# METHODS FOR TREATING HYPERCHOLESTEROLEMIA

## FIELD OF THE INVENTION

Methods are provided for lowering LDL-C levels in an individual having elevated LDL-C levels. Such methods are further useful to treat hypercholesterolemia, and to reduce the risk of coronary heart disease.

## BACKGROUND

Atherosclerosis is a complex, polygenic disease of arterial degeneration that can lead to coronary heart disease (CHD). In Western societies, complications arising from atherosclerosis are the most common causes of death. Several risk factors for CHD have been well-established, and include elevated low density lipoprotein-cholesterol (LDL-C), low levels of high density lipoprotein cholesterol (HDL-C), cigarette smoking, hypertension, age, and family history of early CHD. Given the abundant clinical data and epidemiological studies indicating that lowering LDL-C is beneficial for the prevention of adverse coronary events, the primary target of pharmacological intervention in the treatment and prevention of CHD is lowered LDL-C.

In individuals with autosomal dominant hypercholesterolemia (ADH), elevated LDL-C levels have been linked to mutations in the genes encoding LDL-receptor (LDL-R), apolipoprotein B (apoB), or proprotein convertase subtilisin/kexin type 9 (PCSK9) (Abifadel et al., Nat. Genet., 2003, 34:154-156). The PCSK9 gene (also known as FH3; NARC1; NARC-1; and HCHOLA3) was mapped to Chromosome 1 at location 1p32.3. PCSK9 was identified as a third locus associated with ADH when gain-of-function mutations in PCSK9 were found to be linked to elevated LDL-C levels. ApoB-100 participates in the intracellular assembly and secretion of triglyceride-rich lipoproteins and is a ligand for the LDL-R. PCSK9 is proposed to reduce LDL-R expression levels in the liver. Reduced LDL-R expression results in reduced hepatic uptake of circulating apoB-100-containing lipoproteins, which in turn leads to elevated cholesterol.

Familial hypercholesterolemia (FH) is caused by hundreds of different mutations in the LDL-R, and is phenotypically characterized by elevated plasma LDL-C levels and deposits of LDL-C in tendons, skin and arteries, leading to premature cardiovascular disease. Homozygous and heterozygous mutations in the LDL-R are associated with FH. Likewise, heterozygous and homozygous mutations in the ligand-binding domain of PCSK9 are associated with the FH

phenotype. Mutations in this gene have been associated with a third form of autosomal dominant FH.

In mice genetically deficient in PCSK9, a marked increase in LDL-R expression and increased plasma LDL clearance rate were observed. Conversely, overexpression in mice of wild-type PCSK9, or certain PCSK9 mutants, promotes decreased LDL-R expression and elevated LDL-C levels.

## SUMMARY OF THE INVENTION

Provided herein are methods for the treatment of hypercholesterolemia and/or atherosclerosis, as well as methods for the reduction of elevated LDL-C levels and CHD risk. Methods for treating hypercholesterolemia comprise administering to an individual an antisense compound targeted to a PCSK9 nucleic acid. In such methods, an antisense compound targeted to a PCSK9 nucleic acid may be targeted to sequences as set forth in GENBANK® Accession No. NM_174936.2, nucleotides 25475000 to 25504000 of GENBANK® Accession No. NT_032977.8, or GENBANK® Accession No. AK124635.1.

Methods for treating and/or preventing atherosclerosis comprise administering to an individual an antisense compound targeted to a PCSK9 nucleic acid. Methods for reducing LDL-C levels comprise administering to an individual an antisense compound targeted to a PCSK9 nucleic acid. Methods for reducing CHD risk comprise administering to an individual an antisense compound targeted to a PCSK9 nucleic acid. Such methods may comprise the administration of a therapeutically effective amount of an antisense compound targeted to a PCSK9 nucleic acid.

Methods are provided for reducing LDL-C levels in an individual having elevated LDL-C levels, comprising administering to the individual a therapeutically effective amount of an antisense oligonucleotide targeted to a PCSK9 nucleic acid, thereby reducing LDL-C levels. Also provided are methods for reducing LDL-C levels in an individual comprising selecting an individual having elevated LDL-C levels, and administering to the individual a therapeutically effective amount of an antisense compound targeted to a PCSK9 nucleic acid, and additionally monitoring LDL-cholesterol levels. Further provided are methods for treating atherosclerosis in an individual, comprising selecting an individual diagnosed with atherosclerosis, administering to the individual a therapeutically effective amount of an antisense compound targeted to a PCSK9 nucleic acid, and monitoring atherosclerosis. Also provided are methods for reducing coronary heart disease risk, comprising selecting an individual having elevated LDL-C levels and one or

more additional indicators of coronary heart disease, administering to the individual a therapeutically effective amount of an antisense compound targeted to a PCSK9 nucleic acid, and monitoring LDL-C levels. Additionally provided are methods for treating hypercholesterolemia, comprising administering to an individual diagnosed with hypercholesterolemia a therapeutically effective amount of an antisense oligonucleotide targeted to a PCSK9 nucleic acid, thereby reducing cholesterol levels.

In any of the methods provided, a PCSK9 nucleic acid may be the sequence set forth in SEQ ID NO: 1. Thus, the antisense compound may be targeted to a PCSK9 nucleic acid as set forth in SEQ ID NO: 1.

Any of the methods provided herein may further comprise monitoring LDL-C levels.

An individual may be selected for administration of an antisense compound targeted to a PCSK9 nucleic acid when the individual exhibits an LDL-C level above 100 mg/dL, above 130 mg/dL, above 160 mg/dL, or above 190 mg/dL. Administration of an antisense compound targeted to a PCSK9 nucleic acid may result in an LDL-C level below 190 mg/dL, below 160 mg/dL, below 130 mg/dL, below 100 mg/dL, below 70 mg/dL, or below 50 mg/dL.

In any of the aforementioned methods, administration of the antisense compound may comprise parenteral administration. The parenteral administration may further comprise subcutaneous or intravenous administration.

In any of the methods provided herein, the antisense compound may have least 80%, at least 90%, or at least 95% complementarity to SEQ ID NO: 1. Alternatively, the antisense compound may have 100% complementarity to SEQ ID NO: 1.

The antisense compounds provided herein and employed in any of the described methods may be 8 to 80 subunits in length, 12 to 50 subunits in length, 12 to 30 subunits in length, 15 to 30 subunits in length, 18 to 24 subunits in length, 19 to 22 subunits in length, or 20 subunits in length. Further, the antisense compounds employed in any of the described methods may be antisense oligonucleotides 8 to 80 nucleotides in length, 12 to 50 nucleotides in length, 12 to 30 nucleotides in length 15 to 30 nucleotides in length, 18 to 24 nucleotides in length, 19 to 22 nucleotides in length, or 20 nucleotides in length.

In any of the methods provided, the antisense compound may be an antisense oligonucleotide. Moreover, the antisense oligonucleotide may be a gapmer antisense oligonucleotide. The gapmer antisense oligonucleotide may comprise a gap segment of ten 2'-deoxynucleotides positioned between wing segments of five 2'-MOE nucleotides. The gapmer antisense oligonucleotide may be a gap-widened antisense oligonucleotide, comprising a gap

segment of fourteen 2'-deoxynucleotides positioned between wing segments of three 2'-MOE nucleotides.

In any of the methods provided, the antisense compounds may have at least one modified internucleoside linkage. Additionally, each internucleoside linkage may be a phosphorothioate internucleoside linkage. Each cytosine may be a 5-methyl cytosine.

Also provided herein are antisense compounds targeted to a PCSK9 nucleic acid. Further provided are antisense oligonucleotides targeted to a PCSK9 nucleic acid. The antisense compounds, including antisense oligonucleotides, may be targeted to PCSK9 nucleic acids, which include the sequences as set forth in GENBANK® Accession No. NM_174936.2, nucleotides 25475000 to 25504000 of GENBANK® Accession No. NT_032977.8, or GENBANK® Accession No. AK124635.1. The antisense compounds, including antisense oligonucleotides, may have at least 70%, at least 80%, at least 90%, or at least 95% complementarity to a PCSK9 nucleic acid. The antisense compounds, including antisense oligonucleotides, may have 99% complementarity to a PCSK9 nucleic acid. The antisense compounds, including antisense oligonucleotides, may have 100% complementarity to a PCSK9 nucleic acid. For any of the antisense compounds provided, including antisense oligonucleotides, the PCSK9 nucleic acid may be the sequence set forth in SEQ ID NO: 1.

Antisense compounds targeted to a PCSK9 nucleic acid may be 8 to 80 subunits in length, 12 to 50 subunits in length, 12 to 30 subunits in length, 15 to 30 subunits in length, 18 to 24 subunits in length, 19 to 22 subunits in length, or 20 subunits in length. Antisense oligonucleotides targeted to a PCSK9 nucleic acid may be 8 to 80 subunits in length, 12 to 50 subunits in length, 12 to 30 subunits in length, 15 to 30 subunits in length, 18 to 24 subunits in length, 19 to 22 subunits in length, or 20 subunits in length.

Moreover, the antisense compound may be a gapmer antisense oligonucleotide. The gapmer antisense oligonucleotide may comprise a gap segment of ten 2'-deoxynucleotides positioned between wing segments of five 2'-MOE nucleotides. The gapmer antisense oligonucleotide may be a gap-widened antisense oligonucleotide, comprising a gap segment of fourteen 2'-deoxynucleotides positioned between wing segments of three 2'-MOE nucleotides.

Antisense compounds, including antisense oligonucleotides, targeted to a PCSK9 nucleic acid may have at least one modified internucleoside linkage. Additionally, each internucleoside linkage may be a phosphorothioate internucleoside linkage. Each cytosine may be a 5-methyl cytosine.

Antisense compounds, including antisense oligonucleotides, targeted to a PCSK9 nucleic acid may have at least one modified nucleoside. In certain embodiments, a modified nucleoside is a sugar-modified nucleoside. In certain such embodiments, the sugar-modified nucleosides can further comprise a natural or modified heterocyclic base moiety and/or a natural or modified internucleoside linkage and may include further modifications independent from the sugar modification. In certain embodiments, a sugar modified nucleoside is a 2'-modified nucleoside, wherein the sugar ring is modified at the 2' carbon from natural ribose or 2'-deoxy-ribose.

In certain embodiments, a 2' modified nucleoside has a 2'-F, 2'-$OCH_2$ (2'-OMe) or a 2'-$O(CH_2)_2$-$OCH_3$ (2'-O-methoxyethyl or 2'-MOE) substituent group

In certain embodiments, a 2'-modified nucleoside has a bicyclic sugar moiety. In certain such embodiments, the bicyclic sugar moiety is a D sugar in the alpha configuration. In certain such embodiments, the bicyclic sugar moiety is a D sugar in the beta configuration. In certain such embodiments, the bicyclic sugar moiety is an L sugar in the alpha configuration. In certain such embodiments, the bicyclic sugar moiety is an L sugar in the beta configuration.

In certain embodiments, the bicyclic sugar moiety comprises a bridge group between the 2' and the 4'-carbon atoms. In certain such embodiments, the bridge group comprises from 1 to 8 linked biradical groups. In certain embodiments, the bicyclic sugar moiety comprises from 1 to 4 linked biradical groups. In certain embodiments, the bicyclic sugar moiety comprises 2 or 3 linked biradical groups. In certain embodiments, the bicyclic sugar moiety comprises 2 linked biradical groups. In certain embodiments, a linked biradical group is selected from -O-, -S-, -N(R1)-, -C(R1)(R2)-, -C(R1)=C(R1)-, -C(R1)=N-, -C(=NR1)-, -Si(R1)(R2)-, -S(=O)2-, -S(=O)-, -C(=O)- and -C(=S)-; where each R1 and R2 is, independently, H, hydroxyl, C1-C12 alkyl, substituted C1-C12 alkyl, C2-C12 alkenyl, substituted C2-C12 alkenyl, C2-C12 alkynyl, substituted C2-C12 alkynyl, C5-C20 aryl, substituted C5-C20 aryl, a heterocycle radical, a substituted hetero-cycle radical, heteroaryl, substituted heteroaryl, C5-C7 alicyclic radical, substituted C5-C7 alicyclic radical, halogen, substituted oxy (-O-), amino, substituted amino, azido, carboxyl, substituted carboxyl, acyl, substituted acyl, CN, thiol, substituted thiol, sulfonyl (S(=O)2-H), substituted sulfonyl, sulfoxyl (S(=O)-H) or substituted sulfoxyl; and each substituent group is, independently, halogen, C1-C12 alkyl, substituted C1-C12 alkyl, C2-C12 alkenyl, substituted C2-C12 alkenyl, C2-C12 alkynyl, substituted C2-C12 alkynyl, amino, substituted amino, acyl, substituted acyl, C1-C12 aminoalkyl, C1-C12 aminoalkoxy, substituted C1-C12 aminoalkyl, substituted C1-C12 aminoalkoxy or a protecting group.

In some embodiments, the bicyclic sugar moiety is bridged between the 2' and 4' carbon atoms with a biradical group selected from –O-(CH2)p-, –O-CH2-,–O-CH2CH2-, –O-CH(alkyl)-, -NH-(CH2)p-, -N(alkyl)-(CH2)p-, -O-CH(alkyl)-, -(CH(alkyl))-(CH2)p-, -NH-O-(CH2)p-, -N(alkyl)-O-(CH2)p-, or -O-N(alkyl)-(CH2)p-, wherein p is 1, 2, 3, 4 or 5 and each alkyl group can be further substituted. In certain embodiments, p is 1, 2 or 3.

In one aspect, each of said bridges is, independently, -[C(R1)(R2)]n-, -[C(R1)(R2)]n-O-, -C(R1R2)-N(R1)-O- or –C(R1R2)-O-N(R1)-. In another aspect, each of said bridges is, independently, 4'-(CH2)3-2', 4'-(CH2)2-2', 4'-CH2-O-2', 4'-(CH2)2-O-2', 4'-CH2-O-N(R1)-2' and 4'-CH2-N(R1)-O-2'- wherein each R1 is, independently, H, a protecting group or C1-C12 alkyl.

*Definitions*

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by on of skill in the art to which the invention(s) belong. Unless specific definitions are provided, the nomenclature utilized in connection with, and the procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques may be used for chemical synthesis, chemical analysis, pharmaceutical preparation, formulation and delivery, and treatment of subjects. Certain such techniques and procedures may be found for example in "Antisense Drug Technology: Principles, Strategies, and Applications." by Stanley Crooke, Boca Raton: Taylor & Francis Group, 2008; "Carbohydrate Modifications in Antisense Research" Edited by Sangvi and Cook, American Chemical Society , Washington D.C., 1994; and "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, Pa., 18th edition, 1990; and which is hereby incorporated by reference for any purpose. Where permitted, all patents, patent applications, published applications and publications, GENBANK sequences, websites and other published materials referred to throughout the entire disclosure herein, unless noted otherwise, are incorporated by reference in their entirety. All of the in GENBANK® Accession Nos. along with their associated sequence and structural data pertaining to such sequences including gene organization and structural elements and SNP information that may be found in sequence databases such as the National Center for Biotechnology Information (NCBI) are incorporated herein by reference in their entirety. In the event that there is a plurality of definitions for terms herein, those in this section prevail. Where reference is made to a URL or other such identifier or address, it is understood that such identifiers can change and particular information on the internet can come and go, but

equivalent information can be found by searching the internet. Reference thereto evidences the availability and public dissemination of such information.

A "pharmaceutical composition" means a mixture of substances suitable for administering to an individual. For example, a pharmaceutical composition may comprise an antisense oligonucleotide and a sterile aqueous solution.

"Administering" means providing a pharmaceutical agent to an individual, and includes, but is not limited to administering by a medical professional and self-administering.

"Individual" means a human or non-human animal selected for treatment or therapy.

"Duration" means the period of time during which an activity or event continues. In certain embodiments, the duration of treatment is the period of time during which doses of a pharmaceutical agent are administered.

"Parenteral administration," means administration through injection or infusion. Parenteral administration includes, but is not limited to, subcutaneous administration, intravenous administration, or intramuscular administration.

"Subcutaneous administration" means administration just below the skin. "Intravenous administration" means administration into a vein.

"Dose" means a specified quantity of a pharmaceutical agent provided in a single administration. In certain embodiments, a dose may be administered in two or more boluses, tablets, or injections. For example, in certain embodiments, where subcutaneous administration is desired, the desired dose requires a volume not easily accommodated by a single injection. In such embodiments, two or more injections may be used to achieve the desired dose. In certain embodiments, a dose may be administered in two or more injections to minimize injection site reaction in a individual.

"Dosage unit" means a form in which a pharmaceutical agent is provided. In certain embodiments, a dosage unit is a vial containing lyophilized antisense oligonucleotide. In certain embodiments, a dosage unit is a vial containing reconstituted antisense oligonucleotide.

"Pharmaceutical agent" means a substance provides a therapeutic benefit when administered to a individual. For example, in certain embodiments, an antisense oligonucleotide targeted to PCSK9 is pharmaceutical agent.

"Diluent" means an ingredient in a composition that lacks pharmacological activity, but is pharmaceutically necessary or desirable. For example, in drugs that are injected the diluent may be a liquid, e.g. saline solution.

"Active pharmaceutical ingredient" means the substance in a pharmaceutical composition that provides a desired effect.

"Pharmaceutically acceptable carrier" means a medium or diluent that does not interfere with the structure of the oligonucleotide. Certain, of such carries enable pharmaceutical compositions to be formulated as, for example, tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspension and lozenges for the oral ingestion by a subject.

"Therapeutically effective amount" means an amount of a pharmaceutical agent that provides a therapeutic benefit to an individual. In certain embodiments, a therapeutically effective amount of antisense compound targeted to a PCSK9 nucleic acid is an amount that decreases LDL-C in the individual.

"Hypercholesterolemia" means a condition characterized by elevated serum cholesterol.

"Hyperlipidemia" means a condition characterized by elevated serum lipids.

"Hypertriglyceridemia" means a condition characterized by elevated triglyceride levels.

"Non-familial hypercholesterolemia" means a condition characterized by elevated cholesterol that is not the result of a single gene mutation.

"Polygenic hypercholesterolemia" means a condition characterized by elevated cholesterol that results from the influence of a variety of genetic factors. In certain embodiments, polygenic hypercholesterolemia may be exacerbated by dietary intake of lipids.

"Familial hypercholesterolemia (FH)" means an autosomal dominant metabolic disorder characterized by a mutation in the LDL-receptor (LDL-R) gene, markedly elevated LDL-C and premature onset of atherosclerosis. A diagnosis of familial hypercholesterolemia is made when a individual meets one or more of the following criteria: genetic testing confirming 2 mutated LDL-receptor genes; genetic testing confirming one mutated LDL-receptor gene; document history of untreated serum LDL-cholesterol greater than 500 mg/dL; tendinous and/or cutaneous xanthoma prior to age 10 years; or, both parents have documented elevated serum LDL-cholesterol prior to lipid-lowering therapy consistent with heterozygous familial hypercholesterolemia.

"Homozygous familial hypercholesterolemia" or "HoFH" means a condition characterized by a mutation in both maternal and paternal LDL-R genes.

"Heterozygous familial hypercholesterolemia" or "HeFH" means a condition characterized by a mutation in either the maternal or paternal LDL-R gene.

"Mixed dyslipidemia" means a condition characterized by elevated serum cholesterol and elevated serum triglycerides.

"Diabetic dyslipidemia" or "Type II diabetes with dyslipidemia" means a condition characterized by Type II diabetes, reduced HDL-C, elevated serum triglycerides, and elevated small, dense LDL particles.

"CHD risk equivalents," means indicators of clinical atherosclerotic disease that confer a high risk for coronary heart disease, and include clinical coronary heart disease, symptomatic carotid artery disease, peripheral arterial disease, and/or abdominal aortic aneurysm.

"Metabolic syndrome" means a condition characterized by a clustering of lipid and non-lipid cardiovascular risk factors of metabolic origin. In certain embodiments, metabolic syndrome is identified by the presence of any 3 of the following factors: waist circumference of greater than 102 cm in men or greater than 88 cm in women; serum triglyceride of at least 150 mg/dL; HDL-C less than 40 mg/dL in men or less than 50 mg/dL in women; blood pressure of at least 130/85 mmHg; and fasting glucose of at least 110 mg/dL.

"Non-alcholic fatty liver disease (NAFLD)" means a condition characterized by fatty inflammation of the liver that is not due to excessive alcohol use (for example, alcohol consumption of over 20 g/day). In certain embodiments, NAFLD is related to insulin resistance and the metabolic syndrome.

"Non-alcoholic steatohepatitis (NASH)" means a condition characterized by inflammation and the accumulation of fat and fibrous tissue in the liver, that is not due to excessive alcohol use. NASH is an extreme form of NAFLD.

"Major risk factors" mean factors that contribute to a high risk for coronary heart disease, and include without limitation cigarette smoking, hypertension, low HDL-C, family history of coronary heart disease, and age.

"CHD risk factors" mean CHD risk equivalents and major risk factors.

"Coronary heart disease (CHD)" means a narrowing of the small blood vessels that supply blood and oxygen to the heart, which is often a result of atherosclerosis.

"Reduced coronary heart disease risk" means a reduction in the likelihood that a individual will develop coronary heart disease. In certain embodiments, a reduction in coronary heart disease risk is measured by an improvement in one or more CHD risk factors, for example, a decrease in LDL-C levels.

"Atherosclerosis" means a hardening of the arteries affecting large and medium-sized arteries and is characterized by the presence of fatty deposits. The fatty deposits are called "atheromas" or "plaques," which consist mainly of cholesterol and other fats, calcium and scar tissue, and damage the lining of arteries.

"History of coronary heart disease" means the occurrence of clinically evident coronary heart disease in the medical history of a individual or a individual's family member.

"Early onset coronary heart disease" means a diagnosis of coronary heart disease prior to age 50.

"Statin intolerant individual" means a individual who as a result of statin therapy experiences one or more of creatine kinase increases, liver function test abnormalities, muscle aches, or central nervous system side effects.

"Efficacy" means the ability to produce a desired effect. For example, efficacy of a lipid-lowering therapy may be reduction in the concentration of one or more of LDL-C, VLDL-C, IDL-C, non-HDL-C, ApoB, lipoprotein(a), or triglycerides.

"Acceptable safety profile" means a pattern of side effects that is within clinically acceptable limits.

"Side effects" means physiological responses attributable to a treatment other than desired effects. In certain embodiments, side effects include, without limitation, injection site reactions, liver function test abnormalities, renal function abnormalities, liver toxicity, renal toxicity, central nervous system abnormalities, and myopathies. For example, increased aminotransferase levels in serum may indicate liver toxicity or liver function abnormality. For example, increased bilirubin may indicate liver toxicity or liver function abnormality.

"Injection site reaction" means inflammation or abnormal redness of skin at a site of injection in an individual.

"Individual compliance" means adherence to a recommended or prescribed therapy by a individual.

"Lipid-lowering therapy" means a therapeutic regimen provided to a individual to reduce one or more lipids in a individual. In certain embodiments, a lipid-lowering therapy is provide to reduce one or more of ApoB, total cholesterol, LDL-C, VLDL-C, IDL-C, non-HDL-C, triglycerides, small dense LDL particles, and Lp(a) in a individual.

"Lipid-lowering agent" means a pharmaceutical agent provided to a individual to achieve a lowering of lipids in the individual. For example, in certain embodiments, a lipid-lowering agent is provided to a individual to reduce one or more of ApoB, LDL-C, total cholesterol, and triglycerides.

"LDL-C target" means an LDL-C level that is desired following lipid-lowering therapy.

"Comply" means the adherence with a recommended therapy by a individual.

"Recommended therapy" means a therapeutic regimen recommended by a medical professional for the treatment, amelioration, or prevention of a disease.

"Low LDL-receptor activity" means LDL-receptor activity that is not sufficiently high to maintain clinically acceptable levels of LDL-C in the bloodstream.

"Cardiovascular outcome" means the occurrence of major adverse cardiovascular events.

"Improved cardiovascular outcome" means a reduction in the occurrence of major adverse cardiovascular events, or the risk thereof. Examples of major adverse cardiovascular events include, without limitation, death, reinfarction, stroke, cardiogenic shock, pulmonary edema, cardiac arrest, and atrial dysrhythmia.

"Surrogate markers of cardiovascular outcome" means indirect indicators of cardiovascular events, or the risk thereof. For example, surrogate markers of cardiovascular outcome include carotid intimal media thickness (CIMT). Another example of a surrogate marker of cardiovascular outcome includes atheroma size. Atheroma size may be determined by intravascular ultrasound (IVUS).

"Increased HDL-C" means an increase in serum HDL-C in a individual over time.

"Lipid-lowering" means a reduction in one or more serum lipids in an individual over time.

"Co-administration" means administration of two or more pharmaceutical agents to a individual. The two or more pharmaceutical agents may be in a single pharmaceutical composition, or may be in separate pharmaceutical compositions. Each of the two or more pharmaceutical agents may be administered through the same or different routes of administration. Co-administration encompasses administration in parallel or sequentially.

"Administered concomitantly" refers to the administration of two agents at the same therapeutic time frame, in any manner in which the pharmacological effects of both are manifest in the patient at the same time. Concomitant administration does not require that both agents be administered in a single pharmaceutical composition, in the same dosage form, or by the same route of administration.

"Therapeutic lifestyle change" means dietary and lifestyle changes intended to lower cholesterol and reduce the risk of developing heart disease, and includes recommendations for dietary intake of total daily calories, total fat, saturated fat, polyunsaturated fat, monounsaturated fat, carbohydrate, protein, cholesterol, insoluble fiber, as well as recommendations for physical activity.

"Statin" means a pharmaceutical agent that inhibits the activity of HMG-CoA reductase.

"HMG-CoA reductase inhibitor" means a pharmaceutical agent that acts through the inhibition of the enzyme HMG-CoA reductase.

"Cholesterol absorption inhibitor" means a pharmaceutical agent that inhibits the absorption of exogenous cholesterol obtained from diet.

"LDL apheresis" means a form of apheresis by which LDL-C is removed from blood. Typically, a individual's blood is removed from a vein, and separated into red cells and plasma. LDL-C is filtered out of the plasma prior to return of the plasma and red blood cells to the individual.

"MTP inhibitor" means a pharmaceutical agent that inhibits the enzyme microsomal triglyceride transfer protein.

"Low density lipoprotein-cholesterol (LDL-C)" means cholesterol carried in low density lipoprotein particles. Concentration of LDL-C in serum (or plasma) is typically quantified in mg/dL or nmol/L. "Serum LDL-C" and "plasma LDL-C" mean LDL-C in the serum and plasma, respectively.

"Very low density lipoprotein-cholesterol (VLDL-C)" means cholesterol associated with very low density lipoprotein particles. Concentration of VLDL-C in serum (or plasma) is typically quantified in mg/dL or nmol/L. "Serum VLDL-C" and "plasma VLDL-C" mean VLDL-C in the serum or plasma, respectively.

"Intermediate low density lipoprotein-cholesterol (IDL-C)" means cholesterol associated with intermediate density lipoprotein. Concentration of IDL-C in serum (or plasma) is typically quantified in mg/mL or nmol/L. "Serum IDL-C" and "plasma IDL-C" mean IDL-C in the serum or plasma, respectively.

"Non-high density lipoprotein-cholesterol (Non-HDL-C)" means cholesterol associated with lipoproteins other than high density lipoproteins, and includes, without limitation, LDL-C, VLDL-C, and IDL-C.

"High density lipoprotein-C (HDL-C)" means cholesterol associated with high density lipoprotein particles. Concentration of HDL-C in serum (or plasma) is typically quantified in mg/dL or nmol/L. "Serum HDL-C" and "plasma HDL-C" mean HDL-C in the serum and plasma, respectively.

"Total cholesterol" means all types of cholesterol, including, but not limited to, LDL-C, HDL-C, IDL-C and VLDL-C. Concentration of total cholesterol in serum (or plasma) is typically quantified in mg/dL or nmol/L.

"Lipoprotein(a)" or "Lp(a)" means a lipoprotein particle that is comprised of LDL-C, an apolipoprotein(a) particle, and an apolipoproteinB-100 particle.

"ApoA1" means apolipoprotein-A1 protein in serum. Concentration of ApoA1 in serum is typically quantified in mg/dL or nmol/L.

"ApoB:ApoA1 ratio" means the ratio of ApoB concentration to ApoA1 concentration.

"ApoB-containing lipoprotein" means any lipoprotein that has apolipoprotein B as its protein component, and is understood to include LDL, VLDL, IDL, and lipoprotein(a).

"Small LDL particle" means a subclass of LDL particles characterized by a smaller, denser size compared to other LDL particles. In certain embodiments, intermediate LDL particles are 23-27 nm in diameter. In certain embodiments, large LDL particles are 21.2-23 nm in diameter. In certain embodiments, small LDL particles are 18-21.2 nm in diameter. In certain embodiments, particle size is measured by nuclear magnetic resonance analysis.

"Small VLDL particle" means a subclass of VLDL particles characterized by a smaller, denser size compared to other VLDL particles. In certain embodiments, large VLDL particles are greater than 60 nm in diameter. In certain embodiments, medium VLDL particles are 35-60 nm in diameter. In certain embodiments, small VLDL particles are 27-35 nm in diameter. In certain embodiments, particle size is measured by nuclear magnetic resonance analysis.

"Triglycerides" means lipids that are the triesters of glycerol. "Serum triglycerides" mean triglycerides present in serum. "Liver triglycerides" mean triglycerides present in liver tissue.

"Serum lipids" mean cholesterol and triglycerides in the serum.

"Elevated total cholesterol" means total cholesterol at a concentration in a individual at which lipid-lowering therapy is recommended, and includes, without limitation, elevated LDL-C", "elevated VLDL-C," "elevated IDL-C," and "elevated non-HDL-C." In certain embodiments, total cholesterol concentrations of less than 200 mg/dL, 200-239 mg/dL, and greater than 240 mg/dL are considered desirable, borderline high, and high, respectively. In certain embodiments, LDL-C concentrations of 100 mg/dL, 100-129 mg/dL, 130-159 mg/dL, 160-189 mg/dL, and greater than 190 mg/dL are considered optimal, near optimal/above optimal, borderline high, high, and very high, respectively.

"Elevated triglyceride" means concentrations of triglyceride in the serum or liver at which lipid-lowering therapy is recommended, and includes "elevated serum triglyceride" and "elevated liver triglyceride." In certain embodiments, serum triglyceride concentration of 150-199 mg/dL, 200-499 mg/dL, and greater than or equal to 500 mg/dL is considered borderline high, high, and very high, respectively.

"Elevated small LDL particles" means a concentration of small LDL particles in a individual at which lipid-lowering therapy is recommended.

"Elevated small VLDL particles" means a concentration of small VLDL particles in a individual at which lipid-lowering therapy is recommended.

"Elevated lipoprotein(a)" means a concentration of lipoprotein(a) in a individual at which lipid-lowering therapy is recommended.

"Low HDL-C" means a concentration of HDL-C in a individual at which lipid-lowering therapy is recommended. In certain embodiments lipid-lowering therapy is recommended when low HDL-C is accompanied by elevations in non-HDL-C and/or elevations in triglyceride. In certain embodiments, HDL-C concentrations of less than 40 mg/dL are considered low. In certain embodiments, HDL-C concentrations of less than 50 mg/dL are considered low.

"ApoB" means apolipoprotein B-100 protein. Concentration of ApoB in serum (or plasma) is typically quantified in mg/dL or nmol/L. "Serum ApoB" and "plasma ApoB" mean ApoB in the serum and plasma, respectively.

"LDL/HDL ratio" means the ratio of LDL-C to HDL-C.

"Oxidized-LDL" or "Ox-LDL-C" means LDL-C that is oxidized following exposure to free radicals.

"Individual having elevated LDL-C levels" means an individual who has been identified by a medical professional (e.g. a physician) as having LDL-C levels near or above the level at which therapeutic intervention is recommended, according to guidelines recognized by medical professionals. Such an individual may also be considered "in need of treatment" to decrease LDL-C levels.

"Individual having elevated apoB-100 levels" means an individual who has been identified as having apoB-100 levels near or below the level at which therapeutic intervention is recommended, according to guidelines recognized by medical professionals. Such an individual may also be considered "in need of treatment" to decrease apoB-100 levels.

"Treatment of elevated LDL-C levels" means administration of an antisense compound targeted to a PCSK9 nucleic acid to an individual having elevated LDL-C levels.

"Treatment of atherosclerosis" means administration of an antisense compound targeted to a PCSK9 nucleic acid to an individual who, based upon a physician's assessment, has or is likely to have atherosclerosis. "Prevention of atherosclerosis" means administration of an antisense compound targeted to a PCSK9 nucleic acid to an individual who, based upon a physician's assessment, is susceptible to atherosclerosis.

"Target nucleic acid," "target RNA," "target RNA transcript" and "nucleic acid target" all mean any nucleic acid capable of being targeted by antisense compounds.

"PCSK9 nucleic acid" means any nucleic acid encoding PCSK9. For example, in certain embodiments, a PCSK9 nucleic acid includes, without limitation, a DNA sequence encoding PCSK9, an RNA sequence transcribed from DNA encoding PCSK9, and an mRNA sequence encoding PCSK9. "PCSK9 mRNA" means an mRNA encoding a PCSK9 protein.

"Targeting" means the process of design and selection of an antisense compound that will specifically hybridize to a target nucleic acid and induce a desired effect.

"Targeted" means having a nucleobase sequence that will allow specific hybridization of an antisense compound to a target nucleic acid to induce a desired effect. In certain embodiments, a desired effect is reduction of a target nucleic acid. In certain such embodiments, a desired effect is reduction of PCSK9 mRNA.

"Antisense inhibition" means reduction of a target nucleic acid levels in the presence of an antisense compound complementary to a target nucleic acid compared to target nucleic acid levels in the absence of the antisense compound.

"Target region" means a fragment of a target nucleic acid to which one or more antisense compounds is targeted.

"Target segment" means the sequence of nucleotides of a target nucleic acid to which an antisense compound is targeted. "5' target site" refers to the 5'-most nucleotide of a target segment. "3' target site" refers to the 3'-most nucleotide of a target segment.

"Active target region" means a target region to which one or more active antisense compounds is targeted. "Active antisense compounds" means antisense compounds that reduce target nucleic acid levels.

"Hybridization" means the annealing of complementary nucleic acid molecules. In certain embodiments, complementary nucleic acid molecules include, but are not limited to, an antisense compound and a nucleic acid target. In certain such embodiments, complementary nucleic acid molecules include, but are not limited to, an antisense oligonucleotide and a nucleic acid target

"Stringent hybridization conditions" means conditions under which a nucleic acid molecule, such as an antisense compound, will hybridize to a target nucleic acid sequence, but to a minimal number of other sequences.

"Specifically hybridizable" means an antisense compound that hybridizes to a target nucleic acid to induce a desired effect, while exhibiting minimal or no effects on non-target nucleic acids.

"Complementarity" means the capacity for pairing between nucleobases of a first nucleic acid and a second nucleic acid.

"Fully complementary" means each nucleobase of a first nucleic acid is capable of pairing with each nucleobase of a second nucleic acid. In certain embodiments, a first nucleic acid is an antisense compound and a target nucleic acid is a second nucleic acid. In certain such embodiments, an antisense oligonucleotide is a first nucleic acid and a target nucleic acid is a second nucleic acid.

"Non-complementary nucleobase" means a nucleobase of first nucleic acid that is not capable of pairing with the corresponding nucleobase of a target nucleic acid. "Mismatch" a nucleobase of first nucleic acid that is not capable of pairing with the corresponding nucleobase of a target nucleic acid.

"Portion" means a defined number of contiguous (i.e. linked) nucleobases of a target nucleic acid. In certain embodiments, a portion is a defined number of contiguous nucleobases of a target nucleic acid. In certain embodiments, a portion is a defined number of contiguous nucleobases of an antisense compound.

"Oligomeric compound" means a polymer of linked monomeric subunits which is capable of hybridizing to at least a region of an RNA molecule.

"Antisense compound" means an oligomeric compound that is is capable of undergoing hybridization to a target nucleic acid through hydrogen bonding.

"Oligonucleotide" means a polymer of linked nucleosides each of which can be modified or unmodified, independent one from another.

"Oligonucleoside" means an oligonucleotide in which the internucleoside linkages do not contain a phosphorus atom.

"Unmodified nucleotide" means a nucleotide composed of naturally occuring nucleobases, sugar moieties and internucleoside linkages. In certain embodiments, an unmodified nucleotide is an RNA nucleotide (i.e., β-D-ribonucleosides) or a DNA nucleotide (i.e., β-D-deoxyribonucleoside).

"Antisense oligonucleotide" means a single-stranded oligonucleotide having a nucleobase sequence that will permits hybridization to a corresponding region of a target nucleic acid.

"Motif" means the pattern of unmodified and modified nucleosides in an antisense compound.

"Chimeric antisense compounds" means an antisense compounds that have at least 2 chemically distinct regions, each region having a plurality of subunits. A "gapmer" means an

antisense compound in which an internal position having a plurality of nucleotides that supports RNaseH cleavage is positioned between external regions having one or more nucleotides that are chemically distinct from the nucleosides of the internal region. A "gap segment" means the plurality of nucleotides that make up the internal region of a gapmer. A "wing segment" means the external region of a gapmer.

"Gap-widened" means an antisense compound has a gap segment of 12 or more contiguous 2'-deoxyribonucleotides positioned between 5' and 3' wing segments having from one to six nucleotides having modified sugar moieties.

"Nucleoside" means a nucleobase linked to a sugar.

"Nucleobase" means a heterocyclic base moiety capable of pairing with a base of another nucleic acid.

"Nucleotide" means a nucleoside having a phosphate group covalently linked to the sugar portion of the nucleoside.

"Nucleobase sequence" means the order of contiguous nucleobases independent of any sugar, linkage, and/or nucleobase modification.

"Modified nucleotide" means a nucleotide having, independently, a modified sugar moiety, modified internucleoside linkage, or modified nucleobase.

"Modified nucleoside" means a nucleotide having, independently, a modified sugar moiety or modified nucleobase.

"Contiguous nucleobases" means nucleobases immediately adjacent to each other.

"Modified oligonucleotide" means an oligonucleotide comprising a modified internucleoside linkage, a modified sugar, and/or a modified nucleobase.

"Single-stranded modified oligonucleotide" means a modified oligonucleotide which is not hybridized to a complementary strand.

"Internucleoside linkage" refers to the chemical bond between nucleosides.

"Linked nucleoside" means adjacent nucleosides which are bonded together.

"Linked deoxynucleoside" means a nucleic acid base (A, G, C, T, U) substituted by deoxyribose linked by a phosphate ester to form a nucleotide.

"Naturally occurring internucleoside linkage" means a 3' to 5' phosphodiester linkage.

"Modified internucleoside linkage" means substitution and/or any change from a naturally occurring internucleoside bond. In certain instances, the modified internucleoside linkage refers to a phosphodiester internucleoside bond.

"Phosphorothioate linkage" means a linkage between nucleosides where the phosphodiester bond is modified by replacing one of the non-bridging oxygen atoms with a sulfur atom. A phosphorothioate linkage is a modified internucleoside linkage.

"Modified sugar moiety" means substitution and/or any change from a natural sugar moiety. For the purposes of this disclosure, a "natural sugar moiety" is a sugar moiety found in DNA (2'-H) or RNA (2'-OH).

"Modified sugar" refers to a substitution and /or any change from a natural sugar.

"Bicyclic sugar" means a furosyl ring modified by the bridging of the two non-geminal ring atoms. A bicyclic sugar is a modified sugar.

"Modified nucleobase" means any nucleobase other than adenine, cytosine, guanine, thymidine, or uracil. An "unmodified nucleobase" means the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U).

"Modified sugar moiety" means a sugar moiety having a substitution and/or any change from a natural sugar moiety.

"Natural sugar moiety" means a sugar moiety found in DNA (2'-H) or RNA (2'-OH).

"2'-O-methoxyethyl sugar moiety" means a 2'-substituted furosyl ring having a 2'-$O(CH2)_2$-$OCH_3$ (2'-O-methoxyethyl or 2'-MOE) substituent group.

"2'-O-methoxyethyl nucleotide" means a nucleotide comprising a 2'-O-methoxyethyl modified sugar moiety.

"2'-O-methoxyethyl" refers to an O-methoxy-ethyl modification of the 2' position of a furosyl ring. A 2'-O-methoxyethyl modified sugar is a modified sugar.

"Bicyclic nucleic acid sugar moiety" means a furosyl ring modified by the bridging of two non-geminal ring atoms.

"5-methylcytosine" means a cytosine modified with a methyl group attached to the 5' position. A 5-methylcytosine is a modified nucleobase.

"Prodrug" means a therapeutic agent that is prepared in an inactive form that is converted to an active form (i.e., drug) within the body or cells thereof by the action of endogenous enzymes or other chemicals and/or conditions.

"Pharmaceutically acceptable salts" means physiologically and pharmaceutically acceptable salts of antisense compounds, i.e., salts that retain the desired biological activity of the parent oligonucleotide and do not impart undesired toxicological effects thereto.

"Salts" refers to physiologically and pharmaceutically acceptable salts of antisense compounds, i.e., salts that retain the desired biological activity of the parent oligonucleotide and do not impart undesired toxicological effects thereto.

"Cures" means a method or course that restores health or a prescribed treatment for an illness.

"Slows progression" means decrease in the development of the said disease.

"Cap structure" or "terminal cap moiety" means chemical modifications, which have been incorporated at either terminus of an antisense compound.

"ISIS 301012" means a lipid-lowering agent that is an antisense oligonucleotide having the sequence "GCCTCAGTCTGCTTCGCACC" (SEQ ID NO: 457), where each internucleoside linkage is a phosphorothioate internucleoside linkage, each cytosine is a 5-methylcytosine, nucleotides 6-15 are 2'-deoxynucleotides, and nucleotides 1-5 and 16-20 are 2'-O-methoxyethyl nucleotides.

*Overview*

Elevated levels of LDL-cholesterol (HDL-C) are recognized as a major independent risk factor for coronary heart disease (CHD). Even in individuals undergoing aggressive treatment with currently available cholesterol-lowering agents to reduce LDL-cholesterol (LDL-C) levels, coronary events still occur, and elevated LDL-C levels remain a major risk factor for coronary heart disease in these individuals. Furthermore, many individuals undergoing LDL-lowering therapy do not reach their target LDL-C levels, and thus remain at risk for CHD. Accordingly, there is a need for additional LDL-C lowering agents.

The antisense compounds and methods provided herein are useful for the treatment of hypercholesterolemia. Treatment of hypercholesterolemia encompasses a therapeutic regimen that results in a clinically desirable outcome. For example, the antisense compounds and methods provided herein are useful for the treatment of elevated cholesterol, such as elevated LDL-C. In addition, the antisense compounds and methods provided herein may be used to reduce the risk of CHD, in individuals exhibiting one or more risk factors for CHD. Furthermore, the antisense compounds and methods provided herein may be used to treat and/or prevent atherosclerosis.

As illustrated herein, administration of an antisense oligonucleotide targeted to PCSK9 to animals fed a high-fat diet (an experimental model of hyperlipidemia) resulted in antisense inhibition of PCSK9, upregulation of the LDL-R, reduction of LDL-C levels, and reduction of liver triglycerides. Thus, it is demonstrated that in an experimental model of hyperlipidemia,

antisense inhibition of PCSK9 results in lowering LDL-C levels. Accordingly, provided herein are methods for the treatment of reducing LDL-C levels through the administration of an antisense compound targeted to a PCSK9 nucleic acid. Increased LDL-C levels are considered a risk factor for CHD, and are also linked to atherosclerosis. Accordingly, also provided herein are methods for the reduction of CHD risk, and for the prevention and/or treatment of atherosclerosis. Also provided herein are methods for the treatment of conditions characterized by elevated liver triglycerides, such as hepatic steatosis.

*Certain Indications*

In certain embodiments, the invention provides methods of treating an individual comprising administering one or more pharmaceutical compositions of the present invention. In certain embodiments, the individual has hypercholesterolemia, mixed dyslipidemia, atherosclerosis, a risk of developing atherosclerosis, coronary heart disease, a history of coronary heart disease, early onset coronary heart disease, acute coronary syndrome, one or more risk factors for coronary heart disease, type II diabetes, type II diabetes with dyslipidemia, dyslipidemia, hypertriglyceridemia, hyperlipidemia, hyperfattyacidemia, hepatic steatosis, non-alcoholic steatohepatitis, or non-alcoholic fatty liver disease.

Guidelines for lipid-lowering therapy were established in 2001 by Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP), and updated in 2004 (Grundy et al., Circulation, 2004, 110, 227-239). The guidelines include obtaining a complete lipoprotein profile, typically after a 9 to 12 hour fast, for determination of LDL-C, total cholesterol, and HDL-C levels. According to the most recently established guidelines, LDL-C levels of 130-159 mg/dL, 160-189 mg/dL, and greater than or equal to 190 mg/dL are considered borderline high, high, and very high, respectively. Total cholesterol levels of 200-239 and greater than or equal to 240 mg/dL are considered borderline high and high, respectively. HDL-C levels of less than 40 mg/dL are considered low.

In certain embodiments, the individual has been identified as in need of lipid-lowering therapy. In certain such embodiments, the individual has been identified as in need of lipid-lowering therapy according to the guidelines established in 2001 by Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP), and updated in 2004 (Grundy et al., Circulation, 2004, 110, 227-239). In certain such embodiments, the individual in need of lipid-lowering therapy has LDL-C above 190 mg/dL. In certain such embodiments, the individual in need of lipid-lowering therapy has LDL-C above 160 mg/dL. In certain such

embodiments, the individual in need of lipid-lowering therapy has LDL-C above 130 mg/dL. In certain such embodiments, the individual in need of lipid-lowering therapy has LDL-C above 100 mg/dL. In certain such embodiments, the individual in need of lipid-lowering therapy should maintain LDL-C below 160 mg/dL. In certain such embodiments, the individual in need of lipid-lowering therapy should maintain LDL-C below 130 mg/dL. In certain such embodiments, the individual in need of lipid-lowering therapy should maintain LDL-C below 100 mg/dL. In certain such embodiments, the individual should maintain LDL-C below 70 mg/dL or even below 50 mg/dL.

In certain embodiments, the invention provides methods for reducing ApoB in an individual. In certain embodiments, the invention provides methods for reducing ApoB-containing lipoprotein in an individual. In certain embodiments, the invention provides methods for reducing LDL-C in an individual. In certain embodiments, the invention provides methods for reducing VLDL-C in an individual. In certain embodiments, the invention provides methods for reducing IDL-C in an individual. In certain embodiments, the invention provides methods for reducing non-HDL-C in an individual. In certain embodiments the invention provides methods for reducing Lp(a) in an individual. In certain embodiments, the invention provides methods for reducing serum triglyceride in an individual. In certain embodiments, the invention provides methods for reducing liver triglyceride in an individual. In certain embodiments, the invention provides methods for reducing Ox-LDL-C in an individual. In certain embodiments, the invention provides methods for reducing small LDL particles in an individual. In certain embodiments, the invention provides methods for reducing small VLDL particles in an individual. In certain embodiments, the invention provides methods for reducing phospholipids in an individual. In certain embodiments, the invention provides methods for reducing oxidized phospholipids in an individual.

In certain embodiments, the methods provided by the present invention do not lower HDL-C. In certain embodiments, the methods provided by the present invention do not result in accumulation of lipids in the liver.

In one embodiment are methods for decreasing LDL-C levels, or alternatively methods for treating hypercholesterolemia, by administering to an individual suffering from elevated LDL-C levels a therapeutically effective amount of an antisense compound targeted to a PCSK9 nucleic acid. In another embodiment, a method of decreasing LDL-C levels comprises selecting an individual in need of a decrease in LDL-C levels, and administering to the individual a therapeutically effective amount of an antisense compound targeted to a PCSK9 nucleic acid. In

a further embodiment, a method of reducing coronary heart disease risk includes selecting an individual having elevated LDL-C levels and one or more additional indicators of coronary heart disease risk, and administering to the individual a therapeutically effective amount of an antisense compound targeted to a PCSK9 nucleic acid.

In other embodiments, the LDL-C level is from 100-129 mg/dL, from 130 to 159 mg/dL, from 160-189 mg/dL, or greater than or equal to 190 mg/dL.

In one embodiment, administration of a therapeutically effective amount of an antisense compound targeted to a PCSK9 nucleic acid is accompanied by monitoring of LDL-C levels in the serum of an individual, to determine an individual's response to administration of the antisense compound. An individual's response to administration of the antisense compound is used by a physician to determine the amount and duration of therapeutic intervention.

In one embodiment, administration of an antisense compound targeted to a PCSK9 nucleic acid results in LDL-C levels below 190 mg/dL, below 160 mg/dL, below 130 mg/dL, below 100 mg/dL, below 70 mg/dL, or below 50 mg/dL. In another embodiment, administration of an antisense compound targeted to a PCSK9 nucleic acid decreases LDL-C by at least 15%, by at least 25%, by at least 50%, by at least 60%, by at least 70%, by at least 75%, by at least 80%, by at least 85%, by at least 90%, or by at least 95%.

An individual having elevated LDL-C levels may also exhibit reduced HDL-C levels and/or elevated total cholesterol levels. Accordingly, in one embodiment a therapeutically effective amount of an antisense compound targeted to a PCSK9 nucleic acid is administered to an individual having elevated LDL-C levels, who also has reduced HDL-C levels and/or elevated total cholesterol levels.

Individuals having elevated LDL-C levels may also exhibit elevated triglyceride levels. Accordingly, in one embodiment a therapeutically effective amount of an antisense compound targeted to a PCSK9 nucleic acid is administered to an individual having elevated LDL-C levels, and also having elevated triglyceride levels.

Atherosclerosis can lead to coronary heart disease, stroke, or peripheral vascular disease. Elevated LDL-C levels are considered a risk factor in the development and progression of atherosclerosis. Accordingly, in one embodiment, a therapeutically effective amount of an antisense compound targeted to a PCSK9 nucleic acid is administered to an individual having atherosclerosis. In a further embodiment, a therapeutically effective amount of antisense compound targeted to a PCSK9 nucleic acid is administered to an individual susceptible to atherosclerosis. Atherosclerosis is assessed directly through routine imaging techniques such as,

for example, ultrasound imaging techniques that reveal carotid intimomedial thickness. Accordingly, treatment and/or prevention of atherosclerosis further include monitoring atherosclerosis through routine imaging techniques. In one embodiment, administration of an antisense compound targeted to a PCSK9 nucleic acid leads to a lessening of the severity of atherosclerosis, as indicated by, for example, a reduction of carotid intimomedial thickness in arteries.

Measurements of cholesterol, lipoproteins and triglycerides are obtained using serum or plasma collected from an individual. Methods of obtaining serum or plasma samples are routine, as are methods of preparation of the serum samples for analysis of cholesterol, triglycerides, and other serum markers.

A physician may determine the need for therapeutic intervention for individuals in cases where more or less aggressive LDL-lowering therapy is needed. The practice of the methods herein may be applied to any altered guidelines provided by the NCEP, or other entities that establish guidelines for physicians used in treating any of the diseases or conditions listed herein, for determining coronary heart disease risk and diagnosing metabolic syndrome.

In one embodiment, administration of an antisense compound targeted to a PCSK9 nucleic acid is parenteral administration. Parenteral administration may be intravenous or subcutaneous administration. Accordingly, in another embodiment, administration of an antisense compound targeted to a PCSK9 nucleic acid is intravenous or subcutaneous administration. Administration may include multiple doses of an antisense compound targeted to a PCSK9 nucleic acid.

In certain embodiments, a pharmaceutical composition comprising an antisense compound targeted to PCSK9 is for use in therapy. In certain embodiments, the therapy is the reduction of LDL-C, ApoB, VLDL-C, IDL-C, non-HDL-C, Lp(a) , serum triglyceride, liver triglyceride, Ox-LDL-C, small LDL particles, small VLDL, phospholipids, or oxidized phospholipids in an individual. In certain embodiments, the therapy is the treatment of hypercholesterolemia, mixed dyslipidemia, atherosclerosis, a risk of developing atherosclerosis, coronary heart disease, acute coronary syndrome, a history of coronary heart disease, early onset coronary heart disease, one or more risk factors for coronary heart disease, type II diabetes, type II diabetes with dyslipidemia, dyslipidemia, hypertriglyceridemia, hyperlipidemia, hyperfattyacidemia, hepatic steatosis, non-alcoholic steatohepatitis, or non-alcoholic fatty liver disease. In additional embodiments, the therapy is the reduction of CHD risk. In certain aspects,

the therapy is prevention of atherosclerosis. In certain embodiments, the therapy is the prevention of coronary heart disease.

In certain embodiments, a pharmaceutical composition comprising an antisense compound targeted to PCSK9 is used for the preparation of a medicament for reducing LDL-C, ApoB, VLDL-C, IDL-C, non-HDL-C, Lp(a), serum triglyceride, liver triglyceride, Ox-LDL-C, small LDL particles, small VLDL, phospholipids, or oxidized phospholipids in an individual. In certain embodiments pharmaceutical composition comprising an antisense compound targeted to PCKS9 is used for the preparation of a medicament for reducing coronary heart disease risk. In certain embodiments, an antisense compound targeted to PCSK9 is used for the preparation of a medicament for the treatment of hypercholesterolemia, mixed dyslipidemia, atherosclerosis, a risk of developing atherosclerosis, coronary heart disease, a history of coronary heart disease, early onset coronary heart disease, one or more risk factors for coronary heart disease, type II diabetes, type II diabetes with dyslipidemia, dyslipidemia, hypertriglyceridemia, hyperlipidemia, hyperfattyacidemia, hepatic steatosis, non-alcoholic steatohepatitis, or non-alcoholic fatty liver disease.

*Certain Combination Therapies*

In certain embodiments, one or more pharmaceutical compositions of the present invention are co-administered with one or more other pharmaceutical agents. In certain embodiments, such one or more other pharmaceutical agents are designed to treat the same disease or condition as the one or more pharmaceutical compositions of the present invention. In certain embodiments, such one or more other pharmaceutical agents are designed to treat a different disease or condition as the one or more pharmaceutical compositions of the present invention. In certain embodiments, such one or more other pharmaceutical agents are designed to treat an undesired effect of one or more pharmaceutical compositions of the present invention. In certain embodiments, one or more pharmaceutical compositions of the present invention are co-administered with another pharmaceutical agent to treat an undesired effect of that other pharmaceutical agent. In certain embodiments, one or more pharmaceutical compositions of the present invention and one or more other pharmaceutical agents are administered at the same time. In certain embodiments, one or more pharmaceutical compositions of the present invention and one or more other pharmaceutical agents are administered at different times. In certain embodiments, one or more pharmaceutical compositions of the present invention and one or more other pharmaceutical agents are prepared together in a single formulation. In certain

embodiments, one or more pharmaceutical compositions of the present invention and one or more other pharmaceutical agents are prepared separately.

In certain embodiments, pharmaceutical agents that may be co-administered with a pharmaceutical composition of the present invention include lipid-lowering agents or LXR agonists. In certain such embodiments, pharmaceutical agents that may be co-administered with a pharmaceutical composition of the present invention include, but are not limited to atorvastatin, simvastatin, rosuvastatin, and ezetimibe. In certain such embodiments, the lipid-lowering agent is administered prior to administration of a pharmaceutical composition of the present invention. In certain such embodiments, the lipid-lowering agent is administered following administration of a pharmaceutical composition of the present invention. In certain such embodiments the lipid-lowering agent is administered at the same time as a pharmaceutical composition of the present invention. In certain such embodiments the dose of a co-administered lipid-lowering agent is the same as the dose that would be administered if the lipid-lowering agent was administered alone. In certain such embodiments the dose of a co-administered lipid-lowering agent is lower than the dose that would be administered if the lipid-lowering agent was administered alone. In certain such embodiments the dose of a co-administered lipid-lowering agent is greater than the dose that would be administered if the lipid-lowering agent was administered alone.

In certain embodiments, a co-administered lipid-lowering agent is a HMG-CoA reductase inhibitor. In certain such embodiments the HMG-CoA reductase inhibitor is a statin. In certain such embodiments, the statin is selected from, for example, atorvastatin, simvastatin, pravastatin, fluvastatin, and rosuvastatin.

In certain embodiments, a co-administered lipid-lowering agent is a cholesterol absorption inhibitor. In certain such embodiments, cholesterol absorption inhibitor is ezetimibe.

In certain embodiments, a co-administered lipid-lowering agent is a co-formulated HMG-CoA reductase inhibitor and cholesterol absorption inhibitor. In certain such embodiments the co-formulated lipid-lowering agent is ezetimibe/simvastatin.

In certain embodiments, a co-administered lipid-lowering agent is a microsomal triglyceride transfer protein inhibitor (MTP inhibitor).

In certain embodiments, a co-administered lipid-lowering agent is an oligonucleotide targeted to ApoB.

In certain embodiments, a co-administered pharmaceutical agent is a bile acid sequestrant. In certain such embodiments, the bile acid sequestrant is selected from cholestyramine, colestipol, and colesevelam.

In certain embodiments, a co-administered pharmaceutical agent is a nicotinic acid. In certain such embodiments, the nicotinic acid is selected from immediate release nicotinic acid, extended release nicotinic acid, and sustained release nicotinic acid.

In certain embodiments, a co-administered pharmaceutical agent is a fibric acid. In certain such embodiments, a fibric acid is selected from gemfibrozil, fenofibrate, clofibrate, bezafibrate, and ciprofibrate.

Further examples of pharmaceutical agents that may be co-administered with a pharmaceutical composition of the present invention include, but are not limited to, corticosteroids, including but not limited to prednisone; LXR agonists; immunoglobulins, including, but not limited to intravenous immunoglobulin (IVIg); analgesics (e.g., acetaminophen); anti-inflammatory agents, including, but not limited to non-steroidal anti-inflammatory drugs (e.g., ibuprofen, COX-1 inhibitors, and COX-2, inhibitors); salicylates; antibiotics; antivirals; antifungal agents; antidiabetic agents (e.g., biguanides, glucosidase inhibitors, insulins, sulfonylureas, and thiazolidenediones); adrenergic modifiers; diuretics; hormones (e.g., anabolic steroids, androgen, estrogen, calcitonin, progestin, somatostan, and thyroid hormones); immunomodulators; muscle relaxants; antihistamines; osteoporosis agents (e.g., biphosphonates, calcitonin, and estrogens); prostaglandins, antineoplastic agents; psychotherapeutic agents; sedatives; poison oak or poison sumac products; antibodies; and vaccines.

In certain embodiments, the pharmaceutical compositions of the present invention may be administered in conjunction with a lipid-lowering therapy. In certain such embodiments, a lipid-lowering therapy is therapeutic lifestyle change. In certain such embodiments, a lipid-lowering therapy is LDL apheresis.

*Antisense Compounds*

Oligomeric compounds include, but are not limited to, oligonucleotides, oligonucleosides, oligonucleotide analogs, oligonucleotide mimetics, antisense compounds, antisense oligonucleotides, and siRNAs. An oligomeric compound may be "antisense" to a target nucleic acid, meaning that is is capable of undergoing hybridization to a target nucleic acid through hydrogen bonding.

In certain embodiments, an antisense compound has a nucleobase sequence that, when written in the 5' to 3' direction, comprises the reverse complement of the target segment of a target nucleic acid to which it is targeted. In certain such embodiments, an antisense

oligonucleotide has a nucleobase sequence that, when written in the 5' to 3' direction, comprises the reverse complement of the target segment of a target nucleic acid to which it is targeted.

In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid is 8 to 80, 12 to 50, 12 to 30 or 15 to 30 subunits in length. In other words, antisense compounds are from 8 to 80, 12 to 50, 12 to 30 or 15 to 30 linked subunits. In certain such embodiments, the antisense compounds are 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 subunits in length.

In certain embodiments, an antisense oligonucleotide targeted to a PCSK9 nucleic acid is 12 to 30 nucleotides in length. In certain such embodiments, an antisense oligonucleotide targeted to a PCSK9 nucleic acid is 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length.

In certain embodiment, an antisense compound targeted to a PCSK9 nucleic acid is 15 to 30 subunits in length. In other words, antisense compounds are from 15 to 30 linked subunits. In certain such embodiments, the antisense compounds are 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 subunits in length.

In certain embodiments, an antisense oligonucleotide targeted to a PCSK9 nucleic acid is 15 to 30 nucleotides in length. In certain such embodiments, an antisense oligonucleotide targeted to a PCSK9 nucleic acid is 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length.

In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid is 18 to 24 subunits in length. In other words, antisense compounds are from 18 to 24 linked subunits. In one embodiment, the antisense compounds are 18, 19, 20, 21, 22, 23, or 24 subunits in length.

In certain embodiments, an antisense oligonucleotide targeted to a PCSK9 nucleic acid is 18 to 24 nucleotides in length. In certain such embodiments, an antisense oligonucleotide targeted to a PCSK9 nucleic acid is 18, 19, 20, 21, 22, 23, or 24 nucleotides in length.

In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid is 19 to 22 subunits in length. In other words, antisense compounds are from 19 to 22 linked subunits. This embodies antisense compounds of 19, 20, 21, or 22 subunits in length.

In certain embodiments, an antisense oligonucleotide targeted to a PCSK9 nucleic acid is 19 to 22 nucleotides in length. In certain such embodiments, an antisense oligonucleotide targeted to a PCSK9 nucleic acid is 19, 20, 21, or 22 nucleotides in length.

In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid is 20 subunits in length. In certain such embodiments, antisense compounds are 20 linked subunits in length.

In certain embodiments, an antisense oligonucleotide targeted to a PCSK9 nucleic acid is 20 nucleotides in length. In certain such embodiments, an antisense oligonucleotide targeted to an PCSK9 nucleic acid is 20 linked nucleotides in length.

In certain embodiments, antisense compounds target a range of a PCSK9 nucleic acid. In certain embodiment, such compounds contain at least an 8 nucleotide core sequence in common. In certain embodiments, such compounds sharing at least an 8 nucleotide core sequence target a region identified herein.

In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid may target the following nucleotide regions of SEQ ID NO: 1: 294-317, 406-440, 406-526, 410-436, 410-499, 446-526, 545-581, 591-619, 591-704, 591-743, 595-622, 600-626, 600-639, 600-670, 601-628, 602-628, 603-630, 611-636, 620-647, 638-665, 648-674, 657-684, 705-743, 782-810, 821-859, 835-859, 835-917, 835-942, 860-887, 860-899, 860-909, 860-917, 869-895, 878-905, 888-909, 923-952, 960-1034, 960-1173, 960-986, 967-991, 970-1023, 970-1064, 970-1117, 970-996, 977-1004, 985-1011, 989-1016, 992-1019, 997-1024, 997-1024, 998-1025, 999-1026, 1000-1027, 1001-1028, 1002-1029, 1003-1029, 1004-1029, 1005-1029, 1006-1029, 1007-1034, 1036-1061, 1045-1072, 1076-1096, 1088-1115, 1098-1123, 1200-1251, 1210-1237, 1219-1245, 1228-1251, 1273-1444, 1295-1316, 1318-1345, 1328-1354, 1337-1361, 1344-1371, 1354-1377, 1380-1406, 1389-1416, 1400-1426, 1409-1434, 1465-1491, 1465-1602, 1474-1499, 1482-1519, 1513-1540, 1523-1549, 1526-1602, 1526-1624, 1532-1558, 1541-1568, 1552-1579, 1560-1587, 1561-1589, 1564-1591, 1565-1592, 1566-1592, 1567-1592, 1570-1597, 1571-1599, 1605-1706, 1628-1706, 1640-1666, 1672-1698, 1681-1706, 1735-1761, 1735-1765, 1740-1765, 1849-1876, 1849-1879, 1850-1877, 1851-1877, 1852-1878, 1852-1879, 1853-1879, 1854-1879, 1905-1955, 1915-1942, 1916-1943, 1917-1944, 1918-1945, 1919-1946, 1920-1939, 1920-1947, 1921-1948, 1922-1949, 1923-1950, 1924-1951, 1925-1952, 1926-1952, 1927-1952, 1928-1955, 1962-2059, 2040-2126, 2100-2126, 2100-2139, 2100-2206, 2101-2126, 2305-2332, 2305-2354, 2306-2333, 2307-2334, 2308-2334, 2309-2334, 2310-2334, 2410-2434, 2504-2528, 2509-2528, 2582-2625, 2606-2668, 2828-2855, 2832-2851, 2900-2927, 2900-2929, 2902-2927, 2983-3007, 2983-3013, 3227-3252, 3227-3456, 3472-3496, or 3543-3569.

In certain embodiments, antisense compounds target a range of a PCSK9 nucleic acid. In certain embodiment, such compounds contain at least an 8 nucleotide core sequence in common.

In certain embodiments, such compounds sharing at least an 8 nucleotide core sequence targets the following nucleotide regions of SEQ ID: 1: 294-317, 406-440, 406-526, 410-436, 410-499, 446-526, 545-581, 591-619, 591-704, 591-743, 595-622, 600-626, 600-639, 600-670, 601-628, 602-628, 603-630, 611-636, 620-647, 638-665, 648-674, 657-684, 705-743, 782-810, 821-859, 835-859, 835-917, 835-942, 860-887, 860-899, 860-909, 860-917, 869-895, 878-905, 888-909, 923-952, 960-1034, 960-1173, 960-986, 967-991, 970-1023, 970-1064, 970-1117, 970-996, 977-1004, 985-1011, 989-1016, 992-1019, 997-1024, 997-1024, 998-1025, 999-1026, 1000-1027, 1001-1028, 1002-1029, 1003-1029, 1004-1029, 1005-1029, 1006-1029, 1007-1034, 1036-1061, 1045-1072, 1076-1096, 1088-1115, 1098-1123, 1200-1251, 1210-1237, 1219-1245, 1228-1251, 1273-1444, 1295-1316, 1318-1345, 1328-1354, 1337-1361, 1344-1371, 1354-1377, 1380-1406, 1389-1416, 1400-1426, 1409-1434, 1465-1491, 1465-1602, 1474-1499, 1482-1519, 1513-1540, 1523-1549, 1526-1602, 1526-1624, 1532-1558, 1541-1568, 1552-1579, 1560-1587, 1561-1589, 1564-1591, 1565-1592, 1566-1592, 1567-1592, 1570-1597, 1571-1599, 1605-1706, 1628-1706, 1640-1666, 1672-1698, 1681-1706, 1735-1761, 1735-1765, 1740-1765, 1849-1876, 1849-1879, 1850-1877, 1851-1877, 1852-1878, 1852-1879, 1853-1879, 1854-1879, 1905-1955, 1915-1942, 1916-1943, 1917-1944, 1918-1945, 1919-1946, 1920-1939, 1920-1947, 1921-1948, 1922-1949, 1923-1950, 1924-1951, 1925-1952, 1926-1952, 1927-1952, 1928-1955, 1962-2059, 2040-2126, 2100-2126, 2100-2139, 2100-2206, 2101-2126, 2305-2332, 2305-2354, 2306-2333, 2307-2334, 2308-2334, 2309-2334, 2310-2334, 2410-2434, 2504-2528, 2509-2528, 2582-2625, 2606-2668, 2828-2855, 2832-2851, 2900-2927, 2900-2929, 2902-2927, 2983-3007, 2983-3013, 3227-3252, 3227-3456, 3472-3496, or 3543-3569.

In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid may target the following nucleotide regions of SEQ ID NO: 2: 2274-2400, 2274-2575, 2433-2570, 2433-2579, 2549-2575, 2552-2579, 2585-2638, 2605-2638, 3056-3075, 4150-5159, 4306-4325, 5590-5618, 5667-5686, 6444-6463, 6482-6518, 6492-6518, 6528-6555, 6528-6623, 6534-6561, 6535-6562, 6536-6563, 6537-6563, 6538-6565, 6539-6565, 6540-6567, 6541-6567, 6542-6569, 6546-6573, 6557-6584, 6575-6602, 6585-6611, 6594-6621, 6596-6623, 6652-6671, 7099-7118, 7556-7584, 8836-8855, 8948-8967, 9099-9118, 9099-9168, 9130-9168, 9207-9233, 9207-9235, 9209-9235, 10252-10271, 10633-10652, 11308-11491, 12715-12734, 12928-12947, 13681-13700, 13746-13779, 13816-13847, 13903-13945, 13977-14141, 14179-14198, 14267-14286, 14397-14423, 14441-14460, 14494-14513, 14494-14543, 14524-14543, 14601-14650, 14670-14700, 14675-14700, 14801-14828, 14877-14912, 14877-14915, 14877-14973, 14916-14943, 14916-14973, 14925-14951, 14934-14963, 14946-14973, 14979-14998, 15254-15280, 15254-

15328, 15264-15290, 15279-15305, 15291-15318, 15292-15319, 15293-15320, 15294-15321, 15294-15321, 15295-15322, 15296-15323, 15297-15323, 15298-15323, 15299-15323, 15300-15323, 15301-15328, 15330-15355, 15330-15490, 15339-15366, 15358-15490, 16134-16153, 16668-16687, 17267-17286, 18377-18427, 18561-18580, 18591-18618, 18591-18646, 18591-18668, 18695-18746, 18705-18730, 18709-18736, 18719-18746, 19203-20080, 19931-19952, 19954-19981, 19964-19990, 19973-19999, 19982-20009, 19992-20016, 20016-20042, 20025-20052, 20036-20062, 20045-20070, 20100-20119, 20188-20207, 20624-20650, 20624-20759, 20629-20804, 20633-20660, 20635-20781, 20643-20662, 20657-20676, 20670-20697, 20680-20706, 20683-20781, 20689-20715, 20698-20725, 20709-20736, 20717-20744, 20718-20745, 20719-20746, 20720-20747, 20721-20748, 20722-20749, 20727-20752, 20735-20759, 20762-21014, 20785-21014, 21082-21107, 21082-21152, 21091-21114, 21118-21144, 21127-21152, 21181-21209, 21181-21211, 21183-21211, 21481-21500, 21589-21608, 21692-21719, 22000-22227, 22096-22115, 22096-22223, 22096-22311, 22133-22160, 22133-22163, 22134-22161, 22135-22162, 22136-22163, 22137-22163, 22138-22163, 22189-22239, 22199-22226, 22199-22227, 22200-22227, 22201-22228, 22202-22229, 22203-22230, 22204-22231, 22205-22232, 22206-22233, 22207-22234, 22208-22235, 22209-22236, 22210-22236, 22210-22239, 22211-22236, 22212-22239, 22292-22311, 23985-24054, 24035-24134, 24095-24121, 24858-24877, 24907-24926, 25413-25432, 25994-26013, 26112-26139, 26112-26161, 26112-27303, 26113-26140, 26114-26141, 26115-26141, 26116-26141, 26117-26141, 26117-26475, 26118-26141, 26120-26141, 26132-26151, 26142-26161, 26217-26241, 26311-26335, 26389-26432, 26456-26576, 26635-26662, 26707-26734, 26707-26736, 26790-26820, 27034-27263, 27279-27303, or 27350-27376.

In certain embodiments, antisense compounds target a range of a PCSK9 nucleic acid. In certain embodiment, such compounds contain at least an 8 nucleotide core sequence in common. In certain embodiments, such compounds sharing at least an 8 nucleotide core sequence targets the following nucleotide regions of SEQ ID: 2: 2274-2400, 2274-2575, 2433-2570, 2433-2579, 2549-2575, 2552-2579, 2585-2638, 2605-2638, 3056-3075, 4150-5159, 4306-4325, 5590-5618, 5667-5686, 6444-6463, 6482-6518, 6492-6518, 6528-6555, 6528-6623, 6534-6561, 6535-6562, 6536-6563, 6537-6563, 6538-6565, 6539-6565, 6540-6567, 6541-6567, 6542-6569, 6546-6573, 6557-6584, 6575-6602, 6585-6611, 6594-6621, 6596-6623, 6652-6671, 7099-7118, 7556-7584, 8836-8855, 8948-8967, 9099-9118, 9099-9168, 9130-9168, 9207-9233, 9207-9235, 9209-9235, 10252-10271, 10633-10652, 11308-11491, 12715-12734, 12928-12947, 13681-13700, 13746-13779, 13816-13847, 13903-13945, 13977-14141, 14179-14198, 14267-14286, 14397-14423,

14441-14460, 14494-14513, 14494-14543, 14524-14543, 14601-14650, 14670-14700, 14675-14700, 14801-14828, 14877-14912, 14877-14915, 14877-14973, 14916-14943, 14916-14973, 14925-14951, 14934-14963, 14946-14973, 14979-14998, 15254-15280, 15254-15328, 15264-15290, 15279-15305, 15291-15318, 15292-15319, 15293-15320, 15294-15321, 15294-15321, 15295-15322, 15296-15323, 15297-15323, 15298-15323, 15299-15323, 15300-15323, 15301-15328, 15330-15355, 15330-15490, 15339-15366, 15358-15490, 16134-16153, 16668-16687, 17267-17286, 18377-18427, 18561-18580, 18591-18618, 18591-18646, 18591-18668, 18695-18746, 18705-18730, 18709-18736, 18719-18746, 19203-20080, 19931-19952, 19954-19981, 19964-19990, 19973-19999, 19982-20009, 19992-20016, 20016-20042, 20025-20052, 20036-20062, 20045-20070, 20100-20119, 20188-20207, 20624-20650, 20624-20759, 20629-20804, 20633-20660, 20635-20781, 20643-20662, 20657-20676, 20670-20697, 20680-20706, 20683-20781, 20689-20715, 20698-20725, 20709-20736, 20717-20744, 20718-20745, 20719-20746, 20720-20747, 20721-20748, 20722-20749, 20727-20752, 20735-20759, 20762-21014, 20785-21014, 21082-21107, 21082-21152, 21091-21114, 21118-21144, 21127-21152, 21181-21209, 21181-21211, 21183-21211, 21481-21500, 21589-21608, 21692-21719, 22000-22227, 22096-22115, 22096-22223, 22096-22311, 22133-22160, 22133-22163, 22134-22161, 22135-22162, 22136-22163, 22137-22163, 22138-22163, 22189-22239, 22199-22226, 22199-22227, 22200-22227, 22201-22228, 22202-22229, 22203-22230, 22204-22231, 22205-22232, 22206-22233, 22207-22234, 22208-22235, 22209-22236, 22210-22236, 22210-22239, 22211-22236, 22212-22239, 22292-22311, 23985-24054, 24035-24134, 24095-24121, 24858-24877, 24907-24926, 25413-25432, 25994-26013, 26112-26139, 26112-26161, 26112-27303, 26113-26140, 26114-26141, 26115-26141, 26116-26141, 26117-26141, 26117-26475, 26118-26141, 26120-26141, 26132-26151, 26142-26161, 26217-26241, 26311-26335, 26389-26432, 26456-26576, 26635-26662, 26707-26734, 26707-26736, 26790-26820, 27034-27263, 27279-27303, or 27350-27376.

In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid may target the following nucleotide regions of SEQ ID NO: 3: 220-253, 290-321, 377-419, 451-615, 653-672, 741-760, 871-897, 915-934, 968-1017, 1075-1124, 1075-1174, 1144-1174, 1275-1302, 1315-1341, 1351-1389, 1351-1447, 1365-1439, 1390-1417, 1390-1429, 1390-1439, 1399-1425, 1408-1435, 1420-1447, 1453-1482, 1490-1516, 1490-1564, 1500-1526, 1515-1541, 1527-1553, 1527-1554, 1528-1554, 1529-1555, 1529-1556, 1530-1556, 1530-1557, 1531-1557, 1532-1558, 1533-1559, 1534-1559, 1535-1559, 1536-1559, 1537-1564, 1566-1602, 1566-1681, 1606-1626, 1618-1645, 1626-1653, 1684-1703, 1730-1781, 1740-1767, 1749-1775, 1758-1781, 1820-1847, 1820-1877, 1822-2198, 1830-1856, 1839-1865, 1840-1867, 1898-1924, 1898-2035, 1903-2127,

1907-1934, 1911-1938, 1946-1971, 1954-1980, 1959-2035, 1959-2057, 1963-1988, 1967-2035, 1972-1999, 1982-2008, 1991-2018, 1993-2019, 1995-2022, 1996-2023, 1997-2024, 1998-2025, 1999-2025, 2000-2025, 2009-2035, 2038-2139, 2061-2139, 2073-2099, 2078-2104, 2105-2131, 2112-2139, 2168-2198, 2170-2177, 2245-2284, 2295-2394, 2355-2381, 2355-2394, 2405-2461, 2560-2587, 2560-2609, 2561-2588, 2562-2589, 2563-2589, 2564-2589, 2565-2589, 2566-2589, 2567-2589, 2568-2589, 2665-2689, 2759-2783, 2837-2880, 2904-2923, 3005-3024, 3005-3174, 3083-3110, 3155-3184, 3238-3268, 3482-3711, 3727-3751, or 3798-3824.

In certain embodiments, antisense compounds target a range of a PCSK9 nucleic acid. In certain embodiment, such compounds contain at least an 8 nucleotide core sequence in common. In certain embodiments, such compounds sharing at least an 8 nucleotide core sequence targets the following nucleotide regions of SEQ ID: 3: 220-253, 290-321, 377-419, 451-615, 653-672, 741-760, 871-897, 915-934, 968-1017, 1075-1124, 1075-1174, 1144-1174, 1275-1302, 1315-1341, 1351-1389, 1351-1447, 1365-1439, 1390-1417, 1390-1429, 1390-1439, 1399-1425, 1408-1435, 1420-1447, 1453-1482, 1490-1516, 1490-1564, 1500-1526, 1515-1541, 1527-1553, 1527-1554, 1528-1554, 1529-1555, 1529-1556, 1530-1556, 1530-1557, 1531-1557, 1532-1558, 1533-1559, 1534-1559, 1535-1559, 1536-1559, 1537-1564, 1566-1602, 1566-1681, 1606-1626, 1618-1645, 1626-1653, 1684-1703, 1730-1781, 1740-1767, 1749-1775, 1758-1781, 1820-1847, 1820-1877, 1822-2198, 1830-1856, 1839-1865, 1840-1867, 1898-1924, 1898-2035, 1903-2127, 1907-1934, 1911-1938, 1946-1971, 1954-1980, 1959-2035, 1959-2057, 1963-1988, 1967-2035, 1972-1999, 1982-2008, 1991-2018, 1993-2019, 1995-2022, 1996-2023, 1997-2024, 1998-2025, 1999-2025, 2000-2025, 2009-2035, 2038-2139, 2061-2139, 2073-2099, 2078-2104, 2105-2131, 2112-2139, 2168-2198, 2170-2177, 2245-2284, 2295-2394, 2355-2381, 2355-2394, 2405-2461, 2560-2587, 2560-2609, 2561-2588, 2562-2589, 2563-2589, 2564-2589, 2565-2589, 2566-2589, 2567-2589, 2568-2589, 2665-2689, 2759-2783, 2837-2880, 2904-2923, 3005-3024, 3005-3174, 3083-3110, 3155-3184, 3238-3268, 3482-3711, 3727-3751, or 3798-3824.

In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid may target the following nucleotide regions of SEQ ID NO: 1: 320-405, 441-445, 527-544, 582-590, 744-781, 811-820, 918-922, 953-959, 1034-1036, 1152-1153, 1174-1199, 1251-1272, 1445-1464, 1603-1604, 1625-1627, 1707-1734, 1766-1811, 1832-1848, 1880-1904, 1956-1961, 1982-1939, 2030-2039, 2060-2099, 2140-2149, 2170-2186, 2207-2304, 2355-2409, 2435-2503, 2529-2581, 2626-2648, 2669-2749, 2770-2827, 2856-2876, 2891-2899, 2930-2982, 3014-3226, 3253-3436, 3457-3471, or 3497-3542.

In certain embodiments, antisense compounds target a range of a PCSK9 nucleic acid. In certain embodiment, such compounds contain at least an 8 nucleotide core sequence in common. In certain embodiments, such compounds sharing at least an 8 nucleotide core sequence targets the following nucleotide regions of SEQ ID: 1: 320-405, 441-445, 527-544, 582-590, 744-781, 811-820, 918-922, 953-959, 1034-1036, 1152-1153, 1174-1199, 1251-1272, 1445-1464, 1603-1604, 1625-1627, 1707-1734, 1766-1811, 1832-1848, 1880-1904, 1956-1961, 1982-1939, 2030-2039, 2060-2099, 2140-2149, 2170-2186, 2207-2304, 2355-2409, 2435-2503, 2529-2581, 2626-2648, 2669-2749, 2770-2827, 2856-2876, 2891-2899, 2930-2982, 3014-3226, 3253-3436, 3457-3471, or 3497-3542.

In certain embodiments, a shortened or truncated antisense compound targeted to a PCSK9 nucleic acid has a single subunit deleted from the 5' end (5' truncation), or alternatively from the 3' end (3' truncation). A shortened or truncated antisense compound targeted to a PCSK9 nucleic acid may have two subunits deleted from the 5' end, or alternatively may have two subunits deleted from the 3' end, of the antisense compound. Alternatively, the deleted nucleosides may be dispersed throughout the antisense compound, for example, in an antisense compound having one nucleoside deleted from the 5' end and one nucleoside deleted from the 3' end.

When a single additional subunit is present in a lengthened antisense compound, the additional subunit may be located at the 5' or 3' end of the antisense compound. When two are more additional subunits are present, the added subunits may be adjacent to each other, for example, in an antisense compound having two subunits added to the 5' end (5' addition), or alternatively to the 3' end (3' addition), of the antisense compound. Alternatively, the added subunits may be dispersed throughout the antisense compound, for example, in an antisense compound having one subunit added to the 5' end and one subunit added to the 3' end.

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

Gautschi et al (J. Natl. Cancer Inst. 93:463-471, March 2001) demonstrated the ability of an oligonucleotide having 100% complementarity to the bcl-2 mRNA and having 3 mismatches to the bcl-xL mRNA to reduce the expression of both bcl-2 and bcl-xL *in vitro* and *in vivo*. Furthermore, this oligonucleotide demonstrated potent anti-tumor activity *in vivo*.

Maher and Dolnick (Nuc. Acid. Res. 16:3341-3358,1988) tested a series of tandem 14 nucleobase antisense oligonucleotides, and a 28 and 42 nucleobase antisense oligonucleotides comprised of the sequence of two or three of the tandem antisense oligonucleotides, respectively, for their ability to arrest translation of human DHFR in a rabbit reticulocyte assay. Each of the three 14 nucleobase antisense oligonucleotides alone was able to inhibit translation, albeit at a more modest level than the 28 or 42 nucleobase antisense oligonucleotides.

PCT/US2007/068404 describes incorporation of chemically-modified high-affinity nucleotides into short antisense compounds about 8-16 nucleobases in length and that such compounds are useful in the reduction of target RNAs in animals with increased potency and improved therapeutic index.

In certain embodiments, antisense compounds targeted to a PCSK9 nucleic acid are short antisense compounds. In certain embodiments, such short antisense compounds are oligonucleotide compounds. In certain embodiments, such short antisense compounds are about 8 to 16, preferably 9 to 15, more preferably 9 to 14, more preferably 10 to 14 nucleotides in length and comprises a gap region flanked on each side by a wing, wherein each wing independently consists of 1 to 3 nucleotides. Preferred motifs include but are not limited to wing – deoxy gap –wing motifs selected from 3-10-3, 2-10-3, 2-10-2, 1-10-1, 2-8-2, 1-8-1, 3-6-3 or 1-6-1.

Antisense compounds targeted to a PCSK9 nucleic acid are synthesized in vitro and do not include antisense compositions of biological origin, or genetic vector constructs designed to direct the in vivo synthesis of antisense molecules.

In certain embodiments, an antisense compound is targeted to a region of a PCSK9 nucleic acid that does not contain a single nucleotide polymorphism (SNPs). Incertain embodiments, an antisense compound is targeted to a region of a PCSK9 nucleic acid that does contain a single nucleotide polymorph (SNPs). A single nucleotide polymorphism refers to polymorphisms that are the result of a single nucleotide alteration or the existence of two or more alternative sequences which can be, for example, different allelic forms of a gene. A polymorphism may comprise one or more base changes including, for example, an insertion, a repeat, or a deletion. In certain embodiments, an antisense oligonucleotide targeted to a PCSK9

nucleic acid overlaps with a SNP at the following positions: 428, 432, 449, 996, 1011, 1044, 1317, 1565, 1617, 1618, 1671, 1711, 1722, 1836, 1911. In certain embodiments, the compounds provided herein that target a region of a PCSK9 nucleic acid that contains one or more SNPs will contain the appropriate base substitution, insertion, repeat or deletion such that the compound is fully complementary to the altered PCSK9 nucleic acid sequence.

*Antisense Compound Motifs*

In certain embodiments, antisense compounds targeted to a PCSK9 nucleic acid have chemically modified subunits arranged in patterns, or motifs, to confer to the antisense compounds properties such as enhanced the inhibitory activity, increased binding affinity for a target nucleic acid, or resistance to degradation by *in vivo* nucleases.

Chimeric antisense compounds typically contain at least one region modified so as to confer increased resistance to nuclease degradation, increased cellular uptake, increased binding affinity for the target nucleic acid, and/or increased inhibitory activity. A second region of a chimeric antisense compound may serve as a substrate for the cellular endonuclease RNase H, which cleaves the RNA strand of an RNA:DNA duplex.

Antisense compounds having a gapmer motif are considered chimeric antisense compounds. In a gapmer an internal position having a plurality of nucleotides that supports RNaseH cleavage is positioned between external regions having a plurality of nucleotides that are chemically distinct from the nucleosides of the internal region. In the case of an antisense oligonucleotide having a gapmer motif, the gap segment generally serves as the substrate for endonuclease cleavage, while the wing segments comprise modified nucleosides. The regions of a gapmer are differentiated by the types of sugar moieties comprising each distinct region. The types of sugar moieties that are used to differentiate the regions of a gapmer may in some embodiments include β-D-ribonucleosides, β-D-deoxyribonucleosides, 2'-modified nucleosides (such 2'-modified nucleosides may include 2'-MOE, and 2'-O-$CH_3$, among others), and bicyclic sugar modified nucleosides (such bicyclic sugar modified nucleosides may include those having a 4'-(CH2)n-O-2' bridge, where n=1 or n=2). In general, each distinct region comprises uniform sugar moieties. The wing-gap-wing motif is frequently described as "X-Y-Z", where "X" represents the length of the 5' wing region, "Y" represents the length of the gap region, and "Z" represents the length of the 3' wing region.

In some embodiments, an antisense compound targeted to a PCSK9 nucleic acid has a gap-widened motif. In other embodiments, an antisense oligonucleotide targeted to a PCSK9 nucleic acid has a gap-widened motif.

The gap-widened antisense oligonucleotides described herein may have various wing-gap-wing motifs selected from: 1-16-1, 2-15-1, 1-15-2, 1-14-3, 3-14-1, 2-14-2, 1-13-4, 4-13-1, 2-13-3, 3-13-2, 1-12-5, 5-12-1, 2-12-4, 4-12-2, 3-12-3, 1-11-6, 6-11-1, 2-11-5, 5-11-2, 3-11-4, 4-11-3, 1-17-1, 2-16-1, 1-16-2, 1-15-3, 3-15-1, 2-15-2, 1-14-4, 4-14-1, 2-14-3, 3-14-2, 1-13-5, 5-13-1, 2-13-4, 4-13-2, 3-13-3, 1-12-6, 6-12-1, 2-12-5, 5-12-2, 3-12-4, 4-12-3, 1-11-7, 7-11-1, 2-11-6, 6-11-2, 3-11-5, 5-11-3, 4-11-4, 1-18-1, 1-17-2, 2-17-1, 1-16-3, 1-16-3, 2-16-2, 1-15-4, 4-15-1, 2-15-3, 3-15-2, 1-14-5, 5-14-1, 2-14-4, 4-14-2, 3-14-3, 1-13-6, 6-13-1, 2-13-5, 5-13-2, 3-13-4, 4-13-3, 1-12-7, 7-12-1, 2-12-6, 6-12-2, 3-12-5, 5-12-3, 4-12-4, 1-11-8, 8-11-1, 2-11-7, 7-11-2, 3-11-6, 6-11-3, 4-11-5, 5-11-4, 1-18-1, 1-17-2, 2-17-1, 1-16-3, 3-16-1, 2-16-2, 1-15-4, 4-15-1, 2-15-3, 3-15-2, 1-14-5, 2-14-4, 4-14-2, 3-14-3, 1-13-6, 6-13-1, 2-13-5, 5-13-2, 3-13-4, 4-13-3, 1-12-7, 7-12-1, 2-12-6, 6-12-2, 3-12-5, 5-12-3, 4-12-4, 1-11-8, 8-11-1, 2-11-7, 7-11-2, 3-11-6, 6-11-3, 4-11-5, 5-11-4, 1-19-1, 1-18-2, 2-18-1, 1-17-3, 3-17-1, 2-17-2, 1-16-4, 4-16-1, 2-16-3, 3-16-2, 1-15-5, 2-15-4, 4-15-2, 3-15-3, 1-14-6, 6-14-1, 2-14-5, 5-14-2, 3-14-4, 4-14-3, 1-13-7, 7-13-1, 2-13-6, 6-13-2, 3-13-5, 5-13-3, 4-13-4, 1-12-8, 8-12-1, 2-12-7, 7-12-2, 3-12-6, 6-12-3, 4-12-5, 5-12-4, 2-11-8, 8-11-2, 3-11-7, 7-11-3, 4-11-6, 6-11-4, 5-11-5, 1-20-1, 1-19-2, 2-19-1, 1-18-3, 3-18-1, 2-18-2, 1-17-4, 4-17-1, 2-17-3, 3-17-2, 1-16-5, 2-16-4, 4-16-2, 3-16-3, 1-15-6, 6-15-1, 2-15-5, 5-15-2, 3-15-4, 4-15-3, 1-14-7, 7-14-1, 2-14-6, 6-14-2, 3-14-5, 5-14-3, 4-14-4, 1-13-8, 8-13-1, 2-13-7, 7-13-2, 3-13-6, 6-13-3, 4-13-5, 5-13-4, 2-12-8, 8-12-2, 3-12-7, 7-12-3, 4-12-6, 6-12-4, 5-12-5, 3-11-8, 8-11-3, 4-11-7, 7-11-4, 5-11-6, 6-11-5, 1-21-1, 1-20-2, 2-20-1, 1-20-3, 3-19-1, 2-19-2, 1-18-4, 4-18-1, 2-18-3, 3-18-2, 1-17-5, 2-17-4, 4-17-2, 3-17-3, 1-16-6, 6-16-1, 2-16-5, 5-16-2, 3-16-4, 4-16-3, 1-15-7, 7-15-1, 2-15-6, 6-15-2, 3-15-5, 5-15-3, 4-15-4, 1-14-8, 8-14-1, 2-14-7, 7-14-2, 3-14-6, 6-14-3, 4-14-5, 5-14-4, 2-13-8, 8-13-2, 3-13-7, 7-13-3, 4-13-6, 6-13-4, 5-13-5, 1-12-10, 10-12-1, 2-12-9, 9-12-2, 3-12-8, 8-12-3, 4-12-7, 7-12-4, 5-12-6, 6-12-5, 4-11-8, 8-11-4, 5-11-7, 7-11-5, 6-11-6, 1-22-1, 1-21-2, 2-21-1, 1-21-3, 3-20-1, 2-20-2, 1-19-4, 4-19-1, 2-19-3, 3-19-2, 1-18-5, 2-18-4, 4-18-2, 3-18-3, 1-17-6, 6-17-1, 2-17-5, 5-17-2, 3-17-4, 4-17-3, 1-16-7, 7-16-1, 2-16-6, 6-16-2, 3-16-5, 5-16-3, 4-16-4, 1-15-8, 8-15-1, 2-15-7, 7-15-2, 3-15-6, 6-15-3, 4-15-5, 5-15-4, 2-14-8, 8-14-2, 3-14-7, 7-14-3, 4-14-6, 6-14-4, 5-14-5, 3-13-8, 8-13-3, 4-13-7, 7-13-4, 5-13-6, 6-13-5, 4-12-8, 8-12-4, 5-12-7, 7-12-5, 6-12-6, 5-11-8, 8-11-5, 6-11-7, or 7-11-6. In certain preferred embodiments, a gap-widened motif includes, but is not limited to, 2-13-5, 3-14-3, 3-14-4 gapmer motif.

In one embodiment, a gap-widened antisense oligonucleotide targeted to a PCSK9 nucleic acid has a gap segment of fourteen 2'-deoxyribonucleotides positioned between wing segments of three chemically modified nucleosides. In one embodiment, the chemical modification comprises a 2'-sugar modification. In another embodiment, the chemical modification comprises a 2'-MOE sugar modification.

In one embodiment, antisense compounds targeted to a PCSK9 nucleic acid possess a 5-10-5 gapmer motif.

*Target Nucleic Acids, Target Regions and Nucleotide Sequences*

Nucleotide sequences that encode PCSK9 include, without limitation, the following: GENBANK® Accession No. NM_174936.2, first deposited with GENBANK® on June 1, 2003, and incorporated herein as SEQ ID NO: 1; nucleotides 25475000 to 25504000 of GENBANK® Accession No. NT_032977.8, first deposited with GENBANK® on February 26, 2006, and incorporated herein as SEQ ID NO: 2; and GENBANK® Accession No. AK124635.1, first deposited with GENBANK® on September 8, 2003, and incorporated herein as SEQ ID NO: 3.

It is noted that some portions of these nucleotide sequences share identical sequence. For example, portions of SEQ ID NO: 1 are identical to portions of SEQ ID NO: 2; portions of SEQ ID NO: 1 are identical to portions of SEQ ID NO: 3; and portions of SEQ ID NO: 2 are identical to portions of SEQ ID NO: 3. Accordingly, antisense compounds targeted to SEQ ID NO: 1 may also target SEQ ID NO: 2 and/or SEQ ID NO: 3; antisense compounds targeted to SEQ ID NO: 2 may also target SEQ ID NO: 1 and/or SEQ ID NO: 3; and antisense compounds targeted to SEQ ID NO: 3 may also target SEQ ID NO: 1 and/or SEQ ID NO: 2. Examples of such antisense compounds are shown in the following tables.

In certain embodiments, antisense compounds target a PCSK9 nucleic acid having the sequence of GENBANK® Accession No. NM_174936.2, first deposited with GENBANK® on June 1, 2003, and incorporated herein as SEQ ID NO: 1. In certain such embodiments, an antisense oligonucleotide targets SEQ ID NO: 1. In certain such embodiments, an antisense oligonucleotide that is targeted to SEQ ID NO: 1 is at least 90% complementary to SEQ ID NO: 1. In certain such embodiments, an antisense oligonucleotide that is targeted to SEQ ID NO: 1 is at least 95% complementary to SEQ ID NO: 1. In certain such embodiments, an antisense oligonucleotide that is targeted to SEQ ID NO: 1 is 100% complementary to SEQ ID NO: 1. In certain embodiments, an antisense oligonucleotide targeted to SEQ ID NO: 1 comprises a nucleotide sequence selected from the nucleotide sequences set forth in Table 1.

**Table 1: Nucleotide sequences targeted to NM_174936.2 (SEQ ID NO: 1)**

| SEQ ID NO | 5' Target Site on SEQ ID NO: 1 | 3' Target Site on SEQ ID NO: 1 | Sequence (5'-3') |
|---|---|---|---|
| 4 | 135 | 154 | GCGCGGAATCCTGGCTGGGA |
| 5 | 242 | 261 | GAGGAGACCTAGAGGCCGTG |
| 159 | 294 | 313 | GCCTGGAGCTGACGGTGCCC |
| 160 | 298 | 317 | GACCGCCTGGAGCTGACGGT |
| 6 | 300 | 319 | AGGACCGCCTGGAGCTGACG |
| 162 | 406 | 425 | AAGGCTAGCACCAGCTCCTC |
| 163 | 407 | 426 | CAAGGCTAGCACCAGCTCCT |
| 164 | 408 | 427 | GCAAGGCTAGCACCAGCTCC |
| 165 | 409 | 428 | CGCAAGGCTAGCACCAGCTC |
| 7 | 410 | 429 | ACGCAAGGCTAGCACCAGCT |
| 166 | 411 | 430 | AACGCAAGGCTAGCACCAGC |
| 167 | 412 | 431 | GAACGCAAGGCTAGCACCAG |
| 168 | 413 | 432 | GGAACGCAAGGCTAGCACCA |
| 169 | 414 | 433 | CGGAACGCAAGGCTAGCACC |
| 8 | 417 | 436 | CCTCGGAACGCAAGGCTAGC |
| 170 | 421 | 440 | TCCTCCTCGGAACGCAAGGC |
| 171 | 446 | 465 | GTGCTCGGGTGCTTCGGCCA |
| 172 | 466 | 485 | TGGAAGGTGGCTGTGGTTCC |
| 9 | 480 | 499 | CCTTGGCGCAGCGGTGGAAG |
| 173 | 482 | 501 | ATCCTTGGCGCAGCGGTGGA |
| 174 | 484 | 503 | GGATCCTTGGCGCAGCGGTG |
| 175 | 488 | 507 | CCACGGATCCTTGGCGCAGC |
| 176 | 507 | 526 | CGTAGGTGCCAGGCAACCTC |
| 177 | 545 | 564 | TGACTGCGAGAGGTGGGTCT |
| 178 | 555 | 574 | CAGTGCGCTCTGACTGCGAG |
| 179 | 557 | 576 | GGCAGTGCGCTCTGACTGCG |
| 180 | 559 | 578 | CGGGCAGTGCGCTCTGACTG |
| 10 | 561 | 580 | GGCGGGCAGTGCGCTCTGAC |
| 181 | 562 | 581 | CGGCGGGCAGTGCGCTCTGA |
| 182 | 591 | 610 | ATCCCCGGCGGGCAGCCTGG |
| 183 | 595 | 614 | AGGTATCCCCGGCGGGCAGC |
| 184 | 597 | 616 | TGAGGTATCCCCGGCGGGCA |
| 185 | 598 | 617 | GTGAGGTATCCCCGGCGGGC |
| 186 | 599 | 618 | GGTGAGGTATCCCCGGCGGG |
| 11 | 600 | 619 | TGGTGAGGTATCCCCGGCGG |
| 187 | 601 | 620 | TTGGTGAGGTATCCCCGGCG |
| 188 | 602 | 621 | CTTGGTGAGGTATCCCCGGC |
| 189 | 603 | 622 | TCTTGGTGAGGTATCCCCGG |
| 190 | 604 | 623 | ATCTTGGTGAGGTATCCCCG |
| 191 | 605 | 624 | GATCTTGGTGAGGTATCCCC |
| 12 | 606 | 625 | GGATCTTGGTGAGGTATCCC |
| 192 | 607 | 626 | AGGATCTTGGTGAGGTATCC |
| 193 | 609 | 628 | GCAGGATCTTGGTGAGGTAT |

| SEQ ID NO | 5' Target Site on SEQ ID NO: 1 | 3' Target Site on SEQ ID NO: 1 | Sequence (5'-3') |
|---|---|---|---|
| 194 | 611 | 630 | ATGCAGGATCTTGGTGAGGT |
| 195 | 613 | 632 | ACATGCAGGATCTTGGTGAG |
| 13 | 615 | 634 | AGACATGCAGGATCTTGGTG |
| 196 | 617 | 636 | GAAGACATGCAGGATCTTGG |
| 14 | 620 | 639 | ATGGAAGACATGCAGGATCT |
| 197 | 628 | 647 | AGAAGGCCATGGAAGACATG |
| 198 | 638 | 657 | GAAGCCAGGAAGAAGGCCAT |
| 15 | 646 | 665 | TTCACCAGGAAGCCAGGAAG |
| 199 | 648 | 667 | TCTTCACCAGGAAGCCAGGA |
| 16 | 651 | 670 | TCATCTTCACCAGGAAGCCA |
| 200 | 653 | 672 | ACTCATCTTCACCAGGAAGC |
| 201 | 655 | 674 | CCACTCATCTTCACCAGGAA |
| 202 | 657 | 676 | CGCCACTCATCTTCACCAGG |
| 203 | 659 | 678 | GTCGCCACTCATCTTCACCA |
| 204 | 661 | 680 | AGGTCGCCACTCATCTTCAC |
| 205 | 663 | 682 | GCAGGTCGCCACTCATCTTC |
| 206 | 665 | 684 | CAGCAGGTCGCCACTCATCT |
| 207 | 667 | 686 | TCCAGCAGGTCGCCACTCAT |
| 208 | 685 | 704 | GGCAACTTCAAGGCCAGCTC |
| 17 | 705 | 724 | CCTCGATGTAGTCGACATGG |
| 209 | 724 | 743 | GCAAAGACAGAGGAGTCCTC |
| 210 | 782 | 801 | TTCATCCGCCCGGTACCGTG |
| 211 | 784 | 803 | TATTCATCCGCCCGGTACCG |
| 18 | 785 | 804 | GTATTCATCCGCCCGGTACC |
| 212 | 787 | 806 | TGGTATTCATCCGCCCGGTA |
| 213 | 789 | 808 | GCTGGTATTCATCCGCCCGG |
| 214 | 791 | 810 | GGGCTGGTATTCATCCGCCC |
| 215 | 821 | 840 | ATACACCTCCACCAGGCTGC |
| 216 | 832 | 851 | GTGTCTAGGAGATACACCTC |
| 19 | 835 | 854 | CTGGTGTCTAGGAGATACAC |
| 217 | 837 | 856 | TGCTGGTGTCTAGGAGATAC |
| 20 | 840 | 859 | GTATGCTGGTGTCTAGGAGA |
| 21 | 860 | 879 | GATTTCCCGGTGGTCACTCT |
| 218 | 862 | 881 | TCGATTTCCCGGTGGTCACT |
| 219 | 863 | 882 | CTCGATTTCCCGGTGGTCAC |
| 220 | 864 | 883 | CCTCGATTTCCCGGTGGTCA |
| 221 | 865 | 884 | CCCTCGATTTCCCGGTGGTC |
| 22 | 866 | 885 | GCCCTCGATTTCCCGGTGGT |
| 222 | 867 | 886 | TGCCCTCGATTTCCCGGTGG |
| 223 | 868 | 887 | CTGCCCTCGATTTCCCGGTG |
| 224 | 869 | 888 | CCTGCCCTCGATTTCCCGGT |
| 225 | 870 | 889 | CCCTGCCCTCGATTTCCCGG |
| 226 | 874 | 893 | ATGACCCTGCCCTCGATTTC |
| 227 | 876 | 895 | CCATGACCCTGCCCTCGATT |
| 228 | 878 | 897 | GACCATGACCCTGCCCTCGA |
| 23 | 880 | 899 | GTGACCATGACCCTGCCCTC |
| 229 | 882 | 901 | CGGTGACCATGACCCTGCCC |
| 230 | 884 | 903 | GTCGGTGACCATGACCCTGC |

| SEQ ID NO | 5' Target Site on SEQ ID NO: 1 | 3' Target Site on SEQ ID NO: 1 | Sequence (5'-3') |
|---|---|---|---|
| 231 | 886 | 905 | AAGTCGGTGACCATGACCCT |
| 232 | 888 | 907 | CGAAGTCGGTGACCATGACC |
| 24 | 890 | 909 | CTCGAAGTCGGTGACCATGA |
| 233 | 898 | 917 | GGCACATTCTCGAAGTCGGT |
| 25 | 923 | 942 | GTGGAAGCGGGTCCCGTCCT |
| 234 | 933 | 952 | TGGCCTGTCTGTGGAAGCGG |
| 235 | 960 | 979 | GGTGGGTGCCATGACTGTCA |
| 236 | 963 | 982 | CCAGGTGGGTGCCATGACTG |
| 237 | 967 | 986 | CCTGCCAGGTGGGTGCCATG |
| 26 | 970 | 989 | ACCCCTGCCAGGTGGGTGCC |
| 238 | 972 | 991 | CCACCCCTGCCAGGTGGGTG |
| 27 | 975 | 994 | TGACCACCCCTGCCAGGTGG |
| 239 | 977 | 996 | GCTGACCACCCCTGCCAGGT |
| 240 | 985 | 1004 | TCCCGGCCGCTGACCACCCC |
| 241 | 989 | 1008 | GGCATCCCGGCCGCTGACCA |
| 242 | 992 | 1011 | GCCGGCATCCCGGCCGCTGA |
| 243 | 997 | 1016 | GCCACGCCGGCATCCCGGCC |
| 244 | 998 | 1017 | GGCCACGCCGGCATCCCGGC |
| 245 | 999 | 1018 | TGGCCACGCCGGCATCCCGG |
| 246 | 1000 | 1019 | TTGGCCACGCCGGCATCCCG |
| 247 | 1001 | 1020 | CTTGGCCACGCCGGCATCCC |
| 248 | 1002 | 1021 | CCTTGGCCACGCCGGCATCC |
| 249 | 1003 | 1022 | CCCTTGGCCACGCCGGCATC |
| 28 | 1004 | 1023 | ACCCTTGGCCACGCCGGCAT |
| 447 | 1004 | 1023 | ACCCTTGGTCACGCCGGCAT |
| 250 | 1005 | 1024 | CACCCTTGGCCACGCCGGCA |
| 251 | 1006 | 1025 | GCACCCTTGGCCACGCCGGC |
| 252 | 1007 | 1026 | GGCACCCTTGGCCACGCCGG |
| 253 | 1008 | 1027 | TGGCACCCTTGGCCACGCCG |
| 254 | 1009 | 1028 | CTGGCACCCTTGGCCACGCC |
| 255 | 1010 | 1029 | GCTGGCACCCTTGGCCACGC |
| 256 | 1015 | 1034 | CGCATGCTGGCACCCTTGGC |
| 257 | 1036 | 1055 | CAGTTGAGCACGCGCAGGCT |
| 258 | 1038 | 1057 | GGCAGTTGAGCACGCGCAGG |
| 29 | 1040 | 1059 | TTGGCAGTTGAGCACGCGCA |
| 259 | 1042 | 1061 | CCTTGGCAGTTGAGCACGCG |
| 30 | 1045 | 1064 | TTCCCTTGGCAGTTGAGCAC |
| 260 | 1047 | 1066 | CCTTCCCTTGGCAGTTGAGC |
| 261 | 1051 | 1070 | GTGCCCTTCCCTTGGCAGTT |
| 262 | 1053 | 1072 | CCGTGCCCTTCCCTTGGCAG |
| 263 | 1064 | 1083 | GGTGCCGCTAACCGTGCCCT |
| 264 | 1076 | 1095 | CAGGCCTATGAGGGTGCCGC |
| 31 | 1077 | 1096 | CCAGGCCTATGAGGGTGCCG |
| 458 | 1079 | 1092 | GCCTATGAGGGTGC |
| 459 | 1084 | 1097 | TCCAGGCCTATGAG |
| 265 | 1088 | 1107 | CCGAATAAACTCCAGGCCTA |
| 266 | 1096 | 1115 | TGGCTTTTCCGAATAAACTC |
| 32 | 1098 | 1117 | GCTGGCTTTTCCGAATAAAC |

| SEQ ID NO | 5' Target Site on SEQ ID NO: 1 | 3' Target Site on SEQ ID NO: 1 | Sequence (5'-3') |
|---|---|---|---|
| 267 | 1100 | 1119 | CAGCTGGCTTTTCCGAATAA |
| 268 | 1102 | 1121 | ACCAGCTGGCTTTTCCGAAT |
| 269 | 1104 | 1123 | GGACCAGCTGGCTTTTCCGA |
| 270 | 1108 | 1127 | GGCTGGACCAGCTGGCTTTT |
| 271 | 1119 | 1138 | GTGGCCCCACAGGCTGGACC |
| 272 | 1132 | 1151 | AGCAGCACCACCAGTGGCCC |
| 273 | 1154 | 1173 | GCTGTACCCACCCGCCAGGG |
| 274 | 1200 | 1219 | CGACCCCAGCCCTCGCCAGG |
| 33 | 1210 | 1229 | GTGACCAGCACGACCCCAGC |
| 275 | 1212 | 1231 | CGGTGACCAGCACGACCCCA |
| 276 | 1214 | 1233 | AGCGGTGACCAGCACGACCC |
| 277 | 1216 | 1235 | GCAGCGGTGACCAGCACGAC |
| 278 | 1218 | 1237 | CGGCAGCGGTGACCAGCACG |
| 279 | 1219 | 1238 | CCGGCAGCGGTGACCAGCAC |
| 280 | 1222 | 1241 | TTGCCGGCAGCGGTGACCAG |
| 281 | 1224 | 1243 | AGTTGCCGGCAGCGGTGACC |
| 282 | 1226 | 1245 | GAAGTTGCCGGCAGCGGTGA |
| 283 | 1228 | 1247 | CGGAAGTTGCCGGCAGCGGT |
| 284 | 1230 | 1249 | CCCGGAAGTTGCCGGCAGCG |
| 285 | 1232 | 1251 | GTCCCGGAAGTTGCCGGCAG |
| 286 | 1273 | 1292 | ATGACCTCGGGAGCTGAGGC |
| 287 | 1283 | 1302 | CCCAACTGTGATGACCTCGG |
| 288 | 1295 | 1314 | GGCATTGGTGGCCCCAACTG |
| 149 | 1297 | 1316 | TGGGCATTGGTGGCCCCAAC |
| 289 | 1305 | 1324 | GCTGGTCTTGGGCATTGGTG |
| 290 | 1318 | 1337 | CCCAGGGTCACCGGCTGGTC |
| 291 | 1320 | 1339 | TCCCCAGGGTCACCGGCTGG |
| 292 | 1322 | 1341 | AGTCCCCAGGGTCACCGGCT |
| 293 | 1324 | 1343 | AAAGTCCCCAGGGTCACCGG |
| 34 | 1326 | 1345 | CCAAAGTCCCCAGGGTCACC |
| 294 | 1328 | 1347 | CCCCAAAGTCCCCAGGGTCA |
| 128 | 1330 | 1349 | GTCCCCAAAGTCCCCAGGGT |
| 295 | 1333 | 1352 | TTGGTCCCCAAAGTCCCCAG |
| 35 | 1335 | 1354 | AGTTGGTCCCCAAAGTCCCC |
| 296 | 1337 | 1356 | AAAGTTGGTCCCCAAAGTCC |
| 36 | 1340 | 1359 | GCCAAAGTTGGTCCCCAAAG |
| 297 | 1342 | 1361 | CGGCCAAAGTTGGTCCCCAA |
| 298 | 1344 | 1363 | AGCGGCCAAAGTTGGTCCCC |
| 299 | 1346 | 1365 | ACAGCGGCCAAAGTTGGTCC |
| 300 | 1348 | 1367 | ACACAGCGGCCAAAGTTGGT |
| 301 | 1350 | 1369 | CCACACAGCGGCCAAAGTTG |
| 37 | 1352 | 1371 | GTCCACACAGCGGCCAAAGT |
| 302 | 1354 | 1373 | AGGTCCACACAGCGGCCAAA |
| 303 | 1356 | 1375 | AGAGGTCCACACAGCGGCCA |
| 304 | 1358 | 1377 | AAAGAGGTCCACACAGCGGC |
| 38 | 1361 | 1380 | GGCAAAGAGGTCCACACAGC |
| 305 | 1380 | 1399 | CAATGATGTCCTCCCCTGGG |
| 306 | 1387 | 1406 | GAGGCACCAATGATGTCCTC |

| SEQ ID NO | 5' Target Site on SEQ ID NO: 1 | 3' Target Site on SEQ ID NO: 1 | Sequence (5'-3') |
|---|---|---|---|
| 39 | 1389 | 1408 | TGGAGGCACCAATGATGTCC |
| 307 | 1391 | 1410 | GCTGGAGGCACCAATGATGT |
| 308 | 1393 | 1412 | TCGCTGGAGGCACCAATGAT |
| 309 | 1395 | 1414 | AGTCGCTGGAGGCACCAATG |
| 310 | 1397 | 1416 | GCAGTCGCTGGAGGCACCAA |
| 40 | 1400 | 1419 | GCTGCAGTCGCTGGAGGCAC |
| 311 | 1402 | 1421 | GTGCTGCAGTCGCTGGAGGC |
| 312 | 1404 | 1423 | AGGTGCTGCAGTCGCTGGAG |
| 313 | 1406 | 1425 | GCAGGTGCTGCAGTCGCTGG |
| 314 | 1407 | 1426 | AGCAGGTGCTGCAGTCGCTG |
| 315 | 1409 | 1428 | AAAGCAGGTGCTGCAGTCGC |
| 41 | 1411 | 1430 | ACAAAGCAGGTGCTGCAGTC |
| 316 | 1413 | 1432 | ACACAAAGCAGGTGCTGCAG |
| 317 | 1415 | 1434 | TGACACAAAGCAGGTGCTGC |
| 318 | 1425 | 1444 | TCCCACTCTGTGACACAAAG |
| 101 | 1465 | 1484 | ATGGCTGCAATGCCAGCCAC |
| 319 | 1467 | 1486 | TCATGGCTGCAATGCCAGCC |
| 42 | 1470 | 1489 | GCATCATGGCTGCAATGCCA |
| 320 | 1472 | 1491 | CAGCATCATGGCTGCAATGC |
| 321 | 1474 | 1493 | GACAGCATCATGGCTGCAAT |
| 322 | 1476 | 1495 | CAGACAGCATCATGGCTGCA |
| 43 | 1478 | 1497 | GGCAGACAGCATCATGGCTG |
| 323 | 1480 | 1499 | TCGGCAGACAGCATCATGGC |
| 324 | 1482 | 1501 | GCTCGGCAGACAGCATCATG |
| 325 | 1484 | 1503 | CGGCTCGGCAGACAGCATCA |
| 326 | 1486 | 1505 | TCCGGCTCGGCAGACAGCAT |
| 327 | 1500 | 1519 | CGGCCAGGGTGAGCTCCGGC |
| 328 | 1513 | 1532 | CTCTGCCTCAACTCGGCCAG |
| 329 | 1515 | 1534 | GTCTCTGCCTCAACTCGGCC |
| 330 | 1517 | 1536 | CAGTCTCTGCCTCAACTCGG |
| 331 | 1519 | 1538 | ATCAGTCTCTGCCTCAACTC |
| 332 | 1521 | 1540 | GGATCAGTCTCTGCCTCAAC |
| 333 | 1523 | 1542 | GTGGATCAGTCTCTGCCTCA |
| 334 | 1525 | 1544 | AAGTGGATCAGTCTCTGCCT |
| 44 | 1526 | 1545 | GAAGTGGATCAGTCTCTGCC |
| 335 | 1528 | 1547 | GAGAAGTGGATCAGTCTCTG |
| 336 | 1530 | 1549 | CAGAGAAGTGGATCAGTCTC |
| 337 | 1532 | 1551 | GGCAGAGAAGTGGATCAGTC |
| 45 | 1534 | 1553 | TTGGCAGAGAAGTGGATCAG |
| 338 | 1536 | 1555 | CTTTGGCAGAGAAGTGGATC |
| 46 | 1539 | 1558 | CATCTTTGGCAGAGAAGTGG |
| 339 | 1541 | 1560 | GACATCTTTGGCAGAGAAGT |
| 340 | 1543 | 1562 | ATGACATCTTTGGCAGAGAA |
| 47 | 1545 | 1564 | TGATGACATCTTTGGCAGAG |
| 341 | 1547 | 1566 | ATTGATGACATCTTTGGCAG |
| 342 | 1549 | 1568 | TCATTGATGACATCTTTGGC |
| 48 | 1552 | 1571 | GCCTCATTGATGACATCTTT |
| 343 | 1554 | 1573 | AGGCCTCATTGATGACATCT |

| SEQ ID NO | 5' Target Site on SEQ ID NO: 1 | 3' Target Site on SEQ ID NO: 1 | Sequence (5'-3') |
|---|---|---|---|
| 344 | 1556 | 1575 | CCAGGCCTCATTGATGACAT |
| 345 | 1558 | 1577 | AACCAGGCCTCATTGATGAC |
| 346 | 1560 | 1579 | GGAACCAGGCCTCATTGATG |
| 347 | 1561 | 1580 | GGGAACCAGGCCTCATTGAT |
| 348 | 1562 | 1581 | AGGGAACCAGGCCTCATTGA |
| 349 | 1563 | 1582 | CAGGGAACCAGGCCTCATTG |
| 49 | 1564 | 1583 | TCAGGGAACCAGGCCTCATT |
| 49 | 1564 | 1583 | TCAGGGAACCAGGCCTCATT |
| 350 | 1565 | 1584 | CTCAGGGAACCAGGCCTCAT |
| 351 | 1566 | 1585 | CCTCAGGGAACCAGGCCTCA |
| 352 | 1567 | 1586 | TCCTCAGGGAACCAGGCCTC |
| 353 | 1568 | 1587 | GTCCTCAGGGAACCAGGCCT |
| 50 | 1569 | 1588 | GGTCCTCAGGGAACCAGGCC |
| 354 | 1570 | 1589 | TGGTCCTCAGGGAACCAGGC |
| 355 | 1571 | 1590 | CTGGTCCTCAGGGAACCAGG |
| 356 | 1572 | 1591 | GCTGGTCCTCAGGGAACCAG |
| 357 | 1573 | 1592 | CGCTGGTCCTCAGGGAACCA |
| 87 | 1576 | 1595 | ACCCGCTGGTCCTCAGGGAA |
| 358 | 1578 | 1597 | GTACCCGCTGGTCCTCAGGG |
| 359 | 1580 | 1599 | CAGTACCCGCTGGTCCTCAG |
| 51 | 1583 | 1602 | GGTCAGTACCCGCTGGTCCT |
| 119 | 1605 | 1624 | GCAGGGCGGCCACCAGGTTG |
| 360 | 1628 | 1647 | ACCTGCCCCATGGGTGCTGG |
| 52 | 1640 | 1659 | AAACAGCTGCCAACCTGCCC |
| 361 | 1642 | 1661 | CAAAACAGCTGCCAACCTGC |
| 53 | 1645 | 1664 | CTGCAAAACAGCTGCCAACC |
| 362 | 1647 | 1666 | TCCTGCAAAACAGCTGCCAA |
| 363 | 1649 | 1668 | AGTCCTGCAAAACAGCTGCC |
| 364 | 1660 | 1679 | GCTGACCATACAGTCCTGCA |
| 365 | 1672 | 1691 | GGCCCCGAGTGTGCTGACCA |
| 54 | 1675 | 1694 | GTAGGCCCCGAGTGTGCTGA |
| 366 | 1677 | 1696 | GTGTAGGCCCCGAGTGTGCT |
| 367 | 1679 | 1698 | CCGTGTAGGCCCCGAGTGTG |
| 368 | 1681 | 1700 | ATCCGTGTAGGCCCCGAGTG |
| 369 | 1683 | 1702 | CCATCCGTGTAGGCCCCGAG |
| 370 | 1685 | 1704 | GGCCATCCGTGTAGGCCCCG |
| 371 | 1687 | 1706 | GTGGCCATCCGTGTAGGCCC |
| 372 | 1735 | 1754 | CTGGAGCAGCTCAGCAGCTC |
| 460 | 1735 | 1748 | CAGCTCAGCAGCTC |
| 373 | 1737 | 1756 | AACTGGAGCAGCTCAGCAGC |
| 55 | 1740 | 1759 | AGAAACTGGAGCAGCTCAGC |
| 374 | 1742 | 1761 | GGAGAAACTGGAGCAGCTCA |
| 375 | 1744 | 1763 | CTGGAGAAACTGGAGCAGCT |
| 56 | 1746 | 1765 | TCCTGGAGAAACTGGAGCAG |
| 57 | 1812 | 1831 | CGTTGTGGGCCCGGCAGACC |
| 376 | 1849 | 1868 | CACCTGGCAATGGCGTAGAC |
| 377 | 1850 | 1869 | GCACCTGGCAATGGCGTAGA |
| 378 | 1851 | 1870 | AGCACCTGGCAATGGCGTAG |

| SEQ ID NO | 5' Target Site on SEQ ID NO: 1 | 3' Target Site on SEQ ID NO: 1 | Sequence (5'-3') |
|---|---|---|---|
| 379 | 1852 | 1871 | CAGCACCTGGCAATGGCGTA |
| 380 | 1853 | 1872 | GCAGCACCTGGCAATGGCGT |
| 381 | 1854 | 1873 | GGCAGCACCTGGCAATGGCG |
| 382 | 1855 | 1874 | AGGCAGCACCTGGCAATGGC |
| 383 | 1856 | 1875 | CAGGCAGCACCTGGCAATGG |
| 384 | 1857 | 1876 | GCAGGCAGCACCTGGCAATG |
| 58 | 1858 | 1877 | AGCAGGCAGCACCTGGCAAT |
| 385 | 1859 | 1878 | TAGCAGGCAGCACCTGGCAA |
| 386 | 1860 | 1879 | GTAGCAGGCAGCACCTGGCA |
| 387 | 1905 | 1924 | TGGCCTCAGCTGGTGGAGCT |
| 388 | 1915 | 1934 | GTCCCCATGCTGGCCTCAGC |
| 389 | 1916 | 1935 | GGTCCCCATGCTGGCCTCAG |
| 390 | 1917 | 1936 | GGGTCCCCATGCTGGCCTCA |
| 391 | 1918 | 1937 | CGGGTCCCCATGCTGGCCTC |
| 392 | 1919 | 1938 | ACGGGTCCCCATGCTGGCCT |
| 59 | 1920 | 1939 | CACGGGTCCCCATGCTGGCC |
| 59 | 1920 | 1939 | CACGGGTCCCCATGCTGGCC |
| 393 | 1921 | 1940 | ACACGGGTCCCCATGCTGGC |
| 394 | 1922 | 1941 | GACACGGGTCCCCATGCTGG |
| 395 | 1923 | 1942 | GGACACGGGTCCCCATGCTG |
| 396 | 1924 | 1943 | TGGACACGGGTCCCCATGCT |
| 397 | 1925 | 1944 | GTGGACACGGGTCCCCATGC |
| 398 | 1926 | 1945 | AGTGGACACGGGTCCCCATG |
| 399 | 1927 | 1946 | CAGTGGACACGGGTCCCCAT |
| 400 | 1928 | 1947 | GCAGTGGACACGGGTCCCCA |
| 401 | 1929 | 1948 | GGCAGTGGACACGGGTCCCC |
| 402 | 1930 | 1949 | TGGCAGTGGACACGGGTCCC |
| 403 | 1931 | 1950 | GTGGCAGTGGACACGGGTCC |
| 404 | 1932 | 1951 | GGTGGCAGTGGACACGGGTC |
| 405 | 1933 | 1952 | TGGTGGCAGTGGACACGGGT |
| 406 | 1936 | 1955 | TGTTGGTGGCAGTGGACACG |
| 407 | 1962 | 1981 | AGCTGCAGCCTGTGAGGACG |
| 408 | 1990 | 2009 | GTGCCAAGGTCCTCCACCTC |
| 409 | 2010 | 2029 | TCAGCACAGGCGGCTTGTGG |
| 410 | 2040 | 2059 | CCACGCACTGGTTGGGCTGA |
| 60 | 2100 | 2119 | CTTTGCATTCCAGACCTGGG |
| 411 | 2101 | 2120 | ACTTTGCATTCCAGACCTGG |
| 412 | 2102 | 2121 | GACTTTGCATTCCAGACCTG |
| 413 | 2103 | 2122 | TGACTTTGCATTCCAGACCT |
| 414 | 2104 | 2123 | TTGACTTTGCATTCCAGACC |
| 61 | 2105 | 2124 | CTTGACTTTGCATTCCAGAC |
| 415 | 2107 | 2126 | TCCTTGACTTTGCATTCCAG |
| 416 | 2120 | 2139 | CGGGATTCCATGCTCCTTGA |
| 417 | 2150 | 2169 | GCAGGCCACGGTCACCTGCT |
| 418 | 2187 | 2206 | GGAGGGCACTGCAGCCAGTC |
| 419 | 2305 | 2324 | CAGATGGCAACGGCTGTCAC |
| 420 | 2306 | 2325 | GCAGATGGCAACGGCTGTCA |
| 421 | 2307 | 2326 | AGCAGATGGCAACGGCTGTC |

| SEQ ID NO | 5' Target Site on SEQ ID NO: 1 | 3' Target Site on SEQ ID NO: 1 | Sequence (5'-3') |
|---|---|---|---|
| 422 | 2308 | 2327 | CAGCAGATGGCAACGGCTGT |
| 423 | 2309 | 2328 | GCAGCAGATGGCAACGGCTG |
| 62 | 2310 | 2329 | GGCAGCAGATGGCAACGGCT |
| 424 | 2311 | 2330 | CGGCAGCAGATGGCAACGGC |
| 425 | 2312 | 2331 | CCGGCAGCAGATGGCAACGG |
| 426 | 2313 | 2332 | TCCGGCAGCAGATGGCAACG |
| 427 | 2314 | 2333 | CTCCGGCAGCAGATGGCAAC |
| 428 | 2315 | 2334 | GCTCCGGCAGCAGATGGCAA |
| 429 | 2325 | 2344 | CCAGGTGCCGGCTCCGGCAG |
| 430 | 2335 | 2354 | GAGGCCTGCGCCAGGTGCCG |
| 154 | 2410 | 2429 | TTTTAAAGCTCAGCCCCAGC |
| 63 | 2415 | 2434 | AACCATTTTAAAGCTCAGCC |
| 64 | 2504 | 2523 | TCAAGGGCCAGGCCAGCAGC |
| 65 | 2509 | 2528 | CCCACTCAAGGGCCAGGCCA |
| 122 | 2582 | 2601 | GGAGGGAGCTTCCTGGCACC |
| 66 | 2597 | 2616 | ATGCCCCACAGTGAGGGAGG |
| 67 | 2606 | 2625 | AATGGTGAAATGCCCCACAG |
| 153 | 2649 | 2668 | TTGGGAGCAGCTGGCAGCAC |
| 68 | 2750 | 2769 | CATGGGAAGAATCCTGCCTC |
| 431 | 2828 | 2847 | ATGAGGGCCATCAGCACCTT |
| 432 | 2829 | 2848 | GATGAGGGCCATCAGCACCT |
| 433 | 2830 | 2849 | AGATGAGGGCCATCAGCACC |
| 434 | 2831 | 2850 | GAGATGAGGGCCATCAGCAC |
| 69 | 2832 | 2851 | GGAGATGAGGGCCATCAGCA |
| 435 | 2833 | 2852 | TGGAGATGAGGGCCATCAGC |
| 436 | 2834 | 2853 | CTGGAGATGAGGGCCATCAG |
| 437 | 2835 | 2854 | GCTGGAGATGAGGGCCATCA |
| 438 | 2836 | 2855 | AGCTGGAGATGAGGGCCATC |
| 461 | 2877 | 2890 | TTAATCAGGGAGCC |
| 70 | 2900 | 2919 | TAGATGCCATCCAGAAAGCT |
| 439 | 2902 | 2921 | GCTAGATGCCATCCAGAAAG |
| 440 | 2903 | 2922 | GGCTAGATGCCATCCAGAAA |
| 441 | 2904 | 2923 | TGGCTAGATGCCATCCAGAA |
| 442 | 2905 | 2924 | CTGGCTAGATGCCATCCAGA |
| 71 | 2906 | 2925 | TCTGGCTAGATGCCATCCAG |
| 443 | 2907 | 2926 | CTCTGGCTAGATGCCATCCA |
| 444 | 2908 | 2927 | CCTCTGGCTAGATGCCATCC |
| 445 | 2909 | 2928 | GCCTCTGGCTAGATGCCATC |
| 446 | 2910 | 2929 | AGCCTCTGGCTAGATGCCAT |
| 72 | 2983 | 3002 | GGCATAGAGCAGAGTAAAGG |
| 73 | 2988 | 3007 | AGCCTGGCATAGAGCAGAGT |
| 135 | 2994 | 3013 | TAGCACAGCCTGGCATAGAG |
| 112 | 3227 | 3246 | GAAGAGGCTTGGCTTCAGAG |
| 74 | 3233 | 3252 | AAGTAAGAAGAGGCTTGGCT |
| 75 | 3437 | 3456 | GCTCAAGGAGGGACAGTTGT |
| 76 | 3472 | 3491 | AAAGATAAATGTCTGCTTGC |
| 77 | 3477 | 3496 | ACCCAAAAGATAAATGTCTG |
| 78 | 3543 | 3562 | TCTTCAAGTTACAAAAGCAA |

| SEQ ID NO | 5' Target Site on SEQ ID NO: 1 | 3' Target Site on SEQ ID NO: 1 | Sequence (5'-3') |
|---|---|---|---|
| 99 | 3550 | 3569 | ATAAATATCTTCAAGTTACA |

In certain embodiments, gapmer antisense compounds are targeted to a PCSK9 nucleic acid. In certain such embodiments, gapmer antisense compounds are targeted to SEQ ID NO: 1. In certain such embodiments, the nucleotide sequences illustrated in Table 1 have a 5-10-5 gapmer motif. Table 2 illustrates gapmer antisense compounds targeted to SEQ ID NO: 1, having a 5-10-5 motif, where the gap segment comprises 2'-deoxynucleotides and each wing segment comprises nucleotides comprising a 2'-O-methoxyethyl sugar modification. Internucleoside linkages are phosphorthioate, and cytidines are 5-methylcytidines.

**Table 2: Gapmer antisense compounds having a 5-10-5 motif targeted to SEQ ID NO: 1**

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO: 1 | 3' Target Site on SEQ ID NO: 1 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 395149 | 5-10-5 | 4 | 135 | 154 | 0 | GCGCGGAATCCTGGCTGGGA |
| 395150 | 5-10-5 | 5 | 242 | 261 | 0 | GAGGAGACCTAGAGGCCGTG |
| 395151 | 5-10-5 | 6 | 300 | 319 | 0 | AGGACCGCCTGGAGCTGACG |
| 395152 | 5-10-5 | 7 | 410 | 429 | 0 | ACGCAAGGCTAGCACCAGCT |
| 399793 | 5-10-5 | 8 | 417 | 436 | 0 | CCTCGGAACGCAAGGCTAGC |
| 395153 | 5-10-5 | 9 | 480 | 499 | 0 | CCTTGGCGCAGCGGTGGAAG |
| 395154 | 5-10-5 | 10 | 561 | 580 | 0 | GGCGGGCAGTGCGCTCTGAC |
| 395155 | 5-10-5 | 11 | 600 | 619 | 0 | TGGTGAGGTATCCCCGGCGG |
| 399794 | 5-10-5 | 12 | 606 | 625 | 0 | GGATCTTGGTGAGGTATCCC |
| 399795 | 5-10-5 | 13 | 615 | 634 | 0 | AGACATGCAGGATCTTGGTG |
| 395156 | 5-10-5 | 14 | 620 | 639 | 0 | ATGGAAGACATGCAGGATCT |
| 395157 | 5-10-5 | 15 | 646 | 665 | 0 | TTCACCAGGAAGCCAGGAAG |
| 399796 | 5-10-5 | 16 | 651 | 670 | 0 | TCATCTTCACCAGGAAGCCA |
| 395158 | 5-10-5 | 17 | 705 | 724 | 0 | CCTCGATGTAGTCGACATGG |
| 395159 | 5-10-5 | 18 | 785 | 804 | 0 | GTATTCATCCGCCCGGTACC |
| 395160 | 5-10-5 | 19 | 835 | 854 | 0 | CTGGTGTCTAGGAGATACAC |
| 399797 | 5-10-5 | 20 | 840 | 859 | 0 | GTATGCTGGTGTCTAGGAGA |
| 395161 | 5-10-5 | 21 | 860 | 879 | 0 | GATTTCCCGGTGGTCACTCT |
| 399798 | 5-10-5 | 22 | 866 | 885 | 0 | GCCCTCGATTTCCCGGTGGT |
| 399799 | 5-10-5 | 23 | 880 | 899 | 0 | GTGACCATGACCCTGCCCTC |
| 395162 | 5-10-5 | 24 | 890 | 909 | 0 | CTCGAAGTCGGTGACCATGA |
| 395163 | 5-10-5 | 25 | 923 | 942 | 0 | GTGGAAGCGGGTCCCGTCCT |
| 395164 | 5-10-5 | 26 | 970 | 989 | 0 | ACCCCTGCCAGGTGGGTGCC |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO: 1 | 3' Target Site on SEQ ID NO: 1 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 399800 | 5-10-5 | 27 | 975 | 994 | 0 | TGACCACCCCTGCCAGGTGG |
| 395165 | 5-10-5 | 28 | 1004 | 1023 | 0 | ACCCTTGGCCACGCCGGCAT |
| 395166 | 5-10-5 | 29 | 1040 | 1059 | 0 | TTGGCAGTTGAGCACGCGCA |
| 399801 | 5-10-5 | 30 | 1045 | 1064 | 0 | TTCCCTTGGCAGTTGAGCAC |
| 395167 | 5-10-5 | 31 | 1077 | 1096 | 0 | CCAGGCCTATGAGGGTGCCG |
| 395168 | 5-10-5 | 32 | 1098 | 1117 | 0 | GCTGGCTTTTCCGAATAAAC |
| 395169 | 5-10-5 | 33 | 1210 | 1229 | 0 | GTGACCAGCACGACCCCAGC |
| 395170 | 5-10-5 | 149 | 1297 | 1316 | 0 | TGGGCATTGGTGGCCCCAAC |
| 395171 | 5-10-5 | 34 | 1326 | 1345 | 0 | CCAAAGTCCCCAGGGTCACC |
| 395172 | 5-10-5 | 128 | 1330 | 1349 | 0 | GTCCCCAAAGTCCCCAGGGT |
| 399802 | 5-10-5 | 35 | 1335 | 1354 | 0 | AGTTGGTCCCCAAAGTCCCC |
| 395173 | 5-10-5 | 36 | 1340 | 1359 | 0 | GCCAAAGTTGGTCCCCAAAG |
| 399803 | 5-10-5 | 37 | 1352 | 1371 | 0 | GTCCACACAGCGGCCAAAGT |
| 395174 | 5-10-5 | 38 | 1361 | 1380 | 0 | GGCAAAGAGGTCCACACAGC |
| 395175 | 5-10-5 | 39 | 1389 | 1408 | 0 | TGGAGGCACCAATGATGTCC |
| 399804 | 5-10-5 | 40 | 1400 | 1419 | 0 | GCTGCAGTCGCTGGAGGCAC |
| 399805 | 5-10-5 | 41 | 1411 | 1430 | 0 | ACAAAGCAGGTGCTGCAGTC |
| 395176 | 5-10-5 | 101 | 1465 | 1484 | 0 | ATGGCTGCAATGCCAGCCAC |
| 399806 | 5-10-5 | 42 | 1470 | 1489 | 0 | GCATCATGGCTGCAATGCCA |
| 399807 | 5-10-5 | 43 | 1478 | 1497 | 0 | GGCAGACAGCATCATGGCTG |
| 399808 | 5-10-5 | 44 | 1526 | 1545 | 0 | GAAGTGGATCAGTCTCTGCC |
| 395177 | 5-10-5 | 45 | 1534 | 1553 | 0 | TTGGCAGAGAAGTGGATCAG |
| 399809 | 5-10-5 | 46 | 1539 | 1558 | 0 | CATCTTTGGCAGAGAAGTGG |
| 399810 | 5-10-5 | 47 | 1545 | 1564 | 0 | TGATGACATCTTTGGCAGAG |
| 399811 | 5-10-5 | 48 | 1552 | 1571 | 0 | GCCTCATTGATGACATCTTT |
| 399812 | 5-10-5 | 49 | 1564 | 1583 | 0 | TCAGGGAACCAGGCCTCATT |
| 395178 | 5-10-5 | 50 | 1569 | 1588 | 0 | GGTCCTCAGGGAACCAGGCC |
| 395179 | 5-10-5 | 87 | 1576 | 1595 | 0 | ACCCGCTGGTCCTCAGGGAA |
| 399813 | 5-10-5 | 51 | 1583 | 1602 | 0 | GGTCAGTACCCGCTGGTCCT |
| 395180 | 5-10-5 | 119 | 1605 | 1624 | 0 | GCAGGGCGGCCACCAGGTTG |
| 395181 | 5-10-5 | 52 | 1640 | 1659 | 0 | AAACAGCTGCCAACCTGCCC |
| 399814 | 5-10-5 | 53 | 1645 | 1664 | 0 | CTGCAAAACAGCTGCCAACC |
| 395182 | 5-10-5 | 54 | 1675 | 1694 | 0 | GTAGGCCCCGAGTGTGCTGA |
| 399815 | 5-10-5 | 55 | 1740 | 1759 | 0 | AGAAACTGGAGCAGCTCAGC |
| 399816 | 5-10-5 | 56 | 1746 | 1765 | 0 | TCCTGGAGAAACTGGAGCAG |
| 395183 | 5-10-5 | 57 | 1812 | 1831 | 0 | CGTTGTGGGCCCGGCAGACC |
| 395184 | 5-10-5 | 58 | 1858 | 1877 | 0 | AGCAGGCAGCACCTGGCAAT |
| 395185 | 5-10-5 | 59 | 1920 | 1939 | 0 | CACGGGTCCCCATGCTGGCC |
| 395186 | 5-10-5 | 60 | 2100 | 2119 | 0 | CTTTGCATTCCAGACCTGGG |
| 399817 | 5-10-5 | 61 | 2105 | 2124 | 0 | CTTGACTTTGCATTCCAGAC |
| 395187 | 5-10-5 | 62 | 2310 | 2329 | 0 | GGCAGCAGATGGCAACGGCT |
| 395188 | 5-10-5 | 154 | 2410 | 2429 | 0 | TTTTAAAGCTCAGCCCCAGC |
| 399818 | 5-10-5 | 63 | 2415 | 2434 | 0 | AACCATTTTAAAGCTCAGCC |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO: 1 | 3' Target Site on SEQ ID NO: 1 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 395189 | 5-10-5 | 64 | 2504 | 2523 | 0 | TCAAGGGCCAGGCCAGCAGC |
| 399819 | 5-10-5 | 65 | 2509 | 2528 | 0 | CCCACTCAAGGGCCAGGCCA |
| 399820 | 5-10-5 | 122 | 2582 | 2601 | 0 | GGAGGGAGCTTCCTGGCACC |
| 395190 | 5-10-5 | 66 | 2597 | 2616 | 0 | ATGCCCCACAGTGAGGGAGG |
| 395191 | 5-10-5 | 67 | 2606 | 2625 | 0 | AATGGTGAAATGCCCCACAG |
| 395192 | 5-10-5 | 153 | 2649 | 2668 | 0 | TTGGGAGCAGCTGGCAGCAC |
| 395193 | 5-10-5 | 68 | 2750 | 2769 | 0 | CATGGGAAGAATCCTGCCTC |
| 395194 | 5-10-5 | 69 | 2832 | 2851 | 0 | GGAGATGAGGGCCATCAGCA |
| 395195 | 5-10-5 | 70 | 2900 | 2919 | 0 | TAGATGCCATCCAGAAAGCT |
| 399821 | 5-10-5 | 71 | 2906 | 2925 | 0 | TCTGGCTAGATGCCATCCAG |
| 395196 | 5-10-5 | 72 | 2983 | 3002 | 0 | GGCATAGAGCAGAGTAAAGG |
| 399822 | 5-10-5 | 73 | 2988 | 3007 | 0 | AGCCTGGCATAGAGCAGAGT |
| 399823 | 5-10-5 | 135 | 2994 | 3013 | 0 | TAGCACAGCCTGGCATAGAG |
| 395197 | 5-10-5 | 112 | 3227 | 3246 | 0 | GAAGAGGCTTGGCTTCAGAG |
| 399824 | 5-10-5 | 74 | 3233 | 3252 | 0 | AAGTAAGAAGAGGCTTGGCT |
| 395198 | 5-10-5 | 75 | 3437 | 3456 | 0 | GCTCAAGGAGGGACAGTTGT |
| 395199 | 5-10-5 | 76 | 3472 | 3491 | 0 | AAAGATAAATGTCTGCTTGC |
| 399825 | 5-10-5 | 77 | 3477 | 3496 | 0 | ACCCAAAAGATAAATGTCTG |
| 395200 | 5-10-5 | 78 | 3543 | 3562 | 0 | TCTTCAAGTTACAAAAGCAA |
| 399826 | 5-10-5 | 99 | 3550 | 3569 | 0 | ATAAATATCTTCAAGTTACA |
| 405861 | 5-10-5 | 162 | 406 | 425 | 0 | AAGGCTAGCACCAGCTCCTC |
| 405862 | 5-10-5 | 163 | 407 | 426 | 0 | CAAGGCTAGCACCAGCTCCT |
| 405863 | 5-10-5 | 164 | 408 | 427 | 0 | GCAAGGCTAGCACCAGCTCC |
| 405864 | 5-10-5 | 165 | 409 | 428 | 0 | CGCAAGGCTAGCACCAGCTC |
| 405865 | 5-10-5 | 166 | 411 | 430 | 0 | AACGCAAGGCTAGCACCAGC |
| 405866 | 5-10-5 | 167 | 412 | 431 | 0 | GAACGCAAGGCTAGCACCAG |
| 405867 | 5-10-5 | 168 | 413 | 432 | 0 | GGAACGCAAGGCTAGCACCA |
| 405868 | 5-10-5 | 169 | 414 | 433 | 0 | CGGAACGCAAGGCTAGCACC |
| 405869 | 5-10-5 | 218 | 862 | 881 | 0 | TCGATTTCCCGGTGGTCACT |
| 405870 | 5-10-5 | 219 | 863 | 882 | 0 | CTCGATTTCCCGGTGGTCAC |
| 405871 | 5-10-5 | 220 | 864 | 883 | 0 | CCTCGATTTCCCGGTGGTCA |
| 405872 | 5-10-5 | 221 | 865 | 884 | 0 | CCCTCGATTTCCCGGTGGTC |
| 405873 | 5-10-5 | 222 | 867 | 886 | 0 | TGCCCTCGATTTCCCGGTGG |
| 405874 | 5-10-5 | 223 | 868 | 887 | 0 | CTGCCCTCGATTTCCCGGTG |
| 405875 | 5-10-5 | 224 | 869 | 888 | 0 | CCTGCCCTCGATTTCCCGGT |
| 405876 | 5-10-5 | 225 | 870 | 889 | 0 | CCCTGCCCTCGATTTCCCGG |
| 405877 | 5-10-5 | 246 | 1000 | 1019 | 0 | TTGGCCACGCCGGCATCCCG |
| 405878 | 5-10-5 | 247 | 1001 | 1020 | 0 | CTTGGCCACGCCGGCATCCC |
| 405879 | 5-10-5 | 248 | 1002 | 1021 | 0 | CCTTGGCCACGCCGGCATCC |
| 405880 | 5-10-5 | 249 | 1003 | 1022 | 0 | CCCTTGGCCACGCCGGCATC |
| 405881 | 5-10-5 | 250 | 1005 | 1024 | 0 | CACCCTTGGCCACGCCGGCA |
| 405882 | 5-10-5 | 251 | 1006 | 1025 | 0 | GCACCCTTGGCCACGCCGGC |
| 405883 | 5-10-5 | 252 | 1007 | 1026 | 0 | GGCACCCTTGGCCACGCCGG |
| 405884 | 5-10-5 | 253 | 1008 | 1027 | 0 | TGGCACCCTTGGCCACGCCG |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO: 1 | 3' Target Site on SEQ ID NO: 1 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 405885 | 5-10-5 | 346 | 1560 | 1579 | 0 | GGAACCAGGCCTCATTGATG |
| 405886 | 5-10-5 | 347 | 1561 | 1580 | 0 | GGGAACCAGGCCTCATTGAT |
| 405887 | 5-10-5 | 348 | 1562 | 1581 | 0 | AGGGAACCAGGCCTCATTGA |
| 405888 | 5-10-5 | 349 | 1563 | 1582 | 0 | CAGGGAACCAGGCCTCATTG |
| 405889 | 5-10-5 | 350 | 1565 | 1584 | 0 | CTCAGGGAACCAGGCCTCAT |
| 405890 | 5-10-5 | 351 | 1566 | 1585 | 0 | CCTCAGGGAACCAGGCCTCA |
| 405891 | 5-10-5 | 352 | 1567 | 1586 | 0 | TCCTCAGGGAACCAGGCCTC |
| 405892 | 5-10-5 | 353 | 1568 | 1587 | 0 | GTCCTCAGGGAACCAGGCCT |
| 405893 | 5-10-5 | 431 | 2828 | 2847 | 0 | ATGAGGGCCATCAGCACCTT |
| 405894 | 5-10-5 | 432 | 2829 | 2848 | 0 | GATGAGGGCCATCAGCACCT |
| 405895 | 5-10-5 | 433 | 2830 | 2849 | 0 | AGATGAGGGCCATCAGCACC |
| 405896 | 5-10-5 | 434 | 2831 | 2850 | 0 | GAGATGAGGGCCATCAGCAC |
| 405897 | 5-10-5 | 435 | 2833 | 2852 | 0 | TGGAGATGAGGGCCATCAGC |
| 405898 | 5-10-5 | 436 | 2834 | 2853 | 0 | CTGGAGATGAGGGCCATCAG |
| 405899 | 5-10-5 | 437 | 2835 | 2854 | 0 | GCTGGAGATGAGGGCCATCA |
| 405900 | 5-10-5 | 438 | 2836 | 2855 | 0 | AGCTGGAGATGAGGGCCATC |
| 405901 | 5-10-5 | 439 | 2902 | 2921 | 0 | GCTAGATGCCATCCAGAAAG |
| 405902 | 5-10-5 | 440 | 2903 | 2922 | 0 | GGCTAGATGCCATCCAGAAA |
| 405903 | 5-10-5 | 441 | 2904 | 2923 | 0 | TGGCTAGATGCCATCCAGAA |
| 405904 | 5-10-5 | 442 | 2905 | 2924 | 0 | CTGGCTAGATGCCATCCAGA |
| 405905 | 5-10-5 | 443 | 2907 | 2926 | 0 | CTCTGGCTAGATGCCATCCA |
| 405906 | 5-10-5 | 444 | 2908 | 2927 | 0 | CCTCTGGCTAGATGCCATCC |
| 405907 | 5-10-5 | 445 | 2909 | 2928 | 0 | GCCTCTGGCTAGATGCCATC |
| 405908 | 5-10-5 | 446 | 2910 | 2929 | 0 | AGCCTCTGGCTAGATGCCAT |
| 405909 | 5-10-5 | 267 | 1100 | 1119 | 0 | CAGCTGGCTTTTCCGAATAA |
| 405910 | 5-10-5 | 268 | 1102 | 1121 | 0 | ACCAGCTGGCTTTTCCGAAT |
| 405911 | 5-10-5 | 269 | 1104 | 1123 | 0 | GGACCAGCTGGCTTTTCCGA |
| 405912 | 5-10-5 | 270 | 1108 | 1127 | 0 | GGCTGGACCAGCTGGCTTTT |
| 405913 | 5-10-5 | 275 | 1212 | 1231 | 0 | CGGTGACCAGCACGACCCCA |
| 405914 | 5-10-5 | 276 | 1214 | 1233 | 0 | AGCGGTGACCAGCACGACCC |
| 405915 | 5-10-5 | 277 | 1216 | 1235 | 0 | GCAGCGGTGACCAGCACGAC |
| 405916 | 5-10-5 | 278 | 1218 | 1237 | 0 | CGGCAGCGGTGACCAGCACG |
| 405917 | 5-10-5 | 280 | 1222 | 1241 | 0 | TTGCCGGCAGCGGTGACCAG |
| 405918 | 5-10-5 | 281 | 1224 | 1243 | 0 | AGTTGCCGGCAGCGGTGACC |
| 405919 | 5-10-5 | 282 | 1226 | 1245 | 0 | GAAGTTGCCGGCAGCGGTGA |
| 405920 | 5-10-5 | 283 | 1228 | 1247 | 0 | CGGAAGTTGCCGGCAGCGGT |
| 405921 | 5-10-5 | 284 | 1230 | 1249 | 0 | CCCGGAAGTTGCCGGCAGCG |
| 405922 | 5-10-5 | 285 | 1232 | 1251 | 0 | GTCCCGGAAGTTGCCGGCAG |
| 405923 | 5-10-5 | 288 | 1295 | 1314 | 0 | GGCATTGGTGGCCCCAACTG |
| 405924 | 5-10-5 | 290 | 1318 | 1337 | 0 | CCCAGGGTCACCGGCTGGTC |
| 405925 | 5-10-5 | 292 | 1322 | 1341 | 0 | AGTCCCCAGGGTCACCGGCT |
| 405926 | 5-10-5 | 293 | 1324 | 1343 | 0 | AAAGTCCCCAGGGTCACCGG |
| 405927 | 5-10-5 | 294 | 1328 | 1347 | 0 | CCCCAAAGTCCCCAGGGTCA |
| 405928 | 5-10-5 | 295 | 1333 | 1352 | 0 | TTGGTCCCCAAAGTCCCCAG |
| 405929 | 5-10-5 | 296 | 1337 | 1356 | 0 | AAAGTTGGTCCCCAAAGTCC |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO: 1 | 3' Target Site on SEQ ID NO: 1 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 405930 | 5-10-5 | 297 | 1342 | 1361 | 0 | CGGCCAAAGTTGGTCCCCAA |
| 405931 | 5-10-5 | 298 | 1344 | 1363 | 0 | AGCGGCCAAAGTTGGTCCCC |
| 405932 | 5-10-5 | 299 | 1346 | 1365 | 0 | ACAGCGGCCAAAGTTGGTCC |
| 405933 | 5-10-5 | 300 | 1348 | 1367 | 0 | ACACAGCGGCCAAAGTTGGT |
| 405934 | 5-10-5 | 301 | 1350 | 1369 | 0 | CCACACAGCGGCCAAAGTTG |
| 405935 | 5-10-5 | 302 | 1354 | 1373 | 0 | AGGTCCACACAGCGGCCAAA |
| 405936 | 5-10-5 | 304 | 1358 | 1377 | 0 | AAAGAGGTCCACACAGCGGC |
| 405937 | 5-10-5 | 306 | 1387 | 1406 | 0 | GAGGCACCAATGATGTCCTC |
| 405938 | 5-10-5 | 307 | 1391 | 1410 | 0 | GCTGGAGGCACCAATGATGT |
| 405939 | 5-10-5 | 308 | 1393 | 1412 | 0 | TCGCTGGAGGCACCAATGAT |
| 405940 | 5-10-5 | 309 | 1395 | 1414 | 0 | AGTCGCTGGAGGCACCAATG |
| 405941 | 5-10-5 | 310 | 1397 | 1416 | 0 | GCAGTCGCTGGAGGCACCAA |
| 405942 | 5-10-5 | 311 | 1402 | 1421 | 0 | GTGCTGCAGTCGCTGGAGGC |
| 405943 | 5-10-5 | 312 | 1404 | 1423 | 0 | AGGTGCTGCAGTCGCTGGAG |
| 405944 | 5-10-5 | 314 | 1407 | 1426 | 0 | AGCAGGTGCTGCAGTCGCTG |
| 405945 | 5-10-5 | 315 | 1409 | 1428 | 0 | AAAGCAGGTGCTGCAGTCGC |
| 405946 | 5-10-5 | 316 | 1413 | 1432 | 0 | ACACAAAGCAGGTGCTGCAG |
| 405947 | 5-10-5 | 317 | 1415 | 1434 | 0 | TGACACAAAGCAGGTGCTGC |
| 405948 | 5-10-5 | 319 | 1467 | 1486 | 0 | TCATGGCTGCAATGCCAGCC |
| 405949 | 5-10-5 | 320 | 1472 | 1491 | 0 | CAGCATCATGGCTGCAATGC |
| 405950 | 5-10-5 | 321 | 1474 | 1493 | 0 | GACAGCATCATGGCTGCAAT |
| 405951 | 5-10-5 | 322 | 1476 | 1495 | 0 | CAGACAGCATCATGGCTGCA |
| 405952 | 5-10-5 | 323 | 1480 | 1499 | 0 | TCGGCAGACAGCATCATGGC |
| 405953 | 5-10-5 | 325 | 1484 | 1503 | 0 | CGGCTCGGCAGACAGCATCA |
| 405954 | 5-10-5 | 326 | 1486 | 1505 | 0 | TCCGGCTCGGCAGACAGCAT |
| 405955 | 5-10-5 | 328 | 1513 | 1532 | 0 | CTCTGCCTCAACTCGGCCAG |
| 405956 | 5-10-5 | 329 | 1515 | 1534 | 0 | GTCTCTGCCTCAACTCGGCC |
| 405957 | 5-10-5 | 330 | 1517 | 1536 | 0 | CAGTCTCTGCCTCAACTCGG |
| 405958 | 5-10-5 | 331 | 1519 | 1538 | 0 | ATCAGTCTCTGCCTCAACTC |
| 405959 | 5-10-5 | 332 | 1521 | 1540 | 0 | GGATCAGTCTCTGCCTCAAC |
| 405960 | 5-10-5 | 333 | 1523 | 1542 | 0 | GTGGATCAGTCTCTGCCTCA |
| 405961 | 5-10-5 | 334 | 1525 | 1544 | 0 | AAGTGGATCAGTCTCTGCCT |
| 405962 | 5-10-5 | 335 | 1528 | 1547 | 0 | GAGAAGTGGATCAGTCTCTG |
| 405963 | 5-10-5 | 337 | 1532 | 1551 | 0 | GGCAGAGAAGTGGATCAGTC |
| 405964 | 5-10-5 | 338 | 1536 | 1555 | 0 | CTTTGGCAGAGAAGTGGATC |
| 405965 | 5-10-5 | 339 | 1541 | 1560 | 0 | GACATCTTTGGCAGAGAAGT |
| 405966 | 5-10-5 | 340 | 1543 | 1562 | 0 | ATGACATCTTTGGCAGAGAA |
| 405967 | 5-10-5 | 341 | 1547 | 1566 | 0 | ATTGATGACATCTTTGGCAG |
| 405968 | 5-10-5 | 342 | 1549 | 1568 | 0 | TCATTGATGACATCTTTGGC |
| 405969 | 5-10-5 | 343 | 1554 | 1573 | 0 | AGGCCTCATTGATGACATCT |
| 405970 | 5-10-5 | 344 | 1556 | 1575 | 0 | CCAGGCCTCATTGATGACAT |
| 405971 | 5-10-5 | 355 | 1571 | 1590 | 0 | CTGGTCCTCAGGGAACCAGG |
| 405972 | 5-10-5 | 357 | 1573 | 1592 | 0 | CGCTGGTCCTCAGGGAACCA |
| 405973 | 5-10-5 | 358 | 1578 | 1597 | 0 | GTACCCGCTGGTCCTCAGGG |
| 405974 | 5-10-5 | 359 | 1580 | 1599 | 0 | CAGTACCCGCTGGTCCTCAG |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO: 1 | 3' Target Site on SEQ ID NO: 1 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 405975 | 5-10-5 | 361 | 1642 | 1661 | 0 | CAAAACAGCTGCCAACCTGC |
| 405976 | 5-10-5 | 362 | 1647 | 1666 | 0 | TCCTGCAAAACAGCTGCCAA |
| 405977 | 5-10-5 | 363 | 1649 | 1668 | 0 | AGTCCTGCAAAACAGCTGCC |
| 405978 | 5-10-5 | 365 | 1672 | 1691 | 0 | GGCCCCGAGTGTGCTGACCA |
| 405979 | 5-10-5 | 366 | 1677 | 1696 | 0 | GTGTAGGCCCCGAGTGTGCT |
| 405980 | 5-10-5 | 367 | 1679 | 1698 | 0 | CCGTGTAGGCCCCGAGTGTG |
| 405981 | 5-10-5 | 368 | 1681 | 1700 | 0 | ATCCGTGTAGGCCCCGAGTG |
| 405982 | 5-10-5 | 370 | 1685 | 1704 | 0 | GGCCATCCGTGTAGGCCCCG |
| 405983 | 5-10-5 | 371 | 1687 | 1706 | 0 | GTGGCCATCCGTGTAGGCCC |
| 405984 | 5-10-5 | 372 | 1735 | 1754 | 0 | CTGGAGCAGCTCAGCAGCTC |
| 405985 | 5-10-5 | 373 | 1737 | 1756 | 0 | AACTGGAGCAGCTCAGCAGC |
| 405986 | 5-10-5 | 374 | 1742 | 1761 | 0 | GGAGAAACTGGAGCAGCTCA |
| 405987 | 5-10-5 | 375 | 1744 | 1763 | 0 | CTGGAGAAACTGGAGCAGCT |
| 405988 | 5-10-5 | 381 | 1854 | 1873 | 0 | GGCAGCACCTGGCAATGGCG |
| 405989 | 5-10-5 | 383 | 1856 | 1875 | 0 | CAGGCAGCACCTGGCAATGG |
| 405990 | 5-10-5 | 386 | 1860 | 1879 | 0 | GTAGCAGGCAGCACCTGGCA |
| 405991 | 5-10-5 | 394 | 1922 | 1941 | 0 | GACACGGGTCCCCATGCTGG |
| 405992 | 5-10-5 | 396 | 1924 | 1943 | 0 | TGGACACGGGTCCCCATGCT |
| 405993 | 5-10-5 | 398 | 1926 | 1945 | 0 | AGTGGACACGGGTCCCCATG |
| 405994 | 5-10-5 | 400 | 1928 | 1947 | 0 | GCAGTGGACACGGGTCCCCA |
| 405995 | 5-10-5 | 402 | 1930 | 1949 | 0 | TGGCAGTGGACACGGGTCCC |
| 405996 | 5-10-5 | 412 | 2102 | 2121 | 0 | GACTTTGCATTCCAGACCTG |
| 405997 | 5-10-5 | 415 | 2107 | 2126 | 0 | TCCTTGACTTTGCATTCCAG |
| 405998 | 5-10-5 | 426 | 2313 | 2332 | 0 | TCCGGCAGCAGATGGCAACG |
| 405999 | 5-10-5 | 160 | 298 | 317 | 0 | GACCGCCTGGAGCTGACGGT |
| 406000 | 5-10-5 | 173 | 482 | 501 | 0 | ATCCTTGGCGCAGCGGTGGA |
| 406001 | 5-10-5 | 174 | 484 | 503 | 0 | GGATCCTTGGCGCAGCGGTG |
| 406002 | 5-10-5 | 175 | 488 | 507 | 0 | CCACGGATCCTTGGCGCAGC |
| 406003 | 5-10-5 | 178 | 555 | 574 | 0 | CAGTGCGCTCTGACTGCGAG |
| 406004 | 5-10-5 | 179 | 557 | 576 | 0 | GGCAGTGCGCTCTGACTGCG |
| 406005 | 5-10-5 | 180 | 559 | 578 | 0 | CGGGCAGTGCGCTCTGACTG |
| 406006 | 5-10-5 | 181 | 562 | 581 | 0 | CGGCGGGCAGTGCGCTCTGA |
| 406007 | 5-10-5 | 183 | 595 | 614 | 0 | AGGTATCCCCGGCGGGCAGC |
| 406008 | 5-10-5 | 188 | 602 | 621 | 0 | CTTGGTGAGGTATCCCCGGC |
| 406009 | 5-10-5 | 190 | 604 | 623 | 0 | ATCTTGGTGAGGTATCCCCG |
| 406010 | 5-10-5 | 193 | 609 | 628 | 0 | GCAGGATCTTGGTGAGGTAT |
| 406011 | 5-10-5 | 194 | 611 | 630 | 0 | ATGCAGGATCTTGGTGAGGT |
| 406012 | 5-10-5 | 195 | 613 | 632 | 0 | ACATGCAGGATCTTGGTGAG |
| 406013 | 5-10-5 | 196 | 617 | 636 | 0 | GAAGACATGCAGGATCTTGG |
| 406014 | 5-10-5 | 199 | 648 | 667 | 0 | TCTTCACCAGGAAGCCAGGA |
| 406015 | 5-10-5 | 200 | 653 | 672 | 0 | ACTCATCTTCACCAGGAAGC |
| 406016 | 5-10-5 | 201 | 655 | 674 | 0 | CCACTCATCTTCACCAGGAA |
| 406017 | 5-10-5 | 203 | 659 | 678 | 0 | GTCGCCACTCATCTTCACCA |
| 406018 | 5-10-5 | 204 | 661 | 680 | 0 | AGGTCGCCACTCATCTTCAC |
| 406019 | 5-10-5 | 205 | 663 | 682 | 0 | GCAGGTCGCCACTCATCTTC |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO: 1 | 3' Target Site on SEQ ID NO: 1 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 406020 | 5-10-5 | 206 | 665 | 684 | 0 | CAGCAGGTCGCCACTCATCT |
| 406021 | 5-10-5 | 210 | 782 | 801 | 0 | TTCATCCGCCCGGTACCGTG |
| 406022 | 5-10-5 | 211 | 784 | 803 | 0 | TATTCATCCGCCCGGTACCG |
| 406023 | 5-10-5 | 212 | 787 | 806 | 0 | TGGTATTCATCCGCCCGGTA |
| 406024 | 5-10-5 | 213 | 789 | 808 | 0 | GCTGGTATTCATCCGCCCGG |
| 406025 | 5-10-5 | 216 | 832 | 851 | 0 | GTGTCTAGGAGATACACCTC |
| 406026 | 5-10-5 | 217 | 837 | 856 | 0 | TGCTGGTGTCTAGGAGATAC |
| 406027 | 5-10-5 | 226 | 874 | 893 | 0 | ATGACCCTGCCCTCGATTTC |
| 406028 | 5-10-5 | 227 | 876 | 895 | 0 | CCATGACCCTGCCCTCGATT |
| 406029 | 5-10-5 | 228 | 878 | 897 | 0 | GACCATGACCCTGCCCTCGA |
| 406030 | 5-10-5 | 229 | 882 | 901 | 0 | CGGTGACCATGACCCTGCCC |
| 406031 | 5-10-5 | 230 | 884 | 903 | 0 | GTCGGTGACCATGACCCTGC |
| 406032 | 5-10-5 | 232 | 888 | 907 | 0 | CGAAGTCGGTGACCATGACC |
| 406033 | 5-10-5 | 237 | 967 | 986 | 0 | CCTGCCAGGTGGGTGCCATG |
| 406034 | 5-10-5 | 238 | 972 | 991 | 0 | CCACCCCTGCCAGGTGGGTG |
| 406035 | 5-10-5 | 239 | 977 | 996 | 0 | GCTGACCACCCCTGCCAGGT |
| 406036 | 5-10-5 | 241 | 989 | 1008 | 0 | GGCATCCCGGCCGCTGACCA |
| 406037 | 5-10-5 | 242 | 992 | 1011 | 0 | GCCGGCATCCCGGCCGCTGA |
| 406038 | 5-10-5 | 245 | 999 | 1018 | 0 | TGGCCACGCCGGCATCCCGG |
| 406039 | 5-10-5 | 257 | 1036 | 1055 | 0 | CAGTTGAGCACGCGCAGGCT |
| 406040 | 5-10-5 | 258 | 1038 | 1057 | 0 | GGCAGTTGAGCACGCGCAGG |
| 406041 | 5-10-5 | 259 | 1042 | 1061 | 0 | CCTTGGCAGTTGAGCACGCG |
| 406042 | 5-10-5 | 260 | 1047 | 1066 | 0 | CCTTCCCTTGGCAGTTGAGC |
| 406043 | 5-10-5 | 261 | 1051 | 1070 | 0 | GTGCCCTTCCCTTGGCAGTT |
| 406044 | 5-10-5 | 262 | 1053 | 1072 | 0 | CCGTGCCCTTCCCTTGGCAG |
| 406045 | 5-10-5 | 266 | 1096 | 1115 | 0 | TGGCTTTTCCGAATAAACTC |
| 408642 | 5-10-5 | 264 | 1076 | 1095 | 0 | CAGGCCTATGAGGGTGCCGC |
| 408653 | 5-10-5 | 354 | 1570 | 1589 | 0 | TGGTCCTCAGGGAACCAGGC |
| 409126 | 5-10-5 | 447 | 1004 | 1023 | 1 | ACCCTTGGTCACGCCGGCAT |
| 410529 | 5-10-5 | 184 | 597 | 616 | 0 | TGAGGTATCCCCGGCGGGCA |
| 410530 | 5-10-5 | 185 | 598 | 617 | 0 | GTGAGGTATCCCCGGCGGGC |
| 410531 | 5-10-5 | 186 | 599 | 618 | 0 | GGTGAGGTATCCCCGGCGGG |
| 410532 | 5-10-5 | 187 | 601 | 620 | 0 | TTGGTGAGGTATCCCCGGCG |
| 410533 | 5-10-5 | 189 | 603 | 622 | 0 | TCTTGGTGAGGTATCCCCGG |
| 410534 | 5-10-5 | 191 | 605 | 624 | 0 | GATCTTGGTGAGGTATCCCC |
| 410535 | 5-10-5 | 192 | 607 | 626 | 0 | AGGATCTTGGTGAGGTATCC |
| 410536 | 5-10-5 | 243 | 997 | 1016 | 0 | GCCACGCCGGCATCCCGGCC |
| 410537 | 5-10-5 | 244 | 998 | 1017 | 0 | GGCCACGCCGGCATCCCGGC |
| 410538 | 5-10-5 | 254 | 1009 | 1028 | 0 | CTGGCACCCTTGGCCACGCC |
| 410539 | 5-10-5 | 255 | 1010 | 1029 | 0 | GCTGGCACCCTTGGCCACGC |
| 410540 | 5-10-5 | 356 | 1572 | 1591 | 0 | GCTGGTCCTCAGGGAACCAG |
| 410541 | 5-10-5 | 376 | 1849 | 1868 | 0 | CACCTGGCAATGGCGTAGAC |
| 410542 | 5-10-5 | 377 | 1850 | 1869 | 0 | GCACCTGGCAATGGCGTAGA |
| 410543 | 5-10-5 | 378 | 1851 | 1870 | 0 | AGCACCTGGCAATGGCGTAG |
| 410544 | 5-10-5 | 379 | 1852 | 1871 | 0 | CAGCACCTGGCAATGGCGTA |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO: 1 | 3' Target Site on SEQ ID NO: 1 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 410545 | 5-10-5 | 380 | 1853 | 1872 | 0 | GCAGCACCTGGCAATGGCGT |
| 410546 | 5-10-5 | 382 | 1855 | 1874 | 0 | AGGCAGCACCTGGCAATGGC |
| 410547 | 5-10-5 | 384 | 1857 | 1876 | 0 | GCAGGCAGCACCTGGCAATG |
| 410548 | 5-10-5 | 385 | 1859 | 1878 | 0 | TAGCAGGCAGCACCTGGCAA |
| 410549 | 5-10-5 | 388 | 1915 | 1934 | 0 | GTCCCCATGCTGGCCTCAGC |
| 410550 | 5-10-5 | 389 | 1916 | 1935 | 0 | GGTCCCCATGCTGGCCTCAG |
| 410551 | 5-10-5 | 390 | 1917 | 1936 | 0 | GGGTCCCCATGCTGGCCTCA |
| 410552 | 5-10-5 | 391 | 1918 | 1937 | 0 | CGGGTCCCCATGCTGGCCTC |
| 410553 | 5-10-5 | 392 | 1919 | 1938 | 0 | ACGGGTCCCCATGCTGGCCT |
| 410554 | 5-10-5 | 393 | 1921 | 1940 | 0 | ACACGGGTCCCCATGCTGGC |
| 410555 | 5-10-5 | 395 | 1923 | 1942 | 0 | GGACACGGGTCCCCATGCTG |
| 410556 | 5-10-5 | 397 | 1925 | 1944 | 0 | GTGGACACGGGTCCCCATGC |
| 410557 | 5-10-5 | 399 | 1927 | 1946 | 0 | CAGTGGACACGGGTCCCCAT |
| 410558 | 5-10-5 | 401 | 1929 | 1948 | 0 | GGCAGTGGACACGGGTCCCC |
| 410559 | 5-10-5 | 403 | 1931 | 1950 | 0 | GTGGCAGTGGACACGGGTCC |
| 410560 | 5-10-5 | 404 | 1932 | 1951 | 0 | GGTGGCAGTGGACACGGGTC |
| 410561 | 5-10-5 | 405 | 1933 | 1952 | 0 | TGGTGGCAGTGGACACGGGT |
| 410562 | 5-10-5 | 411 | 2101 | 2120 | 0 | ACTTTGCATTCCAGACCTGG |
| 410563 | 5-10-5 | 413 | 2103 | 2122 | 0 | TGACTTTGCATTCCAGACCT |
| 410564 | 5-10-5 | 414 | 2104 | 2123 | 0 | TTGACTTTGCATTCCAGACC |
| 410565 | 5-10-5 | 419 | 2305 | 2324 | 0 | CAGATGGCAACGGCTGTCAC |
| 410566 | 5-10-5 | 420 | 2306 | 2325 | 0 | GCAGATGGCAACGGCTGTCA |
| 410567 | 5-10-5 | 421 | 2307 | 2326 | 0 | AGCAGATGGCAACGGCTGTC |
| 410568 | 5-10-5 | 422 | 2308 | 2327 | 0 | CAGCAGATGGCAACGGCTGT |
| 410569 | 5-10-5 | 423 | 2309 | 2328 | 0 | GCAGCAGATGGCAACGGCTG |
| 410570 | 5-10-5 | 424 | 2311 | 2330 | 0 | CGGCAGCAGATGGCAACGGC |
| 410571 | 5-10-5 | 425 | 2312 | 2331 | 0 | CCGGCAGCAGATGGCAACGG |
| 410572 | 5-10-5 | 427 | 2314 | 2333 | 0 | CTCCGGCAGCAGATGGCAAC |
| 410573 | 5-10-5 | 428 | 2315 | 2334 | 0 | GCTCCGGCAGCAGATGGCAA |
| 410730 | 5-10-5 | 202 | 657 | 676 | 0 | CGCCACTCATCTTCACCAGG |
| 410731 | 5-10-5 | 207 | 667 | 686 | 0 | TCCAGCAGGTCGCCACTCAT |
| 410732 | 5-10-5 | 214 | 791 | 810 | 0 | GGGCTGGTATTCATCCGCCC |
| 410733 | 5-10-5 | 231 | 886 | 905 | 0 | AAGTCGGTGACCATGACCCT |
| 410734 | 5-10-5 | 279 | 1219 | 1238 | 0 | CCGGCAGCGGTGACCAGCAC |
| 410735 | 5-10-5 | 291 | 1320 | 1339 | 0 | TCCCCAGGGTCACCGGCTGG |
| 410736 | 5-10-5 | 303 | 1356 | 1375 | 0 | AGAGGTCCACACAGCGGCCA |
| 410737 | 5-10-5 | 313 | 1406 | 1425 | 0 | GCAGGTGCTGCAGTCGCTGG |
| 410738 | 5-10-5 | 324 | 1482 | 1501 | 0 | GCTCGGCAGACAGCATCATG |
| 410739 | 5-10-5 | 336 | 1530 | 1549 | 0 | CAGAGAAGTGGATCAGTCTC |
| 410740 | 5-10-5 | 345 | 1558 | 1577 | 0 | AACCAGGCCTCATTGATGAC |
| 410741 | 5-10-5 | 369 | 1683 | 1702 | 0 | CCATCCGTGTAGGCCCCGAG |
| 410742 | 5-10-5 | 159 | 294 | 313 | 0 | GCCTGGAGCTGACGGTGCCC |
| 410743 | 5-10-5 | 170 | 421 | 440 | 0 | TCCTCCTCGGAACGCAAGGC |
| 410744 | 5-10-5 | 171 | 446 | 465 | 0 | GTGCTCGGGTGCTTCGGCCA |
| 410745 | 5-10-5 | 172 | 466 | 485 | 0 | TGGAAGGTGGCTGTGGTTCC |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO: 1 | 3' Target Site on SEQ ID NO: 1 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 410746 | 5-10-5 | 176 | 507 | 526 | 0 | CGTAGGTGCCAGGCAACCTC |
| 410747 | 5-10-5 | 177 | 545 | 564 | 0 | TGACTGCGAGAGGTGGGTCT |
| 410748 | 5-10-5 | 182 | 591 | 610 | 0 | ATCCCCGGCGGGCAGCCTGG |
| 410749 | 5-10-5 | 197 | 628 | 647 | 0 | AGAAGGCCATGGAAGACATG |
| 410750 | 5-10-5 | 198 | 638 | 657 | 0 | GAAGCCAGGAAGAAGGCCAT |
| 410751 | 5-10-5 | 208 | 685 | 704 | 0 | GGCAACTTCAAGGCCAGCTC |
| 410752 | 5-10-5 | 209 | 724 | 743 | 0 | GCAAAGACAGAGGAGTCCTC |
| 410753 | 5-10-5 | 215 | 821 | 840 | 0 | ATACACCTCCACCAGGCTGC |
| 410754 | 5-10-5 | 233 | 898 | 917 | 0 | GGCACATTCTCGAAGTCGGT |
| 410755 | 5-10-5 | 234 | 933 | 952 | 0 | TGGCCTGTCTGTGGAAGCGG |
| 410756 | 5-10-5 | 235 | 960 | 979 | 0 | GGTGGGTGCCATGACTGTCA |
| 410757 | 5-10-5 | 240 | 985 | 1004 | 0 | TCCCGGCCGCTGACCACCCC |
| 410758 | 5-10-5 | 256 | 1015 | 1034 | 0 | CGCATGCTGGCACCCTTGGC |
| 410759 | 5-10-5 | 263 | 1064 | 1083 | 0 | GGTGCCGCTAACCGTGCCCT |
| 410760 | 5-10-5 | 265 | 1088 | 1107 | 0 | CCGAATAAACTCCAGGCCTA |
| 410761 | 5-10-5 | 271 | 1119 | 1138 | 0 | GTGGCCCCACAGGCTGGACC |
| 410762 | 5-10-5 | 272 | 1132 | 1151 | 0 | AGCAGCACCACCAGTGGCCC |
| 410763 | 5-10-5 | 273 | 1154 | 1173 | 0 | GCTGTACCCACCCGCCAGGG |
| 410764 | 5-10-5 | 274 | 1200 | 1219 | 0 | CGACCCCAGCCCTCGCCAGG |
| 410765 | 5-10-5 | 286 | 1273 | 1292 | 0 | ATGACCTCGGGAGCTGAGGC |
| 410766 | 5-10-5 | 287 | 1283 | 1302 | 0 | CCCAACTGTGATGACCTCGG |
| 410767 | 5-10-5 | 289 | 1305 | 1324 | 0 | GCTGGTCTTGGGCATTGGTG |
| 410768 | 5-10-5 | 305 | 1380 | 1399 | 0 | CAATGATGTCCTCCCCTGGG |
| 410769 | 5-10-5 | 318 | 1425 | 1444 | 0 | TCCCACTCTGTGACACAAAG |
| 410770 | 5-10-5 | 327 | 1500 | 1519 | 0 | CGGCCAGGGTGAGCTCCGGC |
| 410771 | 5-10-5 | 360 | 1628 | 1647 | 0 | ACCTGCCCCATGGGTGCTGG |
| 410772 | 5-10-5 | 364 | 1660 | 1679 | 0 | GCTGACCATACAGTCCTGCA |
| 410773 | 5-10-5 | 387 | 1905 | 1924 | 0 | TGGCCTCAGCTGGTGGAGCT |
| 410774 | 5-10-5 | 406 | 1936 | 1955 | 0 | TGTTGGTGGCAGTGGACACG |
| 410775 | 5-10-5 | 407 | 1962 | 1981 | 0 | AGCTGCAGCCTGTGAGGACG |
| 410776 | 5-10-5 | 408 | 1990 | 2009 | 0 | GTGCCAAGGTCCTCCACCTC |
| 410777 | 5-10-5 | 409 | 2010 | 2029 | 0 | TCAGCACAGGCGGCTTGTGG |
| 410778 | 5-10-5 | 410 | 2040 | 2059 | 0 | CCACGCACTGGTTGGGCTGA |
| 410779 | 5-10-5 | 416 | 2120 | 2139 | 0 | CGGGATTCCATGCTCCTTGA |
| 410780 | 5-10-5 | 417 | 2150 | 2169 | 0 | GCAGGCCACGGTCACCTGCT |
| 410781 | 5-10-5 | 418 | 2187 | 2206 | 0 | GGAGGGCACTGCAGCCAGTC |
| 410782 | 5-10-5 | 429 | 2325 | 2344 | 0 | CCAGGTGCCGGCTCCGGCAG |
| 410783 | 5-10-5 | 430 | 2335 | 2354 | 0 | GAGGCCTGCGCCAGGTGCCG |

In certain embodiments, gap-widened antisense compounds are targeted to a PCSK9 nucleic acid. In certain such embodiments, gap-widened antisense compounds are targeted to SEQ ID NO: 1. In certain such embodiments, the nucleotide sequences illustrated in Table 1 have a 3-14-3 gap-widened motif. Table 3 illustrates gap-widened antisense compounds targeted to

SEQ ID NO: 1, having a 3-14-3 motif, where the gap segment comprises 2'-deoxynucleotides and each wing segment comprises nucleotides comprising a 2'-O-methoxyethyl sugar modification. Internucleoside linkages are phosphorthioate, and cytidines are 5-methylcytidines.

**Table 3: Gapmer antisense compounds having a 3-14-3 motif targeted to SEQ ID NO: 1**

| Isis No | Motif | SEQ ID NO | 5' Target Site to SEQ ID NO: 1 | 3' Target Site to SEQ ID NO: 1 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 399871 | 3-14-3 | 4 | 135 | 154 | 0 | GCGCGGAATCCTGGCTGGGA |
| 399872 | 3-14-3 | 5 | 242 | 261 | 0 | GAGGAGACCTAGAGGCCGTG |
| 399873 | 3-14-3 | 6 | 300 | 319 | 0 | AGGACCGCCTGGAGCTGACG |
| 399874 | 3-14-3 | 7 | 410 | 429 | 0 | ACGCAAGGCTAGCACCAGCT |
| 399949 | 3-14-3 | 8 | 417 | 436 | 0 | CCTCGGAACGCAAGGCTAGC |
| 399875 | 3-14-3 | 9 | 480 | 499 | 0 | CCTTGGCGCAGCGGTGGAAG |
| 399876 | 3-14-3 | 10 | 561 | 580 | 0 | GGCGGGCAGTGCGCTCTGAC |
| 399877 | 3-14-3 | 11 | 600 | 619 | 0 | TGGTGAGGTATCCCCGGCGG |
| 399950 | 3-14-3 | 12 | 606 | 625 | 0 | GGATCTTGGTGAGGTATCCC |
| 399951 | 3-14-3 | 13 | 615 | 634 | 0 | AGACATGCAGGATCTTGGTG |
| 399878 | 3-14-3 | 14 | 620 | 639 | 0 | ATGGAAGACATGCAGGATCT |
| 399879 | 3-14-3 | 15 | 646 | 665 | 0 | TTCACCAGGAAGCCAGGAAG |
| 399952 | 3-14-3 | 16 | 651 | 670 | 0 | TCATCTTCACCAGGAAGCCA |
| 399880 | 3-14-3 | 17 | 705 | 724 | 0 | CCTCGATGTAGTCGACATGG |
| 399881 | 3-14-3 | 18 | 785 | 804 | 0 | GTATTCATCCGCCCGGTACC |
| 399882 | 3-14-3 | 19 | 835 | 854 | 0 | CTGGTGTCTAGGAGATACAC |
| 399953 | 3-14-3 | 20 | 840 | 859 | 0 | GTATGCTGGTGTCTAGGAGA |
| 399883 | 3-14-3 | 21 | 860 | 879 | 0 | GATTTCCCGGTGGTCACTCT |
| 399954 | 3-14-3 | 22 | 866 | 885 | 0 | GCCCTCGATTTCCCGGTGGT |
| 399955 | 3-14-3 | 23 | 880 | 899 | 0 | GTGACCATGACCCTGCCCTC |
| 399884 | 3-14-3 | 24 | 890 | 909 | 0 | CTCGAAGTCGGTGACCATGA |
| 399885 | 3-14-3 | 25 | 923 | 942 | 0 | GTGGAAGCGGGTCCCGTCCT |
| 399886 | 3-14-3 | 26 | 970 | 989 | 0 | ACCCCTGCCAGGTGGGTGCC |
| 399956 | 3-14-3 | 27 | 975 | 994 | 0 | TGACCACCCCTGCCAGGTGG |
| 399887 | 3-14-3 | 28 | 1004 | 1023 | 0 | ACCCTTGGCCACGCCGGCAT |
| 399888 | 3-14-3 | 29 | 1040 | 1059 | 0 | TTGGCAGTTGAGCACGCGCA |
| 399957 | 3-14-3 | 30 | 1045 | 1064 | 0 | TTCCCTTGGCAGTTGAGCAC |
| 399889 | 3-14-3 | 31 | 1077 | 1096 | 0 | CCAGGCCTATGAGGGTGCCG |
| 399890 | 3-14-3 | 32 | 1098 | 1117 | 0 | GCTGGCTTTTCCGAATAAAC |
| 399891 | 3-14-3 | 33 | 1210 | 1229 | 0 | GTGACCAGCACGACCCCAGC |
| 399892 | 3-14-3 | 149 | 1297 | 1316 | 0 | TGGGCATTGGTGGCCCCAAC |
| 399893 | 3-14-3 | 34 | 1326 | 1345 | 0 | CCAAAGTCCCCAGGGTCACC |
| 399894 | 3-14-3 | 128 | 1330 | 1349 | 0 | GTCCCCAAAGTCCCCAGGGT |
| 399958 | 3-14-3 | 35 | 1335 | 1354 | 0 | AGTTGGTCCCCAAAGTCCCC |
| 399895 | 3-14-3 | 36 | 1340 | 1359 | 0 | GCCAAAGTTGGTCCCCAAAG |
| 399959 | 3-14-3 | 37 | 1352 | 1371 | 0 | GTCCACACAGCGGCCAAAGT |
| 399896 | 3-14-3 | 38 | 1361 | 1380 | 0 | GGCAAAGAGGTCCACACAGC |
| 399897 | 3-14-3 | 39 | 1389 | 1408 | 0 | TGGAGGCACCAATGATGTCC |
| 399960 | 3-14-3 | 40 | 1400 | 1419 | 0 | GCTGCAGTCGCTGGAGGCAC |
| 399961 | 3-14-3 | 41 | 1411 | 1430 | 0 | ACAAAGCAGGTGCTGCAGTC |
| 399898 | 3-14-3 | 101 | 1465 | 1484 | 0 | ATGGCTGCAATGCCAGCCAC |

| Isis No | Motif | SEQ ID NO | 5' Target Site to SEQ ID NO: 1 | 3' Target Site to SEQ ID NO: 1 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 399962 | 3-14-3 | 42 | 1470 | 1489 | 0 | GCATCATGGCTGCAATGCCA |
| 399963 | 3-14-3 | 43 | 1478 | 1497 | 0 | GGCAGACAGCATCATGGCTG |
| 399964 | 3-14-3 | 44 | 1526 | 1545 | 0 | GAAGTGGATCAGTCTCTGCC |
| 399899 | 3-14-3 | 45 | 1534 | 1553 | 0 | TTGGCAGAGAAGTGGATCAG |
| 399965 | 3-14-3 | 46 | 1539 | 1558 | 0 | CATCTTTGGCAGAGAAGTGG |
| 399966 | 3-14-3 | 47 | 1545 | 1564 | 0 | TGATGACATCTTTGGCAGAG |
| 399967 | 3-14-3 | 48 | 1552 | 1571 | 0 | GCCTCATTGATGACATCTTT |
| 399968 | 3-14-3 | 49 | 1564 | 1583 | 0 | TCAGGGAACCAGGCCTCATT |
| 399900 | 3-14-3 | 50 | 1569 | 1588 | 0 | GGTCCTCAGGGAACCAGGCC |
| 399901 | 3-14-3 | 87 | 1576 | 1595 | 0 | ACCCGCTGGTCCTCAGGGAA |
| 399969 | 3-14-3 | 51 | 1583 | 1602 | 0 | GGTCAGTACCCGCTGGTCCT |
| 399902 | 3-14-3 | 119 | 1605 | 1624 | 0 | GCAGGGCGGCCACCAGGTTG |
| 399903 | 3-14-3 | 52 | 1640 | 1659 | 0 | AAACAGCTGCCAACCTGCCC |
| 399970 | 3-14-3 | 53 | 1645 | 1664 | 0 | CTGCAAAACAGCTGCCAACC |
| 399904 | 3-14-3 | 54 | 1675 | 1694 | 0 | GTAGGCCCCGAGTGTGCTGA |
| 399971 | 3-14-3 | 55 | 1740 | 1759 | 0 | AGAAACTGGAGCAGCTCAGC |
| 399972 | 3-14-3 | 56 | 1746 | 1765 | 0 | TCCTGGAGAAACTGGAGCAG |
| 399905 | 3-14-3 | 57 | 1812 | 1831 | 0 | CGTTGTGGGCCCGGCAGACC |
| 399906 | 3-14-3 | 58 | 1858 | 1877 | 0 | AGCAGGCAGCACCTGGCAAT |
| 399907 | 3-14-3 | 59 | 1920 | 1939 | 0 | CACGGGTCCCCATGCTGGCC |
| 399908 | 3-14-3 | 60 | 2100 | 2119 | 0 | CTTTGCATTCCAGACCTGGG |
| 399973 | 3-14-3 | 61 | 2105 | 2124 | 0 | CTTGACTTTGCATTCCAGAC |
| 399909 | 3-14-3 | 62 | 2310 | 2329 | 0 | GGCAGCAGATGGCAACGGCT |
| 399910 | 3-14-3 | 154 | 2410 | 2429 | 0 | TTTTAAAGCTCAGCCCCAGC |
| 399974 | 3-14-3 | 63 | 2415 | 2434 | 0 | AACCATTTTAAAGCTCAGCC |
| 399911 | 3-14-3 | 64 | 2504 | 2523 | 0 | TCAAGGGCCAGGCCAGCAGC |
| 399975 | 3-14-3 | 65 | 2509 | 2528 | 0 | CCCACTCAAGGGCCAGGCCA |
| 399976 | 3-14-3 | 122 | 2582 | 2601 | 0 | GGAGGGAGCTTCCTGGCACC |
| 399912 | 3-14-3 | 66 | 2597 | 2616 | 0 | ATGCCCCACAGTGAGGGAGG |
| 399913 | 3-14-3 | 67 | 2606 | 2625 | 0 | AATGGTGAAATGCCCCACAG |
| 399914 | 3-14-3 | 153 | 2649 | 2668 | 0 | TTGGGAGCAGCTGGCAGCAC |
| 399915 | 3-14-3 | 68 | 2750 | 2769 | 0 | CATGGGAAGAATCCTGCCTC |
| 399916 | 3-14-3 | 69 | 2832 | 2851 | 0 | GGAGATGAGGGCCATCAGCA |
| 399917 | 3-14-3 | 70 | 2900 | 2919 | 0 | TAGATGCCATCCAGAAAGCT |
| 399977 | 3-14-3 | 71 | 2906 | 2925 | 0 | TCTGGCTAGATGCCATCCAG |
| 399918 | 3-14-3 | 72 | 2983 | 3002 | 0 | GGCATAGAGCAGAGTAAAGG |
| 399978 | 3-14-3 | 73 | 2988 | 3007 | 0 | AGCCTGGCATAGAGCAGAGT |
| 399979 | 3-14-3 | 135 | 2994 | 3013 | 0 | TAGCACAGCCTGGCATAGAG |
| 399919 | 3-14-3 | 112 | 3227 | 3246 | 0 | GAAGAGGCTTGGCTTCAGAG |
| 399980 | 3-14-3 | 74 | 3233 | 3252 | 0 | AAGTAAGAAGAGGCTTGGCT |
| 399920 | 3-14-3 | 75 | 3437 | 3456 | 0 | GCTCAAGGAGGGACAGTTGT |
| 399921 | 3-14-3 | 76 | 3472 | 3491 | 0 | AAAGATAAATGTCTGCTTGC |
| 399981 | 3-14-3 | 77 | 3477 | 3496 | 0 | ACCCAAAAGATAAATGTCTG |
| 399922 | 3-14-3 | 78 | 3543 | 3562 | 0 | TCTTCAAGTTACAAAAGCAA |
| 399982 | 3-14-3 | 99 | 3550 | 3569 | 0 | ATAAATATCTTCAAGTTACA |
| 410574 | 3-14-3 | 184 | 597 | 616 | 0 | TGAGGTATCCCCGGCGGGCA |
| 410575 | 3-14-3 | 185 | 598 | 617 | 0 | GTGAGGTATCCCCGGCGGGC |
| 410576 | 3-14-3 | 186 | 599 | 618 | 0 | GGTGAGGTATCCCCGGCGGG |
| 410577 | 3-14-3 | 187 | 601 | 620 | 0 | TTGGTGAGGTATCCCCGGCG |

| Isis No | Motif | SEQ ID NO | 5' Target Site to SEQ ID NO: 1 | 3' Target Site to SEQ ID NO: 1 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 410578 | 3-14-3 | 188 | 602 | 621 | 0 | CTTGGTGAGGTATCCCCGGC |
| 410579 | 3-14-3 | 189 | 603 | 622 | 0 | TCTTGGTGAGGTATCCCCGG |
| 410580 | 3-14-3 | 190 | 604 | 623 | 0 | ATCTTGGTGAGGTATCCCCG |
| 410581 | 3-14-3 | 191 | 605 | 624 | 0 | GATCTTGGTGAGGTATCCCC |
| 410582 | 3-14-3 | 192 | 607 | 626 | 0 | AGGATCTTGGTGAGGTATCC |
| 405604 | 3-14-3 | 236 | 963 | 982 | 0 | CCAGGTGGGTGCCATGACTG |
| 410583 | 3-14-3 | 243 | 997 | 1016 | 0 | GCCACGCCGGCATCCCGGCC |
| 410584 | 3-14-3 | 244 | 998 | 1017 | 0 | GGCCACGCCGGCATCCCGGC |
| 410585 | 3-14-3 | 245 | 999 | 1018 | 0 | TGGCCACGCCGGCATCCCGG |
| 410586 | 3-14-3 | 246 | 1000 | 1019 | 0 | TTGGCCACGCCGGCATCCCG |
| 410587 | 3-14-3 | 247 | 1001 | 1020 | 0 | CTTGGCCACGCCGGCATCCC |
| 410588 | 3-14-3 | 248 | 1002 | 1021 | 0 | CCTTGGCCACGCCGGCATCC |
| 410589 | 3-14-3 | 249 | 1003 | 1022 | 0 | CCCTTGGCCACGCCGGCATC |
| 410590 | 3-14-3 | 250 | 1005 | 1024 | 0 | CACCCTTGGCCACGCCGGCA |
| 410591 | 3-14-3 | 251 | 1006 | 1025 | 0 | GCACCCTTGGCCACGCCGGC |
| 410592 | 3-14-3 | 252 | 1007 | 1026 | 0 | GGCACCCTTGGCCACGCCGG |
| 410593 | 3-14-3 | 253 | 1008 | 1027 | 0 | TGGCACCCTTGGCCACGCCG |
| 410594 | 3-14-3 | 254 | 1009 | 1028 | 0 | CTGGCACCCTTGGCCACGCC |
| 410595 | 3-14-3 | 255 | 1010 | 1029 | 0 | GCTGGCACCCTTGGCCACGC |
| 410596 | 3-14-3 | 348 | 1562 | 1581 | 0 | AGGGAACCAGGCCTCATTGA |
| 410597 | 3-14-3 | 349 | 1563 | 1582 | 0 | CAGGGAACCAGGCCTCATTG |
| 410598 | 3-14-3 | 350 | 1565 | 1584 | 0 | CTCAGGGAACCAGGCCTCAT |
| 410599 | 3-14-3 | 351 | 1566 | 1585 | 0 | CCTCAGGGAACCAGGCCTCA |
| 410600 | 3-14-3 | 352 | 1567 | 1586 | 0 | TCCTCAGGGAACCAGGCCTC |
| 410601 | 3-14-3 | 353 | 1568 | 1587 | 0 | GTCCTCAGGGAACCAGGCCT |
| 410602 | 3-14-3 | 354 | 1570 | 1589 | 0 | TGGTCCTCAGGGAACCAGGC |
| 410603 | 3-14-3 | 355 | 1571 | 1590 | 0 | CTGGTCCTCAGGGAACCAGG |
| 410604 | 3-14-3 | 356 | 1572 | 1591 | 0 | GCTGGTCCTCAGGGAACCAG |
| 405641 | 3-14-3 | 373 | 1737 | 1756 | 0 | AACTGGAGCAGCTCAGCAGC |
| 410605 | 3-14-3 | 376 | 1849 | 1868 | 0 | CACCTGGCAATGGCGTAGAC |
| 410606 | 3-14-3 | 377 | 1850 | 1869 | 0 | GCACCTGGCAATGGCGTAGA |
| 410607 | 3-14-3 | 378 | 1851 | 1870 | 0 | AGCACCTGGCAATGGCGTAG |
| 410608 | 3-14-3 | 379 | 1852 | 1871 | 0 | CAGCACCTGGCAATGGCGTA |
| 410609 | 3-14-3 | 380 | 1853 | 1872 | 0 | GCAGCACCTGGCAATGGCGT |
| 410610 | 3-14-3 | 381 | 1854 | 1873 | 0 | GGCAGCACCTGGCAATGGCG |
| 410611 | 3-14-3 | 382 | 1855 | 1874 | 0 | AGGCAGCACCTGGCAATGGC |
| 410612 | 3-14-3 | 383 | 1856 | 1875 | 0 | CAGGCAGCACCTGGCAATGG |
| 410613 | 3-14-3 | 384 | 1857 | 1876 | 0 | GCAGGCAGCACCTGGCAATG |
| 410614 | 3-14-3 | 385 | 1859 | 1878 | 0 | TAGCAGGCAGCACCTGGCAA |
| 410615 | 3-14-3 | 388 | 1915 | 1934 | 0 | GTCCCCATGCTGGCCTCAGC |
| 410616 | 3-14-3 | 389 | 1916 | 1935 | 0 | GGTCCCCATGCTGGCCTCAG |
| 410617 | 3-14-3 | 390 | 1917 | 1936 | 0 | GGGTCCCCATGCTGGCCTCA |
| 410618 | 3-14-3 | 391 | 1918 | 1937 | 0 | CGGGTCCCCATGCTGGCCTC |
| 410619 | 3-14-3 | 392 | 1919 | 1938 | 0 | ACGGGTCCCCATGCTGGCCT |
| 410620 | 3-14-3 | 393 | 1921 | 1940 | 0 | ACACGGGTCCCCATGCTGGC |
| 410621 | 3-14-3 | 394 | 1922 | 1941 | 0 | GACACGGGTCCCCATGCTGG |
| 410622 | 3-14-3 | 395 | 1923 | 1942 | 0 | GGACACGGGTCCCCATGCTG |
| 410623 | 3-14-3 | 396 | 1924 | 1943 | 0 | TGGACACGGGTCCCCATGCT |
| 410624 | 3-14-3 | 397 | 1925 | 1944 | 0 | GTGGACACGGGTCCCCATGC |

| Isis No | Motif | SEQ ID NO | 5' Target Site to SEQ ID NO: 1 | 3' Target Site to SEQ ID NO: 1 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 410625 | 3-14-3 | 398 | 1926 | 1945 | 0 | AGTGGACACGGGTCCCCATG |
| 410626 | 3-14-3 | 399 | 1927 | 1946 | 0 | CAGTGGACACGGGTCCCCAT |
| 410627 | 3-14-3 | 400 | 1928 | 1947 | 0 | GCAGTGGACACGGGTCCCCA |
| 410628 | 3-14-3 | 401 | 1929 | 1948 | 0 | GGCAGTGGACACGGGTCCCC |
| 410629 | 3-14-3 | 402 | 1930 | 1949 | 0 | TGGCAGTGGACACGGGTCCC |
| 410630 | 3-14-3 | 403 | 1931 | 1950 | 0 | GTGGCAGTGGACACGGGTCC |
| 410631 | 3-14-3 | 404 | 1932 | 1951 | 0 | GGTGGCAGTGGACACGGGTC |
| 410632 | 3-14-3 | 405 | 1933 | 1952 | 0 | TGGTGGCAGTGGACACGGGT |
| 410633 | 3-14-3 | 411 | 2101 | 2120 | 0 | ACTTTGCATTCCAGACCTGG |
| 410634 | 3-14-3 | 412 | 2102 | 2121 | 0 | GACTTTGCATTCCAGACCTG |
| 410635 | 3-14-3 | 413 | 2103 | 2122 | 0 | TGACTTTGCATTCCAGACCT |
| 410636 | 3-14-3 | 414 | 2104 | 2123 | 0 | TTGACTTTGCATTCCAGACC |
| 410637 | 3-14-3 | 419 | 2305 | 2324 | 0 | CAGATGGCAACGGCTGTCAC |
| 410638 | 3-14-3 | 420 | 2306 | 2325 | 0 | GCAGATGGCAACGGCTGTCA |
| 410639 | 3-14-3 | 421 | 2307 | 2326 | 0 | AGCAGATGGCAACGGCTGTC |
| 410640 | 3-14-3 | 422 | 2308 | 2327 | 0 | CAGCAGATGGCAACGGCTGT |
| 410641 | 3-14-3 | 423 | 2309 | 2328 | 0 | GCAGCAGATGGCAACGGCTG |
| 410642 | 3-14-3 | 424 | 2311 | 2330 | 0 | CGGCAGCAGATGGCAACGGC |
| 410643 | 3-14-3 | 425 | 2312 | 2331 | 0 | CCGGCAGCAGATGGCAACGG |
| 410644 | 3-14-3 | 426 | 2313 | 2332 | 0 | TCCGGCAGCAGATGGCAACG |
| 410645 | 3-14-3 | 427 | 2314 | 2333 | 0 | CTCCGGCAGCAGATGGCAAC |
| 410646 | 3-14-3 | 428 | 2315 | 2334 | 0 | GCTCCGGCAGCAGATGGCAA |

In certain embodiments, gap-widened antisense compounds are targeted to a PCSK9 nucleic acid. In certain such embodiments, gap-widened antisense compounds are targeted to SEQ ID NO: 1. In certain such embodiments, the nucleotide sequences illustrated in Table 1 have a 2-13-5 gap-widened motif. Table 4 illustrates gap-widened antisense compounds targeted to SEQ ID NO: 1, having a 2-13-5 motif, where the gap segment comprises 2'-deoxynucleotides and each wing segment comprises nucleotides comprising a 2'-O-methoxyethyl sugar modification. Internucleoside linkages are phosphorthioate, and cytidines are 5-methylcytidines.

**Table 4: Gapmer antisense compounds having a 2-13-5 motif targeted to SEQ ID NO: 1**

| ISIS No. | Motif | SEQ ID NO | 5' start site to SEQ ID NO: 1 | 3' Start Site to SEQ ID NO: 1 | Mismatches | Sequences (5' to 3') |
|---|---|---|---|---|---|---|
| 410647 | 2-13-5 | 184 | 597 | 616 | 0 | TGAGGTATCCCCGGCGGGCA |
| 410648 | 2-13-5 | 185 | 598 | 617 | 0 | GTGAGGTATCCCCGGCGGGC |
| 410649 | 2-13-5 | 186 | 599 | 618 | 0 | GGTGAGGTATCCCCGGCGGG |
| 410650 | 2-13-5 | 11 | 600 | 619 | 0 | TGGTGAGGTATCCCCGGCGG |
| 410651 | 2-13-5 | 187 | 601 | 620 | 0 | TTGGTGAGGTATCCCCGGCG |
| 410652 | 2-13-5 | 188 | 602 | 621 | 0 | CTTGGTGAGGTATCCCCGGC |
| 410653 | 2-13-5 | 189 | 603 | 622 | 0 | TCTTGGTGAGGTATCCCCGG |

| ISIS No. | Motif | SEQ ID NO | 5' start site to SEQ ID NO: 1 | 3' Start Site to SEQ ID NO: 1 | Mismatches | Sequences (5' to 3') |
|---|---|---|---|---|---|---|
| 410654 | 2-13-5 | 190 | 604 | 623 | 0 | ATCTTGGTGAGGTATCCCCG |
| 410655 | 2-13-5 | 191 | 605 | 624 | 0 | GATCTTGGTGAGGTATCCCC |
| 410656 | 2-13-5 | 12 | 606 | 625 | 0 | GGATCTTGGTGAGGTATCCC |
| 410657 | 2-13-5 | 192 | 607 | 626 | 0 | AGGATCTTGGTGAGGTATCC |
| 410658 | 2-13-5 | 243 | 997 | 1016 | 0 | GCCACGCCGGCATCCCGGCC |
| 410659 | 2-13-5 | 244 | 998 | 1017 | 0 | GGCCACGCCGGCATCCCGGC |
| 410660 | 2-13-5 | 245 | 999 | 1018 | 0 | TGGCCACGCCGGCATCCCGG |
| 410661 | 2-13-5 | 246 | 1000 | 1019 | 0 | TTGGCCACGCCGGCATCCCG |
| 410662 | 2-13-5 | 247 | 1001 | 1020 | 0 | CTTGGCCACGCCGGCATCCC |
| 410663 | 2-13-5 | 248 | 1002 | 1021 | 0 | CCTTGGCCACGCCGGCATCC |
| 410664 | 2-13-5 | 249 | 1003 | 1022 | 0 | CCCTTGGCCACGCCGGCATC |
| 410665 | 2-13-5 | 28 | 1004 | 1023 | 0 | ACCCTTGGCCACGCCGGCAT |
| 410666 | 2-13-5 | 250 | 1005 | 1024 | 0 | CACCCTTGGCCACGCCGGCA |
| 410667 | 2-13-5 | 251 | 1006 | 1025 | 0 | GCACCCTTGGCCACGCCGGC |
| 410668 | 2-13-5 | 252 | 1007 | 1026 | 0 | GGCACCCTTGGCCACGCCGG |
| 410669 | 2-13-5 | 253 | 1008 | 1027 | 0 | TGGCACCCTTGGCCACGCCG |
| 410670 | 2-13-5 | 254 | 1009 | 1028 | 0 | CTGGCACCCTTGGCCACGCC |
| 410671 | 2-13-5 | 255 | 1010 | 1029 | 0 | GCTGGCACCCTTGGCCACGC |
| 410672 | 2-13-5 | 348 | 1562 | 1581 | 0 | AGGGAACCAGGCCTCATTGA |
| 410673 | 2-13-5 | 349 | 1563 | 1582 | 0 | CAGGGAACCAGGCCTCATTG |
| 410674 | 2-13-5 | 49 | 1564 | 1583 | 0 | TCAGGGAACCAGGCCTCATT |
| 410675 | 2-13-5 | 350 | 1565 | 1584 | 0 | CTCAGGGAACCAGGCCTCAT |
| 410676 | 2-13-5 | 351 | 1566 | 1585 | 0 | CCTCAGGGAACCAGGCCTCA |
| 410677 | 2-13-5 | 352 | 1567 | 1586 | 0 | TCCTCAGGGAACCAGGCCTC |
| 410678 | 2-13-5 | 353 | 1568 | 1587 | 0 | GTCCTCAGGGAACCAGGCCT |
| 410679 | 2-13-5 | 50 | 1569 | 1588 | 0 | GGTCCTCAGGGAACCAGGCC |
| 410680 | 2-13-5 | 354 | 1570 | 1589 | 0 | TGGTCCTCAGGGAACCAGGC |
| 410681 | 2-13-5 | 355 | 1571 | 1590 | 0 | CTGGTCCTCAGGGAACCAGG |
| 410682 | 2-13-5 | 356 | 1572 | 1591 | 0 | GCTGGTCCTCAGGGAACCAG |
| 410683 | 2-13-5 | 376 | 1849 | 1868 | 0 | CACCTGGCAATGGCGTAGAC |
| 410684 | 2-13-5 | 377 | 1850 | 1869 | 0 | GCACCTGGCAATGGCGTAGA |
| 410685 | 2-13-5 | 378 | 1851 | 1870 | 0 | AGCACCTGGCAATGGCGTAG |
| 410686 | 2-13-5 | 379 | 1852 | 1871 | 0 | CAGCACCTGGCAATGGCGTA |
| 410687 | 2-13-5 | 380 | 1853 | 1872 | 0 | GCAGCACCTGGCAATGGCGT |
| 410688 | 2-13-5 | 381 | 1854 | 1873 | 0 | GGCAGCACCTGGCAATGGCG |
| 410689 | 2-13-5 | 382 | 1855 | 1874 | 0 | AGGCAGCACCTGGCAATGGC |
| 410690 | 2-13-5 | 383 | 1856 | 1875 | 0 | CAGGCAGCACCTGGCAATGG |
| 410691 | 2-13-5 | 384 | 1857 | 1876 | 0 | GCAGGCAGCACCTGGCAATG |
| 410692 | 2-13-5 | 58 | 1858 | 1877 | 0 | AGCAGGCAGCACCTGGCAAT |
| 410693 | 2-13-5 | 385 | 1859 | 1878 | 0 | TAGCAGGCAGCACCTGGCAA |
| 410694 | 2-13-5 | 388 | 1915 | 1934 | 0 | GTCCCCATGCTGGCCTCAGC |
| 410695 | 2-13-5 | 389 | 1916 | 1935 | 0 | GGTCCCCATGCTGGCCTCAG |
| 410696 | 2-13-5 | 390 | 1917 | 1936 | 0 | GGGTCCCCATGCTGGCCTCA |
| 410697 | 2-13-5 | 391 | 1918 | 1937 | 0 | CGGGTCCCCATGCTGGCCTC |
| 410698 | 2-13-5 | 392 | 1919 | 1938 | 0 | ACGGGTCCCCATGCTGGCCT |
| 410699 | 2-13-5 | 59 | 1920 | 1939 | 0 | CACGGGTCCCCATGCTGGCC |
| 410700 | 2-13-5 | 393 | 1921 | 1940 | 0 | ACACGGGTCCCCATGCTGGC |
| 410701 | 2-13-5 | 394 | 1922 | 1941 | 0 | GACACGGGTCCCCATGCTGG |
| 410702 | 2-13-5 | 395 | 1923 | 1942 | 0 | GGACACGGGTCCCCATGCTG |

| ISIS No. | Motif | SEQ ID NO | 5' start site to SEQ ID NO: 1 | 3' Start Site to SEQ ID NO: 1 | Mismatches | Sequences (5' to 3') |
|---|---|---|---|---|---|---|
| 410703 | 2-13-5 | 396 | 1924 | 1943 | 0 | TGGACACGGGTCCCCATGCT |
| 410704 | 2-13-5 | 397 | 1925 | 1944 | 0 | GTGGACACGGGTCCCCATGC |
| 410705 | 2-13-5 | 398 | 1926 | 1945 | 0 | AGTGGACACGGGTCCCCATG |
| 410706 | 2-13-5 | 399 | 1927 | 1946 | 0 | CAGTGGACACGGGTCCCCAT |
| 410707 | 2-13-5 | 400 | 1928 | 1947 | 0 | GCAGTGGACACGGGTCCCCA |
| 410708 | 2-13-5 | 401 | 1929 | 1948 | 0 | GGCAGTGGACACGGGTCCCC |
| 410709 | 2-13-5 | 402 | 1930 | 1949 | 0 | TGGCAGTGGACACGGGTCCC |
| 410710 | 2-13-5 | 403 | 1931 | 1950 | 0 | GTGGCAGTGGACACGGGTCC |
| 410711 | 2-13-5 | 404 | 1932 | 1951 | 0 | GGTGGCAGTGGACACGGGTC |
| 410712 | 2-13-5 | 405 | 1933 | 1952 | 0 | TGGTGGCAGTGGACACGGGT |
| 410713 | 2-13-5 | 60 | 2100 | 2119 | 0 | CTTTGCATTCCAGACCTGGG |
| 410714 | 2-13-5 | 411 | 2101 | 2120 | 0 | ACTTTGCATTCCAGACCTGG |
| 410715 | 2-13-5 | 412 | 2102 | 2121 | 0 | GACTTTGCATTCCAGACCTG |
| 410716 | 2-13-5 | 413 | 2103 | 2122 | 0 | TGACTTTGCATTCCAGACCT |
| 410717 | 2-13-5 | 414 | 2104 | 2123 | 0 | TTGACTTTGCATTCCAGACC |
| 410718 | 2-13-5 | 61 | 2105 | 2124 | 0 | CTTGACTTTGCATTCCAGAC |
| 410719 | 2-13-5 | 419 | 2305 | 2324 | 0 | CAGATGGCAACGGCTGTCAC |
| 410720 | 2-13-5 | 420 | 2306 | 2325 | 0 | GCAGATGGCAACGGCTGTCA |
| 410721 | 2-13-5 | 421 | 2307 | 2326 | 0 | AGCAGATGGCAACGGCTGTC |
| 410722 | 2-13-5 | 422 | 2308 | 2327 | 0 | CAGCAGATGGCAACGGCTGT |
| 410723 | 2-13-5 | 423 | 2309 | 2328 | 0 | GCAGCAGATGGCAACGGCTG |
| 410724 | 2-13-5 | 62 | 2310 | 2329 | 0 | GGCAGCAGATGGCAACGGCT |
| 410725 | 2-13-5 | 424 | 2311 | 2330 | 0 | CGGCAGCAGATGGCAACGGC |
| 410726 | 2-13-5 | 425 | 2312 | 2331 | 0 | CCGGCAGCAGATGGCAACGG |
| 410727 | 2-13-5 | 426 | 2313 | 2332 | 0 | TCCGGCAGCAGATGGCAACG |
| 410728 | 2-13-5 | 427 | 2314 | 2333 | 0 | CTCCGGCAGCAGATGGCAAC |
| 410729 | 2-13-5 | 428 | 2315 | 2334 | 0 | GCTCCGGCAGCAGATGGCAA |

In certain embodiments, gap-widened antisense compounds are targeted to a PCSK9 nucleic acid. In certain such embodiments, gap-widened antisense compounds are targeted to SEQ ID NO: 1. In certain such embodiments, the nucleotide sequences illustrated in Table 1 have a 3-13-4 gap-widened motif. Table 5 illustrates gap-widened antisense compounds targeted to SEQ ID NO: 1, having a 3-13-4 motif, where the gap segment comprises 2'-deoxynucleotides and each wing segment comprises nucleotides comprising a 2'-O-methoxyethyl sugar modification. Internucleoside linkages are phosphorthioate, and cytidines are 5-methylcytidines.

**Table 5: Gapmer antisense compounds having a 3-13-4 motif targeted to SEQ ID NO: 1**

| Oligo | Motif | SEQ ID NO: | 5' start site | 3' Start Site | Mismatches | OligoSeq |
|---|---|---|---|---|---|---|
| 405526 | 3-13-4 | 236 | 963 | 982 | 0 | CCAGGTGGGTGCCATGACTG |
| 405557 | 3-13-4 | 50 | 1569 | 1588 | 0 | GGTCCTCAGGGAACCAGGCC |
| 405564 | 3-13-4 | 373 | 1737 | 1756 | 0 | AACTGGAGCAGCTCAGCAGC |

The following embodiments set forth target regions of PCSK9 nucleic acids. Also illustrated are examples of antisense compounds targeted to the target regions. It is understood that the sequence set forth in each SEQ ID NO is independent of any modification to a sugar moiety, an internucleoside linkage, or a nucleobase. As such, antisense compounds defined by a SEQ ID NO may comprise, independently, one or more modifications to a sugar moiety, an internucleoside linkage, or a nucleobase. Antisense compounds described by Isis Number (Isis No) indicate a combination of nucleobase sequence and motif.

In certain embodiments, antisense compounds target a range of a PCSK9 nucleic acid. In certain embodiment, such compounds contain at least an 8 nucleotide core sequence in common. In certain embodiments, such compounds sharing at least an 8 nucleotide core sequence targets the following nucleotide regions of SEQ ID: 1: 294-317, 406-440, 406-526, 410-436, 410-499, 446-526, 545-581, 591-619, 591-704, 591-743, 595-622, 600-626, 600-639, 600-670, 601-628, 602-628, 603-630, 611-636, 620-647, 638-665, 648-674, 657-684, 705-743, 782-810, 821-859, 835-859, 835-917, 835-942, 860-887, 860-899, 860-909, 860-917, 869-895, 878-905, 888-909, 923-952, 960-1034, 960-1173, 960-986, 967-991, 970-1023, 970-1064, 970-1117, 970-996, 977-1004, 985-1011, 989-1016, 992-1019, 997-1024, 997-1024, 998-1025, 999-1026, 1000-1027, 1001-1028, 1002-1029, 1003-1029, 1004-1029, 1005-1029, 1006-1029, 1007-1034, 1036-1061, 1045-1072, 1076-1096, 1088-1115, 1098-1123, 1200-1251, 1210-1237, 1219-1245, 1228-1251, 1273-1444, 1295-1316, 1318-1345, 1328-1354, 1337-1361, 1344-1371, 1354-1377, 1380-1406, 1389-1416, 1400-1426, 1409-1434, 1465-1491, 1465-1602, 1474-1499, 1482-1519, 1513-1540, 1523-1549, 1526-1602, 1526-1624, 1532-1558, 1541-1568, 1552-1579, 1560-1587, 1561-1589, 1564-1591, 1565-1592, 1566-1592, 1567-1592, 1570-1597, 1571-1599, 1605-1706, 1628-1706, 1640-1666, 1672-1698, 1681-1706, 1735-1761, 1735-1765, 1740-1765, 1849-1876, 1849-1879, 1850-1877, 1851-1877, 1852-1878, 1852-1879, 1853-1879, 1854-1879, 1905-1955, 1915-1942, 1916-1943, 1917-1944, 1918-1945, 1919-1946, 1920-1939, 1920-1947, 1921-1948, 1922-1949, 1923-1950, 1924-1951, 1925-1952, 1926-1952, 1927-1952, 1928-1955, 1962-2059, 2040-2126, 2100-2126, 2100-2139, 2100-2206, 2101-2126, 2305-2332, 2305-2354, 2306-2333, 2307-2334, 2308-2334, 2309-2334, 2310-2334, 2410-2434, 2504-2528, 2509-2528, 2582-2625, 2606-2668, 2828-2855, 2832-2851, 2900-2927, 2900-2929, 2902-2927, 2983-3007, 2983-3013, 3227-3252, 3227-3456, 3472-3496, or 3543-3569.

In certain embodiments, a target region is nucleotides 294-317 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 294-317 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a

nucleotide sequence selected from SEQ ID NOs: 159 or 160. In certain such embodiments, an antisense compound targeted to nucleotides 294-317 of SEQ ID NO: 1 is selected from ISIS NOs: 410742 or 405999.

In certain embodiments, a target region is nucleotides 406-440 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 406-440 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 7, 8, 162, 163, 164, 165, 166, 167, 168, 169 or 170. In certain such embodiments, an antisense compound targeted to nucleotides 406-440 of SEQ ID NO: 1 is selected from ISIS NOs: 405861, 405862, 405863, 405864, 395152, 399874, 405865, 405866, 405867, 405868, 399793, 399949, or 410743.

In certain embodiments, a target region is nucleotides 406-526 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 406-526 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 7, 8, 9, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, or 176. In certain such embodiments, an antisense compound targeted to nucleotides 406-526 of SEQ ID NO: 1 is selected from ISIS NOs: 405861, 405862, 405863, 405864, 395152, 399874, 405865, 405866, 405867, 405868, 399793, 399950, 410743, 410744, 410745, 395153, 399875, 406000, 406001, 406002 or 410746.

In certain embodiments, a target region is nucleotides 410-436 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 410-436 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 7, 8, 166, 167, 168, 169 or 169. In certain such embodiments, an antisense compound targeted to nucleotides 410-436 of SEQ ID NO: 1 is selected from ISIS NOs: 395152, 399874, 405865, 405866, 405867, 405868, or 399793.

In certain embodiments, a target region is nucleotides 410-499 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 410-499 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 7, 8, 9, 166, 167, 169, 170, 171 or 172. In certain such embodiments, an antisense compound targeted to nucleotides 410-499 of SEQ ID NO: 1 is selected from ISIS NOs: 395152, 399874, 405865, 405866, 405867, 405868, 399793, 399949, 410743, 410744, 410745, 395153, or 399875.

In certain embodiments, a target region is nucleotides 446-526 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 446-526 SEQ ID NO: 1.

In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 9, 171, 172, 173, 174, 175 or 176. In certain such embodiments, an antisense compound targeted to nucleotides 446-526 of SEQ ID NO: 1 is selected from ISIS NOs: 410744, 410745, 395153, 399875, 406000, 406001, 406002, or 410746.

In certain embodiments, a target region is nucleotides 545-581 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 545-581 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 10, 177, 178, 179, 180 or 181. In certain such embodiments, an antisense compound targeted to nucleotides 545-581 of SEQ ID NO: 1 is selected from ISIS NOs: 410747, 406003, 406004, 406005, 395154, 399876, or 406006.

In certain embodiments, a target region is nucleotides 591-619 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 591-619 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 11, 182, 183, 184, 185 or 186. In certain such embodiments, an antisense compound targeted to nucleotides 591-619 of SEQ ID NO: 1 is selected from ISIS NOs: 410748, 406007, 410529, 410574, 410647, 410530, 410575, 410648, 410531, 410576, 410649, 395155, 399877, or 410650.

In certain embodiments, a target region is nucleotides 591-704 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 591-704 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 11, 12, 13, 14, 15, 16, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, or 208. In certain such embodiments, an antisense compound targeted to nucleotides 591-704 of SEQ ID NO: 1 is selected from ISIS NOs: 410748, 406007, 410529, 410574, 410647, 410530, 410575, 410648, 410531, 410576, 410649, 395155, 399877, 410650, 410532, 410577, 410651, 406008, 410578, 410652, 410533, 410579, 410653, 406009, 410580, 410654, 410534, 410581, 410655, 399794, 399950, 410656, or 410751.

In certain embodiments, a target region is nucleotides 591-743 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 591-743 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 11, 12, 13, 14, 15, 16, 17, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, or 209. In certain such embodiments, an antisense compound targeted to

nucleotides 591-743 of SEQ ID NO: 1 is selected from ISIS NOs: 410748, 406007, 410529, 410574, 410647, 410530, 410575, 410648, 410531, 410576, 410649, 395155, 399877, 410650, 410532, 410577, 410651, 406008, 410578, 410652, 410533, 410579, 410653, 406009, 410580, 410654, 410534, 410581, 410655, 399794, 399950, 410656, or 410752.

In certain embodiments, a target region is nucleotides 595-622 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 595-622 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 11, 183, 184, 185, 186, 187, 188, or 189. In certain such embodiments, an antisense compound targeted to nucleotides 595-622 of SEQ ID NO: 1 is selected from ISIS NOs: 406007, 410529, 410574, 410647, 410530, 410575, 410648, 410531, 410576, 410649, 395155, 399877, 410650, 410532, 410577, 410651, 406008, 410578, 410652, 410533, 410579, or 410653.

In certain embodiments, a target region is nucleotides 600-626 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 600-626 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 11, 12, 87, 188, 189, 190, 191, or 192. In certain such embodiments, an antisense compound targeted to nucleotides 600-626 of SEQ ID NO: 1 is selected from ISIS NOs: 395155, 399877, 410650, 410532, 410577, 410651, 406008, 410578, 410652, 410533, 410579, 410653, 406009, 410580, 410654, 410534, 410581, 410655, 399794, 399950, 410656, 410535, 410582, or 410657.

In certain embodiments, a target region is nucleotides 600-639 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 600-639 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 11, 12, 13, 14, 187, 188, 189, 190, 191, 192, 193, 194, 195, or 196. In certain such embodiments, an antisense compound targeted to nucleotides 600-639 of SEQ ID NO: 1 is selected from ISIS NOs: 395155, 399877, 410650, 410532, 410577, 410651, 406008, 410578, 410652, 410533, 410579, 410653, 406009, 410580, 410654, 410534, 410581, 410655, 399794, 399950, 410656, 410535, 410582, 410657, 406010, 406011, 406012, 399795, 399951, 406013, 395156, or 399878.

In certain embodiments, a target region is nucleotides 600-670 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 600-670 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 11, 12, 13, 14, 15, 16, 187, 188, 189, 190, 191,

192, 193, 194, 195, 196, 197, 198, or 199. In certain such embodiments, an antisense compound targeted to nucleotides 600-670 of SEQ ID NO: 1 is selected from ISIS NOs: 395155, 399877, 410650, 410532, 410577, 410651, 406008, 410578, 410652, 410533, 410579, 410653, 406009, 410580, 410654, 410534, 410581, 410655, 399794, 399950, 410656, 410535, 410582, 410657, 406010, 406011, 406012, 399795, 399951, 406013, 395156, 399878, or 399952.

In certain embodiments, a target region is nucleotides 601-628 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 601-628 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 12, 187, 188, 189, 190, 191, 192 or 193. In certain such embodiments, an antisense compound targeted to nucleotides 601-628 of SEQ ID NO: 1 is selected from ISIS NOs: 410532, 410577, 410651, 406008, 410578, 410652, 410533, 410579, 410653, 406009, 410580, 410654, 410534, 410581, 410655, 399794, 399950, 410656, 410535, 410582, 410657, or 406010.

In certain embodiments, a target region is nucleotides 602-628 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 602-628 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 12, 188, 189, 190, 191, 192 or 193. In certain such embodiments, an antisense compound targeted to nucleotides 602-628 of SEQ ID NO: 1 is selected from ISIS NOs: 406008, 410578, 410652, 410533, 410579, 410653, 406009, 410580, 410654, 410534, 410581, 410655, 399794, 399950, 410656, 410535, 410582, 410657, or 406010.

In certain embodiments, a target region is nucleotides 603-630 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 603-630 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 12, 189, 190, 191, 192, 193 or 194. In certain such embodiments, an antisense compound targeted to nucleotides 603-630 of SEQ ID NO: 1 is selected from ISIS NOs: 410533, 410579, 410653, 406009, 410580, 410654, 410534, 410581, 410655, 399794, 399950, 410656, 410535, 410582, 410657, 406010, or 406011.

In certain embodiments, a target region is nucleotides 611-636 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 611-636 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 13, 194, 195 or 196. In certain such

embodiments, an antisense compound targeted to nucleotides 611-636 of SEQ ID NO: 1 is selected from ISIS NOs: 406011, 406012, 399795, 399951, or 406013.

In certain embodiments, a target region is nucleotides 620-647 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 620-647 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 14 or 197. In certain such embodiments, an antisense compound targeted to nucleotides 620-647 of SEQ ID NO: 1 is selected from ISIS NOs: 395156, 399878, or 410749.

In certain embodiments, a target region is nucleotides 638-665 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 638-665 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 15 or 198. In certain such embodiments, an antisense compound targeted to nucleotides 638-665 of SEQ ID NO: 1 is selected from ISIS NOs: 410750, 395157, or 399879.

In certain embodiments, a target region is nucleotides 648-674 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 648-674 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 16, 199, 200, or 201. In certain such embodiments, an antisense compound targeted to nucleotides 648-674 of SEQ ID NO: 1 is selected from ISIS NOs: 406014, 399796, 399952, 406015, or 406016.

In certain embodiments, a target region is nucleotides 657-684 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 657-684 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 202, 203, 204, 205, or 206. In certain such embodiments, an antisense compound targeted to nucleotides 657-684 of SEQ ID NO: 1 is selected from ISIS NOs: 410730, 406017, 406018, 406019, or 406020.

In certain embodiments, a target region is nucleotides 705-743 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 705-743 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 17 or 209. In certain such embodiments, an antisense compound targeted to nucleotides 705-743 of SEQ ID NO: 1 is selected from ISIS NOs: 395158, 399880, or 410752.

In certain embodiments, a target region is nucleotides 782-810 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 782-810 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 18, 210, 211, 212, 213, or 214. In certain such embodiments, an antisense compound targeted to nucleotides 782-810 of SEQ ID NO: 1 is selected from ISIS NOs: 406021, 406022, 395159, 399881, 406023, 406024, or 410732.

In certain embodiments, a target region is nucleotides 821-859 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 821-859 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 19, 20, 215, 216 or 217. In certain such embodiments, an antisense compound targeted to nucleotides 821-859 of SEQ ID NO: 1 is selected from ISIS NOs: 410753, 406025, 395160, 399882, 406026, 399797, or 399953.

In certain embodiments, a target region is nucleotides 835-859 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 835-859 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 19, 20 or 217. In certain such embodiments, an antisense compound targeted to nucleotides 835-859 of SEQ ID NO: 1 is selected from ISIS NOs: 395160, 399882, 406026, 399797, or 399953.

In certain embodiments, a target region is nucleotides 835-917 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 835-917 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 19, 20 ,21, 22, 23, 24, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232 or 233. In certain such embodiments, an antisense compound targeted to nucleotides 835-917 of SEQ ID NO: 1 is selected from ISIS NOs: 395160, 399882, 406026, 399797, 399953, 395161, 399883, 405869, 405870, 405871, 405872, 399798, 399954, 405873, 405874, 405875, 405876, 406027, 406028, 406029, 399799, 399955, 406030, 406031, 410733, 406032, 395162, 399884, or 410754.

In certain embodiments, a target region is nucleotides 835-942 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 835-942 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 19, 20 ,21, 22, 23, 24, 25, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, or 233. In certain such embodiments, an antisense compound targeted to nucleotides 835-942 of SEQ ID NO: 1 is selected from ISIS

NOs: 395160, 399882, 406026, 399797, 399953, 395161, 399883, 405869, 405870, 405871, 405872, 399798, 399954, 405873, 405874, 405875, 405876, 406027, 406028, 406029, 399799, 399955, 406030, 406031, 410733, 406032, 395162, 399884, 410754, 395163, or 399885.

In certain embodiments, a target region is nucleotides 860-887 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 860-887 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 21, 22, 218, 219, 220, 221, 222 or 223. In certain such embodiments, an antisense compound targeted to nucleotides 860-887 of SEQ ID NO: 1 is selected from ISIS NOs: 395161, 399883, 405869, 405870, 405871, 405872, 399798, 399954, 405873, or 405874.

In certain embodiments, a target region is nucleotides 860-899 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 860-899 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 21, 22, 23, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227 or 228. In certain such embodiments, an antisense compound targeted to nucleotides 860-899 of SEQ ID NO: 1 is selected from ISIS NOs: 395161, 399883, 405869, 405870, 405871, 405872, 399798, 399954, 405873, 405874, 405875, 405876, 406027, 406028, 406029, 399799, or 399955.

In certain embodiments, a target region is nucleotides 860-909 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 860-909 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 21, 22, 23, 24, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231 or 232. In certain such embodiments, an antisense compound targeted to nucleotides 860-909 of SEQ ID NO: 1 is selected from ISIS NOs: 395161, 399883, 405869, 405870, 405871, 405872, 399798, 399954, 405873, 405874, 405875, 405876, 406027, 406028, 406029, 399799, 399955, 406030, 406031, 410733, 406032, 395162, or 399884.

In certain embodiments, a target region is nucleotides 860-917 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 860-917 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 21, 22, 23, 24, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, or 233. In certain such embodiments, an antisense compound targeted to nucleotides 860-917 of SEQ ID NO: 1 is selected from ISIS NOs: 395161,

399883, 405869, 405870, 405871, 405872, 399798, 399954, 405873, 405874, 405875, 405876, 406027, 406028, 406029, 399799, 399955, 406030, 406031, 410733, 406032, 395162, 399884, or 410754.

In certain embodiments, a target region is nucleotides 869-895 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 869-895 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 224, 225, 226, or 227. In certain such embodiments, an antisense compound targeted to nucleotides 869-895 of SEQ ID NO: 1 is selected from ISIS NOs: 405875, 405876, 406027, or 406028.

In certain embodiments, a target region is nucleotides 878-905 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 878-905 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 23, 228, 229, 230, or 231. In certain such embodiments, an antisense compound targeted to nucleotides 878-905 of SEQ ID NO: 1 is selected from ISIS NOs: 406029, 399799, 399955, 406030, 406031, or 410733.

In certain embodiments, a target region is nucleotides 888-909 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 888-909 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 24 or 232. In certain such embodiments, an antisense compound targeted to nucleotides 888-909 of SEQ ID NO: 1 is selected from ISIS NOs: 406032, 395162, or 399884.

In certain embodiments, a target region is nucleotides 923-952 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 923-952 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 25 or 234. In certain such embodiments, an antisense compound targeted to nucleotides 923-952 of SEQ ID NO: 1 is selected from ISIS NOs: 395163, 399885, or 410755.

In certain embodiments, a target region is nucleotides 960-1034 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 960-1034 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 26, 27, 28, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, or 256. In certain such embodiments, an antisense compound targeted to nucleotides 960-1034 of SEQ ID NO: 1 is

selected from ISIS NOs: 410756, 405526, 405604, 406033, 395164, 399886, 406034, 399800, 399956, 406035, 410757, 406036, 406037, 410536, 410583, 410658, 410537, 410584, 410659, 406038, 410585, 410660, 405877, 410586, 410661, 405878, 410587, 410662, 405879, 410588, 410663, 405880, or 410758.

In certain embodiments, a target region is nucleotides 960-1173 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 960-1173 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 26, 27, 28, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, or 273. In certain such embodiments, an antisense compound targeted to nucleotides 960-1173 of SEQ ID NO: 1 is selected from ISIS NOs: 410756, 405526, 405604, 406033, 395164, 399886, 406034, 399800, 399956, 406035, 410757, 406036, 406037, 410536, 410583, 410658, 410537, 410584, 410659, 406038, 410585, 410660, 405877, 410586, 410661, 405878, 410587, 410662, 405879, 410588, 410663, 405880, or 410763.

In certain embodiments, a target region is nucleotides 960-986 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 960-986 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 235, 236, or 237. In certain such embodiments, an antisense compound targeted to nucleotides 960-986 of SEQ ID NO: 1 is selected from ISIS NOs: 410756, 405526, 405604, or 406033.

In certain embodiments, a target region is nucleotides 967-991 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 967-991 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 237 or 238. In certain such embodiments, an antisense compound targeted to nucleotides 967-991 of SEQ ID NO: 1 is selected from ISIS NOs: 406033 or 406034.

In certain embodiments, a target region is nucleotides 970-1023 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 970-1023 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 26, 27, 28, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, or 249. In certain such embodiments, an antisense compound targeted to nucleotides 970-1023 of SEQ ID NO: 1 is selected from ISIS NOs: 395164, 399886, 406034,

399800, 399956, 406035, 410757, 406036, 406037, 410536, 410583, 410658, 410537, 410584, 410659, 406038, 410585, 410660, 405877, 410586, 410661, 405878, 410587, 410662, 405879, 410588, 410663, 405880, 410589, 410664, 395165, 399887, or 410665.

In certain embodiments, a target region is nucleotides 970-1064 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 970-1064 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 26, 27, 28, 29, 30, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 149, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, or 263. In certain such embodiments, an antisense compound targeted to nucleotides 970-1064 of SEQ ID NO: 1 is selected from ISIS NOs: 395164, 399886, 406034, 399800, 399956, 406035, 410757, 406036, 406037, 410536, 410583, 410658, 410537, 410584, 410659, 406038, 410585, 410660, 405877, 410586, 410661, 405878, 410587, 410662, 405879, 410588, 410663, 405880, 410589, 410664, 395165, 399887, or 399957.

In certain embodiments, a target region is nucleotides 970-1117 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 970-1117 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 26, 27, 28, 29, 30, 31, 32, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 149, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, or 266. In certain such embodiments, an antisense compound targeted to nucleotides 970-1117 of SEQ ID NO: 1 is selected from ISIS NOs: 395164, 399886, 406034, 399800, 399956, 406035, 410757, 406036, 406037, 410536, 410583, 410658, 410537, 410584, 410659, 406038, 410585, 410660, 405877, 410586, 410661, 405878, 410587, 410662, 405879, 410588, 410663, 405880, 410589, 410664, 395165, 399887, or 399890.

In certain embodiments, a target region is nucleotides 970-996 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 970-996 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 26, 27, or 238. In certain such embodiments, an antisense compound targeted to nucleotides 970-996 of SEQ ID NO: 1 is selected from ISIS NOs: 395164, 399886, 406034, 399800, 399956, or 406035.

In certain embodiments, a target region is nucleotides 977-1004 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 977-1004 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 239 or 240. In certain such embodiments, an

antisense compound targeted to nucleotides 977-1004 of SEQ ID NO: 1 is selected from ISIS NOs: 406035 or 410757.

In certain embodiments, a target region is nucleotides 985-1011 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 985-1011 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 240, 241, or 242. In certain such embodiments, an antisense compound targeted to nucleotides 985-1011 of SEQ ID NO: 1 is selected from ISIS NOs: 410757, 406036, or 406037.

In certain embodiments, a target region is nucleotides 989-1016 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 989-1016 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 241, 242, or 243. In certain such embodiments, an antisense compound targeted to nucleotides 989-1016 of SEQ ID NO: 1 is selected from ISIS NOs: 406036, 406037, 410536, 410583, or 410658.

In certain embodiments, a target region is nucleotides 992-1019 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 992-1019 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 242, 243, 244, 245, or 246. In certain such embodiments, an antisense compound targeted to nucleotides 992-1019 of SEQ ID NO: 1 is selected from ISIS NOs: 406037, 410536, 410583, 410658, 410537, 410584, 410659, 406038, 410585, 410660, 405877, 410586, or 410661.

In certain embodiments, a target region is nucleotides 997-1024 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 997-1024 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 243, 244, 245, 246, 247, 248, 249, or 250. In certain such embodiments, an antisense compound targeted to nucleotides 997-1024 of SEQ ID NO: 1 is selected from ISIS NOs: 410536, 410583, 410658, 410537, 410584, 410659, 406038, 410585, 410660, 405877, 410586, 410661, 405878, 410587, 410662, 405879, 410588, 410663, 405880, 410589, 410664, 395165, 399887, 409126, 410665, 405881, 410590, or 410666.

In certain embodiments, a target region is nucleotides 997-1024 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 997-1024 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 243, 244, 245, 246, 247, 248, 249, or 250. In

certain such embodiments, an antisense compound targeted to nucleotides 997-1024 of SEQ ID NO: 1 is selected from ISIS NOs: 410536, 410583, 410658, 410537, 410584, 410659, 406038, 410585, 410660, 405877, 410586, 410661, 405878, 410587, 410662, 405879, 410588, 410663, 405880, 410589, 410664, 395165, 399887, 409126, 410665, 405881, 410590, or 410666.

In certain embodiments, a target region is nucleotides 998-1025 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 998-1025 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 28, 244, 245, 246, 247, 248, 249, 250, or 251. In certain such embodiments, an antisense compound targeted to nucleotides 998-1025 of SEQ ID NO: 1 is selected from ISIS NOs: 410537, 410584, 410659, 406038, 410585, 410660, 405877, 410586, 410661, 405878, 410587, 410662, 405879, 410588, 410663, 405880, 410589, 410664, 395165, 399887, 410665, 405881, 410590, 410666, 405882, 410591, or 410667.

In certain embodiments, a target region is nucleotides 999-1026 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 999-1026 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 28, 245, 246, 247, 248, 249, 250, 251, or 252. In certain such embodiments, an antisense compound targeted to nucleotides 999-1026 of SEQ ID NO: 1 is selected from ISIS NOs: 406038, 410585, 410660, 405877, 410586, 410661, 405878, 410587, 410662, 405879, 410588, 410663, 405880, 410589, 410664, 395165, 399887, 410665, 405881, 410590, 410666, 405882, 410591, 410667, 405833, 410592, or 410668.

In certain embodiments, a target region is nucleotides 1000-1027 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1000-1027 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 28, 246, 247, 248, 249, 250, 251, 252, or 253. In certain such embodiments, an antisense compound targeted to nucleotides 1000-1027 of SEQ ID NO: 1 is selected from ISIS NOs: 405877, 410586, 410661, 405878, 410587, 410662, 405879, 410588, 410663, 405880, 410589, 410664, 395165, 399887, 410665, 405881, 410590, 410666, 405882, 410591, 410667, 405833, 410592, 410668, 405884, 410593, or 410669.

In certain embodiments, a target region is nucleotides 1001-1028 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1001-1028 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 28, 247, 248, 249, 250, 251, 252, 253, or 254. In certain such embodiments, an antisense compound targeted to nucleotides 1001-1028 of SEQ

ID NO: 1 is selected from ISIS NOs: 405878, 410587, 410662, 405879, 410588, 410663, 405880, 410589, 410664, 395165, 399887, 410665, 405881, 410590, 410666, 405882, 410591, 410667, 405833, 410592, 410668, 405884, 410593, 410669, 410538, 410594, or 410670.

In certain embodiments, a target region is nucleotides 1002-1029 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1002-1029 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 28, 248, 249, 250, 251, 252, 253, 254, or 255. In certain such embodiments, an antisense compound targeted to nucleotides 1002-1029 of SEQ ID NO: 1 is selected from ISIS NOs: 405879, 410588, 410663, 405880, 410589, 410664, 395165, 399887, 410665, 405881, 410590, 410666, 405882, 410591, 410667, 405833, 410592, 410668, 405884, 410593, 410669, 410538, 410594, 410670, 410539, 410595, or 410671.

In certain embodiments, a target region is nucleotides 1003-1029 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1003-1029 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 28, 249, 250, 251,252, 253, 254, or 255. In certain such embodiments, an antisense compound targeted to nucleotides 1003-1029 of SEQ ID NO: 1 is selected from ISIS NOs: 405880, 410589, 410664, 395165, 399887, 409126, 410665, 405881, 410590, 410666, 405882, 410591, 410667, 405883, 410592, 410668, 405884, 410593, 410669, 410538, 410594, 410670, 410539, 410595, or 410671.

In certain embodiments, a target region is nucleotides 1004-1029 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1004-1029 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 28, 250, 251,252, 253, 254, or 255. In certain such embodiments, an antisense compound targeted to nucleotides 1004-1029 of SEQ ID NO: 1 is selected from ISIS NOs: 395165, 399887, 409126, 410665, 405881, 410590, 410666, 405882, 410591, 410667, 405883, 410592, 410668, 405884, 410593, 410669, 410538, 410594, 410670, 410539, 410595, or 410671.

In certain embodiments, a target region is nucleotides 1005-1029 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1005-1029 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 250, 251,252, 253, 254, or 255. In certain such embodiments, an antisense compound targeted to nucleotides 1005-1029 of SEQ ID NO: 1 is selected from ISIS NOs: 410665, 405881, 410590, 410666, 405882, 410591, 410667, 405883,

410592, 410668, 405884, 410593, 410669, 410538, 410594, 410670, 410539, 410595, or 410671.

In certain embodiments, a target region is nucleotides 1006-1029 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1006-1029 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 251,252, 253, 254, or 255. In certain such embodiments, an antisense compound targeted to nucleotides 1006-1029 of SEQ ID NO: 1 is selected from ISIS NOs: 405882, 410591, 410667, 405883, 410592, 410668, 405884, 410593, 410669, 410538, 410594, 410670, 410539, 410595, or 410671.

In certain embodiments, a target region is nucleotides 1007-1034 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1007-1034 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 252, 253, 254, 255, or 256. In certain such embodiments, an antisense compound targeted to nucleotides 1007-1034 of SEQ ID NO: 1 is selected from ISIS NOs: 405883, 410592, 410668, 405884, 410593, 410669, 410538, 410594, 410670, 410539, 410595, 410671, or 410758.

In certain embodiments, a target region is nucleotides 1036-1061 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1036-1061 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 29, 257, 258, or 259. In certain such embodiments, an antisense compound targeted to nucleotides 1036-1061 of SEQ ID NO: 1 is selected from ISIS NOs: 406039, 406040, 395166, 399888, or 406041.

In certain embodiments, a target region is nucleotides 1045-1072 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1045-1072 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 30, 260, 261, or 262. In certain such embodiments, an antisense compound targeted to nucleotides 1045-1072 of SEQ ID NO: 1 is selected from ISIS NOs: 399801, 399957, 406042, 406043, or 406044.

In certain embodiments, a target region is nucleotides 1076-1096 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1076-1096 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 31 or 264. In certain such embodiments, an

antisense compound targeted to nucleotides 1076-1096 of SEQ ID NO: 1 is selected from ISIS NOs: 408642, 395167, or 399889.

In certain embodiments, a target region is nucleotides 1088-1115 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1088-1115 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 265 or 266. In certain such embodiments, an antisense compound targeted to nucleotides 1088-1115 of SEQ ID NO: 1 is selected from ISIS NOs: 410760 or 406045.

In certain embodiments, a target region is nucleotides 1098-1123 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1098-1123 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 32, 267, 268, or 269. In certain such embodiments, an antisense compound targeted to nucleotides 1098-1123 of SEQ ID NO: 1 is selected from ISIS NOs: 395168, 399890, 405909, 405910, or 405911.

In certain embodiments, a target region is nucleotides 1200-1251 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1200-1251 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 33, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, or 285. In certain such embodiments, an antisense compound targeted to nucleotides 1200-1251 of SEQ ID NO: 1 is selected from ISIS NOs: 410764, 395169, 399891, 405913, 405914, 405915, 405916, 410734, 405917, 405918, 405919, 405920, 405921, or 405922.

In certain embodiments, a target region is nucleotides 1210-1237 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1210-1237 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 33, 275, 276, 277, or 278. In certain such embodiments, an antisense compound targeted to nucleotides 1210-1237 of SEQ ID NO: 1 is selected from ISIS NOs: 395169, 399891, 405913, 405914, 405915, or 405916.

In certain embodiments, a target region is nucleotides 1219-1245 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1219-1245 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 279, 280, 281 or 282. In certain such embodiments, an antisense compound targeted to nucleotides 1219-1245 of SEQ ID NO: 1 is selected from ISIS NOs: 410734, 405917, 405918, or 405919.

In certain embodiments, a target region is nucleotides 1228-1251 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1228-1251 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 283, 284, or 285. In certain such embodiments, an antisense compound targeted to nucleotides 1228-1251 of SEQ ID NO: 1 is selected from ISIS NOs: 405920, 405921, or 405922.

In certain embodiments, a target region is nucleotides 1273-1444 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1273-1444 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 34, 35, 36, 37, 38, 39, 40, 41, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307,308, 309, 310, 311, 312, 313, 314, 315, 316, 316, and 318. In certain such embodiments, an antisense compound targeted to nucleotides 1273-1444 of SEQ ID NO: 1 is selected from ISIS NOs: 410765, 410766, 405923, 395170, 399892, 410767, 405924, 410735, 405925, 405926, 395171, 399893, 405927, 395172, 399894, 405928, 399802, 399958, 405929, 395173, 399895, 405930, 405931, 405932, 405933, 405934, 399803, 399959, 405935, 410736, 405936, 395174, or 410769.

In certain embodiments, a target region is nucleotides 1295-1316 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1295-1316 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 149 or 288. In certain such embodiments, an antisense compound targeted to nucleotides 1295-1316 of SEQ ID NO: 1 is selected from ISIS NOs: 405923, 395170, or 399892.

In certain embodiments, a target region is nucleotides 1318-1345 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1318-1345 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 34, 290, 291, 292 or 293. In certain such embodiments, an antisense compound targeted to nucleotides 1318-1345 of SEQ ID NO: 1 is selected from ISIS NOs: 405924, 410735, 405925, 405926, 395171, or 399893.

In certain embodiments, a target region is nucleotides 1328-1354 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1328-1354 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 35, 128, 294 or 295. In certain such

embodiments, an antisense compound targeted to nucleotides 1328-1354 of SEQ ID NO: 1 is selected from ISIS NOs: 405927, 395172, 399894, 405928, 399802, or 399958.

In certain embodiments, a target region is nucleotides 1337-1361 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1337-1361 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 36, 296, or 297. In certain such embodiments, an antisense compound targeted to nucleotides 1337-1361 of SEQ ID NO: 1 is selected from ISIS NOs: 405929, 395173, 399895, or 405930.

In certain embodiments, a target region is nucleotides 1344-1371 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1344-1371 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 37, 298, 299, 300, or 301. In certain such embodiments, an antisense compound targeted to nucleotides 1344-1371 of SEQ ID NO: 1 is selected from ISIS NOs: 405931, 405932, 405933, 405934, 399803, or 399959.

In certain embodiments, a target region is nucleotides 1354-1377 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1354-1377 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 302, 303, or 304. In certain such embodiments, an antisense compound targeted to nucleotides 1354-1377 of SEQ ID NO: 1 is selected from ISIS NOs: 405935, 410736, or 405936.

In certain embodiments, a target region is nucleotides 1380-1406 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1380-1406 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 305 or 306. In certain such embodiments, an antisense compound targeted to nucleotides 1380-1406 of SEQ ID NO: 1 is selected from ISIS NOs: 410768 or 405937.

In certain embodiments, a target region is nucleotides 1389-1416 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1389-1416 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 39, 307, 308, 309 or 310. In certain such embodiments, an antisense compound targeted to nucleotides 1389-1416 of SEQ ID NO: 1 is selected from ISIS NOs: 395175, 399897, 405938, 405939, 405940, or 405941.

In certain embodiments, a target region is nucleotides 1400-1426 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1400-1426 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 40, 311, 312, 313, or 314. In certain such embodiments, an antisense compound targeted to nucleotides 1400-1426 of SEQ ID NO: 1 is selected from ISIS NOs: 399804, 399960, 405942, 405943, 410737, or 405944.

In certain embodiments, a target region is nucleotides 1409-1434 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1409-1434 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 41, 315, 316, or 317. In certain such embodiments, an antisense compound targeted to nucleotides 1409-1434 of SEQ ID NO: 1 is selected from ISIS NOs: 405945, 399805, 399961, 405946, or 405947.

In certain embodiments, a target region is nucleotides 1465-1491 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1465-1491 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 42, 101, 319, or 320. In certain such embodiments, an antisense compound targeted to nucleotides 1465-1491 of SEQ ID NO: 1 is selected from ISIS NOs: 395176, 399898, 405948, 399806, 399962, or 405949.

In certain embodiments, a target region is nucleotides 1465-1602 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1465-1602 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 87, 101, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, or 359. In certain such embodiments, an antisense compound targeted to nucleotides 1465-1602 of SEQ ID NO: 1 is selected from ISIS NOs: 395176, 399898, 405948, 399806, 399962, 405949, 405950, 405951, 399807, 399963, 405952, 410738, 405953, 405954, 410770, 405955, 405956, 405957, 405958, 405959, 405960, 405961, 399808, 399964, 405962, 410739, 405963, 395177, 399899, 405964, 399809, 399965, or 399969.

In certain embodiments, a target region is nucleotides 1474-1499 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1474-1499 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 43, 321, 322, or 323. In certain such

embodiments, an antisense compound targeted to nucleotides 1474-1499 of SEQ ID NO: 1 is selected from ISIS NOs: 405950, 405951, 399807, 399963, or 405952.

In certain embodiments, a target region is nucleotides 1482-1519 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1482-1519 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 324, 325, 326, or 327. In certain such embodiments, an antisense compound targeted to nucleotides 1482-1519 of SEQ ID NO: 1 is selected from ISIS NOs: 410738, 405953, 405954, or 410770.

In certain embodiments, a target region is nucleotides 1513-1540 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1513-1540 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 328, 329, 330, 331, or 332. In certain such embodiments, an antisense compound targeted to nucleotides 1513-1540 of SEQ ID NO: 1 is selected from ISIS NOs: 405955, 405956, 405957, 405958, or 405959.

In certain embodiments, a target region is nucleotides 1523-1549 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1523-1549 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 44, 333, 334, 335, or 336. In certain such embodiments, an antisense compound targeted to nucleotides 1523-1549 of SEQ ID NO: 1 is selected from ISIS NOs: 405960, 405961, 399808, 399964, 405962, or 410739.

In certain embodiments, a target region is nucleotides 1526-1602 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1526-1602 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 44, 45, 46, 47, 48, 49, 50, 51, 87, 335, 336, 337, 338, 339, 340, 341, 342, 343, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, or 359. In certain such embodiments, an antisense compound targeted to nucleotides 1526-1602 of SEQ ID NO: 1 is selected from ISIS NOs: 399808, 399964, 405962, 410739, 405963, 395177, 399899, 405964, 399809, 399965, 405965, 405966, 399810, 399966, 405967, 405968, 399811, 399967, 405969, 405970, 410740, 405885, 405886, 405887, 410596, 410672, 405888, 410597, 410673, 399812, 399968, 410674, or 399969.

In certain embodiments, a target region is nucleotides 1526-1624 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1526-1624 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a

nucleotide sequence selected from SEQ ID NOs: 44, 45, 46, 47, 48, 49, 50, 51, 87, 119, 335, 336, 337, 338, 339, 340, 341, 342, 343, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, or 359. In certain such embodiments, an antisense compound targeted to nucleotides 1526-1624 of SEQ ID NO: 1 is selected from ISIS NOs: 399808, 399964, 405962, 410739, 405963, 395177, 399899, 405964, 399809, 399965, 405965, 405966, 399810, 399966, 405967, 405968, 399811, 399967, 405969, 405970, 410740, 405885, 405886, 405887, 410596, 410672, 405888, 410597, 410673, 399812, 399968, 410674, or 399902.

In certain embodiments, a target region is nucleotides 1532-1558 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1532-1558 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 45, 46, 337, or 338. In certain such embodiments, an antisense compound targeted to nucleotides 1532-1558 of SEQ ID NO: 1 is selected from ISIS NOs: 405963, 395177, 399899, 405964, 399809, or 399965.

In certain embodiments, a target region is nucleotides 1541-1568 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1541-1568 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 47, 340, 341, or 342. In certain such embodiments, an antisense compound targeted to nucleotides 1541-1568 of SEQ ID NO: 1 is selected from ISIS NOs: 405965, 405966, 399810, 399966, 405967, or 405968.

In certain embodiments, a target region is nucleotides 1552-1579 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1552-1579 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 48, 343, 344, 345, or 346. In certain such embodiments, an antisense compound targeted to nucleotides 1552-1579 of SEQ ID NO: 1 is selected from ISIS NOs: 399811, 399967, 405969, 405970, 410740, or 405885.

In certain embodiments, a target region is nucleotides 1560-1587 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1560-1587 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 49, 346, 347 ,348 ,349, 350, 351, 352, or 353. In certain such embodiments, an antisense compound targeted to nucleotides 1560-1587 of SEQ ID NO: 1 is selected from ISIS NOs: 405885, 405886, 405887, 410596, 410672, 405888, 410597, 410673, 399812, 399968, 410674, 405889, 410598, 410675, 405890, 410599, 410676, 405891, 410600, 410677, 405892, 410601, or 410678.

In certain embodiments, a target region is nucleotides 1561-1589 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1561-1589 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 49, 50, 346, 347 ,348 ,349, 350, 351, 352, 353, or 354. In certain such embodiments, an antisense compound targeted to nucleotides 1561-1589 of SEQ ID NO: 1 is selected from ISIS NOs: 405886, 405887, 410596, 410672, 405888, 410597, 410673, 399812, 399968, 410674, 405889, 410598, 410675, 405890, 410599, 410676, 405891, 410600, 410677, 405892, 410601, 410678, 395178, 399900, 405557, 410679, 408653, 410602, or 410680.

In certain embodiments, a target region is nucleotides 1564-1591 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1564-1591 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 49, 50, 350, 351, 352, 353, 354, 355, or 356. In certain such embodiments, an antisense compound targeted to nucleotides 1564-1591 of SEQ ID NO: 1 is selected from ISIS NOs: 399812, 399968, 410674, 405889, 410598, 410675, 405890, 410599, 410676, 405891, 410600, 410677, 405892, 410601, 410678, 395178, 399900, 405557, 410679, 408653, 410602, 410680, 405971, 410603, 410681, 410540, 410604, or 410682.

In certain embodiments, a target region is nucleotides 1565-1592 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1565-1592 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 50, 350, 351, 352, 353, 354, 355, 356, or 357. In certain such embodiments, an antisense compound targeted to nucleotides 1565-1592 of SEQ ID NO: 1 is selected from ISIS NOs: 405889, 410598, 410675, 405890, 410599, 410676, 405891, 410600, 410677, 405892, 410601, 410678, 395178, 399900, 405557, 410679, 408653, 410602, 410680, 405971, 410603, 410681, 410540, 410604, 410682, or 405972.

In certain embodiments, a target region is nucleotides 1566-1592 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1566-1592 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 50, 351, 352, 353, 354, 355, 356, or 357. In certain such embodiments, an antisense compound targeted to nucleotides 1566-1592 of SEQ ID NO: 1 is selected from ISIS NOs: 405890, 410599, 410676, 405891, 410600, 410677, 405892, 410601, 410678, 395178, 399900, 405557, 410679, 408653, 410602, 410680, 405971, 410603, 410681, 410540, 410604, 410682, or 405972.

In certain embodiments, a target region is nucleotides 1567-1592 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1567-1592 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 50, 352, 353, 354, 355, 356, or 357. In certain such embodiments, an antisense compound targeted to nucleotides 1567-1592 of SEQ ID NO: 1 is selected from ISIS NOs: 405891, 410600, 410677, 405892, 410601, 410678, 395178, 399900, 405557, 410679, 408653, 410602, 410680, 405971, 410603, 410681, 410540, 410604, 410682, or 405972.

In certain embodiments, a target region is nucleotides 1570-1597 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1570-1597 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 354, 355, 356, 357 or 358. In certain such embodiments, an antisense compound targeted to nucleotides 1570-1597 of SEQ ID NO: 1 is selected from ISIS NOs: 408653, 410602, 410680, 405971, 410603, 410681, 410540, 410604, 410682, 405972 or 405973.

In certain embodiments, a target region is nucleotides 1571-1599 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1571-1599 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 87, 356, 357, 358, or 359. In certain such embodiments, an antisense compound targeted to nucleotides 1571-1599 of SEQ ID NO: 1 is selected from ISIS NOs: 405971, 410603, 410681, 410540, 410604, 410682, 405972, 395179, 399901, 405973, or 405974.

In certain embodiments, a target region is nucleotides 1605-1706 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1605-1706 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 52, 53, 54, 119, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, or 371. In certain such embodiments, an antisense compound targeted to nucleotides 1605-1706 of SEQ ID NO: 1 is selected from ISIS NOs: 395180, 399902, 410771, 395181, 399903, 405975, 399814, 399970, 405976, 405977, 410772, 405978, 395182, 399904, 405979, 405980, 405981, 410741, 405982, or 405983.

In certain embodiments, a target region is nucleotides 1628-1706 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1628-1706 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a

nucleotide sequence selected from SEQ ID NOs: 52, 53, 54, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, or 371. In certain such embodiments, an antisense compound targeted to nucleotides 1628-1706 of SEQ ID NO: 1 is selected from ISIS NOs: 410771, 395181, 399903, 405975, 399814, 399970, 405976, 405977, 410772, 405978, 395182, 399904, 405979, 405980, 405981, 410741, 405982, or 405983.

In certain embodiments, a target region is nucleotides 1640-1666 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1640-1666 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 52, 53, 361, or 362. In certain such embodiments, an antisense compound targeted to nucleotides 1640-1666 of SEQ ID NO: 1 is selected from ISIS NOs: 395181, 399903, 405975, 399814, 399970, or 405976.

In certain embodiments, a target region is nucleotides 1672-1698 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1672-1698 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 54, 365, 366, or 367. In certain such embodiments, an antisense compound targeted to nucleotides 1672-1698 of SEQ ID NO: 1 is selected from ISIS NOs: 405978, 395182, 399904, 405979, or 405980.

In certain embodiments, a target region is nucleotides 1681-1706 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1681-1706 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 368, 369, 370, or 371. In certain such embodiments, an antisense compound targeted to nucleotides 1681-1706 of SEQ ID NO: 1 is selected from ISIS NOs: 405981, 410741, 405982, or 405983.

In certain embodiments, a target region is nucleotides 1735-1761 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1735-1761 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 55, 372, 373, or 374. In certain such embodiments, an antisense compound targeted to nucleotides 1735-1761 of SEQ ID NO: 1 is selected from ISIS NOs: 405984, 405564, 405641, 405985, 399815, 399971, or 405986.

In certain embodiments, a target region is nucleotides 1735-1765 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1735-1765 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 55, 56, 372, 373, 374, or 375. In certain such

embodiments, an antisense compound targeted to nucleotides 1735-1765 of SEQ ID NO: 1 is selected from ISIS NOs: 405984, 405564, 405641, 405985, 399815, 399971, 405986, 405987, 399816 or 399972.

In certain embodiments, a target region is nucleotides 1740-1765 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1740-1765 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 55, 56, 374, or 375. In certain such embodiments, an antisense compound targeted to nucleotides 1740-1765 of SEQ ID NO: 1 is selected from ISIS NOs: 399815, 399971, 405986, 405987, 399816, or 399972.

In certain embodiments, a target region is nucleotides 1849-1876 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1849-1876 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 376, 377, 378, 379, 380, 381, 382, 383, or 384. In certain such embodiments, an antisense compound targeted to nucleotides 1849-1876 of SEQ ID NO: 1 is selected from ISIS NOs: 410541, 410605, 410683, 410542, 410606, 410684, 410543, 410607, 410685, 410544, 410608, 410686, 410545, 410609, 410687, 405988, 410610, 410688, 410546, 410611, 410689, 405989, 410612, 410690, 410547, 410613, or 410691.

In certain embodiments, a target region is nucleotides 1849-1879 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1849-1879 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 58, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, or 386. In certain such embodiments, an antisense compound targeted to nucleotides 1849-1879 of SEQ ID NO: 1 is selected from ISIS NOs: 410541, 410605, 410683, 410542, 410606, 410684, 410543, 410607, 410685, 410544, 410608, 410686, 410545, 410609, 410687, 405988, 410610, 410688, 410546, 410611, 410689, 405989, 410612, 410690, 410547, 410613, 395184, 410691, 399906, 410692, 410548, 410614, or 405990.

In certain embodiments, a target region is nucleotides 1850-1877 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1850-1877 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 58, 377, 378, 379, 380, 381, 382, 383 or 384. In certain such embodiments, an antisense compound targeted to nucleotides 1850-1877 of SEQ ID NO: 1 is selected from ISIS NOs: 410542, 410606, 410684, 410543, 410607, 410685,

410544, 410608, 410686, 410545, 410609, 410687, 405988, 410610, 410688, 410546, 410611, 410689, 405989, 410612, 410690, 410547, 410613, 395184, 410691, 399906, or 410692.

In certain embodiments, a target region is nucleotides 1851-1877 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1851-1877 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 58, 378, 379, 380, 381, 382, 383, or 384. In certain such embodiments, an antisense compound targeted to nucleotides 1851-1877 of SEQ ID NO: 1 is selected from ISIS NOs: 410543, 410607, 410685, 410544, 410608, 410686, 410545, 410609, 410687, 405988, 410610, 410688, 410546, 410611, 410689, 405989, 410612, 410690, 410547, 410613, 395184, 410691, 399906, or 410692.

In certain embodiments, a target region is nucleotides 1852-1878 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1852-1878 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 58, 379, 380, 381, 382, 383, 384, or 385. In certain such embodiments, an antisense compound targeted to nucleotides 1852-1878 of SEQ ID NO: 1 is selected from ISIS NOs: 410544, 410608, 410686, 410545, 410609, 410687, 405988, 410610, 410688, 410546, 410611, 410689, 405989, 410612, 410690, 410547, 410613, 395184, 410691, 399906, 410692, 410548, 410614, or 410693.

In certain embodiments, a target region is nucleotides 1852-1879 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1852-1879 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 58, 379, 380, 381, 382, 383, 384, 385, or 386. In certain such embodiments, an antisense compound targeted to nucleotides 1852-1879 of SEQ ID NO: 1 is selected from ISIS NOs: 410544, 410608, 410686, 410545, 410609, 410687, 405988, 410610, 410688, 410546, 410611, 410689, 405989, 410612, 410690, 410547, 410613, 395184, 410691, 399906, 410692, 410548, 410614, 410693, or 405990.

In certain embodiments, a target region is nucleotides 1853-1879 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1853-1879 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 58, 380, 381, 382, 383, 384, 385 or 386. In certain such embodiments, an antisense compound targeted to nucleotides 1853-1879 of SEQ ID NO: 1 is selected from ISIS NOs: 410545, 410609, 410687, 405988, 410610, 410688, 410546,

410611, 410689, 405989, 410612, 410690, 410547, 410613, 395184, 410691, 399906, 410692, 410548, 410614, 410693, or 405990.

In certain embodiments, a target region is nucleotides 1854-1879 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1854-1879 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 58, 381, 382, 383, 384, 385, or 386. In certain such embodiments, an antisense compound targeted to nucleotides 1854-1879 of SEQ ID NO: 1 is selected from ISIS NOs: 405988, 410610, 410688, 410546, 410611, 410689, 405989, 410612, 410690, 410547, 410613, 395184, 410691, 399906, 410692, 410548, 410614, 410693, or 405990.

In certain embodiments, a target region is nucleotides 1905-1955 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1905-1955 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 59, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, or 406. In certain such embodiments, an antisense compound targeted to nucleotides 1905-1955 of SEQ ID NO: 1 is selected from ISIS NOs: 410773, 410549, 410615, 410694, 410550, 410616, 410695, 410551, 410617, 410696, 410552, 410618, 410697, 410553, 410619, 410698, 395185, 399907, 410699, 410554, 410620, 410700, 405991, 410621, 410701, 410555, 410622, 410702, 405992, 410623, 410703, 410556, or 410774.

In certain embodiments, a target region is nucleotides 1915-1942 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1915-1942 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 59, 388, 389, 390, 391, 392, 393, 394, or 395. In certain such embodiments, an antisense compound targeted to nucleotides 1915-1942 of SEQ ID NO: 1 is selected from ISIS NOs: 410549, 410615, 410694, 410550, 410616, 410695, 410551, 410617, 410696, 410552, 410618, 410697, 410553, 410619, 410698, 395185, 399907, 410699, 410554, 410620, 410700, 405991, 410621, 410701, 410555, 410622, or 410702.

In certain embodiments, a target region is nucleotides 1916-1943 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1916-1943 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 59, 389, 390, 391, 392, 393, 394, 395, or 396. In certain such embodiments, an antisense compound targeted to nucleotides 1916-1943 of SEQ

ID NO: 1 is selected from ISIS NOs: 410550, 410616, 410695, 410551, 410617, 410696, 410552, 410618, 410697, 410553, 410619, 410698, 395185, 399907, 410699, 410554, 410620, 410700, 405991, 410621, 410701, 410555, 410622, 410702, 405992, 410623, or 410703.

In certain embodiments, a target region is nucleotides 1917-1944 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1917-1944 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 59, 390, 391, 392, 393, 394, 395, 396, or 397. In certain such embodiments, an antisense compound targeted to nucleotides 1917-1944 of SEQ ID NO: 1 is selected from ISIS NOs: 410551, 410617, 410696, 410552, 410618, 410697, 410553, 410619, 410698, 395185, 399907, 410699, 410554, 410620, 410700, 405991, 410621, 410701, 410555, 410622, 410702, 405992, 410623, 410703, 410556, 410624, or 410704.

In certain embodiments, a target region is nucleotides 1918-1945 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1918-1945 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 59, 391, 392, 393, 394, 395, 396, 397, or 398. In certain such embodiments, an antisense compound targeted to nucleotides 1918-1945 of SEQ ID NO: 1 is selected from ISIS NOs: 410552, 410618, 410697, 410553, 410619, 410698, 395185, 399907, 410699, 410554, 410620, 410700, 405991, 410621, 410701, 410555, 410622, 410702, 405992, 410623, 410703, 410556, 410624, 410704, 405993, 410625, or 410705.

In certain embodiments, a target region is nucleotides 1919-1946 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1919-1946 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 59, 392, 393, 394, 395, 396, 397, or 399. In certain such embodiments, an antisense compound targeted to nucleotides 1919-1946 of SEQ ID NO: 1 is selected from ISIS NOs: 410553, 410619, 410698, 395185, 399907, 410699, 410554, 410620, 410700, 405991, 410621, 410701, 410555, 410622, 410702, 405992, 410623, 410703, 410556, 410624, 410704, 405993, 410625, 410705, 410557, 410626, or 410706.

In certain embodiments, a target region is nucleotides 1920-1939 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1920-1939 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 59. In certain such embodiments, an antisense compound targeted to nucleotides 1920-1939 of SEQ ID NO: 1 is selected from ISIS NOs: 395185, 399907, or 410699.

In certain embodiments, a target region is nucleotides 1920-1947 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1920-1947 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 59, 393, 394, 395, 396, 397, 398, 399, or 400. In certain such embodiments, an antisense compound targeted to nucleotides 1920-1947 of SEQ ID NO: 1 is selected from ISIS NOs: 395185, 399907, 410699, 410554, 410620, 410700, 405991, 410621, 410701, 410555, 410622, 410702, 405992, 410623, 410703, 410556, 410624, 410704, 405993, 410625, 410705, 410557, 410626, 410706, 405944, 410627, or 410707.

In certain embodiments, a target region is nucleotides 1921-1948 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1921-1948 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 393, 394, 395, 396, 397, 398, 399, 400, or 401. In certain such embodiments, an antisense compound targeted to nucleotides 1921-1948 of SEQ ID NO: 1 is selected from ISIS NOs: 410554, 410620, 410700, 405991, 410621, 410701, 410555, 410622, 410702, 405992, 410623, 410703, 410556, 410624, 410704, 405993, 410625, 410705, 410557, 410626, 410706, 405944, 410627, 410707, 410558, 410628, or 410708.

In certain embodiments, a target region is nucleotides 1922-1949 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1922-1949 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 394, 395, 396, 397, 398, 399, 400, 401, or 402. In certain such embodiments, an antisense compound targeted to nucleotides 1922-1949 of SEQ ID NO: 1 is selected from ISIS NOs: 405991, 410621, 410701, 410555, 410622, 410702, 405992, 410623, 410703, 410556, 410624, 410704, 405993, 410625, 410705, 410557, 410626, 410706, 405944, 410627, 410707, 410558, 410628, 410708, 405995, 410629, or 410709.

In certain embodiments, a target region is nucleotides 1923-1950 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1923-1950 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 395, 396, 397, 398, 399, 400, 401, 402, or 403. In certain such embodiments, an antisense compound targeted to nucleotides 1923-1950 of SEQ ID NO: 1 is selected from ISIS NOs: 410555, 410622, 410702, 405992, 410623, 410703, 410556, 410624, 410704, 405993, 410625, 410705, 410557, 410626, 410706, 405944, 410627, 410707, 410558, 410628, 410708, 405995, 410629, 410709, 410559, 410630, or 410710.

In certain embodiments, a target region is nucleotides 1924-1951 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1924-1951 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 396, 397, 398, 399, 400, 401, 402, 403, or 404. In certain such embodiments, an antisense compound targeted to nucleotides 1924-1951 of SEQ ID NO: 1 is selected from ISIS NOs: 405992, 410623, 410703, 410556, 410624, 410704, 405993, 410625, 410705, 410557, 410626, 410706, 405994, 410627, 410707, 410558, 410628, 410708, 405995, 410629, 410709, 410559, 410630, 410710, 410560, 410631, or 410711.

In certain embodiments, a target region is nucleotides 1925-1952 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1925-1952 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 397, 398, 399, 400, 401, 402, 403, 404, or 405. In certain such embodiments, an antisense compound targeted to nucleotides 1925-1952 of SEQ ID NO: 1 is selected from ISIS NOs: 410556, 410624, 410704, 405993, 410625, 410705, 410557, 410626, 410706, 405994, 410627, 410707, 410558, 410628, 410708, 405995, 410629, 410709, 410559, 410630, 410710, 410560, 410631, 410711, 410561, 410632, or 410712.

In certain embodiments, a target region is nucleotides 1926-1952 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1926-1952 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 398, 399, 400, 401, 402, 403, 404, or 405. In certain such embodiments, an antisense compound targeted to nucleotides 1926-1952 of SEQ ID NO: 1 is selected from ISIS NOs: 405993, 410625, 410705, 410557, 410626, 410706, 405994, 410627, 410707, 410558, 410628, 410708, 405995, 410629, 410709, 410559, 410630, 410710, 410560, 410631, 410711, 410561, 410632, or 410712.

In certain embodiments, a target region is nucleotides 1927-1952 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1927-1952 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 399, 400, 401, 402, 403, 404, or 405. In certain such embodiments, an antisense compound targeted to nucleotides 1927-1952 of SEQ ID NO: 1 is selected from ISIS NOs: 410557, 410626, 410706, 405994, 410627, 410707, 410558, 410628, 410708, 405995, 410629, 410709, 410559, 410630, 410710, 410560, 410631, 410711, 410561, 410632, or 410712.

In certain embodiments, a target region is nucleotides 1928-1955 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1928-1955 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 400, 401, 402, 403, 404, 405, or 406. In certain such embodiments, an antisense compound targeted to nucleotides 1928-1955 of SEQ ID NO: 1 is selected from ISIS NOs: 405994, 410627, 410707, 410558, 410628, 410708, 405995, 410629, 410709, 410559, 410630, 410710, 410560, 410631, 410711, 410561, 410632, 410712, or 410774.

In certain embodiments, a target region is nucleotides 1962-2059 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 1962-2059 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 407, 408, 409, or 410. In certain such embodiments, an antisense compound targeted to nucleotides 1962-2059 of SEQ ID NO: 1 is selected from ISIS NOs: 410775, 410776, 410777, or 410778.

In certain embodiments, a target region is nucleotides 2040-2126 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 2040-2126 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 60, 61, 410, 411, 412, 413, 414, or 415. In certain such embodiments, an antisense compound targeted to nucleotides 2040-2126 of SEQ ID NO: 1 is selected from ISIS NOs: 410778, 395186, 399908, 410713, 410562, 410633, 410714, 405996, 410634, 410715, 410563, 410635, 410716, 410564, 410636, 410717, 399817, 399973, 410718, or 405997.

In certain embodiments, a target region is nucleotides 2100-2126 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 2100-2126 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 60, 61, 411, 412, 413, 414, or 415. In certain such embodiments, an antisense compound targeted to nucleotides 2100-2126 of SEQ ID NO: 1 is selected from ISIS NOs: 395186, 399908, 410713, 410562, 410633, 410714, 405996, 410634, 410715, 410563, 410635, 410716, 410564, 410636, 410717, 399817, 399973, 410718 or 405997.

In certain embodiments, a target region is nucleotides 2100-2139 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 2100-2139 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 60, 61, 411, 412, 413, 414, 415, or 416. In

certain such embodiments, an antisense compound targeted to nucleotides 2100-2139 of SEQ ID NO: 1 is selected from ISIS NOs: 395186, 399908, 410713, 410562, 410633, 410714, 405996, 410634, 410715, 410563, 410635, 410716, 410564, 410636, 410717, 399817, 399973, 410718, 405997 or 410779.

In certain embodiments, a target region is nucleotides 2100-2206 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 2100-2206 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 60, 61, 411, 412, 413, 414, 415, 416, 417, or 418. In certain such embodiments, an antisense compound targeted to nucleotides 2100-2206 of SEQ ID NO: 1 is selected from ISIS NOs: 395186, 399908, 410713, 410562, 410633, 410714, 405996, 410634, 410715, 410563, 410635, 410716, 410564, 410636, 410717, 399817, 399973, 410718, 405997, 405997, 410780, or 410781.

In certain embodiments, a target region is nucleotides 2101-2126 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 2101-2126 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 61, 411, 412, 413, 414, or 415. In certain such embodiments, an antisense compound targeted to nucleotides 2101-2126 of SEQ ID NO: 1 is selected from ISIS NOs: 410562, 410633, 410714, 405996, 410634, 410715, 410563, 410635, 410716, 410564, 410636, 410717, 399817, 399973, 410718, or 405997.

In certain embodiments, a target region is nucleotides 2305-2332 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 2305-2332 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 62, 419, 420, 421, 422, 423, 424, 425, or 426. In certain such embodiments, an antisense compound targeted to nucleotides 2305-2332 of SEQ ID NO: 1 is selected from ISIS NOs: 410565, 410637, 410719, 410566, 410638, 410720, 410567, 410639, 410721, 410568, 410640, 410722, 410569, 410641, 410723, 395187, 399909, 410724, 410570, 410642, 410725, 410571, 410643, 410726, 405998, 410644, or 410727.

In certain embodiments, a target region is nucleotides 2305-2354 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 2305-2354 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 62, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, or 430. In certain such embodiments, an antisense compound targeted to nucleotides 2305-2354 of SEQ ID NO: 1 is selected from ISIS NOs: 410565, 410637, 410719, 410566,

410638, 410720, 410567, 410639, 410721, 410568, 410640, 410722, 410569, 410641, 410723, 395187, 399909, 410724, 410570, 410642, 410725, 410571, 410643, 410726, 405998, 410644, 410727, 410572, 410645, 410728, 410573, 410646, or 410783.

In certain embodiments, a target region is nucleotides 2306-2333 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 2306-2333 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 62, 420, 421, 422, 423, 424, 425, 426, or 427. In certain such embodiments, an antisense compound targeted to nucleotides 2306-2333 of SEQ ID NO: 1 is selected from ISIS NOs: 410566, 410638, 410720, 410567, 410639, 410721, 410568, 410640, 410722, 410569, 410641, 410723, 395187, 399909, 410724, 410570, 410642, 410725, 410571, 410643, 410726, 405998, 410644, 410727, 410572, 410645, or 410728.

In certain embodiments, a target region is nucleotides 2307-2334 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 2307-2334 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 62, 421, 422, 423, 424, 425, 426, 427, or 428. In certain such embodiments, an antisense compound targeted to nucleotides 2307-2334 of SEQ ID NO: 1 is selected from ISIS NOs: 410567, 410639, 410721, 410568, 410640, 410722, 410569, 410641, 410723, 395187, 399909, 410724, 410570, 410642, 410725, 410571, 410643, 410726, 405998, 410644, 410727, 410572, 410645, 410728, 410573, 410646, or 410729.

In certain embodiments, a target region is nucleotides 2308-2334 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 2308-2334 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 62, 422, 423, 424, 425, 426, 427, or 428. In certain such embodiments, an antisense compound targeted to nucleotides 2308-2334 of SEQ ID NO: 1 is selected from ISIS NOs: 410568, 410640, 410722, 410569, 410641, 410723, 395187, 399909, 410724, 410570, 410642, 410725, 410571, 410643, 410726, 405998, 410644, 410727, 410572, 410645, 410728, 410573, 410646, or 410729.

In certain embodiments, a target region is nucleotides 2309-2334 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 2309-2334 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 62, 423, 424, 425, 426, 427, or 428. In certain such embodiments, an antisense compound targeted to nucleotides 2309-2334 of SEQ ID NO: 1 is selected from ISIS NOs: 410569, 410641, 410723, 395187, 399909, 410724, 410570, 410642,

410725, 410571, 410643, 410726, 405998, 410644, 410727, 410572, 410645, 410728, 410573, 410646, or 410729.

In certain embodiments, a target region is nucleotides 2310-2334 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 2310-2334 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 62, 424, 425, 426, 427, or 428. In certain such embodiments, an antisense compound targeted to nucleotides 2310-2334 of SEQ ID NO: 1 is selected from ISIS NOs: 395187, 399909, 410724, 410570, 410642, 410725, 410571, 410643, 410726, 405998, 410644, 410727, 410572, 410645, 410728, 410573, 410646, or 410729.

In certain embodiments, a target region is nucleotides 2410-2434 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 2410-2434 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 63 or 154. In certain such embodiments, an antisense compound targeted to nucleotides 2410-2434 of SEQ ID NO: 1 is selected from ISIS NOs: 395188, 399910, 399818, or 399974.

In certain embodiments, a target region is nucleotides 2504-2528 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 2504-2528 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 64 or 65. In certain such embodiments, an antisense compound targeted to nucleotides 2504-2528 of SEQ ID NO: 1 is selected from ISIS NOs: 395189, 399911, 399819, or 399975.

In certain embodiments, a target region is nucleotides 2509-2528 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 2509-2528 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 65. In certain such embodiments, an antisense compound targeted to nucleotides 2509-2528 of SEQ ID NO: 1 is selected from ISIS NOs: 399819 or 399975.

In certain embodiments, a target region is nucleotides 2582-2625 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 2582-2625 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 66, 67 or 122. In certain such embodiments, an antisense compound targeted to nucleotides 2582-2625 of SEQ ID NO: 1 is selected from ISIS NOs: 399820, 399976, 395190, 399912, 395191, or 399913.

In certain embodiments, a target region is nucleotides 2606-2668 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 2606-2668 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 67 or 153. In certain such embodiments, an antisense compound targeted to nucleotides 2606-2668 of SEQ ID NO: 1 is selected from ISIS NOs: 395191, 399913, 395192, or 399914.

In certain embodiments, a target region is nucleotides 2828-2855 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 2828-2855 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 69, 431, 432, 433, 434, 435, 436, 437 or 438. In certain such embodiments, an antisense compound targeted to nucleotides 2828-2855 of SEQ ID NO: 1 is selected from ISIS NOs: 405893, 405894, 405895, 405896, 395194, 399916, 405897, 405898, 405899, or 405900.

In certain embodiments, a target region is nucleotides 2832-2851 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 2832-2851 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 69. In certain such embodiments, an antisense compound targeted to nucleotides 2832-2851 of SEQ ID NO: 1 is selected from ISIS NOs: 395194, or 399916.

In certain embodiments, a target region is nucleotides 2900-2927 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 2900-2927 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 70, 71, 439, 440, 441, 442, 443 or 444. In certain such embodiments, an antisense compound targeted to nucleotides 2900-2927 of SEQ ID NO: 1 is selected from ISIS NOs: 395195, 399917, 405901, 405902, 405903, 405904, 399821, 399977, 405905, or 405906.

In certain embodiments, a target region is nucleotides 2900-2929 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 2900-2929 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 70, 71, 439, 440, 441, 442, 443, 444, 446 or 446. In certain such embodiments, an antisense compound targeted to nucleotides 2900-2929 of SEQ ID NO: 1 is selected from ISIS NOs: 395195, 399917, 405901, 405902, 405903, 405904, 399821, 399977, 405905, 405906, 405907, or 405908.

In certain embodiments, a target region is nucleotides 2902-2927 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 2902-2927 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 71, 439, 440, 441, 442, 443 or 444. In certain such embodiments, an antisense compound targeted to nucleotides 2902-2927 of SEQ ID NO: 1 is selected from ISIS NOs: 405901, 405902, 405903, 405904, 399821, 399977, 405905, or 405906.

In certain embodiments, a target region is nucleotides 2983-3007 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 2983-3007 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 72 or 73. In certain such embodiments, an antisense compound targeted to nucleotides 2983-3007 of SEQ ID NO: 1 is selected from ISIS NOs: 395196, 399918, 399822, or 399978.

In certain embodiments, a target region is nucleotides 2983-3013 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 2983-3013 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 72, 73 or 135. In certain such embodiments, an antisense compound targeted to nucleotides 2983-3013 of SEQ ID NO: 1 is selected from ISIS NOs: 395196, 399918, 399822, 399978, 399823, or 399979.

In certain embodiments, a target region is nucleotides 3227-3252 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 3227-3252 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 74 or 112. In certain such embodiments, an antisense compound targeted to nucleotides 3227-3252 of SEQ ID NO: 1 is selected from ISIS NOs: 395197, 399919, 399824, or 399980.

In certain embodiments, a target region is nucleotides 3227-3456 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 3227-3456 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 74, 75 or 112. In certain such embodiments, an antisense compound targeted to nucleotides 3227-3456 of SEQ ID NO: 1 is selected from ISIS NOs: 395197, 399919, 399824, 399980, 395198, or 399920.

In certain embodiments, a target region is nucleotides 3472-3496 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 3472-3496 SEQ ID NO:

1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 76 or 77. In certain such embodiments, an antisense compound targeted to nucleotides 3472-3496 of SEQ ID NO: 1 is selected from ISIS NOs: 395199, 399921, 399825 or 399981.

In certain embodiments, a target region is nucleotides 3543-3569 of SEQ ID NO: 1. In certain embodiments, an antisense compound is targeted to nucleotides 3543-3569 SEQ ID NO: 1. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 78 or 99. In certain such embodiments, an antisense compound targeted to nucleotides 3543-3569 of SEQ ID NO: 1 is selected from ISIS NOs: 395200, 399922, 399826 or 399982.

In certain embodiments, antisense compound target a PCSK9 nucleic acid having the sequence of nucleotides 25475000 to 25504000 of GENBANK® Accession No. NT_032977.8, first deposited with GENBANK® on February 26, 2006, and incorporated herein as SEQ ID NO: 2. In certain such embodiments, an antisense oligonucleotide is targeted to SEQ ID NO: 2. In certain such embodiments, an antisense oligonucleotide that is targeted to SEQ ID NO: 2 is at least 90% complementary to SEQ ID NO: 2. In certain such embodiments, an antisense oligonucleotide that is targeted to SEQ ID NO: 2 is at least 95% complementary to SEQ ID NO: 2. In certain such embodiments, an antisense oligonucleotide that is targeted to SEQ ID NO: 1 is 100% complementary to SEQ ID NO: 1. In certain such embodiments, an antisense oligonucleotide comprises a nucleotide sequence selected from a nucleotide sequence set forth in Table 6.

**Table 6: Antisense sequences targeted to NT_032977.8 (SEQ ID NO: 2)**

| SEQ ID NO | 5' Start Site to SEQ ID NO: 2 | 3' Start Site to SEQ ID NO: 2 | Sequence (5' to 3') |
|---|---|---|---|
| 4 | 2274 | 2293 | GCGCGGAATCCTGGCTGGGA |
| 5 | 2381 | 2400 | GAGGAGACCTAGAGGCCGTG |
| 159 | 2433 | 2452 | GCCTGGAGCTGACGGTGCCC |
| 160 | 2437 | 2456 | GACCGCCTGGAGCTGACGGT |
| 6 | 2439 | 2458 | AGGACCGCCTGGAGCTGACG |
| 162 | 2545 | 2564 | AAGGCTAGCACCAGCTCCTC |
| 163 | 2546 | 2565 | CAAGGCTAGCACCAGCTCCT |
| 164 | 2547 | 2566 | GCAAGGCTAGCACCAGCTCC |
| 165 | 2548 | 2567 | CGCAAGGCTAGCACCAGCTC |
| 7 | 2549 | 2568 | ACGCAAGGCTAGCACCAGCT |
| 166 | 2550 | 2569 | AACGCAAGGCTAGCACCAGC |
| 167 | 2551 | 2570 | GAACGCAAGGCTAGCACCAG |

| SEQ ID NO | 5' Start Site to SEQ ID NO: 2 | 3' Start Site to SEQ ID NO: 2 | Sequence (5' to 3') |
|---|---|---|---|
| 168 | 2552 | 2571 | GGAACGCAAGGCTAGCACCA |
| 169 | 2553 | 2572 | CGGAACGCAAGGCTAGCACC |
| 8 | 2556 | 2575 | CCTCGGAACGCAAGGCTAGC |
| 170 | 2560 | 2579 | TCCTCCTCGGAACGCAAGGC |
| 171 | 2585 | 2604 | GTGCTCGGGTGCTTCGGCCA |
| 172 | 2605 | 2624 | TGGAAGGTGGCTGTGGTTCC |
| 9 | 2619 | 2638 | CCTTGGCGCAGCGGTGGAAG |
| 107 | 3056 | 3075 | CCCACTATAATGGCAAGCCC |
| 80 | 4306 | 4325 | AACCCAGTTCTAATGCACCT |
| 106 | 5140 | 5159 | CCAGTCAGAGTAGAACAGAG |
| 102 | 5590 | 5609 | ATGTGCAGAGATCAATCACA |
| 121 | 5599 | 5618 | GGAGCCTACATGTGCAGAGA |
| 94 | 5667 | 5686 | AGCATGGCACCAGCATCTGC |
| 176 | 6444 | 6463 | CGTAGGTGCCAGGCAACCTC |
| 177 | 6482 | 6501 | TGACTGCGAGAGGTGGGTCT |
| 178 | 6492 | 6511 | CAGTGCGCTCTGACTGCGAG |
| 179 | 6494 | 6513 | GGCAGTGCGCTCTGACTGCG |
| 180 | 6496 | 6515 | CGGGCAGTGCGCTCTGACTG |
| 10 | 6498 | 6517 | GGCGGGCAGTGCGCTCTGAC |
| 181 | 6499 | 6518 | CGGCGGGCAGTGCGCTCTGA |
| 182 | 6528 | 6547 | ATCCCCGGCGGGCAGCCTGG |
| 183 | 6532 | 6551 | AGGTATCCCCGGCGGGCAGC |
| 184 | 6534 | 6553 | TGAGGTATCCCCGGCGGGCA |
| 185 | 6535 | 6554 | GTGAGGTATCCCCGGCGGGC |
| 186 | 6536 | 6555 | GGTGAGGTATCCCCGGCGGG |
| 11 | 6537 | 6556 | TGGTGAGGTATCCCCGGCGG |
| 187 | 6538 | 6557 | TTGGTGAGGTATCCCCGGCG |
| 188 | 6539 | 6558 | CTTGGTGAGGTATCCCCGGC |
| 189 | 6540 | 6559 | TCTTGGTGAGGTATCCCCGG |
| 190 | 6541 | 6560 | ATCTTGGTGAGGTATCCCCG |
| 191 | 6542 | 6561 | GATCTTGGTGAGGTATCCCC |
| 12 | 6543 | 6562 | GGATCTTGGTGAGGTATCCC |
| 192 | 6544 | 6563 | AGGATCTTGGTGAGGTATCC |
| 193 | 6546 | 6565 | GCAGGATCTTGGTGAGGTAT |
| 194 | 6548 | 6567 | ATGCAGGATCTTGGTGAGGT |
| 195 | 6550 | 6569 | ACATGCAGGATCTTGGTGAG |
| 13 | 6552 | 6571 | AGACATGCAGGATCTTGGTG |
| 196 | 6554 | 6573 | GAAGACATGCAGGATCTTGG |
| 14 | 6557 | 6576 | ATGGAAGACATGCAGGATCT |
| 197 | 6565 | 6584 | AGAAGGCCATGGAAGACATG |
| 198 | 6575 | 6594 | GAAGCCAGGAAGAAGGCCAT |
| 15 | 6583 | 6602 | TTCACCAGGAAGCCAGGAAG |
| 199 | 6585 | 6604 | TCTTCACCAGGAAGCCAGGA |
| 16 | 6588 | 6607 | TCATCTTCACCAGGAAGCCA |
| 200 | 6590 | 6609 | ACTCATCTTCACCAGGAAGC |
| 201 | 6592 | 6611 | CCACTCATCTTCACCAGGAA |
| 202 | 6594 | 6613 | CGCCACTCATCTTCACCAGG |
| 203 | 6596 | 6615 | GTCGCCACTCATCTTCACCA |
| 204 | 6598 | 6617 | AGGTCGCCACTCATCTTCAC |
| 205 | 6600 | 6619 | GCAGGTCGCCACTCATCTTC |
| 206 | 6602 | 6621 | CAGCAGGTCGCCACTCATCT |
| 207 | 6604 | 6623 | TCCAGCAGGTCGCCACTCAT |
| 108 | 6652 | 6671 | CCCAGCCCTATCAGGAAGTG |

| SEQ ID NO | 5' Start Site to SEQ ID NO: 2 | 3' Start Site to SEQ ID NO: 2 | Sequence (5' to 3') |
|---|---|---|---|
| 144 | 7099 | 7118 | TGACATCCAGGAGGGAGGAG |
| 91 | 7556 | 7575 | AGACTGATGGAAGGCATTGA |
| 131 | 7565 | 7584 | GTGTTGAGCAGACTGATGGA |
| 145 | 8836 | 8855 | TGACATCTTGTCTGGGAGCC |
| 90 | 8948 | 8967 | AGACTAGGAGCCTGAGTTTT |
| 125 | 9099 | 9118 | GGCCTGCAGAAGCCAGAGAG |
| 17 | 9130 | 9149 | CCTCGATGTAGTCGACATGG |
| 209 | 9149 | 9168 | GCAAAGACAGAGGAGTCCTC |
| 210 | 9207 | 9226 | TTCATCCGCCCGGTACCGTG |
| 211 | 9209 | 9228 | TATTCATCCGCCCGGTACCG |
| 18 | 9210 | 9229 | GTATTCATCCGCCCGGTACC |
| 212 | 9212 | 9231 | TGGTATTCATCCGCCCGGTA |
| 213 | 9214 | 9233 | GCTGGTATTCATCCGCCCGG |
| 214 | 9216 | 9235 | GGGCTGGTATTCATCCGCCC |
| 148 | 10252 | 10271 | TGGCAGCAACTCAGACATAT |
| 127 | 10633 | 10652 | GGTGGTAATTTGTCACAGCA |
| 84 | 11308 | 11327 | AAGGTCACACAGTTAAGAGT |
| 79 | 11472 | 11491 | AAATGCAGGGCTAAAATCAC |
| 88 | 12715 | 12734 | ACTGGATACATTGGCAGACA |
| 111 | 12928 | 12947 | CTAGAGGAACCACTAGATAT |
| 85 | 13681 | 13700 | ACAAATTCCCAGACTCAGCA |
| 100 | 13746 | 13765 | ATCTCAGGACAGGTGAGCAA |
| 116 | 13760 | 13779 | GAGTAGAGATTCTCATCTCA |
| 129 | 13816 | 13835 | GTGCCATCTGAACAGCACCT |
| 117 | 13828 | 13847 | GAGTCTTCTGAAGTGCCATC |
| 81 | 13903 | 13922 | AAGCAGGGCCTCAGGTGGAA |
| 110 | 13926 | 13945 | CCTGGAACCCCTGCAGCCAG |
| 152 | 13977 | 13996 | TTCAGGCAGGTTGCTGCTAG |
| 83 | 13986 | 14005 | AAGGAAGACTTCAGGCAGGT |
| 140 | 13998 | 14017 | TCAGCCAGGCCAAAGGAAGA |
| 137 | 14112 | 14131 | TAGGGAGAGCTCACAGATGC |
| 136 | 14122 | 14141 | TAGGAGAAAGTAGGGAGAGC |
| 132 | 14179 | 14198 | TAAAAGCTGCAAGAGACTCA |
| 139 | 14267 | 14286 | TCAGAGAAAACAGTCACCGA |
| 92 | 14397 | 14416 | AGAGACAGGAAGCTGCAGCT |
| 142 | 14404 | 14423 | TCATTTTAGAGACAGGAAGC |
| 113 | 14441 | 14460 | GAATAACAGTGATGTCTGGC |
| 138 | 14494 | 14513 | TCACAGCTCACCGAGTCTGC |
| 98 | 14524 | 14543 | AGTGTAAAATAAAGCCCCTA |
| 96 | 14601 | 14620 | AGGACCCAAGTCATCCTGCT |
| 124 | 14631 | 14650 | GGCCATCAGCTGGCAATGCT |
| 82 | 14670 | 14689 | AAGGAAAGGGAGGCCTAGAG |
| 133 | 14675 | 14694 | TAGACAAGGAAAGGGAGGCC |
| 103 | 14681 | 14700 | ATTTCATAGACAAGGAAAGG |
| 155 | 14801 | 14820 | CTTATAGTTAACACACAGAA |
| 156 | 14809 | 14828 | AAGTCAACCTTATAGTTAAC |
| 215 | 14877 | 14896 | ATACACCTCCACCAGGCTGC |
| 216 | 14888 | 14907 | GTGTCTAGGAGATACACCTC |
| 19 | 14891 | 14910 | CTGGTGTCTAGGAGATACAC |
| 217 | 14893 | 14912 | TGCTGGTGTCTAGGAGATAC |
| 20 | 14896 | 14915 | GTATGCTGGTGTCTAGGAGA |
| 21 | 14916 | 14935 | GATTTCCCGGTGGTCACTCT |
| 218 | 14918 | 14937 | TCGATTTCCCGGTGGTCACT |

| SEQ ID NO | 5' Start Site to SEQ ID NO: 2 | 3' Start Site to SEQ ID NO: 2 | Sequence (5' to 3') |
|---|---|---|---|
| 219 | 14919 | 14938 | CTCGATTTCCCGGTGGTCAC |
| 220 | 14920 | 14939 | CCTCGATTTCCCGGTGGTCA |
| 221 | 14921 | 14940 | CCCTCGATTTCCCGGTGGTC |
| 22 | 14922 | 14941 | GCCCTCGATTTCCCGGTGGT |
| 222 | 14923 | 14942 | TGCCCTCGATTTCCCGGTGG |
| 223 | 14924 | 14943 | CTGCCCTCGATTTCCCGGTG |
| 224 | 14925 | 14944 | CCTGCCCTCGATTTCCCGGT |
| 225 | 14926 | 14945 | CCCTGCCCTCGATTTCCCGG |
| 226 | 14930 | 14949 | ATGACCCTGCCCTCGATTTC |
| 227 | 14932 | 14951 | CCATGACCCTGCCCTCGATT |
| 228 | 14934 | 14953 | GACCATGACCCTGCCCTCGA |
| 23 | 14936 | 14955 | GTGACCATGACCCTGCCCTC |
| 229 | 14938 | 14957 | CGGTGACCATGACCCTGCCC |
| 230 | 14940 | 14959 | GTCGGTGACCATGACCCTGC |
| 231 | 14942 | 14961 | AAGTCGGTGACCATGACCCT |
| 232 | 14944 | 14963 | CGAAGTCGGTGACCATGACC |
| 24 | 14946 | 14965 | CTCGAAGTCGGTGACCATGA |
| 233 | 14954 | 14973 | GGCACATTCTCGAAGTCGGT |
| 25 | 14979 | 14998 | GTGGAAGCGGGTCCCGTCCT |
| 235 | 15254 | 15273 | GGTGGGTGCCATGACTGTCA |
| 236 | 15257 | 15276 | CCAGGTGGGTGCCATGACTG |
| 237 | 15261 | 15280 | CCTGCCAGGTGGGTGCCATG |
| 26 | 15264 | 15283 | ACCCCTGCCAGGTGGGTGCC |
| 238 | 15266 | 15285 | CCACCCCTGCCAGGTGGGTG |
| 27 | 15269 | 15288 | TGACCACCCCTGCCAGGTGG |
| 239 | 15271 | 15290 | GCTGACCACCCCTGCCAGGT |
| 240 | 15279 | 15298 | TCCCGGCCGCTGACCACCCC |
| 241 | 15283 | 15302 | GGCATCCCGGCCGCTGACCA |
| 242 | 15286 | 15305 | GCCGGCATCCCGGCCGCTGA |
| 243 | 15291 | 15310 | GCCACGCCGGCATCCCGGCC |
| 244 | 15292 | 15311 | GGCCACGCCGGCATCCCGGC |
| 245 | 15293 | 15312 | TGGCCACGCCGGCATCCCGG |
| 246 | 15294 | 15313 | TTGGCCACGCCGGCATCCCG |
| 247 | 15295 | 15314 | CTTGGCCACGCCGGCATCCC |
| 248 | 15296 | 15315 | CCTTGGCCACGCCGGCATCC |
| 249 | 15297 | 15316 | CCCTTGGCCACGCCGGCATC |
| 28 | 15298 | 15317 | ACCCTTGGCCACGCCGGCAT |
| 447 | 15298 | 15317 | ACCCTTGGTCACGCCGGCAT |
| 250 | 15299 | 15318 | CACCCTTGGCCACGCCGGCA |
| 251 | 15300 | 15319 | GCACCCTTGGCCACGCCGGC |
| 252 | 15301 | 15320 | GGCACCCTTGGCCACGCCGG |
| 253 | 15302 | 15321 | TGGCACCCTTGGCCACGCCG |
| 254 | 15303 | 15322 | CTGGCACCCTTGGCCACGCC |
| 255 | 15304 | 15323 | GCTGGCACCCTTGGCCACGC |
| 256 | 15309 | 15328 | CGCATGCTGGCACCCTTGGC |
| 257 | 15330 | 15349 | CAGTTGAGCACGCGCAGGCT |
| 258 | 15332 | 15351 | GGCAGTTGAGCACGCGCAGG |
| 29 | 15334 | 15353 | TTGGCAGTTGAGCACGCGCA |
| 259 | 15336 | 15355 | CCTTGGCAGTTGAGCACGCG |
| 30 | 15339 | 15358 | TTCCCTTGGCAGTTGAGCAC |
| 260 | 15341 | 15360 | CCTTCCCTTGGCAGTTGAGC |
| 261 | 15345 | 15364 | GTGCCCTTCCCTTGGCAGTT |
| 262 | 15347 | 15366 | CCGTGCCCTTCCCTTGGCAG |

| SEQ ID NO | 5' Start Site to SEQ ID NO: 2 | 3' Start Site to SEQ ID NO: 2 | Sequence (5' to 3') |
|---|---|---|---|
| 263 | 15358 | 15377 | GGTGCCGCTAACCGTGCCCT |
| 86 | 15471 | 15490 | ACAGCATTCTTGGTTAGGAG |
| 97 | 16134 | 16153 | AGTCAAGCTGCTGCCCAGAG |
| 120 | 16668 | 16687 | GCTAGTTATTAAGCACCTGC |
| 150 | 17267 | 17286 | TGTGAGCTCTGGCCCAGTGG |
| 115 | 18377 | 18396 | GAGTAAGGCAGGTTACTCTC |
| 134 | 18408 | 18427 | TAGATGTGACTAACATTTAA |
| 157 | 18561 | 18580 | AGGAACAAAGCCAAGGTCAC |
| 266 | 18591 | 18610 | TGGCTTTTCCGAATAAACTC |
| 32 | 18593 | 18612 | GCTGGCTTTTCCGAATAAAC |
| 267 | 18595 | 18614 | CAGCTGGCTTTTCCGAATAA |
| 268 | 18597 | 18616 | ACCAGCTGGCTTTTCCGAAT |
| 269 | 18599 | 18618 | GGACCAGCTGGCTTTTCCGA |
| 270 | 18603 | 18622 | GGCTGGACCAGCTGGCTTTT |
| 271 | 18614 | 18633 | GTGGCCCCACAGGCTGGACC |
| 272 | 18627 | 18646 | AGCAGCACCACCAGTGGCCC |
| 273 | 18649 | 18668 | GCTGTACCCACCCGCCAGGG |
| 274 | 18695 | 18714 | CGACCCCAGCCCTCGCCAGG |
| 33 | 18705 | 18724 | GTGACCAGCACGACCCCAGC |
| 275 | 18707 | 18726 | CGGTGACCAGCACGACCCCA |
| 276 | 18709 | 18728 | AGCGGTGACCAGCACGACCC |
| 277 | 18711 | 18730 | GCAGCGGTGACCAGCACGAC |
| 278 | 18713 | 18732 | CGGCAGCGGTGACCAGCACG |
| 279 | 18714 | 18733 | CCGGCAGCGGTGACCAGCAC |
| 280 | 18717 | 18736 | TTGCCGGCAGCGGTGACCAG |
| 281 | 18719 | 18738 | AGTTGCCGGCAGCGGTGACC |
| 282 | 18721 | 18740 | GAAGTTGCCGGCAGCGGTGA |
| 283 | 18723 | 18742 | CGGAAGTTGCCGGCAGCGGT |
| 284 | 18725 | 18744 | CCCGGAAGTTGCCGGCAGCG |
| 285 | 18727 | 18746 | GTCCCGGAAGTTGCCGGCAG |
| 105 | 19203 | 19222 | CACATTAGCCTTGCTCAAGT |
| 151 | 19913 | 19932 | TGTGATGACCTGGAAAGGTG |
| 288 | 19931 | 19950 | GGCATTGGTGGCCCCAACTG |
| 149 | 19933 | 19952 | TGGGCATTGGTGGCCCCAAC |
| 289 | 19941 | 19960 | GCTGGTCTTGGGCATTGGTG |
| 290 | 19954 | 19973 | CCCAGGGTCACCGGCTGGTC |
| 291 | 19956 | 19975 | TCCCCAGGGTCACCGGCTGG |
| 292 | 19958 | 19977 | AGTCCCCAGGGTCACCGGCT |
| 293 | 19960 | 19979 | AAAGTCCCCAGGGTCACCGG |
| 34 | 19962 | 19981 | CCAAAGTCCCCAGGGTCACC |
| 294 | 19964 | 19983 | CCCCAAAGTCCCCAGGGTCA |
| 128 | 19966 | 19985 | GTCCCCAAAGTCCCCAGGGT |
| 295 | 19969 | 19988 | TTGGTCCCCAAAGTCCCCAG |
| 35 | 19971 | 19990 | AGTTGGTCCCCAAAGTCCCC |
| 296 | 19973 | 19992 | AAAGTTGGTCCCCAAAGTCC |
| 36 | 19976 | 19995 | GCCAAAGTTGGTCCCCAAAG |
| 297 | 19978 | 19997 | CGGCCAAAGTTGGTCCCCAA |
| 298 | 19980 | 19999 | AGCGGCCAAAGTTGGTCCCC |
| 299 | 19982 | 20001 | ACAGCGGCCAAAGTTGGTCC |
| 300 | 19984 | 20003 | ACACAGCGGCCAAAGTTGGT |
| 301 | 19986 | 20005 | CCACACAGCGGCCAAAGTTG |
| 37 | 19988 | 20007 | GTCCACACAGCGGCCAAAGT |
| 302 | 19990 | 20009 | AGGTCCACACAGCGGCCAAA |

| SEQ ID NO | 5' Start Site to SEQ ID NO: 2 | 3' Start Site to SEQ ID NO: 2 | Sequence (5' to 3') |
|---|---|---|---|
| 303 | 19992 | 20011 | AGAGGTCCACACAGCGGCCA |
| 304 | 19994 | 20013 | AAAGAGGTCCACACAGCGGC |
| 38 | 19997 | 20016 | GGCAAAGAGGTCCACACAGC |
| 305 | 20016 | 20035 | CAATGATGTCCTCCCCTGGG |
| 306 | 20023 | 20042 | GAGGCACCAATGATGTCCTC |
| 39 | 20025 | 20044 | TGGAGGCACCAATGATGTCC |
| 307 | 20027 | 20046 | GCTGGAGGCACCAATGATGT |
| 308 | 20029 | 20048 | TCGCTGGAGGCACCAATGAT |
| 309 | 20031 | 20050 | AGTCGCTGGAGGCACCAATG |
| 310 | 20033 | 20052 | GCAGTCGCTGGAGGCACCAA |
| 40 | 20036 | 20055 | GCTGCAGTCGCTGGAGGCAC |
| 311 | 20038 | 20057 | GTGCTGCAGTCGCTGGAGGC |
| 312 | 20040 | 20059 | AGGTGCTGCAGTCGCTGGAG |
| 313 | 20042 | 20061 | GCAGGTGCTGCAGTCGCTGG |
| 314 | 20043 | 20062 | AGCAGGTGCTGCAGTCGCTG |
| 315 | 20045 | 20064 | AAAGCAGGTGCTGCAGTCGC |
| 41 | 20047 | 20066 | ACAAAGCAGGTGCTGCAGTC |
| 316 | 20049 | 20068 | ACACAAAGCAGGTGCTGCAG |
| 317 | 20051 | 20070 | TGACACAAAGCAGGTGCTGC |
| 318 | 20061 | 20080 | TCCCACTCTGTGACACAAAG |
| 158 | 20100 | 20119 | GTGGTGACTTACCAGCCACG |
| 109 | 20188 | 20207 | CCCCTGCACAGAGCCTGGCA |
| 141 | 20624 | 20643 | TCATGGCTGCAATGCCTGGT |
| 320 | 20629 | 20648 | CAGCATCATGGCTGCAATGC |
| 321 | 20631 | 20650 | GACAGCATCATGGCTGCAAT |
| 322 | 20633 | 20652 | CAGACAGCATCATGGCTGCA |
| 43 | 20635 | 20654 | GGCAGACAGCATCATGGCTG |
| 323 | 20637 | 20656 | TCGGCAGACAGCATCATGGC |
| 324 | 20639 | 20658 | GCTCGGCAGACAGCATCATG |
| 325 | 20641 | 20660 | CGGCTCGGCAGACAGCATCA |
| 326 | 20643 | 20662 | TCCGGCTCGGCAGACAGCAT |
| 327 | 20657 | 20676 | CGGCCAGGGTGAGCTCCGGC |
| 328 | 20670 | 20689 | CTCTGCCTCAACTCGGCCAG |
| 329 | 20672 | 20691 | GTCTCTGCCTCAACTCGGCC |
| 330 | 20674 | 20693 | CAGTCTCTGCCTCAACTCGG |
| 331 | 20676 | 20695 | ATCAGTCTCTGCCTCAACTC |
| 332 | 20678 | 20697 | GGATCAGTCTCTGCCTCAAC |
| 333 | 20680 | 20699 | GTGGATCAGTCTCTGCCTCA |
| 334 | 20682 | 20701 | AAGTGGATCAGTCTCTGCCT |
| 44 | 20683 | 20702 | GAAGTGGATCAGTCTCTGCC |
| 335 | 20685 | 20704 | GAGAAGTGGATCAGTCTCTG |
| 336 | 20687 | 20706 | CAGAGAAGTGGATCAGTCTC |
| 337 | 20689 | 20708 | GGCAGAGAAGTGGATCAGTC |
| 45 | 20691 | 20710 | TTGGCAGAGAAGTGGATCAG |
| 338 | 20693 | 20712 | CTTTGGCAGAGAAGTGGATC |
| 46 | 20696 | 20715 | CATCTTTGGCAGAGAAGTGG |
| 339 | 20698 | 20717 | GACATCTTTGGCAGAGAAGT |
| 340 | 20700 | 20719 | ATGACATCTTTGGCAGAGAA |
| 47 | 20702 | 20721 | TGATGACATCTTTGGCAGAG |
| 341 | 20704 | 20723 | ATTGATGACATCTTTGGCAG |
| 342 | 20706 | 20725 | TCATTGATGACATCTTTGGC |
| 48 | 20709 | 20728 | GCCTCATTGATGACATCTTT |
| 343 | 20711 | 20730 | AGGCCTCATTGATGACATCT |

| SEQ ID NO | 5' Start Site to SEQ ID NO: 2 | 3' Start Site to SEQ ID NO: 2 | Sequence (5' to 3') |
|---|---|---|---|
| 344 | 20713 | 20732 | CCAGGCCTCATTGATGACAT |
| 345 | 20715 | 20734 | AACCAGGCCTCATTGATGAC |
| 346 | 20717 | 20736 | GGAACCAGGCCTCATTGATG |
| 347 | 20718 | 20737 | GGGAACCAGGCCTCATTGAT |
| 348 | 20719 | 20738 | AGGGAACCAGGCCTCATTGA |
| 349 | 20720 | 20739 | CAGGGAACCAGGCCTCATTG |
| 49 | 20721 | 20740 | TCAGGGAACCAGGCCTCATT |
| 350 | 20722 | 20741 | CTCAGGGAACCAGGCCTCAT |
| 351 | 20723 | 20742 | CCTCAGGGAACCAGGCCTCA |
| 352 | 20724 | 20743 | TCCTCAGGGAACCAGGCCTC |
| 353 | 20725 | 20744 | GTCCTCAGGGAACCAGGCCT |
| 50 | 20726 | 20745 | GGTCCTCAGGGAACCAGGCC |
| 354 | 20727 | 20746 | TGGTCCTCAGGGAACCAGGC |
| 355 | 20728 | 20747 | CTGGTCCTCAGGGAACCAGG |
| 356 | 20729 | 20748 | GCTGGTCCTCAGGGAACCAG |
| 357 | 20730 | 20749 | CGCTGGTCCTCAGGGAACCA |
| 87 | 20733 | 20752 | ACCCGCTGGTCCTCAGGGAA |
| 358 | 20735 | 20754 | GTACCCGCTGGTCCTCAGGG |
| 359 | 20737 | 20756 | CAGTACCCGCTGGTCCTCAG |
| 51 | 20740 | 20759 | GGTCAGTACCCGCTGGTCCT |
| 119 | 20762 | 20781 | GCAGGGCGGCCACCAGGTTG |
| 360 | 20785 | 20804 | ACCTGCCCCATGGGTGCTGG |
| 93 | 20995 | 21014 | AGAGAGGAGGGCTTAAAGAA |
| 95 | 21082 | 21101 | AGCTGCCAACCTGCAAAAAG |
| 361 | 21088 | 21107 | CAAAACAGCTGCCAACCTGC |
| 53 | 21091 | 21110 | CTGCAAAACAGCTGCCAACC |
| 362 | 21093 | 21112 | TCCTGCAAAACAGCTGCCAA |
| 363 | 21095 | 21114 | AGTCCTGCAAAACAGCTGCC |
| 364 | 21106 | 21125 | GCTGACCATACAGTCCTGCA |
| 365 | 21118 | 21137 | GGCCCCGAGTGTGCTGACCA |
| 54 | 21121 | 21140 | GTAGGCCCCGAGTGTGCTGA |
| 366 | 21123 | 21142 | GTGTAGGCCCCGAGTGTGCT |
| 367 | 21125 | 21144 | CCGTGTAGGCCCCGAGTGTG |
| 368 | 21127 | 21146 | ATCCGTGTAGGCCCCGAGTG |
| 369 | 21129 | 21148 | CCATCCGTGTAGGCCCCGAG |
| 370 | 21131 | 21150 | GGCCATCCGTGTAGGCCCCG |
| 371 | 21133 | 21152 | GTGGCCATCCGTGTAGGCCC |
| 372 | 21181 | 21200 | CTGGAGCAGCTCAGCAGCTC |
| 460 | 21181 | 21194 | CAGCTCAGCAGCTC |
| 373 | 21183 | 21202 | AACTGGAGCAGCTCAGCAGC |
| 55 | 21186 | 21205 | AGAAACTGGAGCAGCTCAGC |
| 374 | 21188 | 21207 | GGAGAAACTGGAGCAGCTCA |
| 375 | 21190 | 21209 | CTGGAGAAACTGGAGCAGCT |
| 56 | 21192 | 21211 | TCCTGGAGAAACTGGAGCAG |
| 143 | 21481 | 21500 | TGAAAATCCATCCAGCACTG |
| 89 | 21589 | 21608 | AGAACCATGGAGCACCTGAG |
| 448 | 21692 | 21711 | CTGCCCTTCCACCAAAATGC |
| 449 | 21693 | 21712 | ACTGCCCTTCCACCAAAATG |
| 450 | 21694 | 21713 | CACTGCCCTTCCACCAAAAT |
| 451 | 21695 | 21714 | GCACTGCCCTTCCACCAAAA |
| 123 | 21696 | 21715 | GGCACTGCCCTTCCACCAAA |
| 452 | 21697 | 21716 | GGGCACTGCCCTTCCACCAA |
| 453 | 21698 | 21717 | TGGGCACTGCCCTTCCACCA |

| SEQ ID NO | 5' Start Site to SEQ ID NO: 2 | 3' Start Site to SEQ ID NO: 2 | Sequence (5' to 3') |
|---|---|---|---|
| 454 | 21699 | 21718 | CTGGGCACTGCCCTTCCACC |
| 455 | 21700 | 21719 | GCTGGGCACTGCCCTTCCAC |
| 57 | 22096 | 22115 | CGTTGTGGGCCCGGCAGACC |
| 376 | 22133 | 22152 | CACCTGGCAATGGCGTAGAC |
| 377 | 22134 | 22153 | GCACCTGGCAATGGCGTAGA |
| 378 | 22135 | 22154 | AGCACCTGGCAATGGCGTAG |
| 379 | 22136 | 22155 | CAGCACCTGGCAATGGCGTA |
| 380 | 22137 | 22156 | GCAGCACCTGGCAATGGCGT |
| 381 | 22138 | 22157 | GGCAGCACCTGGCAATGGCG |
| 382 | 22139 | 22158 | AGGCAGCACCTGGCAATGGC |
| 383 | 22140 | 22159 | CAGGCAGCACCTGGCAATGG |
| 384 | 22141 | 22160 | GCAGGCAGCACCTGGCAATG |
| 58 | 22142 | 22161 | AGCAGGCAGCACCTGGCAAT |
| 385 | 22143 | 22162 | TAGCAGGCAGCACCTGGCAA |
| 386 | 22144 | 22163 | GTAGCAGGCAGCACCTGGCA |
| 387 | 22189 | 22208 | TGGCCTCAGCTGGTGGAGCT |
| 388 | 22199 | 22218 | GTCCCCATGCTGGCCTCAGC |
| 389 | 22200 | 22219 | GGTCCCCATGCTGGCCTCAG |
| 390 | 22201 | 22220 | GGGTCCCCATGCTGGCCTCA |
| 391 | 22202 | 22221 | CGGGTCCCCATGCTGGCCTC |
| 392 | 22203 | 22222 | ACGGGTCCCCATGCTGGCCT |
| 59 | 22204 | 22223 | CACGGGTCCCCATGCTGGCC |
| 393 | 22205 | 22224 | ACACGGGTCCCCATGCTGGC |
| 394 | 22206 | 22225 | GACACGGGTCCCCATGCTGG |
| 395 | 22207 | 22226 | GGACACGGGTCCCCATGCTG |
| 396 | 22208 | 22227 | TGGACACGGGTCCCCATGCT |
| 397 | 22209 | 22228 | GTGGACACGGGTCCCCATGC |
| 398 | 22210 | 22229 | AGTGGACACGGGTCCCCATG |
| 399 | 22211 | 22230 | CAGTGGACACGGGTCCCCAT |
| 400 | 22212 | 22231 | GCAGTGGACACGGGTCCCCA |
| 401 | 22213 | 22232 | GGCAGTGGACACGGGTCCCC |
| 402 | 22214 | 22233 | TGGCAGTGGACACGGGTCCC |
| 403 | 22215 | 22234 | GTGGCAGTGGACACGGGTCC |
| 404 | 22216 | 22235 | GGTGGCAGTGGACACGGGTC |
| 405 | 22217 | 22236 | TGGTGGCAGTGGACACGGGT |
| 406 | 22220 | 22239 | TGTTGGTGGCAGTGGACACG |
| 126 | 22292 | 22311 | GGTGCATAAGGAGAAAGAGA |
| 408 | 23985 | 24004 | GTGCCAAGGTCCTCCACCTC |
| 409 | 24005 | 24024 | TCAGCACAGGCGGCTTGTGG |
| 410 | 24035 | 24054 | CCACGCACTGGTTGGGCTGA |
| 60 | 24095 | 24114 | CTTTGCATTCCAGACCTGGG |
| 411 | 24096 | 24115 | ACTTTGCATTCCAGACCTGG |
| 412 | 24097 | 24116 | GACTTTGCATTCCAGACCTG |
| 413 | 24098 | 24117 | TGACTTTGCATTCCAGACCT |
| 414 | 24099 | 24118 | TTGACTTTGCATTCCAGACC |
| 61 | 24100 | 24119 | CTTGACTTTGCATTCCAGAC |
| 415 | 24102 | 24121 | TCCTTGACTTTGCATTCCAG |
| 416 | 24115 | 24134 | CGGGATTCCATGCTCCTTGA |
| 147 | 24858 | 24877 | TGAGTTCATTTAAGAGTGGA |
| 118 | 24907 | 24926 | GCACCATCCAGACCAGAATC |
| 114 | 25413 | 25432 | GAGAGGTTCAGATCCAGGCC |
| 418 | 25994 | 26013 | GGAGGGCACTGCAGCCAGTC |
| 419 | 26112 | 26131 | CAGATGGCAACGGCTGTCAC |

| SEQ ID NO | 5' Start Site to SEQ ID NO: 2 | 3' Start Site to SEQ ID NO: 2 | Sequence (5' to 3') |
|---|---|---|---|
| 420 | 26113 | 26132 | GCAGATGGCAACGGCTGTCA |
| 421 | 26114 | 26133 | AGCAGATGGCAACGGCTGTC |
| 422 | 26115 | 26134 | CAGCAGATGGCAACGGCTGT |
| 423 | 26116 | 26135 | GCAGCAGATGGCAACGGCTG |
| 62 | 26117 | 26136 | GGCAGCAGATGGCAACGGCT |
| 424 | 26118 | 26137 | CGGCAGCAGATGGCAACGGC |
| 425 | 26119 | 26138 | CCGGCAGCAGATGGCAACGG |
| 426 | 26120 | 26139 | TCCGGCAGCAGATGGCAACG |
| 427 | 26121 | 26140 | CTCCGGCAGCAGATGGCAAC |
| 428 | 26122 | 26141 | GCTCCGGCAGCAGATGGCAA |
| 429 | 26132 | 26151 | CCAGGTGCCGGCTCCGGCAG |
| 430 | 26142 | 26161 | GAGGCCTGCGCCAGGTGCCG |
| 154 | 26217 | 26236 | TTTTAAAGCTCAGCCCCAGC |
| 63 | 26222 | 26241 | AACCATTTTAAAGCTCAGCC |
| 64 | 26311 | 26330 | TCAAGGGCCAGGCCAGCAGC |
| 65 | 26316 | 26335 | CCCACTCAAGGGCCAGGCCA |
| 122 | 26389 | 26408 | GGAGGGAGCTTCCTGGCACC |
| 66 | 26404 | 26423 | ATGCCCCACAGTGAGGGAGG |
| 67 | 26413 | 26432 | AATGGTGAAATGCCCCACAG |
| 153 | 26456 | 26475 | TTGGGAGCAGCTGGCAGCAC |
| 68 | 26557 | 26576 | CATGGGAAGAATCCTGCCTC |
| 431 | 26635 | 26654 | ATGAGGGCCATCAGCACCTT |
| 432 | 26636 | 26655 | GATGAGGGCCATCAGCACCT |
| 433 | 26637 | 26656 | AGATGAGGGCCATCAGCACC |
| 434 | 26638 | 26657 | GAGATGAGGGCCATCAGCAC |
| 69 | 26639 | 26658 | GGAGATGAGGGCCATCAGCA |
| 435 | 26640 | 26659 | TGGAGATGAGGGCCATCAGC |
| 436 | 26641 | 26660 | CTGGAGATGAGGGCCATCAG |
| 437 | 26642 | 26661 | GCTGGAGATGAGGGCCATCA |
| 438 | 26643 | 26662 | AGCTGGAGATGAGGGCCATC |
| 461 | 26684 | 26697 | TTAATCAGGGAGCC |
| 70 | 26707 | 26726 | TAGATGCCATCCAGAAAGCT |
| 439 | 26709 | 26728 | GCTAGATGCCATCCAGAAAG |
| 440 | 26710 | 26729 | GGCTAGATGCCATCCAGAAA |
| 441 | 26711 | 26730 | TGGCTAGATGCCATCCAGAA |
| 442 | 26712 | 26731 | CTGGCTAGATGCCATCCAGA |
| 71 | 26713 | 26732 | TCTGGCTAGATGCCATCCAG |
| 443 | 26714 | 26733 | CTCTGGCTAGATGCCATCCA |
| 444 | 26715 | 26734 | CCTCTGGCTAGATGCCATCC |
| 445 | 26716 | 26735 | GCCTCTGGCTAGATGCCATC |
| 446 | 26717 | 26736 | AGCCTCTGGCTAGATGCCAT |
| 72 | 26790 | 26809 | GGCATAGAGCAGAGTAAAGG |
| 73 | 26795 | 26814 | AGCCTGGCATAGAGCAGAGT |
| 135 | 26801 | 26820 | TAGCACAGCCTGGCATAGAG |
| 112 | 27034 | 27053 | GAAGAGGCTTGGCTTCAGAG |
| 74 | 27040 | 27059 | AAGTAAGAAGAGGCTTGGCT |
| 75 | 27244 | 27263 | GCTCAAGGAGGGACAGTTGT |
| 76 | 27279 | 27298 | AAAGATAAATGTCTGCTTGC |
| 77 | 27284 | 27303 | ACCCAAAAGATAAATGTCTG |
| 78 | 27350 | 27369 | TCTTCAAGTTACAAAAGCAA |
| 99 | 27357 | 27376 | ATAAATATCTTCAAGTTACA |

In certain embodiments, gapmer antisense compounds are targeted to a PCSK9 nucleic acid. In certain such embodiments, gapmer antisense compounds are targeted to SEQ ID NO: 2. In certain such embodiments, the nucleotide sequences illustrated in Table 6 have a 5-10-5 gapmer motif. Table 7 illustrates gapmer antisense compounds targeted to SEQ ID NO: 2, having a 5-10-5 motif, where the gap segment comprises 2'-deoxynucleotides and each wing segment comprises nucleotides comprising a 2'-O-methoxyethyl sugar modification. Internucleoside linkages are phosphorthioate, and cytidines are 5-methylcytidines.

**Table 7: Gapmer antisense compounds having a 5-10-5 motif targeted to SEQ ID NO: 2**

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO:2 | 3' Target Site on SEQ ID NO: 2 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 395149 | 5-10-5 | 4 | 2274 | 2293 | 0 | GCGCGGAATCCTGGCTGGGA |
| 395150 | 5-10-5 | 5 | 2381 | 2400 | 0 | GAGGAGACCTAGAGGCCGTG |
| 395151 | 5-10-5 | 6 | 2439 | 2458 | 0 | AGGACCGCCTGGAGCTGACG |
| 395152 | 5-10-5 | 7 | 2549 | 2568 | 0 | ACGCAAGGCTAGCACCAGCT |
| 399793 | 5-10-5 | 8 | 2556 | 2575 | 0 | CCTCGGAACGCAAGGCTAGC |
| 395153 | 5-10-5 | 9 | 2619 | 2638 | 0 | CCTTGGCGCAGCGGTGGAAG |
| 399837 | 5-10-5 | 107 | 3056 | 3075 | 0 | CCCACTATAATGGCAAGCCC |
| 399838 | 5-10-5 | 80 | 4306 | 4325 | 0 | AACCCAGTTCTAATGCACCT |
| 399839 | 5-10-5 | 106 | 5140 | 5159 | 0 | CCAGTCAGAGTAGAACAGAG |
| 395221 | 5-10-5 | 102 | 5590 | 5609 | 0 | ATGTGCAGAGATCAATCACA |
| 399840 | 5-10-5 | 121 | 5599 | 5618 | 0 | GGAGCCTACATGTGCAGAGA |
| 399841 | 5-10-5 | 94 | 5667 | 5686 | 0 | AGCATGGCACCAGCATCTGC |
| 395154 | 5-10-5 | 10 | 6498 | 6517 | 0 | GGCGGGCAGTGCGCTCTGAC |
| 395155 | 5-10-5 | 11 | 6537 | 6556 | 0 | TGGTGAGGTATCCCCGGCGG |
| 399794 | 5-10-5 | 12 | 6543 | 6562 | 0 | GGATCTTGGTGAGGTATCCC |
| 399795 | 5-10-5 | 13 | 6552 | 6571 | 0 | AGACATGCAGGATCTTGGTG |
| 395156 | 5-10-5 | 14 | 6557 | 6576 | 0 | ATGGAAGACATGCAGGATCT |
| 395157 | 5-10-5 | 15 | 6583 | 6602 | 0 | TTCACCAGGAAGCCAGGAAG |
| 399796 | 5-10-5 | 16 | 6588 | 6607 | 0 | TCATCTTCACCAGGAAGCCA |
| 399842 | 5-10-5 | 108 | 6652 | 6671 | 0 | CCCAGCCCTATCAGGAAGTG |
| 399843 | 5-10-5 | 144 | 7099 | 7118 | 0 | TGACATCCAGGAGGGAGGAG |
| 399844 | 5-10-5 | 91 | 7556 | 7575 | 0 | AGACTGATGGAAGGCATTGA |
| 399845 | 5-10-5 | 131 | 7565 | 7584 | 0 | GTGTTGAGCAGACTGATGGA |
| 399846 | 5-10-5 | 145 | 8836 | 8855 | 0 | TGACATCTTGTCTGGGAGCC |
| 399847 | 5-10-5 | 90 | 8948 | 8967 | 0 | AGACTAGGAGCCTGAGTTTT |
| 399848 | 5-10-5 | 125 | 9099 | 9118 | 0 | GGCCTGCAGAAGCCAGAGAG |
| 395158 | 5-10-5 | 17 | 9130 | 9149 | 0 | CCTCGATGTAGTCGACATGG |
| 395159 | 5-10-5 | 18 | 9210 | 9229 | 0 | GTATTCATCCGCCCGGTACC |
| 399849 | 5-10-5 | 148 | 10252 | 10271 | 0 | TGGCAGCAACTCAGACATAT |
| 395222 | 5-10-5 | 127 | 10633 | 10652 | 0 | GGTGGTAATTTGTCACAGCA |
| 395223 | 5-10-5 | 84 | 11308 | 11327 | 0 | AAGGTCACACAGTTAAGAGT |
| 399850 | 5-10-5 | 79 | 11472 | 11491 | 0 | AAATGCAGGGCTAAAATCAC |
| 399851 | 5-10-5 | 88 | 12715 | 12734 | 0 | ACTGGATACATTGGCAGACA |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO:2 | 3' Target Site on SEQ ID NO: 2 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 399852 | 5-10-5 | 111 | 12928 | 12947 | 0 | CTAGAGGAACCACTAGATAT |
| 395201 | 5-10-5 | 85 | 13681 | 13700 | 0 | ACAAATTCCCAGACTCAGCA |
| 399827 | 5-10-5 | 100 | 13746 | 13765 | 0 | ATCTCAGGACAGGTGAGCAA |
| 399828 | 5-10-5 | 116 | 13760 | 13779 | 0 | GAGTAGAGATTCTCATCTCA |
| 395202 | 5-10-5 | 129 | 13816 | 13835 | 0 | GTGCCATCTGAACAGCACCT |
| 399829 | 5-10-5 | 117 | 13828 | 13847 | 0 | GAGTCTTCTGAAGTGCCATC |
| 399830 | 5-10-5 | 81 | 13903 | 13922 | 0 | AAGCAGGGCCTCAGGTGGAA |
| 395203 | 5-10-5 | 110 | 13926 | 13945 | 0 | CCTGGAACCCCTGCAGCCAG |
| 395204 | 5-10-5 | 152 | 13977 | 13996 | 0 | TTCAGGCAGGTTGCTGCTAG |
| 399831 | 5-10-5 | 83 | 13986 | 14005 | 0 | AAGGAAGACTTCAGGCAGGT |
| 395205 | 5-10-5 | 140 | 13998 | 14017 | 0 | TCAGCCAGGCCAAAGGAAGA |
| 399832 | 5-10-5 | 137 | 14112 | 14131 | 0 | TAGGGAGAGCTCACAGATGC |
| 395206 | 5-10-5 | 136 | 14122 | 14141 | 0 | TAGGAGAAAGTAGGGAGAGC |
| 395207 | 5-10-5 | 132 | 14179 | 14198 | 0 | TAAAAGCTGCAAGAGACTCA |
| 395208 | 5-10-5 | 139 | 14267 | 14286 | 0 | TCAGAGAAAACAGTCACCGA |
| 399833 | 5-10-5 | 92 | 14397 | 14416 | 0 | AGAGACAGGAAGCTGCAGCT |
| 395209 | 5-10-5 | 142 | 14404 | 14423 | 0 | TCATTTTAGAGACAGGAAGC |
| 395210 | 5-10-5 | 113 | 14441 | 14460 | 0 | GAATAACAGTGATGTCTGGC |
| 395211 | 5-10-5 | 138 | 14494 | 14513 | 0 | TCACAGCTCACCGAGTCTGC |
| 395212 | 5-10-5 | 98 | 14524 | 14543 | 0 | AGTGTAAAATAAAGCCCCTA |
| 395213 | 5-10-5 | 96 | 14601 | 14620 | 0 | AGGACCCAAGTCATCCTGCT |
| 395214 | 5-10-5 | 124 | 14631 | 14650 | 0 | GGCCATCAGCTGGCAATGCT |
| 399834 | 5-10-5 | 82 | 14670 | 14689 | 0 | AAGGAAAGGGAGGCCTAGAG |
| 395215 | 5-10-5 | 133 | 14675 | 14694 | 0 | TAGACAAGGAAAGGGAGGCC |
| 395216 | 5-10-5 | 103 | 14681 | 14700 | 0 | ATTTCATAGACAAGGAAAGG |
| 395217 | 5-10-5 | 155 | 14801 | 14820 | 0 | CTTATAGTTAACACACAGAA |
| 399835 | 5-10-5 | 156 | 14809 | 14828 | 0 | AAGTCAACCTTATAGTTAAC |
| 395160 | 5-10-5 | 19 | 14891 | 14910 | 0 | CTGGTGTCTAGGAGATACAC |
| 399797 | 5-10-5 | 20 | 14896 | 14915 | 0 | GTATGCTGGTGTCTAGGAGA |
| 395161 | 5-10-5 | 21 | 14916 | 14935 | 0 | GATTTCCCGGTGGTCACTCT |
| 399798 | 5-10-5 | 22 | 14922 | 14941 | 0 | GCCCTCGATTTCCCGGTGGT |
| 399799 | 5-10-5 | 23 | 14936 | 14955 | 0 | GTGACCATGACCCTGCCCTC |
| 395162 | 5-10-5 | 24 | 14946 | 14965 | 0 | CTCGAAGTCGGTGACCATGA |
| 395163 | 5-10-5 | 25 | 14979 | 14998 | 0 | GTGGAAGCGGGTCCCGTCCT |
| 395164 | 5-10-5 | 26 | 15264 | 15283 | 0 | ACCCCTGCCAGGTGGGTGCC |
| 399800 | 5-10-5 | 27 | 15269 | 15288 | 0 | TGACCACCCCTGCCAGGTGG |
| 395165 | 5-10-5 | 28 | 15298 | 15317 | 0 | ACCCTTGGCCACGCCGGCAT |
| 395166 | 5-10-5 | 29 | 15334 | 15353 | 0 | TTGGCAGTTGAGCACGCGCA |
| 399801 | 5-10-5 | 30 | 15339 | 15358 | 0 | TTCCCTTGGCAGTTGAGCAC |
| 399853 | 5-10-5 | 86 | 15471 | 15490 | 0 | ACAGCATTCTTGGTTAGGAG |
| 399854 | 5-10-5 | 97 | 16134 | 16153 | 0 | AGTCAAGCTGCTGCCCAGAG |
| 399855 | 5-10-5 | 120 | 16668 | 16687 | 0 | GCTAGTTATTAAGCACCTGC |
| 399856 | 5-10-5 | 150 | 17267 | 17286 | 0 | TGTGAGCTCTGGCCCAGTGG |
| 399857 | 5-10-5 | 115 | 18377 | 18396 | 0 | GAGTAAGGCAGGTTACTCTC |
| 399858 | 5-10-5 | 134 | 18408 | 18427 | 0 | TAGATGTGACTAACATTTAA |
| 395224 | 5-10-5 | 157 | 18561 | 18580 | 0 | AGGAACAAAGCCAAGGTCAC |
| 395168 | 5-10-5 | 32 | 18593 | 18612 | 0 | GCTGGCTTTTCCGAATAAAC |
| 395169 | 5-10-5 | 33 | 18705 | 18724 | 0 | GTGACCAGCACGACCCCAGC |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO:2 | 3' Target Site on SEQ ID NO: 2 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 399859 | 5-10-5 | 105 | 19203 | 19222 | 0 | CACATTAGCCTTGCTCAAGT |
| 399860 | 5-10-5 | 151 | 19913 | 19932 | 0 | TGTGATGACCTGGAAAGGTG |
| 395170 | 5-10-5 | 149 | 19933 | 19952 | 0 | TGGGCATTGGTGGCCCCAAC |
| 395171 | 5-10-5 | 34 | 19962 | 19981 | 0 | CCAAAGTCCCCAGGGTCACC |
| 395172 | 5-10-5 | 128 | 19966 | 19985 | 0 | GTCCCCAAAGTCCCCAGGGT |
| 399802 | 5-10-5 | 35 | 19971 | 19990 | 0 | AGTTGGTCCCCAAAGTCCCC |
| 395173 | 5-10-5 | 36 | 19976 | 19995 | 0 | GCCAAAGTTGGTCCCCAAAG |
| 399803 | 5-10-5 | 37 | 19988 | 20007 | 0 | GTCCACACAGCGGCCAAAGT |
| 395174 | 5-10-5 | 38 | 19997 | 20016 | 0 | GGCAAAGAGGTCCACACAGC |
| 395175 | 5-10-5 | 39 | 20025 | 20044 | 0 | TGGAGGCACCAATGATGTCC |
| 399804 | 5-10-5 | 40 | 20036 | 20055 | 0 | GCTGCAGTCGCTGGAGGCAC |
| 399805 | 5-10-5 | 41 | 20047 | 20066 | 0 | ACAAAGCAGGTGCTGCAGTC |
| 399861 | 5-10-5 | 158 | 20100 | 20119 | 0 | GTGGTGACTTACCAGCCACG |
| 399862 | 5-10-5 | 109 | 20188 | 20207 | 0 | CCCCTGCACAGAGCCTGGCA |
| 399863 | 5-10-5 | 141 | 20624 | 20643 | 0 | TCATGGCTGCAATGCCTGGT |
| 399807 | 5-10-5 | 43 | 20635 | 20654 | 0 | GGCAGACAGCATCATGGCTG |
| 399808 | 5-10-5 | 44 | 20683 | 20702 | 0 | GAAGTGGATCAGTCTCTGCC |
| 395177 | 5-10-5 | 45 | 20691 | 20710 | 0 | TTGGCAGAGAAGTGGATCAG |
| 399809 | 5-10-5 | 46 | 20696 | 20715 | 0 | CATCTTTGGCAGAGAAGTGG |
| 399810 | 5-10-5 | 47 | 20702 | 20721 | 0 | TGATGACATCTTTGGCAGAG |
| 399811 | 5-10-5 | 48 | 20709 | 20728 | 0 | GCCTCATTGATGACATCTTT |
| 399812 | 5-10-5 | 49 | 20721 | 20740 | 0 | TCAGGGAACCAGGCCTCATT |
| 395178 | 5-10-5 | 50 | 20726 | 20745 | 0 | GGTCCTCAGGGAACCAGGCC |
| 395179 | 5-10-5 | 87 | 20733 | 20752 | 0 | ACCCGCTGGTCCTCAGGGAA |
| 399813 | 5-10-5 | 51 | 20740 | 20759 | 0 | GGTCAGTACCCGCTGGTCCT |
| 395180 | 5-10-5 | 119 | 20762 | 20781 | 0 | GCAGGGCGGCCACCAGGTTG |
| 399864 | 5-10-5 | 93 | 20995 | 21014 | 0 | AGAGAGGAGGGCTTAAAGAA |
| 399865 | 5-10-5 | 95 | 21082 | 21101 | 0 | AGCTGCCAACCTGCAAAAAG |
| 399814 | 5-10-5 | 53 | 21091 | 21110 | 0 | CTGCAAAACAGCTGCCAACC |
| 395182 | 5-10-5 | 54 | 21121 | 21140 | 0 | GTAGGCCCCGAGTGTGCTGA |
| 399815 | 5-10-5 | 55 | 21186 | 21205 | 0 | AGAAACTGGAGCAGCTCAGC |
| 399816 | 5-10-5 | 56 | 21192 | 21211 | 0 | TCCTGGAGAAACTGGAGCAG |
| 399866 | 5-10-5 | 143 | 21481 | 21500 | 0 | TGAAAATCCATCCAGCACTG |
| 399867 | 5-10-5 | 89 | 21589 | 21608 | 0 | AGAACCATGGAGCACCTGAG |
| 399868 | 5-10-5 | 123 | 21696 | 21715 | 0 | GGCACTGCCCTTCCACCAAA |
| 395183 | 5-10-5 | 57 | 22096 | 22115 | 0 | CGTTGTGGGCCCGGCAGACC |
| 395184 | 5-10-5 | 58 | 22142 | 22161 | 0 | AGCAGGCAGCACCTGGCAAT |
| 395185 | 5-10-5 | 59 | 22204 | 22223 | 0 | CACGGGTCCCCATGCTGGCC |
| 395225 | 5-10-5 | 126 | 22292 | 22311 | 0 | GGTGCATAAGGAGAAAGAGA |
| 395186 | 5-10-5 | 60 | 24095 | 24114 | 0 | CTTTGCATTCCAGACCTGGG |
| 399817 | 5-10-5 | 61 | 24100 | 24119 | 0 | CTTGACTTTGCATTCCAGAC |
| 395226 | 5-10-5 | 147 | 24858 | 24877 | 0 | TGAGTTCATTTAAGAGTGGA |
| 399869 | 5-10-5 | 118 | 24907 | 24926 | 0 | GCACCATCCAGACCAGAATC |
| 399870 | 5-10-5 | 114 | 25413 | 25432 | 0 | GAGAGGTTCAGATCCAGGCC |
| 395187 | 5-10-5 | 62 | 26117 | 26136 | 0 | GGCAGCAGATGGCAACGGCT |
| 395188 | 5-10-5 | 154 | 26217 | 26236 | 0 | TTTTAAAGCTCAGCCCCAGC |
| 399818 | 5-10-5 | 63 | 26222 | 26241 | 0 | AACCATTTTAAAGCTCAGCC |
| 395189 | 5-10-5 | 64 | 26311 | 26330 | 0 | TCAAGGGCCAGGCCAGCAGC |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO:2 | 3' Target Site on SEQ ID NO: 2 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 399819 | 5-10-5 | 65 | 26316 | 26335 | 0 | CCCACTCAAGGGCCAGGCCA |
| 399820 | 5-10-5 | 122 | 26389 | 26408 | 0 | GGAGGGAGCTTCCTGGCACC |
| 395190 | 5-10-5 | 66 | 26404 | 26423 | 0 | ATGCCCCACAGTGAGGGAGG |
| 395191 | 5-10-5 | 67 | 26413 | 26432 | 0 | AATGGTGAAATGCCCCACAG |
| 395192 | 5-10-5 | 153 | 26456 | 26475 | 0 | TTGGGAGCAGCTGGCAGCAC |
| 395193 | 5-10-5 | 68 | 26557 | 26576 | 0 | CATGGGAAGAATCCTGCCTC |
| 395194 | 5-10-5 | 69 | 26639 | 26658 | 0 | GGAGATGAGGGCCATCAGCA |
| 395195 | 5-10-5 | 70 | 26707 | 26726 | 0 | TAGATGCCATCCAGAAAGCT |
| 399821 | 5-10-5 | 71 | 26713 | 26732 | 0 | TCTGGCTAGATGCCATCCAG |
| 395196 | 5-10-5 | 72 | 26790 | 26809 | 0 | GGCATAGAGCAGAGTAAAGG |
| 399822 | 5-10-5 | 73 | 26795 | 26814 | 0 | AGCCTGGCATAGAGCAGAGT |
| 399823 | 5-10-5 | 135 | 26801 | 26820 | 0 | TAGCACAGCCTGGCATAGAG |
| 395197 | 5-10-5 | 112 | 27034 | 27053 | 0 | GAAGAGGCTTGGCTTCAGAG |
| 399824 | 5-10-5 | 74 | 27040 | 27059 | 0 | AAGTAAGAAGAGGCTTGGCT |
| 395198 | 5-10-5 | 75 | 27244 | 27263 | 0 | GCTCAAGGAGGGACAGTTGT |
| 395199 | 5-10-5 | 76 | 27279 | 27298 | 0 | AAAGATAAATGTCTGCTTGC |
| 399825 | 5-10-5 | 77 | 27284 | 27303 | 0 | ACCCAAAAGATAAATGTCTG |
| 395200 | 5-10-5 | 78 | 27350 | 27369 | 0 | TCTTCAAGTTACAAAAGCAA |
| 399826 | 5-10-5 | 99 | 27357 | 27376 | 0 | ATAAATATCTTCAAGTTACA |
| 405861 | 5-10-5 | 162 | 2545 | 2564 | 0 | AAGGCTAGCACCAGCTCCTC |
| 405862 | 5-10-5 | 163 | 2546 | 2565 | 0 | CAAGGCTAGCACCAGCTCCT |
| 405863 | 5-10-5 | 164 | 2547 | 2566 | 0 | GCAAGGCTAGCACCAGCTCC |
| 405864 | 5-10-5 | 165 | 2548 | 2567 | 0 | CGCAAGGCTAGCACCAGCTC |
| 405865 | 5-10-5 | 166 | 2550 | 2569 | 0 | AACGCAAGGCTAGCACCAGC |
| 405866 | 5-10-5 | 167 | 2551 | 2570 | 0 | GAACGCAAGGCTAGCACCAG |
| 405867 | 5-10-5 | 168 | 2552 | 2571 | 0 | GGAACGCAAGGCTAGCACCA |
| 405868 | 5-10-5 | 169 | 2553 | 2572 | 0 | CGGAACGCAAGGCTAGCACC |
| 405869 | 5-10-5 | 218 | 14918 | 14937 | 0 | TCGATTTCCCGGTGGTCACT |
| 405870 | 5-10-5 | 219 | 14919 | 14938 | 0 | CTCGATTTCCCGGTGGTCAC |
| 405871 | 5-10-5 | 220 | 14920 | 14939 | 0 | CCTCGATTTCCCGGTGGTCA |
| 405872 | 5-10-5 | 221 | 14921 | 14940 | 0 | CCCTCGATTTCCCGGTGGTC |
| 405873 | 5-10-5 | 222 | 14923 | 14942 | 0 | TGCCCTCGATTTCCCGGTGG |
| 405874 | 5-10-5 | 223 | 14924 | 14943 | 0 | CTGCCCTCGATTTCCCGGTG |
| 405875 | 5-10-5 | 224 | 14925 | 14944 | 0 | CCTGCCCTCGATTTCCCGGT |
| 405876 | 5-10-5 | 225 | 14926 | 14945 | 0 | CCCTGCCCTCGATTTCCCGG |
| 405877 | 5-10-5 | 246 | 15294 | 15313 | 0 | TTGGCCACGCCGGCATCCCG |
| 405878 | 5-10-5 | 247 | 15295 | 15314 | 0 | CTTGGCCACGCCGGCATCCC |
| 405879 | 5-10-5 | 248 | 15296 | 15315 | 0 | CCTTGGCCACGCCGGCATCC |
| 405880 | 5-10-5 | 249 | 15297 | 15316 | 0 | CCCTTGGCCACGCCGGCATC |
| 405881 | 5-10-5 | 250 | 15299 | 15318 | 0 | CACCCTTGGCCACGCCGGCA |
| 405882 | 5-10-5 | 251 | 15300 | 15319 | 0 | GCACCCTTGGCCACGCCGGC |
| 405883 | 5-10-5 | 252 | 15301 | 15320 | 0 | GGCACCCTTGGCCACGCCGG |
| 405884 | 5-10-5 | 253 | 15302 | 15321 | 0 | TGGCACCCTTGGCCACGCCG |
| 405885 | 5-10-5 | 346 | 20717 | 20736 | 0 | GGAACCAGGCCTCATTGATG |
| 405886 | 5-10-5 | 347 | 20718 | 20737 | 0 | GGGAACCAGGCCTCATTGAT |
| 405887 | 5-10-5 | 348 | 20719 | 20738 | 0 | AGGGAACCAGGCCTCATTGA |
| 405888 | 5-10-5 | 349 | 20720 | 20739 | 0 | CAGGGAACCAGGCCTCATTG |
| 405889 | 5-10-5 | 350 | 20722 | 20741 | 0 | CTCAGGGAACCAGGCCTCAT |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO:2 | 3' Target Site on SEQ ID NO: 2 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 405890 | 5-10-5 | 351 | 20723 | 20742 | 0 | CCTCAGGGAACCAGGCCTCA |
| 405891 | 5-10-5 | 352 | 20724 | 20743 | 0 | TCCTCAGGGAACCAGGCCTC |
| 405892 | 5-10-5 | 353 | 20725 | 20744 | 0 | GTCCTCAGGGAACCAGGCCT |
| 405893 | 5-10-5 | 431 | 26635 | 26654 | 0 | ATGAGGGCCATCAGCACCTT |
| 405894 | 5-10-5 | 432 | 26636 | 26655 | 0 | GATGAGGGCCATCAGCACCT |
| 405895 | 5-10-5 | 433 | 26637 | 26656 | 0 | AGATGAGGGCCATCAGCACC |
| 405896 | 5-10-5 | 434 | 26638 | 26657 | 0 | GAGATGAGGGCCATCAGCAC |
| 405897 | 5-10-5 | 435 | 26640 | 26659 | 0 | TGGAGATGAGGGCCATCAGC |
| 405898 | 5-10-5 | 436 | 26641 | 26660 | 0 | CTGGAGATGAGGGCCATCAG |
| 405899 | 5-10-5 | 437 | 26642 | 26661 | 0 | GCTGGAGATGAGGGCCATCA |
| 405900 | 5-10-5 | 438 | 26643 | 26662 | 0 | AGCTGGAGATGAGGGCCATC |
| 405901 | 5-10-5 | 439 | 26709 | 26728 | 0 | GCTAGATGCCATCCAGAAAG |
| 405902 | 5-10-5 | 440 | 26710 | 26729 | 0 | GGCTAGATGCCATCCAGAAA |
| 405903 | 5-10-5 | 441 | 26711 | 26730 | 0 | TGGCTAGATGCCATCCAGAA |
| 405904 | 5-10-5 | 442 | 26712 | 26731 | 0 | CTGGCTAGATGCCATCCAGA |
| 405905 | 5-10-5 | 443 | 26714 | 26733 | 0 | CTCTGGCTAGATGCCATCCA |
| 405906 | 5-10-5 | 444 | 26715 | 26734 | 0 | CCTCTGGCTAGATGCCATCC |
| 405907 | 5-10-5 | 445 | 26716 | 26735 | 0 | GCCTCTGGCTAGATGCCATC |
| 405908 | 5-10-5 | 446 | 26717 | 26736 | 0 | AGCCTCTGGCTAGATGCCAT |
| 405909 | 5-10-5 | 267 | 18595 | 18614 | 0 | CAGCTGGCTTTTCCGAATAA |
| 405910 | 5-10-5 | 268 | 18597 | 18616 | 0 | ACCAGCTGGCTTTTCCGAAT |
| 405911 | 5-10-5 | 269 | 18599 | 18618 | 0 | GGACCAGCTGGCTTTTCCGA |
| 405912 | 5-10-5 | 270 | 18603 | 18622 | 0 | GGCTGGACCAGCTGGCTTTT |
| 405913 | 5-10-5 | 275 | 18707 | 18726 | 0 | CGGTGACCAGCACGACCCCA |
| 405914 | 5-10-5 | 276 | 18709 | 18728 | 0 | AGCGGTGACCAGCACGACCC |
| 405915 | 5-10-5 | 277 | 18711 | 18730 | 0 | GCAGCGGTGACCAGCACGAC |
| 405916 | 5-10-5 | 278 | 18713 | 18732 | 0 | CGGCAGCGGTGACCAGCACG |
| 405917 | 5-10-5 | 280 | 18717 | 18736 | 0 | TTGCCGGCAGCGGTGACCAG |
| 405918 | 5-10-5 | 281 | 18719 | 18738 | 0 | AGTTGCCGGCAGCGGTGACC |
| 405919 | 5-10-5 | 282 | 18721 | 18740 | 0 | GAAGTTGCCGGCAGCGGTGA |
| 405920 | 5-10-5 | 283 | 18723 | 18742 | 0 | CGGAAGTTGCCGGCAGCGGT |
| 405921 | 5-10-5 | 284 | 18725 | 18744 | 0 | CCCGGAAGTTGCCGGCAGCG |
| 405922 | 5-10-5 | 285 | 18727 | 18746 | 0 | GTCCCGGAAGTTGCCGGCAG |
| 405923 | 5-10-5 | 288 | 19931 | 19950 | 0 | GGCATTGGTGGCCCCAACTG |
| 405924 | 5-10-5 | 290 | 19954 | 19973 | 0 | CCCAGGGTCACCGGCTGGTC |
| 405925 | 5-10-5 | 292 | 19958 | 19977 | 0 | AGTCCCCAGGGTCACCGGCT |
| 405926 | 5-10-5 | 293 | 19960 | 19979 | 0 | AAAGTCCCCAGGGTCACCGG |
| 405927 | 5-10-5 | 294 | 19964 | 19983 | 0 | CCCCAAAGTCCCCAGGGTCA |
| 405928 | 5-10-5 | 295 | 19969 | 19988 | 0 | TTGGTCCCCAAAGTCCCCAG |
| 405929 | 5-10-5 | 296 | 19973 | 19992 | 0 | AAAGTTGGTCCCCAAAGTCC |
| 405930 | 5-10-5 | 297 | 19978 | 19997 | 0 | CGGCCAAAGTTGGTCCCCAA |
| 405931 | 5-10-5 | 298 | 19980 | 19999 | 0 | AGCGGCCAAAGTTGGTCCCC |
| 405932 | 5-10-5 | 299 | 19982 | 20001 | 0 | ACAGCGGCCAAAGTTGGTCC |
| 405933 | 5-10-5 | 300 | 19984 | 20003 | 0 | ACACAGCGGCCAAAGTTGGT |
| 405934 | 5-10-5 | 301 | 19986 | 20005 | 0 | CCACACAGCGGCCAAAGTTG |
| 405935 | 5-10-5 | 302 | 19990 | 20009 | 0 | AGGTCCACACAGCGGCCAAA |
| 405936 | 5-10-5 | 304 | 19994 | 20013 | 0 | AAAGAGGTCCACACAGCGGC |
| 405937 | 5-10-5 | 306 | 20023 | 20042 | 0 | GAGGCACCAATGATGTCCTC |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO:2 | 3' Target Site on SEQ ID NO: 2 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 405938 | 5-10-5 | 307 | 20027 | 20046 | 0 | GCTGGAGGCACCAATGATGT |
| 405939 | 5-10-5 | 308 | 20029 | 20048 | 0 | TCGCTGGAGGCACCAATGAT |
| 405940 | 5-10-5 | 309 | 20031 | 20050 | 0 | AGTCGCTGGAGGCACCAATG |
| 405941 | 5-10-5 | 310 | 20033 | 20052 | 0 | GCAGTCGCTGGAGGCACCAA |
| 405942 | 5-10-5 | 311 | 20038 | 20057 | 0 | GTGCTGCAGTCGCTGGAGGC |
| 405943 | 5-10-5 | 312 | 20040 | 20059 | 0 | AGGTGCTGCAGTCGCTGGAG |
| 405944 | 5-10-5 | 314 | 20043 | 20062 | 0 | AGCAGGTGCTGCAGTCGCTG |
| 405945 | 5-10-5 | 315 | 20045 | 20064 | 0 | AAAGCAGGTGCTGCAGTCGC |
| 405946 | 5-10-5 | 316 | 20049 | 20068 | 0 | ACACAAAGCAGGTGCTGCAG |
| 405947 | 5-10-5 | 317 | 20051 | 20070 | 0 | TGACACAAAGCAGGTGCTGC |
| 405949 | 5-10-5 | 320 | 20629 | 20648 | 0 | CAGCATCATGGCTGCAATGC |
| 405950 | 5-10-5 | 321 | 20631 | 20650 | 0 | GACAGCATCATGGCTGCAAT |
| 405951 | 5-10-5 | 322 | 20633 | 20652 | 0 | CAGACAGCATCATGGCTGCA |
| 405952 | 5-10-5 | 323 | 20637 | 20656 | 0 | TCGGCAGACAGCATCATGGC |
| 405953 | 5-10-5 | 325 | 20641 | 20660 | 0 | CGGCTCGGCAGACAGCATCA |
| 405954 | 5-10-5 | 326 | 20643 | 20662 | 0 | TCCGGCTCGGCAGACAGCAT |
| 405955 | 5-10-5 | 328 | 20670 | 20689 | 0 | CTCTGCCTCAACTCGGCCAG |
| 405956 | 5-10-5 | 329 | 20672 | 20691 | 0 | GTCTCTGCCTCAACTCGGCC |
| 405957 | 5-10-5 | 330 | 20674 | 20693 | 0 | CAGTCTCTGCCTCAACTCGG |
| 405958 | 5-10-5 | 331 | 20676 | 20695 | 0 | ATCAGTCTCTGCCTCAACTC |
| 405959 | 5-10-5 | 332 | 20678 | 20697 | 0 | GGATCAGTCTCTGCCTCAAC |
| 405960 | 5-10-5 | 333 | 20680 | 20699 | 0 | GTGGATCAGTCTCTGCCTCA |
| 405961 | 5-10-5 | 334 | 20682 | 20701 | 0 | AAGTGGATCAGTCTCTGCCT |
| 405962 | 5-10-5 | 335 | 20685 | 20704 | 0 | GAGAAGTGGATCAGTCTCTG |
| 405963 | 5-10-5 | 337 | 20689 | 20708 | 0 | GGCAGAGAAGTGGATCAGTC |
| 405964 | 5-10-5 | 338 | 20693 | 20712 | 0 | CTTTGGCAGAGAAGTGGATC |
| 405965 | 5-10-5 | 339 | 20698 | 20717 | 0 | GACATCTTTGGCAGAGAAGT |
| 405966 | 5-10-5 | 340 | 20700 | 20719 | 0 | ATGACATCTTTGGCAGAGAA |
| 405967 | 5-10-5 | 341 | 20704 | 20723 | 0 | ATTGATGACATCTTTGGCAG |
| 405968 | 5-10-5 | 342 | 20706 | 20725 | 0 | TCATTGATGACATCTTTGGC |
| 405969 | 5-10-5 | 343 | 20711 | 20730 | 0 | AGGCCTCATTGATGACATCT |
| 405970 | 5-10-5 | 344 | 20713 | 20732 | 0 | CCAGGCCTCATTGATGACAT |
| 405971 | 5-10-5 | 355 | 20728 | 20747 | 0 | CTGGTCCTCAGGGAACCAGG |
| 405972 | 5-10-5 | 357 | 20730 | 20749 | 0 | CGCTGGTCCTCAGGGAACCA |
| 405973 | 5-10-5 | 358 | 20735 | 20754 | 0 | GTACCCGCTGGTCCTCAGGG |
| 405974 | 5-10-5 | 359 | 20737 | 20756 | 0 | CAGTACCCGCTGGTCCTCAG |
| 405975 | 5-10-5 | 361 | 21088 | 21107 | 0 | CAAAACAGCTGCCAACCTGC |
| 405976 | 5-10-5 | 362 | 21093 | 21112 | 0 | TCCTGCAAAACAGCTGCCAA |
| 405977 | 5-10-5 | 363 | 21095 | 21114 | 0 | AGTCCTGCAAAACAGCTGCC |
| 405978 | 5-10-5 | 365 | 21118 | 21137 | 0 | GGCCCCGAGTGTGCTGACCA |
| 405979 | 5-10-5 | 366 | 21123 | 21142 | 0 | GTGTAGGCCCCGAGTGTGCT |
| 405980 | 5-10-5 | 367 | 21125 | 21144 | 0 | CCGTGTAGGCCCCGAGTGTG |
| 405981 | 5-10-5 | 368 | 21127 | 21146 | 0 | ATCCGTGTAGGCCCCGAGTG |
| 405982 | 5-10-5 | 370 | 21131 | 21150 | 0 | GGCCATCCGTGTAGGCCCCG |
| 405983 | 5-10-5 | 371 | 21133 | 21152 | 0 | GTGGCCATCCGTGTAGGCCC |
| 405984 | 5-10-5 | 372 | 21181 | 21200 | 0 | CTGGAGCAGCTCAGCAGCTC |
| 405985 | 5-10-5 | 373 | 21183 | 21202 | 0 | AACTGGAGCAGCTCAGCAGC |
| 405986 | 5-10-5 | 374 | 21188 | 21207 | 0 | GGAGAAACTGGAGCAGCTCA |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO:2 | 3' Target Site on SEQ ID NO: 2 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 405987 | 5-10-5 | 375 | 21190 | 21209 | 0 | CTGGAGAAACTGGAGCAGCT |
| 405988 | 5-10-5 | 381 | 22138 | 22157 | 0 | GGCAGCACCTGGCAATGGCG |
| 405989 | 5-10-5 | 383 | 22140 | 22159 | 0 | CAGGCAGCACCTGGCAATGG |
| 405990 | 5-10-5 | 386 | 22144 | 22163 | 0 | GTAGCAGGCAGCACCTGGCA |
| 405991 | 5-10-5 | 394 | 22206 | 22225 | 0 | GACACGGGTCCCCATGCTGG |
| 405992 | 5-10-5 | 396 | 22208 | 22227 | 0 | TGGACACGGGTCCCCATGCT |
| 405993 | 5-10-5 | 398 | 22210 | 22229 | 0 | AGTGGACACGGGTCCCCATG |
| 405994 | 5-10-5 | 400 | 22212 | 22231 | 0 | GCAGTGGACACGGGTCCCCA |
| 405995 | 5-10-5 | 402 | 22214 | 22233 | 0 | TGGCAGTGGACACGGGTCCC |
| 405996 | 5-10-5 | 412 | 24097 | 24116 | 0 | GACTTTGCATTCCAGACCTG |
| 405997 | 5-10-5 | 415 | 24102 | 24121 | 0 | TCCTTGACTTTGCATTCCAG |
| 405998 | 5-10-5 | 426 | 26120 | 26139 | 0 | TCCGGCAGCAGATGGCAACG |
| 405999 | 5-10-5 | 160 | 2437 | 2456 | 0 | GACCGCCTGGAGCTGACGGT |
| 406003 | 5-10-5 | 178 | 6492 | 6511 | 0 | CAGTGCGCTCTGACTGCGAG |
| 406004 | 5-10-5 | 179 | 6494 | 6513 | 0 | GGCAGTGCGCTCTGACTGCG |
| 406005 | 5-10-5 | 180 | 6496 | 6515 | 0 | CGGGCAGTGCGCTCTGACTG |
| 406006 | 5-10-5 | 181 | 6499 | 6518 | 0 | CGGCGGGCAGTGCGCTCTGA |
| 406007 | 5-10-5 | 183 | 6532 | 6551 | 0 | AGGTATCCCCGGCGGGCAGC |
| 406008 | 5-10-5 | 188 | 6539 | 6558 | 0 | CTTGGTGAGGTATCCCCGGC |
| 406009 | 5-10-5 | 190 | 6541 | 6560 | 0 | ATCTTGGTGAGGTATCCCCG |
| 406010 | 5-10-5 | 193 | 6546 | 6565 | 0 | GCAGGATCTTGGTGAGGTAT |
| 406011 | 5-10-5 | 194 | 6548 | 6567 | 0 | ATGCAGGATCTTGGTGAGGT |
| 406012 | 5-10-5 | 195 | 6550 | 6569 | 0 | ACATGCAGGATCTTGGTGAG |
| 406013 | 5-10-5 | 196 | 6554 | 6573 | 0 | GAAGACATGCAGGATCTTGG |
| 406014 | 5-10-5 | 199 | 6585 | 6604 | 0 | TCTTCACCAGGAAGCCAGGA |
| 406015 | 5-10-5 | 200 | 6590 | 6609 | 0 | ACTCATCTTCACCAGGAAGC |
| 406016 | 5-10-5 | 201 | 6592 | 6611 | 0 | CCACTCATCTTCACCAGGAA |
| 406017 | 5-10-5 | 203 | 6596 | 6615 | 0 | GTCGCCACTCATCTTCACCA |
| 406018 | 5-10-5 | 204 | 6598 | 6617 | 0 | AGGTCGCCACTCATCTTCAC |
| 406019 | 5-10-5 | 205 | 6600 | 6619 | 0 | GCAGGTCGCCACTCATCTTC |
| 406020 | 5-10-5 | 206 | 6602 | 6621 | 0 | CAGCAGGTCGCCACTCATCT |
| 406021 | 5-10-5 | 210 | 9207 | 9226 | 0 | TTCATCCGCCCGGTACCGTG |
| 406022 | 5-10-5 | 211 | 9209 | 9228 | 0 | TATTCATCCGCCCGGTACCG |
| 406023 | 5-10-5 | 212 | 9212 | 9231 | 0 | TGGTATTCATCCGCCCGGTA |
| 406024 | 5-10-5 | 213 | 9214 | 9233 | 0 | GCTGGTATTCATCCGCCCGG |
| 406025 | 5-10-5 | 216 | 14888 | 14907 | 0 | GTGTCTAGGAGATACACCTC |
| 406026 | 5-10-5 | 217 | 14893 | 14912 | 0 | TGCTGGTGTCTAGGAGATAC |
| 406027 | 5-10-5 | 226 | 14930 | 14949 | 0 | ATGACCCTGCCCTCGATTTC |
| 406028 | 5-10-5 | 227 | 14932 | 14951 | 0 | CCATGACCCTGCCCTCGATT |
| 406029 | 5-10-5 | 228 | 14934 | 14953 | 0 | GACCATGACCCTGCCCTCGA |
| 406030 | 5-10-5 | 229 | 14938 | 14957 | 0 | CGGTGACCATGACCCTGCCC |
| 406031 | 5-10-5 | 230 | 14940 | 14959 | 0 | GTCGGTGACCATGACCCTGC |
| 406032 | 5-10-5 | 232 | 14944 | 14963 | 0 | CGAAGTCGGTGACCATGACC |
| 406033 | 5-10-5 | 237 | 15261 | 15280 | 0 | CCTGCCAGGTGGGTGCCATG |
| 406034 | 5-10-5 | 238 | 15266 | 15285 | 0 | CCACCCCTGCCAGGTGGGTG |
| 406035 | 5-10-5 | 239 | 15271 | 15290 | 0 | GCTGACCACCCCTGCCAGGT |
| 406036 | 5-10-5 | 241 | 15283 | 15302 | 0 | GGCATCCCGGCCGCTGACCA |
| 406037 | 5-10-5 | 242 | 15286 | 15305 | 0 | GCCGGCATCCCGGCCGCTGA |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO:2 | 3' Target Site on SEQ ID NO: 2 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 406038 | 5-10-5 | 245 | 15293 | 15312 | 0 | TGGCCACGCCGGCATCCCGG |
| 406039 | 5-10-5 | 257 | 15330 | 15349 | 0 | CAGTTGAGCACGCGCAGGCT |
| 406040 | 5-10-5 | 258 | 15332 | 15351 | 0 | GGCAGTTGAGCACGCGCAGG |
| 406041 | 5-10-5 | 259 | 15336 | 15355 | 0 | CCTTGGCAGTTGAGCACGCG |
| 406042 | 5-10-5 | 260 | 15341 | 15360 | 0 | CCTTCCCTTGGCAGTTGAGC |
| 406043 | 5-10-5 | 261 | 15345 | 15364 | 0 | GTGCCCTTCCCTTGGCAGTT |
| 406044 | 5-10-5 | 262 | 15347 | 15366 | 0 | CCGTGCCCTTCCCTTGGCAG |
| 406045 | 5-10-5 | 266 | 18591 | 18610 | 0 | TGGCTTTTCCGAATAAACTC |
| 406478 | 5-10-5 | 448 | 21692 | 21711 | 0 | CTGCCCTTCCACCAAAATGC |
| 406479 | 5-10-5 | 449 | 21693 | 21712 | 0 | ACTGCCCTTCCACCAAAATG |
| 406480 | 5-10-5 | 450 | 21694 | 21713 | 0 | CACTGCCCTTCCACCAAAAT |
| 406481 | 5-10-5 | 451 | 21695 | 21714 | 0 | GCACTGCCCTTCCACCAAAA |
| 406482 | 5-10-5 | 452 | 21697 | 21716 | 0 | GGGCACTGCCCTTCCACCAA |
| 406483 | 5-10-5 | 453 | 21698 | 21717 | 0 | TGGGCACTGCCCTTCCACCA |
| 406484 | 5-10-5 | 454 | 21699 | 21718 | 0 | CTGGGCACTGCCCTTCCACC |
| 406485 | 5-10-5 | 455 | 21700 | 21719 | 0 | GCTGGGCACTGCCCTTCCAC |
| 408653 | 5-10-5 | 354 | 20727 | 20746 | 0 | TGGTCCTCAGGGAACCAGGC |
| 409126 | 5-10-5 | 447 | 15298 | 15317 | 1 | ACCCTTGGTCACGCCGGCAT |
| 410529 | 5-10-5 | 184 | 6534 | 6553 | 0 | TGAGGTATCCCCGGCGGGCA |
| 410530 | 5-10-5 | 185 | 6535 | 6554 | 0 | GTGAGGTATCCCCGGCGGGC |
| 410531 | 5-10-5 | 186 | 6536 | 6555 | 0 | GGTGAGGTATCCCCGGCGGG |
| 410532 | 5-10-5 | 187 | 6538 | 6557 | 0 | TTGGTGAGGTATCCCCGGCG |
| 410533 | 5-10-5 | 189 | 6540 | 6559 | 0 | TCTTGGTGAGGTATCCCCGG |
| 410534 | 5-10-5 | 191 | 6542 | 6561 | 0 | GATCTTGGTGAGGTATCCCC |
| 410535 | 5-10-5 | 192 | 6544 | 6563 | 0 | AGGATCTTGGTGAGGTATCC |
| 410536 | 5-10-5 | 243 | 15291 | 15310 | 0 | GCCACGCCGGCATCCCGGCC |
| 410537 | 5-10-5 | 244 | 15292 | 15311 | 0 | GGCCACGCCGGCATCCCGGC |
| 410538 | 5-10-5 | 254 | 15303 | 15322 | 0 | CTGGCACCCTTGGCCACGCC |
| 410539 | 5-10-5 | 255 | 15304 | 15323 | 0 | GCTGGCACCCTTGGCCACGC |
| 410540 | 5-10-5 | 356 | 20729 | 20748 | 0 | GCTGGTCCTCAGGGAACCAG |
| 410541 | 5-10-5 | 376 | 22133 | 22152 | 0 | CACCTGGCAATGGCGTAGAC |
| 410542 | 5-10-5 | 377 | 22134 | 22153 | 0 | GCACCTGGCAATGGCGTAGA |
| 410543 | 5-10-5 | 378 | 22135 | 22154 | 0 | AGCACCTGGCAATGGCGTAG |
| 410544 | 5-10-5 | 379 | 22136 | 22155 | 0 | CAGCACCTGGCAATGGCGTA |
| 410545 | 5-10-5 | 380 | 22137 | 22156 | 0 | GCAGCACCTGGCAATGGCGT |
| 410546 | 5-10-5 | 382 | 22139 | 22158 | 0 | AGGCAGCACCTGGCAATGGC |
| 410547 | 5-10-5 | 384 | 22141 | 22160 | 0 | GCAGGCAGCACCTGGCAATG |
| 410548 | 5-10-5 | 385 | 22143 | 22162 | 0 | TAGCAGGCAGCACCTGGCAA |
| 410549 | 5-10-5 | 388 | 22199 | 22218 | 0 | GTCCCCATGCTGGCCTCAGC |
| 410550 | 5-10-5 | 389 | 22200 | 22219 | 0 | GGTCCCCATGCTGGCCTCAG |
| 410551 | 5-10-5 | 390 | 22201 | 22220 | 0 | GGGTCCCCATGCTGGCCTCA |
| 410552 | 5-10-5 | 391 | 22202 | 22221 | 0 | CGGGTCCCCATGCTGGCCTC |
| 410553 | 5-10-5 | 392 | 22203 | 22222 | 0 | ACGGGTCCCCATGCTGGCCT |
| 410554 | 5-10-5 | 393 | 22205 | 22224 | 0 | ACACGGGTCCCCATGCTGGC |
| 410555 | 5-10-5 | 395 | 22207 | 22226 | 0 | GGACACGGGTCCCCATGCTG |
| 410556 | 5-10-5 | 397 | 22209 | 22228 | 0 | GTGGACACGGGTCCCCATGC |
| 410557 | 5-10-5 | 399 | 22211 | 22230 | 0 | CAGTGGACACGGGTCCCCAT |
| 410558 | 5-10-5 | 401 | 22213 | 22232 | 0 | GGCAGTGGACACGGGTCCCC |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO:2 | 3' Target Site on SEQ ID NO: 2 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 410559 | 5-10-5 | 403 | 22215 | 22234 | 0 | GTGGCAGTGGACACGGGTCC |
| 410560 | 5-10-5 | 404 | 22216 | 22235 | 0 | GGTGGCAGTGGACACGGGTC |
| 410561 | 5-10-5 | 405 | 22217 | 22236 | 0 | TGGTGGCAGTGGACACGGGT |
| 410562 | 5-10-5 | 411 | 24096 | 24115 | 0 | ACTTTGCATTCCAGACCTGG |
| 410563 | 5-10-5 | 413 | 24098 | 24117 | 0 | TGACTTTGCATTCCAGACCT |
| 410564 | 5-10-5 | 414 | 24099 | 24118 | 0 | TTGACTTTGCATTCCAGACC |
| 410565 | 5-10-5 | 419 | 26112 | 26131 | 0 | CAGATGGCAACGGCTGTCAC |
| 410566 | 5-10-5 | 420 | 26113 | 26132 | 0 | GCAGATGGCAACGGCTGTCA |
| 410567 | 5-10-5 | 421 | 26114 | 26133 | 0 | AGCAGATGGCAACGGCTGTC |
| 410568 | 5-10-5 | 422 | 26115 | 26134 | 0 | CAGCAGATGGCAACGGCTGT |
| 410569 | 5-10-5 | 423 | 26116 | 26135 | 0 | GCAGCAGATGGCAACGGCTG |
| 410570 | 5-10-5 | 424 | 26118 | 26137 | 0 | CGGCAGCAGATGGCAACGGC |
| 410571 | 5-10-5 | 425 | 26119 | 26138 | 0 | CCGGCAGCAGATGGCAACGG |
| 410572 | 5-10-5 | 427 | 26121 | 26140 | 0 | CTCCGGCAGCAGATGGCAAC |
| 410573 | 5-10-5 | 428 | 26122 | 26141 | 0 | GCTCCGGCAGCAGATGGCAA |
| 410730 | 5-10-5 | 202 | 6594 | 6613 | 0 | CGCCACTCATCTTCACCAGG |
| 410731 | 5-10-5 | 207 | 6604 | 6623 | 0 | TCCAGCAGGTCGCCACTCAT |
| 410732 | 5-10-5 | 214 | 9216 | 9235 | 0 | GGGCTGGTATTCATCCGCCC |
| 410733 | 5-10-5 | 231 | 14942 | 14961 | 0 | AAGTCGGTGACCATGACCCT |
| 410734 | 5-10-5 | 279 | 18714 | 18733 | 0 | CCGGCAGCGGTGACCAGCAC |
| 410735 | 5-10-5 | 291 | 19956 | 19975 | 0 | TCCCCAGGGTCACCGGCTGG |
| 410736 | 5-10-5 | 303 | 19992 | 20011 | 0 | AGAGGTCCACACAGCGGCCA |
| 410737 | 5-10-5 | 313 | 20042 | 20061 | 0 | GCAGGTGCTGCAGTCGCTGG |
| 410738 | 5-10-5 | 324 | 20639 | 20658 | 0 | GCTCGGCAGACAGCATCATG |
| 410739 | 5-10-5 | 336 | 20687 | 20706 | 0 | CAGAGAAGTGGATCAGTCTC |
| 410740 | 5-10-5 | 345 | 20715 | 20734 | 0 | AACCAGGCCTCATTGATGAC |
| 410741 | 5-10-5 | 369 | 21129 | 21148 | 0 | CCATCCGTGTAGGCCCCGAG |
| 410742 | 5-10-5 | 159 | 2433 | 2452 | 0 | GCCTGGAGCTGACGGTGCCC |
| 410743 | 5-10-5 | 170 | 2560 | 2579 | 0 | TCCTCCTCGGAACGCAAGGC |
| 410744 | 5-10-5 | 171 | 2585 | 2604 | 0 | GTGCTCGGGTGCTTCGGCCA |
| 410745 | 5-10-5 | 172 | 2605 | 2624 | 0 | TGGAAGGTGGCTGTGGTTCC |
| 410746 | 5-10-5 | 176 | 6444 | 6463 | 0 | CGTAGGTGCCAGGCAACCTC |
| 410747 | 5-10-5 | 177 | 6482 | 6501 | 0 | TGACTGCGAGAGGTGGGTCT |
| 410748 | 5-10-5 | 182 | 6528 | 6547 | 0 | ATCCCCGGCGGGCAGCCTGG |
| 410749 | 5-10-5 | 197 | 6565 | 6584 | 0 | AGAAGGCCATGGAAGACATG |
| 410750 | 5-10-5 | 198 | 6575 | 6594 | 0 | GAAGCCAGGAAGAAGGCCAT |
| 410752 | 5-10-5 | 209 | 9149 | 9168 | 0 | GCAAAGACAGAGGAGTCCTC |
| 410753 | 5-10-5 | 215 | 14877 | 14896 | 0 | ATACACCTCCACCAGGCTGC |
| 410754 | 5-10-5 | 233 | 14954 | 14973 | 0 | GGCACATTCTCGAAGTCGGT |
| 410756 | 5-10-5 | 235 | 15254 | 15273 | 0 | GGTGGGTGCCATGACTGTCA |
| 410757 | 5-10-5 | 240 | 15279 | 15298 | 0 | TCCCGGCCGCTGACCACCCC |
| 410758 | 5-10-5 | 256 | 15309 | 15328 | 0 | CGCATGCTGGCACCCTTGGC |
| 410759 | 5-10-5 | 263 | 15358 | 15377 | 0 | GGTGCCGCTAACCGTGCCCT |
| 410761 | 5-10-5 | 271 | 18614 | 18633 | 0 | GTGGCCCCACAGGCTGGACC |
| 410762 | 5-10-5 | 272 | 18627 | 18646 | 0 | AGCAGCACCACCAGTGGCCC |
| 410763 | 5-10-5 | 273 | 18649 | 18668 | 0 | GCTGTACCCACCCGCCAGGG |
| 410764 | 5-10-5 | 274 | 18695 | 18714 | 0 | CGACCCCAGCCCTCGCCAGG |
| 410767 | 5-10-5 | 289 | 19941 | 19960 | 0 | GCTGGTCTTGGGCATTGGTG |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO:2 | 3' Target Site on SEQ ID NO: 2 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 410768 | 5-10-5 | 305 | 20016 | 20035 | 0 | CAATGATGTCCTCCCCTGGG |
| 410769 | 5-10-5 | 318 | 20061 | 20080 | 0 | TCCCACTCTGTGACACAAAG |
| 410770 | 5-10-5 | 327 | 20657 | 20676 | 0 | CGGCCAGGGTGAGCTCCGGC |
| 410771 | 5-10-5 | 360 | 20785 | 20804 | 0 | ACCTGCCCCATGGGTGCTGG |
| 410772 | 5-10-5 | 364 | 21106 | 21125 | 0 | GCTGACCATACAGTCCTGCA |
| 410773 | 5-10-5 | 387 | 22189 | 22208 | 0 | TGGCCTCAGCTGGTGGAGCT |
| 410774 | 5-10-5 | 406 | 22220 | 22239 | 0 | TGTTGGTGGCAGTGGACACG |
| 410776 | 5-10-5 | 408 | 23985 | 24004 | 0 | GTGCCAAGGTCCTCCACCTC |
| 410777 | 5-10-5 | 409 | 24005 | 24024 | 0 | TCAGCACAGGCGGCTTGTGG |
| 410778 | 5-10-5 | 410 | 24035 | 24054 | 0 | CCACGCACTGGTTGGGCTGA |
| 410779 | 5-10-5 | 416 | 24115 | 24134 | 0 | CGGGATTCCATGCTCCTTGA |
| 410781 | 5-10-5 | 418 | 25994 | 26013 | 0 | GGAGGGCACTGCAGCCAGTC |
| 410782 | 5-10-5 | 429 | 26132 | 26151 | 0 | CCAGGTGCCGGCTCCGGCAG |
| 410783 | 5-10-5 | 430 | 26142 | 26161 | 0 | GAGGCCTGCGCCAGGTGCCG |

In certain embodiments, gap-widened antisense compounds are targeted to a PCSK9 nucleic acid. In certain such embodiments, gap-widened antisense compounds are targeted to SEQ ID NO: 2. In certain such embodiments, the nucleotide sequences illustrated in Table 6 have a 3-14-3 gap-widened motif. Table 8 illustrates gap-widened antisense compounds targeted to SEQ ID NO: 2, having a 3-14-3 motif, where the gap segment comprises 2'-deoxynucleotides and each wing segment comprises nucleotides comprising a 2'-O-methoxyethyl sugar modification. Internucleoside linkages are phosphorthioate, and cytidines are 5-methylcytidines.

**Table 8: Gapmer antisense compounds having a 3-14-3 motif targeted to SEQ ID NO: 2**

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO: 2 | 3' Target Site on SEQ ID NO: 2 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 399871 | 3-14-3 | 4 | 2274 | 2293 | 0 | GCGCGGAATCCTGGCTGGGA |
| 399872 | 3-14-3 | 5 | 2381 | 2400 | 0 | GAGGAGACCTAGAGGCCGTG |
| 399873 | 3-14-3 | 6 | 2439 | 2458 | 0 | AGGACCGCCTGGAGCTGACG |
| 399874 | 3-14-3 | 7 | 2549 | 2568 | 0 | ACGCAAGGCTAGCACCAGCT |
| 399875 | 3-14-3 | 9 | 2619 | 2638 | 0 | CCTTGGCGCAGCGGTGGAAG |
| 399876 | 3-14-3 | 10 | 6498 | 6517 | 0 | GGCGGGCAGTGCGCTCTGAC |
| 399877 | 3-14-3 | 11 | 6537 | 6556 | 0 | TGGTGAGGTATCCCCGGCGG |
| 399878 | 3-14-3 | 14 | 6557 | 6576 | 0 | ATGGAAGACATGCAGGATCT |
| 399879 | 3-14-3 | 15 | 6583 | 6602 | 0 | TTCACCAGGAAGCCAGGAAG |
| 399880 | 3-14-3 | 17 | 9130 | 9149 | 0 | CCTCGATGTAGTCGACATGG |
| 399881 | 3-14-3 | 18 | 9210 | 9229 | 0 | GTATTCATCCGCCCGGTACC |
| 399882 | 3-14-3 | 19 | 14891 | 14910 | 0 | CTGGTGTCTAGGAGATACAC |
| 399883 | 3-14-3 | 21 | 14916 | 14935 | 0 | GATTTCCCGGTGGTCACTCT |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO: 2 | 3' Target Site on SEQ ID NO: 2 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 399884 | 3-14-3 | 24 | 14946 | 14965 | 0 | CTCGAAGTCGGTGACCATGA |
| 399885 | 3-14-3 | 25 | 14979 | 14998 | 0 | GTGGAAGCGGGTCCCGTCCT |
| 399886 | 3-14-3 | 26 | 15264 | 15283 | 0 | ACCCCTGCCAGGTGGGTGCC |
| 399887 | 3-14-3 | 28 | 15298 | 15317 | 0 | ACCCTTGGCCACGCCGGCAT |
| 399888 | 3-14-3 | 29 | 15334 | 15353 | 0 | TTGGCAGTTGAGCACGCGCA |
| 399890 | 3-14-3 | 32 | 18593 | 18612 | 0 | GCTGGCTTTTCCGAATAAAC |
| 399891 | 3-14-3 | 33 | 18705 | 18724 | 0 | GTGACCAGCACGACCCCAGC |
| 399892 | 3-14-3 | 149 | 19933 | 19952 | 0 | TGGGCATTGGTGGCCCCAAC |
| 399893 | 3-14-3 | 34 | 19962 | 19981 | 0 | CCAAAGTCCCCAGGGTCACC |
| 399894 | 3-14-3 | 128 | 19966 | 19985 | 0 | GTCCCCAAAGTCCCCAGGGT |
| 399895 | 3-14-3 | 36 | 19976 | 19995 | 0 | GCCAAAGTTGGTCCCCAAAG |
| 399896 | 3-14-3 | 38 | 19997 | 20016 | 0 | GGCAAAGAGGTCCACACAGC |
| 399897 | 3-14-3 | 39 | 20025 | 20044 | 0 | TGGAGGCACCAATGATGTCC |
| 399899 | 3-14-3 | 45 | 20691 | 20710 | 0 | TTGGCAGAGAAGTGGATCAG |
| 399900 | 3-14-3 | 50 | 20726 | 20745 | 0 | GGTCCTCAGGGAACCAGGCC |
| 399901 | 3-14-3 | 87 | 20733 | 20752 | 0 | ACCCGCTGGTCCTCAGGGAA |
| 399902 | 3-14-3 | 119 | 20762 | 20781 | 0 | GCAGGGCGGCCACCAGGTTG |
| 399904 | 3-14-3 | 54 | 21121 | 21140 | 0 | GTAGGCCCCGAGTGTGCTGA |
| 399905 | 3-14-3 | 57 | 22096 | 22115 | 0 | CGTTGTGGGCCCGGCAGACC |
| 399906 | 3-14-3 | 58 | 22142 | 22161 | 0 | AGCAGGCAGCACCTGGCAAT |
| 399907 | 3-14-3 | 59 | 22204 | 22223 | 0 | CACGGGTCCCCATGCTGGCC |
| 399908 | 3-14-3 | 60 | 24095 | 24114 | 0 | CTTTGCATTCCAGACCTGGG |
| 399909 | 3-14-3 | 62 | 26117 | 26136 | 0 | GGCAGCAGATGGCAACGGCT |
| 399910 | 3-14-3 | 154 | 26217 | 26236 | 0 | TTTTAAAGCTCAGCCCCAGC |
| 399911 | 3-14-3 | 64 | 26311 | 26330 | 0 | TCAAGGGCCAGGCCAGCAGC |
| 399912 | 3-14-3 | 66 | 26404 | 26423 | 0 | ATGCCCCACAGTGAGGGAGG |
| 399913 | 3-14-3 | 67 | 26413 | 26432 | 0 | AATGGTGAAATGCCCCACAG |
| 399914 | 3-14-3 | 153 | 26456 | 26475 | 0 | TTGGGAGCAGCTGGCAGCAC |
| 399915 | 3-14-3 | 68 | 26557 | 26576 | 0 | CATGGGAAGAATCCTGCCTC |
| 399916 | 3-14-3 | 69 | 26639 | 26658 | 0 | GGAGATGAGGGCCATCAGCA |
| 399917 | 3-14-3 | 70 | 26707 | 26726 | 0 | TAGATGCCATCCAGAAAGCT |
| 399918 | 3-14-3 | 72 | 26790 | 26809 | 0 | GGCATAGAGCAGAGTAAAGG |
| 399919 | 3-14-3 | 112 | 27034 | 27053 | 0 | GAAGAGGCTTGGCTTCAGAG |
| 399920 | 3-14-3 | 75 | 27244 | 27263 | 0 | GCTCAAGGAGGGACAGTTGT |
| 399921 | 3-14-3 | 76 | 27279 | 27298 | 0 | AAAGATAAATGTCTGCTTGC |
| 399922 | 3-14-3 | 78 | 27350 | 27369 | 0 | TCTTCAAGTTACAAAAGCAA |
| 399923 | 3-14-3 | 85 | 13681 | 13700 | 0 | ACAAATTCCCAGACTCAGCA |
| 399924 | 3-14-3 | 129 | 13816 | 13835 | 0 | GTGCCATCTGAACAGCACCT |
| 399925 | 3-14-3 | 110 | 13926 | 13945 | 0 | CCTGGAACCCCTGCAGCCAG |
| 399926 | 3-14-3 | 152 | 13977 | 13996 | 0 | TTCAGGCAGGTTGCTGCTAG |
| 399927 | 3-14-3 | 140 | 13998 | 14017 | 0 | TCAGCCAGGCCAAAGGAAGA |
| 399928 | 3-14-3 | 136 | 14122 | 14141 | 0 | TAGGAGAAAGTAGGGAGAGC |
| 399929 | 3-14-3 | 132 | 14179 | 14198 | 0 | TAAAAGCTGCAAGAGACTCA |
| 399930 | 3-14-3 | 139 | 14267 | 14286 | 0 | TCAGAGAAAACAGTCACCGA |
| 399931 | 3-14-3 | 142 | 14404 | 14423 | 0 | TCATTTTAGAGACAGGAAGC |
| 399932 | 3-14-3 | 113 | 14441 | 14460 | 0 | GAATAACAGTGATGTCTGGC |
| 399933 | 3-14-3 | 138 | 14494 | 14513 | 0 | TCACAGCTCACCGAGTCTGC |
| 399934 | 3-14-3 | 98 | 14524 | 14543 | 0 | AGTGTAAAATAAAGCCCCTA |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO: 2 | 3' Target Site on SEQ ID NO: 2 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 399935 | 3-14-3 | 96 | 14601 | 14620 | 0 | AGGACCCAAGTCATCCTGCT |
| 399936 | 3-14-3 | 124 | 14631 | 14650 | 0 | GGCCATCAGCTGGCAATGCT |
| 399937 | 3-14-3 | 133 | 14675 | 14694 | 0 | TAGACAAGGAAAGGGAGGCC |
| 399938 | 3-14-3 | 103 | 14681 | 14700 | 0 | ATTTCATAGACAAGGAAAGG |
| 399939 | 3-14-3 | 155 | 14801 | 14820 | 0 | CTTATAGTTAACACACAGAA |
| 399943 | 3-14-3 | 102 | 5590 | 5609 | 0 | ATGTGCAGAGATCAATCACA |
| 399944 | 3-14-3 | 127 | 10633 | 10652 | 0 | GGTGGTAATTTGTCACAGCA |
| 399945 | 3-14-3 | 84 | 11308 | 11327 | 0 | AAGGTCACACAGTTAAGAGT |
| 399946 | 3-14-3 | 157 | 18561 | 18580 | 0 | AGGAACAAAGCCAAGGTCAC |
| 399947 | 3-14-3 | 126 | 22292 | 22311 | 0 | GGTGCATAAGGAGAAAGAGA |
| 399948 | 3-14-3 | 147 | 24858 | 24877 | 0 | TGAGTTCATTTAAGAGTGGA |
| 399949 | 3-14-3 | 8 | 2556 | 2575 | 0 | CCTCGGAACGCAAGGCTAGC |
| 399950 | 3-14-3 | 12 | 6543 | 6562 | 0 | GGATCTTGGTGAGGTATCCC |
| 399951 | 3-14-3 | 13 | 6552 | 6571 | 0 | AGACATGCAGGATCTTGGTG |
| 399952 | 3-14-3 | 16 | 6588 | 6607 | 0 | TCATCTTCACCAGGAAGCCA |
| 399953 | 3-14-3 | 20 | 14896 | 14915 | 0 | GTATGCTGGTGTCTAGGAGA |
| 399954 | 3-14-3 | 22 | 14922 | 14941 | 0 | GCCCTCGATTTCCCGGTGGT |
| 399955 | 3-14-3 | 23 | 14936 | 14955 | 0 | GTGACCATGACCCTGCCCTC |
| 399956 | 3-14-3 | 27 | 15269 | 15288 | 0 | TGACCACCCCTGCCAGGTGG |
| 399957 | 3-14-3 | 30 | 15339 | 15358 | 0 | TTCCCTTGGCAGTTGAGCAC |
| 399958 | 3-14-3 | 35 | 19971 | 19990 | 0 | AGTTGGTCCCCAAAGTCCCC |
| 399959 | 3-14-3 | 37 | 19988 | 20007 | 0 | GTCCACACAGCGGCCAAAGT |
| 399960 | 3-14-3 | 40 | 20036 | 20055 | 0 | GCTGCAGTCGCTGGAGGCAC |
| 399961 | 3-14-3 | 41 | 20047 | 20066 | 0 | ACAAAGCAGGTGCTGCAGTC |
| 399963 | 3-14-3 | 43 | 20635 | 20654 | 0 | GGCAGACAGCATCATGGCTG |
| 399964 | 3-14-3 | 44 | 20683 | 20702 | 0 | GAAGTGGATCAGTCTCTGCC |
| 399965 | 3-14-3 | 46 | 20696 | 20715 | 0 | CATCTTTGGCAGAGAAGTGG |
| 399966 | 3-14-3 | 47 | 20702 | 20721 | 0 | TGATGACATCTTTGGCAGAG |
| 399967 | 3-14-3 | 48 | 20709 | 20728 | 0 | GCCTCATTGATGACATCTTT |
| 399968 | 3-14-3 | 49 | 20721 | 20740 | 0 | TCAGGGAACCAGGCCTCATT |
| 399969 | 3-14-3 | 51 | 20740 | 20759 | 0 | GGTCAGTACCCGCTGGTCCT |
| 399970 | 3-14-3 | 53 | 21091 | 21110 | 0 | CTGCAAAACAGCTGCCAACC |
| 399971 | 3-14-3 | 55 | 21186 | 21205 | 0 | AGAAACTGGAGCAGCTCAGC |
| 399972 | 3-14-3 | 56 | 21192 | 21211 | 0 | TCCTGGAGAAACTGGAGCAG |
| 399973 | 3-14-3 | 61 | 24100 | 24119 | 0 | CTTGACTTTGCATTCCAGAC |
| 399974 | 3-14-3 | 63 | 26222 | 26241 | 0 | AACCATTTTAAAGCTCAGCC |
| 399975 | 3-14-3 | 65 | 26316 | 26335 | 0 | CCCACTCAAGGGCCAGGCCA |
| 399976 | 3-14-3 | 122 | 26389 | 26408 | 0 | GGAGGGAGCTTCCTGGCACC |
| 399977 | 3-14-3 | 71 | 26713 | 26732 | 0 | TCTGGCTAGATGCCATCCAG |
| 399978 | 3-14-3 | 73 | 26795 | 26814 | 0 | AGCCTGGCATAGAGCAGAGT |
| 399979 | 3-14-3 | 135 | 26801 | 26820 | 0 | TAGCACAGCCTGGCATAGAG |
| 399980 | 3-14-3 | 74 | 27040 | 27059 | 0 | AAGTAAGAAGAGGCTTGGCT |
| 399981 | 3-14-3 | 77 | 27284 | 27303 | 0 | ACCCAAAAGATAAATGTCTG |
| 399982 | 3-14-3 | 99 | 27357 | 27376 | 0 | ATAAATATCTTCAAGTTACA |
| 399983 | 3-14-3 | 100 | 13746 | 13765 | 0 | ATCTCAGGACAGGTGAGCAA |
| 399984 | 3-14-3 | 116 | 13760 | 13779 | 0 | GAGTAGAGATTCTCATCTCA |
| 399985 | 3-14-3 | 117 | 13828 | 13847 | 0 | GAGTCTTCTGAAGTGCCATC |
| 399986 | 3-14-3 | 81 | 13903 | 13922 | 0 | AAGCAGGGCCTCAGGTGGAA |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO: 2 | 3' Target Site on SEQ ID NO: 2 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 399987 | 3-14-3 | 83 | 13986 | 14005 | 0 | AAGGAAGACTTCAGGCAGGT |
| 399988 | 3-14-3 | 137 | 14112 | 14131 | 0 | TAGGGAGAGCTCACAGATGC |
| 399989 | 3-14-3 | 92 | 14397 | 14416 | 0 | AGAGACAGGAAGCTGCAGCT |
| 399990 | 3-14-3 | 82 | 14670 | 14689 | 0 | AAGGAAAGGGAGGCCTAGAG |
| 399991 | 3-14-3 | 156 | 14809 | 14828 | 0 | AAGTCAACCTTATAGTTAAC |
| 399993 | 3-14-3 | 107 | 3056 | 3075 | 0 | CCCACTATAATGGCAAGCCC |
| 399994 | 3-14-3 | 80 | 4306 | 4325 | 0 | AACCCAGTTCTAATGCACCT |
| 399995 | 3-14-3 | 106 | 5140 | 5159 | 0 | CCAGTCAGAGTAGAACAGAG |
| 399996 | 3-14-3 | 121 | 5599 | 5618 | 0 | GGAGCCTACATGTGCAGAGA |
| 399997 | 3-14-3 | 94 | 5667 | 5686 | 0 | AGCATGGCACCAGCATCTGC |
| 399998 | 3-14-3 | 108 | 6652 | 6671 | 0 | CCCAGCCCTATCAGGAAGTG |
| 399999 | 3-14-3 | 144 | 7099 | 7118 | 0 | TGACATCCAGGAGGGAGGAG |
| 400000 | 3-14-3 | 91 | 7556 | 7575 | 0 | AGACTGATGGAAGGCATTGA |
| 400001 | 3-14-3 | 131 | 7565 | 7584 | 0 | GTGTTGAGCAGACTGATGGA |
| 400002 | 3-14-3 | 145 | 8836 | 8855 | 0 | TGACATCTTGTCTGGGAGCC |
| 400003 | 3-14-3 | 90 | 8948 | 8967 | 0 | AGACTAGGAGCCTGAGTTTT |
| 400004 | 3-14-3 | 125 | 9099 | 9118 | 0 | GGCCTGCAGAAGCCAGAGAG |
| 400005 | 3-14-3 | 148 | 10252 | 10271 | 0 | TGGCAGCAACTCAGACATAT |
| 400006 | 3-14-3 | 79 | 11472 | 11491 | 0 | AAATGCAGGGCTAAAATCAC |
| 400007 | 3-14-3 | 88 | 12715 | 12734 | 0 | ACTGGATACATTGGCAGACA |
| 400008 | 3-14-3 | 111 | 12928 | 12947 | 0 | CTAGAGGAACCACTAGATAT |
| 400009 | 3-14-3 | 86 | 15471 | 15490 | 0 | ACAGCATTCTTGGTTAGGAG |
| 400010 | 3-14-3 | 97 | 16134 | 16153 | 0 | AGTCAAGCTGCTGCCCAGAG |
| 400011 | 3-14-3 | 120 | 16668 | 16687 | 0 | GCTAGTTATTAAGCACCTGC |
| 400012 | 3-14-3 | 150 | 17267 | 17286 | 0 | TGTGAGCTCTGGCCCAGTGG |
| 400013 | 3-14-3 | 115 | 18377 | 18396 | 0 | GAGTAAGGCAGGTTACTCTC |
| 400014 | 3-14-3 | 134 | 18408 | 18427 | 0 | TAGATGTGACTAACATTTAA |
| 400015 | 3-14-3 | 105 | 19203 | 19222 | 0 | CACATTAGCCTTGCTCAAGT |
| 400016 | 3-14-3 | 151 | 19913 | 19932 | 0 | TGTGATGACCTGGAAAGGTG |
| 400017 | 3-14-3 | 158 | 20100 | 20119 | 0 | GTGGTGACTTACCAGCCACG |
| 400018 | 3-14-3 | 109 | 20188 | 20207 | 0 | CCCCTGCACAGAGCCTGGCA |
| 400019 | 3-14-3 | 141 | 20624 | 20643 | 0 | TCATGGCTGCAATGCCTGGT |
| 400020 | 3-14-3 | 93 | 20995 | 21014 | 0 | AGAGAGGAGGGCTTAAAGAA |
| 400021 | 3-14-3 | 95 | 21082 | 21101 | 0 | AGCTGCCAACCTGCAAAAAG |
| 400022 | 3-14-3 | 143 | 21481 | 21500 | 0 | TGAAAATCCATCCAGCACTG |
| 400023 | 3-14-3 | 89 | 21589 | 21608 | 0 | AGAACCATGGAGCACCTGAG |
| 400024 | 3-14-3 | 123 | 21696 | 21715 | 0 | GGCACTGCCCTTCCACCAAA |
| 400025 | 3-14-3 | 118 | 24907 | 24926 | 0 | GCACCATCCAGACCAGAATC |
| 400026 | 3-14-3 | 114 | 25413 | 25432 | 0 | GAGAGGTTCAGATCCAGGCC |
| 405604 | 3-14-3 | 236 | 15257 | 15276 | 0 | CCAGGTGGGTGCCATGACTG |
| 405641 | 3-14-3 | 373 | 21183 | 21202 | 0 | AACTGGAGCAGCTCAGCAGC |
| 410574 | 3-14-3 | 184 | 6534 | 6553 | 0 | TGAGGTATCCCCGGCGGGCA |
| 410575 | 3-14-3 | 185 | 6535 | 6554 | 0 | GTGAGGTATCCCCGGCGGGC |
| 410576 | 3-14-3 | 186 | 6536 | 6555 | 0 | GGTGAGGTATCCCCGGCGGG |
| 410577 | 3-14-3 | 187 | 6538 | 6557 | 0 | TTGGTGAGGTATCCCCGGCG |
| 410578 | 3-14-3 | 188 | 6539 | 6558 | 0 | CTTGGTGAGGTATCCCCGGC |
| 410579 | 3-14-3 | 189 | 6540 | 6559 | 0 | TCTTGGTGAGGTATCCCCGG |
| 410580 | 3-14-3 | 190 | 6541 | 6560 | 0 | ATCTTGGTGAGGTATCCCCG |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO: 2 | 3' Target Site on SEQ ID NO: 2 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 410581 | 3-14-3 | 191 | 6542 | 6561 | 0 | GATCTTGGTGAGGTATCCCC |
| 410582 | 3-14-3 | 192 | 6544 | 6563 | 0 | AGGATCTTGGTGAGGTATCC |
| 410583 | 3-14-3 | 243 | 15291 | 15310 | 0 | GCCACGCCGGCATCCCGGCC |
| 410584 | 3-14-3 | 244 | 15292 | 15311 | 0 | GGCCACGCCGGCATCCCGGC |
| 410585 | 3-14-3 | 245 | 15293 | 15312 | 0 | TGGCCACGCCGGCATCCCGG |
| 410586 | 3-14-3 | 246 | 15294 | 15313 | 0 | TTGGCCACGCCGGCATCCCG |
| 410587 | 3-14-3 | 247 | 15295 | 15314 | 0 | CTTGGCCACGCCGGCATCCC |
| 410588 | 3-14-3 | 248 | 15296 | 15315 | 0 | CCTTGGCCACGCCGGCATCC |
| 410589 | 3-14-3 | 249 | 15297 | 15316 | 0 | CCCTTGGCCACGCCGGCATC |
| 410590 | 3-14-3 | 250 | 15299 | 15318 | 0 | CACCCTTGGCCACGCCGGCA |
| 410591 | 3-14-3 | 251 | 15300 | 15319 | 0 | GCACCCTTGGCCACGCCGGC |
| 410592 | 3-14-3 | 252 | 15301 | 15320 | 0 | GGCACCCTTGGCCACGCCGG |
| 410593 | 3-14-3 | 253 | 15302 | 15321 | 0 | TGGCACCCTTGGCCACGCCG |
| 410594 | 3-14-3 | 254 | 15303 | 15322 | 0 | CTGGCACCCTTGGCCACGCC |
| 410595 | 3-14-3 | 255 | 15304 | 15323 | 0 | GCTGGCACCCTTGGCCACGC |
| 410596 | 3-14-3 | 348 | 20719 | 20738 | 0 | AGGGAACCAGGCCTCATTGA |
| 410597 | 3-14-3 | 349 | 20720 | 20739 | 0 | CAGGGAACCAGGCCTCATTG |
| 410598 | 3-14-3 | 350 | 20722 | 20741 | 0 | CTCAGGGAACCAGGCCTCAT |
| 410599 | 3-14-3 | 351 | 20723 | 20742 | 0 | CCTCAGGGAACCAGGCCTCA |
| 410600 | 3-14-3 | 352 | 20724 | 20743 | 0 | TCCTCAGGGAACCAGGCCTC |
| 410601 | 3-14-3 | 353 | 20725 | 20744 | 0 | GTCCTCAGGGAACCAGGCCT |
| 410602 | 3-14-3 | 354 | 20727 | 20746 | 0 | TGGTCCTCAGGGAACCAGGC |
| 410603 | 3-14-3 | 355 | 20728 | 20747 | 0 | CTGGTCCTCAGGGAACCAGG |
| 410604 | 3-14-3 | 356 | 20729 | 20748 | 0 | GCTGGTCCTCAGGGAACCAG |
| 410605 | 3-14-3 | 376 | 22133 | 22152 | 0 | CACCTGGCAATGGCGTAGAC |
| 410606 | 3-14-3 | 377 | 22134 | 22153 | 0 | GCACCTGGCAATGGCGTAGA |
| 410607 | 3-14-3 | 378 | 22135 | 22154 | 0 | AGCACCTGGCAATGGCGTAG |
| 410608 | 3-14-3 | 379 | 22136 | 22155 | 0 | CAGCACCTGGCAATGGCGTA |
| 410609 | 3-14-3 | 380 | 22137 | 22156 | 0 | GCAGCACCTGGCAATGGCGT |
| 410610 | 3-14-3 | 381 | 22138 | 22157 | 0 | GGCAGCACCTGGCAATGGCG |
| 410611 | 3-14-3 | 382 | 22139 | 22158 | 0 | AGGCAGCACCTGGCAATGGC |
| 410612 | 3-14-3 | 383 | 22140 | 22159 | 0 | CAGGCAGCACCTGGCAATGG |
| 410613 | 3-14-3 | 384 | 22141 | 22160 | 0 | GCAGGCAGCACCTGGCAATG |
| 410614 | 3-14-3 | 385 | 22143 | 22162 | 0 | TAGCAGGCAGCACCTGGCAA |
| 410615 | 3-14-3 | 388 | 22199 | 22218 | 0 | GTCCCCATGCTGGCCTCAGC |
| 410616 | 3-14-3 | 389 | 22200 | 22219 | 0 | GGTCCCCATGCTGGCCTCAG |
| 410617 | 3-14-3 | 390 | 22201 | 22220 | 0 | GGGTCCCCATGCTGGCCTCA |
| 410618 | 3-14-3 | 391 | 22202 | 22221 | 0 | CGGGTCCCCATGCTGGCCTC |
| 410619 | 3-14-3 | 392 | 22203 | 22222 | 0 | ACGGGTCCCCATGCTGGCCT |
| 410620 | 3-14-3 | 393 | 22205 | 22224 | 0 | ACACGGGTCCCCATGCTGGC |
| 410621 | 3-14-3 | 394 | 22206 | 22225 | 0 | GACACGGGTCCCCATGCTGG |
| 410622 | 3-14-3 | 395 | 22207 | 22226 | 0 | GGACACGGGTCCCCATGCTG |
| 410623 | 3-14-3 | 396 | 22208 | 22227 | 0 | TGGACACGGGTCCCCATGCT |
| 410624 | 3-14-3 | 397 | 22209 | 22228 | 0 | GTGGACACGGGTCCCCATGC |
| 410625 | 3-14-3 | 398 | 22210 | 22229 | 0 | AGTGGACACGGGTCCCCATG |
| 410626 | 3-14-3 | 399 | 22211 | 22230 | 0 | CAGTGGACACGGGTCCCCAT |
| 410627 | 3-14-3 | 400 | 22212 | 22231 | 0 | GCAGTGGACACGGGTCCCCA |
| 410628 | 3-14-3 | 401 | 22213 | 22232 | 0 | GGCAGTGGACACGGGTCCCC |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO: 2 | 3' Target Site on SEQ ID NO: 2 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 410629 | 3-14-3 | 402 | 22214 | 22233 | 0 | TGGCAGTGGACACGGGTCCC |
| 410630 | 3-14-3 | 403 | 22215 | 22234 | 0 | GTGGCAGTGGACACGGGTCC |
| 410631 | 3-14-3 | 404 | 22216 | 22235 | 0 | GGTGGCAGTGGACACGGGTC |
| 410632 | 3-14-3 | 405 | 22217 | 22236 | 0 | TGGTGGCAGTGGACACGGGT |
| 410633 | 3-14-3 | 411 | 24096 | 24115 | 0 | ACTTTGCATTCCAGACCTGG |
| 410634 | 3-14-3 | 412 | 24097 | 24116 | 0 | GACTTTGCATTCCAGACCTG |
| 410635 | 3-14-3 | 413 | 24098 | 24117 | 0 | TGACTTTGCATTCCAGACCT |
| 410636 | 3-14-3 | 414 | 24099 | 24118 | 0 | TTGACTTTGCATTCCAGACC |
| 410637 | 3-14-3 | 419 | 26112 | 26131 | 0 | CAGATGGCAACGGCTGTCAC |
| 410638 | 3-14-3 | 420 | 26113 | 26132 | 0 | GCAGATGGCAACGGCTGTCA |
| 410639 | 3-14-3 | 421 | 26114 | 26133 | 0 | AGCAGATGGCAACGGCTGTC |
| 410640 | 3-14-3 | 422 | 26115 | 26134 | 0 | CAGCAGATGGCAACGGCTGT |
| 410641 | 3-14-3 | 423 | 26116 | 26135 | 0 | GCAGCAGATGGCAACGGCTG |
| 410642 | 3-14-3 | 424 | 26118 | 26137 | 0 | CGGCAGCAGATGGCAACGGC |
| 410643 | 3-14-3 | 425 | 26119 | 26138 | 0 | CCGGCAGCAGATGGCAACGG |
| 410644 | 3-14-3 | 426 | 26120 | 26139 | 0 | TCCGGCAGCAGATGGCAACG |
| 410645 | 3-14-3 | 427 | 26121 | 26140 | 0 | CTCCGGCAGCAGATGGCAAC |
| 410646 | 3-14-3 | 428 | 26122 | 26141 | 0 | GCTCCGGCAGCAGATGGCAA |

In certain embodiments, gap-widened antisense compounds are targeted to a PCSK9 nucleic acid. In certain such embodiments, gap-widened antisense compounds are targeted to SEQ ID NO: 2. In certain such embodiments, the nucleotide sequences illustrated in Table 6 have a 2-13-5 gap-widened motif. Table 9 illustrates gap-widened antisense compounds targeted to SEQ ID NO: 2, having a 2-13-5 motif, where the gap segment comprises 2'-deoxynucleotides and each wing segment comprises nucleotides comprising a 2'-O-methoxyethyl sugar modification. Internucleoside linkages are phosphorthioate, and cytidines are 5-methylcytidines.

**Table 9: Gapmer antisense compounds having a 2-13-5 motif targeted to SEQ ID NO: 2**

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO:2 | 3' Target Site on SEQ ID NO: 2 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 410647 | 2-13-5 | 184 | 6534 | 6553 | 0 | TGAGGTATCCCCGGCGGGCA |
| 410648 | 2-13-5 | 185 | 6535 | 6554 | 0 | GTGAGGTATCCCCGGCGGGC |
| 410649 | 2-13-5 | 186 | 6536 | 6555 | 0 | GGTGAGGTATCCCCGGCGGG |
| 410650 | 2-13-5 | 11 | 6537 | 6556 | 0 | TGGTGAGGTATCCCCGGCGG |
| 410651 | 2-13-5 | 187 | 6538 | 6557 | 0 | TTGGTGAGGTATCCCCGGCG |
| 410652 | 2-13-5 | 188 | 6539 | 6558 | 0 | CTTGGTGAGGTATCCCCGGC |
| 410653 | 2-13-5 | 189 | 6540 | 6559 | 0 | TCTTGGTGAGGTATCCCCGG |
| 410654 | 2-13-5 | 190 | 6541 | 6560 | 0 | ATCTTGGTGAGGTATCCCCG |
| 410655 | 2-13-5 | 191 | 6542 | 6561 | 0 | GATCTTGGTGAGGTATCCCC |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO:2 | 3' Target Site on SEQ ID NO: 2 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 410656 | 2-13-5 | 12 | 6543 | 6562 | 0 | GGATCTTGGTGAGGTATCCC |
| 410657 | 2-13-5 | 192 | 6544 | 6563 | 0 | AGGATCTTGGTGAGGTATCC |
| 410658 | 2-13-5 | 243 | 15291 | 15310 | 0 | GCCACGCCGGCATCCCGGCC |
| 410659 | 2-13-5 | 244 | 15292 | 15311 | 0 | GGCCACGCCGGCATCCCGGC |
| 410660 | 2-13-5 | 245 | 15293 | 15312 | 0 | TGGCCACGCCGGCATCCCGG |
| 410661 | 2-13-5 | 246 | 15294 | 15313 | 0 | TTGGCCACGCCGGCATCCCG |
| 410662 | 2-13-5 | 247 | 15295 | 15314 | 0 | CTTGGCCACGCCGGCATCCC |
| 410663 | 2-13-5 | 248 | 15296 | 15315 | 0 | CCTTGGCCACGCCGGCATCC |
| 410664 | 2-13-5 | 249 | 15297 | 15316 | 0 | CCCTTGGCCACGCCGGCATC |
| 410665 | 2-13-5 | 28 | 15298 | 15317 | 0 | ACCCTTGGCCACGCCGGCAT |
| 410666 | 2-13-5 | 250 | 15299 | 15318 | 0 | CACCCTTGGCCACGCCGGCA |
| 410667 | 2-13-5 | 251 | 15300 | 15319 | 0 | GCACCCTTGGCCACGCCGGC |
| 410668 | 2-13-5 | 252 | 15301 | 15320 | 0 | GGCACCCTTGGCCACGCCGG |
| 410669 | 2-13-5 | 253 | 15302 | 15321 | 0 | TGGCACCCTTGGCCACGCCG |
| 410670 | 2-13-5 | 254 | 15303 | 15322 | 0 | CTGGCACCCTTGGCCACGCC |
| 410671 | 2-13-5 | 255 | 15304 | 15323 | 0 | GCTGGCACCCTTGGCCACGC |
| 410672 | 2-13-5 | 348 | 20719 | 20738 | 0 | AGGGAACCAGGCCTCATTGA |
| 410673 | 2-13-5 | 349 | 20720 | 20739 | 0 | CAGGGAACCAGGCCTCATTG |
| 410674 | 2-13-5 | 49 | 20721 | 20740 | 0 | TCAGGGAACCAGGCCTCATT |
| 410675 | 2-13-5 | 350 | 20722 | 20741 | 0 | CTCAGGGAACCAGGCCTCAT |
| 410676 | 2-13-5 | 351 | 20723 | 20742 | 0 | CCTCAGGGAACCAGGCCTCA |
| 410677 | 2-13-5 | 352 | 20724 | 20743 | 0 | TCCTCAGGGAACCAGGCCTC |
| 410678 | 2-13-5 | 353 | 20725 | 20744 | 0 | GTCCTCAGGGAACCAGGCCT |
| 410679 | 2-13-5 | 50 | 20726 | 20745 | 0 | GGTCCTCAGGGAACCAGGCC |
| 410680 | 2-13-5 | 354 | 20727 | 20746 | 0 | TGGTCCTCAGGGAACCAGGC |
| 410681 | 2-13-5 | 355 | 20728 | 20747 | 0 | CTGGTCCTCAGGGAACCAGG |
| 410682 | 2-13-5 | 356 | 20729 | 20748 | 0 | GCTGGTCCTCAGGGAACCAG |
| 410683 | 2-13-5 | 376 | 22133 | 22152 | 0 | CACCTGGCAATGGCGTAGAC |
| 410684 | 2-13-5 | 377 | 22134 | 22153 | 0 | GCACCTGGCAATGGCGTAGA |
| 410685 | 2-13-5 | 378 | 22135 | 22154 | 0 | AGCACCTGGCAATGGCGTAG |
| 410686 | 2-13-5 | 379 | 22136 | 22155 | 0 | CAGCACCTGGCAATGGCGTA |
| 410687 | 2-13-5 | 380 | 22137 | 22156 | 0 | GCAGCACCTGGCAATGGCGT |
| 410688 | 2-13-5 | 381 | 22138 | 22157 | 0 | GGCAGCACCTGGCAATGGCG |
| 410689 | 2-13-5 | 382 | 22139 | 22158 | 0 | AGGCAGCACCTGGCAATGGC |
| 410690 | 2-13-5 | 383 | 22140 | 22159 | 0 | CAGGCAGCACCTGGCAATGG |
| 410691 | 2-13-5 | 384 | 22141 | 22160 | 0 | GCAGGCAGCACCTGGCAATG |
| 410692 | 2-13-5 | 58 | 22142 | 22161 | 0 | AGCAGGCAGCACCTGGCAAT |
| 410693 | 2-13-5 | 385 | 22143 | 22162 | 0 | TAGCAGGCAGCACCTGGCAA |
| 410694 | 2-13-5 | 388 | 22199 | 22218 | 0 | GTCCCCATGCTGGCCTCAGC |
| 410695 | 2-13-5 | 389 | 22200 | 22219 | 0 | GGTCCCCATGCTGGCCTCAG |
| 410696 | 2-13-5 | 390 | 22201 | 22220 | 0 | GGGTCCCCATGCTGGCCTCA |
| 410697 | 2-13-5 | 391 | 22202 | 22221 | 0 | CGGGTCCCCATGCTGGCCTC |
| 410698 | 2-13-5 | 392 | 22203 | 22222 | 0 | ACGGGTCCCCATGCTGGCCT |
| 410699 | 2-13-5 | 59 | 22204 | 22223 | 0 | CACGGGTCCCCATGCTGGCC |
| 410700 | 2-13-5 | 393 | 22205 | 22224 | 0 | ACACGGGTCCCCATGCTGGC |
| 410701 | 2-13-5 | 394 | 22206 | 22225 | 0 | GACACGGGTCCCCATGCTGG |
| 410702 | 2-13-5 | 395 | 22207 | 22226 | 0 | GGACACGGGTCCCCATGCTG |
| 410703 | 2-13-5 | 396 | 22208 | 22227 | 0 | TGGACACGGGTCCCCATGCT |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO:2 | 3' Target Site on SEQ ID NO: 2 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 410704 | 2-13-5 | 397 | 22209 | 22228 | 0 | GTGGACACGGGTCCCCATGC |
| 410705 | 2-13-5 | 398 | 22210 | 22229 | 0 | AGTGGACACGGGTCCCCATG |
| 410706 | 2-13-5 | 399 | 22211 | 22230 | 0 | CAGTGGACACGGGTCCCCAT |
| 410707 | 2-13-5 | 400 | 22212 | 22231 | 0 | GCAGTGGACACGGGTCCCCA |
| 410708 | 2-13-5 | 401 | 22213 | 22232 | 0 | GGCAGTGGACACGGGTCCCC |
| 410709 | 2-13-5 | 402 | 22214 | 22233 | 0 | TGGCAGTGGACACGGGTCCC |
| 410710 | 2-13-5 | 403 | 22215 | 22234 | 0 | GTGGCAGTGGACACGGGTCC |
| 410711 | 2-13-5 | 404 | 22216 | 22235 | 0 | GGTGGCAGTGGACACGGGTC |
| 410712 | 2-13-5 | 405 | 22217 | 22236 | 0 | TGGTGGCAGTGGACACGGGT |
| 410713 | 2-13-5 | 60 | 24095 | 24114 | 0 | CTTTGCATTCCAGACCTGGG |
| 410714 | 2-13-5 | 411 | 24096 | 24115 | 0 | ACTTTGCATTCCAGACCTGG |
| 410715 | 2-13-5 | 412 | 24097 | 24116 | 0 | GACTTTGCATTCCAGACCTG |
| 410716 | 2-13-5 | 413 | 24098 | 24117 | 0 | TGACTTTGCATTCCAGACCT |
| 410717 | 2-13-5 | 414 | 24099 | 24118 | 0 | TTGACTTTGCATTCCAGACC |
| 410718 | 2-13-5 | 61 | 24100 | 24119 | 0 | CTTGACTTTGCATTCCAGAC |
| 410719 | 2-13-5 | 419 | 26112 | 26131 | 0 | CAGATGGCAACGGCTGTCAC |
| 410720 | 2-13-5 | 420 | 26113 | 26132 | 0 | GCAGATGGCAACGGCTGTCA |
| 410721 | 2-13-5 | 421 | 26114 | 26133 | 0 | AGCAGATGGCAACGGCTGTC |
| 410722 | 2-13-5 | 422 | 26115 | 26134 | 0 | CAGCAGATGGCAACGGCTGT |
| 410723 | 2-13-5 | 423 | 26116 | 26135 | 0 | GCAGCAGATGGCAACGGCTG |
| 410724 | 2-13-5 | 62 | 26117 | 26136 | 0 | GGCAGCAGATGGCAACGGCT |
| 410725 | 2-13-5 | 424 | 26118 | 26137 | 0 | CGGCAGCAGATGGCAACGGC |
| 410726 | 2-13-5 | 425 | 26119 | 26138 | 0 | CCGGCAGCAGATGGCAACGG |
| 410727 | 2-13-5 | 426 | 26120 | 26139 | 0 | TCCGGCAGCAGATGGCAACG |
| 410728 | 2-13-5 | 427 | 26121 | 26140 | 0 | CTCCGGCAGCAGATGGCAAC |
| 410729 | 2-13-5 | 428 | 26122 | 26141 | 0 | GCTCCGGCAGCAGATGGCAA |

In certain embodiments, gap-widened antisense compounds are targeted to a PCSK9 nucleic acid. In certain such embodiments, gap-widened antisense compounds are targeted to SEQ ID NO: 2. In certain such embodiments, the nucleotide sequences illustrated in Table 6 have a 3-13-4 gap-widened motif. Table 10 illustrates gap-widened antisense compounds targeted to SEQ ID NO: 2, having a 3-13-4 motif, where the gap segment comprises 2'-deoxynucleotides and each wing segment comprises nucleotides comprising a 2'-O-methoxyethyl sugar modification. Internucleoside linkages are phosphorthioate, and cytidines are 5-methylcytidines.

**Table 10: Gapmer antisense compounds having a 3-13-4 motif targeted to SEQ ID NO: 2**

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO:2 | 3' Target Site on SEQ ID NO: 2 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO:2 | 3' Target Site on SEQ ID NO: 2 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 405526 | 3-13-4 | 236 | 15257 | 15276 | 0 | CCAGGTGGGTGCCATGACTG |
| 405557 | 3-13-4 | 50 | 20726 | 20745 | 0 | GGTCCTCAGGGAACCAGGCC |
| 405564 | 3-13-4 | 373 | 21183 | 21202 | 0 | AACTGGAGCAGCTCAGCAGC |

The following embodiments set forth target regions of PCSK9 nucleic acids. Also illustrated are examples of antisense compounds targeted to the target regions. It is understood that the sequence set forth in each SEQ ID NO is independent of any modification to a sugar moiety, an internucleoside linkage, or a nucleobase. As such, antisense compounds defined by a SEQ ID NO may comprise, independently, one or more modifications to a sugar moiety, an internucleoside linkage, or a nucleobase. Antisense compounds described by Isis Number (Isis No) indicate a combination of nucleobase sequence and motif.

In certain embodiments, antisense compounds target a range of a PCSK9 nucleic acid. In certain embodiment, such compounds contain at least an 8 nucleotide core sequence in common. In certain embodiments, such compounds sharing at least an 8 nucleotide core sequence targets the following nucleotide regions of SEQ ID: 2: 2274-2400, 2274-2575, 2433-2570, 2433-2579, 2549-2575, 2552-2579, 2585-2638, 2605-2638, 3056-3075, 4150-5159, 4306-4325, 5590-5618, 5667-5686, 6444-6463, 6482-6518, 6492-6518, 6528-6555, 6528-6623, 6534-6561, 6535-6562, 6536-6563, 6537-6563, 6538-6565, 6539-6565, 6540-6567, 6541-6567, 6542-6569, 6546-6573, 6557-6584, 6575-6602, 6585-6611, 6594-6621, 6596-6623, 6652-6671, 7099-7118, 7556-7584, 8836-8855, 8948-8967, 9099-9118, 9099-9168, 9130-9168, 9207-9233, 9207-9235, 9209-9235, 10252-10271, 10633-10652, 11308-11491, 12715-12734, 12928-12947, 13681-13700, 13746-13779, 13816-13847, 13903-13945, 13977-14141, 14179-14198, 14267-14286, 14397-14423, 14441-14460, 14494-14513, 14494-14543, 14524-14543, 14601-14650, 14670-14700, 14675-14700, 14801-14828, 14877-14912, 14877-14915, 14877-14973, 14916-14943, 14916-14973, 14925-14951, 14934-14963, 14946-14973, 14979-14998, 15254-15280, 15254-15328, 15264-15290, 15279-15305, 15291-15318, 15292-15319, 15293-15320, 15294-15321, 15294-15321, 15295-15322, 15296-15323, 15297-15323, 15298-15323, 15299-15323, 15300-15323, 15301-15328, 15330-15355, 15330-15490, 15339-15366, 15358-15490, 16134-16153, 16668-16687, 17267-17286, 18377-18427, 18561-18580, 18591-18618, 18591-18646, 18591-18668, 18695-18746, 18705-18730, 18709-18736, 18719-18746, 19203-20080, 19931-19952, 19954-19981, 19964-19990, 19973-19999, 19982-20009, 19992-20016, 20016-20042, 20025-20052, 20036-20062, 20045-20070, 20100-20119, 20188-20207, 20624-20650, 20624-20759, 20629-20804,

20633-20660, 20635-20781, 20643-20662, 20657-20676, 20670-20697, 20680-20706, 20683-20781, 20689-20715, 20698-20725, 20709-20736, 20717-20744, 20718-20745, 20719-20746, 20720-20747, 20721-20748, 20722-20749, 20727-20752, 20735-20759, 20762-21014, 20785-21014, 21082-21107, 21082-21152, 21091-21114, 21118-21144, 21127-21152, 21181-21209, 21181-21211, 21183-21211, 21481-21500, 21589-21608, 21692-21719, 22000-22227, 22096-22115, 22096-22223, 22096-22311, 22133-22160, 22133-22163, 22134-22161, 22135-22162, 22136-22163, 22137-22163, 22138-22163, 22189-22239, 22199-22226, 22199-22227, 22200-22227, 22201-22228, 22202-22229, 22203-22230, 22204-22231, 22205-22232, 22206-22233, 22207-22234, 22208-22235, 22209-22236, 22210-22236, 22210-22239, 22211-22236, 22212-22239, 22292-22311, 23985-24054, 24035-24134, 24095-24121, 24858-24877, 24907-24926, 25413-25432, 25994-26013, 26112-26139, 26112-26161, 26112-27303, 26113-26140, 26114-26141, 26115-26141, 26116-26141, 26117-26141, 26117-26475, 26118-26141, 26120-26141, 26132-26151, 26142-26161, 26217-26241, 26311-26335, 26389-26432, 26456-26576, 26635-26662, 26707-26734, 26707-26736, 26790-26820, 27034-27263, 27279-27303, or 27350-27376.

In certain embodiments, a target region is nucleotides 2274-2400 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 2274-2400 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 4 or 5. In certain such embodiments, an antisense compound targeted to nucleotides 2274-2400 of SEQ ID NO: 2 is selected from ISIS NOs: 395149, 399871, 395150 or 399872.

In certain embodiments, a target region is nucleotides 2274-2575 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 2274-2575 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 4, 5, 6, 7, 8, 159, 160, 162, 163, 164, 165, 166, 167, 168 or 169. In certain such embodiments, an antisense compound targeted to nucleotides 2274-2575 of SEQ ID NO: 2 is selected from ISIS NOs: 395149, 399871, 395150, 399872, 410742, 405999, 395151, 399873, 405861, 405862, 405863, 405864, 395152, 399874, 405865, 405866, 405867, 405868, 399793, or 399949.

In certain embodiments, a target region is nucleotides 2433-2570 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 2433-2570 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 6, 7, 159, 160, 162, 163, 164, 165, 166, or 167. In certain such embodiments, an antisense compound targeted to nucleotides 2433-2570 of SEQ

ID NO: 2 is selected from ISIS NOs: 395151, 395152, 399873, 399874, 405861, 405862, 405863, 405864, 405865, 405866, 405999, or 410742.

In certain embodiments, a target region is nucleotides 2433-2579 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 2433-2579 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 6, 7, 8, 159, 160, 162, 163, 164, 165, 166, 167, 168, 169, or 170. In certain such embodiments, an antisense compound targeted to nucleotides 2433-2579 of SEQ ID NO: 2 is selected from ISIS NOs: 395151, 395152, 399793, 399873, 399874, 399949, 405861, 405862, 405863, 405864, 405865, 405866, 405867, 405868, 405999, 410742, or 410743.

In certain embodiments, a target region is nucleotides 2549-2575 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 2549-2575 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 7, 8, 166, 167, 168 or 169. In certain such embodiments, an antisense compound targeted to nucleotides 2549-2575 of SEQ ID NO: 2 is selected from ISIS NOs: 395152, 399793, 399874, 399949, 405865, 405866, 405867, or 405868.

In certain embodiments, a target region is nucleotides 2552-2579 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 2552-2579 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 8, 168, 169 or 170. In certain such embodiments, an antisense compound targeted to nucleotides 2552-2579 of SEQ ID NO: 2 is selected from ISIS NOs: 399793, 399949, 405867, 405868, or 410743.

In certain embodiments, a target region is nucleotides 2585-2638 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 2585-2638 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 9, 171 or 172. In certain such embodiments, an antisense compound targeted to nucleotides 2585-2638 of SEQ ID NO: 2 is selected from ISIS NOs: 395153, 399875, 410744, or 410745.

In certain embodiments, a target region is nucleotides 2605-2638 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 2605-2638 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 8, 168 or 169. In certain such embodiments, an

antisense compound targeted to nucleotides 2605-2638 of SEQ ID NO: 2 is selected from ISIS NOs: 410745, 395153, or 399875.

In certain embodiments, a target region is nucleotides 3056-3075 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 3056-3075 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 107. In certain such embodiments, an antisense compound targeted to nucleotides 3056-3075 of SEQ ID NO: 2 is selected from ISIS NOs: 399837 or 399993.

In certain embodiments, a target region is nucleotides 4150-5159 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 4150-5159 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 106. In certain such embodiments, an antisense compound targeted to nucleotides 4150-5159 of SEQ ID NO: 2 is selected from ISIS NOs: 399839 or 399995.

In certain embodiments, a target region is nucleotides 4306-4325 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 4306-4325 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 80. In certain such embodiments, an antisense compound targeted to nucleotides 4306-4325 of SEQ ID NO: 2 is selected from ISIS NOs: 399838 or 399994.

In certain embodiments, a target region is nucleotides 5590-5618 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 5590-5618 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 102 or 121. In certain such embodiments, an antisense compound targeted to nucleotides 5590-5618 of SEQ ID NO: 2 is selected from ISIS NOs: 395221, 399840, 399943, or 399996.

In certain embodiments, a target region is nucleotides 5667-5686 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 5667-5686 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 94. In certain such embodiments, an antisense compound targeted to nucleotides 5667-5686 of SEQ ID NO: 2 is selected from ISIS NOs: 399841 or 399997.

In certain embodiments, a target region is nucleotides 6444-6463 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 6444-6463 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 176. In certain such embodiments, an antisense compound targeted to nucleotides 6444-6463 of SEQ ID NO: 2 is selected from ISIS NOs: 410746.

In certain embodiments, a target region is nucleotides 6482-6518 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 6482-6518 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 10, 177, 178, 179, 180 or 181. In certain such embodiments, an antisense compound targeted to nucleotides 6482-6518 of SEQ ID NO: 2 is selected from ISIS NOs: 395154, 399876, 406003, 406004, 406005, 406006 or 410747.

In certain embodiments, a target region is nucleotides 6492-6518 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 6492-6518 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 10, 178, 179, 180 or 181. In certain such embodiments, an antisense compound targeted to nucleotides 6492-6518 of SEQ ID NO: 2 is selected from ISIS NOs: 395154, 399876, 406003, 406004, 406005 or 406006.

In certain embodiments, a target region is nucleotides 6528-6555 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 6528-6555 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 182, 183, 184, 185 or 186. In certain such embodiments, an antisense compound targeted to nucleotides 6528-6555 of SEQ ID NO: 2 is selected from ISIS NOs: 406007, 410529, 410530, 410531, 410574, 410575, 410576, 410647, 410648, 410649 or 410748.

In certain embodiments, a target region is nucleotides 6528-6623 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 6528-6623 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 11, 12, 13, 13, 14, 15, 16, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, or 207. In certain such embodiments, an antisense compound targeted to nucleotides 6528-6623 of SEQ ID NO: 2 is selected from ISIS NOs: 395155, 395156, 395157, 399794, 399795, 399796, 399877, 399878, 399879, 399950, 399951, 399952, 406007, 406008,

406009, 406010, 406011, 406012, 406013, 406014, 406015, 406016, 406017, 406018, 406019, 406020, 410529, 410530, 410531, 410532, 410533, 410534, 410535, 410574, 410575, 410576, 410577, 410578, 410579, 410580, 410581, 410582, 410647, 410648, 410649, 410650, 410651, 410652, 410653, 410654, 410655, 410656, 410657, 410730, 410731, 410748, 410749, or 410750.

In certain embodiments, a target region is nucleotides 6534-6561 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 6534-6561 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 11, 184, 185, 186, 187, 188, 189, 190 or 191. In certain such embodiments, an antisense compound targeted to nucleotides 6534-6561 of SEQ ID NO: 2 is selected from ISIS NOs: 395155, 399877, 406008, 406009, 410529, 410530, 410531, 410532, 410533, 410534, 410574, 410575, 410576, 410577, 410578, 410579, 410580, 410581, 410647, 410648, 410649, 410650, 410651, 410652, 410653, 410654, or 410655.

In certain embodiments, a target region is nucleotides 6535-6562 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 6535-6562 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 11, 12, 185, 186, 187, 188, 189, 190 or 191. In certain such embodiments, an antisense compound targeted to nucleotides 6535-6562 of SEQ ID NO: 2 is selected from ISIS NOs: 395155, 399794, 399877, 399950, 406008, 406009, 410530, 410531, 410532, 410533, 410534, 410575, 410576, 410577, 410578, 410579, 410580, 410581, 410648, 410649, 410650, 410651, 410652, 410653, 410654, 410655 or 410656.

In certain embodiments, a target region is nucleotides 6536-6563 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 6536-6563 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 11, 12, 186, 187, 188, 189, 190, 191 or 192. In certain such embodiments, an antisense compound targeted to nucleotides 6536-6563 of SEQ ID NO: 2 is selected from ISIS NOs: 395155, 399794, 399877, 399950, 406008, 406009, 410531, 410532, 410533, 410534, 410535, 410576, 410577, 410578, 410579, 410580, 410581, 410582, 410649, 410650, 410651, 410652, 410653, 410654, 410655, 410656 or 410657.

In certain embodiments, a target region is nucleotides 6537-6563 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 6537-6563 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 11, 12, 187, 188, 189, 190, 191 or 192. In

certain such embodiments, an antisense compound targeted to nucleotides 6537-6563 of SEQ ID NO: 2 is selected from ISIS NOs: 395155, 399794, 399877, 399950, 406008, 406009, 410532, 410533, 410534, 410535, 410577, 410578, 410579, 410580, 410581, 410582, 410650, 410651, 410652, 410653, 410654, 410655, 410656 or 410657.

In certain embodiments, a target region is nucleotides 6538-6565 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 6538-6565 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 12, 187, 188, 189, 190, 191, 192 or 193. In certain such embodiments, an antisense compound targeted to nucleotides 6538-6565 of SEQ ID NO: 2 is selected from ISIS NOs: 399794, 399950, 406008, 406009, 406010, 410532, 410533, 410534, 410535, 410577, 410578, 410579, 410580, 410581, 410582, 410651, 410652, 410653, 410654, 410655, 410656 or 410657.

In certain embodiments, a target region is nucleotides 6539-6565 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 6539-6565 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 12, 188, 189, 190, 191, 192 or 193. In certain such embodiments, an antisense compound targeted to nucleotides 6539-6565 of SEQ ID NO: 2 is selected from ISIS NOs: 399794, 399950, 406008, 406009, 406010, 410533, 410534, 410535, 410578, 410579, 410580, 410581, 410582, 410652, 410653, 410654, 410655, 410656 or 410657.

In certain embodiments, a target region is nucleotides 6540-6567 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 6540-6567 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 12, 189, 190, 191, 192, 193 or 194. In certain such embodiments, an antisense compound targeted to nucleotides 6540-6567 of SEQ ID NO: 2 is selected from ISIS NOs: 399794, 399950, 406009, 406010, 406011, 410533, 410534, 410535, 410579, 410580, 410581, 410582, 410653, 410654, 410655, 410656 or 410657.

In certain embodiments, a target region is nucleotides 6541-6567 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 6541-6567 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 12, 190, 191, 192, 193 or 194. In certain such embodiments, an antisense compound targeted to nucleotides 6541-6567 of SEQ ID NO: 2 is selected from ISIS NOs: 399794, 399950, 406009, 406010, 406011, 410534, 410535, 410580, 410581, 410582, 410654, 410655, 410656 or 410657.

In certain embodiments, a target region is nucleotides 6542-6569 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 6542-6569 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 12, 191, 192, 193, 194 or 195. In certain such embodiments, an antisense compound targeted to nucleotides 6542-6569 of SEQ ID NO: 2 is selected from ISIS NOs: 399794, 399950, 406010, 406011, 406012, 410534, 410535, 410581, 410582, 410655, 410656 or 410657.

In certain embodiments, a target region is nucleotides 6546-6573 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 6546-6573 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 13, 193, 194, 195 or 196. In certain such embodiments, an antisense compound targeted to nucleotides 6546-6573 of SEQ ID NO: 2 is selected from ISIS NOs: 399795, 399951, 406010, 406011, 406012 or 406013.

In certain embodiments, a target region is nucleotides 6557-6584 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 6557-6584 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 14, 197 or 198. In certain such embodiments, an antisense compound targeted to nucleotides 6557-6584 of SEQ ID NO: 2 is selected from ISIS NOs: 395156, 399878, 410749 or 410750.

In certain embodiments, a target region is nucleotides 6575-6602 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 6575-6602 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 15 or 198. In certain such embodiments, an antisense compound targeted to nucleotides 6575-6602 of SEQ ID NO: 2 is selected from ISIS NOs: 395157, 399879 or 410750.

In certain embodiments, a target region is nucleotides 6585-6611 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 6585-6611 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 16, 199, 200 or 201. In certain such embodiments, an antisense compound targeted to nucleotides 6585-6611 of SEQ ID NO: 2 is selected from ISIS NOs: 399796, 399952, 406014, 406015 or 406016.

In certain embodiments, a target region is nucleotides 6594-6621 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 6594-6621 SEQ ID NO:

2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 202, 203, 204, 205 or 206. In certain such embodiments, an antisense compound targeted to nucleotides 6594-6621 of SEQ ID NO: 2 is selected from ISIS NOs: 406017, 406018, 406019, 406020 or 410730.

In certain embodiments, a target region is nucleotides 6596-6623 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 6596-6623 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 203, 204, 205, 206 or 207. In certain such embodiments, an antisense compound targeted to nucleotides 6596-6623 of SEQ ID NO: 2 is selected from ISIS NOs: 406017, 406018, 406019, 406020 or 410731.

In certain embodiments, a target region is nucleotides 6652-6671 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 6652-6671 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 108. In certain such embodiments, an antisense compound targeted to nucleotides 6652-6671 of SEQ ID NO: 2 is selected from ISIS NOs: 399842 or 399998.

In certain embodiments, a target region is nucleotides 7099-7118 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 7099-7118 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 114. In certain such embodiments, an antisense compound targeted to nucleotides 7099-7118 of SEQ ID NO: 2 is selected from ISIS NOs: 399843 or 399999.

In certain embodiments, a target region is nucleotides 7556-7584 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 7556-7584 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 91 or 131. In certain such embodiments, an antisense compound targeted to nucleotides 7556-7584 of SEQ ID NO: 2 is selected from ISIS NOs: 399844, 399845, 400000 or 400001.

In certain embodiments, a target region is nucleotides 8836-8855 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 8836-8855 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 145. In certain such embodiments, an antisense

compound targeted to nucleotides 8836-8855 of SEQ ID NO: 2 is selected from ISIS NOs: 399846 or 400002.

In certain embodiments, a target region is nucleotides 8948-8967 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 8948-8967 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 90. In certain such embodiments, an antisense compound targeted to nucleotides 8948-8967 of SEQ ID NO: 2 is selected from ISIS NOs: 399847 or 400003.

In certain embodiments, a target region is nucleotides 9099-9118 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 9099-9118 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 125. In certain such embodiments, an antisense compound targeted to nucleotides 9099-9118 of SEQ ID NO: 2 is selected from ISIS NOs: 399848 or 400004.

In certain embodiments, a target region is nucleotides 9099-9168 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 9099-9168 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 17, 125 or 209. In certain such embodiments, an antisense compound targeted to nucleotides 9099-9168 of SEQ ID NO: 2 is selected from ISIS NOs: 395158, 399848, 399880, 400004 or 410752.

In certain embodiments, a target region is nucleotides 9130-9168 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 9130-9168 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 17. In certain such embodiments, an antisense compound targeted to nucleotides 9130-9168 of SEQ ID NO: 2 is selected from ISIS NOs: 395158 or 399880.

In certain embodiments, a target region is nucleotides 9207-9233 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 9207-9233 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 18, 210, 211, 212 or 213. In certain such embodiments, an antisense compound targeted to nucleotides 9207-9233 of SEQ ID NO: 2 is selected from ISIS NOs: 395159, 399881, 406021, 406022, 406023 or 406024.

In certain embodiments, a target region is nucleotides 9207-9235 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 9207-9235 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 18, 210, 211, 212, 213 or 214. In certain such embodiments, an antisense compound targeted to nucleotides 9207-9235 of SEQ ID NO: 2 is selected from ISIS NOs: 395159, 399881, 406021, 406022, 406023, 406024 or 410732.

In certain embodiments, a target region is nucleotides 9209-9235 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 9209-9235 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 18, 211, 212, 213 or 214. In certain such embodiments, an antisense compound targeted to nucleotides 9209-9235 of SEQ ID NO: 2 is selected from ISIS NOs: 395159, 399881, 406022, 406023, 406024 or 410732.

In certain embodiments, a target region is nucleotides 10252-10271 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 10252-10271 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 148. In certain such embodiments, an antisense compound targeted to nucleotides 10252-10271 of SEQ ID NO: 2 is selected from ISIS NOs: 399849 or 400005.

In certain embodiments, a target region is nucleotides 10633-10652 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 10633-10652 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 127. In certain such embodiments, an antisense compound targeted to nucleotides 10633-10652 of SEQ ID NO: 2 is selected from ISIS NOs: 395222 or 399944.

In certain embodiments, a target region is nucleotides 11308-11491 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 11308-11491 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 79 or 84. In certain such embodiments, an antisense compound targeted to nucleotides 11308-11491 of SEQ ID NO: 2 is selected from ISIS NOs: 395223, 399850, 399945 or 400006.

In certain embodiments, a target region is nucleotides 12715-12734 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 12715-12734 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid

comprises a nucleotide sequence selected from SEQ ID NOs: 88. In certain such embodiments, an antisense compound targeted to nucleotides 12715-12734 of SEQ ID NO: 2 is selected from ISIS NOs: 399851 or 400007.

In certain embodiments, a target region is nucleotides 12928-12947 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 12928-12947 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 111. In certain such embodiments, an antisense compound targeted to nucleotides 12928-12947 of SEQ ID NO: 2 is selected from ISIS NOs: 399852 or 400008.

In certain embodiments, a target region is nucleotides 13681-13700 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 13681-13700 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 85. In certain such embodiments, an antisense compound targeted to nucleotides 13681-13700 of SEQ ID NO: 2 is selected from ISIS NOs: 395201 or 399923.

In certain embodiments, a target region is nucleotides 13746-13779 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 13746-13779 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 100 or 116. In certain such embodiments, an antisense compound targeted to nucleotides 13746-13779 of SEQ ID NO: 2 is selected from ISIS NOs: 399827, 399828, 399983 or 399984.

In certain embodiments, a target region is nucleotides 13816-13847 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 13816-13847 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 117 or 129. In certain such embodiments, an antisense compound targeted to nucleotides 13816-13847 of SEQ ID NO: 2 is selected from ISIS NOs: 395202, 399829, 399924 or 399985.

In certain embodiments, a target region is nucleotides 13903-13945 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 13903-13945 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 81 or 110. In certain such embodiments, an antisense compound targeted to nucleotides 13903-13945 of SEQ ID NO: 2 is selected from ISIS NOs: 395203, 399830, 399925 or 399986.

In certain embodiments, a target region is nucleotides 13977-14141 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 13977-14141 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 83, 136, 137, 140 or 152. In certain such embodiments, an antisense compound targeted to nucleotides 13977-14141 of SEQ ID NO: 2 is selected from ISIS NOs: 395204, 395205, 395206, 399831, 399832, 399926, 399927, 399928, 399987 or 399988.

In certain embodiments, a target region is nucleotides 14179-14198 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 14179-14198 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 132. In certain such embodiments, an antisense compound targeted to nucleotides 14179-14198 of SEQ ID NO: 2 is selected from ISIS NOs: 395207 or 399929.

In certain embodiments, a target region is nucleotides 14267-14286 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 14267-14286 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 139. In certain such embodiments, an antisense compound targeted to nucleotides 14267-14286 of SEQ ID NO: 2 is selected from ISIS NOs: 395208 or 399930.

In certain embodiments, a target region is nucleotides 14397-14423 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 14397-14423 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 92 or 142. In certain such embodiments, an antisense compound targeted to nucleotides 14397-14423 of SEQ ID NO: 2 is selected from ISIS NOs: 395209, 399833, 399931 or 399989.

In certain embodiments, a target region is nucleotides 14441-14460 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 14441-14460 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 113. In certain such embodiments, an antisense compound targeted to nucleotides 14441-14460 of SEQ ID NO: 2 is selected from ISIS NOs: 395210 or 399932.

In certain embodiments, a target region is nucleotides 14494-14513 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 14494-14513 SEQ ID

NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 138. In certain such embodiments, an antisense compound targeted to nucleotides 14494-14513 of SEQ ID NO: 2 is selected from ISIS NOs: 395211 or 399933.

In certain embodiments, a target region is nucleotides 14494-14543 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 14494-14543 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 98 or 138. In certain such embodiments, an antisense compound targeted to nucleotides 14494-14543 of SEQ ID NO: 2 is selected from ISIS NOs: 395211, 395212, 399933 or 399934.

In certain embodiments, a target region is nucleotides 14524-14543 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 14524-14543 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 98. In certain such embodiments, an antisense compound targeted to nucleotides 14524-14543 of SEQ ID NO: 2 is selected from ISIS NOs: 395212 or 399934.

In certain embodiments, a target region is nucleotides 14601-14650 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 14601-14650 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 96 or 124. In certain such embodiments, an antisense compound targeted to nucleotides 14601-14650 of SEQ ID NO: 2 is selected from ISIS NOs: 395213, 395214, 399935 or 399936.

In certain embodiments, a target region is nucleotides 14670-14700 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 14670-14700 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 82, 103 or 133. In certain such embodiments, an antisense compound targeted to nucleotides 14670-14700 of SEQ ID NO: 2 is selected from ISIS NOs: 395215, 395216, 399834, 399937, 399938 or 399990.

In certain embodiments, a target region is nucleotides 14675-14700 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 14675-14700 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 103 or 133. In certain such

embodiments, an antisense compound targeted to nucleotides 14675-14700 of SEQ ID NO: 2 is selected from ISIS NOs: 395215, 395216, 399937 or 399938.

In certain embodiments, a target region is nucleotides 14801-14828 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 14801-14828 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 155 or 156. In certain such embodiments, an antisense compound targeted to nucleotides 14801-14828 of SEQ ID NO: 2 is selected from ISIS NOs: 395217, 399835, 399939 or 399991.

In certain embodiments, a target region is nucleotides 14877-14912 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 14877-14912 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 19, 215, 216 or 217. In certain such embodiments, an antisense compound targeted to nucleotides 14877-14912 of SEQ ID NO: 2 is selected from ISIS NOs: 395160, 399882, 406025, 406026 or 410753.

In certain embodiments, a target region is nucleotides 14877-14915 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 14877-14915 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 19, 20, 215, 216 or 217. In certain such embodiments, an antisense compound targeted to nucleotides 14877-14915 of SEQ ID NO: 2 is selected from ISIS NOs: 395160, 399797, 399882, 399953, 406025, 406026 or 410753.

In certain embodiments, a target region is nucleotides 14877-14973 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 14877-14973 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 19, 20, 21, 22, 23, 24, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, or 233. In certain such embodiments, an antisense compound targeted to nucleotides 14877-14973 of SEQ ID NO: 2 is selected from ISIS NOs: 395160, 395161, 395162, 399797, 399798, 399799, 399882, 399883, 399884, 399953, 399954, 399955, 405869, 405870, 405871, 405872, 405873, 405874, 405875, 405876, 406025, 406026, 406027, 406028, 406029, 406030, 406031, 406032, 410733, 410753, or 410754.

In certain embodiments, a target region is nucleotides 14916-14943 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 14916-14943 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid

comprises a nucleotide sequence selected from SEQ ID NOs: 21, 22, 218, 219, 220, 221, 222 or 223. In certain such embodiments, an antisense compound targeted to nucleotides 14916-14943 of SEQ ID NO: 2 is selected from ISIS NOs: 395161, 399798, 399883, 399954, 405869, 405870, 405871, 405872, 405873 or 405874.

In certain embodiments, a target region is nucleotides 14916-14973 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 14916-14973 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 21, 22, 23, 24, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, or 223. In certain such embodiments, an antisense compound targeted to nucleotides 14916-14973 of SEQ ID NO: 2 is selected from ISIS NOs: 395161, 395162, 399798, 399799, 399883, 399884, 399954, 399955, 405869, 405870, 405871, 405872, 405873, 405874, 405875, 405876, 406027, 406028, 406029, 406030, 406031, 406032, 410733, or 410754.

In certain embodiments, a target region is nucleotides 14925-14951 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 14925-14951 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 224, 225, 226 or 227. In certain such embodiments, an antisense compound targeted to nucleotides 14925-14951 of SEQ ID NO: 2 is selected from ISIS NOs: 405875, 405876, 406027 or 406028.

In certain embodiments, a target region is nucleotides 14934-14963 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 14934-14963 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 23, 228, 229, 230, 231 or 232. In certain such embodiments, an antisense compound targeted to nucleotides 14934-14963 of SEQ ID NO: 2 is selected from ISIS NOs: 399799, 399955, 406029, 406030, 406031, 406032 or 410733.

In certain embodiments, a target region is nucleotides 14946-14973 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 14946-14973 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 24 or 233. In certain such embodiments, an antisense compound targeted to nucleotides 14946-14973 of SEQ ID NO: 2 is selected from ISIS NOs: 395162, 399884 or 410754.

In certain embodiments, a target region is nucleotides 14979-14998 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 14979-14998 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 25. In certain such embodiments, an antisense compound targeted to nucleotides 14979-14998 of SEQ ID NO: 2 is selected from ISIS NOs: 395163 or 399885.

In certain embodiments, a target region is nucleotides 15254-15280 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 15254-15280 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 235, 236 or 237. In certain such embodiments, an antisense compound targeted to nucleotides 15254-15280 of SEQ ID NO: 2 is selected from ISIS NOs: 405526, 405604, 406033 or 410756.

In certain embodiments, a target region is nucleotides 15254-15328 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 15254-15328 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 26, 27, 28, 235, 236, 237, 238, 239, 240, 241, 242, 243, 243, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, or 447. In certain such embodiments, an antisense compound targeted to nucleotides 15254-15328 of SEQ ID NO: 2 is selected from ISIS NOs: 395164, 395165, 399800, 399886, 399887, 399956, 405526, 405604, 405877, 405878, 405879, 405880, 405881, 405882, 405883, 405884, 406033, 406034, 406035, 406036, 406037, 406038, 409126, 410536, 410537, 410538, 410539, 410583, 410584, 410585, 410586, 410587, 410588, 410589, 410590, 410591, 410592, 410593, 410594, 410595, 410658, 410659, 410660, 410661, 410662, 410663, 410664, 410665, 410666, 410667, 410668, 410669, 410670, 410671, 410756, 410757, or 410758.

In certain embodiments, a target region is nucleotides 15264-15290 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 15264-15290 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 26, 27, 238 or 239. In certain such embodiments, an antisense compound targeted to nucleotides 15264-15290 of SEQ ID NO: 2 is selected from ISIS NOs: 395164, 399800, 399886, 399956, 406034, or 406035.

In certain embodiments, a target region is nucleotides 15279-15305 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 15279-15305 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid

comprises a nucleotide sequence selected from SEQ ID NOs: 240, 241 or 242. In certain such embodiments, an antisense compound targeted to nucleotides 15279-15305 of SEQ ID NO: 2 is selected from ISIS NOs: 406036, 406037, or 410757.

In certain embodiments, a target region is nucleotides 15291-15318 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 15291-15318 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 28, 243, 244, 245, 246, 247, 248, 249, 250, or 447. In certain such embodiments, an antisense compound targeted to nucleotides 15291-15318 of SEQ ID NO: 2 is selected from ISIS NOs: 395165, 399887, 405877, 405878, 405879, 405880, 405881, 406038, 409126, 410536, 410537, 410583, 410584, 410585, 410586, 410587, 410588, 410589, 410590, 410658, 410659, 410660, 410661, 410662, 410663, 410664, 410665, or 410666.

In certain embodiments, a target region is nucleotides 15292-15319 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 15292-15319 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 28, 244, 245, 246, 247, 248, 249, 250 or 447. In certain such embodiments, an antisense compound targeted to nucleotides 15292-15319 of SEQ ID NO: 2 is selected from ISIS NOs: 395165, 399887, 405877, 405878, 405879, 405880, 405881, 406038, 409126, 410537, 410584, 410585, 410586, 410587, 410588, 410589, 410590, 410659, 410660, 410661, 410662, 410663, 410664, 410665, or 410666.

In certain embodiments, a target region is nucleotides 15293-15320 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 15293-15320 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 28, 245, 246, 247, 248, 249, 250, 251, 252 or 447. In certain such embodiments, an antisense compound targeted to nucleotides 15293-15320 of SEQ ID NO: 2 is selected from ISIS NOs: 395165, 399887, 405877, 405878, 405879, 405880, 405881, 405882, 405883, 406038, 409126, 410585, 410586, 410587, 410588, 410589, 410590, 410591, 410592, 410660, 410661, 410662, 410663, 410664, 410665, 410666, 410667, or 410668.

In certain embodiments, a target region is nucleotides 15294-15321 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 15294-15321 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 28, 246, 247, 248, 249, 250, 251,

252, 253 or 447. In certain such embodiments, an antisense compound targeted to nucleotides 15294-15321 of SEQ ID NO: 2 is selected from ISIS NOs: 395165, 399887, 405877, 405878, 405879, 405880, 405881, 405882, 405883, 405884, 409126, 410586, 410587, 410588, 410589, 410590, 410591, 410592, 410593, 410661, 410662, 410663, 410664, 410665, 410666, 410667, 410668 or 410669.

In certain embodiments, a target region is nucleotides 15294-15321 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 15294-15321 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 28, 246, 247, 248, 249, 250, 251, 252, 253 or 447. In certain such embodiments, an antisense compound targeted to nucleotides 15294-15321 of SEQ ID NO: 2 is selected from ISIS NOs: 395165, 399887, 405877, 405878, 405879, 405880, 405881, 405882, 405883, 405884, 409126, 410586, 410587, 410588, 410589, 410590, 410591, 410592, 410593, 410661, 410662, 410663, 410664, 410665, 410666, 410667, 410668 or 410669.

In certain embodiments, a target region is nucleotides 15295-15322 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 15295-15322 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 28, 247, 248, 249, 250, 250, 251, 252, 253, 254 or 447. In certain such embodiments, an antisense compound targeted to nucleotides 15295-15322 of SEQ ID NO: 2 is selected from ISIS NOs: 395165, 399887, 405878, 405879, 405880, 405881, 405882, 405883, 405884, 409126, 410538, 410587, 410588, 410589, 410590, 410591, 410592, 410593, 410594, 410662, 410663, 410664, 410665, 410666, 410667, 410668, 410669 or 410670.

In certain embodiments, a target region is nucleotides 15296-15323 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 15296-15323 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 28, 248, 249, 250, 251, 252, 253, 254, 255 or 447. In certain such embodiments, an antisense compound targeted to nucleotides 15296-15323 of SEQ ID NO: 2 is selected from ISIS NOs: 395165, 399887, 405879, 405880, 405881, 405882, 405883, 405884, 409126, 410538, 410539, 410588, 410589, 410590, 410591, 410592, 410593, 410594, 410595, 410663, 410664, 410665, 410666, 410667, 410668, 410669, 410670 or 410671.

In certain embodiments, a target region is nucleotides 15297-15323 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 15297-15323 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 28, 249, 250, 251, 252, 253, 254, 255 or 447. In certain such embodiments, an antisense compound targeted to nucleotides 15297-15323 of SEQ ID NO: 2 is selected from ISIS NOs: 395165, 399887, 405880, 405881, 405882, 405883, 405884, 409126, 410538, 410539, 410589, 410590, 410591, 410592, 410593, 410594, 410595, 410664, 410665, 410666, 410667, 410668, 410669, 410670 or 410671.

In certain embodiments, a target region is nucleotides 15298-15323 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 15298-15323 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 28, 250, 251, 252, 253, 254, 255 or 447. In certain such embodiments, an antisense compound targeted to nucleotides 15298-15323 of SEQ ID NO: 2 is selected from ISIS NOs: 395165, 399887, 405881, 405882, 405883, 405884, 409126, 410538, 410539, 410590, 410591, 410592, 410593, 410594, 410595, 410665, 410666, 410667, 410668, 410669, 410670 or 410671.

In certain embodiments, a target region is nucleotides 15299-15323 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 15299-15323 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 250, 251, 252, 253, 254 or 255. In certain such embodiments, an antisense compound targeted to nucleotides 15299-15323 of SEQ ID NO: 2 is selected from ISIS NOs: 405881, 405882, 405883, 405884, 410538, 410539, 410590, 410591, 410592, 410593, 410594, 410595, 410666, 410667, 410668, 410669, 410670 or 410671.

In certain embodiments, a target region is nucleotides 15300-15323 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 15300-15323 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 251, 252, 253, 254 or 255. In certain such embodiments, an antisense compound targeted to nucleotides 15300-15323 of SEQ ID NO: 2 is selected from ISIS NOs: 405882, 405883, 405884, 410538, 410539, 410591, 410592, 410593, 410594, 410595, 410667, 410668, 410669, 410670 or 410671.

In certain embodiments, a target region is nucleotides 15301-15328 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 15301-15328 SEQ ID

NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 252, 253, 254, 255 or 256. In certain such embodiments, an antisense compound targeted to nucleotides 15301-15328 of SEQ ID NO: 2 is selected from ISIS NOs: 405883, 405884, 410538, 410539, 410592, 410593, 410594, 410595, 410668, 410669, 410670, 410671 or 410758.

In certain embodiments, a target region is nucleotides 15330-15355 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 15330-15355 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 29, 257, 258 or 259. In certain such embodiments, an antisense compound targeted to nucleotides 15330-15355 of SEQ ID NO: 2 is selected from ISIS NOs: 395166, 399888, 406039, 406040 or 406041.

In certain embodiments, a target region is nucleotides 15330-15490 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 15330-15490 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 29, 30, 86, 257, 258, 259, 260, 261, 262 or 263. In certain such embodiments, an antisense compound targeted to nucleotides 15330-15490 of SEQ ID NO: 2 is selected from ISIS NOs: 395166, 399801, 399853, 399888, 399957, 400009, 406039, 406040, 406041, 406042, 406043, 406044 or 410759.

In certain embodiments, a target region is nucleotides 15339-15366 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 15339-15366 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 30, 260, 261 or 262. In certain such embodiments, an antisense compound targeted to nucleotides 15339-15366 of SEQ ID NO: 2 is selected from ISIS NOs: 399801, 399957, 406042, 406043 or 406044.

In certain embodiments, a target region is nucleotides 15358-15490 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 15358-15490 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 86 or 263. In certain such embodiments, an antisense compound targeted to nucleotides 15358-15490 of SEQ ID NO: 2 is selected from ISIS NOs: 399853, 400009 or 410759.

In certain embodiments, a target region is nucleotides 16134-16153 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 16134-16153 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid

comprises a nucleotide sequence selected from SEQ ID NOs: 97. In certain such embodiments, an antisense compound targeted to nucleotides 16134-16153 of SEQ ID NO: 2 is selected from ISIS NOs: 399854 or 400010.

In certain embodiments, a target region is nucleotides 16668-16687 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 16668-16687 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 120. In certain such embodiments, an antisense compound targeted to nucleotides 16668-16687 of SEQ ID NO: 2 is selected from ISIS NOs: 399855 or 400011.

In certain embodiments, a target region is nucleotides 17267-17286 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 17267-17286 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 150. In certain such embodiments, an antisense compound targeted to nucleotides 17267-17286 of SEQ ID NO: 2 is selected from ISIS NOs: 399856 or 400012.

In certain embodiments, a target region is nucleotides 18377-18427 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 18377-18427 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 115 or 134. In certain such embodiments, an antisense compound targeted to nucleotides 18377-18427 of SEQ ID NO: 2 is selected from ISIS NOs: 399857, 399858, 400013 or 400014.

In certain embodiments, a target region is nucleotides 18561-18580 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 18561-18580 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 157. In certain such embodiments, an antisense compound targeted to nucleotides 18561-18580 of SEQ ID NO: 2 is selected from ISIS NOs: 395224 or 399946.

In certain embodiments, a target region is nucleotides 18591-18618 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 18591-18618 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 32, 266, 267, 268 or 269. In certain such embodiments, an antisense compound targeted to nucleotides 18591-18618 of SEQ ID NO: 2 is selected from ISIS NOs: 395168, 399890, 405909, 405910, 405911 or 406045.

In certain embodiments, a target region is nucleotides 18591-18646 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 18591-18646 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 32, 32, 266, 267, 268, 269, 270, 271 or 272. In certain such embodiments, an antisense compound targeted to nucleotides 18591-18646 of SEQ ID NO: 2 is selected from ISIS NOs: 395168, 399890, 405909, 405910, 405911, 405912, 406045, 410761 or 410762.

In certain embodiments, a target region is nucleotides 18591-18668 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 18591-18668 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 32, 266, 267, 268, 269, 270, 271, 272 or 273. In certain such embodiments, an antisense compound targeted to nucleotides 18591-18668 of SEQ ID NO: 2 is selected from ISIS NOs: 395168, 399890, 405909, 405910, 405911, 405912, 406045, 410761, 410762 or 410763.

In certain embodiments, a target region is nucleotides 18695-18746 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 18695-18746 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 33, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284 or 285. In certain such embodiments, an antisense compound targeted to nucleotides 18695-18746 of SEQ ID NO: 2 is selected from ISIS NOs: 395169, 399891, 405913, 405914, 405915, 405916, 405917, 405918, 405919, 405920, 405921, 405922, 410734 or 410764.

In certain embodiments, a target region is nucleotides 18705-18730 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 18705-18730 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 33, 275, 276 or 277. In certain such embodiments, an antisense compound targeted to nucleotides 18705-18730 of SEQ ID NO: 2 is selected from ISIS NOs: 395169, 399891, 405913, 405914 or 405915.

In certain embodiments, a target region is nucleotides 18709-18736 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 18709-18736 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 276, 277, 278, 279 or 280. In certain such embodiments, an antisense compound targeted to nucleotides 18709-18736 of SEQ ID NO: 2 is selected from ISIS NOs: 405914, 405915, 405916, 405917 or 410734.

In certain embodiments, a target region is nucleotides 18719-18746 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 18719-18746 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 281, 282, 283, 284 or 285. In certain such embodiments, an antisense compound targeted to nucleotides 18719-18746 of SEQ ID NO: 2 is selected from ISIS NOs: 405918, 405919, 405920, 405921 or 405922.

In certain embodiments, a target region is nucleotides 19203-20080 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 19203-20080 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 34, 35, 36, 37, 38, 39, 40, 41, 105, 128, 149, 151, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317 or 318. In certain such embodiments, an antisense compound targeted to nucleotides 19203-20080 of SEQ ID NO: 2 is selected from ISIS NOs: 395170, 395171, 395172, 395173, 395174, 395175, 399802, 399803, 399804, 399805, 399859, 399860, 399892, 399893, 399894, 399895, 399896, 399897, 399958, 399959, 399960, 399961, 400015, 400016, 405923, 405924, 405925, 405926, 405927, 405928, 405929, 405930, 405931, 405932, 405933, 405934, 405935, 405936, 405937, 405938, 405939, 405940, 405941, 405942, 405943, 405944, 405945, 405946, 405947, 410735, 410736, 410737, 410767, 410768 or 410769.

In certain embodiments, a target region is nucleotides 19931-19952 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 19931-19952 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 149 or 188. In certain such embodiments, an antisense compound targeted to nucleotides 19931-19952 of SEQ ID NO: 2 is selected from ISIS NOs: 395170, 399892 or 405923.

In certain embodiments, a target region is nucleotides 19954-19981 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 19954-19981 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 34, 290, 291, 292 or 293. In certain such embodiments, an antisense compound targeted to nucleotides 19954-19981 of SEQ ID NO: 2 is selected from ISIS NOs: 395171, 399893, 405924, 405925, 405926 or 410735.

In certain embodiments, a target region is nucleotides 19964-19990 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 19964-19990 SEQ ID

NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 35, 128, 128, 294 or 295. In certain such embodiments, an antisense compound targeted to nucleotides 19964-19990 of SEQ ID NO: 2 is selected from ISIS NOs: 395172, 399802, 399894, 399958, 405927 or 405928.

In certain embodiments, a target region is nucleotides 19973-19999 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 19973-19999 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 36, 296, 297 or 298. In certain such embodiments, an antisense compound targeted to nucleotides 19973-19999 of SEQ ID NO: 2 is selected from ISIS NOs: 395173, 399895, 405929, 405930 or 405931.

In certain embodiments, a target region is nucleotides 19982-20009 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 19982-20009 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 37, 299, 300, 301 or 302. In certain such embodiments, an antisense compound targeted to nucleotides 19982-20009 of SEQ ID NO: 2 is selected from ISIS NOs: 399803, 399959, 405932, 405933, 405934 or 405935.

In certain embodiments, a target region is nucleotides 19992-20016 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 19992-20016 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 38, 303 or 304. In certain such embodiments, an antisense compound targeted to nucleotides 19992-20016 of SEQ ID NO: 2 is selected from ISIS NOs: 395174, 399896, 405936 or 410736.

In certain embodiments, a target region is nucleotides 20016-20042 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 20016-20042 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 305 or 306. In certain such embodiments, an antisense compound targeted to nucleotides 20016-20042 of SEQ ID NO: 2 is selected from ISIS NOs: 405937 or 410768.

In certain embodiments, a target region is nucleotides 20025-20052 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 20025-20052 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 39, 307, 308, 309 or 310. In

certain such embodiments, an antisense compound targeted to nucleotides 20025-20052 of SEQ ID NO: 2 is selected from ISIS NOs: 395175, 399897, 405938, 405939, 405940 or 405941.

In certain embodiments, a target region is nucleotides 20036-20062 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 20036-20062 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 40, 311, 312, 313 or 314. In certain such embodiments, an antisense compound targeted to nucleotides 20036-20062 of SEQ ID NO: 2 is selected from ISIS NOs: 399804, 399960, 405942, 405943, 405944 or 410737.

In certain embodiments, a target region is nucleotides 20045-20070 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 20045-20070 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 41, 315, 316 or 317. In certain such embodiments, an antisense compound targeted to nucleotides 20045-20070 of SEQ ID NO: 2 is selected from ISIS NOs: 399805, 399961, 405945, 405946 or 405947.

In certain embodiments, a target region is nucleotides 20100-20119 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 20100-20119 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 158. In certain such embodiments, an antisense compound targeted to nucleotides 20100-20119 of SEQ ID NO: 2 is selected from ISIS NOs: 399861 or 400017.

In certain embodiments, a target region is nucleotides 20188-20207 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 20188-20207 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 109. In certain such embodiments, an antisense compound targeted to nucleotides 20188-20207 of SEQ ID NO: 2 is selected from ISIS NOs: 399862 or 400018.

In certain embodiments, a target region is nucleotides 20624-20650 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 20624-20650 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 141, 320 or 321. In certain such embodiments, an antisense compound targeted to nucleotides 20624-20650 of SEQ ID NO: 2 is selected from ISIS NOs: 399863, 400019, 405949 or 405950.

In certain embodiments, a target region is nucleotides 20624-20759 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 20624-20759 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 43, 44, 45, 46, 47, 48, 49, 50, 51, 87, 141, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358 or 359. In certain such embodiments, an antisense compound targeted to nucleotides 20624-20759 of SEQ ID NO: 2 is selected from ISIS NOs: 395177, 395178, 395179, 399807, 399808, 399809, 399810, 399811, 399812, 399813, 399863, 399899, 399900, 399901, 399963, 399964, 399965, 399966, 399967, 399968, 399969, 400019, 405557, 405885, 405886, 405887, 405888, 405889, 405890, 405891, 405892, 405949, 405950, 405951, 405952, 405953, 405954, 405955, 405956, 405957, 405958, 405959, 405960, 405961, 405962, 405963, 405964, 405965, 405966, 405967, 405968, 405969, 405970, 405971, 405972, 405973, 405974, 408653, 410540, 410596, 410597, 410598, 410599, 410600, 410601, 410602, 410603, 410604, 410672, 410673, 410674, 410675, 410676, 410677, 410678, 410679, 410680, 410681, 410682, 410738, 410739, 410740 or 410770.

In certain embodiments, a target region is nucleotides 20629-20804 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 20629-20804 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 43, 44, 45, 46, 47, 48, 49, 50, 51, 87, 119, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 356, 357, 358, 359 or 360. In certain such embodiments, an antisense compound targeted to nucleotides 20629-20804 of SEQ ID NO: 2 is selected from ISIS NOs: 395177, 395178, 395179, 395180, 399807, 399808, 399809, 399810, 399811, 399812, 399813, 399899, 399900, 399901, 399902, 399963, 399964, 399965, 399966, 399967, 399968, 399969, 405557, 405885, 405886, 405887, 405888, 405889, 405890, 405891, 405892, 405949, 405950, 405951, 405952, 405953, 405954, 405955, 405956, 405957, 405958, 405959, 405960, 405961, 405962, 405963, 405964, 405965, 405966, 405967, 405968, 405969, 405970, 405971, 405972, 405973, 405974, 408653, 410540, 410596, 410597, 410598, 410599, 410600, 410601, 410602, 410603, 410604, 410672, 410673, 410674, 410675, 410676, 410677, 410678, 410679, 410680, 410681, 410682, 410738, 410739, 410740, 410770 or 410771.

In certain embodiments, a target region is nucleotides 20633-20660 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 20633-20660 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 43, 322, 323, 324 or 325. In certain such embodiments, an antisense compound targeted to nucleotides 20633-20660 of SEQ ID NO: 2 is selected from ISIS NOs: 399807, 399963, 405951, 405952, 405953 or 410738.

In certain embodiments, a target region is nucleotides 20635-20781 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 20635-20781 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 43, 44, 45, 46, 47, 48, 49, 50, 51, 87, 119, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358 or 359. In certain such embodiments, an antisense compound targeted to nucleotides 20635-20781 of SEQ ID NO: 2 is selected from ISIS NOs: 395177, 395178, 395179, 395180, 399807, 399808, 399809, 399810, 399811, 399812, 399813, 399899, 399900, 399901, 399902, 399963, 399964, 399965, 399966, 399967, 399968, 399969, 405557, 405885, 405886, 405887, 405888, 405889, 405890, 405891, 405892, 405952, 405953, 405954, 405955, 405956, 405957, 405958, 405959, 405960, 405961, 405962, 405963, 405964, 405965, 405966, 405967, 405968, 405969, 405970, 405971, 405972, 405973, 405974, 408653, 410540, 410596, 410597, 410598, 410599, 410600, 410601, 410602, 410603, 410604, 410672, 410673, 410674, 410675, 410676, 410677, 410678, 410679, 410680, 410681, 410682, 410738, 410739, 410740 or 410770.

In certain embodiments, a target region is nucleotides 20643-20662 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 20643-20662 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 326. In certain such embodiments, an antisense compound targeted to nucleotides 20643-20662 of SEQ ID NO: 2 is selected from ISIS NOs: 405954.

In certain embodiments, a target region is nucleotides 20657-20676 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 20657-20676 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 327. In certain such embodiments, an antisense compound targeted to nucleotides 20657-20676 of SEQ ID NO: 2 is selected from ISIS NOs: 410770.

In certain embodiments, a target region is nucleotides 20670-20697 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 20670-20697 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 328, 329, 330, 331 or 332. In certain such embodiments, an antisense compound targeted to nucleotides 20670-20697 of SEQ ID NO: 2 is selected from ISIS NOs: 405955, 405956, 405957, 405958 or 405959.

In certain embodiments, a target region is nucleotides 20680-20706 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 20680-20706 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 44, 333, 334, 335 or 336. In certain such embodiments, an antisense compound targeted to nucleotides 20680-20706 of SEQ ID NO: 2 is selected from ISIS NOs: 399808, 399964, 405960, 405961, 405962 or 410739.

In certain embodiments, a target region is nucleotides 20683-20781 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 20683-20781 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 44, 45, 46, 47, 48, 49, 50, 51, 87, 119, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358 or 359. In certain such embodiments, an antisense compound targeted to nucleotides 20683-20781 of SEQ ID NO: 2 is selected from ISIS NOs: 395177, 395178, 395179, 395180, 399808, 399809, 399810, 399811, 399812, 399813, 399899, 399900, 399901, 399902, 399964, 399965, 399966, 399967, 399968, 399969, 405557, 405885, 405886, 405887, 405888, 405889, 405890, 405891, 405892, 405962, 405963, 405964, 405965, 405966, 405967, 405968, 405969, 405970, 405971, 405972, 405973, 405974, 408653, 410540, 410596, 410597, 410598, 410599, 410600, 410601, 410602, 410603, 410604, 410672, 410673, 410674, 410675, 410676, 410677, 410678, 410679, 410680, 410681, 410682, 410739 or 410740.

In certain embodiments, a target region is nucleotides 20689-20715 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 20689-20715 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 45, 46, 337 or 338. In certain such embodiments, an antisense compound targeted to nucleotides 20689-20715 of SEQ ID NO: 2 is selected from ISIS NOs: 395177, 399809, 399899, 399965, 405963 or 405964.

In certain embodiments, a target region is nucleotides 20698-20725 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 20698-20725 SEQ ID

NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 47, 47, 339, 340, 341 or 342. In certain such embodiments, an antisense compound targeted to nucleotides 20698-20725 of SEQ ID NO: 2 is selected from ISIS NOs: 399810, 399966, 405965, 405966, 405967 or 405968.

In certain embodiments, a target region is nucleotides 20709-20736 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 20709-20736 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 48, 48, 343, 344, 345 or 346. In certain such embodiments, an antisense compound targeted to nucleotides 20709-20736 of SEQ ID NO: 2 is selected from ISIS NOs: 399811, 399967, 405885, 405969, 405970 or 410740.

In certain embodiments, a target region is nucleotides 20717-20744 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 20717-20744 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 49, 346, 347, 348, 349, 350, 351, 352 or 353. In certain such embodiments, an antisense compound targeted to nucleotides 20717-20744 of SEQ ID NO: 2 is selected from ISIS NOs: 399812, 399968, 405885, 405886, 405887, 405888, 405889, 405890, 405891, 405892, 410596, 410597, 410598, 410599, 410600, 410601, 410672, 410673, 410674, 410675, 410676, 410677 or 410678.

In certain embodiments, a target region is nucleotides 20718-20745 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 20718-20745 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 49, 50, 347, 348, 349, 350, 351, 352 or 353. In certain such embodiments, an antisense compound targeted to nucleotides 20718-20745 of SEQ ID NO: 2 is selected from ISIS NOs: 395178, 399812, 399900, 399968, 405557, 405886, 405887, 405888, 405889, 405890, 405891, 405892, 410596, 410597, 410598, 410599, 410600, 410601, 410672, 410673, 410674, 410675, 410676, 410677, 410678 or 410679.

In certain embodiments, a target region is nucleotides 20719-20746 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 20719-20746 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 49, 50, 348, 349, 350, 351, 352, 353 or 354. In certain such embodiments, an antisense compound targeted to nucleotides 20719-20746 of SEQ ID NO: 2 is selected from ISIS NOs: 395178, 399812, 399900, 399968, 405557, 405887, 405888, 405889, 405890, 405891, 405892, 408653, 410596, 410597, 410598, 410599,

410600, 410601, 410602, 410672, 410673, 410674, 410675, 410676, 410677, 410678, 410679 or 410680.

In certain embodiments, a target region is nucleotides 20720-20747 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 20720-20747 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 49, 50, 349, 350, 351, 352, 353, 354 or 355. In certain such embodiments, an antisense compound targeted to nucleotides 20720-20747 of SEQ ID NO: 2 is selected from ISIS NOs: 395178, 399812, 399900, 399968, 405557, 405888, 405889, 405890, 405891, 405892, 405971, 408653, 410597, 410598, 410599, 410600, 410601, 410602, 410603, 410673, 410674, 410675, 410676, 410677, 410678, 410679, 410680 or 410681.

In certain embodiments, a target region is nucleotides 20721-20748 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 20721-20748 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 49, 50, 350, 351, 352, 353, 354, 355 or 356. In certain such embodiments, an antisense compound targeted to nucleotides 20721-20748 of SEQ ID NO: 2 is selected from ISIS NOs: 395178, 399812, 399900, 399968, 405557, 405889, 405890, 405891, 405892, 405971, 408653, 410540, 410598, 410599, 410600, 410601, 410602, 410603, 410604, 410674, 410675, 410676, 410677, 410678, 410679, 410680, 410681 or 410682.

In certain embodiments, a target region is nucleotides 20722-20749 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 20722-20749 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 50, 350, 351, 352, 353, 354, 355, 356 or 357. In certain such embodiments, an antisense compound targeted to nucleotides 20722-20749 of SEQ ID NO: 2 is selected from ISIS NOs: 395178, 399900, 405557, 405889, 405890, 405891, 405892, 405971, 405972, 408653, 410540, 410598, 410599, 410600, 410601, 410602, 410603, 410604, 410675, 410676, 410677, 410678, 410679, 410680, 410681 or 410682.

In certain embodiments, a target region is nucleotides 20727-20752 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 20727-20752 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 87, 354, 355, 356 or 357. In certain such embodiments, an antisense compound targeted to nucleotides 20727-20752 of SEQ

ID NO: 2 is selected from ISIS NOs: 395179, 399901, 405971, 405972, 408653, 410540, 410602, 410603, 410604, 410680, 410681 or 410682.

In certain embodiments, a target region is nucleotides 20735-20759 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 20735-20759 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 51, 358 or 359. In certain such embodiments, an antisense compound targeted to nucleotides 20735-20759 of SEQ ID NO: 2 is selected from ISIS NOs: 399813, 399969, 405973 or 405974.

In certain embodiments, a target region is nucleotides 20762-21014 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 20762-21014 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 93, 119 or 360. In certain such embodiments, an antisense compound targeted to nucleotides 20762-21014 of SEQ ID NO: 2 is selected from ISIS NOs: 395180, 399864, 399902, 400020 or 410771.

In certain embodiments, a target region is nucleotides 20785-21014 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 20785-21014 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 93 or 360. In certain such embodiments, an antisense compound targeted to nucleotides 20785-21014 of SEQ ID NO: 2 is selected from ISIS NOs: 399864, 400020 or 410771.

In certain embodiments, a target region is nucleotides 21082-21107 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 21082-21107 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 95 or 361. In certain such embodiments, an antisense compound targeted to nucleotides 21082-21107 of SEQ ID NO: 2 is selected from ISIS NOs: 399865, 400021 or 405975.

In certain embodiments, a target region is nucleotides 21082-21152 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 21082-21152 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 53, 54, 95, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370 or 371. In certain such embodiments, an antisense compound targeted to nucleotides 21082-21152 of SEQ ID NO: 2 is selected from ISIS NOs: 395182, 399814, 399865,

399904, 399970, 400021, 405975, 405976, 405977, 405978, 405979, 405980, 405981, 405982, 405983, 410741 or 410772.

In certain embodiments, a target region is nucleotides 21091-21114 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 21091-21114 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 53, 362 or 363. In certain such embodiments, an antisense compound targeted to nucleotides 21091-21114 of SEQ ID NO: 2 is selected from ISIS NOs: 399814, 399970, 405976 or 405977.

In certain embodiments, a target region is nucleotides 21118-21144 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 21118-21144 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 54, 365, 366 or 367. In certain such embodiments, an antisense compound targeted to nucleotides 21118-21144 of SEQ ID NO: 2 is selected from ISIS NOs: 395182, 399904, 405978, 405979 or 405980.

In certain embodiments, a target region is nucleotides 21127-21152 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 21127-21152 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 368, 369, 370 or 371. In certain such embodiments, an antisense compound targeted to nucleotides 21127-21152 of SEQ ID NO: 2 is selected from ISIS NOs: 405981, 405982, 405983 or 410741.

In certain embodiments, a target region is nucleotides 21181-21209 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 21181-21209 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 55, 372, 373, 374 or 375. In certain such embodiments, an antisense compound targeted to nucleotides 21181-21209 of SEQ ID NO: 2 is selected from ISIS NOs: 399815, 399971, 405564, 405641, 405984, 405985, 405986 or 405987.

In certain embodiments, a target region is nucleotides 21181-21211 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 21181-21211 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 55, 56, 372, 373, 374 or 375. In certain such embodiments, an antisense compound targeted to nucleotides 21181-21211 of SEQ

ID NO: 2 is selected from ISIS NOs: 399815, 399816, 399971, 399972, 405564, 405641, 405984, 405985, 405986 or 405987.

In certain embodiments, a target region is nucleotides 21183-21211 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 21183-21211 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 55, 56, 373, 374 or 375. In certain such embodiments, an antisense compound targeted to nucleotides 21183-21211 of SEQ ID NO: 2 is selected from ISIS NOs: 399815, 399816, 399971, 399972, 405564, 405641, 405985, 405986 or 405987.

In certain embodiments, a target region is nucleotides 21481-21500 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 21481-21500 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 143. In certain such embodiments, an antisense compound targeted to nucleotides 21481-21500 of SEQ ID NO: 2 is selected from ISIS NOs: 399866 or 400022.

In certain embodiments, a target region is nucleotides 21589-21608 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 21589-21608 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 89. In certain such embodiments, an antisense compound targeted to nucleotides 21589-21608 of SEQ ID NO: 2 is selected from ISIS NOs: 399867 or 400023.

In certain embodiments, a target region is nucleotides 21692-21719 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 21692-21719 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 123, 448, 449, 450, 451, 452, 453, 454 or 455. In certain such embodiments, an antisense compound targeted to nucleotides 21692-21719 of SEQ ID NO: 2 is selected from ISIS NOs: 399868, 400024, 406478, 406479, 406480, 406481, 406482, 406483, 406484 or 406485.

In certain embodiments, a target region is nucleotides 22000-22227 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 22000-22227 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 59, 389, 390, 391, 392, 393, 394, 395 or 396. In certain such embodiments, an antisense compound targeted to nucleotides 22000-

22227 of SEQ ID NO: 2 is selected from ISIS NOs: 395185, 399907, 405991, 405992, 410550, 410551, 410552, 410553, 410554, 410555, 410616, 410617, 410618, 410619, 410620, 410621, 410622, 410623, 410695, 410696, 410697, 410698, 410699, 410700, 410701, 410702 or 410703.

In certain embodiments, a target region is nucleotides 22096-22115 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 22096-22115 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 57. In certain such embodiments, an antisense compound targeted to nucleotides 22096-22115 of SEQ ID NO: 2 is selected from ISIS NOs: 395183 or 399905.

In certain embodiments, a target region is nucleotides 22096-22223 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 22096-22223 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 57, 58, 59, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391 or 392. In certain such embodiments, an antisense compound targeted to nucleotides 22096-22223 of SEQ ID NO: 2 is selected from ISIS NOs: 395183, 395184, 395185, 399905, 399906, 399907, 405988, 405989, 405990, 410541, 410542, 410543, 410544, 410545, 410546, 410547, 410548, 410549, 410550, 410551, 410552, 410553, 410605, 410606, 410607, 410608, 410609, 410610, 410611, 410612, 410613, 410614, 410615, 410616, 410617, 410618, 410619, 410683, 410684, 410685, 410686, 410687, 410688, 410689, 410690, 410691, 410692, 410693, 410694, 410695, 410696, 410697, 410698, 410699 or 410773.

In certain embodiments, a target region is nucleotides 22096-22311 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 22096-22311 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 57, 58, 59, 126, 126, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 401, 401, 402, 402, 402, 403, 403, 403, 404, 404, 404, 405, 405, 405 or 406. In certain such embodiments, an antisense compound targeted to nucleotides 22096-22311 of SEQ ID NO: 2 is selected from ISIS NOs: 395183, 395184, 395185, 395225, 399905, 399906, 399907, 399947, 405988, 405989, 405990, 405991, 405992, 405993, 405994, 405995, 410541, 410542, 410543, 410544, 410545, 410546, 410547, 410548, 410549, 410550, 410551, 410552, 410553, 410554, 410555, 410556, 410557, 410558, 410559, 410560, 410561, 410605, 410606, 410607, 410608, 410609, 410610, 410611, 410612, 410613, 410614, 410615, 410616, 410617,

410618, 410619, 410620, 410621, 410622, 410623, 410624, 410625, 410626, 410627, 410628, 410629, 410630, 410631, 410632, 410683, 410684, 410685, 410686, 410687, 410688, 410689, 410690, 410691, 410692, 410693, 410694, 410695, 410696, 410697, 410698, 410699, 410700, 410701, 410702, 410703, 410704, 410705, 410706, 410707, 410708, 410709, 410710, 410711, 410712, 410773 or 410774.

In certain embodiments, a target region is nucleotides 22133-22160 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 22133-22160 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 376, 377, 378, 379, 380, 381, 382, 383 or 384. In certain such embodiments, an antisense compound targeted to nucleotides 22133-22160 of SEQ ID NO: 2 is selected from ISIS NOs: 405988, 405989, 410541, 410542, 410543, 410544, 410545, 410546, 410547, 410605, 410606, 410607, 410608, 410609, 410610, 410611, 410612, 410613, 410683, 410684, 410685, 410686, 410687, 410688, 410689, 410690 or 410691.

In certain embodiments, a target region is nucleotides 22133-22163 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 22133-22163 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 58, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385 or 386. In certain such embodiments, an antisense compound targeted to nucleotides 22133-22163 of SEQ ID NO: 2 is selected from ISIS NOs: 395184, 399906, 405988, 405989, 405990, 410541, 410542, 410543, 410544, 410545, 410546, 410547, 410548, 410605, 410606, 410607, 410608, 410609, 410610, 410611, 410612, 410613, 410614, 410683, 410684, 410685, 410686, 410687, 410688, 410689, 410690, 410691, 410692 or 410693.

In certain embodiments, a target region is nucleotides 22134-22161 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 22134-22161 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 58, 377, 378, 379, 380, 381, 382, 383 or 384. In certain such embodiments, an antisense compound targeted to nucleotides 22134-22161 of SEQ ID NO: 2 is selected from ISIS NOs: 395184, 399906, 405988, 405989, 410542, 410543, 410544, 410545, 410546, 410547, 410606, 410607, 410608, 410609, 410610, 410611, 410612, 410613, 410684, 410685, 410686, 410687, 410688, 410689, 410690, 410691 or 410692.

In certain embodiments, a target region is nucleotides 22135-22162 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 22135-22162 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid

comprises a nucleotide sequence selected from SEQ ID NOs: 58, 378, 379, 380, 381, 382, 383, 384 or 385. In certain such embodiments, an antisense compound targeted to nucleotides 22135-22162 of SEQ ID NO: 2 is selected from ISIS NOs: 395184, 399906, 405988, 405989, 410543, 410544, 410545, 410546, 410547, 410548, 410607, 410608, 410609, 410610, 410611, 410612, 410613, 410614, 410685, 410686, 410687, 410688, 410689, 410690, 410691, 410692 or 410693.

In certain embodiments, a target region is nucleotides 22136-22163 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 22136-22163 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 58, 379, 380, 381, 382, 383, 384, 385 or 386. In certain such embodiments, an antisense compound targeted to nucleotides 22136-22163 of SEQ ID NO: 2 is selected from ISIS NOs: 395184, 399906, 405988, 405989, 405990, 410544, 410545, 410546, 410547, 410548, 410608, 410609, 410610, 410611, 410612, 410613, 410614, 410686, 410687, 410688, 410689, 410690, 410691, 410692 or 410693.

In certain embodiments, a target region is nucleotides 22137-22163 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 22137-22163 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 58, 380, 381, 382, 383, 384, 385 or 386. In certain such embodiments, an antisense compound targeted to nucleotides 22137-22163 of SEQ ID NO: 2 is selected from ISIS NOs: 395184, 399906, 405988, 405989, 405990, 410545, 410546, 410547, 410548, 410609, 410610, 410611, 410612, 410613, 410614, 410687, 410688, 410689, 410690, 410691, 410692 or 410693.

In certain embodiments, a target region is nucleotides 22138-22163 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 22138-22163 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 58, 381, 382, 383, 384, 385 or 386. In certain such embodiments, an antisense compound targeted to nucleotides 22138-22163 of SEQ ID NO: 2 is selected from ISIS NOs: 395184, 399906, 405988, 405989, 405990, 410546, 410547, 410548, 410610, 410611, 410612, 410613, 410614, 410688, 410689, 410690, 410691, 410692 or 410693.

In certain embodiments, a target region is nucleotides 22189-22239 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 22189-22239 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 59, 387, 388, 389, 390, 391, 392,

393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405 or 406. In certain such embodiments, an antisense compound targeted to nucleotides 22189-22239 of SEQ ID NO: 2 is selected from ISIS NOs: 395185, 399907, 405991, 405992, 405993, 405994, 405995, 410549, 410550, 410551, 410552, 410553, 410554, 410555, 410556, 410557, 410558, 410559, 410560, 410561, 410615, 410616, 410617, 410618, 410619, 410620, 410621, 410622, 410623, 410624, 410625, 410626, 410627, 410628, 410629, 410630, 410631, 410632, 410694, 410695, 410696, 410697, 410698, 410699, 410700, 410701, 410702, 410703, 410704, 410705, 410706, 410707, 410708, 410709, 410710, 410711, 410712, 410773 or 410774.

In certain embodiments, a target region is nucleotides 22199-22226 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 22199-22226 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 59, 388, 389, 390, 391, 392, 393, 394 or 395. In certain such embodiments, an antisense compound targeted to nucleotides 22199-22226 of SEQ ID NO: 2 is selected from ISIS NOs: 395185, 399907, 405991, 410549, 410550, 410551, 410552, 410553, 410554, 410555, 410615, 410616, 410617, 410618, 410619, 410620, 410621, 410622, 410694, 410695, 410696, 410697, 410698, 410699, 410700, 410701 or 410702.

In certain embodiments, a target region is nucleotides 22199-22227 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 22199-22227 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 59, 388, 389, 390, 391, 392, 393, 394, 395 or 396. In certain such embodiments, an antisense compound targeted to nucleotides 22199-22227 of SEQ ID NO: 2 is selected from ISIS NOs: 395185, 399907, 405991, 405992, 410549, 410550, 410551, 410552, 410553, 410554, 410555, 410615, 410616, 410617, 410618, 410619, 410620, 410621, 410622, 410623, 410694, 410695, 410696, 410697, 410698, 410699, 410700, 410701, 410702 or 410703.

In certain embodiments, a target region is nucleotides 22200-22227 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 22200-22227 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 59, 389, 390, 391, 392, 393, 394, 395 or 396. In certain such embodiments, an antisense compound targeted to nucleotides 22200-22227 of SEQ ID NO: 2 is selected from ISIS NOs: 395185, 399907, 405991, 405992, 410550, 410551, 410552, 410553, 410554, 410555, 410616, 410617, 410618, 410619, 410620, 410621, 410622, 410623, 410695, 410696, 410697, 410698, 410699, 410700, 410701, 410702 or 410703.

In certain embodiments, a target region is nucleotides 22201-22228 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 22201-22228 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 59, 390, 391, 392, 393, 394, 395, 396 or 397. In certain such embodiments, an antisense compound targeted to nucleotides 22201-22228 of SEQ ID NO: 2 is selected from ISIS NOs: 395185, 399907, 405991, 405992, 410551, 410552, 410553, 410554, 410555, 410556, 410617, 410618, 410619, 410620, 410621, 410622, 410623, 410624, 410696, 410697, 410698, 410699, 410700, 410701, 410702, 410703 or 410704.

In certain embodiments, a target region is nucleotides 22202-22229 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 22202-22229 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 59, 391, 392, 393, 394, 395, 396, 397 or 398. In certain such embodiments, an antisense compound targeted to nucleotides 22202-22229 of SEQ ID NO: 2 is selected from ISIS NOs: 395185, 399907, 405991, 405992, 405993, 410552, 410553, 410554, 410555, 410556, 410618, 410619, 410620, 410621, 410622, 410623, 410624, 410625, 410697, 410698, 410699, 410700, 410701, 410702, 410703, 410704 or 410705.

In certain embodiments, a target region is nucleotides 22203-22230 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 22203-22230 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 59, 392, 393, 394, 395, 396, 397, 398 or 399. In certain such embodiments, an antisense compound targeted to nucleotides 22203-22230 of SEQ ID NO: 2 is selected from ISIS NOs: 395185, 399907, 405991, 405992, 405993, 410553, 410554, 410555, 410556, 410557, 410619, 410620, 410621, 410622, 410623, 410624, 410625, 410626, 410698, 410699, 410700, 410701, 410702, 410703, 410704, 410705 or 410706.

In certain embodiments, a target region is nucleotides 22204-22231 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 22204-22231 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 59, 393, 394, 395, 396, 397, 398, 399 or 400. In certain such embodiments, an antisense compound targeted to nucleotides 22204-22231 of SEQ ID NO: 2 is selected from ISIS NOs: 395185, 399907, 405991, 405992, 405993, 405994, 410554, 410555, 410556, 410557, 410620, 410621, 410622, 410623, 410624, 410625, 410626, 410627, 410699, 410700, 410701, 410702, 410703, 410704, 410705, 410706 or 410707.

In certain embodiments, a target region is nucleotides 22205-22232 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 22205-22232 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 393, 394, 395, 396, 397, 398, 399, 400 or 401. In certain such embodiments, an antisense compound targeted to nucleotides 22205-22232 of SEQ ID NO: 2 is selected from ISIS NOs: 405991, 405992, 405993, 405994, 410554, 410555, 410556, 410557, 410558, 410620, 410621, 410622, 410623, 410624, 410625, 410626, 410627, 410628, 410700, 410701, 410702, 410703, 410704, 410705, 410706, 410707 or 410708.

In certain embodiments, a target region is nucleotides 22206-22233 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 22206-22233 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 394, 395, 396, 397, 398, 399, 400, 401 or 402. In certain such embodiments, an antisense compound targeted to nucleotides 22206-22233 of SEQ ID NO: 2 is selected from ISIS NOs: 405991, 405992, 405993, 405994, 405995, 410555, 410556, 410557, 410558, 410621, 410622, 410623, 410624, 410625, 410626, 410627, 410628, 410629, 410701, 410702, 410703, 410704, 410705, 410706, 410707, 410708 or 410709.

In certain embodiments, a target region is nucleotides 22207-22234 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 22207-22234 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 395, 396, 397, 398, 399, 400, 401, 402 or 403. In certain such embodiments, an antisense compound targeted to nucleotides 22207-22234 of SEQ ID NO: 2 is selected from ISIS NOs: 405992, 405993, 405994, 405995, 410555, 410556, 410557, 410558, 410559, 410622, 410623, 410624, 410625, 410626, 410627, 410628, 410629, 410630, 410702, 410703, 410704, 410705, 410706, 410707, 410708, 410709 or 410710.

In certain embodiments, a target region is nucleotides 22208-22235 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 22208-22235 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 396, 397, 398, 399, 400, 401, 402, 403 or 404. In certain such embodiments, an antisense compound targeted to nucleotides 22208-22235 of SEQ ID NO: 2 is selected from ISIS NOs: 405992, 405993, 405994, 405995, 410556, 410557, 410558, 410559, 410560, 410623, 410624, 410625, 410626, 410627, 410628, 410629, 410630, 410631, 410703, 410704, 410705, 410706, 410707, 410708, 410709, 410710 or 410711.

In certain embodiments, a target region is nucleotides 22209-22236 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 22209-22236 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 397, 398, 399, 400, 401, 402, 403, 404 or 405. In certain such embodiments, an antisense compound targeted to nucleotides 22209-22236 of SEQ ID NO: 2 is selected from ISIS NOs: 405993, 405994, 405995, 410556, 410557, 410558, 410559, 410560, 410561, 410624, 410625, 410626, 410627, 410628, 410629, 410630, 410631, 410632, 410704, 410705, 410706, 410707, 410708, 410709, 410710, 410711 or 410712.

In certain embodiments, a target region is nucleotides 22210-22236 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 22210-22236 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 398, 399, 400, 401, 402, 403, 404 or 405. In certain such embodiments, an antisense compound targeted to nucleotides 22210-22236 of SEQ ID NO: 2 is selected from ISIS NOs: 405993, 405994, 405995, 410557, 410558, 410559, 410560, 410561, 410625, 410626, 410627, 410628, 410629, 410630, 410631, 410632, 410705, 410706, 410707, 410708, 410709, 410710, 410711 or 410712.

In certain embodiments, a target region is nucleotides 22210-22239 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 22210-22239 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 398, 399, 400, 401, 402, 403, 404, 405 or 405. In certain such embodiments, an antisense compound targeted to nucleotides 22210-22239 of SEQ ID NO: 2 is selected from ISIS NOs: 405993, 405994, 405995, 410557, 410558, 410559, 410560, 410561, 410625, 410626, 410627, 410628, 410629, 410630, 410631, 410632, 410705, 410706, 410707, 410708, 410709, 410710, 410711, 410712 or 410774.

In certain embodiments, a target region is nucleotides 22211-22236 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 22211-22236 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 399, 400, 401, 402, 403, 404 or 405. In certain such embodiments, an antisense compound targeted to nucleotides 22211-22236 of SEQ ID NO: 2 is selected from ISIS NOs: 405994, 405995, 410557, 410558, 410559, 410560, 410561, 410626, 410627, 410628, 410629, 410630, 410631, 410632, 410706, 410707, 410708, 410709, 410710, 410711 or 410712.

In certain embodiments, a target region is nucleotides 22212-22239 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 22212-22239 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 400, 401, 402, 403, 404, 405 or 406. In certain such embodiments, an antisense compound targeted to nucleotides 22212-22239 of SEQ ID NO: 2 is selected from ISIS NOs: 405994, 405995, 410558, 410559, 410560, 410561, 410627, 410628, 410629, 410630, 410631, 410632, 410707, 410708, 410709, 410710, 410711, 410712 or 410774.

In certain embodiments, a target region is nucleotides 22292-22311 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 22292-22311 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 126. In certain such embodiments, an antisense compound targeted to nucleotides 22292-22311 of SEQ ID NO: 2 is selected from ISIS NOs: 395225 or 399947.

In certain embodiments, a target region is nucleotides 23985-24054 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 23985-24054 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 408, 409 or 410. In certain such embodiments, an antisense compound targeted to nucleotides 23985-24054 of SEQ ID NO: 2 is selected from ISIS NOs: 410776, 410777 or 410778.

In certain embodiments, a target region is nucleotides 24035-24134 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 24035-24134 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 60, 61, 410, 411, 412, 413, 414, 415 or 416. In certain such embodiments, an antisense compound targeted to nucleotides 24035-24134 of SEQ ID NO: 2 is selected from ISIS NOs: 395186, 399817, 399908, 399973, 405996, 405997, 410562, 410563, 410564, 410633, 410634, 410635, 410636, 410713, 410714, 410715, 410716, 410717, 410718, 410778 or 410779.

In certain embodiments, a target region is nucleotides 24095-24121 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 24095-24121 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 60, 61, 411, 412, 413, 414 or 415. In certain such embodiments, an antisense compound targeted to nucleotides 24095-24121 of

SEQ ID NO: 2 is selected from ISIS NOs: 395186, 399817, 399908, 399973, 405996, 405997, 410562, 410563, 410564, 410633, 410634, 410635, 410636, 410713, 410714, 410715, 410716, 410717 or 410718.

In certain embodiments, a target region is nucleotides 24858-24877 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 24858-24877 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 147. In certain such embodiments, an antisense compound targeted to nucleotides 24858-24877 of SEQ ID NO: 2 is selected from ISIS NOs: 395226 or 399948.

In certain embodiments, a target region is nucleotides 24907-24926 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 24907-24926 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 118. In certain such embodiments, an antisense compound targeted to nucleotides 24907-24926 of SEQ ID NO: 2 is selected from ISIS NOs: 399869 or 400025.

In certain embodiments, a target region is nucleotides 25413-25432 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 25413-25432 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 114. In certain such embodiments, an antisense compound targeted to nucleotides 25413-25432 of SEQ ID NO: 2 is selected from ISIS NOs: 399870 or 400026.

In certain embodiments, a target region is nucleotides 25994-26013 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 25994-26013 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 418. In certain such embodiments, an antisense compound targeted to nucleotides 25994-26013 of SEQ ID NO: 2 is selected from ISIS NOs: 410781.

In certain embodiments, a target region is nucleotides 26112-26139 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 26112-26139 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 62, 419, 420, 421, 422, 423, 424, 425 or 426. In certain such embodiments, an antisense compound targeted to nucleotides 26112-26139 of SEQ ID NO: 2 is selected from ISIS NOs: 395187, 399909, 405998, 410565, 410566,

410567, 410568, 410569, 410570, 410571, 410637, 410638, 410639, 410640, 410641, 410642, 410643, 410644, 410719, 410720, 410721, 410722, 410723, 410724, 410725, 410726 or 410727.

In certain embodiments, a target region is nucleotides 26112-26161 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 26112-26161 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 62, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429 or 430. In certain such embodiments, an antisense compound targeted to nucleotides 26112-26161 of SEQ ID NO: 2 is selected from ISIS NOs: 395187, 399909, 405998, 410565, 410566, 410567, 410568, 410569, 410570, 410571, 410572, 410573, 410637, 410638, 410639, 410640, 410641, 410642, 410643, 410644, 410645, 410646, 410719, 410720, 410721, 410722, 410723, 410724, 410725, 410726, 410727, 410728, 410729, 410782 or 410783.

In certain embodiments, a target region is nucleotides 26112-27303 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 26112-27303 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 112, 122, 135, 153, 154, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445 or 446. In certain such embodiments, an antisense compound targeted to nucleotides 26112-27303 of SEQ ID NO: 2 is selected from ISIS NOs: 395187, 395188, 395189, 395190, 395191, 395192, 395193, 395194, 395195, 395196, 395197, 395198, 395199, 399818, 399819, 399820, 399821, 399822, 399823, 399824, 399825, 399909, 399910, 399911, 399912, 399913, 399914, 399915, 399916, 399917, 399918, 399919, 399920, 399921, 399974, 399975, 399976, 399977, 399978, 399979, 399980, 399981, 405893, 405894, 405895, 405896, 405897, 405898, 405899, 405900, 405901, 405902, 405903, 405904, 405905, 405906, 405907, 405908, 405998, 410565, 410566, 410567, 410568, 410569, 410570, 410571, 410572, 410573, 410637, 410638, 410639, 410640, 410641, 410642, 410643, 410644, 410645, 410646, 410719, 410720, 410721, 410722, 410723, 410724, 410725, 410726, 410727, 410728, 410729, 410782 or 410783.

In certain embodiments, a target region is nucleotides 26113-26140 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 26113-26140 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 62, 420, 421, 422, 423, 424, 425, 426 or 427. In certain such embodiments, an antisense compound targeted to nucleotides 26113-26140 of SEQ ID NO: 2 is selected from ISIS NOs: 395187, 399909, 405998, 410566, 410567,

410568, 410569, 410570, 410571, 410572, 410638, 410639, 410640, 410641, 410642, 410643, 410644, 410645, 410720, 410721, 410722, 410723, 410724, 410725, 410726, 410727 or 410728.

In certain embodiments, a target region is nucleotides 26114-26141 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 26114-26141 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 62, 421, 422, 423, 424, 425, 426, 427 or 248. In certain such embodiments, an antisense compound targeted to nucleotides 26114-26141 of SEQ ID NO: 2 is selected from ISIS NOs: 395187, 399909, 405998, 410567, 410568, 410569, 410570, 410571, 410572, 410573, 410639, 410640, 410641, 410642, 410643, 410644, 410645, 410646, 410721, 410722, 410723, 410724, 410725, 410726, 410727, 410728 or 410729.

In certain embodiments, a target region is nucleotides 26115-26141 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 26115-26141 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 62, 422, 423, 424, 425, 426, 427 or 248. In certain such embodiments, an antisense compound targeted to nucleotides 26115-26141 of SEQ ID NO: 2 is selected from ISIS NOs: 395187, 399909, 405998, 410568, 410569, 410570, 410571, 410572, 410573, 410640, 410641, 410642, 410643, 410644, 410645, 410646, 410722, 410723, 410724, 410725, 410726, 410727, 410728 or 410729.

In certain embodiments, a target region is nucleotides 26116-26141 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 26116-26141 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 62, 423, 424, 425, 426, 427 or 428. In certain such embodiments, an antisense compound targeted to nucleotides 26116-26141 of SEQ ID NO: 2 is selected from ISIS NOs: 395187, 399909, 405998, 410569, 410570, 410571, 410572, 410573, 410641, 410642, 410643, 410644, 410645, 410646, 410723, 410724, 410725, 410726, 410727 or 410728.

In certain embodiments, a target region is nucleotides 26117-26141 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 26117-26141 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 62, 424, 425, 426, 427 or 428. In certain such embodiments, an antisense compound targeted to nucleotides 26117-26141 of SEQ ID NO: 2 is selected from ISIS NOs: 395187, 399909, 405998, 410570, 410571, 410572,

410573, 410642, 410643, 410644, 410645, 410646, 410724, 410725, 410726, 410727, 410728 or 410729.

In certain embodiments, a target region is nucleotides 26117-26475 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 26117-26475 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 62, 63, 64, 65, 66, 67, 122, 153, 154, 424, 425, 426, 427, 428, 429 or 430. In certain such embodiments, an antisense compound targeted to nucleotides 26117-26475 of SEQ ID NO: 2 is selected from ISIS NOs: 395187, 395188, 395189, 395190, 395191, 395192, 399818, 399819, 399820, 399909, 399910, 399911, 399912, 399913, 399914, 399974, 399975, 399976, 405998, 410570, 410571, 410572, 410573, 410642, 410643, 410644, 410645, 410646, 410724, 410725, 410726, 410727, 410728, 410729, 410782 or 410783.

In certain embodiments, a target region is nucleotides 26118-26141 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 26118-26141 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 424, 425, 426, 427 or 428. In certain such embodiments, an antisense compound targeted to nucleotides 26118-26141 of SEQ ID NO: 2 is selected from ISIS NOs: 405998, 410570, 410571, 410572, 410573, 410642, 410643, 410644, 410645, 410646, 410725, 410726, 410727, 410728 or 410729.

In certain embodiments, a target region is nucleotides 26120-26141 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 26120-26141 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 426, 427 or 428. In certain such embodiments, an antisense compound targeted to nucleotides 26120-26141 of SEQ ID NO: 2 is selected from ISIS NOs: 405998, 410572, 410573, 410644, 410645, 410646, 410727, 410728 or 410729.

In certain embodiments, a target region is nucleotides 26132-26151 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 26132-26151 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 429. In certain such embodiments, an antisense compound targeted to nucleotides 26132-26151 of SEQ ID NO: 2 is selected from ISIS NOs: 410782.

In certain embodiments, a target region is nucleotides 26142-26161 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 26142-26161 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 430. In certain such embodiments, an antisense compound targeted to nucleotides 26142-26161 of SEQ ID NO: 2 is selected from ISIS NOs: 410783.

In certain embodiments, a target region is nucleotides 26217-26241 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 26217-26241 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 63 or 154. In certain such embodiments, an antisense compound targeted to nucleotides 26217-26241 of SEQ ID NO: 2 is selected from ISIS NOs: 395188, 399818 or 399910.

In certain embodiments, a target region is nucleotides 26311-26335 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 26311-26335 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 64 or 65. In certain such embodiments, an antisense compound targeted to nucleotides 26311-26335 of SEQ ID NO: 2 is selected from ISIS NOs: 395189, 399819, 399911 or 399975.

In certain embodiments, a target region is nucleotides 26389-26432 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 26389-26432 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 66, 67 or 122. In certain such embodiments, an antisense compound targeted to nucleotides 26389-26432 of SEQ ID NO: 2 is selected from ISIS NOs: 395190, 395191, 399820, 399912, 399913 or 399976.

In certain embodiments, a target region is nucleotides 26456-26576 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 26456-26576 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 68 or 153. In certain such embodiments, an antisense compound targeted to nucleotides 26456-26576 of SEQ ID NO: 2 is selected from ISIS NOs: 395192, 395193, 399914 or 399915.

In certain embodiments, a target region is nucleotides 26635-26662 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 26635-26662 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid

comprises a nucleotide sequence selected from SEQ ID NOs: 69, 431, 432, 433, 434, 435, 436, 437 or 438. In certain such embodiments, an antisense compound targeted to nucleotides 26635-26662 of SEQ ID NO: 2 is selected from ISIS NOs: 395194, 399916, 405893, 405894, 405895, 405896, 405897, 405898, 405899 or 405900.

In certain embodiments, a target region is nucleotides 26707-26734 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 26707-26734 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 70, 71, 439, 440, 441, 442, 443 or 444. In certain such embodiments, an antisense compound targeted to nucleotides 26707-26734 of SEQ ID NO: 2 is selected from ISIS NOs: 395195, 399821, 399917, 399977, 405901, 405902, 405903, 405904, 405905 or 405906.

In certain embodiments, a target region is nucleotides 26707-26736 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 26707-26736 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 70, 71, 439, 440, 441, 442, 443, 444, 445 or 446. In certain such embodiments, an antisense compound targeted to nucleotides 26707-26736 of SEQ ID NO: 2 is selected from ISIS NOs: 395195, 399821, 399917, 399977, 405901, 405902, 405903, 405904, 405905, 405906, 405907 or 405908.

In certain embodiments, a target region is nucleotides 26790-26820 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 26790-26820 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 72, 73 or 135. In certain such embodiments, an antisense compound targeted to nucleotides 26790-26820 of SEQ ID NO: 2 is selected from ISIS NOs: 395196, 399822, 399823, 399918, 399978 or 399979.

In certain embodiments, a target region is nucleotides 27034-27263 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 27034-27263 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 74, 75 or 112. In certain such embodiments, an antisense compound targeted to nucleotides 27034-27263 of SEQ ID NO: 2 is selected from ISIS NOs: 395197, 395198, 399824, 399919, 399920 or 399980.

In certain embodiments, a target region is nucleotides 27279-27303 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 27279-27303 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid

comprises a nucleotide sequence selected from SEQ ID NOs: 76 or 77. In certain such embodiments, an antisense compound targeted to nucleotides 27279-27303 of SEQ ID NO: 2 is selected from ISIS NOs: 395199, 399825, 399921 or 399981.

In certain embodiments, a target region is nucleotides 27350-27376 of SEQ ID NO: 2. In certain embodiments, an antisense compound is targeted to nucleotides 27350-27376 SEQ ID NO: 2. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 78 or 99. In certain such embodiments, an antisense compound targeted to nucleotides 27350-27376 of SEQ ID NO: 2 is selected from ISIS NOs: 395200, 399826, 399922 or 399982.

In certain embodiments, antisense compounds target a PCSK9 nucleic acid having the sequence of GENBANK® Accession No. AK124635.1, first deposited with GENBANK® on September 8, 2003, and incorporated herein as SEQ ID NO: 3. In certain such embodiments, an antisense oligonucleotide is targeted to SEQ ID NO: 3. In certain such embodiments, an antisense oligonucleotide that is targeted to SEQ ID NO: 3 is at least 90% complementary to SEQ ID NO: 1. In certain such embodiments, an antisense oligonucleotide that is targeted to SEQ ID NO: 3 is at least 95% complementary to SEQ ID NO: 3. In certain such embodiments, an antisense oligonucleotide that is targeted to SEQ ID NO: 3 is 100% complementary to SEQ ID NO: 3. In certain such embodiments, an antisense oligonucleotide comprises a nucleotide sequence selected from a nucleotide sequence set forth in Table 11.

**Table 11: Nucleotide sequences targeted to AK124635.1 (SEQ ID NO: 3)**

| SEQ ID NO | 5' Target Site on SEQ ID NO: 3 | 3' Target Site on SEQ ID NO: 3 | Sequences (5'-3') |
|---|---|---|---|
| 85 | 155 | 174 | ACAAATTCCCAGACTCAGCA |
| 100 | 220 | 239 | ATCTCAGGACAGGTGAGCAA |
| 116 | 234 | 253 | GAGTAGAGATTCTCATCTCA |
| 129 | 290 | 309 | GTGCCATCTGAACAGCACCT |
| 117 | 302 | 321 | GAGTCTTCTGAAGTGCCATC |
| 81 | 377 | 396 | AAGCAGGGCCTCAGGTGGAA |
| 110 | 400 | 419 | CCTGGAACCCCTGCAGCCAG |
| 152 | 451 | 470 | TTCAGGCAGGTTGCTGCTAG |
| 83 | 460 | 479 | AAGGAAGACTTCAGGCAGGT |
| 140 | 472 | 491 | TCAGCCAGGCCAAAGGAAGA |
| 137 | 586 | 605 | TAGGGAGAGCTCACAGATGC |
| 136 | 596 | 615 | TAGGAGAAAGTAGGGAGAGC |
| 132 | 653 | 672 | TAAAAGCTGCAAGAGACTCA |
| 139 | 741 | 760 | TCAGAGAAAACAGTCACCGA |

| SEQ ID NO | 5' Target Site on SEQ ID NO: 3 | 3' Target Site on SEQ ID NO: 3 | Sequences (5'-3') |
|---|---|---|---|
| 92 | 871 | 890 | AGAGACAGGAAGCTGCAGCT |
| 142 | 878 | 897 | TCATTTTAGAGACAGGAAGC |
| 113 | 915 | 934 | GAATAACAGTGATGTCTGGC |
| 138 | 968 | 987 | TCACAGCTCACCGAGTCTGC |
| 98 | 998 | 1017 | AGTGTAAAATAAAGCCCCTA |
| 96 | 1075 | 1094 | AGGACCCAAGTCATCCTGCT |
| 124 | 1105 | 1124 | GGCCATCAGCTGGCAATGCT |
| 82 | 1144 | 1163 | AAGGAAAGGGAGGCCTAGAG |
| 133 | 1149 | 1168 | TAGACAAGGAAAGGGAGGCC |
| 103 | 1155 | 1174 | ATTTCATAGACAAGGAAAGG |
| 155 | 1275 | 1294 | CTTATAGTTAACACACAGAA |
| 156 | 1283 | 1302 | AAGTCAACCTTATAGTTAAC |
| 146 | 1315 | 1334 | TGACATTTGTGGGAGAGGAG |
| 161 | 1322 | 1341 | TCCAAGGTGACATTTGTGGG |
| 215 | 1351 | 1370 | ATACACCTCCACCAGGCTGC |
| 216 | 1362 | 1381 | GTGTCTAGGAGATACACCTC |
| 19 | 1365 | 1384 | CTGGTGTCTAGGAGATACAC |
| 217 | 1367 | 1386 | TGCTGGTGTCTAGGAGATAC |
| 20 | 1370 | 1389 | GTATGCTGGTGTCTAGGAGA |
| 21 | 1390 | 1409 | GATTTCCCGGTGGTCACTCT |
| 218 | 1392 | 1411 | TCGATTTCCCGGTGGTCACT |
| 219 | 1393 | 1412 | CTCGATTTCCCGGTGGTCAC |
| 220 | 1394 | 1413 | CCTCGATTTCCCGGTGGTCA |
| 221 | 1395 | 1414 | CCCTCGATTTCCCGGTGGTC |
| 22 | 1396 | 1415 | GCCCTCGATTTCCCGGTGGT |
| 222 | 1397 | 1416 | TGCCCTCGATTTCCCGGTGG |
| 223 | 1398 | 1417 | CTGCCCTCGATTTCCCGGTG |
| 224 | 1399 | 1418 | CCTGCCCTCGATTTCCCGGT |
| 225 | 1400 | 1419 | CCCTGCCCTCGATTTCCCGG |
| 226 | 1404 | 1423 | ATGACCCTGCCCTCGATTTC |
| 227 | 1406 | 1425 | CCATGACCCTGCCCTCGATT |
| 228 | 1408 | 1427 | GACCATGACCCTGCCCTCGA |
| 23 | 1410 | 1429 | GTGACCATGACCCTGCCCTC |
| 229 | 1412 | 1431 | CGGTGACCATGACCCTGCCC |
| 230 | 1414 | 1433 | GTCGGTGACCATGACCCTGC |
| 231 | 1416 | 1435 | AAGTCGGTGACCATGACCCT |
| 232 | 1418 | 1437 | CGAAGTCGGTGACCATGACC |
| 24 | 1420 | 1439 | CTCGAAGTCGGTGACCATGA |
| 233 | 1428 | 1447 | GGCACATTCTCGAAGTCGGT |
| 25 | 1453 | 1472 | GTGGAAGCGGGTCCCGTCCT |
| 234 | 1463 | 1482 | TGGCCTGTCTGTGGAAGCGG |
| 235 | 1490 | 1509 | GGTGGGTGCCATGACTGTCA |
| 236 | 1493 | 1512 | CCAGGTGGGTGCCATGACTG |
| 237 | 1497 | 1516 | CCTGCCAGGTGGGTGCCATG |
| 26 | 1500 | 1519 | ACCCCTGCCAGGTGGGTGCC |
| 238 | 1502 | 1521 | CCACCCCTGCCAGGTGGGTG |
| 27 | 1505 | 1524 | TGACCACCCCTGCCAGGTGG |
| 239 | 1507 | 1526 | GCTGACCACCCCTGCCAGGT |

| SEQ ID NO | 5' Target Site on SEQ ID NO: 3 | 3' Target Site on SEQ ID NO: 3 | Sequences (5'-3') |
|---|---|---|---|
| 240 | 1515 | 1534 | TCCCGGCCGCTGACCACCCC |
| 241 | 1519 | 1538 | GGCATCCCGGCCGCTGACCA |
| 242 | 1522 | 1541 | GCCGGCATCCCGGCCGCTGA |
| 243 | 1527 | 1546 | GCCACGCCGGCATCCCGGCC |
| 244 | 1528 | 1547 | GGCCACGCCGGCATCCCGGC |
| 245 | 1529 | 1548 | TGGCCACGCCGGCATCCCGG |
| 246 | 1530 | 1549 | TTGGCCACGCCGGCATCCCG |
| 247 | 1531 | 1550 | CTTGGCCACGCCGGCATCCC |
| 248 | 1532 | 1551 | CCTTGGCCACGCCGGCATCC |
| 249 | 1533 | 1552 | CCCTTGGCCACGCCGGCATC |
| 28 | 1534 | 1553 | ACCCTTGGCCACGCCGGCAT |
| 447 | 1534 | 1553 | ACCCTTGGTCACGCCGGCAT |
| 250 | 1535 | 1554 | CACCCTTGGCCACGCCGGCA |
| 251 | 1536 | 1555 | GCACCCTTGGCCACGCCGGC |
| 252 | 1537 | 1556 | GGCACCCTTGGCCACGCCGG |
| 253 | 1538 | 1557 | TGGCACCCTTGGCCACGCCG |
| 254 | 1539 | 1558 | CTGGCACCCTTGGCCACGCC |
| 255 | 1540 | 1559 | GCTGGCACCCTTGGCCACGC |
| 256 | 1545 | 1564 | CGCATGCTGGCACCCTTGGC |
| 257 | 1566 | 1585 | CAGTTGAGCACGCGCAGGCT |
| 258 | 1568 | 1587 | GGCAGTTGAGCACGCGCAGG |
| 29 | 1570 | 1589 | TTGGCAGTTGAGCACGCGCA |
| 259 | 1572 | 1591 | CCTTGGCAGTTGAGCACGCG |
| 30 | 1575 | 1594 | TTCCCTTGGCAGTTGAGCAC |
| 260 | 1577 | 1596 | CCTTCCCTTGGCAGTTGAGC |
| 261 | 1581 | 1600 | GTGCCCTTCCCTTGGCAGTT |
| 262 | 1583 | 1602 | CCGTGCCCTTCCCTTGGCAG |
| 263 | 1594 | 1613 | GGTGCCGCTAACCGTGCCCT |
| 264 | 1606 | 1625 | CAGGCCTATGAGGGTGCCGC |
| 31 | 1607 | 1626 | CCAGGCCTATGAGGGTGCCG |
| 458 | 1609 | 1622 | GCCTATGAGGGTGC |
| 459 | 1614 | 1627 | TCCAGGCCTATGAG |
| 265 | 1618 | 1637 | CCGAATAAACTCCAGGCCTA |
| 266 | 1626 | 1645 | TGGCTTTTCCGAATAAACTC |
| 32 | 1628 | 1647 | GCTGGCTTTTCCGAATAAAC |
| 267 | 1630 | 1649 | CAGCTGGCTTTTCCGAATAA |
| 268 | 1632 | 1651 | ACCAGCTGGCTTTTCCGAAT |
| 269 | 1634 | 1653 | GGACCAGCTGGCTTTTCCGA |
| 270 | 1638 | 1657 | GGCTGGACCAGCTGGCTTTT |
| 271 | 1649 | 1668 | GTGGCCCCACAGGCTGGACC |
| 272 | 1662 | 1681 | AGCAGCACCACCAGTGGCCC |
| 273 | 1684 | 1703 | GCTGTACCCACCCGCCAGGG |
| 274 | 1730 | 1749 | CGACCCCAGCCCTCGCCAGG |
| 33 | 1740 | 1759 | GTGACCAGCACGACCCCAGC |
| 275 | 1742 | 1761 | CGGTGACCAGCACGACCCCA |
| 276 | 1744 | 1763 | AGCGGTGACCAGCACGACCC |
| 277 | 1746 | 1765 | GCAGCGGTGACCAGCACGAC |
| 278 | 1748 | 1767 | CGGCAGCGGTGACCAGCACG |

| SEQ ID NO | 5' Target Site on SEQ ID NO: 3 | 3' Target Site on SEQ ID NO: 3 | Sequences (5'-3') |
|---|---|---|---|
| 279 | 1749 | 1768 | CCGGCAGCGGTGACCAGCAC |
| 280 | 1752 | 1771 | TTGCCGGCAGCGGTGACCAG |
| 281 | 1754 | 1773 | AGTTGCCGGCAGCGGTGACC |
| 282 | 1756 | 1775 | GAAGTTGCCGGCAGCGGTGA |
| 283 | 1758 | 1777 | CGGAAGTTGCCGGCAGCGGT |
| 284 | 1760 | 1779 | CCCGGAAGTTGCCGGCAGCG |
| 285 | 1762 | 1781 | GTCCCGGAAGTTGCCGGCAG |
| 306 | 1820 | 1839 | GAGGCACCAATGATGTCCTC |
| 39 | 1822 | 1841 | TGGAGGCACCAATGATGTCC |
| 307 | 1824 | 1843 | GCTGGAGGCACCAATGATGT |
| 308 | 1826 | 1845 | TCGCTGGAGGCACCAATGAT |
| 309 | 1828 | 1847 | AGTCGCTGGAGGCACCAATG |
| 310 | 1830 | 1849 | GCAGTCGCTGGAGGCACCAA |
| 40 | 1833 | 1852 | GCTGCAGTCGCTGGAGGCAC |
| 311 | 1835 | 1854 | GTGCTGCAGTCGCTGGAGGC |
| 312 | 1837 | 1856 | AGGTGCTGCAGTCGCTGGAG |
| 313 | 1839 | 1858 | GCAGGTGCTGCAGTCGCTGG |
| 314 | 1840 | 1859 | AGCAGGTGCTGCAGTCGCTG |
| 315 | 1842 | 1861 | AAAGCAGGTGCTGCAGTCGC |
| 41 | 1844 | 1863 | ACAAAGCAGGTGCTGCAGTC |
| 316 | 1846 | 1865 | ACACAAAGCAGGTGCTGCAG |
| 317 | 1848 | 1867 | TGACACAAAGCAGGTGCTGC |
| 318 | 1858 | 1877 | TCCCACTCTGTGACACAAAG |
| 101 | 1898 | 1917 | ATGGCTGCAATGCCAGCCAC |
| 319 | 1900 | 1919 | TCATGGCTGCAATGCCAGCC |
| 42 | 1903 | 1922 | GCATCATGGCTGCAATGCCA |
| 320 | 1905 | 1924 | CAGCATCATGGCTGCAATGC |
| 321 | 1907 | 1926 | GACAGCATCATGGCTGCAAT |
| 322 | 1909 | 1928 | CAGACAGCATCATGGCTGCA |
| 43 | 1911 | 1930 | GGCAGACAGCATCATGGCTG |
| 323 | 1913 | 1932 | TCGGCAGACAGCATCATGGC |
| 324 | 1915 | 1934 | GCTCGGCAGACAGCATCATG |
| 325 | 1917 | 1936 | CGGCTCGGCAGACAGCATCA |
| 326 | 1919 | 1938 | TCCGGCTCGGCAGACAGCAT |
| 327 | 1933 | 1952 | CGGCCAGGGTGAGCTCCGGC |
| 328 | 1946 | 1965 | CTCTGCCTCAACTCGGCCAG |
| 329 | 1948 | 1967 | GTCTCTGCCTCAACTCGGCC |
| 330 | 1950 | 1969 | CAGTCTCTGCCTCAACTCGG |
| 331 | 1952 | 1971 | ATCAGTCTCTGCCTCAACTC |
| 332 | 1954 | 1973 | GGATCAGTCTCTGCCTCAAC |
| 333 | 1956 | 1975 | GTGGATCAGTCTCTGCCTCA |
| 334 | 1958 | 1977 | AAGTGGATCAGTCTCTGCCT |
| 44 | 1959 | 1978 | GAAGTGGATCAGTCTCTGCC |
| 335 | 1961 | 1980 | GAGAAGTGGATCAGTCTCTG |
| 336 | 1963 | 1982 | CAGAGAAGTGGATCAGTCTC |
| 337 | 1965 | 1984 | GGCAGAGAAGTGGATCAGTC |
| 45 | 1967 | 1986 | TTGGCAGAGAAGTGGATCAG |
| 338 | 1969 | 1988 | CTTTGGCAGAGAAGTGGATC |

| SEQ ID NO | 5' Target Site on SEQ ID NO: 3 | 3' Target Site on SEQ ID NO: 3 | Sequences (5'-3') |
|---|---|---|---|
| 46 | 1972 | 1991 | CATCTTTGGCAGAGAAGTGG |
| 339 | 1974 | 1993 | GACATCTTTGGCAGAGAAGT |
| 340 | 1976 | 1995 | ATGACATCTTTGGCAGAGAA |
| 47 | 1978 | 1997 | TGATGACATCTTTGGCAGAG |
| 341 | 1980 | 1999 | ATTGATGACATCTTTGGCAG |
| 342 | 1982 | 2001 | TCATTGATGACATCTTTGGC |
| 48 | 1985 | 2004 | GCCTCATTGATGACATCTTT |
| 343 | 1987 | 2006 | AGGCCTCATTGATGACATCT |
| 344 | 1989 | 2008 | CCAGGCCTCATTGATGACAT |
| 345 | 1991 | 2010 | AACCAGGCCTCATTGATGAC |
| 346 | 1993 | 2012 | GGAACCAGGCCTCATTGATG |
| 347 | 1994 | 2013 | GGGAACCAGGCCTCATTGAT |
| 348 | 1995 | 2014 | AGGGAACCAGGCCTCATTGA |
| 349 | 1996 | 2015 | CAGGGAACCAGGCCTCATTG |
| 49 | 1997 | 2016 | TCAGGGAACCAGGCCTCATT |
| 350 | 1998 | 2017 | CTCAGGGAACCAGGCCTCAT |
| 351 | 1999 | 2018 | CCTCAGGGAACCAGGCCTCA |
| 352 | 2000 | 2019 | TCCTCAGGGAACCAGGCCTC |
| 353 | 2001 | 2020 | GTCCTCAGGGAACCAGGCCT |
| 50 | 2002 | 2021 | GGTCCTCAGGGAACCAGGCC |
| 354 | 2003 | 2022 | TGGTCCTCAGGGAACCAGGC |
| 355 | 2004 | 2023 | CTGGTCCTCAGGGAACCAGG |
| 356 | 2005 | 2024 | GCTGGTCCTCAGGGAACCAG |
| 357 | 2006 | 2025 | CGCTGGTCCTCAGGGAACCA |
| 87 | 2009 | 2028 | ACCCGCTGGTCCTCAGGGAA |
| 358 | 2011 | 2030 | GTACCCGCTGGTCCTCAGGG |
| 359 | 2013 | 2032 | CAGTACCCGCTGGTCCTCAG |
| 51 | 2016 | 2035 | GGTCAGTACCCGCTGGTCCT |
| 119 | 2038 | 2057 | GCAGGGCGGCCACCAGGTTG |
| 360 | 2061 | 2080 | ACCTGCCCCATGGGTGCTGG |
| 52 | 2073 | 2092 | AAACAGCTGCCAACCTGCCC |
| 361 | 2075 | 2094 | CAAAACAGCTGCCAACCTGC |
| 53 | 2078 | 2097 | CTGCAAAACAGCTGCCAACC |
| 362 | 2080 | 2099 | TCCTGCAAAACAGCTGCCAA |
| 363 | 2082 | 2101 | AGTCCTGCAAAACAGCTGCC |
| 104 | 2085 | 2104 | CACAGTCCTGCAAAACAGCT |
| 130 | 2095 | 2114 | GTGCTGACCACACAGTCCTG |
| 365 | 2105 | 2124 | GGCCCCGAGTGTGCTGACCA |
| 54 | 2108 | 2127 | GTAGGCCCCGAGTGTGCTGA |
| 366 | 2110 | 2129 | GTGTAGGCCCCGAGTGTGCT |
| 367 | 2112 | 2131 | CCGTGTAGGCCCCGAGTGTG |
| 368 | 2114 | 2133 | ATCCGTGTAGGCCCCGAGTG |
| 369 | 2116 | 2135 | CCATCCGTGTAGGCCCCGAG |
| 370 | 2118 | 2137 | GGCCATCCGTGTAGGCCCCG |
| 371 | 2120 | 2139 | GTGGCCATCCGTGTAGGCCC |
| 372 | 2168 | 2187 | CTGGAGCAGCTCAGCAGCTC |
| 460 | 2168 | 2181 | CAGCTCAGCAGCTC |
| 373 | 2170 | 2189 | AACTGGAGCAGCTCAGCAGC |

| SEQ ID NO | 5' Target Site on SEQ ID NO: 3 | 3' Target Site on SEQ ID NO: 3 | Sequences (5'-3') |
|---|---|---|---|
| 55 | 2173 | 2192 | AGAAACTGGAGCAGCTCAGC |
| 374 | 2175 | 2194 | GGAGAAACTGGAGCAGCTCA |
| 375 | 2177 | 2196 | CTGGAGAAACTGGAGCAGCT |
| 56 | 2179 | 2198 | TCCTGGAGAAACTGGAGCAG |
| 408 | 2245 | 2264 | GTGCCAAGGTCCTCCACCTC |
| 409 | 2265 | 2284 | TCAGCACAGGCGGCTTGTGG |
| 410 | 2295 | 2314 | CCACGCACTGGTTGGGCTGA |
| 60 | 2355 | 2374 | CTTTGCATTCCAGACCTGGG |
| 411 | 2356 | 2375 | ACTTTGCATTCCAGACCTGG |
| 412 | 2357 | 2376 | GACTTTGCATTCCAGACCTG |
| 413 | 2358 | 2377 | TGACTTTGCATTCCAGACCT |
| 414 | 2359 | 2378 | TTGACTTTGCATTCCAGACC |
| 61 | 2360 | 2379 | CTTGACTTTGCATTCCAGAC |
| 415 | 2362 | 2381 | TCCTTGACTTTGCATTCCAG |
| 416 | 2375 | 2394 | CGGGATTCCATGCTCCTTGA |
| 417 | 2405 | 2424 | GCAGGCCACGGTCACCTGCT |
| 418 | 2442 | 2461 | GGAGGGCACTGCAGCCAGTC |
| 419 | 2560 | 2579 | CAGATGGCAACGGCTGTCAC |
| 420 | 2561 | 2580 | GCAGATGGCAACGGCTGTCA |
| 421 | 2562 | 2581 | AGCAGATGGCAACGGCTGTC |
| 422 | 2563 | 2582 | CAGCAGATGGCAACGGCTGT |
| 423 | 2564 | 2583 | GCAGCAGATGGCAACGGCTG |
| 62 | 2565 | 2584 | GGCAGCAGATGGCAACGGCT |
| 424 | 2566 | 2585 | CGGCAGCAGATGGCAACGGC |
| 425 | 2567 | 2586 | CCGGCAGCAGATGGCAACGG |
| 426 | 2568 | 2587 | TCCGGCAGCAGATGGCAACG |
| 427 | 2569 | 2588 | CTCCGGCAGCAGATGGCAAC |
| 428 | 2570 | 2589 | GCTCCGGCAGCAGATGGCAA |
| 429 | 2580 | 2599 | CCAGGTGCCGGCTCCGGCAG |
| 430 | 2590 | 2609 | GAGGCCTGCGCCAGGTGCCG |
| 154 | 2665 | 2684 | TTTTAAAGCTCAGCCCCAGC |
| 63 | 2670 | 2689 | AACCATTTTAAAGCTCAGCC |
| 64 | 2759 | 2778 | TCAAGGGCCAGGCCAGCAGC |
| 65 | 2764 | 2783 | CCCACTCAAGGGCCAGGCCA |
| 122 | 2837 | 2856 | GGAGGGAGCTTCCTGGCACC |
| 66 | 2852 | 2871 | ATGCCCCACAGTGAGGGAGG |
| 67 | 2861 | 2880 | AATGGTGAAATGCCCCACAG |
| 153 | 2904 | 2923 | TTGGGAGCAGCTGGCAGCAC |
| 68 | 3005 | 3024 | CATGGGAAGAATCCTGCCTC |
| 431 | 3083 | 3102 | ATGAGGGCCATCAGCACCTT |
| 432 | 3084 | 3103 | GATGAGGGCCATCAGCACCT |
| 433 | 3085 | 3104 | AGATGAGGGCCATCAGCACC |
| 434 | 3086 | 3105 | GAGATGAGGGCCATCAGCAC |
| 69 | 3087 | 3106 | GGAGATGAGGGCCATCAGCA |
| 435 | 3088 | 3107 | TGGAGATGAGGGCCATCAGC |
| 436 | 3089 | 3108 | CTGGAGATGAGGGCCATCAG |
| 437 | 3090 | 3109 | GCTGGAGATGAGGGCCATCA |
| 438 | 3091 | 3110 | AGCTGGAGATGAGGGCCATC |

| SEQ ID NO | 5' Target Site on SEQ ID NO: 3 | 3' Target Site on SEQ ID NO: 3 | Sequences (5'-3') |
|---|---|---|---|
| 461 | 3132 | 3145 | TTAATCAGGGAGCC |
| 70 | 3155 | 3174 | TAGATGCCATCCAGAAAGCT |
| 439 | 3157 | 3176 | GCTAGATGCCATCCAGAAAG |
| 440 | 3158 | 3177 | GGCTAGATGCCATCCAGAAA |
| 441 | 3159 | 3178 | TGGCTAGATGCCATCCAGAA |
| 442 | 3160 | 3179 | CTGGCTAGATGCCATCCAGA |
| 71 | 3161 | 3180 | TCTGGCTAGATGCCATCCAG |
| 443 | 3162 | 3181 | CTCTGGCTAGATGCCATCCA |
| 444 | 3163 | 3182 | CCTCTGGCTAGATGCCATCC |
| 445 | 3164 | 3183 | GCCTCTGGCTAGATGCCATC |
| 446 | 3165 | 3184 | AGCCTCTGGCTAGATGCCAT |
| 72 | 3238 | 3257 | GGCATAGAGCAGAGTAAAGG |
| 73 | 3243 | 3262 | AGCCTGGCATAGAGCAGAGT |
| 135 | 3249 | 3268 | TAGCACAGCCTGGCATAGAG |
| 112 | 3482 | 3501 | GAAGAGGCTTGGCTTCAGAG |
| 74 | 3488 | 3507 | AAGTAAGAAGAGGCTTGGCT |
| 75 | 3692 | 3711 | GCTCAAGGAGGGACAGTTGT |
| 76 | 3727 | 3746 | AAAGATAAATGTCTGCTTGC |
| 77 | 3732 | 3751 | ACCCAAAAGATAAATGTCTG |
| 78 | 3798 | 3817 | TCTTCAAGTTACAAAAGCAA |
| 99 | 3805 | 3824 | ATAAATATCTTCAAGTTACA |

In certain embodiments, gapmer antisense compounds are targeted to a PCSK9 nucleic acid. In certain such embodiments, gapmer antisense compounds are targeted to SEQ ID NO: 3. In certain such embodiments, the nucleotide sequences illustrated in Table 11 have a 5-10-5 gapmer motif. Table 12 illustrates gapmer antisense compounds targeted to SEQ ID NO: 3, having a 5-10-5 motif, where the gap segment comprises 2'-deoxynucleotides and each wing segment comprises nucleotides comprising a 2'-O-methoxyethyl sugar modification. Internucleoside linkages are phosphorthioate, and cytidines are 5-methylcytidines.

**Table 12: Gapmer antisense compounds having a 5-10-5 motif targeted to SEQ ID NO: 3**

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO: 3 | 3' Target Site on SEQ ID NO: 3 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 395201 | 5-10-5 | 85 | 155 | 174 | 0 | ACAAATTCCCAGACTCAGCA |
| 399827 | 5-10-5 | 100 | 220 | 239 | 0 | ATCTCAGGACAGGTGAGCAA |
| 399828 | 5-10-5 | 116 | 234 | 253 | 0 | GAGTAGAGATTCTCATCTCA |
| 395202 | 5-10-5 | 129 | 290 | 309 | 0 | GTGCCATCTGAACAGCACCT |
| 399829 | 5-10-5 | 117 | 302 | 321 | 0 | GAGTCTTCTGAAGTGCCATC |
| 399830 | 5-10-5 | 81 | 377 | 396 | 0 | AAGCAGGGCCTCAGGTGGAA |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO: 3 | 3' Target Site on SEQ ID NO: 3 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 395203 | 5-10-5 | 110 | 400 | 419 | 0 | CCTGGAACCCCTGCAGCCAG |
| 395204 | 5-10-5 | 152 | 451 | 470 | 0 | TTCAGGCAGGTTGCTGCTAG |
| 399831 | 5-10-5 | 83 | 460 | 479 | 0 | AAGGAAGACTTCAGGCAGGT |
| 395205 | 5-10-5 | 140 | 472 | 491 | 0 | TCAGCCAGGCCAAAGGAAGA |
| 399832 | 5-10-5 | 137 | 586 | 605 | 0 | TAGGGAGAGCTCACAGATGC |
| 395206 | 5-10-5 | 136 | 596 | 615 | 0 | TAGGAGAAAGTAGGGAGAGC |
| 395207 | 5-10-5 | 132 | 653 | 672 | 0 | TAAAAGCTGCAAGAGACTCA |
| 395208 | 5-10-5 | 139 | 741 | 760 | 0 | TCAGAGAAAACAGTCACCGA |
| 399833 | 5-10-5 | 92 | 871 | 890 | 0 | AGAGACAGGAAGCTGCAGCT |
| 395209 | 5-10-5 | 142 | 878 | 897 | 0 | TCATTTTAGAGACAGGAAGC |
| 395210 | 5-10-5 | 113 | 915 | 934 | 0 | GAATAACAGTGATGTCTGGC |
| 395211 | 5-10-5 | 138 | 968 | 987 | 0 | TCACAGCTCACCGAGTCTGC |
| 395212 | 5-10-5 | 98 | 998 | 1017 | 0 | AGTGTAAAATAAAGCCCCTA |
| 395213 | 5-10-5 | 96 | 1075 | 1094 | 0 | AGGACCCAAGTCATCCTGCT |
| 395214 | 5-10-5 | 124 | 1105 | 1124 | 0 | GGCCATCAGCTGGCAATGCT |
| 399834 | 5-10-5 | 82 | 1144 | 1163 | 0 | AAGGAAAGGGAGGCCTAGAG |
| 395215 | 5-10-5 | 133 | 1149 | 1168 | 0 | TAGACAAGGAAAGGGAGGCC |
| 395216 | 5-10-5 | 103 | 1155 | 1174 | 0 | ATTTCATAGACAAGGAAAGG |
| 395217 | 5-10-5 | 155 | 1275 | 1294 | 0 | CTTATAGTTAACACACAGAA |
| 399835 | 5-10-5 | 156 | 1283 | 1302 | 0 | AAGTCAACCTTATAGTTAAC |
| 395218 | 5-10-5 | 146 | 1315 | 1334 | 0 | TGACATTTGTGGGAGAGGAG |
| 395219 | 5-10-5 | 161 | 1322 | 1341 | 0 | TCCAAGGTGACATTTGTGGG |
| 395160 | 5-10-5 | 19 | 1365 | 1384 | 0 | CTGGTGTCTAGGAGATACAC |
| 399797 | 5-10-5 | 20 | 1370 | 1389 | 0 | GTATGCTGGTGTCTAGGAGA |
| 395161 | 5-10-5 | 21 | 1390 | 1409 | 0 | GATTTCCCGGTGGTCACTCT |
| 399798 | 5-10-5 | 22 | 1396 | 1415 | 0 | GCCCTCGATTTCCCGGTGGT |
| 399799 | 5-10-5 | 23 | 1410 | 1429 | 0 | GTGACCATGACCCTGCCCTC |
| 395162 | 5-10-5 | 24 | 1420 | 1439 | 0 | CTCGAAGTCGGTGACCATGA |
| 395163 | 5-10-5 | 25 | 1453 | 1472 | 0 | GTGGAAGCGGGTCCCGTCCT |
| 395164 | 5-10-5 | 26 | 1500 | 1519 | 0 | ACCCCTGCCAGGTGGGTGCC |
| 399800 | 5-10-5 | 27 | 1505 | 1524 | 0 | TGACCACCCCTGCCAGGTGG |
| 395165 | 5-10-5 | 28 | 1534 | 1553 | 0 | ACCCTTGGCCACGCCGGCAT |
| 395166 | 5-10-5 | 29 | 1570 | 1589 | 0 | TTGGCAGTTGAGCACGCGCA |
| 399801 | 5-10-5 | 30 | 1575 | 1594 | 0 | TTCCCTTGGCAGTTGAGCAC |
| 395167 | 5-10-5 | 31 | 1607 | 1626 | 0 | CCAGGCCTATGAGGGTGCCG |
| 395168 | 5-10-5 | 32 | 1628 | 1647 | 0 | GCTGGCTTTTCCGAATAAAC |
| 395169 | 5-10-5 | 33 | 1740 | 1759 | 0 | GTGACCAGCACGACCCCAGC |
| 395175 | 5-10-5 | 39 | 1822 | 1841 | 0 | TGGAGGCACCAATGATGTCC |
| 399804 | 5-10-5 | 40 | 1833 | 1852 | 0 | GCTGCAGTCGCTGGAGGCAC |
| 399805 | 5-10-5 | 41 | 1844 | 1863 | 0 | ACAAAGCAGGTGCTGCAGTC |
| 395176 | 5-10-5 | 101 | 1898 | 1917 | 0 | ATGGCTGCAATGCCAGCCAC |
| 399806 | 5-10-5 | 42 | 1903 | 1922 | 0 | GCATCATGGCTGCAATGCCA |
| 399807 | 5-10-5 | 43 | 1911 | 1930 | 0 | GGCAGACAGCATCATGGCTG |
| 399808 | 5-10-5 | 44 | 1959 | 1978 | 0 | GAAGTGGATCAGTCTCTGCC |
| 395177 | 5-10-5 | 45 | 1967 | 1986 | 0 | TTGGCAGAGAAGTGGATCAG |
| 399809 | 5-10-5 | 46 | 1972 | 1991 | 0 | CATCTTTGGCAGAGAAGTGG |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO: 3 | 3' Target Site on SEQ ID NO: 3 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 399810 | 5-10-5 | 47 | 1978 | 1997 | 0 | TGATGACATCTTTGGCAGAG |
| 399811 | 5-10-5 | 48 | 1985 | 2004 | 0 | GCCTCATTGATGACATCTTT |
| 399812 | 5-10-5 | 49 | 1997 | 2016 | 0 | TCAGGGAACCAGGCCTCATT |
| 395178 | 5-10-5 | 50 | 2002 | 2021 | 0 | GGTCCTCAGGGAACCAGGCC |
| 395179 | 5-10-5 | 87 | 2009 | 2028 | 0 | ACCCGCTGGTCCTCAGGGAA |
| 399813 | 5-10-5 | 51 | 2016 | 2035 | 0 | GGTCAGTACCCGCTGGTCCT |
| 395180 | 5-10-5 | 119 | 2038 | 2057 | 0 | GCAGGGCGGCCACCAGGTTG |
| 395181 | 5-10-5 | 52 | 2073 | 2092 | 0 | AAACAGCTGCCAACCTGCCC |
| 399814 | 5-10-5 | 53 | 2078 | 2097 | 0 | CTGCAAAACAGCTGCCAACC |
| 395220 | 5-10-5 | 104 | 2085 | 2104 | 0 | CACAGTCCTGCAAAACAGCT |
| 399836 | 5-10-5 | 130 | 2095 | 2114 | 0 | GTGCTGACCACACAGTCCTG |
| 395182 | 5-10-5 | 54 | 2108 | 2127 | 0 | GTAGGCCCCGAGTGTGCTGA |
| 399815 | 5-10-5 | 55 | 2173 | 2192 | 0 | AGAAACTGGAGCAGCTCAGC |
| 399816 | 5-10-5 | 56 | 2179 | 2198 | 0 | TCCTGGAGAAACTGGAGCAG |
| 395186 | 5-10-5 | 60 | 2355 | 2374 | 0 | CTTTGCATTCCAGACCTGGG |
| 399817 | 5-10-5 | 61 | 2360 | 2379 | 0 | CTTGACTTTGCATTCCAGAC |
| 395187 | 5-10-5 | 62 | 2565 | 2584 | 0 | GGCAGCAGATGGCAACGGCT |
| 395188 | 5-10-5 | 154 | 2665 | 2684 | 0 | TTTTAAAGCTCAGCCCCAGC |
| 399818 | 5-10-5 | 63 | 2670 | 2689 | 0 | AACCATTTTAAAGCTCAGCC |
| 395189 | 5-10-5 | 64 | 2759 | 2778 | 0 | TCAAGGGCCAGGCCAGCAGC |
| 399819 | 5-10-5 | 65 | 2764 | 2783 | 0 | CCCACTCAAGGGCCAGGCCA |
| 399820 | 5-10-5 | 122 | 2837 | 2856 | 0 | GGAGGGAGCTTCCTGGCACC |
| 395190 | 5-10-5 | 66 | 2852 | 2871 | 0 | ATGCCCCACAGTGAGGGAGG |
| 395191 | 5-10-5 | 67 | 2861 | 2880 | 0 | AATGGTGAAATGCCCCACAG |
| 395192 | 5-10-5 | 153 | 2904 | 2923 | 0 | TTGGGAGCAGCTGGCAGCAC |
| 395193 | 5-10-5 | 68 | 3005 | 3024 | 0 | CATGGGAAGAATCCTGCCTC |
| 395194 | 5-10-5 | 69 | 3087 | 3106 | 0 | GGAGATGAGGGCCATCAGCA |
| 395195 | 5-10-5 | 70 | 3155 | 3174 | 0 | TAGATGCCATCCAGAAAGCT |
| 399821 | 5-10-5 | 71 | 3161 | 3180 | 0 | TCTGGCTAGATGCCATCCAG |
| 395196 | 5-10-5 | 72 | 3238 | 3257 | 0 | GGCATAGAGCAGAGTAAAGG |
| 399822 | 5-10-5 | 73 | 3243 | 3262 | 0 | AGCCTGGCATAGAGCAGAGT |
| 399823 | 5-10-5 | 135 | 3249 | 3268 | 0 | TAGCACAGCCTGGCATAGAG |
| 395197 | 5-10-5 | 112 | 3482 | 3501 | 0 | GAAGAGGCTTGGCTTCAGAG |
| 399824 | 5-10-5 | 74 | 3488 | 3507 | 0 | AAGTAAGAAGAGGCTTGGCT |
| 395198 | 5-10-5 | 75 | 3692 | 3711 | 0 | GCTCAAGGAGGGACAGTTGT |
| 395199 | 5-10-5 | 76 | 3727 | 3746 | 0 | AAAGATAAATGTCTGCTTGC |
| 399825 | 5-10-5 | 77 | 3732 | 3751 | 0 | ACCCAAAAGATAAATGTCTG |
| 395200 | 5-10-5 | 78 | 3798 | 3817 | 0 | TCTTCAAGTTACAAAAGCAA |
| 399826 | 5-10-5 | 99 | 3805 | 3824 | 0 | ATAAATATCTTCAAGTTACA |
| 405869 | 5-10-5 | 218 | 1392 | 1411 | 0 | TCGATTTCCCGGTGGTCACT |
| 405870 | 5-10-5 | 219 | 1393 | 1412 | 0 | CTCGATTTCCCGGTGGTCAC |
| 405871 | 5-10-5 | 220 | 1394 | 1413 | 0 | CCTCGATTTCCCGGTGGTCA |
| 405872 | 5-10-5 | 221 | 1395 | 1414 | 0 | CCCTCGATTTCCCGGTGGTC |
| 405873 | 5-10-5 | 222 | 1397 | 1416 | 0 | TGCCCTCGATTTCCCGGTGG |
| 405874 | 5-10-5 | 223 | 1398 | 1417 | 0 | CTGCCCTCGATTTCCCGGTG |
| 405875 | 5-10-5 | 224 | 1399 | 1418 | 0 | CCTGCCCTCGATTTCCCGGT |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO: 3 | 3' Target Site on SEQ ID NO: 3 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 405876 | 5-10-5 | 225 | 1400 | 1419 | 0 | CCCTGCCCTCGATTTCCCGG |
| 405877 | 5-10-5 | 246 | 1530 | 1549 | 0 | TTGGCCACGCCGGCATCCCG |
| 405878 | 5-10-5 | 247 | 1531 | 1550 | 0 | CTTGGCCACGCCGGCATCCC |
| 405879 | 5-10-5 | 248 | 1532 | 1551 | 0 | CCTTGGCCACGCCGGCATCC |
| 405880 | 5-10-5 | 249 | 1533 | 1552 | 0 | CCCTTGGCCACGCCGGCATC |
| 405881 | 5-10-5 | 250 | 1535 | 1554 | 0 | CACCCTTGGCCACGCCGGCA |
| 405882 | 5-10-5 | 251 | 1536 | 1555 | 0 | GCACCCTTGGCCACGCCGGC |
| 405883 | 5-10-5 | 252 | 1537 | 1556 | 0 | GGCACCCTTGGCCACGCCGG |
| 405884 | 5-10-5 | 253 | 1538 | 1557 | 0 | TGGCACCCTTGGCCACGCCG |
| 405885 | 5-10-5 | 346 | 1993 | 2012 | 0 | GGAACCAGGCCTCATTGATG |
| 405886 | 5-10-5 | 347 | 1994 | 2013 | 0 | GGGAACCAGGCCTCATTGAT |
| 405887 | 5-10-5 | 348 | 1995 | 2014 | 0 | AGGGAACCAGGCCTCATTGA |
| 405888 | 5-10-5 | 349 | 1996 | 2015 | 0 | CAGGGAACCAGGCCTCATTG |
| 405889 | 5-10-5 | 350 | 1998 | 2017 | 0 | CTCAGGGAACCAGGCCTCAT |
| 405890 | 5-10-5 | 351 | 1999 | 2018 | 0 | CCTCAGGGAACCAGGCCTCA |
| 405891 | 5-10-5 | 352 | 2000 | 2019 | 0 | TCCTCAGGGAACCAGGCCTC |
| 405892 | 5-10-5 | 353 | 2001 | 2020 | 0 | GTCCTCAGGGAACCAGGCCT |
| 405893 | 5-10-5 | 431 | 3083 | 3102 | 0 | ATGAGGGCCATCAGCACCTT |
| 405894 | 5-10-5 | 432 | 3084 | 3103 | 0 | GATGAGGGCCATCAGCACCT |
| 405895 | 5-10-5 | 433 | 3085 | 3104 | 0 | AGATGAGGGCCATCAGCACC |
| 405896 | 5-10-5 | 434 | 3086 | 3105 | 0 | GAGATGAGGGCCATCAGCAC |
| 405897 | 5-10-5 | 435 | 3088 | 3107 | 0 | TGGAGATGAGGGCCATCAGC |
| 405898 | 5-10-5 | 436 | 3089 | 3108 | 0 | CTGGAGATGAGGGCCATCAG |
| 405899 | 5-10-5 | 437 | 3090 | 3109 | 0 | GCTGGAGATGAGGGCCATCA |
| 405900 | 5-10-5 | 438 | 3091 | 3110 | 0 | AGCTGGAGATGAGGGCCATC |
| 405901 | 5-10-5 | 439 | 3157 | 3176 | 0 | GCTAGATGCCATCCAGAAAG |
| 405902 | 5-10-5 | 440 | 3158 | 3177 | 0 | GGCTAGATGCCATCCAGAAA |
| 405903 | 5-10-5 | 441 | 3159 | 3178 | 0 | TGGCTAGATGCCATCCAGAA |
| 405904 | 5-10-5 | 442 | 3160 | 3179 | 0 | CTGGCTAGATGCCATCCAGA |
| 405905 | 5-10-5 | 443 | 3162 | 3181 | 0 | CTCTGGCTAGATGCCATCCA |
| 405906 | 5-10-5 | 444 | 3163 | 3182 | 0 | CCTCTGGCTAGATGCCATCC |
| 405907 | 5-10-5 | 445 | 3164 | 3183 | 0 | GCCTCTGGCTAGATGCCATC |
| 405908 | 5-10-5 | 446 | 3165 | 3184 | 0 | AGCCTCTGGCTAGATGCCAT |
| 405909 | 5-10-5 | 267 | 1630 | 1649 | 0 | CAGCTGGCTTTTCCGAATAA |
| 405910 | 5-10-5 | 268 | 1632 | 1651 | 0 | ACCAGCTGGCTTTTCCGAAT |
| 405911 | 5-10-5 | 269 | 1634 | 1653 | 0 | GGACCAGCTGGCTTTTCCGA |
| 405912 | 5-10-5 | 270 | 1638 | 1657 | 0 | GGCTGGACCAGCTGGCTTTT |
| 405913 | 5-10-5 | 275 | 1742 | 1761 | 0 | CGGTGACCAGCACGACCCCA |
| 405914 | 5-10-5 | 276 | 1744 | 1763 | 0 | AGCGGTGACCAGCACGACCC |
| 405915 | 5-10-5 | 277 | 1746 | 1765 | 0 | GCAGCGGTGACCAGCACGAC |
| 405916 | 5-10-5 | 278 | 1748 | 1767 | 0 | CGGCAGCGGTGACCAGCACG |
| 405917 | 5-10-5 | 280 | 1752 | 1771 | 0 | TTGCCGGCAGCGGTGACCAG |
| 405918 | 5-10-5 | 281 | 1754 | 1773 | 0 | AGTTGCCGGCAGCGGTGACC |
| 405919 | 5-10-5 | 282 | 1756 | 1775 | 0 | GAAGTTGCCGGCAGCGGTGA |
| 405920 | 5-10-5 | 283 | 1758 | 1777 | 0 | CGGAAGTTGCCGGCAGCGGT |
| 405921 | 5-10-5 | 284 | 1760 | 1779 | 0 | CCCGGAAGTTGCCGGCAGCG |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO: 3 | 3' Target Site on SEQ ID NO: 3 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 405922 | 5-10-5 | 285 | 1762 | 1781 | 0 | GTCCCGGAAGTTGCCGGCAG |
| 405937 | 5-10-5 | 306 | 1820 | 1839 | 0 | GAGGCACCAATGATGTCCTC |
| 405938 | 5-10-5 | 307 | 1824 | 1843 | 0 | GCTGGAGGCACCAATGATGT |
| 405939 | 5-10-5 | 308 | 1826 | 1845 | 0 | TCGCTGGAGGCACCAATGAT |
| 405940 | 5-10-5 | 309 | 1828 | 1847 | 0 | AGTCGCTGGAGGCACCAATG |
| 405941 | 5-10-5 | 310 | 1830 | 1849 | 0 | GCAGTCGCTGGAGGCACCAA |
| 405942 | 5-10-5 | 311 | 1835 | 1854 | 0 | GTGCTGCAGTCGCTGGAGGC |
| 405943 | 5-10-5 | 312 | 1837 | 1856 | 0 | AGGTGCTGCAGTCGCTGGAG |
| 405944 | 5-10-5 | 314 | 1840 | 1859 | 0 | AGCAGGTGCTGCAGTCGCTG |
| 405945 | 5-10-5 | 315 | 1842 | 1861 | 0 | AAAGCAGGTGCTGCAGTCGC |
| 405946 | 5-10-5 | 316 | 1846 | 1865 | 0 | ACACAAAGCAGGTGCTGCAG |
| 405947 | 5-10-5 | 317 | 1848 | 1867 | 0 | TGACACAAAGCAGGTGCTGC |
| 405948 | 5-10-5 | 319 | 1900 | 1919 | 0 | TCATGGCTGCAATGCCAGCC |
| 405949 | 5-10-5 | 320 | 1905 | 1924 | 0 | CAGCATCATGGCTGCAATGC |
| 405950 | 5-10-5 | 321 | 1907 | 1926 | 0 | GACAGCATCATGGCTGCAAT |
| 405951 | 5-10-5 | 322 | 1909 | 1928 | 0 | CAGACAGCATCATGGCTGCA |
| 405952 | 5-10-5 | 323 | 1913 | 1932 | 0 | TCGGCAGACAGCATCATGGC |
| 405953 | 5-10-5 | 325 | 1917 | 1936 | 0 | CGGCTCGGCAGACAGCATCA |
| 405954 | 5-10-5 | 326 | 1919 | 1938 | 0 | TCCGGCTCGGCAGACAGCAT |
| 405955 | 5-10-5 | 328 | 1946 | 1965 | 0 | CTCTGCCTCAACTCGGCCAG |
| 405956 | 5-10-5 | 329 | 1948 | 1967 | 0 | GTCTCTGCCTCAACTCGGCC |
| 405957 | 5-10-5 | 330 | 1950 | 1969 | 0 | CAGTCTCTGCCTCAACTCGG |
| 405958 | 5-10-5 | 331 | 1952 | 1971 | 0 | ATCAGTCTCTGCCTCAACTC |
| 405959 | 5-10-5 | 332 | 1954 | 1973 | 0 | GGATCAGTCTCTGCCTCAAC |
| 405960 | 5-10-5 | 333 | 1956 | 1975 | 0 | GTGGATCAGTCTCTGCCTCA |
| 405961 | 5-10-5 | 334 | 1958 | 1977 | 0 | AAGTGGATCAGTCTCTGCCT |
| 405962 | 5-10-5 | 335 | 1961 | 1980 | 0 | GAGAAGTGGATCAGTCTCTG |
| 405963 | 5-10-5 | 337 | 1965 | 1984 | 0 | GGCAGAGAAGTGGATCAGTC |
| 405964 | 5-10-5 | 338 | 1969 | 1988 | 0 | CTTTGGCAGAGAAGTGGATC |
| 405965 | 5-10-5 | 339 | 1974 | 1993 | 0 | GACATCTTTGGCAGAGAAGT |
| 405966 | 5-10-5 | 340 | 1976 | 1995 | 0 | ATGACATCTTTGGCAGAGAA |
| 405967 | 5-10-5 | 341 | 1980 | 1999 | 0 | ATTGATGACATCTTTGGCAG |
| 405968 | 5-10-5 | 342 | 1982 | 2001 | 0 | TCATTGATGACATCTTTGGC |
| 405969 | 5-10-5 | 343 | 1987 | 2006 | 0 | AGGCCTCATTGATGACATCT |
| 405970 | 5-10-5 | 344 | 1989 | 2008 | 0 | CCAGGCCTCATTGATGACAT |
| 405971 | 5-10-5 | 355 | 2004 | 2023 | 0 | CTGGTCCTCAGGGAACCAGG |
| 405972 | 5-10-5 | 357 | 2006 | 2025 | 0 | CGCTGGTCCTCAGGGAACCA |
| 405973 | 5-10-5 | 358 | 2011 | 2030 | 0 | GTACCCGCTGGTCCTCAGGG |
| 405974 | 5-10-5 | 359 | 2013 | 2032 | 0 | CAGTACCCGCTGGTCCTCAG |
| 405975 | 5-10-5 | 361 | 2075 | 2094 | 0 | CAAAACAGCTGCCAACCTGC |
| 405976 | 5-10-5 | 362 | 2080 | 2099 | 0 | TCCTGCAAAACAGCTGCCAA |
| 405977 | 5-10-5 | 363 | 2082 | 2101 | 0 | AGTCCTGCAAAACAGCTGCC |
| 405978 | 5-10-5 | 365 | 2105 | 2124 | 0 | GGCCCCGAGTGTGCTGACCA |
| 405979 | 5-10-5 | 366 | 2110 | 2129 | 0 | GTGTAGGCCCCGAGTGTGCT |
| 405980 | 5-10-5 | 367 | 2112 | 2131 | 0 | CCGTGTAGGCCCCGAGTGTG |
| 405981 | 5-10-5 | 368 | 2114 | 2133 | 0 | ATCCGTGTAGGCCCCGAGTG |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO: 3 | 3' Target Site on SEQ ID NO: 3 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 405982 | 5-10-5 | 370 | 2118 | 2137 | 0 | GGCCATCCGTGTAGGCCCCG |
| 405983 | 5-10-5 | 371 | 2120 | 2139 | 0 | GTGGCCATCCGTGTAGGCCC |
| 405984 | 5-10-5 | 372 | 2168 | 2187 | 0 | CTGGAGCAGCTCAGCAGCTC |
| 405985 | 5-10-5 | 373 | 2170 | 2189 | 0 | AACTGGAGCAGCTCAGCAGC |
| 405986 | 5-10-5 | 374 | 2175 | 2194 | 0 | GGAGAAACTGGAGCAGCTCA |
| 405987 | 5-10-5 | 375 | 2177 | 2196 | 0 | CTGGAGAAACTGGAGCAGCT |
| 405996 | 5-10-5 | 412 | 2357 | 2376 | 0 | GACTTTGCATTCCAGACCTG |
| 405997 | 5-10-5 | 415 | 2362 | 2381 | 0 | TCCTTGACTTTGCATTCCAG |
| 405998 | 5-10-5 | 426 | 2568 | 2587 | 0 | TCCGGCAGCAGATGGCAACG |
| 406025 | 5-10-5 | 216 | 1362 | 1381 | 0 | GTGTCTAGGAGATACACCTC |
| 406026 | 5-10-5 | 217 | 1367 | 1386 | 0 | TGCTGGTGTCTAGGAGATAC |
| 406027 | 5-10-5 | 226 | 1404 | 1423 | 0 | ATGACCCTGCCCTCGATTTC |
| 406028 | 5-10-5 | 227 | 1406 | 1425 | 0 | CCATGACCCTGCCCTCGATT |
| 406029 | 5-10-5 | 228 | 1408 | 1427 | 0 | GACCATGACCCTGCCCTCGA |
| 406030 | 5-10-5 | 229 | 1412 | 1431 | 0 | CGGTGACCATGACCCTGCCC |
| 406031 | 5-10-5 | 230 | 1414 | 1433 | 0 | GTCGGTGACCATGACCCTGC |
| 406032 | 5-10-5 | 232 | 1418 | 1437 | 0 | CGAAGTCGGTGACCATGACC |
| 406033 | 5-10-5 | 237 | 1497 | 1516 | 0 | CCTGCCAGGTGGGTGCCATG |
| 406034 | 5-10-5 | 238 | 1502 | 1521 | 0 | CCACCCCTGCCAGGTGGGTG |
| 406035 | 5-10-5 | 239 | 1507 | 1526 | 0 | GCTGACCACCCCTGCCAGGT |
| 406036 | 5-10-5 | 241 | 1519 | 1538 | 0 | GGCATCCCGGCCGCTGACCA |
| 406037 | 5-10-5 | 242 | 1522 | 1541 | 0 | GCCGGCATCCCGGCCGCTGA |
| 406038 | 5-10-5 | 245 | 1529 | 1548 | 0 | TGGCCACGCCGGCATCCCGG |
| 406039 | 5-10-5 | 257 | 1566 | 1585 | 0 | CAGTTGAGCACGCGCAGGCT |
| 406040 | 5-10-5 | 258 | 1568 | 1587 | 0 | GGCAGTTGAGCACGCGCAGG |
| 406041 | 5-10-5 | 259 | 1572 | 1591 | 0 | CCTTGGCAGTTGAGCACGCG |
| 406042 | 5-10-5 | 260 | 1577 | 1596 | 0 | CCTTCCCTTGGCAGTTGAGC |
| 406043 | 5-10-5 | 261 | 1581 | 1600 | 0 | GTGCCCTTCCCTTGGCAGTT |
| 406044 | 5-10-5 | 262 | 1583 | 1602 | 0 | CCGTGCCCTTCCCTTGGCAG |
| 406045 | 5-10-5 | 266 | 1626 | 1645 | 0 | TGGCTTTTCCGAATAAACTC |
| 408642 | 5-10-5 | 264 | 1606 | 1625 | 0 | CAGGCCTATGAGGGTGCCGC |
| 408653 | 5-10-5 | 354 | 2003 | 2022 | 0 | TGGTCCTCAGGGAACCAGGC |
| 409126 | 5-10-5 | 447 | 1534 | 1553 | 1 | ACCCTTGGTCACGCCGGCAT |
| 410536 | 5-10-5 | 243 | 1527 | 1546 | 0 | GCCACGCCGGCATCCCGGCC |
| 410537 | 5-10-5 | 244 | 1528 | 1547 | 0 | GGCCACGCCGGCATCCCGGC |
| 410538 | 5-10-5 | 254 | 1539 | 1558 | 0 | CTGGCACCCTTGGCCACGCC |
| 410539 | 5-10-5 | 255 | 1540 | 1559 | 0 | GCTGGCACCCTTGGCCACGC |
| 410540 | 5-10-5 | 356 | 2005 | 2024 | 0 | GCTGGTCCTCAGGGAACCAG |
| 410562 | 5-10-5 | 411 | 2356 | 2375 | 0 | ACTTTGCATTCCAGACCTGG |
| 410563 | 5-10-5 | 413 | 2358 | 2377 | 0 | TGACTTTGCATTCCAGACCT |
| 410564 | 5-10-5 | 414 | 2359 | 2378 | 0 | TTGACTTTGCATTCCAGACC |
| 410565 | 5-10-5 | 419 | 2560 | 2579 | 0 | CAGATGGCAACGGCTGTCAC |
| 410566 | 5-10-5 | 420 | 2561 | 2580 | 0 | GCAGATGGCAACGGCTGTCA |
| 410567 | 5-10-5 | 421 | 2562 | 2581 | 0 | AGCAGATGGCAACGGCTGTC |
| 410568 | 5-10-5 | 422 | 2563 | 2582 | 0 | CAGCAGATGGCAACGGCTGT |
| 410569 | 5-10-5 | 423 | 2564 | 2583 | 0 | GCAGCAGATGGCAACGGCTG |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO: 3 | 3' Target Site on SEQ ID NO: 3 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 410570 | 5-10-5 | 424 | 2566 | 2585 | 0 | CGGCAGCAGATGGCAACGGC |
| 410571 | 5-10-5 | 425 | 2567 | 2586 | 0 | CCGGCAGCAGATGGCAACGG |
| 410572 | 5-10-5 | 427 | 2569 | 2588 | 0 | CTCCGGCAGCAGATGGCAAC |
| 410573 | 5-10-5 | 428 | 2570 | 2589 | 0 | GCTCCGGCAGCAGATGGCAA |
| 410733 | 5-10-5 | 231 | 1416 | 1435 | 0 | AAGTCGGTGACCATGACCCT |
| 410734 | 5-10-5 | 279 | 1749 | 1768 | 0 | CCGGCAGCGGTGACCAGCAC |
| 410737 | 5-10-5 | 313 | 1839 | 1858 | 0 | GCAGGTGCTGCAGTCGCTGG |
| 410738 | 5-10-5 | 324 | 1915 | 1934 | 0 | GCTCGGCAGACAGCATCATG |
| 410739 | 5-10-5 | 336 | 1963 | 1982 | 0 | CAGAGAAGTGGATCAGTCTC |
| 410740 | 5-10-5 | 345 | 1991 | 2010 | 0 | AACCAGGCCTCATTGATGAC |
| 410741 | 5-10-5 | 369 | 2116 | 2135 | 0 | CCATCCGTGTAGGCCCCGAG |
| 410753 | 5-10-5 | 215 | 1351 | 1370 | 0 | ATACACCTCCACCAGGCTGC |
| 410754 | 5-10-5 | 233 | 1428 | 1447 | 0 | GGCACATTCTCGAAGTCGGT |
| 410755 | 5-10-5 | 234 | 1463 | 1482 | 0 | TGGCCTGTCTGTGGAAGCGG |
| 410756 | 5-10-5 | 235 | 1490 | 1509 | 0 | GGTGGGTGCCATGACTGTCA |
| 410757 | 5-10-5 | 240 | 1515 | 1534 | 0 | TCCCGGCCGCTGACCACCCC |
| 410758 | 5-10-5 | 256 | 1545 | 1564 | 0 | CGCATGCTGGCACCCTTGGC |
| 410759 | 5-10-5 | 263 | 1594 | 1613 | 0 | GGTGCCGCTAACCGTGCCCT |
| 410760 | 5-10-5 | 265 | 1618 | 1637 | 0 | CCGAATAAACTCCAGGCCTA |
| 410761 | 5-10-5 | 271 | 1649 | 1668 | 0 | GTGGCCCCACAGGCTGGACC |
| 410762 | 5-10-5 | 272 | 1662 | 1681 | 0 | AGCAGCACCACCAGTGGCCC |
| 410763 | 5-10-5 | 273 | 1684 | 1703 | 0 | GCTGTACCCACCCGCCAGGG |
| 410764 | 5-10-5 | 274 | 1730 | 1749 | 0 | CGACCCCAGCCCTCGCCAGG |
| 410769 | 5-10-5 | 318 | 1858 | 1877 | 0 | TCCCACTCTGTGACACAAAG |
| 410770 | 5-10-5 | 327 | 1933 | 1952 | 0 | CGGCCAGGGTGAGCTCCGGC |
| 410771 | 5-10-5 | 360 | 2061 | 2080 | 0 | ACCTGCCCCATGGGTGCTGG |
| 410776 | 5-10-5 | 408 | 2245 | 2264 | 0 | GTGCCAAGGTCCTCCACCTC |
| 410777 | 5-10-5 | 409 | 2265 | 2284 | 0 | TCAGCACAGGCGGCTTGTGG |
| 410778 | 5-10-5 | 410 | 2295 | 2314 | 0 | CCACGCACTGGTTGGGCTGA |
| 410779 | 5-10-5 | 416 | 2375 | 2394 | 0 | CGGGATTCCATGCTCCTTGA |
| 410780 | 5-10-5 | 417 | 2405 | 2424 | 0 | GCAGGCCACGGTCACCTGCT |
| 410781 | 5-10-5 | 418 | 2442 | 2461 | 0 | GGAGGGCACTGCAGCCAGTC |
| 410782 | 5-10-5 | 429 | 2580 | 2599 | 0 | CCAGGTGCCGGCTCCGGCAG |
| 410783 | 5-10-5 | 430 | 2590 | 2609 | 0 | GAGGCCTGCGCCAGGTGCCG |

In certain embodiments, gap-widened antisense compounds are targeted to a PCSK9 nucleic acid. In certain such embodiments, gap-widened antisense compounds are targeted to SEQ ID NO: 3. In certain such embodiments, the nucleotide sequences illustrated in Table 11 have a 3-14-3 gap-widened motif. Table 13 illustrates gap-widened antisense compounds targeted to SEQ ID NO: 3, having a 3-14-3 motif, where the gap segment comprises 2'-deoxynucleotides and each wing segment comprises nucleotides comprising a 2'-O-

methoxyethyl sugar modification. Internucleoside linkages are phosphorthioate, and cytidines are 5-methylcytidines.

**Table 13: Gapmer antisense compounds having a 3-14-3 motif targeted to SEQ ID NO: 3**

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO: 3 | 3' Target Site on SEQ ID NO: 3 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 399923 | 3-14-3 | 85 | 155 | 174 | 0 | ACAAATTCCCAGACTCAGCA |
| 399983 | 3-14-3 | 100 | 220 | 239 | 0 | ATCTCAGGACAGGTGAGCAA |
| 399984 | 3-14-3 | 116 | 234 | 253 | 0 | GAGTAGAGATTCTCATCTCA |
| 399924 | 3-14-3 | 129 | 290 | 309 | 0 | GTGCCATCTGAACAGCACCT |
| 399985 | 3-14-3 | 117 | 302 | 321 | 0 | GAGTCTTCTGAAGTGCCATC |
| 399986 | 3-14-3 | 81 | 377 | 396 | 0 | AAGCAGGGCCTCAGGTGGAA |
| 399925 | 3-14-3 | 110 | 400 | 419 | 0 | CCTGGAACCCCTGCAGCCAG |
| 399926 | 3-14-3 | 152 | 451 | 470 | 0 | TTCAGGCAGGTTGCTGCTAG |
| 399987 | 3-14-3 | 83 | 460 | 479 | 0 | AAGGAAGACTTCAGGCAGGT |
| 399927 | 3-14-3 | 140 | 472 | 491 | 0 | TCAGCCAGGCCAAAGGAAGA |
| 399988 | 3-14-3 | 137 | 586 | 605 | 0 | TAGGGAGAGCTCACAGATGC |
| 399928 | 3-14-3 | 136 | 596 | 615 | 0 | TAGGAGAAAGTAGGGAGAGC |
| 399929 | 3-14-3 | 132 | 653 | 672 | 0 | TAAAAGCTGCAAGAGACTCA |
| 399930 | 3-14-3 | 139 | 741 | 760 | 0 | TCAGAGAAAACAGTCACCGA |
| 399989 | 3-14-3 | 92 | 871 | 890 | 0 | AGAGACAGGAAGCTGCAGCT |
| 399931 | 3-14-3 | 142 | 878 | 897 | 0 | TCATTTTAGAGACAGGAAGC |
| 399932 | 3-14-3 | 113 | 915 | 934 | 0 | GAATAACAGTGATGTCTGGC |
| 399933 | 3-14-3 | 138 | 968 | 987 | 0 | TCACAGCTCACCGAGTCTGC |
| 399934 | 3-14-3 | 98 | 998 | 1017 | 0 | AGTGTAAAATAAAGCCCCTA |
| 399935 | 3-14-3 | 96 | 1075 | 1094 | 0 | AGGACCCAAGTCATCCTGCT |
| 399936 | 3-14-3 | 124 | 1105 | 1124 | 0 | GGCCATCAGCTGGCAATGCT |
| 399990 | 3-14-3 | 82 | 1144 | 1163 | 0 | AAGGAAAGGGAGGCCTAGAG |
| 399937 | 3-14-3 | 133 | 1149 | 1168 | 0 | TAGACAAGGAAAGGGAGGCC |
| 399938 | 3-14-3 | 103 | 1155 | 1174 | 0 | ATTTCATAGACAAGGAAAGG |
| 399939 | 3-14-3 | 155 | 1275 | 1294 | 0 | CTTATAGTTAACACACAGAA |
| 399991 | 3-14-3 | 156 | 1283 | 1302 | 0 | AAGTCAACCTTATAGTTAAC |
| 399940 | 3-14-3 | 146 | 1315 | 1334 | 0 | TGACATTTGTGGGAGAGGAG |
| 399941 | 3-14-3 | 161 | 1322 | 1341 | 0 | TCCAAGGTGACATTTGTGGG |
| 399882 | 3-14-3 | 19 | 1365 | 1384 | 0 | CTGGTGTCTAGGAGATACAC |
| 399953 | 3-14-3 | 20 | 1370 | 1389 | 0 | GTATGCTGGTGTCTAGGAGA |
| 399883 | 3-14-3 | 21 | 1390 | 1409 | 0 | GATTTCCCGGTGGTCACTCT |
| 399954 | 3-14-3 | 22 | 1396 | 1415 | 0 | GCCCTCGATTTCCCGGTGGT |
| 399955 | 3-14-3 | 23 | 1410 | 1429 | 0 | GTGACCATGACCCTGCCCTC |
| 399884 | 3-14-3 | 24 | 1420 | 1439 | 0 | CTCGAAGTCGGTGACCATGA |
| 399885 | 3-14-3 | 25 | 1453 | 1472 | 0 | GTGGAAGCGGGTCCCGTCCT |
| 399886 | 3-14-3 | 26 | 1500 | 1519 | 0 | ACCCCTGCCAGGTGGGTGCC |
| 399956 | 3-14-3 | 27 | 1505 | 1524 | 0 | TGACCACCCCTGCCAGGTGG |
| 399887 | 3-14-3 | 28 | 1534 | 1553 | 0 | ACCCTTGGCCACGCCGGCAT |
| 399888 | 3-14-3 | 29 | 1570 | 1589 | 0 | TTGGCAGTTGAGCACGCGCA |
| 399957 | 3-14-3 | 30 | 1575 | 1594 | 0 | TTCCCTTGGCAGTTGAGCAC |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO: 3 | 3' Target Site on SEQ ID NO: 3 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 399889 | 3-14-3 | 31 | 1607 | 1626 | 0 | CCAGGCCTATGAGGGTGCCG |
| 399890 | 3-14-3 | 32 | 1628 | 1647 | 0 | GCTGGCTTTTCCGAATAAAC |
| 399891 | 3-14-3 | 33 | 1740 | 1759 | 0 | GTGACCAGCACGACCCCAGC |
| 399897 | 3-14-3 | 39 | 1822 | 1841 | 0 | TGGAGGCACCAATGATGTCC |
| 399960 | 3-14-3 | 40 | 1833 | 1852 | 0 | GCTGCAGTCGCTGGAGGCAC |
| 399961 | 3-14-3 | 41 | 1844 | 1863 | 0 | ACAAAGCAGGTGCTGCAGTC |
| 399898 | 3-14-3 | 101 | 1898 | 1917 | 0 | ATGGCTGCAATGCCAGCCAC |
| 399962 | 3-14-3 | 42 | 1903 | 1922 | 0 | GCATCATGGCTGCAATGCCA |
| 399963 | 3-14-3 | 43 | 1911 | 1930 | 0 | GGCAGACAGCATCATGGCTG |
| 399964 | 3-14-3 | 44 | 1959 | 1978 | 0 | GAAGTGGATCAGTCTCTGCC |
| 399899 | 3-14-3 | 45 | 1967 | 1986 | 0 | TTGGCAGAGAAGTGGATCAG |
| 399965 | 3-14-3 | 46 | 1972 | 1991 | 0 | CATCTTTGGCAGAGAAGTGG |
| 399966 | 3-14-3 | 47 | 1978 | 1997 | 0 | TGATGACATCTTTGGCAGAG |
| 399967 | 3-14-3 | 48 | 1985 | 2004 | 0 | GCCTCATTGATGACATCTTT |
| 399968 | 3-14-3 | 49 | 1997 | 2016 | 0 | TCAGGGAACCAGGCCTCATT |
| 399900 | 3-14-3 | 50 | 2002 | 2021 | 0 | GGTCCTCAGGGAACCAGGCC |
| 399901 | 3-14-3 | 87 | 2009 | 2028 | 0 | ACCCGCTGGTCCTCAGGGAA |
| 399969 | 3-14-3 | 51 | 2016 | 2035 | 0 | GGTCAGTACCCGCTGGTCCT |
| 399902 | 3-14-3 | 119 | 2038 | 2057 | 0 | GCAGGGCGGCCACCAGGTTG |
| 399903 | 3-14-3 | 52 | 2073 | 2092 | 0 | AAACAGCTGCCAACCTGCCC |
| 399970 | 3-14-3 | 53 | 2078 | 2097 | 0 | CTGCAAAACAGCTGCCAACC |
| 399942 | 3-14-3 | 104 | 2085 | 2104 | 0 | CACAGTCCTGCAAAACAGCT |
| 399992 | 3-14-3 | 130 | 2095 | 2114 | 0 | GTGCTGACCACACAGTCCTG |
| 399904 | 3-14-3 | 54 | 2108 | 2127 | 0 | GTAGGCCCCGAGTGTGCTGA |
| 399971 | 3-14-3 | 55 | 2173 | 2192 | 0 | AGAAACTGGAGCAGCTCAGC |
| 399972 | 3-14-3 | 56 | 2179 | 2198 | 0 | TCCTGGAGAAACTGGAGCAG |
| 399908 | 3-14-3 | 60 | 2355 | 2374 | 0 | CTTTGCATTCCAGACCTGGG |
| 399973 | 3-14-3 | 61 | 2360 | 2379 | 0 | CTTGACTTTGCATTCCAGAC |
| 399909 | 3-14-3 | 62 | 2565 | 2584 | 0 | GGCAGCAGATGGCAACGGCT |
| 399910 | 3-14-3 | 154 | 2665 | 2684 | 0 | TTTTAAAGCTCAGCCCCAGC |
| 399974 | 3-14-3 | 63 | 2670 | 2689 | 0 | AACCATTTTAAAGCTCAGCC |
| 399911 | 3-14-3 | 64 | 2759 | 2778 | 0 | TCAAGGGCCAGGCCAGCAGC |
| 399975 | 3-14-3 | 65 | 2764 | 2783 | 0 | CCCACTCAAGGGCCAGGCCA |
| 399976 | 3-14-3 | 122 | 2837 | 2856 | 0 | GGAGGGAGCTTCCTGGCACC |
| 399912 | 3-14-3 | 66 | 2852 | 2871 | 0 | ATGCCCCACAGTGAGGGAGG |
| 399913 | 3-14-3 | 67 | 2861 | 2880 | 0 | AATGGTGAAATGCCCCACAG |
| 399914 | 3-14-3 | 153 | 2904 | 2923 | 0 | TTGGGAGCAGCTGGCAGCAC |
| 399915 | 3-14-3 | 68 | 3005 | 3024 | 0 | CATGGGAAGAATCCTGCCTC |
| 399916 | 3-14-3 | 69 | 3087 | 3106 | 0 | GGAGATGAGGGCCATCAGCA |
| 399917 | 3-14-3 | 70 | 3155 | 3174 | 0 | TAGATGCCATCCAGAAAGCT |
| 399977 | 3-14-3 | 71 | 3161 | 3180 | 0 | TCTGGCTAGATGCCATCCAG |
| 399918 | 3-14-3 | 72 | 3238 | 3257 | 0 | GGCATAGAGCAGAGTAAAGG |
| 399978 | 3-14-3 | 73 | 3243 | 3262 | 0 | AGCCTGGCATAGAGCAGAGT |
| 399979 | 3-14-3 | 135 | 3249 | 3268 | 0 | TAGCACAGCCTGGCATAGAG |
| 399919 | 3-14-3 | 112 | 3482 | 3501 | 0 | GAAGAGGCTTGGCTTCAGAG |
| 399980 | 3-14-3 | 74 | 3488 | 3507 | 0 | AAGTAAGAAGAGGCTTGGCT |
| 399920 | 3-14-3 | 75 | 3692 | 3711 | 0 | GCTCAAGGAGGGACAGTTGT |
| 399921 | 3-14-3 | 76 | 3727 | 3746 | 0 | AAAGATAAATGTCTGCTTGC |

| Isis No | Motif | SEQ ID NO | 5' Target Site on SEQ ID NO: 3 | 3' Target Site on SEQ ID NO: 3 | Mismatches | Sequence (5'-3') |
|---|---|---|---|---|---|---|
| 399981 | 3-14-3 | 77 | 3732 | 3751 | 0 | ACCCAAAAGATAAATGTCTG |
| 399922 | 3-14-3 | 78 | 3798 | 3817 | 0 | TCTTCAAGTTACAAAAGCAA |
| 399982 | 3-14-3 | 99 | 3805 | 3824 | 0 | ATAAATATCTTCAAGTTACA |
| 405604 | 3-14-3 | 236 | 1493 | 1512 | 0 | CCAGGTGGGTGCCATGACTG |
| 405641 | 3-14-3 | 373 | 2170 | 2189 | 0 | AACTGGAGCAGCTCAGCAGC |
| 410583 | 3-14-3 | 243 | 1527 | 1546 | 0 | GCCACGCCGGCATCCCGGCC |
| 410584 | 3-14-3 | 244 | 1528 | 1547 | 0 | GGCCACGCCGGCATCCCGGC |
| 410585 | 3-14-3 | 245 | 1529 | 1548 | 0 | TGGCCACGCCGGCATCCCGG |
| 410586 | 3-14-3 | 246 | 1530 | 1549 | 0 | TTGGCCACGCCGGCATCCCG |
| 410587 | 3-14-3 | 247 | 1531 | 1550 | 0 | CTTGGCCACGCCGGCATCCC |
| 410588 | 3-14-3 | 248 | 1532 | 1551 | 0 | CCTTGGCCACGCCGGCATCC |
| 410589 | 3-14-3 | 249 | 1533 | 1552 | 0 | CCCTTGGCCACGCCGGCATC |
| 410590 | 3-14-3 | 250 | 1535 | 1554 | 0 | CACCCTTGGCCACGCCGGCA |
| 410591 | 3-14-3 | 251 | 1536 | 1555 | 0 | GCACCCTTGGCCACGCCGGC |
| 410592 | 3-14-3 | 252 | 1537 | 1556 | 0 | GGCACCCTTGGCCACGCCGG |
| 410593 | 3-14-3 | 253 | 1538 | 1557 | 0 | TGGCACCCTTGGCCACGCCG |
| 410594 | 3-14-3 | 254 | 1539 | 1558 | 0 | CTGGCACCCTTGGCCACGCC |
| 410595 | 3-14-3 | 255 | 1540 | 1559 | 0 | GCTGGCACCCTTGGCCACGC |
| 410596 | 3-14-3 | 348 | 1995 | 2014 | 0 | AGGGAACCAGGCCTCATTGA |
| 410597 | 3-14-3 | 349 | 1996 | 2015 | 0 | CAGGGAACCAGGCCTCATTG |
| 410598 | 3-14-3 | 350 | 1998 | 2017 | 0 | CTCAGGGAACCAGGCCTCAT |
| 410599 | 3-14-3 | 351 | 1999 | 2018 | 0 | CCTCAGGGAACCAGGCCTCA |
| 410600 | 3-14-3 | 352 | 2000 | 2019 | 0 | TCCTCAGGGAACCAGGCCTC |
| 410601 | 3-14-3 | 353 | 2001 | 2020 | 0 | GTCCTCAGGGAACCAGGCCT |
| 410602 | 3-14-3 | 354 | 2003 | 2022 | 0 | TGGTCCTCAGGGAACCAGGC |
| 410603 | 3-14-3 | 355 | 2004 | 2023 | 0 | CTGGTCCTCAGGGAACCAGG |
| 410604 | 3-14-3 | 356 | 2005 | 2024 | 0 | GCTGGTCCTCAGGGAACCAG |
| 410633 | 3-14-3 | 411 | 2356 | 2375 | 0 | ACTTTGCATTCCAGACCTGG |
| 410634 | 3-14-3 | 412 | 2357 | 2376 | 0 | GACTTTGCATTCCAGACCTG |
| 410635 | 3-14-3 | 413 | 2358 | 2377 | 0 | TGACTTTGCATTCCAGACCT |
| 410636 | 3-14-3 | 414 | 2359 | 2378 | 0 | TTGACTTTGCATTCCAGACC |
| 410637 | 3-14-3 | 419 | 2560 | 2579 | 0 | CAGATGGCAACGGCTGTCAC |
| 410638 | 3-14-3 | 420 | 2561 | 2580 | 0 | GCAGATGGCAACGGCTGTCA |
| 410639 | 3-14-3 | 421 | 2562 | 2581 | 0 | AGCAGATGGCAACGGCTGTC |
| 410640 | 3-14-3 | 422 | 2563 | 2582 | 0 | CAGCAGATGGCAACGGCTGT |
| 410641 | 3-14-3 | 423 | 2564 | 2583 | 0 | GCAGCAGATGGCAACGGCTG |
| 410642 | 3-14-3 | 424 | 2566 | 2585 | 0 | CGGCAGCAGATGGCAACGGC |
| 410643 | 3-14-3 | 425 | 2567 | 2586 | 0 | CCGGCAGCAGATGGCAACGG |
| 410644 | 3-14-3 | 426 | 2568 | 2587 | 0 | TCCGGCAGCAGATGGCAACG |
| 410645 | 3-14-3 | 427 | 2569 | 2588 | 0 | CTCCGGCAGCAGATGGCAAC |
| 410646 | 3-14-3 | 428 | 2570 | 2589 | 0 | GCTCCGGCAGCAGATGGCAA |

In certain embodiments, gap-widened antisense compounds are targeted to a PCSK9 nucleic acid. In certain such embodiments, gap-widened antisense compounds are targeted to SEQ ID NO: 3. In certain such embodiments, the nucleotide sequences illustrated in Table 11 have a 2-13-5 gap-widened motif. Table 14 illustrates gap-widened antisense compounds

targeted to SEQ ID NO: 3, having a 2-13-5 motif, where the gap segment comprises 2'-deoxynucleotides and each wing segment comprises nucleotides comprising a 2'-O-methoxyethyl sugar modification. Internucleoside linkages are phosphorthioate, and cytidines are 5-methylcytidines.

**Table 14: Gapmer antisense compounds having a 2-13-5 motif targeted to SEQ ID NO: 3**

| ISIS No | Motiff | SEQ ID NO | 5' Target Site to SEQ ID NO: 3 | 3' Target Site to SEQ ID NO: 3 | Mismatches | Sequences (5'- 3') |
|---|---|---|---|---|---|---|
| 410658 | 2-13-5 | 243 | 1527 | 1546 | 0 | GCCACGCCGGCATCCCGGCC |
| 410659 | 2-13-5 | 244 | 1528 | 1547 | 0 | GGCCACGCCGGCATCCCGGC |
| 410660 | 2-13-5 | 245 | 1529 | 1548 | 0 | TGGCCACGCCGGCATCCCGG |
| 410661 | 2-13-5 | 246 | 1530 | 1549 | 0 | TTGGCCACGCCGGCATCCCG |
| 410662 | 2-13-5 | 247 | 1531 | 1550 | 0 | CTTGGCCACGCCGGCATCCC |
| 410663 | 2-13-5 | 248 | 1532 | 1551 | 0 | CCTTGGCCACGCCGGCATCC |
| 410664 | 2-13-5 | 249 | 1533 | 1552 | 0 | CCCTTGGCCACGCCGGCATC |
| 410665 | 2-13-5 | 28 | 1534 | 1553 | 0 | ACCCTTGGCCACGCCGGCAT |
| 410666 | 2-13-5 | 250 | 1535 | 1554 | 0 | CACCCTTGGCCACGCCGGCA |
| 410667 | 2-13-5 | 251 | 1536 | 1555 | 0 | GCACCCTTGGCCACGCCGGC |
| 410668 | 2-13-5 | 252 | 1537 | 1556 | 0 | GGCACCCTTGGCCACGCCGG |
| 410669 | 2-13-5 | 253 | 1538 | 1557 | 0 | TGGCACCCTTGGCCACGCCG |
| 410670 | 2-13-5 | 254 | 1539 | 1558 | 0 | CTGGCACCCTTGGCCACGCC |
| 410671 | 2-13-5 | 255 | 1540 | 1559 | 0 | GCTGGCACCCTTGGCCACGC |
| 410672 | 2-13-5 | 348 | 1995 | 2014 | 0 | AGGGAACCAGGCCTCATTGA |
| 410673 | 2-13-5 | 349 | 1996 | 2015 | 0 | CAGGGAACCAGGCCTCATTG |
| 410674 | 2-13-5 | 49 | 1997 | 2016 | 0 | TCAGGGAACCAGGCCTCATT |
| 410675 | 2-13-5 | 350 | 1998 | 2017 | 0 | CTCAGGGAACCAGGCCTCAT |
| 410676 | 2-13-5 | 351 | 1999 | 2018 | 0 | CCTCAGGGAACCAGGCCTCA |
| 410677 | 2-13-5 | 352 | 2000 | 2019 | 0 | TCCTCAGGGAACCAGGCCTC |
| 410678 | 2-13-5 | 353 | 2001 | 2020 | 0 | GTCCTCAGGGAACCAGGCCT |
| 410679 | 2-13-5 | 50 | 2002 | 2021 | 0 | GGTCCTCAGGGAACCAGGCC |
| 410680 | 2-13-5 | 354 | 2003 | 2022 | 0 | TGGTCCTCAGGGAACCAGGC |
| 410681 | 2-13-5 | 355 | 2004 | 2023 | 0 | CTGGTCCTCAGGGAACCAGG |
| 410682 | 2-13-5 | 356 | 2005 | 2024 | 0 | GCTGGTCCTCAGGGAACCAG |
| 410713 | 2-13-5 | 60 | 2355 | 2374 | 0 | CTTTGCATTCCAGACCTGGG |
| 410714 | 2-13-5 | 411 | 2356 | 2375 | 0 | ACTTTGCATTCCAGACCTGG |
| 410715 | 2-13-5 | 412 | 2357 | 2376 | 0 | GACTTTGCATTCCAGACCTG |
| 410716 | 2-13-5 | 413 | 2358 | 2377 | 0 | TGACTTTGCATTCCAGACCT |
| 410717 | 2-13-5 | 414 | 2359 | 2378 | 0 | TTGACTTTGCATTCCAGACC |
| 410718 | 2-13-5 | 61 | 2360 | 2379 | 0 | CTTGACTTTGCATTCCAGAC |
| 410719 | 2-13-5 | 419 | 2560 | 2579 | 0 | CAGATGGCAACGGCTGTCAC |
| 410720 | 2-13-5 | 420 | 2561 | 2580 | 0 | GCAGATGGCAACGGCTGTCA |
| 410721 | 2-13-5 | 421 | 2562 | 2581 | 0 | AGCAGATGGCAACGGCTGTC |
| 410722 | 2-13-5 | 422 | 2563 | 2582 | 0 | CAGCAGATGGCAACGGCTGT |
| 410723 | 2-13-5 | 423 | 2564 | 2583 | 0 | GCAGCAGATGGCAACGGCTG |

| ISIS No | Motiff | SEQ ID NO | 5' Target Site to SEQ ID NO: 3 | 3' Target Site to SEQ ID NO: 3 | Mismatches | Sequences (5'- 3') |
|---|---|---|---|---|---|---|
| 410724 | 2-13-5 | 62 | 2565 | 2584 | 0 | GGCAGCAGATGGCAACGGCT |
| 410725 | 2-13-5 | 424 | 2566 | 2585 | 0 | CGGCAGCAGATGGCAACGGC |
| 410726 | 2-13-5 | 425 | 2567 | 2586 | 0 | CCGGCAGCAGATGGCAACGG |
| 410727 | 2-13-5 | 426 | 2568 | 2587 | 0 | TCCGGCAGCAGATGGCAACG |
| 410728 | 2-13-5 | 427 | 2569 | 2588 | 0 | CTCCGGCAGCAGATGGCAAC |
| 410729 | 2-13-5 | 428 | 2570 | 2589 | 0 | GCTCCGGCAGCAGATGGCAA |

The following embodiments set forth target regions of PCSK9 nucleic acids. Also illustrated are examples of antisense compounds targeted to the target regions. It is understood that the sequence set forth in each SEQ ID NO is independent of any modification to a sugar moiety, an internucleoside linkage, or a nucleobase. As such, antisense compounds defined by a SEQ ID NO may comprise, independently, one or more modifications to a sugar moiety, an internucleoside linkage, or a nucleobase. Antisense compounds described by Isis Number (Isis No) indicate a combination of nucleobase sequence and motif.

In certain embodiments, antisense compounds target a range of a PCSK9 nucleic acid. In certain embodiment, such compounds contain at least an 8 nucleotide core sequence in common. In certain embodiments, such compounds sharing at least an 8 nucleotide core sequence targets the following nucleotide regions of SEQ ID: 3: 220-253, 290-321, 377-419, 451-615, 653-672, 741-760, 871-897, 915-934, 968-1017, 1075-1124, 1075-1174, 1144-1174, 1275-1302, 1315-1341, 1351-1389, 1351-1447, 1365-1439, 1390-1417, 1390-1429, 1390-1439, 1399-1425, 1408-1435, 1420-1447, 1453-1482, 1490-1516, 1490-1564, 1500-1526, 1515-1541, 1527-1553, 1527-1554, 1528-1554, 1529-1555, 1529-1556, 1530-1556, 1530-1557, 1531-1557, 1532-1558, 1533-1559, 1534-1559, 1535-1559, 1536-1559, 1537-1564, 1566-1602, 1566-1681, 1606-1626, 1618-1645, 1626-1653, 1684-1703, 1730-1781, 1740-1767, 1749-1775, 1758-1781, 1820-1847, 1820-1877, 1822-2198, 1830-1856, 1839-1865, 1840-1867, 1898-1924, 1898-2035, 1903-2127, 1907-1934, 1911-1938, 1946-1971, 1954-1980, 1959-2035, 1959-2057, 1963-1988, 1967-2035, 1972-1999, 1982-2008, 1991-2018, 1993-2019, 1995-2022, 1996-2023, 1997-2024, 1998-2025, 1999-2025, 2000-2025, 2009-2035, 2038-2139, 2061-2139, 2073-2099, 2078-2104, 2105-2131, 2112-2139, 2168-2198, 2170-2177, 2245-2284, 2295-2394, 2355-2381, 2355-2394, 2405-2461, 2560-2587, 2560-2609, 2561-2588, 2562-2589, 2563-2589, 2564-2589, 2565-2589, 2566-2589, 2567-2589, 2568-2589, 2665-2689, 2759-2783, 2837-2880, 2904-2923, 3005-3024, 3005-3174, 3083-3110, 3155-3184, 3238-3268, 3482-3711, or 3727-3751, or 3798-3824.

In certain embodiments, a target region is nucleotides 290-321 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 290-321 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 117 or 129. In certain such embodiments, an antisense compound targeted to nucleotides 290-321 of SEQ ID NO: 3 is selected from ISIS NOs: 395202, 399924, 399829 or 399985.

In certain embodiments, a target region is nucleotides 220-253 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 220-253 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 100 or 116. In certain such embodiments, an antisense compound targeted to nucleotides 220-253 of SEQ ID NO: 3 is selected from ISIS NOs: 399827, 399983, 399828 or 399984.

In certain embodiments, a target region is nucleotides 377-419 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 377-419 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 81 or 110. In certain such embodiments, an antisense compound targeted to nucleotides 377-419 of SEQ ID NO: 3 is selected from ISIS NOs: 399830, 399986, 395203 or 399925.

In certain embodiments, a target region is nucleotides 451-615 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 451-615 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 152, 140, 137 or 136. In certain such embodiments, an antisense compound targeted to nucleotides 451-615 of SEQ ID NO: 3 is selected from ISIS NOs: 395204, 399926, 399831, 399987, 395205, 399927, 399832, 399988, 395206 or 399928.

In certain embodiments, a target region is nucleotides 653-672 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 653-672 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 132. In certain such embodiments, an antisense compound targeted to nucleotides 653-672 of SEQ ID NO: 3 is selected from ISIS NOs: 395207 or 399929.

In certain embodiments, a target region is nucleotides 741-760 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 741-760 SEQ ID NO: 3.

In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 139. In certain such embodiments, an antisense compound targeted to nucleotides 741-760 of SEQ ID NO: 3 is selected from ISIS NOs: 395208 or 399930.

In certain embodiments, a target region is nucleotides 871-897 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 871-897 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 92 or 142. In certain such embodiments, an antisense compound targeted to nucleotides 871-897 of SEQ ID NO: 3 is selected from ISIS NOs: 399833, 399989, 395209 or 399931.

In certain embodiments, a target region is nucleotides 915-934 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 915-934 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 113. In certain such embodiments, an antisense compound targeted to nucleotides 915-934 of SEQ ID NO: 3 is selected from ISIS NOs: 395210 or 399932.

In certain embodiments, a target region is nucleotides 968-1017 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 968-1017 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 98 or 138. In certain such embodiments, an antisense compound targeted to nucleotides 968-1017 of SEQ ID NO: 3 is selected from ISIS NOs: 395211, 399933, 395212, or 399934.

In certain embodiments, a target region is nucleotides 1075-1124 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1075-1124 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 96 or 124. In certain such embodiments, an antisense compound targeted to nucleotides 1075-1124 of SEQ ID NO: 3 is selected from ISIS NOs: 395213, 399935, 395214, or 399936.

In certain embodiments, a target region is nucleotides 1075-1174 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1075-1174 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 82, 96, 103, 124, or 133. In certain such embodiments, an antisense compound targeted to nucleotides 1075-1174 of SEQ ID NO: 3 is

selected from ISIS NOs: 395213, 399935, 395214, 399936, 399834, 399990, 395215, 399937, 395216, or 399938.

In certain embodiments, a target region is nucleotides 1144-1174 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1144-1174 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 82, 133 or 103. In certain such embodiments, an antisense compound targeted to nucleotides 1144-1174 of SEQ ID NO: 3 is selected from ISIS NOs: 399834, 399990, 395215, 399937, 395216 or 399938.

In certain embodiments, a target region is nucleotides 1275-1302 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1275-1302 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 155 or 156. In certain such embodiments, an antisense compound targeted to nucleotides 1275-1302 of SEQ ID NO: 3 is selected from ISIS NOs: 395217, 399939, 399835 or 399991.

In certain embodiments, a target region is nucleotides 1315-1341 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1315-1341 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 146 or 161. In certain such embodiments, an antisense compound targeted to nucleotides 1315-1341 of SEQ ID NO: 3 is selected from ISIS NOs: 395218, 399940, 395219 or 399941.

In certain embodiments, a target region is nucleotides 1351-1389 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1351-1389 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 215, 216, 19, 217 or 20. In certain such embodiments, an antisense compound targeted to nucleotides 1351-1389 of SEQ ID NO: 3 is selected from ISIS NOs: 410753, 406025, 395160, 399882, 406026, 399797 or 399953.

In certain embodiments, a target region is nucleotides 1351-1447 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1351-1447 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 215, 216, 19, 217, 20, 21, 218, 219, 220, 221, 22,222, 223, 224, 225, 226, 227, 228, 23, 229, 230,231, 232, 24, or 233. In certain such embodiments, an antisense compound targeted to nucleotides 1351-1447 of SEQ ID NO: 3 is selected from ISIS NOs: 410753, 406025, 395160, 399882, 406026, 399797, 399953, 395161,

399883, 405869, 405870, 405871, 405872, 399798, 399954, 405873, 405874, 405875, 405876, 406027, 406028, 406029, 399799, 399955, 406030, 406031, 410733, 406032, 395162, 399884 or 410754.

In certain embodiments, a target region is nucleotides 1365-1439 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1365-1439 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 19, 20, 21, 22, 23, 24, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, or 232. In certain such embodiments, an antisense compound targeted to nucleotides 1365-1439 of SEQ ID NO: 3 is selected from ISIS NOs: 395160, 399882, 406026, 399797, 399953, 395161, 399883, 405869, 405870, 405871, 405872, 399798, 399954, 405873, 405874, 405875, 405876, 406027, 406028, 406029, 399799, 399955, 406030, 406031, 410733, 406032, 395162, or 399884.

In certain embodiments, a target region is nucleotides 1390-1417 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1390-1417 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 21, 218, 219, 220, 221, 22, 222 or 223. In certain such embodiments, an antisense compound targeted to nucleotides 1390-1417 of SEQ ID NO: 3 is selected from ISIS NOs: 395161, 399883, 405869, 405870, 405871, 405872, 399798, 399954, 405873 or 405874.

In certain embodiments, a target region is nucleotides 1390-1429 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1390-1429 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 21, 22, 23, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, or 228. In certain such embodiments, an antisense compound targeted to nucleotides 1390-1429 of SEQ ID NO: 3 is selected from ISIS NOs: 395160, 399882, 406026, 399797, 399953, 395161, 399883, 405869, 405870, 405871, 405872, 399798, 399954, 405873, 405874, 405875, 405876, 406027, 406028, 406029, 399799, or 399955.

In certain embodiments, a target region is nucleotides 1390-1439 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1390-1439 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 21, 22, 23, 24, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, or 232. In certain such embodiments, an antisense compound targeted to nucleotides 1390-1439 of SEQ ID NO: 3 is selected from ISIS NOs:

395160, 399882, 406026, 399797, 399953, 395161, 399883, 405869, 405870, 405871, 405872, 399798, 399954, 405873, 405874, 405875, 405876, 406027, 406028, 406029, 399799, 399955, 406030, 406031, 410733, 406032, 395162, or 399884.

In certain embodiments, a target region is nucleotides 1399-1425 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1399-1425 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 224, 225, 226 or 227. In certain such embodiments, an antisense compound targeted to nucleotides 1399-1425 of SEQ ID NO: 3 is selected from ISIS NOs: 405875, 405876, 406027 or 406028.

In certain embodiments, a target region is nucleotides 1408-1435 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1408-1435 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 228, 23, 229, 230 or 231. In certain such embodiments, an antisense compound targeted to nucleotides 1408-1435 of SEQ ID NO: 3 is selected from ISIS NOs: 406029, 399799, 399955, 406030, 406031 or 410733.

In certain embodiments, a target region is nucleotides 1420-1447 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1420-1447 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 24 or 233. In certain such embodiments, an antisense compound targeted to nucleotides 1420-1447 of SEQ ID NO: 3 is selected from ISIS NOs: 395162, 399884 or 410754.

In certain embodiments, a target region is nucleotides 1453-1482 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1453-1482 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 25 or 234. In certain such embodiments, an antisense compound targeted to nucleotides 1453-1482 of SEQ ID NO: 3 is selected from ISIS NOs: 395163, 399885 or 410755.

In certain embodiments, a target region is nucleotides 1490-1516 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1490-1516 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 235, 236, or 237. In certain such embodiments, an antisense compound targeted to nucleotides 1490-1516 of SEQ ID NO: 3 is selected from ISIS NOs: 410756, 405604, or 406033.

In certain embodiments, a target region is nucleotides 1490-1564 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1490-1564 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 235, 236, 237, 26, 238, 27, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 447, 28, 250, 251, 252, 253, 254, 255, or 256. In certain such embodiments, an antisense compound targeted to nucleotides 1490-1564 of SEQ ID NO: 3 is selected from ISIS NOs: 410756, 405604, 406033, 395164, 399886, 406034, 399800, 399956, 406035, 410757, 406036, 406037, 410536, 410583, 410658, 410537, 410584, 410659, 406038, 410585, 410660, 405877, 410586, 410661, 405878, 410587, 410662, 405879, 410588, 410663, 405880, 410589, or 410758.

In certain embodiments, a target region is nucleotides 1500-1526 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1500-1526 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 26, 238, 27, or 239. In certain such embodiments, an antisense compound targeted to nucleotides 1500-1526 of SEQ ID NO: 3 is selected from ISIS NOs: 395164, 399886, 406034, 399800, 399956, or 406035.

In certain embodiments, a target region is nucleotides 1515-1541 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1515-1541 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 240, 241, or 242. In certain such embodiments, an antisense compound targeted to nucleotides 1515-1541 of SEQ ID NO: 3 is selected from ISIS NOs: 399886, 406034, 399800, 399956, or 406035.

In certain embodiments, a target region is nucleotides 1527-1553 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1527-1553 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 243, 244, 245, 246, 247, 248, 447, 28 or 249. In certain such embodiments, an antisense compound targeted to nucleotides 1527-1553 of SEQ ID NO: 3 is selected from ISIS NOs: 410536, 410583, 410658, 410537, 410584, 410659, 406038, 410585, 410660, 405877, 410586, 410661, 405878, 410587, 410662, 405879, 410588, 410663, 405880, 410589, 410664, 395165, 399887, or 410665.

In certain embodiments, a target region is nucleotides 1527-1554 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1527-1554 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a

nucleotide sequence selected from SEQ ID NOs: 243, 244, 245, 246, 247, 248, 249, 447, 28, or 250. In certain such embodiments, an antisense compound targeted to nucleotides 1527-1554 of SEQ ID NO: 3 is selected from ISIS NOs: 410536, 410583, 410658, 410537, 410584, 410659, 406038, 410585, 410660, 405877, 410586, 410661, 405878, 410587, 410662, 405879, 410588, 410663, 405880, 410589, 410664, 395165, 399887, 405881, 410590, 410666, or 410665.

In certain embodiments, a target region is nucleotides 1528-1554 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1528-1554 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 244, 245, 246, 247, 248, 249, 447, 28, or 250. In certain such embodiments, an antisense compound targeted to nucleotides 1528-1554 of SEQ ID NO: 3 is selected from ISIS NOs: 410537, 410584, 410659, 406038, 410585, 410660, 405877, 410586, 410661, 405878, 410587, 410662, 405879, 410588, 410663, 405880, 410589, 410664, 395165, 399887, 409126, 410665, or 405881.

In certain embodiments, a target region is nucleotides 1529-1555 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1529-1555 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 245, 246, 247, 248, 249, 447, 28, 250 or 251. In certain such embodiments, an antisense compound targeted to nucleotides 1529-1555 of SEQ ID NO: 3 is selected from ISIS NOs: 406038, 395165, 399887, 405877, 405878, 405879, 405880, 405881, 405882, 409126, 410585, 410586, 410587, 410588, 410589, 410590, 410591, 410660, 410661, 410662, 410663, 410664, 410665, 410666, 410667, or 410667.

In certain embodiments, a target region is nucleotides 1529-1556 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1529-1556 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 245, 246, 247, 248, 249, 447, 28, 250, 251, or 252. In certain such embodiments, an antisense compound targeted to nucleotides 1529-1556 of SEQ ID NO: 3 is selected from ISIS NOs: 406038, 395165, 399887, 405877, 405878, 405879, 405880, 405881, 405882, 405883, 409126, 410585, 410586, 410587, 410588, 410589, 410590, 410591, 410592, 410660, 410661, 410662, 410663, 410664, 410665, 410666, 410667, or 410668.

In certain embodiments, a target region is nucleotides 1530-1556 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1530-1556 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a

nucleotide sequence selected from SEQ ID NOs: 246, 247, 248, 249, 447, 28, 250, 251, or 252. In certain such embodiments, an antisense compound targeted to nucleotides 1530-1556 of SEQ ID NO: 3 is selected from ISIS NOs: 406038, 395165, 399887, 405877, 405878, 405879, 405880, 405881, 405882, 405883, 409126, 410585, 410586, 410587, 410588, 410589, 410590, 410591, 410592, 410660, 410661, 410662, 410663, 410664, 410665, 410666, 410667, 405884, 410593, 410669 or 410668.

In certain embodiments, a target region is nucleotides 1530-1557 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1530-1557 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 28, 246, 247, 248, 249, 250, 251, 252, 253, or 447. In certain such embodiments, an antisense compound targeted to nucleotides 1530-1557 of SEQ ID NO: 3 is selected from ISIS NOs: 395165, 399887, 405877, 405878, 405879, 405880, 405881, 405882, 405883, 405884, 409126, 410586, 410587, 410588, 410589, 410590, 410591, 410592, 410593, 410661, 410662, 410663, 410664, 410665, 410666, 410667, 410668, or 410669.

In certain embodiments, a target region is nucleotides 1531-1557 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1531-1557 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 28, 247, 248, 249, 250, 251, 252, 253, or 447. In certain such embodiments, an antisense compound targeted to nucleotides 1531-1557 of SEQ ID NO: 3 is selected from ISIS NOs: 395165, 399887, 405878, 405879, 405880, 405881, 405882, 405883, 405884, 409126, 410587, 410588, 410589, 410590, 410591, 410592, 410593, 410662, 410663, 410664, 410665, 410666, 410667, 410668, or 410669.

In certain embodiments, a target region is nucleotides 1532-1558 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1532-1558 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 28, 248, 249, 250, 251, 252, 253, 254 or 447. In certain such embodiments, an antisense compound targeted to nucleotides 1532-1558 of SEQ ID NO: 3 is selected from ISIS NOs: 405879, 410588, 410663, 405880, 410589, 410664, 395165, 399887, 410665, 405881, 410590, 410666, 405882, 410591, 410667, 405883, 410592, 410668, 405884, 410593, 410669, 410538, 410594, or 410670.

In certain embodiments, a target region is nucleotides 1533-1559 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1533-1559 SEQ ID NO:

3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 28, 249, 250, 251, 252, 253, 254, 255 or 447. In certain such embodiments, an antisense compound targeted to nucleotides 1533-1559 of SEQ ID NO: 3 is selected from ISIS NOs: 405880, 410589, 410664, 395165, 399887, 410665, 405881, 410590, 410666, 405882, 410591, 410667, 405883, 410592, 410668, 405884, 410593, 410669, 410538, 410594, 410670, 410539, 410595, or 410671.

In certain embodiments, a target region is nucleotides 1534-1559 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1534-1559 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 28, 250, 251, 252, 253, 254, 255 or 447. In certain such embodiments, an antisense compound targeted to nucleotides 1534-1559 of SEQ ID NO: 3 is selected from ISIS NOs: 395165, 399887, 410665, 405881, 410590, 410666, 405882, 410591, 410667, 405883, 410592, 410668, 405884, 410593, 410669, 410538, 410594, 410670, or 410671.

In certain embodiments, a target region is nucleotides 1535-1559 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1535-1559 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 250, 251, 252, 253, 254, 255 or 447. In certain such embodiments, an antisense compound targeted to nucleotides 1535-1559 of SEQ ID NO: 3 is selected from ISIS NOs: 405881, 410590, 410666, 405882, 410591, 410667, 405883, 410592, 410668, 405884, 410593, 410669, 410538, 410594 or 410671.

In certain embodiments, a target region is nucleotides 1536-1559 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1536-1559 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 251, 252, 253, 254, or 255. In certain such embodiments, an antisense compound targeted to nucleotides 1536-1559 of SEQ ID NO: 3 is selected from ISIS NOs: 405882, 410591, 410667, 405883, 410592, 410668, 405884, 410593, 410669, 410538, 410594, 410670, 410539, 410595, or 410671.

In certain embodiments, a target region is nucleotides 1537-1564 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1537-1564 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 251, 252, 253, 254, 255, or 256. In certain such embodiments, an antisense compound targeted to nucleotides 1537-1564 of SEQ ID NO: 3 is

selected from ISIS NOs: 405882, 410591, 410667, 405883, 410592, 410668, 405884, 410593, 410669, 410538, 410594, 410670, 410539, 410595, 410671, or 410758.

In certain embodiments, a target region is nucleotides 1566-1602 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1566-1602 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 29, 30, 31, 32, 257, 258, 259, 260, 261, or 262. In certain such embodiments, an antisense compound targeted to nucleotides 1566-1602 of SEQ ID NO: 3 is selected from ISIS NOs: 395166, 395167, 395168, 399801, 399888, 399889, 399890, 399957, 405909, 405910, 405911, 405912, 406039, 406040, 406041, 406042, 406043, or 406044.

In certain embodiments, a target region is nucleotides 1566-1681 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1566-1681 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 29, 30, 31, 32, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, or 272. In certain such embodiments, an antisense compound targeted to nucleotides 1566-1681 of SEQ ID NO: 3 is selected from ISIS NOs: 395166, 395167, 395168, 399801, 399888, 399889, 399890, 399957, 405909, 405910, 405911, 405912, 406039, 406040, 406041, 406042, 406043, 406044, 406045, 408642, 410759, 410760, 410761, or 410762.

In certain embodiments, a target region is nucleotides 1606-1626 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1606-1626 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 264 or 31. In certain such embodiments, an antisense compound targeted to nucleotides 1606-1626 of SEQ ID NO: 3 is selected from ISIS NOs: 408642, 395167, or 399889.

In certain embodiments, a target region is nucleotides 1618-1645 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1618-1645 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 265 or 266. In certain such embodiments, an antisense compound targeted to nucleotides 1618-1645 of SEQ ID NO: 3 is selected from ISIS NOs: 410760 or 406045.

In certain embodiments, a target region is nucleotides 1626-1653 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1626-1653 SEQ ID NO:

3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 32, 266, 267, 268, or 269. In certain such embodiments, an antisense compound targeted to nucleotides 1626-1653 of SEQ ID NO: 3 is selected from ISIS NOs: 395168, 399890, 405909, 405910, 405911, or 406045.

In certain embodiments, a target region is nucleotides 1684-1703 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1684-1703 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 273. In certain such embodiments, an antisense compound targeted to nucleotides 1684-1703 of SEQ ID NO: 3 is selected from ISIS NOs: 410763.

In certain embodiments, a target region is nucleotides 1730-1781 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1730-1781 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 33, 33, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, or 285. In certain such embodiments, an antisense compound targeted to nucleotides 1730-1781 of SEQ ID NO: 3 is selected from ISIS NOs: 395169, 399891, 405913, 405914, 405915, 405916, 405917, 405918, 405919, 405920, 405921, 405922, 410734, or 410764.

In certain embodiments, a target region is nucleotides 1740-1767 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1740-1767 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 33, 275, 276, 277, or 278. In certain such embodiments, an antisense compound targeted to nucleotides 1740-1767 of SEQ ID NO: 3 is selected from ISIS NOs: 395169, 399891, 405913, 405914, 405915, or 405916.

In certain embodiments, a target region is nucleotides 1749-1775 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1749-1775 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 279, 280, 281 or 282. In certain such embodiments, an antisense compound targeted to nucleotides 1749-1775 of SEQ ID NO: 3 is selected from ISIS NOs: 410734, 405917, 405918 or 405919.

In certain embodiments, a target region is nucleotides 1758-1781 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1758-1781 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a

nucleotide sequence selected from SEQ ID NOs: 283, 284, or 285. In certain such embodiments, an antisense compound targeted to nucleotides 1758-1781 of SEQ ID NO: 3 is selected from ISIS NOs: 405920, 405921, or 405922.

In certain embodiments, a target region is nucleotides 1820-1847 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1820-1847 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 39, 306, 307, 308, or 309. In certain such embodiments, an antisense compound targeted to nucleotides 1820-1847 of SEQ ID NO: 3 is selected from ISIS NOs: 395175, 399897, 405937, 405938, 405939, or 405940.

In certain embodiments, a target region is nucleotides 1820-1877 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1820-1877 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 39, 40, 41, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, or 318. In certain such embodiments, an antisense compound targeted to nucleotides 1820-1877 of SEQ ID NO: 3 is selected from ISIS NOs: 395175, 399804, 399805, 399897, 399960, 399961, 405937, 405938, 405939, 405940, 405941, 405942, 405943, 405944, 405945, 405946, 405947, 410737, or 410769.

In certain embodiments, a target region is nucleotides 1822-2198 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1822-2198 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 39, 307, 308, 309, 310, 40, 311, 312, 313, 314, 315, 41, 41, 316, 317, 318, 101, 319, 42, 320, 321, 322, 43, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 44, 335, 336, 337, 45, 338, 46, 339, 340, 47, 341, 342, 48, 343, 344, 345, 346, 347, 3, or 366. In certain such embodiments, an antisense compound targeted to nucleotides 1822-2198 of SEQ ID NO: 3 is selected from ISIS NOs: 395175, 399897, 405938, 405939, 405940, 405941, 399804, 399960, 405942, 405943, 410737, 405944, 405945, 399805, 399961, 405946, 405947, 410769, 395176, 399898, 405948, 399806, 399962, 405949, 405950, 405951, 399807, 399963, 405952, 410738, 405953, 405954, or 405979.

In certain embodiments, a target region is nucleotides 1830-1856 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1830-1856 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 40, 310, 311, or 312. In certain such

embodiments, an antisense compound targeted to nucleotides 1830-1856 of SEQ ID NO: 3 is selected from ISIS NOs: 399804, 399960, 405941, 405942, or 405943.

In certain embodiments, a target region is nucleotides 1839-1865 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1839-1865 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 41, 313, 314, 315, or 316. In certain such embodiments, an antisense compound targeted to nucleotides 1839-1865 of SEQ ID NO: 3 is selected from ISIS NOs: 399805, 399961, 405944, 405945, 405946, or 410737.

In certain embodiments, a target region is nucleotides 1840-1867 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1840-1867 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 314, 315, 316, or 317. In certain such embodiments, an antisense compound targeted to nucleotides 1840-1867 of SEQ ID NO: 3 is selected from ISIS NOs: 399961, 405944, 405945, 405946, 410737, or 405947.

In certain embodiments, a target region is nucleotides 1898-1924 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1898-1924 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 42, 101, 319, or 320. In certain such embodiments, an antisense compound targeted to nucleotides 1898-1924 of SEQ ID NO: 3 is selected from ISIS NOs: 395176, 399898, 405948, 399806, 399962, 405949, or 405949.

In certain embodiments, a target region is nucleotides 1898-2035 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1898-2035 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 87, 101, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, or 359. In certain such embodiments, an antisense compound targeted to nucleotides 1898-2035 of SEQ ID NO: 3 is selected from ISIS NOs: 395176, 395177, 395178, 395179, 399806, 399807, 399808, 399809, 399810, 399811, 399812, 399813, 399898, 399899, 399900, 399901, 399962, 399963, 399964, 399965, 399966, 399967, 399968, 399969, 405885, 405886, 405887, 405888, 405889, 405890, 405891, 405892, 405948, 405949, 405950, 405951, 405952, 405953, 405954, 405955, 405956, 405957, 405958, 405959, 405960, 405961, 405962, 405963, 405964, 405965, 405966, 405967, 405968, 405969, 405970, 405971, 405972, 405973, 405974,

408653, 410540, 410596, 410597, 410598, 410599, 410600, 410601, 410602, 410603, 410604, 410672, 410673, 410674, 410675, 410676, 410677, 410678, 410679, 410680, 410681, 410682, 410738, 410739, 410740, or 410770.

In certain embodiments, a target region is nucleotides 1903-2127 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1903-2127 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 42, 320, 321, 322, 43, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 44, 335, 336, 337, 45, 338, 46, 339, 340, 47, 341, 342, 48, 343, 344, 345, 346, 347, 348, 349, 49, 350, 351, 352, 353, 50, 354, 355, 356, 357, 87, 358, 359, 51, 119, 360, or 54. In certain such embodiments, an antisense compound targeted to nucleotides 1903-2127 of SEQ ID NO: 3 is selected from ISIS NOs: 399806, 399962, 405949, 405950, 405951, 399807, 399963, 405952, 410738, 405953, 405954, 410770, 405955, 405956, 405957, 405958, 405959, 405960, 405961, 399808, 399964, 405962, 410739, 405963, 395177, 399899, 405964, 399809, 399965, 405965, 405966, 399810, or 399967.

In certain embodiments, a target region is nucleotides 1907-1934 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1907-1934 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 43, 321, 322, 323, or 324. In certain such embodiments, an antisense compound targeted to nucleotides 1907-1934 of SEQ ID NO: 3 is selected from ISIS NOs: 405950, 405951, 399807, 399963, 405952, or 410738.

In certain embodiments, a target region is nucleotides 1911-1938 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1911-1938 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 43, 323, 324, 325, or 326. In certain such embodiments, an antisense compound targeted to nucleotides 1911-1938 of SEQ ID NO: 3 is selected from ISIS NOs: 399807, 399963, 405952, 410738, 405953, or 405954.

In certain embodiments, a target region is nucleotides 1946-1971 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1946-1971 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 328, 329, 330, or 331. In certain such embodiments, an antisense compound targeted to nucleotides 1946-1971 of SEQ ID NO: 3 is selected from ISIS NOs: 405955, 405956, 405957, or 405958.

In certain embodiments, a target region is nucleotides 1954-1980 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1954-1980 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 44, 332, 333, 334, or 335. In certain such embodiments, an antisense compound targeted to nucleotides 1954-1980 of SEQ ID NO: 3 is selected from ISIS NOs: 405959, 405960, 405961, 399808, 399964, or 405962.

In certain embodiments, a target region is nucleotides 1959-2035 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1959-2035 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 44, 335, 336, 337, 45, 338, 46, 339, 340, 47, 341, 342, 48, 343, 344, 345, 346, 347, 348, 349, 49, 350, 351, 352, 353, 50, 354, 355, 356, 357, 87, 358, 359, or 51. In certain such embodiments, an antisense compound targeted to nucleotides 1959-2035 of SEQ ID NO: 3 is selected from ISIS NOs: 399808, 399964, 405962, 410739, 405963, 395177, 399899, 405964, 399809, 399965, 405965, 405966, 399810, 399966, 405967, 405968, 399811, 399967, 405969, 405970, 410740, 405885, 405886, 405887, 410596, 410672, 405888, 410597, 410673, 399812, 399968, 410674, or 399969.

In certain embodiments, a target region is nucleotides 1959-2057 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1959-2057 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 44, 335, 336, 337, 45, 338, 46, 339, 340, 47, 341, 342, 48, 343, 344, 345, 346, 347, 348, 349, 49, 350, 351, 352, 353, 50, 354, 355, 356, 357, 87, 358, 359, 51, or 119. In certain such embodiments, an antisense compound targeted to nucleotides 1959-2057 of SEQ ID NO: 3 is selected from ISIS NOs: 399808, 399964, 405962, 410739, 405963, 395177, 399899, 405964, 399809, 399965, 405965, 405966, 399810, 399966, 405967, 405968, 399811, 399967, 405969, 405970, 410740, 405885, 405886, 405887, 410596, 410672, 405888, 410597, 410673, 399812, 399968, 410674, or 399902.

In certain embodiments, a target region is nucleotides 1963-1988 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1963-1988 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 45, 336, 337 or 338. In certain such embodiments, an antisense compound targeted to nucleotides 1963-1988 of SEQ ID NO: 3 is selected from ISIS NOs: 410739, 405963, 395177, 399899, or 405964.

In certain embodiments, a target region is nucleotides 1967-2035 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1967-2035 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 45, 338, 46, 339, 340, 47, 341, 342, 48, 343, 344, 345, 346, 347, 348, 349, 49, 350, 351, 352, 353, 50, 354, 355, 356, 357, 87, 358, 359 or 51. In certain such embodiments, an antisense compound targeted to nucleotides 1967-2035 of SEQ ID NO: 3 is selected from ISIS NOs: 395177, 399899, 405964, 399809, 399965, 405965, 405966, 399810, 399966, 405967, 405968, 399811, 399967, 405969, 405970, 410740, 405885, 405886, 405887, 410596, 410672, 405888, 410597, 410673, 399812, 399968, 410674, 405889, 410598, 410675, 405890, 410599, or 399969.

In certain embodiments, a target region is nucleotides 1972-1999 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1972-1999 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 46, 47, 339, 340, or 341. In certain such embodiments, an antisense compound targeted to nucleotides 1972-1999 of SEQ ID NO: 3 is selected from ISIS NOs: 399809, 399965, 405965, 405966, 399810, 399966, or 405967.

In certain embodiments, a target region is nucleotides 1982-2008 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1982-2008 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 48, 342, 343, or 344. In certain such embodiments, an antisense compound targeted to nucleotides 1982-2008 of SEQ ID NO: 3 is selected from ISIS NOs: 405968, 399811, 399967, 405969, or 405970.

In certain embodiments, a target region is nucleotides 1991-2018 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1991-2018 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 49, 345, 346, 347, 348, 349, 350, or 351. In certain such embodiments, an antisense compound targeted to nucleotides 1991-2018 of SEQ ID NO: 3 is selected from ISIS NOs: 399812, 399968, 405885, 405886, 405887, 405888, 405889, 405890, 410596, 410597, 410598, 410599, 410672, 410673, 410674, 410675, 410676, or 410740.

In certain embodiments, a target region is nucleotides 1993-2019 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1993-2019 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a

nucleotide sequence selected from SEQ ID NOs: 49, 346, 347, 348, 349, 350, or 354. In certain such embodiments, an antisense compound targeted to nucleotides 1993-2019 of SEQ ID NO: 3 is selected from ISIS NOs: 405885, 405887, 410596, 410672, 405888, 410597, 410673, 399812, 399968, 410674, 405889, 410598, 410675, 405890, 410599, 410676, 405891, 410600, or 410677.

In certain embodiments, a target region is nucleotides 1995-2022 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1995-2022 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 348, 349, 350, 351, 352, 353, 50, or 351 In certain such embodiments, an antisense compound targeted to nucleotides 1995-2022 of SEQ ID NO: 3 is selected from ISIS NOs: 405887, 410596, 410672, 405888, 410597, 410673, 399812, 399968, 410674, 405889, 410598, 410675, 405890, 410599, 410676, 405891, 410600, 405892, 410601, 410678, 395178, 399900, 410679, 408653, 410602, or 410680.

In certain embodiments, a target region is nucleotides 1996-2023 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1996-2023 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 49, 50, 349, 350, 351, 352, 353, 354, or 355. In certain such embodiments, an antisense compound targeted to nucleotides 1996-2023 of SEQ ID NO: 3 is selected from ISIS NOs: 395178, 399812, 399900, 399968, 405888, 405889, 405890, 405891, 405892, 405971, 408653, 410597, 410598, 410599, 410600, 410601, 410602, 410603, 410673, 410674, 410675, 410676, 410677, 410678, 410679, 410680, or 410681.

In certain embodiments, a target region is nucleotides 1997-2024 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1997-2024 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 49, 50, 350, 351, 352, 353, 354, 355, or 356. In certain such embodiments, an antisense compound targeted to nucleotides 1997-2024 of SEQ ID NO: 3 is selected from ISIS NOs: 399812, 399968, 410674, 405889, 410598, 410675, 405890, 410599, 410676, 405891, 410600, 410677, 405892, 410601, 410678, 395178, 399900, 410679, 408653, 410602, 410680, 405971, 410603, 410681, 410540, 410604, or 410682.

In certain embodiments, a target region is nucleotides 1998-2025 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1998-2025 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 50, 350, 351, 352, 353, 354, 355, 356 or 357.

In certain such embodiments, an antisense compound targeted to nucleotides 1998-2025 of SEQ ID NO: 3 is selected from ISIS NOs: 405889, 410598, 410675, 405890, 410599, 410676, 405891, 410600, 410677, 405892, 410601, 410678, 395178, 399900, 410679, 408653, 410602, 410680, 405971, 410603, 410681, 410540, 410604, 410682, or 405972.

In certain embodiments, a target region is nucleotides 1999-2025 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 1999-2025 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 50, 351, 352, 353, 354, 355, 356, or 357. In certain such embodiments, an antisense compound targeted to nucleotides 1999-2025 of SEQ ID NO: 3 is selected from ISIS NOs: 405889, 410598, 410675, 405890, 410599, 410676, 405891, 410600, 410677, 405892, 410601, 410678, 395178, 399900, 410679, 408653, 410602, 410680, 405971, 410603, 410681, 410540, 410604, 410682, or 405972.

In certain embodiments, a target region is nucleotides 2000-2025 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 2000-2025 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 351, 352, 353, 354, 355, 356, or 357. In certain such embodiments, an antisense compound targeted to nucleotides 2000-2025 of SEQ ID NO: 3 is selected from ISIS NOs: 405890, 410599, 410676, 405891, 410600, 410677, 405892, 410601, 410678, 395178, 399900, 410679, 408653, 410602, 410680, 405971, 410603, 410681, 410540, 410604, 410682, or 405972.

In certain embodiments, a target region is nucleotides 2009-2035 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 2009-2035 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 51, 87, 358, or 359. In certain such embodiments, an antisense compound targeted to nucleotides 2009-2035 of SEQ ID NO: 3 is selected from ISIS NOs: 395179, 399813, 399901, 399969, 405973, or 405974.

In certain embodiments, a target region is nucleotides 2038-2139 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 2038-2139 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 52, 53, 54, 104, 119, 130, 360, 361, 362, 363, 365, 366, 367, 368, 369, 370, or 371. In certain such embodiments, an antisense compound targeted to nucleotides 2038-2139 of SEQ ID NO: 3 is selected from ISIS NOs: 395180, 395181,

395182, 395220, 399814, 399836, 399902, 399903, 399904, 399942, 399970, 399992, 405975, 405976, 405977, 405978, 405979, 405980, 405981, 405982, 405983, 410741, or 410771.

In certain embodiments, a target region is nucleotides 2061-2139 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 2061-2139 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 52, 53, 54, 104, 130, 360, 361, 362, 363, 365, 366, 367, 368, 369, 370, or 371. In certain such embodiments, an antisense compound targeted to nucleotides 2061-2139 of SEQ ID NO: 3 is selected from ISIS NOs: 395181, 395182, 395220, 399814, 399836, 399903, 399904, 399942, 399970, 399992, 405975, 405976, 405977, 405978, 405979, 405980, 405981, 405982, 405983, 410741, or 410771.

In certain embodiments, a target region is nucleotides 2073-2099 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 2073-2099 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 52, 53, 361, or 362. In certain such embodiments, an antisense compound targeted to nucleotides 2073-2099 of SEQ ID NO: 3 is selected from ISIS NOs: 395181, 399814, 399903, 399970, 405975, or 405976.

In certain embodiments, a target region is nucleotides 2078-2104 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 2078-2104 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 53, 104, 362, or 363. In certain such embodiments, an antisense compound targeted to nucleotides 2078-2104 of SEQ ID NO: 3 is selected from ISIS NOs: 395220, 399814, 399942, 399970, 405976, or 405977.

In certain embodiments, a target region is nucleotides 2105-2131 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 2105-2131 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 54, 365, 366, or 367. In certain such embodiments, an antisense compound targeted to nucleotides 2105-2131 of SEQ ID NO: 3 is selected from ISIS NOs: 395182, 399904, 405978, 405979, or 405980.

In certain embodiments, a target region is nucleotides 2112-2139 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 2112-2139 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 367, 368, 369, 370, or 371. In certain such

embodiments, an antisense compound targeted to nucleotides 2112-2139 of SEQ ID NO: 3 is selected from ISIS NOs: 405980, 405981, 410741, 405982, or 405983.

In certain embodiments, a target region is nucleotides 2168-2198 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 2168-2198 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 55, 56, 372, 373, 374, or 375. In certain such embodiments, an antisense compound targeted to nucleotides 2168-2198 of SEQ ID NO: 3 is selected from ISIS NOs: 399815, 399816, 399971, 399972, 405641, 405984, 405985, 405986, or 405987.

In certain embodiments, a target region is nucleotides 2170-2177 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 2170-2177 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 55, 373, 374, or 375. In certain such embodiments, an antisense compound targeted to nucleotides 2170-2177 of SEQ ID NO: 3 is selected from ISIS NOs: 399815, 399971, 405641, 405985, 405986, or 405987.

In certain embodiments, a target region is nucleotides 2245-2284 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 2245-2284 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 408 or 409. In certain such embodiments, an antisense compound targeted to nucleotides 2245-2284 of SEQ ID NO: 3 is selected from ISIS NOs: 410776 or 410777.

In certain embodiments, a target region is nucleotides 2295-2394 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 2295-2394 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 60, 61, 410, 411, 412, 413, 414, 415, or 416. In certain such embodiments, an antisense compound targeted to nucleotides 2295-2394 of SEQ ID NO: 3 is selected from ISIS NOs: 395186, 399817, 399908, 399973, 405996, 405997, 410562, 410563, 410564, 410633, 410634, 410635, 410636, 410713, 410714, 410715, 410716, 410717, 410718, 410778, or 410779.

In certain embodiments, a target region is nucleotides 2355-2381 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 2355-2381 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 60, 61, 411, 412, 413, 414, or 415. In certain

such embodiments, an antisense compound targeted to nucleotides 2355-2381 of SEQ ID NO: 3 is selected from ISIS NOs: 395186, 399817, 399908, 399973, 405996, 405997, 410562, 410563, 410564, 410633, 410634, 410635, 410636, 410713, 410714, 410715, 410716, 410717, or 410718.

In certain embodiments, a target region is nucleotides 2355-2394 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 2355-2394 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 60, 61, 411, 412, 413, 414, 415, or 416. In certain such embodiments, an antisense compound targeted to nucleotides 2355-2394 of SEQ ID NO: 3 is selected from ISIS NOs: 395186, 399817, 399908, 399973, 405996, 405997, 410562, 410563, 410564, 410633, 410634, 410635, 410636, 410713, 410714, 410715, 410716, 410717, 410718, or 410779.

In certain embodiments, a target region is nucleotides 2405-2461 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 2405-2461 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 417 or 418. In certain such embodiments, an antisense compound targeted to nucleotides 2405-2461 of SEQ ID NO: 3 is selected from ISIS NOs: 410780 or 410781.

In certain embodiments, a target region is nucleotides 2560-2587 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 2560-2587 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 62, 419, 420, 421, 422, 423, 424, 425, or 426. In certain such embodiments, an antisense compound targeted to nucleotides 2560-2587 of SEQ ID NO: 3 is selected from ISIS NOs: 395187, 399909, 405998, 410565, 410566, 410567, 410568, 410569, 410570, 410571, 410637, 410638, 410639, 410640, 410641, 410642, 410643, 410644, 410719, 410720, 410721, 410722, 410723, 410724, 410725, 410726, or 410727.

In certain embodiments, a target region is nucleotides 2560-2609 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 2560-2609 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 62, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, or 430. In certain such embodiments, an antisense compound targeted to nucleotides 2560-2609 of SEQ ID NO: 3 is selected from ISIS NOs: 395187, 399909, 405998, 410565, 410566, 410567, 410568, 410569, 410570, 410571, 410572, 410573, 410637, 410638, 410639,

410640, 410641, 410642, 410643, 410644, 410645, 410646, 410719, 410720, 410721, 410722, 410723, 410724, 410725, 410726, 410727, 410728, or 410783.

In certain embodiments, a target region is nucleotides 2561-2588 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 2561-2588 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 420, 421, 422, 423, 424, 425, 426, 427, or 62. In certain such embodiments, an antisense compound targeted to nucleotides 2561-2588 of SEQ ID NO: 3 is selected from ISIS NOs: 410566, 410638, 410720, 410567, 410639, 410721, 410568, 410640, 410722, 410569, 410641, 410723, 395187, 399909, 410724, 410570, 410642, 410725, 410571, 410643, 410726, 405988, 405998, 410644, 410727, 410572, 410645, or 410728.

In certain embodiments, a target region is nucleotides 2562-2589 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 2562-2589 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 62, 421, 422, 423, 424, 425, 426, 427, or 428. In certain such embodiments, an antisense compound targeted to nucleotides 2562-2589 of SEQ ID NO: 3 is selected from ISIS NOs: 395187, 399909, 405998, 410567, 410568, 410569, 410570, 410571, 410572, 410573, 410639, 410640, 410641, 410642, 410643, 410644, 410645, 410646, 410721, 410722, 410723, 410724, 410725, 410726, 410727, 410728, or 410729.

In certain embodiments, a target region is nucleotides 2563-2589 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 2563-2589 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 422, 423, 424, 425, 426, 427, 428 or 62. In certain such embodiments, an antisense compound targeted to nucleotides 2563-2589 of SEQ ID NO: 3 is selected from ISIS NOs: 410568, 410640, 410722, 410569, 410641, 410723, 395187, 399909, 410724, 410570, 410642, 410725, 410571, 410643, 410726, 405988, 405998, 410644, 410727, 410572, 410645, 410728, 410573, 410646, or 410729.

In certain embodiments, a target region is nucleotides 2564-2589 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 2564-2589 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 423, 424, 425, 426, 427, 428 or 62. In certain such embodiments, an antisense compound targeted to nucleotides 2564-2589 of SEQ ID NO: 3 is selected from ISIS NOs: 410569, 410641, 410723, 395187, 399909, 410724, 410570, 410642,

410725, 410571, 410643, 410726, 405988, 405998, 410644, 410727, 410572, 410645, 410728, 410573, 410646, or 410729.

In certain embodiments, a target region is nucleotides 2565-2589 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 2565-2589 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 424, 425, 426, 427, 428 or 62. In certain such embodiments, an antisense compound targeted to nucleotides 2565-2589 of SEQ ID NO: 3 is selected from ISIS NOs: 395187, 399909, 410724, 410570, 410642, 410725, 410571, 410643, 410726, 405988, 405998, 410644, 410727, 410572, 410645, 410728, 410573, 410646, or 410729.

In certain embodiments, a target region is nucleotides 2566-2589 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 2566-2589 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 424, 425, 426, 427, or 428. In certain such embodiments, an antisense compound targeted to nucleotides 2566-2589 of SEQ ID NO: 3 is selected from ISIS NOs: 410570, 410642, 410725, 410571, 410643, 410726, 405988, 405998, 410644, 410727, 410572, 410645, 410728, 410573, 410646, or 410729.

In certain embodiments, a target region is nucleotides 2567-2589 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 2567-2589 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 425, 426, 427, or 428. In certain such embodiments, an antisense compound targeted to nucleotides 2567-2589 of SEQ ID NO: 3 is selected from ISIS NOs: 410571, 410643, 410726, 405988, 405998, 410644, 410727, 410572, 410645, 410728, 410573, 410646, or 410729.

In certain embodiments, a target region is nucleotides 2568-2589 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 2568-2589 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 426, 427 or 428. In certain such embodiments, an antisense compound targeted to nucleotides 2568-2589 of SEQ ID NO: 3 is selected from ISIS NOs: 405988, 405998, 410644, 410727, 410572, 410645, 410728, 410573, 410646, or 410729.

In certain embodiments, a target region is nucleotides 2665-2689 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 2665-2689 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a

nucleotide sequence selected from SEQ ID NOs: 63 or 154. In certain such embodiments, an antisense compound targeted to nucleotides 2665-2689 of SEQ ID NO: 3 is selected from ISIS NOs: 395188, 399910, 399818, or 399974.

In certain embodiments, a target region is nucleotides 2759-2783 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 2759-2783 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 64 or 65. In certain such embodiments, an antisense compound targeted to nucleotides 2759-2783 of SEQ ID NO: 3 is selected from ISIS NOs: 395189, 399911, 399819, or 399975.

In certain embodiments, a target region is nucleotides 2837-2880 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 2837-2880 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 66, 67, or 122. In certain such embodiments, an antisense compound targeted to nucleotides 2837-2880 of SEQ ID NO: 3 is selected from ISIS NOs: 399820, 399976, 395190, 399912, 395191, or 399913.

In certain embodiments, a target region is nucleotides 2904-2923 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 2904-2923 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 153. In certain such embodiments, an antisense compound targeted to nucleotides 2904-2923 of SEQ ID NO: 3 is selected from ISIS NOs: 395192 or 399914.

In certain embodiments, a target region is nucleotides 3005-3024 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 3005-3024 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 68. In certain such embodiments, an antisense compound targeted to nucleotides 3005-3024 of SEQ ID NO: 3 is selected from ISIS NOs: 395193 or 399915.

In certain embodiments, a target region is nucleotides 3005-3174 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 3005-3174 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 68, 431, 432, 433, 434, 69, 435, 436, 437, 438 or 70. In certain such embodiments, an antisense compound targeted to nucleotides 3005-3174

of SEQ ID NO: 3 is selected from ISIS NOs: 395193, 399915, 405893, 405894, 405895, 405896, 395194, 399916, 405897, 405898, 405899, 405900, 395195, or 399917.

In certain embodiments, a target region is nucleotides 3083-3110 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 3083-3110 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 69, 69, 431, 432, 433, 434, 435, 436, 437, or 438. In certain such embodiments, an antisense compound targeted to nucleotides 3083-3110 of SEQ ID NO: 3 is selected from ISIS NOs: 395194, 399916, 405893, 405894, 405895, 405896, 405897, 405898, 405899, or 405900.

In certain embodiments, a target region is nucleotides 3155-3184 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 3155-3184 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 70, 71, 439, 440, 441, 442, 443, 444, 445, or 446. In certain such embodiments, an antisense compound targeted to nucleotides 3155-3184 of SEQ ID NO: 3 is selected from ISIS NOs: 395195, 399821, 399917, 399977, 405901, 405902, 405903, 405904, 405905, 405906, 405907, or 405908.

In certain embodiments, a target region is nucleotides 3238-3268 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 3238-3268 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 72, 73, or 135. In certain such embodiments, an antisense compound targeted to nucleotides 3238-3268 of SEQ ID NO: 3 is selected from ISIS NOs: 395196, 399822, 399823, 399918, 399978, or 399979.

In certain embodiments, a target region is nucleotides 3482-3711 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 3482-3711 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 74, 75, or 112. In certain such embodiments, an antisense compound targeted to nucleotides 3482-3711 of SEQ ID NO: 3 is selected from ISIS NOs: 395197, 395198, 399824, 399919, 399920, or 399980.

In certain embodiments, a target region is nucleotides 3727-3751 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 3727-3751 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 76 or 77. In certain such embodiments, an

antisense compound targeted to nucleotides 3727-3751 of SEQ ID NO: 3 is selected from ISIS NOs: 395199, 399921, 399825, or 399981.

In certain embodiments, a target region is nucleotides 3798-3824 of SEQ ID NO: 3. In certain embodiments, an antisense compound is targeted to nucleotides 3798-3824 SEQ ID NO: 3. In certain embodiments, an antisense compound targeted to a PCSK9 nucleic acid comprises a nucleotide sequence selected from SEQ ID NOs: 78 or 99. In certain such embodiments, an antisense compound targeted to nucleotides 3798-3824 of SEQ ID NO: 3 is selected from ISIS NOs: 395200, 399922, 399826, or 399982.

In certain embodiments, short gapmer antisense compounds are targeted to a PCSK9 nucleic acid. In certain such embodiments, gapmer antisense compounds are targeted to SEQ ID NO: 1, SEQ ID NO: 2 and/or SEQ ID NO: 3. In certain such embodiments, the nucleotide sequences illustrated in Table 14.1 have a 2-10-2 gapmer motif. Table 14.1 illustrates gapmer antisense compounds targeted to SEQ ID NO: 1, SEQ ID NO: 2 and/or SEQ ID NO: 3, having a 2-10-2 motif, where the gap segment comprises 2'-deoxynucleotides and each wing segment comprises nucleotides comprising a 2'-O-methoxyethyl sugar modification. Internucleoside linkages are phosphorthioate, and cytidines are 5-methylcytidines.

**Table 14.1: Gapmer antisense compounds having a 2-10-2 motif targeted to SEQ ID NO: 1, SEQ ID NO: 2 and/or SEQ ID NO: 3**

| Target SEQ ID NO | ISIS NO | Motif | OligoSeq | 5' Target Site on SEQ ID NO:1 | 3' Target Site on SEQ ID NO:1 | SEQ ID NO |
|---|---|---|---|---|---|---|
| 1 | 406539 | 2-10-2 | GCCTATGAGGGTGC | 1079 | 1092 | 458 |
| 1 | 406540 | 2-10-2 | TCCAGGCCTATGAG | 1084 | 1097 | 459 |
| 1 | 406551 | 2-10-2 | CAGCTCAGCAGCTC | 1735 | 1748 | 460 |
| 1 | 406595 | 2-10-2 | TTAATCAGGGAGCC | 2877 | 2890 | 461 |
| 2 | 406551 | 2-10-2 | CAGCTCAGCAGCTC | 21181 | 21194 | 460 |
| 2 | 406595 | 2-10-2 | TTAATCAGGGAGCC | 26684 | 26697 | 461 |
| 3 | 406539 | 2-10-2 | GCCTATGAGGGTGC | 1609 | 1622 | 458 |
| 3 | 406540 | 2-10-2 | TCCAGGCCTATGAG | 1614 | 1627 | 459 |
| 3 | 406551 | 2-10-2 | CAGCTCAGCAGCTC | 2168 | 2181 | 460 |
| 3 | 406595 | 2-10-2 | TTAATCAGGGAGCC | 3132 | 3145 | 461 |

In a certain embodiment, a short antisense compound has increased potency compared to a 20 nucleotide compound. In a certain embodiment such short antisense compound and 20

nucleotide compound target the same region. In a certain embodiment, a short antisense compound has increased potency compared to a 20 nucleotide coumpound containing the sequence of the short antisense compound.

In certain embodiments, the desired effect is a reduction in mRNA target nucleic acid levels. In other embodiments, the desired effect is reduction of levels of protein encoded by the target nucleic acid or a phenotypic change associated with the target nucleic acid.

In one embodiment, a target region is a structurally defined region of the nucleic acid. For example, a target region may encompass a 3' UTR, a 5' UTR, an exon, an intron, a coding region, a translation initiation region, translation termination region, or other defined nucleic acid region. In other embodiments, a target region may encompass the sequence from a 5' target site of one target segment within the target region to a 3' target site of another target segment within the target region.

Targeting includes determination of at least one target segment to which an antisense compound hybridizes, such that a desired effect occurs. A target region may contain one or more target segments. Multiple target segments within a target region may be overlapping. Alternatively, they may be non-overlapping. In one embodiment, target segments within a target region are separated by no more than about 10 nucleotides on the target nucleic acid. In another embodiment, target segments within a target region are separated by no more than about 5 nucleotides on the target nucleic acid. In additional embodiments, target segments are contiguous.

Suitable target segments may be found within a 5' UTR, a coding region, a 3' UTR, an intron, or an exon. Target segments containing a start codon or a stop codon are also suitable target segments.

The determination of suitable target segments may include a comparison of the sequence of a target nucleic acid to other sequences throughout the genome. For example, the BLAST algorithm may be used to identify regions of similarity amongst different nucleic acids. This comparison can prevent the selection of antisense compound sequences that may hybridize in a non-specific manner to sequences other than a selected target nucleic acid (i.e., non-target or off-target sequences).

There may be variation in activity (e.g., as defined by percent reduction of target nucleic acid levels) of the antisense compounds within an active target region. In one embodiment, reductions in PCSK9 mRNA levels are indicative of inhibition of PCSK9 expression. Reductions in levels of a PCSK9 protein are also indicative of inhibition of target mRNA expression.

Further, phenotypic changes are indicative of inhibition of PCSK9 expression. For example, a decrease in LDL-C levels is indicative of inhibition of PCSK9 expression.

*Hybridization*

For example, hybridization may occur between an antisense compound disclosed herein and a PCSK9 nucleic acid. The most common mechanism of hybridization involves hydrogen bonding (e.g., Watson-Crick, Hoogsteen or reversed Hoogsteen hydrogen bonding) between complementary nucleobases of the nucleic acid molecules.

Hybridization can occur under varying conditions. Stringent conditions are sequence-dependent and are determined by the nature and composition of the nucleic acid molecules to be hybridized.

Methods of determining whether a sequence is specifically hybridizable to a target nucleic acid are well known in the art. In one embodiment, the antisense compounds provided herein are specifically hybridizable with a PCSK9 nucleic acid.

*Complementarity*

An antisense compound and a target nucleic acid are complementary to each other when a sufficient number of nucleobases of the antisense compound can hydrogen bond with the corresponding nucleobases of the target nucleic acid, such that à desired effect will occur (e.g., antisense inhibition of a target nucleic acid, such as a PCSK9 nucleic acid).

Non-complementary nucleobases between an antisense compound and a PCSK9 nucleic acid may be tolerated provided that the antisense compound remains able to specifically hybridize to a target nucleic acid. Moreover, an antisense compound may hybridize over one or more segments of a PCSK9 nucleic acid such that intervening or adjacent segments are not involved in the hybridization event (e.g., a loop structure, mismatch or hairpin structure).

In some embodiments, the antisense compounds provided herein are at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% complementary to a PCSK9 nucleic acid. Percent complementarity of an antisense compound with a target nucleic acid can be determined using routine methods.

In other embodiments, the antisense compounds provided herein are fully complementary (i.e, 100% complementary) to a target nucleic acid. For example, antisense compound may be fully complementary to a PCSK9 nucleic acid. As used herein, "fully

complementary" means each nucleobase of an antisense compound is capable of precise base pairing with the corresponding nucleobases of a target nucleic acid.

The location of a non-complementary nucleobase may be at the 5' end or 3' end of the antisense compound. Alternatively, the non-complementary nucleobase or nucleobases may be at an internal position of the antisense compound. When two or more non-complementary nucleobases are present, they may be contiguous (i.e. linked) or non-contiguous. In one embodiment, a non-complementary nucleobase is located in the wing segment of a gapmer antisense oligonucleotide.

In one embodiment, antisense compounds up to 20 nucleobases in length comprise no more than 4, no more than 3, no more than 2 or no more than 1 non-complementary nucleobase(s) relative to a target nucleic acid, such as a PCSK9 nucleic acid.

In another embodiment, antisense compounds up to 30 nucleobases in length comprise no more than 6, no more than 5, no more than 4, no more than 3, no more than 2 or no more than 1 non-complementary nucleobase(s) relative to a target nucleic acid, such as a PCSK9 nucleic acid.

The antisense compounds provided herein also include those which are complementary to a portion of a target nucleic acid. As used herein, "portion" refers to a defined number of contiguous (i.e. linked) nucleobases within a region or segment of a target nucleic acid. A "portion" can also refer to a defined number of contiguous nucleobases of an antisense compound. In one embodiment, the antisense compounds are complementary to at least an 8 nucleobase portion of a target segment. In another embodiment, the antisense compounds are complementary to at least a 12 nucleobase portion of a target segment. In yet another embodiment, the antisense compounds are complementary to at least a 15 nucleobase portion of a target segment.

*Identity*

The antisense compounds provided herein may also have a defined percent identity to a particular nucleotide sequence, SEQ ID NO, or compound represented by a specific Isis number. As used herein, an antisense compound is identical to the sequence disclosed herein if it has the same nucleobase pairing ability. For example, a RNA which contains uracil in place of thymidine in a disclosed DNA sequence would be considered identical to the DNA sequence since both uracil and thymidine pair with adenine. Shortened and lengthened versions of the antisense compounds described herein as well as compounds having non-identical bases relative to the

antisense compounds provided herein also are contemplated. The non-identical bases may be adjacent to each other or dispersed throughout the antisense compound. Percent identity of an antisense compound is calculated according to the number of bases that have identical base pairing relative to the sequence to which it is being compared.

In one embodiment, the antisense compounds are at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or 100% identical to one or more of the antisense compounds disclosed herein.

*Modifications*

A nucleoside is a base-sugar combination. The nucleobase (also known as base) portion of the nucleoside is normally a heterocyclic base moiety. Nucleotides are nucleosides that further include a phosphate group covalently linked to the sugar portion of the nucleoside. For those nucleosides that include a pentofuranosyl sugar, the phosphate group can be linked to the 2', 3' or 5' hydroxyl moiety of the sugar. Oligonucleotides are formed through the covalent linkage of adjacent nucleosides to one another, to form a linear polymeric oligonucleotide. Within the oligonucleotide structure, the phosphate groups are commonly referred to as forming the internucleoside linkages of the oligonucleotide.

Modifications to antisense compounds encompass substitutions or changes to internucleoside linkages, sugar moieties, or nucleobases. Modified antisense compounds are often preferred over native forms because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for nucleic acid target, increased stability in the presence of nucleases, or increased inhibitory activity.

Chemically modified nucleosides may also be employed to increase the binding affinity of a shortened or truncated antisense oligonucleotide for its target nucleic acid. Consequently, comparable results can often be obtained with shorter antisense compounds that have such chemically modified nucleosides.

*Modified Internucleoside Linkages*

The naturally occuring internucleoside linkage of RNA and DNA is a 3' to 5' phosphodiester linkage. Antisense compounds having one or more modified, i.e. non-naturally occurring, internucleoside linkages are often selected over antisense compounds having naturally occurring internucleoside linkages because of desirable properties such as, for example,

enhanced cellular uptake, enhanced affinity for target nucleic acids, and increased stability in the presence of nucleases.

Oligonucleotides having modified internucleoside linkages include internucleoside linkages that retain a phosphorus atom as well as internucleoside linkages that do not have a phosphorus atom. Representative phosphorus containing internucleoside linkages include, but are not limited to, phosphodiesters, phosphotriesters, methylphosphonates, phosphoramidate, and phosphorothioates. Methods of preparation of phosphorous-containing and non-phosphorous-containing linkages are well known.

In one embodiment, antisense compounds targeted to a PCSK9 nucleic acid comprise one or more modified internucleoside linkages. In some embodiments, the modified internucleoside linkages are phosphorothioate linkages. In other embodiments, each internucleoside linkage of an antisense compound is a phosphorothioate internucleoside linkage.

*Modified Sugar Moieties*

Antisense compounds targeted to a PCSK9 nucleic acid may contain one or more nucleotides having modified sugar moieties. Sugar modifications may impart nuclease stability, binding affinity or some other beneficial biological property to the antisense compounds. The furanosyl sugar ring of a nucleoside can be modified in a number of ways including, but not limited to: addition of a substituent group, particularly at the 2' position; bridging of two non-geminal ring atoms to form a bicyclic nucleic acid (BNA); and substitution of an atom or group such as -S-, -N(R)- or $-C(R_1)(R_2)$ for the ring oxygen at the 4'-position. Modified sugars include, but are not limited to: substituted sugars, especially 2'-substituted sugars having a 2'-F, 2'-$OCH_2$ (2'-OMe) or a 2'-$O(CH_2)_2$-$OCH_3$ (2'-O-methoxyethyl or 2'-MOE) substituent group; and bicyclic modified sugars (BNAs), having a 4'-$(CH_2)_n$-O-2' bridge, where n=1 or n=2, including α-L-methyleneoxy (4'-CH2-O-2') BNA , β-D-methyleneoxy (4'-CH2-O-2') BNA and ethyleneoxy (4'-$(CH2)_2$-O-2') BNA. Bicyclic modified sugars also include (6'S)-6'methyl BNA, aminooxy (4'-CH2-O-N(R)-2') BNA, oxyamino (4'-CH2-N(R)-O-2') BNA wherein R is, independently, H, a protecting group or C1-C12 alkyl. The substituent at the 2' position can also be selected from allyl, amino, azido, thio, O-allyl, O-C1-C10 alkyl, $OCF_3$, $O(CH_2)_2SCH_3$, $O(CH_2)_2$-O-N(Rm)(Rn), and O-$CH_2$-C(=O)-N(Rm)(Rn), where each Rm and Rn is, independently, H or substituted or unsubstituted C1-C10 alkyl. In certain embodiments, such BNA modified nucleotides are high-affinity nucleotides and their incorporation into antisense compounds allows for increased potency and improved therapeutic index. Methods for the preparations of modified sugars are

well known to those skilled in the art.

In nucleotides having modified sugar moieties, the nucleobase moieties (natural, modified or a combination thereof) are maintained for hybridization with an appropriate nucleic acid target.

In one embodiment, antisense compounds targeted to a PCSK9 nucleic acid comprise one or more nucleotides having modified sugar moieties. In a suitable embodiment, the modified sugar moiety is 2'-MOE. In other embodiments, the 2'-MOE modified nucleotides are arranged in a gapmer motif.

*Modified Nucleobases*

Nucleobase (or base) modifications or substitutions are structurally distinguishable from, yet functionally interchangeable with, naturally occurring or synthetic unmodified nucleobases. Both natural and modified nucleobases are capable of participating in hydrogen bonding. Such nucleobase modifications may impart nuclease stability, binding affinity or some other beneficial biological property to antisense compounds. Modified nucleobases include synthetic and natural nucleobases such as, for example, 5-methylcytosine (5-me-C). Certain nucleobase substitutions, including 5-methylcytosine substitutions, are particularly useful for increasing the binding affinity of an antisense compound for a target nucleic acid. For example, 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2°C (Sanghvi, Y.S., Crooke, S.T. and Lebleu, B., eds., *Antisense Research and Applications*, CRC Press, Boca Raton, **1993**, pp. 276-278).

Additional unmodified nucleobases include 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl (-C≡C-$CH_3$) uracil and cytosine and other alkynyl derivatives of pyrimidine bases, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 2-F-adenine, 2-amino-adenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-deazaadenine and 3-deazaguanine and 3-deazaadenine.

Heterocyclic base moieties 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. Nucleobases that are particularly useful for increasing the binding affinity of antisense compounds include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2 aminopropyladenine, 5-propynyluracil and 5-propynylcytosine.

In one embodiment, antisense compounds targeted to a PCSK9 nucleic acid comprise one or more modified nucleobases. In an additional embodiment, gap-widened antisense oligonucleotides targeted to a PCSK9 nucleic acid comprise one or more modified nucleobases. In some embodiments, the modified nucleobase is 5-methylcytosine. In further embodiments, each cytosine is a 5-methylcytosine.

*Compositions and Methods for Formulating Pharmaceutical Compositions*

Antisense oligonucleotides may be admixed with pharmaceutically acceptable active and/or inert substances for the preparation of pharmaceutical compositions or formulations. Compositions and methods for the formulation of pharmaceutical compositions are dependent upon a number of criteria, including, but not limited to, route of administration, extent of disease, or dose to be administered.

Antisense compound targeted to a PCSK9 nucleic acid can be utilized in pharmaceutical compositions by combining the antisense compound with a suitable pharmaceutically acceptable diluent or carrier. A pharmaceutically acceptable diluent includes phosphate-buffered saline (PBS). PBS is a diluent suitable for use in compositions to be delivered parenterally. Accordingly, in one embodiment, employed in the methods described herein is a pharmaceutical composition comprising an antisense compound targeted to a PCSK9 nucleic acid and a pharmaceutically acceptable diluent. In one embodiment, the pharmaceutically acceptable diluent is PBS. In other embodiments, the antisense compound is an antisense oligonucleotide.

Pharmaceutical compositions comprising antisense compounds encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or any other oligonucleotide which, upon administration to an animal, including a human, is capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. Accordingly, for example, the disclosure is also drawn to pharmaceutically acceptable salts of antisense compounds, prodrugs, pharmaceutically acceptable salts of such prodrugs, and other bioequivalents. Suitable pharmaceutically acceptable salts include, but are not limited to, sodium and potassium salts.

A prodrug can include the incorporation of additional nucleosides at one or both ends of an antisense compound which are cleaved by endogenous nucleases within the body, to form the active antisense compound.

In certain embodiments, pharmaceutical compositions of the present invention comprise one or more oligonucleotides and one or more excipients. In certain such embodiments, excipients are selected from water, salt solutions, alcohol, polyethylene glycols, gelatin, lactose, amylase, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulosem and polyvinylpyrrolidone.

In certain embodiments, a pharmaceutical composition of the present invention is prepared using known techniques, including, but not limited to mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tabletting processes.

In certain embodiments, a pharmaceutical composition of the present invention is a liquid (e.g., a suspension, elixir and/or solution). In certain of such embodiments, a liquid pharmaceutical composition is prepared using ingredients known in the art, including, but not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents.

In certain embodiments, a pharmaceutical composition of the present invention is a solid (e.g., a powder, tablet, and/or capsule). In certain of such embodiments, a solid pharmaceutical composition comprising one or more oligonucleotides is prepared using ingredients known in the art, including, but not limited to, starches, sugars, diluents, granulating agents, lubricants, binders, and disintegrating agents.

In certain embodiments, a pharmaceutical composition of the present invention is formulated as a depot preparation. Certain such depot preparations are typically longer acting than non-depot preparations. In certain embodiments, such preparations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. In certain embodiments, depot preparations are prepared using suitable polymeric or hydrophobic materials (for example an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

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

In certain embodiments, a pharmaceutical composition of the present invention comprises

one or more tissue-specific delivery molecules designed to deliver the one or more pharmaceutical agents of the present invention to specific tissues or cell types. For example, in certain embodiments, pharmaceutical compositions include liposomes coated with a tissue-specific antibody.

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

In certain embodiments, a pharmaceutical composition of the present invention comprises a sustained-release system. A non-limiting example of such a sustained-release system is a semi-permeable matrix of solid hydrophobic polymers. In certain embodiments, sustained-release systems may, depending on their chemical nature, release pharmaceutical agents over a period of hours, days, weeks or months.

In certain embodiments, a pharmaceutical composition of the present invention is prepared for oral administration. In certain of such embodiments, a pharmaceutical composition is formulated by combining one or more oligonucleotides with one or more pharmaceutically acceptable carriers. Certain of such carriers enable pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a subject. In certain embodiments, pharmaceutical compositions for oral use are obtained by mixing oligonucleotide and one or more solid excipient. Suitable excipients include, but are not limited to, fillers, such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). In certain embodiments, such a mixture is optionally ground and auxiliaries are optionally added. In certain embodiments,

pharmaceutical compositions are formed to obtain tablets or dragee cores. In certain embodiments, disintegrating agents (e.g., cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate) are added.

In certain embodiments, dragee cores are provided with coatings. In certain such embodiments, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to tablets or dragee coatings.

In certain embodiments, pharmaceutical compositions for oral administration are push-fit capsules made of gelatin. Certain of such push-fit capsules comprise one or more pharmaceutical agents of the present invention in admixture with one or more filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In certain embodiments, pharmaceutical compositions for oral administration are soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. In certain soft capsules, one or more pharmaceutical agents of the present invention are be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added.

In certain embodiments, pharmaceutical compositions are prepared for buccal administration. Certain of such pharmaceutical compositions are tablets or lozenges formulated in conventional manner.

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

and liposomes. Aqueous injection suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, such suspensions may also contain suitable stabilizers or agents that increase the solubility of the pharmaceutical agents to allow for the preparation of highly concentrated solutions.

In certain embodiments, a pharmaceutical composition is prepared for transmucosal administration. In certain of such embodiments penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

In certain embodiments, a pharmaceutical composition is prepared for administration by inhalation. Certain of such pharmaceutical compositions for inhalation are prepared in the form of an aerosol spray in a pressurized pack or a nebulizer. Certain of such pharmaceutical compositions comprise a propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In certain embodiments using a pressurized aerosol, the dosage unit may be determined with a valve that delivers a metered amount. In certain embodiments, capsules and cartridges for use in an inhaler or insufflator may be formulated. Certain of such formulations comprise a powder mixture of a pharmaceutical agent of the invention and a suitable powder base such as lactose or starch.

In certain embodiments, a pharmaceutical composition is prepared for rectal administration, such as a suppositories or retention enema. Certain of such pharmaceutical compositions comprise known ingredients, such as cocoa butter and/or other glycerides.

In certain embodiments, a pharmaceutical composition is prepared for topical administration. Certain of such pharmaceutical compositions comprise bland moisturizing bases, such as ointments or creams. Exemplary suitable ointment bases include, but are not limited to, petrolatum, petrolatum plus volatile silicones, lanolin and water in oil emulsions such as Eucerin™, available from Beiersdorf (Cincinnati, Ohio). Exemplary suitable cream bases include, but are not limited to, Nivea™ Cream, available from Beiersdorf (Cincinnati, Ohio), cold cream (USP), Purpose Cream™, available from Johnson & Johnson (New Brunswick, N.J.), hydrophilic ointment (USP) and Lubriderm™, available from Pfizer (Morris Plains, N.J.).

In certain embodiments, a pharmaceutical composition of the present invention comprises an oligonucleotide in a therapeutically effective amount. In certain embodiments, the therapeutically effective amount is sufficient to prevent, alleviate or ameliorate symptoms of a disease or to prolong the survival of the subject being treated. Determination of a therapeutically effective amount is well within the capability of those skilled in the art.

In certain embodiments, one or more oligonucleotides of the present invention is

formulated as a prodrug. In certain embodiments, upon in vivo administration, a prodrug is chemically converted to the biologically, pharmaceutically or therapeutically more active form of the oligonucleotide. In certain embodiments, prodrugs are useful because they are easier to administer than the corresponding active form. For example, in certain instances, a prodrug may be more bioavailable (e.g., through oral administration) than is the corresponding active form. In certain instances, a prodrug may have improved solubility compared to the corresponding active form. In certain embodiments, prodrugs are less water soluble than the corresponding active form. In certain instances, such prodrugs possess superior transmittal across cell membranes, where water solubility is detrimental to mobility. In certain embodiments, a prodrug is an ester. In certain such embodiments, the ester is metabolically hydrolyzed to carboxylic acid upon administration. In certain instances the carboxylic acid containing compound is the corresponding active form. In certain embodiments, a prodrug comprises a short peptide (polyaminoacid) bound to an acid group. In certain of such embodiments, the peptide is cleaved upon administration to form the corresponding active form.

In certain embodiments, a prodrug is produced by modifying a pharmaceutically active compound such that the active compound will be regenerated upon in vivo administration. The prodrug can be designed to alter the metabolic stability or the transport characteristics of a drug, to mask side effects or toxicity, to improve the flavor of a drug or to alter other characteristics or properties of a drug. By virtue of knowledge of pharmacodynamic processes and drug metabolism *in vivo*, those of skill in this art, once a pharmaceutically active compound is known, can design prodrugs of the compound (see, e.g., Nogrady (1985) Medicinal Chemistry A Biochemical Approach, Oxford University Press, New York, pages 388-392).

In certain embodiments, a pharmaceutical composition comprising one or more pharmaceutical agents of the present invention is useful for treating a conditions or disorders in a mammalian, and particularly in a human, subject. Suitable administration routes include, but are not limited to, oral, rectal, transmucosal, intestinal, enteral, topical, suppository, through inhalation, intrathecal, intraventricular, intraperitoneal, intranasal, intraocular and parenteral (e.g., intravenous, intramuscular, intramedullary, and subcutaneous). In certain embodiments, pharmaceutical intrathecals are administered to achieve local rather than systemic exposures. For example, pharmaceutical compositions may be injected directly in the area of desired effect (e.g., in the renal or cardiac area).

In certain embodiments, a pharmaceutical composition of the present invention is administered in the form of a dosage unit (e.g., tablet, capsule, bolus, etc.). In certain

embodiments, such pharmaceutical compositions comprise an oligonucleotide in a dose selected from 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, 150 mg, 155 mg, 160 mg, 165 mg, 170 mg, 175 mg, 180 mg, 185 mg, 190 mg, 195 mg, 200 mg, 205 mg, 210 mg, 215 mg, 220 mg, 225 mg, 230 mg, 235 mg, 240 mg, 245 mg, 250 mg, 255 mg, 260 mg, 265 mg, 270 mg, 270 mg, 280 mg, 285 mg, 290 mg, 295 mg, 300 mg, 305 mg, 310 mg, 315 mg, 320 mg, 325 mg, 330 mg, 335 mg, 340 mg, 345 mg, 350 mg, 355 mg, 360 mg, 365 mg, 370 mg, 375 mg, 380 mg, 385 mg, 390 mg, 395 mg, 400 mg, 405 mg, 410 mg, 415 mg, 420 mg, 425 mg, 430 mg, 435 mg, 440 mg, 445 mg, 450 mg, 455 mg, 460 mg, 465 mg, 470 mg, 475 mg, 480 mg, 485 mg, 490 mg, 495 mg, 500 mg, 505 mg, 510 mg, 515 mg, 520 mg, 525 mg, 530 mg, 535 mg, 540 mg, 545 mg, 550 mg, 555 mg, 560 mg, 565 mg, 570 mg, 575 mg, 580 mg, 585 mg, 590 mg, 595 mg, 600 mg, 605 mg, 610 mg, 615 mg, 620 mg, 625 mg, 630 mg, 635 mg, 640 mg, 645 mg, 650 mg, 655 mg, 660 mg, 665 mg, 670 mg, 675 mg, 680 mg, 685 mg, 690 mg, 695 mg, 700 mg, 705 mg, 710 mg, 715 mg, 720 mg, 725 mg, 730 mg, 735 mg, 740 mg, 745 mg, 750 mg, 755 mg, 760 mg, 765 mg, 770 mg, 775 mg, 780 mg, 785 mg, 790 mg, 795 mg, and 800 mg. In certain such embodiments, a pharmaceutical composition of the present invention comprises a dose of oligonucleotide selected from 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 500 mg, 600 mg, 700 mg, and 800mg. In certain embodiments, a pharmaceutical composition is comprises a dose of oligonucleotide selected from 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, and 400 mg. In certain embodiments the dose is administered at intervals ranging from more than once per day, once per day, once per week, twice per week, three times per week, four times per week, five times per week, 6 times per week, once per month to once per three months, for as long as needed to sustain the desired effect.

In a further aspect, a pharmaceutical agent is sterile lyophilized oligonucleotide that is reconstituted with a suitable diluent, e.g., sterile water for injection. The reconstituted product is administered as a subcutaneous injection or as an intravenous infusion after dilution into saline. The lyophilized drug product consists of the oligonucleotide which has been prepared in water for injection, adjusted to pH 7.0-9.0 with acid or base during preparation, and then lyophilized. The lyophilized oligonucleotide may be 25-800 mg of the oligonucleotide. It is understood that this encompasses 25, 50, 75, 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 425, 450, 475, 500, 525, 550, 575, 600, 625, 650, 675, 700, 725, 750, 775, and 800 mg of lyophilized oligonucleotide. The lyophilized drug product may be packaged in a 2 mL Type I, clear glass

vial (ammonium sulfate-treated), stoppered with a bromobutyl rubber closure and sealed with an aluminum FLIP-OFF® overseal. In one embodiment, the lyophilized pharmaceutical agent comprises ISIS 301012.

The compositions of the present invention may additionally contain other adjunct components conventionally found in pharmaceutical compositions, at their art-established usage levels. Thus, for example, the compositions may contain additional, compatible, pharmaceutically-active materials such as, for example, antipruritics, astringents, local anesthetics or anti-inflammatory agents, or may contain additional materials useful in physically formulating various dosage forms of the compositions of the present invention, such as dyes, flavoring agents, preservatives, antioxidants, opacifiers, thickening agents and stabilizers. However, such materials, when added, should not unduly interfere with the biological activities of the components of the compositions of the present invention. The formulations can be sterilized and, if desired, mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavorings and/or aromatic substances and the like which do not deleteriously interact with the oligonucleotide(s) of the formulation.

*Conjugated Antisense Compounds*

Antisense compounds may be covalently linked to one or more moieties or conjugates which enhance the activity, cellular distribution or cellular uptake of the resulting antisense oligonucleotides. Typical conjugate groups include cholesterol moieties and lipid moieties. Additional conjugate groups include carbohydrates, phospholipids, biotin, phenazine, folate, phenanthridine, anthraquinone, acridine, fluoresceins, rhodamines, coumarins, and dyes.

Antisense compounds can also be modified to have one or more stabilizing groups that are generally attached to one or both termini of antisense compounds to enhance properties such as, for example, nuclease stability. Included in stabilizing groups are cap structures. These terminal modifications protect the antisense compound having terminal nucleic acid from exonuclease degradation, and can help in delivery and/or localization within a cell. The cap can be present at the 5'-terminus (5'-cap), or at the 3'-terminus (3'-cap), or can be present on both termini. Cap structures are well known in the art and include, for example, inverted deoxy abasic caps. Further 3' and 5'-stabilizing groups that can be used to cap one or both ends of an antisense compound to impart nuclease stability include those disclosed in WO 03/004602 published on January 16, 2003.

*Cell Culture and Antisense Compounds Treatment*

The effects of antisense compounds on the level, activity or expression of PCSK9 nucleic acids can be tested *in vitro* in a variety of cell types. Cell types used for such analyses are available from commerical vendors (*e.g.* American Type Culture Collection, Manassus, VA; Zen-Bio, Inc., Research Triangle Park, NC; Clonetics Corporation, Walkersville, MD) and cells are cultured according to the vendor's instructions using commercially available reagents (e.g. Invitrogen Life Technologies, Carlsbad, CA). Illustrative cell types include, but are not limited to, HepG2 cells, HepB3 cells, and primary hepatocytes.

*In vitro Testing of Antisense Oligonucleotides*

Described herein are methods for treatment of cells with antisense oligonucleotides, which can be modified appropriately for treatment with other antisense compounds.

In general, cells are treated with antisense oligonucleotides when they cells reach approximately 60-80% confluency in culture.

One reagent commonly used to introduce antisense oligonucleotides into cultured cells includes the cationic lipid transfection reagent LIPOFECTIN® (Invitrogen, Carlsbad, CA). Antisense oligonucleotides are mixed with LIPOFECTIN® in OPTI-MEM® 1 (Invitrogen, Carlsbad, CA) to achieve the desired final concentration of antisense oligonucleotide and a LIPOFECTIN® concentration that typically ranges 2 to 12 ug/mL per 100 nM antisense oligonucleotide.

Another reagent used to introduce antisense oligonucleotides into cultured cells includes LIPOFECTAMINE® (Invitrogen, Carlsbad, CA). Antisense oligonucleotide is mixed with LIPOFECTAMINE® in OPTI-MEM® 1 reduced serum medium (Invitrogen, Carlsbad, CA) to achieve the desired concentration of antisense oligonucleotide and a LIPOFECTAMINE® concentration that typically ranges 2 to 12 ug/mL per 100 nM antisense oligonucleotide.

Cells are treated with antisense oligonucleotides by routine methods. Cells are typically harvested 16-24 hours after antisense oligonucleotide treatment, at which time RNA or protein levels of target nucleic acids are measured by methods known in the art and described herein. In general, when treatments are performed in multiple replicates, the data are presented as the average of the replicate treatments.

The concentration of antisense oligonucleotide used varies from cell line to cell line. Methods to determine the optimal antisense oligonucleotide concentration for a particular cell

line are well known in the art. Antisense oligonucleotides are typically used at concentrations ranging from 1 nM to 300 nM.

*RNA Isolation*

RNA analysis can be performed on total cellular RNA or poly(A)+ mRNA. Methods of RNA isolation are well known in the art. RNA is prepared using methods well known in the art, for example, using the TRIZOL® Reagent (Invitrogen, Carlsbad, CA) according to the manufacturer's recommended protocols.

*Analysis of Inhibition of Target Levels or Expression*

Inhibition of levels or expression of a PCSK9 nucleic acid can be assayed in a variety of ways known in the art. For example, target nucleic acid levels can be quantitated by, e.g., Northern blot analysis, competitive polymerase chain reaction (PCR), or quantitaive real-time PCR. RNA analysis can be performed on total cellular RNA or poly(A)+ mRNA. Methods of RNA isolation are well known in the art. Northern blot analysis is also routine in the art. Quantitative real-time PCR can be conveniently accomplished using the commercially available ABI PRISM® 7600, 7700, or 7900 Sequence Detection System, available from PE-Applied Biosystems, Foster City, CA and used according to manufacturer's instructions.

*Quantitative Real-Time PCR Analysis of Target RNA Levels*

Quantitation of target RNA levels may be accomplished by quantitative real-time PCR using the ABI PRISM® 7600, 7700, or 7900 Sequence Detection System (PE-Applied Biosystems, Foster City, CA) according to manufacturer's instructions. Methods of quantitative real-time PCR are well known in the art.

Prior to real-time PCR, the isolated RNA is subjected to a reverse transcriptase (RT) reaction, which produces complementary DNA (cDNA) that is then used as the substrate for the real-time PCR amplification. The RT and real-time PCR reactions are performed sequentially in the same sample well. RT and real-time PCR reagents are obtained from Invitrogen (Carlsbad, CA). RT, real-time-PCR reactions are carried out by methods well known to those skilled in the art.

Gene (or RNA) target quantities obtained by real time PCR are normalized using either the expression level of a gene whose expression is constant, such as GAPDH, or by quantifying total RNA using RIBOGREEN® (Invetrogen, Inc. Carlsbad, CA). GAPDH expression is

quantified by real time PCR, by being run simultaneously with the target, multiplexing, or separately. Total RNA is quantified using RIBOGREEN® RNA quantification reagent (Invetrogen, Inc. Eugene, OR). Methods of RNA quantification by RIBOGREEN® are taught in Jones, L.J., et al, (Analytical Biochemistry, 1998, 265, 368-374). A CYTOFLUOR® 4000 instrument (PE Applied Biosystems) is used to measure RIBOGREEN® fluorescence.

Probes and primers are designed to hybridize to a PCSK9 nucleic acid. Methods for designing real-time PCR probes and primers are well known in the art, and may include the use of software such as PRIMER EXPRESS® Software (Applied Biosystems, Foster City, CA).

*Analysis of Protein Levels*

Antisense inhibition of PCSK9 nucleic acids can be assessed by measuring PCSK9 protein levels. Protein levels of PCSK9 can be evaluated or quantitated in a variety of ways well known in the art, such as immunoprecipitation, Western blot analysis (immunoblotting), enzyme-linked immunosorbent assay (ELISA), quantitative protein assays, protein activity assays (for example, caspase activity assays), immunohistochemistry, immunocytochemistry or fluorescence-activated cell sorting (FACS). Antibodies directed to a target can be identified and obtained from a variety of sources, such as the MSRS catalog of antibodies (Aerie Corporation, Birmingham, MI), or can be prepared via conventional monoclonal or polyclonal antibody generation methods well known in the art. Antibodies useful for the detection of human and rat PCSK9 are commercially available.

*In vivo Testing of Antisense Compounds*

Antisense compounds, for example, antisense oligonucleotides, are tested in animals to assess their ability to inhibit expression of PCSK9 and produce phenotypic changes, such as decreases in LDL-C. Testing may be performed in normal animals, or in experimental disease models. For administration to animals, antisense oligonucleotides are formulated in a pharmaceutically acceptable diluent, such as phosphate-buffered saline. Administration includes parenteral routes of administration, such as intraperitoneal, intravenous, and subcutaneous. Calculation of antisense oligonucleotide dosage and dosing frequency is within the abilities of those skilled in the art, and depends upon factors such as route of administration and animal body weight. Following a period of treatment with antisense oligonucleotides, RNA is isolated from various tissues and changes in PCSK9 nucleic acid expression are measured. Changes in PCSK9 protein levels may also be measured.

*Animal Models of Atherosclerosis*

**Nonlimiting disclosure and incorporation by reference**

The following examples serve only to illustrate the methods, antisense oligonucleotides, and compositions provided and are not intended to limit the same. Each of the references, GENBANK® accession numbers, and the like recited in the present application is incorporated herein by reference in its entirety.

## EXAMPLES

**Example 1: Antisense inhibition of human PCSK9: A549 cells**

Antisense oligonucleotides targeted to a PCSK9 nucleic acid were tested for their effects on PCSK9 mRNA *in vitro*. Cultured A549 cells at a density of 4000 cells per well in a 96-well plate were treated with 60 nM of antisense oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and PCSK9 mRNA levels were measured by quantitative real-time PCR, as described herein. PCSK9 mRNA levels were adjusted according to total RNA content as measured by RIBOGREEN®. Results are presented as percent inhibition of PCSK9, relative to untreated control cells. Antisense oligonucleotides that exhibited at least 30% inhibition of PCSK9 expression are shown in Table 15.

The motif column indicates the wing-gap-wing motif of each antisense oligonucleotide. Antisense oligonucleotides were designed as 5-10-5 gapmers, or alternatively as 3-14-3 gapmers, where the gap segment comprises 2'-deoxynucleotides and each wing segment comprises 2'-MOE nucleotides. As illustrated in Table 15, a single nucleobase sequence may be represented by a 5-10-5 motif as well as a 3-14-3 motif. "5' target site" indicates the 5'-most nucleotide which the antisense oligonucleotide is targeted on the indicated GENBANK Accession No.

**Table 15: Antisense inhibition of PCSK9 in human cells (Cell type A549)**

| IsisNo | SEQ ID NO | 5' Target Site | Target Nucleic Acid | Sequence | Motif | % Inhibition |
|---|---|---|---|---|---|---|
| 395150 | 5 | 242 | NM_174936.2 | GAGGAGACCTAGAGGCCGTG | 5-10-5 | 57 |
| 395151 | 6 | 300 | NM_174936.2 | AGGACCGCCTGGAGCTGACG | 5-10-5 | 77 |
| 395152 | 7 | 410 | NM_174936.2 | ACGCAAGGCTAGCACCAGCT | 5-10-5 | 81 |

| IsisNo | SEQ ID NO | 5' Target Site | Target Nucleic Acid | Sequence | Motif | % Inhibition |
|---|---|---|---|---|---|---|
| 395153 | 9 | 480 | NM_174936.2 | CCTTGGCGCAGCGGTGGAAG | 5-10-5 | 51 |
| 395154 | 10 | 561 | NM_174936.2 | GGCGGGCAGTGCGCTCTGAC | 5-10-5 | 40 |
| 395155 | 11 | 600 | NM_174936.2 | TGGTGAGGTATCCCCGGCGG | 5-10-5 | 79 |
| 395156 | 14 | 620 | NM_174936.2 | ATGGAAGACATGCAGGATCT | 5-10-5 | 75 |
| 395157 | 15 | 646 | NM_174936.2 | TTCACCAGGAAGCCAGGAAG | 5-10-5 | 72 |
| 395158 | 17 | 705 | NM_174936.2 | CCTCGATGTAGTCGACATGG | 5-10-5 | 61 |
| 395159 | 18 | 785 | NM_174936.2 | GTATTCATCCGCCCGGTACC | 5-10-5 | 35 |
| 395160 | 19 | 835 | NM_174936.2 | CTGGTGTCTAGGAGATACAC | 5-10-5 | 47 |
| 395161 | 21 | 860 | NM_174936.2 | GATTTCCCGGTGGTCACTCT | 5-10-5 | 70 |
| 395162 | 24 | 890 | NM_174936.2 | CTCGAAGTCGGTGACCATGA | 5-10-5 | 52 |
| 395163 | 25 | 923 | NM_174936.2 | GTGGAAGCGGGTCCCGTCCT | 5-10-5 | 73 |
| 395164 | 26 | 970 | NM_174936.2 | ACCCCTGCCAGGTGGGTGCC | 5-10-5 | 69 |
| 395165 | 28 | 1004 | NM_174936.2 | ACCCTTGGCCACGCCGGCAT | 5-10-5 | 81 |
| 395166 | 29 | 1040 | NM_174936.2 | TTGGCAGTTGAGCACGCGCA | 5-10-5 | 65 |
| 395167 | 31 | 1077 | NM_174936.2 | CCAGGCCTATGAGGGTGCCG | 5-10-5 | 34 |
| 395168 | 32 | 1098 | NM_174936.2 | GCTGGCTTTTCCGAATAAAC | 5-10-5 | 69 |
| 395169 | 33 | 1210 | NM_174936.2 | GTGACCAGCACGACCCCAGC | 5-10-5 | 61 |
| 395171 | 34 | 1326 | NM_174936.2 | CCAAAGTCCCCAGGGTCACC | 5-10-5 | 38 |
| 395173 | 36 | 1340 | NM_174936.2 | GCCAAAGTTGGTCCCCAAAG | 5-10-5 | 64 |
| 395174 | 38 | 1361 | NM_174936.2 | GGCAAAGAGGTCCACACAGC | 5-10-5 | 72 |
| 395175 | 39 | 1389 | NM_174936.2 | TGGAGGCACCAATGATGTCC | 5-10-5 | 41 |
| 395177 | 45 | 1534 | NM_174936.2 | TTGGCAGAGAAGTGGATCAG | 5-10-5 | 41 |
| 395178 | 50 | 1569 | NM_174936.2 | GGTCCTCAGGGAACCAGGCC | 5-10-5 | 67 |
| 395181 | 52 | 1640 | NM_174936.2 | AAACAGCTGCCAACCTGCCC | 5-10-5 | 37 |
| 395182 | 54 | 1675 | NM_174936.2 | GTAGGCCCCGAGTGTGCTGA | 5-10-5 | 51 |
| 395183 | 57 | 1812 | NM_174936.2 | CGTTGTGGGCCCGGCAGACC | 5-10-5 | 74 |
| 395184 | 58 | 1858 | NM_174936.2 | AGCAGGCAGCACCTGGCAAT | 5-10-5 | 61 |
| 395185 | 59 | 1920 | NM_174936.2 | CACGGGTCCCCATGCTGGCC | 5-10-5 | 73 |
| 395186 | 60 | 2100 | NM_174936.2 | CTTTGCATTCCAGACCTGGG | 5-10-5 | 83 |
| 395187 | 62 | 2310 | NM_174936.2 | GGCAGCAGATGGCAACGGCT | 5-10-5 | 80 |
| 395189 | 64 | 2504 | NM_174936.2 | TCAAGGGCCAGGCCAGCAGC | 5-10-5 | 65 |
| 395190 | 66 | 2597 | NM_174936.2 | ATGCCCCACAGTGAGGGAGG | 5-10-5 | 60 |
| 395191 | 67 | 2606 | NM_174936.2 | AATGGTGAAATGCCCCACAG | 5-10-5 | 76 |
| 395193 | 68 | 2750 | NM_174936.2 | CATGGGAAGAATCCTGCCTC | 5-10-5 | 48 |
| 395194 | 69 | 2832 | NM_174936.2 | GGAGATGAGGGCCATCAGCA | 5-10-5 | 64 |
| 395195 | 70 | 2900 | NM_174936.2 | TAGATGCCATCCAGAAAGCT | 5-10-5 | 44 |
| 395196 | 72 | 2983 | NM_174936.2 | GGCATAGAGCAGAGTAAAGG | 5-10-5 | 39 |
| 395198 | 75 | 3437 | NM_174936.2 | GCTCAAGGAGGGACAGTTGT | 5-10-5 | 73 |
| 395199 | 76 | 3472 | NM_174936.2 | AAAGATAAATGTCTGCTTGC | 5-10-5 | 83 |
| 395200 | 78 | 3543 | NM_174936.2 | TCTTCAAGTTACAAAAGCAA | 5-10-5 | 40 |
| 395202 | 129 | 13816 | NT_032977.8 | GTGCCATCTGAACAGCACCT | 5-10-5 | 36 |
| 395203 | 110 | 13926 | NT_032977.8 | CCTGGAACCCCTGCAGCCAG | 5-10-5 | 64 |
| 395204 | 152 | 13977 | NT_032977.8 | TTCAGGCAGGTTGCTGCTAG | 5-10-5 | 55 |
| 395206 | 136 | 14122 | NT_032977.8 | TAGGAGAAAGTAGGGAGAGC | 5-10-5 | 45 |
| 395207 | 132 | 14179 | NT_032977.8 | TAAAAGCTGCAAGAGACTCA | 5-10-5 | 49 |
| 395208 | 139 | 14267 | NT_032977.8 | TCAGAGAAAACAGTCACCGA | 5-10-5 | 56 |
| 395209 | 142 | 14404 | NT_032977.8 | TCATTTTAGAGACAGGAAGC | 5-10-5 | 73 |
| 395210 | 113 | 14441 | NT_032977.8 | GAATAACAGTGATGTCTGGC | 5-10-5 | 82 |

| IsisNo | SEQ ID NO | 5' Target Site | Target Nucleic Acid | Sequence | Motif | % Inhibition |
|---|---|---|---|---|---|---|
| 395211 | 138 | 14494 | NT_032977.8 | TCACAGCTCACCGAGTCTGC | 5-10-5 | 60 |
| 395212 | 98 | 14524 | NT_032977.8 | AGTGTAAAATAAAGCCCCTA | 5-10-5 | 50 |
| 395213 | 96 | 14601 | NT_032977.8 | AGGACCCAAGTCATCCTGCT | 5-10-5 | 57 |
| 395214 | 124 | 14631 | NT_032977.8 | GGCCATCAGCTGGCAATGCT | 5-10-5 | 50 |
| 395215 | 133 | 14675 | NT_032977.8 | TAGACAAGGAAAGGGAGGCC | 5-10-5 | 60 |
| 395216 | 103 | 14681 | NT_032977.8 | ATTTCATAGACAAGGAAAGG | 5-10-5 | 51 |
| 395218 | 146 | 1315 | AK124635.1 | TGACATTTGTGGGAGAGGAG | 5-10-5 | 35 |
| 395220 | 104 | 2085 | AK124635.1 | CACAGTCCTGCAAAACAGCT | 5-10-5 | 54 |
| 395221 | 102 | 5590 | NT_032977.8 | ATGTGCAGAGATCAATCACA | 5-10-5 | 69 |
| 395222 | 127 | 10633 | NT_032977.8 | GGTGGTAATTTGTCACAGCA | 5-10-5 | 64 |
| 395223 | 84 | 11308 | NT_032977.8 | AAGGTCACACAGTTAAGAGT | 5-10-5 | 55 |
| 395226 | 147 | 24858 | NT_032977.8 | TGAGTTCATTTAAGAGTGGA | 5-10-5 | 42 |
| 399793 | 8 | 417 | NM_174936.2 | CCTCGGAACGCAAGGCTAGC | 5-10-5 | 71 |
| 399794 | 12 | 606 | NM_174936.2 | GGATCTTGGTGAGGTATCCC | 5-10-5 | 42 |
| 399795 | 13 | 615 | NM_174936.2 | AGACATGCAGGATCTTGGTG | 5-10-5 | 54 |
| 399796 | 16 | 651 | NM_174936.2 | TCATCTTCACCAGGAAGCCA | 5-10-5 | 50 |
| 399797 | 20 | 840 | NM_174936.2 | GTATGCTGGTGTCTAGGAGA | 5-10-5 | 38 |
| 399798 | 22 | 866 | NM_174936.2 | GCCCTCGATTTCCCGGTGGT | 5-10-5 | 54 |
| 399799 | 23 | 880 | NM_174936.2 | GTGACCATGACCCTGCCCTC | 5-10-5 | 75 |
| 399800 | 27 | 975 | NM_174936.2 | TGACCACCCCTGCCAGGTGG | 5-10-5 | 67 |
| 399801 | 30 | 1045 | NM_174936.2 | TTCCCTTGGCAGTTGAGCAC | 5-10-5 | 79 |
| 399802 | 35 | 1335 | NM_174936.2 | AGTTGGTCCCCAAAGTCCCC | 5-10-5 | 71 |
| 399803 | 37 | 1352 | NM_174936.2 | GTCCACACAGCGGCCAAAGT | 5-10-5 | 63 |
| 399804 | 40 | 1400 | NM_174936.2 | GCTGCAGTCGCTGGAGGCAC | 5-10-5 | 46 |
| 399805 | 41 | 1411 | NM_174936.2 | ACAAAGCAGGTGCTGCAGTC | 5-10-5 | 46 |
| 399806 | 42 | 1470 | NM_174936.2 | GCATCATGGCTGCAATGCCA | 5-10-5 | 85 |
| 399807 | 43 | 1478 | NM_174936.2 | GGCAGACAGCATCATGGCTG | 5-10-5 | 71 |
| 399808 | 44 | 1526 | NM_174936.2 | GAAGTGGATCAGTCTCTGCC | 5-10-5 | 38 |
| 399809 | 46 | 1539 | NM_174936.2 | CATCTTTGGCAGAGAAGTGG | 5-10-5 | 53 |
| 399810 | 47 | 1545 | NM_174936.2 | TGATGACATCTTTGGCAGAG | 5-10-5 | 63 |
| 399811 | 48 | 1552 | NM_174936.2 | GCCTCATTGATGACATCTTT | 5-10-5 | 61 |
| 399812 | 49 | 1564 | NM_174936.2 | TCAGGGAACCAGGCCTCATT | 5-10-5 | 46 |
| 399813 | 51 | 1583 | NM_174936.2 | GGTCAGTACCCGCTGGTCCT | 5-10-5 | 72 |
| 399814 | 53 | 1645 | NM_174936.2 | CTGCAAAACAGCTGCCAACC | 5-10-5 | 88 |
| 399815 | 55 | 1740 | NM_174936.2 | AGAAACTGGAGCAGCTCAGC | 5-10-5 | 38 |
| 399816 | 56 | 1746 | NM_174936.2 | TCCTGGAGAAACTGGAGCAG | 5-10-5 | 51 |
| 399817 | 61 | 2105 | NM_174936.2 | CTTGACTTTGCATTCCAGAC | 5-10-5 | 84 |
| 399818 | 63 | 2415 | NM_174936.2 | AACCATTTTAAAGCTCAGCC | 5-10-5 | 68 |
| 399819 | 65 | 2509 | NM_174936.2 | CCCACTCAAGGGCCAGGCCA | 5-10-5 | 87 |
| 399821 | 71 | 2906 | NM_174936.2 | TCTGGCTAGATGCCATCCAG | 5-10-5 | 83 |
| 399822 | 73 | 2988 | NM_174936.2 | AGCCTGGCATAGAGCAGAGT | 5-10-5 | 70 |
| 399824 | 74 | 3233 | NM_174936.2 | AAGTAAGAAGAGGCTTGGCT | 5-10-5 | 43 |
| 399825 | 77 | 3477 | NM_174936.2 | ACCCAAAAGATAAATGTCTG | 5-10-5 | 61 |
| 399827 | 100 | 13746 | NT_032977.8 | ATCTCAGGACAGGTGAGCAA | 5-10-5 | 81 |
| 399828 | 116 | 13760 | NT_032977.8 | GAGTAGAGATTCTCATCTCA | 5-10-5 | 73 |
| 399829 | 117 | 13828 | NT_032977.8 | GAGTCTTCTGAAGTGCCATC | 5-10-5 | 65 |
| 399831 | 83 | 13986 | NT_032977.8 | AAGGAAGACTTCAGGCAGGT | 5-10-5 | 52 |
| 399833 | 92 | 14397 | NT_032977.8 | AGAGACAGGAAGCTGCAGCT | 5-10-5 | 54 |

| IsisNo | SEQ ID NO | 5' Target Site | Target Nucleic Acid | Sequence | Motif | % Inhibition |
|---|---|---|---|---|---|---|
| 399834 | 82 | 14670 | NT_032977.8 | AAGGAAAGGGAGGCCTAGAG | 5-10-5 | 44 |
| 399836 | 130 | 2095 | AK124635.1 | GTGCTGACCACACAGTCCTG | 5-10-5 | 96 |
| 399837 | 107 | 3056 | NT_032977.8 | CCCACTATAATGGCAAGCCC | 5-10-5 | 83 |
| 399838 | 80 | 4306 | NT_032977.8 | AACCCAGTTCTAATGCACCT | 5-10-5 | 81 |
| 399839 | 106 | 5140 | NT_032977.8 | CCAGTCAGAGTAGAACAGAG | 5-10-5 | 68 |
| 399840 | 121 | 5599 | NT_032977.8 | GGAGCCTACATGTGCAGAGA | 5-10-5 | 46 |
| 399841 | 94 | 5667 | NT_032977.8 | AGCATGGCACCAGCATCTGC | 5-10-5 | 59 |
| 399842 | 108 | 6652 | NT_032977.8 | CCCAGCCCTATCAGGAAGTG | 5-10-5 | 67 |
| 399843 | 144 | 7099 | NT_032977.8 | TGACATCCAGGAGGGAGGAG | 5-10-5 | 33 |
| 399844 | 91 | 7556 | NT_032977.8 | AGACTGATGGAAGGCATTGA | 5-10-5 | 56 |
| 399845 | 131 | 7565 | NT_032977.8 | GTGTTGAGCAGACTGATGGA | 5-10-5 | 48 |
| 399846 | 145 | 8836 | NT_032977.8 | TGACATCTTGTCTGGGAGCC | 5-10-5 | 58 |
| 399847 | 90 | 8948 | NT_032977.8 | AGACTAGGAGCCTGAGTTTT | 5-10-5 | 38 |
| 399849 | 148 | 10252 | NT_032977.8 | TGGCAGCAACTCAGACATAT | 5-10-5 | 74 |
| 399851 | 88 | 12715 | NT_032977.8 | ACTGGATACATTGGCAGACA | 5-10-5 | 62 |
| 399852 | 111 | 12928 | NT_032977.8 | CTAGAGGAACCACTAGATAT | 5-10-5 | 66 |
| 399854 | 97 | 16134 | NT_032977.8 | AGTCAAGCTGCTGCCCAGAG | 5-10-5 | 82 |
| 399855 | 120 | 16668 | NT_032977.8 | GCTAGTTATTAAGCACCTGC | 5-10-5 | 71 |
| 399856 | 150 | 17267 | NT_032977.8 | TGTGAGCTCTGGCCCAGTGG | 5-10-5 | 64 |
| 399857 | 115 | 18377 | NT_032977.8 | GAGTAAGGCAGGTTACTCTC | 5-10-5 | 79 |
| 399858 | 134 | 18408 | NT_032977.8 | TAGATGTGACTAACATTTAA | 5-10-5 | 57 |
| 399859 | 105 | 19203 | NT_032977.8 | CACATTAGCCTTGCTCAAGT | 5-10-5 | 75 |
| 399860 | 151 | 19913 | NT_032977.8 | TGTGATGACCTGGAAAGGTG | 5-10-5 | 36 |
| 399862 | 109 | 20188 | NT_032977.8 | CCCCTGCACAGAGCCTGGCA | 5-10-5 | 59 |
| 399863 | 141 | 20624 | NT_032977.8 | TCATGGCTGCAATGCCTGGT | 5-10-5 | 46 |
| 399864 | 93 | 20995 | NT_032977.8 | AGAGAGGAGGGCTTAAAGAA | 5-10-5 | 30 |
| 399865 | 95 | 21082 | NT_032977.8 | AGCTGCCAACCTGCAAAAAG | 5-10-5 | 75 |
| 399866 | 143 | 21481 | NT_032977.8 | TGAAAATCCATCCAGCACTG | 5-10-5 | 74 |
| 399867 | 89 | 21589 | NT_032977.8 | AGAACCATGGAGCACCTGAG | 5-10-5 | 84 |
| 399868 | 123 | 21696 | NT_032977.8 | GGCACTGCCCTTCCACCAAA | 5-10-5 | 53 |
| 399869 | 118 | 24907 | NT_032977.8 | GCACCATCCAGACCAGAATC | 5-10-5 | 49 |
| 399870 | 114 | 25413 | NT_032977.8 | GAGAGGTTCAGATCCAGGCC | 5-10-5 | 66 |
| 399871 | 4 | 135 | NM_174936.2 | GCGCGGAATCCTGGCTGGGA | 3-14-3 | 40 |
| 399872 | 5 | 242 | NM_174936.2 | GAGGAGACCTAGAGGCCGTG | 3-14-3 | 64 |
| 399873 | 6 | 300 | NM_174936.2 | AGGACCGCCTGGAGCTGACG | 3-14-3 | 65 |
| 399874 | 7 | 410 | NM_174936.2 | ACGCAAGGCTAGCACCAGCT | 3-14-3 | 80 |
| 399875 | 9 | 480 | NM_174936.2 | CCTTGGCGCAGCGGTGGAAG | 3-14-3 | 67 |
| 399876 | 10 | 561 | NM_174936.2 | GGCGGGCAGTGCGCTCTGAC | 3-14-3 | 62 |
| 399877 | 11 | 600 | NM_174936.2 | TGGTGAGGTATCCCCGGCGG | 3-14-3 | 73 |
| 399878 | 14 | 620 | NM_174936.2 | ATGGAAGACATGCAGGATCT | 3-14-3 | 54 |
| 399879 | 15 | 646 | NM_174936.2 | TTCACCAGGAAGCCAGGAAG | 3-14-3 | 75 |
| 399880 | 17 | 705 | NM_174936.2 | CCTCGATGTAGTCGACATGG | 3-14-3 | 80 |
| 399881 | 18 | 785 | NM_174936.2 | GTATTCATCCGCCCGGTACC | 3-14-3 | 63 |
| 399882 | 19 | 835 | NM_174936.2 | CTGGTGTCTAGGAGATACAC | 3-14-3 | 66 |
| 399883 | 21 | 860 | NM_174936.2 | GATTTCCCGGTGGTCACTCT | 3-14-3 | 59 |
| 399884 | 24 | 890 | NM_174936.2 | CTCGAAGTCGGTGACCATGA | 3-14-3 | 71 |
| 399885 | 25 | 923 | NM_174936.2 | GTGGAAGCGGGTCCCGTCCT | 3-14-3 | 73 |
| 399886 | 26 | 970 | NM_174936.2 | ACCCCTGCCAGGTGGGTGCC | 3-14-3 | 76 |

| IsisNo | SEQ ID NO | 5' Target Site | Target Nucleic Acid | Sequence | Motif | % Inhibition |
|---|---|---|---|---|---|---|
| 399887 | 28 | 1004 | NM_174936.2 | ACCCTTGGCCACGCCGGCAT | 3-14-3 | 54 |
| 399888 | 29 | 1040 | NM_174936.2 | TTGGCAGTTGAGCACGCGCA | 3-14-3 | 75 |
| 399889 | 31 | 1077 | NM_174936.2 | CCAGGCCTATGAGGGTGCCG | 3-14-3 | 84 |
| 399890 | 32 | 1098 | NM_174936.2 | GCTGGCTTTTCCGAATAAAC | 3-14-3 | 73 |
| 399891 | 33 | 1210 | NM_174936.2 | GTGACCAGCACGACCCCAGC | 3-14-3 | 99 |
| 399892 | 149 | 1297 | NM_174936.2 | TGGGCATTGGTGGCCCCAAC | 3-14-3 | 61 |
| 399893 | 34 | 1326 | NM_174936.2 | CCAAAGTCCCCAGGGTCACC | 3-14-3 | 54 |
| 399894 | 128 | 1330 | NM_174936.2 | GTCCCCAAAGTCCCCAGGGT | 3-14-3 | 80 |
| 399895 | 36 | 1340 | NM_174936.2 | GCCAAAGTTGGTCCCCAAAG | 3-14-3 | 82 |
| 399896 | 38 | 1361 | NM_174936.2 | GGCAAAGAGGTCCACACAGC | 3-14-3 | 83 |
| 399897 | 39 | 1389 | NM_174936.2 | TGGAGGCACCAATGATGTCC | 3-14-3 | 70 |
| 399898 | 101 | 1465 | NM_174936.2 | ATGGCTGCAATGCCAGCCAC | 3-14-3 | 37 |
| 399899 | 45 | 1534 | NM_174936.2 | TTGGCAGAGAAGTGGATCAG | 3-14-3 | 64 |
| 399900 | 50 | 1569 | NM_174936.2 | GGTCCTCAGGGAACCAGGCC | 3-14-3 | 82 |
| 399901 | 87 | 1576 | NM_174936.2 | ACCCGCTGGTCCTCAGGGAA | 3-14-3 | 76 |
| 399902 | 119 | 1605 | NM_174936.2 | GCAGGGCGGCCACCAGGTTG | 3-14-3 | 39 |
| 399903 | 52 | 1640 | NM_174936.2 | AAACAGCTGCCAACCTGCCC | 3-14-3 | 73 |
| 399904 | 54 | 1675 | NM_174936.2 | GTAGGCCCCGAGTGTGCTGA | 3-14-3 | 81 |
| 399905 | 57 | 1812 | NM_174936.2 | CGTTGTGGGCCCGGCAGACC | 3-14-3 | 80 |
| 399906 | 58 | 1858 | NM_174936.2 | AGCAGGCAGCACCTGGCAAT | 3-14-3 | 92 |
| 399907 | 59 | 1920 | NM_174936.2 | CACGGGTCCCCATGCTGGCC | 3-14-3 | 95 |
| 399908 | 60 | 2100 | NM_174936.2 | CTTTGCATTCCAGACCTGGG | 3-14-3 | 84 |
| 399909 | 62 | 2310 | NM_174936.2 | GGCAGCAGATGGCAACGGCT | 3-14-3 | 73 |
| 399910 | 154 | 2410 | NM_174936.2 | TTTTAAAGCTCAGCCCCAGC | 3-14-3 | 57 |
| 399911 | 64 | 2504 | NM_174936.2 | TCAAGGGCCAGGCCAGCAGC | 3-14-3 | 82 |
| 399912 | 66 | 2597 | NM_174936.2 | ATGCCCCACAGTGAGGGAGG | 3-14-3 | 68 |
| 399913 | 67 | 2606 | NM_174936.2 | AATGGTGAAATGCCCCACAG | 3-14-3 | 92 |
| 399914 | 153 | 2649 | NM_174936.2 | TTGGGAGCAGCTGGCAGCAC | 3-14-3 | 59 |
| 399915 | 68 | 2750 | NM_174936.2 | CATGGGAAGAATCCTGCCTC | 3-14-3 | 78 |
| 399916 | 69 | 2832 | NM_174936.2 | GGAGATGAGGGCCATCAGCA | 3-14-3 | 71 |
| 399917 | 70 | 2900 | NM_174936.2 | TAGATGCCATCCAGAAAGCT | 3-14-3 | 81 |
| 399918 | 72 | 2983 | NM_174936.2 | GGCATAGAGCAGAGTAAAGG | 3-14-3 | 82 |
| 399919 | 112 | 3227 | NM_174936.2 | GAAGAGGCTTGGCTTCAGAG | 3-14-3 | 57 |
| 399920 | 75 | 3437 | NM_174936.2 | GCTCAAGGAGGGACAGTTGT | 3-14-3 | 84 |
| 399921 | 76 | 3472 | NM_174936.2 | AAAGATAAATGTCTGCTTGC | 3-14-3 | 78 |
| 399922 | 78 | 3543 | NM_174936.2 | TCTTCAAGTTACAAAAGCAA | 3-14-3 | 61 |
| 399923 | 85 | 13681 | NT_032977.8 | ACAAATTCCCAGACTCAGCA | 3-14-3 | 82 |
| 399924 | 129 | 13816 | NT_032977.8 | GTGCCATCTGAACAGCACCT | 3-14-3 | 84 |
| 399925 | 110 | 13926 | NT_032977.8 | CCTGGAACCCCTGCAGCCAG | 3-14-3 | 73 |
| 399926 | 152 | 13977 | NT_032977.8 | TTCAGGCAGGTTGCTGCTAG | 3-14-3 | 47 |
| 399927 | 140 | 13998 | NT_032977.8 | TCAGCCAGGCCAAAGGAAGA | 3-14-3 | 78 |
| 399928 | 136 | 14122 | NT_032977.8 | TAGGAGAAAGTAGGGAGAGC | 3-14-3 | 47 |
| 399929 | 132 | 14179 | NT_032977.8 | TAAAAGCTGCAAGAGACTCA | 3-14-3 | 69 |
| 399930 | 139 | 14267 | NT_032977.8 | TCAGAGAAAACAGTCACCGA | 3-14-3 | 82 |
| 399931 | 142 | 14404 | NT_032977.8 | TCATTTTAGAGACAGGAAGC | 3-14-3 | 79 |
| 399932 | 113 | 14441 | NT_032977.8 | GAATAACAGTGATGTCTGGC | 3-14-3 | 83 |
| 399933 | 138 | 14494 | NT_032977.8 | TCACAGCTCACCGAGTCTGC | 3-14-3 | 78 |
| 399934 | 98 | 14524 | NT_032977.8 | AGTGTAAAATAAAGCCCCTA | 3-14-3 | 79 |

| IsisNo | SEQ ID NO | 5' Target Site | Target Nucleic Acid | Sequence | Motif | % Inhibition |
|---|---|---|---|---|---|---|
| 399935 | 96 | 14601 | NT_032977.8 | AGGACCCAAGTCATCCTGCT | 3-14-3 | 89 |
| 399936 | 124 | 14631 | NT_032977.8 | GGCCATCAGCTGGCAATGCT | 3-14-3 | 70 |
| 399937 | 133 | 14675 | NT_032977.8 | TAGACAAGGAAAGGGAGGCC | 3-14-3 | 78 |
| 399938 | 103 | 14681 | NT_032977.8 | ATTTCATAGACAAGGAAAGG | 3-14-3 | 67 |
| 399940 | 146 | 1315 | AK124635.1 | TGACATTTGTGGGAGAGGAG | 3-14-3 | 35 |
| 399942 | 104 | 2085 | AK124635.1 | CACAGTCCTGCAAAACAGCT | 3-14-3 | 75 |
| 399943 | 102 | 5590 | NT_032977.8 | ATGTGCAGAGATCAATCACA | 3-14-3 | 64 |
| 399944 | 127 | 10633 | NT_032977.8 | GGTGGTAATTTGTCACAGCA | 3-14-3 | 73 |
| 399945 | 84 | 11308 | NT_032977.8 | AAGGTCACACAGTTAAGAGT | 3-14-3 | 89 |
| 399947 | 126 | 22292 | NT_032977.8 | GGTGCATAAGGAGAAAGAGA | 3-14-3 | 70 |
| 399948 | 147 | 24858 | NT_032977.8 | TGAGTTCATTTAAGAGTGGA | 3-14-3 | 46 |
| 399949 | 8 | 417 | NM_174936.2 | CCTCGGAACGCAAGGCTAGC | 3-14-3 | 74 |
| 399950 | 12 | 606 | NM_174936.2 | GGATCTTGGTGAGGTATCCC | 3-14-3 | 68 |
| 399951 | 13 | 615 | NM_174936.2 | AGACATGCAGGATCTTGGTG | 3-14-3 | 67 |
| 399952 | 16 | 651 | NM_174936.2 | TCATCTTCACCAGGAAGCCA | 3-14-3 | 74 |
| 399953 | 20 | 840 | NM_174936.2 | GTATGCTGGTGTCTAGGAGA | 3-14-3 | 59 |
| 399954 | 22 | 866 | NM_174936.2 | GCCCTCGATTTCCCGGTGGT | 3-14-3 | 83 |
| 399955 | 23 | 880 | NM_174936.2 | GTGACCATGACCCTGCCCTC | 3-14-3 | 62 |
| 399956 | 27 | 975 | NM_174936.2 | TGACCACCCCTGCCAGGTGG | 3-14-3 | 78 |
| 399957 | 30 | 1045 | NM_174936.2 | TTCCCTTGGCAGTTGAGCAC | 3-14-3 | 82 |
| 399958 | 35 | 1335 | NM_174936.2 | AGTTGGTCCCCAAAGTCCCC | 3-14-3 | 78 |
| 399959 | 37 | 1352 | NM_174936.2 | GTCCACACAGCGGCCAAAGT | 3-14-3 | 89 |
| 399960 | 40 | 1400 | NM_174936.2 | GCTGCAGTCGCTGGAGGCAC | 3-14-3 | 64 |
| 399961 | 41 | 1411 | NM_174936.2 | ACAAAGCAGGTGCTGCAGTC | 3-14-3 | 63 |
| 399962 | 42 | 1470 | NM_174936.2 | GCATCATGGCTGCAATGCCA | 3-14-3 | 68 |
| 399963 | 43 | 1478 | NM_174936.2 | GGCAGACAGCATCATGGCTG | 3-14-3 | 70 |
| 399964 | 44 | 1526 | NM_174936.2 | GAAGTGGATCAGTCTCTGCC | 3-14-3 | 70 |
| 399965 | 46 | 1539 | NM_174936.2 | CATCTTTGGCAGAGAAGTGG | 3-14-3 | 49 |
| 399966 | 47 | 1545 | NM_174936.2 | TGATGACATCTTTGGCAGAG | 3-14-3 | 78 |
| 399967 | 48 | 1552 | NM_174936.2 | GCCTCATTGATGACATCTTT | 3-14-3 | 82 |
| 399968 | 49 | 1564 | NM_174936.2 | TCAGGGAACCAGGCCTCATT | 3-14-3 | 71 |
| 399969 | 51 | 1583 | NM_174936.2 | GGTCAGTACCCGCTGGTCCT | 3-14-3 | 82 |
| 399970 | 53 | 1645 | NM_174936.2 | CTGCAAAACAGCTGCCAACC | 3-14-3 | 74 |
| 399971 | 55 | 1740 | NM_174936.2 | AGAAACTGGAGCAGCTCAGC | 3-14-3 | 48 |
| 399972 | 56 | 1746 | NM_174936.2 | TCCTGGAGAAACTGGAGCAG | 3-14-3 | 63 |
| 399973 | 61 | 2105 | NM_174936.2 | CTTGACTTTGCATTCCAGAC | 3-14-3 | 74 |
| 399974 | 63 | 2415 | NM_174936.2 | AACCATTTTAAAGCTCAGCC | 3-14-3 | 71 |
| 399975 | 65 | 2509 | NM_174936.2 | CCCACTCAAGGGCCAGGCCA | 3-14-3 | 91 |
| 399976 | 122 | 2582 | NM_174936.2 | GGAGGGAGCTTCCTGGCACC | 3-14-3 | 67 |
| 399977 | 71 | 2906 | NM_174936.2 | TCTGGCTAGATGCCATCCAG | 3-14-3 | 89 |
| 399978 | 73 | 2988 | NM_174936.2 | AGCCTGGCATAGAGCAGAGT | 3-14-3 | 80 |
| 399979 | 135 | 2994 | NM_174936.2 | TAGCACAGCCTGGCATAGAG | 3-14-3 | 83 |
| 399980 | 74 | 3233 | NM_174936.2 | AAGTAAGAAGAGGCTTGGCT | 3-14-3 | 50 |
| 399981 | 77 | 3477 | NM_174936.2 | ACCCAAAAGATAAATGTCTG | 3-14-3 | 55 |
| 399982 | 99 | 3550 | NM_174936.2 | ATAAATATCTTCAAGTTACA | 3-14-3 | 36 |
| 399983 | 100 | 13746 | NT_032977.8 | ATCTCAGGACAGGTGAGCAA | 3-14-3 | 96 |
| 399984 | 116 | 13760 | NT_032977.8 | GAGTAGAGATTCTCATCTCA | 3-14-3 | 71 |
| 399985 | 117 | 13828 | NT_032977.8 | GAGTCTTCTGAAGTGCCATC | 3-14-3 | 76 |

| IsisNo | SEQ ID NO | 5' Target Site | Target Nucleic Acid | Sequence | Motif | % Inhibition |
|---|---|---|---|---|---|---|
| 399986 | 81 | 13903 | NT_032977.8 | AAGCAGGGCCTCAGGTGGAA | 3-14-3 | 68 |
| 399987 | 83 | 13986 | NT_032977.8 | AAGGAAGACTTCAGGCAGGT | 3-14-3 | 59 |
| 399988 | 137 | 14112 | NT_032977.8 | TAGGGAGAGCTCACAGATGC | 3-14-3 | 31 |
| 399989 | 92 | 14397 | NT_032977.8 | AGAGACAGGAAGCTGCAGCT | 3-14-3 | 65 |
| 399990 | 82 | 14670 | NT_032977.8 | AAGGAAAGGGAGGCCTAGAG | 3-14-3 | 59 |
| 399992 | 130 | 2095 | AK124635.1 | GTGCTGACCACACAGTCCTG | 3-14-3 | 94 |
| 399993 | 107 | 3056 | NT_032977.8 | CCCACTATAATGGCAAGCCC | 3-14-3 | 76 |
| 399994 | 80 | 4306 | NT_032977.8 | AACCCAGTTCTAATGCACCT | 3-14-3 | 82 |
| 399995 | 106 | 5140 | NT_032977.8 | CCAGTCAGAGTAGAACAGAG | 3-14-3 | 74 |
| 399996 | 121 | 5599 | NT_032977.8 | GGAGCCTACATGTGCAGAGA | 3-14-3 | 65 |
| 399997 | 94 | 5667 | NT_032977.8 | AGCATGGCACCAGCATCTGC | 3-14-3 | 77 |
| 399998 | 108 | 6652 | NT_032977.8 | CCCAGCCCTATCAGGAAGTG | 3-14-3 | 78 |
| 399999 | 144 | 7099 | NT_032977.8 | TGACATCCAGGAGGGAGGAG | 3-14-3 | 43 |
| 400000 | 91 | 7556 | NT_032977.8 | AGACTGATGGAAGGCATTGA | 3-14-3 | 84 |
| 400001 | 131 | 7565 | NT_032977.8 | GTGTTGAGCAGACTGATGGA | 3-14-3 | 73 |
| 400002 | 145 | 8836 | NT_032977.8 | TGACATCTTGTCTGGGAGCC | 3-14-3 | 82 |
| 400003 | 90 | 8948 | NT_032977.8 | AGACTAGGAGCCTGAGTTTT | 3-14-3 | 48 |
| 400004 | 125 | 9099 | NT_032977.8 | GGCCTGCAGAAGCCAGAGAG | 3-14-3 | 45 |
| 400005 | 148 | 10252 | NT_032977.8 | TGGCAGCAACTCAGACATAT | 3-14-3 | 73 |
| 400006 | 79 | 11472 | NT_032977.8 | AAATGCAGGGCTAAAATCAC | 3-14-3 | 78 |
| 400007 | 88 | 12715 | NT_032977.8 | ACTGGATACATTGGCAGACA | 3-14-3 | 77 |
| 400008 | 111 | 12928 | NT_032977.8 | CTAGAGGAACCACTAGATAT | 3-14-3 | 78 |
| 400009 | 86 | 15471 | NT_032977.8 | ACAGCATTCTTGGTTAGGAG | 3-14-3 | 73 |
| 400010 | 97 | 16134 | NT_032977.8 | AGTCAAGCTGCTGCCCAGAG | 3-14-3 | 74 |
| 400011 | 120 | 16668 | NT_032977.8 | GCTAGTTATTAAGCACCTGC | 3-14-3 | 75 |
| 400012 | 150 | 17267 | NT_032977.8 | TGTGAGCTCTGGCCCAGTGG | 3-14-3 | 64 |
| 400013 | 115 | 18377 | NT_032977.8 | GAGTAAGGCAGGTTACTCTC | 3-14-3 | 88 |
| 400014 | 134 | 18408 | NT_032977.8 | TAGATGTGACTAACATTTAA | 3-14-3 | 58 |
| 400015 | 105 | 19203 | NT_032977.8 | CACATTAGCCTTGCTCAAGT | 3-14-3 | 89 |
| 400018 | 109 | 20188 | NT_032977.8 | CCCCTGCACAGAGCCTGGCA | 3-14-3 | 62 |
| 400019 | 141 | 20624 | NT_032977.8 | TCATGGCTGCAATGCCTGGT | 3-14-3 | 47 |
| 400020 | 93 | 20995 | NT_032977.8 | AGAGAGGAGGGCTTAAAGAA | 3-14-3 | 66 |
| 400021 | 95 | 21082 | NT_032977.8 | AGCTGCCAACCTGCAAAAAG | 3-14-3 | 61 |
| 400022 | 143 | 21481 | NT_032977.8 | TGAAAATCCATCCAGCACTG | 3-14-3 | 90 |
| 400023 | 89 | 21589 | NT_032977.8 | AGAACCATGGAGCACCTGAG | 3-14-3 | 83 |
| 400024 | 123 | 21696 | NT_032977.8 | GGCACTGCCCTTCCACCAAA | 3-14-3 | 79 |
| 400025 | 118 | 24907 | NT_032977.8 | GCACCATCCAGACCAGAATC | 3-14-3 | 78 |
| 400026 | 114 | 25413 | NT_032977.8 | GAGAGGTTCAGATCCAGGCC | 3-14-3 | 81 |

Antisense oligonucleotides with the following ISIS Nos exhibited at least 80% inhibition of PCSK9 mRNA levels: 399806, 399814, 399817, 399819, 399821, 399827, 399836, 399837, 399854, 399867, 399889, 399891, 399906, 399907, 399908, 399913, 399920, 399924, 399935, 399945, 399959, 399975, 399977, 399983, 399992, 400000, 400013, 400015, 400022, and 400023. The target segments to which these antisense oligonucleotides are targeted are active

target segments. The target regions to which these antisense oligonucleotides are targeted are active target regions.

ISIS Nos 399814, 399819, 399836, 399891, 399906, 399907, 399913, 399935, 399945, 399959, 399975, 399977, 399983, 399992, 400013, 400015, and 400022 each exhibited at least 85% inhibition of PCSK9 mRNA levels.

ISIS Nos 399836, 399891, 399906, 399907, 399913, 399975, 399983, 399992, and 400022 each exhibited at least 90% inhibition of PCSK9 mRNA levels.

**Example 2: Antisense inhibition of human PCSK9 in HepG2 cells**

Antisense oligonucleotides were tested for their ability to inhibit the expression of PCSK9 mRNA in cultured HepG2 cells. HepG2 cells at a density of 10000 cells per well in a 96-well plate were treated with 1500 nM of antisense oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and PCSK9 mRNA levels were measured by quantitative real-time PCR, as described herein. PCSK9 mRNA levels were adjusted according to total RNA content as measured by RIBOGREEN®. Results are presented as percent inhibition of PCSK9, relative to untreated control cells.

Isis Nos. 399819, 395149, 395150, 395151, 395152, 395153, 395154, 395155, 395156, 395157, 395158, 395161, 395162, 395163, 395164, 395165, 395166, 395167, 395168, 395172, 395173, 395174, 395178, 395179, 395182, 395183, 395185, 395186, 395187, 395189, 395190, 395191, 395193, 395194, 395195, 395198, 395199, 395203, 395207, 395210, 395211, 395213, 395214, 395221, 395222, 399793, 399794, 399795, 399798, 399801, 399803, 399804, 399806, 399807, 399812, 399813, 399814, 399816, 399817, 399820, 399821, 399822, 399823, 399827, 399828, 399829, 399833, 399834, 399836, 399837, 399841, 399844, 399846, 399848, 399849, 399851, 399852, 399854, 399855, 399856, 399857, 399862, 399865, 399867, 399868, 399872, 399873, 399874, 399875, 399876, 399877, 399879, 399880, 399883, 399884, 399885, 399886, 399887, 399888, 399889, 399890, 399891, 399892, 399894, 399895, 399896, 399900, 399901, 399902, 399904, 399905, 399906, 399907, 399908, 399909, 399911, 399912, 399913, 399915, 399916, 399918, 399920, 399921, 399924, 399925, 399929, 399931, 399935, 399936, 399937, 399943, 399944, 399945, 399949, 399950, 399954, 399957, 399959, 399960, 399962, 399963, 399966, 399967, 399968, 399969, 399970, 399972, 399973, 399975, 399976, 399977, 399978, 399979, 399983, 399984, 399985, 399986, 399989, 399990, 399992, 399996, 399997, 399998, 400000, 400001, 400002, 400004, 400005, 400007, 400008, 400009, 400010, 400012, 400013, 400015, 400018, 400021, 400023, 400024, 400025, and 400026 each inhibited PCSK9 by at

least 70% in this experiment. The target segments to which these antisense oligonucleotides are targeted are active target segments. The target regions to which these antisense oligonucleotides are targeted are active target regions.

Isis Nos 399819, 395150, 395152, 395153, 395154, 395155, 395156, 395158, 395163, 395164, 395165, 395166, 395167, 395168, 395173, 395178, 395183, 395185, 395186, 395187, 395189, 395190, 395193, 395194, 395199, 395203, 395210, 395213, 395214, 399793, 399798, 399801, 399804, 399806, 399813, 399816, 399820, 399821, 399822, 399836, 399849, 399856, 399857, 399862, 399868, 399875, 399877, 399880, 399885, 399886, 399887, 399888, 399889, 399890, 399894, 399896, 399900, 399901, 399904, 399905, 399906, 399907, 399911, 399912, 399916, 399920, 399925, 399935, 399936, 399937, 399945, 399954, 399957, 399959, 399960, 399962, 399968, 399969, 399973, 399976, 399977, 399978, 399989, 399992, 400002, 400004, 400007, 400012, 400013, 400023, and 400024 each inhibited PCSK9 by at least 80% in this experiment.

Isis Nos 399819, 395152, 395153, 395155, 395156, 395158, 395163, 395164, 395165, 395166, 395168, 395178, 395183, 395185, 395187, 395189, 395190, 395194, 395199, 395203, 395214, 399793, 399804, 399813, 399821, 399822, 399836, 399856, 399868, 399877, 399887, 399888, 399890, 399900, 399904, 399905, 399907, 399911, 399912, 399916, 399925, 399936, 399954, 399960, 399962, 399969, 399976, 399977, 399978, 399989, 399992, 400012, 400013, 400023, and 400024 each inhibited PCSK9 by at least 85% in this experiment.

Isis Nos 399819, 395165, 395183, 395185, 399868, 399900, 399907, 399911, 399912, 399916, 399936, 399969, and 400024 each inhibited PCSK9 by at least 90% in this experiment.

**Example 3: Antisense inhibition of human PSCK9 (HepB3 cells)**

Antisense oligonucleotides targeted to a PCSK9 nucleic acid were tested for their effects on PCSK9 mRNA *in vitro*. Cultured HepB3 cells at a density of 4000 cells per well in a 96-well plate were treated with 75 nM of antisense oligonucleotide. After a treatment period of approximately 24 hours, RNA was isolated from the cells and PCSK9 mRNA levels were measured by quantitative real-time PCR, as described herein. PCSK9 mRNA levels were adjusted according to total RNA content as measured by RIBOGREEN®. Results are presented as percent inhibition of PCSK9, relative to untreated control cells. Antisense oligonucleotides that exhibited at least 30% inhibition of PCSK9 expression are shown in Tables 16, 17 and 18.

The motif column indicates the wing-gap-wing motif of each antisense oligonucleotide. Antisense oligonucleotides were designed as 5-10-5 gapmers, or alternatively as 3-14-3 gapmers,

or alternatively as 2-13-5 gapmers where the gap segment comprises 2'-deoxynucleotides and each wing segment comprises 2'-MOE nucleotides. As illustrated in Table 16, 17 and 18, a single nucleobase sequence may be represented by a 5-10-5 motif as well as a 3-14-3 motif as well as a 2-13-5 motif. "5' target site" indicates the 5'-most nucleotide which the antisense oligonucleotide is targeted on the indicated GENBANK Accession No.

**Table 16: Antisense inhibition of PCSK9 in human cells (HepB3) targeting SEQ ID NO: 1**

| Isis No. | 5' Target Site to SEQ ID NO: 1 | 3' Target Site to SEQ ID NO: 1 | Sequence 5'-3' | Motif | % inhibition | SEQ ID NO |
|---|---|---|---|---|---|---|
| 410742 | 294 | 313 | GCCTGGAGCTGACGGTGCCC | 5-10-5 | 75.1 | 159 |
| 405999 | 298 | 317 | GACCGCCTGGAGCTGACGGT | 5-10-5 | 70.3 | 160 |
| 395151 | 300 | 319 | AGGACCGCCTGGAGCTGACG | 5-10-5 | 57.3 | 6 |
| 405861 | 406 | 425 | AAGGCTAGCACCAGCTCCTC | 5-10-5 | 90.5 | 162 |
| 405862 | 407 | 426 | CAAGGCTAGCACCAGCTCCT | 5-10-5 | 92.3 | 163 |
| 405863 | 408 | 427 | GCAAGGCTAGCACCAGCTCC | 5-10-5 | 82.6 | 164 |
| 405864 | 409 | 428 | CGCAAGGCTAGCACCAGCTC | 5-10-5 | 91.8 | 165 |
| 395152 | 410 | 429 | ACGCAAGGCTAGCACCAGCT | 5-10-5 | 93.3 | 7 |
| 405865 | 411 | 430 | AACGCAAGGCTAGCACCAGC | 5-10-5 | 84.6 | 166 |
| 405866 | 412 | 431 | GAACGCAAGGCTAGCACCAG | 5-10-5 | 81.8 | 167 |
| 405867 | 413 | 432 | GGAACGCAAGGCTAGCACCA | 5-10-5 | 74.0 | 168 |
| 405868 | 414 | 433 | CGGAACGCAAGGCTAGCACC | 5-10-5 | 76.8 | 169 |
| 399793 | 417 | 436 | CCTCGGAACGCAAGGCTAGC | 5-10-5 | 77.9 | 8 |
| 410743 | 421 | 440 | TCCTCCTCGGAACGCAAGGC | 5-10-5 | 76.7 | 170 |
| 410744 | 446 | 465 | GTGCTCGGGTGCTTCGGCCA | 5-10-5 | 76.9 | 171 |
| 410745 | 466 | 485 | TGGAAGGTGGCTGTGGTTCC | 5-10-5 | 41.7 | 172 |
| 395153 | 480 | 499 | CCTTGGCGCAGCGGTGGAAG | 5-10-5 | 81.1 | 9 |
| 406000 | 482 | 501 | ATCCTTGGCGCAGCGGTGGA | 5-10-5 | 79.1 | 173 |
| 406001 | 484 | 503 | GGATCCTTGGCGCAGCGGTG | 5-10-5 | 63.1 | 174 |
| 406002 | 488 | 507 | CCACGGATCCTTGGCGCAGC | 5-10-5 | 80.8 | 175 |
| 410746 | 507 | 526 | CGTAGGTGCCAGGCAACCTC | 5-10-5 | 44.8 | 176 |
| 410747 | 545 | 564 | TGACTGCGAGAGGTGGGTCT | 5-10-5 | NA | 177 |
| 406003 | 555 | 574 | CAGTGCGCTCTGACTGCGAG | 5-10-5 | 84.2 | 178 |
| 406004 | 557 | 576 | GGCAGTGCGCTCTGACTGCG | 5-10-5 | 56.4 | 179 |
| 406005 | 559 | 578 | CGGGCAGTGCGCTCTGACTG | 5-10-5 | 83.4 | 180 |
| 406006 | 562 | 581 | CGGCGGGCAGTGCGCTCTGA | 5-10-5 | 71.0 | 181 |
| 410748 | 591 | 610 | ATCCCCGGCGGGCAGCCTGG | 5-10-5 | 56.0 | 182 |
| 406007 | 595 | 614 | AGGTATCCCCGGCGGGCAGC | 5-10-5 | 76.3 | 183 |
| 410574 | 597 | 616 | TGAGGTATCCCCGGCGGGCA | 3-14-3 | 69.1 | 184 |
| 410529 | 597 | 616 | TGAGGTATCCCCGGCGGGCA | 5-10-5 | 77.4 | 184 |
| 410647 | 597 | 616 | TGAGGTATCCCCGGCGGGCA | 2-13-5 | 90.7 | 184 |
| 410575 | 598 | 617 | GTGAGGTATCCCCGGCGGGC | 3-14-3 | 71.5 | 185 |
| 410648 | 598 | 617 | GTGAGGTATCCCCGGCGGGC | 2-13-5 | 82.8 | 185 |
| 410530 | 598 | 617 | GTGAGGTATCCCCGGCGGGC | 5-10-5 | 83.2 | 185 |
| 410649 | 599 | 618 | GGTGAGGTATCCCCGGCGGG | 2-13-5 | 53.5 | 186 |
| 410576 | 599 | 618 | GGTGAGGTATCCCCGGCGGG | 3-14-3 | 56.2 | 186 |
| 410531 | 599 | 618 | GGTGAGGTATCCCCGGCGGG | 5-10-5 | 63.6 | 186 |
| 410650 | 600 | 619 | TGGTGAGGTATCCCCGGCGG | 2-13-5 | 86.1 | 11 |
| 399877 | 600 | 619 | TGGTGAGGTATCCCCGGCGG | 3-14-3 | 92.6 | 11 |

| Isis No. | 5' Target Site to SEQ ID NO: 1 | 3' Target Site to SEQ ID NO: 1 | Sequence 5'-3' | Motif | % inhibition | SEQ ID NO |
|---|---|---|---|---|---|---|
| 395155 | 600 | 619 | TGGTGAGGTATCCCCGGCGG | 5-10-5 | 92.7 | 11 |
| 410577 | 601 | 620 | TTGGTGAGGTATCCCCGGCG | 3-14-3 | 62.4 | 187 |
| 410532 | 601 | 620 | TTGGTGAGGTATCCCCGGCG | 5-10-5 | 63.5 | 187 |
| 410651 | 601 | 620 | TTGGTGAGGTATCCCCGGCG | 2-13-5 | 75.5 | 187 |
| 410652 | 602 | 621 | CTTGGTGAGGTATCCCCGGC | 2-13-5 | 81.2 | 188 |
| 410578 | 602 | 621 | CTTGGTGAGGTATCCCCGGC | 3-14-3 | 83.3 | 188 |
| 406008 | 602 | 621 | CTTGGTGAGGTATCCCCGGC | 5-10-5 | 95.2 | 188 |
| 410653 | 603 | 622 | TCTTGGTGAGGTATCCCCGG | 2-13-5 | 68.9 | 189 |
| 410579 | 603 | 622 | TCTTGGTGAGGTATCCCCGG | 3-14-3 | 74.0 | 189 |
| 410533 | 603 | 622 | TCTTGGTGAGGTATCCCCGG | 5-10-5 | 79.0 | 189 |
| 410580 | 604 | 623 | ATCTTGGTGAGGTATCCCCG | 3-14-3 | 62.3 | 190 |
| 410654 | 604 | 623 | ATCTTGGTGAGGTATCCCCG | 2-13-5 | 65.2 | 190 |
| 406009 | 604 | 623 | ATCTTGGTGAGGTATCCCCG | 5-10-5 | 90.7 | 190 |
| 410534 | 605 | 624 | GATCTTGGTGAGGTATCCCC | 5-10-5 | 59.8 | 191 |
| 410581 | 605 | 624 | GATCTTGGTGAGGTATCCCC | 3-14-3 | 72.9 | 191 |
| 410655 | 605 | 624 | GATCTTGGTGAGGTATCCCC | 2-13-5 | 77.4 | 191 |
| 399794 | 606 | 625 | GGATCTTGGTGAGGTATCCC | 5-10-5 | 56.5 | 12 |
| 410656 | 606 | 625 | GGATCTTGGTGAGGTATCCC | 2-13-5 | 68.0 | 12 |
| 399950 | 606 | 625 | GGATCTTGGTGAGGTATCCC | 3-14-3 | 74.4 | 12 |
| 410535 | 607 | 626 | AGGATCTTGGTGAGGTATCC | 5-10-5 | 65.7 | 192 |
| 410582 | 607 | 626 | AGGATCTTGGTGAGGTATCC | 3-14-3 | 69.5 | 192 |
| 410657 | 607 | 626 | AGGATCTTGGTGAGGTATCC | 2-13-5 | 73.1 | 192 |
| 406010 | 609 | 628 | GCAGGATCTTGGTGAGGTAT | 5-10-5 | 56.9 | 193 |
| 406011 | 611 | 630 | ATGCAGGATCTTGGTGAGGT | 5-10-5 | 70.7 | 194 |
| 406012 | 613 | 632 | ACATGCAGGATCTTGGTGAG | 5-10-5 | 69.1 | 195 |
| 406013 | 617 | 636 | GAAGACATGCAGGATCTTGG | 5-10-5 | 77.4 | 196 |
| 395156 | 620 | 639 | ATGGAAGACATGCAGGATCT | 5-10-5 | 76.7 | 14 |
| 410749 | 628 | 647 | AGAAGGCCATGGAAGACATG | 5-10-5 | 59.4 | 197 |
| 410750 | 638 | 657 | GAAGCCAGGAAGAAGGCCAT | 5-10-5 | 57.5 | 198 |
| 399879 | 646 | 665 | TTCACCAGGAAGCCAGGAAG | 3-14-3 | 91.9 | 15 |
| 406014 | 648 | 667 | TCTTCACCAGGAAGCCAGGA | 5-10-5 | 94.0 | 199 |
| 406015 | 653 | 672 | ACTCATCTTCACCAGGAAGC | 5-10-5 | 78.8 | 200 |
| 406016 | 655 | 674 | CCACTCATCTTCACCAGGAA | 5-10-5 | 87.2 | 201 |
| 410730 | 657 | 676 | CGCCACTCATCTTCACCAGG | 5-10-5 | 85.4 | 202 |
| 406017 | 659 | 678 | GTCGCCACTCATCTTCACCA | 5-10-5 | 76.3 | 203 |
| 406018 | 661 | 680 | AGGTCGCCACTCATCTTCAC | 5-10-5 | 63.2 | 204 |
| 406019 | 663 | 682 | GCAGGTCGCCACTCATCTTC | 5-10-5 | 68.1 | 205 |
| 406020 | 665 | 684 | CAGCAGGTCGCCACTCATCT | 5-10-5 | 83.7 | 206 |
| 410731 | 667 | 686 | TCCAGCAGGTCGCCACTCAT | 5-10-5 | 72.9 | 207 |
| 410751 | 685 | 704 | GGCAACTTCAAGGCCAGCTC | 5-10-5 | 84.6 | 208 |
| 395158 | 705 | 724 | CCTCGATGTAGTCGACATGG | 5-10-5 | 93.9 | 17 |
| 410752 | 724 | 743 | GCAAAGACAGAGGAGTCCTC | 5-10-5 | 76.3 | 209 |
| 406021 | 782 | 801 | TTCATCCGCCCGGTACCGTG | 5-10-5 | 79.6 | 210 |
| 406022 | 784 | 803 | TATTCATCCGCCCGGTACCG | 5-10-5 | 78.7 | 211 |
| 406023 | 787 | 806 | TGGTATTCATCCGCCCGGTA | 5-10-5 | 92.5 | 212 |
| 406024 | 789 | 808 | GCTGGTATTCATCCGCCCGG | 5-10-5 | 69.7 | 213 |
| 410732 | 791 | 810 | GGGCTGGTATTCATCCGCCC | 5-10-5 | 30.4 | 214 |
| 410753 | 821 | 840 | ATACACCTCCACCAGGCTGC | 5-10-5 | 72.8 | 215 |
| 406025 | 832 | 851 | GTGTCTAGGAGATACACCTC | 5-10-5 | 74.2 | 216 |
| 406026 | 837 | 856 | TGCTGGTGTCTAGGAGATAC | 5-10-5 | 80.5 | 217 |
| 405869 | 862 | 881 | TCGATTTCCCGGTGGTCACT | 5-10-5 | 87.6 | 218 |
| 405870 | 863 | 882 | CTCGATTTCCCGGTGGTCAC | 5-10-5 | 83.3 | 219 |
| 405871 | 864 | 883 | CCTCGATTTCCCGGTGGTCA | 5-10-5 | 87.0 | 220 |

| Isis No. | 5' Target Site to SEQ ID NO: 1 | 3' Target Site to SEQ ID NO: 1 | Sequence 5'-3' | Motif | % inhibition | SEQ ID NO |
|---|---|---|---|---|---|---|
| 405872 | 865 | 884 | CCCTCGATTTCCCGGTGGTC | 5-10-5 | 88.2 | 221 |
| 399798 | 866 | 885 | GCCCTCGATTTCCCGGTGGT | 5-10-5 | 84.3 | 22 |
| 399954 | 866 | 885 | GCCCTCGATTTCCCGGTGGT | 3-14-3 | 90.3 | 22 |
| 405873 | 867 | 886 | TGCCCTCGATTTCCCGGTGG | 5-10-5 | 90.0 | 222 |
| 405874 | 868 | 887 | CTGCCCTCGATTTCCCGGTG | 5-10-5 | 91.4 | 223 |
| 405875 | 869 | 888 | CCTGCCCTCGATTTCCCGGT | 5-10-5 | 93.5 | 224 |
| 405876 | 870 | 889 | CCCTGCCCTCGATTTCCCGG | 5-10-5 | 90.1 | 225 |
| 406027 | 874 | 893 | ATGACCCTGCCCTCGATTTC | 5-10-5 | 73.9 | 226 |
| 406028 | 876 | 895 | CCATGACCCTGCCCTCGATT | 5-10-5 | 92.3 | 227 |
| 406029 | 878 | 897 | GACCATGACCCTGCCCTCGA | 5-10-5 | 91.4 | 228 |
| 406030 | 882 | 901 | CGGTGACCATGACCCTGCCC | 5-10-5 | 95.6 | 229 |
| 406031 | 884 | 903 | GTCGGTGACCATGACCCTGC | 5-10-5 | 89.6 | 230 |
| 410733 | 886 | 905 | AAGTCGGTGACCATGACCCT | 5-10-5 | 65.7 | 231 |
| 406032 | 888 | 907 | CGAAGTCGGTGACCATGACC | 5-10-5 | 88.5 | 232 |
| 410754 | 898 | 917 | GGCACATTCTCGAAGTCGGT | 5-10-5 | 80.1 | 233 |
| 395163 | 923 | 942 | GTGGAAGCGGGTCCCGTCCT | 5-10-5 | 83.9 | 25 |
| 410755 | 933 | 952 | TGGCCTGTCTGTGGAAGCGG | 5-10-5 | NA | 234 |
| 410756 | 960 | 979 | GGTGGGTGCCATGACTGTCA | 5-10-5 | 67.1 | 235 |
| 406033 | 967 | 986 | CCTGCCAGGTGGGTGCCATG | 5-10-5 | 91.2 | 237 |
| 406034 | 972 | 991 | CCACCCCTGCCAGGTGGGTG | 5-10-5 | 59.3 | 238 |
| 406035 | 977 | 996 | GCTGACCACCCCTGCCAGGT | 5-10-5 | 91.7 | 239 |
| 410757 | 985 | 1004 | TCCCGGCCGCTGACCACCCC | 5-10-5 | 88.9 | 240 |
| 406036 | 989 | 1008 | GGCATCCCGGCCGCTGACCA | 5-10-5 | 84.0 | 241 |
| 406037 | 992 | 1011 | GCCGGCATCCCGGCCGCTGA | 5-10-5 | 55.9 | 242 |
| 410536 | 997 | 1016 | GCCACGCCGGCATCCCGGCC | 5-10-5 | 63.7 | 243 |
| 410658 | 997 | 1016 | GCCACGCCGGCATCCCGGCC | 2-13-5 | 82.0 | 243 |
| 410583 | 997 | 1016 | GCCACGCCGGCATCCCGGCC | 3-14-3 | 87.3 | 243 |
| 410537 | 998 | 1017 | GGCCACGCCGGCATCCCGGC | 5-10-5 | 58.5 | 244 |
| 410659 | 998 | 1017 | GGCCACGCCGGCATCCCGGC | 2-13-5 | 73.7 | 244 |
| 410584 | 998 | 1017 | GGCCACGCCGGCATCCCGGC | 3-14-3 | 79.5 | 244 |
| 410660 | 999 | 1018 | TGGCCACGCCGGCATCCCGG | 2-13-5 | 63.0 | 245 |
| 410585 | 999 | 1018 | TGGCCACGCCGGCATCCCGG | 3-14-3 | 73.2 | 245 |
| 406038 | 999 | 1018 | TGGCCACGCCGGCATCCCGG | 5-10-5 | 86.3 | 245 |
| 410661 | 1000 | 1019 | TTGGCCACGCCGGCATCCCG | 2-13-5 | 53.3 | 246 |
| 410586 | 1000 | 1019 | TTGGCCACGCCGGCATCCCG | 3-14-3 | 60.3 | 246 |
| 405877 | 1000 | 1019 | TTGGCCACGCCGGCATCCCG | 5-10-5 | 83.2 | 246 |
| 410587 | 1001 | 1020 | CTTGGCCACGCCGGCATCCC | 3-14-3 | 63.2 | 247 |
| 410662 | 1001 | 1020 | CTTGGCCACGCCGGCATCCC | 2-13-5 | 67.3 | 247 |
| 405878 | 1001 | 1020 | CTTGGCCACGCCGGCATCCC | 5-10-5 | 91.4 | 247 |
| 410588 | 1002 | 1021 | CCTTGGCCACGCCGGCATCC | 3-14-3 | 65.3 | 248 |
| 410663 | 1002 | 1021 | CCTTGGCCACGCCGGCATCC | 2-13-5 | 67.9 | 248 |
| 405879 | 1002 | 1021 | CCTTGGCCACGCCGGCATCC | 5-10-5 | 94.1 | 248 |
| 410589 | 1003 | 1022 | CCCTTGGCCACGCCGGCATC | 3-14-3 | 80.1 | 249 |
| 410664 | 1003 | 1022 | CCCTTGGCCACGCCGGCATC | 2-13-5 | 81.9 | 249 |
| 405880 | 1003 | 1022 | CCCTTGGCCACGCCGGCATC | 5-10-5 | 93.5 | 249 |
| 410665 | 1004 | 1023 | ACCCTTGGCCACGCCGGCAT | 2-13-5 | 78.7 | 28 |
| 399887 | 1004 | 1023 | ACCCTTGGCCACGCCGGCAT | 3-14-3 | 91.9 | 28 |
| 395165 | 1004 | 1023 | ACCCTTGGCCACGCCGGCAT | 5-10-5 | 96.7 | 28 |
| 410590 | 1005 | 1024 | CACCCTTGGCCACGCCGGCA | 3-14-3 | 82.2 | 250 |
| 410666 | 1005 | 1024 | CACCCTTGGCCACGCCGGCA | 2-13-5 | 82.7 | 250 |
| 405881 | 1005 | 1024 | CACCCTTGGCCACGCCGGCA | 5-10-5 | 98.3 | 250 |
| 410667 | 1006 | 1025 | GCACCCTTGGCCACGCCGGC | 2-13-5 | 84.7 | 251 |
| 410591 | 1006 | 1025 | GCACCCTTGGCCACGCCGGC | 3-14-3 | 86.3 | 251 |

| Isis No. | 5' Target Site to SEQ ID NO: 1 | 3' Target Site to SEQ ID NO: 1 | Sequence 5'-3' | Motif | % inhibition | SEQ ID NO |
|---|---|---|---|---|---|---|
| 405882 | 1006 | 1025 | GCACCCTTGGCCACGCCGGC | 5-10-5 | 91.6 | 251 |
| 410668 | 1007 | 1026 | GGCACCCTTGGCCACGCCGG | 2-13-5 | 91.4 | 252 |
| 405883 | 1007 | 1026 | GGCACCCTTGGCCACGCCGG | 5-10-5 | 92.5 | 252 |
| 410592 | 1007 | 1026 | GGCACCCTTGGCCACGCCGG | 3-14-3 | 93.4 | 252 |
| 410669 | 1008 | 1027 | TGGCACCCTTGGCCACGCCG | 2-13-5 | 69.0 | 253 |
| 410593 | 1008 | 1027 | TGGCACCCTTGGCCACGCCG | 3-14-3 | 88.8 | 253 |
| 405884 | 1008 | 1027 | TGGCACCCTTGGCCACGCCG | 5-10-5 | 90.8 | 253 |
| 410670 | 1009 | 1028 | CTGGCACCCTTGGCCACGCC | 2-13-5 | 74.9 | 254 |
| 410594 | 1009 | 1028 | CTGGCACCCTTGGCCACGCC | 3-14-3 | 75.2 | 254 |
| 410538 | 1009 | 1028 | CTGGCACCCTTGGCCACGCC | 5-10-5 | 78.2 | 254 |
| 410539 | 1010 | 1029 | GCTGGCACCCTTGGCCACGC | 5-10-5 | 61.9 | 255 |
| 410595 | 1010 | 1029 | GCTGGCACCCTTGGCCACGC | 3-14-3 | 83.1 | 255 |
| 410671 | 1010 | 1029 | GCTGGCACCCTTGGCCACGC | 2-13-5 | 83.3 | 255 |
| 410758 | 1015 | 1034 | CGCATGCTGGCACCCTTGGC | 5-10-5 | 73.6 | 256 |
| 406039 | 1036 | 1055 | CAGTTGAGCACGCGCAGGCT | 5-10-5 | 91.2 | 257 |
| 406040 | 1038 | 1057 | GGCAGTTGAGCACGCGCAGG | 5-10-5 | 96.5 | 258 |
| 399888 | 1040 | 1059 | TTGGCAGTTGAGCACGCGCA | 3-14-3 | 90.9 | 29 |
| 395166 | 1040 | 1059 | TTGGCAGTTGAGCACGCGCA | 5-10-5 | 96.2 | 29 |
| 406041 | 1042 | 1061 | CCTTGGCAGTTGAGCACGCG | 5-10-5 | 96.6 | 259 |
| 399801 | 1045 | 1064 | TTCCCTTGGCAGTTGAGCAC | 5-10-5 | 95.6 | 30 |
| 406042 | 1047 | 1066 | CCTTCCCTTGGCAGTTGAGC | 5-10-5 | 92.0 | 260 |
| 406043 | 1051 | 1070 | GTGCCCTTCCCTTGGCAGTT | 5-10-5 | 91.9 | 261 |
| 406044 | 1053 | 1072 | CCGTGCCCTTCCCTTGGCAG | 5-10-5 | 95.4 | 262 |
| 410759 | 1064 | 1083 | GGTGCCGCTAACCGTGCCCT | 5-10-5 | 83.7 | 263 |
| 410760 | 1088 | 1107 | CCGAATAAACTCCAGGCCTA | 5-10-5 | 96.7 | 265 |
| 406045 | 1096 | 1115 | TGGCTTTTCCGAATAAACTC | 5-10-5 | 88.4 | 266 |
| 395168 | 1098 | 1117 | GCTGGCTTTTCCGAATAAAC | 5-10-5 | 91.9 | 32 |
| 405909 | 1100 | 1119 | CAGCTGGCTTTTCCGAATAA | 5-10-5 | 80.3 | 267 |
| 405910 | 1102 | 1121 | ACCAGCTGGCTTTTCCGAAT | 5-10-5 | 90.9 | 268 |
| 405911 | 1104 | 1123 | GGACCAGCTGGCTTTTCCGA | 5-10-5 | 88.0 | 269 |
| 405912 | 1108 | 1127 | GGCTGGACCAGCTGGCTTTT | 5-10-5 | 78.2 | 270 |
| 410761 | 1119 | 1138 | GTGGCCCCACAGGCTGGACC | 5-10-5 | 53.7 | 271 |
| 410762 | 1132 | 1151 | AGCAGCACCACCAGTGGCCC | 5-10-5 | 57.6 | 272 |
| 410763 | 1154 | 1173 | GCTGTACCCACCCGCCAGGG | 5-10-5 | 68.8 | 273 |
| 410764 | 1200 | 1219 | CGACCCCAGCCCTCGCCAGG | 5-10-5 | 66.3 | 274 |
| 399891 | 1210 | 1229 | GTGACCAGCACGACCCCAGC | 3-14-3 | 91.1 | 33 |
| 405913 | 1212 | 1231 | CGGTGACCAGCACGACCCCA | 5-10-5 | 93.8 | 275 |
| 405914 | 1214 | 1233 | AGCGGTGACCAGCACGACCC | 5-10-5 | 90.4 | 276 |
| 405915 | 1216 | 1235 | GCAGCGGTGACCAGCACGAC | 5-10-5 | 86.8 | 277 |
| 405916 | 1218 | 1237 | CGGCAGCGGTGACCAGCACG | 5-10-5 | 91.3 | 278 |
| 410734 | 1219 | 1238 | CCGGCAGCGGTGACCAGCAC | 5-10-5 | 65.8 | 279 |
| 405917 | 1222 | 1241 | TTGCCGGCAGCGGTGACCAG | 5-10-5 | 62.0 | 280 |
| 405918 | 1224 | 1243 | AGTTGCCGGCAGCGGTGACC | 5-10-5 | 33.5 | 281 |
| 405919 | 1226 | 1245 | GAAGTTGCCGGCAGCGGTGA | 5-10-5 | 68.2 | 282 |
| 405920 | 1228 | 1247 | CGGAAGTTGCCGGCAGCGGT | 5-10-5 | 86.2 | 283 |
| 405921 | 1230 | 1249 | CCCGGAAGTTGCCGGCAGCG | 5-10-5 | 85.5 | 284 |
| 405922 | 1232 | 1251 | GTCCCGGAAGTTGCCGGCAG | 5-10-5 | 86.0 | 285 |
| 410765 | 1273 | 1292 | ATGACCTCGGGAGCTGAGGC | 5-10-5 | 50.4 | 286 |
| 410766 | 1283 | 1302 | CCCAACTGTGATGACCTCGG | 5-10-5 | 70.6 | 287 |
| 405923 | 1295 | 1314 | GGCATTGGTGGCCCCAACTG | 5-10-5 | 94.3 | 288 |
| 410767 | 1305 | 1324 | GCTGGTCTTGGGCATTGGTG | 5-10-5 | 65.1 | 289 |
| 405924 | 1318 | 1337 | CCCAGGGTCACCGGCTGGTC | 5-10-5 | 93.1 | 290 |
| 410735 | 1320 | 1339 | TCCCCAGGGTCACCGGCTGG | 5-10-5 | 78.1 | 291 |

| Isis No. | 5' Target Site to SEQ ID NO: 1 | 3' Target Site to SEQ ID NO: 1 | Sequence 5'-3' | Motif | % inhibition | SEQ ID NO |
|---|---|---|---|---|---|---|
| 405925 | 1322 | 1341 | AGTCCCCAGGGTCACCGGCT | 5-10-5 | 93.5 | 292 |
| 405926 | 1324 | 1343 | AAAGTCCCCAGGGTCACCGG | 5-10-5 | 94.6 | 293 |
| 405927 | 1328 | 1347 | CCCCAAAGTCCCCAGGGTCA | 5-10-5 | 94.5 | 294 |
| 405928 | 1333 | 1352 | TTGGTCCCCAAAGTCCCCAG | 5-10-5 | 90.0 | 295 |
| 405929 | 1337 | 1356 | AAAGTTGGTCCCCAAAGTCC | 5-10-5 | 85.5 | 296 |
| 399895 | 1340 | 1359 | GCCAAAGTTGGTCCCCAAAG | 3-14-3 | 84.6 | 36 |
| 395173 | 1340 | 1359 | GCCAAAGTTGGTCCCCAAAG | 5-10-5 | 94.8 | 36 |
| 405930 | 1342 | 1361 | CGGCCAAAGTTGGTCCCCAA | 5-10-5 | 92.9 | 297 |
| 405931 | 1344 | 1363 | AGCGGCCAAAGTTGGTCCCC | 5-10-5 | 88.8 | 298 |
| 405932 | 1346 | 1365 | ACAGCGGCCAAAGTTGGTCC | 5-10-5 | 90.6 | 299 |
| 405933 | 1348 | 1367 | ACACAGCGGCCAAAGTTGGT | 5-10-5 | NA | 300 |
| 405934 | 1350 | 1369 | CCACACAGCGGCCAAAGTTG | 5-10-5 | 92.7 | 301 |
| 405935 | 1354 | 1373 | AGGTCCACACAGCGGCCAAA | 5-10-5 | 86.0 | 302 |
| 410736 | 1356 | 1375 | AGAGGTCCACACAGCGGCCA | 5-10-5 | 73.8 | 303 |
| 405936 | 1358 | 1377 | AAAGAGGTCCACACAGCGGC | 5-10-5 | 93.9 | 304 |
| 410768 | 1380 | 1399 | CAATGATGTCCTCCCCTGGG | 5-10-5 | 79.7 | 305 |
| 405937 | 1387 | 1406 | GAGGCACCAATGATGTCCTC | 5-10-5 | 77.7 | 306 |
| 405938 | 1391 | 1410 | GCTGGAGGCACCAATGATGT | 5-10-5 | 75.5 | 307 |
| 405939 | 1393 | 1412 | TCGCTGGAGGCACCAATGAT | 5-10-5 | 70.6 | 308 |
| 405940 | 1395 | 1414 | AGTCGCTGGAGGCACCAATG | 5-10-5 | 84.4 | 309 |
| 405941 | 1397 | 1416 | GCAGTCGCTGGAGGCACCAA | 5-10-5 | 90.1 | 310 |
| 399804 | 1400 | 1419 | GCTGCAGTCGCTGGAGGCAC | 5-10-5 | 80.8 | 40 |
| 399960 | 1400 | 1419 | GCTGCAGTCGCTGGAGGCAC | 3-14-3 | 82.4 | 40 |
| 405942 | 1402 | 1421 | GTGCTGCAGTCGCTGGAGGC | 5-10-5 | 69.8 | 311 |
| 405943 | 1404 | 1423 | AGGTGCTGCAGTCGCTGGAG | 5-10-5 | 83.6 | 312 |
| 410737 | 1406 | 1425 | GCAGGTGCTGCAGTCGCTGG | 5-10-5 | 49.8 | 313 |
| 405944 | 1407 | 1426 | AGCAGGTGCTGCAGTCGCTG | 5-10-5 | 80.7 | 314 |
| 405945 | 1409 | 1428 | AAAGCAGGTGCTGCAGTCGC | 5-10-5 | 41.1 | 315 |
| 405946 | 1413 | 1432 | ACACAAAGCAGGTGCTGCAG | 5-10-5 | 70.4 | 316 |
| 405947 | 1415 | 1434 | TGACACAAAGCAGGTGCTGC | 5-10-5 | 72.5 | 317 |
| 410769 | 1425 | 1444 | TCCCACTCTGTGACACAAAG | 5-10-5 | 84.9 | 318 |
| 405948 | 1467 | 1486 | TCATGGCTGCAATGCCAGCC | 5-10-5 | 45.9 | 319 |
| 399806 | 1470 | 1489 | GCATCATGGCTGCAATGCCA | 5-10-5 | 82.8 | 42 |
| 399962 | 1470 | 1489 | GCATCATGGCTGCAATGCCA | 3-14-3 | 86.1 | 42 |
| 405949 | 1472 | 1491 | CAGCATCATGGCTGCAATGC | 5-10-5 | 84.9 | 320 |
| 405950 | 1474 | 1493 | GACAGCATCATGGCTGCAAT | 5-10-5 | 76.9 | 321 |
| 405951 | 1476 | 1495 | CAGACAGCATCATGGCTGCA | 5-10-5 | 75.4 | 322 |
| 405952 | 1480 | 1499 | TCGGCAGACAGCATCATGGC | 5-10-5 | 85.1 | 323 |
| 410738 | 1482 | 1501 | GCTCGGCAGACAGCATCATG | 5-10-5 | 68.4 | 324 |
| 405953 | 1484 | 1503 | CGGCTCGGCAGACAGCATCA | 5-10-5 | 93.6 | 325 |
| 405954 | 1486 | 1505 | TCCGGCTCGGCAGACAGCAT | 5-10-5 | 87.5 | 326 |
| 410770 | 1500 | 1519 | CGGCCAGGGTGAGCTCCGGC | 5-10-5 | 68.5 | 327 |
| 405955 | 1513 | 1532 | CTCTGCCTCAACTCGGCCAG | 5-10-5 | 94.2 | 328 |
| 405956 | 1515 | 1534 | GTCTCTGCCTCAACTCGGCC | 5-10-5 | 94.3 | 329 |
| 405958 | 1519 | 1538 | ATCAGTCTCTGCCTCAACTC | 5-10-5 | 80.3 | 331 |
| 405959 | 1521 | 1540 | GGATCAGTCTCTGCCTCAAC | 5-10-5 | 95.4 | 332 |
| 405960 | 1523 | 1542 | GTGGATCAGTCTCTGCCTCA | 5-10-5 | 90.1 | 333 |
| 405961 | 1525 | 1544 | AAGTGGATCAGTCTCTGCCT | 5-10-5 | 88.8 | 334 |
| 405962 | 1528 | 1547 | GAGAAGTGGATCAGTCTCTG | 5-10-5 | 56.1 | 335 |
| 410739 | 1530 | 1549 | CAGAGAAGTGGATCAGTCTC | 5-10-5 | NA | 336 |
| 405963 | 1532 | 1551 | GGCAGAGAAGTGGATCAGTC | 5-10-5 | 59.7 | 337 |
| 405964 | 1536 | 1555 | CTTTGGCAGAGAAGTGGATC | 5-10-5 | 45.3 | 338 |
| 405965 | 1541 | 1560 | GACATCTTTGGCAGAGAAGT | 5-10-5 | 55.9 | 339 |

| Isis No. | 5' Target Site to SEQ ID NO: 1 | 3' Target Site to SEQ ID NO: 1 | Sequence 5'-3' | Motif | % inhibition | SEQ ID NO |
|---|---|---|---|---|---|---|
| 405966 | 1543 | 1562 | ATGACATCTTTGGCAGAGAA | 5-10-5 | 51.3 | 340 |
| 405967 | 1547 | 1566 | ATTGATGACATCTTTGGCAG | 5-10-5 | 64.4 | 341 |
| 405968 | 1549 | 1568 | TCATTGATGACATCTTTGGC | 5-10-5 | 74.6 | 342 |
| 399967 | 1552 | 1571 | GCCTCATTGATGACATCTTT | 3-14-3 | 80.1 | 48 |
| 405969 | 1554 | 1573 | AGGCCTCATTGATGACATCT | 5-10-5 | 63.0 | 343 |
| 405970 | 1556 | 1575 | CCAGGCCTCATTGATGACAT | 5-10-5 | 66.8 | 344 |
| 410740 | 1558 | 1577 | AACCAGGCCTCATTGATGAC | 5-10-5 | 46.8 | 345 |
| 405885 | 1560 | 1579 | GGAACCAGGCCTCATTGATG | 5-10-5 | 73.4 | 346 |
| 410596 | 1562 | 1581 | AGGGAACCAGGCCTCATTGA | 3-14-3 | NA | 348 |
| 410672 | 1562 | 1581 | AGGGAACCAGGCCTCATTGA | 2-13-5 | NA | 348 |
| 405887 | 1562 | 1581 | AGGGAACCAGGCCTCATTGA | 5-10-5 | NA | 348 |
| 410597 | 1563 | 1582 | CAGGGAACCAGGCCTCATTG | 3-14-3 | NA | 349 |
| 405888 | 1563 | 1582 | CAGGGAACCAGGCCTCATTG | 5-10-5 | NA | 349 |
| 410673 | 1563 | 1582 | CAGGGAACCAGGCCTCATTG | 2-13-5 | NA | 349 |
| 410674 | 1564 | 1583 | TCAGGGAACCAGGCCTCATT | 2-13-5 | 60.7 | 49 |
| 399812 | 1564 | 1583 | TCAGGGAACCAGGCCTCATT | 5-10-5 | 68.7 | 49 |
| 399968 | 1564 | 1583 | TCAGGGAACCAGGCCTCATT | 3-14-3 | 84.5 | 49 |
| 410598 | 1565 | 1584 | CTCAGGGAACCAGGCCTCAT | 3-14-3 | 74.5 | 350 |
| 410675 | 1565 | 1584 | CTCAGGGAACCAGGCCTCAT | 2-13-5 | 76.9 | 350 |
| 405889 | 1565 | 1584 | CTCAGGGAACCAGGCCTCAT | 5-10-5 | 80.2 | 350 |
| 410599 | 1566 | 1585 | CCTCAGGGAACCAGGCCTCA | 3-14-3 | 70.6 | 351 |
| 410676 | 1566 | 1585 | CCTCAGGGAACCAGGCCTCA | 2-13-5 | 77.8 | 351 |
| 405890 | 1566 | 1585 | CCTCAGGGAACCAGGCCTCA | 5-10-5 | 87.7 | 351 |
| 410600 | 1567 | 1586 | TCCTCAGGGAACCAGGCCTC | 3-14-3 | 76.5 | 352 |
| 410677 | 1567 | 1586 | TCCTCAGGGAACCAGGCCTC | 2-13-5 | 88.4 | 352 |
| 405891 | 1567 | 1586 | TCCTCAGGGAACCAGGCCTC | 5-10-5 | 96.1 | 352 |
| 405892 | 1568 | 1587 | GTCCTCAGGGAACCAGGCCT | 5-10-5 | 71.4 | 353 |
| 410601 | 1568 | 1587 | GTCCTCAGGGAACCAGGCCT | 3-14-3 | 72.7 | 353 |
| 410678 | 1568 | 1587 | GTCCTCAGGGAACCAGGCCT | 2-13-5 | 75.0 | 353 |
| 395178 | 1569 | 1588 | GGTCCTCAGGGAACCAGGCC | 5-10-5 | 76.7 | 50 |
| 410679 | 1569 | 1588 | GGTCCTCAGGGAACCAGGCC | 2-13-5 | 77.6 | 50 |
| 399900 | 1569 | 1588 | GGTCCTCAGGGAACCAGGCC | 3-14-3 | 92.0 | 50 |
| 408653 | 1570 | 1589 | TGGTCCTCAGGGAACCAGGC | 5-10-5 | 42.5 | 354 |
| 410602 | 1570 | 1589 | TGGTCCTCAGGGAACCAGGC | 3-14-3 | 66.5 | 354 |
| 410680 | 1570 | 1589 | TGGTCCTCAGGGAACCAGGC | 2-13-5 | 71.6 | 354 |
| 410603 | 1571 | 1590 | CTGGTCCTCAGGGAACCAGG | 3-14-3 | 40.8 | 355 |
| 410681 | 1571 | 1590 | CTGGTCCTCAGGGAACCAGG | 2-13-5 | 44.4 | 355 |
| 405971 | 1571 | 1590 | CTGGTCCTCAGGGAACCAGG | 5-10-5 | 65.5 | 355 |
| 410540 | 1572 | 1591 | GCTGGTCCTCAGGGAACCAG | 5-10-5 | 50.9 | 356 |
| 410682 | 1572 | 1591 | GCTGGTCCTCAGGGAACCAG | 2-13-5 | 54.1 | 356 |
| 410604 | 1572 | 1591 | GCTGGTCCTCAGGGAACCAG | 3-14-3 | 62.5 | 356 |
| 405972 | 1573 | 1592 | CGCTGGTCCTCAGGGAACCA | 5-10-5 | 77.6 | 357 |
| 405973 | 1578 | 1597 | GTACCCGCTGGTCCTCAGGG | 5-10-5 | 83.8 | 358 |
| 405974 | 1580 | 1599 | CAGTACCCGCTGGTCCTCAG | 5-10-5 | 89.0 | 359 |
| 399813 | 1583 | 1602 | GGTCAGTACCCGCTGGTCCT | 5-10-5 | 72.4 | 51 |
| 399969 | 1583 | 1602 | GGTCAGTACCCGCTGGTCCT | 3-14-3 | 93.4 | 51 |
| 410771 | 1628 | 1647 | ACCTGCCCCATGGGTGCTGG | 5-10-5 | NA | 360 |
| 395181 | 1640 | 1659 | AAACAGCTGCCAACCTGCCC | 5-10-5 | 87.5 | 52 |
| 405975 | 1642 | 1661 | CAAAACAGCTGCCAACCTGC | 5-10-5 | 77.4 | 361 |
| 405976 | 1647 | 1666 | TCCTGCAAAACAGCTGCCAA | 5-10-5 | 81.2 | 362 |
| 405977 | 1649 | 1668 | AGTCCTGCAAAACAGCTGCC | 5-10-5 | 89.5 | 363 |
| 410772 | 1660 | 1679 | GCTGACCATACAGTCCTGCA | 5-10-5 | 91.2 | 364 |
| 405978 | 1672 | 1691 | GGCCCCGAGTGTGCTGACCA | 5-10-5 | 95.3 | 365 |

| Isis No. | 5' Target Site to SEQ ID NO: 1 | 3' Target Site to SEQ ID NO: 1 | Sequence 5'-3' | Motif | % inhibition | SEQ ID NO |
|---|---|---|---|---|---|---|
| 399904 | 1675 | 1694 | GTAGGCCCCGAGTGTGCTGA | 3-14-3 | 92.6 | 54 |
| 405979 | 1677 | 1696 | GTGTAGGCCCCGAGTGTGCT | 5-10-5 | 85.5 | 366 |
| 405980 | 1679 | 1698 | CCGTGTAGGCCCCGAGTGTG | 5-10-5 | 86.5 | 367 |
| 405981 | 1681 | 1700 | ATCCGTGTAGGCCCCGAGTG | 5-10-5 | 77.8 | 368 |
| 410741 | 1683 | 1702 | CCATCCGTGTAGGCCCCGAG | 5-10-5 | 78.4 | 369 |
| 405982 | 1685 | 1704 | GGCCATCCGTGTAGGCCCCG | 5-10-5 | 86.7 | 370 |
| 405983 | 1687 | 1706 | GTGGCCATCCGTGTAGGCCC | 5-10-5 | 73.1 | 371 |
| 405984 | 1735 | 1754 | CTGGAGCAGCTCAGCAGCTC | 5-10-5 | 83.4 | 372 |
| 405985 | 1737 | 1756 | AACTGGAGCAGCTCAGCAGC | 5-10-5 | 50.7 | 373 |
| 405986 | 1742 | 1761 | GGAGAAACTGGAGCAGCTCA | 5-10-5 | 75.6 | 374 |
| 405987 | 1744 | 1763 | CTGGAGAAACTGGAGCAGCT | 5-10-5 | 88.0 | 375 |
| 399905 | 1812 | 1831 | CGTTGTGGGCCCGGCAGACC | 3-14-3 | 91.2 | 57 |
| 395183 | 1812 | 1831 | CGTTGTGGGCCCGGCAGACC | 5-10-5 | 93.1 | 57 |
| 410541 | 1849 | 1868 | CACCTGGCAATGGCGTAGAC | 5-10-5 | 46.1 | 376 |
| 410605 | 1849 | 1868 | CACCTGGCAATGGCGTAGAC | 3-14-3 | 67.4 | 376 |
| 410683 | 1849 | 1868 | CACCTGGCAATGGCGTAGAC | 2-13-5 | 71.8 | 376 |
| 410606 | 1850 | 1869 | GCACCTGGCAATGGCGTAGA | 3-14-3 | 74.3 | 377 |
| 410542 | 1850 | 1869 | GCACCTGGCAATGGCGTAGA | 5-10-5 | 75.5 | 377 |
| 410684 | 1850 | 1869 | GCACCTGGCAATGGCGTAGA | 2-13-5 | 78.7 | 377 |
| 410543 | 1851 | 1870 | AGCACCTGGCAATGGCGTAG | 5-10-5 | 76.4 | 378 |
| 410685 | 1851 | 1870 | AGCACCTGGCAATGGCGTAG | 2-13-5 | 76.9 | 378 |
| 410607 | 1851 | 1870 | AGCACCTGGCAATGGCGTAG | 3-14-3 | 77.1 | 378 |
| 410544 | 1852 | 1871 | CAGCACCTGGCAATGGCGTA | 5-10-5 | 62.7 | 379 |
| 410608 | 1852 | 1871 | CAGCACCTGGCAATGGCGTA | 3-14-3 | 69.6 | 379 |
| 410686 | 1852 | 1871 | CAGCACCTGGCAATGGCGTA | 2-13-5 | 81.0 | 379 |
| 410545 | 1853 | 1872 | GCAGCACCTGGCAATGGCGT | 5-10-5 | 75.5 | 380 |
| 410687 | 1853 | 1872 | GCAGCACCTGGCAATGGCGT | 2-13-5 | 79.2 | 380 |
| 410609 | 1853 | 1872 | GCAGCACCTGGCAATGGCGT | 3-14-3 | 83.2 | 380 |
| 410610 | 1854 | 1873 | GGCAGCACCTGGCAATGGCG | 3-14-3 | 67.5 | 381 |
| 410688 | 1854 | 1873 | GGCAGCACCTGGCAATGGCG | 2-13-5 | 89.3 | 381 |
| 405988 | 1854 | 1873 | GGCAGCACCTGGCAATGGCG | 5-10-5 | 95.9 | 381 |
| 410546 | 1855 | 1874 | AGGCAGCACCTGGCAATGGC | 5-10-5 | 74.8 | 382 |
| 410689 | 1855 | 1874 | AGGCAGCACCTGGCAATGGC | 2-13-5 | 83.9 | 382 |
| 410611 | 1855 | 1874 | AGGCAGCACCTGGCAATGGC | 3-14-3 | 88.2 | 382 |
| 410612 | 1856 | 1875 | CAGGCAGCACCTGGCAATGG | 3-14-3 | 72.8 | 383 |
| 410690 | 1856 | 1875 | CAGGCAGCACCTGGCAATGG | 2-13-5 | 74.8 | 383 |
| 405989 | 1856 | 1875 | CAGGCAGCACCTGGCAATGG | 5-10-5 | 88.1 | 383 |
| 410547 | 1857 | 1876 | GCAGGCAGCACCTGGCAATG | 5-10-5 | 63.0 | 384 |
| 410691 | 1857 | 1876 | GCAGGCAGCACCTGGCAATG | 2-13-5 | 70.2 | 384 |
| 410613 | 1857 | 1876 | GCAGGCAGCACCTGGCAATG | 3-14-3 | 76.7 | 384 |
| 395184 | 1858 | 1877 | AGCAGGCAGCACCTGGCAAT | 5-10-5 | 68.5 | 58 |
| 410692 | 1858 | 1877 | AGCAGGCAGCACCTGGCAAT | 2-13-5 | 69.1 | 58 |
| 399906 | 1858 | 1877 | AGCAGGCAGCACCTGGCAAT | 3-14-3 | 94.2 | 58 |
| 410614 | 1859 | 1878 | TAGCAGGCAGCACCTGGCAA | 3-14-3 | 36.6 | 385 |
| 410548 | 1859 | 1878 | TAGCAGGCAGCACCTGGCAA | 5-10-5 | 75.0 | 385 |
| 410693 | 1859 | 1878 | TAGCAGGCAGCACCTGGCAA | 2-13-5 | 82.0 | 385 |
| 405990 | 1860 | 1879 | GTAGCAGGCAGCACCTGGCA | 5-10-5 | 96.8 | 386 |
| 410773 | 1905 | 1924 | TGGCCTCAGCTGGTGGAGCT | 5-10-5 | 61.3 | 387 |
| 410549 | 1915 | 1934 | GTCCCCATGCTGGCCTCAGC | 5-10-5 | 63.0 | 388 |
| 410615 | 1915 | 1934 | GTCCCCATGCTGGCCTCAGC | 3-14-3 | 72.5 | 388 |
| 410694 | 1915 | 1934 | GTCCCCATGCTGGCCTCAGC | 2-13-5 | 74.8 | 388 |
| 410550 | 1916 | 1935 | GGTCCCCATGCTGGCCTCAG | 5-10-5 | 69.4 | 389 |
| 410616 | 1916 | 1935 | GGTCCCCATGCTGGCCTCAG | 3-14-3 | 80.7 | 389 |

| Isis No. | 5' Target Site to SEQ ID NO: 1 | 3' Target Site to SEQ ID NO: 1 | Sequence 5'-3' | Motif | % inhibition | SEQ ID NO |
|---|---|---|---|---|---|---|
| 410695 | 1916 | 1935 | GGTCCCCATGCTGGCCTCAG | 2-13-5 | 85.5 | 389 |
| 410551 | 1917 | 1936 | GGGTCCCCATGCTGGCCTCA | 5-10-5 | 68.7 | 390 |
| 410696 | 1917 | 1936 | GGGTCCCCATGCTGGCCTCA | 2-13-5 | 86.3 | 390 |
| 410617 | 1917 | 1936 | GGGTCCCCATGCTGGCCTCA | 3-14-3 | 86.5 | 390 |
| 410552 | 1918 | 1937 | CGGGTCCCCATGCTGGCCTC | 5-10-5 | 77.9 | 391 |
| 410618 | 1918 | 1937 | CGGGTCCCCATGCTGGCCTC | 3-14-3 | 86.7 | 391 |
| 410697 | 1918 | 1937 | CGGGTCCCCATGCTGGCCTC | 2-13-5 | 87.0 | 391 |
| 410553 | 1919 | 1938 | ACGGGTCCCCATGCTGGCCT | 5-10-5 | 72.8 | 392 |
| 410619 | 1919 | 1938 | ACGGGTCCCCATGCTGGCCT | 3-14-3 | 84.1 | 392 |
| 410698 | 1919 | 1938 | ACGGGTCCCCATGCTGGCCT | 2-13-5 | 87.0 | 392 |
| 410699 | 1920 | 1939 | CACGGGTCCCCATGCTGGCC | 2-13-5 | 79.5 | 59 |
| 395185 | 1920 | 1939 | CACGGGTCCCCATGCTGGCC | 5-10-5 | 92.7 | 59 |
| 399907 | 1920 | 1939 | CACGGGTCCCCATGCTGGCC | 3-14-3 | 93.7 | 59 |
| 410620 | 1921 | 1940 | ACACGGGTCCCCATGCTGGC | 3-14-3 | 74.4 | 393 |
| 410554 | 1921 | 1940 | ACACGGGTCCCCATGCTGGC | 5-10-5 | 79.7 | 393 |
| 410700 | 1921 | 1940 | ACACGGGTCCCCATGCTGGC | 2-13-5 | 84.4 | 393 |
| 410621 | 1922 | 1941 | GACACGGGTCCCCATGCTGG | 3-14-3 | 76.0 | 394 |
| 410701 | 1922 | 1941 | GACACGGGTCCCCATGCTGG | 2-13-5 | 83.4 | 394 |
| 405991 | 1922 | 1941 | GACACGGGTCCCCATGCTGG | 5-10-5 | 91.9 | 394 |
| 410555 | 1923 | 1942 | GGACACGGGTCCCCATGCTG | 5-10-5 | 77.0 | 395 |
| 410622 | 1923 | 1942 | GGACACGGGTCCCCATGCTG | 3-14-3 | 79.8 | 395 |
| 410702 | 1923 | 1942 | GGACACGGGTCCCCATGCTG | 2-13-5 | 85.0 | 395 |
| 410703 | 1924 | 1943 | TGGACACGGGTCCCCATGCT | 2-13-5 | 70.4 | 396 |
| 410623 | 1924 | 1943 | TGGACACGGGTCCCCATGCT | 3-14-3 | 78.9 | 396 |
| 405992 | 1924 | 1943 | TGGACACGGGTCCCCATGCT | 5-10-5 | 89.3 | 396 |
| 410704 | 1925 | 1944 | GTGGACACGGGTCCCCATGC | 2-13-5 | 78.6 | 397 |
| 410556 | 1925 | 1944 | GTGGACACGGGTCCCCATGC | 5-10-5 | 81.4 | 397 |
| 410624 | 1925 | 1944 | GTGGACACGGGTCCCCATGC | 3-14-3 | 82.8 | 397 |
| 410625 | 1926 | 1945 | AGTGGACACGGGTCCCCATG | 3-14-3 | 64.4 | 398 |
| 410705 | 1926 | 1945 | AGTGGACACGGGTCCCCATG | 2-13-5 | 74.7 | 398 |
| 405993 | 1926 | 1945 | AGTGGACACGGGTCCCCATG | 5-10-5 | 85.5 | 398 |
| 410706 | 1927 | 1946 | CAGTGGACACGGGTCCCCAT | 2-13-5 | 70.8 | 399 |
| 410557 | 1927 | 1946 | CAGTGGACACGGGTCCCCAT | 5-10-5 | 74.2 | 399 |
| 410626 | 1927 | 1946 | CAGTGGACACGGGTCCCCAT | 3-14-3 | 76.8 | 399 |
| 410627 | 1928 | 1947 | GCAGTGGACACGGGTCCCCA | 3-14-3 | 71.4 | 400 |
| 410707 | 1928 | 1947 | GCAGTGGACACGGGTCCCCA | 2-13-5 | 72.8 | 400 |
| 405994 | 1928 | 1947 | GCAGTGGACACGGGTCCCCA | 5-10-5 | 95.2 | 400 |
| 410708 | 1929 | 1948 | GGCAGTGGACACGGGTCCCC | 2-13-5 | 79.0 | 401 |
| 410628 | 1929 | 1948 | GGCAGTGGACACGGGTCCCC | 3-14-3 | 88.1 | 401 |
| 410558 | 1929 | 1948 | GGCAGTGGACACGGGTCCCC | 5-10-5 | 88.9 | 401 |
| 410629 | 1930 | 1949 | TGGCAGTGGACACGGGTCCC | 3-14-3 | 66.5 | 402 |
| 410709 | 1930 | 1949 | TGGCAGTGGACACGGGTCCC | 2-13-5 | 66.9 | 402 |
| 405995 | 1930 | 1949 | TGGCAGTGGACACGGGTCCC | 5-10-5 | 92.4 | 402 |
| 410630 | 1931 | 1950 | GTGGCAGTGGACACGGGTCC | 3-14-3 | 54.1 | 403 |
| 410710 | 1931 | 1950 | GTGGCAGTGGACACGGGTCC | 2-13-5 | 61.4 | 403 |
| 410559 | 1931 | 1950 | GTGGCAGTGGACACGGGTCC | 5-10-5 | 77.5 | 403 |
| 410711 | 1932 | 1951 | GGTGGCAGTGGACACGGGTC | 2-13-5 | NA | 404 |
| 410631 | 1932 | 1951 | GGTGGCAGTGGACACGGGTC | 3-14-3 | NA | 404 |
| 410560 | 1932 | 1951 | GGTGGCAGTGGACACGGGTC | 5-10-5 | 42.5 | 404 |
| 410712 | 1933 | 1952 | TGGTGGCAGTGGACACGGGT | 2-13-5 | NA | 405 |
| 410632 | 1933 | 1952 | TGGTGGCAGTGGACACGGGT | 3-14-3 | NA | 405 |
| 410561 | 1933 | 1952 | TGGTGGCAGTGGACACGGGT | 5-10-5 | NA | 405 |
| 410774 | 1936 | 1955 | TGTTGGTGGCAGTGGACACG | 5-10-5 | 47.8 | 406 |

| Isis No. | 5' Target Site to SEQ ID NO: 1 | 3' Target Site to SEQ ID NO: 1 | Sequence 5'-3' | Motif | % inhibition | SEQ ID NO |
|---|---|---|---|---|---|---|
| 410775 | 1962 | 1981 | AGCTGCAGCCTGTGAGGACG | 5-10-5 | 36.3 | 407 |
| 410776 | 1990 | 2009 | GTGCCAAGGTCCTCCACCTC | 5-10-5 | 77.3 | 408 |
| 410777 | 2010 | 2029 | TCAGCACAGGCGGCTTGTGG | 5-10-5 | 40.0 | 409 |
| 410778 | 2040 | 2059 | CCACGCACTGGTTGGGCTGA | 5-10-5 | 52.7 | 410 |
| 399908 | 2100 | 2119 | CTTTGCATTCCAGACCTGGG | 3-14-3 | 74.9 | 60 |
| 410713 | 2100 | 2119 | CTTTGCATTCCAGACCTGGG | 2-13-5 | 84.9 | 60 |
| 395186 | 2100 | 2119 | CTTTGCATTCCAGACCTGGG | 5-10-5 | 93.7 | 60 |
| 410714 | 2101 | 2120 | ACTTTGCATTCCAGACCTGG | 2-13-5 | 82.4 | 411 |
| 410633 | 2101 | 2120 | ACTTTGCATTCCAGACCTGG | 3-14-3 | 83.8 | 411 |
| 410562 | 2101 | 2120 | ACTTTGCATTCCAGACCTGG | 5-10-5 | 87.3 | 411 |
| 410715 | 2102 | 2121 | GACTTTGCATTCCAGACCTG | 2-13-5 | 80.5 | 412 |
| 410634 | 2102 | 2121 | GACTTTGCATTCCAGACCTG | 3-14-3 | 81.8 | 412 |
| 405996 | 2102 | 2121 | GACTTTGCATTCCAGACCTG | 5-10-5 | 91.0 | 412 |
| 410563 | 2103 | 2122 | TGACTTTGCATTCCAGACCT | 5-10-5 | 75.4 | 413 |
| 410635 | 2103 | 2122 | TGACTTTGCATTCCAGACCT | 3-14-3 | 75.9 | 413 |
| 410716 | 2103 | 2122 | TGACTTTGCATTCCAGACCT | 2-13-5 | 88.3 | 413 |
| 410636 | 2104 | 2123 | TTGACTTTGCATTCCAGACC | 3-14-3 | 61.3 | 414 |
| 410564 | 2104 | 2123 | TTGACTTTGCATTCCAGACC | 5-10-5 | 71.3 | 414 |
| 410717 | 2104 | 2123 | TTGACTTTGCATTCCAGACC | 2-13-5 | 76.7 | 414 |
| 410718 | 2105 | 2124 | CTTGACTTTGCATTCCAGAC | 2-13-5 | 55.8 | 61 |
| 399973 | 2105 | 2124 | CTTGACTTTGCATTCCAGAC | 3-14-3 | 82.1 | 61 |
| 399817 | 2105 | 2124 | CTTGACTTTGCATTCCAGAC | 5-10-5 | 93.6 | 61 |
| 405997 | 2107 | 2126 | TCCTTGACTTTGCATTCCAG | 5-10-5 | 95.6 | 415 |
| 410779 | 2120 | 2139 | CGGGATTCCATGCTCCTTGA | 5-10-5 | 79.7 | 416 |
| 410780 | 2150 | 2169 | GCAGGCCACGGTCACCTGCT | 5-10-5 | 60.9 | 417 |
| 410781 | 2187 | 2206 | GGAGGGCACTGCAGCCAGTC | 5-10-5 | 66.0 | 418 |
| 410719 | 2305 | 2324 | CAGATGGCAACGGCTGTCAC | 2-13-5 | 61.0 | 419 |
| 410637 | 2305 | 2324 | CAGATGGCAACGGCTGTCAC | 3-14-3 | 66.0 | 419 |
| 410565 | 2305 | 2324 | CAGATGGCAACGGCTGTCAC | 5-10-5 | 71.6 | 419 |
| 410638 | 2306 | 2325 | GCAGATGGCAACGGCTGTCA | 3-14-3 | 71.9 | 420 |
| 410720 | 2306 | 2325 | GCAGATGGCAACGGCTGTCA | 2-13-5 | 75.1 | 420 |
| 410566 | 2306 | 2325 | GCAGATGGCAACGGCTGTCA | 5-10-5 | 77.7 | 420 |
| 410639 | 2307 | 2326 | AGCAGATGGCAACGGCTGTC | 3-14-3 | 67.7 | 421 |
| 410721 | 2307 | 2326 | AGCAGATGGCAACGGCTGTC | 2-13-5 | 68.8 | 421 |
| 410567 | 2307 | 2326 | AGCAGATGGCAACGGCTGTC | 5-10-5 | 72.1 | 421 |
| 410568 | 2308 | 2327 | CAGCAGATGGCAACGGCTGT | 5-10-5 | 54.2 | 422 |
| 410640 | 2308 | 2327 | CAGCAGATGGCAACGGCTGT | 3-14-3 | 57.7 | 422 |
| 410722 | 2308 | 2327 | CAGCAGATGGCAACGGCTGT | 2-13-5 | 59.2 | 422 |
| 410569 | 2309 | 2328 | GCAGCAGATGGCAACGGCTG | 5-10-5 | 57.7 | 423 |
| 410641 | 2309 | 2328 | GCAGCAGATGGCAACGGCTG | 3-14-3 | 66.1 | 423 |
| 410723 | 2309 | 2328 | GCAGCAGATGGCAACGGCTG | 2-13-5 | 81.1 | 423 |
| 399909 | 2310 | 2329 | GGCAGCAGATGGCAACGGCT | 3-14-3 | 69.9 | 62 |
| 410724 | 2310 | 2329 | GGCAGCAGATGGCAACGGCT | 2-13-5 | 87.4 | 62 |
| 395187 | 2310 | 2329 | GGCAGCAGATGGCAACGGCT | 5-10-5 | 92.7 | 62 |
| 410642 | 2311 | 2330 | CGGCAGCAGATGGCAACGGC | 3-14-3 | 70.4 | 424 |
| 410725 | 2311 | 2330 | CGGCAGCAGATGGCAACGGC | 2-13-5 | 75.6 | 424 |
| 410570 | 2311 | 2330 | CGGCAGCAGATGGCAACGGC | 5-10-5 | 78.3 | 424 |
| 410571 | 2312 | 2331 | CCGGCAGCAGATGGCAACGG | 5-10-5 | 52.8 | 425 |
| 410643 | 2312 | 2331 | CCGGCAGCAGATGGCAACGG | 3-14-3 | 59.8 | 425 |
| 410726 | 2312 | 2331 | CCGGCAGCAGATGGCAACGG | 2-13-5 | 69.8 | 425 |
| 410644 | 2313 | 2332 | TCCGGCAGCAGATGGCAACG | 3-14-3 | 59.0 | 426 |
| 410727 | 2313 | 2332 | TCCGGCAGCAGATGGCAACG | 2-13-5 | 68.3 | 426 |
| 405998 | 2313 | 2332 | TCCGGCAGCAGATGGCAACG | 5-10-5 | 75.6 | 426 |

| Isis No. | 5' Target Site to SEQ ID NO: 1 | 3' Target Site to SEQ ID NO: 1 | Sequence 5'-3' | Motif | % inhibition | SEQ ID NO |
|---|---|---|---|---|---|---|
| 410572 | 2314 | 2333 | CTCCGGCAGCAGATGGCAAC | 5-10-5 | 40.9 | 427 |
| 410728 | 2314 | 2333 | CTCCGGCAGCAGATGGCAAC | 2-13-5 | 56.4 | 427 |
| 410645 | 2314 | 2333 | CTCCGGCAGCAGATGGCAAC | 3-14-3 | 70.2 | 427 |
| 410729 | 2315 | 2334 | GCTCCGGCAGCAGATGGCAA | 2-13-5 | 67.7 | 428 |
| 410573 | 2315 | 2334 | GCTCCGGCAGCAGATGGCAA | 5-10-5 | 71.8 | 428 |
| 410646 | 2315 | 2334 | GCTCCGGCAGCAGATGGCAA | 3-14-3 | 72.8 | 428 |
| 410782 | 2325 | 2344 | CCAGGTGCCGGCTCCGGCAG | 5-10-5 | 43.2 | 429 |
| 410783 | 2335 | 2354 | GAGGCCTGCGCCAGGTGCCG | 5-10-5 | 63.7 | 430 |
| 399819 | 2509 | 2528 | CCCACTCAAGGGCCAGGCCA | 5-10-5 | 93.4 | 65 |
| 399912 | 2597 | 2616 | ATGCCCCACAGTGAGGGAGG | 3-14-3 | 84.3 | 66 |
| 405893 | 2828 | 2847 | ATGAGGGCCATCAGCACCTT | 5-10-5 | 93.9 | 431 |
| 405894 | 2829 | 2848 | GATGAGGGCCATCAGCACCT | 5-10-5 | 93.9 | 432 |
| 405895 | 2830 | 2849 | AGATGAGGGCCATCAGCACC | 5-10-5 | 91.8 | 433 |
| 405896 | 2831 | 2850 | GAGATGAGGGCCATCAGCAC | 5-10-5 | 88.5 | 434 |
| 395194 | 2832 | 2851 | GGAGATGAGGGCCATCAGCA | 5-10-5 | 90.0 | 69 |
| 399916 | 2832 | 2851 | GGAGATGAGGGCCATCAGCA | 3-14-3 | 94.5 | 69 |
| 405897 | 2833 | 2852 | TGGAGATGAGGGCCATCAGC | 5-10-5 | 85.1 | 435 |
| 405898 | 2834 | 2853 | CTGGAGATGAGGGCCATCAG | 5-10-5 | 86.9 | 436 |
| 405899 | 2835 | 2854 | GCTGGAGATGAGGGCCATCA | 5-10-5 | 91.5 | 437 |
| 405900 | 2836 | 2855 | AGCTGGAGATGAGGGCCATC | 5-10-5 | 83.7 | 438 |
| 405901 | 2902 | 2921 | GCTAGATGCCATCCAGAAAG | 5-10-5 | 88.4 | 439 |
| 405902 | 2903 | 2922 | GGCTAGATGCCATCCAGAAA | 5-10-5 | 89.3 | 440 |
| 405903 | 2904 | 2923 | TGGCTAGATGCCATCCAGAA | 5-10-5 | 92.6 | 441 |
| 405904 | 2905 | 2924 | CTGGCTAGATGCCATCCAGA | 5-10-5 | 90.4 | 442 |
| 399821 | 2906 | 2925 | TCTGGCTAGATGCCATCCAG | 5-10-5 | 91.7 | 71 |
| 405905 | 2907 | 2926 | CTCTGGCTAGATGCCATCCA | 5-10-5 | 90.7 | 443 |
| 405906 | 2908 | 2927 | CCTCTGGCTAGATGCCATCC | 5-10-5 | 93.3 | 444 |
| 405907 | 2909 | 2928 | GCCTCTGGCTAGATGCCATC | 5-10-5 | 90.2 | 445 |
| 405908 | 2910 | 2929 | AGCCTCTGGCTAGATGCCAT | 5-10-5 | 83.3 | 446 |
| 399978 | 2988 | 3007 | AGCCTGGCATAGAGCAGAGT | 3-14-3 | 96.4 | 73 |

Antisense oligonucleotides that exhibited less than 30% inhibition of PCSK9 mRNA levels were marked with "NA".

Antisense oligonucleotides with the following ISIS Nos exhibited at least 80% inhibition of PCSK9 mRNA levels: 395152, 395153, 395155, 395158, 395163, 395165, 395166, 395168, 395173, 395181, 395183, 395185, 395186, 395187, 395194, 399798, 399801, 399804, 399806, 399817, 399819, 399821, 399877, 399879, 399887, 399888, 399891, 399895, 399900, 399904, 399905, 399906, 399907, 399912, 399916, 399954, 399960, 399962, 399967, 399968, 399969, 399973, 399978, 405861, 405862, 405863, 405864, 405865, 405866, 405869, 405870, 405871, 405872, 405873, 405874, 405875, 405876, 405877, 405878, 405879, 405880, 405881, 405882, 405883, 405884, 405889, 405890, 405891, 405893, 405894, 405895, 405896, 405897, 405898, 405899, 405900, 405901, 405902, 405903, 405904, 405905, 405906, 405907, 405908, 405909, 405910, 405911, 405913, 405914, 405915, 405916, 405920, 405921, 405922, 405923, 405924,

405925, 405926, 405927, 405928, 405929, 405930, 405931, 405932, 405934, 405935, 405936, 405940, 405941, 405943, 405944, 405949, 405952, 405953, 405954, 405955, 405956, 405958, 405959, 405960, 405961, 405973, 405974, 405976, 405977, 405978, 405979, 405980, 405982, 405984, 405987, 405988, 405989, 405990, 405991, 405992, 405993, 405994, 405995, 405996, 405997, 406002, 406003, 406005, 406008, 406009, 406014, 406016, 406020, 406023, 406026, 406028, 406029, 406030, 406031, 406032, 406033, 406035, 406036, 406038, 406039, 406040, 406041, 406042, 406043, 406044, 406045, 410530, 410556, 410558, 410562, 410578, 410583, 410589, 410590, 410591, 410592, 410593, 410595, 410609, 410611, 410616, 410617, 410618, 410619, 410624, 410628, 410633, 410634, 410647, 410648, 410650, 410652, 410658, 410664, 410666, 410667, 410668, 410671, 410677, 410686, 410688, 410689, 410693, 410695, 410696, 410697, 410698, 410700, 410701, 410702, 410713, 410714, 410715, 410716, 410723, 410724, 410730, 410751, 410754, 410757, 410759, 410760, 410769, and 410772. The target segments to which these antisense oligonucleotides are targeted are active target segments. The target regions to which these antisense oligonucleotides are targeted are active target regions.

ISIS Nos 395152, 395155, 395158, 395165, 395166, 395168, 395173, 395181, 395183, 395185, 395186, 395187, 395194, 399801, 399817, 399819, 399821, 399877, 399879, 399887, 399888, 399891, 399900, 399904, 399905, 399906, 399907, 399916, 399954, 399962, 399969, 399978, 405861, 405862, 405864, 405869, 405871, 405872, 405873, 405874, 405875, 405876, 405878, 405879, 405880, 405881, 405882, 405883, 405884, 405890, 405891, 405893, 405894, 405895, 405896, 405897, 405898, 405899, 405901, 405902, 405903, 405904, 405905, 405906, 405907, 405910, 405911, 405913, 405914, 405915, 405916, 405920, 405921, 405922, 405923, 405924, 405925, 405926, 405927, 405928, 405929, 405930, 405931, 405932, 405934, 405935, 405936, 405941, 405952, 405953, 405954, 405955, 405956, 405959, 405960, 405961, 405974, 405977, 405978, 405979, 405980, 405982, 405987, 405988, 405989, 405990, 405991, 405992, 405993, 405994, 405995, 405996, 405997, 406008, 406009, 406014, 406016, 406023, 406028, 406029, 406030, 406031, 406032, 406033, 406035, 406038, 406039, 406040, 406041, 406042, 406043, 406044, 406045, 410558, 410562, 410583, 410591, 410592, 410593, 410611, 410617, 410618, 410628, 410647, 410650, 410668, 410677, 410688, 410695, 410696, 410697, 410698, 410702, 410716, 410724, 410730, 410757, 410760, and 410772 each exhibited at least 85% inhibition of PCSK9 mRNA levels.

ISIS Nos 395152, 395155, 395158, 395165, 395166, 395168, 395173, 395183, 395185, 395186, 395187, 395194, 399801, 399817, 399819, 399821, 399877, 399879, 399887, 399888, 399891, 399900, 399904, 399905, 399906, 399907, 399916, 399954, 399969, 399978, 405861,

405862, 405864, 405873, 405874, 405875, 405876, 405878, 405879, 405880, 405881, 405882, 405883, 405884, 405891, 405893, 405894, 405895, 405899, 405903, 405904, 405905, 405906, 405907, 405910, 405913, 405914, 405916, 405923, 405924, 405925, 405926, 405927, 405928, 405930, 405932, 405934, 405936, 405941, 405953, 405955, 405956, 405959, 405960, 405978, 405988, 405990, 405991, 405994, 405995, 405996, 405997, 406008, 406009, 406014, 406023, 406028, 406029, 406030, 406033, 406035, 406039, 406040, 406041, 406042, 406043, 406044, 410592, 410647, 410668, 410760, and 410772 each exhibited at least 90% inhibition of PCSK9 mRNA levels.

ISIS Nos 395165, 395166, 399801, 399978, 405881, 405891, 405959, 405978, 405988, 405990, 405994, 405997, 406008, 406030, 406040, 406041, 406044, and 410760 each exhibited at least 95% inhibition of PCSK9 mRNA levels.

**Table 17: Antisense inhibition of PCSK9 in human cells (HepB3) targeting SEQ ID NO: 2**

| Isis No. | 5' Target Site to SEQ ID NO: 2 | 3' Target Site to SEQ ID NO: 2 | Sequence 5'-3' | Motif | % inhibition | SEQ ID NO: |
|---|---|---|---|---|---|---|
| 410742 | 2433 | 2452 | GCCTGGAGCTGACGGTGCCC | 5-10-5 | 75.1 | 159 |
| 405999 | 2437 | 2456 | GACCGCCTGGAGCTGACGGT | 5-10-5 | 70.3 | 160 |
| 395151 | 2439 | 2458 | AGGACCGCCTGGAGCTGACG | 5-10-5 | 57.3 | 6 |
| 405861 | 2545 | 2564 | AAGGCTAGCACCAGCTCCTC | 5-10-5 | 90.5 | 162 |
| 405862 | 2546 | 2565 | CAAGGCTAGCACCAGCTCCT | 5-10-5 | 92.3 | 163 |
| 405863 | 2547 | 2566 | GCAAGGCTAGCACCAGCTCC | 5-10-5 | 82.6 | 164 |
| 405864 | 2548 | 2567 | CGCAAGGCTAGCACCAGCTC | 5-10-5 | 91.8 | 165 |
| 395152 | 2549 | 2568 | ACGCAAGGCTAGCACCAGCT | 5-10-5 | 93.3 | 7 |
| 405865 | 2550 | 2569 | AACGCAAGGCTAGCACCAGC | 5-10-5 | 84.6 | 166 |
| 405866 | 2551 | 2570 | GAACGCAAGGCTAGCACCAG | 5-10-5 | 81.8 | 167 |
| 405867 | 2552 | 2571 | GGAACGCAAGGCTAGCACCA | 5-10-5 | 74.0 | 168 |
| 405868 | 2553 | 2572 | CGGAACGCAAGGCTAGCACC | 5-10-5 | 76.8 | 169 |
| 399793 | 2556 | 2575 | CCTCGGAACGCAAGGCTAGC | 5-10-5 | 77.9 | 8 |
| 410743 | 2560 | 2579 | TCCTCCTCGGAACGCAAGGC | 5-10-5 | 76.7 | 170 |
| 410744 | 2585 | 2604 | GTGCTCGGGTGCTTCGGCCA | 5-10-5 | 76.9 | 171 |
| 410745 | 2605 | 2624 | TGGAAGGTGGCTGTGGTTCC | 5-10-5 | 41.7 | 172 |
| 395153 | 2619 | 2638 | CCTTGGCGCAGCGGTGGAAG | 5-10-5 | 81.1 | 9 |
| 410746 | 6444 | 6463 | CGTAGGTGCCAGGCAACCTC | 5-10-5 | 44.8 | 176 |
| 410747 | 6482 | 6501 | TGACTGCGAGAGGTGGGTCT | 5-10-5 | NA | 177 |
| 406003 | 6492 | 6511 | CAGTGCGCTCTGACTGCGAG | 5-10-5 | 84.2 | 178 |
| 406004 | 6494 | 6513 | GGCAGTGCGCTCTGACTGCG | 5-10-5 | 56.4 | 179 |
| 406005 | 6496 | 6515 | CGGGCAGTGCGCTCTGACTG | 5-10-5 | 83.4 | 180 |
| 406006 | 6499 | 6518 | CGGCGGGCAGTGCGCTCTGA | 5-10-5 | 71.0 | 181 |
| 410748 | 6528 | 6547 | ATCCCCGGCGGGCAGCCTGG | 5-10-5 | 56.0 | 182 |
| 406007 | 6532 | 6551 | AGGTATCCCCGGCGGGCAGC | 5-10-5 | 76.3 | 183 |
| 410574 | 6534 | 6553 | TGAGGTATCCCCGGCGGGCA | 3-14-3 | 69.1 | 184 |
| 410529 | 6534 | 6553 | TGAGGTATCCCCGGCGGGCA | 5-10-5 | 77.4 | 184 |
| 410647 | 6534 | 6553 | TGAGGTATCCCCGGCGGGCA | 2-13-5 | 90.7 | 184 |
| 410575 | 6535 | 6554 | GTGAGGTATCCCCGGCGGGC | 3-14-3 | 71.5 | 185 |

| Isis No. | 5' Target Site to SEQ ID NO: 2 | 3' Target Site to SEQ ID NO: 2 | Sequence 5'-3' | Motif | % inhibition | SEQ ID NO: |
|---|---|---|---|---|---|---|
| 410648 | 6535 | 6554 | GTGAGGTATCCCCGGCGGGC | 2-13-5 | 82.8 | 185 |
| 410530 | 6535 | 6554 | GTGAGGTATCCCCGGCGGGC | 5-10-5 | 83.2 | 185 |
| 410649 | 6536 | 6555 | GGTGAGGTATCCCCGGCGGG | 2-13-5 | 53.5 | 186 |
| 410576 | 6536 | 6555 | GGTGAGGTATCCCCGGCGGG | 3-14-3 | 56.2 | 186 |
| 410531 | 6536 | 6555 | GGTGAGGTATCCCCGGCGGG | 5-10-5 | 63.6 | 186 |
| 410650 | 6537 | 6556 | TGGTGAGGTATCCCCGGCGG | 2-13-5 | 86.1 | 11 |
| 399877 | 6537 | 6556 | TGGTGAGGTATCCCCGGCGG | 3-14-3 | 92.6 | 11 |
| 395155 | 6537 | 6556 | TGGTGAGGTATCCCCGGCGG | 5-10-5 | 92.7 | 11 |
| 410577 | 6538 | 6557 | TTGGTGAGGTATCCCCGGCG | 3-14-3 | 62.4 | 187 |
| 410532 | 6538 | 6557 | TTGGTGAGGTATCCCCGGCG | 5-10-5 | 63.5 | 187 |
| 410651 | 6538 | 6557 | TTGGTGAGGTATCCCCGGCG | 2-13-5 | 75.5 | 187 |
| 410652 | 6539 | 6558 | CTTGGTGAGGTATCCCCGGC | 2-13-5 | 81.2 | 188 |
| 410578 | 6539 | 6558 | CTTGGTGAGGTATCCCCGGC | 3-14-3 | 83.3 | 188 |
| 406008 | 6539 | 6558 | CTTGGTGAGGTATCCCCGGC | 5-10-5 | 95.2 | 188 |
| 410653 | 6540 | 6559 | TCTTGGTGAGGTATCCCCGG | 2-13-5 | 68.9 | 189 |
| 410579 | 6540 | 6559 | TCTTGGTGAGGTATCCCCGG | 3-14-3 | 74.0 | 189 |
| 410533 | 6540 | 6559 | TCTTGGTGAGGTATCCCCGG | 5-10-5 | 79.0 | 189 |
| 410580 | 6541 | 6560 | ATCTTGGTGAGGTATCCCCG | 3-14-3 | 62.3 | 190 |
| 410654 | 6541 | 6560 | ATCTTGGTGAGGTATCCCCG | 2-13-5 | 65.2 | 190 |
| 406009 | 6541 | 6560 | ATCTTGGTGAGGTATCCCCG | 5-10-5 | 90.7 | 190 |
| 410534 | 6542 | 6561 | GATCTTGGTGAGGTATCCCC | 5-10-5 | 59.8 | 191 |
| 410581 | 6542 | 6561 | GATCTTGGTGAGGTATCCCC | 3-14-3 | 72.9 | 191 |
| 410655 | 6542 | 6561 | GATCTTGGTGAGGTATCCCC | 2-13-5 | 77.4 | 191 |
| 399794 | 6543 | 6562 | GGATCTTGGTGAGGTATCCC | 5-10-5 | 56.5 | 12 |
| 410656 | 6543 | 6562 | GGATCTTGGTGAGGTATCCC | 2-13-5 | 68.0 | 12 |
| 399950 | 6543 | 6562 | GGATCTTGGTGAGGTATCCC | 3-14-3 | 74.4 | 12 |
| 410535 | 6544 | 6563 | AGGATCTTGGTGAGGTATCC | 5-10-5 | 65.7 | 192 |
| 410582 | 6544 | 6563 | AGGATCTTGGTGAGGTATCC | 3-14-3 | 69.5 | 192 |
| 410657 | 6544 | 6563 | AGGATCTTGGTGAGGTATCC | 2-13-5 | 73.1 | 192 |
| 406010 | 6546 | 6565 | GCAGGATCTTGGTGAGGTAT | 5-10-5 | 56.9 | 193 |
| 406011 | 6548 | 6567 | ATGCAGGATCTTGGTGAGGT | 5-10-5 | 70.7 | 194 |
| 406012 | 6550 | 6569 | ACATGCAGGATCTTGGTGAG | 5-10-5 | 69.1 | 195 |
| 406013 | 6554 | 6573 | GAAGACATGCAGGATCTTGG | 5-10-5 | 77.4 | 196 |
| 395156 | 6557 | 6576 | ATGGAAGACATGCAGGATCT | 5-10-5 | 76.7 | 14 |
| 410749 | 6565 | 6584 | AGAAGGCCATGGAAGACATG | 5-10-5 | 59.4 | 197 |
| 410750 | 6575 | 6594 | GAAGCCAGGAAGAAGGCCAT | 5-10-5 | 57.5 | 198 |
| 399879 | 6583 | 6602 | TTCACCAGGAAGCCAGGAAG | 3-14-3 | 91.9 | 15 |
| 406014 | 6585 | 6604 | TCTTCACCAGGAAGCCAGGA | 5-10-5 | 94.0 | 199 |
| 406015 | 6590 | 6609 | ACTCATCTTCACCAGGAAGC | 5-10-5 | 78.8 | 200 |
| 406016 | 6592 | 6611 | CCACTCATCTTCACCAGGAA | 5-10-5 | 87.2 | 201 |
| 410730 | 6594 | 6613 | CGCCACTCATCTTCACCAGG | 5-10-5 | 85.4 | 202 |
| 406017 | 6596 | 6615 | GTCGCCACTCATCTTCACCA | 5-10-5 | 76.3 | 203 |
| 406018 | 6598 | 6617 | AGGTCGCCACTCATCTTCAC | 5-10-5 | 63.2 | 204 |
| 406019 | 6600 | 6619 | GCAGGTCGCCACTCATCTTC | 5-10-5 | 68.1 | 205 |
| 406020 | 6602 | 6621 | CAGCAGGTCGCCACTCATCT | 5-10-5 | 83.7 | 206 |
| 410731 | 6604 | 6623 | TCCAGCAGGTCGCCACTCAT | 5-10-5 | 72.9 | 207 |
| 395158 | 9130 | 9149 | CCTCGATGTAGTCGACATGG | 5-10-5 | 93.9 | 17 |
| 410752 | 9149 | 9168 | GCAAAGACAGAGGAGTCCTC | 5-10-5 | 76.3 | 209 |
| 406021 | 9207 | 9226 | TTCATCCGCCCGGTACCGTG | 5-10-5 | 79.6 | 210 |
| 406022 | 9209 | 9228 | TATTCATCCGCCCGGTACCG | 5-10-5 | 78.7 | 211 |
| 406023 | 9212 | 9231 | TGGTATTCATCCGCCCGGTA | 5-10-5 | 92.5 | 212 |
| 406024 | 9214 | 9233 | GCTGGTATTCATCCGCCCGG | 5-10-5 | 69.7 | 213 |
| 410732 | 9216 | 9235 | GGGCTGGTATTCATCCGCCC | 5-10-5 | 30.4 | 214 |

| Isis No. | 5' Target Site to SEQ ID NO: 2 | 3' Target Site to SEQ ID NO: 2 | Sequence 5'-3' | Motif | % inhibition | SEQ ID NO: |
|---|---|---|---|---|---|---|
| 399935 | 14601 | 14620 | AGGACCCAAGTCATCCTGCT | 3-14-3 | 81.1 | 96 |
| 399936 | 14631 | 14650 | GGCCATCAGCTGGCAATGCT | 3-14-3 | 89.0 | 124 |
| 410753 | 14877 | 14896 | ATACACCTCCACCAGGCTGC | 5-10-5 | 72.8 | 315 |
| 406025 | 14888 | 14907 | GTGTCTAGGAGATACACCTC | 5-10-5 | 74.2 | 216 |
| 406026 | 14893 | 14912 | TGCTGGTGTCTAGGAGATAC | 5-10-5 | 80.5 | 217 |
| 405869 | 14918 | 14937 | TCGATTTCCCGGTGGTCACT | 5-10-5 | 87.6 | 218 |
| 405870 | 14919 | 14938 | CTCGATTTCCCGGTGGTCAC | 5-10-5 | 83.3 | 219 |
| 405871 | 14920 | 14939 | CCTCGATTTCCCGGTGGTCA | 5-10-5 | 87.0 | 220 |
| 405872 | 14921 | 14940 | CCCTCGATTTCCCGGTGGTC | 5-10-5 | 88.2 | 221 |
| 399798 | 14922 | 14941 | GCCCTCGATTTCCCGGTGGT | 5-10-5 | 84.3 | 22 |
| 399954 | 14922 | 14941 | GCCCTCGATTTCCCGGTGGT | 3-14-3 | 90.3 | 22 |
| 405873 | 14923 | 14942 | TGCCCTCGATTTCCCGGTGG | 5-10-5 | 90.0 | 222 |
| 405874 | 14924 | 14943 | CTGCCCTCGATTTCCCGGTG | 5-10-5 | 91.4 | 223 |
| 405875 | 14925 | 14944 | CCTGCCCTCGATTTCCCGGT | 5-10-5 | 93.5 | 224 |
| 405876 | 14926 | 14945 | CCCTGCCCTCGATTTCCCGG | 5-10-5 | 90.1 | 225 |
| 406027 | 14930 | 14949 | ATGACCCTGCCCTCGATTTC | 5-10-5 | 73.9 | 226 |
| 406028 | 14932 | 14951 | CCATGACCCTGCCCTCGATT | 5-10-5 | 92.3 | 227 |
| 406029 | 14934 | 14953 | GACCATGACCCTGCCCTCGA | 5-10-5 | 91.4 | 228 |
| 406030 | 14938 | 14957 | CGGTGACCATGACCCTGCCC | 5-10-5 | 95.6 | 229 |
| 406031 | 14940 | 14959 | GTCGGTGACCATGACCCTGC | 5-10-5 | 89.6 | 230 |
| 410733 | 14942 | 14961 | AAGTCGGTGACCATGACCCT | 5-10-5 | 65.7 | 231 |
| 406032 | 14944 | 14963 | CGAAGTCGGTGACCATGACC | 5-10-5 | 88.5 | 232 |
| 410754 | 14954 | 14973 | GGCACATTCTCGAAGTCGGT | 5-10-5 | 80.1 | 233 |
| 395163 | 14979 | 14998 | GTGGAAGCGGGTCCCGTCCT | 5-10-5 | 83.9 | 25 |
| 410756 | 15254 | 15273 | GGTGGGTGCCATGACTGTCA | 5-10-5 | 67.1 | 235 |
| 406033 | 15261 | 15280 | CCTGCCAGGTGGGTGCCATG | 5-10-5 | 91.2 | 237 |
| 406034 | 15266 | 15285 | CCACCCCTGCCAGGTGGGTG | 5-10-5 | 59.3 | 238 |
| 406035 | 15271 | 15290 | GCTGACCACCCCTGCCAGGT | 5-10-5 | 91.7 | 239 |
| 410757 | 15279 | 15298 | TCCCGGCCGCTGACCACCCC | 5-10-5 | 88.9 | 240 |
| 406036 | 15283 | 15302 | GGCATCCCGGCCGCTGACCA | 5-10-5 | 84.0 | 241 |
| 406037 | 15286 | 15305 | GCCGGCATCCCGGCCGCTGA | 5-10-5 | 55.9 | 242 |
| 410536 | 15291 | 15310 | GCCACGCCGGCATCCCGGCC | 5-10-5 | 63.7 | 243 |
| 410658 | 15291 | 15310 | GCCACGCCGGCATCCCGGCC | 2-13-5 | 82.0 | 243 |
| 410583 | 15291 | 15310 | GCCACGCCGGCATCCCGGCC | 3-14-3 | 87.3 | 243 |
| 410537 | 15292 | 15311 | GGCCACGCCGGCATCCCGGC | 5-10-5 | 58.5 | 244 |
| 410659 | 15292 | 15311 | GGCCACGCCGGCATCCCGGC | 2-13-5 | 73.7 | 244 |
| 410584 | 15292 | 15311 | GGCCACGCCGGCATCCCGGC | 3-14-3 | 79.5 | 244 |
| 410660 | 15293 | 15312 | TGGCCACGCCGGCATCCCGG | 2-13-5 | 63.0 | 245 |
| 410585 | 15293 | 15312 | TGGCCACGCCGGCATCCCGG | 3-14-3 | 73.2 | 245 |
| 406038 | 15293 | 15312 | TGGCCACGCCGGCATCCCGG | 5-10-5 | 86.3 | 245 |
| 410661 | 15294 | 15313 | TTGGCCACGCCGGCATCCCG | 2-13-5 | 53.3 | 246 |
| 410586 | 15294 | 15313 | TTGGCCACGCCGGCATCCCG | 3-14-3 | 60.3 | 246 |
| 405877 | 15294 | 15313 | TTGGCCACGCCGGCATCCCG | 5-10-5 | 83.2 | 246 |
| 410587 | 15295 | 15314 | CTTGGCCACGCCGGCATCCC | 3-14-3 | 63.2 | 247 |
| 410662 | 15295 | 15314 | CTTGGCCACGCCGGCATCCC | 2-13-5 | 67.3 | 247 |
| 405878 | 15295 | 15314 | CTTGGCCACGCCGGCATCCC | 5-10-5 | 91.4 | 247 |
| 410588 | 15296 | 15315 | CCTTGGCCACGCCGGCATCC | 3-14-3 | 65.3 | 248 |
| 410663 | 15296 | 15315 | CCTTGGCCACGCCGGCATCC | 2-13-5 | 67.9 | 248 |
| 405879 | 15296 | 15315 | CCTTGGCCACGCCGGCATCC | 5-10-5 | 94.1 | 248 |
| 410589 | 15297 | 15316 | CCCTTGGCCACGCCGGCATC | 3-14-3 | 80.1 | 249 |
| 410664 | 15297 | 15316 | CCCTTGGCCACGCCGGCATC | 2-13-5 | 81.9 | 249 |
| 405880 | 15297 | 15316 | CCCTTGGCCACGCCGGCATC | 5-10-5 | 93.5 | 249 |
| 410665 | 15298 | 15317 | ACCCTTGGCCACGCCGGCAT | 2-13-5 | 78.7 | 28 |

| Isis No. | 5' Target Site to SEQ ID NO: 2 | 3' Target Site to SEQ ID NO: 2 | Sequence 5'-3' | Motif | % inhibition | SEQ ID NO: |
|---|---|---|---|---|---|---|
| 399887 | 15298 | 15317 | ACCCTTGGCCACGCCGGCAT | 3-14-3 | 91.9 | 28 |
| 395165 | 15298 | 15317 | ACCCTTGGCCACGCCGGCAT | 5-10-5 | 96.7 | 28 |
| 410590 | 15299 | 15318 | CACCCTTGGCCACGCCGGCA | 3-14-3 | 82.2 | 250 |
| 410666 | 15299 | 15318 | CACCCTTGGCCACGCCGGCA | 2-13-5 | 82.7 | 250 |
| 405881 | 15299 | 15318 | CACCCTTGGCCACGCCGGCA | 5-10-5 | 98.3 | 250 |
| 410667 | 15300 | 15319 | GCACCCTTGGCCACGCCGGC | 2-13-5 | 84.7 | 251 |
| 410591 | 15300 | 15319 | GCACCCTTGGCCACGCCGGC | 3-14-3 | 86.3 | 251 |
| 405882 | 15300 | 15319 | GCACCCTTGGCCACGCCGGC | 5-10-5 | 91.6 | 251 |
| 410668 | 15301 | 15320 | GGCACCCTTGGCCACGCCGG | 2-13-5 | 91.4 | 252 |
| 405883 | 15301 | 15320 | GGCACCCTTGGCCACGCCGG | 5-10-5 | 92.5 | 252 |
| 410592 | 15301 | 15320 | GGCACCCTTGGCCACGCCGG | 3-14-3 | 93.4 | 252 |
| 410669 | 15302 | 15321 | TGGCACCCTTGGCCACGCCG | 2-13-5 | 69.0 | 253 |
| 410593 | 15302 | 15321 | TGGCACCCTTGGCCACGCCG | 3-14-3 | 88.8 | 253 |
| 405884 | 15302 | 15321 | TGGCACCCTTGGCCACGCCG | 5-10-5 | 90.8 | 253 |
| 410670 | 15303 | 15322 | CTGGCACCCTTGGCCACGCC | 2-13-5 | 74.9 | 254 |
| 410594 | 15303 | 15322 | CTGGCACCCTTGGCCACGCC | 3-14-3 | 75.2 | 254 |
| 410538 | 15303 | 15322 | CTGGCACCCTTGGCCACGCC | 5-10-5 | 78.2 | 254 |
| 410539 | 15304 | 15323 | GCTGGCACCCTTGGCCACGC | 5-10-5 | 61.9 | 255 |
| 410595 | 15304 | 15323 | GCTGGCACCCTTGGCCACGC | 3-14-3 | 83.1 | 255 |
| 410671 | 15304 | 15323 | GCTGGCACCCTTGGCCACGC | 2-13-5 | 83.3 | 255 |
| 410758 | 15309 | 15328 | CGCATGCTGGCACCCTTGGC | 5-10-5 | 73.6 | 256 |
| 406039 | 15330 | 15349 | CAGTTGAGCACGCGCAGGCT | 5-10-5 | 91.2 | 257 |
| 406040 | 15332 | 15351 | GGCAGTTGAGCACGCGCAGG | 5-10-5 | 96.5 | 258 |
| 399888 | 15334 | 15353 | TTGGCAGTTGAGCACGCGCA | 3-14-3 | 90.9 | 29 |
| 395166 | 15334 | 15353 | TTGGCAGTTGAGCACGCGCA | 5-10-5 | 96.2 | 29 |
| 406041 | 15336 | 15355 | CCTTGGCAGTTGAGCACGCG | 5-10-5 | 96.6 | 259 |
| 399801 | 15339 | 15358 | TTCCCTTGGCAGTTGAGCAC | 5-10-5 | 95.6 | 30 |
| 406042 | 15341 | 15360 | CCTTCCCTTGGCAGTTGAGC | 5-10-5 | 92.0 | 260 |
| 406043 | 15345 | 15364 | GTGCCCTTCCCTTGGCAGTT | 5-10-5 | 91.9 | 261 |
| 406044 | 15347 | 15366 | CCGTGCCCTTCCCTTGGCAG | 5-10-5 | 95.4 | 262 |
| 410759 | 15358 | 15377 | GGTGCCGCTAACCGTGCCCT | 5-10-5 | 83.7 | 263 |
| 406045 | 18591 | 18610 | TGGCTTTTCCGAATAAACTC | 5-10-5 | 88.4 | 266 |
| 395168 | 18593 | 18612 | GCTGGCTTTTCCGAATAAAC | 5-10-5 | 91.9 | 32 |
| 405909 | 18595 | 18614 | CAGCTGGCTTTTCCGAATAA | 5-10-5 | 80.3 | 267 |
| 405910 | 18597 | 18616 | ACCAGCTGGCTTTTCCGAAT | 5-10-5 | 90.9 | 268 |
| 405911 | 18599 | 18618 | GGACCAGCTGGCTTTTCCGA | 5-10-5 | 88.0 | 269 |
| 405912 | 18603 | 18622 | GGCTGGACCAGCTGGCTTTT | 5-10-5 | 78.2 | 270 |
| 410761 | 18614 | 18633 | GTGGCCCCACAGGCTGGACC | 5-10-5 | 53.7 | 271 |
| 410762 | 18627 | 18646 | AGCAGCACCACCAGTGGCCC | 5-10-5 | 57.6 | 272 |
| 410763 | 18649 | 18668 | GCTGTACCCACCCGCCAGGG | 5-10-5 | 68.8 | 273 |
| 410764 | 18695 | 18714 | CGACCCCAGCCCTCGCCAGG | 5-10-5 | 66.3 | 274 |
| 399891 | 18705 | 18724 | GTGACCAGCACGACCCCAGC | 3-14-3 | 91.1 | 33 |
| 405913 | 18707 | 18726 | CGGTGACCAGCACGACCCCA | 5-10-5 | 93.8 | 275 |
| 405914 | 18709 | 18728 | AGCGGTGACCAGCACGACCC | 5-10-5 | 90.4 | 276 |
| 405915 | 18711 | 18730 | GCAGCGGTGACCAGCACGAC | 5-10-5 | 86.8 | 277 |
| 405916 | 18713 | 18732 | CGGCAGCGGTGACCAGCACG | 5-10-5 | 91.3 | 278 |
| 410734 | 18714 | 18733 | CCGGCAGCGGTGACCAGCAC | 5-10-5 | 65.8 | 279 |
| 405917 | 18717 | 18736 | TTGCCGGCAGCGGTGACCAG | 5-10-5 | 62.0 | 280 |
| 405918 | 18719 | 18738 | AGTTGCCGGCAGCGGTGACC | 5-10-5 | 33.5 | 281 |
| 405919 | 18721 | 18740 | GAAGTTGCCGGCAGCGGTGA | 5-10-5 | 68.2 | 282 |
| 405920 | 18723 | 18742 | CGGAAGTTGCCGGCAGCGGT | 5-10-5 | 86.2 | 283 |
| 405921 | 18725 | 18744 | CCCGGAAGTTGCCGGCAGCG | 5-10-5 | 85.5 | 284 |
| 405922 | 18727 | 18746 | GTCCCGGAAGTTGCCGGCAG | 5-10-5 | 86.0 | 285 |

| Isis No. | 5' Target Site to SEQ ID NO: 2 | 3' Target Site to SEQ ID NO: 2 | Sequence 5'-3' | Motif | % inhibition | SEQ ID NO: |
|---|---|---|---|---|---|---|
| 405923 | 19931 | 19950 | GGCATTGGTGGCCCCAACTG | 5-10-5 | 94.3 | 288 |
| 410767 | 19941 | 19960 | GCTGGTCTTGGGCATTGGTG | 5-10-5 | 65.1 | 289 |
| 405924 | 19954 | 19973 | CCCAGGGTCACCGGCTGGTC | 5-10-5 | 93.1 | 290 |
| 410735 | 19956 | 19975 | TCCCCAGGGTCACCGGCTGG | 5-10-5 | 78.1 | 291 |
| 405925 | 19958 | 19977 | AGTCCCCAGGGTCACCGGCT | 5-10-5 | 93.5 | 292 |
| 405926 | 19960 | 19979 | AAAGTCCCCAGGGTCACCGG | 5-10-5 | 94.6 | 293 |
| 405927 | 19964 | 19983 | CCCCAAAGTCCCCAGGGTCA | 5-10-5 | 94.5 | 294 |
| 405928 | 19969 | 19988 | TTGGTCCCCAAAGTCCCCAG | 5-10-5 | 90.0 | 295 |
| 405929 | 19973 | 19992 | AAAGTTGGTCCCCAAAGTCC | 5-10-5 | 85.5 | 296 |
| 399895 | 19976 | 19995 | GCCAAAGTTGGTCCCCAAAG | 3-14-3 | 84.6 | 36 |
| 395173 | 19976 | 19995 | GCCAAAGTTGGTCCCCAAAG | 5-10-5 | 94.8 | 36 |
| 405930 | 19978 | 19997 | CGGCCAAAGTTGGTCCCCAA | 5-10-5 | 92.9 | 297 |
| 405931 | 19980 | 19999 | AGCGGCCAAAGTTGGTCCCC | 5-10-5 | 88.8 | 298 |
| 405932 | 19982 | 20001 | ACAGCGGCCAAAGTTGGTCC | 5-10-5 | 90.6 | 299 |
| 405933 | 19984 | 20003 | ACACAGCGGCCAAAGTTGGT | 5-10-5 | NA | 300 |
| 405934 | 19986 | 20005 | CCACACAGCGGCCAAAGTTG | 5-10-5 | 92.7 | 301 |
| 405935 | 19990 | 20009 | AGGTCCACACAGCGGCCAAA | 5-10-5 | 86.0 | 302 |
| 410736 | 19992 | 20011 | AGAGGTCCACACAGCGGCCA | 5-10-5 | 73.8 | 303 |
| 405936 | 19994 | 20013 | AAAGAGGTCCACACAGCGGC | 5-10-5 | 93.9 | 304 |
| 410768 | 20016 | 20035 | CAATGATGTCCTCCCCTGGG | 5-10-5 | 79.7 | 305 |
| 405937 | 20023 | 20042 | GAGGCACCAATGATGTCCTC | 5-10-5 | 77.7 | 306 |
| 405938 | 20027 | 20046 | GCTGGAGGCACCAATGATGT | 5-10-5 | 75.5 | 307 |
| 405939 | 20029 | 20048 | TCGCTGGAGGCACCAATGAT | 5-10-5 | 70.6 | 308 |
| 405940 | 20031 | 20050 | AGTCGCTGGAGGCACCAATG | 5-10-5 | 84.4 | 309 |
| 405941 | 20033 | 20052 | GCAGTCGCTGGAGGCACCAA | 5-10-5 | 90.1 | 310 |
| 399804 | 20036 | 20055 | GCTGCAGTCGCTGGAGGCAC | 5-10-5 | 80.8 | 40 |
| 399960 | 20036 | 20055 | GCTGCAGTCGCTGGAGGCAC | 3-14-3 | 82.4 | 40 |
| 405942 | 20038 | 20057 | GTGCTGCAGTCGCTGGAGGC | 5-10-5 | 69.8 | 311 |
| 405943 | 20040 | 20059 | AGGTGCTGCAGTCGCTGGAG | 5-10-5 | 83.6 | 312 |
| 410737 | 20042 | 20061 | GCAGGTGCTGCAGTCGCTGG | 5-10-5 | 49.8 | 313 |
| 405944 | 20043 | 20062 | AGCAGGTGCTGCAGTCGCTG | 5-10-5 | 80.7 | 314 |
| 405945 | 20045 | 20064 | AAAGCAGGTGCTGCAGTCGC | 5-10-5 | 41.1 | 315 |
| 405946 | 20049 | 20068 | ACACAAAGCAGGTGCTGCAG | 5-10-5 | 70.4 | 316 |
| 405947 | 20051 | 20070 | TGACACAAAGCAGGTGCTGC | 5-10-5 | 72.5 | 317 |
| 410769 | 20061 | 20080 | TCCCACTCTGTGACACAAAG | 5-10-5 | 84.9 | 318 |
| 405949 | 20629 | 20648 | CAGCATCATGGCTGCAATGC | 5-10-5 | 84.9 | 320 |
| 405950 | 20631 | 20650 | GACAGCATCATGGCTGCAAT | 5-10-5 | 76.9 | 321 |
| 405951 | 20633 | 20652 | CAGACAGCATCATGGCTGCA | 5-10-5 | 75.4 | 322 |
| 405952 | 20637 | 20656 | TCGGCAGACAGCATCATGGC | 5-10-5 | 85.1 | 323 |
| 410738 | 20639 | 20658 | GCTCGGCAGACAGCATCATG | 5-10-5 | 68.4 | 324 |
| 405953 | 20641 | 20660 | CGGCTCGGCAGACAGCATCA | 5-10-5 | 93.6 | 325 |
| 405954 | 20643 | 20662 | TCCGGCTCGGCAGACAGCAT | 5-10-5 | 87.5 | 326 |
| 410770 | 20657 | 20676 | CGGCCAGGGTGAGCTCCGGC | 5-10-5 | 68.5 | 327 |
| 405955 | 20670 | 20689 | CTCTGCCTCAACTCGGCCAG | 5-10-5 | 94.2 | 328 |
| 405956 | 20672 | 20691 | GTCTCTGCCTCAACTCGGCC | 5-10-5 | 94.3 | 329 |
| 405958 | 20676 | 20695 | ATCAGTCTCTGCCTCAACTC | 5-10-5 | 80.3 | 331 |
| 405959 | 20678 | 20697 | GGATCAGTCTCTGCCTCAAC | 5-10-5 | 95.4 | 332 |
| 405960 | 20680 | 20699 | GTGGATCAGTCTCTGCCTCA | 5-10-5 | 90.1 | 333 |
| 405961 | 20682 | 20701 | AAGTGGATCAGTCTCTGCCT | 5-10-5 | 88.8 | 334 |
| 405962 | 20685 | 20704 | GAGAAGTGGATCAGTCTCTG | 5-10-5 | 56.1 | 335 |
| 410739 | 20687 | 20706 | CAGAGAAGTGGATCAGTCTC | 5-10-5 | NA | 336 |
| 405963 | 20689 | 20708 | GGCAGAGAAGTGGATCAGTC | 5-10-5 | 59.7 | 337 |
| 405964 | 20693 | 20712 | CTTTGGCAGAGAAGTGGATC | 5-10-5 | 45.3 | 338 |

| Isis No. | 5' Target Site to SEQ ID NO: 2 | 3' Target Site to SEQ ID NO: 2 | Sequence 5'-3' | Motif | % inhibition | SEQ ID NO: |
|---|---|---|---|---|---|---|
| 405965 | 20698 | 20717 | GACATCTTTGGCAGAGAAGT | 5-10-5 | 55.9 | 339 |
| 405966 | 20700 | 20719 | ATGACATCTTTGGCAGAGAA | 5-10-5 | 51.3 | 340 |
| 405967 | 20704 | 20723 | ATTGATGACATCTTTGGCAG | 5-10-5 | 64.4 | 341 |
| 405968 | 20706 | 20725 | TCATTGATGACATCTTTGGC | 5-10-5 | 74.6 | 342 |
| 399967 | 20709 | 20728 | GCCTCATTGATGACATCTTT | 3-14-3 | 80.1 | 48 |
| 405969 | 20711 | 20730 | AGGCCTCATTGATGACATCT | 5-10-5 | 63.0 | 343 |
| 405970 | 20713 | 20732 | CCAGGCCTCATTGATGACAT | 5-10-5 | 66.8 | 344 |
| 410740 | 20715 | 20734 | AACCAGGCCTCATTGATGAC | 5-10-5 | 46.8 | 345 |
| 405885 | 20717 | 20736 | GGAACCAGGCCTCATTGATG | 5-10-5 | 73.4 | 346 |
| 410596 | 20719 | 20738 | AGGGAACCAGGCCTCATTGA | 3-14-3 | NA | 348 |
| 410672 | 20719 | 20738 | AGGGAACCAGGCCTCATTGA | 2-13-5 | NA | 348 |
| 405887 | 20719 | 20738 | AGGGAACCAGGCCTCATTGA | 5-10-5 | NA | 348 |
| 410597 | 20720 | 20739 | CAGGGAACCAGGCCTCATTG | 3-14-3 | NA | 349 |
| 405888 | 20720 | 20739 | CAGGGAACCAGGCCTCATTG | 5-10-5 | NA | 349 |
| 410673 | 20720 | 20739 | CAGGGAACCAGGCCTCATTG | 2-13-5 | NA | 349 |
| 410674 | 20721 | 20740 | TCAGGGAACCAGGCCTCATT | 2-13-5 | 60.7 | 49 |
| 399812 | 20721 | 20740 | TCAGGGAACCAGGCCTCATT | 5-10-5 | 68.7 | 49 |
| 399968 | 20721 | 20740 | TCAGGGAACCAGGCCTCATT | 3-14-3 | 84.5 | 49 |
| 410598 | 20722 | 20741 | CTCAGGGAACCAGGCCTCAT | 3-14-3 | 74.5 | 350 |
| 410675 | 20722 | 20741 | CTCAGGGAACCAGGCCTCAT | 2-13-5 | 76.9 | 350 |
| 405889 | 20722 | 20741 | CTCAGGGAACCAGGCCTCAT | 5-10-5 | 80.2 | 350 |
| 410599 | 20723 | 20742 | CCTCAGGGAACCAGGCCTCA | 3-14-3 | 70.6 | 351 |
| 410676 | 20723 | 20742 | CCTCAGGGAACCAGGCCTCA | 2-13-5 | 77.8 | 351 |
| 405890 | 20723 | 20742 | CCTCAGGGAACCAGGCCTCA | 5-10-5 | 87.7 | 351 |
| 410600 | 20724 | 20743 | TCCTCAGGGAACCAGGCCTC | 3-14-3 | 76.5 | 352 |
| 410677 | 20724 | 20743 | TCCTCAGGGAACCAGGCCTC | 2-13-5 | 88.4 | 352 |
| 405891 | 20724 | 20743 | TCCTCAGGGAACCAGGCCTC | 5-10-5 | 96.1 | 352 |
| 405892 | 20725 | 20744 | GTCCTCAGGGAACCAGGCCT | 5-10-5 | 71.4 | 353 |
| 410601 | 20725 | 20744 | GTCCTCAGGGAACCAGGCCT | 3-14-3 | 72.7 | 353 |
| 410678 | 20725 | 20744 | GTCCTCAGGGAACCAGGCCT | 2-13-5 | 75.0 | 353 |
| 395178 | 20726 | 20745 | GGTCCTCAGGGAACCAGGCC | 5-10-5 | 76.7 | 50 |
| 410679 | 20726 | 20745 | GGTCCTCAGGGAACCAGGCC | 2-13-5 | 77.6 | 50 |
| 399900 | 20726 | 20745 | GGTCCTCAGGGAACCAGGCC | 3-14-3 | 92.0 | 50 |
| 408653 | 20727 | 20746 | TGGTCCTCAGGGAACCAGGC | 5-10-5 | 42.5 | 354 |
| 410602 | 20727 | 20746 | TGGTCCTCAGGGAACCAGGC | 3-14-3 | 66.5 | 354 |
| 410680 | 20727 | 20746 | TGGTCCTCAGGGAACCAGGC | 2-13-5 | 71.6 | 354 |
| 410603 | 20728 | 20747 | CTGGTCCTCAGGGAACCAGG | 3-14-3 | 40.8 | 355 |
| 410681 | 20728 | 20747 | CTGGTCCTCAGGGAACCAGG | 2-13-5 | 44.4 | 355 |
| 405971 | 20728 | 20747 | CTGGTCCTCAGGGAACCAGG | 5-10-5 | 65.5 | 355 |
| 410540 | 20729 | 20748 | GCTGGTCCTCAGGGAACCAG | 5-10-5 | 50.9 | 356 |
| 410682 | 20729 | 20748 | GCTGGTCCTCAGGGAACCAG | 2-13-5 | 54.1 | 356 |
| 410604 | 20729 | 20748 | GCTGGTCCTCAGGGAACCAG | 3-14-3 | 62.5 | 356 |
| 405972 | 20730 | 20749 | CGCTGGTCCTCAGGGAACCA | 5-10-5 | 77.6 | 357 |
| 405973 | 20735 | 20754 | GTACCCGCTGGTCCTCAGGG | 5-10-5 | 83.8 | 358 |
| 405974 | 20737 | 20756 | CAGTACCCGCTGGTCCTCAG | 5-10-5 | 89.0 | 359 |
| 399813 | 20740 | 20759 | GGTCAGTACCCGCTGGTCCT | 5-10-5 | 72.4 | 51 |
| 399969 | 20740 | 20759 | GGTCAGTACCCGCTGGTCCT | 3-14-3 | 93.4 | 51 |
| 410771 | 20785 | 20804 | ACCTGCCCCATGGGTGCTGG | 5-10-5 | NA | 360 |
| 405975 | 21088 | 21107 | CAAAACAGCTGCCAACCTGC | 5-10-5 | 77.4 | 361 |
| 405976 | 21093 | 21112 | TCCTGCAAAACAGCTGCCAA | 5-10-5 | 81.2 | 362 |
| 405977 | 21095 | 21114 | AGTCCTGCAAAACAGCTGCC | 5-10-5 | 89.5 | 363 |
| 410772 | 21106 | 21125 | GCTGACCATACAGTCCTGCA | 5-10-5 | 91.2 | 264 |
| 405978 | 21118 | 21137 | GGCCCCGAGTGTGCTGACCA | 5-10-5 | 95.3 | 365 |

| Isis No. | 5' Target Site to SEQ ID NO: 2 | 3' Target Site to SEQ ID NO: 2 | Sequence 5'-3' | Motif | % inhibition | SEQ ID NO: |
|---|---|---|---|---|---|---|
| 399904 | 21121 | 21140 | GTAGGCCCCGAGTGTGCTGA | 3-14-3 | 92.6 | 54 |
| 405979 | 21123 | 21142 | GTGTAGGCCCCGAGTGTGCT | 5-10-5 | 85.5 | 366 |
| 405980 | 21125 | 21144 | CCGTGTAGGCCCCGAGTGTG | 5-10-5 | 86.5 | 367 |
| 405981 | 21127 | 21146 | ATCCGTGTAGGCCCCGAGTG | 5-10-5 | 77.8 | 368 |
| 410741 | 21129 | 21148 | CCATCCGTGTAGGCCCCGAG | 5-10-5 | 78.4 | 369 |
| 405982 | 21131 | 21150 | GGCCATCCGTGTAGGCCCCG | 5-10-5 | 86.7 | 370 |
| 405983 | 21133 | 21152 | GTGGCCATCCGTGTAGGCCC | 5-10-5 | 73.1 | 371 |
| 405984 | 21181 | 21200 | CTGGAGCAGCTCAGCAGCTC | 5-10-5 | 83.4 | 372 |
| 405985 | 21183 | 21202 | AACTGGAGCAGCTCAGCAGC | 5-10-5 | 50.7 | 373 |
| 405986 | 21188 | 21207 | GGAGAAACTGGAGCAGCTCA | 5-10-5 | 75.6 | 374 |
| 405987 | 21190 | 21209 | CTGGAGAAACTGGAGCAGCT | 5-10-5 | 88.0 | 375 |
| 399868 | 21696 | 21715 | GGCACTGCCCTTCCACCAAA | 5-10-5 | 85.8 | 123 |
| 399905 | 22096 | 22115 | CGTTGTGGGCCCGGCAGACC | 3-14-3 | 91.2 | 57 |
| 395183 | 22096 | 22115 | CGTTGTGGGCCCGGCAGACC | 5-10-5 | 93.1 | 57 |
| 410541 | 22133 | 22152 | CACCTGGCAATGGCGTAGAC | 5-10-5 | 46.1 | 376 |
| 410605 | 22133 | 22152 | CACCTGGCAATGGCGTAGAC | 3-14-3 | 67.4 | 376 |
| 410683 | 22133 | 22152 | CACCTGGCAATGGCGTAGAC | 2-13-5 | 71.8 | 376 |
| 410606 | 22134 | 22153 | GCACCTGGCAATGGCGTAGA | 3-14-3 | 74.3 | 377 |
| 410542 | 22134 | 22153 | GCACCTGGCAATGGCGTAGA | 5-10-5 | 75.5 | 377 |
| 410684 | 22134 | 22153 | GCACCTGGCAATGGCGTAGA | 2-13-5 | 78.7 | 377 |
| 410543 | 22135 | 22154 | AGCACCTGGCAATGGCGTAG | 5-10-5 | 76.4 | 378 |
| 410685 | 22135 | 22154 | AGCACCTGGCAATGGCGTAG | 2-13-5 | 76.9 | 378 |
| 410607 | 22135 | 22154 | AGCACCTGGCAATGGCGTAG | 3-14-3 | 77.1 | 378 |
| 410544 | 22136 | 22155 | CAGCACCTGGCAATGGCGTA | 5-10-5 | 62.7 | 379 |
| 410608 | 22136 | 22155 | CAGCACCTGGCAATGGCGTA | 3-14-3 | 69.6 | 379 |
| 410686 | 22136 | 22155 | CAGCACCTGGCAATGGCGTA | 2-13-5 | 81.0 | 379 |
| 410545 | 22137 | 22156 | GCAGCACCTGGCAATGGCGT | 5-10-5 | 75.5 | 380 |
| 410687 | 22137 | 22156 | GCAGCACCTGGCAATGGCGT | 2-13-5 | 79.2 | 380 |
| 410609 | 22137 | 22156 | GCAGCACCTGGCAATGGCGT | 3-14-3 | 83.2 | 380 |
| 410610 | 22138 | 22157 | GGCAGCACCTGGCAATGGCG | 3-14-3 | 67.5 | 381 |
| 410688 | 22138 | 22157 | GGCAGCACCTGGCAATGGCG | 2-13-5 | 89.3 | 381 |
| 405988 | 22138 | 22157 | GGCAGCACCTGGCAATGGCG | 5-10-5 | 95.9 | 381 |
| 410546 | 22139 | 22158 | AGGCAGCACCTGGCAATGGC | 5-10-5 | 74.8 | 382 |
| 410689 | 22139 | 22158 | AGGCAGCACCTGGCAATGGC | 2-13-5 | 83.9 | 382 |
| 410611 | 22139 | 22158 | AGGCAGCACCTGGCAATGGC | 3-14-3 | 88.2 | 382 |
| 410612 | 22140 | 22159 | CAGGCAGCACCTGGCAATGG | 3-14-3 | 72.8 | 383 |
| 410690 | 22140 | 22159 | CAGGCAGCACCTGGCAATGG | 2-13-5 | 74.8 | 383 |
| 405989 | 22140 | 22159 | CAGGCAGCACCTGGCAATGG | 5-10-5 | 88.1 | 383 |
| 410547 | 22141 | 22160 | GCAGGCAGCACCTGGCAATG | 5-10-5 | 63.0 | 384 |
| 410691 | 22141 | 22160 | GCAGGCAGCACCTGGCAATG | 2-13-5 | 70.2 | 384 |
| 410613 | 22141 | 22160 | GCAGGCAGCACCTGGCAATG | 3-14-3 | 76.7 | 384 |
| 395184 | 22142 | 22161 | AGCAGGCAGCACCTGGCAAT | 5-10-5 | 68.5 | 58 |
| 410692 | 22142 | 22161 | AGCAGGCAGCACCTGGCAAT | 2-13-5 | 69.1 | 58 |
| 399906 | 22142 | 22161 | AGCAGGCAGCACCTGGCAAT | 3-14-3 | 94.2 | 58 |
| 410614 | 22143 | 22162 | TAGCAGGCAGCACCTGGCAA | 3-14-3 | 36.6 | 385 |
| 410548 | 22143 | 22162 | TAGCAGGCAGCACCTGGCAA | 5-10-5 | 75.0 | 385 |
| 410693 | 22143 | 22162 | TAGCAGGCAGCACCTGGCAA | 2-13-5 | 82.0 | 385 |
| 405990 | 22144 | 22163 | GTAGCAGGCAGCACCTGGCA | 5-10-5 | 96.8 | 386 |
| 410773 | 22189 | 22208 | TGGCCTCAGCTGGTGGAGCT | 5-10-5 | 61.3 | 387 |
| 410549 | 22199 | 22218 | GTCCCCATGCTGGCCTCAGC | 5-10-5 | 63.0 | 388 |
| 410615 | 22199 | 22218 | GTCCCCATGCTGGCCTCAGC | 3-14-3 | 72.5 | 388 |
| 410694 | 22199 | 22218 | GTCCCCATGCTGGCCTCAGC | 2-13-5 | 74.8 | 388 |
| 410550 | 22200 | 22219 | GGTCCCCATGCTGGCCTCAG | 5-10-5 | 69.4 | 389 |

| Isis No. | 5' Target Site to SEQ ID NO: 2 | 3' Target Site to SEQ ID NO: 2 | Sequence 5'-3' | Motif | % inhibition | SEQ ID NO: |
|---|---|---|---|---|---|---|
| 410616 | 22200 | 22219 | GGTCCCCATGCTGGCCTCAG | 3-14-3 | 80.7 | 389 |
| 410695 | 22200 | 22219 | GGTCCCCATGCTGGCCTCAG | 2-13-5 | 85.5 | 389 |
| 410551 | 22201 | 22220 | GGGTCCCCATGCTGGCCTCA | 5-10-5 | 68.7 | 390 |
| 410696 | 22201 | 22220 | GGGTCCCCATGCTGGCCTCA | 2-13-5 | 86.3 | 390 |
| 410617 | 22201 | 22220 | GGGTCCCCATGCTGGCCTCA | 3-14-3 | 86.5 | 390 |
| 410552 | 22202 | 22221 | CGGGTCCCCATGCTGGCCTC | 5-10-5 | 77.9 | 391 |
| 410618 | 22202 | 22221 | CGGGTCCCCATGCTGGCCTC | 3-14-3 | 86.7 | 391 |
| 410697 | 22202 | 22221 | CGGGTCCCCATGCTGGCCTC | 2-13-5 | 87.0 | 391 |
| 410553 | 22203 | 22222 | ACGGGTCCCCATGCTGGCCT | 5-10-5 | 72.8 | 392 |
| 410619 | 22203 | 22222 | ACGGGTCCCCATGCTGGCCT | 3-14-3 | 84.1 | 392 |
| 410698 | 22203 | 22222 | ACGGGTCCCCATGCTGGCCT | 2-13-5 | 87.0 | 392 |
| 410699 | 22204 | 22223 | CACGGGTCCCCATGCTGGCC | 2-13-5 | 79.5 | 59 |
| 395185 | 22204 | 22223 | CACGGGTCCCCATGCTGGCC | 5-10-5 | 92.7 | 59 |
| 399907 | 22204 | 22223 | CACGGGTCCCCATGCTGGCC | 3-14-3 | 93.7 | 59 |
| 410620 | 22205 | 22224 | ACACGGGTCCCCATGCTGGC | 3-14-3 | 74.4 | 393 |
| 410554 | 22205 | 22224 | ACACGGGTCCCCATGCTGGC | 5-10-5 | 79.7 | 393 |
| 410700 | 22205 | 22224 | ACACGGGTCCCCATGCTGGC | 2-13-5 | 84.4 | 393 |
| 410621 | 22206 | 22225 | GACACGGGTCCCCATGCTGG | 3-14-3 | 76.0 | 394 |
| 410701 | 22206 | 22225 | GACACGGGTCCCCATGCTGG | 2-13-5 | 83.4 | 394 |
| 405991 | 22206 | 22225 | GACACGGGTCCCCATGCTGG | 5-10-5 | 91.9 | 394 |
| 410555 | 22207 | 22226 | GGACACGGGTCCCCATGCTG | 5-10-5 | 77.0 | 395 |
| 410622 | 22207 | 22226 | GGACACGGGTCCCCATGCTG | 3-14-3 | 79.8 | 395 |
| 410702 | 22207 | 22226 | GGACACGGGTCCCCATGCTG | 2-13-5 | 85.0 | 395 |
| 410703 | 22208 | 22227 | TGGACACGGGTCCCCATGCT | 2-13-5 | 70.4 | 396 |
| 410623 | 22208 | 22227 | TGGACACGGGTCCCCATGCT | 3-14-3 | 78.9 | 396 |
| 405992 | 22208 | 22227 | TGGACACGGGTCCCCATGCT | 5-10-5 | 89.3 | 396 |
| 410704 | 22209 | 22228 | GTGGACACGGGTCCCCATGC | 2-13-5 | 78.6 | 397 |
| 410556 | 22209 | 22228 | GTGGACACGGGTCCCCATGC | 5-10-5 | 81.4 | 397 |
| 410624 | 22209 | 22228 | GTGGACACGGGTCCCCATGC | 3-14-3 | 82.8 | 397 |
| 410625 | 22210 | 22229 | AGTGGACACGGGTCCCCATG | 3-14-3 | 64.4 | 398 |
| 410705 | 22210 | 22229 | AGTGGACACGGGTCCCCATG | 2-13-5 | 74.7 | 398 |
| 405993 | 22210 | 22229 | AGTGGACACGGGTCCCCATG | 5-10-5 | 85.5 | 398 |
| 410706 | 22211 | 22230 | CAGTGGACACGGGTCCCCAT | 2-13-5 | 70.8 | 399 |
| 410557 | 22211 | 22230 | CAGTGGACACGGGTCCCCAT | 5-10-5 | 74.2 | 399 |
| 410626 | 22211 | 22230 | CAGTGGACACGGGTCCCCAT | 3-14-3 | 76.8 | 399 |
| 410627 | 22212 | 22231 | GCAGTGGACACGGGTCCCCA | 3-14-3 | 71.4 | 400 |
| 410707 | 22212 | 22231 | GCAGTGGACACGGGTCCCCA | 2-13-5 | 72.8 | 400 |
| 405994 | 22212 | 22231 | GCAGTGGACACGGGTCCCCA | 5-10-5 | 95.2 | 400 |
| 410708 | 22213 | 22232 | GGCAGTGGACACGGGTCCCC | 2-13-5 | 79.0 | 401 |
| 410628 | 22213 | 22232 | GGCAGTGGACACGGGTCCCC | 3-14-3 | 88.1 | 401 |
| 410558 | 22213 | 22232 | GGCAGTGGACACGGGTCCCC | 5-10-5 | 88.9 | 401 |
| 410629 | 22214 | 22233 | TGGCAGTGGACACGGGTCCC | 3-14-3 | 66.5 | 402 |
| 410709 | 22214 | 22233 | TGGCAGTGGACACGGGTCCC | 2-13-5 | 66.9 | 402 |
| 405995 | 22214 | 22233 | TGGCAGTGGACACGGGTCCC | 5-10-5 | 92.4 | 402 |
| 410630 | 22215 | 22234 | GTGGCAGTGGACACGGGTCC | 3-14-3 | 54.1 | 403 |
| 410710 | 22215 | 22234 | GTGGCAGTGGACACGGGTCC | 2-13-5 | 61.4 | 403 |
| 410559 | 22215 | 22234 | GTGGCAGTGGACACGGGTCC | 5-10-5 | 77.5 | 403 |
| 410711 | 22216 | 22235 | GGTGGCAGTGGACACGGGTC | 2-13-5 | NA | 404 |
| 410631 | 22216 | 22235 | GGTGGCAGTGGACACGGGTC | 3-14-3 | NA | 404 |
| 410560 | 22216 | 22235 | GGTGGCAGTGGACACGGGTC | 5-10-5 | 42.5 | 404 |
| 410712 | 22217 | 22236 | TGGTGGCAGTGGACACGGGT | 2-13-5 | NA | 405 |
| 410632 | 22217 | 22236 | TGGTGGCAGTGGACACGGGT | 3-14-3 | NA | 405 |
| 410561 | 22217 | 22236 | TGGTGGCAGTGGACACGGGT | 5-10-5 | NA | 405 |

| Isis No. | 5' Target Site to SEQ ID NO: 2 | 3' Target Site to SEQ ID NO: 2 | Sequence 5'-3' | Motif | % inhibition | SEQ ID NO: |
|---|---|---|---|---|---|---|
| 410774 | 22220 | 22239 | TGTTGGTGGCAGTGGACACG | 5-10-5 | 47.8 | 406 |
| 410776 | 23985 | 24004 | GTGCCAAGGTCCTCCACCTC | 5-10-5 | 77.3 | 408 |
| 410777 | 24005 | 24024 | TCAGCACAGGCGGCTTGTGG | 5-10-5 | 40.0 | 409 |
| 410778 | 24035 | 24054 | CCACGCACTGGTTGGGCTGA | 5-10-5 | 52.7 | 410 |
| 399908 | 24095 | 24114 | CTTTGCATTCCAGACCTGGG | 3-14-3 | 74.9 | 60 |
| 410713 | 24095 | 24114 | CTTTGCATTCCAGACCTGGG | 2-13-5 | 84.9 | 60 |
| 395186 | 24095 | 24114 | CTTTGCATTCCAGACCTGGG | 5-10-5 | 93.7 | 60 |
| 410714 | 24096 | 24115 | ACTTTGCATTCCAGACCTGG | 2-13-5 | 82.4 | 411 |
| 410633 | 24096 | 24115 | ACTTTGCATTCCAGACCTGG | 3-14-3 | 83.8 | 411 |
| 410562 | 24096 | 24115 | ACTTTGCATTCCAGACCTGG | 5-10-5 | 87.3 | 411 |
| 410715 | 24097 | 24116 | GACTTTGCATTCCAGACCTG | 2-13-5 | 80.5 | 412 |
| 410634 | 24097 | 24116 | GACTTTGCATTCCAGACCTG | 3-14-3 | 81.8 | 412 |
| 405996 | 24097 | 24116 | GACTTTGCATTCCAGACCTG | 5-10-5 | 91.0 | 412 |
| 410563 | 24098 | 24117 | TGACTTTGCATTCCAGACCT | 5-10-5 | 75.4 | 413 |
| 410635 | 24098 | 24117 | TGACTTTGCATTCCAGACCT | 3-14-3 | 75.9 | 413 |
| 410716 | 24098 | 24117 | TGACTTTGCATTCCAGACCT | 2-13-5 | 88.3 | 413 |
| 410636 | 24099 | 24118 | TTGACTTTGCATTCCAGACC | 3-14-3 | 61.3 | 414 |
| 410564 | 24099 | 24118 | TTGACTTTGCATTCCAGACC | 5-10-5 | 71.3 | 414 |
| 410717 | 24099 | 24118 | TTGACTTTGCATTCCAGACC | 2-13-5 | 76.7 | 414 |
| 410718 | 24100 | 24119 | CTTGACTTTGCATTCCAGAC | 2-13-5 | 55.8 | 61 |
| 399973 | 24100 | 24119 | CTTGACTTTGCATTCCAGAC | 3-14-3 | 82.1 | 61 |
| 399817 | 24100 | 24119 | CTTGACTTTGCATTCCAGAC | 5-10-5 | 93.6 | 61 |
| 405997 | 24102 | 24121 | TCCTTGACTTTGCATTCCAG | 5-10-5 | 95.6 | 415 |
| 410779 | 24115 | 24134 | CGGGATTCCATGCTCCTTGA | 5-10-5 | 79.7 | 416 |
| 410781 | 25994 | 26013 | GGAGGGCACTGCAGCCAGTC | 5-10-5 | 66.0 | 418 |
| 410719 | 26112 | 26131 | CAGATGGCAACGGCTGTCAC | 2-13-5 | 61.0 | 419 |
| 410637 | 26112 | 26131 | CAGATGGCAACGGCTGTCAC | 3-14-3 | 66.0 | 419 |
| 410565 | 26112 | 26131 | CAGATGGCAACGGCTGTCAC | 5-10-5 | 71.6 | 419 |
| 410638 | 26113 | 26132 | GCAGATGGCAACGGCTGTCA | 3-14-3 | 71.9 | 420 |
| 410720 | 26113 | 26132 | GCAGATGGCAACGGCTGTCA | 2-13-5 | 75.1 | 420 |
| 410566 | 26113 | 26132 | GCAGATGGCAACGGCTGTCA | 5-10-5 | 77.7 | 420 |
| 410639 | 26114 | 26133 | AGCAGATGGCAACGGCTGTC | 3-14-3 | 67.7 | 421 |
| 410721 | 26114 | 26133 | AGCAGATGGCAACGGCTGTC | 2-13-5 | 68.8 | 421 |
| 410567 | 26114 | 26133 | AGCAGATGGCAACGGCTGTC | 5-10-5 | 72.1 | 421 |
| 410568 | 26115 | 26134 | CAGCAGATGGCAACGGCTGT | 5-10-5 | 54.2 | 422 |
| 410640 | 26115 | 26134 | CAGCAGATGGCAACGGCTGT | 3-14-3 | 57.7 | 422 |
| 410722 | 26115 | 26134 | CAGCAGATGGCAACGGCTGT | 2-13-5 | 59.2 | 422 |
| 410569 | 26116 | 26135 | GCAGCAGATGGCAACGGCTG | 5-10-5 | 57.7 | 423 |
| 410641 | 26116 | 26135 | GCAGCAGATGGCAACGGCTG | 3-14-3 | 66.1 | 423 |
| 410723 | 26116 | 26135 | GCAGCAGATGGCAACGGCTG | 2-13-5 | 81.1 | 423 |
| 399909 | 26117 | 26136 | GGCAGCAGATGGCAACGGCT | 3-14-3 | 69.9 | 62 |
| 410724 | 26117 | 26136 | GGCAGCAGATGGCAACGGCT | 2-13-5 | 87.4 | 62 |
| 395187 | 26117 | 26136 | GGCAGCAGATGGCAACGGCT | 5-10-5 | 92.7 | 62 |
| 410642 | 26118 | 26137 | CGGCAGCAGATGGCAACGGC | 3-14-3 | 70.4 | 424 |
| 410725 | 26118 | 26137 | CGGCAGCAGATGGCAACGGC | 2-13-5 | 75.6 | 424 |
| 410570 | 26118 | 26137 | CGGCAGCAGATGGCAACGGC | 5-10-5 | 78.3 | 424 |
| 410571 | 26119 | 26138 | CCGGCAGCAGATGGCAACGG | 5-10-5 | 52.8 | 425 |
| 410643 | 26119 | 26138 | CCGGCAGCAGATGGCAACGG | 3-14-3 | 59.8 | 425 |
| 410726 | 26119 | 26138 | CCGGCAGCAGATGGCAACGG | 2-13-5 | 69.8 | 425 |
| 410644 | 26120 | 26139 | TCCGGCAGCAGATGGCAACG | 3-14-3 | 59.0 | 426 |
| 410727 | 26120 | 26139 | TCCGGCAGCAGATGGCAACG | 2-13-5 | 68.3 | 426 |
| 405998 | 26120 | 26139 | TCCGGCAGCAGATGGCAACG | 5-10-5 | 75.6 | 426 |
| 410572 | 26121 | 26140 | CTCCGGCAGCAGATGGCAAC | 5-10-5 | 40.9 | 427 |

| Isis No. | 5' Target Site to SEQ ID NO: 2 | 3' Target Site to SEQ ID NO: 2 | Sequence 5'-3' | Motif | % inhibition | SEQ ID NO: |
|---|---|---|---|---|---|---|
| 410728 | 26121 | 26140 | CTCCGGCAGCAGATGGCAAC | 2-13-5 | 56.4 | 427 |
| 410645 | 26121 | 26140 | CTCCGGCAGCAGATGGCAAC | 3-14-3 | 70.2 | 427 |
| 410729 | 26122 | 26141 | GCTCCGGCAGCAGATGGCAA | 2-13-5 | 67.7 | 428 |
| 410573 | 26122 | 26141 | GCTCCGGCAGCAGATGGCAA | 5-10-5 | 71.8 | 428 |
| 410646 | 26122 | 26141 | GCTCCGGCAGCAGATGGCAA | 3-14-3 | 72.8 | 428 |
| 410782 | 26132 | 26151 | CCAGGTGCCGGCTCCGGCAG | 5-10-5 | 43.2 | 429 |
| 410783 | 26142 | 26161 | GAGGCCTGCGCCAGGTGCCG | 5-10-5 | 63.7 | 430 |
| 399819 | 26316 | 26335 | CCCACTCAAGGGCCAGGCCA | 5-10-5 | 93.4 | 65 |
| 399912 | 26404 | 26423 | ATGCCCCACAGTGAGGGAGG | 3-14-3 | 84.3 | 66 |
| 405893 | 26635 | 26654 | ATGAGGGCCATCAGCACCTT | 5-10-5 | 93.9 | 431 |
| 405894 | 26636 | 26655 | GATGAGGGCCATCAGCACCT | 5-10-5 | 93.9 | 432 |
| 405895 | 26637 | 26656 | AGATGAGGGCCATCAGCACC | 5-10-5 | 91.8 | 433 |
| 405896 | 26638 | 26657 | GAGATGAGGGCCATCAGCAC | 5-10-5 | 88.5 | 434 |
| 395194 | 26639 | 26658 | GGAGATGAGGGCCATCAGCA | 5-10-5 | 90.0 | 69 |
| 399916 | 26639 | 26658 | GGAGATGAGGGCCATCAGCA | 3-14-3 | 94.5 | 69 |
| 405897 | 26640 | 26659 | TGGAGATGAGGGCCATCAGC | 5-10-5 | 85.1 | 435 |
| 405898 | 26641 | 26660 | CTGGAGATGAGGGCCATCAG | 5-10-5 | 86.9 | 436 |
| 405899 | 26642 | 26661 | GCTGGAGATGAGGGCCATCA | 5-10-5 | 91.5 | 437 |
| 405900 | 26643 | 26662 | AGCTGGAGATGAGGGCCATC | 5-10-5 | 83.7 | 438 |
| 405901 | 26709 | 26728 | GCTAGATGCCATCCAGAAAG | 5-10-5 | 88.4 | 439 |
| 405902 | 26710 | 26729 | GGCTAGATGCCATCCAGAAA | 5-10-5 | 89.3 | 440 |
| 405903 | 26711 | 26730 | TGGCTAGATGCCATCCAGAA | 5-10-5 | 92.6 | 441 |
| 405904 | 26712 | 26731 | CTGGCTAGATGCCATCCAGA | 5-10-5 | 90.4 | 442 |
| 399821 | 26713 | 26732 | TCTGGCTAGATGCCATCCAG | 5-10-5 | 91.7 | 71 |
| 405905 | 26714 | 26733 | CTCTGGCTAGATGCCATCCA | 5-10-5 | 90.7 | 443 |
| 405906 | 26715 | 26734 | CCTCTGGCTAGATGCCATCC | 5-10-5 | 93.3 | 444 |
| 405907 | 26716 | 26735 | GCCTCTGGCTAGATGCCATC | 5-10-5 | 90.2 | 445 |
| 405908 | 26717 | 26736 | AGCCTCTGGCTAGATGCCAT | 5-10-5 | 83.3 | 446 |
| 399978 | 26795 | 26814 | AGCCTGGCATAGAGCAGAGT | 3-14-3 | 96.4 | 73 |

Antisense oligonucleotides that exhibited less than 30% inhibition of PCSK9 mRNA levels were marked with "NA".

Antisense oligonucleotides with the following ISIS Nos exhibited at least 80% inhibition of PCSK9 mRNA levels: 395152, 395153, 395155, 395158, 395163, 395165, 395166, 395168, 395173, 395183, 395185, 395186, 395187, 395194, 399798, 399801, 399804, 399817, 399819, 399821, 399868, 399877, 399879, 399887, 399888, 399891, 399895, 399900, 399904, 399905, 399906, 399907, 399912, 399916, 399935, 399936, 399954, 399960, 399967, 399968, 399969, 399973, 399978, 405861, 405862, 405863, 405864, 405865, 405866, 405869, 405870, 405871, 405872, 405873, 405874, 405875, 405876, 405877, 405878, 405879, 405880, 405881, 405882, 405883, 405884, 405889, 405890, 405891, 405893, 405894, 405895, 405896, 405897, 405898, 405899, 405900, 405901, 405902, 405903, 405904, 405905, 405906, 405907, 405908, 405909, 405910, 405911, 405913, 405914, 405915, 405916, 405920, 405921, 405922, 405923, 405924, 405925, 405926, 405927, 405928, 405929, 405930, 405931, 405932, 405934, 405935, 405936,

405940, 405941, 405943, 405944, 405949, 405952, 405953, 405954, 405955, 405956, 405958, 405959, 405960, 405961, 405973, 405974, 405976, 405977, 405978, 405979, 405980, 405982, 405984, 405987, 405988, 405989, 405990, 405991, 405992, 405993, 405994, 405995, 405996, 405997, 406003, 406005, 406008, 406009, 406014, 406016, 406020, 406023, 406026, 406028, 406029, 406030, 406031, 406032, 406033, 406035, 406036, 406038, 406039, 406040, 406041, 406042, 406043, 406044, 406045, 410530, 410556, 410558, 410562, 410578, 410583, 410589, 410590, 410591, 410592, 410593, 410595, 410609, 410611, 410616, 410617, 410618, 410619, 410624, 410628, 410633, 410634, 410647, 410648, 410650, 410652, 410658, 410664, 410666, 410667, 410668, 410671, 410677, 410686, 410688, 410689, 410693, 410695, 410696, 410697, 410698, 410700, 410701, 410702, 410713, 410714, 410715, 410716, 410723, 410724, 410730, 410754, 410757, 410759, 410769, and 410772. The target segments to which these antisense oligonucleotides are targeted are active target segments. The target regions to which these antisense oligonucleotides are targeted are active target regions.

ISIS Nos 395152, 395155, 395158, 395165, 395166, 395168, 395173, 395183, 395185, 395186, 395187, 395194, 399801, 399817, 399819, 399821, 399868, 399877, 399879, 399887, 399888, 399891, 399900, 399904, 399905, 399906, 399907, 399916, 399936, 399954, 399969, 399978, 405861, 405862, 405864, 405869, 405871, 405872, 405873, 405874, 405875, 405876, 405878, 405879, 405880, 405881, 405882, 405883, 405884, 405890, 405891, 405893, 405894, 405895, 405896, 405897, 405898, 405899, 405901, 405902, 405903, 405904, 405905, 405906, 405907, 405910, 405911, 405913, 405914, 405915, 405916, 405920, 405921, 405922, 405923, 405924, 405925, 405926, 405927, 405928, 405929, 405930, 405931, 405932, 405934, 405935, 405936, 405941, 405952, 405953, 405954, 405955, 405956, 405959, 405960, 405961, 405974, 405977, 405978, 405979, 405980, 405982, 405987, 405988, 405989, 405990, 405991, 405992, 405993, 405994, 405995, 405996, 405997, 406008, 406009, 406014, 406016, 406023, 406028, 406029, 406030, 406031, 406032, 406033, 406035, 406038, 406039, 406040, 406041, 406042, 406043, 406044, 406045, 410558, 410562, 410583, 410591, 410592, 410593, 410611, 410617, 410618, 410628, 410647, 410650, 410668, 410677, 410688, 410695, 410696, 410697, 410698, 410702, 410716, 410724, 410730, 410757, and 410772 each exhibited at least 85% inhibition of PCSK9 mRNA levels.

ISIS Nos 395152, 395155, 395158, 395165, 395166, 395168, 395173, 395183, 395185, 395186, 395187, 399801, 399817, 399819, 399821, 399877, 399879, 399887, 399888, 399891, 399900, 399904, 399905, 399906, 399907, 399916, 399969, 399978, 405862, 405864, 405874, 405875, 405878, 405879, 405880, 405881, 405882, 405883, 405884, 405891, 405893, 405894,

405895, 405899, 405903, 405906, 405910, 405913, 405916, 405923, 405924, 405925, 405926, 405927, 405930, 405934, 405936, 405953, 405955, 405956, 405959, 405978, 405988, 405990, 405991, 405994, 405995, 405996, 405997, 406008, 406014, 406023, 406028, 406029, 406030, 406033, 406035, 406039, 406040, 406041, 406042, 406043, 406044, 410592, 410647, 410668, and 410772 each exhibited at least 90% inhibition of PCSK9 mRNA levels.

ISIS Nos 395165, 395166, 399801, 399978, 405881, 405891, 405959, 405978, 405988, 405990, 405994, 405997, 406008, 406030, 406040, 406041, and 406044 each exhibited at least 95% inhibition of PCSK9 mRNA levels.

**Table 18: Antisense inhibition of PCSK9 in human cells (HepB3) targeting SEQ ID NO: 3**

| Isis No. | 5' Target Site to SEQ ID NO: 3 | 3' Target Site to SEQ ID NO: 3 | Sequence 5'-3' | Motif | % inhibition | SEQ ID NO: |
|---|---|---|---|---|---|---|
| 399935 | 1075 | 1094 | AGGACCCAAGTCATCCTGCT | 3-14-3 | 81.1 | 96 |
| 399936 | 1105 | 1124 | GGCCATCAGCTGGCAATGCT | 3-14-3 | 89.0 | 124 |
| 410753 | 1351 | 1370 | ATACACCTCCACCAGGCTGC | 5-10-5 | 72.8 | 215 |
| 406025 | 1362 | 1381 | GTGTCTAGGAGATACACCTC | 5-10-5 | 74.2 | 216 |
| 406026 | 1367 | 1386 | TGCTGGTGTCTAGGAGATAC | 5-10-5 | 80.5 | 217 |
| 405869 | 1392 | 1411 | TCGATTTCCCGGTGGTCACT | 5-10-5 | 87.6 | 218 |
| 405870 | 1393 | 1412 | CTCGATTTCCCGGTGGTCAC | 5-10-5 | 83.3 | 219 |
| 405871 | 1394 | 1413 | CCTCGATTTCCCGGTGGTCA | 5-10-5 | 87.0 | 220 |
| 405872 | 1395 | 1414 | CCCTCGATTTCCCGGTGGTC | 5-10-5 | 88.2 | 221 |
| 399798 | 1396 | 1415 | GCCCTCGATTTCCCGGTGGT | 5-10-5 | 84.3 | 22 |
| 399954 | 1396 | 1415 | GCCCTCGATTTCCCGGTGGT | 3-14-3 | 90.3 | 22 |
| 405873 | 1397 | 1416 | TGCCCTCGATTTCCCGGTGG | 5-10-5 | 90.0 | 222 |
| 405874 | 1398 | 1417 | CTGCCCTCGATTTCCCGGTG | 5-10-5 | 91.4 | 223 |
| 405875 | 1399 | 1418 | CCTGCCCTCGATTTCCCGGT | 5-10-5 | 93.5 | 224 |
| 405876 | 1400 | 1419 | CCCTGCCCTCGATTTCCCGG | 5-10-5 | 90.1 | 225 |
| 406027 | 1404 | 1423 | ATGACCCTGCCCTCGATTTC | 5-10-5 | 73.9 | 226 |
| 406028 | 1406 | 1425 | CCATGACCCTGCCCTCGATT | 5-10-5 | 92.3 | 227 |
| 406029 | 1408 | 1427 | GACCATGACCCTGCCCTCGA | 5-10-5 | 91.4 | 228 |
| 406030 | 1412 | 1431 | CGGTGACCATGACCCTGCCC | 5-10-5 | 95.6 | 229 |
| 406031 | 1414 | 1433 | GTCGGTGACCATGACCCTGC | 5-10-5 | 89.6 | 230 |
| 410733 | 1416 | 1435 | AAGTCGGTGACCATGACCCT | 5-10-5 | 65.7 | 231 |
| 406032 | 1418 | 1437 | CGAAGTCGGTGACCATGACC | 5-10-5 | 88.5 | 232 |
| 410754 | 1428 | 1447 | GGCACATTCTCGAAGTCGGT | 5-10-5 | 80.1 | 233 |
| 395163 | 1453 | 1472 | GTGGAAGCGGGTCCCGTCCT | 5-10-5 | 83.9 | 25 |
| 410755 | 1463 | 1482 | TGGCCTGTCTGTGGAAGCGG | 5-10-5 | NA | 234 |
| 410756 | 1490 | 1509 | GGTGGGTGCCATGACTGTCA | 5-10-5 | 67.1 | 235 |
| 406033 | 1497 | 1516 | CCTGCCAGGTGGGTGCCATG | 5-10-5 | 91.2 | 237 |
| 406034 | 1502 | 1521 | CCACCCCTGCCAGGTGGGTG | 5-10-5 | 59.3 | 238 |
| 406035 | 1507 | 1526 | GCTGACCACCCCTGCCAGGT | 5-10-5 | 91.7 | 239 |
| 410757 | 1515 | 1534 | TCCCGGCCGCTGACCACCCC | 5-10-5 | 88.9 | 240 |
| 406036 | 1519 | 1538 | GGCATCCCGGCCGCTGACCA | 5-10-5 | 84.0 | 241 |
| 406037 | 1522 | 1541 | GCCGGCATCCCGGCCGCTGA | 5-10-5 | 55.9 | 242 |
| 410536 | 1527 | 1546 | GCCACGCCGGCATCCCGGCC | 5-10-5 | 63.7 | 243 |
| 410658 | 1527 | 1546 | GCCACGCCGGCATCCCGGCC | 2-13-5 | 82.0 | 243 |

| Isis No. | 5' Target Site to SEQ ID NO: 3 | 3' Target Site to SEQ ID NO: 3 | Sequence 5'-3' | Motif | % inhibition | SEQ ID NO: |
|---|---|---|---|---|---|---|
| 410583 | 1527 | 1546 | GCCACGCCGGCATCCCGGCC | 3-14-3 | 87.3 | 243 |
| 410537 | 1528 | 1547 | GGCCACGCCGGCATCCCGGC | 5-10-5 | 58.5 | 244 |
| 410659 | 1528 | 1547 | GGCCACGCCGGCATCCCGGC | 2-13-5 | 73.7 | 244 |
| 410584 | 1528 | 1547 | GGCCACGCCGGCATCCCGGC | 3-14-3 | 79.5 | 244 |
| 410660 | 1529 | 1548 | TGGCCACGCCGGCATCCCGG | 2-13-5 | 63.0 | 245 |
| 410585 | 1529 | 1548 | TGGCCACGCCGGCATCCCGG | 3-14-3 | 73.2 | 245 |
| 406038 | 1529 | 1548 | TGGCCACGCCGGCATCCCGG | 5-10-5 | 86.3 | 245 |
| 410661 | 1530 | 1549 | TTGGCCACGCCGGCATCCCG | 2-13-5 | 53.3 | 246 |
| 410586 | 1530 | 1549 | TTGGCCACGCCGGCATCCCG | 3-14-3 | 60.3 | 246 |
| 405877 | 1530 | 1549 | TTGGCCACGCCGGCATCCCG | 5-10-5 | 83.2 | 246 |
| 410587 | 1531 | 1550 | CTTGGCCACGCCGGCATCCC | 3-14-3 | 63.2 | 247 |
| 410662 | 1531 | 1550 | CTTGGCCACGCCGGCATCCC | 2-13-5 | 67.3 | 247 |
| 405878 | 1531 | 1550 | CTTGGCCACGCCGGCATCCC | 5-10-5 | 91.4 | 247 |
| 410588 | 1532 | 1551 | CCTTGGCCACGCCGGCATCC | 3-14-3 | 65.3 | 248 |
| 410663 | 1532 | 1551 | CCTTGGCCACGCCGGCATCC | 2-13-5 | 67.9 | 248 |
| 405879 | 1532 | 1551 | CCTTGGCCACGCCGGCATCC | 5-10-5 | 94.1 | 248 |
| 410589 | 1533 | 1552 | CCCTTGGCCACGCCGGCATC | 3-14-3 | 80.1 | 249 |
| 410664 | 1533 | 1552 | CCCTTGGCCACGCCGGCATC | 2-13-5 | 81.9 | 249 |
| 405880 | 1533 | 1552 | CCCTTGGCCACGCCGGCATC | 5-10-5 | 93.5 | 249 |
| 410665 | 1534 | 1553 | ACCCTTGGCCACGCCGGCAT | 2-13-5 | 78.7 | 28 |
| 399887 | 1534 | 1553 | ACCCTTGGCCACGCCGGCAT | 3-14-3 | 91.9 | 28 |
| 395165 | 1534 | 1553 | ACCCTTGGCCACGCCGGCAT | 5-10-5 | 96.7 | 28 |
| 410590 | 1535 | 1554 | CACCCTTGGCCACGCCGGCA | 3-14-3 | 82.2 | 250 |
| 410666 | 1535 | 1554 | CACCCTTGGCCACGCCGGCA | 2-13-5 | 82.7 | 250 |
| 405881 | 1535 | 1554 | CACCCTTGGCCACGCCGGCA | 5-10-5 | 98.3 | 250 |
| 410667 | 1536 | 1555 | GCACCCTTGGCCACGCCGGC | 2-13-5 | 84.7 | 251 |
| 410591 | 1536 | 1555 | GCACCCTTGGCCACGCCGGC | 3-14-3 | 86.3 | 251 |
| 405882 | 1536 | 1555 | GCACCCTTGGCCACGCCGGC | 5-10-5 | 91.6 | 251 |
| 410668 | 1537 | 1556 | GGCACCCTTGGCCACGCCGG | 2-13-5 | 91.4 | 252 |
| 405883 | 1537 | 1556 | GGCACCCTTGGCCACGCCGG | 5-10-5 | 92.5 | 252 |
| 410592 | 1537 | 1556 | GGCACCCTTGGCCACGCCGG | 3-14-3 | 93.4 | 252 |
| 410669 | 1538 | 1557 | TGGCACCCTTGGCCACGCCG | 2-13-5 | 69.0 | 253 |
| 410593 | 1538 | 1557 | TGGCACCCTTGGCCACGCCG | 3-14-3 | 88.8 | 253 |
| 405884 | 1538 | 1557 | TGGCACCCTTGGCCACGCCG | 5-10-5 | 90.8 | 253 |
| 410670 | 1539 | 1558 | CTGGCACCCTTGGCCACGCC | 2-13-5 | 74.9 | 254 |
| 410594 | 1539 | 1558 | CTGGCACCCTTGGCCACGCC | 3-14-3 | 75.2 | 254 |
| 410538 | 1539 | 1558 | CTGGCACCCTTGGCCACGCC | 5-10-5 | 78.2 | 254 |
| 410539 | 1540 | 1559 | GCTGGCACCCTTGGCCACGC | 5-10-5 | 61.9 | 255 |
| 410595 | 1540 | 1559 | GCTGGCACCCTTGGCCACGC | 3-14-3 | 83.1 | 255 |
| 410671 | 1540 | 1559 | GCTGGCACCCTTGGCCACGC | 2-13-5 | 83.3 | 255 |
| 410758 | 1545 | 1564 | CGCATGCTGGCACCCTTGGC | 5-10-5 | 73.6 | 256 |
| 406039 | 1566 | 1585 | CAGTTGAGCACGCGCAGGCT | 5-10-5 | 91.2 | 257 |
| 406040 | 1568 | 1587 | GGCAGTTGAGCACGCGCAGG | 5-10-5 | 96.5 | 258 |
| 399888 | 1570 | 1589 | TTGGCAGTTGAGCACGCGCA | 3-14-3 | 90.9 | 29 |
| 395166 | 1570 | 1589 | TTGGCAGTTGAGCACGCGCA | 5-10-5 | 96.2 | 29 |
| 406041 | 1572 | 1591 | CCTTGGCAGTTGAGCACGCG | 5-10-5 | 96.6 | 259 |
| 399801 | 1575 | 1594 | TTCCCTTGGCAGTTGAGCAC | 5-10-5 | 95.6 | 30 |
| 406042 | 1577 | 1596 | CCTTCCCTTGGCAGTTGAGC | 5-10-5 | 92.0 | 260 |
| 406043 | 1581 | 1600 | GTGCCCTTCCCTTGGCAGTT | 5-10-5 | 91.9 | 261 |
| 406044 | 1583 | 1602 | CCGTGCCCTTCCCTTGGCAG | 5-10-5 | 95.4 | 262 |
| 410759 | 1594 | 1613 | GGTGCCGCTAACCGTGCCCT | 5-10-5 | 83.7 | 263 |
| 410760 | 1618 | 1637 | CCGAATAAACTCCAGGCCTA | 5-10-5 | 96.7 | 265 |
| 406045 | 1626 | 1645 | TGGCTTTTCCGAATAAACTC | 5-10-5 | 88.4 | 266 |

| Isis No. | 5' Target Site to SEQ ID NO: 3 | 3' Target Site to SEQ ID NO: 3 | Sequence 5'-3' | Motif | % inhibition | SEQ ID NO: |
|---|---|---|---|---|---|---|
| 395168 | 1628 | 1647 | GCTGGCTTTTCCGAATAAAC | 5-10-5 | 91.9 | 32 |
| 405909 | 1630 | 1649 | CAGCTGGCTTTTCCGAATAA | 5-10-5 | 80.3 | 267 |
| 405910 | 1632 | 1651 | ACCAGCTGGCTTTTCCGAAT | 5-10-5 | 90.9 | 268 |
| 405911 | 1634 | 1653 | GGACCAGCTGGCTTTTCCGA | 5-10-5 | 88.0 | 269 |
| 405912 | 1638 | 1657 | GGCTGGACCAGCTGGCTTTT | 5-10-5 | 78.2 | 270 |
| 410761 | 1649 | 1668 | GTGGCCCCACAGGCTGGACC | 5-10-5 | 53.7 | 271 |
| 410762 | 1662 | 1681 | AGCAGCACCACCAGTGGCCC | 5-10-5 | 57.6 | 272 |
| 410763 | 1684 | 1703 | GCTGTACCCACCCGCCAGGG | 5-10-5 | 68.8 | 273 |
| 410764 | 1730 | 1749 | CGACCCCAGCCCTCGCCAGG | 5-10-5 | 66.3 | 274 |
| 399891 | 1740 | 1759 | GTGACCAGCACGACCCCAGC | 3-14-3 | 91.1 | 33 |
| 405913 | 1742 | 1761 | CGGTGACCAGCACGACCCCA | 5-10-5 | 93.8 | 275 |
| 405914 | 1744 | 1763 | AGCGGTGACCAGCACGACCC | 5-10-5 | 90.4 | 276 |
| 405915 | 1746 | 1765 | GCAGCGGTGACCAGCACGAC | 5-10-5 | 86.8 | 277 |
| 405916 | 1748 | 1767 | CGGCAGCGGTGACCAGCACG | 5-10-5 | 91.3 | 278 |
| 410734 | 1749 | 1768 | CCGGCAGCGGTGACCAGCAC | 5-10-5 | 65.8 | 249 |
| 405917 | 1752 | 1771 | TTGCCGGCAGCGGTGACCAG | 5-10-5 | 62.0 | 280 |
| 405918 | 1754 | 1773 | AGTTGCCGGCAGCGGTGACC | 5-10-5 | 33.5 | 281 |
| 405919 | 1756 | 1775 | GAAGTTGCCGGCAGCGGTGA | 5-10-5 | 68.2 | 282 |
| 405920 | 1758 | 1777 | CGGAAGTTGCCGGCAGCGGT | 5-10-5 | 86.2 | 283 |
| 405921 | 1760 | 1779 | CCCGGAAGTTGCCGGCAGCG | 5-10-5 | 85.5 | 284 |
| 405922 | 1762 | 1781 | GTCCCGGAAGTTGCCGGCAG | 5-10-5 | 86.0 | 285 |
| 405937 | 1820 | 1839 | GAGGCACCAATGATGTCCTC | 5-10-5 | 77.7 | 306 |
| 405938 | 1824 | 1843 | GCTGGAGGCACCAATGATGT | 5-10-5 | 75.5 | 307 |
| 405939 | 1826 | 1845 | TCGCTGGAGGCACCAATGAT | 5-10-5 | 70.6 | 308 |
| 405940 | 1828 | 1847 | AGTCGCTGGAGGCACCAATG | 5-10-5 | 84.4 | 309 |
| 405941 | 1830 | 1849 | GCAGTCGCTGGAGGCACCAA | 5-10-5 | 90.1 | 310 |
| 399804 | 1833 | 1852 | GCTGCAGTCGCTGGAGGCAC | 5-10-5 | 80.8 | 40 |
| 399960 | 1833 | 1852 | GCTGCAGTCGCTGGAGGCAC | 3-14-3 | 82.4 | 40 |
| 405942 | 1835 | 1854 | GTGCTGCAGTCGCTGGAGGC | 5-10-5 | 69.8 | 311 |
| 405943 | 1837 | 1856 | AGGTGCTGCAGTCGCTGGAG | 5-10-5 | 83.6 | 312 |
| 410737 | 1839 | 1858 | GCAGGTGCTGCAGTCGCTGG | 5-10-5 | 49.8 | 313 |
| 405944 | 1840 | 1859 | AGCAGGTGCTGCAGTCGCTG | 5-10-5 | 80.7 | 314 |
| 405945 | 1842 | 1861 | AAAGCAGGTGCTGCAGTCGC | 5-10-5 | 41.1 | 315 |
| 405946 | 1846 | 1865 | ACACAAAGCAGGTGCTGCAG | 5-10-5 | 70.4 | 316 |
| 405947 | 1848 | 1867 | TGACACAAAGCAGGTGCTGC | 5-10-5 | 72.5 | 317 |
| 410769 | 1858 | 1877 | TCCCACTCTGTGACACAAAG | 5-10-5 | 84.9 | 318 |
| 405948 | 1900 | 1919 | TCATGGCTGCAATGCCAGCC | 5-10-5 | 45.9 | 319 |
| 399806 | 1903 | 1922 | GCATCATGGCTGCAATGCCA | 5-10-5 | 82.8 | 42 |
| 399962 | 1903 | 1922 | GCATCATGGCTGCAATGCCA | 3-14-3 | 86.1 | 42 |
| 405949 | 1905 | 1924 | CAGCATCATGGCTGCAATGC | 5-10-5 | 84.9 | 320 |
| 405950 | 1907 | 1926 | GACAGCATCATGGCTGCAAT | 5-10-5 | 76.9 | 321 |
| 405951 | 1909 | 1928 | CAGACAGCATCATGGCTGCA | 5-10-5 | 75.4 | 322 |
| 405952 | 1913 | 1932 | TCGGCAGACAGCATCATGGC | 5-10-5 | 85.1 | 323 |
| 410738 | 1915 | 1934 | GCTCGGCAGACAGCATCATG | 5-10-5 | 68.4 | 324 |
| 405953 | 1917 | 1936 | CGGCTCGGCAGACAGCATCA | 5-10-5 | 93.6 | 325 |
| 405954 | 1919 | 1938 | TCCGGCTCGGCAGACAGCAT | 5-10-5 | 87.5 | 326 |
| 410770 | 1933 | 1952 | CGGCCAGGGTGAGCTCCGGC | 5-10-5 | 68.5 | 327 |
| 405955 | 1946 | 1965 | CTCTGCCTCAACTCGGCCAG | 5-10-5 | 94.2 | 328 |
| 405956 | 1948 | 1967 | GTCTCTGCCTCAACTCGGCC | 5-10-5 | 94.3 | 329 |
| 405958 | 1952 | 1971 | ATCAGTCTCTGCCTCAACTC | 5-10-5 | 80.3 | 331 |
| 405959 | 1954 | 1973 | GGATCAGTCTCTGCCTCAAC | 5-10-5 | 95.4 | 332 |
| 405960 | 1956 | 1975 | GTGGATCAGTCTCTGCCTCA | 5-10-5 | 90.1 | 333 |
| 405961 | 1958 | 1977 | AAGTGGATCAGTCTCTGCCT | 5-10-5 | 88.8 | 334 |

| Isis No. | 5' Target Site to SEQ ID NO: 3 | 3' Target Site to SEQ ID NO: 3 | Sequence 5'-3' | Motif | % inhibition | SEQ ID NO: |
|---|---|---|---|---|---|---|
| 405962 | 1961 | 1980 | GAGAAGTGGATCAGTCTCTG | 5-10-5 | 56.1 | 335 |
| 410739 | 1963 | 1982 | CAGAGAAGTGGATCAGTCTC | 5-10-5 | NA | 336 |
| 405963 | 1965 | 1984 | GGCAGAGAAGTGGATCAGTC | 5-10-5 | 59.7 | 337 |
| 405964 | 1969 | 1988 | CTTTGGCAGAGAAGTGGATC | 5-10-5 | 45.3 | 338 |
| 405965 | 1974 | 1993 | GACATCTTTGGCAGAGAAGT | 5-10-5 | 55.9 | 339 |
| 405966 | 1976 | 1995 | ATGACATCTTTGGCAGAGAA | 5-10-5 | 51.3 | 340 |
| 405967 | 1980 | 1999 | ATTGATGACATCTTTGGCAG | 5-10-5 | 64.4 | 341 |
| 405968 | 1982 | 2001 | TCATTGATGACATCTTTGGC | 5-10-5 | 74.6 | 342 |
| 399967 | 1985 | 2004 | GCCTCATTGATGACATCTTT | 3-14-3 | 80.1 | 48 |
| 405969 | 1987 | 2006 | AGGCCTCATTGATGACATCT | 5-10-5 | 63.0 | 343 |
| 405970 | 1989 | 2008 | CCAGGCCTCATTGATGACAT | 5-10-5 | 66.8 | 344 |
| 410740 | 1991 | 2010 | AACCAGGCCTCATTGATGAC | 5-10-5 | 46.8 | 345 |
| 405885 | 1993 | 2012 | GGAACCAGGCCTCATTGATG | 5-10-5 | 73.4 | 346 |
| 410596 | 1995 | 2014 | AGGGAACCAGGCCTCATTGA | 3-14-3 | NA | 348 |
| 410672 | 1995 | 2014 | AGGGAACCAGGCCTCATTGA | 2-13-5 | NA | 348 |
| 405887 | 1995 | 2014 | AGGGAACCAGGCCTCATTGA | 5-10-5 | NA | 348 |
| 410597 | 1996 | 2015 | CAGGGAACCAGGCCTCATTG | 3-14-3 | NA | 349 |
| 405888 | 1996 | 2015 | CAGGGAACCAGGCCTCATTG | 5-10-5 | NA | 349 |
| 410673 | 1996 | 2015 | CAGGGAACCAGGCCTCATTG | 2-13-5 | NA | 349 |
| 410674 | 1997 | 2016 | TCAGGGAACCAGGCCTCATT | 2-13-5 | 60.7 | 49 |
| 399812 | 1997 | 2016 | TCAGGGAACCAGGCCTCATT | 5-10-5 | 68.7 | 49 |
| 399968 | 1997 | 2016 | TCAGGGAACCAGGCCTCATT | 3-14-3 | 84.5 | 49 |
| 410598 | 1998 | 2017 | CTCAGGGAACCAGGCCTCAT | 3-14-3 | 74.5 | 350 |
| 410675 | 1998 | 2017 | CTCAGGGAACCAGGCCTCAT | 2-13-5 | 76.9 | 350 |
| 405889 | 1998 | 2017 | CTCAGGGAACCAGGCCTCAT | 5-10-5 | 80.2 | 350 |
| 410599 | 1999 | 2018 | CCTCAGGGAACCAGGCCTCA | 3-14-3 | 70.6 | 351 |
| 410676 | 1999 | 2018 | CCTCAGGGAACCAGGCCTCA | 2-13-5 | 77.8 | 351 |
| 405890 | 1999 | 2018 | CCTCAGGGAACCAGGCCTCA | 5-10-5 | 87.7 | 351 |
| 410600 | 2000 | 2019 | TCCTCAGGGAACCAGGCCTC | 3-14-3 | 76.5 | 352 |
| 410677 | 2000 | 2019 | TCCTCAGGGAACCAGGCCTC | 2-13-5 | 88.4 | 352 |
| 405891 | 2000 | 2019 | TCCTCAGGGAACCAGGCCTC | 5-10-5 | 96.1 | 352 |
| 405892 | 2001 | 2020 | GTCCTCAGGGAACCAGGCCT | 5-10-5 | 71.4 | 353 |
| 410601 | 2001 | 2020 | GTCCTCAGGGAACCAGGCCT | 3-14-3 | 72.7 | 353 |
| 410678 | 2001 | 2020 | GTCCTCAGGGAACCAGGCCT | 2-13-5 | 75.0 | 353 |
| 395178 | 2002 | 2021 | GGTCCTCAGGGAACCAGGCC | 5-10-5 | 76.7 | 50 |
| 410679 | 2002 | 2021 | GGTCCTCAGGGAACCAGGCC | 2-13-5 | 77.6 | 50 |
| 399900 | 2002 | 2021 | GGTCCTCAGGGAACCAGGCC | 3-14-3 | 92.0 | 50 |
| 408653 | 2003 | 2022 | TGGTCCTCAGGGAACCAGGC | 5-10-5 | 42.5 | 354 |
| 410602 | 2003 | 2022 | TGGTCCTCAGGGAACCAGGC | 3-14-3 | 66.5 | 354 |
| 410680 | 2003 | 2022 | TGGTCCTCAGGGAACCAGGC | 2-13-5 | 71.6 | 354 |
| 410603 | 2004 | 2023 | CTGGTCCTCAGGGAACCAGG | 3-14-3 | 40.8 | 355 |
| 410681 | 2004 | 2023 | CTGGTCCTCAGGGAACCAGG | 2-13-5 | 44.4 | 355 |
| 405971 | 2004 | 2023 | CTGGTCCTCAGGGAACCAGG | 5-10-5 | 65.5 | 355 |
| 410540 | 2005 | 2024 | GCTGGTCCTCAGGGAACCAG | 5-10-5 | 50.9 | 356 |
| 410682 | 2005 | 2024 | GCTGGTCCTCAGGGAACCAG | 2-13-5 | 54.1 | 356 |
| 410604 | 2005 | 2024 | GCTGGTCCTCAGGGAACCAG | 3-14-3 | 62.5 | 356 |
| 405972 | 2006 | 2025 | CGCTGGTCCTCAGGGAACCA | 5-10-5 | 77.6 | 357 |
| 405973 | 2011 | 2030 | GTACCCGCTGGTCCTCAGGG | 5-10-5 | 83.8 | 358 |
| 405974 | 2013 | 2032 | CAGTACCCGCTGGTCCTCAG | 5-10-5 | 89.0 | 359 |
| 399813 | 2016 | 2035 | GGTCAGTACCCGCTGGTCCT | 5-10-5 | 72.4 | 51 |
| 399969 | 2016 | 2035 | GGTCAGTACCCGCTGGTCCT | 3-14-3 | 93.4 | 51 |
| 410771 | 2061 | 2080 | ACCTGCCCCATGGGTGCTGG | 5-10-5 | NA | 360 |
| 395181 | 2073 | 2092 | AAACAGCTGCCAACCTGCCC | 5-10-5 | 87.5 | 52 |

| Isis No. | 5' Target Site to SEQ ID NO: 3 | 3' Target Site to SEQ ID NO: 3 | Sequence 5'-3' | Motif | % inhibition | SEQ ID NO: |
|---|---|---|---|---|---|---|
| 405975 | 2075 | 2094 | CAAAACAGCTGCCAACCTGC | 5-10-5 | 77.4 | 361 |
| 405976 | 2080 | 2099 | TCCTGCAAAACAGCTGCCAA | 5-10-5 | 81.2 | 362 |
| 405977 | 2082 | 2101 | AGTCCTGCAAAACAGCTGCC | 5-10-5 | 89.5 | 363 |
| 399992 | 2095 | 2114 | GTGCTGACCACACAGTCCTG | 3-14-3 | 92.6 | 130 |
| 405978 | 2105 | 2124 | GGCCCCGAGTGTGCTGACCA | 5-10-5 | 95.3 | 365 |
| 399904 | 2108 | 2127 | GTAGGCCCCGAGTGTGCTGA | 3-14-3 | 92.6 | 54 |
| 405979 | 2110 | 2129 | GTGTAGGCCCCGAGTGTGCT | 5-10-5 | 85.5 | 366 |
| 405980 | 2112 | 2131 | CCGTGTAGGCCCCGAGTGTG | 5-10-5 | 86.5 | 367 |
| 405981 | 2114 | 2133 | ATCCGTGTAGGCCCCGAGTG | 5-10-5 | 77.8 | 368 |
| 410741 | 2116 | 2135 | CCATCCGTGTAGGCCCCGAG | 5-10-5 | 78.4 | 369 |
| 405982 | 2118 | 2137 | GGCCATCCGTGTAGGCCCCG | 5-10-5 | 86.7 | 370 |
| 405983 | 2120 | 2139 | GTGGCCATCCGTGTAGGCCC | 5-10-5 | 73.1 | 371 |
| 405984 | 2168 | 2187 | CTGGAGCAGCTCAGCAGCTC | 5-10-5 | 83.4 | 372 |
| 405985 | 2170 | 2189 | AACTGGAGCAGCTCAGCAGC | 5-10-5 | 50.7 | 373 |
| 405986 | 2175 | 2194 | GGAGAAACTGGAGCAGCTCA | 5-10-5 | 75.6 | 374 |
| 405987 | 2177 | 2196 | CTGGAGAAACTGGAGCAGCT | 5-10-5 | 88.0 | 375 |
| 410776 | 2245 | 2264 | GTGCCAAGGTCCTCCACCTC | 5-10-5 | 77.3 | 408 |
| 410777 | 2265 | 2284 | TCAGCACAGGCGGCTTGTGG | 5-10-5 | 40.0 | 409 |
| 410778 | 2295 | 2314 | CCACGCACTGGTTGGGCTGA | 5-10-5 | 52.7 | 410 |
| 399908 | 2355 | 2374 | CTTTGCATTCCAGACCTGGG | 3-14-3 | 74.9 | 60 |
| 410713 | 2355 | 2374 | CTTTGCATTCCAGACCTGGG | 2-13-5 | 84.9 | 60 |
| 395186 | 2355 | 2374 | CTTTGCATTCCAGACCTGGG | 5-10-5 | 93.7 | 60 |
| 410714 | 2356 | 2375 | ACTTTGCATTCCAGACCTGG | 2-13-5 | 82.4 | 411 |
| 410633 | 2356 | 2375 | ACTTTGCATTCCAGACCTGG | 3-14-3 | 83.8 | 411 |
| 410562 | 2356 | 2375 | ACTTTGCATTCCAGACCTGG | 5-10-5 | 87.3 | 411 |
| 410715 | 2357 | 2376 | GACTTTGCATTCCAGACCTG | 2-13-5 | 80.5 | 412 |
| 410634 | 2357 | 2376 | GACTTTGCATTCCAGACCTG | 3-14-3 | 81.8 | 412 |
| 405996 | 2357 | 2376 | GACTTTGCATTCCAGACCTG | 5-10-5 | 91.0 | 412 |
| 410563 | 2358 | 2377 | TGACTTTGCATTCCAGACCT | 5-10-5 | 75.4 | 413 |
| 410635 | 2358 | 2377 | TGACTTTGCATTCCAGACCT | 3-14-3 | 75.9 | 413 |
| 410716 | 2358 | 2377 | TGACTTTGCATTCCAGACCT | 2-13-5 | 88.3 | 413 |
| 410636 | 2359 | 2378 | TTGACTTTGCATTCCAGACC | 3-14-3 | 61.3 | 414 |
| 410564 | 2359 | 2378 | TTGACTTTGCATTCCAGACC | 5-10-5 | 71.3 | 414 |
| 410717 | 2359 | 2378 | TTGACTTTGCATTCCAGACC | 2-13-5 | 76.7 | 414 |
| 410718 | 2360 | 2379 | CTTGACTTTGCATTCCAGAC | 2-13-5 | 55.8 | 61 |
| 399973 | 2360 | 2379 | CTTGACTTTGCATTCCAGAC | 3-14-3 | 82.1 | 61 |
| 399817 | 2360 | 2379 | CTTGACTTTGCATTCCAGAC | 5-10-5 | 93.6 | 61 |
| 405997 | 2362 | 2381 | TCCTTGACTTTGCATTCCAG | 5-10-5 | 95.6 | 415 |
| 410779 | 2375 | 2394 | CGGGATTCCATGCTCCTTGA | 5-10-5 | 79.7 | 416 |
| 410780 | 2405 | 2424 | GCAGGCCACGGTCACCTGCT | 5-10-5 | 60.9 | 417 |
| 410781 | 2442 | 2461 | GGAGGGCACTGCAGCCAGTC | 5-10-5 | 66.0 | 418 |
| 410719 | 2560 | 2579 | CAGATGGCAACGGCTGTCAC | 2-13-5 | 61.0 | 419 |
| 410637 | 2560 | 2579 | CAGATGGCAACGGCTGTCAC | 3-14-3 | 66.0 | 419 |
| 410565 | 2560 | 2579 | CAGATGGCAACGGCTGTCAC | 5-10-5 | 71.6 | 419 |
| 410638 | 2561 | 2580 | GCAGATGGCAACGGCTGTCA | 3-14-3 | 71.9 | 420 |
| 410720 | 2561 | 2580 | GCAGATGGCAACGGCTGTCA | 2-13-5 | 75.1 | 420 |
| 410566 | 2561 | 2580 | GCAGATGGCAACGGCTGTCA | 5-10-5 | 77.7 | 420 |
| 410639 | 2562 | 2581 | AGCAGATGGCAACGGCTGTC | 3-14-3 | 67.7 | 421 |
| 410721 | 2562 | 2581 | AGCAGATGGCAACGGCTGTC | 2-13-5 | 68.8 | 421 |
| 410567 | 2562 | 2581 | AGCAGATGGCAACGGCTGTC | 5-10-5 | 72.1 | 421 |
| 410568 | 2563 | 2582 | CAGCAGATGGCAACGGCTGT | 5-10-5 | 54.2 | 422 |
| 410640 | 2563 | 2582 | CAGCAGATGGCAACGGCTGT | 3-14-3 | 57.7 | 422 |
| 410722 | 2563 | 2582 | CAGCAGATGGCAACGGCTGT | 2-13-5 | 59.2 | 422 |

| Isis No. | 5' Target Site to SEQ ID NO: 3 | 3' Target Site to SEQ ID NO: 3 | Sequence 5'-3' | Motif | % inhibition | SEQ ID NO: |
|---|---|---|---|---|---|---|
| 410569 | 2564 | 2583 | GCAGCAGATGGCAACGGCTG | 5-10-5 | 57.7 | 423 |
| 410641 | 2564 | 2583 | GCAGCAGATGGCAACGGCTG | 3-14-3 | 66.1 | 423 |
| 410723 | 2564 | 2583 | GCAGCAGATGGCAACGGCTG | 2-13-5 | 81.1 | 423 |
| 399909 | 2565 | 2584 | GGCAGCAGATGGCAACGGCT | 3-14-3 | 69.9 | 62 |
| 410724 | 2565 | 2584 | GGCAGCAGATGGCAACGGCT | 2-13-5 | 87.4 | 62 |
| 395187 | 2565 | 2584 | GGCAGCAGATGGCAACGGCT | 5-10-5 | 92.7 | 62 |
| 410642 | 2566 | 2585 | CGGCAGCAGATGGCAACGGC | 3-14-3 | 70.4 | 424 |
| 410725 | 2566 | 2585 | CGGCAGCAGATGGCAACGGC | 2-13-5 | 75.6 | 424 |
| 410570 | 2566 | 2585 | CGGCAGCAGATGGCAACGGC | 5-10-5 | 78.3 | 424 |
| 410571 | 2567 | 2586 | CCGGCAGCAGATGGCAACGG | 5-10-5 | 52.8 | 425 |
| 410643 | 2567 | 2586 | CCGGCAGCAGATGGCAACGG | 3-14-3 | 59.8 | 425 |
| 410726 | 2567 | 2586 | CCGGCAGCAGATGGCAACGG | 2-13-5 | 69.8 | 425 |
| 410644 | 2568 | 2587 | TCCGGCAGCAGATGGCAACG | 3-14-3 | 59.0 | 426 |
| 410727 | 2568 | 2587 | TCCGGCAGCAGATGGCAACG | 2-13-5 | 68.3 | 426 |
| 405998 | 2568 | 2587 | TCCGGCAGCAGATGGCAACG | 5-10-5 | 75.6 | 426 |
| 405988 | 2568 | 2587 | TCCGGCAGCAGATGGCAACG | 5-10-5 | 84.5 | 426 |
| 410572 | 2569 | 2588 | CTCCGGCAGCAGATGGCAAC | 5-10-5 | 40.9 | 427 |
| 410728 | 2569 | 2588 | CTCCGGCAGCAGATGGCAAC | 2-13-5 | 56.4 | 427 |
| 410645 | 2569 | 2588 | CTCCGGCAGCAGATGGCAAC | 3-14-3 | 70.2 | 427 |
| 410729 | 2570 | 2589 | GCTCCGGCAGCAGATGGCAA | 2-13-5 | 67.7 | 428 |
| 410573 | 2570 | 2589 | GCTCCGGCAGCAGATGGCAA | 5-10-5 | 71.8 | 428 |
| 410646 | 2570 | 2589 | GCTCCGGCAGCAGATGGCAA | 3-14-3 | 72.8 | 428 |
| 410782 | 2580 | 2599 | CCAGGTGCCGGCTCCGGCAG | 5-10-5 | 43.2 | 429 |
| 410783 | 2590 | 2609 | GAGGCCTGCGCCAGGTGCCG | 5-10-5 | 63.7 | 430 |
| 399819 | 2764 | 2783 | CCCACTCAAGGGCCAGGCCA | 5-10-5 | 93.4 | 65 |
| 399912 | 2852 | 2871 | ATGCCCCACAGTGAGGGAGG | 3-14-3 | 84.3 | 66 |
| 405893 | 3083 | 3102 | ATGAGGGCCATCAGCACCTT | 5-10-5 | 93.9 | 431 |
| 405894 | 3084 | 3103 | GATGAGGGCCATCAGCACCT | 5-10-5 | 93.9 | 432 |
| 405895 | 3085 | 3104 | AGATGAGGGCCATCAGCACC | 5-10-5 | 91.8 | 433 |
| 405896 | 3086 | 3105 | GAGATGAGGGCCATCAGCAC | 5-10-5 | 88.5 | 434 |
| 395194 | 3087 | 3106 | GGAGATGAGGGCCATCAGCA | 5-10-5 | 90.0 | 69 |
| 399916 | 3087 | 3106 | GGAGATGAGGGCCATCAGCA | 3-14-3 | 94.5 | 69 |
| 405897 | 3088 | 3107 | TGGAGATGAGGGCCATCAGC | 5-10-5 | 85.1 | 435 |
| 405898 | 3089 | 3108 | CTGGAGATGAGGGCCATCAG | 5-10-5 | 86.9 | 436 |
| 405899 | 3090 | 3109 | GCTGGAGATGAGGGCCATCA | 5-10-5 | 91.5 | 437 |
| 405900 | 3091 | 3110 | AGCTGGAGATGAGGGCCATC | 5-10-5 | 83.7 | 438 |
| 405901 | 3157 | 3176 | GCTAGATGCCATCCAGAAAG | 5-10-5 | 88.4 | 439 |
| 405902 | 3158 | 3177 | GGCTAGATGCCATCCAGAAA | 5-10-5 | 89.3 | 440 |
| 405903 | 3159 | 3178 | TGGCTAGATGCCATCCAGAA | 5-10-5 | 92.6 | 441 |
| 405904 | 3160 | 3179 | CTGGCTAGATGCCATCCAGA | 5-10-5 | 90.4 | 442 |
| 399821 | 3161 | 3180 | TCTGGCTAGATGCCATCCAG | 5-10-5 | 91.7 | 71 |
| 405905 | 3162 | 3181 | CTCTGGCTAGATGCCATCCA | 5-10-5 | 90.7 | 443 |
| 405906 | 3163 | 3182 | CCTCTGGCTAGATGCCATCC | 5-10-5 | 93.3 | 444 |
| 405907 | 3164 | 3183 | GCCTCTGGCTAGATGCCATC | 5-10-5 | 90.2 | 445 |
| 405908 | 3165 | 3184 | AGCCTCTGGCTAGATGCCAT | 5-10-5 | 83.3 | 446 |
| 399978 | 3243 | 3262 | AGCCTGGCATAGAGCAGAGT | 3-14-3 | 96.4 | 73 |

Antisense oligonucleotides that exhibited less than 30% inhibition of PCSK9 mRNA levels were marked with "NA".

Antisense oligonucleotides with the following ISIS Nos exhibited at least 80% inhibition of PCSK9 mRNA levels: 395163, 395165, 395166, 395168, 395181, 395186, 395187, 395194, 399798, 399801, 399804, 399806, 399817, 399819, 399821, 399887, 399888, 399891, 399900, 399904, 399912, 399916, 399935, 399936, 399954, 399960, 399962, 399967, 399968, 399969, 399973, 399978, 399992, 405869, 405870, 405871, 405872, 405873, 405874, 405875, 405876, 405877, 405878, 405879, 405880, 405881, 405882, 405883, 405884, 405889, 405890, 405891, 405893, 405894, 405895, 405896, 405897, 405898, 405899, 405900, 405901, 405902, 405903, 405904, 405905, 405906, 405907, 405908, 405909, 405910, 405911, 405913, 405914, 405915, 405916, 405920, 405921, 405922, 405940, 405941, 405943, 405944, 405949, 405952, 405953, 405954, 405955, 405956, 405958, 405959, 405960, 405961, 405973, 405974, 405976, 405977, 405978, 405979, 405980, 405982, 405984, 405987, 405988, 405996, 405997, 406026, 406028, 406029, 406030, 406031, 406032, 406033, 406035, 406036, 406038, 406039, 406040, 406041, 406042, 406043, 406044, 406045, 410562, 410583, 410589, 410590, 410591, 410592, 410593, 410595, 410633, 410634, 410658, 410664, 410666, 410667, 410668, 410671, 410677, 410713, 410714, 410715, 410716, 410723, 410724, 410754, 410757, 410759, 410760, and 410769. The target segments to which these antisense oligonucleotides are targeted are active target segments. The target regions to which these antisense oligonucleotides are targeted are active target regions.

ISIS Nos 395165, 395166, 395168, 395181, 395186, 395187, 395194, 399801, 399817, 399819, 399821, 399887, 399888, 399891, 399900, 399904, 399916, 399936, 399954, 399962, 399969, 399978, 399992, 405869, 405871, 405872, 405873, 405874, 405875, 405876, 405878, 405879, 405880, 405881, 405882, 405883, 405884, 405890, 405891, 405893, 405894, 405895, 405896, 405897, 405898, 405899, 405901, 405902, 405903, 405904, 405905, 405906, 405907, 405910, 405911, 405913, 405914, 405915, 405916, 405920, 405921, 405922, 405941, 405952, 405953, 405954, 405955, 405956, 405959, 405960, 405961, 405974, 405977, 405978, 405979, 405980, 405982, 405987, 405996, 405997, 406028, 406029, 406030, 406031, 406032, 406033, 406035, 406038, 406039, 406040, 406041, 406042, 406043, 406044, 406045, 410562, 410583, 410591, 410592, 410593, 410668, 410677, 410716, 410724, 410757, and 410760 each exhibited at least 85% inhibition of PCSK9 mRNA levels.

ISIS Nos 395165, 395166, 395168, 395186, 395187, 395194, 399801, 399817, 399819, 399821, 399887, 399888, 399891, 399900, 399904, 399916, 399954, 399969, 399978, 399992, 405873, 405874, 405875, 405876, 405878, 405879, 405880, 405881, 405882, 405883, 405884, 405891, 405893, 405894, 405895, 405899, 405903, 405904, 405905, 405906, 405907, 405910,

405913, 405914, 405916, 405941, 405953, 405955, 405956, 405959, 405960, 405978, 405996, 405997, 406028, 406029, 406030, 406033, 406035, 406039, 406040, 406041, 406042, 406043, 406044, 410592, 410668, and 410760 each exhibited at least 90% inhibition of PCSK9 mRNA levels.

ISIS Nos 395165, 395166, 399801, 399978, 405881, 405891, 405959, 405978, 405997, 406030, 406040, 406041, 406044, and 410760 each exhibited at least 95% inhibition of PCSK9 mRNA levels.

**Example 4: Antisense inhibition of human PSCK9 in HepG2 cells: dose response experiment**

Antisense oligonucleotides targeted to PCSK9 were tested at various doses in HepG2 cells. Cells were plated at densities of 10,000 cells per well and treated with nM concentrations of antisense oligonucleotide as indicated in Tables 19 and 20. After a treatment period of approximately 24 hours, RNA was isolated from the cells and PCSK9 mRNA levels were measured by quantitative real-time PCR, as described herein. Two different human PCSK9 primer probe sets were used to measure mRNA levels. Results with Primer Probe Set 2740 are shown in Table 19, and mRNA levels measured using primer probe set 2823 are shown in Table 20. PCSK9 mRNA levels were adjusted according to total RNA content as measured by RIBOGREEN®. Results are presented as percent inhibition of PCSK9, relative to untreated control cells. As illustrated in Tables 19 and 20, PCSK9 mRNA levels were reduced in a dose-dependent manner.

**Table 19: Antisense Inhibition of PCSK9 in HepG2 cells, Primer Probe Set 2740**

| Isis No | 6.25 nM | 12.5 nM | 25.0 nM | 50.0 nM | 100.0 nM | 200.0 nM |
|---|---|---|---|---|---|---|
| 399819 | 93 | 113 | 84 | 71 | 26 | 12 |
| 395185 | 81 | 64 | 50 | 35 | 24 | 13 |
| 399916 | 65 | 56 | 41 | 18 | 20 | 25 |
| 399907 | 68 | 66 | 42 | 26 | 30 | 25 |
| 399954 | 71 | 63 | 38 | 22 | 16 | 15 |
| 395165 | 71 | 67 | 47 | 29 | 21 | 10 |
| 399936 | 65 | 51 | 31 | 20 | 30 | 28 |
| 399793 | 61 | 57 | 44 | 31 | 39 | 15 |
| 399969 | 57 | 54 | 40 | 27 | 25 | 19 |
| 395152 | 75 | 58 | 58 | 49 | 24 | 28 |

**Table 20: Antisense inhibition of PCSK9 in HepG2 cells, Primer Probe Set 2823**

| Isis No | 6.25 nM | 12.5 nM | 25.0 nM | 50.0 nM | 100.0 nM | 200.0 nM |
|---|---|---|---|---|---|---|
| 399819 | 80 | 264 | 87 | 85 | 34 | 15 |
| 395185 | 86 | 66 | 57 | 45 | 29 | 22 |
| 399916 | 75 | 47 | 45 | 20 | 30 | 45 |
| 399907 | 67 | 72 | 47 | 29 | 31 | 32 |
| 399954 | 59 | 50 | 35 | 17 | 22 | 27 |
| 395165 | 74 | 54 | 41 | 37 | 26 | 22 |
| 399936 | 62 | 41 | 33 | 32 | 28 | 42 |
| 399793 | 62 | 51 | 38 | 36 | 44 | 27 |
| 399969 | 73 | 40 | 58 | 28 | 29 | 35 |
| 395152 | 78 | 53 | 64 | 49 | 22 | 35 |

**Example 5: Antisense inhibition of human PSCK9 in HepB3 cells: dose response experiment**

Antisense oligonucleotides targeted to PCSK9 were tested at various doses in HepB3 cells. Cells were plated at densities of 4,500 cells per well and treated with nM concentrations of antisense oligonucleotide as indicated in Tables 21. After a treatment period of approximately 24 hours, RNA was isolated from the cells and PCSK9 mRNA levels were measured by quantitative real-time PCR, as described herein. Two different human PCSK9 primer probe sets were used to measure mRNA levels. Results with Primer Probe Set 2740 are shown in Table 21. PCSK9 mRNA levels were adjusted according to total RNA content as measured by RIBOGREEN®. Results are presented as percent inhibition of PCSK9, relative to untreated control cells. As illustrated in Tables 21, PCSK9 mRNA levels were reduced in a dose-dependent manner.

**Table 21: Antisense inhibition of PCSK9 in HepB3 cells, Primer Probe Set 2740**

| Isis No. | 2.78 nM | 8.33 nM | 25.0 nM | 75.0 nM |
|---|---|---|---|---|
| 399819 | 127.5 | 85.0 | 36.1 | 21.9 |
| 405891 | 133.7 | 111.4 | 40.2 | 27.2 |
| 406008 | 144.6 | 108.3 | 49.9 | 17.7 |
| 395186 | 124.4 | 106.4 | 42.2 | 30.7 |
| 395185 | 150.7 | 106.6 | 53.6 | 38.1 |
| 405994 | 141.9 | 101.2 | 49.3 | 30.8 |
| 405988 | 148.1 | 117.4 | 47.8 | 25.2 |
| 406033 | 138.1 | 109.9 | 62.4 | 35.3 |
| 395187 | 133.0 | 115.6 | 59.9 | 31.6 |
| 405995 | 124.1 | 109.2 | 57.8 | 42.9 |
| 406023 | 130.0 | 103.5 | 67.1 | 28.0 |
| 399900 | 131.2 | 95.7 | 81.1 | 30.9 |
| 301012 | 121.2 | 100.1 | 63.8 | 49.6 |
| 395165 | 113.2 | 86.9 | 41.6 | 13.3 |

| | | | | |
|---|---|---|---|---|
| 405879 | 124.6 | 88.8 | 44.1 | 13.1 |
| 405991 | 100.6 | 101.4 | 95.9 | 41.0 |
| 405923 | 130.4 | 115.0 | 68.9 | 35.1 |
| 395152 | 143.8 | 98.6 | 61.3 | 59.0 |
| 405881 | 100.7 | 77.4 | 50.2 | 4.5 |
| 141923 | 131.4 | 131.9 | 144.0 | 167.3 |

**Example 6: Antisense inhibition of human PSCK9 in HeLa cells: dose response experiment**

Antisense oligonucleotides targeted to PCSK9 were tested at various doses in HeLa cells. Cells were plated at densities of 5,000 cells per well and treated with nM concentrations of antisense oligonucleotide as indicated in Tables 22. After a treatment period of approximately 24 hours, RNA was isolated from the cells and PCSK9 mRNA levels were measured by quantitative real-time PCR, as described herein. Two different human PCSK9 primer probe sets were used to measure mRNA levels. Results with Primer Probe Set 2740 are shown in Table 22. PCSK9 mRNA levels were adjusted according to total RNA content as measured by RIBOGREEN®. Results are presented as percent inhibition of PCSK9, relative to untreated control cells. As illustrated in Tables 22, PCSK9 mRNA levels were reduced in a dose-dependent manner.

**Table 22: Antisense inhibition of PCSK9 in HeLa cells, Primer Probe Set 2740**

| Isis No. | 2.963 nM | 8.8889 nM | 26.6667 nM | 80.0 nM |
|---|---|---|---|---|
| 399819 | 57 | 32 | 16 | 14 |
| 405891 | 57 | 46 | 17 | 18 |
| 406008 | 45 | 27 | 11 | 5.3 |
| 395186 | 40 | 28 | 11 | 6.6 |
| 395185 | 53 | 32 | 21 | 17 |
| 405994 | 48 | 34 | 20 | 13 |
| 405988 | 44 | 32 | 12 | 7.3 |
| 406033 | 61 | 42 | 25 | 12 |
| 395187 | 42 | 35 | 12 | 6.6 |
| 405995 | 54 | 39 | 21 | 15 |
| 406023 | 76 | 46 | 25 | 6.2 |
| 399900 | 85 | 48 | 23 | 6.4 |
| 301012 | 121 | 109 | 76 | 65 |
| 395165 | 61 | 30 | 10 | 2 |
| 405879 | 64 | 32 | 9.7 | 1 |
| 405991 | 64 | 35 | 24 | 10 |
| 405923 | 71 | 45 | 22 | 5 |
| 395152 | 73 | 34 | 13 | 3.1 |
| 405881 | 58 | 33 | 19 | 2.8 |
| 141923 | 122 | 118 | 131 | 140 |

**Example 7: Antisense inhibition of PSCK9 in primary hepatocytes**

Antisense oligonucleotides targeted to PCSK9 were tested for antisense inhibition of PCSK9 in human primary hepatocytes. Human primary hepatocytes were purchased from a commercial supplier, and cultured according to routine culture procedures. Cells were treated with 10, 25, 50, 150, or 300 nM of antisense oligonucleotide for a period of 24 hours, after which RNA was isolated and PCSK9 mRNA was measured by real-time PCR as described herein.

The antisense oligonucleotides tested in human primary hepatocytes were Isis 395152, 395155, 395165, 395185, 399819, 399821, 399916, 399954, 399978, and 399992. The antisense oligonucleotides inhibited PCSK9 in a dose-dependent manner in human primary hepatocytes.

Monkey primary hepatocytes were similarly treated with 10, 25, 50, 150, or 300 nM concentrations of antisense oligonucleotide targeted to PCSK9. The antisense oligonucleotides tested in monkey primary hepatocytes were Isis 395152, 395155, 395165, 395185, 399819, 399821, 399916, 399954, 399978, and 399992. Each of these antisense oligonucleotides is fully complementary to a monkey PCSK9 nucleic acid. The antisense oligonucleotides inhibited PCSK9 in a dose-dependent manner in monkey primary hepatocytes.

**Example 8: Additional Antisense inhibition of PSCK9 in primary hepatocytes**

Antisense oligonucleotides targeted to PCSK9 were tested for antisense inhibition of PCSK9 in human primary hepatocytes. Human primary hepatocytes were purchased from a commercial supplier, and cultured according to routine culture procedures. Cells were treated with 10, 25, 50, 150, or 300 nM of antisense oligonucleotide for a period of 24 hours, after which RNA was isolated and PCSK9 mRNA was measured by real-time PCR as described herein.

The antisense oligonucleotides tested in human primary hepatocytes were Isis 395165, 395185, 395186, 395187, 405879, 405881, 405891, 405988, 405994, and 406008. The antisense oligonucleotides inhibited PCSK9 in a dose-dependent manner in human primary hepatocytes as shown in Table 23.

**Table 23: Dose-dependent Reduction in Human PCSK9 mRNA Expression in Human Primary Hepatocytes**

| ISIS No. | 10 nM | 25 nM | 50 nM | 150 nM | 300 nM |
|---|---|---|---|---|---|
| 395165 | 16.2 | 20.2 | 22.5 | 48.7 | 76 |
| 395185 | 15.7 | 25.5 | 52.6 | 42.9 | 74.5 |
| 395186 | 19.9 | 21 | 34.4 | 58.3 | 123.8 |
| 395187 | 21.1 | 17.4 | 29.7 | 43.5 | 98.7 |
| 405879 | 47.7 | 48.4 | 64.9 | 176.6 | 119.2 |
| 405881 | 79.3 | 22.3 | 49.5 | 115.3 | 222.4 |

| | | | | | |
|---|---|---|---|---|---|
| 405891 | 48.7 | 86.9 | 73.9 | 138.7 | 169.9 |
| 405988 | 43.8 | 43.9 | 67.8 | 105.4 | 85.2 |
| 405994 | 10.5 | 24.6 | 43.5 | 83.3 | 95.7 |
| 406008 | 32.4 | 41.7 | 116 | 101.7 | 155 |

**Example 9: Antisense inhibition of PSCK9 in Cyno Primary hepatocytes**

Antisense oligonucleotides targeted to PCSK9 were tested for antisense inhibition of PCSK9 in human cyno primary hepatocytes. Human Cyno primary hepatocytes were purchased from a commercial supplier, and cultured according to routine culture procedures. Cells were treated with 10, 25, 50, 150, or 300 nM of antisense oligonucleotide for a period of 24 hours, after which RNA was isolated and PCSK9 mRNA was measured by real-time PCR as described herein.

The antisense oligonucleotides tested in human primary hepatocytes were Isis 395165, 395185, 395186, 395187, 405879, 405881, 405891, 405988, 405994, and 406008. The antisense oligonucleotides inhibited PCSK9 in a dose-dependent manner in human primary hepatocytes as shown in Table 24.

**Table 24: Dose-dependent PCSK9 mRNA Inhibition in Cyno Primary Hepatocytes**

| ISIS No. | 10 nM | 25 nM | 50 nM | 150 nM | 300 nM |
|---|---|---|---|---|---|
| 395165 | 36.3 | 29.9 | 14.9 | 8.6 | 3.2 |
| 395185 | 65.0 | 31.9 | 35.1 | 16.6 | 12.0 |
| 395186 | 65.8 | 42.3 | 21.6 | 23.3 | 16.7 |
| 395187 | 61.3 | 32.9 | 13.2 | 7.7 | 9.02 |
| 405879 | 24.3 | 21.9 | 7.7 | 7.1 | 3.0 |
| 405881 | 75.0 | 33.5 | 26.5 | 11.2 | 4.9 |
| 405891 | 52.4 | 24.8 | 11.2 | 10.8 | 6.7 |
| 405988 | 59.4 | 23.7 | 22.5 | 10.7 | 8.2 |
| 405994 | 64.8 | 52.7 | 22.2 | 7.9 | 6.5 |
| 406008 | 56.3 | 28.2 | 26.5 | 13.4 | 13.3 |

**Example 10: Antisense inhibition of mouse PCSK9 *in vitro***

Antisense oligonucleotides were designed to target murine PCSK9, and were evaluated for their ability to reduce PCSK9 mRNA in primary mouse hepatocytes.

Primary mouse hepatocytes were treated with antisense oligonucleotides at doses of 50, 150, or 300 nM, for a period of 24 hours. RNA was isolated using QIAGEN® RNeasy isolation kits and subjected to quantitative real-time PCR using commercially available reagents

(Invitrogen, Carlsbad, CA). PCSK9 mRNA levels were measured using a mouse PCSK9 primer probe set, and normalized to G3PDH mRNA levels and/or RIBOGREEN® levels.

ISIS 394814 (GAGCAACTTCGGAGGCAGC, SEQ ID NO: 456) was identified as a potent inhibitor of mouse PCSK9. PCSK9 mRNA levels ISIS 394814 yielded a 50% reduction in PCSK9 mRNA at a concentration of 25 nM (i.e., an IC50 of 25 nM) after a 24 hour incubation with primary mouse hepatocytes. No effect on cultured cell viability was observed.

**Example 11: Antisense inhibition of PCSK9 in an animal model of hyperlipidemia: high fat fed mice**

*Treatment*

C57BL/6 mice fed a high-fat diet are routinely employed as an animal model of hyperlipidemia, as well as an animal model of atherosclerosis. Accordingly, to evaluate the effects of PCSK9 antisense inhibition on serum lipid levels *in vivo*, ISIS 394814 was evaluated in C57BL/6 mice fed a high-fat diet. C57BL/6 mice 4-5 weeks of age were obtained from the Jackson Laboratory and maintained on a diet consisting of 60% fat. Treatment groups of 5 mice each were as follows: a group treated with ISIS 394814; a control group treated with saline; and control group treated with an oligonucleotide not complementary to any known gene sequence (ISIS 141923). Oligonucleotide or saline was administered intraperitoneally twice weekly, for a period of 6 weeks; oligonucleotide doses were 50 mg/kg. After the treatment period, whole blood was collected for analysis of serum parameters, and whole liver was collected for RNA analysis, protein analysis, and histological evaluation. Statistical analyses included a nonparametric, two-tailed t-test comparison of experimental samples (ISIS 394814) to control samples (saline or control oligonucleotide).

*RNA Analysis*

Liver RNA was isolated for real-time PCR analysis of PCSK9, LDL-receptor and apolipoprotein B mRNA levels. Treatment with ISIS 394814 resulted in a 92% reduction in PCSK9 mRNA levels, while no significant reduction in PCSK9 mRNA levels was observed in ISIS 141923-treated or saline-treated mice. Antisense inhibition of PCSK9 expression did not significantly affect liver LDL-receptor or liver apolipoprotein B mRNA levels.

*Protein Analysis*

Immunoblotting was performed to assess the effects of PCSK9 antisense inhibition on LDL-receptor protein and apolipoprotein B levels. Protein isolated from mouse liver was subjected to electrophoresis, transferred to a polyvinylidene-fluoride membrane, and

subsequently probed with an anti-mouse LDL-receptor antibody and a scavenger receptor B1 (SR-B1) antibody. Mouse plasma was similarly subjected to electrophoresis and immunoblotting using an anti-mouse apolipoprotein B antibody. Secondary antibodies conjugated to peroxidase were used to detect primary antibodies. Protein bands were visualized using the ECL plus Western blot detection kit (Amersham Biosciences, UK) and quantified using ImageQuant™ analysis software (MolecularDynamics, Santa Clara, CA).

While LDL-receptor mRNA levels were not significantly affected, antisense inhibition of PCSK9 resulted in an approximate 2-fold increase in the level of hepatic LDL-receptor protein relative to 141923-treated controls. No changes in SR-B1 protein were observed. Furthermore, serum apoB-100 levels were significantly reduced by 50%, relative to 141923-treated controls. Serum apoB-48 levels were significantly increased by approximately 3-fold relative to 141923-treated controls. No significant changes in apoA-I protein were observed, relative to 141923-treated controls.

The mRNA levels of the RNA editing enzyme apobec-1 were also measured. Apobec-1 is responsible for the RNA editing that produces apoB-48 in murine liver and intestine. Human apobec-1 is expressed only in intestinal cells, thus these cells are the source of apoB-48 in humans. Antisense inhibition of PCSK9 resulted in an increase in murine hepatic apobec-1 mRNA levels by approximately 2.7 fold compared to saline-treated controls

*Serum Lipid Analysis*

Plasma concentrations of total cholesterol, LDL-C, HDL-C, free cholesterol, triglycerides, glucose, ketones, transaminases, and phospholipids were measured using an automated clinical chemistry analyzer (Hitachi Olympus AU400e, Melville, NY). Serum lipoprotein and cholesterol profiling was performed as described by Crooke et al. (> Lipid Res., 2005, 46, 872-884) using a Beckman System Gold 126 HPLC system, a 507e refrigerated autosampler, a 126 photodiode array detector (Beckman Instruments, Fullerton, CA), and a Superose 6 HR 10/30 column (Pfizer, Chicago, IL). HDL, LDL and VLDL fractions were measured at a wavelength of 505 nm and validated with a cholesterol calibration kit. (Sigma).

Administration of ISIS 394814 resulted in a 52% reduction in total cholesterol (saline, 183 mg/dL ± 18; ISIS 141923, 194 mg/dL ± 14; ISIS 394814, 87 mg/dL ± 19, $p < 0.005$) and a 36% reduction in LDL-C (saline 22 mg/dL ± 4; ISIS 141923, 25 mg/dL ± 2; ISIS 394814, 14 mg/dL ± 2, $p < 0.005$). Serum free cholesterol was reduced by 25% (saline 41 mg/dL ± 10; ISIS 141923, 58 mg/dL ± 3; ISIS 394814, 31 mg/dL ± 5, $p < 0.005$) and phospholipids were reduced 54% (saline, 354 mg/dL ± 29; ISIS 141923, 383 mg/dL ± 21; ISIS 394814, 169 mg/dL ± 35, p

< 0.0001). HDL-C was also reduced by approximately 54% (saline, 183 mg/dL ± 18; ISIS 141923, 194 mg/dL ± 14; ISIS 394814, 87 mg/dL ± 19; p < 0.0001). HPLC profiling confirmed the reduction of LDL and HDL lipid classes.

*Liver Triglyceride Analysis*

Liver triglyceride content was measured according to routine experimental procedures, for example, per procedures described by Desai et al., Diabetes, 2001, 50:2287-2295.

Antisense inhibition of PCSK9 for 6 weeks reduced liver triglyceride content by approximately 65% (p = 0.01) relative to saline controls. No statistically significant changes in liver triglyceride content following 141923 treatment were observed.

Accordingly, one embodiment is a method of lowering LDL-C levels through the administration of an antisense oligonucleotide targeted to a PCSK9 nucleic acid. An additional embodiment includes a method of lowering total cholesterol through the administration of an antisense oligonucleotide targeted to a PCSK9 nucleic acid. An addition embodiment is lowering liver triglycerides by administering an antisense oligonucleotide targeted to a PCSK9 target nucleic acid.

**Example 12: Antisense inhibition of PCSK9 in LDL-R deficient/apoB-100 animals**

LDL-receptor (LDL-R)-deficient/apoB-100 animals do not express the LDL-R gene, and express only the apoB-100 form of apoB. PCSK9 antisense oligonucleotide was administered to LDL-R deficient/apoB-100 mice, to evaluate the effects of antisense inhibition of PCSK9 in the absence of the LDL-R. Mice 4-5 weeks of age were maintained on a standard mouse diet. Treatment groups of 5 mice each were as follows: a group treated with ISIS 394814; a control group treated with saline; and control group treated with an oligonucleotide not complementary to any known gene sequence (ISIS 141923). Oligonucleotide or saline was administered intraperitoneally twice weekly, for a period of 6 weeks; oligonucleotide doses were 50 mg/kg (100 mg/kg/wk total). Real-time PCR of liver mRNA and serum analyses were performed as described for the C57Bl/6 study.

Antisense inhibition of PCSK9 reduced liver PCSK9 mRNA by approximately 90%, relative to saline controls. However, no reduction in serum cholesterol was observed. Liver triglyceride levels were unaffected by antisense inhibition of PCKS9 in these mice. An 80% increase in liver apobec1 mRNA levels was observed, relative to saline controls. These data suggest that a functioning LDL-R is required for cholesterol and liver triglyceride reduction via PCSK9 antisense inhibition.

**Example 13: Antisense inhibition of PSCK9 in Mouse Primary Hepatocytes**

Antisense oligonucleotides targeted to PCSK9 were tested for antisense inhibition of PCSK9 in mouse primary hepatocytes. Mouse primary hepatocytes were purchased from a commercial supplier, and cultured according to routine culture procedures. Cells were treated with 6.25, 12.5, 25, 50, 100, or 200 nM of antisense oligonucleotide for a period of 24 hours, after which RNA was isolated and PCSK9 mRNA was measured by real-time PCR as described herein.

The antisense oligonucleotides tested in human primary hepatocytes were Isis 395165, 395185, 395186, 395187, 405879, 405881, 405891, 405988, 405994, and 406008. The antisense oligonucleotides inhibited PCSK9 in a dose-dependent manner in human primary hepatocytes as shown in Table 25.

**Table 25: Dose-dependent PCSK9 mRNA Inhibition in Mouse Primary Hepatocytes**

| ISIS No | 6.25 nM | 12.5 nM | 25.0 nM | 50.0 nM | 100.0 nM | 200.0 nM |
|---|---|---|---|---|---|---|
| 395165 | 95.2 | 94.9 | 81.7 | 66.3 | 57.5 | 29.9 |
| 395185 | 109.2 | 100 | 90.5 | 81.2 | 64.7 | 35.8 |
| 395186 | 101.9 | 91.5 | 77.8 | 59.1 | 39.5 | 13.7 |
| 395187 | 102.4 | 96.1 | 83.9 | 66.4 | 40 | 15.3 |
| 405879 | 107.3 | 97.5 | 87.8 | 76.6 | 63 | 43.1 |
| 405881 | 104.8 | 102.1 | 98.1 | 84.9 | 68.7 | 48.9 |
| 405891 | 104.9 | 103.3 | 101.5 | 88.9 | 79.6 | 49.5 |
| 405988 | 97.3 | 101.1 | 91.7 | 82.3 | 61.2 | 34.8 |
| 405994 | 110.2 | 101 | 111.6 | 94.4 | 80.1 | 57.7 |
| 406008 | 99.5 | 91.3 | 83.9 | 73.7 | 61.8 | 39.4 |
| 157700 | 97.8 | 98.3 | 96.2 | 94.3 | 83.2 | 76.4 |
| 141923 | 84.3 | 80 | 79.9 | 77.3 | 98.8 | 64.2 |

## CLAIMS

What is claimed is:

1. A compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising a portion which consists of at least 8 contiguous nucleobases complementary to an equal-length portion of 294-317, 406-440, 406-526, 410-436, 410-499, 446-526, 545-581, 591-619, 591-704, 591-743, 595-622, 600-626, 600-639, 600-670, 601-628, 602-628, 603-630, 611-636, 620-647, 638-665, 648-674, 657-684, 705-743, 782-810, 821-859, 835-859, 835-917, 835-942, 860-887, 860-899, 860-909, 860-917, 869-895, 878-905, 888-909, 923-952, 960-1034, 960-1173, 960-986, 967-991, 970-1023, 970-1064, 970-1117, 970-996, 977-1004, 985-1011, 989-1016, 992-1019, 997-1024, 997-1024, 998-1025, 999-1026, 1000-1027, 1001-1028, 1002-1029, 1003-1029, 1004-1029, 1005-1029, 1006-1029, 1007-1034, 1036-1061, 1045-1072, 1076-1096, 1088-1115, 1098-1123, 1200-1251, 1210-1237, 1219-1245, 1228-1251, 1273-1444, 1295-1316, 1318-1345, 1328-1354, 1337-1361, 1344-1371, 1354-1377, 1380-1406, 1389-1416, 1400-1426, 1409-1434, 1465-1491, 1465-1602, 1474-1499, 1482-1519, 1513-1540, 1523-1549, 1526-1602, 1526-1624, 1532-1558, 1541-1568, 1552-1579, 1560-1587, 1561-1589, 1564-1591, 1565-1592, 1566-1592, 1567-1592, 1570-1597, 1571-1599, 1605-1706, 1628-1706, 1640-1666, 1672-1698, 1681-1706, 1735-1761, 1735-1765, 1740-1765, 1849-1876, 1849-1879, 1850-1877, 1851-1877, 1852-1878, 1852-1879, 1853-1879, 1854-1879, 1905-1955, 1915-1942, 1916-1943, 1917-1944, 1918-1945, 1919-1946, 1920-1939, 1920-1947, 1921-1948, 1922-1949, 1923-1950, 1924-1951, 1925-1952, 1926-1952, 1927-1952, 1928-1955, 1962-2059, 2040-2126, 2100-2126, 2100-2139, 2100-2206, 2101-2126, 2305-2332, 2305-2354, 2306-2333, 2307-2334, 2308-2334, 2309-2334, 2310-2334, 2410-2434, 2504-2528, 2509-2528, 2582-2625, 2606-2668, 2828-2855, 2832-2851, 2900-2927, 2900-2929, 2902-2927, 2983-3007, 2983-3013, 3227-3252, 3227-3456, 3472-3496, or 3543-3569 of SEQ ID NO: 1, and wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to SEQ ID NO: 1.

2. The compound of claim 1, wherein the modified oligonucleotide is at least 95% complementary to SEQ ID NO: 1.

3. The compound of claim 2, wherein the modified oligonucleotide is 100% complementary to SEQ ID NO: 1.

4. The compound of claim 1, wherein the modified oligonucleotide hybridizes exclusively within 294-317, 406-440, 406-526, 410-436, 410-499, 446-526, 545-581, 591-619, 591-704, 591-743, 595-622, 600-626, 600-639, 600-670, 601-628, 602-628, 603-630, 611-636, 620-647, 638-665, 648-674, 657-684, 705-743, 782-810, 821-859, 835-859, 835-917, 835-942, 860-887, 860-899, 860-909, 860-917, 869-895, 878-905, 888-909, 923-952, 960-1034, 960-1173, 960-986, 967-991, 970-1023, 970-1064, 970-1117, 970-996, 977-1004, 985-1011, 989-1016, 992-1019, 997-1024, 997-1024, 998-1025, 999-1026, 1000-1027, 1001-1028, 1002-1029, 1003-1029, 1004-1029, 1005-1029, 1006-1029, 1007-1034, 1036-1061, 1045-1072, 1076-1096, 1088-1115, 1098-1123, 1200-1251, 1210-1237, 1219-1245, 1228-1251, 1273-1444, 1295-1316, 1318-1345, 1328-1354, 1337-1361, 1344-1371, 1354-1377, 1380-1406, 1389-1416, 1400-1426, 1409-1434, 1465-1491, 1465-1602, 1474-1499, 1482-1519, 1513-1540, 1523-1549, 1526-1602, 1526-1624, 1532-1558, 1541-1568, 1552-1579, 1560-1587, 1561-1589, 1564-1591, 1565-1592, 1566-1592, 1567-1592, 1570-1597, 1571-1599, 1605-1706, 1628-1706, 1640-1666, 1672-1698, 1681-1706, 1735-1761, 1735-1765, 1740-1765, 1849-1876, 1849-1879, 1850-1877, 1851-1877, 1852-1878, 1852-1879, 1853-1879, 1854-1879, 1905-1955, 1915-1942, 1916-1943, 1917-1944, 1918-1945, 1919-1946, 1920-1939, 1920-1947, 1921-1948, 1922-1949, 1923-1950, 1924-1951, 1925-1952, 1926-1952, 1927-1952, 1928-1955, 1962-2059, 2040-2126, 2100-2126, 2100-2139, 2100-2206, 2101-2126, 2305-2332, 2305-2354, 2306-2333, 2307-2334, 2308-2334, 2309-2334, 2310-2334, 2410-2434, 2504-2528, 2509-2528, 2582-2625, 2606-2668, 2828-2855, 2832-2851, 2900-2927, 2900-2929, 2902-2927, 2983-3007, 2983-3013, 3227-3252, 3227-3456, 3472-3496, or 3543-3569 of SEQ ID NO: 1, and wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to SEQ ID NO: 1.

5. The compound of claim 2, wherein the modified oligonucleotide hybridizes exclusively within 294-317, 406-440, 406-526, 410-436, 410-499, 446-526, 545-581, 591-619, 591-704, 591-743, 595-622, 600-626, 600-639, 600-670, 601-628, 602-628, 603-630, 611-636, 620-647, 638-665, 648-674, 657-684, 705-743, 782-810, 821-859, 835-859, 835-917, 835-942, 860-887, 860-899, 860-909, 860-917, 869-895, 878-905, 888-909, 923-952, 960-1034, 960-1173, 960-986, 967-991, 970-1023, 970-1064, 970-1117, 970-996, 977-1004, 985-1011, 989-1016, 992-1019, 997-1024, 997-1024, 998-1025, 999-1026, 1000-1027, 1001-1028, 1002-1029, 1003-1029, 1004-1029, 1005-1029, 1006-1029, 1007-1034, 1036-1061, 1045-1072, 1076-1096, 1088-1115, 1098-1123, 1200-1251, 1210-1237, 1219-1245, 1228-1251, 1273-1444, 1295-1316, 1318-

1345, 1328-1354, 1337-1361, 1344-1371, 1354-1377, 1380-1406, 1389-1416, 1400-1426, 1409-1434, 1465-1491, 1465-1602, 1474-1499, 1482-1519, 1513-1540, 1523-1549, 1526-1602, 1526-1624, 1532-1558, 1541-1568, 1552-1579, 1560-1587, 1561-1589, 1564-1591, 1565-1592, 1566-1592, 1567-1592, 1570-1597, 1571-1599, 1605-1706, 1628-1706, 1640-1666, 1672-1698, 1681-1706, 1735-1761, 1735-1765, 1740-1765, 1849-1876, 1849-1879, 1850-1877, 1851-1877, 1852-1878, 1852-1879, 1853-1879, 1854-1879, 1905-1955, 1915-1942, 1916-1943, 1917-1944, 1918-1945, 1919-1946, 1920-1939, 1920-1947, 1921-1948, 1922-1949, 1923-1950, 1924-1951, 1925-1952, 1926-1952, 1927-1952, 1928-1955, 1962-2059, 2040-2126, 2100-2126, 2100-2139, 2100-2206, 2101-2126, 2305-2332, 2305-2354, 2306-2333, 2307-2334, 2308-2334, 2309-2334, 2310-2334, 2410-2434, 2504-2528, 2509-2528, 2582-2625, 2606-2668, 2828-2855, 2832-2851, 2900-2927, 2900-2929, 2902-2927, 2983-3007, 2983-3013, 3227-3252, 3227-3456, 3472-3496, or 3543-3569 of SEQ ID NO: 1, and wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to SEQ ID NO: 1.

6. The compound of claim 3, wherein the modified oligonucleotide hybridizes exclusively within 294-317, 406-440, 406-526, 410-436, 410-499, 446-526, 545-581, 591-619, 591-704, 591-743, 595-622, 600-626, 600-639, 600-670, 601-628, 602-628, 603-630, 611-636, 620-647, 638-665, 648-674, 657-684, 705-743, 782-810, 821-859, 835-859, 835-917, 835-942, 860-887, 860-899, 860-909, 860-917, 869-895, 878-905, 888-909, 923-952, 960-1034, 960-1173, 960-986, 967-991, 970-1023, 970-1064, 970-1117, 970-996, 977-1004, 985-1011, 989-1016, 992-1019, 997-1024, 997-1024, 998-1025, 999-1026, 1000-1027, 1001-1028, 1002-1029, 1003-1029, 1004-1029, 1005-1029, 1006-1029, 1007-1034, 1036-1061, 1045-1072, 1076-1096, 1088-1115, 1098-1123, 1200-1251, 1210-1237, 1219-1245, 1228-1251, 1273-1444, 1295-1316, 1318-1345, 1328-1354, 1337-1361, 1344-1371, 1354-1377, 1380-1406, 1389-1416, 1400-1426, 1409-1434, 1465-1491, 1465-1602, 1474-1499, 1482-1519, 1513-1540, 1523-1549, 1526-1602, 1526-1624, 1532-1558, 1541-1568, 1552-1579, 1560-1587, 1561-1589, 1564-1591, 1565-1592, 1566-1592, 1567-1592, 1570-1597, 1571-1599, 1605-1706, 1628-1706, 1640-1666, 1672-1698, 1681-1706, 1735-1761, 1735-1765, 1740-1765, 1849-1876, 1849-1879, 1850-1877, 1851-1877, 1852-1878, 1852-1879, 1853-1879, 1854-1879, 1905-1955, 1915-1942, 1916-1943, 1917-1944, 1918-1945, 1919-1946, 1920-1939, 1920-1947, 1921-1948, 1922-1949, 1923-1950, 1924-1951, 1925-1952, 1926-1952, 1927-1952, 1928-1955, 1962-2059, 2040-2126, 2100-2126, 2100-2139, 2100-2206, 2101-2126, 2305-2332, 2305-2354, 2306-2333, 2307-2334, 2308-2334, 2309-2334, 2310-2334, 2410-2434, 2504-2528, 2509-2528, 2582-2625, 2606-2668, 2828-2855, 2832-2851, 2900-

2927, 2900-2929, 2902-2927, 2983-3007, 2983-3013, 3227-3252, 3227-3456, 3472-3496, or 3543-3569 of SEQ ID NO: 1, and wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to SEQ ID NO: 1.

7. A compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising a portion of at least 8 contiguous nucleobases fully complementary to an equal length portion of nucleobases 294-317, 406-440, 406-526, 410-436, 410-499, 446-526, 545-581, 591-619, 591-704, 591-743, 595-622, 600-626, 600-639, 600-670, 601-628, 602-628, 603-630, 611-636, 620-647, 638-665, 648-674, 657-684, 705-743, 782-810, 821-859, 835-859, 835-917, 835-942, 860-887, 860-899, 860-909, 860-917, 869-895, 878-905, 888-909, 923-952, 960-1034, 960-1173, 960-986, 967-991, 970-1023, 970-1064, 970-1117, 970-996, 977-1004, 985-1011, 989-1016, 992-1019, 997-1024, 997-1024, 998-1025, 999-1026, 1000-1027, 1001-1028, 1002-1029, 1003-1029, 1004-1029, 1005-1029, 1006-1029, 1007-1034, 1036-1061, 1045-1072, 1076-1096, 1088-1115, 1098-1123, 1200-1251, 1210-1237, 1219-1245, 1228-1251, 1273-1444, 1295-1316, 1318-1345, 1328-1354, 1337-1361, 1344-1371, 1354-1377, 1380-1406, 1389-1416, 1400-1426, 1409-1434, 1465-1491, 1465-1602, 1474-1499, 1482-1519, 1513-1540, 1523-1549, 1526-1602, 1526-1624, 1532-1558, 1541-1568, 1552-1579, 1560-1587, 1561-1589, 1564-1591, 1565-1592, 1566-1592, 1567-1592, 1570-1597, 1571-1599, 1605-1706, 1628-1706, 1640-1666, 1672-1698, 1681-1706, 1735-1761, 1735-1765, 1740-1765, 1849-1876, 1849-1879, 1850-1877, 1851-1877, 1852-1878, 1852-1879, 1853-1879, 1854-1879, 1905-1955, 1915-1942, 1916-1943, 1917-1944, 1918-1945, 1919-1946, 1920-1939, 1920-1947, 1921-1948, 1922-1949, 1923-1950, 1924-1951, 1925-1952, 1926-1952, 1927-1952, 1928-1955, 1962-2059, 2040-2126, 2100-2126, 2100-2139, 2100-2206, 2101-2126, 2305-2332, 2305-2354, 2306-2333, 2307-2334, 2308-2334, 2309-2334, 2310-2334, 2410-2434, 2504-2528, 2509-2528, 2582-2625, 2606-2668, 2828-2855, 2832-2851, 2900-2927, 2900-2929, 2902-2927, 2983-3007, 2983-3013, 3227-3252, 3227-3456, 3472-3496, or 3543-3569 of SEQ ID NO: 1, and wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to SEQ ID NO: 1.

8. The compound of claim 7, wherein the modified oligonucleotide is at least 95% complementary to SEQ ID NO: 1.

9. The compound of claim 7, wherein the modified oligonucleotide is 100% complementary to SEQ ID NO: 1.

10. The compound of claim 7, wherein the modified oligonucleotide hybridizes exclusively within 294-317, 406-440, 406-526, 410-436, 410-499, 446-526, 545-581, 591-619, 591-704, 591-743, 595-622, 600-626, 600-639, 600-670, 601-628, 602-628, 603-630, 611-636, 620-647, 638-665, 648-674, 657-684, 705-743, 782-810, 821-859, 835-859, 835-917, 835-942, 860-887, 860-899, 860-909, 860-917, 869-895, 878-905, 888-909, 923-952, 960-1034, 960-1173, 960-986, 967-991, 970-1023, 970-1064, 970-1117, 970-996, 977-1004, 985-1011, 989-1016, 992-1019, 997-1024, 997-1024, 998-1025, 999-1026, 1000-1027, 1001-1028, 1002-1029, 1003-1029, 1004-1029, 1005-1029, 1006-1029, 1007-1034, 1036-1061, 1045-1072, 1076-1096, 1088-1115, 1098-1123, 1200-1251, 1210-1237, 1219-1245, 1228-1251, 1273-1444, 1295-1316, 1318-1345, 1328-1354, 1337-1361, 1344-1371, 1354-1377, 1380-1406, 1389-1416, 1400-1426, 1409-1434, 1465-1491, 1465-1602, 1474-1499, 1482-1519, 1513-1540, 1523-1549, 1526-1602, 1526-1624, 1532-1558, 1541-1568, 1552-1579, 1560-1587, 1561-1589, 1564-1591, 1565-1592, 1566-1592, 1567-1592, 1570-1597, 1571-1599, 1605-1706, 1628-1706, 1640-1666, 1672-1698, 1681-1706, 1735-1761, 1735-1765, 1740-1765, 1849-1876, 1849-1879, 1850-1877, 1851-1877, 1852-1878, 1852-1879, 1853-1879, 1854-1879, 1905-1955, 1915-1942, 1916-1943, 1917-1944, 1918-1945, 1919-1946, 1920-1939, 1920-1947, 1921-1948, 1922-1949, 1923-1950, 1924-1951, 1925-1952, 1926-1952, 1927-1952, 1928-1955, 1962-2059, 2040-2126, 2100-2126, 2100-2139, 2100-2206, 2101-2126, 2305-2332, 2305-2354, 2306-2333, 2307-2334, 2308-2334, 2309-2334, 2310-2334, 2410-2434, 2504-2528, 2509-2528, 2582-2625, 2606-2668, 2828-2855, 2832-2851, 2900-2927, 2900-2929, 2902-2927, 2983-3007, 2983-3013, 3227-3252, 3227-3456, 3472-3496, or 3543-3569 of SEQ ID NO: 1, and wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to SEQ ID NO: 1.

11. The compound of claim 8, wherein the modified oligonucleotide hybridizes exclusively within 294-317, 406-440, 406-526, 410-436, 410-499, 446-526, 545-581, 591-619, 591-704, 591-743, 595-622, 600-626, 600-639, 600-670, 601-628, 602-628, 603-630, 611-636, 620-647, 638-665, 648-674, 657-684, 705-743, 782-810, 821-859, 835-859, 835-917, 835-942, 860-887, 860-899, 860-909, 860-917, 869-895, 878-905, 888-909, 923-952, 960-1034, 960-1173, 960-986, 967-991, 970-1023, 970-1064, 970-1117, 970-996, 977-1004, 985-1011, 989-1016, 992-1019, 997-1024, 997-1024, 998-1025, 999-1026, 1000-1027, 1001-1028, 1002-1029, 1003-

1029, 1004-1029, 1005-1029, 1006-1029, 1007-1034, 1036-1061, 1045-1072, 1076-1096, 1088-1115, 1098-1123, 1200-1251, 1210-1237, 1219-1245, 1228-1251, 1273-1444, 1295-1316, 1318-1345, 1328-1354, 1337-1361, 1344-1371, 1354-1377, 1380-1406, 1389-1416, 1400-1426, 1409-1434, 1465-1491, 1465-1602, 1474-1499, 1482-1519, 1513-1540, 1523-1549, 1526-1602, 1526-1624, 1532-1558, 1541-1568, 1552-1579, 1560-1587, 1561-1589, 1564-1591, 1565-1592, 1566-1592, 1567-1592, 1570-1597, 1571-1599, 1605-1706, 1628-1706, 1640-1666, 1672-1698, 1681-1706, 1735-1761, 1735-1765, 1740-1765, 1849-1876, 1849-1879, 1850-1877, 1851-1877, 1852-1878, 1852-1879, 1853-1879, 1854-1879, 1905-1955, 1915-1942, 1916-1943, 1917-1944, 1918-1945, 1919-1946, 1920-1939, 1920-1947, 1921-1948, 1922-1949, 1923-1950, 1924-1951, 1925-1952, 1926-1952, 1927-1952, 1928-1955, 1962-2059, 2040-2126, 2100-2126, 2100-2139, 2100-2206, 2101-2126, 2305-2332, 2305-2354, 2306-2333, 2307-2334, 2308-2334, 2309-2334, 2310-2334, 2410-2434, 2504-2528, 2509-2528, 2582-2625, 2606-2668, 2828-2855, 2832-2851, 2900-2927, 2900-2929, 2902-2927, 2983-3007, 2983-3013, 3227-3252, 3227-3456, 3472-3496, or 3543-3569 of SEQ ID NO: 1, and wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to SEQ ID NO: 1.

12. The compound of claim 9, wherein the modified oligonucleotide hybridizes exclusively within 294-317, 406-440, 406-526, 410-436, 410-499, 446-526, 545-581, 591-619, 591-704, 591-743, 595-622, 600-626, 600-639, 600-670, 601-628, 602-628, 603-630, 611-636, 620-647, 638-665, 648-674, 657-684, 705-743, 782-810, 821-859, 835-859, 835-917, 835-942, 860-887, 860-899, 860-909, 860-917, 869-895, 878-905, 888-909, 923-952, 960-1034, 960-1173, 960-986, 967-991, 970-1023, 970-1064, 970-1117, 970-996, 977-1004, 985-1011, 989-1016, 992-1019, 997-1024, 997-1024, 998-1025, 999-1026, 1000-1027, 1001-1028, 1002-1029, 1003-1029, 1004-1029, 1005-1029, 1006-1029, 1007-1034, 1036-1061, 1045-1072, 1076-1096, 1088-1115, 1098-1123, 1200-1251, 1210-1237, 1219-1245, 1228-1251, 1273-1444, 1295-1316, 1318-1345, 1328-1354, 1337-1361, 1344-1371, 1354-1377, 1380-1406, 1389-1416, 1400-1426, 1409-1434, 1465-1491, 1465-1602, 1474-1499, 1482-1519, 1513-1540, 1523-1549, 1526-1602, 1526-1624, 1532-1558, 1541-1568, 1552-1579, 1560-1587, 1561-1589, 1564-1591, 1565-1592, 1566-1592, 1567-1592, 1570-1597, 1571-1599, 1605-1706, 1628-1706, 1640-1666, 1672-1698, 1681-1706, 1735-1761, 1735-1765, 1740-1765, 1849-1876, 1849-1879, 1850-1877, 1851-1877, 1852-1878, 1852-1879, 1853-1879, 1854-1879, 1905-1955, 1915-1942, 1916-1943, 1917-1944, 1918-1945, 1919-1946, 1920-1939, 1920-1947, 1921-1948, 1922-1949, 1923-1950, 1924-1951, 1925-1952, 1926-1952, 1927-1952, 1928-1955, 1962-2059, 2040-2126, 2100-2126, 2100-2139, 2100-

2206, 2101-2126, 2305-2332, 2305-2354, 2306-2333, 2307-2334, 2308-2334, 2309-2334, 2310-2334, 2410-2434, 2504-2528, 2509-2528, 2582-2625, 2606-2668, 2828-2855, 2832-2851, 2900-2927, 2900-2929, 2902-2927, 2983-3007, 2983-3013, 3227-3252, 3227-3456, 3472-3496, or 3543-3569 of SEQ ID NO: 1, and wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to SEQ ID NO: 1.

13. The compound of claim 1, consisting of a single-stranded modified oligonucleotide.

14. The compound of claim 13, wherein at least one internucleoside linkage is a phosphorothioate internucleoside linkage.

15. The compound of claim 1, wherein each internucleoside linkage is a phosphorothioate internucleoside linkage.

16. The compound of claim 15, wherein at least one nucleoside comprises a modified sugar.

17. The compound of claim 16, wherein at least one modified sugar is a bicyclic sugar.

18. The compound of claim 17, wherein at least one modified sugar comprises a 2'-O-methoxyethyl.

19. The compound of claim 15, wherein at least one nucleoside comprises a modified nucleobase.

20. The compound of claim 19, wherein the modified nucleobase is a 5-methylcytosine.

21. The compound of claim 1, wherein the modified oligonucleotide comprises:
a gap segment consisting of linked deoxynucleosides;
a 5' wing segment consisting of linked nucleosides; and

a 3' wing segment consisting of linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment; and wherein each nucleoside of each wing segment comprises a modified sugar.

22. The compound of claim 21, wherein the modified oligonucleotide comprises:

a gap segment consisting of ten linked deoxynucleosides;

a 5' wing segment consisting of five linked nucleosides; and

a 3' wing segment consisting of five linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar; and wherein each internucleoside linkage is a phosphorothioate linkage.

23. The antisense compound of claim 21, wherein the antisense compound is a chimeric oligonucleotide consisting of:

a gap segment consisting of from 10 to 18 linked 2'-deoxynucleosides;

a 5' wing segment consisting of from 1 to 5 linked nucleosides; and

a 3' wing segment consisting of from 1 to 5 linked nucleosides;

wherein each nucleoside of the 5' wing segment is a sugar-modified nucleoside, each nucleoside of the 3' wing segment is a sugar-modified nucleoside, and each internucleoside linkage is a phosphorothioate internucleoside linkage.

24. The compound of claim 2, wherein the modified oligonucleotide consists of 20 linked nucleosides.

25. A composition comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of a nucleobase sequence selected from among the nucleobase sequences recited in 294-317, 406-440, 406-526, 410-436, 410-499, 446-526, 545-581, 591-619, 591-704, 591-743, 595-622, 600-626, 600-639, 600-670, 601-628, 602-628, 603-630, 611-636, 620-647, 638-665, 648-674, 657-684, 705-743, 782-810, 821-859, 835-859, 835-917, 835-942, 860-887, 860-899, 860-909, 860-917, 869-895, 878-905, 888-909, 923-952, 960-1034, 960-1173, 960-986, 967-991, 970-1023, 970-1064, 970-1117, 970-996, 977-1004, 985-1011, 989-1016, 992-1019, 997-1024, 997-1024, 998-1025, 999-1026, 1000-1027, 1001-1028, 1002-1029, 1003-1029, 1004-1029,

1005-1029, 1006-1029, 1007-1034, 1036-1061, 1045-1072, 1076-1096, 1088-1115, 1098-1123, 1200-1251, 1210-1237, 1219-1245, 1228-1251, 1273-1444, 1295-1316, 1318-1345, 1328-1354, 1337-1361, 1344-1371, 1354-1377, 1380-1406, 1389-1416, 1400-1426, 1409-1434, 1465-1491, 1465-1602, 1474-1499, 1482-1519, 1513-1540, 1523-1549, 1526-1602, 1526-1624, 1532-1558, 1541-1568, 1552-1579, 1560-1587, 1561-1589, 1564-1591, 1565-1592, 1566-1592, 1567-1592, 1570-1597, 1571-1599, 1605-1706, 1628-1706, 1640-1666, 1672-1698, 1681-1706, 1735-1761, 1735-1765, 1740-1765, 1849-1876, 1849-1879, 1850-1877, 1851-1877, 1852-1878, 1852-1879, 1853-1879, 1854-1879, 1905-1955, 1915-1942, 1916-1943, 1917-1944, 1918-1945, 1919-1946, 1920-1939, 1920-1947, 1921-1948, 1922-1949, 1923-1950, 1924-1951, 1925-1952, 1926-1952, 1927-1952, 1928-1955, 1962-2059, 2040-2126, 2100-2126, 2100-2139, 2100-2206, 2101-2126, 2305-2332, 2305-2354, 2306-2333, 2307-2334, 2308-2334, 2309-2334, 2310-2334, 2410-2434, 2504-2528, 2509-2528, 2582-2625, 2606-2668, 2828-2855, 2832-2851, 2900-2927, 2900-2929, 2902-2927, 2983-3007, 2983-3013, 3227-3252, 3227-3456, 3472-3496, and 3543-3569 of SEQ ID NO: 1, or a salt thereof and a pharmaceutically acceptable carrier or diluent.

26. The composition of claim 25, wherein the modified oligonucleotide is a single-stranded oligonucleotide.

27. The composition of claim 25, wherein the modified oligonucleotide consists of 20 linked nucleosides.

28. A method comprising administering to an animal a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising a portion which consists of at least 8 contiguous nucleobases complementary to an equal-length portion of 294-317, 406-440, 406-526, 410-436, 410-499, 446-526, 545-581, 591-619, 591-704, 591-743, 595-622, 600-626, 600-639, 600-670, 601-628, 602-628, 603-630, 611-636, 620-647, 638-665, 648-674, 657-684, 705-743, 782-810, 821-859, 835-859, 835-917, 835-942, 860-887, 860-899, 860-909, 860-917, 869-895, 878-905, 888-909, 923-952, 960-1034, 960-1173, 960-986, 967-991, 970-1023, 970-1064, 970-1117, 970-996, 977-1004, 985-1011, 989-1016, 992-1019, 997-1024, 997-1024, 998-1025, 999-1026, 1000-1027, 1001-1028, 1002-1029, 1003-1029, 1004-1029, 1005-1029, 1006-1029, 1007-1034, 1036-1061, 1045-1072, 1076-1096, 1088-1115, 1098-1123, 1200-1251, 1210-1237, 1219-1245, 1228-1251, 1273-1444, 1295-1316, 1318-1345, 1328-1354, 1337-1361, 1344-1371, 1354-1377, 1380-1406, 1389-1416, 1400-1426, 1409-1434, 1465-1491,

1465-1602, 1474-1499, 1482-1519, 1513-1540, 1523-1549, 1526-1602, 1526-1624, 1532-1558, 1541-1568, 1552-1579, 1560-1587, 1561-1589, 1564-1591, 1565-1592, 1566-1592, 1567-1592, 1570-1597, 1571-1599, 1605-1706, 1628-1706, 1640-1666, 1672-1698, 1681-1706, 1735-1761, 1735-1765, 1740-1765, 1849-1876, 1849-1879, 1850-1877, 1851-1877, 1852-1878, 1852-1879, 1853-1879, 1854-1879, 1905-1955, 1915-1942, 1916-1943, 1917-1944, 1918-1945, 1919-1946, 1920-1939, 1920-1947, 1921-1948, 1922-1949, 1923-1950, 1924-1951, 1925-1952, 1926-1952, 1927-1952, 1928-1955, 1962-2059, 2040-2126, 2100-2126, 2100-2139, 2100-2206, 2101-2126, 2305-2332, 2305-2354, 2306-2333, 2307-2334, 2308-2334, 2309-2334, 2310-2334, 2410-2434, 2504-2528, 2509-2528, 2582-2625, 2606-2668, 2828-2855, 2832-2851, 2900-2927, 2900-2929, 2902-2927, 2983-3007, 2983-3013, 3227-3252, 3227-3456, 3472-3496, or 3543-3569 of SEQ ID NO: 1, and wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to SEQ ID NO: 1.

29. The method of claim 28, wherein the animal is a human.

30. The method of claim 29, wherein administering the compound slows progression and/or ameliorates hypercholesterolemia, acute coronary syndrome, polygenic hypercholesterolemia, mixed dyslipidemia, coronary heart disease, early onset coronary heart disease, type II diabetes, type II diabetes with dyslipidemia, hepatic steatosis, non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, hypertriglyceridemia, hyperfattyacidemia, hyperlipidemia, metabolic syndrome, atherosclerosis, or improves cardiovascular outcome, or any combination thereof.

31. The method of claim 28 comprising co-administering the compound and at least one additional therapy.

32. The method of claim 31, wherein the compound and additional therapy are administered concomitantly.

33. The method of claim 31, wherein the compound and the additional therapy are administered in the same formulation.

34. The method of claim 31, wherein the additional therapy is a lipid lowering therapy.

35. The method of claim 34, wherein the lipid lowering therapy is a therapeutic lifestyle change, HMG-CoA reductase inhibitor, cholesterol absorption inhibitor, MTP inhibitor, antisense compound targeted to ApoB, or any combination thereof.

36. The method of claim 35, wherein the HMG-CoA reductase inhibitor is atorvastatin, rosuvastatin, or simvastatin.

37. The method of claim 35, wherein the cholesterol absorption inhibitor is ezetimibe.

38. The method of claims 35, wherein the additional lipid lowering therapy comprises an HMG-CoA reductase inhibitor that is simivastatin, and a cholesterol absorption inhibitor that is ezetimibe.

39. The method of claim 35, wherein the antisense compound is ISIS 301012.

40. The method of claim 28, wherein the administering is parenteral administration.

41. The method of claim 40, wherein the parenteral administration comprises subcutaneous or intravenous administration.

42. The method of claim 28, wherein the administering comprises oral administration.

43. A method comprising administering to a human with hypercholesterolemia, polygenic hypercholesterolemia, mixed dyslipidemia, coronary heart disease, acute coronary syndrome, early onset coronary heart disease, type II diabetes, type II diabetes with dyslipidemia, hepatic steatosis, non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, hypertriglyceridemia, hyperfattyacidemia, hyperlipidemia, metabolic syndrome, atherosclerosis, elevated ApoB, elevated cholesterol, elevated LDL-cholesterol, elevated VLDL-cholesterol, or elevated non-HDL cholesterol, a therapeutically effective amount of a composition comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase

sequence comprising at least 8 contiguous nucleobases complementary to an equal-length portion of 294-317, 406-440, 406-526, 410-436, 410-499, 446-526, 545-581, 591-619, 591-704, 591-743, 595-622, 600-626, 600-639, 600-670, 601-628, 602-628, 603-630, 611-636, 620-647, 638-665, 648-674, 657-684, 705-743, 782-810, 821-859, 835-859, 835-917, 835-942, 860-887, 860-899, 860-909, 860-917, 869-895, 878-905, 888-909, 923-952, 960-1034, 960-1173, 960-986, 967-991, 970-1023, 970-1064, 970-1117, 970-996, 977-1004, 985-1011, 989-1016, 992-1019, 997-1024, 997-1024, 998-1025, 999-1026, 1000-1027, 1001-1028, 1002-1029, 1003-1029, 1004-1029, 1005-1029, 1006-1029, 1007-1034, 1036-1061, 1045-1072, 1076-1096, 1088-1115, 1098-1123, 1200-1251, 1210-1237, 1219-1245, 1228-1251, 1273-1444, 1295-1316, 1318-1345, 1328-1354, 1337-1361, 1344-1371, 1354-1377, 1380-1406, 1389-1416, 1400-1426, 1409-1434, 1465-1491, 1465-1602, 1474-1499, 1482-1519, 1513-1540, 1523-1549, 1526-1602, 1526-1624, 1532-1558, 1541-1568, 1552-1579, 1560-1587, 1561-1589, 1564-1591, 1565-1592, 1566-1592, 1567-1592, 1570-1597, 1571-1599, 1605-1706, 1628-1706, 1640-1666, 1672-1698, 1681-1706, 1735-1761, 1735-1765, 1740-1765, 1849-1876, 1849-1879, 1850-1877, 1851-1877, 1852-1878, 1852-1879, 1853-1879, 1854-1879, 1905-1955, 1915-1942, 1916-1943, 1917-1944, 1918-1945, 1919-1946, 1920-1939, 1920-1947, 1921-1948, 1922-1949, 1923-1950, 1924-1951, 1925-1952, 1926-1952, 1927-1952, 1928-1955, 1962-2059, 2040-2126, 2100-2126, 2100-2139, 2100-2206, 2101-2126, 2305-2332, 2305-2354, 2306-2333, 2307-2334, 2308-2334, 2309-2334, 2310-2334, 2410-2434, 2504-2528, 2509-2528, 2582-2625, 2606-2668, 2828-2855, 2832-2851, 2900-2927, 2900-2929, 2902-2927, 2983-3007, 2983-3013, 3227-3252, 3227-3456, 3472-3496, or 3543-3569 of SEQ ID NO: 1, and wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to SEQ ID NO: 1.

44. The method of claim 28, wherein the animal has hypercholesterolemia, polygenic hypercholesterolemia, mixed dyslipidemia, a history of coronary heart disease, coronary heart disease, acute coronary syndrome, early onset coronary heart disease, one or more risk factors for coronary heart disease, type II diabetes, type II diabetes with dyslipidemia, hepatic steatosis, non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, hypertriglyceridemia, hyperfattyacidemia, hyperlipidemia, metabolic syndrome, atherosclerosis, elevated ApoB, elevated cholesterol, elevated LDL-cholesterol, elevated VLDL-cholesterol, elevated IDL-cholesterol, or elevated non-HDL cholesterol.

45. The method of claim 44, wherein the elevated LDL-cholesterol level is above a target level of at least about 100 mg/dL, 130 mg/dL, 160 mg/dL, or 190 mg/dL.

46. The method of claim 44, wherein the administering the compound to the animal reduces LDL-cholesterol levels.

47. The method of claim 46, wherein administering the compound results in an LDL-cholesterol level below a target level of at least about 190 mg/dL, 160 mg/dL, 130 mg/dL, 100 mg/dL, 70 mg/dL, or 50 mg/dL.

48. The method of claim 44, wherein the one or more risk factors is selected from age, smoking, hypertension, low HDL-cholesterol, and a family history of early coronary heart disease.

49. The method of claim 44, wherein the animal failed to meet the LDL-cholesterol target level on lipid-lowering therapy, did not comply with the recommend therapy, experienced side effects of therapy, or any combination thereof.

50. The method of claim 49, wherein the lipid-lowering therapy is a statin.

51. The method of claim 49, wherein the lipid-lowering therapy is ezetimibe.

52. The method of claim 28, wherein administering results in a reduction of ApoB, LDL-cholesterol, VLDL-cholesterol, Lp(a), small LDL-particle, small VLDL-particle, non-HDL-cholesterol, liver triglyceride level, serum triglycerides, serum phospholipids, or any combination thereof.

53. The method of claim 52, wherein the ApoB reduction is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

54. The method of claim 53, wherein the ApoB reduction is between 10% and 80%, between 20% and 70%, between 30% and 60%, or between 30% and 70%.

55. The method of claim 52, wherein the LDL-cholesterol reduction is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

56. The method of claim 52, wherein the VLDL-cholesterol reduction is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

57. The method of claim 52, wherein the Lp(a) reduction is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

58. The method of claim 52, wherein the small LDL-particle reduction is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

59. The method of claim 52, wherein the small VLDL-particle reduction is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

60. The method of claim 52, wherein the non-HDL-cholesterol reduction is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

61. The method of claim 52, wherein the liver triglyceride level reduction is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

62. The method of claim 52, wherein the administering of the pharmaceutical composition results in a serum triglyceride reduction of at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

63. The method of claim 52, wherein the administering of the pharmaceutical composition results in a serum phospholipid reduction of at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

64. The method of claims 52 or 53, wherein the serum phospholipid is serum oxidized phospholipid.

65. The method of claim 28, wherein administering results in reduced coronary heart disease risk, or slows, stops or prevents the progression of atherosclerosis, or any combination thereof.

66. The method of claim 28, wherein administering results in improved cardiovascular outcome of the human.

67. The method of claim 66, wherein the improved cardiovascular outcome is improved carotid intimal media thickness, improved atheroma thickness, increased HDL-cholesterol, or any combination thereof.

68. The method of claim 28, wherein administering ameliorates hepatic steatosis, results in lipid lowering, improves LDL/HDL ration, or any combination thereof.

69. A compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising a portion which consists of at least 8 contiguous nucleobases complementary to an equal-length portion of 2274-2400, 2274-2575, 2433-2570, 2433-2579, 2549-2575, 2552-2579, 2585-2638, 2605-2638, 3056-3075, 4150-5159, 4306-4325, 5590-5618, 5667-5686, 6444-6463, 6482-6518, 6492-6518, 6528-6555, 6528-6623, 6534-6561, 6535-6562, 6536-6563, 6537-6563, 6538-6565, 6539-6565, 6540-6567, 6541-6567, 6542-6569, 6546-6573, 6557-6584, 6575-6602, 6585-6611, 6594-6621, 6596-6623, 6652-6671, 7099-7118, 7556-7584, 8836-8855, 8948-8967, 9099-9118, 9099-9168, 9130-9168, 9207-9233, 9207-9235, 9209-9235, 10252-10271, 10633-10652, 11308-11491, 12715-12734, 12928-12947, 13681-13700, 13746-13779, 13816-13847, 13903-13945, 13977-14141, 14179-14198, 14267-14286, 14397-14423, 14441-14460, 14494-14513, 14494-14543, 14524-14543, 14601-14650, 14670-14700, 14675-14700, 14801-14828, 14877-14912, 14877-14915, 14877-14973, 14916-14943, 14916-14973, 14925-14951, 14934-14963, 14946-14973, 14979-14998, 15254-15280, 15254-15328, 15264-15290, 15279-15305, 15291-15318, 15292-15319, 15293-15320, 15294-15321, 15294-15321, 15295-15322, 15296-15323, 15297-15323, 15298-15323, 15299-15323, 15300-15323, 15301-15328, 15330-15355, 15330-15490, 15339-15366, 15358-15490, 16134-16153, 16668-16687, 17267-17286, 18377-18427, 18561-18580, 18591-18618, 18591-18646, 18591-18668, 18695-18746, 18705-18730, 18709-18736, 18719-18746, 19203-20080, 19931-19952, 19954-19981, 19964-19990, 19973-19999, 19982-20009, 19992-20016, 20016-20042, 20025-20052, 20036-20062, 20045-20070, 20100-20119, 20188-20207, 20624-20650, 20624-20759, 20629-20804, 20633-20660, 20635-20781, 20643-20662, 20657-20676, 20670-20697, 20680-20706, 20683-20781, 20689-20715, 20698-20725, 20709-20736, 20717-20744, 20718-20745, 20719-20746, 20720-20747, 20721-20748, 20722-20749, 20727-20752, 20735-20759, 20762-21014, 20785-21014, 21082-21107, 21082-21152, 21091-21114, 21118-21144, 21127-21152, 21181-21209, 21181-21211, 21183-21211, 21481-21500, 21589-21608, 21692-21719, 22000-22227, 22096-22115, 22096-22223, 22096-22311, 22133-22160, 22133-22163, 22134-22161, 22135-22162, 22136-22163, 22137-22163, 22138-22163, 22189-22239, 22199-22226, 22199-22227, 22200-22227, 22201-22228, 22202-22229, 22203-22230, 22204-22231, 22205-22232, 22206-22233, 22207-22234, 22208-22235, 22209-22236, 22210-22236, 22210-22239, 22211-22236, 22212-22239, 22292-22311, 23985-24054, 24035-24134, 24095-24121, 24858-24877, 24907-24926, 25413-25432, 25994-26013, 26112-26139, 26112-26161, 26112-27303, 26113-26140, 26114-26141, 26115-26141, 26116-26141, 26117-26141, 26117-26475, 26118-

26141, 26120-26141, 26132-26151, 26142-26161, 26217-26241, 26311-26335, 26389-26432, 26456-26576, 26635-26662, 26707-26734, 26707-26736, 26790-26820, 27034-27263, 27279-27303, or 27350-27376 of SEQ ID NO: 2, and wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to SEQ ID NO: 2.

70. The compound of claim 69, wherein the modified oligonucleotide is at least 95% complementary to SEQ ID NO: 2.

71. The compound of claim 70, wherein the modified oligonucleotide is 100% complementary to SEQ ID NO: 2.

72. The compound of claim 69, wherein the modified oligonucleotide hybridizes exclusively within 2274-2400, 2274-2575, 2433-2570, 2433-2579, 2549-2575, 2552-2579, 2585-2638, 2605-2638, 3056-3075, 4150-5159, 4306-4325, 5590-5618, 5667-5686, 6444-6463, 6482-6518, 6492-6518, 6528-6555, 6528-6623, 6534-6561, 6535-6562, 6536-6563, 6537-6563, 6538-6565, 6539-6565, 6540-6567, 6541-6567, 6542-6569, 6546-6573, 6557-6584, 6575-6602, 6585-6611, 6594-6621, 6596-6623, 6652-6671, 7099-7118, 7556-7584, 8836-8855, 8948-8967, 9099-9118, 9099-9168, 9130-9168, 9207-9233, 9207-9235, 9209-9235, 10252-10271, 10633-10652, 11308-11491, 12715-12734, 12928-12947, 13681-13700, 13746-13779, 13816-13847, 13903-13945, 13977-14141, 14179-14198, 14267-14286, 14397-14423, 14441-14460, 14494-14513, 14494-14543, 14524-14543, 14601-14650, 14670-14700, 14675-14700, 14801-14828, 14877-14912, 14877-14915, 14877-14973, 14916-14943, 14916-14973, 14925-14951, 14934-14963, 14946-14973, 14979-14998, 15254-15280, 15254-15328, 15264-15290, 15279-15305, 15291-15318, 15292-15319, 15293-15320, 15294-15321, 15294-15321, 15295-15322, 15296-15323, 15297-15323, 15298-15323, 15299-15323, 15300-15323, 15301-15328, 15330-15355, 15330-15490, 15339-15366, 15358-15490, 16134-16153, 16668-16687, 17267-17286, 18377-18427, 18561-18580, 18591-18618, 18591-18646, 18591-18668, 18695-18746, 18705-18730, 18709-18736, 18719-18746, 19203-20080, 19931-19952, 19954-19981, 19964-19990, 19973-19999, 19982-20009, 19992-20016, 20016-20042, 20025-20052, 20036-20062, 20045-20070, 20100-20119, 20188-20207, 20624-20650, 20624-20759, 20629-20804, 20633-20660, 20635-20781, 20643-20662, 20657-20676, 20670-20697, 20680-20706, 20683-20781, 20689-20715, 20698-20725, 20709-20736, 20717-20744, 20718-20745, 20719-20746, 20720-20747, 20721-20748, 20722-20749, 20727-20752, 20735-20759, 20762-21014, 20785-21014, 21082-21107, 21082-

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73. The compound of claim 70, wherein the modified oligonucleotide hybridizes exclusively within 2274-2400, 2274-2575, 2433-2570, 2433-2579, 2549-2575, 2552-2579, 2585-2638, 2605-2638, 3056-3075, 4150-5159, 4306-4325, 5590-5618, 5667-5686, 6444-6463, 6482-6518, 6492-6518, 6528-6555, 6528-6623, 6534-6561, 6535-6562, 6536-6563, 6537-6563, 6538-6565, 6539-6565, 6540-6567, 6541-6567, 6542-6569, 6546-6573, 6557-6584, 6575-6602, 6585-6611, 6594-6621, 6596-6623, 6652-6671, 7099-7118, 7556-7584, 8836-8855, 8948-8967, 9099-9118, 9099-9168, 9130-9168, 9207-9233, 9207-9235, 9209-9235, 10252-10271, 10633-10652, 11308-11491, 12715-12734, 12928-12947, 13681-13700, 13746-13779, 13816-13847, 13903-13945, 13977-14141, 14179-14198, 14267-14286, 14397-14423, 14441-14460, 14494-14513, 14494-14543, 14524-14543, 14601-14650, 14670-14700, 14675-14700, 14801-14828, 14877-14912, 14877-14915, 14877-14973, 14916-14943, 14916-14973, 14925-14951, 14934-14963, 14946-14973, 14979-14998, 15254-15280, 15254-15328, 15264-15290, 15279-15305, 15291-15318, 15292-15319, 15293-15320, 15294-15321, 15294-15321, 15295-15322, 15296-15323, 15297-15323, 15298-15323, 15299-15323, 15300-15323, 15301-15328, 15330-15355, 15330-15490, 15339-15366, 15358-15490, 16134-16153, 16668-16687, 17267-17286, 18377-18427, 18561-18580, 18591-18618, 18591-18646, 18591-18668, 18695-18746, 18705-18730, 18709-18736, 18719-18746, 19203-20080, 19931-19952, 19954-19981, 19964-19990, 19973-19999, 19982-20009, 19992-20016, 20016-20042, 20025-20052, 20036-20062, 20045-20070, 20100-20119, 20188-20207, 20624-20650, 20624-20759, 20629-20804, 20633-20660, 20635-20781,

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74. The compound of claim 71, wherein the modified oligonucleotide hybridizes exclusively within 2274-2400, 2274-2575, 2433-2570, 2433-2579, 2549-2575, 2552-2579, 2585-2638, 2605-2638, 3056-3075, 4150-5159, 4306-4325, 5590-5618, 5667-5686, 6444-6463, 6482-6518, 6492-6518, 6528-6555, 6528-6623, 6534-6561, 6535-6562, 6536-6563, 6537-6563, 6538-6565, 6539-6565, 6540-6567, 6541-6567, 6542-6569, 6546-6573, 6557-6584, 6575-6602, 6585-6611, 6594-6621, 6596-6623, 6652-6671, 7099-7118, 7556-7584, 8836-8855, 8948-8967, 9099-9118, 9099-9168, 9130-9168, 9207-9233, 9207-9235, 9209-9235, 10252-10271, 10633-10652, 11308-11491, 12715-12734, 12928-12947, 13681-13700, 13746-13779, 13816-13847, 13903-13945, 13977-14141, 14179-14198, 14267-14286, 14397-14423, 14441-14460, 14494-14513, 14494-14543, 14524-14543, 14601-14650, 14670-14700, 14675-14700, 14801-14828, 14877-14912, 14877-14915, 14877-14973, 14916-14943, 14916-14973, 14925-14951, 14934-14963, 14946-14973, 14979-14998, 15254-15280, 15254-15328, 15264-15290, 15279-15305, 15291-15318, 15292-15319, 15293-15320, 15294-15321, 15294-15321, 15295-15322, 15296-15323, 15297-15323, 15298-15323, 15299-15323, 15300-15323, 15301-15328, 15330-15355, 15330-15490, 15339-15366, 15358-15490, 16134-16153, 16668-16687, 17267-17286, 18377-18427, 18561-18580, 18591-18618, 18591-18646, 18591-18668, 18695-18746, 18705-18730, 18709-

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75. A compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising a portion of at least 8 contiguous nucleobases fully complementary to an equal length portion of nucleobases 2274-2400, 2274-2575, 2433-2570, 2433-2579, 2549-2575, 2552-2579, 2585-2638, 2605-2638, 3056-3075, 4150-5159, 4306-4325, 5590-5618, 5667-5686, 6444-6463, 6482-6518, 6492-6518, 6528-6555, 6528-6623, 6534-6561, 6535-6562, 6536-6563, 6537-6563, 6538-6565, 6539-6565, 6540-6567, 6541-6567, 6542-6569, 6546-6573, 6557-6584, 6575-6602, 6585-6611, 6594-6621, 6596-6623, 6652-6671, 7099-7118, 7556-7584, 8836-8855, 8948-8967, 9099-9118, 9099-9168, 9130-9168, 9207-9233, 9207-9235, 9209-9235, 10252-10271, 10633-10652, 11308-11491, 12715-12734, 12928-12947, 13681-13700, 13746-13779, 13816-13847, 13903-13945, 13977-14141, 14179-14198, 14267-14286, 14397-14423, 14441-14460, 14494-14513, 14494-14543, 14524-14543, 14601-14650, 14670-14700, 14675-14700, 14801-14828, 14877-14912, 14877-14915, 14877-14973, 14916-14943, 14916-14973, 14925-14951, 14934-14963, 14946-14973, 14979-14998, 15254-

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76. The compound of claim 75, wherein the modified oligonucleotide is at least 95% complementary to SEQ ID NO: 2.

77. The compound of claim 75, wherein the modified oligonucleotide is 100% complementary to SEQ ID NO: 2.

78. The compound of claim 75, wherein the modified oligonucleotide hybridizes exclusively within 2274-2400, 2274-2575, 2433-2570, 2433-2579, 2549-2575, 2552-2579, 2585-2638, 2605-2638, 3056-3075, 4150-5159, 4306-4325, 5590-5618, 5667-5686, 6444-6463, 6482-

6518, 6492-6518, 6528-6555, 6528-6623, 6534-6561, 6535-6562, 6536-6563, 6537-6563, 6538-6565, 6539-6565, 6540-6567, 6541-6567, 6542-6569, 6546-6573, 6557-6584, 6575-6602, 6585-6611, 6594-6621, 6596-6623, 6652-6671, 7099-7118, 7556-7584, 8836-8855, 8948-8967, 9099-9118, 9099-9168, 9130-9168, 9207-9233, 9207-9235, 9209-9235, 10252-10271, 10633-10652, 11308-11491, 12715-12734, 12928-12947, 13681-13700, 13746-13779, 13816-13847, 13903-13945, 13977-14141, 14179-14198, 14267-14286, 14397-14423, 14441-14460, 14494-14513, 14494-14543, 14524-14543, 14601-14650, 14670-14700, 14675-14700, 14801-14828, 14877-14912, 14877-14915, 14877-14973, 14916-14943, 14916-14973, 14925-14951, 14934-14963, 14946-14973, 14979-14998, 15254-15280, 15254-15328, 15264-15290, 15279-15305, 15291-15318, 15292-15319, 15293-15320, 15294-15321, 15294-15321, 15295-15322, 15296-15323, 15297-15323, 15298-15323, 15299-15323, 15300-15323, 15301-15328, 15330-15355, 15330-15490, 15339-15366, 15358-15490, 16134-16153, 16668-16687, 17267-17286, 18377-18427, 18561-18580, 18591-18618, 18591-18646, 18591-18668, 18695-18746, 18705-18730, 18709-18736, 18719-18746, 19203-20080, 19931-19952, 19954-19981, 19964-19990, 19973-19999, 19982-20009, 19992-20016, 20016-20042, 20025-20052, 20036-20062, 20045-20070, 20100-20119, 20188-20207, 20624-20650, 20624-20759, 20629-20804, 20633-20660, 20635-20781, 20643-20662, 20657-20676, 20670-20697, 20680-20706, 20683-20781, 20689-20715, 20698-20725, 20709-20736, 20717-20744, 20718-20745, 20719-20746, 20720-20747, 20721-20748, 20722-20749, 20727-20752, 20735-20759, 20762-21014, 20785-21014, 21082-21107, 21082-21152, 21091-21114, 21118-21144, 21127-21152, 21181-21209, 21181-21211, 21183-21211, 21481-21500, 21589-21608, 21692-21719, 22000-22227, 22096-22115, 22096-22223, 22096-22311, 22133-22160, 22133-22163, 22134-22161, 22135-22162, 22136-22163, 22137-22163, 22138-22163, 22189-22239, 22199-22226, 22199-22227, 22200-22227, 22201-22228, 22202-22229, 22203-22230, 22204-22231, 22205-22232, 22206-22233, 22207-22234, 22208-22235, 22209-22236, 22210-22236, 22210-22239, 22211-22236, 22212-22239, 22292-22311, 23985-24054, 24035-24134, 24095-24121, 24858-24877, 24907-24926, 25413-25432, 25994-26013, 26112-26139, 26112-26161, 26112-27303, 26113-26140, 26114-26141, 26115-26141, 26116-26141, 26117-26141, 26117-26475, 26118-26141, 26120-26141, 26132-26151, 26142-26161, 26217-26241, 26311-26335, 26389-26432, 26456-26576, 26635-26662, 26707-26734, 26707-26736, 26790-26820, 27034-27263, 27279-27303, or 27350-27376 of SEQ ID NO: 2, and wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to SEQ ID NO: 2.

79. The compound of claim 76, wherein the modified oligonucleotide hybridizes exclusively within 2274-2400, 2274-2575, 2433-2570, 2433-2579, 2549-2575, 2552-2579, 2585-2638, 2605-2638, 3056-3075, 4150-5159, 4306-4325, 5590-5618, 5667-5686, 6444-6463, 6482-6518, 6492-6518, 6528-6555, 6528-6623, 6534-6561, 6535-6562, 6536-6563, 6537-6563, 6538-6565, 6539-6565, 6540-6567, 6541-6567, 6542-6569, 6546-6573, 6557-6584, 6575-6602, 6585-6611, 6594-6621, 6596-6623, 6652-6671, 7099-7118, 7556-7584, 8836-8855, 8948-8967, 9099-9118, 9099-9168, 9130-9168, 9207-9233, 9207-9235, 9209-9235, 10252-10271, 10633-10652, 11308-11491, 12715-12734, 12928-12947, 13681-13700, 13746-13779, 13816-13847, 13903-13945, 13977-14141, 14179-14198, 14267-14286, 14397-14423, 14441-14460, 14494-14513, 14494-14543, 14524-14543, 14601-14650, 14670-14700, 14675-14700, 14801-14828, 14877-14912, 14877-14915, 14877-14973, 14916-14943, 14916-14973, 14925-14951, 14934-14963, 14946-14973, 14979-14998, 15254-15280, 15254-15328, 15264-15290, 15279-15305, 15291-15318, 15292-15319, 15293-15320, 15294-15321, 15294-15321, 15295-15322, 15296-15323, 15297-15323, 15298-15323, 15299-15323, 15300-15323, 15301-15328, 15330-15355, 15330-15490, 15339-15366, 15358-15490, 16134-16153, 16668-16687, 17267-17286, 18377-18427, 18561-18580, 18591-18618, 18591-18646, 18591-18668, 18695-18746, 18705-18730, 18709-18736, 18719-18746, 19203-20080, 19931-19952, 19954-19981, 19964-19990, 19973-19999, 19982-20009, 19992-20016, 20016-20042, 20025-20052, 20036-20062, 20045-20070, 20100-20119, 20188-20207, 20624-20650, 20624-20759, 20629-20804, 20633-20660, 20635-20781, 20643-20662, 20657-20676, 20670-20697, 20680-20706, 20683-20781, 20689-20715, 20698-20725, 20709-20736, 20717-20744, 20718-20745, 20719-20746, 20720-20747, 20721-20748, 20722-20749, 20727-20752, 20735-20759, 20762-21014, 20785-21014, 21082-21107, 21082-21152, 21091-21114, 21118-21144, 21127-21152, 21181-21209, 21181-21211, 21183-21211, 21481-21500, 21589-21608, 21692-21719, 22000-22227, 22096-22115, 22096-22223, 22096-22311, 22133-22160, 22133-22163, 22134-22161, 22135-22162, 22136-22163, 22137-22163, 22138-22163, 22189-22239, 22199-22226, 22199-22227, 22200-22227, 22201-22228, 22202-22229, 22203-22230, 22204-22231, 22205-22232, 22206-22233, 22207-22234, 22208-22235, 22209-22236, 22210-22236, 22210-22239, 22211-22236, 22212-22239, 22292-22311, 23985-24054, 24035-24134, 24095-24121, 24858-24877, 24907-24926, 25413-25432, 25994-26013, 26112-26139, 26112-26161, 26112-27303, 26113-26140, 26114-26141, 26115-26141, 26116-26141, 26117-26141, 26117-26475, 26118-26141, 26120-26141, 26132-26151, 26142-26161, 26217-26241, 26311-26335, 26389-26432, 26456-26576, 26635-26662, 26707-26734, 26707-26736, 26790-26820, 27034-27263, 27279-27303, or 27350-27376 of SEQ ID NO: 2, and

wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to SEQ ID NO: 2.

80. The compound of claim 77, wherein the modified oligonucleotide hybridizes exclusively within 2274-2400, 2274-2575, 2433-2570, 2433-2579, 2549-2575, 2552-2579, 2585-2638, 2605-2638, 3056-3075, 4150-5159, 4306-4325, 5590-5618, 5667-5686, 6444-6463, 6482-6518, 6492-6518, 6528-6555, 6528-6623, 6534-6561, 6535-6562, 6536-6563, 6537-6563, 6538-6565, 6539-6565, 6540-6567, 6541-6567, 6542-6569, 6546-6573, 6557-6584, 6575-6602, 6585-6611, 6594-6621, 6596-6623, 6652-6671, 7099-7118, 7556-7584, 8836-8855, 8948-8967, 9099-9118, 9099-9168, 9130-9168, 9207-9233, 9207-9235, 9209-9235, 10252-10271, 10633-10652, 11308-11491, 12715-12734, 12928-12947, 13681-13700, 13746-13779, 13816-13847, 13903-13945, 13977-14141, 14179-14198, 14267-14286, 14397-14423, 14441-14460, 14494-14513, 14494-14543, 14524-14543, 14601-14650, 14670-14700, 14675-14700, 14801-14828, 14877-14912, 14877-14915, 14877-14973, 14916-14943, 14916-14973, 14925-14951, 14934-14963, 14946-14973, 14979-14998, 15254-15280, 15254-15328, 15264-15290, 15279-15305, 15291-15318, 15292-15319, 15293-15320, 15294-15321, 15294-15321, 15295-15322, 15296-15323, 15297-15323, 15298-15323, 15299-15323, 15300-15323, 15301-15328, 15330-15355, 15330-15490, 15339-15366, 15358-15490, 16134-16153, 16668-16687, 17267-17286, 18377-18427, 18561-18580, 18591-18618, 18591-18646, 18591-18668, 18695-18746, 18705-18730, 18709-18736, 18719-18746, 19203-20080, 19931-19952, 19954-19981, 19964-19990, 19973-19999, 19982-20009, 19992-20016, 20016-20042, 20025-20052, 20036-20062, 20045-20070, 20100-20119, 20188-20207, 20624-20650, 20624-20759, 20629-20804, 20633-20660, 20635-20781, 20643-20662, 20657-20676, 20670-20697, 20680-20706, 20683-20781, 20689-20715, 20698-20725, 20709-20736, 20717-20744, 20718-20745, 20719-20746, 20720-20747, 20721-20748, 20722-20749, 20727-20752, 20735-20759, 20762-21014, 20785-21014, 21082-21107, 21082-21152, 21091-21114, 21118-21144, 21127-21152, 21181-21209, 21181-21211, 21183-21211, 21481-21500, 21589-21608, 21692-21719, 22000-22227, 22096-22115, 22096-22223, 22096-22311, 22133-22160, 22133-22163, 22134-22161, 22135-22162, 22136-22163, 22137-22163, 22138-22163, 22189-22239, 22199-22226, 22199-22227, 22200-22227, 22201-22228, 22202-22229, 22203-22230, 22204-22231, 22205-22232, 22206-22233, 22207-22234, 22208-22235, 22209-22236, 22210-22236, 22210-22239, 22211-22236, 22212-22239, 22292-22311, 23985-24054, 24035-24134, 24095-24121, 24858-24877, 24907-24926, 25413-25432, 25994-26013, 26112-26139, 26112-26161, 26112-27303, 26113-26140, 26114-26141, 26115-26141, 26116-

26141, 26117-26141, 26117-26475, 26118-26141, 26120-26141, 26132-26151, 26142-26161, 26217-26241, 26311-26335, 26389-26432, 26456-26576, 26635-26662, 26707-26734, 26707-26736, 26790-26820, 27034-27263, 27279-27303, or 27350-27376 of SEQ ID NO: 2, and wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to SEQ ID NO: 2.

81. The compound of claim 69, consisting of a single-stranded modified oligonucleotide.

82. The compound of claim 81, wherein at least one internucleoside linkage is a phosphorothioate internucleoside linkage.

83. The compound of claim 69, wherein each internucleoside linkage is a phosphorothioate internucleoside linkage.

84. The compound of claim 83, wherein at least one nucleoside comprises a modified sugar.

85. The compound of claim 84, wherein at least one modified sugar is a bicyclic sugar.

86. The compound of claim 85, wherein at least one modified sugar comprises a 2'-O-methoxyethyl.

87. The compound of claim 83, wherein at least one nucleoside comprises a modified nucleobase.

88. The compound of claim 87, wherein the modified nucleobase is a 5-methylcytosine.

89. The compound of claim 69, wherein the modified oligonucleotide comprises:
a gap segment consisting of linked deoxynucleosides;
a 5' wing segment consisting of linked nucleosides; and

a 3' wing segment consisting of linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment; and wherein each nucleoside of each wing segment comprises a modified sugar.

90. The compound of claim 89, wherein the modified oligonucleotide comprises:

a gap segment consisting of ten linked deoxynucleosides;

a 5' wing segment consisting of five linked nucleosides; and

a 3' wing segment consisting of five linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar; and wherein each internucleoside linkage is a phosphorothioate linkage.

91. The antisense compound of claim 89, wherein the antisense compound is a chimeric oligonucleotide consisting of:

a gap segment consisting of from 10 to 18 linked 2'-deoxynucleosides;

a 5' wing segment consisting of from 1 to 5 linked nucleosides; and

a 3' wing segment consisting of from 1 to 5 linked nucleosides;

wherein each nucleoside of the 5' wing segment is a sugar-modified nucleoside, each nucleoside of the 3' wing segment is a sugar-modified nucleoside, and each internucleoside linkage is a phosphorothioate internucleoside linkage.

92. The compound of claim 70, wherein the modified oligonucleotide consists of 20 linked nucleosides.

93. A composition comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of a nucleobase sequence selected from among the nucleobase sequences recited in 2274-2400, 2274-2575, 2433-2570, 2433-2579, 2549-2575, 2552-2579, 2585-2638, 2605-2638, 3056-3075, 4150-5159, 4306-4325, 5590-5618, 5667-5686, 6444-6463, 6482-6518, 6492-6518, 6528-6555, 6528-6623, 6534-6561, 6535-6562, 6536-6563, 6537-6563, 6538-6565, 6539-6565, 6540-6567, 6541-6567, 6542-6569, 6546-6573, 6557-6584, 6575-6602, 6585-6611, 6594-6621, 6596-6623, 6652-6671, 7099-7118, 7556-7584, 8836-8855, 8948-8967, 9099-9118, 9099-9168, 9130-9168, 9207-9233, 9207-9235, 9209-9235, 10252-10271, 10633-10652, 11308-11491,

12715-12734, 12928-12947, 13681-13700, 13746-13779, 13816-13847, 13903-13945, 13977-14141, 14179-14198, 14267-14286, 14397-14423, 14441-14460, 14494-14513, 14494-14543, 14524-14543, 14601-14650, 14670-14700, 14675-14700, 14801-14828, 14877-14912, 14877-14915, 14877-14973, 14916-14943, 14916-14973, 14925-14951, 14934-14963, 14946-14973, 14979-14998, 15254-15280, 15254-15328, 15264-15290, 15279-15305, 15291-15318, 15292-15319, 15293-15320, 15294-15321, 15294-15321, 15295-15322, 15296-15323, 15297-15323, 15298-15323, 15299-15323, 15300-15323, 15301-15328, 15330-15355, 15330-15490, 15339-15366, 15358-15490, 16134-16153, 16668-16687, 17267-17286, 18377-18427, 18561-18580, 18591-18618, 18591-18646, 18591-18668, 18695-18746, 18705-18730, 18709-18736, 18719-18746, 19203-20080, 19931-19952, 19954-19981, 19964-19990, 19973-19999, 19982-20009, 19992-20016, 20016-20042, 20025-20052, 20036-20062, 20045-20070, 20100-20119, 20188-20207, 20624-20650, 20624-20759, 20629-20804, 20633-20660, 20635-20781, 20643-20662, 20657-20676, 20670-20697, 20680-20706, 20683-20781, 20689-20715, 20698-20725, 20709-20736, 20717-20744, 20718-20745, 20719-20746, 20720-20747, 20721-20748, 20722-20749, 20727-20752, 20735-20759, 20762-21014, 20785-21014, 21082-21107, 21082-21152, 21091-21114, 21118-21144, 21127-21152, 21181-21209, 21181-21211, 21183-21211, 21481-21500, 21589-21608, 21692-21719, 22000-22227, 22096-22115, 22096-22223, 22096-22311, 22133-22160, 22133-22163, 22134-22161, 22135-22162, 22136-22163, 22137-22163, 22138-22163, 22189-22239, 22199-22226, 22199-22227, 22200-22227, 22201-22228, 22202-22229, 22203-22230, 22204-22231, 22205-22232, 22206-22233, 22207-22234, 22208-22235, 22209-22236, 22210-22236, 22210-22239, 22211-22236, 22212-22239, 22292-22311, 23985-24054, 24035-24134, 24095-24121, 24858-24877, 24907-24926, 25413-25432, 25994-26013, 26112-26139, 26112-26161, 26112-27303, 26113-26140, 26114-26141, 26115-26141, 26116-26141, 26117-26141, 26117-26475, 26118-26141, 26120-26141, 26132-26151, 26142-26161, 26217-26241, 26311-26335, 26389-26432, 26456-26576, 26635-26662, 26707-26734, 26707-26736, 26790-26820, 27034-27263, 27279-27303, and 27350-27376 of SEQ ID NO: 2, or a salt thereof, and a pharmaceutically acceptable carrier or diluent.

94. The composition of claim 93, wherein the modified oligonucleotide is a single-stranded oligonucleotide.

95. The composition of claim 93, wherein the modified oligonucleotide consists of 20 linked nucleosides.

96. A method comprising administering to an animal a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising a portion which consists of at least 8 contiguous nucleobases complementary to an equal-length portion of 2274-2400, 2274-2575, 2433-2570, 2433-2579, 2549-2575, 2552-2579, 2585-2638, 2605-2638, 3056-3075, 4150-5159, 4306-4325, 5590-5618, 5667-5686, 6444-6463, 6482-6518, 6492-6518, 6528-6555, 6528-6623, 6534-6561, 6535-6562, 6536-6563, 6537-6563, 6538-6565, 6539-6565, 6540-6567, 6541-6567, 6542-6569, 6546-6573, 6557-6584, 6575-6602, 6585-6611, 6594-6621, 6596-6623, 6652-6671, 7099-7118, 7556-7584, 8836-8855, 8948-8967, 9099-9118, 9099-9168, 9130-9168, 9207-9233, 9207-9235, 9209-9235, 10252-10271, 10633-10652, 11308-11491, 12715-12734, 12928-12947, 13681-13700, 13746-13779, 13816-13847, 13903-13945, 13977-14141, 14179-14198, 14267-14286, 14397-14423, 14441-14460, 14494-14513, 14494-14543, 14524-14543, 14601-14650, 14670-14700, 14675-14700, 14801-14828, 14877-14912, 14877-14915, 14877-14973, 14916-14943, 14916-14973, 14925-14951, 14934-14963, 14946-14973, 14979-14998, 15254-15280, 15254-15328, 15264-15290, 15279-15305, 15291-15318, 15292-15319, 15293-15320, 15294-15321, 15294-15321, 15295-15322, 15296-15323, 15297-15323, 15298-15323, 15299-15323, 15300-15323, 15301-15328, 15330-15355, 15330-15490, 15339-15366, 15358-15490, 16134-16153, 16668-16687, 17267-17286, 18377-18427, 18561-18580, 18591-18618, 18591-18646, 18591-18668, 18695-18746, 18705-18730, 18709-18736, 18719-18746, 19203-20080, 19931-19952, 19954-19981, 19964-19990, 19973-19999, 19982-20009, 19992-20016, 20016-20042, 20025-20052, 20036-20062, 20045-20070, 20100-20119, 20188-20207, 20624-20650, 20624-20759, 20629-20804, 20633-20660, 20635-20781, 20643-20662, 20657-20676, 20670-20697, 20680-20706, 20683-20781, 20689-20715, 20698-20725, 20709-20736, 20717-20744, 20718-20745, 20719-20746, 20720-20747, 20721-20748, 20722-20749, 20727-20752, 20735-20759, 20762-21014, 20785-21014, 21082-21107, 21082-21152, 21091-21114, 21118-21144, 21127-21152, 21181-21209, 21181-21211, 21183-21211, 21481-21500, 21589-21608, 21692-21719, 22000-22227, 22096-22115, 22096-22223, 22096-22311, 22133-22160, 22133-22163, 22134-22161, 22135-22162, 22136-22163, 22137-22163, 22138-22163, 22189-22239, 22199-22226, 22199-22227, 22200-22227, 22201-22228, 22202-22229, 22203-22230, 22204-22231, 22205-22232, 22206-22233, 22207-22234, 22208-22235, 22209-22236, 22210-22236, 22210-22239, 22211-22236, 22212-22239, 22292-22311, 23985-24054, 24035-24134, 24095-24121, 24858-24877, 24907-24926, 25413-25432, 25994-26013, 26112-26139, 26112-26161, 26112-27303, 26113-26140, 26114-26141, 26115-26141, 26116-26141, 26117-

26141, 26117-26475, 26118-26141, 26120-26141, 26132-26151, 26142-26161, 26217-26241, 26311-26335, 26389-26432, 26456-26576, 26635-26662, 26707-26734, 26707-26736, 26790-26820, 27034-27263, 27279-27303, or 27350-27376 of SEQ ID NO: 2, and wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to SEQ ID NO: 2.

97. The method of claim 96, wherein the animal is a human.

98. The method of claim 97, wherein administering the compound slows progression and/or ameliorates hypercholesterolemia, polygenic hypercholesterolemia, mixed dyslipidemia, coronary heart disease, acute coronary syndrome, early onset coronary heart disease, type II diabetes, type II diabetes with dyslipidemia, hepatic steatosis, non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, hypertriglyceridemia, hyperfattyacidemia , hyperlipidemia, metabolic syndrome, atherosclerosis, or improves cardiovascular outcome, or any combination thereof .

99. The method of claim 96, comprising co-administering the compound and at least one additional therapy.

100. The method of claim 99, wherein the compound and additional therapy are administered concomitantly.

101. The method of claim 99, wherein the compound and the additional therapy are administered in the same formulation.

102. The method of claim 99, wherein the additional therapy is a lipid lowering therapy.

103. The method of claim 102, wherein the lipid lowering therapy is a therapeutic lifestyle change, HMG-CoA reductase inhibitor, cholesterol absorption inhibitor, MTP inhibitor, antisense compound targeted to ApoB or any combination thereof.

104. The method of claim 103, wherein the HMG-CoA reductase inhibitor is atorvastatin, rosuvastatin, or simvastatin.

105. The method of claim 103, wherein the cholesterol absorption inhibitor is ezetimibe.

106. The method of claims 103, wherein the additional lipid lowering therapy comprises an HMG-CoA reductase inhibitor that is simivastatin and a cholesterol absorption inhibitor that is ezetimibe.

107. The method of claim 103, wherein the antisense compound is ISIS 301012.

108. The method of claim 96, wherein the administering is parenteral administration.

109. The method of claim 108, wherein the parenteral administration comprises subcutaneous or intravenous administration.

110. The method of claim 96, wherein the administering comprises oral administration.

111. A method comprising administering to a human with hypercholesterolemia, polygenic hypercholesterolemia, mixed dyslipidemia, coronary heart disease, acute coronary syndrome, early onset coronary heart disease, type II diabetes, type II diabetes with dyslipidemia, hepatic steatosis, non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, hypertriglyceridemia, hyperfattyacidemia, hyperlipidemia, metabolic syndrome, atherosclerosis, elevated ApoB, elevated cholesterol, elevated LDL-cholesterol, elevated VLDL-cholesterol, or elevated non-HDL cholesterol, a therapeutically effective amount of a composition comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases complementary to an equal-length portion of 2274-2400, 2274-2575, 2433-2570, 2433-2579, 2549-2575, 2552-2579, 2585-2638, 2605-2638, 3056-3075, 4150-5159, 4306-4325, 5590-5618, 5667-5686, 6444-6463, 6482-6518, 6492-6518, 6528-6555, 6528-6623, 6534-6561, 6535-6562, 6536-6563, 6537-6563, 6538-6565, 6539-6565, 6540-6567, 6541-6567, 6542-6569, 6546-6573, 6557-6584, 6575-6602, 6585-6611, 6594-6621, 6596-6623, 6652-6671, 7099-7118, 7556-7584, 8836-8855, 8948-8967, 9099-9118, 9099-

9168, 9130-9168, 9207-9233, 9207-9235, 9209-9235, 10252-10271, 10633-10652, 11308-11491, 12715-12734, 12928-12947, 13681-13700, 13746-13779, 13816-13847, 13903-13945, 13977-14141, 14179-14198, 14267-14286, 14397-14423, 14441-14460, 14494-14513, 14494-14543, 14524-14543, 14601-14650, 14670-14700, 14675-14700, 14801-14828, 14877-14912, 14877-14915, 14877-14973, 14916-14943, 14916-14973, 14925-14951, 14934-14963, 14946-14973, 14979-14998, 15254-15280, 15254-15328, 15264-15290, 15279-15305, 15291-15318, 15292-15319, 15293-15320, 15294-15321, 15294-15321, 15295-15322, 15296-15323, 15297-15323, 15298-15323, 15299-15323, 15300-15323, 15301-15328, 15330-15355, 15330-15490, 15339-15366, 15358-15490, 16134-16153, 16668-16687, 17267-17286, 18377-18427, 18561-18580, 18591-18618, 18591-18646, 18591-18668, 18695-18746, 18705-18730, 18709-18736, 18719-18746, 19203-20080, 19931-19952, 19954-19981, 19964-19990, 19973-19999, 19982-20009, 19992-20016, 20016-20042, 20025-20052, 20036-20062, 20045-20070, 20100-20119, 20188-20207, 20624-20650, 20624-20759, 20629-20804, 20633-20660, 20635-20781, 20643-20662, 20657-20676, 20670-20697, 20680-20706, 20683-20781, 20689-20715, 20698-20725, 20709-20736, 20717-20744, 20718-20745, 20719-20746, 20720-20747, 20721-20748, 20722-20749, 20727-20752, 20735-20759, 20762-21014, 20785-21014, 21082-21107, 21082-21152, 21091-21114, 21118-21144, 21127-21152, 21181-21209, 21181-21211, 21183-21211, 21481-21500, 21589-21608, 21692-21719, 22000-22227, 22096-22115, 22096-22223, 22096-22311, 22133-22160, 22133-22163, 22134-22161, 22135-22162, 22136-22163, 22137-22163, 22138-22163, 22189-22239, 22199-22226, 22199-22227, 22200-22227, 22201-22228, 22202-22229, 22203-22230, 22204-22231, 22205-22232, 22206-22233, 22207-22234, 22208-22235, 22209-22236, 22210-22236, 22210-22239, 22211-22236, 22212-22239, 22292-22311, 23985-24054, 24035-24134, 24095-24121, 24858-24877, 24907-24926, 25413-25432, 25994-26013, 26112-26139, 26112-26161, 26112-27303, 26113-26140, 26114-26141, 26115-26141, 26116-26141, 26117-26141, 26117-26475, 26118-26141, 26120-26141, 26132-26151, 26142-26161, 26217-26241, 26311-26335, 26389-26432, 26456-26576, 26635-26662, 26707-26734, 26707-26736, 26790-26820, 27034-27263, 27279-27303, or 27350-27376 of SEQ ID NO: 2, and wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to SEQ ID NO: 2.

112. The method of claim 96, wherein the animal has hypercholesterolemia, polygenic hypercholesterolemia, mixed dyslipidemia, a history of coronary heart disease, coronary heart disease, acute coronary syndrome, early onset coronary heart disease, one or more risk factors for

coronary heart disease, type II diabetes, type II diabetes with dyslipidemia, hepatic steatosis, non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, hypertriglyceridemia, hyperfattyacidemia, hyperlipidemia, metabolic syndrome, atherosclerosis, elevated ApoB, elevated cholesterol, elevated LDL-cholesterol, elevated VLDL-cholesterol, elevated IDL-cholesterol, or elevated non-HDL cholesterol.

113. The method of claim 112, wherein the elevated LDL-cholesterol level is above a target level of at least about 100 mg/dL, 130 mg/dL, 160 mg/dL, or 190 mg/dL.

114. The method of claim 112, wherein the administering the compound to the animal reduces LDL-cholesterol levels.

115. The method of claim 114, wherein administering the compound results in an LDL-cholesterol level below a target level of at least about 190 mg/dL, 160 mg/dL, 130 mg/dL, 100 mg/dL, 70 mg/dL, or 50 mg/dL.

116. The method of claim 112, wherein the one or more risk factors is selected from age, smoking, hypertension, low HDL-cholesterol, and a family history of early coronary heart disease.

117. The method of claim 112, wherein the animal failed to meet the LDL-cholesterol target level on lipid-lowering therapy, did not comply with the recommend therapy, experienced side effects of therapy, or any combination thereof.

118. The method of claim 117, wherein the lipid-lowering therapy is a statin.

119. The method of claim 117, wherein the lipid-lowering therapy is ezetimibe.

120. The method of claim 96, wherein administering results in a reduction of ApoB, LDL-cholesterol, VLDL-cholesterol, Lp(a), small LDL-particle, small VLDL-particle, non-HDL-cholesterol, liver triglyceride level, serum triglycerides, serum phospholipids, or any combination thereof.

121. The method of claim 120, wherein the ApoB reduction is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

122. The method of claim 121, wherein the ApoB reduction is between 10% and 80%, between 20% and 70%, between 30% and 60%, or between 30% and 70%.

123. The method of claim 120, wherein the LDL-cholesterol reduction is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

124. The method of claim 120, wherein the VLDL-cholesterol reduction is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

125. The method of claim 120, wherein the Lp(a) reduction is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

126. The method of claim 120, wherein the small LDL-particle reduction is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

127. The method of claim 120, wherein the small VLDL-particle reduction is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

128. The method of claim 120, wherein the non-HDL-cholesterol reduction is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

129. The method of claim 120, wherein the liver triglyceride level reduction is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

130. The method of claim 120, wherein the administering of the pharmaceutical composition results in a serum triglyceride reduction of at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

131. The method of claim 120, wherein the administering of the pharmaceutical composition results in a serum phospholipid reduction of at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

132. The method of claims 120 or 131, wherein the serum phospholipid is serum oxidized phospholipid.

133. The method of claim 96, wherein administering results in reduced coronary heart disease risk, or slows, stops or prevents the progression of atherosclerosis, or any combination thereof.

134. The method of claim 96, wherein administering results in improved cardiovascular outcome of the human.

135. The method of claim 134, wherein the improved cardiovascular outcome is improved carotid intimal media thickness, improved atheroma thickness, increased HDL-cholesterol, or any combination thereof.

136. The method of claim 96, wherein administering ameliorates hepatic steatosis, results in lipid lowering, improves LDL/HDL ration, or any combination thereof.

137. A compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising a portion which consists of at least 8 contiguous nucleobases complementary to an equal-length portion of 220-253, 290-321, 377-419, 451-615, 653-672, 741-760, 871-897, 915-934, 968-1017, 1075-1124, 1075-1174, 1144-1174, 1275-1302, 1315-1341, 1351-1389, 1351-1447, 1365-1439, 1390-1417, 1390-1429, 1390-1439, 1399-1425, 1408-1435, 1420-1447, 1453-1482, 1490-1516, 1490-1564, 1500-1526, 1515-1541, 1527-1553, 1527-1554, 1528-1554, 1529-1555, 1529-1556, 1530-1556, 1530-1557, 1531-1557, 1532-1558, 1533-1559, 1534-1559, 1535-1559, 1536-1559, 1537-1564, 1566-1602, 1566-1681, 1606-1626, 1618-1645, 1626-1653, 1684-1703, 1730-1781, 1740-1767, 1749-1775, 1758-1781, 1820-1847, 1820-1877, 1822-2198, 1830-1856, 1839-1865, 1840-1867, 1898-1924, 1898-2035, 1903-2127, 1907-1934, 1911-1938, 1946-1971, 1954-1980, 1959-2035, 1959-2057, 1963-1988, 1967-2035, 1972-1999, 1982-2008, 1991-2018, 1993-2019, 1995-2022, 1996-2023, 1997-2024, 1998-2025, 1999-2025, 2000-2025, 2009-2035, 2038-2139, 2061-2139, 2073-2099, 2078-2104, 2105-2131, 2112-2139, 2168-2198, 2170-2177, 2245-2284, 2295-2394, 2355-2381, 2355-2394, 2405-2461, 2560-2587, 2560-2609, 2561-2588, 2562-2589, 2563-2589, 2564-2589, 2565-2589, 2566-2589, 2567-2589, 2568-2589, 2665-2689, 2759-2783, 2837-2880, 2904-2923, 3005-3024, 3005-3174, 3083-3110, 3155-3184, 3238-3268, 3482-3711, 3727-3751, or 3798-3824 of SEQ ID NO: 3, and wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to SEQ ID NO: 3.

138. The compound of claim 137, wherein the modified oligonucleotide is at least 95% complementary to SEQ ID NO: 3.

139. The compound of claim 138, wherein the modified oligonucleotide is 100% complementary to SEQ ID NO: 3.

140. The compound of claim 137, wherein the modified oligonucleotide hybridizes exclusively within 220-253, 290-321, 377-419, 451-615, 653-672, 741-760, 871-897, 915-934, 968-1017, 1075-1124, 1075-1174, 1144-1174, 1275-1302, 1315-1341, 1351-1389, 1351-1447, 1365-1439, 1390-1417, 1390-1429, 1390-1439, 1399-1425, 1408-1435, 1420-1447, 1453-1482, 1490-1516, 1490-1564, 1500-1526, 1515-1541, 1527-1553, 1527-1554, 1528-1554, 1529-1555, 1529-1556, 1530-1556, 1530-1557, 1531-1557, 1532-1558, 1533-1559, 1534-1559, 1535-1559, 1536-1559, 1537-1564, 1566-1602, 1566-1681, 1606-1626, 1618-1645, 1626-1653, 1684-1703, 1730-1781, 1740-1767, 1749-1775, 1758-1781, 1820-1847, 1820-1877, 1822-2198, 1830-1856, 1839-1865, 1840-1867, 1898-1924, 1898-2035, 1903-2127, 1907-1934, 1911-1938, 1946-1971, 1954-1980, 1959-2035, 1959-2057, 1963-1988, 1967-2035, 1972-1999, 1982-2008, 1991-2018, 1993-2019, 1995-2022, 1996-2023, 1997-2024, 1998-2025, 1999-2025, 2000-2025, 2009-2035, 2038-2139, 2061-2139, 2073-2099, 2078-2104, 2105-2131, 2112-2139, 2168-2198, 2170-2177, 2245-2284, 2295-2394, 2355-2381, 2355-2394, 2405-2461, 2560-2587, 2560-2609, 2561-2588, 2562-2589, 2563-2589, 2564-2589, 2565-2589, 2566-2589, 2567-2589, 2568-2589, 2665-2689, 2759-2783, 2837-2880, 2904-2923, 3005-3024, 3005-3174, 3083-3110, 3155-3184, 3238-3268, 3482-3711, 3727-3751, or 3798-3824 of SEQ ID NO: 3, and wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to SEQ ID NO: 3.

141. The compound of claim 138, wherein the modified oligonucleotide hybridizes exclusively within 220-253, 290-321, 377-419, 451-615, 653-672, 741-760, 871-897, 915-934, 968-1017, 1075-1124, 1075-1174, 1144-1174, 1275-1302, 1315-1341, 1351-1389, 1351-1447, 1365-1439, 1390-1417, 1390-1429, 1390-1439, 1399-1425, 1408-1435, 1420-1447, 1453-1482, 1490-1516, 1490-1564, 1500-1526, 1515-1541, 1527-1553, 1527-1554, 1528-1554, 1529-1555, 1529-1556, 1530-1556, 1530-1557, 1531-1557, 1532-1558, 1533-1559, 1534-1559, 1535-1559, 1536-1559, 1537-1564, 1566-1602, 1566-1681, 1606-1626, 1618-1645, 1626-1653, 1684-1703, 1730-1781, 1740-1767, 1749-1775, 1758-1781, 1820-1847, 1820-1877, 1822-2198, 1830-1856, 1839-1865, 1840-1867, 1898-1924, 1898-2035, 1903-2127, 1907-1934, 1911-1938, 1946-1971, 1954-1980, 1959-2035, 1959-2057, 1963-1988, 1967-2035, 1972-1999, 1982-2008, 1991-2018, 1993-2019, 1995-2022, 1996-2023, 1997-2024, 1998-2025, 1999-2025, 2000-2025, 2009-2035, 2038-2139, 2061-2139, 2073-2099, 2078-2104, 2105-2131, 2112-2139, 2168-2198, 2170-2177, 2245-2284, 2295-2394, 2355-2381, 2355-2394, 2405-2461, 2560-2587, 2560-2609, 2561-2588, 2562-2589, 2563-2589, 2564-2589, 2565-2589, 2566-2589, 2567-2589, 2568-2589, 2665-2689, 2759-2783, 2837-2880, 2904-2923, 3005-3024, 3005-3174, 3083-3110, 3155-3184, 3238-3268,

3482-3711, 3727-3751, or 3798-3824 of SEQ ID NO: 3, and wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to SEQ ID NO: 3.

142. The compound of claim 139, wherein the modified oligonucleotide hybridizes exclusively within 220-253, 290-321, 377-419, 451-615, 653-672, 741-760, 871-897, 915-934, 968-1017, 1075-1124, 1075-1174, 1144-1174, 1275-1302, 1315-1341, 1351-1389, 1351-1447, 1365-1439, 1390-1417, 1390-1429, 1390-1439, 1399-1425, 1408-1435, 1420-1447, 1453-1482, 1490-1516, 1490-1564, 1500-1526, 1515-1541, 1527-1553, 1527-1554, 1528-1554, 1529-1555, 1529-1556, 1530-1556, 1530-1557, 1531-1557, 1532-1558, 1533-1559, 1534-1559, 1535-1559, 1536-1559, 1537-1564, 1566-1602, 1566-1681, 1606-1626, 1618-1645, 1626-1653, 1684-1703, 1730-1781, 1740-1767, 1749-1775, 1758-1781, 1820-1847, 1820-1877, 1822-2198, 1830-1856, 1839-1865, 1840-1867, 1898-1924, 1898-2035, 1903-2127, 1907-1934, 1911-1938, 1946-1971, 1954-1980, 1959-2035, 1959-2057, 1963-1988, 1967-2035, 1972-1999, 1982-2008, 1991-2018, 1993-2019, 1995-2022, 1996-2023, 1997-2024, 1998-2025, 1999-2025, 2000-2025, 2009-2035, 2038-2139, 2061-2139, 2073-2099, 2078-2104, 2105-2131, 2112-2139, 2168-2198, 2170-2177, 2245-2284, 2295-2394, 2355-2381, 2355-2394, 2405-2461, 2560-2587, 2560-2609, 2561-2588, 2562-2589, 2563-2589, 2564-2589, 2565-2589, 2566-2589, 2567-2589, 2568-2589, 2665-2689, 2759-2783, 2837-2880, 2904-2923, 3005-3024, 3005-3174, 3083-3110, 3155-3184, 3238-3268, 3482-3711, 3727-3751, or 3798-3824 of SEQ ID NO: 3, and wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to SEQ ID NO: 3.

143. A compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising a portion of at least 8 contiguous nucleobases fully complementary to an equal length portion of nucleobases 220-253, 290-321, 377-419, 451-615, 653-672, 741-760, 871-897, 915-934, 968-1017, 1075-1124, 1075-1174, 1144-1174, 1275-1302, 1315-1341, 1351-1389, 1351-1447, 1365-1439, 1390-1417, 1390-1429, 1390-1439, 1399-1425, 1408-1435, 1420-1447, 1453-1482, 1490-1516, 1490-1564, 1500-1526, 1515-1541, 1527-1553, 1527-1554, 1528-1554, 1529-1555, 1529-1556, 1530-1556, 1530-1557, 1531-1557, 1532-1558, 1533-1559, 1534-1559, 1535-1559, 1536-1559, 1537-1564, 1566-1602, 1566-1681, 1606-1626, 1618-1645, 1626-1653, 1684-1703, 1730-1781, 1740-1767, 1749-1775, 1758-1781, 1820-1847, 1820-1877, 1822-2198, 1830-1856, 1839-1865, 1840-1867, 1898-1924, 1898-2035, 1903-2127, 1907-1934, 1911-1938, 1946-1971, 1954-1980, 1959-2035, 1959-2057, 1963-1988, 1967-2035, 1972-1999, 1982-2008, 1991-2018, 1993-2019, 1995-2022, 1996-2023,

1997-2024, 1998-2025, 1999-2025, 2000-2025, 2009-2035, 2038-2139, 2061-2139, 2073-2099, 2078-2104, 2105-2131, 2112-2139, 2168-2198, 2170-2177, 2245-2284, 2295-2394, 2355-2381, 2355-2394, 2405-2461, 2560-2587, 2560-2609, 2561-2588, 2562-2589, 2563-2589, 2564-2589, 2565-2589, 2566-2589, 2567-2589, 2568-2589, 2665-2689, 2759-2783, 2837-2880, 2904-2923, 3005-3024, 3005-3174, 3083-3110, 3155-3184, 3238-3268, 3482-3711, 3727-3751, or 3798-3824 of SEQ ID NO: 3, and wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to SEQ ID NO: 3.

144. The compound of claim 143, wherein the modified oligonucleotide is at least 95% complementary to SEQ ID NO: 3.

145. The compound of claim 143, wherein the modified oligonucleotide is 100% complementary to SEQ ID NO: 3.

146. The compound of claim 143, wherein the modified oligonucleotide hybridizes exclusively within 220-253, 290-321, 377-419, 451-615, 653-672, 741-760, 871-897, 915-934, 968-1017, 1075-1124, 1075-1174, 1144-1174, 1275-1302, 1315-1341, 1351-1389, 1351-1447, 1365-1439, 1390-1417, 1390-1429, 1390-1439, 1399-1425, 1408-1435, 1420-1447, 1453-1482, 1490-1516, 1490-1564, 1500-1526, 1515-1541, 1527-1553, 1527-1554, 1528-1554, 1529-1555, 1529-1556, 1530-1556, 1530-1557, 1531-1557, 1532-1558, 1533-1559, 1534-1559, 1535-1559, 1536-1559, 1537-1564, 1566-1602, 1566-1681, 1606-1626, 1618-1645, 1626-1653, 1684-1703, 1730-1781, 1740-1767, 1749-1775, 1758-1781, 1820-1847, 1820-1877, 1822-2198, 1830-1856, 1839-1865, 1840-1867, 1898-1924, 1898-2035, 1903-2127, 1907-1934, 1911-1938, 1946-1971, 1954-1980, 1959-2035, 1959-2057, 1963-1988, 1967-2035, 1972-1999, 1982-2008, 1991-2018, 1993-2019, 1995-2022, 1996-2023, 1997-2024, 1998-2025, 1999-2025, 2000-2025, 2009-2035, 2038-2139, 2061-2139, 2073-2099, 2078-2104, 2105-2131, 2112-2139, 2168-2198, 2170-2177, 2245-2284, 2295-2394, 2355-2381, 2355-2394, 2405-2461, 2560-2587, 2560-2609, 2561-2588, 2562-2589, 2563-2589, 2564-2589, 2565-2589, 2566-2589, 2567-2589, 2568-2589, 2665-2689, 2759-2783, 2837-2880, 2904-2923, 3005-3024, 3005-3174, 3083-3110, 3155-3184, 3238-3268, 3482-3711, 3727-3751, or 3798-3824 of SEQ ID NO: 3, and wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to SEQ ID NO: 3.

147. The compound of claim 144, wherein the modified oligonucleotide hybridizes exclusively within 220-253, 290-321, 377-419, 451-615, 653-672, 741-760, 871-897, 915-934, 968-1017, 1075-1124, 1075-1174, 1144-1174, 1275-1302, 1315-1341, 1351-1389, 1351-1447, 1365-1439, 1390-1417, 1390-1429, 1390-1439, 1399-1425, 1408-1435, 1420-1447, 1453-1482, 1490-1516, 1490-1564, 1500-1526, 1515-1541, 1527-1553, 1527-1554, 1528-1554, 1529-1555, 1529-1556, 1530-1556, 1530-1557, 1531-1557, 1532-1558, 1533-1559, 1534-1559, 1535-1559, 1536-1559, 1537-1564, 1566-1602, 1566-1681, 1606-1626, 1618-1645, 1626-1653, 1684-1703, 1730-1781, 1740-1767, 1749-1775, 1758-1781, 1820-1847, 1820-1877, 1822-2198, 1830-1856, 1839-1865, 1840-1867, 1898-1924, 1898-2035, 1903-2127, 1907-1934, 1911-1938, 1946-1971, 1954-1980, 1959-2035, 1959-2057, 1963-1988, 1967-2035, 1972-1999, 1982-2008, 1991-2018, 1993-2019, 1995-2022, 1996-2023, 1997-2024, 1998-2025, 1999-2025, 2000-2025, 2009-2035, 2038-2139, 2061-2139, 2073-2099, 2078-2104, 2105-2131, 2112-2139, 2168-2198, 2170-2177, 2245-2284, 2295-2394, 2355-2381, 2355-2394, 2405-2461, 2560-2587, 2560-2609, 2561-2588, 2562-2589, 2563-2589, 2564-2589, 2565-2589, 2566-2589, 2567-2589, 2568-2589, 2665-2689, 2759-2783, 2837-2880, 2904-2923, 3005-3024, 3005-3174, 3083-3110, 3155-3184, 3238-3268, 3482-3711, 3727-3751, or 3798-3824 of SEQ ID NO: 3, and wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to SEQ ID NO: 3.

148. The compound of claim 145, wherein the modified oligonucleotide hybridizes exclusively within 220-253, 290-321, 377-419, 451-615, 653-672, 741-760, 871-897, 915-934, 968-1017, 1075-1124, 1075-1174, 1144-1174, 1275-1302, 1315-1341, 1351-1389, 1351-1447, 1365-1439, 1390-1417, 1390-1429, 1390-1439, 1399-1425, 1408-1435, 1420-1447, 1453-1482, 1490-1516, 1490-1564, 1500-1526, 1515-1541, 1527-1553, 1527-1554, 1528-1554, 1529-1555, 1529-1556, 1530-1556, 1530-1557, 1531-1557, 1532-1558, 1533-1559, 1534-1559, 1535-1559, 1536-1559, 1537-1564, 1566-1602, 1566-1681, 1606-1626, 1618-1645, 1626-1653, 1684-1703, 1730-1781, 1740-1767, 1749-1775, 1758-1781, 1820-1847, 1820-1877, 1822-2198, 1830-1856, 1839-1865, 1840-1867, 1898-1924, 1898-2035, 1903-2127, 1907-1934, 1911-1938, 1946-1971, 1954-1980, 1959-2035, 1959-2057, 1963-1988, 1967-2035, 1972-1999, 1982-2008, 1991-2018, 1993-2019, 1995-2022, 1996-2023, 1997-2024, 1998-2025, 1999-2025, 2000-2025, 2009-2035, 2038-2139, 2061-2139, 2073-2099, 2078-2104, 2105-2131, 2112-2139, 2168-2198, 2170-2177, 2245-2284, 2295-2394, 2355-2381, 2355-2394, 2405-2461, 2560-2587, 2560-2609, 2561-2588, 2562-2589, 2563-2589, 2564-2589, 2565-2589, 2566-2589, 2567-2589, 2568-2589, 2665-2689, 2759-2783, 2837-2880, 2904-2923, 3005-3024, 3005-3174, 3083-3110, 3155-3184, 3238-3268,

3482-3711, 3727-3751, or 3798-3824 of SEQ ID NO: 3, and wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to SEQ ID NO: 3.

149. The compound of claim 137, consisting of a single-stranded modified oligonucleotide.

150. The compound of claim 149, wherein at least one internucleoside linkage is a phosphorothioate internucleoside linkage.

151. The compound of claim 137, wherein each internucleoside linkage is a phosphorothioate internucleoside linkage.

152. The compound of claim 151, wherein at least one nucleoside comprises a modified sugar.

153. The compound of claim 152, wherein at least one modified sugar is a bicyclic sugar.

154. The compound of claim 153, wherein at least one modified sugar comprises a 2'-O-methoxyethyl.

155. The compound of claim 151, wherein at least one nucleoside comprises a modified nucleobase.

156. The compound of claim 155, wherein the modified nucleobase is a 5-methylcytosine.

157. The compound of claim 137, wherein the modified oligonucleotide comprises:

a gap segment consisting of linked deoxynucleosides;

a 5' wing segment consisting of linked nucleosides; and

a 3' wing segment consisting of linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment; and wherein each nucleoside of each wing segment comprises a modified sugar.

158. The compound of claim 157, wherein the modified oligonucleotide comprises:

a gap segment consisting of ten linked deoxynucleosides;

a 5' wing segment consisting of five linked nucleosides; and

a 3' wing segment consisting of five linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar; and wherein each internucleoside linkage is a phosphorothioate linkage.

159. The antisense compound of claim 157, wherein the antisense compound is a chimeric oligonucleotide consisting of:

a gap segment consisting of from 10 to 18 linked 2'-deoxynucleosides;

a 5' wing segment consisting of from 1 to 5 linked nucleosides; and

a 3' wing segment consisting of from 1 to 5 linked nucleosides;

wherein each nucleoside of the 5' wing segment is a sugar-modified nucleoside, each nucleoside of the 3' wing segment is a sugar-modified nucleoside, and each internucleoside linkage is a phosphorothioate internucleoside linkage.

160. The compound of claim 137, wherein the modified oligonucleotide consists of 20 linked nucleosides.

161. A composition comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases of a nucleobase sequence selected from among the nucleobase sequences recited in 220-253, 290-321, 377-419, 451-615, 653-672, 741-760, 871-897, 915-934, 968-1017, 1075-1124, 1075-1174, 1144-1174, 1275-1302, 1315-1341, 1351-1389, 1351-1447, 1365-1439, 1390-1417, 1390-1429, 1390-1439, 1399-1425, 1408-1435, 1420-1447, 1453-1482, 1490-1516, 1490-1564, 1500-1526, 1515-1541, 1527-1553, 1527-1554, 1528-1554, 1529-1555, 1529-1556, 1530-1556, 1530-1557, 1531-1557, 1532-1558, 1533-1559, 1534-1559, 1535-1559, 1536-1559, 1537-1564, 1566-1602, 1566-1681, 1606-1626, 1618-1645, 1626-1653, 1684-1703, 1730-1781, 1740-1767, 1749-1775, 1758-1781, 1820-1847, 1820-1877, 1822-2198, 1830-1856, 1839-1865, 1840-1867, 1898-1924, 1898-2035, 1903-2127, 1907-1934, 1911-1938, 1946-1971, 1954-1980, 1959-2035, 1959-2057, 1963-1988, 1967-2035, 1972-1999, 1982-2008, 1991-2018, 1993-2019, 1995-

2022, 1996-2023, 1997-2024, 1998-2025, 1999-2025, 2000-2025, 2009-2035, 2038-2139, 2061-2139, 2073-2099, 2078-2104, 2105-2131, 2112-2139, 2168-2198, 2170-2177, 2245-2284, 2295-2394, 2355-2381, 2355-2394, 2405-2461, 2560-2587, 2560-2609, 2561-2588, 2562-2589, 2563-2589, 2564-2589, 2565-2589, 2566-2589, 2567-2589, 2568-2589, 2665-2689, 2759-2783, 2837-2880, 2904-2923, 3005-3024, 3005-3174, 3083-3110, 3155-3184, 3238-3268, 3482-3711, 3727-3751, or 3798-3824 of SEQ ID NO: 3 or a salt thereof, and a pharmaceutically acceptable carrier or diluent.

162. The composition of claim 161, wherein the modified oligonucleotide is a single-stranded oligonucleotide.

163. The composition of claim 161, wherein the modified oligonucleotide consists of 20 linked nucleosides.

164. A method comprising administering to an animal a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising a portion which consists of at least 8 contiguous nucleobases complementary to an equal-length portion of 220-253, 290-321, 377-419, 451-615, 653-672, 741-760, 871-897, 915-934, 968-1017, 1075-1124, 1075-1174, 1144-1174, 1275-1302, 1315-1341, 1351-1389, 1351-1447, 1365-1439, 1390-1417, 1390-1429, 1390-1439, 1399-1425, 1408-1435, 1420-1447, 1453-1482, 1490-1516, 1490-1564, 1500-1526, 1515-1541, 1527-1553, 1527-1554, 1528-1554, 1529-1555, 1529-1556, 1530-1556, 1530-1557, 1531-1557, 1532-1558, 1533-1559, 1534-1559, 1535-1559, 1536-1559, 1537-1564, 1566-1602, 1566-1681, 1606-1626, 1618-1645, 1626-1653, 1684-1703, 1730-1781, 1740-1767, 1749-1775, 1758-1781, 1820-1847, 1820-1877, 1822-2198, 1830-1856, 1839-1865, 1840-1867, 1898-1924, 1898-2035, 1903-2127, 1907-1934, 1911-1938, 1946-1971, 1954-1980, 1959-2035, 1959-2057, 1963-1988, 1967-2035, 1972-1999, 1982-2008, 1991-2018, 1993-2019, 1995-2022, 1996-2023, 1997-2024, 1998-2025, 1999-2025, 2000-2025, 2009-2035, 2038-2139, 2061-2139, 2073-2099, 2078-2104, 2105-2131, 2112-2139, 2168-2198, 2170-2177, 2245-2284, 2295-2394, 2355-2381, 2355-2394, 2405-2461, 2560-2587, 2560-2609, 2561-2588, 2562-2589, 2563-2589, 2564-2589, 2565-2589, 2566-2589, 2567-2589, 2568-2589, 2665-2689, 2759-2783, 2837-2880, 2904-2923, 3005-3024, 3005-3174, 3083-3110, 3155-3184, 3238-3268, 3482-3711, 3727-3751, or 3798-3824 of SEQ ID NO: 3, and wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to SEQ ID NO: 3.

165. The method of claim 164, wherein the animal is a human.

166. The method of claim 165, wherein administering the compound slows progression and/or ameliorates hypercholesterolemia, polygenic hypercholesterolemia, mixed dyslipidemia, coronary heart disease, acute coronary syndrome, early onset coronary heart disease, type II diabetes, type II diabetes with dyslipidemia, hepatic steatosis, non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, hypertriglyceridemia, hyperfattyacidemia, hyperlipidemia, metabolic syndrome, atherosclerosis, or improves cardiovascular outcome, or any combination thereof.

167. The method of claim 164, comprising co-administering the compound and at least one additional therapy.

168. The method of claim 167, wherein the compound and additional therapy are administered concomitantly.

169. The method of claim 167, wherein the compound and the additional therapy are administered in the same formulation.

170. The method of claim 167, wherein the additional therapy is a lipid lowering therapy.

171. The method of claim 170, wherein the lipid lowering therapy is a therapeutic lifestyle change, HMG-CoA reductase inhibitor, cholesterol absorption inhibitor, MTP inhibitor, antisense compound targeted to ApoB, or any combination thereof.

172. The method of claim 171, wherein the HMG-CoA reductase inhibitor is atorvastatin, rosuvastatin, or simvastatin.

173. The method of claim 171, wherein the cholesterol absorption inhibitor is ezetimibe.

174. The method of claims 171, wherein the additional lipid lowering therapy comprises an HMG-CoA reductase inhibitor that is simivastatin, and a cholesterol absorption inhibitor that is ezetimibe.

175. The method of claim 171, wherein the antisense compound is ISIS 301012.

176. The method of claim 164, wherein the administering is parenteral administration.

177. The method of claim 176, wherein the parenteral administration comprises subcutaneous or intravenous administration.

178. The method of claim 164, wherein the administering comprises oral administration.

179. A method comprising administering to a human with hypercholesterolemia, polygenic hypercholesterolemia, mixed dyslipidemia, coronary heart disease, early onset coronary heart disease, acute coronary syndrome, type II diabetes, type II diabetes with dyslipidemia, hepatic steatosis, non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, hypertriglyceridemia, hyperfattyacidemia, hyperlipidemia, metabolic syndrome, atherosclerosis, elevated ApoB, elevated cholesterol, elevated LDL-cholesterol, elevated VLDL-cholesterol, or elevated non-HDL cholesterol, a therapeutically effective amount of a composition comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 8 contiguous nucleobases complementary to an equal-length portion of 220-253, 290-321, 377-419, 451-615, 653-672, 741-760, 871-897, 915-934, 968-1017, 1075-1124, 1075-1174, 1144-1174, 1275-1302, 1315-1341, 1351-1389, 1351-1447, 1365-1439, 1390-1417, 1390-1429, 1390-1439, 1399-1425, 1408-1435, 1420-1447, 1453-1482, 1490-1516, 1490-1564, 1500-1526, 1515-1541, 1527-1553, 1527-1554, 1528-1554, 1529-1555, 1529-1556, 1530-1556, 1530-1557, 1531-1557, 1532-1558, 1533-1559, 1534-1559, 1535-1559, 1536-1559, 1537-1564, 1566-1602, 1566-1681, 1606-1626, 1618-1645, 1626-1653, 1684-1703, 1730-1781, 1740-1767, 1749-1775, 1758-1781, 1820-1847, 1820-1877, 1822-2198, 1830-1856, 1839-1865, 1840-1867, 1898-1924, 1898-2035, 1903-2127, 1907-1934, 1911-1938, 1946-1971, 1954-1980, 1959-2035, 1959-2057, 1963-1988, 1967-2035, 1972-1999, 1982-2008, 1991-2018, 1993-2019, 1995-2022, 1996-2023, 1997-2024, 1998-2025, 1999-2025, 2000-2025, 2009-2035, 2038-2139, 2061-

2139, 2073-2099, 2078-2104, 2105-2131, 2112-2139, 2168-2198, 2170-2177, 2245-2284, 2295-2394, 2355-2381, 2355-2394, 2405-2461, 2560-2587, 2560-2609, 2561-2588, 2562-2589, 2563-2589, 2564-2589, 2565-2589, 2566-2589, 2567-2589, 2568-2589, 2665-2689, 2759-2783, 2837-2880, 2904-2923, 3005-3024, 3005-3174, 3083-3110, 3155-3184, 3238-3268, 3482-3711, 3727-3751, or 3798-3824 of SEQ ID NO: 3, and wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to SEQ ID NO: 3.

180. The method of claim 164, wherein the animal has hypercholesterolemia, polygenic hypercholesterolemia, mixed dyslipidemia, a history of coronary heart disease, coronary heart disease, acute coronary syndrome, early onset coronary heart disease, one or more risk factors for coronary heart disease, type II diabetes, type II diabetes with dyslipidemia, hepatic steatosis, non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, hypertriglyceridemia, hyperfattyacidemia, hyperlipidemia, metabolic syndrome, atherosclerosis, elevated ApoB, elevated cholesterol, elevated LDL-cholesterol, elevated VLDL-cholesterol, elevated IDL-cholesterol, or elevated non-HDL cholesterol.

181. The method of claim 180, wherein the elevated LDL-cholesterol level is above a target level of at least about 100 mg/dL, 130 mg/dL, 160 mg/dL, or 190 mg/dL.

182. The method of claim 180, wherein the administering the compound to the animal reduces LDL-cholesterol levels.

183. The method of claim 182, wherein administering the compound results in an LDL-cholesterol level below a target level of at least about 190 mg/dL, 160 mg/dL, 130 mg/dL, 100 mg/dL, 70 mg/dL, or 50 mg/dL.

184. The method of claim 180, wherein the one or more risk factors is selected from age, smoking, hypertension, low HDL-cholesterol, and a family history of early coronary heart disease.

185. The method of claim 180, wherein the animal failed to meet the LDL-cholesterol target level on lipid-lowering therapy, did not comply with the recommend therapy, experienced side effects of therapy, or any combination thereof.

186. The method of claim 185, wherein the lipid-lowering therapy is a statin.

187. The method of claim 185, wherein the lipid-lowering therapy is ezetimibe.

188. The method of claim 164, wherein administering results in a reduction of ApoB, LDL-cholesterol, VLDL-cholesterol, Lp(a), small LDL-particle, small VLDL-particle, non-HDL-cholesterol, liver triglyceride level, serum triglycerides, serum phospholipids, or any combination thereof.

189. The method of claim 188, wherein the ApoB reduction is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

190. The method of claim 189 wherein the ApoB reduction is between 10% and 80%, between 20% and 70%, between 30% and 60%, or between 30% and 70%.

191. The method of claim 188, wherein the LDL-cholesterol reduction is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

192. The method of claim 188, wherein the VLDL-cholesterol reduction is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

193. The method of claim 188, wherein the Lp(a) reduction is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

194. The method of claim 188, wherein the small LDL-particle reduction is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

195. The method of claim 188, wherein the small VLDL-particle reduction is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

196. The method of claim 188, wherein the non-HDL-cholesterol reduction is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

197. The method of claim 188, wherein the liver triglyceride level reduction is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

198. The method of claim 188, wherein the administering of the pharmaceutical composition results in a serum triglyceride reduction of at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

199. The method of claim 188, wherein the administering of the pharmaceutical composition results in a serum phospholipid reduction of at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

200. The method of claims 188 or 199, wherein the serum phospholipid is serum oxidized phospholipid.

201. The method of claim 164, wherein administering results in reduced coronary heart disease risk, or slows, stops or prevents the progression of atherosclerosis, or any combination thereof.

202. The method of claim 164, wherein administering results in improved cardiovascular outcome of the human.

203. The method of claim 202, wherein the improved cardiovascular outcome is improved carotid intimal media thickness, improved atheroma thickness, increased HDL-cholesterol, or any combination thereof.

204. The method of claim 164, wherein administering ameliorates hepatic steatosis, results in lipid lowering, improves LDL/HDL ration, or any combination thereof.

205. A compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12 contiguous nucleobases of a nucleobase sequence selected from among the nucleobase sequences recited in SEQ ID NOs: 4 - 457.

206. The compound of claim 205 consisting of a single-stranded modified oligonucleotide.

207. The compound of claim 206, wherein the nucleobase sequence of the modified oligonucleotide is 80% complementary to a nucleic acid sequence encoding human PCSK9 selected from among the nucleic acid sequences recited in SEQ ID NOs: 1-3.

208. The compound of claim 206, wherein the nucleobase sequence of the modified oligonucleotide is 85% complementary to a nucleic acid sequence encoding human PCSK9 selected from among the nucleic acid sequences recited in SEQ ID NOs: 1-3.

209. The compound of claim 206, wherein the nucleobase sequence of the modified oligonucleotide is 90% complementary to a nucleic acid sequence encoding human PCSK9 selected from among the nucleic acid sequences recited in SEQ ID NOs: 1-3.

210. The compound of claim 206, wherein the nucleobase sequence of the modified oligonucleotide is 95% complementary to a nucleic acid sequence encoding human PCSK9 selected from among the nucleic acid sequences recited in SEQ ID NOs: 1-3.

211. The compound of claim 206, wherein the nucleobase sequence of the modified oligonucleotide is 99% complementary to a nucleic acid sequence encoding human PCSK9 selected from among the nucleic acid sequences recited in SEQ ID NOs: 1-3.

212. The compound of claim 206, wherein the nucleobase sequence of the modified oligonucleotide is 100% complementary to a nucleic acid sequence encoding human PCSK9 selected from among the nucleic acid sequences recited in SEQ ID NOs: 1-3.

213. The compound of claim 206, wherein at least one internucleoside linkage is a phosphorothioate internucleoside linkage.

214. The compound of claim 213, wherein each internucleoside linkage is a phosphorothioate internucleoside linkage.

215. The compound of claim 206, wherein at least one nucleoside comprises a modified sugar.

216. The compound of claim 215, wherein at least one modified sugar is a bicyclic sugar.

217. The compound of claim 215, wherein at least one modified sugar comprises a 2'-O-methoxyethyl.

218. The compound of claim 206, wherein at least one nucleoside comprises a modified nucleobase.

219. The compound of claim 218, wherein the modified nucleobase is a 5-methylcytosine.

220. The compound of claim 205, wherein the modified oligonucleotide comprises:
a gap segment consisting of linked deoxynucleosides;
a 5' wing segment consisting of linked nucleosides; and
a 3' wing segment consisting of linked nucleosides;
wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment; and wherein each nucleoside of each wing segment comprises a modified sugar.

221. The compound of claim 220, wherein the modified oligonucleotide comprises:
a gap segment consisting of ten linked deoxynucleosides;
a 5' wing segment consisting of five linked nucleosides; and
a 3' wing segment consisting of five linked nucleosides;
wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment; wherein each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar; and wherein each internucleoside linkage is a phosphorothioate linkage.

222. The antisense compound of claim 220, wherein the antisense compound is a chimeric oligonucleotide consisting of:
a gap segment consisting of from 10 to 18 linked 2'-deoxynucleosides;
a 5' wing segment consisting of from 1 to 5 linked nucleosides; and
a 3' wing segment consisting of from 1 to 5 linked nucleosides;
wherein each nucleoside of the 5' wing segment is a sugar-modified nucleoside, each nucleoside of the 3' wing segment is a sugar-modified nucleoside, and each internucleoside linkage is a phosphorothioate internucleoside linkage.

223. The compound of claim 206, wherein the modified oligonucleotide consists of 20 linked nucleosides.

224. A composition comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12 contiguous

nucleobases of a nucleobase sequence selected from among the nucleobase sequences recited in SEQ ID NOs: 4 - 457 or a salt thereof and a pharmaceutically acceptable carrier or diluent.

225. The composition of claim 224, wherein the modified oligonucleotide is a single-stranded oligonucleotide.

226. The composition of claim 224, wherein the modified oligonucleotide consists of 20 linked nucleosides.

227. A method comprising administering to an animal a compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides and having a nucleobase sequence comprising at least 12 contiguous nucleobases of a nucleobase sequence selected from among the nucleobase sequences recited in SEQ ID NOs: 4 - 457.

228. The method of claim 227, wherein the animal is a human.

229. The method of claim 228, wherein administering the compound slows progression and/or ameliorates hypercholesterolemia, polygenic hypercholesterolemia, mixed dyslipidemia, coronary heart disease, acute coronary syndrome, early onset coronary heart disease, type II diabetes, type II diabetes with dyslipidemia, hepatic steatosis, non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, hypertriglyceridemia, hyperfattyacidemia, hyperlipidemia, metabolic syndrome, atherosclerosis, or improves cardiovascular outcome, or any combination thereof.

230. The method of claim 228, comprising co-administering the compound and at least one additional therapy.

231. The method of claim 230, wherein the compound and additional therapy are administered concomitantly.

232. The method of claim 230, wherein the compound and the additional therapy are administered in the same formulation.

233. The method of claim 230, wherein the additional therapy is a lipid lowering therapy.

234. The method of claim 233, wherein the lipid lowering therapy is a therapeutic lifestyle change, HMG-CoA reductase inhibitor, cholesterol absorption inhibitor, MTP inhibitor, antisense compound targeted to ApoB, or any combination thereof.

235. The method of claim 234, wherein the HMG-CoA reductase inhibitor is atorvastatin, rosuvastatin, or simvastatin.

236. The method of claim 234, wherein the cholesterol absorption inhibitor is ezetimibe.

237. The method of claim 234, wherein the antisense compound is ISIS 301012.

238. The method of claim 227, wherein the administering is parenteral administration.

239. The method of claim 228, wherein the parenteral administration comprises subcutaneous or intravenous administration.

240. The method of claim 227, wherein the administering comprises oral administration.

241. The method of claim 227, wherein the animal has hypercholesterolemia, polygenic hypercholesterolemia, mixed dyslipidemia, a history of coronary heart disease, coronary heart disease, acute coronary syndrome, early onset coronary heart disease, one or more risk factors for coronary heart disease, type II diabetes, type II diabetes with dyslipidemia, hepatic steatosis, non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, hypertriglyceridemia, hyperfattyacidemia, hyperlipidemia, metabolic syndrome, atherosclerosis, elevated ApoB, elevated cholesterol, elevated LDL-cholesterol, elevated VLDL-cholesterol, elevated LDL-cholesterol, elevated non-HDL cholesterol, or any combination thereof.

242. The method of claim 241, wherein the elevated LDL-cholesterol level is above a target level of at least about 100 mg/dL, at least 130 mg/dL, at least 160 mg/dL, or at least 190 mg/dL.

243. The method of claim 241, wherein the one or more risk factors is selected from age, smoking, hypertension, low HDL-cholesterol, and a family history of early coronary heart disease.

244. The method of claim 227, wherein the animal failed to meet a LDL-cholesterol target level on lipid-lowering therapy, did not comply with the recommend therapy, experienced side effects of therapy, or any combination thereof.

245. The method of claim 244, wherein the lipid-lowering therapy is a statin or ezetimibe.

246. The method of claim 227, wherein administering results in a reduction of ApoB, LDL-cholesterol, VLDL-cholesterol, Lp(a), small LDL-particle, small VLDL-particle, non-HDL-cholesterol, liver triglyceride level, serum triglycerides, serum phospholipids, or any combination thereof.

247. The method of claim 246, wherein administering the compound results in a reduction of LDL-cholesterol level below a target level of at least about 190 mg/dL, at least 160 mg/dL, at least 130 mg/dL, at least 100 mg/dL, 70 mg/dL, or 50 mg/dL.

248. The method of claim 247, wherein the reduction is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

249. The method of claim 248, wherein the reduction is between 10% and 80%, between 20% and 70%, between 30% and 60%, or between 30% and 70%.

250. The method of claims 246, wherein the serum phospholipid is serum oxidized phospholipid.

251. The method of claim 229, wherein the improved cardiovascular outcome is improved carotid intimal media thickness, improved atheroma thickness, increased HDL-cholesterol, or any combination thereof.

252. The method of any of claims 227-251, comprising administering the pharmaceutical composition every day, every two days, every three days, every four days, every five days, every six days, or every 7 days.

253. The method of any of claims 227-251, comprising administering the pharmaceutical composition every week, every two weeks, every three weeks, or every four weeks.

254. The method of any of claims 227-251, comprising administering the pharmaceutical composition every month, every two months, every three months, every four months, or every six months.

255. The method of any of claims 227-251, wherein the dose is 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, 220, 225, 230, 235, 240, 245, 250, 255, 260, 265, 270, 270, 280, 285, 290, 295, 300, 305, 310, 315, 320, 325, 330, 335, 340, 345, 350, 355, 360, 365, 370, 375, 380, 385, 390, 395, 400, 405, 410, 415, 420, 425, 430, 435, 440, 445, 450, 455, 460, 465, 470, 475, 480, 485, 490, 495, 500, 505, 510, 515, 520, 525, 530, 535, 540, 545, 550, 555, 560, 565, 570, 575, 580, 585, 590, 595, 600, 605, 610, 615, 620, 625, 630, 635, 640, 645, 650, 655, 660, 665, 670, 675, 680, 685, 690, 695, 700, 705, 710, 715, 720, 725, 730, 735, 740, 745, 750, 755, 760, 765, 770, 775, 780, 785, 790, 795, or 800 mg.

256. The method of any of claims 227-251, wherein the dose is 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, 220, 225, 230, 235, 240, 245, 250, 255, 260, 265, 270, 270, 280, 285, 290, 295, or 300 mg.

257. The method of any of claims 227-251, wherein the dose is 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, or 400 mg.

258. The method of any of claims 227-251, wherein the pharmaceutical composition comprises an antisense oligonucleotide concentration of about 50 mg/ml, about 75 mg/ml, about 100 mg/ml, about 125 mg/ml, about 150 mg/ml, about 175 mg/ml, about 200 mg/ml, about 225 mg/ml, or about 250 mg/ml.

259. A method of inhibiting the expression of PCSK9 in human cells or tissues comprising contacting said cells or tissues with a compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides targeted to a nucleic acid molecule encoding human PCSK9.

260. A method of treating hypercholesterolemia, polygenic hypercholesterolemia, mixed dyslipidemia, a history of coronary heart disease, coronary heart disease, early onset coronary heart disease, acute coronary syndrome, one or more risk factors for coronary heart disease, type II diabetes, type II diabetes with dyslipidemia, hepatic steatosis, non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, hypertriglyceridemia, hyperfattyacidemia, hyperlipidemia, metabolic syndrome, elevated ApoB, elevated cholesterol, elevated LDL-cholesterol, elevated VLDL-cholesterol, elevated LDL-cholesterol, atherosclerosis, elevated non-HDL cholesterol, or any combination thereof, by administering to a human having hypercholesterolemia, polygenic hypercholesterolemia, mixed dyslipidemia, a history of coronary heart disease, coronary heart disease, early onset coronary heart disease, one or more risk factors for coronary heart disease, type II diabetes, type II diabetes with dyslipidemia, hepatic steatosis, non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, hypertriglyceridemia, hyperfattyacidemia, hyperlipidemia, metabolic syndrome, elevated ApoB, elevated cholesterol, elevated LDL-cholesterol, elevated VLDL-cholesterol, elevated ILDL-cholesterol, elevated non-HDL cholesterol, or any combination thereof, a compound comprising a modified oligonucleotide consisting of 12 to 30 linked nucleosides targeted to a nucleic acid molecule encoding human PCSK9.

261. The method of claim 259, wherein treating results in slowed progression and/or amelioration of hypercholesterolemia, polygenic hypercholesterolemia, mixed dyslipidemia, a

history of coronary heart disease, acute coronary syndrome, coronary heart disease, early onset coronary heart disease, one or more risk factors for coronary heart disease, type II diabetes, type II diabetes with dyslipidemia, hepatic steatosis, non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, hypertriglyceridemia, hyperfattyacidemia, hyperlipidemia, metabolic syndrome, elevated ApoB, elevated cholesterol, elevated LDL-cholesterol, elevated VLDL-cholesterol, elevated IDL-cholesterol, atherosclerosis, elevated non-HDL cholesterol, or any combination thereof.

262. The method of claim 259, wherein the compound is 80% complementary to a nucleic acid sequence encoding human PCSK9 selected from among the nucleic acid sequences recited in SEQ ID NOs: 1-3.

263. The method of claim 259, wherein the compound is 85% complementary to a nucleic acid sequence encoding human PCSK9 selected from among the nucleic acid sequences recited in SEQ ID NOs: 1-3.

264. The method of claim 259, wherein the compound is 90% complementary to a nucleic acid sequence encoding human PCSK9 selected from among the nucleic acid sequences recited in SEQ ID NOs: 1-3.

265. The method of claim 259, wherein the compound is 95% complementary to a nucleic acid sequence encoding human PCSK9 selected from among the nucleic acid sequences recited in SEQ ID NOs: 1-3.

266. The method of claim 259, wherein the compound is 99% complementary to a nucleic acid sequence encoding PCSK9 selected from among the nucleic acid sequences recited in SEQ ID NOs: 1-3.

267. The method of claim 259, wherein the compound is 100% complementary to a nucleic acid sequence encoding human PCSK9 selected from among the nucleic acid sequences recited in SEQ ID NOs: 1-3.

268. The method of claim 259, wherein the compound consists of a single-stranded modified oligonucleotide.

269. The method of claim 259, wherein the compound comprises at least one phosphorothioate internucleoside linkage.

270. The method of claim 269, wherein each internucleoside linkage in the compound is a phosphorothioate internucleoside linkage.

271. The method of claim 259, wherein the compound comprises a modified sugar.

272. The method of claim 271, wherein the modified sugar is a bicyclic sugar.

273. The method of claim 272, wherein the modified sugar is a 2'-O-methoxyethyl.

274. The method of claim 259, wherein at least one nucleoside of the compound comprises a modified nucleobase.

275. The method of claim 274, wherein the modified nucleobase is a 5-methylcytosine.

276. The method of claim 259, wherein the modified oligonucleotide comprises:
a gap segment consisting of linked deoxynucleosides;
a 5' wing segment consisting of linked nucleosides; and
a 3' wing segment consisting of linked nucleosides;
wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment; and wherein each nucleoside of each wing segment comprises a modified sugar.

277. The method of claim 259, wherein the modified oligonucleotide comprises:
a gap segment consisting of ten linked deoxynucleosides;
a 5' wing segment consisting of five linked nucleosides; and
a 3' wing segment consisting of five linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment; wherein each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar; and wherein each internucleoside linkage is a phosphorothioate linkage.

278. The method of claim 259, wherein the modified oligonucleotide consists of 20 linked nucleosides.

279. The method of claim 259, wherein the administering is parenteral administration.

280. The method of claim 259, wherein the paternteral administration comprises subcutaneous or intravenous administration.

281. The method of claim 259, wherein the administering is an oral administration.