# PCSK9 INHIBITORS AND METHODS OF USE THEREOF TO TREAT CHOLESTEROL-RELATED DISORDERS

## REFERENCE TO RELATED APPLICATIONS

**[0001]** This Application claims priority to U.S. Provisional Application No. 63/032451, filed May 29, 2020, the entirety of which is incorporated herein by reference.

## REFERENCE TO SEQUENCE LISTING

**[0002]** The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled APMOL025WO.txt created on May 5, 2021, which is 149,410 bytes in size. The information in the electronic format of the Sequence Listing is incorporated herein by reference in its entirety.

## BACKGROUND

Field

**[0003]** The present disclosure relates to Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) inhibitors, and to therapies targeting PCSK9 to treat cholesterol-related disorders such as heterozygous familial hypercholesterolemia (HeFH).

## SUMMARY

**[0003a]** In one aspect, provided herein is a use of an anti-PCSK9 antibody in the manufacture of a medicament for lowering serum LDL cholesterol (LDL-C) in a pediatric subject having heterozygous familial hypercholesterolemia (HeFH), wherein the subject has a baseline LDL-C of about 200 mg/dL or greater, said medicament comprising theanti-PCSK9 antibody at a dose from about 350 to about 500 mg, to thereby lower the subject's LDL-C.

**[0003b]** In another aspect, provided herein is a use of a PCSK9 antibody in the manufacture of a medicament for lowering serum LDL cholesterol (LDL-C) in a pediatric subject having heterozygous familial hypercholesterolemia (HeFH), wherein the subject has a baseline LDL-C of about 210 mg/dL or less, said medicament comprising the PCSK9

antibody at a dose of about 350 to about 500 mg, to thereby lower the subject's LDL-C, wherein the subject's LDL-C is lowered by at least 40%.

**[0003c]** In another aspect, provided herein is a use of a PCSK9 inhibitor in the manufacture of a medicament for treating or preventing heterozygous familial hypercholesterolemia (HeFH) or symptoms in a pediatric subject in need of treatment or prevention of HeFH or symptoms thereof, wherein the subject has a baseline LDL-C at or above an upper quartile of baseline LDL-C values among a pediatric HeFH patient cohort, wherein the PCSK9 inhibitor is for use in an enhanced dosage regimen of the PCSK9 inhibitor, to thereby treat or prevent HeFH or symptoms thereof, wherein the enhanced dosage regimen comprises the PCSK9 inhibitor which is to be administered at a mean dose that is about 20% to about 500% greater than a reference mean dose of the PCSK9 inhibitor for treating or preventing HeFH or symptoms thereof in pediatric HeFH patients having a baseline LDL-C value that is less than the upper quartile.

**[0003d]** In another aspect, provided herein is a use of an anti-PCSK9 antibody in the manufacture of a medicament for lowering serum LDL cholesterol (LDL-C) in a pediatric subject having HeFH, wherein the subject has a baseline LDL-C of about 200 mg/dL or greater, wherein the anti-PCSK9 antibody is for use at a dosing frequency of about once a month, and at an amount from about 400 mg to about 450 mg; wherein the anti-PCSK9 antibody is for use with at least one statin; and wherein the anti-PCSK9 antibody is for use with at least one other LDL cholesterol-lowering therapy that is different from the anti-PCSK9 antibody and the at least one statin, to thereby lower the subject's LDL-C by at least 30%.

**[0004]** Also provided herein is a method of lowering serum LDL cholesterol (LDL-C) in a pediatric subject, comprising: identifying a pediatric subject having heterozygous familial hypercholesterolemia (HeFH), wherein the subject has a baseline LDL-C of about 200 mg/dL or greater; and administering to the subject an anti-PCSK9 antibody at a dose from about 350 to about 500 mg, to thereby lower the subject's LDL-C. Optionally, the baseline LDL-C is from about 200 mg/dL to about 550 mg/dL. In some examples, the baseline LDL-C is 208 mg/dL or more. In some examples, the subject's LDL-C is lowered by at least 20%, at least 30%, at least 40%, about 30% to about 50%, about 20% to about 50%, about 20% to about 80%, about 30% to about 50%, or about 30% to about 80%. In some examples, the subject's LDL-C is lowered by at least 30%. In some examples, the subject's LDL-C is lowered by about 30% to about 80%. In some

examples, the anti-PCSK9 antibody is administered every two weeks to every four weeks, every two weeks, or every four weeks. Unless explicitly stated otherwise herein, "every four weeks," "monthly," and "QM" as used herein shall be interchangeable. As such, administration "every four weeks" shall encompass "monthly" and "QM" administration. In some examples, the anti-PCSK9 antibody is administered every four weeks, and the subject's LDL-C is lowered by at least 20%. In some examples, the anti-PCSK9 antibody is administered every two weeks, and the subject's LDL-C is lowered by at least 30%.

**[0005]** Also provided herein is a method of lowering serum LDL cholesterol (LDL-C) in a pediatric subject, comprising: identifying a pediatric subject having heterozygous familial hypercholesterolemia (HeFH), wherein the subject has a baseline LDL-C of about 210 mg/dL or less; and administering to the subject a PCSK9 antibody, at a dose of about 350 to about 500 mg, to thereby lower the subject's LDL-C, wherein the subject's LDL-C is lowered by at least 40%. Optionally, the baseline LDL-C is less than 208 mg/dL. In some examples, the subject's LDL-C is lowered by at least 40%, at least 50%, at least 60%, about 40% to about 60%, about 40% to about 80%, about 50% to about 60%, or about 50% to about 80%. In some examples, the subject's LDL-C is lowered by at least 45%. In some examples, the anti-PCSK9 antibody is administered every two weeks to every four weeks, every two weeks, or every four weeks. In some examples, the anti-PCSK9 antibody is administered every four weeks, and the subject's LDL-C is lowered by at least 40%. In some examples, the anti-PCSK9 antibody is administered every two weeks, and the subject's LDL-C is lowered by at least 50%.

**[0006]** In some examples, the anti-PCSK9 antibody comprises: a heavy chain variable region (VH) comprising: a CDRH1, CDRH2, and a CDRH3 of a CDRH1, CDRH2, and a CDRH3, respectively, of a VH of evolocumab; and a light chain variable region (VL) comprising: a CDRL1, CDRL2, and a CDRL3 of a CDRL1, CDRL2, and a CDRL3, respectively, of a VL of evolocumab. In some examples, the anti-PCSK9 antibody comprises: a heavy chain variable region (VH) comprising an amino acid sequence at least 90% identical to the VH of evolocumab; and a light chain variable region (VL) comprising an amino acid sequence at least 90% identical to the VL of evolocumab. In some examples, the anti-PCSK9 antibody comprises: a heavy chain variable region (VH)

comprising an amino acid sequence at least 95% identical to the VH of evolocumab; and a light chain variable region (VL) comprising an amino acid sequence at least 95% identical to the VL of evolocumab. In some examples, the anti-PCSK9 antibody comprises: a heavy chain variable region (VH) comprising: a CDRH1, CDRH2, and a CDRH3 of a CDRH1, CDRH2, and a CDRH3, respectively, of a VH of evolocumab; and an amino acid sequence at least 90% identical to the VH of evolocumab; and a light chain variable region (VL) comprising: a CDRL1, CDRL2, and a CDRL3 of a CDRL1, CDRL2, and a CDRL3, respectively, of a VL of evolocumab; and an amino acid sequence at least 90% identical to the VL of evolocumab. Optionally, the anti-PCSK9 antibody is evolocumab.

**[0007]** In some examples, the dose is about 420 mg. In some examples, the dose is about 490 mg.

**[0008]** In some examples, the subject's LDL-C is lowered by at least week 20 of administration of the PCSK9 antibody.

**[0009]** Provided herein is a method of lowering serum LDL cholesterol (LDL-C) in a pediatric subject, comprising: identifying a pediatric subject having heterozygous familial hypercholesterolemia (HeFH), wherein the subject has a baseline LDL-C at or above an upper quartile of baseline LDL-C values among a pediatric HeFH patient cohort; and administering to the subject an enhanced dosage regimen of a PCSK9 inhibitor, wherein the enhanced dosage regimen comprises an amount and/or dosing frequency that is each independently about 20% to about 500% greater than an average amount and/or average dosing frequency of the PCSK9 inhibitor for pediatric HeFH patients having a baseline LDL-C value that is less than the upper quartile, whereby the subject's LDL-C is lowered. Optionally, the amount of the PCSK9 inhibitor is about 5% to about 100% greater than the average amount. In some examples, the dosing frequency of the PCSK9 inhibitor is about 15% to about 400% greater than the average dosing frequency. In some examples, the average dosing frequency is a dosing frequency of the PCSK9 inhibitor for pediatric HeFH patients having a baseline LDL-C value that is less than a median of baseline LDL-C values among the cohort. In some examples, the average amount is an amount of the PCSK9 inhibitor for pediatric HeFH patients having a baseline LDL-C value that is less than a median of baseline LDL-C values among the cohort. In some examples, the subject's LDL-C is lowered by at least 30%. In some examples, the subject's LDL-C is lowered

by from about 30% to about 80%. In some examples, the reduction in the subject's LDL-C is at least 70% of the average reduction in LDL-C achieved in pediatric HeFH patients having a baseline LDL-C value that is less than the upper quartile and receiving the PCSK9 inhibitor at the average frequency of administration. In some examples, the subject's LDL-C is lowered by at least week 20 of administration of the PCSK9 inhibitor.

**[0010]** Also provided is a method of treating or preventing heterozygous familial hypercholesterolemia (HeFH) or symptoms thereof, comprising: identifying a pediatric subject in need of treatment or prevention of HeFH or symptoms thereof, wherein the subject has a baseline LDL-C at or above an upper quartile of baseline LDL-C values among a pediatric HeFH patient cohort; and administering to the subject an enhanced dosage regimen of a PCSK9 inhibitor, to thereby treat or prevent HeFH or symptoms thereof, wherein the enhanced dosage regimen comprises administering the PCSK9 inhibitor at a mean dose that is about 20% to about 500% greater than a reference mean dose of the PCSK9 inhibitor for treating or preventing HeFH or symptoms thereof in pediatric HeFH patients having a baseline LDL-C value that is less than the upper quartile. Optionally, the reference mean dose is a dose of the PCSK9 inhibitor for pediatric HeFH patients having a baseline LDL-C value that is less than a median of baseline LDL-C values among the cohort. In some examples, the enhanced dosage regimen comprises an increase in a dosing frequency and/or an amount of the PCSK9 inhibitor administered to the subject. In some examples, the upper quartile is in a range of about 190 mg/dL to about 220 mg/dL. In some examples, the upper quartile is about 200 mg/dL. In some examples, the subject's baseline LDL-C is about 200 mg/dL or greater. In some examples, the baseline LDL-C is from about 200 mg/dL to about 550 mg/dL. In some examples, the baseline LDL-C is 208 mg/dL or greater. In some examples, the PCSK9 inhibitor is approved by a government regulatory agency for lowering serum LDL cholesterol levels in a human patient. In some examples, the average dosing frequency is a dosing frequency of the PCSK9 inhibitor for pediatric HeFH patients having a baseline LDL-C value that is less than a median of baseline LDL-C values among the cohort. In some examples, the PCSK9 inhibitor is an antibody, small-molecule inhibitor, or an inhibitory nucleic acid. Optionally, the PCSK9 inhibitor is an anti-PCSK9 antibody, a siRNA or shRNA. Optionally, the PCSK9 inhibitor comprises one or more of evolocumab, alirocumab, bococizumab, 1D05-IgG2, RG-

7652, LGT209, REGN728, LY3015014, 1B20, inclisiran, ISIS 394814, ALN-PCS02, SX-PCK9, and BMS-962476. In some examples, the average dosing frequency is in a range from about once every 2 weeks to about once every 12 weeks. In some examples, the method further comprises determining quartiles of the baseline LDL-C values of the cohort. In some examples, the cohort comprises at least 25 pediatric HeFH patients. In some examples, the baseline LDL-C values among the cohort is at least 130 mg/dL.

**[0011]** In some examples, the method further comprises measuring the baseline LDL-C of the subject. In some examples, the identifying comprises diagnosing and/or genotyping the subject for HeFH. In some examples, the identifying comprises diagnosing and/or genotyping the patient for compound HeFH.

**[0012]** Also provided herein is a method of lowering serum LDL-cholesterol (LDL-C) in a pediatric subject, the method comprising: administering to a pediatric subject an enhanced dosage regimen of a PCSK9 inhibitor, wherein the subject has heterozygous familial hypercholesterolemia (HeFH) or symptoms thereof, wherein the enhanced dosage regimen of the PCSK9 inhibitor comprises an amount of the PCSK9 inhibitor that is about 20% to about 500% greater than a standard-of-care average amount for adults having HeFH, and/or a dosing frequency of the PCSK9 inhibitor that is about 20% to about 500% greater than a standard-of-care average frequency for adults having HeFH, whereby the subject's LDL-C is lowered. Optionally, the enhanced dosage regimen lowers LDL-C in the subject by at least 30%. In some examples, the enhanced dosage regimen lowers LDL-C in the subject by 30%-80%. In some examples, the amount of the PCSK9 inhibitor is increased by about 5% to about 100% than the standard-of-care amount. In some examples, the dosing frequency of the PCSK9 inhibitor is increased by about 15% to about 400% than the standard-of-care dosing frequency. In some examples, the enhanced dosage regimen is continued until a therapeutically acceptable end point for HeFH is achieved. In some examples, the PCSK9 inhibitor is approved by government regulatory agency for lowering LDL-C in a human patient. In some examples, the standard-of-care dosing frequency is between once every 2 weeks to once every 12 weeks. In some examples, the PCSK9 inhibitor is an anti-PCSK9 antibody. Optionally, the anti-PCSK9 antibody comprises: a heavy chain variable region (VH) comprising: a CDRH1, CDRH2, and a CDRH3 of a CDRH1, CDRH2, and a CDRH3, respectively, of a VH of evolocumab; and an

amino acid sequence at least 90% identical to the VH of evolocumab; and a light chain variable region (VL) comprising: a CDRL1, CDRL2, and a CDRL3 of a CDRL1, CDRL2, and a CDRL3, respectively, of a VL of evolocumab; and an amino acid sequence at least 90% identical to the VL of evolocumab. In some examples, the anti-PCSK9 antibody is evolocumab.

**[0013]** In some examples, the standard-of-care amount is between 400 and 500 mg/dose. In some examples, the standard-of-care amount and/or frequency is about 420 mg/month.

**[0014]** In some examples, the subject's LDL-C is lowered by at least week 20 of administration of the PCSK9 inhibitor.

**[0015]** Provided herein is a method of treating or preventing heterozygous familial hypercholesterolemia (HeFH) or symptoms thereof, comprising: identifying a pediatric subject in need of treatment or prevention of HeFH or symptoms thereof; and administering to the subject an enhanced dosage regimen of a PCSK9 inhibitor, to thereby treat or prevent HeFH or symptoms thereof, wherein the enhanced dosage regimen comprises administering the PCSK9 inhibitor at an mean dose that is about 20% to about 500% greater than a standard-of-care mean dose of the PCSK9 inhibitor to treat or prevent HeFH or symptoms thereof in an adult patient. Optionally, the enhanced dosage regimen comprises a higher dosing frequency of the PCSK9 inhibitor than a standard-of-care dosing frequency. In some examples, the enhanced dosage regimen comprises a higher amount of the PCSK9 inhibitor than a standard-of-care amount. In some examples, the PCSK9 inhibitor is an antibody, small-molecule inhibitor, or an inhibitory nucleic acid. Optionally, the PCSK9 inhibitor is an anti-PCSK9 antibody. Optionally, the PCSK9 inhibitor is a siRNA or shRNA. Optionally, the PCSK9 inhibitor comprises one or more of evolocumab, alirocumab, bococizumab, 1D05-IgG2, RG-7652, LGT209, inclisiran, ISIS 394814, SX-PCK9, and BMS-962476.

**[0016]** In some examples, the method further comprises administering one or more other LDL cholesterol-lowering therapy to the subject. Optionally, the other LDL cholesterol-lowering therapy comprises a statin, a fibrate, a bile acid sequestrant, niacin, an antiplatelet agent, an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, an acylCoA cholesterol acetyltransferase (ACAT) inhibitor, a cholesterol

absorption inhibitor, a cholesterol ester transfer protein (CETP) inhibitor, a microsomal triglyceride transfer protein (MTTP) inhibitor, a cholesterol modulator, a bile acid modulator, a peroxisome proliferation activated receptor (PPAR) agonist, a gene-based therapy, a composite vascular protectant, a glycoprotein Ilb/IIIa inhibitor, aspirin or an aspirin-like compound, an IB AT inhibitor, a squalene synthase inhibitor, or a monocyte chemoattractant protein (MCP)-I inhibitor.

**[0017]** Also provided is a method of lowering serum LDL cholesterol (LDL-C) in a pediatric subject, comprising: administering to a pediatric subject having HeFH, wherein the subject has a baseline LDL-C of about 200 mg/dL or greater: a PCSK9 antibody at a dosing frequency of about once a month, and at an amount from about 400 mg to about 450 mg; at least one statin; and at least one other LDL cholesterol-lowering therapy that is different from the PCSK9 antibody and the at least one statin, to thereby lower the subject's LDL-C by at least 30%. Optionally, the anti-PCSK9 antibody comprises: a heavy chain variable region (VH) comprising: a CDRH1, CDRH2, and a CDRH3 of a CDRH1, CDRH2, and a CDRH3, respectively, of a VH of evolocumab; and an amino acid sequence at least 90% identical to the VH of evolocumab; and a light chain variable region (VL) comprising: a CDRL1, CDRL2, and a CDRL3 of a CDRL1, CDRL2, and a CDRL3, respectively, of a VL of evolocumab; and an amino acid sequence at least 90% identical to the VL of evolocumab. Optionally, the anti-PCSK9 antibody is evolocumab. In some examples, the amount is about 420 mg.

**[0018]** Also provided herein is a method of treating or preventing heterozygous familial hypercholesterolemia (HeFH) or symptoms thereof, comprising: administering to a pediatric subject having HeFH and a baseline serum LDL cholesterol (LDL-C) at or above an upper quartile of baseline LDL-C values among a pediatric HeFH patient cohort: a PCSK9 inhibitor; at least one statin; and at least one other LDL cholesterol-lowering therapy that is different from the PCSK9 inhibitor and the at least one statin, to thereby treat or prevent HeFH or symptoms thereof, wherein the PCSK9 inhibitor is administered according to a dosage regimen of the PCSK9 inhibitor for pediatric HeFH patients having a baseline LDL-C value that is less than the upper quartile. Optionally, the upper quartile is in a range of about 190 mg/dL to about 220 mg/dL. In some examples, the baseline LDL-C is about 200 mg/dL or greater. In some examples, the PCSK9 inhibitor is administered according to a

dosage regimen of the PCSK9 inhibitor for pediatric HeFH patients having a baseline LDL-C value that is less than a median of baseline LDL-C values among the cohort.

**[0019]** Provided herein is a method of treating or preventing heterozygous familial hypercholesterolemia (HeFH) or symptoms thereof, comprising: administering to a pediatric subject having HeFH: a PCSK9 inhibitor, wherein the PCSK9 inhibitor is administered according to a standard-of-care dosage regimen to treat or prevent HeFH or symptoms thereof in an adult patient; at least one statin; and at least one other LDL cholesterol-lowering therapy that is different from the PCSK9 inhibitor and the at least one statin, to thereby treat or prevent HeFH or symptoms thereof. Optionally, the at least one other LDL cholesterol-lowering therapy is administered according to an enhanced dosage regimen comprising an mean dose of the at least one other LDL cholesterol-lowering therapy that is about 20% to about 500% greater than a standard-of-care mean dose of the at least one other LDL cholesterol-lowering therapy to treat or prevent HeFH or symptoms thereof in a pediatric patient. Optionally, the enhanced dosage regiment comprises an increase in a dosing frequency and/or an increase in an amount of the PCSK9 inhibitor.

**[0020]** In some examples, the PCSK9 inhibitor is an antibody, small-molecule inhibitor, or an inhibitory nucleic acid. Optionally, the PCSK9 inhibitor comprises one or more of evolocumab, alirocumab, bococizumab, 1D05-IgG2, RG-7652, LGT209, REGN728, LY3015014, 1B20, inclisiran, ISIS 394814, SX-PCK9, and BMS-962476. In some examples, the at least one other LDL cholesterol-lowering therapy comprises a second PCSK9 inhibitor. Optionally, the second PCSK9 inhibitor is a small-molecule inhibitor, or an inhibitory nucleic acid. Optionally, the second PCSK9 inhibitor comprises one or more of evolocumab, alirocumab, bococizumab, 1D05-IgG2, RG-7652, LGT209, REGN728, LY3015014, 1B20, inclisiran, ISIS 394814, SX-PCK9, and BMS-962476.

**[0021]** In some examples, the at least one other LDL cholesterol-lowering therapy comprises a statin, a fibrate, a bile acid sequestrant, niacin, an antiplatelet agent, an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, an acylCoA cholesterol acetyltransferase (ACAT) inhibitor, a cholesterol absorption inhibitor, a cholesterol ester transfer protein (CETP) inhibitor, a microsomal triglyceride transfer protein (MTTP) inhibitor, a cholesterol modulator, a bile acid modulator, a peroxisome proliferation activated receptor (PPAR) agonist, a gene-based therapy, a composite vascular protectant, a

glycoprotein Ilb/IIIa inhibitor, aspirin or an aspirin-like compound, an IB AT inhibitor, a squalene synthase inhibitor, or a monocyte chemoattractant protein (MCP)-I inhibitor.

**[0022]** In some examples, the age of the subject is 17 years old or younger. In some examples, the age of the subject is between 10 and 17 years old. In some examples, the subject has compound HeFH. In some examples, the subject is receiving at least one other LDL cholesterol-lowering therapy. In some examples, the PCSK9 inhibitor or anti-PCSK9 antibody is administered subcutaneously or intravenously.

**[0023]** Provided herein is a kit for treating a pediatric subject in need of treating or preventing heterozygous familial hypercholesterolemia (HeFH) or symptoms thereof, comprising: a dosage form comprising a PCSK9 inhibitor in an amount sufficient to administer the PCSK9 inhibitor to a pediatric subject having HeFH an enhanced dosage regimen comprising administering to the subject the PCSK9 inhibitor at a dosing frequency that is at least 2 fold greater than an average dosing frequency of the PCSK9 inhibitor for pediatric HeFH patients having a baseline LDL-C value that is less than the upper quartile. Optionally, the average dosing frequency is a dosing frequency of the PCSK9 inhibitor for pediatric HeFH patients having a baseline LDL-C value that is less than a median of baseline LDL-C values among the cohort.

**[0024]** Also provided is a kit for treating a pediatric subject in need of treating or preventing heterozygous familial hypercholesterolemia (HeFH) or symptoms thereof, comprising: a dosage form comprising a PCSK9 inhibitor in an amount sufficient to administer the PCSK9 inhibitor to a pediatric subject an enhanced dosage regimen comprising administering to the subject the PCSK9 inhibitor at a dosage that is about 20% to about 500% greater than a standard-of-care dosage of the PCSK9 inhibitor to treat or prevent the cholesterol-related disorder in an adult HeFH patient.

**[0025]** Also provided herein is a method of lowering serum LDL cholesterol (LDL-C), comprising: administering to a subject a PCSK9 inhibitor, wherein the subject has heterozygous familial hypercholesterolemia, wherein the subject is a pediatric subject, wherein the PCSK9 inhibitor is administered in an amount that is at least as effective as 420 mg of evolocumab, wherein the PCSK9 inhibitor is administered at a frequency of every two weeks or more, whereby the subject's LDL-C is reduced by more than 30%.

**[0026]** Provided herein is a method of lowering serum LDL cholesterol (LDL-C) in a subject, comprising: identifying a pediatric subject having heterozygous familial hypercholesterolemia (HeFH), wherein the subject has a baseline LDL-C above an upper quartile of baseline LDL-C values among a pediatric HeFH patient cohort; and administering to the subject an enhanced dosage regimen of a PCSK9 inhibitor, wherein the enhanced dosage regimen comprises a dosing frequency and/or an amount that is from 20% to 500% greater than an average dosing frequency and/or average amount in a government regulatory agency-approved label for the PCSK9 inhibitor, whereby the subject's LDL-C is lowered by at least 30%. Optionally, the enhanced dosage regimen comprises a dosing frequency that is at least 2 fold greater than the average dosing frequency.

**[0027]** In some examples, the PCSK9 inhibitor comprises one or more of evolocumab, alirocumab, bococizumab, 1D05-IgG2, RG-7652, LGT209, REGN728, LY3015014, 1B20, inclisiran, ISIS 394814, ALN-PCS02, SX-PCK9, and BMS-962476.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0028]** FIG. 1 shows a schematic diagram of a study design for evolocumab for low density lipoprotein-cholesterol (LDL-C) reduction in pediatric subjects with heterozygous familial hypercholesterolemia (HeFH).

**[0029]** FIGS. 2A and 2B show schematic diagrams of methods of lowering serum LDL cholesterol (LDL-C) in a pediatric subject, according to some embodiments of the present disclosure.

**[0030]** FIG. 3 shows a schematic diagram of a method of lowering serum LDL cholesterol (LDL-C) in a pediatric subject, according to some embodiments of the present disclosure.

**[0031]** FIG. 4 shows a schematic diagram of a method of treating or preventing heterozygous familial hypercholesterolemia (HeFH) or symptoms thereof, according to some embodiments of the present disclosure.

**[0032]** FIG. 5 shows a schematic diagram of a method of lowering serum LDL cholesterol (LDL-C) in a pediatric subject, according to some embodiments of the present disclosure.

WHAT IS CLAIMED IS:

1. Use of an anti-PCSK9 antibody in the manufacture of a medicament for lowering serum LDL cholesterol (LDL-C) in a pediatric subject

having heterozygous familial hypercholesterolemia (HeFH), wherein the subject has a baseline LDL-C of about 200 mg/dL or greater,

said medicament comprising theanti-PCSK9 antibody at a dose from about 350 to about 500 mg, to thereby lower the subject's LDL-C.

2. The use of claim 1, wherein the baseline LDL-C is from about 200 mg/dL to about 550 mg/dL.

3. The use of claim 1 or 2, wherein the baseline LDL-C is 208 mg/dL or more.

4. The use of any one of the preceding claims, wherein the subject's LDL-C is lowered by at least 20%, at least 30%, at least 40%, about 30% to about 50%, about 20% to about 50%, about 20% to about 80%, about 30% to about 50%, or about 30% to about 80%.

5. The use of any one of the preceding claims, wherein the subject's LDL-C is lowered by at least 30%.

6. The use of any one of the preceding claims, wherein the subject's LDL-C is lowered by about 30% to about 80%.

7. The use of any one of the preceding claims, wherein the anti-PCSK9 antibody is to be administered every two weeks to every four weeks, every two weeks, or every four weeks.

8. The use of any one of claims 1-3, wherein the anti-PCSK9 antibody is to be administered every four weeks, and wherein the subject's LDL-C is lowered by at least 20%.

9. The use of any one of claims 1-3, wherein the anti-PCSK9 antibody is to be administered every two weeks, and wherein the subject's LDL-C is lowered by at least 30%.

10. Use of a PCSK9 antibody in the manufacture of a medicament for lowering serum LDL cholesterol (LDL-C) in a pediatric subject

having heterozygous familial hypercholesterolemia (HeFH), wherein the subject has a baseline LDL-C of about 210 mg/dL or less,

said medicament comprising the PCSK9 antibody at a dose of about 350 to about 500 mg, to thereby lower the subject's LDL-C, wherein the subject's LDL-C is lowered by at least 40%.

11. The use of claim 10, wherein the baseline LDL-C is less than 208 mg/dL.

12. The use of claim 10 or 11, wherein the subject's LDL-C is lowered by at least 40%, at least 50%, at least 60%, about 40% to about 60%, about 40% to about 80%, about 50% to about 60%, or about 50% to about 80%.

13. The use of any one of claims 10-12, wherein the subject's LDL-C is lowered by at least 45%.

14. The use of any one of claims 10-13, wherein the anti-PCSK9 antibody is to be administered every two weeks to every four weeks, every two weeks, or every four weeks.

15. The use of any one of claims 10-13, wherein the anti-PCSK9 antibody is to be administered every four weeks, and wherein the subject's LDL-C is lowered by at least 40%.

16. The use of any one of claims 10-13, wherein the anti-PCSK9 antibody is to be administered every two weeks, and wherein the subject's LDL-C is lowered by at least 50%.

17. The use of any one of the preceding claims, wherein the anti-PCSK9 antibody comprises:

a heavy chain variable region (VH) comprising:

a CDRH1, CDRH2, and a CDRH3 of a CDRH1, CDRH2, and a CDRH3, respectively, of a VH of evolocumab; and

an amino acid sequence at least 90% identical to the VH of evolocumab; and

a light chain variable region (VL) comprising:

a CDRL1, CDRL2, and a CDRL3 of a CDRL1, CDRL2, and a CDRL3, respectively, of a VL of evolocumab; and

an amino acid sequence at least 90% identical to the VL of evolocumab.

18. The use of any one of the preceding claims, wherein the anti-PCSK9 antibody is evolocumab.

19. The use of any one of the preceding claims, wherein the dose is about 420 mg.

20. The use of any one of claims 1-18, wherein the dose is about 490 mg.

21. The use of any one of the preceding claims, wherein the subject's LDL-C is lowered by at least week 20 of administration of the PCSK9 antibody.

22. Use of a PCSK9 inhibitor in the manufacture of a medicament for treating or preventing heterozygous familial hypercholesterolemia (HeFH) or symptoms

in a pediatric subject in need of treatment or prevention of HeFH or symptoms thereof, wherein the subject has a baseline LDL-C at or above an upper quartile of baseline LDL-C values among a pediatric HeFH patient cohort,

wherein the PCSK9 inhibitor is for use in an enhanced dosage regimen of the PCSK9 inhibitor, to thereby treat or prevent HeFH or symptoms thereof,

wherein the enhanced dosage regimen comprises the PCSK9 inhibitor which is to be administered at a mean dose that is about 20% to about 500% greater than a reference mean dose of the PCSK9 inhibitor for treating or preventing HeFH or symptoms thereof in pediatric HeFH patients having a baseline LDL-C value that is less than the upper quartile.

23. The use of claim 22, wherein the reference mean dose is a dose of the PCSK9 inhibitor for pediatric HeFH patients having a baseline LDL-C value that is less than a median of baseline LDL-C values among the cohort.

24. The use of claim 22 or 23, wherein the enhanced dosage regimen comprises an increase in a dosing frequency and/or an amount of the PCSK9 inhibitor which is to be administered to the subject.

25. The use of any one of claims 22-24, wherein the upper quartile is in a range of about 190 mg/dL to about 220 mg/dL.

26. The use of any one of claims 22-25, wherein the upper quartile is about 200 mg/dL.

27. The use of any one of claims 22-26, wherein the subject's baseline LDL-C is about 200 mg/dL or greater.

28. The use of any one of claims 22-27, wherein the baseline LDL-C is from about 200 mg/dL to about 550 mg/dL.

29. The use of any one of claims 22-28, wherein the baseline LDL-C is 208 mg/dL or greater.

30. The use of any one of claims 22-29, wherein the PCSK9 inhibitor is approved by a government regulatory agency for lowering serum LDL cholesterol levels in a human patient.

31. The use of any one of claims 22-30, wherein the average dosing frequency is a dosing frequency of the PCSK9 inhibitor for pediatric HeFH patients having a baseline LDL-C value that is less than a median of baseline LDL-C values among the cohort.

32. The use of any one of claims 22-31, wherein the PCSK9 inhibitor is an antibody, small-molecule inhibitor, or an inhibitory nucleic acid.

33. The use of claim 32, wherein the PCSK9 inhibitor is an anti-PCSK9 antibody, a siRNA or shRNA.

34. The use of claim 32, wherein the PCSK9 inhibitor comprises one or more of evolocumab, alirocumab, bococizumab, 1D05-IgG2, RG-7652, LGT209, REGN728, LY3015014, 1B20, inclisiran, ISIS 394814, ALN-PCS02, SX-PCK9, and BMS-962476.

35. The use of any one of claims 22-34, wherein the average dosing frequency is in a range from about once every 2 weeks to about once every 12 weeks.

36. The use of any one of claims 22-35, further comprising determining quartiles of the baseline LDL-C values of the cohort.

37. The use of any one of claims 22-36, wherein the cohort comprises at least 25 pediatric HeFH patients.

38. The use any one of claims 22-37, wherein the baseline LDL-C values among the cohort is at least 130 mg/dL.

39. The use of any one of the preceding claims, further comprising measuring the baseline LDL-C of the subject.

40. The use of any one of the preceding claims, wherein the identifying comprises diagnosing and/or genotyping the subject for HeFH.

41. The use of any one of the preceding claims, wherein the identifying comprises diagnosing and/or genotyping the patient for compound HeFH.

42. Use of an anti-PCSK9 antibody in the manufacture of a medicament for lowering serum LDL cholesterol (LDL-C) in a pediatric subject

having HeFH, wherein the subject has a baseline LDL-C of about 200 mg/dL or greater,

wherein the anti-PCSK9 antibody is for use at a dosing frequency of about once a month, and at an amount from about 400 mg to about 450 mg;

wherein the anti-PCSK9 antibody is for use with at least one statin; and

wherein the anti-PCSK9 antibody is for use with at least one other LDL cholesterol-lowering therapy that is different from the anti-PCSK9 antibody and the at least one statin,

to thereby lower the subject's LDL-C by at least 30%.

43. The use of claim 42, wherein the anti-PCSK9 antibody comprises:

a heavy chain variable region (VH) comprising:

a CDRH1, CDRH2, and a CDRH3 of a CDRH1, CDRH2, and a CDRH3, respectively, of a VH of evolocumab; and

an amino acid sequence at least 90% identical to the VH of evolocumab; and

a light chain variable region (VL) comprising:

a CDRL1, CDRL2, and a CDRL3 of a CDRL1, CDRL2, and a CDRL3, respectively, of a VL of evolocumab; and

an amino acid sequence at least 90% identical to the VL of evolocumab.

44. The use of claim 42 or 43, wherein the anti-PCSK9 antibody is evolocumab.

45. The use of any one of claims 42-44, wherein the amount is about 420 mg.

46. The use of any one of the preceding claims, wherein the age of the subject is 17 years old or younger.

47. The use of any one of the preceding claims, wherein the age of the subject is between 10 and 17 years old.

48. The use of any one of the preceding claims, wherein the subject has compound HeFH.

49. The use of any one of the preceding claims, wherein the subject is receiving at least one other LDL cholesterol-lowering therapy.

50. The use of any one of the preceding claims, wherein the PCSK9 inhibitor or anti-PCSK9 antibody is to be administered subcutaneously or intravenously.