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] ~~Provided~~ 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 ~~embodiments~~examples, the baseline LDL-C is 208 mg/dL or more. In some ~~embodiment~~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 ~~embodiment~~examples, the subject's LDL-C is lowered by at least 30%. In some ~~embodiment~~examples, the subject's LDL-C is lowered by about 30% to about 80%. In some

~~embodiment~~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 ~~embodiment~~examples, the anti-PCSK9 antibody is administered every four weeks, and the subject's LDL-C is lowered by at least 20%. In some ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~examples, the subject's LDL-C is lowered by at least 45%. In some ~~embodiment~~examples, the anti-PCSK9 antibody is administered every two weeks to every four weeks, every two weeks, or every four weeks. In some ~~embodiment~~examples, the anti-PCSK9 antibody is administered every four weeks, and the subject's LDL-C is lowered by at least 40%. In some ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~examples, the dose is about 420 mg. In some ~~embodiment~~examples, the dose is about 490 mg.

[0008] In some ~~embodiment~~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 ~~embodiment~~examples, the dosing frequency of the PCSK9 inhibitor is about 15% to about 400% greater than the average dosing frequency. In some ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~examples, the subject's LDL-C is lowered by at least 30%. In some ~~embodiment~~examples, the subject's LDL-C is lowered

by from about 30% to about 80%. In some ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~examples, the upper quartile is in a range of about 190 mg/dL to about 220 mg/dL. In some ~~embodiment~~examples, the upper quartile is about 200 mg/dL. In some ~~embodiment~~examples, the subject's baseline LDL-C is about 200 mg/dL or greater. In some ~~embodiment~~examples, the baseline LDL-C is from about 200 mg/dL to about 550 mg/dL. In some ~~embodiment~~examples, the baseline LDL-C is 208 mg/dL or greater. In some ~~embodiment~~examples, the PCSK9 inhibitor is approved by a government regulatory agency for lowering serum LDL cholesterol levels in a human patient. In some ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~examples, the average dosing frequency is in a range from about once every 2 weeks to about once every 12 weeks. In some ~~embodiment~~examples, the method further comprises determining quartiles of the baseline LDL-C values of the cohort. In some ~~embodiment~~examples, the cohort comprises at least 25 pediatric HeFH patients. In some ~~embodiment~~examples, the baseline LDL-C values among the cohort is at least 130 mg/dL.

[0011] In some ~~embodiment~~examples, the method further comprises measuring the baseline LDL-C of the subject. In some ~~embodiment~~examples, the identifying comprises diagnosing and/or genotyping the subject for HeFH. In some ~~embodiment~~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 ~~embodiment~~examples, the enhanced dosage regimen lowers LDL-C in the subject by 30%-80%. In some ~~embodiment~~examples, the amount of the PCSK9 inhibitor is increased by about 5% to about 100% than the standard-of-care amount. In some ~~embodiment~~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 ~~embodiment~~examples, the enhanced dosage regimen is continued until a therapeutically acceptable end point for HeFH is achieved. In some ~~embodiment~~examples, the PCSK9 inhibitor is approved by government regulatory agency for lowering LDL-C in a human patient. In some ~~embodiment~~examples, the standard-of-care dosing frequency is between once every 2 weeks to once every 12 weeks. In some ~~embodiment~~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 ~~embodiment~~examples, the anti-PCSK9 antibody is evolocumab.

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

[0014] In some ~~embodiment~~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 ~~embodiment~~examples, the enhanced dosage regimen comprises a higher amount of the PCSK9 inhibitor than a standard-of-care amount. In some ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~examples, the baseline LDL-C is about 200 mg/dL or greater. In some ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~examples, the age of the subject is 17 years old or younger. In some ~~embodiment~~examples, the age of the subject is between 10 and 17 years old. In some ~~embodiment~~examples, the subject has compound HeFH. In some ~~embodiment~~examples, the subject is receiving at least one other LDL cholesterol-lowering therapy. In some ~~embodiment~~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 ~~embodiment~~example**s**, 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 ~~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~~,

said medicament comprising the~~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.

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

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

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

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

7. The ~~method~~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 ~~method~~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 ~~method~~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 ~~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,~~

said medicament comprising the~~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%.

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

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

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

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

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

21. The ~~method~~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. 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.~~

~~23. The method of claim 22, wherein the amount of the PCSK9 inhibitor is about 5% to about 100% greater than the average amount.~~

~~24. The method of claim 22 or 23, wherein the dosing frequency of the PCSK9 inhibitor is about 15% to about 400% greater than the average dosing frequency.~~

~~25. The method of any one of claims 22-24, 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.~~

~~26. The method of any one of claims 22-25, wherein 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.~~

~~27. The method of any one of claims 22-26, wherein the subject's LDL-C is lowered by at least 30%.~~

~~28. The method of any one of claims 22-27, wherein the subject's LDL-C is lowered by from about 30% to about 80%.~~

~~29. The method of any one of claims 22-28, wherein 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.~~

~~30. The method of any one of claims 22-29, wherein the subject's LDL-C is lowered by at least week 20 of administration of the PCSK9 inhibitor.~~

~~31.~~22. Use of a PCSK9 inhibitor in the manufacture of a medicament for ~~A method of~~ treating or preventing heterozygous familial hypercholesterolemia (HeFH) or symptoms ~~thereof, comprising:~~

~~identifying~~ 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~~; and~~,

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

wherein the enhanced dosage regimen comprises ~~administering~~ 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.

~~32.~~23. The ~~method~~ use of claim ~~31~~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.

~~33.~~24. The ~~method~~use of claim ~~31~~ 22 or ~~32~~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.

~~34.~~25. The ~~method~~use of any one of claims 22-~~33~~24, wherein the upper quartile is in a range of about 190 mg/dL to about 220 mg/dL.

~~35.~~26. The ~~method~~use of any one of claims 22-~~34~~25, wherein the upper quartile is about 200 mg/dL.

~~36.~~27. The ~~method~~use of any one of claims 22-~~35~~26, wherein the subject's baseline LDL-C is about 200 mg/dL or greater.

~~37.~~28. The ~~method~~use of any one of claims 22-~~36~~27, wherein the baseline LDL-C is from about 200 mg/dL to about 550 mg/dL.

~~38.~~29. The ~~method~~use of any one of claims 22-~~37~~28, wherein the baseline LDL-C is 208 mg/dL or greater.

~~39.~~30. The ~~method~~use of any one of claims 22-~~38~~29, wherein the PCSK9 inhibitor is approved by a government regulatory agency for lowering serum LDL cholesterol levels in a human patient.

~~40.~~31. The ~~method~~use of any one of claims 22-~~39~~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.

~~41.~~32. The ~~method~~use of any one of claims 22-~~40~~31, wherein the PCSK9 inhibitor is an antibody, small-molecule inhibitor, or an inhibitory nucleic acid.

~~42.~~33. The ~~method~~use of claim ~~41~~32, wherein the PCSK9 inhibitor is an anti-PCSK9 antibody, a siRNA or shRNA.

~~43.~~34. The ~~method~~use of claim ~~41~~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.

~~44.~~35. The ~~method~~use of any one of claims 22-~~43~~34, wherein the average dosing frequency is in a range from about once every 2 weeks to about once every 12 weeks.

~~45.~~36. The ~~method~~use of any one of claims 22-~~44~~35, further comprising determining quartiles of the baseline LDL-C values of the cohort.

~~46.~~37. The ~~method~~use of any one of claims 22-~~45~~36, wherein the cohort comprises at least 25 pediatric HeFH patients.

~~47.~~38. The ~~method~~use any one of claims 22-~~46~~37, wherein the baseline LDL-C values among the cohort is at least 130 mg/dL.

~~48.~~39. The ~~method~~use of any one of the preceding claims, further comprising measuring the baseline LDL-C of the subject.

~~49.~~40. The ~~method~~use of any one of the preceding claims, wherein the identifying comprises diagnosing and/or genotyping the subject for HeFH.

~~50.~~41. The ~~method~~use of any one of the preceding claims, wherein the identifying comprises diagnosing and/or genotyping the patient for compound HeFH.

~~51. 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.~~

~~52. The method of claim 51, wherein the enhanced dosage regimen lowers LDL-C in the subject by at least 30%.~~

~~53. The method of claim 51 or 52, wherein the enhanced dosage regimen lowers LDL-C in the subject by 30%-80%.~~

~~54. The method of any one of claims 51-53, wherein the amount of the PCSK9 inhibitor is increased by about 5% to about 100% than the standard-of-care amount.~~

~~55. The method of any one of claims 51-54, wherein the dosing frequency of the PCSK9 inhibitor is increased by about 15% to about 400% than the standard-of-care dosing frequency.~~

~~56. The method of any one of claims 51-55, wherein the enhanced dosage regimen is continued until a therapeutically acceptable end point for HeFH is achieved.~~

~~57. The method of any one of claims 51-56, wherein the PCSK9 inhibitor is approved by government regulatory agency for lowering LDL-C in a human patient.~~

~~58. The method of any one of claims 51-57, wherein the standard-of-care dosing frequency is between once every 2 weeks to once every 12 weeks.~~

~~59. The method of any one of claims 51-58, wherein the PCSK9 inhibitor is an anti-PCSK9 antibody.~~

~~60. The method of claim 59, 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.~~

~~61. The method of claim 59 or 60, wherein the anti-PCSK9 antibody is evolocumab.~~

~~62. The method of any one of claims 59-61, wherein the standard-of-care amount is between 400 and 500 mg/dose.~~

~~63. The method of any one of claims 59-62, wherein the standard-of-care amount and/or frequency is about 420 mg/month.~~

~~64. The method of any one of claims 51-63, wherein the subject's LDL-C is lowered by at least week 20 of administration of the PCSK9 inhibitor.~~

~~65. 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.~~

~~66. The method of claim 65, wherein the enhanced dosage regimen comprises a higher dosing frequency of the PCSK9 inhibitor than a standard-of-care dosing frequency.~~

~~67. The method of claim 65 or 66, wherein the enhanced dosage regimen comprises a higher amount of the PCSK9 inhibitor than a standard-of-care amount.~~

~~68. The method of any one of claims 51-67, wherein the PCSK9 inhibitor is an antibody, small-molecule inhibitor, or an inhibitory nucleic acid.~~

~~69. The method of claim 68, wherein the PCSK9 inhibitor is an anti-PCSK9 antibody.~~

~~70. The method of claim 68, wherein the PCSK9 inhibitor is a siRNA or shRNA.~~

~~71. The method of claim 68, wherein the PCSK9 inhibitor comprises one or more of evolocumab, alirocumab, bococizumab, 1D05-IgG2, RG-7652, LGT209, inclisiran, ISIS 394814, SX-PCK9, and BMS-962476.~~

~~72. The method of any one of the preceding claims, further comprising administering one or more other LDL cholesterol-lowering therapy to the subject.~~

~~73. The method of claim 72, wherein 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 IIb/IIIa inhibitor, aspirin or an aspirin-like compound, an IB AT inhibitor, a squalene synthase inhibitor, or a monocyte chemoattractant protein (MCP)-I inhibitor.~~

~~74.~~42. Use of an anti-PCSK9 antibody in the manufacture of a medicament for ~~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~~ 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%.

~~75.~~43. The ~~method~~ use of claim ~~74~~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.

~~76.~~44. The ~~method~~ use of claim ~~74~~ 42 or ~~75~~43, wherein the anti-PCSK9 antibody is evolocumab.

~~77.~~45. The ~~method~~ use of any one of claims ~~74~~42-~~76~~44, wherein the amount is about 420 mg.

~~78. 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.

79. The method of claim 78, wherein the upper quartile is in a range of about 190 mg/dL to about 220 mg/dL.

80. The method of claim 78 or 79, wherein the baseline LDL-C is about 200 mg/dL or greater.

81. The method of any one of claims 78-80, 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 a median of baseline LDL-C values among the cohort.

82. 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.

83. The method of claim 82, wherein 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.

~~84. The method of claim 83, wherein the enhanced dosage regiment comprises an increase in a dosing frequency and/or an increase in an amount of the PCSK9 inhibitor.~~

~~85. The method of any one of claims 78-84, wherein the PCSK9 inhibitor is an antibody, small molecule inhibitor, or an inhibitory nucleic acid.~~

~~86. The method of claim 85, wherein 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.~~

~~87. The method of any one of claims 74-86, wherein the at least one other LDL cholesterol-lowering therapy comprises a second PCSK9 inhibitor.~~

~~88. The method of claim 87, wherein the second PCSK9 inhibitor is a small molecule inhibitor, or an inhibitory nucleic acid.~~

~~89. The method of claim 88, wherein 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.~~

~~90. The method of any one of claims 74-89, wherein 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 IIb/IIIa inhibitor, aspirin or an aspirin-like compound, an IB AT inhibitor, a squalene synthase inhibitor, or a monocyte chemoattractant protein (MCP) I inhibitor.~~

~~91.~~46. The ~~method~~ use of any one of the preceding claims ~~or claims 99-102~~, wherein the age of the subject is 17 years old or younger.

~~92.~~47. The ~~method~~use of any one of the preceding claims ~~or claims 99-102~~, wherein the age of the subject is between 10 and 17 years old.

~~93.~~48. The ~~method~~use of any one of the preceding claims ~~or claims 99-102~~, wherein the subject has compound HeFH.

~~94.~~49. The ~~method~~use of any one of the preceding claims ~~or claims 99-102~~, wherein the subject is receiving at least one other LDL cholesterol-lowering therapy.

~~95.~~50. The ~~method~~use of any one of the preceding claims ~~or claims 99-102~~, wherein the PCSK9 inhibitor or anti-PCSK9 antibody is to be administered subcutaneously or intravenously.

~~96. 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.~~

~~97. The kit of claim 96, 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.~~

~~98. 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.~~

~~99. 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%.~~

~~100. 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 %.~~

~~101. The method of claim 100, wherein the enhanced dosage regimen comprises a dosing frequency that is at least 2-fold greater than the average dosing frequency.~~

~~102. The method of any one of claims 99-101, 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.~~