of SEQ ID NO: 175, a CDRH3 comprising the amino acid sequence of SEQ ID NO: 180; d) a light chain complementarity determining region (CDR) CDRL1 comprising the amino acid sequence of SEQ ID NO: 305, a CDRL2 comprising the amino acid sequence of SEQ ID NO: 312, a CDRL3 comprising the amino acid sequence of SEQ ID NO: 319; and a heavy chain complementarity determining region (CDR) CDRH1 comprising the amino acid sequence of SEQ ID NO: 308, a CDRH2 comprising the amino acid sequence of SEQ ID NO: 320, a CDRH3 comprising the amino acid sequence of SEQ ID NO: 310; or e) a light chain variable region that comprises the amino acid sequence of SEQ ID NO: 23 and a heavy chain variable region comprises the amino acid sequence of SEQ ID NO:49, wherein the CDRs are according to Kabat, Chothia, or AbM, in the manufacture of a medicament for lowering serum LDL cholesterol in a human patient by at least 15%; and/or treating or preventing a cholesterol related disorder in a human patient having an elevated serum LDL cholesterol level; wherein the use comprises that the monoclonal antibody is to be administered to the human patient in need thereof at a dose of 70 mg to 450 mg. In another aspect, the present invention refers to the use of a monoclonal antibody as defined in the present invention in the manufacture of a medicament for use in combinatorial therapy in a human patient for treating a condition as defined in the present invention, wherein the medicament is to be administered to the human patient before, after or with at least one other cholesterol-lowering agent.

Also described herein is a stable formulation comprising at least one monoclonal antibody that specifically binds to PCSK9, wherein PCSK9 comprises the amino acids of SEQ ID NO 1, the monoclonal antibody in an amount of about 40 mg/ml to about 300 mg/ml, and a pharmaceutically acceptable buffer in an amount of about .05 mM to about 40 mM, and a pharmaceutically acceptable surfactant in an amount that is about .01% w/v to about 20% w/v, and at least one pharmaceutically acceptable stabilizer of about 0.5% w/v to about 10% w/v, wherein the stable formulation has a pH of between about 4.0 to about 6.0 is provided. In some examples the above stable formulation comprises a pharmaceutically acceptable buffer chosen from thee group consisting of glutamate, phosphate, phosphate buffered saline, sodium acetate, sodium citrate, and Tris buffer. In particular examples the pharmaceutically acceptable buffer of the above stable formulation is present in an

CLAIMS

1. Use of a monoclonal antibody that specifically binds to PCSK9 comprising

a) a light chain variable region that comprises an amino acid sequence that is at least 90% identical to that of SEQ ID NO: 23 and a heavy chain variable region that comprises an amino acid sequence that is at least 90% identical to that of SEQ ID NO:49;

b) a light chain complementarity determining region (CDR) of the CDRL1 sequence in SEQ ID NO:23, a CDRL2 of the CDRL2 sequence in SEQ ID NO:23, and a CDRL3 of the CDRL3 sequence in SEQ ID NO:23; and

a heavy chain complementarity determining region (CDR) of the CDRH1 sequence in SEQ ID NO:49, a CDRH2 of the CDRH2 sequence in SEQ ID NO:49, and a CDRH3 of the CDRH3 sequence in SEQ ID NO:49;

c) a light chain complementarity determining region (CDR) CDRL1 comprising the amino acid sequence of SEQ ID NO: 158, a CDRL2 comprising the amino acid sequence of SEQ ID NO: 162, a CDRL3 comprising the amino acid sequence of SEQ ID NO: 395; and

a heavy chain complementarity determining region (CDR) CDRH1 comprising the amino acid sequence of SEQ ID NO: 368, a CDRH2 comprising the amino acid sequence of SEQ ID NO: 175, a CDRH3 comprising the amino acid sequence of SEQ ID NO: 180;

d) a light chain complementarity determining region (CDR) CDRL1 comprising the amino acid sequence of SEQ ID NO: 305, a CDRL2 comprising the amino acid sequence of SEQ ID NO: 312, a CDRL3 comprising the amino acid sequence of SEQ ID NO: 319; and

a heavy chain complementarity determining region (CDR) CDRH1 comprising the amino acid sequence of SEQ ID NO: 308, a CDRH2 comprising the amino acid sequence of SEQ ID NO: 320, a CDRH3 comprising the amino acid sequence of SEQ ID NO: 310;

or

e) a light chain variable region that comprises the amino acid sequence of SEQ ID NO: 23 and a heavy chain variable region comprises the amino acid sequence of SEQ ID NO:49,

wherein the CDRs are according to Kabat, Chothia, or AbM,

in the manufacture of a medicament for

(i) lowering serum LDL cholesterol in a human patient by at least 15%; and/or

(ii) treating or preventing a cholesterol related disorder in a human patient having an elevated serum LDL cholesterol level;

wherein the use comprises that the monoclonal antibody is to be administered to the human patient in need thereof at a dose of 70 mg to 450 mg.

2. The use of claim 1(ii), wherein the cholesterol related disorder is selected from the group consisting of familial hypercholesterolemia including heterozygous familial hypercholesterolemia and homozygous familial hypercholesterolemia, non-familial hypercholesterolemia, elevated lipoprotein (a), heart disease, metabolic syndrome, diabetes, coronary heart disease, stroke, cardiovascular disease, Alzheimer's disease, peripheral arterial disease, hyperlipidemia and dyslipidemia.

3. The use of claims 1 or 2, wherein the serum LDL cholesterol level of said human patient is lowered by at least 15%.

4. The use of claims 1 or 2, wherein the serum LDL cholesterol level of said human patient is lowered by an amount selected from the group consisting of a) at least 30%, b) at least 40%, c) at least 50%, and d) at least 60%.

5. The use of claims 1 or 2, wherein the monoclonal antibody is to be administered to a human patient at a dose selected from the group consisting of: a) 70 mg to 450 mg, b) 140 mg to 200 mg, c) 140 mg to 180 mg, d) 140 mg to 170 mg, e) 140 mg, f) 150 mg, g) 420 mg, h) 450 mg.

6. The use of any one of claims 1-5, wherein the monoclonal antibody is to be administered to a human patient on a schedule selected from the group consisting of: (1) once a week, (2) once every two weeks, (3) once a month, (4) once every other month, (5) once every three months (6) once every six months and (7) once every twelve months.

7. The use of any one of claims 1-6, wherein the monoclonal antibody is to be administered to a human patient on a schedule selected from the group consisting of:
(a) 70 mg to 420 mg to be administered once every 2 weeks (Q2W);
(b) 140 mg to 280 mg to be administered once every two weeks (Q2W);
h(c) at least an amount of 140 mg every two weeks or every other week (Q2W);
(d) 280 mg to 420 mg to be administered once every 4 weeks (Q4W); and
(e) up to 420 mg every two weeks (Q2W); and
(f) at least an amount of 420 mg every four weeks (Q4W).

8. The use of any one of claims 1-7, wherein the administration comprises that the monoclonal antibody is to be administered parenterally, optionally wherein the administration comprises that the monoclonal antibody is to be administered intravenously or subcutaneously.

9. The use of claim 1, wherein the monoclonal antibody is to be administered to a human patient:
(a) at a dose of 105 mg to 280 mg subcutaneously once every two weeks, and wherein the serum LDL cholesterol level of the human patient is lowered at least 30 - 50% for 7-14 days, optionally wherein the dose is 140 mg;
(b) at a dose of 280 to 450 mg subcutaneously once every month, and wherein the serum LDL cholesterol level of the human patient is lowered at least 30 -50% for 21 to 31 days, optionally wherein the dose is 420 mg.

10. Use of a monoclonal antibody as defined in any one of claims 1 to 9 in the manufacture of a medicament for use in combinatorial therapy in a human patient for treating a condition as defined in any one of claims 1 to 9, wherein the medicament is to be administered to the human patient before, after or with at least one other cholesterol-lowering agent.

11. The use of claim 10, wherein the at least one other cholesterol lowering agent is selected from the group consisting of: statins, including, atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, Nicotinic acid, Fibric acid, Bile acid sequestrants, Cholesterol absorption inhibitor, lipid modifying agents, PPAR gamma agonists, PPAR alpha/gamma agonists,

squalene synthase inhibitors, CETP inhibitors, anti-hypertensives, anti-diabetic agents, including sulphonyl ureas, insulin, GLP-1 analogs, DDPIV inhibitors, ApoB modulators, MTP inhibitors and /or arteriosclerosis obliterans treatments, oncostatin M, estrogen, berberine and a therapeutic agent for an immune-related disorder.

METHODS OF TREATING OR PREVENTING CHOLESTEROL RELATED DISORDERS

Abstract

The present invention relates to methods of treating or preventing cholesterol related disorders, such as hypercholesterolemia, hyperlipidemia or dyslipidemia, using antibodies against proprotein convertase subtilisin/kexin type 9 (PCSK9). Formulations and methods of producing said formulations are also described.

No Suitable Figure