

CLAIMS:

1. An antibody or fragment comprising a binding site which specifically binds to Proprotein Convertase Subtilisin Kexin type 9 (PCSK9), wherein the binding site comprises

(i) a VH domain comprising a CDRH1 comprising SEQ ID NO: 263 or 277, a CDRH2 comprising SEQ ID NO: 267 or 281, and a CDRH3 comprising SEQ ID NO: 271 or 285;

and

a VL domain comprising a CDRL1 comprising SEQ ID NO: 293 or 307, a CDRL2 comprising SEQ ID NO: 297 or 311, and CDRL3 comprising SEQ ID NO: 301 or 315; or

(ii) a VH domain comprising a CDRH1 comprising SEQ ID NO: 323 or 337, a CDRH2 comprising SEQ ID NO: 327 or 341, and a CDRH3 comprising SEQ ID NO: 331 or 345;

and

a VL domain comprising a CDRL1 comprising SEQ ID NO: 353 or 367, a CDRL2 comprising SEQ ID NO: 357 or 371, and a CDRL3 comprising SEQ ID NO: 361 or 375; or

(iii) a VH domain comprising a CDRH1 comprising SEQ ID NO: 7 or 21, a CDRH2 comprising SEQ ID NO: 11 or 25, and a CDRH3 comprising SEQ ID NO: 15 or 29;

and

a VL domain comprising a CDRL1 comprising SEQ ID NO: 39 or 53, a CDRL2 comprising SEQ ID NO: 43 or 57, and a CDRL3 comprising SEQ ID NO: 47 or 61; or

(iv) a VH domain comprising a CDRH1 comprising SEQ ID NO: 69 or 83, a CDRH2 comprising SEQ ID NO: 73 or 87, and a CDRH3 comprising SEQ ID NO: 77 or 91;

and

a VL domain comprising a CDRL1 comprising SEQ ID NO: 99 or 113, a CDRL2 comprising SEQ ID NO: 103 or 117, and a CDRL3 comprising SEQ ID NO: 107 or 121; or

(v) a VH domain comprising a CDRH1 comprising SEQ ID NO: 203 or 217, a CDRH2 comprising SEQ ID NO: 207 or 221, and a CDRH3 comprising SEQ ID NO: 211 or 225;

and

a VL domain comprising a CDRL1 comprising SEQ ID NO: 233 or 247, a CDRL2 comprising SEQ ID NO: 237 or 251, and a CDRL3 comprising SEQ ID NO: 241 or 255.

2. The antibody or fragment according to claim 1, wherein the binding site comprises:
- (i) a VH domain comprising SEQ ID NO: 259, 319, 1, 65 or 199; or an amino acid that is at least 70% identical thereto; and/or
 - (ii) a VL domain comprising SEQ ID NO: 289, 349, 33, 95 or 229; or an amino acid that is at least 70% identical thereto; or
 - (iii) a VH domain comprising SEQ ID NO: 259 paired with a VL domain comprising SEQ ID NO: 289; or
 - (iv) a VH domain comprising SEQ ID NO: 319 paired with a VL domain comprising SEQ ID NO: 349.
3. The antibody or fragment according to claim 1 or 2 comprising first and second copies of said VH domain.
4. An antibody or fragment according to any preceding claim, which specifically binds to a PCSK9 comprising an amino acid sequence selected from SEQ ID NOs: 189-194.
5. The antibody or fragment according to any preceding claim, wherein the antibody or fragment comprises a human constant region.
6. The antibody or fragment according to claim 5, wherein the constant region is an IgG4-PE constant region.
7. The antibody or fragment according to any preceding claim, further comprising an antigen-binding site that specifically binds another target antigen.
8. An agent comprising the anti-PCSK9 antibody or fragment as defined in any preceding claim, for use in treating or preventing a PCSK9-mediated disease or condition in a subject.
9. The agent of claim 8, wherein the disease or condition is selected from hypercholesterolemia, hyperlipidemia, dyslipidemia, cholestatic liver disease, nephrotic syndrome, hypothyroidism, obesity, diabetes, atherosclerosis or a cardiovascular disease.

10. The agent of claim 8 or 9, wherein the agent is to be administered to the subject simultaneously or sequentially with a statin.
- 5 11. A combination of an amount of an anti-PCSK9 antibody or fragment and an amount of a statin, wherein the antibody or fragment is according to any one of claims 1 to 7.
- 10 12. An agent comprising the antibody or fragment according to any one of claims 1 to 7 or combination according to claim 11, the agent or combination for use in treating or preventing hypercholesterolaemia in a subject that has previously been on a statin treatment regime at a first dose, wherein the dose of statin that is to be administered to the subject is reduced relative to the first dose or wherein no statin is to be administered to the subject.
- 15 13. The combination for use according to claim 12, wherein the dose of statin that is to be administered to the subject is reduced relative to the first dose to a daily dose of 10 to 20mg; or <60mg.
- 20 14. An agent comprising the antibody or fragment of any one of claims 1 to 7 or combination of claim 11, the agent or combination for use in decreasing cholesterol in a human or animal subject suffering from elevated cholesterol, wherein the agent or combination is to be administered to the human or animal subject, or in lowering plasma low density lipoprotein cholesterol (LDL-C) level in the subject after the subject has received the anti-PCSK9 antibody or fragment.
- 25 15. A combination as defined in claim 11 for use in treating or preventing a PCSK9-mediated disease or condition.
- 30 16. The combination for use according to claim 15, wherein the PCSK9-mediated disease or condition is hypercholesterolaemia.
17. The agent or combination for use according to any one of claims 8 to 16, wherein the subject is to be further administered a further therapy.

18. A pharmaceutical composition comprising an antibody or fragment of any one of claims 1 to 7 or a combination as defined in claim 11 and a pharmaceutically acceptable excipient, diluent or carrier.

19. The pharmaceutical composition according to claim 18 for use in treating and/or preventing a PCSK9-mediated condition or disease.

20. The pharmaceutical composition according to claim 19 in combination with a label or instructions.

21. A nucleic acid that encodes a VH domain and/or a VL domain of an antibody or fragment as defined in any one of claims 1 to 7.

22. A nucleic acid according to Claim 21, wherein the nucleic acid:

- (a) encodes a VH domain comprising the amino acid sequence of a VH domain comprising SEQ ID NO: 259, 319, 1, 65 or 199; or an amino acid that is at least 70% identical thereto;
- (b) encodes a VL domain comprising the amino acid sequence of a VL domain comprising SEQ ID NO: 289, 349, 33, 95 or 229; or an amino acid that is at least 70% identical thereto; or
- (c) has a nucleotide sequence that is at least 70% identical to the sequence of SEQ ID NO: 260 or 320; or
- (d) encodes a heavy chain and/or a light chain of an antibody or fragment as defined in any one of claims 1 to 7; or
- (e) encodes a heavy chain comprising a VH amino acid sequence that is at least 70% identical to SEQ ID NO: 259 or 319; and a C region amino acid sequence that is at least 70% identical to a IGHG4 sequence; or
- (f) encodes a light chain comprising a VL amino acid sequence that is at least 70% identical to SEQ ID NO: 289 or 349; and a C region amino acid sequence that is at least 70% identical to a IGKC sequence.

23. A vector comprising the nucleic acid(s) of claim 21 or 22.

24. A host cell comprising the nucleic acid(s) of claim 21 or 22 or the vector of claim 23.

25. The antibody or fragment according to claim 5, wherein the human constant region is an IgG4 constant region or an IgG1 constant region.

26. The antibody or fragment according to claim 6, wherein the IgG4-PE constant region comprises the amino acid sequence of SEQ ID NO: 3 or 152.

27. The antibody or fragment according to claim 7, wherein the target antigen is ANGPTL3.

28. The combination of claim 11, wherein the combination comprises multiple doses of said antibody and/or statin.

29. The combination of claim 13, wherein the daily dose is 10 mg or 40 mg.

30. The agent or combination for use according to claim 17, wherein the further therapy is a further therapeutic agent.

31. The agent or combination for use according to claim 30, wherein the further therapeutic agent is selected from the group consisting of a:

- a. Statin;
- b. An ANGPTL3 inhibitor
- c. Fibrate;
- d. Bile acid sequestrant;
- e. Nicotinic acid; and
- f. Niacin.

32. The agent or combination for use according to claim 31, wherein the ANGPTL3 inhibitor is an anti-ANGPTL3 antibody or evinacumab.

33. The pharmaceutical composition according to claim 18, wherein the pharmaceutical composition is in combination with a further therapeutic agent selected from an agent recited in claim 31 or 32.

34. The pharmaceutical composition for use according to claim 19, the PCSK9-mediated condition or disease is hypercholesterolaemia.

35. The pharmaceutical composition for use according to claim 20, wherein the label or instructions comprise a marketing authorisation number.

5 36. The pharmaceutical composition for use according to claim 35, wherein the marketing authorisation number is an FDA or EMA authorisation number.

37. The pharmaceutical composition for use according to claim 36, wherein the composition is also in combination with an IV or injection device that comprises the antibody or fragment.

10

38. The nucleic acid according to claim 22, wherein the C region amino acid sequence of the heavy chain is at least at least 70% identical to SEQ ID NO: 3 or 152.

15

39. The nucleic acid according to claim 22, wherein the C region amino acid sequence of the light chain is at least 70% identical to SEQ ID NO: 156.

40. Use of an agent comprising the anti-PCSK9 antibody or fragment as defined in any of claims 1-7 in the manufacture of a medicament for treating or preventing a PCSK9-mediated disease or condition in a subject.

20

41. The use of claim 40, wherein the disease or condition is selected from hypercholesterolemia, hyperlipidemia, dyslipidemia, cholestatic liver disease, nephrotic syndrome, hypothyroidism, obesity, diabetes, atherosclerosis or a cardiovascular disease.

25

42. The use of claim 40 or 41, wherein the agent is to be administered to the subject simultaneously or sequentially with a statin.

30

43. Use of an agent comprising the antibody or fragment according to any one of claims 1 to 7 or combination according to claim 11 in the manufacture of a medicament for treating or preventing hypercholesterolaemia in a subject that has previously been on a statin treatment regime at a first dose, wherein the dose of statin that is to be administered to the subject is reduced relative to the first dose or wherein no statin is to be administered to the subject.

44. The use according to claim 43, wherein the dose of statin that is to be administered to the subject is reduced relative to the first dose to a daily dose of 10 to 20mg; or <60mg.

45. Use of an agent comprising the antibody or fragment of any one of claims 1 to 7 or combination of claim 11 in the manufacture of a medicament for decreasing cholesterol in a human or animal subject suffering from elevated cholesterol, wherein the agent or combination is to be administered to the human or animal subject, or for lowering plasma low density lipoprotein cholesterol (LDL-C) level in the subject after the subject has received the anti-PCSK9 antibody or fragment.

46. Use of a combination as defined in claim 11 in the manufacture of a medicament for treating or preventing a PCSK9-mediated disease or condition.

47. The use according to claim 46, wherein the PCSK9-mediated disease or condition is hypercholesterolaemia.

48. The use according to any one of claims 40 to 47, wherein the subject is to be further administered a further therapy.

49. Use of the pharmaceutical composition according to claim 18 in the manufacture of a medicament for treating and/or preventing a PCSK9-mediated condition or disease.

50. The use according to claim 49 in combination with a label or instructions.

51. The use according to claim 44, wherein the daily dose is 10 mg or 40 mg.

52. The use according to claim 48, wherein the further therapy is a further therapeutic agent.

53. The use according to claim 52, wherein the further therapeutic agent is selected from the group consisting of a:

- a. Statin;
- b. An ANGPTL3 inhibitor
- c. Fibrate;
- d. Bile acid sequestrant;

- e. Nicotinic acid; and
- f. Niacin.

54. The use according to claim 53, wherein the ANGPTL3 inhibitor is an anti-ANGPTL3 antibody or evinacumab.

55. The use according to claim 49, the PCSK9-mediated condition or disease is hypercholesterolaemia.

56. The use according to claim 50, wherein the label or instructions comprise a marketing authorisation number.

57. The use according to claim 56, wherein the marketing authorisation number is an FDA or EMA authorisation number.

58. The use according to claim 57, wherein the composition is also in combination with an IV or injection device that comprises the antibody or fragment.