

cardiovascular disease attack and death risk in patients with hyperlipidemia. Anti-PCSK9 antibodies are potent lipid-lowering agents, of which the efficacy in preventing cardiovascular disease attack and reducing the death risk in patients with hyperlipidemia has also been demonstrated. The clinical research results of anti-PCSK9 antibody evolocumab demonstrated that receiving evolocumab treatment can significantly reduce the risk of cardiovascular disease attack in patients with hyperlipidemia, and compared with the placebo control group, the incidences of myocardial infarction, stroke and conditions requiring coronary revascularization procedure are significantly reduced in the patients receiving evolocumab treatment. Large-scale clinical studies of another marketed anti-PCSK9 antibody, alirocumab, also demonstrated a protective effect on the cardiovascular system. Compared with the placebo control, the anti-PCSK9 antibody can reduce the overall risk of developing major adverse cardiovascular events, including acute myocardial infarction, ischemic stroke, death of coronary heart disease (CHD), or unstable angina requiring hospitalization, by 15%. Based on the results of these clinical studies, the two anti-PCSK9 antibodies were approved by the FDA in 2017 and 2019, respectively, for preventing heart disease and stroke in adult patients with cardiovascular disease.

SUMMARY

One aspectexample of the present application provides an inhibitor of the interaction between PCSK9 and LDLR, preferably an anti-PCSK9 antibody or an antigen-binding fragment thereof, for treating hypercholesterolemia (more preferably homozygous familial hypercholesterolemia or "HoFH", or heterozygous familial hypercholesterolemia or "HeFH", or hypercholesterolemia in a patient with extremely high or high risk of cardiovascular disease).

In one aspect, the present disclosure refers to an anti-PCSK9 antibody or an antigen-binding fragment thereof for use in treating hypercholesterolemia.

In some specific embodimentexamples, the antibody or the antigen-binding fragment thereof is a monoclonal antibody or an antigen-binding fragment thereof that specifically binds to human PCSK9 and blocks the binding of human PCSK9 to LDLR.

In some embodiment examples, the anti-PCSK9 antibody is a humanized antibody.

In some embodiment examples, the anti-PCSK9 antibody comprises:
a heavy chain variable region comprising an amino acid sequence set forth in SEQ ID NO: 2 or an amino acid sequence having at least 80% homology, preferably at least 85% homology, more preferably at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% homology thereto; and
a light chain variable region comprising an amino acid sequence set forth in SEQ ID NO: 4 or an amino acid sequence having at least 80% homology, preferably at least 85% homology, more preferably at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% homology thereto.

In some embodiment examples, the CDR sequences of the antibody are as follows:

HCDR1: GFTFSSYS (SEQ ID NO: 5);

HCDR2: ISSSSSYI (SEQ ID NO: 6);

HCDR3: EYDFWSAYYDAFDV (SEQ ID NO: 7);

LCDR1: SRNIGGGND (SEQ ID NO: 8);

LCDR2: GVI (SEQ ID NO: 9); and

LCDR3: QSF DGSLSGSV (SEQ ID NO: 10).

Another aspect example of the present application provides a pharmaceutical composition, preferably for treating hypercholesterolemia (more preferably HoFH, HeFH or hypercholesterolemia in a patient with extremely high or high risk of cardiovascular disease), comprising: an inhibitor of the interaction between PCSK9 and LDLR (and a statin), and a pharmaceutically acceptable carrier.

In one aspect, the present disclosure refers to a pharmaceutical composition, preferably for use in treating hypercholesterolemia, comprising: the anti-PCSK9 antibody or the antigen-binding fragment thereof disclosed herein, and a pharmaceutically acceptable carrier.

In some embodiment examples, the inhibitor of the interaction between PCSK9 and LDLR is in a form suitable for a parenteral or non-parenteral route of administration.

Another aspect example of the present application provides a kit, preferably for treating hypercholesterolemia (more preferably HoFH, HeFH or hypercholesterolemia in a patient with extremely high or high risk of cardiovascular disease), comprising the anti-PCSK9 antibody or the antigen-binding fragment thereof

disclosed herein. In some embodimentexamples, the kit further comprises a statin, and/or ezetimibe.

In one aspect, the present disclosure refers to a kit, preferably for treating hypercholesterolemia, comprising the anti-PCSK9 antibody or the antigen-binding fragment thereof disclosed herein, wherein preferably, the kit further comprises a statin (preferably a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, more preferably selected from lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin and pitavastatin), and/or ezetimibe.

The present application is further intended to at least provide a method for treating hypercholesterolemia (more preferably HoFH, HeFH or hypercholesterolemia in a patient with extremely high or high risk of cardiovascular disease), comprising: administering (e.g., parenterally or non-parenterally) to a subject in need a therapeutically effective amount of the inhibitor of the interaction between PCSK9 and LDLR disclosed herein (preferably the anti-PCSK9 antibody or the antigen-binding fragment thereof). Preferably, a statin is administered to the subject in combination. More preferably, a statin and ezetimibe are administered to the subject in combination. In some embodimentexamples, the inhibitor, the statin and/or ezetimibe are administered simultaneously or separately.

In one aspect, the present disclosure refers to use of a therapeutically effective amount of the anti-PCSK9 antibody or the antigen-binding fragment thereof disclosed herein, in the manufacture of a medicament for treating hypercholesterolemia, wherein the anti-PCSK9 antibody or the antigen-binding fragment thereof is to be administered (e.g., parenterally or non-parenterally) to a subject in need, wherein preferably, a statin is to be co-administered to the subject, and more preferably, a statin and ezetimibe are to be co-administered to the subject.

In some embodimentexamples, the statin is a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor.

In some embodimentexamples, the statin, i.e., the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, includes lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin and pitavastatin or any combination thereof, etc.

In certain embodimentexamples, the hypercholesterolemia (more preferably HoFH, HeFH or hypercholesterolemia in a patient with extremely high or high risk of cardiovascular disease) is caused by 1 (pair of) or more (pairs of) allelic or non-allelic gene mutations in LDLR, apolipoprotein B (ApoB), PCSK9 or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) genes, etc., wherein the allelic gene mutation includes LDLR dysfunctional mutation, ApoB gene mutation affecting the binding of LDL to LDLR, functional mutation resulting in increased affinity of PCSK9 for LDLR, LDLRAP1 dysfunctional mutation resulting in decreased LDL internalization activity, etc. Variants known to cause FH in the LDLR, APOB or PCSK9 genes are described, for example, in *Canadian Journal of Cardiology*, 34, (2018), 1553–1563, Canadian

Cardiovascular Society Position Statement on Familial Hypercholesterolemia: Update 2018.

In certain embodiment examples, the hypercholesterolemia (more preferably HoFH, HeFH or hypercholesterolemia in a patient with extremely high or high risk of cardiovascular disease) exhibits LDL-C > 13 mmol/L (500 mg/dL) when previously untreated or LDL-C $\geq$ 8 mmol/L (300 mg/dL) when previously treated (with a high dose/maximum tolerated dose of a statin in combination with ezetimibe), combined with skin or tendon xanthoma before age of 10 or both parents carrying 1 (pair of) or more (pairs of) allelic gene mutations in LDLR, ApoB, PCSK9 or LDLRAP1 genes, etc.

In certain embodiment examples, the hypercholesterolemia (more preferably HeFH) satisfies the following a) and b): a) the hypercholesterolemia is caused by 1 (pair of) or more (pairs of) unpaired allelic gene mutations in LDLR, apolipoprotein B (ApoB), PCSK9 or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) genes, etc., as described above, b) the patient has a serum LDL-C level $\geq$ 4.7 mmol/L (180 mg/dL) when previously untreated with a lipid regulating drug; or satisfies at least 1 of the following c) and d) simultaneously: c) a patient having skin or tendon xanthoma or a patient aged < 45 years with arcus lipoides corneae, and d) having a first-degree relative with FH or early adult atherosclerotic cardiovascular disease (ASCVD), particularly coronary heart disease.

The present application is further intended to at least provide use of the inhibitor of the interaction between PCSK9 and LDLR disclosed herein (preferably the anti-PCSK9 antibody or the antigen-binding fragment thereof) in preparing a medicament for treating hypercholesterolemia (more preferably HoFH, HeFH or hypercholesterolemia in a patient with extremely high or high risk of cardiovascular disease).

The present application further provides a method for treating a patient with hypercholesterolemia (more preferably HoFH, HeFH or hypercholesterolemia in a patient with extremely high or high risk of cardiovascular disease),

comprising: (i) genotyping the patient, (ii) measuring LDL-C level in a sample from the patient, and (iii) administering to the patient, when the patient is identified with homozygous (or heterozygous) familial hypercholesterolemia, a therapeutically effective amount of the anti-PCSK9 antibody or the antigen-binding portion thereof disclosed herein, preferably in combination with a statin, more preferably in combination with a statin and ezetimibe.

In one aspect, the present disclosure refers to use of a therapeutically effective amount of an anti-PCSK9 antibody or an antigen-binding fragment thereof, in the manufacture of a medicament for treating a patient with hypercholesterolemia, wherein: (i) the patient is to be genotyped, (ii) the LDL-C level in a sample (preferably serum, plasma or whole blood) from the patient is to be measured, and (iii) the anti-PCSK9 antibody or the antigen-binding fragment thereof is to be administered to the patient, when the patient is identified with homozygous or heterozygous familial hypercholesterolemia, preferably in combination with a statin, more preferably in combination with a statin and ezetimibe, wherein preferably the therapeutically effective amount is 0.1 mg/kg or higher, preferably 0.1–60 mg/kg, based on the weight of the patient.

In some ~~embodiment~~examples, the sample is serum, plasma or whole blood.

In certain ~~embodiment~~examples of the present ~~invention~~disclosure, the hypercholesterolemia in the patient with extremely high or high risk of cardiovascular disease refers to simultaneously satisfying the following condition 1 and condition 2, wherein the condition 1 is satisfying any of a) to h) (refer to *Guidelines for Prevention and Treatment of Dyslipidemia in Chinese Adults* (2016 Edition): a) a history of coronary artery disease (e.g. acute coronary syndrome, stable coronary heart disease, post-revascularization, ischemic cardiomyopathy), b) a history of ischemic stroke (excluding lacunar infarction), c) transient ischemic attack, d) peripheral atherosclerosis (e.g. carotid atherosclerosis, post-carotid endarterectomy, post-carotid stent placement, post-revascularization, lower limb atherosclerotic disease, post-lower limb artery revascularization), e) $\text{LDL-C} \geq 4.9 \text{ mmol/L}$ (190 mg/dL) or $\text{TC} \geq 7.2 \text{ mmol/L}$, f) type 2 diabetes patients aged 40 years and above with 1.8 mmol/L (70 mg/dL) $\leq \text{LDL-C} < 4.9 \text{ mmol/L}$ (190 mg/dL), g) chronic renal disease in stage 3 (i.e., with measured and calculated glomerular filtration rate $30 \text{ mL/min/1.73 m}^2 \leq \text{eGFR} < 60 \text{ mL/min/1.73 m}^2$), h) at least 3 of the following risk factors: male aged ≥ 45 and female aged ≥ 55 ; hypertension; smoking; a family history of CVD (for first-degree relatives: male aged < 55 and female aged < 65); HDL cholesterol $< 40 \text{ mg/dL}$; obesity ($\text{BMI} \geq 28 \text{ kg/m}^2$); and the condition 2 is satisfying either a) or b): after 4 weeks of stable basal lipid-lowering agent treatment: a) $\text{LDL-C level} > 1.8 \text{ mmol/L}$ (70 mg/dL) for patients with extremely high risk, or b) $\text{LDL-C level} > 2.6 \text{ mmol/L}$ (100 mg/dL) for patients with high risk.

The present application is further intended to at least provide a method for

preparing a pharmaceutical formulation (pharmaceutical composition) of an inhibitor of the interaction between PCSK9 and LDLR (preferably an anti-PCSK9 antibody or an antigen-binding fragment thereof) for treating hypercholesterolemia (preferably HoFH, HeFH or hypercholesterolemia in a patient with extremely high or high risk of cardiovascular disease).

In some [embodimentexamples](#), the anti-PCSK9 antibody is administered in a cycle of 2 weeks (14 days) or 4 weeks (28 days), and preferably, subcutaneously administered on the first day (D1) of each cycle. That is, the anti-PCSK9 antibody is administered once every two weeks (q2w) or four weeks (q4w).

In some [embodimentexamples](#), related is a single dose unit, preferably for treating familial hypercholesterolemia (more preferably HoFH, HeFH or hypercholesterolemia in a patient with extremely high or high risk of cardiovascular disease), comprising: 0.1–60 mg of the anti-PCSK9 antibody or the antigen-binding fragment thereof disclosed herein.

Another [aspectexample](#) of the present [inventiondisclosure](#) relates to use of 0.1–60 mg of the anti-PCSK9 antibody or the antigen-binding fragment thereof disclosed herein in preparing a single dose unit for treating familial hypercholesterolemia (more preferably HoFH, HeFH or hypercholesterolemia in a patient with extremely high or high risk of cardiovascular disease).

In one aspect, the present disclosure refers to use of the anti-PCSK9 antibody or the antigen-binding fragment thereof disclosed herein in the manufacture of a medicament for reducing the risk of attack and death of cardiovascular disease in a patient with hypercholesterolemia at extremely high or high risk of cardiovascular disease.

In one aspect, the present disclosure refers to use of a therapeutically effective amount of the anti-PCSK9 antibody or the antigen-binding fragment thereof disclosed herein, in the manufacture of a medicament for reducing blood cholesterol in a patient with hyperlipidemic cardiovascular disease (more preferably a patient with extremely high/high risk of cardiovascular disease) or for reducing a risk of cardiovascular disease attack in a patient with hyperlipidemic cardiovascular disease, wherein the anti-PCSK9 antibody or the antigen-binding fragment thereof is to be administered (e.g., parenterally or non-parenterally) to the patient, preferably in combination with a statin, more preferably in combination with a statin and ezetimibe, wherein more preferably the statin is selected from lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin and pitavastatin or any combination thereof.

MAB1

As used herein, MAB1 is an anti-PCSK9 monoclonal antibody, the sequence and structure of which can be found in reference Patent No. WO2016/127912A1. In the monoclonal antibody MAB1, the HCDR1 comprises a sequence GFTFSSYS (SEQ ID NO: 5), the HCDR2 comprises a sequence ISSSSSYI (SEQ ID NO: 6), the HCDR3 comprises a sequence EYDFWSAYYDAFDV (SEQ ID NO: 7), the LCDR1 comprises a sequence SRNIGGGND (SEQ ID NO: 8), the LCDR2 comprises a sequence GVI (SEQ ID NO: 9), and the LCDR3 comprises a sequence QSF DGSLSGSV (SEQ ID NO: 10).

Definitions and Descriptions

CLAIMS

1. An anti-PCSK9 antibody or an antigen-binding fragment thereof for use in treating hypercholesterolemia.
2. The anti-PCSK9 antibody or the antigen-binding fragment thereof for use according to claim 1, wherein the anti-PCSK9 antibody comprises:
an HCDR1: GFTFSSYS (SEQ ID NO: 5);
an HCDR2: ISSSSSYI (SEQ ID NO: 6);
an HCDR3: EYDFWSAYYDAFDV (SEQ ID NO: 7);
an LCDR1: SRNIGGGND (SEQ ID NO: 8);
an LCDR2: GVI (SEQ ID NO: 9); and
an LCDR3: QSFDGSLSGSV (SEQ ID NO: 10).
3. The anti-PCSK9 antibody or the antigen-binding fragment thereof for use according to claim 1, wherein the anti-PCSK9 antibody comprises: a heavy chain variable region comprising an amino acid sequence set forth in SEQ ID NO: 2 or an amino acid sequence having at least 80% homology, preferably at least 85% homology, more preferably at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% homology thereto; and
a light chain variable region comprising an amino acid sequence set forth in SEQ ID NO: 4 or an amino acid sequence having at least 80% homology, preferably at least 85% homology, more preferably at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% homology thereto.
4. The anti-PCSK9 antibody or the antigen-binding fragment thereof for use according to claim 1, wherein the antibody is a monoclonal antibody, preferably a humanized antibody.
5. A pharmaceutical composition, preferably for use in treating hypercholesterolemia, comprising: the anti-PCSK9 antibody or the antigen-binding fragment thereof according to any of claims 1–4, and a pharmaceutically acceptable carrier.
6. A kit, preferably for treating hypercholesterolemia, comprising the anti-

PCSK9 antibody or the antigen-binding fragment thereof according to any of claims 1–4, wherein preferably, the kit further comprises a statin (preferably a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, more preferably selected from lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin and pitavastatin), and/or ezetimibe.

7. The kit according to claim 6, wherein the anti-PCSK9 antibody is in a form suitable for a parenteral or non-parenteral route of administration.

8. ~~A method for treating hypercholesterolemia, comprising administering (e.g., parenterally or non-parenterally) to a subject in need~~Use of a therapeutically effective amount of the anti-PCSK9 antibody or the antigen-binding fragment thereof according to any of claims 1–4, in the manufacture of a medicament for treating hypercholesterolemia, wherein the anti-PCSK9 antibody or the antigen-binding fragment thereof is to be administered (e.g., parenterally or non-parenterally) to a subject in need, wherein preferably, a statin is to be co-administered to the subject, and more preferably, a statin and ezetimibe are to be co-administered to the subject.

9. The ~~method-use~~ according to claim 8, wherein the anti-PCSK9 antibody or the antigen-binding fragment thereof, the statin, and/or ezetimibe are to be administered simultaneously or separately.

10. The ~~method-use~~ according to claim 8, wherein the therapeutically effective amount is 0.1 mg/kg or greater, preferably 0.1–60 mg/kg, based on the body weight of the patient.

11. The anti-PCSK9 antibody or the antigen-binding fragment thereof according to any of claims 1–4, the pharmaceutical composition according to claim 5, the kit according to any of claims 6–7, or the ~~method-use~~ according to any of claims 8–9, wherein the hypercholesterolemia is selected from the group consisting of: (i) homozygous familial hypercholesterolemia, wherein more preferably the hypercholesterolemia is caused by 1 (pair of) or more (pairs of) allelic or non-allelic gene mutations in LDLR, apolipoprotein B (ApoB), PCSK9 or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) genes, preferably the

allelic gene mutation including LDLR dysfunctional mutation, ApoB gene mutation affecting the binding of LDL to LDLR, functional mutation resulting in increased affinity of PCSK9 for LDLR, and LDLRAP1 dysfunctional mutation resulting in decreased LDL internalization activity, and/or preferably the hypercholesterolemia (more preferably HoFH) exhibits LDL-C > 13 mmol/L (500 mg/dL) when previously untreated or LDL-C $\geq$ 8 mmol/L (300 mg/dL) when previously treated (with a high dose/maximum tolerated dose of a statin in combination with ezetimibe), combined with skin or tendon xanthoma before age of 10 or both parents carrying 1 or more pairs of allelic gene mutations in LDLR, ApoB, PCSK9 or LDLRAP1 genes;

(ii) heterozygous familial hypercholesterolemia, wherein preferably the heterozygous familial hypercholesterolemia is caused by 1 or more unpaired allelic gene mutations in LDLR, apolipoprotein B (ApoB), PCSK9 or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) genes, and more preferably the allelic gene mutation includes LDLR dysfunctional mutation, ApoB gene mutation affecting the binding of LDL to LDLR, functional mutation resulting in increased affinity of PCSK9 for LDLR, and LDLRAP1 dysfunctional mutation resulting in decreased LDL internalization activity; and

(iii) hypercholesterolemia in a patient with extremely high or high risk of cardiovascular disease, wherein preferably the hypercholesterolemia in the patient with extremely high or high risk of cardiovascular disease refers to simultaneously satisfying the following condition 1 and condition 2, wherein the condition 1 is satisfying any of a) to h): a) a history of coronary artery disease (e.g. acute coronary syndrome, stable coronary heart disease, post-revascularization, ischemic cardiomyopathy), b) a history of ischemic stroke (excluding lacunar infarction), c) transient ischemic attack, d) peripheral atherosclerosis (e.g. carotid atherosclerosis, post-carotid endarterectomy, post-carotid stent placement, post-revascularization, lower limb atherosclerotic disease, post-lower limb artery revascularization), e) LDL-C $\geq$ 4.9 mmol/L (190 mg/dL) or TC $\geq$ 7.2 mmol/L, f) type 2 diabetes patients aged 40 years and above

with 1.8 mmol/L (70 mg/dL) $\leq$ LDL-C $< 4.9 \text{ mmol/L}$ (190 mg/dL), g) chronic renal disease in stage 3 (i.e., with measured and calculated glomerular filtration rate $30 \text{ mL/min/1.73 m}^2 \leq \text{eGFR} < 60 \text{ mL/min/1.73 m}^2$), h) at least 3 of the following risk factors: male aged ≥ 45 and female aged ≥ 55 ; hypertension; smoking; a family history of CVD (for first-degree relatives: male aged < 55 and female aged < 65); HDL cholesterol $< 40 \text{ mg/dL}$; obesity (BMI $\geq 28 \text{ kg/m}^2$); and the condition 2 is satisfying either a) or b): after 4 weeks of stable basal lipid-lowering agent treatment: a) LDL-C level $> 1.8 \text{ mmol/L}$ (70 mg/dL) for patients with extremely high risk, or b) LDL-C level $> 2.6 \text{ mmol/L}$ (100 mg/dL) for patients with high risk.

12. ~~A method for treating a patient with hypercholesterolemia, comprising: (i) genotyping the patient, (ii) measuring LDL-C level in a sample (preferably serum, plasma or whole blood) from the patient, and (iii) administering to the patient, when the patient is identified with homozygous or heterozygous familial hypercholesterolemia,~~Use of a therapeutically effective amount of an anti-PCSK9 antibody or an antigen-binding fragment thereof, in the manufacture of a medicament for treating a patient with hypercholesterolemia, wherein: (i) the patient is to be genotyped, (ii) the LDL-C level in a sample (preferably serum, plasma or whole blood) from the patient is to be measured, and (iii) the anti-PCSK9 antibody or the antigen-binding fragment thereof is to be administered to the patient, when the patient is identified with homozygous or heterozygous familial hypercholesterolemia, preferably in combination with a statin, more preferably in combination with a statin and ezetimibe, wherein preferably the therapeutically effective amount is 0.1 mg/kg or higher, preferably $0.1\text{--}60 \text{ mg/kg}$, based on the weight of the patient.

13. The ~~method-use~~ according to claim 12, wherein the homozygous or heterozygous familial hypercholesterolemia is as defined in claim 11.

14. The ~~method-use~~ according to any of claims 12–13, wherein if the patient is identified with heterozygous familial hypercholesterolemia, the patient has a serum LDL-C level $\geq 4.7 \text{ mmol/L}$ (180 mg/dL) when previously untreated with

a lipid regulating drug, or,

if the patient is identified with heterozygous familial hypercholesterolemia, the patient satisfies at least 1 of the following a) and b) simultaneously: a) a patient having skin or tendon xanthoma or a patient aged < 45 years with arcus lipoides corneae, and b) having a first-degree relative with FH or early adult atherosclerotic cardiovascular disease (ASCVD), particularly coronary heart disease.

15. The ~~method-use~~ according to any of claims 8–12, wherein the anti-PCSK9 antibody or the antigen-binding fragment thereof is to be administered in a cycle of 2 weeks (14 days) or 4 weeks (28 days), and preferably, the anti-PCSK9 antibody or the antigen-binding fragment thereof is to be subcutaneously administered on the first day (D1) of each cycle.

16. Use of the anti-PCSK9 antibody or the antigen-binding fragment thereof according to any of claims 1–4 in ~~preparing a pharmaceutical formulation (or a pharmaceutical composition)~~the manufacture of a medicament for reducing the risk of attack and death of cardiovascular disease in a patient with hypercholesterolemia at extremely high or high risk of cardiovascular disease.

17. ~~A method for reducing blood cholesterol in a patient with hyperlipidemic cardiovascular disease (more preferably a patient with extremely high/high risk of cardiovascular disease) or for reducing a risk of cardiovascular disease attack in a patient with hyperlipidemic cardiovascular disease, comprising: administering (e.g., parenterally or non-parenterally) to the patient~~Use of a therapeutically effective amount of the anti-PCSK9 antibody or the antigen-binding fragment thereof according to any of claims 1–4, in the manufacture of a medicament for reducing blood cholesterol in a patient with hyperlipidemic cardiovascular disease (more preferably a patient with extremely high/high risk of cardiovascular disease) or for reducing a risk of cardiovascular disease attack in a patient with hyperlipidemic cardiovascular disease, wherein the anti-PCSK9 antibody or the antigen-binding fragment thereof is to be administered (e.g., parenterally or non-parenterally) to the patient, preferably in combination with

a statin, more preferably in combination with a statin and ezetimibe, wherein more preferably the statin is selected from lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin and pitavastatin or any combination thereof.

18. The ~~method-use~~ according to claim 17, wherein the anti-PCSK9 antibody is to be administered in a cycle of 2 weeks (14 days) or 4 weeks (28 days), and preferably, the anti-PCSK9 antibody is to be subcutaneously administered on the first day (D1) of each cycle.