# USE OF ANTI-ANGPTL3 ANTIBODY IN TREATING HYPERLIPIDEMIA AND METHOD

The present disclosure claims priority to Patent Application CN202410246641.9, which is incorporated herein by reference in its entirety.

## TECHNICAL FIELD

The present disclosure pertains to the field of pharmaceuticals and relates to a method for treating hyperlipidemia with an anti-ANGPTL3 antibody or an antigen-binding fragment thereof, and pharmaceutical use thereof.

## BACKGROUND

Atherosclerosis cardiovascular disease (CVD) is a major disease threatening human health. Low-density lipoprotein cholesterol (LDL-C) is a major risk factor for the development and progression of atherosclerosis cardiovascular disease (ASCVD). A meta-analysis showed that, within 1 year, each 1.0 mmol/L reduction in LDL-C is associated with an approximately 22% reduction in the risk of major vascular events (including coronary heart disease death, non-fatal myocardial infarction, coronary revascularization, and ischemic stroke) and a 10% reduction in all-cause mortality.

Angiopoietin-like protein 3 (ANGPTL3) is a secreted protein. As a member of the angiopoietin-like protein family, it is mainly expressed in the liver. The amino-terminal coil region of ANGPTL3 is associated with the inhibition of lipoprotein lipase (LPL) activity, and the carboxyl-terminal fibrinogen-like region, which modulates triglyceride (TG), is primarily associated with the modulation of angiogenesis. Thus, the protein has the function of modulating lipid metabolism and promoting angiogenesis.

ANGPTL3 serves primarily to modulate lipoprotein metabolism and, by inhibition of LPL and endothelial lipase (EL), plays a role in modulating lipid metabolism. At present, ANGPTL3 inhibitors fall into 2 categories, one of which is ANGPTL3-ASO, and the other is ANGPTL3 monoclonal antibodies. Their mechanisms and sites of action are different: ANGPTL3-ASO mainly acts on hepatocytes, while ANGPTL3 monoclonal antibodies exert their effects in blood circulation.

Although ANGPTL3 is a promising target for lowering lipid levels, only one monoclonal antibody drug, evinacumab, has been approved for marketing to date. Evinacumab is injected intravenously once every 4 weeks. Long-term intravenous injection may impose a burden on patients and reduce patient compliance. Moreover, based on the package insert for evinacumab, the effect of evinacumab on cardiovascular morbidity and mortality has not yet been established. Therefore, there remains a need in the art to develop new therapeutic approaches targeting ANGPTL3 that are safe, effective, and associated with high patient compliance.

## SUMMARY

The present disclosure provides use of an ANGPTL3 inhibitor (such as an anti-ANGPTL3 antibody or an antigen-binding fragment thereof) in treating hyperlipidemia and a method.

In one aspect, the present disclosure provides use of an anti-ANGPTL3 antibody or an antigen-binding fragment thereof in the manufacture of a medicament for treating a hyperlipidemia patient.

In another aspect, the present disclosure provides an anti-ANGPTL3 antibody or an antigen-binding fragment thereof for use in treating a hyperlipidemia patient.

In another aspect, the present disclosure provides use of an anti-ANGPTL3 antibody or an antigen-binding fragment thereof in combination with a background lipid-lowering therapeutic agent in the manufacture of a medicament for treating a hyperlipidemia patient.

In another aspect, the present disclosure provides use of a combination of an anti-ANGPTL3 antibody or an antigen-binding fragment thereof and a background lipid-lowering therapeutic agent in the manufacture of a medicament for treating a hyperlipidemia patient.

In another aspect, the present disclosure provides an anti-ANGPTL3 antibody or an antigen-binding fragment thereof for use in treating a hyperlipidemia patient, wherein a background lipid-lowering therapeutic agent is also administered to the hyperlipidemia patient.

In another aspect, the present disclosure provides an anti-ANGPTL3 antibody or an antigen-binding fragment thereof for use in treating a hyperlipidemia patient, wherein the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is administered in combination with a background lipid-lowering therapeutic agent.

In another aspect, the present disclosure provides use of an anti-ANGPTL3 antibody or an antigen-binding fragment thereof in the manufacture of a medicament for lowering plasma low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), lipoprotein(a) (Lp(a)), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and/or apolipoprotein A1 (ApoA1) levels in a hyperlipidemia patient.

In another aspect, the present disclosure provides an anti-ANGPTL3 antibody or an antigen-binding fragment thereof for use in lowering plasma low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), lipoprotein(a) (Lp(a)), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and/or apolipoprotein A1 (ApoA1) levels in a hyperlipidemia patient.

In another aspect, the present disclosure provides use of an anti-ANGPTL3 antibody or an antigen-binding fragment thereof in combination with a background lipid-lowering therapeutic agent in the manufacture of a medicament for lowering plasma low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), lipoprotein(a) (Lp(a)), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and/or apolipoprotein

A1 (ApoA1) levels in a hyperlipidemia patient.

In another aspect, the present disclosure provides use of a combination of an anti-ANGPTL3 antibody or an antigen-binding fragment thereof and a background lipid-lowering therapeutic agent in the manufacture of a medicament for lowering plasma low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), lipoprotein(a) (Lp(a)), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and/or apolipoprotein A1 (ApoA1) levels in a hyperlipidemia patient.

In another aspect, the present disclosure provides an anti-ANGPTL3 antibody or an antigen-binding fragment thereof for use in lowering plasma low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), lipoprotein(a) (Lp(a)), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and/or apolipoprotein A1 (ApoA1) levels in a hyperlipidemia patient, wherein a background lipid-lowering therapeutic agent is also administered to the hyperlipidemia patient in combination.

In another aspect, the present disclosure provides an anti-ANGPTL3 antibody or an antigen-binding fragment thereof for use in lowering plasma low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), lipoprotein(a) (Lp(a)), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and/or apolipoprotein A1 (ApoA1) levels in a hyperlipidemia patient, wherein the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is administered in combination with a background lipid-lowering therapeutic agent.

In another aspect, the present disclosure provides a method for treating a hyperlipidemia patient, which comprises administering an anti-ANGPTL3 antibody or an antigen-binding fragment thereof to a subject in need thereof.

In another aspect, the present disclosure provides a method for treating a hyperlipidemia patient, which comprises administering a background lipid-lowering therapeutic agent and an anti-ANGPTL3 antibody or an antigen-binding fragment thereof to a subject in need thereof.

Subject

In some embodiments, the hyperlipidemia patient is at risk of atherosclerosis cardiovascular disease (ASCVD). In some specific embodiments, the hyperlipidemia patient is at moderate or higher ASCVD risk (such as moderate risk, high risk, very high risk, and ultra-high risk) and does not achieve an LDL-C goal after receiving a lipid-lowering drug therapy.

In some embodiments, the hyperlipidemia patient is at moderate or higher ASCVD risk and does not achieve an LDL-C goal after receiving a lipid-lowering drug therapy.

In some embodiments, the hyperlipidemia patient is at moderate or higher ASCVD risk and does not achieve an LDL-C goal after receiving a lipid-lowering drug therapy for at least 4 weeks.

In some embodiments, the hyperlipidemia patient meets the following criteria:

(1) having received a lipid-lowering drug therapy for at least 4 weeks, and having a fasting LDL-C level of ≥ 1.4 mmol/L;

(2) having received a lipid-lowering drug therapy for at least 4 weeks, and having a fasting LDL-C level of ≥ 1.8 mmol/L;

(3) having received a lipid-lowering drug therapy for at least 4 weeks, and having a fasting LDL-C level of ≥ 2.6 mmol/L; or

(4) having a fasting LDL-C level of ≥ 2.6 mmol/L.

In some embodiments, in the hyperlipidemia patient at moderate or higher ASCVD risk not achieving the LDL-C goal after receiving the lipid-lowering drug therapy, the fasting LDL-C levels are as follows:

(1) For hyperlipidemia patients receiving stable treatment with moderate- or higher-intensity statin agents for ≥ 4 weeks: 1) the fasting LDL-C level is ≥ 1.4 mmol/L if the ASCVD risk is classified as ultra-high risk; 2) the fasting LDL-C level is ≥ 1.8 mmol/L if the ASCVD risk is classified as very high risk; and 3) the fasting LDL-C level is ≥ 2.6 mmol/L if the ASCVD risk is classified as moderate and high risk.

(2) For other circumstances where hyperlipidemia patients do not meet the criteria of "receiving stable treatment with moderate- or higher-intensity statin agents for ≥4 weeks", the fasting LDL-C level is ≥ 2.6 mmol/L if the ASCVD risk is classified as: 1) ultra-high risk, 2) very high risk, and 3) moderate and high risk.

In some embodiments, in the hyperlipidemia patient at moderate or higher ASCVD risk not achieving the LDL-C goal after receiving the lipid-lowering drug therapy, the fasting triglyceride level is ≤ 5.6 mmol/L.

In some embodiments, the ASCVD risk assessment is determined according to clinical treatment guidelines, such as the Chinese Guideline for Lipid Management (2023), the 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA Guideline on the Management of Blood Cholesterol: Executive Summary, and the 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk.

In some embodiments, ASCVD risk is determined according to the Chinese Guideline for Lipid Management (2023).

In some embodiments, the lipid-lowering drug therapy refers to a background lipid-lowering drug therapy.

In some embodiments, background lipid-lowering therapeutic agents include statin agents and/or non-statin agents. For example, statin agents include, but are not limited to, atorvastatin, rosuvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, simvastatin, and/or Xuezhikang. Non-statin agents include, but are not limited to, cholesterol absorption inhibitors (e.g., ezetimibe) and/or PCSK9 inhibitors (e.g., alirocumab and evolocumab).

In some embodiments, the selection and dose of a background lipid-lowering therapeutic agent are determined according to clinical treatment guidelines, such as the Chinese

Guideline for Lipid Management (2023), the 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA Guideline on the Management of Blood Cholesterol: Executive Summary, and the 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk.

In some embodiments, the moderate- or higher-intensity statin agents include, but are not limited to, the following statins (daily doses): atorvastatin ≥ about 10 mg; rosuvastatin ≥ about 5 mg; fluvastatin ≥ about 80 mg; lovastatin ≥ about 40 mg; pitavastatin ≥ about 2 mg; pravastatin ≥ about 40 mg; simvastatin ≥ about 20 mg; and Xuezhikang ≥ about 1.2 g.

In some embodiments, the moderate-intensity statin agents include, but are not limited to, the following statins (daily doses): atorvastatin about 10-20 mg; rosuvastatin about 5-10 mg; fluvastatin about 80 mg; lovastatin about 40 mg; pitavastatin about 2-4 mg; pravastatin about 40 mg; simvastatin about 20-40 mg; and Xuezhikang about 1.2 g.

Anti-ANGPTL3 Antibody or Antigen-Binding Fragment thereof

In some embodiments, the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is administered at a frequency selected from the group consisting of once every week, once every 2 weeks, once every 4 weeks, once every 6 weeks, once every 8 weeks, once every 10 weeks, and once every 12 weeks.

In some embodiments, the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is administered at a frequency that is less than once every 4 weeks. Illustratively, the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is administered at a frequency of once every 4 weeks, once every 6 weeks, once every 8 weeks, once every 10 weeks, or once every 12 weeks.

In some embodiments, the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is administered at a frequency of once every 4 weeks or once every 8 weeks.

In some embodiments, the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is administered at a dose selected from the group consisting of about 50 to about 1500 mg, about 100 to about 1000 mg, about 150 to about 600 mg, about 50 to about 800 mg, and about 100 to about 600 mg.

In some embodiments, the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is administered at a dose selected from the group consisting of about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, about 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, about 600 mg, about 610 mg, about 620 mg, about 630 mg, about 640 mg, about 650 mg, about 660 mg, about 670 mg,

about 680 mg, about 690 mg, about 700 mg, about 710 mg, about 720 mg, about 730 mg, about 740 mg, about 750 mg, about 760 mg, about 770 mg, about 780 mg, about 790 mg, about 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg, about 1500 mg, etc. (including any numerical value between any of the point values described above).

In some specific embodiments, the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is administered at a dose selected from the group consisting of about 150 mg, about 300 mg, about 600 mg, and about 1200 mg.

In some specific embodiments, the administration dose and administration frequency of the anti-ANGPTL3 antibody or the antigen-binding fragment thereof are any one selected from the group consisting of the following:

(1) The anti-ANGPTL3 antibody or the antigen-binding fragment thereof is administered at a dose of 150-600 mg per administration (e.g., about 150 mg per administration, about 200 mg per administration, about 250 mg per administration, about 300 mg per administration, about 350 mg per administration, about 400 mg per administration, about 450 mg per administration, about 550 mg per administration, about 550 mg per administration, or about 600 mg per administration) and at a frequency of once every 2 weeks.

(2) The anti-ANGPTL3 antibody or the antigen-binding fragment thereof is administered at a dose of 150-600 mg per administration (e.g., about 150 mg per administration, about 200 mg per administration, about 250 mg per administration, about 300 mg per administration, about 350 mg per administration, about 400 mg per administration, about 450 mg per administration, about 550 mg per administration, about 550 mg per administration, or about 600 mg per administration) and at a frequency of once every 4 weeks.

(3) The anti-ANGPTL3 antibody or the antigen-binding fragment thereof is administered at a dose of 150-600 mg per administration (e.g., about 150 mg per administration, about 200 mg per administration, about 250 mg per administration, about 300 mg per administration, about 350 mg per administration, about 400 mg per administration, about 450 mg per administration, about 550 mg per administration, about 550 mg per administration, or about 600 mg per administration) and at a frequency of once every 6 weeks.

(4) The anti-ANGPTL3 antibody or the antigen-binding fragment thereof is administered at a dose of 150-600 mg per administration (e.g., about 150 mg per administration, about 200 mg per administration, about 250 mg per administration, about 300 mg per administration, about 350 mg per administration, about 400 mg per administration, about 450 mg per administration, about 550 mg per administration, about 550 mg per administration, or about 600 mg per administration) and at a frequency of once every 8 weeks.

(5) The anti-ANGPTL3 antibody or the antigen-binding fragment thereof is

administered at a dose of 150-600 mg per administration (e.g., about 150 mg per administration, about 200 mg per administration, about 250 mg per administration, about 300 mg per administration, about 350 mg per administration, about 400 mg per administration, about 450 mg per administration, about 550 mg per administration, about 550 mg per administration, or about 600 mg per administration) and at a frequency of once every 10 weeks.

(6) The anti-ANGPTL3 antibody or the antigen-binding fragment thereof is administered at a dose of 150-600 mg per administration (e.g., about 150 mg per administration, about 200 mg per administration, about 250 mg per administration, about 300 mg per administration, about 350 mg per administration, about 400 mg per administration, about 450 mg per administration, about 550 mg per administration, about 550 mg per administration, or about 600 mg per administration) and at a frequency of once every 12 weeks.

(7) The anti-ANGPTL3 antibody or the antigen-binding fragment thereof is administered at a dose of 150-1200 mg per administration (e.g., about 150 mg per administration, about 200 mg per administration, about 250 mg per administration, about 300 mg per administration, about 350 mg per administration, about 400 mg per administration, about 450 mg per administration, about 550 mg per administration, about 550 mg per administration, about 600 mg per administration, about 700 mg per administration, about 800 mg per administration, about 1000 mg per administration, or about 1200 mg per administration) and at a frequency of once every 12 weeks.

(8) The anti-ANGPTL3 antibody or the antigen-binding fragment thereof is administered at a dose of 600-1200 mg per administration (e.g., about 600 mg per administration, about 700 mg per administration, about 800 mg per administration, about 1000 mg per administration, or about 1200 mg per administration) and at a frequency of once every 12 weeks.

In some specific embodiments, the administration dose and administration frequency of the anti-ANGPTL3 antibody or the antigen-binding fragment thereof are any one selected from the group consisting of the following:

The anti-ANGPTL3 antibody or the antigen-binding fragment thereof is administered at a dose of about 150 mg per administration, about 300 mg per administration, about 600 mg per administration, about 1000 mg per administration, or about 1200 mg per administration, and at a frequency of once every 4 weeks; or

the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is administered at a dose of about 150 mg per administration, about 300 mg per administration, about 600 mg per administration, about 1000 mg per administration, or about 1200 mg per administration, and at a frequency of once every 8 weeks; or

the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is administered at a dose of about 150 mg per administration, about 300 mg per administration, about 600 mg per administration, about 1000 mg per administration, or about 1200 mg per administration, and at a frequency of once every 12 weeks.

In some embodiments, the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is an anti-ANGPTL3 antibody or an antigen-binding fragment thereof of any class disclosed in WO2023001228 and WO2021147984. The antibody sequences, preparation methods, compositions, and other related contents in the above patents are incorporated herein by reference.

In some embodiments, the anti-ANGPTL3 antibody or the antigen-binding fragment thereof comprises any 1, any 2, any 3, any 4, any 5, or any 6 CDRs selected from the group consisting of a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2, and a LCDR3 set forth in SEQ ID NO: 1 to SEQ ID NO: 6.

In some embodiments, the anti-ANGPTL3 antibody or the antigen-binding fragment thereof comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the anti-ANGPTL3 antibody or the antigen-binding fragment thereof comprises a HCDR1, a HCDR2, and a HCDR3 in the heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 7, and/or the light chain variable region comprises a LCDR1, a LCDR2, and a LCDR3 in the light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 8.

In some embodiments, the anti-ANGPTL3 antibody or the antigen-binding fragment thereof comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the heavy chain variable region comprises a HCDR1, a HCDR2, and a HCDR3 set forth in SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3, respectively, and/or the light chain variable region comprises a LCDR1, a LCDR2, and a LCDR3 set forth in SEQ ID NO: 4, SEQ ID NO: 5, and SEQ ID NO: 6, respectively.

The aforementioned CDR sequences are shown in Table 1 below:

| Antibody molecule P8B | | | |
|---|---|---|---|
| Light chain CDR | | Heavy chain CDR | |
| LCDR1 | RSSQSLLHSNVYTYLD (SEQ ID NO: 4) | HCDR1 | SYDIN (SEQ ID NO: 1) |
| LCDR2 | LGSNRAS (SEQ ID NO: 5) | HCDR2 | LINPREDSTSYAQKFQG (SEQ ID NO: 2) |
| LCDR3 | MQALQTPLT (SEQ ID NO: 6) | HCDR3 | DLGSIREVLYYGMDV (SEQ ID NO: 3) |

The above CDRs are defined according to the Kabat, IMGT, Chothia, AbM, or Contact numbering scheme. In some specific embodiments, the CDRs are defined according to the Kabat numbering scheme.

In some embodiments, the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is a humanized antibody. In some specific embodiments, the VH of the anti-ANGPTL3 antibody or the antigen-binding fragment thereof comprises the amino acid sequence set forth in SEQ ID NO: 7 or an amino acid sequence having at least 80% or

90% sequence identity thereto, and the VL thereof comprises the amino acid sequence set forth in SEQ ID NO: 8 or an amino acid sequence having at least 80% or 90% sequence identity thereto.

> Heavy chain variable region sequence of P8B:

*QVQLVQSGAEVKKPGASVKVSCKASGYTFT*SYDIN*WVRQAPGQGLEWVG*LINPR**E**D STSYAQKFQG*RVTMTRDTSTSTMYMELSSLRSEDTAVYFCAR*DLGSIREVLYYGMD V*WGQGTTVTVSS*

SEQ ID NO: 7

> Light chain variable region sequence of P8B:

*DVVMTQSPLSLPVTPGEPASISC*RSSQSLLHSN**V**YTYLD*WYLQKPGQSPQLLIY*LGS NRAS*GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC*MQALQTPLT*FGQGTRLEIK*

SEQ ID NO: 8

Note: The underlined parts in the sequences represent the CDR sequences determined according to the Kabat numbering scheme, and the italicized parts represent FR sequences.

In some embodiments, the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is a humanized antibody comprising any 1 or 2 of the aforementioned VH and VL.

In some embodiments, the anti-ANGPTL3 antibody or the antigen-binding fragment thereof further comprises an antibody constant region; for example, the heavy chain constant region of the antibody constant region is selected from the group consisting of human IgG1, IgG2, IgG3, and IgG4 constant regions and variants thereof; and the light chain constant region of the antibody constant region is selected from the group consisting of human antibody κ and λ chain constant regions and variants thereof.

Illustratively, the antibody heavy chain constant region is selected from the group consisting of a human IgG4-YTE variant comprising the sequence set forth in SEQ ID NO: 11, and the light chain constant region is selected from the group consisting of the constant region of a human κ chain comprising the sequence set forth in SEQ ID NO: 12.

> Heavy chain constant region sequence of human IgG4-YTE variant:

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA VLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCP APEFLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG K

SEQ ID NO: 11

> Light chain constant region sequence of human κ chain:

RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQE SVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 12

Illustratively, the light/heavy chain constant regions described above were combined with the aforementioned variable regions of P8B to form a complete anti-ANGPTL3 antibody,

P8BG. The light/heavy chain sequences of the antibody are as follows:

> Heavy chain sequence of P8BG:

*QVQLVQSGAEVKKPGASVKVSCKASGYTFT*SYDIN*WVRQAPGQGLEWVG*LINPR**E**D
STSYAQKFQG*RVTMTRDTSTSTMYMELSSLRSEDTAVYFCAR*DLGSIREVLYYGMD
V*WGQGTTVTVSS*ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNS
GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKR
VESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSQEDPEV
QFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALH
NHYTQKSLSLSLGK

SEQ ID NO: 9

> Light chain sequence of P8BG:

*DVVMTQSPLSLPVTPGEPASISC*RSSQSLLHSN**V**YTYLD*WYLQKPGQSPQLLIY*LGS
NRAS*GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC*MQALQTPLT*FGQGTRLEIK*R
TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQES
VTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 10

In some embodiments, the anti-ANGPTL3 antibody or the antigen-binding fragment thereof comprises a heavy chain and a light chain, wherein the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 9 or an amino acid sequence having at least 80% or 90% identity thereto, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 10 or an amino acid sequence having at least 80% or 90% identity thereto.

In some embodiments, the anti-ANGPTL3 antibody or the antigen-binding fragment thereof comprises any 1 or 2 of the aforementioned heavy and light chains.

In the context of the present disclosure, "at least 80%" and "at least 90%" encompass 80% or more, e.g., at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, and any numerical range between any two of these numbers.

In some embodiments, the route of administration of the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is oral administration, parenteral administration, or percutaneous administration. In some specific embodiments, the route of administration of the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is subcutaneous injection.

In some embodiments, the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is formulated into an injectable form. Illustratively, the injectable form of the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is an injection or a freeze-dried powder, which comprises the anti-ANGPTL3 antibody or the antigen-binding fragment thereof and one or more pharmaceutically acceptable excipients.

In some embodiments, the pharmaceutical composition comprising the anti-ANGPTL3 antibody or the antigen-binding fragment thereof further comprises a buffer, a stabilizer, and/or a surfactant.

Illustratively, the aforementioned buffer is any one selected from the group consisting of acetic acid-sodium acetate, histidine-hydrochloride, sodium dihydrogen phosphate-disodium hydrogen phosphate, succinic acid-sodium succinate, and citric acid-sodium citrate buffers. Illustratively, the surfactant may be selected from the group consisting of polysorbate 20, polysorbate 80, poloxamer, Triton, sodium dodecyl sulfonate, sodium lauryl sulfonate, sodium octyl glycoside, lauryl-sulfobetaine, myristyl-sulfobetaine, linoleyl-sulfobetaine, stearyl-sulfobetaine, lauryl-sarcosine, myristyl-sarcosine, linoleyl-sarcosine, stearyl-sarcosine, linoleyl-betaine, myristyl-betaine, cetyl-betaine, lauramidopropyl-betaine, cocamidopropyl-betaine, linoleamidopropyl-betaine, myristamidopropyl betaine, palmitamidopropyl betaine, isostearamidopropyl-betaine, myristamidopropyl-dimethylamine, palmitamidopropyl-dimethylamine, isostearamidopropyl-dimethylamine, sodium methyl cocoyl taurate, sodium methyl oleyl taurate, polyethylene glycol, polypropylene glycol, copolymers of ethylene and propylene glycol, and the like. Illustratively, the stabilizer is selected from the group consisting of sugars and amino acids, wherein sugars comprise general compositions $(CH_2O)_n$ and derivatives thereof, such as monosaccharides, disaccharides, trisaccharides, polysaccharides, sugar alcohols, reducing sugars, non-reducing sugars, and the like. The sugars may be selected from the group consisting of glucose, sucrose, trehalose, lactose, fructose, maltose, dextran, glycerin, erythritol, glycerol, arabitol, xylose, sorbitol, mannitol, melibiose, melezitose, raffinose, mannotriose, stachyose, maltose, lactulose, maltulose, glucitol, maltitol, lactitol, isomaltulose, and the like. The amino acids are, for example, selected from the group consisting of glycine, methionine, and proline. WO2023001228 relates to compositions of the anti-ANGPTL3 antibody, and the patent application is incorporated herein by reference in its entirety.

Combination Administration

In some embodiments, provided is the method or the use according to any one of the foregoing, wherein the hyperlipidemia patient is treated with a background lipid-lowering therapeutic agent and the anti-ANGPTL3 antibody or the antigen-binding fragment thereof.

In some embodiments, provided is the method or the use according to any one of the foregoing, wherein an administration regimen for the hyperlipidemia patient includes:

1) a run-in period during which a background lipid-lowering therapeutic agent is administered to the hyperlipidemia patient; and

2) a treatment period during which a background lipid-lowering therapeutic agent and an anti-ANGPTL3 antibody or an antigen-binding fragment thereof are administered to the hyperlipidemia patient.

In some embodiments, the duration of the run-in period is ≥ 4 weeks, for example, 4

weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 10 weeks, and the like.

In some embodiments, background lipid-lowering therapeutic agents include statin agents, with or without the administration of non-statin agents. In some specific embodiments, the statin agents include, but are not limited to, atorvastatin, rosuvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, simvastatin, and/or Xuezhikang. In some specific embodiments, the non-statin agents are cholesterol absorption inhibitors (e.g., ezetimibe) and/or PCSK9 inhibitors (e.g., alirocumab and evolocumab).

In some embodiments, the selection and dose of a background lipid-lowering therapeutic agent are determined according to clinical treatment guidelines, such as the Chinese Guideline for Lipid Management (2023), the 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA Guideline on the Management of Blood Cholesterol: Executive Summary, and the 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk.

In some specific embodiments, atorvastatin is administered at a dose of about ≥ 10 mg, for example about 10 mg to about 40 mg, about 10 mg to about 50 mg, about 10 mg to about 60 mg, about 10 mg to about 80 mg, or about 10 mg to about 100 mg. In some specific embodiments, atorvastatin is administered at a dose of about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 90 mg, about 100 mg, or the like.

In some specific embodiments, atorvastatin is administered at a frequency of once daily, once every 2 days, or twice daily. In some specific embodiments, atorvastatin is administered at a frequency of once daily.

In some specific embodiments, atorvastatin is administered at a frequency of once daily and at a dose of about ≥ 10 mg, about 10 mg to about 40 mg, about 10 mg to about 50 mg, about 10 mg to about 60 mg, about 10 mg to about 80 mg, or about 10 mg to about 100 mg.

In some specific embodiments, rosuvastatin is administered at a dose of about ≥ 5 mg, for example about 5 mg to about 10 mg, about 5 mg to about 20 mg, about 5 mg to about 40 mg, about 5 mg to about 50 mg, about 5 mg to about 60 mg, about 5 mg to about 80 mg, or about 5 mg to about 100 mg. In some specific embodiments, rosuvastatin is administered at a dose of about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 90 mg, about 100 mg, or the like.

In some specific embodiments, rosuvastatin is administered at a frequency of once daily, once every 2 days, or twice daily. In some specific embodiments, rosuvastatin is administered at a frequency of once daily.

In some specific embodiments, rosuvastatin is administered at a frequency of once daily and at a dose of about ≥ 5 mg, about 5 mg to about 10 mg, about 5 mg to about 20 mg, about 5 mg to about 40 mg, about 5 mg to about 50 mg, about 5 mg to about 60 mg, about 5 mg to about 80 mg, or about 5 mg to about 100 mg.

In some embodiments, after completion of the run-in period treatment, hyperlipidemia patients meeting the following criteria are treated with a background lipid-lowering therapeutic agent and an anti-ANGPTL3 antibody or an antigen-binding fragment thereof:

1) having a fasting LDL-C level of ≥ 1.4 mmol/L before randomization for patients at ultra-high ASCVD risk or a fasting LDL-C level of ≥ 1.8 mmol/L before randomization for patients at very high ASCVD risk or a fasting LDL-C level of ≥ 2.6 mmol/L before randomization for patients at moderate and high ASCVD risk;

2) having a fasting triglyceride level of ≤ 5.6 mmol/L before randomization.

In some embodiments, provided is the method or the use according to any one of the foregoing, wherein, after treatment with the anti-ANGPTL3 antibody or the antigen-binding fragment thereof, the hyperlipidemia patients exhibit at least one of the following improved indicators:

reduced plasma low-density lipoprotein cholesterol (LDL-C) levels;

reduced triglyceride (TG) levels;

reduced non-high-density lipoprotein cholesterol (non-HDL-C) levels;

reduced apolipoprotein B (ApoB) levels;

reduced lipoprotein(a) (Lp(a)) levels;

reduced total cholesterol (TC) levels;

reduced high-density lipoprotein cholesterol (HDL-C) levels; and

reduced apolipoprotein A1 (ApoA1) levels.

For example, according to certain embodiments of the present disclosure, administration of the anti-ANGPTL3 antibody or the antigen-binding fragment thereof to a suitable subject results in:

an average percent reduction of at least about 1%, about 5%, about 10%, about 15%, about 20%, about 25%, 30%, 40%, 50%, 60%, or greater from baseline in serum low-density lipoprotein cholesterol (LDL-C) levels;

an average percent reduction of at least about 1%, about 5%, about 10%, about 15%, about 20%, about 25%, 30%, 40%, 50%, 60%, or greater from baseline in triglyceride (TG) levels;

an average percent reduction of at least about 1%, about 5%, about 10%, about 15%, about 20%, about 25%, 30%, 40%, 50%, 60%, or greater from baseline in non-high-density lipoprotein cholesterol (non-HDL-C) levels;

an average percent reduction of at least about 1%, about 5%, about 10%, about 15%, about 20%, about 25%, 30%, 40%, 50%, 60%, or greater from baseline in apolipoprotein B (ApoB) levels;

an average percent reduction of at least about 1%, about 5%, about 10%, about 15%, about 20%, about 25%, 30%, 40%, 50%, 60%, or greater from baseline in Lp(a) levels;

an average percent reduction of at least about 1%, about 5%, about 10%, about 15%, about 20%, about 25%, 30%, 40%, 50%, 60%, or greater from baseline in total cholesterol (TC) levels;

an average percent reduction of at least about 1%, about 5%, about 10%, about 15%, about 20%, about 25%, 30%, 40%, 50%, 60%, or greater from baseline in high-density lipoprotein cholesterol (HDL-C) levels; and/or

an average percent reduction of at least about 1%, about 5%, about 10%, about 15%, about 20%, about 25%, 30%, 40%, 50%, 60%, or greater from baseline in apolipoprotein A1 levels.

The anti-ANGPTL3 antibody of the present disclosure can reduce LDL-C levels in hyperlipidemia patients, thereby providing the benefit of reducing the risk of cardiovascular events, preventing and controlling ASCVD, and exhibiting good safety and efficacy. In another aspect, the anti-ANGPTL3 antibody is administered via subcutaneous injection at a low frequency, which results in good patient compliance.

In some embodiments, the anti-ANGPTL3 antibody of the present disclosure exhibits good efficacy in terms of LDL-C and TG levels in patients at moderate and high ASCVD risk and shows greater LDL-C reduction effect and enhanced target inhibition efficacy compared with existing treatment methods (e.g., zodasiran). The Q4W/Q8W subcutaneous administration regimen of the anti-ANGPTL3 antibody significantly improves treatment convenience, especially in patients with chronic diseases requiring long-term management. In this study, patient treatment compliance reached up to 97%, with a low incidence of injection site reactions (3.4%). There was no statistically significant difference in the incidence of TRAEs between the anti-ANGPTL3 antibody groups (19.5%) and the placebo group (13.4%). Meanwhile, the anti-ANGPTL3 antibody had minimal impact on liver function (the incidence of alanine transaminase (ALT) elevation was comparable to that of the placebo group), which is in contrast to the risk of liver enzyme abnormalities associated with evinacumab, indicating that the anti-ANGPTL3 antibody in the present disclosure may have a more favorable hepatic safety profile.

**Terminology**

In order to facilitate the understanding of the present disclosure, certain technical and scientific terms are specifically defined below. Unless otherwise specifically defined herein, all other technical and scientific terms used herein have the meanings generally understood by those of ordinary skill in the art to which the present disclosure pertains.

Unless the context clearly requires otherwise, throughout the description and the claims, the words “comprise”, “have”, “include”, etc., are to be understood in an inclusive sense as opposed to an exclusive or exhaustive sense, that is to say, in the sense of “including but not limited to”.

“Optional” or “optionally” means that the event or circumstance subsequently described may, but does not necessarily, occur; this description includes the instance where the event

or circumstance occurs or does not occur.

"About" or "approximately" means that the numerical value is within an acceptable margin of error for the specific value determined by those of ordinary skill in the art, and the numerical value depends in part on how the value is measured or determined (i.e., the limitations of the measurement system). For example, "about" may mean a standard deviation within 1 or greater than 1. Alternatively, "about" or "substantially comprise" may mean a range of at most 20%, e.g., a variation of between 1% and 15%, between 1% and 10%, between 1% and 5%, between 0.5% and 5%, or between 0.5% and 1%. In the present disclosure, every instance where a number or numerical range is preceded by the term "about" also includes embodiments of the given number. Unless otherwise specified, when a specific value is provided in the present application and claims, the meaning of "about" or "substantially comprise" should be assumed to be within an acceptable margin of error for that specific value.

The term "and/or", e.g., "X and/or Y", should be understood to mean "X and Y" or "X or Y" and should be used to provide explicit support for both meanings or either meaning.

The three-letter and single-letter codes for amino acids used in the present disclosure are described in J. Biol. Chem., 243, p3558 (1968).

"Antibody" is used in the broadest sense and encompasses a variety of antibody structures, including but not limited to monoclonal antibodies, polyclonal antibodies, monospecific antibodies, multispecific antibodies (e.g., bispecific antibodies), full-length antibodies, and antibody fragments (or antigen-binding fragments, or antigen-binding moieties), so long as they exhibit the desired antigen-binding activity. An antibody may refer to an immunoglobulin, which is a four-peptide-chain structure formed by linking two identical heavy chains and two identical light chains by interchain disulfide bonds. The heavy chain constant regions of immunoglobulins differ in amino acid composition and arrangement; therefore, they also differ in antigenicity. Accordingly, immunoglobulins can be classified into five classes, also referred to as isotypes of immunoglobulins, namely IgM, IgD, IgG, IgA, and IgE, and their corresponding heavy chains are a μ chain, a δ chain, a γ chain, an α chain, and an ε chain, respectively. Igs of the same class can be classified into different subclasses based on the amino acid composition of their hinge regions and the number and positions of heavy chain disulfide bonds; for example, IgG can be divided into IgG1, IgG2, IgG3, and IgG4. Light chains are classified into κ or λ chains based on their constant regions. Each of the five Ig classes may have a κ chain or λ chain. In the antibody heavy and light chains, the sequences of about 110 amino acids near the N-terminus vary considerably and thus are referred to as variable regions (V regions); the remaining amino acid sequences near the C-terminus are relatively stable and thus are referred to as constant regions (C regions). The variable regions comprise 3 hypervariable regions (CDRs) and 4 framework regions (FRs) with relatively conservative sequences. The 3 hypervariable regions determine the specificity of the antibody and thus are also known as complementarity determining regions (CDRs). Each of the light chain variable regions (VLs) and the heavy chain variable regions (VHs) consists of 3 CDRs and 4 FRs arranged

from the amino-terminus to the carboxyl-terminus as follows: FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. The 3 CDRs of the light chain refer to LCDR1, LCDR2, and LCDR3, and the 3 CDRs of the heavy chain refer to HCDR1, HCDR2, and HCDR3.

For the determination or definition of CDRs, the deterministic depiction of CDRs and identification of residues comprising binding sites of an antibody can be accomplished by resolving the structure of the antibody and/or resolving the structure of the antibody-ligand complex. This can be accomplished by any one of a variety of techniques known to those skilled in the art, such as X-ray crystallography. A variety of analysis methods can be used to identify CDRs, including but not limited to the Kabat numbering scheme, the Chothia numbering scheme, the AbM numbering scheme, the IMGT numbering scheme, the contact definition, and the conformational definition.

The amino acid sequence boundaries of the CDRs can be determined by a variety of well-known schemes, for example, the "Kabat" numbering scheme (see Kabat et al. (1991), "Sequences of Proteins of Immunological Interest", 5th ed., Public Health Service, National Institutes of Health, Bethesda, MD), the "Chothia" numbering scheme, the "ABM" numbering scheme, the "contact" numbering scheme (see Martin, ACR. Protein Sequence and Structure Analysis of Antibody Variable Domains[J]. 2001), and the ImMunoGenTics (IMGT) numbering scheme (Lefranc, M.P. et al., Dev. Comp. Immunol., 27, 55-77 (2003); Front Immunol. 2018 Oct 16; 9: 2278), and the like.

The term "antigen-binding fragment" or "functional fragment" or "antigen-binding moiety" refers to one or more fragments of an intact antibody that retain the ability to specifically bind to an antigen. It has been shown that a fragment of a full-length antibody can be used to achieve the antigen-binding function of the antibody. Illustratively, examples of binding fragments encompassed by the term "antigen-binding fragment" include: (i) a Fab fragment, a monovalent fragment consisting of VL, VH, CL, and CH1 domains; (ii) a $F(ab')_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge in the hinge region; (iii) an Fd fragment consisting of VH and CH1 domains; (iv) an Fv fragment consisting of the VH and VL domains of a single arm of an antibody; (v) a dsFv, a stable antigen-binding fragment formed by linking a VH and a VL by an interchain disulfide bond; (vi) an scFv; (vii) a diabody, a bispecific antibody, and a multispecific antibody comprising fragments such as an scFv, a dsFv, and a Fab.

"Homology" refers to the sequence similarity between two polynucleotide sequences or between two polypeptides. When positions in two sequences being compared are occupied by identical bases or amino acid monomer subunits, for example, if a position is occupied by adenine in both DNA molecules, the molecules are homologous at that position. The homology percentage between two sequences is a function of the number of matching or homologous positions shared by the two sequences divided by the number of positions compared × 100%. For example, in the optimal alignment of sequences, if 6 out of 10 positions of two sequences are matched or homologous, the two sequences are 60% homologous, and if 95 out of 100 positions of two sequences are matched or homologous, the two sequences are 95% homologous. Generally, two sequences, when

aligned, are compared to give the maximum percent homology. For example, the comparison may be made using a BLAST algorithm, wherein parameters are selected for the algorithm to give the maximum match between the reference sequences over the entire length of each sequence. The following references relate to the BLAST algorithm, often used for sequence analysis: the BLAST algorithm: Altschul, S.F. et al., (1990) J. Mol. Biol., 215: 403-410; Gish, W., et al., (1993) Nature Genet., 3: 266-272; Madden, T.L. et al., (1996) Meth. Enzymol., 266: 131-141; Altschul, S.F. et al., (1997) Nucleic Acids Res., 25: 3389-3402; and Zhang, J. et al., (1997) Genome Res., 7: 649-656. Other conventional BLAST algorithms, such as the one provided by NCBI BLAST, are also well known to those skilled in the art.

"Administer", "give", and "treat", when applied to animals, humans, experimental subjects, cells, tissues, organs, or biological fluid, refer to contacting an exogenous drug, a therapeutic agent, a diagnostic agent or composition with the animals, humans, subjects, cells, tissues, organs, or biological fluid. "Administer", "give", and "treat" can refer to, for example, therapeutic, pharmacokinetic, diagnostic, research, and experimental methods. Treatment of cells comprises contact between a reagent and cells, and contact between the reagent and a fluid, wherein the fluid is in contact with the cells. "Administer", "give", and "treat" also mean treating, for example, cells through a reagent, diagnosis, or binding composition, or through another type of cell *in vitro* and *ex vivo*. "Treat", when applied to humans, veterinary subjects, or research subjects, refers to therapeutic treatment, prophylactic or preventive measures, and research and diagnostic applications.

"Treatment" refers to administering a therapeutic agent, such as a composition comprising any one of the conjugation compounds of the present disclosure, either internally or externally, to a patient with one or more disease symptoms on which the therapeutic agent is known to have a therapeutic effect. Generally, the therapeutic agent is administered in an amount effective to alleviate one or more disease symptoms in the patient or population being treated to induce regression of such symptoms or to inhibit the development of such symptoms to any clinically measurable degree. The amount of the therapeutic agent effective to alleviate any specific disease symptom (also known as a "therapeutically effective amount") may vary depending on a variety of factors, such as the disease state, age, and body weight of the patient, and the ability of the drug to produce a desired therapeutic effect in the patient. Whether a disease symptom has been palliated can be evaluated by any clinical test method commonly used by doctors or other health care professionals to evaluate the severity or progression of the symptom. Although an embodiment of the present disclosure (for example, a treatment method or a product) may not be effective in alleviating every disease symptom of interest, it should palliate the disease symptoms of interest in a statistically significant number of patients, as determined by any statistical test method known in the art, such as a Student t-test, a chi-square test, a Mann and Whitney's U test, a Kruskal-Wallis test (H test), a Jonckheere-Terpstra test, and a Wilcoxon test.

"Effective amount" comprises an amount sufficient to ameliorate or prevent a symptom or sign of a medical disease. The effective amount also means an amount sufficient to allow or facilitate diagnosis. The effective amount for a particular patient or veterinary subject may vary depending on factors such as the disorder to be treated, the general health of the patient, the method, route, and dose of administration, and the severity of side effects. The effective amount may be the maximum dose or administration regimen to avoid significant side effects or toxic effects.

The term "subject" and "patient" mean a mammal, particularly a primate, and particularly a human.

**DETAILED DESCRIPTION**

The present disclosure is further described below with reference to examples, which, however, are not intended to limit the scope of the present disclosure. In the examples of the present disclosure, experimental methods in which specific conditions are not indicated were generally carried out under conventional conditions, for example, as described in Antibodies: A Laboratory Manual and Molecular Cloning: A Laboratory Manual by Cold Spring Harbor Laboratory, or in accordance with the conditions recommended by the manufacturers of the starting materials or commercial products. Reagents without specific sources indicated were commercially available conventional reagents.

**Example 1. Preparation of Anti-ANGPTL3 Antibody**

The anti-ANGPTL3 antibody was prepared with reference to the method described in WO2023001228 and was designated as the P8BG antibody. The heavy chain and light chain sequences of the anti-ANGPTL3 antibody are set forth in SEQ ID NO: 9 and SEQ ID NO: 10, respectively, in the present disclosure. The dosage form is an injection with strengths of 150 mg/1.5 mL, 0.3 g/2 mL, and 0.3 g/2 mL.

> Heavy chain sequence of P8BG:

*QVQLVQSGAEVKKPGASVKVSCKASGYTFT*SYDIN*WVRQAPGQGLEWVG*LINPR**E**D STSYAQKFQG*RVTMTRDTSTSTMYMELSSLRSEDTAVYFCAR*DLGSIREVLYYGMD V*WGQGTTVTVSS*ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKR VESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSQEDPEV QFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALH NHYTQKSLSLSLGK

SEQ ID NO: 9

> Light chain sequence of P8BG:

*DVVMTQSPLSLPVTPGEPASISC*RSSQSLLHSN**V**YTYLD*WYLQKPGQSPQLLIY*LGS NRAS*GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC*MQALQTPLT*FGQGTRLEIK*R

TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQES
VTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 10

**Example 2. Evaluation of Efficacy and Safety of Multiple Subcutaneous Administration of ANGPTL3 Injection in Combination with Lipid-Lowering Drugs for Stable Treatment of Hyperlipidemia Patients with Poor Lipid Control**

**1. Investigational drugs**

1) The anti-ANGPTL3 antibody prepared in Example 1.

2) The placebo injection was identical to the anti-ANGPTL3 antibody injection with respect to color and clarity.

**2. Enrolled subjects**

1) Fasting LDL-C level at screening (Table 2):

| | Receiving regular and stable treatment with any one moderate- or higher-intensity* statin for ≥ 4 weeks at screening | Any other circumstances not meeting the criteria of "receiving regular and stable treatment with any one moderate- or higher-intensity* statin for ≥ 4 weeks at screening" |
|---|---|---|
| Ultra-high ASCVD risk | Fasting LDL-C level ≥ 1.4 mmol/L | Fasting LDL-C level ≥ 2.6 mmol/L |
| Very high ASCVD risk | Fasting LDL-C level ≥ 1.8 mmol/L | |
| Moderate and high ASCVD risk | Fasting LDL-C level ≥ 2.6 mmol/L | |

2) Fasting triglyceride level ≤ 5.6 mmol/L;

*Moderate-intensity statin (daily dose): atorvastatin 10-20 mg; rosuvastatin 5-10 mg; fluvastatin 80 mg; lovastatin 40 mg; pitavastatin 2-4 mg; pravastatin 40 mg; simvastatin 20-40 mg; and Xuezhikang 1.2 g.

**3. Study protocol**

This study consists of 5 periods in total, including a screening period, a run-in period, a treatment period (core treatment period and extension treatment period), and a safety follow-up period.

I. Run-in period:

During the run-in period, subjects follow a low-fat diet and undergo adjustments in lifestyle and background lipid-lowering therapy. After a stable state is reached and maintained for ≥ 4 weeks, subjects will be assessed for compliance and against the

randomization/exclusion criteria at the end of the run-in period.

Background lipid-lowering therapy refers to the administration of statins at the specified types and doses in this study, with or without the administration of other lipid-lowering drugs, as detailed below:

(1) Statins and doses specified in this study: atorvastatin calcium tablets ≥ 10 mg qd, or rosuvastatin ≥ 5 mg qd. The type and dose of statin are determined by the investigator based on the subject's conditions.

(2) Non-statin lipid-lowering agents permitted in this study include cholesterol absorption inhibitors (e.g., ezetimibe) and PCSK9 inhibitors (e.g., alirocumab and evolocumab). If a subject is receiving the above lipid-lowering drugs at screening, he/she may continue or discontinue these lipid-lowering drugs under investigator guidance. If continued, the type and dose must remain stable from the run-in period through the end of the extension treatment period.

(3) The types and doses of lipid-lowering drugs permitted in this study shall be adjusted to a stable regimen and maintained unchanged for ≥ 4 weeks (for PCSK9 inhibitors, ≥ 8 weeks is required) during the run-in period.

II. Administration regimen during the treatment period:

Investigational groups:

Anti-ANGPTL3 antibody, 150 mg Q4W, injected subcutaneously;
Anti-ANGPTL3 antibody, 300 mg Q4W, injected subcutaneously;
Anti-ANGPTL3 antibody, 600 mg Q4W, injected subcutaneously; and
Anti-ANGPTL3 antibody, 600 mg Q8W, injected subcutaneously.

Control groups:

Placebo 150 mg Q4W, injected subcutaneously;
Placebo 300 mg Q4W, injected subcutaneously;
Placebo 600 mg Q4W, injected subcutaneously; and
Placebo, 600 mg Q8W, injected subcutaneously.

**4. Outcome evaluations**

**4.1 Patient baseline characteristics**

From November 24, 2023 to April 17, 2024, a total of 335 patients were randomized. Among them, 333 patients received at least one treatment (anti-ANGPTL3 antibody, n = 266; placebo, n = 67) and were included in the efficacy and safety analyses. 93.9% to 97.0% of patients across all groups completed the 16-week study.

Baseline demographic and disease characteristics were generally balanced across all groups (Table 3). In the study cohort, 99.1% of patients were receiving statin therapy, 0.9% (n = 3) had missing data due to unrelated reasons, 12.0% were receiving cholesterol absorption inhibitors, and 0.9% were receiving PCSK9 inhibitors.

Table 3. Patient baseline characteristics

| | **Anti-ANGLPT3 Antibody 150 mg Q4W (N = 67)** | **Anti-ANGPTL3 antibody 300 mg Q4W (N = 66)** | **Anti-ANGPTL3 antibody 600 mg Q4W (N = 66)** | **Anti-ANGPTL3 antibody 600 mg Q8W (N = 67)** | **Placebo (N = 67)** |
|---|---|---|---|---|---|
| Age | 59.2 ±11.2 | 57.2 ±10.1 | 56.4 ±10.6 | 57.2 ±9.9 | 58.6 ±7.7 |
| Male | 39 (58.2) | 40 (60.6) | 46 (69.7) | 42 (62.7) | 36 (53.7) |
| ASCVD risk, n (%) | | | | | |
| Moderate risk | 5 ( 7.5) | 5 ( 7.6) | 11 ( 16.7) | 3 ( 4.5) | 7 ( 10.4) |
| High risk | 20 ( 29.9) | 14 ( 21.2) | 19 ( 28.8) | 20 ( 29.9) | 16 ( 23.9) |
| Very high risk | 19 ( 28.4) | 26 ( 39.4) | 22 ( 33.3) | 24 ( 35.8) | 19 ( 28.4) |
| Ultra-high risk | 23 ( 34.3) | 21 ( 31.8) | 14 ( 21.2) | 20 ( 29.9) | 25 ( 37.3) |
| Lipid-lowering drug therapy | | | | | |
| Statin | 67(100) | 66(100) | 66(100) | 67(100) | 66(98.5) |
| Moderate intensity | 65(97.0) | 62(93.9) | 62(93.9) | 66(98.5) | 63(94.0) |
| High intensity | 2(3.0) | 4(6.1) | 4(6.1) | 1(1.5) | 3(4.4) |
| Cholesterol absorption inhibitors | 9(13.4) | 7 ( 10.6) | 8 ( 12.1) | 8 ( 11.9) | 7 ( 10.4) |
| PCSK9 inhibitors | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 1.5) | 2 ( 3.0) |
| Lipid parameters | | | | | |
| LDL-C, mmol/L | 2.8± 1.0 | 2.7± 0.8 | 2.8±0.9 | 2.9±1.2 | 2.8±1.1 |
| <1.8 | 5 (7.5) | 6 (9.1) | 5 (7.6) | 8 (11.9) | 5 (7.5) |
| 1.8 ≤ LDL-C<2.6 | 29 ( 43.3) | 28 ( 42.4) | 25 (37.9) | 25 (37.3) | 28 (41.8) |
| ≥2.6 | 33 ( 49.3) | 32 (48.5) | 36 (54.5) | 34 (50.7) | 34 (50.7) |
| TG, mmol/L | 1.8±0.9 | 1.7±0.9 | 1.8±0.9 | 1.6±0.8 | 1.7±0.9 |
| <1.7 | 37 ( 55.2) | 42 ( 63.6) | 38 ( 57.6) | 44 ( 65.7) | 42 ( 62.7) |

| | | | | | |
|---|---|---|---|---|---|
| ≥1.7 | 30 ( 44.8) | 24 ( 36.4) | 28 ( 42.4) | 23 ( 34.3) | 25 ( 37.3) |
| TC, mmol/L | 4.9 ±1.1 | 4.7 ±1.0 | 4.8±1.0 | 4.9±1.3 | 4.8 ±1.2 |
| HDL-C, mmol/L | 1.3 ±0.4 | 1.3 ±0.3 | 1.3 ±0.3 | 1.3±0.3 | 1.3±0.3 |
| non-HDL-C, mmol/L | 3.6 ±1.1 | 3.4 ±1.0 | 3.6 ±1.0 | 3.6±1.3 | 3.5±1.2 |
| ApoB, g/L | 1.0 ±0.3 | 0.9 ±0.2 | 1.0 ±0.3 | 1.0 ±0.3 | 1.0 ±0.27 |
| ApoA1, g/L | 1.4 ±0.3 | 1.4 ±0.2 | 1.4 ±0.2 | 1.4 ±0.2 | 1.4 ±0.3 |
| Lp(a), nmol/L | 28.2(11.3, 68.6) | 26.4(9.6, 92.7) | 27.2(10.8, 86.0) | 30.7(8.7, 99.9) | 45.3(13.3 , 124.5) |
| Values are presented as mean ± standard deviation, number of patients (%), or median (quartiles Q1-Q3).<br>High-intensity therapy is defined as atorvastatin ≥ 40 mg/day or rosuvastatin ≥ 20 mg/day; all lower doses are categorized as moderate-intensity therapy. | | | | | |
| ASCVD = atherosclerosis cardiovascular disease; PCSK9 = proprotein convertase subtilisin/kexin type 9;<br>Q4W = once every 4 weeks; Q8W = once every 8 weeks;<br>ApoA1 = apolipoprotein A1; ApoB = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol;<br>LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); TC = total cholesterol; and TG = triglyceride. | | | | | |

**4.2 Efficacy**

After 16 weeks of treatment, the anti-ANGPTL3 antibody injection dose groups 150 mg Q4W, 300 mg Q4W, 600 mg Q4W, and 600 mg Q8W showed significant reductions in LDL-C levels compared with the placebo group. Compared with the placebo group, the least-squares mean changes in LDL-C levels for each anti-ANGPTL3 antibody group were -21.7 (95% CI: -28.5, -14.9), -27.3 (95% CI: -34.1, -20.4), -29.9 (95% CI: -36.7, -23.1), and -22.5 (95% CI: -29.3, -15.7), respectively (Table 4).

Compared with the placebo group, the anti-ANGPTL3 antibody groups showed reductions in LDL-C levels, with least-squares mean absolute changes of -0.6 mmol/L (95% CI: -0.8 to -0.4 mmol/L), -0.7 mmol/L (95% CI: -0.9 to -0.6 mmol/L), -0.9 mmol/L (95% CI: -1.0 to -0.7 mmol/L), and -0.7 mmol/L (95% CI: -0.9 to -0.5 mmol/L) in the 150 mg Q4W, 300 mg Q4W, 600 mg Q4W, and 600 mg Q8W groups, respectively (Table 4). At week 16, LDL-C goal achievement rate in the anti-ANGPTL3 antibody groups ranged from 59.1% to 71.2%, higher than the achievement rate of the placebo group (30.8% to 31.2%), indicating the efficacy of the anti-ANGPTL3 antibody in reducing LDL-C levels. All anti-ANGPTL3 antibody groups showed a sustained increase in percent reduction in LDL-C

from baseline with increasing dose and treatment duration.

Table 4 also presents results for other lipid parameters at week 16. At week 16, compared with the corresponding placebo group, the anti-ANGPTL3 antibody groups showed significant reductions in least-squares mean percentages of TG (difference: -63.2% to -51.7%), non-high-density lipoprotein cholesterol (non-HDL-C) (difference: -34.5% to -26.8%), apolipoprotein B (ApoB) (difference: -19.2% to -13.5%), total cholesterol (TC) (difference: -32.6% to -25.7%), and apolipoprotein A1 (ApoA1) (difference: -36.2% to -29.1%) levels ($P < 0.0001$ for each comparison).

Table 4. Results of primary and some secondary lipid parameters

| | **Anti-ANGPTL3 antibody 150 mg Q4W (N = 67)** | **Anti-ANGPTL3 antibody 300 mg Q4W (N = 66)** | **Anti-ANGPTL3 antibody 600 mg Q4W (N = 66)** | **Anti-ANGPTL3 antibody 600 mg Q8W (N = 67)** | **Placebo (N = 67)** |
|---|---|---|---|---|---|
| Primary endpoint | | | | | |
| % change in LDL-C from baseline to week 16 | -29.8 (-35.0, -24.5) | -35.3 (-40.6, -30.1) | -38.0 (-43.3, -32.7) | -30.5 (-35.8, -25.3) | -8.1 (-13.3, -2.8) |
| Difference; P value | -21.7(-28.5, -14.9); <0.0001 | -27.3 (-34.1, -20.4); <0.0001 | -29.9 (-36.7, -23.1); <0.0001 | -22.5(-29.3, -15.7); <0.0001 | / |
| Key secondary endpoint | | | | | |
| % change in TG from baseline to week 16 | -49.8 (-55.0, -44.7) | -57.5 (-62.8, -52.3) | -61.4 (-66.6, -56.2) | -55.8 (-61.0, -50.6) | 1.8 (-3.4, 7.0) |
| Difference; P value | -51.7(-58.3, -45.0), <0.0001 | -59.4 (-66.0, -52.7), <0.0001 | -63.2(-69.8, -56.6), <0.0001 | -57.6 (-64.2, -51.0), <0.0001 | / |
| Other secondary endpoints | | | | | |
| Absolute change in LDL-C from | -0.9 (-1.1, -0.8) | -1.0 (-1.2, -0.9) | -1.2 (-1.3, -1.0) | -1.0 (-1.1, -0.8) | -0.3 (-0.5, -0.2) |

| | | | | | |
|---|---|---|---|---|---|
| baseline to week 16, mmol/L | | | | | |
| Difference; P value | -0.6(-0.8, -0.4), <0.0001 | -0.7(-0.9, -0.6), <0.0001 | -0.9(-1.0, -0.7), <0.0001 | -0.7(-0.9, -0.5), <0.0001 | / |
| Proportion of patients achieving LDL-C goal at week 16, [a]% (n/N) | 59.7 (40/67) | 59.1 (39/66) | 71.2 (47/66) | 59.7 (40/67) | 31.3 (21/67) |
| % change in secondary lipid variables from baseline to week 16 | | | | | |
| Non–HDL-C | -31.7 (-35.9, -27.5) | -36.3 (-40.5, -32.1) | -39.4 (-43.5, -35.2) | -33.2 (-37.4, -29.0) | -4.9 (-9.1, -0.7) |
| Difference; P value | -26.8 (-32.2, -21.3), <0.0001 | -31.4 (-36.8, -25.9), <0.0001 | -34.5 (-39.9, -29.0), <0.0001 | -28.3 (-33.7, -22.8), <0.0001 | / |
| ApoB | -18.4 (-22.6, -14.3) | -21.7 (-25.9, -17.6) | -24.1 (-28.3, -19.9) | -19.0 (-23.1, -14.8) | -4.9 (-9.1, -0.7) |
| Difference; P value | -13.5(-18.9, -8.1),<0.0001 | -16.8(-22.3, -11.4),<0.0001 | -19.2(-24.6, -13.8),<0.0001 | -14.0 (-19.5, -8.6),<0.0001 | / |
| Lp(a) | -6.2 (-28.3, 9.2) | 0.7 (-5.6, 21.8) | 5.9 (-15.9, 33.9) | 0.0 (-17.4, 18.8) | -2.4 (-15.8, 10.8) |
| Difference; P value | -6.0 (-16.4, 4.4), 0.2562 | 6.4(-4.0, 16.8),0.2257 | 6.7(-3.7, 17.1),0.2061 | 2.5(-7.8, 12.9),0.6352 | / |
| TC | -32.0 (-35.1, -28.9) | -36.0 (-39.1, -32.9) | -39.0 (-42.1, -35.9) | -34.3 (-37.4, -31.2) | -6.4 (-9.4, -3.3) |
| Difference; P value | -25.7(-29.7, -21.7),<0.0001 | -29.6 (-33.7, -25.6),<0.0001 | -32.6(-36.6, -28.6),<0.0001 | -27.9(-31.9, -23.9),<0.0001 | / |
| HDL-C | -29.5 (-33.2, -25.8) | -33.6 (-37.3, -29.8) | -34.2 (-38.0, -30.6) | -34.8 (-38.6, -31.1) | -7.0 (-10.7, -3.3) |

| | | | | | |
|---|---|---|---|---|---|
| Difference; P value | -22.5(-27.2, -17.8), <0.0001 | -26.6(-31.3, -21.8), <0.0001 | -27.3(-32.0, -22.5), <0.0001 | -27.8(-32.6, -23.1), <0.0001 | |
| ApoA1 | -32.1 (-34.9, -29.3) | -36.9 (-39.8, -34.0) | -39.2 (-42.0, -36.3) | -36.9 (-39.7, -34.0) | -3.00 (-5.84, -0.15) |
| Difference; P value | -29.1(-32.7, -25.5), <0.0001 | -33.9 (-37.5, -30.3), <0.0001 | -36.2 (-39.8, -32.5), <0.0001 | -33.9(-37.5, -30.2), <0.0001 | / |

Values are presented as least-squares means (95% confidence intervals) or medians (quartiles Q1-Q3).

a: The LDL-C goal is as defined below: < 1.4 mmol/L for patients at ultra-high ASCVD risk, < 1.8 mmol/L for patients at very high ASCVD risk, and < 2.6 mmol/L for patients at moderate and high ASCVD risk.

Lp(a) was analyzed using robust regression; other variables were analyzed using a mixed model for repeated measures (MMRM).

**4.3 Safety**

During the 16-week treatment period, mean treatment compliance rates were 97.0%-97.8% in the anti-ANGPTL3 antibody groups, 97.8% in the placebo group, and 97.1%-99.7% in the background statin therapy group. Overall, 145 of the 266 patients (54.5%) receiving anti-ANGPTL3 antibody treatment experienced at least 1 treatment-related adverse event (AE) within 16 weeks, while 29 of the 67 patients (43.3%) receiving placebo experienced at least 1 treatment-related adverse event, wherein treatment-related adverse events (TRAEs) were reported in 52 patients (19.5%) in the anti-ANGPTL3 antibody groups and 9 patients (13.4%) in the placebo group (see Table 5). Most TRAEs were mild in severity and had a similar incidence across different administration regimens. No treatment-related deaths occurred during the study. The most common TRAEs were hyperuricemia (2.6% in the anti-ANGPTL3 antibody groups and 3.0% in the placebo group), blood creatine phosphokinase (CPK) increased (0% in the anti-ANGPTL3 antibody groups and 3.0% in the placebo group), and nausea (0.8% in the anti-ANGPTL3 antibody groups and 3.0% in the placebo group).

Table 5. Adverse events (AEs)

| | **Anti-ANGPTL3 antibody (N = 266)** | **Placebo(N = 67)** |
|---|---|---|
| Any TEAE | 145 (54.5) | 29 (43.3) |
| Mild | 108 (40.6) | 24 (35.8) |
| Moderate | 28 (10.5) | 4 (6.0) |

| | | |
|---|---|---|
| Severe | 9 (3.4) | 1 (1.5) |
| TEAEs with an incidence of ≥ 2% in patients receiving anti-ANGPTL3 antibody or placebo | | |
| Hyperuricemia | 19 (7.1) | 6 (9.0) |
| Type 2 diabetes mellitus | 0 (0.0) | 2 (3.0) |
| Injection site reactions | 9 (3.4) | 0 (0.0) |
| Asthenia | 2 (0.8) | 2 (3.0) |
| Blood CPK increased | 10 (3.8) | 4 (6.0) |
| Blood glucose increased | 7 (2.6) | 1 (1.5) |
| ALT increased | 6 (2.3) | 0 (0.0) |
| Proteinuria detected | 6 (2.3) | 0 (0.0) |
| Blood creatinine increased | 3 (1.1) | 2 (3.0) |
| Blood urea increased | 0 (0.0) | 2 (3.0) |
| Dizziness | 6 (2.3) | 2 (3.0) |
| Sinus bradycardia | 8 (3.0) | 2 (3.0) |
| Ventricular extrasystole | 2 (0.8) | 2 (3.0) |
| Upper respiratory tract infection | 7 (2.6) | 2 (3.0) |
| Nausea | 2 (0.8) | 2 (3.0) |
| Any TRAE | 52 (19.5) | 9 (13.4) |
| Mild | 45 (16.9) | 8 (11.9) |
| Moderate | 6 (2.3) | 0 (0.0) |
| Severe | 1 ( 0.4) | 1 (1.5) |
| TRAE leading to treatment discontinuation | 3 (1.1) | 0 (0.0) |
| TRAE leading to death | 0 (0.0) | 0 (0.0) |
| TRAEs with an incidence of ≥ 2% in patients receiving the anti-ANGPTL3 antibody or placebo | | |
| Hyperuricemia | 7 ( 2.6) | 2 ( 3.0) |

| | | |
|---|---|---|
| Injection site reactions | 9 ( 3.4) | 0 ( 0.0) |
| Blood CPK increased | 0 ( 0.0) | 2 ( 3.0) |
| Nausea | 2 ( 0.8) | 2 ( 3.0) |
| Data are presented as numbers (%) | | |
| AE: adverse event;<br>TEAE: treatment-emergent adverse event;<br>TRAE: treatment-related adverse event;<br>ALT: alanine transaminase; and<br>CPK: creatine phosphokinase | | |

**Example 3. A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase II Clinical Study Evaluating Efficacy and Safety of Multiple Subcutaneous Administration of Anti-ANGPTL3 Antibody Injection in Hyperlipidemia Patients with Poor Lipid Control**

**1. Investigational drugs**

1) The anti-ANGPTL3 antibody prepared in Example 1.

2) The placebo injection was identical to the anti-ANGPTL3 antibody injection with respect to color and clarity.

**2. Enrolled subjects**

1) Fasting LDL-C level at screening (Table 2):

| | Receiving regular and stable treatment with any one moderate- or higher-intensity* statin for ≥ 4 weeks at screening | Any other circumstances not meeting the criteria of "receiving regular and stable treatment with any one moderate- or higher-intensity* statin for ≥ 4 weeks at screening" |
|---|---|---|
| Ultra-high ASCVD risk | Fasting LDL-C level ≥ 1.4 mmol/L | Fasting LDL-C level ≥ 2.6 mmol/L |
| Very high ASCVD risk | Fasting LDL-C level ≥ 1.8 mmol/L | |
| Moderate and high ASCVD risk | Fasting LDL-C level ≥ 2.6 mmol/L | |

2) Fasting triglyceride level ≤ 5.6 mmol/L;

*Moderate-intensity statin (daily dose): atorvastatin 10-20 mg; rosuvastatin 5-10 mg; fluvastatin 80 mg; lovastatin 40 mg; pitavastatin 2-4 mg; pravastatin 40 mg; simvastatin 20-40 mg; and Xuezhikang 1.2 g.

**3. Study protocol**

This study consists of 5 periods in total, including a screening period, a run-in period, a treatment period (core treatment period and extension treatment period), and a safety follow-up period.

I. Run-in period

The run-in period lasts 4-8 weeks and begins on the day of the first dose. During the run-in period, subjects follow a low-fat diet and undergo adjustments in lifestyle and background lipid-lowering therapy. After a stable state is reached and maintained for ≥ 4 weeks (8 weeks if PCSK9 inhibitors are used), subjects will be assessed for compliance and against the randomization/exclusion criteria at the end of the run-in period.

Background lipid-lowering therapy refers to the administration of statins at the specified types and doses in this study, with or without the administration of other lipid-lowering drugs, as detailed below:

(1) Statins and doses specified in this study: atorvastatin calcium tablets ≥ 10 mg qd, or rosuvastatin ≥ 5 mg qd. The type and dose of statin are determined by the investigator based on the subject's conditions.

(2) Subjects receiving statins not specified in this study at screening shall be switched to the specified statin regimen under investigator guidance, with dose adjustments made until the specified dose is reached; the regimen is then maintained without further change, which is considered the start of stable treatment.

(3) Non-statin lipid-lowering agents permitted in this study include cholesterol absorption inhibitors (e.g., ezetimibe) and PCSK9 inhibitors (e.g., alirocumab and evolocumab). If a subject is receiving the above lipid-lowering drugs at screening, he/she may continue lipid-lowering drugs under investigator guidance (PCSK9 inhibitors, if used, must not be discontinued), and the type and dose must remain stable from the run-in period through the end of the treatment period.

II. Administration regimen during the treatment period:

Investigational groups:

Anti-ANGPTL3 antibody, 600 mg Q12W, injected subcutaneously;

Anti-ANGPTL3 antibody, 1200 mg Q12W, injected subcutaneously.

Control groups:

Placebo 600 mg Q12W, injected subcutaneously;

Placebo 1200 mg Q12W, injected subcutaneously.

**4. Safety and efficacy evaluation**

Efficacy evaluation: Blood samples were collected from the subjects at the scheduled visits according to the study protocol for efficacy evaluation. The levels of LDL-C, TG, non-HDL-C, ApoB, Lp(a), TC, HDL-C, and ApoA1 were measured. Percent change from baseline and absolute change from baseline in each indicator were calculated and

compared between the anti-ANGPTL3 antibody injection and the placebo, as specified in the protocol.

Safety evaluation: The incidence and severity of adverse events (AEs), adverse events of special interest (AESIs), and serious adverse events (SAEs) in the subjects throughout the study period were collected; vital signs, physical examinations, laboratory tests, 12-lead electrocardiograms, and other examinations were performed; the incidence and severity of injection site reactions were also recorded.

**Example 4. A Randomized, Double-Blind, Placebo-Controlled Phase I Study of Anti-ANGPTL3 Antibody in Healthy Subjects**

1. Study objective:

The purpose of this Phase I single-dose study is to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and immunogenicity of the anti-ANGPTL3 antibody in healthy subjects.

2. Study method:

Six dose groups are planned, including 100 mg, 300 mg, 450 mg, 750 mg, 900 mg (optional), and 1200 mg (optional). Healthy subjects are randomly assigned to receive a single subcutaneous administration of anti-ANGPTL3 antibody or placebo. The subjects will be observed for seven days after administration. The 100 mg group will be followed up to day 148, while the other dose groups will be followed up to day 190. The primary endpoints are safety and tolerability.

3. Study results:

A total of 72 subjects were enrolled across the six dose groups from 100-1200 mg (anti-ANGPTL3 antibody, n = 54; placebo, n = 18). The anti-ANGPTL3 antibody was well tolerated at the tested doses. Reports showed that a total of 49 subjects (90.7%) in the anti-ANGPTL3 antibody groups and 17 subjects (94.4%) in the placebo group experienced treatment-emergent adverse events (TEAEs). All TEAEs were mild or moderate in severity. There were no serious adverse events or TEAEs that led to death. Serum concentrations of the anti-ANGPTL3 antibody were generally elevated with increasing doses. Peak serum concentrations were reached at 8.0-10.0 days post-dose, and mean $t_{1/2}$ values ranged from 29.4 to 53.3 days across dose levels. Exposure to the anti-ANGPTL3 antibody showed a slight supra-proportional increase from 100-1200 mg. Across all anti-ANGPTL3 antibody dose groups, serum LDL-C and TG levels decreased rapidly and significantly. In higher-dose groups, levels remained below baseline until the end of follow-up, whereas in the placebo group, levels were mostly above baseline. In the 750-1200 mg groups, maximum reductions from baseline in low-density lipoprotein cholesterol (LDL-C) were from -46.5% to -49.1%, and in total cholesterol (TG) from -67.4% to -82.8%. On day 85, LDL-C reductions in high-dose groups remained at 36.9%-

39.0% and TG reductions at 59.9%-79.1%. No anti-drug antibodies were detected in subjects receiving the anti-ANGPTL3 antibody.

4. Conclusion:

The anti-ANGPTL3 antibody was well tolerated in healthy subjects and demonstrated significant efficacy.

## CLAIMS

1. Use of an anti-ANGPTL3 antibody or an antigen-binding fragment thereof in the manufacture of a medicament for treating a hyperlipidemia patient, the hyperlipidemia patient being subject to a risk of atherosclerosis cardiovascular disease (ASCVD).

2. The use according to claim 1, wherein the hyperlipidemia patient is a hyperlipidemia patient at moderate or higher ASCVD risk,
preferably a hyperlipidemia patient at moderate or higher ASCVD risk not achieving an LDL-C goal after receiving a lipid-lowering drug therapy, and more preferably a hyperlipidemia patient at moderate or higher ASCVD risk not achieving an LDL-C goal after receiving a background lipid-lowering therapy for at least 4 weeks.

3. The use according to claim 1 or 2, wherein the fasting LDL-C level of the hyperlipidemia patient is selected from the group consisting of: LDL-C < 1.8 mmol/L, 1.8 ≤ LDL-C < 2.6, and LDL-C ≥ 2.6; and/or the fasting triglyceride level of the hyperlipidemia patient is ≤ 5.6 mmol/L.

4. The use according to any one of claims 1-3, wherein the hyperlipidemia patient meets the following criteria:
(1) having received a lipid-lowering drug therapy for at least 4 weeks, and having a fasting LDL-C level of ≥ 1.4 mmol/L;
(2) having received a lipid-lowering drug therapy for at least 4 weeks, and having a fasting LDL-C level of ≥ 1.8 mmol/L;
(3) having received a lipid-lowering drug therapy for at least 4 weeks, and having a fasting LDL-C level of ≥ 2.6 mmol/L; or
(4) having a fasting LDL-C level of ≥ 2.6 mmol/L;
preferably, the lipid-lowering drug is selected from the group consisting of a statin agent and/or a non-statin agent, preferably a moderate- or higher-intensity statin agent.

5. The use according to any one of claims 1-4, wherein the anti-ANGPTL3 antibody or the antigen-binding fragment thereof comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein:
the heavy chain variable region comprises a HCDR1, a HCDR2, and a HCDR3 set forth in SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3, respectively; and
the light chain variable region comprises a LCDR1, a LCDR2, and a LCDR3 set forth in SEQ ID NO: 4, SEQ ID NO: 5, and SEQ ID NO: 6, respectively.

6. The method according to any one of claims 1-5, wherein the anti-ANGPTL3 antibody or the antigen-binding fragment thereof comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the heavy chain variable region comprises

the amino acid sequence set forth in SEQ ID NO: 7 or an amino acid sequence having at least 90% identity thereto, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 8 or an amino acid sequence having at least 90% identity thereto.

7. The method according to any one of claims 1-6, wherein the anti-ANGPTL3 antibody or the antigen-binding fragment thereof comprises a heavy chain and a light chain, wherein the heavy chain comprises the amino acid sequence set forth in SEQ ID NO: 9 or an amino acid sequence having at least 90% identity thereto, and the light chain comprises the amino acid sequence set forth in SEQ ID NO: 10 or an amino acid sequence having at least 90% identity thereto.

8. The method according to any one of claims 1-7, wherein the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is administered via subcutaneous injection.

9. The use according to any one of claims 1-8, wherein the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is administered at a dose of about 50 mg to about 1500 mg, about 50 mg to about 1000 mg, about 100 mg to about 1000 mg, or about 150 mg to about 600 mg; preferably, the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is administered at a dose selected from the group consisting of: about 50 mg, about 150 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 800 mg, about 1000 mg, and about 1200 mg;
the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is administered at a frequency of once every week, once every 2 weeks, once every 4 weeks, once every 6 weeks, once every 8 weeks, once every 10 weeks, or once every 12 weeks, preferably once every 4 weeks or once every 8 weeks;
preferably, an administration regimen of the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is selected from the group consisting of:
administered at a dose of about 150 mg and at a frequency of once every 4 weeks;
administered at a dose of about 300 mg and at a frequency of once every 4 weeks;
administered at a dose of about 600 mg and at a frequency of once every 4 weeks;
administered at a dose of about 600 mg and at a frequency of once every 8 weeks;
administered at a dose of about 600 mg and at a frequency of once every 12 weeks; and
administered at a dose of about 1200 mg and at a frequency of once every 12 weeks.

10. The use according to any one of claims 1-9, wherein the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is used in combination with a background lipid-lowering therapeutic agent;
preferably, the background lipid-lowering therapeutic agent comprises a statin agent and/or a non-statin agent, preferably comprises at least one of a statin agent, a cholesterol absorption inhibitor, and a PCSK9 inhibitor.

11. The use according to any one of claims 1-10, wherein the anti-ANGPTL3 antibody or the antigen-binding fragment thereof lowers at least one of the following indicators in the hyperlipidemia patient:

lowering plasma low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), lipoprotein(a) (Lp(a)), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and apolipoprotein A1 (ApoA1) levels in the hyperlipidemia patient.

12. Use of an anti-ANGPTL3 antibody or an antigen-binding fragment thereof in combination with a background lipid-lowering therapeutic agent in the manufacture of a medicament for treating a hyperlipidemia patient, wherein

preferably, the anti-ANGPTL3 antibody or the antigen-binding fragment thereof comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein:

the heavy chain variable region comprises a HCDR1, a HCDR2, and a HCDR3 set forth in SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3, respectively, and the light chain variable region comprises a LCDR1, a LCDR2, and a LCDR3 set forth in SEQ ID NO: 4, SEQ ID NO: 5, and SEQ ID NO: 6, respectively; or

the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 7 or an amino acid sequence having at least 90% identity thereto, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 8 or an amino acid sequence having at least 90% identity thereto; or

the anti-ANGPTL3 antibody or the antigen-binding fragment thereof comprises a heavy chain and a light chain, wherein the heavy chain comprises the amino acid sequence set forth in SEQ ID NO: 9 or an amino acid sequence having at least 90% identity thereto, and the light chain comprises the amino acid sequence set forth in SEQ ID NO: 10 or an amino acid sequence having at least 90% identity thereto.

13. The use according to claim 12, wherein the background lipid-lowering therapeutic agent comprises a statin agent and/or a non-statin agent, preferably comprises at least one of a statin agent, a cholesterol absorption inhibitor, and a PCSK9 inhibitor.

14. The use according to claim 12 or 13, wherein the hyperlipidemia patient is any one selected from the group consisting of the following:

a hyperlipidemia patient at risk of atherosclerosis cardiovascular disease (ASCVD);

a hyperlipidemia patient at moderate or higher ASCVD risk;

a hyperlipidemia patient at moderate or higher ASCVD risk not achieving an LDL-C goal after receiving a lipid-lowering drug therapy; and

a hyperlipidemia patient at moderate or higher ASCVD risk not achieving an LDL-C goal after receiving a lipid-lowering drug therapy for at least 4 weeks.

15. The use according to any one of claims 12-14, wherein the fasting LDL-C level of the hyperlipidemia patient is selected from the group consisting of: LDL-C < 1.8 mmol/L, 1.8 ≤ LDL-C < 2.6, and LDL-C ≥ 2.6; and/or the fasting triglyceride level of the hyperlipidemia patient is ≤ 5.6 mmol/L.

16. The use according to any one of claims 12-15, wherein the hyperlipidemia patient meets the following criteria:
(1) having received a lipid-lowering drug therapy for at least 4 weeks, and having a fasting LDL-C level of ≥ 1.4 mmol/L;
(2) having received a lipid-lowering drug therapy for at least 4 weeks, and having a fasting LDL-C level of ≥ 1.8 mmol/L;
(3) having received lipid-lowering drug therapy for at least 4 weeks, and having a fasting LDL-C level of ≥ 2.6 mmol/L; or
(4) having a fasting LDL-C level of ≥ 2.6 mmol/L;
preferably, the lipid-lowering drug is selected from the group consisting of a statin agent and/or a non-statin agent, preferably a moderate- or higher-intensity statin agent.

17. The use according to any one of claims 12-16, wherein:
the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is administered at a dose of about 50 mg to about 1500 mg, about 50 mg to about 1000 mg, about 100 mg to about 1000 mg, or about 150 mg to about 600 mg; preferably, the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is administered at a dose selected from the group consisting of: about 50 mg, about 150 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 800 mg, about 1000 mg, and about 1200 mg;
the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is administered at a frequency of once every week, once every 2 weeks, once every 4 weeks, once every 6 weeks, once every 8 weeks, once every 10 weeks, or once every 12 weeks, preferably once every 4 weeks or once every 8 weeks;
preferably, an administration regimen of the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is selected from the group consisting of:
administered at a dose of about 150 mg and at a frequency of once every 4 weeks;
administered at a dose of about 300 mg and at a frequency of once every 4 weeks;
administered at a dose of about 600 mg and at a frequency of once every 4 weeks;
administered at a dose of about 600 mg and at a frequency of once every 8 weeks;
administered at a dose of about 600 mg and at a frequency of once every 12 weeks; and
administered at a dose of about 1200 mg and at a frequency of once every 12 weeks.

18. A method for lowering plasma low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), lipoprotein(a) (Lp(a)), total cholesterol (TC), high-density lipoprotein

cholesterol (HDL-C), and/or apolipoprotein A1 (ApoA1) levels in a hyperlipidemia patient, comprising administering an anti-ANGPTL3 antibody or an antigen-binding fragment thereof to a subject in need thereof, wherein,
the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is as defined in any one of claims 5-9;
preferably, the hyperlipidemia patient is preferably as defined in any one of claims 1-4;
preferably, the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is used in combination with a background lipid-lowering therapeutic agent;
preferably, the background lipid-lowering therapeutic agent comprises a statin agent and/or a non-statin agent, preferably comprises at least one of a statin agent, a cholesterol absorption inhibitor, and a PCSK9 inhibitor.

19. A method for treating hyperlipidemia, comprising administering an anti-ANGPTL3 antibody or an antigen-binding fragment thereof to a subject in need thereof, wherein hyperlipidemia patient is at risk of atherosclerosis cardiovascular disease (ASCVD);
the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is as defined in any one of claims 5-9;
preferably, the hyperlipidemia patient is preferably as defined in any one of claims 1-4;
preferably, the anti-ANGPTL3 antibody or the antigen-binding fragment thereof is used in combination with a background lipid-lowering therapeutic agent;
preferably, the background lipid-lowering therapeutic agent comprises a statin agent and/or a non-statin agent, preferably comprises at least one of a statin agent, a cholesterol absorption inhibitor, and a PCSK9 inhibitor.