Efficacy and Safety of Tafolecimab with Different Dosing Intervals in Patients with Hyperlipidemia

Study Protocol

(Protocol Number: V2.0; Date: November 20, 2025)

Project Name: Efficacy and Safety of Tafolecimab with Different Dosing Intervals in Patients with Hyperlipidemia Study Protocol

Host Department: The First Affiliated Hospital of Shandong First Medical University (Qianfoshan Hospital)

Principal Investigator: Mei Gao

Participating Institutions: None

Investigator’ s

As the principal investigator of this research project, I will adhere to the *Measures for the Ethical Review of Life Science and Medical Research Involving Human Subjects* (2023), the *Measures for the Ethical Review of Biomedical Research Involving Human Subjects* (2016),the WMA *Declaration of Helsinki* (2013), the CIOMS *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (2002), and the ethical principles of Good Clinical Practice (GCP). Under the guidance of the Good Clinical Practice (GCP) guidelines, I

Name:

Signature:

Date:

Protocol Title	Efficacy and Safety of Tafolecimab with Different Dosing Intervals in Patients with Hyperlipidemia
Version Number/Date	Version Number: V2.0 Version Date: November 20, 2025
Principal Investigator	Mei Gao
Study Design	Prospective, observational cohort study
Study Objective	This study aims to systematically evaluate the lipid-lowering efficacy and safety of two dosing regimens—150 mg of Tafolecimab administered every two weeks (Q2W) versus every three weeks (Q3W)—for 12 weeks in patients with hyperlipidemia whose LDL-C levels remain above target after 4 weeks of treatment with moderate-intensity statins ± a

	cholesterol absorption inhibitor.The primary efficacy endpoint is the percentage change in LDL-C from baseline at week 12 of the first treatment cycle.
Sample Size	30 patients in each of Groups A and B, for a total of 60 patients
Study Population	Patients with hyperlipidemia who have been treated with moderate-intensity statins ± a cholesterol absorption inhibitor for at least 4 weeks but whose LDL-C levels still do not meet the lipid-lowering targets recommended by the Chinese Guidelines for Lipid Management (2023) for their corresponding ASCVD risk stratification, and who require combination therapy with a PCSK9 inhibitor and are scheduled to receive Tafolecimab .

Study Methods	This study is a prospective, observational cohort study.The study will be conducted at the Department of Coronary Heart Disease, First Affiliated Hospital of Shandong First Medical University. Grouping will be based on clinical decision-making, and the study will systematically and prospectively collect and compare efficacy and safety data for Tafolecimab across two dosing intervals (Q2W and Q3W) in patients with hyperlipidemia. Data collection will include baseline characteristics, laboratory parameters, and adverse events; all data will be entered into electronic case report forms (CRFs) and subjected to statistical analysis.
Grouping Design	Group A: Tafolecimab 150 mg subcutaneous injection, once every 2 weeks (14 ± 3 days)

	Group B: 150 mg Tafolecimab subcutaneous injection, once every 3 weeks (21 ± 3 days)
Follow-up Schedule	Group A will undergo follow-up visits at Week 2 (V1), Week 6 (V2), and Week 12 (V3) after the first dose, with a window of ±3 days. Group B will undergo follow-up visits at Week 3 (V1), Week 9 (V2), and Week 12 (V3) after the first dose, with a window of ±3 days.
Inclusion Criteria	1) Age ⩾18 years. 2) Diagnosed with hyperlipidemia and on a stable, regular dose of moderate-intensity statins for at least 4 weeks (specifically: Atorvastatin 10 mg/d, Rosuvastatin 5 mg/d, Fluvastatin 80 mg/d, Pitavastatin 2-4 mg/d, Pravastatin 40 mg/d, Simvastatin 20-40 mg/d, or Xuezhikang 1.2 g/d), with or without

	concurrent cholesterol absorption inhibitors. 3) Baseline LDL-C levels failing to reach the therapeutic target corresponding to the patient's ASCVD risk categorization (defined as follows):ASCVD Primary Prevention (Low Risk): LDL-C ⩾ 3.4 mmol/L; ASCVD Primary Prevention (Moderate/High Risk): LDL-C ⩾ 2.6 mmol/L; ASCVD Secondary Prevention (Very High Risk): LDL-C ⩾ 1.8 mmol/L OR reduction from baseline ⩾ 50%; ASCVD Secondary Prevention (Ultra-High Risk): LDL-C ⩾ 1.4 mmol/L OR reduction from baseline ⩾ 50% 4) Meets the standard clinical criteria for PCSK9 inhibitor initiation, OR the treating physician estimates that continuing current moderate-intensity statins

	cholesterol absorption inhibitor therapy will not achieve the target LDL-C levels, thereby requiring combination therapy with a PCSK9 inhibitor. 5) First-time user of tafolecimab (PCSK9 inhibitor-naïve). 6) Voluntarily participates in the study, provides written informed consent, and meets all follow-up compliance requirements. 7) Candidates must meet ALL of the above criteria to be eligible for enrollment in the study.
Exclusion Criteria	1) Marked liver function abnormalities at enrollment: alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels 3 times or more above the upper limit of the normal reference range;

	2) Renal insufficiency at enrollment: serum creatinine levels above the upper limit of the normal reference range and/or endogenous creatinine clearance below the lower limit of the normal reference range; 3) Severe heart failure: left ventricular ejection fraction ≤ 30%; 4) Secondary dyslipidemia caused by factors such as thyroid dysfunction, nephrotic syndrome, or familial hyperlipidemia; 5) Patients with connective tissue diseases, rheumatic or autoimmune diseases, rhabdomyolysis, hematologic disorders, or malignancies, combined with other types of intracranial diseases; 6) Patients who have experienced an allergic reaction while taking oral statins or receiving Tafolecimab

	injections, as well as those with clear contraindications; 7) Patients with a history of major surgery or trauma, or who have developed severe acute or chronic infections during the follow-up period; 8) Pregnant women; 9) Patients with serious illnesses and a life expectancy of ≤3 months, such as those with malignant tumors; 10) Other circumstances deemed unsuitable for participation by the investigators, including any medical or non-medical conditions that may increase the subject’s risk, interfere with study assessments, or affect the subject’s ability to complete the study. 11) Participants meeting any of the above criteria must be excluded.

Study Termination Criteria	The study will end when the last participant completes their final follow-up visit.
Withdrawal/Exclusion Criteria	All study participants who have signed the informed consent form and been screened as eligible for the study are considered dropouts if they withdraw from the clinical study at any time and for any reason, provided they have not completed the observation period specified in the protocol.After a study participant drops out, the investigator should make every effort to contact them to complete as many assessment items as possible and record the participant’s last dose of medication to the best of their ability. The reason for the participant’s dropout should be documented, and the study summary form should be completed. For

	participants who drop out due to an adverse event (AE), this should be recorded in the CRF.
Early Withdrawal Criteria	Poor participant compliance, or self-initiated medication changes or discontinuation ; participants who, for any reason, are unwilling to continue clinical follow-up and request to withdraw from the study and discontinue follow-up to their treating physician; participants who, although they have not explicitly requested to withdraw from the study, are lost to follow-up because they no longer accept medication or undergo examinations.
Primary Outcome Measure	Percentage change in LDL-C from baseline in enrolled patients 12 weeks after the first dose (percentage change from baseline =

	(current value – baseline value)/ baseline value ×100%)
Secondary Endpoints	1. Percentage change in Lp(a) from baseline in enrolled patients at Week 12 after the first dose of treatment (percentage change from baseline = (current value – baseline value)/baseline value × 100%) 2. Comparison of the LDL-C target achievement rates across groups at each follow-up time point. 3. Changes in lipid profile parameters (HDL-C, TC, TG, ApoB, and ApoA1) across groups at each follow-up time point.
Safety Endpoints	1) Injection site reactions (e.g., erythema, swelling, induration, pain, itching, etc.); 2) Elevated transaminases ≥3 ULN or elevated creatine kinase levels ⩾5 ULN;

	3） Systemic reactions (e.g., flu-like symptoms, headache, fatigue); 4） Number of cases and duration of very low LDL-C (LDL-C < 0.5 mmol/L) 5) Other adverse symptoms affecting continued use of the drug.
Statistical Analysis Methods	Statistical analysis was performed using SPSS 26.0 software. To control for baseline confounding and selection bias resulting from grouping based on clinical decision-making, propensity score matching (PSM) was used to balance the baseline characteristics between the two groups of patients. First, baseline variables that might influence decisions regarding dosing intervals and treatment efficacy were systematically collected, including demographic data (age, sex, height, weight, BMI),clinical characteristics (ASCVD risk

	stratification, history of comorbidities, smoking history, alcohol consumption history, family history of cardiovascular disease), as well as the distance from the patient's residence to the hospital (<50 km, ≥50 km), and factors that may influence physician decision-making (such as patient-reported convenience of medical care, treatment preferences, and the physician's primary reason for selecting the Q3W regimen).The group variable was treated as the dependent variable, and all of the aforementioned potential confounding variables were treated as independent variables to calculate the propensity score for each patient. Using the nearest-neighbor matching method, a patient with the closest propensity score in the Q2W

	group was matched 1:1 with each patient in the Q3W group.After matching, baseline characteristics were balanced between groups (standardized difference after matching <10%), and subsequent analyses were primarily based on the matched sample. For primary efficacy endpoints (e.g., percentage change in LDL-C), if the data followed a normal distribution with homogeneous variances, an independent samples t-test was used to compare the two groups; if the conditions for parametric tests were not met, the Mann-Whitney U test was used.Within-group before-and-after comparisons will use either a paired t-test or the Wilcoxon signed-rank test, depending on the distribution of the difference. Categorical data will be analyzed using the chi-square test

	or Fisher’s exact test, while repeated-measure data will be analyzed using repeated-measures analysis of variance (ANOVA) or generalized estimating equations (GEE). Safety endpoints will be described in terms of the number of cases and the number of occurrences of different adverse events; between-group comparisons will use the chi-square test.
Format of Research Publication	We plan to publish one SCI paper

I. Research Objectives

1. Primary Objective

This study aims to systematically evaluate the lipid-lowering efficacy and safety of two dosing regimens—Tafolecimab 150 mg every two weeks (Q2W) and every three weeks (Q3W)—administered for 12 weeks in patients with hyperlipidemia whose LDL-C levels remain above target after 4 weeks of treatment with moderate-intensity statins ± a cholesterol absorption inhibitor.The primary efficacy endpoint is defined as the percentage change in LDL-C from baseline at Week 12 following the first dose.

2. Secondary Objectives

The secondary objectives of this study aim to comprehensively evaluate the clinical value of the two dosing regimens from multiple perspectives:

① To assess the impact of the two regimens on Lp(a)—a key independent residual cardiovascular risk factor—by analyzing the percentage change in Lp(a) relative to baseline at week 12 after the first dose.② To assess the efficiency of lipid control by dynamically monitoring and comparing the LDL-C target achievement rates between the two groups at prespecified follow-up time points (Group A: 2, 6, and 12 weeks after the first dose; Group B: 3, 9, and 12 weeks after the first dose).③ To comprehensively describe the combined effects of the two treatment regimens on lipid metabolism by observing changes from baseline in lipid profile parameters—including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), ApoB, and ApoA1—at each follow-up visit.④ In a real-world clinical setting, systematically monitor the incidence of treatment-related adverse events between the two groups, with a focus on injection site reactions, abnormal elevations in liver transaminases (ALT/AST) and creatine kinase (CK), as well as the number of cases and duration of extremely low LDL-C (LDL-C < 0.5 mmol/L) and other adverse symptoms affecting continued medication use, to provide evidence for clinical drug safety.

3. Exploratory Objectives

① To preliminarily investigate whether the Q3W dosing regimen can achieve efficacy comparable to the standard Q2W regimen in maintaining long-term stable control of LDL-C and Lp(a), thereby providing a viable alternative for patients seeking improved treatment adherence.② To explore the potential value of extending the dosing interval to Q3W (reducing the annual number of injections from 26 to approximately 17) in improving the patient treatment experience, enhancing long-term treatment adherence, and optimizing the utilization of healthcare resources.

II. Research Background

Cardiovascular disease is a leading cause of death and disability worldwide, and its burden continues to increase in both urban and rural areas of China[1]. Atherosclerosis is the common pathological basis for the vast majority of cardiovascular and cerebrovascular events, and hyperlipidemia—particularly elevated low-density lipoprotein cholesterol (LDL-C) levels—is a core risk factor driving the onset and progression of atherosclerosis[2].

A wealth of evidence-based medical data has clearly demonstrated that LDL-C levels exhibit a log-linear relationship with the risk of atherosclerotic cardiovascular disease (ASCVD), and that effectively lowering LDL-C yields significant cardiovascular benefits[3] . Mendelian randomization studies have further confirmed that for every 1 mmol/L reduction in LDL-C, the risk of ASCVD decreases by approximately 50%[4] .To more effectively control residual cardiovascular risk, numerous authoritative guidelines both domestically and internationally have further strengthened lipid-lowering targets for high- and very-high-risk populations. For example, the 2019 ESC/EAS Guidelines on the Management of Dyslipidemia recommend that very-high-risk patients with diagnosed ASCVD maintain LDL-C levels below 1.4 mmol/L, with a reduction of at least 50% from baseline[5];the 2023 “Chinese Cholesterol Education Program (CCEP) Expert Recommendations” also explicitly state that for ultra-high-risk patients with ASCVD, LDL-C should be maintained at <1.4 mmol/L with a reduction of >50%[6].

However, the current status of lipid management among patients with coronary heart disease in China is not encouraging. Studies show that among the ASCVD population in China, the rate of lipid-lowering drug therapy is only 14.5%, and the LDL-C target achievement rate is as low as 6.8%[7] .Doubling the statin dose can only further reduce LDL-C by approximately 6%, and a significant proportion of patients are unable to achieve target levels due to adverse reactions or insufficient efficacy[8] . Therefore, the latest domestic and international consensus guidelines emphasize that for high-risk or very high-risk patients who remain non-compliant with target levels despite statin therapy, non-statin potent lipid-lowering drugs, such as PCSK9 (proprotein convertase subtilisin/kallikrein 9) inhibitors, should be added early in the treatment regimen[9] .

In addition to low-density lipoprotein (LDL), more than 40% of patients have significant residual cardiovascular risk[9][10]. Lipoprotein(a) [Lp(a)] is a genetic risk factor independent of LDL-C; even when its levels are well controlled (e.g., <70 mg/dL), high Lp(a) can still significantly increase the risk of coronary heart disease events[10].Currently, there are no effective means to lower Lp(a) levels; statins not only fail to reduce Lp(a) but may even cause its levels to rise by approximately 11%, further exacerbating cardiovascular risk[11]. Therefore, the development of therapeutic strategies that simultaneously target both LDL-C and Lp(a) has become an urgent need in the field of lipid management.

The clinical application of PCSK9 inhibitors offers a significant breakthrough in addressing this challenge.By inhibiting the PCSK9 protein, these drugs enhance the activity of LDL receptors in liver cells, significantly promoting the clearance of LDL-C[12]错误!不能识别的开关参数。. Multiple large-scale cardiovascular outcome studies (such as FOURIER and ODYSSEY OUTCOMES) have confirmed that adding a PCSK9 inhibitor to statin therapy can further reduce LDL-C by 50%–60% and significantly lower the risk of MACE[13][14].Notably, PCSK9 inhibitors can also reduce Lp(a) by approximately 25%–30%, making them the only widely available therapy currently capable of simultaneously targeting both LDL-C and Lp(a)[15]. Consequently, authoritative guidelines both domestically and internationally have recommended them as the standard of care for patients with coronary heart disease who have not achieved target levels despite statin therapy[16].

Tafolecimab is a fully human anti-PCSK9 monoclonal antibody independently developed in China[17]. It binds to and inhibits circulating PCSK9 with high affinity, blocking the interaction between PCSK9 and the low-density lipoprotein receptor (LDLR). This reduces the lysosomal degradation of LDLR, allowing more LDLR to circulate to the surface of hepatocytes and significantly enhancing their capacity to clear LDL-C[18].

Tafolecimab IgG2 subtype; its Fc segment has been engineered to reduce immunogenicity and weaken its binding affinity to FcγR, further enhancing the drug's safety.Following subcutaneous injection, the drug is well absorbed, takes effect rapidly, and provides long-lasting, stable efficacy[19][20]. Its Phase III clinical trials (the CREDIT series) confirmed that for patients with hypercholesterolemia who did not achieve target levels despite dietary control combined with statin therapy, Tafolecimab 150 mg every two weeks (Q2W),450 mg every four weeks (Q4W), and 600 mg every six weeks (Q6W) all effectively reduced LDL-C levels by 57%–69%, with sustained and stable efficacy. More than 70% of very high-risk patients achieved the target of LDL-C < 1.4 mmol/L, while Lp(a) was significantly reduced by approximately 30%–50%[21] .Notably, the 600 mg Q6W extended-interval dosing regimen greatly enhances dosing convenience and long-term patient adherence while maintaining strong therapeutic efficacy[22] .

Based on the pharmacokinetic properties of Tafolecimab—which has a long half-life of 26.1 days—the theoretical feasibility of a once-every-three-weeks (Q3W) dosing regimen is supported, as blood concentrations are expected to remain above the therapeutic threshold even toward the end of the dosing interval.If the 150 mg Q3W dosing

regimen is validated, the number of annual injections for patients would decrease from 26 to 17 compared to the 150 mg Q2W regimen, which is expected to significantly reduce the treatment burden, improve long-term treatment adherence, lower overall healthcare costs, and provide a new pathway for personalized lipid management strategies.

Currently, there is a lack of prospective clinical studies systematically evaluating whether the Tafolecimab 150 mg Q3W regimen can sustainably inhibit PCSK9 activity throughout the entire dosing cycle and achieve long-term, stable control of low-density lipoprotein cholesterol (LDL-C) and Lp(a).Therefore, this study aims to conduct an exploratory clinical trial to systematically compare the differences in efficacy and safety between the Tafolecimab Q3W regimen and the standard Q2W regimen, with the goal of providing high-level evidence-based medical support for optimizing lipid management strategies in patients with ASCVD, enhancing treatment adherence, and improving long-term prognosis.

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III. Research Basis

1. Preliminary Animal Studies and Literature Review

Tafolecimab was identified through yeast surface display technology, which offers the following distinct advantages: First, high affinity and high specificity—through screening of a yeast display library and affinity maturation optimization, Tafolecimab achieved an affinity for PCSK9 at the picomolar level (1–10 pM), significantly higher than that of antibodies developed using traditional transgenic mouse platforms(such as Evolocumab and

Alirocumab); second, a fully human sequence—this antibody was directly screened from a fully human yeast library, avoiding immunogenicity issues and eliminating the need for subsequent humanization modifications, thereby significantly reducing the risk of clinical immunogenicity[1] ;Third, excellent stability and long duration of action—through engineering optimization, Tafolecimab demonstrates outstanding thermal and pH stability, with an extended half-life (approximately 26.1 days), supporting dosing every 4–6 weeks and greatly improving patient compliance[2].

Preclinical studies conducted in a short-term pharmacodynamic model using crab-eating macaques provided preliminary validation of its long-acting mechanism. The experiment utilized a high-fat diet to induce a mild hypercholesterolemia model, in which healthy adult crab-eating macaques were randomly assigned to a control group, a positive control (Evolocumab) group, and low-, medium-, and high-dose Tafolecimab groups.The results showed that Tafolecimab exhibited a dose-dependent LDL-C-lowering effect. In the high-dose group, the mean reduction in LDL-C reached 68.2% ± 5.1% on day 7 post-administration; this efficacy was not statistically different from that of the positive control group, and the lipid-lowering effect persisted until day 14 post-administration without fully reverting to baseline levels.The pharmacokinetic-time curve indicated that the duration of action of Tafolecimab was longer than that of the positive control, suggesting it may have a longer in vivo half-life, which provides a basis for further clinical exploration of longer dosing intervals (e.g., once monthly)[3].

A Phase I study (NCT03366688) conducted in healthy volunteers and patients with hypercholesterolemia further confirmed that the elimination half-life of Tafolecimab is as long as 26.1 days, significantly longer than that of marketed drugs in the same class, such as Evolocumab (11.4 days) and aliximab (5.5 days)[4].Drug dosing intervals are typically designed to be 1–2 times the half-life; therefore, a half-life of 26.1 days fully supports, from a pharmacokinetic perspective, a 3-week (21-day) or even 4-week dosing regimen.Furthermore, Tafolecimab has an extremely low clearance rate of only 0.162 L/day, which is significantly lower than that of aliximab (0.908 L/day) and Evolocumab (0.256 L/day)[5]. This low clearance rate indicates a longer residence time of the drug in the body, serving as another key parameter supporting the extension of the dosing interval.The current every-two-week (Q2W) dosing regimen represents only a preliminary application of its long-acting potential; extending the dosing interval to every three weeks (Q3W)

is a pharmacokinetically sound and conservative optimization strategy[6].

The Phase II study (NCT03815812) not only validated its efficacy but also provided model predictions and indirect evidence for the Q3W regimen through the exploration of different dosing regimens.Population pharmacokinetic/pharmacodynamic (PopPK/PD) analysis showed that when the serum trough concentration of Tafolecimab reached 5 μg/mL, the LDL-C reduction effect plateaued, suggesting that maintaining a trough concentration above this threshold is key to ensuring efficacy.Based on the established PK model, simulations of the 150 mg Q3W dosing regimen showed that trough concentrations can be maintained stably above 5 μg/mL, theoretically ensuring that lipid-lowering efficacy will not significantly diminish due to the extended dosing interval[7][8].

The Phase III CREDIT-2 study in patients with heterozygous familial hypercholesterolemia (HeFH) demonstrated that Tafolecimab 150 mg administered every 2 weeks reduced LDL-C by 58.4%, with 59.6% of patients achieving an LDL-C reduction of ≥50%[9].In addition, the drug significantly reduced non-HDL-C, apolipoprotein B (ApoB), and Lp(a) by 70.5%, 61.4%, and 43.3%, respectively, demonstrating multifaceted cardiovascular protection[10].The incidence of adverse events with Tafolecimab was 59%, comparable to 58% in the placebo group.The CREDIT series of studies further confirmed the feasibility of longer dosing intervals: the 450 mg Q4W regimen reduced LDL-C by 58.7%, with 75% of patients achieving an LDL-C reduction of ≥50% and a reduction in Lp(a) of approximately 49.6%; the 600 mg Q6W regimen reduced LDL-C by 57.3%,with 71.8% of patients achieving an LDL-C reduction of ≥50% and Lp(a) reduced by approximately 42%[11][12]. Phase III clinical data provide definitive clinical validation for the long-acting dosing regimens of Tafolecimab, completely dispelling doubts regarding the feasibility of its longer dosing intervals, and offering robust supporting evidence and confidence for the successful implementation of the 150 mg Q3W regimen[13].

In summary, preclinical studies laid the molecular foundation for long-acting action; Phase I studies provided key PK parameters, demonstrating its ultra-long half-life; Phase II studies used exposure-response models to predict the efficacy threshold for the Q3W regimen and preliminarily validated the feasibility of Q4W/Q6W regimens; and Phase III studies provided definitive clinical evidence, demonstrating that longer dosing interval regimens remain highly effective[14][15].A complete and logically rigorous chain of evidence has been established, spanning from the underlying

mechanisms to clinical trials at various stages. To further systematically evaluate the efficacy of the Tafolecimab 150 mg Q3W regimen in maintaining long-term, stable target levels of LDL-C and Lp(a),this study aims to systematically evaluate the lipid-lowering efficacy and safety of two dosing regimens—150 mg Tafolecimab every two weeks (Q2W) and every three weeks (Q3W)—over a 12-week period in patients with hyperlipidemia whose LDL-C levels remain uncontrolled after 4 weeks of treatment with moderate-intensity statins ± a cholesterol absorption inhibitor.The goal is to provide a more convenient and compliant individualized treatment strategy for lipid management and to offer high-level evidence-based medical evidence for optimizing long-term lipid-lowering treatment regimens[16].

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2. Criteria for Selecting Study Participants

Although statins are the cornerstone of lipid management, in clinical practice, a large number of patients with hyperlipidemia still fail to achieve LDL-C levels corresponding to their risk categories despite regular statin therapy.Data from China show that even among patients receiving lipid-lowering therapy, doubling the statin dose results in only about a 6% additional reduction, and 56% of patients still fail to meet their targets even after a dose increase, highlighting the limitations of statin monotherapy or traditional combination therapy.Both domestic and international guidelines (such as those from the ACC and ESC) emphasize that for patients with hyperlipidemia at high cardiovascular risk (e.g., those with multiple risk factors, diabetes, or imaging-confirmed atherosclerotic plaques), more aggressive lipid-lowering strategies should be implemented to delay the progression of atherosclerosis.recommending that LDL-C be reduced to <1.8 mmol/L or even <1.4 mmol/L, and explicitly advising early combination therapy with non-statin lipid-lowering agents if statin therapy is insufficient or not tolerated. PCSK9 inhibitors, as a new cornerstone of potent lipid-lowering therapy, provide a critical treatment option for such patients.Therefore, we selected patients with a confirmed diagnosis of hyperlipidemia who, after 4 weeks of treatment with a moderate-intensity statin ± a cholesterol absorption inhibitor, had not achieved the LDL-C target levels corresponding to their ASCVD risk category as defined by the *Chinese Guidelines for Lipid Management (2023)*. We aimed to explore the efficacy and safety of extending the dosing interval to Q3W on top of the standard treatment regimen (toliximab 150 mg Q2W).This study aims to verify whether a more convenient dosing regimen can maintain excellent therapeutic efficacy, thereby providing high-level evidence-based medical

evidence to improve patient adherence and optimize lipid management strategies for primary prevention.

3. Basis for Endpoint Selection

This study is a prospective, observational cohort study designed to preliminarily evaluate the efficacy and safety of the Tafolecimab 150 mg every three weeks (Q3W) dosing regimen compared to the every two weeks (Q2W) regimen.

Rationale for the Primary Endpoint: This study selected “the percentage change in low-density lipoprotein cholesterol (LDL-C) from baseline at week 12 after the first dose” as the primary efficacy endpoint, based on the well-established pathophysiological role of LDL-C as a key factor in the pathogenesis of atherosclerotic cardiovascular disease.as its reduction has been demonstrated by extensive evidence-based medical research to be significantly associated with a decreased risk of cardiovascular events, and is universally recognized by authoritative lipid management guidelines both domestically and internationally as a core surrogate endpoint for evaluating lipid-lowering efficacy. This metric is highly sensitive, effectively distinguishes the lipid-lowering intensity of different treatment regimens, and is easily and accurately assessed within a short 12-week timeframe, aligning closely with the objectives and clinical feasibility requirements of this exploratory study.

Rationale for selecting secondary endpoints: The rate of achieving LDL-C target levels is the most intuitive and clinically meaningful efficacy indicator in clinical practice. Assessing this rate at various time points provides a dynamic reflection of the actual ability of different dosing regimens to help patients achieve guideline-recommended targets in the real world. Lipoprotein(a) is an important genetic risk factor independent of LDL-C, for which there is currently no specific treatment.Toleciumab has been demonstrated to effectively reduce Lp(a); evaluating its effect on Lp(a) reduction helps comprehensively demonstrate the drug’s multi-target benefits, aligning with the current focus on residual risk control in lipid management.Changes in other lipid parameters (HDL-C, TC, TG, ApoB, ApoA1) are intended to comprehensively evaluate the impact of Tafolecimab on the overall lipid profile and its actual efficacy in helping patients achieve treatment goals in real-world clinical practice.

The selection of safety endpoints was based on the known safety profiles of PCSK9 inhibitors and preclinical data. The study will systematically monitor injection site reactions, liver enzymes, creatine kinase, the number and duration of cases with extremely low LDL-C (LDL-C < 0.5 mmol/L), and other adverse events that may affect continued treatment. This is to comprehensively evaluate the safety and tolerability of the drug under an extended dosing interval regimen.

IV. Study Content

1. Study Population

This study enrolled patients diagnosed with hyperlipidemia, who, prior to enrollment, had received lipid-lowering therapy with moderate-intensity statins (including atorvastatin 10-20mg, rosuvastatin 5-10mg, fluvastatin 80mg, lovastatin 40mg, pitavastatin 1-4mg, pravastatin 40mg, simvastatin 20-40mg, Xuezhikang 1.2g, etc.) for at least 4 weeks, with or without combination with cholesterol absorption inhibitors, and according to the "2023 Chinese Guidelines for Lipid Management", their LDL-C levels failed to reach the target values corresponding to their respective ASCVD risk categories (for patients at very high cardiovascular risk: LDL-C ≥ 1.8 mmol/L or a reduction from baseline≥ 50%; for patients at ultra-high cardiovascular risk: LDL-C ≥ 1.4 mmol/L or a reduction from baseline ≤50%; for patients at high risk and below risk categories: LDL-C≥ 2.6 mmol/L or a reduction from base line≤ 50%), or the clinician predicted that the patient's LDL-C level would still fail to reach the target with continued moderate-dose statin lipid-lowering therapy and required combination therapy with a PCSK9 inhibitor, and who were using tafolecimab for the first time.

2. Sample Size

This study is a prospective, observational cohort study designed to preliminarily evaluate the lipid-lowering efficacy and safety of Tafolecimab 150 mg Q2W (standard dosing regimen) versus 150 mg Q3W (extended dosing regimen). Based on the design of other exploratory studies and clinical feasibility, and taking into account factors such as the study duration, resource availability, and subject recruitment, it is anticipated that 30 patients will be enrolled in each group[1][2][3][4].This sample size will facilitate the preliminary collection of trend data on LDL-C reduction under different dosing intervals and provide a reference for sample size estimation in subsequent confirmatory clinical trials. This study will emphasize standardized data collection and follow-up management, strictly

control dropouts, ensure data quality and completeness, and provide preliminary evidence to support the optimization of Tafolecimab dosing regimens.

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3. Specific Study Content

This study is a prospective, observational cohort study.Based on strict inclusion and exclusion criteria, we will recruit and follow up patients who visit the Department of Cardiology at the First Affiliated Hospital of Shandong First Medical University (Qianfoshan Hospital, Shandong Province) and meet the following conditions: This study includes patients diagnosed with hyperlipidemia who, prior to enrollment, had received lipid-lowering therapy with moderate-intensity statins ± a cholesterol absorption inhibitor for at least 4 weeks; according to the *Chinese Guidelines for Lipid Management (2023)*,their LDL-C levels have not reached the target values corresponding to their ASCVD risk category, and clinicians have decided to initiate combination therapy with Tafolecimab based on standard clinical practice guidelines, taking into account the patient’s ASCVD risk stratification, current LDL-C level, and the required reduction. Patients may be enrolled only after they have fully understood and voluntarily signed a written informed consent form.

This study does not alter any established clinical management protocols. All laboratory tests are follow-up examinations conducted during the patient’s treatment with Tafolecimab in accordance with clinical practice guidelines and routine follow-up requirements.The primary objective of this study is to systematically and prospectively collect and analyze these routine clinical data, as detailed below: At predetermined time points during patients’ routine clinical follow-up (i.e., baseline and scheduled visit points), lipid-related laboratory reports already obtained as part of their clinical care will be collected, including: low-density

lipoprotein cholesterol (LDL-C), lipoprotein(a) [Lp(a)], total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), ApoB, and ApoA1 levels. Concurrently, laboratory reports for liver function and creatine kinase—among others—completed at the same follow-up time point for routine medical monitoring purposes will be collected.Core data include: levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatine kinase (CK), as well as the number of cases with extremely low LDL-C (LDL-C < 0.5 mmol/L) and the duration of such cases. These data will be used to systematically monitor patient safety during routine treatment.

This study will use electronic case report forms (CRFs) as the data collection tool. All data entry will be performed by a research physician who has been trained and authorized by the principal investigator. This individual will review the patient's original medical records (including inpatient records and the outpatient electronic medical record system) and official laboratory reports from the hospital's laboratory information system to accurately and completely enter the following information into the CRF system:General information and baseline clinical characteristics, including date of data collection, outpatient registration number, gender, age, height, weight, body mass index (BMI), cardiovascular risk stratification, history of comorbidities, medication history, smoking history, alcohol consumption history, and family history of cardiovascular disease;Distance from the patient's residence to the hospital (<50 km, ≥50 km); the physician's primary rationale for selecting the Q3W dosing regimen (e.g., based on patient preference, anticipated adherence, convenience of medical care, etc.); and baseline laboratory parameters, including a complete lipid profile tested within 1 week prior to the first administration of Tafolecimab [total cholesterol (TC), triglycerides (TG),high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), lipoprotein(a) (Lp(a)), ApoB, ApoA1 ApoB, ApoA1] and safety markers [alanine aminotransferase (ALT),aspartate aminotransferase (AST), creatine kinase (CK), uric acid (UA), and the number of cases with extremely low LDL-C (LDL-C < 0.5 mmol/L) and the duration of such cases]. All entered data must be rigorously cross-checked against the source documents to ensure their authenticity and accuracy, thereby guaranteeing the standardization and consistency of the data collection process.

3.1. Primary Efficacy Endpoint: During the outpatient follow-up visit at Week 12 (±3 days) after the first dose, enter the LDL-C value from the laboratory report into the Case Report Form (CRF) to observe the percentage change in LDL-C from baseline. (Percentage

change from baseline = (Week 12 value – baseline value) / baseline value × 100%).

3.2. Key Secondary Efficacy Endpoints: During the outpatient follow-up visit at Week 12 (±3 days) after the first dose, the Lp(a) value from the laboratory report will be entered into the electronic Case Report Form (CRF), and the percentage change in Lp(a) from baseline for enrolled patients will be observed.(Percentage change from baseline = (Week 12 value – baseline value) / baseline value × 100%).

3.3 LDL-C Target Achievement Rate: During outpatient follow-up visits at each visit point (±3-day window) in Group A (Weeks 2, 6, and 12 after the first dose) and Group B (Weeks 3, 9, and12 weeks) during outpatient follow-up at each visit (within a ±3-day window), the study physician will enter the current LDL-C value and the corresponding patient's cardiovascular risk stratification into the CRF to calculate the proportion of patients achieving the preset lipid-lowering target, thereby dynamically assessing the onset of action and sustained achievement of targets for the two regimens.

3.4. At the same visit time points mentioned above, the investigator must enter values for HDL-C, TC, TG, ApoB, ApoA1, and other parameters from the laboratory reports into the CRF to record their absolute values and changes relative to baseline, for the purpose of comprehensively evaluating the drug's impact on overall lipid metabolism.

3.5. At all outpatient visit points throughout the study period, the investigator must systematically monitor and record the following safety parameters in the designated module of the CRF through medical history, physical examination, and review of current laboratory reports: these include alanine aminotransferase (ALT),aspartate aminotransferase (AST) levels elevated to ≥3 times the upper limit of normal (ULN), or creatine kinase (CK) levels elevated to ≥5 times the ULN, as well as the number of cases and duration of very low LDL-C (LDL-C < 0.5 mmol/L).Adverse Events (AE): Record in detail all observed or patient-reported adverse events, particularly injection site reactions (e.g., erythema, swelling, pain, itching, etc.) and systemic reactions (e.g., flu-like symptoms, headache, fatigue). The time of onset, severity, measures taken, and outcome must be recorded in the CRF, and the relevance to the study drug must be assessed.

V. Study Methods

1. Inclusion Criteria (Diagnostic Criteria, Inclusion Criteria, Exclusion Criteria)

1.1 Inclusion Criteria

Study participants must meet all of the following inclusion criteria:

1) Age ≥ 18 years
2) Patients with hyperlipidemia who were already taking moderate doses of statins on a regular basis prior to enrollment (atorvastatin 10 mg/day, rosuvastatin 5 mg/day, fluvastatin 80 mg/day,pivastatin 2－4 mg/day, pravastatin 40 mg/day, simvastatin 20－40 mg/day, or Xielikang 1.2 g/day) for at least 4 weeks, regardless of whether they were taking a cholesterol absorption inhibitor in combination
3) LDL-C levels have not reached the target values corresponding to the respective ASCVD risk categories, namely: low-risk patients for primary prevention of ASCVD: LDL-C ≥ 3.4 mmol/L; moderate- and high-risk patients for primary prevention of ASCVD: LDL-C ≥ 2.6 mmol/L;Patients at very high risk for ASCVD secondary prevention: LDL-C ≥ 1.8 mmol/L or a reduction from baseline of ≤ 50%; patients at ultra-high risk for ASCVD secondary prevention: LDL-C ≥ 1.4 mmol/L or a reduction from baseline of ≤ 50%
4) Patients who meet the criteria for PCSK9 inhibitor use, or for whom the clinician anticipates that LDL-C levels will remain uncontrolled despite continued treatment with moderate-dose statins ± a cholesterol absorption inhibitor, and who therefore require combination therapy with a PCSK9 inhibitor
5) First-time use of a PCSK9 inhibitor
6) Voluntarily participate and sign an informed consent form, and be able to undergo follow-up
7) All of the above criteria must be met for inclusion in the study
1.2 Exclusion Criteria
Study participants cannot be enrolled if any of the following conditions are present during the pre-enrollment screening:
1) Marked liver function abnormalities at enrollment: alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels 3 times or more above the upper limit of the normal reference range;
2) Renal insufficiency at enrollment: serum creatinine levels above the upper limit of the normal reference range and/or endogenous creatinine clearance below the lower limit of the normal reference range;
3) Severe heart failure: left ventricular ejection fraction ≤ 30%;
4) Secondary dyslipidemia caused by factors such as thyroid dysfunction, nephrotic syndrome, or familial hyperlipidemia;
5) Patients with connective tissue diseases, rheumatic or autoimmune diseases, rhabdomyolysis, hematologic disorders, or malignancies, combined with other types of intracranial diseases;
6) Patients who have experienced an allergic reaction while taking oral statins or receiving Tafolecimab injections, as well as those with clear contraindications;

7) Patients with a history of major surgery or trauma, or who develop severe acute or chronic infections during the follow-up period;
8) Pregnant women;
9) Patients with serious illnesses and a life expectancy of ≤3 months, such as those with malignant tumors;
10) Other circumstances deemed unsuitable for participation by the investigators, including any medical or non-medical conditions that may increase the subject’s risk, interfere with study assessments, or affect the subject’s ability to complete the study.
11) Participants meeting any of the above criteria must be excluded.
2. Study Participant Grouping

This study is a prospective, observational cohort study. All treatment decisions (including the dosing frequency of Tafolecimab) are made independently by clinicians based on the patient’s actual condition, treatment preferences, expected compliance, and clinical judgment.Patients receiving the “toreliximab 150 mg Q2W” regimen will be enrolled in Group A, and patients receiving the “toreliximab 150 mg Q3W” regimen will be enrolled in Group B. The research team will systematically and prospectively collect and compare data on the efficacy and safety of the two dosing regimens.

3. Criteria for Early Withdrawal or Discontinuation of Study Participation

(1) The study participant requests withdrawal or discontinuation;

(2) Study discontinuation due to the occurrence of a serious adverse event (SAE) during the study;

(3) The participant develops another illness during the study that affects the assessment of efficacy and adverse events.

VI. Study Procedures

1. Study Participant Management

1.1 Recruitment of Study Participants

In accordance with the above inclusion and exclusion criteria, patients with hyperlipidemia seeking treatment at the Department of Cardiology, First Affiliated Hospital of Shandong First Medical University (Qianfoshan Hospital, Shandong Province) were selected. These patients were previously treated with moderate-intensity statins (atorvastatin 10 mg/day, rosuvastatin 5 mg/day, fluvastatin 80 mg/day,pivastatin 2–4 mg/day, pravastatin 40 mg/day, simvastatin 20–40 mg/day, or Xielikang 1.2 g/day) for 4 weeks, regardless of whether they were also taking a cholesterol absorption inhibitor. Based on the *Chinese Guidelines for Lipid Management (2023)*,LDL-C levels did not reach the target values corresponding to the

respective ASCVD risk categories (for patients at very high cardiovascular risk: LDL-C ≥ 1.8 mmol/L or a reduction from baseline of ≤ 50%; for patients at extremely high cardiovascular risk: LDL-C ≥ 1.4 mmol/L or a reduction from baseline of ≤ 50%;for patients in the high-risk category and below: LDL-C ≥ 2.6 mmol/L or a reduction from baseline of ≤ 50%), or when the clinician anticipates that the patient's LDL-C levels will remain above target despite continued lipid-lowering therapy with a moderate dose of statins combined with a cholesterol absorption inhibitor, and combination therapy with a PCSK9 inhibitor is required, for patients scheduled to receive Tafolecimab .

1.2 Informed Consent Process

Before study participants enroll in the clinical trial, the investigator or a designated representative will be responsible for explaining to each participant the background of the study, its main objectives, and the benefits and risks of participation, including known and foreseeable risks and potential adverse events.Both the study participant and the investigating physician must sign their names and the date on the informed consent form before the participant enters the study (prior to screening). The final text of the informed consent form must include the following: the purpose of the study, the main study content, the participant's obligations, the benefits and risks of participating in the study, and the confidentiality of the participant's information.

The informed consent form must obtain written approval from the relevant regulatory authorities in accordance with regulations and be written in a language that the research participant can read.Both the research participant and the investigator conducting the informed consent process—or the investigator's representative—must sign and date the informed consent form. The original copy of the informed consent form shall be retained by the investigator, and a duplicate copy shall be provided to the research participant for their retention. If significant new data regarding the investigational drug are discovered, the informed consent form must be amended in writing, submitted to the relevant regulatory authorities for approval, and then re-signed by the research participant.

1.3. Verification of Inclusion and Exclusion Criteria

After obtaining the research participant's signed informed consent form, a research physician authorized by the Principal Investigator (PI) is responsible for conducting the final verification of the research participant's eligibility on the day of enrollment.The verification process involves comparing the research participant's original medical records (including, but not limited to, outpatient medical records, past medical history, and medication

records) as well as laboratory test reports and diagnostic test results from within one week prior to signing the informed consent form against the inclusion and exclusion criteria established in the protocol. Only after verification confirms that the research participant meets all inclusion criteria and does not meet any exclusion criteria may they be formally enrolled in this study.

1.4. Review of Medical History and Concurrent Medication Records

All enrolled patients will undergo the collection of the following information and relevant examinations in accordance with the protocol flowchart: This includes collecting demographic data, taking a medical history (including past medical history and treatment history), and documenting past medication use (within the past 30 days) and current concomitant medications.

2. Risk Control and Management Procedures

2.1. Study Compliance Management

Investigators should diligently implement the informed consent process to ensure that study participants fully understand the significance of the study and the importance of taking medication on time, and that they cooperate with the study. Investigators should thoroughly inquire about participants' medication use, including concomitant medications.

2.2 Safety Evaluation Procedures (Assessment, Detection, and Reporting of Adverse Events)

An adverse event (AE) is defined as an unexpected, adverse medical event occurring in a clinical trial after a patient or study participant receives a study drug, though it does not necessarily have a causal relationship with the treatment. AEs include clinically significant abnormalities in clinical laboratory test results, which may indicate a disease and/or organ damage. All observed adverse events or those voluntarily reported by study participants should be promptly recorded in the source documents and the Case Report Form (CRF).

Adverse events in clinical trials are collected starting from the participant's first administration of the study drug and continuing until the end of the study. For each adverse event, the time of onset, severity, duration, management, and outcome must be described. The causal relationship with the study drug must be analyzed and assessed, as well as whether the event meets the criteria for a serious adverse event. If the criteria for a serious adverse event are met, the event must be documented and reported in accordance with the serious adverse event reporting procedure.

When completing the adverse event form, the investigator will use the CTCAE (Version 1.0) to assess the intensity of the adverse event. To ensure consistency, event intensity is graded as follows:

Grade 1: Mild; asymptomatic or minor; limited to clinical or diagnostic findings; no treatment required.

Grade 2: Moderate; requires minor, local, or non-invasive treatment; age-appropriate limitation in instrumental activities of daily living (instrumental activities of daily living include cooking, shopping for clothing, using the telephone, managing finances, etc.).

Grade 3: Severe or of significant medical importance but not immediately life-threatening; resulting in hospitalization or prolonged hospitalization; leading to disability; or causing limitations in instrumental activities of daily living (instrumental activities of daily living include cooking, shopping for clothes, using the telephone, managing finances, etc., and do not involve being bedridden).

Grade 4: Life-threatening; requires emergency treatment.

Grade 5: Death related to the AE.

The investigator should assess the possible association between the adverse event and the study drug as well as concomitant medications, and rate it according to the following 5-level classification criteria.

Definitely related: The reaction occurs in a reasonable temporal sequence with drug administration, is consistent with the known reaction type of the suspected drug, resolves after discontinuation of the suspected drug, and is unlikely to have occurred due to the participant’s clinical condition or other causes.

Likely related: The reaction occurred within a reasonable time frame after drug administration, is consistent with the known reaction profile of the suspected drug, and resolved significantly after discontinuation of the suspected drug; the participant’s clinical condition or other causes are unlikely to have produced the reaction.

Possibly related: The reaction occurred within a reasonable time frame after drug administration, is consistent with the known reaction types of the suspected drug, and may improve after discontinuation of the suspected drug; however, the participant’s clinical condition or other factors may also have caused the reaction.

Possibly unrelated: The reaction does not occur in a timeline that is reasonably consistent with drug administration, does not fit the known reaction patterns of the suspected drug, shows no improvement after discontinuation of the suspected drug, and may be caused by the study participant’s clinical condition or other factors; the reaction improves after the disease condition improves or other factors are resolved.

Definitely unrelated: The reaction does not occur within a reasonable time frame after drug administration, does not match the known reaction types of the suspected drug, and may be caused by the study participant’s clinical condition or other factors; the reaction subsides after the disease condition improves or other causes are eliminated.

The first three categories are collectively considered adverse events of the test drug, and the incidence of adverse events is calculated accordingly.

Follow-up should be conducted regarding the occurrence of adverse events

(1) Treatment-related AEs of any grade should be followed up until:

1) resolution, or improvement to baseline levels;

2) the relationship to the study drug has been reevaluated, the AE is deemed unrelated to treatment, and the investigator confirms that the AE will not improve further;

(2) Adverse events (AEs) not related to treatment should be followed up until:

1) the investigator confirms that the AE will not improve further;

2) the study database is closed and no further safety data are collected.

(3) Outcome of AEs:

1) Resolution without sequelae: The adverse event has fully resolved without leaving any sequelae;

2) Resolution with sequelae: The adverse event has resolved, but sequelae remain;

3) No resolution: The adverse event persists;

4) Death: The patient died as a result of the adverse event. If possible, the autopsy report should be attached to the CRF;

5) When it is unlikely that further information can be obtained (the patient or healthcare provider refuses to provide further information, or there is evidence that the patient remains lost to follow-up despite best efforts).

Note: The end date and final outcome of all AEs should be recorded on the CRF.

(4) Treatment interventions for AEs and measures taken related to the study drug

Any interventions taken to address an AE must be recorded in the “Concomitant Therapy” section of the CRF, specifying whether they were pharmacological or non-pharmacological.

1) Record the measures taken related to the study drug:

2) None: No measures related to the study drug were taken;

3) Interruption/Adjustment: Discontinuation of the study drug, but resumption of treatment once the patient's symptoms have resolved;

4) Discontinuation: Permanent discontinuation of the study drug

Serious Adverse Event (SAE): An adverse event that meets any of the following criteria: resulting in the patient's death; life-threatening; requiring hospitalization or prolonging an existing hospitalization; resulting in permanent or significant disability or loss of function; constituting a congenital malformation or birth defect; or a medical event that the investigator deems to be a serious adverse event. All SAEs occurring during the clinical trial must be recorded on the SAE Report Form.

When a serious adverse event occurs, the investigator must complete the Serious Adverse Event Report Form and report it to the relevant department within 24 hours of confirmation, in accordance with hospital policies and procedures. At the same time, follow-up must be conducted.

(1) For SAEs not related to treatment, follow-up should continue until:

1) resolution, or improvement to baseline levels;

2) the investigator confirms that the SAE will not improve further or has stabilized.

(2) Treatment-related SAEs should be followed up until:

1) resolution, or improvement to baseline levels;

2) the investigator confirms that the SAE will not improve further or has stabilized.

Take necessary and reasonable medical measures to ensure the safety of study participants; determine whether the serious adverse event is related to the study itself or the study drug; when a potential association with the study drug or comparator is suspected, open the emergency envelope to unblind the study; document and follow up on the serious adverse event; and report it promptly to the relevant authorities in accordance with GCP requirements.

3. Data Collection Procedures

All laboratory data in this study were derived from routine clinical diagnostic and treatment procedures. The collection, processing, and testing of all blood samples (fasting venous blood) were independently performed by the hospital's laboratory department; the research team did not conduct any additional sample collection or perform any tests on its own. The data collection process and validity criteria are defined as follows:

Data Sources and Collection Timepoints: The study systematically collected official laboratory reports issued by the hospital's clinical laboratory during routine follow-up examinations for

patients at baseline (within 1 week prior to the first dose of Tafolecimab) and at each follow-up visit (V1, V2, V3).Core Laboratory Parameters: The routine parameters collected include: lipid profile—total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), lipoprotein(a) (Lp(a)), ApoB, and ApoA1—as well as changes in these lipid parameters;Safety indicators: alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase (CK), and extremely low LDL-C (LDL-C < 0.5 mmol/L). Validity criteria: A valid set of laboratory data must simultaneously meet the following conditions: ① Reliable source: Data must originate from official reports in the hospital's laboratory information system.② Timing compliance: The sample collection date falls within the visit window specified in the protocol (e.g., the V3 visit window is Week 12 ± 3 days). ③ Standardized procedure: The sample is sent to the clinical laboratory for testing in accordance with standard clinical procedures (fasting, standardized collection, and transport).

Example: A patient in Group A is scheduled for the V3 visit at Week 12 (i.e., Day 84). On Day 83 (within the ±3-day window), a fasting blood sample was drawn at the outpatient clinic; the sample was tested by the clinical laboratory, which issued an official report containing results for LDL-C, Lp(a), and other parameters. This report was collected by the research team and entered into the system, and is therefore considered a valid data point.

4. Discontinuation/Withdrawal Procedures

4.1 Discontinuation of the Study Intervention

4.1.1 Under certain circumstances, an investigator may be unable to continue the study. If an investigator terminates a clinical study, they must notify the principal investigator and the ethics committee and provide a clear explanation of the reasons.

4.1.2 Termination Requested by the Principal Investigator

Reasons for the principal investigator to request termination of the study may include, but are not limited to:

(1) Funding issues;

(2) Administrative reasons;

(3) The investigator's failure to comply with the protocol, GCP, etc.;

(4) The investigator is unable to recruit a sufficient number of study participants;

(5) Safety considerations.

4.2 Study Participant Withdrawal or Termination of Participation

(1) The study participant withdraws informed consent;

(2) The study participant develops another illness during the study that affects the assessment of efficacy and adverse events;

(3) Poor treatment response, unwillingness to continue receiving the study treatment, or worsening symptoms that prevent completion of the study;

(4) Discontinuation of the study due to the occurrence of a serious adverse event during the study;

(5) Other reasons.

5. Follow-up Requirements

Includes the screening period, the clinical observation period, adverse event assessments, and follow-up after the study concludes.

5.1. Screening Period (V0)

Before commencing any study-related procedures, the investigator must provide potential study participants with a detailed explanation of the study and obtain their voluntary, signed written informed consent. Immediately after signing the informed consent form, a screening assessment must be conducted. Participants may be enrolled only if they meet all inclusion criteria and do not meet any exclusion criteria. Enrolled participants must complete the following baseline data collection and examinations:

• Collection of demographic data: age, sex, ethnicity;

• Physical measurements: height, weight;

• Medical history interview, including past medical history and treatment history;

• Vital signs;

• Medication history: Record concurrent medications and medication history within the 30 days prior to enrollment;

• Laboratory tests: Complete all baseline laboratory tests specified in the protocol.

• Complete the case report form.

5.2 Treatment and Observation Period

During the treatment period, study participants in both groups will undergo follow-up visits according to different schedules. The specific follow-up content and time points are summarized in the table below:

Visit Point	Weeks Since First Dose	Core Examinations and Assessments
Screening Period (V0)	Pre-enrollment	Informed consent, eligibility screening, collection of all baseline data (demographics, medical history, vital signs, concomitant medications, complete laboratory tests)
First Visit (V1)	Group A: Week 2 (±3 days)	Vital signs, efficacy laboratory tests, review and

	Group B: Week 3 (±3 days)	assessment of adverse events, completion of the CRF
Second Visit (V2)	Group A: Week 6 (±3 days) Group B: Week 9 (±3 days)	Vital signs, efficacy laboratory tests, review and assessment of adverse events, and completion of the CRF
Third Visit (V3)	Both Groups: Week 12 (±3 days)	Vital signs, efficacy laboratory tests, review and assessment of adverse events, and completion of the CRF

Note: Efficacy laboratory tests include: LDL-C, HDL-C, Lp(a), TC, TG, ApoA1, ApoB, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase (CK); very low LDL-C: LDL-C < 0.5 mmol/L.Adverse event (AE) assessment is conducted throughout the entire study period, from the first dose administration until the end of the study, and must be performed at every visit.

5.3 Safety Assessment and Follow-up

Adverse event data collection begins with the first administration of the study drug and continues through the final visit. For any adverse event, follow-up is required until the event resolves, stabilizes, or it is confirmed that no further information is needed. All serious adverse events (SAEs) must be reported within 24 hours of becoming known, in accordance with established procedures.

Specify which study data may be recorded directly as source data in the case report form

Demographic data: age, sex, height, weight, BMI;

Medical history: past medical history, surgical history, medication history, family history;

Laboratory test results: LDL-C, HDL-C, Lp(a), TC, TG, ApoB, ApoA1, ALT, AST, CK, HbA1c, etc.;

Vital signs: blood pressure, heart rate;

Adverse event records: time of occurrence, severity, management measures, and outcome;

Record of concomitant medications;

Status of informed consent form signing.

VII. Study Start and End Dates

The clinical study will commence upon receipt of the approval document from the hospital's Institutional Review Board (IRB). The study will conclude when the last study participant completes their final follow-up. A total of 60 patients are planned for enrollment, with the study scheduled to be completed by December 31, 2028.

Clinical Criteria for Suspension/Termination of the Study

The study may be suspended or terminated under the following circumstances:

1. Safety concerns: The occurrence of serious adverse events (SAEs) related to Tafolecimab at a rate significantly higher than expected;
2. The Ethics Committee or regulatory authorities require suspension or termination;
3. The dropout rate among study participants exceeds 30%, compromising statistical power;
4. The efficacy observed in the study is significantly inferior to expectations, making it impossible to achieve the study objectives;
5. Insufficient funding or resources to continue supporting the study;
6. The investigator deviates from the protocol or GCP principles, and the deviation is deemed uncorrectable following evaluation;
7. Updates to national policies or guidelines render the study no longer compliant with ethical or scientific requirements.

Any decision to suspend or terminate the study must be notified in writing to the Ethics Committee, and follow-up and data collection for enrolled patients must be properly managed.

IX. Compliance with Ethical Principles and Relevant Regulations

The conduct of this study complies with the “Measures for Ethical Review of Biomedical Research Involving Human Subjects” (2023), the “Measures for Ethical Review of Biomedical Research Involving Human Subjects” (2016),the WMA “Declaration of Helsinki” (2013), the CIOMS “International Ethical Guidelines for Biomedical Research Involving Human Subjects” (2002), and the ethical principles of Good Clinical Practice (GCP). Under the guidance of the Good Clinical Practice (GCP) guidelines, the study will be conducted using the protocol approved by the Ethics Committee and in accordance with the requirements of this protocol to ensure the scientific integrity of the study and to protect the health and rights of research participants.Prior to the start of the study, the investigator shall submit the study protocol, informed consent form, participant recruitment procedures, and other written materials to be provided to study participants to the Ethics Committee for review and approval.The principal investigator may only conduct the clinical trial after receiving written approval from the ethics committee. During the course of the trial, if there are any new amendments to the protocol, informed consent form, or other documents, written approval must be obtained again in accordance with regulations. The completion or early termination of the clinical trial must also be reported to the ethics committee.

X. Data Safety and Monitoring Plan

1. Data Recording

This study will use Case Report Forms (CRFs) to collect and manage study data in a timely, accurate, and complete manner.

2. CRF Completion and Amendments

Completion: CRF data is derived from source documents such as original medical records and laboratory test reports and must be consistent with these source documents. All observations and test results specified in the study protocol must be recorded in the CRF in a timely, accurate, complete, clear, standardized, and truthful manner; no arbitrary changes are permitted.

Amendments: If necessary, when correcting data in the CRF, the reason for the amendment must be documented as prompted by the system. The EDC system's logic validation program will perform logical checks on the entered data and flag problematic entries, allowing the Principal Investigator (PI) or data entry personnel to make corrections or provide explanations.

3. Data Entry

Investigators or dedicated data entry personnel shall enter data into the computer system for storage in accordance with the protocol requirements; dual data entry is required. Data entry personnel must verify the completeness and logical consistency of the entered clinical trial data. For data items that are questionable or inconsistent with the original medical records, they must promptly raise a query. They must also follow up with data entry personnel and investigators to resolve the query, verify the data, and correct any inconsistencies.

4. Data Processing

After the data has been checked and cleaned to ensure accuracy, it is submitted to the statistical analysts for statistical analysis in accordance with the requirements of the statistical protocol.

5. Retention of Study Records

In accordance with GCP principles, investigators should maintain all detailed original documentation regarding study participants and record information related to the study progress, medication administration, laboratory test results, safety data, and efficacy assessments in the CRF. The recorded data should be complete, timely, and clear. Original documents, medical records, and other materials should be clear, detailed, and easily identifiable by personnel involved in this clinical study.

6. To ensure the integrity, accuracy, and reliability of the data, the following measures have been implemented in this study:

A. Selection of qualified and experienced investigators;

B. Prior to the start of the study, researchers were provided with a detailed introduction to the study protocol through lectures and written materials

and jointly develop solutions for potential issues;

C. If any data are found to be questionable, they should be promptly communicated to the researchers for confirmation or correction;

D. Conducted blinded verification of the data during the statistical analysis phase. If any discrepancies were found, researchers were responsible for confirming and correcting them;

E. Establish standard operating procedures and quality control protocols for laboratory test parameters;

F. For lipid profile testing, adopt a standardized testing method to minimize measurement errors.

G. To ensure the quality of the trial, prior to the official start of the trial, the project leader (First Affiliated Hospital of Shandong First Medical University) and the principal investigators of the project team shall develop the clinical research protocol and establish relevant contingency plans and SOPs. Provide training on clinical drug trials to the relevant researchers participating in the trial.

X. Statistical Analysis Plan

1. Determination of Study Participant Sample Size

This study aims to evaluate the feasibility of the innovative dosing regimen “Tafolecimab 150 mg Q3W.” This regimen has not yet been systematically evaluated in prospective clinical studies; therefore, precise efficacy parameters (such as mean and standard deviation) comparing it to the Q2W regimen are not available in the published literature.Given the exploratory nature of this study, its objective is not to conduct confirmatory hypothesis testing, but rather to preliminarily obtain trend data on LDL-C reduction under the two dosing regimens, estimate the range of effect sizes, and provide a reference for sample size calculation in subsequent large-scale Phase III studies.Following the precedent set by exploratory studies of similar PCSK9 inhibitors—such as the Phase II dose-finding trial of alirocumab (REGN727), which used a sample size of 15–16 patients per group to successfully evaluate trends in efficacy and safety of different doses (150 mg, 200 mg,300 mg) and dosing intervals (every 2 weeks vs. every 4 weeks) in patients with heterozygous familial hypercholesterolemia. This study provided direct guidance for sample size selection in the early clinical development of PCSK9 inhibitors.According to the “Guidance on the Planning and Reporting of Data Management and Statistical Analysis in Clinical Trials of Drugs,” for exploratory trials, sample size is

typically determined based on a comprehensive assessment of factors such as feasibility, the magnitude of the drug's effect, and the objectives of the exploratory study. Julious SA also noted in *Statistical Issues in Drug Development* that, in the absence of precise prior parameters, it is reasonable and scientific to use a moderate sample size for feasibility assessment.

Taking into comprehensive consideration our center's patient recruitment capacity, study duration, and resource constraints, we set the sample size at 30 patients per group, for a total sample size of 60 patients. This approach ensures clinical feasibility while providing preliminary evidence of clinical value regarding the efficacy and safety of the Q3W dosing regimen for Tafolecimab , and offers reliable parametric support for sample size estimation in subsequent Phase III clinical trials.

2. All statistical tests in this study will use two-sided tests, with a significance level set at 0.05. That is, when the P-value is <0.05, the difference is considered statistically significant. This standard is a conventional setting in biomedical research, and no adjustment to the α level was made in this study.

3. Describe the statistical hypotheses for the primary endpoint, including the null hypothesis and the alternative hypothesis, and briefly outline the specific statistical methods and analysis software to be used.

Statistical Hypotheses: The primary outcome measure of this study is the percentage change in LDL-C from baseline at week 12 of treatment. The statistical hypotheses are as follows:

The null hypothesis (H_0) is that there is no significant difference in the primary outcome between the Tafolecimab 150 mg Q3W regimen and the 150 mg Q2W regimen; the alternative hypothesis is that there is a significant difference between the two regimens.

4. Method for Handling Missing Values

Missing values for the primary efficacy endpoint (percentage change in LDL-C from baseline at Week 12 of treatment) will be handled using the Last Observation Carried Forward (LOCF) method, i.e., replacing the missing value with the participant's most recent available follow-up observation. For missing values in other secondary efficacy and safety endpoints, no data imputation or carry-forward will be performed; analysis will be based solely on the complete data actually collected.All instances of missing data will be described in the study report.

Statistical Methods and Software: Statistical analyses will be performed using SPSS 26.0. To control for baseline confounding and selection bias resulting from clinical decision-based grouping, propensity score matching (PSM) will be used to balance the baseline

characteristics between the two groups.First, baseline variables that may influence decisions regarding dosing intervals and treatment efficacy will be systematically collected, including demographic data (age, sex, height, weight, BMI), clinical characteristics (ASCVD risk stratification, history of comorbidities, smoking history, alcohol consumption history, family history of cardiovascular disease), as well as the distance from the patient's residence to the hospital (<50 km, ≥50 km),factors that may influence physician decision-making (such as patient-reported convenience of care, treatment preferences, and the primary reasons physicians selected the Q3W regimen). The grouping variable will be treated as the dependent variable, and all of the aforementioned potential confounding variables will be treated as independent variables to calculate the propensity score for each patient.Using the nearest-neighbor matching method, a patient with the closest propensity score in the Q2W group was matched to each patient in the Q3W group at a 1:1 ratio. After matching, baseline characteristics were balanced between groups (standardized difference after matching <10%); subsequent analyses were primarily based on the matched sample. Subsequent analyses were primarily based on the matched sample.For continuous variables (e.g., percentage change in LDL-C from baseline at week 12 of treatment, percentage change in Lp(a), and changes in lipid profiles), intergroup comparisons were conducted to assess differences between the Q2W and Q3W groups at the same time points. If the data followed a normal distribution and had homogeneous variances, an independent samples t-test was used, with results expressed as "mean ± standard deviation";if the data do not meet the assumptions for parametric tests, the Mann-Whitney U test will be used, and results will be expressed as "median (interquartile range)." For within-group comparisons: changes relative to baseline before and after treatment within each group will be compared. If the pre- and post-treatment differences follow a normal distribution, a paired t-test will be used. If they do not follow a normal distribution, the Wilcoxon signed-rank test will be used.For categorical variables (e.g., LDL-C target achievement rate), between-group comparisons—specifically, comparisons of differences between the Q2W and Q3W groups at the same time point—use the chi-square test; if more than 20% of the cells have a theoretical frequency <5, or if any cell has a theoretical frequency <1, Fisher's exact test is used, and results are expressed as "number of cases (percentage)." Intra-group comparisons: To compare differences in categorical indicators among patients within the same group at different time points, the "McNemar test" is used when comparing two time points (e.g., the target achievement rates at visit points V1 and V3); for intra-group comparisons involving more

than two related time points (e.g., simultaneously comparing the target achievement rates at visit points V1, V2, and V3), Cochran’s Q test is used.

XII. Format of Research Publication

We plan to publish one related paper in an international journal in the form of an SCI-indexed article.