JACC: ASIA VOL. 3, NO. 4, 2023

ORIGINAL RESEARCH

Tafolecimab in Chinese Patients With Hypercholesterolemia (CREDIT-4)

A Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial

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ABSTRACT

BACKGROUND Tafolecimab is a novel fully human proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibody, developed for the treatment of hypercholesterolemia.

OBJECTIVES The purpose of this study was to assess the efficacy and safety of tafolecimab in Chinese patients at high or very high cardiovascular risk with hypercholesterolemia.

METHODS Patients with diagnoses of heterozygous familial hypercholesterolemia (HeFH) by the Simon Broome criteria or at high or very high cardiovascular risk with nonfamilial hypercholesterolemia, with screening low-density lipoprotein cholesterol (LDL-C) level ≥1.8 mmol/L, were randomized 2:1 to receive tafolecimab or placebo 450 mg every 4 weeks (Q4W) in the 12-week double-blind treatment period. The primary endpoint was the percent change from baseline to week 12 in LDL-C levels.

RESULTS A total of 303 patients were enrolled and received at least 1 dose of tafolecimab (n = 205) or placebo (n = 98). The least squares mean percent change in LDL-C level from baseline to week 12 was -68.9% (SE 1.4%) in the tafolecimab group and -5.8% (1.8%) in the placebo group (difference: -63.0%; [95% CI: -66.5% to -59.6%]; $P < 0.0001$). More patients treated with tafolecimab achieved ≥50% LDL-C reductions, LDL-C <1.8 mmol/L, and LDL-C <1.4 mmol/L at week 12 than did those in the placebo group (all $P < 0.0001$). Furthermore, tafolecimab markedly reduced non-HDL-C, apolipoprotein B, and lipoprotein(a) levels. During the double-blind treatment period, the most commonly reported adverse events included urinary tract infection (5.9% with tafolecimab vs 4.1% with placebo) and hyperuricemia (3.4% vs 4.1%).

CONCLUSIONS Tafolecimab was safe and showed robust lipid-lowering efficacy in Chinese patients at high or very high cardiovascular risk with hypercholesterolemia. (A Study of IBI306 in Participants With Hypercholesterolemia; NCT04709536) (JACC: Asia 2023;3:636-645) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Karol Watson, MD, PhD, served as Guest Associate Editor for this paper.

ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2023.04.011

Cardiovascular disease is the leading cause of death in China.[1] Hypercholesterolemia, characterized by elevated low-density lipoprotein cholesterol (LDL-C), is one of the major causes of cardiovascular disease.[2] The prevalence of hypercholesterolemia is relatively high, and the percentage of adults with controlled blood cholesterol is low in China.[3]

Reducing LDL-C levels is the cornerstone of hypercholesterolemia therapy for cardiovascular disease prevention. Numerous clinical trial outcomes have demonstrated that cholesterol-lowering therapy can reduce the morbidity and mortality of cardiovascular diseases.[4-6] Statins are widely used and have been proven to be effective in reducing LDL-C levels. The current guidelines for the management of dyslipidemia recommend optimizing statin therapy to achieve LDL-C goals for patients at high or very high cardiovascular risk.[7,8] Although moderate-intensity statin therapy is crucial for the attainment of optimal LDL-C goals in China, a proportion of patients at high risk or very high cardiovascular risk with hypercholesterolemia still need additional nonstatin therapy.[9-11] The additional use of ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors is recommended in populations at high or very high cardiovascular risk if statins alone are not sufficient to achieve LDL-C goals,[8] and the addition of PCSK9 to a statin regimen increases the magnitude of LDL-C lowering more than ezetimibe.[12] Although additional nonstatin therapy was recommended, >90% of Chinese patients were still given a moderate dose of statins,[13] suggesting that there is great room for the improvement of cholesterol control in Chinese patients, especially in populations at high or very high cardiovascular risk.

PCSK9 is predominantly expressed in the liver and secreted into the plasma, which interacts with LDL receptors to mediate the degradation of LDL receptors, increasing serum LDL-C concentration.[14] The 2 worldwide approved monoclonal antibodies targeting PCSK9, alirocumab and evolocumab, have demonstrated significant reductions in LDL-C levels ≤60% in Asian populations at high cardiovascular risk with hypercholesterolemia.[15,16] However, clinical evidence of PCSK9 inhibitors in Chinese patients at very high or high cardiovascular risk with hypercholesterolemia is limited. Therefore, more clinical trials are needed to generalize the efficacy and safety of PCSK9 inhibitors in this population.

Tafolecimab is a fully human IgG2 PCSK9 monoclonal antibody developed in China, with a favorable safety and efficacy profile observed in the phase 1 study.[17] Here, we conducted a randomized, placebo-controlled clinical trial, CREDIT-4 (Clinical Research of Developing PCSK9 Inhibitor as Cholesterol-lowering Therapy in Chinese Patients with Dyslipidemia-4), to evaluate the efficacy and safety of tafolecimab in Chinese patients with HeFH or at high or very high cardiovascular risk with non-FH hypercholesterolemia.

ABBREVIATIONS AND ACRONYMS

ETD = estimated treatment difference

HeFH = heterozygous familial hypercholesterolemia

LDL-C = low-density lipoprotein cholesterol

PCSK9 = proprotein convertase subtilisin/kexin type 9

METHODS

ETHICS. The study protocol was approved by each site's institutional review board or independent ethics committee. This study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. The study was registered at clinicaltrials.gov (NCT04709536).

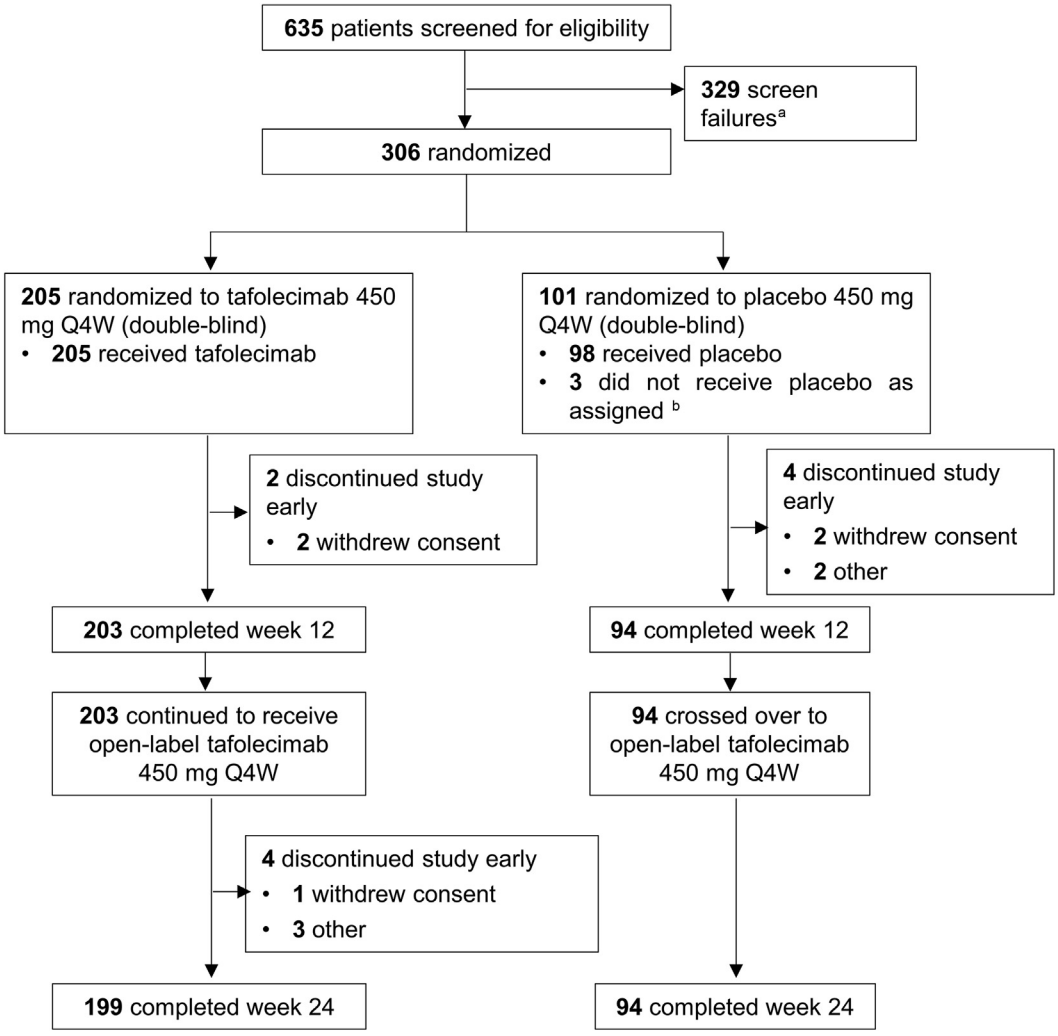
STUDY DESIGN AND PATIENTS. This was a randomized, double-blind, placebo-controlled phase 3 study conducted across 32 study centers in China. Patients (aged 18-75 years) with diagnoses of heterozygous familial hypercholesterolemia (HeFH) by the Simon Broome criteria or at high or very high cardiovascular risk with nonfamilial hypercholesterolemia, with screening LDL-C level ≥1.8 mmol/L and using stable lipid-lowering therapy for at least 4 weeks before randomization, were eligible. Patients were excluded if they had a diagnosis of homozygous familial hypercholesterolemia or had received a PCSK9 monoclonal antibody within 4 months before randomization. The full inclusion and exclusion criteria are listed in Supplemental Table 1. All patients provided written informed consent before to screening.

STUDY PROCEDURES. Eligible patients were randomized in a 2:1 ratio to receive subcutaneous tafolecimab or placebo 450 mg every 4 weeks in combination with statins in the 12-week double-blind treatment period. Randomization was implemented

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received November 16, 2022; revised manuscript received April 5, 2023, accepted April 12, 2023.

FIGURE 1 Patient Flow



[a]Main reasons for screen failure: inclusion criteria not met, exclusion criteria met, consent withdrawn. [b]2 patients withdrew consent, and 1 patient did not receive treatment because of the investigator's operation error. Q4W = every 4 weeks.

by an interactive web response system and was stratified by LDL-C levels at screening (≥ or <3.4 mmol/L) and by heterozygous familial hypercholesterolemia (yes/no). The patients, investigators, and study site personnel involved in treating and assessing patients were masked to treatment allocations.

After the 12-week double-blind treatment period, patients receiving tafolecimab continued to receive open-label tafolecimab 450 mg every 4 weeks, and patients receiving placebo crossed over to receive open-label tafolecimab 450 mg every 4 weeks for 12 weeks, followed by a 4-week safety follow-up period.

Study visits consisted of vital sign and electrocardiogram measurements, adverse events assessment, and sample collection for laboratory measurements. Study visits for assessing the primary efficacy endpoint, percent reduction from baseline in LDL-C, was at week 12, and study visits for assessing other efficacy endpoints were at weeks 2, 4, 8, 12, 16, 20, and 24.

High-density lipoprotein cholesterol (HDL-C, OSR6187, Beckman Coulter), total cholesterol

(OSR6116, Beckman Coulter), and triglycerides (OSR61118, Beckman Coulter) concentrations were measured by commercial kits on a Beckman Coulter AU600 Chemistry Analyzer. Non-HDL cholesterol (non-HDL-C) concentration was calculated by subtracting HDL-C concentration from total cholesterol concentration. Very-low-density lipoprotein cholesterol concentration was calculated by dividing the triglyceride concentration by 5 (when triglyceride was <4.52 mmol/L) or by subtracting HDL-C and LDL-C concentrations from total cholesterol concentration (when triglyceride was ≥4.52 mmol/L). Apolipoprotein A1, apolipoprotein B, and lipoprotein(a) concentrations were analyzed using an immunonephelometric assay, N Latex Reagent (OUED, OSAN and OQHL, respectively, Siemens) and BN ProSpec System (Siemens) was used for detection. Unbound PCSK9 concentrations were measured using a sandwich enzyme-linked immunosorbent assay. All lipids and PCSK9 were tested in a central laboratory (WuXi AppTec, Shanghai).

DNA extracted from blood samples of all enrolled patients was sequenced by Novogene for variants in all exons of *LDLR*, *APOB*, *PCSK9*, and *LDLRAP1* genes.

ENDPOINTS. The primary endpoint was the percent change from baseline to week 12 in LDL-C levels. Key secondary endpoints included the proportion of patients achieving ≥50% LDL-C reductions, LDL-C <1.8 mmol/L, LDL-C <1.4 mmol/L. Other secondary endpoints included the proportion of very-high-risk patients achieving LDL-C <1.4 mmol/L, the proportion of high-risk patients achieving LDL-C <1.8 mmol/L, and the percent change from baseline to week 12 in non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B, and lipoprotein(a) levels.

Safety endpoints were assessed through reported adverse events, vital signs, electrocardiograms, and laboratory results. Adverse events were coded and classified using the Medical Dictionary of Regulatory Activities (version 24.0). The severity and causality of adverse events were assessed by investigators based on prespecified criteria. Immunogenicity was assessed through the detection of antidrug antibodies and neutralizing antibodies in samples drawn at prespecified visits.

STATISTICAL ANALYSIS. A sample size of 300 patients was based on the assumption that a common SD of 40% and a dropout rate of 10% was sufficient to generate 99% power to detect ≥40% mean difference in percent reduction in LDL-C levels between the tafolecimab 450 mg every 4 weeks group and the placebo group with a *t*-test at the 0.05 2-sided significance level.

Efficacy endpoints were analyzed in the efficacy analysis population, defined as patients who received at least 1 dose of tafolecimab or placebo and had assessments at baseline and at least once after baseline. Two estimands (on-treatment and treatment-policy) were used to assess treatment efficacy, either accounting for or regardless of intercurrent events.

The on-treatment estimand assesses treatment efficacy before intercurrent events, defined as study drug discontinuation or background therapy adjustment (such as adjustment of statin dose, addition of new background therapy, or interruption of

TABLE 1 Demographic and Baseline Characteristics

	450 mg Q4W		
	Tafolecimab (n = 205)	Placebo (n = 98)	Overall (N = 303)
Age, y	56.9 ± 9.2	56.8 ± 9.4	56.8 ± 9.2
Asian	205 (100)	98 (100)	303 (100)
Male	147 (71.7)	62 (63.3)	209 (69.0)
BMI, kg/m^2	26.6 ± 4.0	26.3 ± 3.7	26.5 ± 3.9
Screening LDL-C[a]			
<3.4 mmol/L	158 (77.1)	76 (77.6)	234 (77.2)
≥3.4 mmol/L	47 (22.9)	22 (22.4)	69 (22.8)
FH classification[b]			
HeFH	25 (12.2)	13 (13.3)	38 (12.5)
Non-FH	180 (87.8)	85 (86.7)	265 (87.5)
Cardiovascular risk[c]			
High risk	54 (26.3)	23 (23.5)	77 (25.4)
Very high risk	150 (73.2)	75 (76.5)	225 (74.3)
Missing[d]	1 (0.5)	0	1 (0.3)
Concomitant disease			
Cardiovascular disease	105 (51.2)	52 (53.1)	157 (51.8)
Cerebrovascular disease	44 (21.5)	16 (16.3)	60 (19.8)
Type 2 diabetes	68 (33.2)	36 (36.7)	104 (34.3)
Chronic kidney disease	70 (34.1)	31 (31.6)	101 (33.3)
Mixed dyslipidemia	113 (55.1)	57 (58.2)	170 (56.1)
Lipid-regulating medication			
Moderate-dose statin	198 (96.6)	97 (99.0)	295 (97.4)
High-dose statin[e]	7 (3.4)	1 (1.0)	8 (2.6)
Ezetimibe	23 (11.2)	8 (8.2)	31 (10.2)
Lipid parameters			
LDL-C, mmol/L	3.05 ± 0.95	3.10 ± 0.78	3.06 ± 0.90
Apolipoprotein B, g/L	0.90 ± 0.25	0.88 ± 0.22	0.89 ± 0.24
Apolipoprotein B/apolipoprotein A1	0.64 ± 0.23	0.63 ± 0.18	0.63 ± 0.21
Lipoprotein(a), g/L	0.15 (0.08-0.33)	0.16 (0.08-0.34)	0.16 (0.08-0.34)
Non-HDL-C, mmol/L	3.49 ± 1.10	3.52 ± 0.93	3.50 ± 1.05

Values are mean ± SD, median (IQR), or n (%). [a]Randomization stratification factors. [b]By Simon Broome diagnostic criteria. [c]Refer to ESC guideline for criteria for high/very high CV risk. [d]After the patient successfully quit smoking, the patient was no longer characterized to have a high CV risk, and after discussion with the lead PI, the patient was included in the PPS. [e]Defined as atorvastatin 40-80 mg or rosuvastatin 20 mg.

BMI = body mass index; CV = cardiovascular; HDL-C = high-density lipoprotein cholesterol; FH = familial hypercholesterolemia; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; PI = principal investigator; PPS = per protocol set; Q4W = every 4 weeks.

TABLE 2 Main Efficacy Endpoints at Week 12 (On-Treatment Estimand)

	450 mg Q4W		
	Tafolecimab (n = 201)	Placebo (n = 98)	ETD versus placebo
LDL-C			
Percent CFB to week 12 (%)[a]	−68.9 ± 1.4	−5.8 ± 1.8	−63.0 (−66.5 to −59.6)
CFB (mmol/L)	−2.10 ± 0.05	−0.17 ± 0.06	−1.93 (−2.05 to −1.81)
≥50% LDL-C reduction at week 12[a]	182 (90.5)	2 (2.0)	88.6 (83.7-93.5)
LDL-C <1.8 mmol/L at week 12[a]	193 (96.0)	3 (3.1)	93.0 (88.6-97.3)
LDL-C <1.4 mmol/L at week 12[a]	174 (86.6)	1 (1.0)	85.8 (80.7-90.8)
Non-HDL-C			
Percent CFB to week 12 (%)	−70.5 ± 1.4	−6.6 ± 1.8	−63.9 (−67.5 to −60.3)
CFB (mmol/L)	−2.46 ± 0.06	−0.24 ± 0.07	−2.22 (−2.35 to −2.08)
Apolipoprotein B			
Percent CFB to week 12 (%)	−61.4 ± 1.3	−2.45 ± 1.6	−59.0 (−62.1 to −55.8)
CFB (g/L)	−0.56 ± 0.01	−0.04 ± 0.02	−0.52 (−0.55 to −0.49)
Apolipoprotein B/apolipoprotein A1			
Percent CFB to week 12 (%)	−65.1 ± 1.2	−5.25 ± 1.5	−59.8 (−62.8 to −56.8)
CFB	−0.42 ± 0.01	−0.04 ± 0.01	−0.38 (−0.40 to −0.35)
Lipoprotein(a)			
Percent CFB to week 12 (%)	−45.4 ± 3.1	−11.5 ± 3.9	−33.9 (−42.2 to −25.7)
CFB (g/L)	−0.11 ± 0.01	−0.03 ± 0.01	−0.08 (−0.10 to −0.06)

Values are least squares mean ± SE for CFB, and least squares mean (95% CI) for ETD. n (%) for proportion of patients. [a]Controlled for type I error ($\alpha = 0.05$).

CFB = change from baseline; ETD = estimated treatment difference; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Q4W = every 4 weeks.

background therapy). For continuous endpoints, a mixed effect model with a repeated measures model was used. The model included fixed categorical effects of treatment group, visit, treatment-by-visit interaction, and randomization stratification factors, as well as the continuous fixed covariates of baseline LDL-C and baseline LDL-C value-by-visit interaction and ran with an unstructured covariance matrix. For categorical endpoints, the Clopper-Pearson method was used for within-group calculation of CIs, and the Mantel-Haenszel method stratified on randomization stratification factors was used for between-group calculation of CIs and statistical testing, and patients without any available assessment at week 12 were imputed using the last observation carried forward method.

The treatment policy estimand assesses treatment efficacy regardless of any intercurrent event. For continuous endpoints, a pattern-mixture model method was used to impute different reasons for missing data, and analysis of covariance was used to analyze imputed data. For categorical endpoints, statistical testing methods were the same as those of the on-treatment estimand except that patients without any available assessment at week 12 were treated as nonresponders.

The primary endpoint (the percent change from baseline to week 12 in LDL-C levels) and key secondary endpoints (proportion of patients achieving ≥50% reduction in LDL-C level and proportion of patients with LDL-C level <1.8 mmol/L and <1.4 mmol/L at week 12) were assessed by both on-treatment and treatment policy estimands and controlled for type I error. Other secondary efficacy endpoints at week 12 were assessed by on-treatment estimand.

Safety analyses were performed on the safety analysis population, defined as all patients who received at least 1 dose of tafolecimab or placebo. Data from the safety analysis (adverse events, laboratory findings, and vital signs) were descriptively summarized.

All statistical analyses were performed with SAS 9.4.

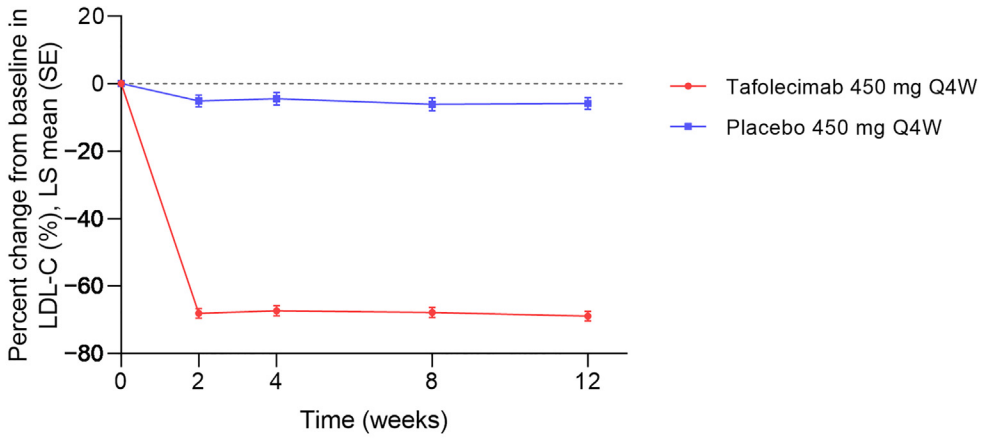
RESULTS

PATIENTS. This study was conducted across 32 study centers in China between February 2021 and January 2022. Of 635 patients screened, 306 were randomized. Of the 303 patients who received at least 1 dose of tafolecimab (n = 205) or placebo (n = 98) during the double-blind treatment period, 297 patients (98.0%) completed the double-blind treatment and received open-label tafolecimab treatment. A total of 293 patients completed the week 24 treatment (Figure 1). A total of 303 patients were included in the safety analysis population, and 301 patients were included in the efficacy analysis population.

The patients' demographic and baseline characteristics were generally balanced between treatment groups (Table 1). The mean age of the patients was 56.8 years, and 69.0% were men; 51.8% had concomitant cardiovascular disease, and 19.8% had concomitant cerebrovascular disease. Overall, 38 patients (12.5%) had HeFH, and the remaining 265 patients (87.5%) were classified as having nonfamilial hypercholesterolemia; 74.3% were at very high cardiovascular risk. At baseline, the mean LDL-C level was 3.06 mmol/L, and the majority of the patients (97.4%) were taking moderate-dose statins, with 31 (10.2%) receiving ezetimibe in addition to statin therapy.

EFFICACY. Tafolecimab treatment resulted in a robust and durable decrease in LDL-C levels (Table 2, Figure 2, Supplemental Figure 1). For the on-treatment estimand, the least squares mean percent change in LDL-C level from baseline to week 12 was -68.9% (SE 1.4%) in the tafolecimab group and -5.8% (1.8%) in the placebo group (estimated treatment difference [ETD]: -63.0% [95% CI: -66.5% to -59.6%], $P < 0.0001$) (Table 2). For the treatment-policy

FIGURE 2 **Percent Change From Baseline in LDL-C Levels Over 12 Weeks**



No. of Patients

Tafolecimab	201	199	200	196	193
Placebo	98	95	97	90	88

On-treatment estimand. LDL-C = low-density lipoprotein cholesterol; LS = least squares; Q4W = every 4 weeks; SE = standard error.

estimand, the least squares mean percent change in LDL-C level from baseline to week 12 was -67.9% (SE 1.5%) in the tafolecimab group and -4.9% (1.9%) in the placebo group (ETD: −63.0% [95% CI: −66.4% to -59.6%], $P < 0.0001$) (Supplemental Table 2). The reduction in LDL-C levels in the tafolecimab group was maintained through week 24 (Supplemental Table 3, Supplemental Figure 2). Moreover, the LDL-C-lowering efficacy of tafolecimab was consistent across most prespecified subgroups and was not related to sex, BMI, baseline LDL-C levels, or the presence of concomitant diseases (cardiovascular disease, cerebrovascular disease, type 2 diabetes, chronic kidney disease, and mixed dyslipidemia) (Supplemental Figure 3).

Significantly more patients receiving tafolecimab achieved ≥50% reduction from baseline to week 12 in LDL-C levels, LDL-C <1.8 mmol/L and LDL-C <1.4 mmol/L at week 12, compared with those receiving placebo ($P < 0.0001$ for all comparisons vs placebo) (**Table 2**, Supplemental Table 2, Supplemental Figure 4). Moreover, in the very-high-risk population, LDL-C <1.4 mmol/L was achieved in 128 patients (87.1%) receiving tafolecimab (n = 147) compared with 1 patient (1.3%) receiving placebo (n = 75). In the high-risk population, LDL-C <1.8 mmol/L was achieved in 50 patients (94.3%) receiving tafolecimab (n = 53) compared with none in patients receiving placebo (n = 23).

Reductions in LDL-C were accompanied by improvement in other lipids, which were achieved at week 12 and maintained through week 24 in the tafolecimab group (**Table 2**, Supplemental Table 3, Supplemental Figure 5). Consistent with LDL-C, tafolecimab treatment led to a significant reduction from baseline in non-HDL-C, total cholesterol, and apolipoprotein B at week 12, (on-treatment estimand, $P < 0.0001$ for all comparisons vs placebo). Of note, the least squares mean percent change from baseline to week 12 in lipoprotein(a) levels was −45.4% (SE 3.1%) in the tafolecimab group compared with −11.5% (3.9%) in the placebo group (ETD: −33.9% [95% CI: −42.2% to −25.7%], on-treatment estimand, $P < 0.0001$). Tafolecimab also resulted in approximately 10% reductions of very-low-density lipoprotein and triglycerides at week 12, similar to other PCSK9 inhibitors; the declines were much less prominent than that of LDL-C.

SAFETY. Tafolecimab was well tolerated and showed an overall favorable safety profile (**Table 3**). During the double-blind treatment period, the incidence of adverse events was lower in the tafolecimab group than in the placebo group (41.5% with tafolecimab vs 54.1% with placebo). The most commonly reported adverse events in the tafolecimab group were urinary tract infection (5.9% vs 4.1%) and hyperuricemia (3.4% vs 4.1%). One patient receiving tafolecimab reported pruritus that was mild in severity but led to discontinuation of the study drug during the double-blind treatment period. During the double-blind treatment period, serious adverse events of urinary tract infection, pneumonia, unstable angina, angina

TABLE 3 TEAE and Laboratory Abnormalities in the Double-Blind Treatment Period

	450 mg Q4W	
	Tafolecimab (n = 205)	Placebo (n = 98)
Adverse events		
Any TEAE	85 (41.5)	53 (54.1)
TESAE	5 (2.4)	4 (4.1)
Leading to treatment discontinuation	1 (0.5)	1 (1.0)
Deaths	0	0
Adverse events >1% of patients receiving tafolecimab		
Urinary tract infection	12 (5.9)	4 (4.1)
Hyperuricemia	7 (3.4)	4 (4.1)
Upper respiratory tract infection	6 (2.9)	3 (3.1)
Toothache	6 (2.9)	1 (1.0)
Weight decreased	5 (2.4)	2 (2.0)
Arthralgia	5 (2.4)	0
Hepatic function abnormal	3 (1.5)	2 (2.0)
Protein urine present	3 (1.5)	1 (1.0)
Blood uric acid increased	3 (1.5)	0
Adverse events of special interest	6 (2.9)	5 (5.1)
Hypersensitivity[a]	2 (1.0)	1 (1.0)
Injection site reaction[b]	2 (1.0)	1 (1.0)
Alanine aminotransferase increased[c]	0	0
Liver damage[d]	0	0
Muscle events[e]	2 (1.0)	3 (3.1)
Laboratory results		
n	204	98
AST >3× ULN (any post-baseline value)	0	0
Creatine kinase >3 × ULN (any post-baseline value)	0	2 (2.0)
Total bilirubin >2 × ULN (any post-baseline value)	1 (0.5)	0

Values are n (%). [a]Acute onset within minutes to hours: cutaneous and/or mucosal symptoms (angioedema, urticaria, eczema), respiratory symptoms (dyspnea, wheezing, bronchospasm), hypotension (SBP <90 mm Hg or >30% decrease from baseline), [b]Symptoms such as swelling, flushing, ecchymosis, pruritus, induration, pain at the injection site. [c]ALT 3 × ULN if baseline was normal; ALT >2 × baseline if baseline >ULN. [d]Refer to the 2015 Chinese Society of Hepatology guideline for the basic conditions and severity grading of DILI. [e]Muscle pain, muscle aches, muscle stiffness, muscle tenderness, muscle cramps, muscle weakness, or flulike symptoms.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; DILI = drug-induced liver injury; Q4W = every 4 weeks; TEAE = treatment-emergent adverse events; ULN = upper limit of normal.

pectoris, and edema were reported in 1 (0.5%) patient each in the tafolecimab group, all of which were judged by the investigator to be unrelated to the study drug. One patient in the tafolecimab group experienced a severe serious adverse event of unstable angina, but the dose remained unchanged and the patient fully recovered afterward. Except for the severe serious adverse event of unstable angina reported in 1 patient, all other serious treatment-emergent adverse events were mild or moderate in severity.

The incidence of the adverse events of special interest, predefined as hypersensitivity, injection site reactions, increased alanine aminotransferase, liver damage, and muscle-related adverse events, were low in both groups (2.9% with tafolecimab vs 5.1% with placebo), all of which were mild to moderate in severity. The incidence of laboratory abnormalities was rare; only 1 patient in the tafolecimab group had total bilirubin elevation >2 times the upper limit of normal (Table 3).

In the double-blind treatment period, 4 patients (2.0%) in the tafolecimab group and none in the placebo group experienced anti-drug antibodies. Neutralizing antibody was negative in both groups.

PCSK9 LEVEL. The maximum reduction of −96.36% in PCSK9 level was observed 8 hours after the first dose of tafolecimab. Furthermore, the PSCK9 level remained approximately 80% below baseline in the tafolecimab group during the double-blind period (Supplemental Figure 6).

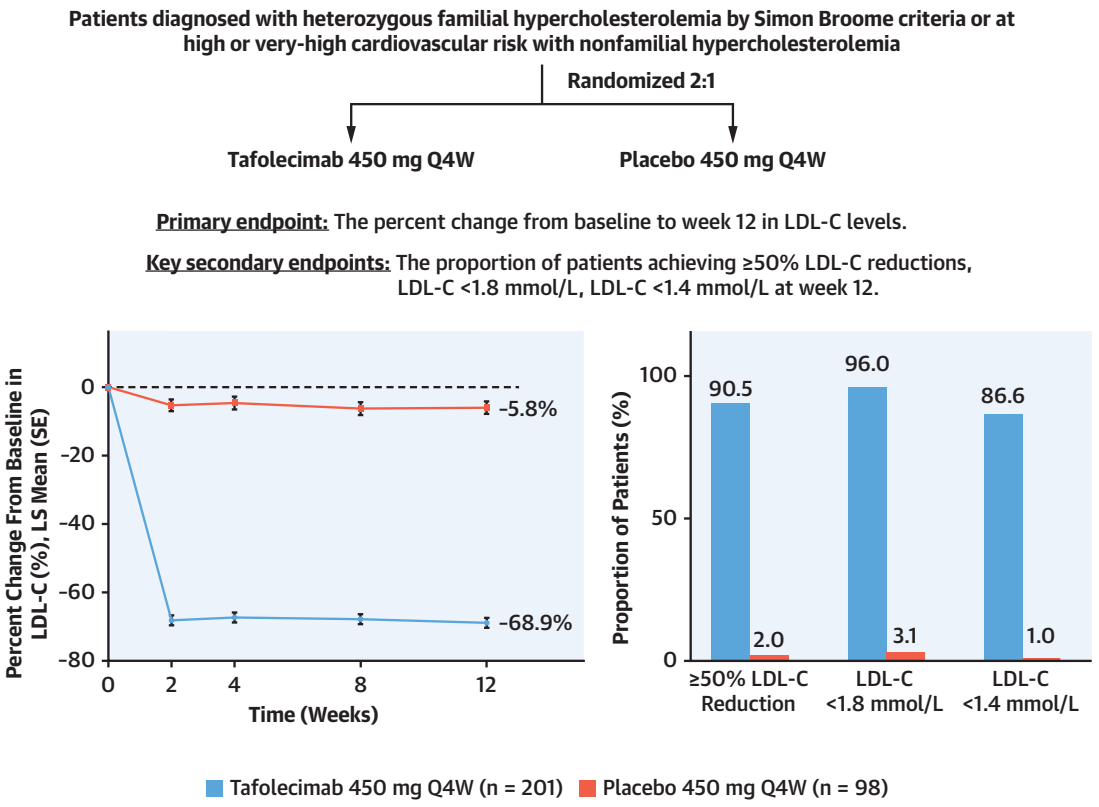
DISCUSSION

The results of this large-scale randomized, placebo-controlled clinical trial demonstrated statistically significant reductions in LDL-C as well as other lipid levels after treatment with tafolecimab every 4 weeks in Chinese patients at high or very high cardiovascular risk with hypercholesterolemia, thus supporting the use of tafolecimab in Chinese patients with HeFH or at high or very high cardiovascular risk with hypercholesterolemia.

In patients at high or very high cardiovascular risk, ezetimibe or PCSK9 inhibitors add-on to statin combination therapy proved to be an effective treatment that led to additional LDL-C lowering.[12] On maximally tolerated statin dose, LDL-C lowering induced by alirocumab is more prominent than that induced by ezetimibe in Chinese patients with hyperlipidemia at high cardiovascular risk.[18] However, clinical evidence of the safety and efficacy of PCSK9 inhibitors in Chinese patients is limited. We conducted a clinical study of a novel PCSK9 inhibitor, tafolecimab, in Chinese patients at high or very high cardiovascular risk with hypercholesterolemia.

The LDL-C-lowering effect of tafolecimab was comparable with those of other approved PCSK9 antibodies observed in the Asian populations. In the ODYSSEY Japan study, alirocumab 75 mg every 2 weeks resulted in a -62.5% change in LDL-C levels from baseline to week 24 in patients with HeFH or at high risk with hypercholesterolemia.[15] In the YUKAWA study, evolocumab 140 mg every 2 weeks and 420 mg every month resulted in changes of −68.6% and −63.9% in LDL-C levels from baseline to week 12, respectively, in hypercholesterolemic, statin-treated Japanese patients at high cardiovascular risk.[16] In our study, the mean percent changes in LDL-C levels were -68.9% and

CENTRAL ILLUSTRATION **Significant Efficacy and Favorable Safety of Tafolecimab**



Tafolecimab substantially reduced LDL-C levels by approximately 70%, and significantly more patients achieved LDL-C <1.8 mmol/L, LDL-C <1.4 mmol/L, and ≥50% reductions in LDL-C levels at week 12. The well-tolerated safety profile was observed in the trial. LDL-C = low-density lipoprotein cholesterol; LS = least squares; Q4W = every 4 weeks; SE = standard error.

-65.7% at week 12 and week 24, respectively, in the group receiving tafolecimab 450 mg every 4 weeks.. In addition, the majority of patients at high or very high cardiovascular risk with hypercholesterolemia achieved the LDL-C goals through additional tafolecimab therapy.

The LDL-C-lowering efficacy of tafolecimab was consistent among patients with HeFH and nonfamilial hypercholesterolemia, and among patients with different concomitant diseases, suggesting the robustness and broad applicability of tabolecimab as a potent PCSK9 inhibitor.

Concurrent reductions in levels of LDL-C and other lipids were well documented with the use of PCSK9 inhibitors (evolocumab and alirocumab) in patients with high and very high cardiovascular risk.[19] Consistently, in addition to LDL-C, rapid and prominent reductions in total cholesterol, non-HDL-C, ApoB, and lipoprotein(a) levels were also observed in our study. Numerous studies have confirmed that total cholesterol level is causally related to atherosclerotic cardiovascular disease.[20] Non-HDL-C and ApoB levels are highly correlated with LDL-C levels, increasing the risk of atherosclerotic cardiovascular disease events.[21] Lipoprotein(a) concentrations were elevated in patients with cardiovascular disease. Cardiovascular outcome trials of alirocumab supported the hypothesis that lowering lipoprotein(a) has the potential to reduce cardiovascular events.[22,23] With comprehensive improvements in lipid levels, tafolecimab may offer enhanced cardiovascular benefits.

Tafolecimab was well tolerated and demonstrated a favorable risk-to-benefit profile, with a safety profile similar to those identified in other PCSK9 inhibitors. No clinically relevant safety issues emerged with the administration of tafolecimab, and the incidence of adverse events was similar between the tafolecimab group and the placebo group. The majority of serious adverse events were mild in severity, and all were judged to be unrelated to the study drug.

STUDY LIMITATIONS. Although the open-label tafolecimab treatment demonstrated sustained efficacy up to week 24, the relatively short duration of the 12-week double-blind treatment period restrains the evaluation of long-term efficacy and safety of tafolecimab in Chinese patients with high or very high cardiovascular risk. Whereas the lipid-lowering effects of tafolecimab are evidenced in this study, the effects of tafolecimab on cardiovascular outcomes warrant further investigation. Furthermore, although about 300 patients were enrolled in our study, it is insufficient to generalize for the Chinese population with high or very high cardiovascular risk. A larger sample size is required to evaluate the efficacy and safety of tafolecimab, and more data will be revealed in other phase 3 studies of tafolecimab.

CONCLUSIONS

In Chinese patients with HeFH or non-FH at high or very high cardiovascular risk, tafolecimab dosed at 450 mg every 4 weeks was safe and demonstrated significant and durable lipid-lowering efficacy (**Central Illustration**). Tafolecimab substantially reduced LDL-C levels by approximately 70%, and significantly more patients achieved LDL-C <1.8 mmol/L, LDL-C <1.4 mmol/L, and ≥50% reductions in LDL-C levels at week 12. The short-term efficacy and safety profile of tafolecimab was comparable with those of other marketed PCSK9 inhibitors. With its robust lipid-lowering efficacy and well-tolerated safety profile, tafolecimab may provide these patients with a novel treatment option.

ACKNOWLEDGMENTS The authors thank all patients, investigators, and study site staff who were involved in the conduct of this trial.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This study was sponsored by Innovent Biologics, Inc. The sponsor was involved in the study design, data collection, data review, data analysis, and drafting of the manuscript. Drs Huo, Qi, D. Liu, Qu, B. Chen, Meng, Zhu, Lipeng Li, Wang, C. Liu, Zheng, Lian, Yin, Lv, Lu, and X. Chen have reported personal fees from Innovent Biologics, Inc, during the conduct of the study. Drs Xue, An, H. Li, Deng, Li Li, and Qian have been employees of Innovent Biologics, Inc.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: A proportion of Chinese patients at high or very high cardiovascular risk with hypercholesterolemia need additional non-statin therapy to achieve LDL-C goals. PCSK9 inhibitor significantly reduced LDL-C levels and was recommended in populations at high or very high cardiovascular risk with hypercholesterolemia. However, clinical evidence of PCSK9 inhibitors in this Chinese population is limited. Tafolecimab is a fully human IgG2 PCSK9 monoclonal antibody developed in China, and we performed this randomized, placebo-controlled clinical trial to evaluate the efficacy and safety of tafolecimab in Chinese patients at high or very high cardiovascular risk with hypercholesterolemia, our results showed tafolecimab dosed at 450 mg every 4 weeks was safe and demonstrated significant and durable lipid-lowering efficacy, may provide a novel treatment option for these patients.

TRANSLATIONAL OUTLOOK: The double-blind treatment period is relatively short in this study. Further, Larger sample sizes and longer double-blind treatment period studies are needed to confirm the long-term efficacy and safety of tafolecimab in the Chinese population.

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KEY WORDS coronary artery disease, hypercholesterolemia, low-density lipoprotein cholesterol, tafolecimab

APPENDIX For supplemental tables and figures, please see the online version of this paper.