Tafolecimab in Chinese patients with non-familial hypercholesterolemia (CREDIT-1): a 48-week randomized, double-blind, placebo-controlled phase 3 trial

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The Lancet Regional Health - Western Pacific 2023;41: 100907

Published Online xxx https://doi.org/10.1016/j.lanwpc.2023.100907

Summary

Background Tafolecimab, a fully human proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibody developed for the treatment of hypercholesterolemia, demonstrated robust lipid-lowering efficacy and favorable safety in previous short-term studies. We aimed to assess the long-term efficacy and safety of tafolecimab in Chinese non-familial hypercholesterolemia (non-FH) patients.

Methods Non-FH patients at high or very-high cardiovascular risk with screening low-density lipoprotein cholesterol (LDL-C) level ≥1.8 mmol/L or non-FH patients with screening LDL-C level ≥3.4 mmol/L and on stable lipid-lowering therapy for at least 4 weeks, were randomized in a 2:2:1:1 ratio to receive subcutaneous tafolecimab 450 mg Q4W, tafolecimab 600 mg Q6W, placebo 450 mg Q4W, or placebo 600 mg Q6W, respectively, in the 48-week double-blind treatment period. The primary endpoint was the percent change from baseline to week 48 in LDL-C levels.

Findings A total of 618 patients were randomized and 614 patients received at least one dose of tafolecimab (n = 411) or placebo (n = 203). At week 48, tafolecimab induced significant reductions in LDL-C levels (treatment differences versus placebo [on-treatment estimand]: −65.0% [97.5% CI: −70.2%, −59.9%] for 450 mg Q4W; −57.3% [97.5% CI: −64.0%, −50.7%] for 600 mg Q6W; both $P < 0.0001$). Significantly more patients treated with tafolecimab achieved ≥50% LDL-C reductions, LDL-C < 1.8 mmol/L, and LDL-C < 1.4 mmol/L than placebo group at both dose regimens (all $P < 0.0001$). Furthermore, tafolecimab significantly reduced non-HDL-C, apolipoprotein B, and lipoprotein(a) levels. The most commonly-reported treatment emergent adverse events in the tafolecimab groups included upper respiratory infection, urinary tract infection and hyperuricemia.

Interpretation Tafolecimab dosed at 450 mg Q4W and 600 mg Q6W was safe and showed superior lipid-lowering efficacy versus placebo, providing a novel treatment option for Chinese hypercholesterolemia patients.

Funding This study was sponsored by Innovent Biologics, Inc.

Abbreviations: PCSK9, Proprotein convertase subtilisin/kexin type 9; Non-FH, Non-familial hypercholesterolemia; LDL-C, Low-density lipoprotein cholesterol; Lipoprotein(a), Lp(a); ETD, Estimated treatment difference; Q4W, Every 4 weeks; Q6W, Every 6 weeks

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Keywords: Cardiovascular disease; Hypercholesterolemia; Low-density lipoprotein cholesterol; Tafolecimab

Research in context

Evidence before this study

During the planning phase for the CREDIT-1 trial, we searched PubMed from database inception to Dec 1, 2019, for pre-clinical and clinical research published using the search terms"Hypercholesterolemia","Cardiovascular disease", "Low-density lipoprotein cholesterol", "Proprotein convertase subtilisin/kexin type 9". Hypercholesterolemia is one of the major causes of cardiovascular disease. Previous studies demonstrated monoclonal antibodies targeting PCSK9 induced significant reductions in LDL-C levels and the incidence of cardiovascular events in patients with hypercholesterolemia, but more clinical evidence of PCSK9 monoclonal antibodies is needed to generalize applicability in the Chinese population. Tafolecimab, a fully human proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibody developed for the treatment of hypercholesterolemia, demonstrated robust lipid-lowering efficacy and favorable safety in previous short-term studies.

Added value of this study

To our knowledge, this is the first study of PCSK9 monoclonal antibody conducted in China to access long-term efficacy and safety and to explore a long-interval dosing regimen from a large population. Patients at high or very high cardiovascular risk with non-familial hypercholesterolemia, with screening LDL-C level ≥1.8 mmol/L or non-familial hypercholesterolemia patients with screening LDL-C level ≥3.4 mmol/L were enrolled in this study. We found at week 48, the mean difference in percent reduction in LDL-C levels between the tafolecimab 450 mg Q4W group and placebo 450 mg Q4W group was −65.0% [97.5% CI: −70.2%, −59.9%], $P < 0.0001$; the mean difference in percent reduction in LDL-C levels between the tafolecimab 600 mg Q6W group and placebo 600 mg Q6W group was −57.3% [97.5% CI: −64.0%, −50.7%], $P < 0.0001$. Significantly 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 48 than the corresponding placebo group at both dose regimens (all $P < 0.0001$).

Implications of all the available evidence

In Chinese patients with non-familial hypercholesterolemia, tafolecimab dosed at both 450 mg Q4W and 600 mg Q6W was safe and demonstrated clinically meaningful lipid-lowering efficacy. Tafolecimab may provide a novel treatment option for Chinese patients with hypercholesterolemia.

Introduction

Hypercholesterolemia, characterized by elevated low-density lipoprotein cholesterol (LDL-C), is one of the major causes of cardiovascular disease.[1] LDL-C lowering is the cornerstone therapy and has proved to be effective in the prevention of cardiovascular events in patients with hypercholesterolemia.[2]

The result of a mega screening project revealed that one seventh of Chinese adults are at high or very high atherosclerotic vascular disease (ASCVD) risk and one sixth require lipid-lowering therapies.[3] Guidelines in China recommended moderate-intensity statins as the mainstay treatment, but only a fraction of patients at high or very high cardiovascular risk achieved targeted LDL-C levels with statins.[3–5] Additional use of ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors was recommended for patients who failed to achieve LDL-C goals by statins alone.[6,7] The two approved monoclonal antibodies (mabs) targeting PCSK9, alirocumab and evolocumab, have demonstrated significant reductions in LDL-C levels and the incidence of cardiovascular events in patients with hypercholesterolemia.[8–11] However, the clinical data of these two mabs are mainly based on western population and the clinical evidence of PCSK9 mabs in Chinese patients with hypercholesterolemia is limited. Thus, more clinical evidence of PCSK9 mabs are needed to generalize its applicability in Chinese population.

Patient adherence is important for sustained reductions in LDL-C levels with lipid-lowering therapies in clinical practice. Poor adherence of patients at high or very high cardiovascular risk is associated with worse cardiovascular outcomes.[12] Patient adherence is affected by dose frequency,[13] thus less frequent dosing might improve the adherence rate, resulting in long-term cardiovascular benefits to patients at high or very high cardiovascular risk. Subcutaneous injection interval of approved PCSK9 mabs is every 2 or 4 weeks, necessitating the exploration of longer dose intervals.

Tafolecimab is a fully human IgG2 PCSK9 mab developed in China, with a favorable safety and efficacy profile observed in patients with heterozygous familial hypercholesterolemia (HeFH) (CREDIT-2)[14] and patients at high or very high cardiovascular risk with non-FH or HeFH (CREDIT-4).[15] Here, we conducted a randomized, placebo-controlled clinical trial, CREDIT-1 (**C**linical **Re**search of **D**eveloping PCSK9 **I**nhibitor as Cholesterol-lowering **T**herapy in Chinese Patients with Dyslipidemia-**1**), to evaluate the long-term efficacy and safety of tafolecimab in Chinese patients with non-FH.

Methods

Study design

This was a randomized, double-blind, placebo-controlled phase 3 study conducted from April 2020 to March 2022 across 64 study centers in China. This study included a 4-week screening period, 48-week treatment period and a 4-week safety follow-up period.

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 (NCT04289285).

Participants

Patients (aged 18–75 years) at high or very high cardiovascular risk (refer to ESC guidelines for criteria) with non-FH, with screening LDL-C level ≥1.8 mmol/L or non-FH patients with screening LDL-C level ≥3.4 mmol/L and on stable lipid-lowering therapy for at least 4 weeks before randomization were eligible. Patients were excluded if they had been diagnosed with familial hypercholesterolemia, or received tafolecimab or other PCSK9 inhibitors. The full inclusion and exclusion criteria were listed in Supplemental Table S1. During the study, patients should remain on a stable dose of moderate or high-intensity statins (except for those intolerant to statins) with or without ezetimibe. Written informed consent was obtained from all study patients.

Randomization and masking

Eligible patients were randomized in a 2:2:1:1 ratio to receive subcutaneous tafolecimab 450 mg Q4W, tafolecimab 600 mg Q6W, placebo 450 mg Q4W, or placebo 600 mg Q6W, respectively, in the 48-week double-blind treatment period. The study drugs (tafolecimab or placebo) were given via autoinjector by clinical staff at the study site up to week 24. After week 24, the patients could choose to self-inject the study drugs under the guidance of clinical staff.

Randomization was implemented by an interactive web response system and was stratified by LDL-C levels at screening (≥ or <3.4 mmol/L) and by ezetimibe use (yes/no) at baseline. Patients, investigators, and study site personnel involved in treating and assessing patients were masked to the study treatment allocations.

Procedures

LDL-C (OSR6183, Beckman Coulter), 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. Apolipoprotein A1, Apolipoprotein B and lipoprotein(a) (Lp(a)) concentrations were analyzed using an immunonephelometric assay, N Latex Reagent (OUED, OSAN and OQHL, respectively, Siemens) and BN ProSpec System (Siemens) were 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).

Outcomes

The primary endpoint was the percent change from baseline to week 48 in LDL-C levels. Key secondary endpoints included the percent change from baseline to week 12 or 24 in LDL-C levels, the proportion of patients achieving ≥50% LDL-C reductions, LDL-C < 1.8 mmol/L, LDL-C < 1.4 mmol/L at week 12, 24, and 48. Other secondary endpoints included the percent change from baseline to week 48 in non-HDL-C, apolipoprotein B, Lp(a) levels and Apolipoprotein B/Apolipoprotein A1 ratio, the proportion of patients achieving ≥30% or ≥50% Lp(a) reductions at week 48, the proportion of patients with decreased LDL-C and Lp(a) at week 48.

Safety endpoints were assessed through reported adverse events (AEs), vital signs, electrocardiogram, and laboratory results. AEs were coded and classified using the Medical Dictionary of Regulatory Activities (version 24.0). The severity and causality of AEs were assessed by investigators based on pre-specified criteria. Immunogenicity was assessed through the detection of anti-drug antibodies (ADA) and neutralizing antibodies (NAb).

Statistical analysis

A sample size of 600 patients (300 for each dose regimen) was based on the assumption that a common standard deviation of 30% and a dropout rate of 10% was sufficient to generate 99% power to detect ≥30% mean difference in percent reduction in LDL-C levels between the tafolecimab group and the corresponding placebo group with overall type I error of 0.05 (type I error for each t-test controlled at 0.025 for each dose group).

Efficacy endpoints were analyzed in the efficacy analysis population, defined as patients who received at least one dose of tafolecimab or placebo and had baseline and at least one post-baseline LDL-C assessment. Two estimands (on-treatment and treatment-policy) were used to assess treatment efficacy from different perspectives and accounted for intercurrent events differently. Intercurrent events included premature study drug discontinuation or background therapy adjustment (such as adjustment of statin dose, the addition of new background therapy, and interruption of background therapy) (Supplemental Table S2).

The on-treatment estimand aims to evaluate the efficacy by considering the impact of intercurrent events, reflecting the efficacy before the occurrence of intercurrent events. For continuous endpoints, a mixed effect model with repeated measures (MMRM) 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 CI calculation and the Mantel-Haenszel method stratified on randomization stratification factors was used for between-group CI calculation and statistical testing, and patients without any available assessment at week 12, 24, and 48 were imputed using the last observation carried forward method.

The treatment policy estimand aims to evaluate the efficacy without considering the impacts of any intercurrent events, reflecting the clinical practice of target population, giving a real-world understanding of the use of a new product. For continuous endpoints, pattern-mixture model method (PMM) was used to impute for missing data and analysis of covariance (ANCOVA) was used to analyze imputed data. For categorical endpoints, statistical testing methods were the same as those of the on-treatment estimand. Additionally, the absence of LDL-C results at corresponding time points (weeks 12, 24, and 48) would be considered as no response.

The primary endpoint (the percent change from baseline to week 48 in LDL-C levels) and key secondary endpoints (the percent change from baseline to week 12 or 24 in LDL-C levels, the 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, 24, and 48) were assessed by both on-treatment and treatment policy estimands and controlled for type I error. Other secondary efficacy endpoints were assessed by on-treatment estimand.

Safety analyses were done on the safety analysis population, defined as all patients who received at least one dose of tafolecimab or placebo. AEs were descriptively summarized.

All statistical analyses were performed with SAS 9.4.

Role of the funding source

This study sponsored by Innovent Biologics, Inc. The funding was used for study design, data collection, data analysis, and data interpretation. All authors verified that this study was done according to the protocol and was attested for data accuracy and completeness. All authors had full access to all the data in the study, contributed to the writing and reviewing of the manuscript, and approved the final submitted version. The corresponding author had final responsibility for the decision to submit for publication.

Results

Participants

Of 1145 patients screened, 618 were randomized. Of the 614 patients who received at least one dose of tafolecimab (n = 411) or placebo (n = 203) during the study, 46 patients (7.4%) discontinued the study, and 572 patients (92.5%) completed the week 48 treatment (Fig. 1). A total of 614 patients were included in the safety analysis population and 608 patients were included in the efficacy analysis population. Patient demographic and baseline characteristics were generally balanced between treatment groups (Table 1).

Efficacy

Tafolecimab treatment resulted in a robust and durable decrease in LDL-C levels (Table 2, Fig. 2). For the on-treatment estimand, the least squares mean percent change in LDL-C level from baseline to week 48 was −64.5% (SE 1.8%) in the tafolecimab 450 mg Q4W group, as compared with 0.5% (2.2%) in the placebo 450 mg Q4W group (estimated treatment difference [ETD]: −65.0% [97.5% CI: −70.2%, −59.9%], P < 0.0001); −55.6% (2.1%) in the tafolecimab 600 mg Q6W group, as compared with 1.8% (2.7%) in the placebo 600 mg Q6W group (ETD: −57.3% [97.5% CI: −64.0%, −50.7%], P < 0.0001) (Table 2). For the treatment-policy estimand, the treatment difference versus placebo was −65.8% [97.5% CI: −71.0%, −60.6%] for tafolecimab 450 mg Q4W group; −53.6% [97.5% CI: −60.3%, −46.8%] for tafolecimab 600 mg Q6W group [both P < 0.0001]) (Supplemental Table S3). Moreover, the LDL-C-lowering efficacy of tafolecimab was not significantly affected by age, sex, BMI, baseline LDL-C levels, baseline PCSK9 levels or the presence of concomitant diseases (cardiovascular disease, cerebrovascular disease, type 2 diabetes, chronic kidney disease, and mixed dyslipidemia) (Supplemental Fig. S1).

Significantly more patients receiving tafolecimab achieved ≥50% reduction, LDL-C<1.8 mmol/L and LDL-C<1.4 mmol/L at week 12, 24, and 48, compared to those receiving placebo at both dose regimens. At week 48, LDL-C ≥ 50% reduction was achieved in 180 patients (87.8%) in tafolecimab 450 mg Q4W group, 140 patients (71.8%) in tafolecimab 600 mg Q6W group, as compared with 1 patient (1.0%) in placebo 450 mg Q4W group, 2 patients (2.0%) in placebo 600 mg Q6W group (both P < 0.0001); LDL-C <1.8 mmol/L was achieved in 188 patients (91.7%) in tafolecimab 450 mg Q4W group and 160 patients (82.1%) in tafolecimab 600 mg Q6W group, as compared with 7 patients (7.1%) in placebo 450 mg Q4W group, 10 patients (9.9%) in placebo 600 mg Q6W group (both P < 0.0001); LDL-C < 1.4 mmol/L was achieved in 177 patients (83.4%) and 134 patients (68.7%) in tafolecimab 450 mg Q4W group and tafolecimab 600 mg Q6W group, respectively, as compared with 1 patient (1.0%) in placebo 450 mg Q4W group, 2 patients (2.0%) in placebo 600 mg Q6W group

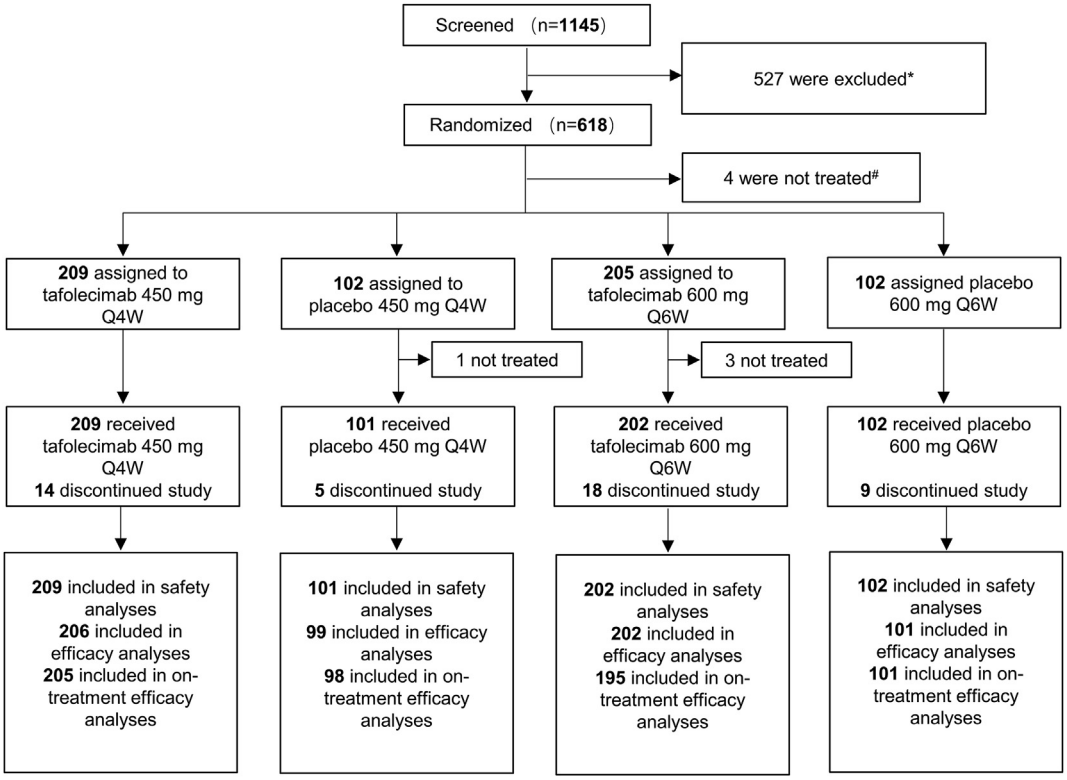


Fig. 1: Patient flow. *243 did not meet inclusion criteria, 195 met exclusion, 62 withdrawal of informed consent, 27 other. # withdrawal of informed consent. Q4W = every 4 weeks; Q6W = every 6 weeks.

(both $P < 0.0001$) (Table 2, Supplemental Figs. S2 and S3 and Table S3).

Moreover, in the very-high cardiovascular risk population ($n = 439$), assessed by on-treatment estimand at week 48, LDL-C <1.4 mmol/L was achieved in 138 patients (84.7%) receiving tafolecimab 450 mg Q4W ($n = 163$), as compared with 1 patient (1.5%) receiving placebo 450 mg Q4W ($n = 67$), and 98 patients (70.0%) receiving tafolecimab 600 mg Q6W ($n = 140$), as compared with 2 patients (2.9%) receiving placebo 600 mg Q6W ($n = 69$) (both $P < 0.0001$); In the high-risk population ($n = 130$), LDL-C <1.8 mmol/L was achieved in 34 patients (89.5%) receiving tafolecimab 450 mg Q4W ($n = 38$), as compared with 2 patients (7.7%) receiving placebo 450 mg Q4W ($n = 26$), and 37 patients (88.1%) receiving tafolecimab 600 mg Q6W ($n = 42$), as compared with 1 patient (4.2%) receiving placebo 600 mg Q6W ($n = 24$) at week 48 (both $P < 0.0001$).

Reductions in LDL-C were accompanied by improvements in other lipids (Table 2). Consistent with LDL-C reductions, tafolecimab treatment led to a rapid reduction from baseline in non-HDL-C and apolipoprotein B at week 48 (on-treatment estimand, $P < 0.0001$ for all comparisons versus placebo). Tafolecimab treatment also markedly reduced Lp(a)levels. The percent change from baseline to week 48 in Lp(a) levels assessed by on-treatment estimand was −28.3% with tafolecimab 450 mg Q4W, as compared with 21.3% with placebo Q4W (treatment difference, −49.6% [95% CI: −59.4%, −39.7%], $P < 0.0001$); −25.8% with tafolecimab 600 mg Q6W, as compared with 16.5% with placebo Q6W (treatment difference, −42.3% [−52.8%, −31.9%], $P < 0.0001$) (Table 2). Significantly more patients receiving tafolecimab achieved ≥30% reduction and ≥50% reduction from baseline to week 48 in Lp(a)levels compared to those receiving placebo at both dose regimens ($P < 0.0001$ for all comparisons versus placebo) (Supplemental Fig. S4a). In addition, a significant positive correlation was observed between reductions in Lp(a) and LDL-C at week 48 (Spearman correlation coefficient, 0.4833, $P < 0.0001$) (Supplemental Fig. S4b). Significantly more patients treated with tafolecimab achieved reductions in both LDL-C and Lp(a), compared with placebo-treated ($P < 0.0001$) (Supplemental Fig. S4c).

The maximum reduction in PCSK9 level was observed 8 h after the first dose of tafolecimab. Furthermore, the PCSK9 level remained approximately 80% below baseline in tafolecimab 450 mg Q4W group and 30% below baseline in tafolecimab 600 mg Q6W group over 48 weeks (Supplemental Fig. S5).

	450 mg Q4W		600 mg Q6W		Overall	
	Tafolecimab (n = 209)	Placebo (n = 101)	Tafolecimab (n = 202)	Placebo (n = 102)	Tafolecimab (n = 411)	Placebo (n = 203)
Age, years	57.9 (9.03)	57.0 (9.15)	57.7 (8.24)	57.0 (9.48)	57.8 (8.64)	57.0 (9.29)
Male sex, n (%)	140 (67.0)	65 (64.4)	133 (65.8)	67 (65.7)	273 (66.4)	132 (65.0)
BMI, kg/m^2	26.68 (3.68)	26.64 (3.33)	26.62 (3.42)	26.66 (3.96)	26.65 (3.55)	26.65 (3.65)
Weight, kg	73.67 (13.33)	73.44 (13.96)	73.59 (12.73)	73.60 (14.32)	73.63 (13.02)	73.52 (14.11)
Screening LDL-C, n (%)[a]						
<3.4 mmol/L	158 (75.6)	77 (76.2)	153 (75.7)	78 (76.5)	311 (75.7)	155 (76.4)
≥3.4 mmol/L	51 (24.4)	24 (23.8)	49 (24.3)	24 (23.5)	100 (24.3)	48 (23.6)
Lipid-regulating medication, n (%)						
High dose statin[b]	13 (6.2)	3 (3.0)	4 (2.0)	7 (6.9)	17 (4.1)	10 (4.9)
Moderate dose statin[c]	194 (92.8)	97 (96.0)	197 (97.5)	94 (92.2)	391 (95.1)	191 (94.1)
Statin with Ezetimibe	21 (10.0)	9 (8.9)	18 (8.9)	9 (8.8)	39 (9.5)	18 (8.9)
Cardiovascular risk[d], n (%)						
High	39 (18.7)	28 (27.7)	45 (22.3)	24 (23.5)	84 (20.4)	52 (25.6)
Very high	166 (79.4)	68 (67.3)	143 (70.8)	70 (68.6)	309 (75.2)	138 (68.0)
Concomitant disease, n (%)						
Coronary artery disease	127 (60.8)	57 (56.4)	111 (55.0)	57 (55.9)	238 (57.9)	114 (56.2)
Cerebrovascular disease	43 (20.6)	20 (19.8)	47 (23.3)	19 (18.6)	90 (21.9)	39 (19.2)
Type 2 diabetes	90 (43.1)	32 (31.7)	68 (33.7)	35 (34.3)	158 (38.4)	67 (33.0)
Hypertension	153 (73.2)	74 (73.3)	149 (73.8)	82 (80.4)	302 (73.5)	156 (76.8)
Chronic kidney disease[e]	63 (30.1)	41 (40.6)	74 (36.6)	34 (33.3)	137 (33.3)	75 (36.9)
Mixed dyslipidemia[f]	134 (64.1)	65 (64.4)	115 (56.9)	64 (62.7)	249 (60.6)	129 (63.5)
Lipid parameters						
LDL-C, mmol/L	2.83 (0.74)	2.83 (0.73)	2.91 (0.80)	2.82 (0.82)	2.87 (0.77)	2.82 (0.77)
Apolipoprotein B, g/L	0.85 (0.22)	0.85 (0.20)	0.86 (0.22)	0.85 (0.24)	0.86 (0.22)	0.85 (0.22)
Apolipoprotein B/apolipoprotein A1	0.62 (0.18)	0.62 (0.17)	0.62 (0.19)	0.60 (0.17)	0.62 (0.18)	0.61 (0.17)
Lp(a), g/L	0.12 (0.04–0.26)	0.13 (0.04–0.29)	0.11 (0.04–0.25)	0.15 (0.04–0.35)	0.12 (0.04–0.26)	0.14 (0.04–0.31)
Non-HDL-C, mmol/L	3.12 (0.87)	3.12 (0.82)	3.19 (0.92)	3.14 (0.97)	3.15 (0.89)	3.13 (0.89)

Data are presented as mean (SD), median (interquartile range), or n (%). BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); Q4W = every 4 weeks; Q6W = every 6 weeks. [a]Randomization stratification factors. [b]Defined as atorvastatin 40–80 mg or rosuvastatin 20 mg. [c]Defined as atorvastatin 10–20 mg, rosuvastatin 5–10 mg, simvastatin 20–40 mg, Lovastatin 40 mg, pravastatin 40 mg, fluvastatin 80 mg, pitavastatin 2–4 mg and Xuezhikang capsule 1.2 g. [d]Refer to ESC guideline for criteria for high/very high CV risk. [e]eGFR < 90 mL/min/1.73 m^2 was defined as chronic kidney disease. [f]Mixed dyslipidemia was defined as non-achievement of 2019 ESC/EAS risk-based LDL-C goals accompanied by abnormal triglycerides or abnormal HDL-C, Abnormal triglyceride refers to triglyceride ≥1.7 mmol/L, abnormal HDL-C refers to HDL-C < 1.0 mmol/L (male), or <1.3 mmol/L (female).

Table 1: **Demographic and baseline characteristics.**

Safety

Tafolecimab was well tolerated and showed an overall favorable safety profile (Table 3). The incidences of treatment-emergent adverse events (TEAEs) were similar in patients who received tafolecimab (85.2%) or placebo (85.7%). The most commonly-reported TEAEs in the tafolecimab group were upper respiratory infection (11.2%), urinary tract infection (10.9%) and hyperuricemia (10.5%). Most TEAEs were mild or moderate in severity. Seven patients (3.3%) receiving tafolecimab 450 mg Q4W and 5 patients (2.5%) receiving tafolecimab 600 mg Q6W discontinued the study drug prematurely due to AEs. Serious adverse events (SAEs) were reported in 36 patients (8.8%) receiving tafolecimab and 21 patients (10.3%) receiving placebo. SAEs of patients receiving tafolecimab were unrelated to the study drug judged by the investigators (most commonly-reported SAE including unstable angina, coronary artery disease and intervertebral disc herniation). AEs leading to death were reported in 2 patients from the tafolecimab 600 mg Q6W group (one acute myocardial infarction and one arrhythmia) and 2 patients from the placebo 600 mg Q6W group (one sudden death and one acute myocardial infarction), all were unrelated to the study drug according to investigators' judgment.

The incidences of hypersensitivity were low and similar between the tafolecimab and placebo groups. The incidence of injection-site adverse events and muscle events were higher in the tafolecimab groups than placebo groups (Table 3).

The incidence of laboratory abnormalities in ALT, AST and creatine kinase was low and similar between the tafoleciamb groups and the placebo groups (Table 3).

For immunogenicity, 22 patients (10.7%) in the tafolecimab 450 mg Q4W group and 22 patients (10.9%) in the tafolecimab 600 mg Q6W group developed anti-drug antibody after tafolecimab treatment. One patient (0.5%)

	450 mg Q4W			600 mg Q6W		
	Tafolecimab (n = 205)	Placebo (n = 98)	ETD	Tafolecimab (n = 195)	Placebo (n = 101)	ETD
LDL-C at week 48						
CFB, mmol/L	−1.80 (0.05)	−0.03 (0.06)	−1.77 (−1.90, −1.65)	−1.62 (0.07)	−0.00 (0.08)	−1.62 (−1.80, −1.44)
Percent CFB, %[a]	−64.5 (1.8)	0.5 (2.2)	−65.0 (−70.2, −59.9)	−55.6 (2.1)	1.8 (2.7)	−57.3 (−64.0, −50.7)
≥50% LDL-C reduction[a]	180 (87.8)	1 (1.0)	86.9 (81.4, 92.5)	140 (71.8)	2 (2.0)	69.7 (61.9, 77.6)
LDL-C < 1.8 mmol/L[a]	188 (91.7)	7 (7.1)	84.9 (78.0, 91.9)	160 (82.1)	10 (9.9)	72.2 (63.2, 81.3)
LDL-C < 1.4 mmol/L[a]	171 (83.4)	1 (1.0)	82.9 (76.8, 89.0)	134 (68.7)	2 (2.0)	66.8 (58.7, 74.8)
LDL-C at week 12						
Percent CFB, %[a]	−65.5 (1.7)	0.04 (2.1)	−65.5 (−70.3, −60.8)	−53.6 (2.1)	1.1 (2.7)	−54.7 (−61.3, −48.1)
≥50% LDL-C reduction[a]	183 (89.3)	1 (1.0)	88.4 (83.1, 93.7)	135 (69.2)	2 (2.0)	67.1 (59.1, 75.1)
LDL-C < 1.8 mmol/L[a]	189 (92.2)	7 (7.1)	85.4 (78.4, 92.3)	159 (81.5)	10 (9.9)	71.7 (62.6, 80.7)
LDL-C < 1.4 mmol/L[a]	176 (85.9)	1 (1.0)	85.1 (79.3, 90.9)	131 (67.2)	0	67.2 (59.7, 74.7)
LDL-C at week 24						
Percent CFB, %[a]	−66.4 (1.7)	2.1 (2.1)	−68.5 (−73.2, −63.9)	−55.9 (2.1)	−2.1 (2.7)	−53.8 (−60.5, −47.2)
≥50% LDL-C reduction[a]	183 (89.3)	1 (1.0)	88.4 (83.0, 93.7)	142 (72.8)	2 (2.0)	70.7 (63.0, 78.5)
LDL-C < 1.8 mmol/L[a]	192 (93.7)	2 (2.0)	91.9 (87.0, 96.7)	155 (79.5)	13 (12.9)	66.7 (56.8, 76.6)
LDL-C < 1.4 mmol/L[a]	175 (85.4)	1 (1.0)	85.0 (79.2, 90.8)	136 (69.7)	1 (1.0)	68.8 (61.2, 76.5)
Non-HDL-C at week 48						
CFB, mmol/L	−2.02 (0.06)	0.07 (0.08)	−2.10 (−2.25, −1.94)	−1.76 (0.08)	0.13 (0.10)	−1.89 (−2.10, −1.68)
Percent CFB, %	−65.9 (2.0)	4.0 (2.5)	−69.9 (−75.1, −64.8)	−54.9 (2.3)	5.7 (3.0)	−60.7 (−67.0, −54.3)
Apolipoprotein B at week 48						
CFB, g/L	−0.50 (0.02)	0.03 (0.02)	−0.52 (−0.56, −0.49)	−0.44 (0.02)	0.04 (0.02)	−0.48 (−0.53, −0.42)
Percent CFB, %	−58.5 (1.6)	4.8 (2.1)	−63.3 (−67.7, −58.9)	−50.4 (2.0)	6.2 (2.6)	−56.5 (−62.3, −50.7)
Apolipoprotein B/Apolipoprotein A1 at week 48						
CFB	−0.38 (0.01)	0.00 (0.01)	−0.39 (−0.41, −0.36)	−0.34 (0.01)	0.00 (0.02)	−0.34 (−0.37, −0.30)
Percent CFB, %	−61.5 (1.6)	2.2 (2.1)	−63.7 (−68.1, −59.3)	−53.9 (2.0)	3.3 (2.6)	−57.2 (−62.9, −51.5)
Lp(a) at week 48[b]						
CFB, g/L	−0.06 (0.01)	0.02 (0.01)	−0.07 (−0.09, −0.05)	−0.04 (0.01)	0.02 (0.01)	−0.07 (−0.09, −0.04)
Percent CFB, %	−28.3 (2.6)	21.3 (4.2)	−49.6 (−59.4, −39.7)	−25.8 (2.9)	16.5 (4.5)	−42.3 (−52.8, −31.9)

Data are presented as least squares mean (standard error) for CFB, n (%) for LDL-C target attainment rates, least squares mean (97.5% CI) for ETD of percent CFB in LDL-C and LDL-C target attainment rates, least squares mean (95% CI) for ETD of CFB in LDL-C, as well as ETD of CFB and percent CFB in other lipid parameters. $P < 0.0001$ for all comparisons versus placebo. CFB = change from baseline; ETD = estimated treatment difference; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); Q4W = every 4 weeks; Q6W = every 6 weeks. [a]Controlled for type I error (pairwise $\alpha = 0.025$). [b]Lp(a) levels analysis using a robust regression estimation.

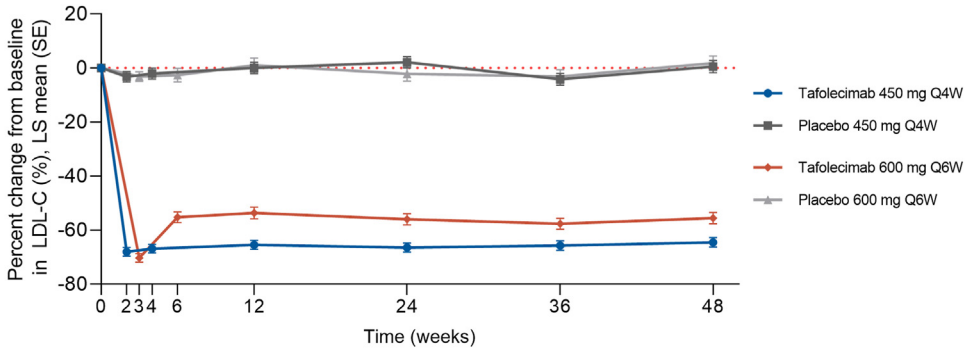
Table 2: **Main efficacy endpoints (on-treatment estimand).**

in the tafolecimab 450 mg Q4W group and 2 patients (1.0%) in the tafolecimab 600 mg Q6W group developed neutralizing antibody after tafolecimab treatment.

Discussion

Results from CREDIT-1 demonstrated tafolecimab dosed at 450 mg Q4W and 600 mg Q6W induced clinically meaningful and statistically significant reductions in LDL-C as well as other lipid levels over 48 weeks in Chinese patients with non-FH, with a favorable safety profile comparable with those of other PCSK9 mabs. These data, together with evidence from other phase 3 studies of tafolecimab (CREDIT-2 and CREDIT-4),[14,15] supported the use of tafolecimab as a new treatment option for the treatment of hypercholesterolemia in the Chinese population.

Tafolecimab treatment induced significant reductions in LDL-C levels (treatment difference versus placebo: –57.4% for 150 mg Q2W; –61.9% for 450 mg Q4W) at week 12 in patients with HeFH in the CREDIT-2 study.[14] Consistently, in the CREDIT-4 study,[15] the mean percent change in LDL-C levels was –68.9% and –65.7% for tafolecimab 450 mg Q4W group at week 12 and week 24, respectively, in Chinese HeFH patients or non-FH patients at high or very high cardiovascular risk. Both CREDIT-2 and CREDIT-4 studies showed robust short-term lipid-lowering efficacy and favorable safety profiles of tafolecimab. In addition, the LDL-C and other lipids-lowering effect of tafolecimab were comparable to those of evolocumab and alirocumab observed in the Asian populations. Of note, tafolecimab showed a long-acting potential compared to evolocumab and alirocumab in dose-ascending studies conducted in Chinese subjects. In studies of evolocumab and alirocumab, the LDL-C and PCSK9 levels remained around the nadir through day 22 for 420 mg evolocumab and through day 29 for 300 mg alirocumab.[16,17] However, the



No. of Patients	W2	W3	W4	W6	W12	W24	W36	W48
Tafolecimab 450 mg Q4W	204			200	180	176	164	153
Placebo 450 mg Q4W	97			96	87	84	78	74
Tafolecimab 600 mg Q6W		195		182	174	164	150	143
Placebo 600 mg Q6W		100		94	91	84	76	74

Fig. 2: Percent change from baseline in LDL-C levels over 48 weeks. On-treatment estimand. LDL-C = low-density lipoprotein cholesterol; LS = least squares; Q4W = every 4 weeks; Q6W = every 6 weeks; SE = standard error.

	450 mg Q4W		600 mg Q6W		Overall	
	Tafolecimab (n = 209)	Placebo (n = 101)	Tafolecimab (n = 202)	Placebo (n = 102)	Tafolecimab (n = 411)	Placebo (n = 203)
TEAE						
Any	177 (84.7)	91 (90.1)	173 (85.6)	83 (81.4)	350 (85.2)	174 (85.7)
Treatment-related	49 (23.4)	16 (15.8)	44 (21.8)	19 (18.6)	93 (22.6)	35 (17.2)
Serious	15 (7.2)	12 (11.9)	21 (10.4)	9 (8.8)	36 (8.8)	21 (10.3)
Deaths	0	0	2 (1.0)	2 (2.0)	2 (0.5)	2 (1.0)
Leading to treatment discontinuation	7 (3.3)	1 (1.0)	5 (2.5)	0	12 (2.9)	1 (0.5)
TEAEs reported in >5% of patients in any group receiving tafolecimab[a]						
Upper respiratory infection	24 (11.5)	11 (10.9)	22 (10.9)	10 (9.8)	46 (11.2)	21 (10.3)
Urinary tract infection	18 (8.6)	12 (11.9)	27 (13.4)	9 (8.8)	45 (10.9)	21 (10.3)
Hyperuricemia[b]	21 (10.0)	15 (14.9)	22 (10.9)	6 (5.9)	43 (10.5)	21 (10.3)
Blood creatine phosphokinase increased	15 (7.2)	11 (10.9)	15 (7.4)	10 (9.8)	30 (7.3)	21 (10.3)
Blood glucose increased	12 (5.7)	7 (6.9)	14 (6.9)	6 (5.9)	26 (6.3)	13 (6.4)
Poor control of diabetes	15 (7.2)	4 (4.0)	8 (4.0)	8 (7.8)	23 (5.6)	12 (5.9)
Hepatic function abnormal	8 (3.8)	3 (3.0)	11 (5.4)	5 (4.9)	19 (4.6)	8 (3.9)
Alanine aminotransferase increased	6 (2.9)	5 (5.0)	12 (5.9)	2 (2.0)	18 (4.4)	7 (3.4)
Adverse events of special interests						
Hypersensitivity[c]	4 (1.9)	1 (1.0)	5 (2.5)	3 (2.9)	9 (2.2)	4 (2.0)
Injection site reaction[d]	13 (6.2)	2 (2.0)	17 (8.4)	3 (2.9)	30 (7.3)	5 (2.5)
Muscle events[e]	12 (5.7)	3 (3.0)	7 (3.5)	2 (2.0)	19 (4.6)	5 (2.5)
Laboratory results (any post-baseline value)						
ALT > 3 × ULN (if ALT at baseline < ULN); ALT > 2 × baseline (if ALT at baseline ≥ ULN)	7 (3.3)	2 (2.0)	3 (1.5)	1 (1.0)	10 (2.4)	3 (1.5)
AST > 3 × ULN	2 (1.0)	2 (2.0)	3 (1.5)	1 (1.0)	5 (1.2)	3 (1.5)
Creatine kinase >5 × ULN	3 (1.4)	1 (1.0)	2 (1.0)	0	5 (1.2)	1 (0.5)
Total bilirubin > 2 × ULN	2 (1.0)	1 (1.0)	0	0	2 (0.5)	1 (0.5)

Data are n (%). TEAE = Treatment emergent adverse events; ALT = alanine aminotransferase; ULN = upper limit of normal; Q4W = every 4 weeks; Q6W = every 6 weeks. [a]By MedDRA (version 24.1) preferred term. [b]Hyperuricemia was recorded if serum uric acid (UA) level >420 μmol/L twice on different days. [c]Acute onset within minutes to hours: cutaneous and/or mucosal symptoms (angioedema, urticaria, eczema), respiratory symptoms (dyspnea, wheezing, bronchospasm), hypotension (SBP < 90 mmHg or >30% decrease from baseline). [d]Symptoms such as swelling, flushing, ecchymosis, pruritus, induration, pain at the injection site. [e]Defined using statin-associated muscle events (ACC/AHA guideline on the management of blood cholesterol [2018]).

Table 3: **TEAE and laboratory results.**

reduction of LDL-C and PCSK9 levels were maintained to more than 6 weeks after a single dose of 450 mg or 600 mg tafolecimab administration,[18] supporting the exploration of a long-interval dosing regimen in further studies. Thus, to evaluate long-term efficacy and safety and explore long-interval dosing regimen, we conducted this CREDIT-1 study. The results demonstrated that tafolecimab dosed at 450 mg Q4W or 600 mg Q6W both lowered LDL-C (treatment difference versus placebo: –65.0% for 450 mg Q4W; –57.3% for 600 mg Q6W) and other lipid levels and maintained to week 48. Additionally, reductions in LDL-C were not significantly affected by factors such as age, weight, baseline LDL-C levels or concomitant diseases, suggesting the robustness and broad applicability of tafolecimab as a potent PCSK9 inhibitor.

LDL-C reduction of ≥50% from baselined and LDL-C goal of <1.4 mmol/L are recommended for patients at very-high cardiovascular risk; LDL-C reduction of ≥50% from baselined and LDL-C goal of <1.8 mmol/L are recommended for patients at high cardiovascular risk by current guidelines for lipid management.[6,7] However, Chinese patients at high or very high cardiovascular risk receiving moderate statin therapy may not be able to achieve these goals,[3–5] A population-based study reported that only 14% of Chinese patients at very high cardiovascular risk receiving moderate statins achieved LDL-C < 1.4 mmol/L[4], and only a fraction of patients were willing to use high-intensity statins to control LDL-C in China possibly due to the potential side-effects.[19] In this study, a reduction of ≥50% was reported in approximately 90% of patients in tafolecimab 450 mg Q4W group and approximately 70% of patients in tafolecimab 600 mg Q6W group over 48 weeks. Approximately 90% of patients at high cardiovascular risk achieved LDL-C < 1.8 mmol/L after receiving tafolecimab, and more than 70% of patients at very high cardiovascular risk achieved LDL-C < 1.4 mmol/L after receiving tafolecimab. These data suggested that tafolecimab was effective in hypercholesterolemia patients with LDL-C inadequately controlled by statins with or without ezetimibe.

Lp(a) concentration is elevated in patients with cardiovascular disease, which is recognized as an independent risk factor for cardiovascular diseases such as myocardial infarction and stroke.[20,21] Cardiovascular outcome trials of alirocumab found that lowering Lp(a) has the potential to reduce cardiovascular events.[22,23] Lp(a) levels are usually featured by a skewed distribution with variable concentrations. The Lp(a) levels detected in our study were within the reported range of Lp (a) concentrations and the baseline were similar to the studies of alirocumab conducted in Japanese population.[11] In our study, tafolecimab treatment reduced the Lp(a) levels in Chinese hypercholesterolemia and a significant correlation was observed between reductions in Lp(a) and LDL-C, consistent with the findings of evolocumab.[24] Given the lower Lp(a) levels in Chinese population and skewed distribution of Lp(a) levels, together with elevations of Lp(a) levels observed in placebo group which was possibly due to the use of statins and concomitant chronic kidney disease of enrolled patients,[25,26] the potential Lp(a) lowering effects of tafolecimab still warrant further investigation.

Sustained LDL-C lowering and long-term cardiovascular benefits largely depend on patients' adherence to LDL-C lowering therapies.[12] While current approved PCSK9 mabs with monthly intervals achieved robust lipid-lowering efficacy, less frequent dosing is highly desirable for chronic administration. Attempts on long-interval dosing of PCSK9 mabs have yielded promising LDL-C lowering efficacy but were either terminated[27] or in early phase clinical development.[28] Inclisiran is a long-acting siRNA approved by EMA and FDA, which is still under review by the National Medical Products Administration (NMPA, China). Inclisiran induced approximately 50% reductions in LDL-C levels under long-interval dosing (every 6 months). However, as the RNA-based drug, the safety of inclisiran requires long-term monitoring with large sample size and it may be challenging to reverse any potential adverse effects due to long activity of inclisiran.[29] In this study, tafolecimab 600 mg Q6W resulted in sustained LDL-C reductions of more than 50% under the premise of good safety, offering a dosing advantage over current approved PCSK9 mabs.

Tafolecimab was well tolerated and demonstrated a favorable risk-benefit profile in this long-term study, with an overall safety profile comparable to other phase 3 trials of tafolecimab.[14,15] The most commonly-reported TEAEs were comparable with approved PCSK9 mabs except for hyperuricemia. Regarding the reason for occurred hyperuricemia, some studies found serum uric acid level is positively associated with chronic and metabolic diseases.[30] Thus, we speculated it might be associated with concomitant metabolic diseases such as hyperuricemia and chronic kidney disease of enrolled patients. The incidence of hyperuricemia was similar between tafolecimab group and placebo group and all reported events of hyperuricemia were mild or moderate in severity.

While the lipid-lowering effects of tafolecimab are evidenced, a limited number of cardiovascular events were observed in the study, thus precluding a clinically relevant analysis of the potential effect of tafolecimab on cardiovascular outcomes. A longer-term study is required to evaluate the cardiovascular benefits of tafolecimab in the future.

Conclusions

In Chinese patients with non-FH, tafolecimab dosed at both 450 mg Q4W and 600 mg Q6W was safe and demonstrated clinically meaningful lipid-lowering

efficacy. Tafolecimab may provide a novel treatment option with a longer-dosing interval for Chinese patients with hypercholesterolemia.

Contributors

Yong Huo, Huan Deng, and Lei Qian designed the study. Beijian Chen, Qiufang Lian, Shuqing Wang, Lu Liu, Di Lu, Yanling Qu, Guanzhong Zheng, Lipeng Li, Yuan Ji, Guotian Yin, Wenjun Huang, Ying Xie, Xinchun Yang and Xiufang Gao did the trial and collected the data. Yong Huo, Pei An, Fengtai Xue, Haoyu Li, and Li Li analyzed the data. Yong Huo, Pei An, Fengtai Xue, Haoyu Li, Li Li, Lijuan Pei, Huan Deng and Lei Qian interpreted the data. Lijuan Pei wrote the manuscript. All authors had full access to all the data in the study and had critically reviewed the manuscript and approved the final manuscript. All authors vouch for data accuracy and fidelity to the protocol.

Data sharing statement

The data analyzed in the study are available from the corresponding author on reasonable request.

Declaration of interests

Yong Huo, Beijian Chen, Qiufang Lian, Shuqing Wang, Lu Liu, Di Lu, Yanling Qu, Guanzhong Zheng, Lipeng Li, Yuan Ji, Guotian Yin, Wenjun Huang, Ying Xie, Xinchun Yang, Xiufang Gao report personal fees from Innovent Biologics, Inc., during the conduct of the study. Pei An, Fengtai Xue, Haoyu Li, Huan Deng, Li Li, Lijuan Pei and Lei Qian were employees of Innovent Biologics, Inc.

Acknowledgements

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

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.100907.

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