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ORIGINAL RESEARCH

Efficacy and Safety of Evolocumab in Chinese Patients with Primary Hypercholesterolemia and Mixed Dyslipidemia: 12-Week Primary Results of the HUA TUO 华佗 Randomized Clinical Trial

Hong Tan · Weimin Li · Zhouqing Huang · Yajun Han · Xuecheng Huang · Dongye Li · Xiaochun Xing · Maria Laura Monsalvo · You Wu · Jackie Mao · Lily Xin · Jiyan Chen on behalf of HUA TUO study investigators

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ABSTRACT

Introduction: Evolocumab, a fully human proprotein convertase/subtilisin kexin type 9 inhibitor antibody, significantly lowers low-density lipoprotein cholesterol (LDL-C) in patients with type 2 diabetes mellitus and hyperlipidemia and mixed dyslipidemia. This 12-week study evaluated the efficacy and safety of evolocumab in Chinese patients with primary hypercholesterolemia and mixed dyslipidemia at different levels of cardiovascular disease risk.

Methods: HUA TUO was a 12-week randomized, double-blind, placebo-controlled study. Chinese patients aged 18 years or older on stable optimized statin therapy were randomized 2:2:1:1 to receive evolocumab 140 mg every 2 weeks (Q2W), evolocumab 420 mg monthly (QM), or a matching placebo. The coprimary endpoints were percent change from baseline in LDL-C at the mean of weeks 10 and 12 and at week 12.

Results: Overall, 241 randomized patients (mean [standard deviation] age, 60.2 [10.3]

HUA TUO investigators are listed in the Supplementary Material.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40119-023-00304-x.

H. Tan · J. Chen (✉)
Guangdong Provincial People's Hospital, Guangzhou 510080, China
e-mail: chen-jiyan@163.com

W. Li
The First Affiliated Hospital of Harbin Medical University, Harbin 150001, China

Z. Huang
The First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, China

Y. Han
Inner Mongolia Autonomous Region People's Hospital, Hohhot 010017, China

X. Huang
The Second Nanning People's Hospital, Nanning 530031, China

D. Li
The Affiliated Hospital of Xuzhou Medical University, Xuzhou 221006, China

X. Xing
Tianjin Fourth Central Hospital, Tianjin 300140, China

M. L. Monsalvo · Y. Wu
Amgen Inc., 1 Amgen Center Drive, Thousand Oaks, CA 91320, USA

J. Mao · L. Xin
Amgen China, Shanghai 200020, China

years) received evolocumab 140 mg Q2W ($n=79$), evolocumab 420 mg QM ($n=80$), placebo Q2W ($n=41$), or placebo QM ($n=41$). At weeks 10 and 12, the placebo-adjusted least-squares mean percent change from baseline in LDL-C for the evolocumab 140 mg Q2W group was −70.7% (95% CI −78.0% to −63.5%); −69.7% (95% CI −76.5% to −63.0%) for the evolocumab 420 mg QM group. Significant improvements in all other lipid parameters were observed with evolocumab. The patient incidence of treatment-emergent adverse events was similar between the treatment groups and across dosing regimens.

Conclusion: In Chinese patients with primary hypercholesterolemia and mixed dyslipidemia, 12-week treatment with evolocumab significantly lowered LDL-C and other lipids, and was safe and well tolerated (NCT03433755).

Graphical Abstract:

EFFICACY AND SAFETY OF EVOLOCUMAB

in Chinese Patients With Primary Hypercholesterolemia and Mixed Dyslipidemia: Primary Results of a Phase 3 Randomized Clinical Trial

Hong Tan, Weimin Li, Zhouqing Huang, Yajun Han, Xuecheng Huang, Dongye Li, Xiaochun Xing, Maria Laura Monsalvo, You Wu, Jackie Mao, Lily Xin, Jiyan Chen, on behalf of HUA TUO study investigators

HUA TUO 华佗 Study

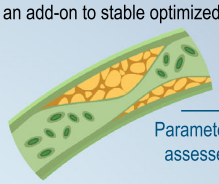
A phase 3, randomized (2:2:1:1), double-blind, placebo-controlled 12-week study (NCT03433755)

Evolocumab (**140 mg SC Q2W and 420 mg SC QM**) vs matched placebo

241 Chinese patients aged ≥ 18 years with **primary hypercholesterolemia and mixed dyslipidemia** at different levels of CV risk

Objective

Evaluate the **efficacy and safety** of evolocumab as an add-on to stable optimized statin therapy



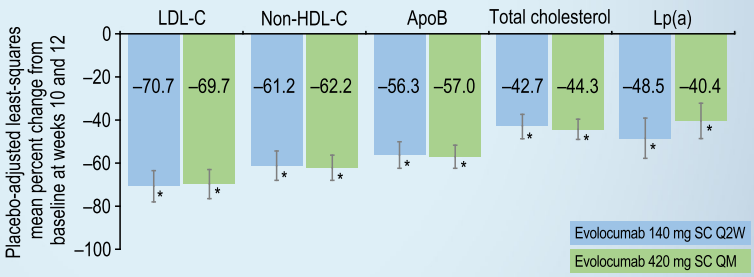
Parameters assessed:
- LDL-C
- Non-HDL-C
- ApoB
- Lp(a)
- Total cholesterol

Patient Characteristics

- Mean (SD) age **60.2 (10.3) years**
- **Once-daily** stable optimized statin therapy ± ezetimibe
- Male **67.6%**
- Mean (SD) LDL-C at baseline **116.1 (34.6) mg/dL**
- Hypertension **62.2%**
- Coronary artery disease **85.9%**
- High / very high risk for CVD **92.1%**
- T2DM **28.6%**
- ≥ 2 risk factors for CVD **50.6%**

Efficacy

- Significant improvement in LDL-C and other lipids was observed with evolocumab 140 mg Q2W and evolocumab 420 mg QM vs matching placebo
- Reductions in LDL-C were maintained throughout the 12-week study in both evolocumab dosing regimens



Error bars depict 95% CIs.
*All treatment differences (evolocumab vs placebo) in the least-squares mean percent change from baseline for all lipid parameters were statistically significant ($P < 0.0001$).

Safety

Evolocumab vs placebo

≥ 1 TEAEs (patient incidence, %): 54.7% vs 54.9%

SAEs (patient incidence, %): 4.4% vs 7.3%

The majority of TEAEs were mild or moderate in severity and no TEAEs led to discontinuation of evolocumab or placebo

Most common TEAEs

- URT infection **8.2% vs 8.5%**
- Hypertension **6.3% vs 6.1%**
- Hyperuricemia **3.8% vs 0.0%**
- Hyperbilirubinemia **2.5% vs 4.9%**

Conclusion

Evolocumab significantly lowered LDL-C and other lipids, and was safe and well tolerated in Chinese patients with primary hypercholesterolemia and mixed dyslipidemia

Adis

PEER-REVIEWED FEATURE

ApoB, apolipoprotein B; **CV**, cardiovascular; **CVD**, cardiovascular disease; **HDL-C**, high-density lipoprotein cholesterol; **LDL-C**, low-density lipoprotein cholesterol; **Lp(a)**, lipoprotein(a); **QM**, once monthly; **Q2W**, once every 2 weeks; **SAE**, serious adverse event; **SC**, subcutaneous; **SD**, standard deviation; **TEAE**, treatment-emergent adverse event; **T2DM**, type 2 diabetes mellitus; **URT**, upper respiratory tract.

Keywords: Evolocumab; Hypercholesterolemia; Mixed dyslipidemia; LDL cholesterol; PCSK9; Hyperlipidemia

Key Summary Points

Evolocumab significantly lowers LDL-C in patients with type 2 diabetes mellitus and hyperlipidemia and mixed dyslipidemia.

HUA TUO was a 12-week, phase 3, double-blind, placebo-controlled confirmatory study that evaluated evolocumab in Chinese patients with primary hypercholesterolemia and mixed dyslipidemia at different levels of cardiovascular disease risk.

Evolocumab significantly reduced LDL cholesterol, improved other lipid parameters, and was safe and well tolerated.

The results of this 12-week study are consistent with previous global studies of evolocumab and confirm the favorable efficacy and safety of evolocumab in Chinese patients with primary hypercholesterolemia and mixed dyslipidemia.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate understanding of the article. The abstract is also available in both Chinese and Japanese. To view all features for this article go to https://doi.org/10.6084/m9.figshare.21896643.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide and continues to rise globally, especially in developing countries [1]. Globally, China has the highest number of CVD-related deaths [1, 2]; in 2015 and 2018, CVD accounted for over 40% of all deaths in China [3, 4]. The incidence has been steadily increasing over the past two decades primarily because of the rapid industrialization and is expected to increase in the future [3–5]. Furthermore, in China, the prevalence of dyslipidemia, an important risk factor for CVD, is over 30% [6]; it has drastically increased since 2002 and is expected to increase because of the increasing prevalence of dyslipidemia in the younger population [6–8].

Since low-density lipoprotein (LDL) cholesterol is an independent and well-known modifiable risk factor for CVD, lowering levels of LDL cholesterol with lipid-lowering therapies has been the main clinical strategy to reduce CVD events [9–11]. Despite the availability of statin therapy in China, many Chinese patients with CVD, including those at high or very high risk for CVD, do not achieve guideline-recommended LDL cholesterol–lowering goals [12, 13].

Evolocumab, a fully human monoclonal antibody, inhibits proprotein convertase/subtilisin kexin type 9 (PCSK9)-mediated degradation of the LDL receptor, which leads to increased levels of LDL receptor on hepatocytes that are available to eliminate LDL cholesterol [14]. Evolocumab is currently approved in over 77 countries/regions for lowering LDL cholesterol and in over 65 countries/regions for the risk reduction of cardiovascular (CV) events. In China, evolocumab is approved for lowering LDL cholesterol in adult and pediatric (aged 12 years and older) patients with homozygous familial hypercholesterolemia, adult patients with primary hypercholesterolemia (including heterozygous familial hypercholesterolemia) and mixed dyslipidemia, and for the prevention of CV events, including reducing the risk of myocardial infarction, stroke, and coronary revascularization in adults with established CVD. The LDL cholesterol-lowering indication in patients with primary hypercholesterolemia and mixed dyslipidemia was supported by the BERSON trial, which enrolled patients with type 2 diabetes and primary hyperlipidemia and mixed dyslipidemia [15, 16]. HUA TUO was a phase 3, randomized, double-blind, placebo-controlled confirmatory study of evolocumab in China. This 12-week study evaluated the efficacy, safety, and tolerability of evolocumab as

an add-on to stable optimized statin therapy in Chinese patients with primary hypercholesterolemia and mixed dyslipidemia at different levels of CV risk.

METHODS

Trial Design and Oversight

HUA TUO was a phase 3, multicenter (31 centers in China), randomized, placebo-controlled, double-blind study evaluating the efficacy, safety, and tolerability of 12 weeks of subcutaneous (SC) injections of evolocumab 140 mg every 2 weeks (Q2W) or evolocumab 420 mg monthly (QM) (Fig. 1) as an adjunct to a stable and optimized (maximum and appropriate) daily dose of an approved statin therapy with or without ezetimibe, in Chinese patients with primary hypercholesterolemia and mixed dyslipidemia. The optimal statin treatment was determined by the investigator's judgment according to the 2016 Chinese guideline for the management of dyslipidemia in adults [17]. For patients in the Q2W regimen, the investigational product (IP; evolocumab or placebo) was administered on day 1, week 2, week 4, week 6, week 8, and week 10. For the QM regimen, the IP was administered on day 1, week 4, and week 8. The last dose of evolocumab or placebo was administered at week 8 for QM patients and at week 10 for Q2W patients. The final study visit for patients on the QM regimen was at week 12; for patients on Q2W, there was a phone call at week 14. The first patient was enrolled on May 9, 2019, and the last patient completed the study on May 9, 2020.

Amgen staff, patients, and study site staff were blinded to the allocated treatment intervention but not to the dosing frequency. To ensure that blinding was maintained during the treatment period, Amgen staff, investigators, and study site staff were blinded to results of lipid parameters, apolipoprotein A1, apolipoprotein B (apoB), lipoprotein(a) [Lp(a)], high-sensitivity C-reactive protein, and PCSK9 tests until unblinding of the clinical database.

A central laboratory, Medpace Reference Laboratories, analyzed all laboratory samples. LDL cholesterol levels were calculated by using

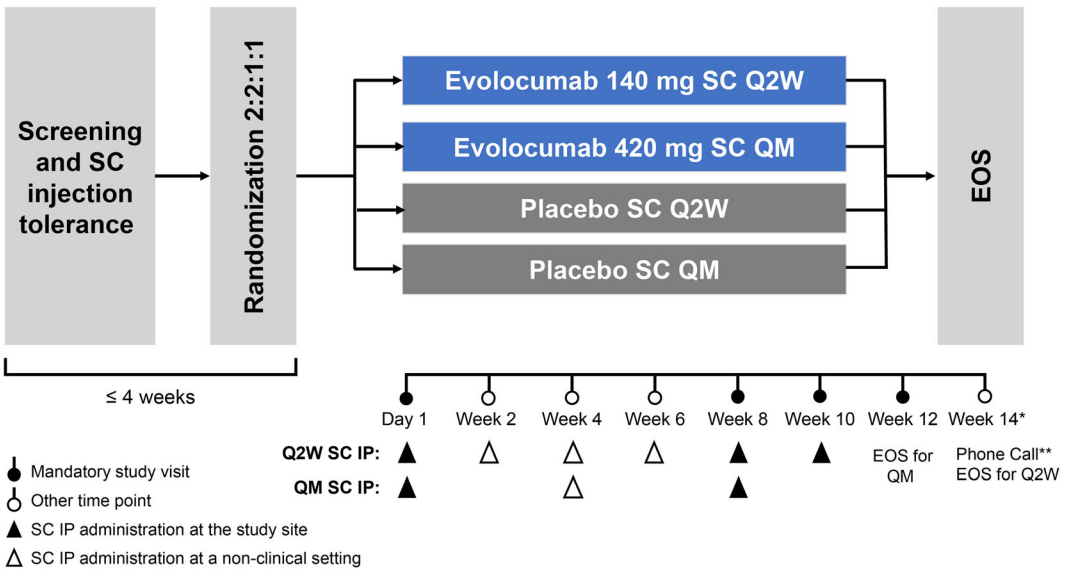


Fig. 1 Study design. *Only for patients receiving IP SC Q2W. **Phone call for AEs, ADEs, SAEs, and DREs among patients receiving IP SC Q2W. *ADE* adverse device effect, *AE* adverse event, *DRE* disease-related event, *EOS* end of study, *IP* investigational product, *QM* monthly, *Q2W* every 2 weeks, *SAE* serious adverse event, *SC* subcutaneous

the Friedewald formula for triglyceride levels of 400 mg/dL or less. For samples with a calculated LDL cholesterol of less than 40 mg/dL or triglyceride levels more than 400 mg/dL, LDL cholesterol was measured by ultracentrifugation.

Amgen sponsored the study. Independent ethics committees at each site reviewed and approved the study protocol and the informed consent form. The investigator collected written informed consent from all participants before any screening procedures were performed.

Patients and Randomization

Eligible patients were randomized 2:2:1:1 to receive evolocumab 140 mg SC Q2W, evolocumab 420 mg SC QM, placebo SC Q2W, or placebo SC QM, respectively, with an interactive voice response system or interactive web response system and a computer-generated randomization schedule. Randomization was stratified by baseline CV risk (high/very high CV risk versus not high/very high CV risk) based on the 2007 Chinese guidelines on the prevention and treatment of dyslipidemia in adults [18] and international guidelines.

The intensity of lipid-lowering therapies in this study was classified as either intensive or non-intensive statin usage on the basis of the 2016 Chinese guidelines recommending only medium-intensity statins and the observation that Chinese patients tend to achieve lower LDL cholesterol levels than do patients from western countries when the same statin and dose are used. Intensive statin usage included atorvastatin (≥40 mg once daily [QD]), rosuvastatin (20 mg QD), simvastatin (80 mg QD), or any statin (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin) plus ezetimibe. Non-intensive statin usage included doses other than those listed under intensive doses.

Details on patient eligibility criteria can be found in the Supplementary Material (Table S1). Briefly, eligible patients were at least 18 years of age, had to be on a stable optimized daily dose of an approved statin therapy with or without ezetimibe (at least 4 weeks before LDL cholesterol screening not requiring uptitration), had to have a fasting screening LDL cholesterol of 80 mg/dL (2.1 mmol/L) or more for patients with high/very high CV risk (see Supplementary Material for criteria) or 130 mg/dL (3.4 mmol/L) or more for patients not meeting the high/very high CV risk criteria, had to have fasting screening triglycerides of 400 mg/dL (4.5 mmol/L) or less, and had to tolerate a placebo injection at screening before randomization. Patients were instructed to maintain their diet and exercise regimen and remain on baseline statin therapy throughout the study unless the investigator deemed it necessary to change the dosage.

Endpoints

The coprimary endpoints were the mean percent change from baseline in LDL cholesterol at weeks 10 and 12 and the percent change from baseline in LDL cholesterol at week 12. The mean of weeks 10 and 12 was included as an endpoint because it better reflects average LDL cholesterol reduction during the dosing interval with QM dosing [19]. Secondary endpoints included the mean change from baseline at weeks 10 and 12 and the change from baseline at week 12 for the following: LDL cholesterol, high-density lipoprotein (HDL) cholesterol (percent change), non-HDL cholesterol (percent change), apoB (percent change), total cholesterol (percent change), achievement of target LDL cholesterol (<70 mg/dL [1.8 mmol/L]), achievement of at least a 50% reduction from baseline in LDL cholesterol, Lp(a) (percent change), triglycerides (percent change), and very low-density lipoprotein (VLDL) cholesterol (percent change). Safety endpoints included the patient incidence of treatment-emergent adverse events (TEAEs) and laboratory values. Details regarding exploratory endpoints are included in the Supplementary Material.

Statistical Analysis

Based on Chinese regulations at the time the study was designed, the initial total sample size was 450 patients randomized 2:2:1:1 to

evolocumab SC Q2W (150 patients), evolocumab SC QM (150 patients), placebo SC Q2W (75 patients), or placebo SC QM (75 patients). This planned sample size would have provided at least 98% power to determine the superiority of evolocumab over placebo for both dosing regimens for the coprimary endpoints, assuming a 10% dropout rate. However, enrollment in the study was disrupted because of the COVID-19 pandemic after 259 patients had already been enrolled. A statistical reassessment determined that a sample size of 259 patients would still maintain the original study power (98%) for the superiority of each evolocumab dosing regimen over placebo for the coprimary endpoints with a conservative assumed difference in mean treatment effect on LDL cholesterol of −40% between evolocumab and placebo, 10% of patients lost to follow-up, and a common standard deviation (SD) of 25%.

Efficacy and safety analyses included all randomized patients who received at least one dose of the IP, except for 17 patients who were excluded from all data analyses for regulatory reasons, and were done independently for each dosing regimen (Q2W and QM). Planned analyses of data from anti-evolocumab antibody tests and PCSK9 assessments were not carried out because the data quality of tested samples could not be confirmed because the regulatory approvals had expired. The coprimary endpoints were assessed by using a repeated measures linear mixed-effects model including treatment group, stratification factor (high/very high CV risk versus not high/very high CV risk), scheduled visit, and the interaction of treatment with scheduled visit. The same model was used for the secondary endpoints if applicable. Multiplicity adjustment was done in each dosing regimen for the coprimary endpoints and secondary endpoints to preserve the family-wise error rate at 0.05 using sequential gatekeeping and Hochberg procedures (Fig. 1 in the Supplementary Material). No imputation was done for missing values in the main analysis, but multiple imputation was applied to handle missing primary variables in the sensitivity analyses. Subgroup analyses of the coprimary endpoints were done using the same methods used for the coprimary endpoints. A total of 12 prespecified subgroups were included in the analyses: age (<65, ≥65 years), sex, medical history of diabetes mellitus, baseline LDL cholesterol level (<median, ≥median), family history of premature coronary heart disease (CHD), baseline PCSK9 (<median, ≥median), body mass index (<25, 25 to <30, ≥30 kg/m^2), hypertension, current smoker, two or more baseline CHD risk factors, baseline triglycerides (<median, ≥median), and a diagnosis of heterozygous familial hypercholesterolemia. Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.1. Analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Patients

Of the 259 randomized patients, 17 were excluded for regulatory reasons and one was excluded because of not receiving the IP. The remaining 241 were included in the full analysis set (FAS) and received at least one dose of evolocumab 140 mg Q2W (n=79), evolocumab 420 mg QM (n=80), placebo Q2W (n=41), or placebo QM (n=41) from May 9, 2019 through May 9, 2020 (Fig. 2). Among the 241 patients in the FAS, 240 (99.2%) completed the study (one patient was lost to follow-up) and 214 (88.4%) completed the IP (24 patients discontinued the IP because of reasons related to the COVID-19 pandemic and three patients discontinued the IP at their request). Baseline demographics and clinical characteristics of patients were generally similar between the treatment groups (Table 1). The mean (SD) age of patients was 60.2 (10.3) years, 163 (67.6%) were male, and 207 (85.9%) had coronary artery disease. The most common risk factors for CVD were hypertension (62.2%), low HDL cholesterol (43.6%), and type 2 diabetes mellitus (28.6%); 122 patients (50.6%) had two or more risk factors for CVD. The vast majority (92.1%) of patients were categorized as having high or very high risk for CVD during randomization stratification. At baseline, most

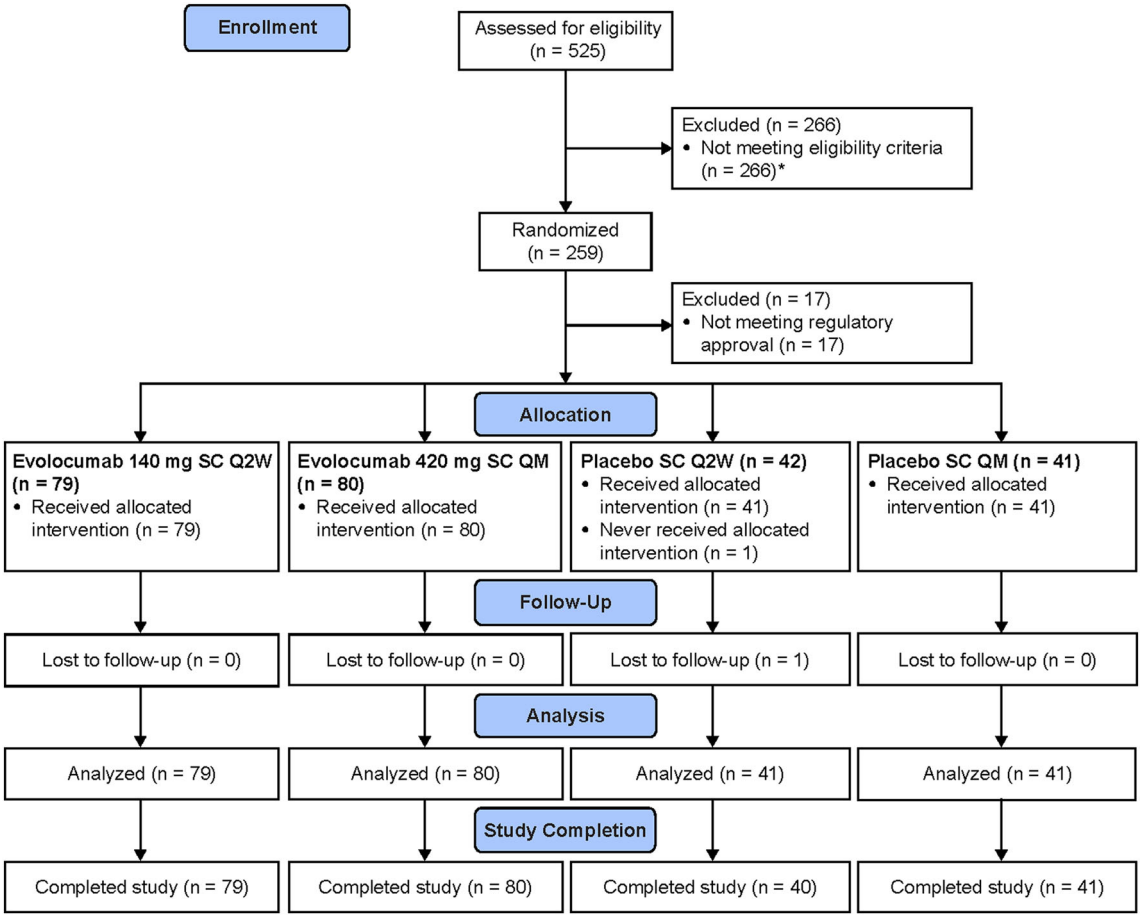


Fig. 2 Patient disposition. *Patients did not meet all eligibility criteria. The number of patients who were assessed for eligibility, enrolled, randomly assigned to treatment arms, received the investigational product, and analyzed for the study are shown. One patient in the placebo SC Q2W group never received the investigational product. *Q2W* every 2 weeks, *QM* monthly, *SC* subcutaneous

patients (72.6%) were using non-intensive statins.

Efficacy

The mean (SD) level of LDL cholesterol at baseline was 116.1 (34.6) mg/dL (3.0 [0.9] mmol/L). Results of the coprimary endpoints demonstrated significantly greater improvements in LDL cholesterol with evolocumab 140 mg Q2W and evolocumab 420 mg QM than with matching placebo (Table 2); both evolocumab dosing regimens resulted in similar reductions in LDL cholesterol. At weeks 10 and 12, the least-squares (LS) mean (95% confidence interval [CI]) percent changes from baseline in LDL cholesterol for the evolocumab 140 mg Q2W and placebo Q2W groups were −68.9% (−75.3%, −62.4%) and 1.9% (−5.5%, 9.2%), respectively, resulting in a difference (95% CI) of −70.7% (−78.0% to −63.5%). The LS mean (95% CI) percent changes from baseline in LDL cholesterol for the evolocumab 420 mg QM and placebo QM groups were −70.1% (−76.5%, −63.7%) and −0.4% (−7.9%, 7.1%), respectively, with a difference of −69.7% (−76.5% to −63.0%). The LS mean (95% CI) change from baseline in LDL cholesterol at weeks 10 and 12 for the evolocumab 140 mg Q2W and placebo Q2W groups were −77.1 (−86.7, −67.5) mg/dL

Table 1 Baseline characteristics

	Evolocumab		Placebo	
	140 mg SC Q2W (*N*=79)	420 mg SC QM (*N*=80)	SC Q2W (*N*=41)	SC QM (*N*=41)
Age				
Mean (SD), years	61.2 (10.6)	60.9 (9.8)	57.8 (9.8)	59.4 (10.9)
<65 years, *n* (%)	43 (54.4)	48 (60.0)	31 (75.6)	25 (61.0)
≥65 years, *n* (%)	36 (45.6)	32 (40.0)	10 (24.4)	16 (39.0)
Male, *n* (%)	51 (64.6)	51 (63.8)	30 (73.2)	31 (75.6)
Height, mean (SD), cm	164.9 (8.5)	164.9 (8.1)	165.4 (8.1)	167.4 (8.1)
Weight, mean (SD), kg	67.9 (13.2)	70.1 (12.8)	70.2 (10.1)	71.7 (13.6)
BMI, mean (SD), kg/m^2	24.9 (3.9)	25.7 (3.3)	25.6 (2.8)	25.4 (3.1)
Coronary artery disease, *n* (%)	69 (87.3)	68 (85.0)	36 (87.8)	34 (82.9)
Cerebrovascular disease, *n* (%)	7 (8.9)	17 (21.3)	6 (14.6)	7 (17.1)
Peripheral arterial disease, *n* (%)	8 (10.1)	8 (10.0)	3 (7.3)	6 (14.6)
Cardiovascular risk factors, *n* (%)				
Current cigarette smoking	10 (12.7)	11 (13.8)	9 (22.0)	8 (19.5)
Type 2 diabetes mellitus	25 (31.6)	25 (31.3)	9 (22.0)	10 (24.4)
Hypertension	46 (58.2)	50 (62.5)	26 (63.4)	28 (68.3)
Family history of premature CHD	2 (2.5)	5 (6.3)	2 (4.9)	3 (7.3)
Low HDL-C[a]	35 (44.3)	26 (32.5)	21 (51.2)	23 (56.1)
Patients with ≥2 risk factors	37 (46.8)	38 (47.5)	24 (58.5)	23 (56.1)
Statin intensity, *n* (%)				
Intensive statin usage[b]	22 (27.8)	17 (21.3)	15 (36.6)	12 (29.3)
Non-intensive statin usage[c]	57 (72.2)	63 (78.8)	26 (63.4)	29 (70.7)
Ezetimibe, *n* (%)	17 (21.5)	11 (13.8)	11 (26.8)	6 (14.6)
Lipid parameters				
LDL-C[d], mean (SD), mg/dL	113.7 (37.7)	115.5 (30.1)	120.9 (42.2)	117.1 (28.2)
Non-HDL-C, mean (SD), mg/dL	141.5 (40.1)	142.2 (31.8)	147.2 (44.6)	144.0 (36.0)
Total cholesterol, mean (SD), mg/dL	189.7 (39.8)	189.9 (33.0)	191.4 (43.0)	186.6 (38.5)
HDL-C, mean (SD), mg/dL	48.2 (15.4)	47.7 (10.6)	44.2 (9.8)	42.6 (10.8)
Triglycerides, median (IQR), mg/dL	133.5 (99.5–168.0)	122.8 (100.5–148.3)	115.0 (91.5–153.0)	123.0 (94.5–150.5)

Table 1 continued

	Evolocumab		Placebo	
	140 mg SC Q2W (*N*=79)	**420 mg SC QM (*N*=80)**	**SC Q2W (*N*=41)**	**SC QM (*N*=41)**
Lp(a), median (IQR), nmol/L	59.0 (25.0–158.0)	80.0 (35.8–169.8)	71.0 (43.5–152.5)	73.5 (29.5–144.0)

BMI body mass index, *CHD* coronary heart disease, *HDL-C* high-density lipoprotein cholesterol, *IQR* interquartile range, *LDL-C* low-density lipoprotein cholesterol, *Lp(a)* lipoprotein(a), *Q2W* every 2 weeks, *QD* once daily, *QM* monthly, *SC* subcutaneous, *SD* standard deviation

[a] Low HDL-C is defined as HDL-C<40 mg/dL in men and<50 mg/dL in women

[b] Intensive statin usage includes one of the following within 4 weeks before screening: atorvastatin ≥ 40 mg QD, rosuvastatin ≥ 20 mg QD, simvastatin ≥ 80 mg QD, or any statin (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin) QD plus ezetimibe

[c] Non-intensive statin usage includes at least weekly doses of statins other than those listed under intensive doses within 4 weeks before screening

[d] When LDL-C<40 mg/dL or triglycerides>400 mg/dL, calculated LDL-C was replaced with ultracentrifugation LDL-C from the same sample

(−2.0 [−2.2, −1.7] mmol/L) and −0.6 (−11.3, 10.1) mg/dL (−0.02 [−0.3, 0.3] mmol/L), respectively, for a difference (95% CI) of −76.5 (−86.6 to −66.4) mg/dL (−2.0 [−2.2 to −1.7] mmol/L). For the evolocumab 420 mg QM and placebo QM groups, the LS mean (95% CI) changes from baseline in LDL cholesterol were −83.0 (−92.9, −73.2) mg/dL and −5.8 (−17.4, 5.8) mg/dL, respectively, for a difference of −77.2 (−87.7 to −66.7) mg/dL (−2.0 [−2.3 to −1.7] mmol/L). At week 12, the extent of placebo-adjusted reduction in LDL cholesterol was similar to that at the mean of weeks 10 and 12 for both evolocumab groups. Reductions in LDL cholesterol were maintained throughout the 12-week study in both evolocumab dosing regimens (Fig. 3).

At weeks 10 and 12, the proportions of patients achieving an LDL cholesterol level of less than 70 mg/dL and those achieving at least a 50% reduction from baseline in LDL cholesterol were significantly higher in the evolocumab groups than in the matching placebo groups (Table 2). The placebo-adjusted responder rate (95% CI) for achieving an LDL cholesterol level of less than 70 mg/dL was 87% (73–93%) for the evolocumab 140 mg Q2W group and 92% (77–96%) for the evolocumab 420 mg QM group. Similarly, the placebo-adjusted responder rate (95% CI) for achieving at least a 50% reduction from baseline in LDL cholesterol at weeks 10 and 12 was 87% (73–93%) for the evolocumab 140 mg Q2W group and 89% (74–94%) for the evolocumab 420 mg QM group. Evolocumab treatment also resulted in favorable efficacy with other lipid parameters, including non-HDL cholesterol, apoB, total cholesterol, Lp(a), triglycerides, HDL cholesterol, and VLDL cholesterol (Table 2; Table S2).

Results of sensitivity analyses, using multiple imputation to handle missing coprimary endpoints, demonstrated the validity of the primary analysis results ($P<0.0001$ for both dosing regimens) (Table S3). Evolocumab also demonstrated favorable efficacy for the coprimary endpoints in all prespecified subgroups (including those for different levels of CV risk), except for the subgroup of family history of premature CHD in which the small sample size prevented proper assessment (Fig. 4). The magnitude of the treatment effect with evolocumab for the coprimary endpoints was also consistent in all subgroups (including those for different levels of CV risk), except for the subgroup of sex in the QM dosing group and the subgroup of baseline LDL cholesterol levels in the Q2W

Table 2 Results of efficacy endpoints

Endpoint	Evolocumab 140 mg SC Q2W (*N*=79)	Placebo SC Q2W (*N*=41)	Evolocumab 420 mg SC QM (*N*=80)	Placebo SC QM (*N*=41)
Mean percent change from baseline in LDL-C at weeks 10 and 12, 95% CI[a], %	−68.9 (−75.3, −62.4)	1.9 (−5.5, 9.2)	−70.1 (−76.5, −63.7)	−0.4 (−7.9, 7.1)
Difference[a,b]	−70.7 (−78.0 to −63.5)		−69.7 (−76.5 to −63.0)	
	P<0.0001		*P*<0.0001	
Percent change from baseline in LDL-C at week 12, 95% CI[a], %	−68.4 (−75.4, −61.4)	2.5 (−5.8, 10.8)	−63.1 (−69.9, −56.3)	2.7 (−5.7, 11.1)
Difference[a,b]	−70.9 (−79.5 to −62.3)		−65.8 (−74.0 to −57.7)	
	P<0.0001		*P*<0.0001	
Mean change from baseline in LDL-C at weeks 10 and 12, 95% CI[a], mg/dL	−77.1 (−86.7, −67.5)	−0.6 (−11.3, 10.1)	−83.0 (−92.9, −73.2)	−5.8 (−17.4, 5.8)
Difference[a,b]	−76.5 (−86.6 to −66.4)		−77.2 (−87.7 to −66.7)	
	P<0.0001		*P*<0.0001	
Change from baseline in LDL-C at week 12, 95% CI[a], mg/dL	−76.7 (−86.7, −66.7)	−0.8 (−12.2, 10.6)	−75.1 (−85.1, −65.1)	−2.1 (−14.1, 9.9)
Difference[a,b]	−75.9 (−87.1 to −64.7)		−73.0 (−84.1 to −61.8)	
	P<0.0001		*P*<0.0001	
Mean percent change from baseline in non-HDL-C at weeks 10 and 12, 95% CI[a], %	−58.8 (−65.0, −52.7)	2.4 (−4.6, 9.3)	−62.2 (−67.8, −56.6)	−0.1 (−6.6, 6.5)
Difference[a,b]	−61.2 (−68.0 to −54.4)		−62.2 (−68.0 to −56.3)	
	P<0.0001		*P*<0.0001	
Percent change from baseline in non-HDL-C at week 12, 95% CI[a], %	−57.6 (−64.1, −51.1)	3.9 (−3.8, 11.5)	−54.9 (−60.8, −49.0)	1.8 (−5.5, 9.1)
Difference[a,b]	−61.5 (−69.3 to −53.7)		−56.7 (−63.7 to −49.6)	
	P<0.0001		*P*<0.0001	
Mean percent change from baseline in apoB at weeks 10 and 12, 95% CI[a], %	−54.5 (−60.0, −48.9)	1.8 (−4.5, 8.1)	−56.9 (−62.0, −51.9)	0.1 (−5.9, 6.0)
Difference[a,b]	−56.3 (−62.4 to −50.1)		−57.0 (−62.4 to −51.7)	
	P<0.0001		*P*<0.0001	
Percent change from baseline in apoB at week 12, 95% CI[a], %	−53.2 (−59.1, −47.2)	2.5 (−4.5, 9.6)	−50.0 (−55.5, −44.5)	1.2 (−5.7, 8.1)

Table 2 continued

Endpoint	Evolocumab 140 mg SC Q2W (*N*=79)	Placebo SC Q2W (*N*=41)	Evolocumab 420 mg SC QM (*N*=80)	Placebo SC QM (*N*=41)
Difference[a,b]	−55.7 (−63.0 to −48.4)		−51.2 (−58.1 to −44.4)	
	P<0.0001		*P*<0.0001	
Mean percent change from baseline in total cholesterol at weeks 10 and 12, 95% CI[a], %	−41.4 (−46.2, −36.6)	1.3 (−4.1, 6.8)	−44.4 (−48.9, −39.9)	−0.1 (−5.4, 5.2)
Difference[a,b]	−42.7 (−48.1 to −37.4)		−44.3 (−49.0 to −39.6)	
	P<0.0001		*P*<0.0001	
Percent change from baseline in total cholesterol at week 12, 95% CI[a], %	−40.4 (−45.4, −35.3)	2.7 (−3.2, 8.6)	−39.3 (−44.0, −34.5)	1.2 (−4.7, 7.0)
Difference[a,b]	−43.1 (−49.1 to −37.0)		−40.4 (−46.0 to −34.9)	
	P<0.0001		*P*<0.0001	
Achievement of mean target LDL-C< 70 mg/dL at weeks 10 and 12, *n* (%), 95% CI[c]	*n*=69	*n*=37	*n*=71	*n*=35
	62 (89.9)	1 (2.7)	69 (97.2)	2 (5.7)
	(80.5, 95.0)	(0.5, 13.8)	(90.3, 99.2)	(1.6, 18.6)
Difference[b]	87.2 (72.6 to 92.8)		91.5 (76.9 to 96.1)	
	P[d]<0.0001		*P*[d]<0.0001	
Achievement of target LDL-C<70 mg/dL at week 12, *n* (%), 95% CI[c]	*n*=64	*n*=34	*n*=66	*n*=27
	58 (90.6)	0 (0.0)	59 (89.4)	1 (3.7)
	(81.0, 95.6)	(0.0, 10.2)	(79.7, 94.8)	(0.7, 18.3)
Difference[b]	90.6 (76.6 to 95.6)		85.7 (68.2 to 91.9)	
	P[d]<0.0001		*P*[d]<0.0001	
Achievement of mean target ≥50% reduction in LDL-C at weeks 10 and 12, *n* (%), 95% CI[c]	*n*=69	*n*=37	*n*=71	*n*=35
	60 (87.0)	0 (0.0)	67 (94.4)	2 (5.7)
	(77.0, 93.0)	(0.0, 9.4)	(86.4, 97.8)	(1.6, 18.6)
Difference[b]	87.0 (73.3 to 93.0)		88.7 (73.5 to 94.0)	
	P[d]<0.0001		*P*[d]<0.0001	
Achievement of target ≥50% reduction in LDL-C at week 12, *n* (%), 95% CI[c]	*n*=64	*n*=34	*n*=66	*n*=27
	53 (82.8)	0 (0.0)	57 (86.4)	1 (3.7)
	(71.8, 90.1)	(0.0, 10.2)	(76.1, 92.7)	(0.7, 18.3)

Table 2 continued

Endpoint	Evolocumab 140 mg SC Q2W (*N*=79)	Placebo SC Q2W (*N*=41)	Evolocumab 420 mg SC QM (*N*=80)	Placebo SC QM (*N*=41)
Difference[b]	82.8 (67.8 to 90.1)		82.7 (64.8 to 89.7)	
	$P^{d}<0.0001$		$P^{d}<0.0001$	
Mean percent change from baseline in Lp(a) at weeks 10 and 12, 95% CI[a], %	−43.5 (−52.3, −34.7)	5.0 (−4.9, 14.8)	−29.2 (−36.2, −22.1)	11.3 (2.6, 19.9)
Difference[a,b]	−48.5 (−57.8 to −39.1)		−40.4 (−48.6 to −32.2)	
	$P<0.0001$		$P<0.0001$	
Percent change from baseline in Lp(a) at week 12, 95% CI[a], %	−42.8 (−51.9, −33.7)	1.9 (−8.5, 12.2)	−23.7 (−32.0, −15.5)	14.5 (3.4, 25.7)
Difference[a,b]	−44.7 (−54.8 to −34.7)		−38.3 (−49.9 to −26.6)	
	$P<0.0001$		$P<0.0001$	

ApoB apolipoprotein B, *CI* confidence interval, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *Lp(a)* lipoprotein(a), *Q2W* every 2 weeks, *QM* monthly, *SC* subcutaneous, *n*=number of patients with observed data

[a] Least-squares means are shown from the repeated measures linear mixed-effects model, which included treatment group, stratification factors, scheduled visit, and the interaction of treatment with scheduled visit as covariates

[b] Treatment differences are within each dose frequency group using placebo as a reference

[c] The 95% CI was calculated by using the Wilson score method

[d] *P* values are based on the Cochran–Mantel–Haenszel test adjusted by the stratification factor

dosing group at week 12. When qualitative interaction *P* values were assessed for the subgroup of sex in the QM group and the subgroup of baseline LDL cholesterol levels in the Q2W dosing group, no significant interactions were observed within subgroups ($P=0.5$ for both subgroups). As such, consistent directionality of treatment effect with evolocumab was demonstrated across sex groups and baseline LDL cholesterol level groups.

Safety

The patient incidence of TEAEs was similar between the evolocumab and placebo groups and across dosing regimens within each group (Table 3). A total of 87 patients (54.7%) in the evolocumab groups and 45 (54.9%) in the placebo groups reported at least one TEAE, of which the majority were Common Terminology Criteria for Adverse Events (CTCAE; version 5.0) grade 1 (mild) or 2 (moderate). Seven patients (4.4%) in the evolocumab groups and six (7.3%) in the placebo groups reported serious AEs. The most common AEs (occurring in at least five patients across all treatment groups and dosing regimens) in the evolocumab and placebo groups, respectively, were upper respiratory tract infection (8.2% versus 8.5%), hypertension (6.3% versus 6.1%), hyperbilirubinemia (2.5% versus 4.9%), hyperuricemia (3.8% versus 0%),

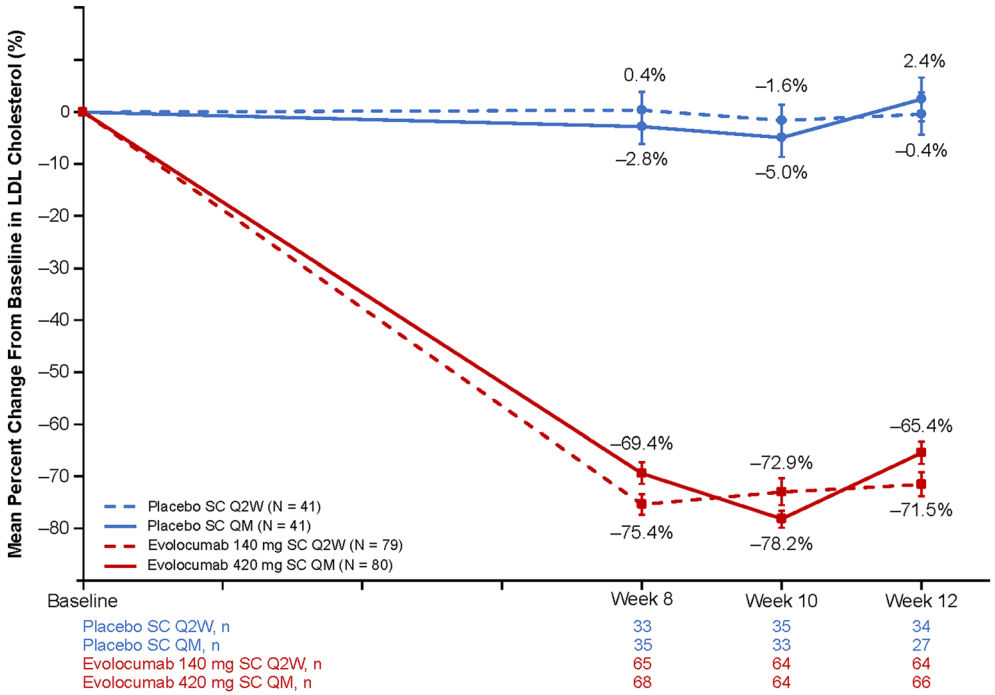


Fig. 3 Mean percent change in LDL cholesterol in the evolocumab and placebo treatment groups throughout the 12-week study. Missing values were not imputed. *n* = the number of patients with observed data. Vertical lines represent the standard error of the mean. *LDL* low-density lipoprotein, *Q2W* every 2 weeks, *QM* monthly, *SC* subcutaneous

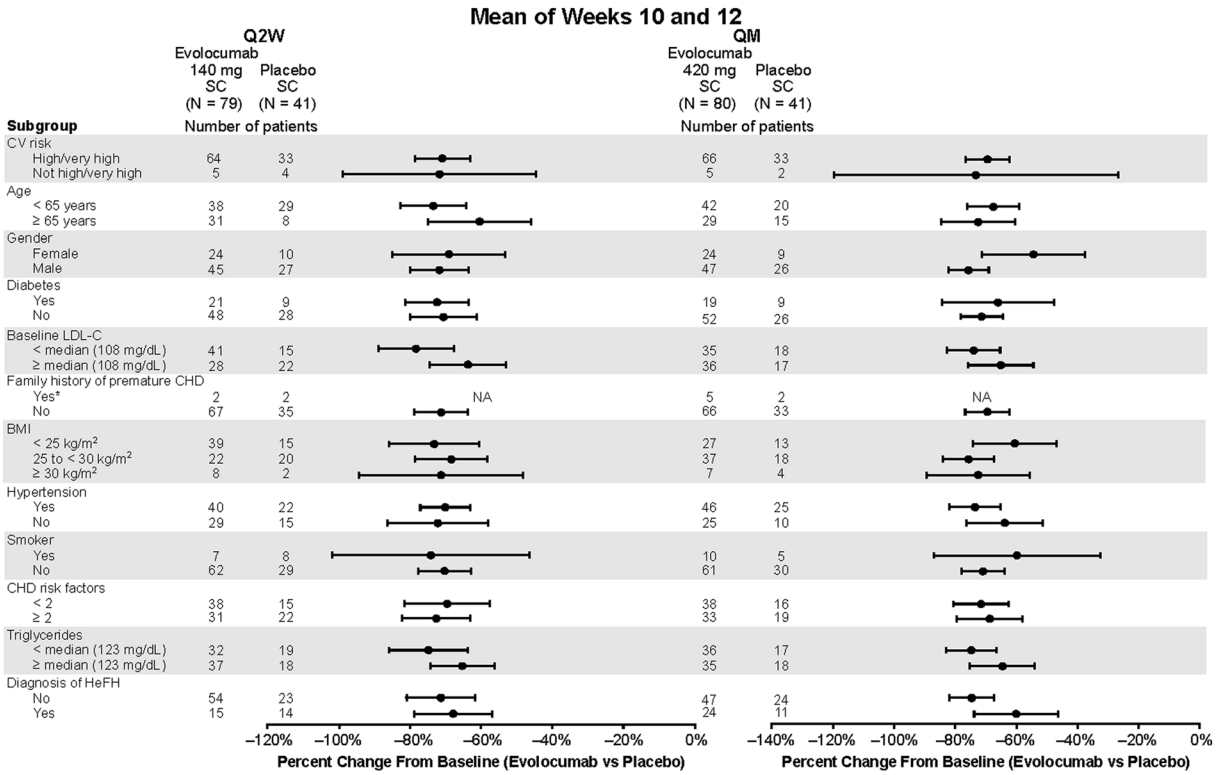
cough (1.9% versus 2.4%), and pyrexia (1.3% versus 3.7%). No AEs led to discontinuation of the IP; no fatal AEs were reported.

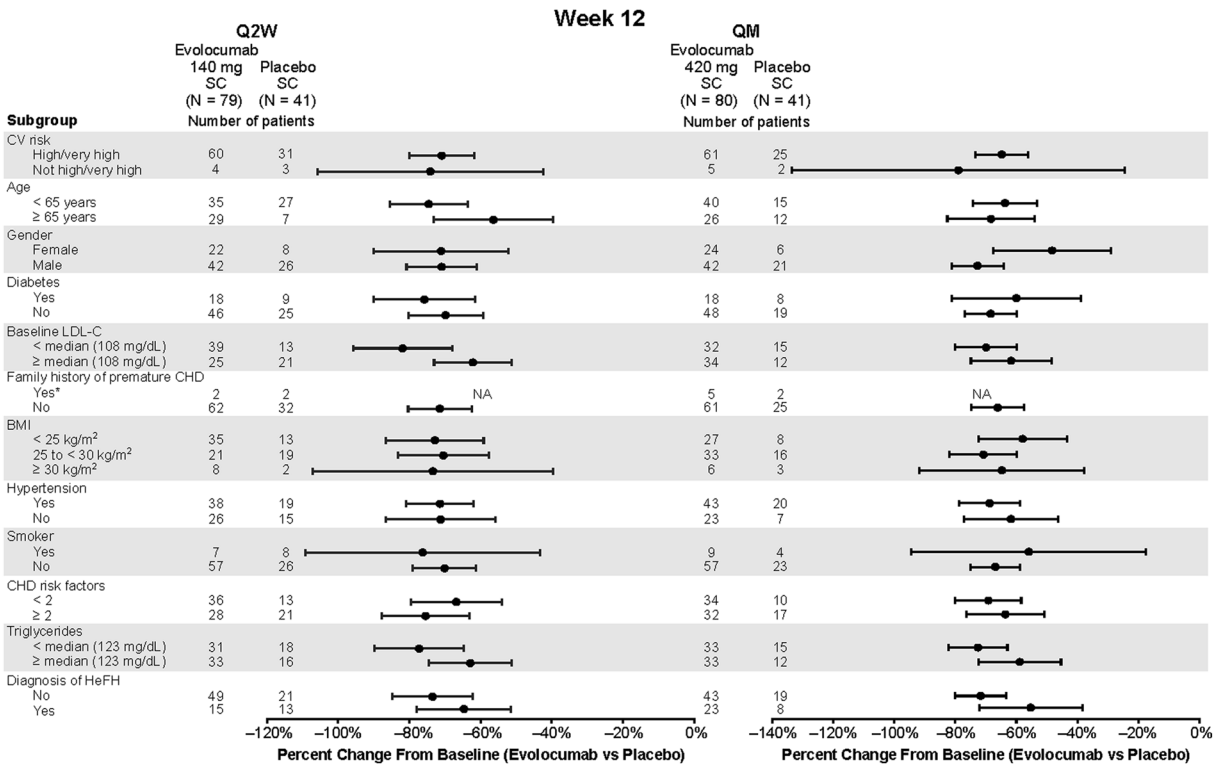
Results of laboratory tests were similar between the treatment groups and did not indicate any clinically important treatment-related abnormalities. No patients had elevated creatine kinase levels (>5 × upper limit of normal) or elevated alanine aminotransferase or aspartate aminotransferase levels (>3 × upper limit of normal).

DISCUSSION

HUA TUO is the first evolocumab study dedicated to patients in China. In this 12-week, phase 3, randomized, double-blind, placebo-controlled study in Chinese patients with primary hypercholesterolemia and mixed dyslipidemia, evolocumab, when added to stable optimized statin therapy with or without ezetimibe, resulted in significant reductions in LDL cholesterol at the mean of weeks 10 and 12 (−70% to −71% versus placebo) and at week 12 (−66% to −71% versus placebo). The magnitude of reduction in LDL cholesterol was similar between both dosing regimens (140 mg Q2W and 420 mg QM), which allows for more options to improve treatment adherence based on patient's preference.

LDL cholesterol is considered a primary target in the management of atherosclerotic CVD and reduction of CV risk. The addition of non-statin therapies in patients who cannot achieve their LDL cholesterol goal with optimal statin therapy is recommended by clinical practice guidelines [7, 10, 11]. Specifically in patients at high risk and very high risk, Chinese guidelines recommend an LDL cholesterol level of less than 2.6 mmol/L (100 mg/dL) and less than 1.8 mmol/L (70 mg/dL), respectively. In HUA TUO, after 12 weeks of treatment with evolocumab Q2W or QM, the vast majority of


Mean of Weeks 10 and 12
Q2W
Evolocumab 140 mg SC (N = 79)
Placebo SC (N = 41)
QM
Evolocumab 420 mg SC (N = 80)
Placebo SC (N = 41)
Subgroup
Number of patients
CV risk
High/very high 64 33 66 33
Not high/very high 5 4 5 2
Age
< 65 years 38 29 42 20
≥ 65 years 31 8 29 15
Gender
Female 24 10 24 9
Male 45 27 47 26
Diabetes
Yes 21 9 19 9
No 48 28 52 26
Baseline LDL-C
< median (108 mg/dL) 41 15 35 18
≥ median (108 mg/dL) 28 22 36 17
Family history of premature CHD
Yes* 2 2 NA 5 2 NA
No 67 35 66 33
BMI
< 25 kg/m2 39 15 27 13
25 to < 30 kg/m2 22 20 37 18
≥ 30 kg/m2 8 2 7 4
Hypertension
Yes 40 22 46 25
No 29 15 25 10
Smoker
Yes 7 8 10 5
No 62 29 61 30
CHD risk factors
< 2 38 15 38 16
≥ 2 31 22 33 19
Triglycerides
< median (123 mg/dL) 32 19 36 17
≥ median (123 mg/dL) 37 18 35 18
Diagnosis of HeFH
No 54 23 47 24
Yes 15 14 24 11
–120% –100% –80% –60% –40% –20% 0%
–140% –120% –100% –80% –60% –40% –20% 0%
Percent Change From Baseline (Evolocumab vs Placebo)
Percent Change From Baseline (Evolocumab vs Placebo)


Week 12
Q2W
Evolocumab 140 mg SC (N = 79)
Placebo SC (N = 41)
QM
Evolocumab 420 mg SC (N = 80)
Placebo SC (N = 41)
Subgroup
Number of patients
CV risk
High/very high 60 31 61 25
Not high/very high 4 3 5 2
Age
< 65 years 35 27 40 15
≥ 65 years 29 7 26 12
Gender
Female 22 8 24 6
Male 42 26 42 21
Diabetes
Yes 18 9 18 8
No 46 25 48 19
Baseline LDL-C
< median (108 mg/dL) 39 13 32 15
≥ median (108 mg/dL) 25 21 34 12
Family history of premature CHD
Yes* 2 2 NA 5 2 NA
No 62 32 61 25
BMI
< 25 kg/m2 35 13 27 8
25 to < 30 kg/m2 21 19 33 16
≥ 30 kg/m2 8 2 6 3
Hypertension
Yes 38 19 43 20
No 26 15 23 7
Smoker
Yes 7 8 9 4
No 57 26 57 23
CHD risk factors
< 2 36 13 34 10
≥ 2 28 21 32 17
Triglycerides
< median (123 mg/dL) 31 18 33 15
≥ median (123 mg/dL) 33 16 33 12
Diagnosis of HeFH
No 49 21 43 19
Yes 15 13 23 8
–120% –100% –80% –60% –40% –20% 0%
–140% –120% –100% –80% –60% –40% –20% 0%
Percent Change From Baseline (Evolocumab vs Placebo)
Percent Change From Baseline (Evolocumab vs Placebo)

◀**Fig. 4** Subgroup analyses of coprimary endpoints. Forest plots are shown of placebo-adjusted (evolocumab minus placebo) least-squares means of the coprimary endpoints for the evolocumab groups by subgroups. Least-squares means are from the repeated measures linear effects model including treatment group, stratification factors, scheduled visit, and the interaction of treatment with scheduled visit as covariates. *The sample size was too small to perform the analysis. Horizontal lines are 95% CIs. *BMI* body mass index, *CHD* coronary heart disease, *CV* cardiovascular, *HeFH* heterozygous familial hypercholesterolemia, *LDL-C* low-density lipoprotein cholesterol, *Q2W* every 2 weeks, *QM* monthly, *SC* subcutaneous

patients achieved an LDL cholesterol level of less than 70 mg/dL (86–91% versus placebo). For patients with high baseline levels of LDL cholesterol who cannot achieve this goal, an alternative goal of at least a 50% reduction in LDL cholesterol should be considered [7]. In this study, 83–89% of patients in the evolocumab groups achieved at least a 50% reduction from baseline in LDL cholesterol compared with the placebo groups. Significant improvements in other lipid parameters (including non-HDL cholesterol, apoB, total cholesterol, Lp(a), triglycerides, HDL cholesterol, and VLDL cholesterol) were also observed for the evolocumab groups compared with the placebo groups. No safety concerns were observed during the study.

Table 3 Safety data

	Evolocumab		**Placebo**	
	140 mg SC Q2W (*N*=79)	**420 mg SC QM (*N*=80)**	**SC Q2W (*N*=41)**	**SC QM (*N*=41)**
All TEAEs, *n* (%)	45 (57.0)	42 (52.5)	22 (53.7)	23 (56.1)
Grade ≥ 2	30 (38.0)	24 (30.0)	13 (31.7)	14 (34.1)
Grade ≥ 3	8 (10.1)	3 (3.8)	0 (0.0)	3 (7.3)
Serious AEs, *n* (%)	6 (7.6)	1 (1.3)	2 (4.9)	4 (9.8)
AEs leading to discontinuation of IP, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Most common TEAEs (>5 patients across all treatment groups and dosing regimens), *n* (%)				
Upper respiratory tract infection	7 (8.9)	6 (7.5)	5 (12.2)	2 (4.9)
Hypertension	6 (7.6)	4 (5.0)	2 (4.9)	3 (7.3)
Hyperbilirubinemia	3 (3.8)	1 (1.3)	2 (4.9)	2 (4.9)
Hyperuricemia	3 (3.8)	3 (3.8)	0 (0.0)	0 (0.0)
Cough	2 (2.5)	1 (1.3)	1 (2.4)	1 (2.4)
Pyrexia	2 (2.5)	0 (0.0)	0 (0.0)	3 (7.3)
Laboratory values at any postbaseline visit, *n* (%)				
CK > 5 × ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ALT or AST > 5 × ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

AE adverse event, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *CK* creatine kinase, *IP* investigational product, *Q2W* every 2 weeks, *QM* monthly, *SC* subcutaneous, *TEAE* treatment-emergent adverse event, *ULN* upper limit of normal

The results of HUA TUO are consistent with prior short-term and long-term global studies with evolocumab in patients with hypercholesterolemia and mixed dyslipidemia and with previous subgroup analyses in both Asian and Chinese patients. In the 12-week, randomized, double-blind, global, phase 3 LAPLACE-2 study, evolocumab significantly reduced LDL cholesterol (63–75% versus placebo) in patients with hypercholesterolemia and mixed dyslipidemia [18]. The YUKAWA-2 study showed mean LDL cholesterol reductions ranging from 67% to 76% after 12 weeks of evolocumab treatment in Japanese patients at high risk [20]. Furthermore, in a pooled analysis including data from 15 phase 2 and phase 3 studies, no significant difference in the treatment effect of evolocumab was observed between White and non-White, and the reduction across patient populations was consistent with that observed in Asian patients (68.9% reduction) [21]. Similar reductions in LDL cholesterol with evolocumab have previously been reported regardless of other demographic and clinical characteristics [21, 22]. A prespecified analysis from the long-term CV outcomes FOURIER trial showed that treatment with evolocumab in Asian patients is at least as effective as it is in non-Asian patients [23]. The results of HUA TUO are also consistent with a prespecified analysis of patients in China ($n=453$) from the global BERSON study, which enrolled patients with type 2 diabetes and hyperlipidemia and mixed dyslipidemia [16]. In the subgroup of patients enrolled in China, evolocumab resulted in an 80–81% placebo-adjusted reduction in LDL cholesterol at the mean of weeks 10 and 12 [16]. The efficacy of another PCSK9 inhibitor (alirocumab) was evaluated in patients from South Korea and Taiwan with hypercholesterolemia at high CV risk on maximally tolerated statin therapy (75 mg Q2W [9.5% of patients increased dosage to 150 mg Q2W at week 12] versus placebo). In that study, treatment with alirocumab, compared with placebo, resulted in statistically significant reductions in LDL cholesterol (57.1% versus 6.3%, respectively) at week 24 [24].

The main limitations of the study are the small number of patients ($N=241$) and the short 12-week duration for the assessment of sustained lowering of LDL cholesterol and safety. However, the results of HUA TUO are consistent with prior global studies and studies with other Asian patients that included larger sample sizes and/or a longer follow-up.

CONCLUSION

This 12-week study confirms the efficacy and safety of evolocumab, as an adjunct to stable statin therapy with or without ezetimibe, to reduce LDL cholesterol and improve other lipid parameters in Chinese patients with primary hypercholesterolemia and mixed dyslipidemia.

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List of Investigators. Please see Supplementary Material.

Prior Publication. Some of the results included here were presented at the 2022 European Atherosclerosis Society (EAS) (Milan, Italy; May 22–25, 2022).

Disclosures. Maria Laura Monsalvo, You Wu, Jackie Mao, and Lily Xin are employees of and hold stock in Amgen. Hong Tan, Weimin Li, Zhouqing Huang, Yajun Han, Xuecheng Huang, Dongye Li, Xiaochun Xing, and Jiyan Chen report no relationships that could be construed as a conflict of interest.

Compliance with Ethics Guidelines. This study involved human patients who provided informed consent to participate in the study and was approved by ethics committees and institutional review boards listed in the Supplementary Material. Oversight and conduct of the study were done in accordance with the ethical guidelines of the Declaration of Helsinki, Good Clinical Practice guidelines of the International Council for Harmonisation, and related regulations in China.

Data Availability. Qualified researchers may request data from Amgen clinical studies. Complete details are available at https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparency-practices/clinical-trial-data-sharing-request.

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