



# 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

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## ABSTRACT

**Introduction:** Evolocumab, a fully human pro-protein 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>.

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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)



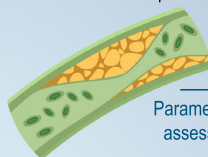
Evolocumab (140 mg SC Q2W and 420 mg SC QM) vs matched placebo

241 Chinese patients aged  $\geq 18$  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  $\pm$  ezetimibe



Male 67.6%



Mean (SD) LDL-C at baseline 116.1 (34.6) mg/dL



Hypertension 62.2%



Coronary artery disease 85.9%

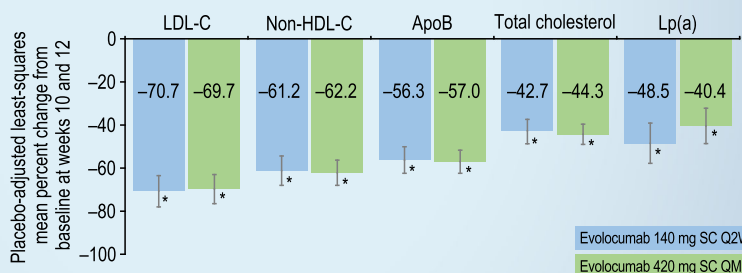


T2DM 28.6%

High / very high risk for CVD 92.1%  
 $\geq 2$  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  $\geq 1$  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**



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.

This graphical abstract represents the opinions of the authors. For a full list of declarations, including funding and author disclosure statements, and copyright information, please see the full text online.

**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

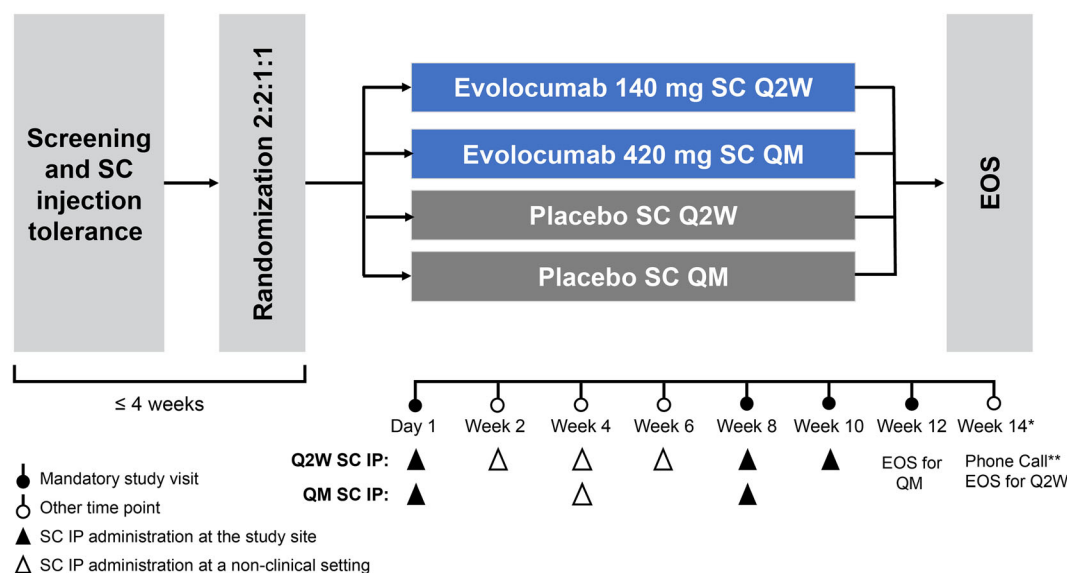
### Trial Design and Oversight

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 ( $\geq 40$  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%.

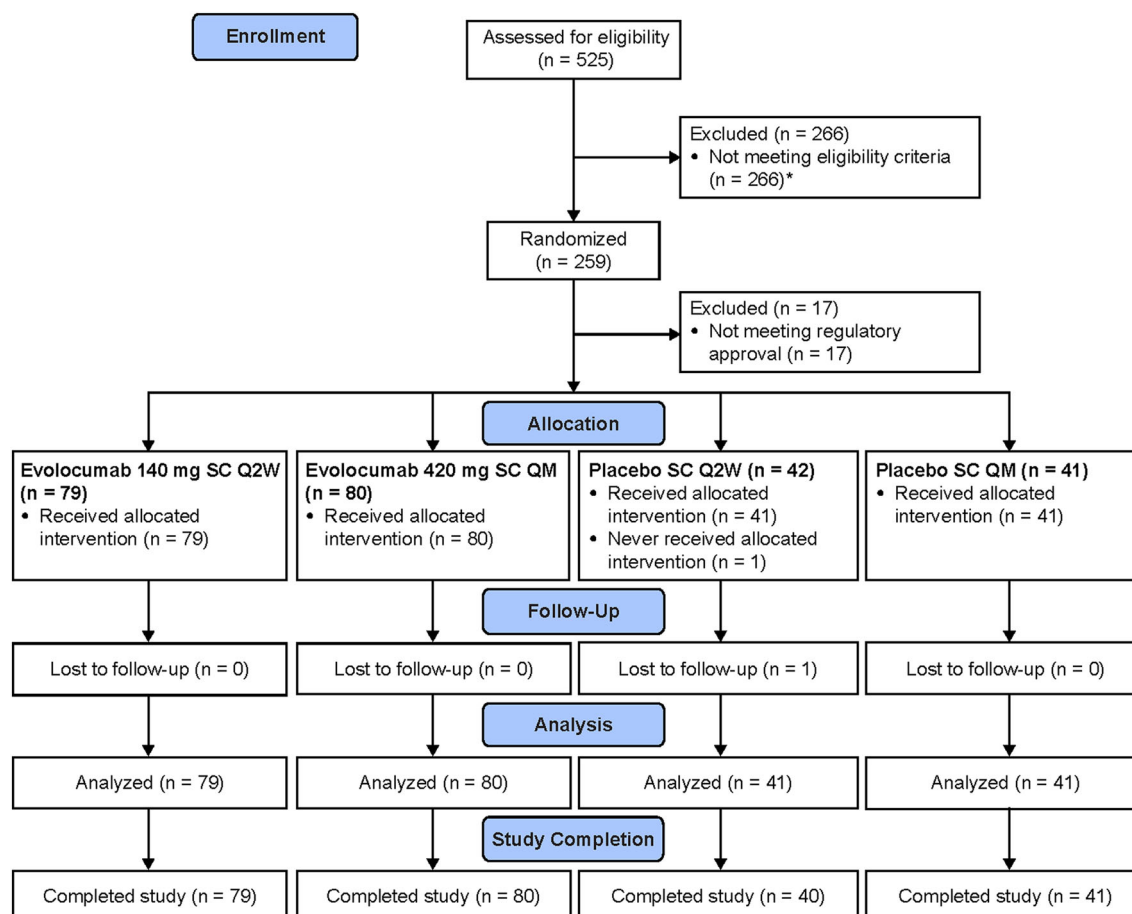
Efficacy and safety analyses included all randomized patients who received at least one dose of the IP, except for 17 patients who were excluded from all data analyses for regulatory reasons, and were done independently for each dosing regimen (Q2W and QM). Planned analyses of data from anti-evolocumab 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,  $\geq$ 65 years), sex, medical history of diabetes mellitus, baseline LDL cholesterol level (<median,  $\geq$ median), family history of premature coronary heart disease (CHD), baseline PCSK9 (<median,  $\geq$ median), body mass index (<25, 25 to <30,  $\geq$ 30 kg/m<sup>2</sup>), hypertension, current smoker, two or more baseline CHD risk factors, baseline triglycerides (<median,  $\geq$ 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

	<b>Evolocumab</b>		<b>Placebo</b>	
	<b>140 mg SC Q2W (N=79)</b>	<b>420 mg SC QM (N=80)</b>	<b>SC Q2W (N=41)</b>	<b>SC QM (N=41)</b>
<b>Age</b>				
Mean (SD), years	61.2 (10.6)	60.9 (9.8)	57.8 (9.8)	59.4 (10.9)
<65 years, <i>n</i> (%)	43 (54.4)	48 (60.0)	31 (75.6)	25 (61.0)
≥65 years, <i>n</i> (%)	36 (45.6)	32 (40.0)	10 (24.4)	16 (39.0)
Male, <i>n</i> (%)	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 <sup>2</sup>	24.9 (3.9)	25.7 (3.3)	25.6 (2.8)	25.4 (3.1)
Coronary artery disease, <i>n</i> (%)	69 (87.3)	68 (85.0)	36 (87.8)	34 (82.9)
Cerebrovascular disease, <i>n</i> (%)	7 (8.9)	17 (21.3)	6 (14.6)	7 (17.1)
Peripheral arterial disease, <i>n</i> (%)	8 (10.1)	8 (10.0)	3 (7.3)	6 (14.6)
<b>Cardiovascular risk factors, <i>n</i> (%)</b>				
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 <sup>a</sup>	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)
<b>Statin intensity, <i>n</i> (%)</b>				
Intensive statin usage <sup>b</sup>	22 (27.8)	17 (21.3)	15 (36.6)	12 (29.3)
Non-intensive statin usage <sup>c</sup>	57 (72.2)	63 (78.8)	26 (63.4)	29 (70.7)
Ezetimibe, <i>n</i> (%)	17 (21.5)	11 (13.8)	11 (26.8)	6 (14.6)
<b>Lipid parameters</b>				
LDL-C <sup>d</sup> , 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

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

<sup>b</sup> 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

<sup>c</sup> Non-intensive statin usage includes at least weekly doses of statins other than those listed under intensive doses within 4 weeks before screening

<sup>d</sup> 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	Placebo	Evolocumab	Placebo
	140 mg SC Q2W (N=79)	SC Q2W (N=41)	420 mg SC QM (N=80)	SC QM (N=41)
Mean percent change from baseline in LDL-C at weeks 10 and 12, 95% CI <sup>a</sup> , %	-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 <sup>a,b</sup>	-70.7 (-78.0 to -63.5)		-69.7 (-76.5 to -63.0)	
	<i>P</i> <0.0001		<i>P</i> <0.0001	
Percent change from baseline in LDL-C at week 12, 95% CI <sup>a</sup> , %	-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 <sup>a,b</sup>	-70.9 (-79.5 to -62.3)		-65.8 (-74.0 to -57.7)	
	<i>P</i> <0.0001		<i>P</i> <0.0001	
Mean change from baseline in LDL-C at weeks 10 and 12, 95% CI <sup>a</sup> , 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 <sup>a,b</sup>	-76.5 (-86.6 to -66.4)		-77.2 (-87.7 to -66.7)	
	<i>P</i> <0.0001		<i>P</i> <0.0001	
Change from baseline in LDL-C at week 12, 95% CI <sup>a</sup> , 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 <sup>a,b</sup>	-75.9 (-87.1 to -64.7)		-73.0 (-84.1 to -61.8)	
	<i>P</i> <0.0001		<i>P</i> <0.0001	
Mean percent change from baseline in non-HDL-C at weeks 10 and 12, 95% CI <sup>a</sup> , %	-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 <sup>a,b</sup>	-61.2 (-68.0 to -54.4)		-62.2 (-68.0 to -56.3)	
	<i>P</i> <0.0001		<i>P</i> <0.0001	
Percent change from baseline in non-HDL-C at week 12, 95% CI <sup>a</sup> , %	-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 <sup>a,b</sup>	-61.5 (-69.3 to -53.7)		-56.7 (-63.7 to -49.6)	
	<i>P</i> <0.0001		<i>P</i> <0.0001	
Mean percent change from baseline in apoB at weeks 10 and 12, 95% CI <sup>a</sup> , %	-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 <sup>a,b</sup>	-56.3 (-62.4 to -50.1)		-57.0 (-62.4 to -51.7)	
	<i>P</i> <0.0001		<i>P</i> <0.0001	
Percent change from baseline in apoB at week 12, 95% CI <sup>a</sup> , %	-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	Placebo	Evolocumab	Placebo
	140 mg SC Q2W (N=79)	SC Q2W (N=41)	420 mg SC QM (N=80)	SC QM (N=41)
Difference <sup>a,b</sup>	-55.7 (-63.0 to -48.4)		-51.2 (-58.1 to -44.4)	
	<i>P</i> <0.0001		<i>P</i> <0.0001	
Mean percent change from baseline in total cholesterol at weeks 10 and 12, 95% CI <sup>a</sup> , %	-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 <sup>a,b</sup>	-42.7 (-48.1 to -37.4)		-44.3 (-49.0 to -39.6)	
	<i>P</i> <0.0001		<i>P</i> <0.0001	
Percent change from baseline in total cholesterol at week 12, 95% CI <sup>a</sup> , %	-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 <sup>a,b</sup>	-43.1 (-49.1 to -37.0)		-40.4 (-46.0 to -34.9)	
	<i>P</i> <0.0001		<i>P</i> <0.0001	
Achievement of mean target LDL-C < 70 mg/dL at weeks 10 and 12, <i>n</i> (%), 95% CI <sup>c</sup>	<i>n</i> =69 62 (89.9) (80.5, 95.0)	<i>n</i> =37 1 (2.7) (0.5, 13.8)	<i>n</i> =71 69 (97.2) (90.3, 99.2)	<i>n</i> =35 2 (5.7) (1.6, 18.6)
Difference <sup>b</sup>	87.2 (72.6 to 92.8)		91.5 (76.9 to 96.1)	
	<i>P</i> <sup>d</sup> <0.0001		<i>P</i> <sup>d</sup> <0.0001	
Achievement of target LDL-C < 70 mg/dL at week 12, <i>n</i> (%), 95% CI <sup>c</sup>	<i>n</i> =64 58 (90.6) (81.0, 95.6)	<i>n</i> =34 0 (0.0) (0.0, 10.2)	<i>n</i> =66 59 (89.4) (79.7, 94.8)	<i>n</i> =27 1 (3.7) (0.7, 18.3)
Difference <sup>b</sup>	90.6 (76.6 to 95.6)		85.7 (68.2 to 91.9)	
	<i>P</i> <sup>d</sup> <0.0001		<i>P</i> <sup>d</sup> <0.0001	
Achievement of mean target ≥ 50% reduction in LDL-C at weeks 10 and 12, <i>n</i> (%), 95% CI <sup>c</sup>	<i>n</i> =69 60 (87.0) (77.0, 93.0)	<i>n</i> =37 0 (0.0) (0.0, 9.4)	<i>n</i> =71 67 (94.4) (86.4, 97.8)	<i>n</i> =35 2 (5.7) (1.6, 18.6)
Difference <sup>b</sup>	87.0 (73.3 to 93.0)		88.7 (73.5 to 94.0)	
	<i>P</i> <sup>d</sup> <0.0001		<i>P</i> <sup>d</sup> <0.0001	
Achievement of target ≥ 50% reduction in LDL-C at week 12, <i>n</i> (%), 95% CI <sup>c</sup>	<i>n</i> =64 53 (82.8) (71.8, 90.1)	<i>n</i> =34 0 (0.0) (0.0, 10.2)	<i>n</i> =66 57 (86.4) (76.1, 92.7)	<i>n</i> =27 1 (3.7) (0.7, 18.3)

Table 2 continued

Endpoint	Evolocumab	Placebo	Evolocumab	Placebo
	140 mg SC Q2W (N=79)	SC Q2W (N=41)	420 mg SC QM (N=80)	SC QM (N=41)
Difference <sup>b</sup>	82.8 (67.8 to 90.1) $P^d < 0.0001$		82.7 (64.8 to 89.7) $P^d < 0.0001$	
Mean percent change from baseline in Lp(a) at weeks 10 and 12, 95% CI <sup>a</sup> , %	-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 <sup>a,b</sup>	-48.5 (-57.8 to -39.1) $P < 0.0001$		-40.4 (-48.6 to -32.2) $P < 0.0001$	
Percent change from baseline in Lp(a) at week 12, 95% CI <sup>a</sup> , %	-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 <sup>a,b</sup>	-44.7 (-54.8 to -34.7) $P < 0.0001$		-38.3 (-49.9 to -26.6) $P < 0.0001$	

*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

<sup>a</sup> 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

<sup>b</sup> Treatment differences are within each dose frequency group using placebo as a reference

<sup>c</sup> The 95% CI was calculated by using the Wilson score method

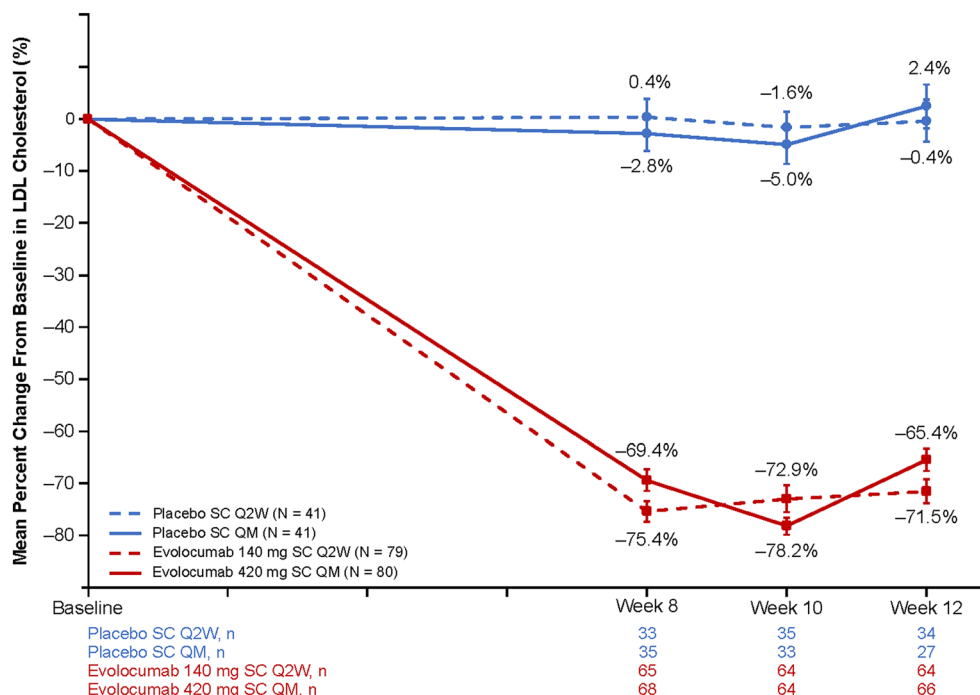
<sup>d</sup> *P* values are based on the Cochran–Mantel–Haenszel test adjusted by the stratification factor

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 ( $>5 \times$  upper limit of normal) or elevated alanine aminotransferase or aspartate aminotransferase levels ( $>3 \times$  upper limit of normal).

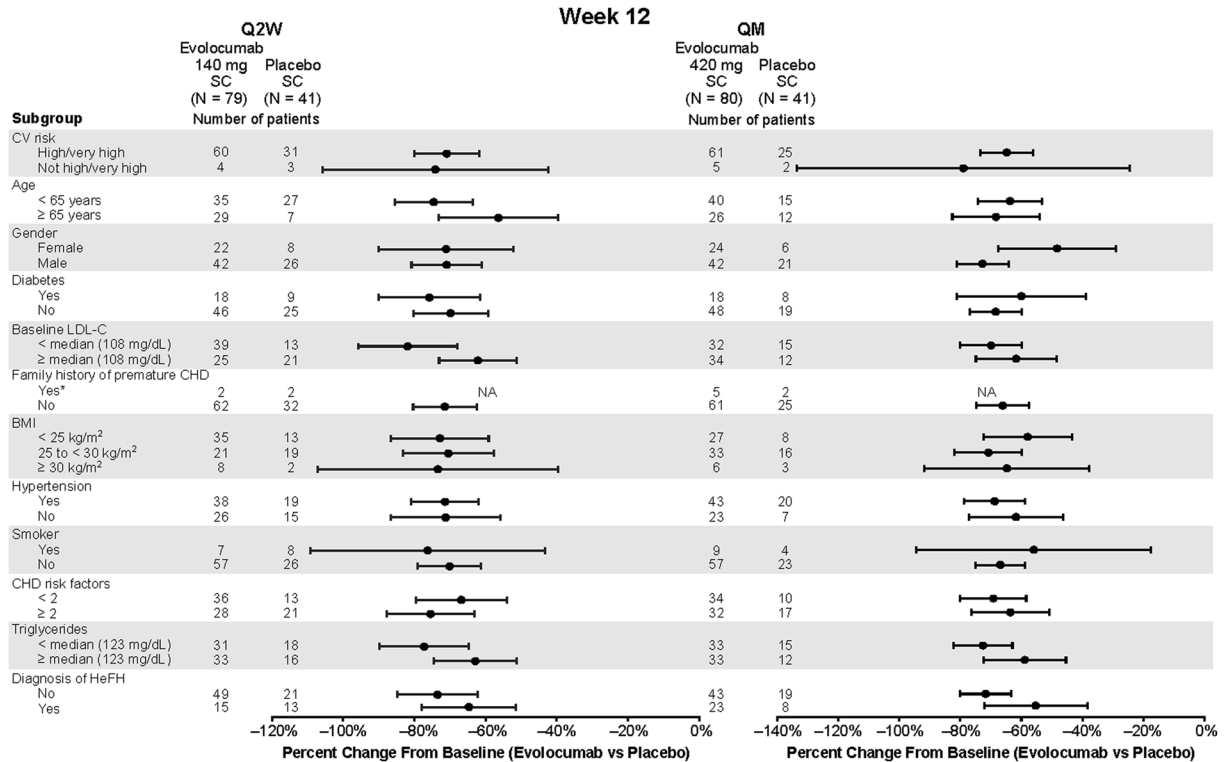
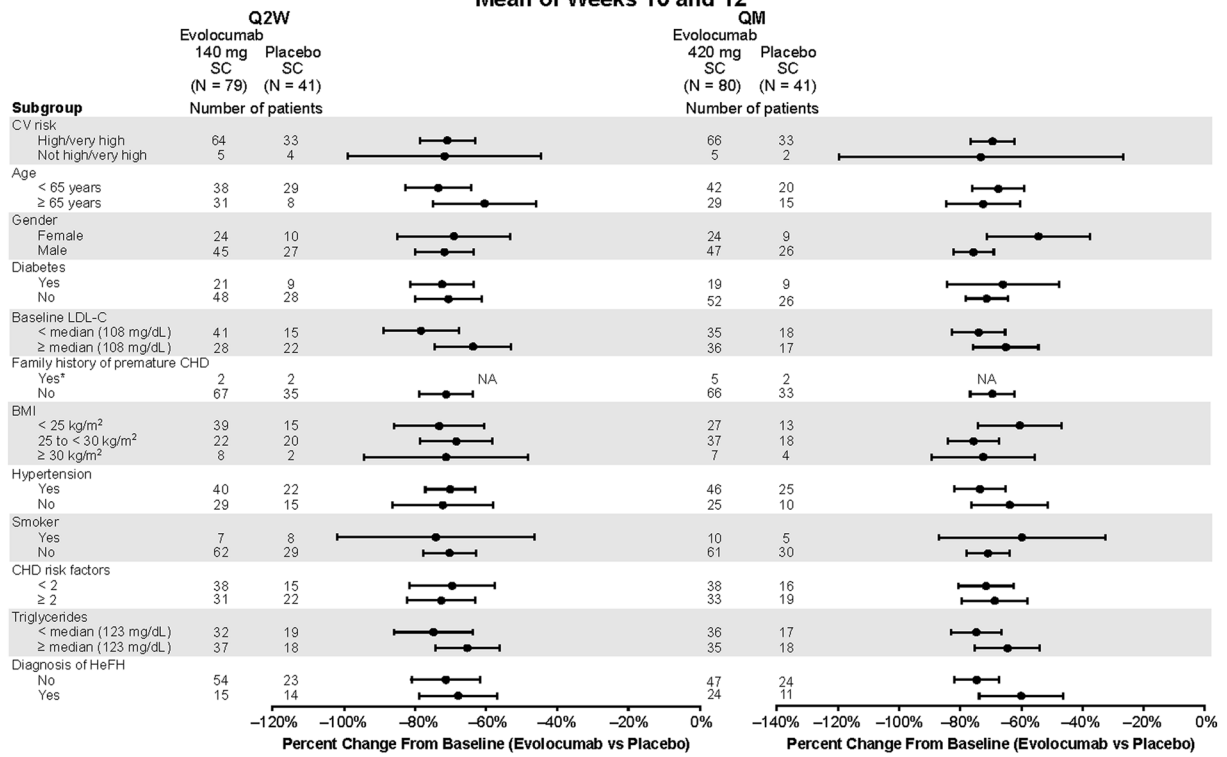
## DISCUSSION

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



◀ **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

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.

patients achieved an LDL cholesterol level of less than 70 mg/dL (86–91% versus placebo).

**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, <i>n</i> (%)	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, <i>n</i> (%)	6 (7.6)	1 (1.3)	2 (4.9)	4 (9.8)
AEs leading to discontinuation of IP, <i>n</i> (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Most common TEAEs (>5 patients across all treatment groups and dosing regimens), <i>n</i> (%)				
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, <i>n</i> (%)				
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 BERSO 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 alicumab, 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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**Author Contributions.** Authors had full access to the data in the study and take full responsibility for the integrity and accuracy of the data. Concept and design: Maria Laura Monsalvo, Jackie Mao, Lily Xin. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: All authors. Critical revision for intellectual content: All authors. Statistical analysis: You Wu. Administrative, technical, or material support: Maria Laura Monsalvo, You Wu, Jackie Mao, Lily Xin. The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

**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 Jiyang 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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