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## **Anti-PCSK9 Antibody Effectively Lowers Cholesterol in Patients with Statin Intolerance: The GAUSS-2 Randomized, Placebo-controlled Phase 3 Clinical Trial of Evolocumab**

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### **Running head: Evolocumab in Statin-intolerant Patients**

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### **Disclosures**

Dr. Stroes reports receiving (non-substantial) lecturing fees from Amgen, Merck, Novartis, Regeneron, and Sanofi.

Dr. Colquhoun reports no conflict of interest that would be biased to this work.

Dr. Sullivan reports receiving research funding from Amgen, Abbott Products, AstraZeneca, Merck Sharp and Dohme, and Sanofi; educational program funding from Abbott Products, AstraZeneca, Merck Sharp and Dohme, Pfizer Australia, and Roche; and travel support from Merck Sharp and Dohme. Dr Sullivan has served on advisory boards for Abbott Products, Merck Sharp and Dohme, and Pfizer Australia.

Dr. Civeira has received a research grant from Merck, consulting fees from Sanofi, and honoraria from Merck and Amgen.

Dr. Rosenson has participated on advisory boards for Aegerion, Amgen, Astra Zeneca, CVS Caremark, GSK, Novartis Pfizer, Regeneron, Sanofi, and Sticars InterACT. Dr. Rosenson has received institutional research grants from Amgen, Novartis, and Sanofi and royalties from UpToDate, Inc. Dr. Rosenson is a stockholder of LipoScience, and Medicines Company.

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Drs. Dent, Knusel, Xue, Scott, and Wasserman are employees and stockholders of Amgen.

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**Abstract**

**Objectives** To evaluate the efficacy and safety of subcutaneous (SC) evolocumab compared with oral ezetimibe in hypercholesterolemic subjects unable to tolerate effective statin doses.

**Background** Statin intolerance, predominantly due to muscle-related side effects, is reported in up to 10%-20% of patients. Evolocumab, a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9), demonstrated marked reductions in plasma LDL cholesterol (LDL-C) in a phase 2 study in statin-intolerant patients.

**Methods** The Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin Intolerant Subjects (GAUSS-2; NCT 01763905), a 12-week, double-blind study, randomized patients (2:2:1:1) to evolocumab 140 mg biweekly (Q2W) or evolocumab 420 mg monthly (QM) both with daily oral placebo (PBO); or SC PBO Q2W or QM both with daily oral ezetimibe 10 mg. Co-primary endpoints were percent change from baseline in LDL cholesterol at week 12 and at the mean of weeks 10 and 12.

**Results** 307 patients (mean [SD] age 62 [10], LDL-C 193 [59] mg/dL) were randomized. Evolocumab reduced LDL-C from baseline by 53% to 56%, corresponding to treatment differences versus ezetimibe of 37% to 39% ( $p < 0.001$ ). Muscle adverse events occurred in 12% of evolocumab- and 23% of ezetimibe-treated patients. Treatment-emergent adverse events and laboratory abnormalities were comparable across treatment groups.

**Conclusions** Robust efficacy combined with favorable tolerability makes evolocumab a promising therapy for addressing the large unmet clinical need in high-risk patients with elevated cholesterol who are statin intolerant.

**Key words:** LDL-cholesterol, statin intolerance, evolocumab, ezetimibe, hypercholesterolemia

**Abbreviations**

CHD, coronary heart disease

CK, creatine kinase

HDL-C, high-density lipoprotein cholesterol

LDL-C, low-density lipoprotein cholesterol

LDLR, low-density lipoprotein receptor

NCEP, National Cholesterol Education Program

PCSK9, proprotein convertase subtilisin/kexin type 9

Q2W, every 2 weeks

QM, monthly

VLDL-C, very low density lipoprotein cholesterol

## INTRODUCTION

Lowering low-density lipoprotein cholesterol with statins reduces cardiovascular risk.(1,2)

Whereas statins are well tolerated, statin-associated side effects have been shown to exceed previous estimates based on randomized trials, reaching up to 10-20%.(3) Although Zhang et al (3) reported that a substantial proportion of patients with side effects to one statin tolerated a rechallenge to a second statin, failure to achieve treatment target in patients intolerant to multiple statins is expected to translate into lower benefits in cardiovascular risk.(1-4) The cholesterol absorption inhibitor, ezetimibe, is well tolerated but yields only a minor reduction in LDL-C. Other therapies include bile acid sequestrants and nicotinic acid, but these agents are usually poorly tolerated. Novel potent LDL-C-lowering therapies such as the apolipoprotein-B synthesis inhibitor and the microsomal triglyceride transfer protein inhibitor are characterized by marked side effects, limiting wider usage.(5,6)

Proprotein convertase subtilisin/kexin type 9 is a protein involved in regulating LDLR recycling.(7-9) Evolocumab (AMG 145) is a fully human monoclonal antibody that binds to PCSK9 and inhibits its interaction with the LDLR, resulting in increased receptor recycling and LDL clearance. In a phase 2 dose-finding study, evolocumab reduced LDL-C in statin-intolerant patients and showed favorable short-term tolerability.(10) We now report the Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin Intolerant Subjects-2 (GAUSS-2) trial,(11) a phase 3 study comparing the effects of evolocumab with ezetimibe in statin-intolerant hypercholesterolemic subjects. Compared to GAUSS, which included patients intolerant to at least one statin, the present phase 3 trial evaluated evolocumab compared to ezetimibe using a placebo-controlled design in patients intolerant to at least 2 statins.

## **METHODS**

### **Patients**

GAUSS-2 enrolled patients aged 18 to 80 years on no or low-dose statin. Participants had LDL-C above their NCEP Adult Treatment Panel III goal.(12) Participants had prior intolerance to  $\geq 2$  statins, defined as inability to tolerate any dose or increase the dose above the smallest tablet strength because of intolerable muscle-related side effects.(11)

### **Study Design and Oversight**

The institutional review boards approved the protocol and all patients provided written informed consent. GAUSS-2 (NCT01763905) was a randomized, double-blind, phase 3, placebo- and ezetimibe-controlled study.(11) Patients were randomized 2:2:1:1 to subcutaneous (SC) evolocumab 140 mg Q2W or evolocumab 420 mg monthly (QM) both with daily oral placebo; or SC PBO Q2W or QM both with daily oral ezetimibe. Patients and all study personnel were blinded to treatment assignment. An independent data monitoring committee reviewed all data.

### **Study Procedures**

Study procedures were similar to those listed in the MENDEL-2 study (Koren, manuscript submitted to JACC).

### **Efficacy and Safety Evaluations**

Co-primary endpoints were percent change from baseline in LDL-C at the mean of weeks 10 and 12 and at week 12. Co-secondary efficacy endpoints at the same time points included change from baseline in LDL-C, percent of patients with LDL-C  $< 70$  mg/dL and percent change from baseline in non-HDL-C, apolipoprotein B, total cholesterol/HDL-C ratio, apolipoprotein B/apolipoprotein A-I ratio, lipoprotein(a), triglycerides, HDL-C, and VLDL-C.(10) Safety

endpoints included treatment-emergent and serious adverse events, CK and hepatic enzyme elevations, and anti-evolocumab antibodies.

### **Statistical Analysis**

Planned enrollment of 300 patients (200 evolocumab) had  $\geq 92\%$  power to detect superiority of evolocumab regimens over ezetimibe based on a 2-sided t-test with 0.05 significance level for co-primary endpoints. Statistical analyses were similar to those in the MENDEL-2 study (Koren, manuscript submitted to JACC).

## **RESULTS**

### **Patients**

Between January and August 2013, 307 patients were randomized to evolocumab (n=205) or ezetimibe (n=102). (Table 1 and Table S1 in the Supplementary Appendix). Patients had mean (SD) baseline LDL-C of 193 (59) mg/dL. Lipid-lowering therapy was used by 33% of patients; 18% received a low-dose statin. Fifty-six percent of patients were at high CHD risk by NCEP. Treatment was completed by 96% of patients on evolocumab and 86% of patients on ezetimibe. Eight patients discontinued evolocumab (4%) for adverse events (n=6), patient request (n=1), or loss to follow-up (n=1). Fourteen patients discontinued ezetimibe (14%) for adverse events (n=11), patient request (n=2), or other reason (n=1). The study was completed by 290 patients (94%; Figure S1 the Supplementary Appendix).

### **Efficacy Outcomes**

#### ***LDL Cholesterol***

Evolocumab yielded significant reductions in LDL-C (Table 2). Mean percent reductions from baseline (95% confidence interval [CI]) at a mean of weeks 10 and 12 were 56.1% (59.7%-52.5%) with 140 mg Q2W and 55.3% (58.3%-52.3%) with 420 mg QM, corresponding to

treatment differences versus ezetimibe of 36.9% (42.3%-31.6%) and 38.7% (43.1%-34.3%), respectively ( $p<0.001$ ). Mean percent reductions from baseline and treatment differences at week 12 were similar ( $p<0.001$ ). Reductions in LDL-C were sustained throughout the trial (Figure 1). Evolocumab-treated patients were more likely to achieve LDL-C target levels than ezetimibe-treated patients (Figure 2).

### ***Other Lipids***

Compared with ezetimibe, evolocumab led to significant reductions in apolipoprotein B, lipoprotein(a), non-HDL-C, and the apolipoprotein B/apolipoprotein A-I and total cholesterol/HDL-C ratios ( $p<0.001$ ; Table 2 and Table S2 in the Supplementary Appendix).

### **Safety Outcomes**

Treatment-emergent adverse events are listed in Table 3 and the Supplementary Appendix.

Adverse events led to study drug discontinuation in 8% (evolocumab) and 13% (ezetimibe) of patients. Myalgia occurred in 8% of evolocumab and 18% of ezetimibe treated patients. Patients using low-dose statin therapy were more likely to develop myalgia in the ezetimibe (statin vs. no statin: 21% vs. 17%) and the evolocumab group (statin vs. no statin: 17% vs 6%).

Discontinuation rates due to musculoskeletal side effects were 5% (evolocumab) and 6% (ezetimibe). No binding or neutralizing antibodies to evolocumab were detected.

### **DISCUSSION**

In the GAUSS-2 study, evolocumab administered over three months yielded a significant reduction in LDL-C in hypercholesterolemic patients unable to tolerate effective doses of at least two statins, reflecting a population with a true unmet need.

Evolocumab treatment resulted in a 53% to 56% reduction in LDL-C, with comparable reductions between dosing regimens. In GAUSS-2, 82% of patients used no statin, leading to



markedly elevated LDL-C levels (mean of 193 mg/dL) comparable to those observed in early secondary prevention trials (13). Of evolocumab-treated patients at high risk, over 75% achieved LDL-C <100 mg/dL compared with less than 10% ezetimibe-treated patients. In the context of the American College of Cardiology/American Heart Association guidelines,(14) these findings imply that evolocumab could be a promising alternative agent to lower LDL-C in statin-intolerant patients with markedly elevated LDL-C levels.

Compared with the dose-finding phase 2 trial (GAUSS; (10)), GAUSS-2 enrolled a higher CV-risk population with more patients intolerant to at least two statins, leading to the inclusion of patients with a truly unmet clinical need. Awaiting the results of the outcome trial with evolocumab (NCT01764633), the observed 100 mg/dL reduction in LDL-C can be expected to reduce cardiovascular risk given the 22% risk reduction per 39 mg/dL LDL-C decrease reported for statins.(1,2)

In GAUSS-2, ezetimibe was selected as comparator based on its favorable tolerability and widespread use in statin-intolerant patients.(15) The vast majority of patients using ezetimibe failed to achieve LDL-C target levels, as evidenced by the 2% rate of LDL-C <70 mg/dL achievement. Moreover, benefit of ezetimibe-induced LDL-C lowering awaits confirmation in the ongoing outcome study (IMPROVE-IT; NCT00202878).(16)

Evolocumab also reduced lipoprotein(a) levels by 27% (Q2W) and 22% (QM) at week 12, consistent with lipoprotein(a) reductions reported in previous studies using PCSK9-targeting programs.(17-19) Further studies on the mechanism of lipoprotein(a) lowering and the benefit of evolocumab in patients with elevated lipoprotein(a) levels are warranted.

Evolocumab was well tolerated with 96% of patients completing treatment. With all patients having historically experienced muscle-related side effects during statin therapy, myalgia

incidence was low (18%, 7%, and 9% of patients in the ezetimibe, evolocumab biweekly, and evolocumab monthly groups, respectively). In the MENDEL-2 study, (Koren, et al, manuscript submitted to JACC) these rates were 1%, 1%, and 1%, respectively. Notwithstanding the higher rate in statin-intolerant patients, there was no increase in muscle-related side effects in the evolocumab- compared to ezetimibe-treated patients. This suggests that the pathways contributing to statin-associated myalgia/myositis(20,21) are distinct from those contributing to PCSK9 antibody-mediated LDL-C lowering. Since the study was short-term, these data await confirmation in the FOURIER outcome study (NCT01764633). The incidence of treatment-emergent adverse events and laboratory abnormalities were comparable across treatment groups. A limitation of this study includes the absence of a blinded statin rechallenge. We used a real-life definition of patients having experienced intolerable muscle-related side effects to  $\geq 2$  statins, with the majority failing to tolerate  $\geq 3$  statins. A placebo-controlled, blinded statin rechallenge has, however, been included in the GAUSS-3 study (NCT01984424). Another limitation is the short study duration in patients needing life-long treatment; however, patients were eligible to enroll in the open-label extension study (NCT01854918) following GAUSS-2.

In conclusion, evolocumab treatment yielded a robust reduction in plasma LDL-C in hypercholesterolemic patients with statin intolerance. The low incidence of muscle-related side effects in GAUSS-2 underscores evolocumab as a useful therapy for hypercholesterolemic patients who presently have few tolerable treatment options, provided that benefit is confirmed in the ongoing endpoint trial (FOURIER, NCT01764633).

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**Figure Legends**

**Figure 1. Mean percent change in LDL-C concentration from baseline to week 12 in patients dosed with evolocumab every 2 weeks (A) and monthly (B).** Vertical lines represent standard error around the mean. No imputation was used for missing data; the plot is based on observed values. BL, baseline; LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 weeks; QM, monthly; SC, subcutaneous

**Figure 2. Percentage of patients achieving LDL-C goal at week 12 and at mean of weeks 10 and 12 stratified by National Cholesterol Education Program risk category.** NCEP risk categories defined as high – diagnosed coronary heart disease or risk equivalent; moderately high – 2 or more risk factors and Framingham risk score  $\leq 20\%$ ; and lower – 0 or 1 risk factor. LDL-C, low-density lipoprotein cholesterol; PBO, placebo; Q2W, every 2 weeks; QD, daily; QM, monthly

**Table 1. Baseline characteristics**

	Evolocumab		Evolocumab	
	Ezetimibe QD	140 mg Q2W	Ezetimibe QD	420 mg QM +
	+ PBO Q2W	+ PBO QD	+ PBO QM	PBO QD
	N = 51	N = 103	N = 51	N = 102
Age, y	62 (10)	61 (10)	60 (9)	63 (10)
Male, n (%)	24 (47)	57 (55)	29 (57)	56 (55)
Race, n (%)				
White	49 (96)	94 (91)	46 (90)	98 (96)
Black	0	3 (3)	1 (2)	3 (3)
Lipid parameters				
LDL-C, mg/dL	195 (64)	192 (57)	195 (52)	192 (61)
Apolipoprotein B, mg/dL	140 (37)	140 (32)	140 (31)	133 (32)
Lipoprotein(a), nmol/L, median (IQR)	57 (22, 205)	39 (10, 101)	26 (7, 181)	31 (9, 80)
Apolipoprotein A-I, mg/dL	154 (34)	149 (29)	144 (23)	153 (24)
HDL-C, mg/dL	52 (18)	51 (16)	48 (11)	54 (16)

Free PCSK9, ng/mL	317 (125)	285 (80)	295 (98)	266 (95)
Statin-related history, n (%)				
Number of intolerable statins				
2	25 (49)	46 (45)	17 (33)	50 (49)
3	13 (26)	37 (36)	22 (43)	32 (31)
≥4	13 (25)	20 (19)	12 (24)	20 (20)
Worst muscle-related side effect <sup>§</sup>				
Myalgia	40 (78)	80 (78)	45 (88)	81 (79)
Myositis	11 (22)	20 (19)	4 (8)	19 (19)
Rhabdomyolysis	0	2 (2)	2 (4)	2 (2)
Lipid-lowering therapy at baseline				
Any	15 (29)	34 (33)	16 (31)	37 (36)
Rosuvastatin	6 (12)	10 (10)	2 (4)	9 (9)



Simvastatin	0	1 (1)	3 (6)	3 (3)
Atorvastatin	1 (2)	1 (1)	2 (4)	2 (2)
Other statin	2 (4)	7 (7)	3 (6)	3 (3)
Cardiovascular risk factors, n (%)				
Current cigarette use	5 (10)	12 (12)	4 (8)	3 (3)
Type 2 diabetes mellitus	11 (22)	20 (19)	16 (31)	15 (15)
Hypertension	30 (59)	57 (55)	38 (75)	56 (55)
Family history of premature CHD <sup>†</sup>	10 (20)	31 (30)	22 (43)	36 (35)
Low HDL-C <sup>§</sup>	18 (35)	37 (36)	18 (35)	29 (28)
≥2 CV risk factors	20 (39)	54 (52)	35 (69)	38 (37)
NCEP risk categories, n (%) <sup>¶</sup>				
High	32 (63)	51 (50)	32 (63)	58 (57)
Moderately high	5 (10)	16 (16)	8 (16)	16 (16)
Moderate	9 (18)	20 (19)	8 (16)	16 (16)

Low	5 (10)	16 (16)	3 (6)	12 (12)
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Data are mean (SD) unless specified. <sup>§</sup>Data missing for one patient in the evolocumab Q2W arm; myalgia, muscle symptoms without creatine kinase (CK) elevation; myositis, muscle symptoms with CK elevation; rhabdomyolysis, muscle symptoms with marked CK elevation.

<sup>l</sup>CHD in male first-degree relative at <55 years of age or in female first-degree relative at <65 years of age; <sup>§</sup>Defined as <40 mg/dL in men and <50 mg/dL in women. <sup>¶</sup>Risk category

definitions: high, diagnosed CHD or risk equivalent; moderately high, 2 or more risk factors and Framingham risk score 10%-20%; moderate, 2 or more risk factors and Framingham risk score <10%; lower, 0 or 1 risk factor. CHD, coronary heart disease; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; NCEP, National Cholesterol Education Program; PBO, placebo; PCSK9, proprotein convertase subtilisin/kexin type 9; Q2W, every 2 weeks; QD, daily; QM, monthly

**Table 2. Efficacy outcomes**

	Ezetimibe QD + PBO Q2W N = 51	Evolocumab 140 mg Q2W + PBO QD N = 103	Ezetimibe QD + PBO QM N = 51	Evolocumab 420 mg QM + PBO QD N = 102
<b>LDL-C, %</b>				
% change from baseline, mean of weeks 10 and 12 <sup>†</sup>	-19.2 (-23.9, -14.5)	-56.1 (-59.7, -52.5)	-16.6 (-20.6, -12.6)	-55.3 (-58.3, -52.3)
Treatment difference vs ezetimibe <sup>‡</sup>		-36.9 (-42.3, -31.6)		-38.7 (-43.1, -34.3)
% change from baseline, week 12 <sup>†</sup>	-18.1 (-23.1, -13.1)	-56.1 (-59.9, -52.4)	-15.1 (-19.3, -10.9)	-52.6 (-55.7, -49.5)
Treatment difference vs ezetimibe <sup>‡</sup>		-38.1 (-43.7, -32.4)		-37.6 (-42.2, -32.9)
<b>LDL-C*, mg/dL</b>				
Change from baseline, mean of weeks 10 and 12, mg/dL	-39.1 (-49.3, -29.0)	-105.4 (-113.1, -97.7)	-33.0 (-41.9, -24.1)	-103.6 (-110.2, 96.9)
Treatment difference vs ezetimibe <sup>‡</sup>		-66.3 (-77.9, -54.7)		-70.6 (-80.5, -60.7)
Change from baseline, week 12, mg/dL	-36.2 (-46.9, -25.5)	-106.0 (-114.0, -97.9)	-30.2 (-39.5, -20.9)	-99.0 (-105.9, -92.1)
Treatment difference vs		-69.7		-68.8

ezetimibe <sup>‡</sup>		(-82.0, -57.5)		(-79.2, -58.4)
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### Other lipid parameters

#### Apolipoprotein B

% change from baseline,	-13.7	-45.9	-11.0	-46.0
mean of weeks 10 and 12	(-17.9, -9.4)	(-49.2, -42.6)	(-15.4, -6.7)	(-49.3, -42.7)
Treatment difference vs		-32.2		-35.0
ezetimibe <sup>‡</sup>		(-36.9, -27.5)		(-39.6, -30.4)
% change from baseline,	-13.0	-45.8	-10.0	-43.1
week 12	(-17.5, -8.4)	(-49.4, -42.3)	(-14.6, -5.4)	(-46.5, -39.7)
Treatment difference vs		-32.9		-33.1
ezetimibe <sup>‡</sup>		(-38.0, -27.7)		(-38.0, -28.2)

#### Lipoprotein(a)

% change from baseline,	-2.3	-26.2	1.6	-23.7
mean of weeks 10 and 12	(-8.9, 4.3)	(-31.4, -21.0)	(-6.4, 9.5)	(-29.6, -17.9)
Treatment difference vs		-23.9		-25.3
ezetimibe <sup>‡</sup>		(-31.3, -16.5)		(-33.8, -16.8)
% change from baseline,	-1.7	-27.0	5.8	-22.1
week 12	(-8.8, 5.3)	(-32.5, -21.5)	(-4.3, 15.9)	(-29.3, -14.8)
Treatment difference vs		-25.3		-27.9
ezetimibe <sup>‡</sup>		(-33.3, -17.3)		(-39.2, -16.6)

## HDL-C

% change from baseline,	0.3	5.5	1.4	7.2
mean of weeks 10 and 12	(-3.6, 4.2)	(2.5, 8.5)	(-2.6, 5.5)	(4.2, 10.2)
Treatment difference vs ezetimibe		5.2 (0.7, 9.6)		5.7 (1.2, 10.2)
% change from baseline,	1.8	5.3	1.6	6.5
week 12	(-2.6, 6.2)	(2.0, 8.6)	(-2.7, 6.0)	(3.3, 9.7)
Treatment difference vs ezetimibe		3.6 (-1.5, 8.6)		4.8 (-0.2, 9.8)

Apolipoprotein A-I<sup>s</sup>

% change from baseline,	-0.1	5.4	2.6	5.3
mean of weeks 10 and 12	(-3.4, 3.3)	(2.7, 8.1)	(-1.1, 6.2)	(2.5, 8.0)
Treatment difference vs ezetimibe		5.5 (1.7, 9.2)		2.7 (-1.2, 6.5)
% change from baseline,	1.1	5.2	3.2	5.5
week 12	(-2.4, 4.6)	(2.4, 7.9)	(-0.9, 7.2)	(2.5, 8.5)
Treatment difference vs ezetimibe		4.1 (0.1, 8.0)		2.3 (-2.1, 6.8)

## LDL-C achievement &lt;70

mg/dL

Mean of weeks 10 and 12, n (%)	1 (2.0)	46 (45.5)	0	42 (42.0)
Treatment difference vs ezetimibe <sup>‡</sup> , %		43.5 (30.9, 53.4)		42.0 (30.3, 51.8)
Week 12, n (%)	1 (2.0)	49 (50.0)	0	36 (37.5)
Treatment difference vs ezetimibe <sup>‡</sup> , %		48.0 (35.0, 57.8)		37.5 (25.5, 47.5)
PCSK9				
% change from baseline, week 10, mean (SD)	-6.4 (38.4)	-61.8 (31.2)	7.9 (61.9)	-93.9 (17.0)
% change from baseline, week 12, mean (SD)	1.1 (30.0)	-61.1 (33.8)	0.7 (60.0)	-27.2 (163.9)

Data are least squares mean (95% CI), unless otherwise specified. Least squares mean is from the repeated measures model, including covariates of stratification factors, treatment group, scheduled visit, and interaction of treatment with scheduled visits. <sup>†</sup>Co-primary endpoint.

<sup>‡</sup>Adjusted p value vs ezetimibe <0.001; multiplicity adjustments within each dose frequency were used to control for the overall significance level for all primary and secondary endpoints.

HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol. PBO, placebo; PCSK9, proprotein convertase subtilisin/kexin type 9; Q2W, every 2 weeks; QD, daily; QM, monthly

**Table 3. Adverse events**

Event	Ezetimibe			Evolocumab		
				140 mg	420 mg	
				Q2W +	QM +	
	QD +	QD +		PBO	PBO	
	PBO	PBO		QD	QD	
	Q2W	QM	All	N =	N =	All
	N = 51	N = 51	N=102	103	102	N=205
<i>n (%)</i>						
Treatment emergent						
Any	35 (69)	39 (77)	74 (73)	63 (61)	72 (71)	135 (66)
Serious	1 (2)	3 (6)	4 (4)*	5 (5)	1 (1)	6 (3) <sup>†</sup>
Leading to discontinuation of investigational product	4 (8)	9 (18)	13 (13)	6 (6)	11 (11)	17 (8)
Deaths	0	0	0	0	0	0
Common treatment emergent <sup>‡</sup>						

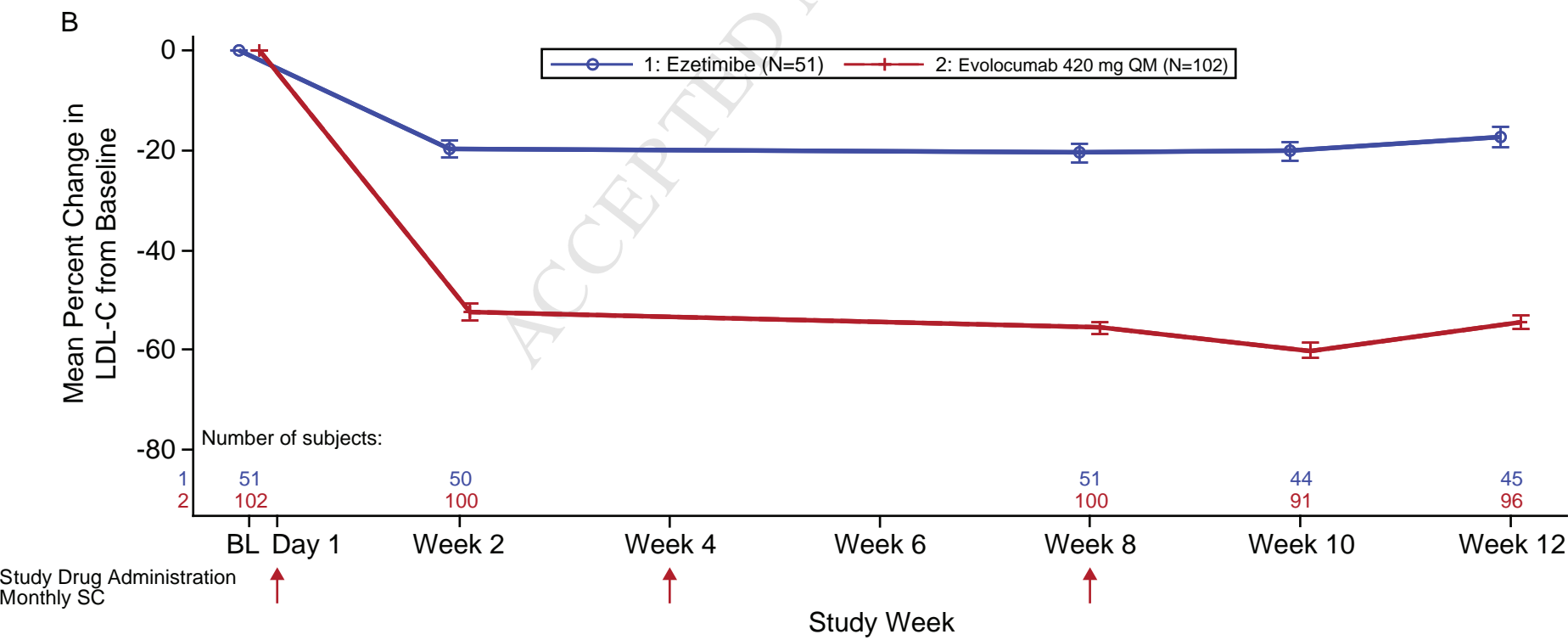
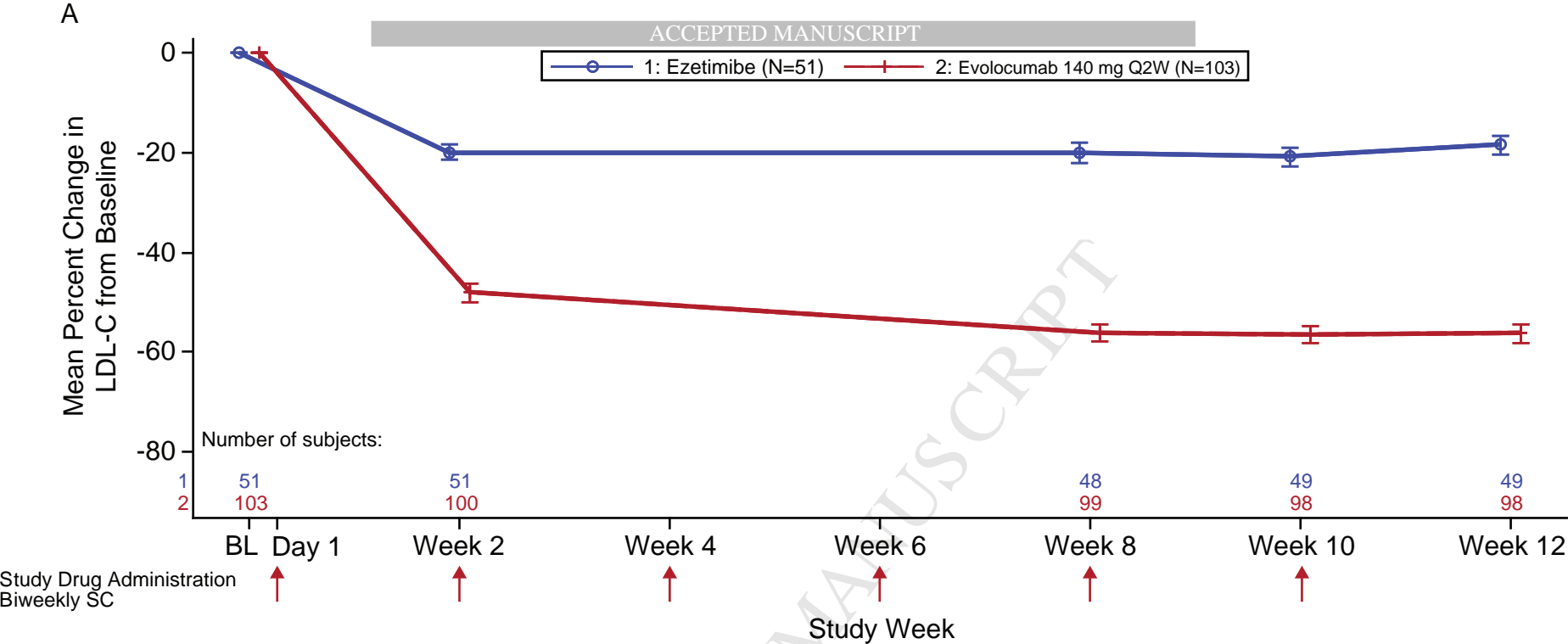
Headache	3 (6)	6 (12)	9 (9)	4 (4)	12 (12)	16 (8)
Myalgia	7 (14)	11 (22)	18 (18)	7 (7)	9 (9)	16 (8)
Pain in extremity	0	1 (2)	1 (1)	2 (2)	12 (12)	14 (7)
Muscle spasms	3 (6)	1 (2)	4 (4)	5 (5)	8 (8)	13 (6)
Fatigue	4 (8)	6 (12)	10 (10)	3 (3)	6 (6)	9 (4)
Nausea	2 (4)	5 (10)	7 (7)	3 (3)	6 (6)	9 (4)
Nasopharyngitis	3 (6)	0	3 (3)	5 (5)	2 (2)	7 (3)
Diarrhea	3 (6)	4 (8)	7 (7)	3 (3)	2 (2)	5 (2)
Injection site erythema	0	3 (6)	3 (3)	2 (2)	2 (2)	4 (2)
Paraesthesia	1 (2)	4 (8)	5 (5)	0	2 (2)	2 (1)
Influenza	3 (6)	0	3 (3)	1 (1)	0	1 (<1)
Pruritus	1 (2)	3 (6)	4 (4)	0	0	0
Abnormal laboratory tests						
CK >5 x ULN	3 (6)	0	3 (3)	0	2 (2)	2 (1)
CK >10 x ULN	1 (2)	0	1 (1)	0	0	0



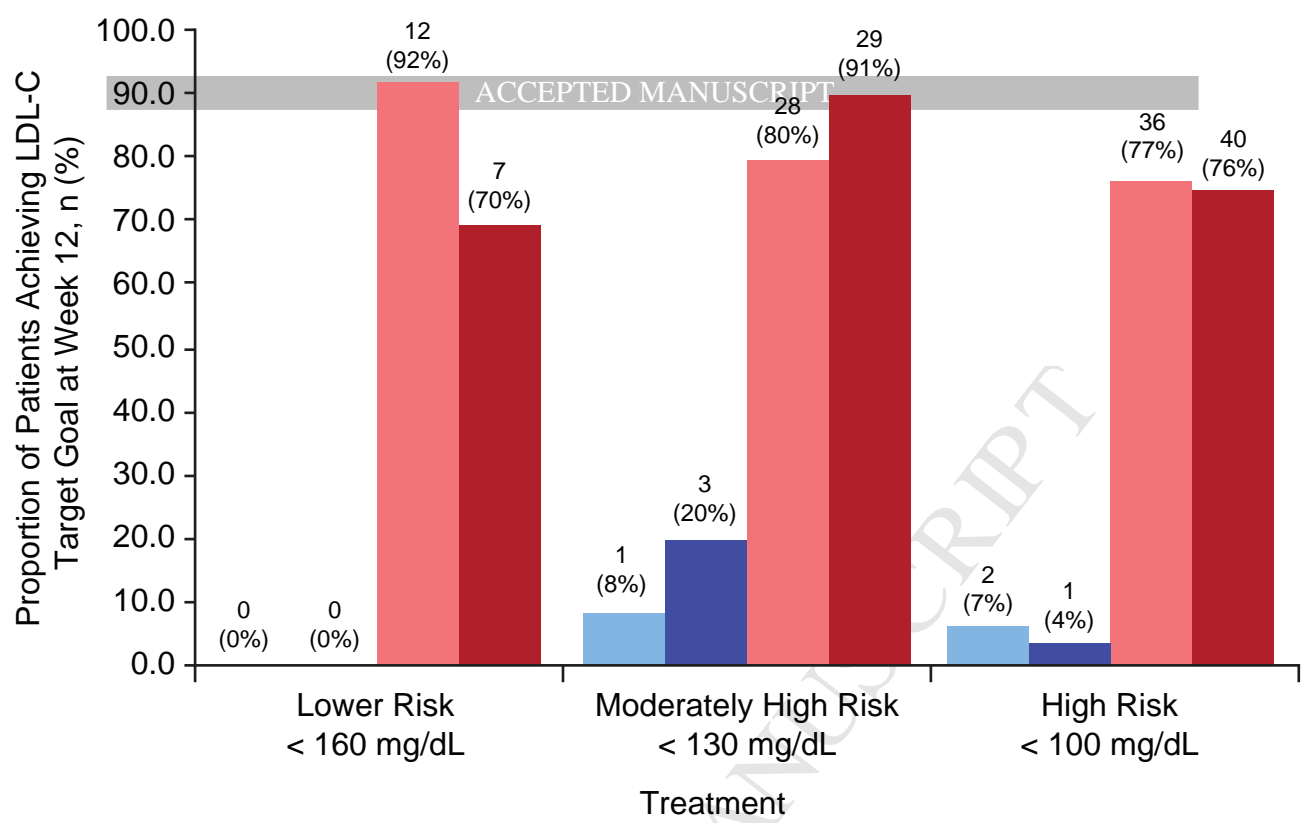
ALT or AST >3 x ULN	0	0	0	0	0	0
Muscle-related SMQ	8 (16)	15 (29)	23 (23)	13 (13)	12 (12)	25 (12)
Myositis	0	0	0	0	1 (1)	1 (<1)
Myalgia	7 (14)	11 (22)	18 (18)	7 (7)	9 (9)	16 (8)
Musculoskeletal pain	1 (2)	2 (4)	3 (3)	1 (1)	2 (2)	3 (2)
Muscular weakness	0	1 (2)	1 (1)	2 (2)	0	2 (1)
Increased plasma creatinine	0	0	0	2 (2)	0	2 (1)
Blood CK increased	0	1 (2)	1 (1)	2 (2)	0	2 (1)
Potential injection site reactions <sup>§</sup>	1 (2)	7 (14)	8 (8)	3 (3)	3 (3)	6 (3) <sup>l</sup>
Antibodies						
Binding	NA	NA	NA	0	0 <sup>¶</sup>	0
Neutralizing	NA	NA	NA	0	0 <sup>¶</sup>	0

Neurocognitive events	0	0	0	0	0	0
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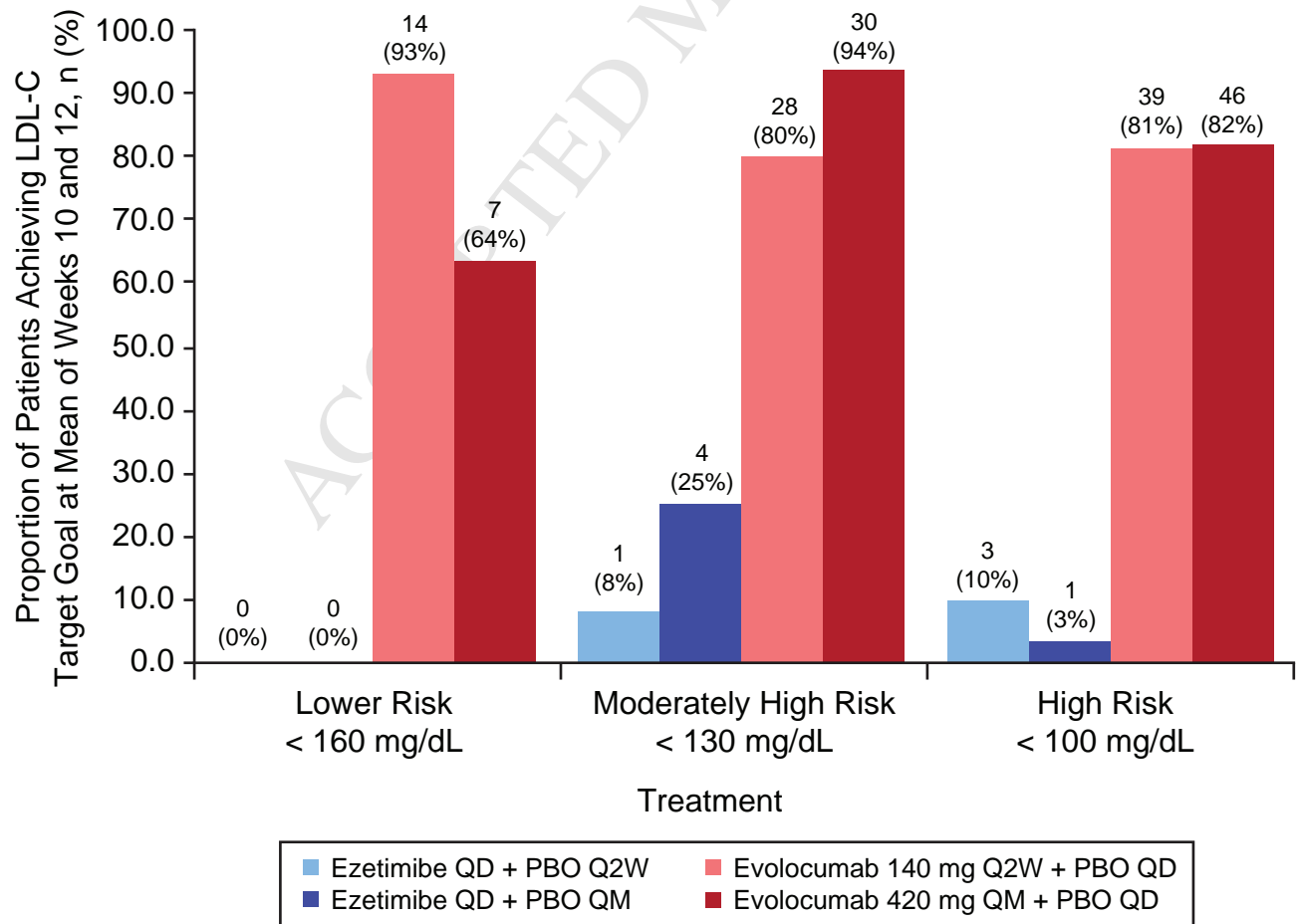
<sup>\*</sup>Gastrointestinal motility disorder (n=1), inguinal hernia (n=1), kidney infection (n=1), spinal decompression (n=1). <sup>†</sup>Increased hepatic enzymes (n=1), back pain (n=1), carcinoma (n=2; bladder and neuroendocrine), lipoma (n=1), and musculoskeletal surgery (n=1). <sup>‡</sup>Reported in  $\geq 5\%$  of patients in one or more treatment arms. <sup>§</sup>Searched using high-level term grouping, which includes injection site (IS) rash, IS inflammation, IS pruritus, IS reaction, and IS urticaria. <sup>||</sup>Reactions consisted of erythema (n=4), pain (n=3), rash (n=2), bruising, irritation, swelling, and urticaria (n=1 each) <sup>¶</sup>Data missing for one patient. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; NA, not assessed; PBO, placebo; Q2W, every 2 weeks; QD, daily; QM, monthly; SMQ, Standard MedDRA Queries; ULN, upper limit of normal



A



B



Rates based on patients with observed values and LDL-C above target goal at baseline

**Anti-PCSK9 Antibody Effectively Lowers Cholesterol in Patients with Statin Intolerance:  
The GAUSS-2 Randomized, Placebo-controlled Phase 3 Clinical Trial of Evolocumab**

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## Supplemental Methods

### Patients

GAUSS-2 enrolled men and women aged 18 to 80 years on no statin, or on a low-dose (weekly dose of 7 times the smallest available tablet strength) statin. Participants had LDL-C above their NCEP Adult Treatment Panel (ATP) III risk category goal(15) ( $\geq 100$  mg/dL with diagnosed CHD or risk equivalent,  $\geq 130$  mg/dL without CHD or risk equivalent and  $\geq 2$  risk factors,  $\geq 160$  mg/dL without CHD or risk equivalent and 1 risk factor, or  $\geq 190$  mg/dL without CHD or risk equivalent and no risk factors) and triglycerides  $\leq 400$  mg/dL. Participants had prior intolerance to  $\geq 2$  statins, defined as inability to tolerate any dose or increase the dose above the smallest tablet strength because of intolerable muscle-related side effects, which resolved or improved significantly upon dose decrease or discontinuation. Major exclusion criteria included New York Heart Association class III or IV heart failure or left ventricular ejection fraction  $< 30\%$ , acute coronary syndrome or serious arrhythmia in the prior 3 months, type 1 diabetes mellitus or type 2 diabetes mellitus that is poorly controlled or diagnosed within the prior 6 months, uncontrolled hypertension or thyroid disease, moderate or severe renal dysfunction (estimated glomerular filtration rate  $< 30$  mL/min/1.73m<sup>2</sup>), liver enzymes  $> 2$  times the upper limit of normal (ULN), CK  $> 3 \times$ ULN or use of systemic steroids (other than hormone replacement) or cyclosporine within the prior 3 months, or use of niacin  $> 200$  mg/day, red yeast rice, or prescription lipid-lowering medications other than low-dose statins, ezetimibe or bile-acid sequestrants in the prior 6 weeks. Discontinuation of ezetimibe was required  $\geq 4$  weeks before LDL-C screening.

## Study Design and Oversight

GAUSS-2 was conducted at 50 sites in North America, Europe, Asia, Africa, and Australia. Injectable study drug was administered either in the clinic at study visits or by self-injection between study visits. Randomization was stratified by screening LDL-C concentration ( $<180$  mg/dL or  $\geq 180$  mg/dL) and baseline statin use (yes or no). Amgen designed the study in collaboration with academic investigators, and was responsible for data collection and analysis.

## Study Procedures

Screening procedures included medical history, physical examination, 12-lead electrocardiogram, fasting ( $\geq 9$  hour) lipids, chemistry including fasting glucose, glycated hemoglobin, liver function tests, and CK, hematology and a placebo injection before randomization to confirm tolerance of SC self-administration using an auto-injector pen.

Study visits occurred on day 1 and at weeks 2, 8, 10, and 12, with fasting lipids collected at each visit. Injectable study drug was administered after sample collection. All samples were analyzed by a central laboratory. Final adverse event information was collected at week 12 for the QM arm and by telephone at week 14 for the Q2W arm. Oral dosing compliance was assessed by tablet count.

Central laboratory reports were reviewed before study drug administration at clinic visits. If CK was  $>5\times\text{ULN}$ , CK was retested. If, upon retest, CK was  $>10\times\text{ULN}$ , study drug was to be discontinued unless elevated due to myocardial infarction; if CK was  $>5\times\text{ULN}$  to  $\leq 10\times\text{ULN}$ , study drug continuation was recommended if there was an alternative explanation; if CK was  $\leq 5\times\text{ULN}$ , study drug continuation was recommended. If subjects had triglyceride values  $>1000$  mg/dL, investigators were informed so that appropriate patient follow-up could be initiated.

### **Efficacy Evaluation**

Co-primary endpoints were percent change from baseline in LDL-C at week 12 and at the mean of weeks 10 and 12. The mean of weeks 10 and 12 endpoint was analyzed to assess the impact of cumulative exposure to evolocumab.

### **Statistical Analysis**

Efficacy and safety analysis included all randomized patients who received at least 1 dose of study drug. Co-primary and co-secondary efficacy endpoints were analyzed using a repeated measures linear effects model for each dose frequency with no imputation of missing data, except for percent of patients with LDL-C <70 mg/dL, which was analyzed using the Cochran-Mantel Haenszel test. Multiplicity adjustments within each dose frequency were used to control for the overall significance level for all primary and secondary endpoints. Safety analyses were conducted using descriptive statistics. Adverse events were classified according to MedDRA (version 16.1).



## Supplemental Results

### Patients

Lipid-lowering therapy was used by 33% of patients; 18% received a low-dose statin (mean weekly doses: rosuvastatin, 23 mg; simvastatin, 94 mg; atorvastatin, 38 mg). The prevalence of coronary artery disease at enrollment was 29% and that of cerebrovascular or peripheral artery disease was 16%. The study was completed by 290 patients (94%); 303 (99%) completed the week 12 visit; Figure S1).

### Safety Summary

Treatment-emergent adverse events occurred in 135 patients (66%) receiving evolocumab and 74 patients (73%) receiving ezetimibe (Table 3 in the full manuscript). Serious adverse events occurred in 6 patients (3%) in the evolocumab arms and 4 patients (4%) in the ezetimibe arms. Serious events in the evolocumab arms were increased hepatic enzymes (n=1), back pain (n=1), carcinoma (n=2; bladder and neuroendocrine), lipoma (n=1), and musculoskeletal surgery (n=1). No deaths or cardiovascular or cerebrovascular events were reported. Adverse events led to study drug discontinuation in 17 patients (8%) on evolocumab and 13 patients (13%) on ezetimibe. The most common adverse events were headache (8%), myalgia (8%), and extremity pain (7%) in the evolocumab arms and myalgia (18%), fatigue (10%), headache (9%), and diarrhea (7%) in the ezetimibe arms. Potential muscle adverse events occurred in 12% (evolocumab) and 23% (ezetimibe) of patients, most commonly myalgia (8%, evolocumab; 18%, ezetimibe). The proportions of patients who discontinued due to musculoskeletal side effects were 5% (evolocumab) and 6% (ezetimibe). Myositis occurred in one patient; this patient received evolocumab 420 mg QM. Other potential muscle events in the evolocumab and ezetimibe arms, respectively, included muscle weakness (1%, 1%), musculoskeletal pain (2%,

3%) and increased blood creatinine (1%, 0). Creatine kinase (CK) elevations >5 times the upper limit of normal were observed in 2 patients (1%) on evolocumab and 3 patients (3%) on ezetimibe. One patient in the ezetimibe arm experienced a CK elevation >10 times the ULN. No CK elevation was sustained over multiple visits and all events were attributed to exercise and were asymptomatic single occurrences that resolved spontaneously without discontinuation of treatment with the exception of one elevation in a patient with a pre-study history of elevated CK. Potential injection site reactions were reported in 3% (evolocumab) and 8% (ezetimibe) of patients. No binding or neutralizing antibodies to evolocumab were detected.

## Supplemental Tables

Table S1. Additional baseline lipids and cardiovascular risk factors

	Ezetimibe QD + PBO Q2W N = 51	Evolocumab 140 mg Q2W + PBO QD N = 103	Ezetimibe QD + PBO QM N = 51	Evolocumab 420 mg QM + PBO QD N = 102
Lipid parameters				
Non-HDL-C, mg/dL	231 (66)	228 (57)	233 (57)	222 (63)
Apolipoprotein B/apolipoprotein A-I ratio	0.9 (0.3)	1.0 (0.3)	1.0 (0.3)	0.9 (0.3)
Triglycerides, mg/dL, median (IQR)	170 (120, 243)	165 (123, 224)	168 (124, 240)	139 (103, 190)
VLDL-C, mg/dL, median (IQR)	34 (24, 49)	33 (25, 44)	34 (25, 48)	28 (21, 38)
Ratio of TC to HDL-C	6 (2)	6 (2)	6 (2)	6 (2)
Metabolic syndrome risk factors, n (%)				
Elevated waist circumference*	31 (61)	67 (65)	29 (57)	56 (55)
Triglycerides $\geq 150$ mg/dL	30 (59)	59 (57)	31 (61)	40 (39)
Hypertension, SBP $\geq 130$ mm Hg, or DBP $\geq 85$ mm Hg	45 (88)	77 (75)	43 (84)	84 (82)
Fasting glucose $\geq 100$ mg/dL	26 (51)	52 (51)	20 (39)	35 (34)
Patients with metabolic syndrome ( $\geq 3$ factors) and without diabetes mellitus	21 (41)	41 (40)	19 (37)	33 (32)

hsCRP, mg/L, median (IQR)	1.7 (0.9, 3.1)	1.4 (0.7, 3.4)	1.8 (0.9, 2.8)	1.8 (0.9, 3.3)
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Data are mean (SD) unless specified. \* Defined as  $\geq 102$  cm for non-Asian men,  $\geq 88$  cm for non-Asian women,  $\geq 90$  cm for Asian men, and  $\geq 80$  cm for Asian women. CHD, coronary heart disease; CV, cardiovascular; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; PBO, placebo; Q2W, every 2 weeks; QD, daily; QM, monthly; SBP, systolic blood pressure; TC, total cholesterol; VLDL-C, very low-density lipoprotein cholesterol

**Table S2. Additional efficacy outcomes**

	Ezetimibe QD + PBO Q2W N = 51	Evolocumab 140 mg Q2W + PBO QD N = 103	Ezetimibe QD + PBO QM N = 51	Evolocumab 420 mg QM + PBO QD N = 102
<b>Other lipid parameters</b>				
<b>Non-HDL-C</b>				
% change from baseline, mean of weeks 10 and 12	-17.2 (-21.4, -12.9)	-48.7 (-52.0, -45.5)	-14.5 (-18.2, -10.9)	-49.1 (-51.9, -46.4)
Treatment difference vs ezetimibe*		-31.5 (-36.3, -26.7)		-34.6 (-38.6, -30.5)
% change from baseline, week 12	-16.5 (-21.1, -12.0)	-48.6 (-52.1, -45.2)	-13.2 (-17.0, -9.4)	-46.2 (-49.0, -43.3)
Treatment difference vs ezetimibe*		-32.1 (-37.3, -26.9)		-33.0 (-37.2, -28.8)
<b>Apolipoprotein B/apolipoprotein A-I ratio</b>				
% change from baseline, mean of weeks 10 and 12	-13.0 (-17.5, -8.5)	-47.9 (-51.4, -44.4)	-11.9 (-17.0, -6.9)	-48.3 (-52.1, -44.5)
Treatment difference vs ezetimibe*		-34.9 (-39.8, -29.9)		-36.4 (-41.7, -31.0)
% change from baseline, week 12	-13.1 (-18.0, -8.3)	-47.7 (-51.4, -43.9)	-11.4 (-16.7, -6.0)	-45.5 (-49.5, -41.5)
Treatment difference vs ezetimibe*		-34.5 (-40.1, -29.0)		-34.1 (-39.9, -28.4)
<b>Triglycerides</b>				
% change from baseline, mean of weeks 10 and 12	-3.7 (-11.4, 3.9)	-6.32 (-12.1, -0.5)	-0.3 (-9.5, 8.9)	-6.7 (-13.5, 0.1)
Treatment difference vs ezetimibe		-2.6 (-11.4, 6.2)		-6.4 (-16.6, 3.7)
% change from baseline, week 12	-5.5 (-13.9, 2.9)	-3.9 (-10.2, 2.4)	2.16 (-8.7, 13.1)	-2.5 (-10.4, 5.3)
Treatment difference vs ezetimibe		1.6 (-8.1, 11.3)		-4.7 (-17.0, 7.7)
<b>VLDL-C</b>				
% change from baseline, mean of weeks 10 and 12	-5.8 (-13.3, 1.8)	-7.6 (-13.3, -1.9)	-2.9 (-11.6, 5.8)	-6.5 (-12.8, -0.1)
Treatment difference vs ezetimibe		-1.8 (-10.4, 6.8)		-3.5 (-13.1, 6.1)
% change from baseline, week 12	-5.5 (-13.5, 2.5)	-6.2 (-12.3, -0.1)	-2.3 (-12.4, 7.8)	-2.2 (-9.3, 4.9)
Treatment difference vs ezetimibe		-0.7 (-10.0, 8.6)		0.1 (-11.2, 11.4)
<b>Ratio of TC to HDL-C</b>				
% change from baseline,	-13.4	-40.8	-11.2	-41.1

mean of weeks 10 and 12	(-17.7, -9.2)	(-44.1, -37.6)	(-15.5, -6.9)	(-44.3, -37.9)
Treatment difference vs ezetimibe*		-27.4		-29.9
% change from baseline, week 12	-14.1	(-32.1, -22.7)	-9.92	(-34.7, -25.2)
	(-18.7, -9.6)	(-43.9, -37.0)	(-14.5, -5.3)	(-42.0, -35.2)
Treatment difference vs ezetimibe*		-26.3		-28.7
		(-31.4, -21.2)		(-33.9, -23.4)

**Other parameters**

hsCRP, mg/L, median (IQR)

Week 12	1.7	1.7	1.6	1.5
	(0.8, 3.6)	(0.9, 5.0)	(0.8, 3.0)	(0.8, 3.2)

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Data are least squares mean (95% CI). Least squares mean is from the repeated measures

model, including covariates of stratification factors, treatment group, scheduled visit, and

interaction of treatment with scheduled visits. \*Adjusted p value vs ezetimibe <0.001; multiplicity

adjustments within each dose frequency were used to control for the overall significance level

for all primary and secondary endpoints. HDL-C, high-density lipoprotein cholesterol; hsCRP,

high-sensitivity C-reactive protein; IQR, interquartile range; PBO, placebo; Q2W, every 2 weeks;

QD, daily; QM, monthly; TC, total cholesterol; VLDL-C, very low-density lipoprotein cholesterol

**Supplemental Figure****Figure S1. Patient allocation and disposition (CONSORT diagram)**

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