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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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Objectives This study sought to evaluate the efficacy and safety of subcutaneous evolocumab compared with oral ezetimibe in hypercholesterolemic patients who are unable to tolerate effective statin doses.

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

Methods The GAUSS-2 (Goal Achievement after Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects) trial was a 12-week, double-blind study of randomized patients (2:2:1:1) to evolocumab 140 mg every two weeks (Q2W) or evolocumab 420 mg once monthly (QM) both with daily oral placebo or subcutaneous placebo Q2W or QM both with daily oral ezetimibe 10 mg. Co-primary endpoints were percent change from baseline in LDL-C at the mean of weeks 10 and 12, and at week 12.

Results Three hundred seven patients (age 62 ± 10 years; 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-treated patients 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 largely unmet clinical need in high-risk patients with elevated cholesterol who are statin intolerant. (Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects-2; NCT01763905)
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Abbreviations and Acronyms

CHD = coronary heart disease

CI = confidence interval

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

Lowering low-density lipoprotein cholesterol (LDL-C) with statins reduces cardiovascular risk (1,2). Although statins are well tolerated, statin-related adverse events have been reported more commonly than in the randomized trials, reaching up to 10% to 20% of patients (3). Although Zhang et al. (3) reported that a substantial proportion of patients with side effects to 1 statin tolerated a re-challenge to a second statin, failure to achieve treatment target in patients intolerant of 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 (PCSK9) is a protein involved in regulating low-density lipoprotein receptor (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 on the GAUSS-2 (Goal Achievement after Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects-2) trial (11), a phase 3 study that compared the effects of evolocumab with ezetimibe in statin-intolerant hypercholesterolemic patients. Compared with GAUSS, which included patients intolerant to at least 1 statin, the present phase 3 trial evaluated evolocumab compared with 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 statins. Participants had LDL-C above their National Cholesterol Education Program (NCEP) Adult Treatment Panel III goal (12). Participants had previous intolerance to ≥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 was a randomized, double-blind, phase 3, placebo- and ezetimibe-controlled study (11). Patients were randomized 2:2:1:1 to subcutaneous evolocumab 140 mg every two weeks (Q2W) or evolocumab 420 mg once monthly (QM) both with daily oral placebo or subcutaneous placebo 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 (Anti-PCKS9 Monotherapy for Hypercholesterolemia: The MENDEL-2 Randomized, Controlled Phase III Clinical Trial of Evolocumab) study (13).

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–high-density lipoprotein cholesterol (HDL-C), apolipoprotein B, total cholesterol/HDL-C ratio, apolipoprotein B/apolipoprotein A-I ratio, lipoprotein(a), triglycerides, HDL-C, and very low-density lipoprotein (VLDL-C) (10). Safety endpoints included treatment-emergent and serious adverse events, creatine kinase (CK) and hepatic enzyme elevations, and anti-evolocumab antibodies.

Statistical analysis. Planned enrollment of 300 patients (200 on evolocumab) had ≥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 (13).

Results

Patients. Between January and August 2013, 307 patients were randomized to evolocumab (n = 205) or ezetimibe (n = 102) (Table 1, Online Table S1). Patients had a 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 risk of coronary heart disease (CHD) according to the 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%) (Online Fig. S1).

Efficacy outcomes. LOW-DENSITY LIPOPROTEIN CHOLESTEROL. Evolocumab yielded significant reductions in LDL-C (Table 2). Mean percent reductions from baseline at a mean of weeks 10 and 12 were 56.1% (95% confidence interval

Table 1 Baseline Characteristics

	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)
Age, yrs	62 ± 10	61 ± 10	60 ± 9	63 ± 10
Male	24 (47)	57 (55)	29 (57)	56 (55)
Race				
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	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				
No. 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*				
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				
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†	10 (20)	31 (30)	22 (43)	36 (35)
Low HDL-C‡	18 (35)	37 (36)	18 (35)	29 (28)
≥2 CV risk factors	20 (39)	54 (52)	35 (69)	38 (37)
NCEP risk categories§				
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)
Lower	5 (10)	16 (16)	3 (6)	12 (12)

Values are mean ± SD or n (%), unless otherwise noted. *Data are missing for 1 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. †CHD in male first-degree relative at <55 years of age or in female first-degree relative at <65 years of age. ‡Defined as <40 mg/dl in men and <50 mg/dl in women. §Risk category definitions: high (diagnosed CHD or risk equivalent); moderately high (2 or more risk factors and Framingham risk score 10% to 20%); moderate (2 or more risk factors and Framingham risk score <10%); and 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.

[CI]: 59.7% to 52.5%) with 140 mg Q2W and 55.3% (95% CI: 58.3% to 52.3%) with 420 mg QM, corresponding to treatment differences versus ezetimibe of 36.9% (95% CI: 42.3% to 31.6%) and 38.7% (95% CI: 43.1% to 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 (Fig 1). Evolocumab-treated patients were more likely to achieve LDL-C target levels than ezetimibe-treated patients (Fig. 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, Online Table S2).

Safety outcomes. Treatment-emergent adverse events are listed in Table 3 and the Online Appendix. Adverse events led to study drug discontinuation in 8% (evolocumab) and 13% (ezetimibe) of patients. Myalgia occurred in 8% of

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)
LDL-C, %				
% change from baseline, mean of weeks 10 and 12*	−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†		−36.9 (−42.3, −31.6)		−38.7 (−43.1, −34.3)
% change from baseline, week 12*	−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†		−38.1 (−43.7, −32.4)		−37.6 (−42.2, −32.9)
LDL-C, mg/dl				
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†		−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. ezetimibe†		−69.7 (−82.0, −57.5)		−68.8 (−79.2, −58.4)
Other lipid parameters				
Apolipoprotein B				
% change from baseline, mean of weeks 10 and 12	−13.7 (−17.9, −9.4)	−45.9 (−49.2, −42.6)	−11.0 (−15.4, −6.7)	−46.0 (−49.3, −42.7)
Treatment difference vs. ezetimibe†		−32.2 (−36.9, −27.5)		−35.0 (−39.6, −30.4)
% change from baseline, week 12	−13.0 (−17.5, −8.4)	−45.8 (−49.4, −42.3)	−10.0 (−14.6, −5.4)	−43.1 (−46.5, −39.7)
Treatment difference vs. ezetimibe†		−32.9 (−38.0, −27.7)		−33.1 (−38.0, −28.2)
Lipoprotein(a)				
% change from baseline, mean of weeks 10 and 12	−2.3 (−8.9, 4.3)	−26.2 (−31.4, −21.0)	1.6 (−6.4, 9.5)	−23.7 (−29.6, −17.9)
Treatment difference vs. ezetimibe†		−23.9 (−31.3, −16.5)		−25.3 (−33.8, −16.8)
% change from baseline, week 12	−1.7 (−8.8, 5.3)	−27.0 (−32.5, −21.5)	5.8 (−4.3, 15.9)	−22.1 (−29.3, −14.8)
Treatment difference vs. ezetimibe†		−25.3 (−33.3, −17.3)		−27.9 (−39.2, −16.6)
HDL-C				
% change from baseline, mean of weeks 10 and 12	0.3 (−3.6, 4.2)	5.5 (2.5, 8.5)	1.4 (−2.6, 5.5)	7.2 (4.2, 10.2)
Treatment difference vs. ezetimibe		5.2 (0.7, 9.6)		5.7 (1.2, 10.2)
% change from baseline, week 12	1.8 (−2.6, 6.2)	5.3 (2.0, 8.6)	1.6 (−2.7, 6.0)	6.5 (3.3, 9.7)
Treatment difference vs. ezetimibe		3.6 (−1.5, 8.6)		4.8 (−0.2, 9.8)
Apolipoprotein A-I				
% change from baseline, mean of weeks 10 and 12	−0.1 (−3.4, 3.3)	5.4 (2.7, 8.1)	2.6 (−1.1, 6.2)	5.3 (2.5, 8.0)
Treatment difference vs. ezetimibe		5.5 (1.7, 9.2)		2.7 (−1.2, 6.5)
% change from baseline, week 12	1.1 (−2.4, 4.6)	5.2 (2.4, 7.9)	3.2 (−0.9, 7.2)	5.5 (2.5, 8.5)
Treatment difference vs. ezetimibe		4.1 (0.1, 8.0)		2.3 (−2.1, 6.8)
LDL-C achievement <70 mg/dl				
Mean of weeks 10 and 12	1 (2.0)	46 (45.5)	0	42 (42.0)
Treatment difference vs. ezetimibe,† %		43.5 (30.9, 53.4)		42.0 (30.3, 51.8)
Week 12	1 (2.0)	49 (50.0)	0	36 (37.5)
Treatment difference vs. ezetimibe,† %		48.0 (35.0, 57.8)		37.5 (25.5, 47.5)
PCSK9				
% change from baseline, week 10	−6.4 ± 38.4	−61.8 ± 31.2	7.9 ± 61.9	−93.9 ± 17.0
% change from baseline, week 12	1.1 ± 30.0	−61.1 ± 33.8	0.7 ± 60.0	−27.2 ± 163.9

Values are mean ± SD or least squares mean (95% confidence interval) 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. *Co-primary endpoint. †Adjusted p value versus ezetimibe <0.001; multiplicity adjustments within each dose frequency were used to control for the overall significance level for all primary and secondary endpoints.

Abbreviations as in Table 1.

evolocumab-treated patients 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 3 months yielded a significant reduction in LDL-C in hypercholesterolemic patients who were unable to tolerate effective doses of at least 2 statins, reflecting a population with a true unmet need.

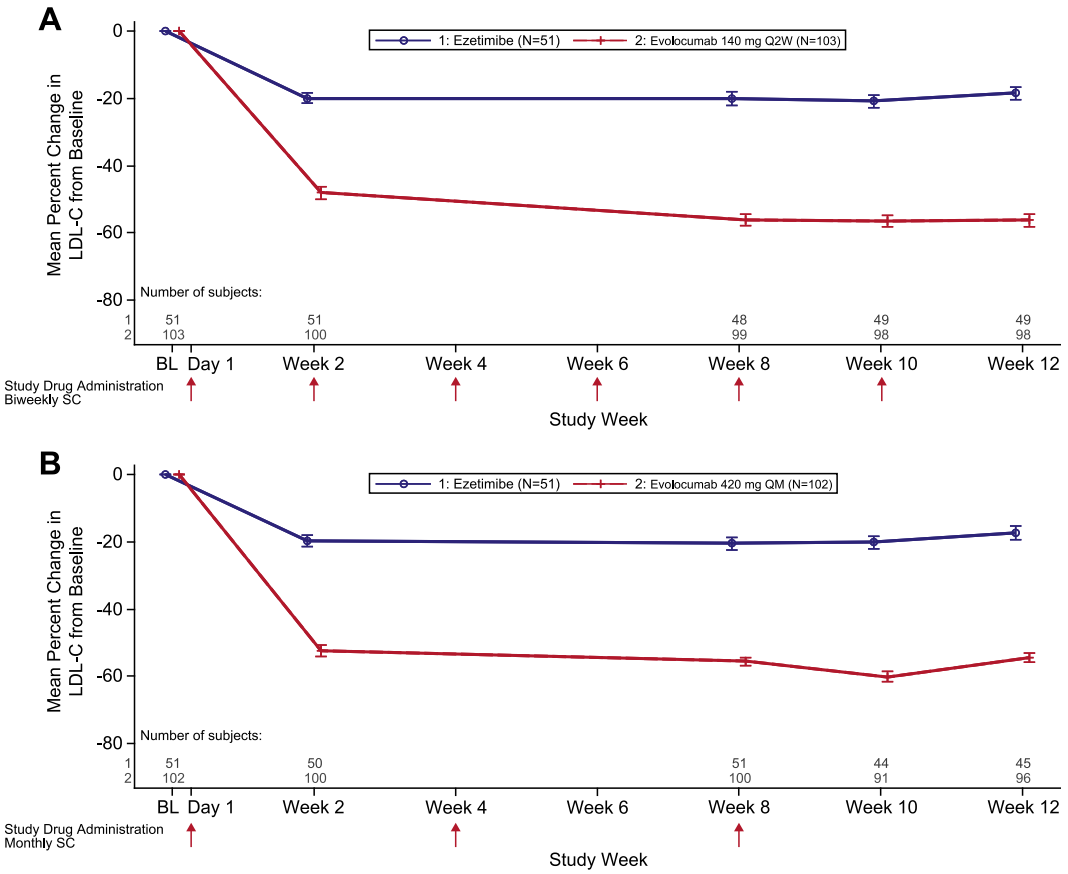

Figure 1 **Mean Percent Change in Low-Density Lipoprotein Cholesterol Concentration from Baseline to Week 12 in Patients Who Received Evolocumab**

Patients who received evolocumab **(A)** every 2 weeks and **(B)** monthly. **Vertical lines** represent SE 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.

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 (14). Of evolocumab-treated patients at high risk, more than 75% achieved LDL-C <100 mg/dl compared with less than 10% of ezetimibe-treated patients. In the context of the American College of Cardiology/American Heart Association guidelines (15), 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 population at a higher cardiovascular risk, with more patients intolerant of at least 2 statins, leading to the inclusion of patients with a truly unmet clinical need. In the upcoming results of the outcome trial with evolocumab (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects with Elevated Risk; 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 (16). The majority of patients using ezetimibe were unable to achieve LDL-C target levels, as evidenced by the 2% rate of achieving LDL-C <70 mg/dl. Moreover, benefit of ezetimibe-induced, LDL-C lowering awaits confirmation in the ongoing outcome study (IMPROVE-IT [Improved Reduction of Outcomes: Vytorin Efficacy International Trial]; NCT00202878) (17).

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 (18–20). Further studies on the mechanism of lipoprotein(a) lowering and the benefit of evolocumab in patients with elevated lipoprotein(a) levels are warranted.

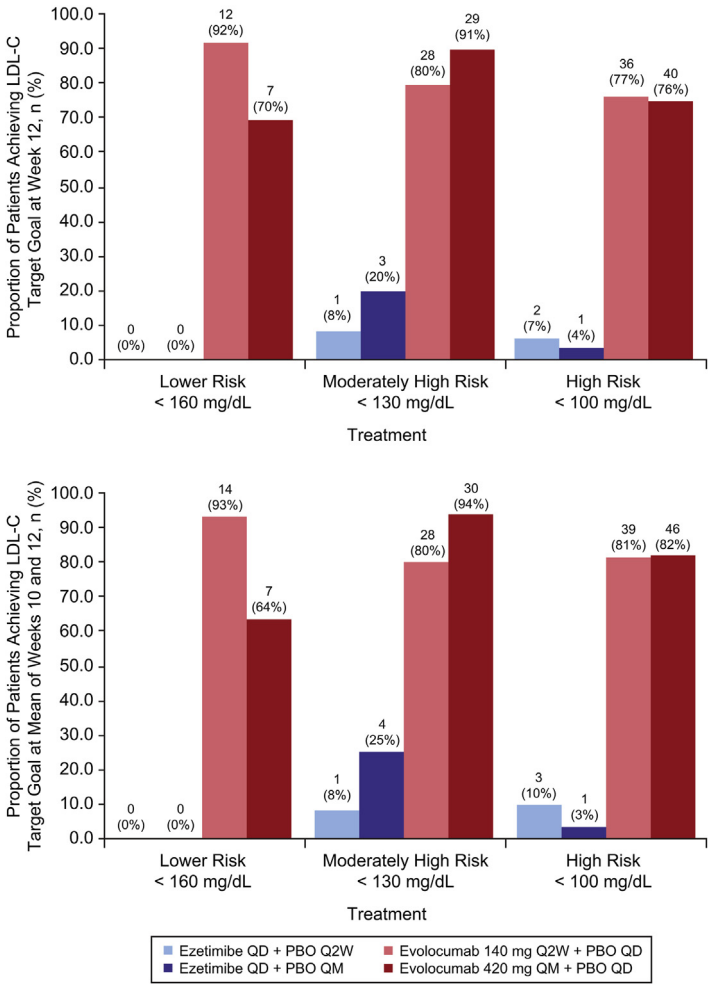

Figure 2 **Percentage of Patients Achieving Low-Density Lipoprotein Cholesterol Goal at Week 12 and at Mean of Weeks 10 and 12 Stratified by National Cholesterol Education Program Risk Category**

Rates based on patients with observed values and LDL-C above target goal at baseline. National Cholesterol Education Program (NCEP) risk categories are defined as high (diagnosed coronary heart disease or risk equivalent), moderately high (2 or more risk factors and Framingham risk score ≤20%), and lower (0 or 1 risk factor). PBO = placebo; other abbreviations as in Figure 1.

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 Q2W, and evolocumab QM groups, respectively). In the MENDEL-2 study (13), 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 with ezetimibe-treated patients. This suggests that the pathways contributing to statin-associated myalgia and/or myositis (21,22) are distinct from those contributing to PCSK9 antibody-mediated LDL-C lowering. Because the study was short term, these data await confirmation in the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; NCT01764633) outcome study. The incidence of treatment-emergent adverse events and laboratory abnormalities were comparable across treatment groups.

Study limitations. A limitation of this study includes the absence of a blinded statin re-challenge. We used a real-life definition of patients who experienced intolerable muscle-related side effects to ≥2 statins, with the majority unable to tolerate ≥3 statins. A placebo-controlled blinded statin re-challenge has, however, been included in the GAUSS-3 (Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects-3; NCT01984424) study. Another limitation is the short study duration in patients needing life-long treatment;

Table 3 Adverse Events

Event	Ezetimibe			Evolocumab		
	QD + PBO Q2W (n = 51)	QD + PBO QM (n = 51)	All (N = 102)	140 mg Q2W + PBO QD (n = 103)	420 mg QM + PBO QD (n = 102)	All (N = 205)
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)†
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‡						
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 × ULN	3 (6)	0	3 (3)	0	2 (2)	2 (1)
CK >10 × ULN	1 (2)	0	1 (1)	0	0	0
ALT or AST >3 × 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§	1 (2)	7 (14)	8 (8)	3 (3)	3 (3)	6 (3)‖
Anti-evolocumab antibodies						
Binding	NA	NA	NA	0	0¶	0
Neutralizing	NA	NA	NA	0	0¶	0
Neurocognitive adverse events#	0	0	0	0	0	0

Values are n (%). *Gastrointestinal motility disorder (n = 1), inguinal hernia (n = 1), kidney infection (n = 1), spinal decompression (n = 1). †Increased hepatic enzymes (n = 1), back pain (n = 1), carcinoma (n = 2; bladder and neuroendocrine), lipoma (n = 1), and musculoskeletal surgery (n = 1). ‡Reported in ≥5% of patients in 1 or more treatment arms. §Searched using high-level term grouping, which includes injection site (IS) rash, IS inflammation, IS pruritus, IS reaction, and IS urticaria. ‖Reactions consisted of erythema (n = 4), pain (n = 3), rash (n = 2), bruising, irritation, swelling, and urticaria (n = 1 each). ¶Data missing for 1 patient. #Searched using HLGT terms: deliria (including confusion); cognitive and attention disorders and disturbances; dementia and amnestic conditions; disturbances in thinking and perception; mental impairment disorders.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; NA = not applicable; SMQ = Standard MedDRA Queries; ULN = upper limit of normal; other abbreviations as in Table 1.

however, patients were eligible to enroll in the open-label extension study (Open Label Study of Long Term Evaluation Against LDL-C Trial-2; NCT01854918) following GAUSS-2.

Conclusions

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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REFERENCES

1. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267–78.
2. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:1670–81.
3. Zhang H, Plutzky J, Skentzos S, et al. Discontinuation of statins in routine care settings: a cohort study. Ann Intern Med 2013;158:526–34.
4. Gomez Sandoval YH, Braganza MV, Daskalopoulou SS. Statin discontinuation in high-risk patients: a systematic review of the evidence. Curr Pharm Des 2011;17:3669–89.
5. Visser ME, Wagener G, Baker BF, et al. Mipomersen, an apolipoprotein B synthesis inhibitor, lowers low-density lipoprotein cholesterol in high-risk statin-intolerant patients: a randomized, double-blind, placebo-controlled trial. Eur Heart J 2012;33:1142–9.
6. Cuchel M, Meagher EA, du Toit Theron H, et al. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. Lancet 2013;381:40–6.
7. Abifadel M, Varret M, Rabès JP, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nat Genet 2003;34:154–6.
8. Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med 2006;354:1264–72.
9. Horton JD, Cohen JC, Hobbs HH. Molecular biology of PCSK9: its role in LDL metabolism. Trends Biochem Sci 2007;32:71–7.
10. Sullivan D, Olsson AG, Scott R, et al. Effect of a monoclonal antibody to PCSK9 on low-density lipoprotein cholesterol levels in statin-intolerant patients: the GAUSS randomized trial. JAMA 2012;308:2497–506.
11. Cho L, Rocco M, Colquhoun D, et al. Design and rationale of the GAUSS-2 study trial: a double-blind, ezetimibe-controlled Phase 3 study of the efficacy and tolerability of evolocumab (AMG 145) in subjects with hypercholesterolemia who are intolerant of statin therapy. Clin Cardiol 2014;37:131–9.
12. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143–421.
13. Koren MJ, Lundqvist P, Bolognese M, et al., for the MENDEL-2 Investigators. Anti-PCSK9 monotherapy for hypercholesterolemia: the MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. J Am Coll Cardiol 2014;63:2531–40.
14. Pedersen TR, Kjekshus J, Berg K, et al. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). 1994. Atheroscler Suppl 2004;5:81–7.
15. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol 2013 Nov 7 [E-pub ahead of print].
16. Knopp RH, Dujovne CA, Le Beaut A, et al. Evaluation of the efficacy, safety, and tolerability of ezetimibe in primary hypercholesterolaemia: a pooled analysis from two controlled phase III clinical studies. Int J Clin Pract 2003;57:363–8.
17. Califf RM, Lokhnygina Y, Cannon CP, et al. An update on the IMProved reduction of outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) design. Am Heart J 2010;159:705–9.
18. Desai NR, Kohli P, Giugliano RP, et al. AMG145, a monoclonal antibody against proprotein convertase subtilisin kexin type 9, significantly reduces lipoprotein(a) in hypercholesterolemic patients receiving statin therapy: an analysis from the LDL-C Assessment With Proprotein Convertase Subtilisin Kexin Type 9 Monoclonal Antibody Inhibition Combined With Statin Therapy (LAPLACE)-Thrombolysis in Myocardial Infarction (TIMI) 57 Trial. Circulation 2013;128:962–9.
19. Raal F, Scott R, Somaratne R, et al. Low-density lipoprotein cholesterol-lowering effects of AMG 145, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease in patients with heterozygous familial hypercholesterolemia: the Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) randomized trial. Circulation 2012;126:2408–17.
20. Stein EA, Mellis S, Yancopoulos GD, et al. Effect of a monoclonal antibody to PCSK9 on LDL cholesterol. N Engl J Med 2012;366:1108–18.
21. Mammen AL, Chung T, Christopher-Stine L, et al. Autoantibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase in patients with statin-associated autoimmune myopathy. Arthritis Rheum 2011;63:713–21.
22. Search Collaborative Group, Link E, Parish S, et al. SLCO1B1 variants and statin-induced myopathy–a genomewide study. N Engl J Med 2008;359:789–99.

Key words: evolocumab ■ ezetimibe ■ hypercholesterolemia ■ LDL-cholesterol ■ statin intolerance.

APPENDIX

For a supplemental figure and tables, please see the online version of this article.