Original Investigation

Efficacy and Tolerability of Evolocumab vs Ezetimibe in Patients With Muscle-Related Statin Intolerance
The GAUSS-3 Randomized Clinical Trial

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IMPORTANCE Muscle-related statin intolerance is reported by 5% to 20% of patients.

OBJECTIVE To identify patients with muscle symptoms confirmed by statin rechallenge and compare lipid-lowering efficacy for 2 nonstatin therapies, ezetimibe and evolocumab.

DESIGN, SETTING, AND PARTICIPANTS Two-stage randomized clinical trial including 511 adult patients with uncontrolled low-density lipoprotein cholesterol (LDL-C) levels and history of intolerance to 2 or more statins enrolled in 2013 and 2014 globally. Phase A used a 24-week crossover procedure with atorvastatin or placebo to identify patients having symptoms only with atorvastatin but not placebo. In phase B, after a 2-week washout, patients were randomized to ezetimibe or evolocumab for 24 weeks.

INTERVENTIONS Phase A: atorvastatin (20 mg) vs placebo. Phase B: randomization 2:1 to subcutaneous evolocumab (420 mg monthly) or oral ezetimibe (10 mg daily).

MAIN OUTCOME AND MEASURES Coprimary end points were the mean percent change in LDL-C level from baseline to the mean of weeks 22 and 24 levels and from baseline to week 24 levels.

RESULTS Of the 491 patients who entered phase A (mean age, 60.7 [SD, 10.2] years; 246 women [50.1%]; 170 with coronary heart disease [34.6%]; entry mean LDL-C level, 212.3 [SD, 67.9] mg/dL), muscle symptoms occurred in 209 of 491 (42.6%) while taking atorvastatin but not while taking placebo. Of these, 199 entered phase B, along with 19 who proceeded directly to phase B for elevated creatine kinase (N = 218, with 73 randomized to ezetimibe and 145 to evolocumab; entry mean LDL-C level, 219.9 [SD, 72] mg/dL). For the mean of weeks 22 and 24, LDL-C level with ezetimibe was 183.0 mg/dL; mean percent LDL-C change, −16.7% (95% CI, −20.5% to −12.9%), absolute change, −31.0 mg/dL and with evolocumab was 103.6 mg/dL; mean percent change, −54.5% (95% CI, −57.2% to −51.8%); absolute change, −106.8 mg/dL ($P < .001$). LDL-C level at week 24 with ezetimibe was 181.5 mg/dL; mean percent change, −16.7% (95% CI, −20.8% to −12.5%); absolute change, −31.2 mg/dL and with evolocumab was 104.1 mg/dL; mean percent change, −52.8% (95% CI, −55.8% to −49.8%); absolute change, −102.9 mg/dL ($P < .001$). For the mean of weeks 22 and 24, between-group difference in LDL-C was −37.8%; absolute difference, −75.8 mg/dL. For week 24, between-group difference in LDL-C was −36.1%; absolute difference, −71.7 mg/dL. Muscle symptoms were reported in 28.8% of ezetimibe-treated patients and 20.7% of evolocumab-treated patients (log-rank $P = .17$). Active study drug was stopped for muscle symptoms in 5 of 73 ezetimibe-treated patients (6.8%) and 1 of 145 evolocumab-treated patients (0.7%).

CONCLUSIONS AND RELEVANCE Among patients with statin intolerance related to muscle-related adverse effects, the use of evolocumab compared with ezetimibe resulted in a significantly greater reduction in LDL-C levels after 24 weeks. Further studies are needed to assess long-term efficacy and safety.

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Group Information: The Goal Achievement after Utilizing an anti-PCSK9 Antibody in Statin-Intolerant Subjects 3 (GAUSS-3) investigators are listed at the end of this article.

Administration of HMG-CoA reductase inhibitors (statins) to reduce levels of low-density lipoprotein cholesterol (LDL-C) represents an essential component of contemporary strategies to reduce morbidity and mortality from atherosclerotic vascular disease.[1] However, a significant proportion of patients with clinical indications for statin treatment report inability to tolerate evidence-based doses, most commonly because of muscle-related adverse effects.[2] These patients typically report muscle pain or weakness when treatment is initiated or dosage increased and relief when the drug is discontinued or the dosage reduced. Although some patients with statin-associated muscle symptoms experience marked elevation in serum creatine kinase (CK) levels, most do not. Accordingly, diagnosis of this disorder remains largely subjective, based on the presence of patient-reported symptoms.[3] The incidence of similar symptoms in placebo-treated patients has resulted in skepticism about the true incidence of statin intolerance.

Patients with muscle-related intolerance often refuse to take statins despite elevated LDL-C levels and a high risk of major cardiovascular events. Current management may include very low or intermittent administration of statins or use of ezetimibe, but these strategies seldom achieve the greater than 50% reduction recommended by current guidelines.[1,4,5] Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors markedly lower LDL-C levels and have shown potential as an alternative therapy for patients who experience intolerable adverse effects during statin therapy.[6-8] Currently available data suggest that muscle-related adverse effects are uncommon with PCSK9 inhibitors, even in patients with a history of such symptoms, but prior trials relied exclusively on medical history to document statin intolerance.

The GAUSS-3 (Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects 3) trial was designed as a 2-stage randomized clinical trial to first identify patients with statin-induced muscle symptoms during a placebo-controlled statin rechallenge procedure and subsequently to compare the effectiveness and tolerability of 2 nonstatin therapies—ezetimibe or evolocumab, a recently approved PCSK9 inhibitor.

Methods

Study Design

The GAUSS-3 trial enrolled patients with elevated LDL-C levels who were unable to tolerate an effective dose of a statin because of muscle-related adverse effects. Local institutional review boards approved the study protocol, and all patients provided written informed consent. The methods are described in greater detail in a design manuscript[9]; the protocol is available in Supplement 1 and the statistical analysis plan in Supplement 2.

Briefly, the study had 2 phases: after an initial 4-week washout period in which any statins, ezetimibe, or other lipid-lowering agents were discontinued, participants were enrolled in phase A, a double-blind, placebo-controlled crossover procedure to rechallenge patients with atorvastatin. Patients were randomly assigned in a 1:1 ratio to receive either atorvastatin (20 mg daily) or matching placebo for the first 10 weeks (period 1), then underwent a 2-week washout period, followed by crossover to the alternate therapy for a second 10-week period (period 2). Patients who experienced intolerable muscle symptoms during the first period did not complete the full 10 weeks of exposure but entered a 2-week washout period before proceeding to period 2.

After completion of phase A, patients who experienced muscle-related adverse effects while taking atorvastatin but not placebo were eligible for phase B, a 24-week, double-blind randomization to ezetimibe or evolocumab using a double-dummy design in which patients received either injectable placebo and oral ezetimibe or injectable evolocumab and oral placebo. Alternatively, patients could proceed directly to phase B if they had a documented history of CK elevation more than 10 times the upper limit of normal accompanied by muscle symptoms while taking statin therapy, with documented resolution of both CK elevation and symptoms at discontinuation. These study procedures were designed to ensure that only patients with reproducible statin-associated muscle symptoms entered phase B of the study. For phase B, patients were randomized 2:1 to receive subcutaneously administered evolocumab (420 mg monthly) or oral ezetimibe (10 mg daily). Randomization for both phases was performed centrally via an interactive web-based or voice recognition system.

In phase A, randomization used a permuted block size of 4. Phase B used a permuted block size of 3, with stratification for LDL-C level (<180 mg/dL vs ≥180 mg/dL [to convert LDL-C values to mmol/L, multiply by 0.0259]). Allocation was concealed using a centralized randomization process. Information on race/ethnicity was self-reported based on fixed, standardized US Census terms and used to determine if outcomes were different for patients from different racial/ethnic subgroups (as routinely required by regulators).

Inclusion Criteria

The main eligibility criteria for phase A included age between 18 and 80 years and inability to tolerate atorvastatin at 10 mg and any other statin at any dose or, alternatively, 3 or more statins, with 1 at the lowest average daily starting dose and 2 other statins at any dose. The lowest average starting dose was defined as 5 mg for rosuvastatin, 10 mg for simvastatin, 40 mg for pravastatin, 20 mg for lovastatin, 40 mg for fluvastatin, or 2 mg for pitavastatin. For patients with diagnosed coronary heart disease, lipid inclusion criteria required an LDL-C level of 100 mg/dL or greater. Patients without coronary heart disease were required to have an LDL-C level of 130 mg/dL or greater with 2 or more risk factors, 160 mg/dL or greater with 1 or more risk factors, or 190 mg/dL or greater with no additional risk factors. Patients were excluded for myocardial infarction, unstable angina, coronary revascularization, or stroke within 3 months before randomization. Other inclusion and exclusion criteria are listed in the protocol (Supplement 1).

Treatments

Atorvastatin (20-mg tablets) and matching placebo were supplied as overencapsulated tablets. Evolocumab (140 mg) and matching placebo were supplied in a single-use, disposable, handheld mechanical (spring-based) 1.0-mL prefilled autoin-

jector pen for subcutaneous administration. Patients were instructed to administer 3 autoinjector doses subcutaneously each month, providing a 420-mg total dosage of evolocumab. Ezetimibe (10-mg tablets) and matching placebo were supplied as overencapsulated tablets for daily administration.

Primary and Secondary End Points

In phase B, to account for the pharmacodynamic effects of a PCSK9 antibody administered monthly (evolocumab), the study prespecified 2 coprimary end points: mean percent change from baseline LDL-C level to the mean of LDL-C levels at weeks 22 and 24, which approximates mean treatment effect, and a more conservative measure, the percent change from baseline LDL-C level to the level at week 24, which reflects effects at the end of the dosing interval. Using the same 2 time points, the tier-1 cosecondary efficacy end points assessed absolute change from baseline in LDL-C level; percent change from baseline in levels of total cholesterol, non–high-density lipoprotein cholesterol (non–HDL-C), and apolipoprotein B (ApoB); percent change from baseline in total cholesterol to HDL-C ratio and ApoB to apolipoprotein A1 ratio; and the percentage of patients achieving an LDL-C level less than 70 mg/dL. Tier-2 cosecondary efficacy end points were also measured as percent change from baseline to the mean of weeks 22 and 24 and at week 24 and included levels of lipoprotein(a), triglycerides, HDL-C, and very low-density lipoprotein cholesterol.

The incidence of treatment-emergent adverse events, serious adverse events, and adverse events leading to discontinuation of study drug were collected for each randomized treatment group. Prespecified safety and tolerability outcomes included the incidence of muscle-related adverse effects during phase A. Adverse events were coded using the current version of the Medical Dictionary for Regulatory Activities. An independent committee adjudicated clinical events including death, myocardial infarction, hospitalization for unstable angina, coronary revascularization, stroke, transient ischemic attack, and hospitalization for heart failure. The incidence of antievolocumab antibodies (binding and neutralizing) at any time was assessed.

Statistical Methods

The analyses of safety and tolerability during the phase A double-blind statin rechallenge included all randomized participants who received 1 or more doses of atorvastatin or placebo. Efficacy and safety analyses for phase B included all randomized patients who received 1 or more doses of ezetimibe or evolocumab. For patients who participated in both phases, baseline lipid values were defined as those taken at the beginning of phase A. For patients who bypassed phase A, the lipid values taken at the beginning of phase B were considered the baseline values. For the coprimary end points, a repeated-measures linear-effects model was used to compare the efficacy of evolocumab with ezetimibe, which included terms for treatment group, stratification by LDL-C level (<180 mg/dL vs ≥180 mg/dL), scheduled visit, and the interaction of treatment with scheduled visit. A positive result for the trial required statistical significance for both coprimary end points. For efficacy end points, for which the analysis method was the repeated-measures linear-effects model, missing lipid measurements were not imputed. The statistical model for the cosecondary efficacy end points was identical to that for the coprimary end points, with the exception of the end point percentage of patients achieving LDL-C levels less than 70 mg/dL, which was analyzed using the Cochran-Mantel Haenszel test adjusted by the LDL-C stratification.

Multiplicity adjustments were applied for analyses of coprimary and cosecondary end points to control the overall familywise error rate at .05 using a combination of sequential testing, the Hochberg procedure, and the fall-back procedure.[10] The statistical approach for control of multiplicity is shown in eFigure 1 in Supplement 3. Cumulative incidence estimates were calculated using the Kaplan-Meier method, with hazard ratios (HRs) calculated using an unstratified Cox model and *P* values calculated using the log-rank test.

Analyses were performed using Statistical Analysis Software version 9.3 (SAS Institute Inc).

Sample Size Determination

The number of participants expected to be enrolled in phase A was 500 to provide 100 patients for phase B, assuming a rate of 20% for muscle-related intolerance in phase A, which was a conservative estimate based on observational studies.[3] The mean for LDL-C reduction for evolocumab compared with ezetimibe was estimated as −35.9% (95% CI, −44.1% to −27.8%) from prior studies.[7,8] Assuming that 15% of phase B randomized patients would end treatment early but remain in the study, 5% would end the study early, and 2% would not receive any study drug, a sample size of 100 provided 98% power for each of the coprimary end points and 96% power to simultaneously detect significant treatment effects for the coprimary end points. The sample size calculation was performed using a 2-sided *t* test with a .05 significance level, an attenuated treatment effect of 21% greater reduction in LDL-C level with evolocumab, and an attenuated common standard deviation of 24%.

Results

Study Participants

Study participants were enrolled between December 10, 2013, and November 28, 2014. The characteristics of patients were similar in phases A and B (**Table 1**). There were approximately equal numbers of men and women, with a mean age of approximately 60 years. More than 80% of patients had a history of intolerance to 3 or more statins before entering the study. Coronary heart disease was present in approximately one-third of patients, hypertension in more than one-half, and the majority were classified in the National Cholesterol Education Program high-risk category.[11] Mean LDL-C levels were 212.3 mg/dL (SD, 67.9) for all patients entering phase A and 219.9 mg/dL (SD, 72.0) for all patients participating in phase B.

Statin Rechallenge Outcomes

The disposition of patients in the trial is shown in **Figure 1**. A total of 492 patients entered phase A, the statin rechallenge procedure, with 491 receiving 1 or more doses of study drug,

Table 1. Baseline Demographics and Laboratory Values

	Phase A			Phase B		
	All Randomized (n = 491)[a]	Atorvastatin Followed by Placebo (n = 245)[a]	Placebo Followed by Atorvastatin (n = 246)	Total Qualifying for Phase B (n = 218)	Ezetimibe (n = 73)	Evolocumab (n = 145)
Sex, No. (%)						
Women	246 (50.1)	120 (49.0)	126 (51.2)	106 (48.6)	39 (53.4)	67 (46.2)
Men	245 (49.9)	125 (51.0)	120 (48.8)	112 (51.4)	34 (46.6)	78 (53.8)
Age, mean (SD), y	60.7 (10.2)	61.5 (10.2)	59.9 (10.2)	58.8 (10.5)	58.5 (9.4)	59.0 (11.1)
Race, No. (%)						
White	465 (94.7)	231 (94.3)	234 (95.1)	207 (95.0)	69 (94.5)	138 (95.2)
Other	26 (5.3)	14 (5.7)	12 (4.9)	11 (5.0)	4 (5.5)	7 (4.8)
BMI, mean (SD)[b]	28.5 (5.7)	28.4 (6.1)	28.5 (5.4)	28.0 (5.0)	28.5 (5.9)	27.8 (4.4)
Coronary heart disease, No. (%)	170 (34.6)	85 (34.7)	85 (34.6)	69 (31.7)	21 (28.8)	48 (33.1)
Cerebrovascular disease or PAD, No. (%)	113 (23.0)	59 (24.1)	54 (22.0)	44 (20.2)	17 (23.3)	27 (18.6)
Cardiovascular risk factors, No. (%)						
Current cigarette use	51 (10.4)	22 (9.0)	29 (11.8)	29 (13.3)	13 (17.8)	16 (11.0)
Type 2 diabetes mellitus	63 (12.8)	29 (11.8)	34 (13.8)	26 (11.9)	10 (13.7)	16 (11.0)
Hypertension	282 (57.4)	147 (60.0)	135 (54.9)	112 (51.4)	43 (58.9)	69 (47.6)
Family history of premature CHD	190 (38.7)	91 (37.1)	99 (40.2)	86 (39.4)	32 (43.8)	54 (37.2)
Low HDL-C	179 (36.5)	92 (37.6)	87 (35.4)	81 (37.2)	33 (45.2)	48 (33.1)
Patients with 2 or more risk factors	236 (48.1)	119 (48.6)	117 (47.6)	104 (47.7)	44 (60.3)	60 (41.4)
NCEP risk categories, No. (%)[c]						
High risk	307 (62.5)	155 (63.3)	152 (61.8)	122 (56.0)	38 (52.1)	84 (57.9)
Moderately high risk	54 (11.0)	26 (10.6)	28 (11.4)	29 (13.3)	8 (11.0)	21 (14.5)
Moderate risk	73 (14.9)	40 (16.3)	33 (13.4)	38 (17.4)	16 (21.9)	22 (15.2)
Lower risk	57 (11.6)	24 (9.8)	33 (13.4)	29 (13.3)	11 (15.1)	18 (12.4)
History of intolerance to statins, No. (%)						
1 statin	0	0	0	6 (2.8)	1 (1.4)	5 (3.4)
2 statins	91 (18.5)	43 (17.6)	48 (19.5)	33 (15.1)	12 (16.4)	21 (14.5)
≥3 statins	400 (81.5)	202 (82.4)	198 (80.5)	179 (82.1)	60 (82.2)	119 (82.1)
Worst muscle-related adverse effect, No. (%)						
Myalgia	410 (83.5)	203 (82.9)	207 (84.1)	173 (79.4)	61 (83.6)	112 (77.2)
Myositis	79 (16.1)	41 (16.7)	38 (15.4)	31 (14.2)	7 (9.6)	24 (16.6)
Rhabdomyolysis	2 (0.4)	1 (0.4)	1 (0.4)	14 (6.4)	5 (6.8)	9 (6.2)
Baseline laboratory values, mean (SD)						
TC, mg/dL	300.5 (71.2)	300.0 (75.3)	301.0 (67.0)	307.0 (74.7)	308.0 (73.8)	306.5 (75.4)
LDL-C, mg/dL	212.3 (67.9)	212.0 (72.2)	212.7 (63.6)	219.9 (72.0)	221.9 (70.2)	218.8 (73.1)
HDL-C, mg/dL	50.9 (15.7)	51.0 (16.3)	50.9 (15.1)	49.8 (15.4)	50.2 (15.5)	49.7 (15.4)
VLDL-C, mg/dL	36.4 (15.3)	36.5 (15.5)	36.3 (15.0)	36.7 (15.1)	35.7 (14.3)	37.1 (15.6)
Non–HDL-C, mg/dL	249.6 (71.1)	249.0 (74.7)	250.2 (67.3)	257.2 (74.5)	257.8 (76.3)	256.9 (73.8)
Apolipoprotein B, mg/dL	154.3 (40.4)	154.5 (44.1)	154.2 (36.5)	157.2 (41.7)	155.0 (42.4)	158.3 (41.5)
TC:HDL-C ratio	6.4 (2.3)	6.4 (2.3)	6.4 (2.3)	6.7 (2.5)	6.7 (2.7)	6.7 (2.3)
ApoB:ApoA1 ratio	1.03 (0.34)	1.03 (0.36)	1.04 (0.32)	1.06 (0.37)	1.06 (0.42)	1.06 (0.34)
Triglycerides, median (IQR), mg/dL	170.0 (121.5-231.0)	168.5 (118.5-228.5)	172.8 (123.5-231.5)	171.3 (127.0-233.0)	162.5 (127.0-231.0)	176.0 (128.0-233.5)
Lipoprotein(a), median (IQR), nmol/L	32.0 (15.0-146.0)	33.5 (15.0-156.5)	28.0 (14.0-144.0)	31.0 (15.0-156.0)	38.0 (18.0-164.0)	29.0 (12.5-152.5)
hs-CRP, median (IQR), mg/L	1.6 (0.8-3.4)	1.4 (0.8-2.8)	1.7 (0.9-4.1)	1.7 (0.9-3.6)	1.7 (0.9-3.8)	1.7 (0.9-3.6)

Abbreviations: ApoB, apolipoprotein B; ApoA1, apolipoprotein A1; BMI, body mass index; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; NCEP, National Cholesterol Education Program; PAD, peripheral arterial disease; VLDL-C, very low-density lipoprotein cholesterol; TC, total cholesterol.

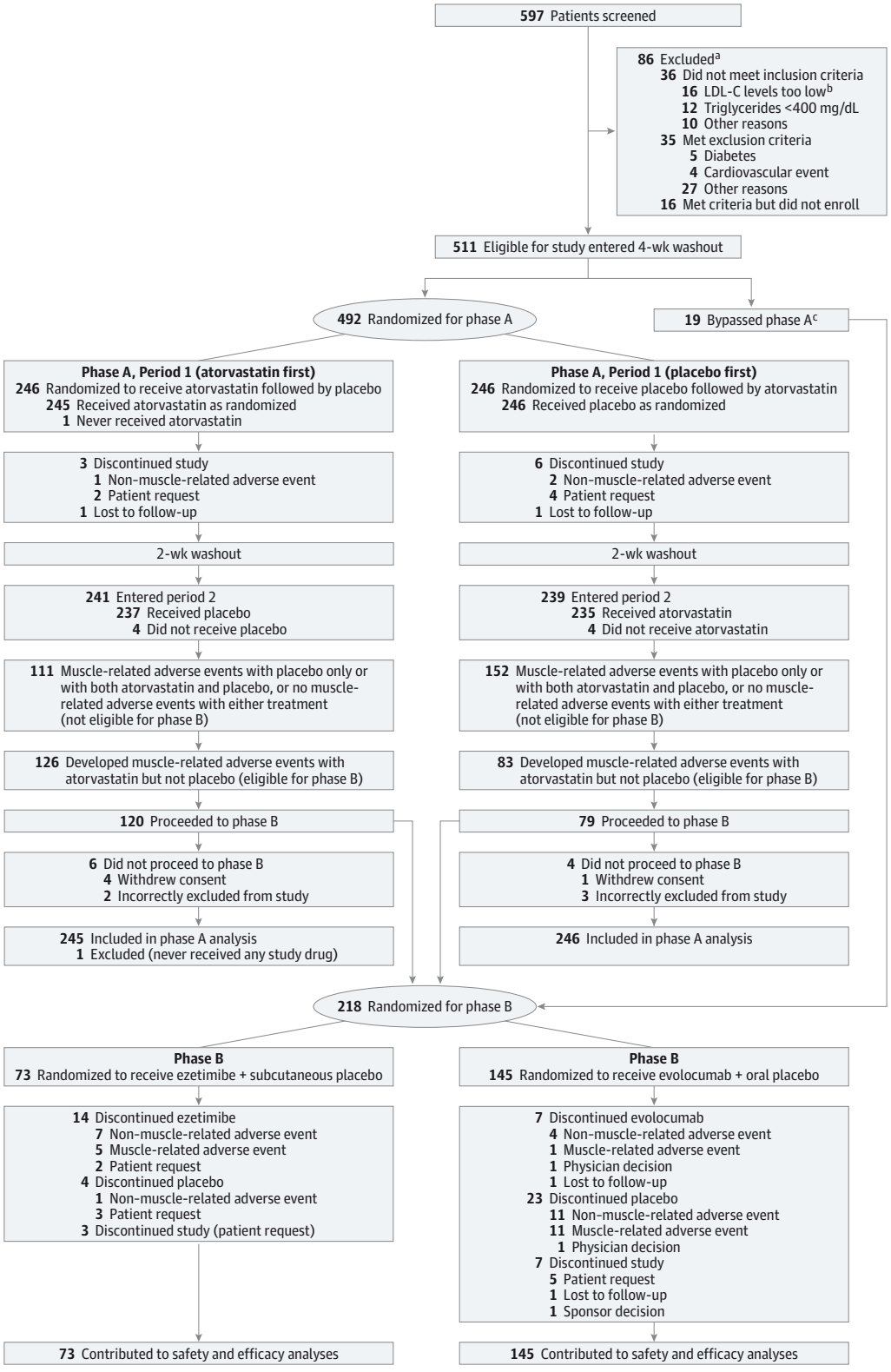
SI conversion factors: To convert TC, LDL-C, HDL-C, VLDL-C, and non–HDL-C values from mg/dL to mmol/L, multiply by 0.0259; triglycerides values from mg/dL to mmol/L, multiply by 0.0113; lipoprotein(a) values from nmol/L to μmol/L, multiply by 0.0357; and hs-CRP values from mg/L to nmol/L, multiply by 9.524.

[a] Does not include 1 patient who never received study drug.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] High risk is defined as CHD or a 10-year Framingham risk greater than 20%, moderate risk as 2 or more cardiovascular risk factors (10%-20% Framingham risk), and low risk as 1 or 0 cardiovascular risk factors.

Figure 1. Flow of Patients in the GAUSS-3 Trial



GAUSS-3 indicates Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects 3.

[a] An individual may have been excluded for more than 1 reason.

[b] See Methods.

[c] Nineteen patients bypassed phase A because of creatine kinase elevation ≥10× the upper limit of normal.

Table 2. Patients Experiencing Intolerable Muscle-Related Symptoms During Phase A of GAUSS-3 Trial[a]

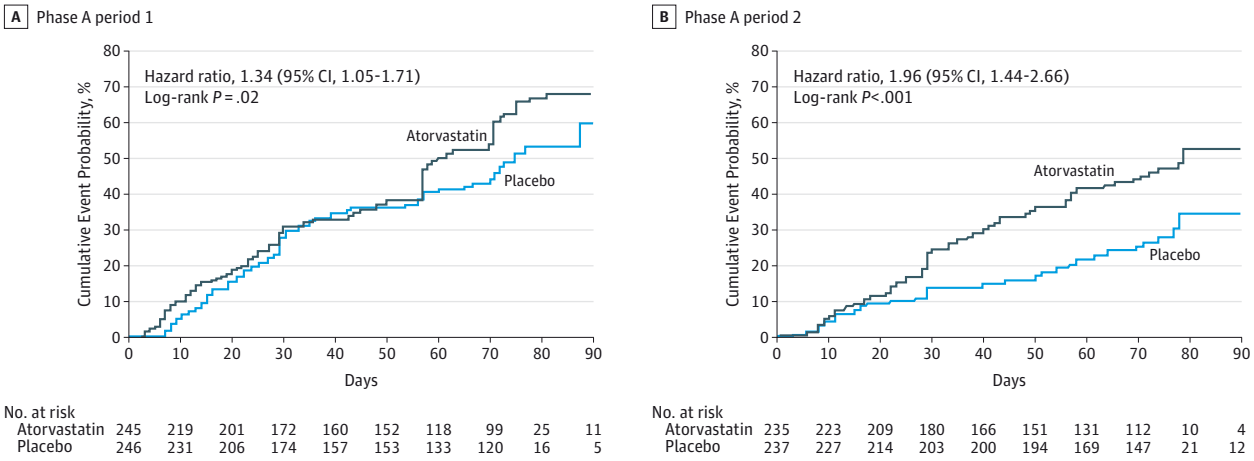
Category, No. (%)	Atorvastatin Followed by Placebo (n = 245)[b]	Placebo Followed by Atovastatin (n = 246)	All Randomized Patients (n = 491)[b]
Symptoms with atorvastatin but not placebo	126 (51.4)	83 (33.7)	209 (42.6)
Symptoms with placebo but not atorvastatin	42 (17.1)	88 (35.8)	130 (26.5)
Symptoms with both placebo and atorvastatin	22 (9.0)	26 (10.6)	48 (9.8)
No symptoms with either treatment	47 (19.2)	38 (15.4)	85 (17.3)
Did not start period 2 treatment	8 (3.3)	11 (4.5)	19 (3.9)

Abbreviation: GAUSS-3, Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects 3.

[a] Nineteen patients bypassed phase A because of creatine kinase elevation ≥10× the upper limit of normal.

[b] Does not include 1 patient who never received study drug.

Figure 2. Time to First Occurrence of a Muscle-Related Adverse Effect Resulting in Discontinuation of Study Drug During Period 1 and Period 2 of Phase A, GAUSS-3 Trial



Atorvastatin dose, 20 mg daily; placebo indicates matching placebo. GAUSS-3 indicates Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects 3.

245 of whom received atorvastatin before placebo and 246 of whom received placebo before atorvastatin.

For those receiving atorvastatin first, 126 (51.4%) developed a muscle-related adverse event with atorvastatin but not placebo, 122 (49.8%) completed phase A, and 120 (49%) proceeded to phase B. For those receiving placebo first, 83 (33.7%) developed a muscle-related adverse event with atorvastatin but not placebo, 80 (32.5%) completed phase A, and 79 (32.1%) proceeded to phase B. Overall, 209 of 491 patients (42.6%) with a history of muscle-related adverse effects reported intolerable symptoms in phase A when given a double-blind, placebo-controlled atorvastatin rechallenge; of these, 199 entered phase B. Conversely, 130 of the 491 patients (26.5%) experienced intolerable muscle symptoms with placebo but not atorvastatin during phase A. The numbers and percentages of patients experiencing a muscle-related adverse effect with atorvastatin, placebo, neither, or both treatments during phase A are shown in **Table 2**, categorized by first treatment received.

The time to first muscle-related adverse effect is shown in **Figure 2** for patients who received 1 or more doses of study drug during phase A. Figure 2A shows the time to muscle-related adverse effect for patients randomized to receive atorvastatin or placebo during the first 10-week period; Figure 2B shows this outcome for patients randomized to receive atorvastatin or placebo during the second 10-week period. During the first period, the HR for developing muscle symptoms with atorvastatin compared with placebo was 1.34 (95% CI, 1.05 to 1.71; P = .02) (Figure 2A). During the second period, the HR for developing muscle symptoms with atorvastatin compared with placebo was 1.96 (95% CI, 1.44 to 2.66; P < .001) (Figure 2B). Nineteen patients bypassed phase A because of myalgia with a documented 10-fold increase in CK level during previous statin administration. A total of 218 patients entered phase B and received 1 or more doses of study drug, 73 of whom were randomized to receive ezetimibe plus subcutaneous placebo and 145 to receive evolocumab plus oral placebo.

Efficacy End Points

Results for the primary and secondary efficacy end points are reported in **Table 3**. Lipid values at week 22 and week 24 during phase B are reported in the eTable in Supplement 3; the effect of ezetimibe and evolocumab on LDL-C levels during phase B is displayed graphically in **Figure 3**. Lipid values were unavailable at 24 weeks for 16 patients in the ezetimibe group and 28 patients in the evolocumab group. For the first coprimary end point, LDL-C level for the mean of weeks 22 and 24 was 183.0 mg/dL (95% CI, 167.4 to 198.6; least-squares mean per-

Table 3. Coprimary and Secondary Efficacy Measures at 2 Time Points (24 Weeks and Mean of 22 and 24 Weeks) in GAUSS-3 Trial

Measure	Ezetimibe (n = 73) LS Mean (95% CI)[a]	Evolocumab (n = 145) LS Mean (95% CI)[a]	Adjusted *P* Value	LS Mean Difference (95% CI)[a]
Coprimary End Points				
Mean % change in LDL-C				
Mean for wk 22 and 24	−16.7 (−20.5 to −12.9)	−54.5 (−57.2 to −51.8)	<.001	−37.8 (−42.3 to −33.3)
At wk 24	−16.7 (−20.8 to −12.5)	−52.8 (−55.8 to −49.8)		−36.1 (−41.1 to −31.1)
Tier 1 Cosecondary Efficacy End Points				
Mean absolute change in LDL-C, mg/dL				
Mean for wk 22 and 24	−31.0 (−38.4 to −23.5)	−106.8 (−112.2 to −101.4)	<.001	−75.8 (−84.7 to −67.0)
At wk 24	−31.2 (−39.2 to −23.3)	−102.9 (−108.7 to −97.2)		−71.7 (−81.3 to −62.2)
Mean % change in mean total cholesterol				
Mean for wk 22 and 24	−11.4 (−14.2 to −8.6)	−38.0 (−40.1 to −36.0)	<.001	−26.6 (−30.0 to −23.3)
At wk 24	−11.6 (−14.6 to −8.6)	−36.6 (−38.8 to −34.5)		−25.1 (−28.7 to −21.5)
Mean % change in mean non-HDL-C				
Mean for wk 22 and 24	−14.4 (−17.8 to −11.0)	−47.4 (−49.9 to −45.0)	<.001	−33.1 (−37.1 to −29.0)
At wk 24	−14.6 (−18.2 to −11.0)	−45.7 (−48.3 to −43.1)		−31.1 (−35.4 to −26.8)
Mean % change in mean ApoB				
Mean for wk 22 and 24	−11.4 (−15.0 to −7.8)	−45.3 (−47.9 to −42.7)	<.001	−33.9 (−38.2 to −29.6)
At wk 24	−11.7 (−15.6 to −7.9)	−43.5 (−46.2 to −40.7)		−31.8 (−36.4 to −27.2)
Mean % change in mean total cholesterol/HDL-C ratio				
Mean for wk 22 and 24	−11.5 (−14.9 to −8.0)	−41.4 (−43.9 to −38.9)	<.001	−29.9 (−34.1 to −25.8)
At wk 24	−12.8 (−16.5 to −9.2)	−40.0 (−42.7 to −37.4)		−27.2 (−31.6 to −22.8)
Mean % change from baseline in ApoB:ApoA1 ratio				
Mean for wk 22 and 24	−11.9 (−15.6 to −8.1)	−46.0 (−48.7 to −43.3)	<.001	−34.1 (−38.6 to −29.7)
At wk 24	−12.6 (−16.5 to −8.7)	−44.6 (−47.4 to −41.8)		−32.0 (−36.6 to −27.3)
Patients achieving mean LDL-C <70 mg/dL, No. (%) [95% CI][b]				
Mean for wk 22 and 24	1 (1.4) [0.3 to 7.7]	41 (29.9) [22.9 to 38.1]	<.001	28.5 (19.1 to 36.7)
At wk 24	0 (0) [0.0 to 6.3]	32 (27.4) [20.1 to 36.1]		27.4 (17.7 to 36.1)
Tier 2 Cosecondary Efficacy End Points				
Mean % change in mean lipoprotein(a)				
Mean for wk 22 and 24	−1.6 (−7.2 to 3.9)	−22.7 (−26.7 to −18.7)	<.001	−21.1 (−27.7 to −14.5)
At wk 24	0.2 (−5.8 to 6.2)	−21.1 (−25.4 to −16.7)		−21.2 (−28.4 to −14.1)
Mean % change in mean triglycerides				
Mean for wk 22 and 24	−1.0 (−8.7 to 6.8)	−5.4 (−11.0 to 0.20)	.37	−4.4 (−13.7 to 4.9)
At wk 24	−1.1 (−10.9 to 8.7)	−2.9 (−9.9 to 4.1)		−1.8 (−13.6 to 10.0)
Mean % change in mean HDL-C				
Mean for wk 22 and 24	1.7 (−1.7 to 5.0)	7.8 (5.4 to 10.3)	.008	6.2 (2.2 to 10.2)
At wk 24	2.9 (−0.8 to 6.6)	7.4 (4.7 to 10.1)		4.5 (0.0 to 9.0)
Mean % change in mean VLDL-C				
Mean for wk 22 and 24	−2.2 (−8.5 to 4.2)	−6.8 (−11.4 to −2.2)	.37	−4.7 (−12.3 to 2.9)
At wk 24	−2.7 (−10.3 to 5.0)	−3.9 (−9.4 to 1.6)		−1.2 (−10.5 to 8.0)

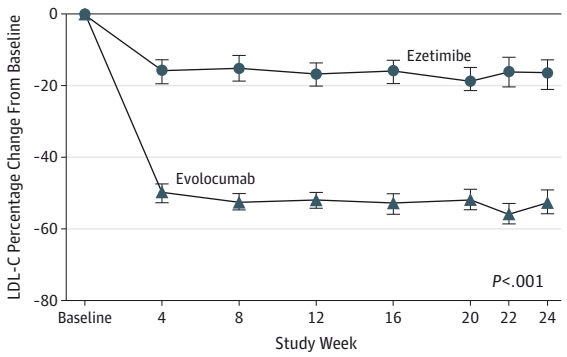
Abbreviations: ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; GAUSS-3, Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects 3; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LS, least squares; VLDL-C, very low-density lipoprotein cholesterol.

[a] Least-squares mean from repeated-measures model, which includes treatment group. LDL-C stratification, scheduled visit, and the interaction of treatment with scheduled visit as covariates. Testing of each co-end-point pair results in a single *P* value; for cosecondary end points, these *P* values are used in the Hochberg procedure.

[b] Analysis of mean LDL-C values <70 mg/dL was based on differences in percentage achievement and tested using the Cochran-Mantel-Haenszel test stratified by LDL-C stratification factor.

cent change from baseline, −16.7% [95% CI, −20.5% to −12.9%]) for ezetimibe and 103.6 mg/dL (95% CI, 92.5 to 114.8; mean percent change, −54.5% [95% CI, −57.2% to −51.8%]) for evolocumab)—a mean difference of −37.8% (95% CI, −42.3% to −33.3%) ($P < .001$). For the other coprimary end point, LDL-C level at week 24 was 181.5 mg/dL (95% CI, 164.9 to 198.0; least-squares mean percent change from baseline, −16.7% [95% CI, −20.8% to −12.5%]) for ezetimibe and 104.1 mg/dL (95% CI, 92.4

Figure 3. Mean Percent Change in Low-Density Lipoprotein Cholesterol Level During Randomized Treatment With Ezetimibe or Evolocumab, GAUSS-3 Trial



No. of patients

Ezetimibe	73	72	70	67	67	64	60	57
Evolocumab	145	142	142	139	137	127	127	117

Ezetimibe dose, 10 mg daily; evolocumab dose, 140 mg 3 times monthly (420 mg total dosage). GAUSS-3 indicates Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects 3. Error bars indicate 95% CIs.

to 115.7; mean percent change, −52.8% [95% CI, −55.8% to −49.8%]) for evolocumab—a mean difference of −36.1% (95% CI, -41.1% to -31.1%) (P < .001). Secondary end points including percent changes in levels of total cholesterol, non-HDL-C, and ApoB; total cholesterol to HDL-C ratio; and ApoB to apolipoprotein A1 ratio showed similar results.

The first cosecondary end point, absolute change in LDL-C level for the mean of weeks 22 and 24, showed a least-squares mean change of −31.0 mg/dL (95% CI, −38.4 to −23.5) for ezetimibe and −106.8 mg/dL (95% CI, −112.2 to −101.4) for evolocumab—a mean difference of −75.8 mg/dL (95% CI, −84.7 to −67.0) (P < .001). The other cosecondary end point, absolute change in LDL-C level at week 24, showed a least-squares mean change of −31.2 mg/dL (95% CI, −39.2 to −23.3) for ezetimibe and −102.9 mg/dL (95% CI, −108.7 to −97.2) for evolocumab—a mean difference of −71.7 mg/dL (95% CI, −81.3 to −62.2) (P < .001).

Mean percent changes for lipoprotein(a) level for the mean of weeks 22 and 24 were −1.6% (95% CI, −7.2% to 3.9%) with ezetimibe and −22.7% (95% CI, −26.7% to −18.7%) with evolocumab (between-group difference, −21.1% [95% CI, −27.7% to −14.5%]). Mean percent changes at week 24 were 0.2% (95% CI, −5.8% to 6.2%) for ezetimibe and −21.1% (95% CI, −25.4% to −16.7%) for evolocumab (between-group difference, −21.2% [95% CI, −28.4% to −14.1%]).

For the mean of weeks 22 and 24, 1.4% (95% CI, 0.3% to 7.7%) of patients achieved an LDL-C level less than 70 mg/dL with ezetimibe and 29.9% (95% CI, 22.9% to 38.1%) with evolocumab (P < .001). At week 24, 0% (95% CI, 0.0% to 6.3%) of patients achieved an LDL-C level less than 70 mg/dL with ezetimibe and 27.4% (95% CI, 20.1% to 36.1%) with evolocumab (P < .001).

Safety and Tolerability Outcomes

During phase B, any muscle-related adverse event occurred in 21 ezetimibe-treated patients (28.8%) and 30 evolocumab-treated patients (20.7%) (**Table 4**). eFigure 2 in Supplement 3 shows nonprespecified analyses of the time to patient-reported muscle symptoms for evolocumab compared with ezetimibe (HR, 0.68 [95% CI, 0.39 to 1.19]; P = .17). Muscle symptoms leading to discontinuation of oral study drug occurred in 5 of 73 ezetimibe-treated patients (6.8%) and 11 of 145 evolocumab-treated patients (7.6%) receiving oral placebo. Muscle symptoms leading to discontinuation of injectable study drug occurred in 1 of 145 evolocumab-treated patients (0.7%) and 0 of 73 ezetimibe-treated patients receiving placebo injections (Table 4).

Any investigator-reported increase in CK level occurred in 1 ezetimibe-treated patient (1.4%) and 4 evolocumab-treated patients (2.8%). Injection site reactions occurred in 2 of 73 subcutaneous placebo-treated patients (2.7%) and 7 of 143 evolocumab-treated patients (4.8%). There were 2 adjudicated major adverse cardiovascular events in the trial: 1 myocardial

Table 4. Most Common Adverse Events During Phase B of the GAUSS-3 Trial

Adverse Event	No. (%) of Patients	
	Ezetimibe (n = 73)	Evolocumab (n = 145)
Total muscle-related events	21 (28.8)	30 (20.7)
Myalgia	16 (21.9)	20 (13.8)
Creatine kinase increase[a]	1 (1.4)	4 (2.8)
Musculoskeletal pain	1 (1.4)	5 (3.4)
Muscle weakness	0	3 (2.1)
Nasopharyngitis	2 (2.7)	14 (9.7)
Arthralgia	1 (1.4)	13 (9.0)
Pain in extremity	1 (1.4)	13 (9.0)
Muscle spasms	5 (6.8)	13 (9.0)
Fatigue	5 (6.8)	12 (8.3)
Headache	7 (9.6)	10 (6.9)
Back pain	6 (8.2)	10 (6.9)
Injection site reactions	2 (2.7)	7 (4.8)
Influenza	1 (1.4)	7 (4.8)
Diarrhea	4 (5.5)	6 (4.1)
Urinary tract infection	4 (5.5)	5 (3.4)
Nausea	3 (4.1)	5 (3.4)
Rash	3 (4.1)	5 (3.4)
Fall	1 (1.4)	5 (3.4)
Gastroesophageal reflux disease	0	5 (3.4)
Insomnia	0	5 (3.4)
Discontinuation of treatment for any reason		
Discontinued oral drug treatment	14 (19.2)	23 (15.9)
Discontinued subcutaneous drug treatment	4 (5.5)	7 (4.8)
Discontinuation of treatment for muscle symptoms		
Discontinued oral drug treatment	5 (6.8)	11 (7.6)
Discontinued subcutaneous drug treatment	0	1 (0.7)
Adjudicated cardiovascular events		
Myocardial infarction	1 (1.4)	1 (0.7)
Percutaneous coronary intervention	2 (2.7)	3 (2.1)

Abbreviation: GAUSS-3, Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects 3.

[a] Any investigator-reported elevation above upper limit of normal.

infarction in each treatment group and no deaths in either group. One patient (0.7%) developed evolocumab-binding antibodies; no patients developed neutralizing antibodies. Other common adverse effects are shown in Table 4.

Discussion

Statin intolerance related to muscle symptoms represents a major unresolved challenge to the delivery of optimal cardiovascular care. The reported incidence of statin-associated muscle symptoms in observational studies ranges from 5% to 29% of treated patients, varying by statin and dose.[2] Often, despite multiple attempts to find a statin regimen acceptable to the patient, practitioners resort to less effective therapies. Alternative approaches typically include use of ezetimibe or administration of statins intermittently or at dosages below the approved starting dose.[4,5,12] These alternative therapeutic strategies provide less LDL-C reduction than recommended by current practice guidelines and result in higher LDL-C levels than most practitioners consider acceptable for optimal reduction of cardiovascular risk. The problem of statin-associated muscle symptoms is particularly vexing for patients with known cardiovascular disease (ie, secondary prevention) or those with very high LDL-C levels (eg, patients with heterozygous familial hyperlipidemia). However, concerns exist about the ability to reliably diagnose this disorder, uncertainty about its true incidence, and absence of clinical outcome data for nonstatin therapies.

In the current trial, we sought to address several of these concerns, first by determining the incidence of statin intolerance due to muscle-related adverse effects with a blinded atorvastatin rechallenge and subsequently by evaluating the tolerability and relative efficacy of 2 potentially useful therapies in these patients—ezetimibe and a recently approved PCSK9 inhibitor, evolocumab. To identify the presence of statin intolerance, the trial design used a 2-stage approach previously tested in a smaller study.[13]

In the first phase of the study, patients with a strong history of muscle-related statin intolerance were administered both atorvastatin and placebo using a crossover procedure to allow identification of patients who developed muscle symptoms during atorvastatin administration but not during placebo administration. During this rechallenge procedure, we observed a 42.6% rate of discontinuation for intolerable muscle symptoms with atorvastatin but not placebo, which was modestly higher than that reported in a smaller prior study using simvastatin.[13] However, 26.5% of patients reported similar symptoms with placebo but not atorvastatin, demonstrating that reported muscle symptoms are not always related to statin use. Since statin-associated muscle symptoms are dose-related, the rate observed in GAUSS-3 for atorvastatin (20 mg) may underestimate the problem, particularly for patients needing high-intensity statin therapy, such as those enrolled in the trial.

During the second phase of the study, patients with reproducible statin-induced muscle symptoms during rechallenge were randomized to 2 nonstatin LDL-C–lowering therapies to assess both efficacy and tolerability. The PCSK9 inhibitor evolocumab produced significantly larger reductions in levels of LDL-C and other atherogenic lipoproteins (Table 3 and Figure 3). Both coprimary end points showed a 16.7% reduction with ezetimibe and a more than 50% reduction with evolocumab. These reductions in LDL-C levels are consistent with current labeling for both products. Despite very high baseline values, the LDL-C goal of less than 70 mg/dL was achieved in nearly 30% of evolocumab-treated patients and 1.4% of ezetimibe-treated patients (Table 3). The LDL-C reduction for both drugs was stable by 4 weeks and sustained during the course of the 24 weeks of treatment (Figure 3).

The study demonstrates the unmet medical need in this population, all of whom had either preexisting cardiovascular disease or multiple risk factors and very high baseline LDL-C levels, which on average exceeded 210 mg/dL. In such patients, LDL-C reduction with statins is considered a particularly important priority in efforts to prevent cardiovascular morbidity and mortality. Because some patients cannot tolerate statins, the need for alternative LDL-C–lowering strategies in such patients is self-evident. Previous trials have suggested that PCSK9 inhibitors are effective at lowering LDL-C levels and well tolerated by patients with a history of statin-associated muscle symptoms.[6-8] Although these initial trials included some patients with a history of extreme CK elevations during statin treatment, the studies did not use a placebo-controlled statin rechallenge procedure to identify the presence of statin intolerance. In retrospect, these studies may have included many patients who would have been able to tolerate 10 weeks of atorvastatin (20 mg) during blinded rechallenge.

Both ezetimibe and evolocumab were well tolerated during the trial, with 5 ezetimibe-treated patients (6.8%) and 1 evolocumab-treated patient (0.7%) discontinuing active treatment because of muscle-related adverse events. However, 11 evolocumab-treated patients (7.6%) discontinued oral placebo for muscle symptoms. These findings demonstrate that both drugs are unlikely to provoke muscle symptoms and can be administered successfully in such patients, although with significant differences in lipid-lowering efficacy. Since a minority of patients achieved optimal LDL-C levels despite treatment with evolocumab, it may be worth exploring the addition of ezetimibe to evolocumab for those patients requiring further LDL-C reduction. It should be noted that neither ezetimibe nor evolocumab is approved for reduction of major adverse cardiovascular events. Although a single outcome trial was completed for ezetimibe and showed modest event reduction, the drug was not approved in the United States for a clinical outcome benefit.[14] Evolocumab and other PCSK9 inhibitors are undergoing study in large clinical outcomes trials that are expected to complete in 2016 or 2017.[15-17]

To our knowledge, the GAUSS-3 trial represents the largest and most comprehensive study using a blinded rechallenge procedure to assess the ability of patients with a history of muscle-related adverse effects to tolerate statins. The trial provides insights into the time course of statin-associated muscle-related adverse effects. As shown in Figure 2A, initial randomization to either atorvastatin or placebo in phase A

resulted in similar rates of muscle symptoms during the first 50 days, with a modest increase in occurrence with atorvastatin near the end of the 10-week exposure (HR, 1.34 [95% CI, 1.05 to 1.71]; $P = .02$). After crossover to period 2, larger numbers of patients experienced symptoms in the atorvastatin treatment group, with differences in event rates occurring relatively early (HR, 1.96 [95% CI, 1.44 to 2.66]; $P < .001$) (Figure 2B). Study participants were aware that they might receive a statin during phase A and frequently reported intolerable muscle symptoms while receiving placebo, clearly demonstrating the importance of patient perceptions on inability to tolerate statins. Although the reported rate of intolerance during atorvastatin administration was higher than that observed with placebo, these differences were modest, reflecting the importance of the "nocebo effect" (adverse effects during placebo administration) among patients with a history of statin intolerance.[18]

The study has important limitations. The study was modest in size, reflecting the clinical challenges of requesting that participants with a strong history of muscle intolerance undergo rechallenge with atorvastatin after experiencing unpleasant adverse effects during prior attempts at statin treatment. The study design also did not permit the use of a common management strategy for patients with muscle-related symptoms—administration of small doses of statins 1 to 3 times weekly. Such a study design would be challenging, because this approach often requires months of careful titration to reach the highest statin dosage tolerable for individual patients. The 24-week duration of therapy was relatively short for patients who require lifetime LDL-C reduction. However, the majority of patients report statin-associated muscle-related adverse effects within the first 3 months of initiating therapy. An additional limitation is that many of these patients with very high baseline LDL-C levels did not achieve optimal LDL-C levels and would require additional therapeutic agents, which may be associated with muscle symptoms. Although preliminary data are promising, definitive data on cardiovascular outcomes with evolocumab are not yet available.[19]

Conclusions

Among patients with statin intolerance related to muscle-related adverse effects, the use of evolocumab compared with ezetimibe resulted in a significantly greater reduction in LDL-C levels after 24 weeks. Further studies are needed to assess long-term efficacy and safety.

ARTICLE INFORMATION

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