PRELIMINARY COMMUNICATION

ONLINE FIRST

Effect of a Monoclonal Antibody to PCSK9 on Low-Density Lipoprotein Cholesterol Levels in Statin-Intolerant Patients

The GAUSS Randomized Trial

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Context An estimated 10% to 20% of patients cannot tolerate statins or adequate doses to achieve treatment goals. Plasma proprotein convertase subtilisin/kexin type 9 (PCSK9) binds to low-density lipoprotein (LDL) receptors, promoting their degradation and increasing LDL cholesterol levels. In phase 1 studies, a human monoclonal antibody to PCSK9, AMG145, was well tolerated and reduced LDL cholesterol levels.

Objective To assess the efficacy and tolerability of AMG145 in patients with statin intolerance due to muscle-related side effects.

Design, Setting, and Patients A 12-week, randomized, double-blind, placebo- and ezetimibe-controlled, dose-ranging study conducted between July 2011 and May 2012 in statin-intolerant adult patients at 33 international sites.

Intervention Patients were randomized equally to 1 of 5 groups: AMG145 alone at doses of 280 mg, 350 mg, or 420 mg; AMG145 at 420 mg plus 10 mg of ezetimibe; or 10 mg of ezetimibe plus placebo. AMG145 or placebo was administered subcutaneously every 4 weeks.

Main Outcome Measures The primary end point was percentage change from baseline to week 12 in ultracentrifugation-measured LDL cholesterol. Other end points included measures of safety and tolerability of different doses of AMG145 and AMG145 plus ezetimibe.

Results Of 236 patients screened, 160 were randomized (mean age, 62 years; 64% female; mean baseline LDL cholesterol, 193 mg/dL); all patients had intolerance to 1 or more statins because of muscle-related events. At week 12, mean changes in LDL cholesterol levels were –67 mg/dL (–41%; 95% CI, –49% to –33%) for the AMG145, 280-mg, group; –70 mg/dL (–43%; 95% CI, –51% to –35%) for the 350-mg group; –91 mg/dL (–51%; 95% CI, –59% to –43%) for the 420-mg group; and –110 mg/dL (–63%; 95% CI, –71% to –55%) for the 420-mg/ezetimibe group compared with –14 mg/dL (–15%; 95% CI, –23% to –7.0%) for the placebo/ezetimibe group ($P < .001$). Four serious adverse events were reported with AMG145 (coronary artery disease, acute pancreatitis, hip fracture, syncope). Myalgia was the most common treatment-emergent adverse event during the study, occurring in 5 patients (15.6%) in the 280-mg group (n=32); 1 patient (3.2%) in the 350-mg group (n=31), 1 patient (3.1%) in the 420-mg group (n=32), 6 patients (20.0%) receiving 420-mg AMG145/ezetimibe, and 1 patient (3.1%) receiving placebo/ezetimibe.

Conclusion In this phase 2 study in statin-intolerant patients, subcutaneous administration of a monoclonal antibody to PCSK9 significantly reduced LDL cholesterol levels and was associated with short-term tolerability.

Trial Registration clinicaltrials.gov Identifier: NCT01375764

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REDUCTION OF LOW-DENSITY LIpoprotein cholesterol (LDL-C) is the cornerstone of cardiovascular risk reduction,[1-3] with specific LDL-C goals based on cardiovascular outcome trials.[1-4] Statins are currently the most effective agents for reducing LDL-C levels.[5] However, of approximately 20 million patients treated with statins,[6] an estimated 10% to 20% are unable to tolerate any statins or the higher doses necessary to achieve current LDL-C goals, primarily because of muscle-related side effects.[7]

The most effective and frequently used alternative is ezetimibe, a cholesterol absorption inhibitor that reduces LDL-C levels by 18%,[8] which alone is unlikely to achieve LDL-C goals and is more commonly used in combination with statins.[9] However statin-intolerant patients have a need for more effective LDL-C–lowering therapies.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) plays a pivotal role in cellular cholesterol homeostasis, in which it mediates the binding and trafficking of LDL receptors.[10] Gain-of-function mutations result in hypercholesterolemia, while loss-of-function mutations are associated with reduction in

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plasma LDL-C levels and decreased risk of cardiovascular disease without detectable adverse effects on other aspects of general health.[11,12] In phase 1 studies, a human monoclonal antibody to PCSK9, designated AMG145, was well tolerated and lowered LDL-C levels.[13] The Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin Intolerant Subjects (GAUSS) study assessed the efficacy and safety of AMG145 in patients with a documented history of muscle-related adverse effects with statins.

METHODS

This global phase 2, randomized, double-blind, placebo- and ezetimibe-controlled, dose-ranging study was conducted at 33 study sites in North America, Australia, and Europe between July 2011 and May 2012. The institutional review board or independent ethics committee at each site approved the protocol and informed consent form. All patients provided written informed consent before study procedures were performed.

The primary end point was the percentage change from baseline at week 12 in LDL-C measured by preparative ultracentrifugation in patients. Other objectives included assessment of the safety and tolerability of 3 different doses of AMG145 and AMG145 plus ezetimibe compared with placebo plus ezetimibe.

The study enrolled adults aged 18 to 75 years with hypercholesterolemia who were considered statin intolerant. Statin intolerance was defined as the inability to tolerate at least 1 statin at any dose or an increase in dose above weekly maximums of rosuvastatin, 35 mg; atorvastatin, 70 mg; simvastatin, 140 mg; pravastatin, 140 mg; lovastatin, 140 mg; or fluvastatin, 280 mg, because of intolerable myalgia (muscle pain, soreness, weakness, or cramps) or myopathy (myalgia plus elevated creatine kinase [CK]) and having symptom improvement or resolution with statin discontinuation.

Patients had LDL-C levels above risk-based goals recommended by the National Cholesterol Education Program: 100 mg/dL or greater with diagnosed coronary heart disease (CHD) or risk equivalent, 130 mg/dL or greater without CHD or risk equivalent and 2 or more risk factors, or 160 mg/dL or greater without CHD or risk equivalent and with 1 or 0 risk factors.[1] (To convert LDL-C to mmol/L, multiply by 0.0259.)

Eligible patients could receive stable doses (≥4 weeks before screening) of 1 or more of the following: statins less than or equal to the weekly maximums listed in a previous paragraph, bile-acid sequestering resins, or plant stanols/sterols. Patients taking ezetimibe at the time of initial screening discontinued ezetimibe for at least 4 weeks before the eligibility visit. All patients were required to have fasting triglyceride values of 400 mg/dL or less at screening. (To convert triglycerides to mmol/L, multiply by 0.0113.)

Exclusion criteria included heart failure (New York Heart Association class III or IV or left ventricular ejection fraction <30%); uncontrolled serious cardiac arrhythmia or hypertension; major cardiac, cerebrovascular, pulmonary, or venous event within 3 months before randomization; type 1 diabetes mellitus or poorly controlled or recently diagnosed type 2 diabetes mellitus; thyroid disease; renal dysfunction, defined as an estimated glomerular filtration rate less than 30 mL/min/1.73 m^2; aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 2× upper limit of normal (ULN); CK greater than 3× ULN; and use of systemic corticosteroids or cyclosporine within the last 3 months.

Study Procedures

Patients were initially assessed for eligibility with a fasting lipid profile. If eligibility was confirmed by laboratory values, patients were randomized within 6 weeks. Randomization was done by interactive voice response system and was stratified by screening levels of LDL-C (<130 mg/dL or ≥130 mg/dL) and statin use at baseline (yes or no). Patients were randomized 1:1:1:1:1 to receive AMG145 alone at doses of 280 mg, 350 mg, or 420 mg, every 4 weeks; AMG145, 420 mg every 4 weeks plus daily oral ezetimibe, 10 mg; or placebo every 4 weeks plus daily oral ezetimibe, 10 mg. Administration of ezetimibe was not blinded. AMG145 or placebo was administered subcutaneously.

The treatment period was 12 weeks, with study visits scheduled at screening and day 1 and at weeks 2, 4, 8, and 12. Patients received subcutaneous AMG145 or placebo on day 1 and at weeks 4 and 8 (3 doses). Blood samples for all assessments were collected after an overnight fast (water only) and analyzed by a central laboratory (eAppendix 1, available at http://www.jama.com). Anti-AMG145 antibody formation was assessed at weeks 0, 4, and 12. After screening, investigators, site staff, and study team members were blinded to all assessment results.

An independent data and safety monitoring committee regularly reviewed unblinded data prepared by an external biostatistical group independent of Amgen. Deaths and major cardiovascular and muscle-related events were adjudicated by an independent clinical events committee.

Statistical Analysis

Data from all patients who received at least 1 dose of investigational product (AMG145 or placebo) were included in the analyses of baseline characteristics and efficacy and safety end points. Patients were analyzed in the treatment group to which they were randomized. The true treatment effect of AMG145 compared with ezetimibe in the percentage reduction in LDL-C was assumed to be approximately 20% (SD, 20%) (an assumption based on Food and Drug Administration statistical reviews of ezetimibe and pitavastatin).

The planned enrollment was 30 patients per group (150 total), which provided approximately 84% power to detect an AMG145 treatment effect of approximately 17.5% in LDL-C reduction, assuming a common SD of 21.93% calculated using a 2-sided *t* test with a

.05 significance level (α). The power calculation for the primary end point (percentage change from baseline in LDL-C measured by ultracentrifugation at week 12) was based on an intent-to-treat analysis that assumed a 15% rate of study drug discontinuation.

Secondary end points, all measured at week 12, included absolute change in LDL-C and percentage changes from baseline in non–high-density lipoprotein cholesterol (non–HDL-C), apolipoprotein B (apo B), and the ratios of total cholesterol/HDL-C and apo B/apo AI. Exploratory end points included the percentage change from baseline in additional lipid parameters including lipoprotein(a) at each study visit and the incidence of adjudicated events of death (all-cause and cardiovascular); cardiac ischemic events (myocardial infarction, hospitalization for unstable angina, and coronary revascularization); hospitalization for heart failure; cerebrovascular events (transient ischemic attack and stroke); and noncoronary revascularization.

Key safety end points included the incidence of treatment-emergent adverse events (AEs), laboratory values, vital signs, and electrocardiographic parameters at each scheduled visit, and the incidence of anti-AMG145 antibodies (binding and neutralizing). Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 15.0.

The primary analysis of the primary efficacy end point was analyzed using an analysis-of-covariance (ANCOVA) model to assess the efficacy of each AMG145-alone dose group compared with placebo/ezetimibe. A hierarchical sequential testing approach was applied to control the family-wise error rate for multiple comparisons, at a significance level of .05 for 2-sided testing, starting from the highest dose group and continuing on to the next highest dose until .05 statistical significance was not met or the lowest dose was tested, whichever occurred first. Additional analyses included an ANCOVA model to access the efficacy of AMG145 plus ezetimibe compared with placebo/ezetimibe, at a significance level of .05.

All efficacy end points were analyzed using last-observation-carried-forward (LOCF) imputation. Sensitivity analyses were performed using the last measured LDL-C value during the treatment period or including only patients who completed the study. The Kruskal-Wallis test (with LOCF) and repeated-measures mixed-effects model (without LOCF) were also performed, including all patients who received at least 1 dose of investigational product. Safety data were reported as observed. Safety analyses were conducted using descriptive statistics.

RESULTS

Of 236 patients screened, 160 were randomized (AMG145 only, n=96; ezetimibe/AMG145, n=31; placebo/ezetimibe, n=33) (FIGURE 1). Three patients did not receive investigational product, discontinued the study, and were excluded from the analyses, leaving a full analysis set of 157 patients who received at least 1 dose of investigational product. Of these, 155 patients (97% of those randomized) completed the study through the final visit, and 150 (94%) received all planned doses (Figure 1). Five patients discontinued treatment after receiving at least 1 dose of investigational product because of muscle-related AEs (none serious): 2 in the placebo/ezetimibe group and 1 each in the groups for AMG145, 350 mg, 420 mg, and 420 mg with ezetimibe.

Patient characteristics at baseline, including PCSK9 levels, were similar among the groups (TABLE 1). Mean age was 62 years, 64% were female, and the mean (SD) baseline LDL-C level was 193 (51) mg/dL. Fifty percent of patients were high risk or moderately high risk according to National Cholesterol Education Program categories. Seventeen percent had coronary artery disease, and 7% had cerebrovascular or peripheral arterial disease (eTable 1). At baseline, 24% of patients used lipid-lowering medications; 16% used statins. All patients were unable to tolerate at least 1 statin because of muscle-related side effects; 77% could not tolerate 2 or more statins; 32%, 3 or more; and 11% could not tolerate 4 or more statins. The worst muscle-related statin side effects were myalgia, reported by 90% of patients; myositis, reported by 9%; and rhabdomyolysis, reported by 1%.

LDL-C Reduction

Administration of AMG145 resulted in a dose-dependent reduction in LDL-C levels (TABLE 2 and FIGURE 2). At week 12, least-squares mean percentage changes in LDL-C from baseline in the AMG145 dose groups were –41% (95% CI, –49% to –33%) in the 280-mg group, –43% (95% CI, –51% to –35%) in the 350-mg group, –51% (95% CI, –59% to –43%) in the 420-mg group, and –63% (95% CI, –71% to –55%) in the 420-mg/ezetimibe group, compared with –15% (95% CI, –23% to –7.0%) in the placebo/ezetimibe group. Absolute changes in LDL-C were –67 mg/dL, 280 mg; –70 mg/dL, 350 mg, –91 mg/dL, 420 mg; –110 mg/dL, 420 mg and ezetimibe; and –14 mg/dL, placebo and ezetimibe.

The maximal reduction in LDL-C level was evident within 2 weeks of commencement of AMG145 therapy, with or without ezetimibe, and the effect was maintained throughout the 12-week study. The reduction in LDL-C level was significantly greater with every dose of AMG145 than with placebo/ezetimibe ($P<.001$). In the AMG145-alone groups, LDL-C goals of less than 100 mg/dL and less than 70 mg/dL were achieved in 54% and 18% of patients, respectively (FIGURE 3), compared with 7% and 0% with ezetimibe. Treatment with AMG145/ezetimibe resulted in 90% and 62% of patients achieving these goals, respectively.

Other Efficacy Results

The effect of AMG145 on LDL-C levels was accompanied by similar changes in total cholesterol, non–HDL-C, apo B, and the ratios of total cholesterol/HDL-C and apo B/apo AI (Table 2 and TABLE 3). Consistent with results in ear-

lier trials,[13] lipoprotein(a) level was reduced by 20% (95% CI, –29% to –11%) to 26% (95% CI, –35% to –17%) with AMG145 and 29% (95% CI, –42% to –16%) with AMG145/ezetimibe (all $P<.01$ to $P<.001$ vs placebo/ezetimibe).

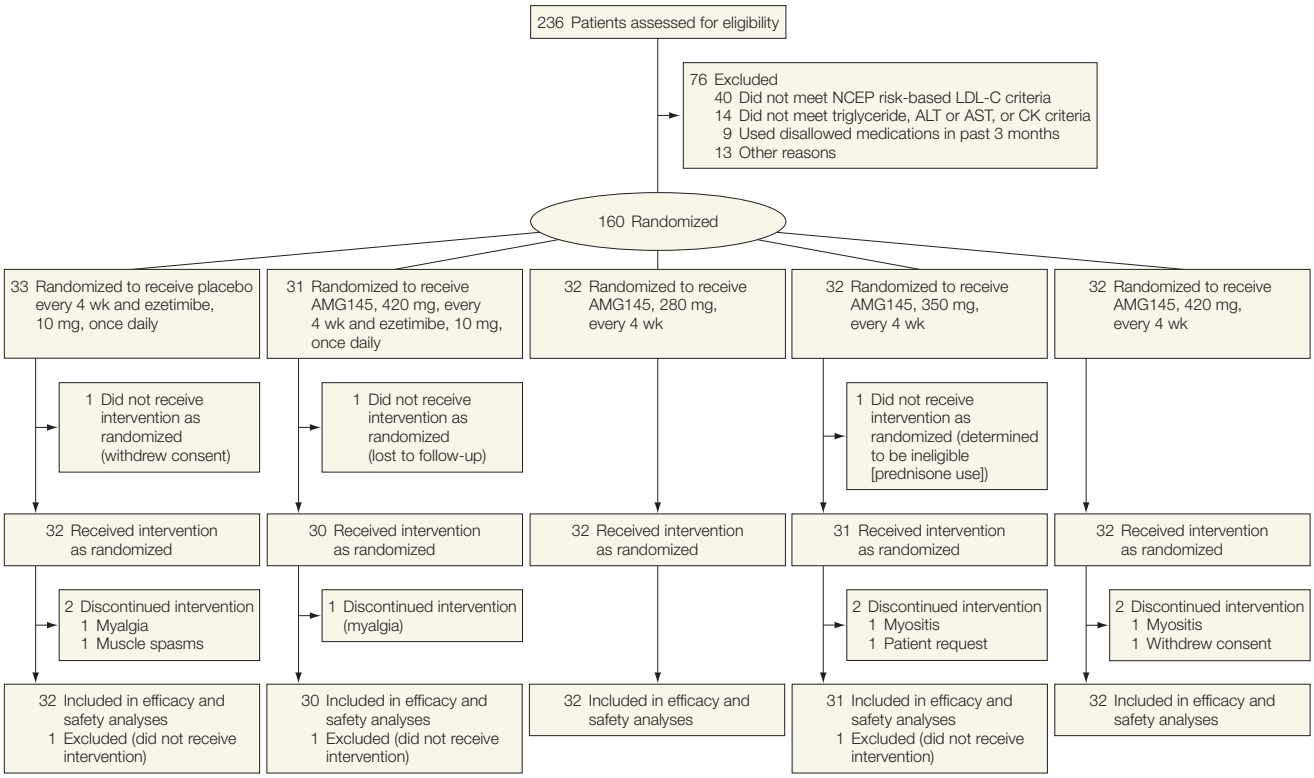
AMG145 increased HDL-C modestly, from 6% (95% CI, –1% to 12%) to 12% (95% CI, 4% to 20%), compared with 1% (95% CI, –8% to 6%) with placebo/ezetimibe. The difference in the effect on HDL-C level between AMG145/ezetimibe and placebo/ezetimibe was statistically significant ($P<.001$). Similar increases were seen in apo AI, with all groups treated with AMG145 showing statistically significantly greater responses than those treated with placebo/ezetimibe ($P<.05$ or $P<.01$). Small, nonsignificant reductions in triglyceride and very low-density lipoprotein cholesterol (VLDL-C) levels were seen with AMG145 compared with placebo/ezetimibe. Mean free PCSK9 levels at week 12 declined by up to 48.4% (95% CI, –54.1% to –42.6%) from pretreatment levels with AMG145 monotherapy and by 1.5% (95% CI, –10.1% to 7.2%) with ezetimibe monotherapy.

Tolerability and Safety

Administration of AMG145 was well tolerated, with no significant safety findings reported in these statin-intolerant patients. Overall, 60% of patients receiving AMG145 and 59% receiving placebo/ezetimibe reported treatment-emergent AEs (eTable 2). Myalgia was the most common treatment-emergent AE during the study, occurring in 7 patients (7.4%) taking AMG145 only (280 mg, 5 patients [15.6%]; 350 mg, 1 patient [3.2%]; 420 mg, 1 patient [3.1%]), 6 patients (20.0%) taking AMG145/ezetimibe, and 1 patient (3.1%) taking placebo/ezetimibe. The other most common treatment-emergent AEs for the AMG145-only, AMG145/ezetimibe, and placebo/ezetimibe groups, respectively, were nasopharyngitis (5.3%, 10.0%, 15.6%), nausea (4.2%, 0%, 3.1%), and fatigue (4.2%, 0%, 6.3%). No relationship was apparent between the incidence of any single treatment-emergent AE and AMG145 dose, and the overall incidence of treatment-related AEs did not appear to be dose related.

Four serious AEs occurred, all in the AMG145-treated groups (coronary artery disease, acute pancreatitis, hip fracture, and syncope); none were considered treatment related. The AE of coronary artery disease was a coronary angiography and stenting procedure planned before study enrollment, without signs or symptoms of instability after enrollment. No deaths were reported. Changes in key laboratory parameters (eTable 2) did not show any

Figure 1. GAUSS Study: Patient Enrollment and Disposition



GAUSS indicates Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin Intolerant Subjects; NCEP, National Cholesterol Education Program; LDL-C, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase.

differences between treatment groups, and laboratory safety results did not appear to be related to the AMG145 dose.

Two patients in the AMG145, 350-mg, group had CK levels greater than 10 × ULN during the study. One of these patients had an isolated CK elevation of 2773 U/L at week 4 the day after an unusually intense weight-lifting workout; the event resolved spontaneously without treatment interruption. This episode was adjudicated not to be a muscle-related event by the clinical events committee. The other patient had an isolated CK elevation of 2030 U/L accompanied by generalized muscular pain at week 2, after his gym routine. Rosuvastatin and AMG145 were discontinued, and subsequent CK values were normal. A muscle biopsy showed a normal pattern. This event was adjudicated positively as a myopathy event. One patient in the placebo/ezetimibe group had a CK level greater than 5 × ULN at week 4.

Two patients in the AMG, 420-mg, group experienced 1 percutaneous intervention each; 1 of these patients had experienced a non-ST segment elevation myocardial infarction that was

Table 1. Baseline Demographic and Disease Characteristics

Characteristic	AMG145 SC Every 4 wk			AMG145 or Placebo Every 4 wk and Ezetimibe, 10 mg, Once Daily		All Patients (N = 157)
	280 mg (n = 32)	350 mg (n = 31)	420 mg (n = 32)	AMG145 SC, 420 mg (n = 30)	Placebo SC (n = 32)	
Age, mean (SD), y	62.2 (10.1)	62.3 (9.1)	60.0 (8.6)	62.0 (7.2)	62.4 (6.6)	61.8 (8.4)
Female, sex, No. (%)	18 (56.3)	21 (67.7)	20 (62.5)	23 (76.7)	18 (56.3)	100 (63.7)
Race/ethnicity, No. (%)						
White	28 (87.5)	29 (93.5)	30 (93.8)	24 (80.0)	28 (87.5)	139 (88.5)
Black	2 (6.3)	2 (6.5)	1 (3.1)	1 (3.3)	2 (6.3)	8 (5.1)
Statin intolerance, No. (%)						
1	4 (12.5)	7 (22.6)	9 (28.1)	9 (30.0)	7 (21.9)	36 (22.9)
2	17 (53.1)	13 (41.9)	11 (34.4)	15 (50.0)	14 (43.8)	70 (44.6)
3	7 (21.9)	8 (25.8)	10 (31.3)	1 (3.3)	8 (25.0)	34 (21.7)
≥4	4 (12.5)	3 (9.7)	2 (6.3)	5 (16.7)	3 (9.4)	17 (10.8)
Worst muscle-related side effect, No. (%)[a]						
Myalgia	29 (90.6)	28 (90.3)	29 (90.6)	28 (93.3)	28 (87.5)	142 (90.4)
Myositis	3 (9.4)	3 (9.7)	2 (6.3)	2 (6.7)	4 (12.5)	14 (8.9)
Rhabdomyolysis	0	0	1 (3.1)	0	0	1 (0.6)
Lipid parameters, mean (SD)						
LDL-C, mg/dL, by ultracentrifugation	194.8 (48.1)	190.3 (47.8)	203.5 (60.3)	194.4 (60.1)	182.9 (36.4)	193.2 (51.0)
LDL-C, mg/dL, calculated	192.1 (47.6)	189.1 (50.9)	202.5 (61.1)	193.6 (59.7)	180.9 (35.8)	191.5 (51.6)
Total cholesterol, mg/dL	284 (55.9)	281.5 (53.4)	292 (57.9)	279.7 (65.3)	274.5 (38.9)	282.4 (54.4)
HDL-C, mg/dL	58.5 (19.6)	58.5 (20)	51.4 (18.7)	59.9 (19.2)	60.8 (18.8)	57.8 (19.3)
Non–HDL-C, mg/dL	225.5 (53.3)	222.9 (55.8)	240.6 (63.9)	219.8 (60.5)	213.7 (40.4)	224.6 (55.3)
Total cholesterol/HDL-C ratio, mg/dL	5.29 (1.82)	5.44 (2.31)	6.44 (2.83)	5.09 (2.42)	4.91 (1.55)	5.44 (2.27)
VLDL-C, mg/dL	30.5 (13.5)	32.5 (19.7)	37.1 (18.8)	25.3 (10.6)	30.8 (14.2)	31.3 (16.0)
Apo B, mg/dL	143 (30.6)	144.9 (33.9)	150.8 (34.1)	138.8 (33.1)	138 (21.7)	143.2 (30.9)
Apo AI, mg/dL	163.5 (31.8)	166.5 (32.6)	151.6 (33)	163.1 (29.0)	170.8 (31.5)	163.1 (31.9)
Apo B/apo AI ratio	0.91 (0.27)	0.92 (0.33)	1.06 (0.39)	0.88 (0.33)	0.84 (0.23)	0.92 (0.32)
Triglycerides, mg/dL	161.7 (66.4)	170.7 (88.7)	190.7 (79.3)	130.9 (55.5)	163.9 (65.7)	163.9 (73.7)
Lipoprotein(a), nmol/L, median (Q1, Q3)	36.5 (10.5, 122.5)	68.3 (31.0, 184.0)	26.0 (9.0, 100.5)	39.0 (14.0, 187.0)	58.5 (5.5, 140.5)	39.0 (11.0, 137.0)
Free PCSK9, ng/mL	383 (97.9)	396.2 (129.2)	371.6 (87.2)	379.4 (110.9)	389.8 (90.9)	384.0 (102.9)
NCEP CHD risk category, No. (%)						
High risk	14 (43.8)	12 (38.7)	11 (34.4)	10 (33.3)	15 (46.9)	62 (39.5)
Moderately high risk	1 (3.1)	5 (16.1)	5 (15.6)	1 (3.3)	4 (12.5)	16 (10.2)
Moderate risk	8 (25.0)	10 (32.3)	7 (21.9)	11 (36.7)	8 (25.0)	44 (28.0)
Lower risk	9 (28.1)	4 (12.9)	9 (28.1)	8 (26.7)	5 (15.6)	35 (22.3)

Abbreviations: apo AI, apolipoprotein AI; apo B, apolipoprotein B; CHD, coronary heart disease; CK, creatine kinase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NCEP, National Cholesterol Education Program; PCSK9, proprotein convertase subtilisin/kexin type 9; Q1, first quartile; Q3, third quartile; SC, subcutaneous; VLDL-C, very low-density lipoprotein cholesterol.

SI conversion factors: To convert LDL-C, HDL-C, and total cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113.

[a] For any statin. Myalgia refers to muscle symptoms without CK elevation; myositis, muscle symptoms with CK elevation; and rhabdomyolysis, muscle symptoms with significant CK elevation.

Table 2. Key Efficacy Outcomes at Week 12: Cholesterol Levels

	Mean (95% CI)				
	AMG145 SC Every 4 wk			AMG145 or Placebo Every 4 wk and Ezetimibe, 10 mg, Once Daily	
	280 mg (n = 32)	350 mg (n = 31)	420 mg (n = 32)	AMG145 SC, 420 mg (n = 30)	Placebo SC (n = 32)
LDL-C (ultracentrifugation)					
Absolute value, mg/dL[a]	112.6 (96.3 to 128.9)	107.2 (93.8 to 120.6)	99.0 (83.6 to 114.5)	70.8 (56.9 to 84.7)	154.3 (140.2 to 168.4)
Change from baseline, mg/dL[b]	–66.8 (–84.5 to –49.2)	–69.7 (–87.7 to –51.8)	–90.8 (–108.5 to –73.0)	–109.8 (–131.9 to –87.7)	–14.2 (–31.7 to 3.3)
% change from baseline[b,c]	–40.8 (–48.6 to –32.9)	–42.6 (–50.5 to –34.7)	–50.7 (–58.6 to –42.8)	–63.0 (–71.4 to –54.5)	–14.8 (–22.6 to –7.0)
Treatment difference vs placebo + ezetimibe, %[b,c]	–26.0 (–34.1 to –17.9)	–27.8 (–36.0 to –19.7)	–35.9 (–44.1 to –27.8)	–47.3 (–53.7 to –40.8)	
P value vs ezetimibe + placebo[b,c]	<.001	<.001	<.001	<.001	
Total cholesterol					
Absolute value, mg/dL[a]	196.4 (178.2 to 214.5)	194.4 (179.0 to 209.8)	179.5 (161.8 to 197.3)	152.8 (136.3 to 169.2)	242.5 (227.5 to 257.6)
Change from baseline, mg/dL[a]	–87.6 (–102.6 to –72.7)	–89.1 (–105.8 to –72.3)	–113.5 (–128.5 to –98.4)	–126.5 (–141.4 to –111.6)	–32.9 (–43.8 to –22.0)
% change from baseline[b]	–29.8 (–35.7 to –23.8)	–30.4 (–36.4 to –24.5)	–37.7 (–43.6 to –31.7)	–44.3 (–50.6 to –37.9)	–10.7 (–16.6 to –4.8)
P value vs ezetimibe + placebo[b]	<.001	<.001	<.001	<.001	
HDL-C					
Absolute value, mg/dL[a]	62.2 (55.4 to 68.9)	63.5 (55.6 to 71.5)	56.1 (48.9 to 63.3)	66.3 (59.3 to 73.3)	62.0 (55.3 to 68.7)
Change from baseline, mg/dL[a]	3.7 (–0.4 to 7.7)	4.6 (2.2 to 6.9)	4.5 (2.2 to 6.7)	6.8 (3.9 to 9.7)	0.9 (–1.4 to 3.1)
% change from baseline[b]	5.9 (–1.0 to 12.7)	5.5 (–1.4 to 12.3)	7.4 (0.6 to 14.3)	12.0 (3.9 to 20.1)	–1.1 (–7.9 to 5.7)
P value vs ezetimibe + placebo[b]	.05	.07	.02	<.001	
Non–HDL-C					
Absolute value, mg/dL[a]	134.2 (117.3 to 151.1)	130.9 (113.9 to 147.9)	123.5 (105.7 to 141.3)	86.5 (72.8 to 100.2)	180.5 (164.5 to 196.6)
Change from baseline, mg/dL[a]	–91.3 (–106.9 to –75.7)	–93.6 (–109.9 to –77.3)	–117.9 (–133.0 to –102.8)	–133.3 (–147.8 to –118.8)	–33.7 (–44.7 to –22.8)
% change from baseline[b]	–39.8 (–46.9 to –32.8)	–41.6 (–48.8 to –34.5)	–48.6 (–55.7 to –41.5)	–59.8 (–67.4 to –52.2)	–15.0 (–22.0 to –8.0)
P value vs ezetimibe + placebo[b]	<.001	<.001	<.001	<.001	
Total cholesterol/HDL-C ratio					
Absolute value[a]	3.34 (2.94 to 3.74)	3.46 (2.85 to 4.07)	3.47 (2.95 to 3.99)	2.42 (2.08 to 2.76)	4.21 (3.72 to 4.70)
Change from baseline[a]	–1.95 (–2.40 to –1.50)	–2.00 (–2.46 to –1.55)	–2.99 (–3.70 to –2.28)	–2.71 (–3.36 to –2.06)	–0.70 (–1.00 to –0.41)
% change from baseline[b]	–32.0 (–38.3 to –25.6)	–33.5 (–40.0 to –27.1)	–40.6 (–47.0 to –34.2)	–49.4 (–57.1 to –41.8)	–9.6 (–15.9 to –3.3)
P value vs ezetimibe + placebo[b]	<.001	<.001	<.001	<.001	
VLDL-C					
Absolute value, mg/dL[a]	21.6 (18.2 to 25.0)	23.4 (17.3 to 29.6)	28.0 (23.0 to 33.0)	16.5 (13.5 to 19.5)	27.9 (22.0 to 33.7)
Change from baseline, mg/dL[a]	–8.9 (–13.2 to –4.5)	–8.8 (–13.6 to –3.9)	–8.3 (–13.4 to –3.1)	–9.2 (–12.0 to –6.4)	–3.1 (–7.9 to 1.7)
% change from baseline[b]	–27.6 (–48.6 to –6.7)	–28.8 (–50.2 to –7.5)	–15.0 (–36.1 to 6.1)	–37.8 (–65.0 to –10.6)	–13.2 (–34.1 to 7.6)
P value vs ezetimibe + placebo[b]	.19	.16	.87	.02	

Abbreviations: apo AI, apolipoprotein AI; apo B, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SC, subcutaneous; PCSK9, proprotein convertase subtilisin/kexin type 9; VLDL-C, very low-density lipoprotein cholesterol.

SI conversion factors: To convert LDL-C, HDL-C, and total cholesterol to mmol/L, multiply by 0.0259.

[a] Observed summary data without imputation for missing values.

[b] Least-squares means of the placebo/ezetimibe group and AMG145-alone groups were from an analysis-of-covariance (ANCOVA) model including placebo/ezetimibe group, AMG145-alone groups, and stratification factors. Least-squares mean of AMG145, 420 mg/ezetimibe was from an ANCOVA model including placebo/ezetimibe group; AMG145, 420 mg/ezetimibe group; and stratification factors. For LDL-C level, missing ultracentrifugation values at week 12 were imputed using last observation carried forward (LOCF) and calculated LDL-C values. For other parameters, missing values at week 12 were imputed using LOCF.

[c] Primary end point.

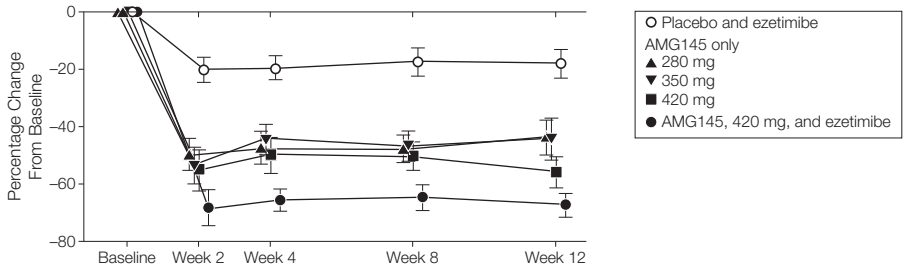
treated with percutaneous coronary intervention. The percutaneous interventions and myocardial infarction were also adjudicated as positive by the clinical events committee. No binding or neutralizing antibodies against AMG145 were detected.

COMMENT

The GAUSS study assessed AMG145, a fully human monoclonal antibody against PCSK9, to reduce LDL-C levels in a difficult-to-treat and increasing patient population: patients at cardiovascular risk who are unable to tolerate effective doses of statins because of muscle-related side effects. In this population, 94% of patients completed all scheduled treatments in the 12-week trial of subcutaneous administration of AMG145 every 4 weeks. Treatment with AMG145 produced LDL-C reductions of 41% to 63%, without significant muscle-related side effects, in patients predisposed to such side effects. These reductions are comparable with those achieved with maximal doses of the most efficacious statins.

Although baseline LDL-C level was on average greater than 190 mg/dL and considerably higher than in prior trials with a PCSK9 monoclonal antibody, the reductions in LDL-C levels with AMG145 administered as monotherapy every 4 weeks were comparable to those obtained with REGN727 given with statins every 2 weeks.[14-16] In addition, in the GAUSS trial, the primary end point of LDL-C level was determined by the reference procedure, ultracentrifugation, which is unlike calculated LDL-C used in prior trials,[14-16] which tends to under-

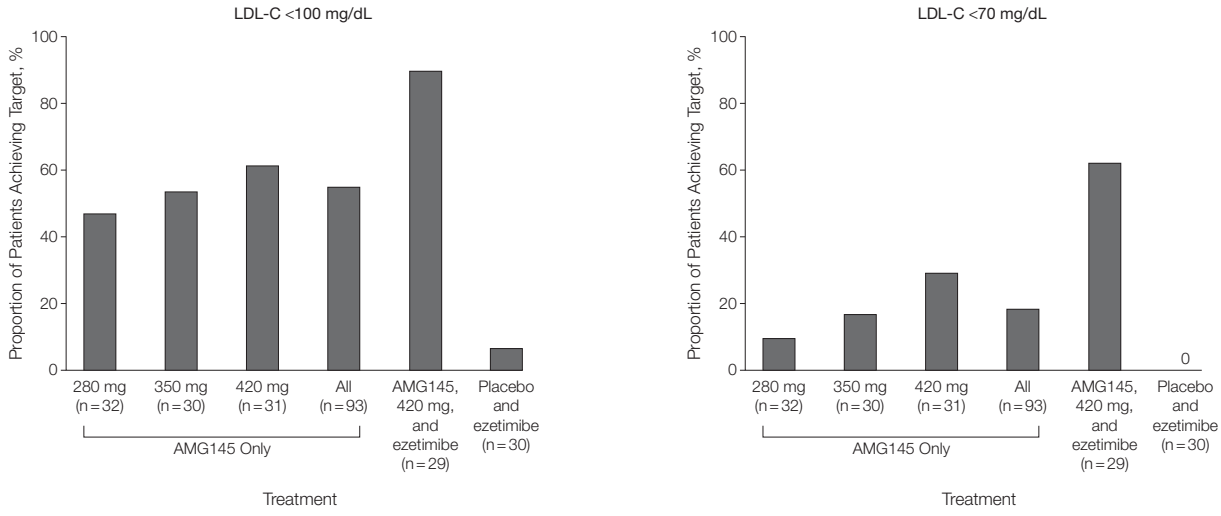
Figure 2. Reductions in Levels of Low-Density Lipoprotein Cholesterol at Week 12



No. of patients					
Placebo and ezetimibe	32	30	32	32	31
AMG145, 280 mg	32	32	32	32	32
AMG145, 350 mg	31	30	29	30	30
AMG145, 420 mg	32	30	30	31	31
AMG145, 420 mg, and ezetimibe	30	29	30	28	29

Mean percentage change in low-density lipoprotein cholesterol from baseline to week 12 (calculated). Patients received AMG145 or placebo subcutaneously every 4 weeks. Oral ezetimibe, 10 mg, was given daily. Error bars indicate 95% CIs.

Figure 3. Percentage of Patients Achieving Recommended Low-Density Lipoprotein Cholesterol Goals



Patients received AMG145 or placebo subcutaneously every 4 weeks. Oral ezetimibe, 10 mg, was given daily. Low-density lipoprotein cholesterol (LDL-C) values at week 12 were measured by preparative ultracentrifugation.

estimate LDL-C when levels decrease below 70 mg/dL[17] and thus overestimate the percentage reduction in LDL-C.[18]

Reports of fatigue, muscle fatigue, or muscle spasm occurred in fewer than 5% of patients taking AMG145, with or without ezetimibe. Patients reported higher rates using the term *myalgia*, with 3.1% with ezetimibe alone, 3.1%

Table 3. Key Efficacy Outcomes at Week 12: Apolipoprotein B, Apolipoprotein AI, Triglycerides, Lipoprotein(a), and Free PCSK9

	Mean (95% CI)				
	AMG145 SC Every 4 wk			AMG145 or Placebo Every 4 wk and Ezetimibe, 10 mg, Once Daily	
	280 mg (n = 32)	350 mg (n = 31)	420 mg (n = 32)	AMG145 SC, 420 mg (n = 30)	Placebo SC (n = 32)
Apo B					
Absolute value, mg/dL[a]	92.8 (82.8 to 102.9)	94.5 (83.8 to 105.2)	85.1 (74.7 to 95.4)	66.3 (57.8 to 74.9)	118.9 (110.5 to 127.4)
Change from baseline, mg/dL[a]	–50.2 (–58.8 to –41.6)	–51.4 (–61.1 to –41.7)	–65.7 (–74.9 to –56.5)	–72.7 (–81.3 to –64.1)	–19.5 (–25.3 to –13.6)
% change from baseline[b]	–33.6 (–40.3 to –26.9)	–34.3 (–41.1 to –27.5)	–42.1 (–48.8 to –35.3)	–49.1 (–56.4 to –41.7)	–12.2 (–18.9 to –5.5)
P value vs ezetimibe + placebo[b]	<.001	<.001	<.001	<.001	
Apo AI					
Absolute value, mg/dL[a]	177.8 (165.8 to 189.8)	182.8 (172.0 to 193.7)	167.0 (155.6 to 178.3)	179.7 (169.2 to 190.3)	174.3 (161.9 to 186.7)
Change from baseline, mg/dL[a]	14.3 (7.0 to 21.7)	15.6 (8.9 to 22.2)	15.0 (10.1 to 19.9)	16.9 (11.9 to 21.9)	3.4 (–3.0 to 9.8)
% change from baseline[b]	6.0 (0.5 to 11.6)	6.9 (1.3 to 12.5)	7.5 (1.9 to 13.1)	8.3 (1.2 to 15.3)	–1.4 (–6.9 to 4.1)
P value vs ezetimibe + placebo[b]	.01	.005	.003	.002	
Apo B/apo AI ratio					
Absolute value[a]	0.54 (0.47 to 0.61)	0.55 (0.46 to 0.64)	0.53 (0.45 to 0.61)	0.38 (0.32 to 0.43)	0.71 (0.64 to 0.79)
Change from baseline[a]	–0.37 (–0.44 to –0.30)	–0.37 (–0.44 to –0.30)	–0.53 (–0.62 to –0.43)	–0.51 (–0.60 to –0.42)	–0.13 (–0.18 to –0.09)
% change from baseline	–36.5 (–42.7 to –30.2)	–38.2 (–44.5 to –31.8)	–45.4 (–51.7 to –39.1)	–52.0 (–59.5 to –44.5)	–11.4 (–17.6 to –5.1)
P value vs ezetimibe + placebo[b]	<.001	<.001	<.001	<.001	
Triglycerides					
Absolute value, mg/dL[a]	129.2 (112.0 to 146.3)	138.0 (111.4 to 164.6)	161.9 (134.3 to 189.5)	110.7 (93.6 to 127.8)	155.9 (126.8 to 185.1)
Change from baseline, mg/dL[a]	–32.5 (–51.2 to –13.9)	–33.1 (–51.7 to –14.4)	–26.3 (–44.2 to –8.3)	–22.2 (–33.2 to –11.3)	–7.6 (–30.6 to 15.4)
% change from baseline[b]	–18.0 (–32.5 to –3.4)	–19.3 (–34.0 to –4.6)	–14.2 (–28.8 to 0.4)	–9.5 (–34.0 to 15.0)	–5.5 (–20.0 to 8.9)
P value vs ezetimibe + placebo[b]	.10	.07	.26	.26	
Lipoprotein(a)					
Absolute value, nmol/L[a]	68.7 (29.0 to 108.3)	99.3 (55.2 to 143.4)	40.8 (20.3 to 61.3)	80.0 (43.6 to 116.5)	73.5 (47.8 to 99.1)
Change from baseline, nmol/L[a]	–24.3 (–37.5 to –11.1)	–23.6 (–35.2 to –12.0)	–17.4 (–27.0 to –7.8)	–22.8 (–34.6 to –10.9)	–7.5 (–12.7 to –2.2)
% change from baseline[b]	–25.9 (–34.9 to –16.9)	–20.3 (–29.4 to –11.1)	–23.6 (–32.6 to –14.5)	–29.1 (–41.9 to –16.3)	–7.9 (–16.8 to 1.0)
P value vs ezetimibe + placebo[b]	<.001	.01	.001	<.001	
Free PCSK9					
Absolute value, ng/mL[a]	196.8 (170.3 to 223.4)	211.5 (172.7 to 250.3)	215.4 (168.9 to 261.8)	163.3 (128.8 to 197.8)	376.2 (343.6 to 408.9)
Change from baseline, ng/mL[a]	–186.4 (–212.7 to –160.2)	–190.3 (–240.5 to –140.1)	–164.8 (–198.2 to –131.4)	–226.3 (–264.7 to –187.8)	–15.6 (–46.4 to 15.2)
% change from baseline[a]	–48.4 (–54.1 to –42.6)	–46.2 (–58.2 to –34.2)	–45.9 (–55.6 to –36.3)	–59.3 (–66.7 to –51.9)	–1.5 (–10.1 to 7.2)
P value vs ezetimibe + placebo[b]	<.001	<.001	<.001	<.001	

Abbreviations: apo A1, apolipoprotein AI; apo B, apolipoprotein B; SC, subcutaneous; PCSK9, proprotein convertase subtilisin/kexin type 9.
SI conversion factors: To convert triglycerides to mmol/L, multiply by 0.0113.
[a] Observed summary data without imputation for missing values.
[b] Least-squares means of the placebo/ezetimibe group and AMG145-alone groups were from an analysis-of-covariance (ANCOVA) model including placebo/ezetimibe group, AMG145-alone groups, and stratification factors. Least-squares mean of AMG145, 420 mg/ezetimibe was from an ANCOVA model including placebo/ezetimibe group; AMG145, 420 mg/ezetimibe group; and stratification factors. For LDL-C level, missing ultracentrifugation values at week 12 were imputed using last observation carried forward (LOCF) and calculated LDL-C values. For other parameters, missing values at week 12 were imputed using LOCF.

to 15.6% with the highest and lowest doses of AMG145, respectively, and 20% with AMG145/ezetimibe. The incidence of muscle-related adverse effects reported with AMG145 appears similar to that seen in patients taking REGN727 who were able to tolerate background statins.[14] Thus, the muscle tolerability profile of AMG145 in this short-term trial in a cohort of statin-intolerant patients, if confirmed in larger and longer-term trials, provides a potential therapeutic option for high-risk patients who currently have few treatment options.

The overall incidence of all adverse effects was similar among patients receiving AMG145 without ezetimibe (58%), those receiving AMG145/ezetimibe (67%), and those receiving placebo/ezetimibe (59%). None of the 4 serious AEs (acute pancreatitis, coronary artery disease, hip fracture, and syncope) prompted discontinuation of AMG145. These events are not known to be linked to the mechanism of action of PCSK9 inhibition, and the accumulated safety record of AMG145 has not raised specific concerns to date. The incidence of all other adverse effects among patients taking AMG145 only was less than 5% except for nasopharyngitis, which occurred in 5% of AMG145 patients and in 16% of patients treated with placebo/ezetimibe.

These results are consistent with the safety and tolerability data from previous studies with AMG145 and another anti-PCSK9 antibody-based therapy.[13-16] In a clinical trial of the apo B synthesis inhibitor mipomersen, high-risk statin-intolerant patients experienced significant, although substantially less, LDL-C reduction than was observed in this trial, but with persistently high rates of muscle symptoms, even among those receiving placebo.[19] In that trial, mipomersen was associated with significantly increased hepatic transaminases and injection site reactions. In comparison, AMG145 was not associated with liver function alterations or high rates of injection site reactions.

Because there is currently no widely accepted definition of statin intolerance, we endeavored to use a practical definition in this study, which resulted in a population with a true unmet medical need, as exemplified by the mean LDL-C in excess of 190 mg/dL, 24% of patients with clinical atherosclerotic disease and 50% at high or moderately high cardiovascular risk.[1] Although patients able to tolerate very low doses of a statin were eligible, 84% of all patients were unable to tolerate even low doses of any statin.

The comparator in this trial, ezetimibe, considered the best alternative for LDL-C reduction and tolerability in statin-intolerant patients, reduced LDL-C an expected 15% and was well tolerated. However, fewer than 7% of patients receiving placebo/ezetimibe achieved the LDL-C goal of less than 100 mg/dL and none achieved LDL-C levels less than 70 mg/dL, compared with the 62% of patients who received AMG145, 420 mg/ezetimibe achieving LDL-C levels less than 70 mg/dL. AMG145 doses of 280 mg, 350 mg, and 420 mg alone reduced LDL-C levels by 41%, 43%, and 51%, respectively. The overall reduction in LDL-C achieved with AMG145 alone or in combination with ezetimibe was quantitatively similar to reductions reported with the most highly efficacious statins.

AMG145 also reduced lipoprotein(a) levels by 20% to 26%, with slightly greater decreases seen with AMG145/ezetimibe. The ability to reduce lipoprotein(a) distinguishes AMG145 from the most commonly available LDL-C–reducing agents, especially those that also up-regulate the LDL receptor. The effect of AMG145 on HDL-C and apo AI levels was modest but consistent, with increases ranging from 5% to 12%. This effect is in the range seen with statins. The increases in apo AI level were significant ($P < .05$ to $P < .01$) vs placebo/ezetimibe, but the HDL-C increase was significant only with the AMG145, 420-mg, dose; the combination of ezetimibe/AMG145 resulted in a 12% increase in HDL-C level ($P < .05$). The mechanisms by which AMG145 might affect lipoprotein(a), HDL-C, and triglyceride-rich lipoprotein metabolism have not been determined.

The limitations of this trial include the short, 12-week study duration for a drug that will need to be taken for longer periods. In addition, the relatively small sample size provides limited information, and both larger and longer-term studies in a similar statin adverse population are needed to confirm the preliminary results of the GAUSS trial. Another potential limitation was the use of unblinded ezetimibe. Patients randomized to subcutaneous AMG145/ezetimibe or placebo/ezetimibe knew they were receiving ezetimibe, which may have contributed to imbalances in AE reporting. Larger studies with blinded ezetimibe will provide more definitive evidence of the safety and tolerability of this combination in statin-intolerant patients. Other limitations include the difficulties of a standard definition and subjective nature of statin intolerance and muscle-related side effects, the lack of a specific biomarker or standardized instrument for detecting or monitoring the condition, and the lack of current regulatory guidance or recognition regarding muscle-related side effects other than rhabdomyolysis.

CONCLUSION

In this phase 2 study of patients selected on the basis of prior statin intolerance, treatment with subcutaneous administration of a monoclonal antibody to PCSK9, AMG145, achieved significant reductions in LDL-C and was associated with short-term tolerability.

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Study concept and design: Sullivan, Olsson, Scott, Kim, Wasserman, Stein.

Acquisition of data: Sullivan, Olsson, Stein.

Analysis and interpretation of data: Sullivan, Olsson, Scott, Kim, Xue, Gebski, Wasserman, Stein.

Drafting of the manuscript: Sullivan, Olsson, Stein.

Critical revision of the manuscript for important intellectual content: Sullivan, Olsson, Scott, Kim, Xue, Wasserman, Stein.

Statistical analysis: Xue, Gebski.
Obtained funding: Scott, Wasserman.
Administrative, technical, or material support: Xue.
Study supervision: Scott, Kim, Wasserman.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Sullivan reported having received research funding from Amgen, Abbott Products, AstraZeneca, Merck Sharp and Dohme, and sanofi-aventis and also having received funding for educational programs from Abbott Products, AstraZeneca, Merck Sharp and Dohme, Pfizer Australia, and Roche and travel support from Merck Sharp and Dohme. Dr Sullivan reported having served on advisory boards for Abbott Products, Merck Sharp and Dohme, and Pfizer Australia. Dr Olsson reported having received research support from Amgen, AstraZeneca, Karobio, Merck Sharp and Dohme, Pfizer, Roche, and sanofi-aventis and consultation fees from AstraZeneca, Karobio, Merck, Pfizer, and Roche. Mr Gebski is employed by the NHMRC Clinical Trials Centre, University of Sydney, which received compensation from Amgen for statistical analysis. Dr Stein reported having received consulting fees from Amgen, Adnexus Therapeutics, and sanofi related to PCSK9 inhibitors, and his institution has received research funding related to PCSK9 clinical trials from Amgen, sanofi, and Regeneron. Drs Scott, Kim, Xue, and Wasserman are employees of Amgen and have received Amgen stock/stock options.

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Online-Only Material: The eAppendixes and eTables are available at http://www.jama.com.

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