The GAUSS-3 Trial

Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin Intolerant Subjects-3

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***Disclosure**

Study Sponsor: Amgen
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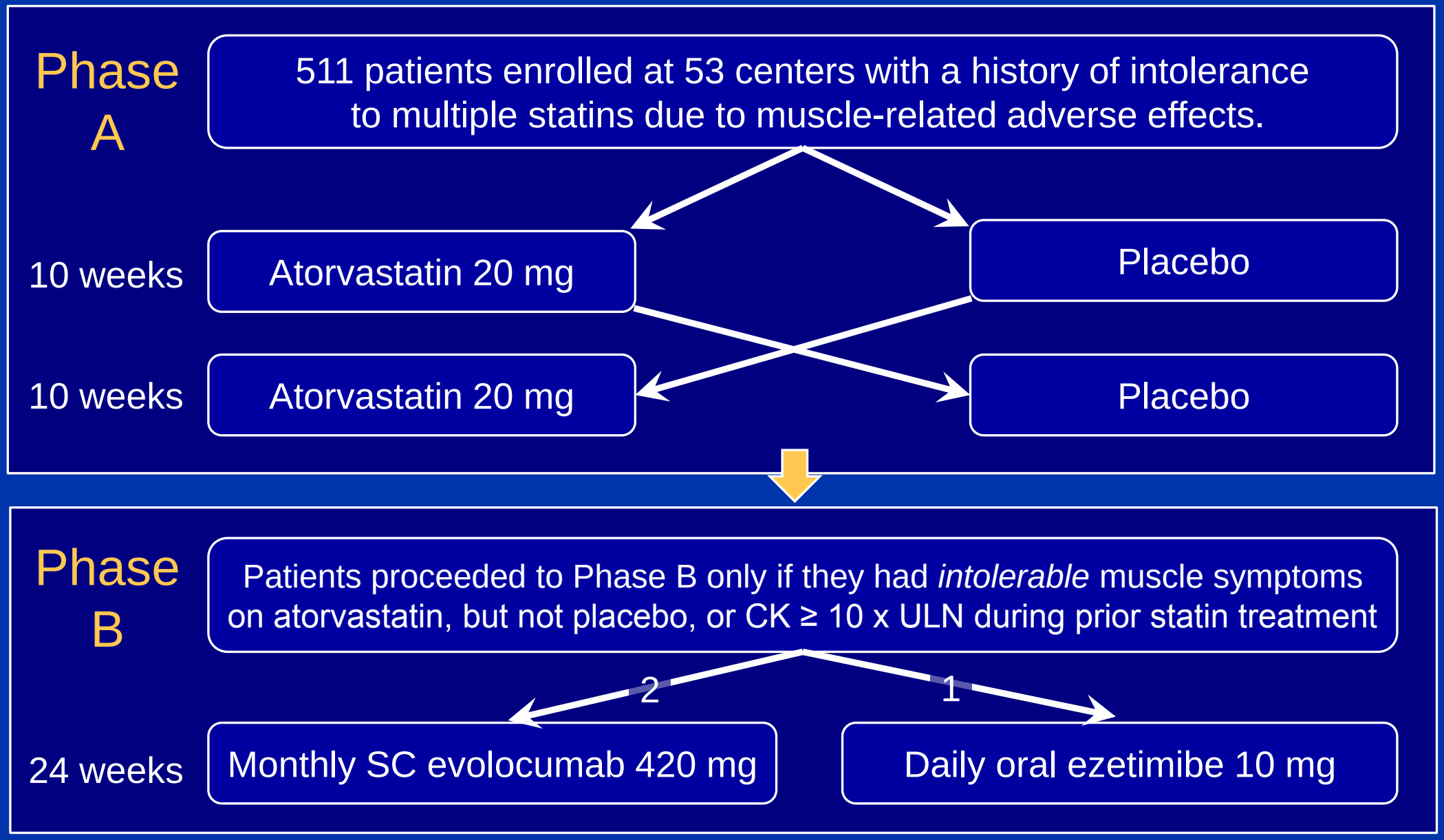
Background

- 5-10% of patients with high CV risk decline (or are reluctant) to take statins after experiencing muscle-related symptoms, creating an unmet clinical need.
- Diagnosis is primarily based on subjective patient complaints, since most patients do not have elevations in CK enzymes.
- Conflicting rates of muscle-related symptoms in observational studies and randomized trials raise questions about the true incidence of statin intolerance.
- We sought to confirm statin-induced muscle intolerance via a blinded, placebo-controlled atorvastatin re-challenge and then compare two alternative therapies, ezetimibe vs. evolocumab.

Study Design: Two Double-Blind Phases



Study Details

- Key inclusion criteria:
  - LDL-C ≥ 100 mg/dL with coronary disease or ≥ 130 mg/dL with ≥ 2 risk factors, ≥160 mg/dL with ≥ 1 risk factor, or ≥ 190 mg/dL with no additional risk factors
  - Inability to tolerate atorvastatin 10 mg plus any other statin, or ≥ 3 statins with 1 at the lowest daily starting dose
- Co-primary endpoints, percent change in LDL-C:
  - Mean of weeks 22 and 24 (mean evolocumab effect)
  - At week 24 (effect at end of dosing interval)

Selected Baseline Characteristics

Characteristic	Phase A (n=491)	Phase B (n=218)	
		Ezetimibe (n=73)	Evolocumab (n=145)
Age (years)	61	59	59
Male Gender	50%	47%	54%
Coronary Heart Disease	35%	29%	33%
NCEP-ATP III High Risk	63%	52%	58%
Intolerance to ≥ 3 statins	82%	82%	82%
Total Cholesterol (mg/dL)	301	308	307
LDL-C (mg/dL)	212	222	219
HDL-C (mg/dL)	51	50	50

Phase A: Study Drug Discontinuation Events

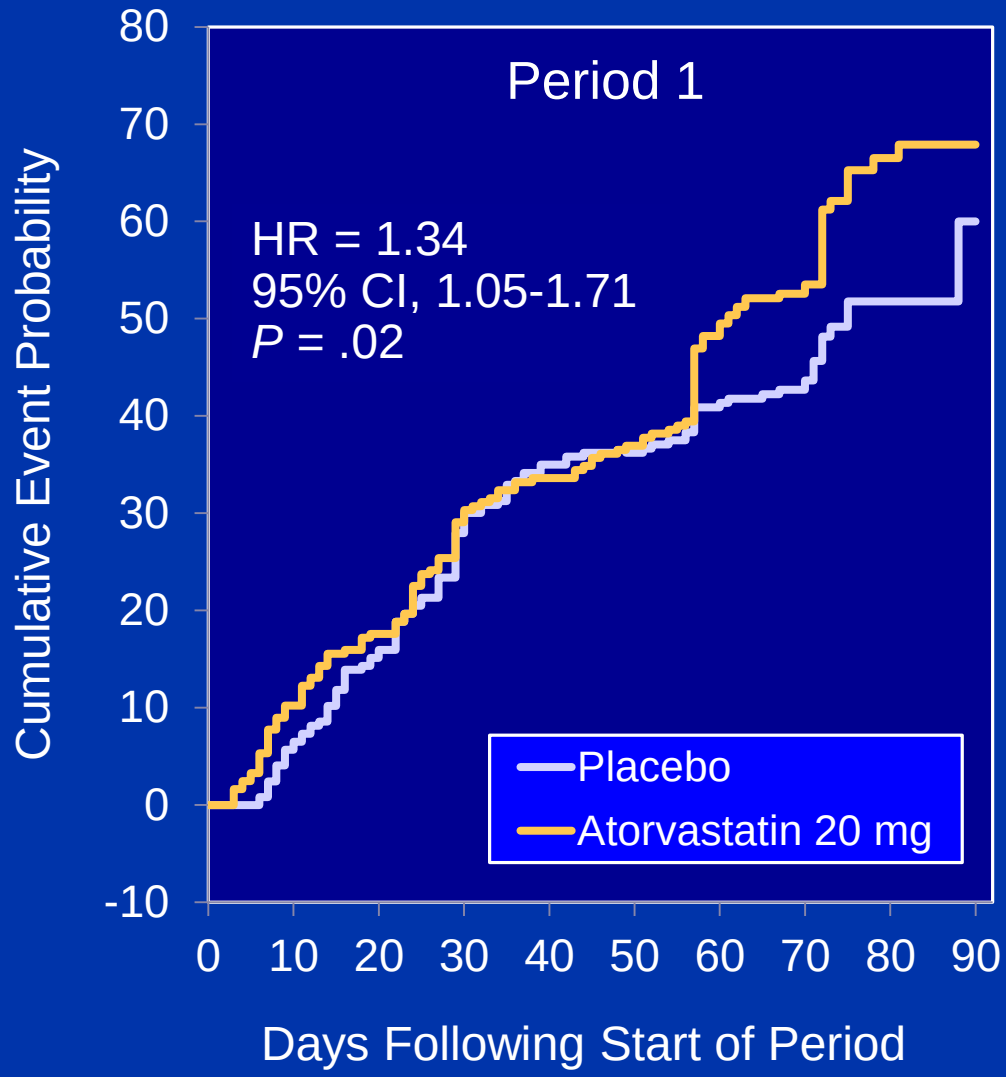
***Intolerable* Muscle Symptoms**	**N = 491**
On atorvastatin, but not placebo	209 (42.6%)*
On placebo, but not atorvastatin	130 (26.5%)
On both placebo and atorvastatin	48 (9.8%)
No symptoms on either treatment	85 (17.3%)
Did not complete Phase A	*20/511*

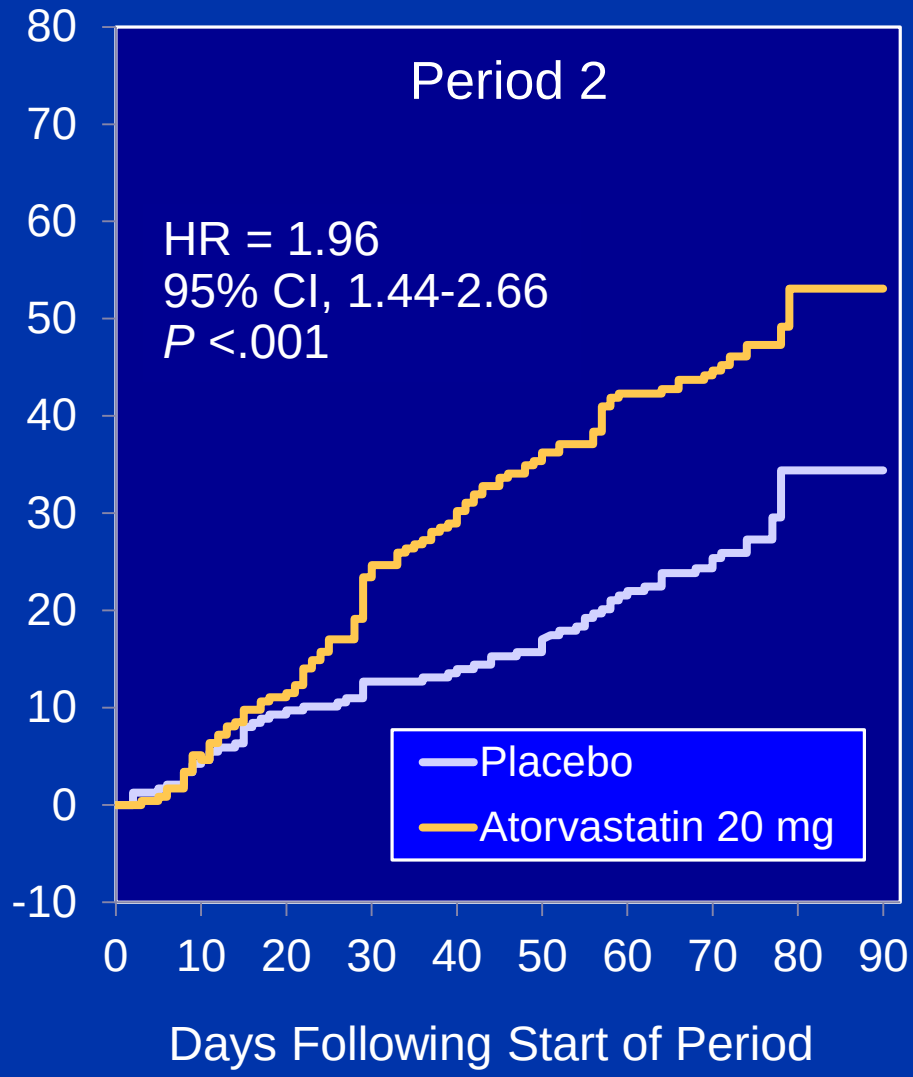
Bypassed Phase A due to CK elevation ≥ 10 x ULN	19 (3.9%)*

**218 of these 228 eligible patients proceeded to Phase B*

Atorvastatin vs. Placebo Re-challenge Outcomes

Time to *Intolerable* Muscle Symptoms Resulting in Drug Discontinuation



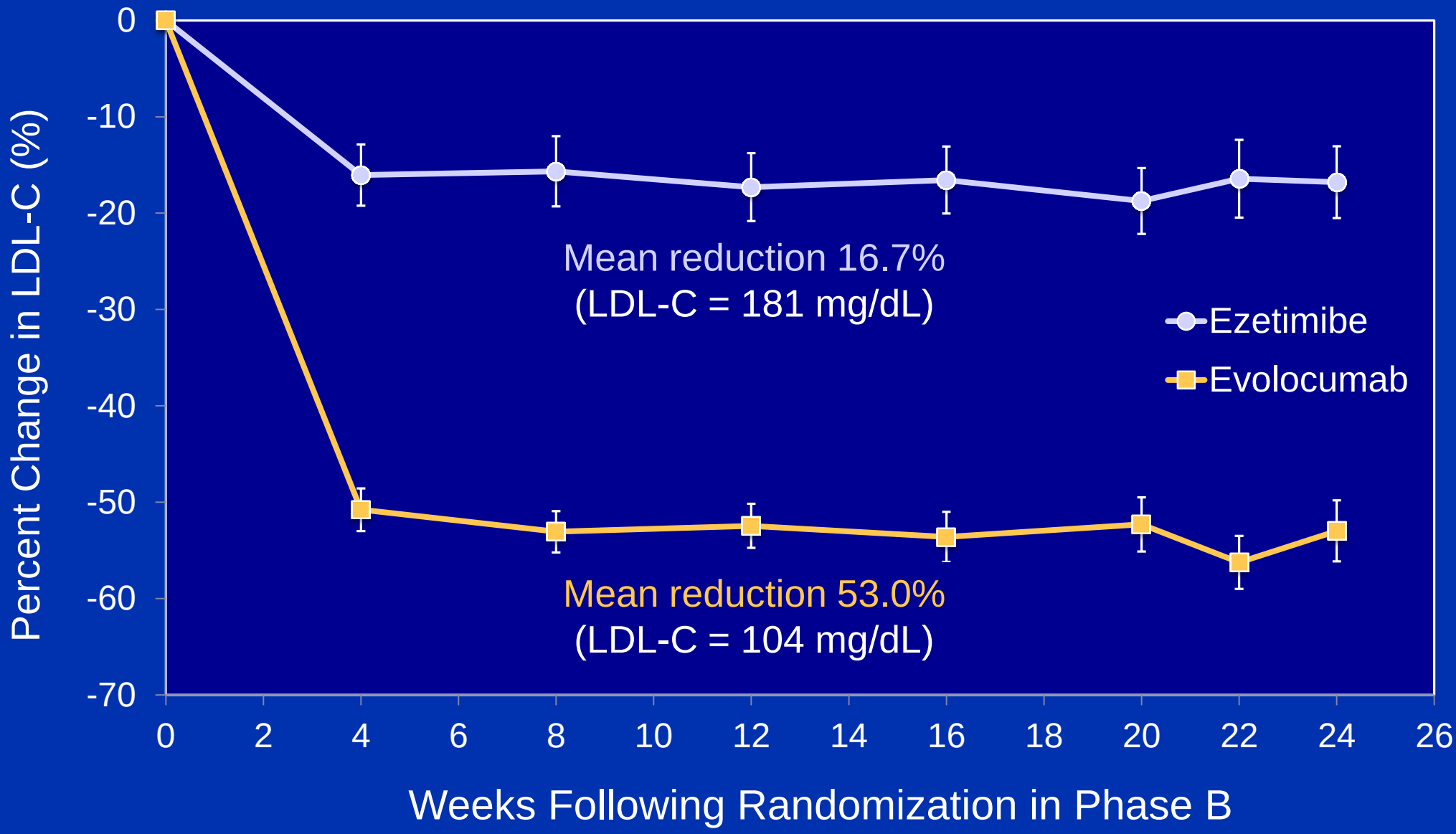


Phase B: Key Primary and Secondary Outcomes

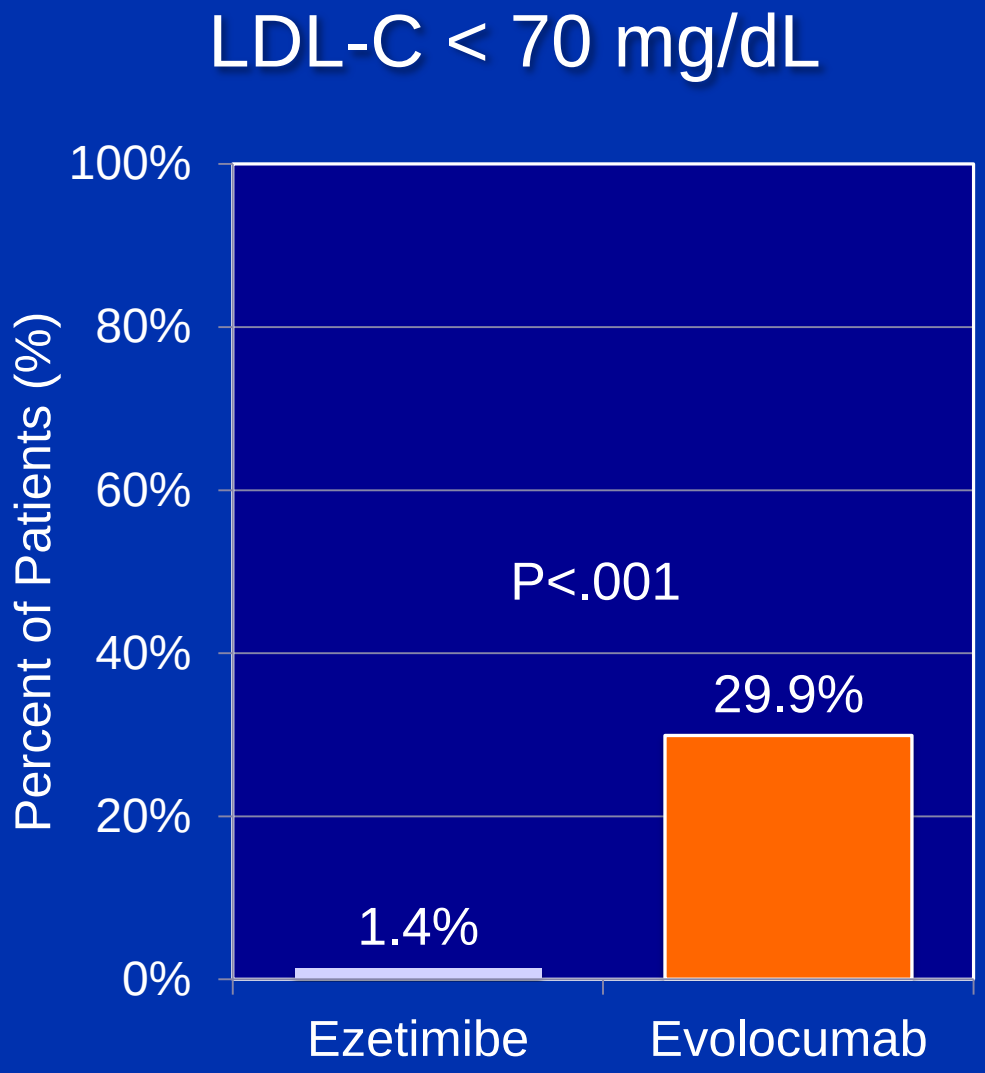
	Ezetimibe (n=73)	Evolocumab (n=145)	*P* value
Co-Primary Primary Endpoints			
LDL-C (week 24)	-16.7%	-52.8%	<.001
LDL-C (mean weeks 22 and 24)	-16.7%	-54.5%	<.001
Selected Secondary Endpoints (Week 24)			
Lipoprotein (a)	+0.2%	-21.1%	<.001
HDL-C	+2.9%	+7.4%	.008
Triglycerides	-1.1%	-2.9%	NS

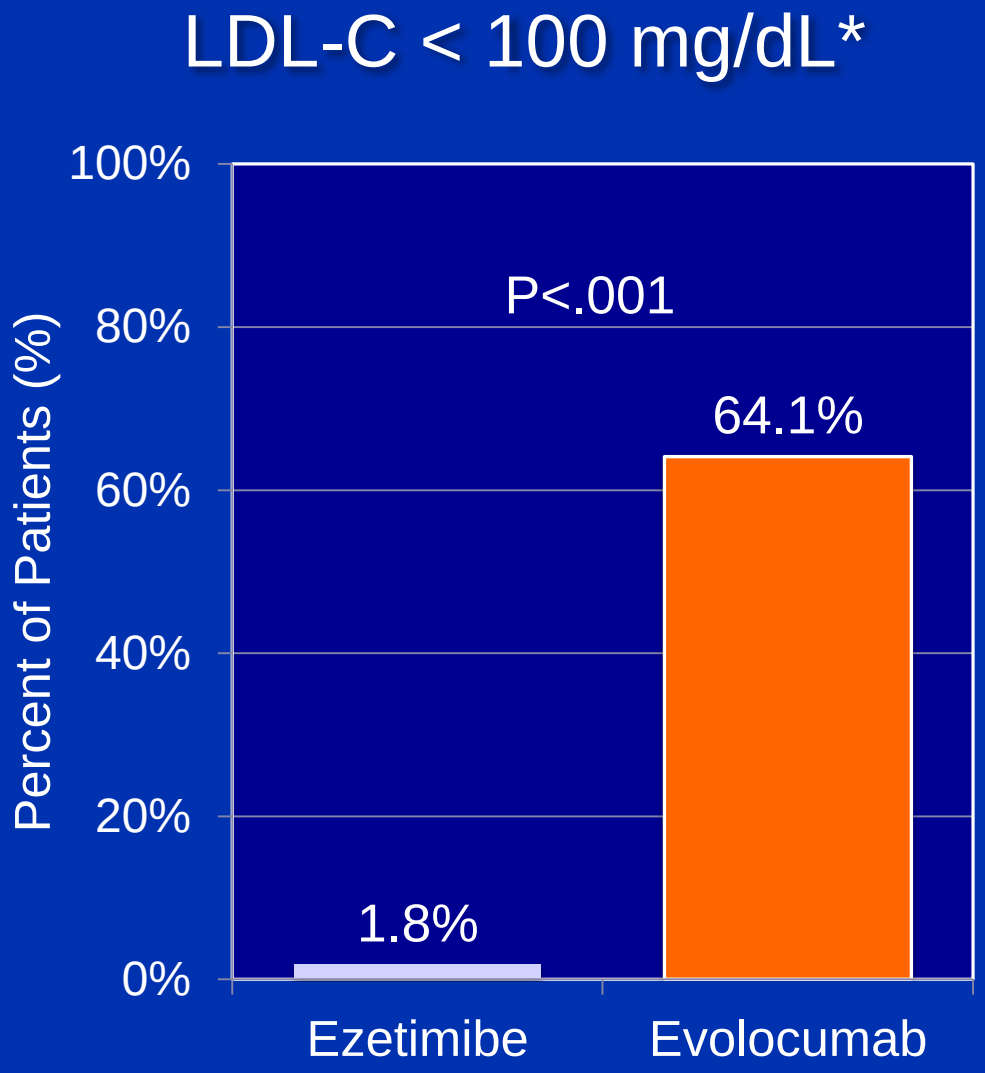
Other secondary endpoints: Changes in total cholesterol, non-HDL-C, Apo B, total cholesterol/HDL-C ratio, Apo B/Apo A1 ratio, significant (*P*<.001)

LDL-C Values Over Time During Phase B



Achievement of Common LDL-C Target Levels



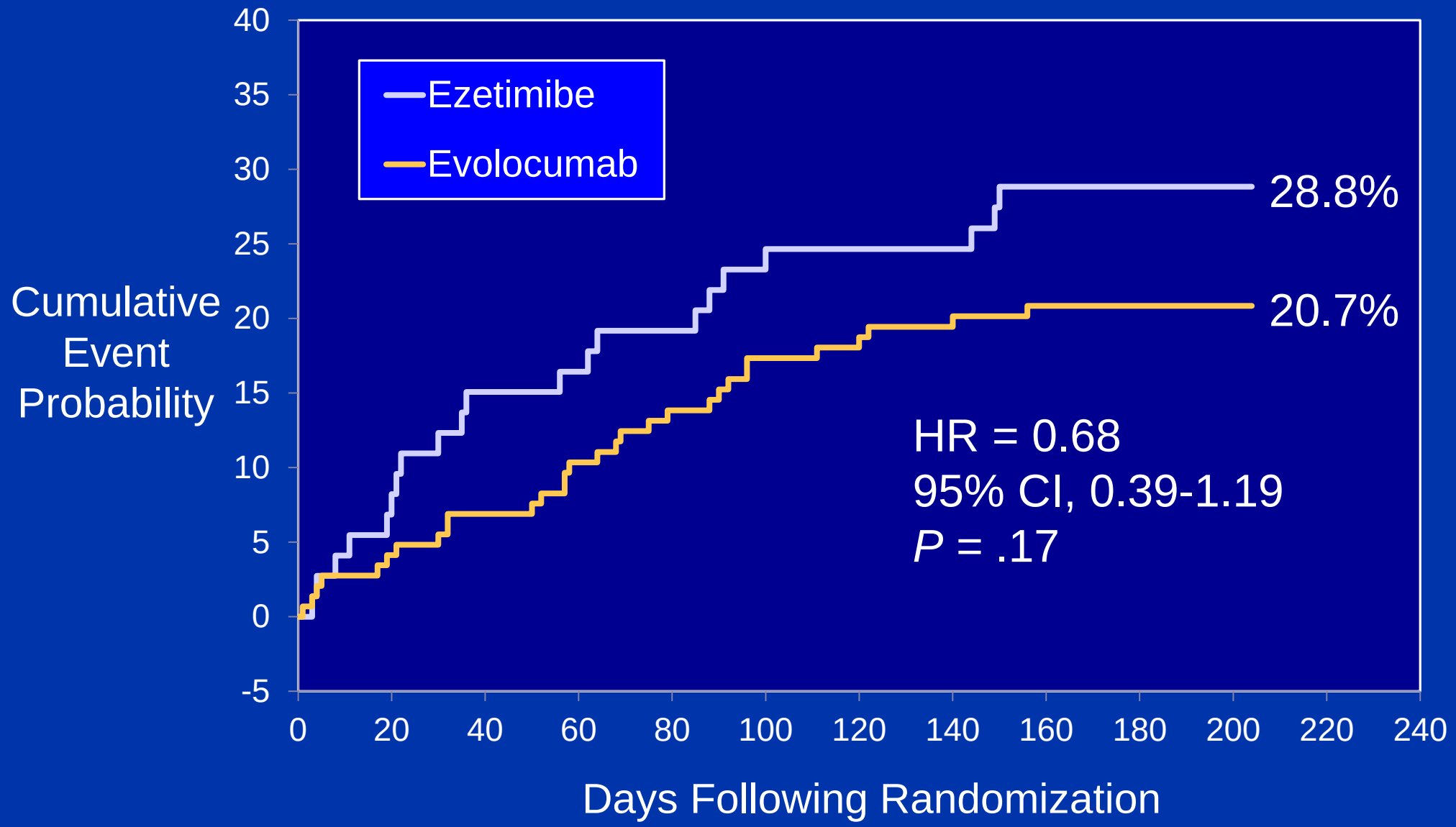


*not a protocol prespecified analysis

Phase B: Adverse Effects and Drug Discontinuations

	Ezetimibe (n=73)	Evolocumab (n=145)
Total muscle-related events	21 (28.8%)	30 (20.7%)
Myalgia, muscle pain or weakness	17 (23.3%)	25 (17.2%)
Investigator reported CK Increase	1 (1.4%)	4 (2.8%)
Discontinuation of Treatment for Any Reason		
Discontinuation of oral treatment	14 (19.2%)	23 (15.9%)
Discontinued SC 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 SC drug treatment	0 (0%)	1 (0.7%)

Phase B: Time to Any Muscle-Related Symptom

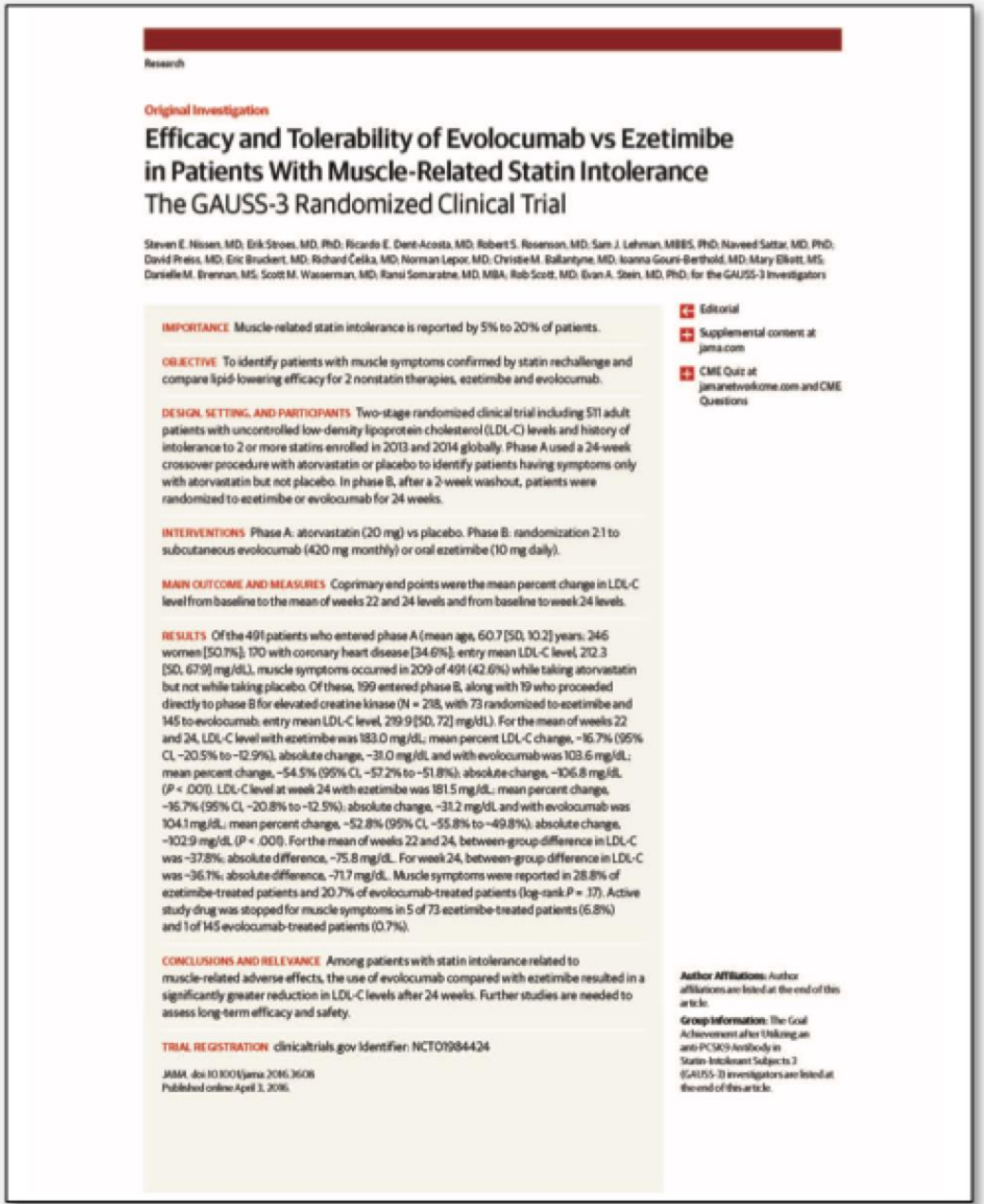


Limitations

- The GAUSS-3 Trial was modest in size, although the largest study to date using a statin rechallenge procedure.
- The design did not permit a common management strategy for patients with muscle symptoms on statins - administration of small doses of statins 1-3 times weekly.
- Atorvastatin 20 mg is lower than the 40 and 80 mg doses recommended for high risk patients, which may underestimate the incidence of muscle symptoms.
- The 24-week duration of therapy was relatively short for patients who require lifelong LDL-C reduction.

Conclusions

- A substantial proportion (42.6%) of patients with a history of muscle-related statin intolerance have symptoms when re-challenged with atorvastatin 20 mg, but not placebo.
- A smaller fraction of patients (26.5%) report muscle-related symptoms when administered placebo, but not atorvastatin.
- In patients with statin-associated muscle symptoms, evolocumab, compared with ezetimibe, produced significantly larger reductions in LDL-C and other atherogenic lipoproteins.
- Both drugs uncommonly induced muscle symptoms leading to discontinuation (ezetimibe 6.8%, evolocumab 0.7%).



Research

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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Editorial

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Author Affiliations: Author affiliations are listed at the end of this article.

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.

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

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A Final Thought

Controversy has surrounded the issue of statin-associated muscle symptoms because of large differences in the incidence of this disorder in randomized trials and observational studies. The GAUSS-3 trial demonstrates that muscle-related intolerance is reproducible during blinded statin rechallenge in a substantial fraction (about 40%) of patients with a history of symptoms. Accordingly, development of alternative approaches to LDL-C reduction for these patients represents an important medical priority.