Comparison of PCSK9 Inhibitor Evolocumab Versus Ezetimibe in Statin-intolerant Patients: Design of the Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects 3 (GAUSS-3) Trial

Short title: Trial Design: Comparison of PCSK9 Inhibitor Evolocumab Versus Ezetimibe in Statin-intolerant Patients

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SUMMARY

Statins are the accepted standard for lowering low-density lipoprotein-cholesterol (LDL-C). However, 5%-10% of statin-treated patients report intolerance, mostly due to muscle-related adverse effects. There are challenges to objective identification of patients with statin intolerance. Evolocumab is a monoclonal antibody that binds proprotein convertase subtilisin/kexin type 9 (PCSK9), resulting in marked LDL-C reduction. We report the design of Goal Achievement after Utilizing an anti-PCSK9 Antibody in Statin Intolerant Subjects 3 (GAUSS-3), a phase 3, multicenter, randomized, double-blind, ezetimibe-controlled study to compare the effectiveness of 24 weeks of evolocumab 420 mg monthly versus ezetimibe 10 mg/day in hypercholesterolemic patients unable to tolerate an effective statin dose. The study incorporates a novel atorvastatin-controlled, double-blind, cross-over phase intended to objectively identify statin intolerance. Eligible patients had LDL-C above the National Cholesterol Education Project Adult Treatment Panel III target level for the appropriate coronary heart disease risk category and were unable to tolerate at least 3 statins or 2 statins (one of which was atorvastatin ≤10 mg/day) or had a history of marked CK elevation accompanied by muscle symptoms while on one statin. This trial has two co-primary endpoints: mean percent change from baseline in LDL-C at Weeks 22 and 24 and percent change from baseline in LDL-C at Week 24. Key secondary efficacy endpoints include change from baseline in LDL-C; percent of patients attaining an LDL-C <70 mg/dL [1.81 mmol/L]); and percent change from baseline in total cholesterol, non-HDL-C, and ApoB. Recruitment of 511 patients was completed on November 28, 2014.

Key Words: evolocumab, hypercholesterolemia, LDL-C, PCSK9, statin intolerance

INTRODUCTION

Clinicians who treat lipid disorders consider the intolerance of patients to effective doses of HMG-CoA reductase inhibitors (statins) one of the most vexing problems in clinical practice. Patients reporting statin intolerance typically describe a variety of muscle symptoms, including muscle pain or weakness, when treated with a statin, and often report relief from the symptoms when the drug is withdrawn or the dose decreased. More severe forms associated with marked elevation in the concentration of creatine kinase (CK), which may in rare cases result in rhabdomyolysis. However, CK elevation is abnormal in only a small fraction of patients. The reported incidence of statin intolerance in observational studies varies widely, but ranges from 5%-10% of patients treated with statins.[1-3] The precise definition of this syndrome has been elusive, in part because of the lack of established biomarkers that identify statin intolerance.[4] Accordingly, the presence of this disorder is subjective and usually based upon patient-reported symptoms rather than objective criteria. Regardless of severity or definition, many at-risk patients stop taking their statins as prescribed, which worsens the impact of hypercholesterolemia-associated morbidity on public health.[3,5,6]

The vague nature of the complaints, lack of consistent diagnostic biomarkers, and incidence of similar symptoms in placebo-treated patients has resulted in skepticism within the healthcare practitioner and regulatory communities about the true incidence of statin intolerance. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors represent a promising approach to lowering low density lipoprotein cholesterol (LDL-C) in patients who experience intolerable adverse effects during statin therapy. These new drugs, which were approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2015, are highly effective in reducing LDL-C. Currently available data demonstrate few untoward muscle-related adverse effects in

patients administered PCSK9 inhibitors.[7,8] In this setting, we designed a rigorous randomized controlled trial to identify patients with reproducible statin-induced symptoms to compare the effectiveness of two therapies—ezetimibe or the recently approved PCSK9 inhibitor, evolocumab.

METHODS

Study Design

The Goal Achievement after Utilizing an anti-PCSK9 Antibody in Statin Intolerant Subjects 3 (GAUSS-3) trial is a phase 3, multicenter, randomized, double-blind, ezetimibe-controlled, parallel group study of the PCSK9 inhibitor evolocumab in hypercholesterolemic patients unable to tolerate an effective dose of a statin (clinicaltrials.gov NCT01984424). The study incorporates a novel double-blind, 2-period, placebo-controlled cross-over design intended to identify patients with objectively documented statin intolerance prior to randomization to evolocumab or ezetimibe (Figure 1).

Prior to randomization, patients undergo a 4-week washout phase, during which ezetimibe and statins are withdrawn. This study has three active parts: Part A is a double-blind, 2-period, placebo-controlled 24-week cross-over phase in which patients with a history of statin intolerance are randomly assigned in a 1:1 ratio to either atorvastatin 20 mg daily or matching placebo for the first 10 weeks (Period 1), then undergo a two-week washout period, with subsequent cross over to the alternate therapy for a second 10-week period (Period 2). Patients who experience intolerable muscle-related symptoms during either period do not need to complete the full 10 weeks of exposure. Patients who experience muscle-related symptoms, which in the clinical judgment of the investigator would lead them to stop the study treatment (or if the symptoms are deemed intolerable by the patient) enter a 2-week washout period prior to entering Period 2 or Part B of the study.

Part B is a 24-week double-blind, double-dummy, active-controlled comparison of subcutaneously (SC) injected evolocumab 420 mg monthly with oral ezetimibe 10 mg daily with a 2:1 ratio of evolocumab to ezetimibe. Two categories of patients can enter Part B of the study: 1) patients from Part A who experience muscle-related symptoms while taking atorvastatin and do not experience these symptoms while taking placebo; and 2) any patient with a documented history of CK elevation >10 times the upper limit of normal (ULN) accompanied by muscle symptoms while on statin therapy with resolution of both CK elevation and muscle symptoms upon discontinuation of statin therapy. These study procedures are designed to ensure that only patients with rigorously documented statin-induced muscle symptoms enter Part B of the study.

Part C is a 2-year open-label extension phase, during which all patients who complete Part B receive evolocumab to evaluate the long-term safety and efficacy of evolocumab in patients with objectively documented statin intolerance. (NCT01854918)

Study Objectives and Endpoints

The primary objective of GAUSS-3 is to evaluate the effect of 24 weeks of evolocumab administered monthly compared with ezetimibe on percent change from baseline in LDL-C in hypercholesterolemic patients unable to tolerate an effective dose of a statin due to muscle-related side effects (MRSE) as confirmed by statin re-challenge. Secondary objectives of the study include evaluation of the safety and tolerability of monthly SC evolocumab compared to ezetimibe; change from baseline in LDL-C; percent change from baseline in total cholesterol, non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol/HDL-C ratio, ApoB/apolipoprotein A1 (ApoA1) ratio, lipoprotein(a) [Lp(a)], triglycerides, HDL-C, and VLDL-C; and percent of patients attaining LDL-C <70 mg/dL (1.81 mmol/L). An exploratory objective of the study is to evaluate the incidence of MRSE during a double-blind, placebo-controlled, cross-over atorvastatin re-challenge. The primary hypothesis of GAUSS-3 is that evolocumab 420

mg monthly will be well tolerated and result in greater reduction of LDL-C than ezetimibe in hypercholesterolemic patients unable to tolerate an effective dose of a statin.

GAUSS-3 has 2 co-primary endpoints: mean percent change from baseline in LDL-C at Weeks 22 and 24 of Part B and percent change from baseline in LDL-C at Week 24 of Part B. Tier 1 co-secondary efficacy endpoints of the means at Weeks 22 and 24 and at Week 24 of Part B include change from baseline in LDL-C; LDL-C response (LDL-C <70 mg/dL [1.81 mmol/L]); and percent change from baseline in total cholesterol, non-HDL-C, ApoB, total cholesterol/HDL-C ratio, and ApoB/ApoA1 ratio. Tier 2 co-secondary efficacy endpoints of the means at Weeks 22 and 24 and at Week 24 of Part B are percent change from baseline in Lp(a), triglycerides, HDL-C, and VLDL-C.

Inclusion and Exclusion Criteria

The major inclusion criteria are summarized in Table 1. Briefly, they include an LDL-C above the target level specified in the National Cholesterol Education Project (NCEP) Adult Treatment Panel III (ATPIII) for the appropriate coronary heart disease risk category and an inability to tolerate at least 3 statins (one of which must be at the lowest approved starting average daily dose) or an inability to tolerate 2 statins (one of which must be atorvastatin at an average daily dose of 10 mg or less). The key exclusion criteria are summarized in Table 2.

Treatments and Key Procedures

At screening, subjects were given placebo SC injections within 5-10 days of the screening LDL-C evaluation via 3 prefilled 1 mL autoinjector pens prior to randomization in Part A. In Part A, patients were assigned to 20 mg atorvastatin or matching placebo taken orally daily for 10 weeks or until considered intolerant. After a 2-week washout, patients switch therapies for an additional 10 weeks. In Part B, the patients were randomized 2:1 to either 420 mg evolocumab SC monthly and placebo orally daily or

placebo SC monthly and daily 10 mg ezetimibe. Injections were administered via 3 prefilled 1mL autoinjector pens containing either 140 mg per milliliter of evolocumab or placebo. In Part C, all patients will receive open-label evolocumab 420 mg SC monthly .

Randomization in Part B was stratified by screening LDL-C level (<180 mg/dL [4.66 mmol/L] vs. ≥180 mg/dL) at study baseline. The following describes procedures during Part B: 1) blinded investigational product (IP), evolocumab or placebo, was administered at the study site using a prefilled autoinjector pen; 2) central laboratory results of the lipid panel, ApoA1, ApoB, Lp(a), and high sensitivity C-reactive protein (hsCRP) were blinded for the duration of the study; 3) investigators were not permitted to perform non-protocol lipid testing until at least 12 weeks after the last blinded IP administration (investigators were informed if triglycerides are >1000 mg/dL (11.3 mmol/L) to enable appropriate management); 4) the last dose of blinded SC IP was given at Week 20 of Part B for all patients.

Patients were encouraged to complete all planned visits regardless of their adherence to IP administration (intention-to-treat approach). In countries where permitted, patients were invited to consent to pharmacogenetic analyses. The study included collection of biomarker samples where approved by the independent ethics committee, applicable regulatory, and other authorities. The study included adjudication of deaths and major cardiovascular (CV) events by an independent Clinical Events Committee (CEC) with oversight by an independent Data Monitoring Committee (DMC). The members of these committees are listed in the Appendix. An independent external biostatistical group provided analyses for the DMC.

Statistical Considerations

The number of patients needed in Part B assumed the smallest treatment effect was approximately 25% with a common standard deviation of 20% based on evolocumab

phase 2 results. It was anticipated that the treatment effect would be attenuated due to: (1) ~15% of randomized subjects stopping IP early (2) ~5% of randomized subjects ending study participation early 3) 2% of randomized subjects not receiving any IP. After accounting for treatment attenuation, the sample size provides approximately 98% power for each co-primary endpoint.

The number of patients needed for Part A was calculated to achieve a planned sample size of 100 patients in Part B. In the double-blind, placebo-controlled statin re-challenge phase, the estimated rate of MRSE by blinded statin re-challenge was 20%. Thus, the expected number of patients to be enrolled in Part A was 500. To ensure that the target number of patients was achieved, enrollment in Part A continued until the Part B target sample size was met. All patients who completed Part B are eligible to participate in Part C. It was estimated that approximately 80% to 100% of patients in Part B would continue to Part C. The 20% estimate of MRSE was selected based on a previous study with a similar crossover design examining the efficacy of co-enzyme Q 10 in statin intolerant patients.[9] This prior single-center study showed a 34% incidence of MRSE by blinded statin re-challenge. We selected a more conservative 20% estimate for our global multicenter study to ensure that sufficient patients were enrolled to adequately test the principal hypotheses.

Efficacy and safety analyses will be performed on all randomized patients in Part B who received at least one dose of IP in Part B. Multiplicity adjustments will be applied for primary analyses of co-primary and co-secondary endpoints to control the overall family-wise error rate at 0.05.

The long-term efficacy and safety analysis will be descriptive and will include all enrolled patients in Part C of the study who received at least one dose of IP in Part C. Events of death, myocardial infarction, hospitalization for unstable angina, coronary

revascularization, stroke, transient ischemic attack, and hospitalization for heart failure will be adjudicated by an independent CEC. Patient incidence of exploratory endpoint events will be summarized for each treatment group.

Analyses of Co-Primary and Co-Secondary Endpoints

To assess the co-primary endpoints of the mean percent change in LDL-C from baseline at Weeks 22 and 24 of Part B and the percent change from baseline at Week 24 of Part B, a repeated measures linear effects model will be used to compare the efficacy of evolocumab with ezetimibe. The repeated measures model will include terms for treatment group, stratification factor, scheduled visit and the interaction of treatment with scheduled visit. Missing values will not be imputed when the repeated measures linear effects model is used. The statistical model for the co-secondary efficacy endpoints will be similar to the co-primary endpoints. However, LDL-C response will be analyzed using the Cochran-Mantel-Haenszel test adjusted by the stratification factors.

Subgroup Analyses

The following baseline covariates were prespecified for subgroup or covariate analyses: age:< 65 years or ≥ 65 years, sex, race, baseline LDL-C < median or ≥ median, family history of premature coronary heart disease, and PCSK9 level < baseline median or ≥ baseline median. Because of the small size of the study, the protocol did not emphasize such analyses.

Safety Analyses

Adverse events (AEs) will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Patient incidence of treatment emergent AEs, serious AEs, and AEs leading to discontinuation of IP will be tabulated by randomized treatment group. Measurements of laboratory parameters and vital signs will be summarized over time. The incidence and percentages of patients who develop anti-evolocumab antibodies (binding and neutralizing) at any time will also be tabulated. Data

for patients with 2 consecutive values < 25 mg/dL are provided to the data Monitoring Committee for their review.

BASELINE DEMOGRAPHICS

The GAUSS-3 study completed enrollment of 511 patients on November 28, 2014, of whom 492 entered Part A and 19 bypassed Part A and directly entered Part B. A majority of randomized patients had high cardiovascular risk and most failed 3 or more statins (Table 3). Median baseline LDL-C was 198 mg/dL (5 mmol/L). The male to female ratio was 1:1 and 94% of patients were white.

DISCUSSION

Patient reported statin intolerance, predominantly due to statin-associated muscle symptoms, is a relatively common and difficult-to-treat disorder that affects millions of patients worldwide. The Prediction of Muscular Risk in Observational Conditions (PRIMO) study reported muscle symptoms in 10.5% of 7924 patients treated with statins.1 Other observational studies suggest an incidence approaching 20% of statin-treated patients in routine clinical practice.[3] In a recent retrospective cohort study involving more than 100,000 patients, 17% had at least one statin-related event documented of which 27% (5% of the total study population) referred to myalgia or myopathy.[3] In the context of strong evidence from randomized controlled trials of the benefits of lowering of LDL-C in both primary and secondary prevention, the inability to treat patients with statin intolerance undermines public health efforts to reduce the burden of cardiovascular disease. Accordingly, development of alternative treatment strategies for lipid management in statin-intolerant patients represents an important unmet medical need.

Current approaches to management of patients with muscle-related statin intolerance have many limitations. Most clinicians first try a series of alternative statins, which is successful in some patients, although recurrent symptoms occur in many others.

Some authorities recommend administration of small doses of a high efficacy statin 1 to 3 times weekly with gradual titration to reach the maximally tolerated dosage.[9] This strategy has proven useful, although many patients are unable to reach a dosage that is both well tolerated and sufficient to reduce LDL-C to desirable levels. Ezetimibe is also commonly prescribed in statin-intolerant patients, but the LDL-C lowering effect of this agent is modest (about 16%-20%) and the effect on cardiovascular outcomes relatively small. The only controlled cardiovascular outcome trial using ezetimibe, demonstrated a 6.4% reduction in cardiovascular events when added to a statin after 7 years of treatment, which was driven by the reduction in nonfatal events.[10]

The identification of patients with MRSE has been challenging due to the subjective nature of symptoms. Most patients do not exhibit either myositis or overt rhabdomyolysis, both of which are characterized by a substantial elevation of CK. Furthermore, successful statin re-challenge in some patients with previously reported statin-related muscle symptoms has led to skepticism about the true incidence of statin intolerance and concerns about over-diagnosis of muscle-related statin intolerance. As a consequence, no pharmacological therapy has received explicit approval from the FDA to lower LDL-C in patients unable to tolerate adequate dosages of statins.

The development of PCSK9 inhibitors represents a potentially important addition to the therapeutic armamentarium for management of statin-intolerant patients. These agents reduce LDL-C by 50% or more when administered SC every 2 to 4 weeks.[11,12] Preliminary studies have shown a low incidence of myalgia or myositis, including trials conducted in patients with a history of statin intolerance.[7,8] In the GAUSS trial, in patients unable to tolerate at least one statin, evolocumab demonstrated robust reductions in LDL-C and was well tolerated with a low incidence of muscle-related adverse effects.[8] A second study, GAUSS-2, compared evolocumab with ezetimibe in patients intolerant to at least two statins, and demonstrated a >50% reduction from baseline in LDL-C with no

differences in muscle-related adverse effects compared with ezetimibe.7 Similar findings have been reported with another PCSK9 inhibitor.[13]

Despite the promise of these agents, regulatory approval in the US for the treatment of statin-intolerant patients will require the highest quality evidence of efficacy in a population with demonstrated statin-intolerance. GAUSS-3 was designed with this goal. In GAUSS-3, screening for enrollment into Part A required the strong evidence of statin-intolerance including either the inability to tolerate an entry dosage of atorvastatin (10mg daily) and another statin at any dose or failure to tolerate three statins with at least one administered at the lowest approved average daily dose. For randomization in Part B, enrollment included only those patients who experienced muscle-related symptoms on atorvastatin, but not placebo or patients with a documented history of CK elevation >10 times ULN accompanied by muscle symptoms while on statin therapy with resolution of both upon discontinuation of statin therapy. Accordingly, GAUSS-3 will provide a high degree of confidence that enrolled patients are truly unable to tolerate effective statin therapy. The study will also provide insights into the incidence of statin intolerance after a blinded statin re-challenge. Although not the primary endpoints, the percentage and characteristics of patients who complete Part A will provide valuable objective data of the incidence on statin intolerance during blinded re-challenge in patients who report prior MRSE.

The enrollment criteria for GAUSS-3 selected a patient population with a particularly high unmet clinical need. As shown in Table 3, the median LDL-C is approximately 200 mg/dL, a level considered unacceptably high, even in primary prevention. Approximately half of the enrolled patients have coronary, cerebrovascular, or peripheral arterial disease, and more than 50% of patients fell into the highest risk category defined by the NCEP ATP III guidelines. The need to substantially reduce LDL-C in such patients is self-evident. The results of GAUSS-3 will inform clinicians about the

relative efficacy of evolocumab compared with ezetimibe in such patients and will provide both clinicians and the regulatory community with a better understanding of the potential role of PCSK9 inhibition in the management of these challenging patients.

APPENDIX

GAUSS-3 Investigators

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REFERENCES

1. Bruckert E, Hayem G, Dejager S, Yau C, Begaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients--the PRIMO study. *Cardiovasc Drugs Ther.* 2005;19:403-14.
2. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA.* 2003;289:1681-90.
3. Zhang H, Plutzky J, Skentzos S et al. Discontinuation of statins in routine care settings: a cohort study. *Ann Intern Med.* 2013;158:526-34.
4. Stroes ES, Thompson PD, Corsini A et al. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. *Eur Heart J.* 2015;36:1012-1022.
5. Avorn J, Monette J, Lacour A et al. Persistence of use of lipid-lowering medications: a cross-national study. *JAMA.* 1998;279:1458-62.
6. Ellis JJ, Erickson SR, Stevenson JG, Bernstein SJ, Stiles RA, Fendrick AM. Suboptimal statin adherence and discontinuation in primary and secondary prevention populations. *J Gen Intern Med.* 2004;19:638-45.
7. Stroes E, Colquhoun D, Sullivan D et al. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. *J Am Coll Cardiol.* 2014;63:2541-8.
8. Sullivan D, Olsson AG, Scott R et al. Effect of a monoclonal antibody to PCSK9 on low-density lipoprotein cholesterol levels in statin-intolerant patients: the GAUSS randomized trial. *JAMA.* 2012;308:2497-506.

9. Taylor BA1, Lorson L2, White CM3, Thompson PD3. A randomized trial of coenzyme Q10 in patients with confirmed statin myopathy. Atherosclerosis. 2015 Feb;238(2):329-35. doi: 10.1016/j.atherosclerosis.2014.12.016. Epub 2014 Dec 17.

10. Backes JM, Venero CV, Gibson CA et al. Effectiveness and tolerability of every-other-day rosuvastatin dosing in patients with prior statin intolerance. *Ann Pharmacother.* 2008;42:341-6.

11. Cannon CP, Blazing MA, Giugliano RP et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med.* 2015;372:2387-97.

12. Blom DJ, Hala T, Bolognese M et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. *N Engl J Med.* 2014;370:1809-19.

13. Robinson JG, Farnier M, Krempf M et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med.* 2015;372:1489-99.

14. Moriarty PM, Thompson PD, Cannon CP et al. Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: The ODYSSEY ALTERNATIVE randomized trial. *J Clin Lipidol.* 2015;August 27:[published online ahead of print].

TABLES

Table 1. Main Inclusion Criteria

Male or female ≥18 to ≤80 years of age at signing of informed consent.
Patient not at LDL-C goal by NCEP ATP III risk category and the following LDL-C levels by central laboratory at screening:
a) Fasting LDL-C ≥100 mg/dL (2.59 mmol/L) for patients with diagnosed CHD or are CHD risk equivalent or
b) Fasting LDL-C ≥130 mg/dL (3.37 mmol/L) for patients without diagnosed CHD or risk equivalent and 2 or more risk factors or
c) Fasting LDL-C ≥160 mg/dL (4.14 mmol/L) for patients without diagnosed CHD or risk equivalent and with 1 or more risk factors or
d) Fasting LDL-C ≥190 mg/dL (4.9 mmol/L) for patients without diagnosed CHD or risk equivalent and with no risk factors
Patient must have a history of statin intolerance as evidenced by the following:
a) Unable to tolerate atorvastatin at an average daily dose of 10 mg and unable to tolerate any other statin at any dose due to skeletal muscle-related symptoms (eg., pain, aches, weakness or cramping)
OR
b) Unable to tolerate at least three statins: one statin at the lowest starting average daily dose (rosuvastatin 5 mg, simvastatin 10 mg, pravastatin 40 mg, lovastatin 20 mg, fluvastatin 40 mg, or pitavastatin 2 mg) and any other two statins at any dose, due to skeletal muscle-related symptoms (eg, pain, aches, weakness or cramping)

OR
c) A documented history of CK elevation >10 x ULN accompanied by muscle symptoms while on statin therapy and documented resolution of both CK elevation and muscle symptoms upon discontinuation of statin therapy
AND
Symptoms resolved or improved when statin dose was decreased or discontinued
Lipid lowering therapy has been stable prior to LDL-C screening for at least 4 weeks if currently on a bile-acid sequestering resin and/or stanol; if patient is on statin or ezetimibe at start of screening, statin or ezetimibe must be discontinued for ≥ 4 weeks before LDL-C screening
Fasting triglycerides ≤400 mg/dL (4.52 mmol/L) by central laboratory at screening

ATP, Adult Treatment Panel III; CHD, coronary heart disease; LDL-C, low density lipoprotein cholesterol; NCEP, National Cholesterol Education Project; ULN, upper limit of normal.

Table 2. Major Exclusion Criteria

History of hemorrhagic stroke
Personal or family history of hereditary muscular disorders
NYHA III or IV heart failure, or last known left ventricular ejection fraction <30%
Uncontrolled serious cardiac arrhythmia in the past 3 months prior to randomization
Myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft or stroke within 3 months prior to randomization
Planned cardiac surgery or revascularization
Type 1 diabetes, poorly controlled type 2 diabetes (HbA1c >8.5%), newly diagnosed type 2 diabetes within 6 months of randomization
Uncontrolled hypertension defined as sitting systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg
Subject who has taken in the last 4 weeks red yeast rice, >200 mg/day niacin, or prescription lipid-regulating drugs (eg, fibrates and derivatives, statins or ezetimibe) other than bile-acid sequestering resin, or stanols and stanol esters
Patient who has taken a cholesterylester transfer protein inhibitor in the last 12 months prior to LDL-C screening, such as: anacetrapib, dalcetrapib or evacetrapib
Treatment in the last 3 months prior to LDL-C screening with any of the following drugs: systemic cyclosporine, systemic corticosteroids
Uncontrolled hypothyroidism or hyperthyroidism
Estimated glomerular filtration rate <30 mL/min/1.73m^2 at screening

Active liver disease or hepatic dysfunction, defined as AST or ALT >3 times the ULN
Known active infection or major hematologic, renal, metabolic, gastrointestinal or endocrine dysfunction in the judgment of the investigator
Diagnosis of deep vein thrombosis or pulmonary embolism within 3 months prior to randomization.
Unreliability as a study participant based on the investigator's (or designee's) knowledge of the patient (eg, alcohol or other drug)
Currently enrolled in another investigational device or drug study, or less than 30 days since ending another investigational device or drug study(s), or receiving other investigational agent(s)
Female patient who has either (1) not used at least 1 highly effective method of contraception for at least 1 month prior to screening or (2) is not willing to use such a method during treatment and for an additional 15 weeks after the end of treatment, unless the patient is sterilized or postmenopausal
Patient who is pregnant or breast feeding, or planning to become pregnant during treatment and/or within weeks after the end of treatment
Patient who has previously received evolocumab or any other investigational therapy to inhibit PCSK9
Malignancy except non-melanoma skin cancers, cervical or breast ductal carcinoma in situ within the last 5 years

ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDL-C, low density lipoprotein cholesterol; NYHA, New York Heart Association; PCSK9, proprotein convertase subtilisin/kexin type 9; ULN, upper limit of normal.

Table 3. Baseline Demographics and Laboratory Values

	All Randomized (N = 511)
Gender, n (%)	
Female	254 (49.7)
Male	257 (50.3)
Age, years, median (IQR)	62.0 (54.0, 68.0)
Race, n (%)	
White	483 (94.5)
Other	28 (5.5)
BMI, kg/m^2, median (IQR)	28.5 (24.9, 30.9)
Coronary artery disease, n (%)	170 (33.3)
Cerebrovascular disease or PAD, n (%)	115 (22.5)
Cardiovascular risk factors, n (%)	
Current cigarette use	54 (10.6)

Type 2 diabetes mellitus	64 (12.5)
Hypertension	283 (55.4)
Family history of premature coronary heart disease	196 (38.4)
Low HDL-C	189 (37.0)
Patients with 2 or more risk factors	242 (47.4)
National cholesterol education program risk categories, n (%)	
High risk	316 (61.8)
Moderately high risk	55 (10.8)
Moderate risk	76 (14.9)
Lower risk	64 (12.5)
History of intolerance to statins, n (%) per patient	
One statin	8 (1.6)
Two statins	102 (20.0)
Three statins	217 (42.5)
Four or more statins	184 (36.0)

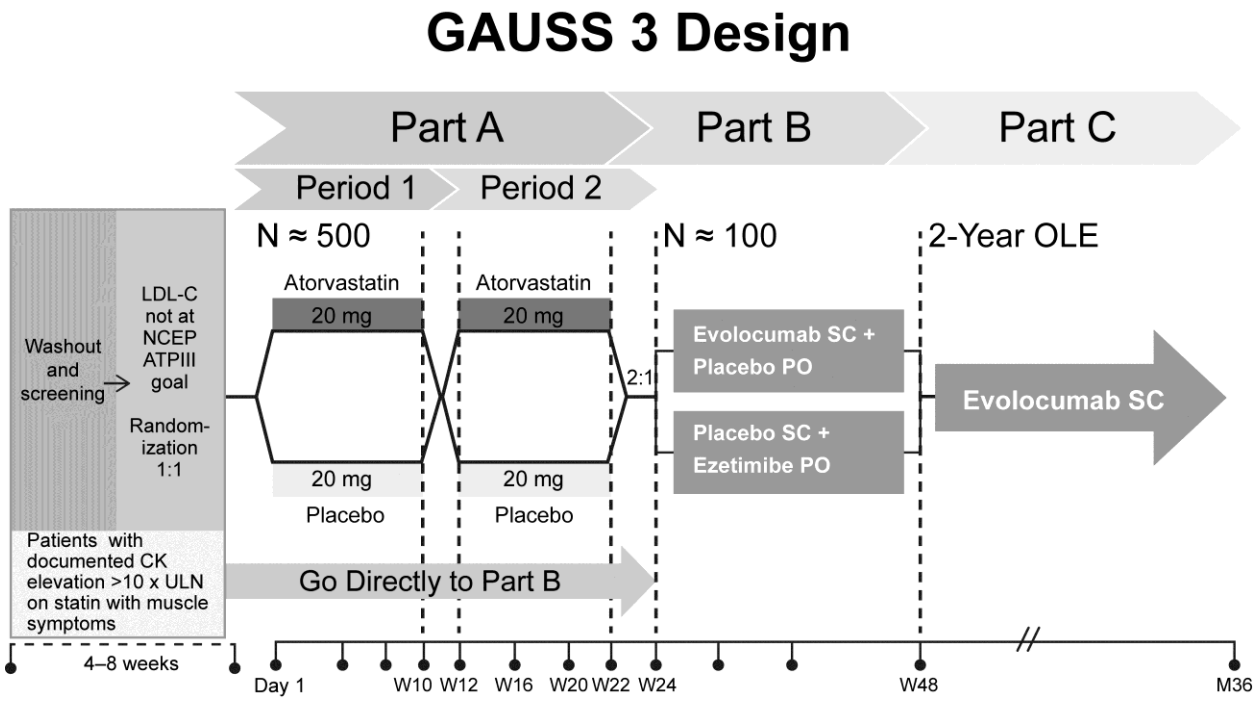
Worst muscle related side effect, n (%)	
Myalgia	412 (80.6)
Myositis	85 (16.6)
Rhabdomyolysis	14 (2.7)
Baseline laboratory values, median (IQR)	
TC, mg/dL	286.5 (254.5, 334.0)
LDL-C, mg/dL,	197.5 (170.3, 243.0)
HDL-C, mg/dL,	48.0 (40.0, 60.0)
Triglycerides, mg/dL,	168.5 (122.0, 231.0)
Lipoprotein(a), nmol/L	32.0 (15.0, 146.0)
hsCRP, mg/L	1.55 (0.83, 3.41)

BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; hsCRP, high sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; PAD, peripheral arterial disease; TC, total cholesterol.

FIGURE LEGENDS

Figure: GAUSS 3 study design. ATP III, Adult Treatment Panel III; CK, creatine kinase; GAUSS 3, Goal Achievement after Utilizing an anti-PCSK9 Antibody in Statin Intolerant Subjects; NCEP, national cholesterol education project; OLE, open-label extension; PO, oral; SC, subcutaneous; ULN, upper limit of normal.

FIGURE


GAUSS 3 Design
Part A
Part B
Part C
Period 1
Period 2
N ≈ 500
N ≈ 100
2-Year OLE
Washout and screening
LDL-C not at NCEP ATPIII goal
Random-ization 1:1
Patients with documented CK elevation >10 x ULN on statin with muscle symptoms
Atorvastatin
20 mg
Atorvastatin
20 mg
20 mg
Placebo
20 mg
Placebo
2:1
Evolocumab SC + Placebo PO
Placebo SC + Ezetimibe PO
Evolocumab SC
Go Directly to Part B
4–8 weeks
Day 1
W10
W12
W16
W20
W22
W24
W48
M36