# Goal Achievement after Utilizing an Anti-PCSK9 Antibody in Statin-Intolerant Subjects (GAUSS): Results from a Randomized, Double-blind, Placebo and Ezetimibe Controlled Study

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# Background: LDL-C Reduction in Statin-Intolerant Patients

- Statins are currently the most effective agents for reducing LDL-C and cardiovascular risk,[1] but 10% to 20% of patients cannot tolerate statins, or higher doses of statins, that are required to achieve recommended LDL-C goals, due primarily to muscle-related side effects.[2]
- Ezetimibe is the most frequently used statin alternative, lowering LDL-C 18%, but even low-risk patients are unlikely to achieve LDL-C goals with ezetimibe alone, or in combination with low-dose statins.[3]
- Statin-intolerant patients, especially those at high cardiovascular risk, need more effective and well tolerated therapies to lower LDL-C.


1. Baigent C, et al/ *Lancet.* 2005;366:1267-1278.
2. Bruckert E, et al. *Cardiovasc Drugs Ther.* 2005;19:403-414.
3. Ballantyne CM, et al. *Am J Cardiol.* 2007;99(5):673-680.

# Background: PCSK9 Inhibition and AMG 145

- Plasma proprotein convertase subtilisin/kexin type 9 (PCSK9) plays a pivotal role in cellular cholesterol homeostasis, by binding to, and mediating the recycling of LDL receptors.[1]
- AMG 145 is a fully human monoclonal antibody that binds to PCSK9 in the circulation and blocks its interaction with LDL-Rs, increasing their recycling and removal of LDL-C.
- In phase 1 studies, AMG 145 was well tolerated and reduced LDL-C up to 64% in healthy subjects and up to 81% in subjects with hypercholesterolemia.[2]


1. Benjannet S, et al. *J Biol Chem.* 2010;285:40965-40978.
2. Dias C. et al. *J Am Coll Cardiol.* 2012;60(19) Published Online First Oct 17, 2012

# GAUSS Background

- **Study objective:**

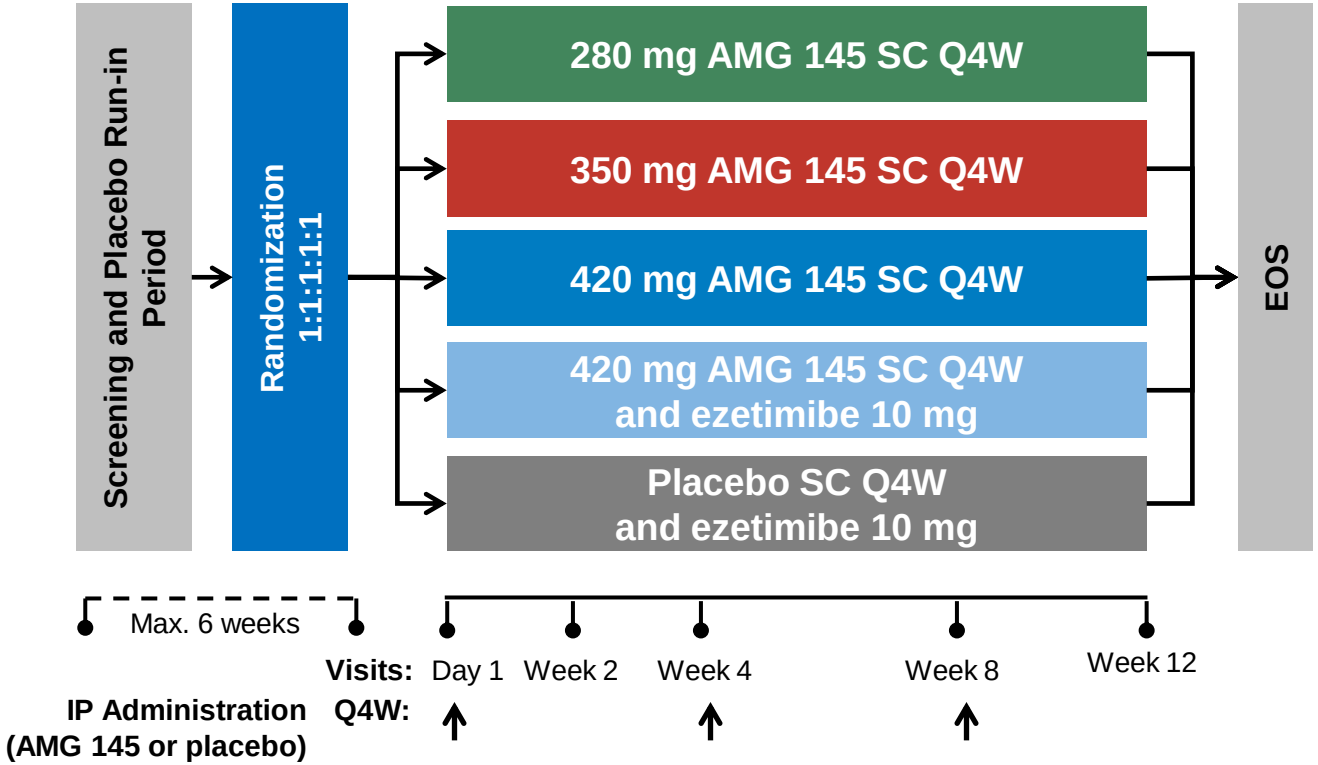
  Evaluate the safety, tolerability, and efficacy of AMG 145 compared to ezetimibe in adult patients, 18-75 years, at cardiovascular risk unable to tolerate effective doses of statins due to muscle-related side effects.

- Global, Randomized, Double-blind, Controlled Study

# GAUSS: Key Entry Criteria

- Statin intolerant: defined as intolerable myalgia (muscle pain, soreness, weakness, or cramps) or myopathy (myalgia plus an elevated creatine kinase level); and having symptom improvement or resolution with statin discontinuation and either
  - unable to tolerate at least 1 statin at any dose or
  - unable to tolerate 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
- Elevated LDL-C: above risk-based goals recommended by the National Cholesterol Education Program (NCEP):
  - ≥ 100 mg/dL (2.59 mmol/L) with diagnosed coronary heart disease (CHD) or risk equivalent
  - ≥ 130 mg/dL (3.4 mmol/L) without CHD or risk equivalent and ≥ 2 risk factors, or
  - ≥ 160 mg/dL (4.1 mmol/L) without CHD or risk equivalent and with ≤ 1 risk factor.
- Background Rx: Eligible patients could receive stable doses (≥ 4 weeks before screening) of one or more of the following: statins less than or equal to the weekly maximums listed above, bile-acid sequestering resins, or plant stanols/sterols.

# GAUSS: Study Design & Entry Criteria




**Primary endpoint:**
Percentage change in LDL-C, *by ultracentrifugation*, from baseline at 12 weeks

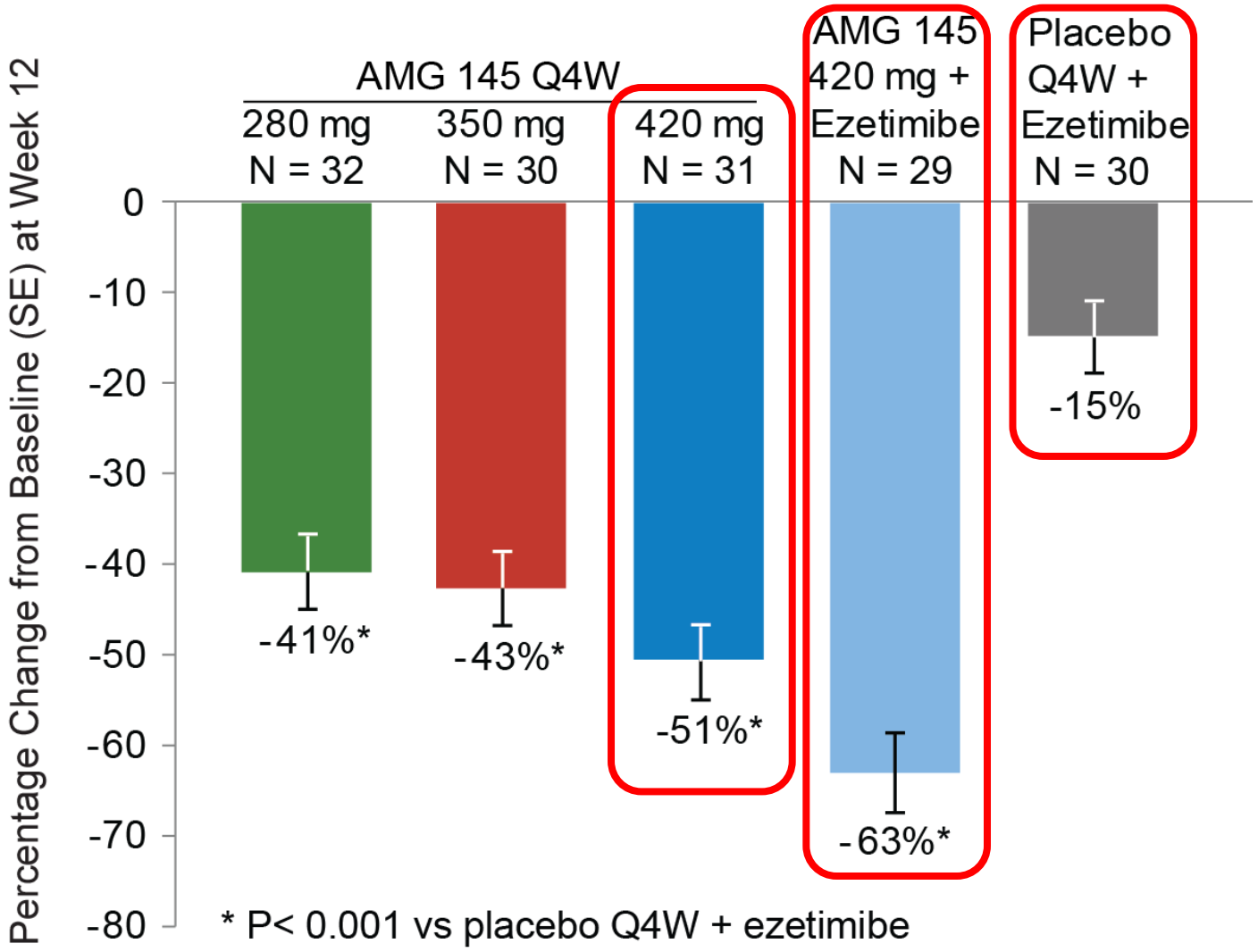
NCEP, National Cholesterol Education Program

# GAUSS: Baseline Characteristics

| Characteristic | AMG 145 Q4W | | | AMG 145 420 mg + Ezetimibe N = 30 | Placebo Q4W + Ezetimibe N = 32 |
|---|---|---|---|---|---|
| | 280 mg N = 32 | 350 mg N = 31 | 420 mg N = 32 | | |
| Sex, female, n (%) | 18 (56) | 21 (68) | 20 (63) | 23 (77) | 18 (56) |
| Age, years, mean (SD) | 62 (10) | 62 (9) | 60 (9) | 62 (7) | 62 (7) |
| LDL-C, mg/dL , mean (SD)* | **195 (48)** | **190 (48)** | **204 (60)** | **194 (60)** | **183 (36)** |
| Free PCSK9, ng/mL, mean (SD) | 383 (98) | 396 (129) | 372 (87) | 379 (111) | 390 (91) |
| NCEP high-risk, n (%) | **14 (44)** | **12 (39)** | **11 (34)** | **10 (33)** | **15 (47)** |
| Coronary artery disease, n (%) | 3 (9) | 5 (16) | 3 (9) | 6 (20) | 10 (31) |
| Statins failed (muscle-related events) | | | | | |
| ≥ 1, n (%) | **32 (100)** | **31 (100)** | **32 (100)** | **30 (100)** | **32 (100)** |
| ≥ 2, n (%) | **28 (53)** | **24 (77)** | **23 (72)** | **21 (70)** | **25 (78)** |
| ≥ 3, n (%) | 11 (34) | 11 (35) | 12 (38) | 6 (20) | 11 (34) |
| Worst statin-related events, any statin | | | | | |
| Myalgia, n (%) | 31 (97) | 30 (97) | 29 (91) | 29 (97) | 29 (91) |
| Myositis, n (%) | 3 (9) | 3 (10) | 2 (6) | 2 (7) | 4 (13) |
| Rhabdomyolysis, n (%) | 0 (0.0) | 0 (0.0) | 1 (3) | 0 (0) | 0 (0) |

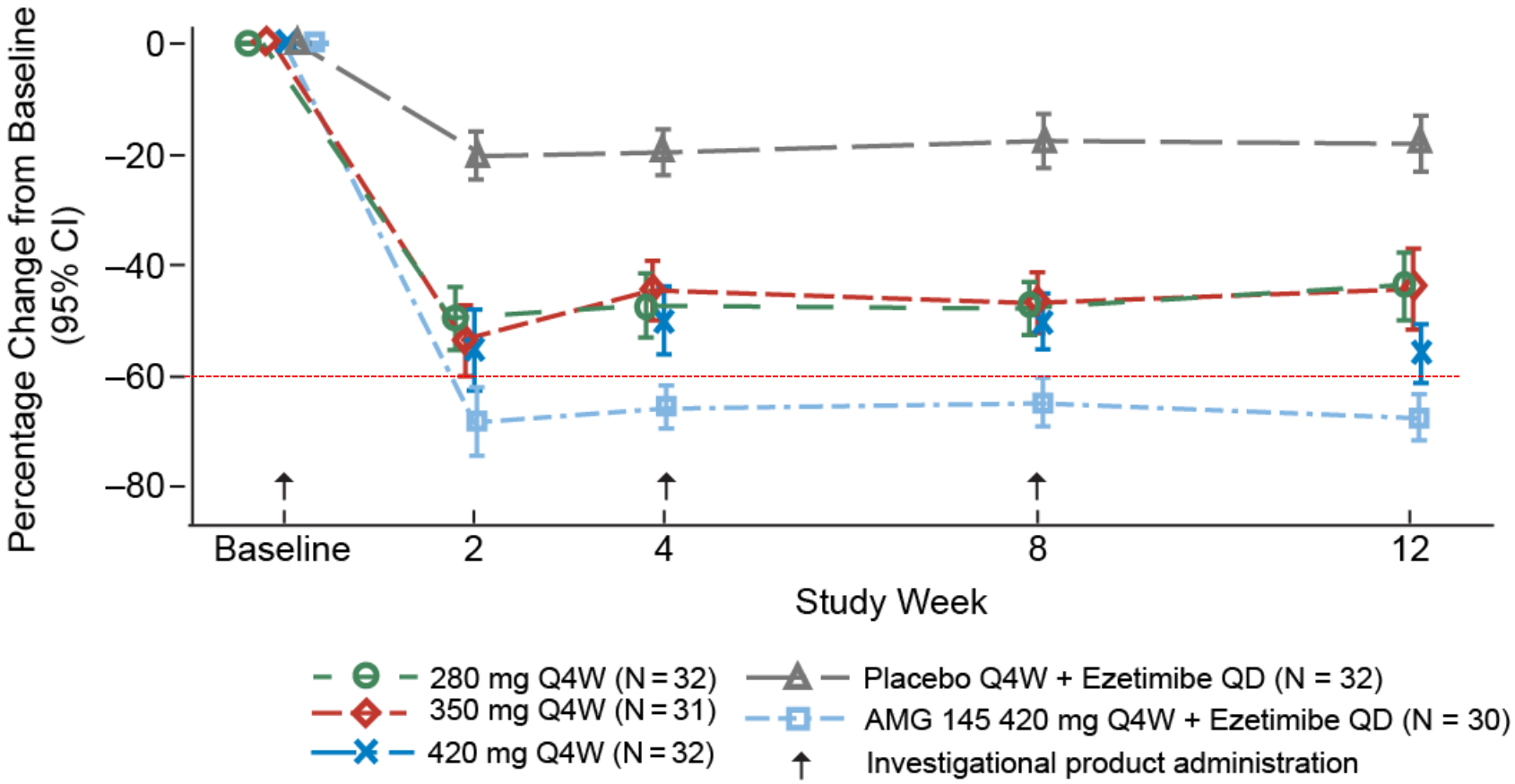
* LDL-C measured by ultracentrifugation.
SD, standard deviation; NCEP, National Cholesterol Education Program

# GAUSS: % Change in LDL-C, by UC, from Baseline at Week 12



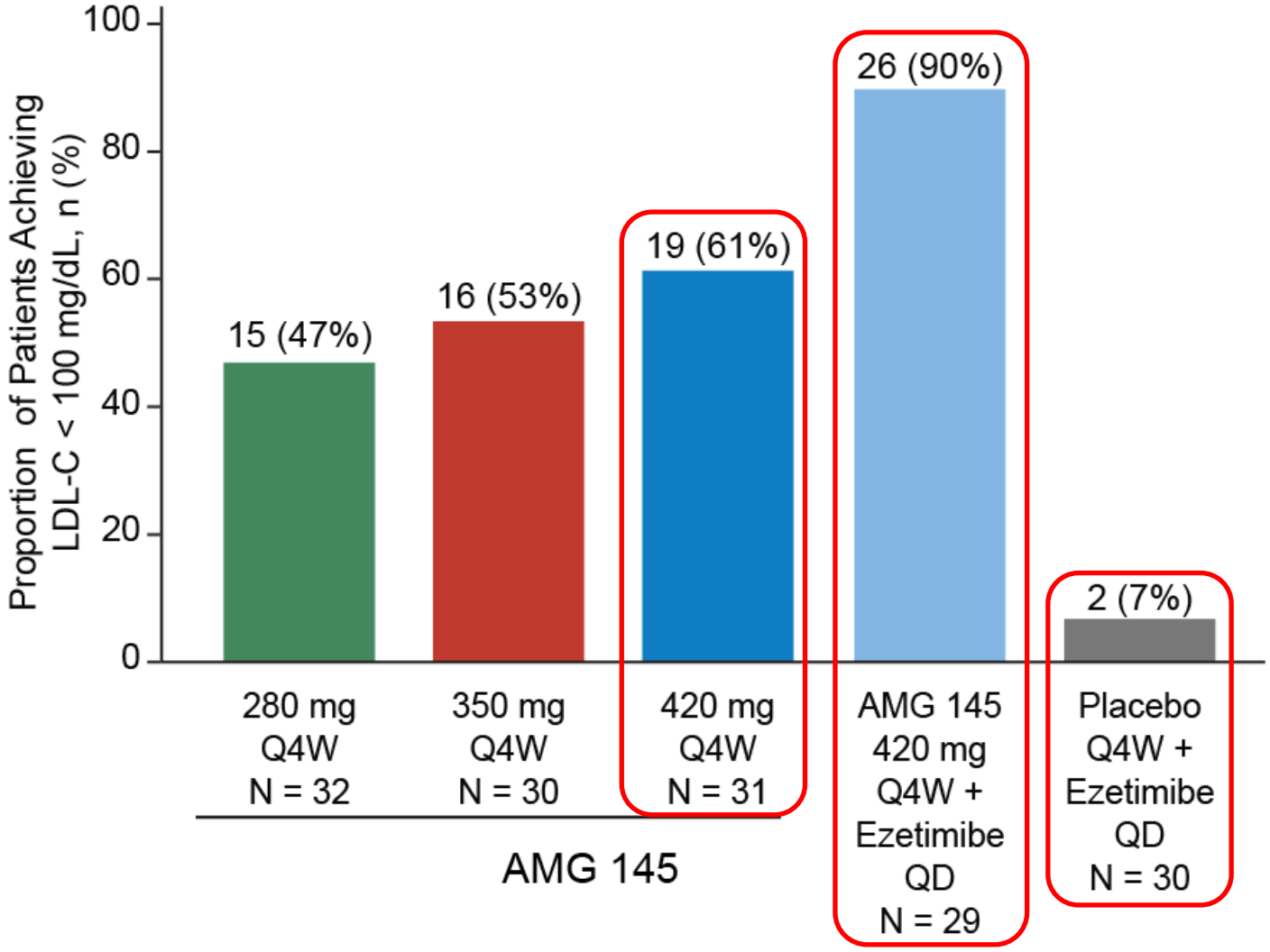

LDL-C values at baseline and week 12 were measured using preparative ultracentrifugation.
Q4W, every 4 weeks; QD, daily; SE, standard error

# GAUSS: % Change from Baseline in Calculated LDL-C* At All Visits



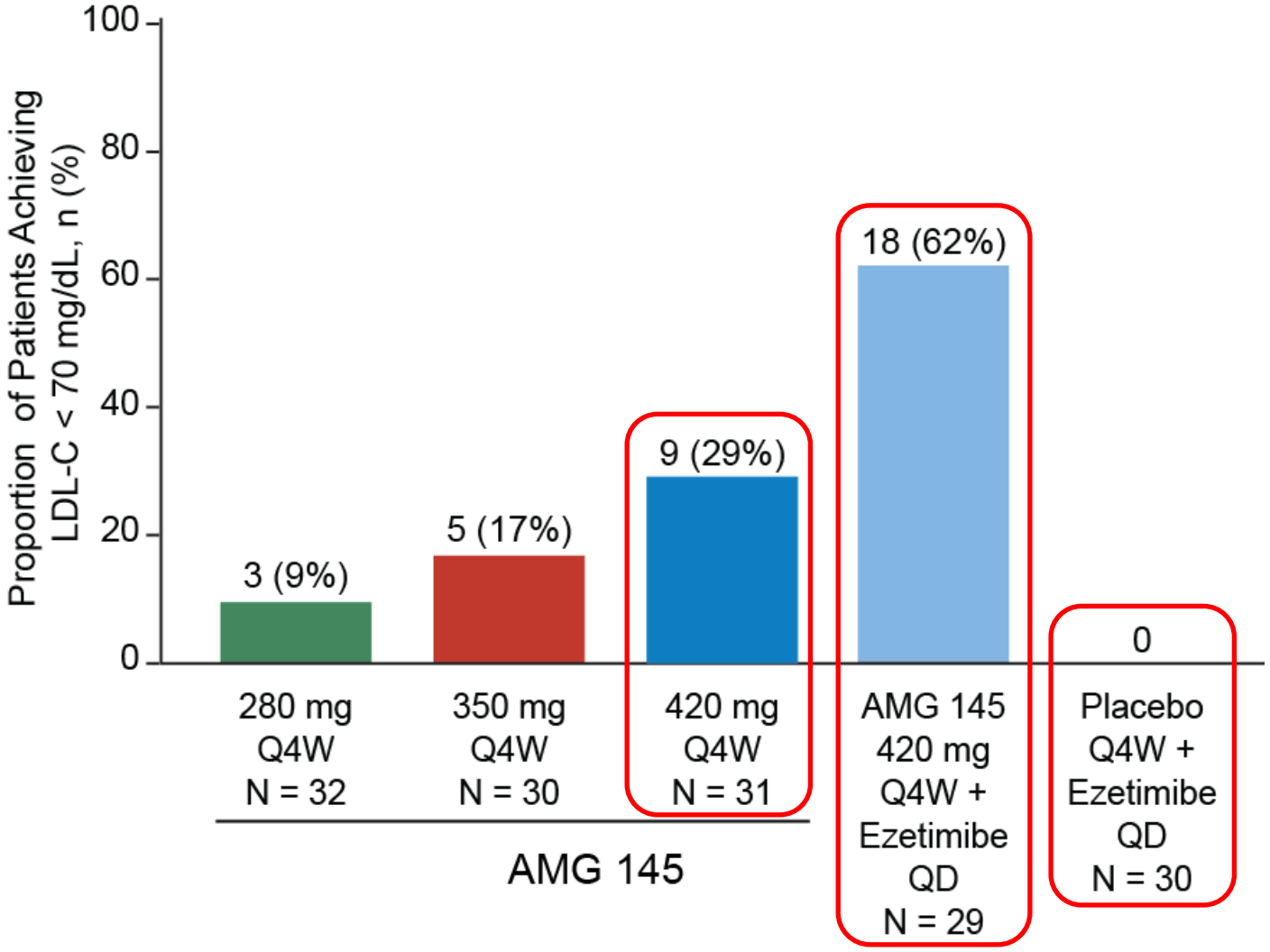

* Calculated LDL-C values.
Q4W, every 4 weeks; QD, daily, CI, confidence intervals

# GAUSS: Achievement of LDL-C* Goal < 100 mg/dL at Week 12



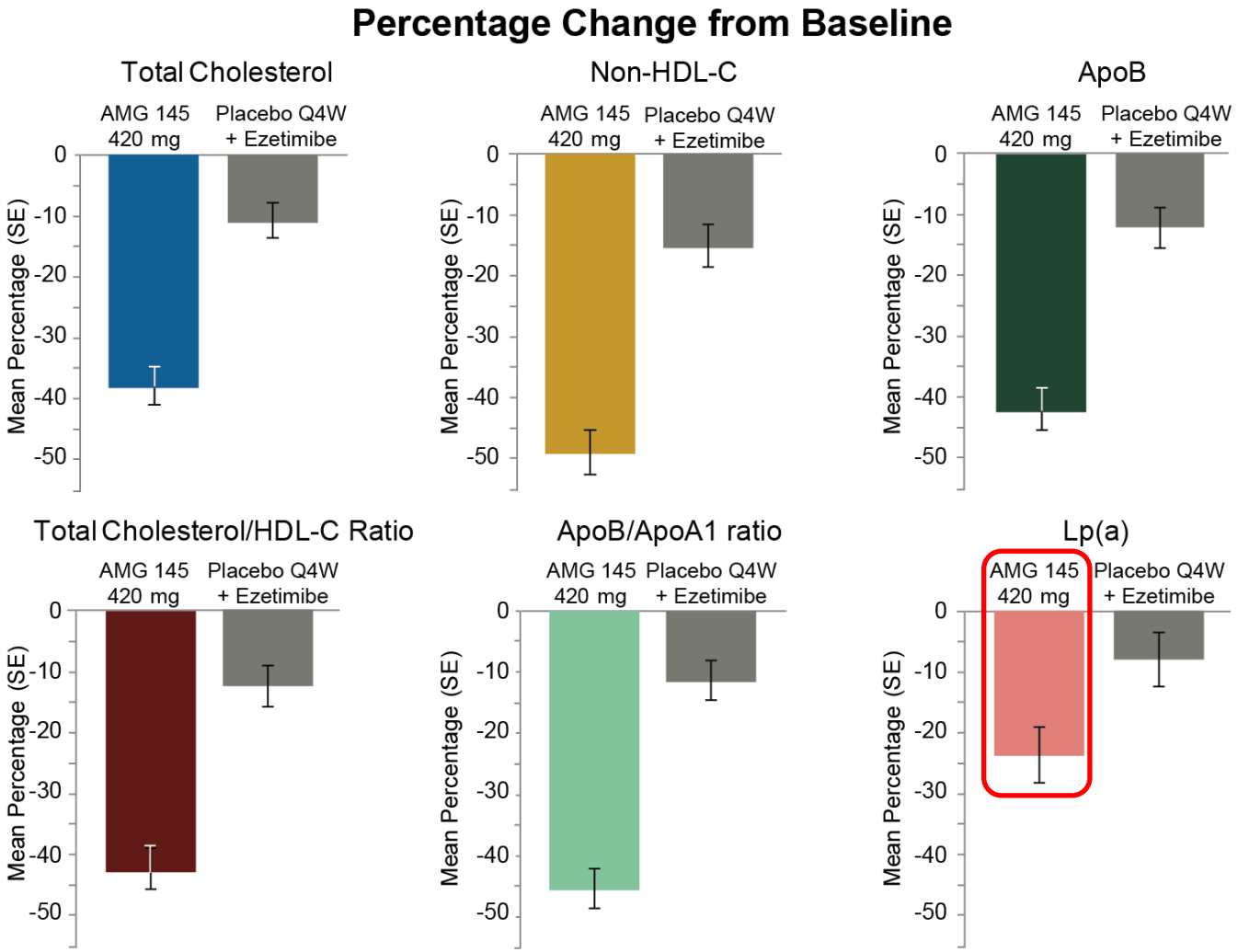

*LDL-C values at baseline and week 12 were measured using preparative ultracentrifugation.

# GAUSS: Achievement of LDL-C* Goal < 70 mg/dL at Week 12




*LDL-C values at baseline and week 12 were measured using preparative ultracentrifugation.

# GAUSS: Effect of AMG 145 on Other Lipid Parameters Compared to Placebo at Week 12




*P* < 0.001 versus placebo Q4W + ezetimibe for all parameters
SE, standard error

# GAUSS: Safety and Tolerability

| Adverse Events, Patient Incidence, n (%) | AMG 145 | | | AMG 145 420 mg + Ezetimibe 10 mg N = 30 | Placebo Q4W + Ezetimibe N = 32 |
|---|---|---|---|---|---|
| | 280 mg N = 32 | 350 mg N = 31 | 420 mg N = 32 | | |
| Treatment-emergent AEs | 22 (68.8) | 15 (48.4) | 18 (56.3) | 20 (66.7) | 19 (59.4) |
| Serious AEs* | 2 (6.3) | 1 (3.2) | 1 (3.1) | 0 (0.0) | 0 (0.0) |
| Deaths | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Treatment-related AEs | 8 (25.0) | 3 (9.7) | 6 (18.8) | 5 (16.7) | 7 (21.9) |
| Muscle-related AEs | | | | | |
| Myalgia | 5 (15.6) | 1 (3.2) | 1 (3.1) | 6 (20.0) | 1 (3.1) |
| Muscle fatigue | 2 (6.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (3.1) |
| Muscle spasms | 1 (3.1) | 2 (6.5) | 0 (0.0) | 0 (0.0) | 3 (9.4) |
| AEs leading to discontinuation | 0 (0.0) | 1 (3.2) | 1 (3.1) | 1 (3.3) | 2 (6.3) |
| Other most commonly reported AEs | | | | | |
| Nasopharyngitis | 2 (6.3) | 2 (6.5) | 1 (3.1) | 3 (10.0) | 5 (15.6) |
| Nausea | 2 (6.3) | 1 (3.2) | 1 (3.1) | 0 (0.0) | 1 (3.1) |
| Fatigue | 4 (12.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (6.3) |

* Four serious adverse events were reported for AMG 145: acute pancreatitis, coronary artery disease, hip fracture, and syncope. **None were considered treatment related.**



AE: Adverse event. Some patients experienced more than 1 AE.

# GAUSS: CK Elevations

| CK Elevations at Any Post-Baseline Visit | AMG 145 280 mg N = 32 | AMG 145 350 mg N = 31 | AMG 145 420 mg N = 32 | AMG 145 420 mg + Ezetimibe 10 mg N = 30 | Placebo Q4W + Ezetimibe N = 32 |
|---|---|---|---|---|---|
| > 5 × ULN, n (%) | 0 (0.0) | **2 (6.5)** | 0 (0.0) | 0 (0.0) | **1 (3.1)** |
| > 10 × ULN, n (%) | 0 (0.0) | **2 (6.5)** | 0 (0.0) | 0 (0.0) | 0 (0.0) |

**Two patients with CK elevations > 10 x ULN:**

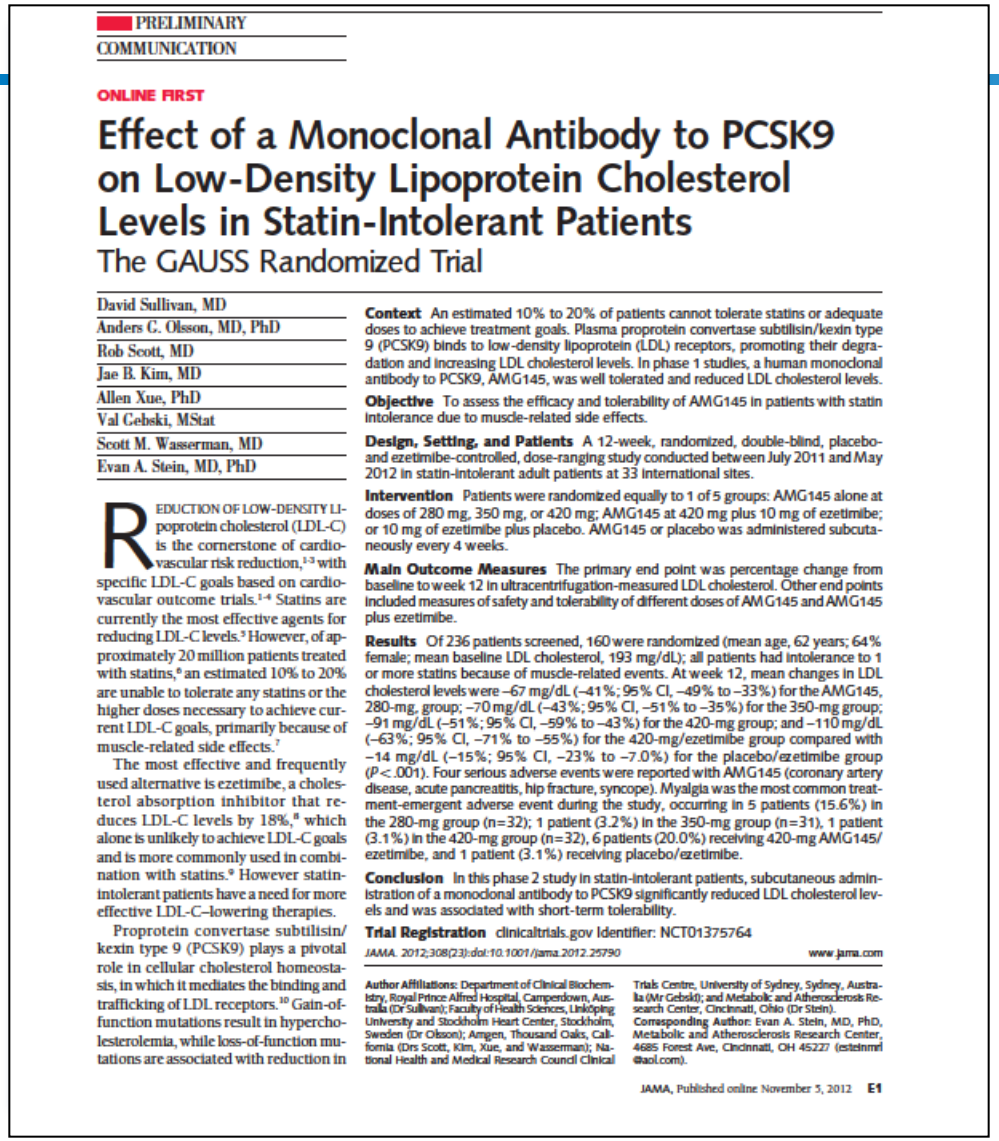
- One patient (AMG 145, 350 mg) had an isolated CK elevation of 2773 U/L at week 4 the day after an intense weight-lifting workout.
  - Resolved spontaneously without treatment interruption by the next study visit
  - Adjudicated not to be a muscle-related event by the Clinical Events Committee
- One patient (AMG 145, 350 mg) had an isolated CK elevation of 2030 U/L accompanied by generalized muscular pain at week 2, following strenuous exercise.
  - Rosuvastatin and AMG 145 were discontinued, and subsequent CK values were normal.
  - Muscle biopsy showed a normal pattern.
  - Adjudicated positively as a myopathy event



CK: creatine kinase

# GAUSS: Conclusions

- Patients with statin-intolerance achieved reductions in LDL-C with AMG 145 in the order of those found with the highest statin doses of the most efficacious statins.
  - 61% of patients who received AMG 145 420 mg achieved an LDL-C goal of < 100 mg/dL; up to 29% reached LDL-C < 70 mg/dL.
  - When combined with ezetimibe, AMG 145 yielded LDL-C <100 mg/dl and <70 mg/dL in 90% and 62% of patients, respectively.
- Improvements were observed in other lipid and lipoprotein parameters, including Lp(a).
- AMG 145, with or without ezetimibe, was well tolerated in this study. Myalgia was the most common treatment-emergent AE, occurring in 7 patients on AMG 145. Complaints of fatigue, muscle fatigue, or muscle spasm were reported in < 5% of patients on AMG 145 with or without ezetimibe, and no liver function abnormalities were observed.



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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