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

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Presenter Disclosure Information

Evan A. Stein

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  - This study was funded by Amgen Inc.
  - E.A. Stein has received consulting fees from Amgen, Adnexus Therapeutics, BMS, Genentech, Regeneron and Sanofi related to PCSK9 inhibitors, and his institution has received research funding for PCSK9 trials from Amgen, BMS, Genentech, Sanofi, and Regeneron. D. Sullivan has received funding for research, educational programs, or travel support from, and/or has served on an advisory board for Amgen, Abbott Products, AstraZeneca, Merck, Sharp and Dohme, Sanofi Aventis, Pfizer Australia, and Roche. A. G. Olsson has received research support and/or consulting fees from Amgen, AstraZeneca, Karobio, MSD, Pfizer, and Roche.
  - R. Scott, J.B. Kim, A. Xue, T. Liu, and S.M. Wasserman are employees of Amgen Inc. and have received Amgen stock/stock options.
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- Unlabeled/unapproved uses disclosure
  - Use of AMG 145 in patients with hyperlipidemia is investigational.

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 statin.[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: PCKS9 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]

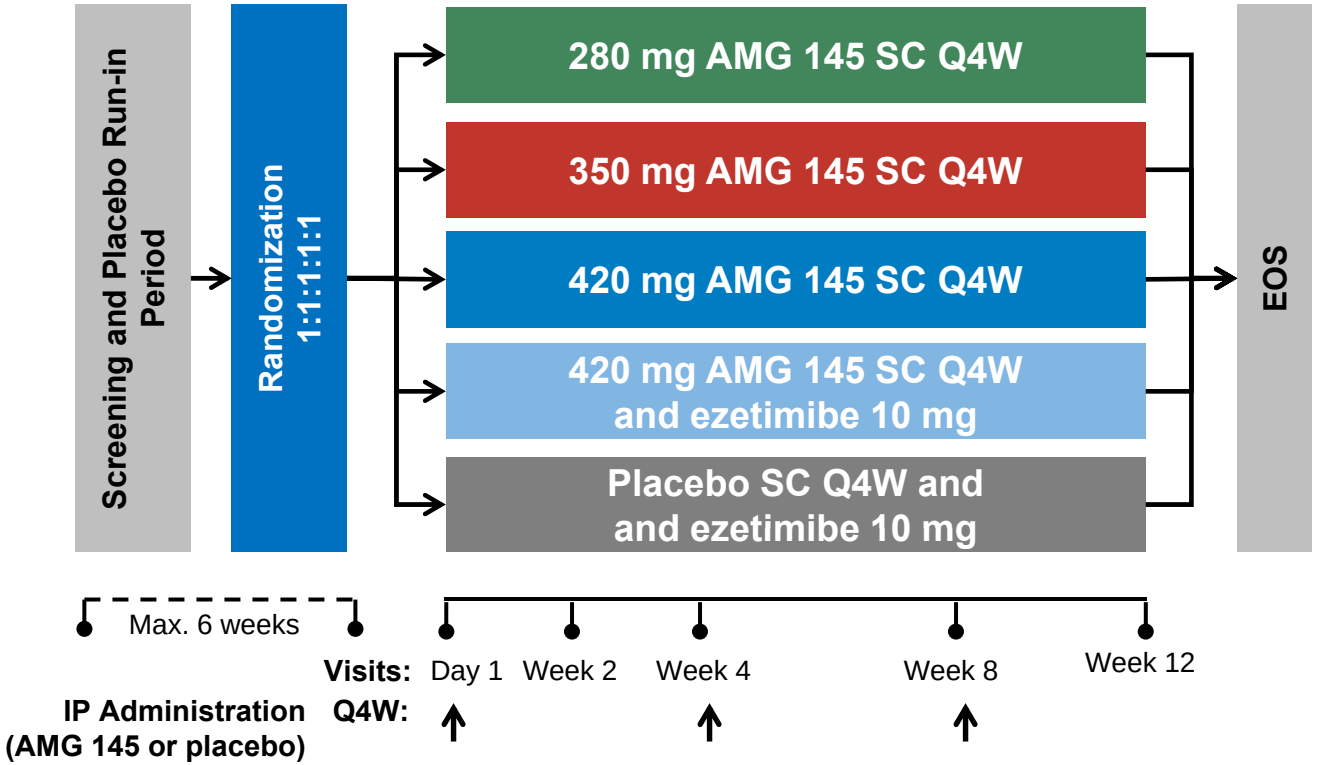
1. Benjannet S, et al. *J Biol Chem.* 2010;285:40965-40978.
2. Dias C. et al. *J Am Coll Cardiol.* 2012;60(19) Published Online First Oct 17, 2012

GAUSS Background

- Goal Achievement after Utilizing an Anti-PCSK9 Antibody in Statin-Intolerant Subjects
- Global, Randomized, Double-blind, Controlled Study
- **Study objective:**

  Evaluate the safety, tolerability, and efficacy of AMG 145 compared to ezetimibe in a difficult-to-treat and growing population: patients at cardiovascular risk who are unable to tolerate effective doses of statins due to muscle-related side effects.

GAUSS: Study Design & Entry Criteria



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

Population

- Adults (18 – 75 years) with LDL-C above goals per NCEP risk level
- Statin-intolerance due to muscle-related side effects

A1

NCEP, National Cholesterol Education Program

Slide 6

A1 Statin intolerant definition added in the notes page.
Author, 10/15/2012

A2

GAUSS: Baseline Characteristics

Characteristic	AMG 145 Q4W			AMG 145 420 mg + Ezetimibe	Placebo + Ezetimibe
	280 mg N = 32	350 mg N = 31	420 mg N = 32	N = 30	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)

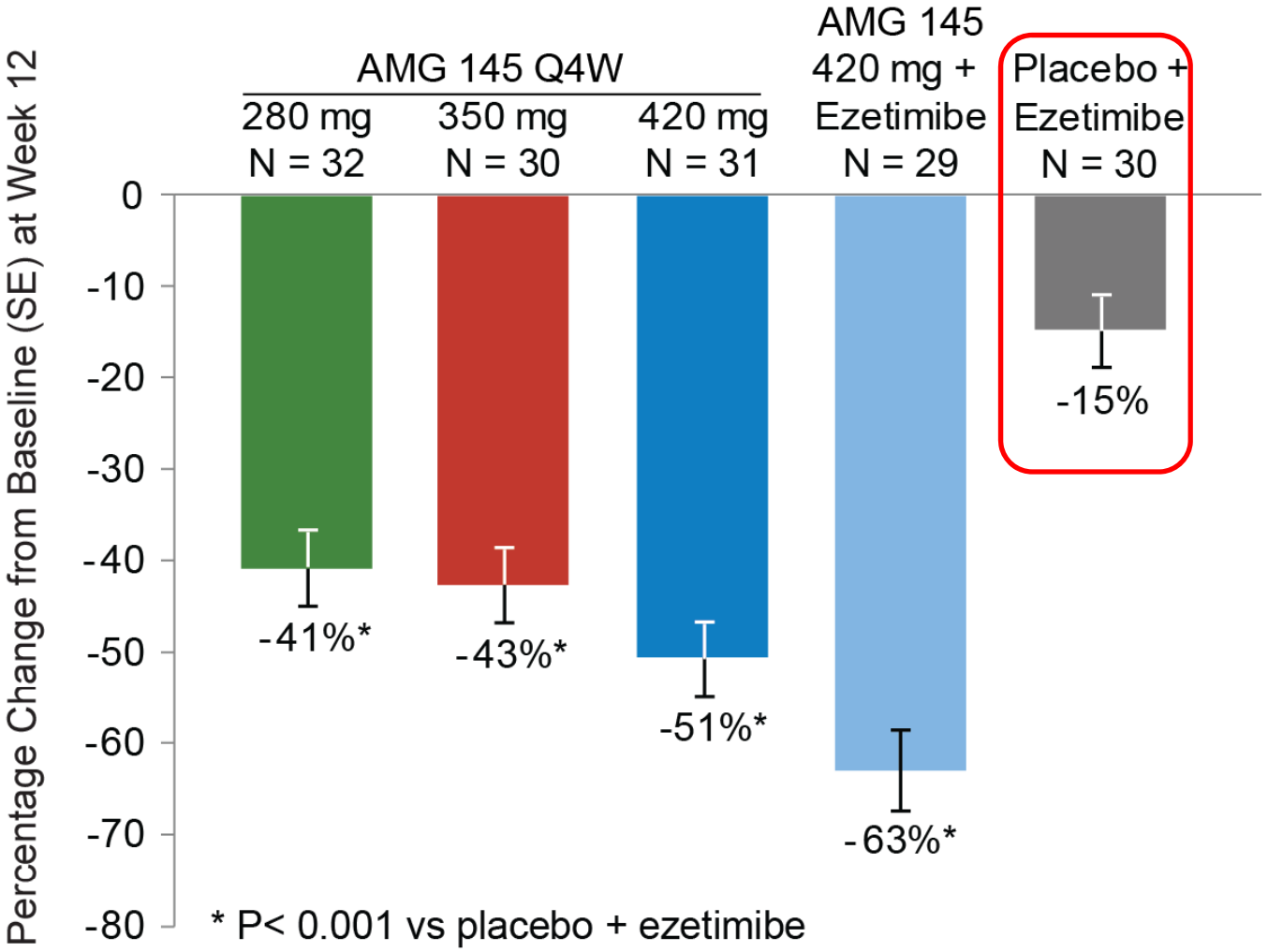
* LDL-C measured by ultracentrifugation.
SD, standard deviation; NCEP, National Cholesterol Education Program

Slide 7

A2 Statin use detail is in notes page

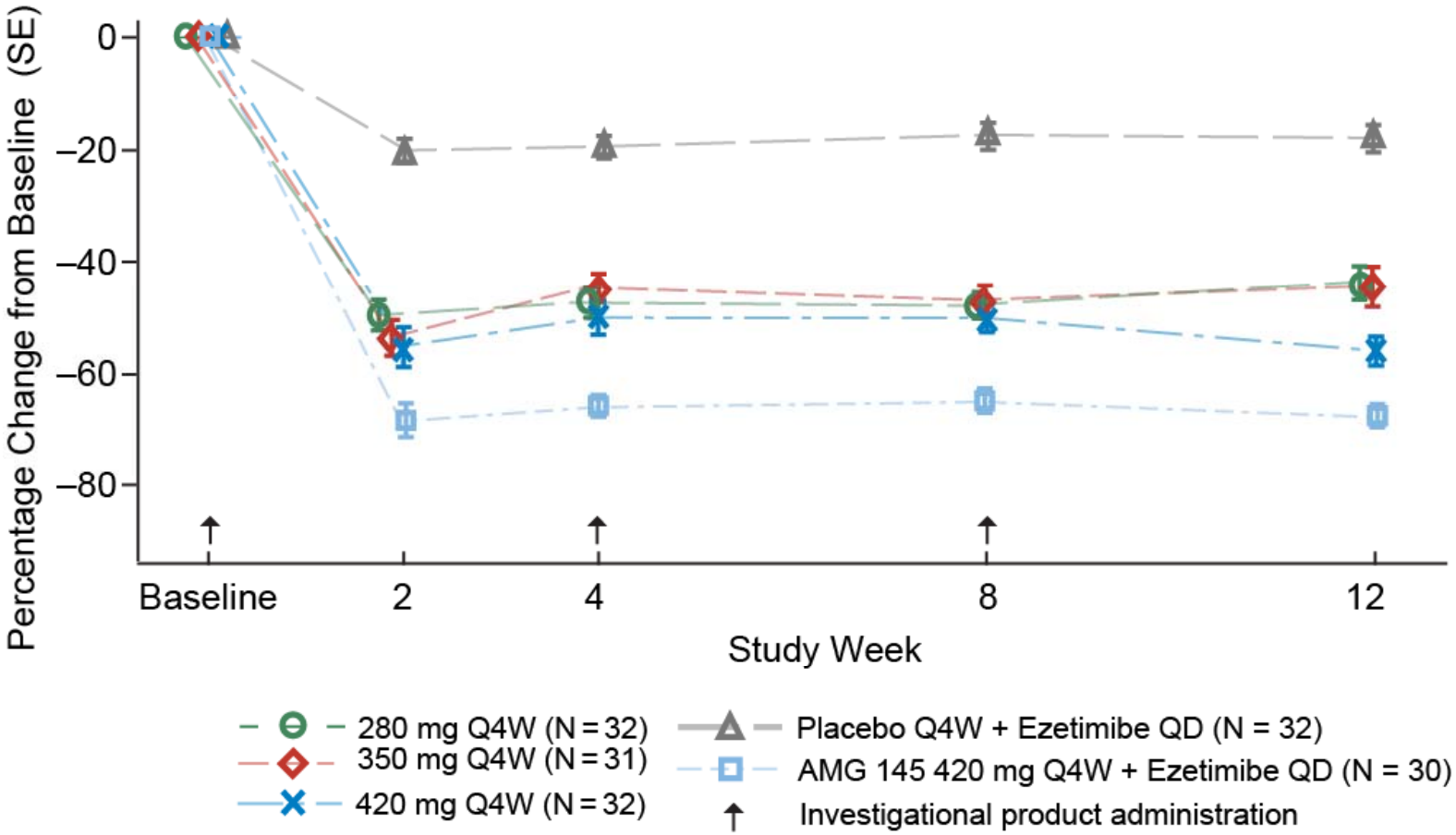
smw: font needs to be 32 for title.
Author, 10/17/2012

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



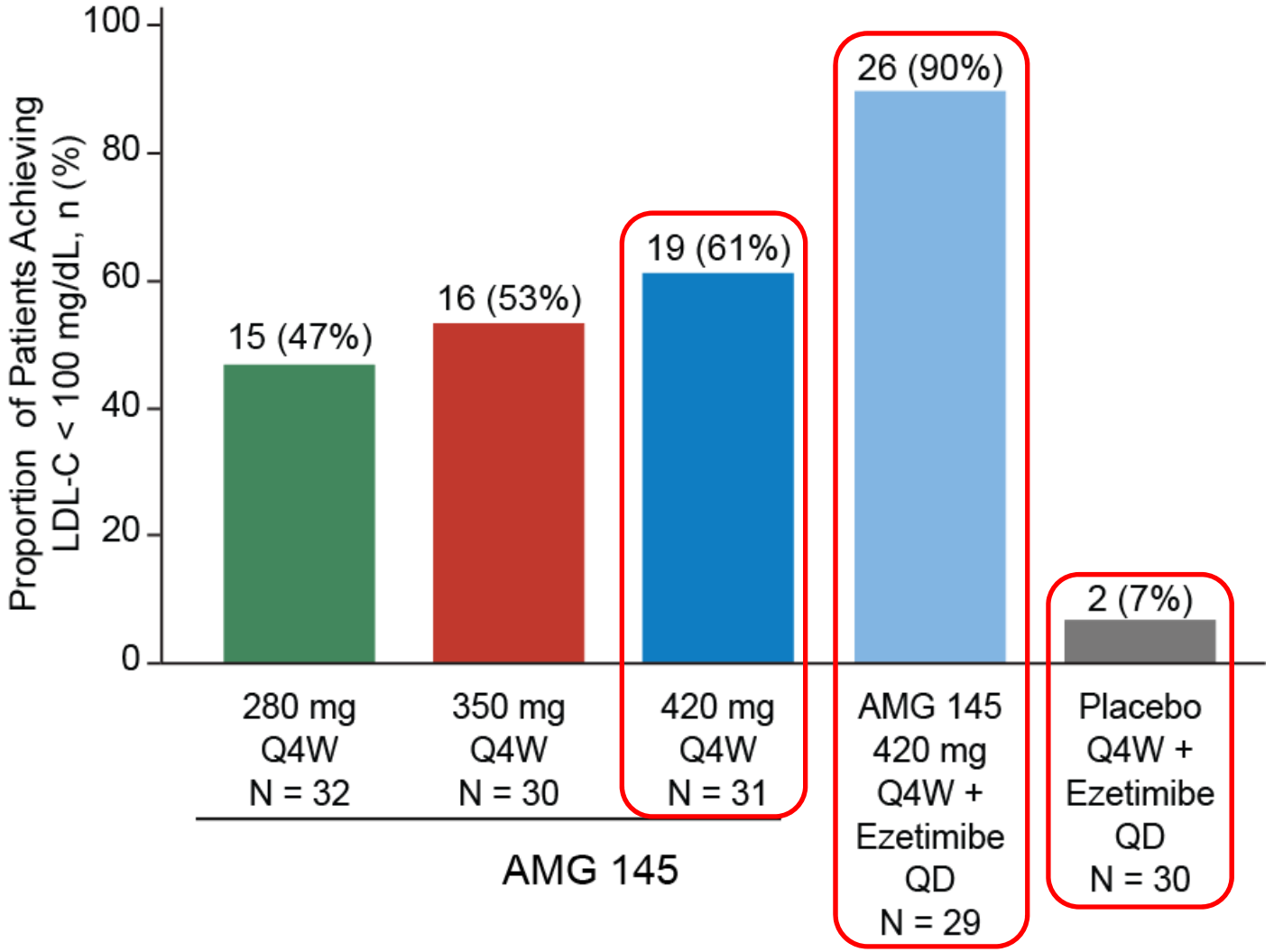
LDL-C values at baseline and week 12 were measured using preparative ultracentrifugation.
Q4W, every 4 weeks; QD, daily; SE, standard error

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



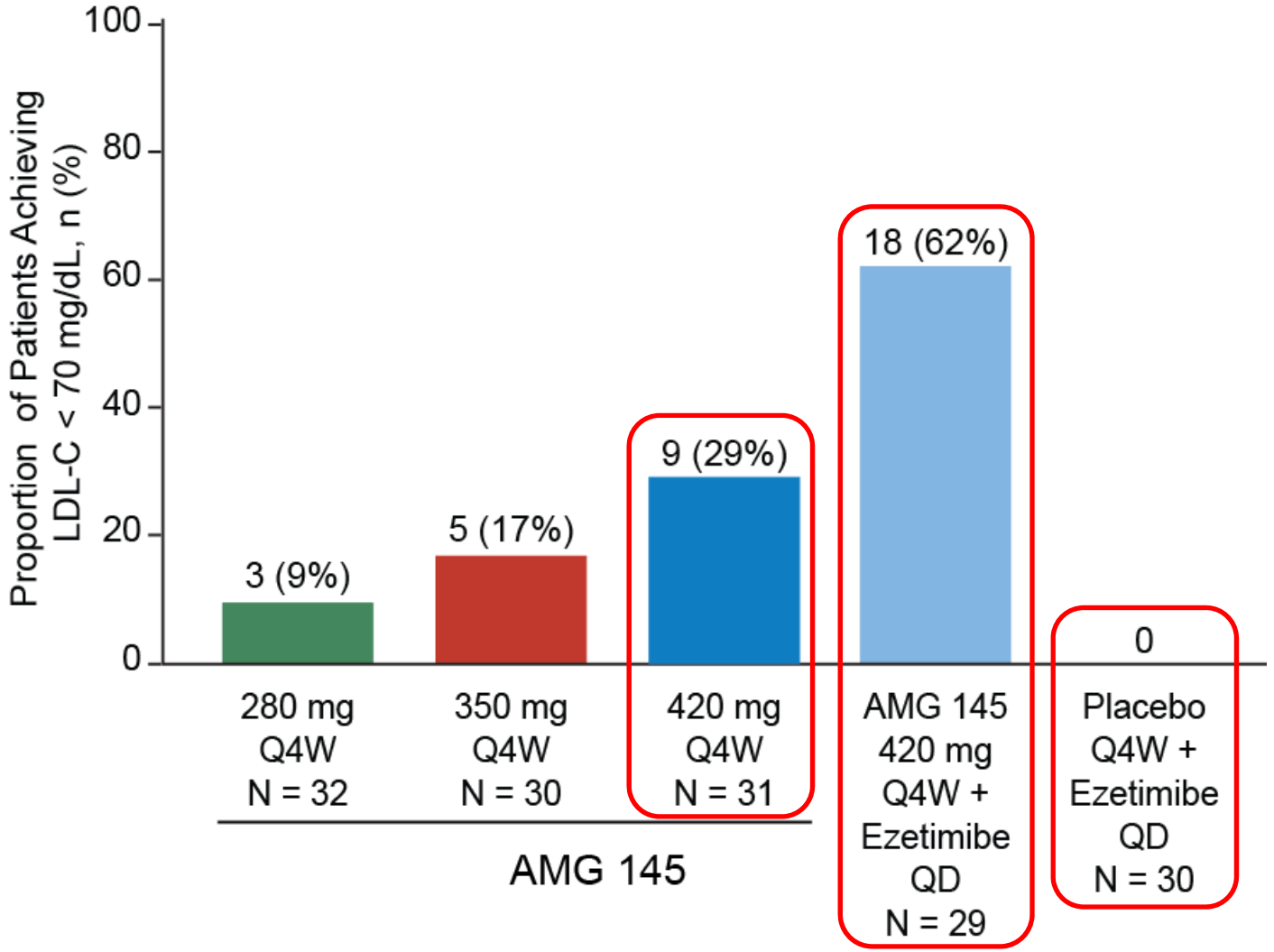
* Calculated LDL-C values.
Q4W, every 4 weeks; QD, daily, CI, confidence intervals

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



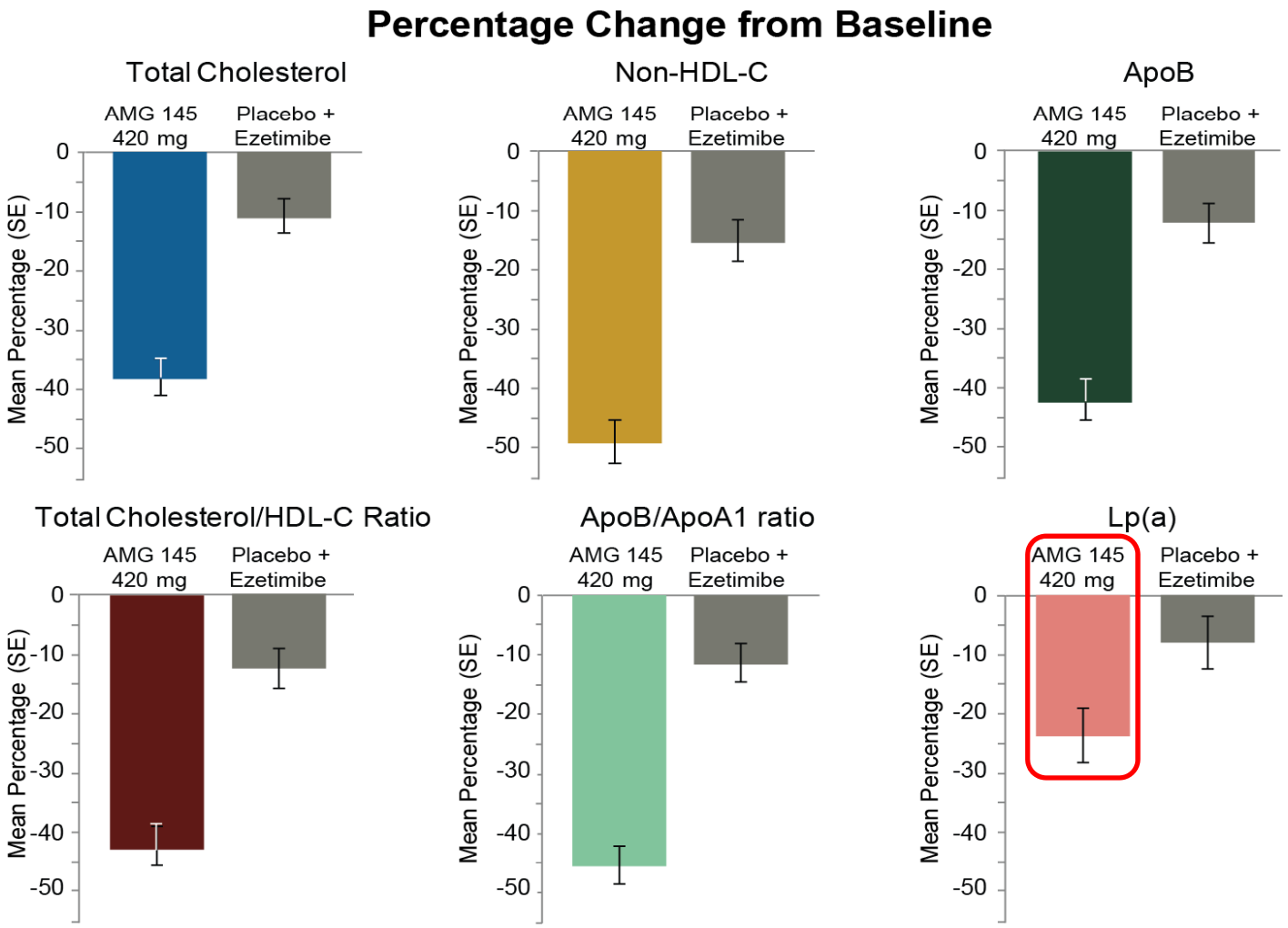
*LDL-C values at baseline and week 12 were measured using preparative ultracentrifugation.

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 + 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	Placebo + Ezetimibe 10 mg
	280 mg N = 32	350 mg N = 31	420 mg N = 32	N = 30	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 + Ezetimibe 10 mg 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

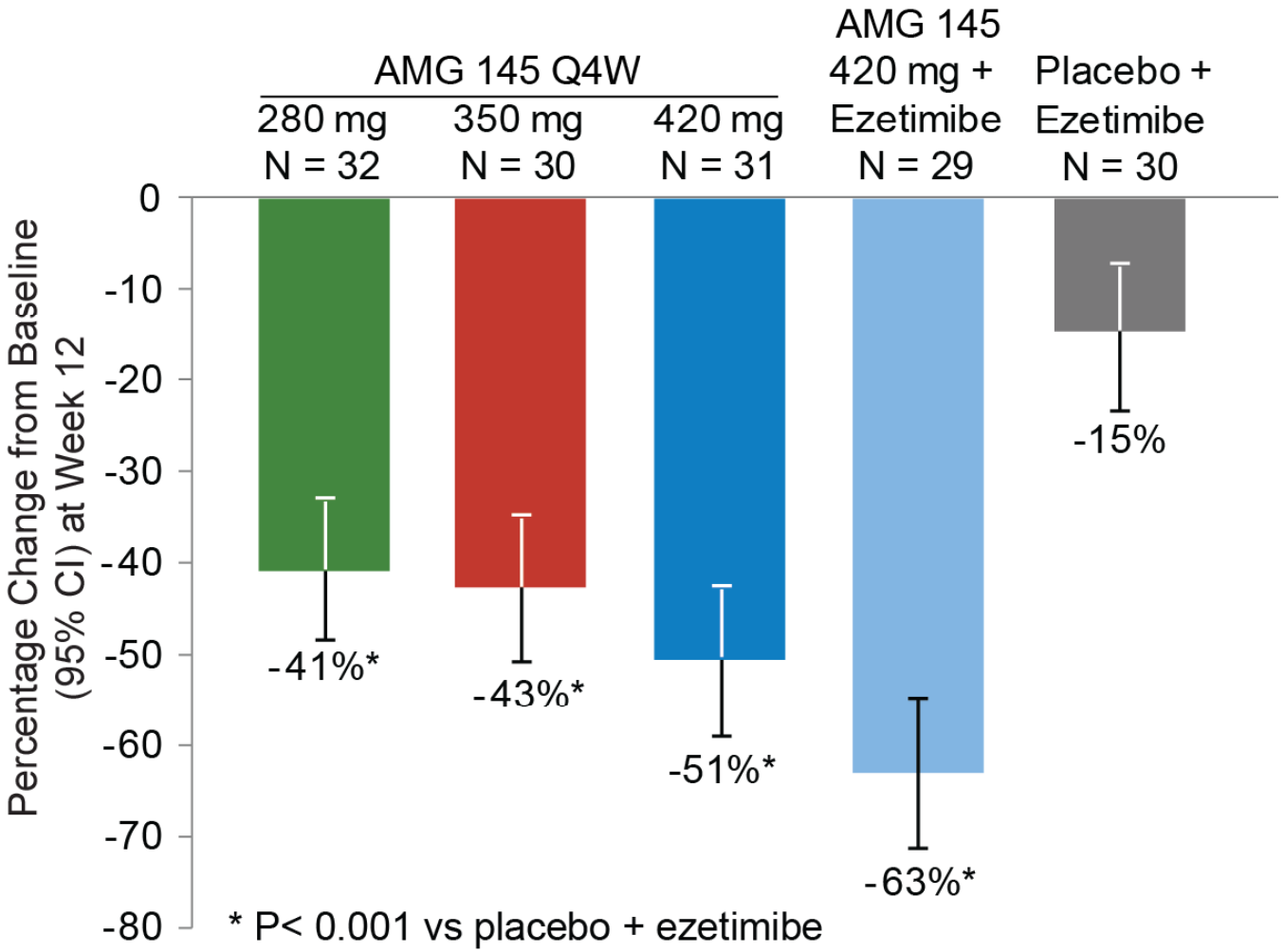
GAUSS: Conclusions

- 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.

Backup Slides

A4
A5

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; CI, confidence intervals; UC, ultracentrifugation

Slide 17

A4 Replaced graph with SEs with 95% CI version for consistency with manuscript

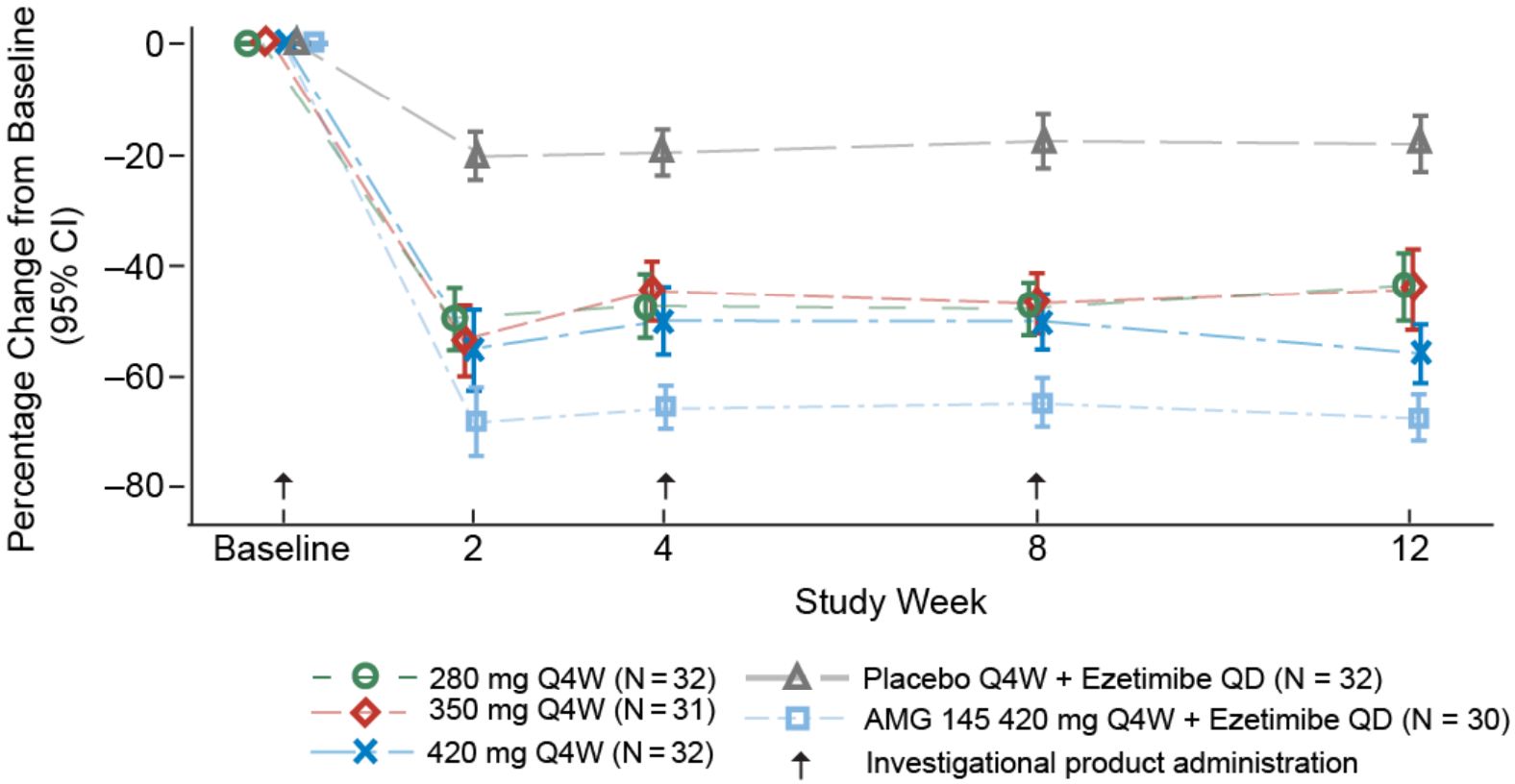
SE version is in backup slides

Also added n for each bar

smw: defer to Evan as to which he wants to show. Try to see if you can increas title font - if possilbe
Author, 10/17/2012

A5 get rid of the animation. it is not necessary and doesn't go over well at aha.
Author, 10/17/2012

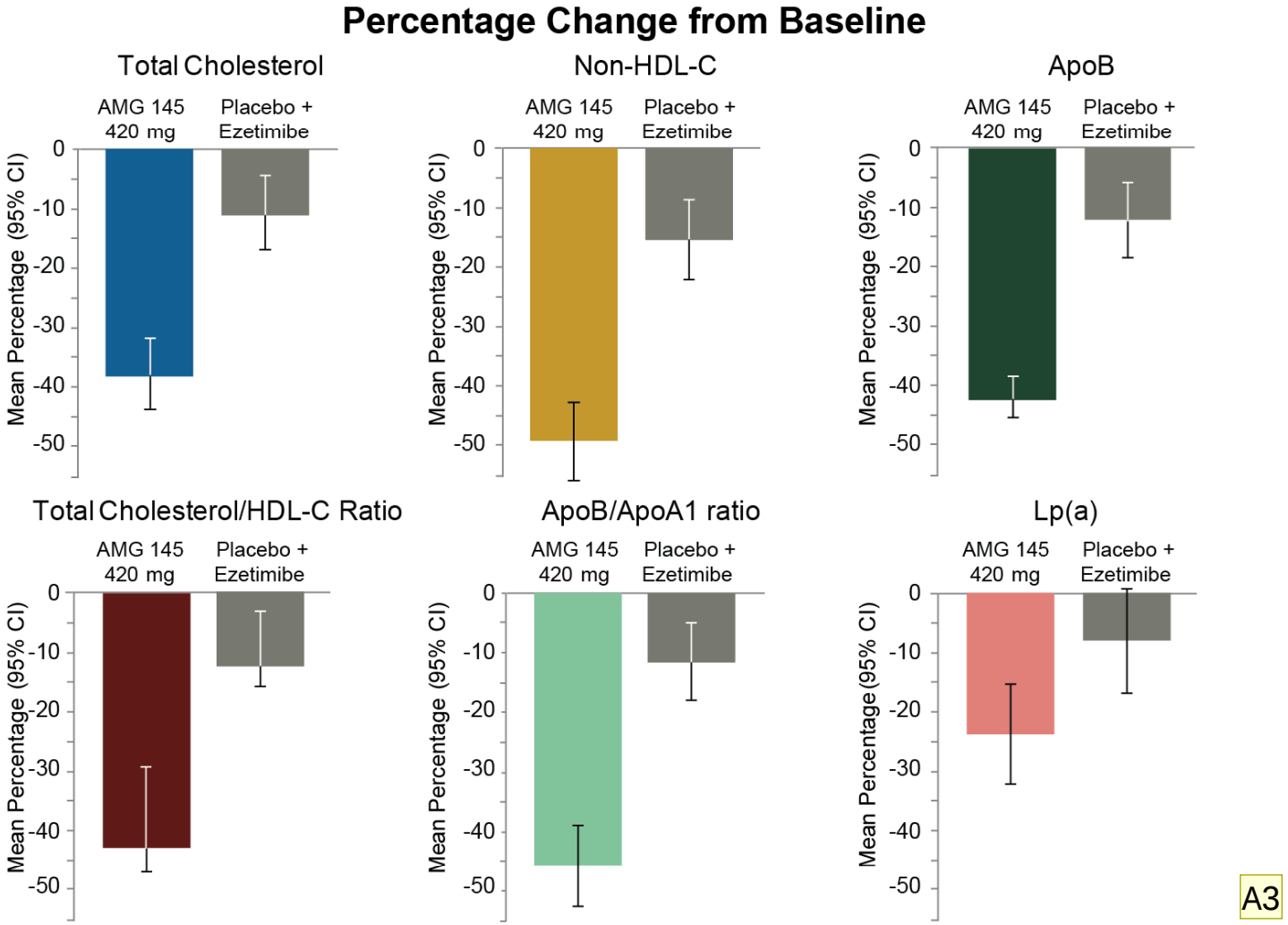
GAUSS: % Change from Baseline in Calculated LDL-C* At All Visits



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

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

A3



A3

P < 0.001 versus placebo + ezetimibe for all parameters
CI, confidence intervals

Slide 19

A3 Replaced SE with 95% CI for consistency with the manuscript. SE version is in the backup slides.
Author, 10/14/2012

A3 ApoA1 and HDL-C changes in the notes page.
Author, 10/16/2012

Patients Using Lipid-Regulating Medications

Lipid-regulating medication use	AMG 145 280 – 420 mg N = 95	AMG 145 420 mg + Ezetimibe N = 30	Placebo + Ezetimibe N = 32
Any statin, n (%)	15 (16)	4 (13)	6 (19)
Atorvastatin, n (%)	0 (0)	1 (3)	1 (3)
Average dose, mg/day	0	10	5
Fluvastatin, n (%)	1 (1)	0 (0)	0 (0)
Average dose, mg/day	40	0	0
Lovastatin, n (%)	0 (0)	1 (3)	0 (0)
Average dose, mg/day	0	20	0
Pravastatin, n (%)	3 (3)	0 (0)	0 (0)
Average dose, mg/day	10	0	0
Rosuvastatin, n (%)	6 (6)	2 (7)	3 (9)
Average dose, mg/day	3	2	2
Simvastatin, n (%)	5 (5)	0 (0)	2 (6)
Average dose, mg/day	16	0	15
Bile-acid sequestrants, n (%)	1 (1)	1 (3)	1 (3)
Omega-3 fish oil supplements, n (%)	6 (6)	4 (13)	1 (3)

Average daily dose calculation for each statin includes only patients taking the statin.

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

Treatment Difference Versus Placebo + Ezetimibe, mean (SE)	AMG 145			AMG 145 420 mg + Ezetimibe 10 mg N = 30
	280 mg N = 32	350 mg N = 31	420 mg N = 32	
Total cholesterol, %	-19.1 (3.1)*	-19.8 (3.1)*	-27.0 (3.1)*	-33.1 (2.4)*
Non-HDL-C, %	-24.9 (3.7)*	-26.7 (3.7)*	-33.6 (3.7)*	-45.0 (2.9)*
Total cholesterol/HDL-C ratio, %	-22.4 (3.3)*	-23.9 (3.3)*	-31.0 (3.3)*	-37.9 (2.9)*
VLDL-C, %	-14.4 (10.9)	-15.6 (11.1)	-1.8 (11.0)	-25.0 (10.4)‡
ApoB, %	-21.4 (3.5)*	-22.1 (3.5)*	-29.9 (3.5)*	-38.2 (2.8)*
ApoA1, %	7.4 (2.9)‡	8.3 (2.9)†	8.9 (2.9)†	8.7 (2.7)†
ApoB/ApoA1 ratio, %	-25.1 (3.3)*	-26.8 (3.3)*	-34.1 (3.3)*	-41.3 (2.9)*
Lp(a) , %	-18.0 (4.7)*	-12.4 (4.8)‡	-15.7 (4.7)†	-21.7 (4.9)*
Free PCSK9, ng/mL	-173.3 (20.8)*	-168.3 (20.8)*	-157.5 (20.8)*	-211.8 (19.5)*

*P<0.001; †P<0.01; ‡ P<0.05