A Phase 3 Double-blind, Randomized Study to Assess Safety and Efficacy of Evolocumab (AMG 145) in Hypercholesterolemic Subjects Unable to Tolerate an Effective Dose of Statin

Erik Stroes[1], David Colquhoun[2], David Sullivan[3], Fernando Civeira[4], Robert S. Rosenson[5], Gerald F. Watts[6], Eric Bruckert[7], Leslie Cho[8], Ricardo Dent[9], Beat Knusel[9], Allen Xue[9], Rob Scott[9], Scott M. Wasserman[9], and Michael Rocco[8] for the GAUSS-2 Investigators

[1]Academic Medical Center, Amsterdam, Netherlands; [2]Wesley Medical Centre, Auchenflower, Australia; [3]Royal Prince Alfred Hospital, Camperdown, Australia; [4]Hospital Universitario Miguel Servet, Zaragoza, Spain; [5]Icahn School of Medicine at Mount Sinai, NY, USA; [6]Royal Perth Hospital, School of Medicine and Pharmacology, University of Western Australia, Australia; [7]Hopital Pitié-Salpêtrière, Paris, France; [8]Cleveland Clinic, Cleveland, OH, USA; [9]Amgen, Thousand Oaks, CA, USA

March 30, 2014, Joint ACC/JAMA Late-breaking Clinical Trials Session 402
American College of Cardiology, Washington DC

Background and Rationale

- LDL-C lowering with statins reduces CV risk
  - ~ 22% CV and ~10% mortality risk reduction for every 39 mg/dL LDL-C decrease[1]
- Statin side effects leading to partial/complete statin intolerance may be present in *10% – 20%* of patients in a real-life setting.[2,3]
- Statin discontinuation and low adherence have been shown to impact survival in both primary and secondary prevention.[4-6]
- Evolocumab, a fully human monoclonal antibody against PCSK9, is a novel therapeutic option for lowering LDL-C.
- In a phase II study, evolocumab reduced LDL-C in patients intolerant to at least *one* statin.[7]

1. *Lancet* 2010;376(9753):1670-1681.
2. *Can J Cardiol* 2011;27:635-62.
3. *Ann Intern Med* 2013;158:526.
4. *JAMA* 2007;297:177.
5. *Eur Heart J* 2013;34:2940-8.
6. *Eur J Clin Pharm* 2009;65:1013.
7. *JAMA* 2012;308:2497-2506.

The GAUSS-2 Study

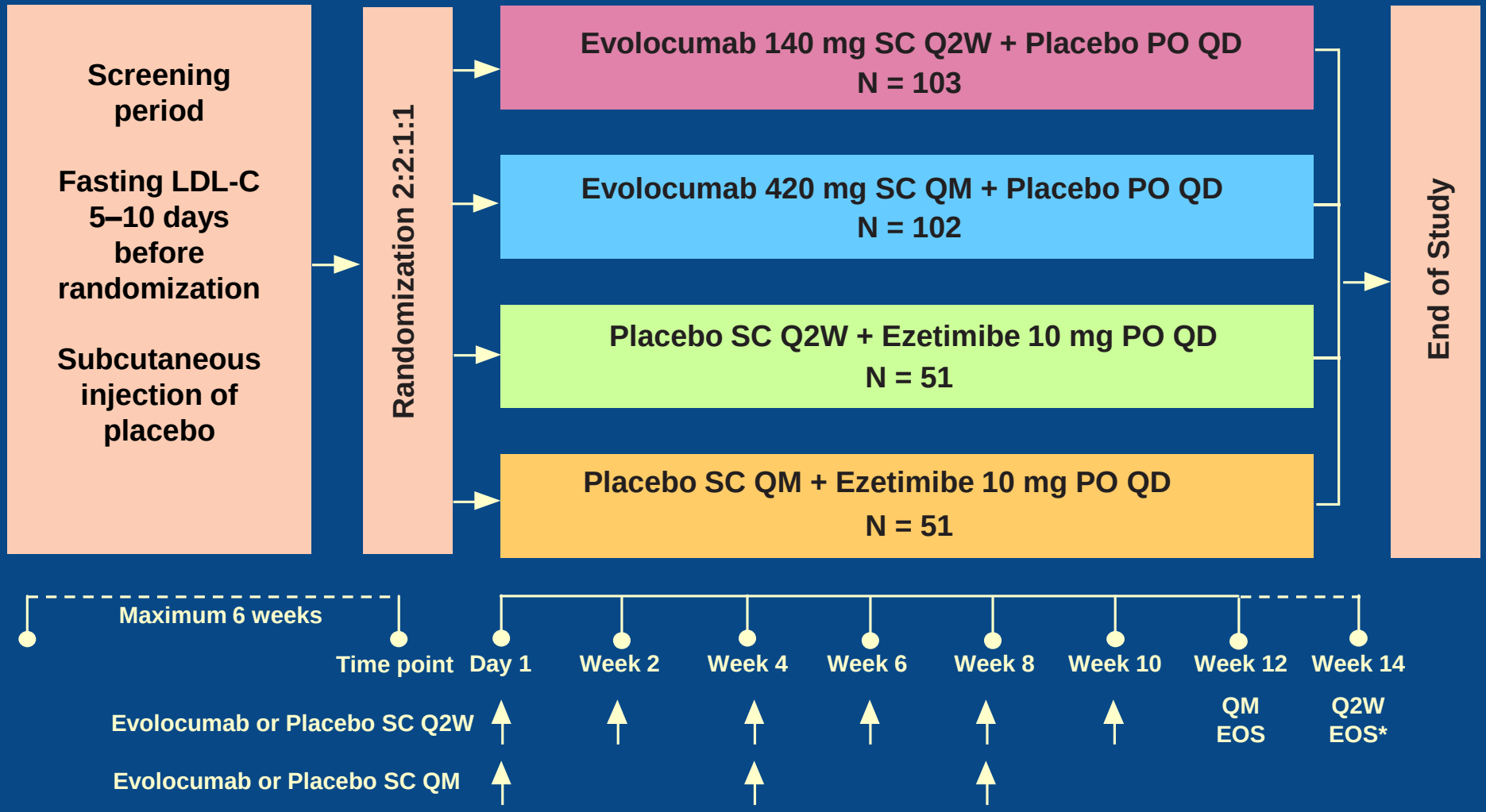
- **G**oal **A**chievement after **U**tilizing an anti-PCSK9 antibody in **S**tatin Intolerant **S**ubjects (NCT01763905)

- **Design**
  A 12-week randomized, double-blind, placebo- and ezetimibe-controlled multicenter phase 3 study[1]

- **Objective**
  To evaluate the efficacy and safety of evolocumab in statin-intolerant hypercholesterolemic patients

1. *Clin Cardiol* 2014. In Press.

GAUSS-2 Study Design



*Phone call for AEs, SAEs. AEs, adverse events; EOS, end of study; LDL-C, low-density lipoprotein cholesterol; SAEs, serious adverse events; SC, subcutaneous; PO, oral; Q2W, every 2 weeks (biweekly); QM, monthly

GAUSS-2: Endpoints

- **Co-primary endpoints**
  Percent change from baseline in LDL-C at mean of weeks 10 and 12 and at week 12

- **Secondary endpoints**
  At mean of weeks 10 and 12 and at week 12:
  - Percent change from baseline in ApoB, ApoA-I, lipoprotein(a), TG, and HDL-C
  - Achievement of LDL-C < 70 mg/dL

- **Key safety endpoints**
  - Treatment-emergent and serious adverse events
  - Muscle and hepatic enzyme elevations
  - Anti-evolocumab antibodies

GAUSS-2: Baseline Characteristics

	Biweekly		Monthly	
	PBO Q2W + EZE QD (N = 51)	Evolocumab 140 mg Q2W + PBO QD (N = 103)	PBO QM + EZE QD (N = 51)	Evolocumab 420 mg QM + PBO QD (N = 102)
Age (years), mean (SD)	62 (10)	61 (10)	60 (9)	63 (10)
Female, %	53	45	43	45
Race, white, %	96	91	90	96
NCEP risk categories*, %				
High	63	50	63	57
Moderately high	10	16	16	16
Moderate	18	19	16	16
Lower	10	16	6	12

*Risk category definitions: high, diagnosed CHD or risk equivalent; moderately high, 2 or more risk factors and Framingham risk score 10%–20%; moderate, 2 or more risk factors and Framingham risk score < 10%; lower, 0 or 1 risk factor. EZE, ezetimibe; PBO, placebo; Q2W, biweekly; QM, monthly; QD, daily

GAUSS-2: Baseline Characteristics II

	Biweekly		Monthly	
	PBO Q2W + EZE QD (N = 51)	Evolocumab 140 mg Q2W + PBO QD (N = 103)	PBO QM + EZE QD (N = 51)	Evolocumab 420 mg QM + PBO QD (N = 102)
Number of intolerable statins, %				
≥ 2	100	100	100	100
≥ 3	51	55	67	51
≥ 4	26	19	24	20
Worst muscle-related side effect*, %				
Myalgia	78	78	88	79
Myositis	22	19	8	19
Rhabdomyolysis	0	2	4	2
Lipid lowering therapy, %	29	33	31	36
Statin use, %	18	18	20	17

*Data missing for one patient in the evolocumab Q2W arm
EZE, ezetimibe; PBO, placebo; Q2W, biweekly; QM, monthly; QD, daily

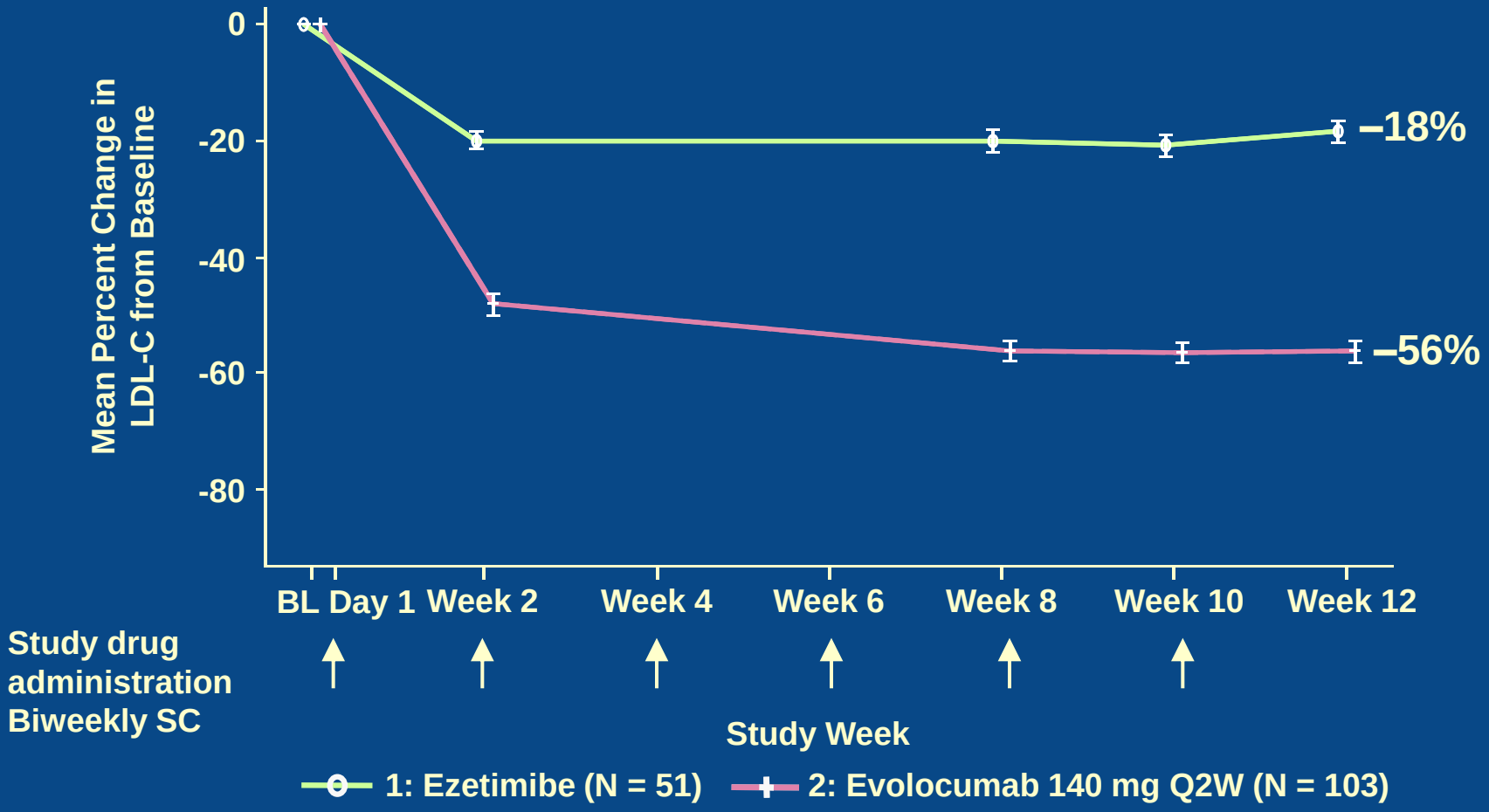
GAUSS-2: Baseline Lipids

	Biweekly		Monthly	
	PBO Q2W EZE QD (N = 51)	Evolocumab 140 mg Q2W + PBO QD (N = 103)	PBO QM + EZE QD (N = 51)	Evolocumab 420 mg QM + PBO QD (N = 102)
LDL-C*, mg/dL, mean (SD)	195 (64)	192 (57)	195 (52)	192 (61)
ApoB, mg/dL, mean (SD)	140 (37)	140 (32)	140 (31)	133 (32)
Lp(a), nmol/L, median (Q1,Q3)	57 (22, 205)	39 (10, 101)	26 (7, 181)	31 (9, 80)
TG, mg/dL, median (Q1,Q3)	170 (120, 243)	165 (123, 224)	168 (124, 240)	139 (103, 190)

*Determined by the Friedewald formula with reflexive testing via preparative ultracentrifugation when calculated LDL-C was <40 mg/dL or triglyceride levels were >400 mg/dL

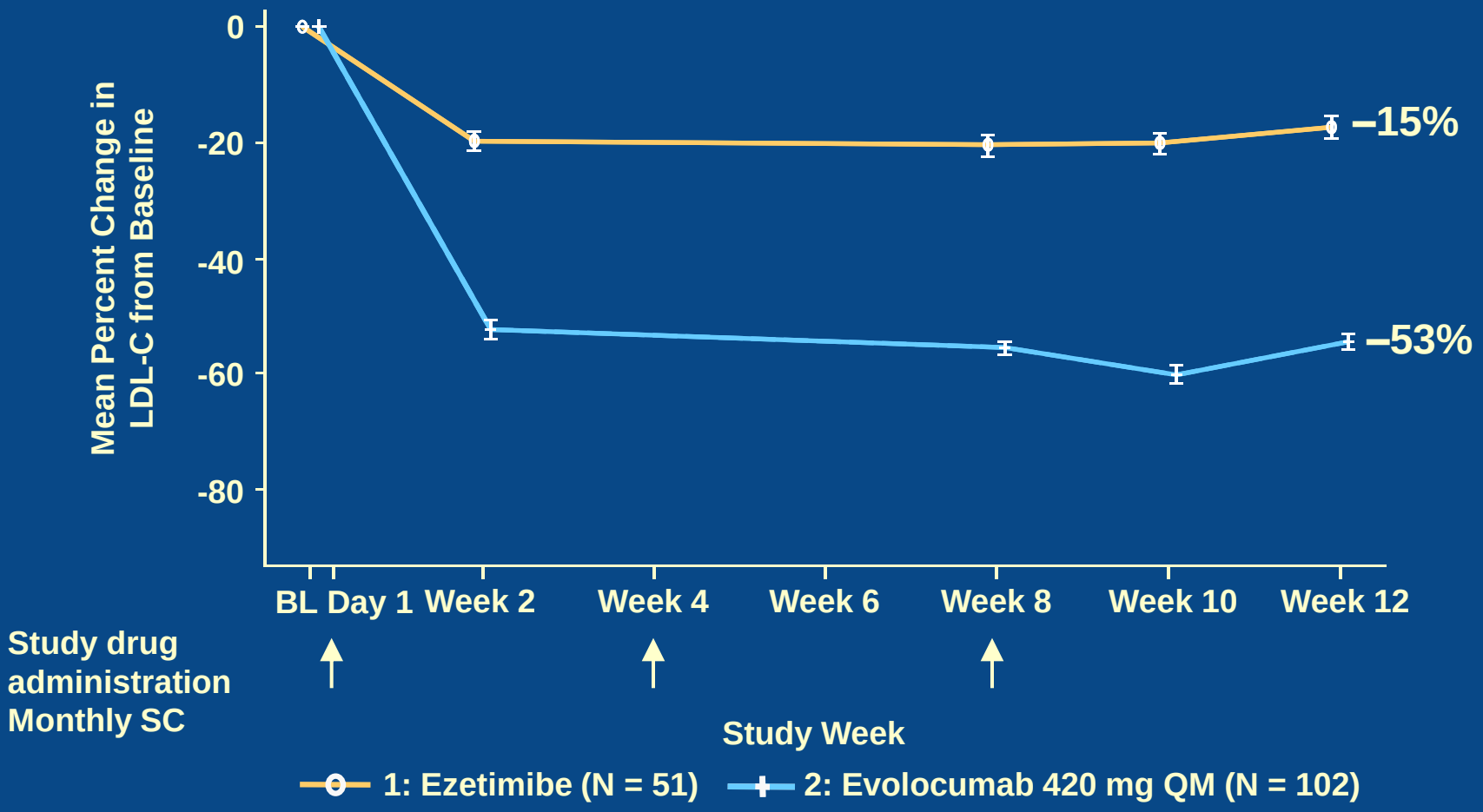
EZE, ezetimibe; PBO, placebo; Q2W, biweekly; QM, monthly; QD, daily; TG, triglycerides

GAUSS-2: Evolocumab
Primary Endpoint *Biweekly* Dose



BL, baseline. Vertical lines represent the standard error around the mean. Plot is based on observed data with no imputation for missing values. *P* value is multiplicity adjusted.

GAUSS-2: Evolocumab
Primary Endpoint *Monthly* Dose

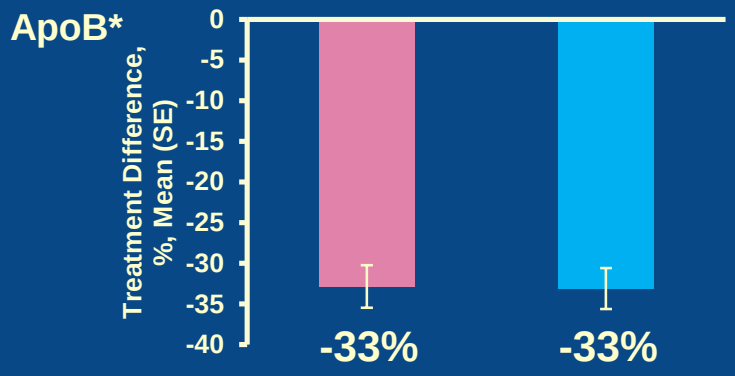


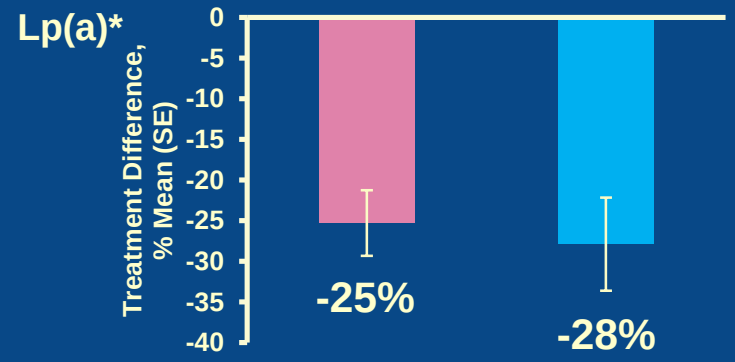
BL, baseline. Vertical lines represent the standard error around the mean. Plot is based on observed data with no imputation for missing values. *P* value is multiplicity adjusted.

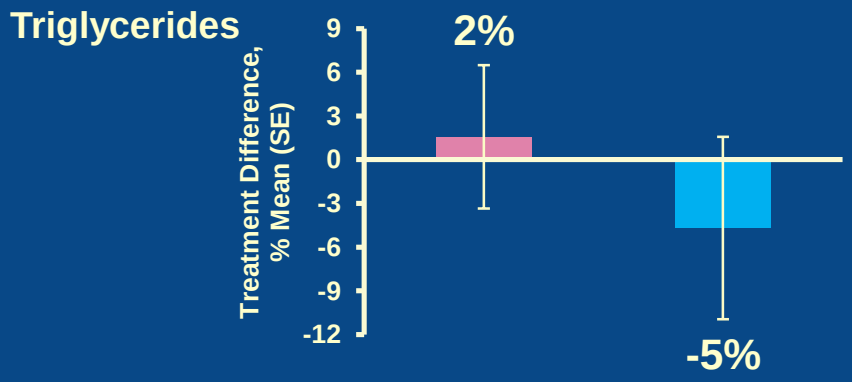
GAUSS-2: LDL-C lowering efficacy
Clinically equivalent between dosing groups

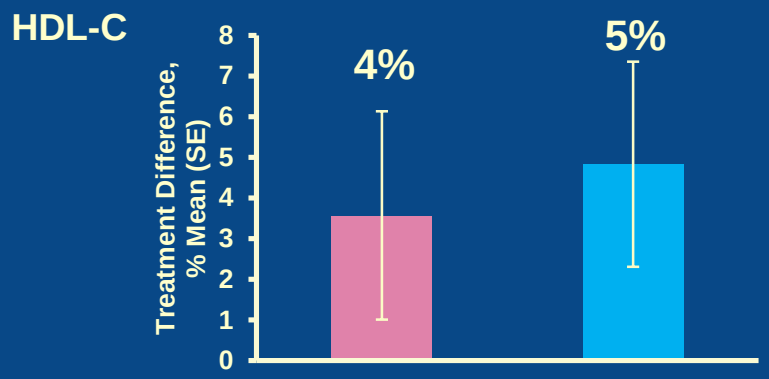
Evolocumab Biweekly			
Treatment Difference *vs* Ezetimibe	**Average at weeks 10 and 12**	**–37%**	***P* < 0.001**
	At week 12	**–38%**	
Evolocumab Monthly			
Treatment Difference *vs* Ezetimibe	**Average at weeks 10 and 12**	**–39%**	***P* < 0.001**
	At week 12	**–38%**	

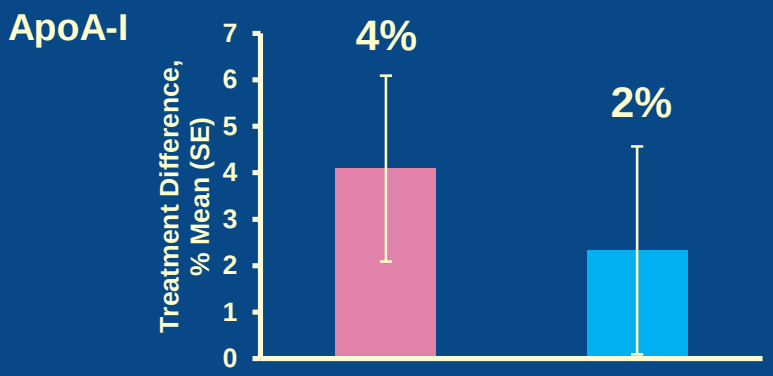
GAUSS-2: Secondary Endpoints at Week 12











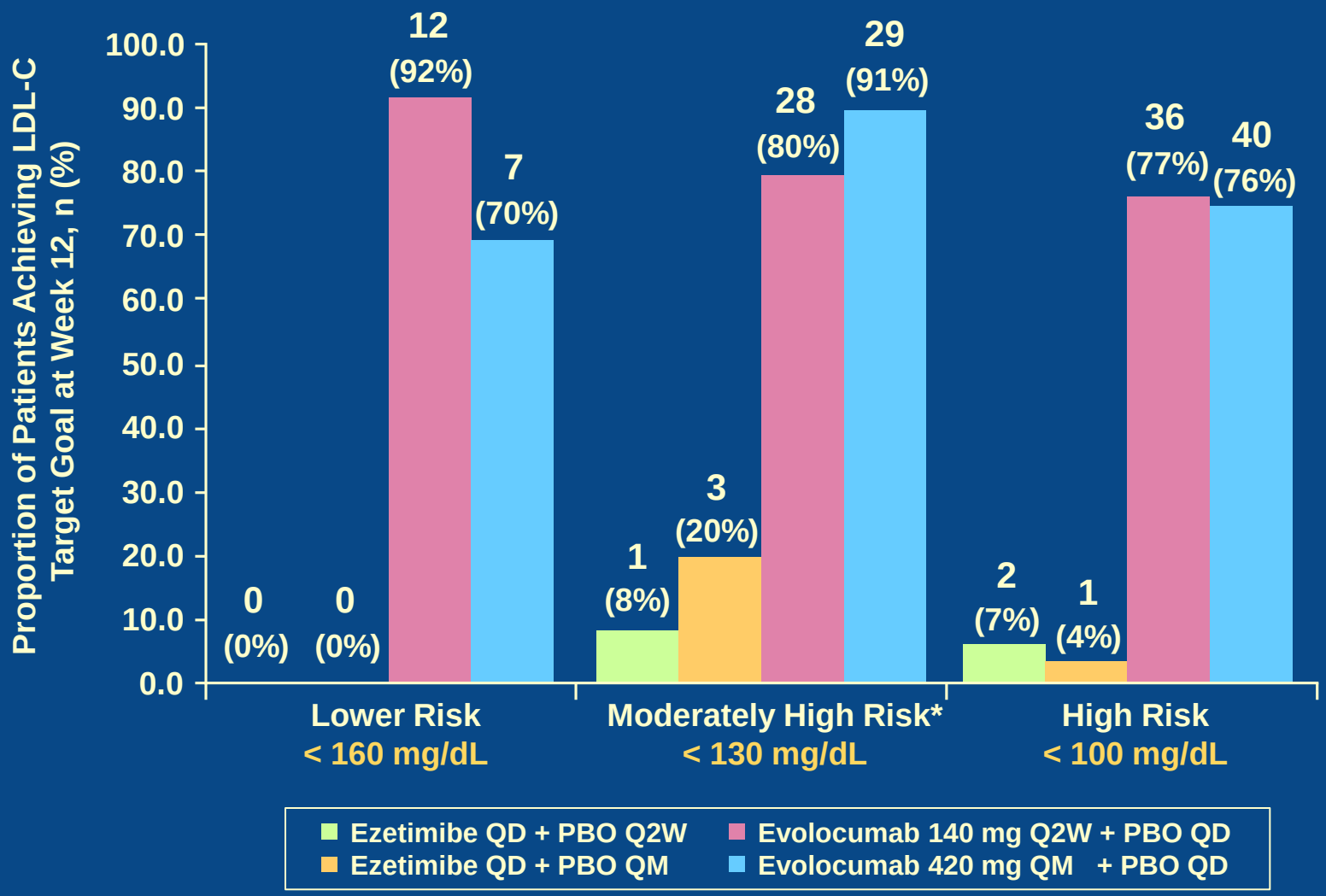
Evolocumab 140 mg Q2W vs ezetimibe

Evolocumab 420 mg QM vs ezetimibe

Treatment difference vs ezetimibe:
*$P < 0.001$; P value adjusted for multiplicity.

No notable difference in results for average at weeks 10 and 12 and week 12

GAUSS-2: LDL-C Goal Achievement at Week 12



*Combination of NCEP ATP III moderate and moderately-high risk categories
Rate based on subjects with observed values at Week 12 and LDL-C above target goal at baseline

GAUSS-2: Safety and Tolerability

Adverse Events (AEs), n(%)	Ezetimibe (N = 102)	Evolocumab (N = 205)
Treatment-emergent AEs	74 (73)	135 (66)
Common treatment-emergent AEs (≥5% of patients in either treatment arm)		
Headache	9 (9)	16 (8)
Myalgia	**18 (18)**	**16 (8)**
Extremity pain	1 (1)	14 (7)
Muscle spasms	4 (4)	13 (6)
Fatigue	10 (10)	9 (4)
Nausea	7 (7)	9 (4)
Diarrhea	7 (7)	5 (2)
Paresthesia	5 (5)	2 (1)
Serious AEs	4 (4)	6 (3)
AEs leading to study drug discontinuation	13 (13)	17 (8)
Deaths	0	0
Potential injection site reactions*	8 (8)	6 (3)
Muscle-related SMQ†	23 (23)	25 (12)
Neurocognitive AEs††	0	0
Anti-evolocumab antibodies‡	-	0

*Reported using high-level term grouping, including IS - rash, inflammation, pruritus, reaction, urticaria. †Standard MedDRA Queries. ††Searched HLGT terms: Deliria (incl confusion); Cognitive and attention disorders and disturbances; dementia and amnestic conditions; disturbances in thinking and perception; mental impairment disorders. ‡Binding or neutralizing; data missing for one patient.

GAUSS-2: Conclusions

- Evolocumab, administered biweekly (140 mg) or monthly (420 mg), yields a potent reduction in LDL-C after 12 weeks in patients with statin intolerance to at least 2 statins.
  - LDL-C reductions are clinically equivalent with biweekly and monthly dosing regimens.
- Evolocumab biweekly (140 mg) or monthly (420 mg) is superior to ezetimibe in lowering LDL-C, ApoB, and Lp(a).
- Evolocumab is well tolerated with low rates of muscle symptoms in this 12-week study in patients intolerant to ≥ 2 statins due to muscle-related side effects.
- The LDL-C lowering efficacy combined with good tolerability make evolocumab a promising option to address the *unmet* clinical need in high-risk hypercholesterolemic patients with statin intolerance.

JACC
Journal of the American College of Cardiology

Anti-PCSK9 Antibody Effectively Lowers Cholesterol in Patients with Statin Intolerance: The GAUSS-2 Randomized, Placebo-controlled Phase 3 Clinical Trial of Evolocumab

Erik Stroes, MD, PhD, David Colquhoun, MD, David Sullivan, MD, Fernando Civeira, MD, Robert S. Rosenson, MD, Gerald F. Watts, DSc, PhD, DM, Eric Bruckert, MD, Leslie Cho, MD, Ricardo Dent, MD, Beat Knusel, PhD, Allen Xue, PhD, Rob Scott, MD, Scott M. Wasserman, MD, Michael Rocco, MD for the GAUSS-2 Investigators

***JACC* 2014: online first.**
Available online at http://content.onlinejacc.org/

Thank you to our investigators and coordinators, data safety committee members, clinical endpoint committee members, core laboratories, operational teams, monitors, and sponsor