Нови терапевтични възможности за редукция на LDL-C Програма PROFICIO с Evolocumab

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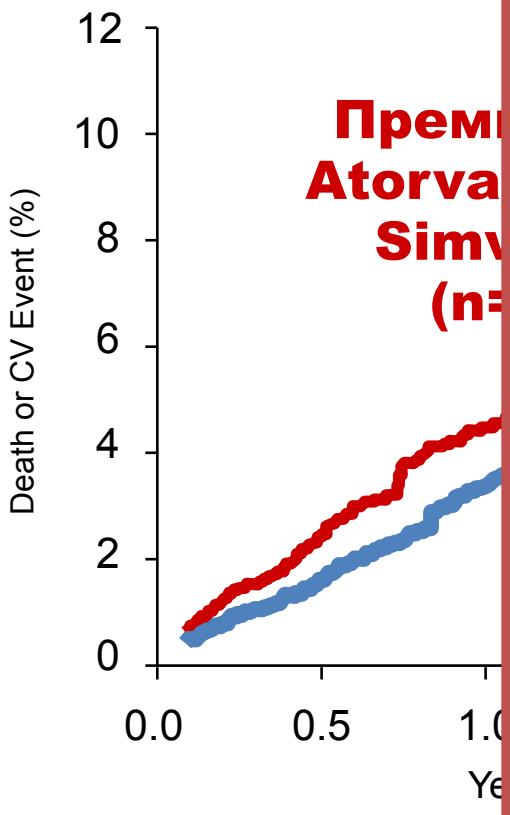
Национална кардиологична болница

UK Switching Study: преминаване от Atorvastatin към Simvastatin



Преми
Atorva
Simv
(n=

33%

Повишена смъртност или СС събития
(P=0.007)

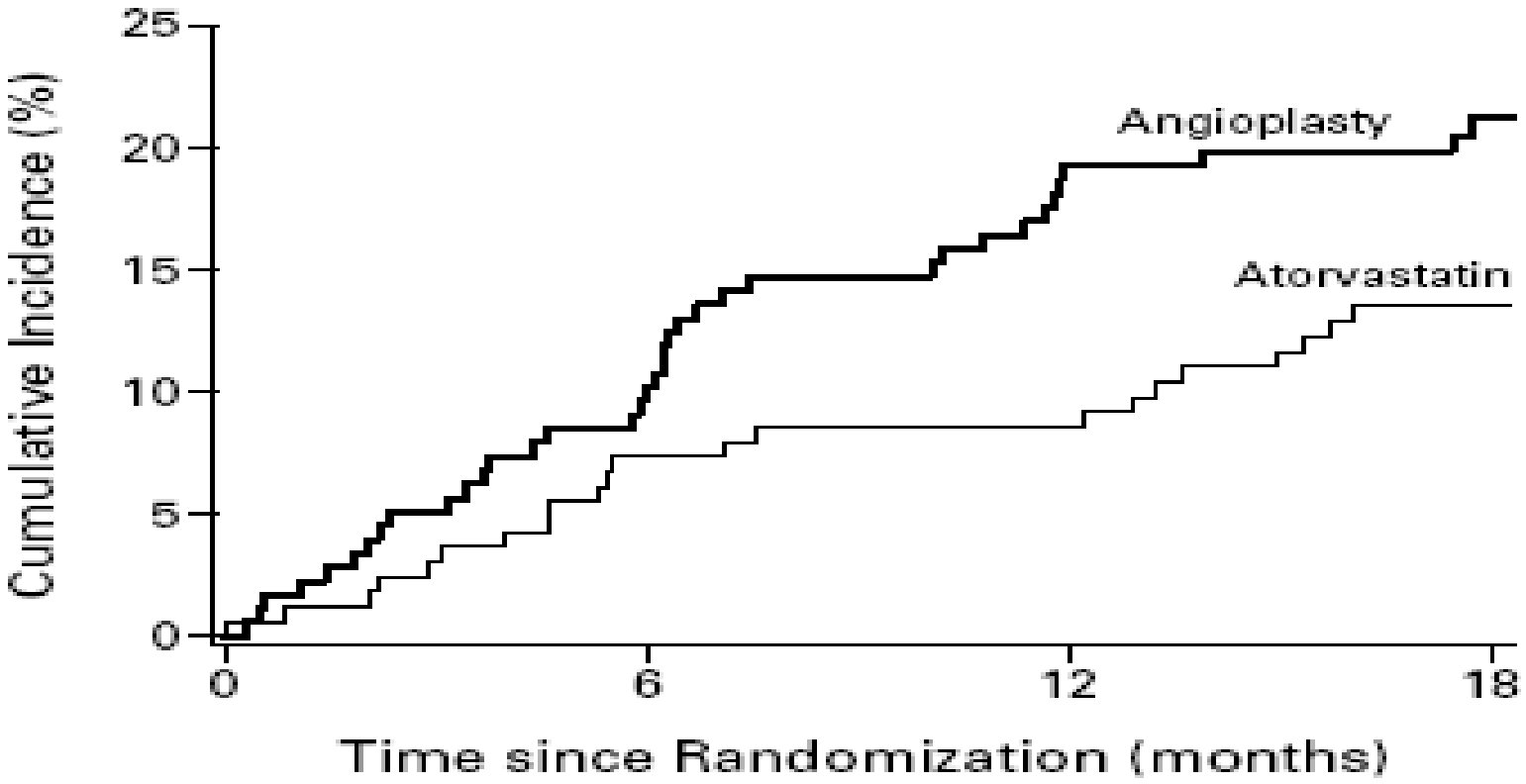
Първична крайна цел: време до смърт или първо голямо СС събитие (МИ, инсулт и реваскуларизация)

on
Sep 1-5, 2007

PHILLIPS B, et al. Poster accepted for presentation at the European Society of Cardiology Congress, Sep 1-5, 2007

Агресивната липидопонижаваща терапия е толкова ефективна колкото ангиопластиката

AVERT

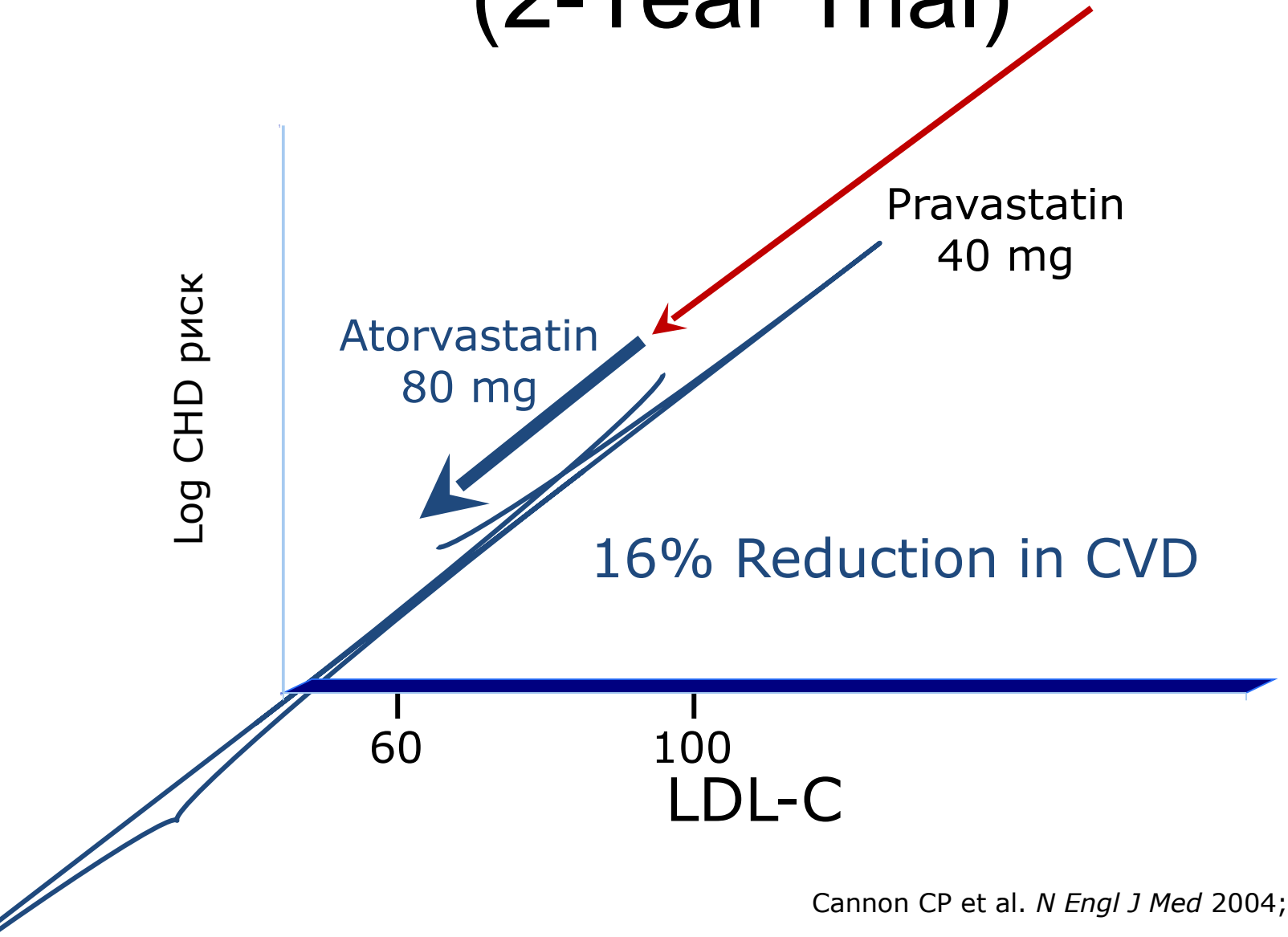


Лечението с atorvastatin, сравнено с ангиопластика, е свързано със значимо удължаване на времето до първото исхемично събитие и с редукция на риска от

36%

Pitt B.et al. AGGRESSIVE LIPID-LOWERING THERAPY COMPARED WITH ANGIOPLASTY IN STABLE CORONARY ARTERY DISEASE. // New Engl. J. Med. 1999;341:70-76.

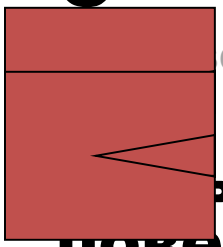
PROVE IT–TIMI 22 (2-Year Trial)



Cannon CP et al. *N Engl J Med* 2004;350:1495-1504.

PCSK9 *(proprotein convertase subtilisin/kexin type 9)*

Ензим свързан с плазмения LDL – С



ed in the liver, intestine and kidney)

ъхекспресията на ген за PCSK9 повече PCSK9 LDL-рецепт намаление (LDL-R неспособен за намали LDL-С) **повишен цркулиращ LDL-С**

Високи нива на PCSK9 = висок LDL-С

Conversely, lacking *Pcsk9 leads to* increased levels of hepatic LDL

receptors,and they remove LDL from the plasma at an accelerated rate)

1.Brown, M.S.,Science, Vol 311, March 24, 2006

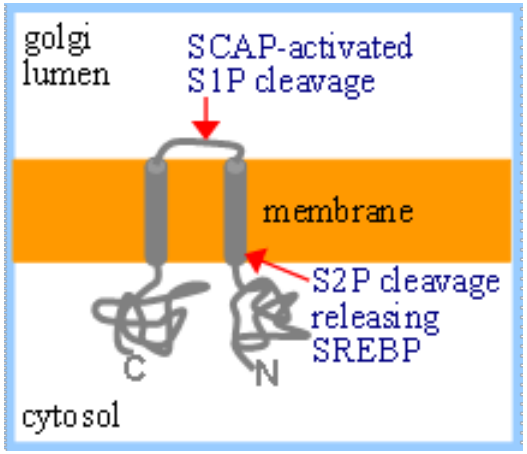
Ниски нива на PCSK9 = нисък LDL-С

2. Cohen J.C. et al, New England Journal of Medicine, Volume 354, 2006 Number 12

LDL-рецепторен път
SREBP Pathway

Michael BROWN

LDL-receptor

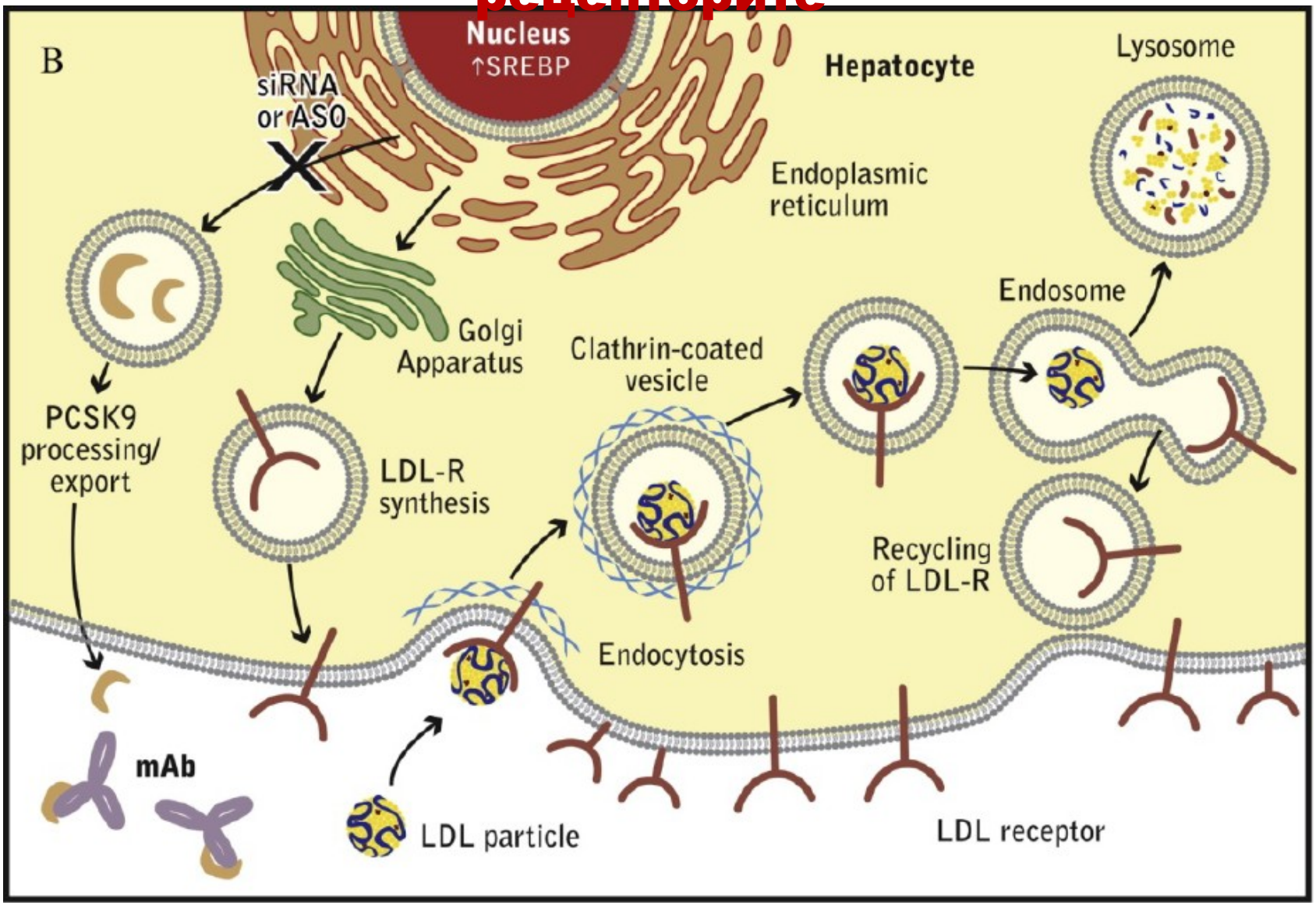


SREBP

Joseph GOLDSTEIN

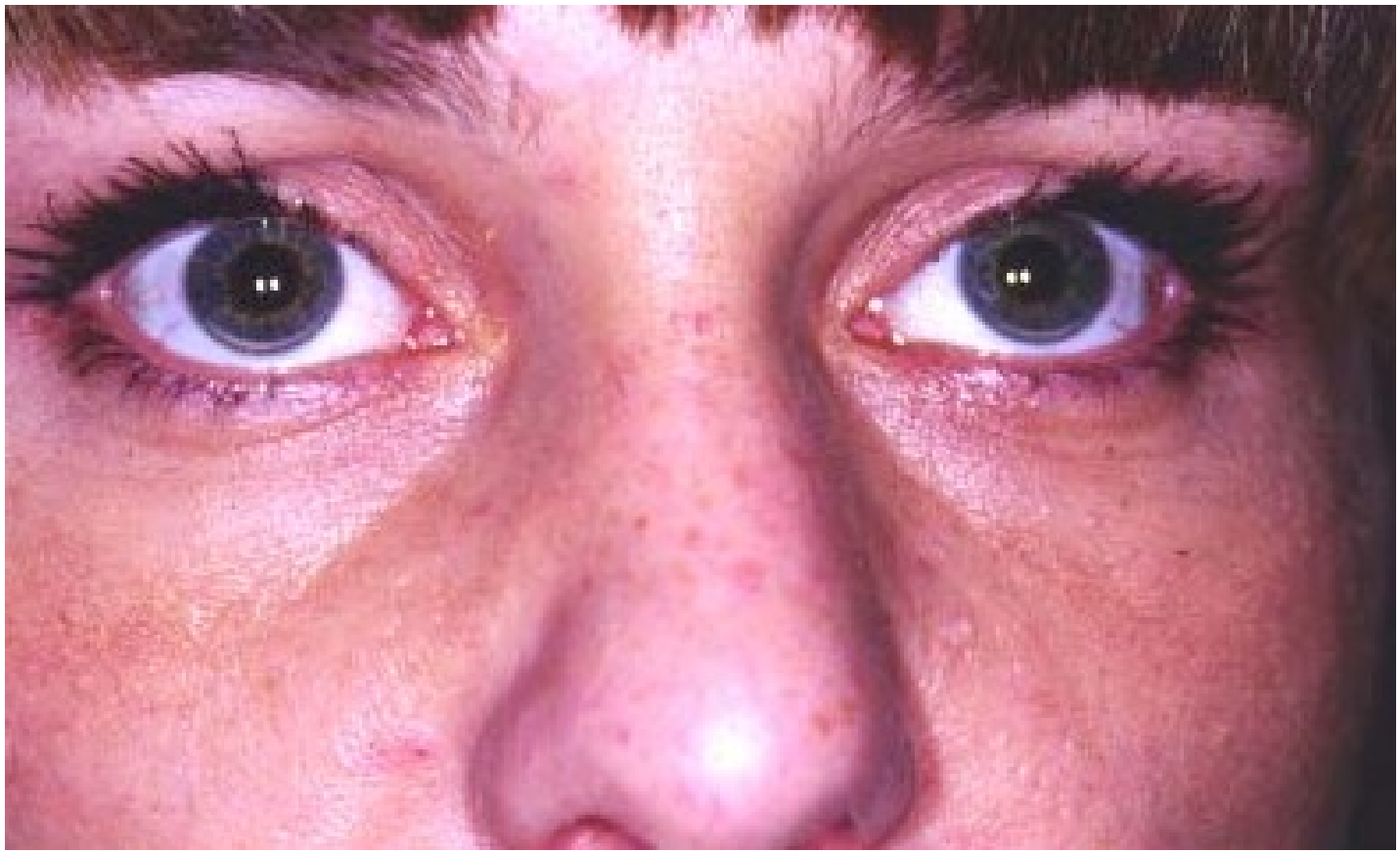
Nobel Prize 1985

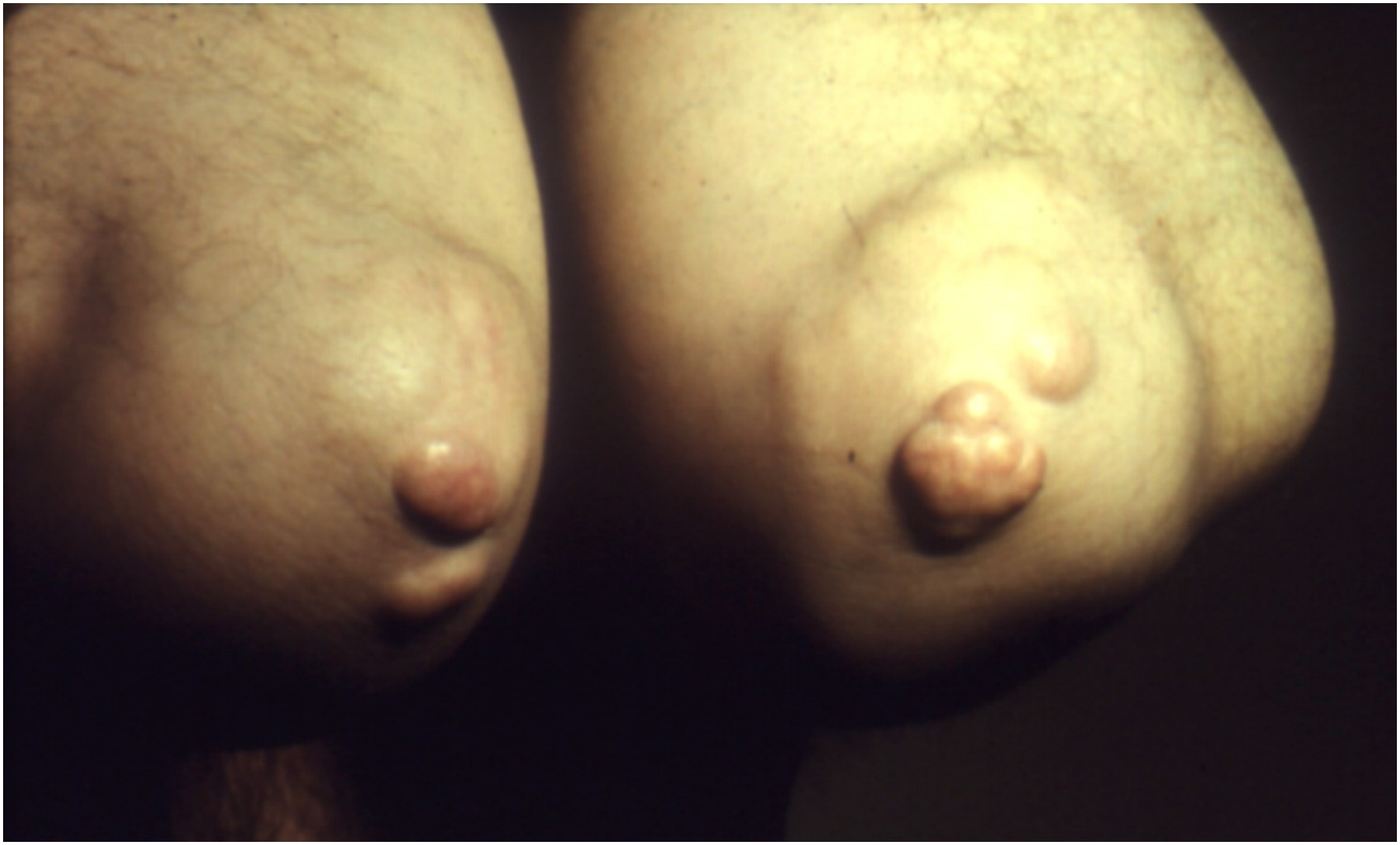
Роля на PCSK9 в регулацията на LDL-рецепторите



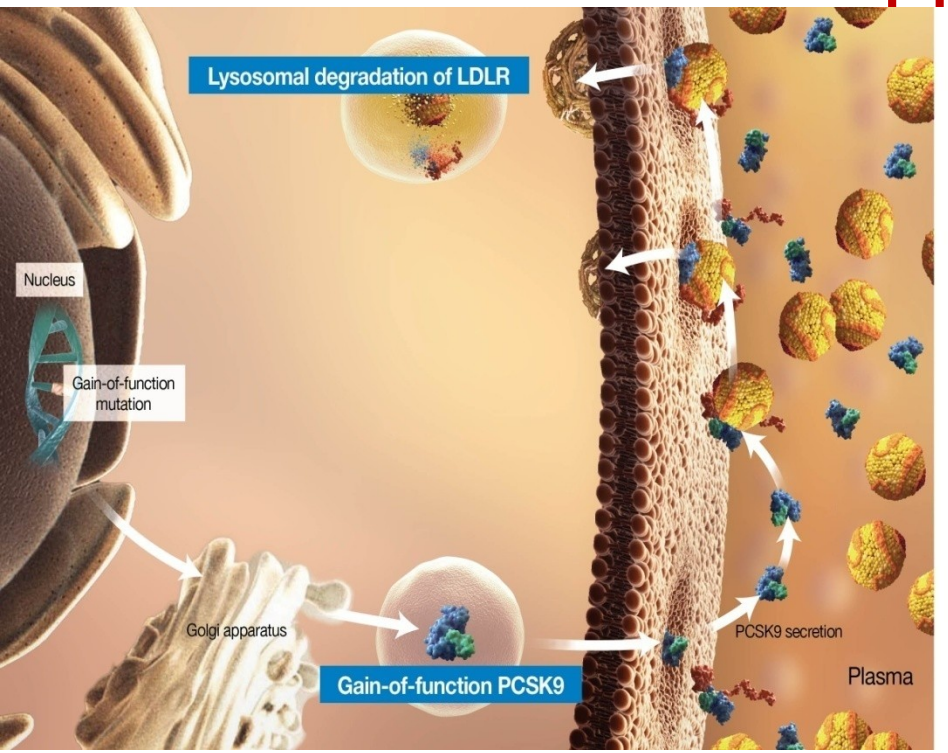
Catapano AL et al.; Atherosclerosis 2013; 228: 18-28

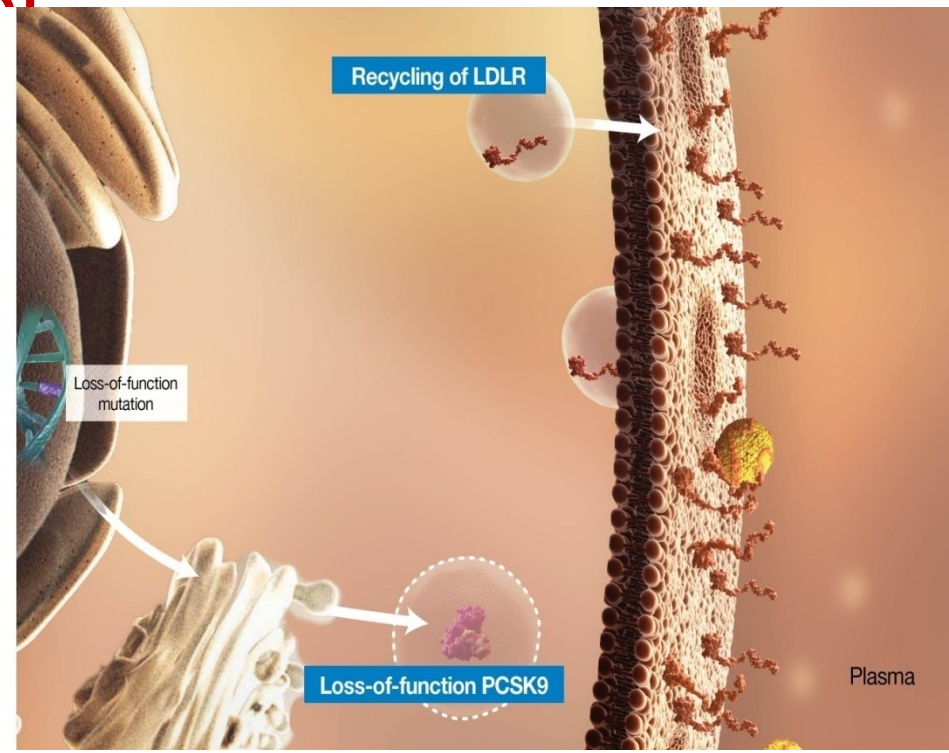
Фамилна хиперхолестеролемия, LDL-C 8,2mmol/l (Ж 27 г.)





Генетични вариации на PCSK9 сочат неговата роля в регулацията на нивата на LDL





PCSK9 Gain of Function (GOF) = <u>Less</u> LDL-Rs1,3,5

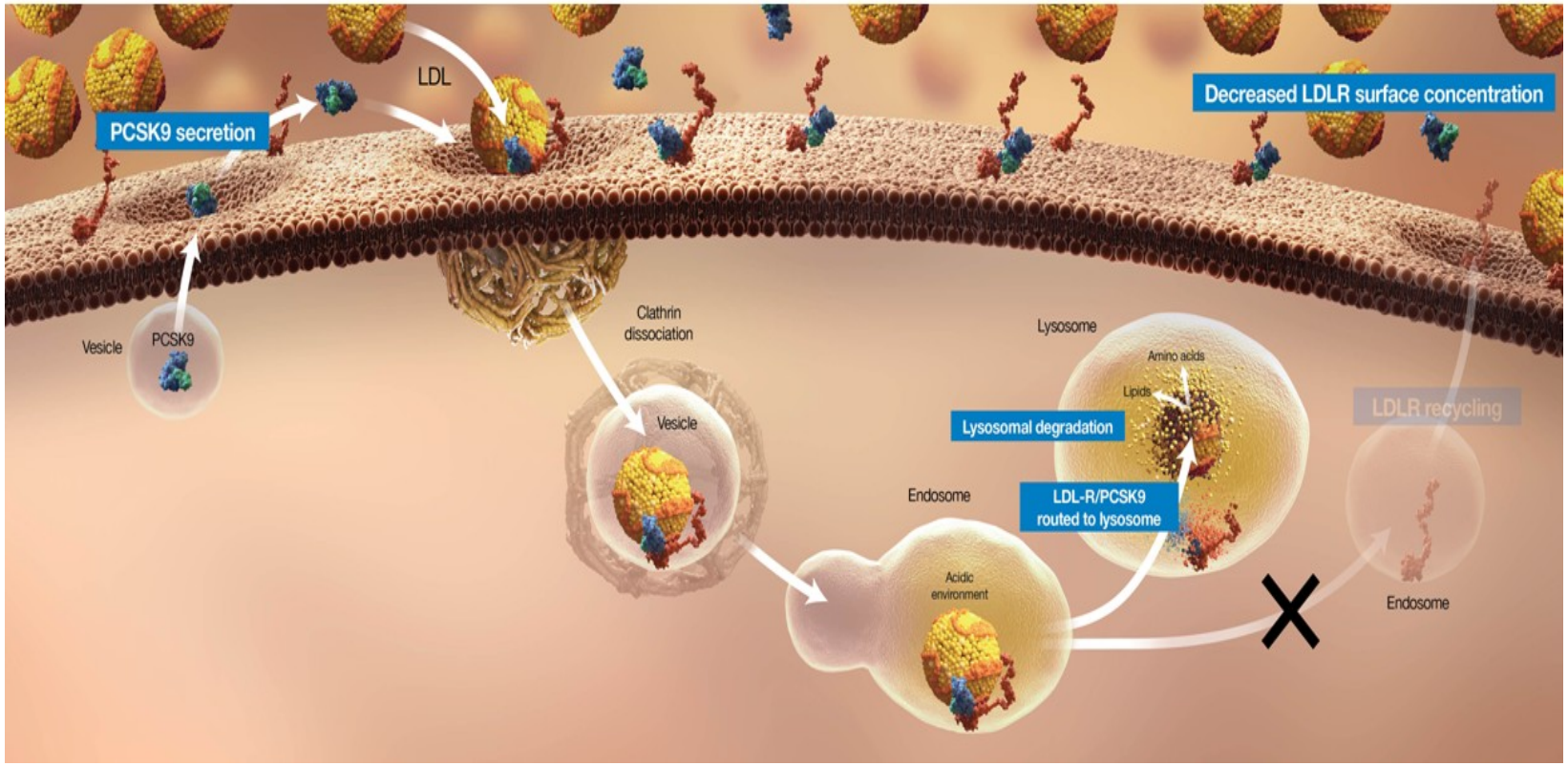
PCSK9 Loss of Function (LOF) = <u>More</u> LDL-Rs2,4,5

- Mutations in the human PCSK9 gene that lead to a loss of PCSK9 function are found in 1% to 3% of the population6,7

1. Horton JD, et al. *J Lipid Res*. 2009;50:S172-S177. **2.** Lakoski SG, et al. *J Clin Endocrinol Metab.* 2009;94: 2537-2543. **3.** Abifadel M, et al. *Hum Mutat.* 2009;30:520-529. **4.** Cohen J, et al. *Nat Genet.* 2005;37:161-165. **5.** Steinberg D, et al. *PNAS*. 2009;106:9546-9547. **6.** Cohen JC, et al. *N Engl J Med*. 2006;354:1264-1272. **7.** Benn M, et al. *J Am Coll Cardiol*. 2010;55:2833-2842.

PCSK9 Is a Key Regulator of LDL-R Recycling

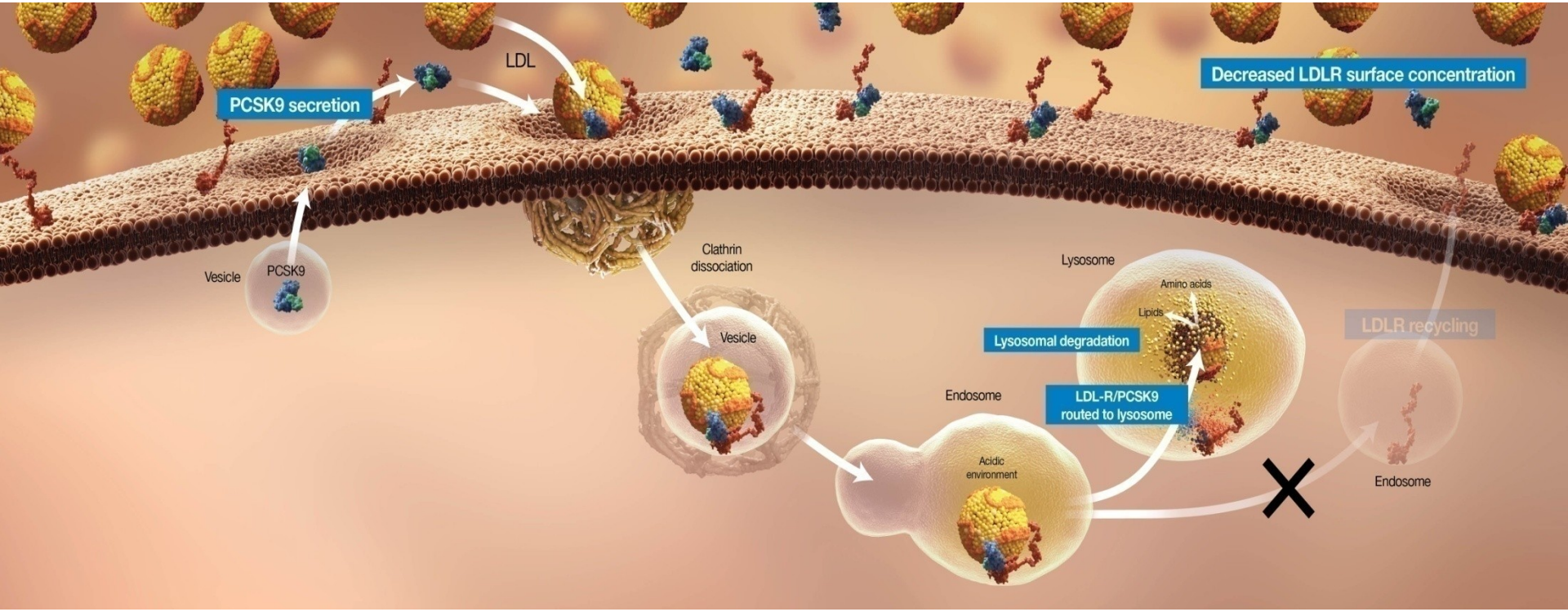
- PCSK9 mediates degradation of the LDL-R by interacting with the extracellular domain and targeting the receptor for degradation1



LDL = low-density lipoprotein.

1. Horton JD, et al. *J Lipid Res*. 2009;50:S172-S177. **2.** Qian YW, et al. *J Lipid Res.* 2007;48:1488-1498.
3. Zhang DW, et al. *J Biol Chem.* 2007;282:18602-18612.

PCSK9 регулира повърхностната експресия на LDLRs чрез повлияване на лизозомната деградация



AMG 145, човешко моноклонално антитяло, което се свързва с PCSK9, е добре поносимо и намалява LDL във фаза Ia и Ib

(Dias CS, JACC published online Oct 17, 2012. http://dx.doi.org/10.1016/j.jacc.2012.08.986)

Brown MS, et al. *Proc Natl Acad Sci U S A*. 1979;76:3330-3337.
Steinberg D, et al. *Proc Natl Acad Sci U S A*. 2009;106:9546-9547.
Goldstein JL, et al. *Arterioscler Thromb Vasc Biol*. 2009;29:431-438.

Qian YW, et al. *J Lipid Res*. 2007;48:1488-1498.
Horton JD, et al. *J Lipid Res*. 2009;50:S172-S177.
Zhang DW, et al. *J Biol Chem*. 2007;282:18602-18612.

The Role of PCSK9 in the Regulation of LDL Cholesterol

AMGEN®

Cardiovascular

PCSK9 инхибитори

молекула	Разработено от	Описание	Клинична фаза
Alirocumab	Regeneron/Sanofi	Човешко IgG1 mAb	Phase 3
Evolocumab	Amgen	Човешко IgG1 mAb	Phase 3
Bococizumab	Pfizer	Хуманизирано IgG1 mAb	Phase 3
RG-7652	Roche	mAb	Phase 3
LY3015014	Eli Lilly	mAb	Phase 2a
ALN-PCS02	Alnylam	RNA interference therapeutic	Phase 1

mAb = monoclonal antibody

Sheridan C. ***Nature Biotechnology.*** **December 12, 2013; V31:1058.**

Фаза I клинични проучвания с PCSK9 инхибитори

Table 1 | Phase I clinical trials of PCSK9 inhibitors

Type of agent	Name	Company	Duration (days)	Change from baseline (%)				
				LDL-C	Lp(a)	apoB	HDL-C	Tg
Small interfering RNA[63]	ALN-PCS	Alnylam (USA)	NA	–41	NA	NA	None	NA
Antibody[64]	Alirocumab	Sanofi (USA) and Regeneron Pharmaceuticals (USA)	64	–61	–27	–48	+18	–16
Antibody[65]	Evolocumab	Amgen (USA)	60	–81	–50	–59	None	None
Antibody[66–70]	Bococizumab	Pfizer (USA)	NR*	NR*	NR*	NR*	NR*	NR*
Antibody[71–73]	LY3015014	Lilly (USA)	NR	NR	NR	NR	NR	NR

*Results reported in abstract form.[60,74] Abbreviations: apoB, apolipoprotein B; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; Lp(a), lipoprotein(a); NA, not available; NR, trial completed, but data not yet published in a peer-reviewed journal; Tg, triglyceride.

Dadu, R. T. & Ballantyne, C. M. (2014) Lipid lowering with PCSK9 inhibitors
Nat. Rev. Cardiol. doi:10.1038/nrcardio.2014.84

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Фаза II клинични проучвания моноклонални антитела срещу

Table 2 | Phase II clinical trials of monoclonal antibodies against PCSK9

Study	PCSK9 inhibitor	Population; *n*	Treatment groups	Change versus placebo (LSM%)*			
				LDL-C	Lp(a)	HDL-C	Tg
McKenney *et al.*[76]	Alirocumab	LDL-C level ≥100 mg/dl with stable-dose atorvastatin; 183	50 mg, 100 mg, or 150 mg every 2 weeks	–34.5 to –67.3	–13.3 to –28.6	+5.1 to +7.7	–15.2 to –28.6
			200 mg or 300 mg every 4 weeks	–38.1 to –42.6	–7.9 to –16.7	+7.3 to +9.5	–18.1 to –20.5
Roth *et al.*[77]	Alirocumab	LDL-C level ≥100 mg/dl with atorvastatin; 92	150 mg every 2 weeks plus atorvastatin 10 mg daily	–48.9	–32.0‡	+6.2	+7.9‡
			150 mg every 2 weeks plus atorvastatin 80 mg daily	–55.9	–28.2‡	+9.4	–12.8‡
Stein *et al.*[78,79]	Alirocumab	LDL-C level ≥100 mg/dl with a statin, with or without ezetimibe; 77	150 mg every 2 weeks	–57.2	–19.5‡	+10.1	–5.7‡
			150 mg, 200 mg, or 300 mg every 4 weeks	–18.2 to –31.5	–3.5 to –11.4‡	+4.3 to +7.8	–6.2 to +5.6‡
LAPLACE–TIMI 57 trial[80]	Evolocumab	LDL-C level ≥85 mg/dl with a statin, with or without ezetimibe; 631	70 mg, 105 mg, or 140 mg every 2 weeks	–41.8 to –66.1	NA	+6.6 to +8.1	–18.1 to –33.7
			280 mg, 350 mg, or 420 mg every 4 weeks	–41.8 to –50.3	NA	+1.6 to +5.5	–13.4 to –19.4
MENDEL trial[81]	Evolocumab	LDL-C level ≥100 mg/dl and ≤190 mg/dl without lipid-lowering therapy; 406	70 mg, 105 mg, or 140 mg every 2 weeks	–37.3 to –47.2	–11.1 to –29.3	+4.2 to +10.2	–7.4 to –12.0
			280 mg, 350 mg, or 420 mg every 4 weeks	–43.6 to –52.5	–21.6 to –29.2	+3.3 to +5.8	–1.7 to –5.3
RUTHERFORD trial[82]	Evolocumab	Heterozygous FH, LDL-C level ≥100 mg/dl with a statin, with or without ezetimibe; 167	350 mg every 4 weeks	–43.8	–23.1	+7.8	–15.0
			420 mg every 4 weeks	–56.4	–31.5	+6.8	–19.9
GAUSS trial[83]	Evolocumab	Statin intolerant (no statin therapy), LDL-C level >ATP III target; 236	280 mg, 350 mg, or 420 mg every 4 weeks	–26.0 to –35.9	–12.4 to –18.0	+6.6 to +8.5	–8.7 to –13.8
			420 mg every 4 weeks plus ezetimibe 10 mg daily	–47.3	–21.2	+13.1	–4.0

Phase II studies of bococizumab have been completed,[86–88] and presented in abstract form,[85] but full reports have not yet been published in peer-reviewed journals. Phase II studies of LY3015014 are ongoing. *Change versus atorvastatin 80 mg monotherapy in Roth *et al.*; change versus ezetimibe 10 mg monotherapy in GAUSS trial. ‡Median. Abbreviations: ATP III, US National Cholesterol Education Program Adult Treatment Panel III; FH, familial hypercholesterolemia; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; Lp(a), lipoprotein(a); LSM, least-squares mean; NA, not available; Tg, triglyceride.

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Фаза III клинични проучвания с

Table 3 | Phase III clinical trials of alirocumab

Study	Population (background statin therapy)	Purpose	Estimated completion
ODYSSEY MONO[90]	Hypercholesterolaemia (with or without statin therapy)	To demonstrate the reduction in LDL-C level by alirocumab versus ezetimibe, after 24 weeks of treatment	Completed
ODYSSEY ALTERNATIVE[91]	Statin intolerance; primary hypercholesterolaemia (heterozygous FH or non-FH); and moderate, high, or very high CVD risk (no statin therapy)	To evaluate the efficacy and safety of alirocumab versus ezetimibe and versus atorvastatin, after 24 weeks of treatment	May 2014
ODYSSEY OPTIONS I[92]	Hypercholesterolaemia (heterozygous FH or non-FH) not adequately controlled (atorvastatin with or without other lipid-modifying therapy), and high CVD risk	To evaluate the reduction in LDL-C level by alirocumab as an add-on therapy to atorvastatin, versus ezetimibe as an add-on therapy to atorvastatin, versus doubling the atorvastatin dose, and versus switching from atorvastatin to rosuvastatin, after 24 weeks of treatment	May 2014
ODYSSEY OPTIONS II[93]	Hypercholesterolaemia not adequately controlled (rosuvastatin with or without other lipid-modifying therapy), and high CVD risk	To evaluate the reduction in LDL-C level by alirocumab as an add-on therapy to rosuvastatin, versus ezetimibe as an add-on therapy to rosuvastatin, and versus doubling the rosuvastatin dose, after 24 weeks of treatment	April 2014
ODYSSEY COMBO I[94]	Hypercholesterolaemia not adequately controlled (with maximum dose of a statin with or without other lipid-modifying therapy), and high CVD risk	To demonstrate the reduction in LDL-C level by alirocumab versus placebo as an add-on therapy to stable, maximally tolerated daily statin therapy with or without other lipid-modifying therapy, after 24 weeks of treatment	April 2014
ODYSSEY COMBO II[95]	Hypercholesterolaemia not adequately controlled (maximum dose of a statin with or without other lipid-modifying therapy), and high CVD risk	To demonstrate the reduction in LDL-C level by alirocumab versus ezetimibe as an add-on therapy to stable, maximally tolerated daily statin therapy in comparison with ezetimibe, after 24 weeks of treatment	July 2015
ODYSSEY CHOICE 1[96]	Hypercholesterolaemia	To evaluate the efficacy and safety of alirocumab every 4 weeks versus placebo with or without statin therapy, after 24 weeks of treatment	May 2014
ODYSSEY FH I[97]	Heterozygous FH not adequately controlled with current lipid-modifying therapy (no specification regarding statin therapy)	To evaluate the effect of alirocumab versus placebo on LDL-C level after 24 weeks of treatment (including background statin or other lipid-modifying therapy)	December 2014
ODYSSEY FH II[98]	Heterozygous FH not adequately controlled (with maximally tolerated statin with or without other lipid-modifying therapy)	To demonstrate the reduction in LDL-C level by alirocumab versus placebo as an add-on therapy to stable, maximally tolerated daily statin (atorvastatin, rosuvastatin, or simvastatin) therapy, with or without other lipid-modifying therapy, after 24 weeks of treatment	December 2014
ODYSSEY HIGH FH[99]	Heterozygous FH not adequately controlled with current lipid-modifying therapy (no specification regarding statin therapy)	To evaluate the effect of alirocumab versus placebo on LDL-C level after 24 weeks of treatment (including background statin or other lipid-modifying therapy)	January 2015
ODYSSEY LONG TERM[100]	Hypercholesterolaemia not adequately controlled with current lipid-modifying therapy, and high CVD risk (no specification regarding statin therapy)	To evaluate the long-term safety and tolerability of alirocumab versus placebo, after 78 weeks of treatment	October 2014
ODYSSEY OUTCOMES[101]	Recent (in the past 4–16 weeks) acute coronary syndrome event requiring hospitalization	To compare the effect of alirocumab versus placebo on CVD events (cardiovascular death, nonfatal myocardial infarction, fatal and nonfatal ischaemic stroke, unstable angina requiring hospitalization), for up to 64 months	March 2018

Abbreviations: CVD, cardiovascular disease; FH, familial hypercholesterolaemia; LDL-C, LDL cholesterol.

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Фаза III клинични проучвания с

Table 4 | Phase III clinical trials of evolocumab

Study	Population (background statin therapy)	Purpose	Estimated completion
MENDEL-2[102]	Framingham Risk Score ≤10% and LDL-C level ≥100 mg/dl (no specification regarding statin therapy)	To evaluate the safety and efficacy of evolocumab every 2 or 4 weeks versus ezetimibe and versus placebo, at 10 and 12 weeks	Completed
GAUSS-2[103]	Statin intolerance; hypercholesterolaemia (no statin or low-dose statin)	To evaluate the safety and efficacy of evolocumab every 2 or 4 weeks versus ezetimibe, at 10 and 12 weeks	Completed
DESCARTES[104]	LDL-C level ≥85 mg/dl and either at ATP III target with background lipid therapy or taking maximum background lipid therapy (no specification regarding statin therapy)	To evaluate the efficacy, safety, and tolerability of evolocumab every 4 weeks versus placebo, at 52 weeks, when added to assigned background lipid-lowering therapy	Completed
LAPLACE-2[105]	Primary hypercholesterolaemia or mixed dyslipidaemia (taking statin therapy with or without ezetimibe)	To evaluate the safety, tolerability, and efficacy of evolocumab every 2 or 4 weeks plus a statin versus a statin plus ezetimibe, at 10 and 12 weeks	Completed
RUTHERFORD-2[106]	Heterozygous FH and LDL-C level ≥100 mg/dl with statin therapy (no specification regarding statin therapy)	To evaluate the safety, tolerability, and efficacy of evolocumab every 2 or 4 weeks versus placebo, at 10 and 12 weeks	Completed
OSLER-2[107]	Hypercholesterolaemia or mixed dyslipidaemia; completion of previous evolocumab study (no specification regarding statin therapy)	To evaluate the long-term safety, tolerability, and efficacy of evolocumab versus usual care, at 104 weeks	January 2017
GLAGOV[108]	Coronary heart disease; clinical indication for coronary catheterization; and LDL-C level ≥80 mg/dl or, with additional risk factors, ≥60 mg/dl and <80 mg/dl (no specification regarding statin therapy)	To determine the effects of evolocumab every 4 weeks on atherosclerotic disease burden (percent atheroma volume measured by intravascular ultrasonography), at 72 weeks	July 2015
FOURIER[109]	Clinical CVD, high risk of recurrent CVD event, and LDL-C level ≥70 mg/dl or non-HDL-C ≥100 mg/dl (no specification regarding statin therapy)	To assess the effect of evolocumab every 2 or 4 weeks plus a statin versus placebo plus a statin on major CVD events (CVD death, nonfatal myocardial infarction, unstable angina requiring hospitalization, stroke, or coronary revascularization), at 5 years	February 2018
TESLA[110]	Homozygous FH and LDL-C level >130 mg/dl with stable lipid therapy (no specification regarding statin therapy)	To determine the safety, tolerability, and efficacy of evolocumab in patients with homozygous FH, at 12 weeks	February 2014
TAUSSIG[111]	Homozygous FH or *PCSK9* mutations; LDL-C level above ATP III target or receiving apheresis; and completion of previous evolocumab study (no specification regarding statin therapy)	To assess the long-term safety and efficacy of evolocumab every 2 or 4 weeks on LDL-C level in patients with severe FH, at 5 years	January 2020
Study of AMG 145 in high-risk Japanese patients[112]	Japanese, high CVD risk, and hypercholesterolaemia or mixed dyslipidaemia (receiving statin therapy)	To evaluate the efficacy, safety, and tolerability of evolocumab every 2 or 4 weeks plus low-dose or high-dose statin versus placebo plus low-dose or high-dose statin, at 10 and 12 weeks	August 2014

Abbreviations: ATP III, US National Cholesterol Education Program Adult Treatment Panel III; CVD, cardiovascular disease; FH, familial hypercholesterolaemia; LDL-C, LDL cholesterol; non-HDL-C, non-HDL cholesterol.

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Фаза III клинични проучвания с bococizumab

Table 5 | Phase III clinical trials of bococizumab

Study	Population (background statin therapy)	Purpose	Estimated completion
SPIRE-HF[113]	Heterozygous FH; high or very high CVD risk; LDL-C level >70 mg/dl and Tg level ≤400 mg/dl (with statin therapy)	To compare the effect of bococizumab and a statin versus placebo and a statin on LDL-C level in patients with heterozygous FH, at 12 weeks	January 2016
SPIRE-HR[114]	High or very high CVD risk; LDL-C level >70 mg/dl and Tg level ≤400 mg/dl (with statin therapy)	To compare the effect of bococizumab and a statin versusxplacebo and a statin on LDL-C level, at 12 weeks	January 2016
SPIRE-LDL[115]	High or very high CVD risk; LDL-C level >70 mg/dl and Tg level ≤400 mg/dl (with statin therapy)	To compare the effect of bococizumab and a statin versusxplacebo and a statin on LDL-C level, at 12 weeks	December 2015
SPIRE-1[116]	High CVD risk; LDL-C level ≥70 mg/dl and <100 mg/dl, or non-HDL-C level ≥100 mg/dl and <130 mg/dl, with lipid-lowering therapy (no specification regarding statin therapy)	To compare the effect of bococizumab versus placebo on reducing the occurrence of major cardiovascular events, including cardiovascular death, myocardial infarction, stroke, and unstable angina requiring urgent revascularization, at 5 years	August 2017
SPIRE-2[117]	High CVD risk; LDL-C level ≥100 mg/dl or non-HDL-C level ≥130 mg/dl, with lipid-lowering therapy (no specification regarding statin therapy)	To compare the effect of bococizumab versus placebo on reducing the occurrence of major cardiovascular events, including cardiovascular death, myocardial infarction, stroke, and unstable angina requiring urgent revascularization, at 5 years	August 2017

Abbreviations: CVD, cardiovascular disease; FH, familial hypercholesterolaemia; LDL-C, LDL cholesterol; non-HDL-C, non-HDL cholesterol; Tg, triglyceride.

nature REVIEWS CARDIOLOGY

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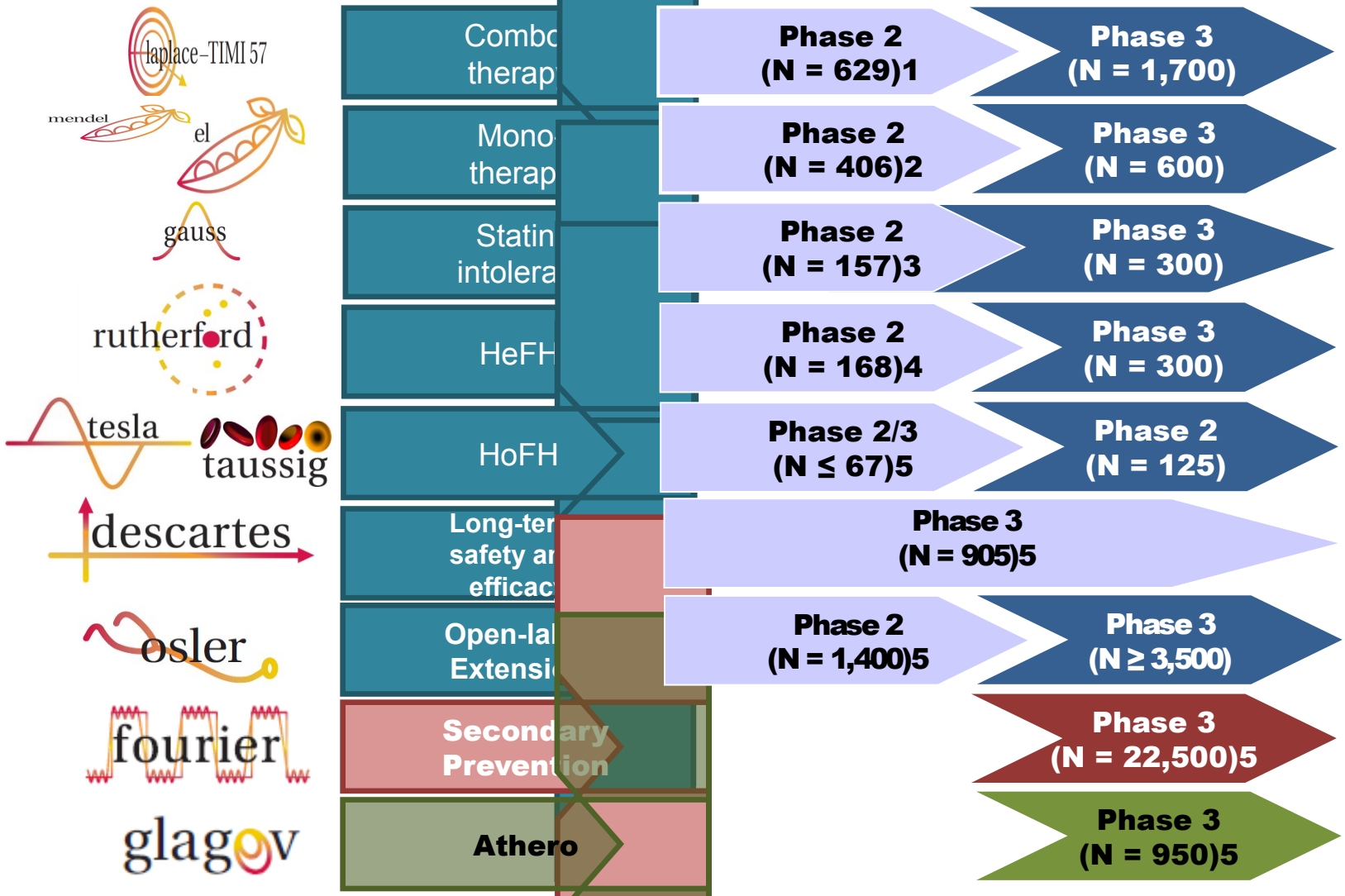
PROFICIO

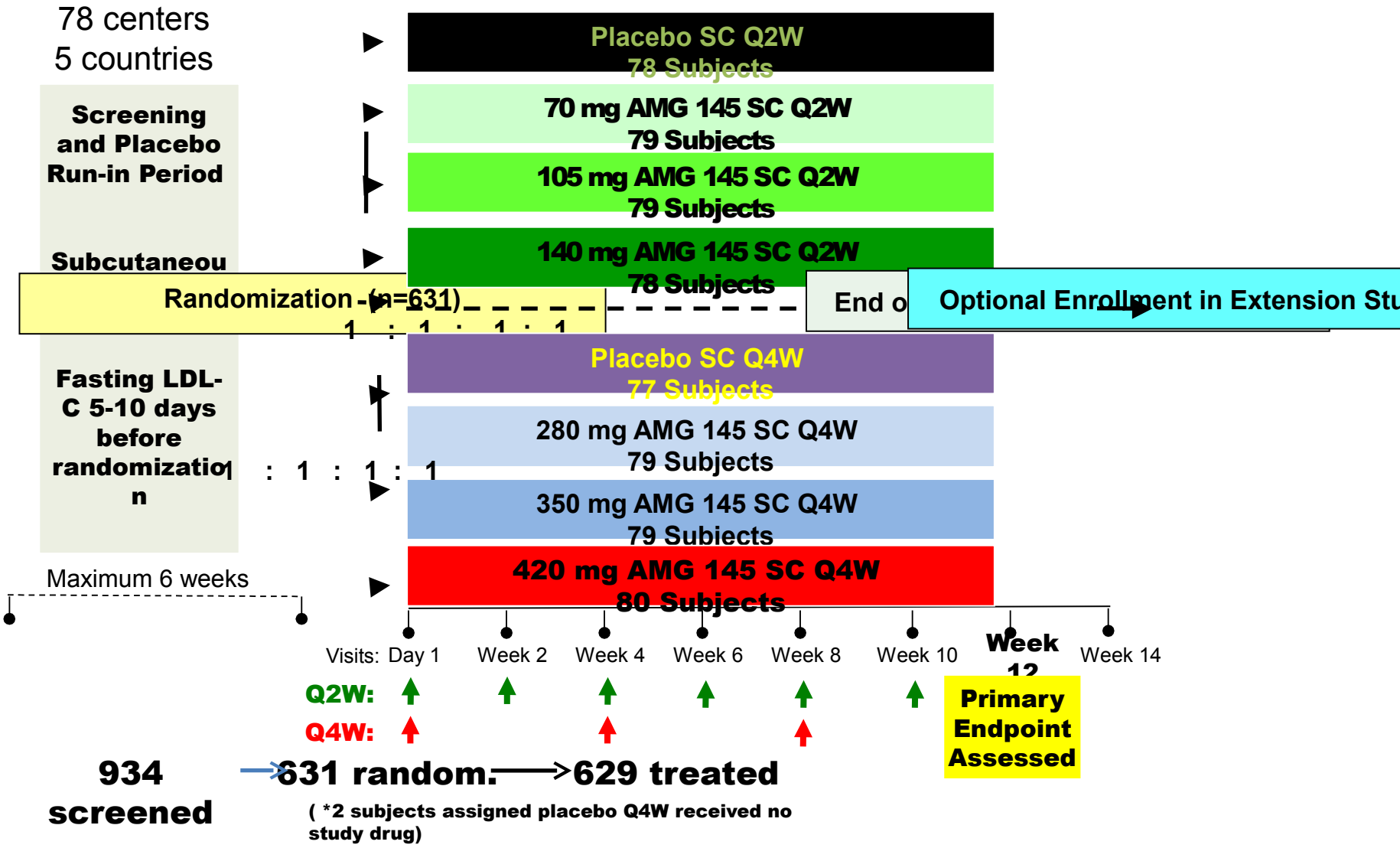
Program to Reduce LDL-C and Cardiovascular Outcomes Following Inhibition of PCSK9 In Different Populations



1. Giugliano RP, et al. *Lancet*. 2012;380:2007-2017. 2. Koren MJ, et al. *Lancet*. 2012:380:1995-2006. 3. Sullivan D, et al. *JAMA*. 2012;308:2497-2506. 4. Raal F, et al. *Circulation*. 2012;126:2408-2417. 5. Clinical Trials.gov. Available at: http://www.clinicaltrials.gov. Accessed April 22, 2013.

Дизайн

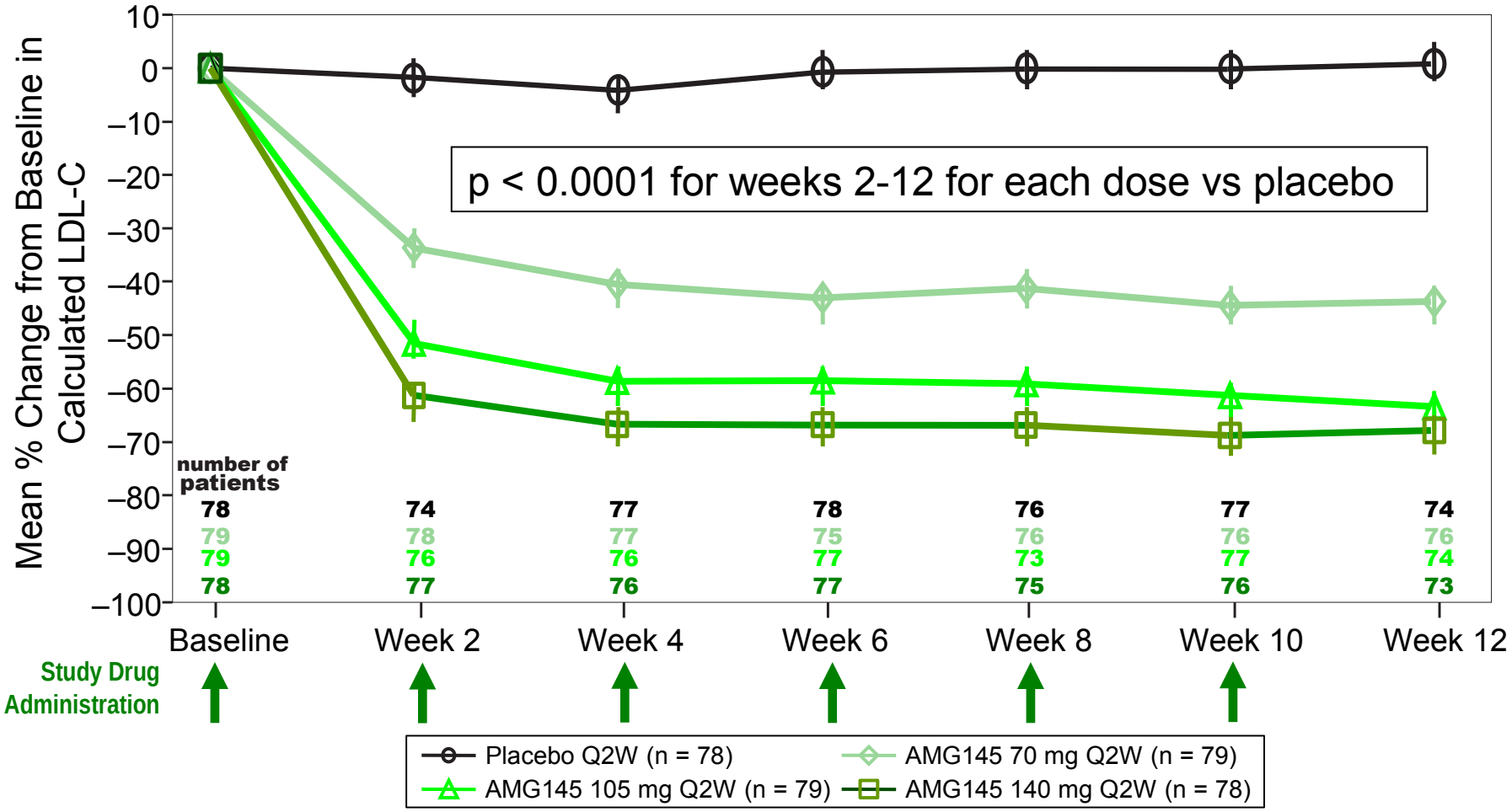
laplace–TIMI 57



Kohli P, et al. *Clin Cardiol*. 2012;35:385-391.

Evolocumab (AMG 145) Q2W отговор:

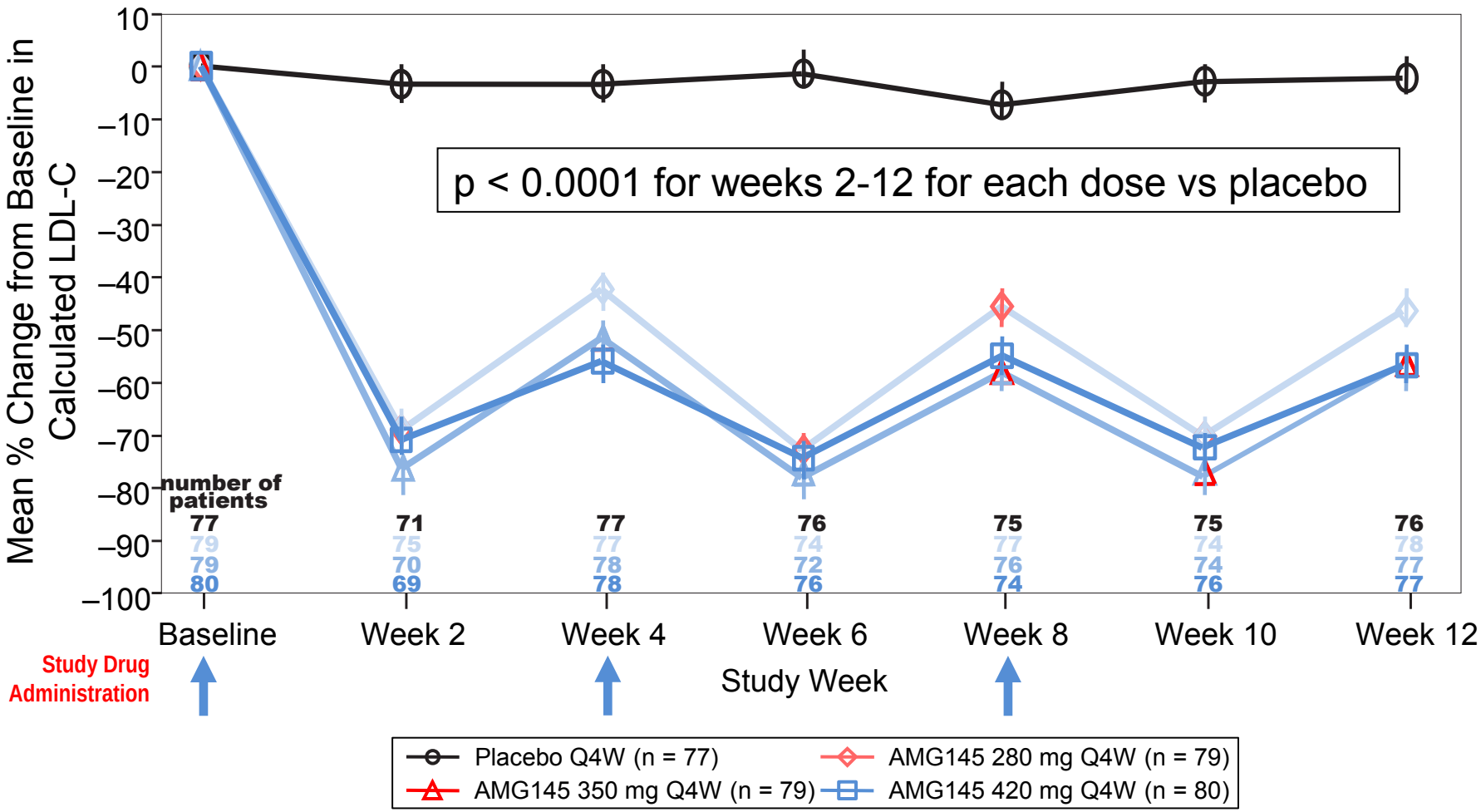
% промяна на LDL-C на 12 седм



LDL-C calculated using the Friedewald equation

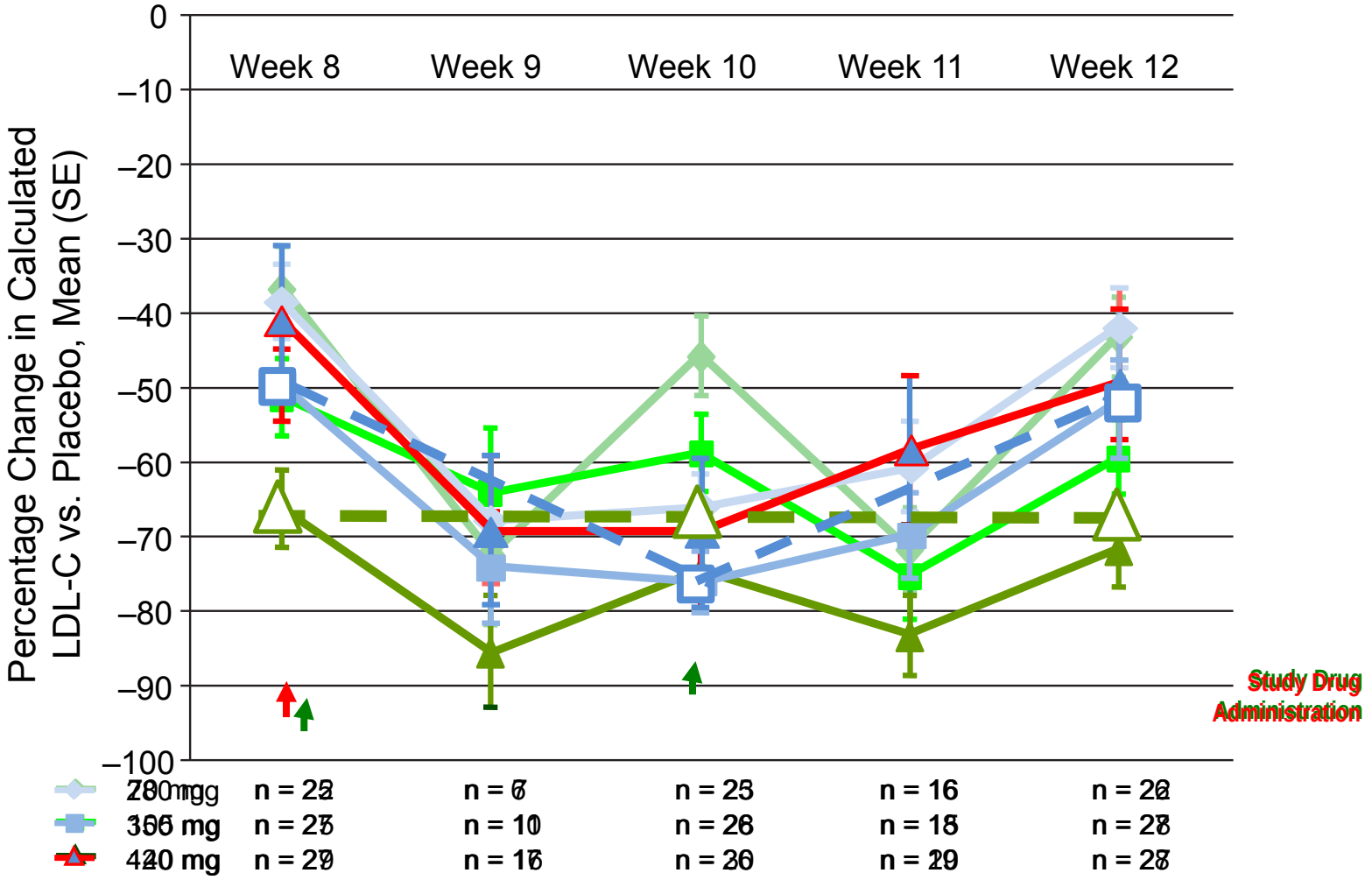
Evolocumab (AMG 145) Q4W отгов
% промяна на LDL-C на 12 седм

laplace–TIMI 57



LDL-C calculated using the Friedewald equation

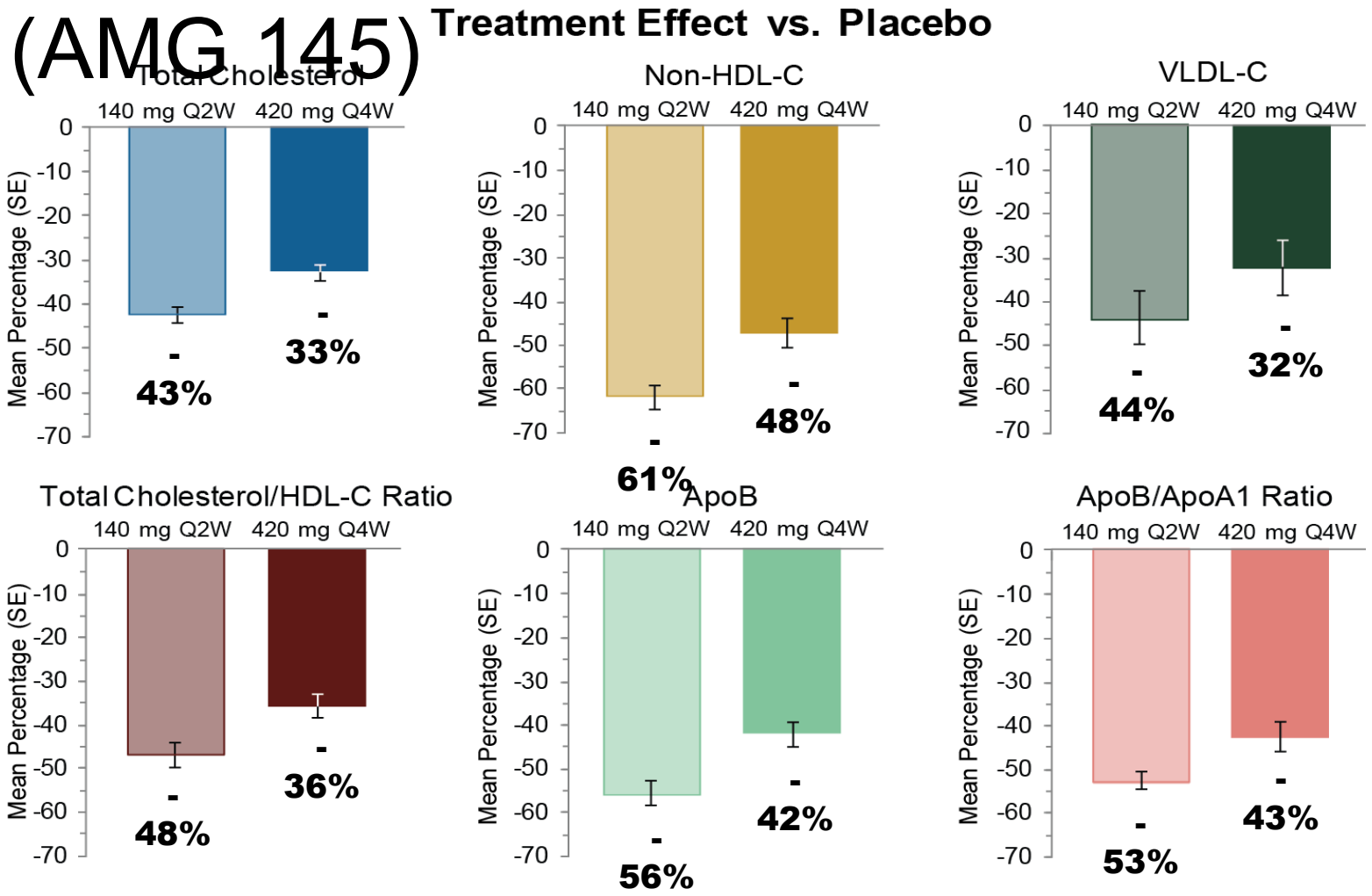
Evolocumab (AMG 145) отговор:
% промяна на LDL-C Wks 8-12 (placebo adjusted)



LDL-C calculated using the Friedewald equation

Вторични резултати на 12 седм с 2 дози Evolocumab (AMG 145)

laplace–TIMI 57



***P* < 0.0001 versus placebo for all parameters**

Q2W, every 2 weeks; Q4W, every 4 weeks; SE, standard error

Безопасност

laplace–TIMI 57

Adverse Events, Patient Incidence, n	Q2W Dose Groups				Q4W Dose Groups				
	Placebo N=78	AMG 145 70 mg N=79	AMG 145 105 mg N=79	AMG 145 140 mg N=78	Placebo N=77	AMG 145 280 mg N=79	AMG 145 350 mg N=79	AMG 145 420 mg N=80	Total N=629
Adverse events	33	41	52	43	38	45	48	48	348
Serious AE	4	0	1	4	0	2	2	2	15
Lead to drug DC	0	0	0	2*	0	0	0	0	2
Drug related AEs	7	4	9	4	4	6	7	9	50†
Lead to drug DC	0	0	0	0	0	0	0	0	0
Injection site rxn	2	1	1	0	1	2	3	1	11
AST or ALT >3x ULN	1	0	0	0	0	0	0	0	1
CPK >5X ULN	0	1	1	1	0	0	0	1	4**
CV events‡	1	1	0	4	0	1	1	0	8
Death	0	0	0	1	0	0	0	0	1

*Both events were reported as non-serious by the investigators.
†All 50 were reported as non-serious by the investigator and none led to discontinuation of drug
** All were asymptomatic ‡Acute coronary syndrome, coronary revascularization, TIA, congestive heart failure requiring hospitalization, or death

THE LANCET

Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-ranging phase 2 study

*Robert P Giugliano, Nihar R Desai, Payal Kohli, William J Rogers, Ransi Somaratne, Fannie Huang, Thomas Liu, Satishkumar Mohanavelu, Elaine B Hoffman, Shannon T McDonald, Timothy E Abrahamsen, Scott M Wasserman, Robert Scott, Marc S Sabatine, for the LAPLACE-TIMI 57 Investigators**

***Lancet* 2012:380 (online first).**
Available on line at www.thelancet.com

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

LAPLACE-2:
A Phase 3, Double-blind, Randomized, Placebo and Ezetimibe Controlled, Multicenter Study to Evaluate Safety, Tolerability and Efficacy of Evolocumab (AMG 145) in Combination With Statin Therapy in Subjects With Primary Hypercholesterolemia and Mixed Dyslipidemia

Jennifer G Robinson, Bettina S Nedergaard, William J Rogers, Jonathan Fialkow, Joel M Neutel, David Ramstad, Ransi Somaratne, Jason C Legg, Patric Nelson, Rob Scott, Scott M Wasserman, and Robert Weiss, *for the LAPLACE-2 Investigators*

LDL-C **A**ssessment with **P**CSK9 Monoclona**L** **A**ntibody Inhibition **C**ombined With Statin Th**E**rapy – 2 (NCT01763866)

30 Mar 2014, Late-breaking Clinical Trials Session 402, American College of Cardiology and JAMA 2014;311:1870–82

Disclaimer: Evolocumab has not been approved for use by the EMA and/or any other regulatory authorities outside of the EU

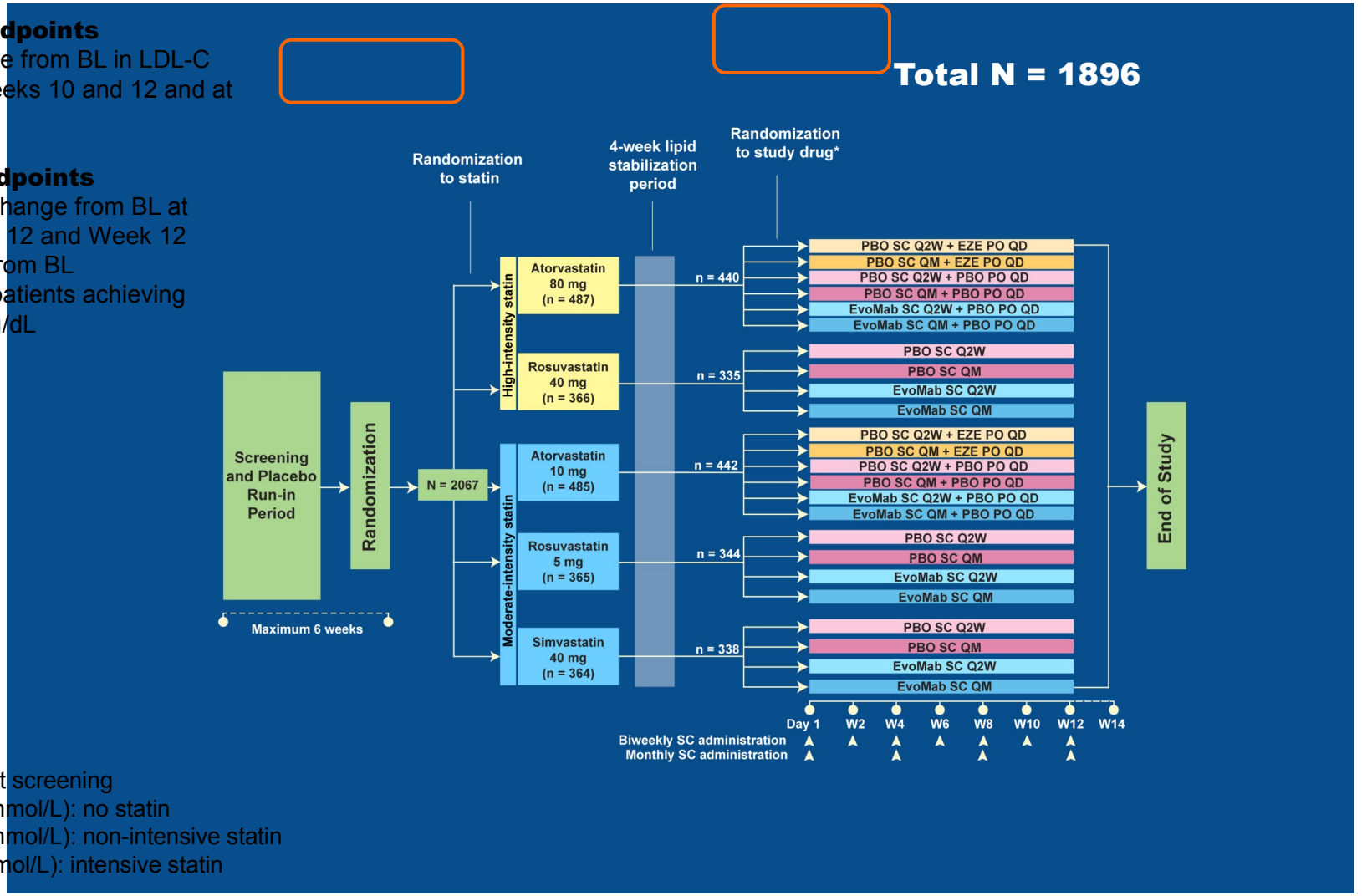
LAPLACE-2: Дизайн

Co-primary endpoints

- Percent change from BL in LDL-C at mean of Weeks 10 and 12 and at Week 12

Secondary endpoints

- Mean LDL-C change from BL at Weeks 10 and 12 and Week 12
- Lipid change from BL
- Proportion of patients achieving LDL-C <70 mg/dL

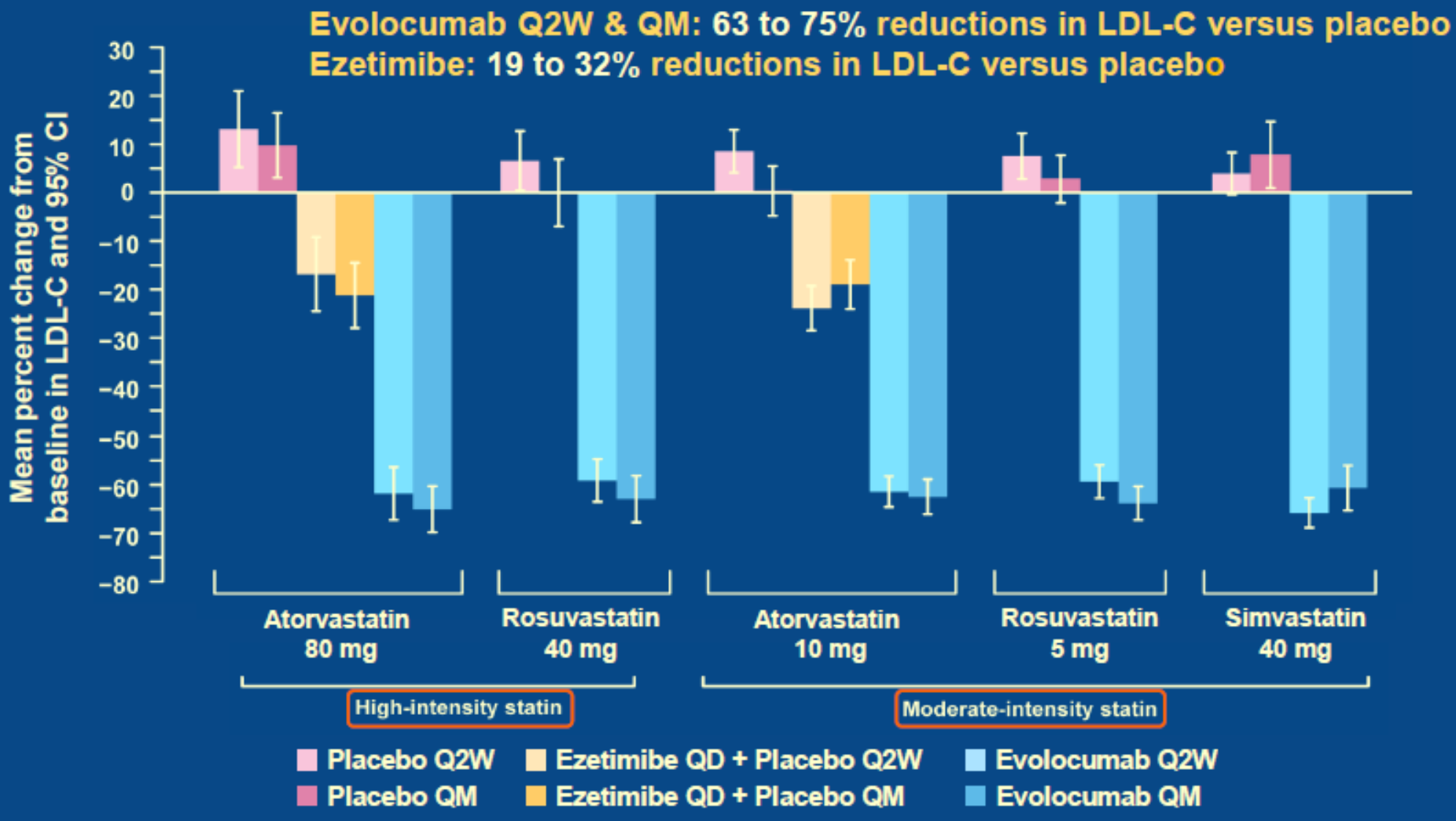


Eligibility: LDL-C at screening
≥150 mg/dL (3.9 mmol/L): no statin
≥100 mg/dL (2.6 mmol/L): non-intensive statin
≥80 mg/dL (2.1 mmol/L): intensive statin

*1896 patients were randomized and received at least one dose of study drug. Three patients did not receive study drug.

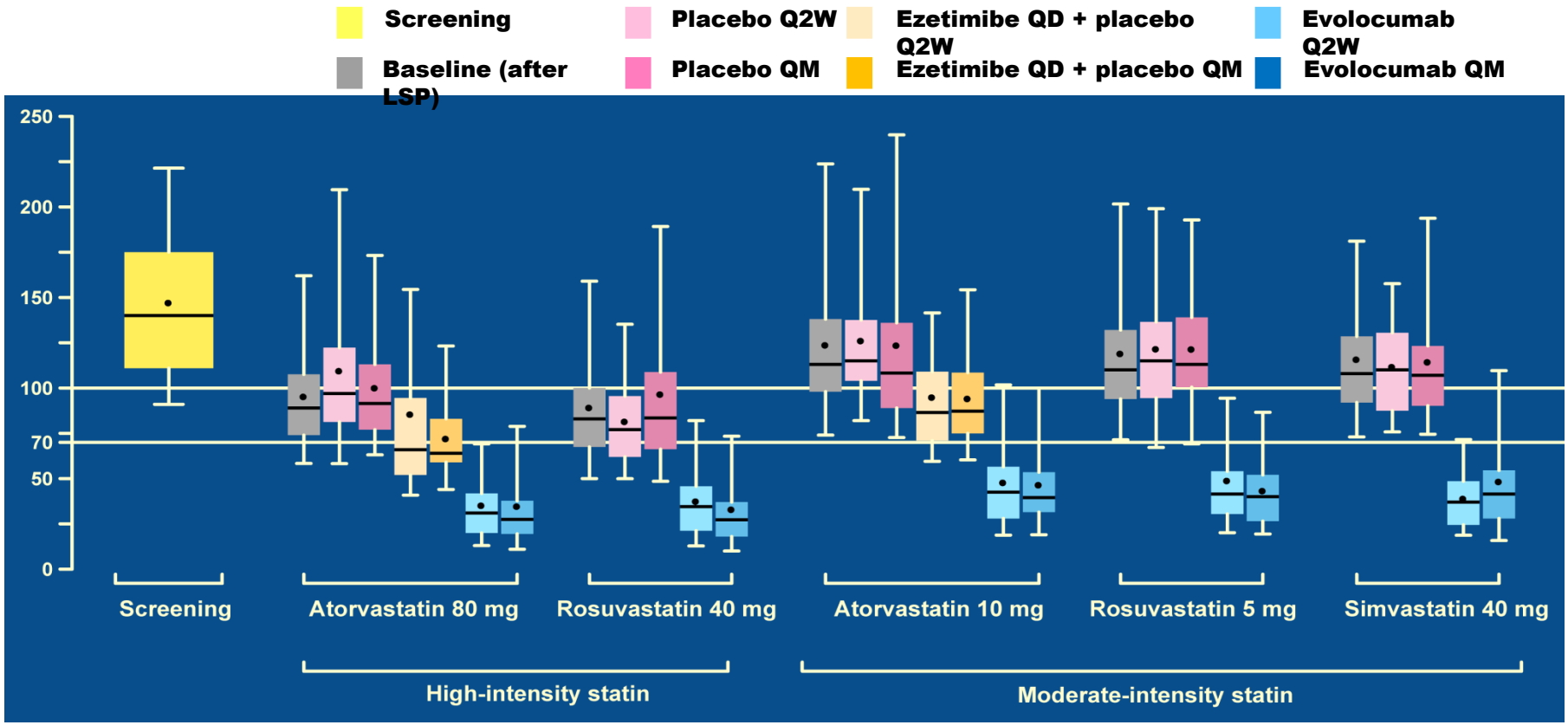
BL, baseline LDL-C, low-density lipoprotein cholesterol; PBO, placebo; EvoMab, evolocumab; EZE, ezetimibe; PO, oral; Q2W, biweekly; QM, monthly; QD, daily; SC, subcutaneous; W, week

LAPLACE-2: LDL-C Response at Mean of Weeks 10 and 12



All treatment differences versus placebo and ezetimibe were statistically significant ($p<0.001$). Vertical lines represent 95% CIs.
No notable differences were observed between the mean of Weeks 10 and 12 and Week 12 alone.
LDL-C, low-density lipoprotein cholesterol; Q2W, biweekly; QM, monthly

LAPLACE-2: Screening, Baseline, and On-treatment LDL-C*



95th percentile
75th percentile
Mean achieved LDL-C
Median achieved LDL-C
25th percentile
5th percentile

% LDL-C <70 mg/dL
High-intensity statin:
Q2W – 94%
QM – 93 to 95%

% LDL-C <70 mg/dL
Moderate-intensity statin:
Q2W – 88 to 94%
QM – 86 to 90%

*Mean of Weeks 10 and 12. No notable differences were observed between the mean of Weeks 10 and 12 and Week 12 alone.
LDL-C, low-density lipoprotein cholesterol; LSP, lipid-stabilization period; Q2W, biweekly; QM, monthly

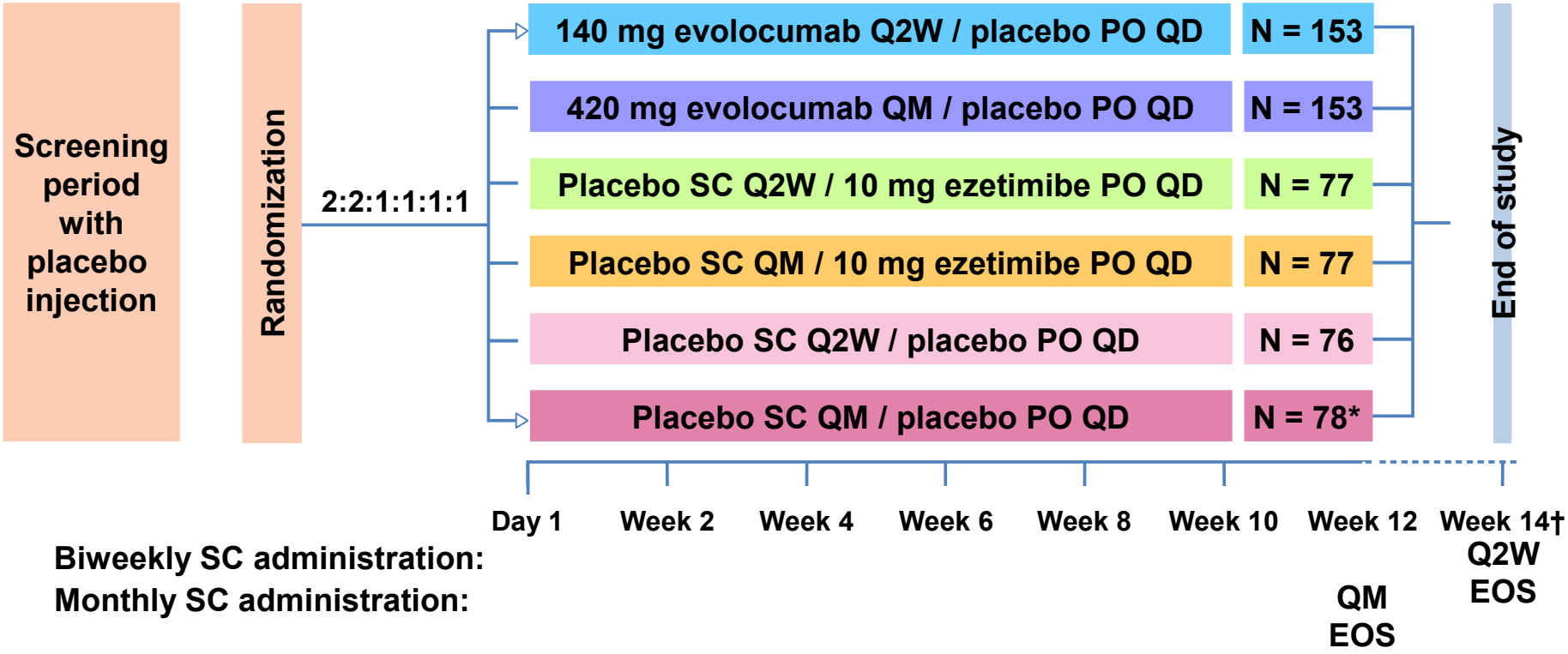
MENDEL-2: Efficacy and Safety of Evolocumab (AMG 145) Monotherapy Compared With Ezetimibe and Placebo in Hypercholesterolemic Subjects: A Phase 3 Randomized Clinical Trial

Michael J Koren, Pernille Lundqvist, Michael Bolognese, Joel M Neutel, Maria Laura Monsalvo, Jingyuan Yang, Jae B Kim, Rob Scott, Scott M Wasserman, Harold Bays
for the MENDEL-2 Investigators

Monoclonal Antibody Against PCSK9 to Reduce **E**levated LDL-C in Patients Currently **N**ot Receiving **D**rug Therapy For **E**asing **L**ipid Levels-2 (NCT01763827)

29 Mar 2014, Featured Clinical Research Session 400, American College of Cardiology and J Am Coll Cardiol 2014;63:2531–40

MENDEL-2: Дизайн



Co-primary endpoints

- Percent change from baseline in LDL-C at Week 12 and mean of Weeks 10 and 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
  - Percent of patients with LDL-C <70 mg/dL

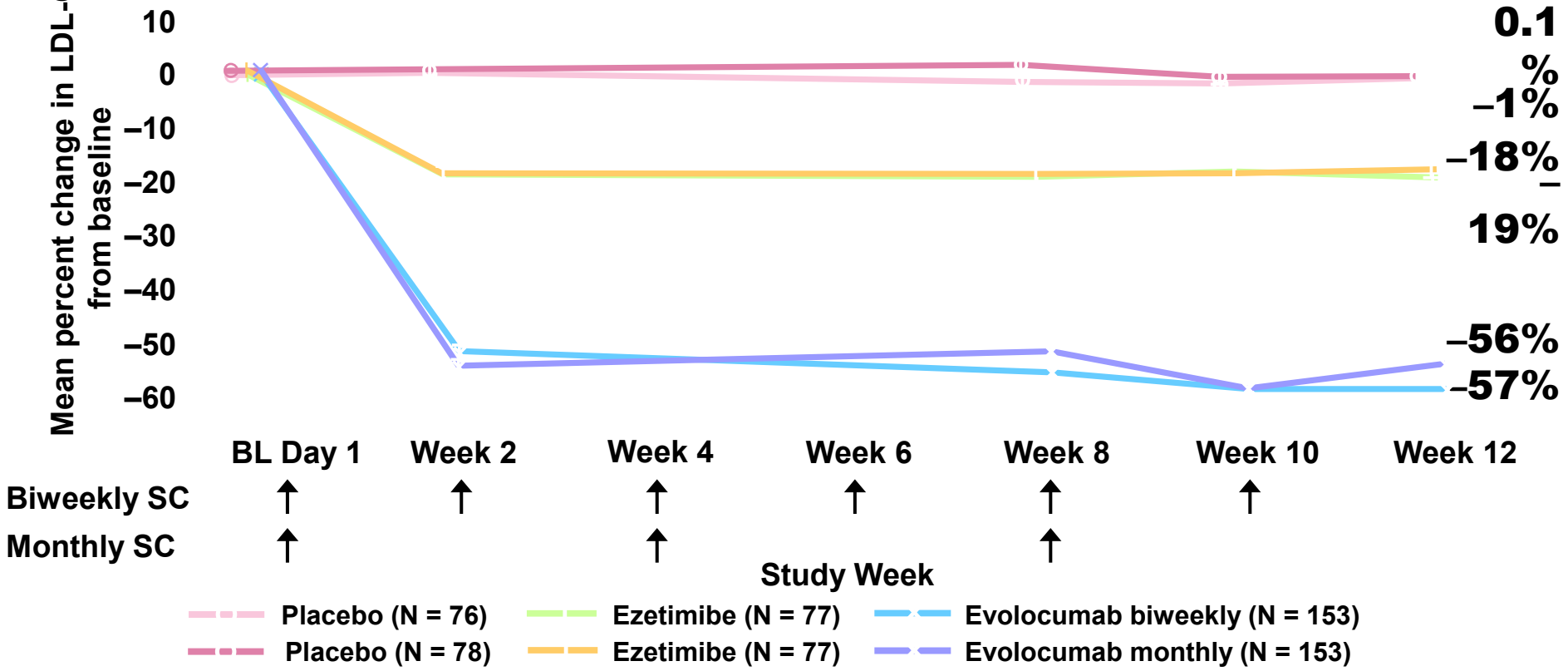
Key safety endpoints

- Treatment-emergent and serious adverse events
- Muscle and hepatic enzyme elevations
- Anti-evolocumab antibodies

*One patient was randomized but not dosed. †Phone call for AEs, SAEs.
AEs, adverse events; EOS, end of study; QD, daily; Q2W, biweekly; QM, monthly

MENDEL-2: Evolocumab

Primary Endpoint *Biweekly* and *Monthly* Doses



- **Evolocumab resulted in significant LDL-C reductions compared with ezetimibe***
  - **Biweekly: –39% and –39%, respectively†**
  - **Monthly: –40% and –38%, respectively†**
- **Biweekly and monthly dosing regimens were clinically equivalent**

Vertical lines represent the standard error around the mean. Plot is based on observed data with no imputation for missing values. p values are multiplicity adjusted. *Average at Weeks 10 and 12 and Week 12; †p<0.001 for both.
BL, baseline

GAUSS-2:
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

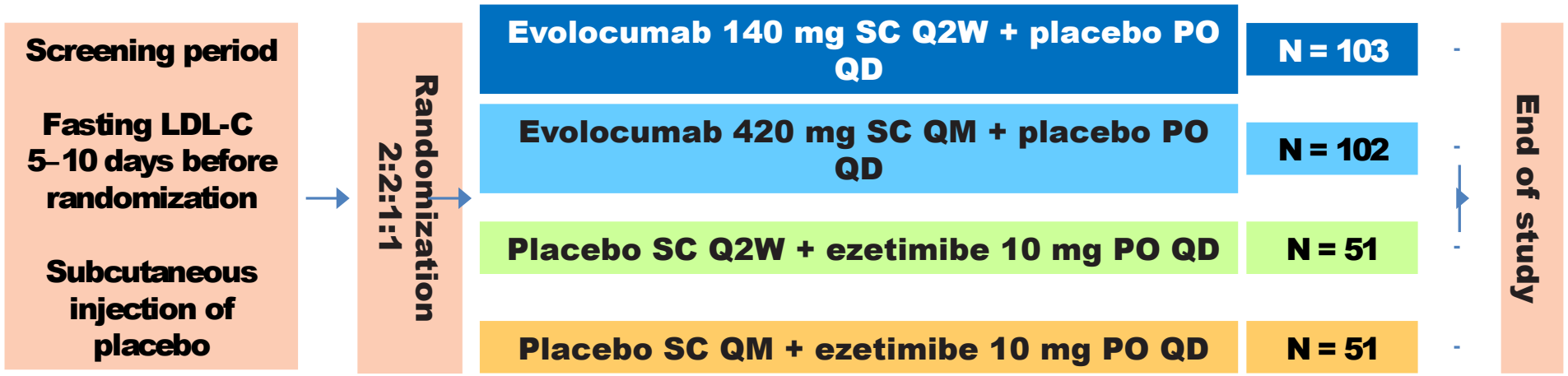
Erik Stroes, David Colquhoun, David Sullivan, Fernando Civeira, Robert S Rosenson, Gerald F Watts, Eric Bruckert, Leslie Cho, Ricardo Dent, Beat Knusel, Allen Xue, Rob Scott, Scott M Wasserman, and Michael Rocco
for the GAUSS-2 Investigators

Goal **A**chievement after **U**tilizing an anti-PCSK9 antibody in **S**tatin Intolerant **S**ubjects-**2** (NCT01763905)

30 Mar 2014, Late-breaking Clinical Trials Session 402, American College of Cardiology and J Am Coll Cardiol 2014;63:2541–8

Disclaimer: Evolocumab has not been approved for use by the EMA and/or any other regulatory authorities outside of the EU

GAUSS-2: Дизайн



Co-primary endpoints

- Percent change from baseline in LDL-C at mean of Weeks 10 and 12 and at Week 12

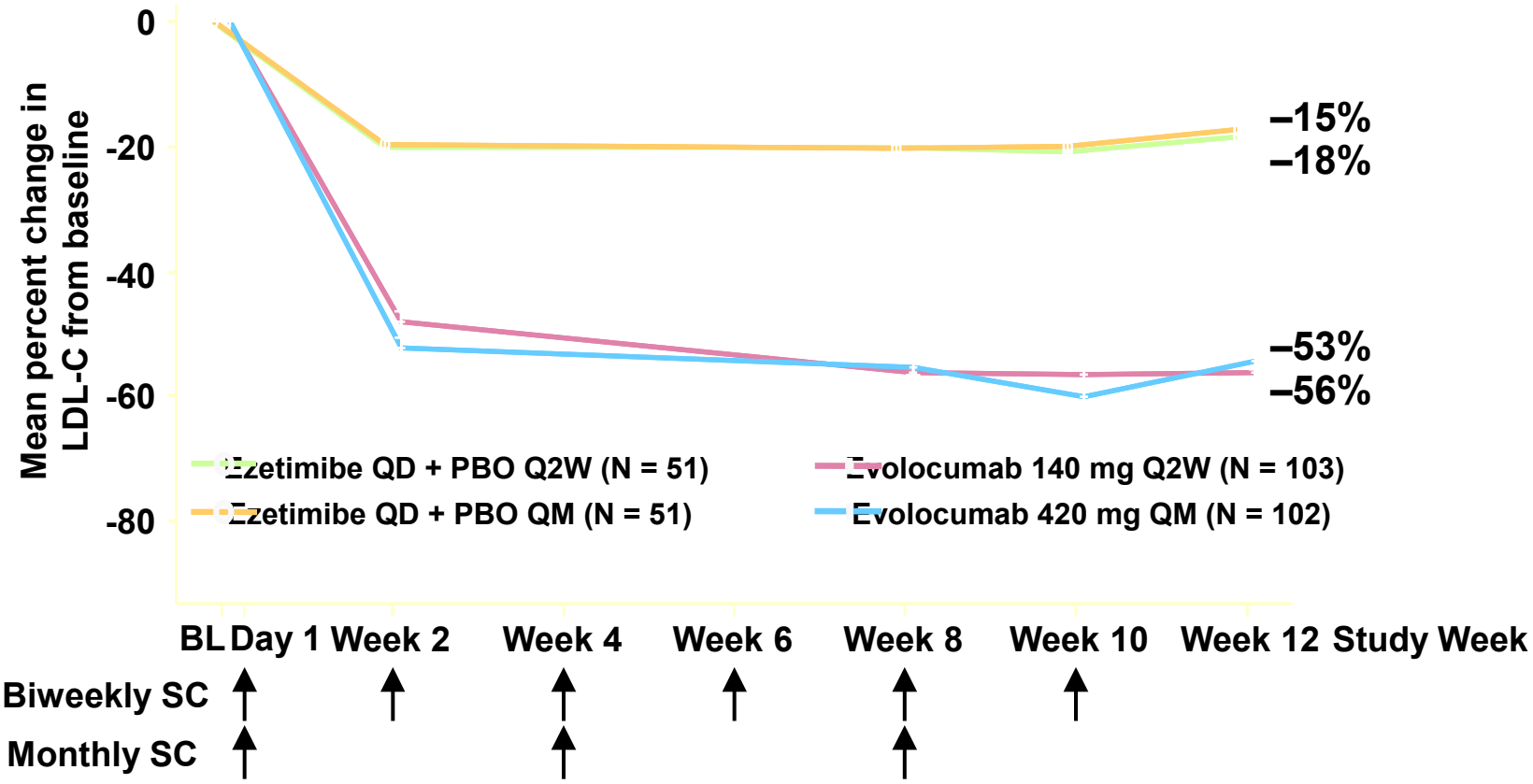
Secondary endpoints

- Change from baseline in ApoB, ApoA-I, lipoprotein(a), TG, and HDL-C
- Achievement of NCEP LDL-C targets
- Safety endpoints

*Phone call for AEs, SAEs.

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

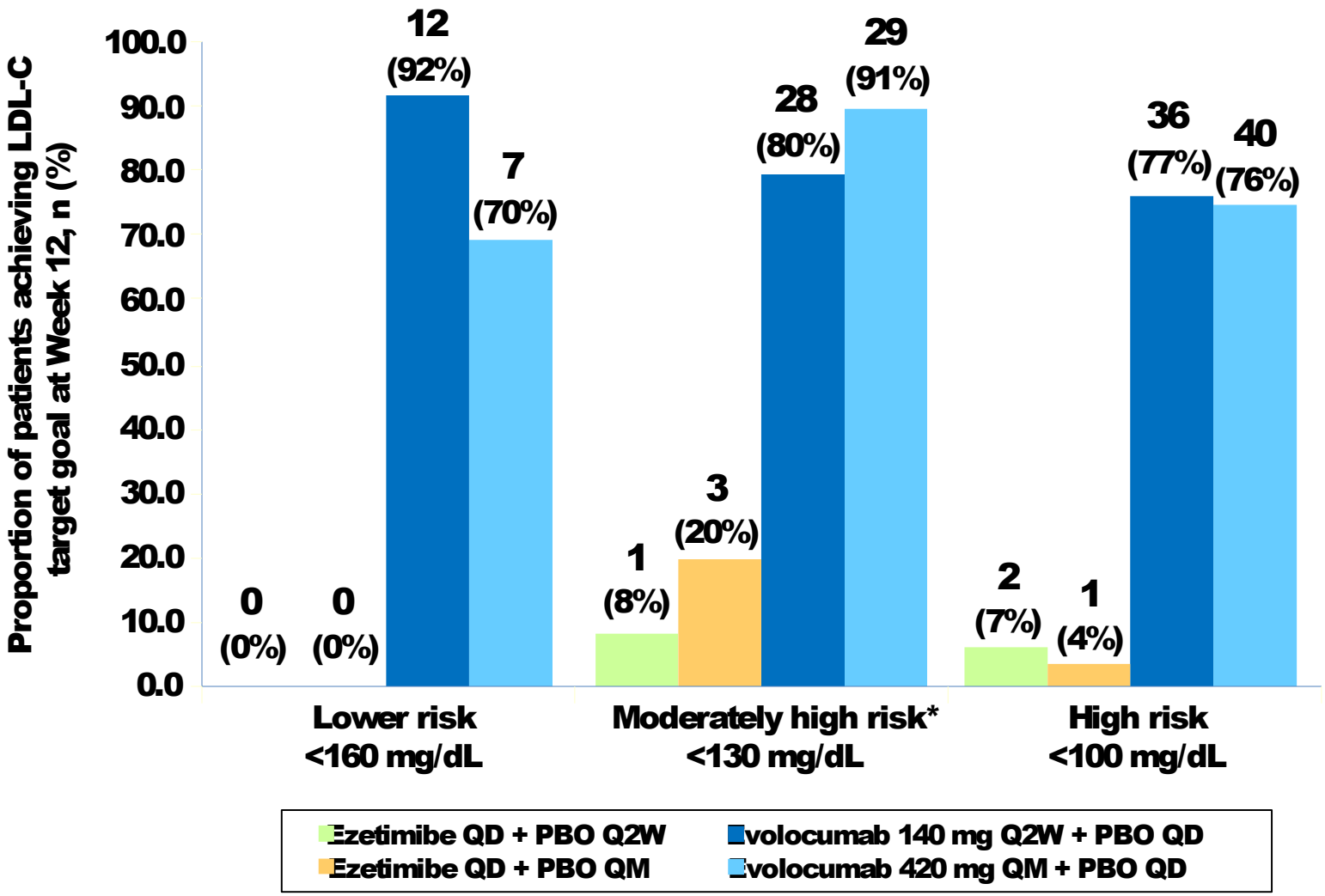
GAUSS-2: Evolocumab Primary Endpoints: Biweekly and Monthly Doses



- **Evolocumab was superior to ezetimibe in reducing LDL-C from baseline***
  - **Biweekly: –37% and –38%, respectively, (p<0.001 for both)**
  - **Monthly: –39% and –38%, respectively, (p<0.001 for both)**
- **Clinical equivalence demonstrated between biweekly 140 mg and monthly 420 mg**

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. *Average at Weeks 10 and 12 and Week 12. BL, baseline

GAUSS-2: постигане на прицел за LDL-C на 12 седмица



*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.

DESCARTES:
Long-term Tolerability and Efficacy of Evolocumab (AMG 145) in Hyperlipidemic Subjects: A 52 Week Phase 3 Double-blind, Randomized, Placebo-controlled Study

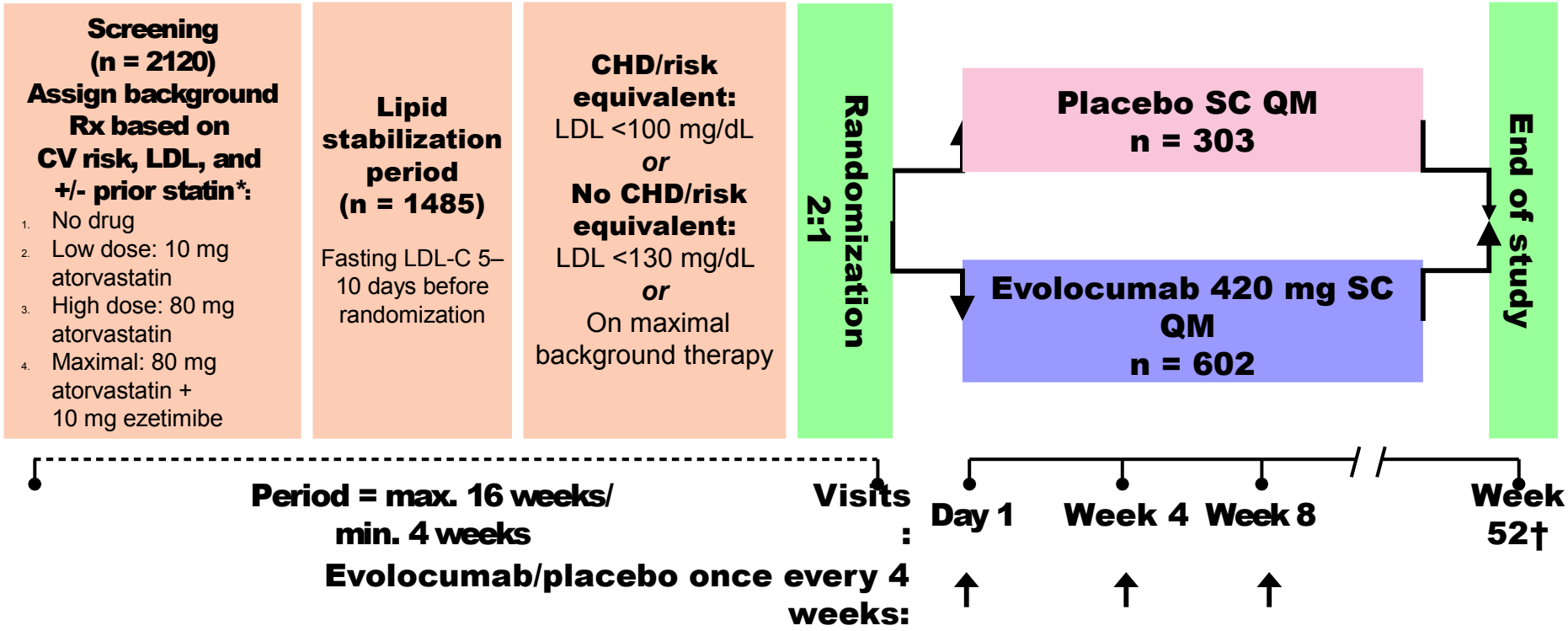
Dirk J. Blom, Tomas Hala, Michael Bolognese, Michael J Lillestol, Phillip D Toth, Lesley Burgess, Richard Ceska, Eli Roth, Michael J Koren, Christie M Ballantyne, Maria Laura Monsalvo, Kate Tsirtsonis, Jae B Kim, Rob Scott, Scott M Wasserman, and Evan A Stein, *for the DESCARTES Investigators*

Durable **E**ffect of PC**S**K9 antibody **C**omp**AR**ed wi**T**h plac**E**bo **S**tudy (NCT01516879)

29 Mar 2014, Featured Clinical Research Session 400, American College of Cardiology and N Engl J Med 2014;370:1809–19

Disclaimer: Evolocumab has not been approved for use by the EMA and/or any other regulatory authorities outside of the EU

DESCARTES: Дизайн



Primary endpoint

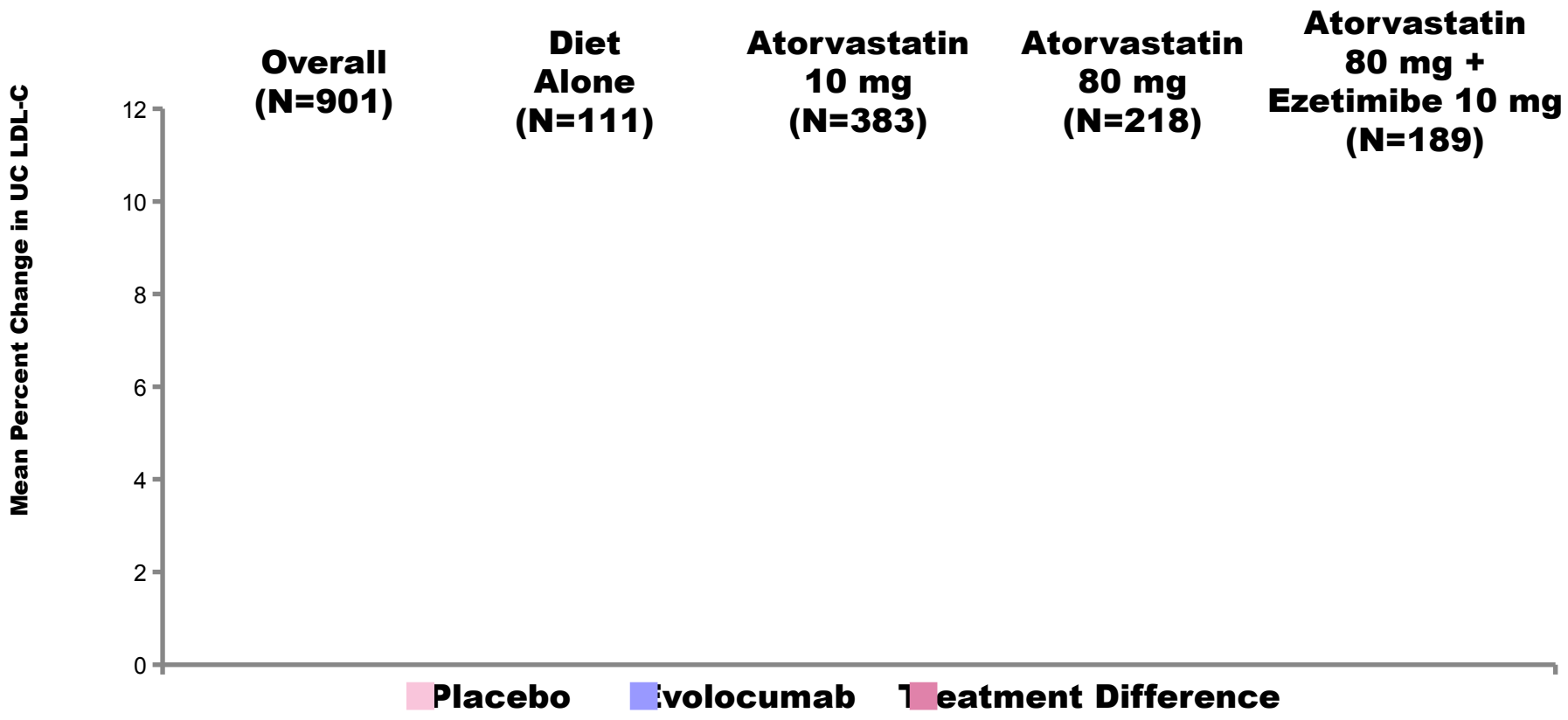
- % change from baseline in UC LDL-C at Week 52

Secondary endpoints

- LDL-C % change from baseline at Week 12
- LDL-C change from baseline at Week 52
- % patients achieving <70 mg/dL LDL-C target at Week 52
- % changes from baseline for TC, HDL-C, non-HDL-C, ApoB, VLDL-C, triglycerides, and Lp(a) at Week 52
- % changes in total cholesterol/HDL cholesterol ratio and apolipoprotein B/apolipoprotein A1 ratio at Week 52

*Run-in treatment was tailored in accordance with CV risk; †Last dose administered at Week 48.

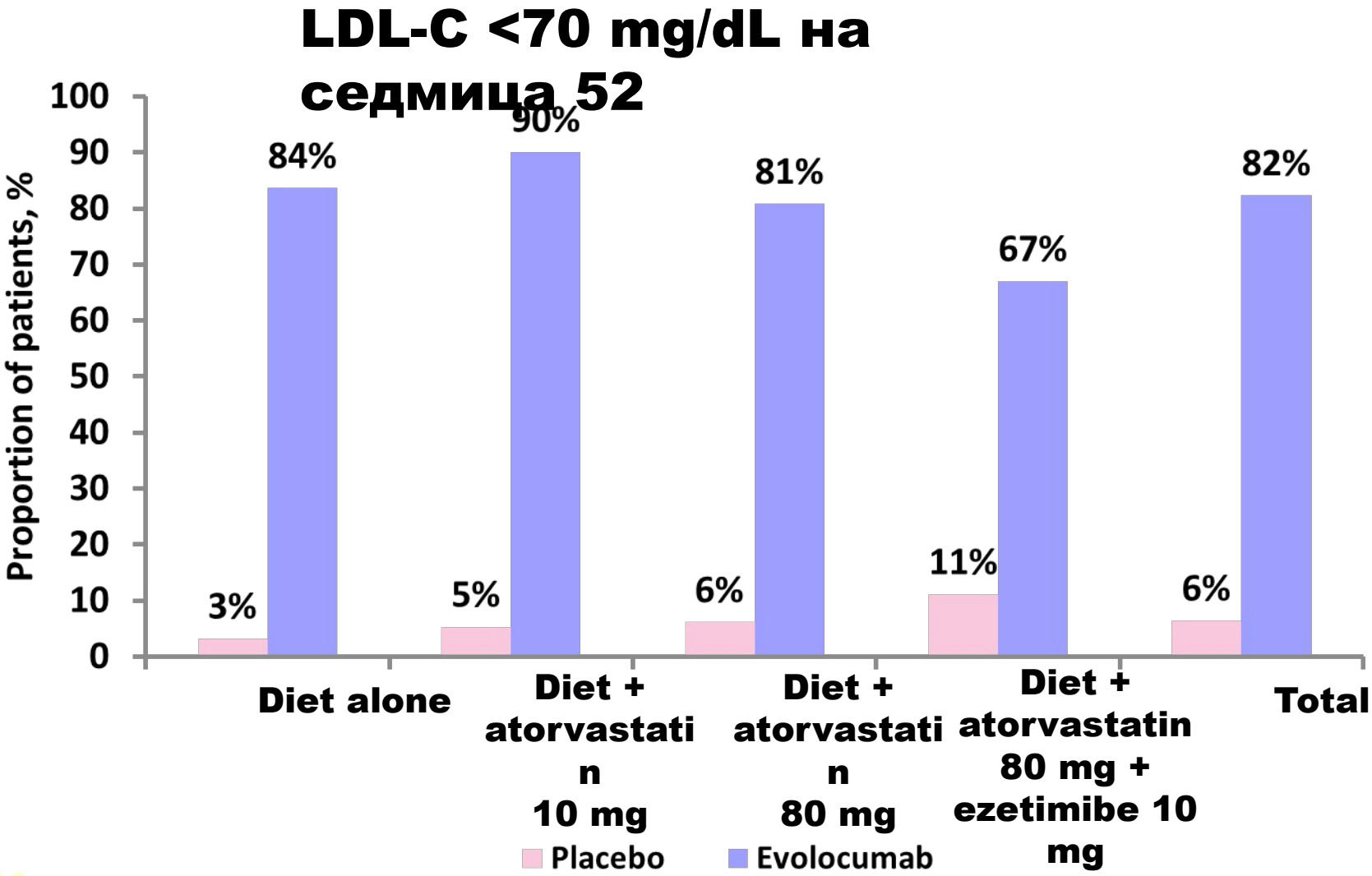
DESCARTES: % промяна на LDL-C на седмица 52



- 6.8% повишаване на LDL-C при placebo (n=302)
- 50.1% намаление на LDL-C при evolocumab (n=599)*
- 57% разлика между групите

Error bars represent standard error for treatment difference. Treatment difference are least squares mean derived from a repeated measures model. *Average of all evolocumab patients. UC, ultracentrifugation

DESCARTES: постигане на прицелен LDL-C



Randomized Comparison of the Safety, Tolerability, and Efficacy of Long-term Administration of AMG 145: 52-Week Results From the OSLER Study

Michael J Koren1, Robert P Giugliano2, Frederick Raal3, David Sullivan4, Michael Bolognese5, Gilles Langslet6, Fernando Civeira7, Ransi Somaratne8, Patric Nelson8, Thomas Liu8, Rob Scott8, Scott M Wasserman8, Marc S Sabatine2 for the OSLER Investigators

1Jacksonville Center for Clinical Research, Jacksonville, FL; 2TIMI Study Group/ Cardiovascular Division, Brigham and Women's Hospital, Boston, MA; 3Carbohydrate & Lipid Metabolism Research Unit, Division of Endocrinology & Metabolism, Department of Medicine, University of the Witwatersrand, Johannesburg, South Africa; 4Department of Clinical Biochemistry, Royal Prince Alfred Hospital, Camperdown, Australia; 5Bethesda Health Research Center, Bethesda, MD; 6Lipid Clinic, Oslo University Hospital, Oslo, Norway; 7Hospital Universitario Miguel Servet, Zaragoza, Spain; 8Amgen, Thousand Oaks, CA

November 19, 2013, Session CS.03
American Heart Association Scientific Sessions, Dallas, TX

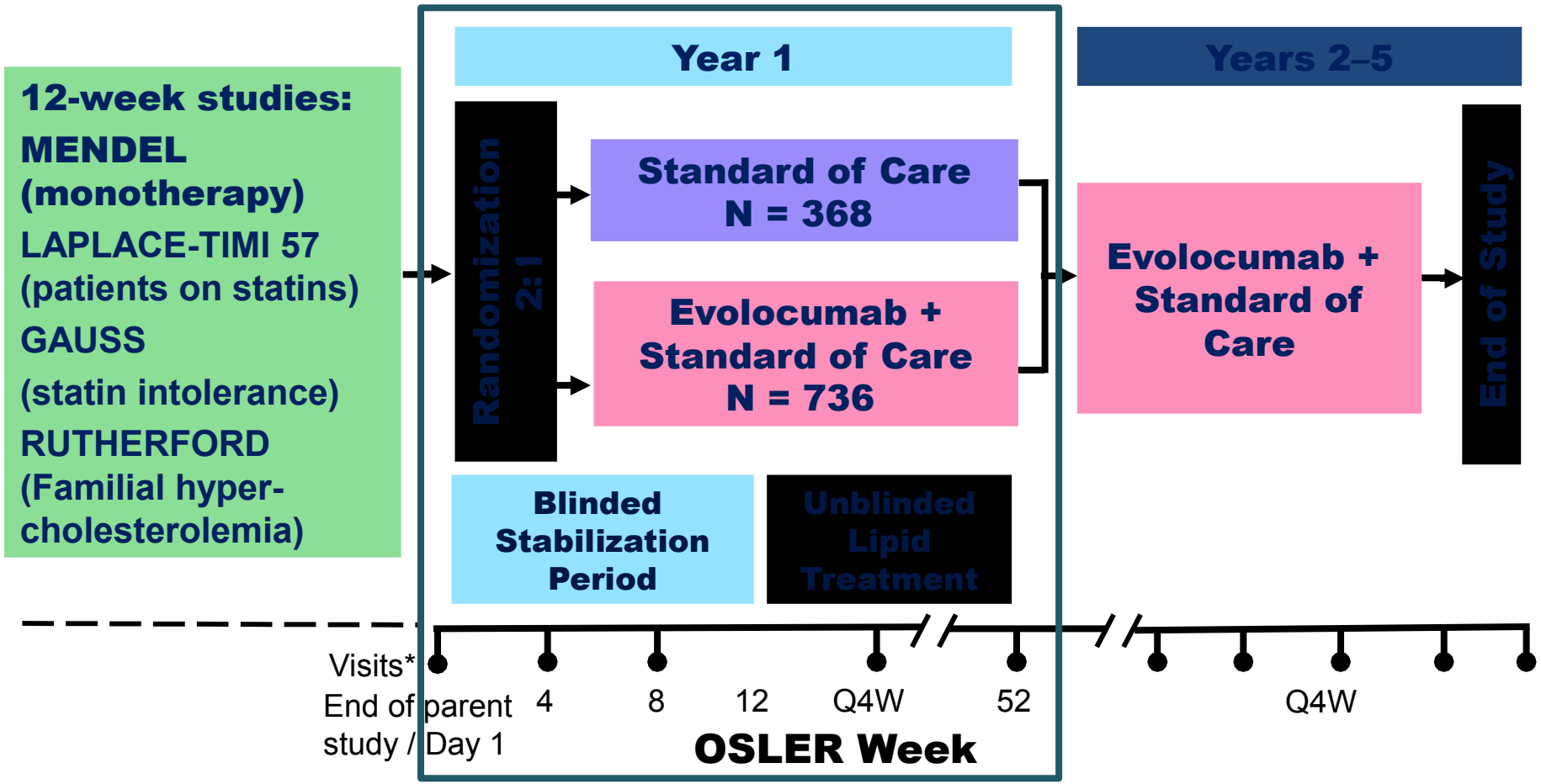
Background: PCSK9 Inhibition For LDL-C Reduction

- PCSK9 inhibition has emerged as a new approach for treating hypercholesterolemia.
- AMG 145 (Evolocumab), a fully human monoclonal antibody against PCSK9, reduced LDL-C by up to 65% and was well tolerated in 4 randomized, placebo-controlled, phase 2 clinical trials of 12 weeks duration in over 1300 hypercholesterolemic patients. 1-4
- Longer-term efficacy and safety of PCSK9 inhibition have not been reported to date.

1. Koren MJ, et al. *Lancet*. 2012;380:1995-2006
2. Raal FJ, et al. *Circulation*. 2012;126:2408-2417
3. Sullivan D, et al. *JAMA*. 2012;308:2497-2506
4. Stein E, et al. *Lancet*. 2012;380:29-36

PCSK9, Proprotein convertase subtilisin/kexin type 9

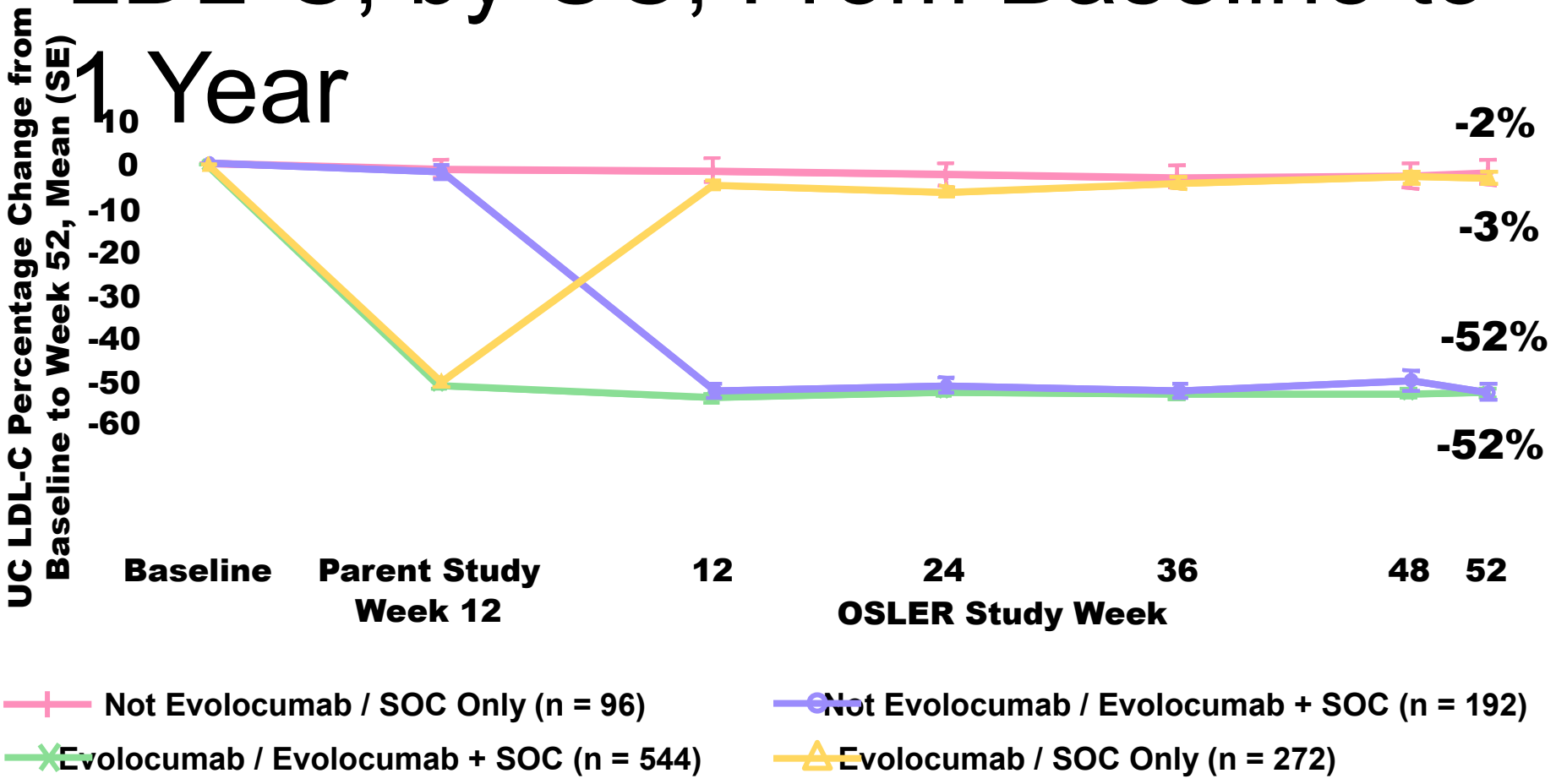
OSLER: Дизайн



Primary Objectives: Effects on LDL-C over 1 year; Safety and Tolerability

Q4W, every 4 weeks. * Patients in the evolocumab + SOC group had in-person visits every 4 weeks. Patients in the SOC group had in-person visits at week 4, then every 3 months, with telephone visits every 4 weeks.

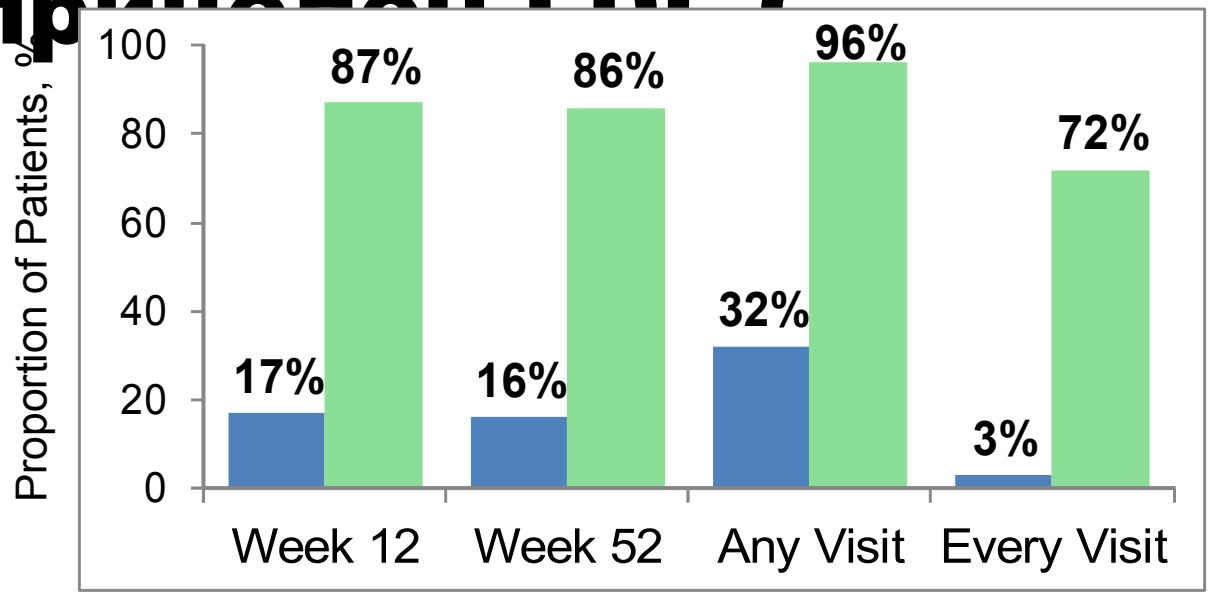
OSLER: Percentage Change in LDL-C, by UC, From Baseline to 1 Year



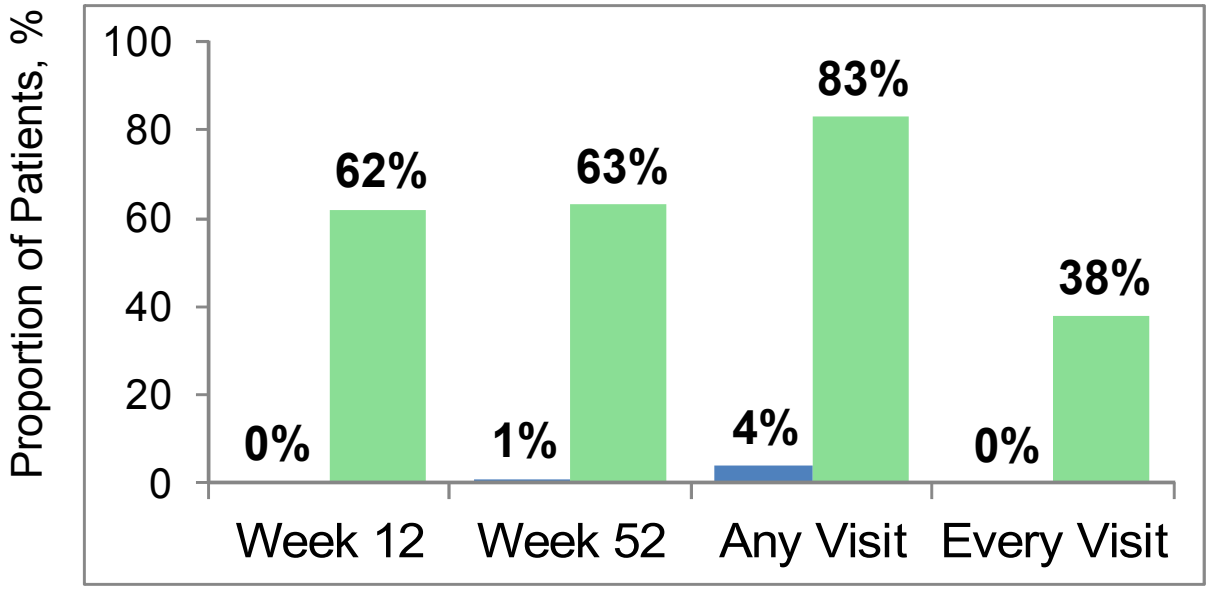
SE, standard error; SOC, standard of care; UC, ultracentrifugation

OSLER: постигане на прицелни LDL-C

< 100 mg/dL



< 70 mg/dL

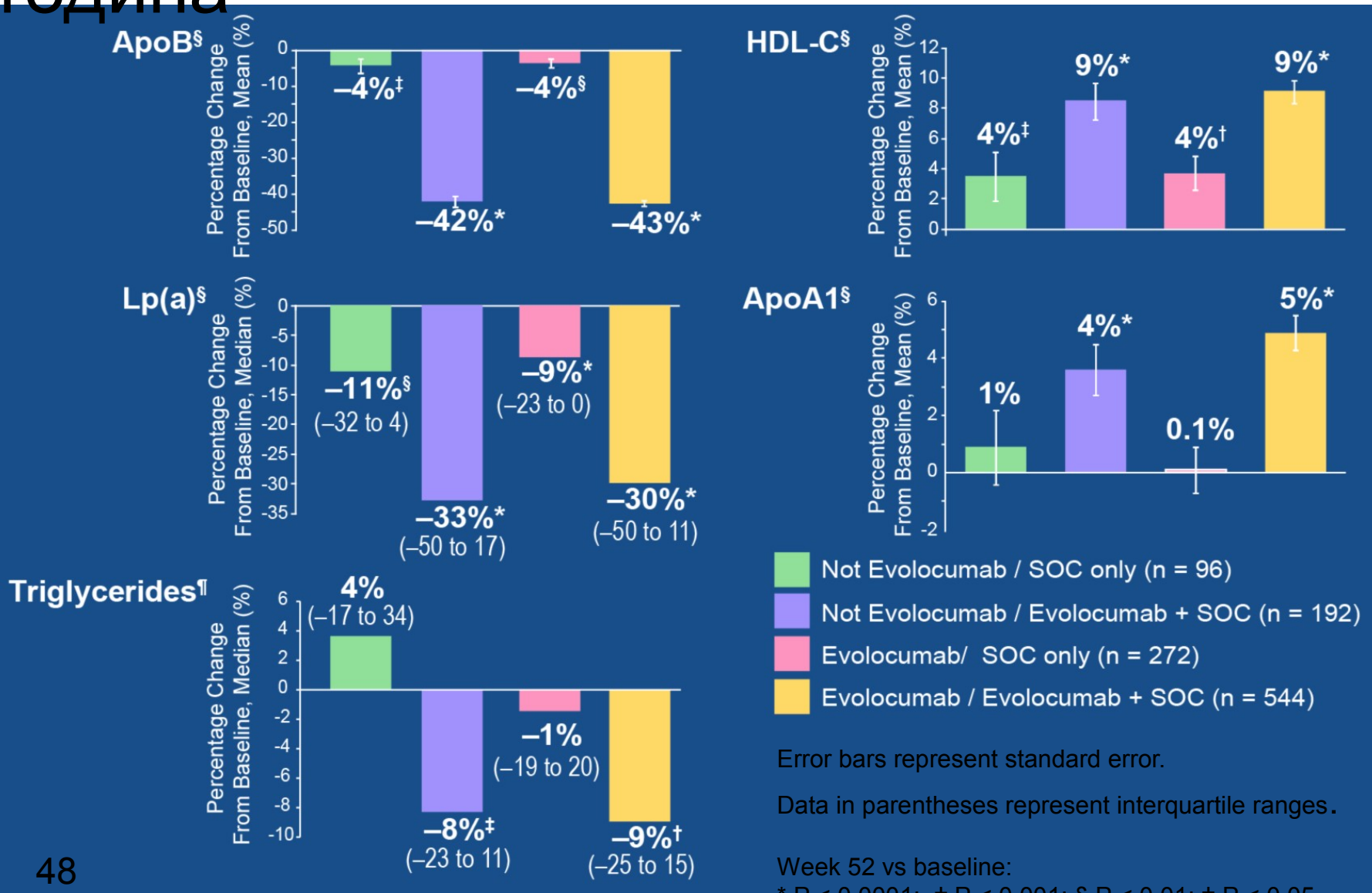


SOC

Evolocumab + SOC

LDL-C values by ultracentrifugation. SOC, standard of care

OSLER: ефекти на Evolocumab след 1 година



Error bars represent standard error.

Data in parentheses represent interquartile ranges.

Week 52 vs baseline:
* P < 0.0001; † P < 0.001; § P < 0.01; ‡ P < 0.05

OSLER: странични ефекти

	LDL-C < 25 mg/dL*	LDL-C < 50 mg/dL*	LDL-C ≥ 50 mg/dL	
Adverse events, %	Evolocumab + SOC N = 98	Evolocumab + SOC N = 409	SOC N = 359	Evolocumab + SOC N = 323
Any AE	81.6	82.2	74.7	81.1
Serious AEs	5.1	6.6	6.1	7.7
Hepatobiliary AE	1.0	0.7	0.8	0.3
Renal and Urinary AE	1.0	2.2	3.1	2.5

AE, adverse event; SOC, standard of care.
*In the SOC group, no patients had LDL-C <25 mg/dL, and 2 patients had LDL-C <50 mg/dL.

OSLER: странични ефекти според LDL-C

Adverse events, n (%)	LDL-C < 25 mg/dL*		LDL-C < 50 mg/dL*		LDL-C ≥ 50 mg/dL	
	Evolocumab + SOC N = 98		Evolocumab + SOC N = 409		SOC N = 359	Evolocumab + SOC N = 323
Nervous System AEs	19 (19.4)		64 (15.6)		37 (10.3)	44 (13.6)
Headache	9 (9.2)		25 (6.1)		10 (2.8)	21 (6.5)
Dizziness	4 (4.1)		11 (2.7)		11 (3.1)	5 (1.5)
Migraine	1 (1.0)		4 (1.0)		1 (0.3)	7 (2.2)
Amnesia	1 (1.0)		1 (0.2)		0 (0.0)	1 (0.3)
Memory impairment†	0 (0.0)		4 (1.0)		0 (0.0)	1 (0.3)
Psychiatric AEs	5 (5.1)		20 (4.9)		12 (3.3)	15 (4.6)
Insomnia	4 (4.1)		9 (2.2)		4 (1.1)	4 (1.2)
Depression	1 (1.0)		6 (1.5)		5 (1.4)	5 (1.5)
Anxiety	0 (0.0)		4 (1.0)		2 (0.6)	5 (1.5)

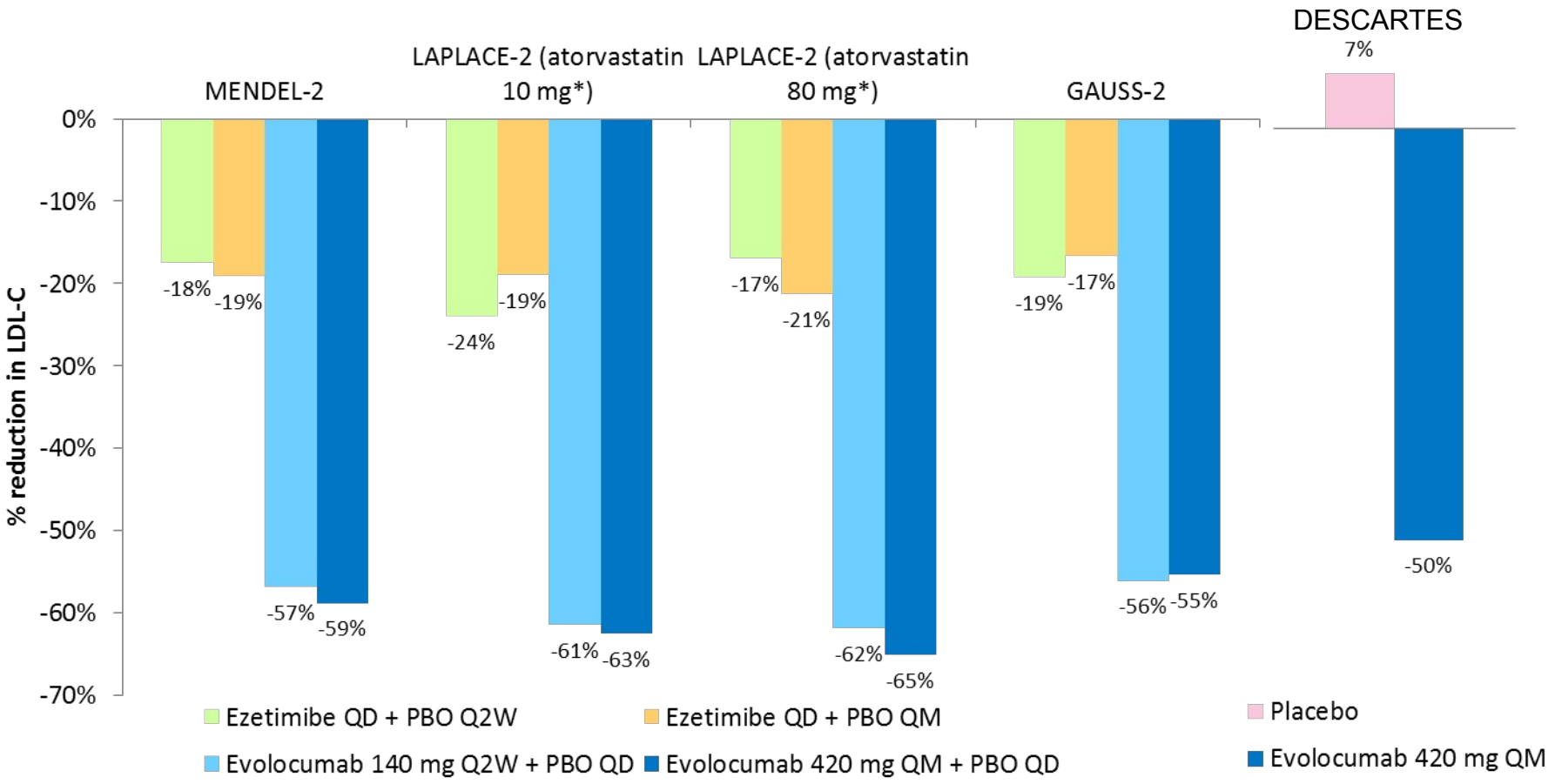
* In the SOC group, no patients had LDL-C <25 mg/dL, and 2 patients had LDL-C <50 mg/dL.
† Includes “memory impairment” and “mental impairment” terms.

OSLER: мускулоскелетни странични ефекти

Adverse events, n (%)	LDL-C < 25 mg/dL* Evolocumab + SOC N = 98	LDL-C < 50 mg/dL* Evolocumab + SOC N = 409	LDL-C ≥ 50 mg/dL SOC N = 359	LDL-C ≥ 50 mg/dL Evolocumab + SOC N = 323
Musculoskeletal and Connective Tissue Disorders	34 (34.7)	135 (33.0)	89 (24.8)	84 (26.0)
Back pain	12 (12.2)	31 (7.6)	20 (5.6)	17 (5.3)
Arthralgia	7 (7.1)	34 (8.3)	16 (4.5)	17 (5.3)
Pain in extremity	7 (7.1)	21 (5.1)	10 (2.8)	15 (4.6)

AE, adverse event; SOC, standard of care.
* In the SOC group, no patients had LDL-C <25 mg/dL, and 2 patients had LDL-C <50 mg/dL.

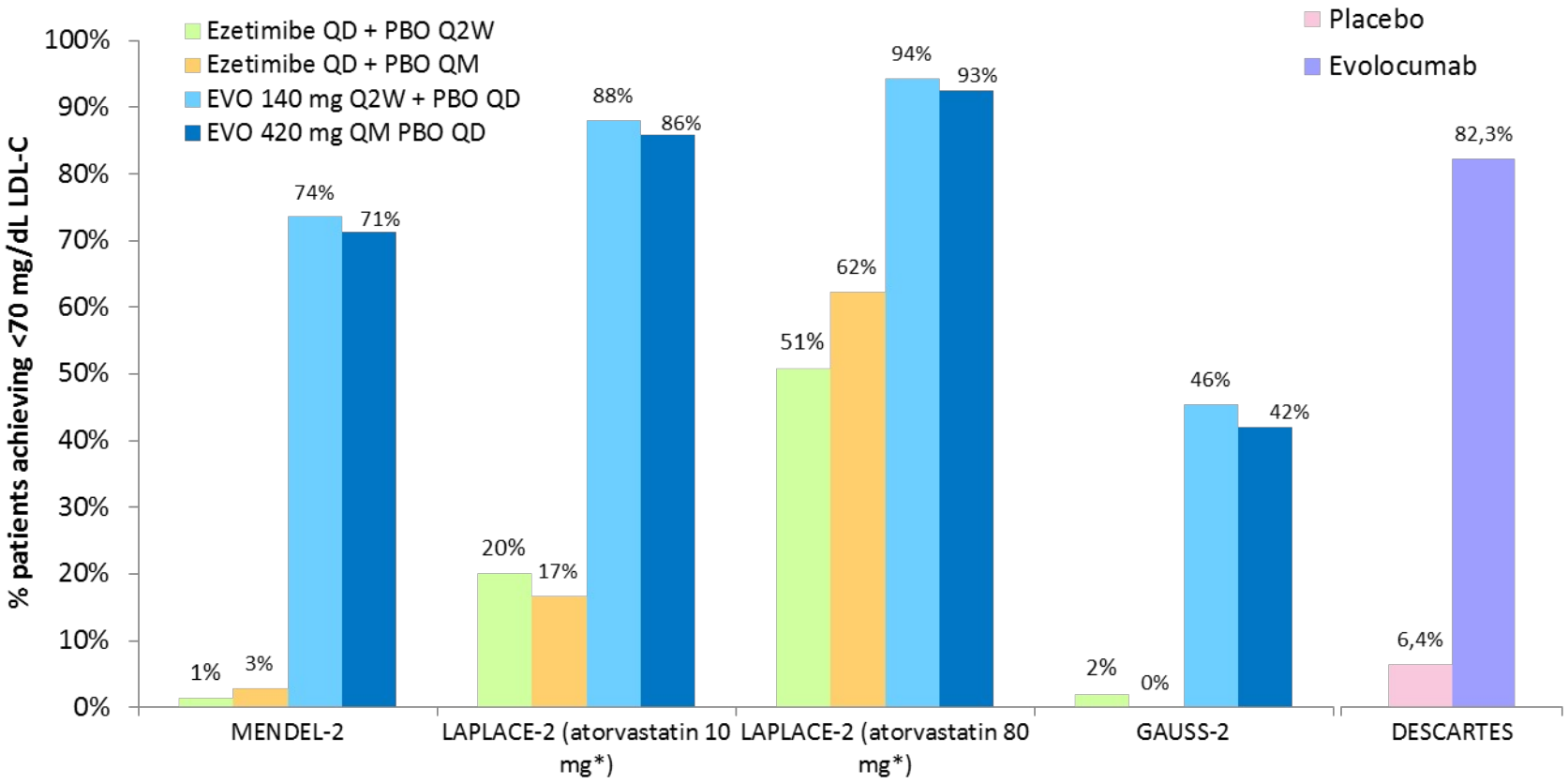
Фаза III проучвания с Evolocumab – намаление на LDL-C



*Only 2 statin dose groups are shown for the LAPLACE-2 study; these indicate the level of LDL-C reductions seen with moderate intensity (atorvastatin 10 mg) and high intensity (atorvastatin 80 mg) statin

Percentage reduction in LDL-C for each trial at mean of Week 10 and Week 12; DESCARTES reduction at Week 52.
LAPLACE-2 patients are grouped by moderate- or high-intensity statin combination therapy.

Фаза III проучвания с Evolocumab – постигане на прицелен LDL-C



*Only 2 statin dose groups are shown for the LAPLACE-2 study; these indicate the level of LDL-C goal fulfilment seen with moderate intensity (atorvastatin 10 mg) and high intensity (atorvastatin 80 mg) statin

Percentage of patients achieving LDL-C treatment goal of <70 mg/dL at a mean of Weeks 10 and 12; DESCARTES patients at Week 52. LAPLACE-2 patients are grouped by moderate- or high-intensity statin combination therapy.