PCSK9 Inhibitors: A View of Clinical Studies

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PCSK9 Inhibitors : A View of Clinical Studies

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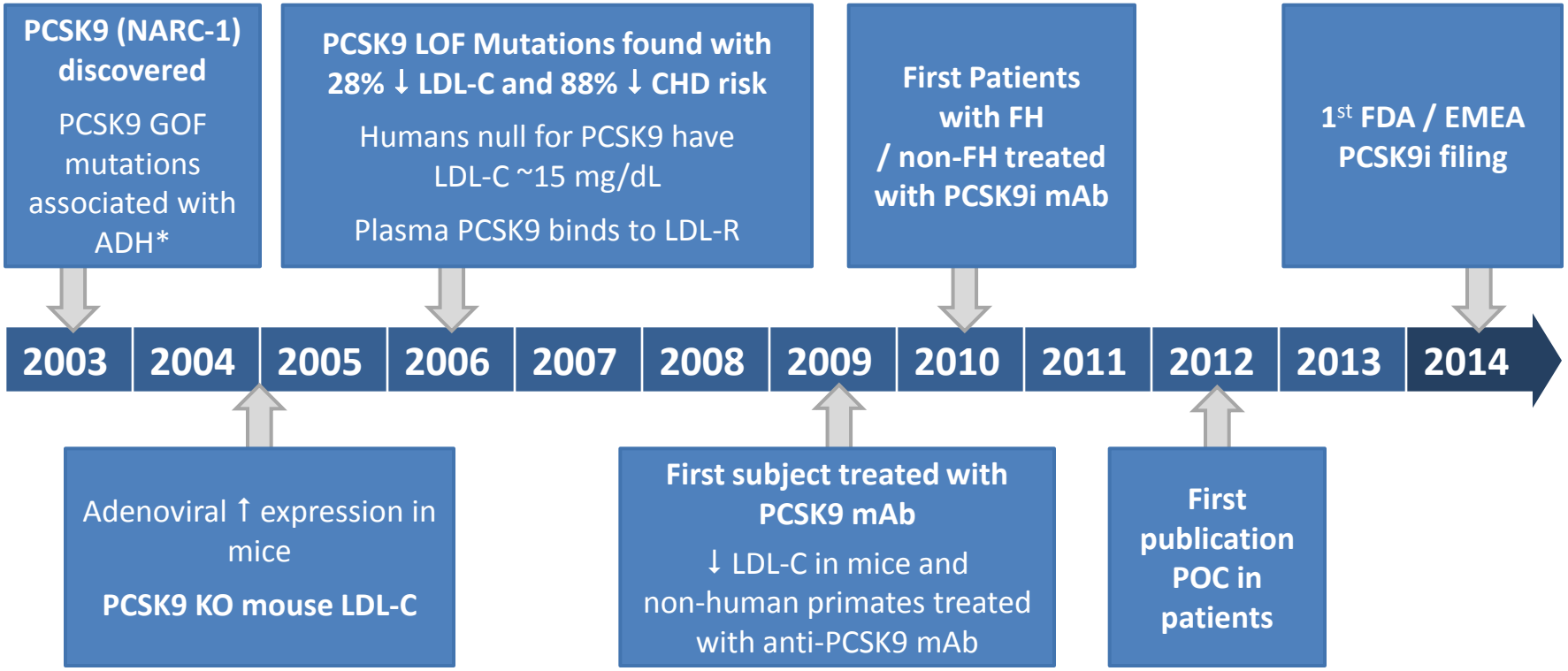
Disclosure

- Honoraria for consulting and speaker activities from
  - Amgen, Biolab, Boehringer-Ingelheim
  - Genzyme, Eli-Lilly, Merck, Pfizer, Praxis, Kowa, Jansen, Torrent & Sanofi/Regeneron

PCSK9 Inhibitors : A View of Clinical Studies

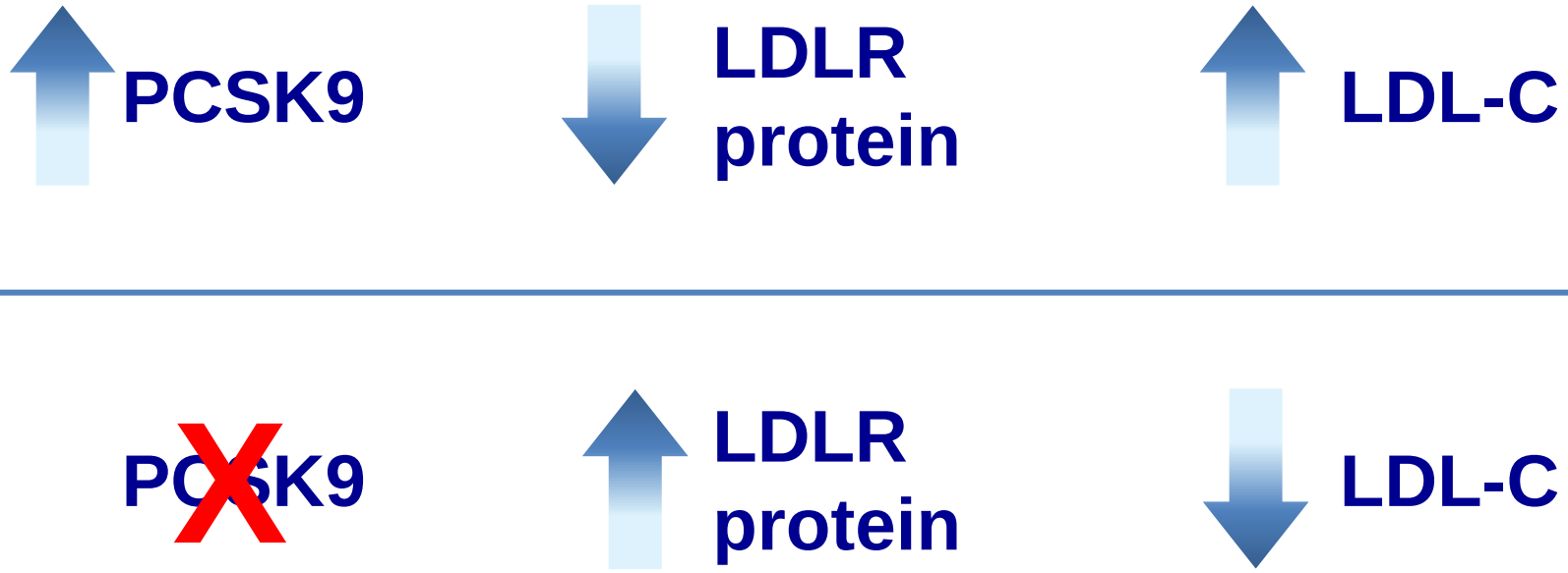
- Efficacy
  - General high risk population
  - Familial Hypercholesterolemia
  - Statin intolerant
- Safety
- CVD prevention?

PCSK9 Inhibitors: From Target Discovery to Phase III in 10 Years



* ADH: Autosomal Dominant Hypercholesterolemia; Seidah NG. Proc Natl Acad Sci US 2003;100(3):928-33, Abifadel M. Nat Genet 2003;34(2):154-6, Maxwell KN. Proc Natl Acad Sci US 2004;101(18):7100-5, Rashid S. Proc Natl Acad Sci US 2005;102(15):5374-79, Lagace TA et al. JCI 2006;116:2995-3005 Cohen JC. N Engl J Med 2006;354(12):1264-72, Zhao Z. Am J Hum Genet 2006;79(3):514-23, Hooper AJ. Atherosderosis 2007;193(2):445-8, Chan JC. Proc Natl Acad Sci US 2009;106(24):9820-5: Stein et at N Engl J Med 2012;366:1108-18; Stein modified from Swergold, Regeneron.

PCSK9 Promotes Degradation of LDLRs



LDL-C=low-density lipoprotein cholesterol; LDLR=low-density lipoprotein receptor.

Phase 3 Program to Support LDL-C Reduction in Targeted Populations

- **High CV Risk Patients**
  - Patients not at LDL-C goal with currently available LLT (even high doses of potent statins) = >persistent risk
- **Familial Hypercholesterolemia**
  - LDL-C levels often far from goal, even with potent statins and combination Tx
  - Life-long exposure to high LDL-C; considered high risk even w/o additional risk factors
- **Statin Intolerant Patients**
  - LDL-C levels often far from goal, due to intolerance
  - Definition: unable to tolerate at least 2 statins, including one at the lowest dose

Overview of ODYSSEY Phase 3 clinical trial program

12 global phase 3 trials
Including more than 23,500 patients across more than 2,000 study centers

HeFH population

Add-on to max tolerated statin (± other LMT)

ODYSSEY FH I (EFC12492) N=471
LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100mg/dL
18 months

ODYSSEY FH II (CL1112) N=250
LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100mg/dL
18 months

ODYSSEY HIGH FH (EFC12732) N=105
LDL-C ≥ 160 mg/dL
18 months

ODYSSEY LONG TERM (LTS11717) N=2,100
LDL-C ≥ 70 mg/dL
18 months

HC in high CV risk population

Add-on to max tolerated statin (± other LMT)

ODYSSEY COMBO I (EFC11568) N=306
LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL
12 months

***ODYSSEY COMBO II (EFC11569)** N=660
LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dl
24 months

ODYSSEY OUTCOMES (EFC11570) N=18,000
LDL-C ≥ 70 mg/dL

Additional populations

ODYSSEY MONO (EFC11716) N=100
Patients on no background LMTs
LDL-C ≥ 100 mg/dL
6 months

ODYSSEY ALTERNATIVE (CL1119) N=250
Patients with defined statin intolerance
LDL-C ≥ 70 mg/dL **OR** LDL-C ≥ 100 mg/dL
6 months

ODYSSEY CHOICE I (CL1308) N=700
LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL
12 months

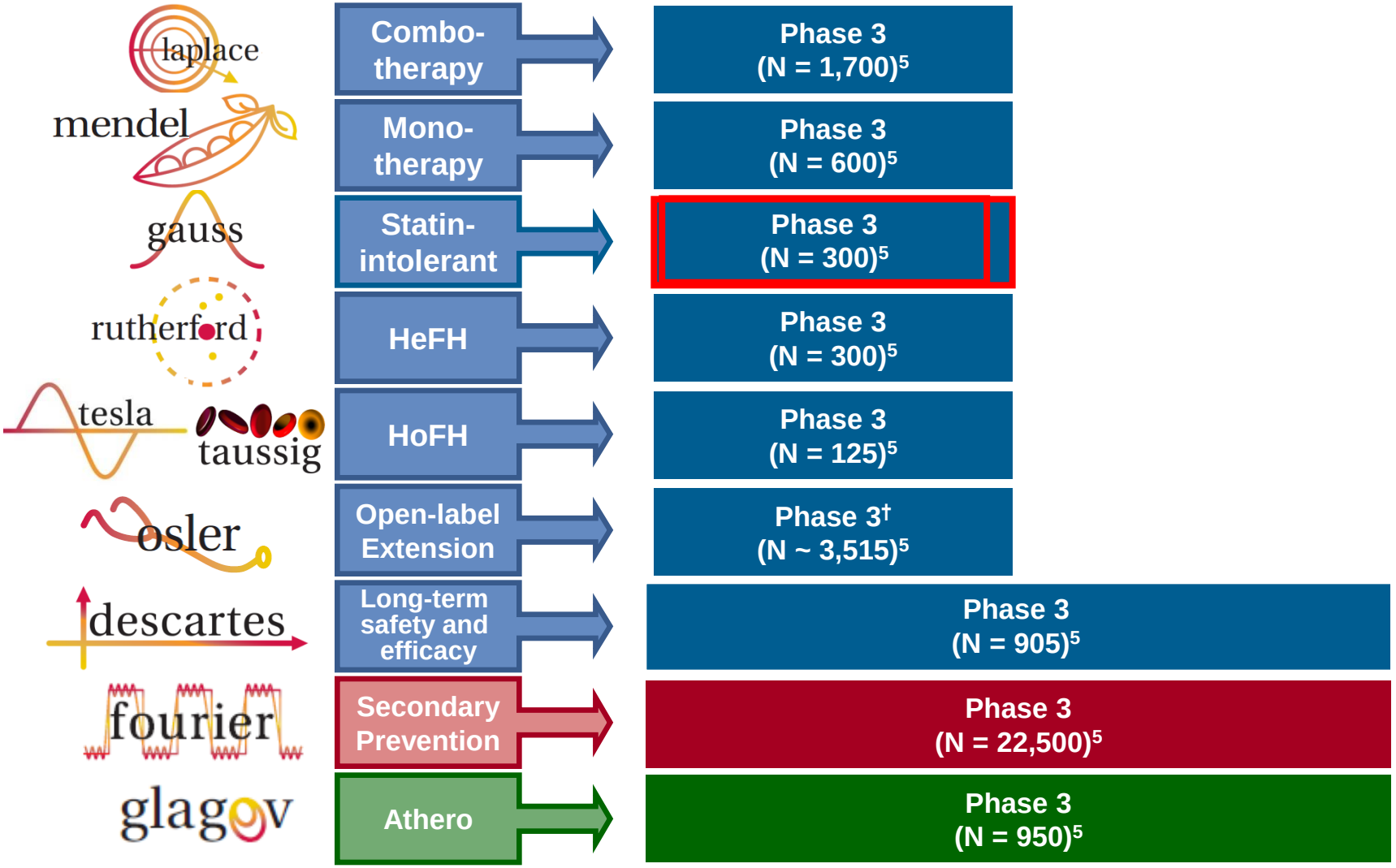
ODYSSEY OPTIONS I (CL1110) N=350
Patients not at goal on moderate dose atorvastatin
LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL
6 months

ODYSSEY OPTIONS II (CL1118) N=300
Patients not at goal on moderate dose rosuvastatin
LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL
6 months

HC = hypercholesterolemia; LMT = lipid-modifying therapy *For the ODYSSEY COMBO II other LMT not allowed at entry

PROFICIO

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



*Subjects completed a qualifying Phase 2 study. †Subjects completed a qualifying Phase 3 study.

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 Oct. 2, 2013.
6. Data on file, Amgen; [AMG 145 Protocol 20120332].

SPIRE Phase 3 Bococizumab Clinical Development Program:
Designed to Address Unmet Needs in the Management of CVD in High Risk Patients

SPIRE (Studies of PCSK9 Inhibition and the Reduction of Vascular Events) N=~30,000

SPIRE Lipid Lowering Studies

SPIRE HR (n=300)
On statin
High risk of CV event
LDL-C ≥70 or ≥100 mg/dL

SPIRE LDL (n=1,932)
On statin
High risk of CV event
LDL-C ≥70 mg/dL

SPIRE FH (n=300)
HeFH (genetic diagnosis or Simon Broome Criteria),
LDL ≥70 mg/dL

SPIRE LL (n=690)
On statin
High / very high risk of CV event
LDL-C ≥100 mg/dL

SPIRE SI (n=150)
Statin intolerant
LDL-C ≥70 mg/dL

SPIRE CV Outcome Studies

SPIRE-1 (n=17,000)
High Risk Primary and Secondary Prevention
LDL-C ≥70 to <100 mg/dL on statins (or statin intolerant)

SPIRE-2 (n=9,000)
High Risk Primary and Secondary Prevention
LDL-C ≥100 mg/dL on statins (or statin intolerant)

SPIRE

Studies on PCSK9 Inhibition and the Reduction of Vascular Events

NCT#: https://clinicaltrials.gov
SPIRE HR: NCT01968954
SPIRE LDL: NCT01968967
SPIRE HF: NCT01968980
SPIRE-LL: NCT02100514
SPIRE-SI: NCT02135029
SPIRE-1: NCT01975376
SPIRE-2: NCT01975389

Studies in Patients at High CV Risk and Not at LDL-C Goal

ODYSSEY COMBO I
ODYSSEY COMBO II

Kereiakes DJ et al. *Am Heart J. 2015 Jun;169(6):906-915.e13*
Cannon CP et al. *Eur Heart J* 2015 36(19):1186-94

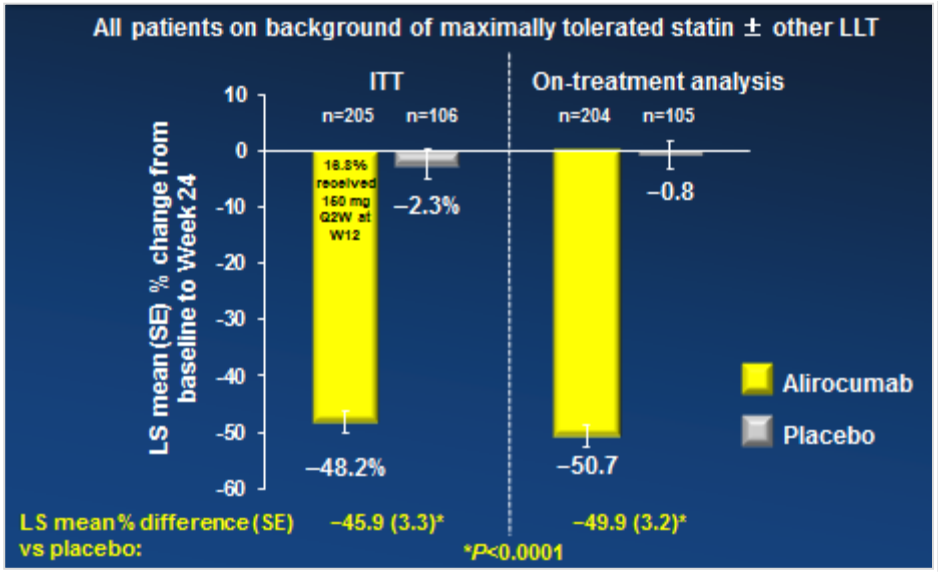
Baseline Characteristics: COMBO I and II

All patients on background maximally tolerated statin ±other LLT	COMBO I		COMBO II	
	Alirocumab (N=209)	**Placebo** (N=107)	**Alirocumab** (n=479)	**Ezetimibe** (n=241)
Age, years, mean (SD)	**63.0** (9.5)	**63.0** (8.8)	**61.7** (*9.4*)	**61.3** (*9.2*)
Male, % (n)	**62.7%** (131)	**72.0%** (77)	**75.2%** (360)	**70.5%** (170)
Race, white, % (n)	**81.3%** (170)	**82.2%** (88)	**84.3%** (404)	**85.5%** (206)
BMI, kg/m^2, mean (SD)	**32.6** (6.3)	**32.0** (7.1)	**30.0** (*5.4*)	**30.3** (*5.1*)
CHD history, % (n)	**78.5%** (164)	**77.6%** (83)	**91.2%** (437)	**88.0%** (212)
Hypertension, % (n)	**88.5%** (185)	**88.8%** (95)	**79.7%** (382)	**82.2%** (198)
Type 2 diabetes, % (n)	**45.0%** (94)	**39.3%** (42)	**30.3%** (145)	**31.5%** (76)
Any statin*,% (n)	**99.5%** (208)	**100%** (107)	**99.8%** (478)	**100%** (241)
High-intensity statin†, % (n)	**61.7%** (129)	**64.5%** (69)	**66.8%** (320)	**66.4%** (160)
LDL-C, calculated mean (*SD*)**, mg/dL**	**100.2** (29.5)	**106.0** (35.3)	**109** (*37*)	**105** (*34*)

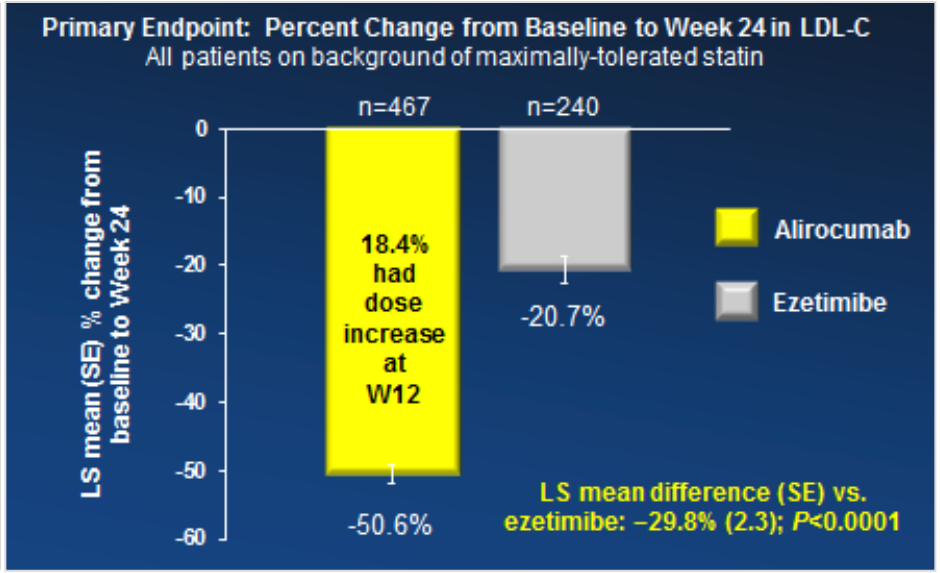
Kereiakes DJ et al. *Am Heart J. 2015 Jun;169(6):906-915.e13*
Cannon CP et al. *Eur Heart J* 2015 36(19):1186-94

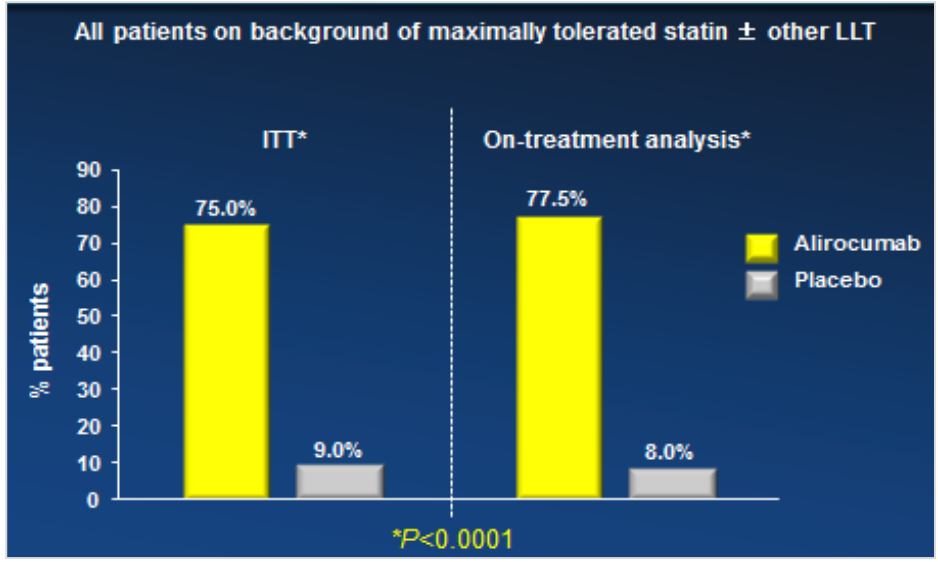
LDL-C Reductions and Goal Achievement

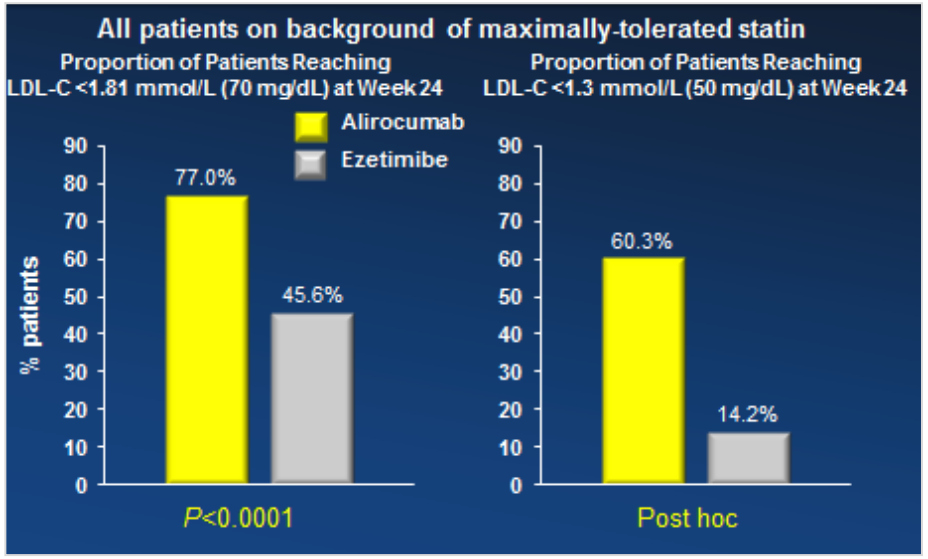
COMBO I



COMBO II

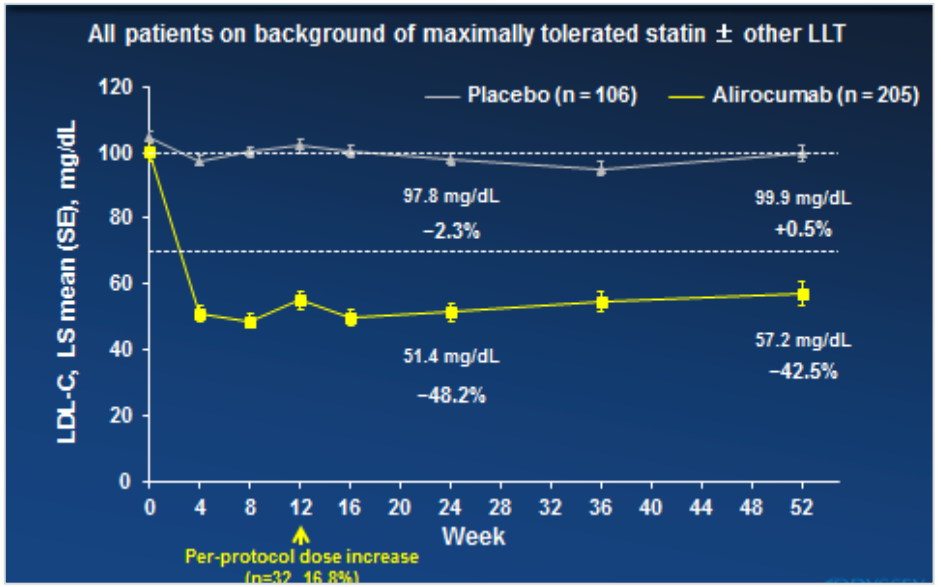




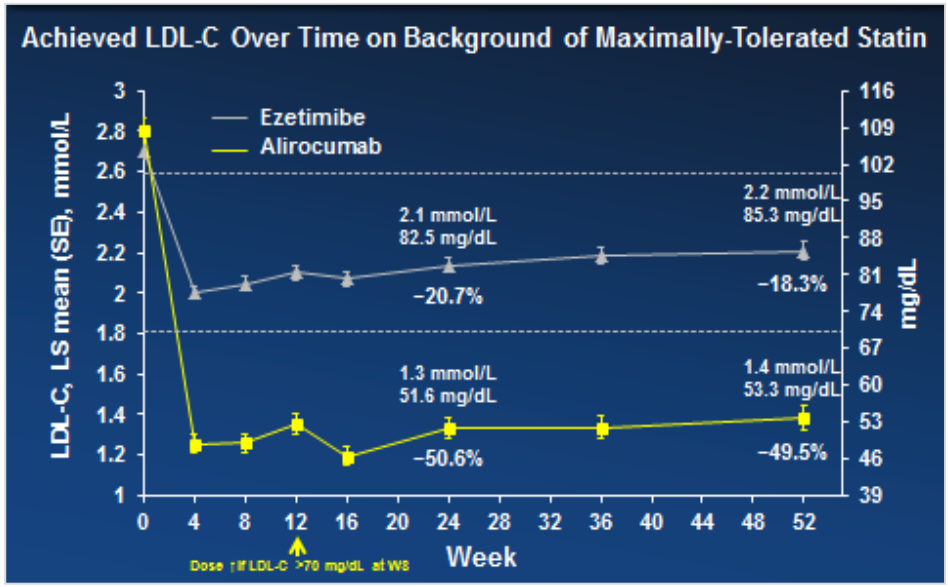


Consistent LDL-C Reductions Over 52 Weeks

COMBO I



COMBO II



- LDL-C ↓ from baseline maintained over 52 weeks with alirocumab
- Mean achieved LDL-C levels of 53.3 mg/dL in COMBO I and 53.3 mg/dL in COMBO II at week 52 with alirocumab
- Consistent effects of alirocumab vs comparator through 52 weeks

Kereiakes DJ et al. *Am Heart J. 2015 Jun;169(6):906-915.e13*
Cannon CP et al. *Eur Heart J* 2015 36(19):1186-94

Alirocumab Dose Selection Based on Patient Needs

A flexible model to address:

- Different baseline LDL-C
- Different background LLT
- Treat to target approach

75 mg Q2W
1 ml

LDL-C
-50%

150 mg Q2W
1 ml

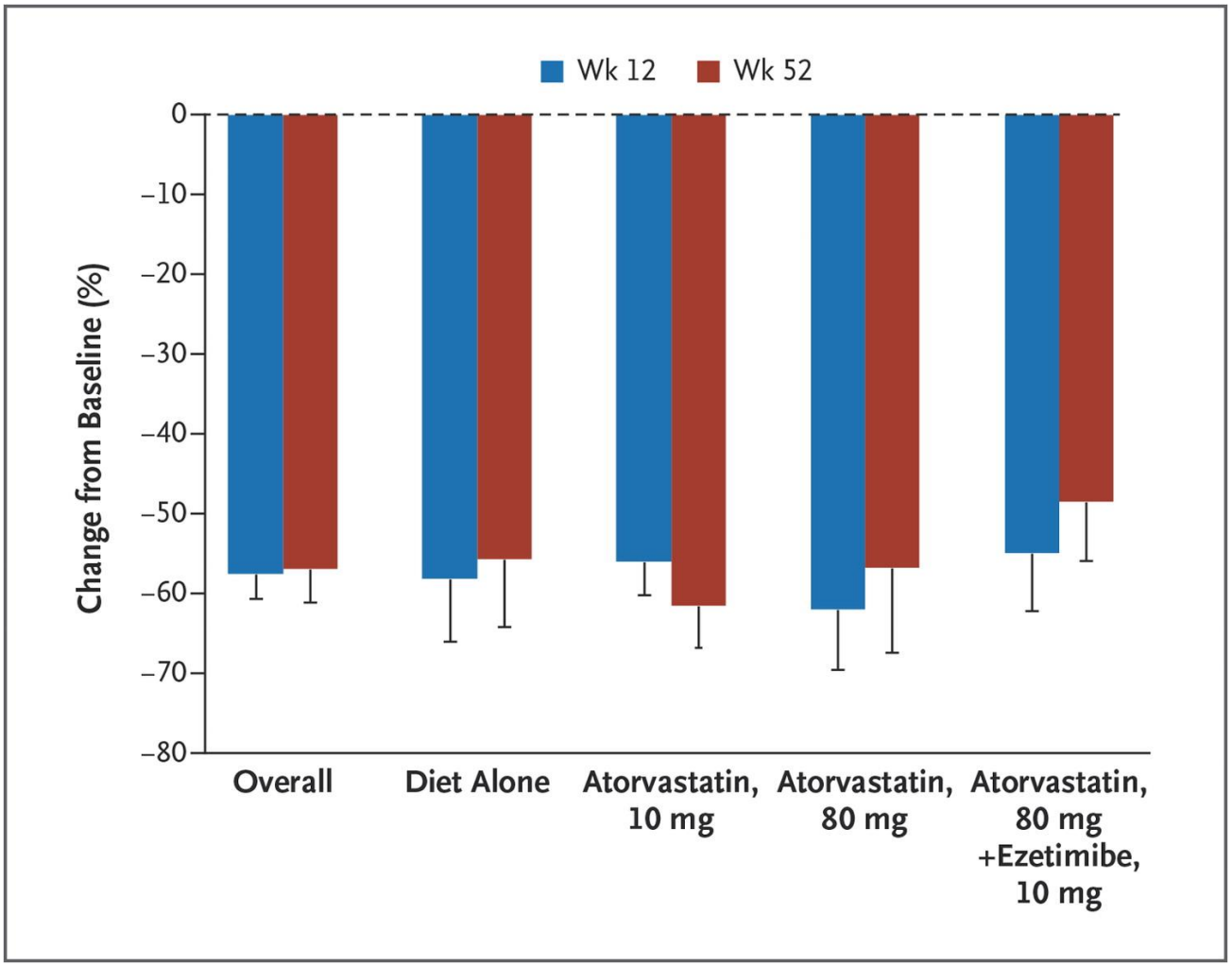
LDL-C
-70%

Additional offer Q4W:

- **300 mg (+ statins)**
- **150 mg (- statins)**

Percent Reduction from Baseline in Low-Density Lipoprotein (LDL) Cholesterol Levels in the Evolocumab Group, as Compared with the Placebo Group, at Weeks 12 and 52, According to Background Lipid-Lowering Therapy.

N=901



Blom DJ et al. N Engl J Med 2014;370:1809-1819.

Results of Bococizumab, A Monoclonal Antibody Against PCSK9, from a Randomized, Placebo-Controlled, Dose-Ranging Study in Statin-Treated Subjects With Hypercholesterolemia

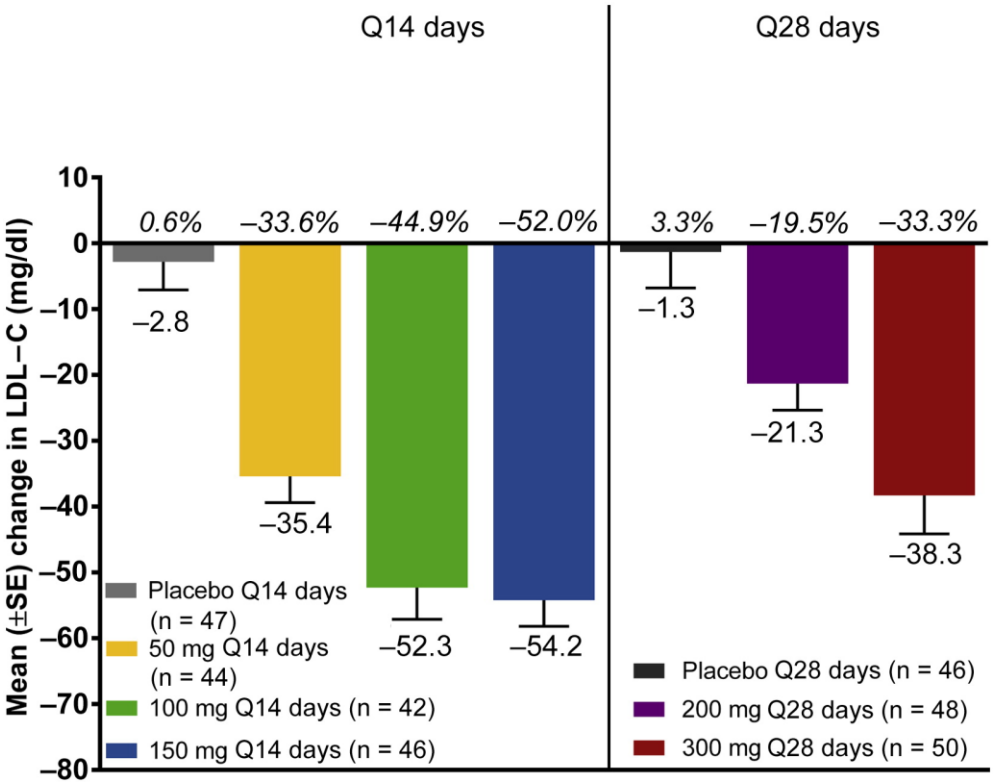


Figure 2 Mean absolute change from baseline in LDL-C at week 12. The placebo and bococizumab Q14 days and Q28 days dose groups are shown, with the corresponding mean percent changes from baseline in italics.

Ballantyne CM et al. The American Journal of Cardiology, Volume 115, Issue 9, 2015, 1212 - 1221

Familial Hypercholesterolemia

Alirocumab Studies in Familial Hypercholesterolemia

ODYSSEY FH I
ODYSSEY FH II
ODYSSEY HIGH FH

Kastelein et al., ESC 2014 oral presentation, Efficacy and safety of alirocumab in patients with heFH not adequately controlled with current lipid-lowering therapy: Results of ODYSSEY FH I and FH II studies

Ginsberg et al. AHA 2014 oral presentation, ODYSSEY HIGH FH: Efficacy and Safety of Alirocumab in Patients with Severe Heterozygous Familial Hypercholesterolemia

Baseline Characteristics

All patients on background of max-tolerated statin ± other lipid-lowering therapy	FH I		FH II		HIGH FH	
	Alirocumab (N=323)	**Placebo (N=163)**	**Alirocumab (N=167)**	**Placebo (N=82)**	**Alirocumab (N=72)**	**Placebo (N=35)**
Diagnosis of HeFH*, % (n) Genotyping Clinical criteria	39.9% (129) 59.8% (193)†	38.0% (62) 62.0% (101)	70.1% (117) 29.9% (50)	81.7% (67) 18.3% (15)	19.4% (14) 80.6% (58)	14.3% (5) 85.7% (30)
Age, years, mean (SD)	52.1 (12.9)	51.7 (12.3)	53.2 (12.9)	53.2 (12.5)	49.8 (14.2)	52.1 (11.2)
Male, % (n)	55.7% (180)	57.7% (94)	51.5% (86)	54.9% (45)	48.6% (35)	62.9% (22)
Race, white, % (n)	92.9% (300)	88.3% (144)	98.2% (164)	97.6% (80)	88.9% (64)	85.7% (30)
BMI, kg/m^2, mean (SD)	29.0 (4.6)	30.0 (5.4)	28.6 (4.6)	27.7 (4.7)	28.8 (5.2)	28.9 (4.2)
CHD history, % (n)	45.5% (147)	47.9% (78)	34.1% (57)	37.8% (31)	43.1% (31)	62.9% (22)
Current smoker, % (n)	12.1% (39)	18.4% (30)	21.6% (36)	15.9% (13)	16.7% (12)	25.7% (9)
Hypertension, % (n)	43.0% (139)	43.6% (71)	34.1% (57)	29.3% (24)	55.6% (40)	60.0% (21)
Type 2 diabetes, % (n)	9.6% (31)	15.3% (25)	4.2% (7)	3.7% (3)	12.5% (9)	17.1% (6)

*Diagnosis of HeFH must be made either by genotyping or by clinical criteria. For those patients not genotyped, the clinical diagnosis may be based on either the Simon Broome criteria for definite FH or the WHO/Dutch Lipid Network criteria with a score of >8 points.

† In FH I, one patient was categorized as "probable" FH by clinical criteria – genotyping results for this patient are pending.

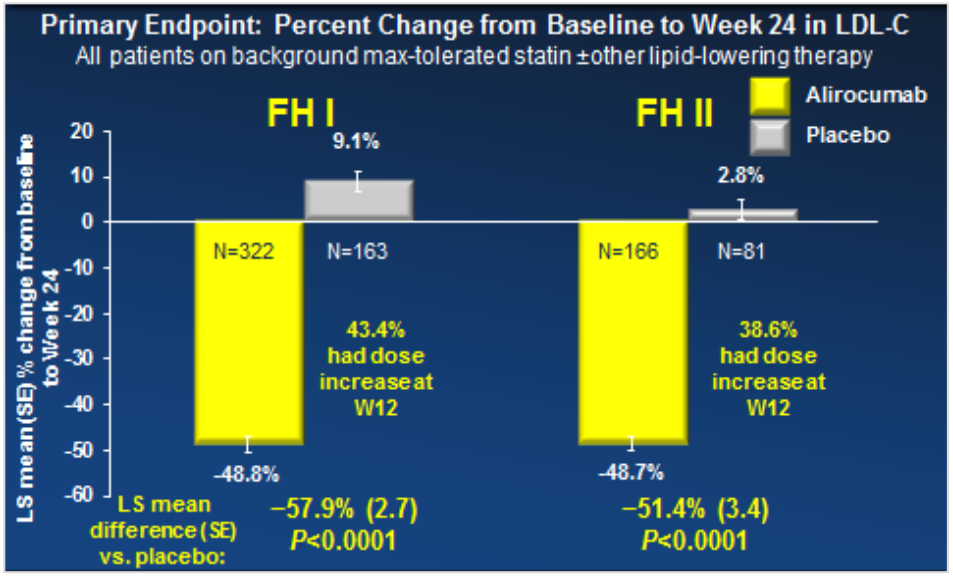
Lipid Medication and LDL-C at Baseline

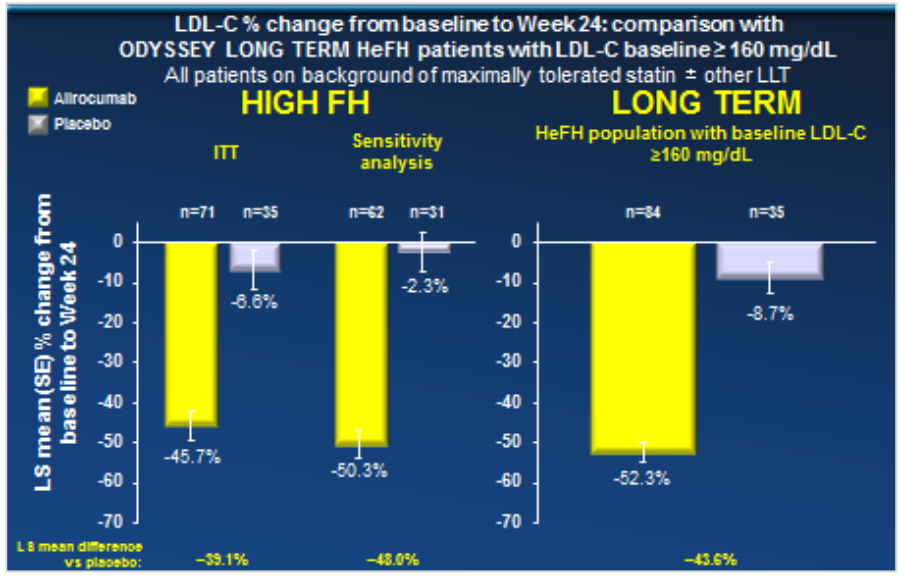
All patients on background of max-tolerated statin ± other lipid-lowering therapy	FH I		FH II		HIGH FH	
	Alirocumab (N=323)	**Placebo** (N=163)	**Alirocumab** (N=167)	**Placebo** (N=82)	**Alirocumab** (N=72)	**Placebo** (N=35)
Any statin*, % (n)	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**
High-intensity statin†, % (n)	**80.8%** (261)	**82.8%** (135)	**86.2%** (144)	**87.8%** (72)	**79.2%** (57)	**80.0%** (28)
Ezetimibe, % (n)	**55.7%** (180)	**59.5%** (97)	**67.1%** (112)	**64.6%** (53)	**19.4%** (14)	**34.3%** (12)
LDL-C, mean (SD), **mg/dL**	**144.7** (51.2)	**144.4** (46.8)	**134.6** (41.3)	**134.0** (41.6)	**196.3** (57.9)	**201.0** (43.4)

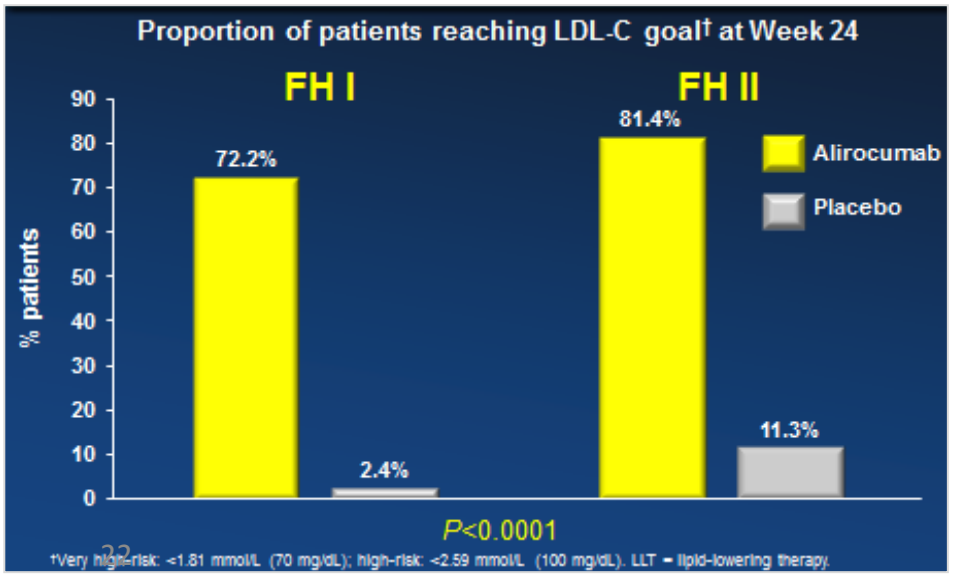
*Patients should receive either rosuvastatin 20-40 mg, atorvastatin 40-80 mg daily, or simvastatin 80 mg daily unless not tolerated and/or appropriate other dose given according to the judgement of the investigator.

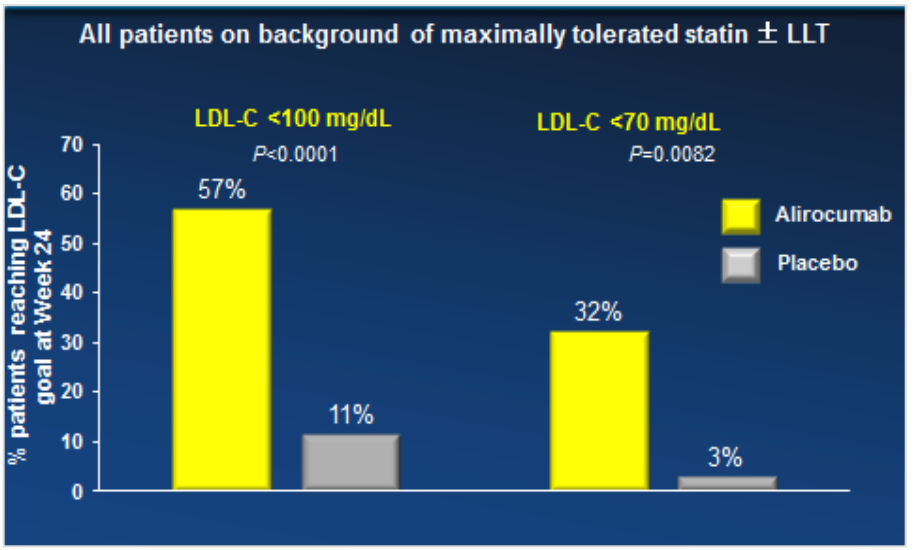
† High-intensity statin: atorvastatin 40-80 mg or rosuvastatin 20-40 mg daily.

LDL-C Reductions and Goal Achievement



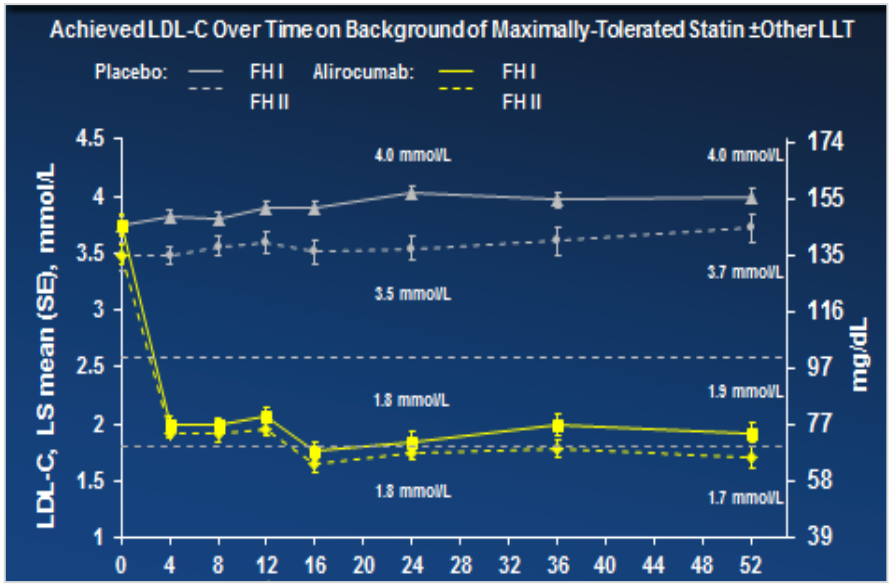




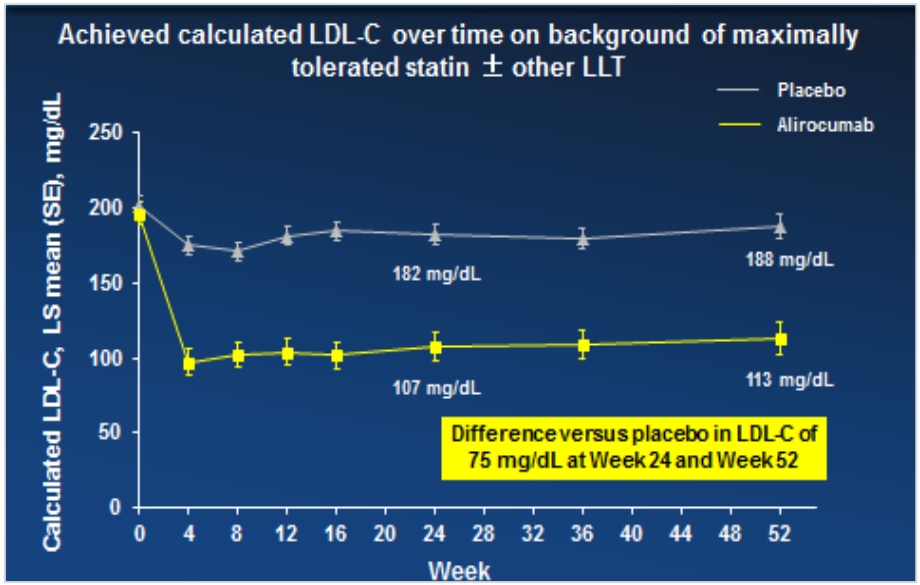


Consistent LDL-C Reductions Over 52 Weeks

FH I and FH II



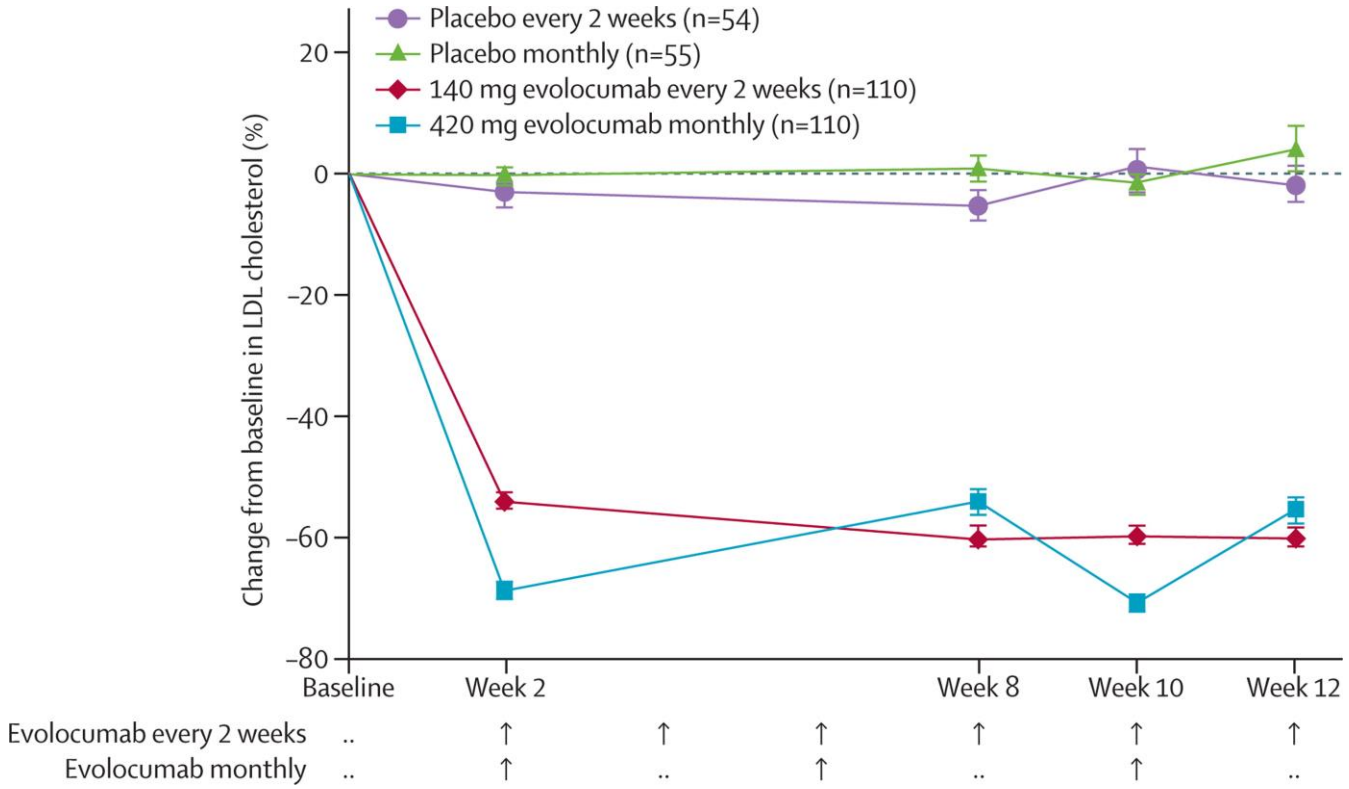
HIGH FH



- Significantly greater LDL-C ↓ vs placebo at week 24 in FH I, FH II, and HIGH FH (P<0.001 for all studies)
- Mean achieved LDL-C levels with alirocumab of 65.9-74.3 mg/dL at week 52 in FH I and II and 107 mg/dL at week 24 in HIGH FH
- In HIGH FH, percentage decrease from baseline informed by high baseline LDL-C (196.3 mg/dL):
  - The absolute mean decrease from baseline in LDL-C was –90.8 mg/dL at Week 24 with alirocumab versus 182 mg/dL with placebo

PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial

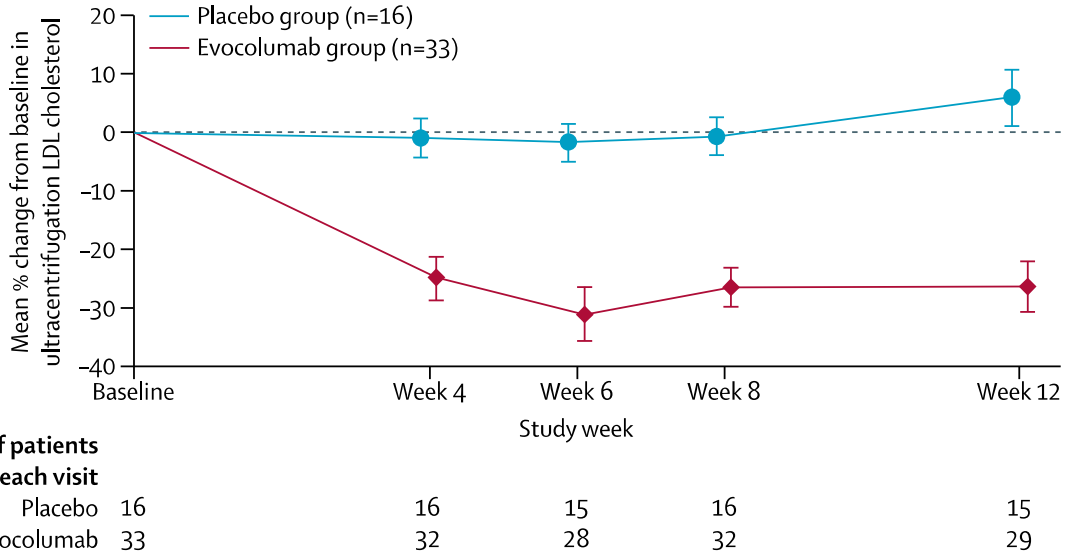
*Frederick J Raal, Evan A Stein, Robert Dufour, Traci Turner, Fernando Civeira, Lesley Burgess, Gisle Langslet, Russell Scott, Anders G Olsson, David Sullivan, G Kees Hovingh, Bertrand Cariou, Ioanna Gouni-Berthold, Ransi Somaratne, Ian Bridges, Rob Scott, Scott M Wasserman, Daniel Gaudet, for the RUTHERFORD-2 Investigators**



Raal FJ et al. Lancet 2015; 385: 331–40

Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial

*Frederick J Raal, Narimon Honarpour, Dirk J Blom, G Kees Hovingh, Feng Xu, Rob Scott, Scott M Wasserman, Evan A Stein, for the TESLA Investigators**



On treament residual LDL= 280 mg/dL

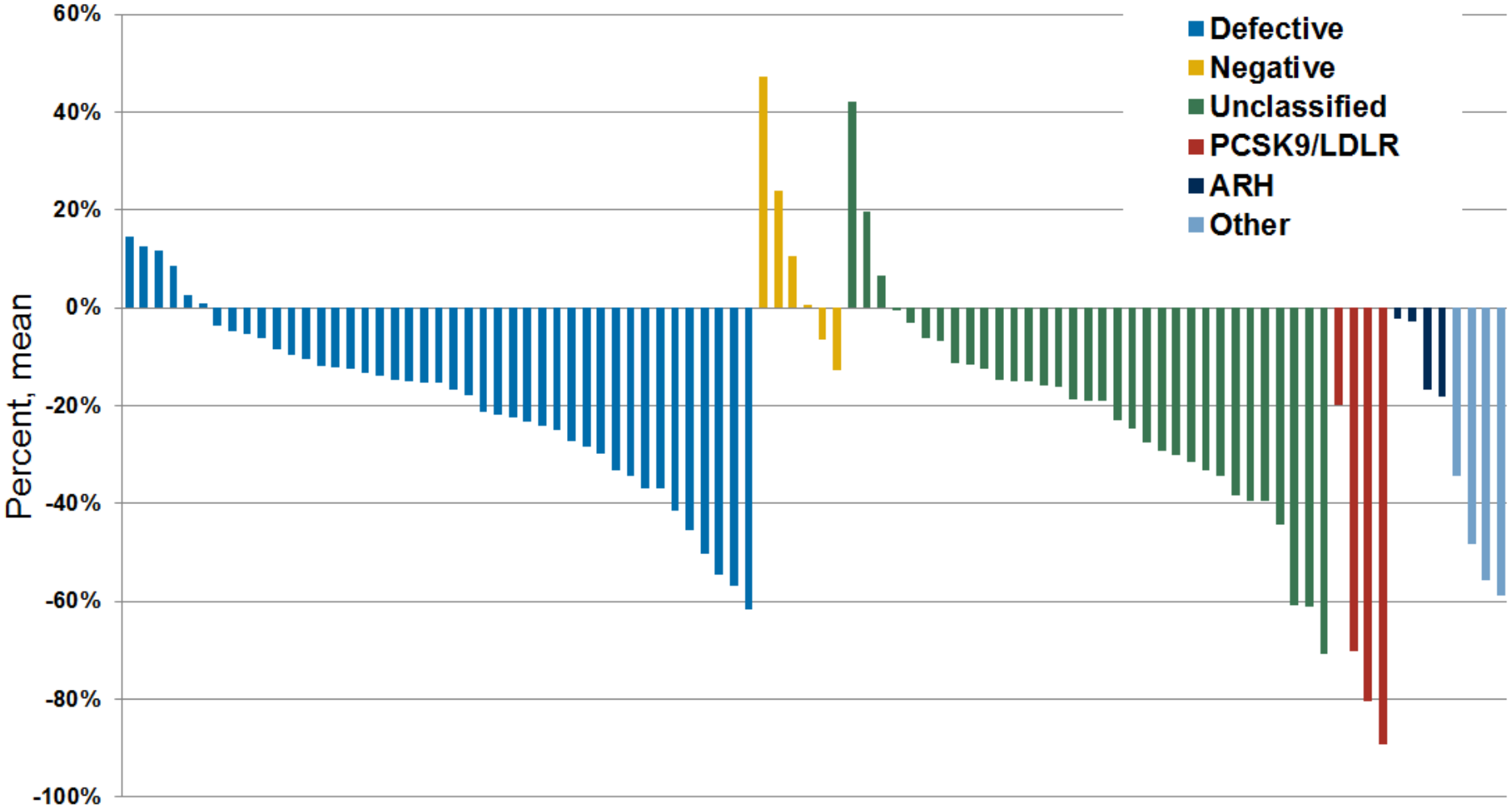
Figure 2: **Mean percentage change in ultracentrifugation LDL cholesterol concentration from baseline to week 12**

Vertical lines represent standard error around the mean. The plot is based on observed values and no imputation was used for missing values. Number of patients represents those analysed for this endpoint at each visit.

www.thelancet.com **Published online October 2, 2014 http://dx.doi.org/10.1016/S0140-6736(14)61374-X**

Individual Percent Change from Baseline to Week 12 in UC LDL-C (N = 94)

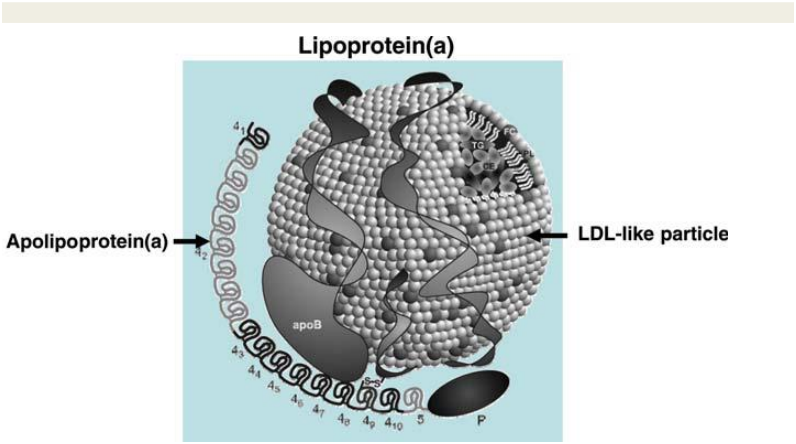
TAUSSIG



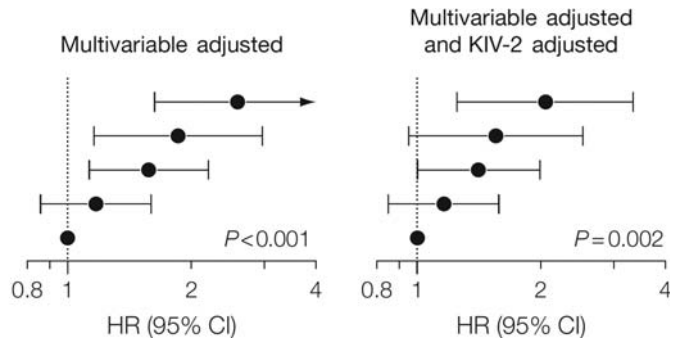
Abbreviations: ARH, autosomal recessive hypercholesterolemia .

Raal et al ISA 2015

Lipoprotein(a) : and independent risk factor for cardiovascular disease



Lipoprotein(a) Percentile	mg/dL	Participants (no.)	Events (no.)
>95th	>117	376	46
90th–95th	77–117	450	46
67th–89th	30–76	1731	155
22nd–66th	5–29	3385	241
<22nd [reference]	<5	1582	104



Kamstrup et al. JAMA 2009; 301:2331 – 2339.

Lipoprotein(a) Levels in Familial Hypercholesterolemia : An Important Predictor of Cardiovascular Disease Independent of the Type of LDL Receptor Mutation

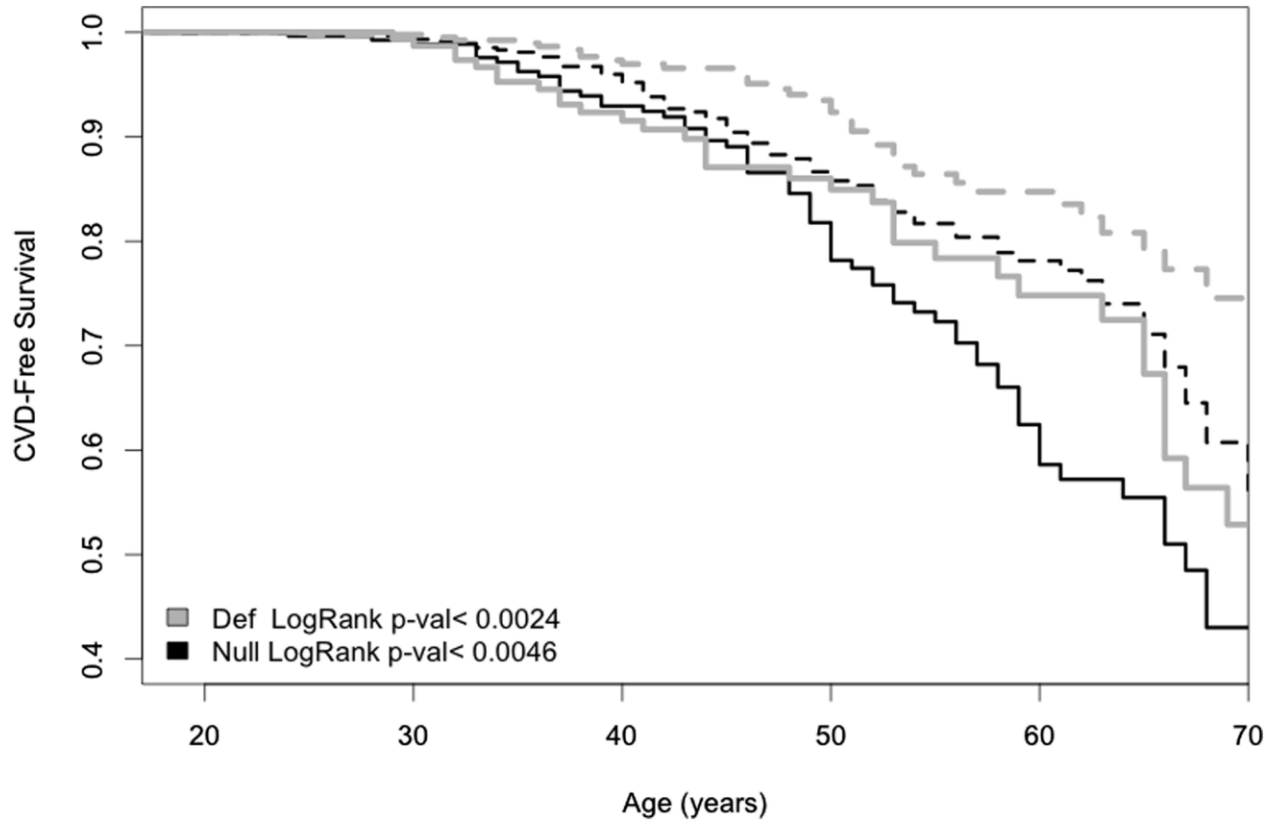
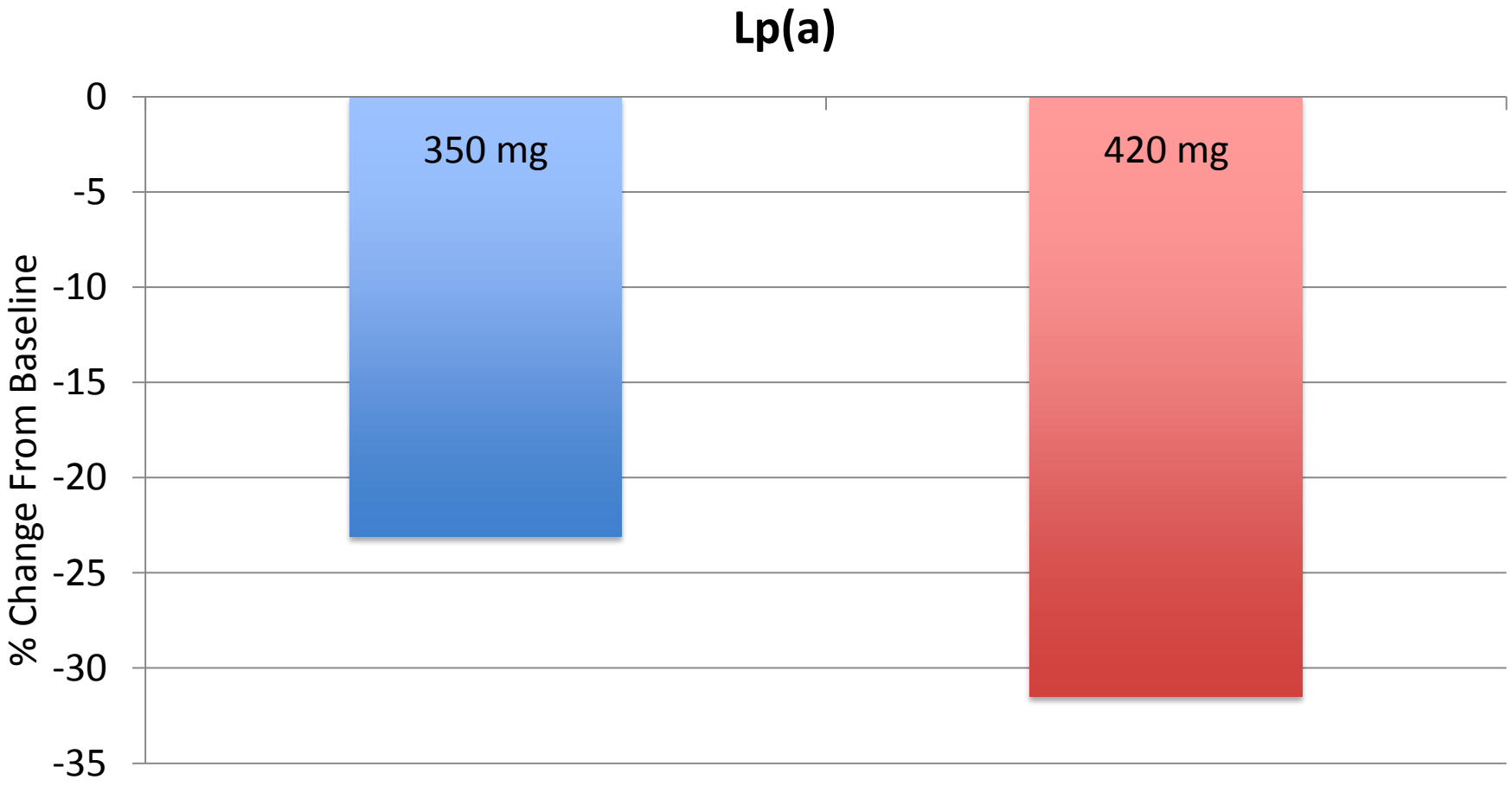


Figure 4 Kaplan-Meier Curves for CVD-Free Survival in Subjects With FH According to Lp(a) Levels and Type of Mutation The black solid line indicates null mutations and Lp(a) levels >50 mg/dl; the black dashed line indicates null mutations and Lp(a)...

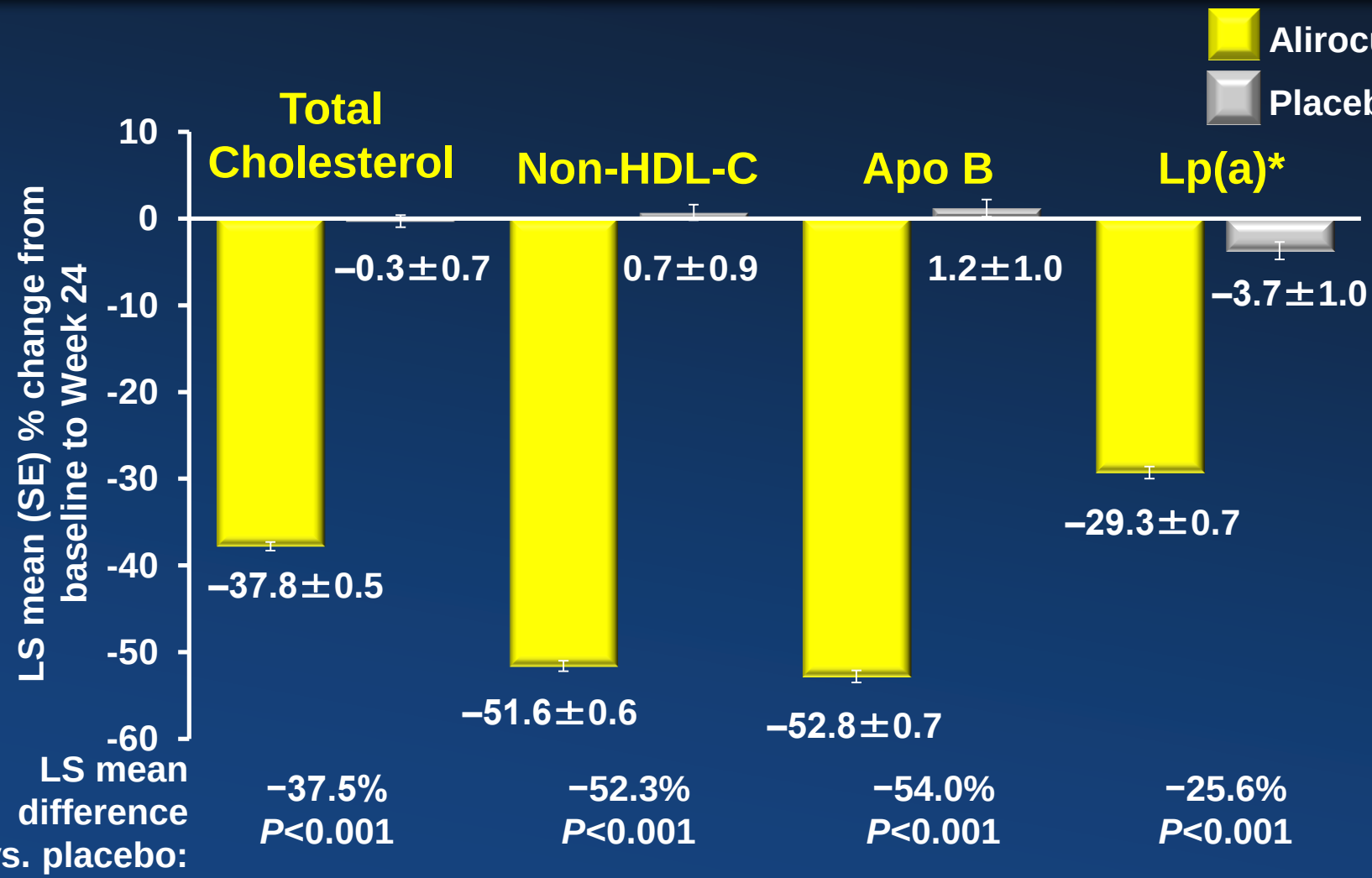
Alonso R et al. Journal of the American College of Cardiology, Volume 63, Issue 19, 2014, 1982 - 1989

Evolocumab Reduces Lp(a) in Heterozygous FH



Raal F et al. Circulation 2012;126:2408-2417

Change from Baseline to Week 24:
Total Cholesterol, Non-HDL-C, Apo B and Lp(a) (ITT)



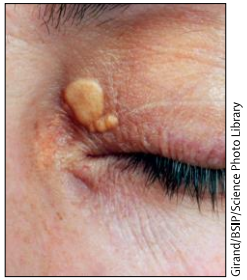
These are secondary endpoints in ITT analysis population. *Analyzed with the use of multiple imputation, followed by robust regression. A combined estimate for adjusted mean (±SE) is shown. Robinson JG et al. *NEJM* 2015; 372:1489-99.

SANOFI

Robinson JG et al. *NEJM* 2015; 372:1489-99.

REGENERON

Familial hypercholesterolaemia: PCSK9 inhibitors are coming



Girard/BSIP/Science Photo Library

Published Online
October 2, 2014
http://dx.doi.org/10.1016/
S0140-6736(14)61702-5

If proven to be safe and efficacious in the long term, as well as cost effective, PCSK9 monoclonal antibodies might be the best standard of care for many patients with severe forms of familial hypercholesterolaemia.

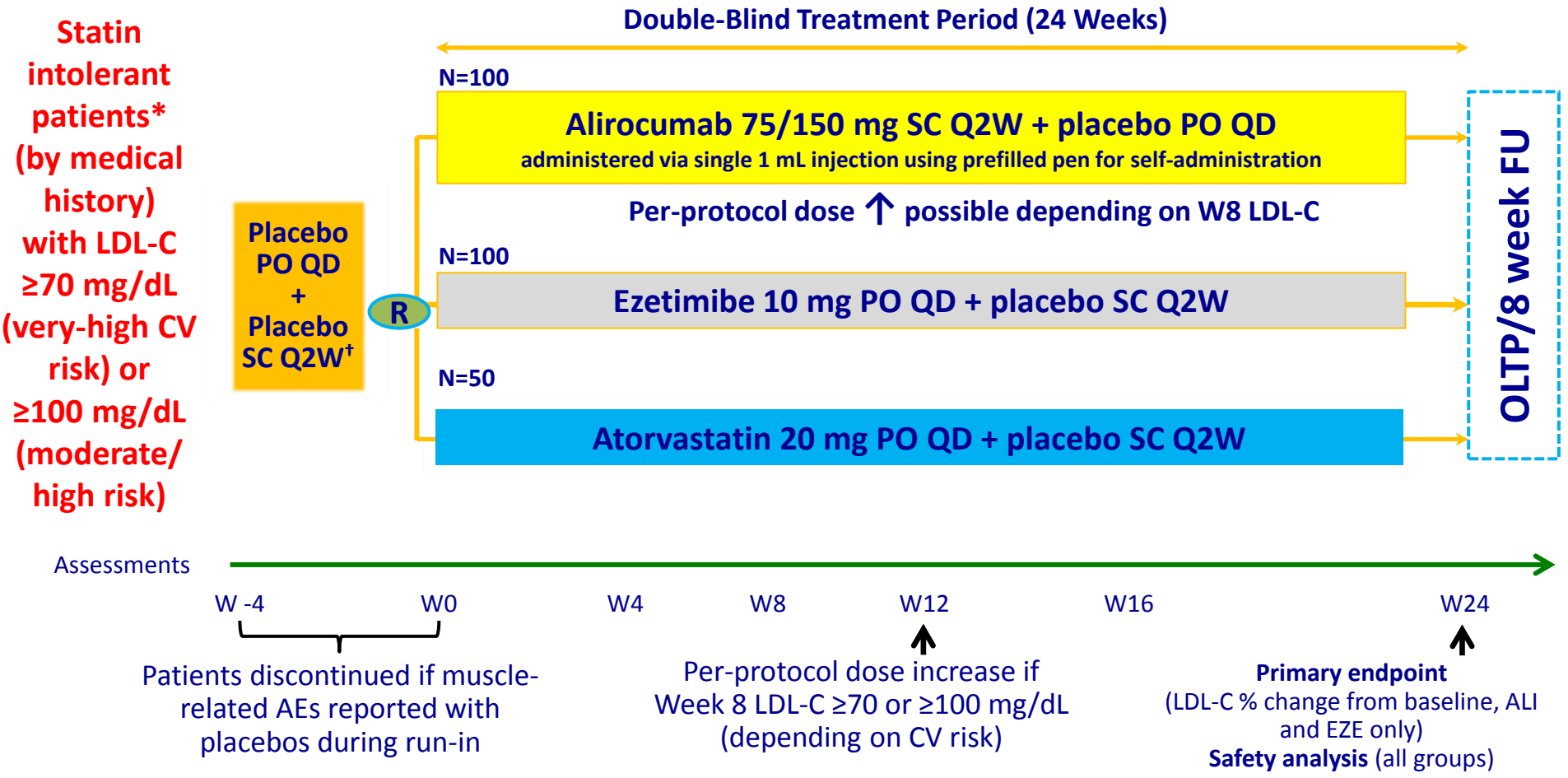
Santos RD & Watts G. Lancet. 2015 ;385:307-10

Studies in Statin Intolerance

ODYSSEY ALTERNATIVE

Moriarty et al. AHA 2014 oral presentation, ODYSSEY ALTERNATIVE:
Efficacy and safety of alirocumab versus ezetimibe, in patients with statin intolerance defined by placebo run-in and statin rechallenge arm

ODYSSEY ALTERNATIVE Study Design

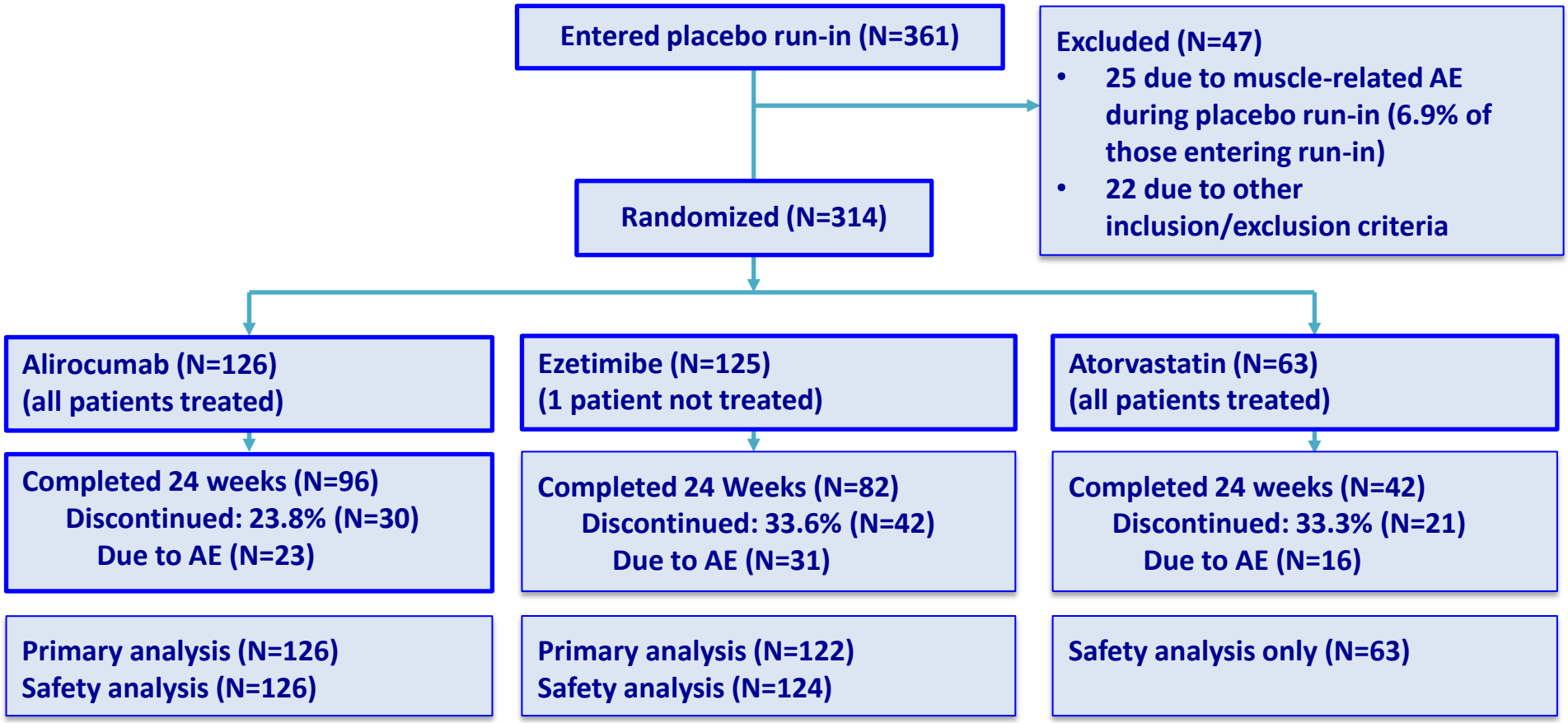


∗Unable to tolerate at least two different statins, including one at the lowest dose, due to muscle-related symptoms

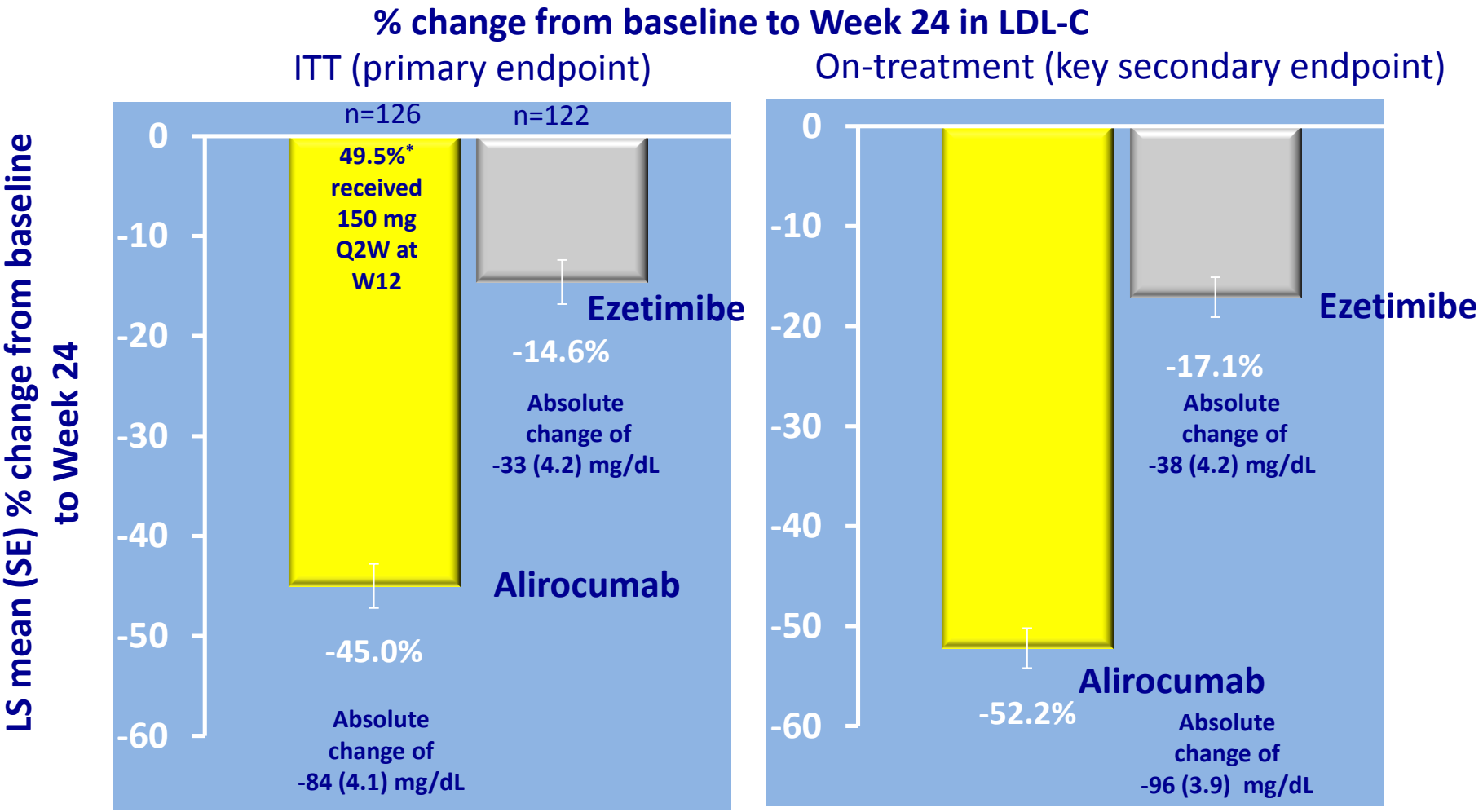
†4-week single-blind placebo run-in follows 2-week washout of statins, ezetimibe and red yeast rice.

OLTP: Alirocumab open-label treatment period; W, Week.

Patient Disposition



Alirocumab Significantly Reduced LDL-C From Baseline to Week 24 vs Ezetimibe



LS mean difference (SE) vs ezetimibe: -30.4 (3.1); *P*<0.0001

LS mean difference (SE) vs ezetimibe: -35.1 (2.8); *P*<0.0001

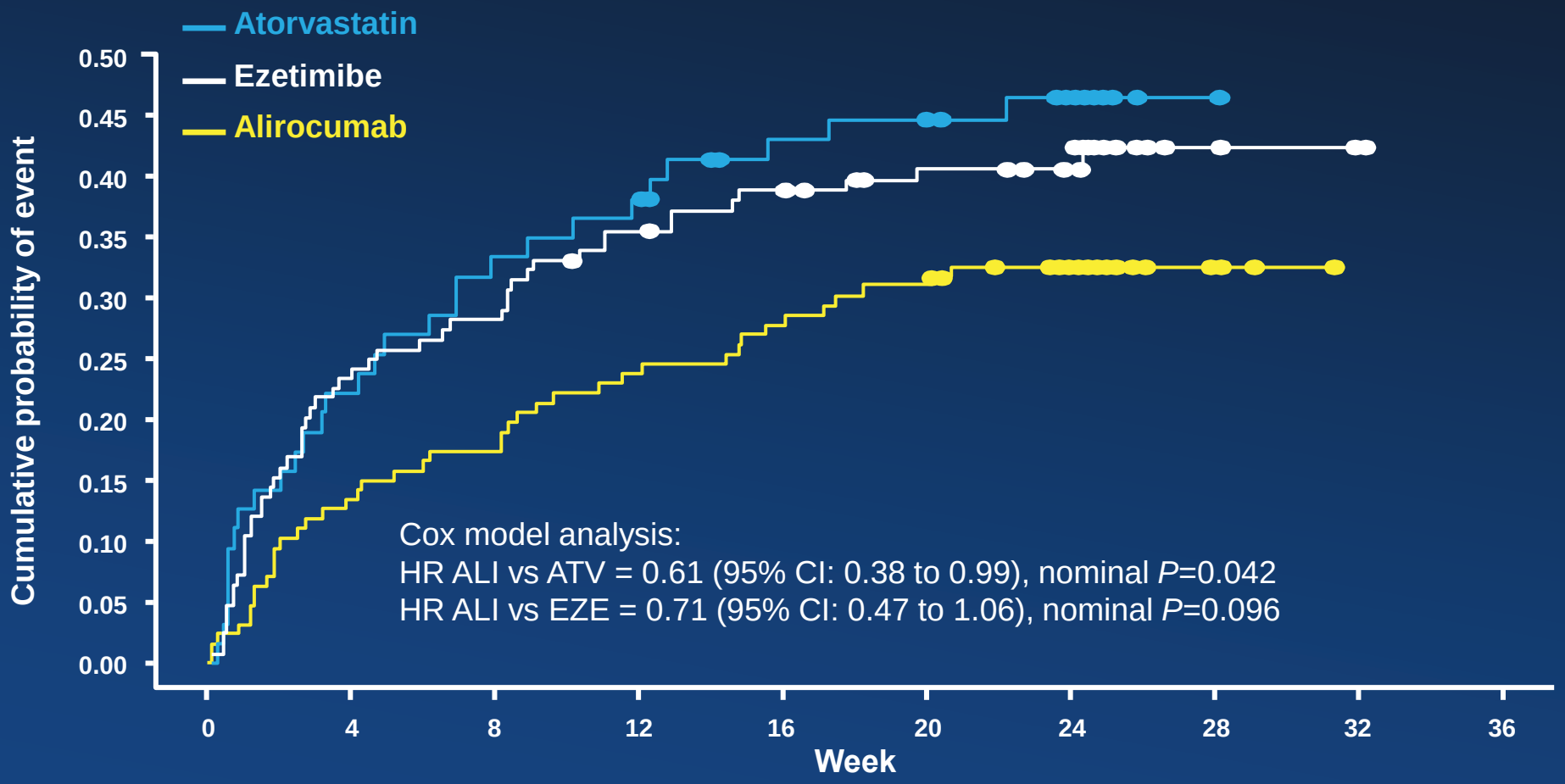
*49.5% of 109 patients who received at least one injection after Week 12 had dose increase.

Safety Analysis

% of patients	Alirocumab (N=126)	Ezetimibe (N=124)	Atorvastatin (N=63)
TEAEs*	82.5%	80.6%	85.7%
Treatment-emergent SAEs	9.5%	8.1%	11.1%
TEAEs leading to death	0	0	0
TEAEs leading to discontinuation	18.3%	25.0%	25.4%
Any skeletal-muscle related TEAE†	32.5%	41.1%	46.0%
HR (95% CI) alirocumab vs comparator	-	0.71 (95% CI: 0.47 to 1.06)	0.61 (95% CI: 0.38 to 0.99)
P-value vs alirocumab‡	-	0.096	0.042
Skeletal-muscle related TEAE leading to discontinuation	15.9%	20.2%	22.2%
HR (95% CI) alirocumab vs comparator	-	0.78 (95% CI: 0.43 to 1.41)	0.67 (95% CI: 0.34 to 1.32)
P-value vs alirocumab‡	-	0.409	0.240

Fewer Skeletal Muscle AEs With Alirocumab Than With Atorvastatin

Kaplan-Meier estimates for time to first skeletal muscle event*



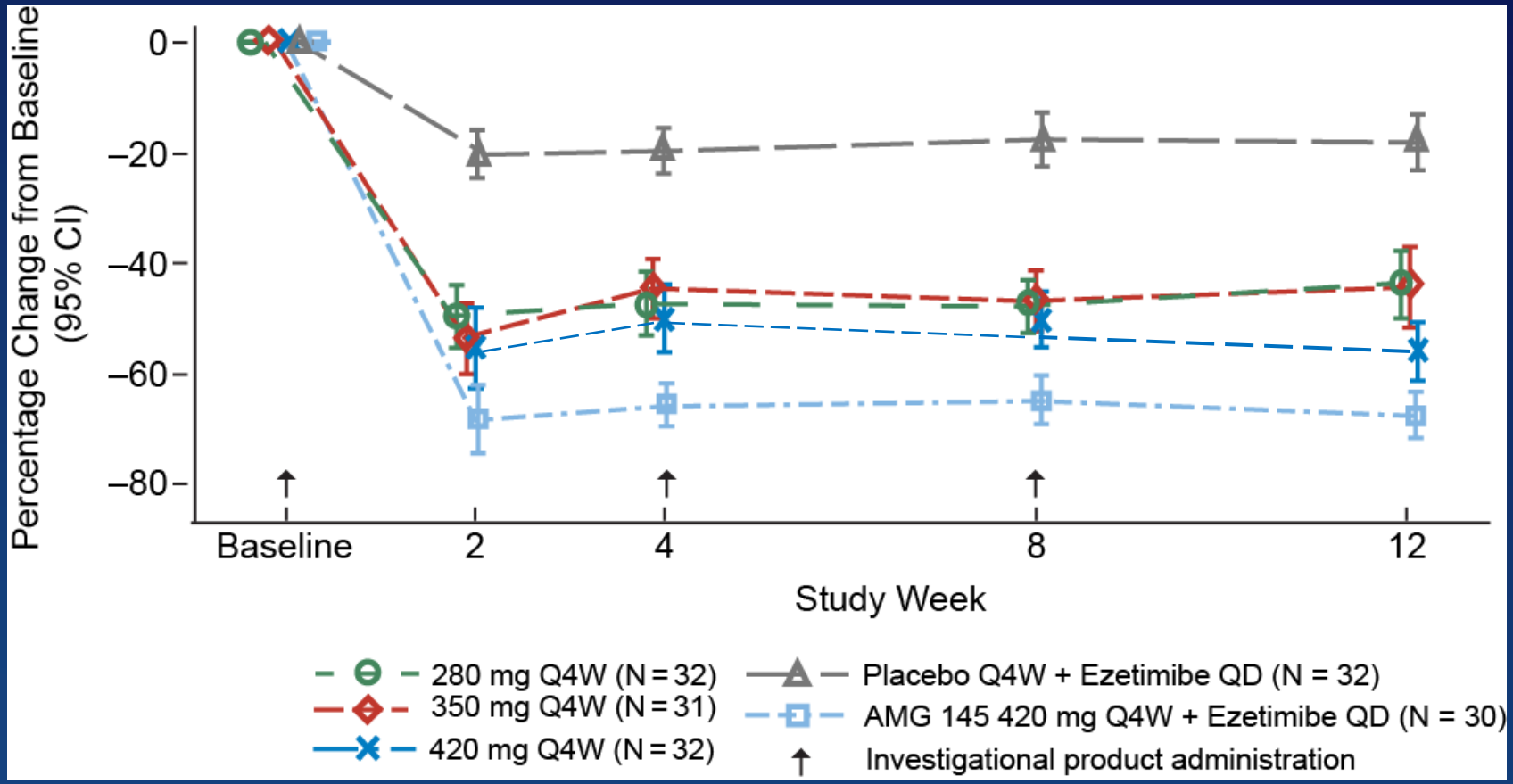
*Pre-defined category including myalgia, muscle spasms, muscular weakness, musculoskeletal stiffness, muscle fatigue.
ALI=alirocumab; ATV= atorvastatin, EZE=ezetimibe.

SANOFI

Moriarty et al AHA 2014

REGENERON

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



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

Sullivan et al JAMA 2012;126:2408-17

GAUSS: Safety and Tolerability

Adverse Events, Patient Incidence, n (%)	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
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.

Sullivan et al JAMA 2012;126:2408-17

Safety

Pooled Safety Across ODYSSEY

TEAEs Occurring in ≥5% Patients in Any Group (Pool of 4x Phase 2 + 10x Phase 3 trials*)

% (n) of patients All pts on background statin	Ezetimibe-controlled pool (N=1482)		Placebo-controlled pool (N=3752)	
TEAEs by preferred term in ≥5% patients	Alirocumab n=864	Ezetimibe n=618	Alirocumab n=2476	Placebo n=1276
Nasopharyngitis	5.4% (37)	5.7% (35)	11.3% (279)	11.1% (141)
Myalgia	6.7% (58)	7.6% (47)	4.2% (104)	3.4% (44)
Upper respiratory tract infection	5.9% (51)	6.0% (37)	6.1% (152)	7.0% (89)
Injection site reaction	2.9% (25)	1.9% (12)	6.7% (166)	4.8% (61)
Influenza	3.7% (32)	2.3% (14)	5.7% (141)	4.6% (59)
Headache	3.9% (34)	3.4% (21)	4.8% (119)	5.2% (66)

*Placebo-controlled studies: phase 3 (LTS11717, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
Ezetimibe-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE).
Includes all data collected to last patient visit at 52 wks for COMBO, FH, HIGH FH and LONG TERM studies.

Pooled Neurocognitive Disorders

Safety Analysis – Total TEAEs

% (n) of patients	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo (N=1276)	Alirocumab (N=2476)	Ezetimibe (N=618)	Alirocumab (N=864)
% (n)	0.7% (9)	0.8% (21)	1.0% (6)	0.9% (8)
95% mid-p CI	0.3% to1.3%	0.5% to1.3%	0.4% to 2.0%	0.4% to 1.8%
Number of patients with an event per 100 patient years*	0.6	0.7	1.3	1.1
95% CI	0.3 to 1.2	0.5 to 1.1	0.5 to 2.8	0.5 to 2.2
Hazard ratio versus control (95% CI)†	1.18 (0.54 to 2.58)		0.94 (0.32 to 2.74)	

* Calculated as number of patients with an event divided by total patient years. For patients with event, number of patient years is calculated up to date of the first event, for patients without event, it corresponds to the length of TEAE period.

† Calculated using a Cox model stratified on the study.

Patients attaining very low LDL levels

Is it bad?

TEAEs (≥2%) in Patients With 2 Consecutive LDL-C <25 mg/dL – by Organ Class

Primary System Organ Class	Control (N=1894) n	Control (N=1894) Rate (%)	Control (N=1894) Rate/ 100 PY	Alirocumab (N=3340) n	Alirocumab (N=3340) Rate (%)	Alirocumab (N=3340) Rate/ 100 PY	Alirocumab LDL-C ≥25mg/dL (N=2544) n	Alirocumab LDL-C ≥25mg/dL (N=2544) Rate (%)	Alirocumab LDL-C ≥25mg/dL (N=2544) Rate/ 100 PY	Alirocumab 2 LDL-C <25mg/dL (N=796) n	Alirocumab 2 LDL-C <25mg/dL (N=796) Rate (%)	Alirocumab 2 LDL-C <25mg/dL (N=796) Rate/ 100 PY
Infections and infestations	687	36.3%	49.1	1286	38.5%	49.7	947	37.2%	49.6	271	34.0%	44.3
Musculoskeletal and connective tissue disorders	478	25.2%	29.8	808	24.2%	27.1	605	23.8%	27.6	168	21.1%	24.6
Gastrointestinal disorders	318	16.8%	18.6	567	17.0%	17.9	426	16.7%	18.4	101	12.7%	13.8
General and administration site conditions	282	14.9%	16.3	504	15.1%	15.8	395	15.5%	17	81	10.2%	10.9
Nervous system disorders	283	14.9%	16.4	497	14.9%	15.4	384	15.1%	16.3	82	10.3%	11
Injury, poisoning, and procedural complications	242	12.8%	13.8	428	12.8%	13	329	12.9%	13.7	80	10.1%	10.7
Respiratory, thoracic, mediastinal	172	9.1%	9.5	325	9.7%	9.6	242	9.5%	9.8	62	7.8%	8.1
Cardiac disorders	159	8.4%	8.7	275	8.2%	8	212	8.3%	8.5	53	6.7%	6.9
Skin and subcutaneous tissue	130	6.9%	7.1	270	8.1%	7.9	203	8.0%	8.2	51	6.4%	6.7
Investigations	127	6.7%	6.9	235	7.0%	6.8	192	7.5%	7.6	34	4.3%	4.4
Metabolism and nutrition	120	6.3%	6.5	232	6.9%	6.7	164	6.4%	6.5	56	7.0%	7.4
Vascular disorders	134	7.1%	7.3	211	6.3%	6.1	164	6.4%	6.5	32	4.0%	4.1
Psychiatric disorders	110	5.8%	5.9	171	5.1%	4.9	137	5.4%	5.4	28	3.5%	3.6
Eye disorders	71	3.7%	3.8	152	4.6%	4.4	103	4.0%	4	42	5.3%	5.4
Renal and urinary disorders	84	4.4%	4.5	128	3.8%	3.6	98	3.9%	3.8	25	3.1%	3.2
Neoplasms benign, malignant, and unspecified	48	2.5%	2.5	85	2.5%	2.4	59	2.3%	2.3	22	2.8%	2.8
Reproductive and breast	40	2.1%	2.1	77	2.3%	2.2	58	2.3%	2.2	15	1.9%	1.9
Blood and lymphatic system	46	2.4%	2.4	72	2.2%	2	55	2.2%	2.1	13	1.6%	1.6
Ear and labyrinth disorders	53	2.8%	2.8	56	1.7%	1.6	44	1.7%	1.7	11	1.4%	1.4

Table S6. Neurocognitive TEAEs: Safety Analysis

	Alirocumab (N = 1550)	Alirocumab with 2 consecutive LDL cholesterol <25 mg/dL (N = 575)	Placebo (N = 788)
Neurocognitive disorders - no. of patients (%)*	18 (1.2)	3 (0.5)	4 (0.5)
Amnesia	5 (0.3)	0	0
Memory impairment	4 (0.3)	0	1 (0.1)
Confusional state	4 (0.3)	1 (0.2)	1 (0.1)
Confusion postoperative	1 (<0.1)	0	0
Dementia	1 (<0.1)	1 (0.2)	1 (0.1)
Disorientation	1 (<0.1)	0	0
Disturbance in attention	1 (<0.1)	0	1 (0.1)
Frontotemporal dementia	1 (<0.1)	1 (0.2)	0
Reading disorder	1 (<0.1)	0	0
Transient global amnesia	1 (<0.1)	0	0
Vascular encephalopathy	1 (<0.1)	0	0

*Neurocognitive events were selected with the use of a custom MedDRA query that was based on the

Robinson JG et al. N Engl J Med. 2015 ;372(16):1489-99

Adverse Events and Achieved LDL-C: Evolocumab

Supplemental Table S2 – Adverse Events and Laboratory Results by Achieved LDL Cholesterol

	Evolocumab subjects stratified by minimum post-baseline (achieved) LDL cholesterol				All evolocumab subjects (N =2976)
Subject incidence, n (%)	**<25 mg/dL (N =773)**	**25 to <40 mg/dL (N = 759)**	**<40 mg/dL (N = 1532)**	**(N= 1426)**	
Adverse event	541 (70.0)	517 (68.1)	1058 (69.1)	1000 (70.1)	2060 (69.2)
Serious adverse event	59 (7.6)	52 (6.9)	111 (7.2)	111 (7.8)	222 (7.5)
Muscle-related adverse event	38 (4.9)	54 (7.1)	92 (6.0)	98 (6.9)	190 (6.4)
CK >5× ULN	3 (0.4)	7 (0.9)	10 (0.7)	7 (0.5)	17 (0.6)
ALT/AST >3× ULN	7 (0.9)	6 (0.8)	13 (0.8)	18 (1.3)	31 (1.0)
Neurocognitive adverse event	4 (0.5)	9 (1.2)	13 (0.8)	14 (1.0)	27 (0.9)

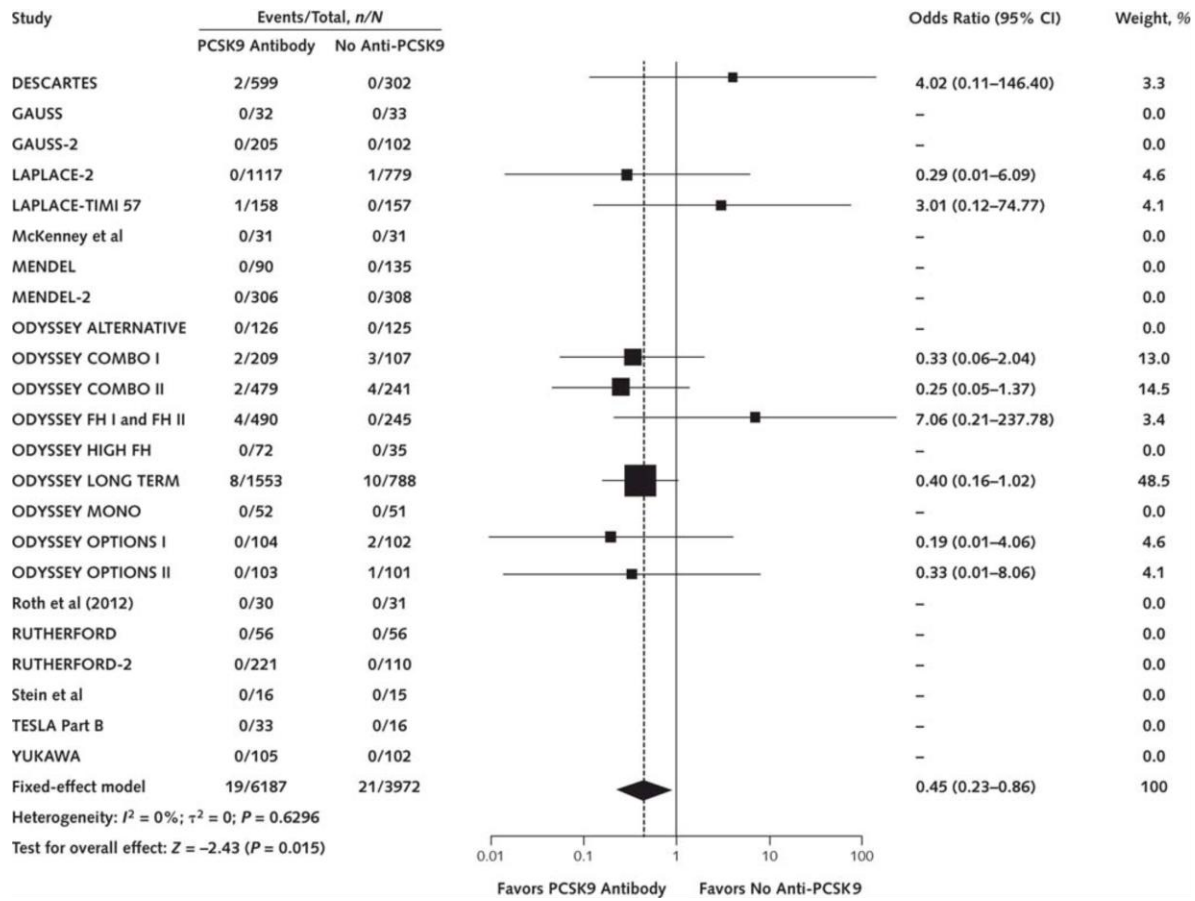
Sabatine MS et al. N Engl J Med 2015. 372(16):1500-9

Cardiovascular Events ?

Annals of Internal Medicine
Established in 1927 by the American College of Physicians

From: Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Antibodies in Adults With Hypercholesterolemia: A Systematic Review and Meta-analysisEffects of PCSK9 Antibodies in Adults With Hypercholesterolemia

Effects of PCSK9 inhibitors on All Cause Mortality



Study	Events/Total, *n/N*		Odds Ratio (95% CI)	Weight, %
	PCSK9 Antibody	No Anti-PCSK9		
DESCARTES	2/599	0/302	4.02 (0.11–146.40)	3.3
GAUSS	0/32	0/33	–	0.0
GAUSS-2	0/205	0/102	–	0.0
LAPLACE-2	0/1117	1/779	0.29 (0.01–6.09)	4.6
LAPLACE-TIMI 57	1/158	0/157	3.01 (0.12–74.77)	4.1
McKenney et al	0/31	0/31	–	0.0
MENDEL	0/90	0/135	–	0.0
MENDEL-2	0/306	0/308	–	0.0
ODYSSEY ALTERNATIVE	0/126	0/125	–	0.0
ODYSSEY COMBO I	2/209	3/107	0.33 (0.06–2.04)	13.0
ODYSSEY COMBO II	2/479	4/241	0.25 (0.05–1.37)	14.5
ODYSSEY FH I and FH II	4/490	0/245	7.06 (0.21–237.78)	3.4
ODYSSEY HIGH FH	0/72	0/35	–	0.0
ODYSSEY LONG TERM	8/1553	10/788	0.40 (0.16–1.02)	48.5
ODYSSEY MONO	0/52	0/51	–	0.0
ODYSSEY OPTIONS I	0/104	2/102	0.19 (0.01–4.06)	4.6
ODYSSEY OPTIONS II	0/103	1/101	0.33 (0.01–8.06)	4.1
Roth et al (2012)	0/30	0/31	–	0.0
RUTHERFORD	0/56	0/56	–	0.0
RUTHERFORD-2	0/221	0/110	–	0.0
Stein et al	0/16	0/15	–	0.0
TESLA Part B	0/33	0/16	–	0.0
YUKAWA	0/105	0/102	–	0.0
Fixed-effect model	19/6187	21/3972	0.45 (0.23–0.86)	100

Heterogeneity: $I^2 = 0\%$; $\tau^2 = 0$; $P = 0.6296$

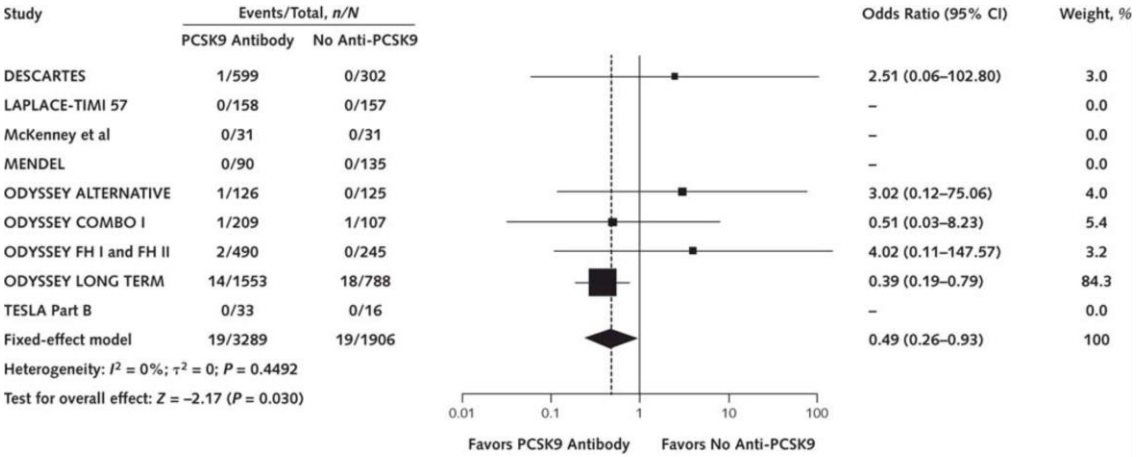
Test for overall effect: $Z = -2.43$ ($P = 0.015$)

Navarese et al. Ann Intern Med. 2015;163(1):40-51.

Annals of Internal Medicine
Established in 1927 by the American College of Physicians

From: Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Antibodies in Adults With Hypercholesterolemia: A Systematic Review and Meta-analysisEffects of PCSK9 Antibodies in Adults With Hypercholesterolemia

Myocardial infarction

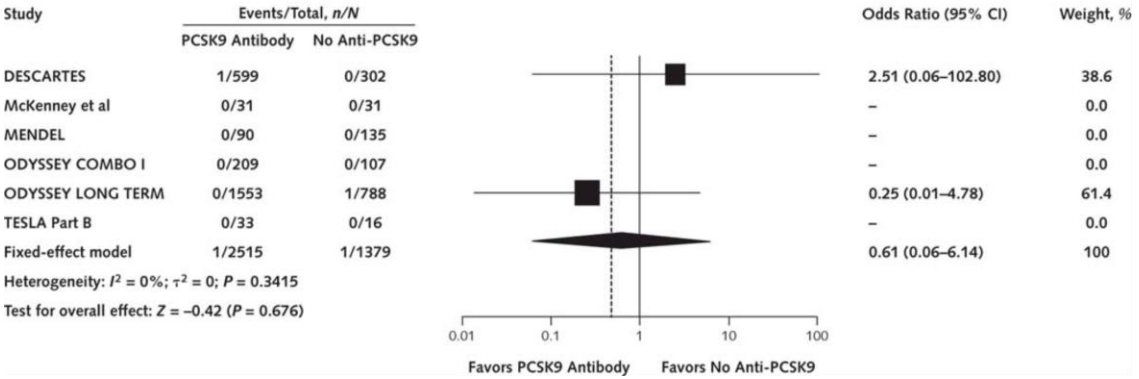


Study	Events/Total, *n/N*		Odds Ratio (95% CI)	Weight, %
	PCSK9 Antibody	No Anti-PCSK9		
DESCARTES	1/599	0/302	2.51 (0.06–102.80)	3.0
LAPLACE-TIMI 57	0/158	0/157	–	0.0
McKenney et al	0/31	0/31	–	0.0
MENDEL	0/90	0/135	–	0.0
ODYSSEY ALTERNATIVE	1/126	0/125	3.02 (0.12–75.06)	4.0
ODYSSEY COMBO I	1/209	1/107	0.51 (0.03–8.23)	5.4
ODYSSEY FH I and FH II	2/490	0/245	4.02 (0.11–147.57)	3.2
ODYSSEY LONG TERM	14/1553	18/788	0.39 (0.19–0.79)	84.3
TESLA Part B	0/33	0/16	–	0.0
Fixed-effect model	19/3289	19/1906	0.49 (0.26–0.93)	100

Heterogeneity: $I^2 = 0\%$; $\tau^2 = 0$; $P = 0.4492$

Test for overall effect: $Z = -2.17$ ($P = 0.030$)

Unstable angina



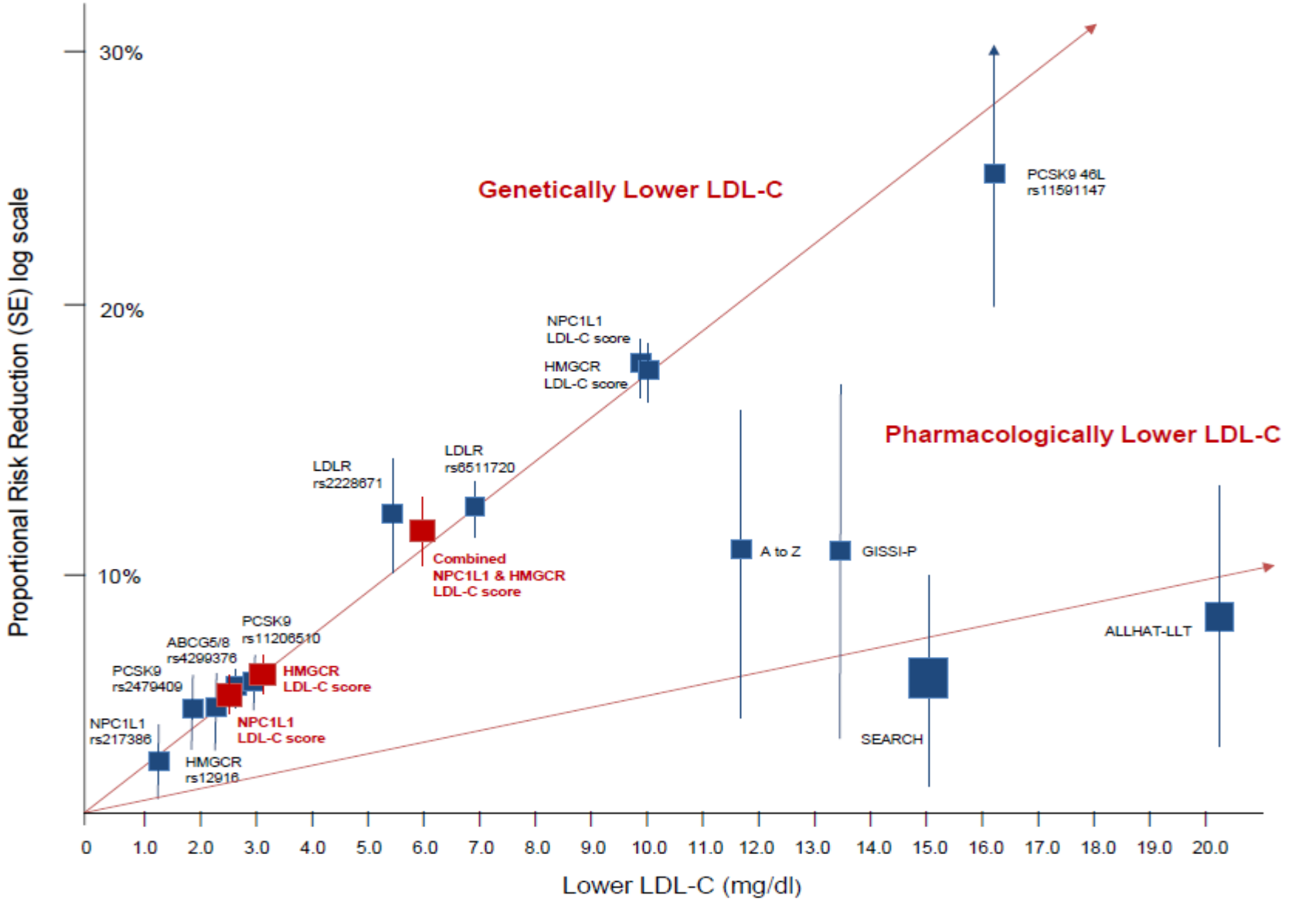
Study	Events/Total, *n/N*		Odds Ratio (95% CI)	Weight, %
	PCSK9 Antibody	No Anti-PCSK9		
DESCARTES	1/599	0/302	2.51 (0.06–102.80)	38.6
McKenney et al	0/31	0/31	–	0.0
MENDEL	0/90	0/135	–	0.0
ODYSSEY COMBO I	0/209	0/107	–	0.0
ODYSSEY LONG TERM	0/1553	1/788	0.25 (0.01–4.78)	61.4
TESLA Part B	0/33	0/16	–	0.0
Fixed-effect model	1/2515	1/1379	0.61 (0.06–6.14)	100

Heterogeneity: $I^2 = 0\%$; $\tau^2 = 0$; $P = 0.3415$

Test for overall effect: $Z = -0.42$ ($P = 0.676$)

Navarese et al. Ann Intern Med. 2015;163(1):40-51.

From Genes to Medical Treatment: Effects of LDL-C Lowering on CVD



Ference, BA et al. J Am Coll Cardiol 2015;doi:10.1016/j.jacc.2015.02.020).

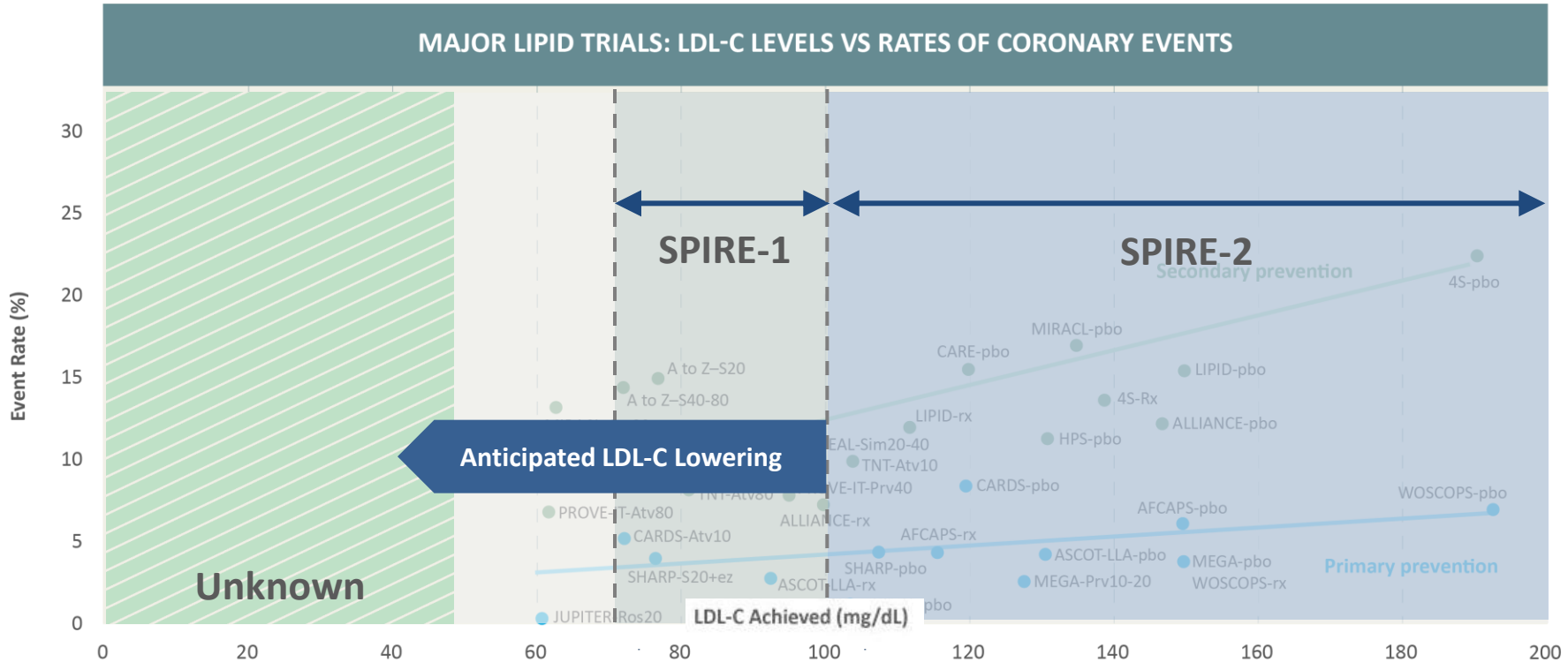
Ference, BA et al. J Am Coll Cardiol 2012;60:2631-9.

Outcomes Trials for Alirocumab and Evolocumab

	ODYSSEY OUTCOMES	FOURIER
Inclusion criteria	ACS within the last 4 to 52 weeks; LDL-C ≥70 (on atorvastatin 40-80 mg or rosuvastatin 20-40 mg)	MI, stroke, or symptomatic PAD + at least 1 major RF or at least 2 minor RFs; LDL-C ≥70 (or non-HDL ≥100) (on atorvastatin 20 to 80 mg or equivalent)
Number of patients	18,000	27,500
Primary endpoint	CV death, MI, stroke, and hospitalization for UA	CV death, MI, stroke, coronary revascularization and hospitalization for UA
Background Therapy	Max tolerated doses of atorvastatin and rosuvastatin	Atorvastatin: 20 (at least), 40 (recommended where locally approved), 80 mg (or equivalent)
Dosing regimen	75 mg → 150 mg Q2W (based on w8 LDL-C level)	140 Q2W (1 ml pen) or 420 QM (3 x 1 ml pen or 3.5 ml via personal injector (9' injection time)

Schwartz et al. Am Heart J 2014;168:682-689.

SPIRE Program Is Only PCSK9i Program with Two CV Outcomes Studies Testing Different Hypotheses



SPIRE-2 is the only PCSK9i study explicitly assessing CV outcomes in high risk patients with an LDL-C >100 mg/dL despite the use of high intensity statins

Raymond C, et al. *Cleve Clin J Med*. 2014;81:11-19.

High risk Primary and Secondary Prevention
N=26,000

Conclusions

- PCSK9 inhibitors
  - Efficacious in lowering LDL-C and Lp(a)
  - Work in different clinical scenarios
  - Well tolerated
  - Will test barriers of clinical practice!!!!
  - Cost effectiveness !!!!!