Evolocumab

Endocrinologic and Metabolic Drugs Advisory Committee

June 10, 2015

AMGEN

Introduction

Rob Scott, MD

Amgen Inc.
Vice President, Global Development

Presentation Agenda

Introduction **Mechanism of Action**	**Rob Scott, MD** Amgen Inc. Vice President, Global Development
Unmet Need	**Marc S. Sabatine, MD, MPH*** Chairman of the Thrombolysis in Myocardial Infarction (TIMI) Study Group Senior Physician in Cardiovascular Medicine at Brigham and Women's Hospital Professor of Medicine at Harvard Medical
Program Overview **Efficacy** **Safety**	**Scott M. Wasserman, MD, FACC** Amgen Inc. Vice President, Global Development
Benefit-Risk	**Rob Scott, MD** Amgen Inc. Vice President, Global Development

***Received consulting fees and had travel expenses covered by Amgen Inc.**

Experts Available to the Committee

Christie M. Ballantyne, MD*	**Expert Topic: Familial Hypercholesterolemia and treatment of hyperlipidemia** Professor of Medicine and Chief of the Section of Atherosclerosis and Vascular Medicine, Baylor College of Medicine Director of the Center for Cardiovascular Disease Prevention Methodist DeBakey Heart and Vascular Center
Evan A. Stein, MD, PhD*	**Expert Topic: Familial Hypercholesterolemia and Lab Methodology** Director Emeritus Voluntary Professor Pathology and Laboratory Medicine University of Cincinnati
Janet Wittes, PhD*	**Expert Topic: Statistics** President, Statistics Collaborative

***Received consulting fees and had travel expenses covered by Amgen Inc.**

Evolocumab

Novel Therapeutic Agent

Evolocumab is a fully human monoclonal antibody against PCSK9 and blocks PCSK9/LDLR interaction

Proposed Patient Populations

1. Hyperlipidemia and mixed dyslipidemia
2. Homozygous familial hypercholesterolemia
   - Orphan designation granted 2013

Primary Hyperlipidemia and Mixed Dyslipidemia

- Evolocumab is indicated in adults with primary hyperlipidemia (heterozygous familial and nonfamilial) or mixed dyslipidemia, as an adjunct to diet to reduce LDL-C, TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/ApoA1, VLDL-C, triglycerides and Lp(a), and to increase HDL-C and ApoA1
  - In combination with a statin or statin with other lipid-lowering therapies (e.g., ezetimibe), or
  - Alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or
  - Alone or in combination with other lipid-lowering therapies in patients for whom a statin is not considered clinically appropriate

Homozygous Familial Hypercholesterolemia

- Evolocumab is indicated in adults and adolescents aged 12 years and older with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C, TC, ApoB, and non-HDL-C in combination with other lipid lowering therapies (e.g., statins, LDL apheresis)

Proposed Dosing and Administration

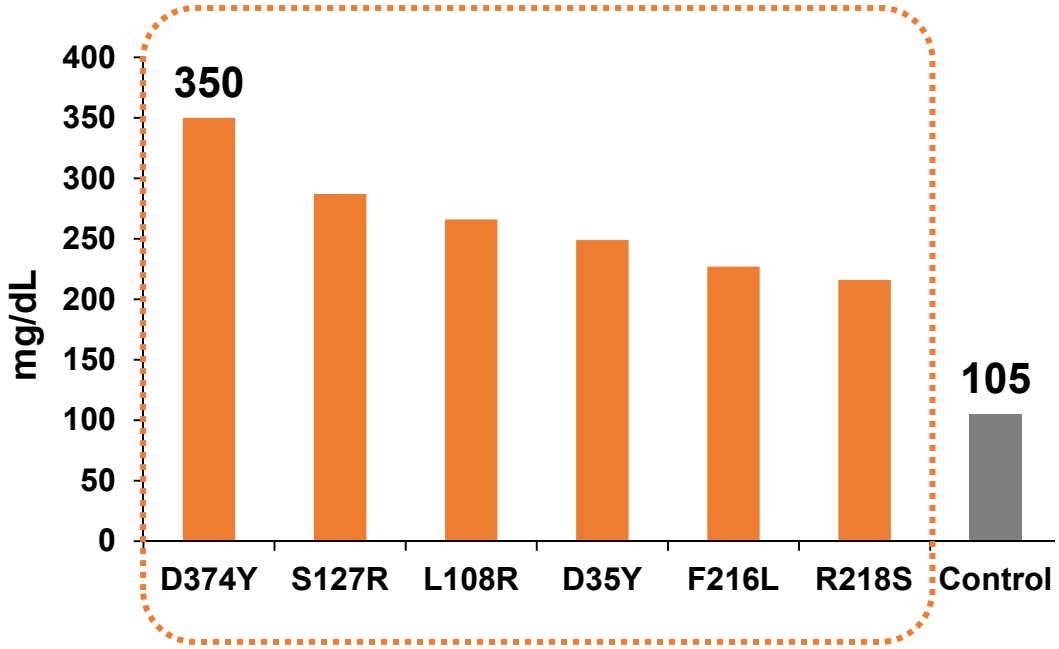
Patient Population	Recommended Dosage Strength and Frequency
Primary Hyperlipidemia and Mixed Dyslipidemia	140 mg every 2 weeks or 420 mg once monthly*
Homozygous Familial Hypercholesterolemia	420 mg once monthly or 420 mg every 2 weeks

*140 mg every 2 weeks or 420 mg once monthly are clinically equivalent

PCSK9 Genetics Were the Impetus to Develop Anti-PCSK9 Antibodies

Rare

- Gain-of-function mutation
- High LDL-C
- Premature cardiovascular disease

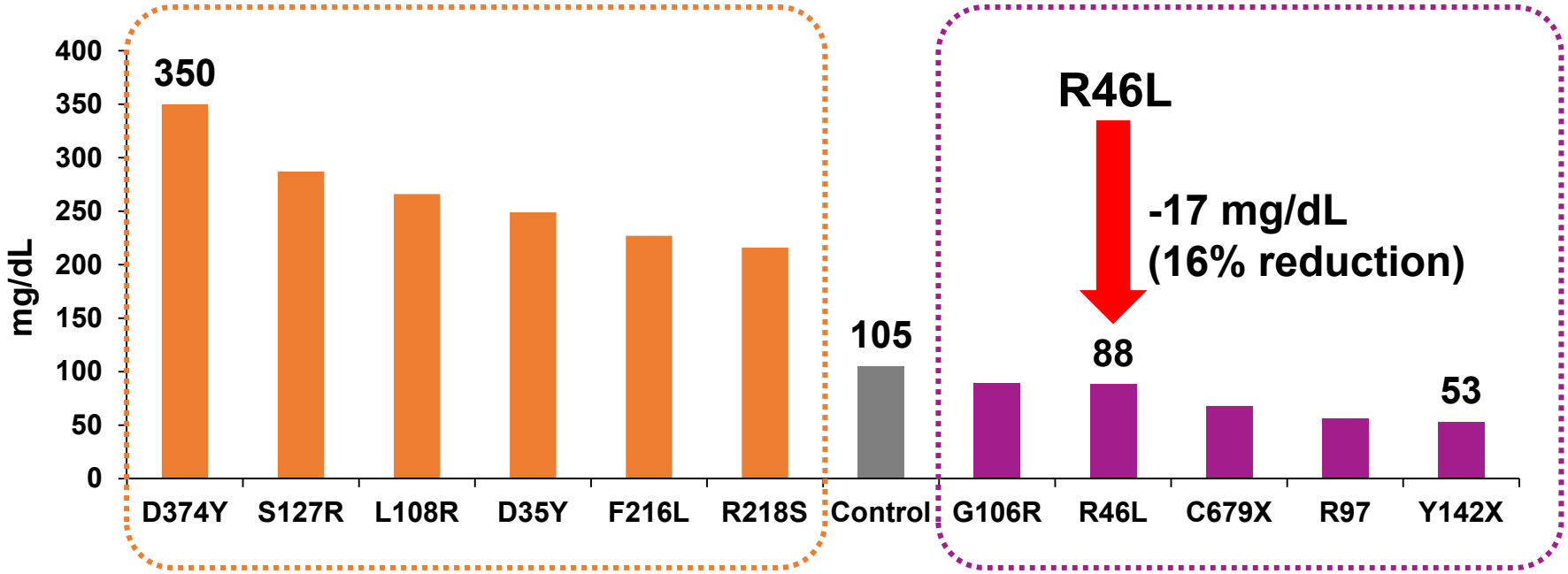


Modified from Poirier, Mayer. *Drug Des Devel Ther.* 2013; 7: 1135-48

PCSK9 Genetics Were the Impetus to Develop Anti-PCSK9 Antibodies

Rare
- Gain-of-function mutation
- High LDL-C
- Premature cardiovascular disease

Common
- Loss-of-function mutation
- Lower LDL-C
- Lower incidence of cardiovascular disease

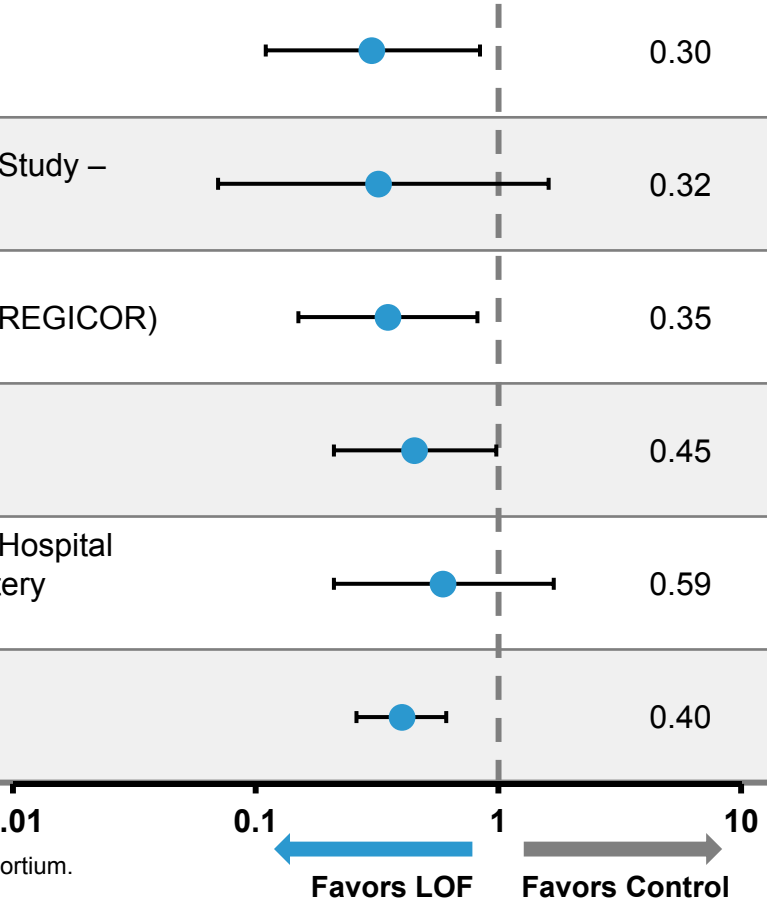


Modified from Poirier, Mayer. *Drug Des Devel Ther.* 2013; 7: 1135-48

The Impact of R46L Missense on Early Onset Myocardial Infarction

Lifelong Impact of 16% Lower LDL translates into 60% Lower Risk

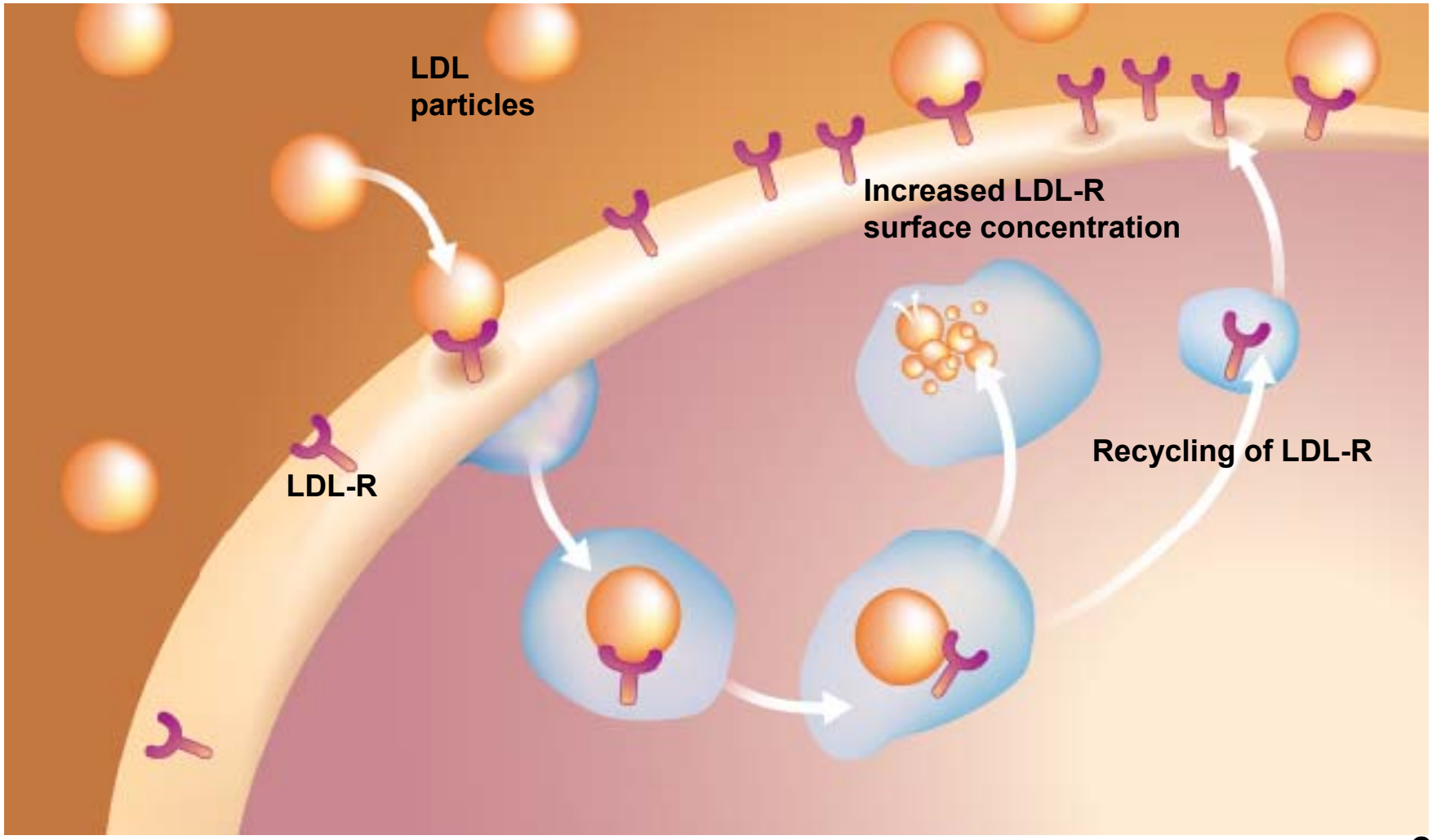
Site	Study	OR for Early Onset MI	95% CI	p-value
Finland	FINRISK	0.30	(0.11, 0.84)	0.02
Sweden	Malmo Diet and Cancer Study – CV cohorts	0.32	(0.07, 1.61)	0.17
Spain	Registre Gironi del Cor (REGICOR)	0.35	(0.15, 0.82)	0.02
Seattle	Heart Attack Risk in Puget Sound	0.45	(0.21, 0.98)	0.049
Boston	Massachusetts General Hospital Pre-mature Coronary Artery Disease Study	0.59	(0.21, 1.69)	0.46
Combined analysis		0.40	(0.26, 0.61)	0.0002



OR=odds ratio; MI=myocardial infarction; CI=95% CI;
Kathiresan S and the Myocardial Infarction Genetics Consortium.
N Engl J Med. 2008;358:2299-2300

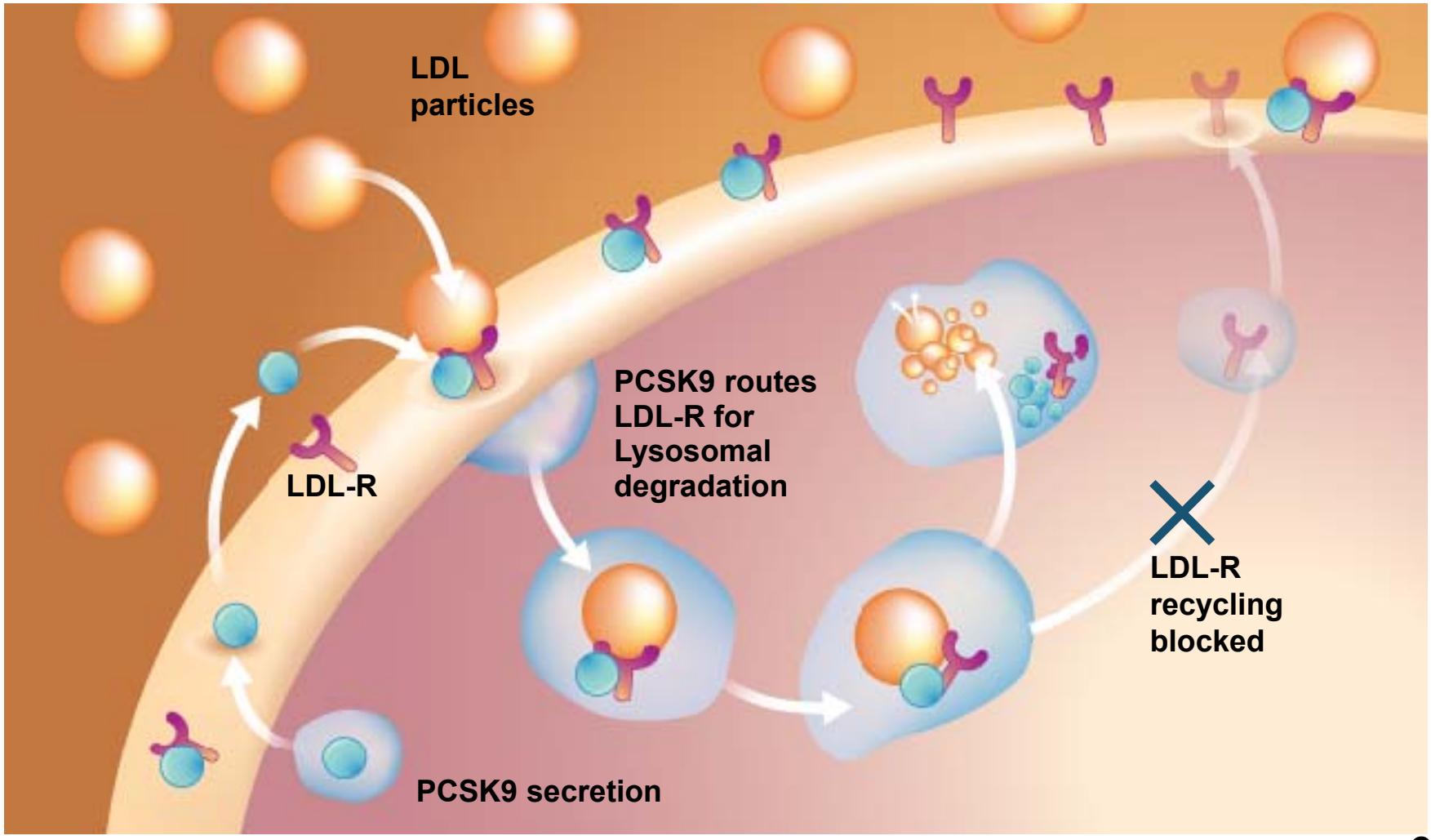
Absence of PCSK9 Enhances LDL-R Recycling and Clearance of LDL Particles

Absence of PCSK9 – More LDL-R / Lower plasma LDL-C



PCSK9 Regulates the Surface Expression of LDL-Rs by Targeting for Lysosomal Degradation

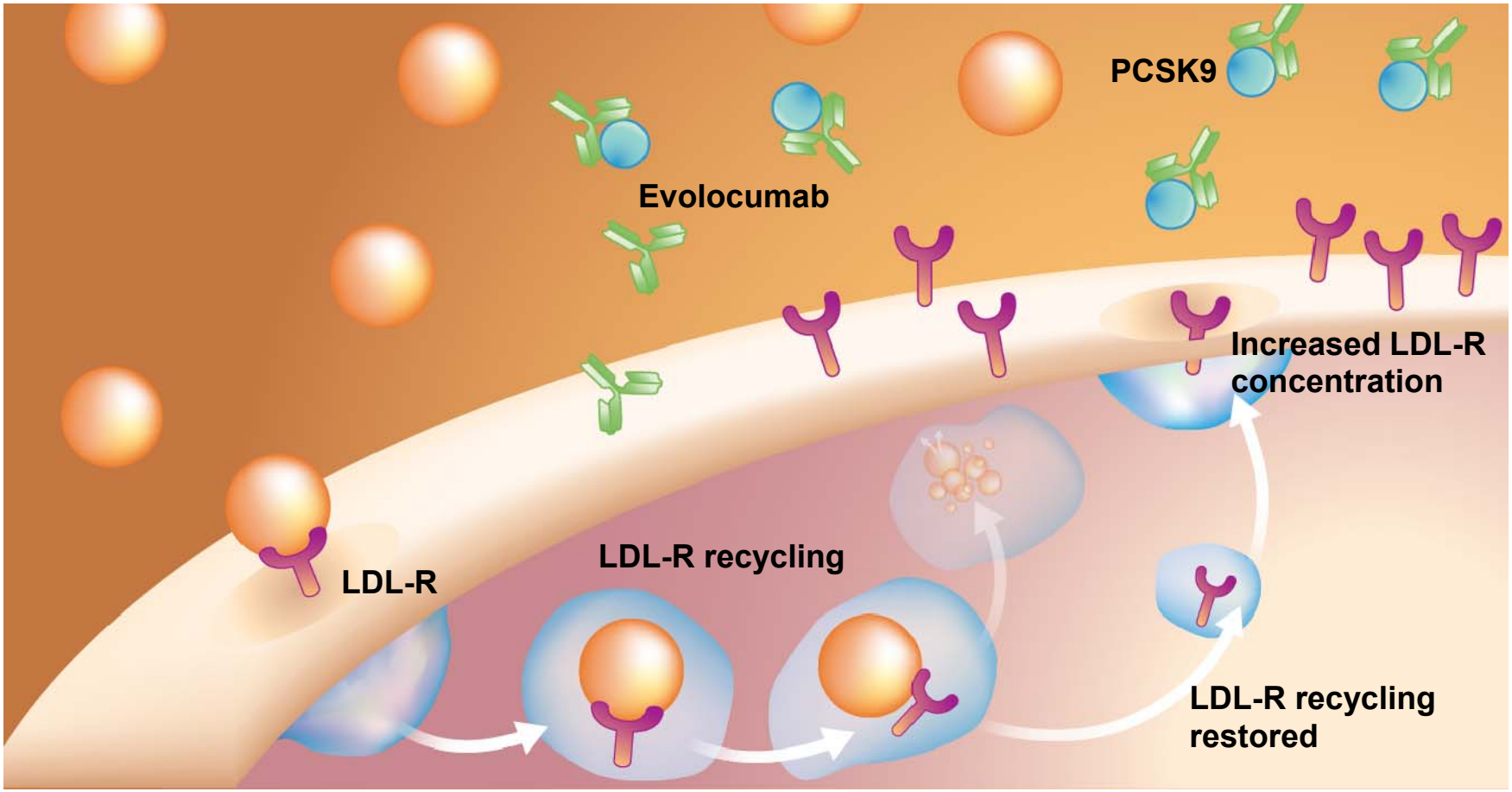
Presence of PCSK9 - Less LDL-R / Higher plasma LDL-C



Evolocumab is a Fully Human Monoclonal Antibody Against PCSK9 and Blocks PCSK9/LDL-R Interaction

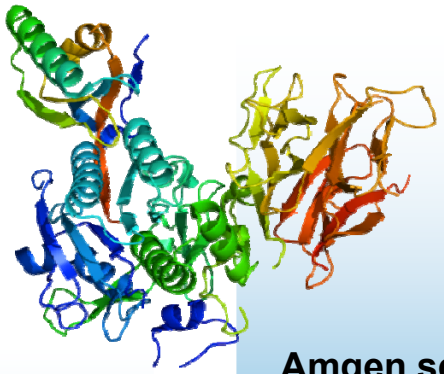
Presence of Evolocumab - Absence of PCSK9

More LDL-R / Lower plasma LDL-C



Chan JC, Piper DE, Cao Q et al. *Proc Natl Acad Sci USA.* 2009;106:9820-9825.

Amgen Innovation: Rapid Translation of a Genetic Discovery into a New Therapy



PCSK9 Crystal Structure

2003 — Role of PCSK9 in LDL metabolism emerges

2005 — Amgen launches PCSK9 program

2006 — Amgen scientists elucidate complete structure of PCSK9 (published 2007)

2007 — Amgen scientists file patent application to Abs that block PCSK9-LDL-R interaction and lower cholesterol *in vivo*

2009 — Evolocumab enters clinical development - first human dosed

2014 — Evolocumab is the first PCSK9 therapy filed

2015 — Evolocumab receives positive CHMP opinion in Europe

Presentation Summary

- LDL-C is a major modifiable risk factor for cardiovascular disease
- Available therapies, while effective, are often not sufficient to adequately control LDL-C
- Evolocumab demonstrated
  - Consistent and significant reduction in LDL-C with favorable changes in other lipid parameters
  - Favorable safety and tolerability profile with no major safety issues identified, including in subjects with very low LDL-C
- Fully enrolled CV outcomes study with 27,500 subjects will complete no later than 2017
- Robust clinical program and ongoing pharmacovigilance prior to the conclusion of cardiovascular outcomes trial
- Benefit-risk assessment for evolocumab is positive

Why Do We Need Another Therapy for Hyperlipidemia?

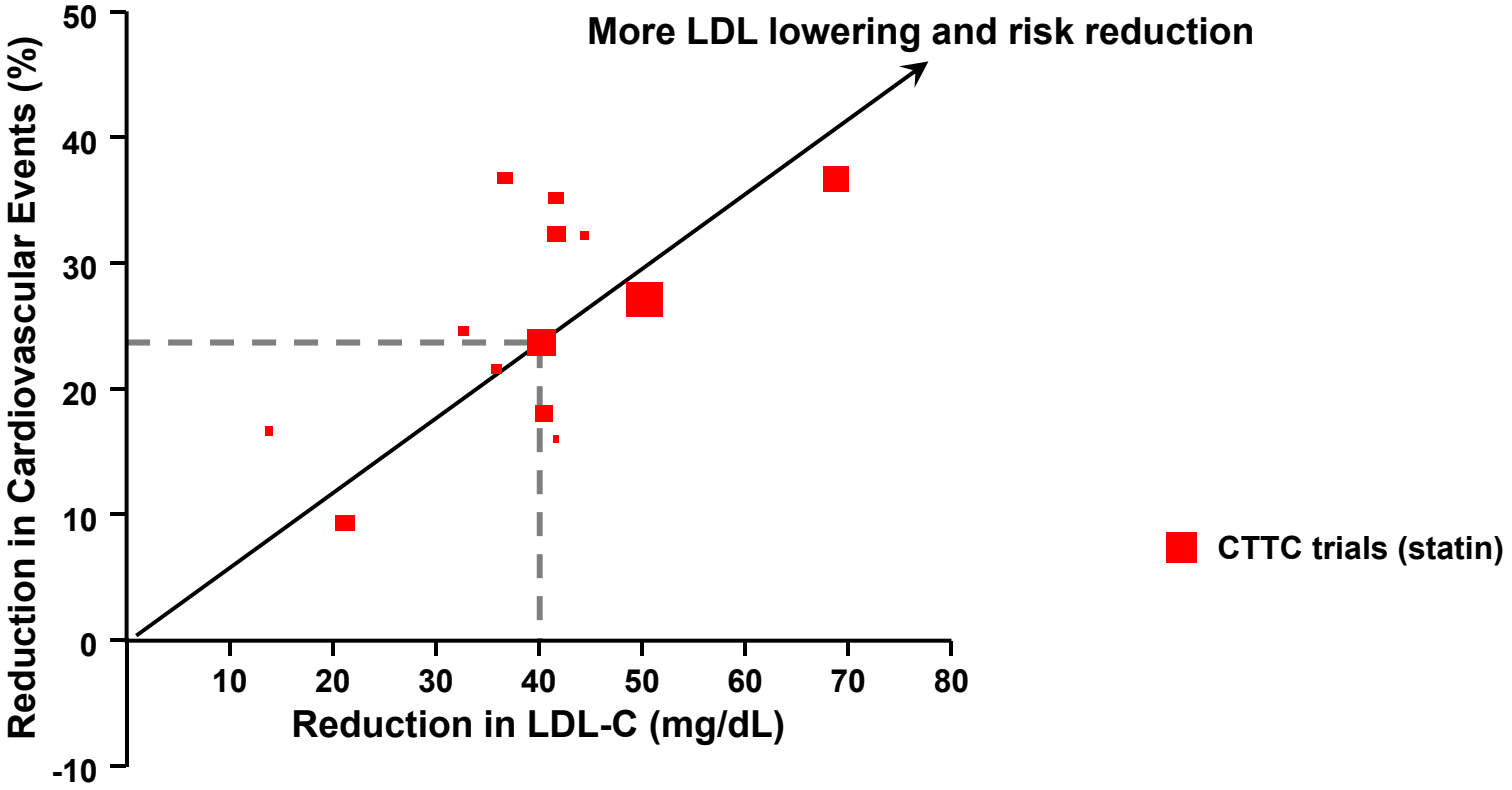
Marc S. Sabatine, MD, MPH

Brigham and Women's Hospital

Burden of Cardiovascular Disease

- Affects ~80 million Americans
- The top cause of death in the United States: 780,000 per year
- Annual cost $320 billion per year
- Well established risk factors including LDL cholesterol, which shows a continuous relationship between LDL and CV risk

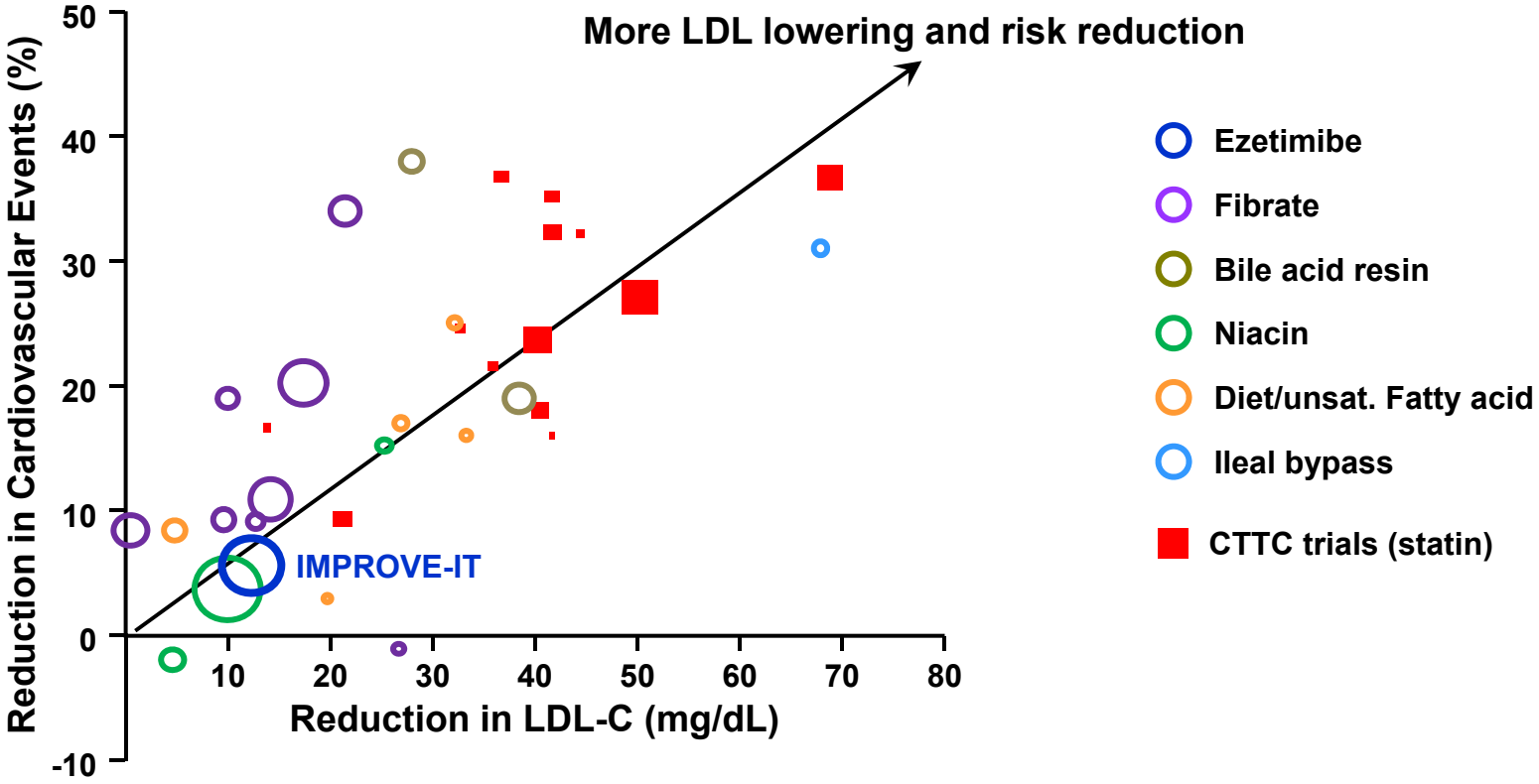
Relative Risk Reduction in Cardiovascular Events vs. Absolute Reduction in LDL-C



Every 40 mg/dL decrease in LDL-C decreases relative risk for CV events by 20-25%

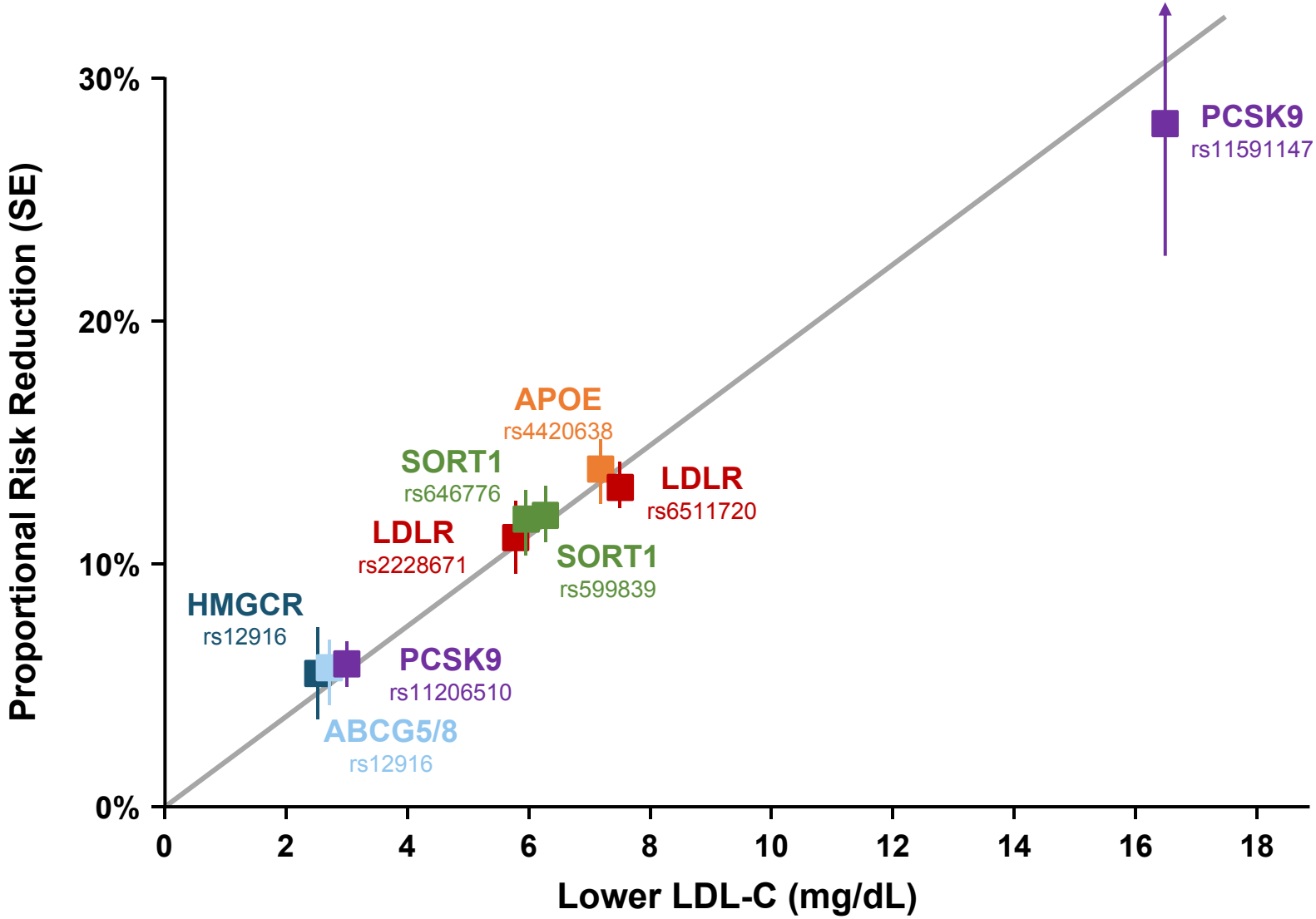
Data from studies of non-statin lipid-lowering medications superimposed upon data from the Cholesterol Treatment Trialist's 2005 meta-analysis suggest that reduction of coronary event risk due to reduction of LDL-C is independent of method

Relative Risk Reduction in Cardiovascular Events vs. Absolute Reduction in LDL-C



Data from studies of non-statin lipid-lowering medications suggest that reduction of coronary event risk due to reduction of LDL-C is independent of method

Lower Risk of Cardiovascular Events via Multiple Genetic Variants Affecting LDL-C



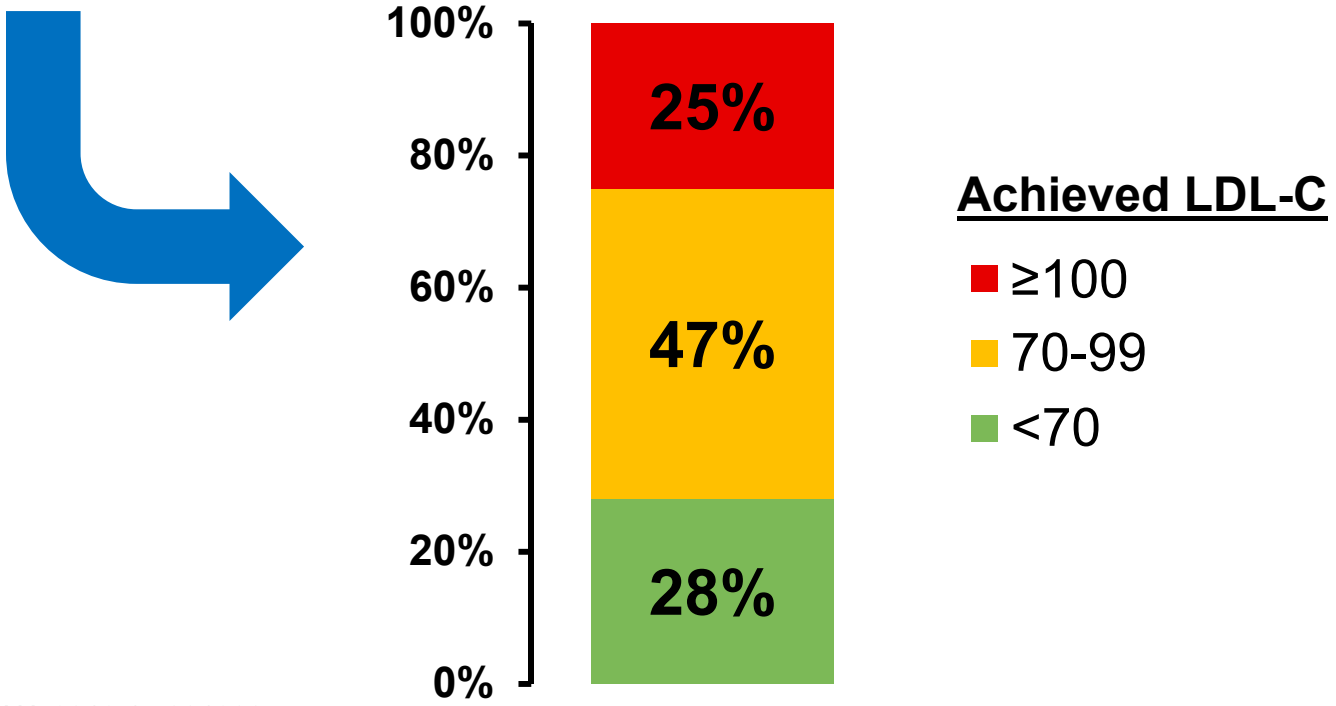
Ference BA et al. JACC 2012;60:2631–9

Who Are The Patients Whose Needs are Not Being Met by Current Therapies?

- Patients whose LDL-C cannot be controlled with intensive statin therapy ± other current therapies
  - High-risk patients in whom we cannot get the LDL-C low enough
  - Most patients with Heterozygous Familial Hypercholesterolemia (HeFH)
  - Almost all patients with Homozygous FH
- Patients who cannot take a statin, or an effective dose
  - Statin intolerance or statins are not clinically appropriate (eg, drug-drug interactions, active liver disease, myopathies)

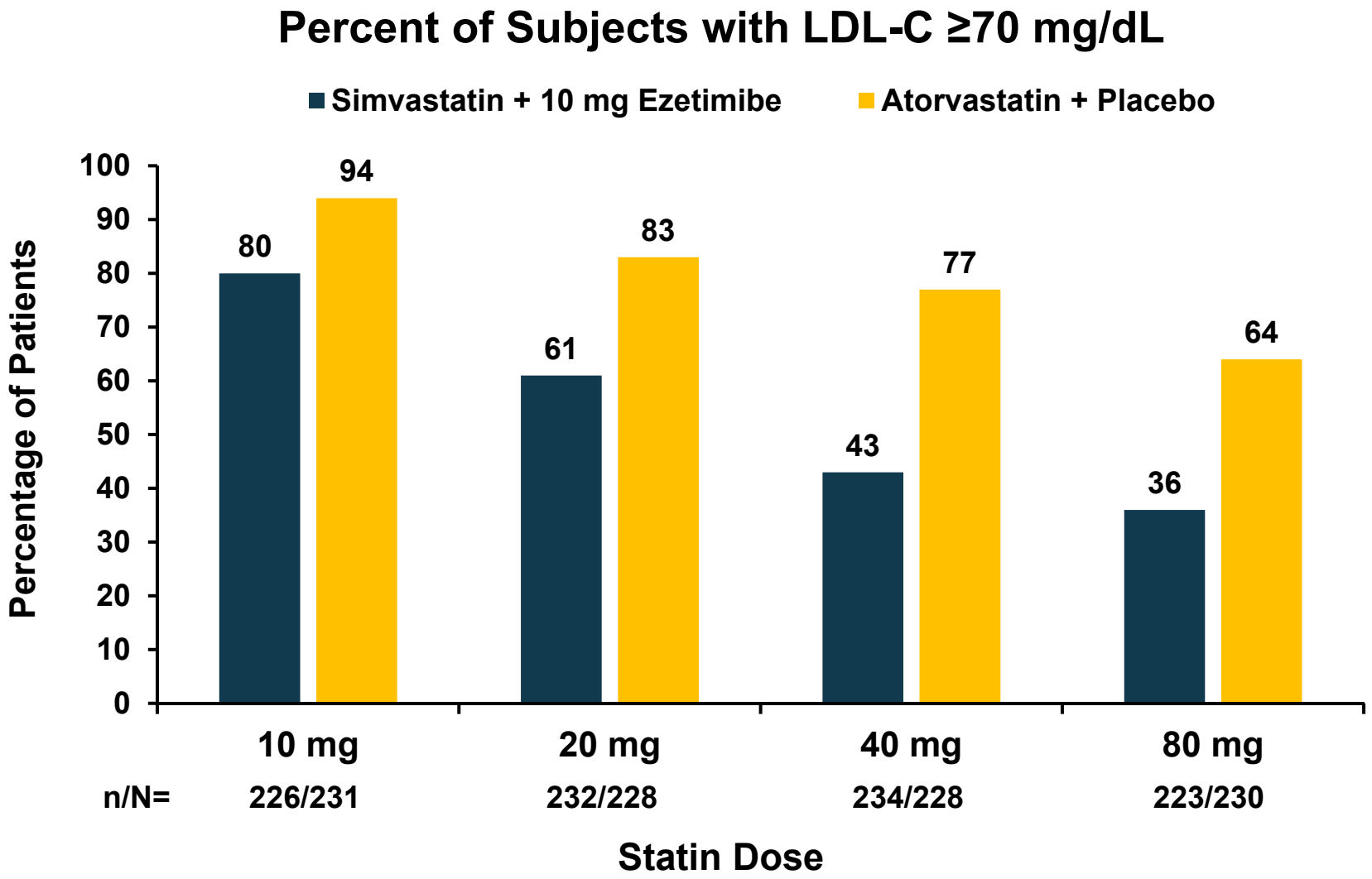
LDL-C Control in High-Risk Patients

- Americans who are high-risk (NCEP) and on lipid-modifying therapy
  - ~½ have diabetes only
  - **~½ have overt vascular disease**



Jones PH et al. JAHA 2012;1:e001800

Even in Clinical Studies Using High Intensity Therapy, Many Do Not Reach Goal

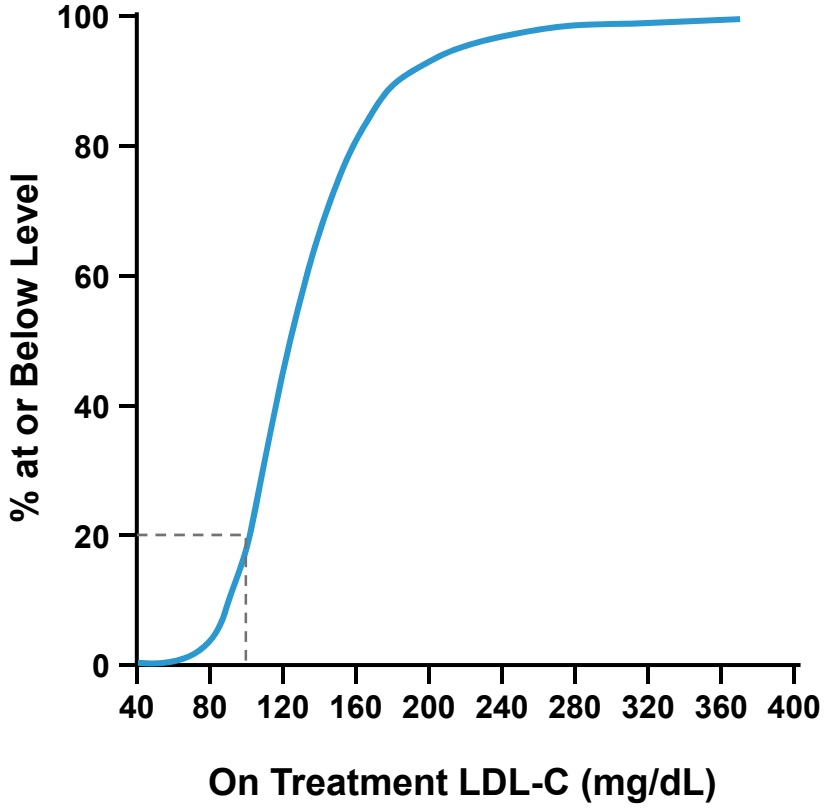


Ballantyne CM, et al. *Am Heart J* 2005;149:464-73.

Heterozygous Familial Hypercholesterolemia (HeFH)

- One mutated LDL-C receptor
- Prevalence
  - 1 in 200 to 500
- LDL-C levels
  - Twice normal
  - 190-350 mg/dL
- Premature CHD
  - Age: 30-40's in men
  - Age: 40-50's in women
  - Lifetime risk ~100% in males

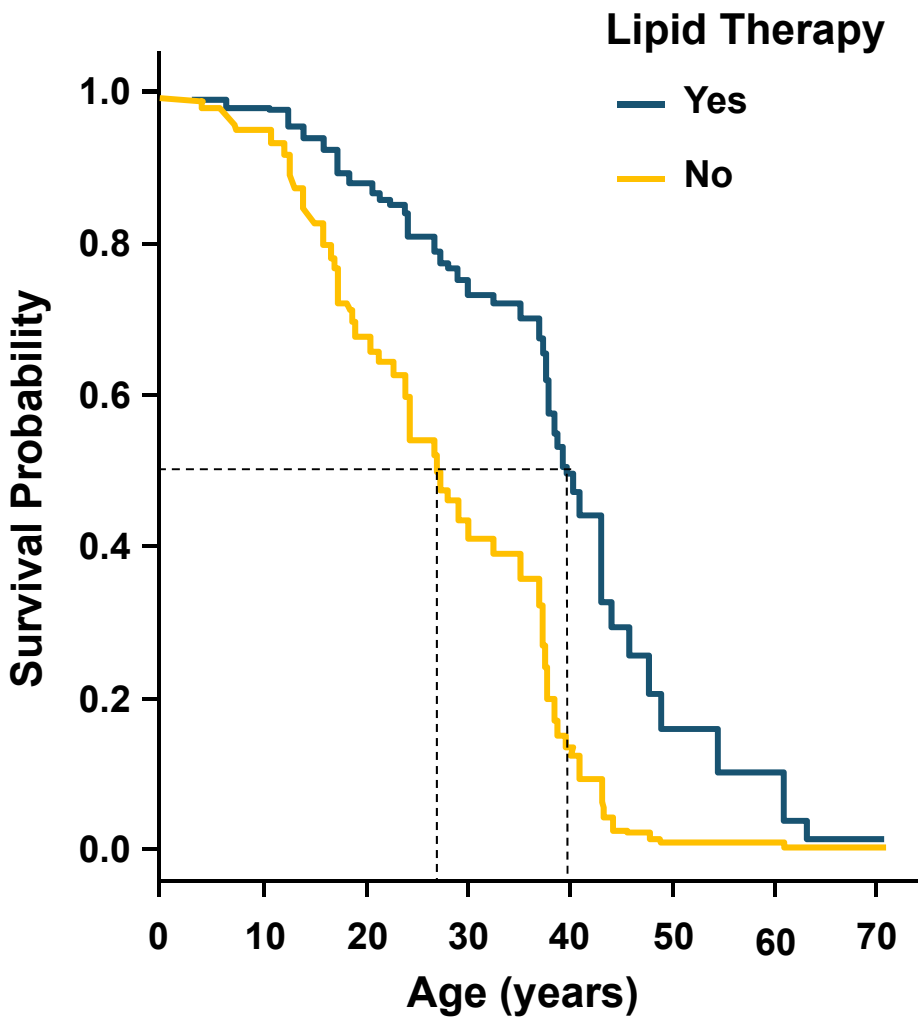
Few HeFH Patients are Currently Able to Achieve Desired Levels of LDL-C



Nordestgaard BG *Eur Heart J*. (2013)34:3478-90
Adapted from: National Cholesterol Education Program (NCEP). *Circulation*. 2002;106:3143-3421.

Homozygous Familial Hypercholesterolemia (HoFH)

- Two mutated LDL-C receptors
- Prevalence
  - 1/1,000,000 US
- LDL-C levels
  - 4-fold increase
  - 400-1,000 mg/dL
- Premature CHD universal
  - Age: Teens or pre-teens
  - Widespread, severe atherosclerosis
  - Aortic valve disease



Nordestgaard BG *Eur Heart J*. (2013)34:3478-90
Adapted from: National Cholesterol Education Program (NCEP). *Circulation*. 2002;106:3143-3421.

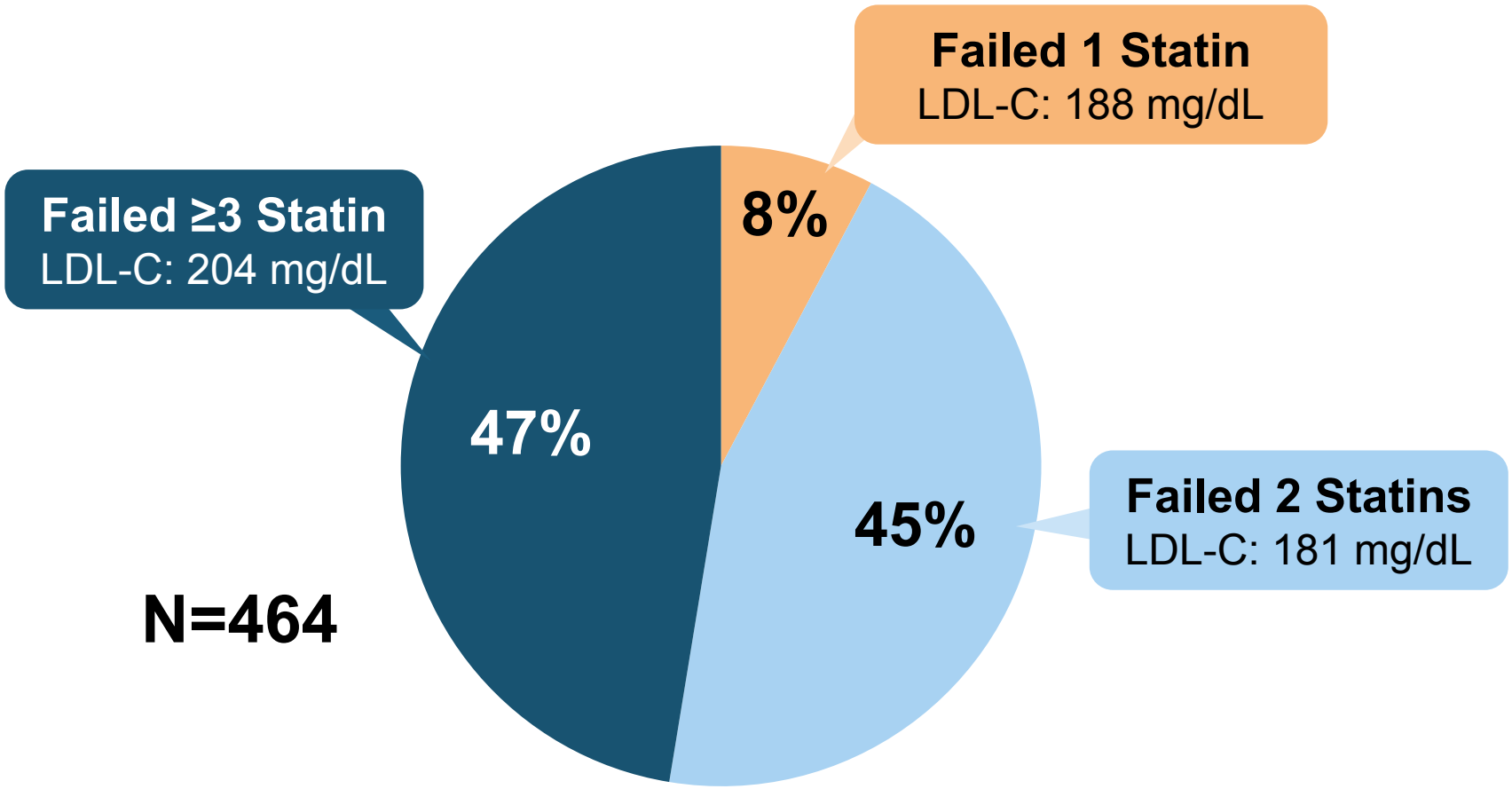
Statin Intolerance

- In clinical trials, rates low
  - Patients willing to participate in a clinical trial
  - Some trials had active run-in phase
- In real-world practice, 5-15% of populations discontinue statin
  - Higher percentage discontinue statin therapy
  - Many can restart when rechallenged, although not always on an optimal dose

Saeed et al. 2013; Zhang et al 2013; Stroes et al 2015

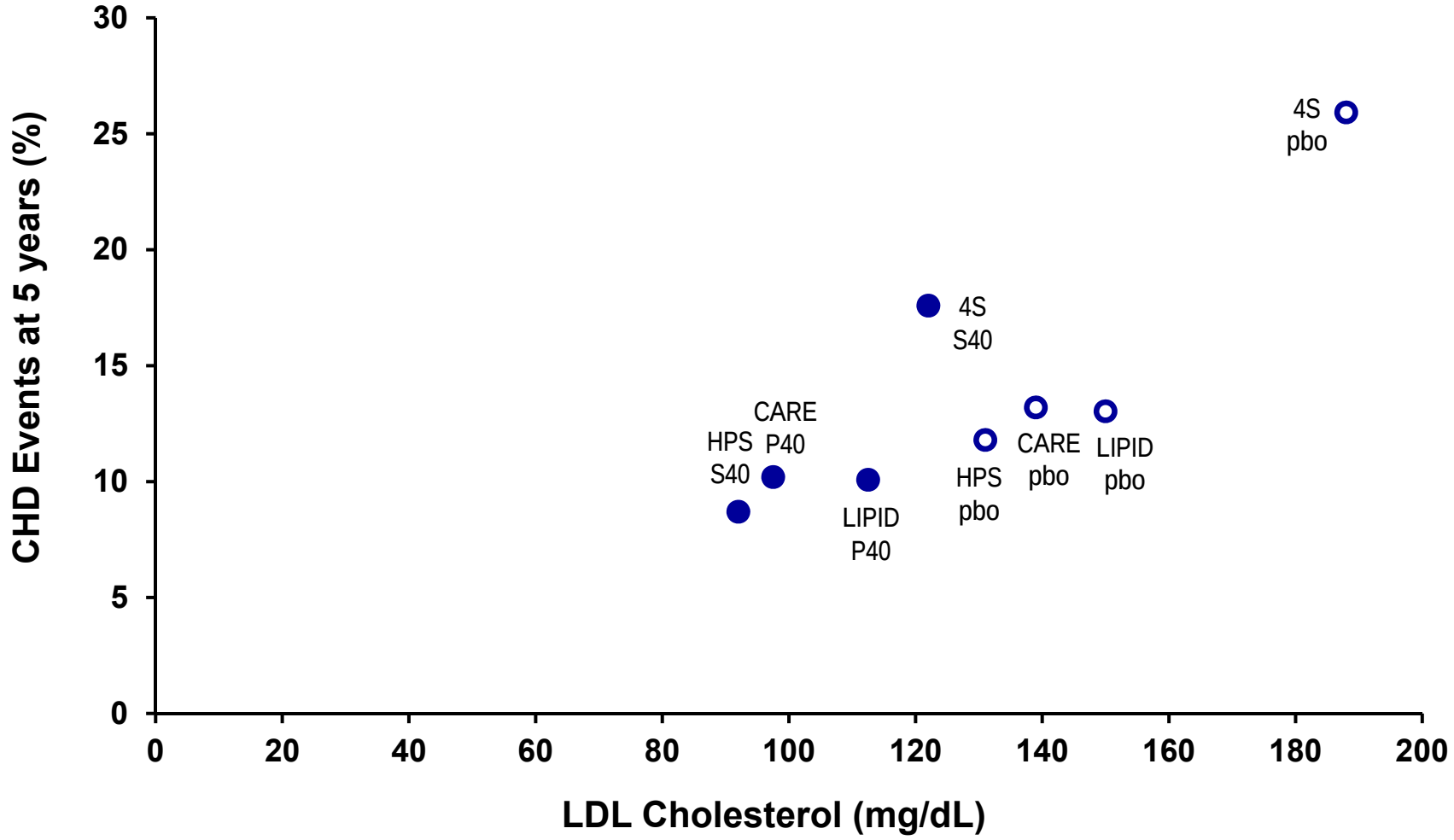
Data from 2 Amgen Studies in Statin Intolerant Patients

Faced with High LDL-C Levels, Physicians do Attempt to Rechallenge



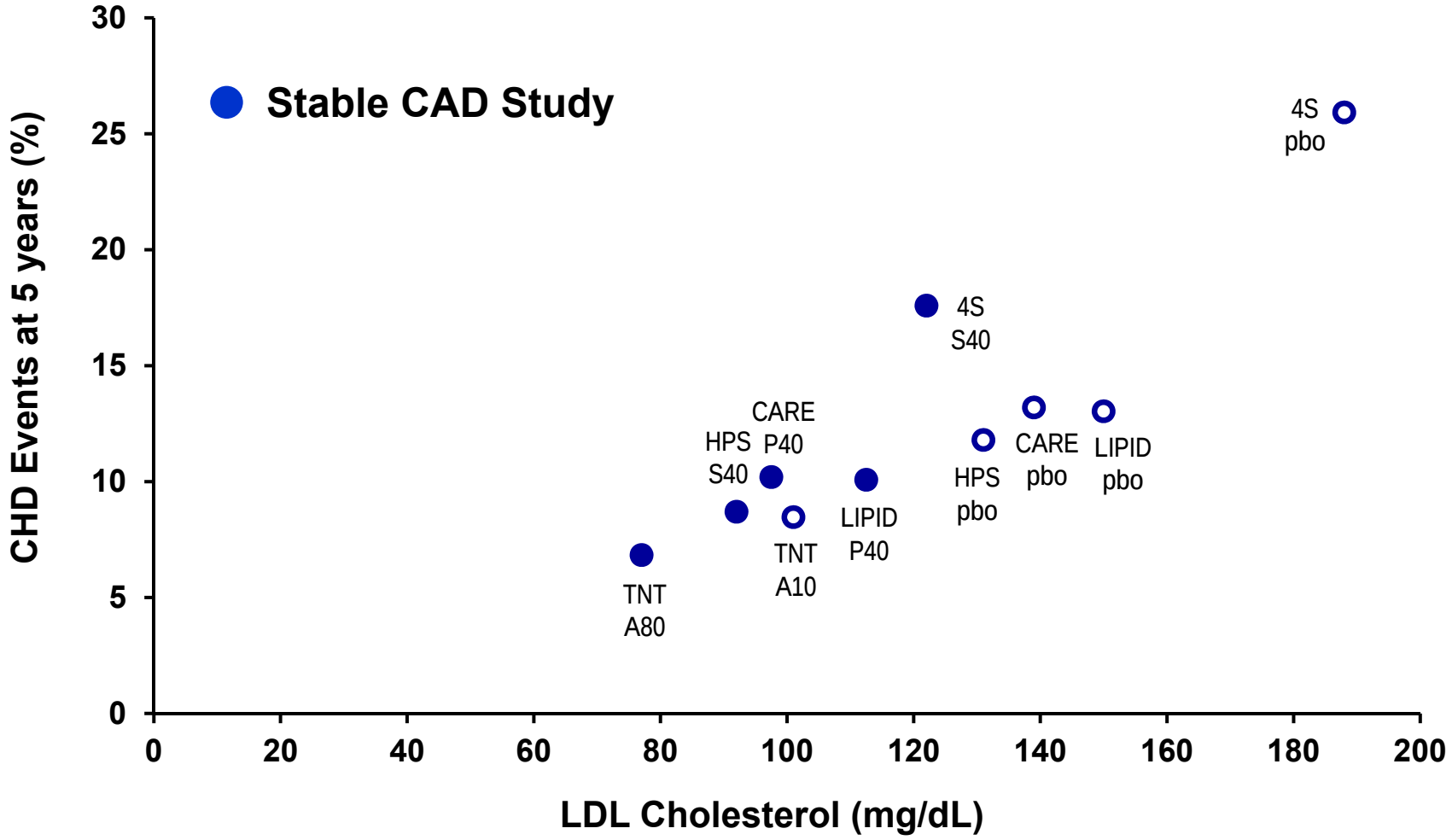
Rationale for Achieving Lower LDL-C

Clinical Trial Data supports Achieving Lower Levels of LDL-C



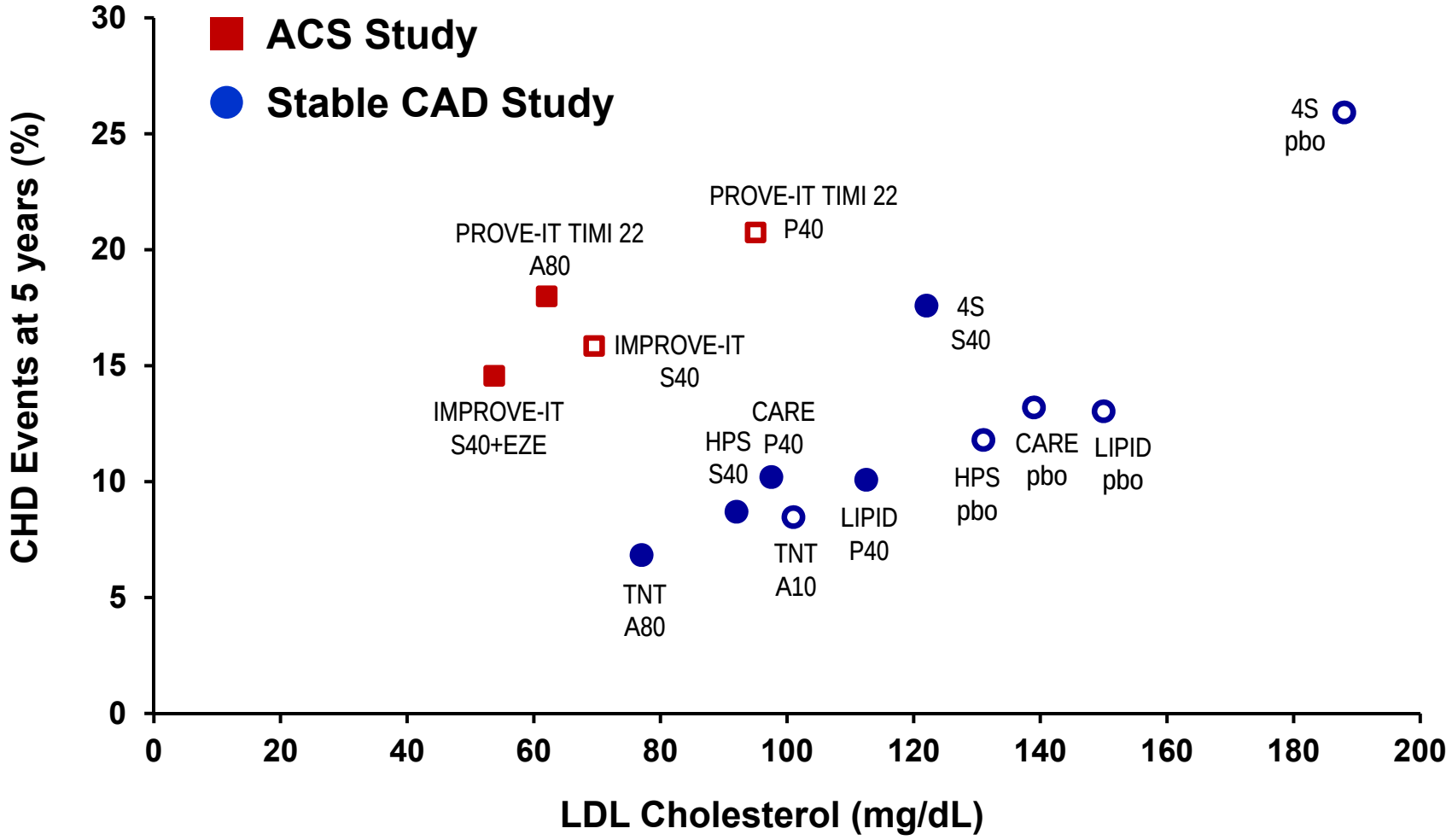
Adapted from Rosensen, Exp Opin Emerg Drugs 2004;9:269; LaRosa J et al, N Engl J Med,2005;352:1425

Clinical Trial Data supports Achieving Lower Levels of LDL-C



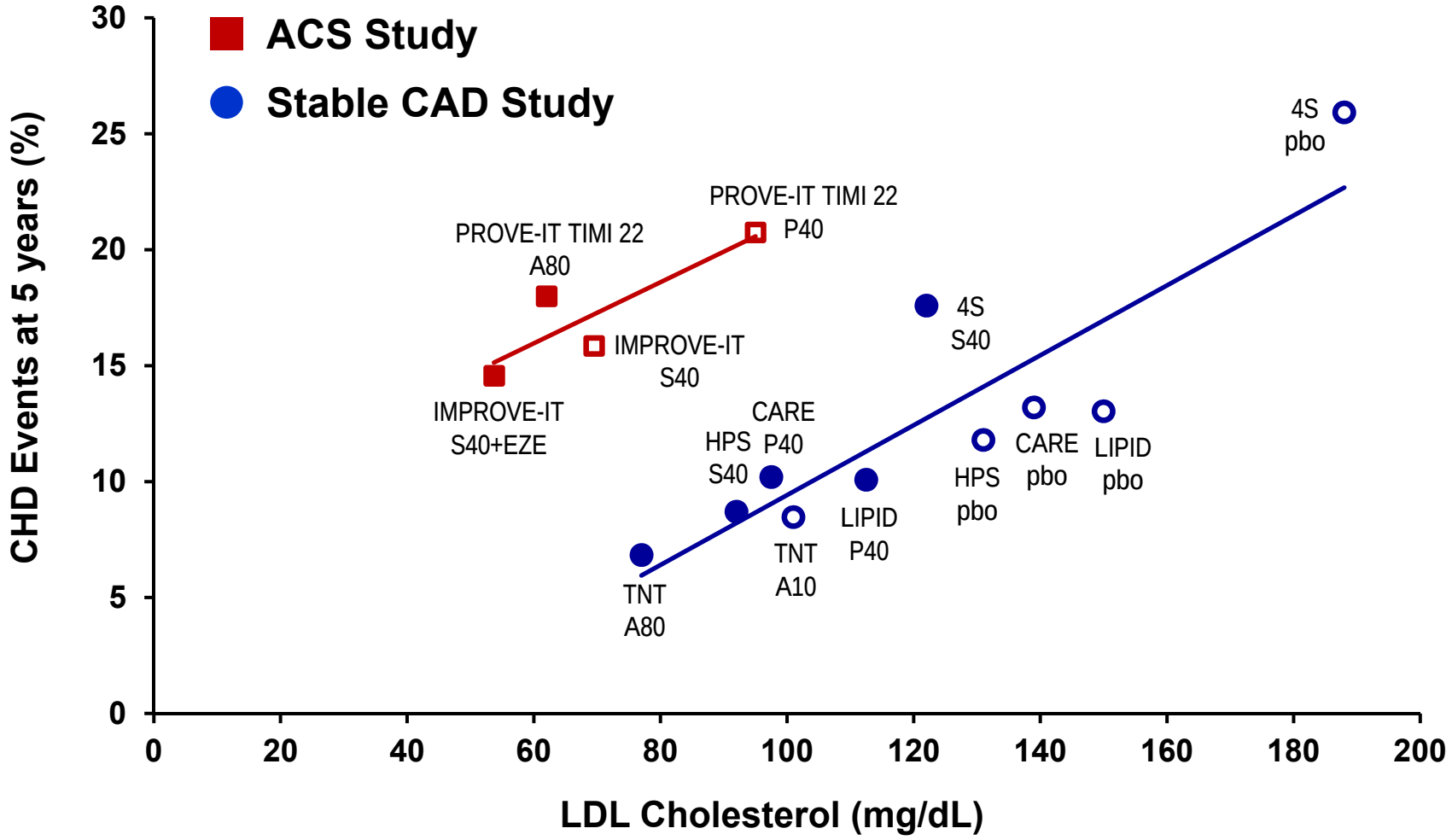
Adapted from Rosensen, Exp Opin Emerg Drugs 2004;9:269; LaRosa J et al, N Engl J Med,2005;352:1425

Clinical Trial Data supports Achieving Lower Levels of LDL-C



Adapted from Rosensen, Exp Opin Emerg Drugs 2004;9:269; LaRosa J et al, N Engl J Med,2005;352:1425

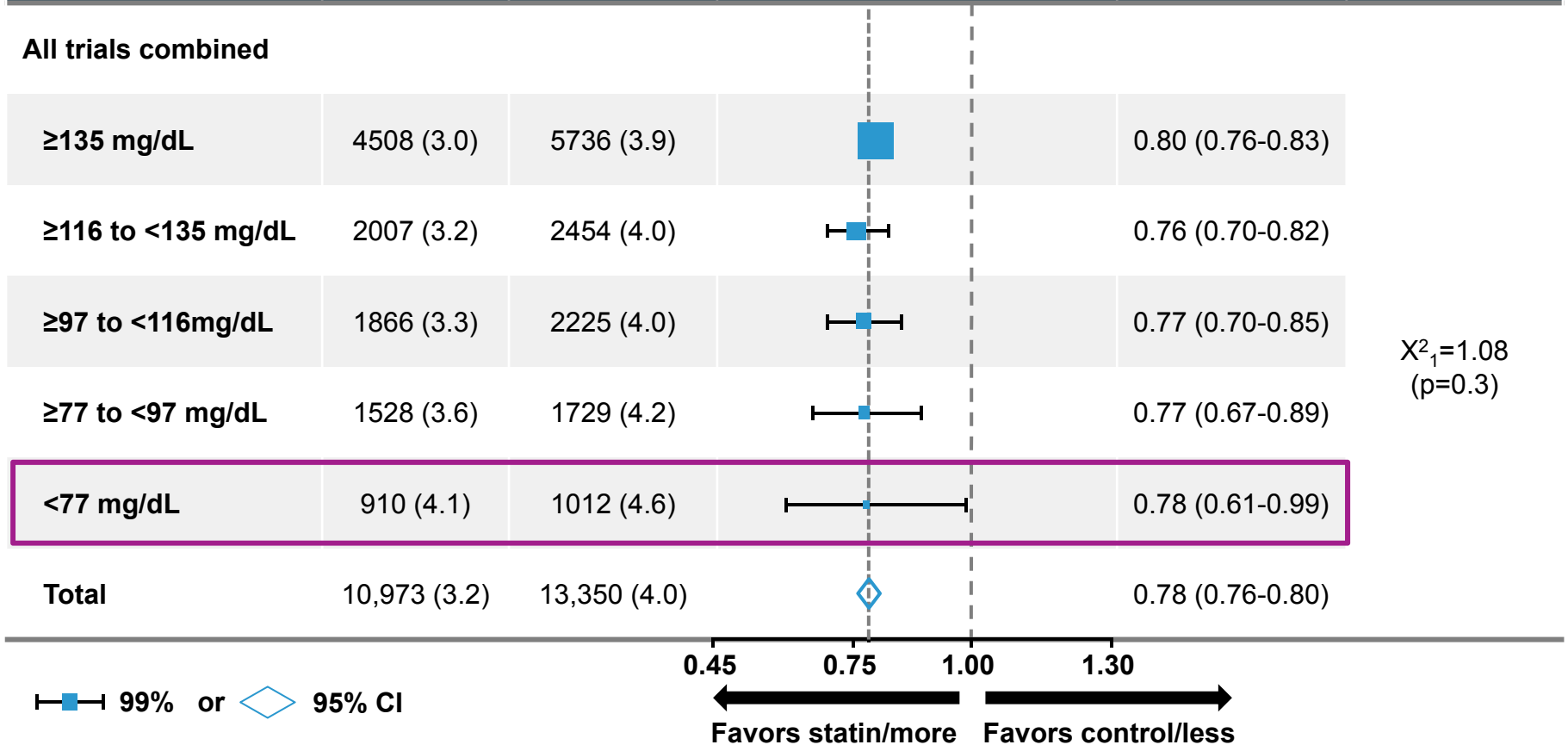
Clinical Trial Data supports Achieving Lower Levels of LDL-C



Adapted from Rosensen, Exp Opin Emerg Drugs 2004;9:269; LaRosa J et al, N Engl J Med,2005;352:1425

Clinical Trial Data Supporting Benefit of Lowering LDL-C, Even When Starting "Low"

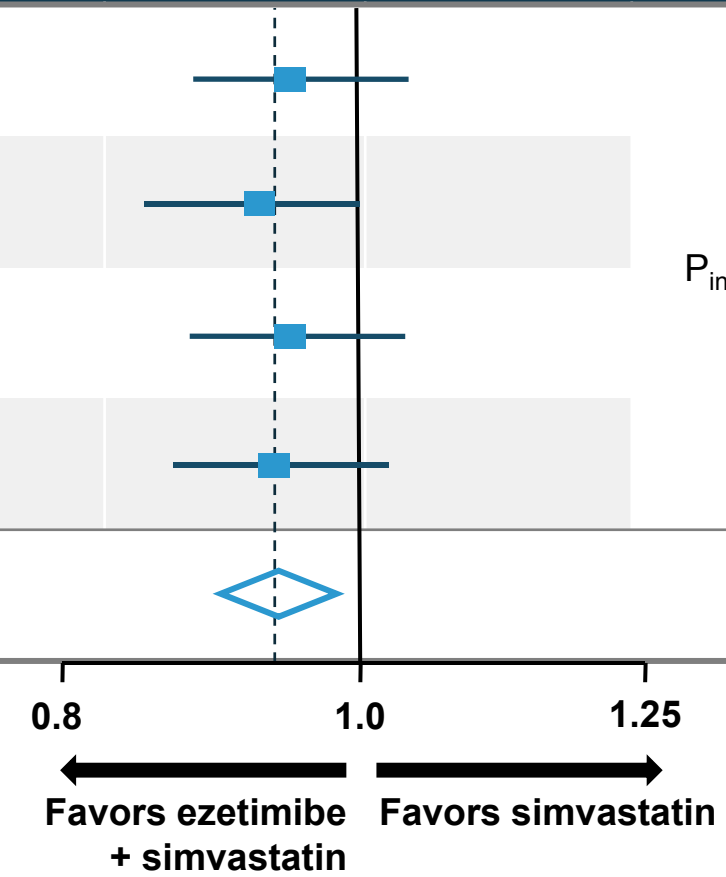
Baseline LDL-C	Events (% per annum) Statin/More	Control/Less	RR (CI) per 1 mmol/L Reduction in LDL-C	Trend Test
All trials combined				
≥135 mg/dL	4508 (3.0)	5736 (3.9)	0.80 (0.76-0.83)	
≥116 to <135 mg/dL	2007 (3.2)	2454 (4.0)	0.76 (0.70-0.82)	
≥97 to <116mg/dL	1866 (3.3)	2225 (4.0)	0.77 (0.70-0.85)	X^2_1=1.08 (p=0.3)
≥77 to <97 mg/dL	1528 (3.6)	1729 (4.2)	0.77 (0.67-0.89)	
<77 mg/dL	910 (4.1)	1012 (4.6)	0.78 (0.61-0.99)	
Total	10,973 (3.2)	13,350 (4.0)	0.78 (0.76-0.80)	



CTT Cycle #2. *Lancet* 2010;376:1670-81

IMPROVE-IT: Hazard Ratios for the Primary Endpoint by Quartiles of LDL-C at Admission

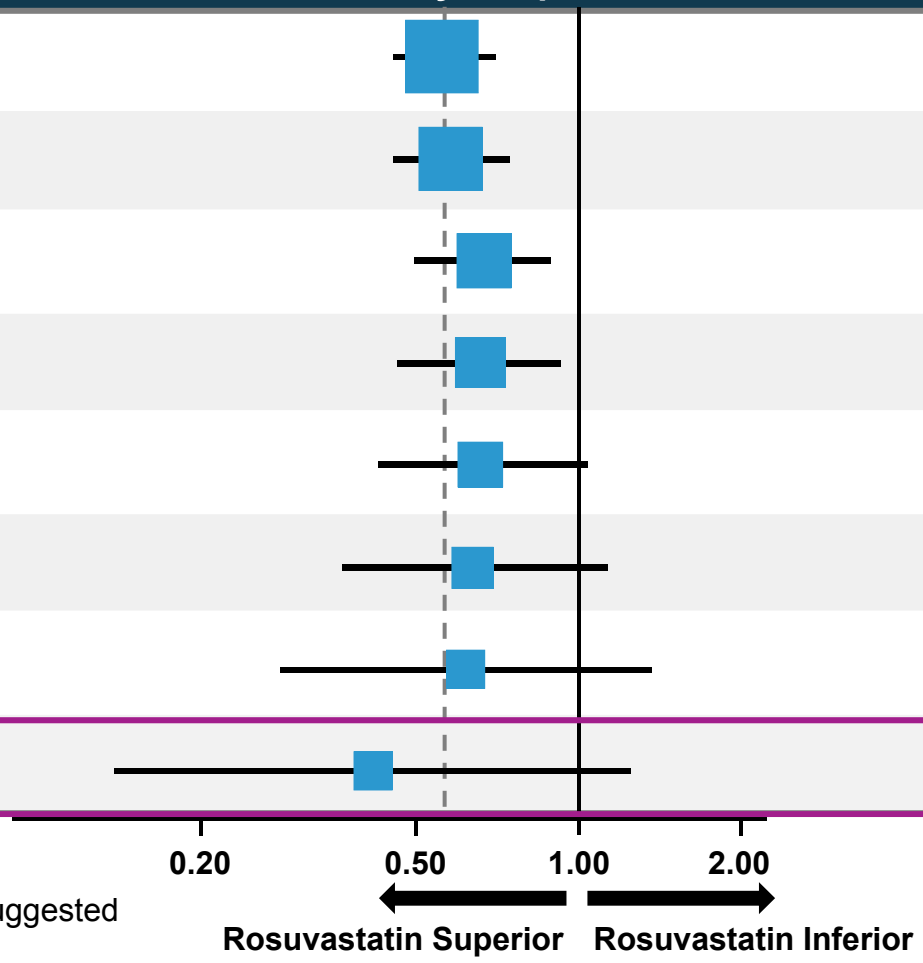
Quartiles (Based on LDL-C at Admission)	Median LDL-C at 4 Months (mg/dL)		HR for Primary Endpoint	P-value
	Ezetimibe + Simvastatin	Simvastatin		
1	45	63		
2	49	69		
3	50	69		P_{int}=0.77
4	53	72		
Overall	49	68		



RP Giugliano et al. *ACC 2015*

Risk Reduction in JUPITER Trial by Baseline LDL-C

Baseline LDL-C	N	HR (95% CI) for Primary Endpoint
≤130 mg/dL	17802	
≤120 mg/dL	13972	
≤110 mg/dL	9784	
≤100 mg/dL	6269	
≤90 mg/dL	3687	
≤80 mg/dL	2033	
≤70 mg/dL	1022	
≤60 mg/dL*	511	

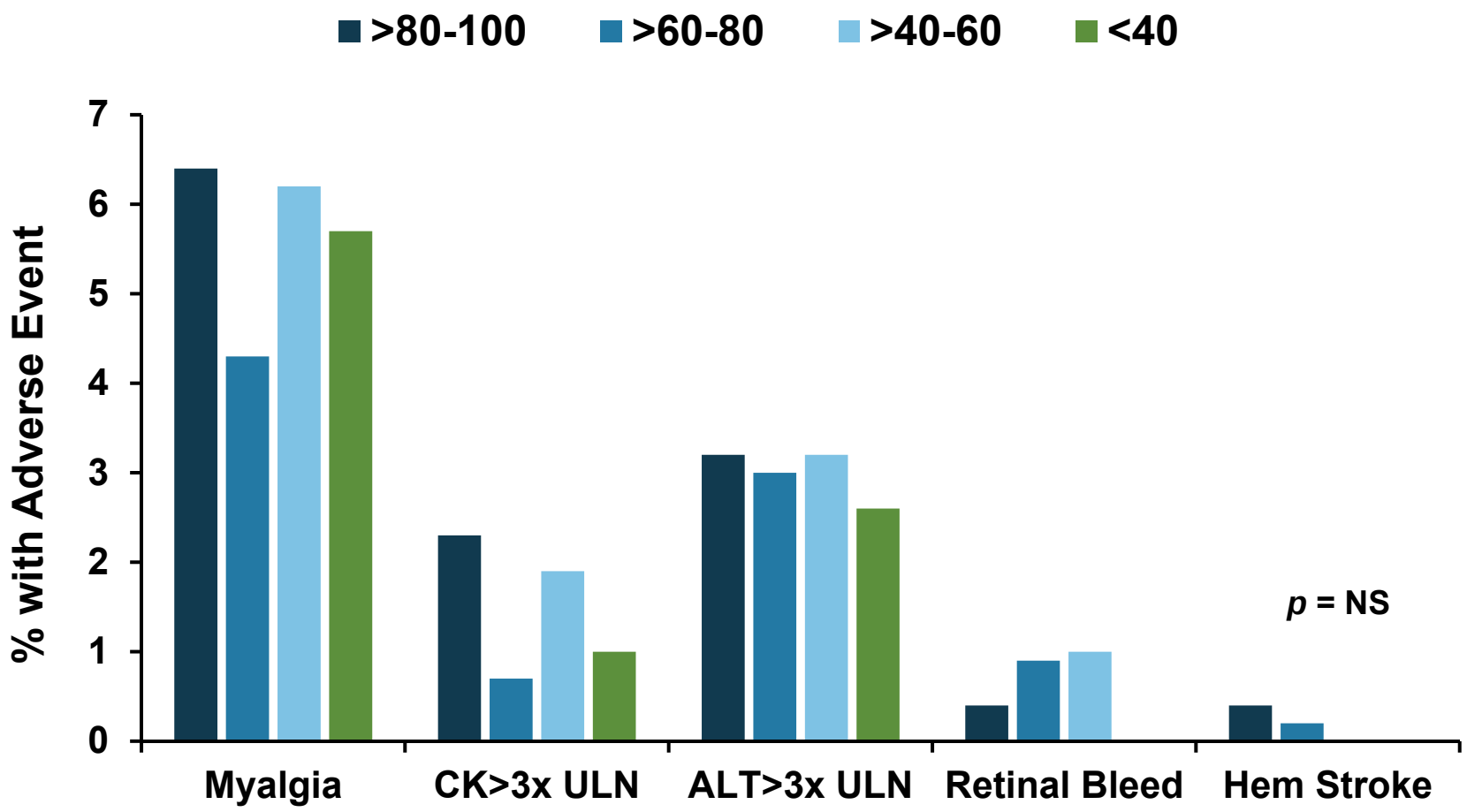


*Overall in trial rosuvastatin reduced LDL-C by 50% suggested achieved LDL-C of ≤30 mg/dL in this subgroup
Hsia J et al. *JACC* 2011.

Are There Substantiated Safety Concerns with Low LDL-C?

- All tissues can synthesize their own cholesterol
- Cholesterol enters the circulation via chylomicrons and VLDL-C
- LDL-C is final product of remodeling of these lipoproteins through interaction with other lipoproteins and the endothelium
- Brain sits behind the blood brain barrier and is independent of circulating lipoproteins
- PCSK9i do not ↓ cholesterol production, they ↑ cholesterol uptake
- Individuals with homozygous PCSK9 deficiency are healthy and have LDL-C between 10-20 mg/dL

Achievement of low LDL-C in PROVE IT-TIMI 22 was not Associated with Safety Concerns



Wiviott SD et al. *J Am Coll Cardiol*. 2005;46:1411-1416.

Summary of Unmet Need (1 of 2)

- There are key groups of patients who still require additional lipid lowering options
  - Patients unable to have LDL-C well controlled on intensive statins:
    - High-risk patients unable to achieve optimally low LDL-C
    - Patients with heterozygous FH
    - Patients with homozygous FH
  - Patients unable to tolerate or cannot be prescribed statins

Summary of Unmet Need (2 of 2)

- LDL-C is a proven modifiable risk factor for cardiovascular events
- The limit below which additional LDL-C lowering is not beneficial has not been established
- LDL-C reduction with PCSK9 inhibition is anticipated to lower CV risk
  - Mechanism of action is upregulating LDL receptor, like statins
  - Genetic validation from individuals with PCSK9 LOF variants
  - Encouraging preliminary CV outcomes data
- There are no identified safety concerns with low LDL-C

Evolocumab Clinical Development Program

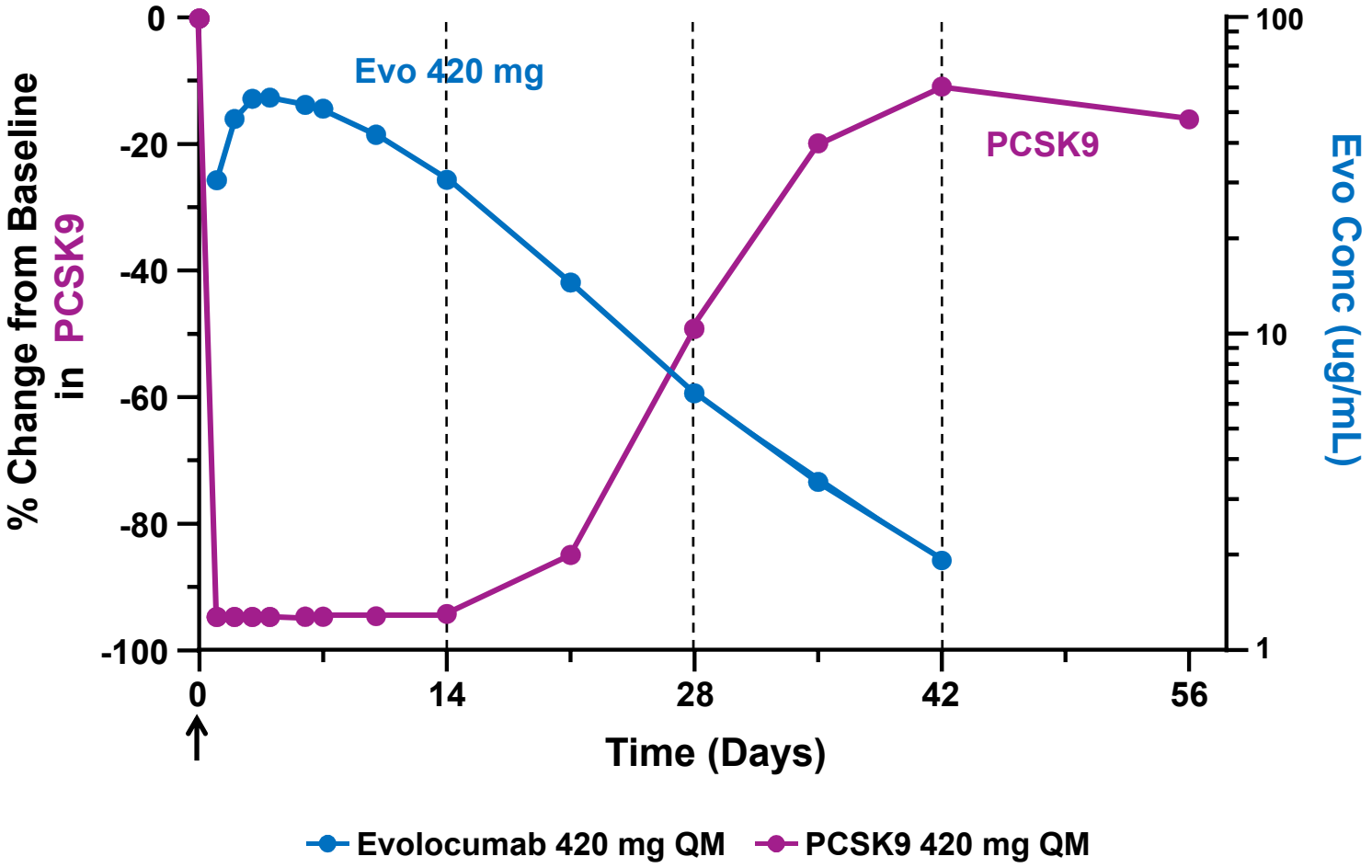
Scott M. Wasserman, MD, FACC

Amgen Inc.
Vice President, Global Development

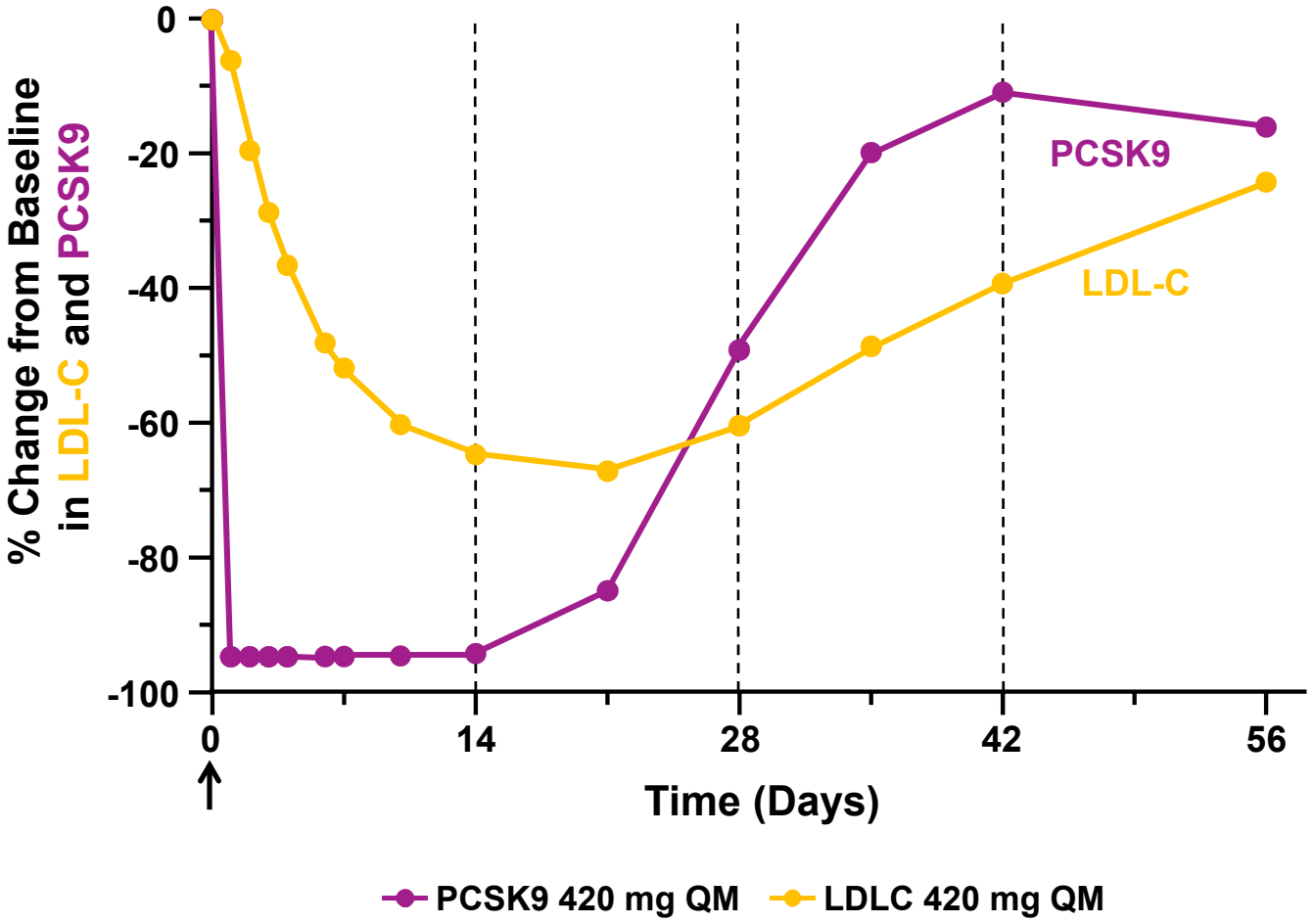
Contents

- Phase 3 Dose Selection
- Clinical Program Overview
- Efficacy
- Safety Evaluation

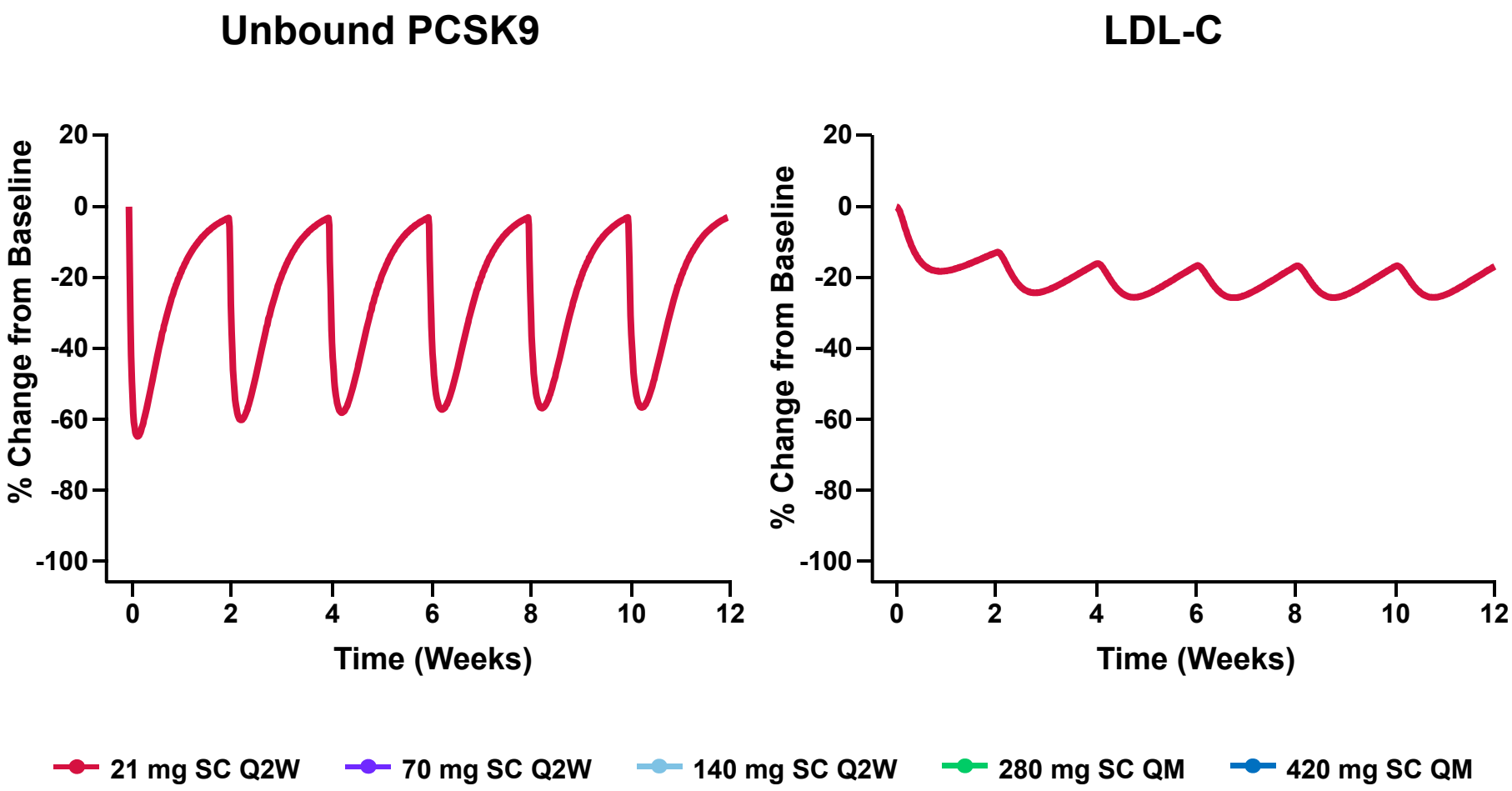
Evolocumab Pharmacokinetics and Pharmacodynamics



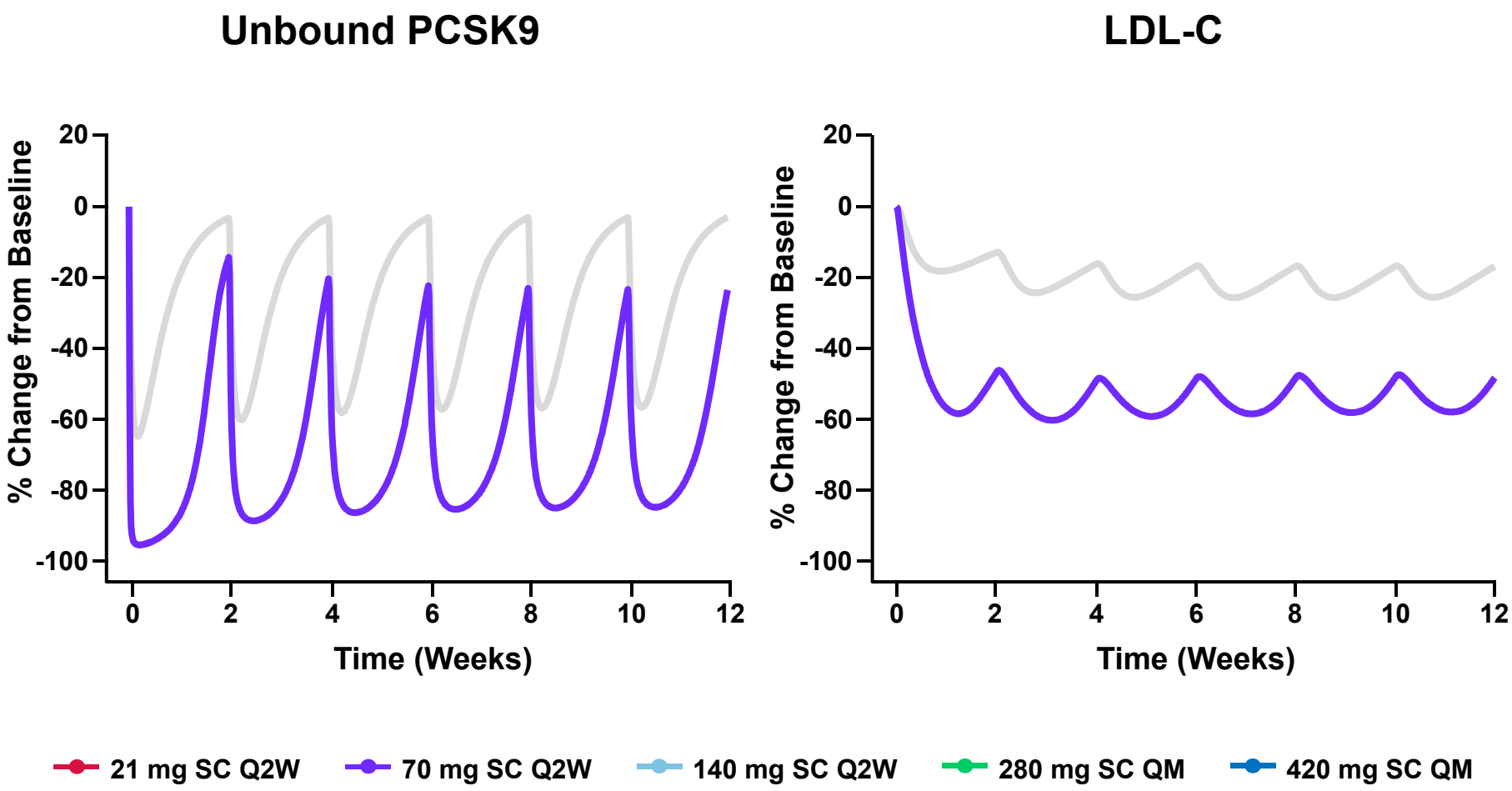
Evolocumab Pharmacokinetics and Pharmacodynamics



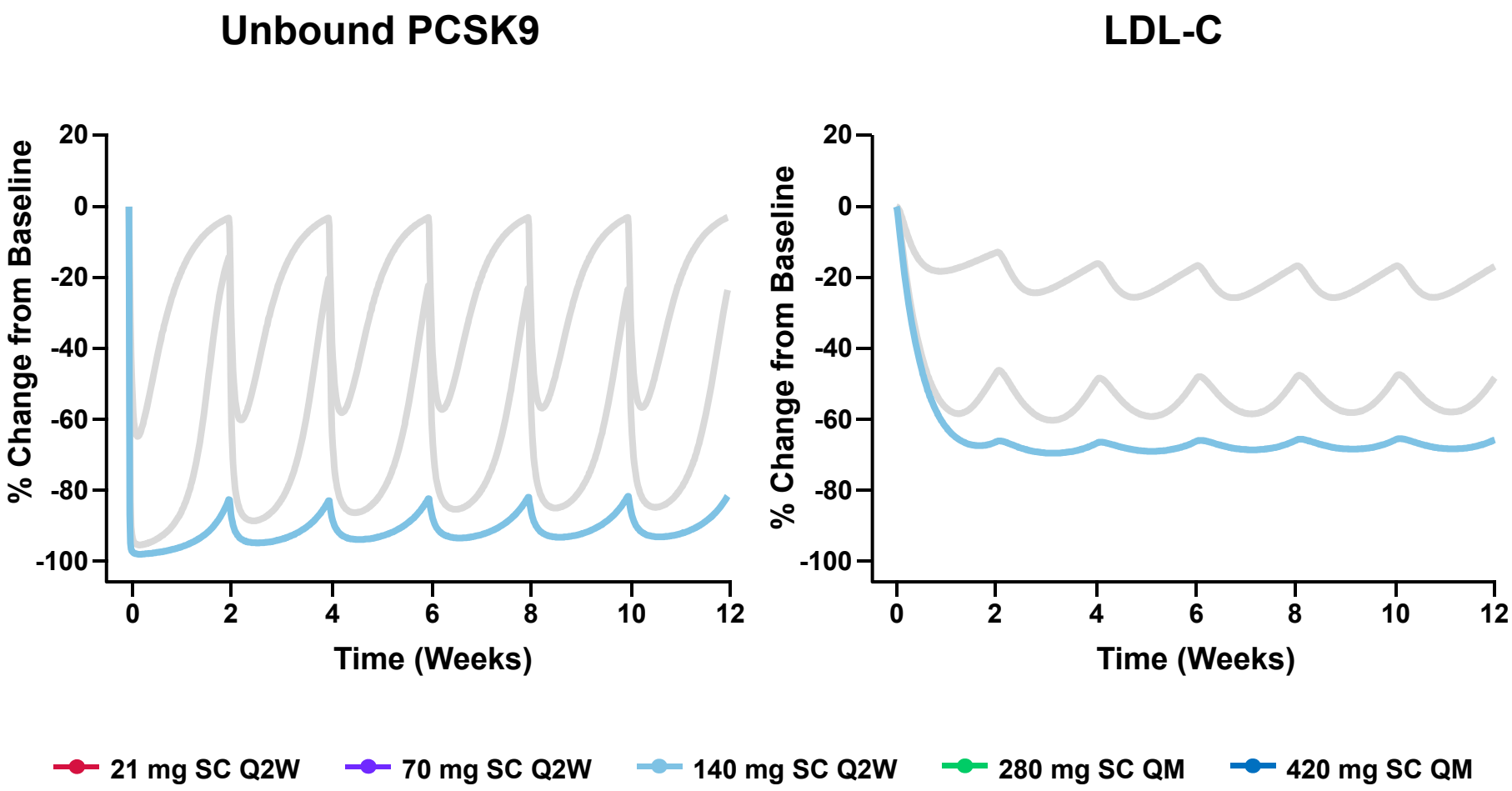
Relationship Between PCSK9 Inhibition and LDL-C Reduction with 21 mg Q2W



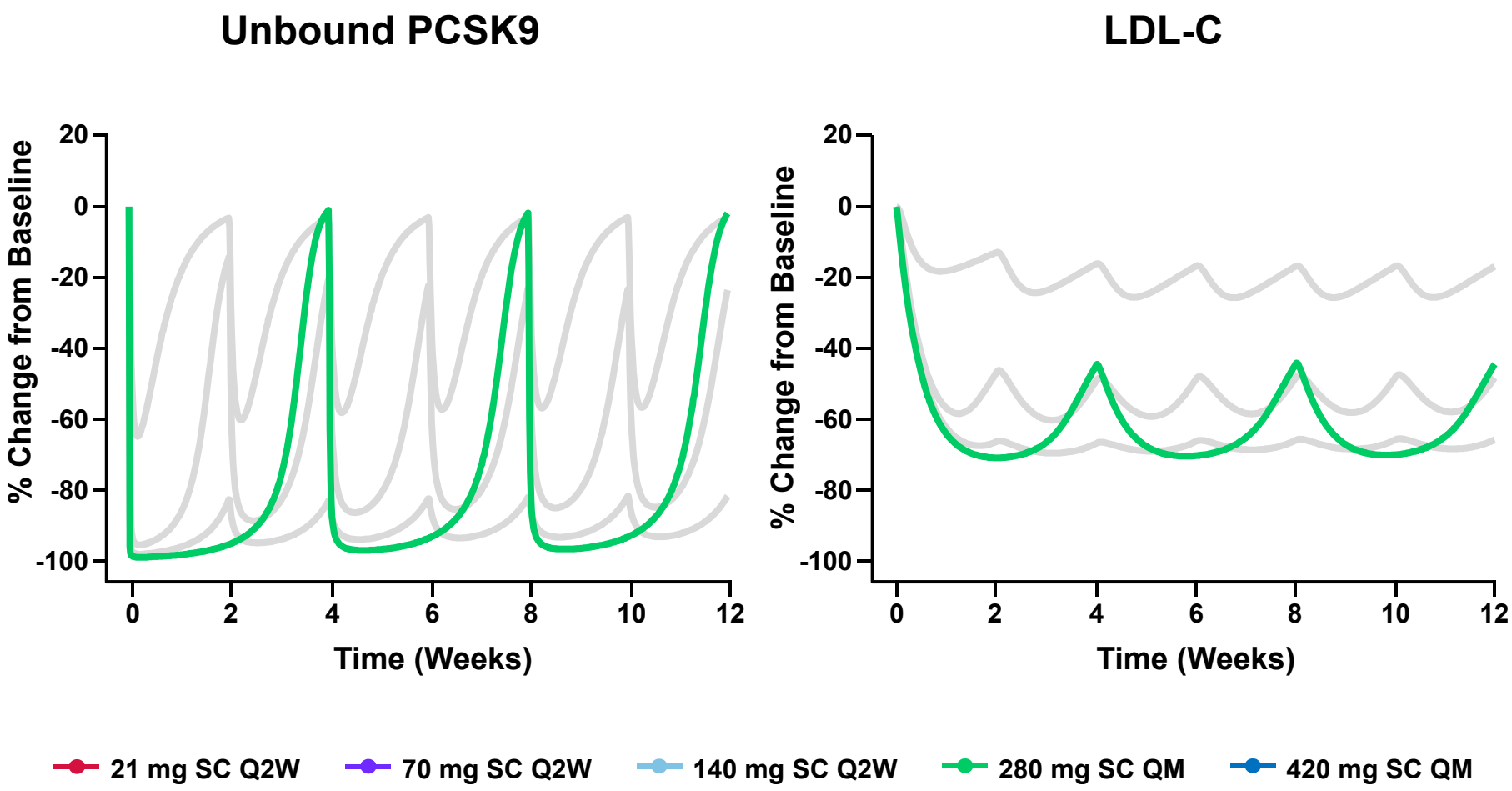
Relationship Between PCSK9 Inhibition and LDL-C Reduction with 70 mg Q2W



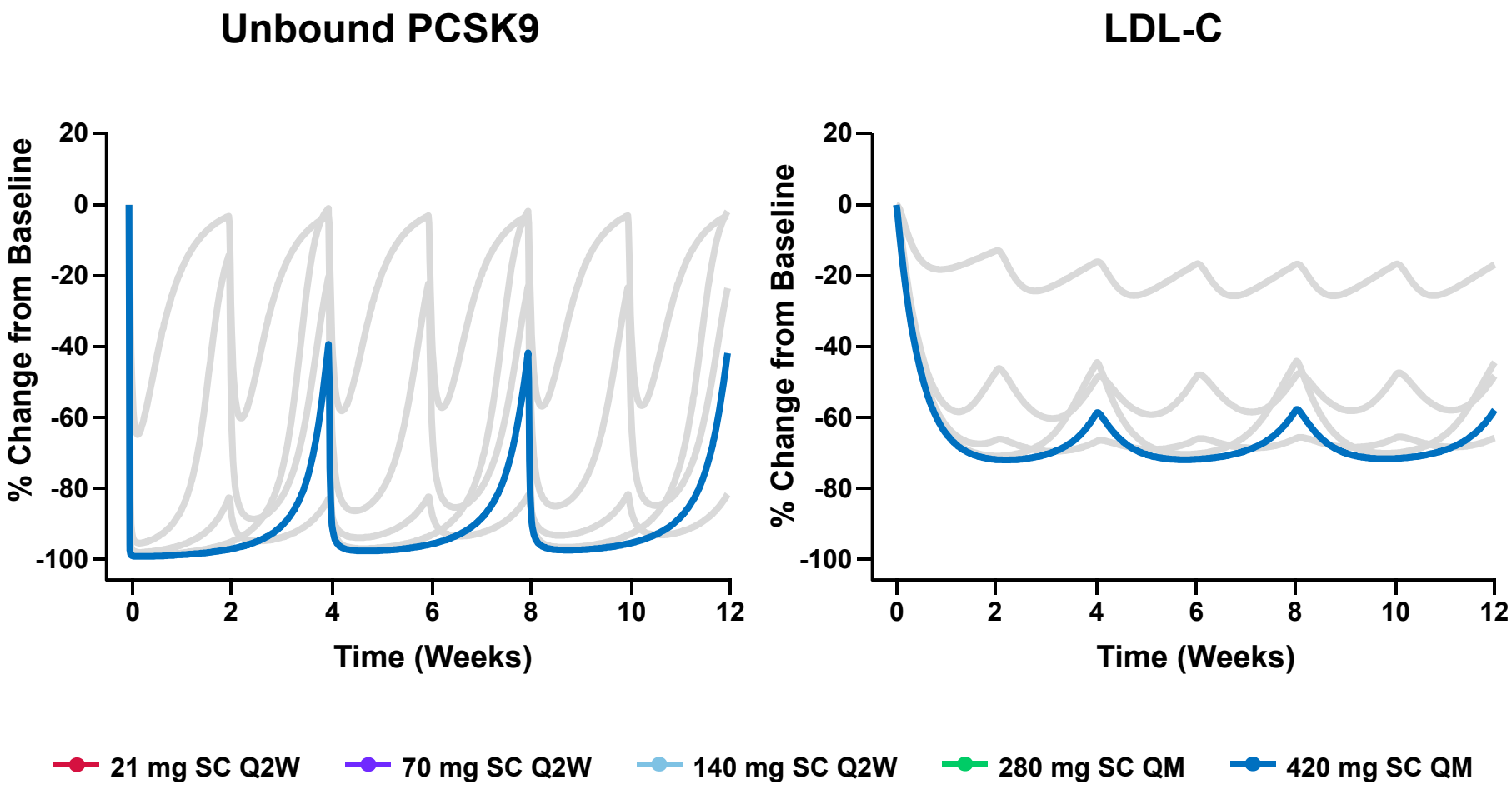
Sustained PCSK9 Inhibition with 140 mg Q2W Leads to Effective, Stable LDL-C Reduction



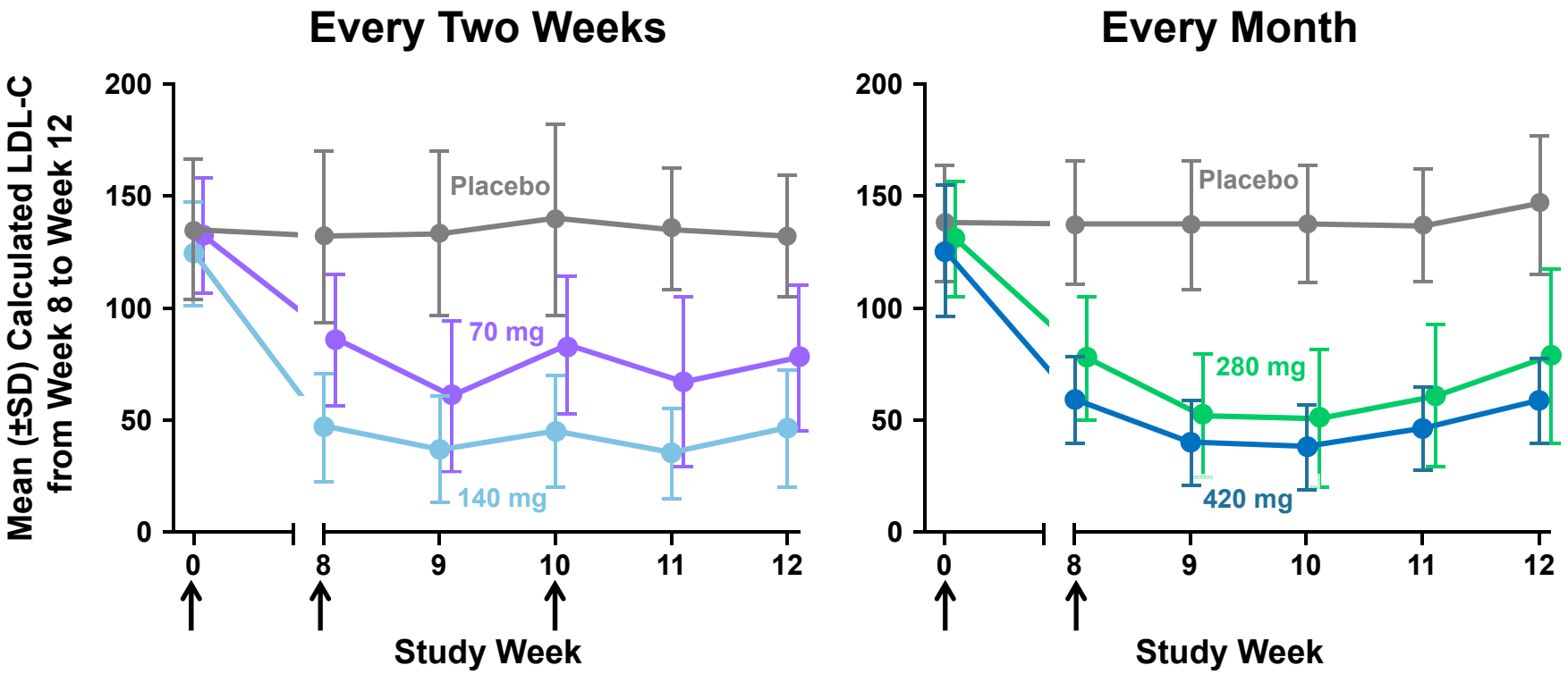
Relationship Between PCSK9 Inhibition and LDL-C Reduction with 280 mg QM



Relationship Between PCSK9 Inhibition and LDL-C Reduction with 420 mg QM



Phase 3 Dose Selection



140 mg Q2W and 420 mg QM

- **Provided most effective reductions in LDL-C per regimen**
- **More stable LDL-C reduction (flatten the U-shape)**

Clinical Program Overview

26 Studies

2 Biopharmaceutic Studies

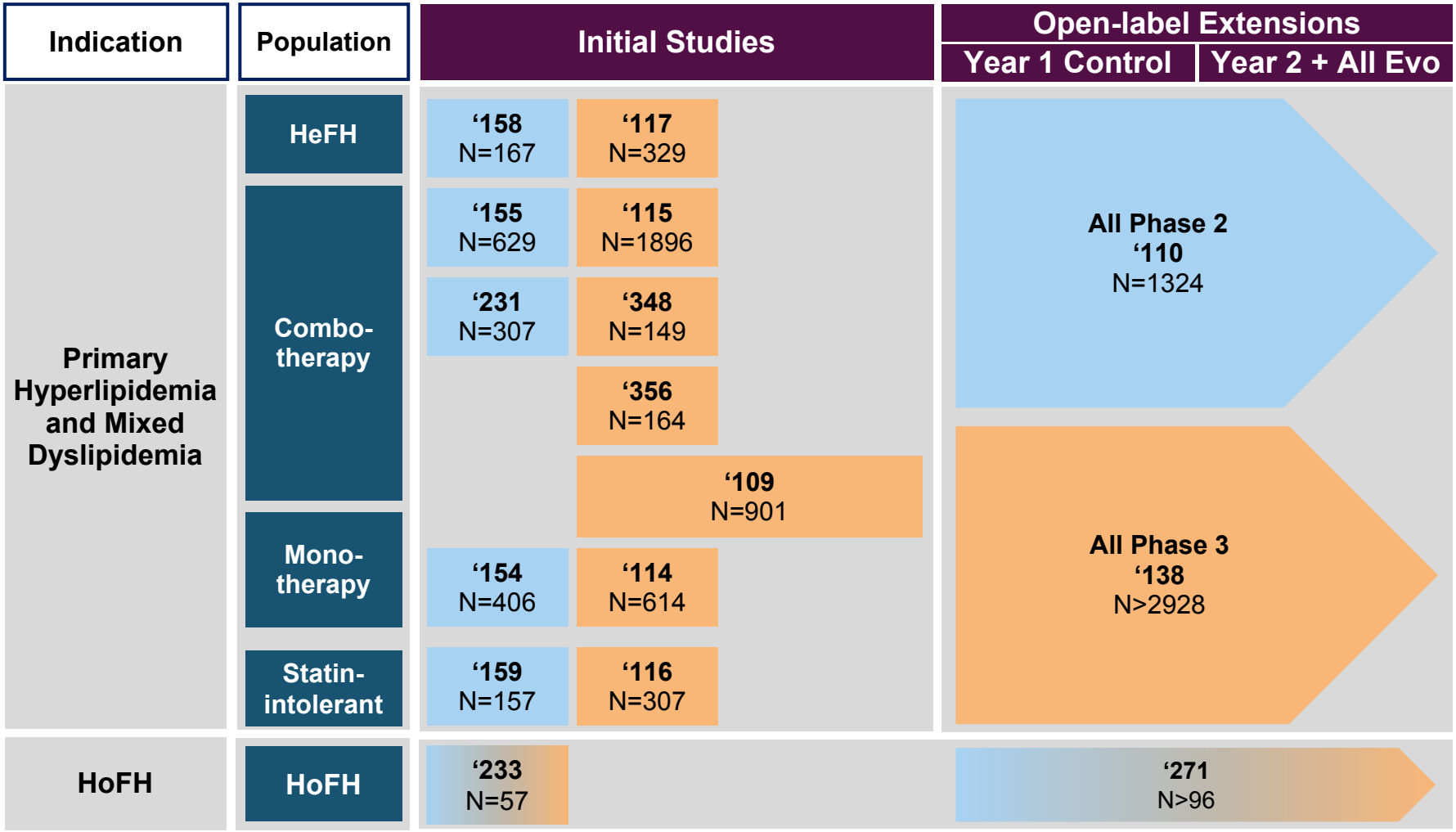
8 Clinical Pharmacology Studies

- 6 Healthy subjects PK/PD and tolerability
- 1 Primary hyperlipidemia and mixed dyslipidemia
- 1 Hepatic impairment

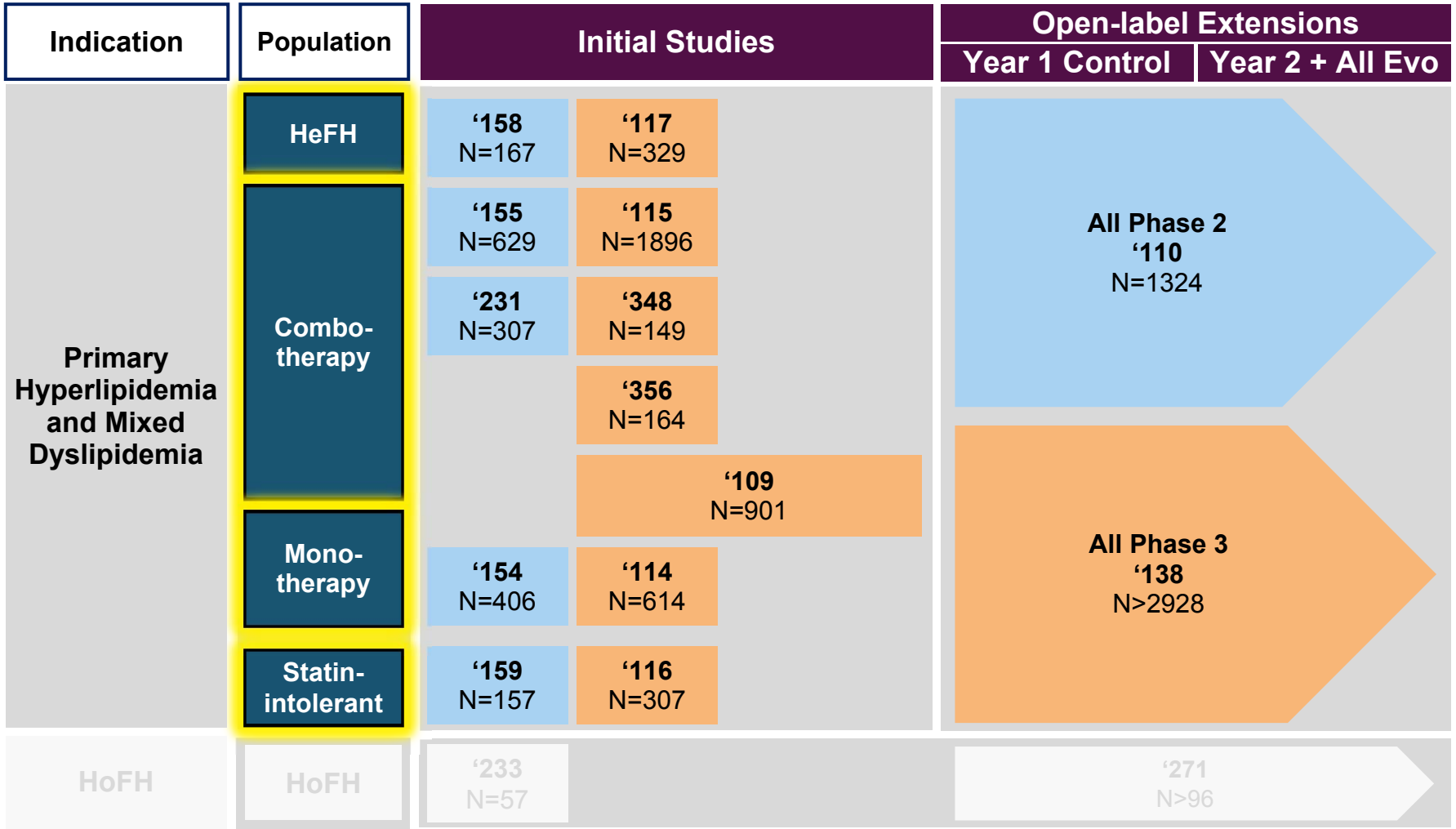
16 Phase 2 and Phase 3 Trials

- 14 Primary hyperlipidemia and mixed dyslipidemia
  - 2 HeFH
  - 5 Combination therapy
  - 2 Monotherapy
  - 2 Statin-intolerant
  - 1 Long-term Combo-monotherapy
  - 2 Long-term open-label extensions
- 2 HoFH
  - 1 RCT
  - 1 Long-term open-label

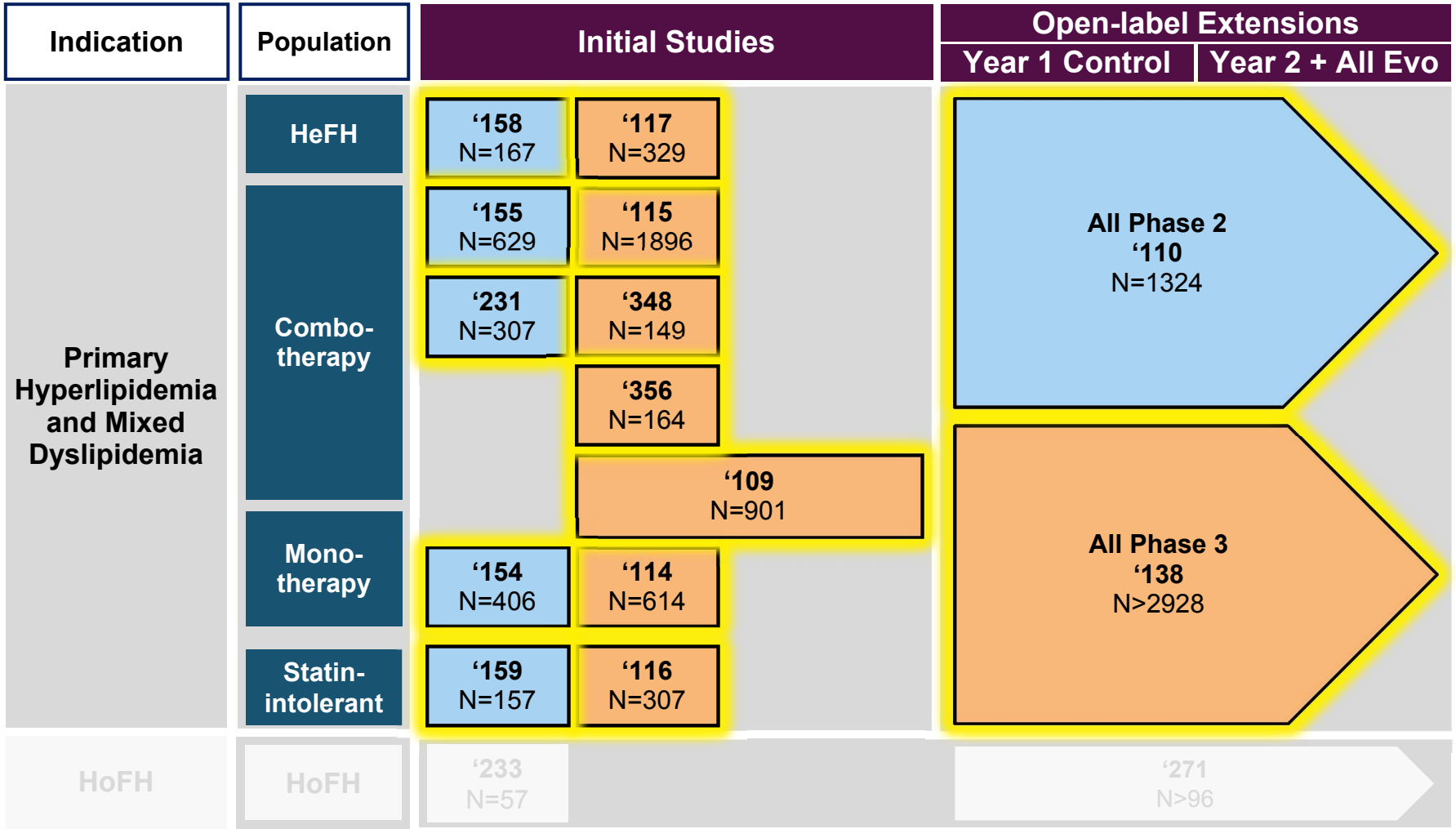
Clinical Development Program



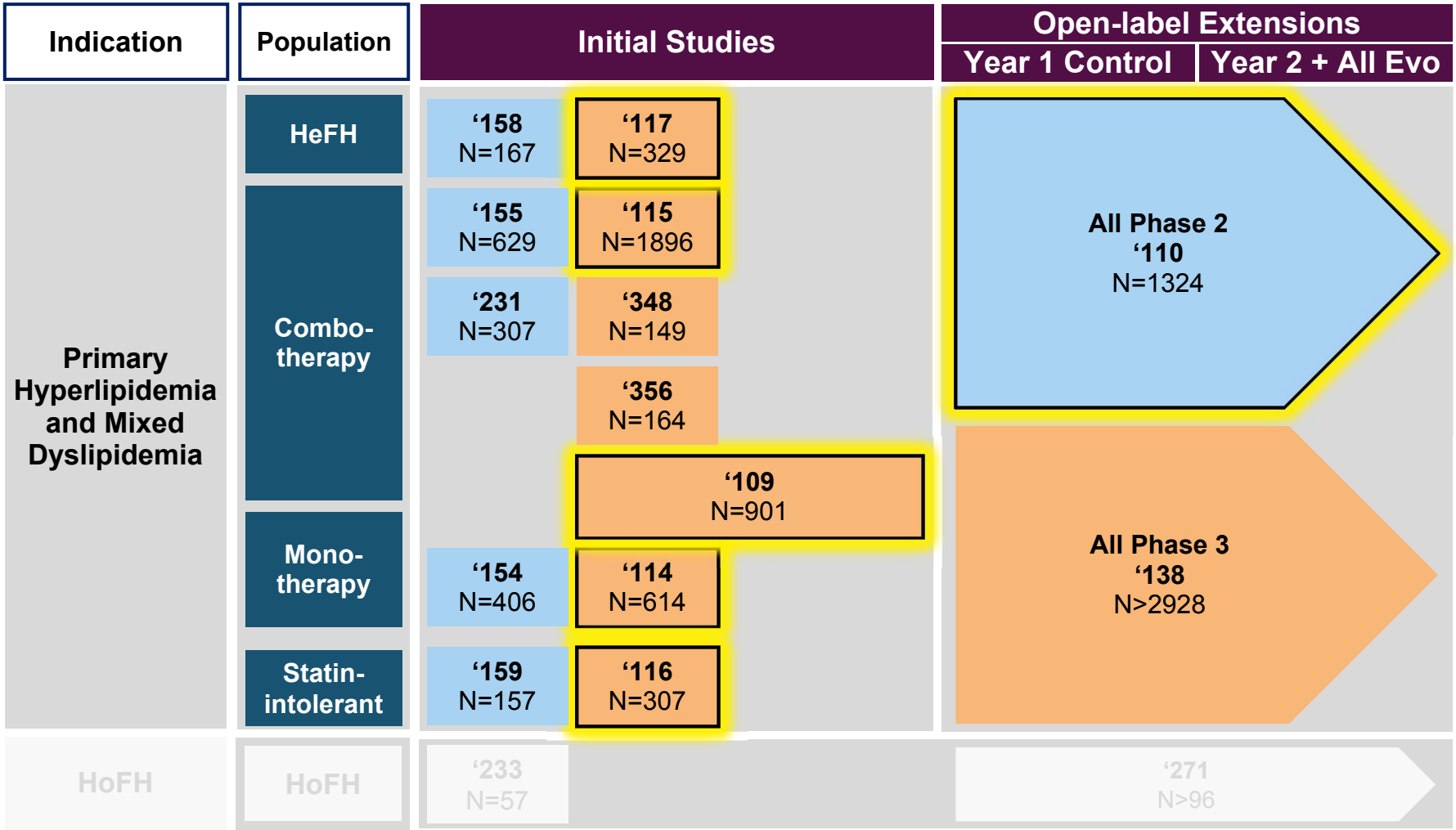
Four Populations in Primary Hyperlipidemia and Mixed Dyslipidemia Indication



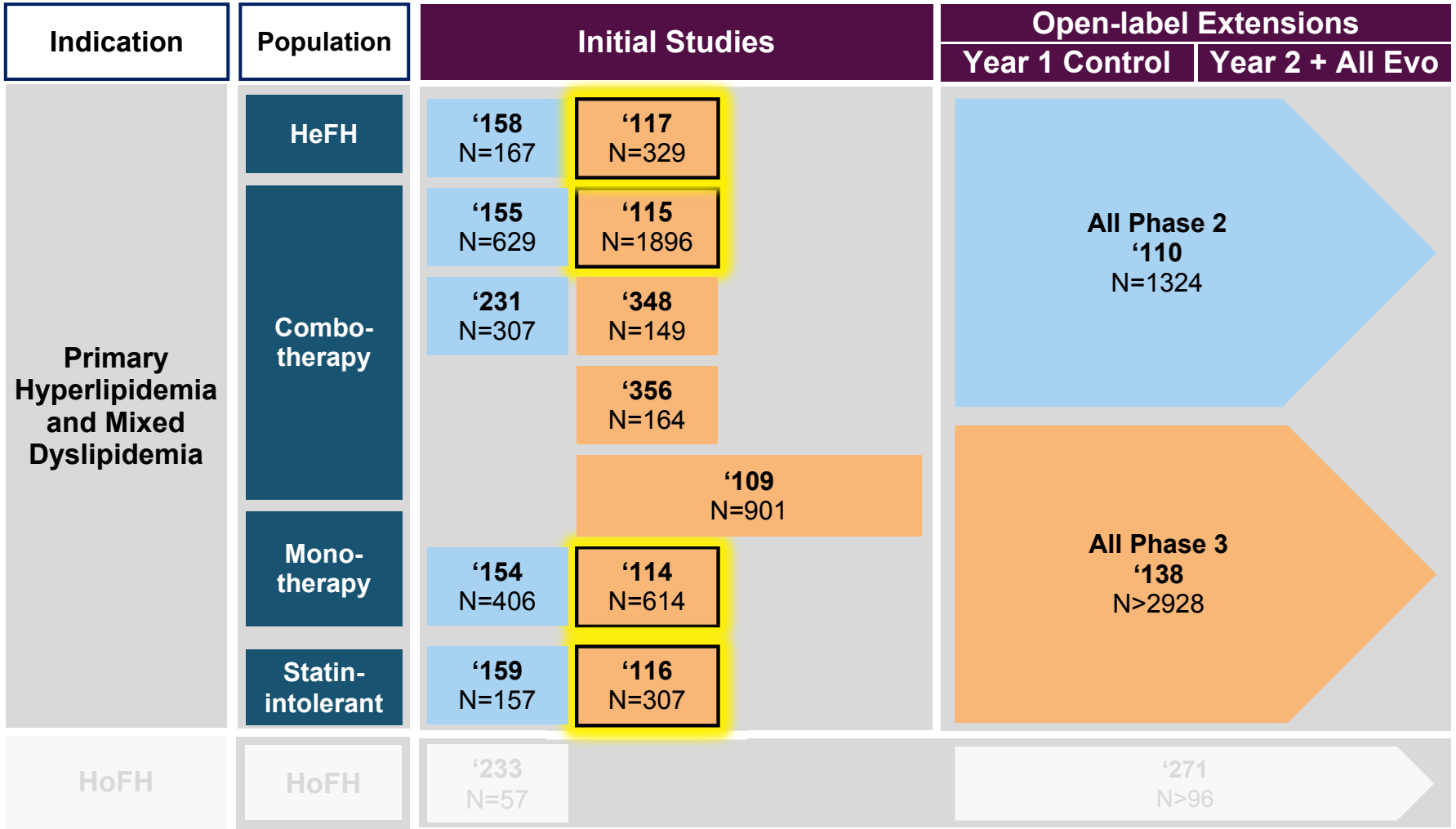
Fourteen Trials



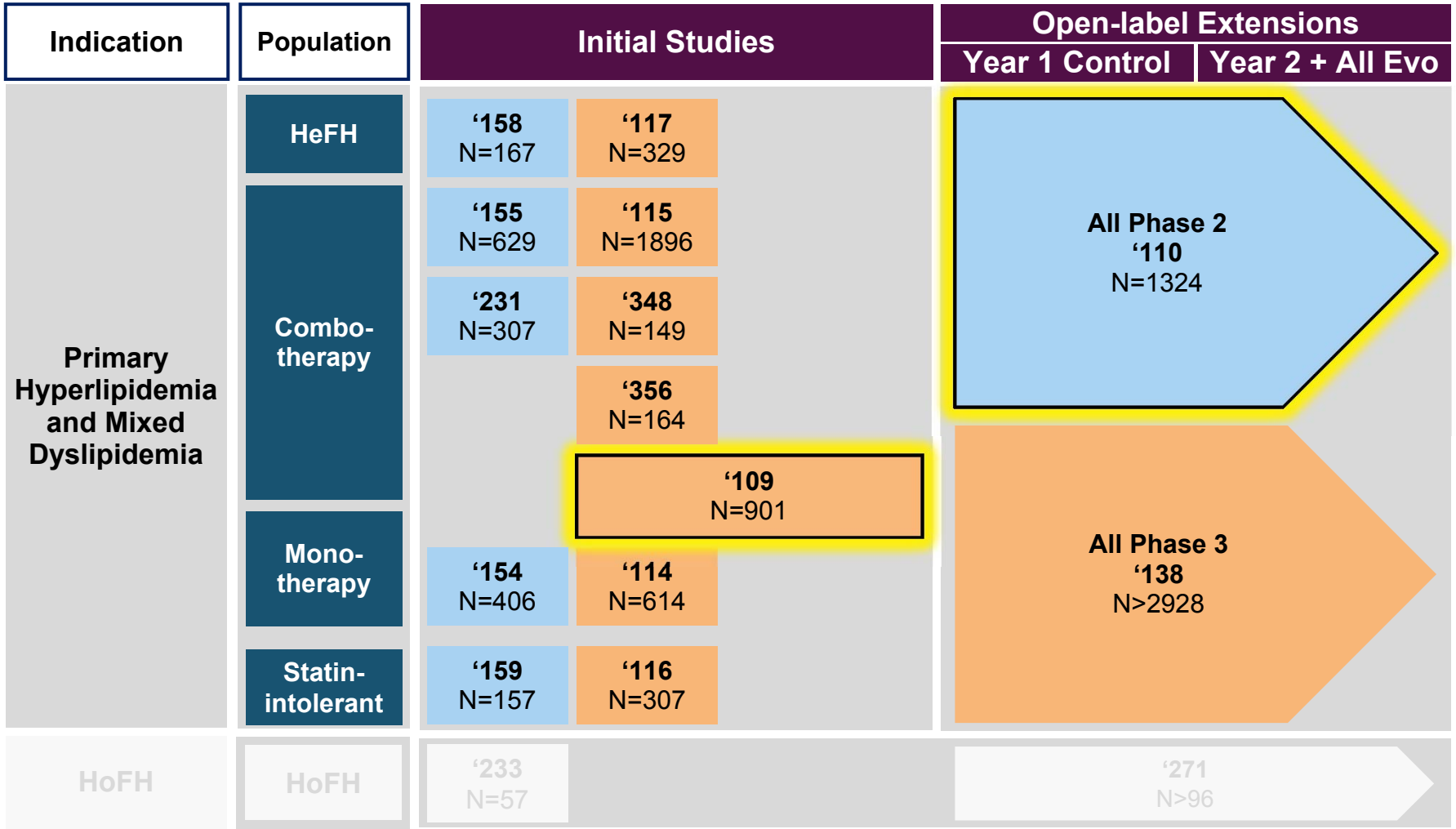
Efficacy Focuses on Six Key Studies



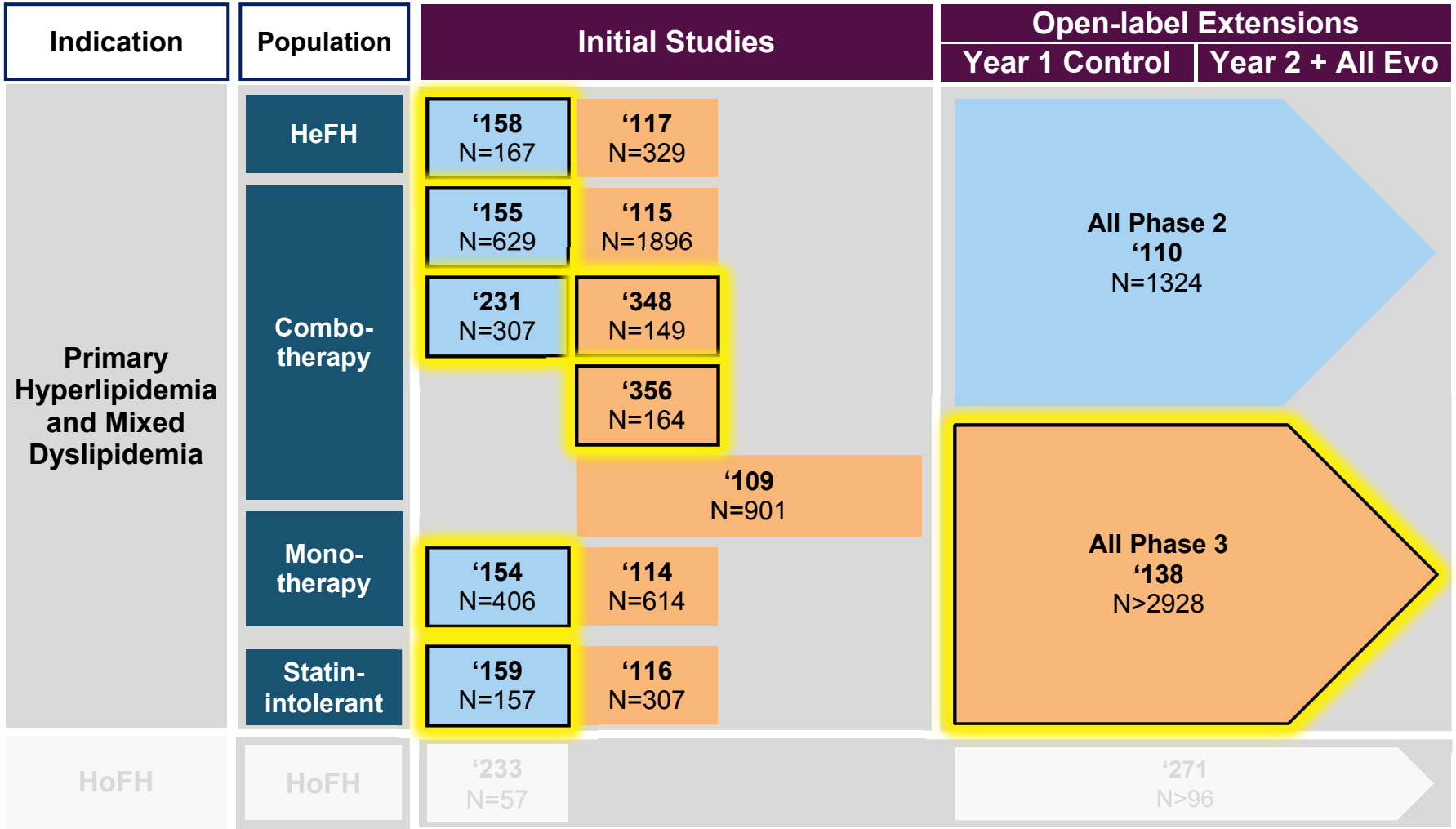
Four 12-week Phase 3 Studies



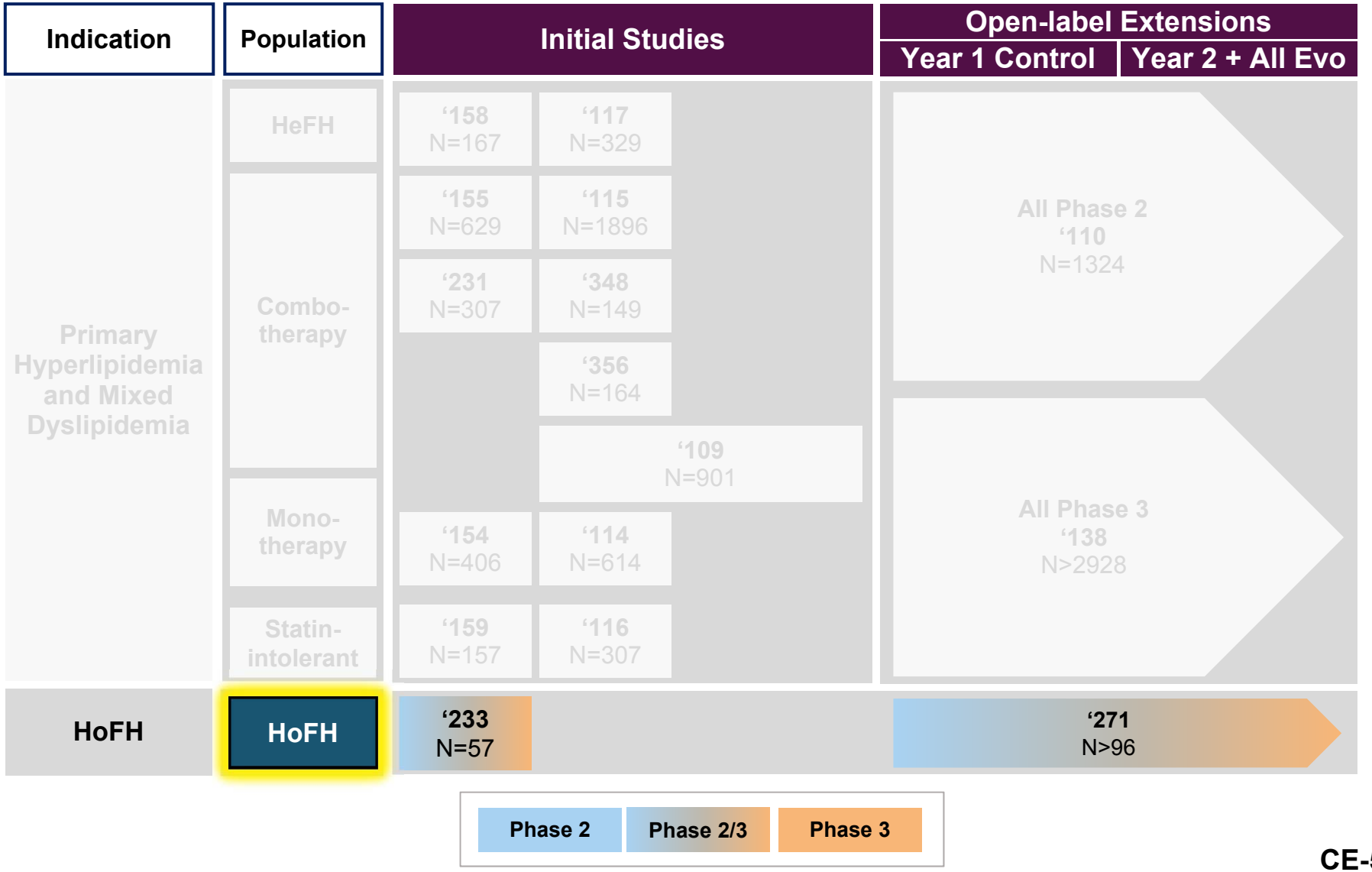
Two Long-term Efficacy Studies



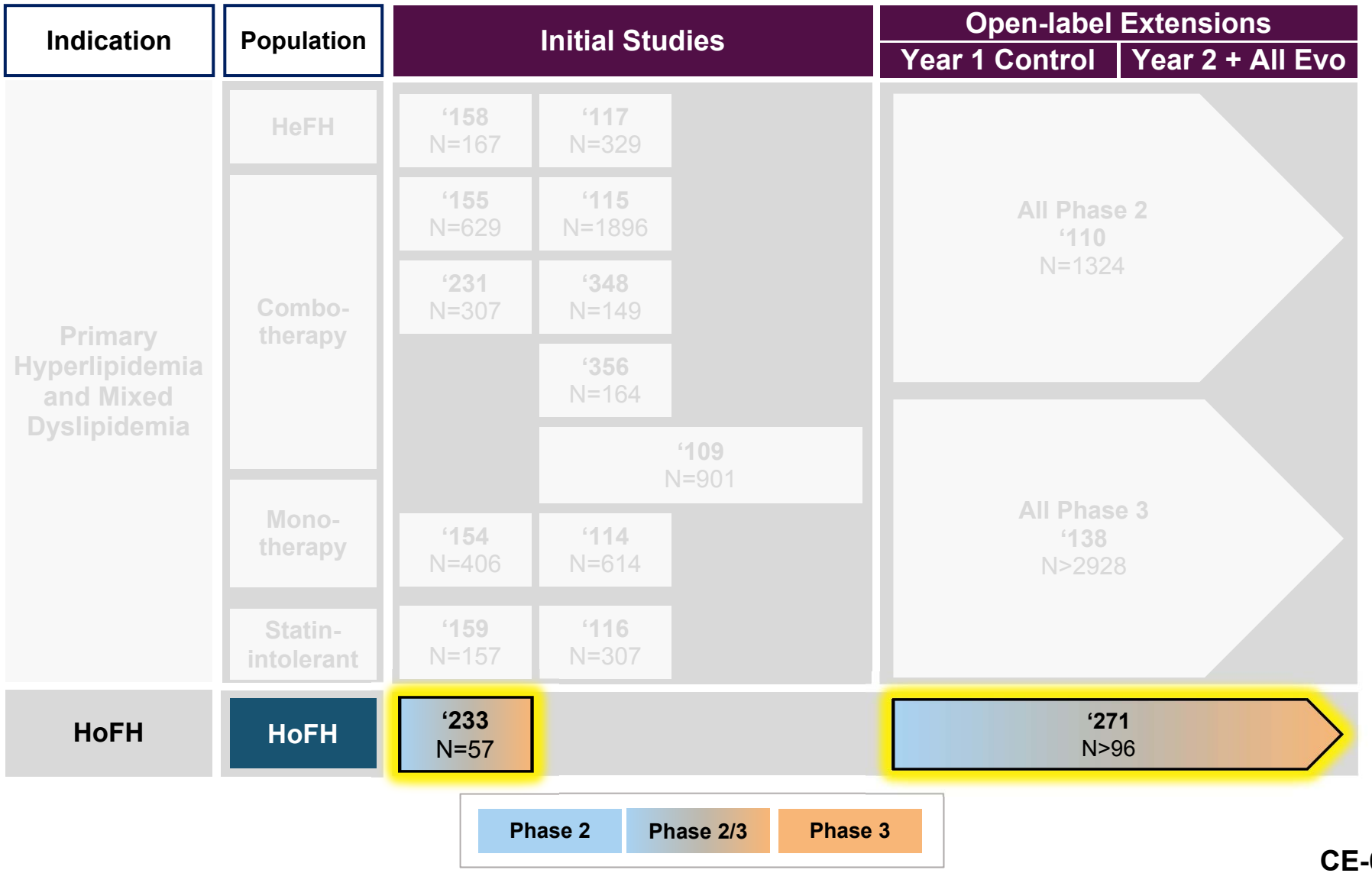
Eight Additional Studies Provide Supportive Data



Homozygous Familial Hypercholesterolemia Indication



Two Studies


Indication
Population
Initial Studies
Open-label Extensions
Year 1 Control
Year 2 + All Evo
Primary Hyperlipidemia and Mixed Dyslipidemia
HeFH
Combo-therapy
Mono-therapy
Statin-intolerant
'158 N=167
'117 N=329
'155 N=629
'115 N=1896
'231 N=307
'348 N=149
'356 N=164
'109 N=901
'154 N=406
'114 N=614
'159 N=157
'116 N=307
All Phase 2 '110 N=1324
All Phase 3 '138 N>2928
HoFH
HoFH
'233 N=57
'271 N>96
Phase 2
Phase 2/3
Phase 3

Study Designs

Primary Hyperlipidemia and Mixed Dyslipidemia

Phase 3 12-Week Trial Designs

Study		HeFH ('117) N=329	Combotherapy ('115) N=1896	Monotherapy ('114) N=614	Statin-intolerant ('116) N=307
Population		HeFH	CV risk on statin	Framingham Risk 10% or less	Intolerant to 2 or more statins
Fasting LDL-C		≥100 mg/dL	≥80 mg/dL	≥100 and <190 mg/dL	≥100 mg/dL
Background Lipid Lowering Therapy		Statin ± ezetimibe	•Rosuvastatin 5 and 40 mg •Atorvastatin 10 and 80 mg •Simvastatin 40 mg	Diet alone	No or low dose statin
Comparators	Placebo	☑	☑	☑	
	Ezetimibe		☑	☑	☑

Key Long-term Trial Designs

Study	Long-term Combo-Mono (‘109) N=901	Open-label (‘110) N=1324
Population	Range of Cardiovascular risk	Completing Phase 2 LDL-C study
Fasting LDL-C	≥75 mg/dL	≥85 mg/dL
Background Lipid Lowering Therapy	• Diet alone • Atorvastatin 10 mg • Atorvastatin 80 mg • Atorvastatin 80 mg+ezetimibe	Standard of care
Comparator	Placebo	Standard of care (Year 1)
Duration	52 weeks	Up to 5 years

Efficacy Endpoints

Co-primary Efficacy Endpoints	• **Percent change in LDL-C from BL to weeks 10 and 12** • **Percent change in LDL-C from BL to week 12**	
Co-secondary Efficacy Endpoints	• Change from BL in LDL-C • LDL-C response (LDL-C <70 mg/dL)	• Percent change from BL in – Non-HDL-C – ApoB – Total cholesterol/HDL-C ratio – ApoB/ApoA1 ratio – Lp(a) – Triglycerides – HDL-C – VLDL-C

- Each evolocumab dose frequency group was compared to corresponding dose frequency control group(s)
- Mixed model repeated measure (MMRM) used all observed data regardless of adherence to study drug
- Overall type I error rate of 0.05 was controlled for multiple comparisons within each dose frequency cohort

Demographics and Disposition

Primary Hyperlipidemia and Mixed Dyslipidemia

Baseline Demographics

Study	HeFH (‘117) N=329 %	Combination Therapy (‘115) N=1896 %	Monotherapy (‘114) N=614 %	Statin-intolerant (‘116) N=307 %	Long-term (‘109) N=901 %	Open-label (‘110) N=1324 %
Female	**42**	**46**	**66**	**46**	**52**	**53**
Age (years), mean (SD)	**51 (13)**	**60 (10)**	**53 (12)**	**62 (10)**	**56 (11)**	**57 (11)**
Race						
Asian	5	1	9	3	6	19
Black or African American	1	4	7	2	8	6
White	90	94	83	94	80	74
Ethnicity						
Hispanic or Latino	1.0	5	11	2	6	4
Region						
North America	23	39	57	37	58	49
Europe	54	58	32	50	27	30
Asia Pacific	23	3	10	13	15	21

Baseline Characteristics

Study	HeFH (‘117) N=329 %	Combination Therapy (‘115) N=1896 %	Monotherapy (‘114) N=614 %	Statin-intolerant (‘116) N=307 %	Long-term (‘109) N=901 %	Open-label (‘110) N=1324 %
LDL-C (mg/dL), mean (SD)	**156 (45)**	**109 (41)**	**143 (23)**	**193 (59)**	**100 (22)**	**141 (37)**
Baseline lipid medication	**100**	**100**	**-**	**33**	**88**	**74**
Statin	100	100	-	18	88	72
High-intensity	76	41	-	0	45	20
Moderate-intensity	22	59	-	4	43	31
Ezetimibe	62	-	-	-	21	13
NCEP CHD risk categories						
High-moderately high	49	50	6	71	35	45
Moderate	27	28	37	17	33	30
Low	24	22	57	12	31	25
ACC/AHA 2013 statin benefit groups	**100**	**69**	**22**	**93**	**50**	**70**

Phase 3 Disposition

Study	HeFH (‘117) N=329 %	Combination Therapy (‘115) N=1896 %	Monotherapy (‘114) N=614 %	Statin-intolerant (‘116) N=307 %	Long-term (‘109) N=901 %
Completed SC injection	**98.5**	**95.3**	**94.6**	**95.4**	**88.8**
Discontinued SC injection	**1.5**	**4.7**	**5.4**	**4.6**	**11.2**
Adverse event	0	1.7	2.0	3.9	1.8
Subject request	1.5	1.8	1.5	0.3	3.6
Lost to follow-up	0	0.2	0.8	0.3	1.2
Completed study or roll-over	**98.8**	**97.3**	**98.7**	**98.7**	**94.9**
Discontinued before study completion or roll-over	**1.2**	**2.6**	**1.3**	**1.3**	**5.1**
Withdraw consent	1.2	2.1	0.3	1.0	2.1
Lost to follow-up	0	0.3	1.0	0.3	1.4
Enrolled in open-label study	**89.1**	**72.9**	**61.6**	**82.7**	**67.9**

Phase 3 Disposition

Study	HeFH (‘117) N=329 %	Combination Therapy (‘115) N=1896 %	Monotherapy (‘114) N=614 %	Statin-intolerant (‘116) N=307 %	Long-term (‘109) N=901 %
Completed SC injection	98.5	95.3	94.6	95.4	88.8
Discontinued SC injection	1.5	4.7	5.4	4.6	11.2
Adverse event	0	1.7	2.0	3.9	1.8
Subject request	1.5	1.8	1.5	0.3	3.6
Lost to follow-up	0	0.2	0.8	0.3	1.2
Completed study or roll-over	**98.8**	**97.3**	**98.7**	**98.7**	**94.9**
Discontinued before study completion or roll-over	**1.2**	**2.6**	**1.3**	**1.3**	**5.1**
Withdraw consent	1.2	2.1	0.3	1.0	2.1
Lost to follow-up	0	0.3	1.0	0.3	1.4
Enrolled in open-label study	89.1	72.9	61.6	82.7	67.9

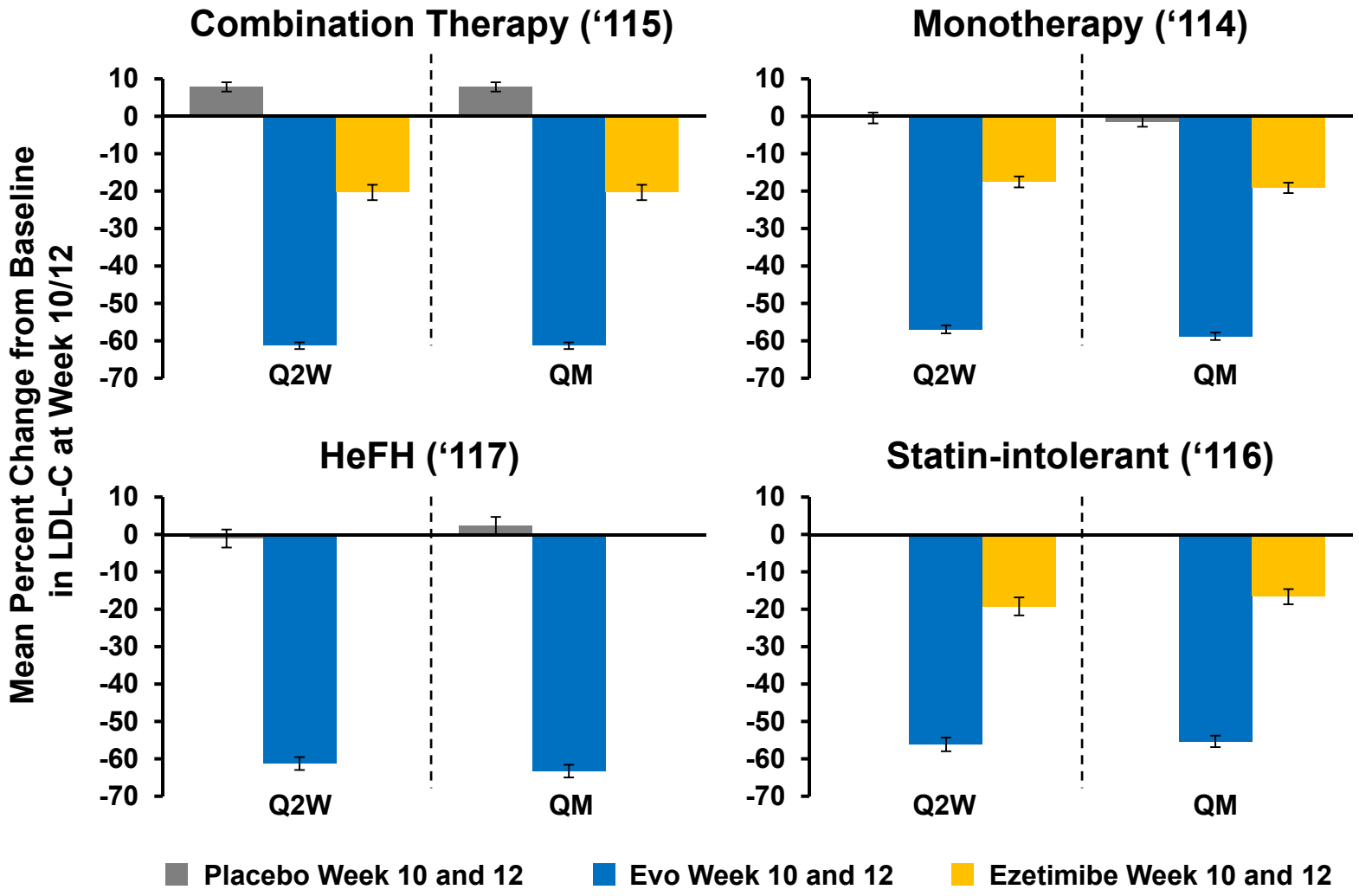
Phase 3 Disposition

Study	HeFH (‘117) N=329 %	Combination Therapy (‘115) N=1896 %	Monotherapy (‘114) N=614 %	Statin-intolerant (‘116) N=307 %	Long-term (‘109) N=901 %
Completed SC injection	98.5	95.3	94.6	95.4	88.8
Discontinued SC injection	1.5	4.7	5.4	4.6	11.2
Adverse event	0	1.7	2.0	3.9	1.8
Subject request	1.5	1.8	1.5	0.3	3.6
Lost to follow-up	0	0.2	0.8	0.3	1.2
Completed study or roll-over	98.8	97.3	98.7	98.7	94.9
Discontinued before study completion or roll-over	1.2	2.6	1.3	1.3	5.1
Withdraw consent	1.2	2.1	0.3	1.0	2.1
Lost to follow-up	0	0.3	1.0	0.3	1.4
Enrolled in open-label study	**89.1**	**72.9**	**61.6**	**82.7**	**67.9**

Efficacy Results

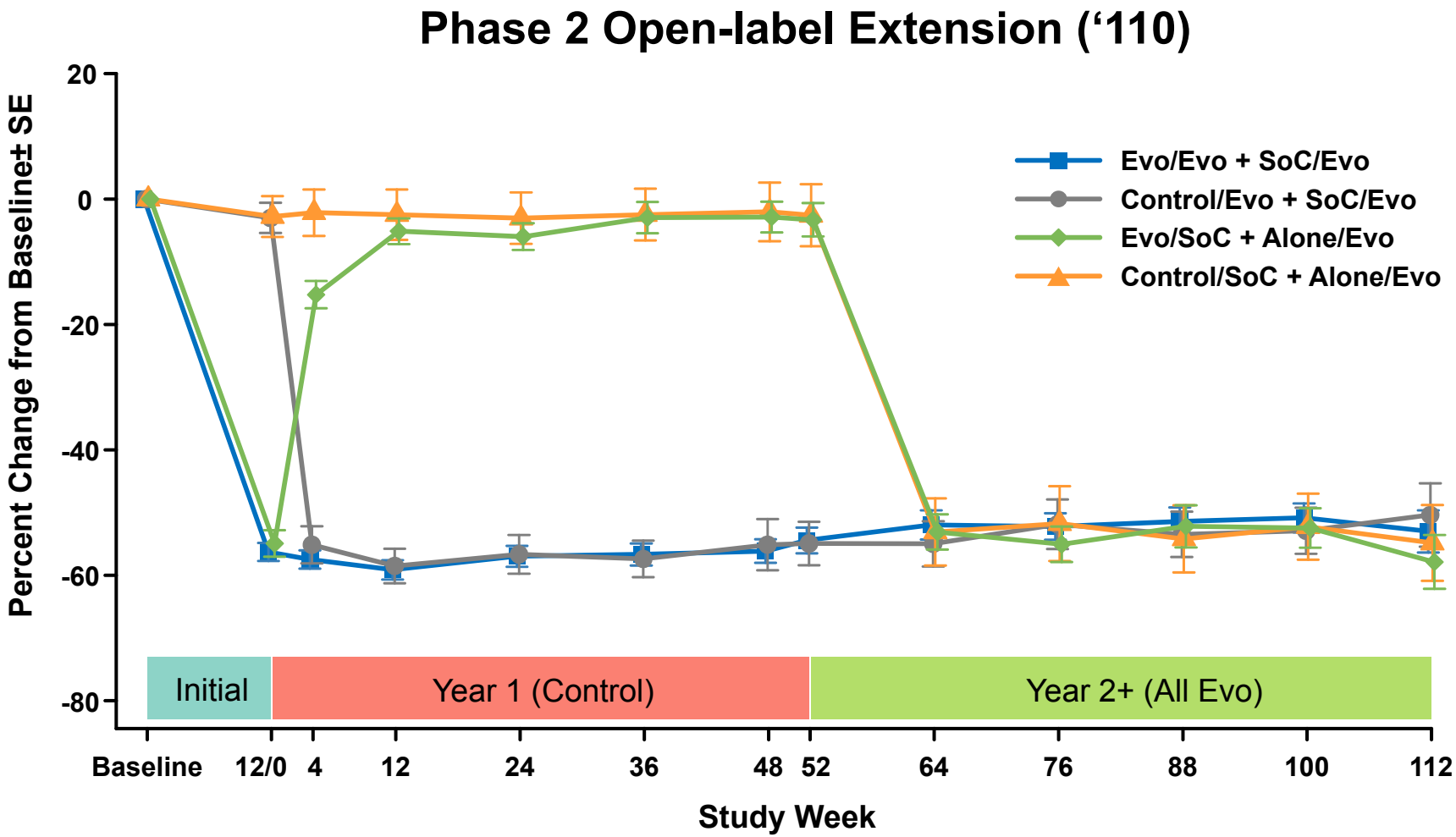
Primary Hyperlipidemia and Mixed Dyslipidemia

Co-primary Endpoint: Consistent, Clinically Equivalent LDL-C Reduction

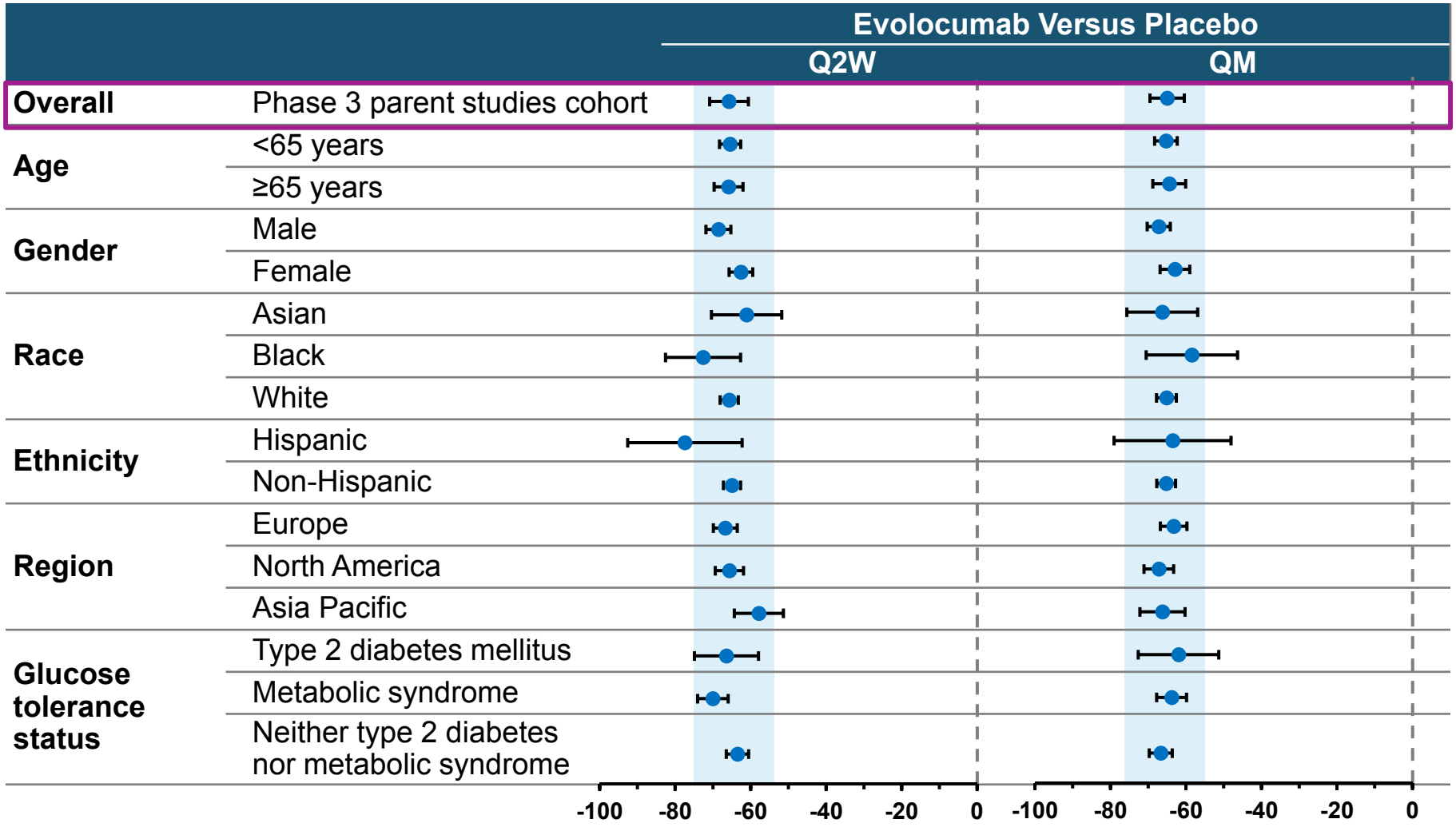


Note: p<0.001 for all comparison versus placebo or ezetimibe

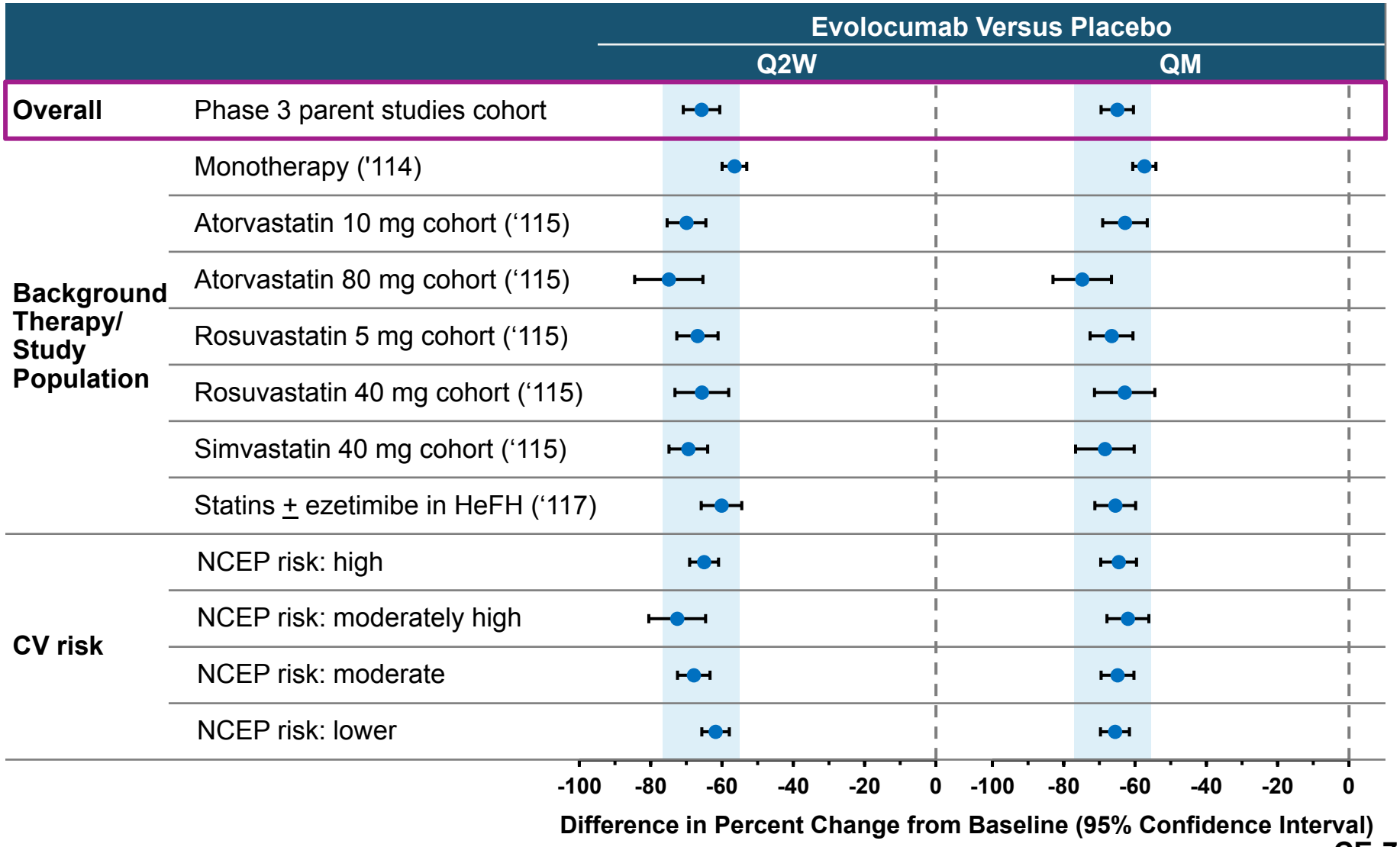
Efficacy Maintained Over 2 Years in the Phase 2 Open-label Study



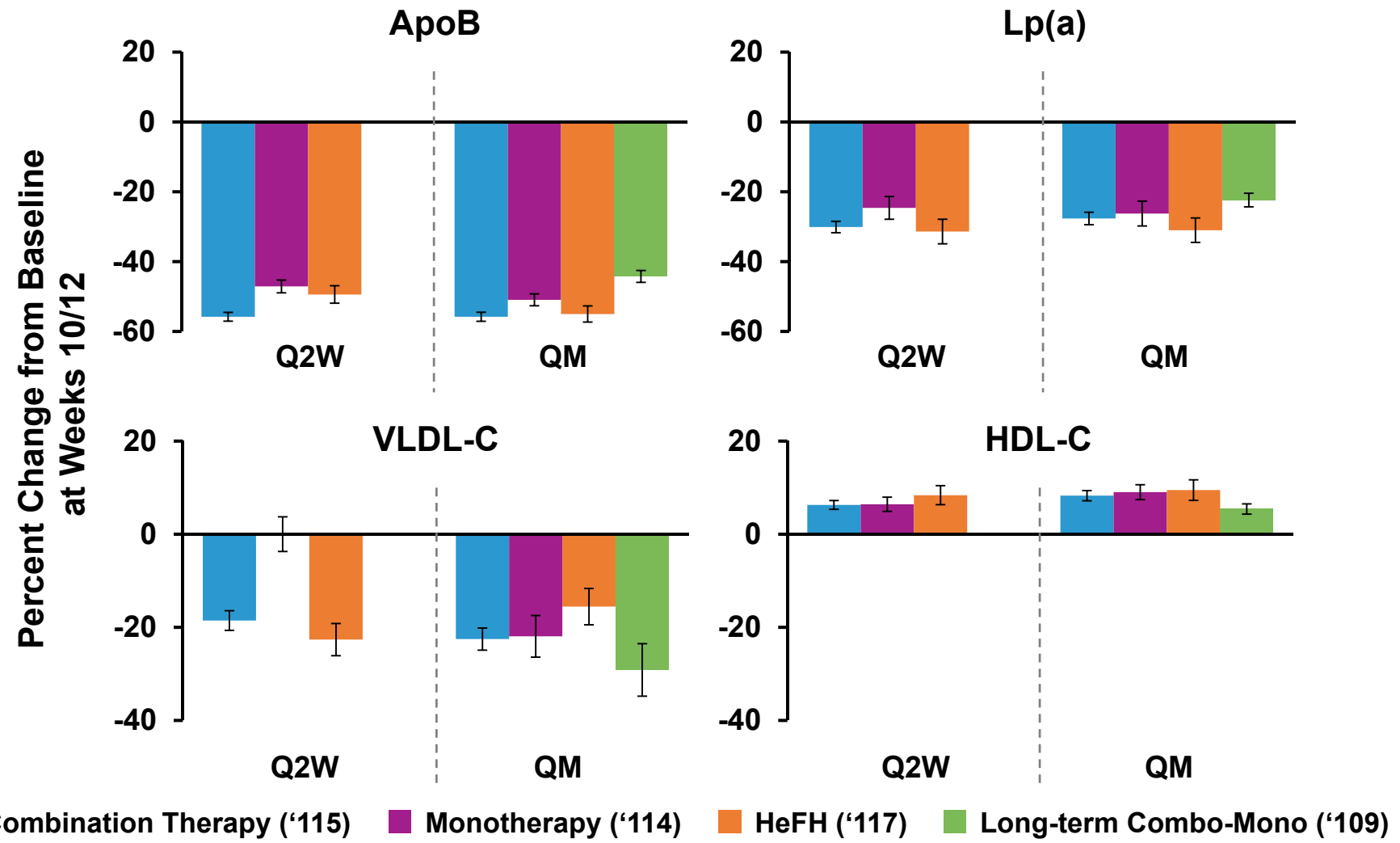
Consistent, Clinically Equivalent LDL-C Reduction Regardless of Demographics



Consistent, Clinically Equivalent Results Regardless of Background Therapy or CV Risk



Effect on Other Lipid Parameters Compared to Placebo



Efficacy

Homozygous Familial Hypercholesterolemia

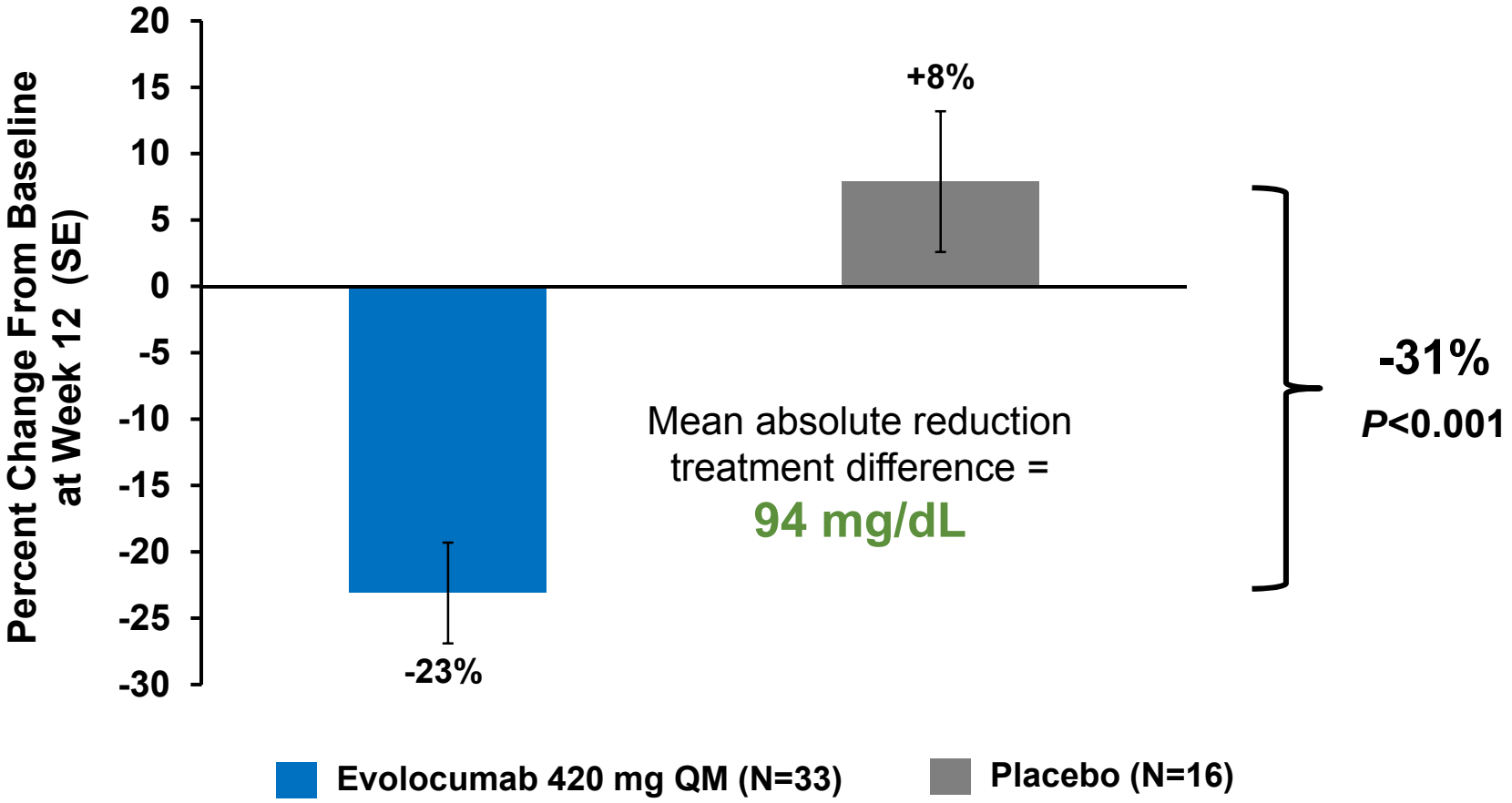
Homozygous FH Trial Designs

Study	Phase 3 Randomized, Placebo-controlled ('233)	Phase 2/3 Open-label ('271)
Total, N	49	96 (31 apheresis)
Adolescent (12-18 years), N	10	13
Fasting LDL-C	≥130 mg/dL	Non-apheresis ≥100 mg/dL Apheresis: no LDL-C requirement
Background Lipid Lowering Therapy	Stable lipid-lowering therapies	Stable lipid-lowering therapies ± apheresis
Evo Doses and Delivery	420 mg QM	420 mg QM or 420 mg Q2W
Treatment Duration	12 weeks	Up to 5 years

HoFH Baseline Characteristics

Study	Phase 3 Randomized, Placebo-controlled ('233)		Phase 2/3 Open-label ('271)
	Placebo N=16 %	Evo N=33 %	All HoFH patients (rollover, de novo incl. apheresis) N=96 %
Female	50	49	47
Age (years), mean (SD)	32 (14)	30 (12)	34 (14)
12-18 years, n	3	7	13
Coronary artery disease	38	46	46
CVD or PAD	0	12	16
Baseline lipid medication			
Statin	100	100	98
Ezetimibe	94	91	90
LDL-C (mg/dL), mean (SD)	336 (146)	356 (135)	321 (131)
PCSK9 (ng/mL), mean (SD)	674 (180)	640 (208)	670 (201)

Phase 3 Primary Endpoint in HoFH: LDL-C Reduction



Other HoFH Efficacy Results

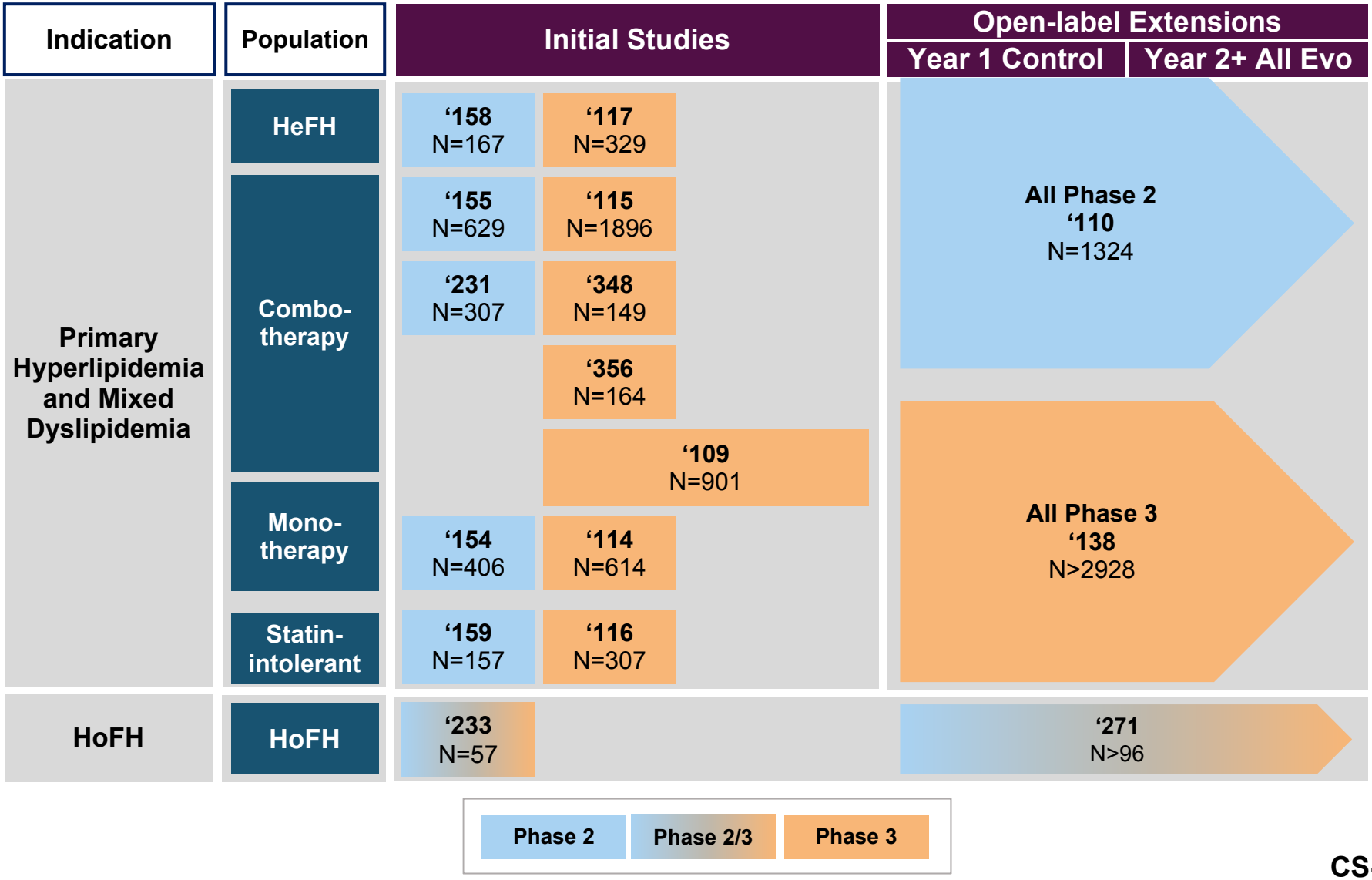
- Reductions in LDL-C, ApoB, and Lp(a)
- Greatest efficacy in LDL-R defective subjects; less efficacy in other subjects and no efficacy in LDL-R negative subject
- Efficacy in apheresis and adolescents is similar to the overall HoFH cohort
- Evolocumab 420 mg Q2W produced an incremental 6% reduction in LDL-C (p=0.02; absolute decrease of 20-30 mg/dL) compared to 420 mg QM

Summary of Evolocumab Efficacy

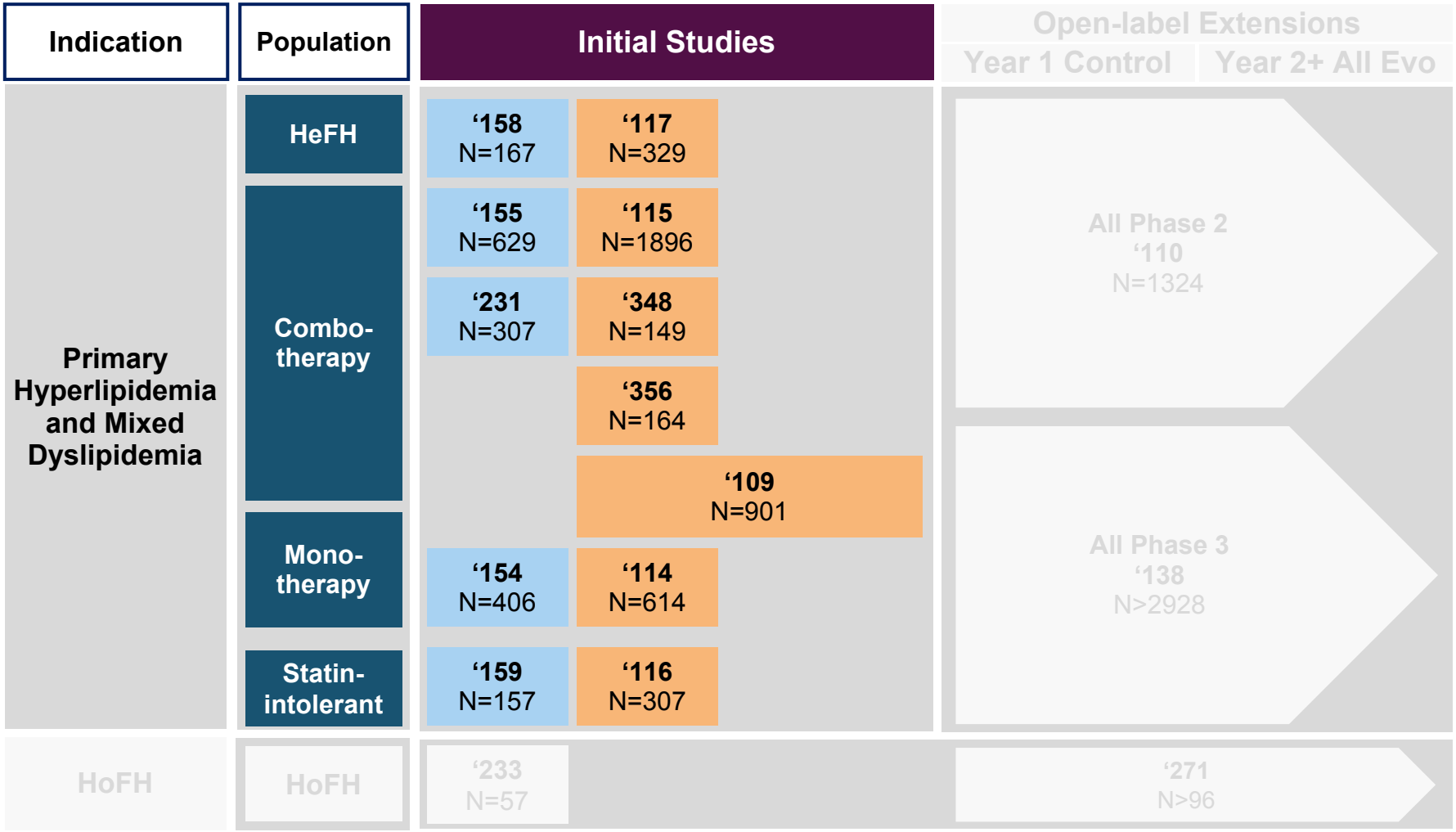
- Consistent, clinically equivalent LDL-C reductions with evolocumab 140 mg Q2W and 420 mg QM in primary hyperlipidemia and mixed dyslipidemia
  - 55-75% compared to placebo
  - 35-45% compared to ezetimibe
- Effects maintained with long-term therapy
- Effective in all subgroups
- In 49 phase 3 HoFH subjects, evolocumab reduced LDL-C by 30% compared to placebo
- Significant improvements in other lipid parameters

Phase 2 and 3 Safety: Overview

Clinical Development Program Safety Database

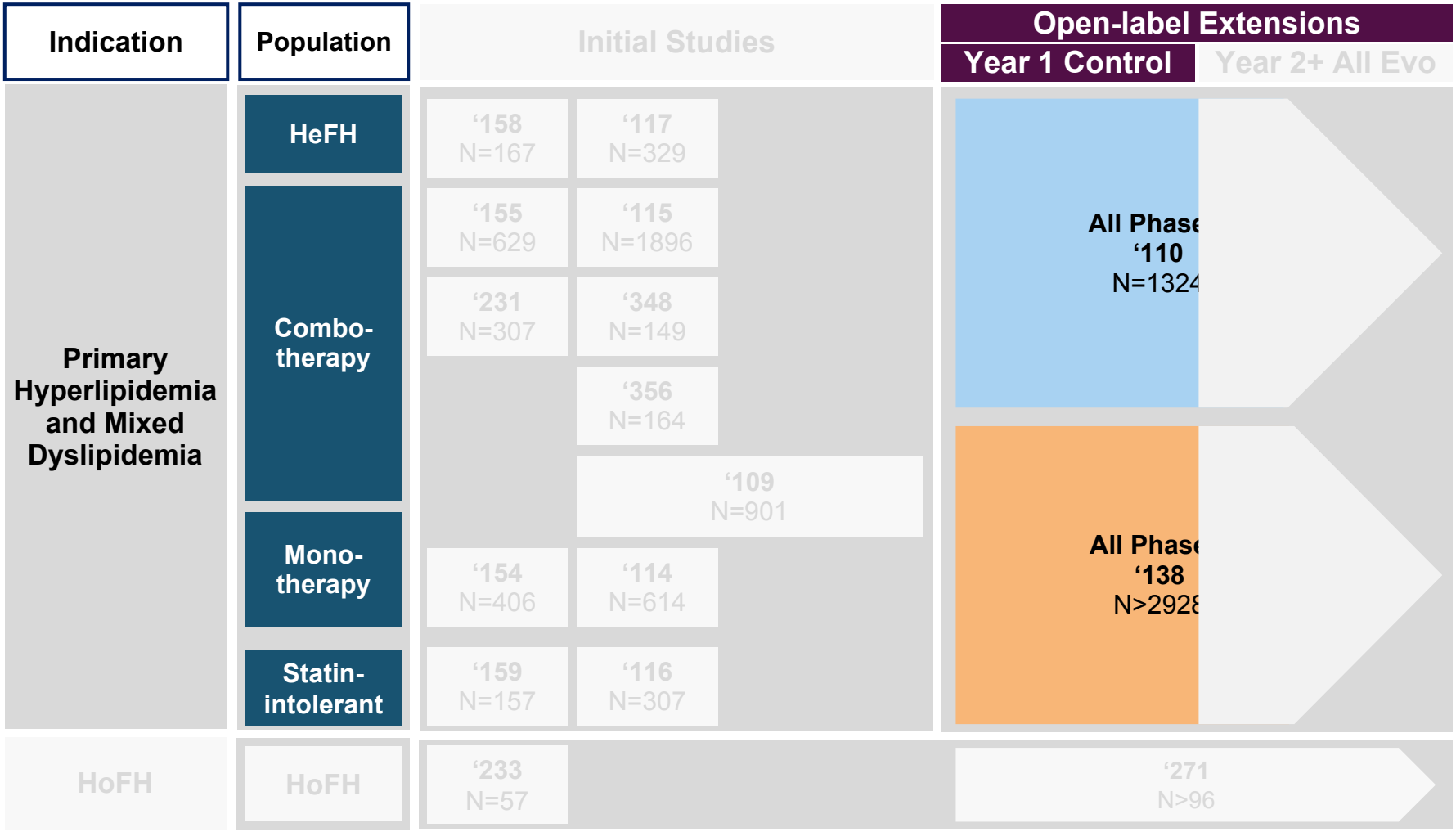


Integrated Safety Analyses From the Initial Phase 2/3 Studies



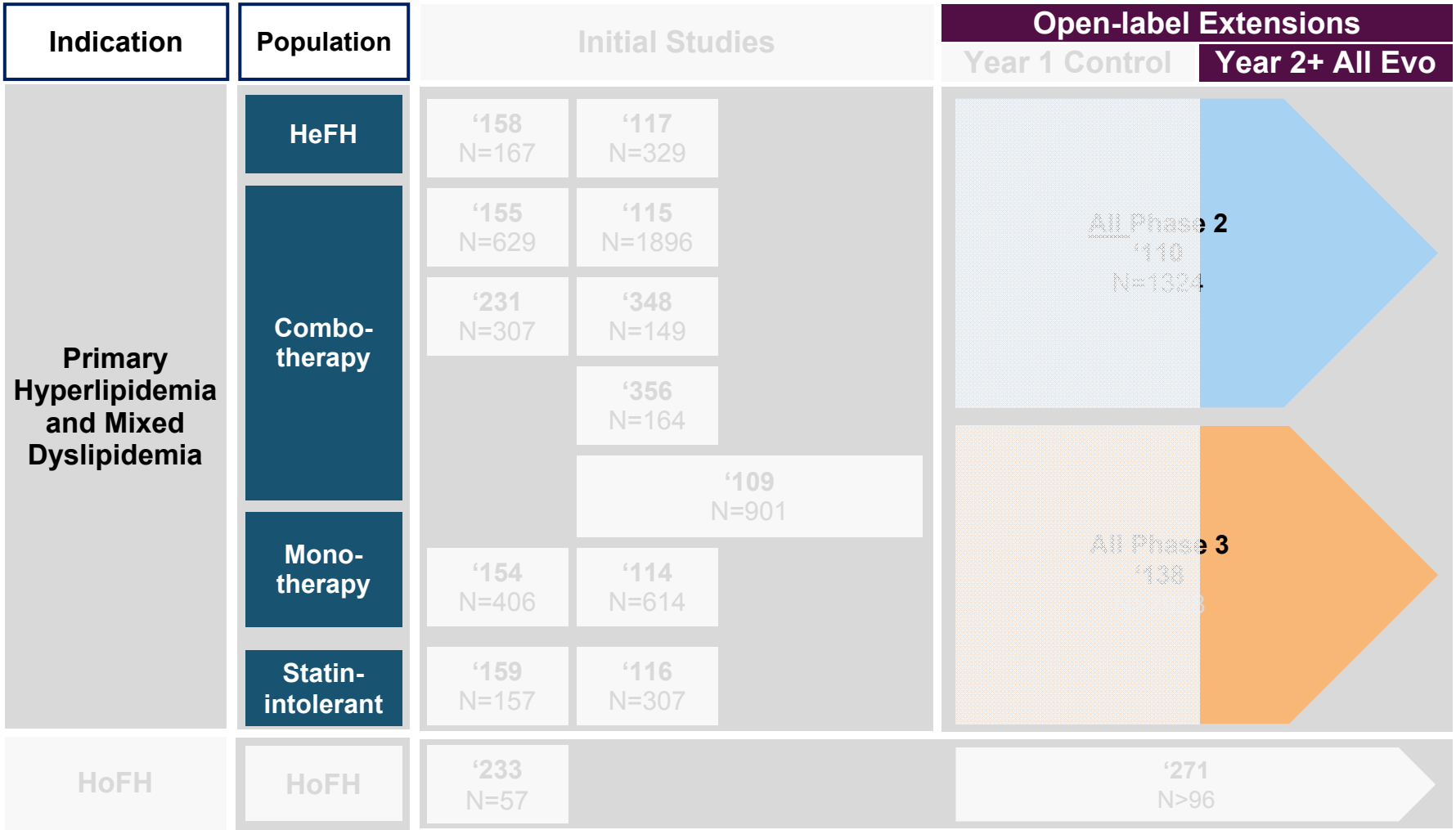
- Pooled data from 12 Phase 2/3 studies
- 8 – 52 week duration

Integrated Safety Analyses for Year 1 Open-label Control Period



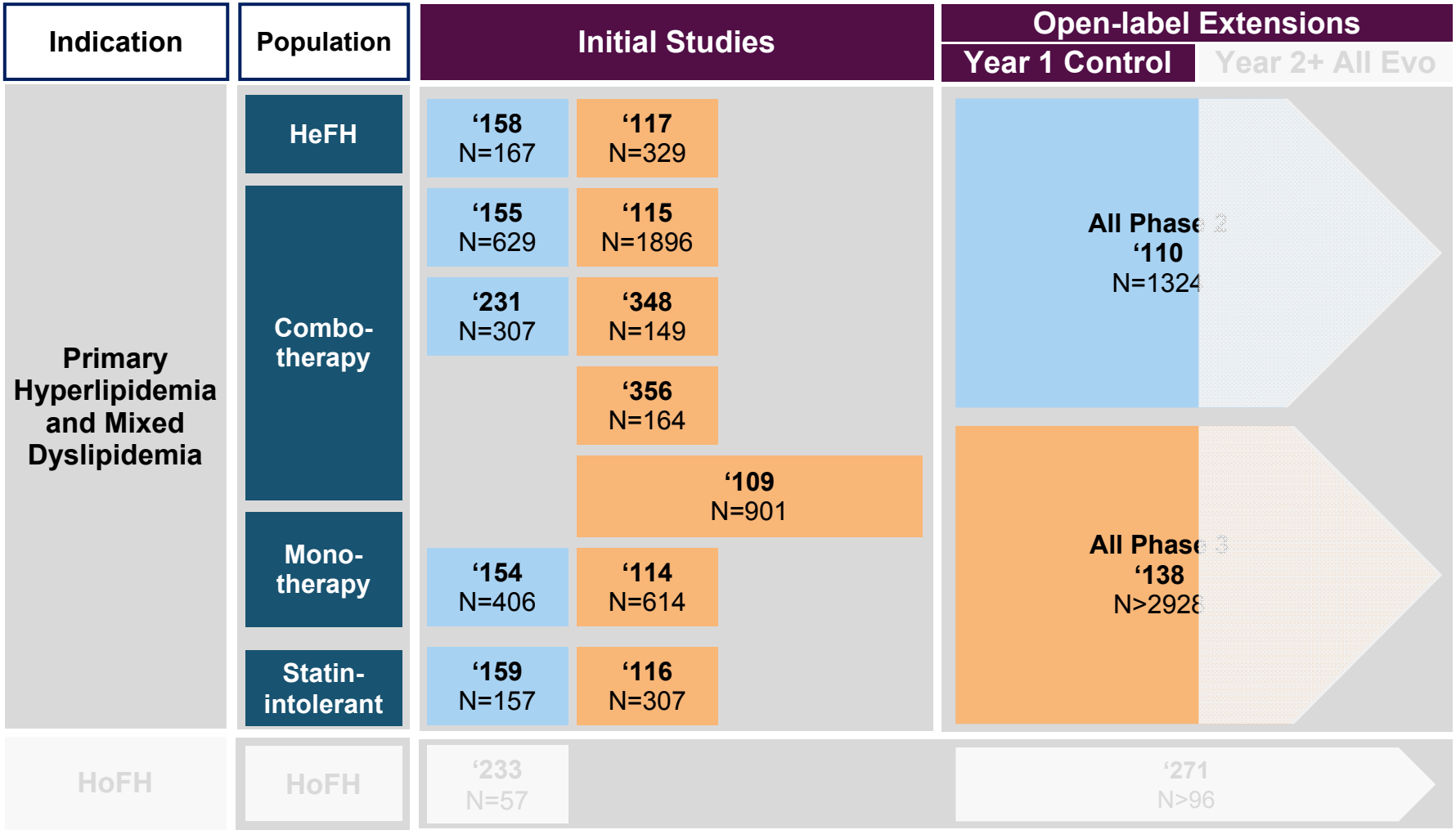
- First year of Open-label studies
- 2:1 randomization to Evo plus SoC vs SOC

Integrated Safety Analyses for Open-label Year 2+ All Evolocumab Period

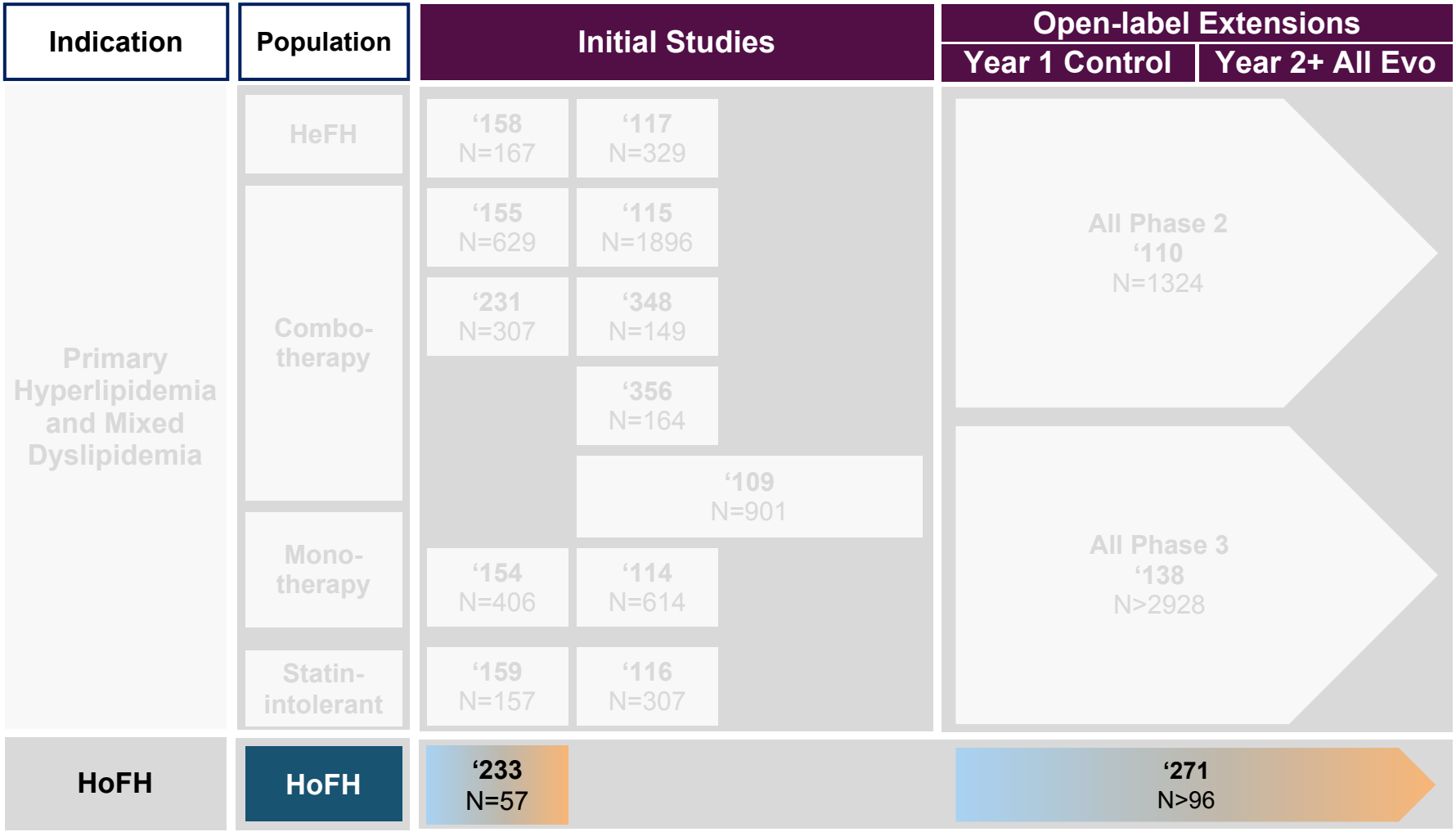


- All subjects on Evo after year 1

Integrated Safety Analyses for Initial Phase 2/3 Studies and Year 1 Open-label Control Period



Safety Dataset for Homozygous FH



Phase 2 and 3 Safety

Primary Hyperlipidemia and Mixed Dyslipidemia

Exposure in Phase 2 and Phase 3 Program

	Any Control	Any Evo	Total
Number of Patients	**3027**	**4971**	**6026**
Total pt-yr exposure	1737	4427	6165
Number of Patients			
≥3 months	2988	4839	5904
≥6 months	1444	3286	4571
≥12 months	718	1797	2430
≥18 months	55	881	1405
≥24 months	1	611	920
≥30 months	0	165	328

120 day update **5246**

120 day update **2495**

- 120 day safety update provides an additional 3 months of safety data

74% of Eligible Initial Phase 2/3 Study Patients Enrolled in Open-label Extensions

6026 Subjects Randomized and Dosed from the Initial Studies
(Control N=2080, Evo N=3946)

26% (n=1581) Not Enrolled
In Open-label Extension Studies

- Due to adverse events: 2% (n=92)
- Patient request: 2% (n=102)
- Patient never intended to roll over due to:
  - Initial study experience: 1% (n=61)
  - Level of commitment: 4% (n=264)
  - Personal reason: 9% (n=559)
- Patient intended to roll over but did not: 6% (n=366)
- Other reasons <1%

74% (n=4445) Enrolled
in Open-label Extension Studies

Overall Safety Summary

Preferred terms	Initial Phase 2/3 Studies		Open-label Year 1 Control	
	Any Control N=2080 %	Any Evo N=3946 %	SoC N=1419 %	Evo + SoC N=2833 %
Median study exposure (mo)	3.2	3.1	7.4	7.4
All adverse events	49.6	51.1	55.0	60.3
Grade ≥3	3.2	3.7	6.0	6.0
Grade ≥4	0.3	0.6	0.6	0.6
Serious adverse events	2.1	2.8	5.8	5.4
Leading to discontinuation of investigational product	2.3	1.9	NA	2.0
All cause mortality	0.1	0.1	0.3	0.1

SoC=standard of care

Adverse Reactions

	Any Control N=2080 %	Any Evo N=3946 %
Median study exposure (mo)	3.2	3.1
AEs ≥2% evo and > control		
Nasopharyngitis	4.8	5.9
Upper respiratory tract infection	2.7	3.2
Back Pain	2.7	3.0
Arthralgia	2.2	2.3
Influenza	2.0	2.1
Nausea	1.8	2.1
Other events		
Injection site reactions (SMQ)	3.0	3.3
Rash	0.7	0.9
Urticaria	0.1	0.4

Most Common Serious Adverse Events Reported in Evolocumab Subjects

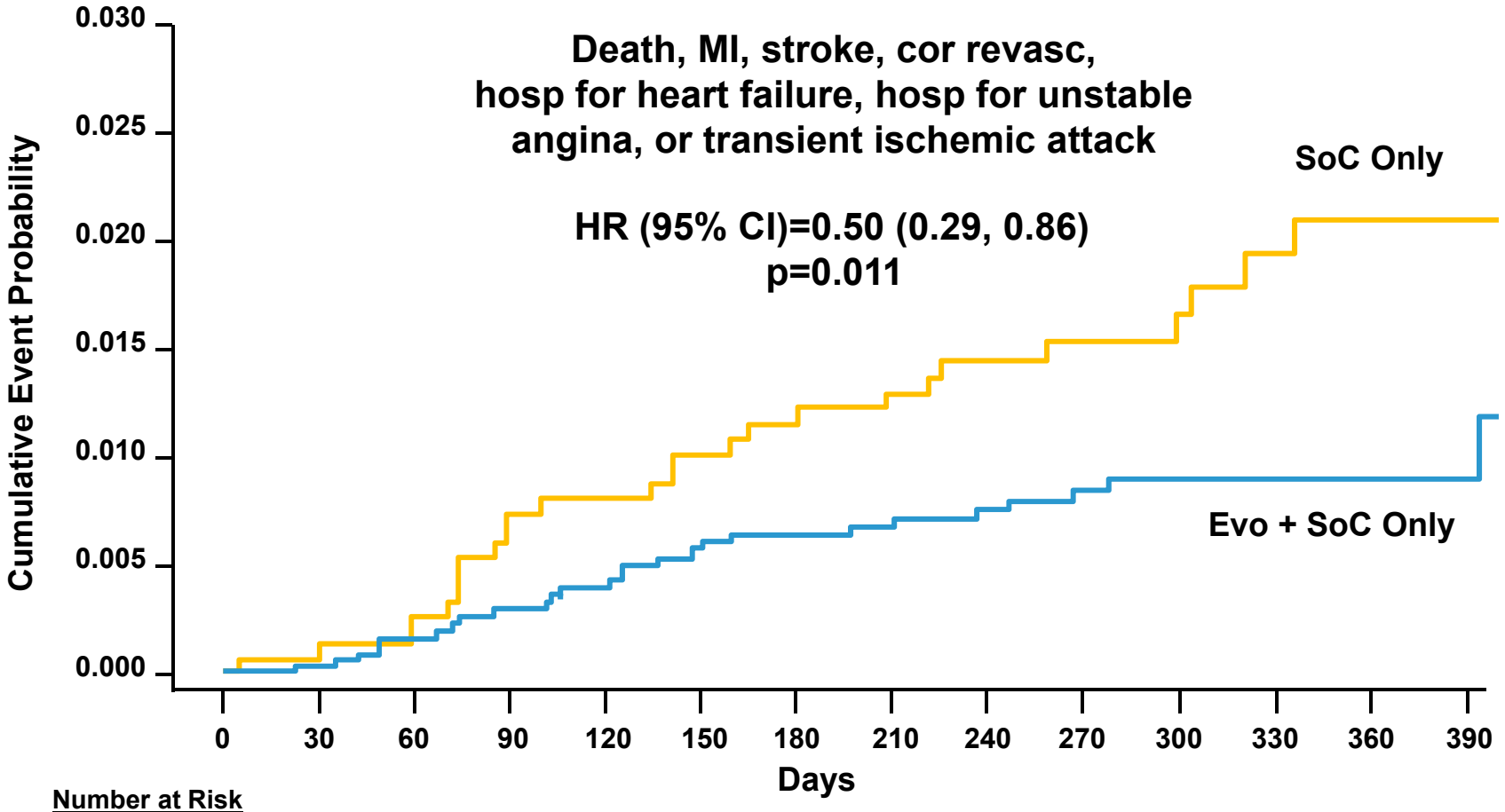
Preferred terms	Initial Phase 2/3 Studies		Open-label Year 1 Control	
	Any Control N=2080 %	Any Evo N=3946 %	SoC N=1419 %	Evo + SoC N=2833 %
Median study exposure (mo)	**3.2**	**3.1**	**7.4**	**7.4**
Overall SAEs	**2.1**	**2.8**	**5.8**	**5.4**
Osteoarthritis	0	<0.1	0.1	0.3
Angina pectoris	0.1	0.1	0.1	0.2
Myocardial infarction	0	0.1	0.2	0.2
Non-cardiac chest pain	0	<0.1	0.1	0.2
Appendicitis	0	0.1	0.1	0.1
Chest pain	<0.1	0	0.2	0.1
Coronary artery disease	<0.1	0.1	0	0.1
Angina unstable	0	0.1	0.5	0.1
Pulmonary embolism	<0.1	0.1	0.4	<0.1

Adjudicated Cardiovascular Events

Subject incidence	Initial Phase 2/3 Studies		Open-label Year 1 Control	
	Any Control N=2080 n (%)	Any Evo N=3946 n (%)	SoC N=1419 n (%)	Evo + SoC N=2833 n (%)
Median study exposure (mo)	3.2	3.1	10.2	10.3
Death, MI, stroke, cor revasc, hosp for heart failure, hosp for unstable angina, or transient ischemic attack	9 (0.4)	25 (0.6)	26 (1.7)	26 (0.9)
Death, MI, stroke	4 (0.2)	14 (0.4)	11 (0.7)	13 (0.4)

MI=myocardial infarction; hosp=hospitalization; cor revasc=coronary revascularization

Cumulative Incidence of Cardiovascular Events in the Year 1 Control Period



Number at Risk

Evo + SoC Only	2976	2696	2960	2936	2921	2881	2780	2696	2424	2062	1622	1313	850	746
SoC Only	1489	1486	1481	1466	1456	1437	1388	1348	1203	1024	802	636	409	349

120-d

CS-97

All Cause Mortality

Subject incidence	Initial Phase 2/3 Studies		Open-label Year 1 Control		Year 2+
	Any Control N=2080 n (%)	Any Evo N=3946 n (%)	SoC N=1419 n (%)	Evo + SoC N=2833 n (%)	Evo + SoC N=1675 n (%)
19 deaths	2 (0.1)	4 (0.1)	5 (0.3)	4 (0.1)	4 (0.2)

- **Reported AE preferred terms for CV deaths (12)**
  - Myocardial infarction (4), Cardiac arrest
  - Cardiac failure (2) (adjudicated negatively for HF)
  - Sudden cardiac death, Sudden death
  - Cerebrovascular accident
  - Peripheral ischemia, Pulmonary embolism
- **Reported AE preferred terms for Non-CV deaths (6) and Undetermined (1)**
  - Lung neoplasm malignant (2), Cholangiocarcinoma, Gastric cancer
  - *Clostridium difficile* infection, Pneumonia
  - Death

Events of Interest with Other Lipid-lowering Therapies

Subject incidence	Initial Phase 2/3 Studies		Open-label Year 1 Control	
	Any Control N=2080 %	Any Evo N=3946 %	SoC N=1489 %	Evo + SoC N=2976 %
Median study exposure (mo)	3.2	3.1	10.2	10.3
Muscle AEs (SMQ)	4.7	5.0	5.6	5.9
CK >5x ULN	0.7	0.7	1.2	0.6
Hepatic disorder AEs (SMQ)	0.8	0.9	1.2	1.2
ALT or AST >3x ULN	1.0	0.4	1.2	1.0
Proteinuria (urine dipstick)	5.3	5.5	9.8	9.3
New onset diabetes	1.7	1.9	2.7	2.9
Neurocognitive AEs (HLGT)	0.3	0.1	0.2	0.8

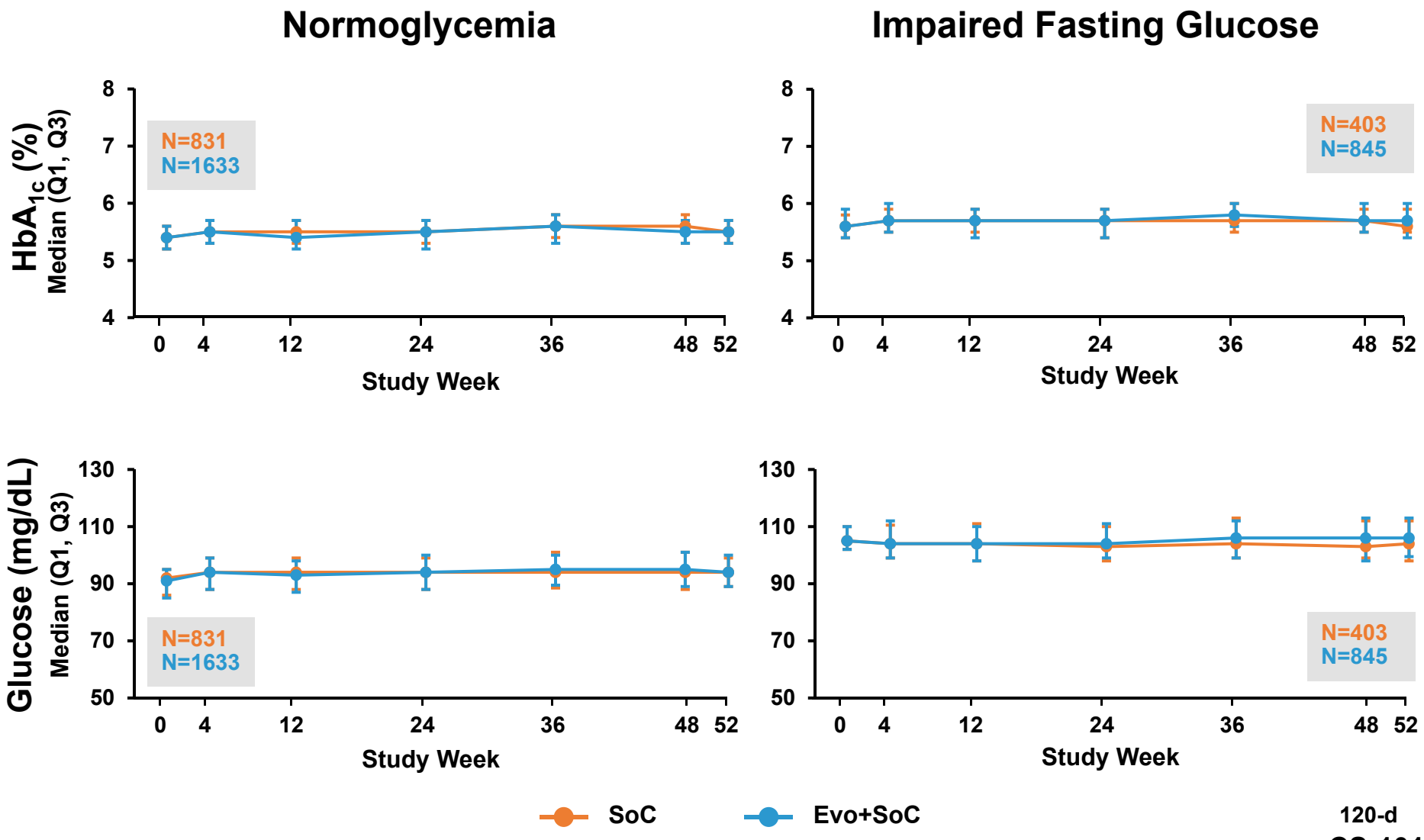
Incidence of Glycemic Changes

	Initial Phase 2/3 Studies		Open-label Year 1 Control	
	Any Control %	Any Evo %	SoC %	Evo + SoC %
Median study exposure (mo)	3.2	3.1	10.2	10.3
Baseline normoglycemia and impaired fasting glucose (FBG <126 mg/dL)	N=1798 1.7	N=3320 1.9	N=1234 2.7	N=2478 2.9
Incidence of new onset diabetes				
Baseline normoglycemia (FBG <100 mg/dL)	N=1234 0.6	N=2161 0.5	N=831 1.4	N=1633 1.1
Baseline impaired fasting glucose (100≤ FBG <126 mg/dL)	N=564 4.1	N=1159 4.6	N=403 5.2	N=845 6.3
Incidence of impaired fasting glucose				
Baseline normoglycemia (FBG <100 mg/dL)	N=1234 11.2	N=2161 12.9	N=731 11.5	N=1428 9.9

120-d

CS-100

Effect of Long-term Treatment on HbA_{1c} and Fasting Blood Glucose: Open-label, Year 1 Control



120-d

CS-101

Incidence of Neurocognitive Adverse Events

Preferred terms	Initial Phase 2/3 Studies		Open-label Year 1 Control	
	Any Control N=2080 n (%)	Any Evo N=3946 n (%)	SoC N=1489 n (%)	Evo + SoC N=2976 n (%)
Median exposure (mo)	3.2	3.1	10.2	10.3
All adverse event	6 (0.3)	5 (0.1)	3 (0.2)	25 (0.8)
By grade				
Grade 1	5 (0.2)	2 (0.1)	2 (0.1)	18 (0.6)
Grade 2	2 (0.1)	3 (0.1)	1 (0.1)	7 (0.2)
Grade 3	-	-	-	2 (0.1)
Serious adverse events	-	1 (<0.1)	-	1 (<0.1)
AEs leading to discontinuation of IP	1 (<0.1)	1 (<0.1)	N/A	3 (0.1)
AE that resolved on IP	2 (0.1)	3 (0.1)	N/A*	8 (0.3)

*Standard of care group did not receive IP; 1 of the 3 resolved on study

Incidence of Neurocognitive Adverse Events by Preferred Term

Preferred terms (Events in ≥2 subjects in any group)	Initial Phase 2/3 Studies		Open-label Year 1 Control	
	Any Control N=2080 n (%)	Any Evo N=3946 n (%)	SoC N=1489 n (%)	Evo + SoC N=2976 n (%)
Median study exposure (mo)	3.2	3.1	10.2	10.3
Number of subjects reporting AEs	6 (0.3)	5 (0.1)	3 (0.2)	25 (0.8)
Memory impairment	1 (<0.1)	1 (<0.1)	2 (0.1)	7 (0.2)
Amnesia	-	2 (0.1)	1 (0.1)	7 (0.2)
Dementia	-	-	-	3 (0.1)
Mental impairment	-	-	-	2 (0.1)
Confusional state	-	-	-	2 (0.1)
Disorientation	2 (0.1)	1 (<0.1)	-	1 (<0.1)

Incidence of Hypersensitivity Adverse Events

Preferred terms (Events in ≥2 subjects in any group)	Initial Phase 2/3 Studies		Open-label Year 1 Control	
	Any Control N=2080 %	Any Evo N=3946 %	SoC N=1489 %	Evo + SoC N=2976 %
Median study exposure (mo)	3.2	3.1	10.2	10.3
Hypersensitivity (SMQ) AEs	2.4	3.2	3.6	4.9
Hypersensitivity (SMQ) SAEs	0	0	0	0.1
Contrast media allergy	0	0	0	0.1
Anaphylactic reaction	0	0	0	<0.1
Angioedema	0	0	0	<0.1

Anti-Evolocumab Antibodies

- Overall incidence of anti-evolocumab binding antibodies after at least one dose of evolocumab was 0.3% (13 out of 4915)
- No neutralizing antibodies
- No impact of binding antibodies on safety, PK, or PD

Low LDL-C Safety: Open-label, Year-1 Control Summary

	Open-label Year 1 Control		
	LDL-C <40 mg/dL	LDL-C ≥40 mg/dL	
	Evo + SoC N=1510 %	Evo + SoC N=1448 %	SOC N=1459 %
Median study exposure (mo)	10.5	10.1	10.2
Adverse events	65.1	66.4	61.8
Serious adverse events	6.4	7.0	6.7
Muscle AEs (SMQ)	5.6	6.3	5.8
CK >5x ULN	0.7	0.5	1.1
Hepatic disorders AEs (SMQ)	1.5	0.9	1.2
ALT or AST >3x ULN	0.8	1.2	1.2
New onset diabetes mellitus	3.5	2.3	2.6
Neurocognitive AEs (HLGT)	0.7	1.0	0.2

Low LDL-C Safety: Open-label, Year-1 Control Summary

	Open-label Year 1 Control			
	LDL-C <25 mg/dL	LDL-C <40 mg/dL	LDL-C ≥40 mg/dL	
	Evo + SoC N=755 %	Evo + SoC N=1510 %	Evo + SoC N=1448 %	SOC N=1459 %
Median study exposure (mo)	10.4	10.5	10.1	10.2
Adverse events	65.3	65.1	66.4	61.8
Serious adverse events	6.5	6.4	7.0	6.7
Muscle AEs (SMQ)	4.8	5.6	6.3	5.8
CK >5x ULN	0.4	0.7	0.5	1.1
Hepatic disorders AEs (SMQ)	1.7	1.5	0.9	1.2
ALT or AST >3x ULN	0.9	0.8	1.2	1.2
New onset diabetes mellitus	3.6	3.5	2.3	2.6
Neurocognitive AEs (HLGT)	0.4	0.7	1.0	0.2

Phase 3 Safety

Homozygous Familial Hypercholesterolemia

Overall Exposure for Homozygous Familial Hypercholesterolemia (HoFH)

	Any Placebo	Any Evo	Total
Number of Patients	16	99	**99**
Total pt-yr exposure	4	63	67
Number of Patients			
≥3 months	16	81	85
≥6 months	0	56	59
≥12 months	0	23	28
≥18 months	0	8	8
≥24 months	0	3	3
≥30 months	0	0	0

120 day update

88

Most Frequent AEs in HoFH Patients are Generally Similar to the Overall Program

Phase 3 RCT Study (‘233)		
Preferred Term	Placebo N=16 n (%)	Evo N=33 n (%)
Median study exposure (months)	2.8	2.8
Adverse events	10 (62.5)	12 (36.4)
Upper respiratory tract infection	1 (6.3)	3 (9.1)
Influenza	0	3 (9.1)
Gastroenteritis	0	2 (6.1)
Nasopharyngitis	0	2 (6.1)

Open-label Study (‘271)			
Preferred Term	Non-apher. N=66 n (%)	Apheresis N=34 n (%)	Total N=100 n (%)
Median study exposure (months)	8.0	7.2	7.5
Adverse events	42 (63.6)	26 (76.5)	68 (68.0)
Nasopharyngitis	4 (6.1)	5 (14.7)	9 (9.0)
Influenza	4 (6.1)	3 (8.8)	7 (7.0)
Anemia	2 (3.0)	3 (8.8)	5 (5.0)
Headache	3 (4.5)	2 (5.9)	5 (5.0)

Summary of Evolocumab Safety

- 4971 subjects received evolocumab (4427 subject-years)
- Appropriate patient population
  - ~75% high to moderate NCEP risk
  - ~75% on statins; of these, 39% high- and 52% moderate-intensity
- Incidence of adverse events was similar to comparator
- Adverse events in long-term studies consistent with findings from initial studies and within expected rate for the population
- No safety risks for events of interest or low/very low LDL-C
- Anti-evolocumab binding antibodies are rare and non-neutralizing; no effect on safety
- Safety profile generally consistent in HoFH population

Benefit-Risk Assessment

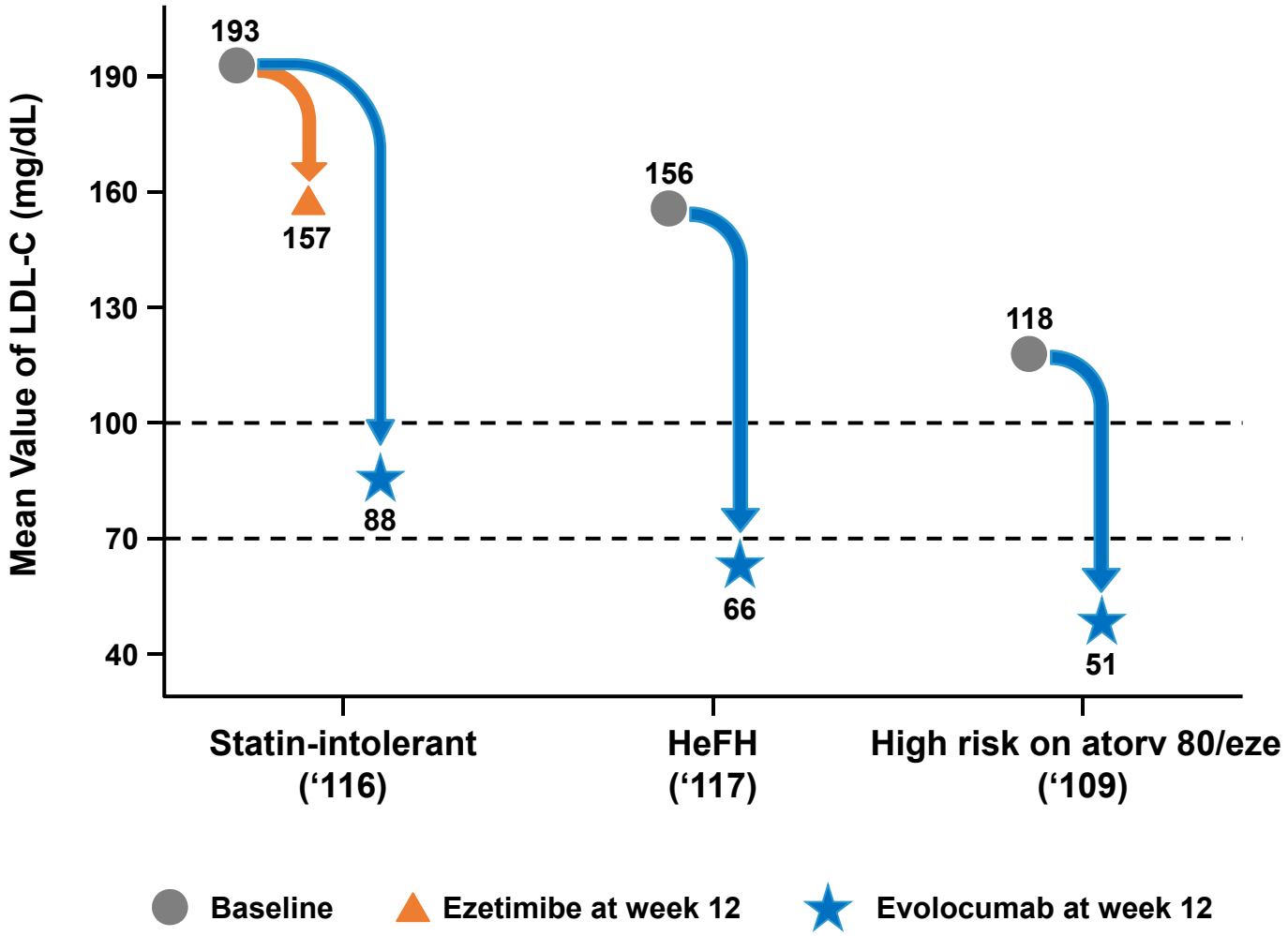
Rob Scott, MD

Amgen Inc.
Vice President, Global Development

Who are the Patients who Could Benefit?

- Patients whose LDL-C cannot be controlled with statins ± other current therapies
- Patients who cannot take a statin, or an effective dose

How Might Evolocumab be Used in Clinical Practice?



Anticipated Benefit as a Factor of Baseline LDL-C and Risk

	Baseline LDL-C				
	70	100	130	160	190
LDL-C Reduction (mg/dL)					
10 year baseline risk					
5%	Low risk				
7.5%	Moderate risk				
15%	High risk				
30%	Very High Risk				

ACC\AHA Guidelines do not recommend calculating risk in HeFH due to very high lifetime risk which mandates therapy

Anticipated Benefit as a Factor of Baseline LDL-C and Risk

	Baseline LDL-C				
	70	100	130	160	190
LDL-C Reduction (mg/dL)	42	60	78	96	114
10 year baseline risk					
5%					
7.5%					
15%					
30%					

- Evolocumab reduces LDL-C by ~60% regardless of baseline LDL-C
- Absolute LDL-C reduction is greater with higher baseline LDL-C
- Each mmol or ~40 mg/dL absolute LDL-C reduction reduces the risk of CV death, non-fatal MI or stroke by 22%

Projecting Anticipated Benefit as a Factor of Baseline LDL-C and Risk

	Baseline LDL-C				
	70	100	130	160	190
LDL-C Reduction (mg/dL)	42	60	78	96	114
10 year baseline risk					
5%	1%				
7.5%					
15%					
30%					19%

42 mg/dL reduction gives 22% relative risk reduction
5% X 0.22 = 1% absolute risk reduction

114 mg/dL reduction gives 63% relative risk reduction
30% X 0.63 = 19% absolute risk reduction

- Evolocumab reduces LDL-C by ~60% regardless of baseline LDL-C
- Absolute LDL-C reduction is greater with higher baseline LDL-C
- Each mmol or ~40 mg/dL absolute LDL-C reduction reduces the risk of CV death, non-fatal MI or stroke by 22%

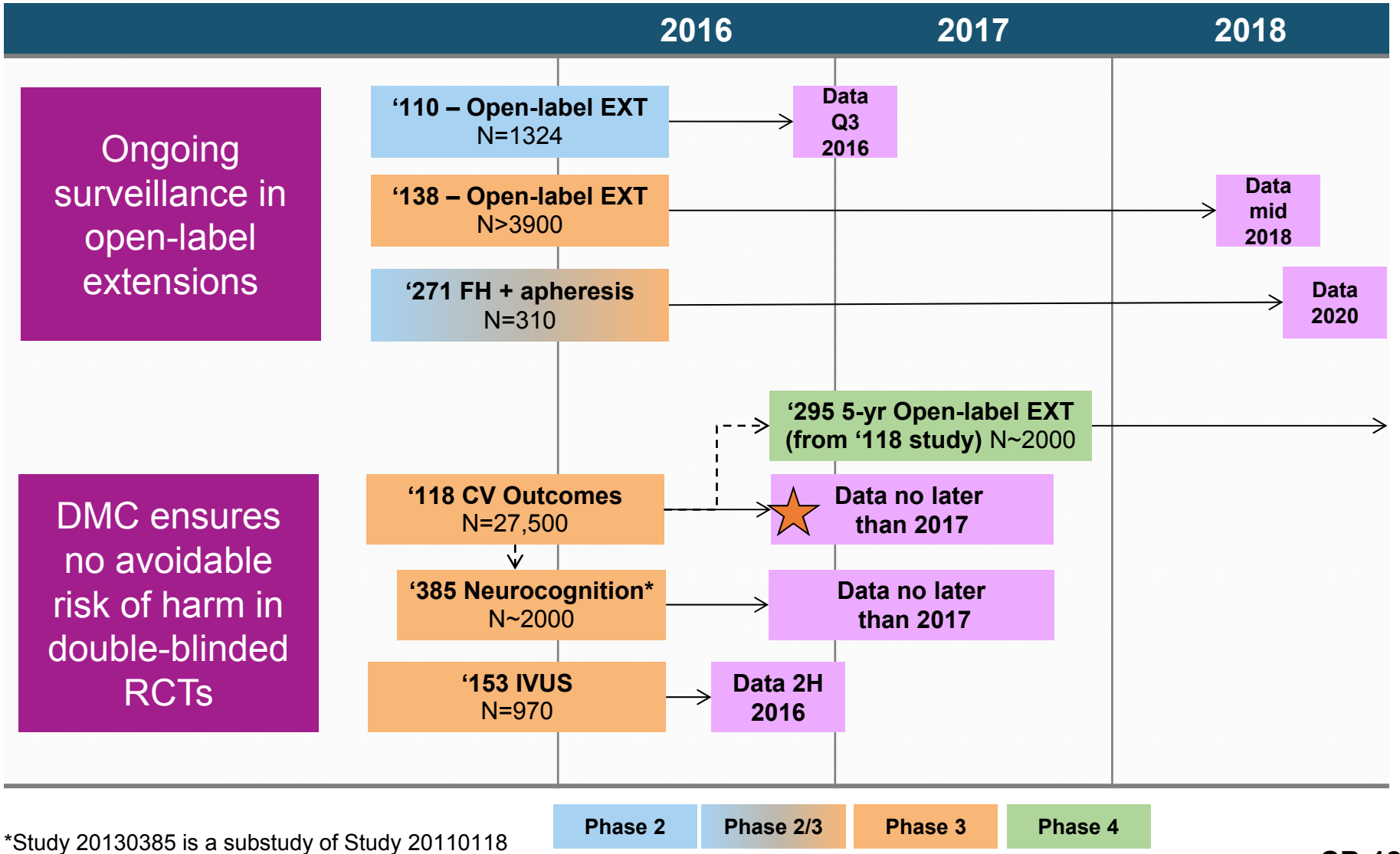
Anticipated Absolute Risk Reduction is a Function of Baseline Risk and LDL-C Level

	Baseline LDL-C				
	70	**100**	**130**	**160**	**190**
LDL-C Reduction (mg/dL)	42	60	78	96	114
10 year baseline risk	**Absolute risk reduction with evolocumab (%)**				
5%	1	2	2	3	3
7.5%	2	2	3	4	5
15%	3	5	6	8	9
30%	7	10	13	16	19

- Patients with moderate baseline risk (7.5%) and high LDL-C (≥160) receive the same benefit as titrating from a moderate intensity to a high intensity statin (e.g. TNT)
- Patients with coronary disease get the same or more benefit from 70-100 mg/dL and higher

Ongoing and Planned Pharmacovigilance

Ongoing Clinical Trial Surveillance Permits Detection of Potential Signals



*Study 20130385 is a substudy of Study 20110118

Comprehensive Pharmacovigilance Plan

Routine PV	Postmarketing Surveillance	• Collection and evaluation of postmarketing adverse event reports using detailed questionnaires • Safety signal detection/ evaluation in various databases
Education and Communication	Risk Communication	• Communication of risks in product label • Patient instructions for use of device

	Education for HCPs and patients	• Amgen voluntary program
		  • HCP and patient education material
		  • Support call center

Additional Studies	Ongoing Safety Assessment (New onset diabetes, muscle events, hepatic events, etc.)	• ~27,500 subjects outcomes study '118 (ongoing) including adjudication of new onset diabetes • Ph2/3 OLE studies (ongoing)
	➢ Neurocognitive safety	• ~2000 subjects cognitive function study (ongoing) with validated neurocognitive instrument (CANTAB)
	Safety beyond 7 years	• ~2000 subjects 5-year '118 OLE
	Pediatrics	• Controlled and open-label studies in FH patients 10 years and older
	Pregnancy	• Observational study in FH patients evaluating pregnancy outcomes

Conclusion

- Cardiovascular disease is the leading cause of death in the US
- LDL-C is a major modifiable risk factor for cardiovascular disease
- Available therapies, while effective, are often not sufficient to adequately control LDL-C
- Evolocumab demonstrated consistent and significant reduction in LDL-C
- No risk identified that would offset the predicted cardiovascular benefit of LDL-C reduction with evolocumab
  - Adverse event profile similar to comparator with no major safety issues identified, including in subjects with very low LDL-C
  - Robust clinical program and ongoing pharmacovigilance
- Evolocumab has favorable benefit:risk and can lower LDL-C in patients that need additional treatment options

Thank You

Q&A Slides Projected

Endocrinologic and Metabolic Drugs Advisory Committee

June 10, 2015

Baseline CRP in Initial Studies

	‘109 N=901 Median (Q1, Q3)	‘114 N=614 Median (Q1, Q3)	’115 N=1896 Median (Q1, Q3)	‘116 N=307 Median (Q1, Q3)	‘117 N=329 Median (Q1, Q3)
Patients with observed data at baseline, n	894	607	1879	302	322
hsCRP mg/L	1.23 (0.64, 2.97)	1.37 (0.69, 2.70)	1.45 (0.76, 3.04)	1.71 (0.84, 3.20)	0.99 (0.52, 2.03)

Baseline Demographics in HoFH (N=100) OLE Study '271 According to Dose Regimen

	QM only (n=25)	Q2W only (n=28)	QM&Q2W (n=47)	Uptitration from QM to Q2W (n=41)
Female, n (%)	15 (60)	12 (43)	22 (47)	18 (44)
Age (years), mean (SD)	38 (15)	34 (15)	31 (13)	31 (12)
LDL-C (mg/dL), mean (SD)	242 (98)	308 (90)	368 (142)	395 (128)
PCSK9 (ng/dL), mean (SD)	596 (204)	717 (225)	678 (176)	678 (172)
MI, n (%)	4 (16)	3 (11)	4 (9)	4 (10)
Peripheral arterial disease, n (%)	--	2 (7)	3 (6)	2 (5)
Baseline lipid medication, n (%)	25 (100)	26 (93)	47 (100)	41 (100)
Statin	25 (100)	26 (93)	47 (100)	41 (100)
High-intensity	22 (88)	22 (79)	46 (98)	41 (100)
Moderate-intensity	3 (12)	4 (14)	1 (2)	--
Ezetimibe	21 (84)	25 (89)	43 (92)	38 (93)

Adverse Events in HoFH OLE Study '271 According to Dose Regimen

Subject incidence of AEs and SAEs according to dosing regimen in OLE HoFH Study '271		
	QM only (n=25)	Uptitration from QM to Q2W (n=41)
Median study exposure (mo)	5.5	13.5
All adverse events	16 (64)	26 (63)
Grade 1	15 (60)	13 (32)
Grade 2	4 (16)	20 (49)
Grade 3	0 (0)	7 (17)
Grade 4	0 (0)	0 (0)
Serious adverse events	--	6 (15)
Leading to discontinuation of investigational product	--	1 (2)
All cause mortality	--	--

120d

CL-457

SAEs in Uptitraters in HoFH OLE Study ‘271

- All SAEs were consistent with the natural history of HoFH (7 events in 6 patients)
  - Complications of FH (6 events)
    - Aortic valve disease (2 events)
      - Aortic stenosis
      - Aortic valve disease
    - Atherosclerosis (4 events)
      - Chest pain
      - Angina pectoris
      - Coronary artery disease
      - Coronary artery occlusion
  - Other (1 event)
    - Non-cardiac chest pain (history prior to study)

Types of CV Outcomes –Cardiovascular Events in the Year 1 Control Period

Endpoint	Evolocumab + stnd of care (N=2976)		Standard of care alone (N=1489)		HR (95% CI)
	n	%	n	%	
All CV Events	26	0.90	26	2.10	0.50 (0.29-0.86)
Death	3	0.10	4	0.33	0.38 (0.08-1.68)
Coronary Events (MI, hosp for UA, or revasc)	20	0.71	15	1.14	0.67 (0.34-1.30
Cerebrovasc Events (Stroke or TIA)	3	0.12	7	0.56	0.21 (0.06-0.83)
Heart failure hospitalization	1	0.03	1	0.07	0.51 (0.03-8.30)

% are KM event rates at 1 year except for HF, which is a crude %

Adjudicated CV Events
NEJM Sabatine et al., March 2015

	Evolocumab Group (N=2976)	Standard-Therapy Group (N=1489)	Hazard Ratio (95% CI)
CV events n(%)			
All	29 (0.95)	31 (2.18)	0.47 (0.28-0.78)
MACE	28 (0.95)	30 (2.11)	0.47 (0.28-0.78)
Death	4 (0.14)	6 (0.41)	
CV or Unknown	4 (0.1)	3 (0.2)	
Non-CV	0 (0.0)	3 (0.2)	
Coronary Events	22 (0.75)	18 (1.30)	
MI	9 (0.3)	5 (0.3)	
UA Hospitalization	3 (0.1)	3 (0.2)	
Coronary Revasc	15 (0.5)	17 (1.1)	
Cerebrovascular events	4 (0.14)	7 (0.47)	
Stroke	3 (0.1)	2 (0.1)	
TIA	1 (0.0)	5 (0.3)	
Heart failure hospitalization	1 (0.03)	1 (0.07)	

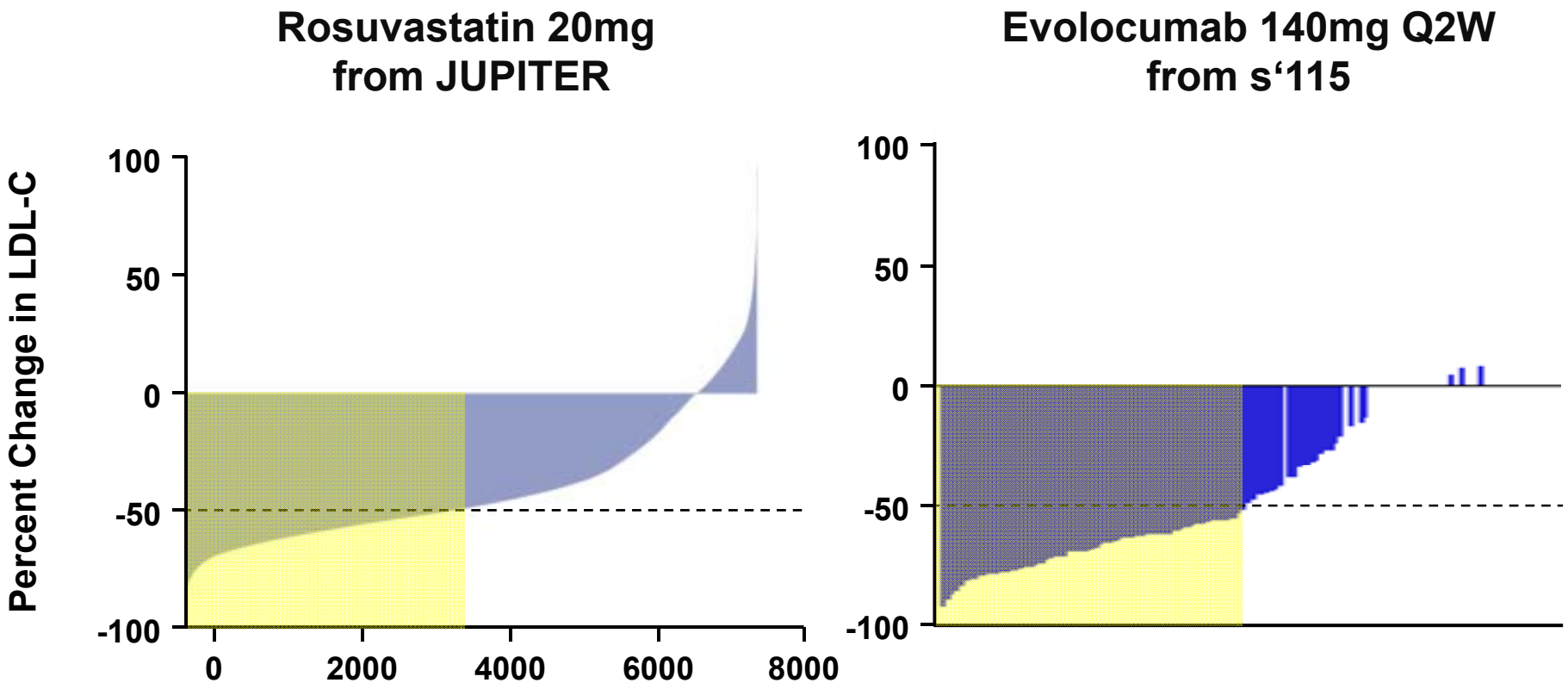
Prevalence of Low LDL-C

	Evolocumab Y1 Control N=2958					
	Any LDL-C below		≥ 2 LDL-C below		All LDL-C below	
	n	%	n	%	n	%
LDL –C < 40 mg/dL	**1510**	**51**	**806**	**27**	**528**	**18**
LDL-C < 25mg/dL	**755**	**26**	**254**	**9**	**134**	**5**
LDL-C < 15mg/dL	**281**	**9**	**59**	**2**	**20**	**0.7**

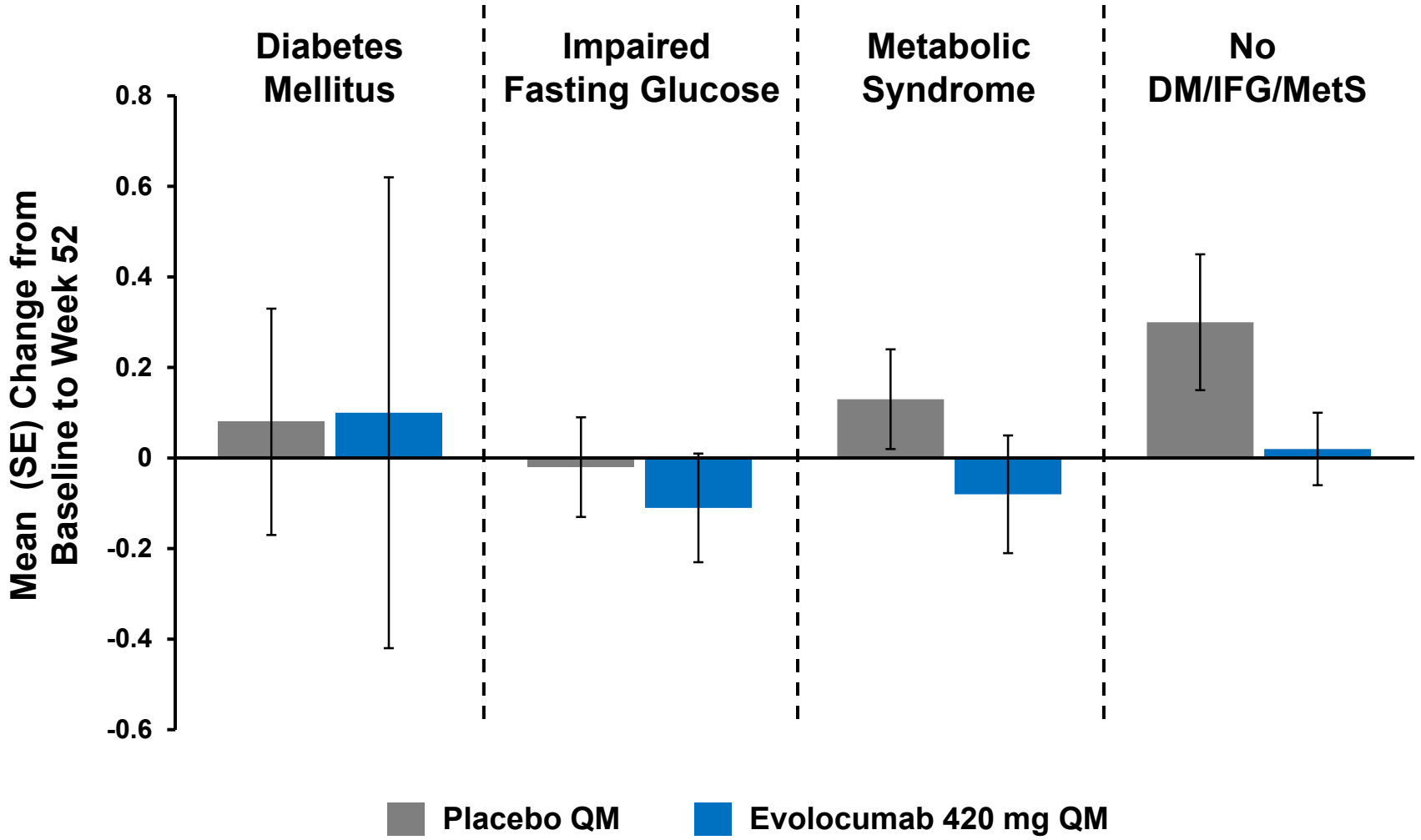
120 Day

CL-284

Individual Response Variability

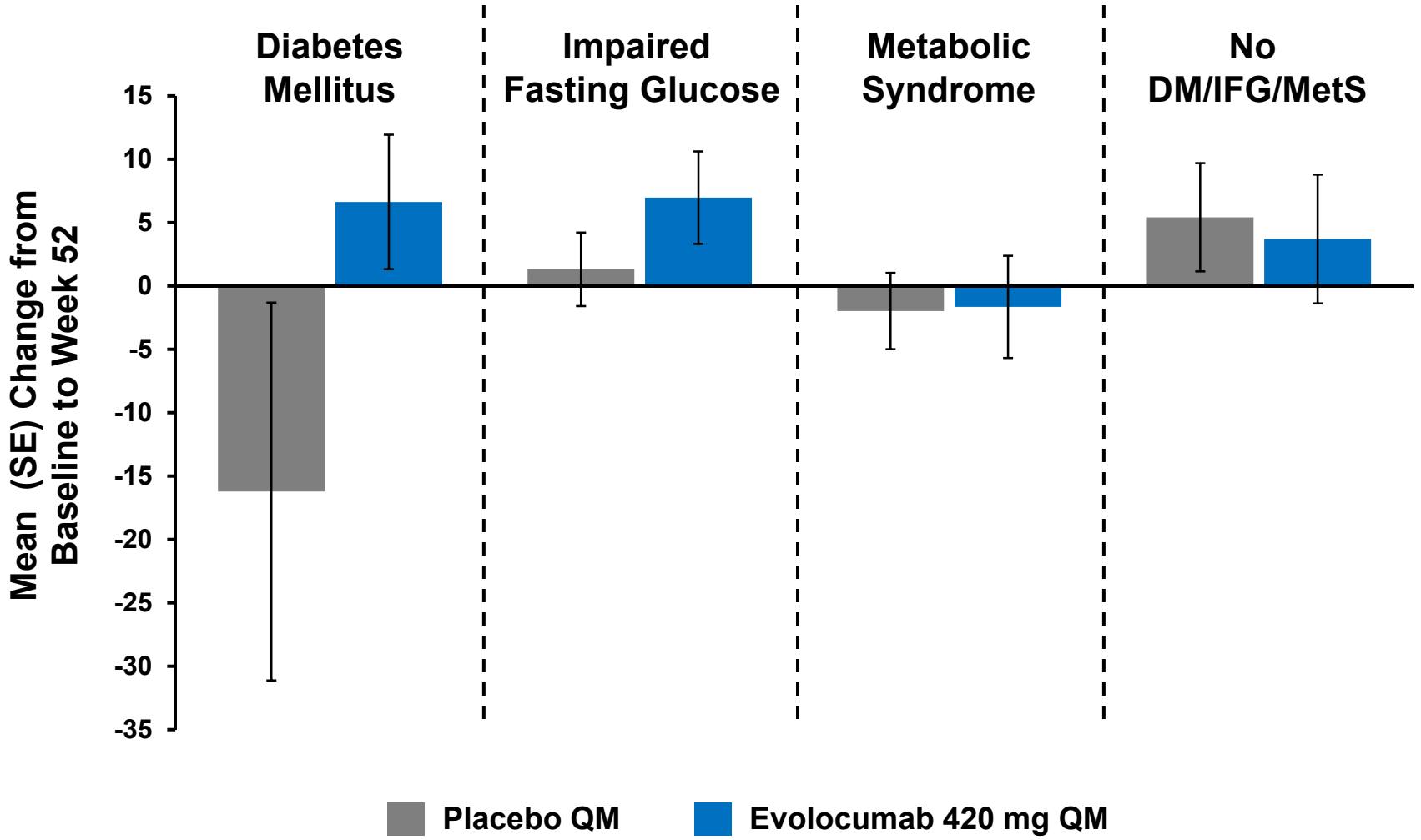


Change in Insulin Resistance at Week 52 in Long-term Study (‘109)



CL-244

Change in Beta Cell Function at Week 52 in Long-term Study (‘109)



CL-245

In Open-label HoFH Study ‘271, Evolocumab Reduced LDL-C in Adolescent Patients

Mean Percent Change from Baseline at OLE Week 12

	All HoFH Subjects n=100	Adolescent HoFH Subjects n=14
UC LDL-C	**-21%**	**-13%**
TC	-15%	-9%
Non-HDL-C	-19%	-12%
ApoB	-15%	-10%
Lp(a)	-8%	-3%

Integrated Parent Analysis Set (IPAS)
Change from Initial Study Baseline in CRP (mg/L)

Parent study		Any Placebo	Any Control	Evo 140 or 420	All Evo
Week 12	n	1171	1707	2198	2923
	median	0	-0.01	0.02	0.02
	Q1, Q3	-0.47, 0.37	-0.53, 0.40	-0.42, 0.53	-0.46, 0.51
Week 24	n	284	284	567	567
	median	0	0	0	0
	Q1, Q3	-0.37, 0.59	-0.37, 0.59	-0.49, 0.50	-0.49, 0.50
Week 52	n	272	272	532	532
	median	0.02	0.02	0	0
	Q1, Q3	-0.41, 0.80	-0.41, 0.80	-0.50, 0.56	-0.50, 0.56

Change in Statin Intensity During Phase 3 Year 1 Controlled Study

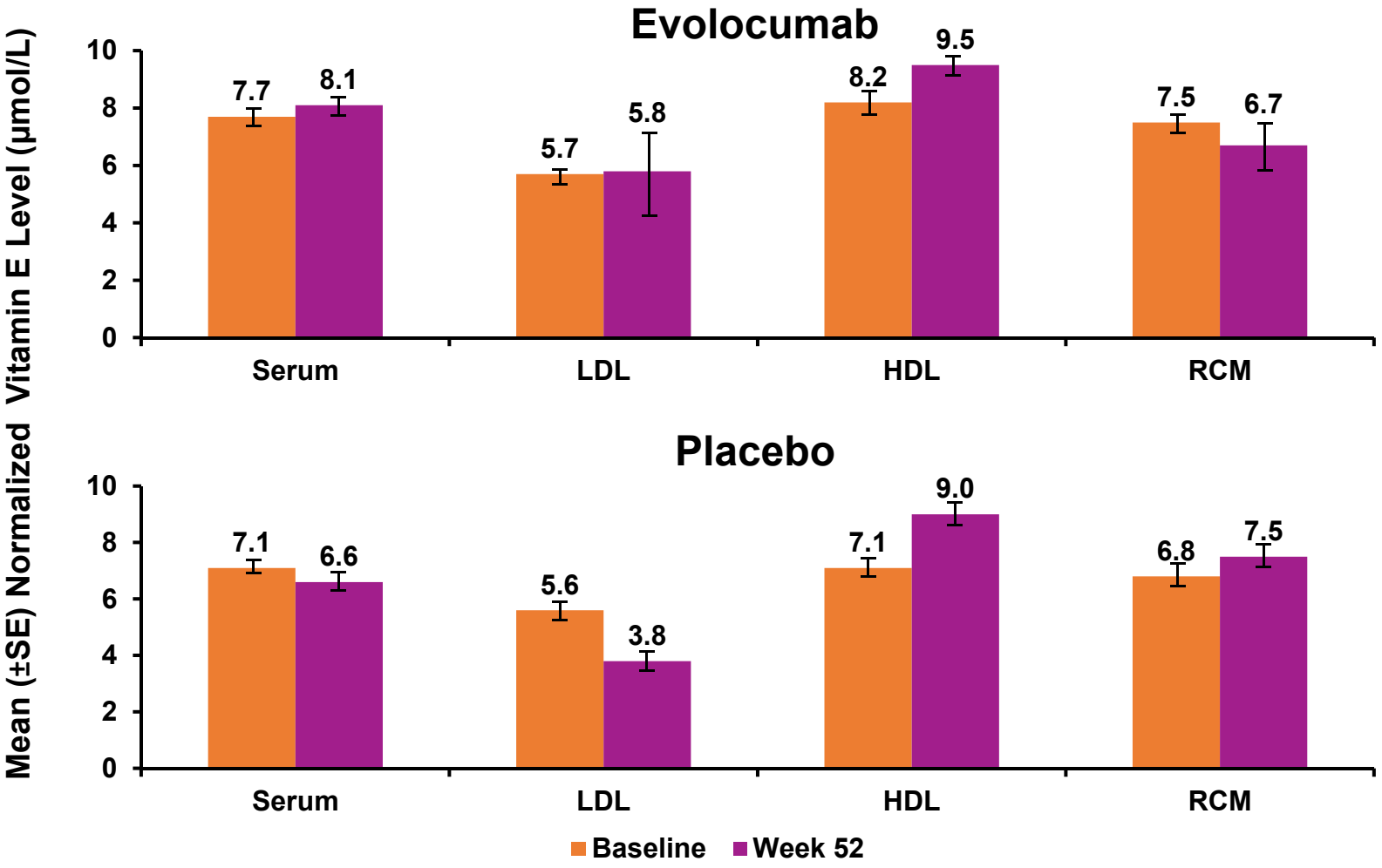
	Year 1 Control	
	SoC Alone N=1047	Evo + SoC N=2094
On statin at any time	N=813	N=1481
Stable statin intensity	88%	90%
Decreased statin intensity	2%	6%
Increased statin intensity	10%	3%

Baseline Demographics and Statin Use in Secondary Prevention in the United States

		Overall Population		On LDL-C Lowering tx*	
		Medicare 2010 N=39,767 %	MarketScan 2012 N=273,926 %	Medicare 2010 N=16,977 %	MarketScan 2012 N=88,616 %
Age categories	18-<65	13.7	46.2	13.1	40.4
	65-<75	31.4	20.2	35.2	23.8
	≥75	54.9	33.6	51.7	35.7
Race	White	83.1	Unavailable	84.8	Unavailable
	Black	10.9		9.0	
	Hispanic	2.6		2.5	
	Asian	1.6		2.0	
	Other	1.8		1.7	
Sex	% male	45.1	59.7	47.3	63.7
Statin prescription filled	High-intensity	14.9	15.9	22.4	29.9
	Mod-intensity	37.7	27.7	54.7	54.2
	Low-intensity	6.2	5.4	8.7	10.1
	None	41.2	51.0	14.1	5.8
Statin titration	Up	2.9	3.1	2.7	2.8
	Down	3.8	3.8	3.0	3.6
	No change	93.3	93.1	94.3	93.6

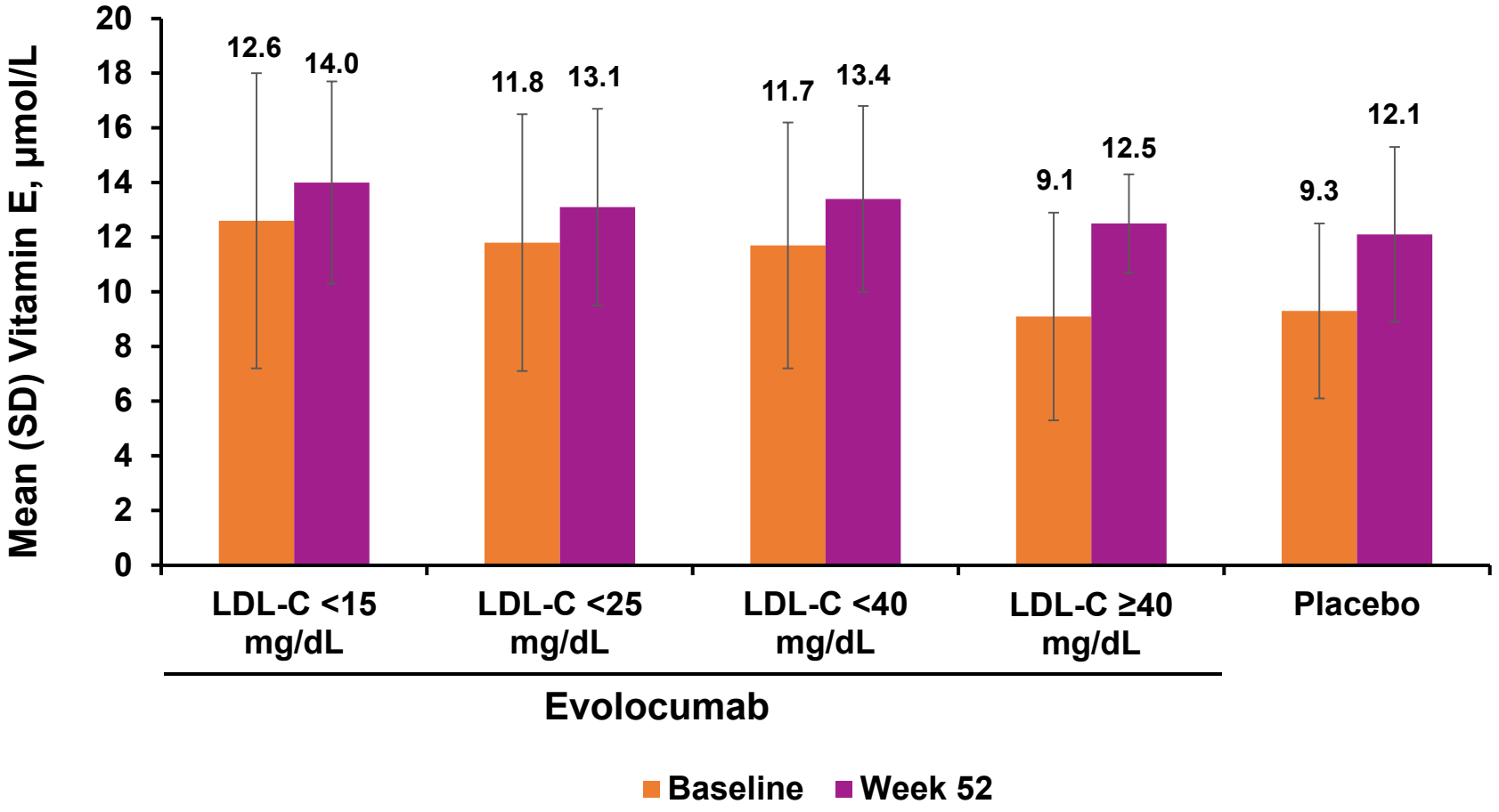
*Among those on LDL-C lowering therapy as of index date

Normalized Vitamin E from Study `109



- 52 weeks of evolocumab exposure showed no significant changes from baseline in Vitamin E when normalized by LDL-C

Absolute Vitamin E in HDL by LDL-C Levels from Study `109

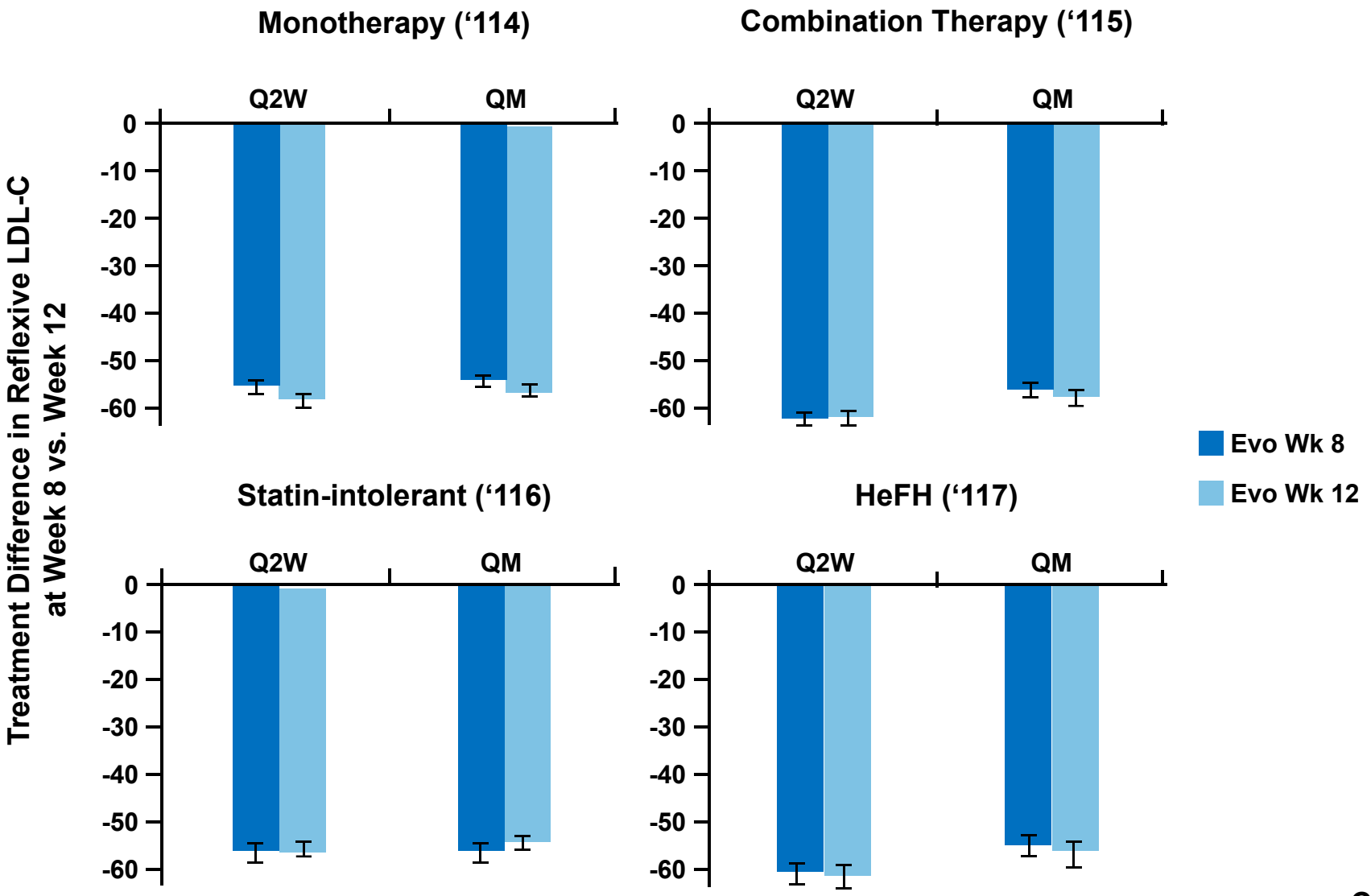


CL-373

Change in Statin Intensity During Phase 2 Year 1 Controlled Study

	Year 1 Control	
	SoC Alone N=442	Evo + SoC N=882
On statin at any time	N=287	N=612
Stable statin intensity	96%	96%
Decreased statin intensity	1%	3%
Increased statin intensity	3%	1%

Comparison of Efficacy at Week 8 (Home) and Week 12 (Clinic) in Phase 3 LDL-C Lowering Trials



CL-189

Statistical Power Considerations (‘118)

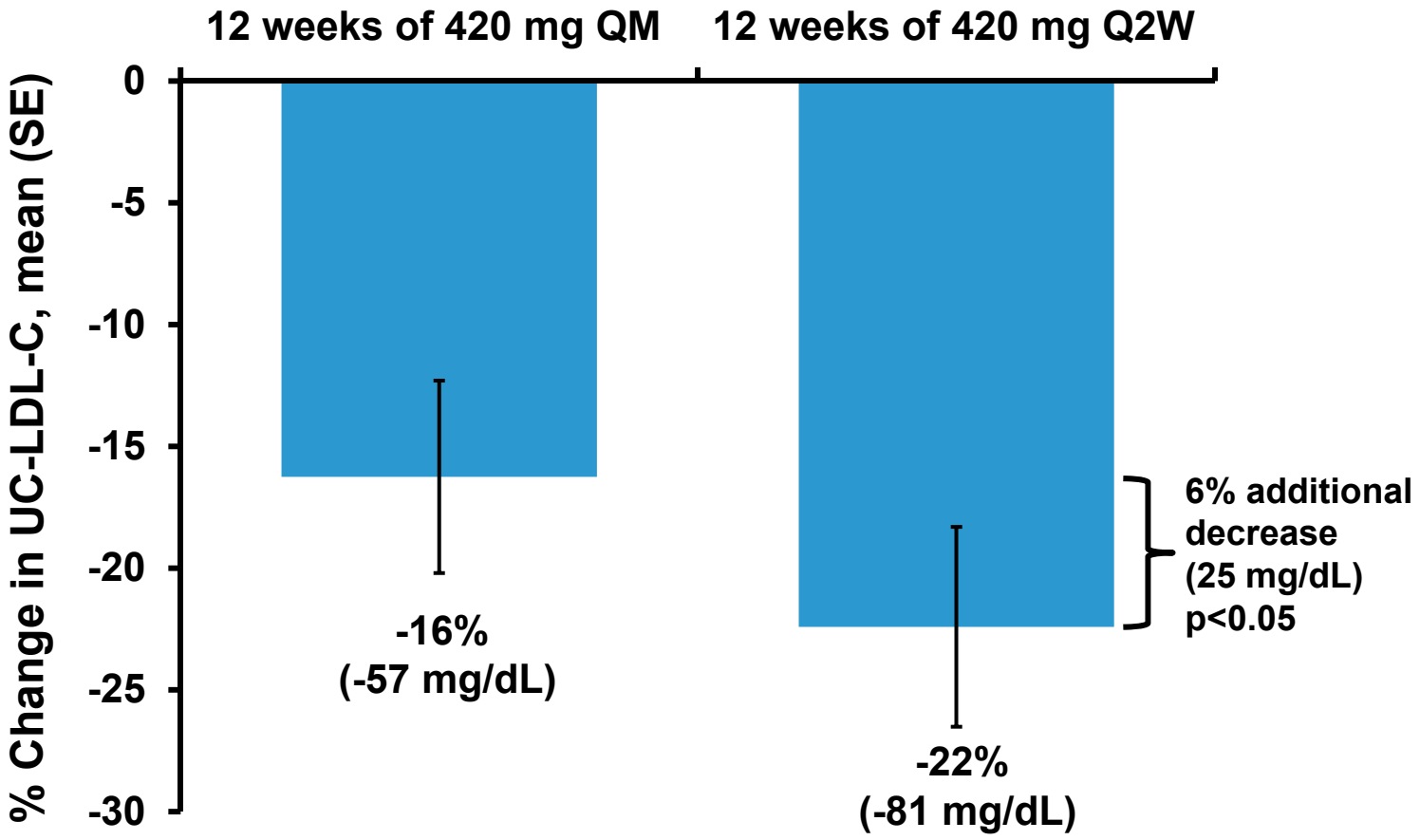
- At least 90% power for detecting tx effect of evomab
  - 1630 subjects having the MI, stroke, or CV death
    - Use ITT data collection
  - ≥15% risk reduction of evomab vs. placebo
    - Account for assumption of non-compliance rate and initial treatment lag
  - 3% lost to follow-up rate 56 months

Consistent with the MOA, LDL Receptor Activity Affects Response in Patients with HoFH

Mutation Status	Treatment Difference for Evolocumab vs. Placebo		
	Percent Change from Baseline at Week 12		
	UC LDL-C	ApoB	Lp(a)[b]
All (n=49)	**-31***	**-23***	**-12**
Defective (n=28) [a]	-41*	-33*	-25**
Other (n=21) [b,c]	-16	-9	3

*p < 0.001
**p = 0.005
[a] Defective = predicted LDLR activity >5% of normal
[b] Indeterminate category includes patients with indeterminate LDLR activity (no published data on LDLR activity associated with mutations), one patient with negative LDLR activity (predicted LDLR activity ≤5% of normal, n=1), and patients with HoFH due to autosomal recessive hypercholesterolemia (n=1) or mutations of both ApoB alleles (n=2).
[c] The single LDLR negative patient received evolocumab; percent changes from baseline at Week 12 for this patient were 10% for UC LDL-C, 9% for ApoB, and 38% for Lp(a).

In Study '271, Increasing Evolocumab from 420 mg QM to 420 mg Q2W Further Reduced LDL-C



120d

CL-124

Rosuvastatin Titration in HoFH: Efficacy

Lipid Parameter	Baseline (mg/dL) mean (SD) N=41	Week 6 Rosuva 20mg %Δ mean (SD) N=41	Week 12 Rosuva 40mg %Δ mean (SD) N=37	Week 18 Rosuva 80mg %Δ mean (SD) N=41 (LOCF)
LDL-C	514 (116)	-19 (16)**	-23 (15)**	-21 (21)**

LDL Receptor Status	N	Baseline (mg/dL) mean (SD)	Week 18 Rosuva 80mg %Δ mean (SD)
Overall	**41**	**515 (13)**	**-21 (21)**
Negative	5	420 (11)	-9 (37)
Defective	28	524 (14)	-22 (18)
Unknown	8	543 (14)	-27 (20)

Note that 23% reduction in LDL-C ≈ 113 mg/dL

*P<0.05 **P<0.001

Marais AD et al Atherosclerosis 2007;197:400-406

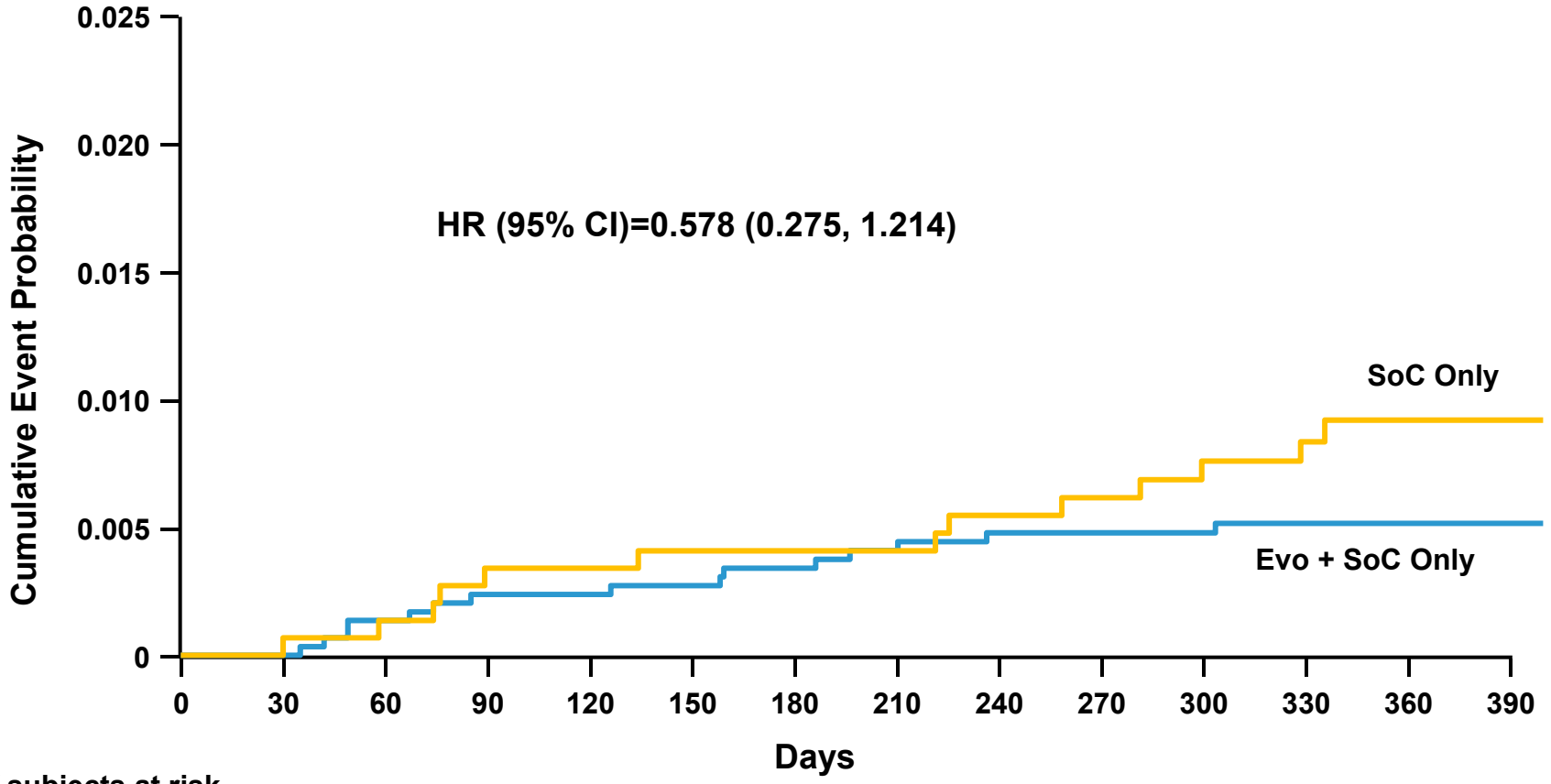
In OLE HoFH Study ‘271, high baseline PCSK9 levels were further reduced by 420 mg Q2W

PCSK9 Values in the Titration Analysis Set (OLE HoFH Study ‘271)			
	Titration Analysis Set (n=28)		
	Baseline	After 12 Weeks of 420 mg QM	After 12 Weeks of 420 mg Q2W
PCSK9 level mean (SD), ng/mL	680 (187)	424 (190)	46 (38)
% reduction from baseline mean (SE)	--	-34 (7)	-93 (1)

120-d

CL-280

Cumulative Incidence of All Cause Death/MI/Stroke in the Year 1 Control Period



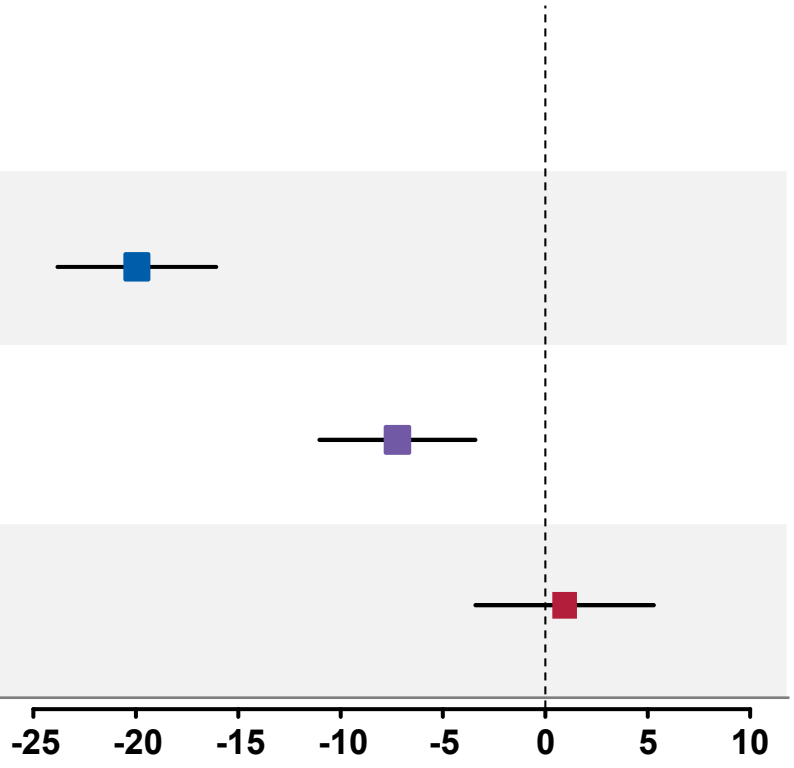
No. of subjects at risk

Evo + SoC	2976	2971	2963	2951	2943	2938	2927	2905	2894	2857	2760	2625	855	750
SoC Alone	1489	1487	1483	1478	1474	1472	1469	1461	1451	1432	1381	1298	414	356

Oct data

Phase 3 Doses Provide Clinically Equivalent LDL-C Reduction

	N	Mean Difference (95% CI)
Calculated LDL-C		
140 mg Q2W vs. 70 mg Q2W	247	-19.94 (-23.82, -16.05)
420 mg QM vs. 280 mg QM	249	-7.22 (-11.02, -3.42)
420 mg QM vs. 140 mg Q2W	248	0.94 (-3.41, 5.28)



Percent Change from Baseline Differences (Week 10 and 12 Means)