



UPDATE ON OUR GENERAL MEDICINE PORTFOLIO

NOVEMBER 7, 2022

AMGEN[®]

SAFE HARBOR STATEMENT

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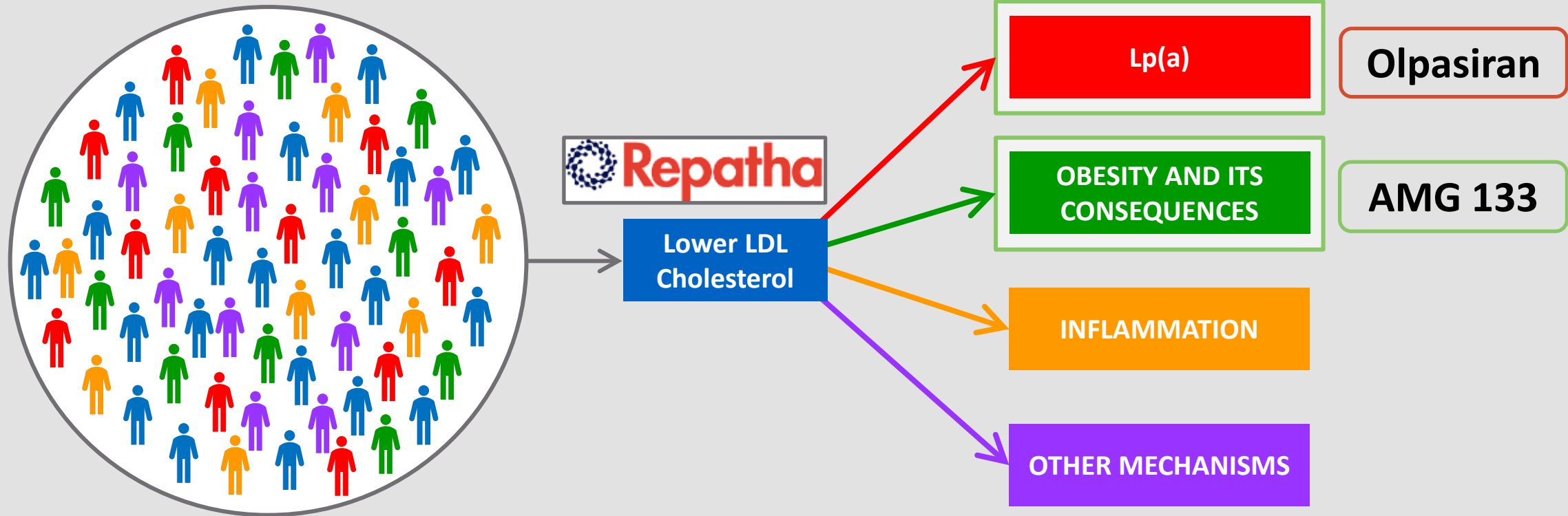


AGENDA

Topic	Presenter
Introduction	David Reese, MD Executive Vice President, Research and Development, Amgen
FOURIER AND FOURIER-OLE (Open-Label Extension) Studies	Marc S. Sabatine, MD, MPH Chair of TIMI Study Group Distinguished Chair in Cardiovascular Medicine, Brigham and Women's Hospital Professor of Medicine, Harvard Medical School
Reduction of Lipoprotein(a) With Small Interfering RNA	
AMG 133 Program Update	Narimon Honarpour MD, PhD Vice President, Clinical Development, Amgen
Concluding Remarks	
Q&A	All

TARGETING MECHANISMS OF RESIDUAL RISK THROUGH INNOVATIVE USE OF HUMAN DATA TO INFORM TARGET DISCOVERY, BIOMARKERS, AND PATIENT SEGMENTATION

High CV and Metabolic Risk Patients



Additional programs coming into the clinical pipeline for metabolic/obesity, heart failure and vascular disease

LDL= low-density lipoprotein; Lp(a)= Lipoprotein(a); CV= cardiovascular.

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Provided November 7, 2022, as part of an oral presentation and qualified by such, contains forward-looking statements, actual results may vary materially; Amgen disclaims any duty to update



FOURIER AND FOURIER-OLE (Open-Label Extension) Studies

Marc S. Sabatine, MD, MPH



An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

This study was funded by Amgen Inc.



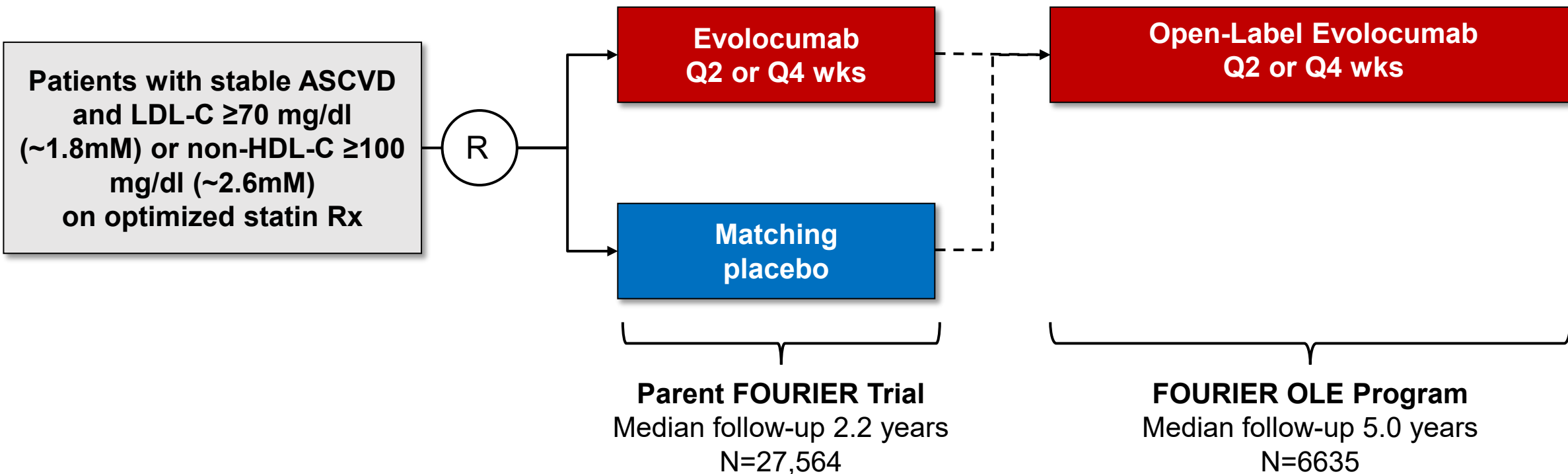
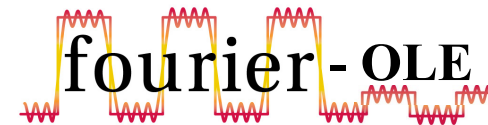
Background

- In the FOURIER trial, 27,564 patients with stable ASCVD were randomized to the PCSK9 inhibitor evolocumab vs. placebo.
- Evolocumab reduced the risk of MACE, but there was no observed effect on CV mortality.
- However, the median follow-up was only 2.2 years.
- Pivotal statin trials had median follow-up of 4-5 years and demonstrated both a lag effect (clinical benefit grew over time) and legacy effect (clinical benefit persisted in extended follow-up after the parent trial ended).
- Thus, very long-term data on safety and efficacy of LDL-C lowering with PCSK9 inhibition are needed.





Study Schema



US & Eastern Europe: NCT02867813
Western Europe: NCT03080935

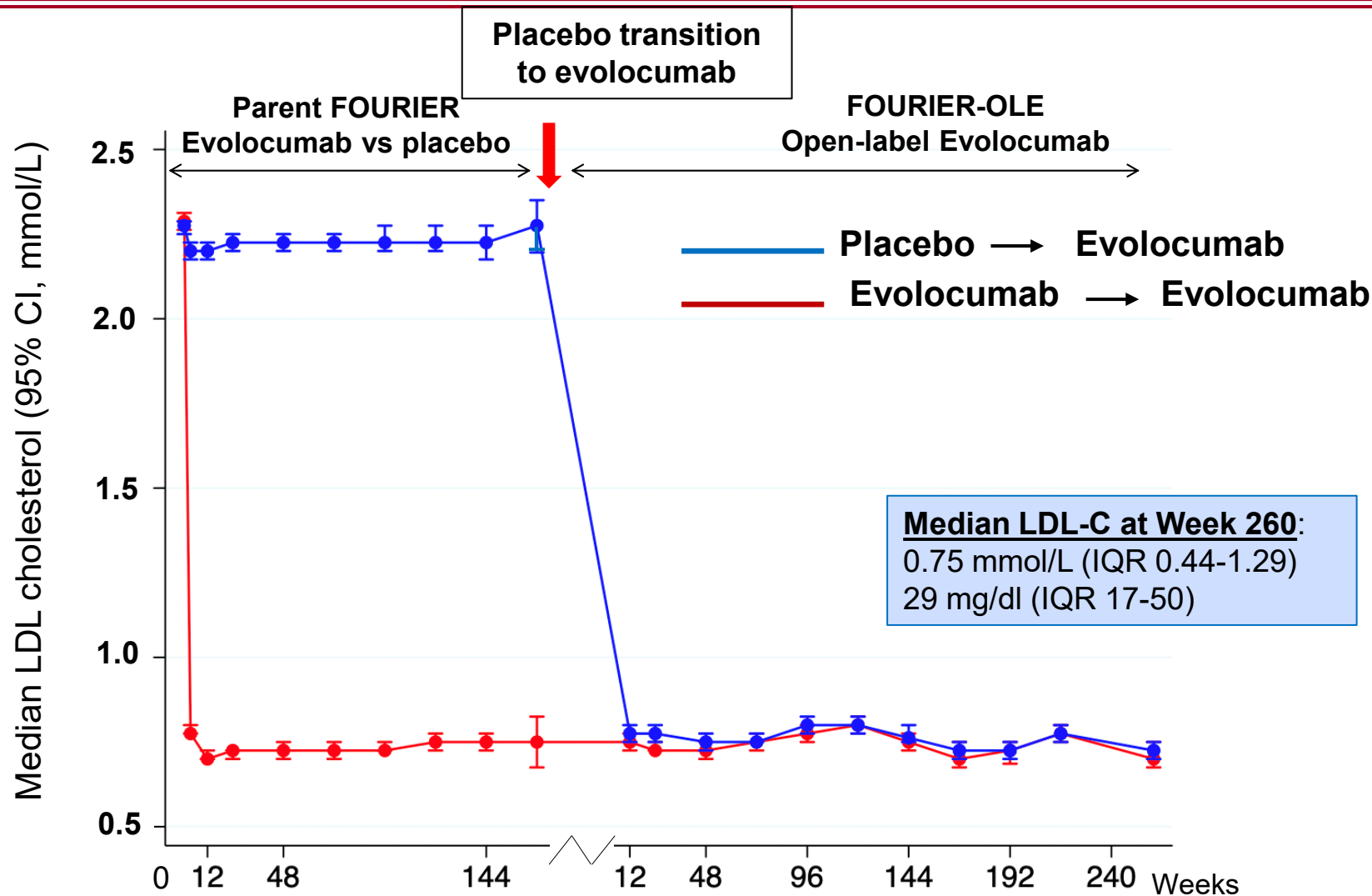
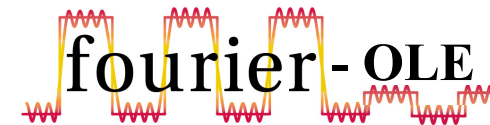


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ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; Rx: medical prescription; Q2W = every two weeks; Q4W = every four weeks; OLE = open label extension.

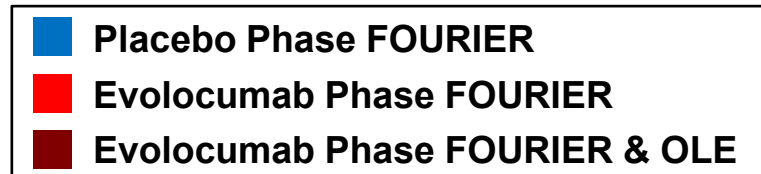
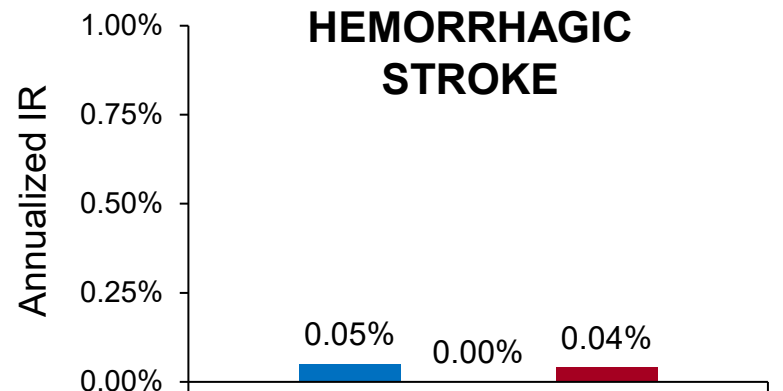
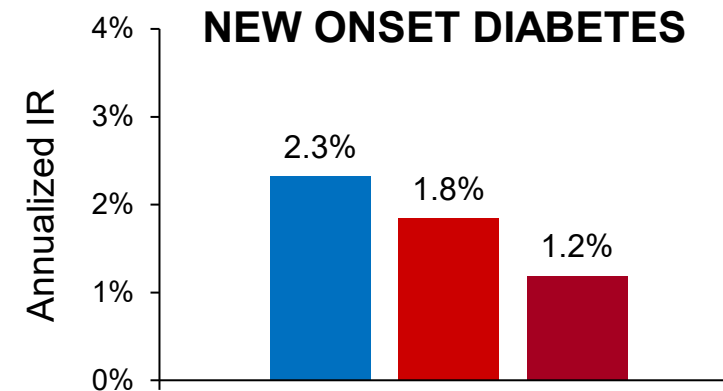
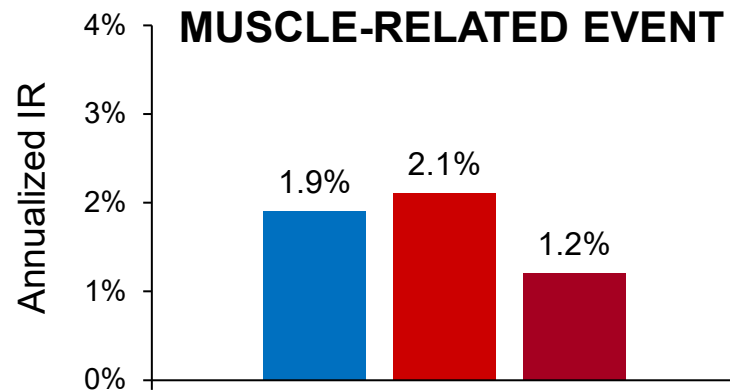
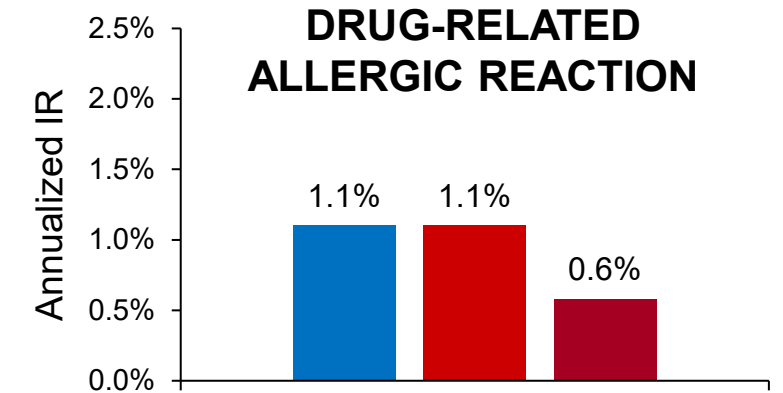
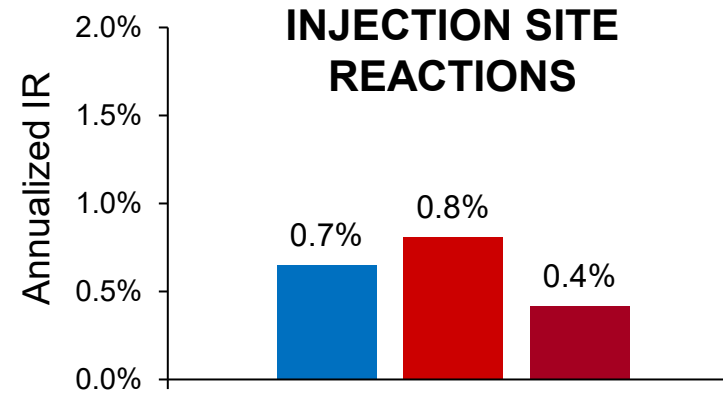
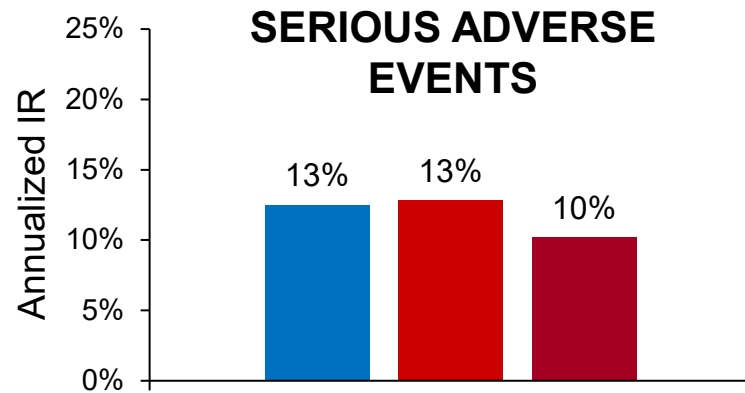
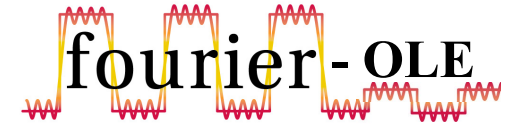


Effect on LDL-C



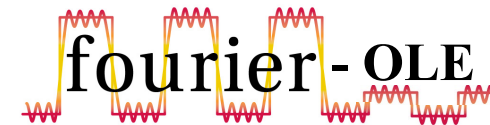


Long-Term Safety

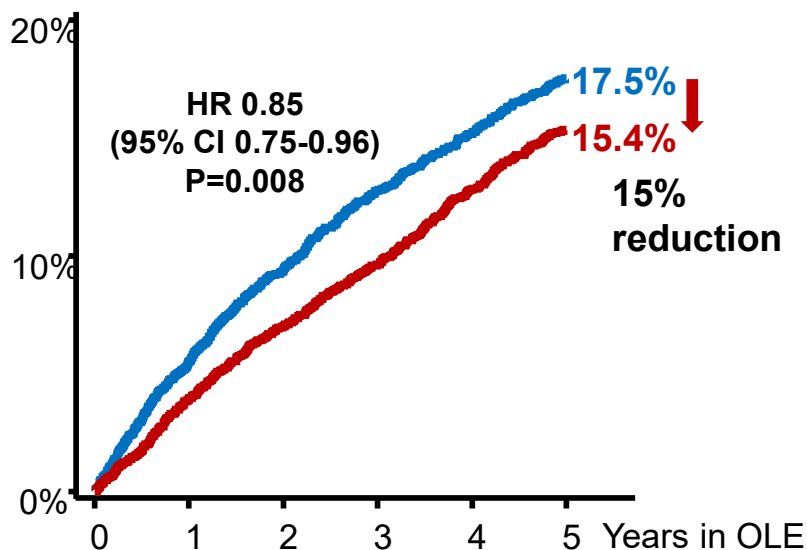




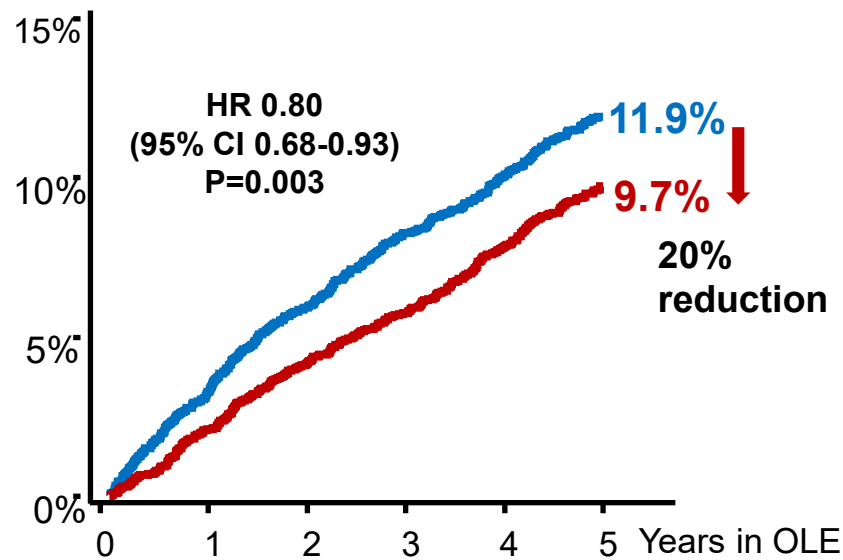
Efficacy during FOURIER-OLE



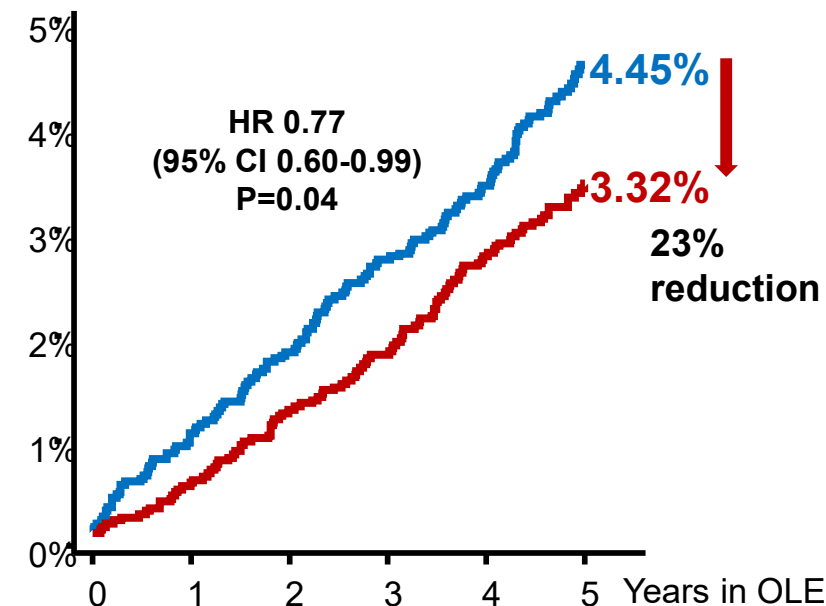
Primary Endpoint: CV death, MI, stroke, unstable angina or coronary revascularization



Key Secondary Endpoint: CV death, MI or stroke



CV death



— Placebo → Evolocumab
— Evolocumab → Evolocumab

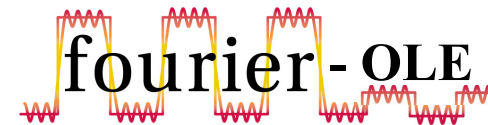


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CV = cardiovascular; MI = myocardial infarction; OLE = open label extension; HR = hazard ratio.



Analyses On Very Low LDL-C

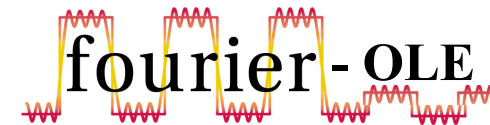


- **The optimal achieved LDL-C level with regards to cardiovascular and safety outcomes in the long-term remains unclear.**
- **We explored the relationship between achieved LDL-C levels and the occurrence of long-term adverse cardiovascular and safety outcomes, down to very low (<20 mg/dL) achieved LDL-C levels.**

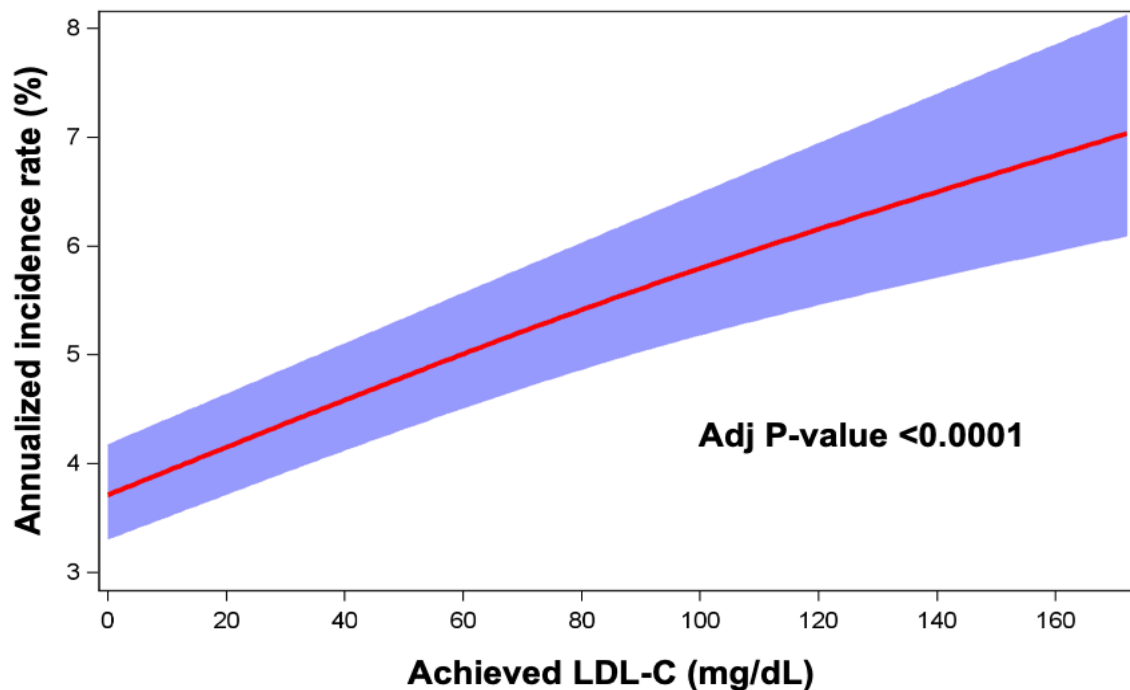




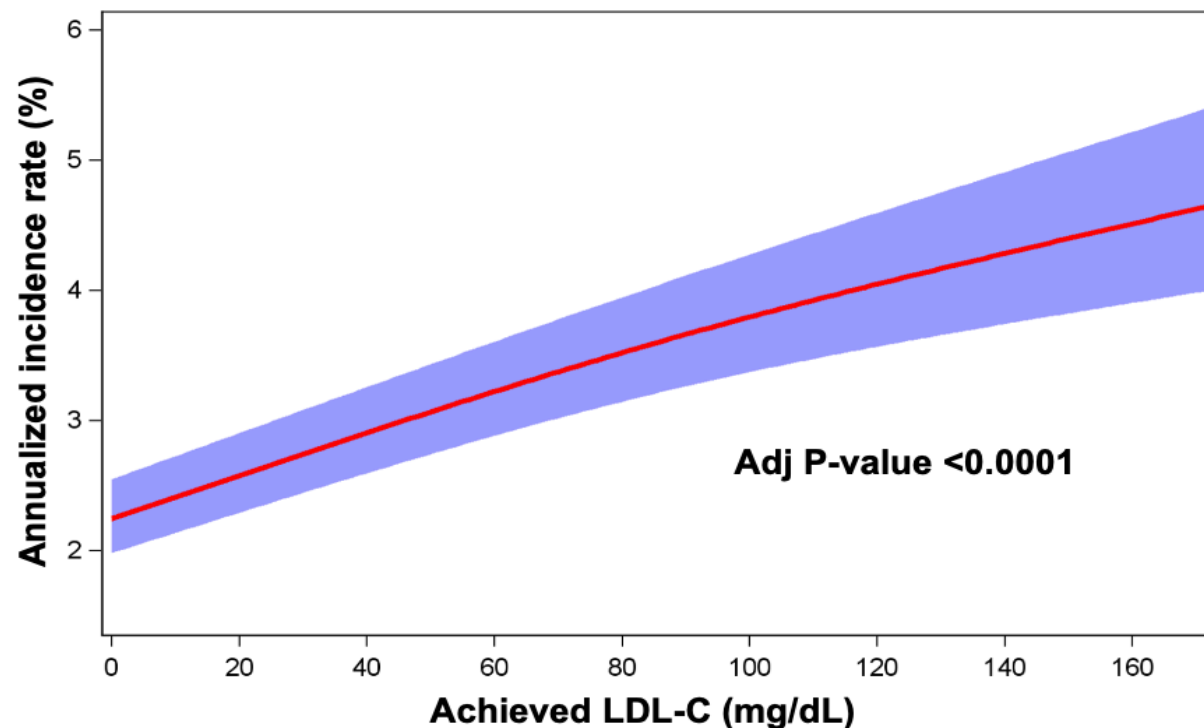
CV Outcomes and Achieved LDL-C



Primary endpoint: CV death, MI, stroke, coronary revascularization or hospitalization for unstable angina



Key secondary endpoint: CV death, MI, or stroke

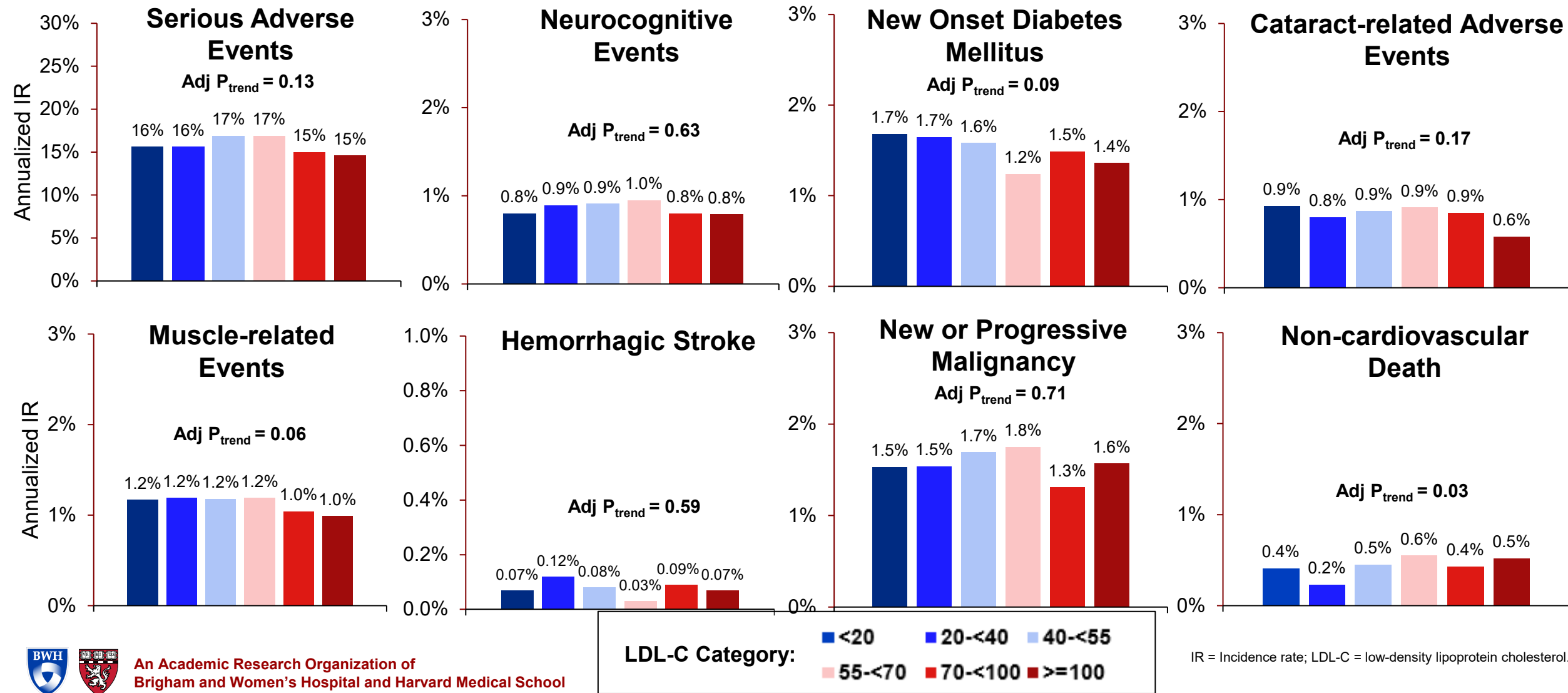
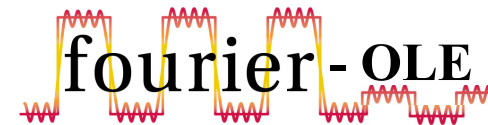


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CV = cardiovascular; MI = myocardial infarction; LDL-C = low-density lipoprotein cholesterol.



Safety and Achieved LDL-C



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IR = Incidence rate; LDL-C = low-density lipoprotein cholesterol.



Summary & Conclusions



- **Long-term use of evolocumab with median follow-up of more than 7 years appears both safe and well-tolerated.**
- **Earlier initiation of evolocumab is associated with continued accrual of cardiovascular benefit, including cardiovascular mortality, over the next several years.**
- **Monotonic relationship between lower achieved LDL-C levels, down to very low LDL-C levels <20 mg/dL, and a lower risk of cardiovascular events up to 8.6 years of follow-up.**
- **“There appears to be no LDL-C level below which benefit ceases”.**
(2022 ACC Expert Consensus Decision Pathway on the Role of Non-statin Therapies for LDL-Cholesterol Lowering)



#AHA22

Reduction of Lipoprotein(a) With Small Interfering RNA: Results of the OCEAN(a)-DOSE (TIMI 67) Trial

Marc S. Sabatine MD MPH:

On Behalf of the OCEAN(a)-DOSE Trial Investigators

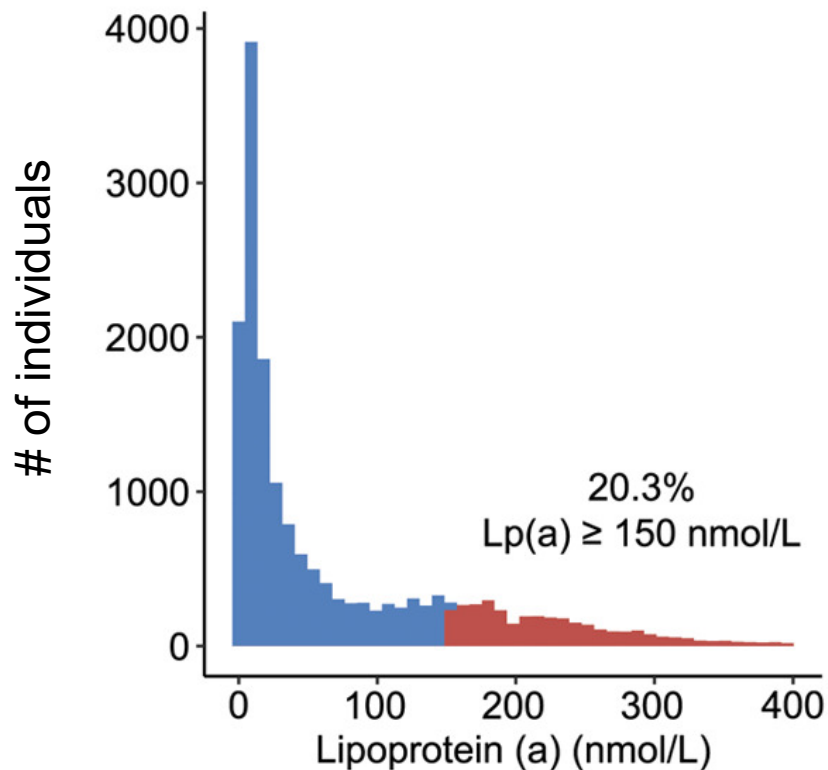


American
Heart
Association.

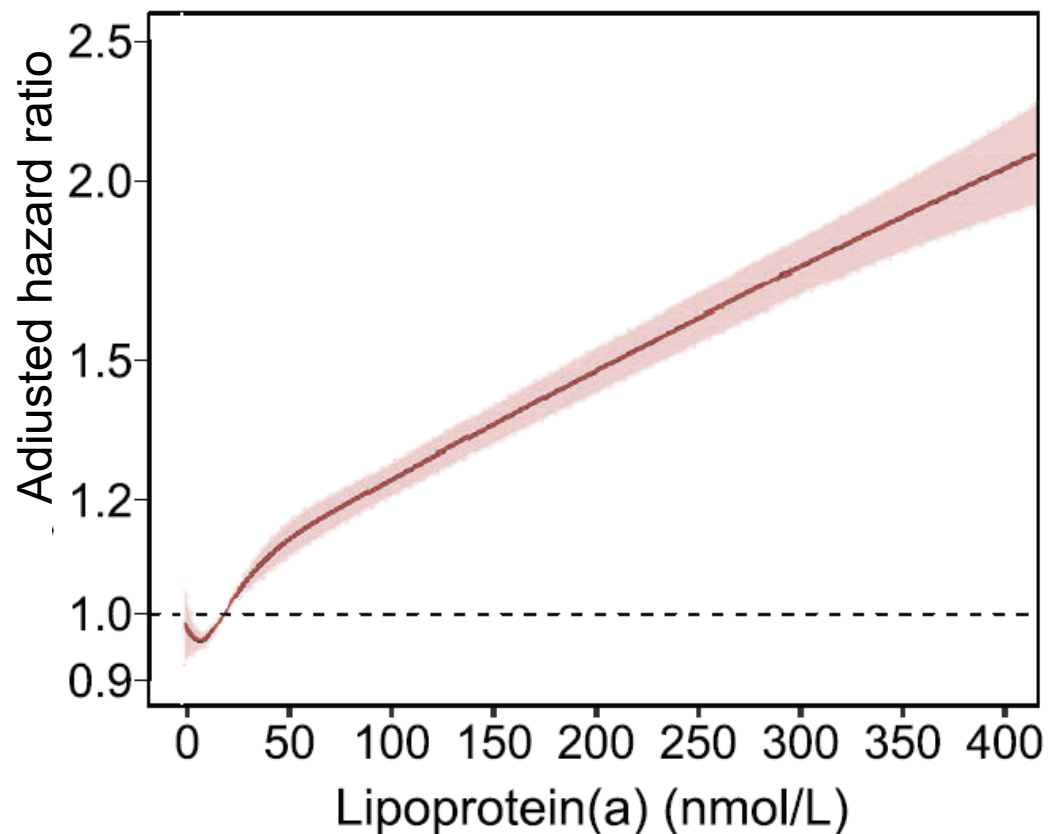


Lp(a) and Coronary Heart Disease Risk

Lp(a) distribution in individuals with established atherosclerotic cardiovascular disease



Lp(a) is associated with atherosclerotic cardiovascular disease risk independent of traditional risk factors





OCEAN(a)-DOSE: STUDY SCHEMA

Clinicaltrials.gov: NCT04270760

Patients aged 18-80 years with atherosclerotic disease
& Lp(a) >150 nmol/L

N=281

RANDOMIZE 1:1:1:1:1

DOUBLE BLIND

Olpasiran
10mg Q12W

Olpasiran
75mg Q12W

Olpasiran
225mg Q12W

Olpasiran
225mg Q24W

Placebo

Primary Endpoint: % Change in Lp(a) from Baseline to Week 36

Key Secondary Endpoint: % Change in Lp(a) from Baseline to Week 48



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Lp(a)= Lipoprotein(a); Q12W = every 12 weeks; Q24W = every 24 weeks.

O'Donoghue ML et al., *Am Heart J* 2022;251:61-69



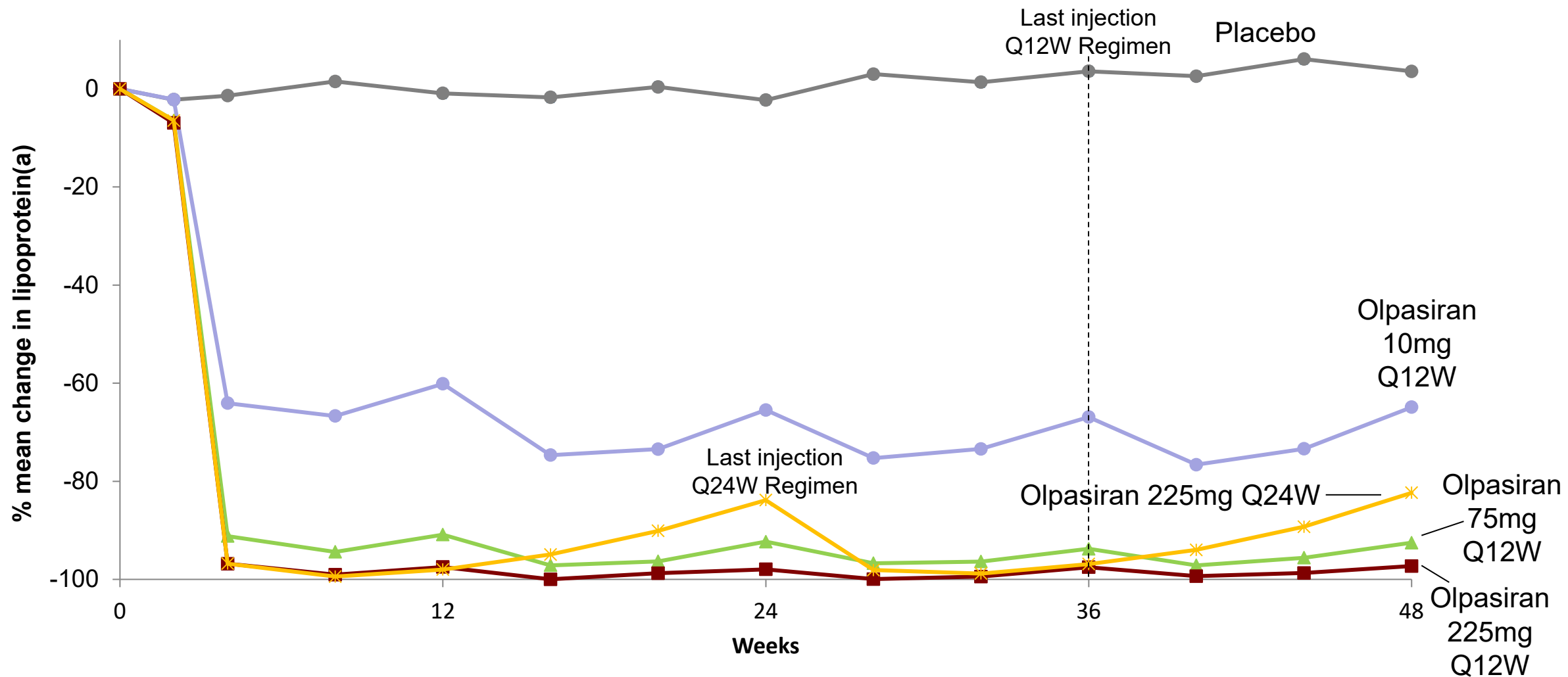
Baseline Characteristics

	Olpasiran Pooled Dose Arms (N=227)	Placebo Q12W SC (N=54)
Age in years, mean (SD)	61.6 (9.6)	63.4 (8.9)
Female sex	32%	33%
Coronary Artery Disease	91%	93%
Myocardial Infarction	27%	37%
Peripheral Artery Disease	12%	6%
Cerebrovascular Disease	20%	22%
Selected lipid lowering therapy use at baseline		
Statin	89%	83%
Ezetimibe	55%	41%
PCSK9 inhibitor	24%	22%
Baseline laboratory values, median (IQR)		
Lipoprotein(a), (nmol/L)	261 (197, 360)	246 (200, 343)
LDL-C, (mg/dl)	68 (52, 87)	65 (48, 81)





Changes in Lp(a) Through Follow-Up



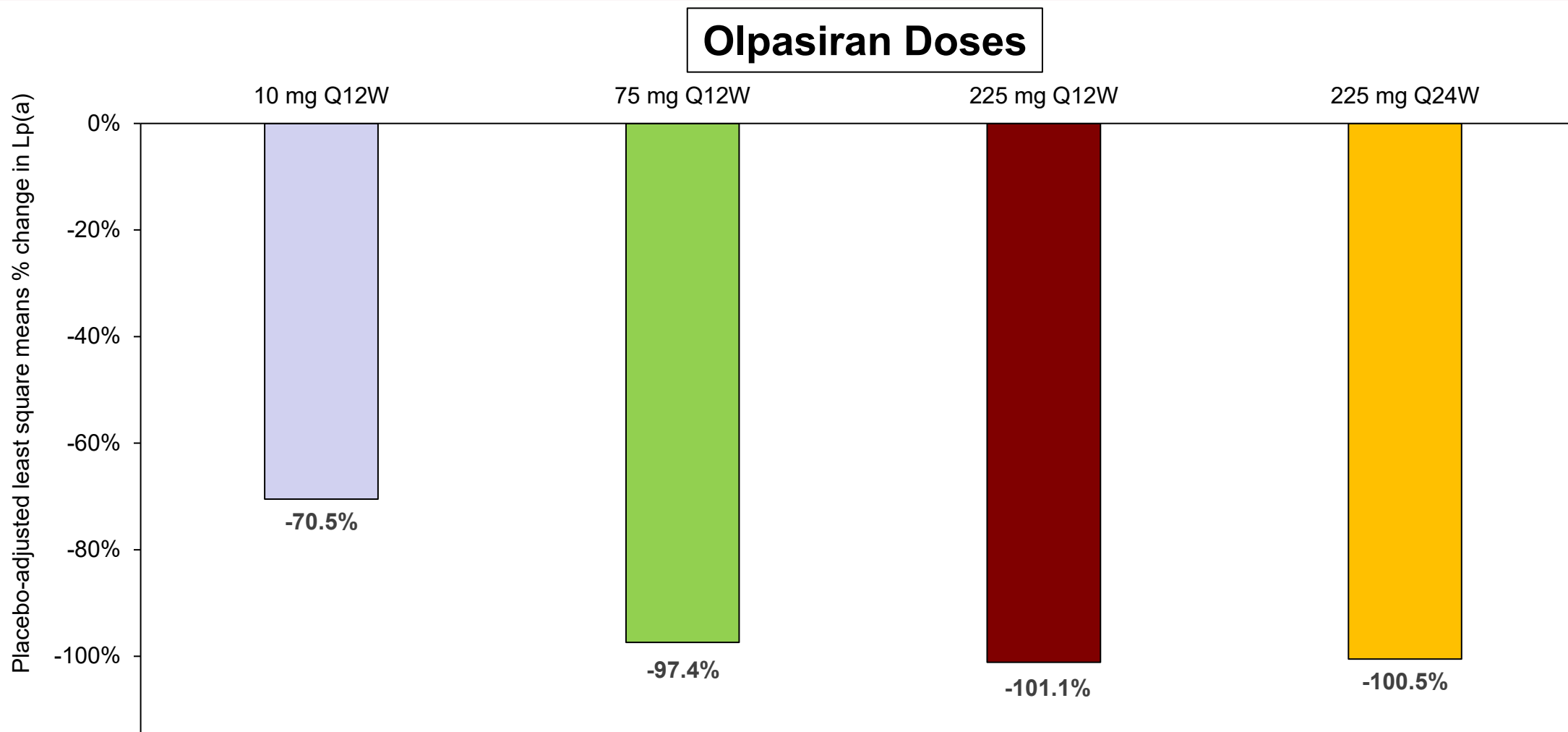
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Lp(a)= Lipoprotein(a); Q12W = every 12 weeks; Q24W = every 24 weeks.

Means reported as least-square means



Primary Endpoint: % Change in Lp(a) at 36 weeks

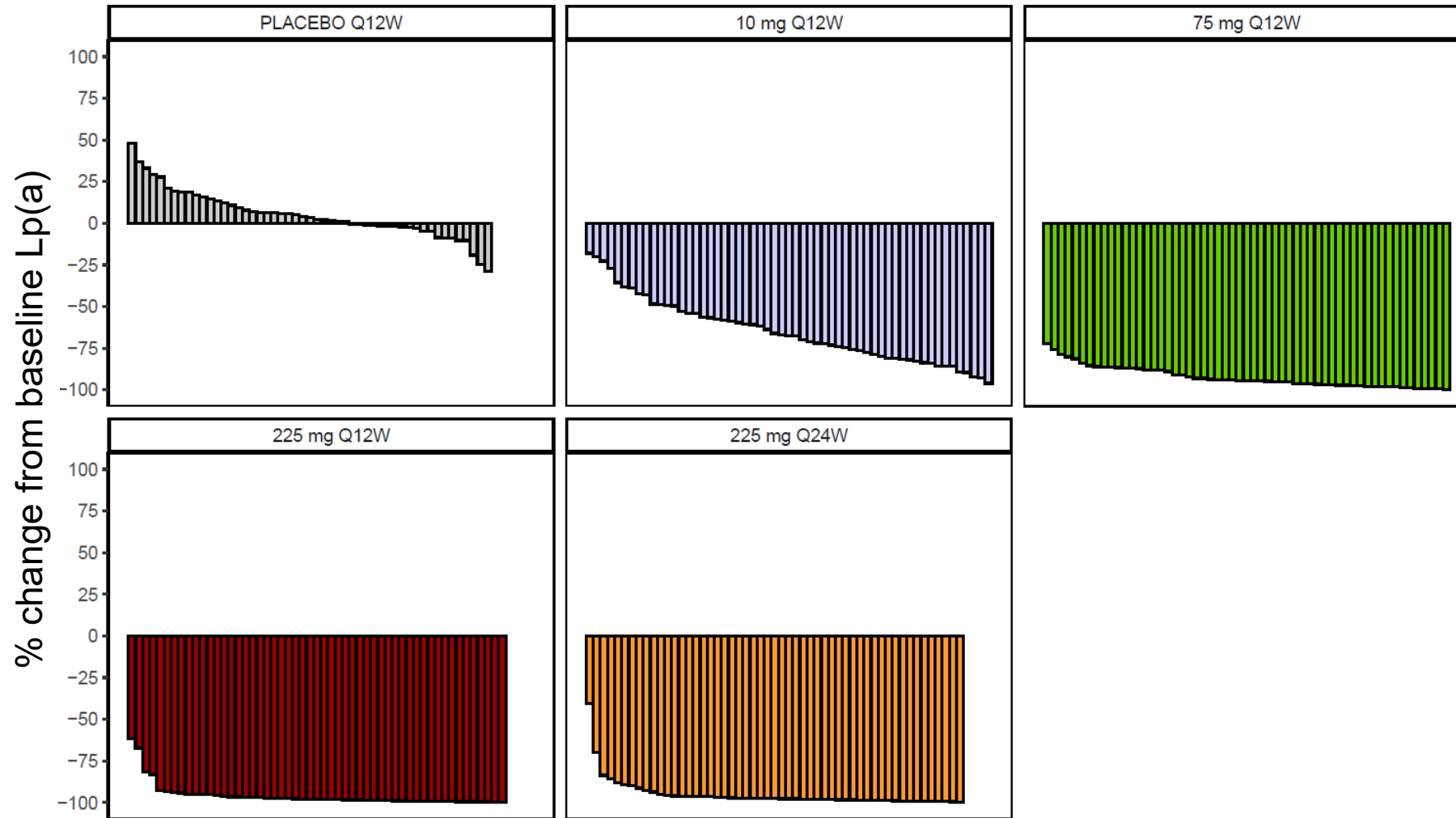


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Lp(a)= Lipoprotein(a); Q12W = every 12 weeks; Q24W = every 24 weeks.



Interindividual Variability in Lp(a) Response at Week 36



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Lp(a)= Lipoprotein(a); Q12W = every 12 weeks; Q24W = every 24 weeks.



Safety & Tolerability

	Olpasiran 10 mg Q12W SC (N=58)	Olpasiran 75 mg Q12W SC (N=58)	Olpasiran 225 mg Q12W SC (N=56)	Olpasiran 225 mg Q24W SC (N=55)	Placebo Q12W SC (N=54)
Treatment Emergent Adverse Events	78%	79%	84%	85%	83%
Serious adverse events	5.2%	5.2%	11%	7.3%	15%
Reported as related to study drug	12%	22%	29%	25%	20%
Leading to discontinuation of study drug	1.7%	1.7%	1.8%	1.8%	1.9%
Myalgia	5.2%	1.7%	7.1%	7.3%	7.4%
Liver-related adverse events	1.7%	3.4%	1.8%	1.8%	3.7%
Hyperglycemia, new-onset or worsening diabetes mellitus	8.6%	5.2%	8.9%	5.5%	5.6%
Injection site reactions*	5.2%	19%	21%	24%	11%
Hypersensitivity reactions**	1.7%	6.9%	5.4%	9.1%	1.9%

*Injection site reactions were generally mild

Q12W = every 12 weeks; Q24W = every 24 weeks.

**Hypersensitivity reactions were generally described as mild injection site pain



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Conclusions

- **Lp(a) is associated with atherosclerotic cardiovascular disease risk independent of traditional risk factors¹**
- **Olpasiran, an siRNA, dosed 75 mg or higher every 12 weeks, reduces Lp(a) concentration by more than 95% in patients with established atherosclerotic cardiovascular disease.**
- **Olpasiran appears both safe and well-tolerated in this study.**
- **These findings set the foundation for Phase 3 testing scheduled to commence later this year (NCT05581303).**





The NEW ENGLAND
JOURNAL of MEDICINE

ORIGINAL ARTICLE

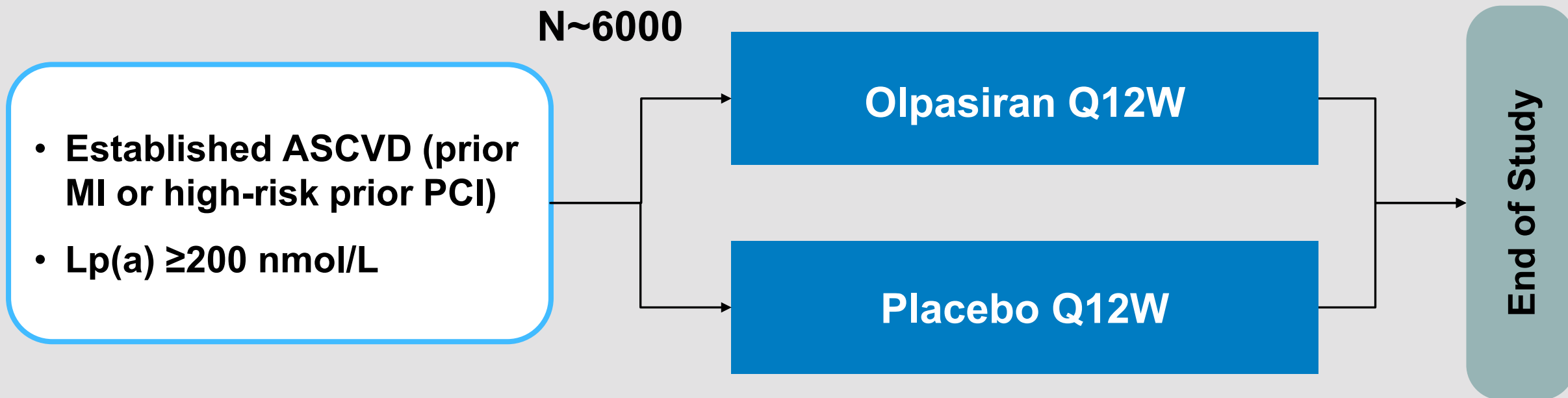
Small Interfering RNA to Reduce Lipoprotein(a) in Cardiovascular Disease

Michelle L. O'Donoghue, M.D., M.P.H., Robert S. Rosenson, M.D.,
Baris Gencer, M.D., J. Antonio G. López, M.D., Norman E. Lepor, M.D.,
Seth J. Baum, M.D., Elmer Stout, M.D., Daniel Gaudet, M.D., Ph.D.,
Beat Knusel, Ph.D., Julia F. Kuder, M.A., Xinhui Ran, M.S.,
Sabina A. Murphy, M.P.H., Huei Wang, Ph.D., You Wu, Ph.D.,
Helina Kassahun, M.D., and Marc S. Sabatine, M.D., M.P.H.,
for the OCEAN(a)-DOSE Trial Investigators*



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PHASE 3 CARDIOVASCULAR OUTCOMES TRIAL SCHEMA



Primary endpoint: time to first CHD, MI or urgent revascularization

Estimated study start in December 2022



AMG 133 PROGRAM UPDATE

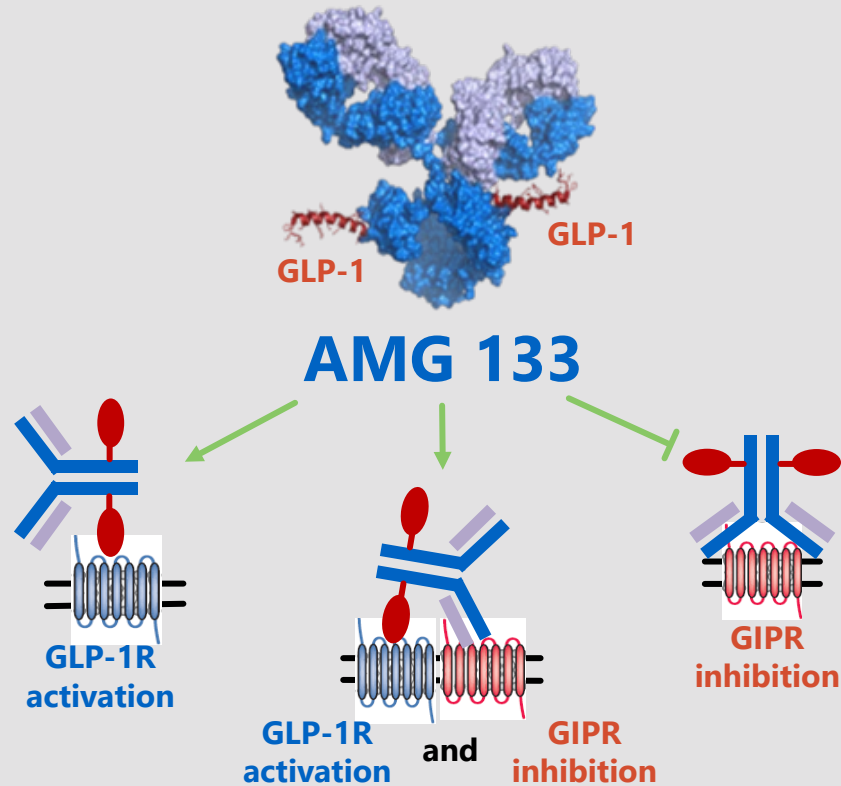
NARIMON HONARPOUR

VICE PRESIDENT CLINICAL DEVELOPMENT

AMGEN[®]

AMG 133, A FIRST-IN-CLASS ANTIBODY-PEPTIDE CONJUGATE TARGETING OBESITY

GIPR INHIBITORY ANTIBODY



STUDY POPULATIONS OF GIPR VARIANTS

Japanese
Genome-wide association study¹

European
Genome-wide association study^{2,3}

Whole exome sequencing
in UK-Biobank and N. America⁴

↓ GIPR
expression

↓ BMI

GIPR= Gastric Inhibitory Polypeptide Receptor; GLP-1= Glucagon-like peptide-1; GLP-1R= Glucagon-like peptide-1 receptor

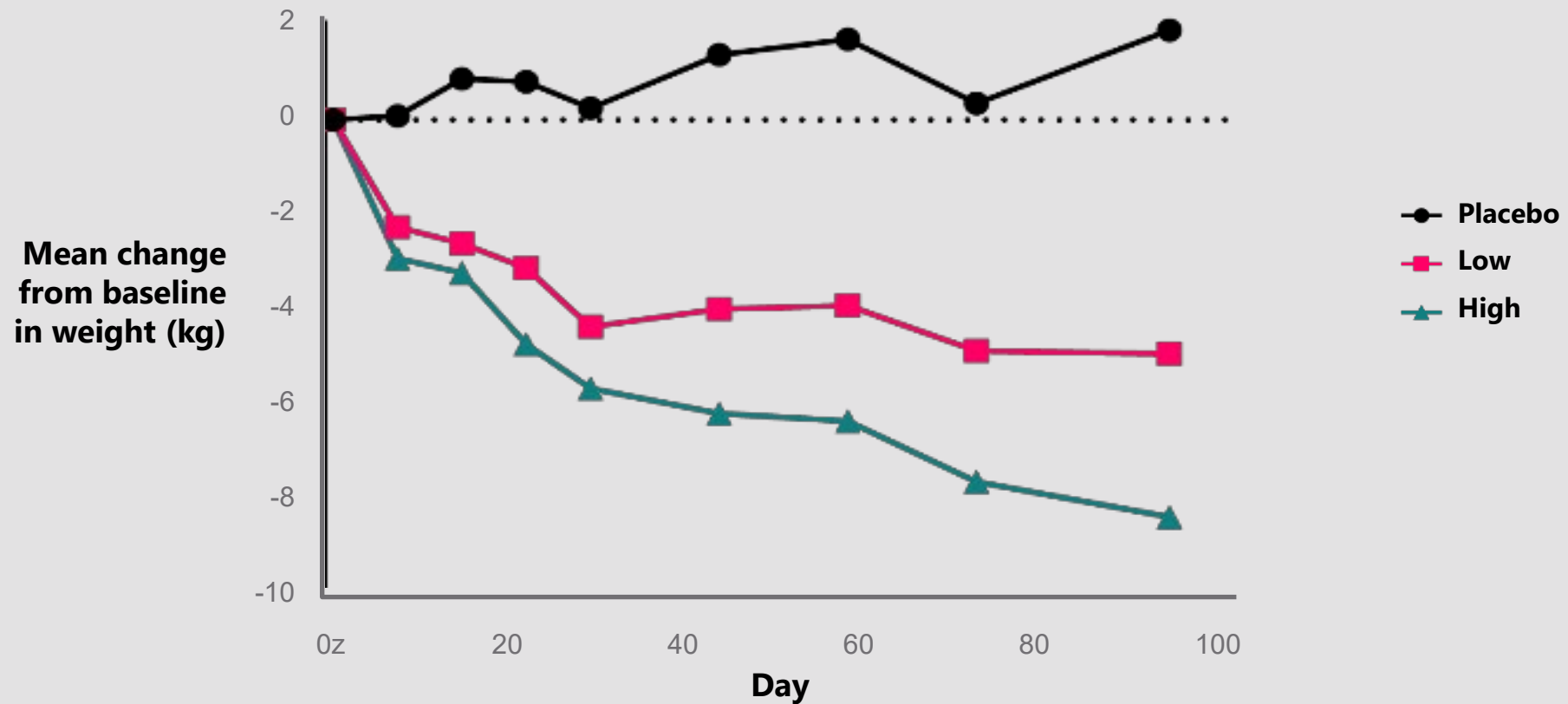
GIPR= Gastric Inhibitory Polypeptide Receptor; BMI= body mass index

1. Nature Genetics 2012; 44 (3):302-6
2. Nature Genetics 2010; 42 (11):937-48 (deCODE is collaborator)
3. Nature Genetics 2013; 45 (5):501-12 (deCODE is collaborator)
4. Science 2021; 373 (6550)

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AMG 133 HAS DEMONSTRATED EARLY CLINICAL EFFICACY IN OBESE PATIENTS

Single Subcutaneous Dose of AMG133



kg= kilogram
Data source: Amgen internal data

SINCE OUR UPDATE IN FEBRUARY, WE'VE CONTINUED TO PROGRESS AMG 133 IN PHASE 1

- **Completed single ascending dose and multiple ascending dose cohorts**
 - Dosed Q4W, subcutaneously.
- **Dose-dependent reductions in mean body weight from baseline.**
 - Multi-dose mean percent change in BW by day 85: -7.19% (low dose) to -14.52% (high dose) in AMG 133-treated vs 1.49% in placebo.
 - Total of three doses, each 4 weeks apart.
 - Plateau on weight reduction not observed.
- **No notable safety concerns were identified; most TEAEs were mild and transient.**
- **The pharmacokinetics were dose-proportional with an extended half-life.**
- **Data from the initial cohorts will be presented at the 20th World Congress on Insulin Resistance, Diabetes and Cardiovascular Disease (WCIRDC) Hybrid Conference in Dec.**

Planning underway to rapidly initiate a Phase 2 trial



CONCLUSIONS

NARIMON HONARPOUR

VICE PRESIDENT CLINICAL DEVELOPMENT

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ROBUST CARDIOMETABOLIC PORTFOLIO PROVIDES POTENTIAL LONG-TERM GROWTH OPPORTUNITIES FOR THE COMPANY

- **Portfolio strategy focuses on genetically validated drivers of risk such as PCSK9, Lp(a) and GIPR (for obesity); results are encouraging.**
- **Repatha FOURIER OLE findings argue for early initiation of a significant and sustained LDL-C reduction to maximize clinical benefit.**
- **Olpasiran treatment resulted in rapid and sustained reduction in Lp(a); plan to initiate Phase 3 in December 2022.**
- **AMG 133 demonstrated significant dose-dependent weight-loss of up to ~14.5% @ d85 in obese patients with Q4W dosing; plan to initiate Phase 2 early 2023.**

PCSK9 = proprotein convertase subtilisin/kexin type 9; Lp(a) = Lipoprotein(a); GIPR = Gastric Inhibitory Polypeptide Receptor; OLE = open label extension; LDL-C = low-density lipoprotein cholesterol; Q4W = every 4 weeks



QUESTIONS?

DAVID REESE, MD

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