

ACC.26

Essence-TIMI 73b CCTA Trial: Effect of APOC3 Inhibition with Olezarsen on Coronary Atherosclerosis

Nicholas Marston, MD, MPH

Investigator, TIMI Study Group

Cardiologist, Brigham and Women's Hospital

Harvard Medical School



AMERICAN
COLLEGE of
CARDIOLOGY®

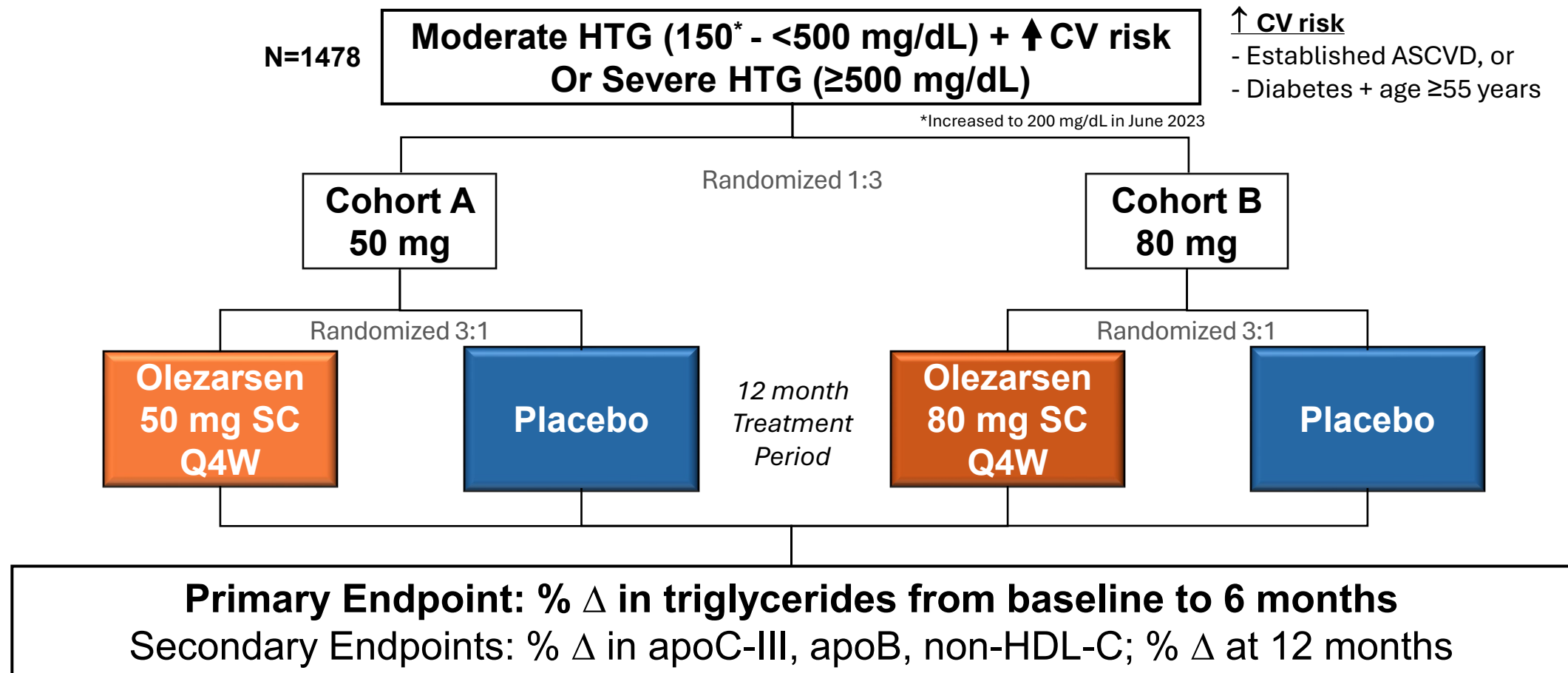
Background

- Triglyceride-rich lipoproteins (TRLs) and the cholesterol they carry, known as remnant cholesterol (RC), are associated with ASCVD
- Some studies have suggested that TRL particles and remnant cholesterol carry outsized risk compared to LDL particles and LDL-C
- Whether lowering TRLs and remnant cholesterol favorably modifies coronary atherosclerosis is unclear

ApoC3 and Olezarsen

- Variants disrupting *APOC3* function are associated with 39% lower triglyceride levels and a 40% lower lifetime risk of CAD
- Olezarsen is an antisense oligonucleotide (ASO) that:
 - Targets apolipoprotein C-III (APOC3) mRNA
 - Significantly reduces triglycerides and remnant cholesterol
 - Has minimal effect on LDL-C in moderate hypertriglyceridemia, but a net reduction in ApoB
- We investigated the effect of olezarsen on coronary atherosclerosis by CT angiography

Parent Trial Schema



CCTA Substudy

Core Lab

- MGH
- Director, Michael Lu, MD, MPH

Key Inclusion Criterion

- Quantifiable NCPV

Imaging Endpoints (pbo-adjusted % Δ)

- **1° EP:** NCPV
- **Key 2° EP:** LAP
- **Other 2° EP's:** total, calcified, fibrous, and fibro-fatty plaque volumes

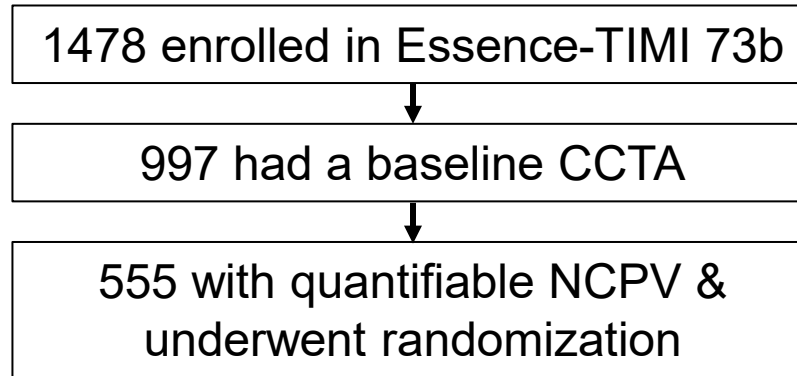
Analytic Approach

- Pooled olezarsen doses
- Power calculations: 400 paired scans provided >80% power to detect a 10% difference (2-sided α of 0.05, SD 30%)

-30-30 HU	31-130 HU	131-350 HU	>350 HU
Necrotic core	Fibrofatty	Fibrous	Calcium (low, medium, high density)
Low-attenuation plaque volume (LAPV)			
Non-calcified plaque volume (NCPV)			Calcified plaque volume (CPV)
Total plaque volume (TPV)			

JACC CV Img. 2025;18:912

Patient Disposition in CCTA Study



Baseline Characteristics

	Overall N=468
Age (yrs)	63 (56, 70)
Female sex	31%
Race/Ethnicity	
White	93%
Hispanic/Latino	16%

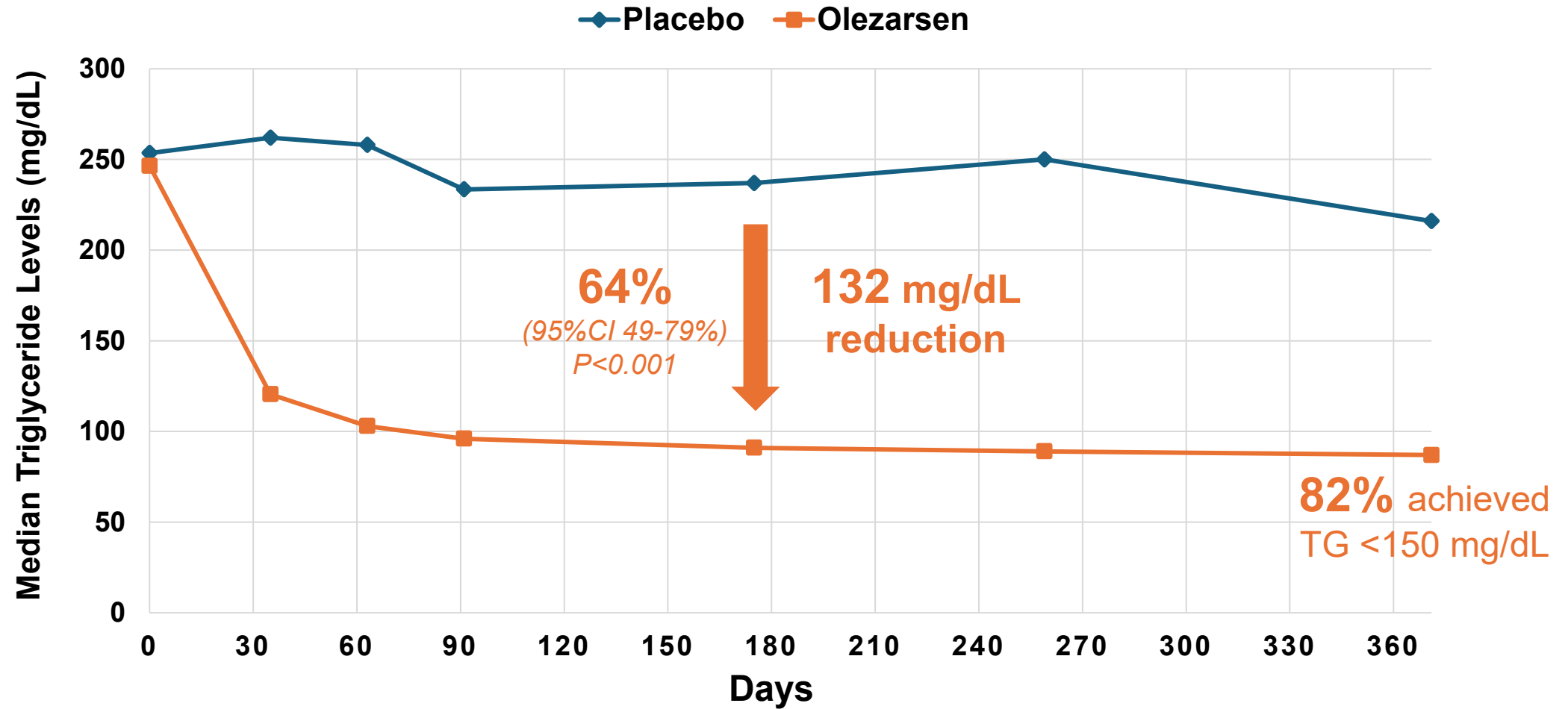
Baseline Lipid Values

Lab Values, mg/dL	Overall N=468
Triglycerides	249 (197–331)
≥500 mg/dL	9%
Non-HDL cholesterol	130 (105–162)
LDL cholesterol	81 (60–109)
Remnant cholesterol	53 (38–76)
VLDL cholesterol	43 (34–57)
Apolipoprotein B	93 (76–111)

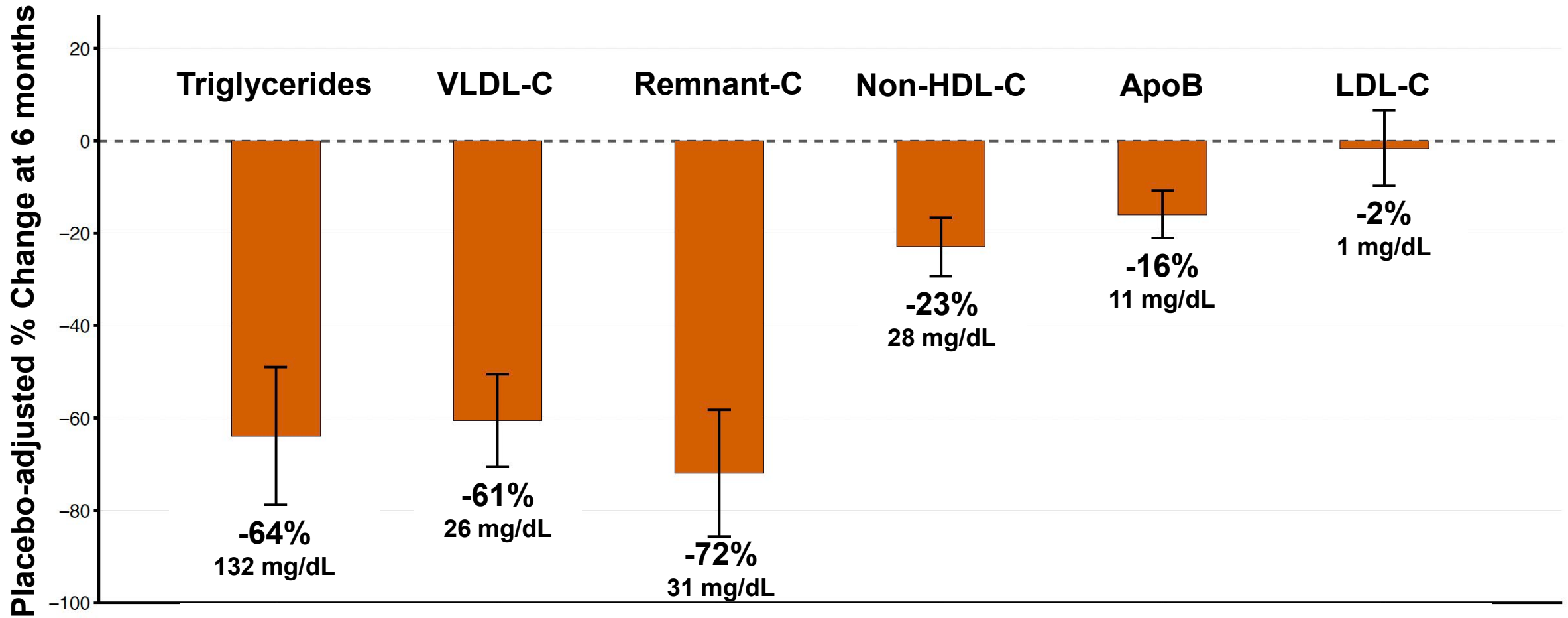
Baseline Plaque Volumes

Plaque Volume (mm ³)	Overall N=468
Non-Calcified	125 (63–213)
Low-Attenuation	4.3 (0.9-14.8)
Calcified	37 (9-102)
Fibrous	107 (53-188)
Fibro-Fatty	5.6 (1.8–13.2)
Total	169 (83-316)

Triglyceride Lowering



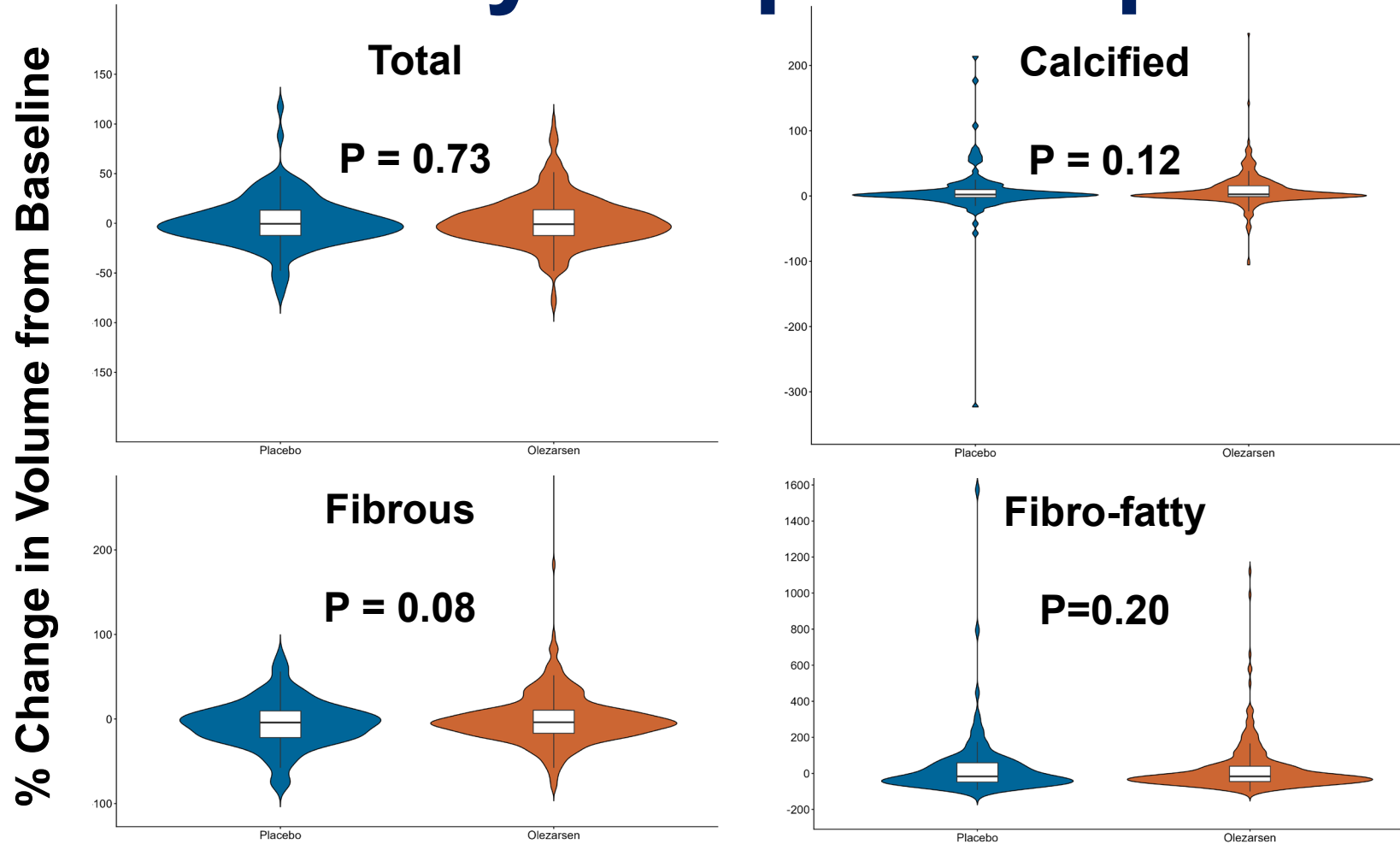
Other Lipid-Lowering Effects



Primary Endpoint: Change in Non-Calcified Plaque Volume

Key Secondary Endpoint: Low Attenuation Plaque Volume

Secondary Plaque Endpoints



Potential Limitations

- Trial duration: 12 month follow up time
- Imaging Modality: CCTA vs invasive imaging (IVUS/OCT)
- Population: No significant plaque progression in the placebo group in the setting of 97% of subjects on background lipid lowering therapy

Summary

Among patients with largely moderate hypertriglyceridemia, treatment with olezarsen on top of standard-of-care lipid-lowering therapy:

- Substantially lowered triglycerides and remnant cholesterol levels
- Modestly lowered apolipoprotein B levels
- Did not affect noncalcified coronary plaque volume at 12 months

Conclusion

- These data do not support the hypothesis that reductions in RC and TRL have an outsized cardiovascular benefit compared with reductions in LDL-C and LDL particles
- Nonetheless, genetic epidemiology links lifelong lower ApoC3 levels with a lower risk of coronary artery disease
- Therefore, a cardiovascular outcomes trial would be required to determine if long-term *APOC3* inhibition reduces CV events



Circulation

Effect of APOC3 Inhibition with Olezarsen on Coronary Atherosclerosis: Essence–TIMI 73b Imaging Study

Nicholas A. Marston, Brian A. Bergmark, Thomas A. Prohaska, Filipe A. Moura, Andre Zimmerman, Veronica J. Alexander, Yu Mi Kang, Julia Weinland, Xinhui Ran, Sabina A. Murphy, Shuanglu Zhang, Dan Li, Maciej Banach, Erik S.G. Stroes, Robert Kiss, Daniel Gaudet, Michal Vrablik, Assen Goudev, Jeroen J. Bax, Matthew J. Budoff, Borek Foldyna, Michael T. Lu, Sotirios Tsimikas, Robert P. Giugliano, Marc S. Sabatine



CIRCULATION. 2026; [PUBLISHED ONLINE AHEAD OF PRINT]. DOI: 10.1161/CIRCULATIONAHA.126.080012

ACC.26