



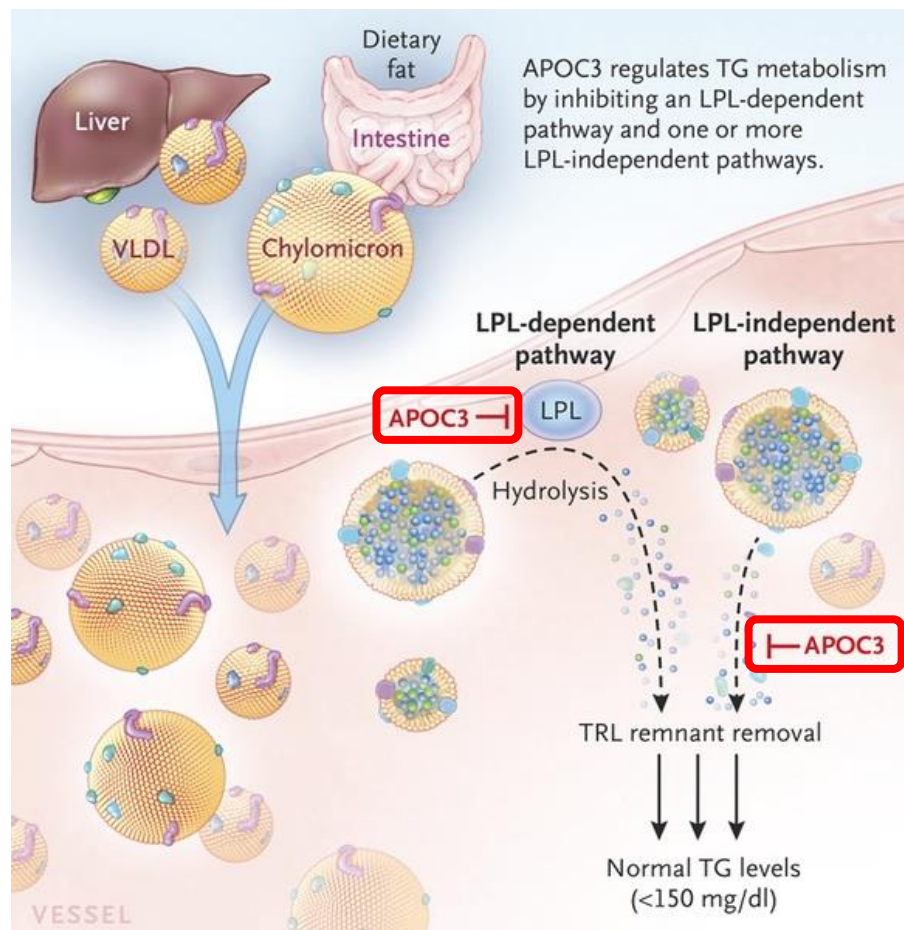
Essence-TIMI 73b

Olezarsen in patients with hypertriglyceridemia at high cardiovascular risk

Brian Bergmark, MD

for the Essence-TIMI 73b Investigators

30 August 2025



Highly effective therapies for reducing levels of TG's are lacking

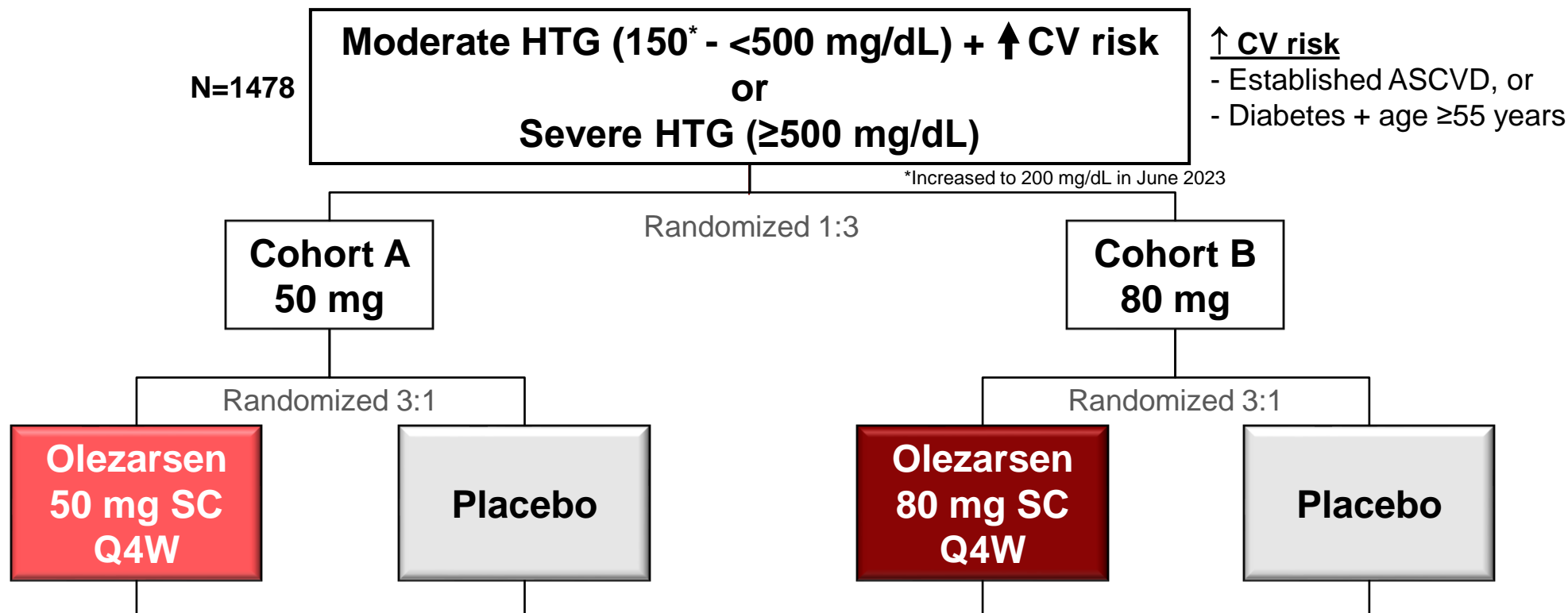
Apolipoprotein C-III

- Synthesized primarily in the liver
- Inhibits metabolism of triglycerides

Olezarsen: GalNAc₃-conjugated ASO targeting APOC3 mRNA

- Approved in the US for TG-lowering in adults with the rare familial chylomicronemia syndrome
- Efficacy and safety in a broader population of patients with hypertriglyceridemia and elevated CV risk are not established

Trial Design



Primary Endpoint: % Δ in triglycerides from baseline to 6 months
Secondary Endpoints: % Δ in apoC-III, apoB, non-HDL-C; % Δ at 12 months
Safety: ALT/AST, renal function, platelets

Primary efficacy analysis population: Patients with baseline triglycerides <500 mg/dL

Primary safety analysis population: All patients receiving at least one dose of study drug

Divide TG value in mg/dL by 88.5 to calculate mmol/L
 Bergmark BA, Marston NA, et al. *Am Heart J*;2025:116-24



Trial Organization



TIMI Study Group

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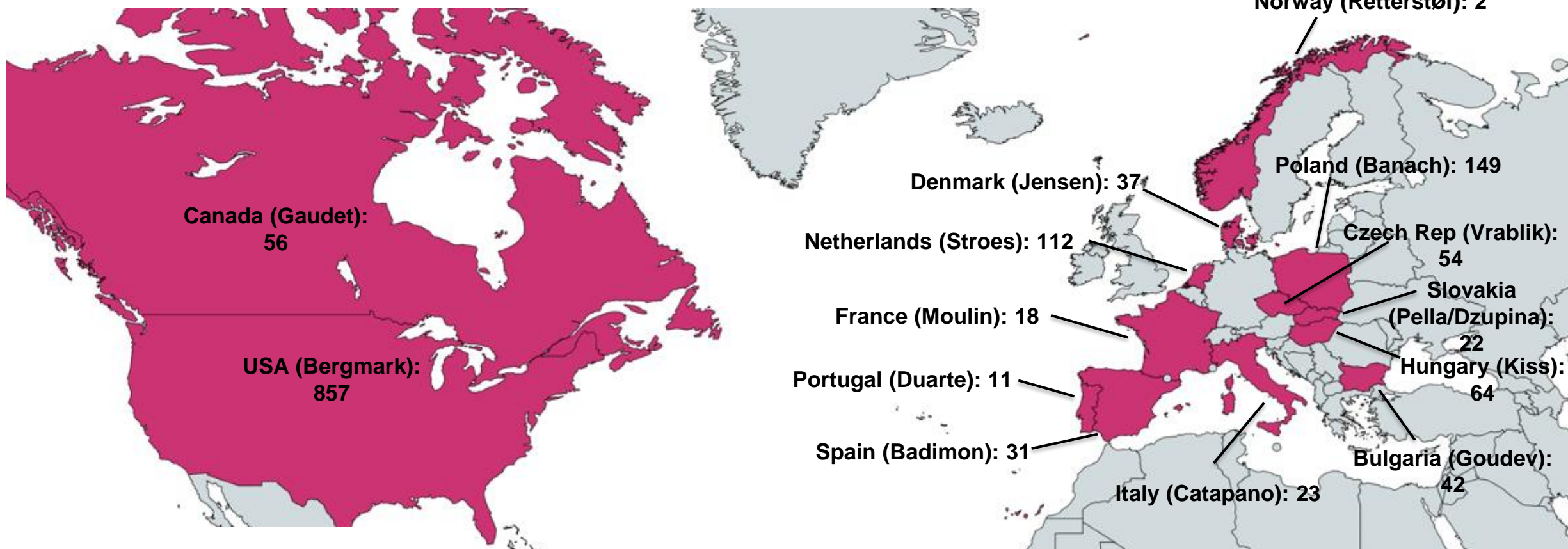
James Freston

Essence-TIMI 73b was supported by a grant from Ionis Pharmaceuticals to Brigham and Women's Hospital.

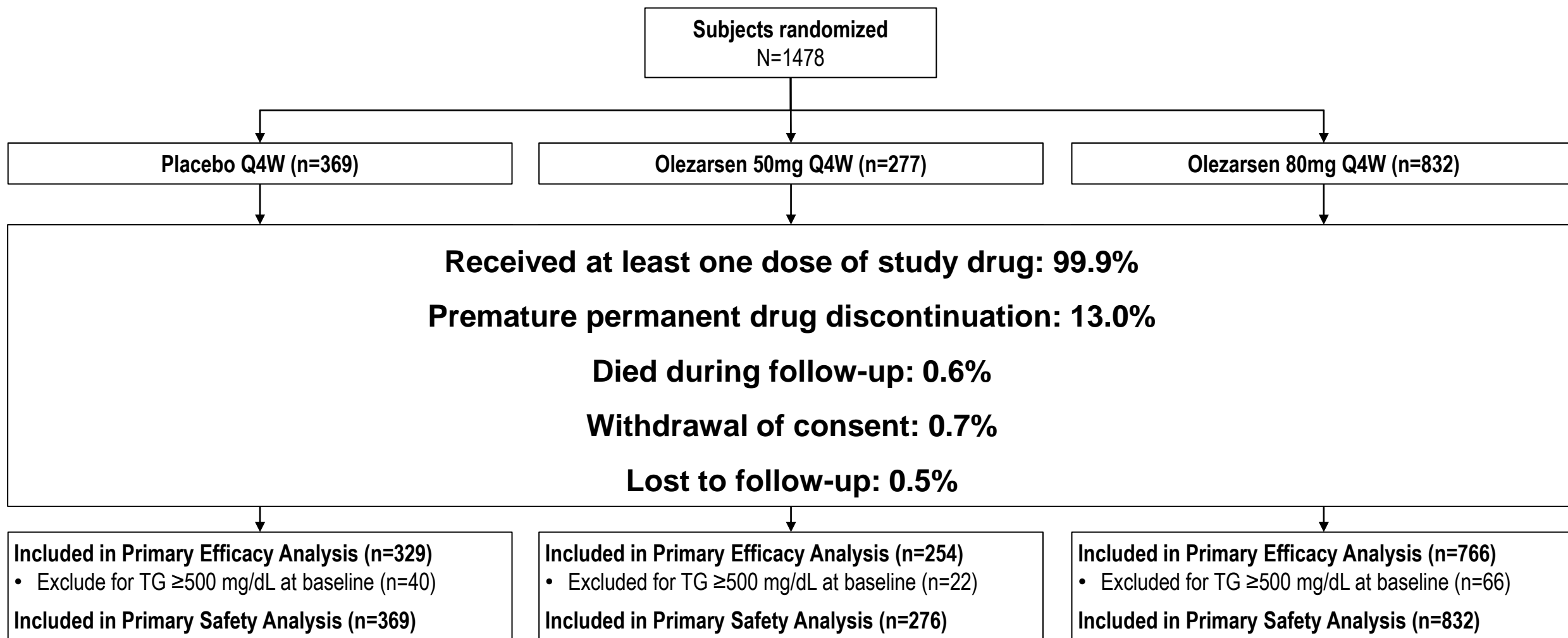


An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

November 2022 – February 2024 | **14 Countries** | **160 Sites** | **1,478 Patients**



Follow-up





Baseline Characteristics



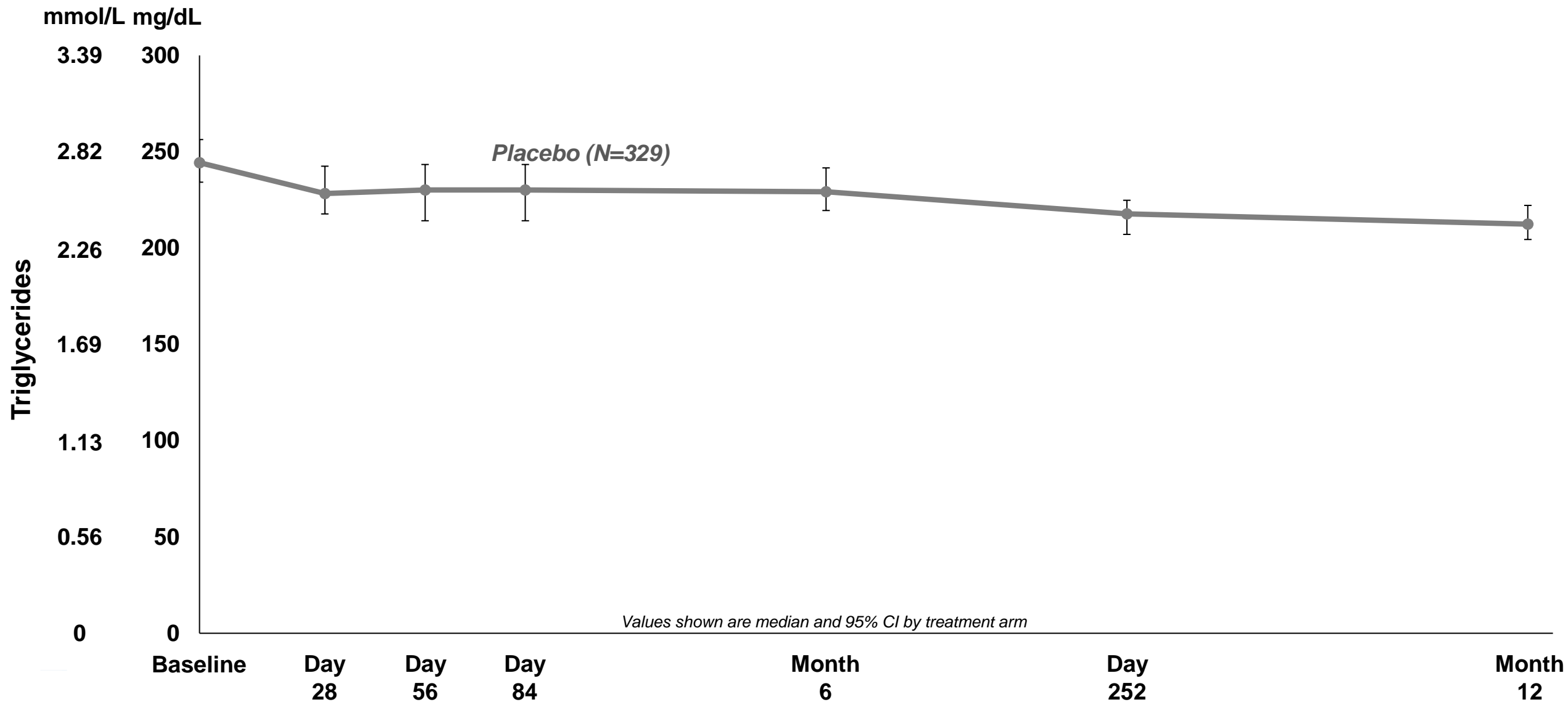
	Overall N=1349
Age (yrs)	64 (56, 70)
Female sex	40
Race/Ethnicity	
White	93
Black	4
Asian	1
Hispanic/Latino	23
Diabetes mellitus	60
Chronic kidney disease	9
Triglycerides (mg/dL)	238.5 (190.5, 307.5)
Triglycerides (mmol/L)	2.7 (2.2, 3.5)
HbA1c (%)	6.2 (5.7, 7.1)

	Overall N=1349
Lipid-lowering therapy	96
Statin	81
Ezetimibe	17
Fibrate	23
Omega-3 fatty acid	17
Niacin	1
PCSK9 inhibitor	5
≥2 therapies	42

Values shown are % or median (IQR) for pooled treatment arms in the primary efficacy cohort
There were no significant differences across treatment arms

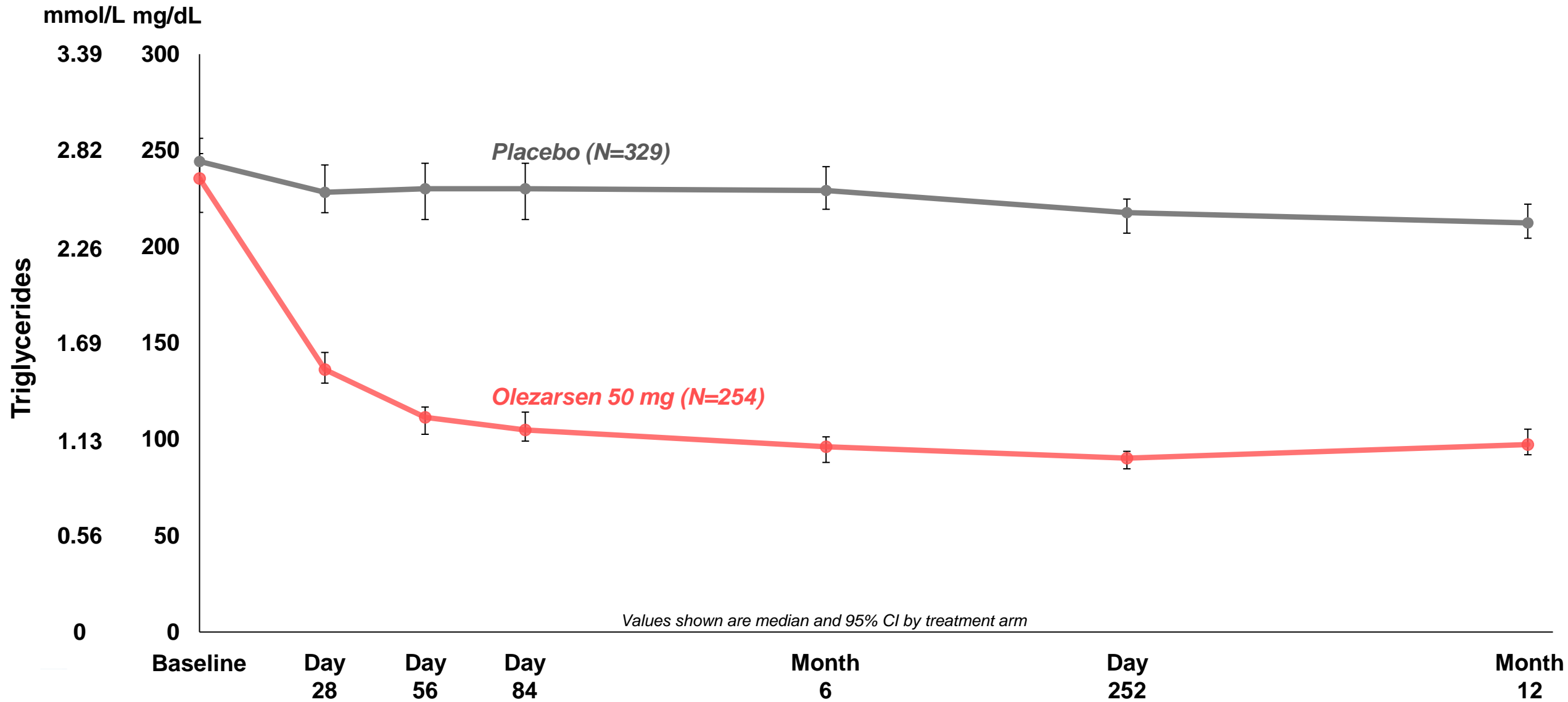


Olezarsen Efficacy



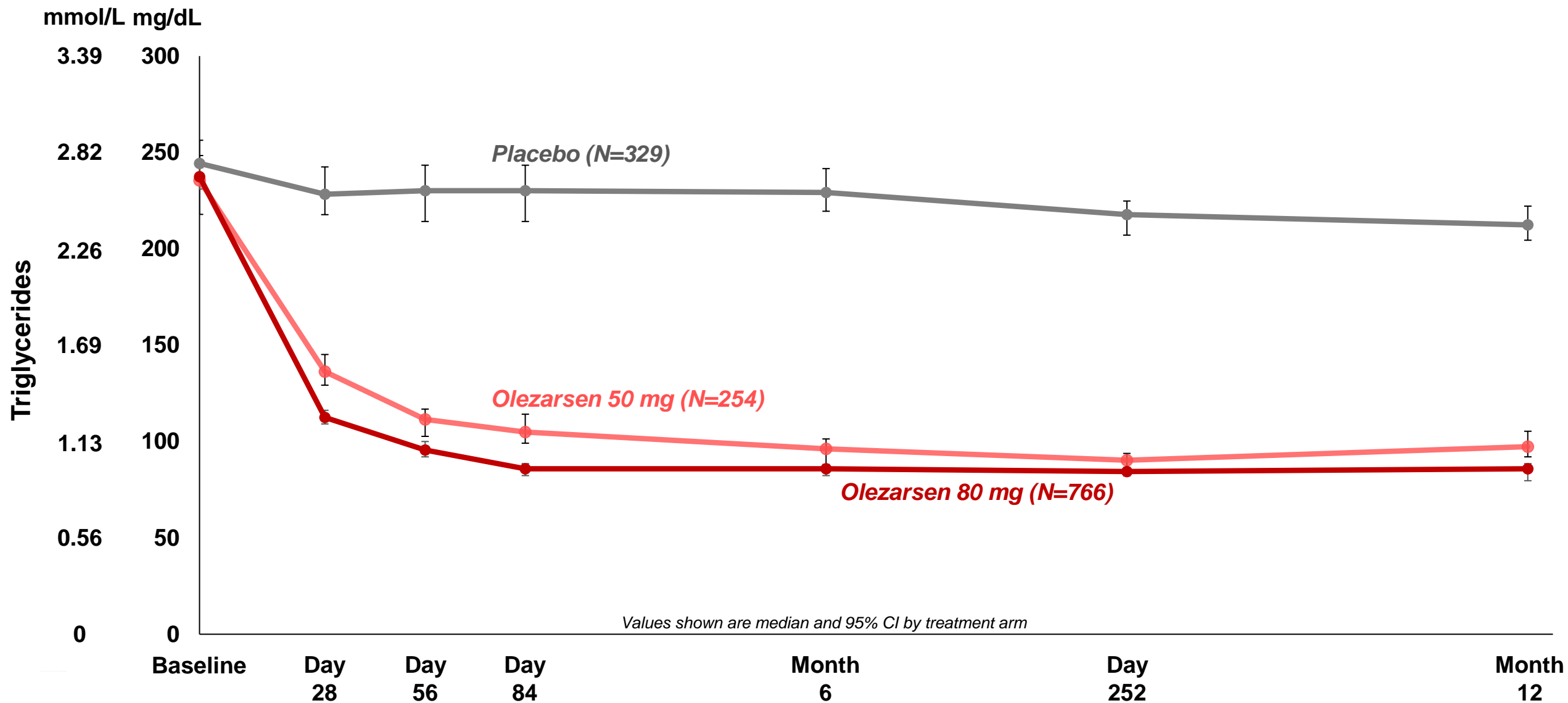


Olezarsen Efficacy



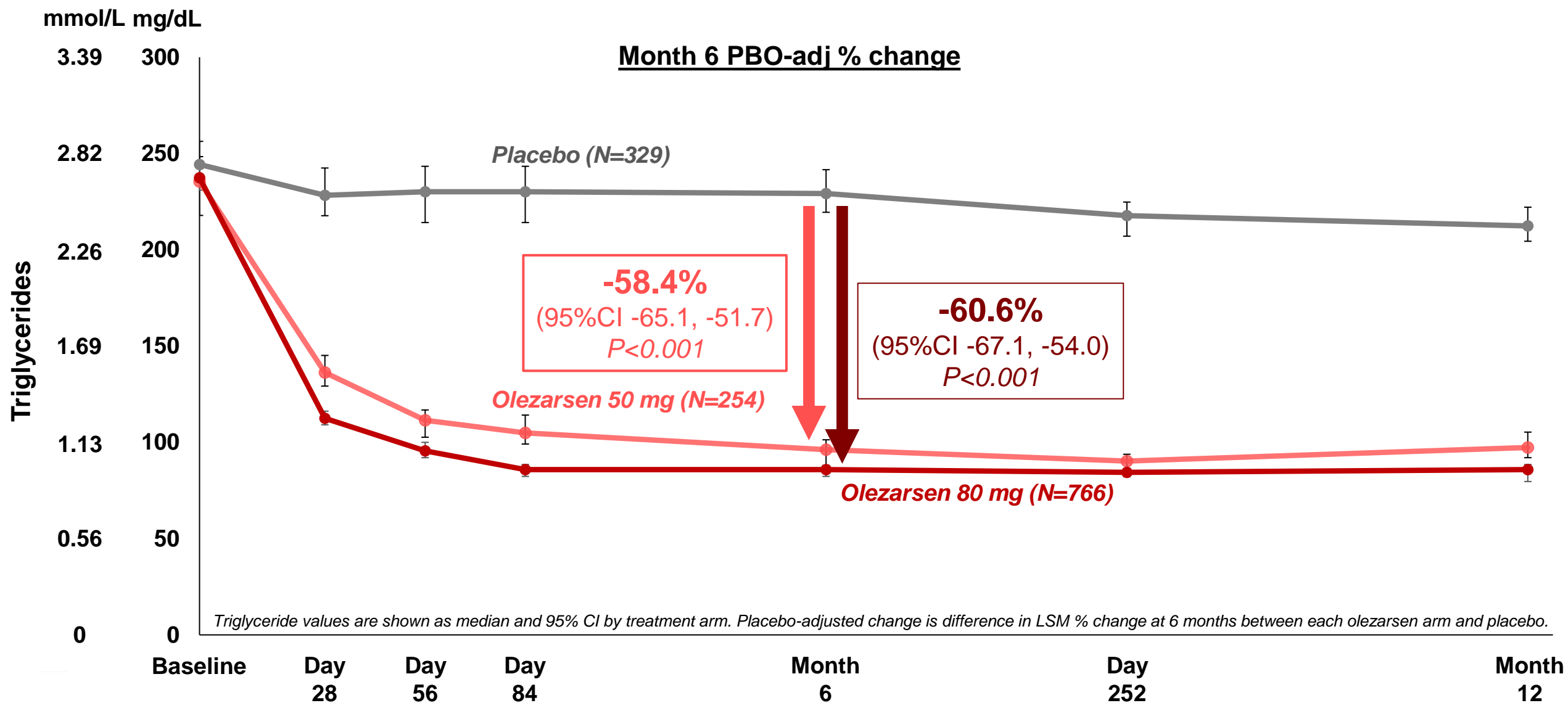


Olezarsen Efficacy



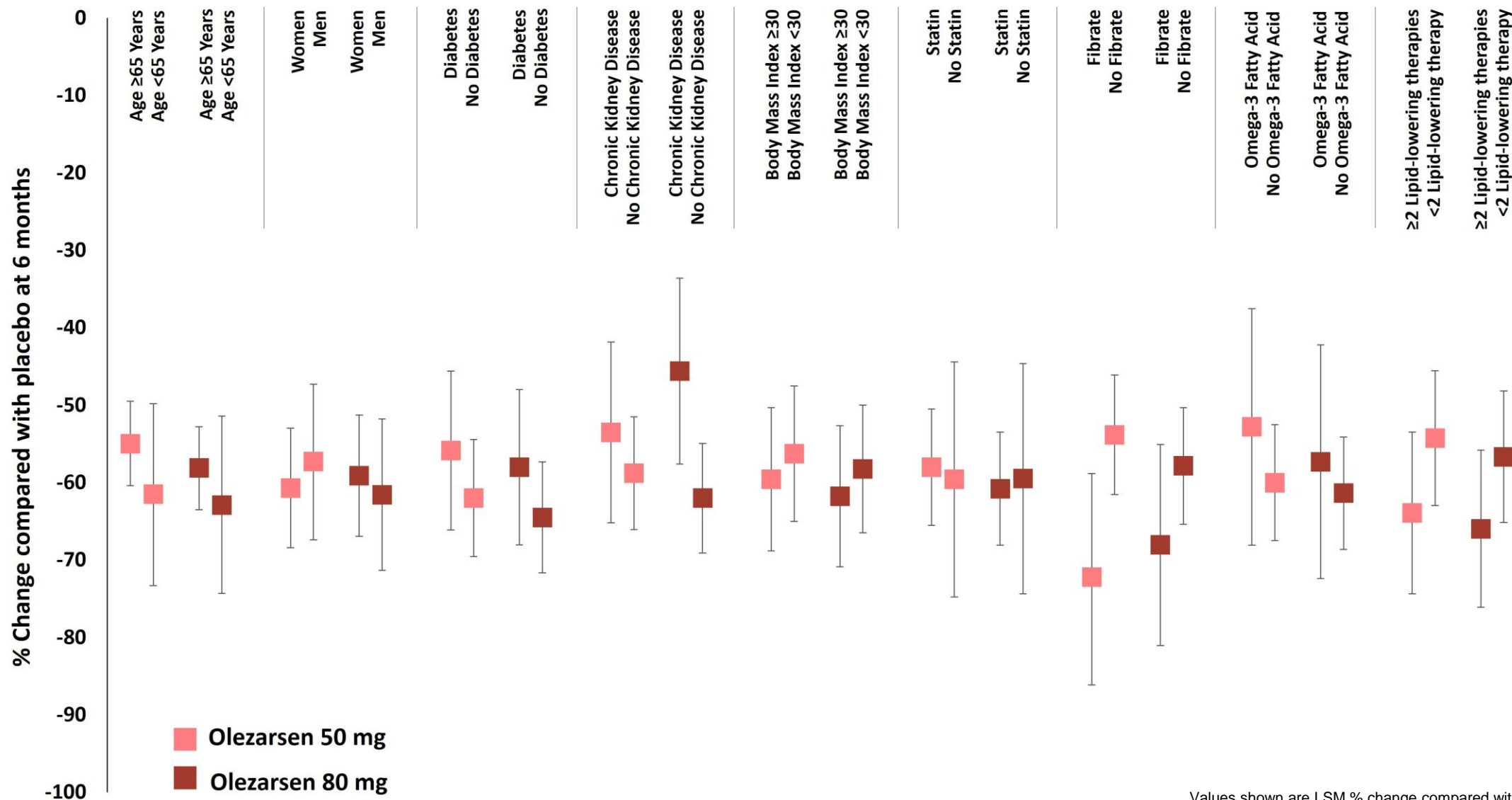


Olezarsen Efficacy





Triglyceride-Lowering in Key Subgroups



Values shown are LSM % change compared with placebo and 95% CI





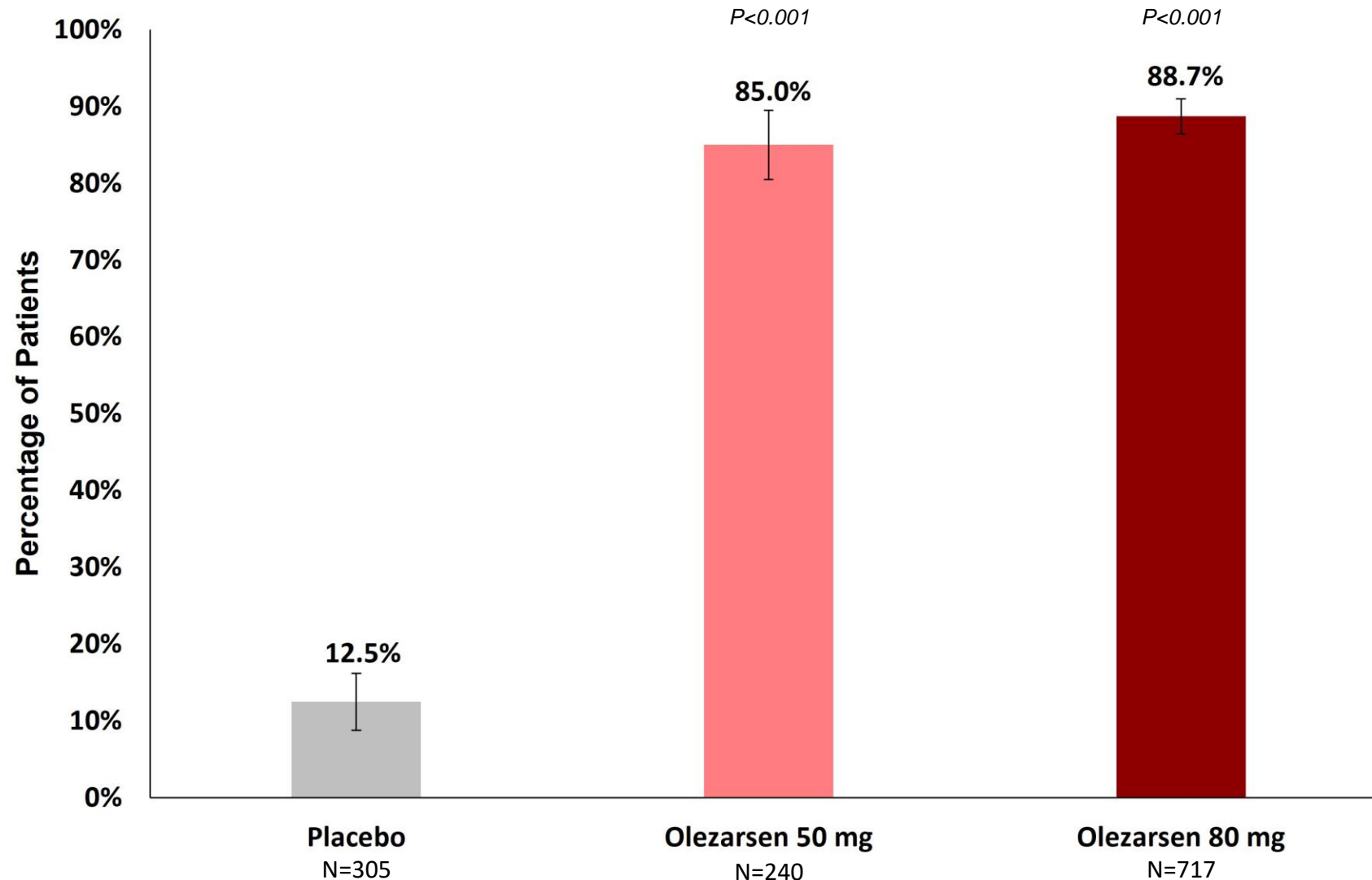
Placebo-adjusted lipid changes at 6 months

Triglycerides





Achieved TG <150 mg/dL (1.69 mmol/L) at 6 months



P values are compared with placebo among patients with available TG values in the primary efficacy cohort





Adjudicated clinical event rates through 12 Months



	Placebo N=329	Olezarsen (pooled) N=1020
Major adverse cardiovascular events		
CV death, MI, ischemic stroke, or arterial revascularization	4.3	5.0
Pancreatitis		
Acute pancreatitis	0	0.3

CV – cardiovascular; MI – myocardial infarction

Event data shown as % in the primary efficacy cohort





Key Safety Parameters



	Placebo N=369	Olezarsen 50 mg N=276	P-value vs Placebo	Olezarsen 80 mg N=832	P-value vs Placebo
Treatment-emergent adverse events					
Any	72	73	0.84	77	0.09
Leading to drug discontinuation	5	4	0.75	7	0.22
Serious	11	9	0.42	14	0.29
Leading to drug discontinuation	1	1	0.70	2	0.49
Injection Site Reaction	2	15	<0.001	16	<0.001
Mild	2	13	<0.001	15	<0.001
Moderate	<1	3	0.006	3	0.002
Severe	0	0	-	0	-

Treatment phase data in the safety cohort shown as %





Key Safety Parameters



	Placebo N=369	Olezarsen 50 mg N=276	P-value vs Placebo	Olezarsen 80 mg N=832	P-value vs Placebo
Hepatic abnormalities*					
ALT or AST ≥ 3 x ULN	1	3	0.12	2	0.15
ALT or AST ≥ 5 x ULN	<1	1	0.58	<1	0.99
Total bilirubin ≥ 2 x ULN	<1	<1	0.99	<1	0.52
Renal abnormalities					
eGFR decline $\geq 50\%$	1	<1	0.99	1	0.73
UPCR ≥ 1000 mg/g	2	1	0.77	2	0.98
UPCR ≥ 3000 mg/g	0	<1	0.43	<1	0.99
Platelet count reductions					
<100K/uL	1	2	0.18	2	0.10
<75K/uL	<1	1	0.32	1	0.68
<50K/uL	<1	0	0.99	<1	0.52

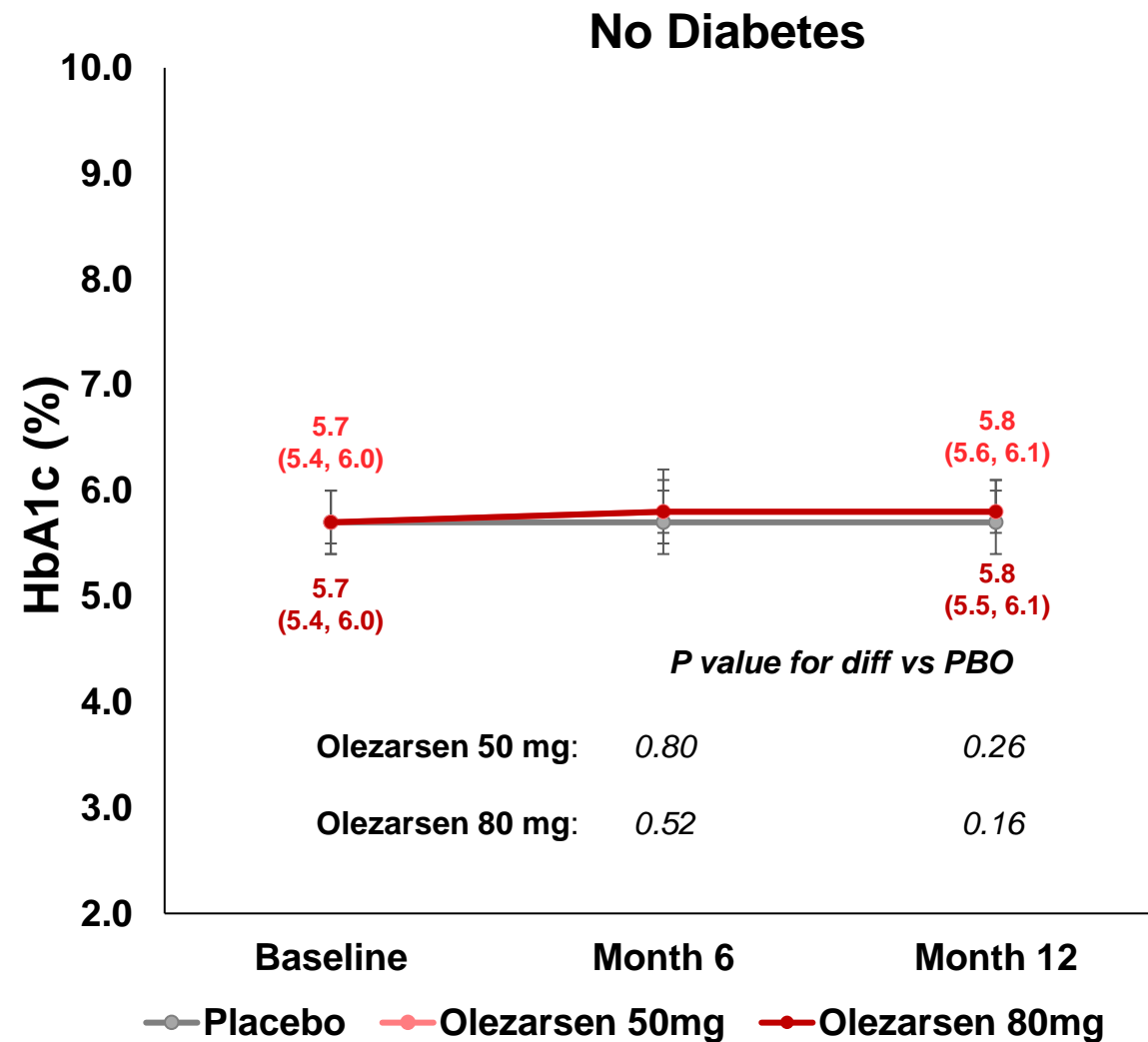
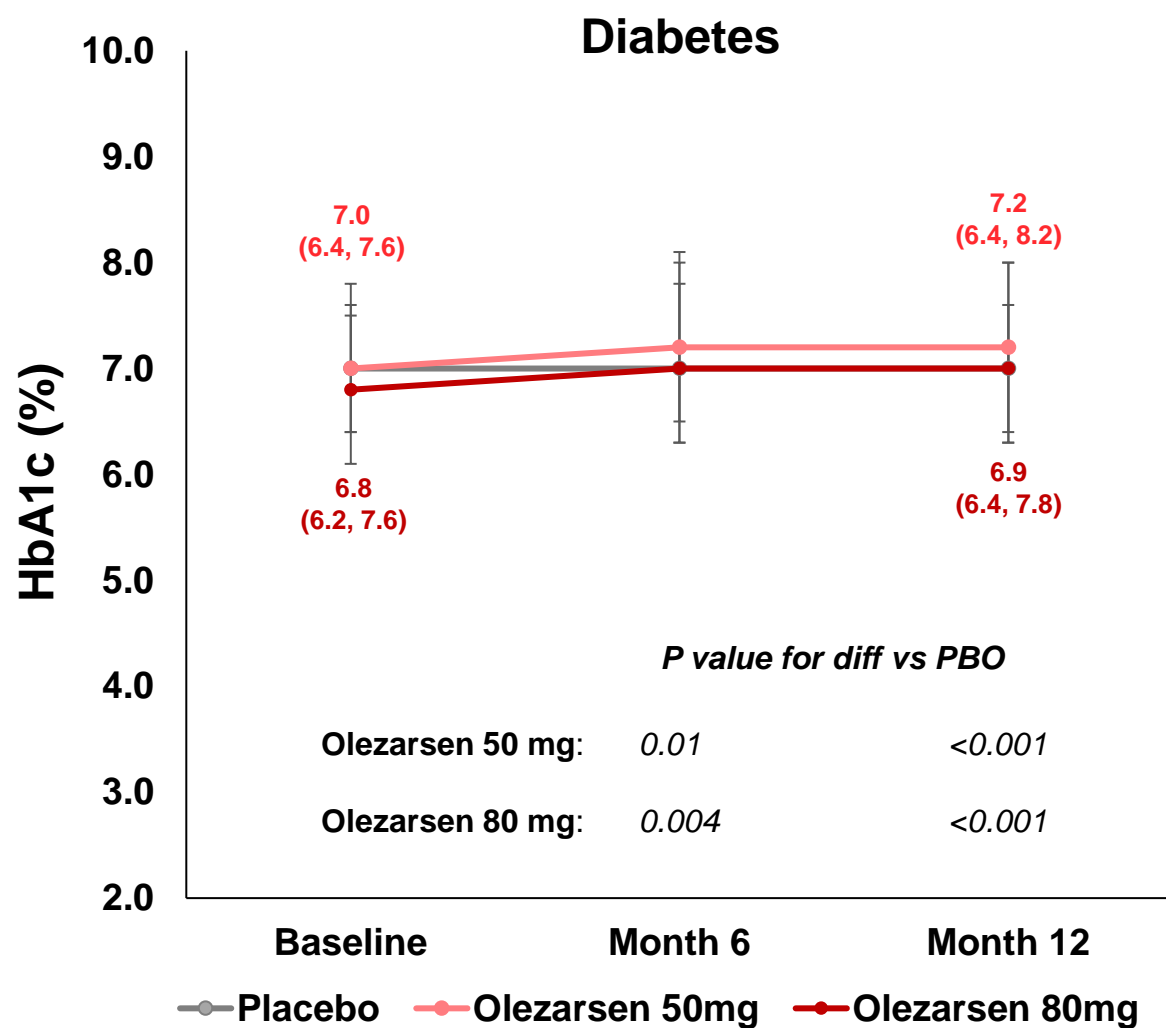
*There were no cases meeting Hy's Law criteria

Treatment phase data in the safety cohort shown as %





Glycemic control



Trial primarily designed to assess olezarsen among patients with moderate hypertriglyceridemia rather than across full range of triglyceride levels

Two phase 3 trials are specifically evaluating olezarsen in patients with severe (≥ 500 mg/dL | 5.65 mmol/L) hypertriglyceridemia (NCT05079919 and NCT05552326)

Efficacy & safety of olezarsen beyond one year of treatment not assessed

A longer-term open-label extension program among patients with severe hypertriglyceridemia is underway (NCT05681351)



Summary and Conclusions



In patients with moderate hypertriglyceridemia and heightened cardiovascular risk, olezarsen reduced triglyceride levels by approximately 60%

- *TG effect was greater than is possible with current standard of care therapies*
- *~70% reduction in remnant cholesterol*
- *Significant reductions in apoB and non-HDL-C*
- *No major safety concerns*

Findings support efficacy & safety of olezarsen for triglyceride-lowering in a broad population of patients with moderately elevated triglycerides





ORIGINAL ARTICLE

Targeting *APOC3* with Olezarsen in Moderate Hypertriglyceridemia

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