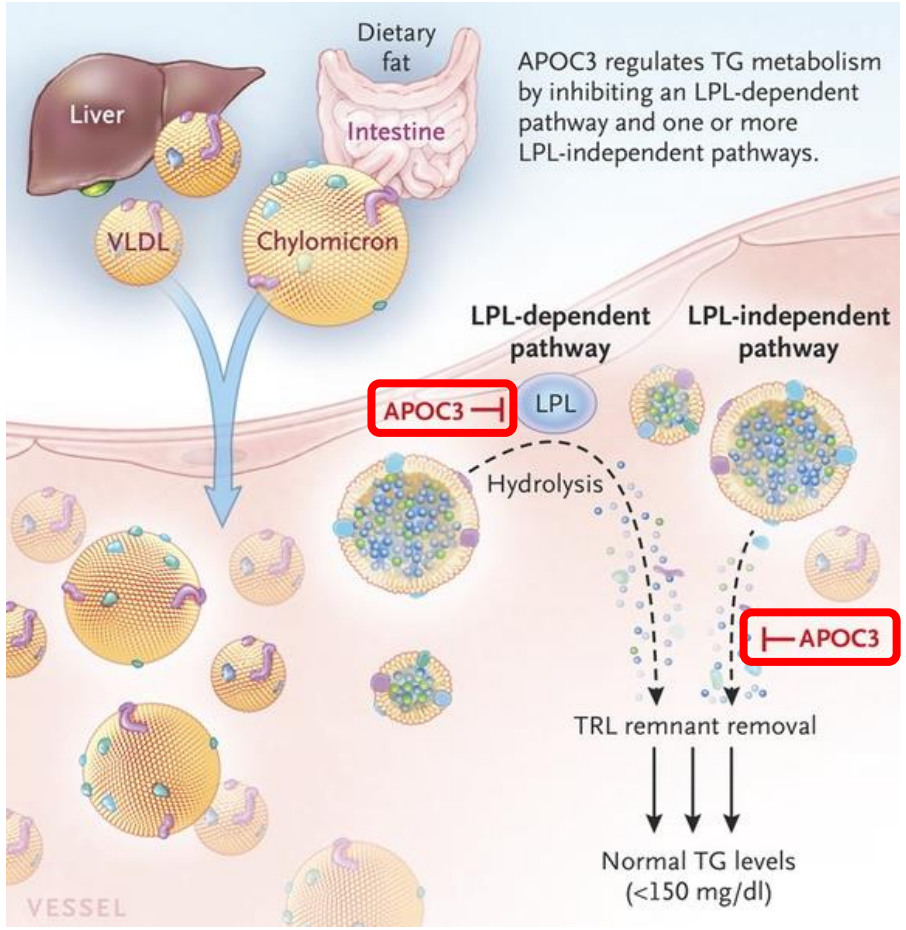
Essence-TIMI 73b

Olezarsen in patients with hypertriglyceridemia at high cardiovascular risk

Brian Bergmark, MD
for the Essence-TIMI 73b Investigators

30 August 2025

Background



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

Apolipoprotein C-III

- Synthesized primarily in the liver
- Inhibits metabolism of triglycerides

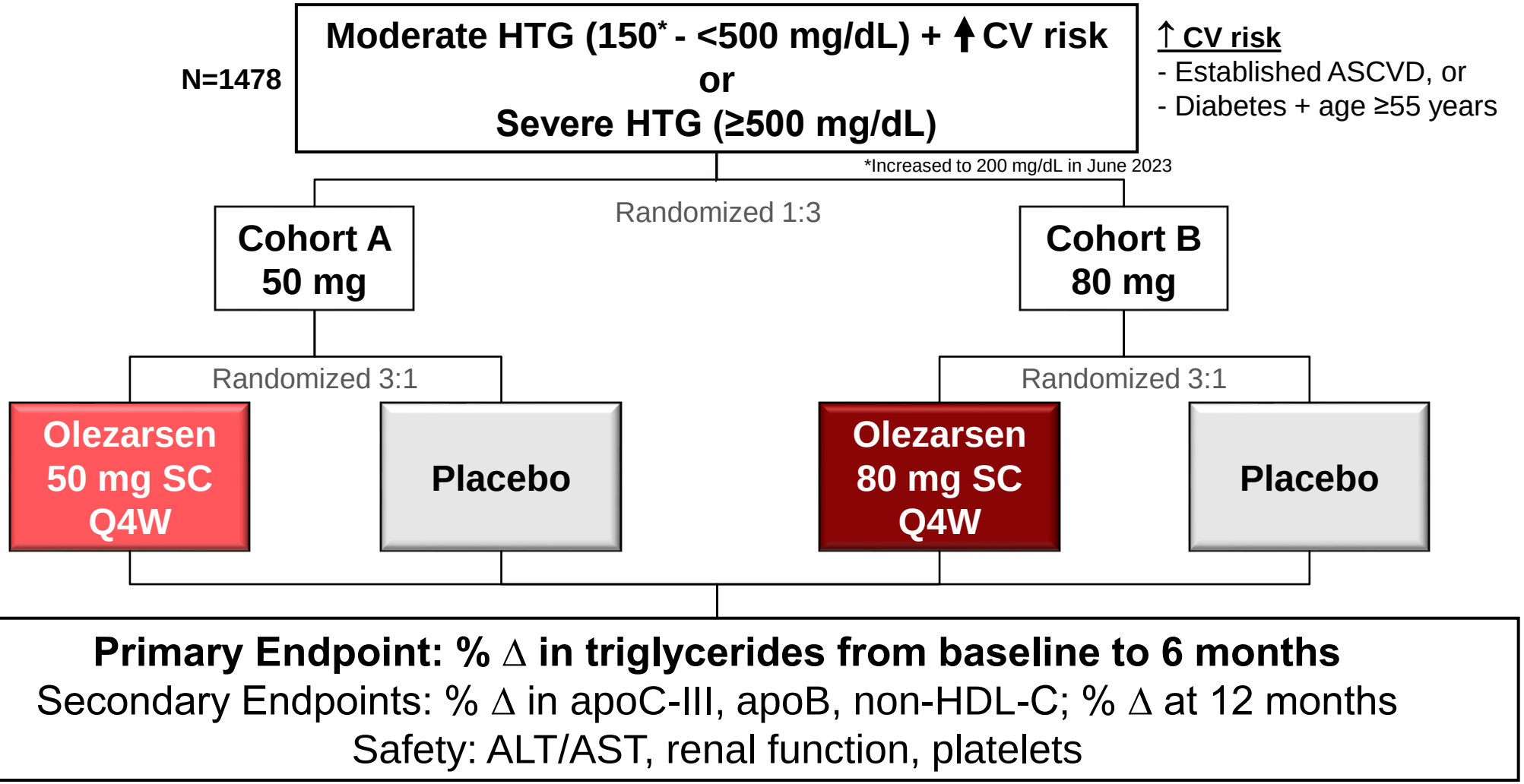
Olezarsen: $GalNAc_3$-conjugated ASO targeting *APOC3* mRNA

- 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

ASO, antisense oligonucleotide
TG, triglycerides

Gaudet D, et al. *N Engl J Med*. 2014;371:2200-6
Stroes ESG, et al. *N Engl J Med*. 2024;390:1781-92
Bergmark BA, et al. *N Engl J Med*. 2024;390:1770-80

Trial Design



***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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Sponsor: Ionis

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Dan Li (Stats)

Independent Data Monitoring Committee

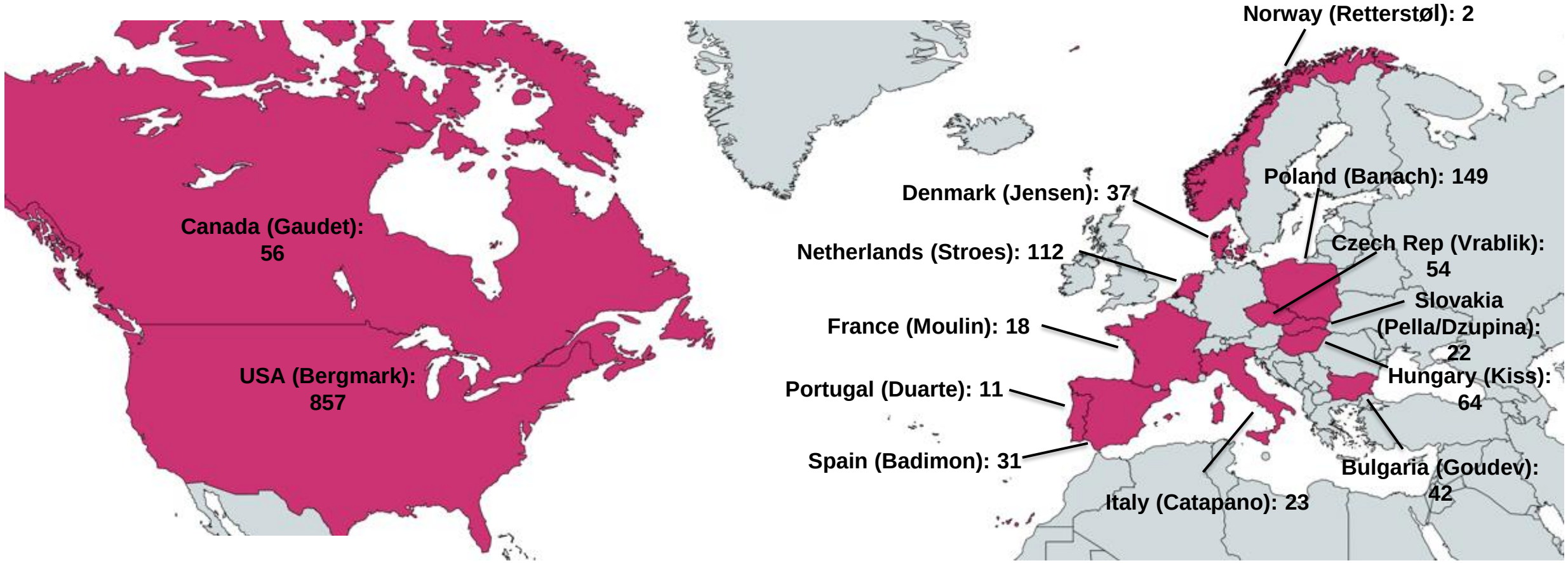
Richard Becker (Chair)
Jamie Dwyer
Willis Maddrey

Charles Davis (Statistician)
François Mach
James Freston

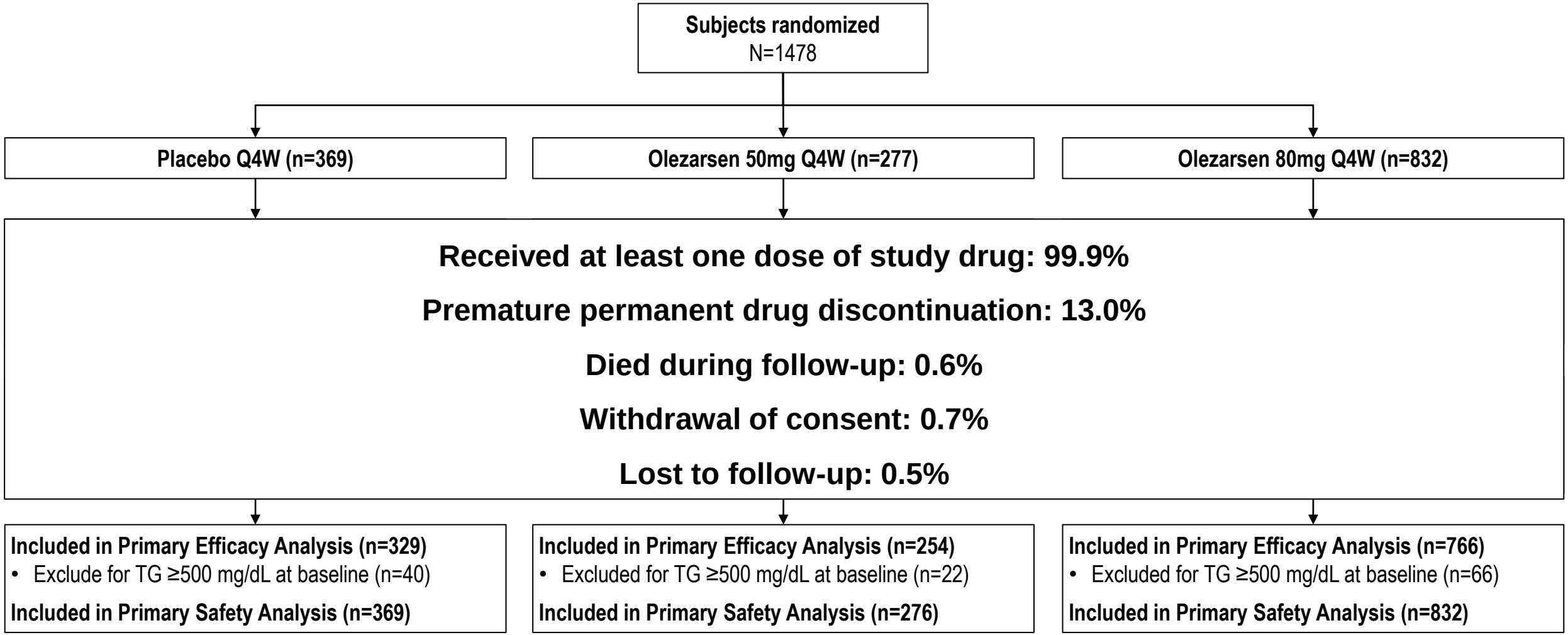
Essence-TIMI 73b was supported by a grant from Ionis Pharmaceuticals to Brigham and Women's Hospital.

Enrollment

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



Follow-up



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
*No deaths attributed to study medication by site investigator

Divide TG value in mg/dL by 88.5 to calculate mmol/L

Baseline Characteristics

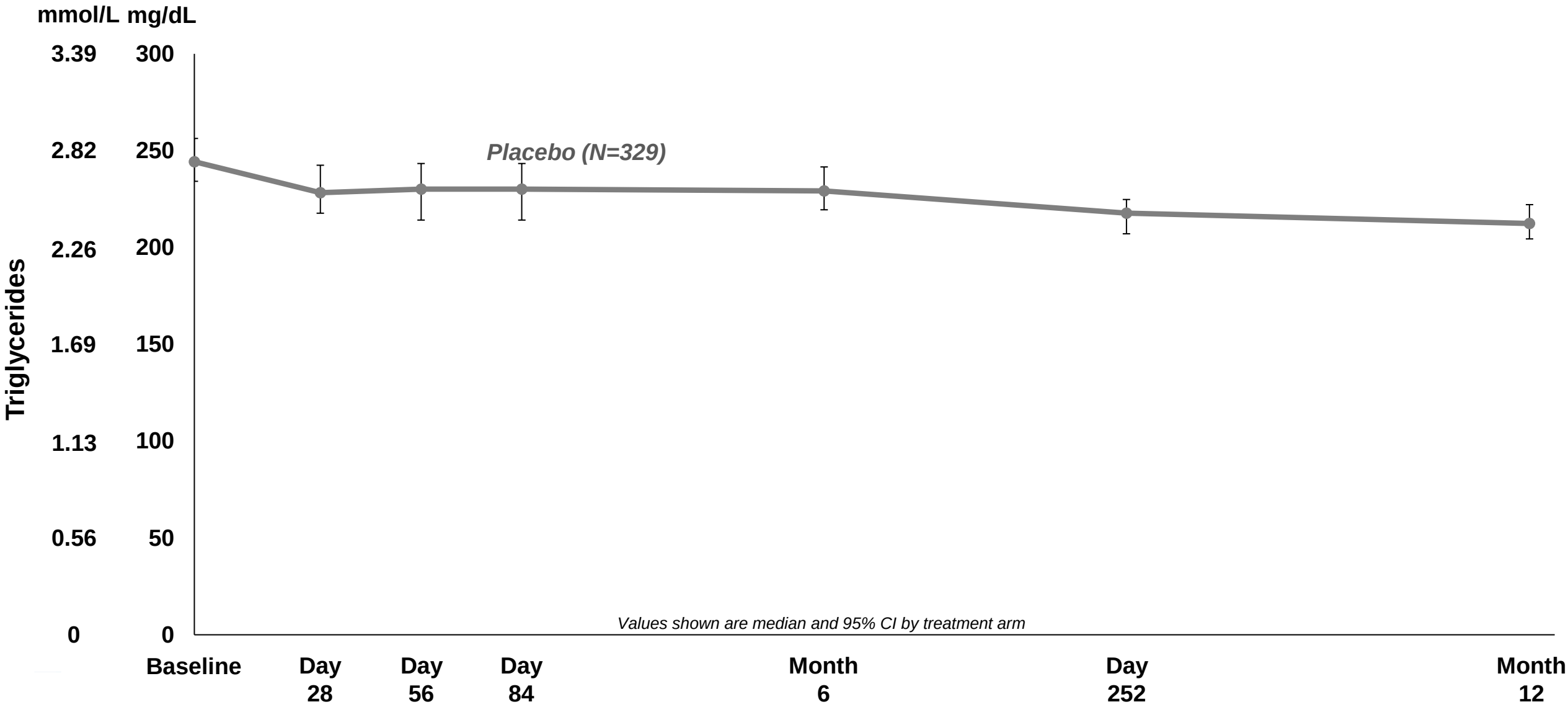
	Overall N=1349
Age (yrs)	64 (56, 70)
Female sex	40
Race/Ethnicity	
White	93
Black	4
Asian	1
Hispanic/Latino	23
Diabetes mellitus	60
Chronic kidney disease	9
Triglycerides (mg/dL)	238.5 (190.5, 307.5)
Triglycerides (mmol/L)	2.7 (2.2, 3.5)
HbA1c (%)	6.2 (5.7, 7.1)

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

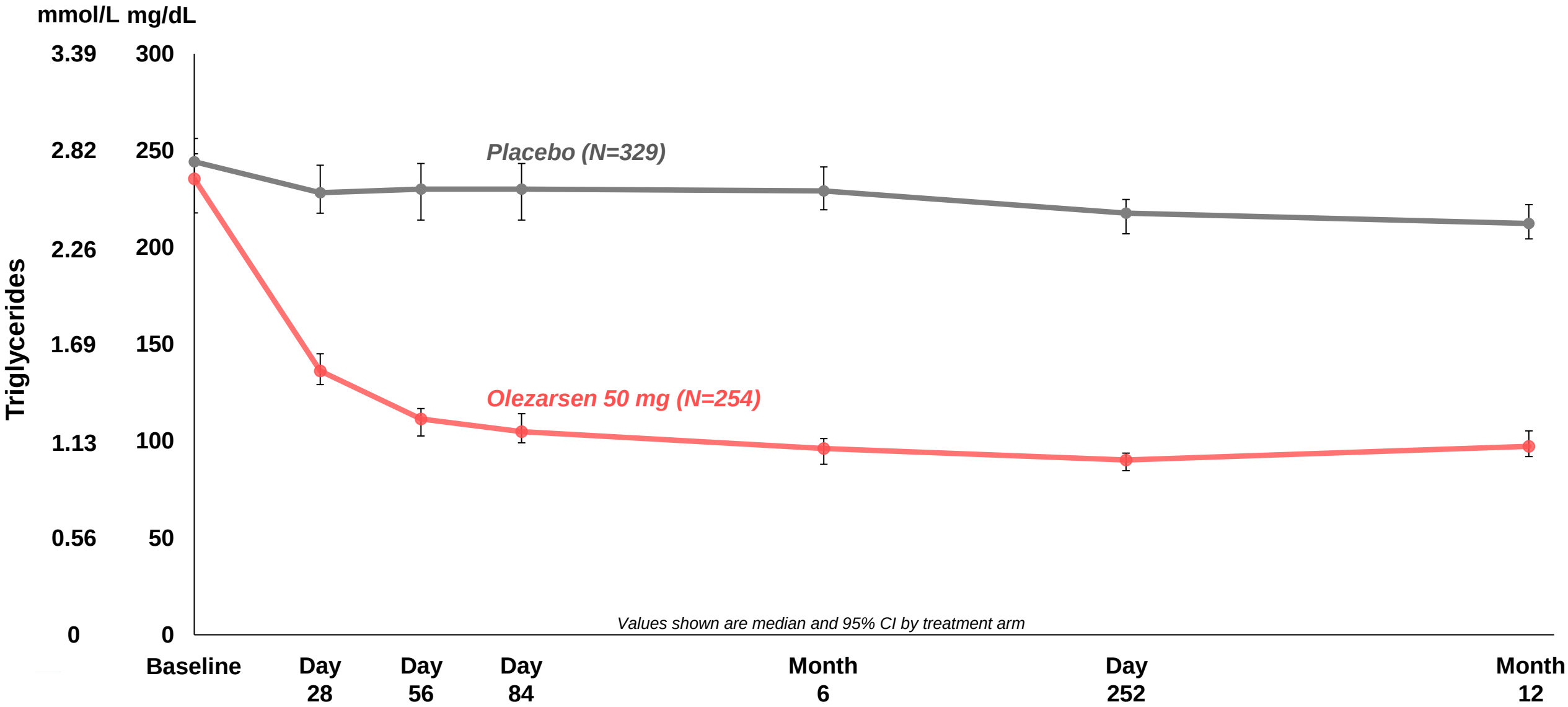
	Overall N=1349
Lipid-lowering therapy	96
Statin	81
Ezetimibe	17
Fibrate	23
Omega-3 fatty acid	17
Niacin	1
PCSK9 inhibitor	5
≥2 therapies	42

Divide TG value in mg/dL by 88.5 to calculate mmol/L

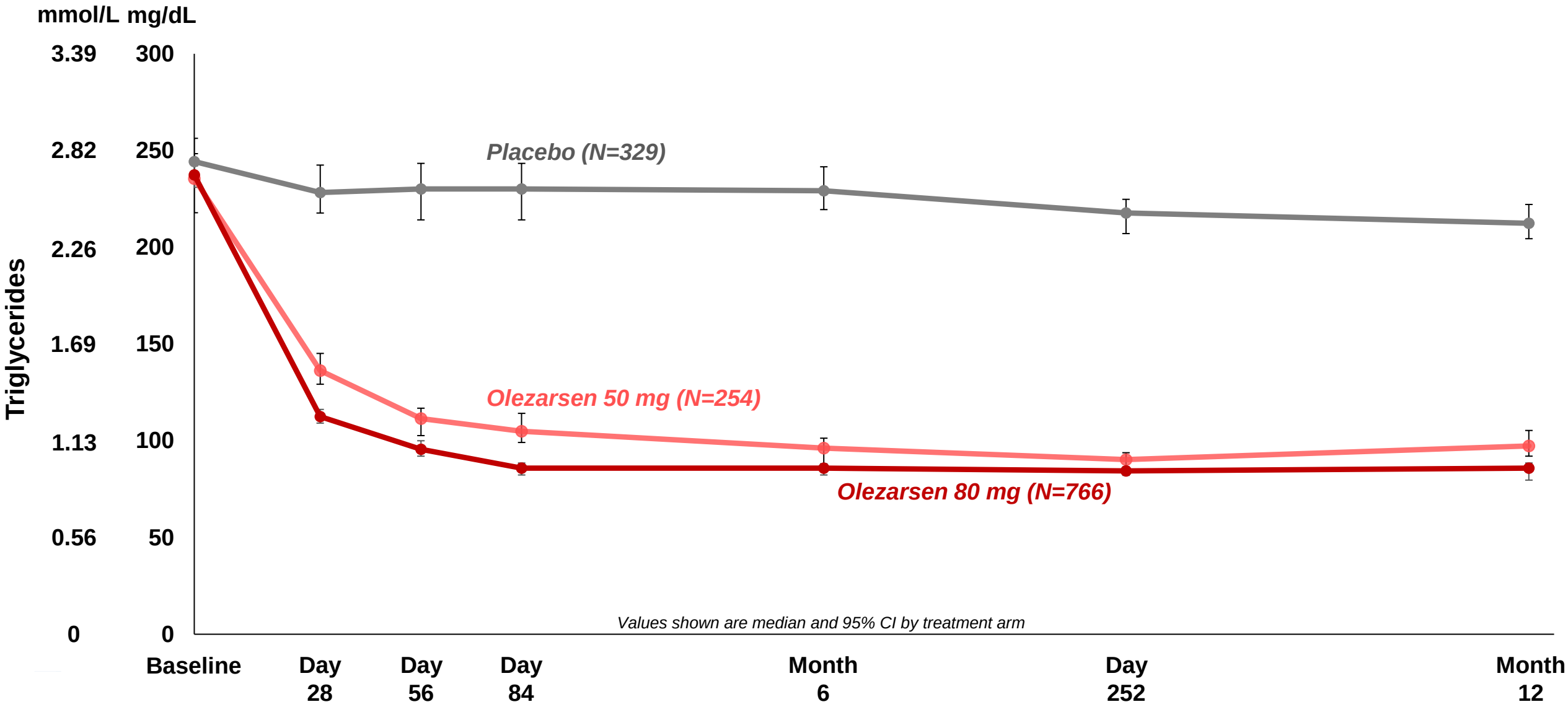
Olezarsen Efficacy



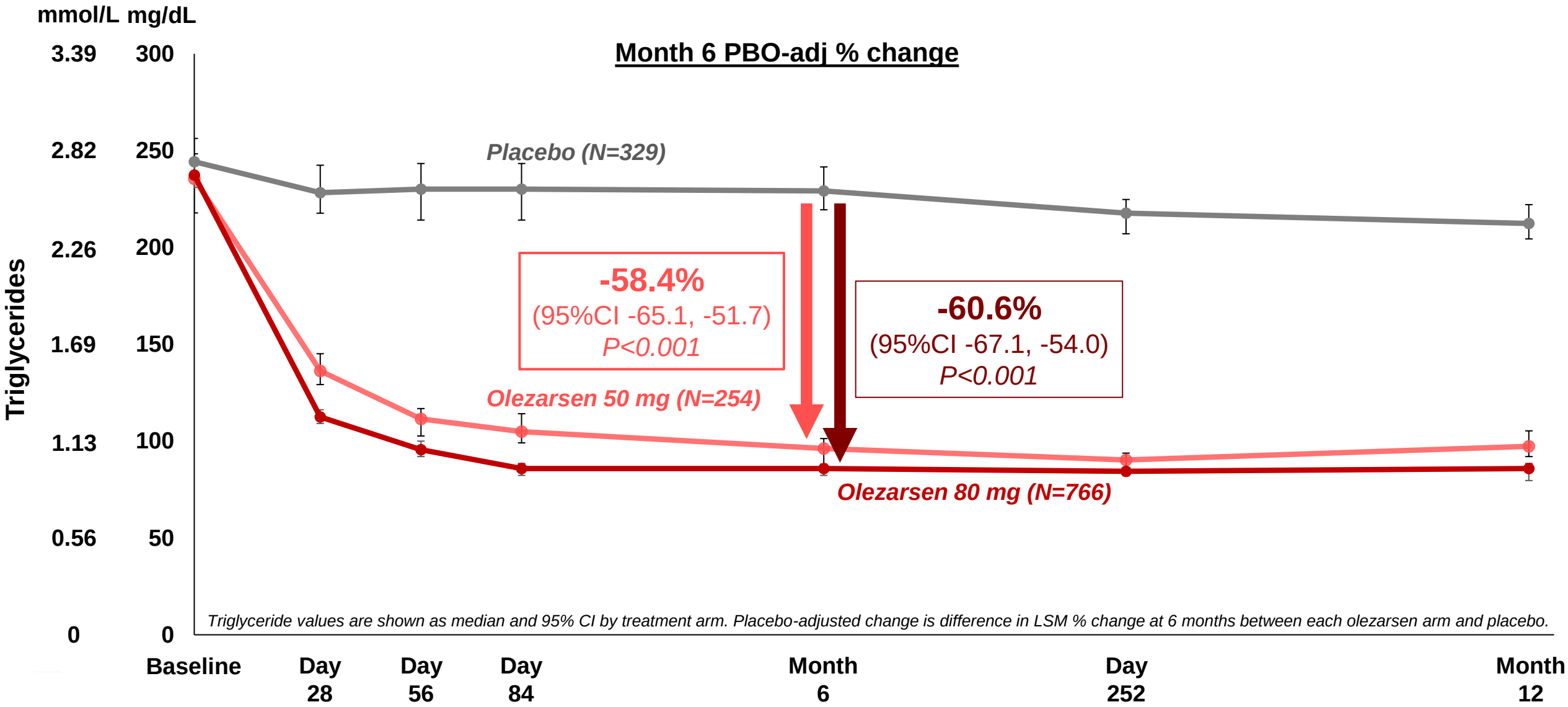
Olezarsen Efficacy



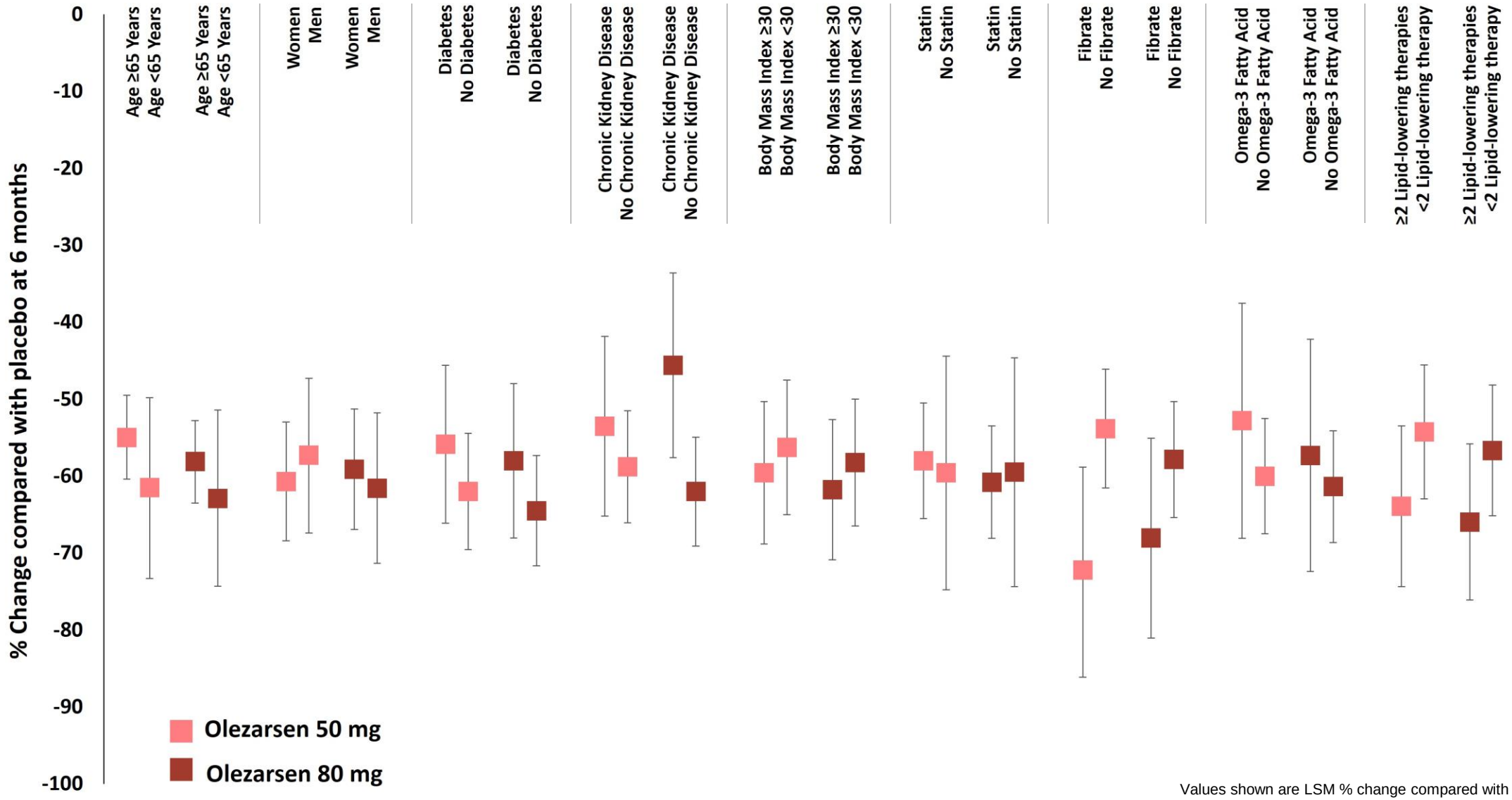
Olezarsen Efficacy



Olezarsen Efficacy



Triglyceride-Lowering in Key Subgroups

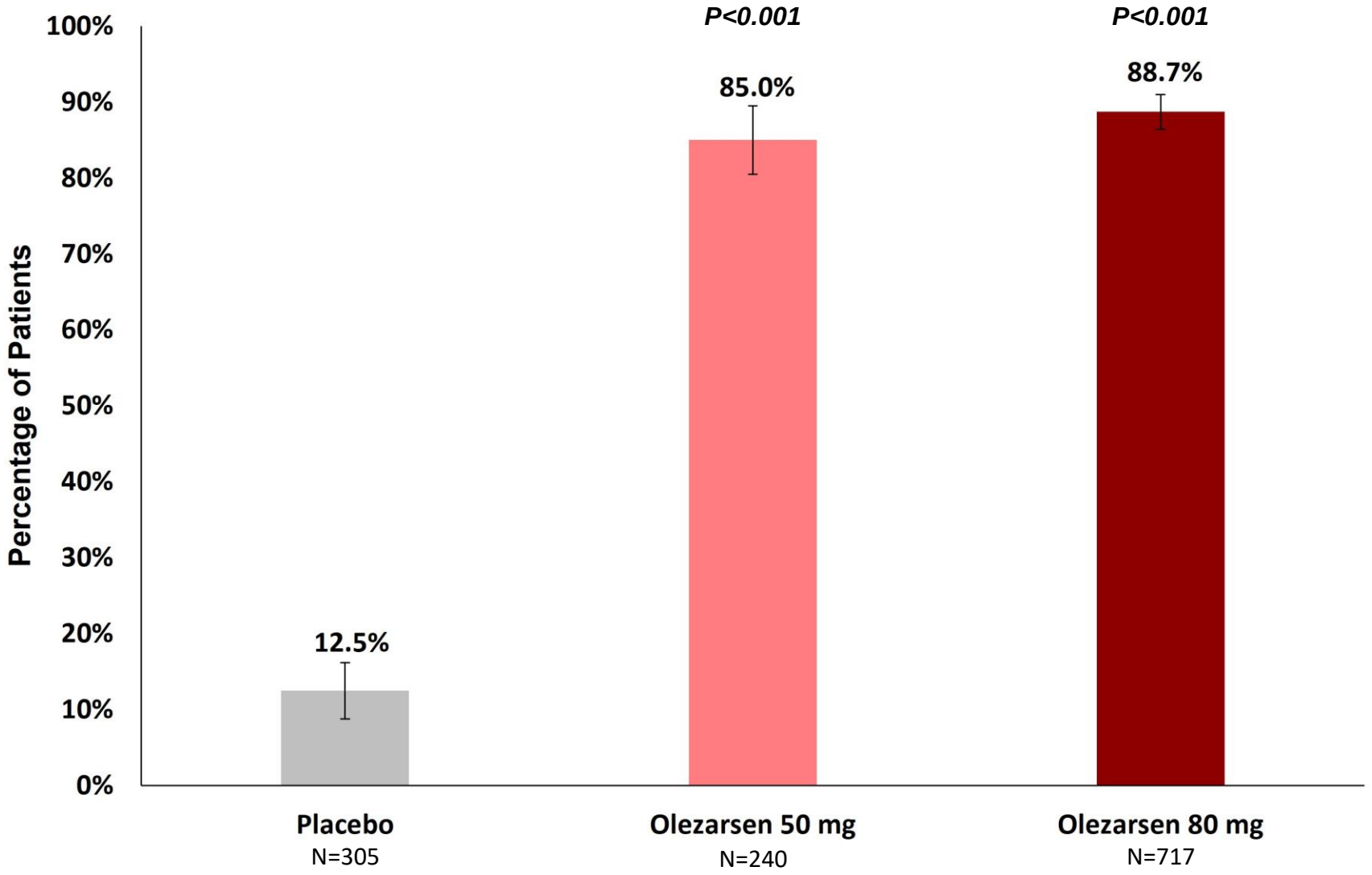


Values shown are LSM % change compared with placebo and 95% CI

Placebo-adjusted lipid changes at 6 months

Values shown are LSM % change compared with placebo and 95% CI in the primary efficacy cohort. Remnant cholesterol was measured directly.

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 %

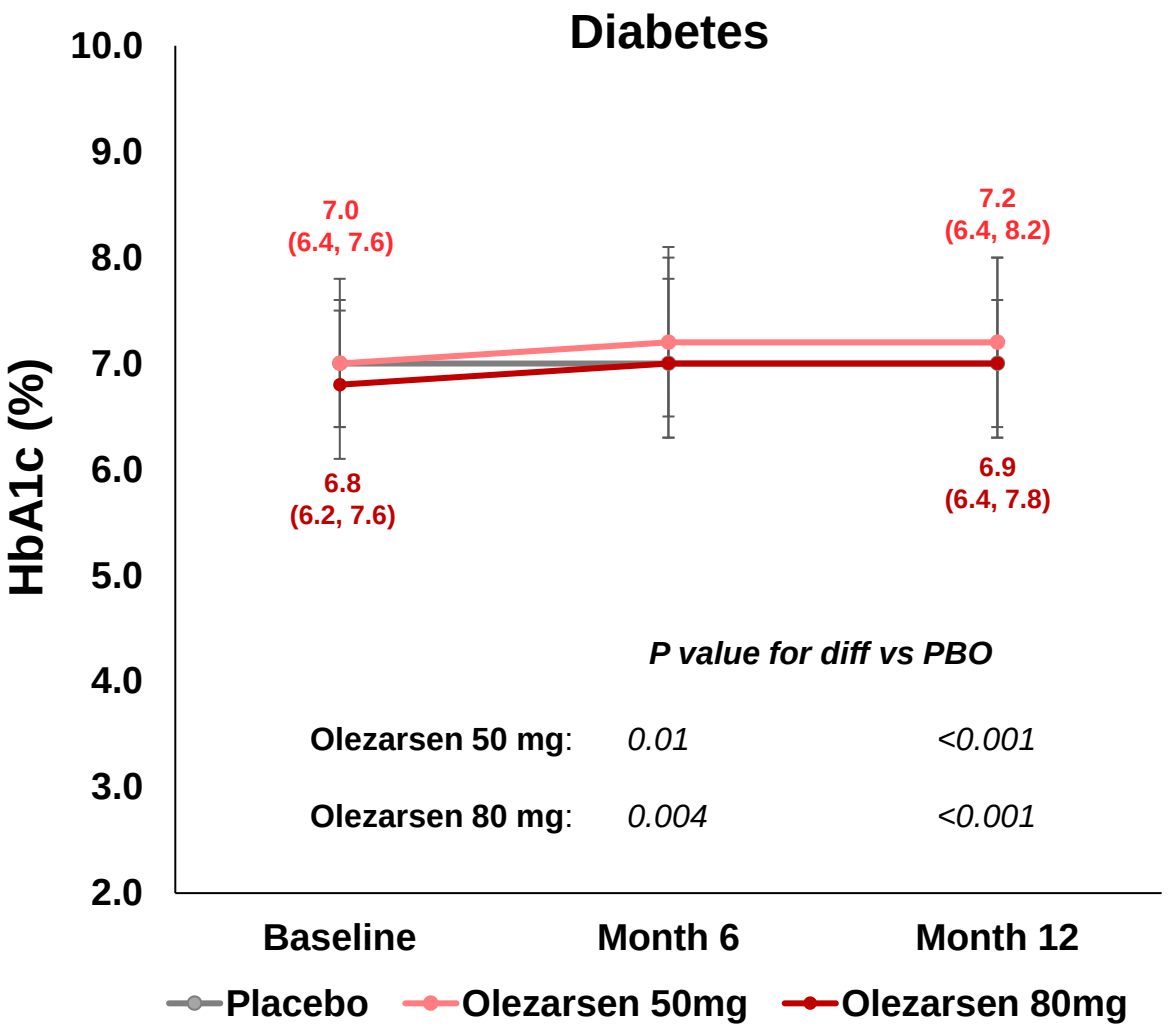
Key Safety Parameters

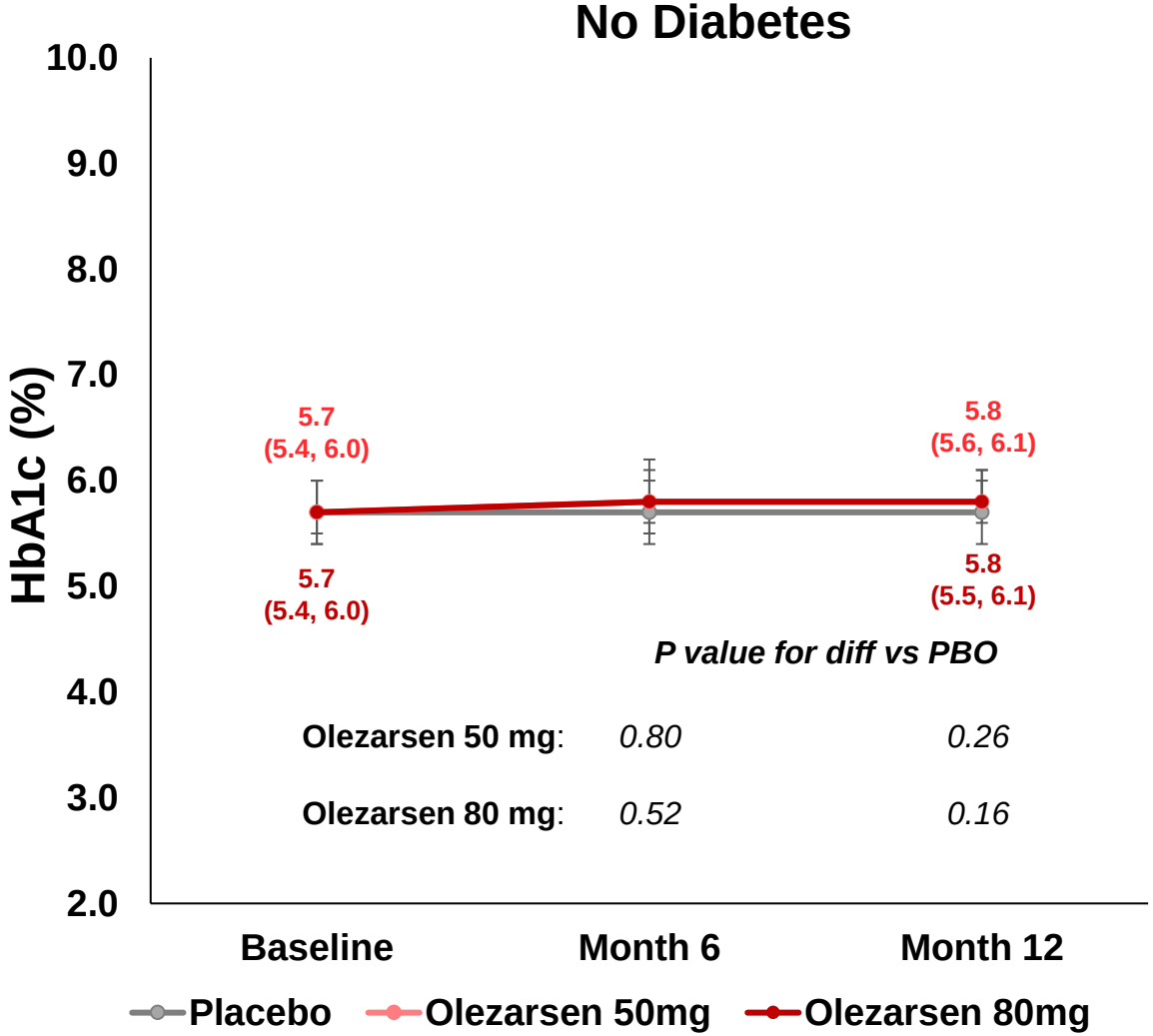
	Placebo N=369	Olezarsen 50 mg N=276	P-value vs Placebo	Olezarsen 80 mg N=832	P-value vs Placebo
Hepatic abnormalities*					
ALT or AST ≥3x ULN	1	3	0.12	2	0.15
ALT or AST ≥5x ULN	<1	1	0.58	<1	0.99
Total bilirubin ≥2x ULN	<1	<1	0.99	<1	0.52
Renal abnormalities					
eGFR decline ≥50%	1	<1	0.99	1	0.73
UPCR ≥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





Median (IQR) shown at each time point

Limitations

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)

Marston N, et al. *Am Heart J*. 2025;286:125-35

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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Targeting *APOC3* with Olezarsen in Moderate Hypertriglyceridemia

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