ACC.24

Bridge – TIMI 73a

Olezarsen in patients with hypertriglyceridemia at high cardiovascular risk

Brian Bergmark, MD

For the Bridge–TIMI 73 Investigators

AMERICAN COLLEGE of CARDIOLOGY

Background

Reducing triglyceride-rich lipoproteins (TRL) remains an unmet clinical need

- Elevated TRLs are associated with ↑ CV risk
- TRLs are at least as atherogenic as LDL
- Hypertriglyceridemia has direct clinical consequences, particularly when severe

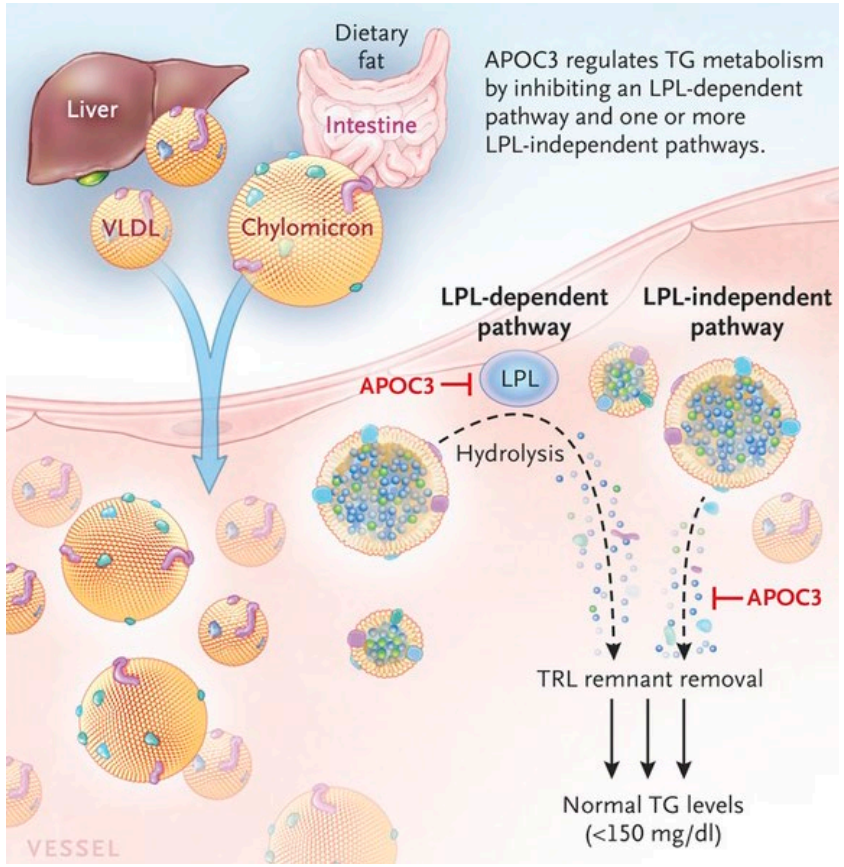
Apolipoprotein C-III

- Synthesized primarily in the liver
- Inhibits lipoprotein lipase
- ↑ triglyceride levels

Loss of function mutations in *APOC3*

- ↓ triglyceride levels
- ↓ CV risk

Olezarsen is a $GalNAc_3$-conjugated antisense oligonucleotide targeting *APOC3* mRNA

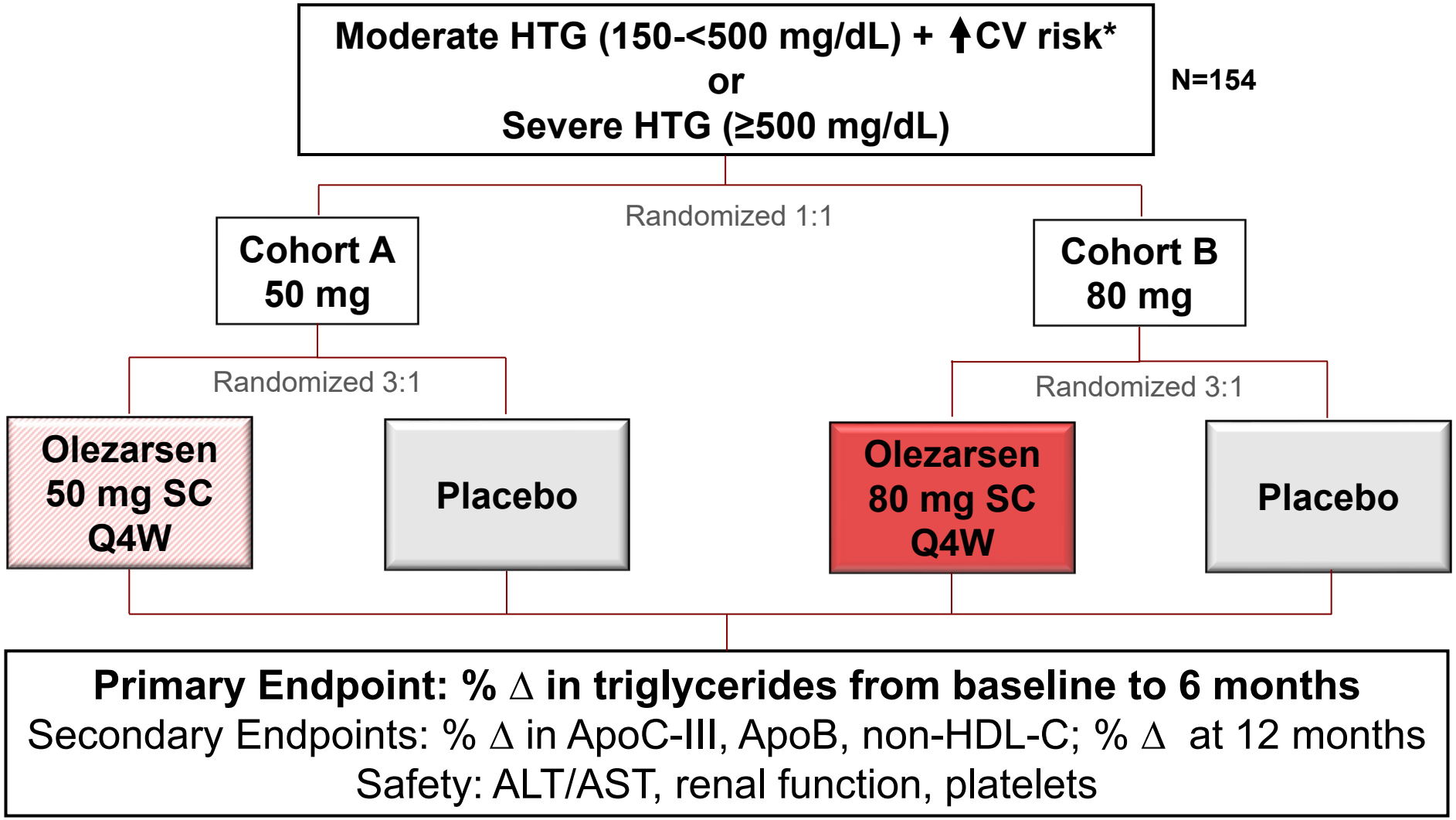


Gaudet D. *N Engl J Med*. 2014;371:2200-6
Alexander VJ, et al. *Eur Heart J*. 2019;40:2785-96
Tardif JC, et al. *Eur Heart J*. 2022;43:1401-12

Objective

Assess the efficacy and safety of olezarsen in patients with moderate hypertriglyceridemia and elevated CV risk or with severe hypertriglyceridemia

Trial Design



* ↑ **CV risk:** Established ASCVD or increased ASCVD risk (T2DM or ≥2 risk factors)

Trial Organization

TIMI Study Group

Marc Sabatine (Chair)
Robert Giugliano (Sr Investigator)
P. Fish & A. Jevne (Ops)
Brian Bergmark (PI)
Nicholas Marston (Investigator)
S. Murphy, E. Goodrich, S. Zhang (Stats)

Sponsor: Ionis

Sotirios Tsimikas (SVP, Global CV Dev)
Ewa Karwatowska-Prokopczuk (VP, CV Med)
Thomas Prohaska (Director, Clin Dev)
Vickie Alexander (Executive Director, Clin Dev)

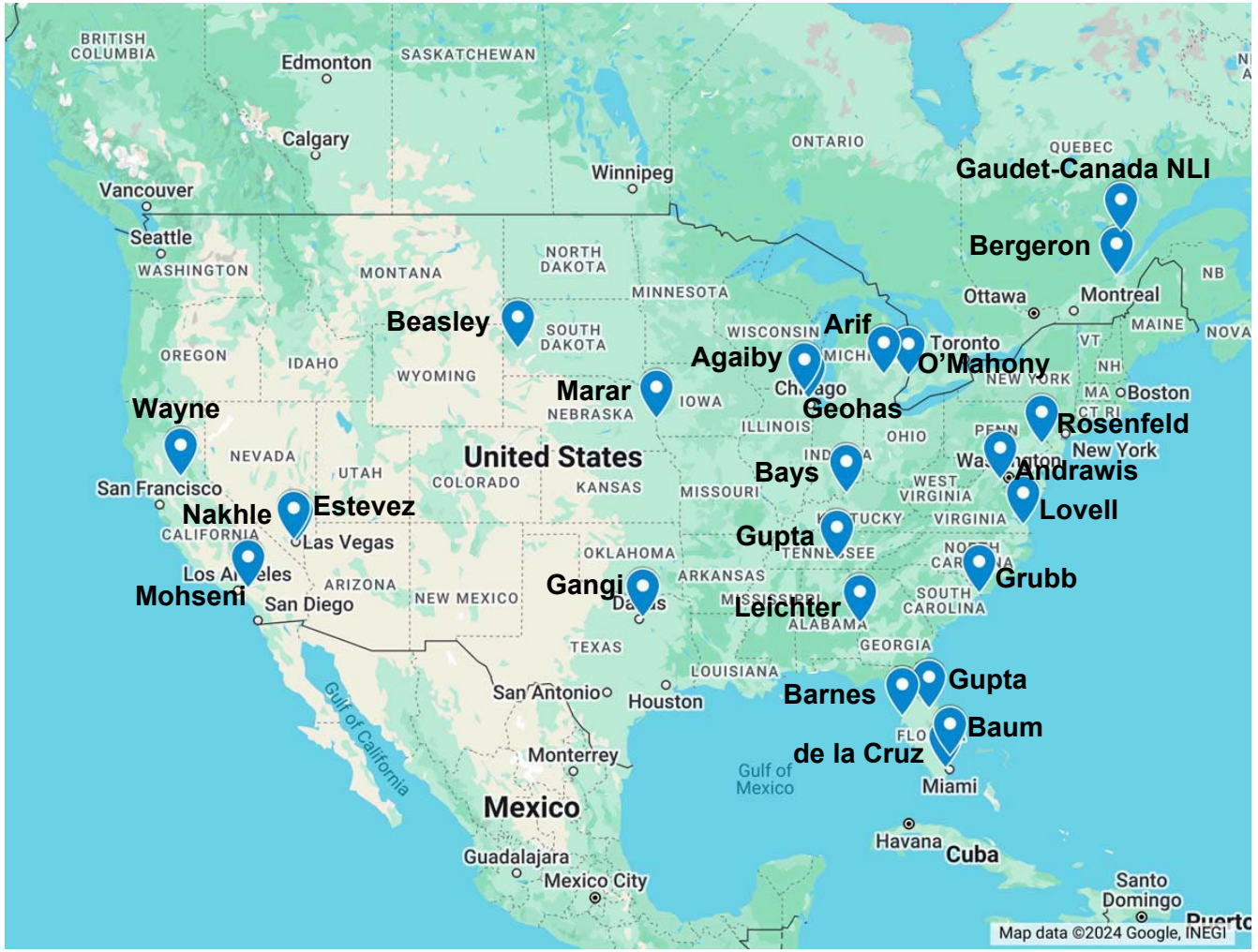
Independent Data Monitoring Committee

Richard Becker (Chair)
Jamie Dwyer
Willis Maddrey
Charles Davis (Statistician)
François Mach

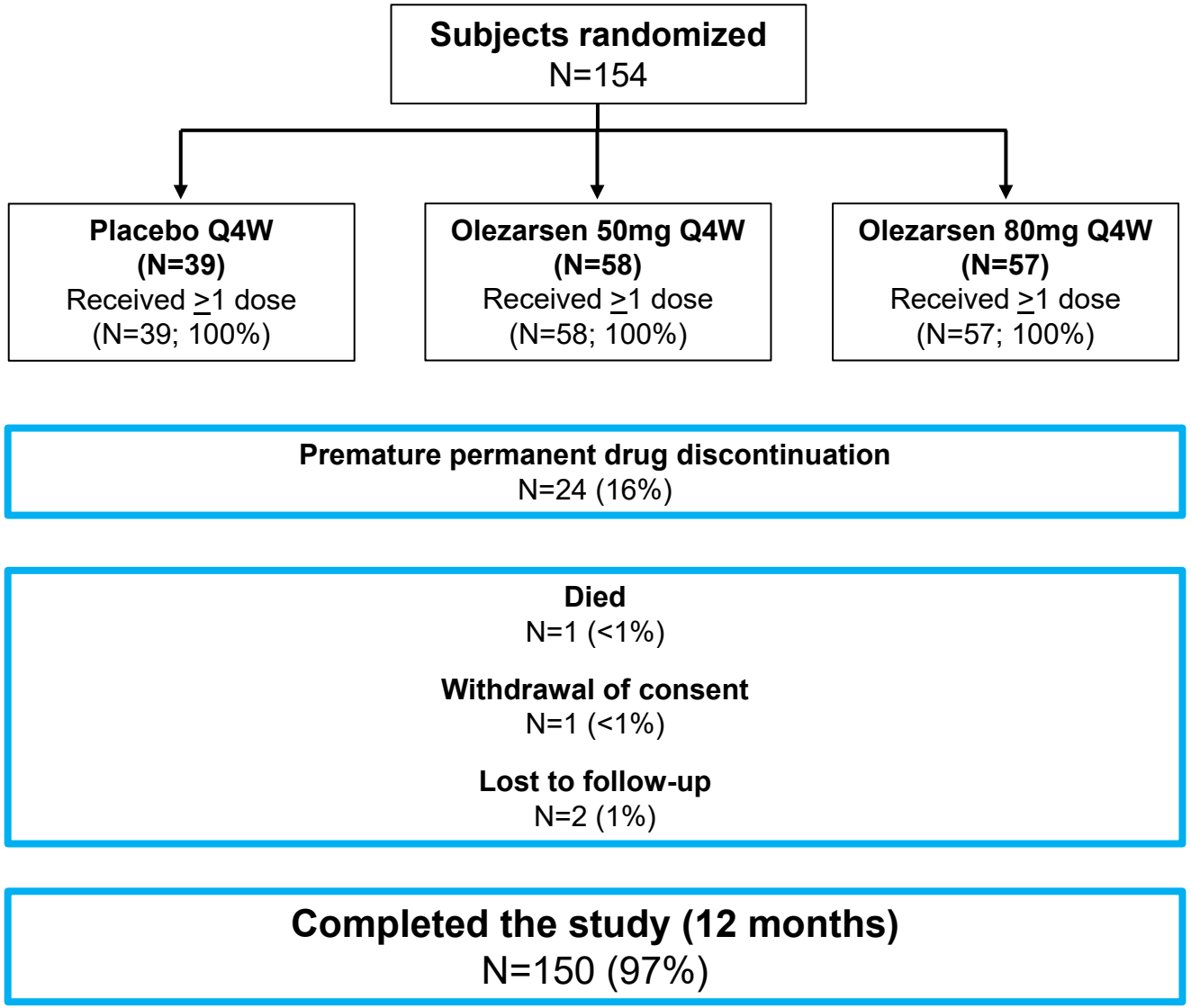
Bridge-TIMI 73a was supported by a grant from Ionis Pharmaceuticals to Brigham and Women's Hospital.

Enrollment

June – September 2022 | **24** Sites | **154** Patients



Follow-up

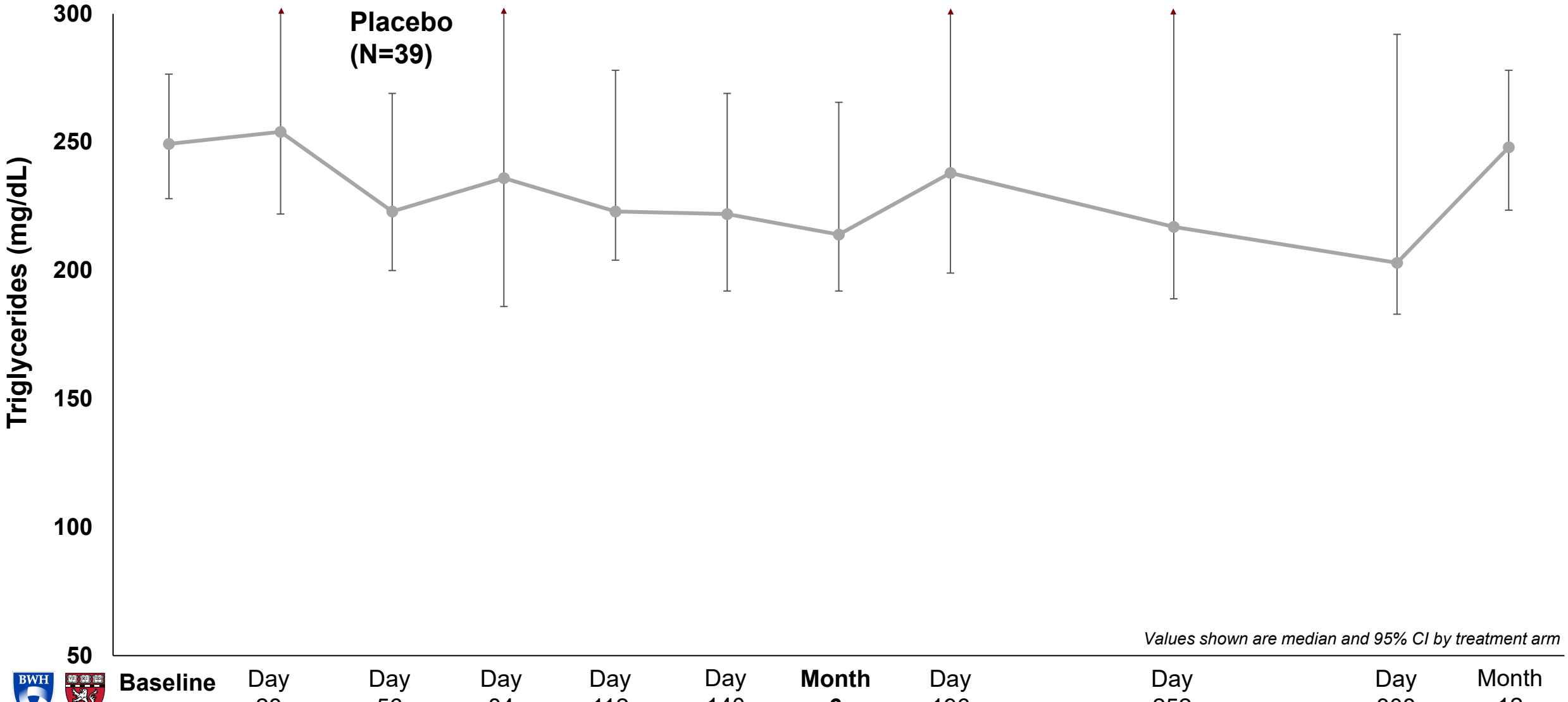

Subjects randomized
N=154
Placebo Q4W
(N=39)
Received ≥1 dose
(N=39; 100%)
Olezarsen 50mg Q4W
(N=58)
Received ≥1 dose
(N=58; 100%)
Olezarsen 80mg Q4W
(N=57)
Received ≥1 dose
(N=57; 100%)
Premature permanent drug discontinuation
N=24 (16%)
Died
N=1 (<1%)
Withdrawal of consent
N=1 (<1%)
Lost to follow-up
N=2 (1%)
Completed the study (12 months)
N=150 (97%)

Baseline Characteristics

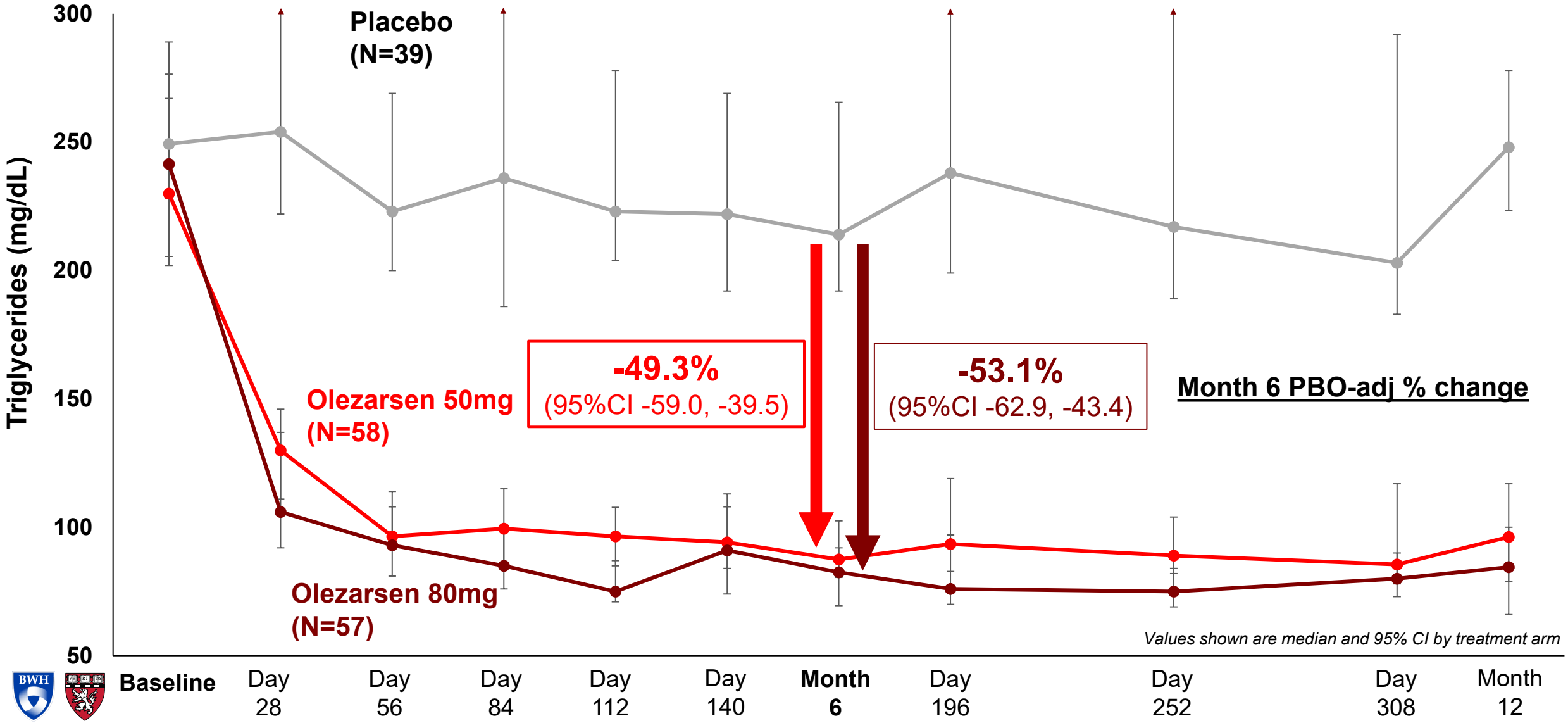
Clinical characteristics	Total N=154
Age (yrs)	62 (55-70)
Female sex	42%
Race/Ethnicity	
White	92%
Hispanic/Latino	38%
Black	8%
Hispanic/Latino	33%
Asian	1%
BMI (kg/m^2)	33 (29-37)
Prior pancreatitis	1%
Diabetes mellitus	68%

Values shown are % or median (IQR)

Olezarsen Efficacy



Olezarsen Efficacy

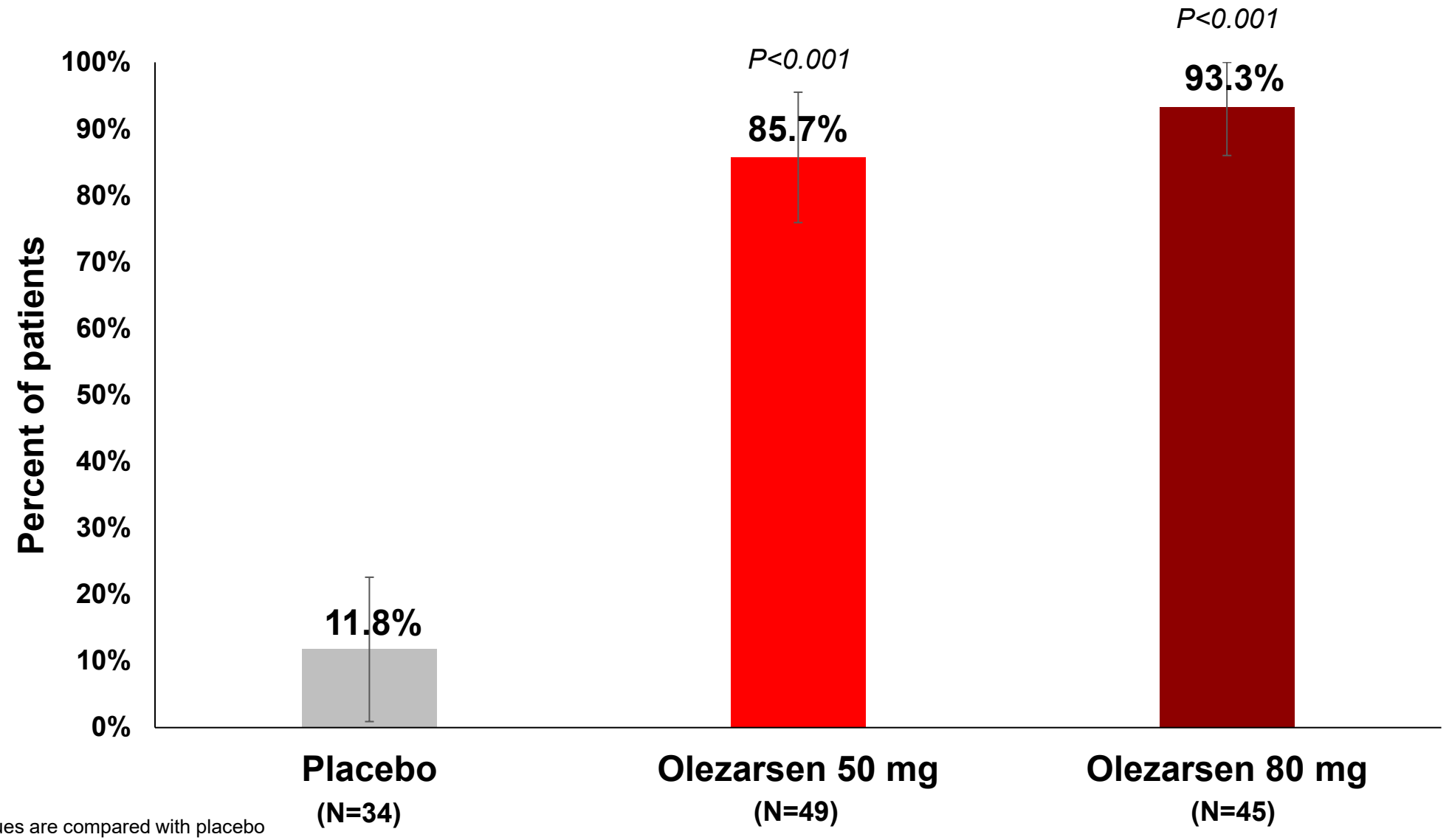


Lipid changes at 6 months

Values shown are placebo-adjusted LSM % changes and 95% CI at 6 months

Achieved TG<150 mg/dL at 6 months

In patients with moderate hypertriglyceridemia at baseline



P values are compared with placebo

Key Safety Parameters

	Placebo N=39	Olezarsen 50 mg N=58	P-value vs Placebo	Olezarsen 80 mg N=57	P-value vs Placebo
Treatment-emergent adverse events					
Any	29 (74.4)	42 (72.4)	0.83	38 (66.7)	0.42
Leading to drug discontinuation	0 (0)	7 (12.1)	0.04	3 (5.3)	0.27
Serious	2 (5.1)	4 (6.9)	>0.99	7 (12.3)	0.30
Leading to drug discontinuation	0 (0)	1 (1.7)	>0.99	1 (1.8)	>0.99
Pancreatitis	0	0	--	0	--
Hepatic abnormalities					
ALT ≥ ULN	1 (2.6)	27 (46.6)	<0.001	21 (36.8)	<0.001
AST ≥ ULN	4 (10.3)	18 (31.0)	0.03	21 (36.8)	0.004
ALT or AST ≥3x ULN	0	4 (6.9)	0.15	1 (1.8)	>0.99
Total bilirubin ≥2x ULN	0	0	--	0	--
Alkaline phosphatase ≥2x ULN	0	0	--	0	--

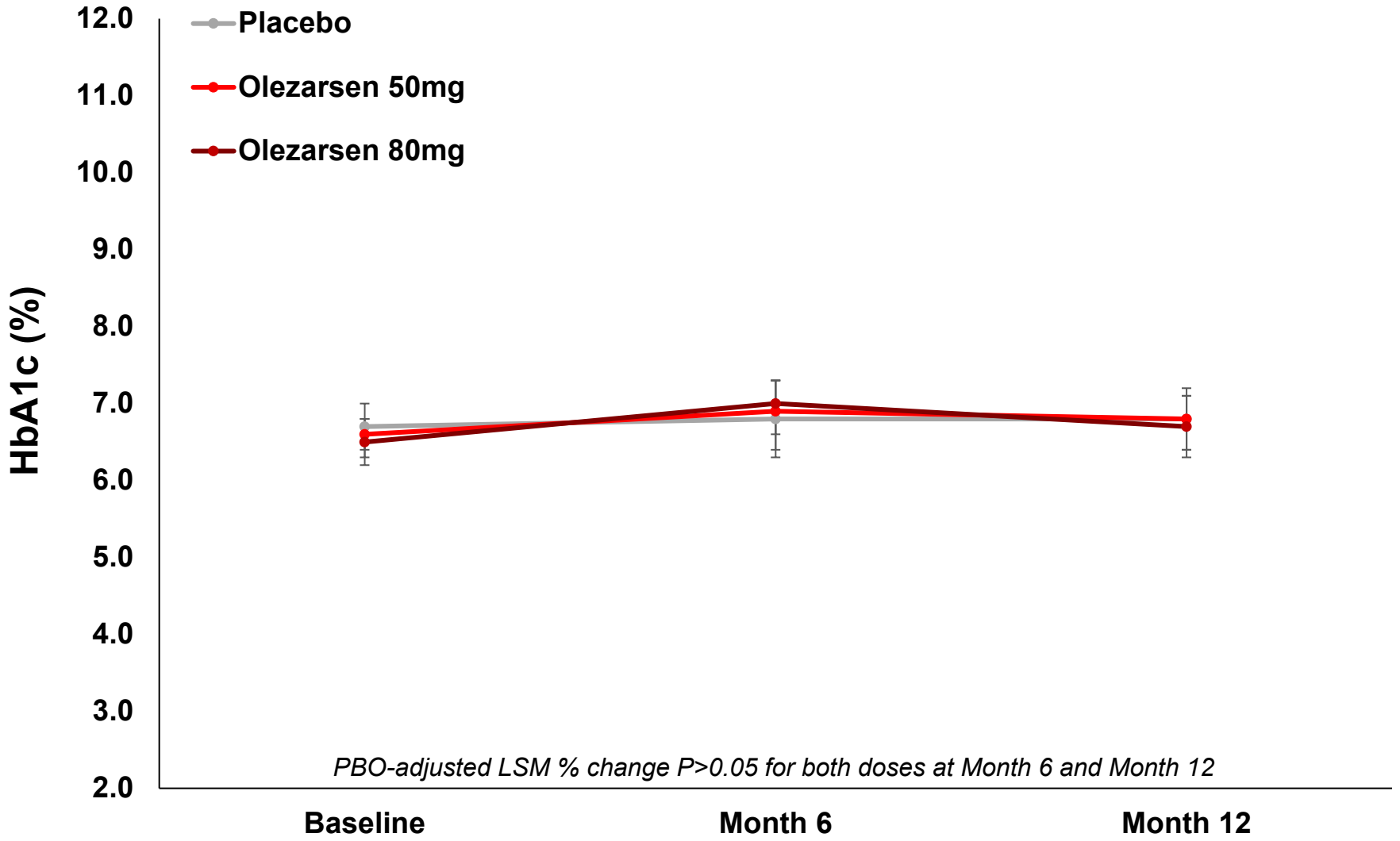
Treatment phase safety data shown

Key Safety Parameters

	Placebo N=39	Olezarsen 50 mg N=58	P-value vs Placebo	Olezarsen 80 mg N=57	P-value vs Placebo
Renal abnormalities					
eGFR decline ≥30%	8 (20.5)	6 (10.3)	0.16	4 (7.0)	0.06
eGFR decline ≥50%	0	0	--	0	--
UPCR ≥1000 mg/g	4 (10.3)	4 (6.9)	0.71	3 (5.3)	0.44
Platelet count					
<140K/uL	1 (2.6)	10 (17.2)	0.05	10 (17.5)	0.03
<100K/uL	1 (2.6)	0	0.40	3 (5.3)	0.64
<75K/uL	0	0	--	0	--

Treatment phase safety data shown

Additional Safety



Olezarsen Program

Mod HTG + CV risk *or* Severe HTG	**Bridge-TIMI 73a**	**Essence-TIMI 73b** • 1478 patients • Coronary CTA substudy
Severe HTG	**CORE-TIMI 72a** • 540 patients • Hepatic MRI substudy	**CORE2-TIMI 72b** • 390 patients • Hepatic MRI substudy
	Open Label Extension	

Limitations

The number of patients with severe hypertriglyceridemia was small, limiting the ability to assess olezarsen's lipid and clinical effects in these patients

Trials of olezarsen in patients with severe hypertriglyceridemia are ongoing

Treatment beyond one year was not evaluated

Open label extension programs with olezarsen are underway

These findings cannot necessarily be applied to patients with specific genetic syndromes or secondary causes of hypertriglyceridemia

Olezarsen's effects in patients with familial chylomicronemia syndrome (Balance trial) will be presented at 9:45 am today in room B313A

Summary and Conclusions

In patients with largely moderate hypertriglyceridemia and elevated cardiovascular risk, olezarsen 50 mg or 80 mg monthly significantly reduced triglyceride levels

- *TG effect was greater than is possible with currently available treatments*
- *There were no major safety concerns in this phase 2b trial*

Olezarsen led to meaningful reductions in apolipoprotein B and non-high-density lipoprotein cholesterol, markers of atherogenic risk

Thank you

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