ACC.24

Bridge – TIMI 73a

Olezarsen in patients with hypertriglyceridemia at high cardiovascular risk

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For the Bridge–TIMI 73a Investigators

AMERICAN COLLEGE of CARDIOLOGY

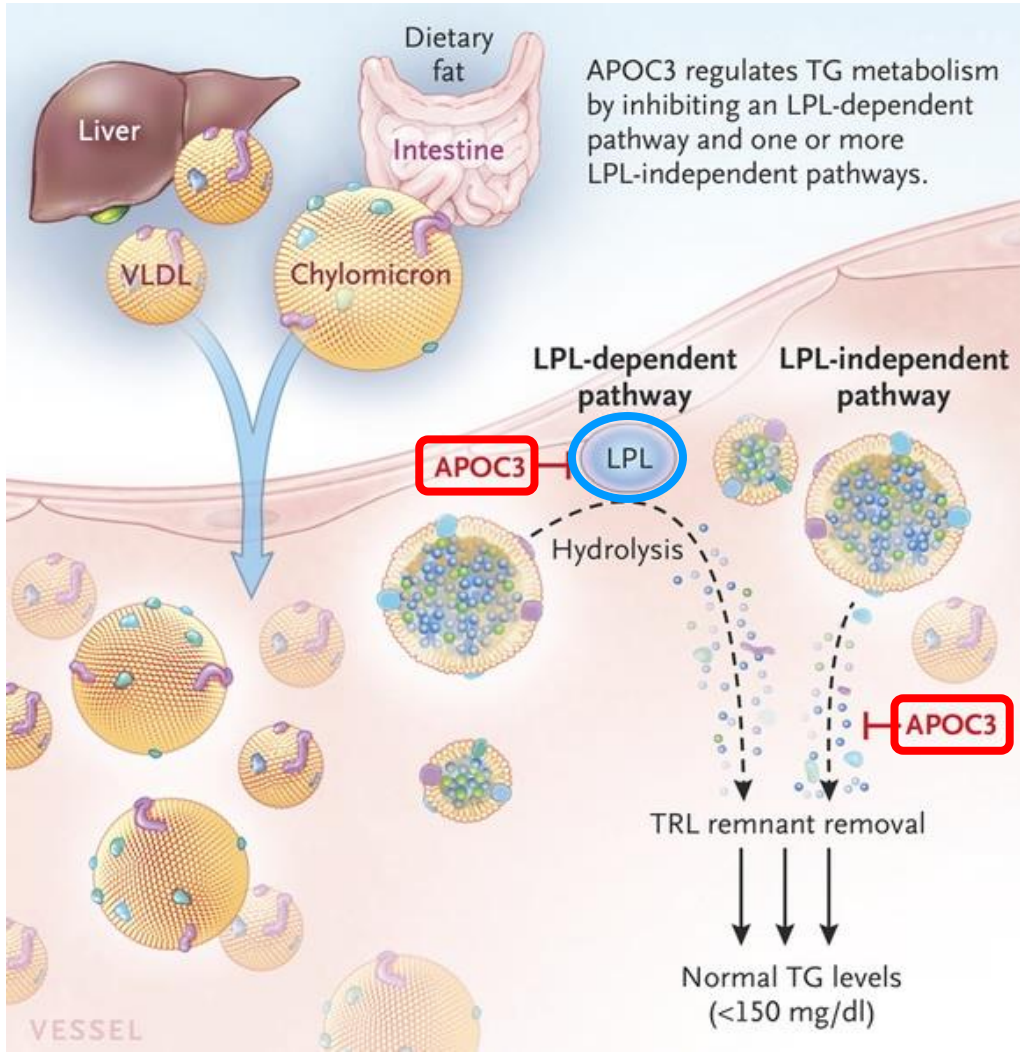
Background

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

- Elevated TRLs (eg, chylomicrons and VLDL) are associated with ↑ CV risk
- TRLs are at least as atherogenic as LDL
- Hypertriglyceridemia, particularly when severe, has direct clinical consequences

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

Background



Lipoprotein Lipase (LPL)

- Hydrolyses triglycerides
- Facilitates clearance of TRLs

Apolipoprotein C-III

- Synthesized primarily in the liver
- Resides on TRLs
- Inhibits LPL
- ↑ triglyceride levels

Loss of function mutations in *APOC3*

- ↓ triglyceride levels
- ↓ CV risk

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

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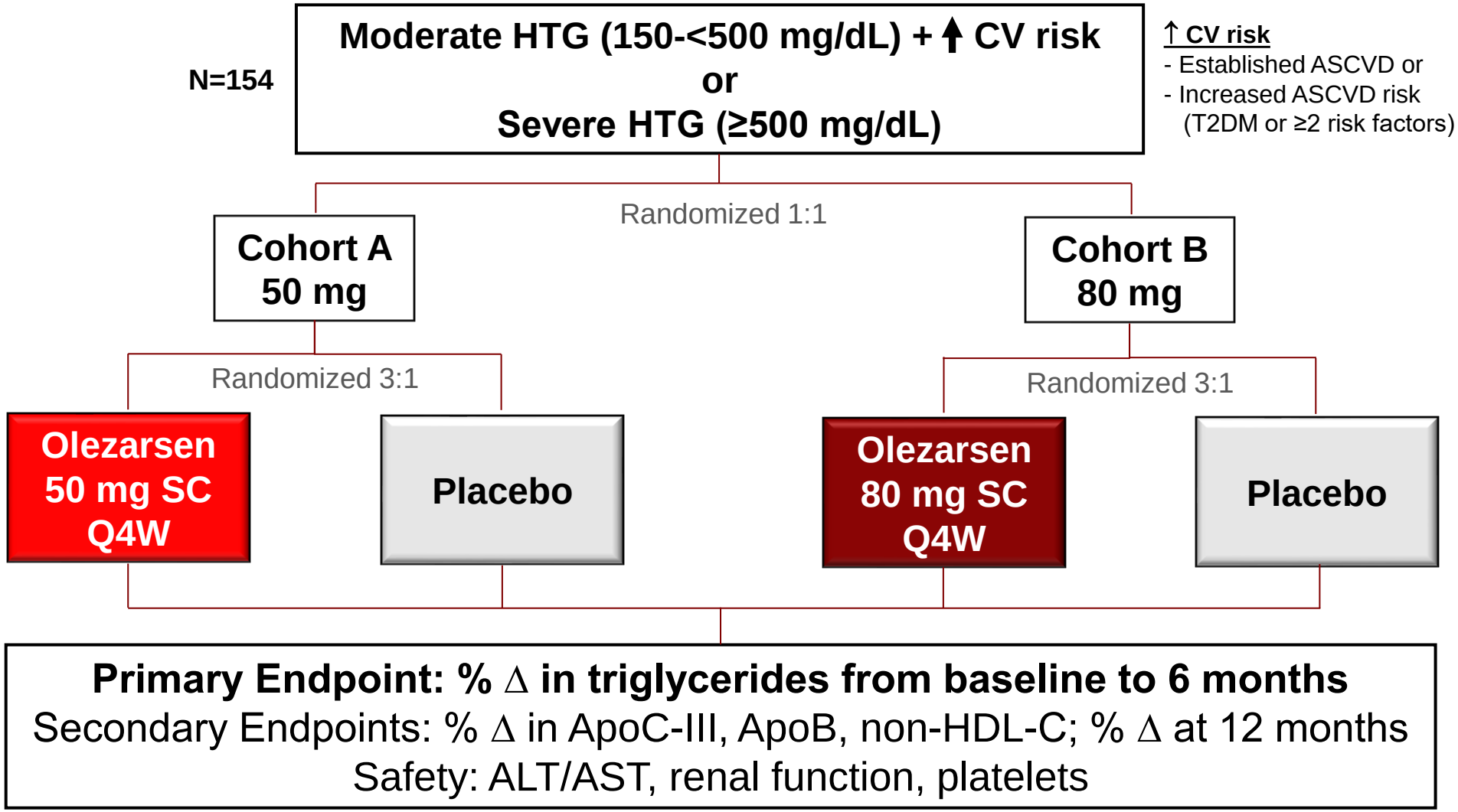
Objective

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

Trial Design



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

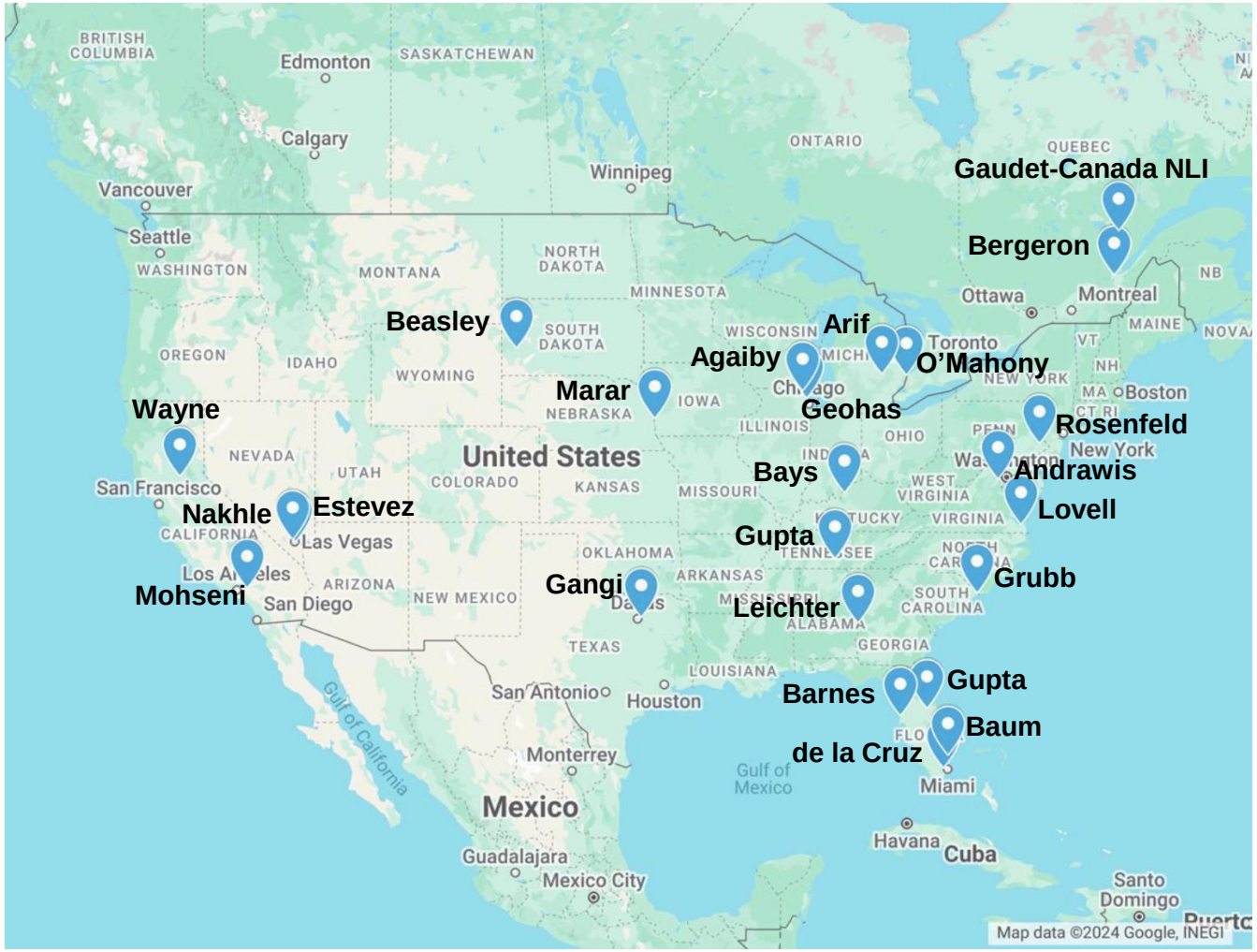
Richard Becker (Chair)
Jamie Dwyer
Willis Maddrey

Charles Davis (Statistician)
François Mach

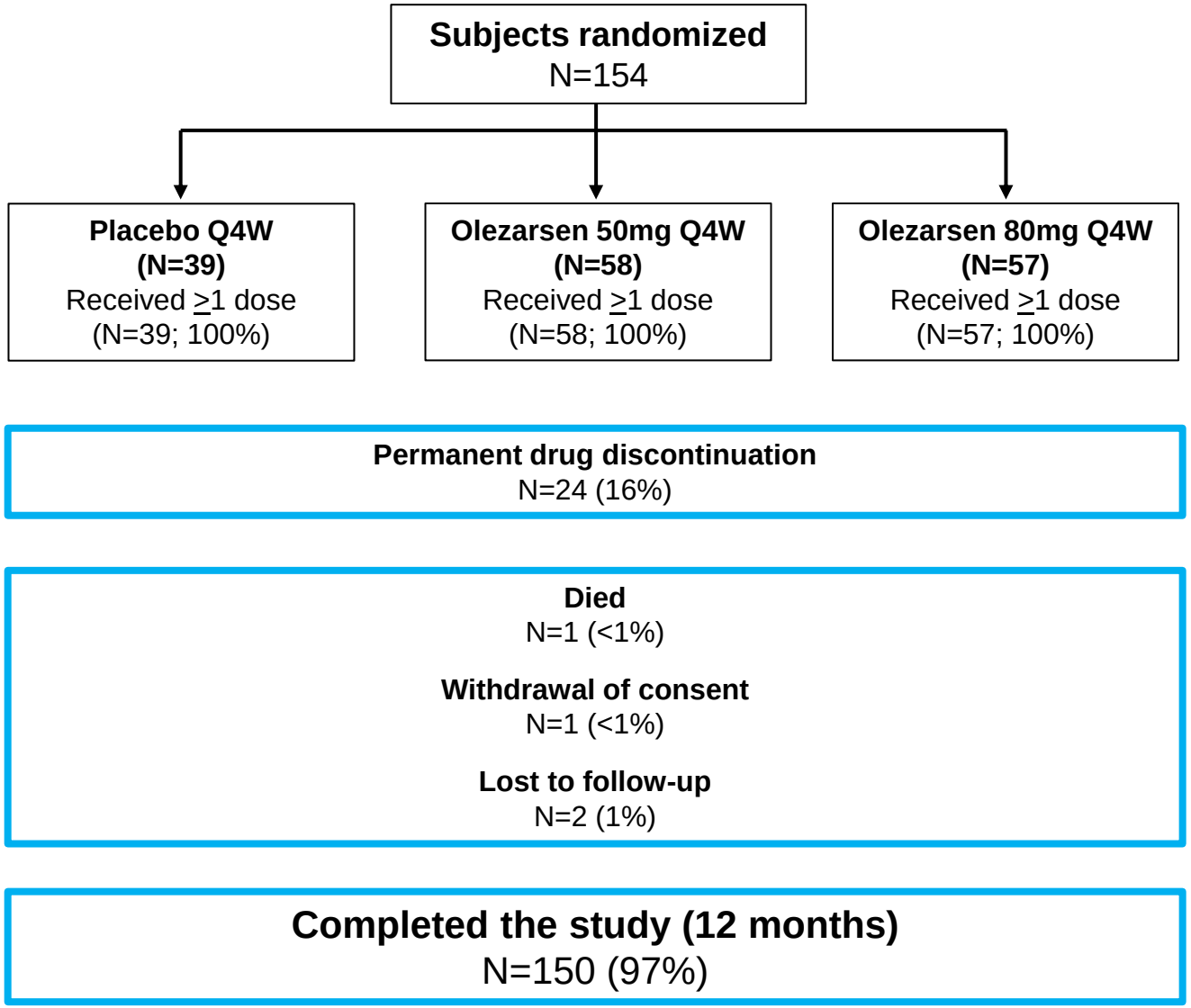
Bridge-TIMI 73a was supported by a grant from Ionis Pharmaceuticals to Brigham and Women's Hospital.

Enrollment

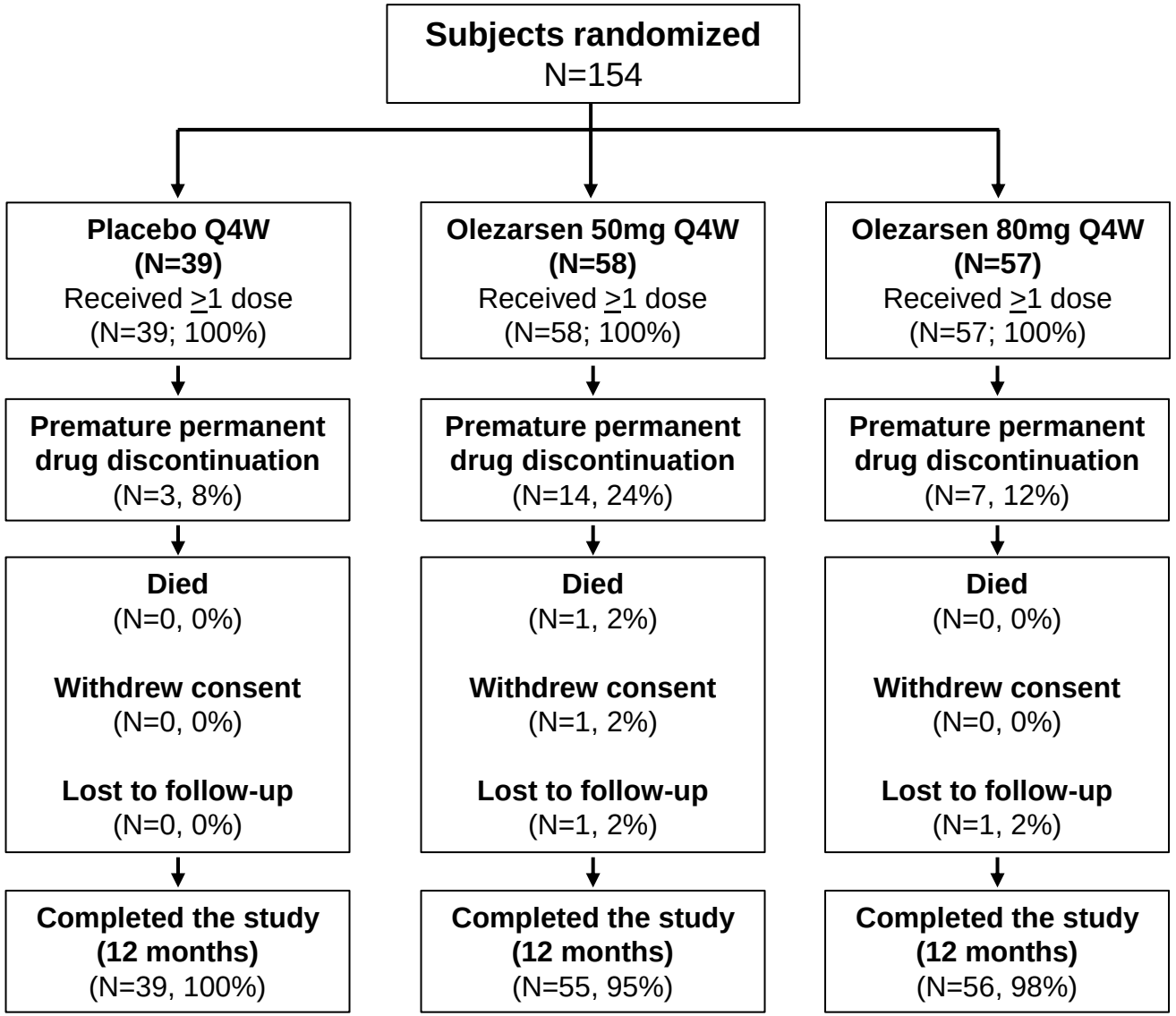
June – September 2022 | **24** Sites | **154** Patients



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%)
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%)

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=3, 8%)
Premature permanent drug discontinuation
(N=14, 24%)
Premature permanent drug discontinuation
(N=7, 12%)
Died
(N=0, 0%)
Withdrew consent
(N=0, 0%)
Lost to follow-up
(N=0, 0%)
Died
(N=1, 2%)
Withdrew consent
(N=1, 2%)
Lost to follow-up
(N=1, 2%)
Died
(N=0, 0%)
Withdrew consent
(N=0, 0%)
Lost to follow-up
(N=1, 2%)
Completed the study
(12 months)
(N=39, 100%)
Completed the study
(12 months)
(N=55, 95%)
Completed the study
(12 months)
(N=56, 98%)

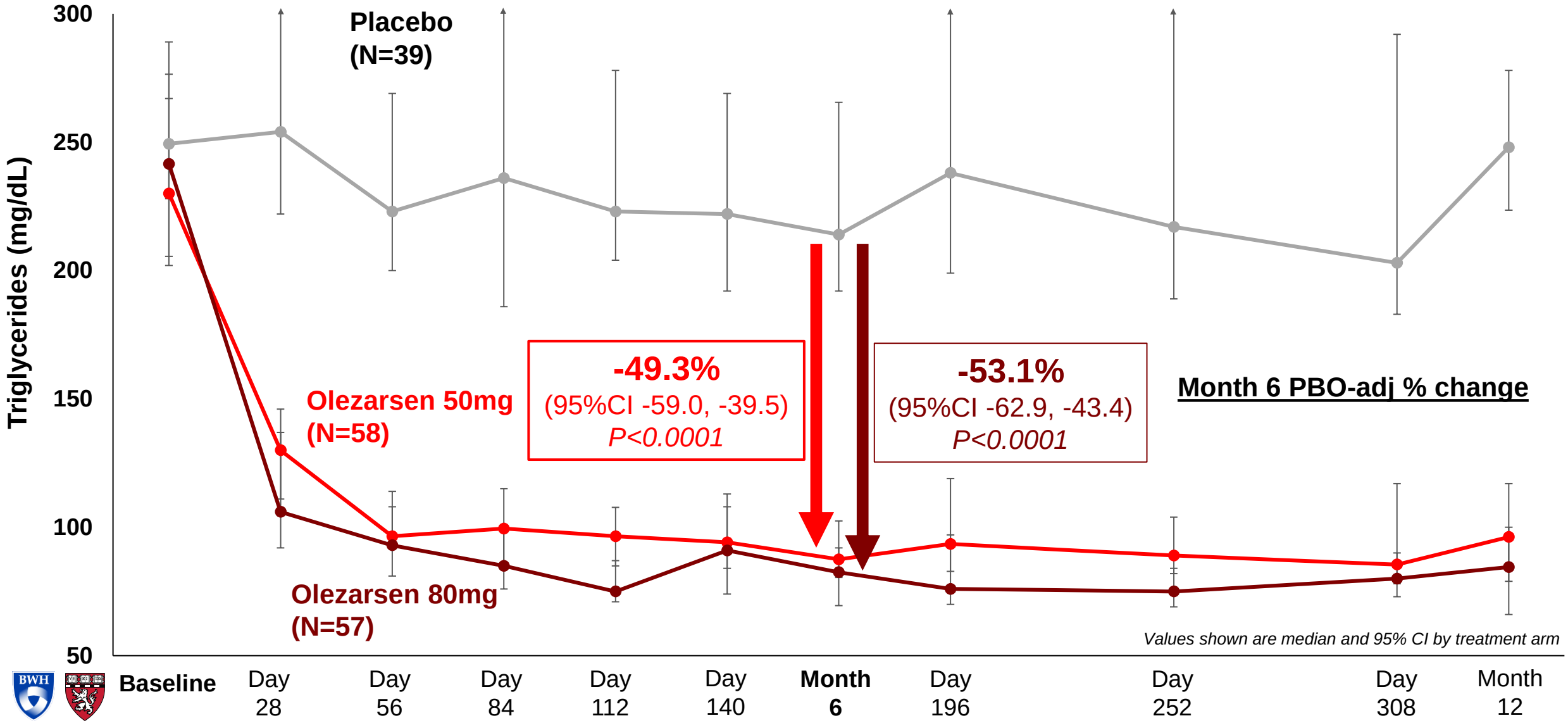
Baseline Characteristics

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

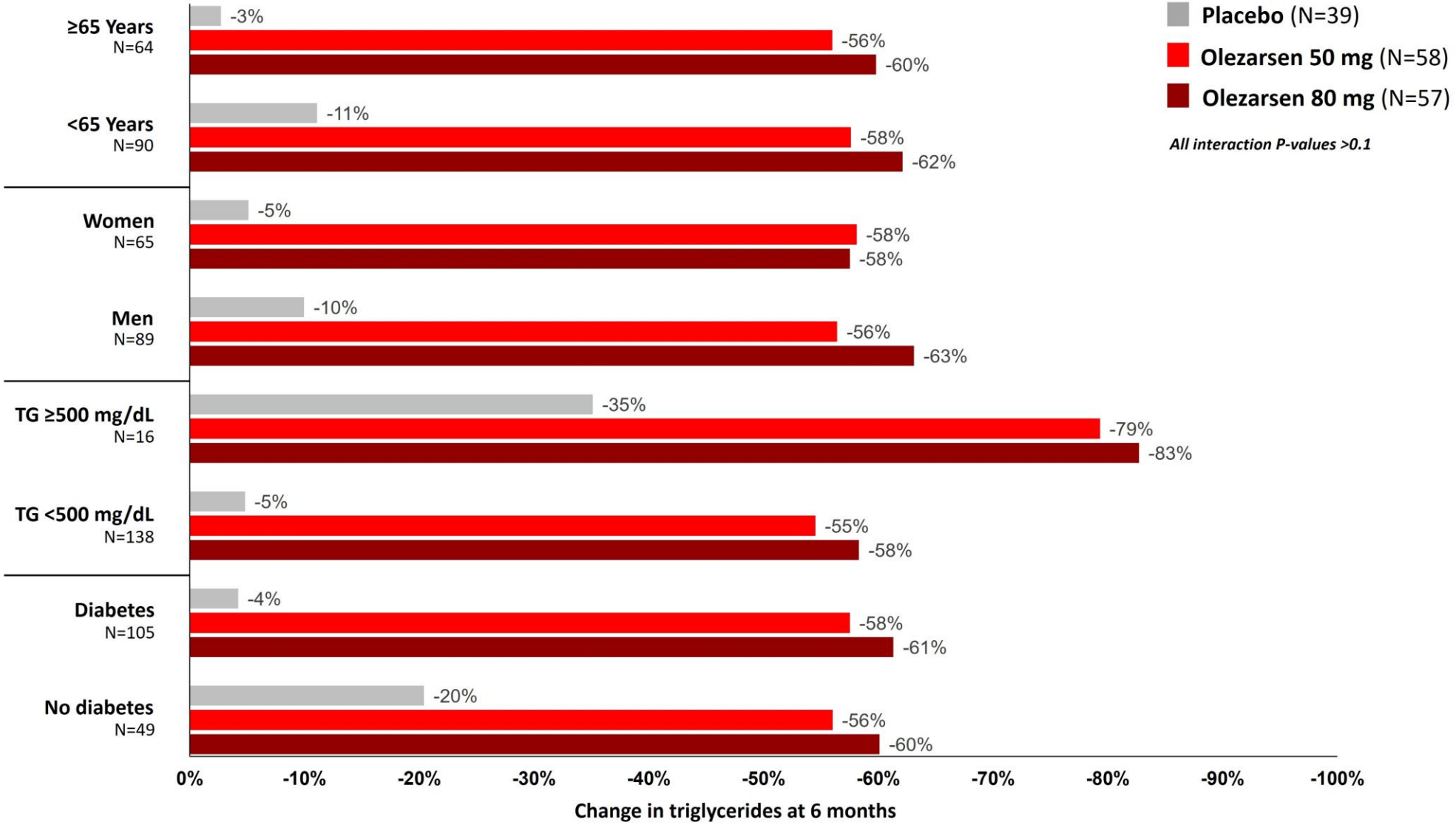
Triglycerides and therapy	Total N=154
Triglycerides (mg/dL)	242 (192-324)
Triglycerides ≥500 mg/dL	10%
Any lipid-lowering therapy	97%
Statin	82%
Ezetimibe	6%
Fibrate	16%
Omega-3 fatty acid	16%
Niacin	1%
PCSK9i	3%
≥2 therapies	31%

Values shown are % or median (IQR)

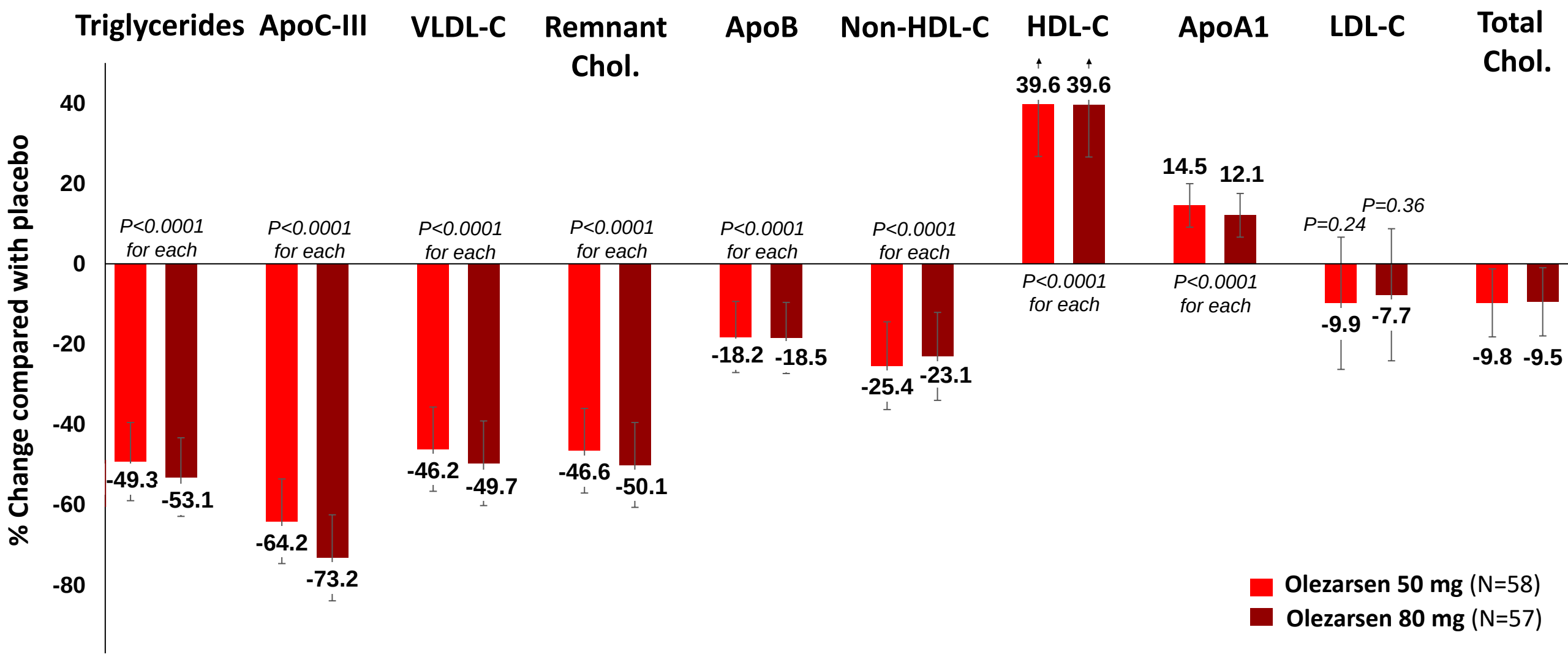
Olezarsen Efficacy



Key subgroups



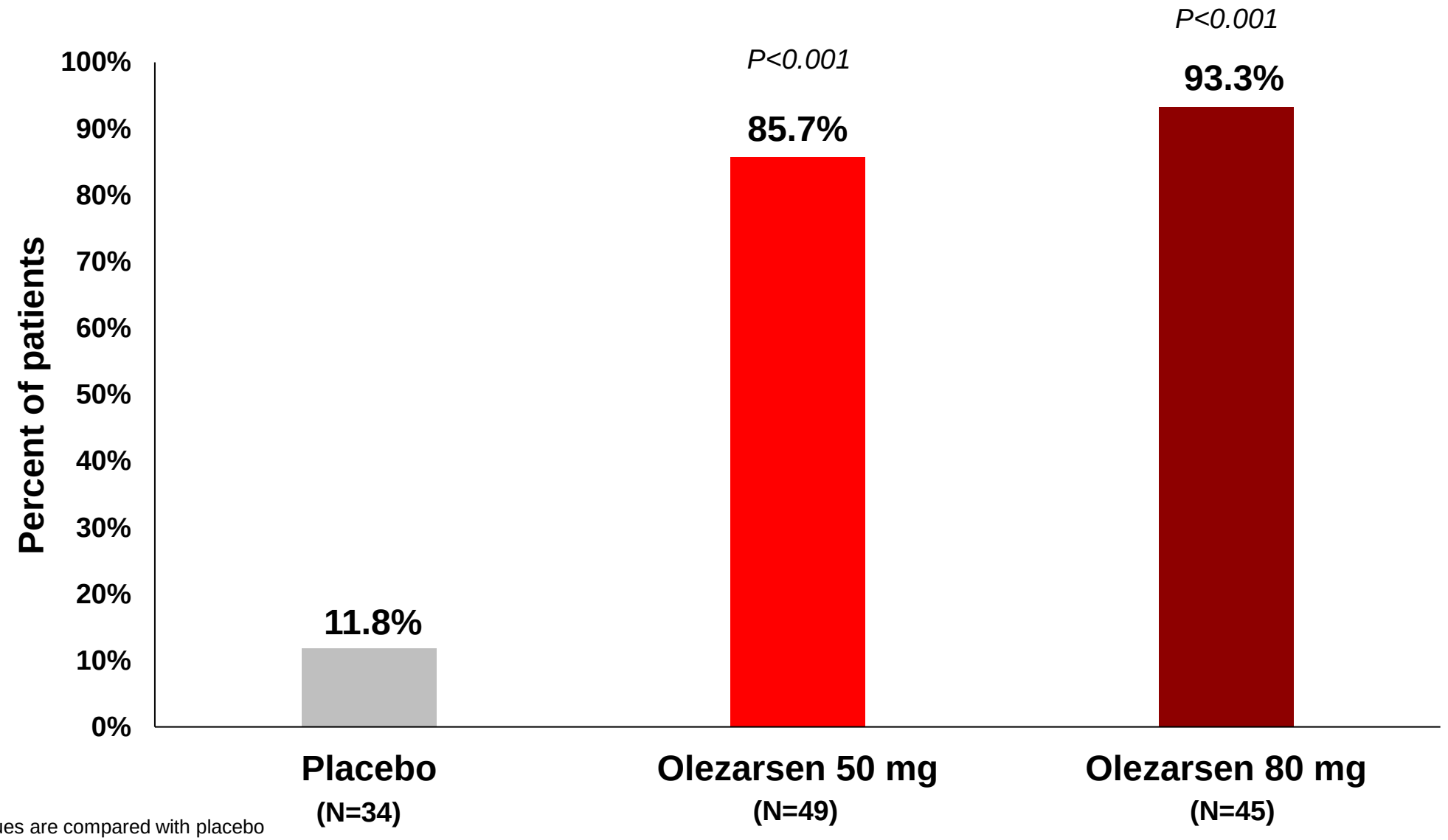
Lipid changes at 6 months



Values shown are placebo-adjusted LSM % changes and 95% CI at 6 months. P values are for comparison with placebo.

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
Hepatic abnormalities					
ALT or AST > ULN	4 (10.3)	28 (48.3)	<0.001	26 (45.6)	<0.001
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	--

Patients were eligible to enroll with ALT or AST up to 3x ULN at baseline. 2 patients (5%) in placebo, 6 patients (10%) in olezarsen 50 mg, and 4 patients (7%) in olezarsen 80 mg had an ALT level > ULN at baseline. 2 patients (5%) in placebo, 3 patients (5%) in olezarsen 50 mg, and 4 patients (7%) in olezarsen 80 mg had an AST level > ULN at baseline.

Treatment phase safety data shown as N (%)

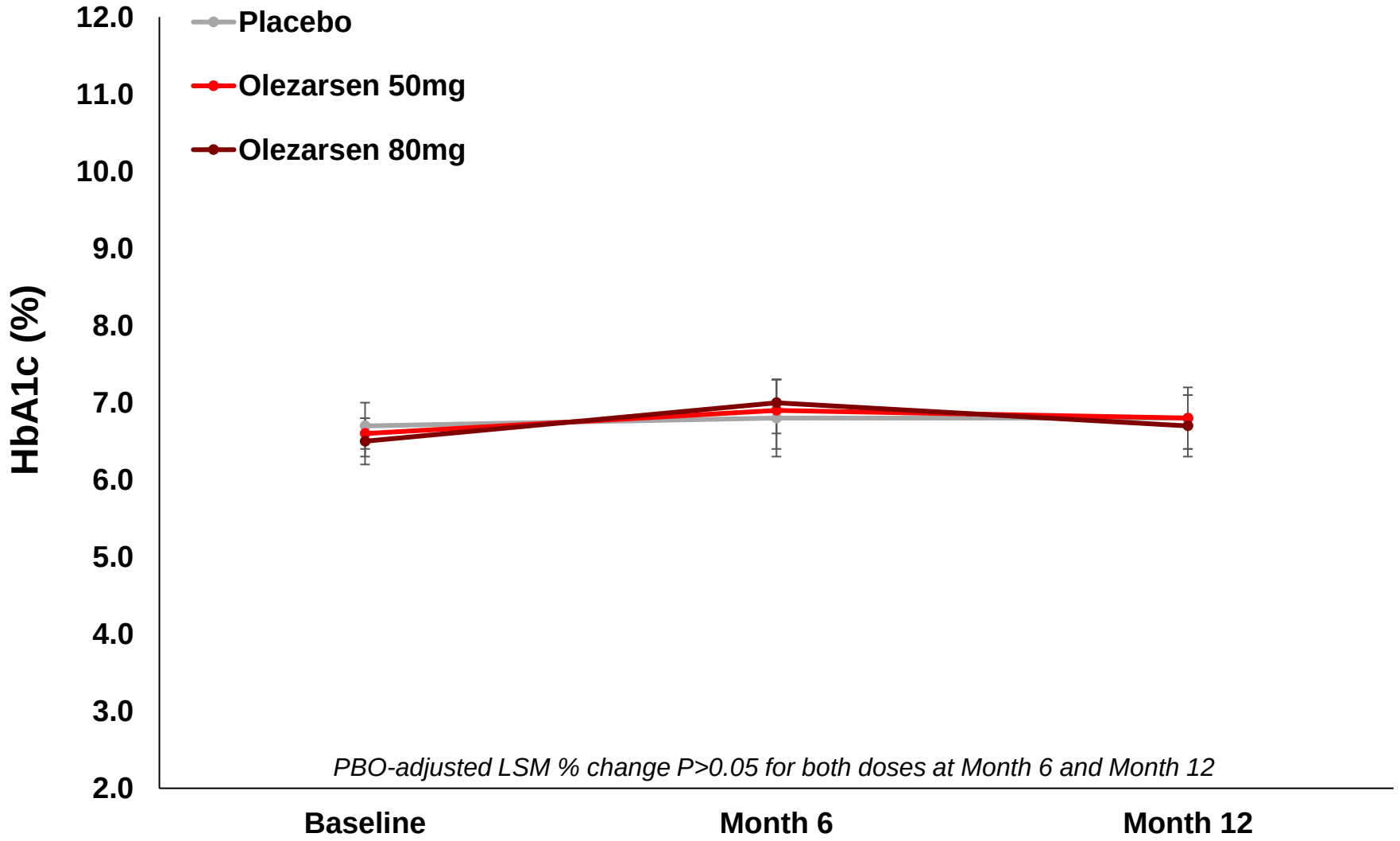
Key Safety Parameters

	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					
Bleeding Event	2 (5.1)	3 (5.2)	>0.99	3 (5.3)	>0.99
<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	--
Injection site reaction	0	10 (17.2)	0.01	3 (5.3)	0.27

There were no exclusion criteria for platelet counts. 1 patient in placebo (3%), 0 patients in olezarsen 50 mg, and 2 patients (4%) in olezarsen 80 mg had a baseline platelet value below 140,000/ul.

Treatment phase safety data shown as N (%)

Glycemic control



PBO-adjusted LSM % change P>0.05 for both doses at Month 6 and Month 12

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

TIMI CORE TIMI 72a CORE2 TIMI 72b Bridge TIMI 73a Essence TIMI 73b

Severe HTG (≥500 mg/dL)	**CORE-TIMI 72a** • 540 patients • Hepatic fat MRI substudy	**CORE2-TIMI 72b** • 390 patients • Hepatic fat MRI substudy
	Open Label Extension	
Mod HTG + CV risk ***or*** **Severe HTG**	**Bridge-TIMI 73a** • 154 patients	**Essence-TIMI 73b** • 1312 patients • Coronary CTA substudy

Summary and Conclusions

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

- *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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Olezarsen for Hypertriglyceridemia in Patients at High Cardiovascular Risk

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*Drs. Bergmark and Marston contributed equally to this article.