

Olezarsen in Patients with Severe Hypertriglyceridemia

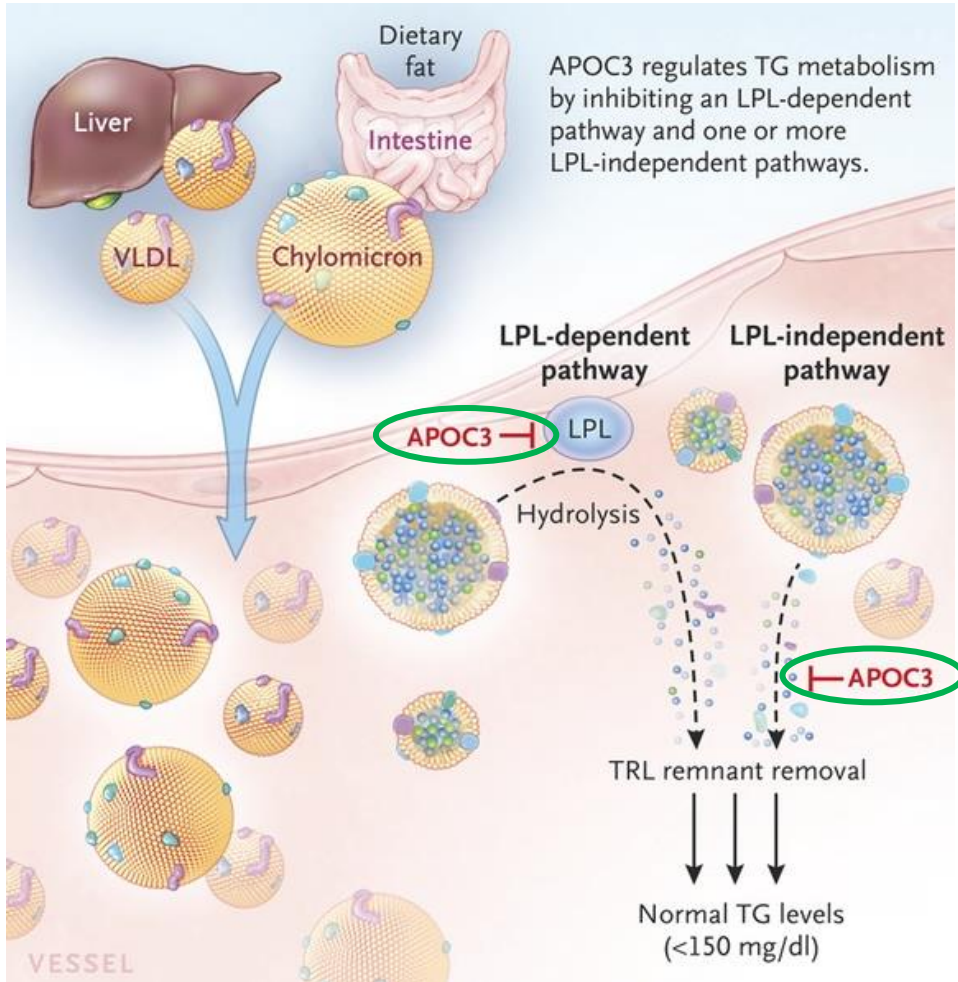
Results of CORE-TIMI 72a & CORE2-TIMI 72b

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TIMI Study Group

Brigham and Women's Hospital

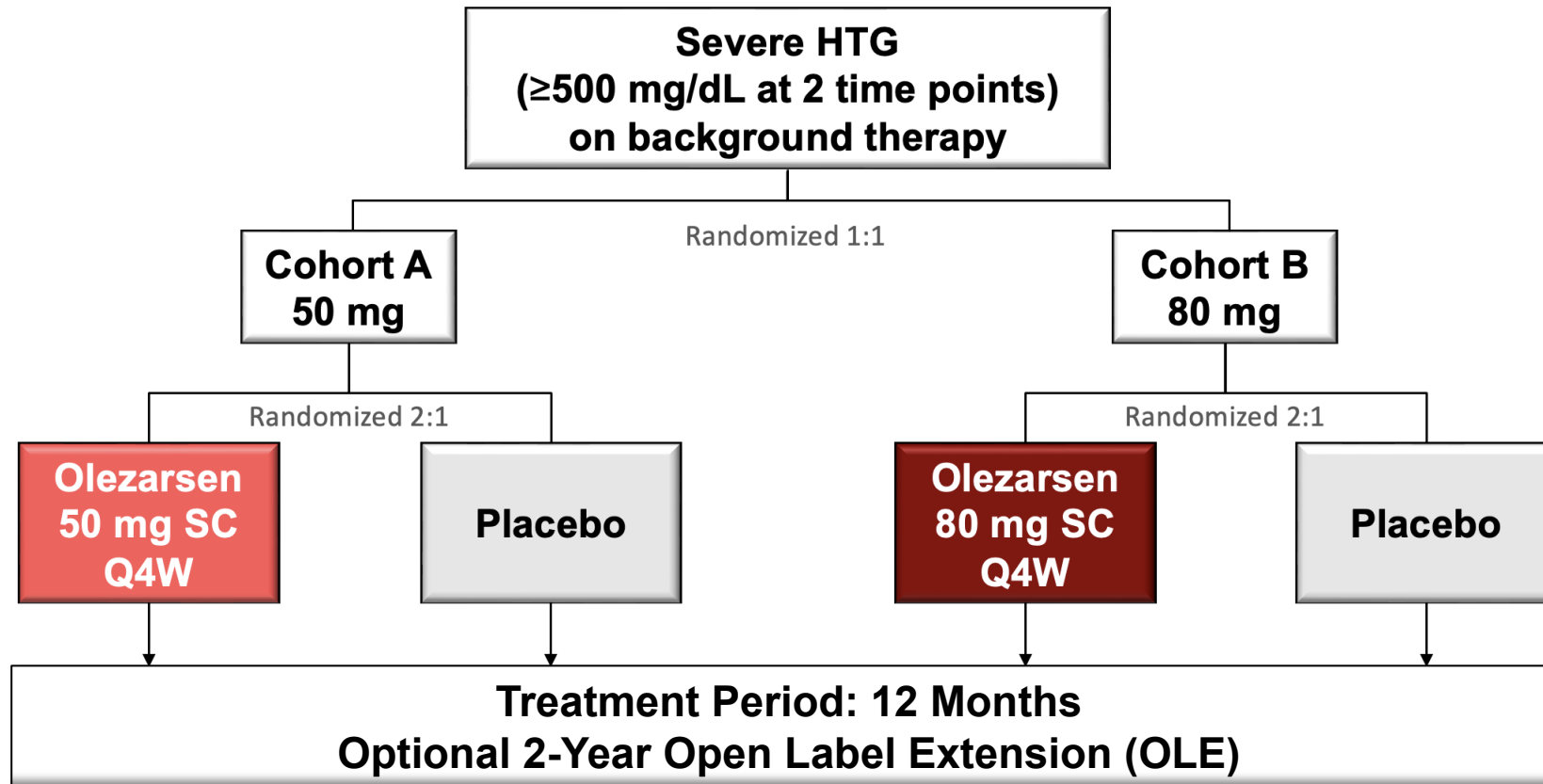
- The CORE and CORE2 trials were funded by Ionis Pharmaceuticals.
- Dr. Marston reports clinical trial involvement with Ionis, Amgen, and Marea, consulting fees from Amgen, Ionis, Verve/Lilly, New Amsterdam, Radence, and Arboretum, and speaking fees from Amgen, Ionis, and Verve/Lilly.



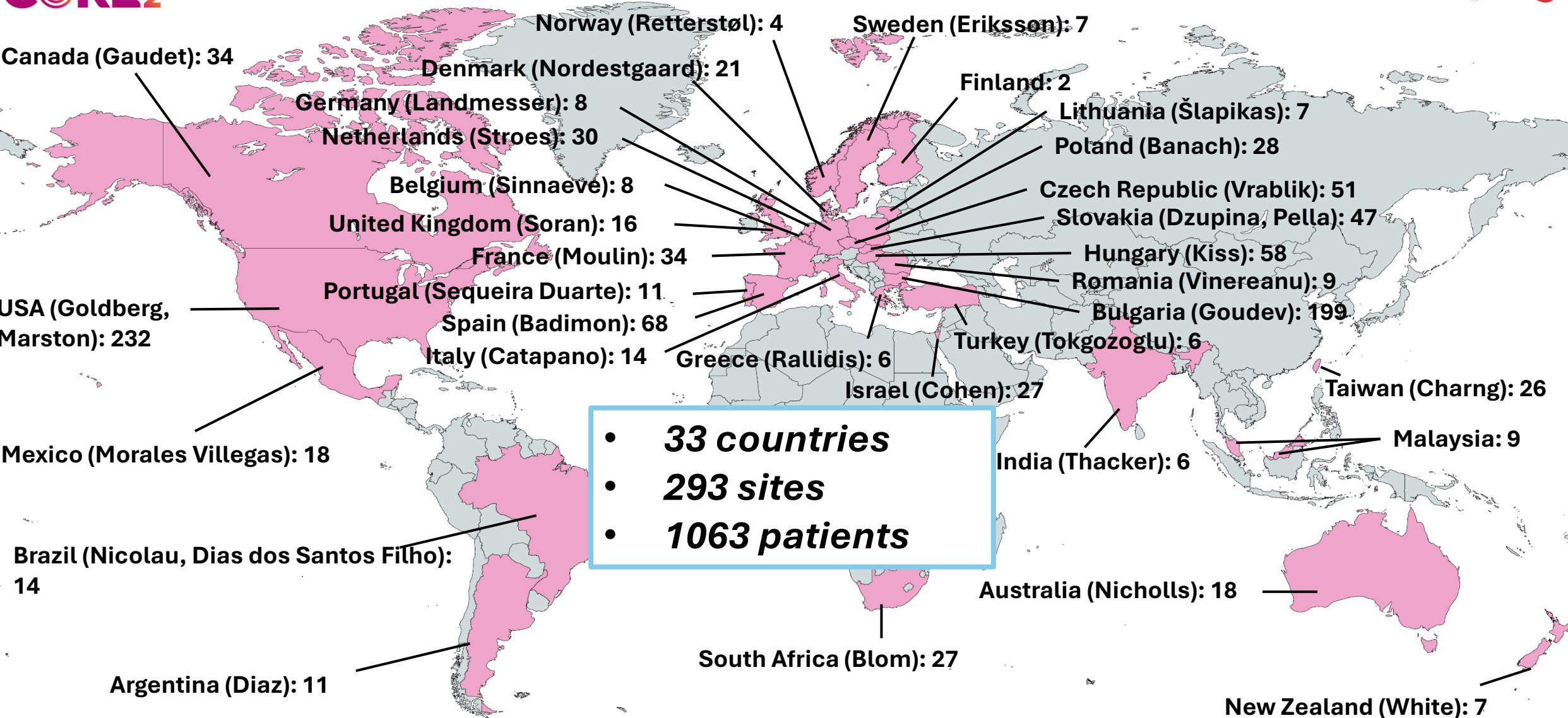
- Severe hypertriglyceridemia (sHTG), defined as triglycerides (TGs) of 500 mg/dL (5.65 mmol/L) or greater, carries an increased risk of acute pancreatitis
- Apolipoprotein C-III (APOC3) inhibits:
 - lipoprotein lipase, a key enzyme in TG metabolism
 - hepatic uptake of TG-rich lipoproteins (TRLs)
- Olezarsen is an antisense oligonucleotide targeting APOC3 that promotes the breakdown and clearance of TRLs, yet its effect on severe hypertriglyceridemia and acute pancreatitis risk was not previously established

CORE-TIMI 72a & CORE2-TIMI 72b

Identically designed

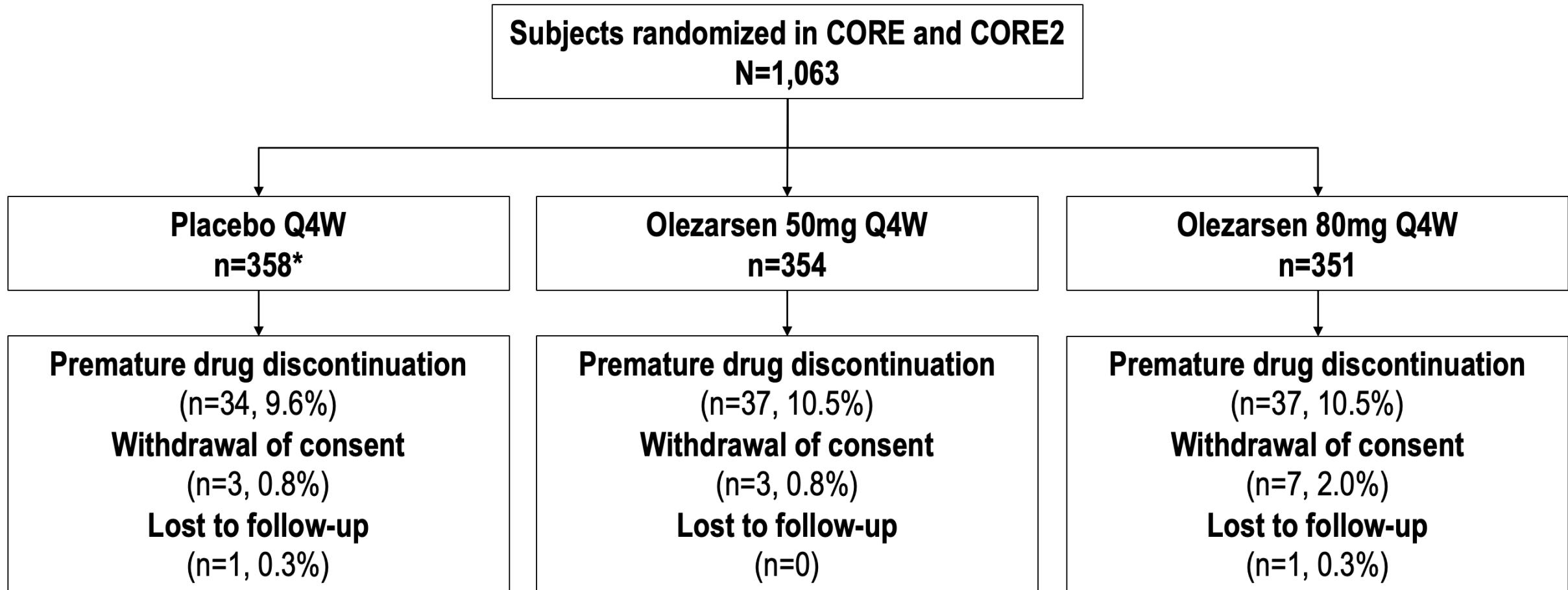


Global Enrollment



- **33 countries**
- **293 sites**
- **1063 patients**

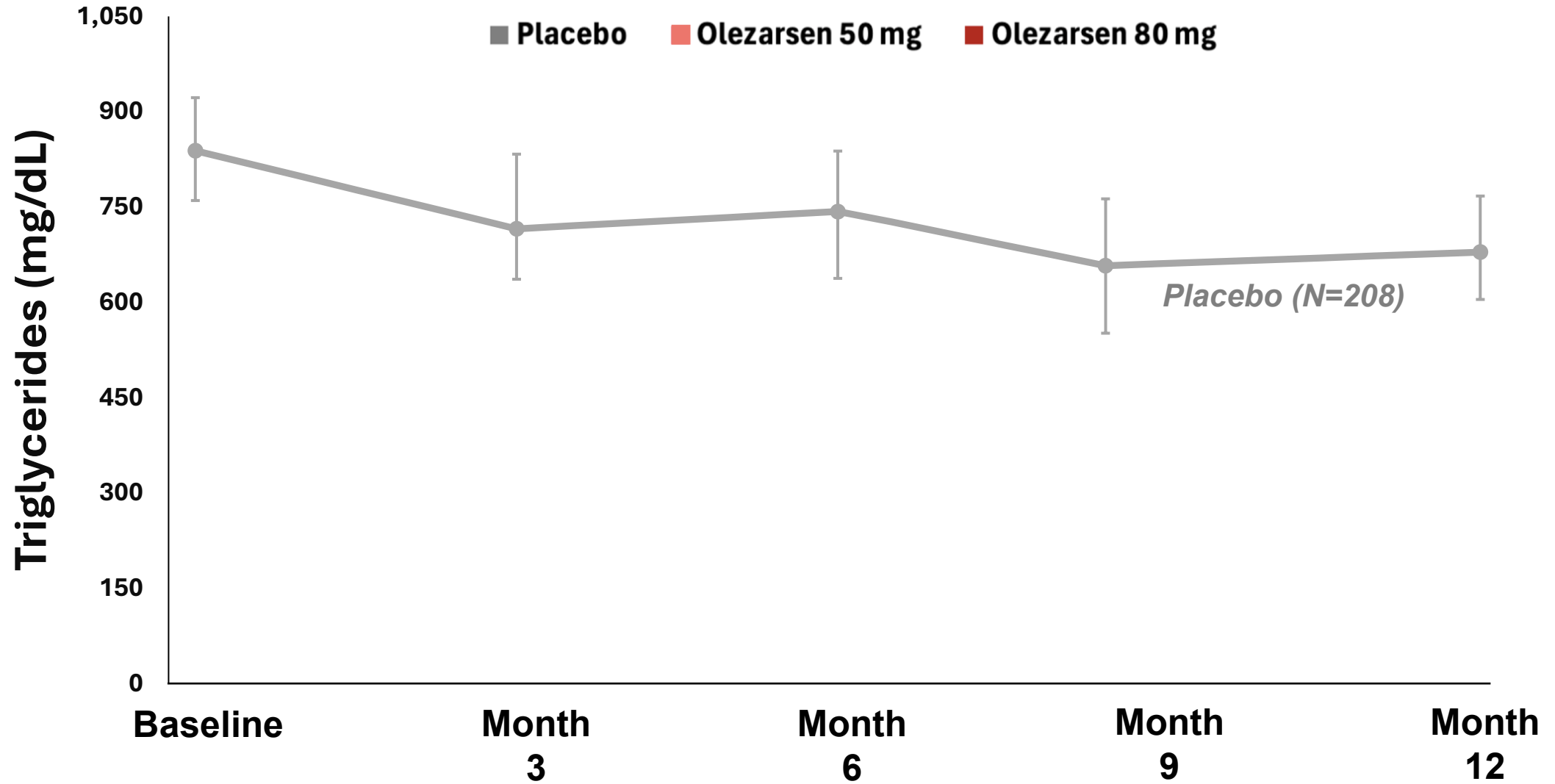
Patient Disposition



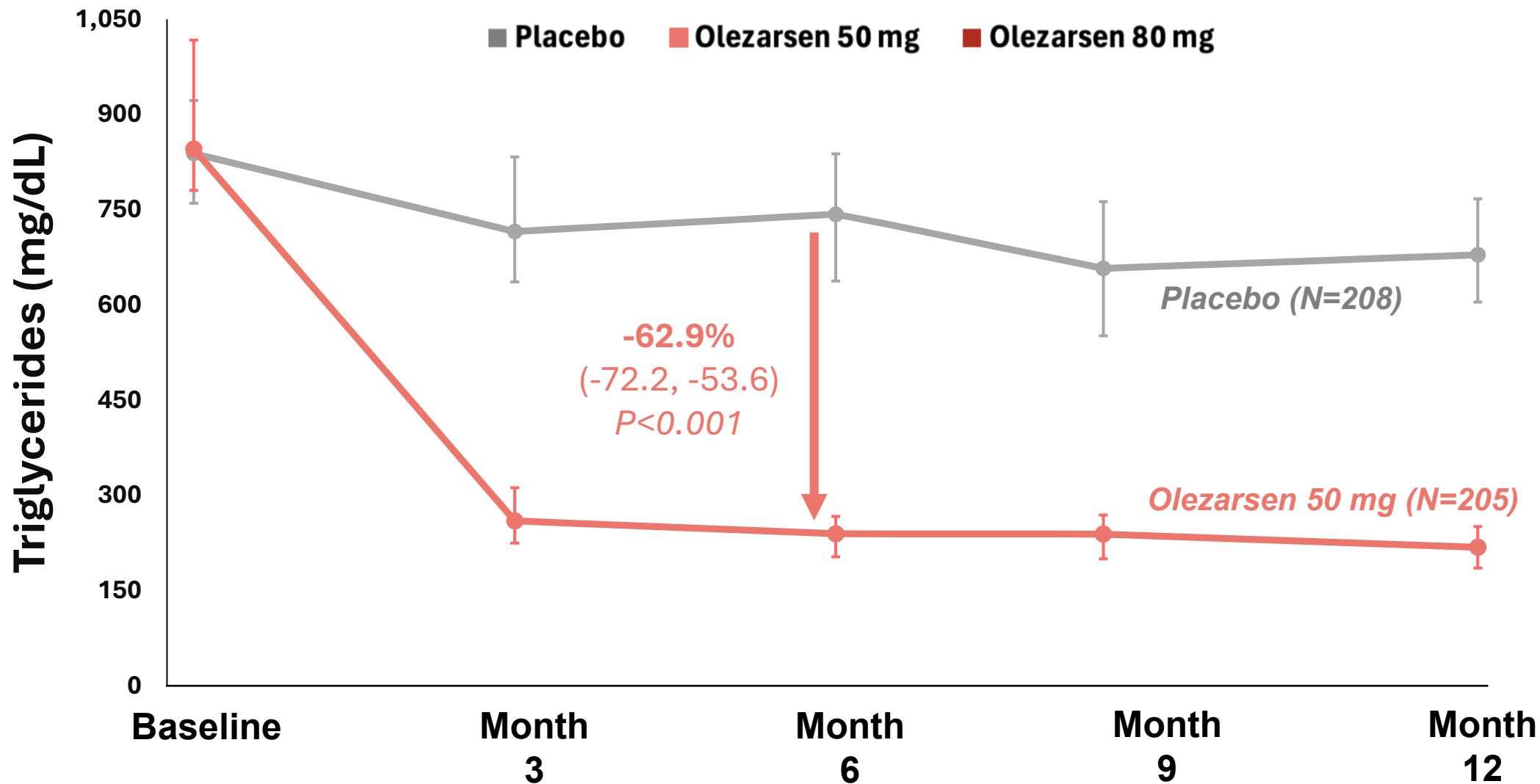
Baseline characteristics

	CORE N=617	CORE2 N=444
Age (yrs)	54 (45, 61)	54 (47, 62)
Female sex	24%	23%
Race/Ethnicity		
White	93%	82%
Hispanic/Latino	5%	22%

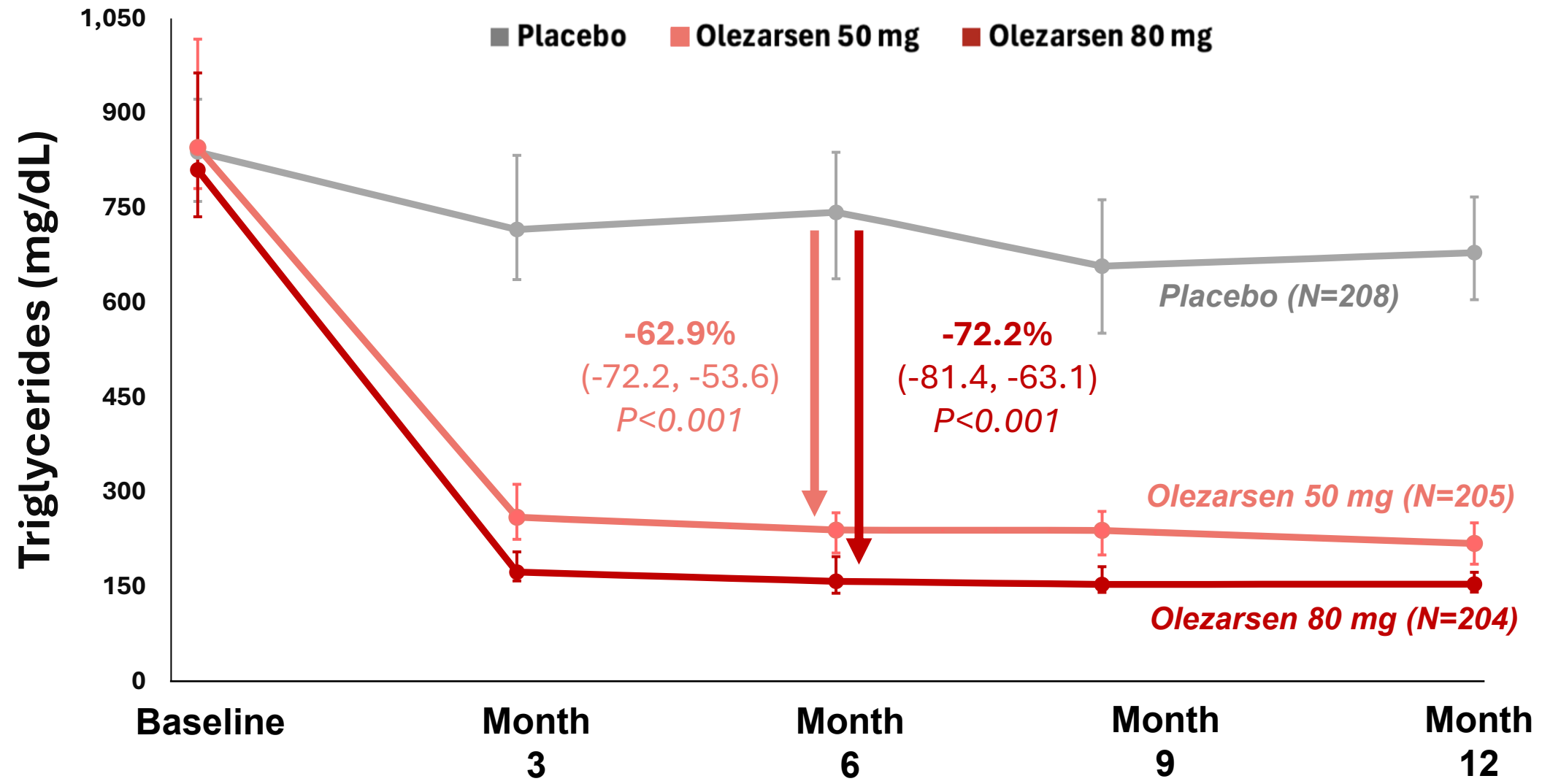
Primary Endpoint: CORE-TIMI 72a



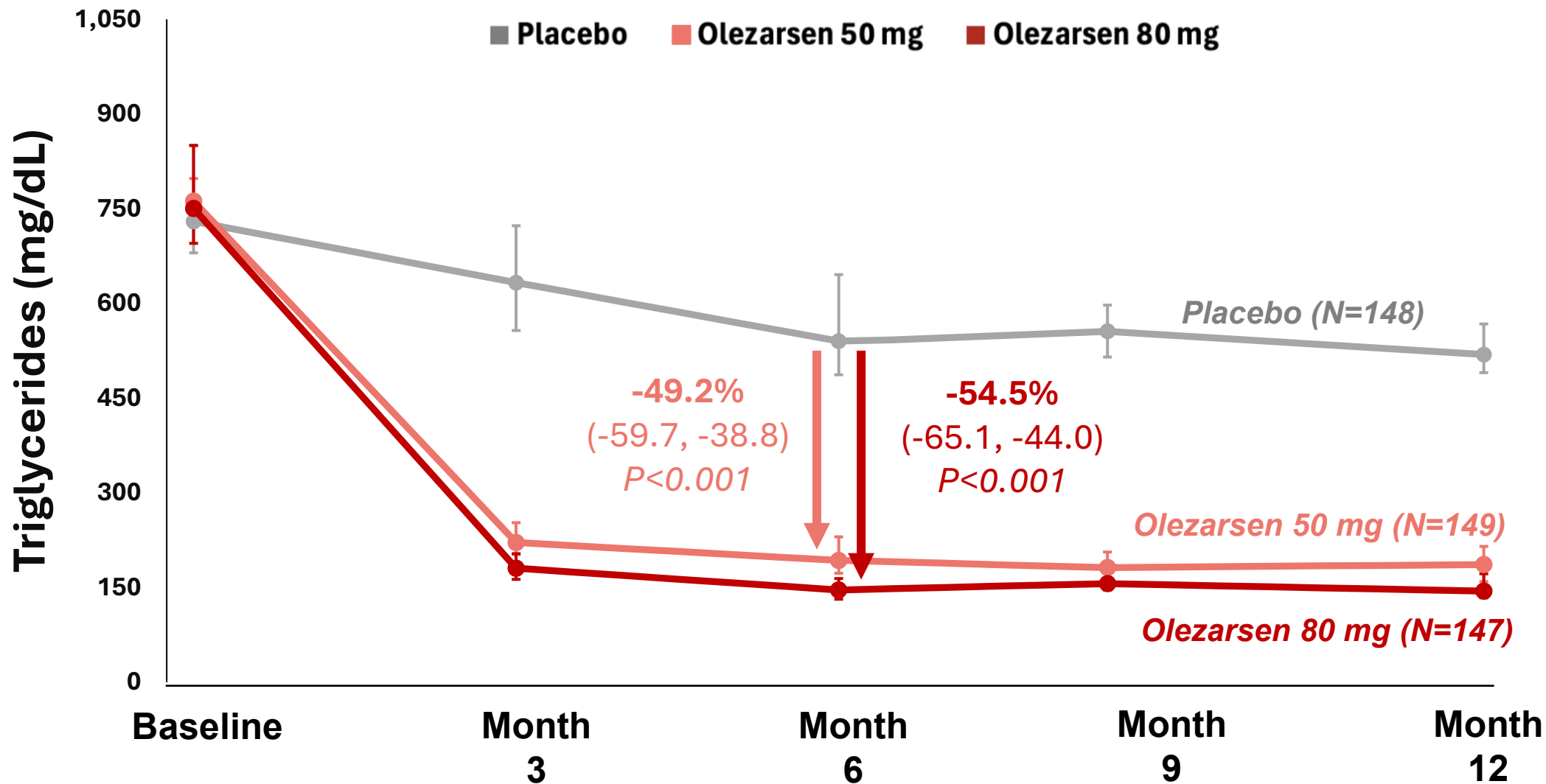
Primary Endpoint: CORE-TIMI 72a



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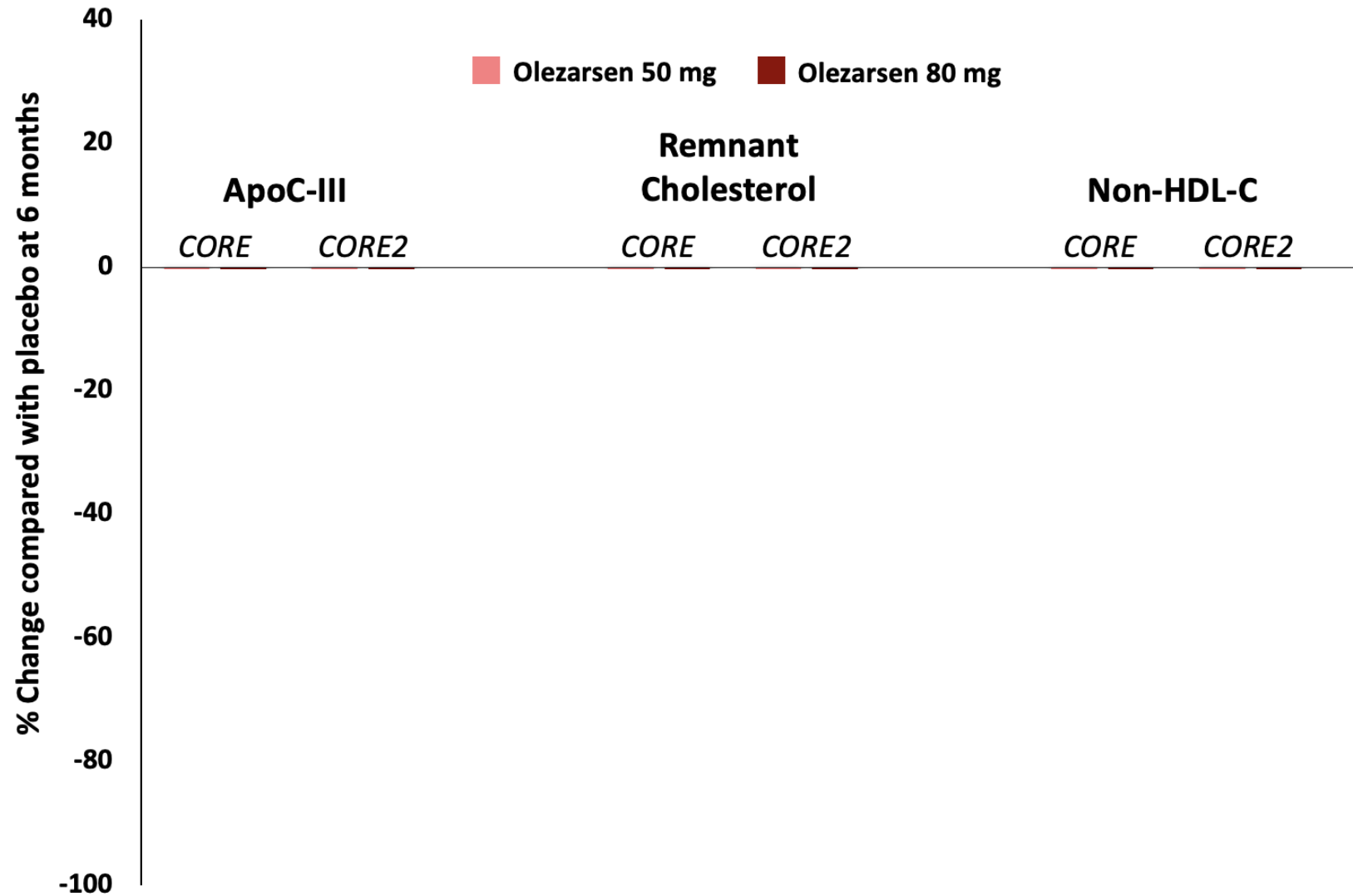


Primary Endpoint: CORE2-TIMI 72b



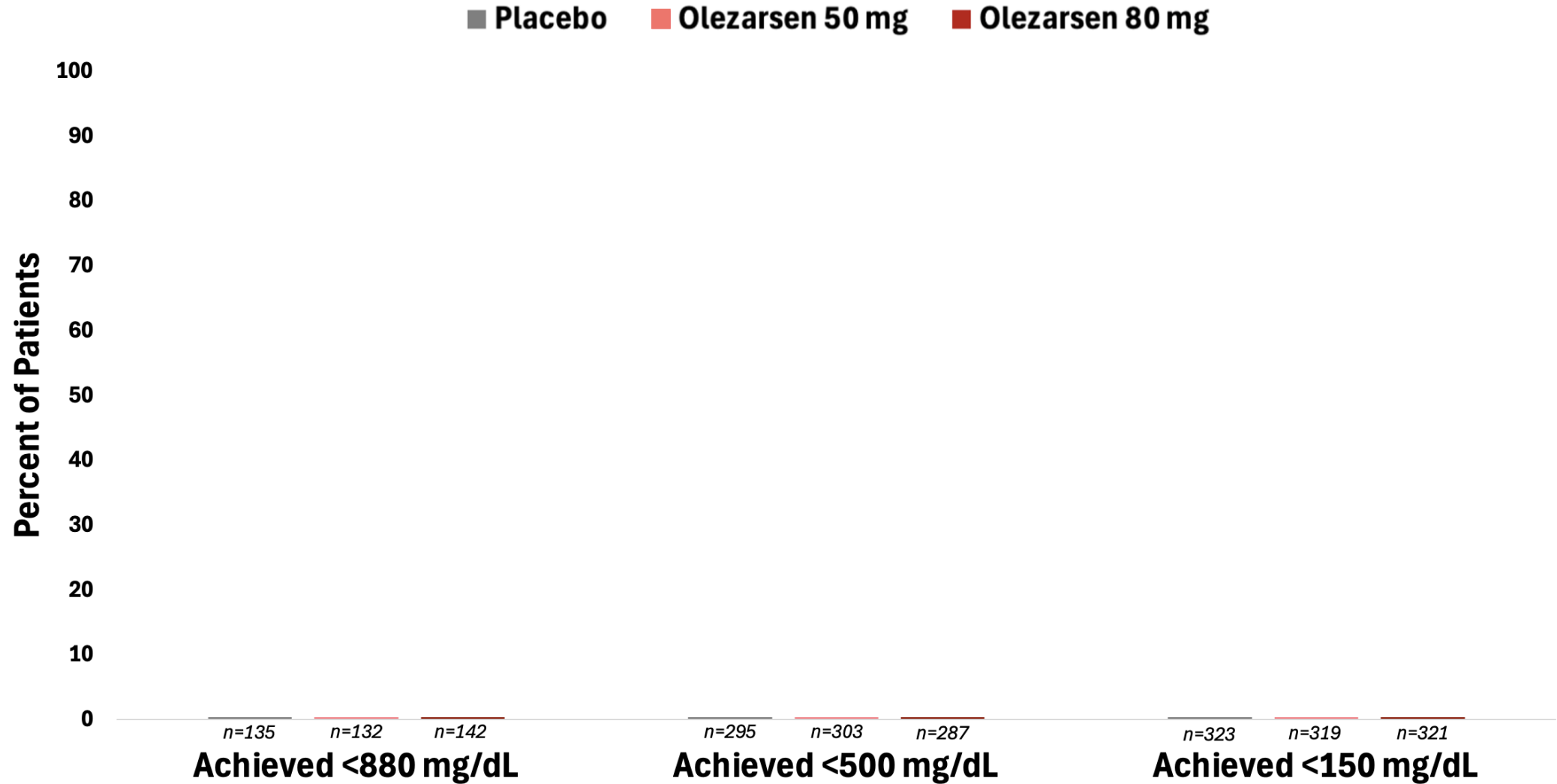
Secondary Lipid Endpoints

at 6 months



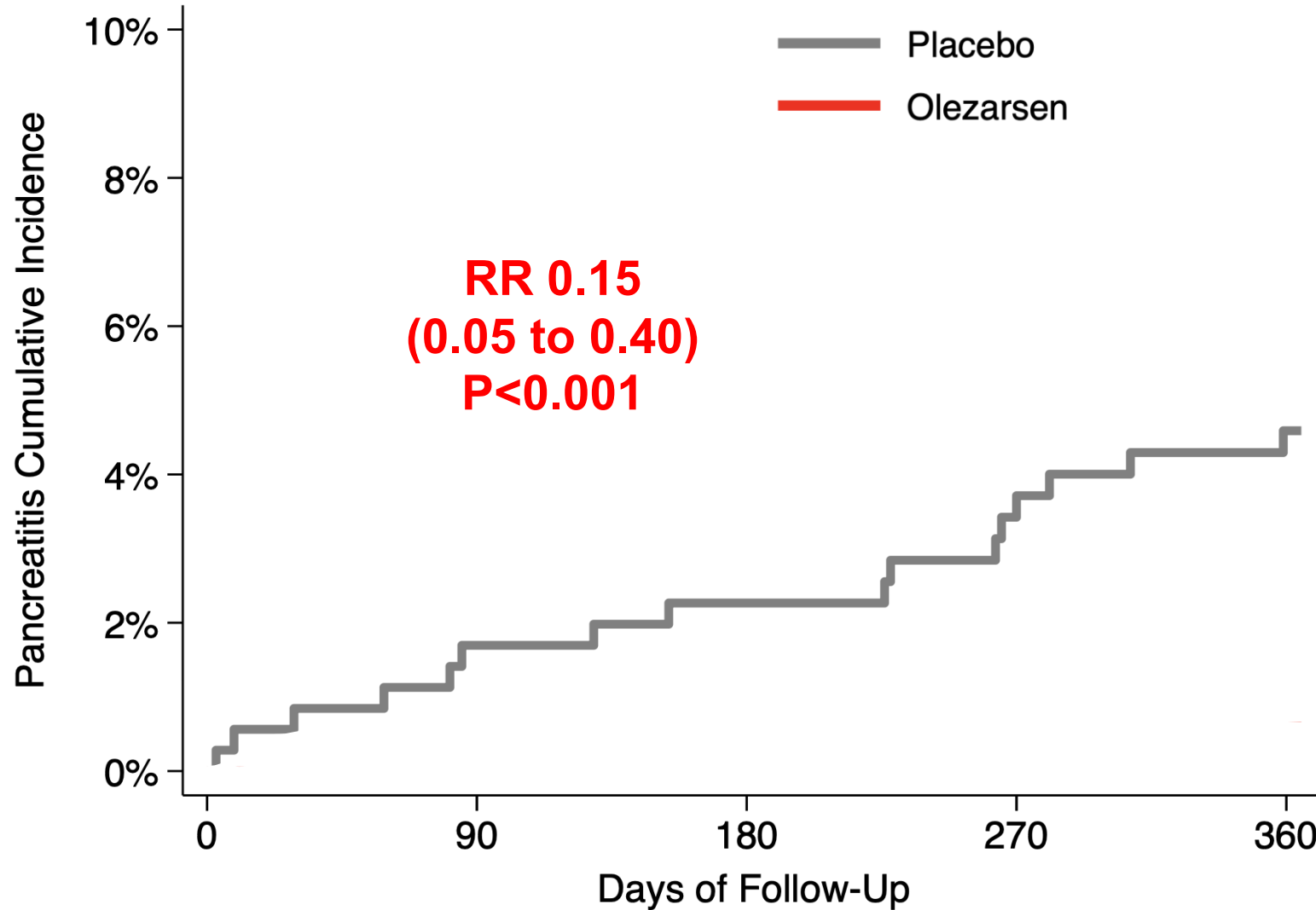
Achieved TG Levels at 12 months

Pooled analysis across trials



Acute Pancreatitis

Pooled analysis across both doses and trials

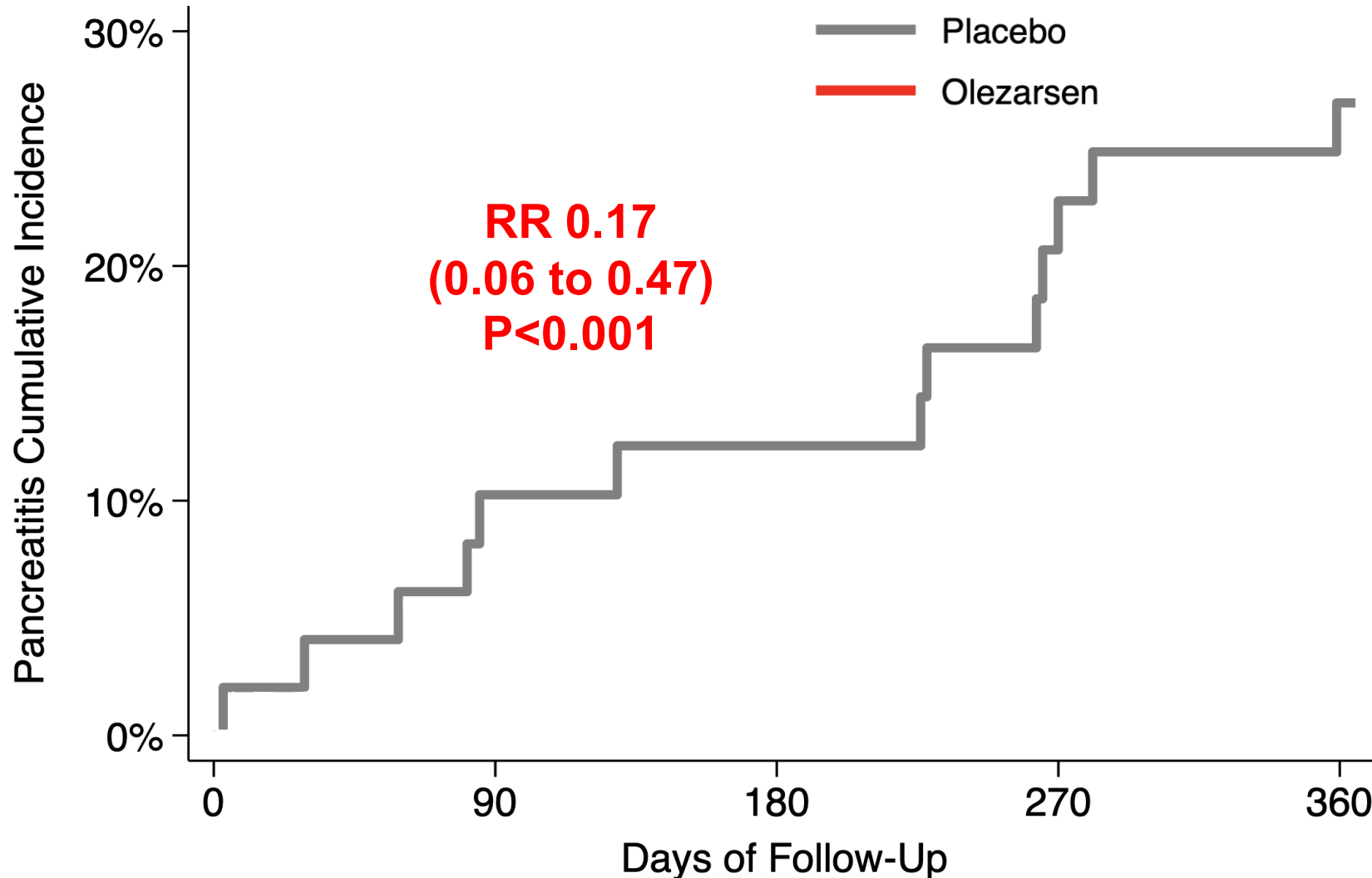


**ARR in incidence of total events
= 5.2%**

**NNT over 1 year
= 20**

Acute Pancreatitis

Prespecified Subgroup with TGs ≥ 880 mg/dL + Prior AP (N=141)



ARR in incidence of total events = 32.5%

NNT over 1 year = 4

Key Safety Parameters

Pooled analysis across trials

Treatment-emergent adverse events	Placebo N=356	Olezarsen 50 mg N=354	P-value vs Placebo	Olezarsen 80 mg N=351	P-value vs Placebo
Any	75%	75%	0.86	76%	0.64
Leading to drug discontinuation	2%	3%	0.25	4%	0.09
Serious	14%	9%	0.04	11%	0.24
Leading to drug discontinuation	0.3%	1%	0.22	0.6%	0.57

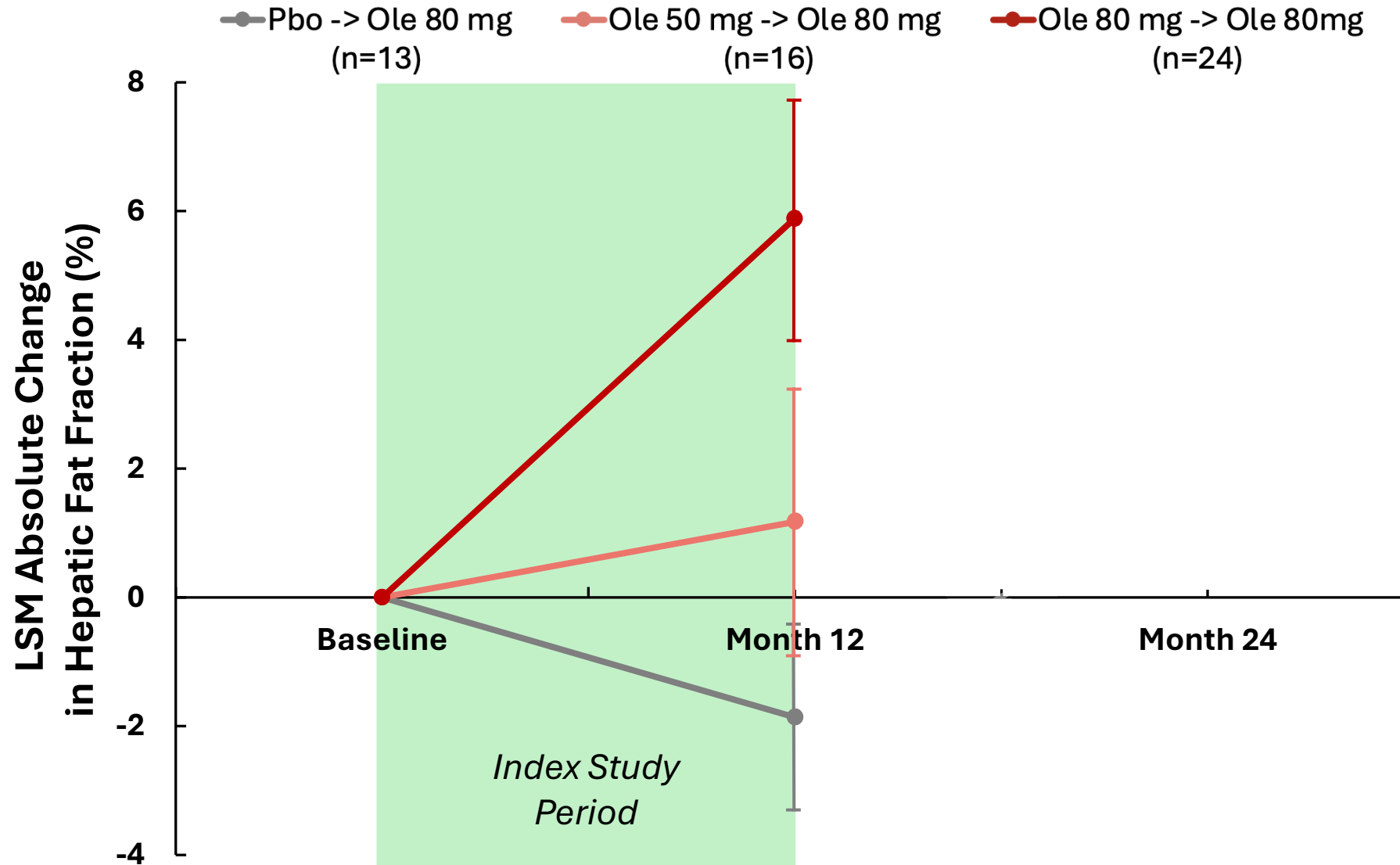
	Placebo	Olezarsen 50 mg	P-value vs Placebo	Olezarsen 80 mg	P-value vs Placebo
Hepatic parameters*					
ALT or AST $\geq 3x$ ULN	2%	3%	0.60	7%	0.003
ALT or AST $\geq 5x$ ULN	1%	1%	0.99	1%	0.47
Total bilirubin $\geq 2x$ ULN	<1%	<1%	0.99	1%	0.56

Patients with ALT/AST $< 3x$ ULN at screening/qualification were allowed to be enrolled

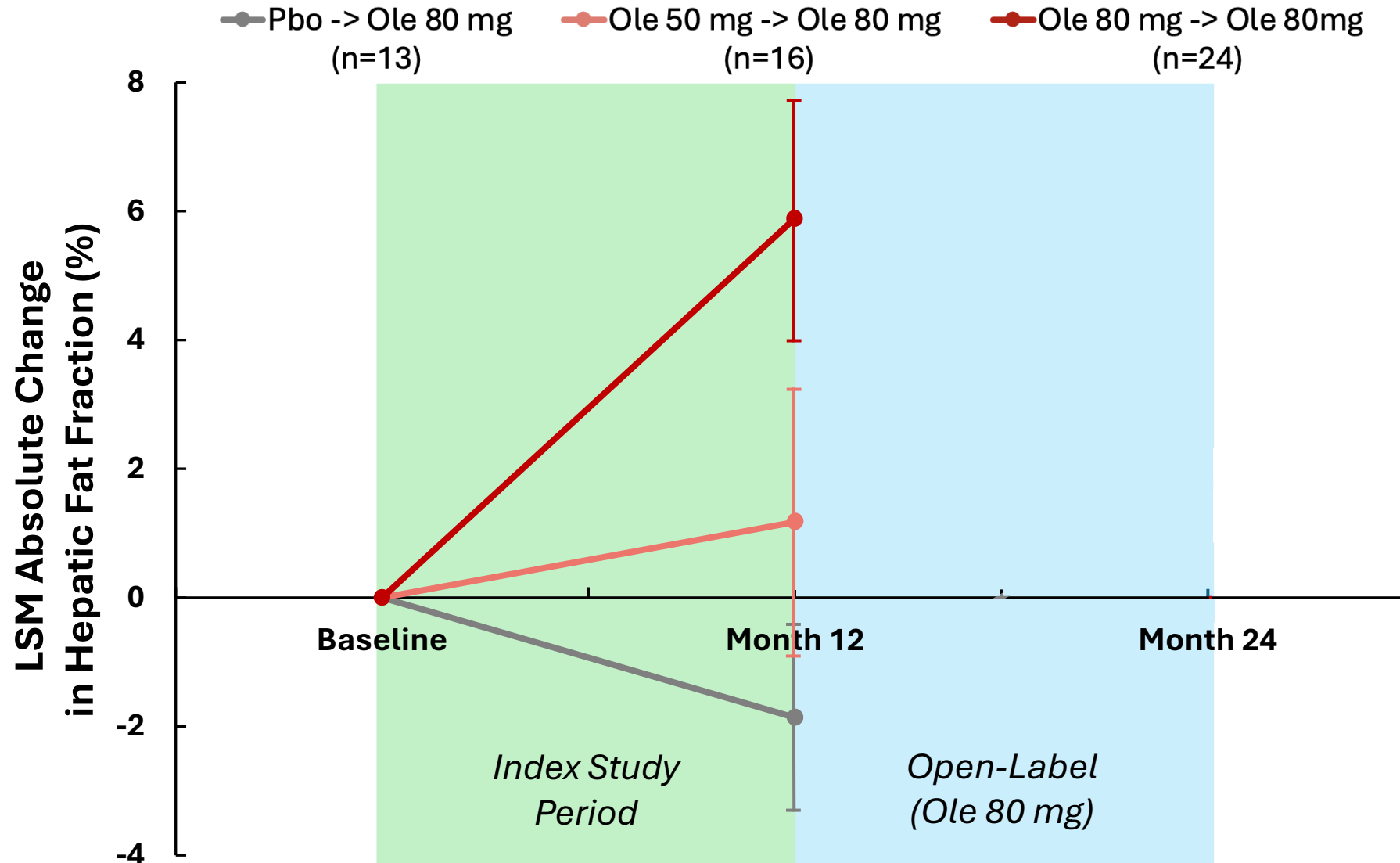
*There were no cases meeting Hy's Law criteria. Changes in HFF were not associated with changes in LFTs.

^No major bleeding events were associated with low platelet counts.

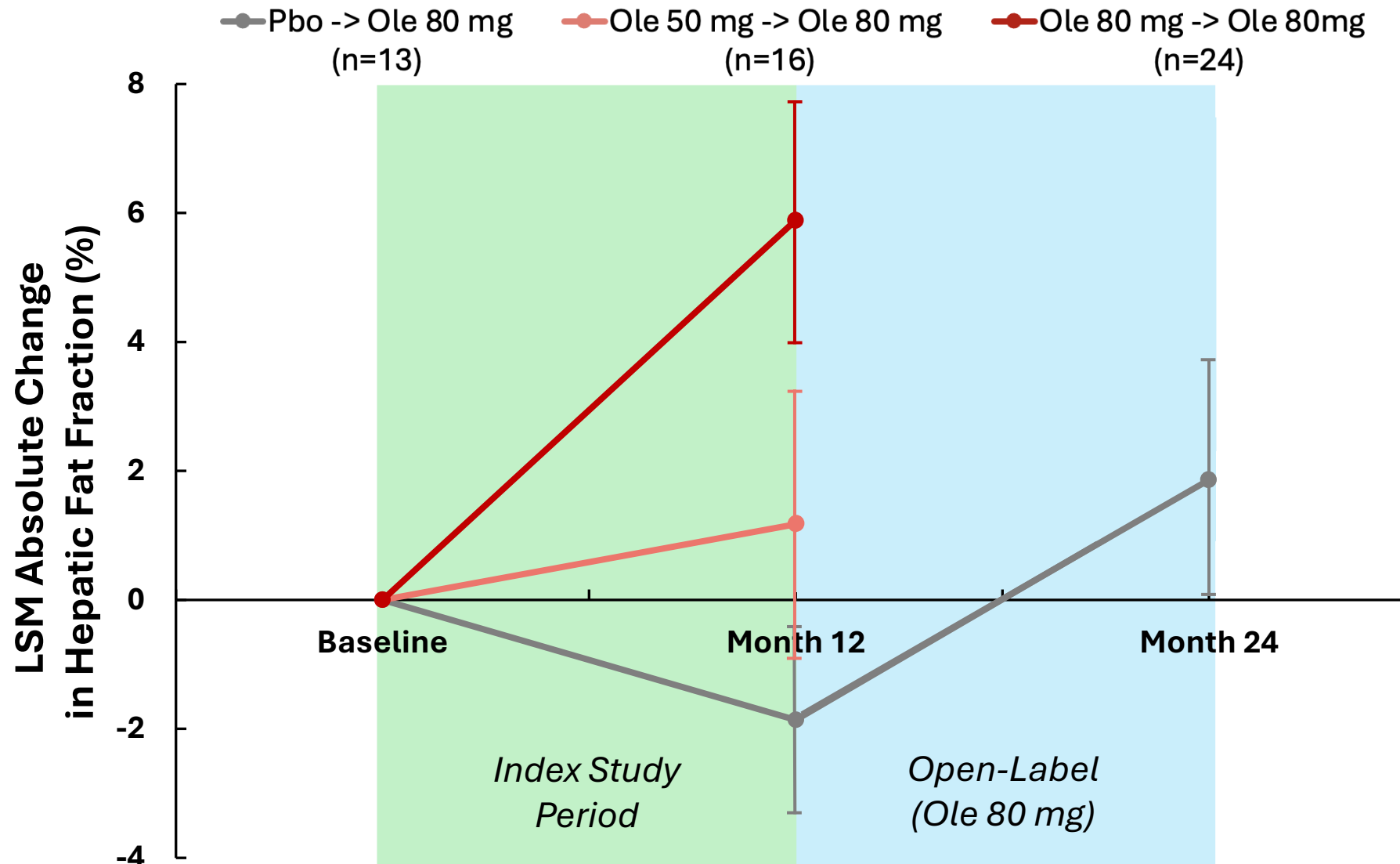
Preliminary 24-month HFF data (n=53)



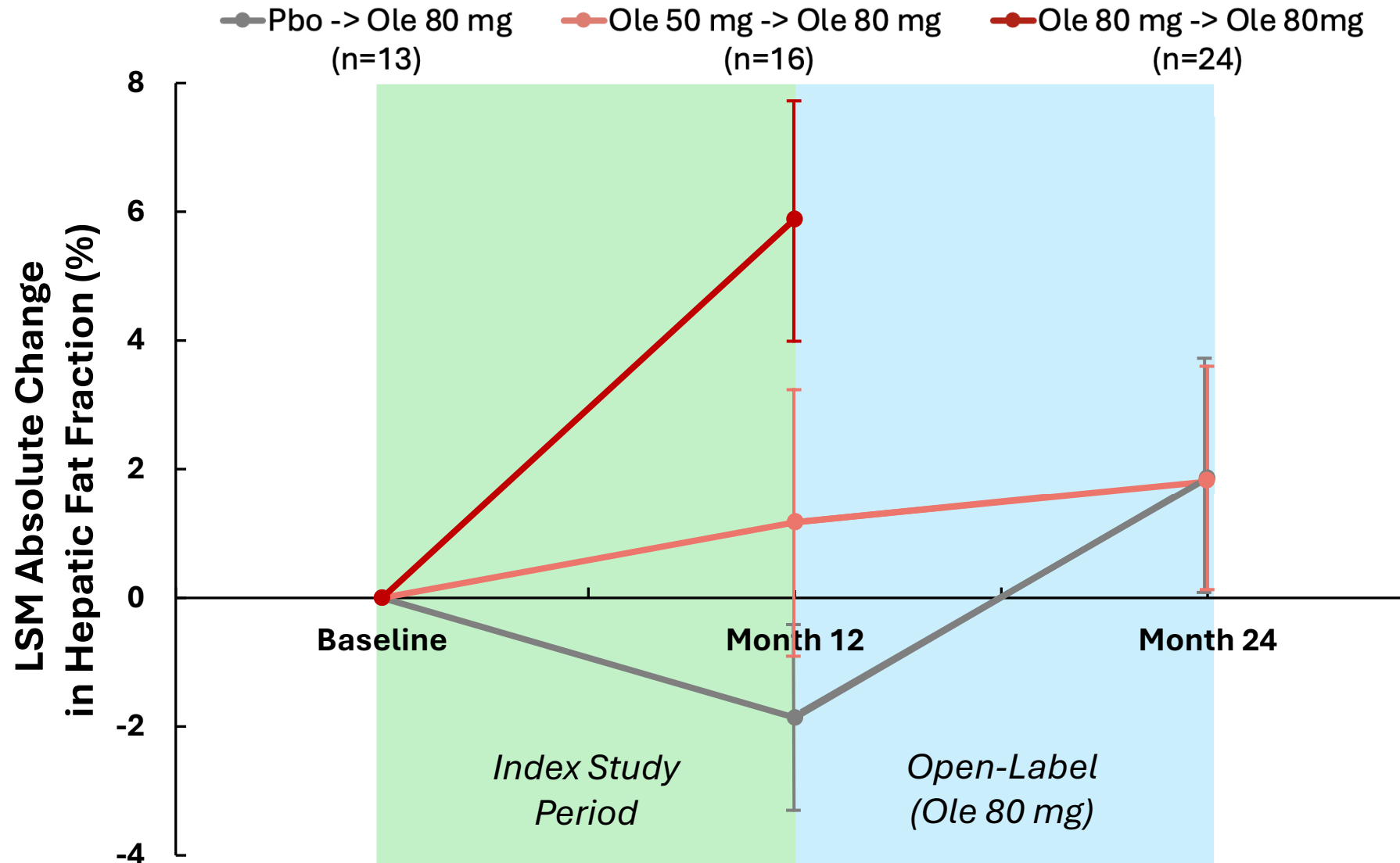
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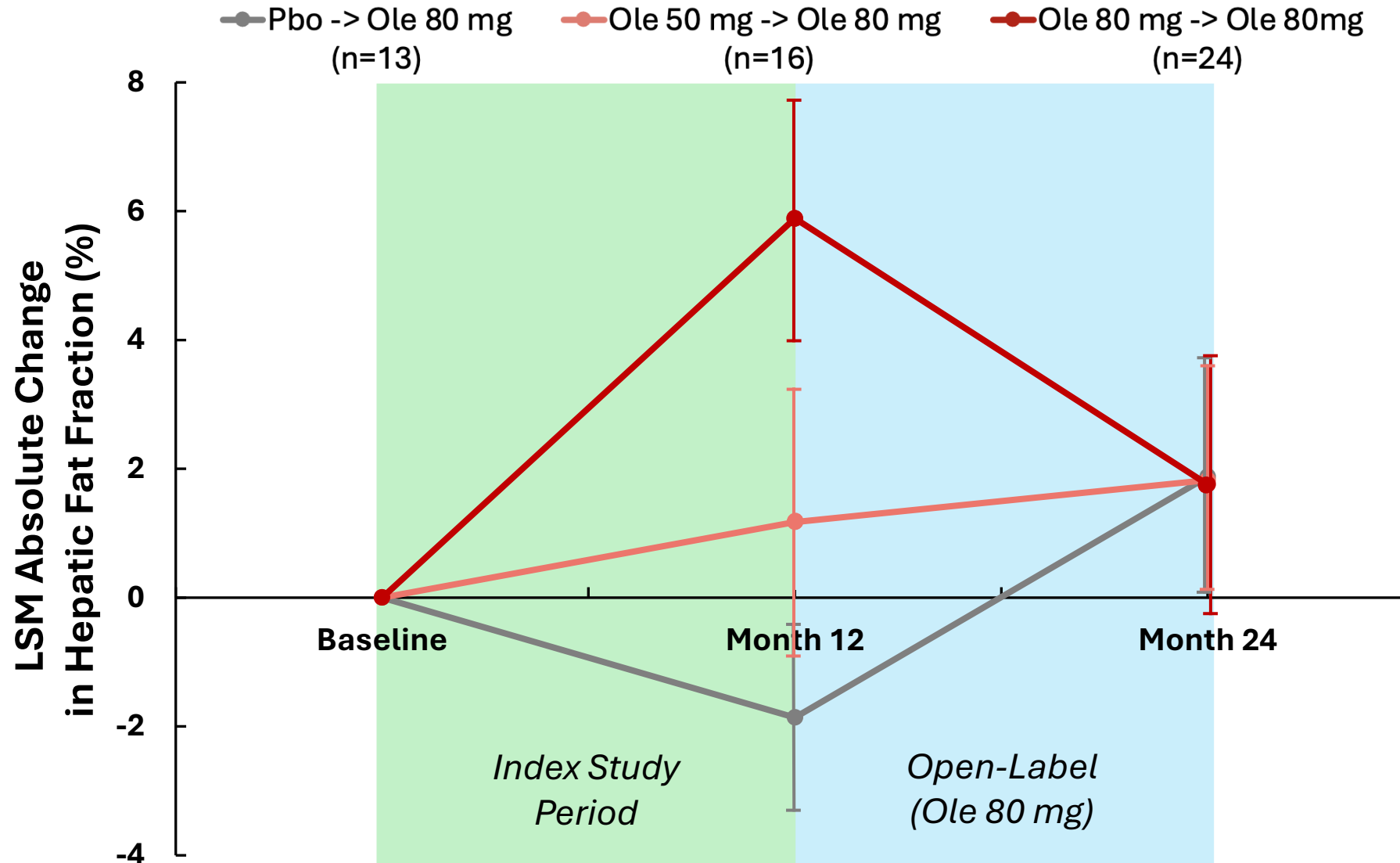
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- **Among patients with severe hypertriglyceridemia, olezarsen:**
 - Lowered triglycerides by 49-72%, which is more than conventional therapies
 - Resulted in >85% of patients achieving levels below 500 mg/dL
 - Reduced the risk of acute pancreatitis by 85%, a first in sHTG
 - Was generally well-tolerated, with ongoing monitoring in the OLE
- **These findings support the use of olezarsen in patients with severe hypertriglyceridemia to reduce triglyceride levels and risk of acute pancreatitis**

Thank You