

# Olezarsen in Patients with Severe Hypertriglyceridemia

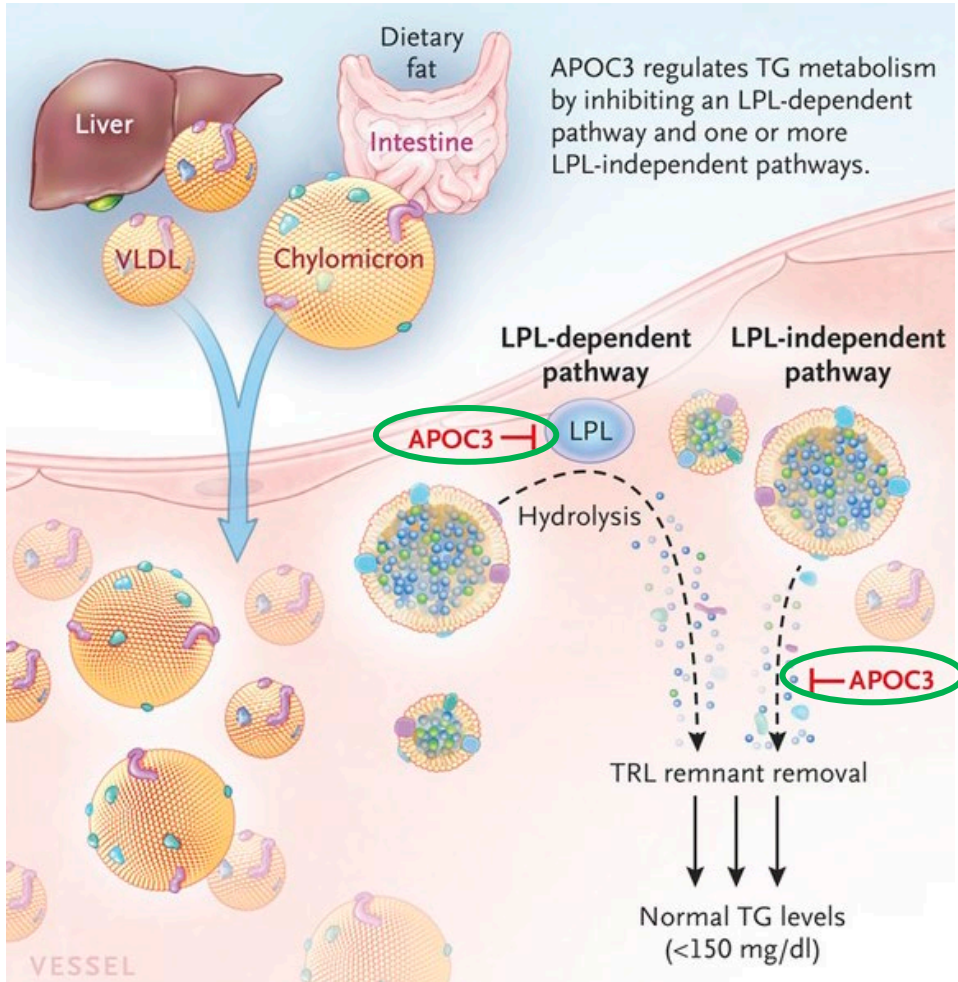
*Results of CORE-TIMI 72a & CORE2-TIMI 72b*

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TIMI Study Group

Brigham and Women's Hospital

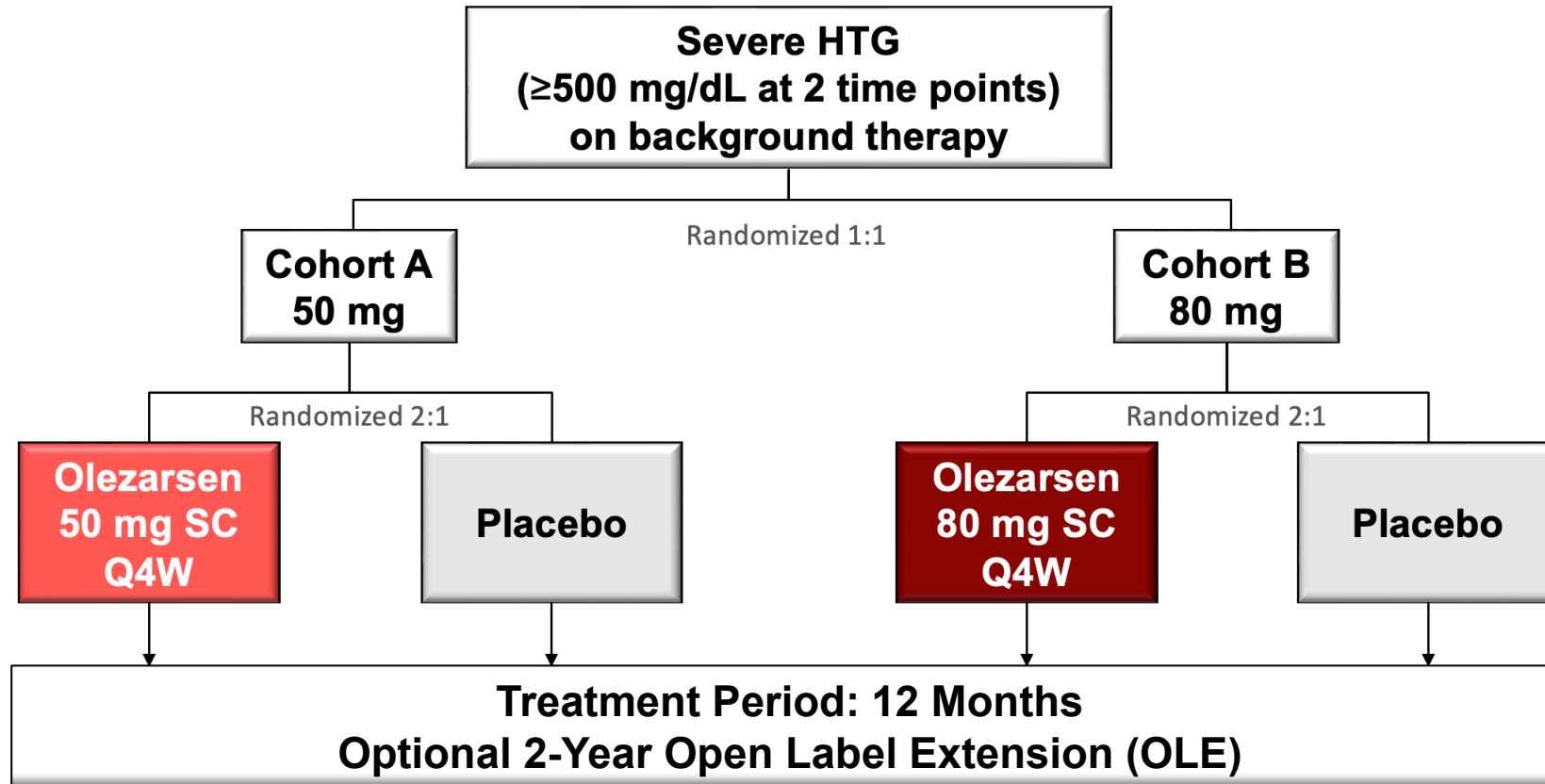
- The CORE and CORE2 trials were funded by Ionis Pharmaceuticals.
- Dr. Marston reports clinical trial involvement with Ionis, Amgen, and Marea, consulting fees from Amgen, Ionis, Verve/Lilly, New Amsterdam, Radence, and Arboretum, and speaking fees from Amgen, Ionis, and Verve/Lilly.



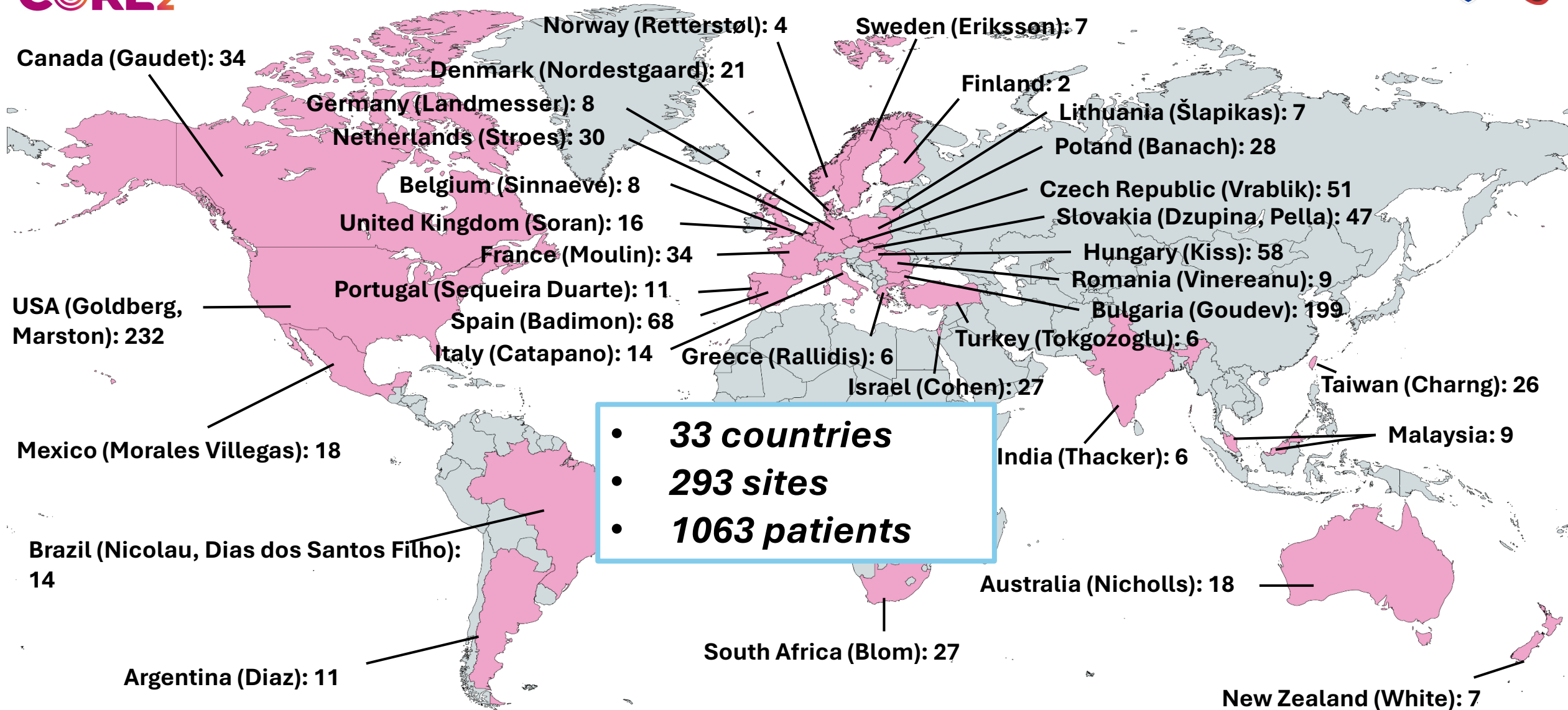
- Severe hypertriglyceridemia (sHTG), defined as triglycerides (TGs) of 500 mg/dL (5.65 mmol/L) or greater, carries an increased risk of acute pancreatitis
- Apolipoprotein C-III (APOC3) inhibits:
  - lipoprotein lipase, a key enzyme in TG metabolism
  - hepatic uptake of TG-rich lipoproteins (TRLs)
- 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*

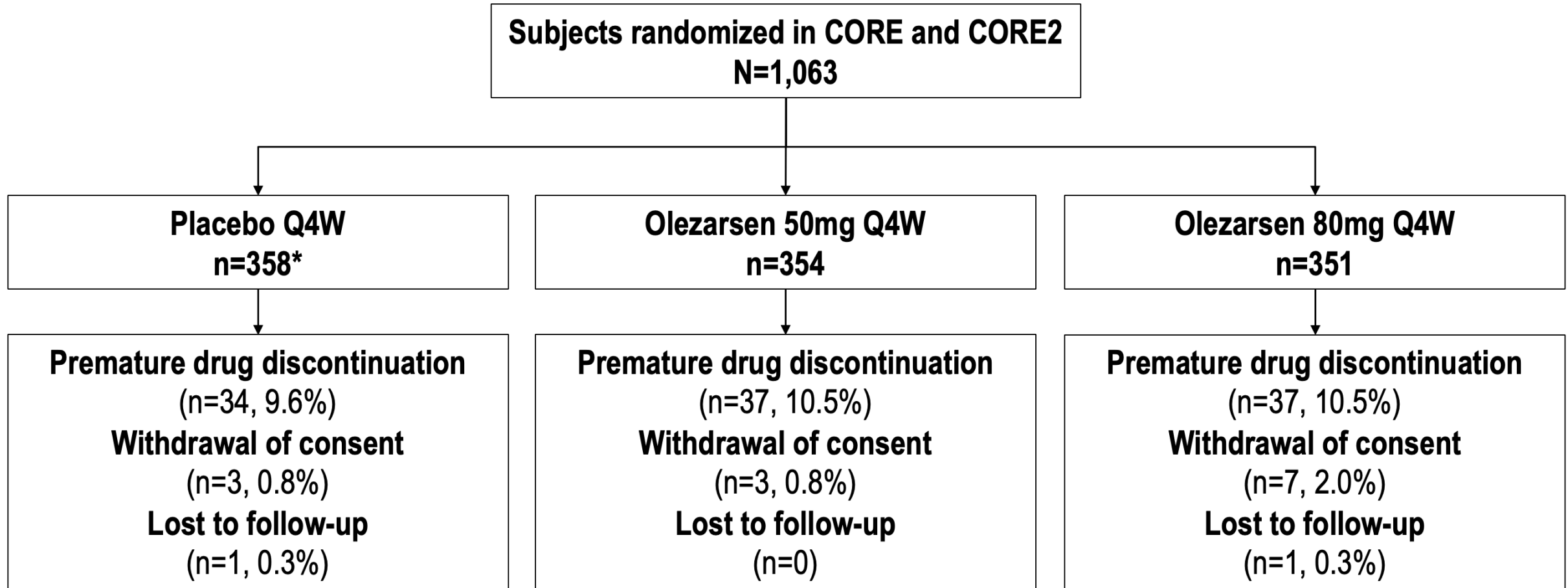


# Global Enrollment



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

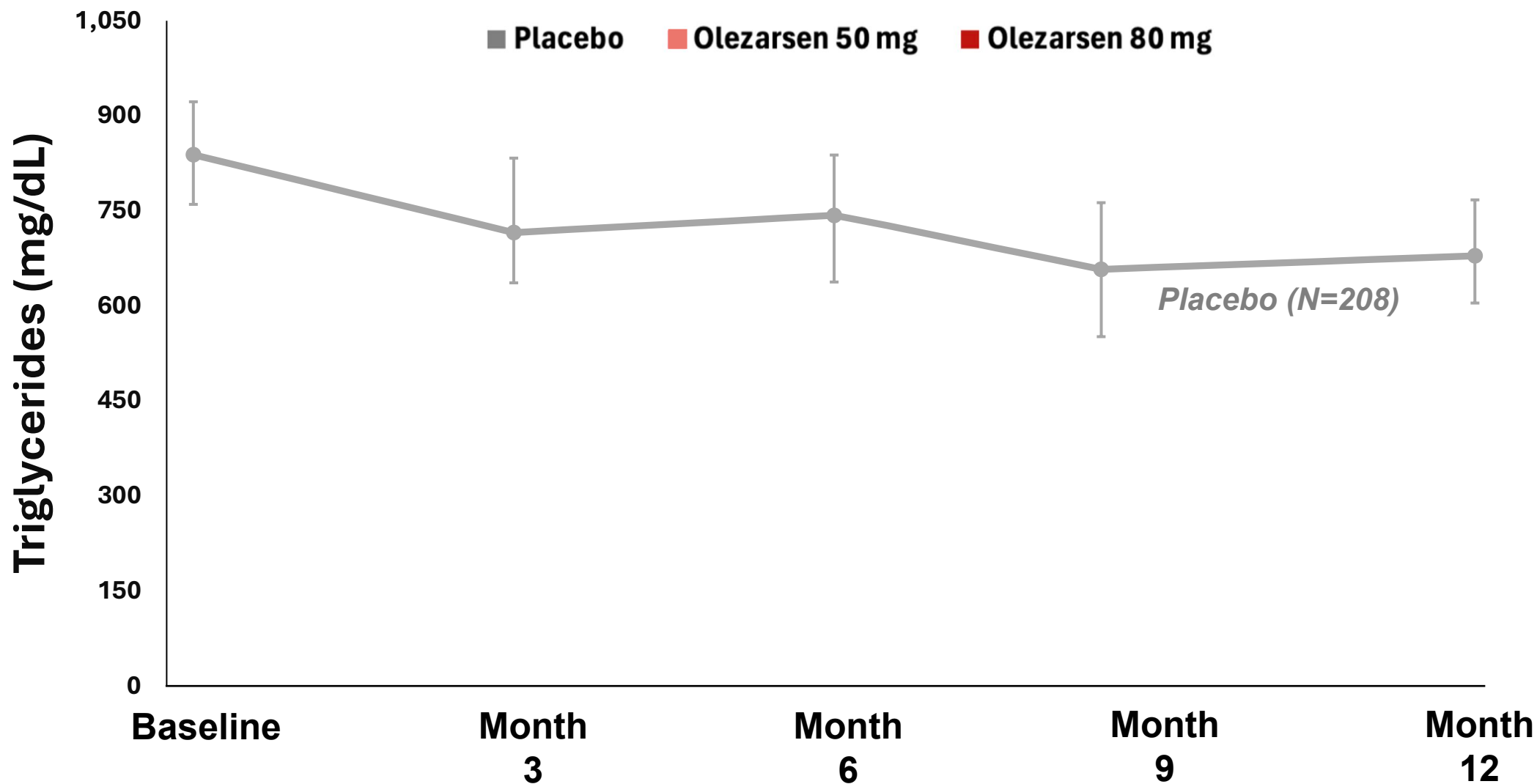
# Patient Disposition



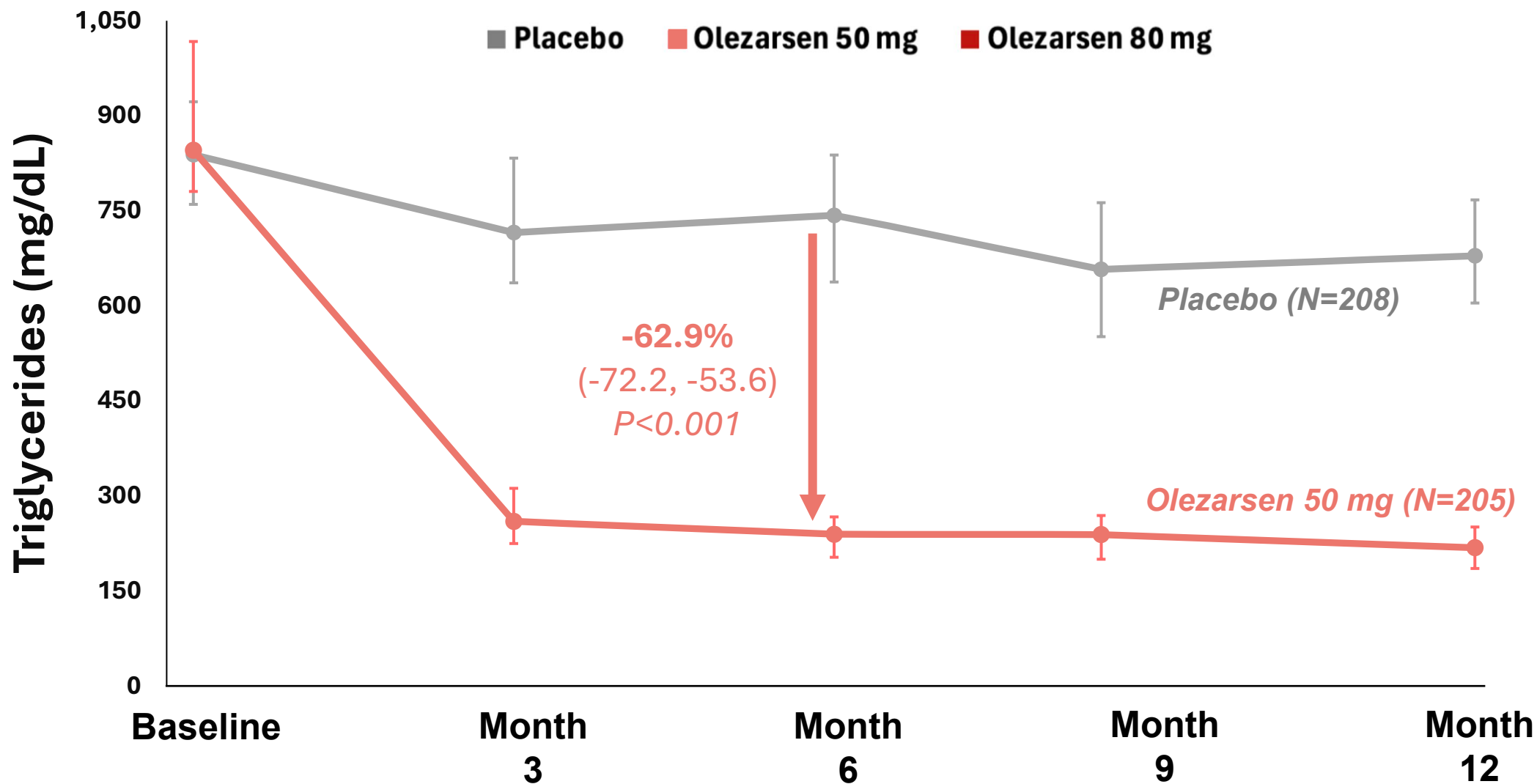
# Baseline characteristics

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

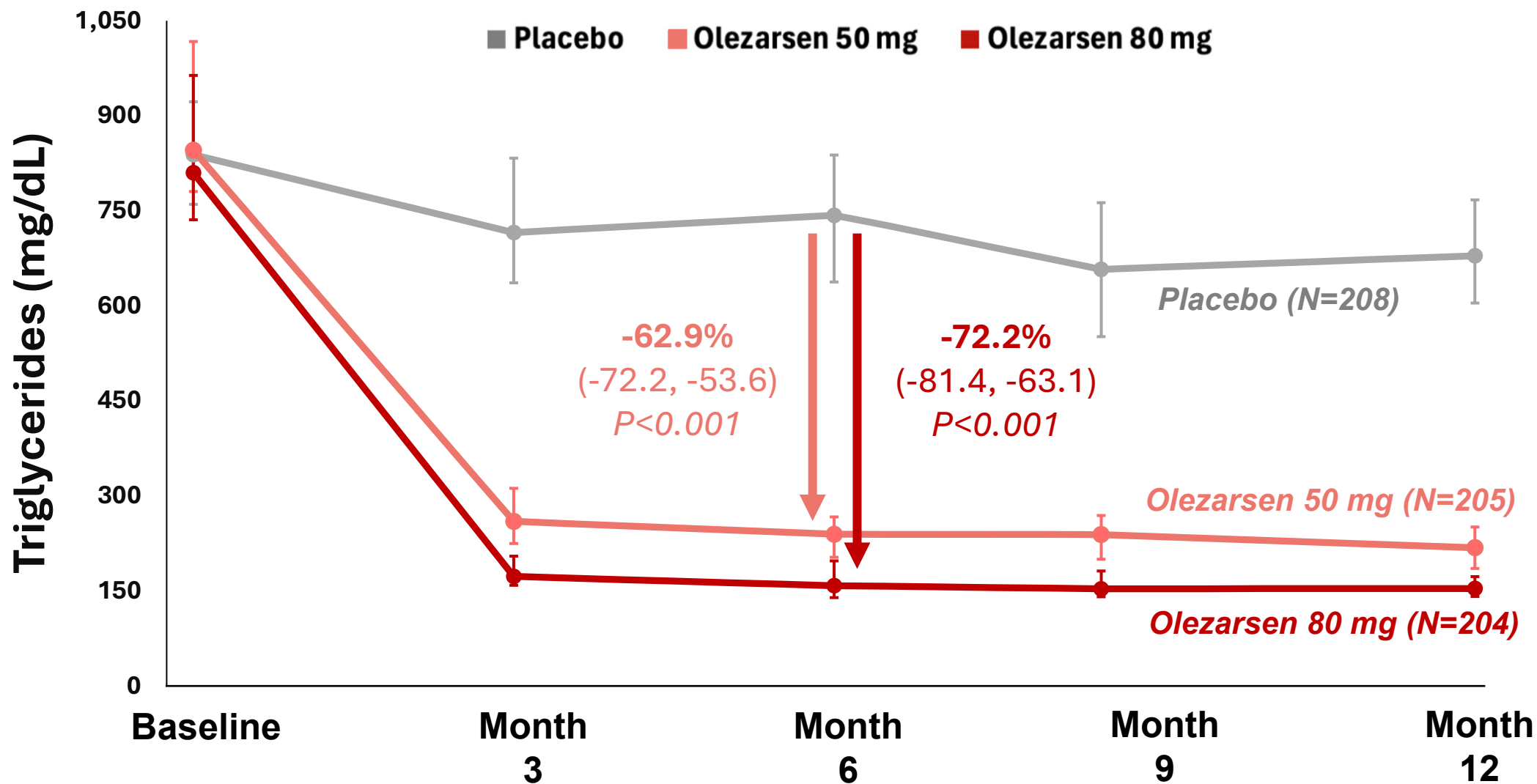
# Primary Endpoint: CORE-TIMI 72A



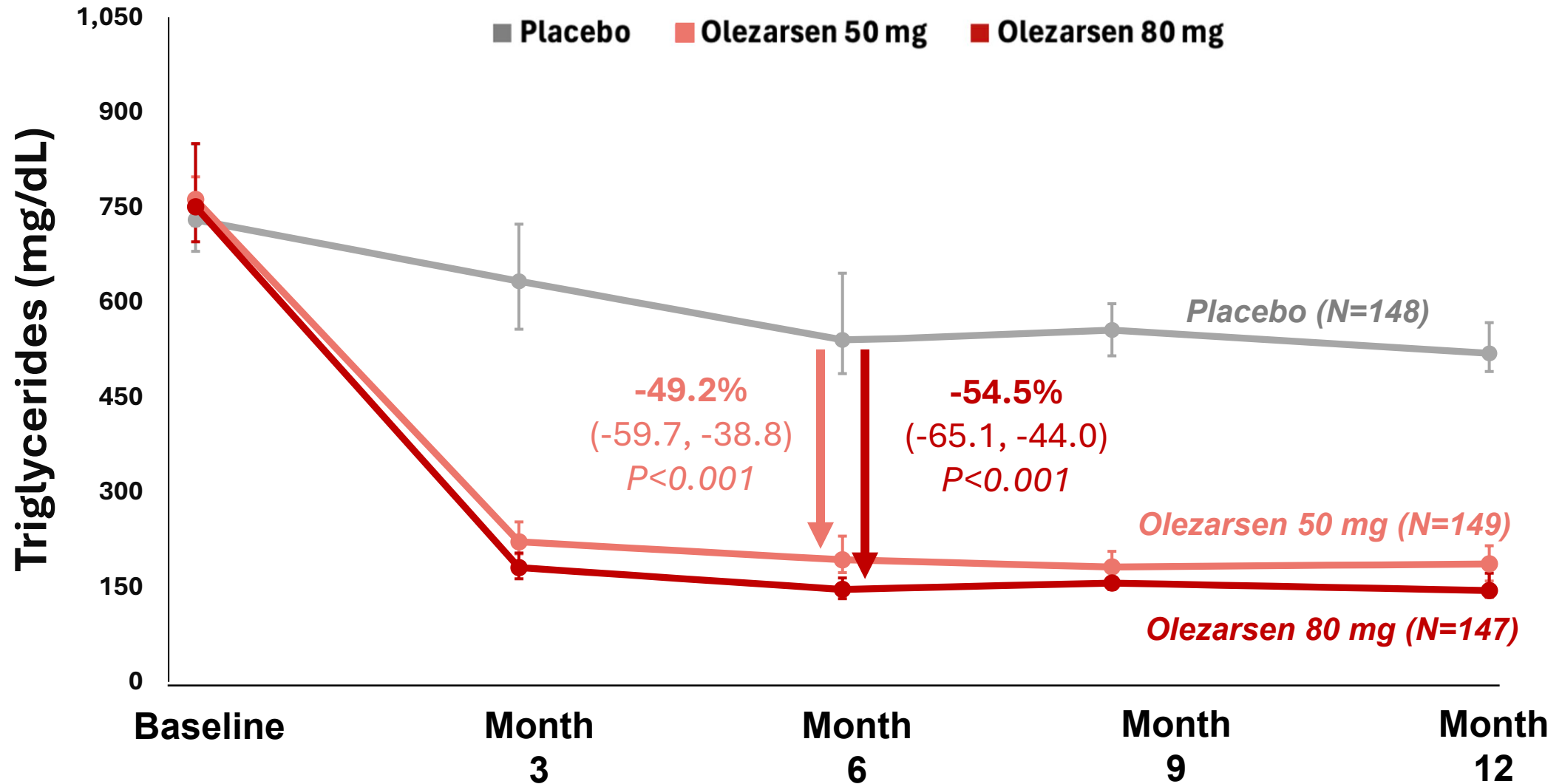
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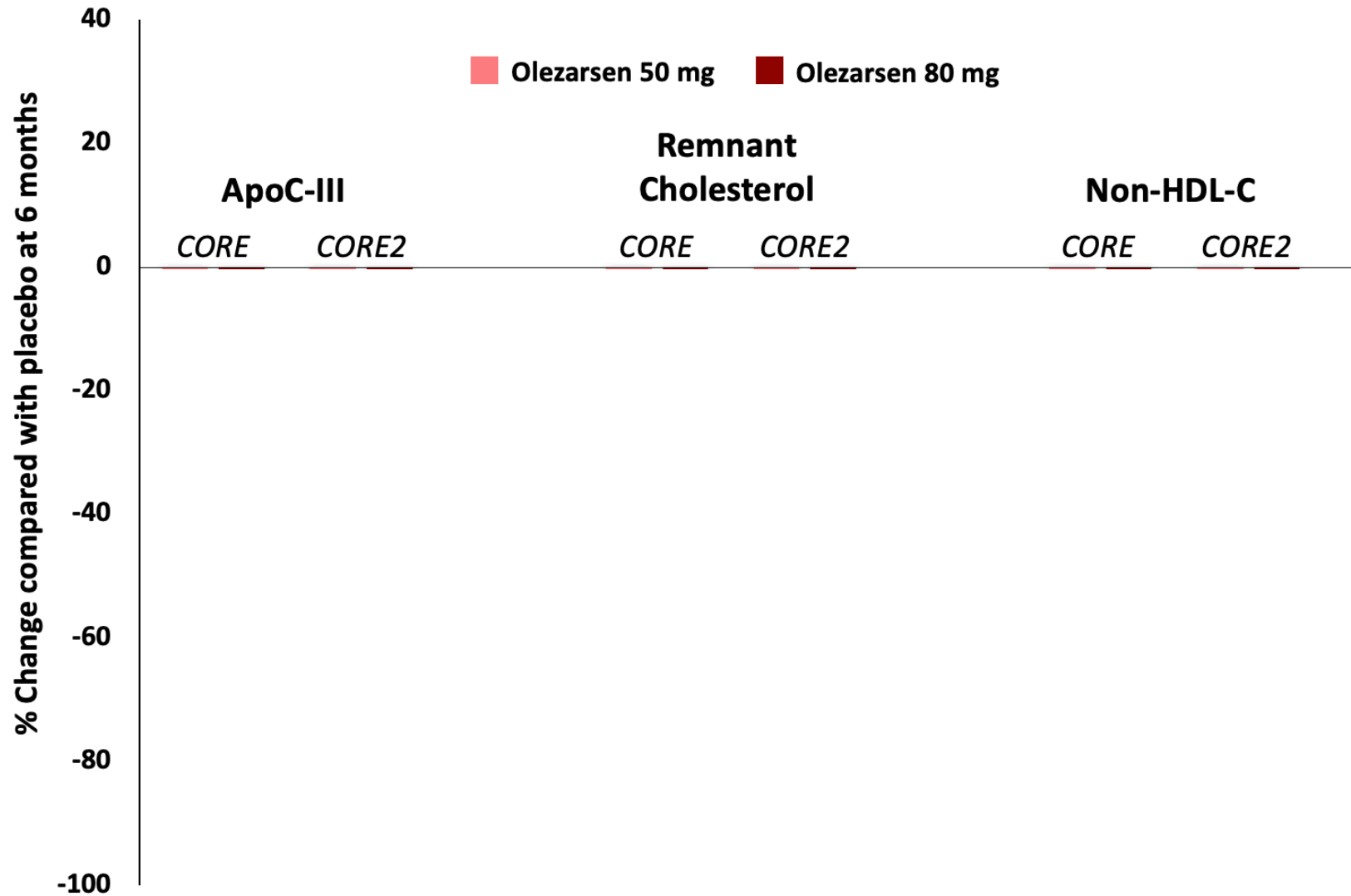


# Primary Endpoint: CORE2-TIMI 72B



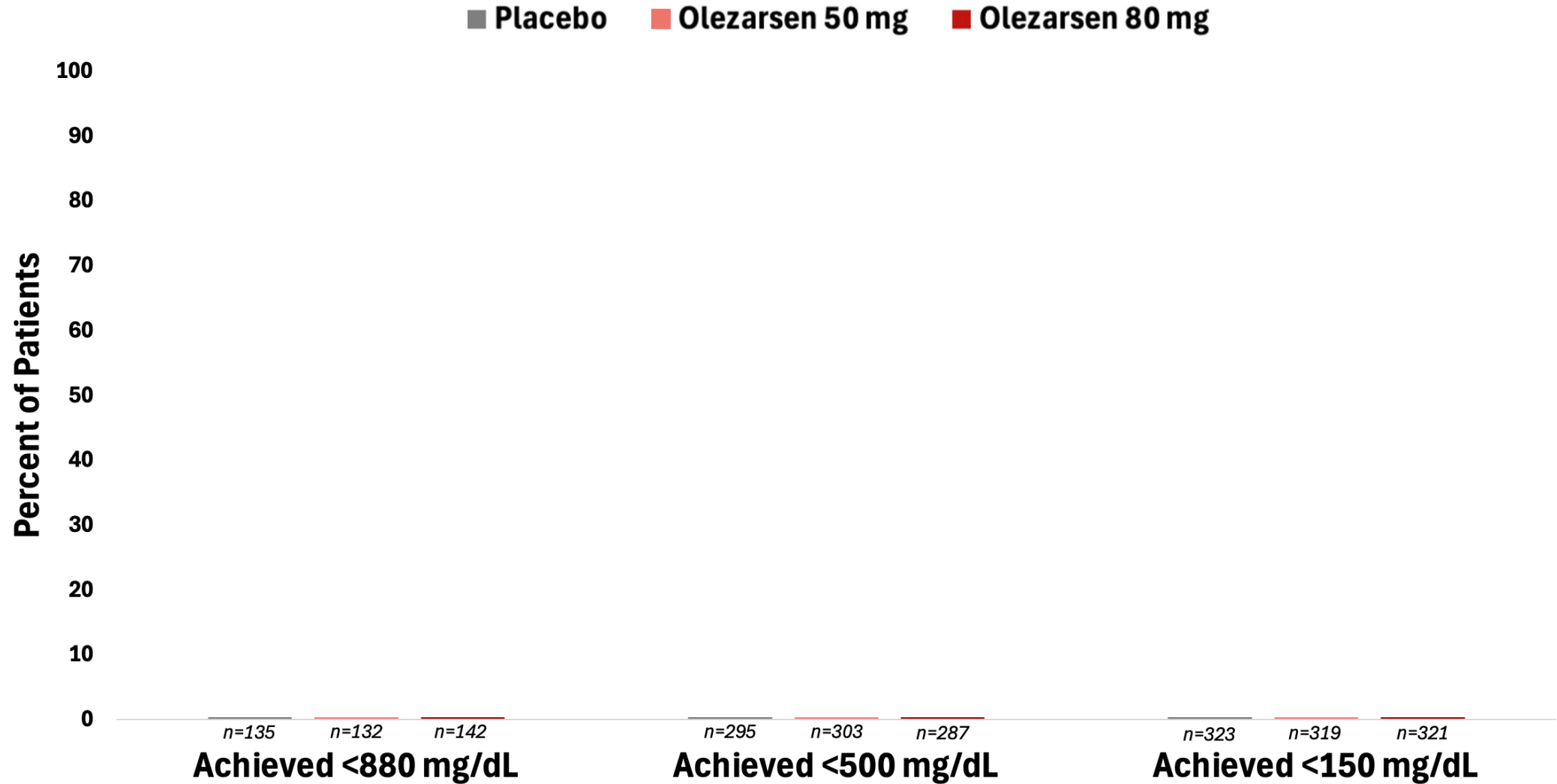
# Secondary Lipid Endpoints

at 6 months



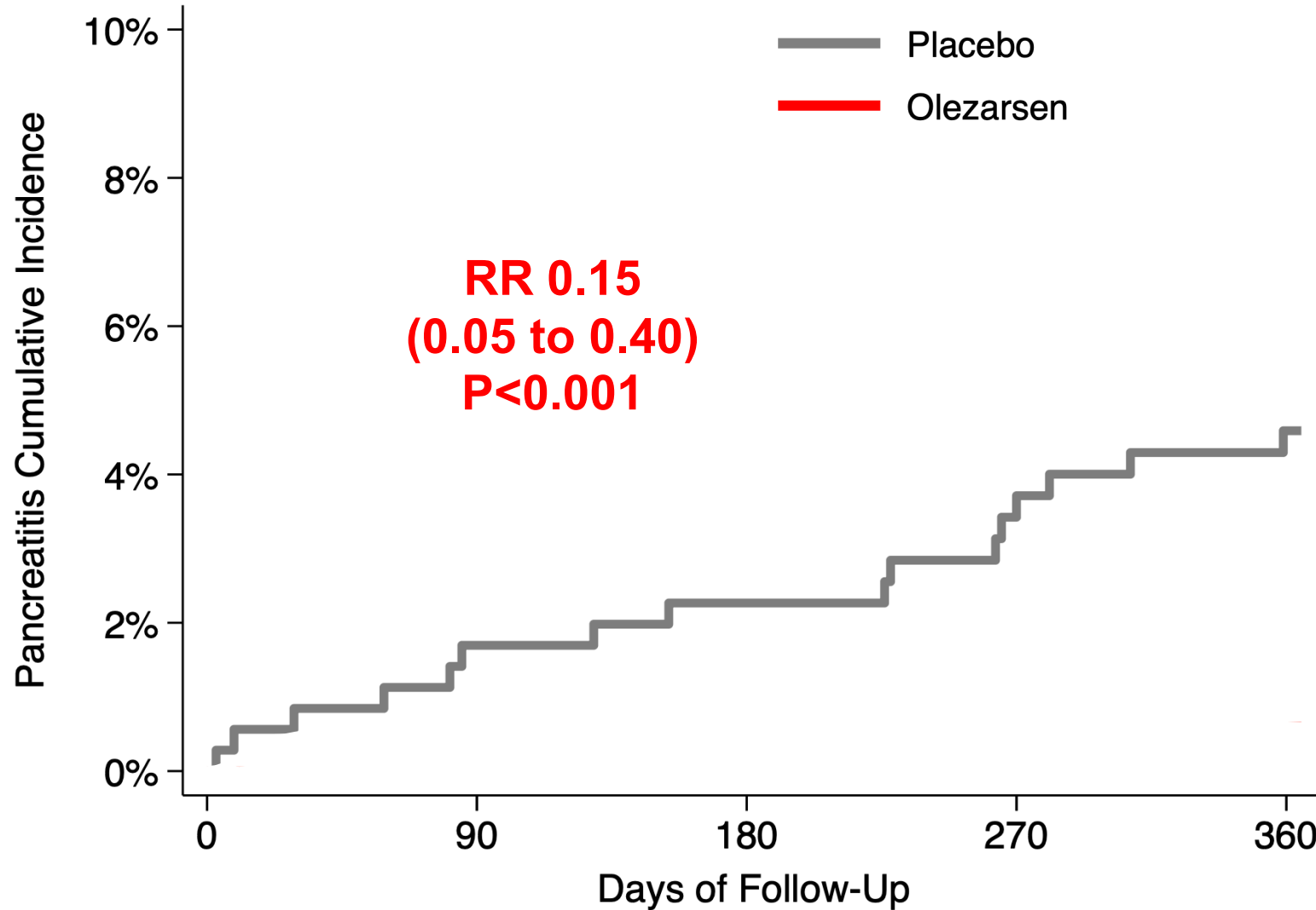
# Achieved TG Levels at 12 months

*Pooled analysis across trials*



# Acute Pancreatitis

*Pooled analysis across both doses and trials*

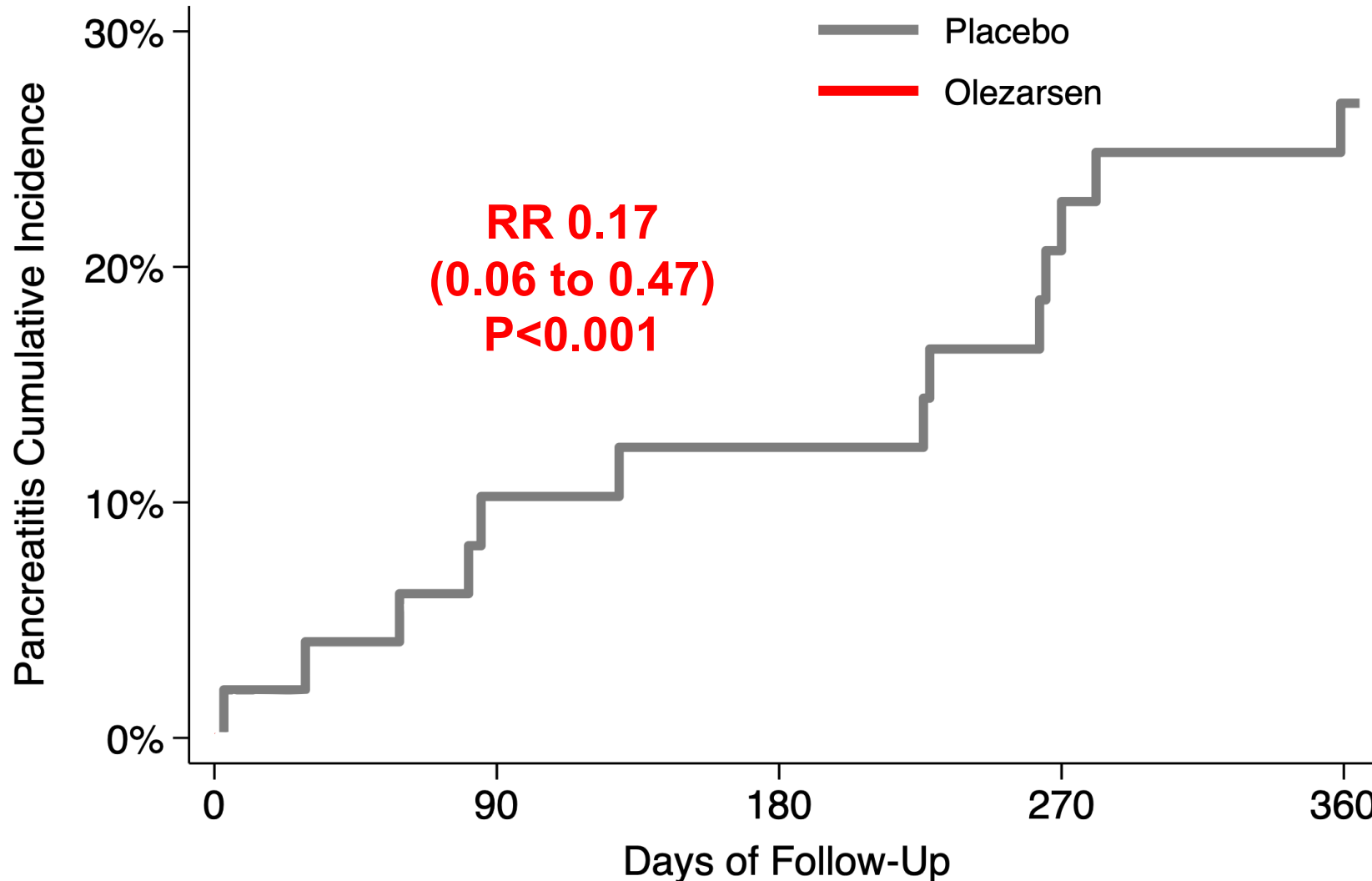


**ARR in incidence of total events**  
**= 5.2%**

**NNT over 1 year**  
**= 20**

# Acute Pancreatitis

Prespecified Subgroup with TGs  $\geq 880$  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

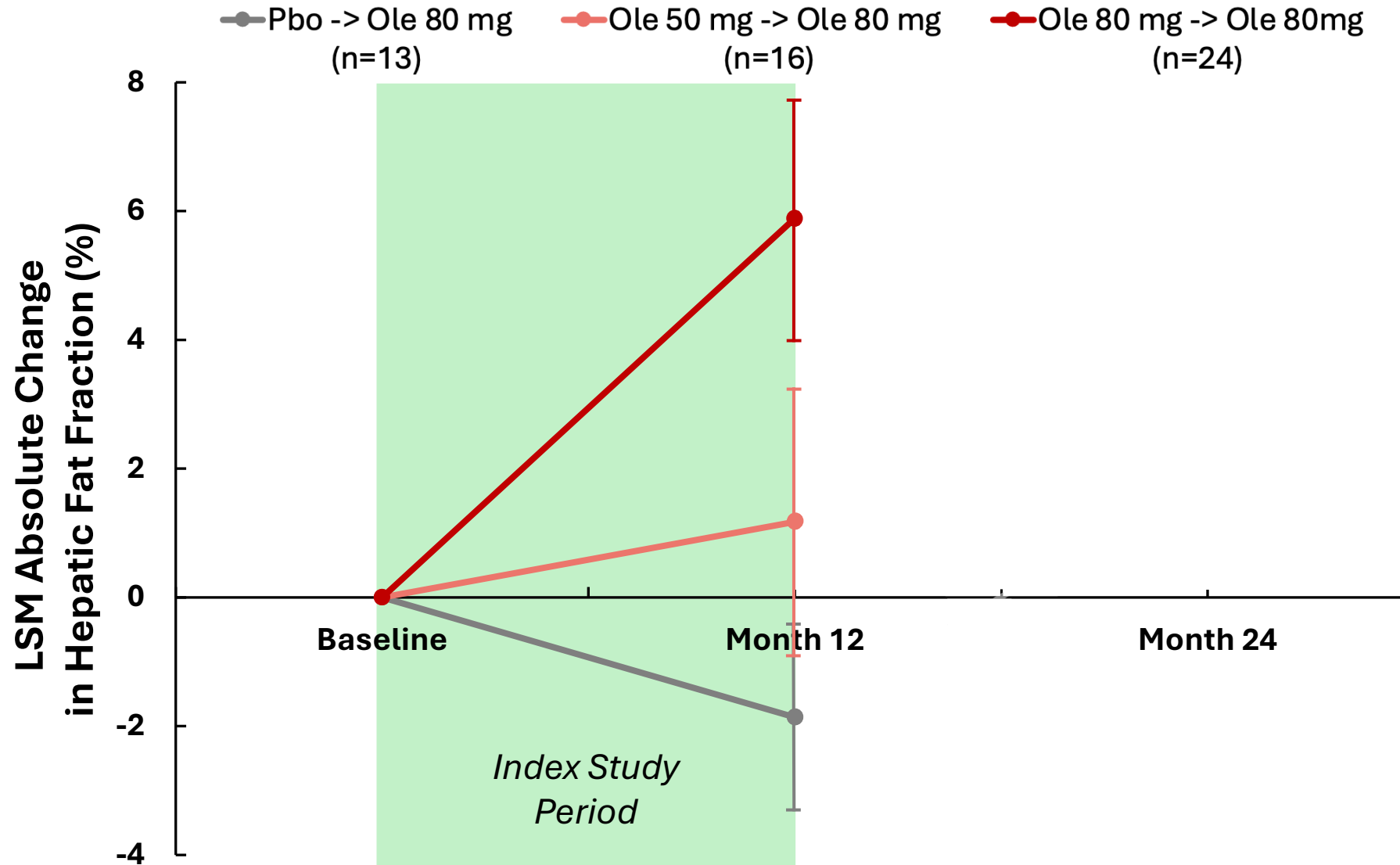
	Placebo	Olezarsen 50 mg	P-value vs Placebo	Olezarsen 80 mg	P-value vs Placebo
<b>Hepatic parameters*</b>					
ALT or AST $\geq 3x$ ULN	2%	3%	0.60	7%	0.003
ALT or AST $\geq 5x$ ULN	1%	1%	0.99	1%	0.47
Total bilirubin $\geq 2x$ ULN	<1%	<1%	0.99	1%	0.56

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

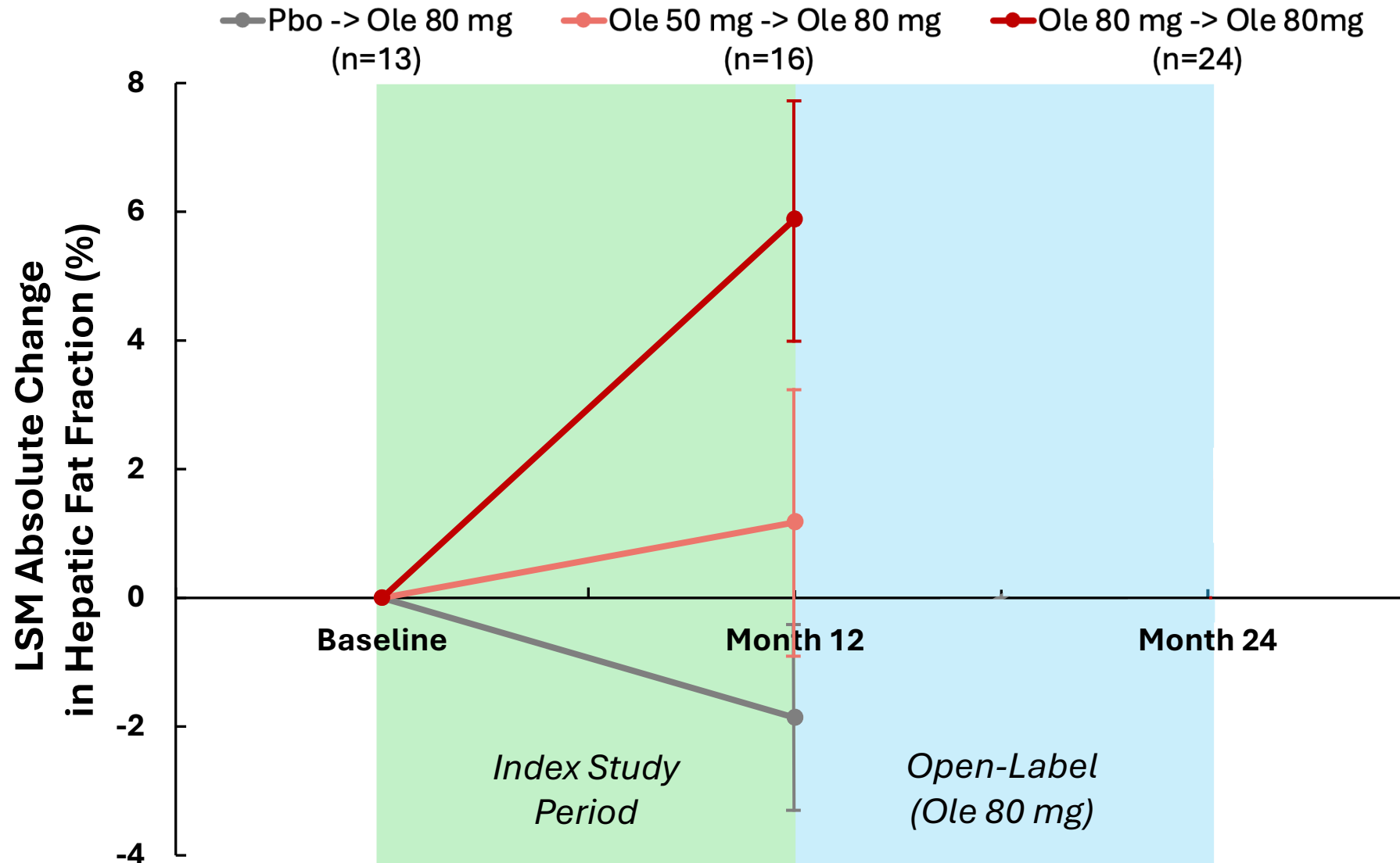
\*There were no cases meeting Hy's Law criteria. Changes in HFF were not associated with changes in LFTs.

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

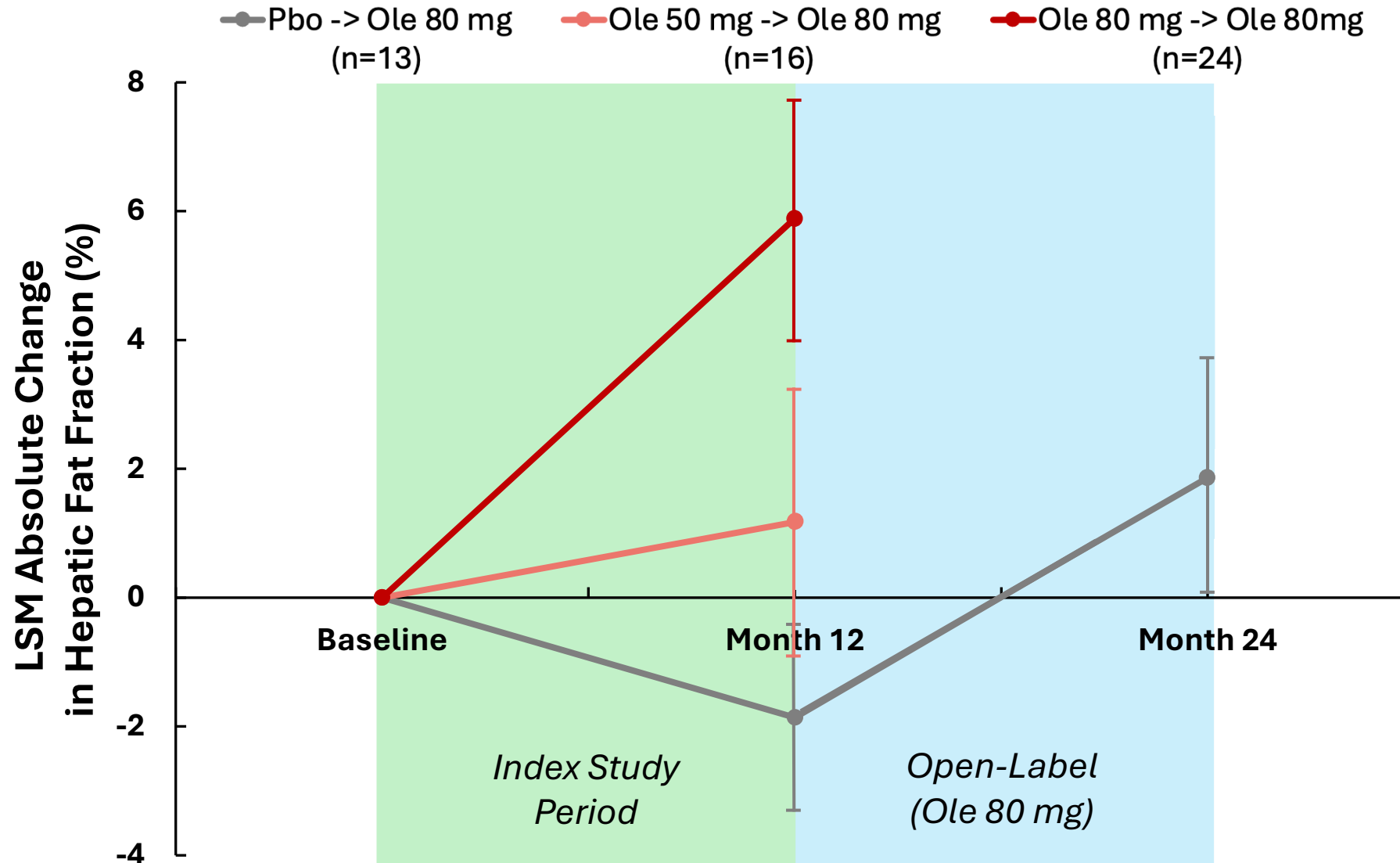
# Preliminary 24-month HFF data (n=53)



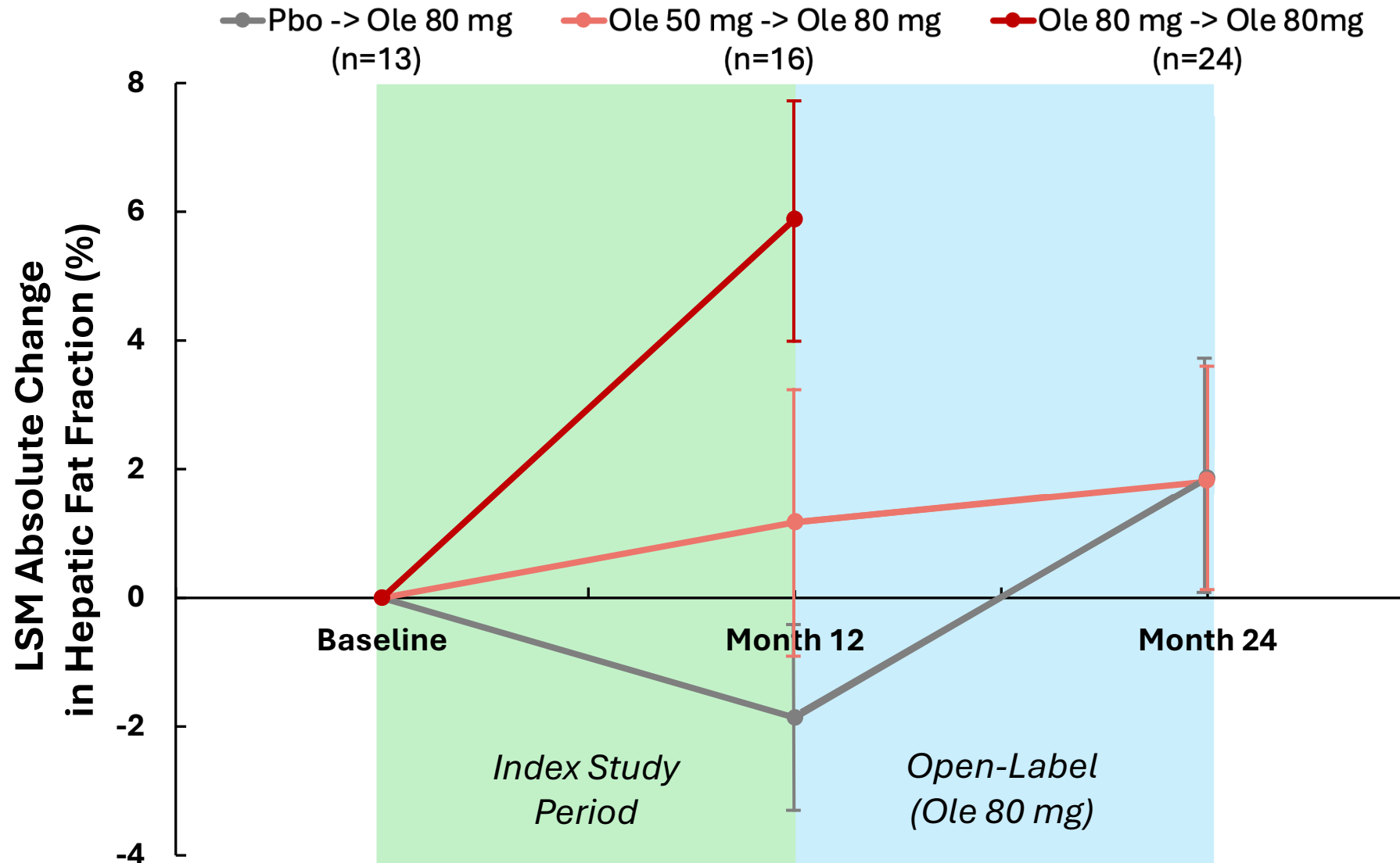
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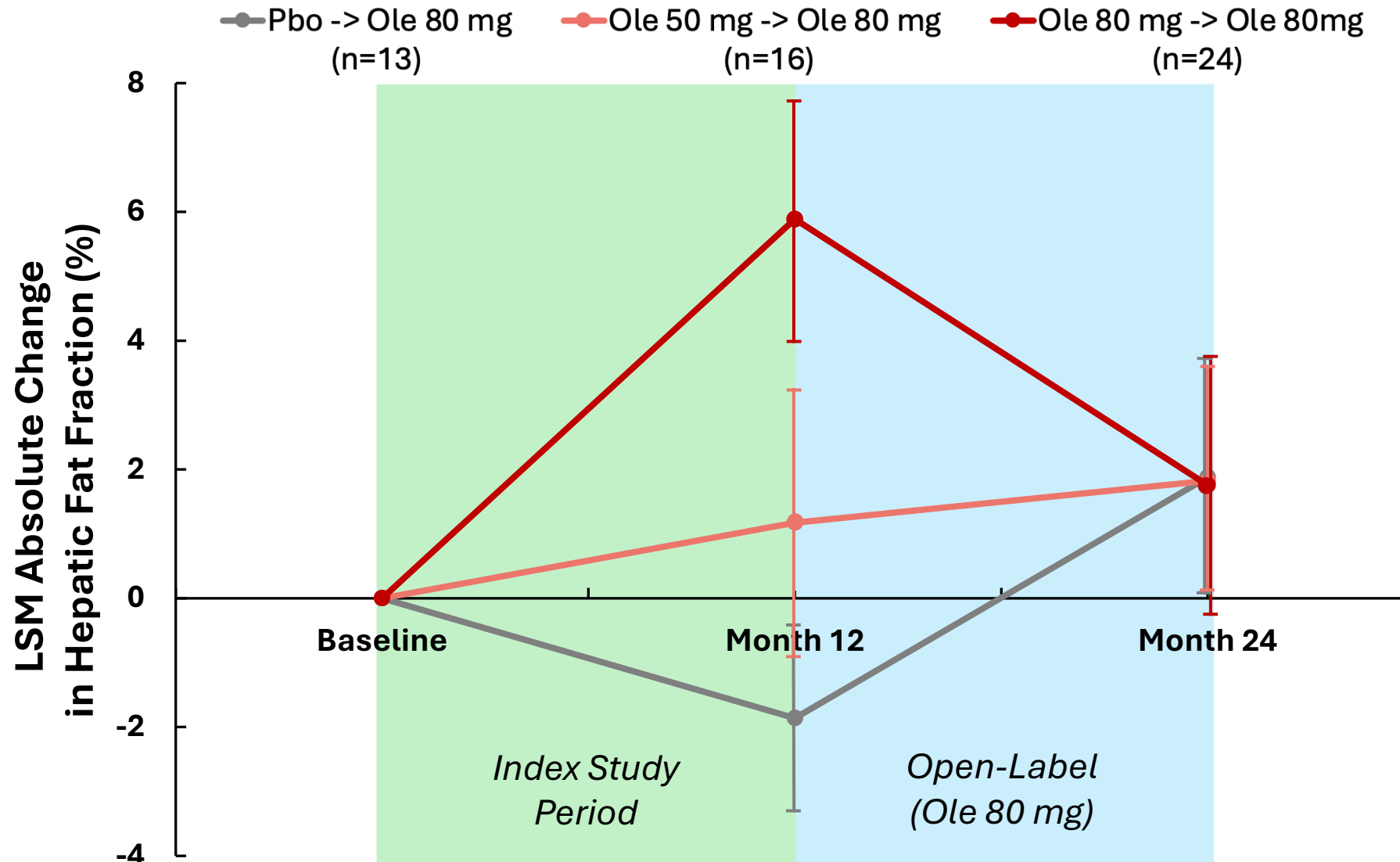
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- **Among patients with severe hypertriglyceridemia, olezarsen:**
  - Lowered triglycerides by 49-72%, which is more than conventional therapies
  - Resulted in >85% of patients achieving levels below 500 mg/dL
  - Reduced the risk of acute pancreatitis 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