Olezarsen in Patients with Severe Hypertriglyceridemia

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

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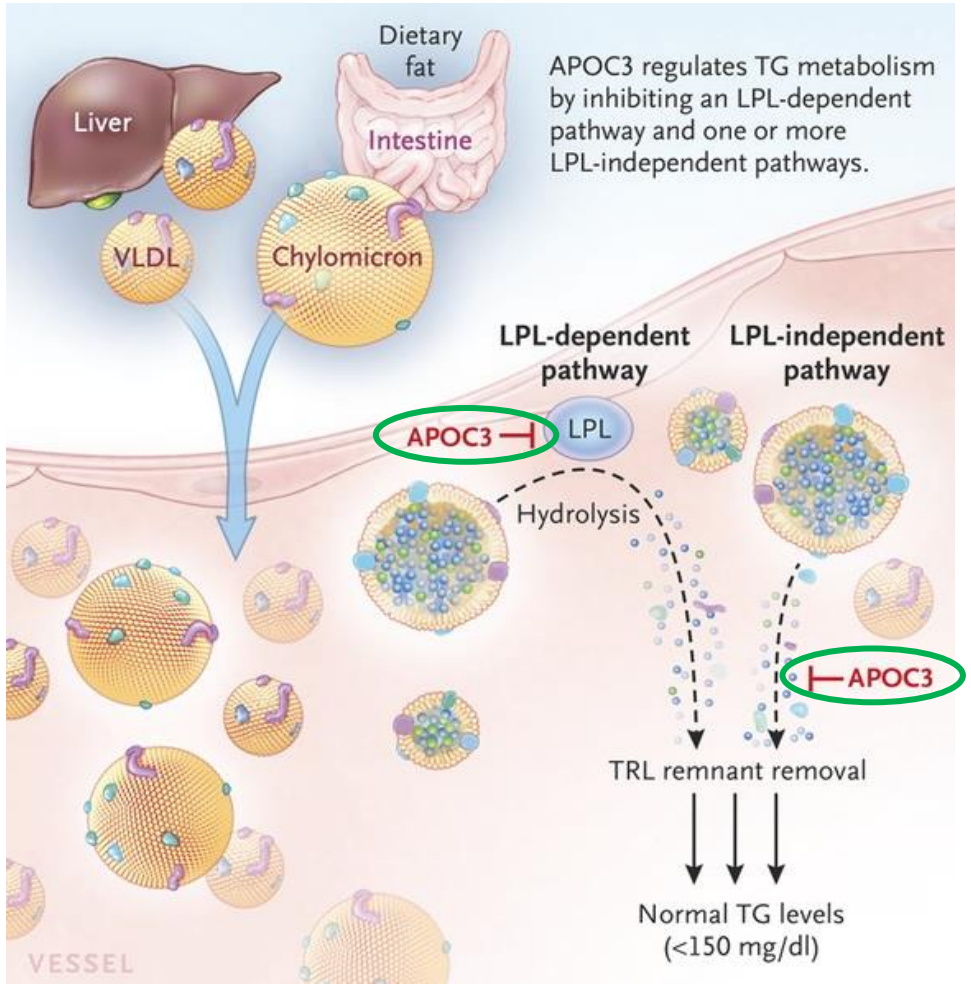
Disclosures

- 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.

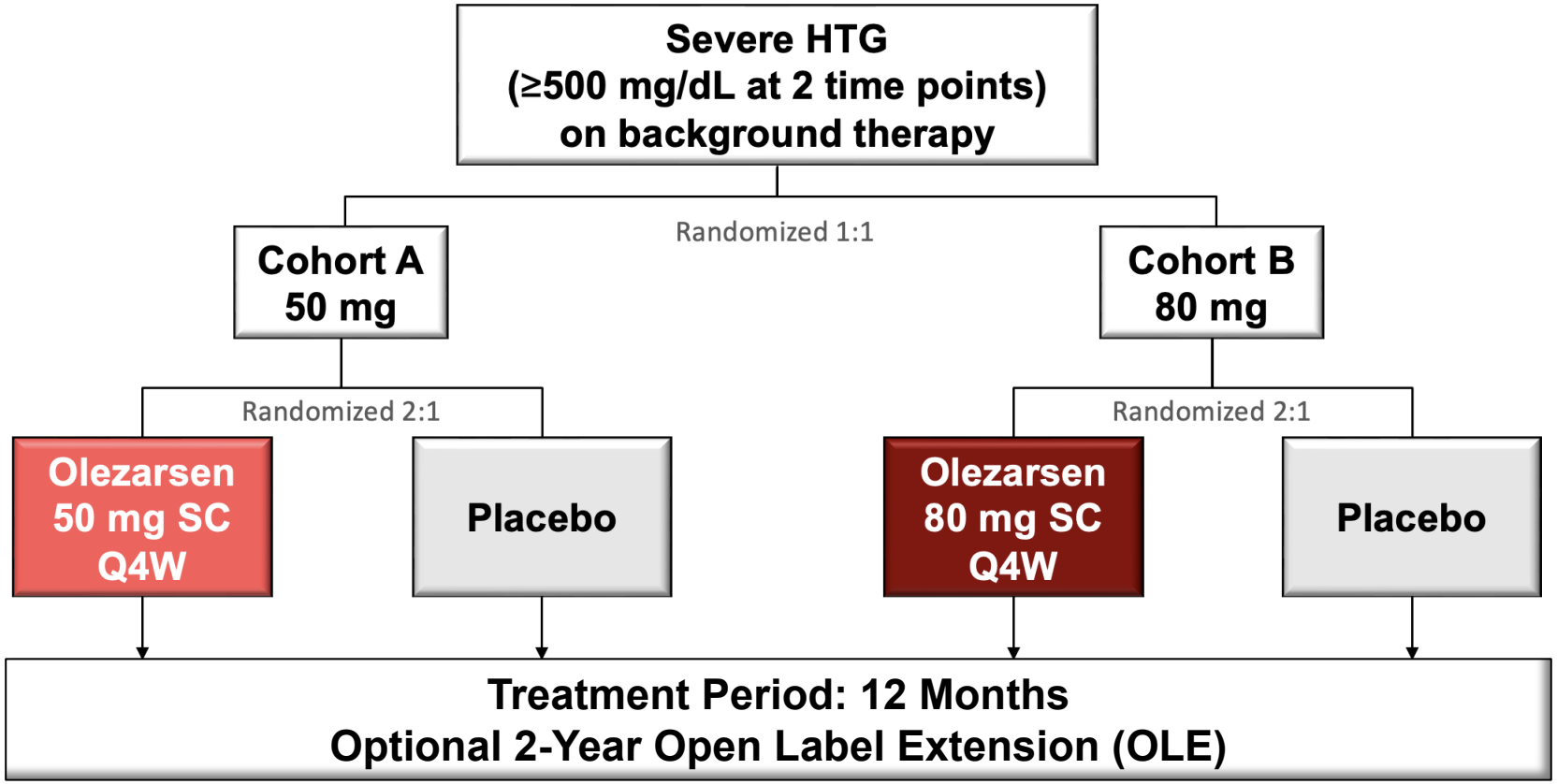
Background



- 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

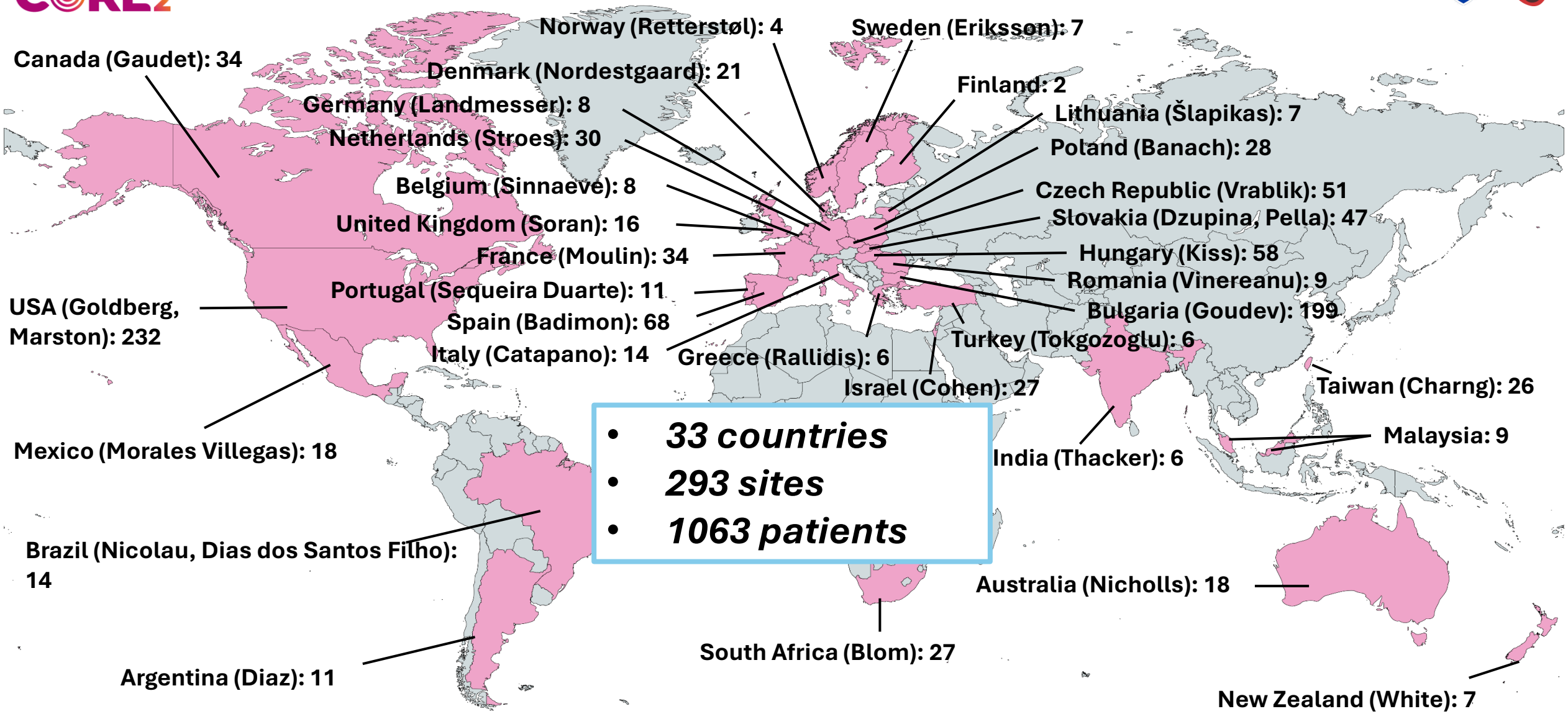
Identically designed



PEP (each trial): Pbo-adj % Δ in triglycerides from baseline to 6 months for each dose
SEP (each trial): % Δ in TGs at 12 mos, % Δ in ApoC-III, Rem-C, non-HDL-C at 6 & 12 mos
SEP (pooled): % achieving <880 & 500 mg/dL, acute pancreatitis, Δ in hepatic fat by MRI
Open-Label Extension: Hepatic fat by MRI at 24 and 36 Months

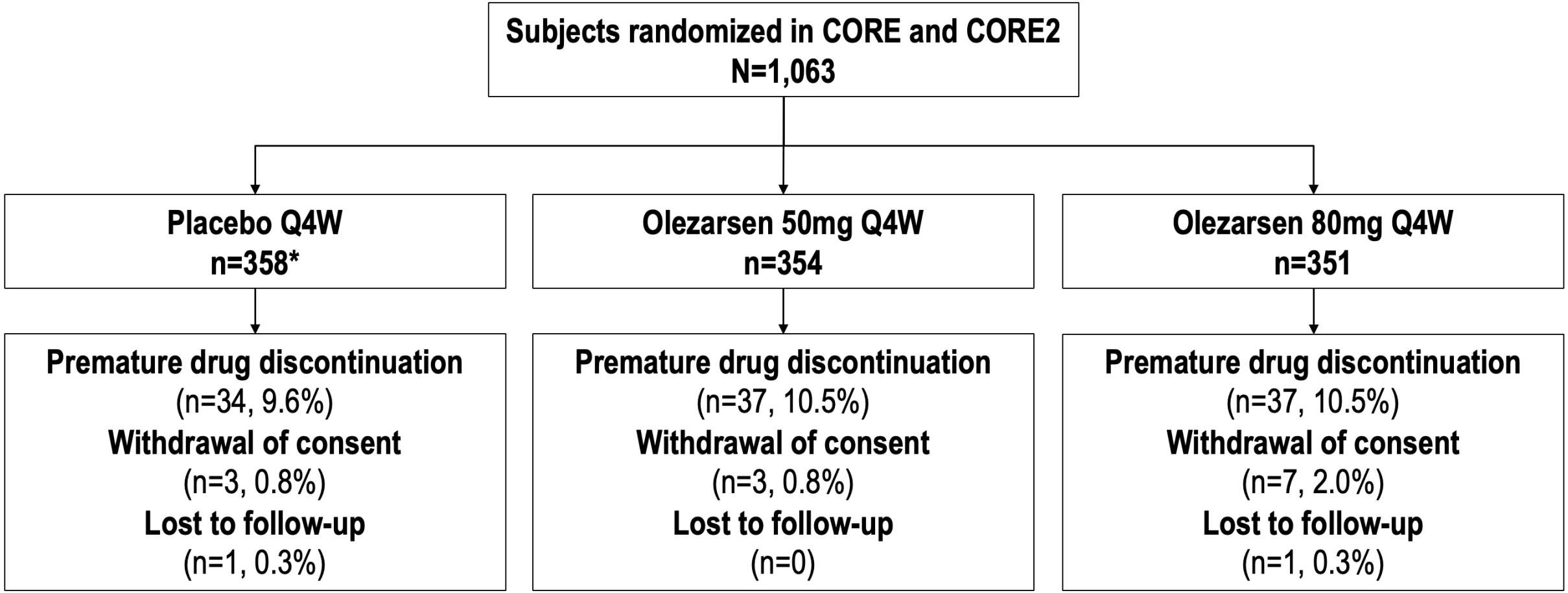
2 trials performed in accordance with regulatory guidance
PEP, primary endpoint; SEP, secondary endpoint

Global Enrollment



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

Patient Disposition



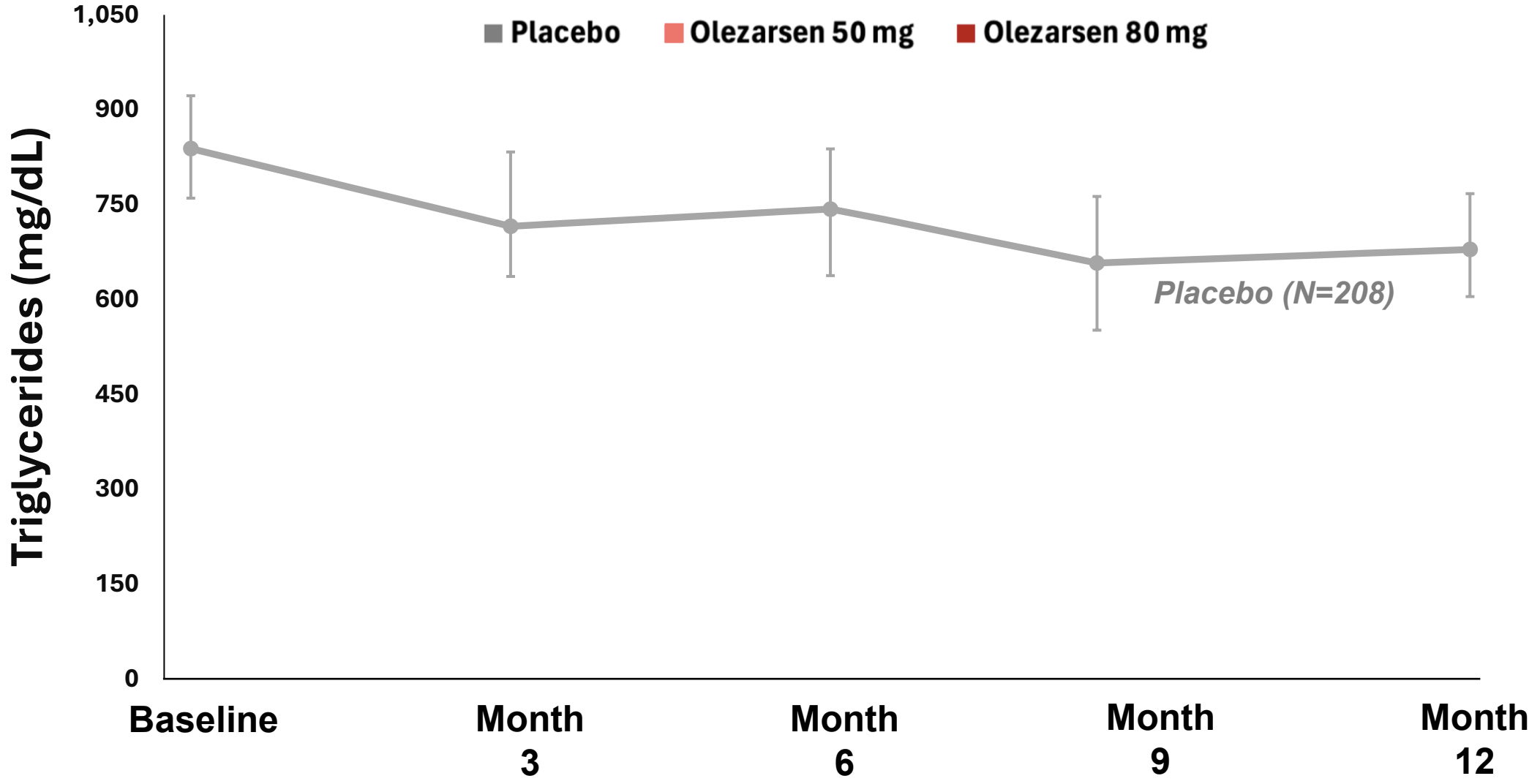
*Two patients in the placebo arm did not receive IP and so were not included in the primary analysis

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%
Body Mass Index (kg/m^2)	31 (28, 35)	31 (28, 35)
Diabetes mellitus	60%	69%
Triglycerides (mg/dL)	832 (602, 1382)	748 (584, 1136)
History of Pancreatitis	23%	13%
Any Lipid Lowering Therapy	99%	99%
Statin	72%	77%
Fibrate	66%	60%
Omega-3 fatty acid	34%	30%
≥2 Lipid-lowering therapies	67%	63%

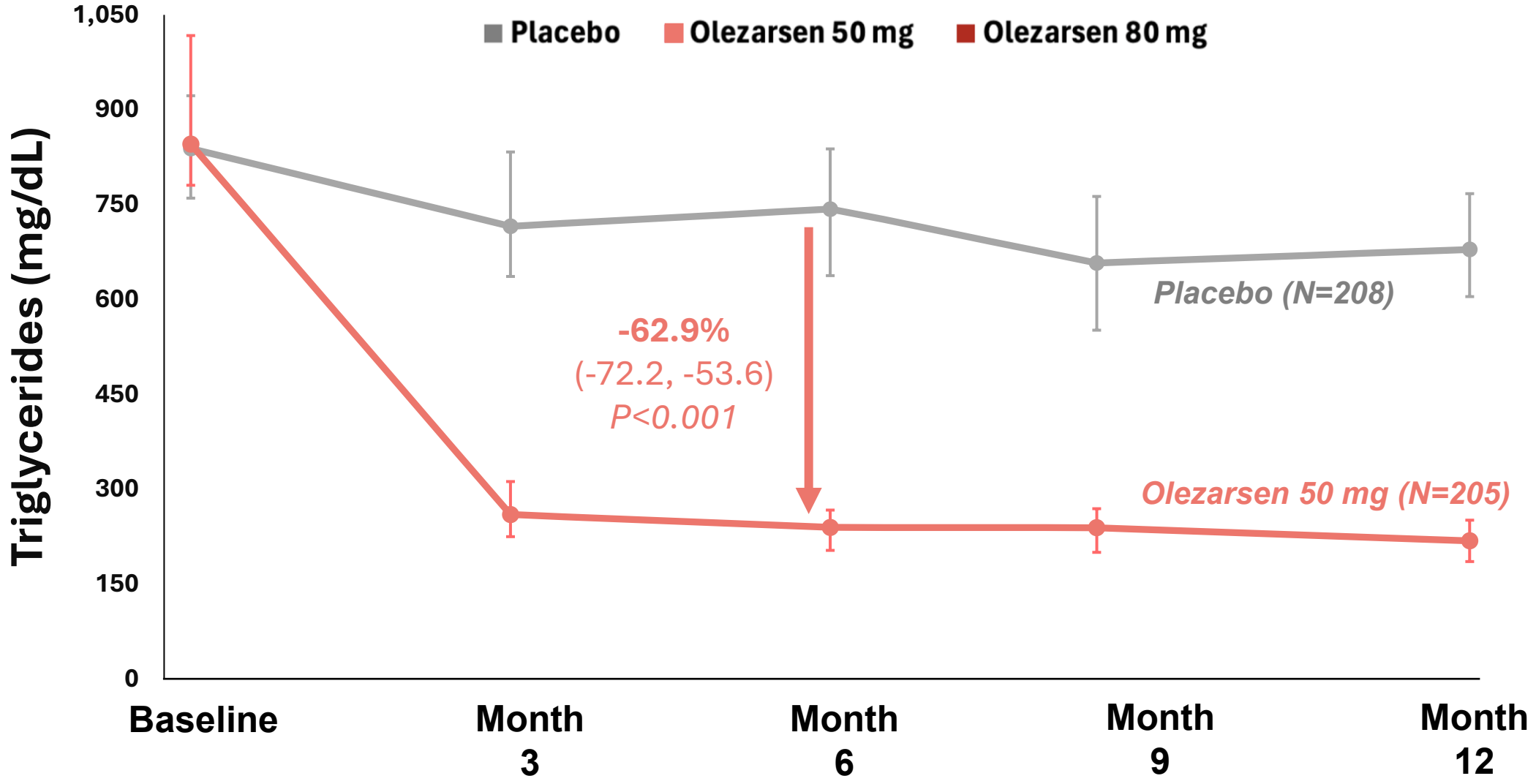
Continuous variables listed as median (IQR)
Baseline variables balanced by treatment arm

Primary Endpoint: CORE-TIMI 72A



Values plotted are median (95% CI). Differences are placebo-adjusted least squares mean change in TG levels.

Primary Endpoint: CORE-TIMI 72A



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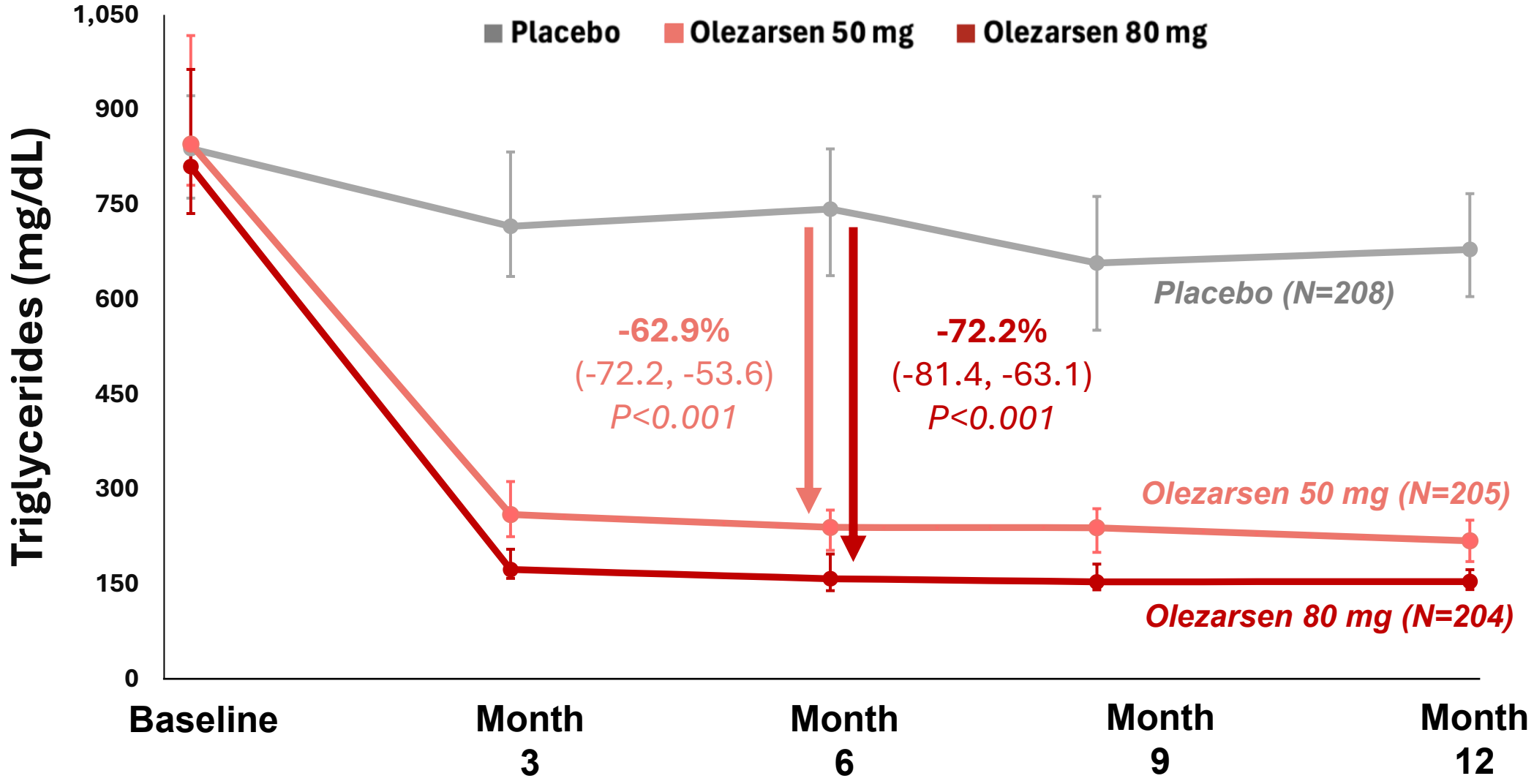
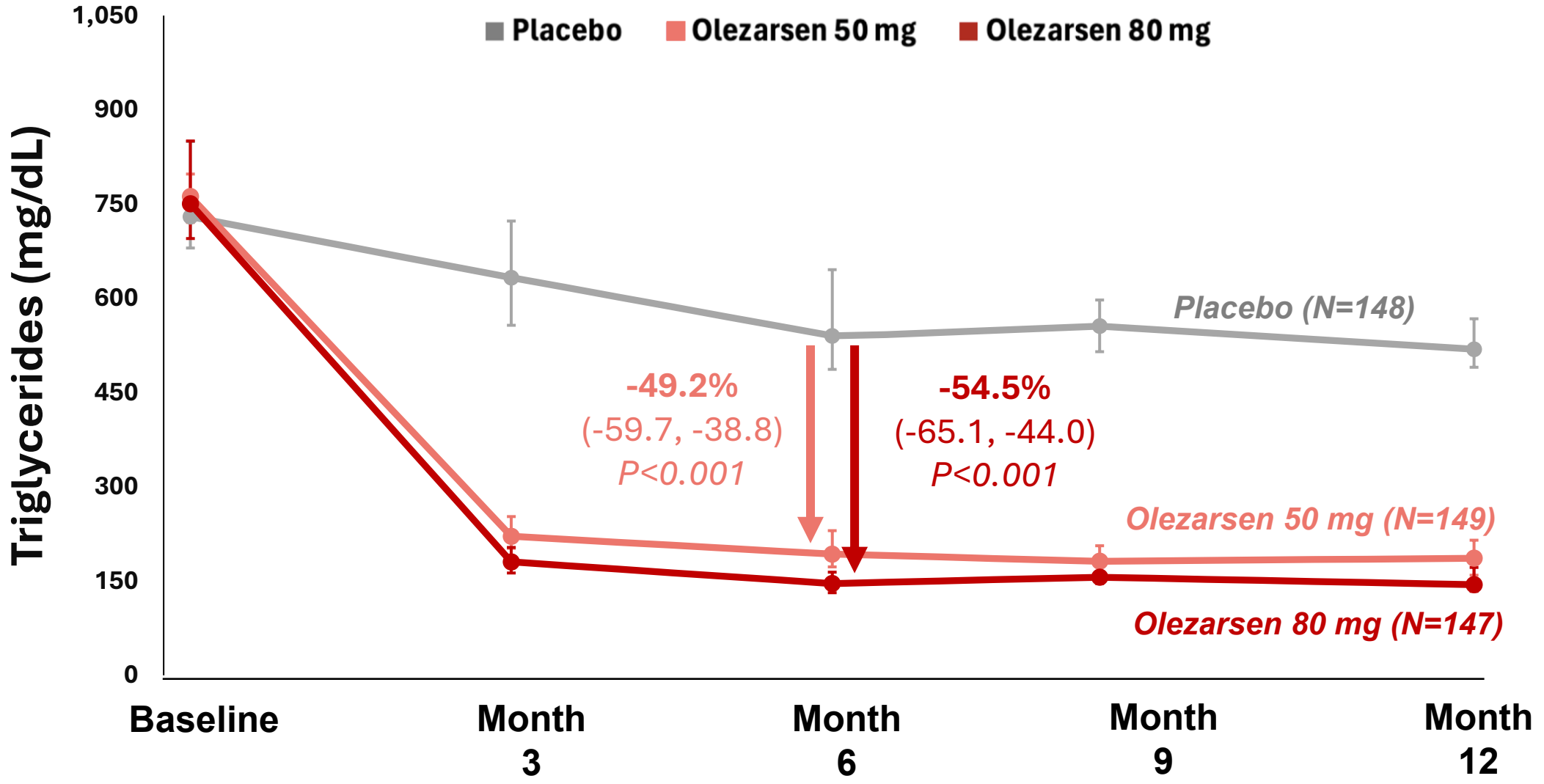
Primary Endpoint: CORE-TIMI 72A



Values plotted are median (95% CI). Differences are placebo-adjusted least squares mean change in TG levels.

Primary Endpoint: CORE2-TIMI 72B



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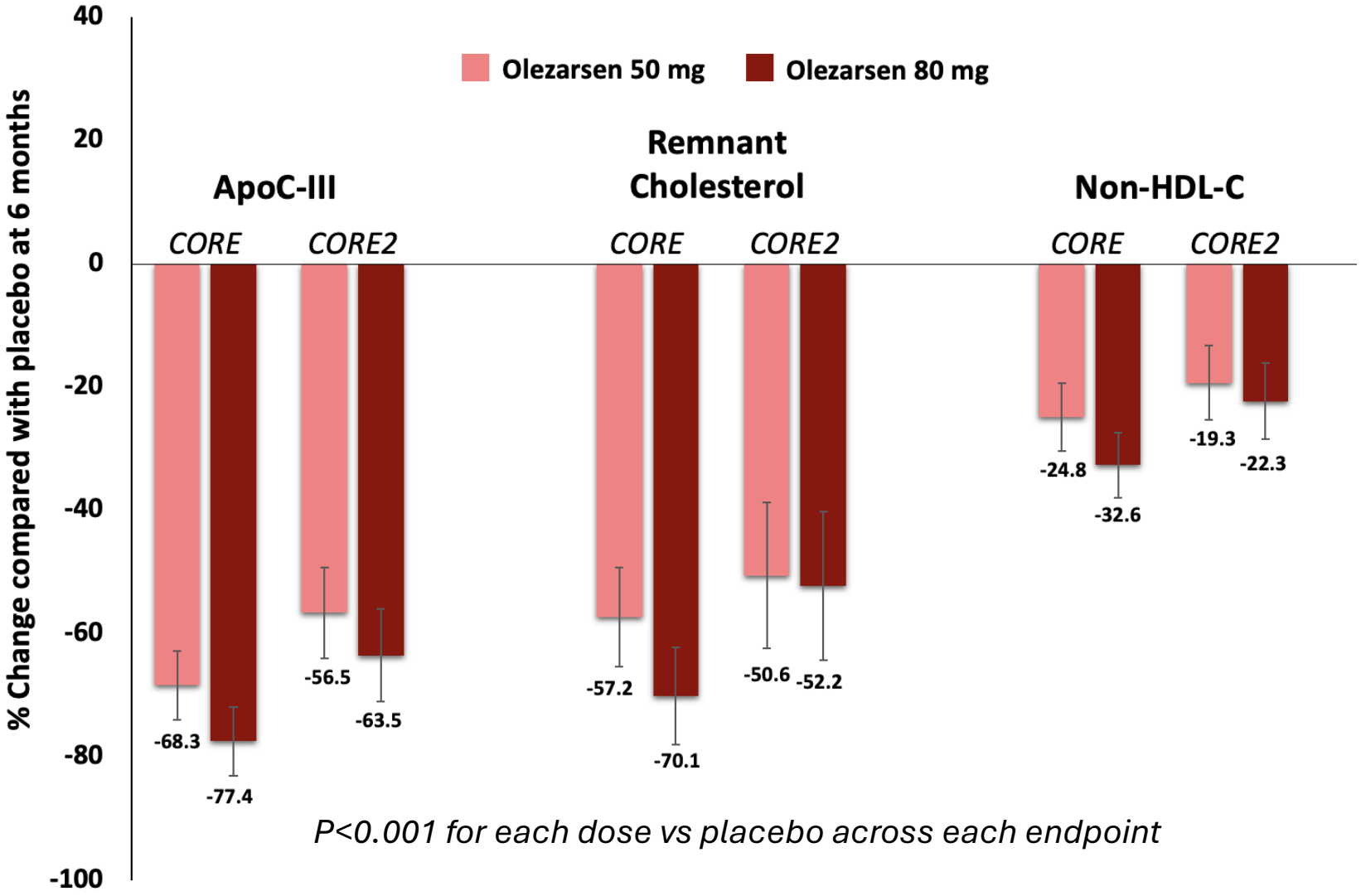
Secondary Lipid Endpoints

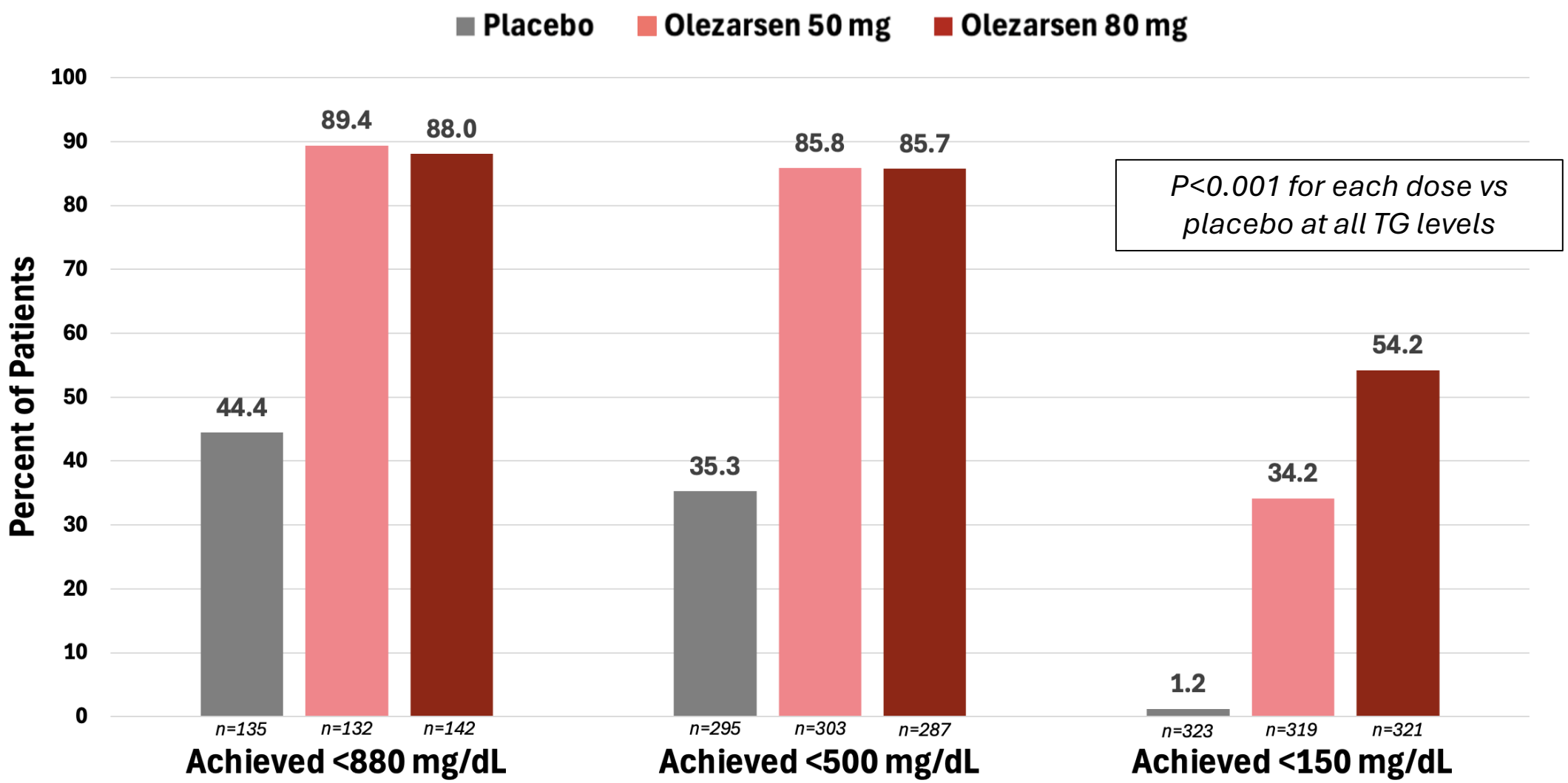
at 6 months



P<0.001 for each dose vs placebo across each endpoint

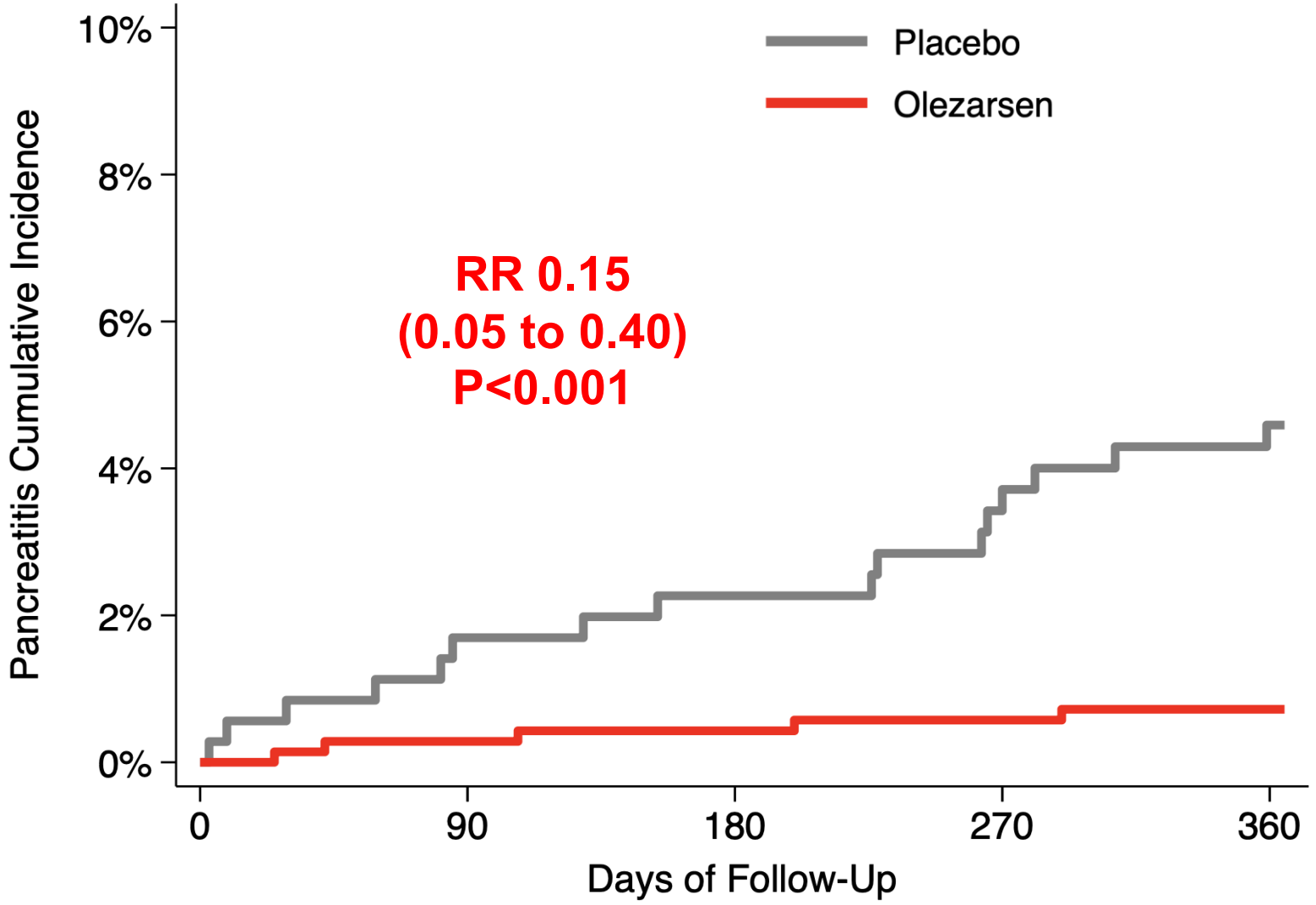
Achieved TG Levels at 12 months

Pooled analysis across trials



Acute Pancreatitis

Pooled analysis across both doses and trials

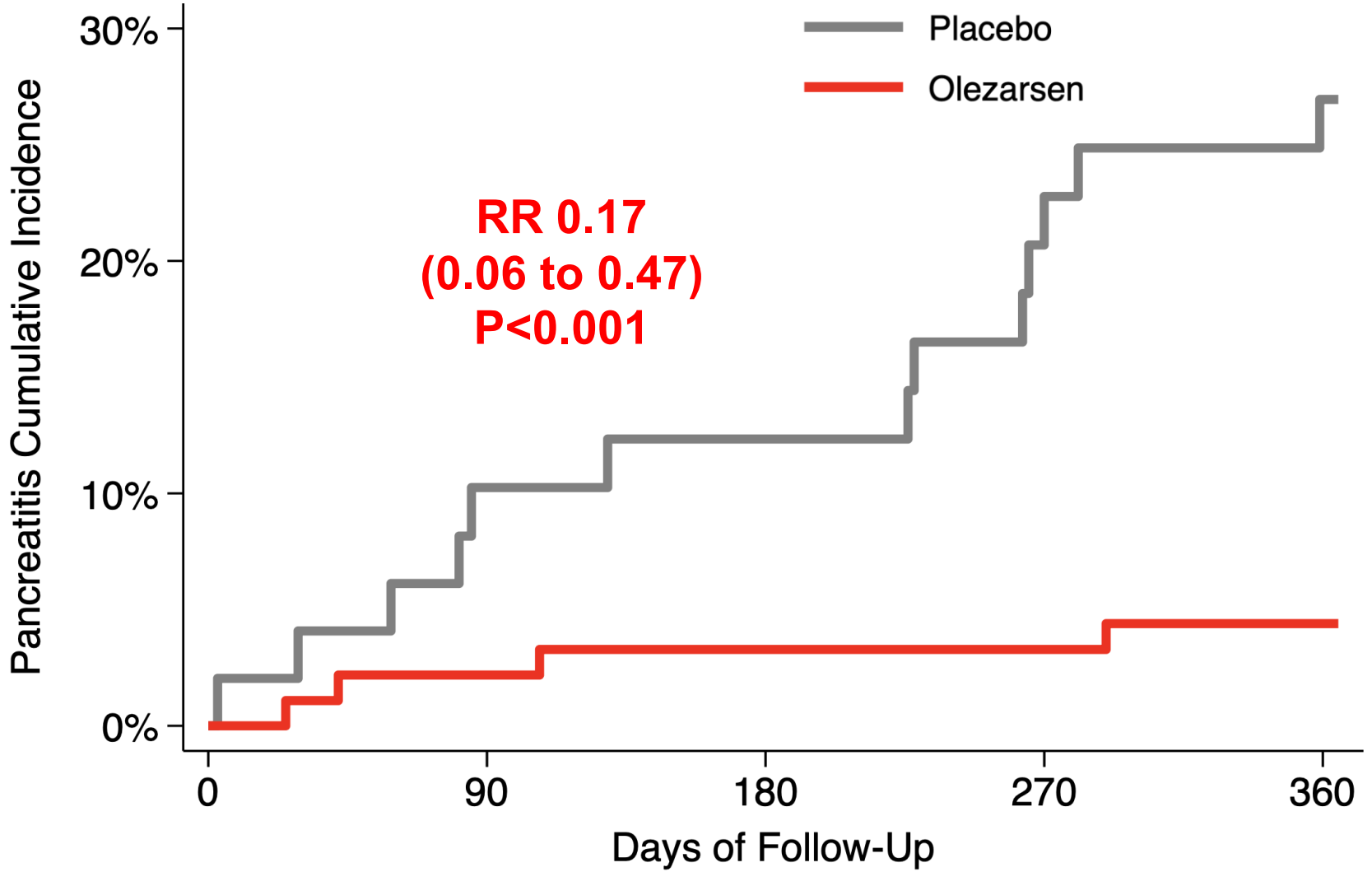


ARR in incidence of total events = 5.2%

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
Any Injection Site Reaction	1%	10%	<0.001	17%	<0.001
Mild	1%	10%		15%	
Moderate	0	1%		3%	
Severe	0	0		0	

Other Parameters

Pooled analysis across trials

	Placebo	Olezarsen 50 mg	P-value vs Placebo	Olezarsen 80 mg	P-value vs Placebo
Hepatic parameters*					
ALT or AST ≥3x ULN	2%	3%	0.60	7%	0.003
ALT or AST ≥5x ULN	1%	1%	0.99	1%	0.47
Total bilirubin ≥2x ULN	<1%	<1%	0.99	1%	0.56
Absolute change in HFF (%)	0.14	2.28	0.052	4.18	<0.001
Platelet count^					
<100K/uL	3%	2%	0.26	7%	0.03
<75K/uL	2%	1%	0.18	2%	0.76
Glycemic measures					
HbA1c (%), pbo-adjusted change		0.25	0.006	0.24	0.009

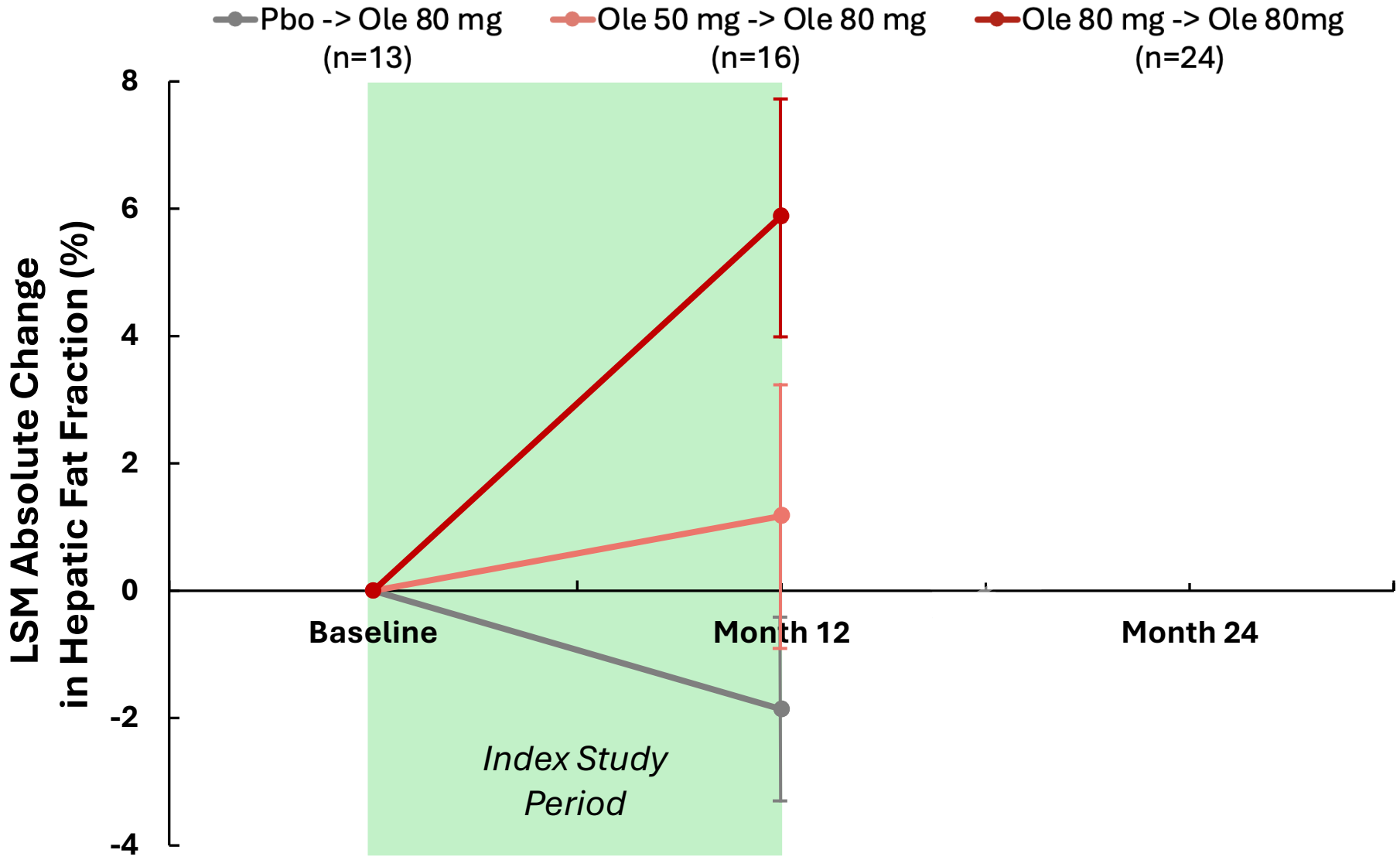
Patients with ALT/AST <3x ULN at screening/qualification were allowed to be enrolled

*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.

HFF = hepatic fat fraction, measured at baseline & 12 months as part of MRI substudy (n=252). Baseline HFF = 14.3%.

Preliminary 24-month HFF data (n=53)



HFF = hepatic fat fraction
Baseline HFF = 13.9% in placebo, 17.6% in 50 mg, 16.0% in 80 mg

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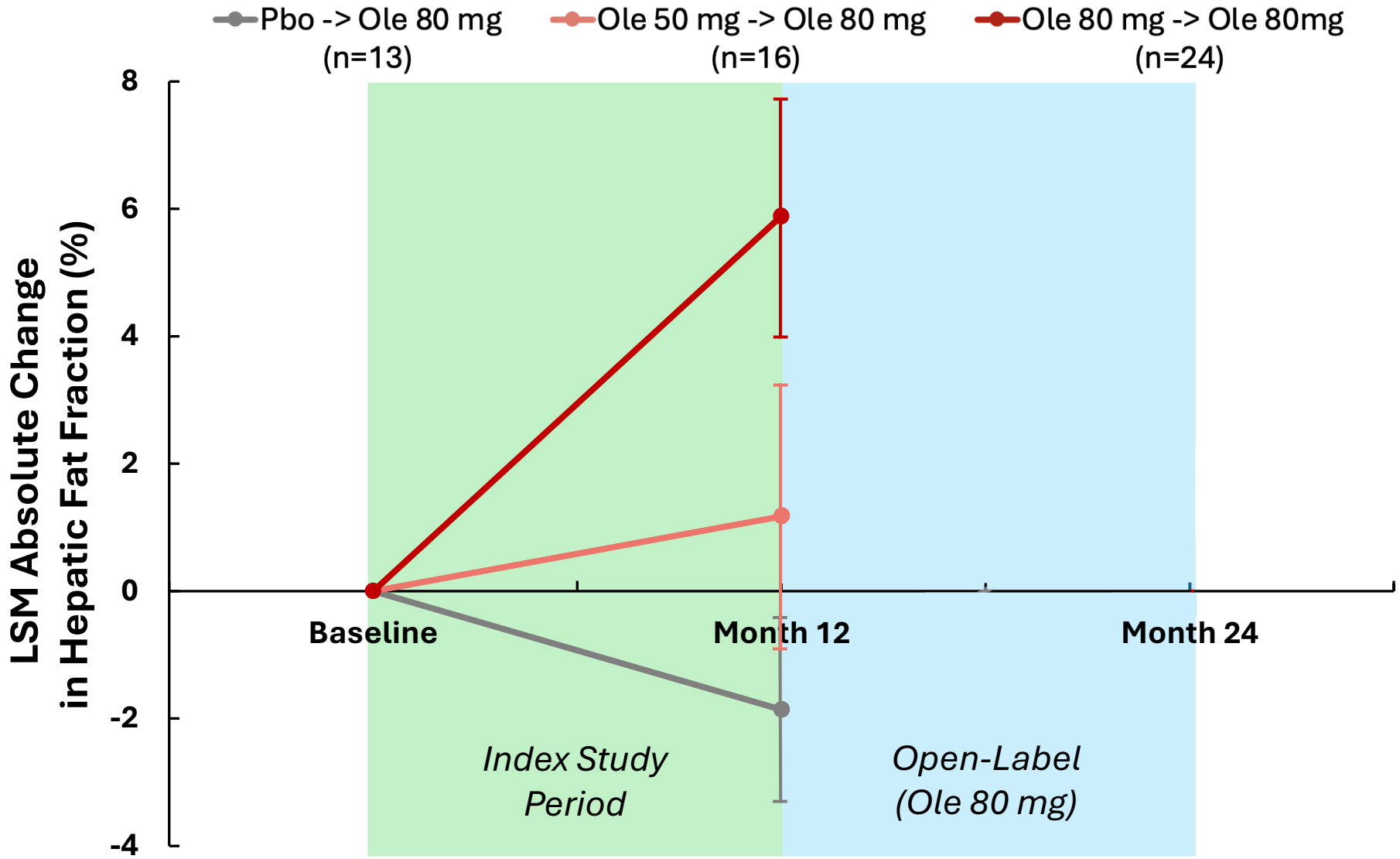

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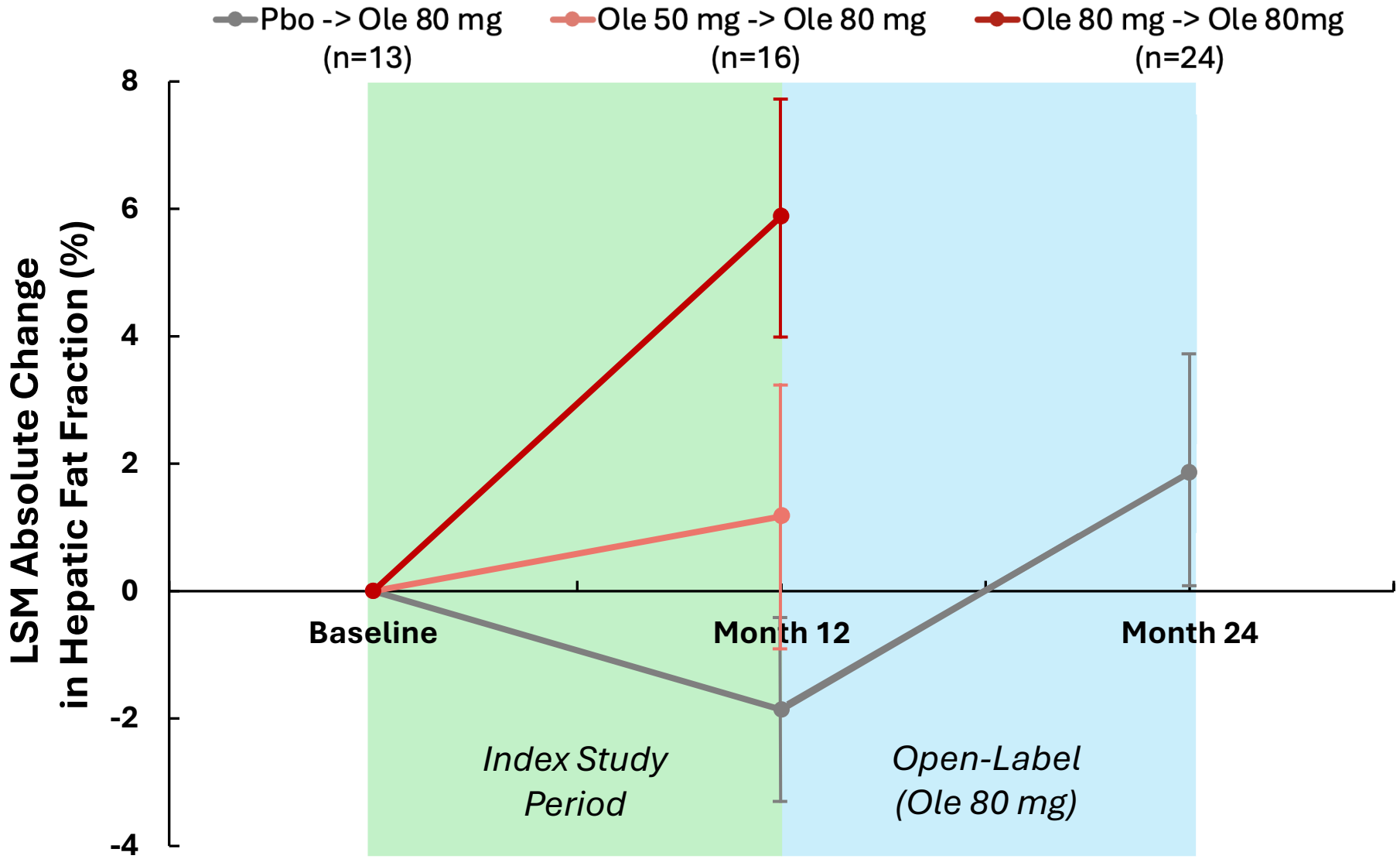

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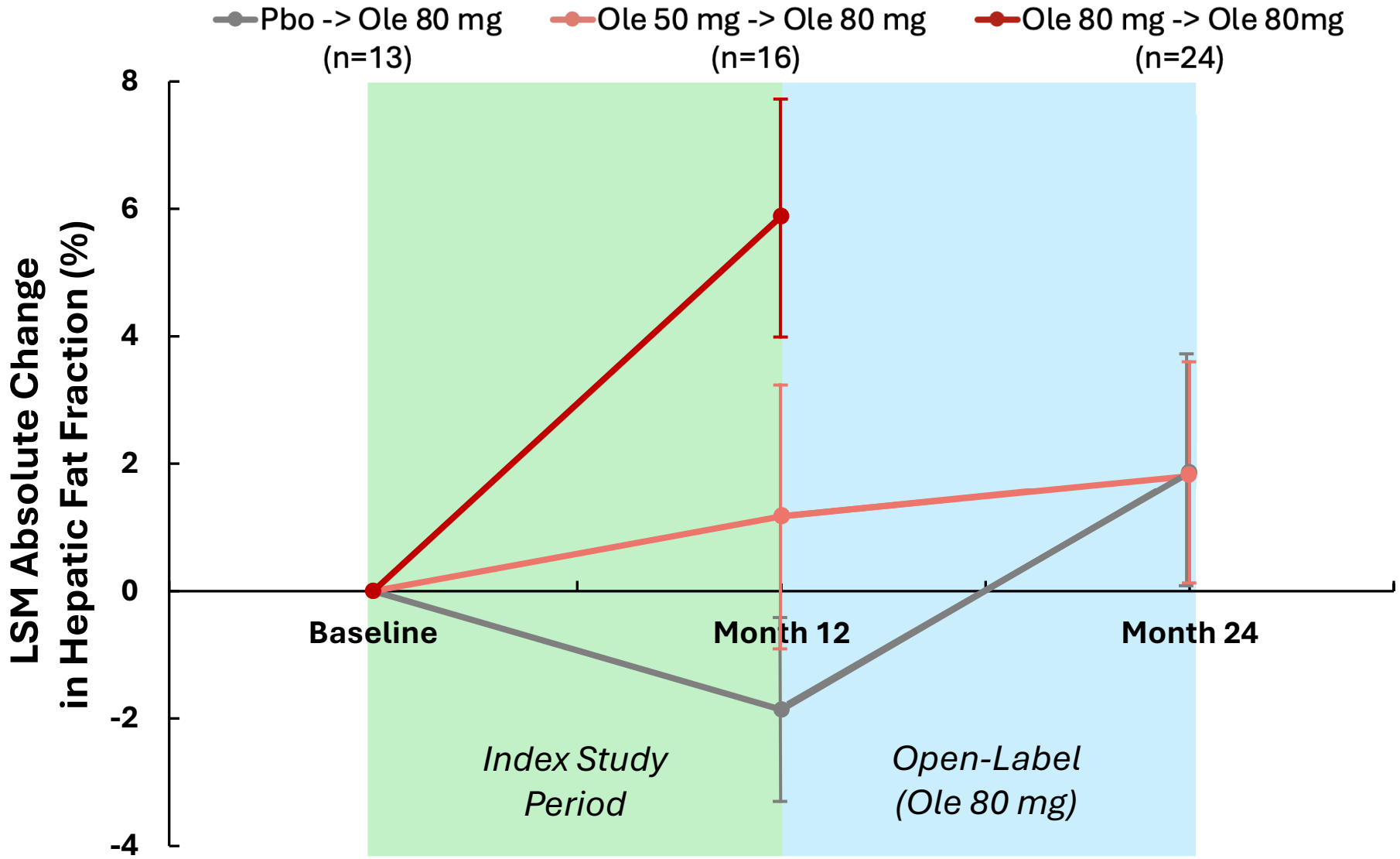

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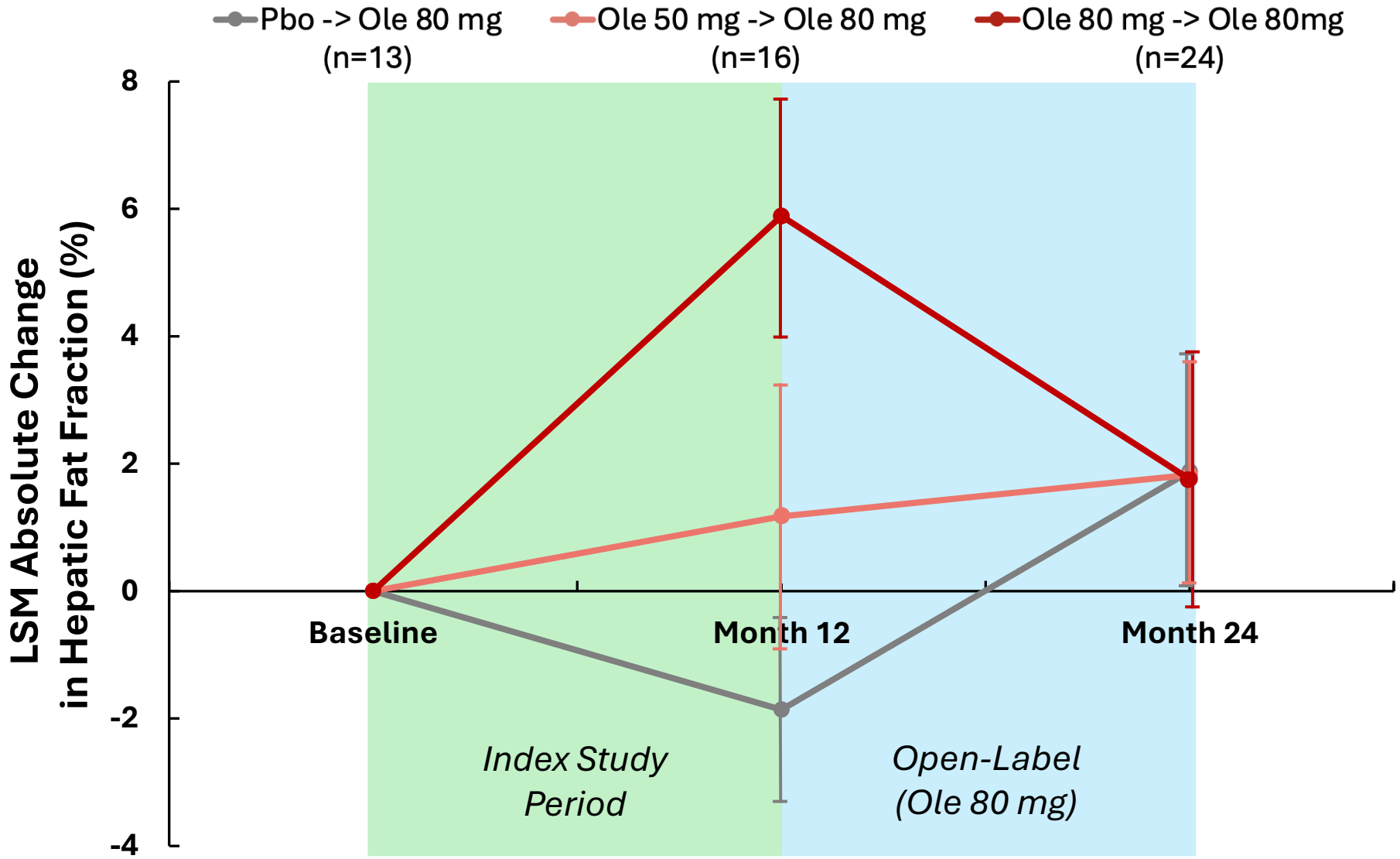

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Summary & Conclusion

- **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