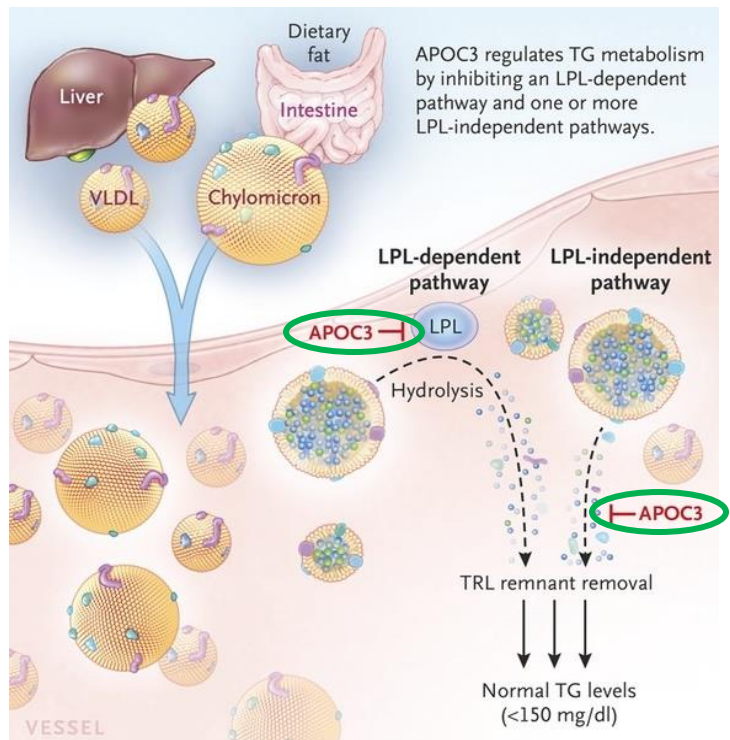


OLEZARSEN IN PATIENTS WITH SEVERE HYPERTRIGLYCERIDEMIA

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

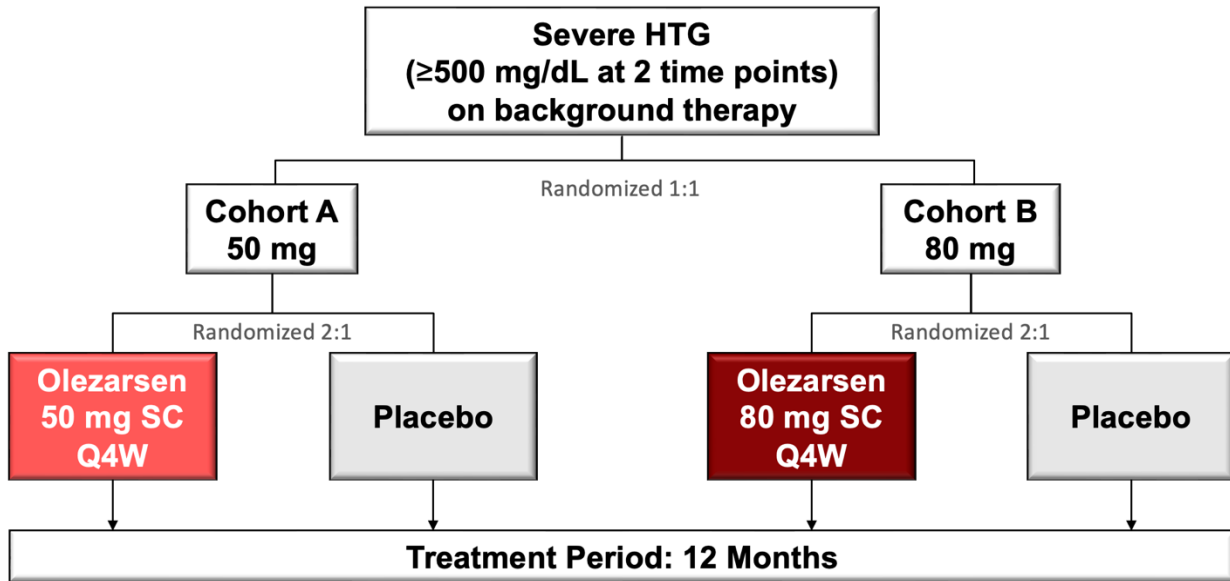
Nicholas A. Marston, Brian A. Bergmark, Veronica J. Alexander, Thomas A. Prohaska, Yu Mi Kang, Filipe Moura, Andre Zimmerman, Elaine Waldman, Julie Weinland, Shuanglu Zhang, Erica L. Goodrich, Sabina A. Murphy, Shuting Xia, Dan Li, Sotirios Tsimikas, Robert P. Giugliano, Marc S. Sabatine on behalf of the CORE and CORE2 Investigators



- 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 is unclear

CORE-TIMI 72A & CORE2-TIMI 72B

Identically designed



PEP (each trial): Pbo-adj % Δ in triglycerides at 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 mo
SEP (pooled): % achieving <880 & 500 mg/dL, acute pancreatitis, Δ in hepatic fat
Safety (pooled): ALT/AST, renal function, platelets

TIMI Study Group

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Robert Giugliano (Sr Investigator)
P. Fish & A. Jevne (Ops)

Nicholas Marston (PI)
Brian Bergmark (Investigator)
S. Murphy, E. Goodrich, S. Zhang, JF. Kuder (Stats)

Sponsor: Ionis

Sotirios Tsimikas (SVP, Global CV Dev)
Vickie Alexander (Exec Director, Clin Dev)

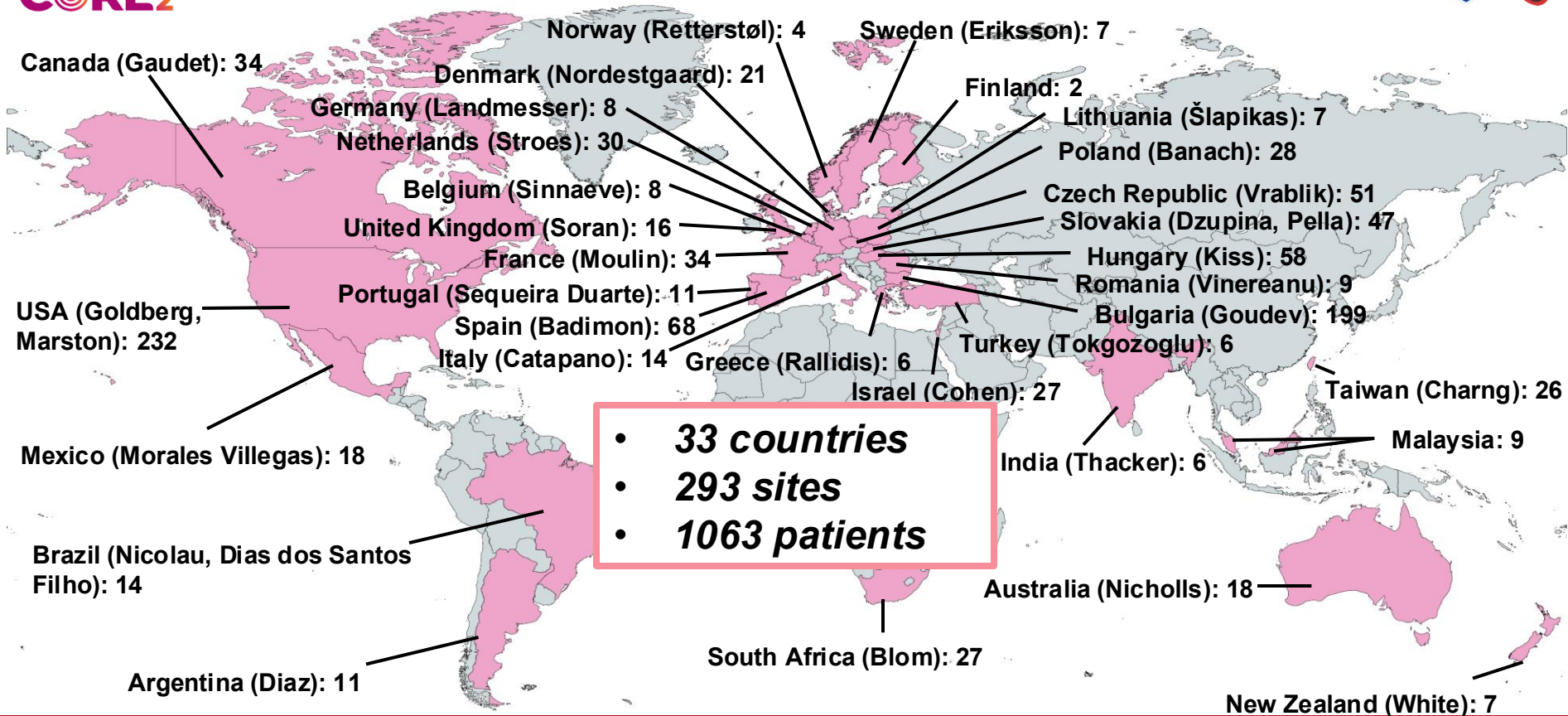
Thomas Prohaska (Medical Director, Clin Dev)
Dan Li, Shuting Xia (Stats)

Independent Data Monitoring Committee

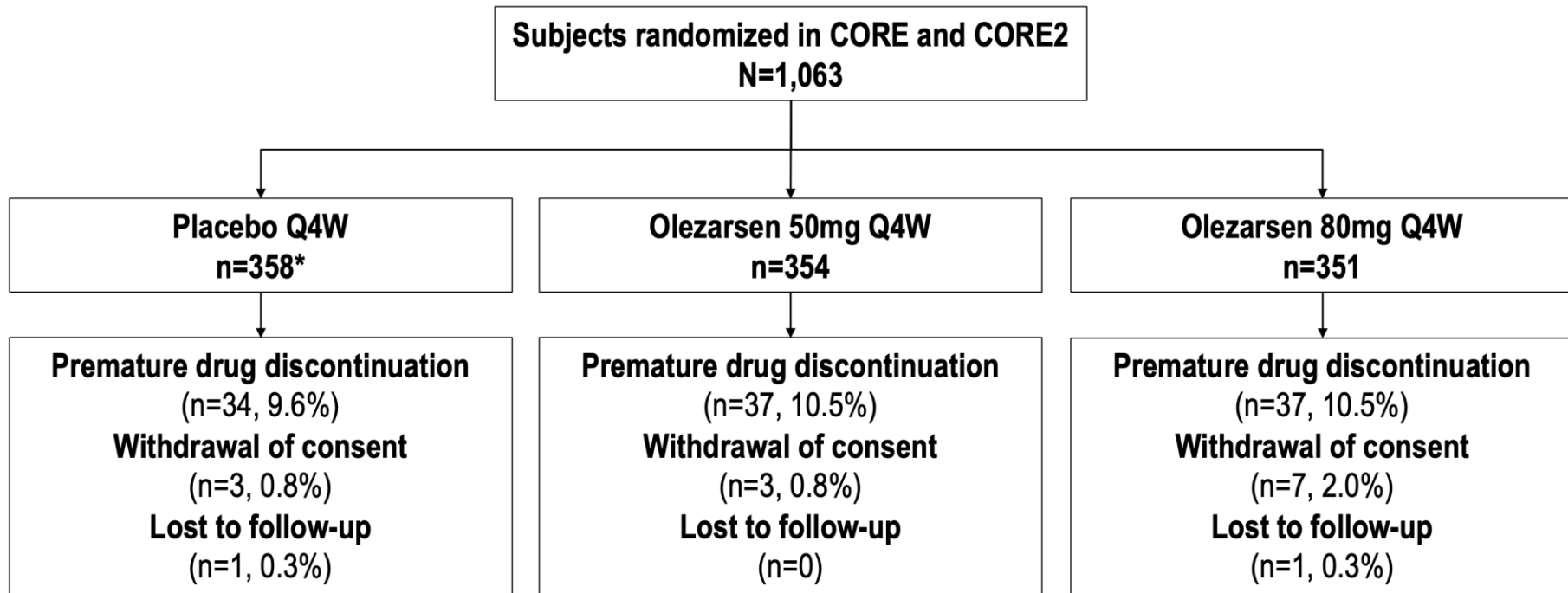
Richard Becker (Chair)
Jamie Dwyer
Willis Maddrey

Charles Davis (Statistician)
François Mach
James Freston

GLOBAL ENROLLMENT



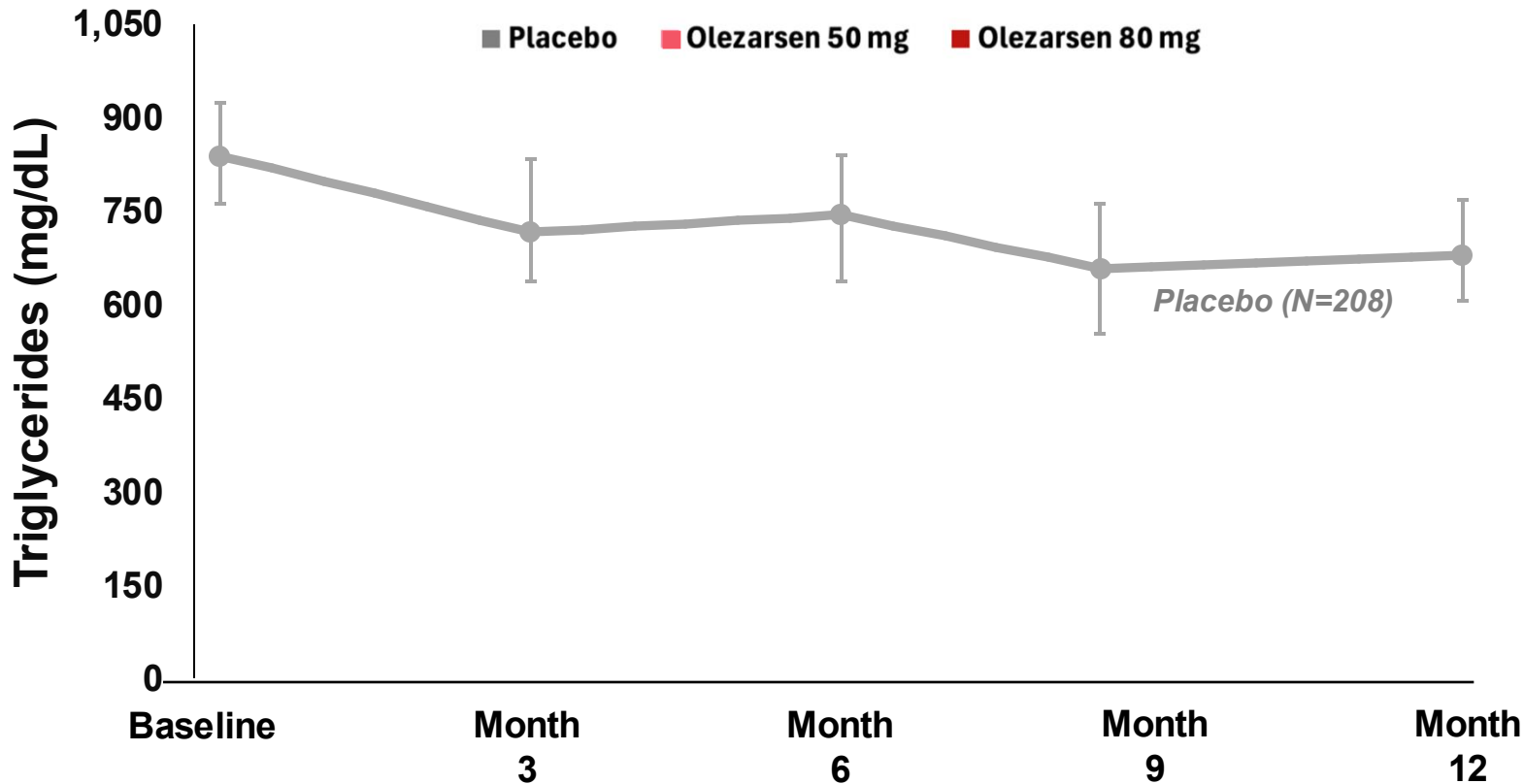
PATIENT DISPOSITION



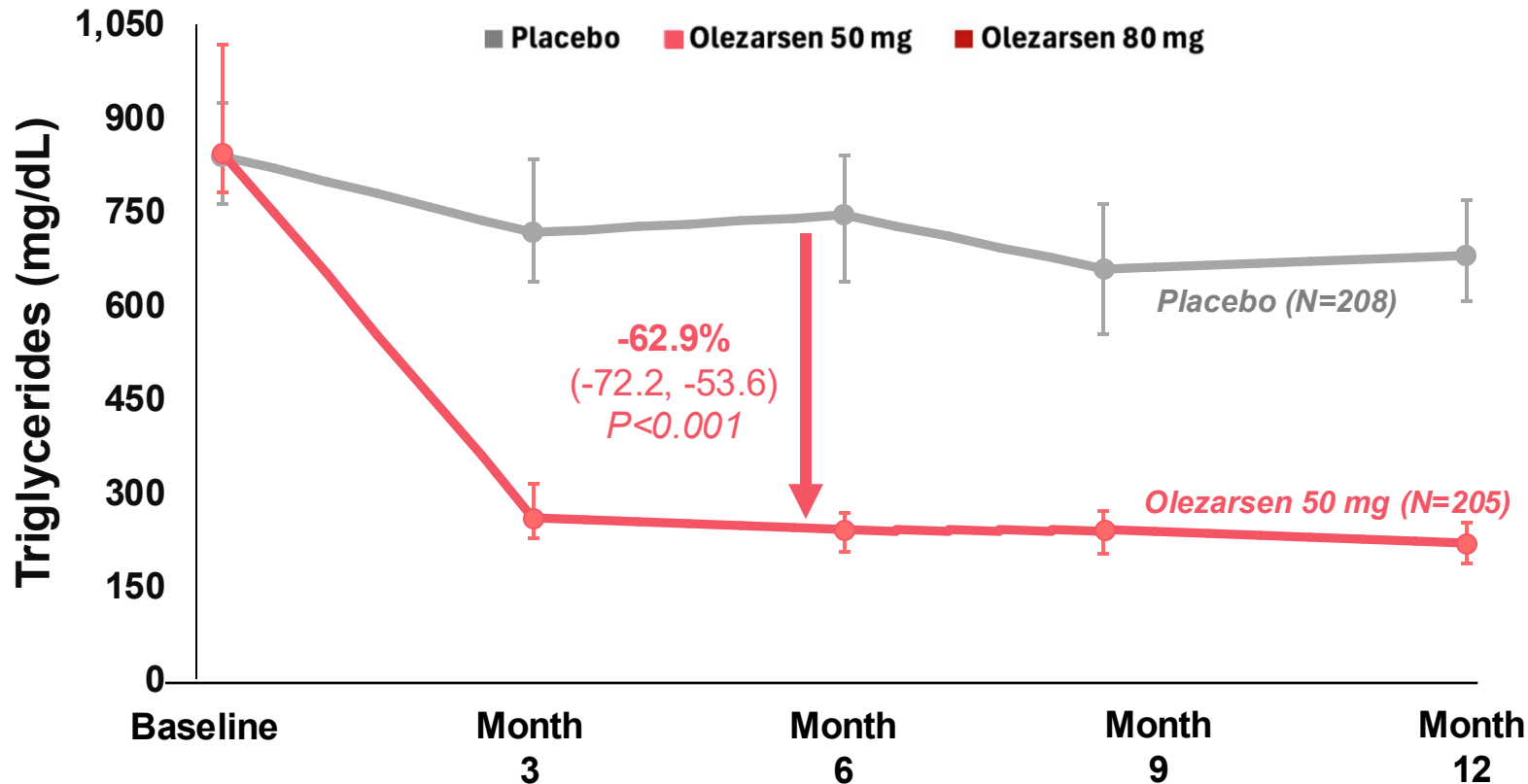
BASELINE CHARACTERISTICS

	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%
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%

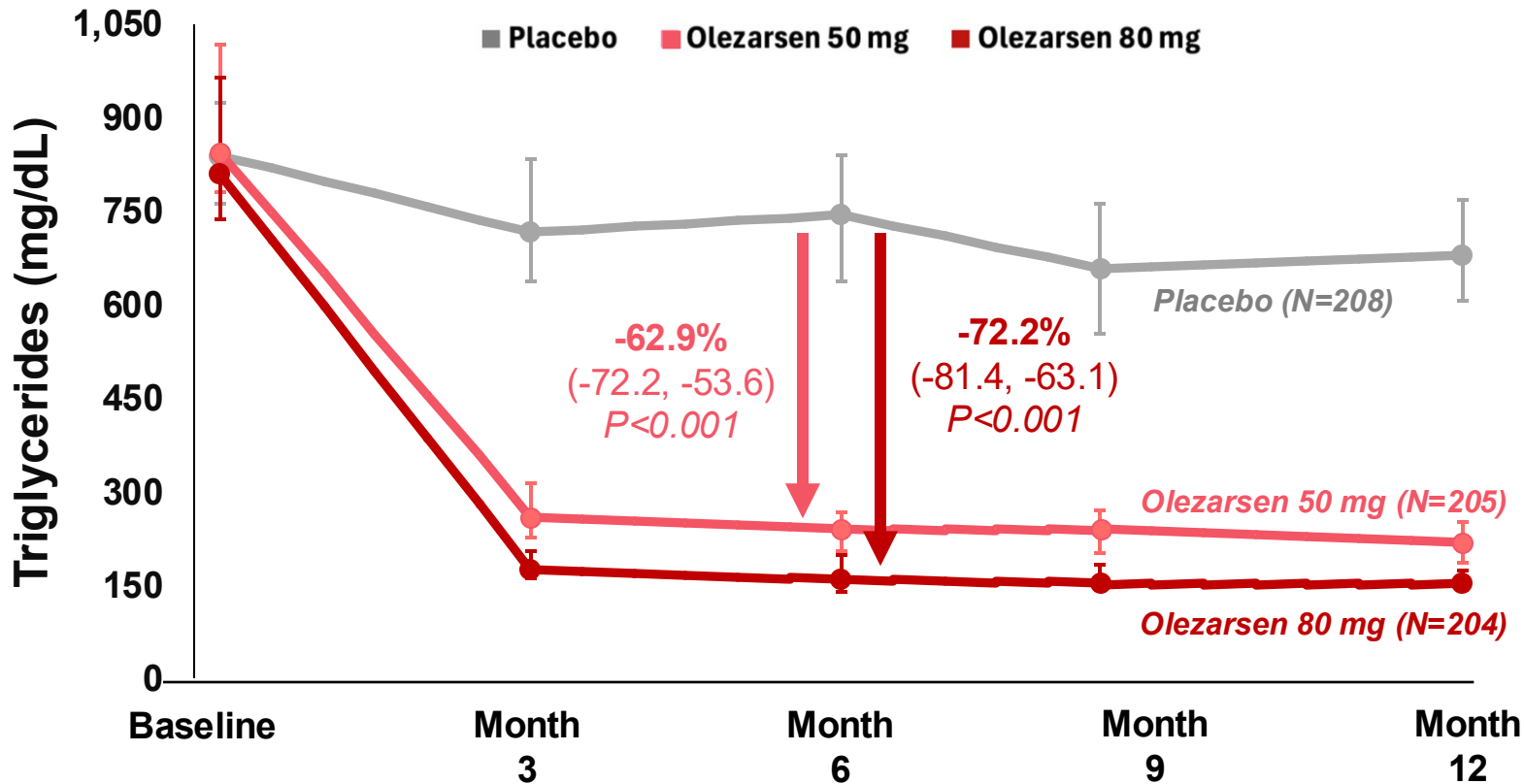
PRIMARY ENDPOINT: CORE-TIMI 72A



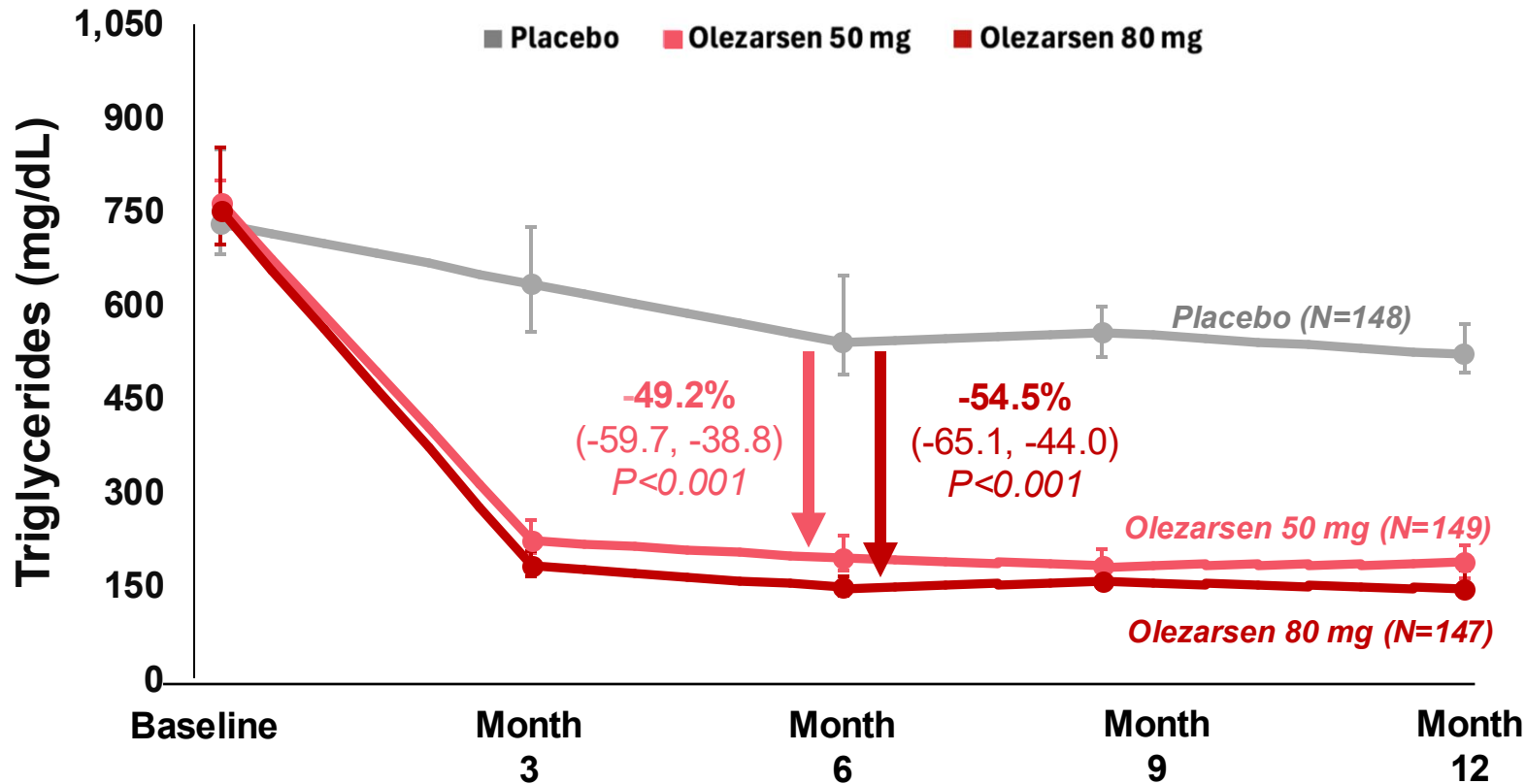
PRIMARY ENDPOINT: CORE-TIMI 72A



PRIMARY ENDPOINT: CORE-TIMI 72A

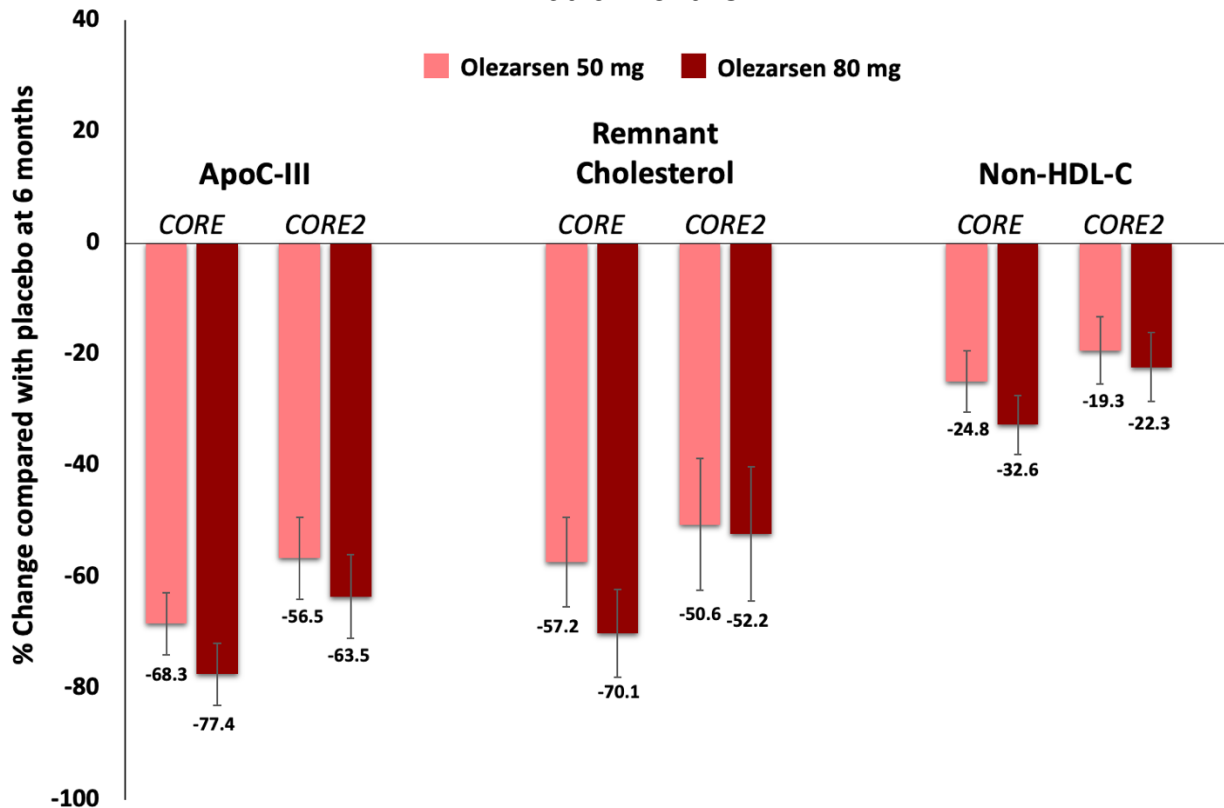


PRIMARY ENDPOINT: CORE2-TIMI 72B



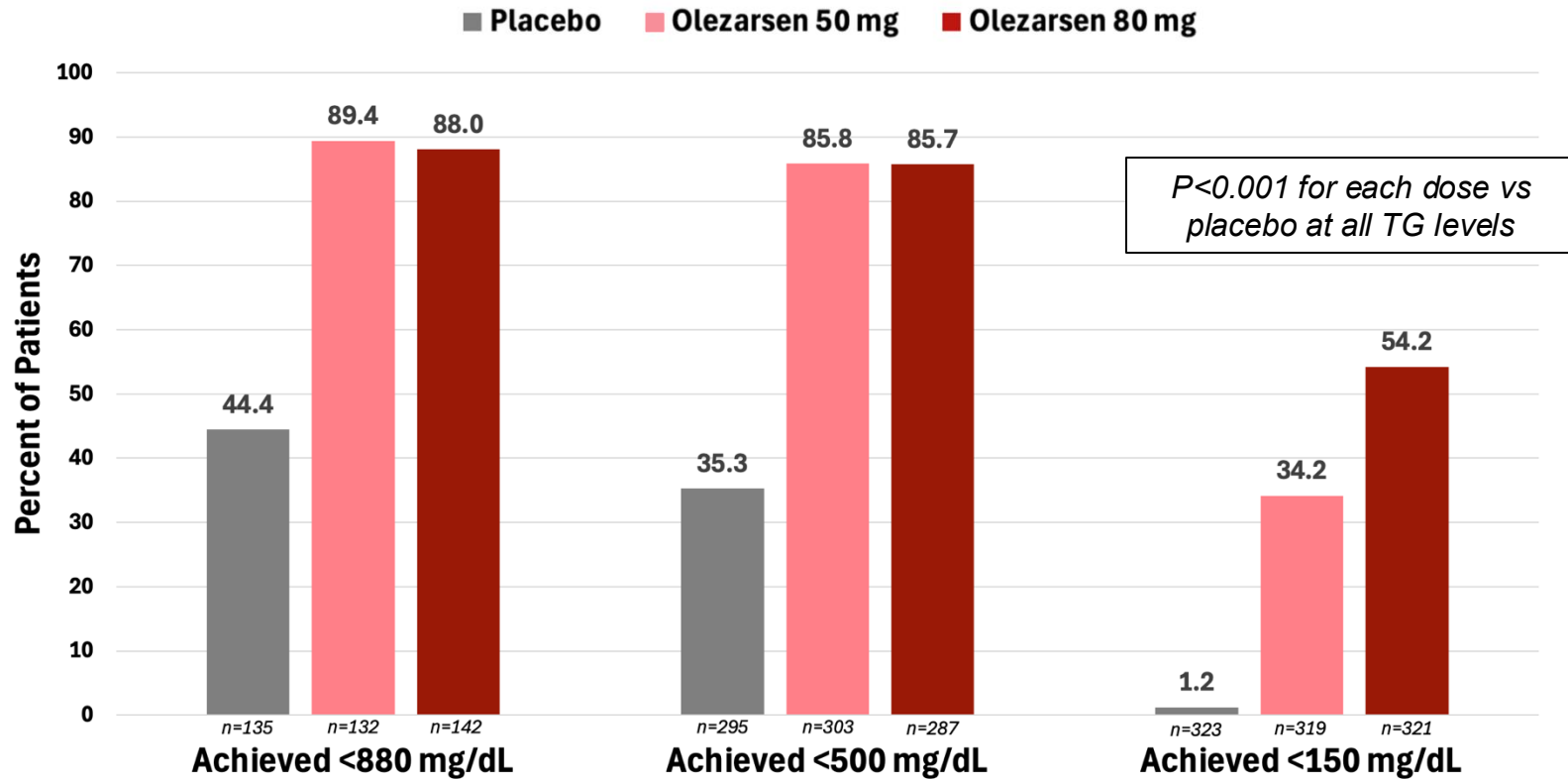
SECONDARY LIPID ENDPOINTS

at 6 months



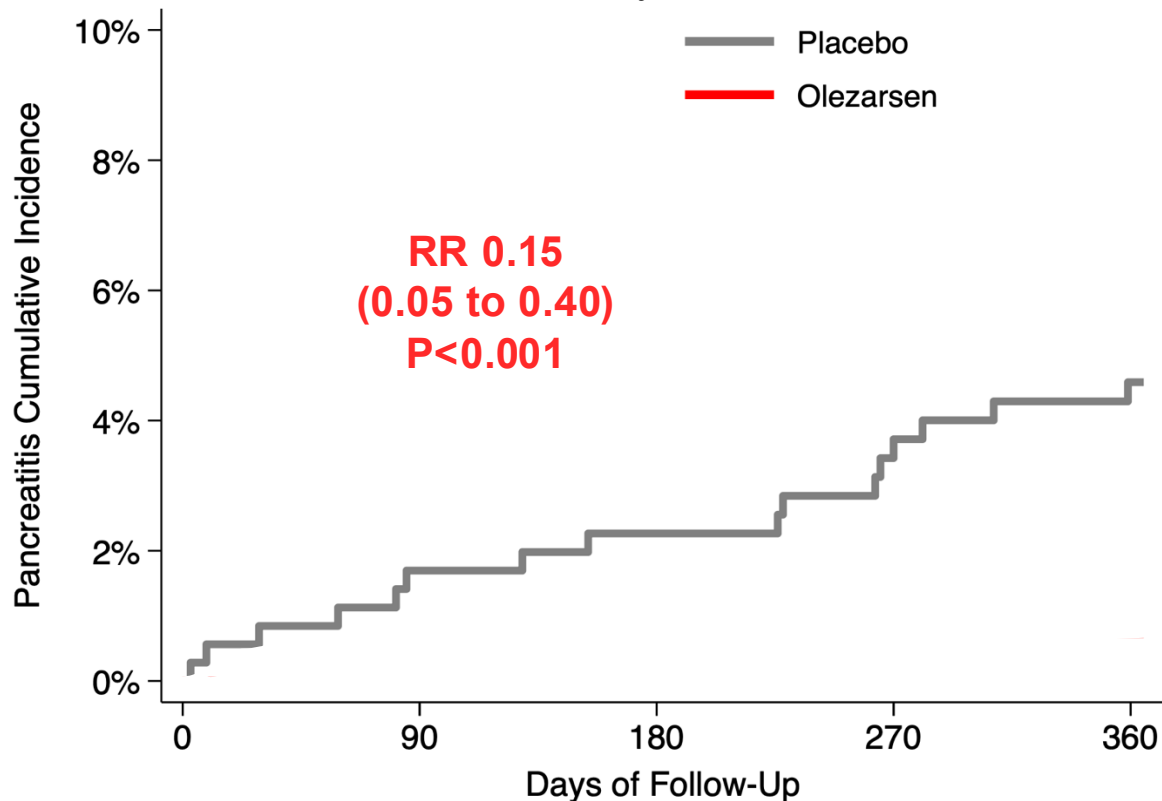
ACHIEVED TG LEVELS AT 12 MONTHS

Pooled analysis across trials



ACUTE PANCREATITIS

Pooled analysis across both doses and trials

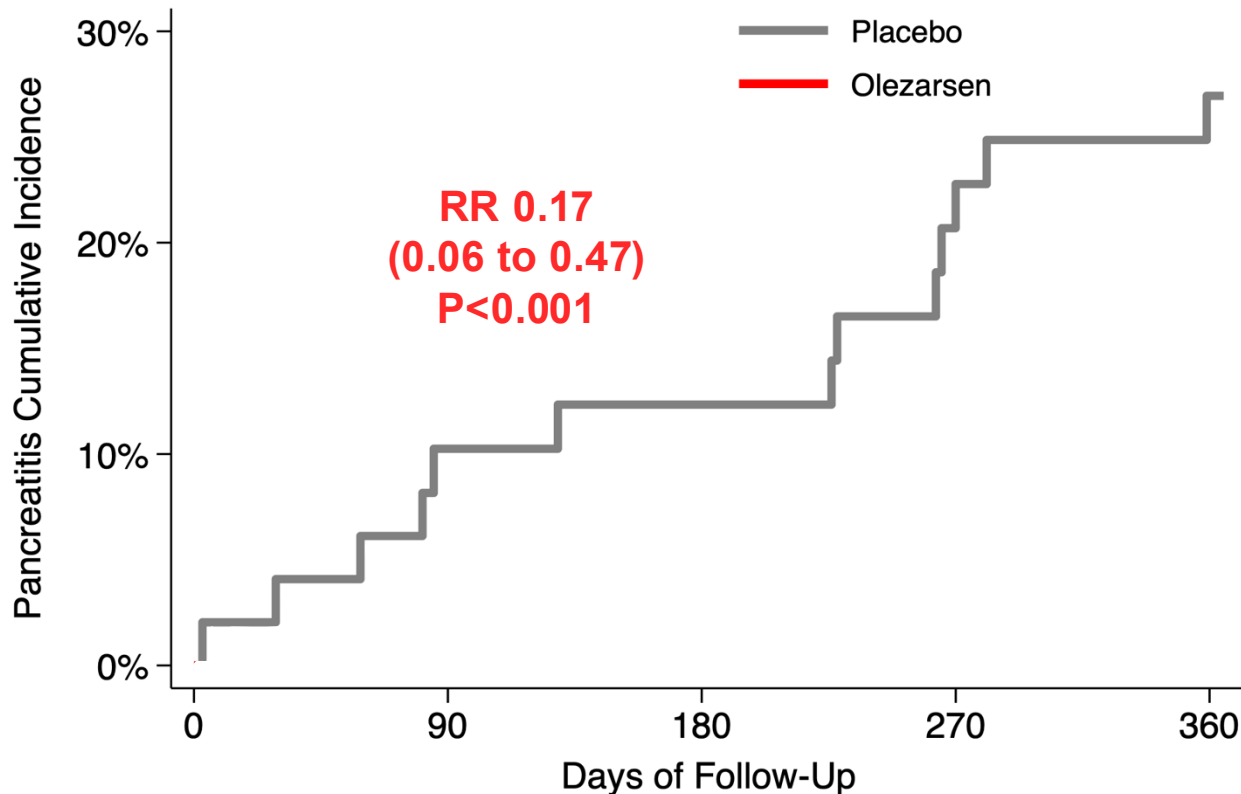


**ARR in incidence
of total events**
= 5.2%

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

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

ORIGINAL ARTICLE

Olezarsen for Managing Severe Hypertriglyceridemia and Pancreatitis Risk

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and Marc S. Sabatine, M.D., MPH,^{1,2}
for the CORE-TIMI 72a and CORE2-TIMI 72b Investigators

