OLEZARSEN IN PATIENTS WITH SEVERE HYPERTRIGLYCERIDEMIA

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

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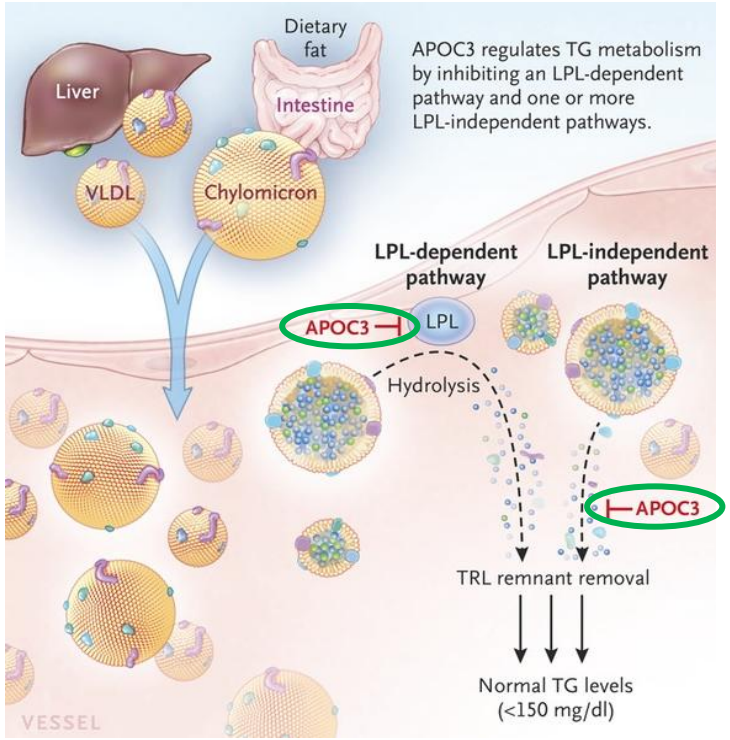
#AHA25

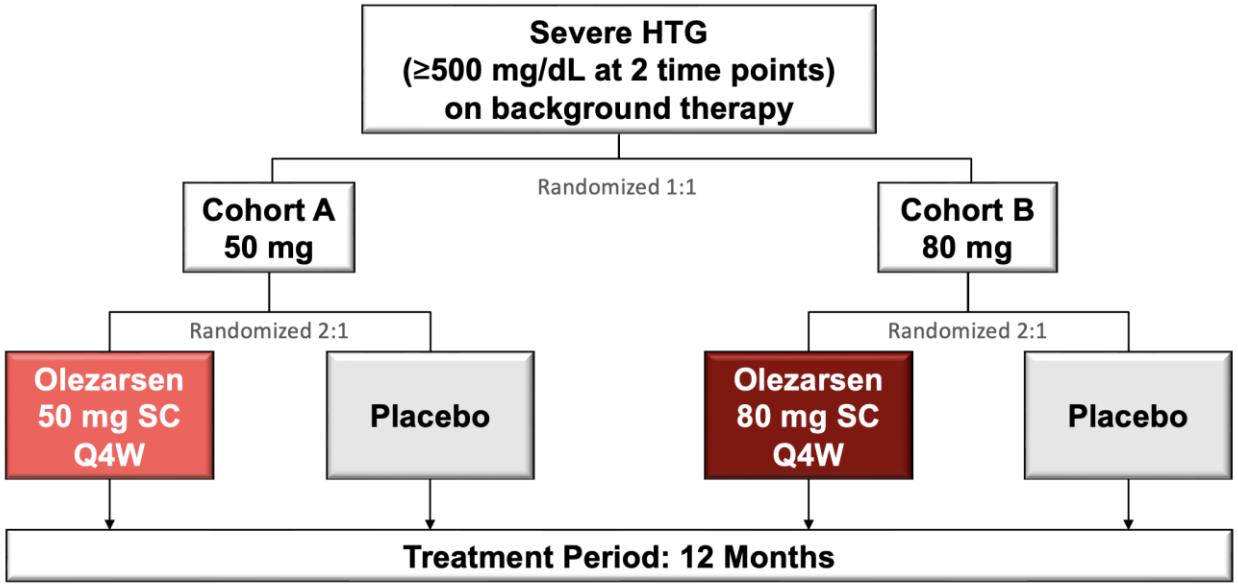
BACKGROUND



- 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 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

TRIAL ORGANIZATION

TIMI Study Group

Marc Sabatine (Chair)
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Independent Data Monitoring Committee

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Jamie Dwyer
Willis Maddrey

Charles Davis (Statistician)
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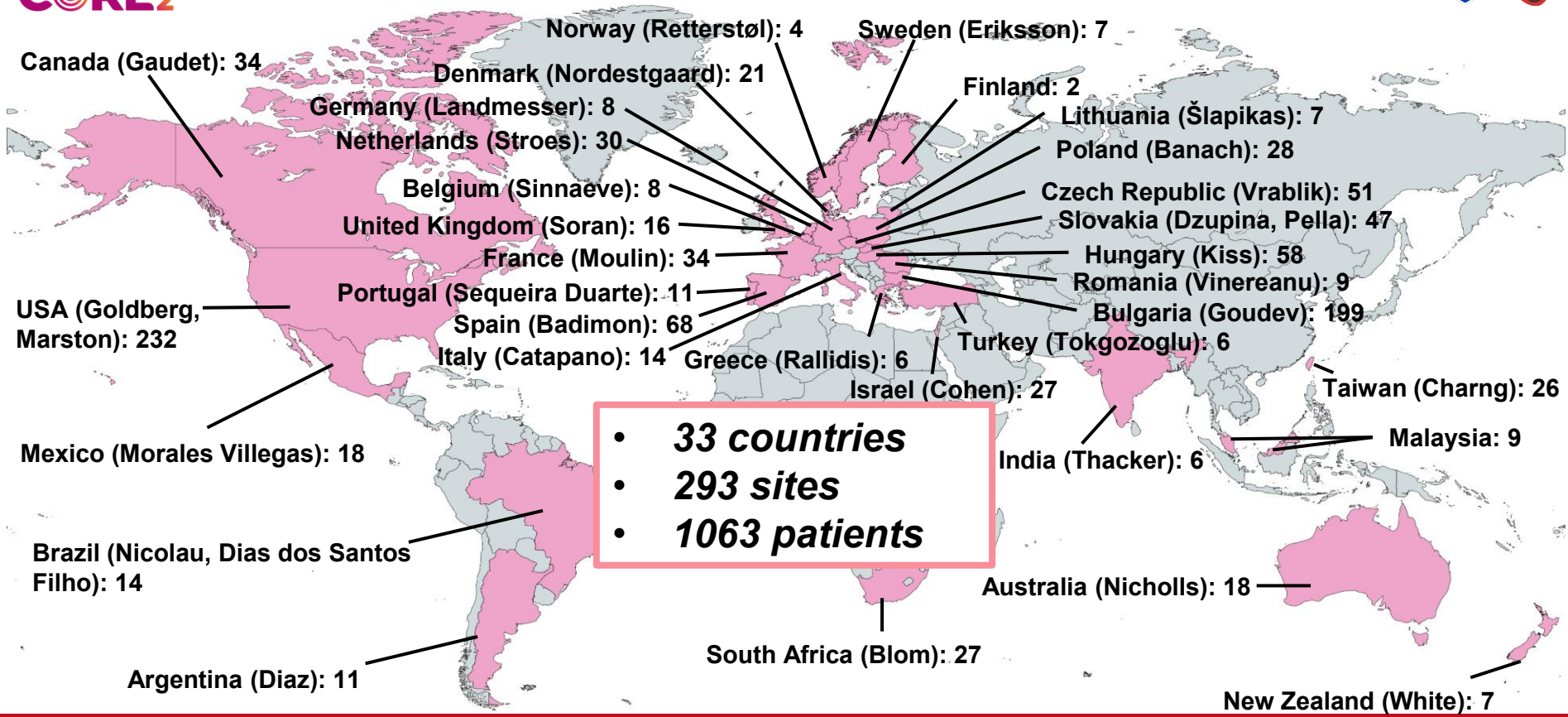
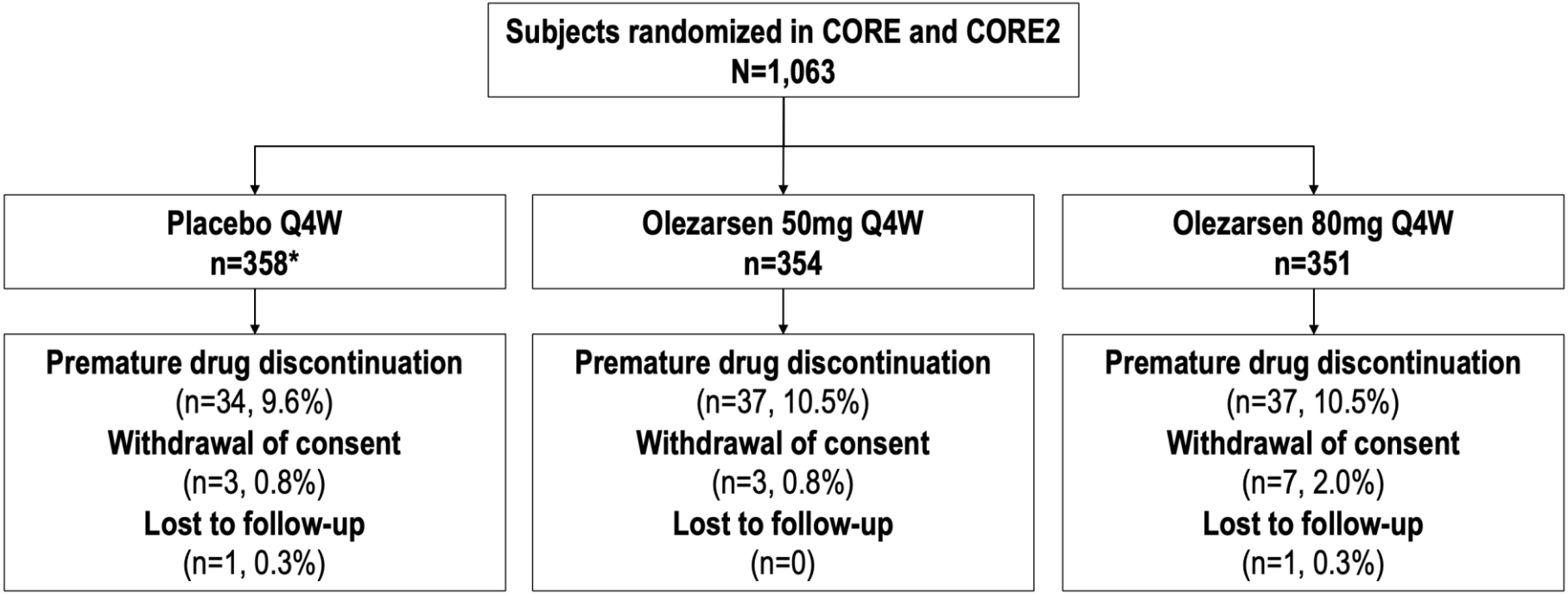
James Freston

GLOBAL ENROLLMENT



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

PATIENT DISPOSITION



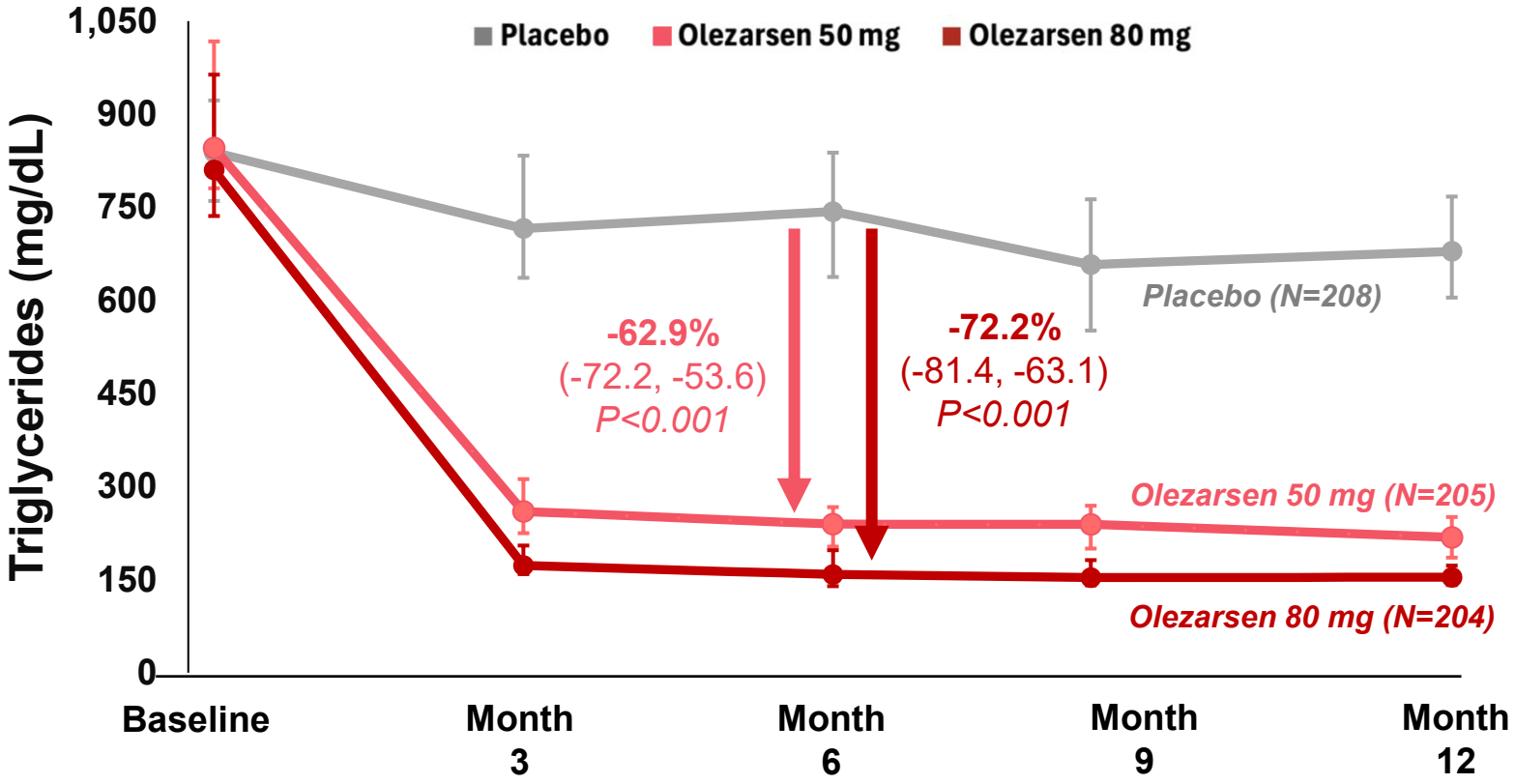
*Two patients in the placebo arm did not receive IP and so were not included in the primary analysis

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%

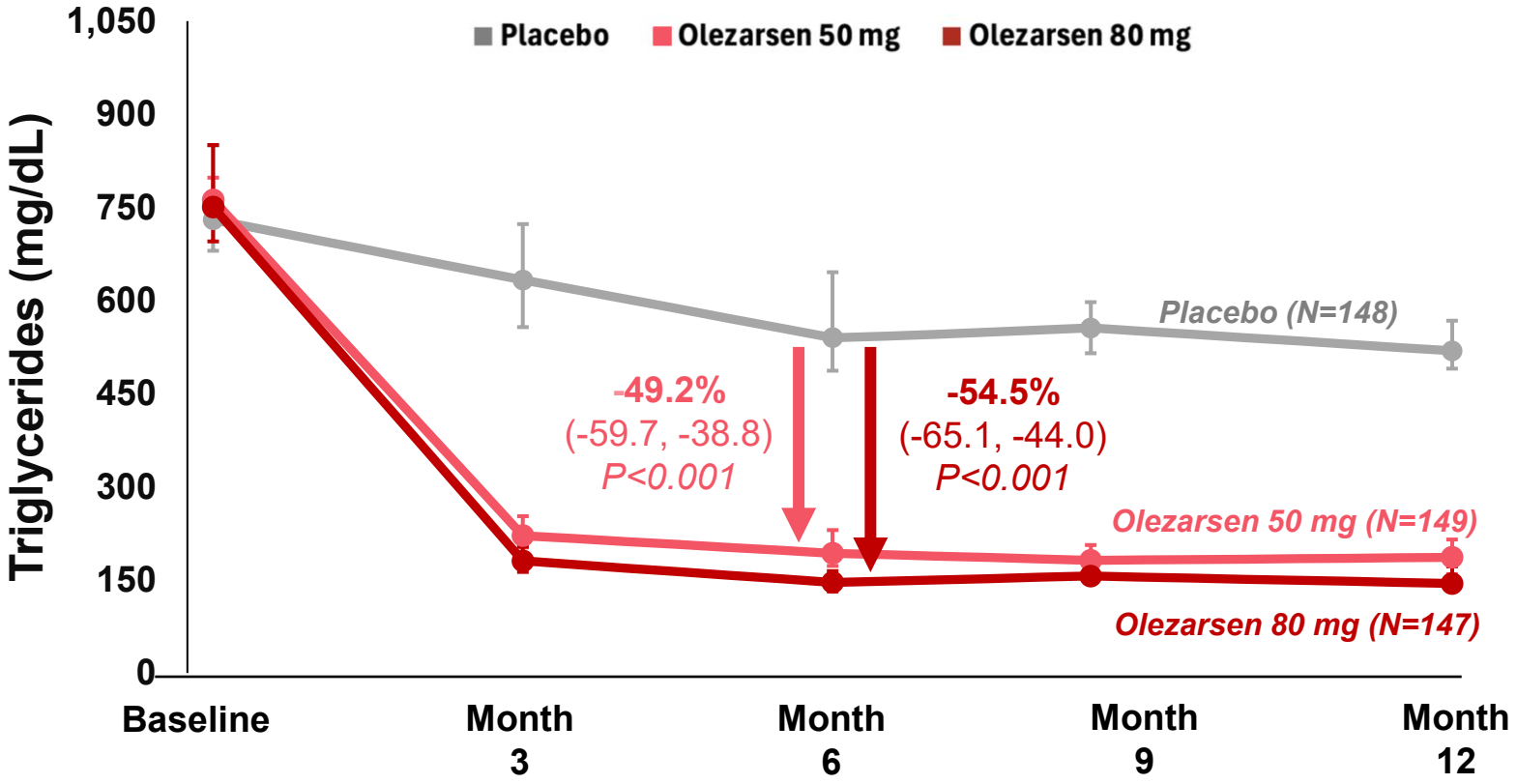
Continuous variables listed as median (IQR)
Baseline variables balanced by treatment arm

PRIMARY ENDPOINT: CORE-TIMI 72A



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

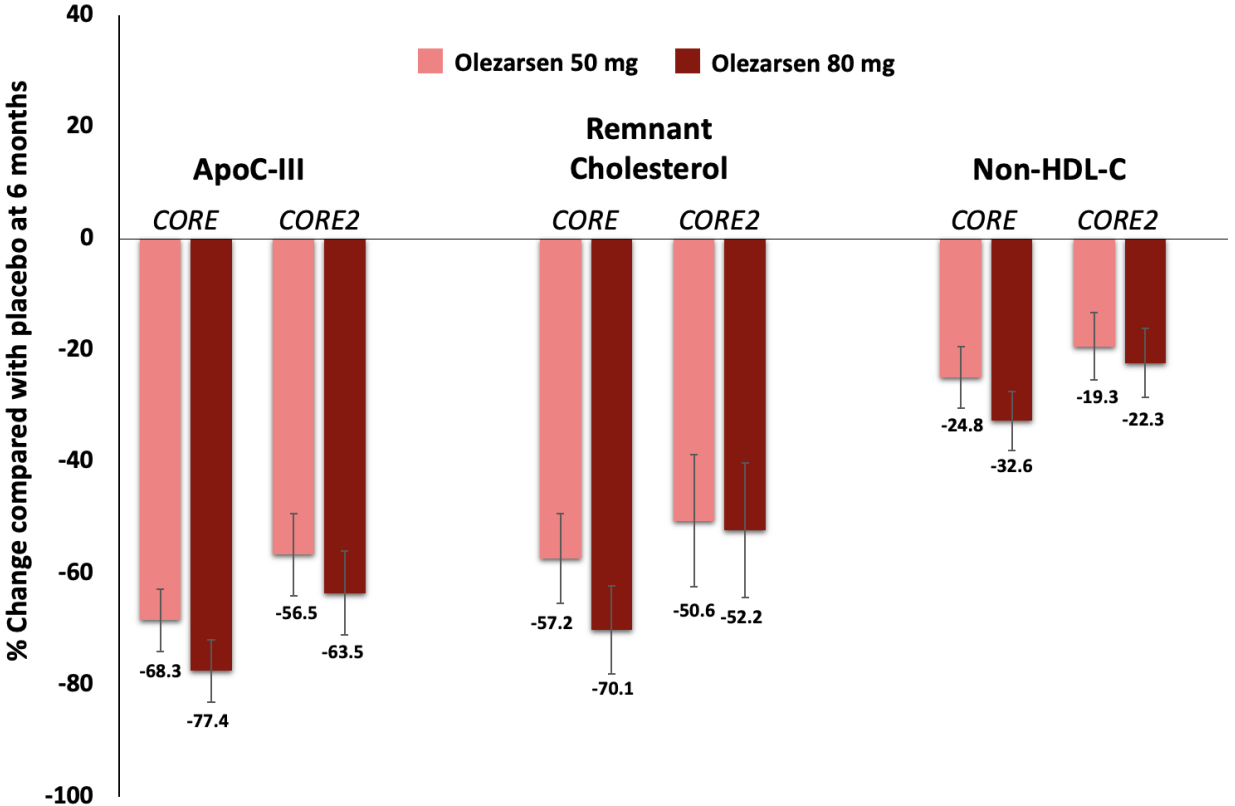
PRIMARY ENDPOINT: CORE2-TIMI 72B



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

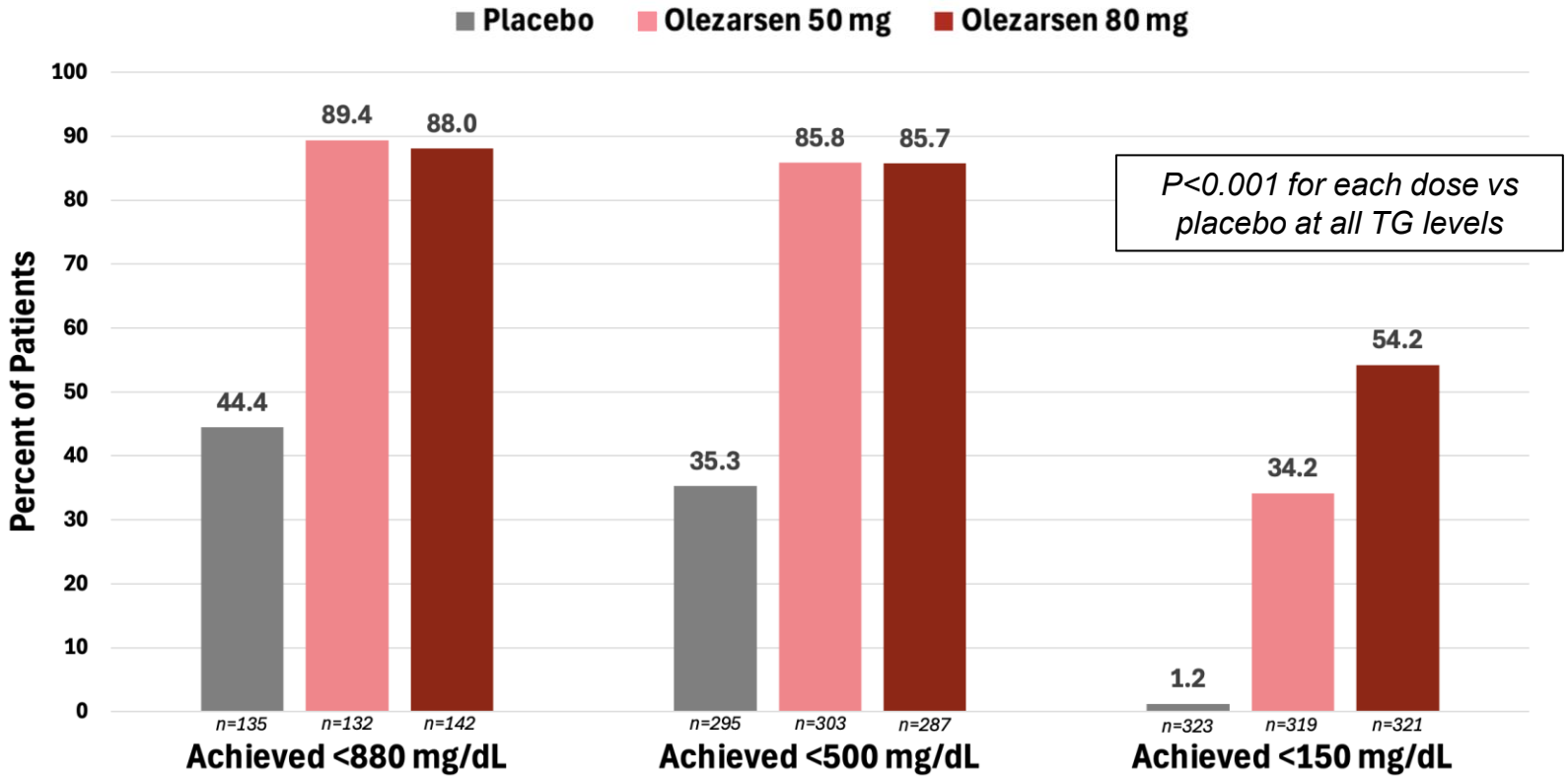
SECONDARY LIPID ENDPOINTS

at 6 months



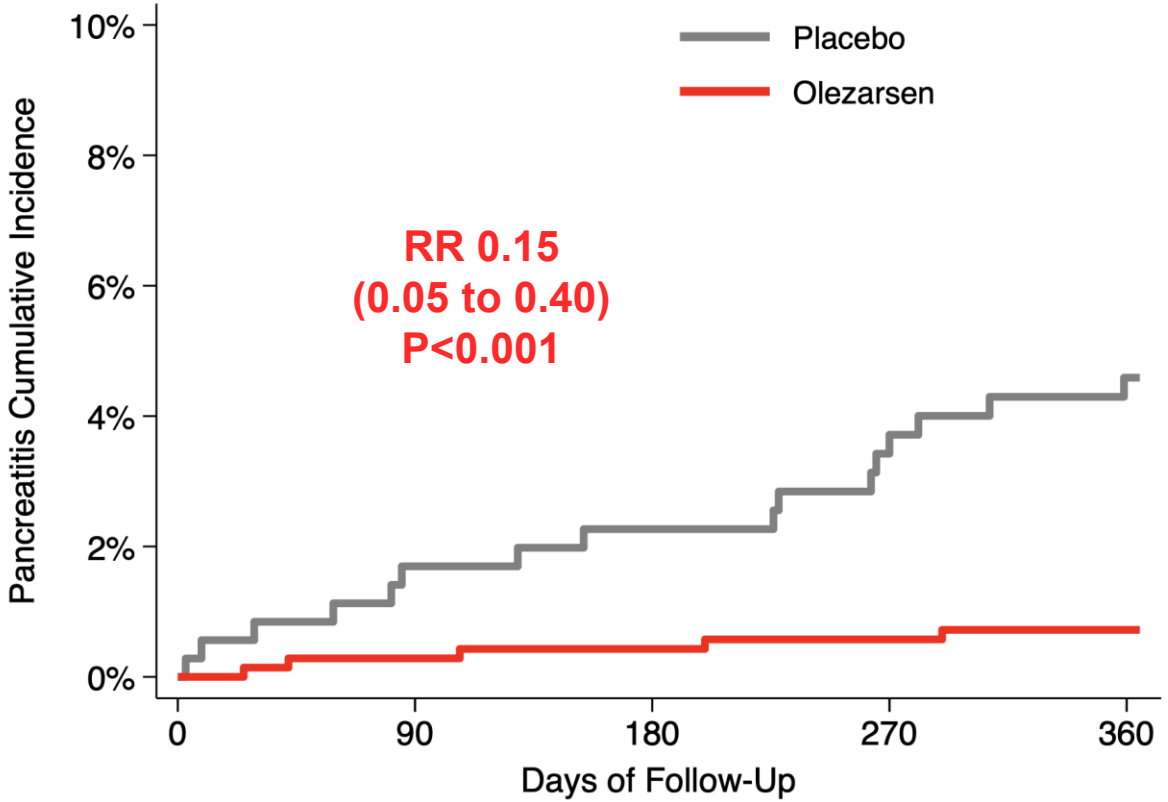
ACHIEVED TG LEVELS AT 12 MONTHS

Pooled analysis across trials



ACUTE PANCREATITIS

Pooled analysis across both doses and trials

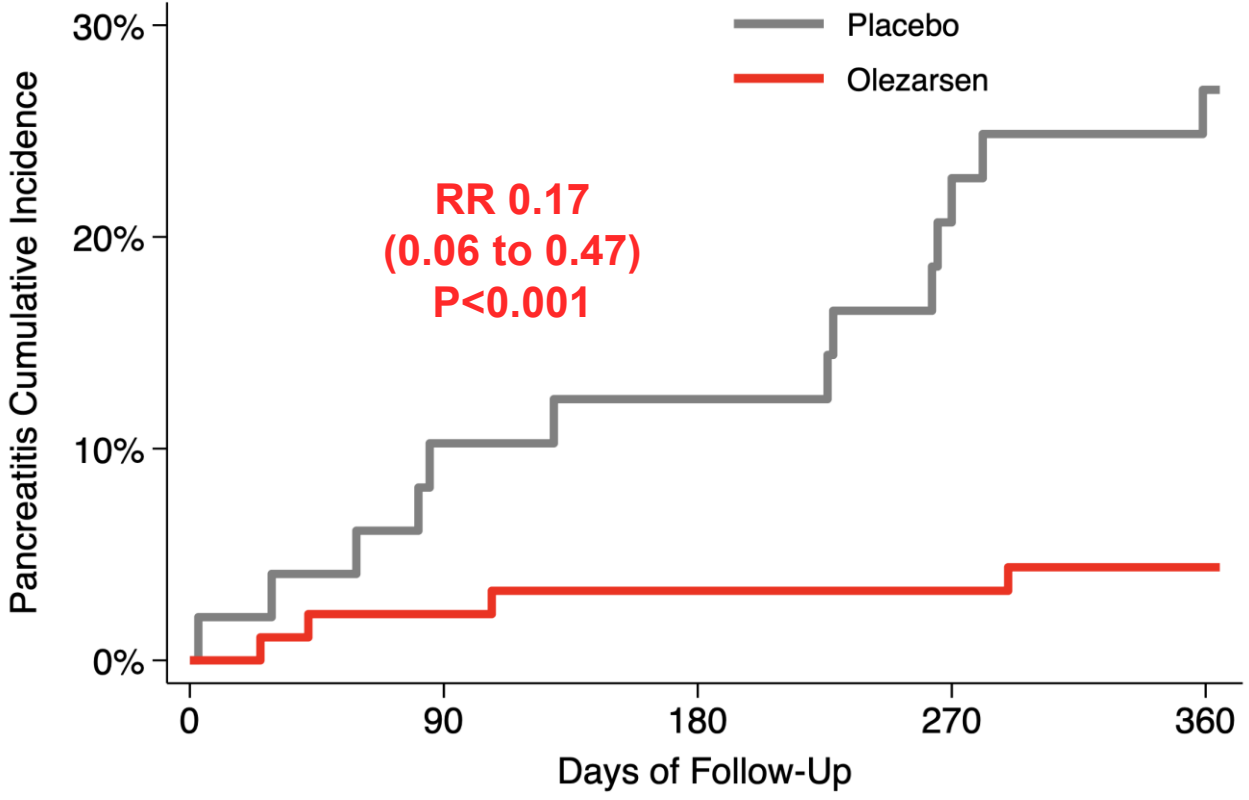


ARR in incidence of total events = 5.2%

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	

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

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

SUMMARY & CONCLUSION

- **Among patients with severe hypertriglyceridemia, olezarsen:**
  - Lowered triglycerides by ~65%, 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**

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ORIGINAL ARTICLE

Olezarsen for Managing Severe Hypertriglyceridemia and Pancreatitis Risk

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