

PREVENTION OF ACUTE PANCREATITIS WITH APOC3 INHIBITION IN SEVERE HYPERTRIGLYCERIDEMIA ACROSS TRIGLYCERIDE LEVELS AND PRIOR PANCREATITIS

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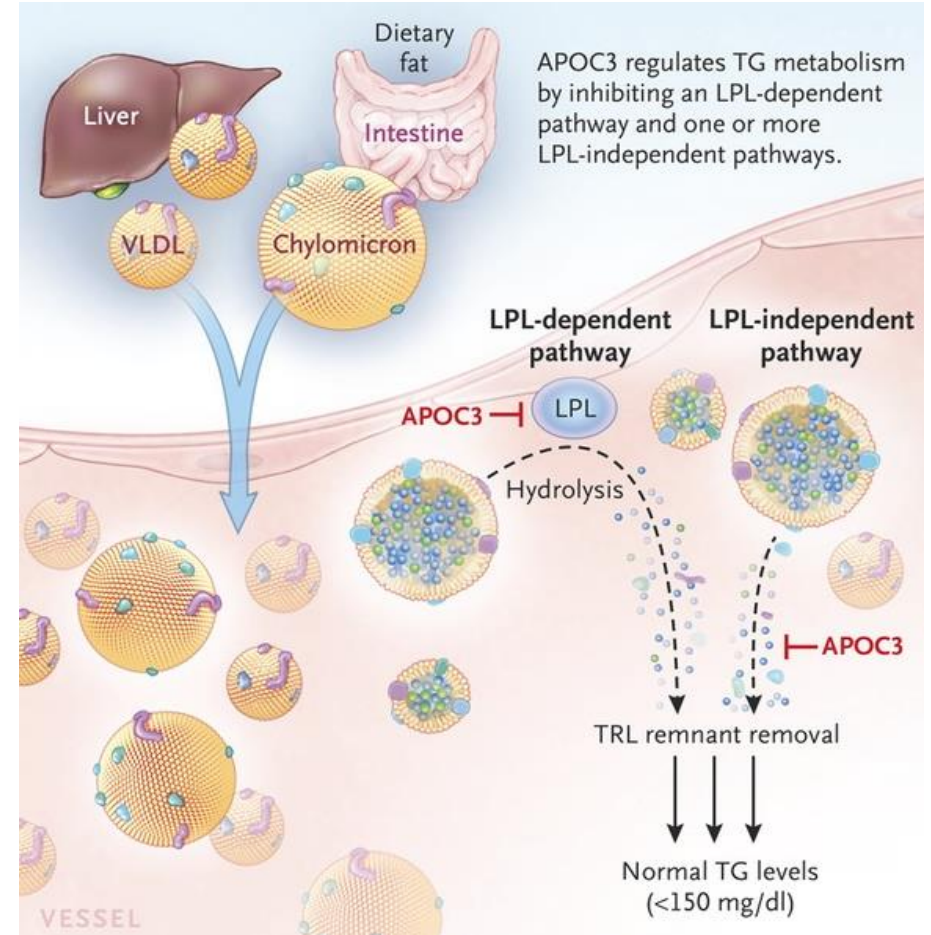


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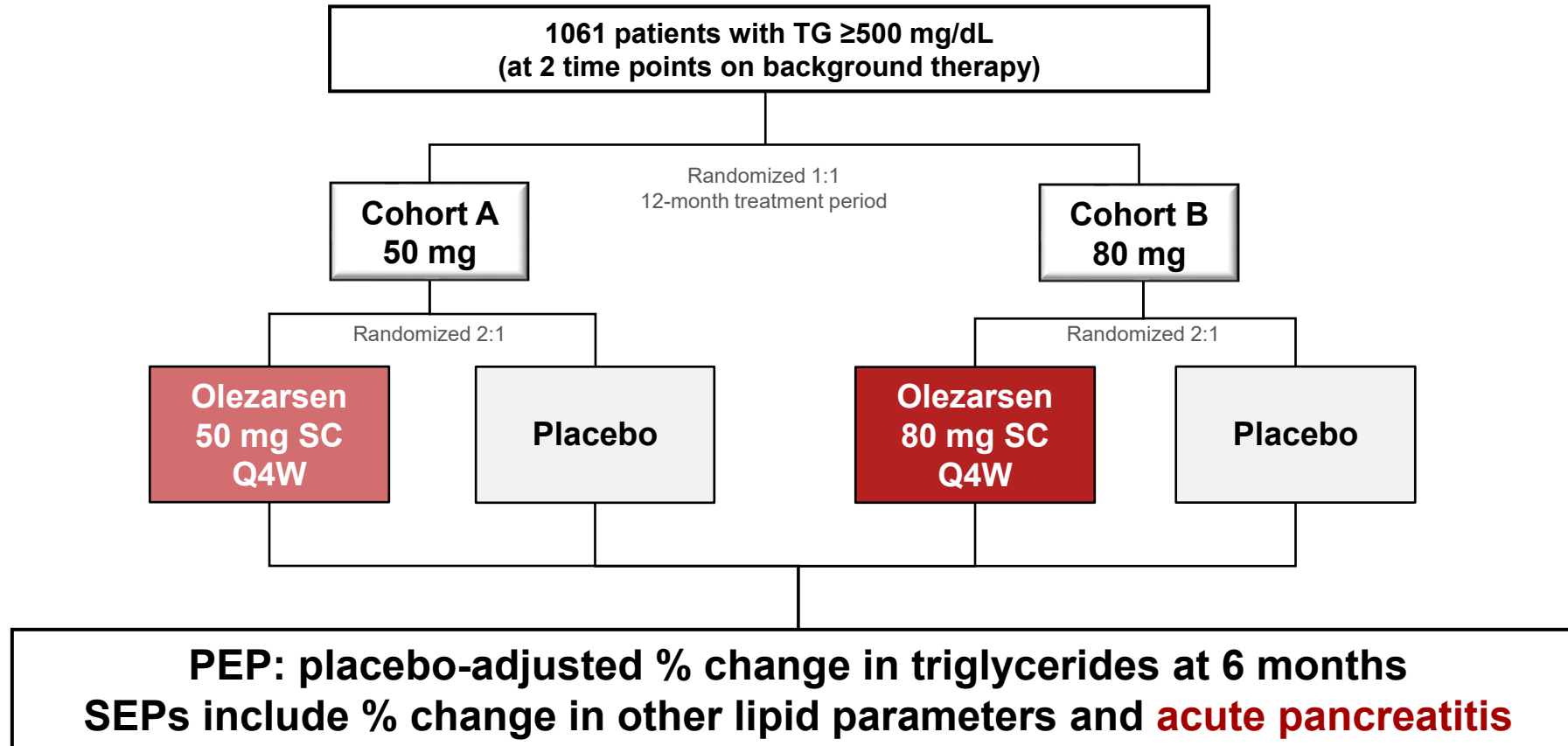
BACKGROUND

- Severe hypertriglyceridemia (sHTG), defined as TG \geq 500 mg/dL, carries an increased risk of acute pancreatitis
- Risk is highly heterogeneous even within the sHTG range and according to prior pancreatitis status
- Apolipoprotein C-III (APOC-III) inhibits lipoprotein lipase, a pivotal enzyme responsible for the catabolism of TGs



Gaudet D et al. NEJM 2014

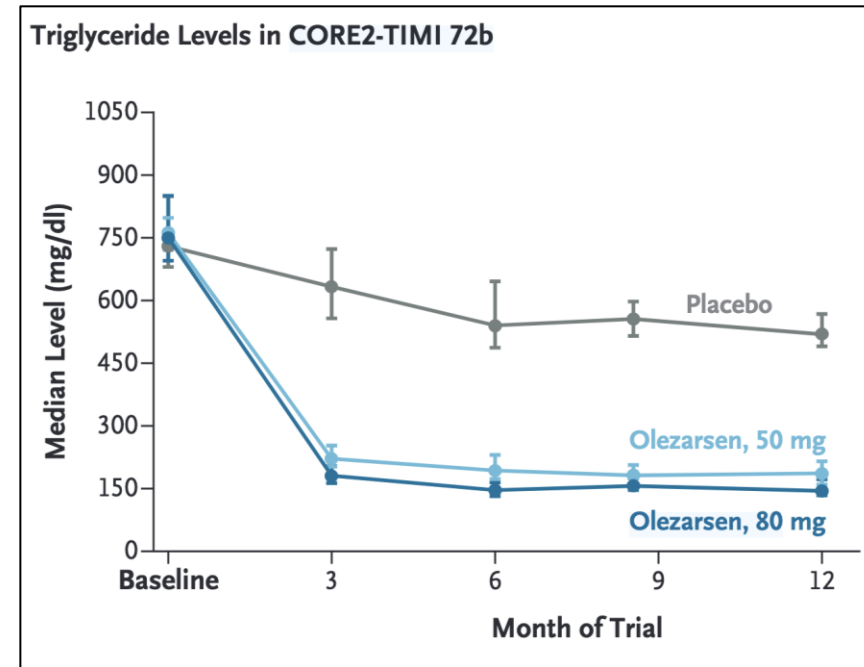
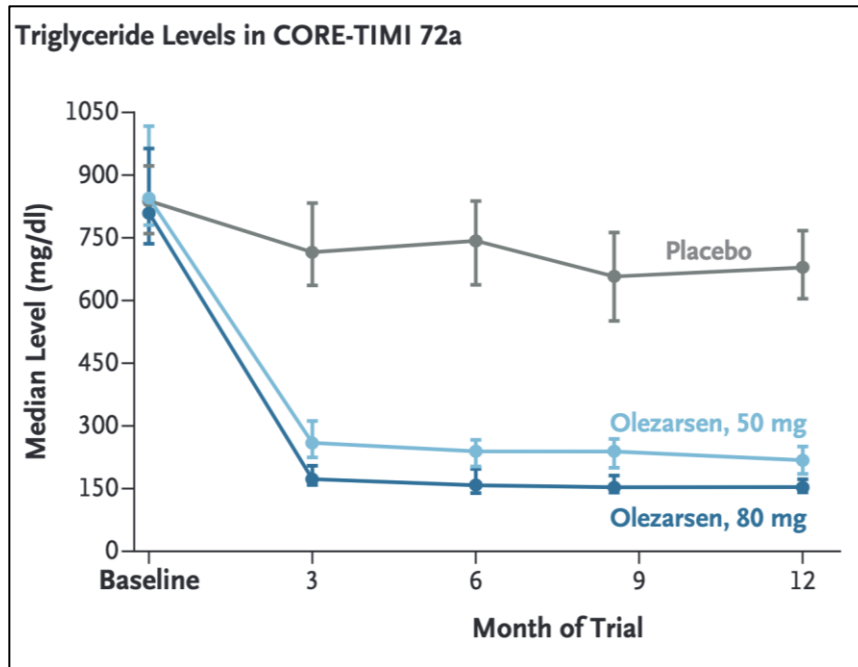
CORE-TIMI 72A & CORE2-TIMI 72B: IDENTICALLY DESIGNED PHASE 3 TRIALS



CORE-TIMI 72a and CORE2-TIMI 72b were identically designed. Data were pooled for this analysis.
 PEP indicates primary endpoint; SEP, secondary endpoint.

BACKGROUND

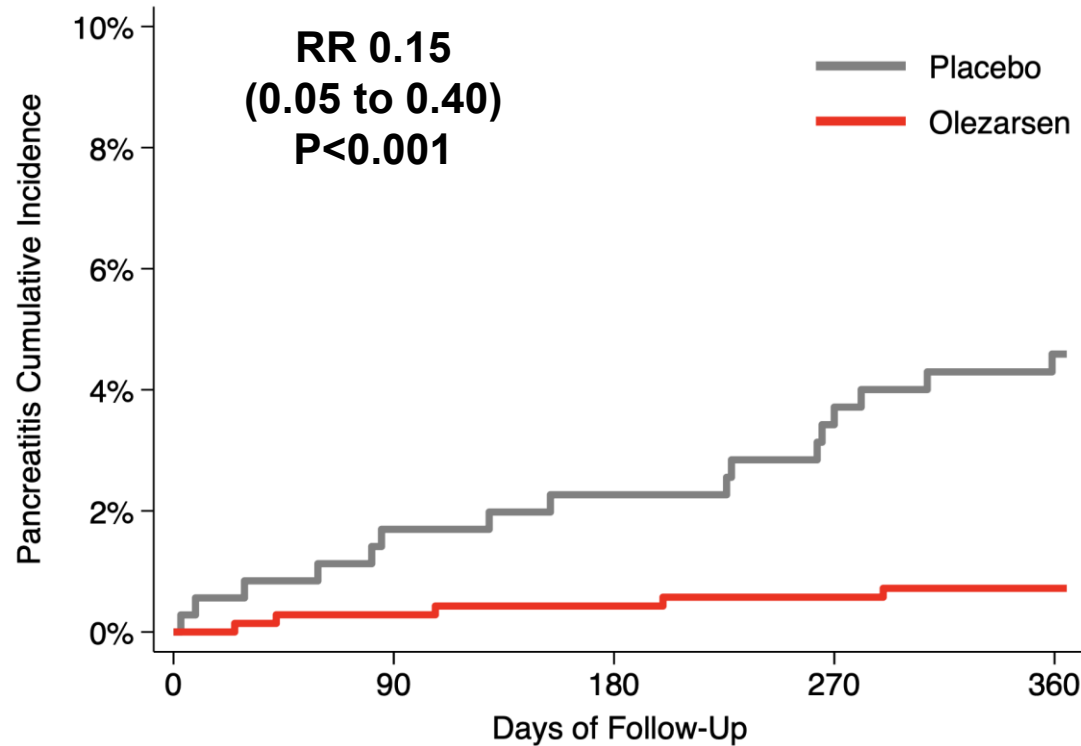
In patients with TG \geq 500 mg/dL, olezarsen, an antisense oligonucleotide that targets APOC3 mRNA, \downarrow TGs by 49–72%



Marston N et al. NEJM 2025

BACKGROUND

In a pooled analysis of both trials and doses, olezarsen ↓ acute pancreatitis by 85%



ARR in incidence of total events = 5.2%

NNT over 1 year = 20

Marston N et al. NEJM 2025

The effect of olezarsen on acute pancreatitis has not been defined across pre-treatment triglyceride levels and prior pancreatitis in patients with severe hypertriglyceridemia

BASELINE CHARACTERISTICS

Characteristic	No acute pancreatitis during follow-up (N=1039)	Acute pancreatitis during follow-up (N=22)	P-value
Demographics			
Age (years)	54 (46–62)	47 (42–57)	0.052
Female	243 (23.4)	7 (31.8)	0.357
BMI (kg/m ²)	31.2 (28.1–34.7)	30.6 (26.9–32.6)	0.268
Current smoking	268 (25.8)	6 (27.3)	0.875
History of CKD	88 (8.5)	1 (5.5)	0.077
History of diabetes	655 (63.0)	18 (81.8)	0.077
History of pancreatitis	181 (17.4)	19 (86.4)	<0.001
Triglycerides (mg/dL)	779.5 (592.5–1220.0)	1638.0 (1150.5–3907.5)	<0.001
≥ 880 mg/dL	434 (41.8)	21 (95.5)	<0.001
Lipid-lowering therapies			
Statin	766 (73.7)	18 (81.8)	0.471
Ezetimibe	233 (22.4)	6 (27.3)	0.590
Fibrate	655 (63.0)	19 (86.4)	0.025
Omega-3 fatty acids	329 (31.7)	11 (50.0)	0.068
≥2 lipid-lowering therapies	674 (64.9)	18 (81.8)	0.116

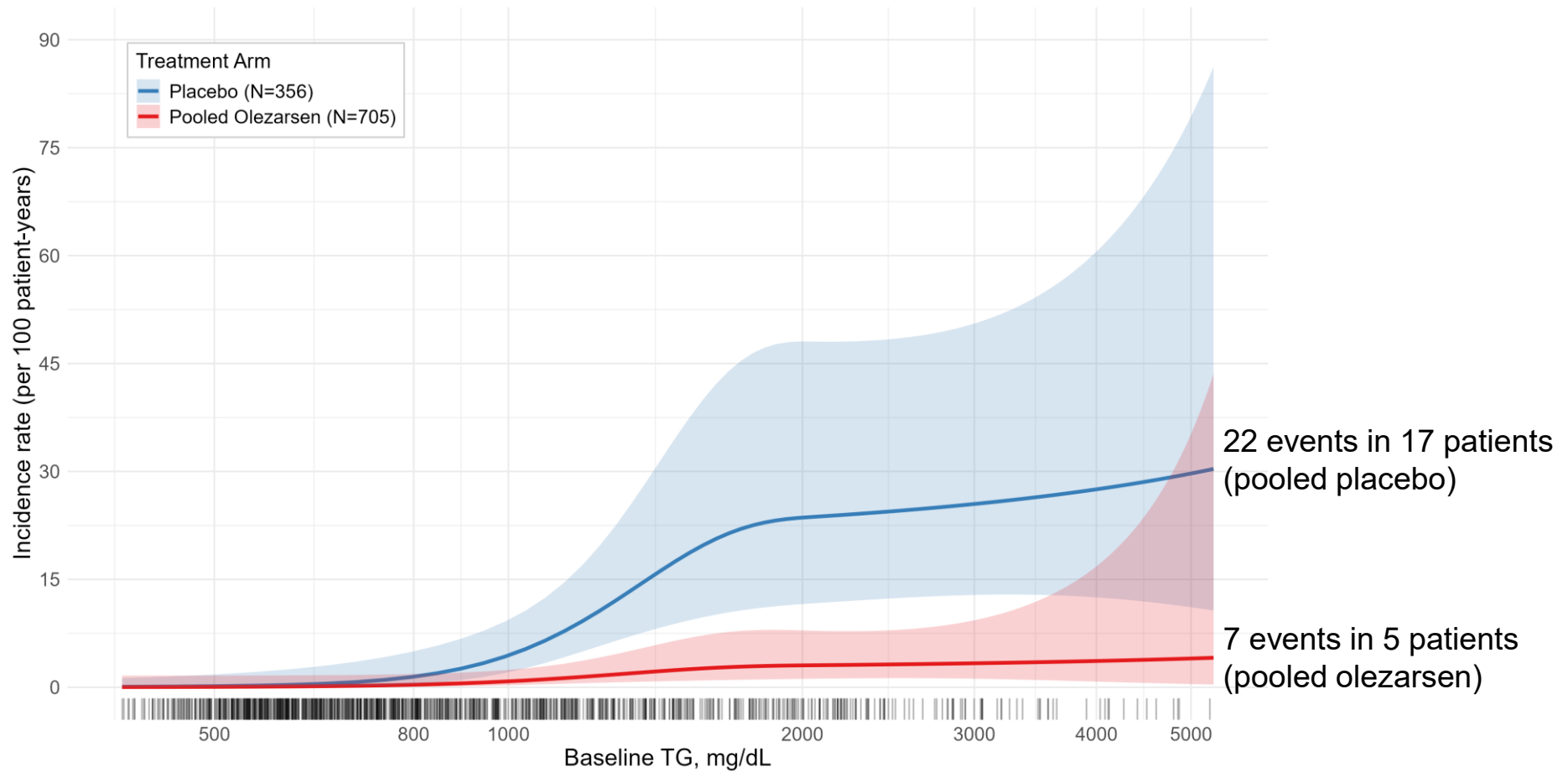
Continuous data are displayed as median (IQR).

PREDICTORS OF ACUTE PANCREATITIS IN SEVERE HYPERTRIGLYCERIDEMIA

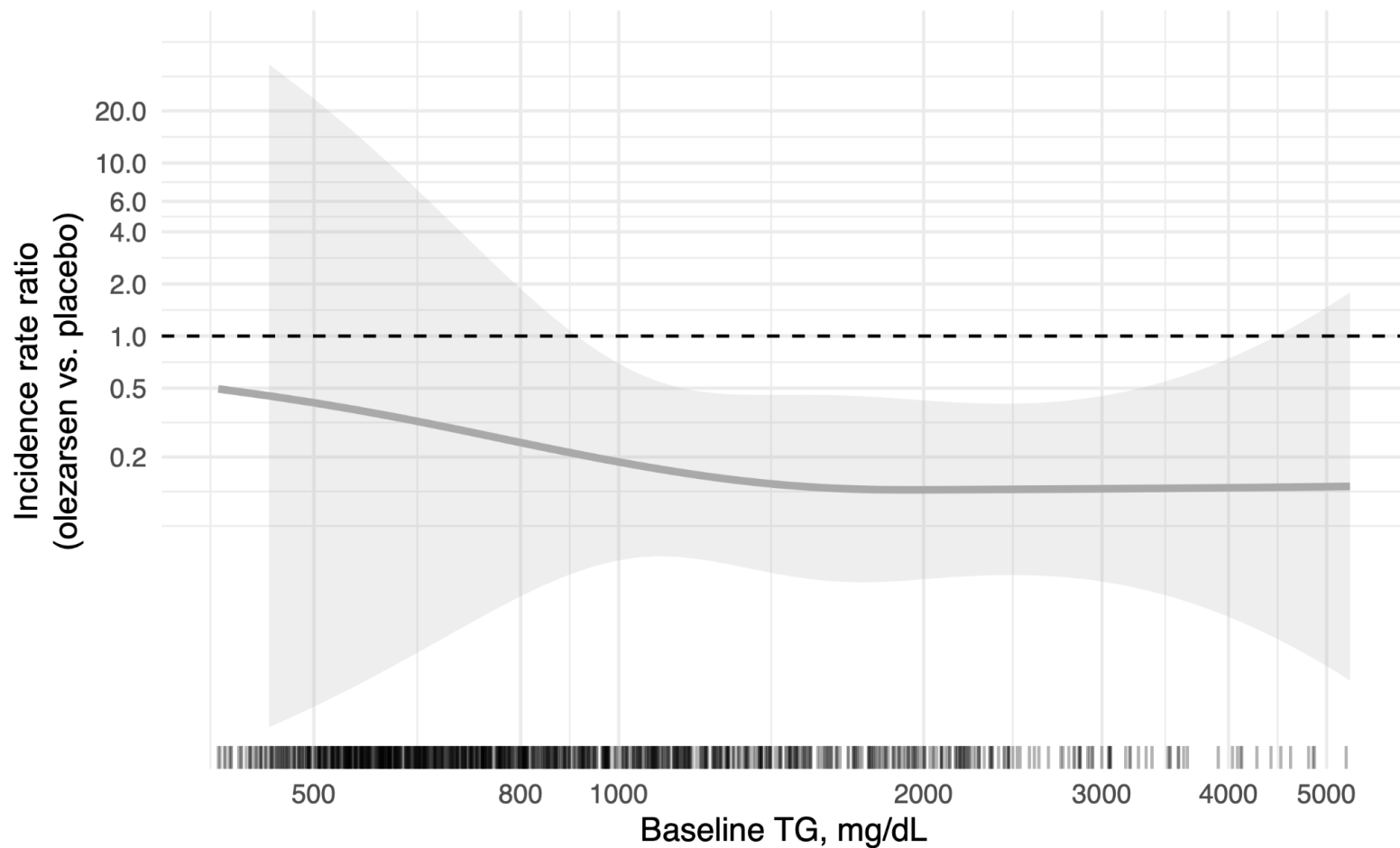
Predictor	Incidence rate ratio (95% CI)	P-value
Prior pancreatitis	41.98 (9.53, 184.85)	<0.001
Triglycerides (per 100 mg/dL)	1.07 (1.02, 1.12)	0.005
Age (per 10 years)	0.65 (0.41, 1.06)	0.082
History of diabetes	2.97 (0.87, 10.20)	0.083
BMI (per 5 kg/m ²)	0.85 (0.52, 1.39)	0.520
Current smoking	1.19 (0.36, 3.91)	0.772
Chronic kidney disease	0.80 (0.07, 8.77)	0.855
Female	0.94 (0.24, 3.61)	0.927

Analysis conducted in placebo group

INCIDENCE OF ACUTE PANCREATITIS BY BASELINE FASTING TRIGLYCERIDE LEVEL

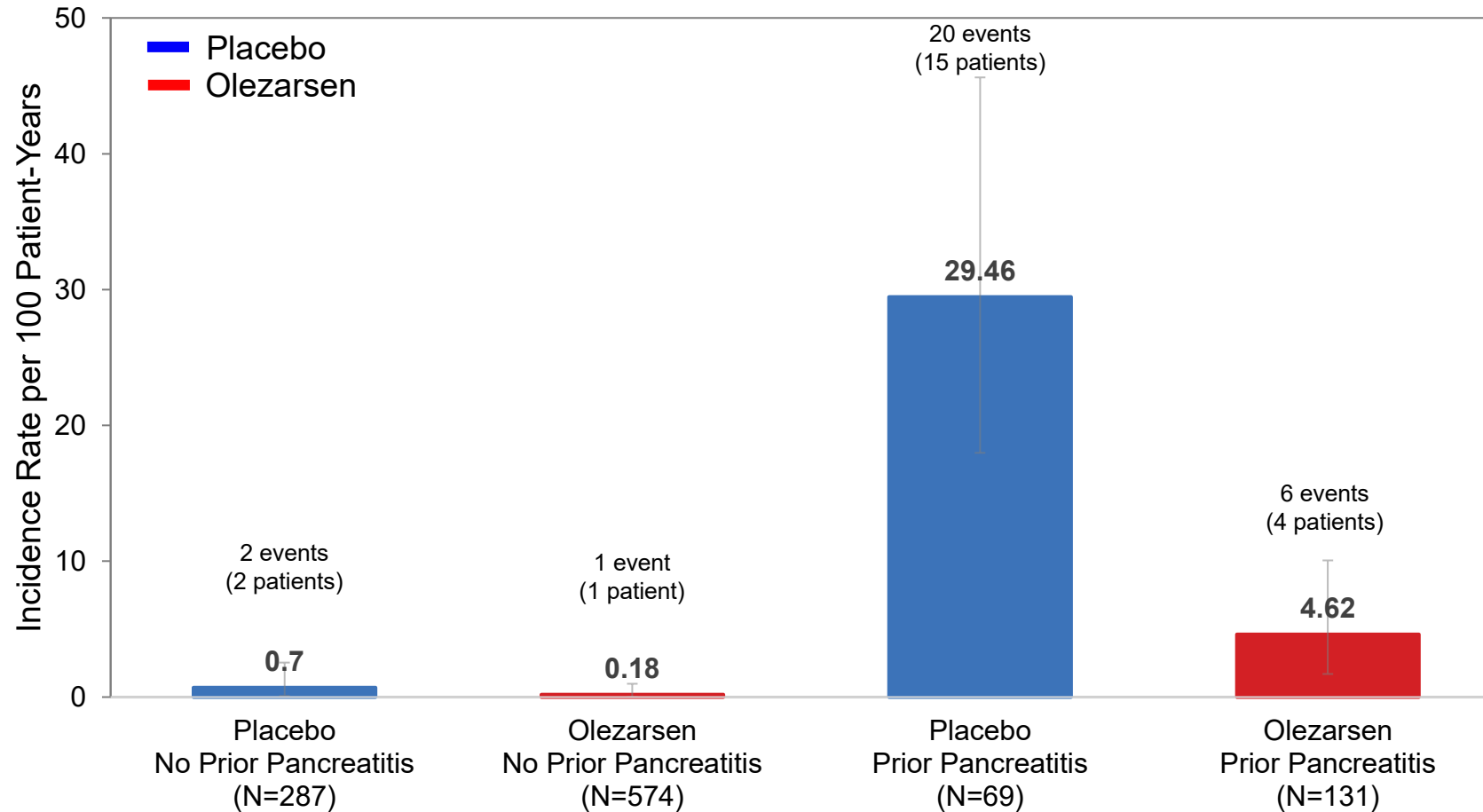


INCIDENCE RATE RATIO OF ACUTE PANCREATITIS BY BASELINE FASTING TRIGLYCERIDE LEVEL



*Overall : IRR_{total events} **0.15** (0.05 to 0.40)

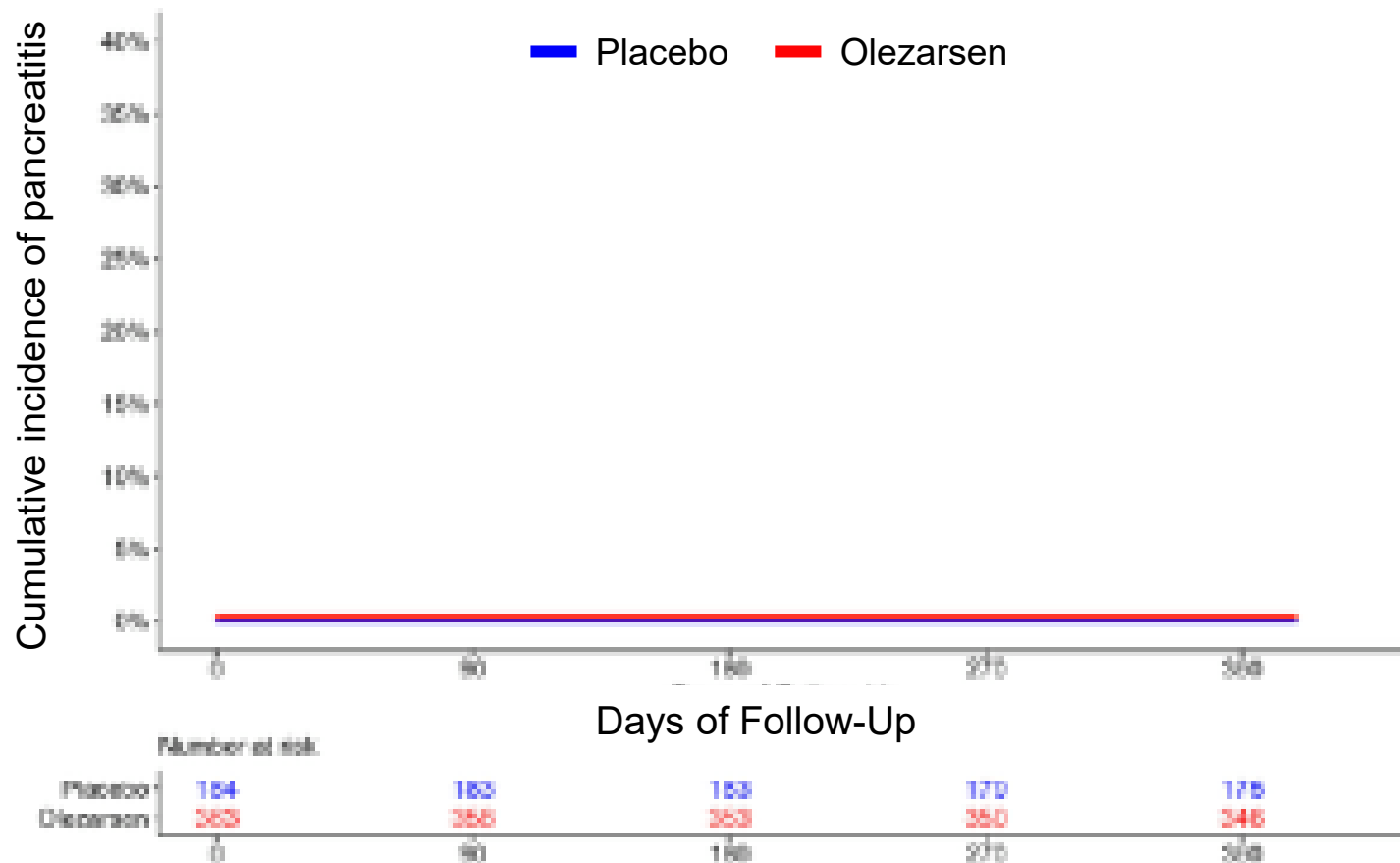
INCIDENCE OF ACUTE PANCREATITIS BY PRIOR PANCREATITIS



ACUTE PANCREATITIS BY BASELINE FASTING TRIGLYCERIDE LEVEL AND HISTORY OF PANCREATITIS



Baseline TG < 880 mg/dL (10 mmol/L), without prior acute pancreatitis



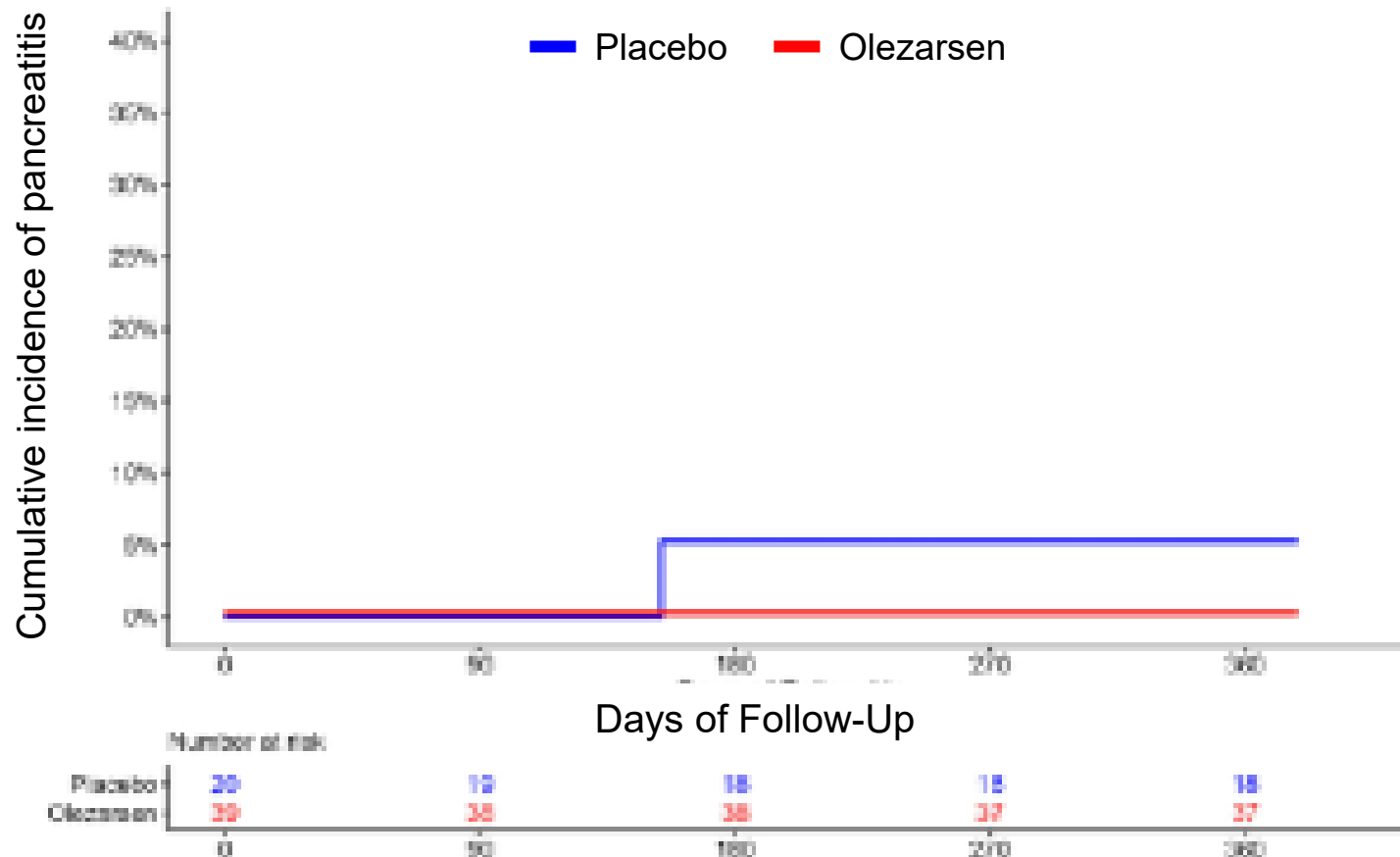
No events

*Overall : **IRR**_{total events} **0.15** (0.05 to 0.40)

ACUTE PANCREATITIS BY BASELINE FASTING TRIGLYCERIDE LEVEL AND HISTORY OF PANCREATITIS



Baseline TG < 880 mg/dL (10 mmol/L), with prior acute pancreatitis



ARR_{total events} 5.2 events/100 pt-years

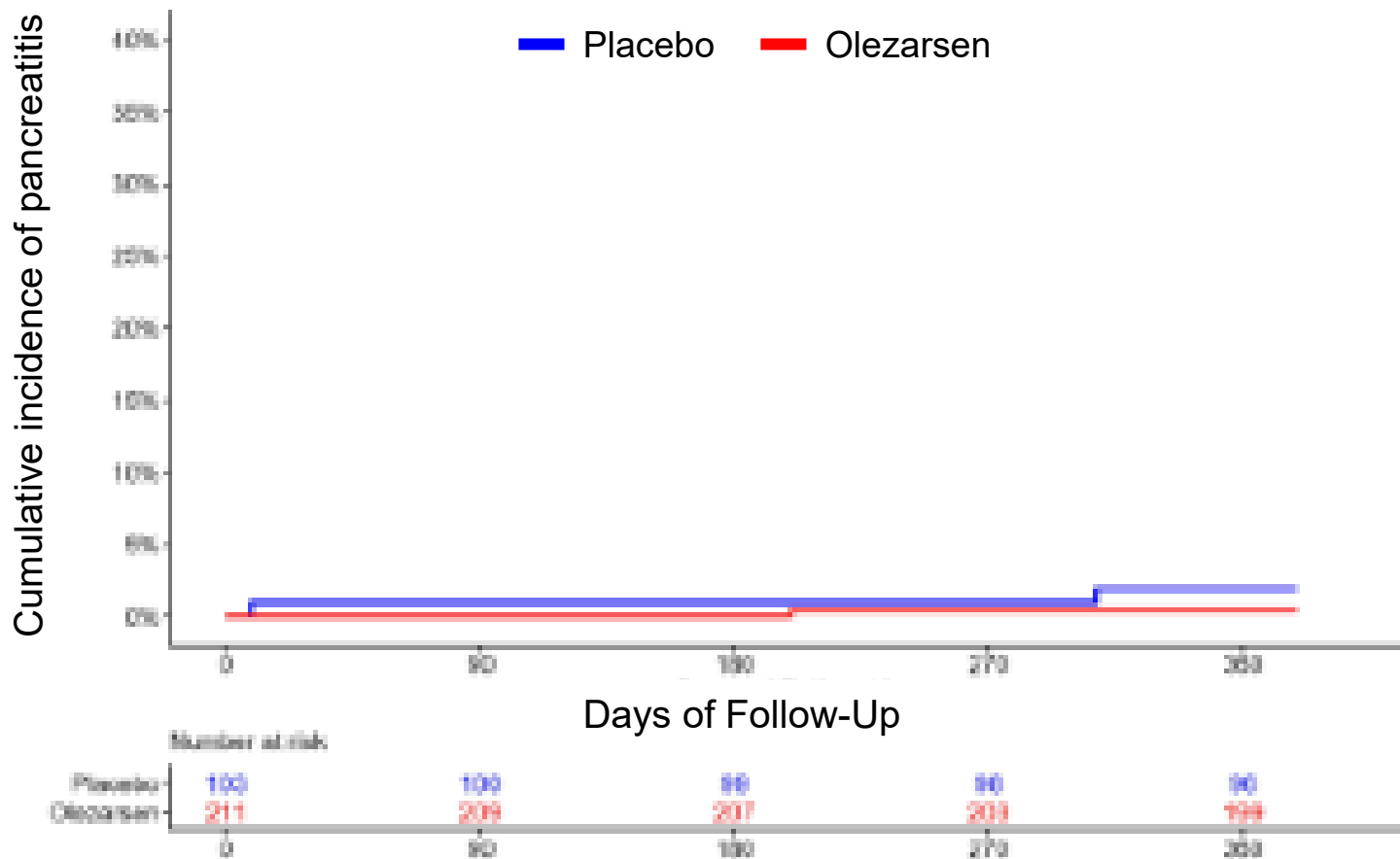
NNT_{1yr} = 20

*Overall : IRR_{total events} 0.15 (0.05 to 0.40)

ACUTE PANCREATITIS BY BASELINE FASTING TRIGLYCERIDE LEVEL AND HISTORY OF PANCREATITIS



Baseline TG \geq 880 mg/dL (10 mmol/L), without prior acute pancreatitis



ARR_{total events} 1.5 events/100 pt-yrs

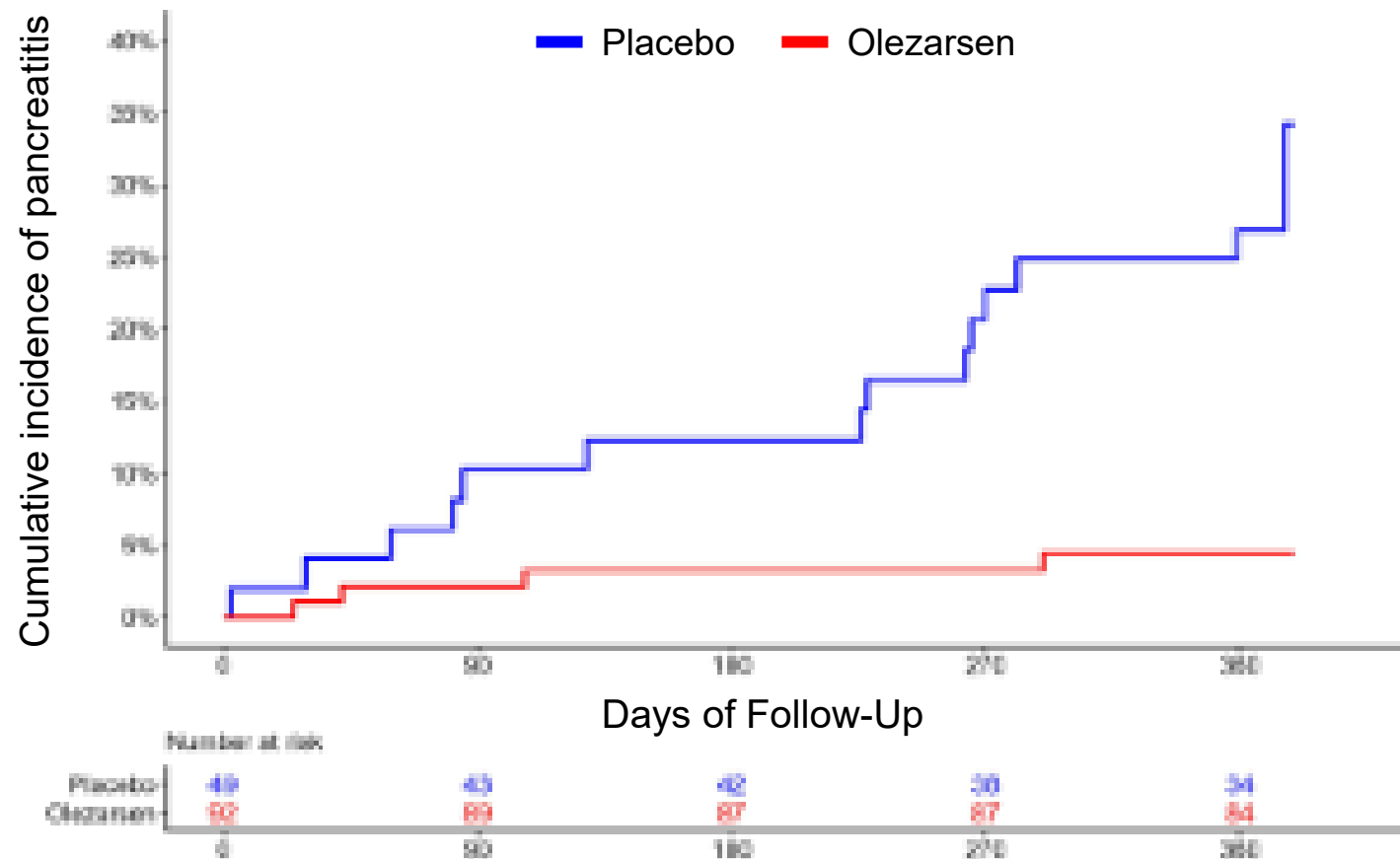
NNT_{1yr} = 67

***Overall : IRR_{total events} 0.15 (0.05 to 0.40)**

ACUTE PANCREATITIS BY BASELINE FASTING TRIGLYCERIDE LEVEL AND HISTORY OF PANCREATITIS



Baseline TG \geq 880 mg/dL (10 mmol/L), with prior acute pancreatitis



ARR_{total events} 32.5 events/100 pt-yrs

NNT_{1yr} = 4

*Overall : IRR_{total events} 0.15 (0.05 to 0.40)

LIMITATIONS

- Follow-up was limited to a year and long-term data are needed
- Participants enrolled had stable background therapy which may not reflect the broader population of patients in clinical practice
- TG subgroup classification was based on averaged baseline TGs, despite known substantial within-patient variability

CONCLUSIONS

In patients with sHTG (triglycerides ≥ 500 mg/dL):

- Olezarsen reduced pancreatitis events by ~85% versus placebo
- Highest pancreatitis risk was observed among those with prior pancreatitis and higher level of TGs
- Relative benefit was consistent across the spectrum of severe hypertriglyceridemia and history of pancreatitis
- These findings support olezarsen as a promising strategy for pancreatitis prevention. The magnitude of absolute risk reduction was related to baseline TG levels and history of pancreatitis

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Funded by Ionis Pharmaceuticals | Moura FA, Zimmerman A, Bergmark BA, Marston NA, et al. | On behalf of the CORE and CORE2 TIMI Study Group | ENDO 2026