



Mass General Brigham



TIMI
Study Group

An Academic Research Organization of
Brigham & Women's Hospital and
an Affiliate of Harvard Medical School

ApoC3 Inhibitor Olezarsen Markedly Reduces Triglycerides & Risk of Pancreatitis in Severe Hypertriglyceridemia Patients with Diabetes Mellitus: Insights from CORE-TIMI 72a and CORE2-TIMI 72b

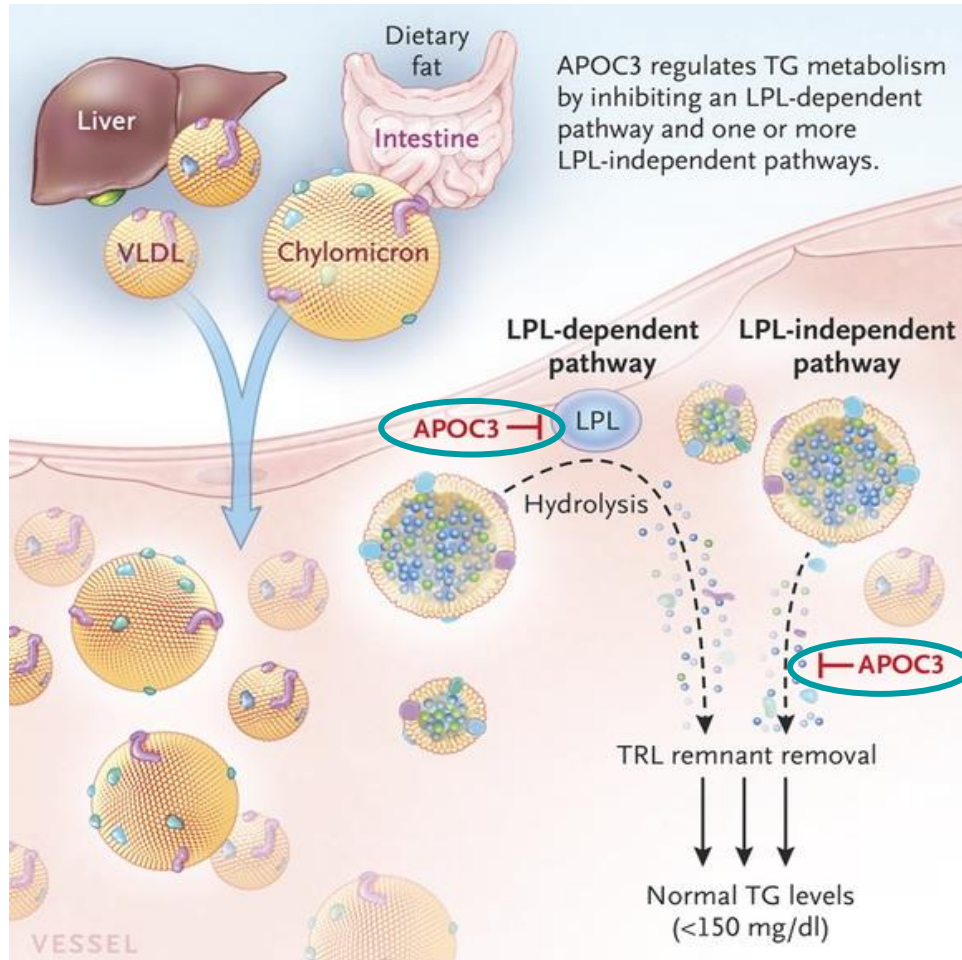
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On Behalf of the CORE-TIMI 72a and CORE2-TIMI 72b Investigators

June 6, 2026

Background

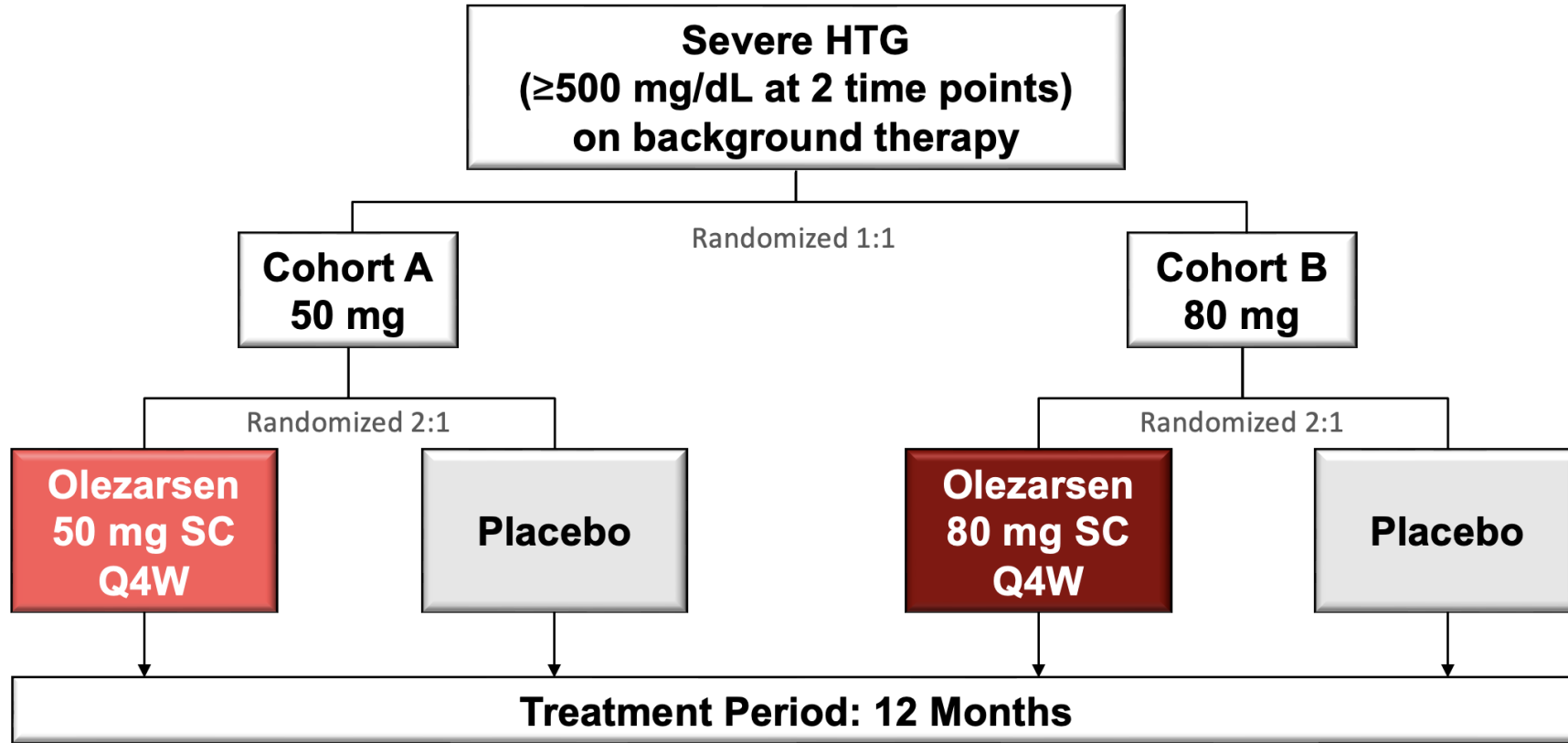
sHTG, APOC3, & olezarsen



- Severe hypertriglyceridemia (sHTG), defined as triglycerides (TGs) ≥ 500 mg/dL (5.65 mmol/L) carries an increased risk of acute pancreatitis
- **Apolipoprotein C-III (APOC3)** inhibits:
 - lipoprotein lipase (LPL), a key enzyme in TG metabolism
 - hepatic uptake of TG-rich lipoproteins (TRLs)
- **Olezarsen** is an antisense oligonucleotide targeting *APOC3* (i.e., APOC3 inhibitor)

CORE-TIMI 72a & CORE2-TIMI 72b

Study design (identical)



Primary endpoint: placebo-adjusted % change in triglycerides at 6 months

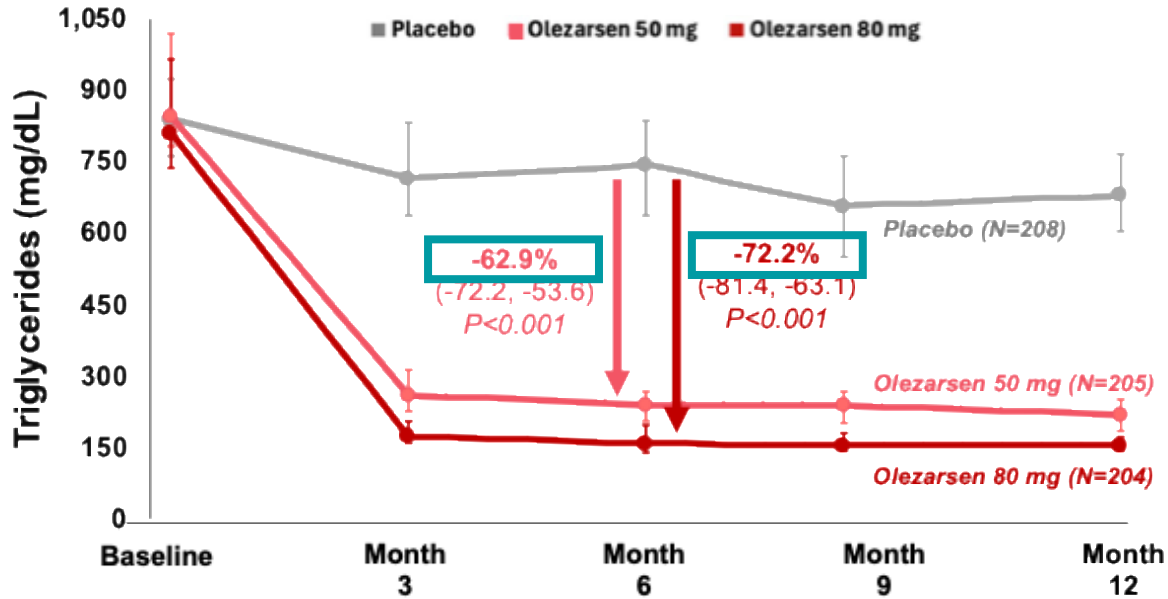
Secondary endpoints include % change in other lipid parameters and acute pancreatitis



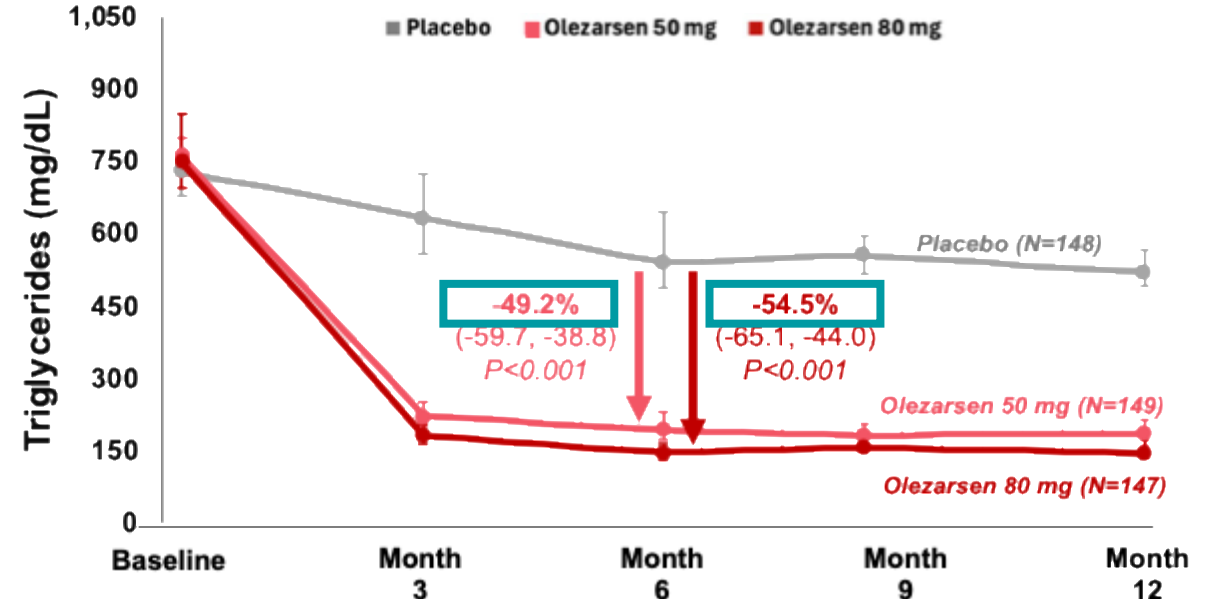
CORE-TIMI 72a & CORE2-TIMI 72b

Primary endpoint: placebo-adjusted % change in TG at 6 months from baseline

CORE-TIMI 72a



CORE2-TIMI 72b

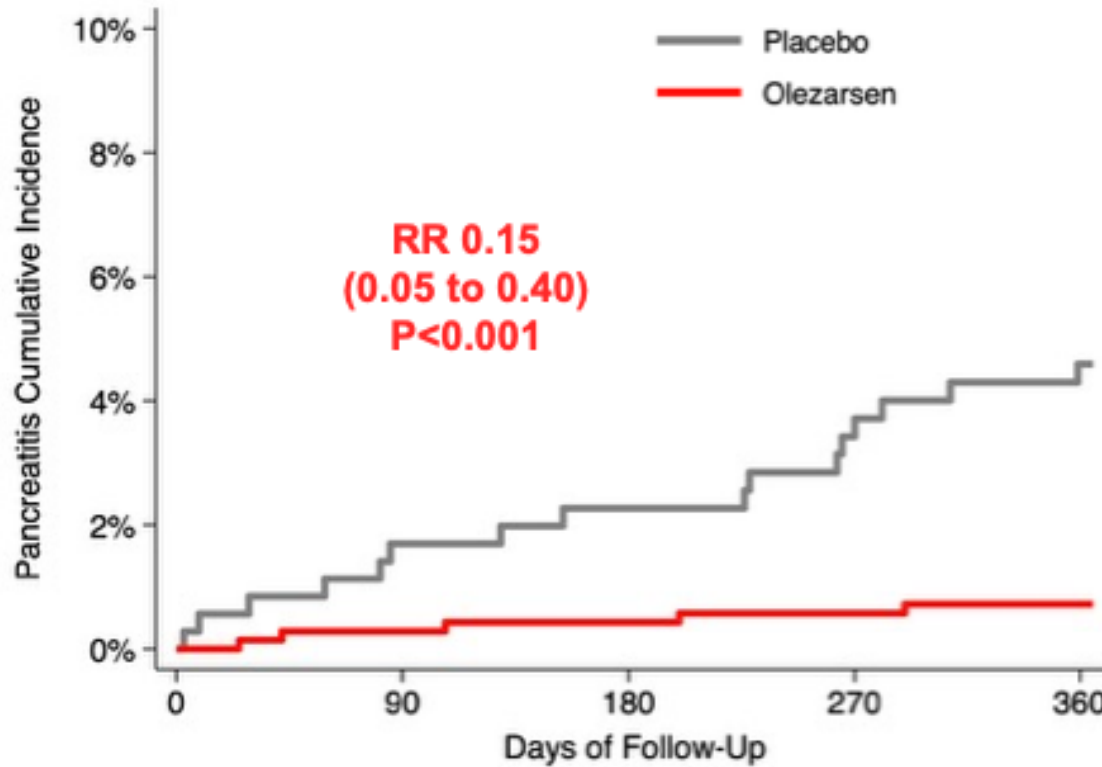


Olezarsen lowered plasma TG levels by **~49-72%**, compared to placebo



CORE-TIMI 72a & CORE2-TIMI 72b

Secondary endpoint: Acute pancreatitis over 12 months (pooled analysis)



ARR in incidence of total events = 5.2%

NNT over 1 year = 20

Abbreviations: ARR, absolute risk reduction; NNT, number needed to treat; RR, rate ratio

Olezarsen reduced the rate of acute pancreatitis by 85%, compared to placebo



Background & Objectives

sHTG & DM

- Insulin resistance, a hallmark of type 2 diabetes mellitus (DM), is a common non-genetic driver of TG dysregulation
- Both **sHTG & DM** are independently associated with high risk for **acute pancreatitis (AP)**, a potentially life-threatening complication
- Therefore, patients with sHTG & DM represent a particularly high-risk subgroup
 - Conventional TG-lowering therapies may not be sufficient to address the risk

**We aimed to evaluate the efficacy & safety of olezarsen
in adults with sHTG & DM**



Methods

- Modified intention-to-treat population (≥ 1 dose study medication)
- Baseline DM was defined as at least one of:
 - Investigator-reported history of DM (dedicated eCRF field)
 - HbA1c $\geq 6.5\%$
 - Use of glucose-lowering medications in the absence of a non-DM indication
- Changes in fasting lipid and glycemic parameters at 6 months were assessed using an analysis of covariance (ANCOVA) model
- Centrally adjudicated AP events over 12 months were compared between pooled olesarsen treatment and placebo groups using a negative binomial regression model



Baseline Characteristics

DM vs No DM

Characteristic	DM (N=689)	No DM (N=372)
Age (years)	56	50
Female	27.6%	16.1%
Body mass index (kg/m ²)	31.6	30.3
History of ASCVD	30.3%	16.9%
History of pancreatitis	21.5%	14.0%
Lipid-lowering therapy		
Statin	80.0%	62.6%
On ≥2 lipid-lowering therapy	67.6%	60.8%
Fasting laboratory results		
Triglycerides (mg/dL)	779.0	823.5
ApoC-III (mg/dL)	35.2	32.9
eGFR (ml/min/1.73 m ²)	93.0	99.0

Characteristic	DM (N=689)
Glucose-lowering medications	
Insulin	36.0%
Basal insulin	32.7%
Rapid-acting insulin	22.1%
GLP-1 receptor agonist	24.1%
DPP-4 inhibitor	12.0%
Sulfonylureas	20.8%
Meglitinides	1.9%
Metformin	80.0%
SGLT-2 inhibitor	47.3%
Thiazolidinediones	3.6%

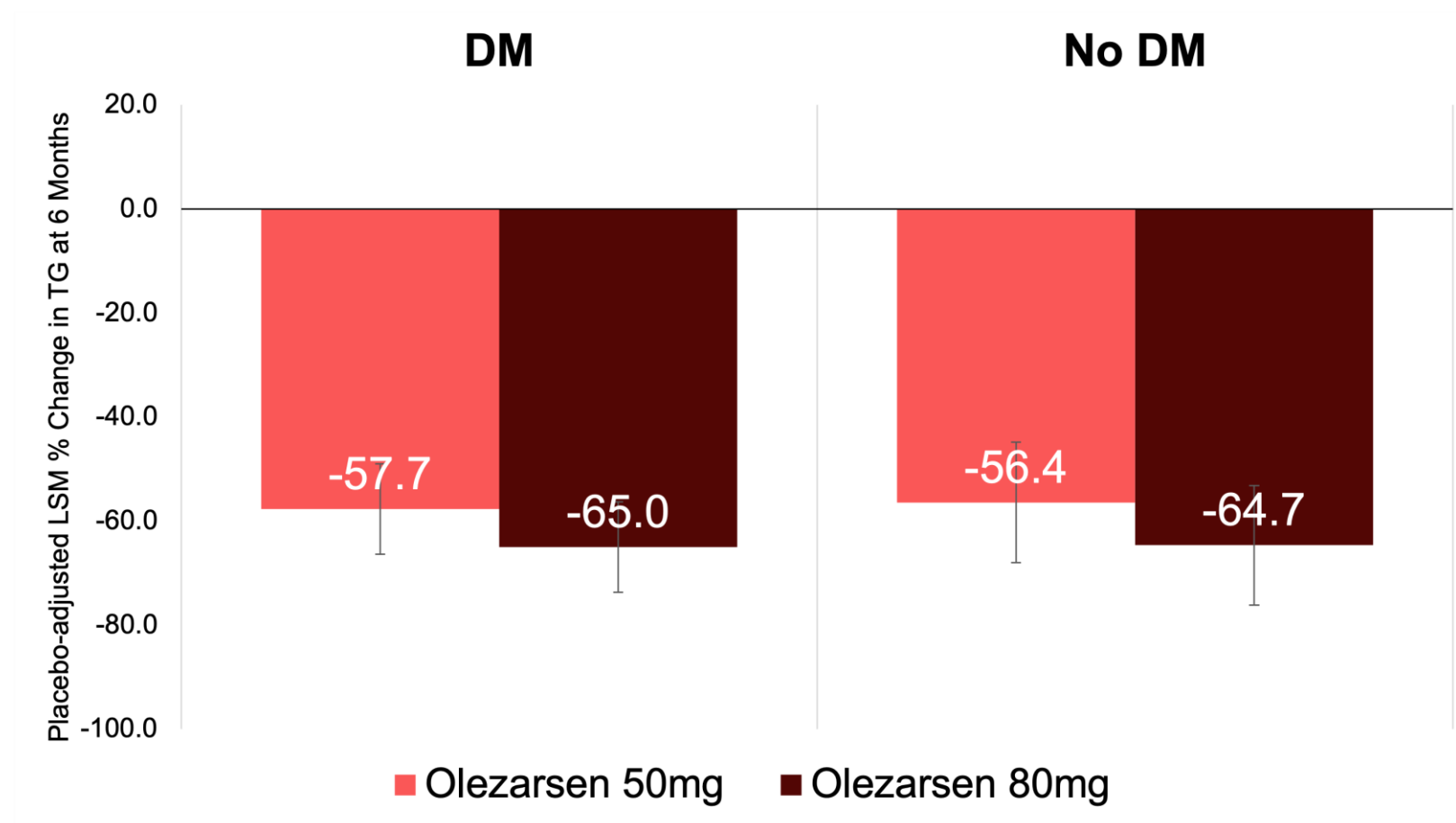
All comparisons between subgroup had P<0.05 except baseline TG level



Continuous variables are presented as the median, and categorical variables are expressed as proportions (%)

TG-Lowering Efficacy of Olezarsen by Baseline DM

At 6 months



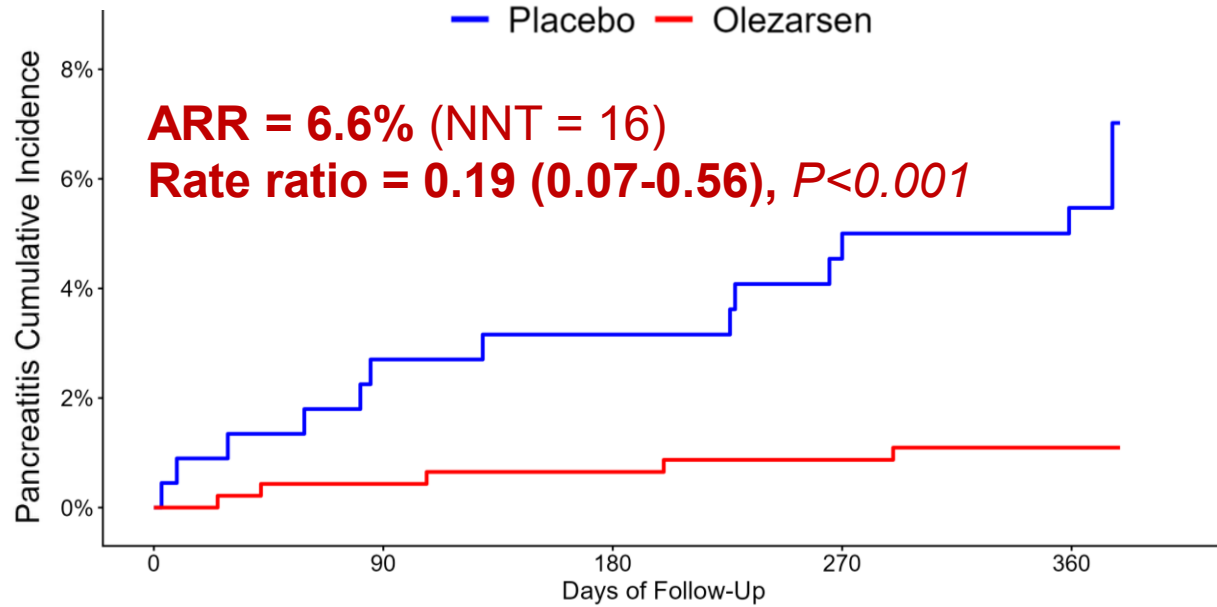
Error bars indicate 95% confidence intervals; $P < 0.0001$ for all comparisons vs. placebo; P -interaction=0.93



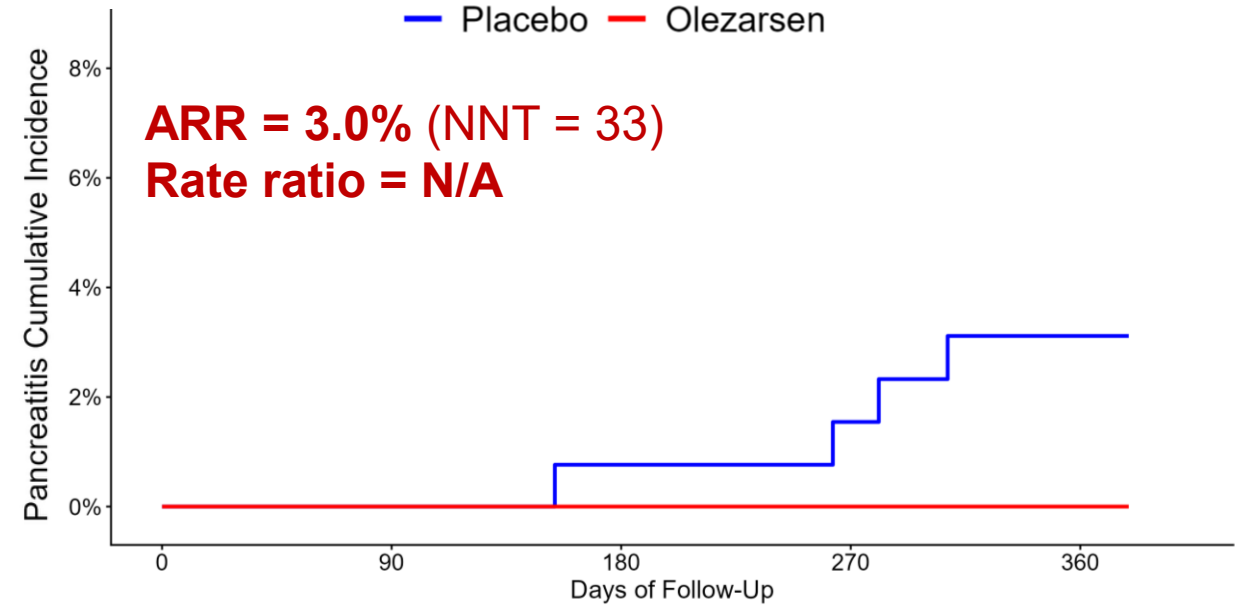
Efficacy of Olezarsen in Acute Pancreatitis Prevention

Total event analysis over 12 months, pooled olezarsen

DM



No DM

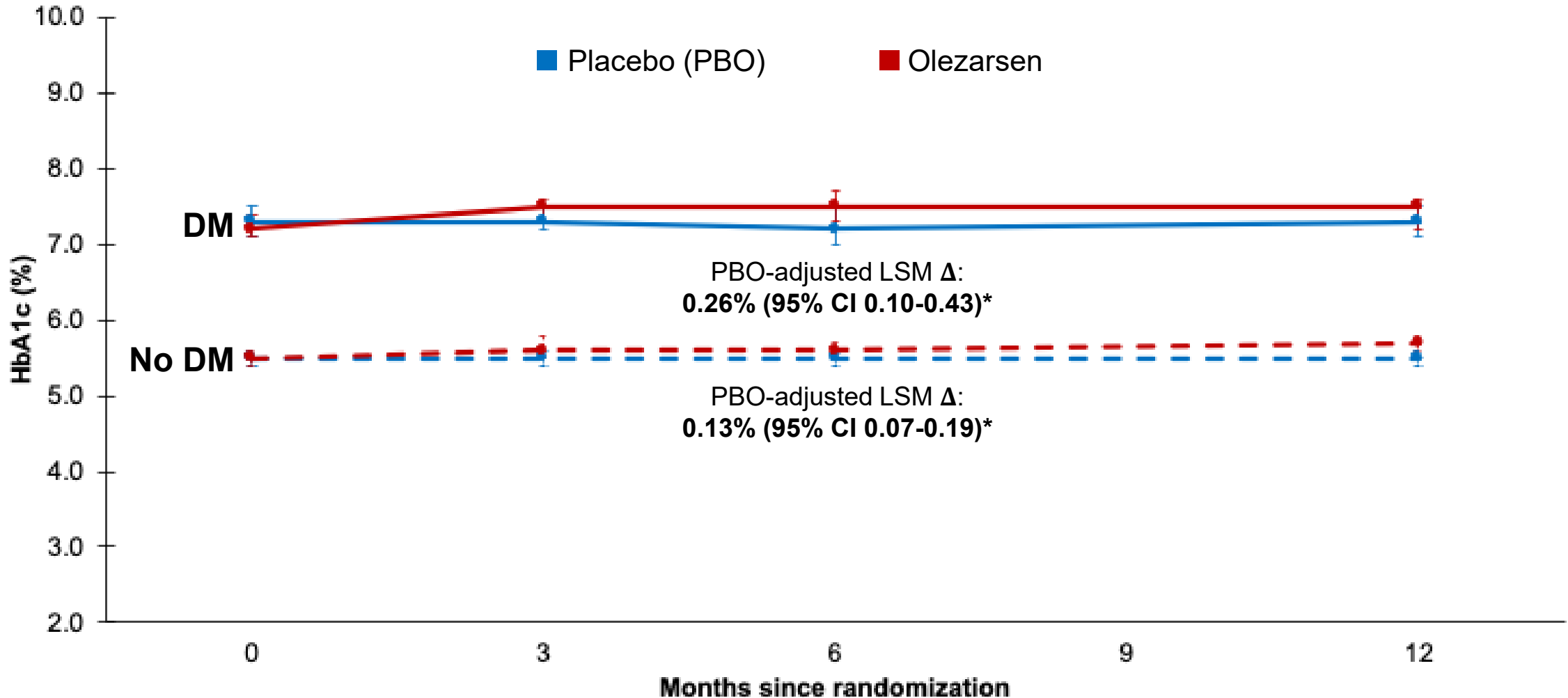


Abbreviations: ARR, absolute rate reduction; CI, confidence interval; NNT, number needed to treat
P for log-rank < 0.01 for both graphs



Glycemic Impact of Olezarsen by DM Status

HbA1c, pooled olezarsen

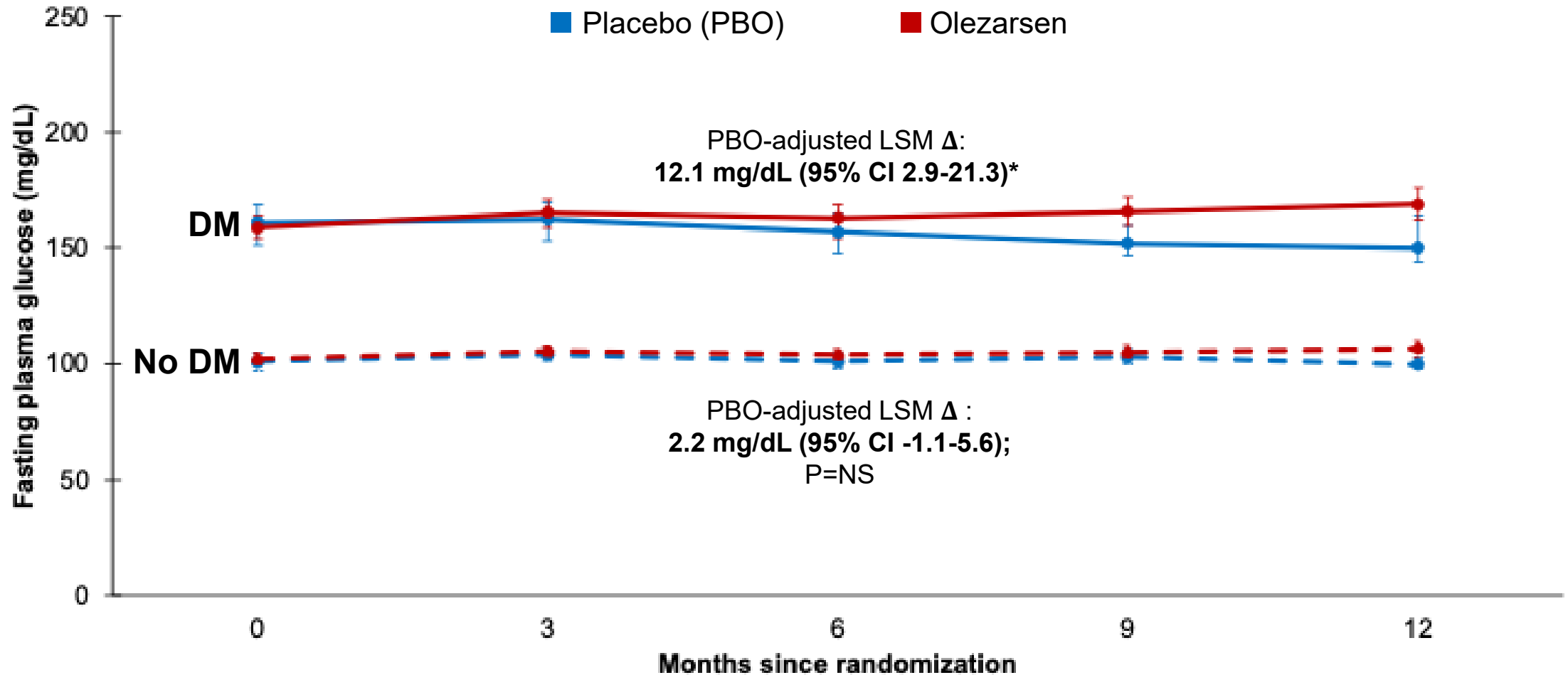


Estimates at each time point are presented as medians, with error bars indicating 95% confidence intervals; *P<0.01
Abbreviation: LSM, least-squares mean; PEP, primary endpoint; PBO, placebo



Glycemic Impact of Olezarsen by DM Status

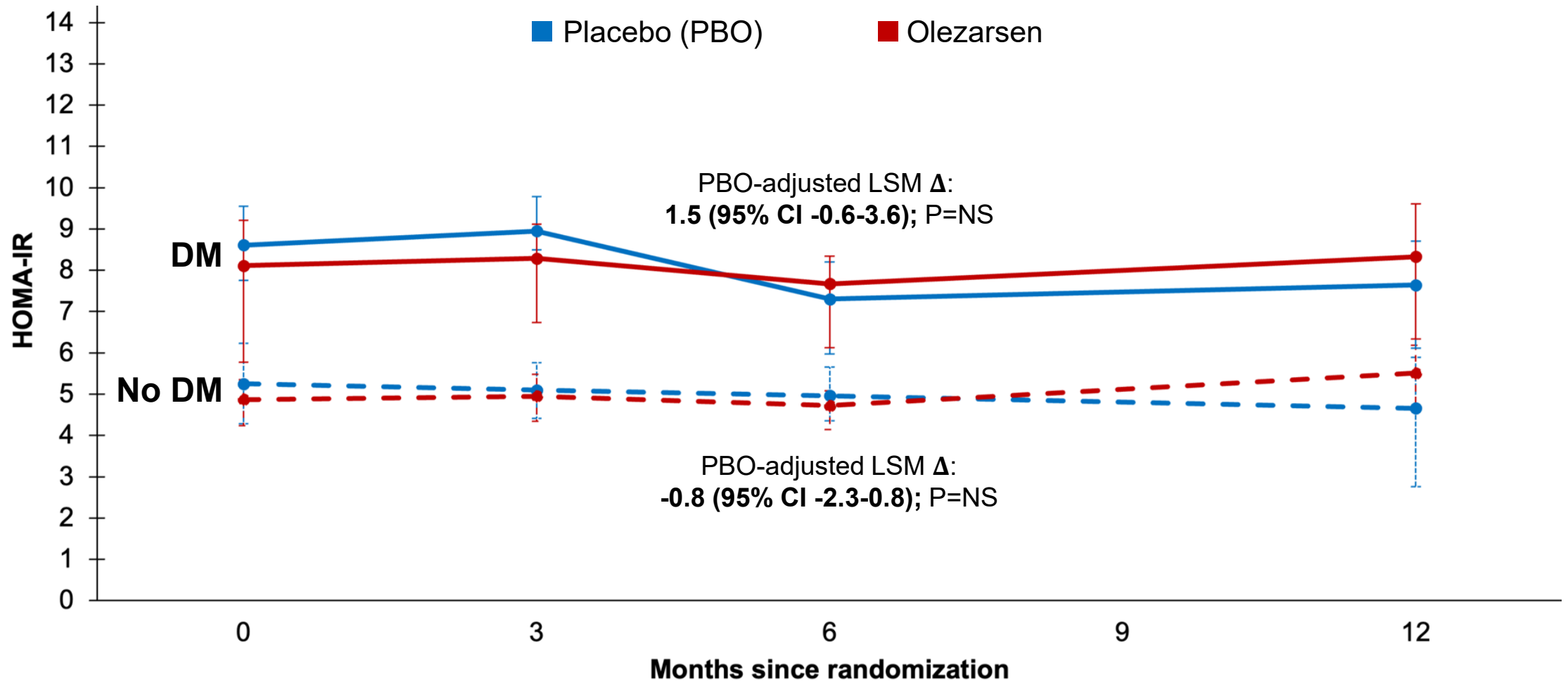
Fasting plasma glucose, pooled olezarsen



Estimates at each time point are presented as medians, with error bars indicating 95% confidence intervals; *P<0.01
Abbreviation: LSM, least-squares mean; PEP, primary endpoint; PBO, placebo

Glycemic Impact of Olezarsen by DM Status

HOMA-IR, pooled olezarsen



Estimates at each time point are presented as medians, with error bars indicating 95% confidence intervals
Abbreviation: LSM, least-squares mean; PEP, primary endpoint; PBO, placebo



Limitations

- Changes in diabetes medications were not assessed in this study
 - Assessment of glycemic profile may not fully capture the extent of dysglycemia
- Not designed to elucidate the mechanistic pathways underlying the glycemic change, but appears to be a class effect
- Assessment of glycemic impact of olesarsen beyond 12 months requires further studies



Summary & Conclusions

- In this high-risk population with **severe HTG & DM**, **olezarsen**;
 - Reduced TG levels by **58–65%** on top of currently available lipid lowering therapies
 - Reduced acute pancreatitis events by **81%**, with an absolute rate reduction of **6.6%**
 - Yielded a number needed to treat of **16** to prevent one event over 12 months
 - Minimally increased HbA1c (by **0.26%**) with **no changes** in HOMA-IR
 - The degree of glycemic excursion observed is unlikely to be clinically meaningful for most sHTG patients
- CORE-OLE (NCT05681351), an open-label extension study of CORE-TIMI 72a & CORE2-TIMI 72b, will further elucidate the long-term effect of olezarsen

