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Balance
a familial chylomicronemia syndrome study

A Randomized, Placebo-Controlled Phase 3 Study of Olezarsen in Patients With Familial Chylomicronemia Syndrome

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Olezarsen is an investigational drug in late-stage development

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Familial Chylomicronemia Syndrome (FCS)

- Rare genetic disease causing severe hypertriglyceridemia[1]
  - Prevalence: 1 to 13 cases per 1,000,000 people in the US[2-4]
- Significant burden of acute (potentially life-threatening) pancreatitis

360-fold increased risk

of **acute pancreatitis** vs normal TG levels[5]

85% report at least 1 episode

of **acute pancreatitis**; 40% experience ≥1 episode[6]

2 times higher mortality

with severe HTG vs normal TG levels[7]

- Minimal to no response to conventional TG-lowering therapies[1]
- **Hypothesis:** olezarsen will decrease TG levels in patients with FCS

Not an actual patient.

Abbreviations: FCS, familial chylomicronemia syndrome; HTG, hypertriglyceridemia; TG, triglyceride.

1. Stroes E, et al. *Atheroscler Suppl*. 2017:23:1-7. 2. Pallazola VA, et al. *Eur J Prev Cardiol*. 2020;27(19):2276-8. 3. Warden BA, et al. *J Clin Lipidol*. 2020;14(2):201-6. 4. Tripathi M, et al. *Endocr Pract*. 2021;27(1):71-6. 5. Gaudet D, et al. *Atheroscler Suppl*. 2010;11(1):55-60. 6. Davidson M, et al. *J Clin Lipidol.* 2018;12L898-907. 7. Nawaz H, et al. *Am J Gastroenterol*. 2015;110(10):1497-503.

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Mechanism of Action of Olezarsen

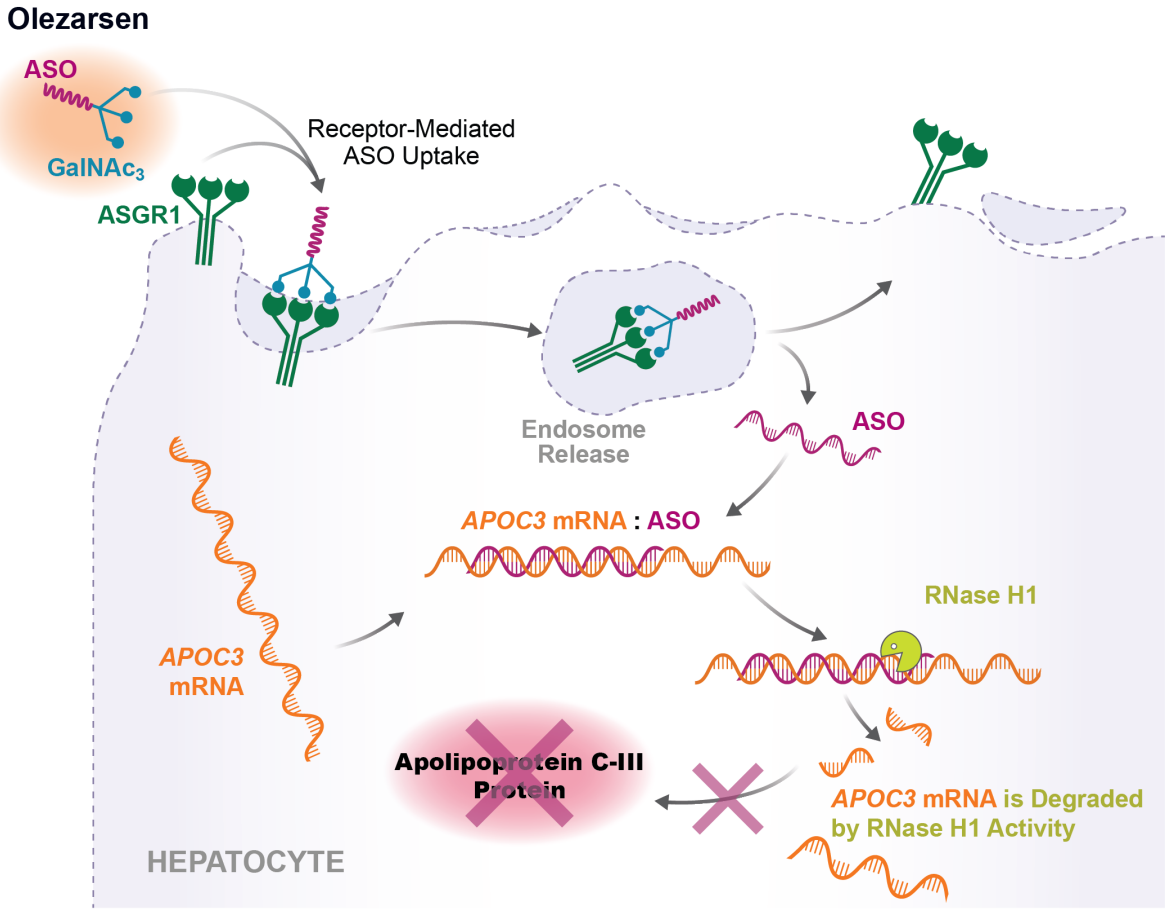
Olezarsen[1,2]

- $GalNAc_3$-conjugated antisense oligonucleotide designed to target *APOC3* mRNA in liver

ApoC-III[3]

- Expressed by hepatocytes
- Inhibits:
  - Lipoprotein and hepatic lipase activity
  - Hepatic clearance of TG-rich lipoproteins

- Lowering of ApoC-III decreases circulating TGs[1,2]



Adapted from Crooke ST, et al. *Nucleic Acid Therapeutics*, 2019;29:16-32.

Abbreviations: *APOC3*, apolipoprotein C-3; ApoC-III, apolipoprotein C-III; ASGR, asialoglycoprotein receptor; ASO, antisense oligonucleotide; $GalNAc_3$, triantennary *N*-acetylgalactosamine; mRNA, messenger RNA; RNase H, ribonuclease H; TG, triglyceride.

1. Alexander VJ, et al. *Eur Heart J*. 2019;40:2785-96. 2. Tardif JC, et al. *Eur Heart J*. 2022;43:1401-12. 3. Gordts PL, et al. *J Clin Invest*. 2016;126(8):2855-66.

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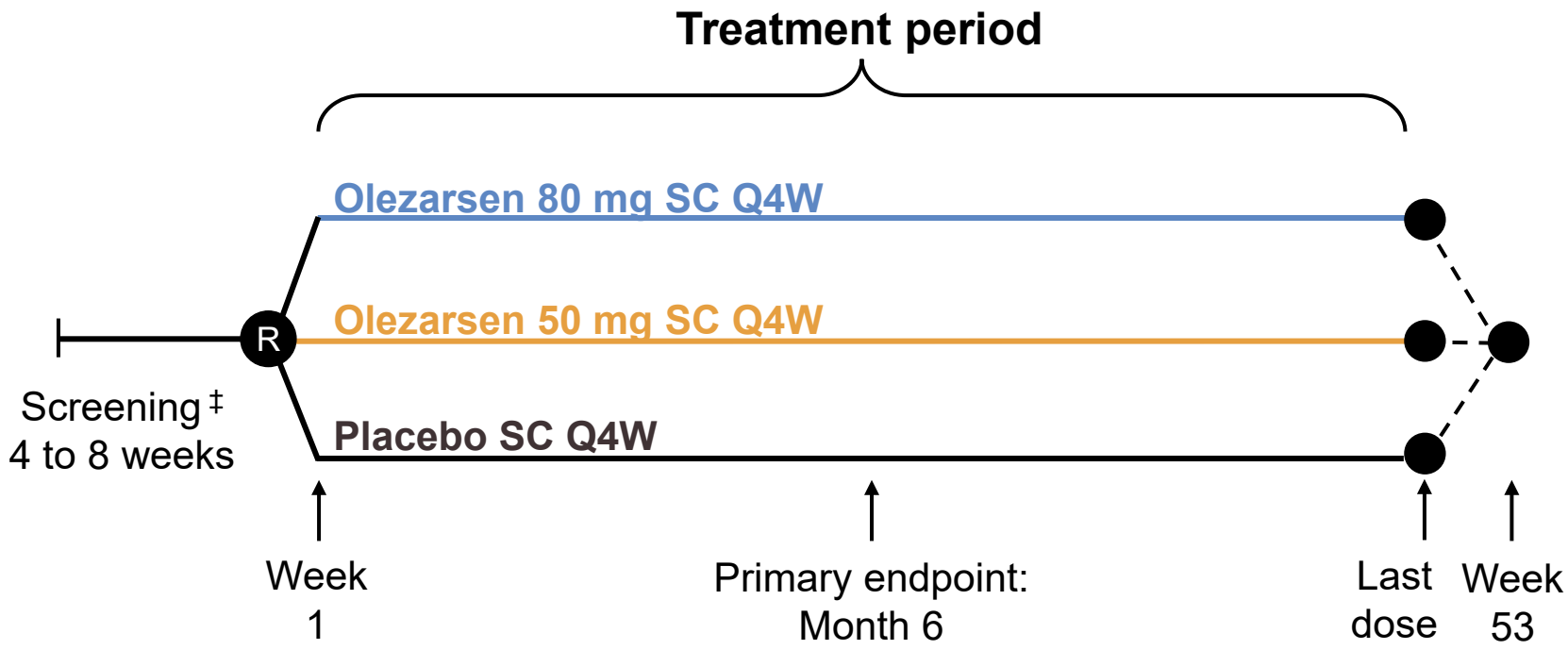
Study Design

Population

- Genetically identified FCS*
- Fasting TG ≥880 mg/dL (10 mmol/L)
- History of pancreatitis within 10 years prior to screening in ≥65% of patients†



*Including pathogenic variants in *LPL*, *APOA5*, *GPIHBP1*, *LMF1*, and *APOC2*.
†Patients with no history of pancreatitis were capped at 35% of enrollment.
‡The screening period includes a 2-week diet stabilization/run-in period for patients not on a stable diet and a 2-week qualification period.
Abbreviations: *APOA5*, apolipoprotein A-5; *APOC2*, apolipoprotein C-2; FCS, familial chylomicronemia syndrome; *GPIHBP1*, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1; *LMF1*, lipase maturation factor 1; *LPL*, lipoprotein lipase; Q4W, every 4 weeks; R, randomization; SC, subcutaneous; TG, triglyceride.

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Statistical Analysis

- Endpoints were tested in a prespecified hierarchical order
  - If any comparison was not statistically significant, analysis of all subsequent endpoints was considered exploratory
- Primary endpoint: % change in fasting TG from baseline to month 6
  - First tested for olezarsen 80 mg vs pooled placebo
  - Then for olezarsen 50 mg vs pooled placebo
- Secondary endpoints

Abbreviations: TG, triglyceride.

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Key Secondary Endpoints in Hierarchical Order

Rank	Parameter	Measure	Time point	Olezarsen dose
1	**TG**	**% change from baseline**	**12 months**	**80 mg**
2	**ApoC-III**	**% change from baseline**	**6 months**	**80 mg**
3	**ApoC-III**	**% change from baseline**	**12 months**	**80 mg**
4	TG	Proportion with ≥40% reduction from baseline	6 months	80 mg
5	Apo B-48	% change from baseline	6 months	80 mg
6	Non-HDL-C	% change from baseline	6 months	80 mg
7	**TG**	**% change from baseline**	**12 months**	**50 mg**
8	**ApoC-III**	**% change from baseline**	**6 months**	**50 mg**
9	**ApoC-III**	**% change from baseline**	**12 months**	**50 mg**
10	TG	Proportion with ≥40% reduction from baseline	6 months	50 mg
11	Apo B-48	% change from baseline	6 months	50 mg
12	Non-HDL-C	% change from baseline	6 months	50 mg
13	**Acute pancreatitis (adjudicated)**	**Event rate, patients with prior history within past 10 years**	**Week 1–53**	**Pooled**
14	**Acute pancreatitis (adjudicated)**	**Event rate, full analysis set**	**Week 1–53**	**Pooled**
25	**Acute pancreatitis (adjudicated)**	**Event rate, patients with ≥2 adjudicated prior events within past 5 years**	**Week 1–53**	**Pooled**

Bold text indicates secondary endpoints reported in the presentation.
Abbreviations: Apo B-48, apolipoprotein B-48; ApoC-III, apolipoprotein C-III; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride.

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Patient Demographics and Baseline Characteristics

	Placebo (n = 23)	Olezarsen 50 mg (n = 21)	Olezarsen 80 mg (n = 22)
Age, years, mean (SD)	44.0 (14.7)	43.2 (12.1)	47.7 (13.3)
Sex, n (%)			
Female	12 (52.2)	15 (71.4)	11 (50.0)
Male	11 (47.8)	6 (28.6)	11 (50.0)
BMI, kg/m^2, mean (SD)	24.2 (4.1)	22.4 (3.5)	25.1 (6.0)
History of acute pancreatitis in prior 10 years, n (%)	15 (65.2)	15 (71.4)	17 (77.3)
Triglycerides, mg/dL, mean (SD)	2596 (1256)	2684 (1235)	2613 (1499)
Apolipoprotein C-III, mg/dL, mean (SD)	27.7 (11.7)	27.7 (10.5)	27.5 (11.6)
Concomitant medications, n (%)			
Fibrate	11 (47.8)	8 (38.1)	11 (50.0)
Omega-3 fatty acid	7 (30.4)	6 (28.6)	12 (54.5)
Statin	7 (30.4)	4 (19.0)	5 (22.7)
Other lipid-lowering agent	3 (13.0)	0	3 (13.6)

Abbreviations: BMI, body mass index; SD, standard deviation.

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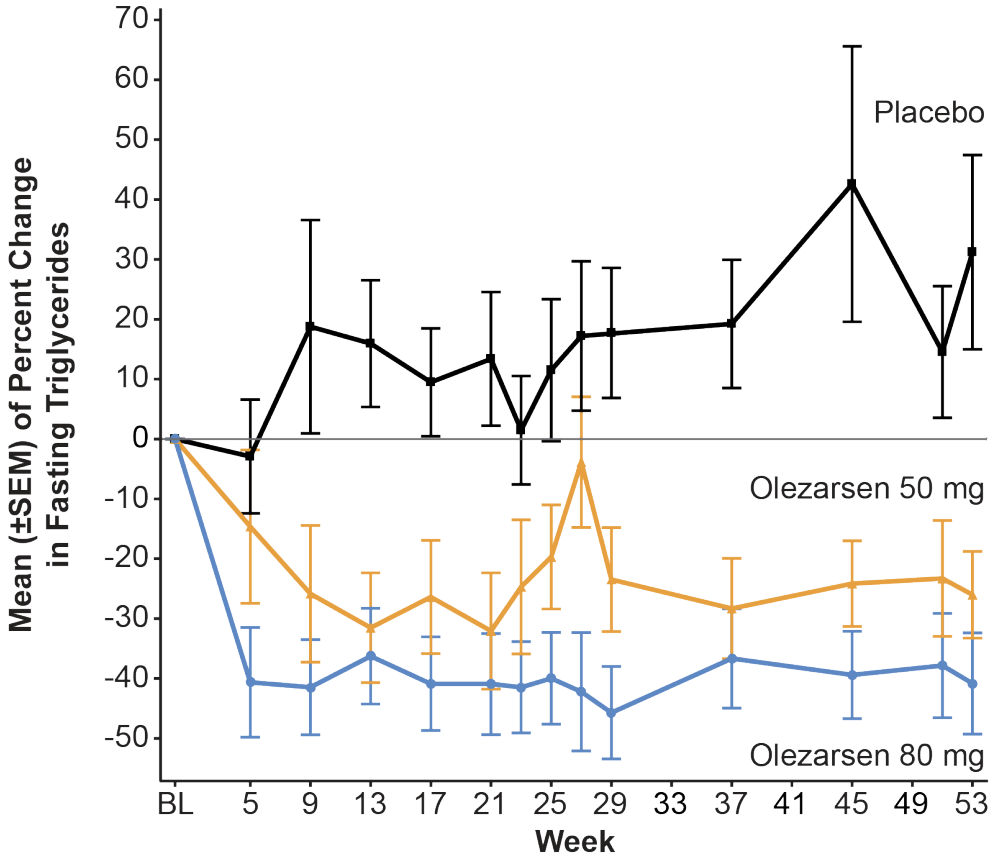
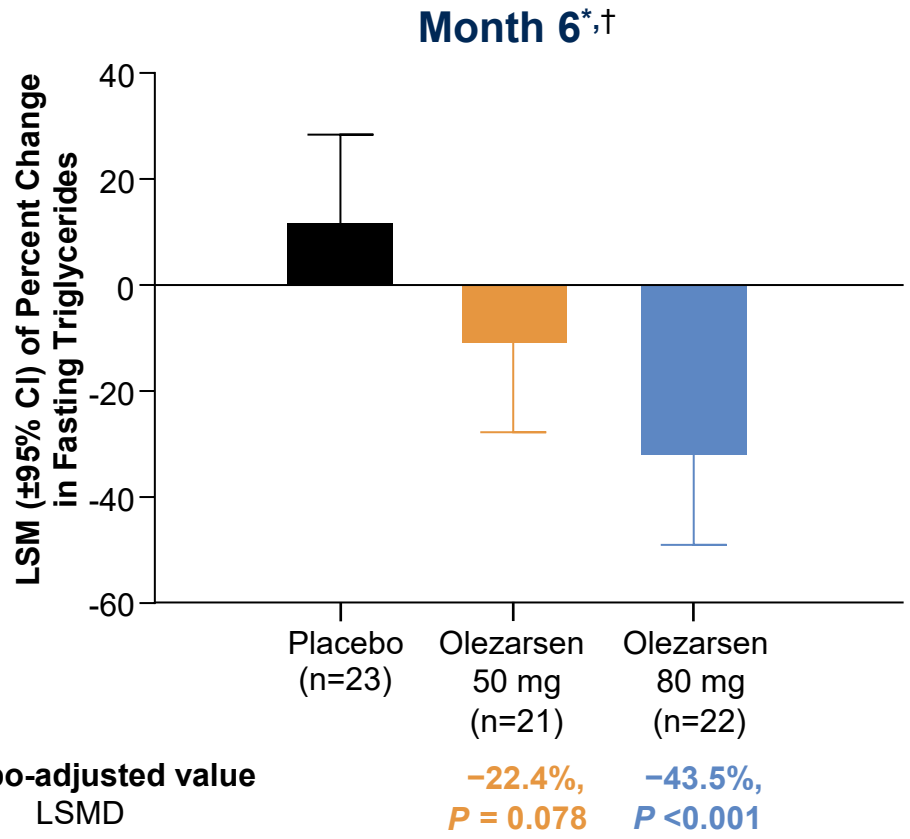
Primary Endpoint: Fasting TG Reduced From Baseline vs Placebo at 6 Months With Olezarsen





*Olezarsen 80 mg monthly (P <0.001), 50 mg monthly (P = 0.078). †Primary endpoint was calculated from an average of weeks 23, 25, and 27.
Abbreviations: BL, baseline; CI, confidence interval; LSM, least squares mean; LSMD, LSM difference; SEM, standard error of the mean; TG, triglyceride.

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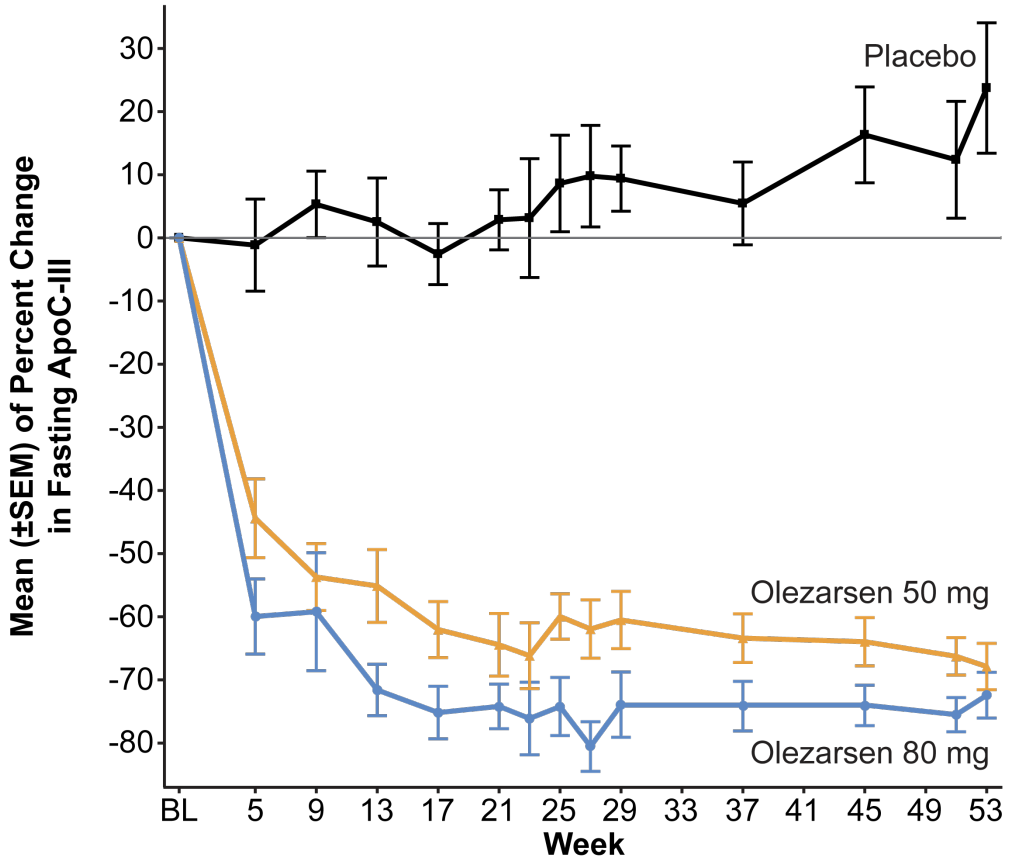
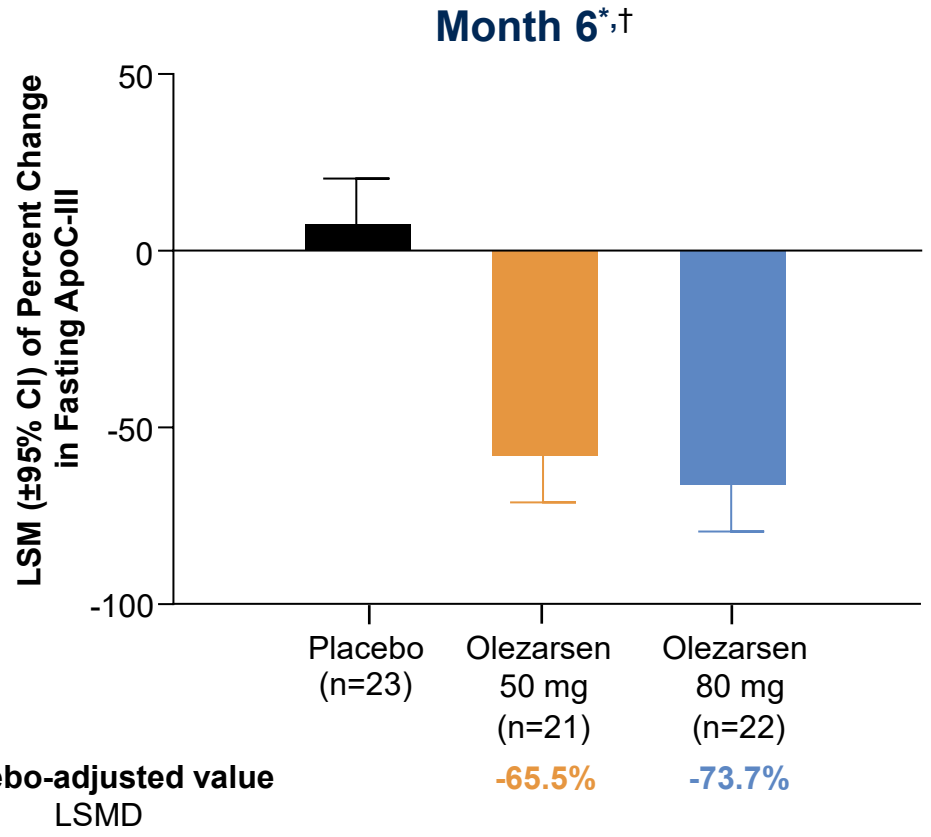
Secondary Endpoint: Fasting ApoC-III Reduced From Baseline vs Placebo at 6 Months With Olezarsen





*Olezarsen 80 mg monthly (LSMD 95% CI: −94.6%, −52.8%); 50 mg monthly (LSMD 95% CI: −82.6%, −48.3%). †Endpoint calculated from an average of weeks 23, 25, and 27. Abbreviations: BL, baseline; CI, confidence interval; ApoC-III, apolipoprotein C-III; LSM, least squares mean; LSMD, LSM difference; SEM, standard error of the mean.

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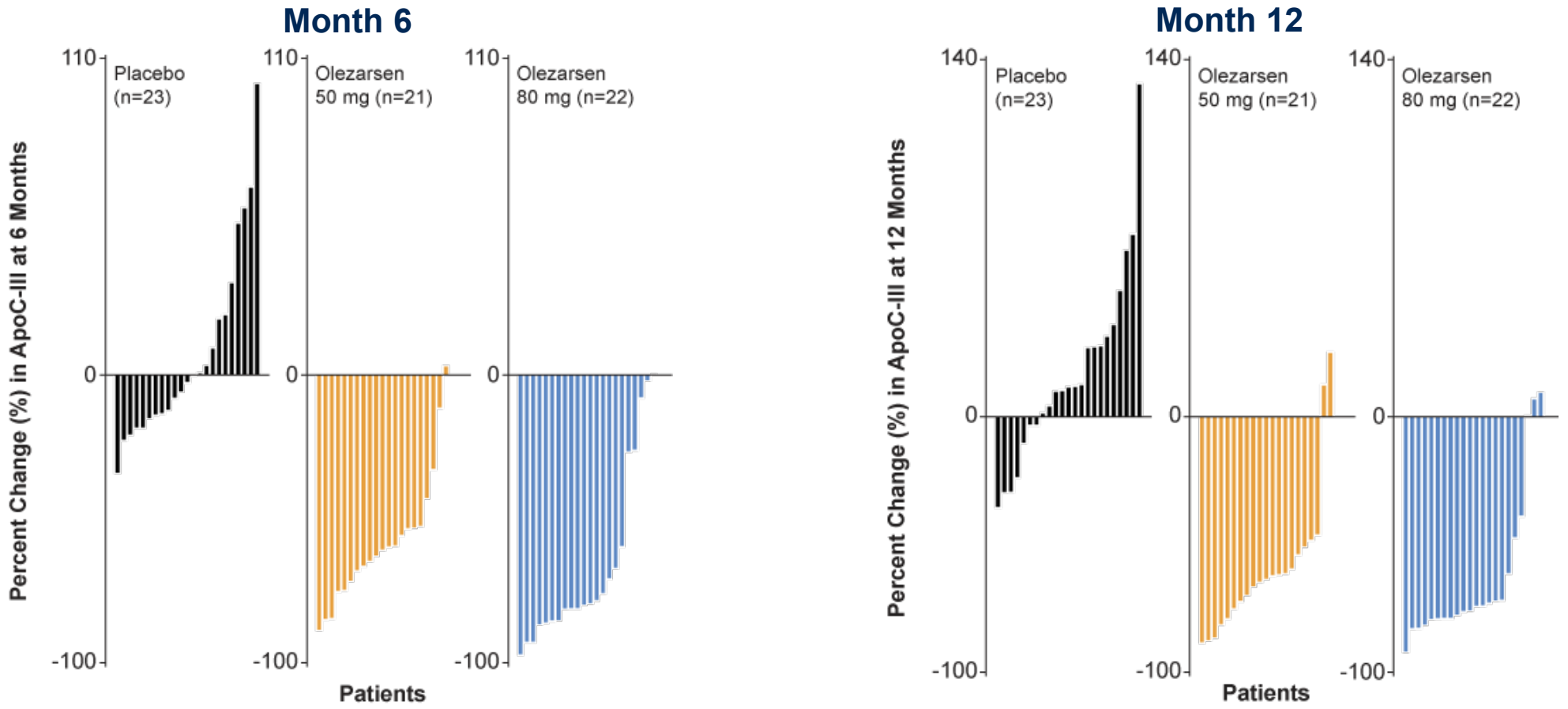
Sustained ApoC-III Reductions Through 12 Months in the Majority of Olezarsen-Treated Patients



Full analysis set.
Abbreviations: ApoC-III, apolipoprotein C-III.

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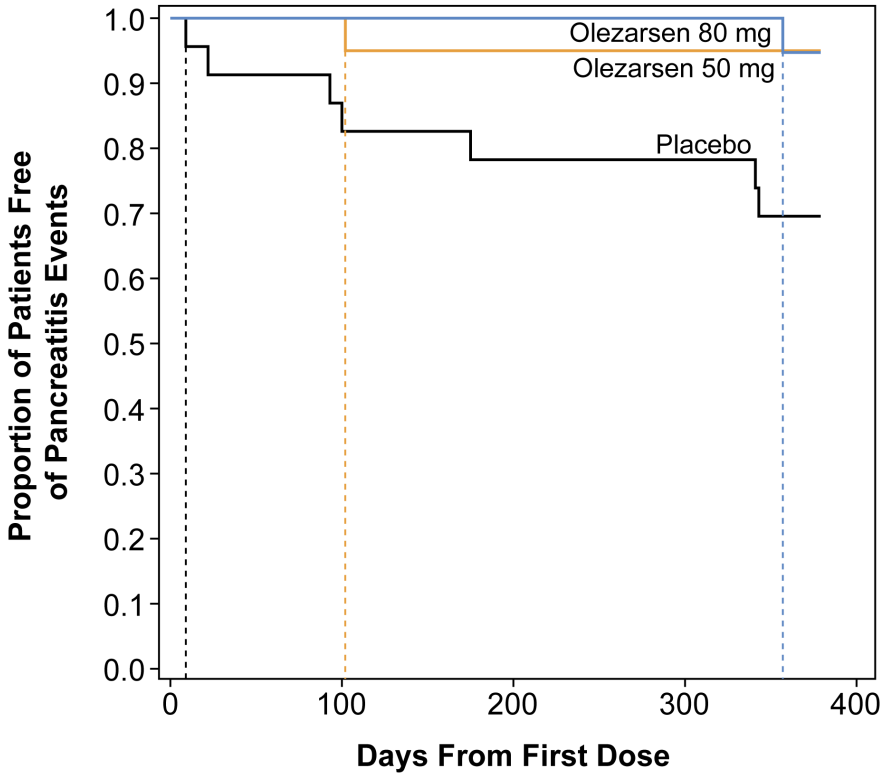
Reduced Incidence of Pancreatitis Events in Olezarsen-Treated Patients

Time to first pancreatitis event per patient



Patients with pancreatitis events

	Placebo (n=23)	Olezarsen 50 mg (n=21)	Olezarsen 80 mg (n=22)
Patients with events, n	7	1	1
Pancreatitis events, n	11	1	1
First pancreatitis event, study day	9	102	357

Selected prespecified secondary endpoints

Adjudicated Acute Pancreatitis Endpoint (Week 1-53)	Event Rate per 100 PY (95% CI)		Mean Rate Ratio* (95% CI)
	Placebo	Pooled Olezarsen	
All patients	36.3 (14.7, 89.7)	4.37 (0.942, 20.3)	0.12 (0.022, 0.656)
Patients with history within last 10 years	66.2 (30.5, 144)	6.73 (1.61, 28.1)	0.10 (0.020, 0.506)
Patients with ≥2 events within last 5 years	119 (61.2, 230)	16.6 (4.05, 67.9)	0.14 (0.029, 0.669)

*Pooled olezarsen vs placebo; exposure-adjusted event rate in the treatment group divided by the exposure-adjusted event rate in the placebo group; a ratio of 1 would indicate no difference.
Abbreviations: CI, confidence interval; PY, patient-year.

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Safety Profile

Adverse Events, n (%)	Placebo (n = 23)	Olezarsen 50 mg (n = 21)	Olezarsen 80 mg (n = 22)
Any	22 (95.7)	18 (85.7)	19 (86.4)
Related to study drug	5 (21.7)	6 (28.6)	7 (31.8)
Mild	3 (13.0)	6 (28.6)	3 (13.6)
Moderate	0	0	4 (18.2)
Severe	2 (8.7)	0	0
Leading to treatment discontinuation	0	1 (4.8)†	2 (9.1)*
Leading to death	0	1 (4.8)†	0
Any serious	9 (39.1)	4 (19.0)	3 (13.6)
Serious related to study drug	0	0	0
Laboratory anomalies, n (%)			
ALT or AST ≥3 × ULN	3 (13.0)	0	1 (4.5)
UPCR ≥1000 mg/g	2 (8.7)	0	0
eGFR decrease ≥30%	4 (17.4)	2 (9.5)	2 (9.1)
eGFR decrease ≥50%	1 (4.3)	0	0
Platelet count <75,000/mm^3	2 (8.7)‡	1 (4.8)	2 (9.1)
Platelet count <50,000/mm^3	1 (4.3)‡	0	0

- A greater proportion of placebo-treated patients experienced SAEs
- No drug-related SAEs
- No clinically meaningful changes in platelet count or in measures of hepatic and renal function

*Adverse events in the 80 mg group leading to treatment discontinuation were diarrhea, vomiting, flushing, and chest discomfort in 1 patient and chills, myalgia, and trismus in the other patient.
†Adverse event leading to death in the 50 mg group was considered unrelated to study treatment by the investigator.
‡One sample was analyzed 25 days after collection and included a note of "gross hemolysis."

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; UPCR, urine protein to creatinine ratio; ULN, upper limit of normal; SAE, serious adverse event.

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Conclusions

- Olezarsen, a $GalNAc_3$-conjugated ASO targeting ApoC-III mRNA, at 80 mg every 4 weeks significantly reduced TG in patients with FCS at 6 months
  - Effects on TG and ApoC-III were sustained through 12 months
- Olezarsen demonstrated a clear signal for reduced pancreatitis events in patients with FCS at 12 months (mean rate ratios 0.10–0.14 vs placebo)
- The safety and tolerability profile of olezarsen was favorable versus placebo
- Olezarsen may represent a novel therapy to reduce plasma TG levels and acute pancreatitis in patients with FCS

Abbreviations: ApoC-III, apolipoprotein C-III; ASO, antisense oligonucleotide; FCS, familial chylomicronemia syndrome; $GalNAc_3$, triantennary *N*-acetylgalactosamine;TG, triglyceride.

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ORIGINAL ARTICLE

Olezarsen, Acute Pancreatitis, and Familial Chylomicronemia Syndrome

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