Olezarsen and plozasiran in the treatment of familial chylomicronemia syndrome (FCS): Results from a matching-adjusted indirect comparison (MAIC)

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BACKGROUND

- FCS is a rare genetic form of primary hypertriglyceridemia with an increased risk of acute pancreatitis (AP).[1]
- Alongside strict adherence to an extremely low-fat diet, emerging data support apolipoprotein C-III (apoC-III) inhibitors such as olezarsen and plozasiran as therapeutic approaches to reduce triglycerides (TG).[2,3]
- Olezarsen 80 mg every four weeks is approved by the United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as an adjunct to diet in FCS, and a new drug approval filing was submitted to the US FDA for plozasiran 25 mg every three months with a decision expected in November of 2025.
- Evidence on the comparative efficacy and safety of apoC-III inhibitors in patients with FCS is currently lacking.
- MAIC is an indirect treatment comparison (ITC) methodology which can reduce bias by addressing imbalances in key baseline characteristics.[4]

OBJECTIVE

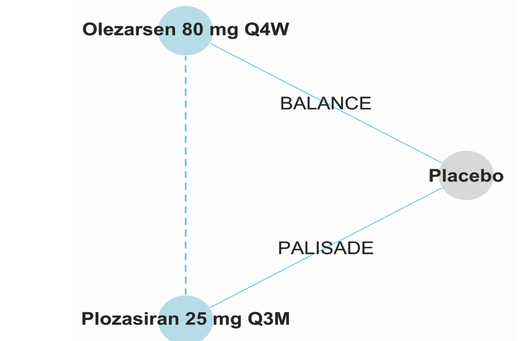
- To indirectly compare the efficacy and safety of olezarsen 80 mg to plozasiran 25 mg for FCS in the BALANCE[2] and PALISADE[3] phase 3 studies.

STUDY DESIGN

- An ITC was conducted using an anchored MAIC to account for cross-trial differences, weighting BALANCE's individual patient data to match published baseline characteristics in PALISADE.
- Matched variables were fasting TG and variables with a significant ($p < 0.2$) treatment-covariate interaction in BALANCE, indicating treatment effect modification, assessed per outcome.
- Outcomes analyzed were percent change in fasting TG, apoC-III, and non-high-density lipoprotein cholesterol (non-HDL-C), and fasting TG threshold achievement, AP risk, and risk of treatment-emergent and serious adverse events (TEAEs and SAEs).
- Sensitivity analyses were conducted using Bucher ITC and alternative scenarios that employed different sets of matching variables (matching on all variables, sex and race, variances of continuous variables, and determinate genetic confirmation). Determinate genetic confirmation was defined as a confirmed FCS genotype in PALISADE and as a positive ("pathogenic/likely pathogenic") test result in BALANCE.

TABLES AND FIGURES

FIGURE 1: Network Diagram



Acute pancreatitis analyses include multiple scenarios including pooled dose analyses with olezarsen 50 mg and 80 mg Q4W and plozasiran 25mg and 50 mg Q3M. Abbreviations:Q3M – Every three months. Q4W – Every four weeks.

TABLE 1: Pre-Matching Baseline Characteristics

Variable	BALANCE			PALISADE		
	OLE 80 mg	OLE 50+80 mg	PBO	PLZ 25 mg	PLZ 25+50 mg	PBO
Sample Size / ESS	22	43	23	26	50	25
Mean Age (years)	47.7	45.5	44	47.9	45.4	47.4
Female sex	50%	60%	52%	54%	54%	44%
White Race	77%	79%	96%	73%	72%	76%
Mean BMI (kg/m^2)	25.1	23.8	24.2	26.1	25.8	25.0
Mean Baseline TG (mg/dL)	2613	2648	2596	2349	2418	2271
10-year AP History	77%	74%	65%	89%	90%	88%

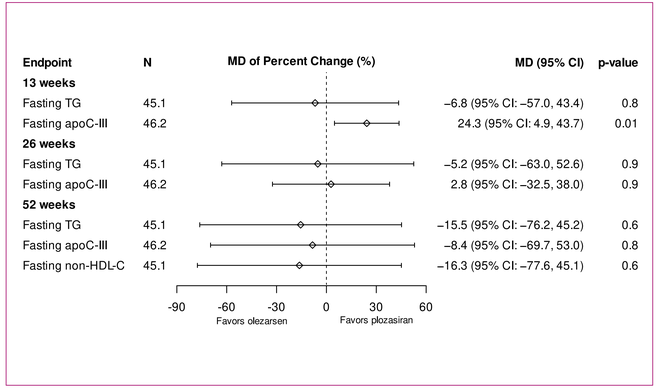
Abbreviations: AP – Acute Pancreatitis, BMI – Body Mass Index, ESS – Effective Sample Size, OLE – Olezarsen, PBO – Placebo, PLZ – Plozasiran, TG – Triglycerides.

TABLE 2: Matching Variables By Outcome

Outcome	Age	Sex	White Race	BMI	Baseline Fasting TG	10-year AP History	% Decrease in ESS	
							OLE 80 mg	PBO
Percent change in fasting TG	✓	✗	✓	✗	✓	✓	13%	56%
Fasting TG ≤ 880 mg/dL	✗	✗	✗	✗	✓	✗	3%	7%
Percent change in fasting apoC-III	✓	✗	✓	✗	✓	✗	8%	50%
Percent change in fasting non-HDL-C	✗	✗	✓	✗	✓	✓	13%	52%
AP, ≥ 1 event	✗	✗	✗	✗	✓	✗	3%	7%
TEAE, any	✗	✗	✗	✗	✓	✗	3%	7%
SAE, any	✗	✗	✗	✗	✓	✗	3%	7%

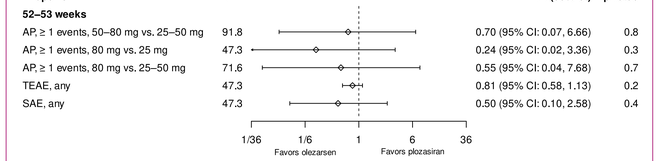
✓ – Variable was used as a matching variable for the outcome in the corresponding row.
✗ – Variable was not used as a matching variable for the outcome in the corresponding row.
Abbreviations: AE – Adverse Event, AP – Acute Pancreatitis, ApoC-III – Apolipoprotein C-III, BMI – Body Mass Index, ESS – Effective Sample Size, HDL-C – High-Density Lipoprotein Cholesterol, OLE – Olezarsen, PBO – Placebo, SAE – Serious AE, TEAE – Treatment-Emergent AE, TG – Triglycerides.

FIGURE 2: Lipid and Apolipoprotein Reduction Results



Note: Percent change is relative to baseline. Sample size may not be an integer due to the weighting of BALANCE patients.
Abbreviations: ApoC-III – Apolipoprotein C-III, CI – Confidence Interval, HDL-C – High-Density Lipoprotein Cholesterol, MD – Mean Difference, N – Sum of the effective sample size in the olezarsen arm and the sample size in the plozasiran arm, Q3M – Every three months, Q4W – Every four weeks, TG – Triglycerides.

FIGURE 3: Acute Pancreatitis and Safety Results



Abbreviations: AE – Adverse Event, AP – Acute Pancreatitis, CI – Confidence Interval, N – Sum of the effective sample size in the olezarsen arm and the sample size in the plozasiran arm, Q3M – Every three months, Q4W – Every four weeks, RR – Risk Ratio, SAE – Serious AE, TEAE – Treatment-Emergent AE, TG – Triglycerides.

RESULTS

- The network and baseline characteristics for BALANCE and PALISADE are displayed in **Figure 1** and **Table 1**, respectively. Both trials enrolled patients with a fasting TG ≥880 mg/dL, and PALISADE enrolled clinically diagnosed in addition to genetically confirmed patients with FCS.
- After weighting, matched baseline variables were identical, and BALANCE's effective sample size reduced by 3–13% and 7–56% for olezarsen and placebo, respectively, depending on the outcome (**Table 2**).
- Reductions in lipid and apolipoprotein parameters were comparable at week 26 and numerically favored olezarsen 80 mg at week 52 but they were not statistically significant (NS) with the exception of fasting apoC-III at the early week 13 time point which favored plozasiran ($p < 0.05$) (**Figure 2**).
- Fasting TG ≤ 880 mg/dL achievement was 77% lower for olezarsen 80 mg at 52 weeks vs plozasiran 25 mg at 43 weeks (RR: 0.23; 95% confidence interval: 0.03, 1.97; NS).
- Pooled dose (50 and 80 mg) olezarsen was associated with 30% lower AP risk compared to pooled dose (25 and 50 mg) plozasiran (NS) (**Figure 3**); dose-stratified AP results also showed lower risk for olezarsen 80 mg compared to pooled dose and 25 mg plozasiran (NS).
- Olezarsen 80 mg was associated with 19% lower risk of a TEAE and 50% lower risk of an SAE compared to plozasiran 25 mg (NS).
- Findings of sensitivity analyses including Bucher ITC and alternate MAICs, were consistent with the primary analysis except the sensitivity MAICs fasting apoC-III at 13 weeks (NS) and TG ≤ 880 mg/dL achievement (favored olezarsen 80 mg Q4W; NS). Matching for patients with determinate genetically confirmed FCS did not materially change the results.

CONCLUSION

- In this ITC, olezarsen demonstrated numerically better efficacy and safety outcomes at 52 weeks compared with plozasiran in patients with FCS, though the differences were not statistically significant. Limitations include differences in follow-up for the TG ≤ 880 mg/dL outcome, and reduced power due to the small sizes of BALANCE and PALISADE.

DISCLOSURES

Asia Sikora Kessler, Sotirios Tsimikas and Montserrat Vera Llonch are employees of Ionis Pharmaceuticals. Seth Baum is employed by Flourish Research. Paul Serafini, Divya Pushkarna and Johnny Zhou are employees of Evidinno Outcomes Research Inc.

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