A Randomized, Placebo-controlled Phase 3 Study of Plozasiran in Patients With FCS: Interim Analysis of Open Label Extension of PALISADE at 1 Year

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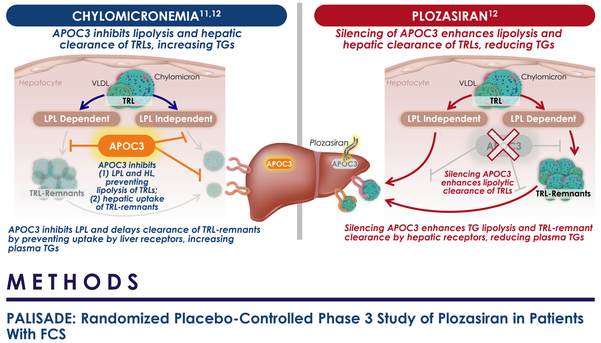
BACKGROUND

Persistent Chylomicronemia

- **Extremely high plasma triglycerides (TG)** (>9.9 mmol/L) in which fat is absorbed as particles, called chylomicrons, cannot be cleared from the circulation[1]
- **Due to ultrarare bi-allelic recessive variants** (Familial Chylomicronemia Syndrome, FCS) **or more common genetic variants that impair the lipolytic enzyme, lipoprotein lipase (LPL)**[1-4]
  - Adults with severe chylomicronemia, a high-risk subset of which, can phenocopy classical FCS
- **Persistent chylomicronemia can cause multiple symptoms** (physical, cognitive, emotional), the most severe being **acute pancreatitis (AP)** and its life-threatening sequelae[5-8]
  - Directly related to TG levels (>5.6 mmol/L)
- **Historically available therapeutic agents** (fibrates, N-3 fatty acids, statins, niacin) are **not sufficient to lower TGs below the thresholds for increased AP risk**
- Current emerging therapies targeting APOC3 have shown promising results to reduce the risk of AP in patients with persistent chylomicronemia,

Plozasiran (ARO-APOC3) is an Investigational siRNA Therapeutic Targeting APOC3, a Key Regulator of TG and TRL Metabolism



METHODS

PALISADE: Randomized Placebo-Controlled Phase 3 Study of Plozasiran in Patients With FCS

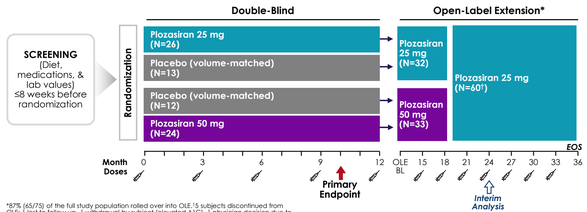
Study Population: Adults with genetically confirmed or clinical FCS who completed the randomized, double-blind period were invited to consent to continue in a 2-part OLE period

Primary Endpoint: Placebo-adjusted median percent change in TGs

Main objective of the OLE: To identify long-term safety signals and insights into long term efficacy

OLE Parts: Subjects received either plozasiran 25 mg or 50 mg as a subcutaneous injection Q3M during Part A; all subjects transitioned to final chosen clinical dose of 25 mg for Part B

Timing: The OLE will provide an additional 24 months of plozasiran treatment (efficacy and safety) evaluation



*87% (65/75) of the full study population rolled over into OLE.†5 subjects discontinued from OLE: 1 lost to follow-up, 1 withdrawal by subject (elevated A1C), 1 physician decision due to AE during the randomization period, 2 other (wanted to become pregnant).

PALISADE Enrolled Patients with FCS Defined Clinically or Genetically Confirmed

Criteria included history of multiple TG measurements >11.3 mmol/L, despite best standard of care; plus at least one of the following:

1. Prior genetic testing diagnostic of FCS* **OR**
2. Recurrent episodes of acute pancreatitis† **OR**
3. Recurrent hospitalizations for severe abdominal pain without other explainable cause **OR**
4. History of childhood pancreatitis **OR**
5. Family history of HTG-induced acute pancreatitis

Genetic testing done on patients who were not previously tested for FCS variants

*Supportive genetic testing includes but is not limited to homozygous, compound heterozygous, or double heterozygote for loss-of-function or otherwise inactivating mutations in genes affecting lipoprotein lipase activity including LPL, APOC2, APOA5, GPIHBP1, GPD1, or LMF1; or evidence of low LPL activity (<20% of normal) based on source-verifiable documentation. †Not caused by alcohol or cholelithiasis.

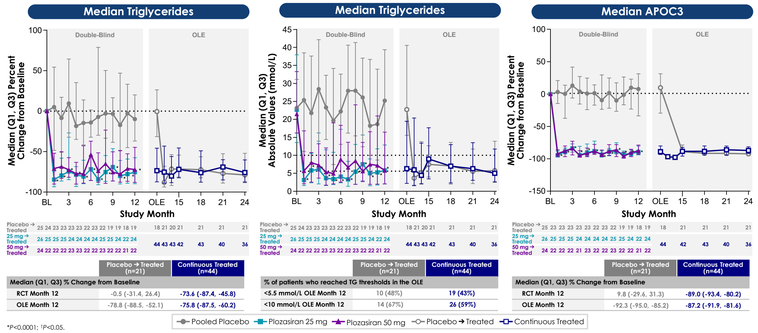
RESULTS

Table 1. PALISADE OLE Baseline Characteristics

	Placebo to Plozasiran (N=21)	Continuous Plozasiran (N=44)	Total (N=65)
Age, years	48.4 (14.2)	44.7 (12.6)	45.9 (13.2)
Male, n (%)	12 (57.1)	21 (47.7)	33 (50.8)
Female, n (%)	9 (42.9)	23 (52.3)	32 (49.2)
White, n (%)	16 (76.2)	32 (72.7)	48 (73.8)
BMI, kg/m²	24.9 (4.1)	25.6 (4.4)	25.4 (4.3)
Triglycerides, mmol/L; Median (Q1, Q3)	25.5 (16.5, 42.1)	24.9 (15.3, 38.1)	25.5 (15.8, 38.3)
APOC3, g/L; Median (Q1, Q3)	0.39 (0.30, 0.48)	0.33 (0.20, 0.42)	0.34 (0.21, 0.44)
VLDL-C, mmol/L	6.43 (4.18)	6.75 (3.78)	6.64 (3.88)
Non-HDL-C, mmol/L	7.14 (4.14)	7.34 (3.73)	7.28 (3.84)
LDL-C (UC), mmol/L	0.73 (0.48)	0.60 (0.44)	0.64 (0.45)
ApoB, g/L	0.74 (0.28)	0.69 (0.29)	0.71 (0.29)
Total cholesterol, mmol/L	7.61 (4.13)	7.75 (3.72)	7.71 (3.82)
HDL-C, mmol/L	0.47 (0.25)	0.41 (0.16)	0.43 (0.20)
HbA1c, %	6.09 (1.15)	5.69 (1.15)	5.82 (1.15)
Genetic confirmation of FCS, n (%)	12 (57.1)	27 (61.4)	39 (60.0)
Anti-Diabetic medications, n (%)	7 (33.3)	11 (25.0)	18 (27.7)
Fibrates, n (%)	1 (4.8)	5 (11.4)	6 (9.2)
Statins, n (%)	1 (4.8)	1 (2.3)	2 (3.1)
Omega-3, n (%)	0 (0.0)	2 (4.5)	2 (3.1)
PCSK9 inhibitors, n (%)	0 (0.0)	1 (2.3)	1 (1.5)

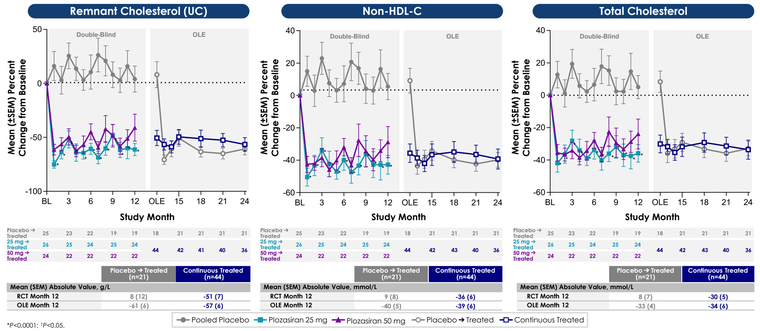
*Data are reported as mean (±SD) unless otherwise noted, true baseline prior to study dosing is presented. Note: Diabetic patients are defined as having HbA1c ≥6.5% or fasting glucose ≥126 mg/dL or with medical history of 'diabetes' or receiving diabetic medications at baseline.

Figure 1. Plozasiran TG and APOC3 Response Persisted Over 12 Months in the OLE[13]



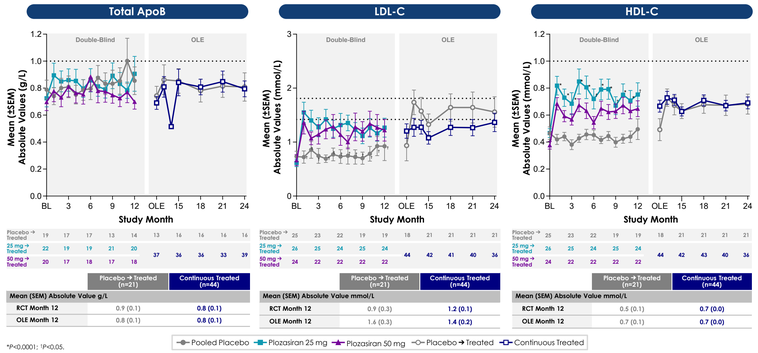
*P<0.0001; †P<0.05.

Figure 2. Plozasiran Reduced Remnant and Non-HDL Cholesterol Levels Over 12 Months in the OLE



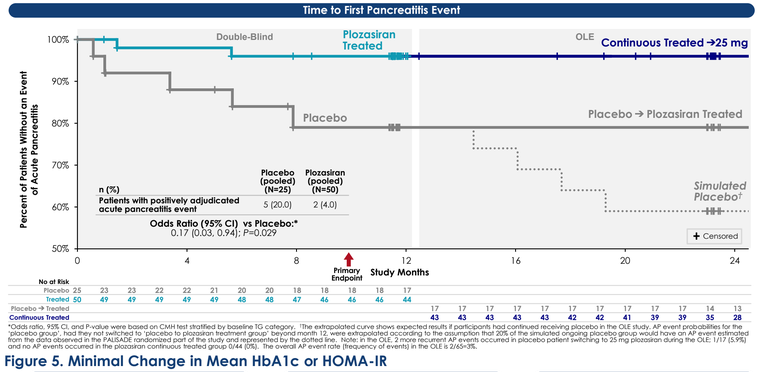
*P<0.0001; †P<0.05.

Figure 3. Plozasiran Did Not Increase Total ApoB Levels Despite Increases in HDL-C and LDL-C



*P<0.0001; †P<0.05.

Figure 4. Plozasiran Reduced the Incidence of Acute Pancreatitis



*Odds ratio, 95% CI, and P-value were based on CMH test stratified by baseline TG category. †The extrapolated curve shows expected results if participants had continued receiving placebo in the OLE study. AP event probabilities for the 'placebo group' had they not switched to 'placebo to plozasiran treatment group' beyond month 12, were extrapolated according to the assumption that 20% of the simulated ongoing placebo group would have an AP event estimated from the data observed in the PALISADE randomized part of the study and represented by the dotted line. Note: In the OLE, 2 more recurrent AP events occurred in placebo patient switching to 25 mg plozasiran during the OLE; 1/17 (5.9%) and no AP events occurred in the plozasiran continuous treated group 0/44 (0%). The overall AP event rate (frequency of events) in the OLE is 2.6/6=3%.

Figure 5. Minimal Change in Mean HbA1c or HOMA-IR

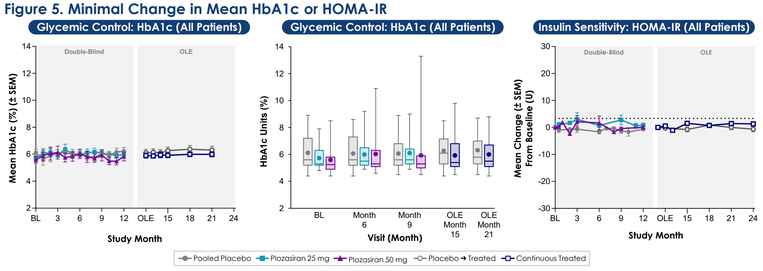


Table 2. Summary of Adverse Events in the OLE*

n (%) OLE	Plozasiran 25mg (N=63)	Plozasiran 50mg (N=33)
All Treatment-Emergent Adverse Events (TEAEs)	29 (46.0)	25 (75.8)
Upper respiratory tract infection	4 (6.3)	4 (12.1)
Urinary tract infection	4 (6.3)	1 (3.0)
Influenza	4 (6.3)	0 (0.0)
Abdominal pain	2 (3.2)	5 (15.2)
Nasopharyngitis	2 (3.2)	2 (6.1)
Vascular disorders	1 (1.6)	3 (9.1)
Lipase increased	1 (1.6)	2 (6.1)
Nausea	0 (0.0)	2 (6.1)
Gastroenteritis	0 (0.0)	2 (6.1)
Treatment-related TEAEs	8 (12.7)	6 (18.2)
Serious TEAEs	3 (4.8)	3 (9.1)
TEAEs leading to study or study drug discontinuation	3 (4.8)	0 (0.0)
Deaths	1 (1.6)†	0 (0.0)

n (%) OLE	Placebo → Treated (n=21)	Continuous Treated (n=44)
Mean (SD) HbA1c (%) at baseline	6.1 (1.1)	5.7 (1.1)
Mean (SD) HbA1c (%) at OLE Month 24	6.3 (1.3)	6.0 (1.4)
Mean (SD) platelet count (10⁹/L) at baseline	207.0 (75.0)	192.1 (56.9)
Mean (SD) platelet count (10⁹/L) at OLE Month 24	206.1 (80.0)	184.8 (51.1)

*AEs are summarized up to each individual subject's 1-year OLE data. All subjects in OLE eventually were dosed with 25 mg. The subjects who transitioned from 50 mg dose to 25 mg dose is also included in this summary. †Death: anti-psychotic drug OD. Subjects who discontinued from OLE: 1 lost to follow-up, 1 withdrawal by subject (elevated A1C), 1 physician decision due to AE, 2 other (wanted to become pregnant).

- TEAEs leading to discontinuation due to AEs remained low (4.8%)
- AEs in OLE were consistent with prior observations with lower incidence of occurrence than in the randomized period
- No cases of anaphylaxis or systemic hypersensitivity
- Minimal changes in HbA1c
- No changes in platelets

CONCLUSIONS

- **Plozasiran (quarterly dosing) significantly reduced median TGs by >70% in patients with persistent chylomicronemia (genetic FCS or clinical FCS*) over time through 12 months in OLE**
- **Reductions in TGs apparent at 1 month in the OLE and sustained thereafter through 12 months of the OLE with similar efficacy to the randomized portion of the trial**
- **69% of patients reached TG <9.95 mmol/L and 57% reached TG <5.65 mmol/L in the OLE**
- **No clinically meaningful changes in atherogenic lipoproteins with ApoB remaining low and unchanged through the OLE**
- **AEs in the OLE consistent with previous observations**
- **Plozasiran is a novel therapeutic candidate, with a reassuring safety and tolerability profile, for reducing plasma TG levels and risk of AP in patients with persistent chylomicronemia**

*High-risk persistent chylomicronemia (patients with prior AP events and exceptionally high TGs)

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DISCLOSURES

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ABBREVIATIONS

AP, acute pancreatitis; **ApoB**, apolipoprotein B; **APOC3**, apolipoprotein C3; **BMI**, body mass index; **CI**, confidence interval; **CMH**, Cochran-Mantel-Haenszel; **EOS**, end of study; **FCS**, familial chylomicronemia syndrome; **HbA1c**, glycosylated hemoglobin; **HDL-C**, high-density lipoprotein cholesterol; **HL**, hepatic lipase; **HOMA-IR**, homeostatic model assessment for insulin resistance; **HTG**, hypertriglyceridemia; **LDL-C**, low-density lipoprotein cholesterol; **LPL**, lipoprotein lipase; **mRNA**, messenger RNA; **N**, number; **OLE**, open-label extension; **Q1**, **Q3**, interquartile range; **SAE**, serious adverse event; **SD**, standard deviation; **SEM**, standard error of mean; **siRNA**, small interfering RNA; **TEAE**, treatment emergent adverse event; **TG**, triglyceride; **TRL**, triglyceride rich lipoproteins; **UC**, ultracentrifuge; **VLDL**, very low-density lipoprotein; **W**, week.