PALISADE: Plozasiran Decreases Risk of Acute Pancreatitis and Improves Indices of QoL in FCS

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CONCLUSIONS

- **In patients with FCS, plozasiran markedly reduced TGs and risk of AP with an associated improvement in indices of Quality of Life**
- **Plozasiran rapidly and durably lowered TGs below AP risk thresholds invariant of FCS genotype**
- **Favorable safety profile compared with placebo**
- **More patients on placebo experienced abdominal pain leading to hospital admissions for AP with a prolonged length of stay**
- **Clinically meaningful improvements in most QoL indices were observed with plozasiran compared with placebo**
- **Plozasiran is a novel investigational therapeutic agent for managing extreme hypertriglyceridemia and significantly preventing risk of AP with improvement in QoL in patients with FCS**

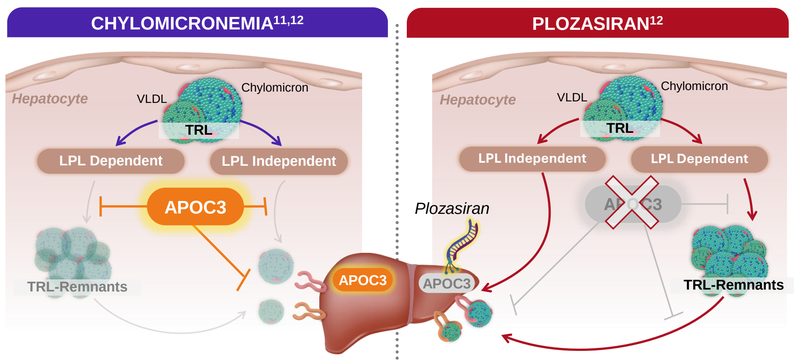
BACKGROUND

Familial Chylomicronemia Syndrome

- **Is reflected by extremely high plasma triglycerides** (>9.9 mmol/L) caused by impaired circulatory clearance of chylomicrons containing TGs derived from the diet[1]
- **Is due to ultrarare bi-allelic recessive variants of LPL; FCS or more common genetic variants** (Multifactorial Chylomicronemia Syndrome)* that **impair triglyceride lipolysis**[1-4]
  - Adults with extreme chylomicronemia can phenocopy classical FCS
- **Chylomicronemia causes multiple symptoms** (physical, cognitive, emotional), the most severe being **acute pancreatitis** and its life-threatening sequelae[5-8]
  - Directly related to triglyceride levels (>5.6 mmol/L)
- **Traditional therapeutic agents** (fibrates, n-3 fatty acids, statins) are **generally ineffective**[9,10]

*High risk multifactorial FCS (patients with prior acute pancreatitis events and exceptionally high triglycerides).

Figure 1. Plozasiran: an Investigational siRNA Therapeutic Targeting APOC3, a Key Regulator of TG and TRL Metabolism



METHODS

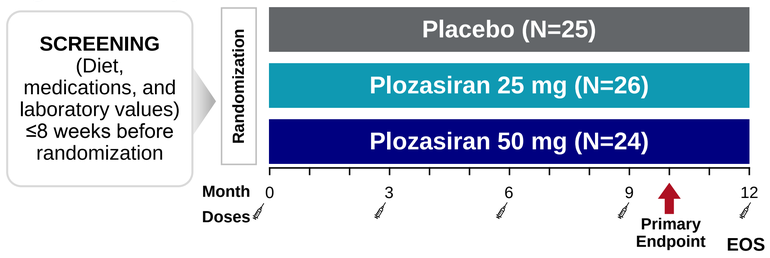
Primary Endpoint:

- Placebo-adjusted median percent change in triglycerides at Month 10

Multiplicity-Controlled Key Secondary Endpoints

1. Percent change from baseline at Months 10 and 12 (averaged) in fasting triglycerides
2. Percent change from baseline at Month 10 and 12 in fasting APOC3
3. Incidence of positively adjudicated AP events during the randomized period

Figure 2. Study Schema



- PALISADE enrolled patients with FCS defined clinically* or genetically† confirmed

Exploratory Endpoints

- European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 is a generalized PRO tool designed to assess the quality of life (QoL)
- While initially developed for cancer patients, the QLQ-C30 has been applied to assess the QoL in other diseases, such as AP and chronic pancreatitis patients. It provides valuable insights into the impact of pancreatitis and its management on patients' overall well-being and functioning[13]

*Clinical criteria included history of multiple triglyceride measurements above 11.3 mmol/L, despite best standard of care; plus at least a prior genetic testing diagnostic of FCS† ***OR,*** recurrent episodes of AP not caused by alcohol or cholelithiasis ***OR*** recurrent hospitalizations for severe abdominal pain without other explainable cause ***OR*** history of childhood AP ***OR*** family history of HTG-induced AP. †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. Genetic testing was done on all patients not previously tested for FCS variants.

RESULTS

Table 1. PALISADE Baseline Characteristics

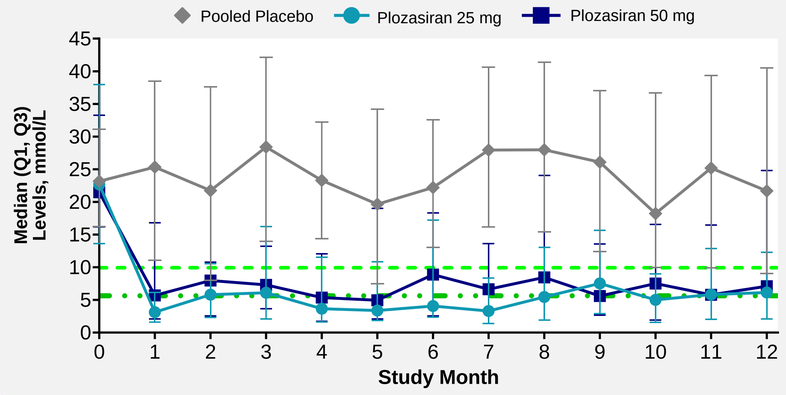
Characteristic	Placebo (pooled) (N=25)	Plozasiran 25 mg (N=26)	Plozasiran 50 mg (N=24)
Mean (SD) age, years	47 (14)	48 (14)	43 (11)
Female, n (%)	11 (44)	14 (54)	13 (54)
White, n (%)	19 (76)	19 (73)	17 (71)
Mean (SD) BMI, kg/m²	25 (4)	26 (4)	25 (5)
Mean (SD) APOC3, mmol/L	1.0 (0.5)	1.0 (0.4)	0.9 (20)
Median (Q1, Q3) triglyceride, mmol/L	23.2 (16.2, 31.1)	22.7 (13.6, 37.9)	21.5 (16.2, 33.3)
Receiving statins n (%)	11 (44)	11 (42)	12 (50)
Fibrates, n (%)	16 (64)	19 (73)	15 (63)
Omega-3 fatty acids, n (%)	6 (24)	9 (35)	7 (29)
Diabetes or pre-diabetes, n (%)	11 (44)	10 (39)	7 (29)
Genetic confirmation of FCS, n (%)	14 (56)	14 (54)	16 (67)
Previous episode of pancreatitis, n (%)	22 (88)	23 (89)	22 (92)

Data are reported as mean (±SD) unless otherwise noted. Diabetic patients are defined as having HbA1c ≥6.5% or fasting glucose ≥7.0 mmol/L or with medical history of 'diabetes' or receiving diabetic medications at baseline. *% = 100 x n/N', N' is the number of diabetic or prediabetic patients at baseline.

REDUCTIONS IN TRIGLYCERIDES TO < 5.6 mmol/L

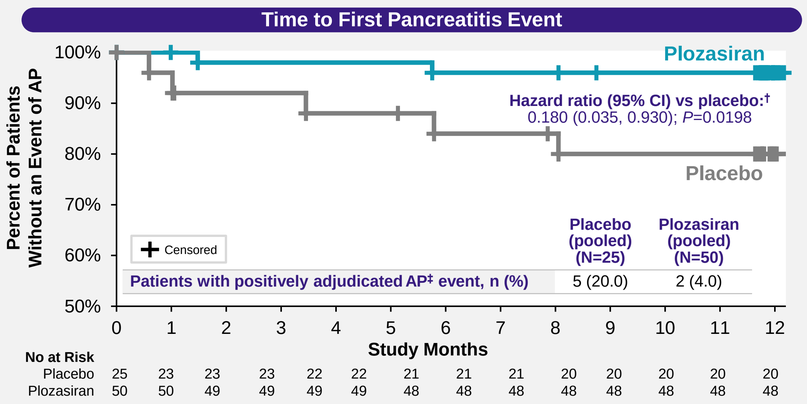
Figure 3. Reductions in Triglycerides Initiate 1 Month After Dose

75% of patients reached triglycerides < 9.9 mmol/L and 50% reached < 5.6 mmol/L at 10 months



82% REDUCTION IN ACUTE PANCREATITIS

Figure 4. Statistically Significant Decrease in Incidence of AP*



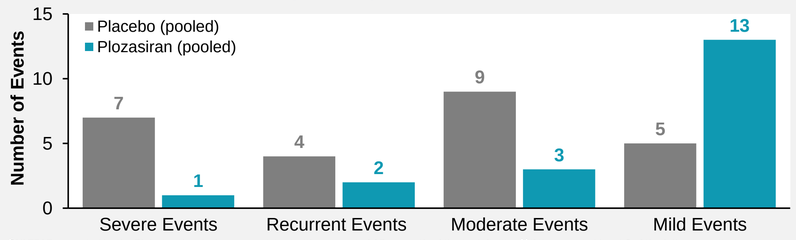
*4 patients with AP events were FCS genotype negative. †Odds ratio, 95% CI, and P-value were based on CMH test stratified by baseline TG category. 7 incident cases occurred in 5 of 25 (20%) participants receiving placebo and 2 incident cases occurred in 2 of 50 (4%) participants in the plozasiran-treated group. ‡6 severe cases and 1 moderate in placebo and 1 moderate and 1 mild in 25 mg were adjudicated; % = 100 x n/N. An AP event is defined based on the 2013 Atlanta definition. TEAEs are AEs that occur following IP administration or a pre-existing condition exacerbated following IP administration. Hospitalizations for abdominal pain are not dependent on AP. Listing of treatment-emergent potential AP / abdominal pain events (randomized period).

Table 2. Reduced Incidence of Hospitalization for Abdominal Pain

	Placebo (pooled) (N=25)	Plozasiran (pooled) (N=50)
Abdominal pain hospitalizations, n (%) E	5 (20.0) 6	2 (4.0) 2
Odds Ratio (95% CI); *p*-value§	0.179 (0.033, 0.967); *p*=0.0279	
Total days in hospital due to AP, n	49	14

%=100*n/N. §Odds ratio vs placebo, corresponding 95% CI and p-value are based on Cochran-Mantel-Haenszel (CMH) test stratified by baseline triglycerides.

Figure 5. Reduced Severity of Any Potential AP/Abdominal Pain TEAE¶



¶All TEAEs reported by the PI during the study are consistent with an event of AP as per the Atlanta definition[14] if they meet at least 2 of the following criteria: **1.** Abdominal pain consistent with AP (acute onset of a persistent, severe, epigastric pain often radiating to the back). **2.** Serum lipase activity (or amylase activity) ≥3 times the upper limit of normal (×ULN). **3.** Characteristic findings of AP on CECT, MRI, or transabdominal ultrasonography.

Table 3. Reductions in Acute Pancreatitis/Abdominal Pain Events

Category, % of Subjects; Number of Events	Placebo (pooled) (N=25)	Plozasiran (pooled) (N=50)
Severe abdominal pain consistent with AP	24%; 12	10%; 6
Serum lipase activity (or amylase activity) ≥3×ULN	20%; 5	4%; 2
CECT or MRI or transabdominal ultrasonography	12%; 4	0%; 0

SAFETY

- A greater proportion of placebo-treated patients compared to pooled plozasiran patients experienced severe TEAEs (20% vs 12%) or serious TEAEs (28% vs 14%)
- Most common reported TEAEs were abdominal pain, COVID-19*, nasopharyngitis, headache, nausea, back pain, URTI, diarrhea
- Fewer premature discontinuations with pooled plozasiran (10%) vs placebo (24%)
- No reductions in platelet counts
- Mean HbA1c at Month 12 was comparable to baseline levels
- No deaths

*The observed difference in COVID-19 occurrence in this trial was not seen in the larger phase 2b trials in mixed hyperlipidemia and severe hypertriglyceridemia also conducted during the COVID-19 pandemic, and likely was a chance finding

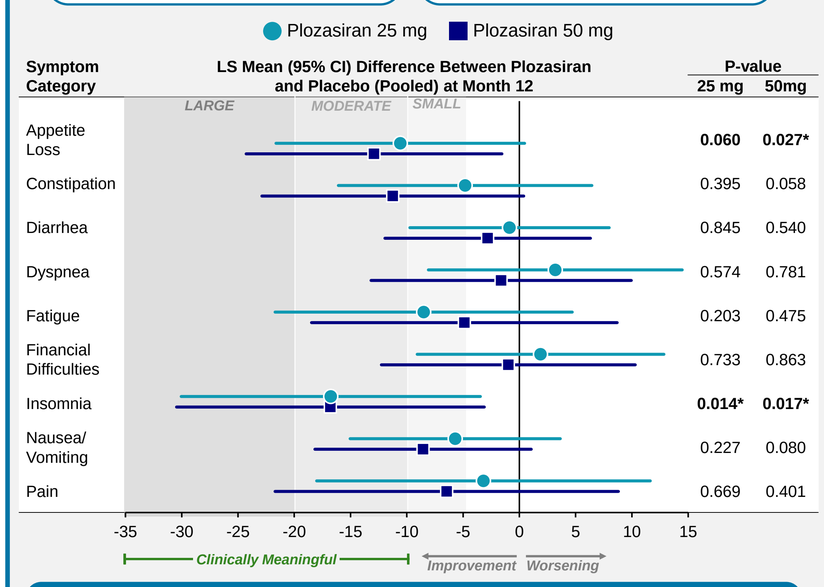
IMPROVEMENTS IN QUALITY OF LIFE

Figure 6. EORTC-QLQ-C30 QoL Exploratory Endpoints at Month 12 and Over Time for Symptom and Function Scales

Most QoL Symptom Domains Improved With Clinically[15] Meaningful Improvements (> -10 Points) in 2 Domains

-13.0 Decrease in Appetite Loss

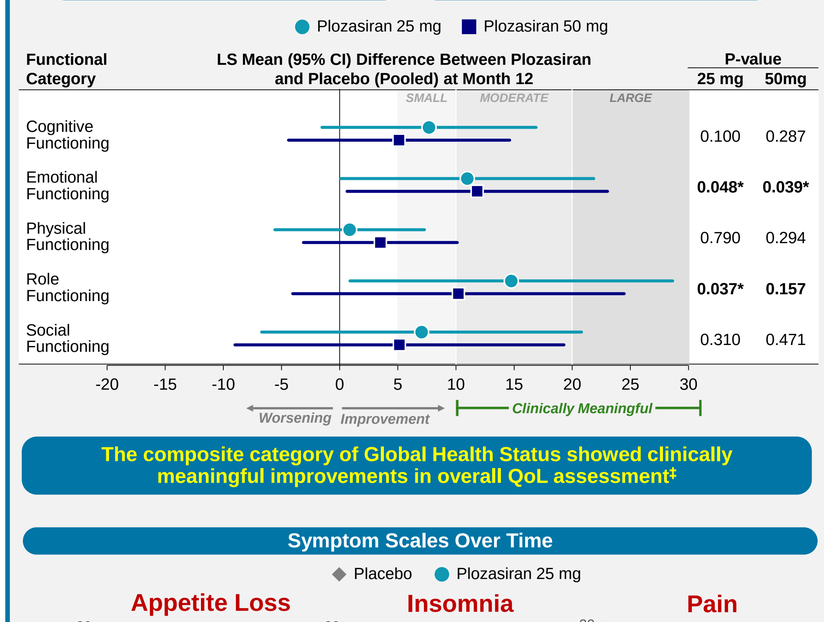
-16.8† Decrease of Insomnia



Most QoL Functional Domains Improved With Clinically[15] Meaningful Improvements (> +10 Points) in 2 Domains

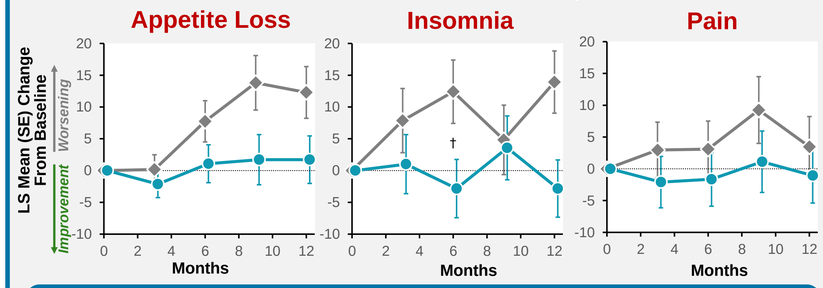
+14.8 Increase in Role Function

+11.8† Increase in Emotional Function

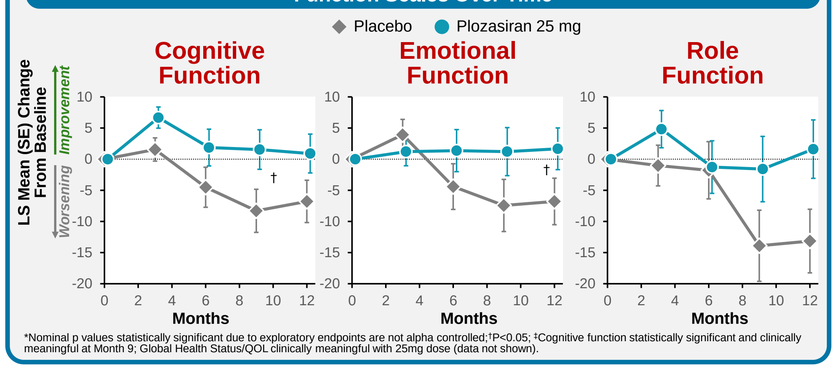


The composite category of Global Health Status showed clinically meaningful improvements in overall QoL assessment‡

Symptom Scales Over Time



Function Scales Over Time



*Nominal p values statistically significant due to exploratory endpoints are not alpha controlled;†P<0.05; ‡Cognitive function statistically significant and clinically meaningful at Month 9; Global Health Status/QOL clinically meaningful with 25mg dose (data not shown).

ABBREVIATIONS

AP, acute pancreatitis; **APOC3**, apolipoprotein C3; **BMI**, body mass index; **CECT,** contrast-enhanced computed tomography; **CI**, confidence interval; **CMH**, Cochran-Mantel-Haenszel; **E** = Number of events; **FCS**, familial chylomicronemia syndrome; **HbA1c**, glycosylated hemoglobin; **HDL-C**, high-density lipoprotein cholesterol; **HL**, hepatic lipase; **HTG**, hypertriglyceridemia; **IP**, investigational product; **LPL**, lipoprotein lipase; **MRI**, magnetic resonance imaging; **N**, number; **PI**, principal investigator; **PRO**, Patient reported outcomes; **Q1**, **Q3**, interquartile range; **QoL**, Quality of Life; **SD**, standard deviation; **SAE**, serious adverse event; **SEM**, standard error of mean; **TG**, triglycerides; **TEAE**, treatment emergent adverse event; **ULN**, upper limit of normal; **URTI**, upper respiratory tract infection; **TRL**, triglyceride rich lipoproteins; **VLDL**, very low-density lipoprotein; **W**, week.

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