A Phase 3 Study to Assess the Efficacy and Safety of Plozasiran in Adults with Genetically or Clinically-Defined FCS at High Risk of Acute Pancreatitis

#0023

Gerald F. Watts, D.Sc., M.D., Ph.D.[1], Robert S. Rosenson, M.D.[2], Robert A. Hegele, M.D.[3], Ira J. Goldberg, M.D.[4], Antonio Gallo, M.D., Ph. D.[5], Ann Mertens, M.D., Ph.D.[6], Alexis Baass, M.D., M.Sc.[7], Rong Zhou, Ph.D.[8], Ma'an Muhsin, M.D.[8], Jennifer Hellawell, M.D.[8], Nicholas J. Leeper, M.D.[9], Daniel Gaudet, M.D., Ph.D.[10], on behalf of the PALISADE Study Group*

[1]School of Medicine, University of Western Australia and Department of Cardiology, Royal Perth Hospital, Perth, Australia (G.F.W.); [2]Metabolism and Lipids Program, Mount Sinai Fuster Heart Hospital, Icahn School of Medicine at Mt Sinai, Mount Sinai, New York, NY, USA (R.S.R.); [3]Robarts Research Institute, London, Ontario, Canada (R.A.H.); [4]NYU School of Medicine, NYU Langone Health, New York City, NY, USA (I.J.G); [5]Sorbonne University, INSERM UMR1166, Lipidology and Cardiovascular Prevention Unit, Department of Nutrition, Pitie-Salpetriere Hospital, AP-HP, Paris, France (A.G.); [6]Department of Endocrinology, University Hospitals Leuven – KU Leuven, Leuven, Belgium (A.M.); [7]Department of Medicine, McGill University and Genetic Dyslipidemia Clinic, Montréal Clinical Research Institute (IRCM), Montréal, Québec, Canada (A.B.); [8]Arrowhead Pharmaceuticals, Pasadena, CA, USA (R.Z., M.M, J.H.); [9]Stanford University, Palo Alto, CA, USA (N.J.L.); [10]Université de Montréal and ECOGENE-21, Montréal, Québec, Canada (D.G)

BACKGROUND

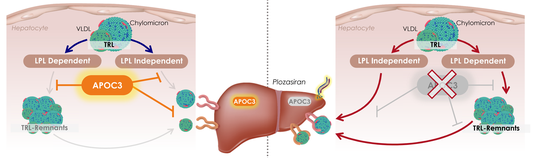
Persistent Chylomicronemia

- **Is reflected by extremely high plasma triglycerides** (>880 mg/dL) caused by impaired circulatory clearance of chylomicrons containing TGs derived from the diet[1]
- **Due to ultrarare bi-allelic recessive variants of lipoprotein lipase** (LPL; Familial Chylomicronemia Syndrome, 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 (>500 mg/dL)
- **Current therapeutic agents** (fibrates, n-3 fatty acids, statins, niacin) are **generally ineffective**

Plozasiran: An Investigational SiRNA Therapeutic Targeting APOC3, a Key Regulator of TG and TRL Metabolism

CHYLOMICRONEMIA[11,12]

APOC3 inhibits LPL and delays clearance of TRL-remnants by preventing uptake by liver receptors, increasing plasma TGs

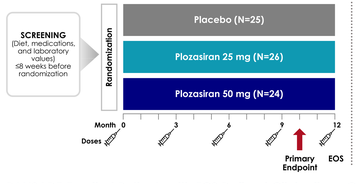


PLOZASIRAN[12]

Silencing APOC3 enhances TG lipolysis and TRL-remnant clearance by hepatic receptors, reducing plasma TGs

METHODS

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



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 in fasting APOC3
3. Percent change from baseline at Month 12 in fasting APOC3
4. Incidence of positively adjudicated events of acute pancreatitis during the randomized period

PALISADE Enrolled Patients with FCS Defined Clinically or Genetically Confirmed

- Criteria included history of multiple TG measurements above 1000 mg/dL, 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 was done on all patients not previously tested for FCS variants

*Supportive genetic testing includes but is not limited to homozygous, compound heterozygous, or double heterozygous 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 Baseline Characteristics

Characteristic	Pooled Placebo (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)
Male, n (%)	14 (56)	12 (46)	11 (46)
White, n (%)	19 (76)	19 (73)	17 (71)
Mean (SD) BMI, kg/m^2	25 (4)	26 (4)	25 (5)
Median (Q1, Q3) APOC3, mg/dL	39 (29, 50)	39 (27, 44)	30 (18, 37)
Mean (SD) APOC3, mg/dL	40 (18)	39 (17)	33 (20)
Median (Q1, Q3) triglyceride, mg/dL	2053 (1435, 2755)	2008 (1204, 3361)	1902 (1434, 2948)
Mean (SD) triglyceride, mg/dL	2272 (1141)	2350 (1375)	2492 (1523)
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. 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.
IE = 100 x n/N, N' is the number of diabetic or prediabetic patients at baseline.

Figure 1. Plozasiran TG Response at 1 Month Persisted Below Thresholds for Risk of Pancreatitis Over 12 months

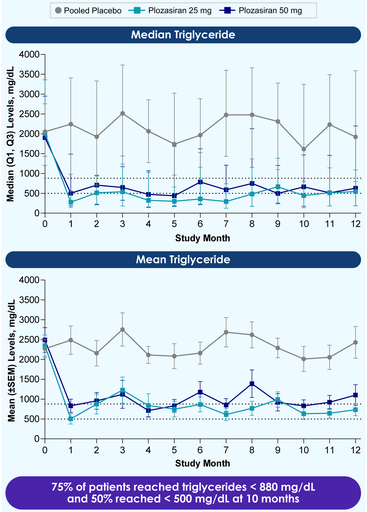
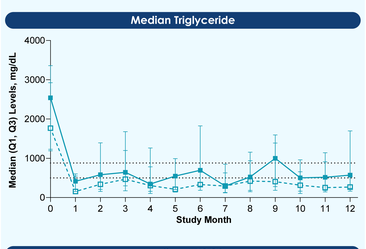
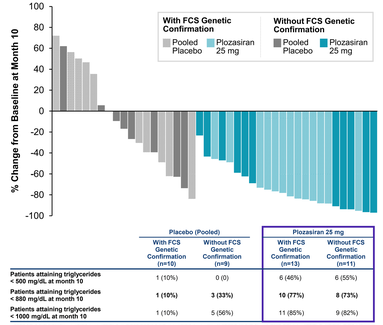


Figure 2. Plozasiran TG and APOC3 Responses Persisted Over 12 Months with No Significant Difference by FCS Genotype



Between group differences are not statistically significant through all time points.

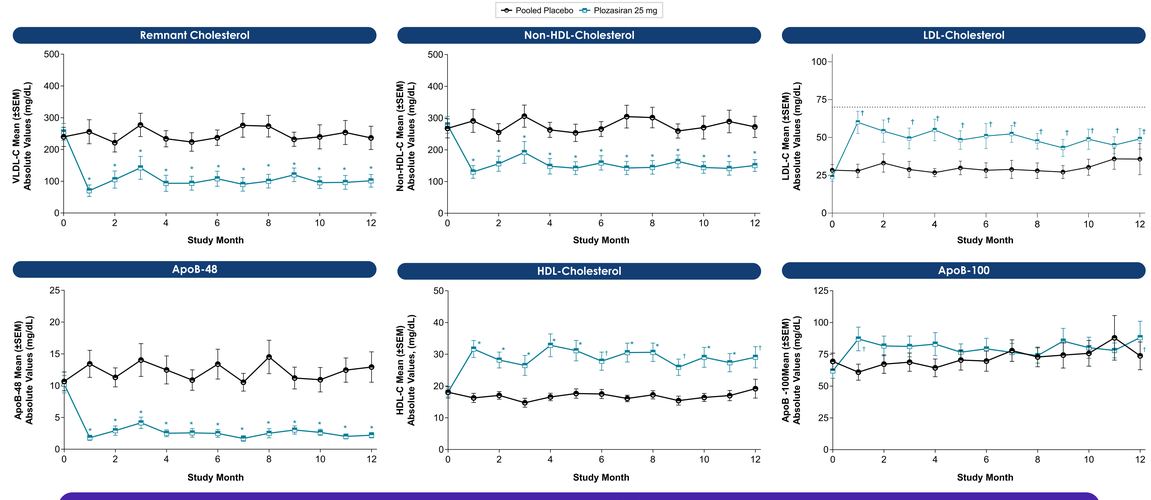
Figure 3. Reductions in TG and % of Patients Attaining TG Below Risk Thresholds for Pancreatitis by FCS Genotype



	Placebo (Pooled)		Plozasiran 25 mg	
	With FCS Genetic Confirmation (n=10)	Without FCS Genetic Confirmation (n=9)	With FCS Genetic Confirmation (n=13)	Without FCS Genetic Confirmation (n=11)
Patients attaining triglycerides < 500 mg/dL at month 10	1 (10%)	0 (0)	6 (46%)	6 (55%)
Patients attaining triglycerides < 880 mg/dL at month 10	1 (10%)	3 (33%)	10 (77%)	8 (73%)
Patients attaining triglycerides < 1000 mg/dL at month 10	1 (10%)	5 (56%)	11 (85%)	9 (82%)

Thresholds above 500 and 880 mg/dL increase risk of AP and CVD; Extremely high TG-levels >1000 mg/dL can lead to "chylomicron syndrome," causing AP.

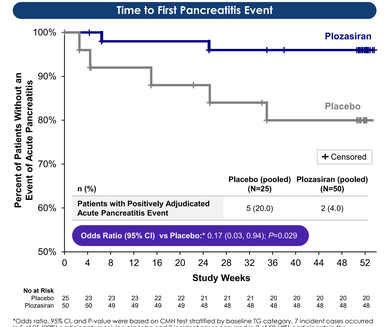
Figure 4. Plozasiran Lowered TG-Rich Lipoproteins and Increased LDL-Cholesterol and HDL-Cholesterol Levels



Responses Were Similar by FCS Genotype

*P<0.0001; †P<0.05. With Plozasiran vs Placebo.

Figure 5. Plozasiran Significantly Reduced the Incidence of Acute Pancreatitis†



*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. 14 patients with AP events were FCS genotype negative.

Table 2. Summary of Adverse Events

	Pooled Placebo (N=25)	Plozasiran 25 mg (N=26)	Plozasiran 50 mg (N=24)
Patients with Any TEAEs	20	23	20
Most Common TEAEs, N (%)			
Abdominal pain	5 (20)	7 (27)	6 (25)
COVID-19 infection*	0 (0)	5 (19)	7 (29)
Nasopharyngitis	3 (12)	5 (19)	2 (8)
Headache	2 (8)	3 (12)	5 (21)
Nausea	2 (8)	4 (15)	3 (13)
Back pain	2 (8)	3 (12)	2 (8)
Upper respiratory tract infection	2 (8)	3 (12)	2 (8)
Diarrhea	2 (8)	1 (4)	4 (17)
Severe TEAEs	5 (20)	3 (12)	3 (13)
Serious TEAEs	7 (28)	5 (19)	2 (8)
Deaths	0 (0)	0 (0)	0 (0)
Premature discontinuations	6 (24)	3 (12)	2 (8)
HbA1c, mean (SD)			
Baseline	6.1 (1.33)	5.7 (0.90)	5.59 (1.15)
Month 12	6.2 (1.17)	5.98 (1.00)	5.83 (1.56)
Platelet count, 10^9/liter, mean (SD)			
Baseline	217.9 (80.5)	204.4 (70.4)	192.9 (50.7)
Change from BL at Month 10	25.9 (38.2)	28.7 (61.2)	-4.4 (48.2)
Change from BL at Month 12	8.6 (47.5)	-4.3 (40.8)	-8.7 (50.8)

*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.

- A greater proportion of placebo-treated patients experienced SAEs
- Fewer premature discontinuations from blinded therapy with plozasiran
- No reductions in platelet counts
- Hyperglycemia with plozasiran confined to patients with pre-diabetes and diabetes
- No deaths

CONCLUSIONS

PALISADE met all alpha-controlled trial endpoints

- **Plozasiran (quarterly dosing) significantly reduced acute pancreatitis**
- **Plozasiran substantially reduced triglycerides in patients with persistent chylomicronemia (FCS or FCS-like syndrome*) and over half achieved TG treatment goals (75% < 880 mg/dL, 50% < 500 mg/dL), invariant of FCS genotype**
- **Reductions in TGs and APOC3 were apparent at 1 month and sustained thereafter over 12 months with comparable efficacy in genetically and clinically-defined patients**
- **Reductions in atherogenic TRLs and minor increase in LDL-C with no change in ApoB**
- **Favorable safety and tolerability comparable to placebo**
- **Plozasiran is a novel therapeutic candidate for reducing plasma TG levels and risk of acute pancreatitis in patients with persistent chylomicronemia**

*High risk MCS (patients with prior acute pancreatitis events and exceptionally high TGs).

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Circulation https://www.ahajournals.org/doi/ 10.1161/CIRCULATIONAHA.124.072860.

ABBREVIATIONS

APOC3, apolipoprotein C3; AP, acute pancreatitis; BL, baseline; 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; HTG, hypertriglyceridemia; LPL, lipoprotein lipase; MCS, Multifactorial Chylomicronemia Syndrome; N, number; Q, quartile; Q1, 1st quartile; Q3, 3rd quartile; SAE, serious adverse event; SD, standard deviation; SEM, standard error of mean; TEAE, treatment emergent adverse event; TG, triglycerides; TRL, triglyceride rich lipoproteins; VLDL-C, very low-density lipoprotein cholesterol; W, week.

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