A RANDOMIZED, PLACEBO-CONTROLLED PHASE 3 STUDY OF PLOZASIRAN IN PATIENTS WITH FAMILIAL CHYLOMICRONEMIA SYNDROME: PALISADE – OPEN LABEL EXTENSION

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PROGRAM DISCLOSURE

Nature of Relationship	Name of the For-profit and/or Not-for-profit Organization(s)	Description of Relationship
Any direct financial payments including receipt of honoraria	General Medicines, GSK, TD Cowen, Life Extension, Lipigon, Novo Nordisk, Amgen, Novartis, Merck Sharp & Dohme, Intercept Pharmaceuticals, Regeneron Pharmaceuticals, Kowa American Corporation, and Rona Therapeutics	consulting fees
	Wolters Kluwer (UptoDate)	royalties
Membership on advisory boards or speakers' bureaus		
Funded grants of clinical trials	89Bio, Amgen, Argo Biopharma, Arrowhead, AstraZeneca, Kalexo Bio, Lilly, Lindus Therapeutics, Mammoth Biosciences, Merck Sharp & Dohme, NIH, Novartis, Novo Nordisk, and Verve Therapeutics	Research funding to institution
Patents on a drug, product or device		
All other investments/relationship that could be seen as having the potential to influence the content of the educational activity	MediMergent, LLC.	stock holdings

FAMILIAL CHYLOMICRONEMIA SYNDROME (FCS)

- FCS is characterized by extremely high plasma triglycerides (>880 mg/dL) caused by impaired metabolism and circulatory clearance of TG-chylomicrons containing TGs derived from the diet[1]
- Traditional standard-of-care therapies (fibrates, n-3 fatty acids, statins, niacin) are generally ineffective in FCS[1]
- Plozasiran (Redemplo®), is an siRNA that silences APOC3 and enhances TG lipolysis and TRL-remnant clearance by hepatic receptors, reducing plasma TGs[2]
- In the Phase 3 PALISADE study, plozasiran demonstrated rapid, deep and durable TG lowering (-80%) and significant reductions in pooled AP risk (82% risk reduction)[3]

1. Baass A, et al. *J Intern Med*. 2020;287(4):340-348. **2.** Ballantyne CM, et al. *New Engl J Med*. **3.** Watts GF, et al. *New Engl J Med*. 2025;392(2):127-137. 2024;391:899-912.

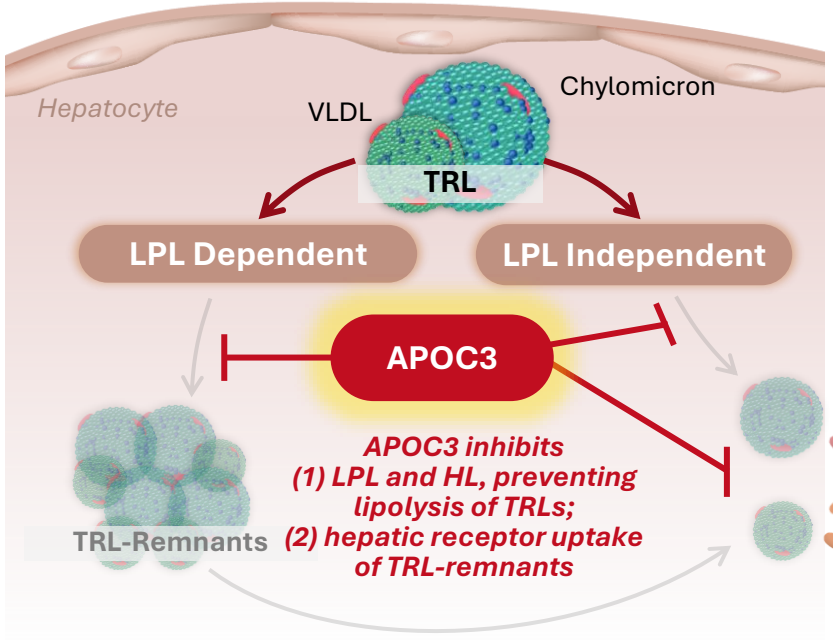
AP, acute pancreatitis; **APOC3,** apolipoprotein C-III; **ASCVD,** atherosclerotic cardiovascular disease; **CV,** cardiovascular; **HTG,** hypertriglyceridemia; **LPL,** lipoprotein lipase; **sHTG,** severe hypertriglyceridemia; **siRNA,** small interfering RNA; **TG,** triglyceride; **TRL,** triglyceride-rich lipoprotein.

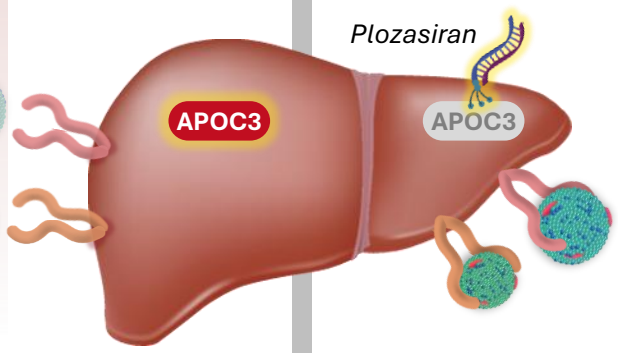
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PLOZASIRAN SILENCES APOC3, A KEY REGULATOR OF TG RICH LIPOPROTEIN METABOLISM AND CLEARANCE

HYPERTRIGLYCERIDEMIA[1,2]

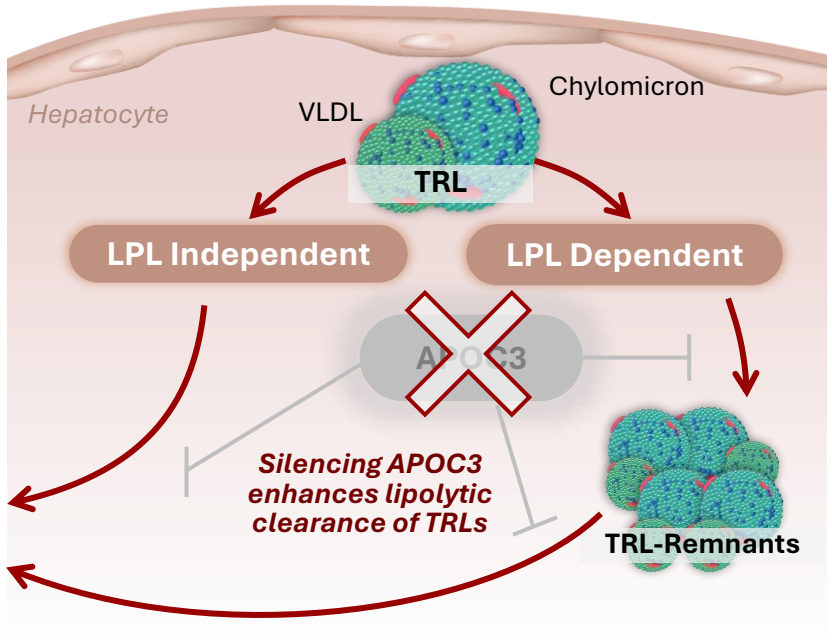
APOC3 inhibits lipolysis and hepatic clearance of TRLs, increasing TGs





PLOZASIRAN[2]

Silencing of APOC3 enhances lipolysis and hepatic clearance of TRLs, reducing TGs



1. Van Zwol W, et al. *J Clin Med.* 2019; 8:1085. **2.** Ballantyne CM, et al. *New Engl J Med.* 2024; Published online: May 28, 2024. DOI: 10.1056/NEJMoa2404143.

APOC3, apolipoprotein C3; **HL**, hepatic lipase; **LPL**, lipoprotein lipase; **siRNA**, small interfering RNA; **TG,** triglycerides; **TRL**, triglyceride rich lipoproteins; **VLDL**, very low-density lipoprotein.

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PALISADE ENROLLED PATIENTS WITH CLINICALLY DIAGNOSED OR GENETICALLY CONFIRMED FCS

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

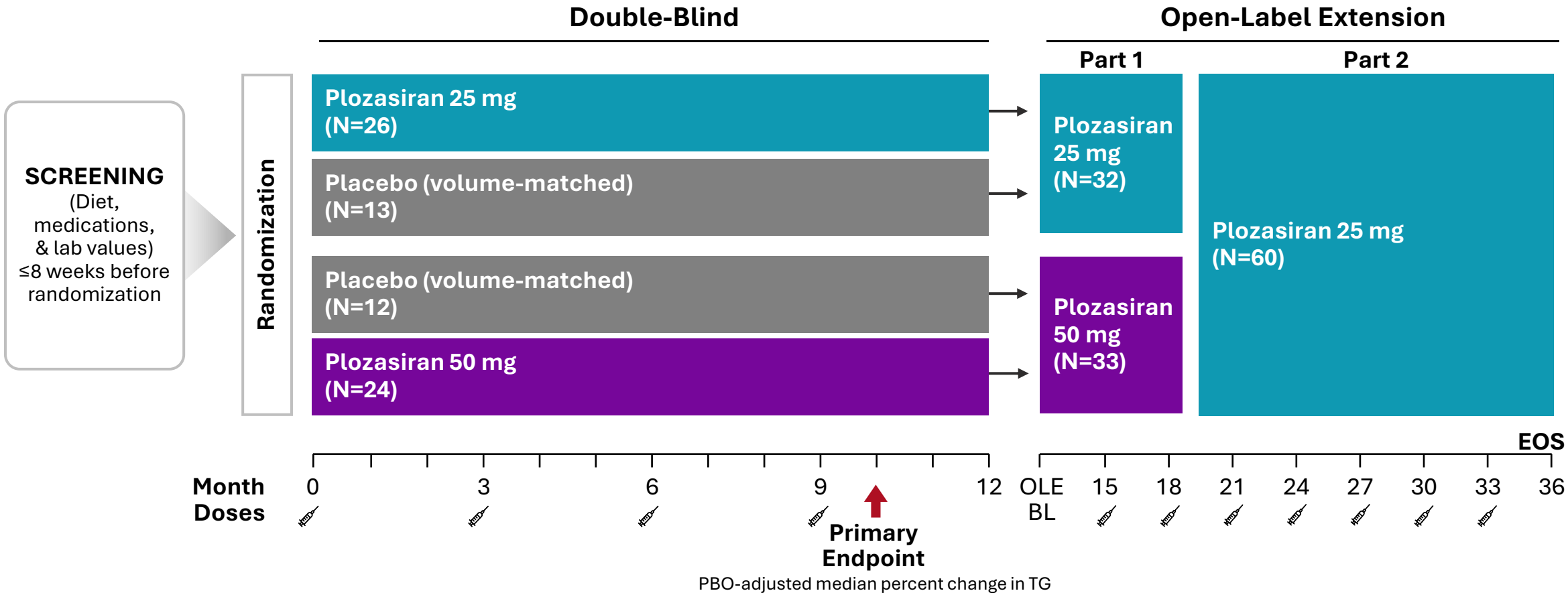
Genetic testing was done on all patients not previously tested for FCS variants

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

FCS, familial chylomicronemia syndrome; **HTG,** hypertriglyceridemia; **TG,** triglycerides.

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PALISADE OLE STUDY DESIGN



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

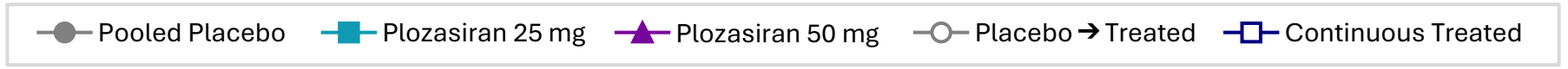
Syringe represents dosing schedule. BL, baseline; EOS, end of study; OLE, open-label extension; PBO, placebo; TG, triglyceride.

PALISADE OLE BASELINE CHARACTERISTICS

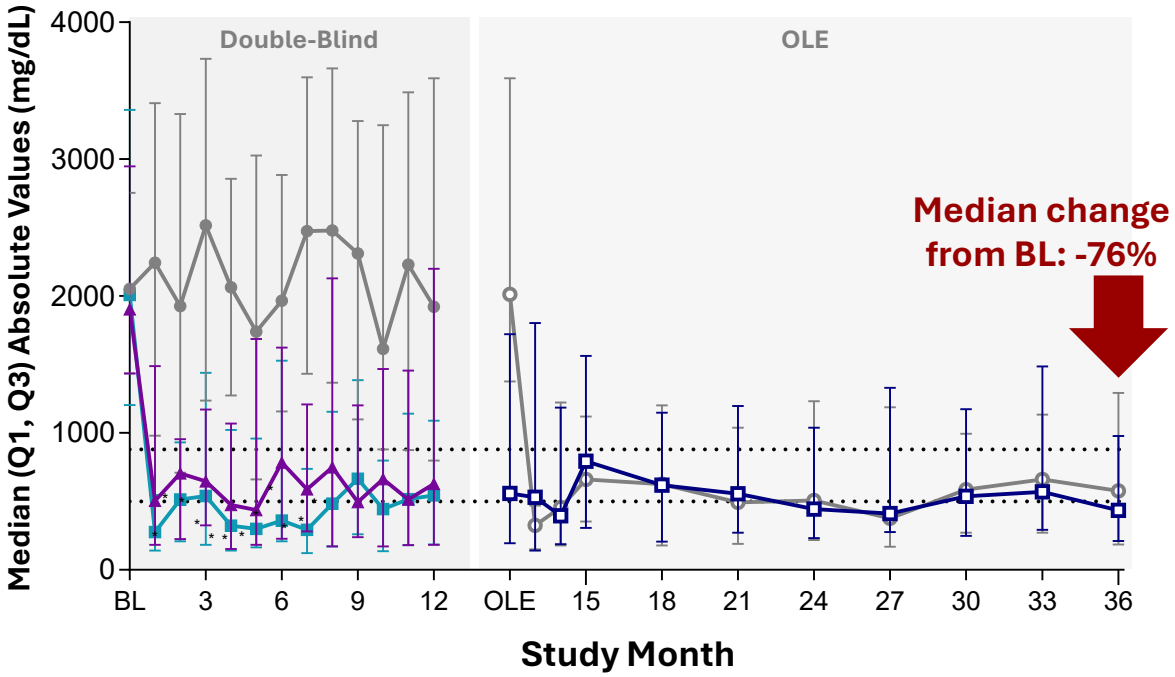
	Placebo to Plozasiran (N=21)	Continuous Plozasiran (N=44)	Total (N=65)
Age, years; Mean (SD)	48.4 (14.2)	44.7 (12.6)	45.9 (13.2)
Male, n (%)	12 (57.1)	21 (47.7)	33 (50.8)
White, n (%)	16 (76.2)	32 (72.7)	48 (73.8)
BMI, kg/m^2; Mean (SD)	24.9 (4.1)	25.6 (4.4)	25.4 (4.3)
Triglycerides, mg/dL; Median (Q1, Q3)	2255 (1459, 3729)	2202 (1354, 3374)	2255 (1398, 3388)
Genetic confirmation of FCS, n (%)	12 (57.1)	27 (61.4)	39 (60.0)
HbA1c, %; Mean (SD)	6.09 (1.15)	5.69 (1.15)	5.82 (1.15)
Lipid Lowering medications, n (%)	15 (71.4)	35 (79.5)	50 (76.9)
Fibrates, n (%)	13 (61.9)	30 (68.2)	43 (66.2)
Statins, n (%)	10 (47.6)	19 (43.2)	29 (44.6)
Omega-3, n (%)	5 (23.8)	14 (31.8)	19 (29.2)

BMI, body mass index; **FCS,** familial chylomicronemia syndrome; **HbA1c,** glycosylated hemoglobin; **N,** number; **OLE,** open-label extension; **Q1, Q3,** interquartile range; **SD,** standard deviation.

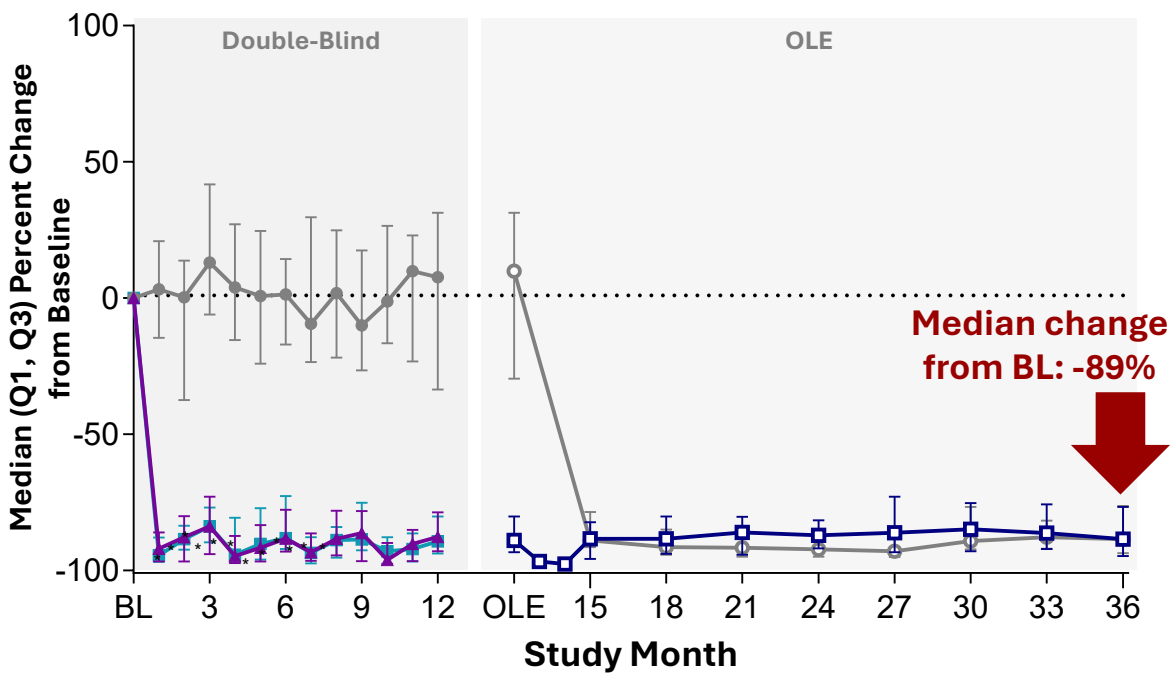
PLOZASIRAN TG AND APOC3 RESPONSE PERSISTED THROUGH 24 MONTHS IN THE OLE



Median Triglycerides



Median APOC3



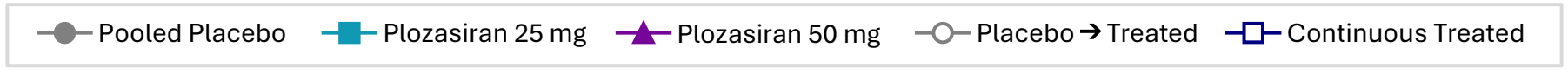
57% of patients achieved TG<880 mg/dL | **48% of patients achieved TG<500 mg/dL**

*P<0.0001; †P<0.05.

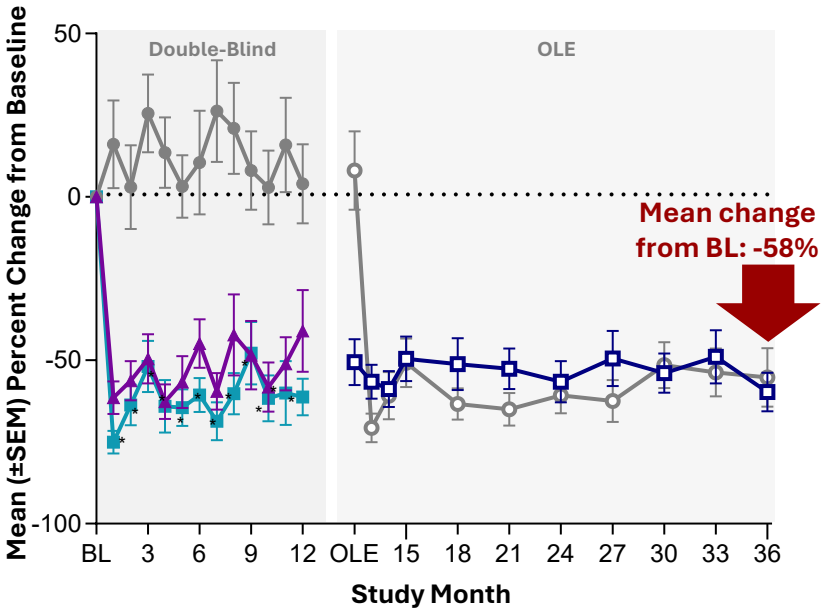
APOC3, apolipoprotein C3; **BL**, baseline; **OLE,** open-label extension; **Q1, Q3,** interquartile range; **RCT,** randomized controlled trial; **TG,** triglyceride.

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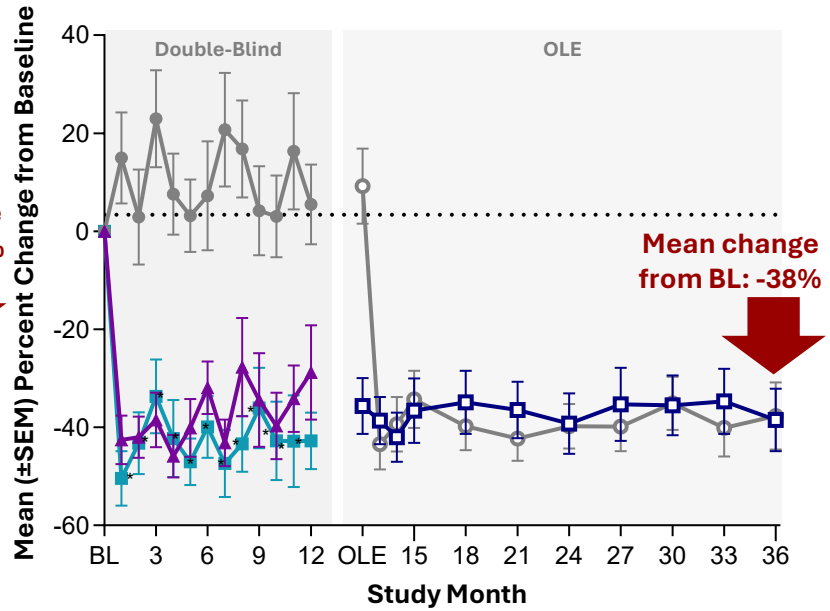
PLOZASIRAN REDUCED REMNANT CHOLESTEROL AND NON-HDL CHOLESTEROL LEVELS OVER 24 MONTHS IN THE OLE



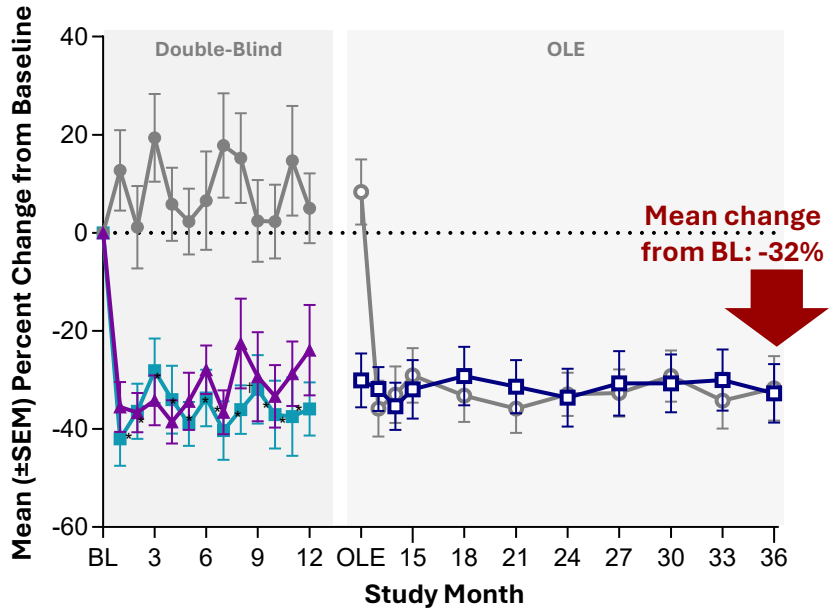
Remnant Cholesterol (UC)



Non-HDL-C



Total Cholesterol

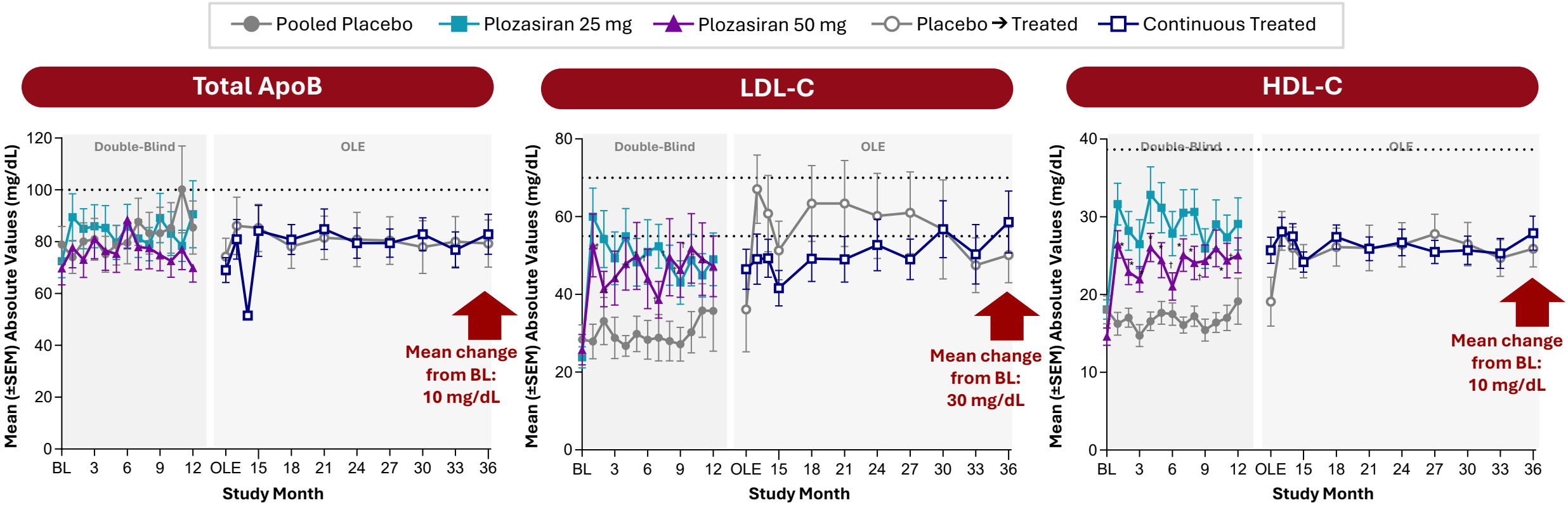


*P<0.0001; †P<0.05.

BL, baseline; **HDL,** high-density lipoprotein; **HDL-C,** high-density lipoprotein cholesterol; **OLE,** open-label extension; **RCT,** randomized controlled trial; **SEM,** standard error of mean; **UC,** ultracentrifuge.

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PLOZASIRAN DID NOT SIGNIFICANTLY INCREASE TOTAL APOB LEVELS



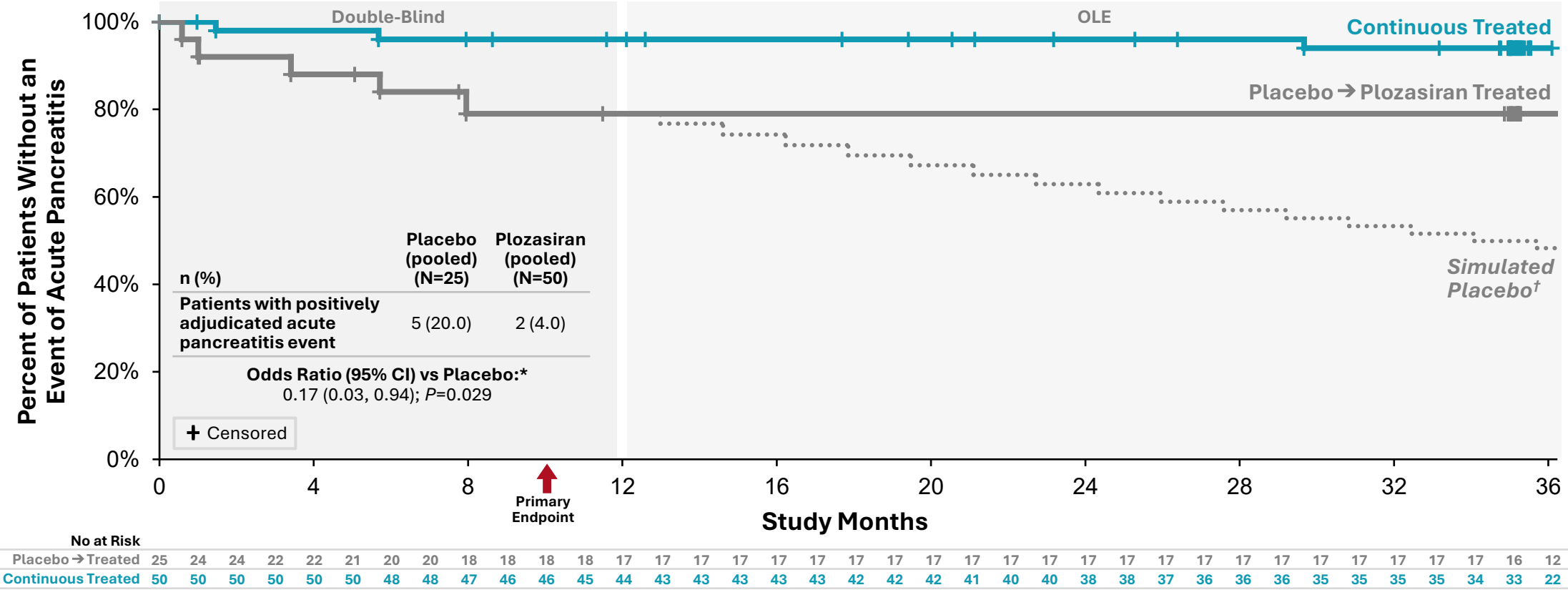
*P<0.0001; †P<0.05.

ApoB, apolipoprotein B; **BL**, baseline; **HDL-C,** high-density lipoprotein cholesterol; **LDL-C,** low-density lipoprotein cholesterol; **OLE,** open-label extension; **RCT,** randomized controlled trial; **SEM,** standard error of mean.

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PLOZASIRAN REDUCED THE RISK OF ACUTE PANCREATITIS, WITH ONLY ONE INCIDENT EVENT DURING THE OLE

Time to First Pancreatitis Event



No at Risk

Placebo → Treated	25	24	24	22	22	21	20	20	18	18	18	18	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	16	12
Continuous Treated	50	50	50	50	50	50	48	48	47	46	46	45	44	43	43	43	43	43	42	42	42	41	40	40	38	38	37	36	36	36	35	35	35	35	34	33	22

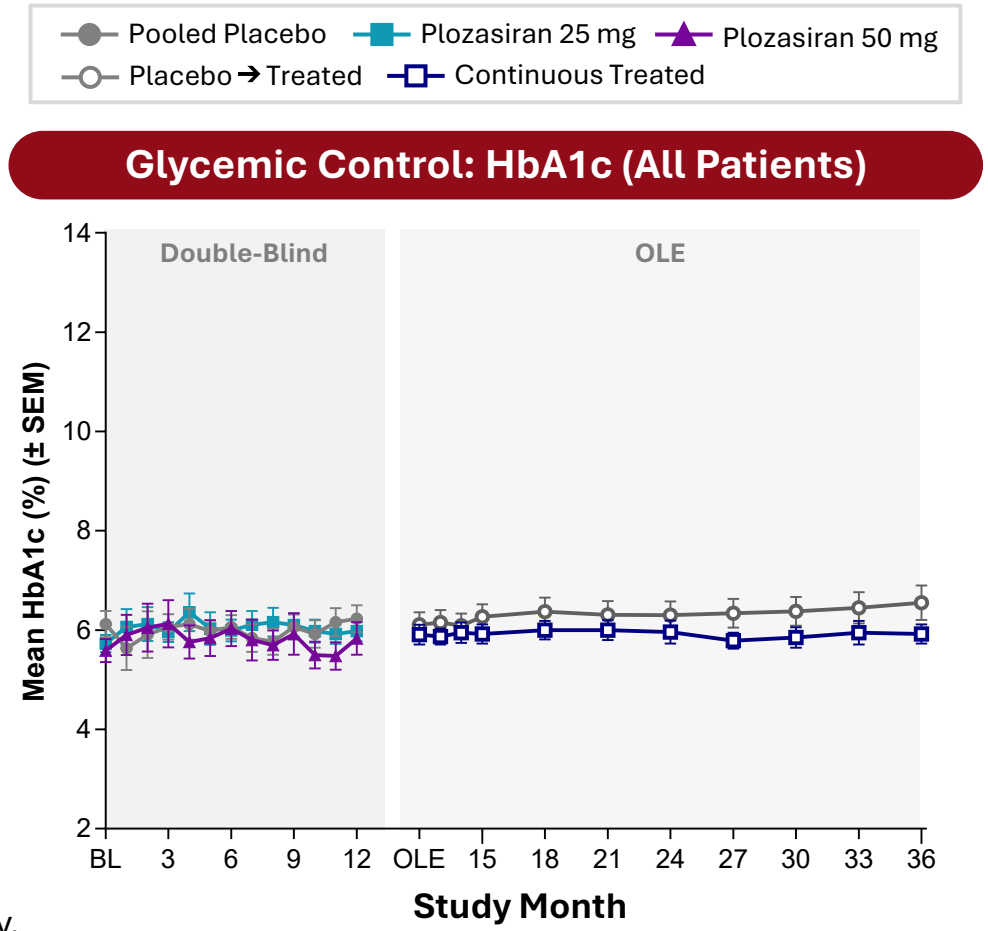
*Odds ratio, 95% CI, and P-value were based on CMH test stratified by baseline TG category. †The extrapolated curve shows predicted results if participants had continued receiving placebo in the OLE study. AP event probabilities for the 'placebo group', had they not switched to 'placebo to plozasiran 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. 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 1 AP event occurred in the plozasiran continuous treated group 1/44 (2.3%), this was a mild case of adjudicated AP. The overall AP event rate (frequency of events) in the OLE is 3/61=5%.

AP, acute pancreatitis; **CI,** confidence interval; **CMH,** Cochran-Mantel-Haenszel; **OLE,** open-label extension; **TG,** triglyceride.

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OVERALL SAFETY SUMMARY OLE (2-YEAR DATA)*: CONSISTENT WITH PRIOR STUDIES OBSERVATIONS

OLE, n (%)	Plozasiran 25mg (N=63)
All TEAEs*	49 (78)
Most common (>5%)	
Upper respiratory tract infection	9 (14)
Anemia	5 (8)
Abdominal pain upper	5 (8)
HbA1c increased	5 (8)
Cough	5 (8)
Diarrhea	4 (6)
COVID-19	4 (6)
Back pain	4 (6)
Dizziness	4 (6)
Treatment-related TEAEs	12 (19)
Serious TEAEs	7 (11)
TEAEs leading to study drug discontinuation	3 (5)†
Deaths	1 (2)‡



No clinically meaningful laboratory findings, including hematologic, hepatic, or renal toxicity, were considered related to plozasiran; no cases meeting Hy's law criteria were identified

*Regardless of causality. AEs are summarized up to each individual subject's 2-year OLE data; All anemia AEs were reported as mild or moderate and were assessed by PI and Sponsor as unrelated to plozasiran. †Subjects who discontinued from OLE due to AE: 1 withdrawal by subject (elevated A1C), 1 physician decision due to AE (elevated A1C) and 1 arrhythmia. ‡Death due to cardiac arrhythmia: Concomitant use of multiple antipsychotics associated with increased arrhythmia risk, assessed by Investigator and Sponsor as unrelated to plozasiran.

AE, adverse event; **HbA1c,** glycosylated hemoglobin; **OLE,** open-label extension; **SEM,** standard error of the mean; **TEAE,** treatment emergent adverse event.

CONCLUSIONS

- Quarterly dosed plozasiran significantly reduced median TGs by 76% in patients with FCS through 24 months in the OLE
  - 57% of patients reached TG<880 mg/dL and 48% reached TG<500 mg/dL at 24 months
- No clinically meaningful adverse changes in ApoB in the OLE
- Plozasiran reduced the risk of AP, with only one incident event during the OLE
- Safety and tolerability in the OLE were consistent with previous observations

24-month open-label treatment (up to 36 months of total treatment) with plozasiran resulted in sustained TG reductions from baseline and a safety profile consistent with the trial's randomized phase

AP, acute pancreatitis; **ApoB,** apolipoprotein B; **FCS,** familial chylomicronemia syndrome; **OLE,** open-label extension; **TG,** triglycerides.

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A RANDOMIZED, PLACEBO-CONTROLLED PHASE 3 STUDY OF PLOZASIRAN IN PATIENTS WITH FAMILIAL CHYLOMICRONEMIA SYNDROME: PALISADE – OPEN LABEL EXTENSION

Gerald F. Watts[1]; Robert S. Rosenson[2]; Robert A. Hegele[3]; Ira J. Goldberg[4]; Antonio Gallo[5]; Ann Mertens[6]; Alexis Baass[7]; Ran Fu[8]; Lalitha Aiyer[8]; Nicholas J. Leeper[9]; Jennifer Hellawell[8]; Daniel Gaudet[10]

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