Plozasiran Across a Spectrum of Hypertriglyceridemia: Final Long-term Efficacy and Safety Results from an Open-label Extension Study

SHASTA-2 MUIR

POSTER 1006-03

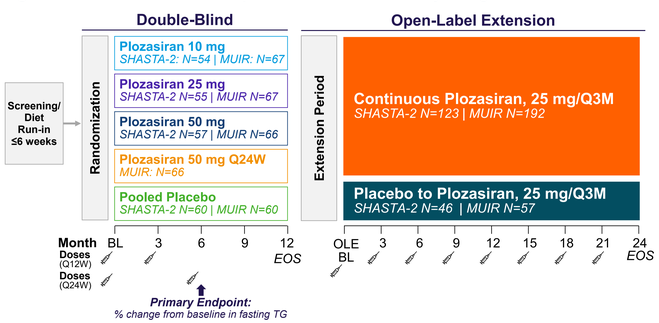
Christie M. Ballantyne[1], Gerald F. Watts[2], Robert S. Rosenson[3], Szilárd Vasas[4], Denes Pall[5], Peter Clifton[6], Stephen Nicholls[7], Ran Fu[8], Stacey Melquist[8], Jennifer Hellawell[8], Daniel Gaudet[9]

[1]The Texas Heart Institute, at Baylor College of Medicine, Houston, TX, USA; [2]School of Medicine, University of Western Australia and Department of Cardiology, Royal Perth Hospital, Perth, Australia; [3]Metabolism and Lipids Program, Mount Sinai Fuster Heart Hospital, Icahn School of Medicine at Mt Sinai, Mount Sinai, New York, NY, USA; [4]Borbanya Praxis Kft.; Nyiregyhaza, Hungary; [5]Department of Medical Clinical Pharmacology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary; [6]Royal Adelaide Hospital; Adelaide, South Australia; [7]Victorian Heart Institute, Monash University, Melbourne, VIC, Australia; [8]Arrowhead Pharmaceuticals, Pasadena, CA, USA; [9]ECOGENE-21 and Dept of Medicine, Université de Montréal, QC, CA

INTRODUCTION

- Hypertriglyceridemia is highly prevalent and clinically heterogeneous, conferring risk for acute pancreatitis at severe triglyceride levels (>500 mg/dL) and increased ASCVD risk across moderate elevations (>150-499 mg/dL) due to atherogenic triglyceride-rich lipoproteins [1,2]
- Apolipoprotein C-III (APOC3) is a key regulator of TRL metabolism, impairing LPL-dependent and independent metabolism and clearance; genetic loss-of-function variants are associated with lower TGs and reduced CV and AP risk, supporting APOC3 as a therapeutic target [3-5]
- Plozasiran, a hepatocyte-targeted GalNAc-conjugated siRNA, selectively reduces APOC3 expression and has demonstrated robust TG and atherogenic lipoprotein reductions across a spectrum of HTG phenotypes (severe and mixed phenotypes), including LPL-independent settings [6,7]
- Prior randomized phase 2b trials (SHASTA-2 and MUIR) established short-term efficacy and safety of plozasiran in sHTG and HTG; however, long-term durability and safety data have been limited [8,9]
- This analysis reports 2-year open-label extension results evaluating the long-term efficacy, safety, and tolerability of plozasiran 25 mg Q3M across mild-to-severe HTG populations

Figure 1. SHASTA-2 and MUIR Open-Label Extension Study Designs



OLE Primary Endpoint	OLE Secondary Endpoints	OLE Exploratory Endpoints	OLE Exploratory Safety Endpoints
Incidence of TEAEs through end-of-study	Change in TGs, ApoC3, non-HDL-C, HDL-C, total ApoB, and LDL-C	Change in total chol, VLDL-C, ApoB-48, ApoB-100, adjudicated AP events	Change in fasting glucose and HbA1c

Table 1. Baseline Characteristics

	SHASTA-2		MUIR	
Demographics/Characteristic	Placebo to Plozasiran (N=46)	Continuous Plozasiran (N=123)	Placebo to Plozasiran (N=57)	Continuous Plozasiran (N=192)
Age (years), mean (SD)	56.4 (10.8)	55.8 (11.2)	60.5 (10.1)	63.3 (11.0)
Male, n (%)	33 (71.7)	97 (78.9)	32 (56.1)	108 (56.3)
Race, White, n (%)	42 (91.3)	111 (90.2)	51 (89.5)	178 (92.7)
BMI (kg/m^2), mean (SD)	30.3 (3.7)	31.7 (4.6)	30.7 (5.5)	32.1 (6.4)
TGs, mg/dL, median (Q1, Q3)	735.9 (551.0, 885.3)	684.7 (549.8, 1057.0)	231.0 (196.9, 279.9)	228.3 (184.2, 309.9)
ApoC-III, mg/dL, mean (SD)	32.6 (16.6)	33.9 (16.4)	15.0 (4.8)	15.3 (5.50)
HDL-C, mg/dL, mean (SD)	28.6 (11.5)	29.4 (10.5)	41.4 (10.9)	43.4 (11.9)
Non-HDL-C, mg/dL, mean (SD)	187.0 (81.5)	211.1 (91.9)	147.0 (40.9)	152.1 (47.3)
VLDL-C (calc), mg/dL, mean (SD)	122.4 (85.0)	138.9 (100.3)	47.9 (16.7)	49.7 (21.5)
LDL-C (Martin-Hopkins), mg/dL, median (Q1, Q3)	79.0 (48.0, 114.0)	93.5 (60.0, 128.0)	103.0 (84.0, 125.0)	107.0 (84.5, 142.5)
ApoB, mg/dL, mean (SD)	95.4 (29.6)	107.1 (47.7)	102.0 (27.6)	102.1 (26.0)
Receiving statins, n (%)	33 (71.7)	84 (68.3)	55 (96.5)	177 (92.2)
Type 2 diabetes, n (%)	29 (63.0)	63 (51.2)	26 (45.6)	107 (55.7)
Receiving GLP-1R agonists, n (%)	5 (10.9)	23 (18.7)	6 (10.5)	18 (9.4)

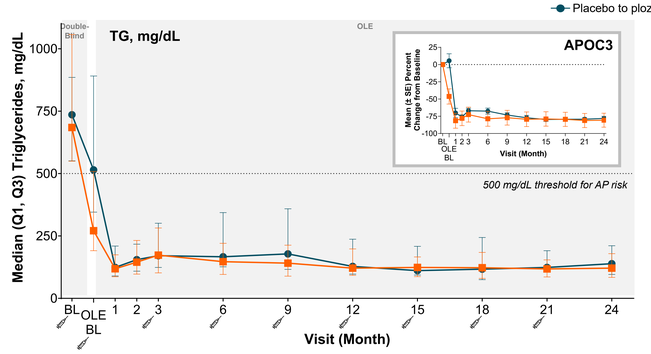
Mean TG value at the parent study baseline is defined as the geometric mean of the last 2 non-missing values prior to the first dose or the last non-missing value prior to the first dose if only a single value is available in the parent study. For other lipid related parameter, Parent Study Baseline is defined as the last non-missing predose value in the parent study (this includes unscheduled visits). If the measured value at baseline visit is below the limit of quantification, then the baseline APOC3 will be missing.

RESULTS

Figure 2. Median absolute values in TG in SHASTA-2 and MUIR OLE

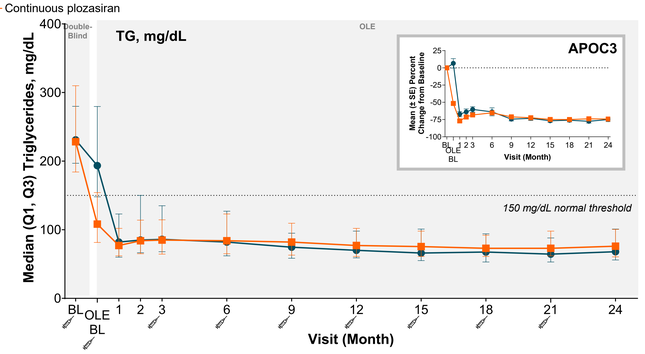
In SHASTA-2, median TG continued to fall by -83 % (-89.5, -73.5)*

96% of patients achieved TG <500 mg/dL and 63% of patients achieved TG <150 mg/dL*



In MUIR, median reductions in TG of -67 % (-73.8, -56.2)*

93% of patients achieved TG <150 mg/dL*



All graphs show median (Q1,Q3) levels or mean (±SE)% change from baseline (inset). Syringe represents dosing schedule. *Relative to Baseline, at Month 24 OLE

Figure 3. Percent Change From Baseline in Lipoproteins in SHASTA-2 and MUIR OLE

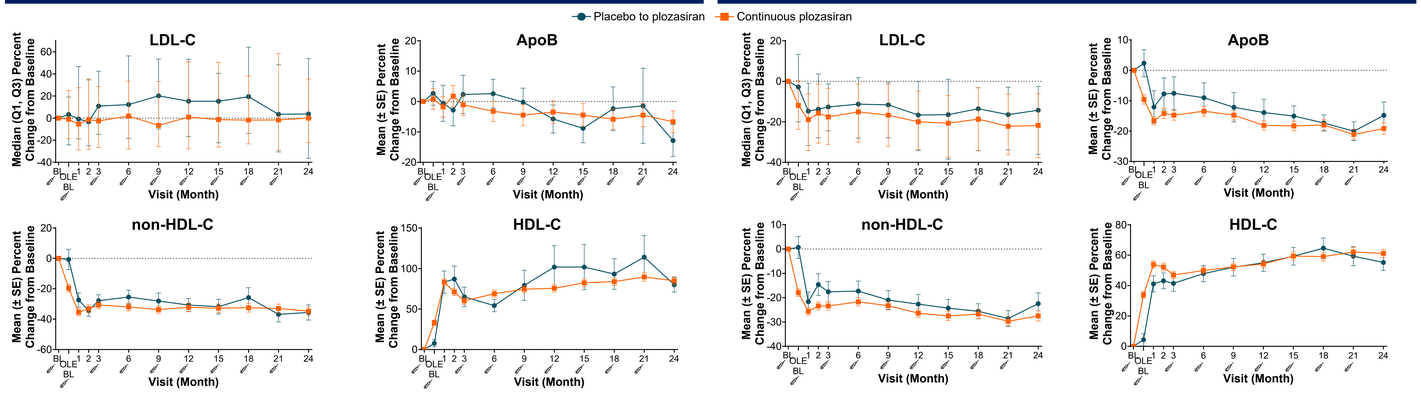
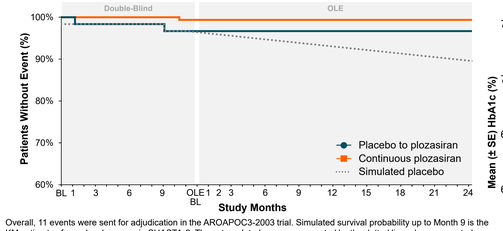


Figure 4. Kaplan-Meier Plot of Time to First Adjudicated AP Event in the OLE

SHASTA-2

Lower rates of AP events were observed with longer duration of plozasiran treatment



Overall, 11 events were sent for adjudication in the AROAPOC3-2003 trial. Simulated survival probability up to Month 9 is the KM estimates from placebo group in SHASTA-2. The extrapolated curve, represented by the dotted line, 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 of a constant hazard rate, that is, we assume patients continue experiencing events at a constant rate post-SHASTA.

Figure 5. Safety Consistent With Index Studies, Including No Clinically Meaningful Changes in HbA1c or Liver Function

SHASTA-2 + MUIR

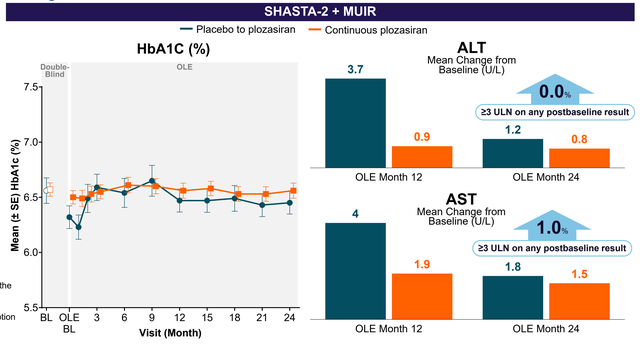


Table 2. Summary of OLE Safety Findings

SHASTA-2 + MUIR, n (%)	Plozasiran Pooled (N=418)
All TEAEs	310 (74.2)
Type 2 diabetes mellitus	40 (9.6)
COVID-19	34 (8.1)
Diabetes mellitus	28 (6.7)
URTI	24 (5.7)
Back pain	22 (5.3)
Treatment-related TEAEs	72 (17.2)
Serious TEAEs	60 (14.4)
TEAEs leading to study drug discontinuation	26 (6.2)*
Deaths	2 (0.5)†

Data reported as n (%) TEAEs occurring >5%. *Drug discontinuations in the OLE due to: diabetes mellitus (9), type 2 diabetes mellitus (5), glycosylated hemoglobin increased (4), sudden cardiac death (1), bladder neoplasm (1), cholangiocarcinoma (1), colorectal cancer metastatic (1), small intestine adenocarcinoma (1), drug abuse (1), renal impairment (1), rash (1). †OLE deaths: sudden cardiac death, cholangiocarcinoma; were not deemed to be related to study drug.

CONCLUSIONS

Long-term treatment with 25 mg Q3M of plozasiran resulted in sustained and clinically meaningful reductions in TG across a broad spectrum of HTG, including severe and mixed phenotypes (-83% in sHTG and -67% in HTG), through 24 months.

Favorable and durable improvements in atherogenic lipoproteins (including Remnant-C, non-HDL-C, and ApoB) and minimal changes (including reductions) in LDL-C were observed, supporting the potential relevance of APOC3 silencing for both AP and ASCVD risk mitigation.

Majority of patients achieved TG levels below thresholds for AP risk or below normal thresholds, 96% of sHTG patients achieved TG <500 mg/dL and 63% of sHTG patients and 93% of HTG patients achieved TG < 150 mg/dL.

There was a reduction in AP events, with no APs occurring in both studies in the OLE.

Plozasiran demonstrated a consistent long-term safety and tolerability profile, with stable glycemic parameters, no clinically meaningful liver/renal function changes and no new safety signals.

DEFINITIONS

AE, adverse events; **AP**, acute pancreatitis; **ApoB**, apolipoprotein B; **ApoC-III**, apolipoprotein C3 gene; **ALT**, alanine aminotransferase; **APOC3,** apolipoprotein C3; **ASCVD**, atherosclerotic cardiovascular disease; **AST**, aspartate aminotransferase; **BMI**, body mass index; **BL,** baseline; **Calc**, calculated; **Chol**, cholesterol; **CV**, cardiovascular; **GLP-1R**, glucagon-like peptide-1 receptor; **HDL-C**, high-density lipoprotein cholesterol; **HTG**, hypertriglyceridemia; **LDL-C**, low-density lipoprotein cholesterol; **LDLR**, low-density lipoprotein receptor; **LPL**, lipoprotein lipase; **OLE**, open-label extension; **Q1, Q3**, interquartile range; **SD**, standard deviation; **SE**, standard error; **sHTG**, severe hypertriglyceridemia; **TEAEs**, treatment emergent adverse events; **TG**, triglyceride; **TRL**, triglyceride-rich lipoprotein; **URTI**, upper respiratory tract infection; **VLDL-C**, very-low-density lipoprotein cholesterol.

REFERENCES

1. Baass A, et al. *J Intern Med.* 2020;287(4):340-348. **2.** Chapman MJ, et al. *Atherosclerosis.* 2025;410:120529. **3.** Ginsberg HN, et al. *J Clin Invest.* 1986;78(5):1287-1295. **4.** Borén J, et al. *Front Endocrinol.* 2020;11:474. **5.** Gaudet D, et al. *N Engl J Med.* 2014;371(23):2200-2206. **6.** Watts GF, et al. *Nature Med.* 2023.10.1038. **7.** Gaudet D, et al. *NEJM Evid.* 2023;2(12): EVIDoa2200325.10.1056. **8.** Gaudet D, et al. *JAMA Cardiol.* 2024;9:620-630. **9.** Ballantyne CM, et al. *N Engl J Med.* 2024;391(10):899-912.

DISCLOSURES

CM Ballantyne reports grants and/or honoraria from Abbott Diagnostic, Akcea, Althera, Amarin, Amgen, Arrowhead, AstraZeneca, Denka Seiken, Esperion, Genentech, Gilead, Illumina, Ionis, Matinas BioPharma Inc, Merck, New Amsterdam, Novartis, Novo Nordisk, Pfizer, Regeneron, Roche Diagnostic, and Sanofi-Synthelabo. **GW Watts** reports grants and/or honoraria from Amgen, Novartis, Arrowhead, Esperion, Astrazeneca, Pfizer, Novo Nordisk, Silence Therapeutics, CSL Seqirus, and Sanofi-Regeneron. **RS Rosenson** reports grant/research support from (all paid to institution, not individual): Amgen, Arrowhead, Novartis, Eli Lilly, Regeneron; consulting fees from Amgen, Arrowhead, CRISPR Therapeutics, Eli Lilly, Lipigon, Novartis, Precision Biosciences, Regeneron, UltraGenyx, Verve; non-promotional speaking fee from Amgen and Kowa; other support from MediMergent, LLC (significant); and is an UpToDate, Inc. stock shareholder (significant). **D Pall,S Vasas** and **P Clifton** have no disclosures. **S Nicholls** reports grants and/or honoraria from Akcea, Amarin, Amgen, Anthera, Arrowhead Pharmaceuticals Inc, AstraZeneca, Boehringer Ingelheim, Cerenis, CSL Behring, Eli Lilly, Esperion, InfraReDx, LipoScience, The Medicines Company, Merck, New Amsterdam Pharma, Novartis, Omthera, Resverlogix, Roche, Sanofi-Regeneron, and Takeda. **D Gaudet** reports grants and/or honoraria from Alnylam, Amgen, Arrowhead, AstraZeneca, Boehringer-Ingelheim, CRISPR Therapeutics, Dalcor Pharma, Eli Lilly, Esperion, Ionis, Kowa, Novartis, Pfizer, Regeneron, Sanofi, Ultragenyx and Verve Therapeutics. **R Fu, S Melquist,** and **J Hellawell,** are current employees of Arrowhead Pharmaceuticals.

ACKNOWLEDGEMENTS

We would like to thank the patients and caregivers who participated in this study. We thank Nathalie Kertesz, PhD of Arrowhead Pharmaceuticals for writing and review; Saudha Parthasarathy, PhD of Innovation Communications Group for editorial support; and Heather Hartley-Thorne of Sephirus Communications for providing graphics support on behalf of Arrowhead Pharmaceuticals.

Full manuscript simultaneously published in AJPC

Download a copy of this poster at www.arrowheadmedicalaffairs.com/ ACC2026/1006-03