Baseline Characteristics and Rationale of the SHASTA-3 and SHASTA-4 Studies: Randomized, Double-Blind, Placebo-Controlled, Phase 3 Studies of Plozasiran in Patients with Severe Hypertriglyceridemia

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BACKGROUND

- Severe hypertriglyceridemia (sHTG) confers an increased risk of acute pancreatitis (AP) and atherosclerotic cardiovascular disease (ASCVD)[1-3]
- sHTG-associated AP is a substantial source of morbidity, mortality, reduced quality of life and financial burden to health care systems[4-6]
- Currently available therapeutic approaches for sHTG are often insufficient to reduce triglyceride (TG) levels and prevent AP[7]
- Plozasiran, an investigational small interfering ribonucleic acid (siRNA) therapeutic, inhibits hepatic production of apolipoprotein C3 (APOC3), a key regulator of lipoprotein lipase (LPL)-mediated TG metabolism and clearance[8]
- In a phase 2 study of sHTG patients [TG ≥500 mg/dL], plozasiran demonstrated durable reductions in TG levels of up to -80%, 12 weeks after the last dose, and 91% achieved a TG below 500 mg/dL (threshold of increased risk for AP)[8]
- The objective of the SHASTA-3 and SHASTA-4 trials will be to evaluate safety and efficacy of plozasiran with TG reductions including AP rates, in patients with sHTG[9-10]

REFERENCES

1. Hegele RA, et al. *Lancet Diabetes Endocrinol.* 2014;2(8):655-666. **2.** Scherer J, et al. *J Clin Gastroenterol.* 2014;48(3):195-203. **3.** Pejic RN, Lee DT. *J Am Board Fam Med.* 2006;19(3):310-316. **4.** Scherer J, et al. *J Clin Gastroenterol.* 2014;48(3):195-203. **5.** Jin M, et al. *J Clin Lipidol.* 2019;13 (6):947-953.e1. **6.** Yang AL, McNabb-Baltar J. *Pancreatology.* 2020;20(5): 795-800. **7.** Gaudet D, et al. *N Engl J Med.* 2014;371(23):2200-2206. **8.** Gaudet D, et al. *JAMA Cardiol.* 2024;9(7):620–630. **9.** SHASTA-3 Clinical Trial. ClinicalTrials.gov, NCT06347003. https://clinicaltrials.gov/study/NCT06347003. **10.** SHASTA-4 Clinical Trial. ClinicalTrials.gov, NCT06347016. https://clinicaltrials.gov/study/NCT06347016. **11**. Food and Drug Administration. Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products: Guidance for Industry (Draft). 2019. https://www.fda.gov/media/133660/download.

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STUDY DESIGN

- SHASTA-3 and SHASTA-4 are phase 3, randomized, double-blind, placebo-controlled, multi-center trials

Key Inclusion Criteria

- Prior sHTG diagnosis and fasting TG ≥500 mg/dL, at screening

Key Exclusion Criteria

- Use of any hepatocyte targeted siRNA treatments that target lipids and/or TGs within 1 year (except inclisiran at least 4 weeks prior to enrollment)
- siRNA or antisense oligonucleotide (ASO) use within 60 days
- Known familial chylomicronemia syndrome (FCS) diagnosis
- AP within 4 weeks of screening

Study Design Elements

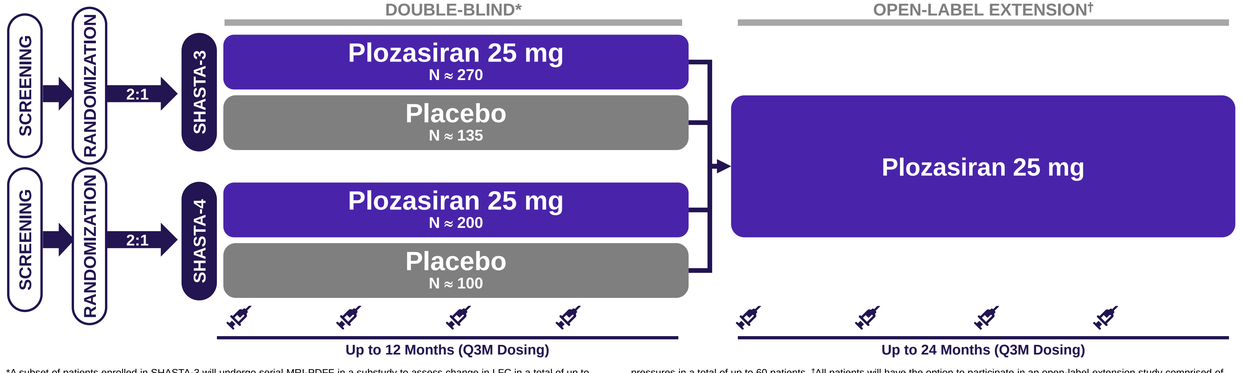
- Planned adult enrollment was 705, with multiple sites across multiple countries participating in two independent trials performed in accordance with regulatory guidance[11]
- Patients randomized 2:1 to receive 4 quarterly subcutaneous injections of plozasiran 25 mg or matching placebo over a 1-year double-blinded period, followed by post-treatment evaluation or entry into the open-label extension study
- The effect of plozasiran on other lipids and lipoproteins and inflammatory biomarkers as well as adjudicated major adverse cardiovascular event rates, safety and tolerability will be assessed

Primary Efficacy Endpoint

- Percent change in fasting serum TG levels from baseline to Month 12

Key Secondary Endpoints

- Percent change in fasting TG levels from baseline to month 10
- Proportion of patients achieving fasting TGs of <500 mg/dL and TGs of <150 mg/dL at month 12
- Percent change in remnant cholesterol (VLDL-C) and non-HDL-C from baseline to Month 12
- Adjudicated AP event rate from Day 1 to Month 12
- Frequency and severity of AEs and SAEs over time through Month 12



*A subset of patients enrolled in SHASTA-3 will undergo serial MRI-PDFF in a substudy to assess change in LFC in a total of up to 60 patients with screening liver fat fraction ≥8% prior to randomization and at screening and Month 12 at sites where MRI-PDFF testing is available. ABPM is a substudy of SHASTA-4 and will be conducted for the evaluation of changes in systolic and diastolic blood pressures in a total of up to 60 patients. †All patients will have the option to participate in an open-label extension study comprised of patients from both studies. Patients who opt out of the OLE will have an additional 3-month follow-up visit at Month 15.

CONCLUSIONS

SHASTA-3 and SHASTA-4 are designed to determine whether the quarterly-dosed APOC3 siRNA plozasiran, added to standard of care, safely reduces TG levels in patients with sHTG.

Baseline Parameters

	SHASTA-3 (N=446)	SHASTA-4 (N=311)	SHASTA-3 + SHASTA-4 (N=757)
Age (Years), mean (SD)	51.9 (11.7)	53.2 (11.6)	52.4 (11.7)
Sex at birth, male n (%)	369 (82.7)	229 (73.6)	598 (79.0)
Race, n (%)			
White	331 (74.2)	271 (87.1)	602 (79.5)
Asian	99 (22.2)	17 (5.5)	116 (15.3)
Black or African American	3 (0.7)	13 (4.2)	16 (2.1)
Other	17 (3.8)	13 (4.2)	30 (3.9)
Ethnicity, n (%)			
Hispanic or Latino	91 (20.4)	60 (19.3)	151 (19.9)
Not Hispanic or Latino	354 (79.4)	249 (80.1)	603 (79.7)
Region, n (%)			
North America	128 (28.7)	120 (38.6)	248 (32.8)
Europe	179 (40.1)	142 (45.7)	321 (42.4)
Asia	85 (19.1)	0 (0.0)	85 (11.2)
Other	54 (12.1)	49 (15.8)	103 (13.6)
BMI (kg/m²), mean (SD)	30.5 (5.2)	31.5 (5.1)	30.9 (5.1)
TG at screening (mg/dL)*			
Mean (SD)	945.3 (535.4)	995.5 (672.4)	965.9 (595.6)
Median (Q1, Q3)	758.5 (597.5, 1095.0)	730.0 (588.5, 1119.0)	741.5 (594.5, 1104.5)
TG at baseline (mg/dL)*			
Mean (SD)	809.0 (491.3)	941.2 (667.0)	863.3 (573.3)
Median (Q1, Q3)	657.2 (516.1, 950.3)	725.5 (544.6, 1094.9)	677.8 (530.9, 1012.5)
TG ≥880 mg/dL, n (%)	164 (36.8)	119 (38.3)	283 (37.4)
ApoC-III (mg/dL), mean (SD)†	32.2 (15.3)	36.4 (17.2)	33.9 (16.2)
non-HDL-C (mg/dL), mean (SD)†	176.3 (72.4)	194.2 (86.3)	183.7 (78.8)
HDL-C (mg/dL), mean (SD)†	28.8 (10.8)	28.0 (10.9)	28.5 (10.9)
LDL-C (UC) (mg/dL), mean (SD)†	66.5 (32.8)	62.5 (31.8)	64.9 (32.4)
ApoB (mg/dL), mean (SD)†	97.2 (27.3)	99.1 (26.6)	98.0 (27.0)
HbA1c (%), mean (SD)‡	6.4 (1.1)	6.5 (1.1)	6.5 (1.1)
Lipid lowering therapy, n (%)	430 (96.4)	297 (95.5)	727 (96.0)
Statin	298 (66.8)	226 (72.7)	524 (69.2)
Fibrate	278 (62.3)	180 (57.9)	458 (60.5)
Omega-3 fatty acid	65 (14.6)	42 (13.5)	107 (14.1)
Ezetimibe	109 (24.4)	64 (20.6)	173 (22.9)
PCSK9 inhibitor	20 (4.5)	9 (2.9)	29 (3.8)
Niacin	8 (1.8)	3 (1.0)	11 (1.5)
Other lipid lowering therapies	61 (13.7)	54 (17.4)	115 (15.2)
≥2 therapies	281 (63.0)	198 (63.7)	479 (63.3)
Medical History			
Diabetes mellitus	273 (61.2)	195 (62.7)	468 (61.8)
Hypertension	277 (62.1)	219 (70.4)	496 (65.5)
Coronary artery disease	29 (6.5)	32 (10.3)	61 (8.1)
Pancreatitis	90 (20.2)	65 (20.9)	155 (20.5)

*Mean TG at screening is defined as the arithmetic mean of the last 2 fasting TG level collected during the screening period. For fasting TG levels, baseline is defined as the average (ie, geometric mean) of Day 1 predose assessment, and the last fasting TG level collected during the screening period. †For non-triglyceride lipid-related, lipoprotein, and serum PD assessments, baseline is defined as the predose value on Day 1. If Day 1 or as otherwise specified values are erroneous or not available and repeat blood draw is not possible, the screening value may be used as baseline. ‡For HbA1c, baseline is defined as the worst value measured during screening and Day 1. **ApoB,** apolipoprotein B; **BMI,** body mass index; **HDL-C,** high density lipoprotein cholesterol; **LDL-C,** low density lipoprotein cholesterol; **NA,** not applicable; **non-HDL-C,** non-high density lipoprotein cholesterol; **Q1,** 1st quartile; **Q3,** 3rd quartile; **SD,** standard deviation; **TG,** triglycerides; **UC**, ultracentrifugation.

For medical inquiries or questions related to this poster, contact: medinfo@arrowheadpharma.com

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