Poster #57

SHASTA-5 Rationale and Design: Randomized, Double-Blind, Placebo-Controlled Outcomes Study to Evaluate Plozasiran Efficacy For Reduction of Pancreatitis Risk

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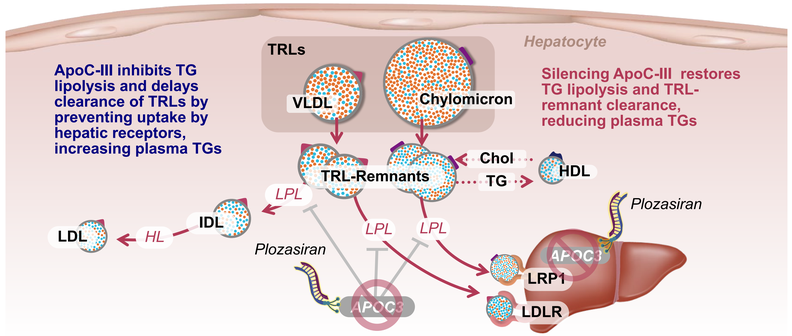
BACKGROUND

- SHTG is a disorder characterized by marked elevations in TG levels and confers an increased risk of AP.
- AP risk correlates with severity of TG elevation and increases with prior history of AP, especially if recent. TG-induced AP can be associated with substantial morbidity, mortality, reduced quality of life and burden to health care systems.[1,2]
- Traditional TG therapies provide modest TG reductions and have not been shown to reduce AP risk in SHTG.[3]
- Plozasiran, an investigational siRNA, inhibits hepatic production of APOC3, a key regulator of LPL-mediated TG metabolism and clearance.

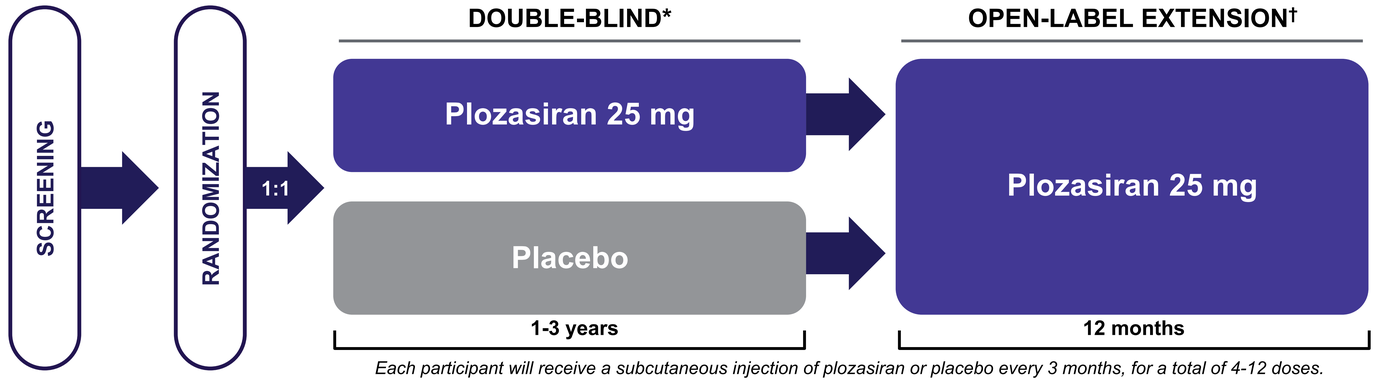
Figure 1. Impact of Plozasiran on Triglycerides and Lipoprotein Metabolism



- In a phase 2 study of severe hypertriglyceridemia (sHTG) patients, TG 500-4000 mg/dL, plozasiran demonstrated durable reductions in TG levels of approximately -80% and in the majority of patients, decreased circulating TG below 500 mg/dL, the threshold for increased risk for AP.[4,5] Also, in a phase 3 study (PALISADE) in FCS, plozasiran was associated with similar reductions from baseline in TG levels with a statistically significant reduction in confirmed, adjudicated AP events.
- SHASTA-5 is an outcomes trial designed to demonstrate reduction in AP in adults with sHTG at high risk of AP.

METHODS

- SHASTA-5 is a randomized, double-blind, placebo-controlled, multi-center outcomes trial.
- Patients will agree to dietary counseling, maintaining a stable low-fat diet and receiving lipid-lowering medications throughout the study.
- In this global time-to-first event study, approximately 140 patients will be randomized 1:1 to receive plozasiran 25 mg subcutaneous dose quarterly or matching placebo with maximum expected follow up of 3 years followed by an optional open label extension.
- Randomization will be stratified based on number of documented AP events within 1-year of screening and baseline TG levels (≥2000 mg/dL vs <2000 mg/dL).



Each participant will receive a subcutaneous injection of plozasiran or placebo every 3 months, for a total of 4-12 doses.

*Target enrollment is 140 patients in 14 countries. Anticipated enrollment period is 2 years. †Participants that experience an AP event will transition into open label extension (1 year). All other participants will transition to OLE when target number of AP events are reached.

Key Eligibility Criteria

- Adults (≥18yo) with mean fasting TG level ≥1000 mg/dL (≥11.3 mmol/L) at 2 separate consecutive visits, at least 7 and no more than 17 days apart during the screening period
- At least 2 prior documented AP events not attributed to other causes, at least one in the 12 months prior to screening
- Agree to dietary counseling and maintaining a stable low-fat diet, and receiving SOC lipid-lowering medications per local guidelines, unless intolerant
- No use of any hepatocyte-targeted siRNA that targets lipids and/or TGs within 365 days of Day 1, except inclisiran; no use of any other hepatocyte-targeted siRNA or ASO within 60 days or 5 half-lives of Day 1 based on plasma PK, whichever is longer

Primary Endpoint

Time to first occurrence of positively-adjudicated* AP event compared with placebo during the double-blind treatment period

Key Secondary & Safety Endpoints

- Percent change in fasting TG levels from baseline to Month 12 compared with placebo
- Proportion of patients who achieve average fasting TG of <880 mg/dL (<10 mmol/L) from Month 3 to the end of double-blind treatment period
- Achievement of average fasting TG of <500 mg/dL (<5.65 mmol/L) and <800 mg/dL (<10 mmol/L) from Month 3 to end of double-blind treatment period
- Time to first major abdominal pain event† occurring >10 days after first dose of study drug compared with placebo
- Change from baseline in patient-reported productivity and activity impairment (WPAI-SHP score) and health status (EQ-5D-5L score)

Positively adjudicated: confirmed by a blinded, independent committee (Abdominal Events Adjudication Committee) according to the Atlanta classification of AP[6] and as outlined in the Abdominal Events Adjudication Committee Charter. Potential events of AP will be categorized as one of the following: Documented AP; Probable AP; Possible AP; Unable to adjudicate; No pancreatitis/other etiology. The criteria for each category will be defined in a separate Abdominal Events Adjudication Committee Charter. For the purpose of the analysis, events adjudicated as documented, probable or possible AP are to be considered positively adjudicated.†Major abdominal pain event defined as adjudicated AP, adjudicated presentation to ER and/or hospitalization with severe abdominal pain not attributed to other etiologies, or need for apheresis.

DISCLOSURES

PM Moriarty reports Research for Amgen, Kowa, Lilly, Novartis, Sanofi, Regeneron, Genzyme, Pfizer, Catabasis, Espirion, B. Braun, and Kaneka; Consultant for Regeneron, Duke Clinical Research Institute, Lilly, Catabasis, B Braun, Kaneka, and Genzyme. **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. **S Romeo** reports consulting AstraZeneca, Novartis, AMGEN, Sanofi, Ribocure Ab **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** and **J Hellawell** are current employees of Arrowhead Pharmaceuticals.

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Download a copy of this poster at www.arrowheadmedicalaffairs.com/NLA2025/SHASTA-5

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ABBREVIATIONS

AP, acute pancreatitis; **Apo A-1**, apolipoprotein A-1; **ApoB**, apolipoprotein B; **ApoC-III**, apolipoprotein C3 gene; **APOC3**, apolipoprotein C3; **Chol**, cholesterol; **EQ-5D-5L**, EuroQol 5-dimension instrument; **ER**, emergency room; **HbA1c**, hemoglobin A1c; **HDL**, high-density lipoprotein; **HL**, hepatic lipase; **HTG**, hypertriglyceridemia; **IDL**, intermediate-density lipoprotein; **LDL**, low-density lipoprotein; **LDLR**, low-density lipoprotein receptor; **LPL**, lipoprotein lipase; **LRP1**, low-density lipoprotein receptor-related protein 1; **SHTG**, Severely high hypertriglyceridemia; **SOC**, standard of care; **TG**, triglyceride; **TRL**, triglyceride-rich lipoprotein; **VLDL**, very low-density lipoprotein; **WPAI-SHP**, Work Productivity and Activity Impairment Questionnaire: Specific Health Problem.