Rationale and Design of the MUIR-3 Study: Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Plozasiran in Adults with Hypertriglyceridemia

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BACKGROUND

- Hypertriglyceridemia (HTG) confers an increased risk of Atherosclerotic cardiovascular disease (ASCVD). ASCVD is the leading cause of mortality worldwide. Elevated triglyceride rich lipoproteins (TRL) are an established risk factor for ASCVD and a target for prevention of major adverse cardiovascular events (MACE)[1,2]
- Apolipoprotein C3 (APOC3) is an important key regulator of triglyceride (TG) metabolism; patients with HTG typically have increased APOC3 levels due to elevation of TRL carrying APOC3 [3-4]
- Small interfering RNAs (siRNA) have advantages such as high specificity and potent activity, and reversibility and have a generally good side-effect profile, features that often allow for durable gene silencing with infrequent dose administration[5]
- Plozasiran is an investigational N-acetylgalactosamine (GalNAc)-conjugated siRNA therapeutic, which inhibits hepatic production of apolipoprotein C3 (APOC3), a key regulator of lipoprotein lipase (LPL)-mediated TG metabolism and clearance through LPL-dependent and independent mechanisms[5,6]
- In a phase 2 study in patients with mixed hyperlipidemia (defined as TG 150 to 499 mg/dL and non-HDL >100 mg/dL or LDL >70 mg/dL), plozasiran demonstrated durable TG reductions of -62% vs placebo, measured 12 weeks after the last dose[7]

OBJECTIVE

- MUIR-3 will evaluate the efficacy and safety of plozasiran in patients with moderate HTG

METHODS

- MUIR-3 is a phase 3, randomized, double-blind, placebo-controlled, multi-center trial

KEY INCLUSION CRITERIA

- Mean fasting TG ≥150 mg/dL and ≤499 mg/dL at screening

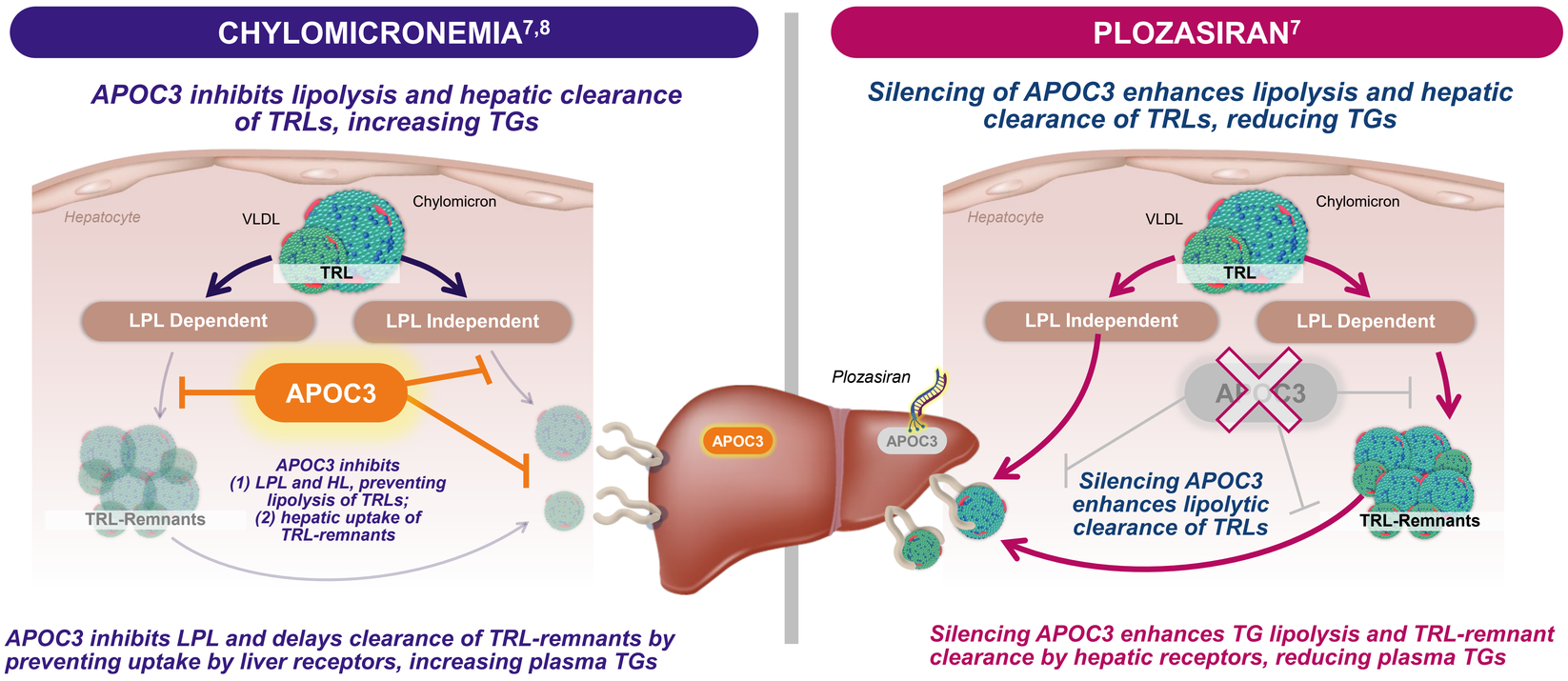
KEY EXCLUSION CRITERIA

- siRNA or ASO use within 60 days or use of any hepatocyte-targeted siRNA treatments that target lipids and/or TG within 1 year (except inclisiran at least 4 weeks prior to enrollment)
- Active acute pancreatitis within 4 weeks of screening
- Body mass index >45 kg/m^2

CONCLUSIONS

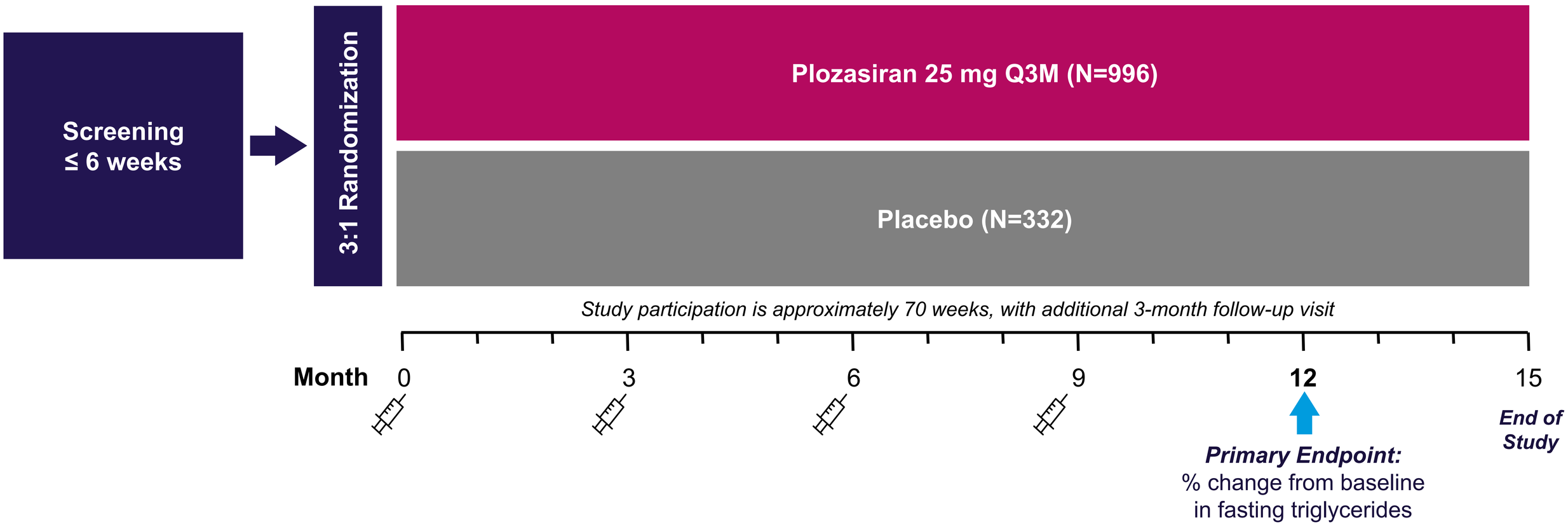
MUIR-3 is designed to determine whether the APOC3 siRNA plozasiran, as an add on to standard of care lipid lowering therapy, safely reduces TG levels thereby contributing to decreasing the residual cardiovascular disease risk in individuals with HTG

Figure 1. Plozasiran (ARO-APOC3) is an Investigational siRNA Therapeutic Targeting APOC3, a Key Regulator of TG and TRL Metabolism



STUDY DESIGN

- 1328 adult patients with HTG will be enrolled at multiple sites and countries and randomized 3:1 to receive four quarterly subcutaneous injections of plozasiran 25 mg or matching placebo over a 1-year double-blinded period, followed by a 3-month follow up post-treatment period evaluation
- The randomization will be stratified based on statin use at screening
- After informed consent, subjects will be assessed for eligibility during the 6-week screening period
- Enrolled subjects will be counseled to remain on the specified low-fat diet and background medications throughout the study
- **The primary efficacy endpoint** is placebo-adjusted % change in fasting TG from baseline to month 12 with plozasiran
- **Secondary endpoints** include placebo-adjusted % change in fasting TG from baseline to month 10 and the percentage of patients achieving fasting TG <150 mg/dL at 10 and 12 months compared to placebo
- Adjudicated MACE rates, safety and tolerability parameters will be assessed
- Percent changes in other lipid and lipoprotein parameters will also be assessed



REFERENCES

1. Ference BA, et al. *Eur Heart J*. 2017;38:2459-2472. **2.** Stone NJ, et al. *J Am Coll Cardiol*. 2014;63:2889-2934. **3.** Wyler von Ballmoos MC. *J Clin Lipidol.* 2015;9:498-510. **4.** Pollin TI, et al. *Science*. 2008;322:1702-1705**. 5.** Gaudet D, et al. *N Engl J Med Evid*. 2023;2(12):EVIDoa2200325. **6.** Gaudet D, et al. *JAMA Cardiol*. 2024;9(7): 620–630 **7.** Ballantyne CM. *N Engl J Med* 2024;391:899-912.**8.** Van Zwol W et al. *J Clin Med*. 2019; 8:1085.

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ABBREVIATIONS

APOC3, apolipoprotein C-III; **ASCVD**, atherosclerotic cardiovascular disease; **ASO**, antisense oligonucleotide; **GalNAc**, N-acetylgalactosamine; **HL**=hepatic lipase; **HTG**, hypertriglyceridemia; **LPL**, lipoprotein lipase; **MACE**, major adverse cardiovascular events; **Q3M**, every 3 months; **RNA**, ribonucleic acid; **siRNA**, small interfering RNA; **TG**, triglyceride; **TRL**, triglyceride rich lipoproteins; **VLDL**=very low-density lipoprotein.