Arrowhead Pharmaceuticals Announces New Phase 2 Data of Plozasiran Published in JAMA Cardiology and Presented at American College of Cardiology 73rd Annual Scientific Session & Expo

April 7, 2024

- Plozasiran reduced triglycerides and APOC3 up to a mean maximum of 86% and 90% respectively in patients with severe hypertriglyceridemia

- SHASTA-3 and SHASTA-4 Phase 3 studies to be initiated

PASADENA, Calif.--(BUSINESS WIRE)--Apr. 7, 2024--

Arrowhead Pharmaceuticals, Inc. (NASDAQ: ARWR) today presented final data from the double-blind treatment period of its Phase 2 SHASTA-2 study of investigational plozasiran (formerly ARO-APOC3) in patients with severe hypertriglyceridemia (SHTG). Results from the SHASTA-2 study showed dramatic, consistent, and sustained reductions in Apolipoprotein C-III (APOC3) and triglycerides and improvement in multiple atherogenic lipoprotein levels. These data were presented in a late-breaking oral presentation today at the American College of Cardiology 73rd Annual Scientific Session & Expo (ACC.24) in Atlanta and simultaneously published in the journal JAMA Cardiology.

“Promising results presented today at ACC.24 and simultaneously published in JAMA Cardiology showed that treatment with plozasiran in the SHASTA-2 study led to significant and sustained reductions in triglyceride levels below the threshold associated with elevated risk for pancreatitis. These are important and exciting data as patients with severe hypertriglyceridemia currently have limited treatment options,” said Daniel Gaudet, M.D., Ph.D., Professor of Medicine at Université de Montréal and Principal Investigator for the SHASTA-2 study.

Select SHASTA-2 Results

Treatment with plozasiran led to dose-dependent placebo-adjusted reductions in triglycerides (primary endpoint) of -49% ($P < 0.001$), -53% ($P < 0.001$), and -57% ($P < 0.001$), driven by placebo-adjusted reductions in APOC3 of -68% ($P < 0.001$), -72% ($P < 0.001$), and -77% ($P < 0.001$) at week 24, after receiving two doses of 10 mg, 25 mg, and 50 mg plozasiran, respectively. Mean maximum, non-placebo adjusted reductions from baseline in triglycerides and APOC3 were up to 86% and 90% and typically occurred around week 16 or week 20.

Significant and durable triglyceride and APOC3 reductions persisted to week 48, 36 weeks after the last dose. There was limited interpatient variability in pharmacodynamic response across all plozasiran treatment groups.

Among patients treated with plozasiran, 90.6% achieved a triglyceride level less than 500 mg/dL, the level associated with increased risk of acute pancreatitis, at week 24. In addition, 48.4% of patients achieved normal triglyceride levels of less than 150 mg/dL at week 24.

Subjects treated with plozasiran also showed improvements in multiple atherogenic lipid and lipoprotein levels, including remnant cholesterol, HDL-cholesterol, and non-HDL cholesterol.

Bruce Given, M.D., interim chief medical scientist at Arrowhead, added, “We continue to be encouraged by the full 48-week data from the SHASTA-2 study of plozasiran in patients with severe hypertriglyceridemia and as a result we are confidently advancing the program into multiple Phase 3 studies. We are pleased that over 90% of patients that received just two doses of plozasiran in the SHASTA-2 study achieved triglyceride levels below the level associated with increased risk of pancreatitis, and almost half of patients achieved triglyceride levels in the normal range, which is surprising given the high mean starting levels of almost 900 mg/dL. Two of Arrowhead’s planned Phase 3 studies are SHASTA-3 and SHASTA-4, which are both pivotal, year-long, placebo-controlled studies to evaluate the efficacy and safety of plozasiran in patients with severe hypertriglyceridemia, the same patient population as SHASTA-2. These studies are both on schedule to begin dosing over the coming months.”

Safety and Tolerability

Plozasiran demonstrated a favorable safety profile in the SHASTA-2 study. The adverse event and serious adverse event profile were similar across treatment groups. Observed adverse events generally reflected the comorbidities and underlying conditions of the study population. All serious treatment emergent adverse events were deemed not related to plozasiran. The most common events occurring in 5 or more patients were COVID-19 infection, worsening glycemic control, diarrhea, urinary tract infection, and headache.

Details about the ACC.24 presentation are listed below.

American College of Cardiology 73rd Annual Scientific Session & Expo – April 6-8, 2024

Title: **Plozasiran (ARO-APOC3), An Investigational RNAi Therapeutic, Demonstrates Profound and Durable Reductions in APOC3 and Triglycerides (TG) in Patients With Severe Hypertriglyceridemia (SHTG), SHASTA-2 Final Results**
Date/Time: April 7, 2024, 9:00 a.m. EDT
Presenter: Daniel Gaudet MD, PhD
Session: Late-Breaking Clinical Trials II

Slides from the late-breaking oral presentation at ACC.24 may be accessed on the Events and Presentations page under the Investors section of the Arrowhead website after the oral presentation concludes.

About SHASTA-2

SHASTA-2 (AROAPOC3-2001) is a double-blind, placebo-controlled Phase 2b study in adults with SHTG. Three dose levels of plozasiran (10 mg, 25 mg and 50 mg) were evaluated against placebo in 229 participants who had mean fasting triglycerides of greater than or equal to 500 mg/dL (5.65 mmol/L) at screening. Participants were randomly assigned in a 3:1 ratio to receive plozasiran or placebo. Each participant received subcutaneous injections on day 1 and week 12. The duration of the study was approximately 54 weeks from screening to the week 48 end-of-study examination. The primary objective of the study was to evaluate the safety and efficacy of plozasiran in adults with SHTG and to select a dosing regimen for later stage

clinical studies in this patient population.

About Severe Hypertriglyceridemia

Severe hypertriglyceridemia (SHTG) is characterized by triglyceride (TG) levels greater than 500 mg/dL[1-3]. Very severe forms (TG greater 880 mg/dl) include familial chylomicronemia syndrome (FCS) and multifactorial chylomicronemia syndrome (MCS)[4-6]. SHTG significantly increases the risk of atherosclerotic cardiovascular disease (ASCVD) and acute pancreatitis (AP), often with recurrent attacks requiring repeat hospital admissions and worsening outcomes[1-3,6]. AP risk is proportional to number, characteristics, and concentration of triglyceride rich lipoproteins (TRLs), particularly chylomicrons, and increases as TGs rise[7]. Limited treatment options exist to sustainably reduce TGs below the pancreatitis risk threshold[1-3].

About Plozasiran

Plozasiran, previously called ARO-APOC3, is a first-in-class investigational RNA interference (RNAi) therapeutic designed to reduce production of Apolipoprotein C-III (APOC3), which is a component of triglyceride rich lipoproteins (TRLs) and a key regulator of triglyceride metabolism. APOC3 increases triglyceride levels in the blood by inhibiting breakdown of TRLs by lipoprotein lipase and uptake of TRL remnants by hepatic receptors in the liver. The goal of treatment with plozasiran is to reduce the level of APOC3, thereby reducing triglycerides and restoring lipids to more normal levels.

In multiple clinical studies, investigational plozasiran demonstrated reductions in triglycerides and multiple atherogenic lipoproteins in patients with familial chylomicronemia syndrome (FCS), severe hypertriglyceridemia (SHTG), and mixed dyslipidemia (MD). Plozasiran has demonstrated a favorable safety profile to date with treatment emergent adverse events reported that reflect the comorbidities and underlying conditions of the study populations. Plozasiran is currently being investigated in the Phase 3 PALISADE clinical study in patients with FCS, which is on schedule to be completed in the middle of 2024. Phase 2 studies in patients with SHTG and MD, SHASTA-2 and MUIR respectively, are complete and additional Phase 3 studies are planned to begin shortly.

Plozasiran has been granted Orphan Drug Designation and Fast Track Designation by the U.S. Food and Drug Administration and Orphan Drug Designation by the European Medicines Agency.

About Arrowhead Pharmaceuticals

Arrowhead Pharmaceuticals develops medicines that treat intractable diseases by silencing the genes that cause them. Using a broad portfolio of RNA chemistries and efficient modes of delivery, Arrowhead therapies trigger the RNA interference mechanism to induce rapid, deep, and durable knockdown of target genes. RNA interference, or RNAi, is a mechanism present in living cells that inhibits the expression of a specific gene, thereby affecting the production of a specific protein. Arrowhead's RNAi-based therapeutics leverage this natural pathway of gene silencing.

For more information, please visit www.arrowheadpharma.com, or follow us on X (formerly Twitter) at @ArrowheadPharma or on LinkedIn. To be added to the Company's email list and receive news directly, please visit http://ir.arrowheadpharma.com/email-alerts.

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This news release contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. Any statements contained in this release except for historical information may be deemed to be forward-looking statements. Without limiting the generality of the foregoing, words such as "may," "will," "expect," "believe," "anticipate," "hope," "intend," "plan," "project," "could," "estimate," "continue," "target," "forecast" or "continue" or the negative of these words or other variations thereof or comparable terminology are intended to identify such forward-looking statements. In addition, any statements that refer to projections of our future financial performance, trends in our business, expectations for our product pipeline or product candidates, including anticipated regulatory submissions and clinical program results, prospects or benefits of our collaborations with other companies, or other characterizations of future events or circumstances are forward-looking statements. These forward-looking statements include, but are not limited to, statements about the initiation, timing, progress and results of our preclinical studies and clinical trials, and our research and development programs; our expectations regarding the potential benefits of the partnership, licensing and/or collaboration arrangements and other strategic arrangements and transactions we have entered into or may enter into in the future; our beliefs and expectations regarding milestone, royalty or other payments that could be due to or from third parties under existing agreements; and our estimates regarding future revenues, research and development expenses, capital requirements and payments to third parties. These statements are based upon our current expectations and speak only as of the date hereof. Our actual results may differ materially and adversely from those expressed in any forward-looking statements as a result of numerous factors and uncertainties, including the impact of the ongoing COVID-19 pandemic on our business, the safety and efficacy of our product candidates, decisions of regulatory authorities and the timing thereof, the duration and impact of regulatory delays in our clinical programs, our ability to finance our operations, the likelihood and timing of the receipt of future milestone and licensing fees, the future success of our scientific studies, our ability to successfully develop and commercialize drug candidates, the timing for starting and completing clinical trials, rapid technological change in our markets, the enforcement of our intellectual property rights, and the other risks and uncertainties described in our most recent Annual Report on Form 10-K, subsequent Quarterly Reports on Form 10-Q and other documents filed with the Securities and Exchange Commission from time to time. We assume no obligation to update or revise forward-looking statements to reflect new events or circumstances.

Source: Arrowhead Pharmaceuticals, Inc.

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