Arrowhead Pharmaceuticals Presents New Phase 2 Data of Plozasiran in Patients with Mixed Hyperlipidemia

May 28, 2024

- Plozasiran significantly lowered triglyceride levels with commensurate reductions in APOC3, non-HDL-C, and remnant cholesterol

- Data presented at European Atherosclerosis Society 92nd Congress and simultaneously published in the New England Journal of Medicine

PASADENA, Calif.--(BUSINESS WIRE)--May 28, 2024-- Arrowhead Pharmaceuticals, Inc. (NASDAQ: ARWR) today announced results from the Phase 2b double blind, randomized MUIR study of investigational plozasiran (formerly ARO-APOC3) in patients with mixed hyperlipidemia. Treatment with plozasiran in the MUIR study achieved reductions in triglyceride rich lipoproteins, a genetically validated target associated with increased risk of atherosclerotic cardiovascular disease (ASCVD)[1,2]. These data were presented in an oral presentation today at the European Atherosclerosis Society (EAS) 92nd Congress and simultaneously published in the New England Journal of Medicine.

“Plozasiran demonstrated potent and durable reductions of atherogenic lipoproteins, such as non-HDL-C, ApoB, and remnant cholesterol in the Phase 2 MUIR study that supports its further development in Phase 3 studies for patients with increased risk for ASCVD,” said Christie M. Ballantyne, M.D., Baylor College of Medicine, and Principal Investigator for the MUIR study. “Despite advances in treatment, patients with mixed hyperlipidemia have elevated and persistent ASCVD risk due in part to high levels of atherogenic triglyceride rich lipoproteins. The promising results from treatment with plozasiran in the MUIR study help to lay the groundwork for a more extensive study to potentially test whether plozasiran reduces ASCVD risk.”

Bruce Given, M.D., interim chief medical scientist at Arrowhead added, “Results from the MUIR study of plozasiran in patients with mixed hyperlipidemia are encouraging and we are excited to present data at EAS and publish the results today in the New England Journal of Medicine. We believe plozasiran shows promise in multiple diseases with substantial unmet need, including familial chylomicronemia syndrome, severe hypertriglyceridemia, and mixed hyperlipidemia, and we are eager to further investigate plozasiran in additional clinical studies.”

Select MUIR Results

By silencing Apolipoprotein C-III (APOC3), plozasiran significantly reduced triglycerides and atherogenic triglyceride rich lipoproteins and increased HDL, across all dose levels at Week 24 in patients with mixed dyslipidemia.

At week 24, representing trough effect after 2 quarterly doses, plozasiran treatment was associated with placebo adjusted reductions in triglycerides of -50%, -56%, and -62% (all $p<0.001$) at the 10, 25, and 50 mg doses, respectively. Fasting triglyceride levels were normalized (achieved levels below 150 mg/dL) in most patients (79-92%) randomized to a treatment arm. Commensurate reductions in APOC3 of -57%, -73%, and -79%, with strong positive correlations with changes in triglyceride levels were observed.

Changes in other atherogenic lipoprotein parameters were also observed. At week 24, for the quarterly doses of 10, 25, and 50 mg, the following placebo adjusted changes were observed: non-HDL-C levels -17%, -18%, and -24%; apoB levels -10%, -13%, and -19%; and remnant cholesterol levels -43%, -49%, and -48% with strong correlations with changes in triglyceride levels.

Safety and Tolerability

Plozasiran demonstrated a favorable safety profile in the MUIR study. The overall rates of occurrence of treatment-emergent adverse events (TEAEs) and discontinuations were similar for plozasiran and placebo throughout the 48 weeks of observation. Observed adverse events generally reflected the comorbidities and underlying conditions of the study population. TEAEs occurring in 5 or more patients were COVID-19, worsening glycemic control, upper respiratory tract infection, urinary tract infection, headache, and bronchitis.

Arrowhead is also presenting data from the SHASTA-2 study of plozasiran and the ARCHES-2 study of zodasiran (formerly ARO-ANG3) at EAS. Details about the EAS presentations are listed below.

European Atherosclerosis Society (EAS) 92nd Congress – May 26-29, 2024

Title: **PLOZASIRAN (ARO-APOC3), DECREASES APOC3 AND TRIGLYCERIDES (TG) IN PATIENTS WITH MIXED DYSLIPIDEMIA: MUIR FINAL RESULTS**
Date/Time: May 28, 2024, 12:04 p.m. CEST
Presenter: Christie M Ballantyne, M.D.
Session: New Therapeutics

Title: **PLOZASIRAN (ARO-APOC3), AN INVESTIGATIONAL RNAI THERAPEUTIC, DEMONSTRATES PROFOUND AND DURABLE REDUCTIONS IN APOC-3 AND TRIGLYCERIDES (TG) IN PATIENTS WITH SEVERE HYPERTRIGLYCERIDEMIA (SHTG), SHASTA-2 FINAL RESULTS**
Date/Time: May 28, 2024, 2:49 p.m. CEST
Presenter: Daniel Gaudet, M.D., Ph.D.
Session: SaaG Session: The Enigmas of TG-rich Lipoproteins

Title: **ZODASIRAN SILENCES HEPATIC ANGPTL3 LEADING TO DEEP AND DURABLE REDUCTIONS IN ATHEROGENIC LIPIDS AND LIPOPROTEINS IN MIXED DYSLIPIDEMIA PATIENTS: FINAL RESULTS FROM ARCHES-2, DOUBLE-BLIND PERIOD**
Date/Time: May 29, 2024, 11:30 a.m. CEST
Presenter: Robert Rosenson, M.D.
Session: Late Breaker Session 2: New Therapeutic Agents

Presentation material may be accessed on the Events and Presentations page under the Investors section of the Arrowhead website after each presentation concludes.

About MUIR

MUIR (NCT04998201) is a double-blind, placebo-controlled Phase 2b clinical study in adults with mixed hyperlipidemia. Plozasiran was evaluated against placebo in 353 participants who had who had fasting triglycerides between 150-499 mg/dL and either LDL-cholesterol greater than 70 mg/dL or non-HDL-cholesterol greater 100 mg/dL. Participants were randomly assigned in a 3:1 ratio to receive 10, 25, or 50 mg plozasiran or placebo by subcutaneous injections on day 1 and week 12, or 50 mg plozaisran or placebo on day 1 and week 24. The primary objective of the study was to evaluate the safety and efficacy of plozasiran in adults with mixed hyperlipidemia.

About Mixed Hyperlipidemia

Mixed hyperlipidemia, also called mixed dyslipidemia, is a highly prevalent disorder characterized by elevated low-density lipoprotein cholesterol (LDL-C) and triglyceride levels. Despite the efficacy of LDL-C-lowering therapies in reducing atherosclerotic cardiovascular disease (ASCVD) risk in mixed hyperlipidemia, there remains substantial residual risk attributed to elevated non-HDL driven by remnant cholesterol in triglyceride-rich lipoproteins[3-6]. Genome-wide association and Mendelian randomization studies also support a causal role for triglyceride rich lipoproteins in ASCVD[7-10].

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 hyperlipidemia. 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 PALISADE Phase 3 clinical study in patients with FCS, which recently completed, and the Phase 3 SHASTA-3 and SHASTA-4 studies in patients with SHTG.

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.

Safe Harbor Statement under the Private Securities Litigation Reform Act:

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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