Arrowhead Pharmaceuticals Presents New Pivotal Phase 3 Data at ESC 2024 from PALISADE Study of Plozasiran in Patients with Familial Chylomicronemia Syndrome

September 2, 2024

- Plozasiran reduced triglycerides by 80% from baseline and reduced the risk of developing acute pancreatitis by 83%

- Similar responses were observed in patients with genetically confirmed and clinically diagnosed FCS

- Based on these findings, Arrowhead plans to file a New Drug Application by year-end 2024

- PALISADE results simultaneously published in The New England Journal of Medicine

- Company hosting a virtual analyst and investor event on September 3, 2024, at 8:00 am EDT to discuss results

PASADENA, Calif.--(BUSINESS WIRE)--Sep. 2, 2024-- Arrowhead Pharmaceuticals, Inc. (NASDAQ: ARWR) today announced results from the Phase 3 PALISADE study of investigational plozasiran in patients with familial chylomicronemia syndrome (FCS), a severe and rare genetic disease which currently has no approved treatments in the U.S. PALISADE successfully met its primary endpoint and all multiplicity-controlled key secondary endpoints, including statistically significant reductions in triglycerides (TGs), apolipoprotein C-III (APOC3), and the incidence of acute pancreatitis (AP). These data were presented today in a late-breaking oral presentation at the European Society of Cardiology (ESC) Congress 2024 and simultaneously published in The New England Journal of Medicine.

Based on these positive findings from the PALISADE study, Arrowhead intends to file a New Drug Application with the United States Food and Drug Administration (FDA) by year-end 2024 and plans to seek regulatory approval with additional global regulatory authorities thereafter.

“People living with extremely high triglyceride levels, like those in the PALISADE study, have a substantially higher risk of developing acute pancreatitis and associated long-term sequelae, including a poor quality of life. There are currently no approved therapies in the U.S. to specifically treat FCS, so as physicians we have very few options to help our patients other than various triglyceride-lowering medications which provide minimal benefit, and very strict diet restrictions that take a significant toll on patients and their families,” said Gerald F. Watts, D.Sc., M.D., Ph.D., Winthrop Professor of Cardio-metabolic Medicine at the University of Western Australia, Perth. “Plozasiran demonstrated very deep reductions in triglycerides in the PALISADE study and is the only investigational medicine to achieve a statistically significant reduction in the risk of developing acute pancreatitis in patients with genetically confirmed and clinically diagnosed FCS in a controlled study. These results are encouraging and offer hope to people living with FCS and their physicians who are in desperate need of new safe and effective treatment options.”

Bruce Given, M.D., chief medical scientist at Arrowhead, added, “We continue to be impressed by the promising results from the SUMMIT program of clinical studies of plozasiran in various patient populations, including SHASTA in patients with severe hypertriglyceridemia, MUIR in patients with mixed hyperlipidemia, and now PALISADE in patients with FCS. Based on the data generated to date, we view plozasiran as potentially best-in-class and supportive of development across the spectrum of triglyceride disorders. Specifically, today we showed that in PALISADE a high proportion of patients receiving plozasiran achieved triglyceride levels below guideline-directed risk thresholds associated with the risk of acute pancreatitis, which is a critical treatment goal that physicians communicate to us frequently. Further, PALISADE included patients with an established genetic diagnosis of FCS and patients with symptomatic, persistent chylomicronemia suggestive of FCS. The consistency of results in PALISADE suggests that plozasiran response may be independent of the presence of known FCS-associated genetic variants. This is supportive of the potential value of plozasiran in patients with clinically diagnosed disease, regardless of genetic status.”

Select PALISADE Results

In PALISADE, 75 patients with persistent chylomicronemia, with or without a genetic diagnosis, were randomly assigned to receive subcutaneous plozasiran at 25 mg (n=26) or 50 mg (n=24) or placebo (n=25) every three months for 12 months. At baseline, the median triglyceride level was 2044 mg/dL. Forty-four patients (59%) had genetically confirmed FCS and 31 patients (41%) had clinically diagnosed persistent chylomicronemia suggestive of FCS.

At month ten, the median reduction from baseline in the fasting triglyceride level (the primary endpoint) was -80% in the 25 mg plozasiran group, -78% in the 50 mg plozasiran group, and -17% in the placebo group ($p<0.001$).

Marked reductions in the median triglyceride level below guideline-directed risk thresholds associated with acute pancreatitis occurred as early as one month after trial initiation and showed modest variation throughout the 12-month blinded treatment period. The mean percentage change in triglyceride level was similar to median values.

At month ten, APOC3 was significantly reduced with median reductions of -93% in the 25 mg plozasiran group, -96% in the 50 mg plozasiran group, and -1% in the placebo group ($p<0.001$).

The final alpha-controlled secondary efficacy end point compared the incidence of positively adjudicated acute pancreatitis in a pre-specified pooled analysis of the 25 mg and the 50 mg plozasiran groups versus the pooled placebo group. Among the 38 suspected cases of acute pancreatitis that were referred for adjudication, nine episodes in seven patients were positively adjudicated.

Plozasiran demonstrated statistical significance for this endpoint, with patients receiving plozasiran achieving an 83% reduction in the risk of developing acute pancreatitis versus placebo. A total of two cases occurred in two of 50 patients (4%) receiving plozasiran, and seven cases occurred in five of 25 patients (20%) receiving placebo (odds ratio, 0.17, $p=0.03$).

Safety and Tolerability

Plozasiran demonstrated a favorable safety profile in the PALISADE study. The most common adverse events were abdominal pain, COVID-19, nasopharyngitis, headache, nausea, back pain, upper respiratory tract infection, and diarrhea. Adverse events among the patients in the two plozasiran dose groups were generally similar to those in the placebo group. Severe and serious adverse events were more common in the placebo

group. Hyperglycemia was observed in a limited number of patients in the treatment groups but was confined to patients with pre-diabetes and diabetes.

ESC 2024 Presentation Details

Title: **A Randomised, Placebo-Controlled Phase 3 Study of Plozasiran in Patients with Familial Chylomicronemia Syndrome**
Date/Time: September 2, 2024, 11:36 am BST
Presenter: Professor Gerald Watts, University of Western Australia
Session: Small trials, trial updates, and other studies on lipid therapy
Session Type: Late Breaking Science

Slides from the late-breaking oral presentation at ESC 2024 may be accessed on the Events and Presentations page in the Investors section of the Arrowhead website after the oral presentation concludes.

Virtual Analyst and Investor Event

The analyst and investor event on September 3, 2024, at 8:00 am EDT will feature an encore presentation of the ESC 2024 data by Professor Watts and will include discussion by Arrowhead management. To register for the event, please visit: https://lifescievents.com/event/arrowheadpharma/.

The live event and an archived webcast may also be accessed on the Events and Presentations page in the Investors section of the Arrowhead website.

About PALISADE Phase 3 Study

The PALISADE study (NCT05089084) is a Phase 3 placebo controlled study to evaluate the efficacy and safety of plozasiran in adults with genetically confirmed or clinically diagnosed FCS. The primary endpoint of the study is percent change from baseline in fasting TG versus placebo at Month 10. A total of 75 subjects distributed across 39 different sites in 18 countries were randomized to receive 25 mg plozasiran, 50 mg plozasiran, or matching placebo once every three months. Participants who completed the randomized period were eligible to continue in a 2-part extension period, where all participants receive plozasiran.

About Familial Chylomicronemia Syndrome

Familial chylomicronemia syndrome (FCS) is a severe and rare genetic disease often caused by various monogenic mutations. FCS leads to extremely high triglyceride (TG) levels, typically over 880 mg/dL. Such severe elevations can lead to various serious signs and symptoms including acute and potentially fatal pancreatitis, chronic abdominal pain, diabetes, hepatic steatosis, and cognitive issues. Currently, the therapeutic options that can adequately treat FCS are limited.

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 generally reflect the comorbidities and underlying conditions of the study populations.

Plozasiran is being investigated in the SUMMIT program of clinical studies, including the PALISADE Phase 3 study in patients with FCS, which recently completed, the SHASTA studies in patients with SHTG, and the MUIR and CAPITAN studies in patients with mixed hyperlipidemia.

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. Arrowhead intends to file a New Drug Application with the FDA in 2024 and plans to seek regulatory approval with additional global regulatory authorities. Investigational plozasiran has not been reviewed or approved to treat any disease.

About Plozasiran EAP

Arrowhead is committed to bringing new investigational medicines to patients with serious diseases as quickly and efficiently as possible. The company has established an expanded access program (EAP) for some individuals living with FCS. As with any investigational medicine that has not been approved by regulatory authorities, investigational plozasiran may or may not be effective in treating your diagnosis or condition, and there may be risks associated with its use. If you are a patient or caregiver wishing to know more about this plozasiran EAP for FCS, please discuss this EAP and all treatment options with your treating physician. If you are a treating physician and are seeking information about the plozasiran EAP or would like to request access for a patient, please contact EAP@arrowheadpharma.com.

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.

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