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

May 29, 2024

- Zodasiran significantly reduced triglycerides and atherogenic triglyceride rich lipoproteins across all dose levels at Week 24

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

PASADENA, Calif.--(BUSINESS WIRE)--May 29, 2024-- Arrowhead Pharmaceuticals, Inc. (NASDAQ: ARWR) today announced results from the Phase 2b double blind, randomized ARCHES-2 study of investigational zodasiran (formerly ARO-ANG3) in patients with mixed hyperlipidemia. Zodasiran was associated with robust and durable reductions in triglycerides, triglyceride rich lipoprotein remnants, and total atherogenic lipoproteins, including LDL-C. These data were presented in a late-breaking oral presentation today at the European Atherosclerosis Society (EAS) 92nd Congress and simultaneously published in the New England Journal of Medicine.

“Results from clinical studies of zodasiran, including those for the ARCHES-2 study in patients with mixed hyperlipidemia presented today at EAS and published in the New England Journal of Medicine, continue to support ANGPTL3 as an exciting target for an RNAi-based gene silencing strategy,” said Bruce Given, M.D., interim chief medical scientist at Arrowhead. “Genetic studies show that ANGPTL3 loss-of-function variants lead to enhanced lipoprotein lipase and endothelial lipase activity, resulting in lower concentrations of most plasma lipoproteins, including triglyceride rich lipoproteins, LDL-C, VLDL/remnant cholesterol, and HDL-C. Individuals with these variants also have demonstrated a markedly reduced risk of ASCVD and have no known adverse clinical phenotypes[1-3].”

Robert Rosenson, M.D., Icahn School of Medicine at Mount Sinai, and Principal Investigator for the ARCHES-2 study added, “The potent reductions in serum lipids and lipoproteins and favorable safety profile seen in the ARCHES-2 clinical study of zodasiran suggest its potential to treat residual ASCVD risk in patients with elevated triglyceride rich lipoproteins. The genetic data around ANGPTL3 as a target are very compelling and support further Phase 3 studies to determine whether the large reductions in triglyceride rich lipoproteins observed after zodasiran treatment can replicate the genetic data and reduce ASCVD risk.”

Select ARCHES-2 Results

Zodasiran treatment was associated with dose-dependent placebo adjusted reductions in triglycerides, remnant cholesterol, LDL-C, ApoB, and Non-HDL-C across all dose levels in patients with mixed hyperlipidemia.

At week 24, representing trough effect, zodasiran treatment at 50, 100, and 200 mg on day 1 and week 12 was associated with placebo adjusted reductions in triglycerides of -51%, -57%, and -63% (all p<0.001) respectively. ANPTL3, the genetic target of zodasiran, was reduced compared with placebo by -54%, -70%, and -74%, and remnant cholesterol levels were reduced by -73%, -76%, and -82%, which strongly correlated with changes in triglyceride levels.

Changes in other atherogenic lipoprotein parameters were also observed across all three dose levels. At week 24, the following placebo adjusted changes were observed for the 200 mg dose: LDL-C -20%, ApoB -22%; Non-HDL-C -36%.

In a subset of patients with baseline liver fat fraction greater than 8%, dose-dependent liver fat reductions, measured by MRI-PDFF, were observed reaching -28% with the 200 mg dose compared with -2% with placebo.

Safety and Tolerability

Zodasiran demonstrated a favorable safety profile in patients with mixed hyperlipidemia in the ARCHES-2 study. Treatment-emergent adverse events (TEAEs) were generally balanced between treatment and placebo groups and generally reflected the comorbidities and underlying conditions of the study population. There were no clinically meaningful changes in laboratory safety evaluations, no changes in mean platelet counts, and modest changes in HbA1c.

Details about the EAS presentation is listed below.

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

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

About ARCHES-2

ARCHES-2 (NCT04832971) is a double-blind, placebo-controlled dose-ranging Phase 2b clinical study of zodasiran in 204 participants with mixed hyperlipidemia. Participants with fasting triglycerides between 150-499 mg/dL and either LDL-cholesterol greater than 70 mg/dL or non-HDL-cholesterol greater 100 mg/dL were randomly assigned in a 3:1 ratio to receive subcutaneous injections of 50, 100, or 200 mg zodasiran or placebo on day 1 and week 12 and followed through week 36. 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[4-7h]. Genome-wide association and Mendelian randomization studies also support a causal role for triglyceride rich lipoproteins in ASCVD[8-11].

About Zodasiran

Zodasiran, previously called ARO-ANG33, is a first-in-class investigational RNA interference (RNAi) therapeutic designed to reduce production of angiopoietin-like protein (ANGPTL3), which is a hepatocyte expressed regulator of lipid and lipoprotein metabolism with multiple potential modes of action, including inhibition of lipoprotein lipase (LPL) and endothelial lipase (EL)[12,13]. Genetic studies suggest that individuals with ANGPTL3 loss-of-function variants have enhanced lipoprotein lipase and endothelial lipase activity, resulting in lower levels atherogenic lipoproteins and a reduced risk of ASCVD[1-3].

In clinical studies, investigational zodasiran demonstrated a favorable safety profile and was associated with dose-dependent reductions in triglycerides, triglyceride rich lipoprotein remnants, and total atherogenic lipoproteins, including LDL-C, in patients with homozygous and heterozygous familial cholesterolemia (HoFH) and mixed hyperlipidemia.

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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1. Dewey, et al. *N Engl J Med.* 2017;377 (3):211-21.
2. Minicocci, et al. *J Lipid Res.* 2013;54(12): 3481-90
3. Musunuru, et al. *N Engl J Med.* 2010; 363(23):2220-7
4. Gugliucci A. J Clin Med. 2023;12:4399.
5. Silverman MG, et al. JAMA. 2016;316(12):1289-1297
6. Langsted A, et al. J Int Med. 2020;288:116–127.
7. Fu L, et al. Diabetes Care. 2022;45(9):2136-2143.
8. Bjornson E, et al. Eur Heart J. 2023;44:4186-4195
9. Nordestgaard BG. Circ Res. 2016;118:547-563.
10. Virani SS, et al. J Am Coll Cardiol. 2021;78(9):960-993
11. Hussain A, et al. Curr Atheroscler Rep. 2020;22:25.
12. Adam, et al. J Lipid Res. 2020;61(9): 1271-86.
13. Rosenson. J Lipid Res. 2021:62:100060.

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Arrowhead Pharmaceuticals, Inc.
Vince Anzalone, CFA
626-304-3400

ir@arrowheadpharma.com

Investors:
LifeSci Advisors, LLC
Brian Ritchie
212-915-2578
britchie@lifesciadvisors.com

Media:
LifeSci Communications, LLC
Kendy Guarinoni, Ph.D.
724-910-9389
kguarinoni@lifescicomms.com

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