Arrowhead Pharmaceuticals Presents New Clinical Data Showing ARO-RAGE Achieves High Level of Gene Knockdown in Patients with Asthma

May 20, 2024

- ARO-RAGE reduced serum sRAGE by up to 88% in patients with asthma

- Additional promising results presented on two preclinical stage programs targeting thymic stromal lymphopoietin (TSLP) and influenza A viruses

PASADENA, Calif.--(BUSINESS WIRE)--May 20, 2024-- Arrowhead Pharmaceuticals, Inc. (NASDAQ: ARWR) today announced that new interim clinical data on ARO-RAGE, an investigational RNAi-based medicine for the treatment of inflammatory lung diseases, such as asthma, were presented at the American Thoracic Society (ATS) 2024 International Conference. Interim results from the ongoing Phase 1/2 study demonstrate that treatment with ARO-RAGE led to a reduction in soluble RAGE (sRAGE) concentration in bronchoalveolar lavage fluid (BALF) and serum in a dose-dependent manner in normal healthy volunteers (NHV) and in patients with mild to moderate asthma.

“These results underscore the potential of our proprietary TRiM ™ platform to enable us to develop impactful new therapies to potentially treat multiple pulmonary diseases with significant unmet needs. Arrowhead was the first company to show that RNAi could be harnessed to achieve high levels of target gene knockdown in the lung in healthy human subjects and these data presented at ATS 2024 build on that success,” said James Hamilton, M.D., chief of discovery and translational medicine at Arrowhead. “Our ARO-RAGE data is first-in-class and demonstrated deep and sustained knockdown in the lung in patients with mild to moderate asthma, a long duration of effect that appears to support every two-month dosing, and a favorable safety and tolerability profile. These results give us further confidence as we move towards the initiation of a Phase 2 study in late 2024.”

Select ARO-RAGE Results

In the ongoing 1001 study, ARO-RAGE achieved the following key results as of 05 April 2024:

- Single and multiple doses of ARO-RAGE in NHVs led to dose dependent reductions in sRAGE in both BALF and in serum
- After two doses of ARO-RAGE in patients with mild to moderate asthma, serum sRAGE was reduced up to 88% with a mean maximum reduction up to 77%
- Serum sRAGE was reduced in a dose-responsive manner with similar reductions observed in NHVs and patients with asthma at each dose level
- Pharmacodynamic effects were long lasting, with a duration that appears to support once every two-month dosing
- ARO-RAGE plasma exposure following a single dose in NHVs was of limited quantity and duration

Safety and Tolerability Results

ARO-RAGE has shown a favorable safety profile to date, with no demonstrated pattern of effect on systemic safety labs and no demonstrated pattern of detrimental effect on lung function (FEV1, FVC, or DLCO) over time. There have been no serious adverse effects related to study drug and no treatment emergent adverse events leading to trial withdrawal or study drug discontinuation.

Arrowhead also presented preclinical data on two additional lung targeted programs that utilize the company’s proprietary Targeted RNAi Molecule (TRiM™) platform. ARO-TSLP is designed to silence the epithelial cytokine thymic stromal lymphopoietin (TSLP), a genetically and clinically validated therapeutic target that activates multiple immune cell lineages to promote asthmatic inflammation. ARO-IAV is designed to silence expression of highly conserved influenza A viruses, including the highly pathogenic avian influenza virus (H5N1).

Details about the ATS presentations are listed below.

American Thoracic Society (ATS) 2024 International Conference – May 17-22, 2024

Title: **A First-in-Human Study of ARO-RAGE, a Novel Inhaled RNA-Interference Therapy for Asthma**
Date/Time: May 19, 2024, 11:30 a.m. PDT
Type: Late-Breaking Poster

Title: **A lung-targeted therapeutic siRNA against highly conserved viral M1 mRNAs effectively limits highly pathogenic influenza A infection in mice**
Date/Time: May 20, 2024, 11:30 a.m. PDT
Type: Poster

Title: **Lung-targeted RNAi molecules silence human TSLP expression in PCLS cultures and humanized mice and suppress pulmonary allergic inflammation**
Date/Time: May 20, 2024, 11:30 a.m. PDT
Type: Poster

Presentation materials may be accessed on the Events and Presentations page in the Investors section of the Arrowhead website.

About Pulmonary TRiM™ Platform

Arrowhead’s pulmonary Targeted RNAi Molecule (TRiM ™) delivery platform facilitates selective delivery of therapeutic small interfering RNAs (siRNAs) to the lung epithelium via an integrin $\alpha_v\beta_6$ targeting moiety, mediating durable gene silencing upon inhalation utilizing a nebulizer.

About ARO-RAGE

ARO-RAGE is an investigational RNAi therapeutic targeting the receptor for advanced glycation end-products (RAGE) as a potential treatment for inflammatory lung diseases. RAGE is implicated as an upstream mediator of Type-2 and non-Type-2 inflammatory cascades and is involved in the pathogenesis of asthma and numerous inflammatory diseases[1,2,3]. Silencing RAGE expression via RNAi is designed to reduce the amount of RAGE protein expressed on pulmonary epithelial cells. Reduced RAGE expression in the pulmonary epithelium may result in reduction of RAGE-dependent inflammatory pathways, leading to decreased exacerbation frequency and improved airflow in patients with asthma.

About the ARORAGE-1001 Phase 1/2 Study

ARORAGE-1001 (NCT05276570) is an ongoing Phase 1/2a, randomized, double-blinded, placebo-controlled study in normal healthy volunteers (NHV) (Part 1), in patients with mild to moderate asthma (Part 2), and in patients with high baseline fractional exhaled nitric oxide (FeNO) (Part 3). Subjects receive ascending doses of ARO-RAGE or placebo via nebulizer on Day 1 in the single-ascending dose cohorts or Days 1 and 29 in the multiple-ascending dose cohorts. The objectives of the study include the assessment of safety and tolerability, pharmacokinetics, and pharmacodynamics of ARO-RAGE in NHVs and patients with asthma.

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. Perkins TN. *Allergy* 2021;76:1350-66.
2. Oczypok EA. *JACI* 2015;136:747-56.
3. Killian KN. *Front Immunol* 2023;14:1039997.

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