Arrowhead Pharmaceuticals' Proprietary Pulmonary TRiM™ Platform Achieves High Levels of Target Gene Knockdown and Long Duration of Effect

April 25, 2023

- Interim Results from Ongoing ARO-RAGE Phase 1/2 Study Demonstrate up to 90% Serum sRAGE Reduction with Mean Maximum Reduction of 80% after Two Doses

- Further Data to be Presented at Upcoming R&D Day

PASADENA, Calif.--(BUSINESS WIRE)--Apr. 25, 2023-- Arrowhead Pharmaceuticals Inc. (NASDAQ: ARWR) today announced interim results from an ongoing Phase 1/2 clinical study of ARO-RAGE, the company's investigational RNA interference (RNAi) therapeutic designed to reduce production of the receptor for advanced glycation end products (RAGE) as a potential treatment for inflammatory pulmonary diseases, such as asthma. These data represent the first clinical demonstration of the potential utility of Arrowhead's proprietary Targeted RNAi Molecule (TRiM ^{TM}) platform optimized for delivery to the lungs.

Matthias Salathe, M.D., Professor, Pulmonary, Critical Care and Sleep Medicine, and Vice Chancellor for Research at the University of Kansas Medical Center, said: "These interim ARO-RAGE Phase 1/2 data are highly encouraging. Unmet need continues to exist for many patients with severe asthma who suffer from persistent symptoms and exacerbations, despite current therapies. Reducing expression of the RAGE protein in pulmonary epithelial cells to the degree that ARO-RAGE has demonstrated to date in this study has the potential to treat patients with asthma and other inflammatory lung diseases in a fundamentally new way. RAGE represents a promising target for intervention as its activation has been implicated as a proximal regulator of the inflammatory cascade in the asthmatic airway, and thus RAGE silencing may result in potent anti-inflammatory effects. I look forward to the availability of additional results from this important trial."

Interim results from ARO-RAGE administration in Part 1 of the ongoing Phase 1/2 study in normal healthy volunteers include:

- Reductions in soluble RAGE (sRAGE) as measured in serum after two doses on Day 1 and Day 29
  - Mean maximum reduction at 92 mg dose was 80% with a maximum reduction of 90%
  - Mean maximum reductions at 10 to 44 mg dose levels showed a dose response ranging from 31% to 59%
- Duration of pharmacologic effect persisted for at least 6 weeks after the second administration of the 92 mg dose with further follow up ongoing
  - Interim results for this cohort are only available through Day 71
- Reductions in sRAGE as measured in bronchoalveolar lavage fluid (BALF) at Day 31 after a single dose
  - Mean reduction at 92 mg dose was 75% with a maximum reduction of 92%
  - Mean reductions at 10 to 44 mg doses ranged from 44% to 52%
- Reductions in serum sRAGE were also observed after a single dose
  - Mean maximum reduction at 92 mg dose was 56% with a maximum reduction of 68%
  - Mean maximum reductions at 10 to 44 mg dose levels showed a dose response and ranged from 23% to 53%
- The pooled placebo groups experienced a mean sRAGE increase of 8% in BALF and a mean decrease of 1% in serum
- Safety and tolerability
  - Overall, no patterns of adverse changes in any clinical safety parameters
  - No reported serious or severe adverse events
  - No dropouts related to drug or related to adverse events
- These results include 4 of 5 escalating dose levels. Data are not yet available for single or multiple dose cohorts at 184 mg, the highest dose being tested

Christopher Anzalone, Ph.D., President and CEO at Arrowhead, said: "We think these interim data with ARO-RAGE represent clinical validation of Arrowhead's inhaled pulmonary TRiM ^{TM} platform and, specifically, of ARO-RAGE as a potential new therapy to treat patients with inflammatory lung diseases. The high level of target gene knockdown, the long duration of effect, and the promising safety and tolerability results are all very encouraging signs for our growing pipeline of RNAi therapeutic candidates that leverage this same platform. We look forward to providing additional data at our upcoming R&D Day on June 1, 2023, and at future medical meetings."

About the Phase 1/2 Study

ARORAGE-1001 (NCT05276570) is a Phase 1/2a, randomized, double-blinded, placebo-controlled study in normal healthy volunteers (NHV), Part 1, and patients with mild-to-moderate asthma, Part 2. The single ascending dose portion of the study includes 5 sequentially enrolled NHV cohorts with escalating single-dose levels. The multiple ascending dose portion of the study includes 5 NHV cohorts and 3 asthma patient 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 RAGE

RAGE is implicated in the pathogenesis of numerous inflammatory diseases, including asthma. Reduction of 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 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 Twitter @ArrowheadPharma. 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.

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