Arrowhead Presents Additional Clinical Data on Investigational ARO-AAT Treatment in Patients with Alpha-1 Liver Disease at EASL International Liver Congress

June 26, 2021

PASADENA, Calif.--(BUSINESS WIRE)--Jun. 26, 2021-- Arrowhead Pharmaceuticals Inc. (NASDAQ: ARWR) today presented additional positive interim 48-week liver biopsy results from the ongoing AROAAT2002 study, an open-label Phase 2 clinical study of ARO-AAT, the company's second generation investigational RNA interference (RNAi) therapeutic being co-developed with Takeda Pharmaceutical Company Limited ("Takeda") as a treatment for the rare genetic liver disease associated with alpha-1 antitrypsin deficiency (AATD), at The International Liver Congress - The Annual Meeting of the European Association for the Study of the Liver (EASL).

The results demonstrate that, in the AROAAT2002 study, investigational ARO-AAT treatment led to improvements in multiple measures of liver health, including fibrosis, with substantial and sustained reductions in the level of mutant AAT protein (Z-AAT). In addition, ARO-AAT treatment was generally well tolerated after up to 1 year of treatment.

Javier San Martin, M.D., chief medical officer at Arrowhead, said: "We believe the interim results that were presented today at EASL represent an important breakthrough for the field and are encouraging for patients with alpha-1 liver disease, who currently have no available treatment options other than liver transplant. The data indicate that treatment with investigational ARO-AAT, being developed in collaboration with Takeda as TAK-999, resulted in substantial, sustained, and consistent reductions in the production of the toxic mutant Z-AAT protein, which has been identified as the cause of progressive liver disease in patients with alpha-1 antitrypsin deficiency. This reduction over 6 and 12 months led to multiple important signals associated with healing of patients' liver disease. Importantly, we believe ARO-AAT is the first investigational therapy to show this type of benefit in patients with alpha-1 liver disease. We want to thank all the investigators and patients for their participation in the study, and we look forward to the availability of additional results from this study and from our ongoing SEQUOIA study of ARO-AAT, which we anticipate will reach full enrollment during the third quarter of 2021."

Pharmacodynamics and Efficacy

After 24 weeks (cohort 1, n=4) and 48 weeks (cohort 2, n=5) of treatment with investigational ARO-AAT in the AROAAT2002 study, the following results were observed:

- Serum Z-AAT levels decreased in all patients
- Median decrease in intra-hepatic Z-AAT levels were:
  - Total Z-AAT -80.1% (range -72 to -97%)
  - Monomer -90% (range -79 to -97%)
  - Polymer -81% (range* -42 to -97%)
    - *Excluding 1 subject in cohort 1 that had very low Z-AAT polymer levels at baseline that increased at week 24
- Histological globule burden was reduced in all nine patients, with two achieving full resolution (total aggregate globule burden score=0)
- Six of the nine patients (2/4 after 24 weeks and 4/5 after 48 weeks) achieved a 1 or greater stage improvement in Metavir fibrosis stage, with no worsening of fibrosis in the other three patients
  - Two patients had baseline F4 fibrosis (cirrhosis), with one patient achieving a two-stage improvement to F2 and the other patient achieving a one-stage improvement to F3
- Multiple biomarkers of liver health improved, including liver stiffness (FibroScan), liver enzymes alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT), and PRO-C3, a marker of collagen formation

Safety and Tolerability

In AROAAT2002, investigational ARO-AAT demonstrated an acceptable safety profile and was generally well tolerated after up to 1 year of treatment. There were no treatment-emergent adverse events leading to drug discontinuation, dose interruptions, or study withdrawal. Lung function was assessed throughout the study and there were no clinically meaningful changes in percent predicted forced expiratory volume in 1 second (ppFEV1). Three serious adverse events (SAEs) were reported, but none were considered related to the study drug. All SAEs were moderate in severity and all resolved.

AROAAT2002 (NCT03946449) is a pilot open-label, multi-dose, Phase 2 study to assess the response to investigational ARO-AAT in 16 patients with AATD associated liver disease and baseline liver fibrosis. All eligible participants receive a pre-dose biopsy and an end of study biopsy. Treated participants will also be offered the opportunity to continue treatment in an open-label extension (OLE). Including the OLE, interim assessments will be made after 6 months, 12 months, 18 months, and 24 months of treatment with ARO-AAT.

Presentation Details

Title: **ARO-AAT an investigational RNAi therapeutic demonstrates improvement in liver fibrosis with reduction in intra-hepatic Z-AAT burden**
Authors: Pavel Strnad, *et al.*

Type: Late-Breaking Oral Presentation
Date and Time: June 26, 2021 at 12:15 CEST

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

About Arrowhead and Takeda Collaboration

In October 2020, Arrowhead and Takeda announced a collaboration and licensing agreement to develop investigational ARO-AAT. Under the terms of the agreement, Arrowhead and Takeda will co-develop ARO-AAT which, if approved, will be co-commercialized in the United States under a 50/50 profit-sharing structure. Outside the U.S., Takeda will lead the global commercialization strategy and receive an exclusive license to commercialize ARO-AAT with Arrowhead eligible to receive tiered royalties of 20-25% on net sales. Arrowhead received an upfront payment of $300 million and is eligible to receive potential development, regulatory and commercial milestones of up to $740 million.

About Alpha-1 Antitrypsin-Associated Liver Disease

Alpha-1 Antitrypsin-Associated Deficiency (AATD) is a rare genetic disorder associated with liver disease in children and adults and pulmonary disease in adults. AATD is estimated to affect 1 per 3,000-5,000 people in the United States and 1 per 2,500 in Europe. The protein AAT is primarily synthesized and secreted by hepatocytes. Its function is to inhibit enzymes that can break down normal connective tissue. The most common disease variant, the Z mutant, has a single amino acid substitution that results in improper folding of the protein. The mutant protein cannot be effectively secreted and accumulates in globules inside the hepatocytes. This triggers continuous hepatocyte injury, leading to fibrosis, cirrhosis, and increased risk of hepatocellular carcinoma.

Individuals with the homozygous PiZZ genotype have severe deficiency of functional AAT leading to pulmonary disease and liver disease. Lung disease is frequently treated with AAT augmentation therapy. However, augmentation therapy does nothing to treat liver disease, and there is no specific therapy for hepatic manifestations. There is a significant unmet need as liver transplant, with its attendant morbidity and mortality, is currently the only available cure.

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.

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," "intend," "plan," "project," "could," "estimate," or "continue" 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, prospects or benefits of our collaborations with other companies, or other characterizations of future events or circumstances are forward-looking statements. 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, 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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