Arrowhead ARO-AAT Phase 2 Interim Results in Patients with Alpha-1 Liver Disease Demonstrate Improvements in Key Parameters after Six Months of Treatment

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- Up to 97% reduction in intra-hepatic Z-AAT polymer
- Up to 95% reduction in intra-hepatic total Z-AAT burden
- Up to 66% and 58% reduction in circulating ALT and GGT levels respectively
- Up to 26% improvement in FibroScan values

PASADENA, Calif.--(BUSINESS WIRE)--Sep. 16, 2020-- Arrowhead Pharmaceuticals Inc. (NASDAQ: ARWR) today announced positive interim 24-week liver biopsy results in four subjects from AROAAT2002, an open-label Phase 2 clinical study of ARO-AAT, the company's second generation investigational RNA interference (RNAi) therapeutic being developed as a treatment for the rare genetic liver disease associated with alpha-1 antitrypsin deficiency (AATD). The results show clear evidence of a meaningful pharmacodynamic effect by ARO-AAT, leading to improvements in relevant biomarkers, including substantial reductions in intra-hepatic mutant AAT protein (Z-AAT), both Z-AAT monomer and Z-AAT polymer; improvements in liver stiffness based on FibroScan; and, a decrease in alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT), both serum biomarkers of liver injury.

After 24 weeks of treatment with investigational ARO-AAT in the AROAAT2002 study, serum and total intra-hepatic Z-AAT decreased in all four patients by up to 93% and 95%, respectively. Three of four patients demonstrated reductions from baseline in intra-hepatic Z-AAT polymer, with a maximum reduction of 97%. All four patients showed reductions in ALT and GGT, with maximum reductions of 66% and 58%, respectively. All patients demonstrated improved transient elastography FibroScan values, with three of four patients exhibiting greater than 20% reductions.

Javier San Martin, M.D., chief medical officer at Arrowhead, said: "While we had anticipated that 6 months of treatment with investigational ARO-AAT in the Phase 2 open label study would likely lead to substantial reductions in Z-AAT monomer, the improvements in additional clinically meaningful biomarkers, including reductions in Z-AAT polymer, improvements in FibroScan values, and decreases in ALT and GGT, were more substantial than we expected. These are very exciting results and provide us with increased confidence in the potential of this program. Based on these important data, we are actively assessing our clinical and regulatory path forward, including engaging with the U.S. Food and Drug Administration and other regulatory agencies, to identify areas where the program could potentially be streamlined and accelerated."

Professor Pavel Strnad, M.D., University Hospital Aachen, Germany, and an investigator on the trial, said: "These data are very encouraging and suggest that ARO-AAT may rapidly ameliorate liver injury. It is particularly reassuring to see the decrease in liver enzymes, which suggests that elevations are related to proteotoxic stress that could be addressed with ARO-AAT therapy rather than reflecting co-morbidities. In addition, no major lung events have occurred in this study to date, which indicates that RNAi-based reduction of Z-AAT in the liver has not negatively affected lung function during the treatment period. I am pleased that all of my patients have opted to continue on study for the 12-month extension, and I am eager to follow their progress."

Miriam O'Day, President & CEO of the Alpha-1 Foundation, stated: "The news regarding the Arrowhead ARO-AAT Phase 2 interim results for liver treatment in Alpha-1 Antitrypsin Deficiency brings hope to the Alpha-1 community in the midst of the COVID-19 pandemic. It is critically important that new treatments for patients who currently do not have therapeutic interventions move forward and encourages our optimism as we reimagine treatment for this condition and its underserved patient population."

Mark Brantly, M.D., Scientific Director, Alpha-1 Foundation, stated: "The Arrowhead ARO-AAT Phase 2 open label clinical trial is exciting for the Alpha-1 community as it brings forward an intervention for the liver disease associated with Alpha-1 Antitrypsin Deficiency. The interim result of this study demonstrates proof of principle that RNA interference is a promising therapy for the liver disease associated with Alpha-1 Antitrypsin Deficiency. Alpha-1 Foundation is devoted to developing treatments for the Alpha-1 community by directly funding research, partnering with industry collaborators and supporting a research registry to accelerate the completion of clinical trials. This news is exciting and offers hope for the Alpha-1 community who joins us in celebrating this accomplishment and each step that moves our community closer to a cure."

Arrowhead submitted a late-breaker abstract on the interim 24-week results for the first cohort of AROAAT2002 in which 4 patients received 200 mg ARO-AAT at Week 1, 4 and 16, and, if accepted, intends to present additional data at the American Association for the Study of Liver Disease (AASLD) Liver Meeting in November 2020.

AROAAT2002 (NCT03946449) is a pilot open-label, multi-dose, Phase 2 study to assess the response to ARO-AAT in approximately 16 patients with AATD associated liver disease and baseline liver fibrosis who will be enrolled in three cohorts. All eligible participants will require 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. Arrowhead is also evaluating ARO-AAT in the ongoing SEQUOIA Phase 2/3 trial, which began in August 2019.

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. 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 various factors and uncertainties, including 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, and the enforcement of our intellectual property rights. Our most recent Annual Report on Form 10-K and subsequent Quarterly Reports on Form 10-Q discuss some of the important risk factors that may affect our business, results of operations and financial condition. We assume no obligation to update or revise forward-looking statements to reflect new events or circumstances.

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