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Arrowhead Completes Dosing Healthy Volunteers and Initiates Transition to Patients in Phase 1 Study of ARC-AAT

PASADENA, Calif.--(BUSINESS WIRE)-- Arrowhead Research Corporation (NASDAQ: ARWR), a biopharmaceutical company developing targeted RNAi therapeutics, today announced that it completed dosing healthy volunteers and will begin dosing patients in an on-going phase 1 study of ARC-AAT, the Company's clinical candidate for the treatment of liver disease associated with Alpha-1 Antitrypsin Deficiency (AATD). AATD is a rare genetic disorder that can severely damage the liver and lungs of affected individuals. The study was designed to begin dose escalation in healthy volunteers (Part A) and transition into patients (Part B) when a predefined knockdown target is achieved. That target is at least 30% reduction of serum AAT levels in 3 subjects or greater than 60% reduction in a single subject. This was met during the third cohort. All three dose levels tested appear to be generally well tolerated and the data safety committee has cleared the study to move into patients with AATD. Dosing in patients may now begin at the highest dose level used in Part A and then continued dose escalation may proceed under the protocol. The company expects to complete the Phase 1 study by the end of 2015.

"We are excited that Part A of the phase 1 study is complete and that we can now begin studying ARC-AAT directly in patients with PiZZ genotype AATD," said Bruce D. Given, M.D., Arrowhead's Chief Operating Officer. "The lung disease associated with AATD is frequently treated with AAT augmentation therapy. However, there is a great need in the field to identify new treatment options for the AATD-related liver disease. Currently, the only option for severe cases is liver transplant, with all of its attendant risks and availability issues. We think ARC-AAT is a very promising program that may potentially provide a better option for patients and physicians."

ARC-AAT is comprised of novel unlocked nucleobase analog containing RNAi trigger molecules (UNA) that are co-administered with Dynamic Polyconjugates (DPCs) to enable the escape of the UNA from endosomes. The ratio of UNA to DPC is 2:1 by weight. In Part A of the study, three cohorts of six participants each received ARC-AAT at doses of 0.38 mg/kg, 1.0 mg/kg, and 2.0 mg/kg of UNA, and 0.19 mg/kg, 0.5 mg/kg, and 1.0 mg/kg of DPC, respectively.

The Phase 1 trial is a multi-center, randomized, placebo-controlled, double-blind, single dose-escalation first-in-human study to evaluate the safety, tolerability and pharmacokinetics of ARC-AAT and the effect on circulating AAT levels. The study has been enrolling in dose cohorts of six participants each, with participants randomized at a ratio of 2:1 (active:placebo) to receive a single intravenous injection of either ARC-AAT or placebo (normal saline). The study consists of two parts; Part A in healthy volunteers, which has been completed, and Part B to be conducted in patients with PiZZ genotype AATD. The study evaluates participants for 28 days following dosing, with additional follow-up if needed every 2 weeks until AAT levels return to baseline.

"The Alpha-1 Foundation and the entire Alpha-1 community are excited to see this program move forward," said John Walsh, president and chief executive officer of the Alpha-1 Foundation. "We and The Alpha-1 Project, the Foundation's venture philanthropy arm, will continue to work closely with Arrowhead on clinical trial recruitment and provide additional assistance to get this potentially life saving therapy to adults and children with liver disease due to Alpha-1."

About Alpha-1 Antitrypsin Deficiency (AATD)

AATD is an autosomal recessive genetic disorder associated with liver disease in children and adults and pulmonary disease in adults. Alpha-1 antitrypsin is a circulating glycoprotein protease inhibitor of the serpin family encoded by the AAT gene and primarily synthesized in the liver. The physiologic function is inhibition of neutrophil proteases to protect healthy tissues during inflammation and prevent tissue damage. The Z mutant is the most common disease variant and has a single amino acid substitution that results in improper protein folding causing severe impairment of secretion from hepatocytes. This lack of secretion leads to accumulation of mutant Z-AAT polymers, which form globules in the hepatocyte endoplasmic reticulum. This triggers continuous hepatocyte injury, leading to fibrosis, cirrhosis, and increased risk of hepatocellular carcinoma.

In clinical practice, approximately 96-98% of AATD-related disease is due to the homozygous PiZZ genotype. PiZZ individuals have severe deficiency of functional AAT leading to pulmonary disease and hepatocyte injury 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 is currently the only available treatment for severe liver manifestations.

The mean estimated prevalence of AATD in the U.S is 1 per 3000-5000, or approximately 100,000 patients. AATD is also an important cause of pediatric liver disease with an estimated prevalence in children of approximately 20,000 patients, and 50-80% likely to manifest liver disease during childhood. It is an orphan disease that appears to be frequently misdiagnosed or undiagnosed. European prevalence is estimated to be 1 per 2500.

About ARC-AAT

Arrowhead's ARC-AAT is being investigated for the treatment of liver disease associated with Alpha-1 Antitrypsin Deficiency (AATD), a rare genetic disease that severely damages the liver and lungs of affected individuals. ARC-AAT employs a novel unlocked nucleobase analog (UNA) containing RNAi trigger molecule designed for systemic delivery using the Dynamic Polyconjugate delivery system. ARC-AAT is highly effective at knocking down the Alpha-1 antitrypsin (AAT) gene transcript and reducing the hepatic production of the mutant AAT (Z-AAT) protein. Reduction of liver production of the inflammatory Z-AAT protein, which is likely a cause of progressive liver disease in AATD patients, is important as it is expected to halt the progression of liver disease and potentially allow fibrotic tissue repair. The Company is conducting a single dose Phase 1 clinical study, with part A in healthy volunteers and part B in AATD patients.

About Arrowhead Research Corporation

Arrowhead Research Corporation is a biopharmaceutical company developing targeted RNAi therapeutics. The company is leveraging its proprietary Dynamic Polyconjugate™ delivery platform to develop targeted drugs based on the RNA interference mechanism that efficiently silences disease-causing genes. Arrowhead's pipeline includes ARC-520 for chronic hepatitis B virus and ARC-AAT for liver disease associated with Alpha-1 antitrypsin deficiency.

For more information please visit http://www.arrowheadresearch.com, or follow us on Twitter @ArrowRes. To be added to the Company's email list and receive news directly, please visit

http://ir.arrowheadresearch.com/alerts.cfm.

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 our ability to finance our operations, the future success of our scientific studies, our ability to successfully develop drug candidates, the timing for starting and completing clinical trials, actions of the U.S. Food and Drug Administration (FDA) and similar global regulatory bodies, rapid technological change in our markets, challenges to the validity of our intellectual property rights, and the enforcement of our intellectual property rights. Arrowhead Research Corporation's 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.

Source: Arrowhead Research Corporation

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