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Arrowhead Begins Phase 1 Trial of ARC-AAT for Treatment of Liver Disease Associated with Alpha-1 Antitrypsin Deficiency

PASADENA, Calif.--(BUSINESS WIRE)-- Arrowhead Research Corporation (NASDAQ: ARWR), a biopharmaceutical company developing targeted RNAi therapeutics, today announced that it has initiated dosing in a Phase 1 clinical trial of ARC-AAT, the company's candidate for the treatment of liver disease associated with Alpha-1 Antitrypsin Deficiency (AATD), a rare genetic disorder that severely damages the liver and lungs of affected individuals. Trial initiation followed successful completion of the Clinical Trial Notification (CTN) regulatory process in Australia. The study will be conducted in two parts, with Part A in healthy volunteers and Part B in patients with AATD. The primary objectives of the study are to determine the safety and tolerability of escalating doses of ARC-AAT, evaluate the pharmacokinetics, and determine the effect on circulating levels of alpha-1 antitrypsin. Initial data from this study is expected in late 2015.

Christopher Anzalone, Ph.D., president and chief executive officer of Arrowhead said, "The ARC-AAT Phase 1 trial is the first human study of an RNAi therapeutic against liver disease associated with AATD, which has no current treatment options, short of liver transplant. ARC-AAT is our second clinical candidate using the DPC delivery system, after ARC-520 targeting the hepatitis B virus, and it is the first candidate that targets an endogenous gene to enter human trials. We expect the Phase 1 study to primarily generate safety and tolerability data, but it should also give a readout on the depth and duration of activity."

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, pharmacokinetics of ARC-AAT and the effect on circulating alpha-1 antitrypsin (AAT) levels. The study plans to enroll 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 will consist of two parts, with Part A planned to be conducted in healthy volunteers and Part B planned to be conducted in patients with PiZZ genotype AATD. In Part A, dose escalation will proceed until the achievement of certain target knockdown parameters. When these AAT knockdown parameters are achieved, dose escalation in healthy volunteers (Part A) is planned to stop and dosing in patients with AATD (Part B) is planned to begin at the highest dose level used in Part A and then dose escalation will proceed. We expect participants will be evaluated for 28 days following dosing with additional follow-up every 2 weeks until AAT levels return to baseline.

"The whole Alpha-1 community is excited to see this landmark clinical trial begin for Alpha-1 liver disease," said John Walsh, president and chief executive officer of the Alpha-1 Foundation. "We're proud that The Alpha-1 Project, the Foundation's venture philanthropy arm, is collaborating with Arrowhead on the development of this potentially lifesaving therapy for both adults and children with liver disease due to Alpha-1."

ARC-AAT is the second clinical candidate to use Arrowhead's proprietary Dynamic Polyconjugate (DPC) delivery platform and includes an optimized RNAi-trigger design that contains an unlocked nucleobase analog (UNA) and various chemical modifications that enhance activity and substantially extend the duration of effect in non-clinical studies. Arrowhead previously reported data from these studies at an analyst day the company held in June 2014 and in a plenary presentation at the AASLD Liver Meeting in November 2014. Injection of ARC-AAT in transgenic mice expressing the inflammatory human Z-AAT protein resulted in prevention and reduction of Z-AAT globules and, importantly, liver inflammation. In primate studies, a 90% reduction of AAT in serum was observed after a single injection, which persisted for over ten weeks with greater than 80 percent knockdown observed at the six-week time point. Multi-dose studies in primates showed a sustained reduction of AAT with once every six weeks dosing. The goal of treatment with ARC-AAT is to reduce the hepatic production of Z-ATT, thereby preventing further accumulation of Z-AAT in the liver and potentially reversing pre-existing liver injury and fibrosis.

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 has been clearly defined as the 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 Alpha-1 Antitrypsin Deficiency (AATD)

AATD is a co-dominant 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 cure.

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 dysfunction during childhood. It is considered to be a relatively high prevalence orphan disease, and it is frequently misdiagnosed or undiagnosed. European prevalence is estimated to be 1 per 2500.

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, ARC-AAT for liver disease associated with Alpha-1 antitrypsin deficiency, and partner-based programs in obesity and oncology.

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, rapid technological change in our markets, 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

Arrowhead Research Corporation
Vince Anzalone, CFA
626-304-3400
ir@arrowres.com
or
Investor Relations:
The Trout Group
Todd James
646-378-2926
ir@arrowres.com
or
Media:
Russo Partners

Matt Middleman, M.D.
212-845-4272
matt.middleman@russopartnersllc.com

Source: Arrowhead Research Corporation

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