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# Arrowhead Announces New Clinical Candidate ARC-AAT for Treatment of Alpha-1 Antitrypsin Deficiency-Associated Liver Disease

- *RNAi Therapeutic ARC-AAT Induces Dose Dependent Reductions in Mutant AAT Protein of Greater than 95 Percent in Preclinical Studies*
- *Long Duration of Effect with AAT Remaining Reduced by More than 80% at 6 Weeks after a Single Dose*
- *Company Receives Funding from The Alpha-1 Project to Support ARC-AAT*

PASADENA, Calif.--(BUSINESS WIRE)-- Arrowhead Research Corporation (NASDAQ: ARWR), a biopharmaceutical company developing targeted RNAi therapeutics, today announced its next clinical candidate ARC-AAT, an RNAi therapeutic designed to treat liver disease associated with Alpha-1 antitrypsin deficiency (AATD). The Company is hosting an analyst day today to discuss ARC-AAT and will present preclinical data starting at 12:30 p.m. EDT. A live webcast of the presentation and archive are available on the Company's website at www.arrowheadresearch.com. To access an audio only live presentation, dial 844-825-4406 toll free from the U.S. or 315-625-3230 for international callers and enter Conference ID 54600551.

A panel of key opinion leaders will join Arrowhead management for the presentation today. Included in the panel are: Jeffrey Teckman, M.D., professor of pediatrics and biochemistry and molecular biology, and director, division of gastroenterology and hepatology, department of pediatrics, St. Louis University School of Medicine; John Walsh, co-founder, president and CEO, Alpha-1 Foundation; and, Jean-Marc Quach, executive director, The Alpha-1 Project.

"ARC-AAT is our second clinical candidate to use the DPC delivery system, and we are excited to build on the success to date of ARC-520, our clinical candidate against chronic hepatitis B infection, which is currently in a Phase 2a study," said Christopher Anzalone, Ph.D., Arrowhead's president and chief executive officer. "ARC-AAT is designed to inhibit the production of mutant AAT protein in the liver and in preclinical studies it has shown high levels of knockdown with long duration of action. AATD patients express mutant AAT, which can accumulate in hepatocytes and damage the liver. Liver disease associated with Alpha-1 antitrypsin deficiency has no current treatment options and patients can progress to cirrhosis, hepatocellular carcinoma, and may require liver transplant."

Arrowhead has developed a novel unlocked nucleobase analog (UNA)-containing RNAi molecule designed for systemic delivery using the Dynamic Polyconjugate (DPC) delivery system. ARC-AAT is highly effective at knocking down the Alpha-1 antitrypsin (AAT) gene transcript and reducing the hepatic production of mutant AAT protein. The Company plans to file an Investigational New Drug (IND) application for ARC-AAT in the fourth quarter of 2014.

In PiZ mice, which are genetically modified to produce the mutant human AAT (Z-AAT), ARC-AAT induced a greater than 95 percent reduction in circulating AAT after a single dose. After eight weeks of treatment in multi-dose studies, soluble (monomeric) and insoluble (polymeric) forms of Z-AAT were greatly reduced in the livers of PiZ mice treated with ARC-AAT. In addition, liver globule burden was substantially reduced from baseline levels and in comparison to treatment with saline, which showed progressive globule formation.

The addition of chemical modifications, including UNAs, slowed the rebound in production of AAT compared to canonical siRNAs, and produced a substantially improved duration of effect. In primate studies, knockdown of AAT in serum persisted for over ten weeks with greater than 80 percent knockdown observed at the six-week time point.

"AATD is one of the most common genetically-based orphan diseases," said Bruce Given, M.D., Arrowhead's chief operating officer. "In the absence of specific therapy other than liver transplant, the liver disease goes largely undiagnosed. As the lung disease is better recognized and treated, leading to longer life spans, the liver disease associated with AATD is becoming a larger clinical problem, for which we believe RNAi holds great potential."

The goal of treatment with ARC-AAT is prevention and possibly reversal of Z-AAT accumulation-related liver injury and fibrosis. Reduction of 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 allow fibrotic tissue repair.

The Company anticipates that initial testing will be in adult patients with signs of liver injury, with the intention of preventing additional injury and improving liver histology. In the future, additional studies may be initiated to investigate treatment of children, including those with severe hepatic disease who may otherwise require liver transplant.

Arrowhead also announced that it has signed an agreement with The Alpha-1 Project (TAP), the venture philanthropy subsidiary of the Alpha-1 Foundation. TAP's mission is to support organizations in pursuit of cures and therapies for lung and liver disease caused by Alpha-1 Antitrypsin Deficiency. Under the terms of the agreement, TAP will partially fund the development of ARC-AAT. In addition to the funding, TAP will make its scientific advisors available to Arrowhead, assist with patient recruitment for clinical trials thanks to the Alpha-1 Foundation Patient Research Registry, and engage in other collaborative efforts that support the development of ARC-AAT.

"On behalf of the Alpha-1 community, I am delighted to see this collaboration between TAP and Arrowhead," said John Walsh, president and CEO of the Alpha-1 Foundation. "This is an exciting effort to develop a therapy that could provide a sorely-needed treatment for both 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 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 disease 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 The Alpha-1 Project**

Mission statement: The Alpha-1 Project will work with patients, academia, pharmaceutical and biotech companies, and public health organizations in the relentless pursuit of cures and therapies for COPD and liver disease caused by Alpha-1 Antitrypsin Deficiency. For more information, visit www.thealpha-1project.com. The Alpha-1 Project is a wholly-owned for-profit subsidiary of the Alpha-1 Foundation. For more information on the Foundation, visit www.alpha-1foundation.org.

**About Arrowhead Research Corporation**

Arrowhead Research Corporation is a biopharmaceutical company developing targeted RNAi therapeutics. The company is leveraging its proprietary drug delivery technologies to develop targeted drugs based on the RNA interference mechanism that efficiently silences disease-causing genes. Arrowhead technologies also enable partners to create peptide-drug conjugates that specifically home to cell types of interest while sparing off-target tissues. Arrowhead's pipeline includes clinical programs in chronic hepatitis B virus 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 to receive news directly, please send an email to ir@arrowres.com.

**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.*

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