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Arrowhead Pharmaceuticals Provides Update on Heparc-2004 Study

PASADENA, Calif.--(BUSINESS WIRE)-- Arrowhead Pharmaceuticals, Inc. (NASDAQ: ARWR) is providing an update on its Heparc-2004 clinical study of ARC-520, its therapeutic candidate under clinical investigation for the treatment of chronic hepatitis B virus (HBV) infection. Heparc-2004 is a multicenter, randomized, double-blind, placebo-controlled, multi-dose study of ARC-520, which is currently being performed in up to 12 patients in the United States under an Investigational New Drug (IND).

Arrowhead was notified today verbally by the United States Food & Drug Administration (FDA) of its decision to place a clinical hold on Heparc-2004. The study is on hold while the company provides responses to questions arising from a nonclinical toxicology study in non-human primates using EX1, the company's liver-targeted, intravenously administered delivery vehicle.

The FDA did not indicate the clinical hold was based on any human findings. To date, EX1 has been administered over 800 times in more than 300 human study subjects and patients. Across this substantial clinical experience, only 3 serious adverse events (SAE) have been observed. Two of these were fevers, treated with acetaminophen, after which the patients continued on the study with no further complications. The other SAE was an instance of hepatic carcinoma in a patient with chronic HBV and cirrhosis, judged by the treating physician to be unrelated to the drug. A small minority (6%) of infusions in ARC-520 studies have been associated with infusion reactions, with 4 patients discontinuing ARC-520 treatment. In addition, across the ARC-520, ARC-521, and ARC-AAT clinical programs, laboratory values have not been deemed indicative of any drug-induced organ toxicity.

Arrowhead has not yet received written notice of the clinical hold from the FDA; however, based on verbal communications the clinical hold was prompted by deaths at the highest dose of an ongoing non-human primate toxicology study. This study involves higher doses of EX1 than those used clinically in humans and higher than those used in the company's previous animal toxicology studies. The cause of these animal deaths is unknown and under investigation. The EX1 delivery vehicle is used in the company's ARC-520, ARC-521, and ARC-AAT programs.

Arrowhead remains committed to working collaboratively with regulatory authorities worldwide. The company has disseminated data from the same animal study to agencies across our development programs and is providing updates as appropriate. The company believes the findings in animal toxicology studies are related to dose level, and that the safety profile seen in human clinical studies across the three programs involving EX1 supports continuing all ongoing clinical studies.

About ARC-520

Arrowhead's ARC-520 is being investigated for its potential to produce functional cures in patients with chronic hepatitis B virus (HBV) infection. ARC-520 intervenes upstream of the reverse transcription process where current standard-of-care nucleotide and nucleoside analogs act, and is designed to silence the production of all HBV gene products. The small interfering RNAs (siRNAs) in ARC-520 engage the body's normal cellular RNAi machinery and direct specific cleavage of HBV RNA transcripts, thereby reducing the levels of HBV proteins and the RNA template used to produce viral DNA. Arrowhead is investigating ARC-520 specifically to determine if significantly reducing circulating and non-circulating viral proteins and RNA will allow for re-constitution of an effective host immune response and ultimately HBsAg seroclearance, resulting in functional cure. As many as 350-400 million people worldwide are chronically infected with the hepatitis B virus, which can lead to cirrhosis of the liver and is responsible for 80% of primary liver cancers globally. Arrowhead is currently conducting Phase 2b multiple dose and combination studies in chronic HBV patients. In clinical studies to date, the most common reported adverse events in all subjects completing treatment were upper respiratory infection and headache.

About ARC-521

Arrowhead's ARC-521 is being investigated for its potential to produce functional cures in patients with chronic hepatitis B virus (HBV) infection. ARC-521 intervenes upstream of the reverse transcription process where current standard-of-care nucleotide and nucleoside analogs act, and is designed to silence the production of all HBV gene products. The small interfering RNAs (siRNAs) in ARC-521 engage the body's normal cellular RNAi machinery and direct specific cleavage of HBV RNA transcripts, thereby reducing the levels of HBV proteins and the RNA template used to produce viral DNA. Designed to complement ARC-520, ARC-521 is a second-generation HBV candidate that targets HBV mRNA transcripts from both cccDNA and integrated DNA and is expected to be most suitable for those patients who tend to have lower levels

of viral cccDNA. Arrowhead is investigating ARC-521 specifically to determine if significantly reducing circulating and non-circulating viral proteins and RNA will allow for re-constitution of an effective host immune response and ultimately HBsAg seroclearance, resulting in functional cure. As many as 350-400 million people worldwide are chronically infected with the hepatitis B virus, which can lead to cirrhosis of the liver and is responsible for 80% of primary liver cancers globally. Arrowhead is conducting a Phase 1/2 single and multiple dose study in healthy volunteers and HBV patients.

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. 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 a rare disease that is frequently misdiagnosed or undiagnosed. ARC-AAT employs a novel unlocked nucleobase analog (UNA) containing an 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 in animal studies. Reduction of liver production of the inflammatory Z-AAT protein, which is believed to be the cause of progressive liver disease in AATD patients, is important as it is expected to halt the progression of liver disease. ARC-AAT was granted orphan drug designation in both the United States and in Europe, the latter being held on Arrowhead's behalf by a local EU representative, Pharma Gateway AB. Arrowhead is conducting a Phase 1 clinical study of ARC-AAT, with part A in healthy volunteers (now complete) and part B in AATD patients, and a Phase 2 multiple dose study in AATD patients.

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. The company's pipeline includes ARC-520 and ARC-521 for chronic hepatitis B virus infection, ARC-AAT for liver disease associated with alpha-1 antitrypsin deficiency, ARC-F12 for hereditary angioedema and thromboembolic disorders, ARC-LPA for cardiovascular disease, and ARC-HIF2 for renal cell carcinoma.

For more information, please visit www.arrowheadpharma.com, or follow us on Twitter [@ArrowheadPharma](https://twitter.com/ArrowheadPharma). To be added to the Company's email list and receive news directly, please visit <http://ir.arrowheadpharma.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 the safety and efficacy of our product candidates, the duration and impact of the clinical hold of Heparc-2004, 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. 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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