October 9, 2014

Arrowhead Issues Open Letter to Shareholders

PASADENA, Calif.--(BUSINESS WIRE)-- Arrowhead Research Corporation (NASDAQ: ARWR), a biopharmaceutical company developing targeted RNAi therapeutics, today issued the following open letter to shareholders from President and CEO, Christopher Anzalone, Ph.D.:

Dear Arrowhead Shareholders,

Market reaction to our AASLD abstract took us by surprise because we have always believed that our public communications surrounding the ARC-520 Phase 2a study have been consistent and, more importantly, properly reflected the data we were seeing in the initial two cohorts. We still believe that, but the market clearly expected something different and/or misunderstood the data. Therefore, I wanted to clarify recent events for our shareholders.

Let us begin with our goal. We have said for some time that our goal was to identify a dose of ARC-520 capable of achieving HBsAg reduction of around 1 log (corresponding with 90% knockdown) after a single administration. This was a somewhat arbitrary goal since it is unknown what level of HBsAg reduction is necessary to de-repress the immune system and potentially enable a functional cure. Indeed, the entire concept of enabling a functional cure by suppressing HBsAg release remains an untested theory, but that is one of the challenges of being a pioneer in the field. We chose 1 log as a goal because, according to the scientific literature, the small number of patients who achieve functional cure from Interferon therapy demonstrate ½ log reduction in HBsAg (approximately 70% knockdown) after 12 weeks and 1 log (90% knockdown) after 24 weeks. We expected that if ARC-520 is active it should lead to more rapid reduction, particularly on repeat dosing, so a full log might not be needed after a single administration. Even so, we believed that a 1 log goal is intellectually honest and we wanted to share our thinking publicly rather than establish an artificially low goal just so we could beat it.

With this goal in hand and on the back of a Phase 1 study that suggested ARC-520 was well tolerated, we embarked on our ongoing Phase 2a dose-finding study. Given our animal data across multiple species we believed that we could achieve our goal, but we did not know what dose level would be needed in humans. As is always appropriate with a new technology, we started on the low end of what we expected to be the active dose range, 1 - 2 mg/kg. We characterized these doses as, in our view, potentially active but always added that we were prepared to go higher. On our August 12th quarterly conference call, we disclosed that the first 2 dose levels tested in patients with chronic HBV would not meet our goal. This was not alarming to us because the safety data from the Phase 1 study in healthy volunteers suggested that we could continue to dose-escalate with little risk of toxicity. Therefore, we began a new cohort at a higher dose: 3 mg/kg. At the time of our August update, the study was still blinded and ongoing but we wanted to provide some information about what we were seeing. Recognizing that we were still blinded to which patients had received ARC-520 and which received placebo, we described the apparent HBsAg knockdown at 1mg/kg as "modest" and 2mg/kg as "moderate." The study is now unblinded with respect to the first two cohorts and, as was reported in the recent AASLD abstract, we now know that the mean peak knockdown was 39% at 1 mg/kg and 51% at 2 mg/kg. Those numbers still feel "modest" and "moderate" to us, as we initially reported. Since the August conference call, we have remained consistent with that terminology.

We also said on the August conference call that we believed the knockdown we were seeing in humans was similar in magnitude to that which we have seen in previous studies with non-human primates at similar doses. More specifically, the chimpanzee with chronic HBV that we treated received two doses of ARC-520: 2 mg/kg on day 1 and then 3 mg/kg on day 15. Prior to receiving the second dose, HBsAg was reduced about 50% from baseline. To repeat, we reported mean peak HBsAg knockdown of 51% in patients receiving 2 mg/kg in the Phase 2a while the chimpanzee knockdown at that dose was approximately 50%. The chimpanzee ultimately experienced 80-85% reduction in HBsAg, but only after receiving the 3 mg/kg dose. That was not the only study with non-human primates that can be referenced. In a paper we published in the scientific journal *Molecular Therapy* in May 2013, we showed that doses around 2 mg/kg (using siRNAs targeting a different liver-expressed gene) inhibit Factor 7 activity between 30-60%. As with the chimpanzee study, this certainly feels similar in magnitude to the 51% HBsAg knockdown we saw in patients receiving 2 mg/kg ARC-520.

So where are we? We have only completed the first two dose levels in an ongoing dose finding study and have not yet identified a dose in humans that will meet our knockdown goal… but we are not yet finished. We now have unblinded Phase 1 safety data in healthy volunteers through 4 mg/kg and we continue to see a favorable safety profile: no dose-limiting toxicities or adverse events rated serious or severe. We have just finished dosing all 8 patients in the 3 mg/kg cohort and as data come

in, we will decide whether to escalate to 4 mg/kg. We do not expect timing of the program to be impacted. We plan to submit regulatory filings by the end of the year in support of the multi-dose Phase 2b study whether or not we escalate to 4mg/kg in the Phase 2a study.

We continue to be excited about ARC-520 and the potential to enable a functional cure for patients with chronic HBV infection. There is still much we do not know about ARC-520 and how effective a therapy it may be one day, but there are some important things that we do know. It appears to be well tolerated at all doses tested in our prior Phase 1 study: 1 mg/kg - 4 mg/kg. The drug appears to do what it is designed to do. We have seen clear knockdown in the first 2 doses tested in patients and the favorable safety profile enables us to increase the dose to see if we can induce deeper knockdown. Interestingly, we have seen unexpectedly durable knockdown in patients, even though the low doses provided relatively shallow depth of HBsAg reductions. At the final time points studied, nearly 3 months after a single injection, we continue to see knockdown. We believe that this is important and quite unique. We expect that it will provide significant advantages, particularly as we increase dose and initiate planned multi-dose studies.

We remain committed to long term value creation for our shareholders, and this includes timely and honest communication. We have always provided as much information as possible and have tried to be transparent about our thinking and planning, and we will continue to do so.

Sincerely,

Christopher Anzalone, Ph.D.
President and CEO

About ARC-520

Arrowhead's RNAi-based candidate ARC-520 is designed to treat chronic HBV infection by reducing the expression and release of new viral particles and key viral proteins. The goal is to achieve a functional cure, which is an immune clearant state characterized by hepatitis B s-antigen negative serum with or without sero-conversion. The siRNAs in ARC-520 intervene at the mRNA level, upstream of where nucleotide and nucleoside analogues act. In transient and transgenic mouse models of HBV infection, a single co-injection of Arrowhead's Dynamic Polyconjugate (DPC) delivery vehicle with cholesterol-conjugated siRNA targeting HBV sequences resulted in multi-log knockdown of HBV RNA, proteins and viral DNA with long duration of effect. Arrowhead has completed enrollment in a Phase 1 single ascending dose study in normal volunteers. The company is conducting a single dose Phase 2a study in chronic HBV patients, and expects to follow with multi-dose, multi-national Phase 2b studies. Approximately 350 million people worldwide are chronically infected with the hepatitis B virus. Chronic HBV infection can lead to cirrhosis of the liver and is responsible for 80% of primary liver cancers globally.

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 achieve targeted levels of efficacy for ARC-520 in our ongoing Phase 2a study in Hepatitis B, as well as our ability to replicate the results seen in earlier preclinical studies in ongoing and future clinical studies, the ability to achieve a functional cure for Hepatitis B at the targeted levels of antigen knockdown, or any level that we are able to achieve, the ability to continue to safely dose patients at higher levels with ARC-520 or other drugs, our ability to finance our operations, the future success of our scientific studies, our ability to successfully develop drug candidates (both in terms of safety and efficacy), 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

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