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Arrowhead Data Reveal Important Considerations for Future Hepatitis B Treatment

- Results May Guide New Clinical Approaches, *Science Translational Medicine* Study Shows -

PASADENA, Calif.--(BUSINESS WIRE)-- Arrowhead Pharmaceuticals Inc. (NASDAQ: ARWR) today announced results from studies of ARC-520, a prior-generation RNAi therapeutic candidate against chronic hepatitis B virus (HBV) infection, in a Phase 2 clinical study in HBV patients and a complementary study in chimpanzees chronically infected with HBV. These studies demonstrated that HBV DNA integrated into the host genome is an under-appreciated source of HBV surface antigen (HBsAg), a key protein implicated in maintaining chronic HBV infection.

In many patients, integrated HBV DNA appeared to be the dominant source of HBsAg production. The findings expand the understanding of HBV biology and host interactions, and could have important implications for future trial design and endpoint expectations for new therapies developed to cure chronic HBV. These data from study, "RNAi-based treatment of chronically infected patients and chimpanzees implicates integrated hepatitis B virus DNA as a source of HBsAg" were published in *Science Translational Medicine.*

Bruce D. Given, M.D., chief operating officer and head of R&D for Arrowhead Pharmaceuticals, said: "Our experience from Arrowhead's multiple clinical studies of our prior therapeutic candidates ARC-520 and ARC-521, and the extensive non-clinical research we completed, have provided us with invaluable insights that guide the development path of follow-on candidate ARO-HBV, a new therapy for patients with chronic HBV that utilizes the company's next generation Targeted RNAi Molecule (TRiM™) platform. We think long-term immune control of HBV will require reduction of HBsAg from both integrated DNA and cccDNA, which ARO-HBV is designed to do. Importantly, the findings described in the Science Translational Medicine paper extend beyond HBsAg in showing reductions in other viral antigens and viral DNA. The ARC-520 and ARC-521 data suggest that an RNAi-based approach, like ARO-HBV, could serve as a cornerstone therapy for combinations intended to cure chronic HBV because it can act as a direct anti-viral against all HBV viral products and has the potential to synergize with other agents."

The paper entitled, "RNAi-based treatment of chronically infected patients and chimpanzees implicates integrated hepatitis B virus DNA as a source of HBsAg," by Christine I. Wooddell and Man-Fung Yuen et al, was made available online ahead of print in the journal Science Translational Medicine (27 September 2017).

In the publication, several independent lines of evidence demonstrate that HBsAg is expressed not only from the episomal covalently closed circular DNA (cccDNA) minichromosome, but also from transcripts arising from HBV DNA integrated into the host genome. The latter was a large source of HBsAg production in HBeAg negative chimpanzees and presumed, by extension, in HBeAg negative and NUC experienced patients.

"This is an important finding with wide-reaching implications for the field because production of viral proteins was previously thought to depend only on transcription of viral cccDNA. We now understand that integrated HBV DNA is a means of producing circulating HBsAg that is not dependent on viral replication, which may contribute to sustained suppression of the immune system and allow for continued virion production," commented Christine I. Wooddell, Ph.D., lead study author. "Just a few cccDNA-containing cells able to escape immune surveillance can maintain chronic infection. Therefore, only complete immune control of HBsAg can be expected to prevent reinfection off therapy and result in a functional cure."

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.

For more information, please visit www.arrowheadpharma.com, or follow us on Twitter @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 regulatory delays in our clinical programs, 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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