



Arrowhead Pharmaceuticals Gains Full Rights to NASH Candidate ARO-PNPLA3 with Promising Phase 1 Results

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- Achieved Up to 40% Mean Reduction in Liver Fat in PNPLA3 I148M Homozygotes After Single-Dose

PASADENA, Calif.--(BUSINESS WIRE)--Feb. 15, 2023-- Arrowhead Pharmaceuticals Inc. (NASDAQ: ARWR) announced today that it has gained rights to ARO-PNPLA3, formerly called JNJ-75220795, which was part of a 2018 research collaboration and option agreement between Arrowhead and Janssen Pharmaceuticals, Inc., one of the Janssen Pharmaceutical Companies of Johnson & Johnson. ARO-PNPLA3 is an investigational RNA interference (RNAi) therapeutic developed using Arrowhead's proprietary TRiM™ platform and designed to reduce liver expression of patatin-like phospholipase domain containing 3 (PNPLA3) as a potential treatment for patients with non-alcoholic steatohepatitis (NASH). ARO-PNPLA3 is currently in a Phase 1 clinical study. PNPLA3 has strong genetic and preclinical validation as a driver of fat accumulation and damage in the livers of patients who carry the common I148M mutation.

"With no FDA approved therapies, NASH remains an area of significant unmet medical need. PNPLA3 is a unique NASH drug target as the I148M disease associated variant increases the risk of NAFLD, NASH, and hepatocellular carcinoma by 4 to 12-fold for homozygotes. The vast human genetic data in support of this target are compelling and supported by a strong pathophysiologic mechanistic understanding," said Rohit Loomba, M.D., MHSc, Professor of Medicine, Director of the NAFLD Research Center at University of California at San Diego. "The Phase 1 data on ARO-PNPLA3 are extremely encouraging and I look forward to seeing this molecule progress to a later stage clinical study."

After a single dose in a Phase 1 clinical study, ARO-PNPLA3 achieved encouraging results, including:

- A dose-dependent mean reduction in liver fat of up to 40% in patients homozygous for the I148M mutation
- No apparent treatment emergent increases in triglycerides or LDL-cholesterol
- Safety and tolerability
 - No clinically meaningful changes or trends in any safety parameters
 - No tolerability issues reported
 - Mostly mild adverse events (AE) reported
 - No serious or severe AEs
 - No AEs leading to treatment or study discontinuation

"We are impressed by the initial Phase 1 clinical data for JNJ-75220795, now called ARO-PNPLA3. We understand that Janssen is undergoing a strategic R&D portfolio review and subsequently advised us of their decision to return full rights to this promising NASH candidate back to Arrowhead," said Christopher Anzalone, Ph.D., Arrowhead's president and CEO. "ARO-PNPLA3 is a potentially complementary addition to our growing pipeline of RNAi candidates in the cardiometabolic space. We look forward to the availability of additional data on ARO-PNPLA3 as we design a Phase 2 study and assess options for communicating full Phase 1 results."

NASH is a subgroup of non-alcoholic fatty liver disease (NAFLD) in which hepatic cell injury and inflammation has developed over background steatosis. Although there are many investigational drugs in clinical study, there are no drugs specifically approved for the treatment of NASH. NAFLD is the most common chronic liver disease with a worldwide prevalence of 20-30%. Up to 30% of those with NAFLD will go on to develop NASH which can progress to liver cirrhosis. The rising prevalence of NASH presents a significant health burden in many developed countries.^{1,2}

The I148M genetic variant in the PNPLA3 gene is involved with the underlying pathophysiology and is a known risk factor for hepatic steatosis, steatohepatitis, elevated plasma liver enzyme levels, hepatic fibrosis and cirrhosis. There are approximately 12.5 million PNPLA3 I148M homozygotes in China, Japan, Germany, Italy, the UK, and the U.S. with approximately 4.5 million in the U.S. alone.³

The Phase 1 study ([NCT04844450](https://clinicaltrials.gov/ct2/show/study/NCT04844450)) is a double-blind, placebo-controlled, randomized, multipart, single and multiple ascending dose study to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of subcutaneously administered JNJ-75220795 in up to 112 participants with certain genetic predisposition to NAFLD and the presence of liver steatosis determined at screening.

About Arrowhead/Janssen Research Collaboration

Arrowhead received written notice from Janssen that they have terminated their rights to JNJ-75220795, now called ARO-PNPLA3, under the October 2018 research collaboration and option agreement. The companies are working to transition the program and associated data to Arrowhead.

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](https://twitter.com/ArrowheadPharma). To be added to the Company's email list and receive news directly, please visit <http://ir.arrowheadpharma.com/email-alerts>.

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. Any statements contained in this release except for historical information may be deemed to be forward-looking statements. Without limiting the generality of the foregoing, words such as "may," "will," "expect," "believe," "anticipate," "hope," "intend," "plan," "project," "could," "estimate," or "continue" are intended to identify such forward-looking statements. In addition, any statements that refer to projections of our future financial performance, trends in our business, expectations for our product pipeline or product candidates, including anticipated regulatory submissions and clinical program results, prospects or benefits of our collaborations with other companies, or other characterizations of future events or circumstances are forward-looking statements. 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 numerous factors and uncertainties, including the impact of the ongoing COVID-19 pandemic on our business, the safety and efficacy of our product candidates, decisions of regulatory authorities and the timing thereof, the duration and impact of regulatory delays in our clinical programs, our ability to finance our operations, the likelihood and timing of the receipt of future milestone and licensing fees, the future success of our scientific studies, our ability to successfully develop and commercialize drug candidates, the timing for starting and completing clinical trials, rapid technological change in our markets, the enforcement of our intellectual property rights, and the other risks and uncertainties described in our most recent Annual Report on Form 10-K, subsequent Quarterly Reports on Form 10-Q and other documents filed with the Securities and Exchange Commission from time to time. We assume no obligation to update or revise forward-looking statements to reflect new events or circumstances.

Source: Arrowhead Pharmaceuticals, Inc.

¹ Ekstedt, M., Nasr, P. & Kechagias, S. Curr Hepatology Rep. 2017;16: 391.

² Vernon, G, Baranova, A. and Younossi, Z. M. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Alimentary Pharmacology & Therapeutics, 2011;34:274-285.

³ Carlsson B, Lindén D, Brölén G, et al. Review article: the emerging role of genetics in precision medicine for patients with non-alcoholic steatohepatitis. Aliment Pharmacol Ther. 2020;00:1–16. <https://doi.org/10.1111/apt.15738>

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