Arrowhead Pharmaceuticals Licenses Clinical MASH Program Targeting PNPLA3 to Madrigal Pharmaceuticals

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- Precision approach targets patients who have a mutation in the PNPLA3 gene, which is highly prevalent among Hispanic patients with MASH

- Phase 1 data published in *The New England Journal of Medicine* demonstrated a 46% reduction in liver fat in homozygous patients and a well-tolerated safety profile

PASADENA, Calif.--(BUSINESS WIRE)--May 5, 2026-- Arrowhead Pharmaceuticals, Inc. (NASDAQ: ARWR) today announced an exclusive worldwide license agreement with Madrigal Pharmaceuticals (NASDAQ: MDGL) for ARO-PNPLA3, Arrowhead's clinical stage RNA interference (RNAi) therapeutic designed to reduce liver expression of patatin-like phospholipase domain containing 3 (PNPLA3) as a potential treatment for patients with metabolic dysfunction-associated steatohepatitis (MASH).

"The early clinical data for ARO-PNPLA3 have been quite compelling and demonstrate reductions in liver fat up to 46% following a single dose in patients homozygous for the PNPLA3 I148M mutation, a well-established genetic contributor to MASH progression," said Christopher Anzalone, Ph.D., President and CEO at Arrowhead. "Madrigal's leadership in the MASH space make them a natural and attractive partner to advance ARO-PNPLA3. Our proprietary TRiM™ platform enables broad targeting of diseases and genes expressed throughout the body generating a deep pipeline of candidates, many of which are well suited for strategic partnerships to accelerate development and commercialization. Today's transaction with Madrigal underscores Arrowhead's disciplined business development strategy, demonstrating our ability to partner high-potential, clinically validated programs with leading organizations in therapeutic areas beyond our core commercial cardiometabolic focus."

PNPLA3 has strong genetic and preclinical validation as a driver of fat accumulation and damage in the livers of patients who carry the I148M mutation. The I148M genetic variant 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.

Phase 1 Trials of ARO-PNPLA3 Provide Potential Proof of Concept

A Phase 1, first-in-human, double-blind, placebo-controlled trial of ARO-PNPLA3 was conducted in the United States in 55 patients with Metabolic dysfunction-associated fatty liver disease (MAFLD) who were either homozygous or heterozygous carriers of the PNPLA3 I148M variant. Approximately 93% of participants were Hispanic or Latino. Data from this study, published in *The New England Journal of Medicine*[1], demonstrated:

- Reductions in liver fat up to 46% (as measured by MRI-PDFF) at 12 weeks following a single dose at the highest dose level tested in PNPLA3 I148M homozygous patients
- Rapid onset of effect, with reductions observed at six weeks and sustained through at least 24 weeks
- No clinically meaningful adverse events were observed
- No effect on liver fat content was observed in heterozygous participants at any of the doses studied
- Results from a second Phase 1 trial conducted in Japan (n=9) support these findings

Summary of License Agreement

Under the terms of the agreement, Madrigal will receive an exclusive global license to develop, manufacture, and commercialize ARO-PNPLA3, a clinical stage program that utilizes Arrowhead's TRiM ™ platform designed to silence hepatocyte expression of PNPLA3 as a potential treatment for patients with MASH.

Summary Financial Terms

Upon closing, Madrigal will make a $25 million upfront payment to Arrowhead. Arrowhead is also eligible to receive development, regulatory, and sales milestone payments of up to $975 million. Arrowhead is further eligible to receive tiered royalties on commercial sales ranging from high-single digits to the mid-teens.

About Arrowhead Pharmaceuticals

Arrowhead Pharmaceuticals (NASDAQ: ARWR) is a commercial-stage pharmaceutical company developing medicines that treat intractable diseases by silencing the genes that cause them, harnessing the natural RNA interference (RNAi) mechanism. The company has built a broad portfolio of clinical and commercial RNAi therapeutics through its industry-leading targeted RNAi molecule (TRiM™) platform, which can precisely silence genes in a wide range of cell types, including liver, lung, muscle, adipose, and central nervous system tissue. At Arrowhead, we rapidly advance potential best- and first-in-class RNAi treatments for diseases with significant unmet medical need, because every day matters to the patients we serve.

For more information, please visit www.arrowheadpharma.com, or follow us on X (formerly Twitter) at @ArrowheadPharma, LinkedIn, Facebook, and Instagram. 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," "continue," "target," "forecast" or "continue" or the negative of these words or other variations thereof or comparable terminology 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 forward-looking statements include, but are not limited to, statements about the initiation, timing, progress and results of our preclinical studies and clinical trials, and our research and development programs; our expectations regarding the potential benefits of the partnership, licensing and/or collaboration arrangements and other strategic arrangements and transactions we have entered into or may enter into in the future; our beliefs and expectations regarding milestone, royalty or other payments that could be due to or from third parties under existing agreements; and our estimates regarding future revenues, research and development expenses, capital requirements and payments to third parties. 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 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.

[1] Fabbrini, E., Rady, B., Koshkina, A., et al. (2024). Phase 1 Trials of PNPLA3 siRNA in I148M Homozygous Patients with MAFLD. The New England Journal of Medicine, 391(5), 475. https://doi.org/10.1056/NEJMc2402341

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