Arrowhead Pharmaceuticals Showcases Two Clinical-Stage RNAi-Based Candidates to Treat Obesity and Metabolic Diseases

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- ARO-INHBE and ARO-ALK7 both target a known pathway that signals the body to store fat in adipose tissue with a novel mechanism of action that may better preserve lean muscle mass compared to currently approved obesity therapies

- Data highlight Arrowhead's leadership in the use of RNA interference to potentially treat Obesity

PASADENA, Calif.--(BUSINESS WIRE)--Mar. 6, 2025-- Arrowhead Pharmaceuticals, Inc. (NASDAQ: ARWR) today announced presentation of preclinical data supporting the advancement of two first-in-class clinical stage, RNAi-based investigational therapeutics being developed for the treatment of obesity and metabolic diseases. The two candidates, ARO-INHBE and ARO-ALK7, have the potential to reduce body weight and fat mass with a novel mechanism of action that may lead to improved preservation of lean muscle mass compared to currently approved obesity therapies. The presentation titled, "Targeting Obesity with RNAi-based Therapies," was included in the Oligo-Based Therapeutics: Clinical Advancements session at the RNA Leaders Europe Congress 2025 held March 4–6, 2025 in Basel, Switzerland.

"Arrowhead is leading the field in the discovery and development of potential new RNAi-based therapies for obesity and metabolic diseases. Our first two programs, ARO-INHBE and ARO-ALK7, both seek to intervene in a known biological pathway with strong support from human genetics studies and compelling preclinical results in mouse models of obesity where INHBE silencing in the liver and ALK7 silencing in adipose tissue led to dramatic reductions in fat mass without reductions in lean mass." said James Hamilton, M.D., MBA, Chief Medical Officer and Head of R&D. "We now move on to Phase 1/2 clinical studies in patients with obesity that are designed to evaluate single- and multiple-ascending doses of ARO-INHBE and ARO-ALK7 as monotherapy, as well as multiple-ascending doses in combination with tirzepatide, a GLP-1/GIP receptor co-agonist."

Select ARO-INHBE Preclinical Results:

In a diet-induced obese (DIO) mouse model, hepatic INHBE silencing with siRNA led to a 19% suppression in body weight gain relative to vehicle controls. Treated mice exhibited improved body composition with a 22% reduction of fat mass while preserving lean mass. Treated mice also demonstrated a trend to improved glycemic control. Hepatic INHBE silencing in DIO mice enhanced catecholamine sensitivity, increasing lipid mobilization and oxidation, which was not associated with liver steatosis. In fact, treated animals showed less liver fat accumulation relative to saline controls.

Select ARO-ALK7 Preclinical Results:

DIO mice treated with an ALK7 siRNA exhibit a 39% suppression in body weight gain relative to controls. Adipose ALK7 silencing reduced fat mass by 50% while preserving lean mass. Similar to INHBE silencing in hepatocytes, ALK7 silencing in adipocytes enhanced catecholamine sensitivity, increasing lipid mobilization and oxidation, which was not associated with liver steatosis. In fact, treated animals showed less liver fat accumulation relative to saline controls. In combination studies with tirzepatide, ALK7 siRNA enhanced the therapeutic benefits versus tirzepatide monotherapy, with additive effects on body weight and fat mass reduction while ameliorating the significant loss of lean mass associated with tirzepatide monotherapy.

Arrowhead believes it is the first company to initiate clinical studies against these two novel targets, INHBE and ALK7. INHBE, and the ligand it encodes Activin E, signals the ALK7 receptor on adipose tissue to store fat and suppress lipolysis. Intervening in this known biological pathway has the potential to improve adipose dysfunction in obesity by increasing lipolysis and reducing adipose hypertrophy and visceral adiposity. In addition, published human genetics studies suggest that loss-of-function variants of INHBE and/or ALK7 are associated with reduced abdominal fat and lower risk of coronary heart disease and type 2 diabetes.

Arrowhead is currently conducting Phase 1/2 clinical studies of ARO-INHBE and ARO-ALK7. Dosing in the ARO-INHBE study was initiated in December 2024 with initial data possible by year end 2025. The company anticipates dosing in the ARO-ALK7 study will begin in the second quarter of 2025 with initial data from the single-ascending dose portion of the study possible by year end 2025.

The presentation may be accessed on the Events and Presentations page in the Investors section of the Arrowhead website.

About ARO-INHBE

ARO-INHBE is designed to reduce the hepatic expression of the INHBE gene and its secreted gene product, Activin E. INHBE is a promising genetically validated target in which loss-of-function INHBE variants in humans are associated with improved fat distribution and lower risk of metabolic diseases, such as type 2 diabetes. Activin E acts as a ligand in a pathway that regulates energy homeostasis in adipose tissue. Inhibiting this pathway with investigational ARO-INHBE treatment has the potential to increase lipolysis, and reduce adipose hypertrophy and dysfunction, visceral adiposity, and insulin resistance.

About the AROINHBE-1001 Phase 1/2 Study

AROINHBE-1001 (NCT06700538) is a Phase 1/2a dose-escalating study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of ARO-INHBE in up to 78 adult volunteers with obesity. Part 1 of the study is designed to assess single and multiple doses of ARO-INHBE monotherapy, and Part 2 of the study is designed to assess ARO-INHBE in combination with tirzepatide, a subcutaneously administered GLP-1/GIP receptor co-agonist that has been approved in the United States and the European Union for management of type 2 diabetes mellitus since 2022 and weight management since 2023/2024 respectively.

About ARO-ALK7

ARO-ALK7 is designed to silence adipocyte expression of the ACVR1C gene to reduce the production of Activin receptor-like kinase 7 (ALK7), which acts as a receptor in a pathway that regulates energy homeostasis in adipose tissue. In large genetic datasets, reduced ACVR1C expression has been associated with healthier adipose distribution and reduced risk of obesity-related metabolic complications. Treatment with investigational ARO-ALK7 has the potential to reduce visceral adiposity and improve lipid and glycemic parameters.

About the AROALK7-1001 Phase 1/2a Study

AROALK7-1001 is a Phase 1/2a first-in-human dose-escalating study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of ARO-ALK7 in up to 90 adult volunteers with obesity. Part 1 of the study is designed to assess single and multiple doses of ARO-ALK7 monotherapy, and Part 2 of the study is designed to assess ARO-ALK7 in combination with tirzepatide, a subcutaneously administered GLP-1/GIP receptor co-agonist that has been approved in the United States and the European Union for management type 2 diabetes mellitus since 2022 and weight management since 2023/2024 respectively.

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 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.

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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 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.

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