



Arrowhead Pharmaceuticals Presents Preclinical Data on ARO-ALK7 for Treatment of Obesity

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PASADENA, Calif.--(BUSINESS WIRE)--Feb. 25, 2025-- Arrowhead Pharmaceuticals, Inc. (NASDAQ: ARWR) today announced preclinical results on ARO-ALK7, the company's investigational RNA interference (RNAi) therapeutic targeting Activin receptor-like kinase 7 (ALK7) being developed as a potential treatment for obesity. The results were presented in a poster at the Keystone Symposia on Obesity and Adipose Tissue held February 23–26, 2025 in Banff, AB, Canada.

ARO-ALK7 is the first RNAi-based therapy to directly target a gene expressed in adipose tissue and highlights Arrowhead's leadership in the delivery of siRNA to multiple tissues and cell types throughout the body utilizing its proprietary and differentiated Targeted RNAi Molecule (TRiM™) platform. Arrowhead received regulatory clearance to initiate a Phase 1/2a clinical trial of ARO-ALK7 in New Zealand, which the company anticipates will begin dosing in the second quarter of 2025.

"Human genetic studies support ALK7 as a promising therapeutic target for the treatment of obesity. Loss-of-function ALK7 variants have been associated with improved body composition, protection from type 2 diabetes, and reduced risk of cardiovascular disease. While incretin-based therapies are the current frontline pharmacotherapeutics for obesity and metabolic outcomes, issues concerning significant loss of lean mass, adverse GI events at high dose levels, and disproportional fat mass gain after cessation of the therapies remain a challenge for many patients," said James Hamilton, M.D., MBA, Chief Medical Officer and Head of R&D. "In preclinical studies in rodents and non-human primates, ARO-ALK7 demonstrated dose-dependent and durable reductions in ALK7 mRNA expression in adipose tissue. Pharmacological studies in diet-induced obese mouse models demonstrate that ALK7 silencing in adipose tissue led to improved body composition, with an approximate 50% reduction in fat mass with preservation of lean mass. Furthermore, co-treatment of tirzepatide, a GLP-1/GIP receptor co-agonist, with 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. Lastly, body fat loss in mice with ALK7 silencing was attributed to increased energy expenditure and lipolysis without a change in food intake, suggesting that the effect was due to fat being metabolized as opposed to caloric reduction."

Select Preclinical Results:

Pharmacodynamic results in non-human primates

- Single subcutaneous doses of ARO-ALK7 led to dose-dependent and durable reductions in ALK7 mRNA in abdominal fat
 - Approximately 80% knockdown achieved at 0.3 mg/kg
 - Approximately 91% knockdown achieved at 1.5 mg/kg with 75% knockdown still observed after 12 weeks

Pharmacological studies in a diet-induced obese (DIO) mouse model

- ALK7 silencing in adipose tissue suppressed body weight gain and improved body composition
 - Body weight gain was suppressed by 40% relative to control
 - Approximately 50% reduction in fat mass with preservation of lean mass by DEXA imaging was observed in treated animals
- Body fat loss in treated animals was mechanistically attributed to lipolysis and increased energy expenditure
 - No change in food intake was observed
 - Increased oxygen consumption and heat production were observed
 - Increased levels of glycerol, NEFAs, and ketones were observed and animals exhibited upregulation in the expression of lipolytic genes
- ALK7 silencing enhanced the therapeutic benefit of tirzepatide
 - Co-treatment of tirzepatide and ALK7 siRNA had additive effects on body weight and fat mass reductions
 - ALK7 siRNA ameliorated the loss of lean mass observed with monotherapy treatment with tirzepatide

Toxicology results

- ARO-ALK7 was generally well-tolerated with no adverse or dose-limiting findings identified in Han Wistar rats

The poster presentation may be accessed on the [Events and Presentations](#) page in the Investors section of the Arrowhead website.

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](https://twitter.com/ArrowheadPharma), [LinkedIn](https://www.linkedin.com/company/arrowheadpharma), [Facebook](https://www.facebook.com/arrowheadpharma), and [Instagram](https://www.instagram.com/arrowheadpharma). 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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