Arrowhead Pharmaceuticals Announces Interim Clinical Data on RNAi-based Obesity Candidates Showing Weight Loss in Obese Patients with Diabetes and Improved Measures of Body Composition

January 6, 2026

- ARO-INHBE in combination with tirzepatide achieved -9.4% weight loss at week 16 in obese patients with type 2 diabetes mellitus, demonstrating an approximately two-fold improvement versus -4.8% on tirzepatide alone

- ARO-INHBE drove robust fat reduction including -23.2% visceral fat, -15.4% total fat, and -76.7% liver fat reduction, representing an approximately three-fold improvement in all these measures versus tirzepatide alone in obese diabetic patients

- ARO-INHBE monotherapy achieved mean visceral fat reduction of -9.9% (single dose, week 16) and -15.6% placebo adjusted (two doses, week 24) with single dose treatment increasing lean muscle tissue by 3.6 %

- ARO-ALK7 is the first RNAi-therapeutic to show knockdown in humans of an adipocyte expressed gene and achieved a mean reduction of -88% in *ALK7* mRNA with a maximum reduction of -94%

- ARO-ALK7 monotherapy achieved a -14.1% (single dose, week 8) placebo adjusted visceral fat reduction

- Company hosting a virtual KOL webinar today, January 6, 2026, at 11:30 am EST to discuss results

PASADENA, Calif.--(BUSINESS WIRE)--Jan. 6, 2026-- Arrowhead Pharmaceuticals, Inc. (NASDAQ: ARWR) today announced interim results from two Phase 1/2a clinical trials of ARO-INHBE and ARO-ALK7, the company's investigational RNA interference (RNAi) therapeutics being developed as potential treatments for obesity. Preliminary results with Arrowhead's promising new approach to treating obesity and metabolic diseases showed meaningful reductions in multiple key measures, including visceral fat, total fat, and liver fat. To date, in combination with tirzepatide, a GLP-1/GIP receptor co-agonist, ARO-INHBE has doubled weight loss and tripled reductions in visceral fat, total fat, and liver fat versus tirzepatide alone in obese patients with type 2 diabetes mellitus. The Phase 1/2a studies of ARO-INHBE and ARO-ALK7 are ongoing, and the Company expects to report and present additional results in 2026.

"The future of obesity care must acknowledge and address the different subtypes of obesity. New therapeutic approaches should focus on reducing visceral fat and combining therapies to achieve a low cardiovascular risk state and improve cardio-renal-metabolic outcomes," said Carel le Roux, M.D., Ph.D., Chair in Chemical Pathology and Metabolic Medicine at University College Dublin School of Medicine. "The interim clinical trial results announced today for Arrowhead's ARO-INHBE and ARO-ALK7 show dramatic and rapid reductions in visceral fat, a key driver in metabolic diseases. Furthermore, ARO-INHBE in combination with tirzepatide almost doubled weight loss and improved multiple measures of body composition versus tirzepatide alone in patients with obesity and type 2 diabetes mellitus. This is promising and demonstrates therapeutic potential for RNAi-based targeting of the Activin E/ALK7 pathway directly in a patient population that typically loses less weight on therapy and experiences worse cardiovascular outcomes compared to non-diabetic patients. This is a clear area of high unmet need."

The interim clinical trial results announced today represent the first demonstration in humans that the Activin E/ALK7 pathway, a genetically validated pathway that regulates adipose fat storage, may potentially be harnessed therapeutically to improve body composition and enhance weigh loss versus tirzepatide treatment alone in obese patients with type 2 diabetes mellitus. This patient population typically experiences less weight loss with incretin therapy, are less likely to reach weight loss targets, and need more effective treatment options.

James Hamilton, M.D., MBA, Chief Medical Officer and Head of R&D at Arrowhead added, "While incretin-based therapies have meaningfully advanced the treatment of obesity and metabolic disease, shortcomings around loss of lean mass, tolerability related to GI effects, reduced response in patients with diabetes, and disproportional fat mass gain after cessation of therapy remains a challenge for many patients. Interim results from the Phase 1/2a studies of ARO-INHBE and ARO-ALK7 provide encouraging early evidence that targeting the Activin E/ALK7 pathway may address some of the limitations in current standard-of-care obesity treatments. The ARO-INHBE and ARO-ALK7 programs are important strategically for Arrowhead, complementing our focus and growing commercial capabilities that enable us to potentially advance multiple novel RNAi-based therapies for cardiometabolic diseases. The impressive early results announced today further demonstrate Arrowhead's leadership in the design and development of potentially best-in-class RNAi-based therapies, utilizing our proprietary and differentiated Targeted RNAi Molecule (TRiM^{TM}) platform, for liver expressed genes such as *INHBE* and now for adipose expressed genes such as *ALK7*."

Select ARO-INHBE Phase 1/2a Results

A single dose of ARO-INHBE in adult volunteers with obesity (n= 4 per dose level) achieved a dose dependent reduction in serum Activin E with a mean maximum reduction of -85% after a single 400 mg dose and a maximum observed reduction of -94%.

Single dose ARO-INHBE monotherapy at week 16 led to:

- Mean visceral fat reduction of -9.9%
- Mean liver fat relative reduction of -38%
- Increased total lean tissue of 3.6%

Two doses of ARO-INHBE monotherapy at Week 24 achieved:

- Mean visceral fat reduction of -15.6%, adjusted for placebo.

ARO-INHBE enhanced weight loss and fat reduction versus tirzepatide alone in obese patients with type 2 diabetes mellitus. Two doses of ARO-INHBE (400 mg) in combination with tirzepatide (n = 4) achieved approximately two-fold weight loss at week 16 and an approximately three-fold reduction in fat, based on the week 12 MRI, versus tirzepatide alone in these patients. Results include the following, measured by mean percent

change from baseline:

	Tirzepatide + Placebo	ARO-INHBE (400 mg) Tirzepatide Combination
Weight Loss (week 16 weight)	-4.8 % (n=5)	-9.4% (n=4)
Visceral Fat (week 12 MRI)	-7.4% (n=5)	-23.2% (n=3)
Total Fat (week 12 MRI)	-5.3% (n=5)	-15.4% (n=3)
Liver Fat (relative reduction on (week 12 MRI)	-20% (n=5)	-76.7% (n=3)

Safety and Tolerability

ARO-INHBE has been generally well tolerated to date as monotherapy and in combination with tirzepatide in participants with obesity with and without type 2 diabetes. Most treatment emergent adverse events (TEAE) were mild in severity. No TEAEs led to study or study drug discontinuation. Injection site reactions were generally mild and self-limited. One SAE of “limb abscess” was reported, managed with bedside drainage, and assessed as unrelated to study treatment by both sponsor and site investigator. Frequency of gastrointestinal (GI) adverse events was similar in combination and tirzepatide monotherapy groups. There we no clinically significant adverse laboratory trends including liver enzymes, glycemic indices, or lipid parameters.

Select ARO-ALK7 Phase 1/2a Results

ARO-ALK7 is the first RNAi-therapeutic to show adipocyte gene target silencing in a clinical trial. ARO-ALK7 achieved dose dependent reductions in adipose *ALK7* mRNA with a mean reduction of -88% at the 200 mg dose at week 8 with a maximum reduction of -94% (n = 4).

In addition, a single dose of ARO-ALK7 led to rapid dose dependent reductions in mean visceral fat with a -14.1% reduction, adjusted for placebo, already observed at Week 8.

Safety and Tolerability

ARO-ALK7 has been generally well tolerated to date as monotherapy in participants with obesity. No clinically significant adverse laboratory trends, including in liver enzymes and glycemic parameters, were identified. Most TEAEs were mild in severity. No TEAEs led to study or study drug discontinuation. No SAEs were reported.

Virtual Analyst and Investor Event

The company is hosting a virtual webinar today, January 6, 2026, at 11:30 am EST featuring Carel le Roux M.D., Ph.D., Chair in Chemical Pathology and Metabolic Medicine at University College Dublin School of Medicine, who will join members of the Arrowhead management team to discuss the interim results of the Company's Phase 1/2a studies of ARO-INHBE and ARO-ALK7. To register for the event, please visit: https://lifescievents.com/event/sa2ymsnv7/.

The live event and an archived webcast may also be accessed on the Events and Presentations page on 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 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. In preclinical animal studies, *ALK7* silencing in adipose tissue led to reduced body weight and fat mass with preservation of lean muscle. Treatment with investigational ARO-ALK7 has the potential to reduce visceral adiposity and improve lipid and glycemic parameters.

About the AROALK7-1001 Phase 1/2 Study

AROALK7-1001 (NCT06937203) 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.

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 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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