

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT
PURSUANT TO SECTION 13 OR 15(D) OF
THE SECURITIES EXCHANGE ACT OF 1934
January 6, 2026
Date of Report
(Date of earliest event reported)

Arrowhead Pharmaceuticals, Inc.
(Exact name of registrant as specified in its charter)

Delaware
(State or other jurisdiction
of incorporation)

001-38042
(Commission
File Number)

46-0408024
(IRS Employer
Identification No.)

177 E. Colorado Blvd, Suite 700, Pasadena, CA 91105
(Address of principal executive offices, including Zip Code)
(626) 304-3400
(Registrant's telephone number, including area code)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

- ☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
- ☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
- ☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
- ☐ Pre-commencement communications pursuant to Rule 13e-4 (c) under the Exchange Act (17 CFR 240.13e-4(c))

Title of each class	Securities registered pursuant to Section 12(b) of the Act:		Name of each exchange on which registered
	Trading Symbol(s)		
Common Stock, par value \$0.001 per share	ARWR		The Nasdaq Global Select Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).
Emerging growth company ☐
If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

On January 6, 2026, Arrowhead Pharmaceuticals, Inc. (the “Company”) issued a press release announcing interim results from its 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. In addition, the Company made publicly available a data presentation announcing interim results from its Phase 1/2a clinical trials of ARO-INHBE and ARO-ALK7. The Company hosted a conference call and webcast today, Tuesday, January 6, 2026, at 11:30 a.m., Eastern Time, to discuss the data results.

The information in Item 7.01 of this Current Report on Form 8-K, including the information in the press release and the presentation attached as Exhibit 99.1 and Exhibit 99.2, respectively, to this Current Report on Form 8-K, is furnished pursuant to Item 7.01 of Form 8-K and shall not be deemed “filed” for the purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or otherwise subject to the liabilities of that section. Furthermore, the information in Item 7.01 of this Current Report on Form 8-K, including the information in the press release and the presentation attached as Exhibit 99.1 and Exhibit 99.2, respectively, to this Current Report on Form 8-K, shall not be deemed to be incorporated by reference in the filings of the Company under the Securities Act of 1933, as amended.

Item 8.01 Other Events.

On January 6, 2026, the Company announced interim results from its Phase 1/2a clinical trials of ARO-INHBE and ARO-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 serious adverse effect (“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 were 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.

Safe Harbor Statement under the Private Securities Litigation Reform Act

This Current Report on Form 8-K 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 the Company's future financial performance, trends in the Company's business, expectations for the Company's product pipeline or product candidates, including anticipated regulatory submissions and clinical program results, prospects or benefits of the Company's 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 potential therapeutic benefits and safety of ARO-INHBE and ARO-ALK7; the potential to advance multiple novel RNAi-based therapies for cardiometabolic diseases; the initiation, timing, progress and results of the Company's preclinical studies and clinical trials, and the Company's research and development programs; the Company's expectations regarding the potential benefits of the partnership, licensing and/or collaboration arrangements and other strategic arrangements and transactions the Company has entered into or may enter into in the future; the Company's beliefs and expectations regarding milestone, royalty or other payments that could be due to or from third parties under existing agreements; and the Company's estimates regarding future revenues, research and development expenses, capital requirements and payments to third parties. These statements are based upon the Company's current expectations and speak only as of the date hereof. The Company's actual results may differ materially and adversely from those expressed in any forward-looking statements as a result of numerous factors and uncertainties, including interim results of a clinical trial are not necessarily indicative of final results and one or more of the clinical outcomes may materially change as patient enrollment continues, following more comprehensive reviews of the data and as more patient data becomes available, the safety and efficacy of the Company's product candidates, decisions of regulatory authorities and the timing thereof, the duration and impact of regulatory delays in the Company's clinical programs, the Company's ability to finance the Company's operations, the likelihood and timing of the receipt of future milestone and licensing fees, the future success of the Company's scientific studies, the Company's ability to successfully develop and commercialize drug candidates, the timing for starting and completing clinical trials, rapid technological change in the Company's markets, the enforcement of the Company's intellectual property rights, and the other risks and uncertainties described in the Company's 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. The Company assumes no obligation to update or revise forward-looking statements to reflect new events or circumstances.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	Description
99.1	Press Release, dated January 6, 2026
99.2	Presentation, dated January 6, 2026
104	Cover Page Interactive Data File (embedded within the Inline XBRL document).

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

Date: September 11, 2025

ARROWHEAD PHARMACEUTICALS, INC.

By: /s/ Daniel Apel
Daniel Apel
Chief Financial Officer



PRESS RELEASE
Jan. 6, 2026

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

- 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., 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 weight 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™) platform, for liver expressed genes such as *INHBE* and now for adipose expressed genes such as *ALK7*."

Select ARO-INHBE Phase 1/2a Results

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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.

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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>.

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 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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Source: Arrowhead Pharmaceuticals, Inc.

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Obesity KOL Webinar ARO-INHBE and ARO-ALK7 Interim Phase 1/2a Clinical Data

January 06, 2026



Introduction and Agenda

Vince Anzalone, CFA

Vice President, Finance and IR



Safe Harbor Statement

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Agenda

Topic	Presenter
Introduction	Vince Anzalone, CFA
The Future: What's Next in Obesity Treatment to Address the Unmet Needs	Carel Le Roux, M.D., Ph.D. University College Dublin, School of Medicine
Therapeutic Rationale for Targeting the Activin E - ALK7 Axis	James Hamilton, M.D., MBA
Interim Results from Phase 1/2a Studies	James Hamilton, M.D., MBA
Key Takeaways	Chris Anzalone, Ph.D.
Q&A	Panel

Obesity Key Opinion Leader

Carel le Roux, M.D., Ph.D.

Chair of Metabolic Medicine, University College Dublin, School of Medicine

Professor Carel le Roux graduated from medical school in Pretoria South Africa, completed his specialist training in metabolic medicine and obtained his PhD from Imperial College London where he later took up a faculty position. He moved to University College Dublin for the Chair in Chemical Pathology and Metabolic Medicine. He also holds the position of Professor of Metabolic Medicine at Ulster University. He currently coordinates an Innovative Medicine Initiative project on obesity.

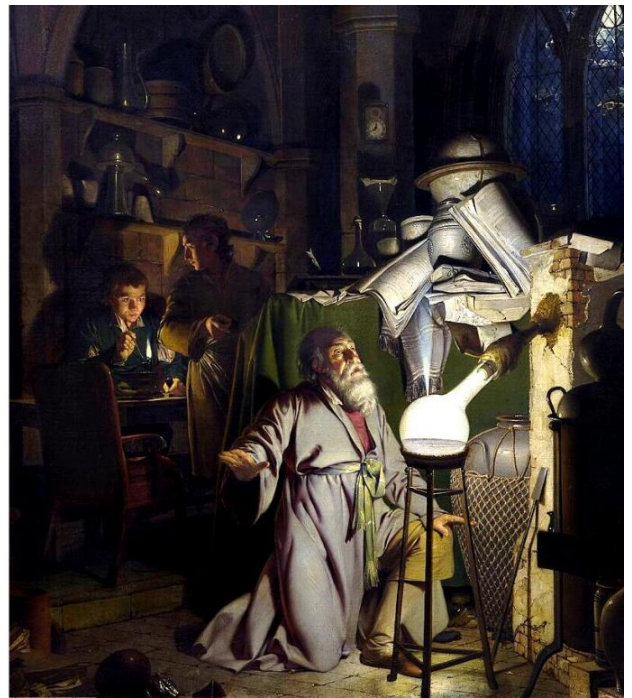


The Future: What's Next in Obesity Treatment to Address the Unmet Needs

Carel le Roux, M.D., Ph.D.

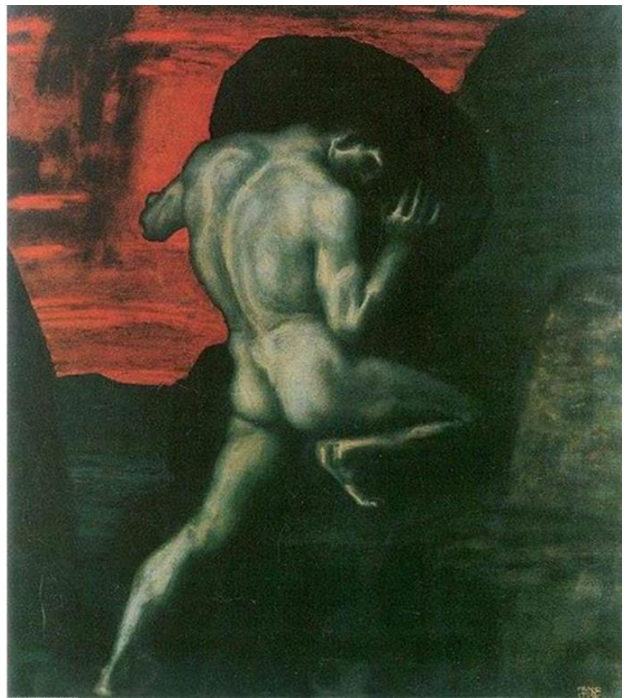
University College Dublin, Ulster University,
University of Pretoria

Joseph Wright of Derby.
The Alchemist Discovering Phosphorus. 1771.
Derby Museum and Art Gallery

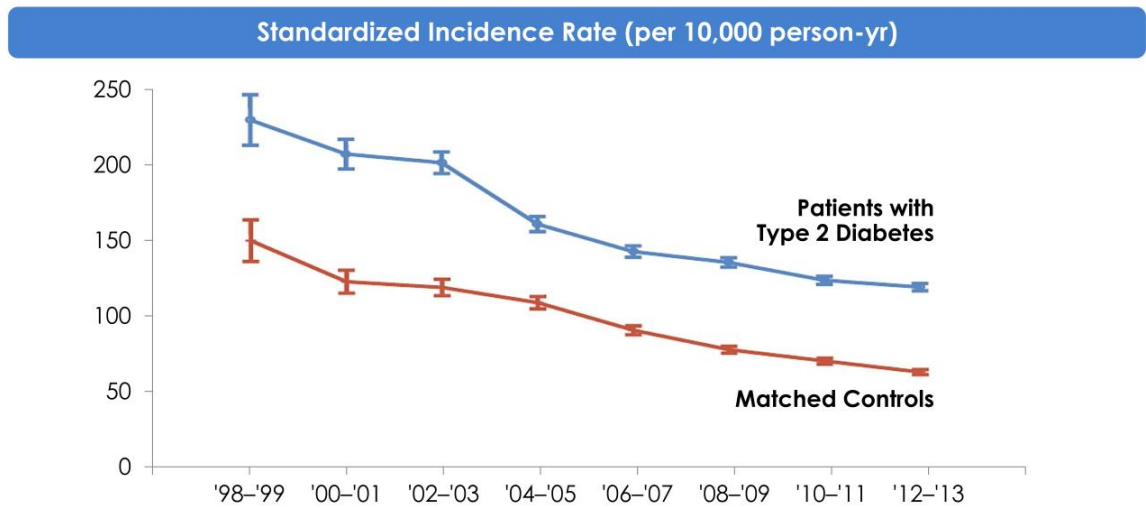


Conflicts of Interest

- Consilient Health
- Novo Nordisk
- Herbalife
- Johnson & Johnson
- Covidien
- Fractyl
- GI Dynamics
- Olympus
- Lilly
- Boehringer Ingelheim
- Keyron
- Astra Zeneca
- Roche
- Arrowhead
- Amgen



Death from Cardiovascular Disease

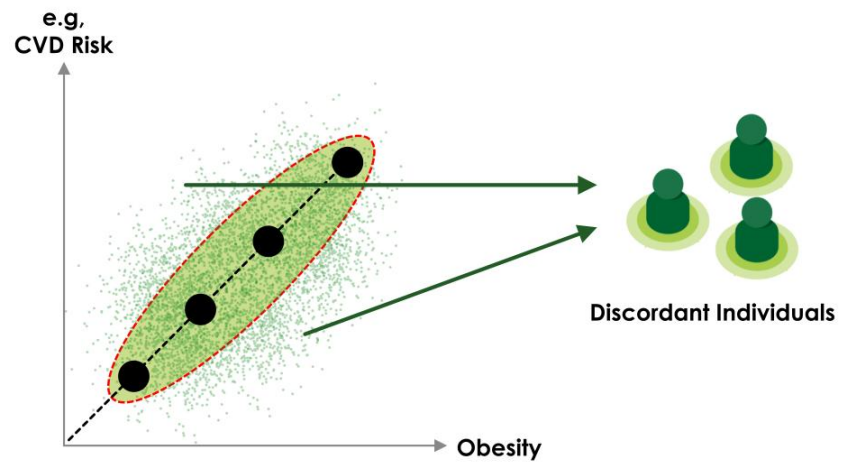


Rawshani et al, NEJM 2017.

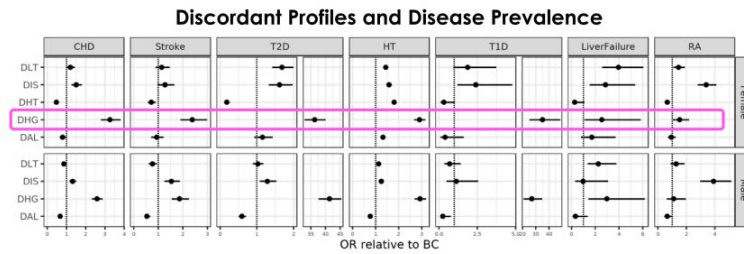
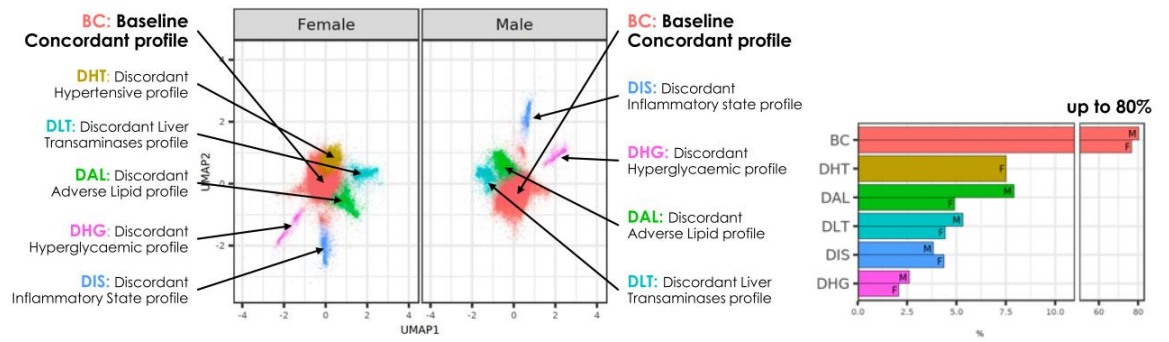
Visceral Fat Drives Metabolic Diseases



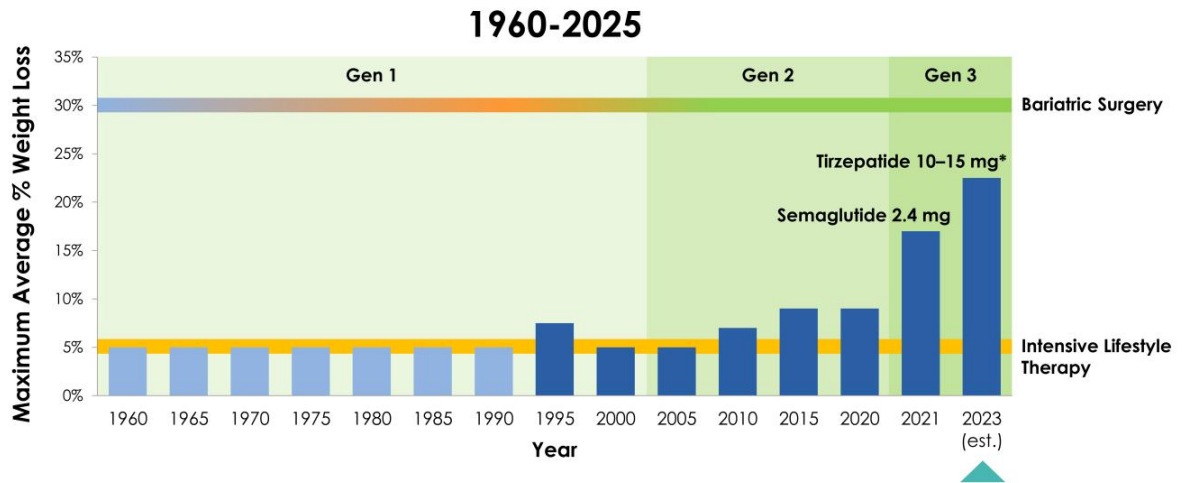
What We Know: Risk Doesn't Always Follow BMI



Coral, le Roux et al Nature Medicine 2024.



Emergence of Highly Effective Obesity Medications



Kaplan LM, 2023.

Weight Change from Baseline (%)



Proposed Obesity Treat to Target Thresholds

- ▶ Busetto, L et al. ECO 2024
- ▶ Investigated changes in BMI and WHtR with 10-year ORC risk
- ▶ >45K UK adults, 41% Overweight, 59% Obesity

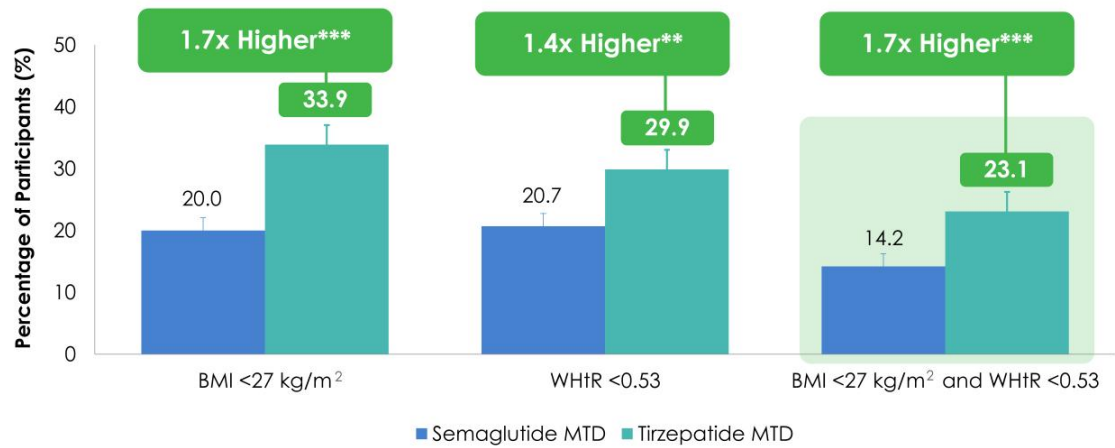


RESULTS: WHtR <0.53 and/or BMI <27 kg/m² After Weight Loss

Predictors of low risk for incident T2D, HTN, hip/knee OA, ASCVD

ASCVD = Atherosclerotic cardiovascular disease; BMI = body mass index; HTN = hypertension; OA = osteoarthritis; ORC = obesity-related complication; T2D = type 2 diabetes; WHtR = waist to height ratio.
Busetto L, et al. AS07.02. Obes Facts 2024; 17 (supp 1):S6.

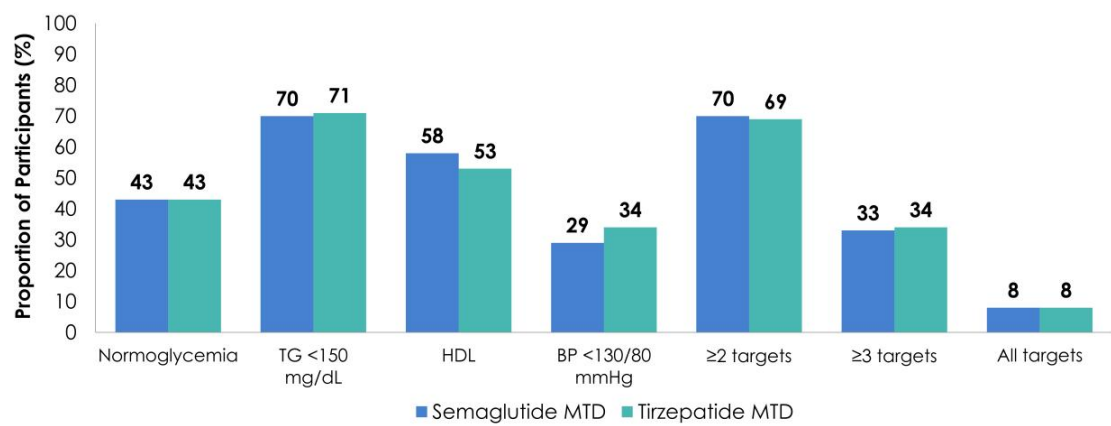
Percent of Participants Reaching Treat to Target Thresholds at Week 72



p<0.01 vs semaglutide. *p<0.001 vs semaglutide.
Note: Week 72 data in participants who discontinued study drug early was imputed by multiple imputation based on missing at random (MAR) assumption using on-treatment data.
Treatment comparisons were made via logistic regression with the aid of Rubin's rule.

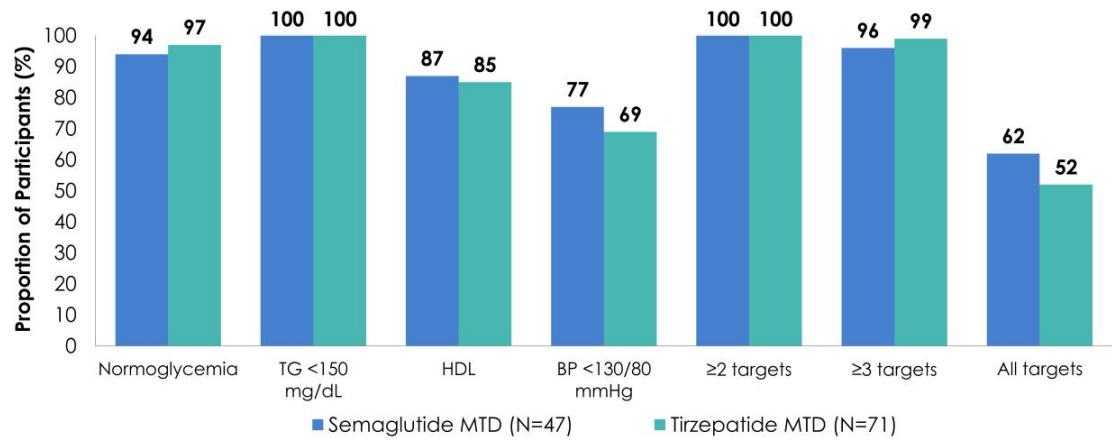
Percent of Participants with Normalization of Cardiometabolic Parameters

Baseline



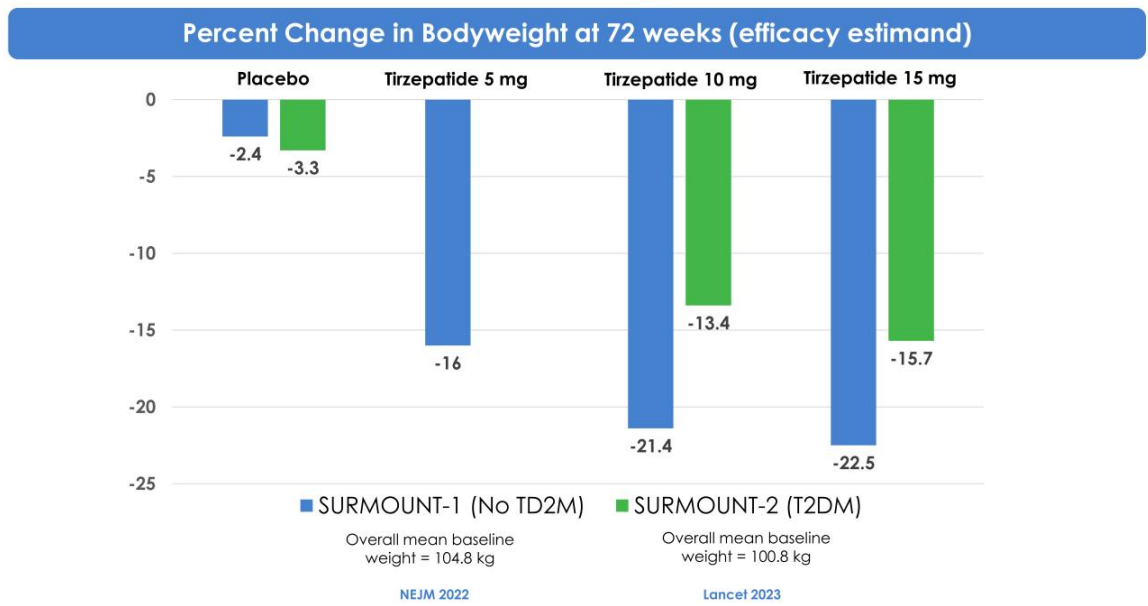
Normoglycemia (HbA1c <5.7% and FSG <100 mg/dL). HDL sex-specific goals (female ≥50 mg/dL, male ≥40 mg/dL). Data are means based on observed data at baseline for participants who completed treatment.

Normalization of Cardiometabolic Parameters in Participants Reaching WHtR <0.53 & BMI <27 at Week 72

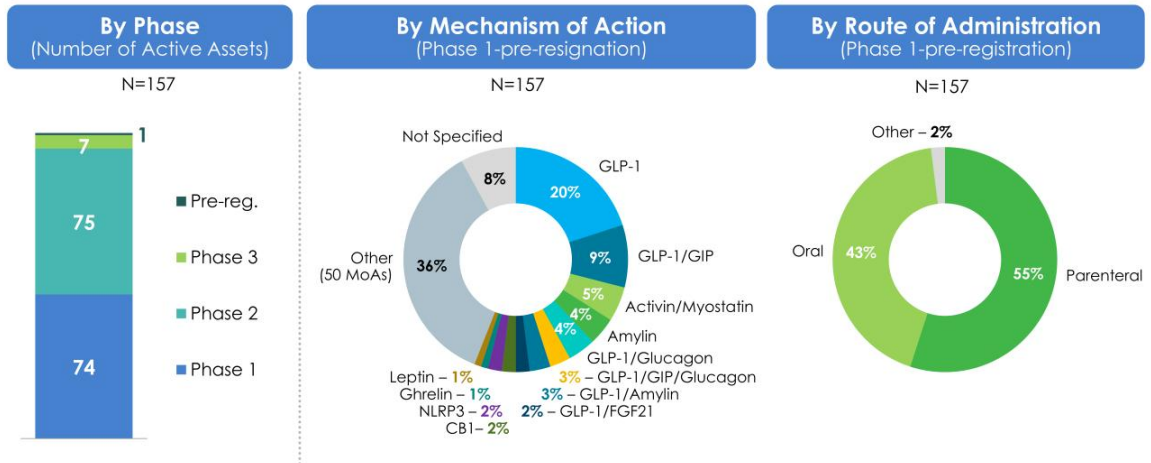


Normoglycemia (HbA1c <5.7% and FSG <100 mg/dL), HDL sex-specific goals (female ≥50 mg/dL, male ≥40 mg/dL). N = number of participants meeting WHtR <0.53 and BMI <27 kg/m² at Week 72. Data are means based on observed data at Week 72 or LOCF for participants who completed treatment.

Patients with Diabetes Lose Less Weight

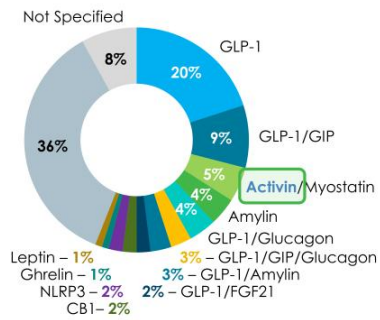


Pipeline: By Phase, MOA, and Administration Route



Source: IQVIA Analytics Link; Clinicaltrials.gov; company reports, press releases, desk research, IQVIA EMEA Thought Leadership analysis; December 2024.
 GLP-1 = glucagon-like peptide 1; GIP = gastric inhibitory polypeptide; GCG = glucagon; MoA = mechanism of action; NLRP3 = 'NACHT', LRR, and PYD domains-containing protein 3;
 CB1 = cannabinoid receptor 1; FGF21 = fibroblast growth factor 21.
 Outlook for obesity in 2025; more than a transition year. Accessed February 5, 2025. <https://www.iqvia.com/locations/emea/blogs/2025/01/outlook-for-obesity-in-2025-more-than-a-transition-year>

Therapeutic Potential for RNAi-based Targeting of the Activin E – ALK7 Pathway



- ▶ Novel mechanism of action targeting metabolically unhealthy adipose tissue
- ▶ Infrequent SC administration to reduce medication burden
- ▶ Potential to complement other weight loss therapies to enhance fat loss and improve metabolic health

Conclusions

The Future of Obesity Care Will Include



Recognising the
different subtypes
of obesity



Reducing visceral fat
to achieve better
cardio-kidney-
metabolic outcomes



Combining therapies
to achieve low
cardiovascular
risk state

ARO-INHBE and ARO-ALK7 Interim Clinical Data Update

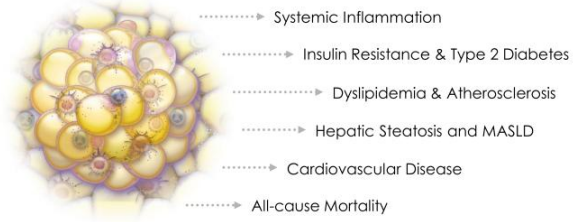
Therapeutic Rationale for Targeting the Activin E – ALK7 Axis

James Hamilton MD, MBA
Chief Medical Officer and Head of R&D

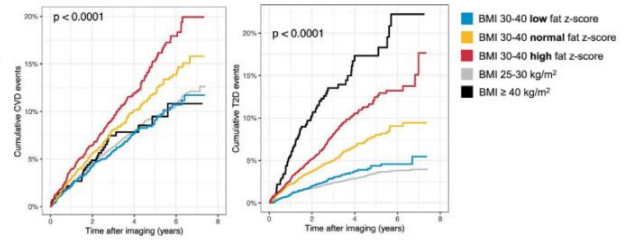


Targeting Visceral Adiposity to Improve Metabolic Health

Excess Visceral Adiposity is Associated with Metabolic Risk^{1,2}



Visceral Fat Burden (measured by z-score) Predicts Incident Cardiovascular Disease and Type 2 Diabetes³



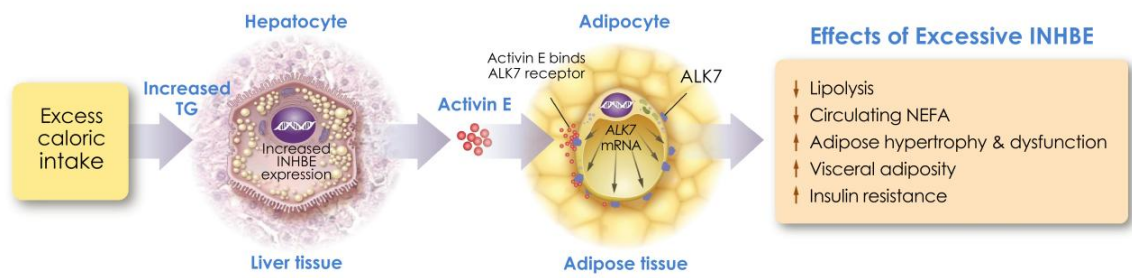
Visceral Fat Reduction is Associated with Improvement in Metabolic Risk Factors^{4,5}

Incretin Therapies Reduce Visceral Fat But Have Tolerability Limitations and High Discontinuation Rates

Therapies Directly Targeting Visceral Fat May Have Potent Cardiometabolic Benefits

1. Naeland et al., *Lancet Diabetes Endocrinol* 2019; 2. Stefan et al., *Lancet Diabetes Endocrinol* 2020; 3. Linge et al., *Surg Obes Relat Dis* 2024; 4. Abdullah et al., *Frontiers in endocrinology* 2025; 5. Okauchi et al., *Diabetes Care* 2007

Hepatic Activin E Encoded by *INHBE* Gene Regulates Energy Homeostasis in Adipose Tissue via the ALK7 Receptor

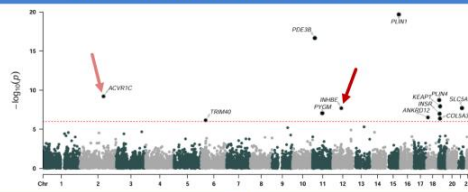


- Inhibin subunit beta E (INHBE) is primarily expressed in hepatocytes
- Activin E (dimeric INHBE protein) is potent hepatokine secreted by the liver
- Circulating Activin E promotes adipose storage of fats by suppressing lipolysis in adipose tissue

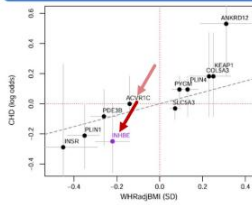
1. Deaton et al., *Nat Commun* 2022; 2. Akbari et al., *Nat Commun* 2022. NEFA = non-esterified fatty acids

pLOF Variants of *INHBE* Are Associated with Reduced Abdominal Fat and Cardiometabolic Risk

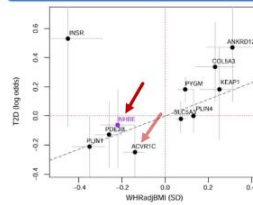
↓ Waist-to-Hip Ratio Adjusted for BMI



↓ ASCVD Risk



↓ T2DM Risk

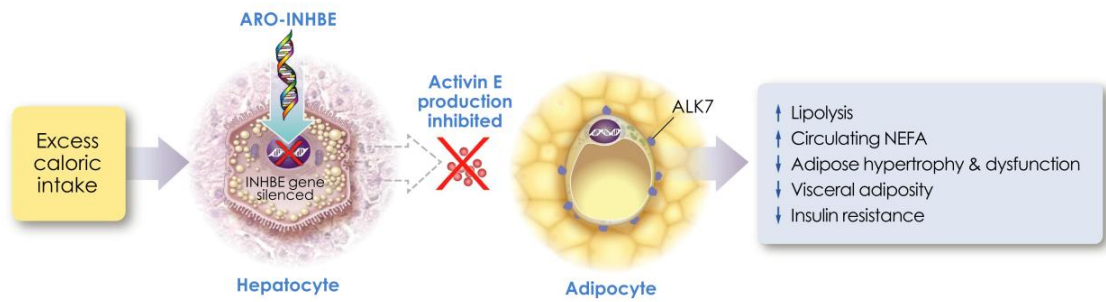


Favorable Cardiometabolic Profile

Trait	Beta (95% CI)
↓ Triglycerides ¹	-0.13 (-0.21, -0.05)
↑ HDL-C ¹	0.10 (0.02, 0.18)
↓ Apolipoprotein B ¹	-0.076 (-0.16, 0.004)
↓ Fasting Glucose ¹	-0.17 (-0.33, -0.02)
↓ HgbA1c ²	-0.053 (-0.11, 0.001)
↓ ALT ²	-0.07 (-0.13, -0.02)
↓ WHR Adjusted for BMI ¹	-0.22 (-0.3, -0.14)
↓ Visceral Fat Volume (MRI) ²	-0.23 (-0.45, -0.011)

¹ Deaton et al., Nat Commun 2022; ² Akbari et al., Nat Commun 2022. ALT = Alanine Aminotransferase; ASCVD = Atherosclerotic Cardiovascular Disease; BMI = Body Mass Index; HDL-C = High-Density Lipoprotein Cholesterol; HgbA1c = Hemoglobin A1c; MRI = Magnetic Resonance Imaging; pLOF = Predicted Loss-of-Function; T2DM = Type 2 Diabetes Mellitus; WHR = Waist to Hip Ratio

Silencing Hepatic *INHBE* May Inhibit Maladaptive Activin E – ALK7 Signaling and Improve Adipose Dysfunction in Obesity



1. Deaton et al., *Nat Commun* 2022; 2. Akbari et al., *Nat Commun* 2022. NEFA = non-esterified fatty acids

ARO-INHBE and ARO-ALK7 Interim Clinical Data Update

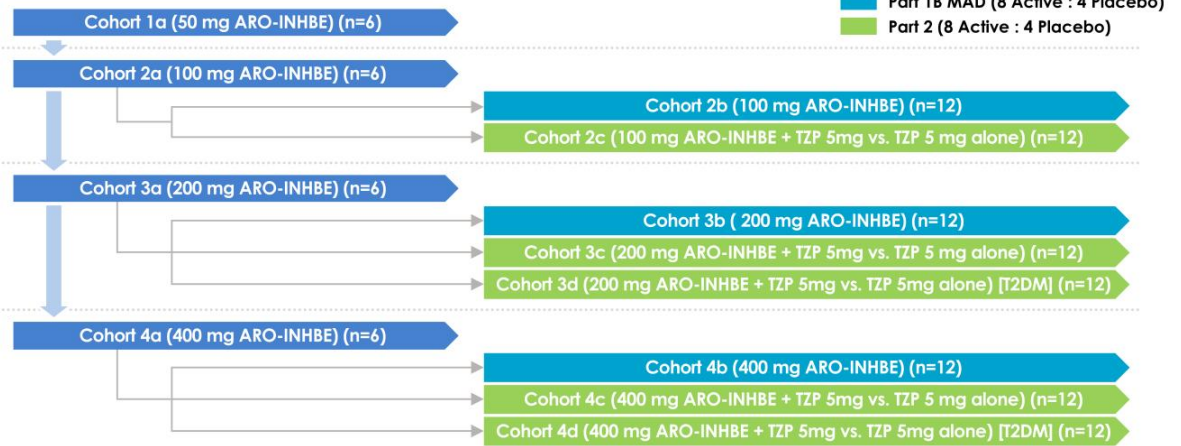
Clinical Study Update from AROINHBE-1001

James Hamilton MD, MBA
Chief Medical Officer and Head of R&D



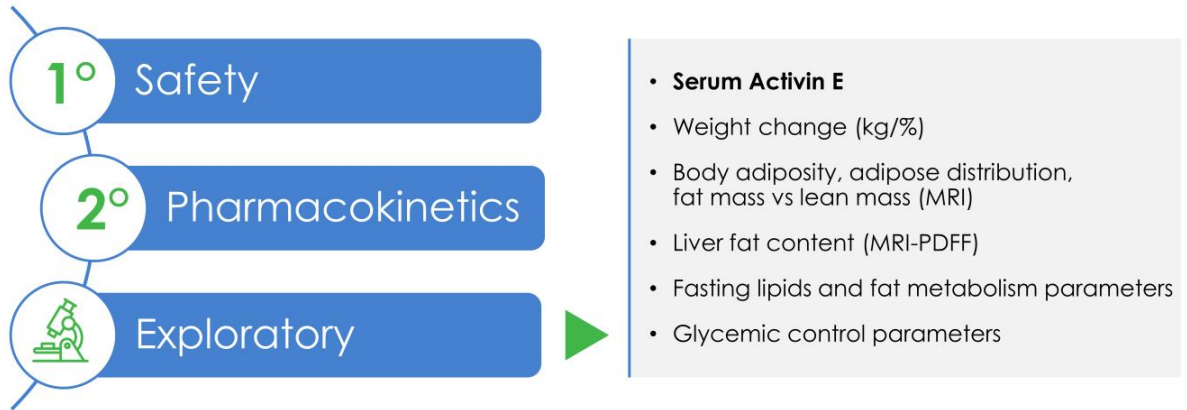
AROINHBE-1001: Phase 1/2a Study of ARO-INHBE in Volunteers with Obesity, with and without Type 2 Diabetes Mellitus

✓ Enrollment Completed for All Cohorts



MAD = Multiple Ascending Dose; SAD = Single Ascending Dose; T2DM = Type 2 Diabetes Mellitus; TZP = Tirzepatide

Key Endpoints



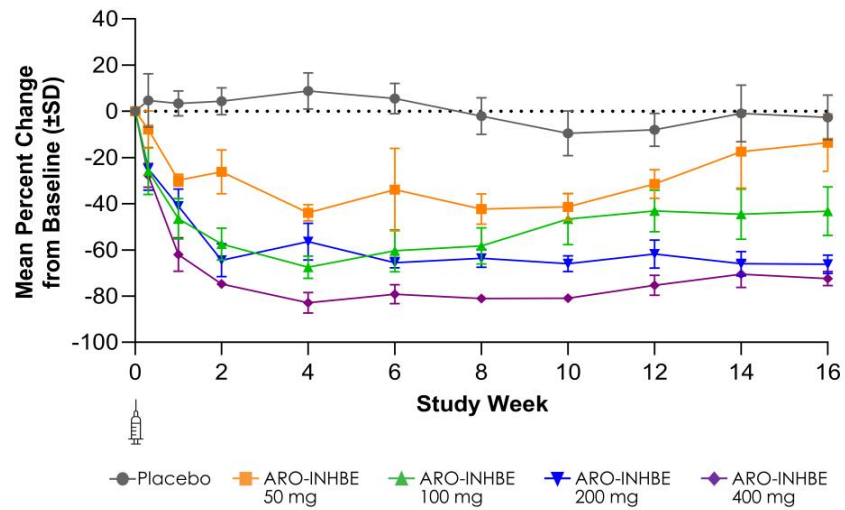
MRI = Magnetic Resonance Imagine; MRI-PDFF = Magnetic Resonance Imaging-Proton Density Fat Fraction

Baseline Characteristics – Participants with Obesity (Monotherapy)

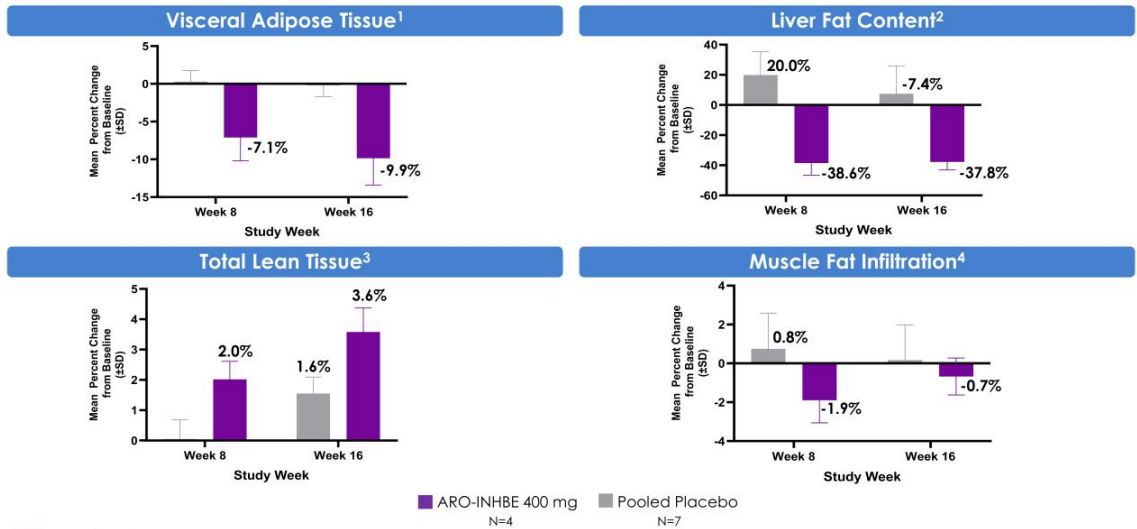
	ARO-INHBE SAD Cohorts (N=25)	ARO-INHBE MAD Cohorts (N=36)
Age, mean (SD)	43 (8.8)	41.6 (11.7)
Sex, female, n (%)	15 (60)	23 (64)
Race		
White, n (%)	17 (68.0)	19 (52.8)
Native Hawaiian or Pacific Islander, n (%)	5 (20.0)	15 (41.7)
Asian, n (%)	3 (12.0)	5 (13.9)
Black or African American, n (%)	0 (0.0)	1 (2.8)
Other, n (%)	3 (12.0)	1 (2.8)
Weight, mean (SD), kg	102.0 (13.2)	105.8 (15.5)
BMI, mean (SD), kg/m ²	35.7 (3.7)	36.8 (5.0)
Liver fat content, mean (SD), %	6.9 (5.6)	7.5 (6.1)
Visceral adipose tissue, mean (SD), L	5.0 (1.9)	4.6 (1.7)
HgbA1c, mean (SD), %	5.4 (0.3)	5.4 (0.4)
Activin E, mean (SD), pg/mL	521.0 (236.7)	466.3 (137.4)

BMI = Body Mass Index; HgbA1c = Hemoglobin A1c; MAD = Multiple Ascending Dose; SAD = Single Ascending Dose; SD = Standard Deviation

ARO-INHBE Achieved Mean Max Activin E Reduction of **85%** with Long Response Duration

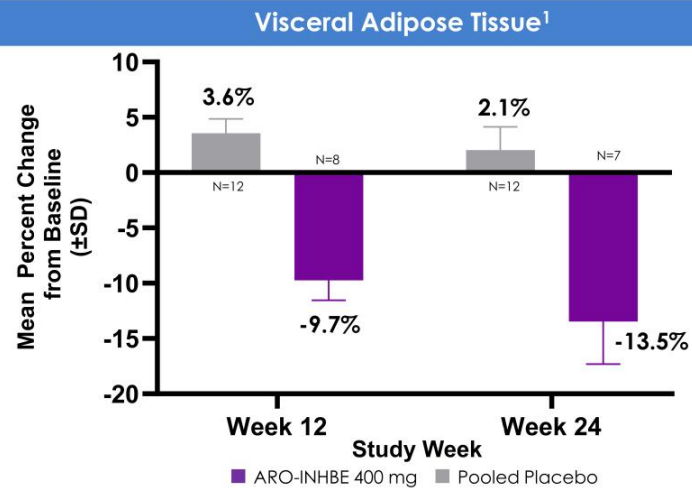


A Single Dose of ARO-INHBE Achieved Mean Visceral Fat Reductions of **9.9%** and Liver Fat Reductions of up to **38.6%**



Body composition measurements obtained using MRI. 1. Visceral adipose tissue in the abdominal cavity; 2. Liver fat measured using MRI-PDFF; 3. Total lean tissue measured from neck to knee images, excluding extremities; 4. Muscle fat infiltration is an average of bilateral anterior thigh measurements.

Repeat Doses of ARO-INHBE Enhanced Mean Placebo Adjusted Visceral Fat Reductions to **15.6%**



Body composition measurements obtained using MRI. 1. Visceral adipose tissue in the abdominal cavity.

Combination Therapy Update – Obesity with Type 2 Diabetes Mellitus



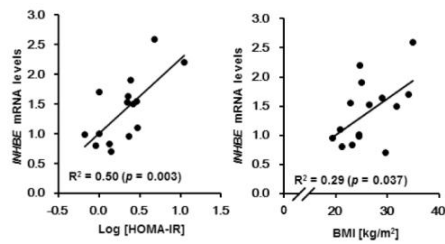
Baseline Characteristics – Participants with Obesity and Type 2 Diabetes Mellitus (Combination with tirzepatide)

	Participants with Obesity and T2DM (N=24)
Age, mean (SD)	52.1 (7.9)
Sex, female, n (%)	12 (50)
Race	
White, n (%)	14 (58.3)
Native Hawaiian or Pacific Islander, n (%)	5 (20.8)
Asian, n (%)	3 (12.5)
Black or African American, n (%)	0 (0.0)
Other, n (%)	3 (12.5)
Weight, mean (SD), kg	103.0 (17.0)
BMI, mean (SD), kg/m ²	36.6 (5.7)
Liver fat content, mean (SD), %	17.1 (1.9)
Visceral adipose tissue, mean (SD), L	6.8 (2.4)
HgbA1c, mean (SD), %	7.4 (0.7)
Activin E, mean (SD), pg/mL	661.6 (234.1)
Metformin Alone, n (%)	18 (75.0)
Metformin + SGLT2 Inhibitor, n (%)	6 (25.0)

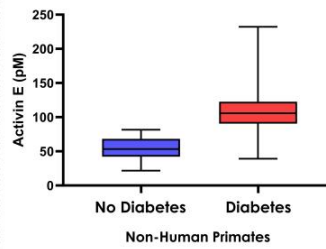
BMI = Body Mass Index; HgbA1c = Hemoglobin A1c; MAD = Multiple Ascending Dose; SAD = Single Ascending Dose; SD = Standard Deviation

Insulin Resistance is Associated with Higher Activin E Levels in Primates and in Humans

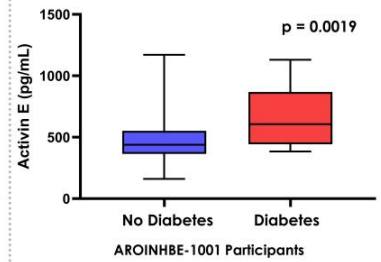
Elevated Hepatic *INHBE* Expression in Human Biopsy Samples¹



Serum Activin E Levels in NHPs with and without Diabetes



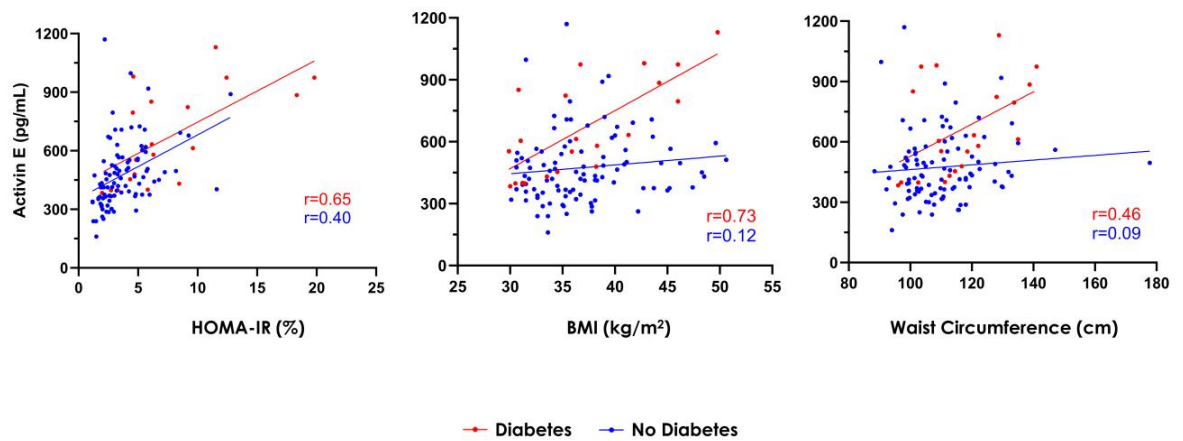
Baseline Serum Activin E Levels in AROINHBE-1001 Participants



1. Sugiyama et al., PLOS ONE 2018



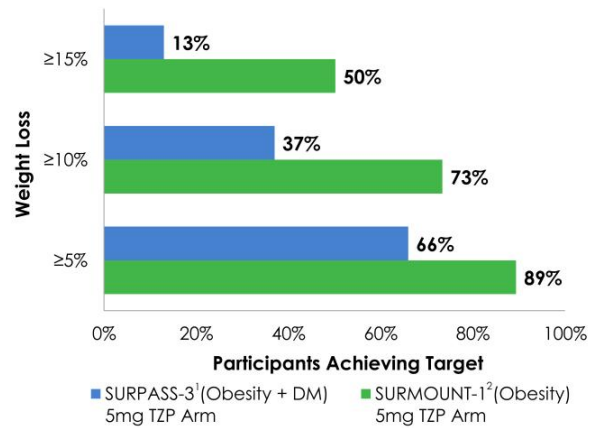
Baseline Activin E Levels Correlate with Insulin Resistance and Anthropometric Measures in Study Participants with Diabetes



Patients with Obesity and Type 2 Diabetes Lose Less Weight On Incretins and Need More Therapeutic Options

Patients with obesity and type 2 diabetes mellitus experience **less weight loss** and are **less likely to reach weight loss targets** with incretin therapy

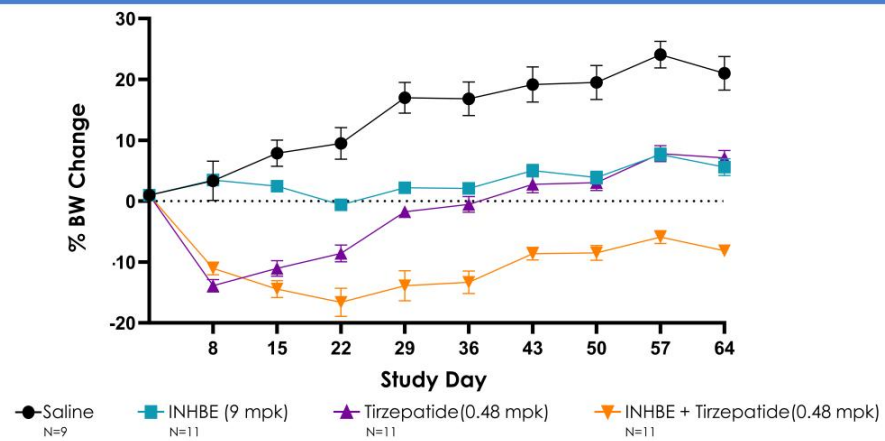
There is unmet need for combination therapies that can synergize with incretins to enhance weight loss and further reduce cardiometabolic risk, particularly in T2DM patients



1. Ludvik et al., *Lancet* 2021; 2. Jastreboff et al., *N Engl J Med* 2022; T2DM = Type 2 Diabetes Mellitus; TZP = Tirzepatide

Preclinical Studies Indicate Enhanced Weight Loss with *INHBE* Silencing Combined with tirzepatide in Diabetic Mice

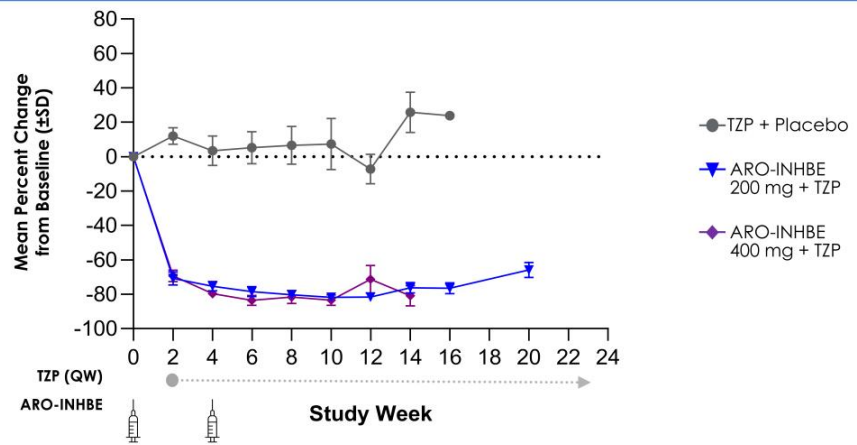
INHBE siRNA + TZP Enhanced Weight Loss in Obese Diabetic db/db Mice



Ngai et al., *Diabetes* 2024. TZP = Tirzepatide; mpk = mg/kg

ARO-INHBE Demonstrated Substantial and Durable Decreases in Serum Activin E up to **84%** in T2DM Combination Cohorts. No Decrease in Activin E with Tirzepatide Alone.

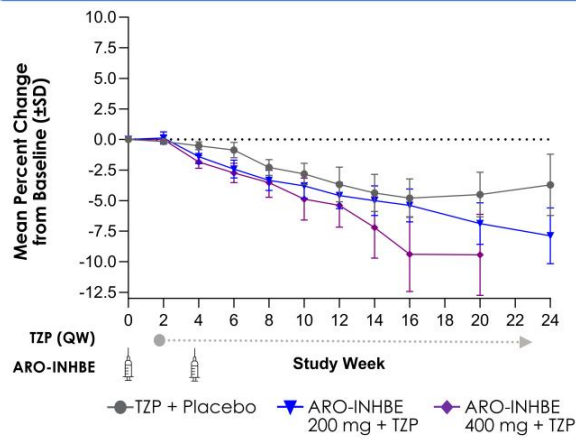
Obesity with T2DM Combination Therapy Cohorts



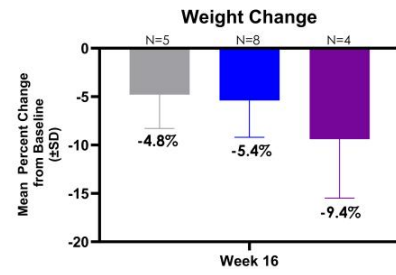
QW = Once weekly dosing; T2DM = Type 2 Diabetes Mellitus; T2P = Tirzepatide

Combination Therapy with ARO-INHBE Enhanced Weight Loss Compared to Tirzepatide Alone in Obese T2DM Patients

Weight Loss – Obesity with T2DM Combination Therapy Cohorts

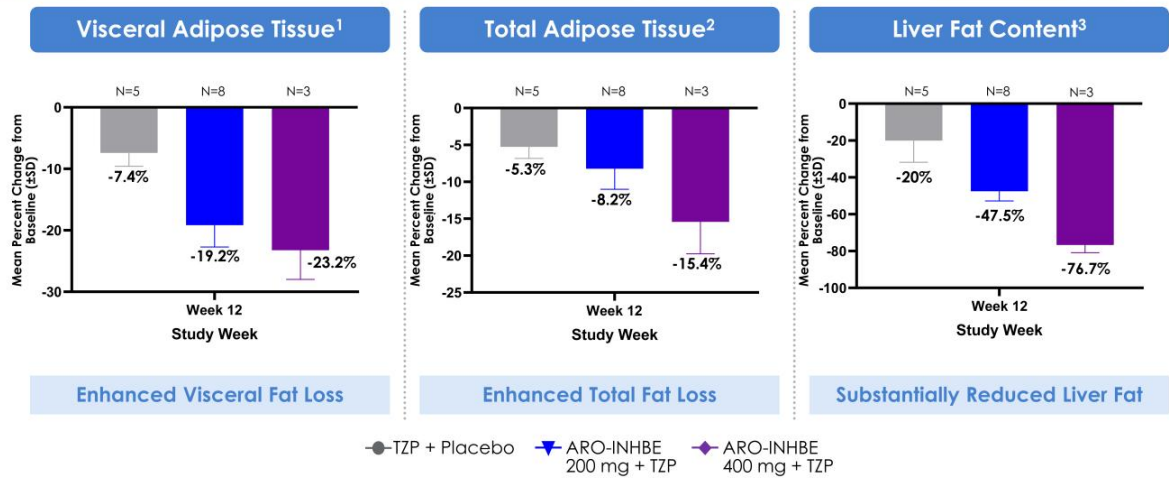


QW = Once weekly dosing; T2DM = Type 2 Diabetes Mellitus; TZP = Tirzepatide



At Week 16, combo therapy weight loss of 9.4% versus 4.8% for TZP alone

Combination Therapy Achieved Synergistic Fat Loss in Study Participants with Obesity and Type 2 Diabetes



Body composition measurements obtained using MRI. 1. Visceral adipose tissue in the abdominal cavity; 2. Total adipose tissue measured from neck to knee images, excluding extremities; 3. Liver fat measured using MRI-PDFF. TZP = Tirzepatide

Visceral Fat and Liver Fat Reductions with ARO-INHBE + Low-dose TZP Compare Favorably with High-dose TZP at 52 Weeks in SURPASS-3

% Reduction	12-week MRI / 16-week Weight Data		52-week Data	
	AROINHBE-1001		SURPASS-3 MRI Substudy ¹	
	ARO-INHBE 400 mg + TZP 5 mg	Placebo + TZP 5 mg	TZP 5 mg	TZP 15 mg
Visceral Adipose Tissue	-23.2%	-7.4%	-16.33%	-23.95%
Liver Fat Content	-76.7%	-20%	-29.78%	-39.59%
VAT to ASAT Ratio	-12.7%	-3.1%	-2.00%	-4.36%
Total Adipose Tissue	-15.4%	-5.3%	Not available	Not available
Body Weight	-9.4%	-4.8%	-8.1%	-13.9%

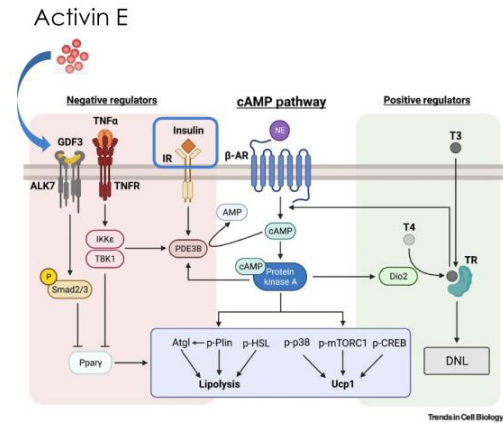
1. Gastaldelli et al., Diabetes & endocrinology 2022; ASAT = Abdominal Subcutaneous Adipose Tissue; TZP = Tirzepatide; VAT = Visceral Adipose Tissue

Targeting Activin E may be More Effective in Conditions of Insulin Resistance: A Plausible Hypothesis

Insulin is a potent inhibitor of lipolysis in adipose tissue

In conditions of insulin resistance or reduced insulin secretion (e.g. T2DM), other regulators, including Activin E, may play a more critical role in modulating fat storage

Silencing hepatic Activin E in obese diabetic patients may result in more pronounced fat loss due to enhanced lipolysis



Guilherme et al., Trends Cell Biol 2023. T2DM = Type 2 Diabetes Mellitus

ARO-INHBE Demonstrates a Favorable Safety Profile

✓ ARO-INHBE was **well tolerated** as monotherapy and in combination with tirzepatide in participants with obesity with and without type 2 diabetes.

- Most TEAEs were mild in severity
- No TEAEs led to study or study drug discontinuation

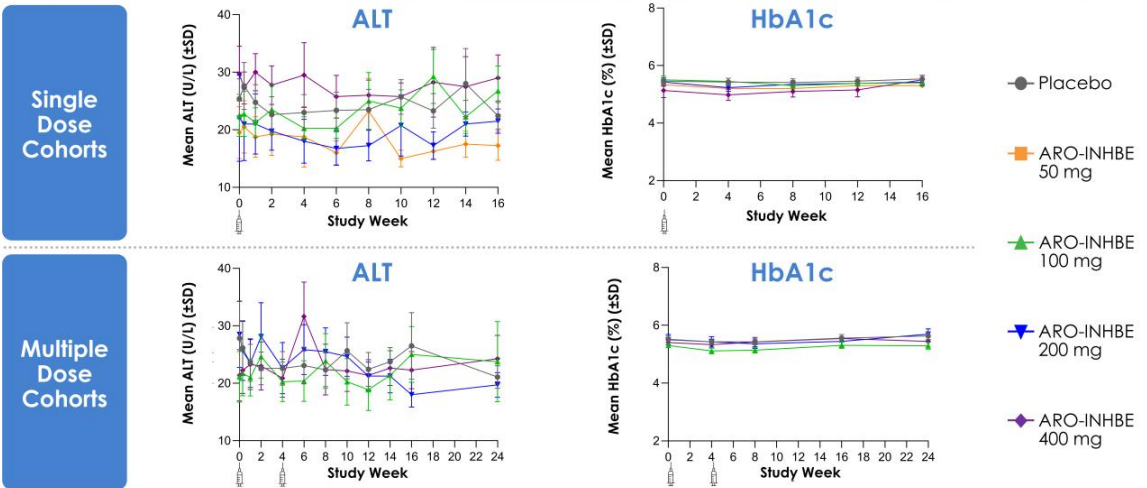
✓ Injection site reactions were generally **mild and self-limited**.

✓ Frequency of GI adverse events was similar in combination and tirzepatide monotherapy groups.

✓ One SAE of "limb abscess" was reported, managed with bedside drainage, and assessed as Unrelated to study treatment by both Sponsor and Site Investigator.

✓ **No clinically significant adverse laboratory trends** including in liver enzymes, glycemic indices, or lipid parameters were identified.

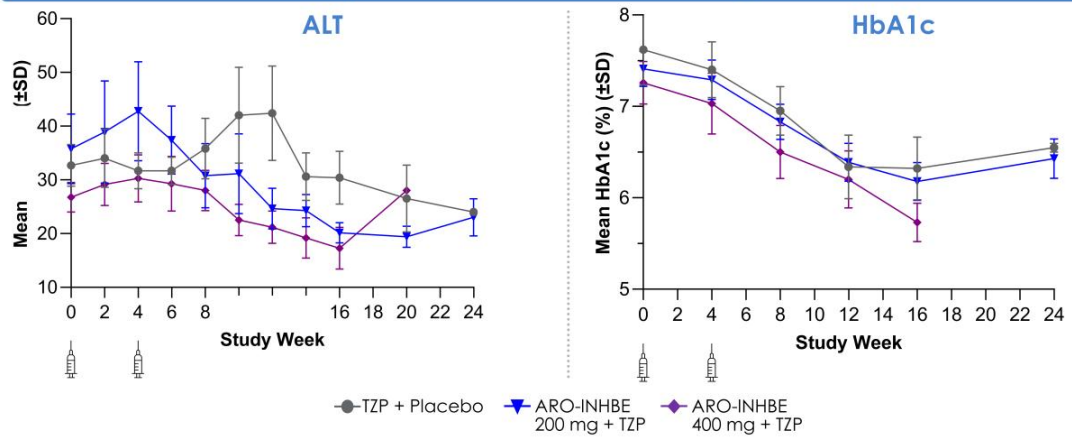
Stable Liver and Glycemic Parameters in Monotherapy Groups with No Adverse Changes in HbA1c or ALT Over Time



ALT = Alanine Aminotransferase; HbA1c = Hemoglobin A1c

Stable Liver Chemistries and Improving Glycemic Parameters in Combination Therapy Groups

Obesity with T2DM Combination Therapy Cohorts



ALT = Alanine Aminotransferase; HbA1c = Hemoglobin A1c; T2DM = Type 2 Diabetes Mellitus; TZP = Tirzepatide

Summary and Next Steps

- ✓ ARO-INHBE was **safe, well-tolerated**, and achieved **robust and sustained reductions in serum Activin E** levels with no adverse changes in transaminases or HbA1c
- ✓ Monotherapy with ARO-INHBE achieved **meaningful reductions in visceral and liver fat** by MRI
- ✓ Combination therapy with tirzepatide in patients with obesity and type 2 diabetes **enhanced fat mass loss and weight loss** compared to tirzepatide alone, representing a unique opportunity for targeting metabolic health in a population that achieves less weight loss with GLP-1/GIP monotherapy
- ✓ Phase 2 study planning in progress

HbA1c = Hemoglobin A1c

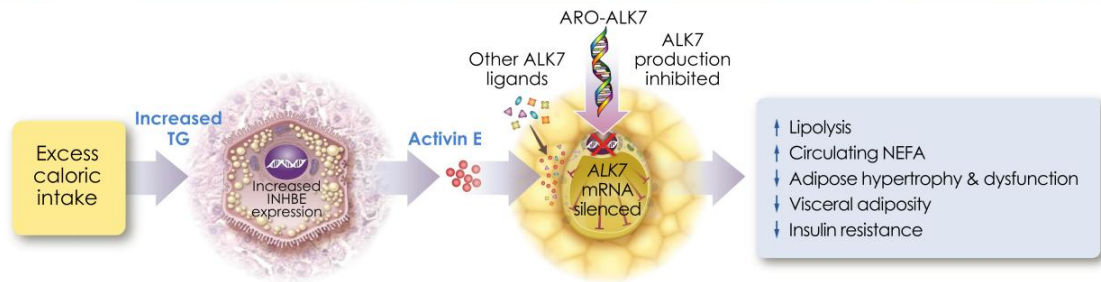
ARO-INHBE and ARO-ALK7 Interim Clinical Data Update

Clinical Study Update from AROALK7-1001

James Hamilton MD, MBA
Chief Medical Officer and Head of R&D



Activin Receptor-like Kinase 7 (ALK7, *ACVR1C*) is a Genetically Validated Adipose Target



- ALK7 is a TGF- β receptor superfamily member preferentially expressed on adipocytes
- Ligands may include: GDF3, GDF11, ActB, ActE, ActAB, ActC, Nodal
- ALK7 signaling suppresses lipolysis, increasing adipocyte size and lipid content

pLOF ALK7 Variants Are Associated with Lower Risks of Obesity and Type 2 Diabetes

Table 2—Association of variants in *ACVR1C* with WHRadBMI and with type 2 diabetes

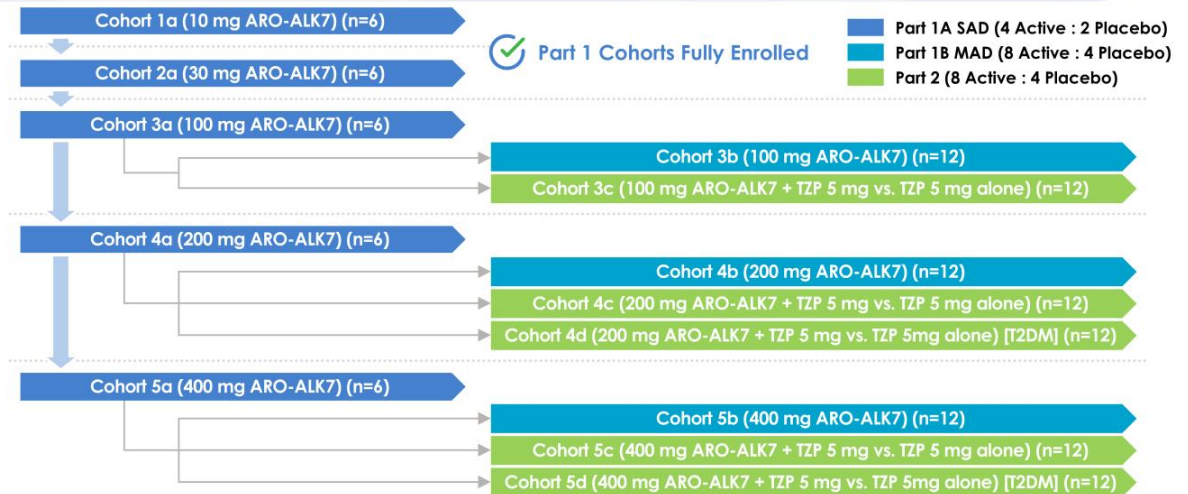
Variant	Minor allele frequency (%)	WHRadBMI		Type 2 diabetes	
		β (95% CI)	P value	OR (95% CI)	P value
Aan150His	1.1	-0.089 (-0.11, -0.067)	3.4×10^{-17}	0.88 (0.83, 0.94)	8.7×10^{-5}
Ile195Thr	0.2	-0.15 (-0.09, 0.19)	1.0×10^{-8}	0.79 (0.67, 0.93)	0.005
Ile482Val	7.2	-0.019 (-0.01, -0.027)	1.6×10^{-5}	0.95 (0.93, 0.97)	4.8×10^{-6}
rs72927479	5.1	-0.035 (-0.045, -0.025)	2.6×10^{-12}	0.93 (0.89, 0.97)	6.0×10^{-4}

Estimates for WHRadBMI were derived through linear regression analysis in UK Biobank. Estimates for type 2 diabetes were derived through meta-analysis of UK Biobank and the DIAGRAM ExText2D Consortium.

Emdin et al., *Diabetes* 2019

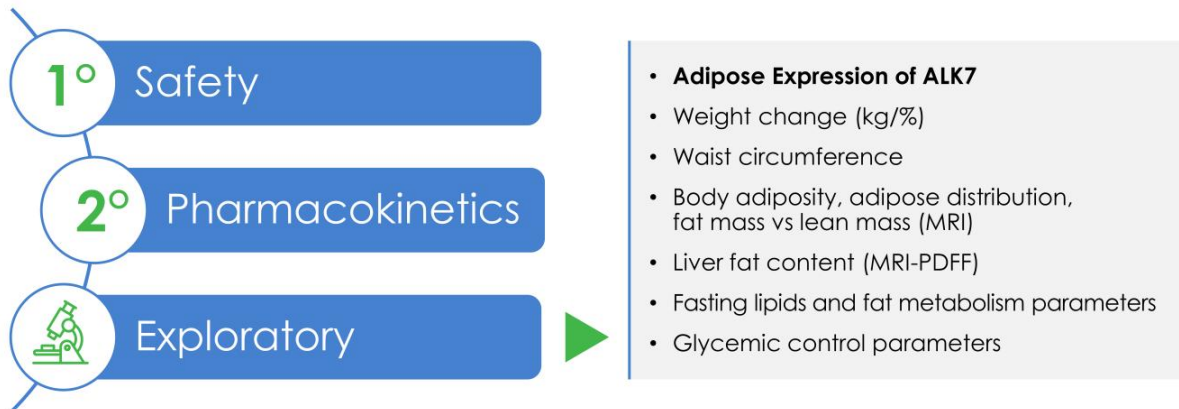


AROALK7-1001: Phase 1/2a Study of **ARO-ALK7** in Volunteers with Obesity, with and without Type 2 Diabetes Mellitus



MAD = Multiple Ascending Dose; SAD = Single Ascending Dose; T2DM = Type 2 Diabetes Mellitus; TZP = Tirzepatide

Key Endpoints



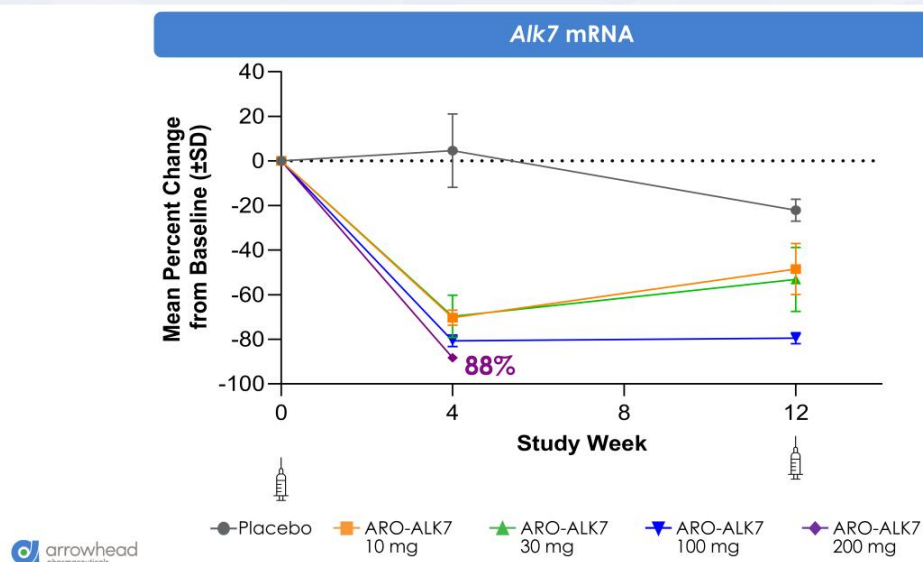
MRI = Magnetic Resonance Imagine; MRI-PDFF = Magnetic Resonance Imaging-Proton Density Fat Fraction

Baseline Characteristics – Volunteers with Obesity (Part 1)

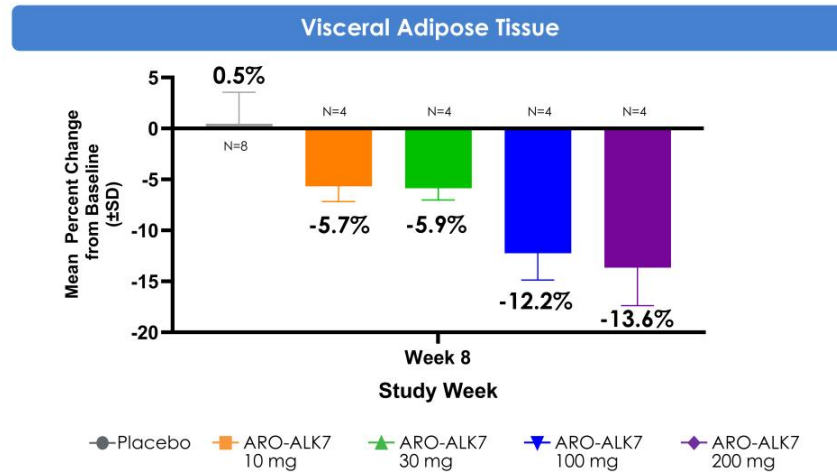
	ARO-ALK7 SAD Cohorts (N=30)	ARO-ALK7 MAD Cohorts (N=24)
Age, mean (SD)	39.0 (13.1)	39.6 (9.5)
Sex, female, n (%)	21 (70.0)	18 (75)
Race		
White, n (%)	18 (60.0)	16 (66.7)
Native Hawaiian or Pacific Islander, n (%)	8 (26.7)	9 (37.5)
Asian, n (%)	3 (10.0)	2 (8.3)
Black or African American, n(%)	1 (3.3)	0 (0.0)
Other, n (%)	4 (13.3)	3 (12.5)
Weight, mean (SD), kg	105.0 (15.9)	105.5 (21.1)
BMI, mean (SD), kg/m ²	36.3 (3.9)	36.8 (5.5)
HgbA1c, mean (SD), %	5.4 (0.3)	5.3 (0.4)

BMI = Body Mass Index; HgbA1c = Hemoglobin A1c; MAD = Multiple Ascending Dose; SAD = Single Ascending Dose; SD = Standard Deviation

ARO-ALK7 Demonstrated Dose Dependent Mean Decreases in Alk7 mRNA up to **88%**, Confirming TRiM Platform Ability to Silence Adipocyte Gene Expression



Rapid Dose-dependent Reductions in Visceral Fat of Up to 14.1% (Placebo-adjusted) After a Single Dose of ARO-ALK7



ARO-ALK7 Demonstrated a Favorable Safety Profile

ARO-ALK7 was **well tolerated** as monotherapy in participants with obesity.



Most TEAEs were
mild in severity



No TEAEs led to
study or study drug
discontinuation



No SAEs were
reported

No clinically significant adverse laboratory trends (including in liver enzymes and glycemic parameters) **were identified.**

Summary and Next Steps



ARO-ALK7 was **safe**, **well-tolerated**, and led to **deep reductions in adipose ALK7 expression** at all clinical doses



SAD and MAD Cohorts **fully enrolled** and Part 2 Cohorts, recruiting participants with obesity with and without type 2 diabetes, are **actively enrolling**



Additional AROALK7-1001 data release throughout **2026**

MAD = Multiple Ascending Dose; SAD = Single Ascending Dose



**We would like to thank the patients,
investigators, and site personnel
who participated in the studies**



Key Takeaways

Chris Anzalone, Ph.D.
President and CEO



Key Early Findings from Ongoing Phase 1/2a Studies

- **ARO-INHBE: dose-dependent reductions in serum Activin E**
 - mean max reduction of **-85%** after a single 400 mg dose
 - max observed reduction of **-94%**
- **ARO-INHBE monotherapy reduced visceral fat**
 - **-9.9%** after a single dose at week 16
 - **-15.6%** after 2 doses at week 24
- **ARO-INHBE + tirzepatide doubled weight loss in obese diabetic patients versus TZP alone**
 - **-9.4%** weight loss at week 16 with ARO-INHBE + TZP
 - **-4.8%** weight loss at week 16 with TZP alone
- **ARO-INHBE + TZP drove *high quality* weight loss in obese diabetic patients**
 - **-23.2%** visceral fat reduction
 - **-15.4%** total fat reduction
 - **-76.7%** liver fat reduction
 - Approximately 3-fold improvement versus TZP alone across these measures
- **ARO-ALK7 is the first RNAi therapeutic to show knockdown of an adipocyte-expressed target in humans**
 - mean reduction of **-88%** ALK7 mRNA
 - max reduction of **-94%**
- **Early data, but ARO-ALK7 could be more active than ARO-INHBE**
 - **-14%** placebo-adjusted reduction in visceral fat after single dose monotherapy at week 8

What We Already Achieved in Phase 1/2a

- ✓ **Established Safety and Tolerability** of single-dose, multi-dose, and combination regimens with tirzepatide
- ✓ Demonstrated **deep and durable knockdown** of Activin E and ALK7
- ✓ Identified signals of **Activin E/ALK7 pathway translation in humans**
- ✓ Measured **favorable changes in body composition**
- ✓ Showed **benefit on weight loss** in a specific population with unmet need

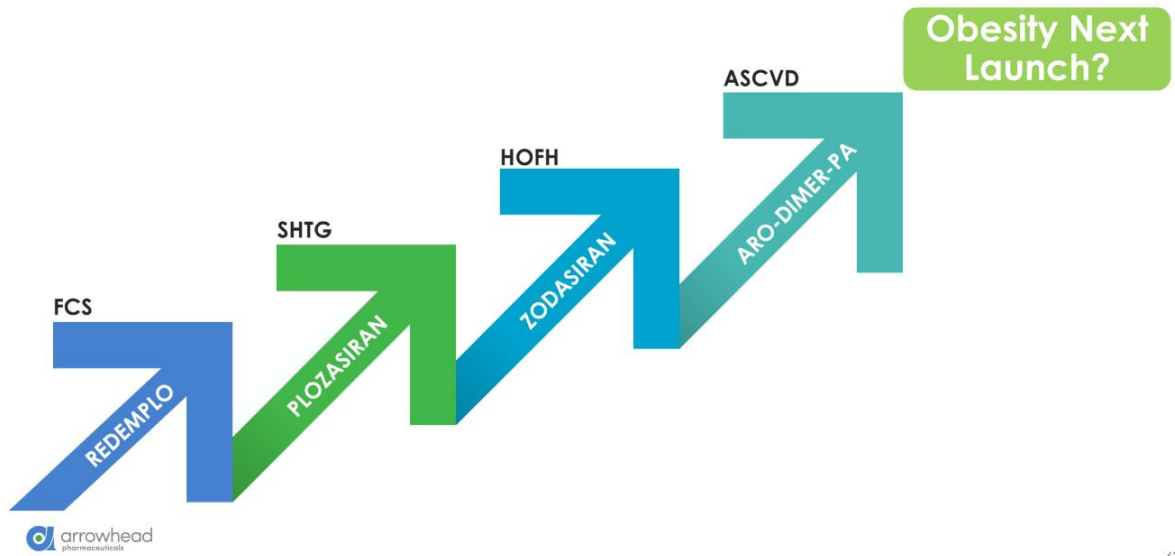
What We Still Hope to Achieve



Next Steps

- **Expanding current studies, including:**
 - Increasing numbers of patients to increase power
 - Extending follow-up to better understand drug durability and activity out to 1 year
 - Initiation of a monotherapy cohort in obese diabetic patients
 - Initiation of additional combination cohorts with other GLPs
- **Initiate Phase 2b studies ASAP (current studies and additions are not gating)**
 - Combination studies (tirzepatide and other GLPs) in obese diabetic patients
 - Studies aimed at use as maintenance therapy (after GLPs are removed)
- **Obesity pipeline expansion**
 - New liver and adipocyte targets
 - Dimers targeting 2 adipocyte targets
 - Dimers targeting 2 liver targets
 - Leveraging our sc CNS platform to address central targets

Obesity Complements our Cardiometabolic Launch Plans



Arrowhead's Growth Drivers in 2026 and Beyond



Arrowhead's first **commercial sales** of **REDEMPLO** in familial chylomicronemia



Phase 3 studies of plozasiran in **severe hypertriglyceridemia (potential multi-billion-dollar opportunity)** on pace to readout in Q3 2026



ARO-DIMER-PA targeting PCSK9 and APOC3 first clinical **readout in 2H 2026**



Obesity franchise will grow with new targets, including dimers. Additional ARO-INHBE and ARO-ALK7 data presented in 2026



Emerging CNS pipeline with systemic delivery via SC administration: early ARO-MAPT data presented in 2026



Funded into fiscal 2028, potentially through **multiple independent and partner launches**

