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

January 06, 2026

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ARO-INHBE and ARO-ALK7 Interim Clinical Data Update
January 2026

Introduction and Agenda

Vince Anzalone, CFA
Vice President, Finance and IR

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Safe Harbor Statement

This presentation contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. 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 various factors and uncertainties, including, without limitation, our developmental stage and limited operating history, our ability to successfully and timely develop products, entering into new collaborations and achieving existing projected milestones, rapid technological changes in our markets, demand for our future products, legislative, regulatory and competitive developments and general economic conditions. Our Annual Report on Form 10-K, recent and forthcoming Quarterly Reports on Form 10-Q, recent Current Reports on Forms 8-K, and other SEC filings discuss some of the important risk factors that may affect our ability to achieve the anticipated results, as well as our business, results of operations and financial condition. Readers are cautioned not to place undue reliance on these forward-looking statements. Additionally, Arrowhead disclaims any intent to update these forward-looking statements to reflect subsequent developments.

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.

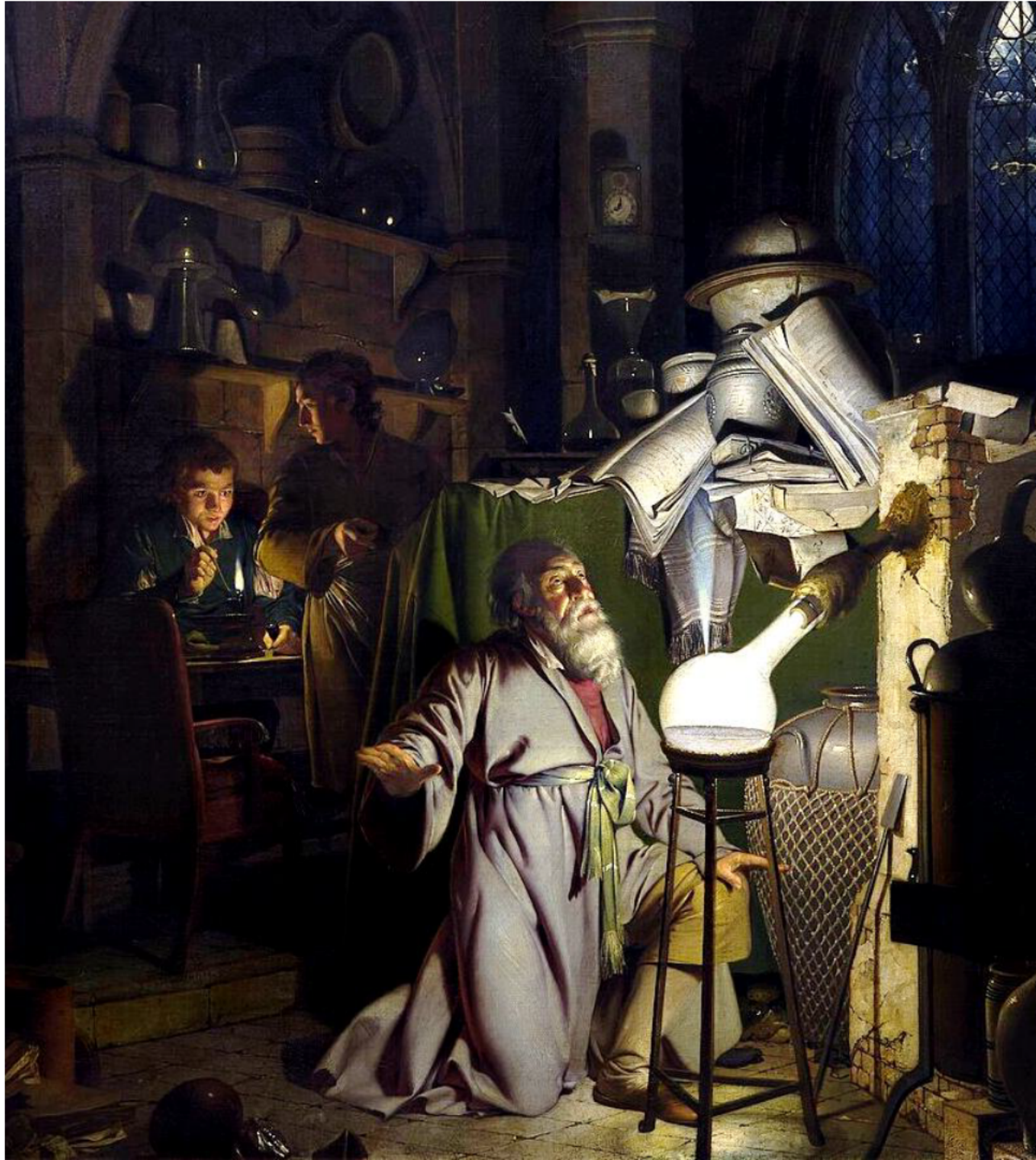
Chair of Metabolic Medicine, University College Dublin, School of Medicine

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.

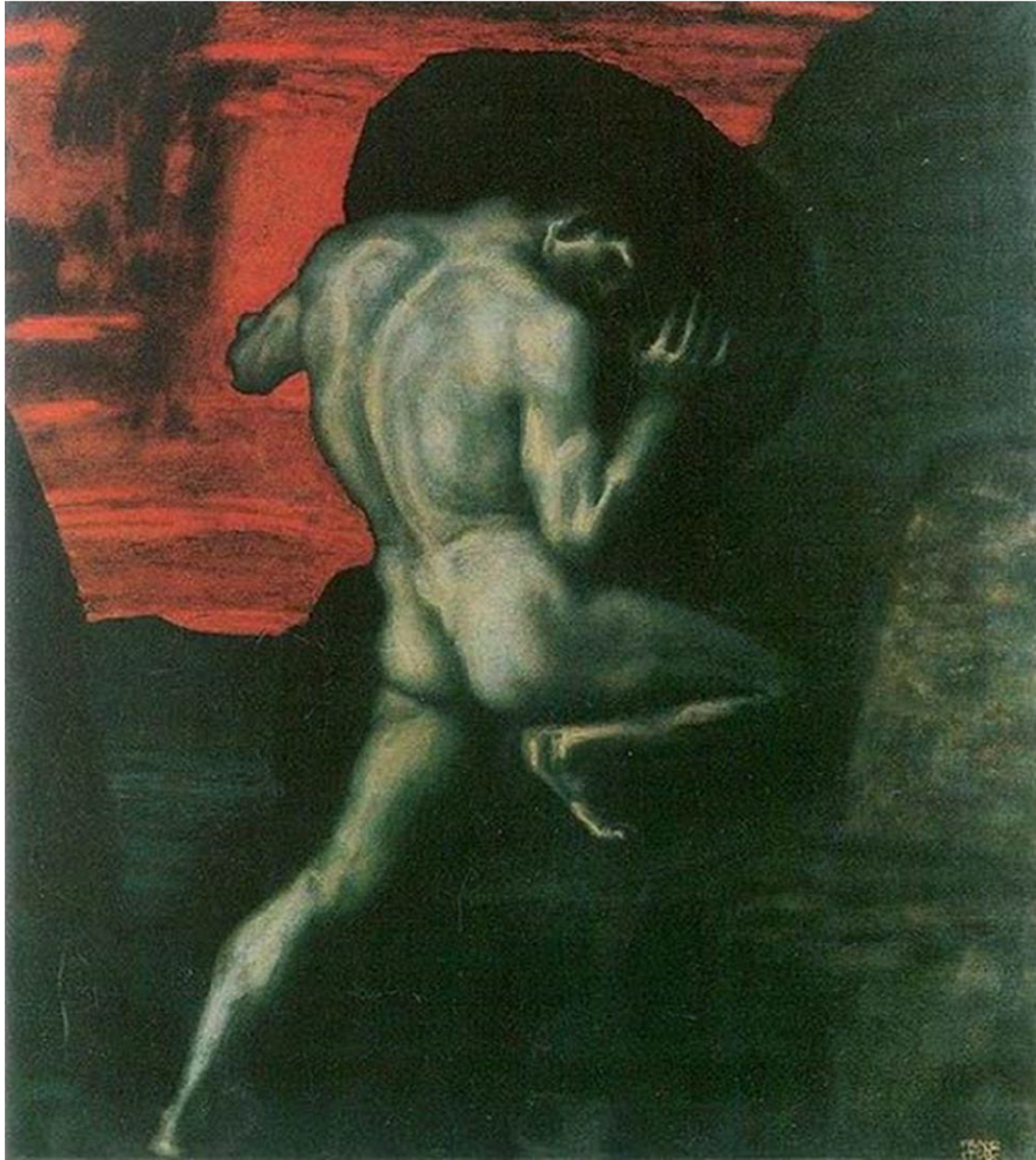
University College Dublin, Ulster University,
University of Pretoria



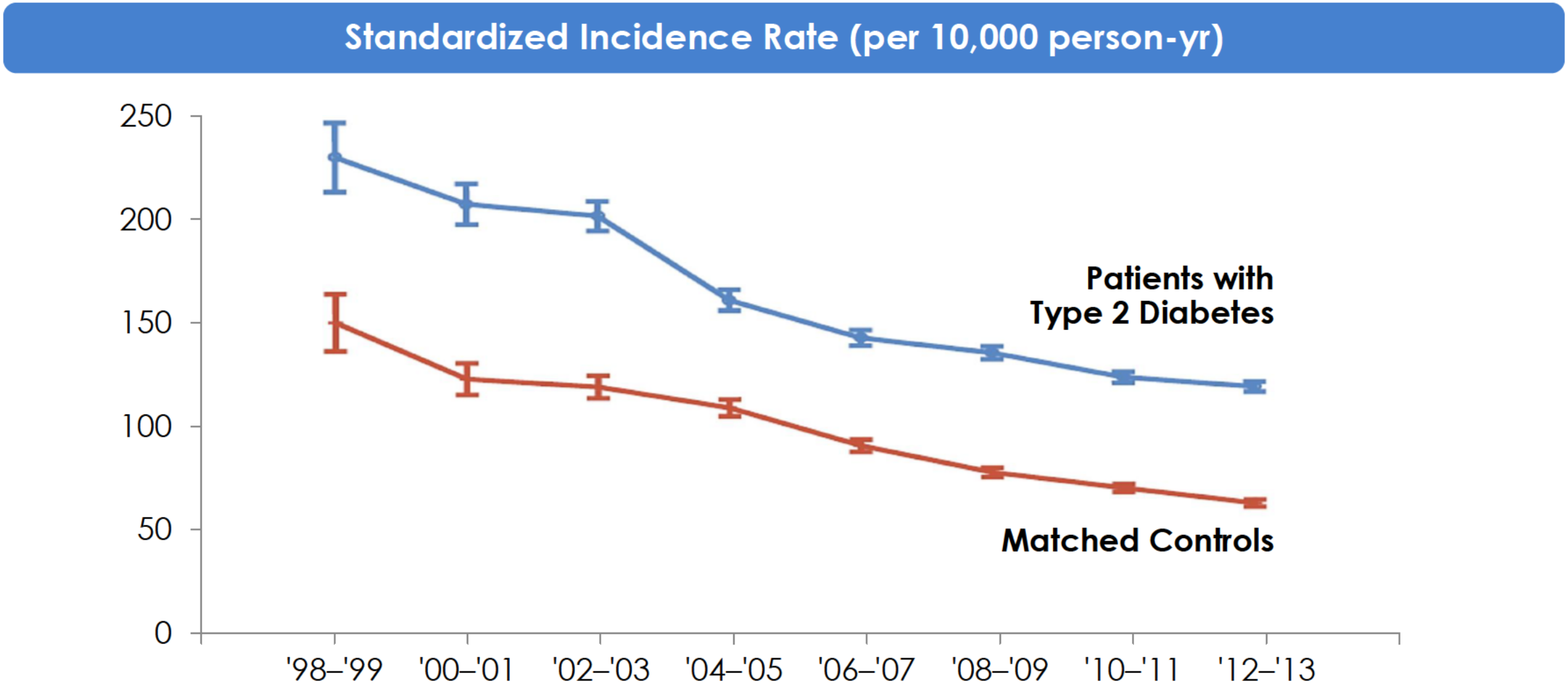
Joseph Wright of Derby.
The Alchemist Discovering Phosphorus. 1771.
Derby Museum and Art Gallery

Conflicts of Interest

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

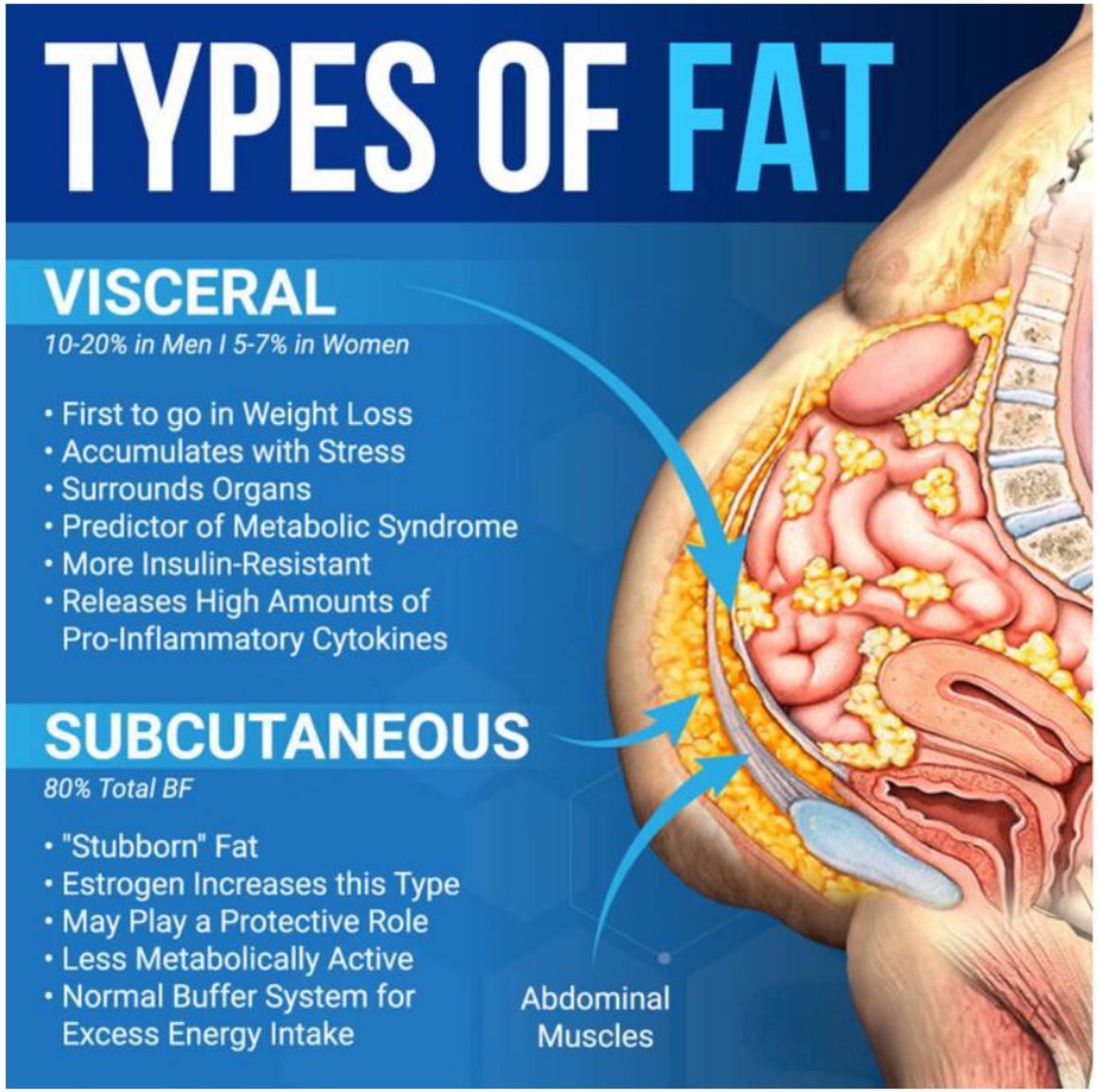


Death from Cardiovascular Disease

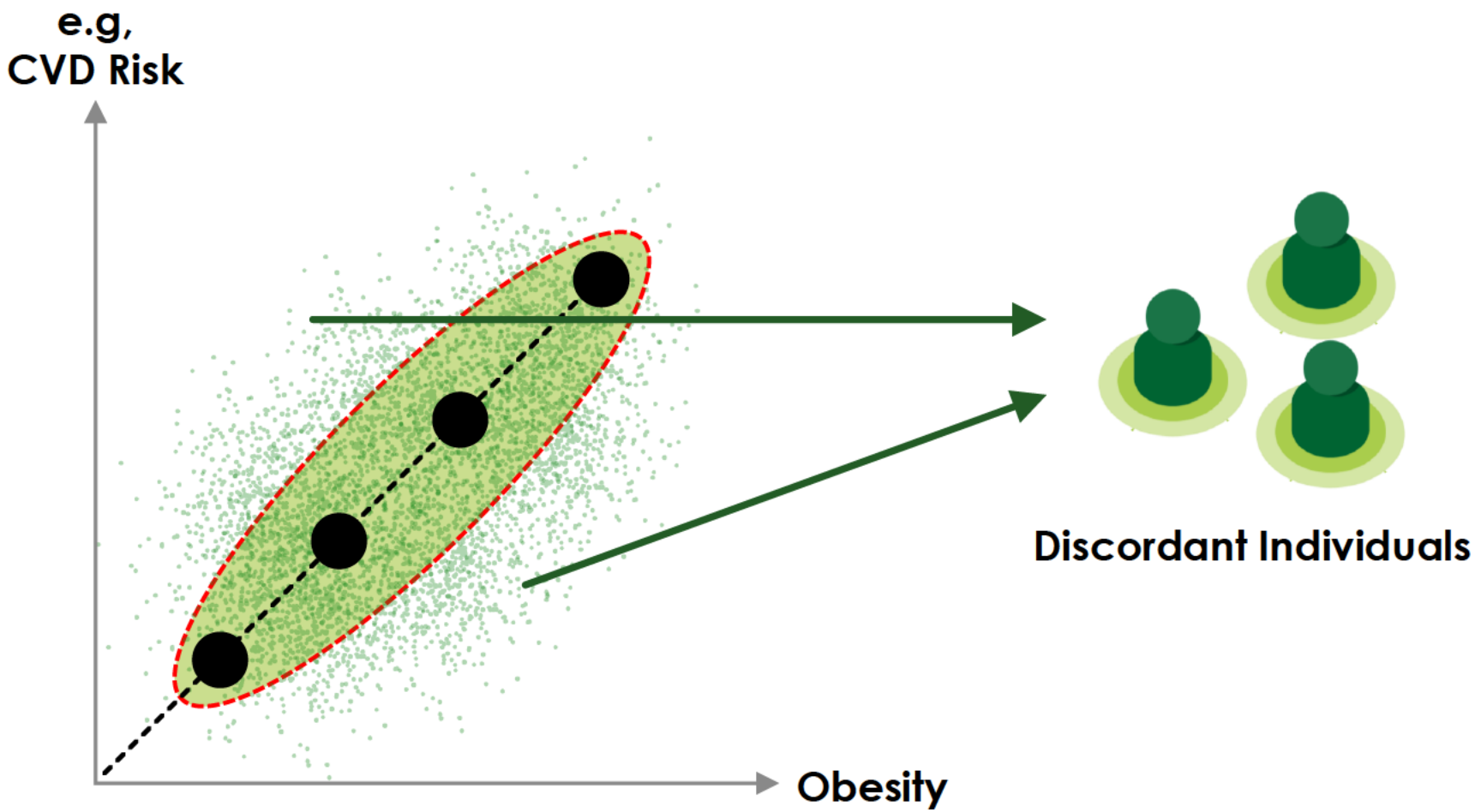


Rawshani et al. *NEJM 2017*.

Visceral Fat Drives Metabolic Diseases



What We Know: Risk Doesn't Always Follow BMI



Coral, le Roux et al *Nature Medicine 2024*.

BC: Baseline Concordant profile

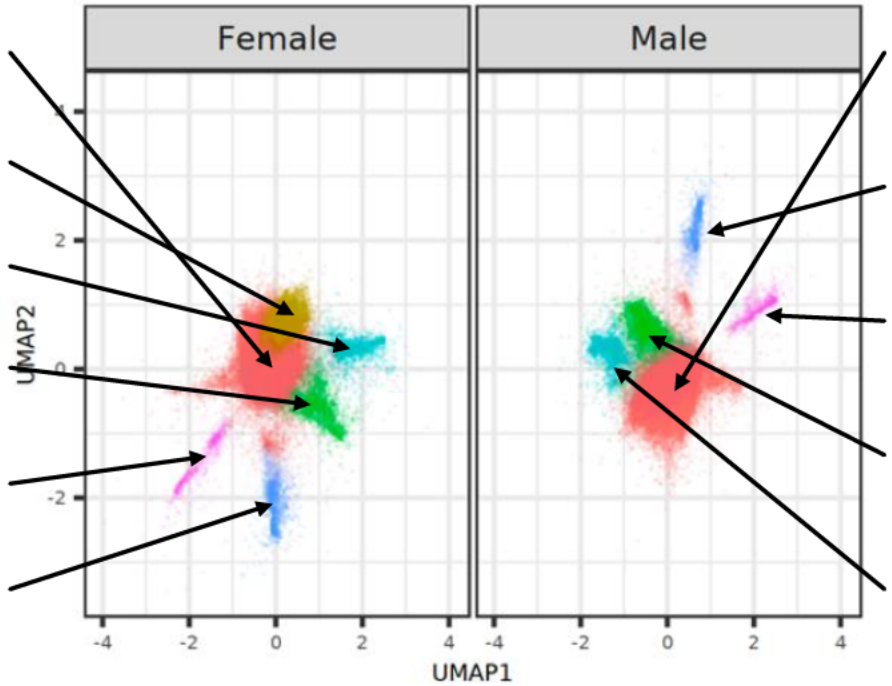
DHT: Discordant Hypertensive profile

DLT: Discordant Liver Transaminases profile

DAL: Discordant Adverse Lipid profile

DHG: Discordant Hyperglycaemic profile

DIS: Discordant Inflammatory State profile



BC: Baseline Concordant profile

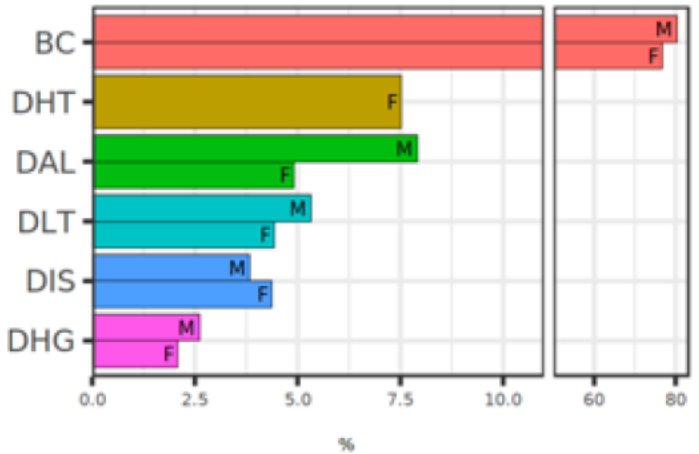
DIS: Discordant Inflammatory state profile

DHG: Discordant Hyperglycaemic profile

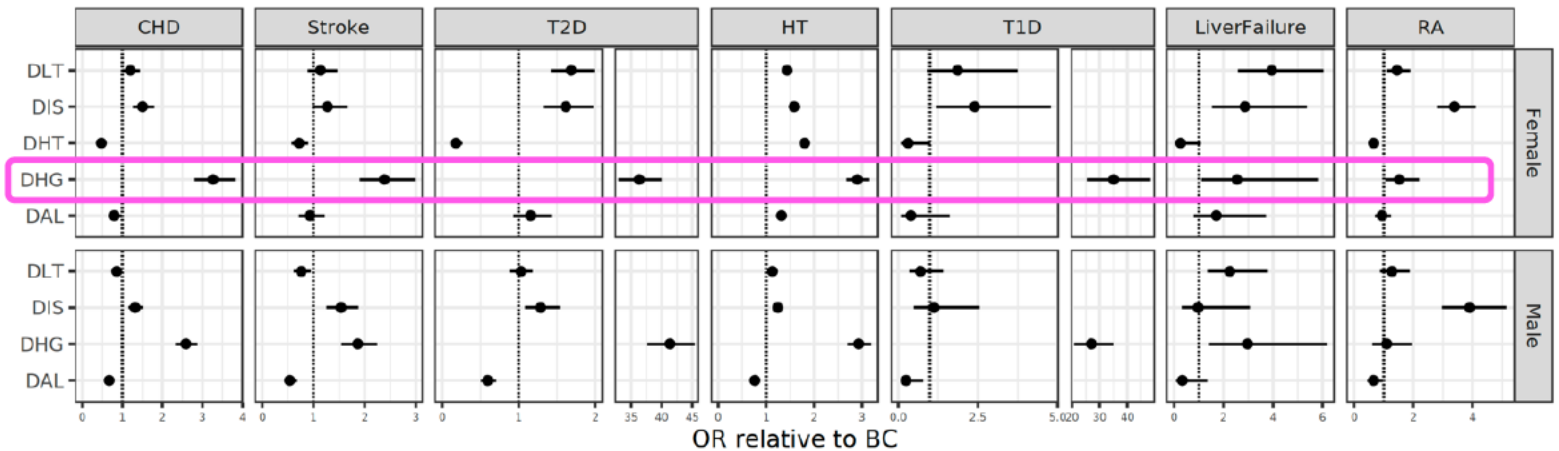
DAL: Discordant Adverse Lipid profile

DLT: Discordant Liver Transaminases profile

up to 80%

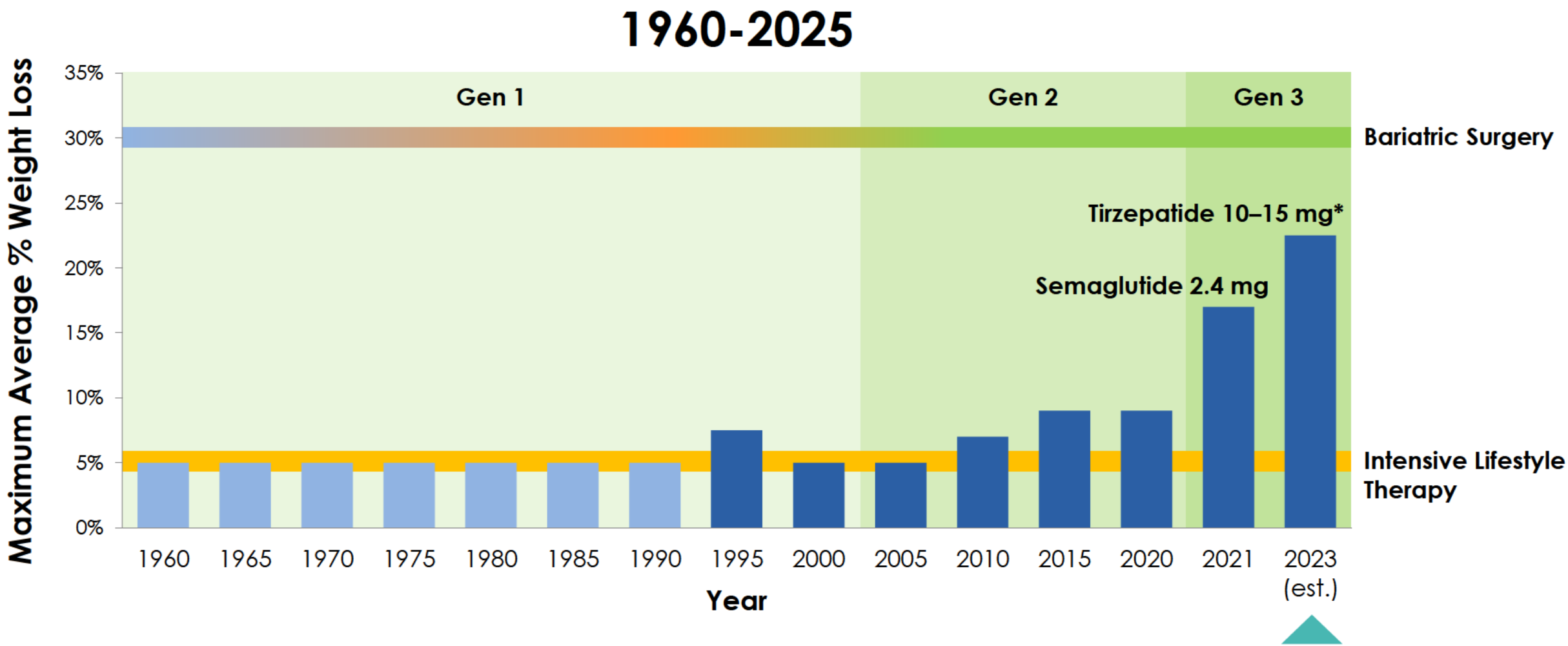


Discordant Profiles and Disease Prevalence



Coral, le Roux et al *Nature Medicine 2024*

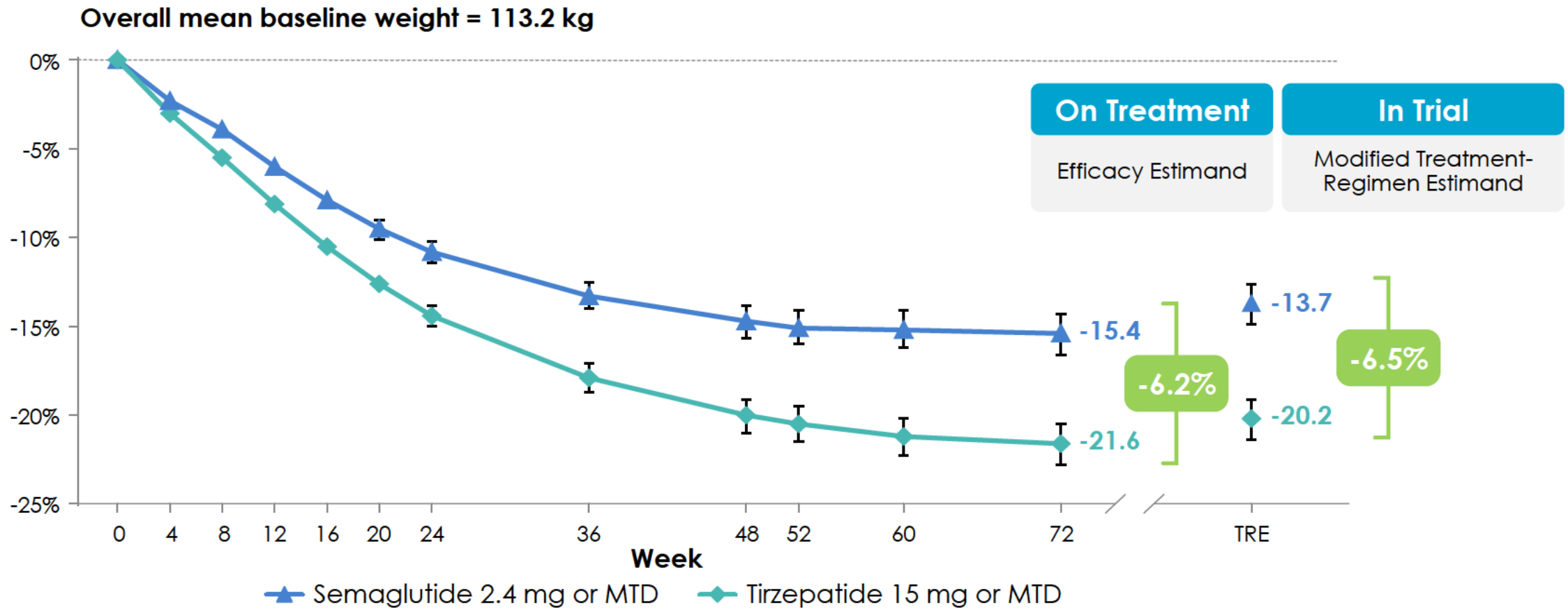
Emergence of Highly Effective Obesity Medications



Kaplan LM, 2023.

Weight Reduction from Baseline to Week 72: Percent Change

Weight Change from Baseline (%)



***p<0.001 vs semaglutide. Data are LSM ± 95% CI. Week 4 through Week 60 data were not controlled for multiplicity.
Data from Aronne LJ, le Roux CW et al. *N Engl J Med* 2025
TRE = Treatment-regimen estimand.

Proposed Obesity Treat to Target Thresholds

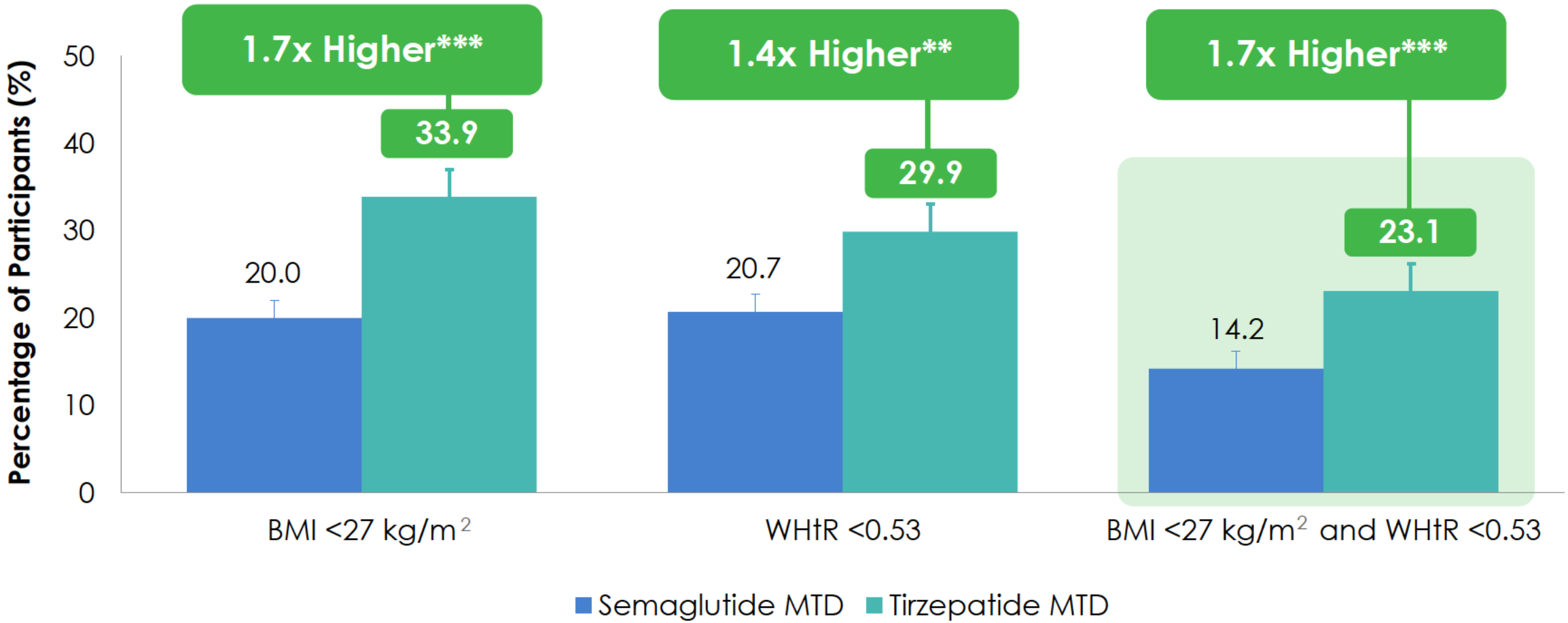
- Busetto, L et al. ECO 2024
- Investigated changes in BMI and WHtR with 10-year ORC risk
- >45K UK adults, 41% Overweight, 59% Obesity

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):56.

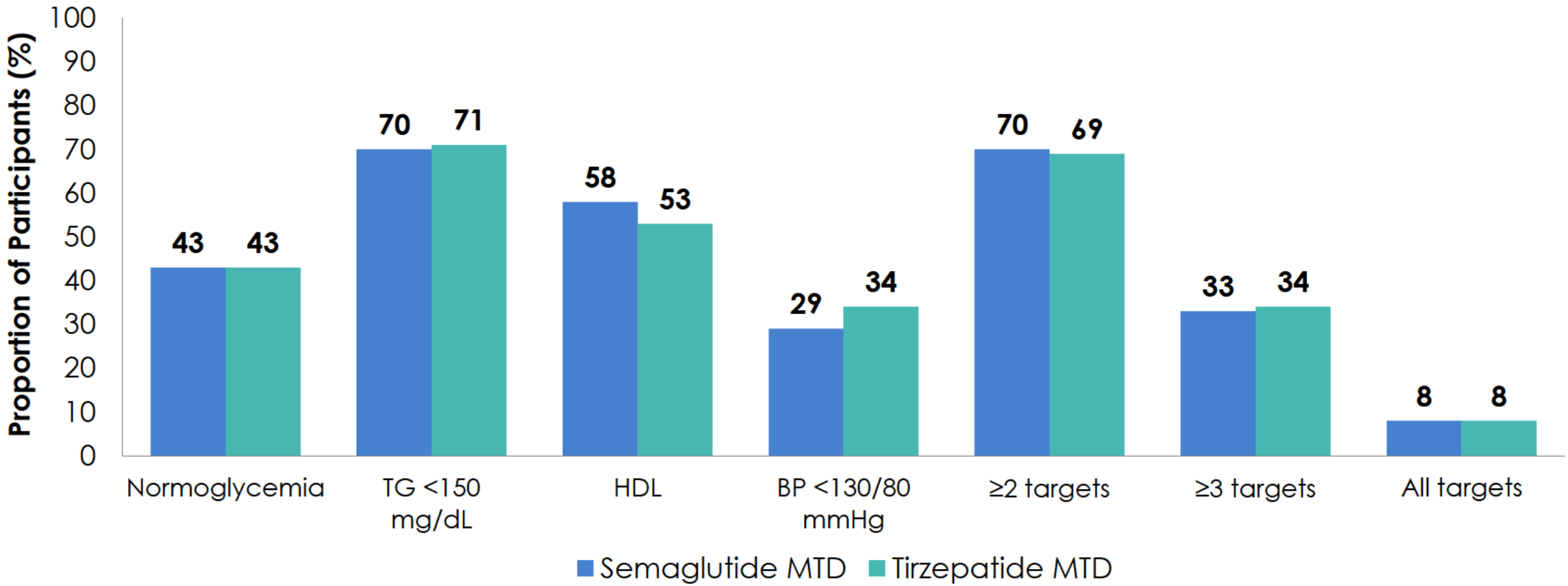
Percent of Participants Reaching Treat to Target Thresholds at Week 72



**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 on-treatment data. Treatment comparisons were made via logistic regression with the aid of Rubin's rule.

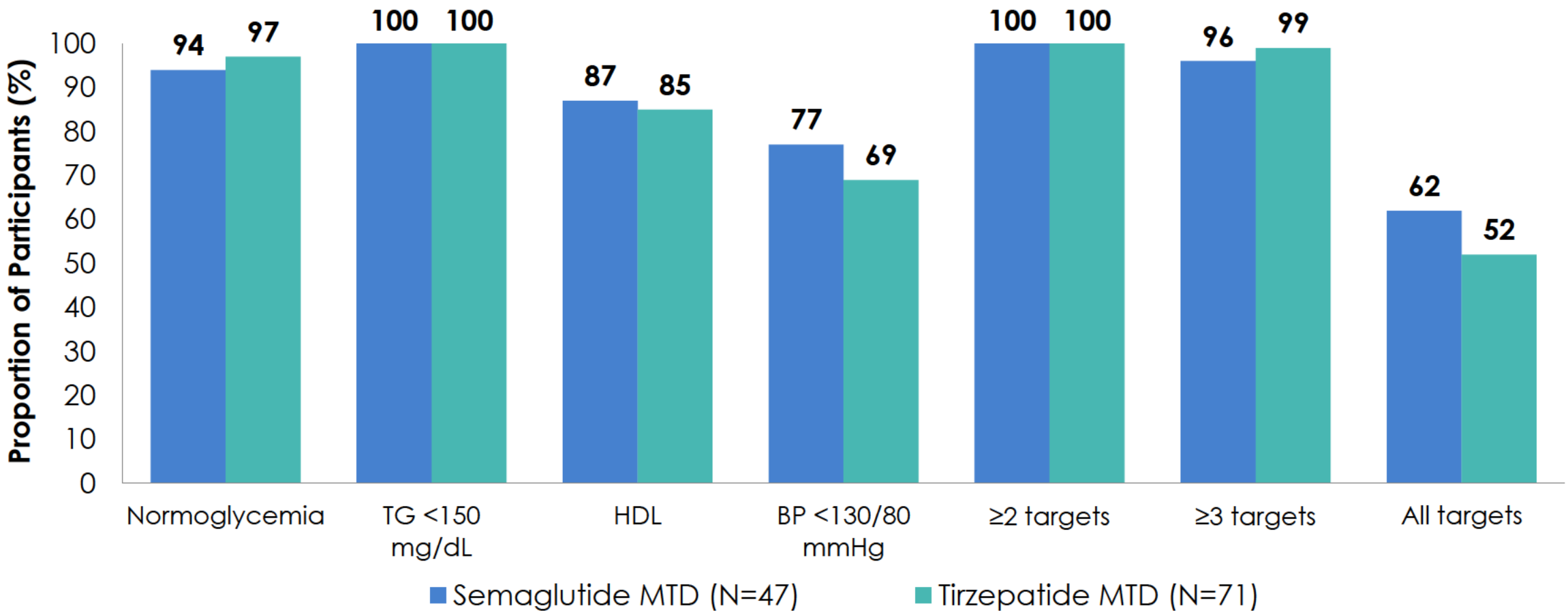
Percent of Participants with Normalization of Cardiometabolic Parameters

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.

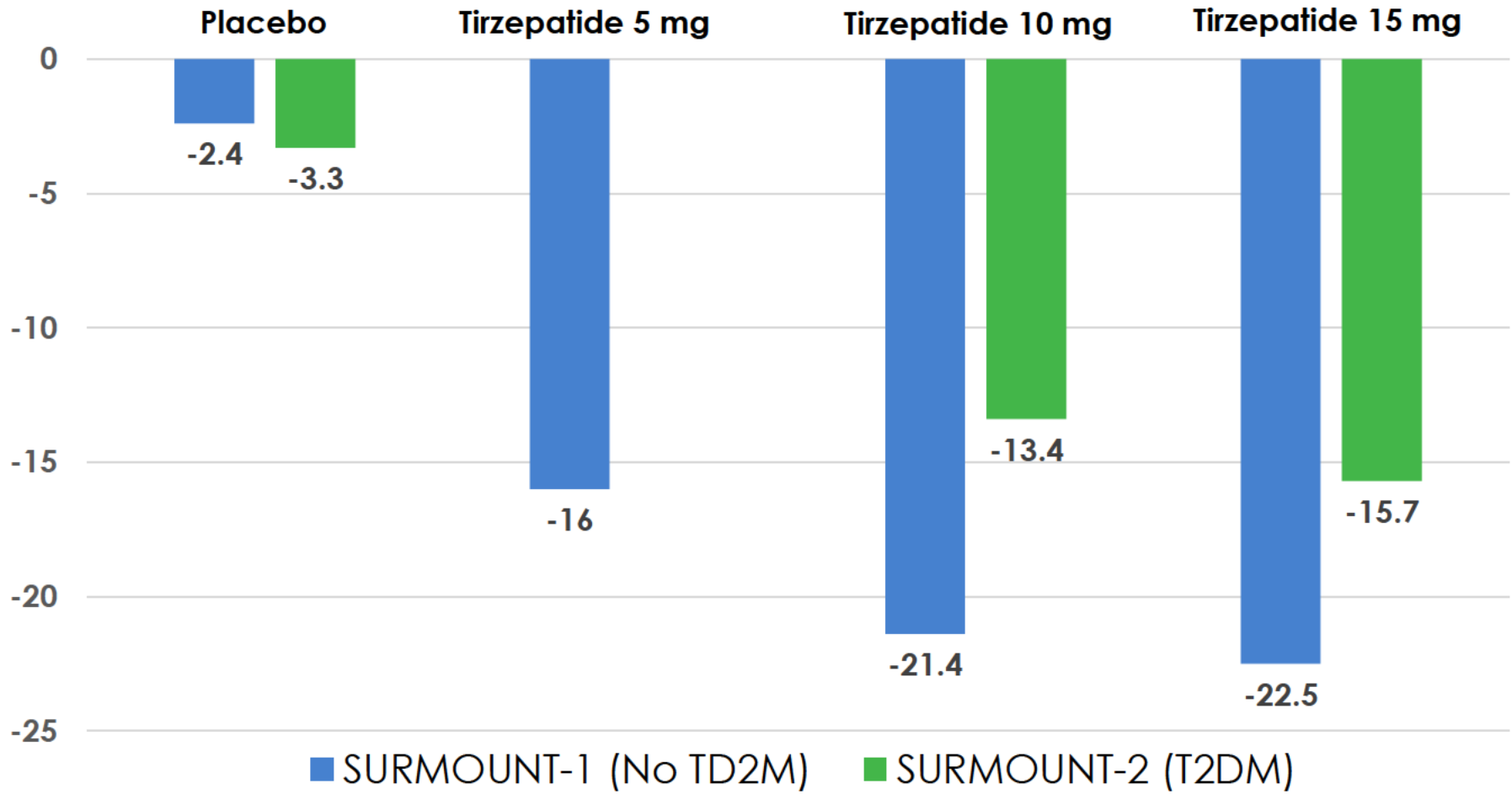
Normalization of Cardiometabolic Parameters in Participants Reaching WHtR <0.53 & BMI <27 at Week 72



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

Percent Change in Bodyweight at 72 weeks (efficacy estimand)



Overall mean baseline weight = 104.8 kg

Overall mean baseline weight = 100.8 kg

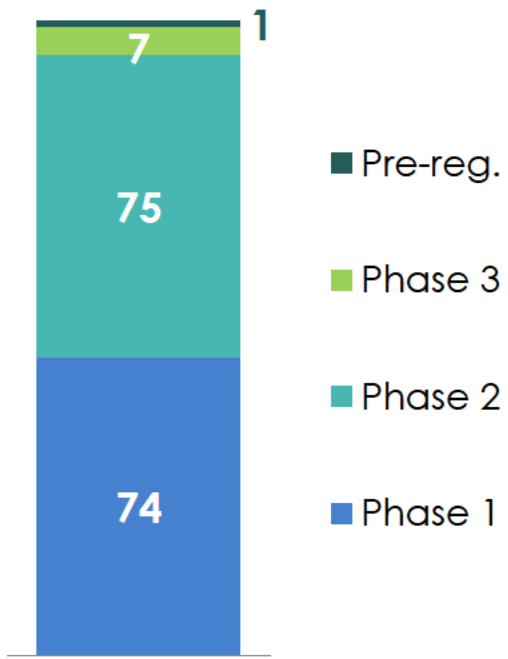
NEJM 2022

Lancet 2023

Pipeline: By Phase, MOA, and Administration Route

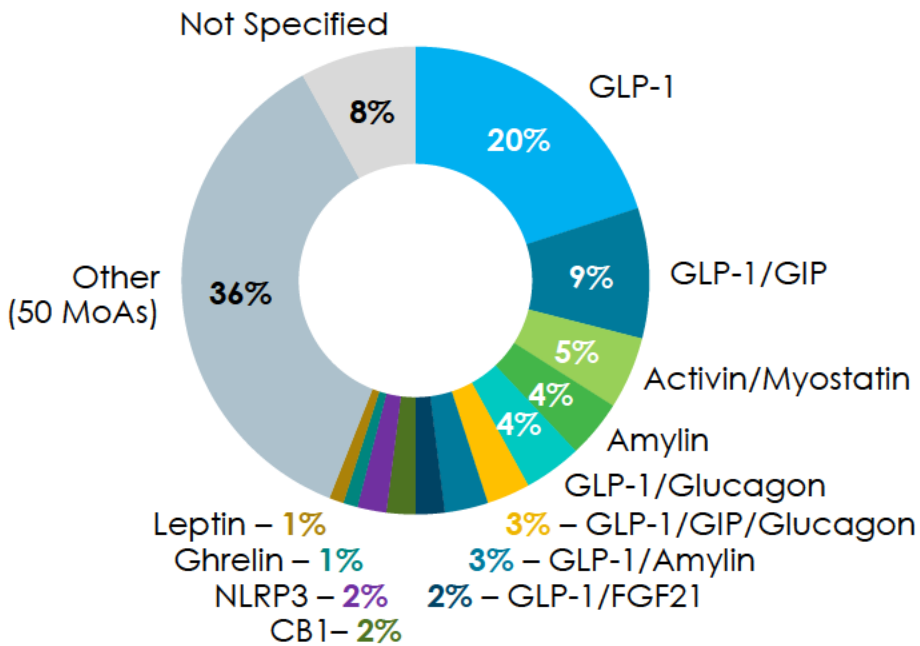
By Phase
(Number of Active Assets)

N=157



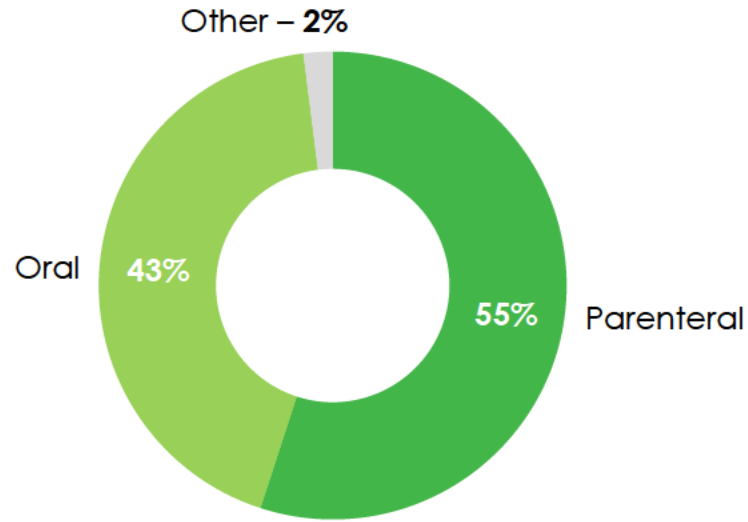
By Mechanism of Action
(Phase 1-pre-resignation)

N=157



By Route of Administration
(Phase 1-pre-registration)

N=157

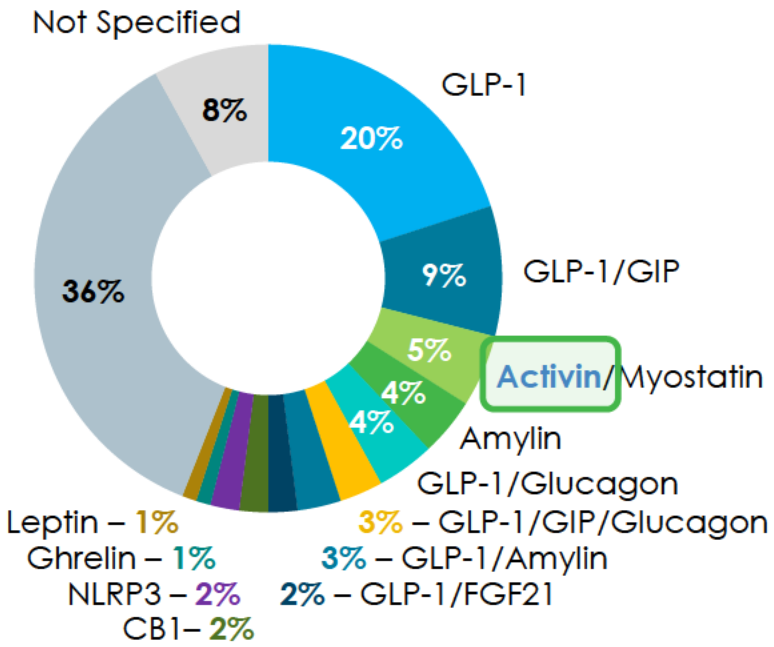


Source: IQVIA Analytics Link; Cinicaltraials.gov; company reports, press releases, desk research, IQVIA EMEA Thought Leadership analysis; December 2024.

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

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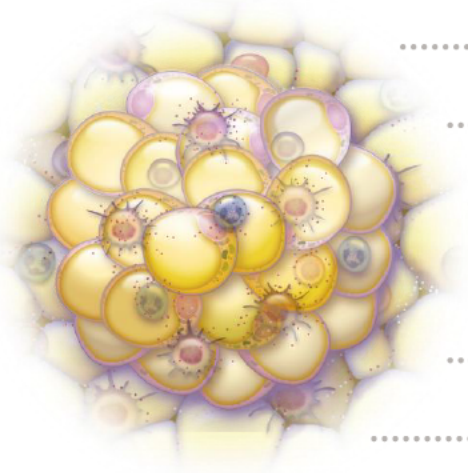
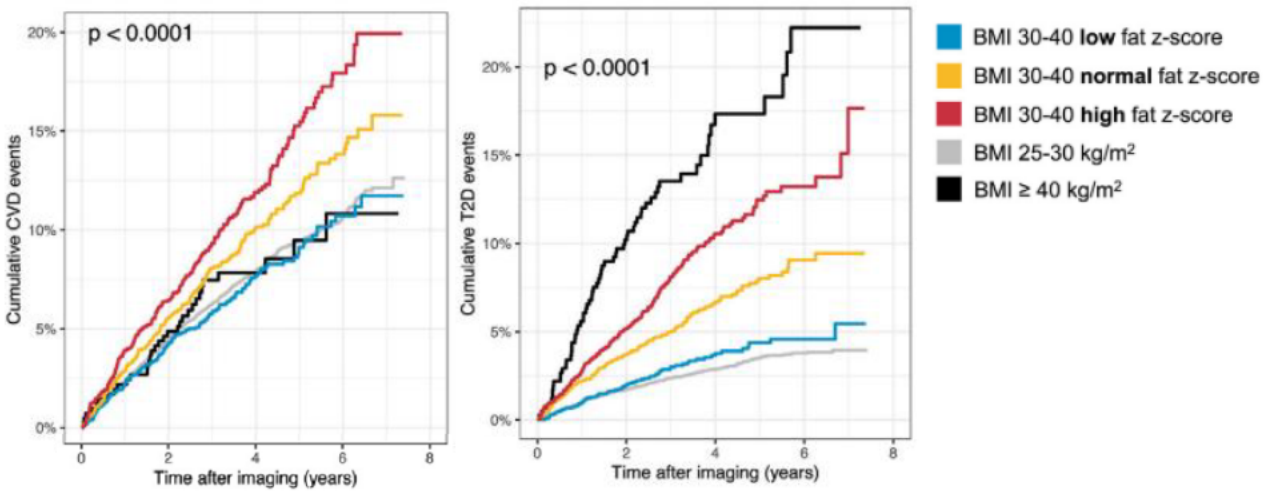
Targeting Visceral Adiposity to Improve Metabolic Health

Excess Visceral Adiposity is Associated with Metabolic Risk[1,2]



- Systemic Inflammation
- Insulin Resistance & Type 2 Diabetes
- Dyslipidemia & Atherosclerosis
- Hepatic Steatosis and MASLD
- Cardiovascular Disease
- All-cause Mortality

Visceral Fat Burden (measured by z-score) Predicts Incident Cardiovascular Disease and Type 2 Diabetes[3]



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. Neeland 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

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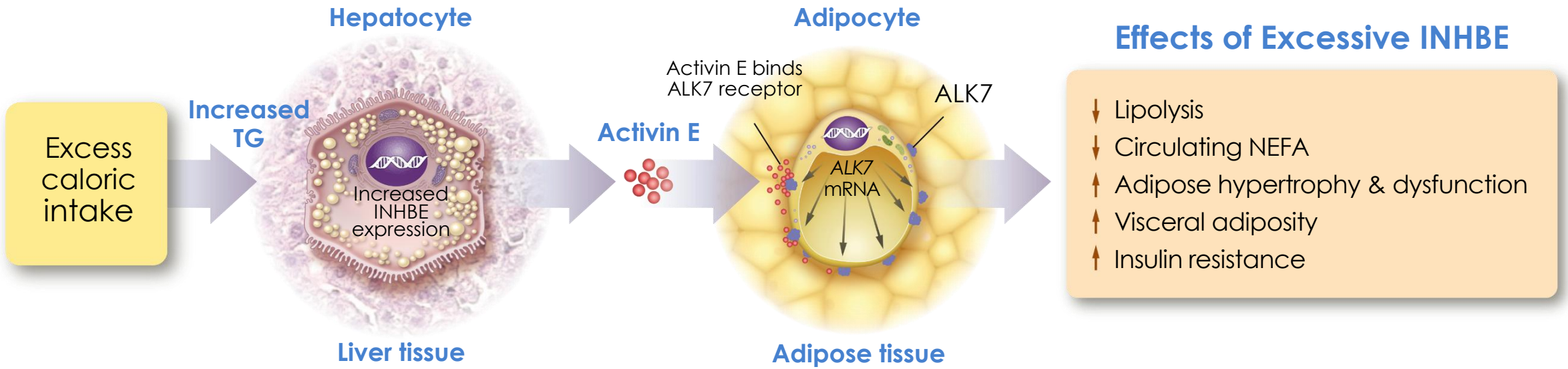
Hepatic Activin E Encoded by *INHBE* Gene Regulates Energy Homeostasis in Adipose Tissue via the ALK7 Receptor



- 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

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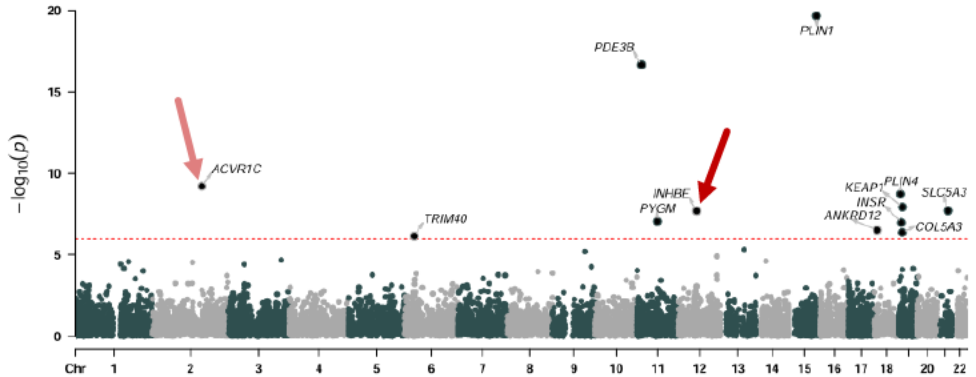
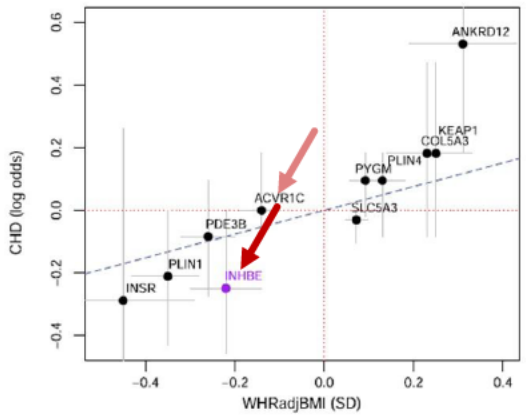
pLOF Variants of *INHBE* Are Associated with Reduced Abdominal Fat and Cardiometabolic Risk

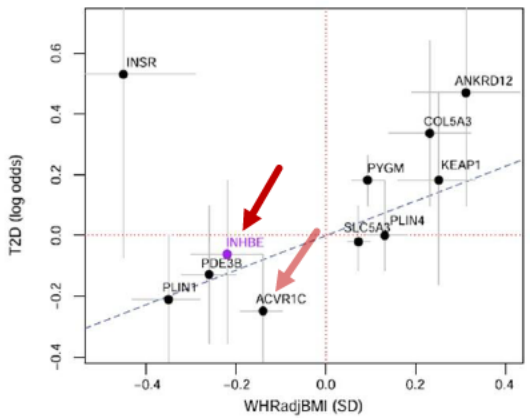
↓ Waist-to-Hip Ratio Adjusted for BMI



↓ 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

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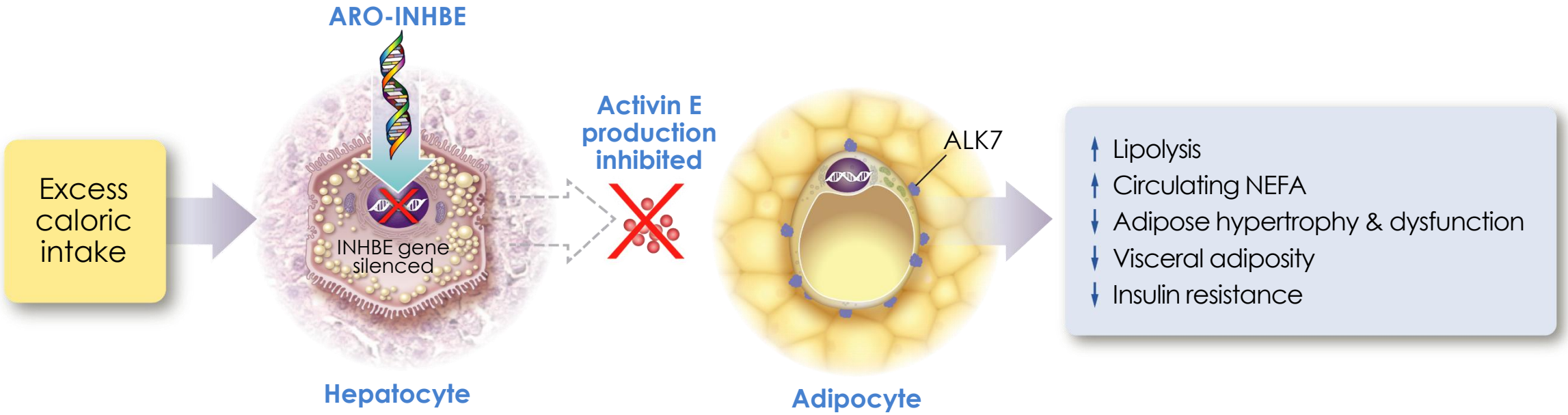
Silencing Hepatic *INHBE* May Inhibit Maladaptive Activin E – ALK7 Signaling and Improve Adipose Dysfunction in Obesity



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

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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

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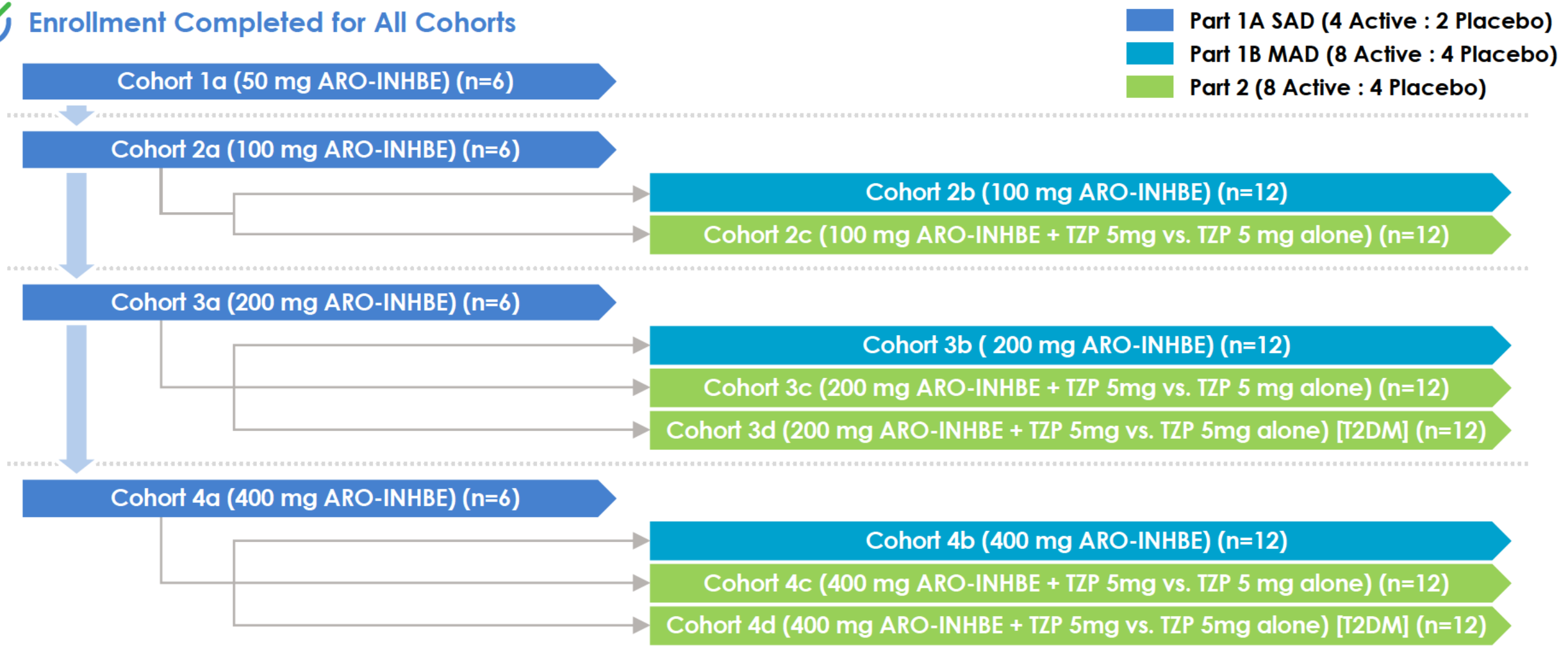
AROINHBE-1001: Phase 1/2a Study of ARO-INHBE in Volunteers with Obesity, with and without Type 2 Diabetes Mellitus

Enrollment Completed for All Cohorts



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

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Key Endpoints

1° Safety

2° Pharmacokinetics

Exploratory

- **Serum Activin E**
- Weight change (kg/%)
- Body adiposity, adipose distribution, fat mass vs lean mass (MRI)
- Liver fat content (MRI-PDFF)
- Fasting lipids and fat metabolism parameters
- Glycemic control parameters

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

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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

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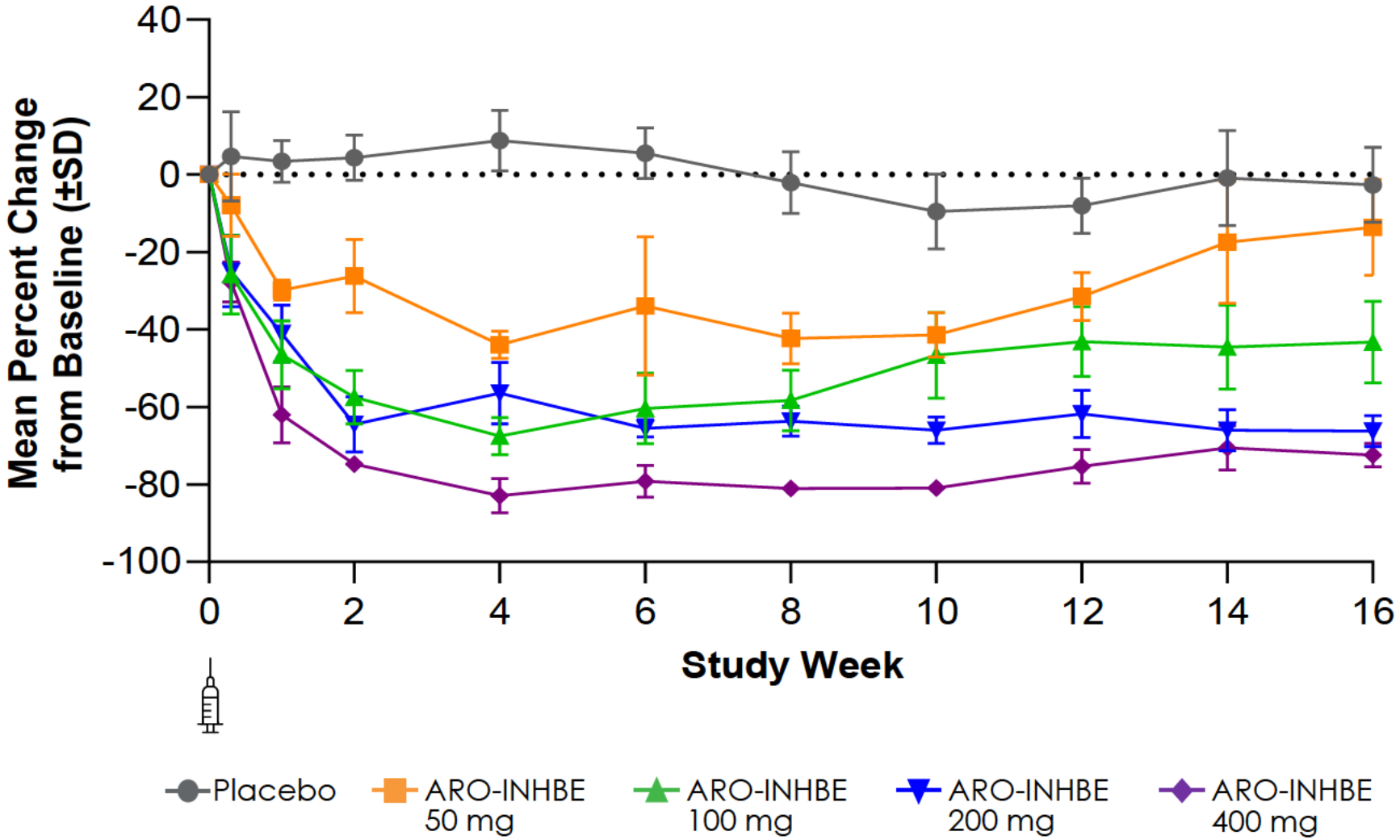
ARO-INHBE Achieved Mean Max Activin E Reduction of **85%** with Long Response Duration



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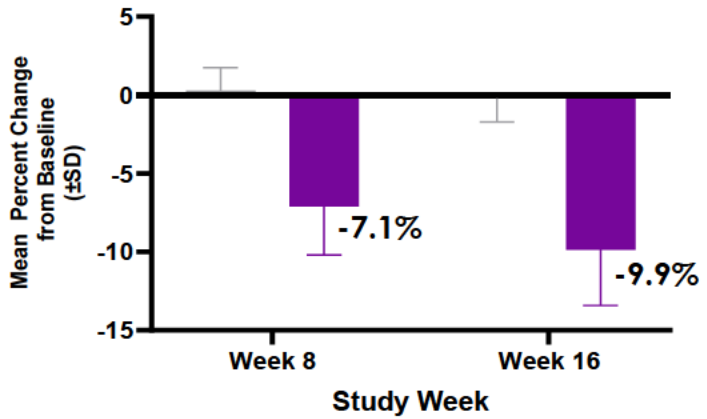
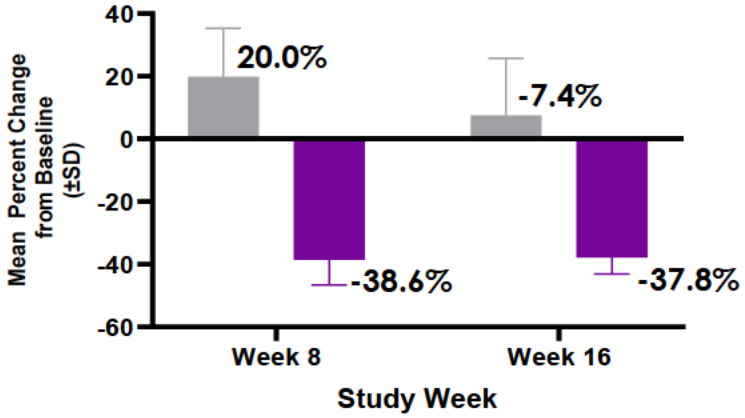
A Single Dose of ARO-INHBE Achieved Mean Visceral Fat Reductions of **9.9%** and Liver Fat Reductions of up to **38.6%**

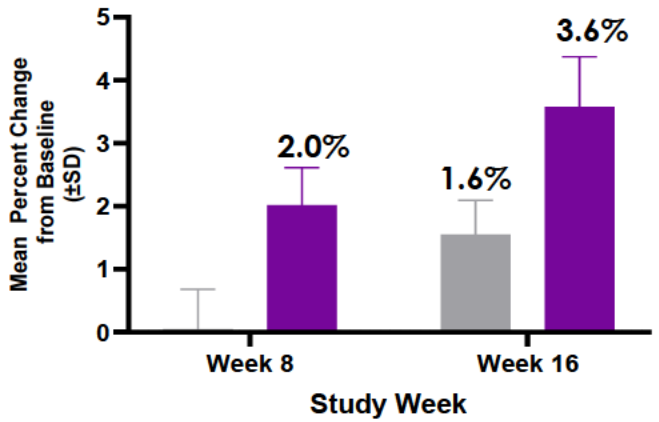
Visceral Adipose Tissue[1]



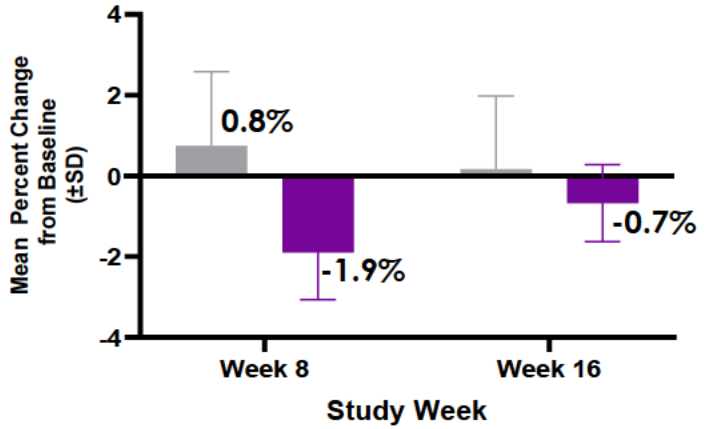
Liver Fat Content[2]



Total Lean Tissue[3]



Muscle Fat Infiltration[4]



ARO-INHBE 400 mg N=4

Pooled Placebo N=7

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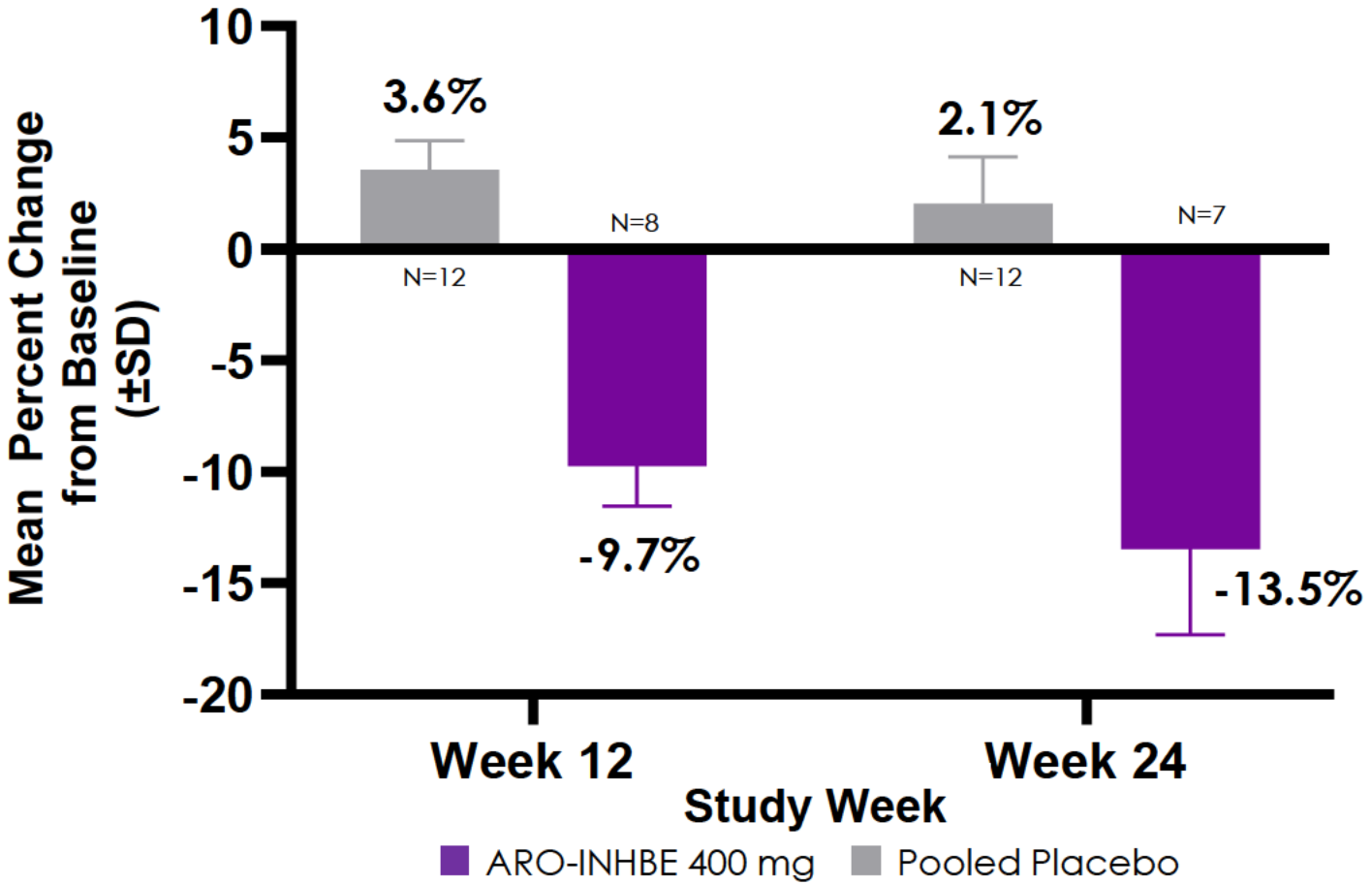
Body composition measurements obtained using MRI. 1. Visceral adipose tissue in the abdominal cavity; 2. Liver fat measured using MRI-PDFF; 3. Total lean tissue measured from neck to knee images, excluding extremities; 4. Muscle fat infiltration is an average of bilateral anterior thigh measurements.

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

Visceral Adipose Tissue[1]



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

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Combination Therapy Update – Obesity with Type 2 Diabetes Mellitus

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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

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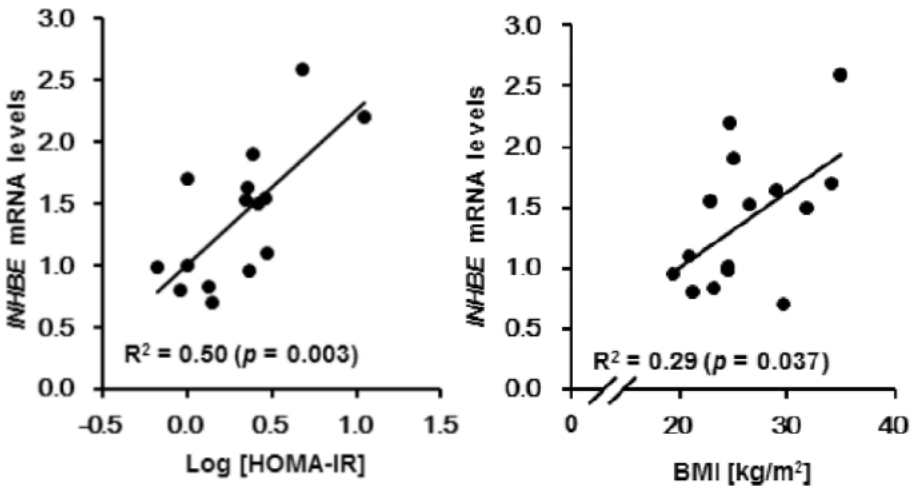
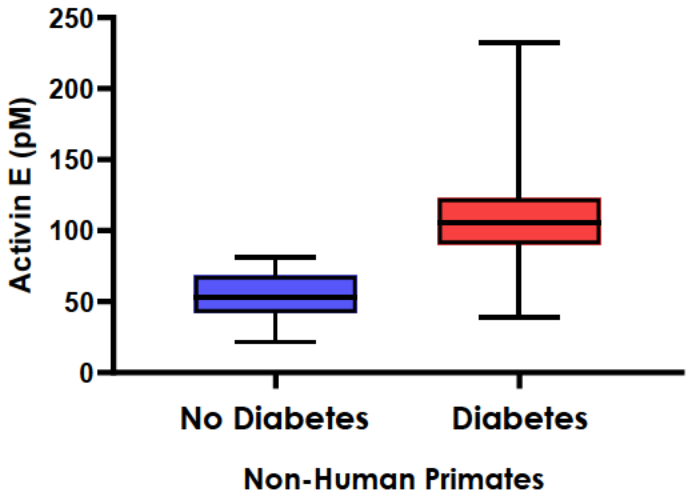
Insulin Resistance is Associated with Higher Activin E Levels in Primates and in Humans

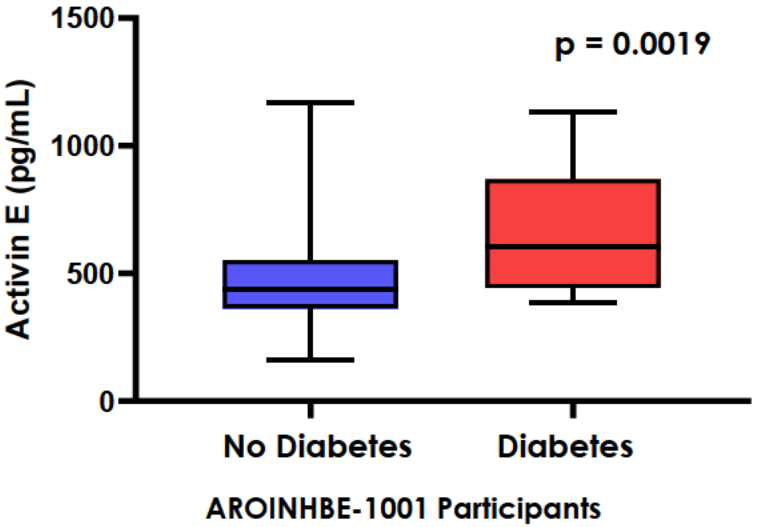
Elevated Hepatic *INHBE* Expression in Human Biopsy Samples[1]



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

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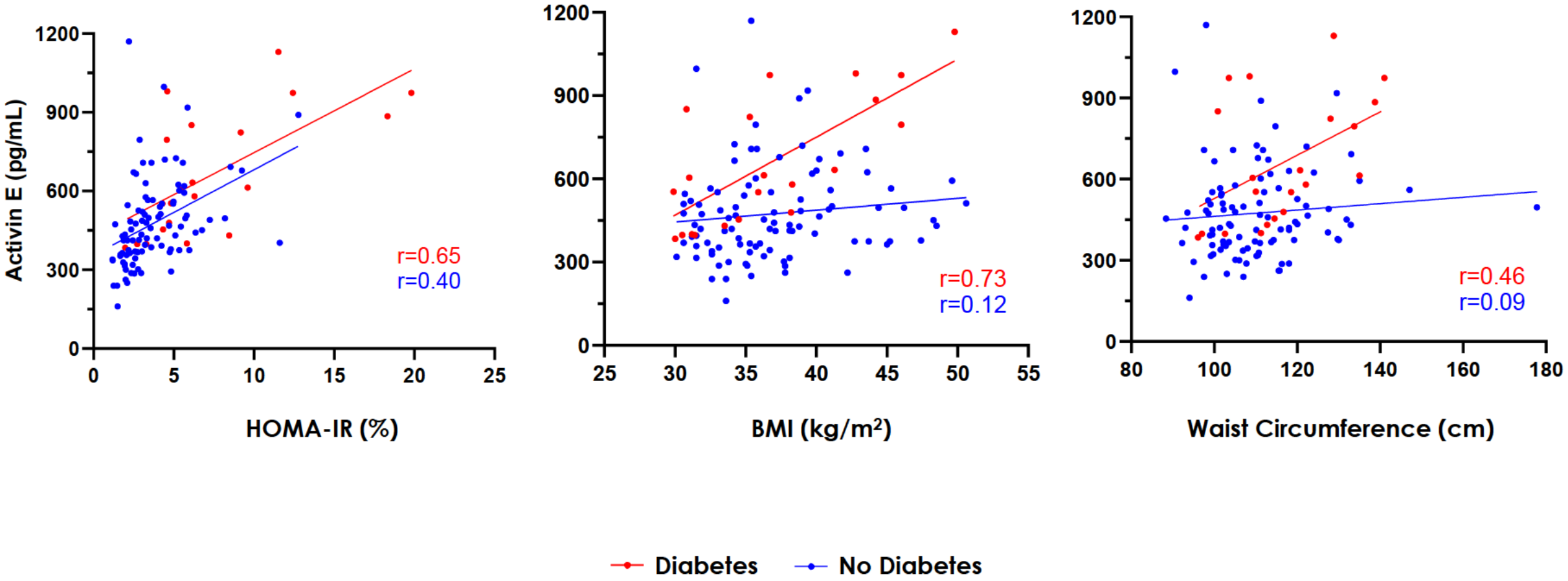
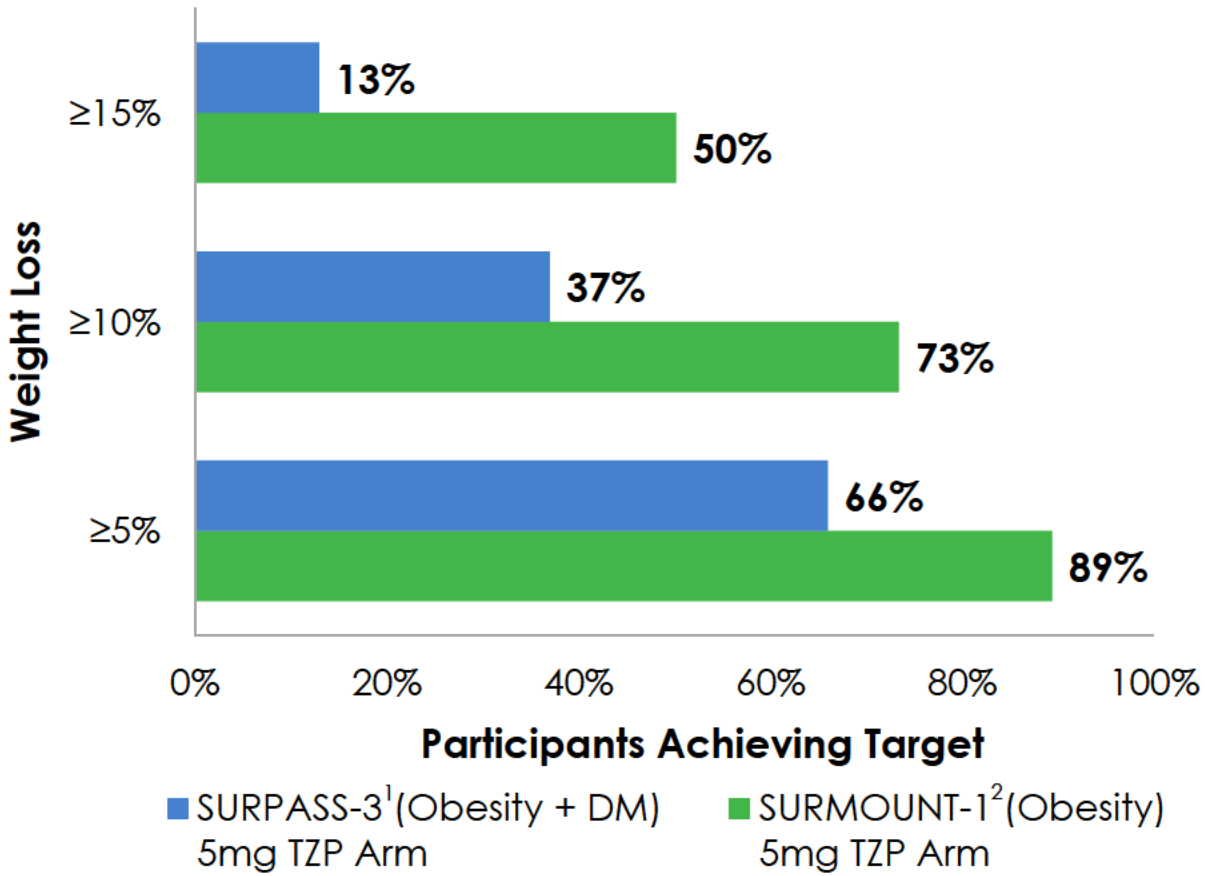
Baseline Activin E Levels Correlate with Insulin Resistance and Anthropometric Measures in Study Participants with Diabetes



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

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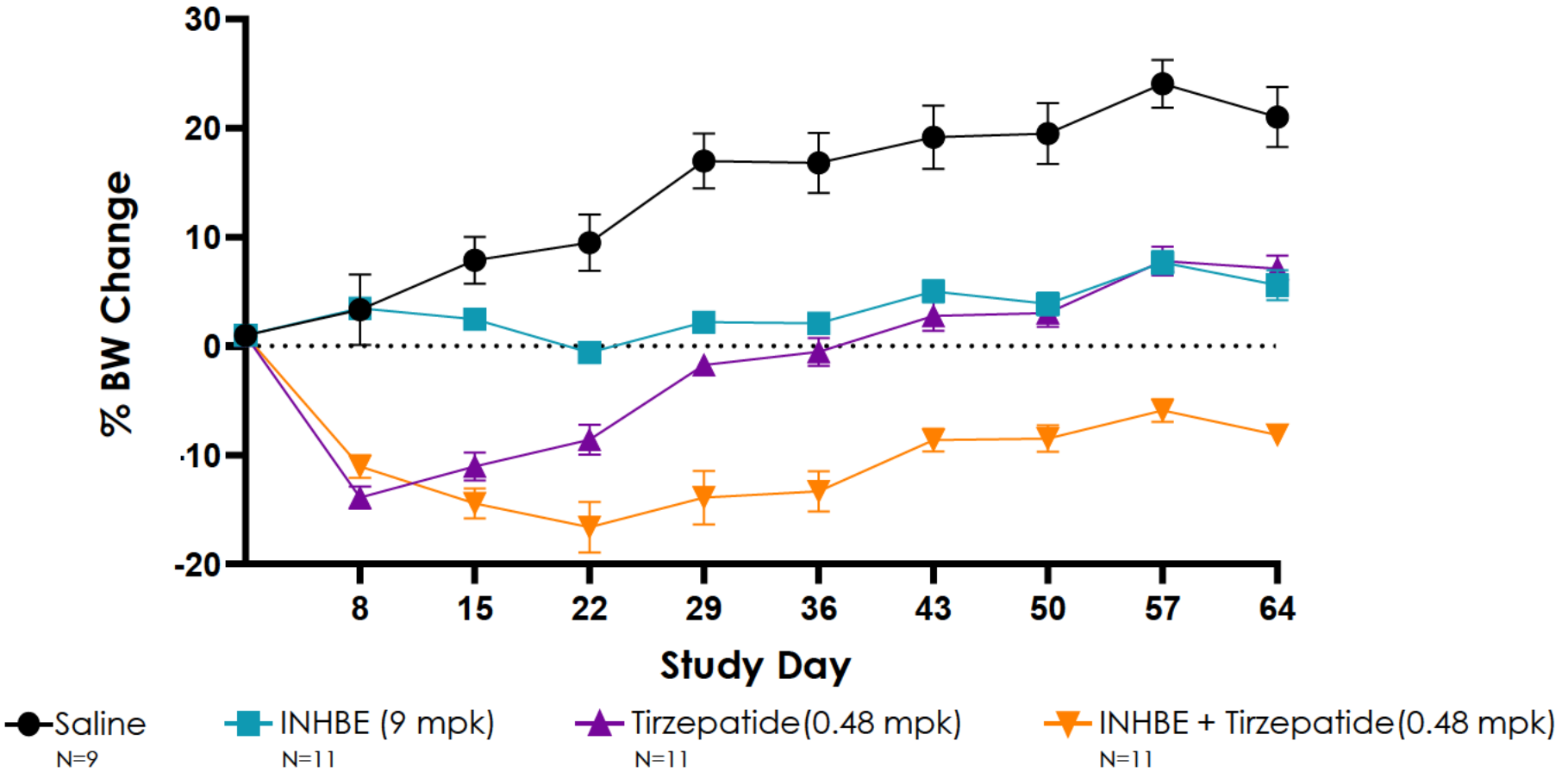
Preclinical Studies Indicate Enhanced Weight Loss with *INHBE* Silencing Combined with tirzepatide in Diabetic Mice

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



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

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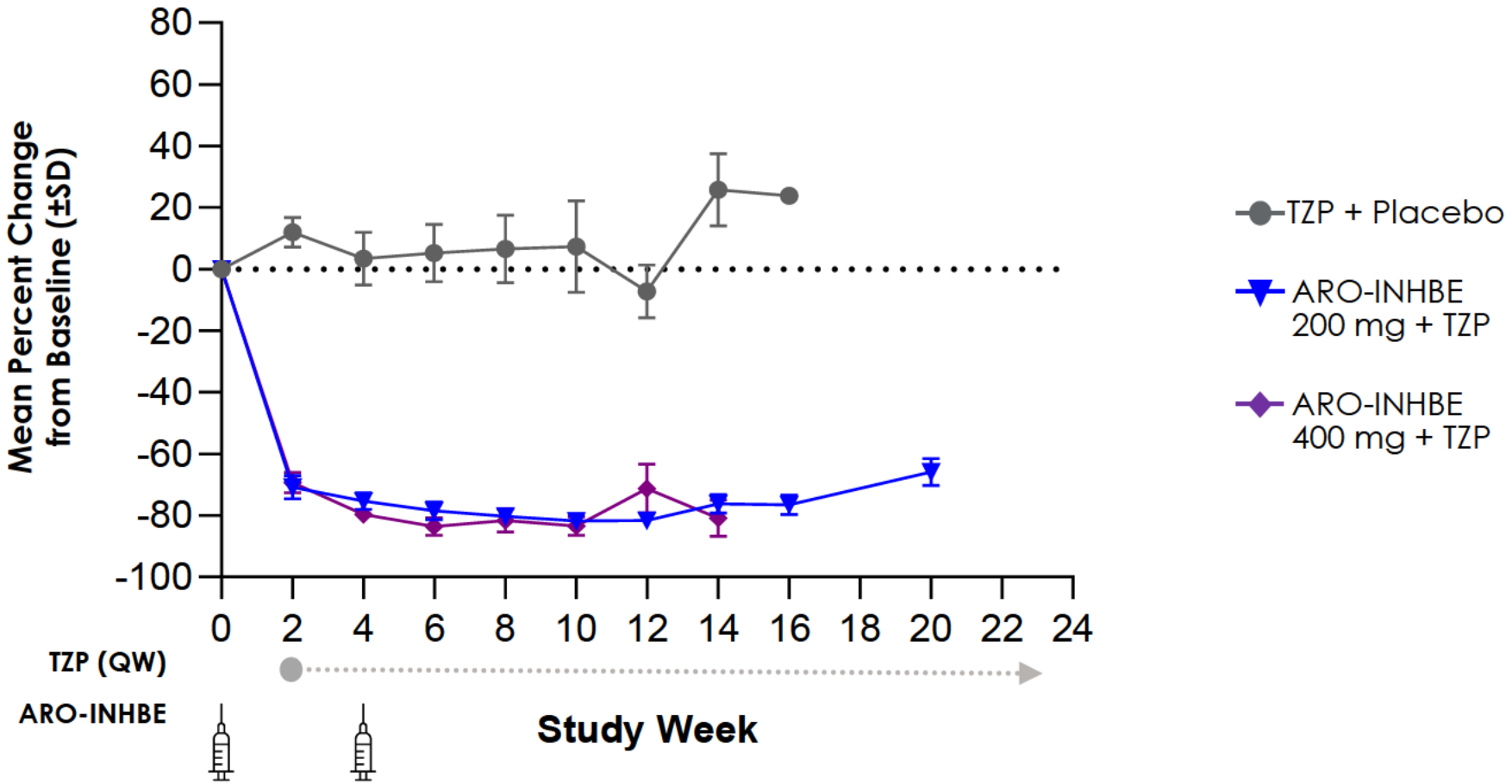
ARO-INHBE Demonstrated Substantial and Durable Decreases in Serum Activin E up to **84%** in T2DM Combination Cohorts. No Decrease in Activin E with Tirzepatide Alone.

Obesity with T2DM Combination Therapy Cohorts



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

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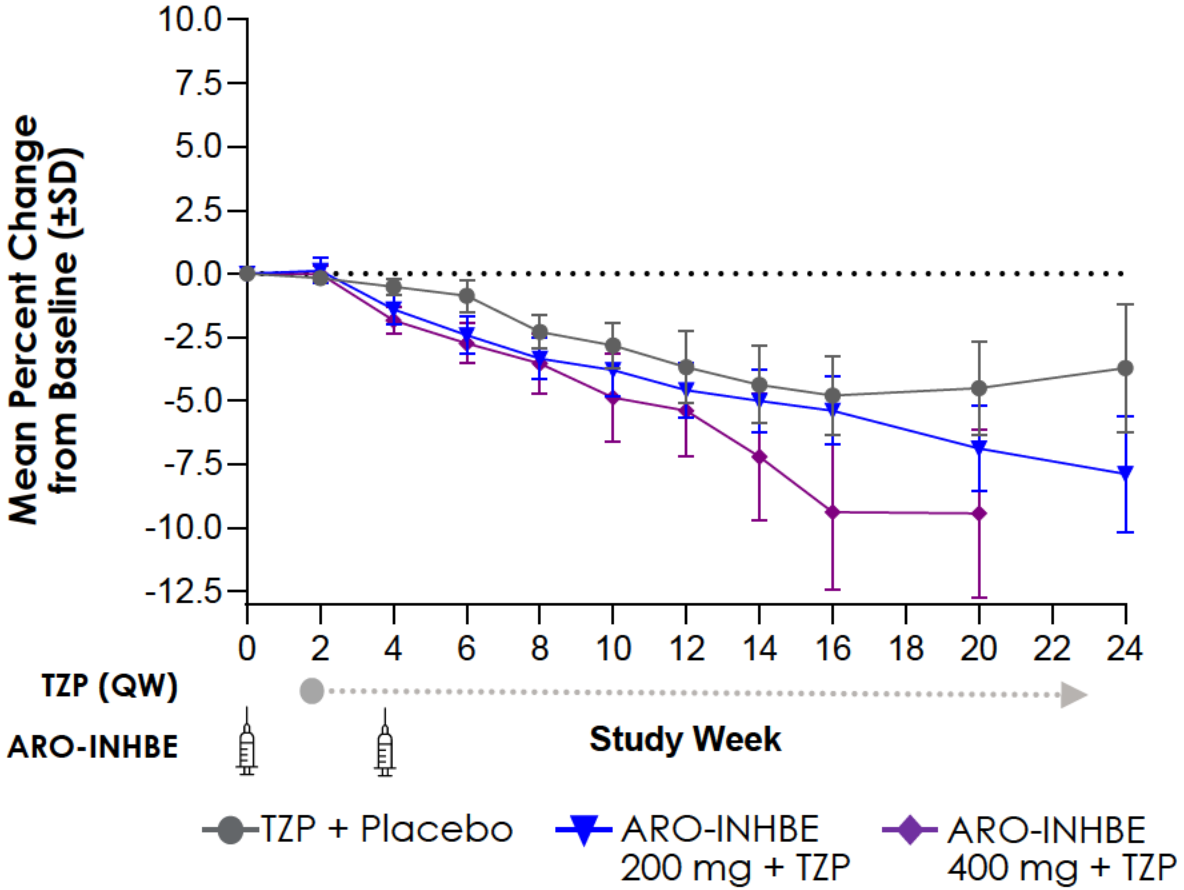
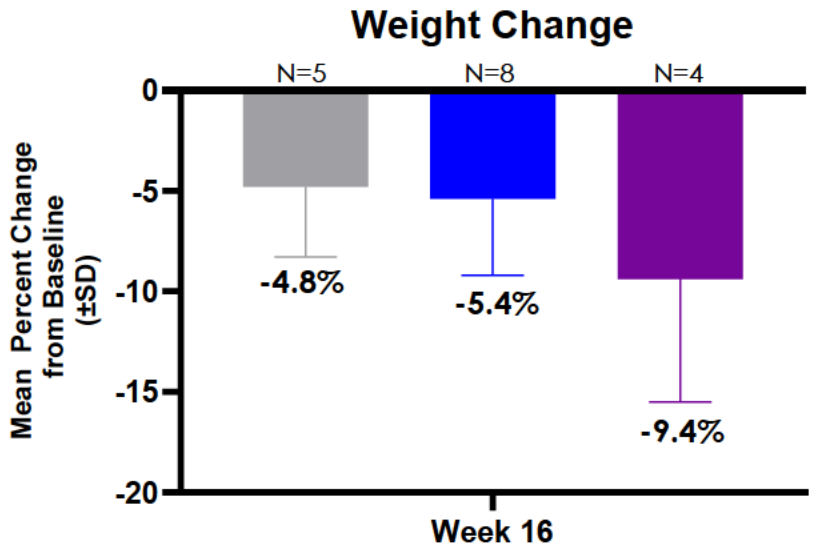
Combination Therapy with ARO-INHBE Enhanced Weight Loss Compared to Tirzepatide Alone in Obese T2DM Patients

Weight Loss – Obesity with T2DM Combination Therapy Cohorts





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

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

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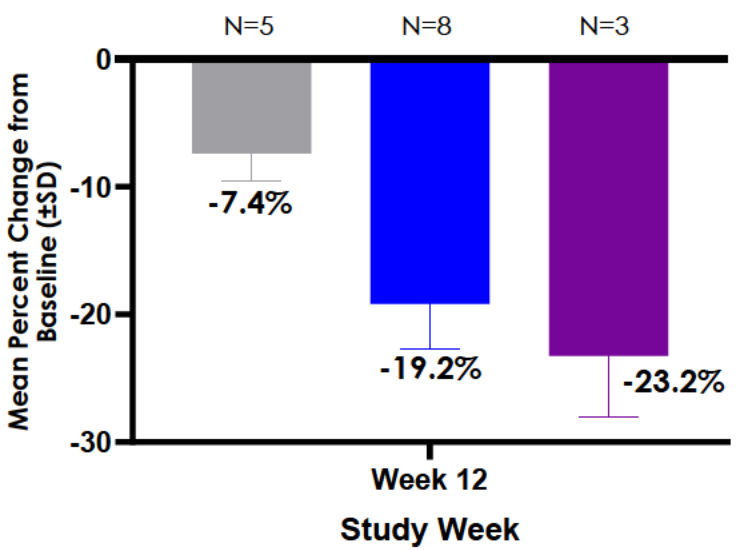
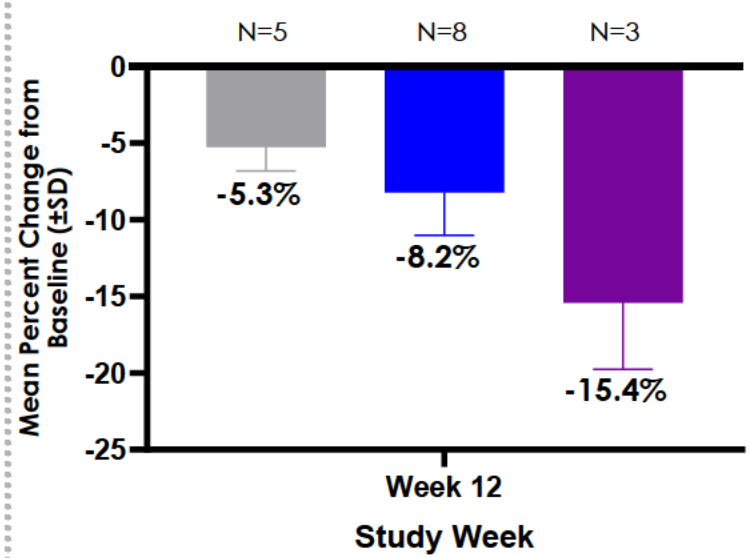
Combination Therapy Achieved Synergistic Fat Loss in Study Participants with Obesity and Type 2 Diabetes

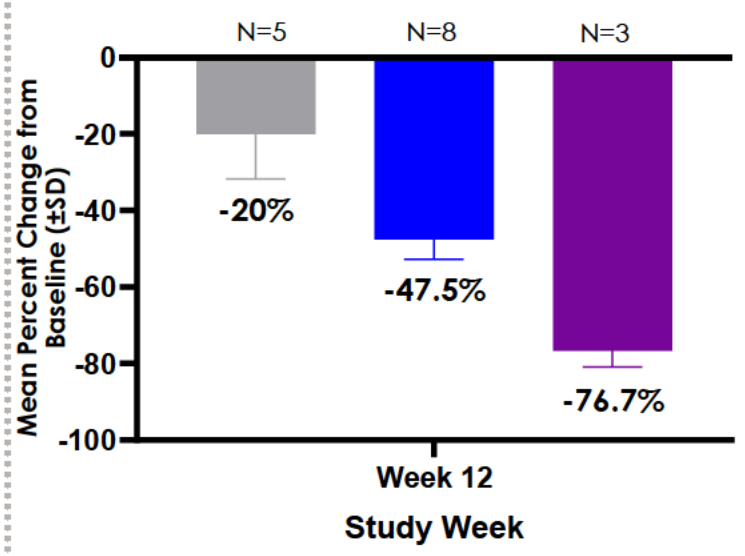
Visceral Adipose Tissue[1]



Total Adipose Tissue[2]



Liver Fat Content[3]



Enhanced Visceral Fat Loss

Enhanced Total Fat Loss

Substantially Reduced Liver Fat

TZP + Placebo

ARO-INHBE 200 mg + TZP

ARO-INHBE 400 mg + TZP

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

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

	12-week MRI / 16-week Weight Data		52-week Data	
	AROINHBE-1001		SURPASS-3 MRI Substudy[1]	
% Reduction	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

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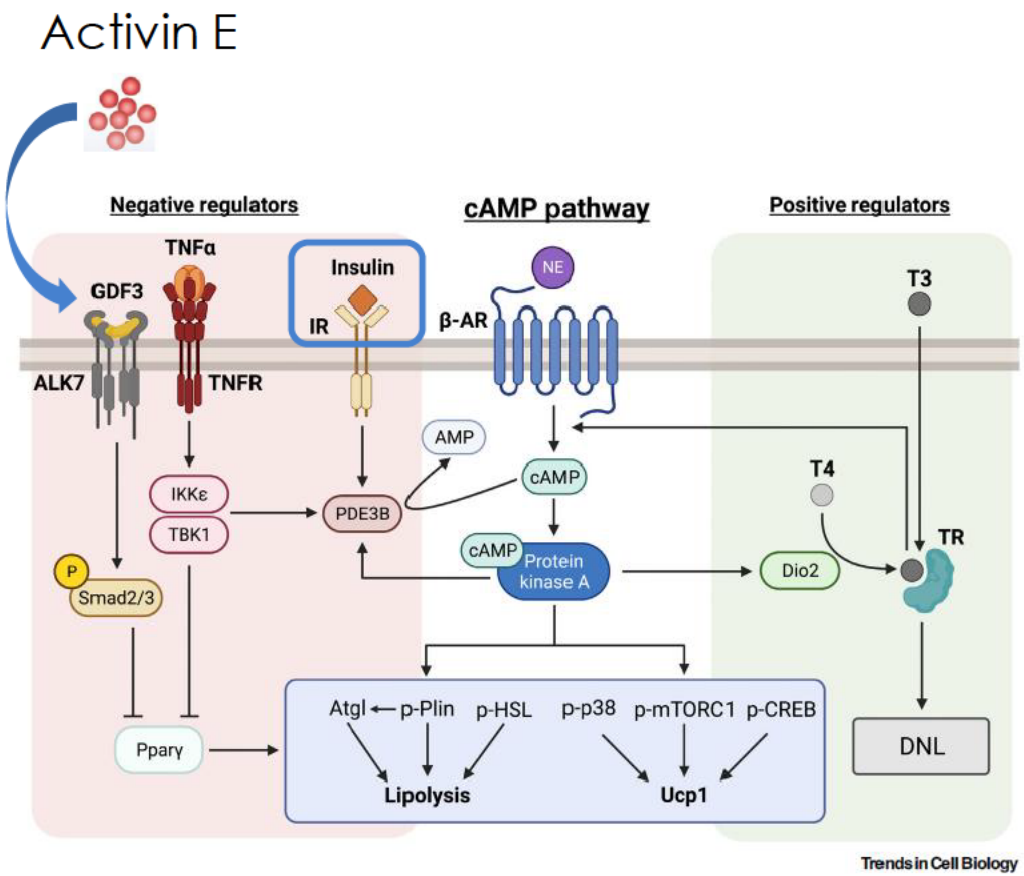
Targeting Activin E may be More Effective in Conditions of Insulin Resistance: A Plausible Hypothesis

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

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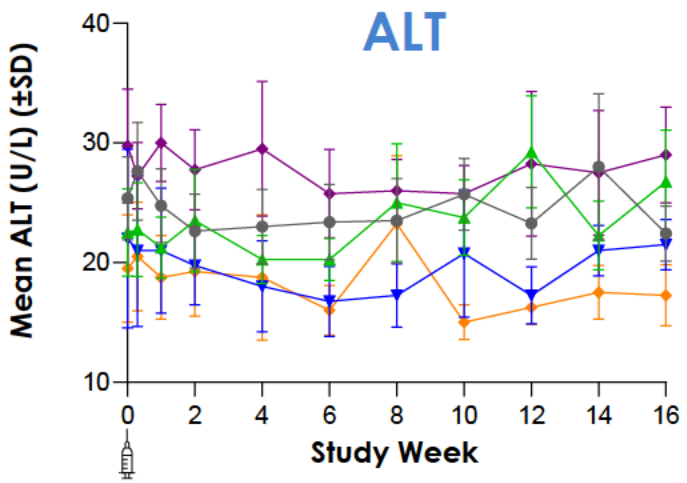
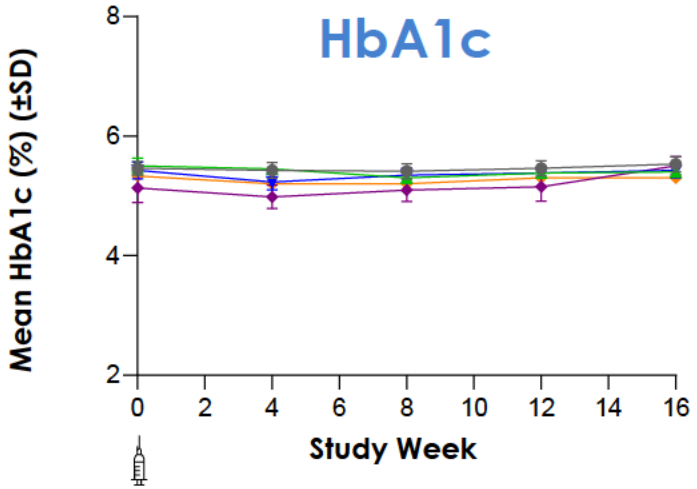
ARO-INHBE Demonstrates a Favorable Safety Profile

- 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.

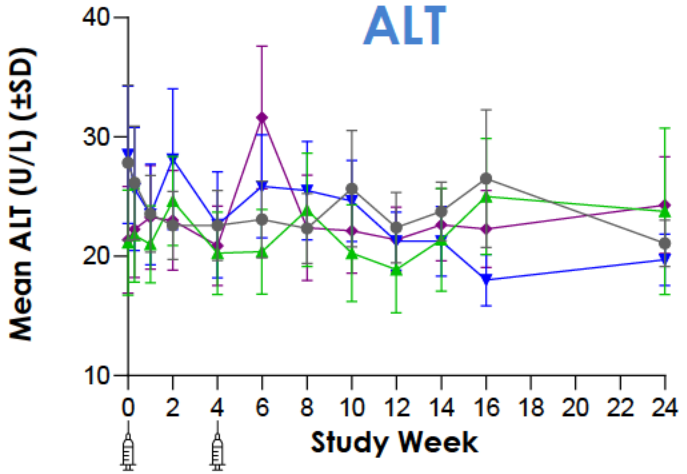
Stable Liver and Glycemic Parameters in Monotherapy Groups with No Adverse Changes in HbA1c or ALT Over Time

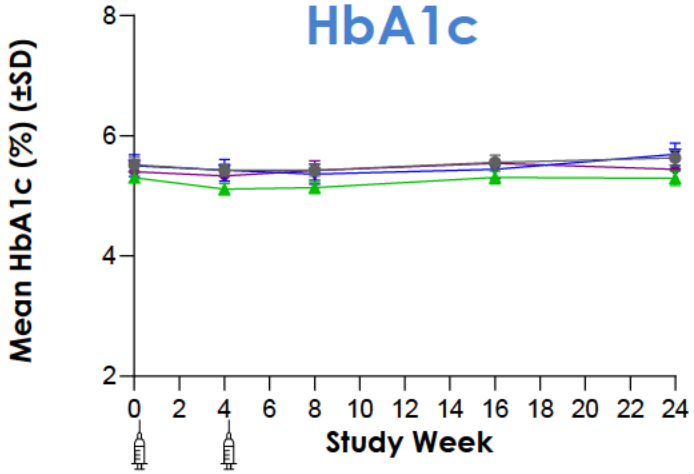
Single Dose Cohorts





Multiple Dose Cohorts





- Placebo
- ARO-INHBE 50 mg
- ARO-INHBE 100 mg
- ARO-INHBE 200 mg
- ARO-INHBE 400 mg

ALT = Alanine Aminotransferase; HbA1c = Hemoglobin A1c

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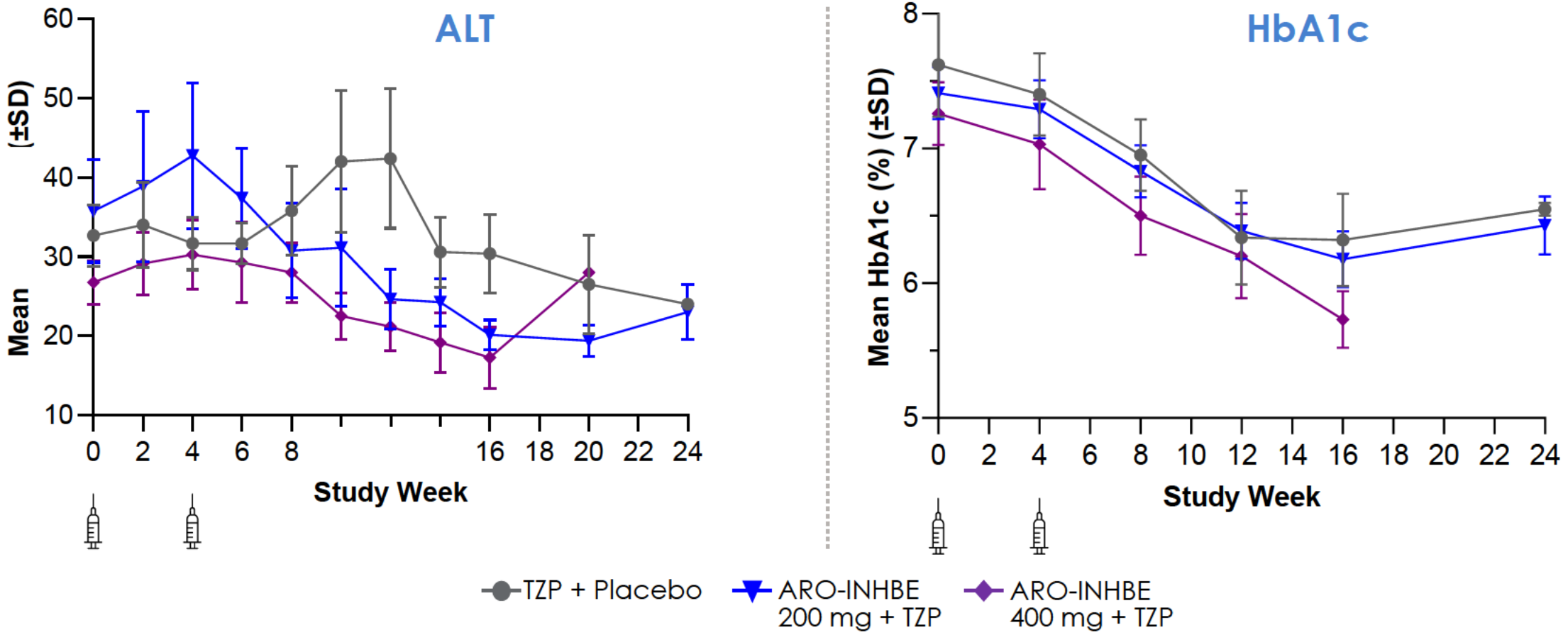
Stable Liver Chemistries and Improving Glycemic Parameters in Combination Therapy Groups

Obesity with T2DM Combination Therapy Cohorts



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

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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

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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

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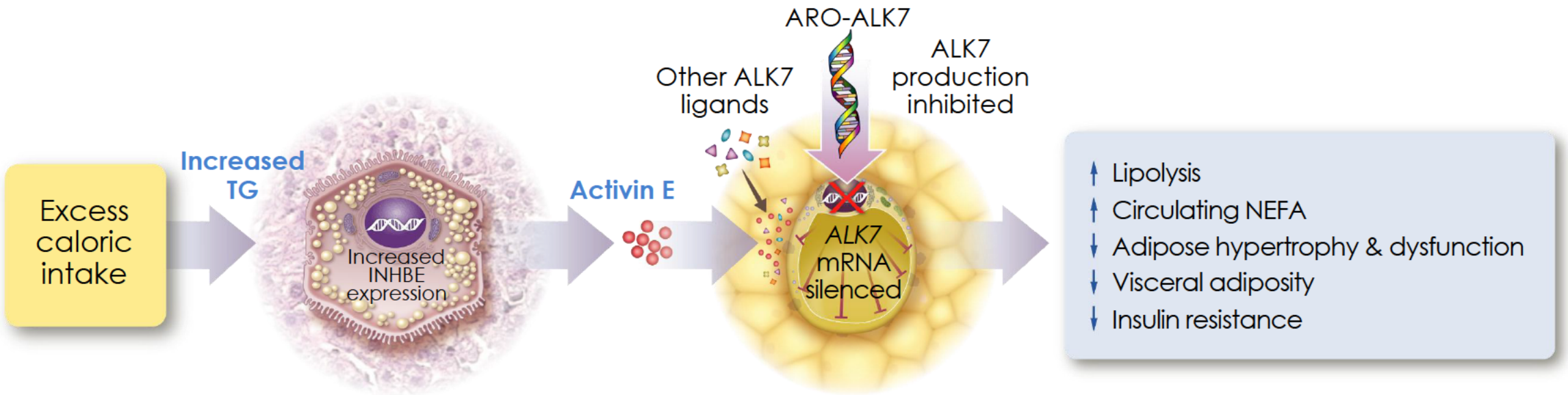
Activin Receptor-like Kinase 7 (ALK7, *ACVR1C*) is a Genetically Validated Adipose Target



- 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 WHRadjBMI and with type 2 diabetes

Variant	Minor allele frequency (%)	WHRadjBMI β (95% CI)	WHRadjBMI *P* value	Type 2 diabetes OR (95% CI)	Type 2 diabetes *P* value
Asn150His	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^{-9}	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 WHRadjBMI 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

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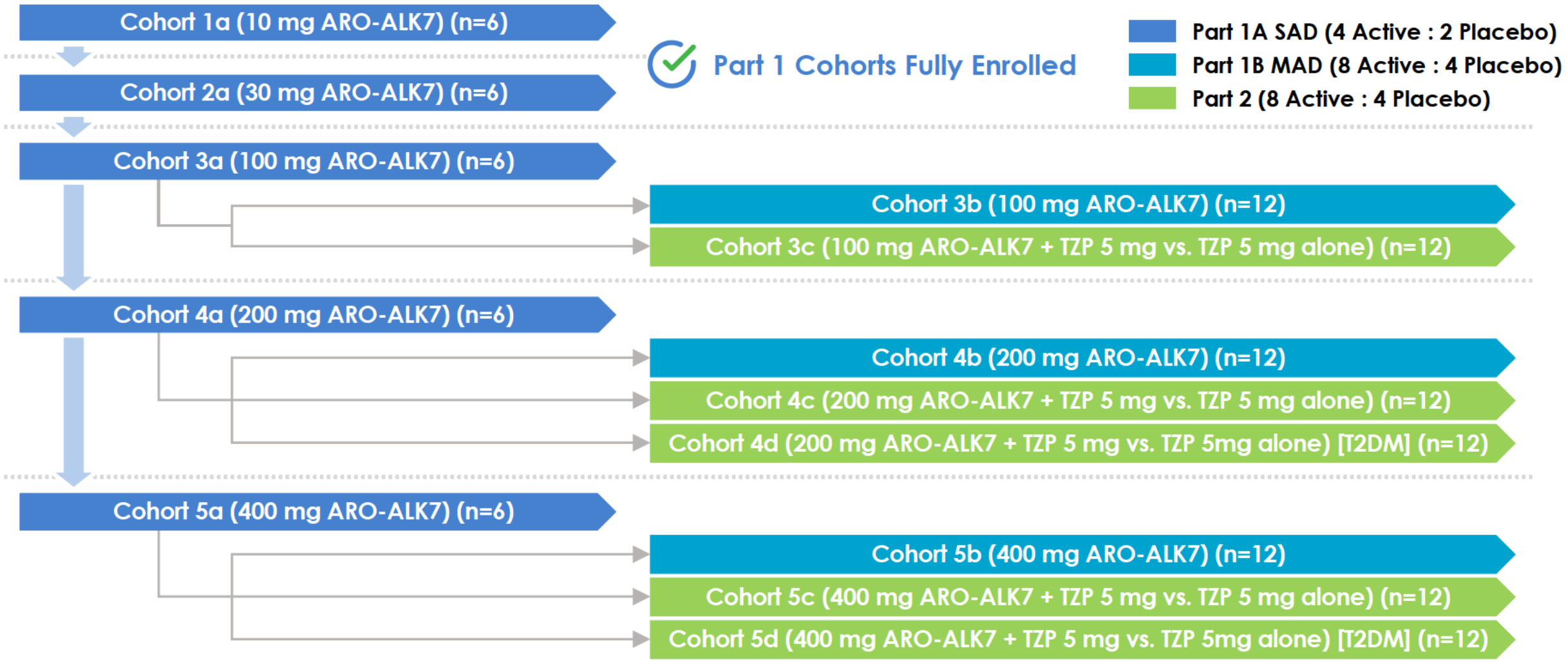
AROALK7-1001: Phase 1/2a Study of **ARO-ALK7** in Volunteers with Obesity, with and without Type 2 Diabetes Mellitus



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

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Key Endpoints

1° Safety

2° Pharmacokinetics

Exploratory

- **Adipose Expression of ALK7**
- Weight change (kg/%)
- Waist circumference
- Body adiposity, adipose distribution, fat mass vs lean mass (MRI)
- Liver fat content (MRI-PDFF)
- Fasting lipids and fat metabolism parameters
- Glycemic control parameters

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

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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

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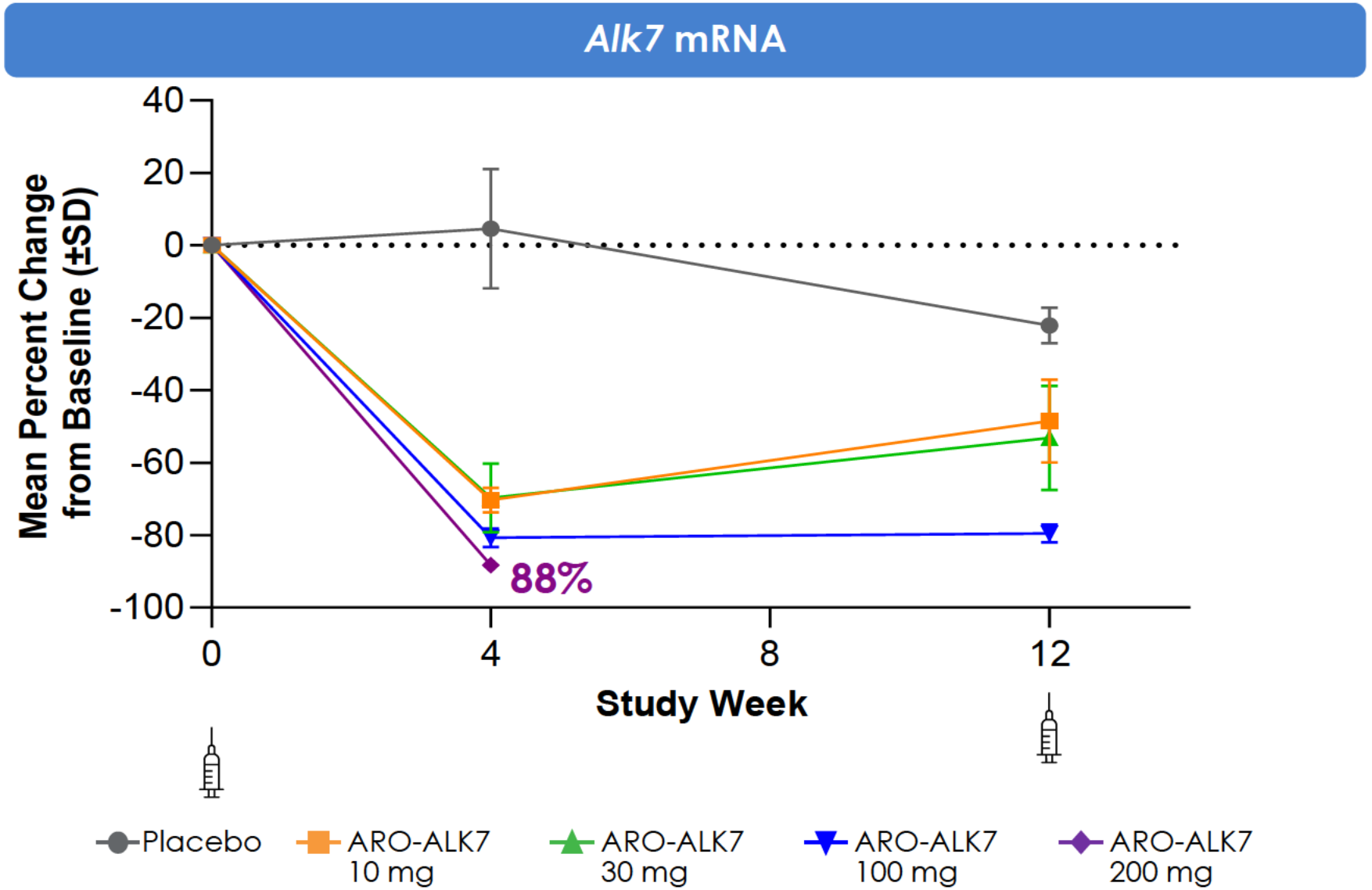
ARO-ALK7 Demonstrated Dose Dependent Mean Decreases in *Alk7* mRNA up to **88%**, Confirming TRiM Platform Ability to Silence Adipocyte Gene Expression



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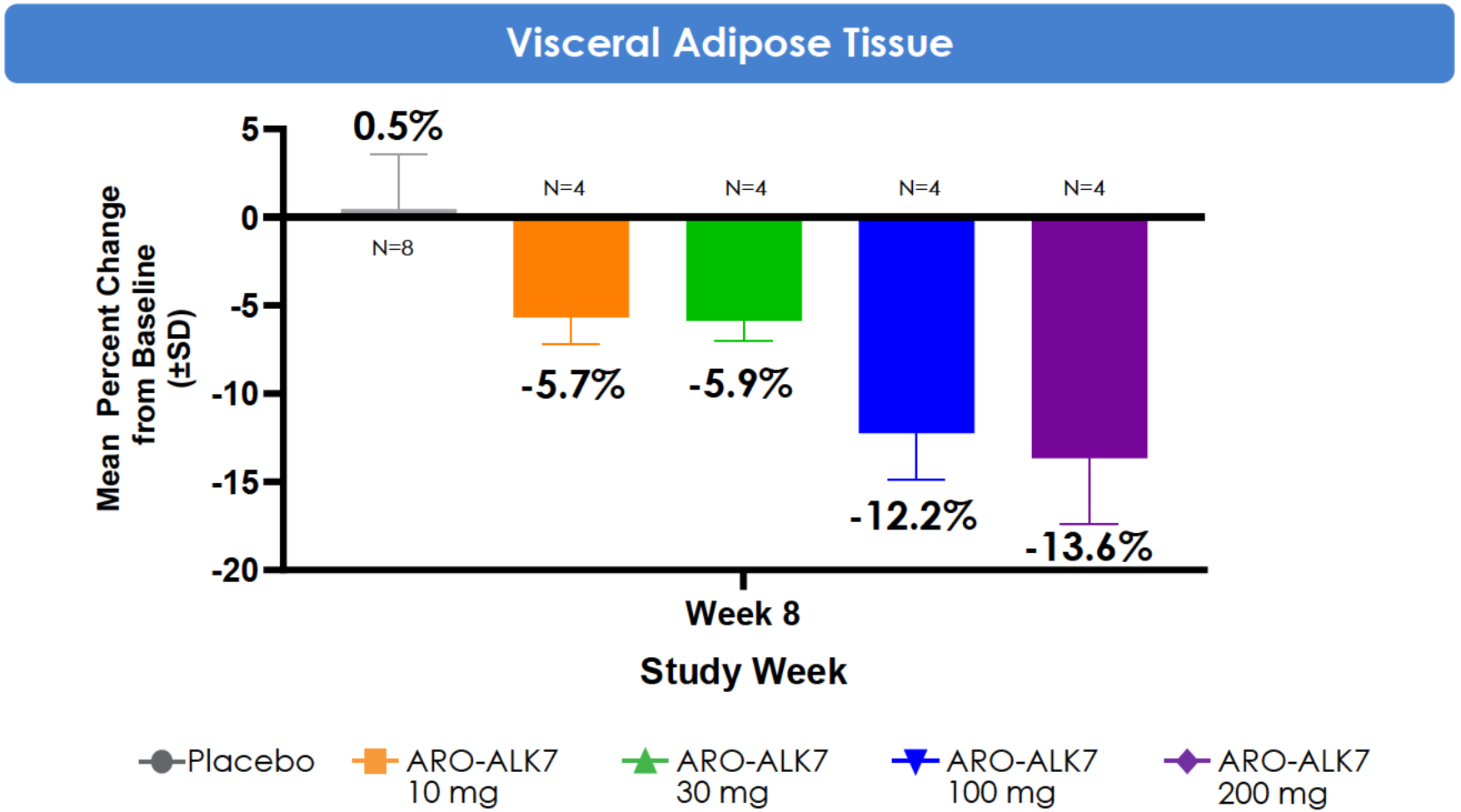
Rapid Dose-dependent Reductions in Visceral Fat of Up to **14.1%** (Placebo-adjusted) After a Single Dose of ARO-ALK7



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.**

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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

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

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ARO-INHBE and ARO-ALK7 Interim Clinical Data Update
January 2026

Key Takeaways

Chris Anzalone, Ph.D.
President and CEO

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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 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

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What We Already Achieved in Phase 1/2a

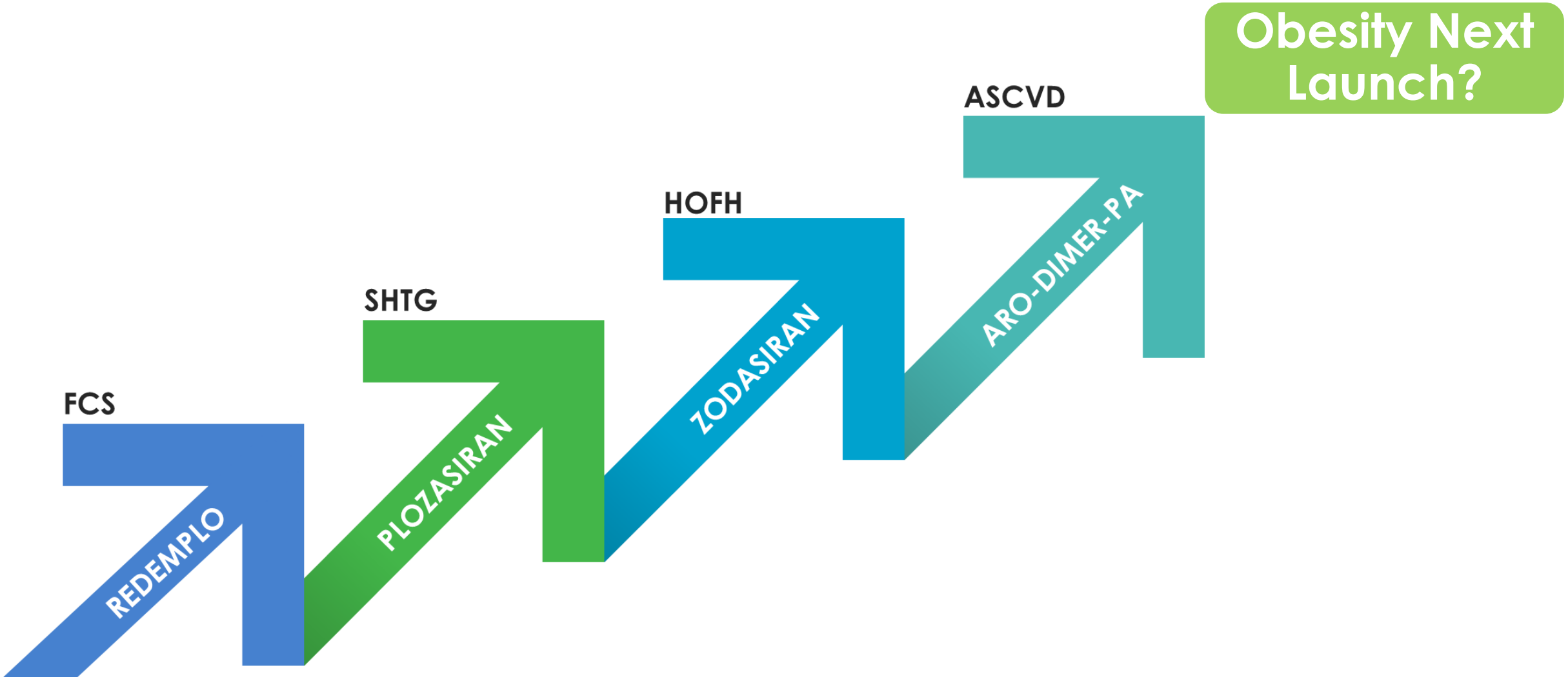
- **Established Safety and Tolerability** of single-dose, multi-dose, and combination regimens with tirzepatide
- Demonstrated **deep and durable knockdown** of Activin E and ALK7
- Identified signals of **Activin E/ALK7 pathway translation in humans**
- Measured **favorable changes in body composition**
- 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 (tirzepitide 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



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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**

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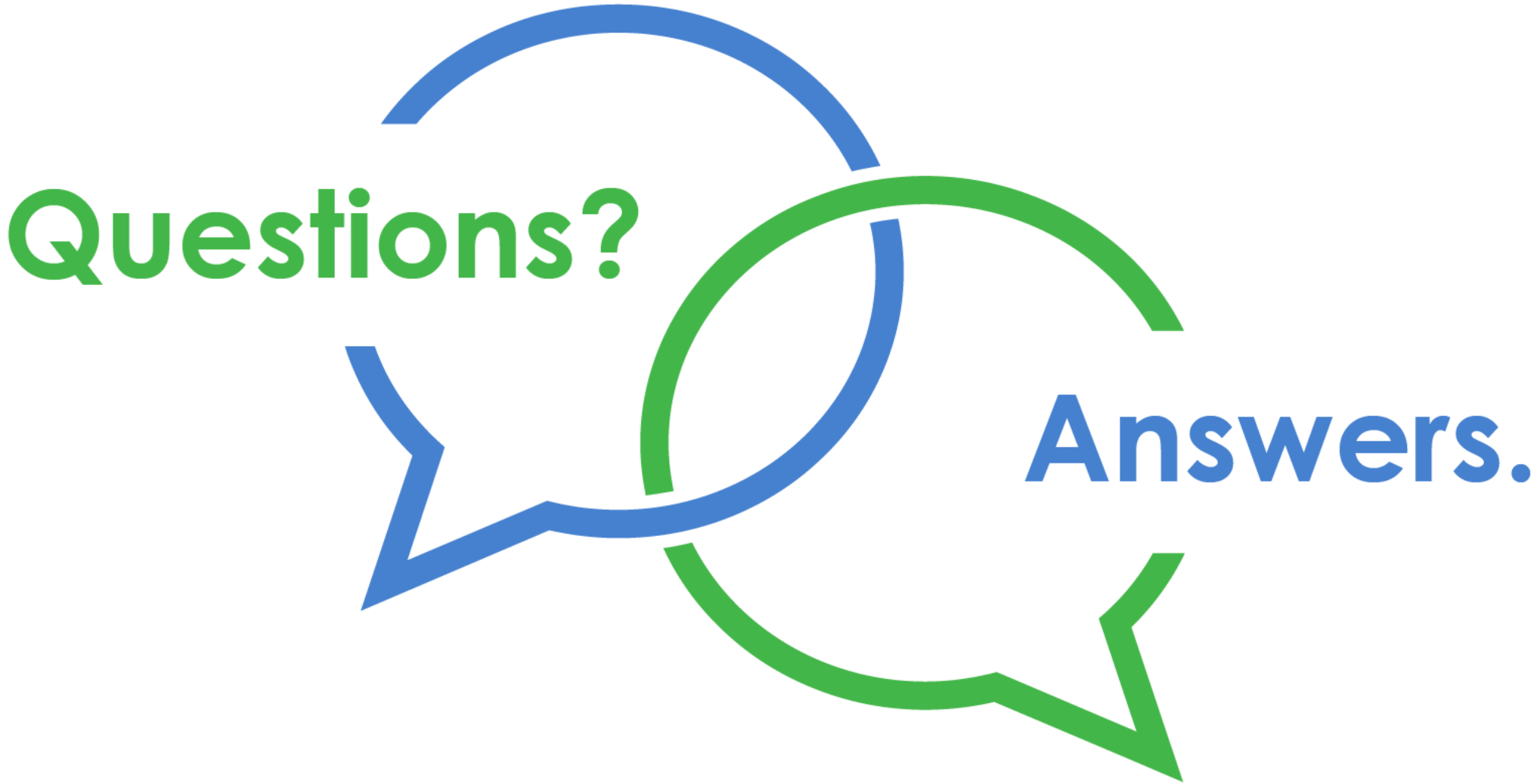

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