2024 Summer Series of R&D Webinars
Part IV – Obesity Programs

August 14, 2024

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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.

Obesity Programs Webinar – August 14, 2024

Welcome and Introductions

Vince Anzalone, CFA
Vice President, Finance and IR

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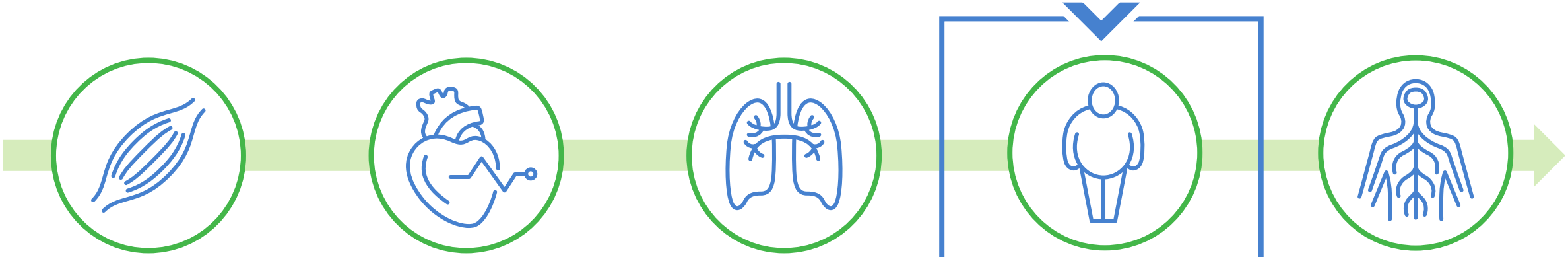
2024 Summer Series of R&D Webinars



Muscle

ARO-DM1 and ARO-DUX4

May 23, 2024

Cardiometabolic

Plozasiran and Zodasiran

June 25, 2024

Pulmonary

ARO-RAGE, ARO-MUC5AC, ARO-MMP7

July 16, 2024

Obesity/ Metabolic

ARO-INHBE and New Adipose Target

August 14, 2024

Central Nervous System

Platform and Pipeline Updates

Sept. 25, 2024

2024 Summer Series Goals

- Provide focused time to cover underappreciated parts of our pipeline
- Detail advances in the TRiM™ platform
- Hear directly from the Arrowhead team that worked on the programs
- Get external physician perspective on each disease area

Obesity Webinar Agenda

Time	Topic	Presenter
11:00–11:05	Introductions and Agenda	Vince Anzalone, CFA
11:05–11:20	Obesity overview and unmet need	Carel Le Roux M.D., Ph.D.
11:20–11:35	ARO-INHBE Preclinical data	Erik Bush Ph.D.
11:35–11:45	TRiM™ Adipose Delivery Platform	Tao Pei Ph.D.
11:45–12:00	ARO-ALK7 Preclinical Data	Erik Bush Ph.D.
12:00–12:05	Clinical trial designs and status	James Hamilton M.D., MBA
12:05–12:10	Key takeaways	Vince Anzalone, CFA
12:10–12:30	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 at St Bartholomew's Hospitals and the Hammersmith Hospitals. He 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 and he is now a Director of the Metabolic Medicine Group. He also holds the position of Professor of Metabolic Medicine at Ulster University and Extra-ordinary Professor of Chemical Pathology at University of Pretoria. He currently coordinates an Innovative Medicine Initiative project on obesity. He previously received the Irish Research Council Researcher of the Year award, a President of Ireland Young Researcher Award, the Irish Research Council Laureate Award, a Clinician Scientist Award from the National Institute Health Research in the UK, and a Wellcome Trust Clinical Research Fellowship for his work on how the gut talks to the brain.

Who We Are

Arrowhead is a **RNAi therapeutics platform company** with a **broad pipeline** of **wholly owned and partnered** product candidates

- **14 clinical stage programs** (10 wholly-owned; 4 partnered)
- Mix of **early, mid, and late-stage** candidates targeting **rare and high-prevalence diseases**
- Growing pipeline with **2–3 new clinical programs planned per year**

- **Targeted RNAi Molecule (TRiM™)** platform achieves **deep and durable gene silencing**
- **Fulfilling the promise** of bringing RNAi therapeutics to diseases **outside of the liver**

- **Non-dilutive capital** from Amgen, Takeda, GSK, and Royalty Pharma as milestones are achieved and royalties are earned
- Potential for **additional** product, platform, and structured finance **deals**

20 in '25: We Expect to Have 20 Individual Drugs in Clinical Trials or At Market in 2025

Arrowhead Clinical Pipeline

Obesity Programs Webinar – August 14, 2024

Obesity Disease Background and Unmet Need

Professor Carel le Roux
Chair of Metabolic Medicine, University College Dublin

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The future for obesity care

Carel le Roux

University College Dublin

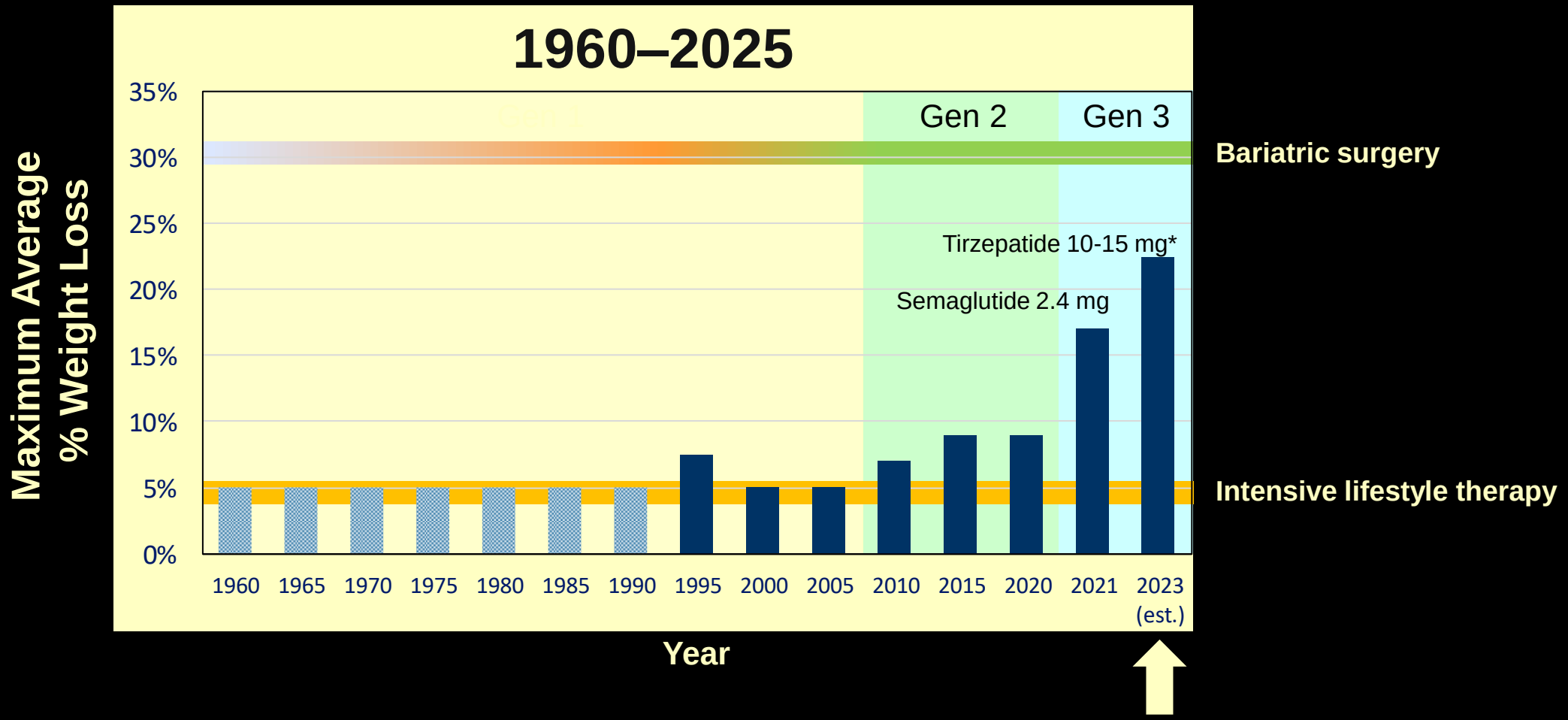
Ulster University

University of Pretoria

Conflicts of interest

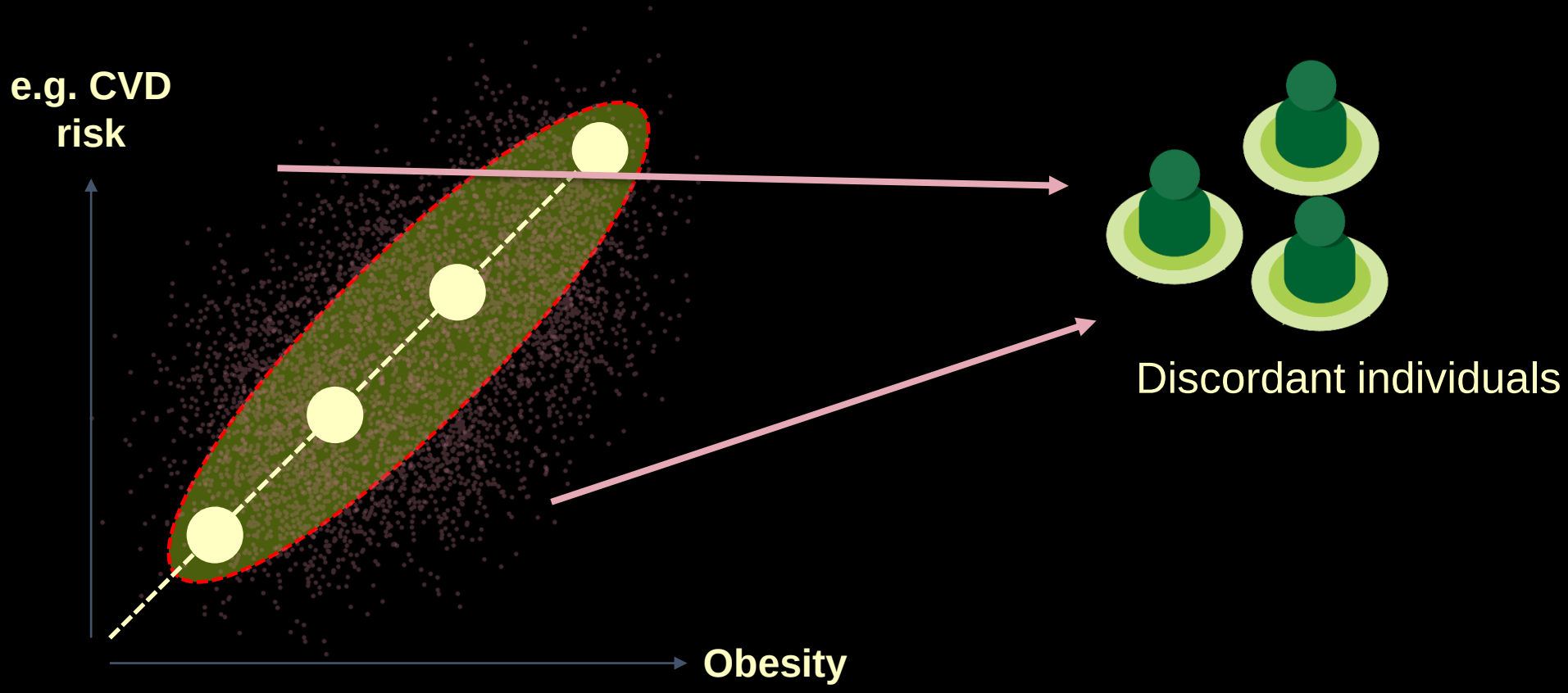
- Consilient Health
- Novo Nordisk
- Herbalife
- Johnson & Johnson
- Covidien
- Fractyl
- GI Dynamics
- Lilly
- Boehringer Ingelheim
- Keyron
- Arrowhead

The emergence of highly effective anti-obesity medications



Kaplan LM, 2023.

Obesity is likely more than one disease



le Roux et al., *Nature Medicine*, 2024, in press.

BC: Baseline Concordant profile

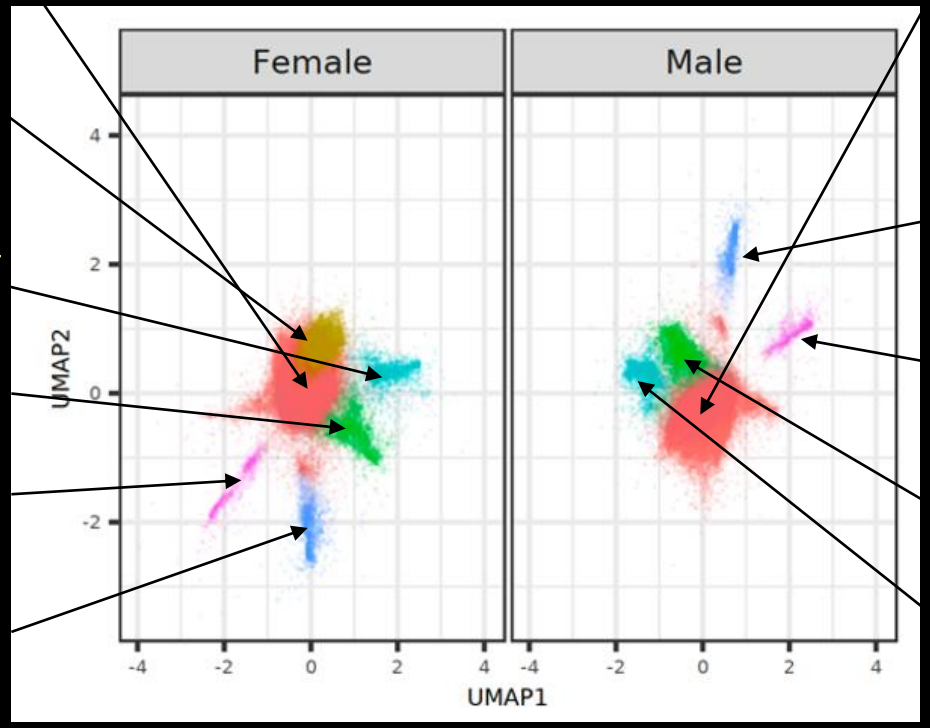
DHT: Discordant Hypertensive profile

DLT: Discordant Liver Transaminases profile

DAL: Discordant Adverse Lipid profile

DHG: Discordant Hyperglycaemic profile

DIS: Discordant Inflammatory State profile



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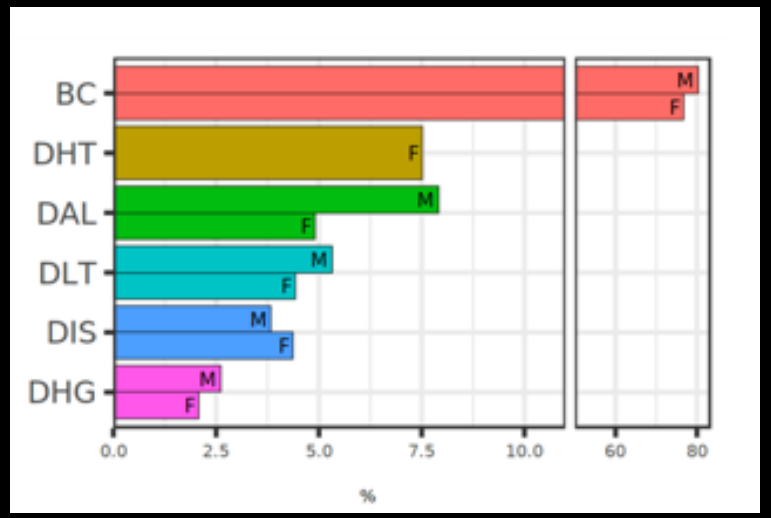
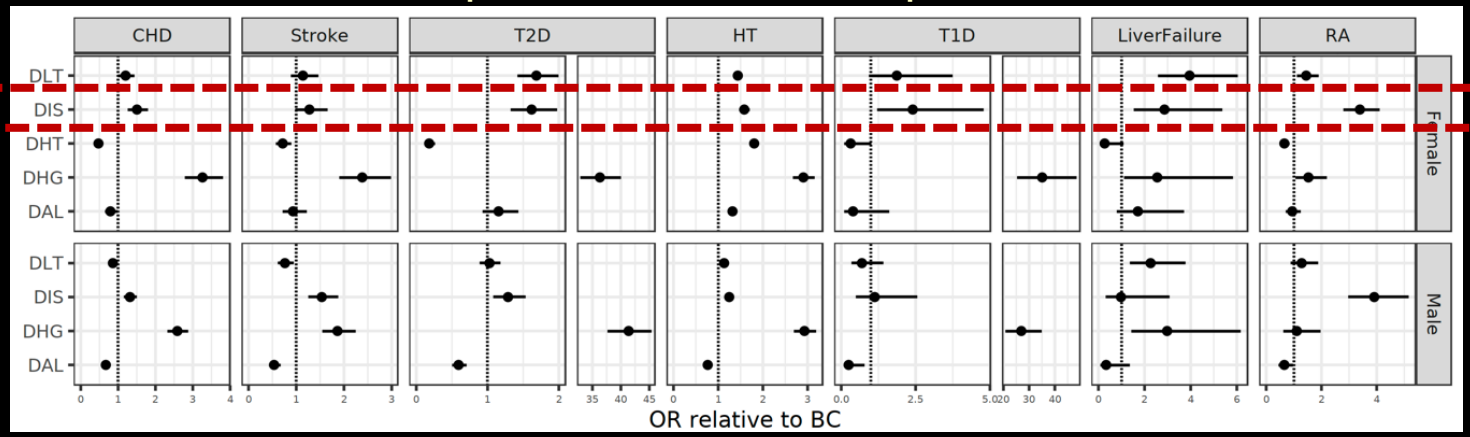


Discordant profiles and disease prevalence

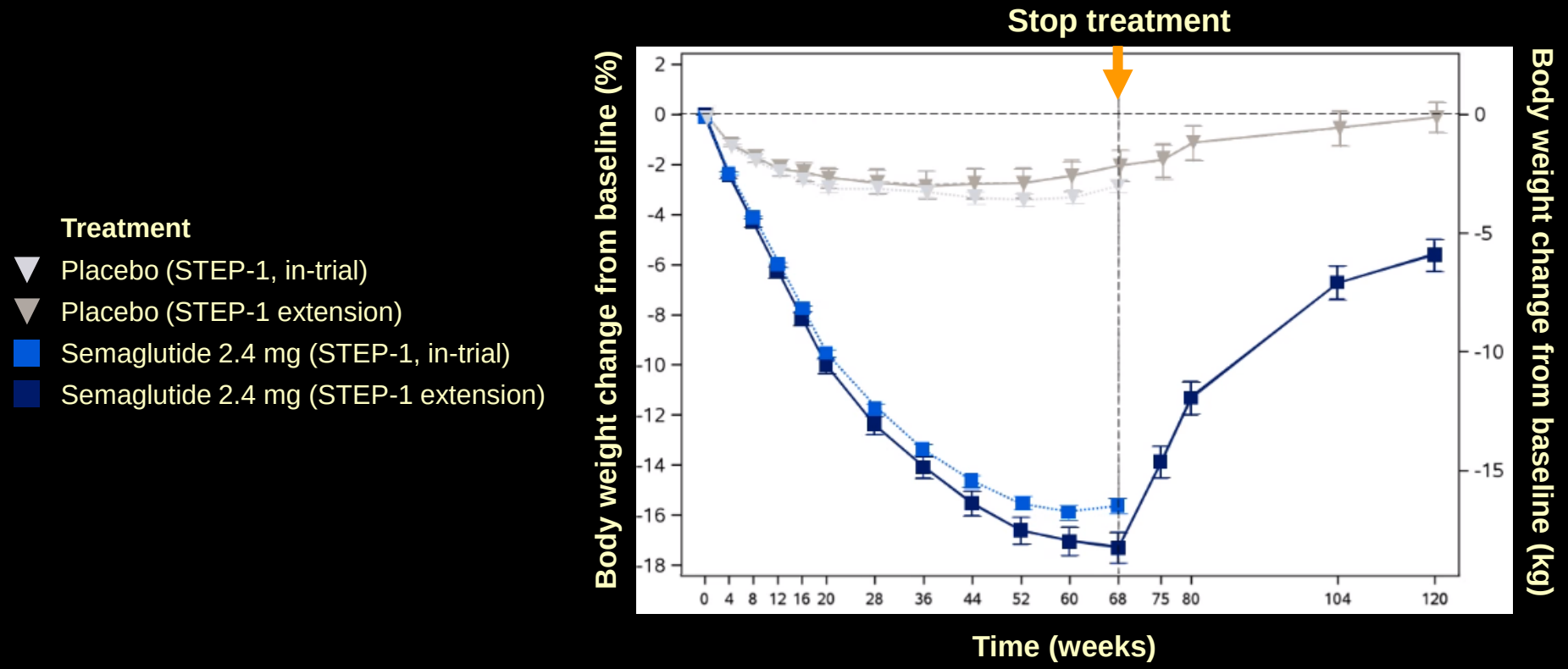


le Roux et al., *Nature Medicine*, 2024, in press.

Re-regulation of fat mass is dependent on the presence of the medication

STEP 1 Trial and Extension

Semaglutide 2.4 mg/wk vs. placebo in participants without diabetes

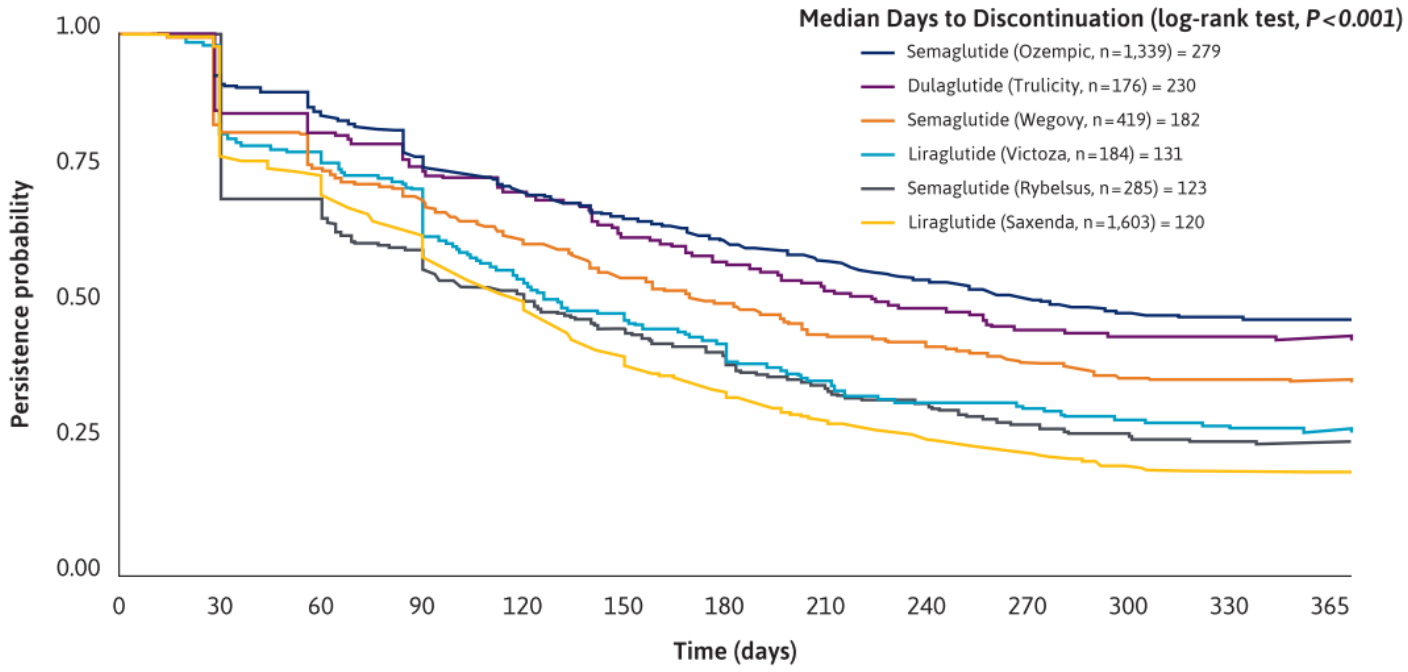


Long-term benefit of anti-obesity medications requires continued treatment

Wilding et al. *N Engl J Med*. 2021; Wilding et al. *Diabetes Obes Metab*. 2022.

1-year discontinuation rates for GLP-1 agonists remain high

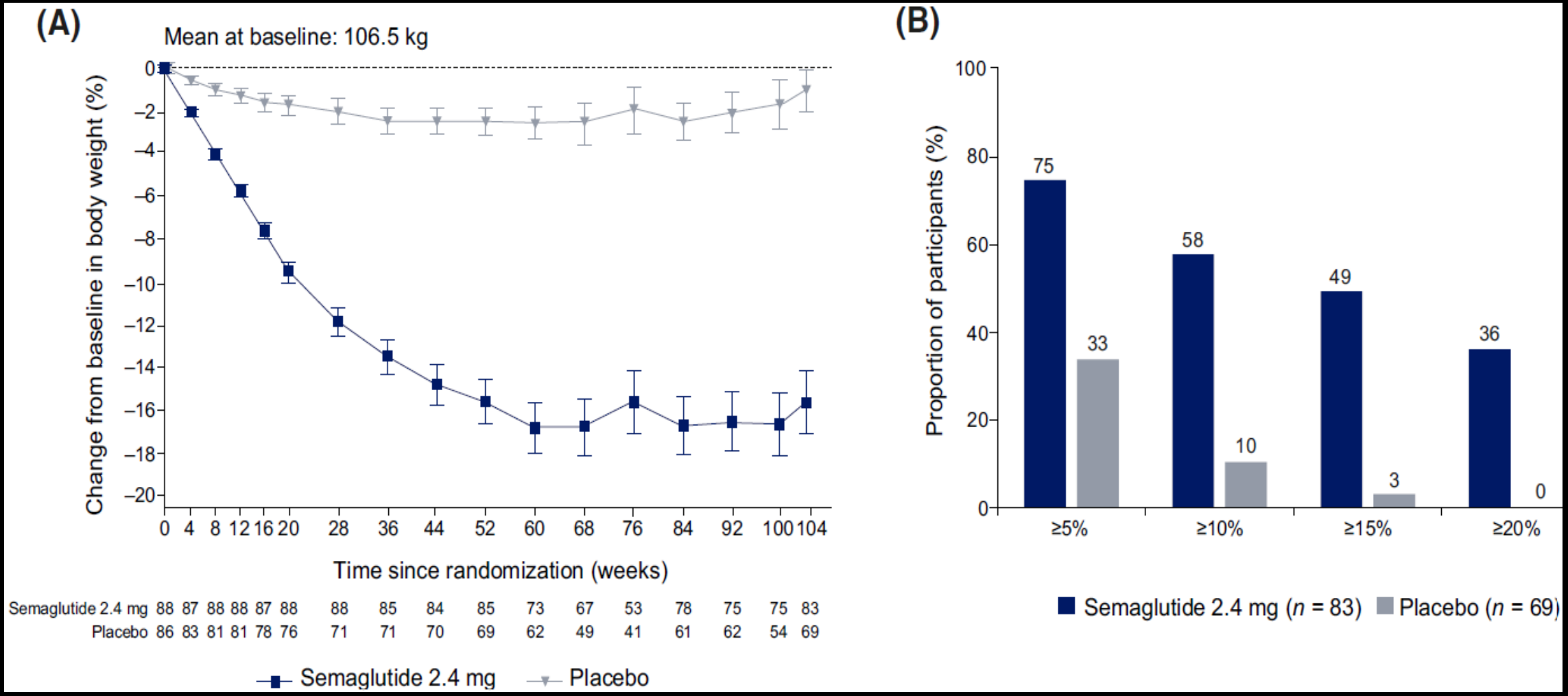
FIGURE 1 Glucagon-Like Peptide-1 Agonists: Kaplan-Meier 1 Year Therapy Persistence (n = 4,066)



Kaplan-Meier curve represents 4,066 obese commercially insured adults without diabetes initiating a GLP-1 product during calendar year 2021. All persistency and adherence measurements were conducted at the GLP-1 product level. Members were considered persistent if they did not have a 60-day gap in therapy and were censored at the end of the 365-day period.

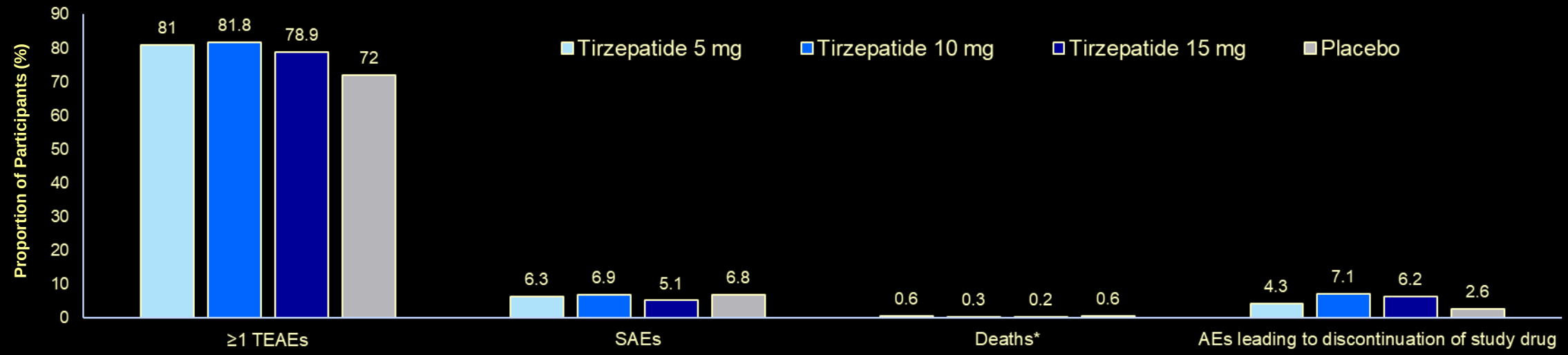
Gleason PP, et al. *J Manag Care Spec Pharm*. 2024; 30(8):860-867.

STEP 5 Semaglutide 2.4mg for 2 years



Wadden et al *Obesity* 2023.

Overview of adverse events

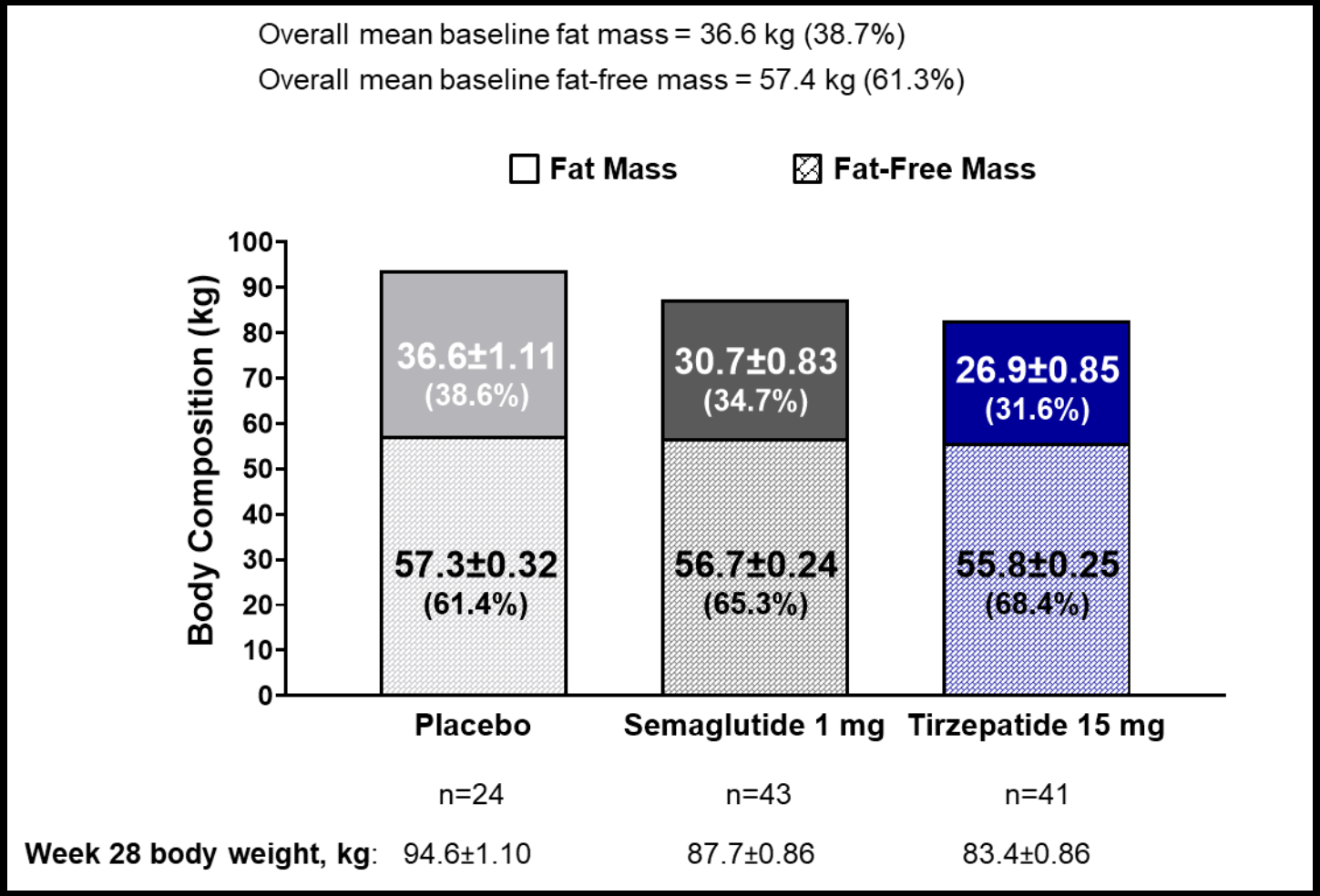


	Tirzepatide 5 mg (N=630)	Tirzepatide 10 mg (N=636)	Tirzepatide 15 mg (N=630)	Placebo (N=643)
Adverse events leading to discontinuation of study drug n (%)	27 (4.3)	45 (7.1)	39 (6.2)	17 (2.6)
Nausea n (%)	6 (1.0)	7 (1.1)	12 (1.9)	2 (0.3)
Diarrhea n (%)	2 (0.3)	5 (0.8)	3 (0.5)	0
Abdominal pain n (%)	0	2 (0.3)	3 (0.5)	0
Vomiting n (%)	0	4 (0.6)	0	0
Discontinuation of study drug due to gastrointestinal events (%)	1.9	4.4	4.1	0.5

AE = Adverse Event; SAE = Serious Adverse Event; TEAE = Treatment-emergent Adverse Event; TZP = Tirzepatide.
*All deaths were adjudicated by an external committee of physicians; n=4, 2, 1, 4 in tirzepatide 5 mg, 10 mg, 15 mg, and placebo groups, respectively. Three deaths in TZP arms were related to COVID-19 and also included as SAEs.

Jastreboff AM, et al. *N Engl J Med*. 2022;387(3):205-216.

Weight reduction at week 28 with tirzepatide is mainly driven by fat mass loss but also muscle mass loss



Data are LSM ± SE for fat or fat-free mass in body mass and for body weight at 28 weeks using ANOVA (baseline) and ANCOVA (week 28). Percent of fat or fat-free mass in body mass are in parentheses. Pharmacodynamic analysis set. ANOVA = analysis of variance; ANCOVA = analysis of covariance; LSM = least squares mean; SE = standard error.

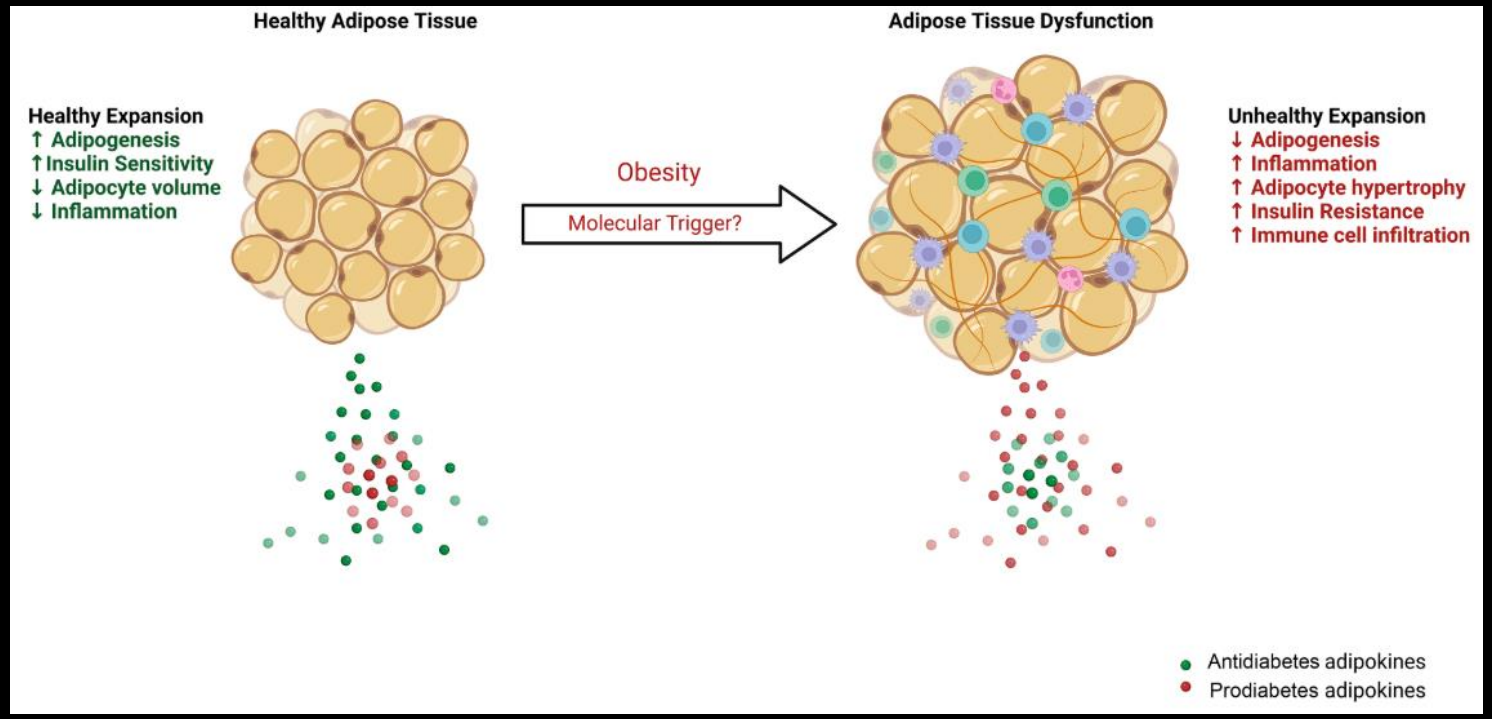
Adipose Dysfunction is Central to Metabolic Disease

Largest endocrine organ in the body

Produces/secretes numerous adipokines (messengers) which regulate numerous physiological functions

Adipose dysfunction has been associated with:

- Obesity
- Type 2 diabetes (T2D)
- Dyslipidemia
- Inflammatory disease
- Cardiovascular disease
- Cancer



Gilani A, et al. *Diabetes*. 2024; 73(2), 169-177.

Conclusions

- The future of obesity care will include
  - Chronic treatment aimed at health gain not weight loss
  - Recognising the biological basis for the disease
  - Needing more and different treatments for the subtypes of the disease

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ARO-INHBE Program – Preclinical Data

Erik Bush, PhD
Senior Vice President of Biology

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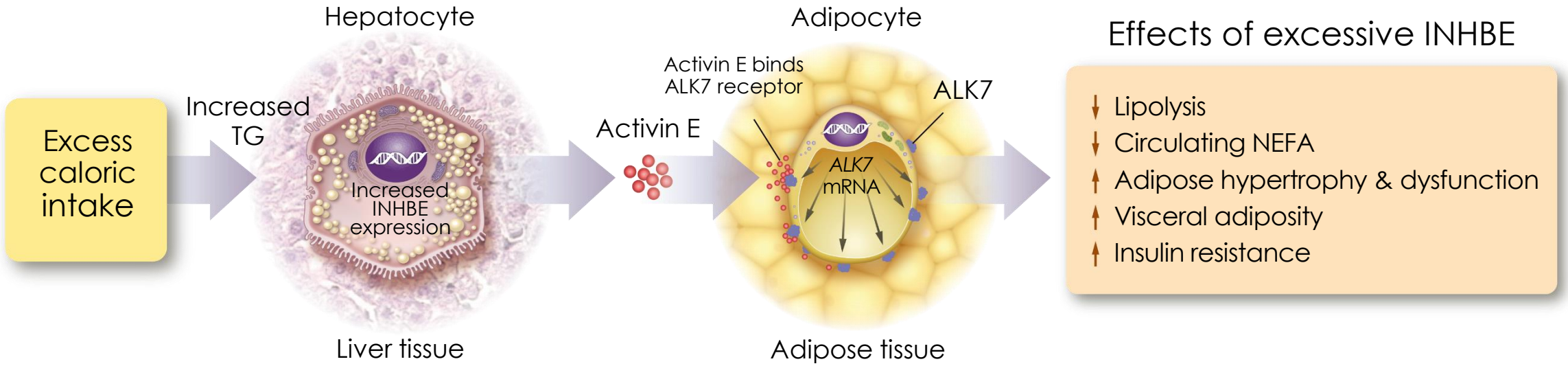
Hepatic Activin E encoded by *INHBE* gene regulates energy homeostasis in adipose tissue

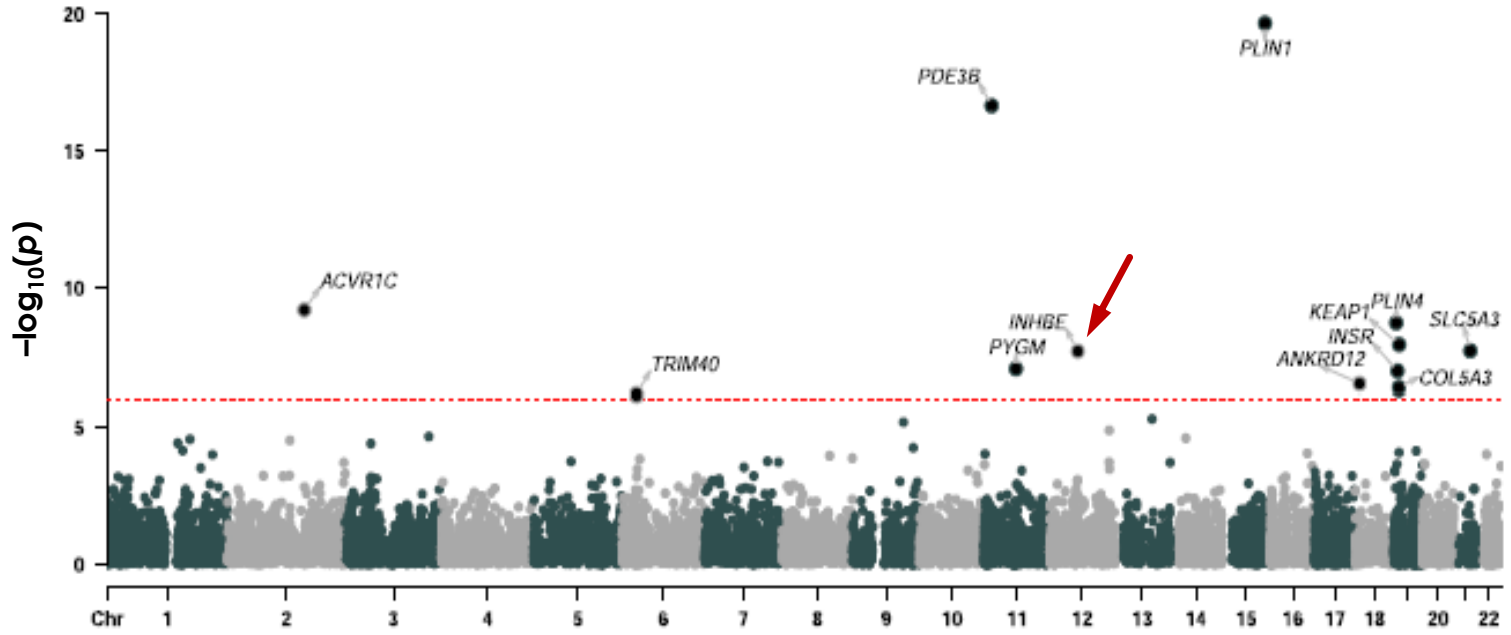


- Inhibin subunit beta E (*INHBE*) is primarily expressed in hepatocytes
- Activin E (dimeric *INHBE* protein) is potent hepatokine secreted by the liver
- Circulating Activin E promotes adipose storage of fats by suppressing lipolysis in adipose tissue

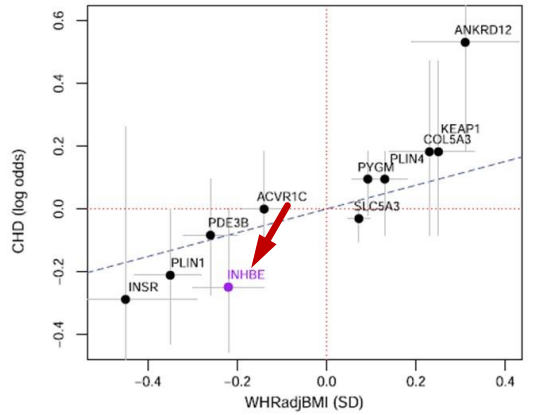
pLOF Variants of INHBE are Associated with Reduced Abdominal Fat and Lower Risk of Coronary Heart Disease and type 2 Diabetes

Human Genome-wide Association Study

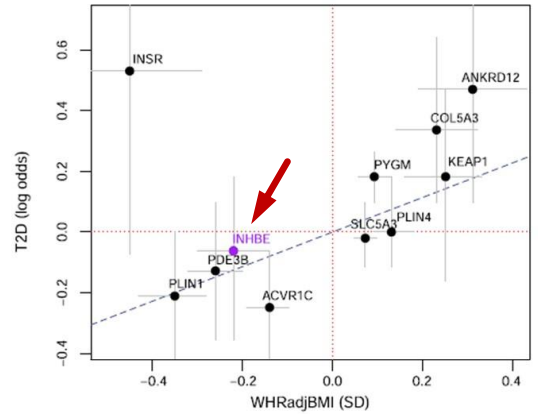
Waist-to-Hip Ratio Adjusted for BMI



CHD Risk



T2D Risk



Nature Communications. (2022)13:4319. https://doi.org/10.1038/s41467-022-31757-8. www.nature.com/naturecommunications.

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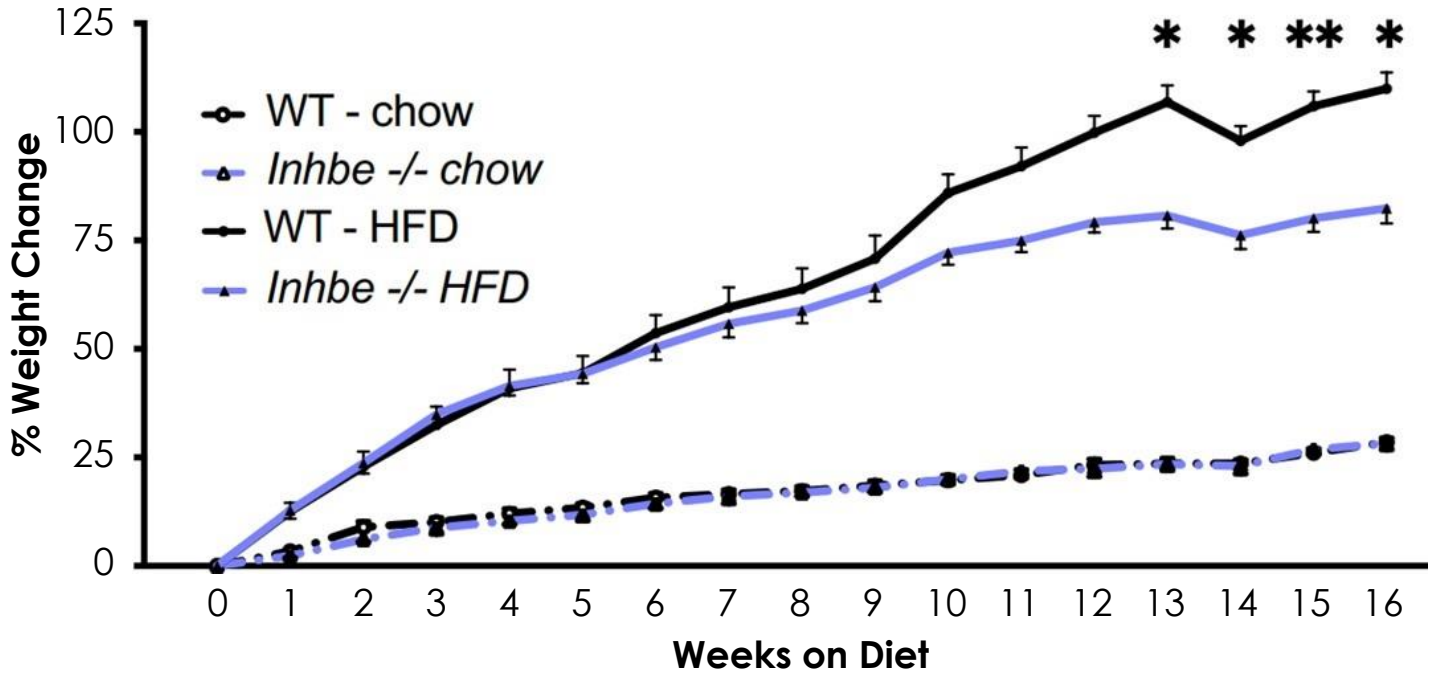
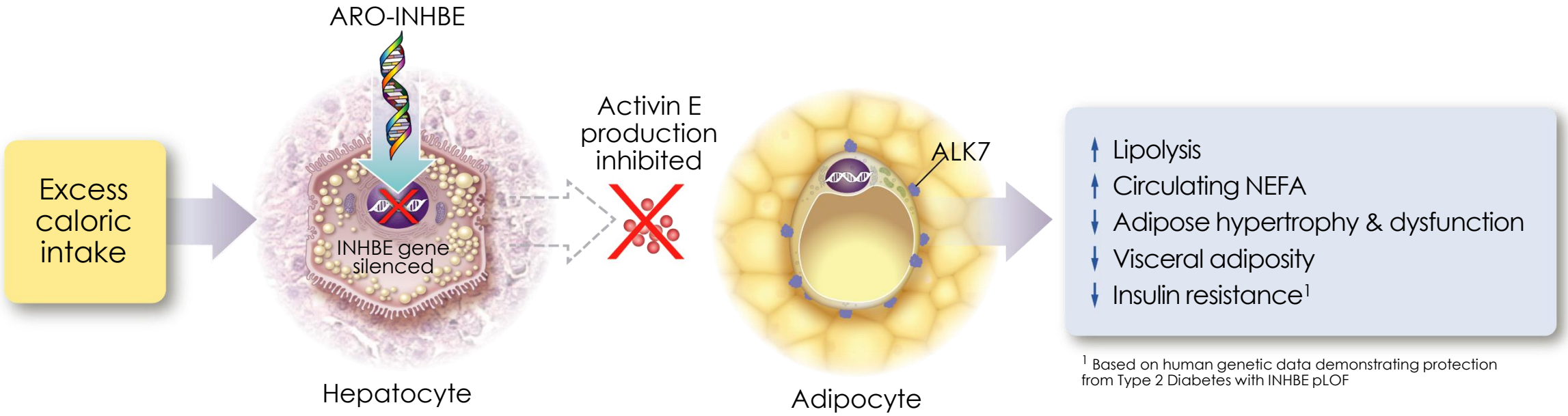
INHBE Knockout Mice on a High-fat Diet Exhibit Reduced Body Weight and Increased Adipose Lipolysis

Body Weight Gain



Adam et al., 2023, PNAS 120. https://www.pnas.org/doi/10.1073/pnas.2309967120.

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

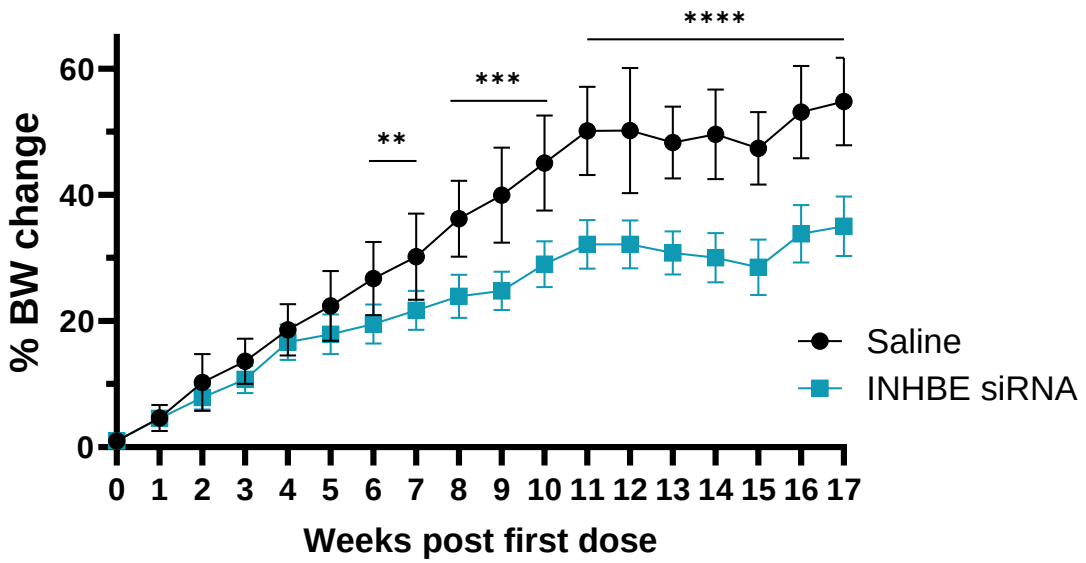


[1] Based on human genetic data demonstrating protection from Type 2 Diabetes with INHBE pLOF

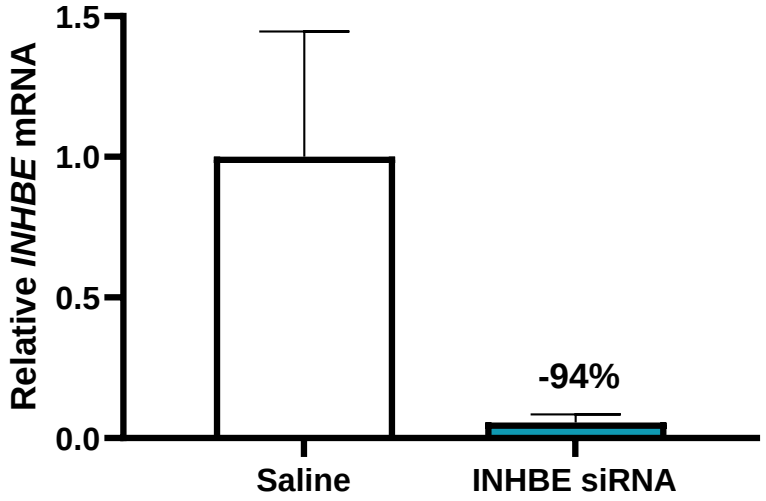
*Based on human genetic data demonstrating protection from Type 2 Diabetes with *INHBE* pLOF.

Hepatic *INHBE* Silencing Limits Weight Gain in a Mouse Model of Diet-induced Obesity (DIO)

Body Weight Change



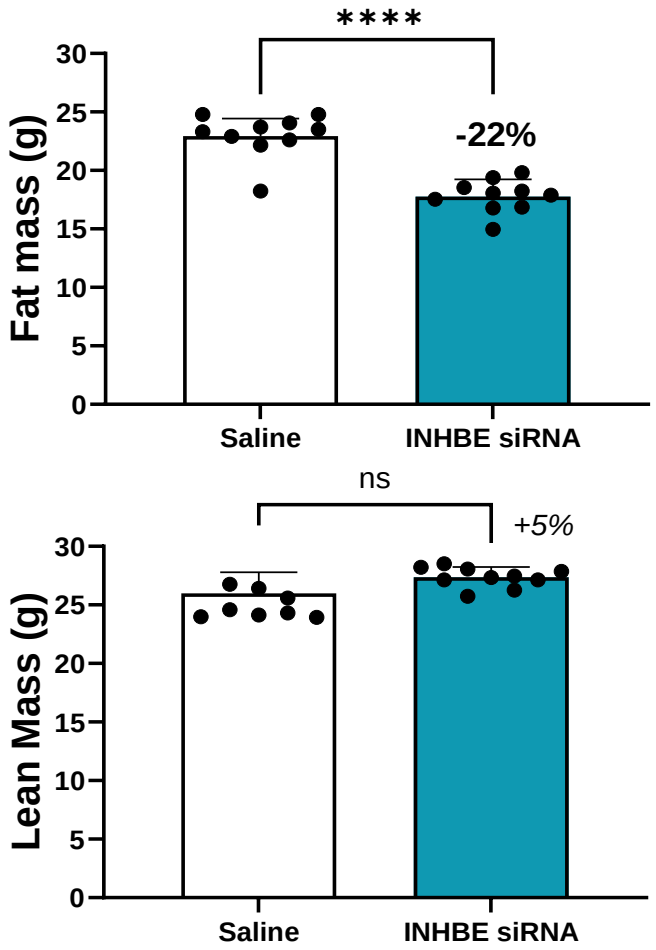
Liver *INHBE mRNA* Expression



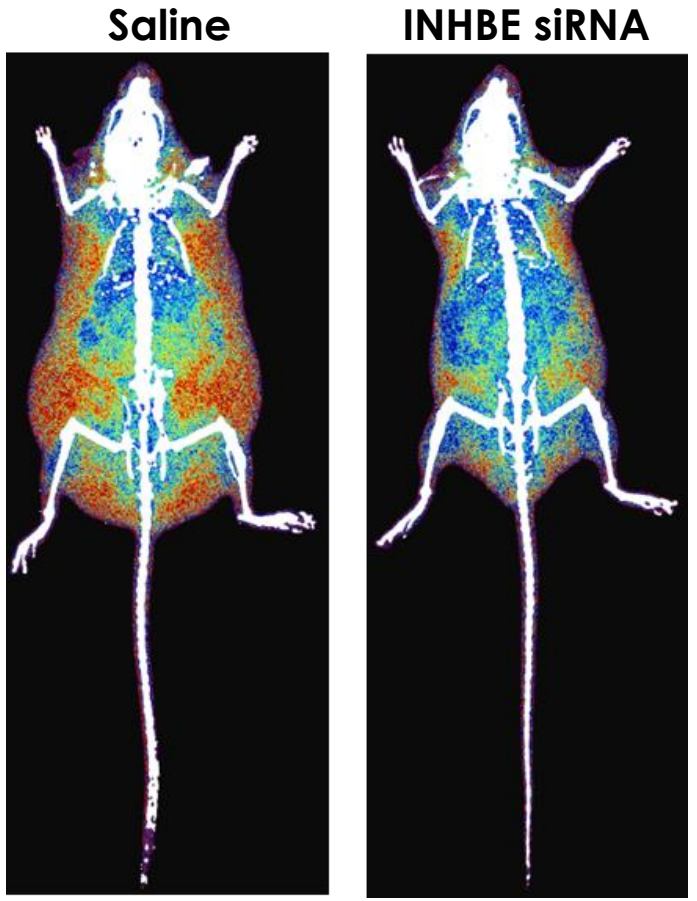
- Mice on a high calorie diet treated with an INHBE siRNA exhibit a **19% suppression** in BW gain relative to vehicle controls
- Mice treated with control RISC loading blocked version of the INHBE siRNA are not protected from BW gain

INHBE Silencing Reduces Fat Mass and Preserves Lean Mass in DIO Mouse Model

Body Composition

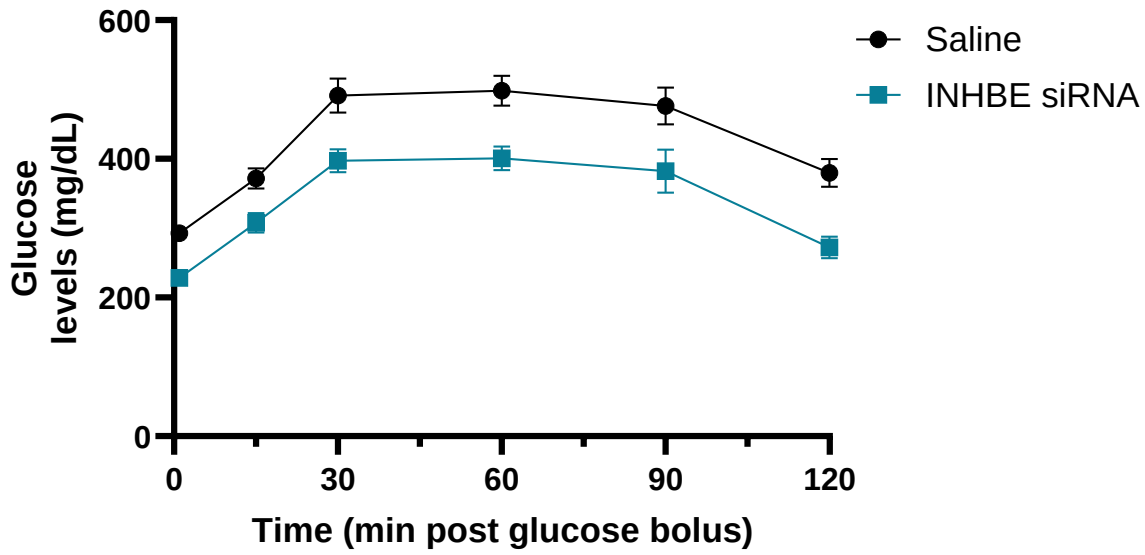


DEXA Images

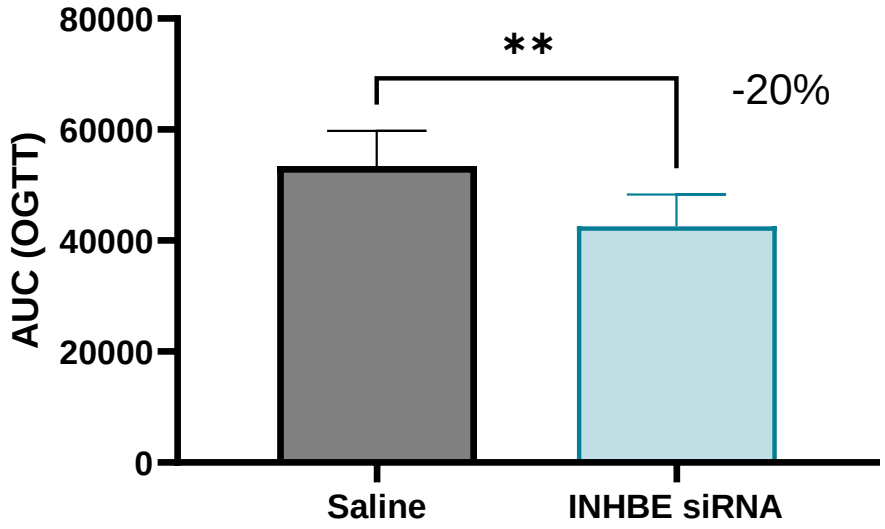


Trend to Improved Glycemic Control in DIO Mice with *INHBE* Silencing

Oral Glucose Tolerance Test



Glucose AUC



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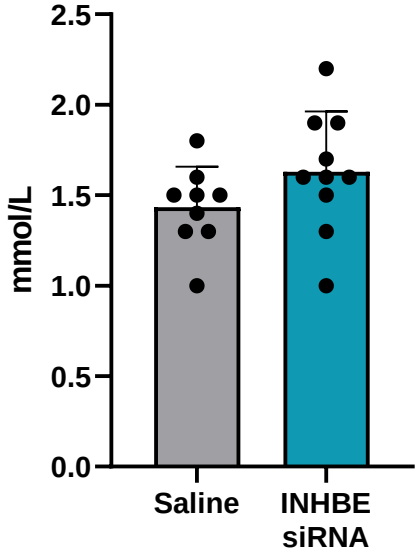
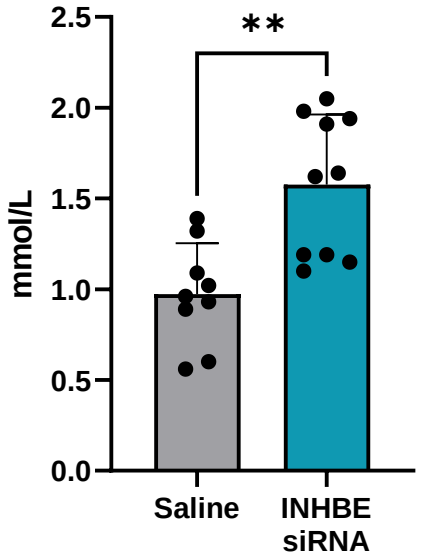
Hepatic *INHBE* Silencing in DIO Mice May Enhance Catecholamine Sensitivity, Increasing Lipid Mobilization and Oxidation

Mice Treated with a Beta 3 Adrenergic Agonist to Stimulate Lipolysis

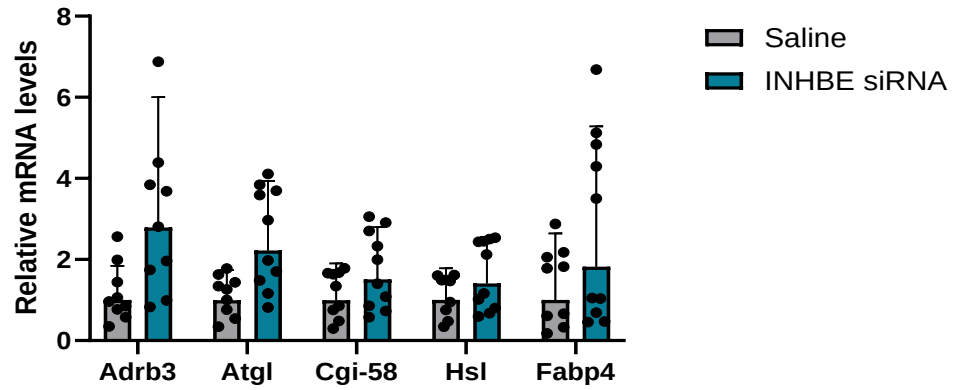
NEFA



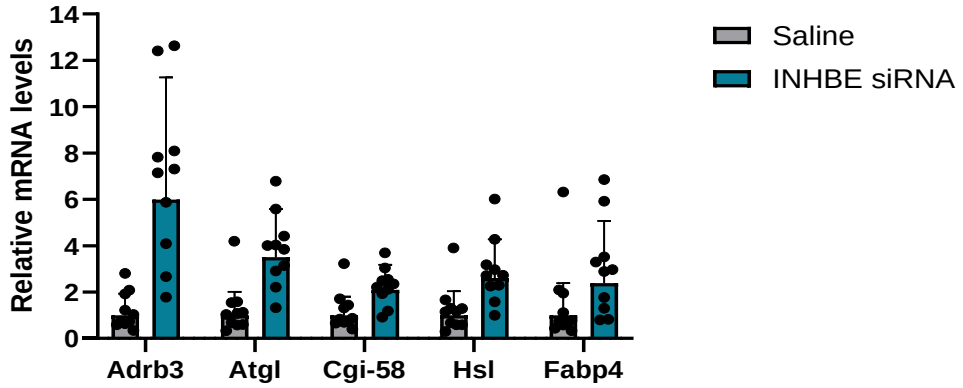
β-hydroxybutyrate



Lipolytic genes in iWAT



Lipolytic genes in pgWAT



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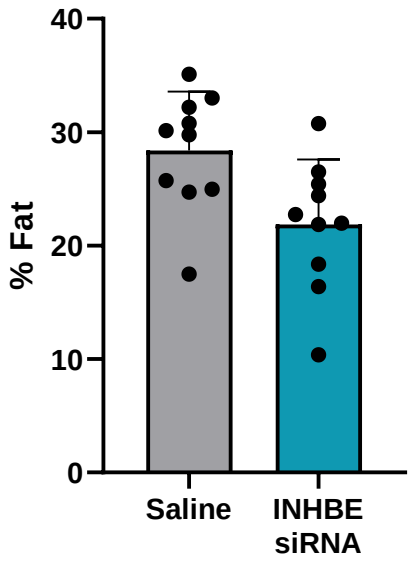
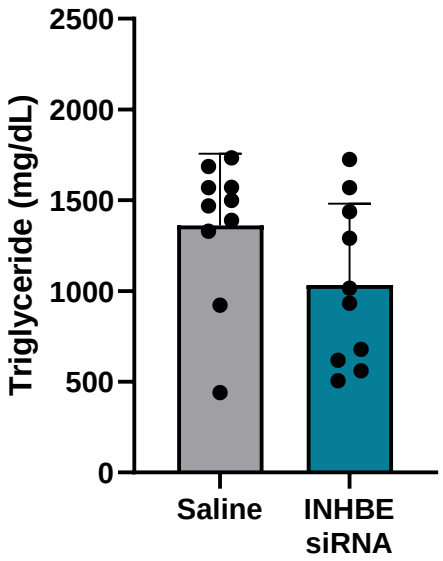
Increased Lipid mobilization in *INHBE*-silenced DIO Mice is not Associated With Liver Steatosis

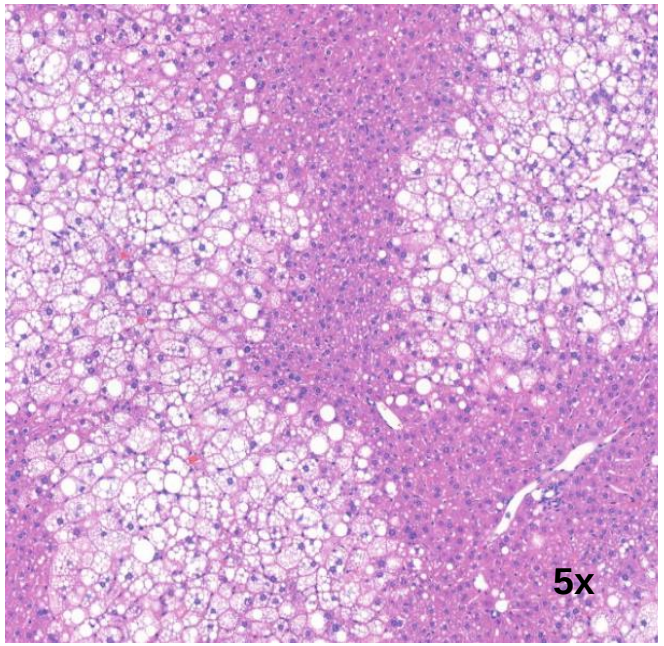
Liver Fat Composition (DEXA)



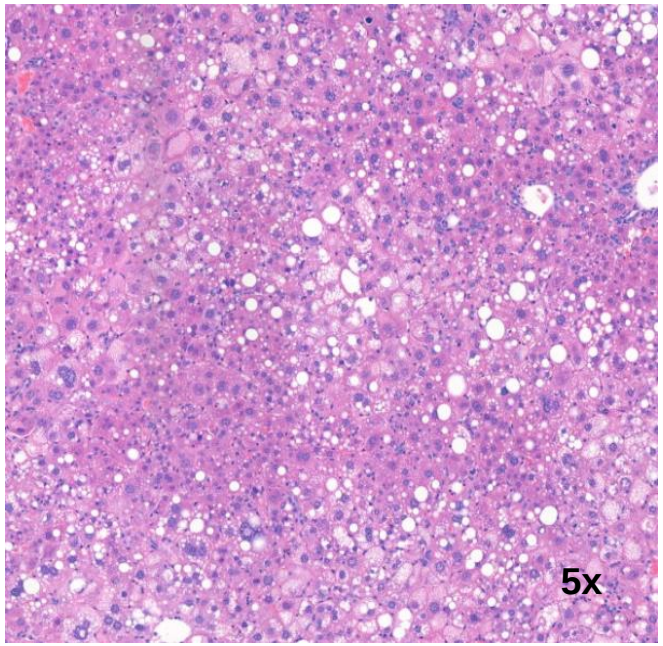
Liver Triglycerides



Saline

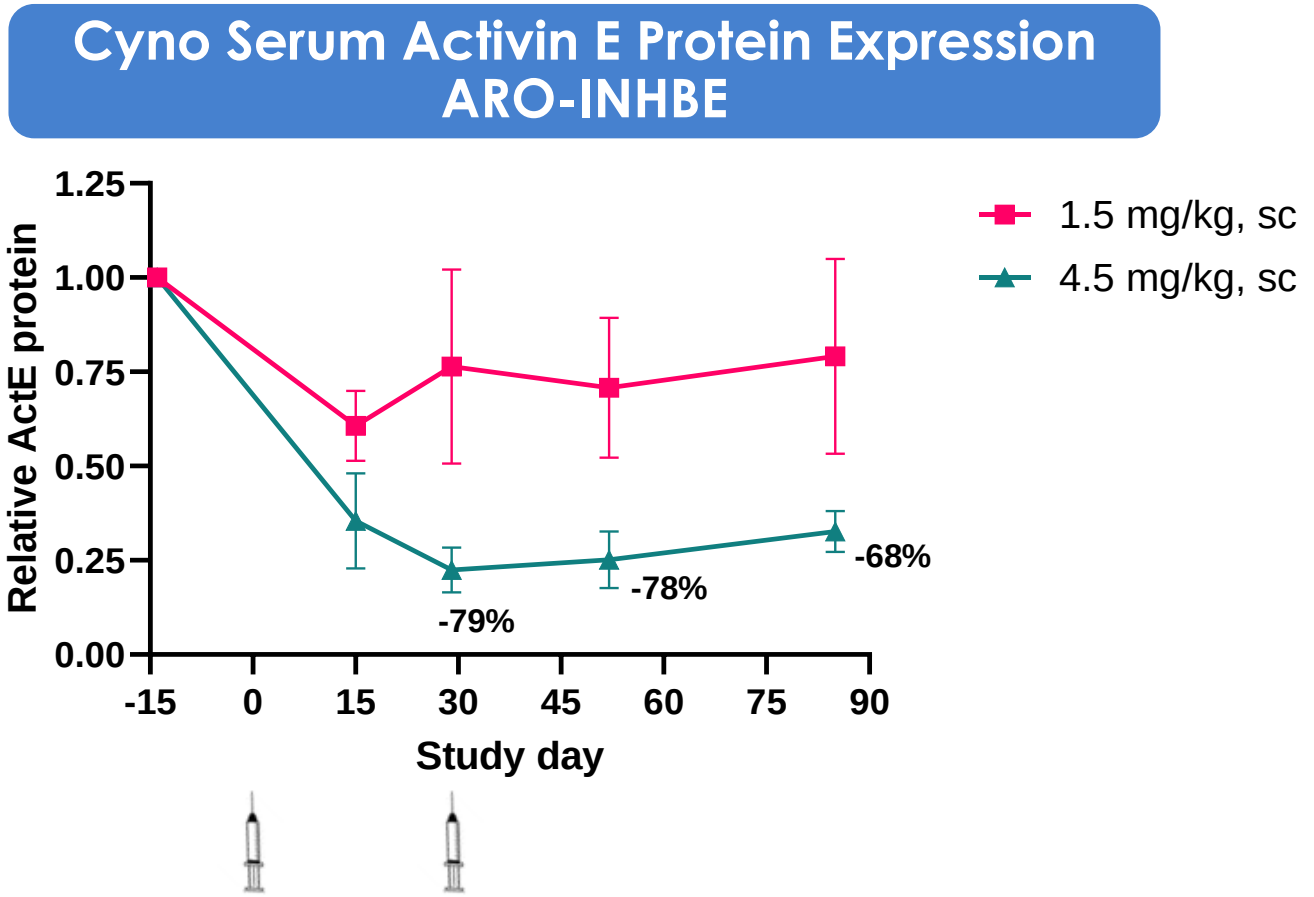


INHBE siRNA



H&E shows less liver fat accumulation with *INHBE* silencing relative to saline controls

ARO-INHBE Effectively Silences Circulating Activin E in Lean Non-human Primates



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TRiM™ Platform for Adipose Delivery

Tao Pei, PhD
Senior Vice President of Chemistry

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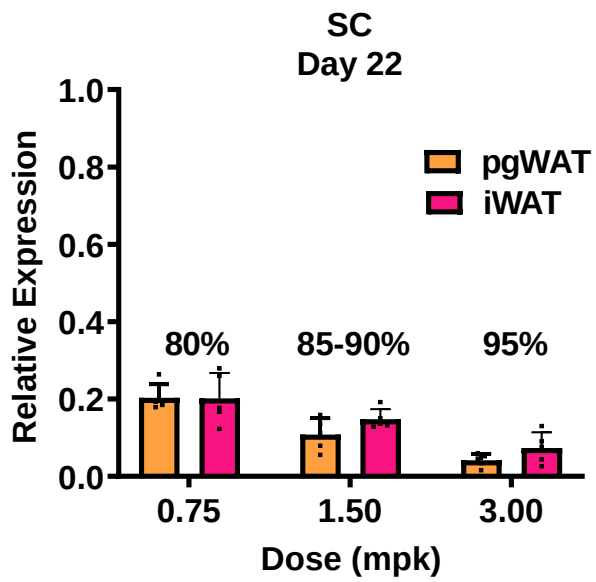
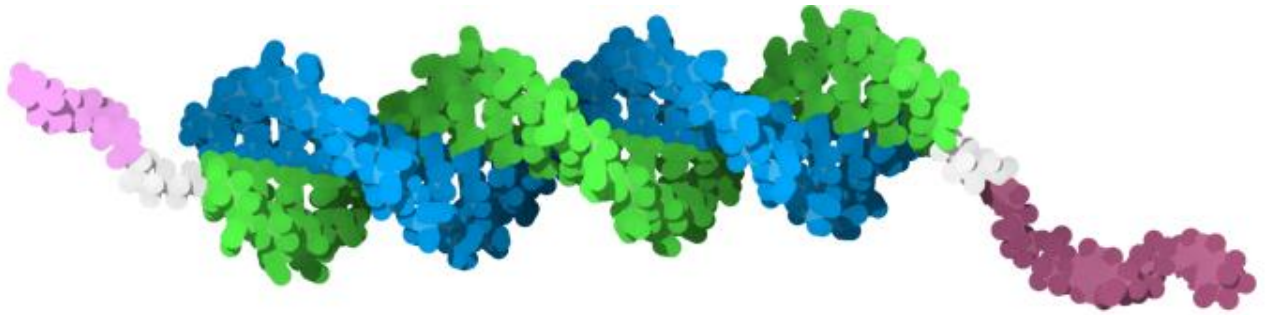
TRiM™ Adipose Platform Achieves Deep Gene Knockdown in Mouse

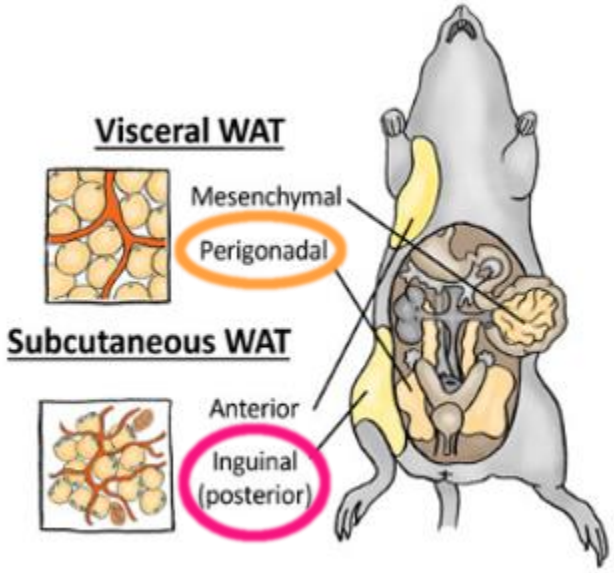
Tissue Adipoq mRNA Expression



- Assessed mRNA gene KD in two different adipose tissues
- Achieved ≥ 80% gene KD in both tissues across dose range at 3 weeks post-dose



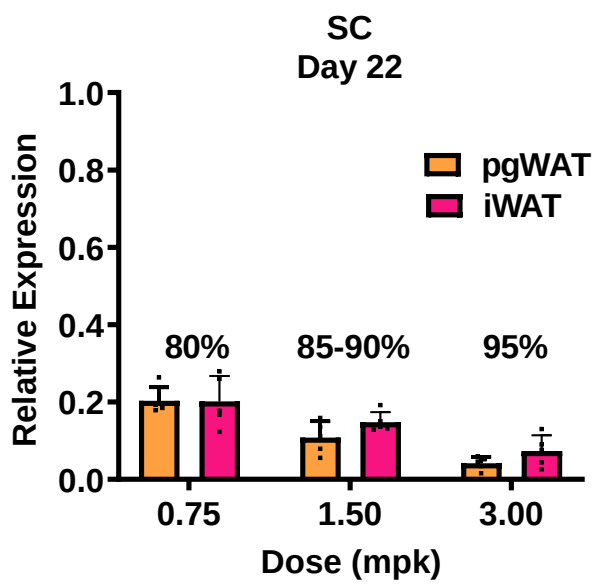
Dual Lipid Conjugate



Börgeson E, et al. *Front. Cell Dev. Biol.* 2022; 10:1003118.

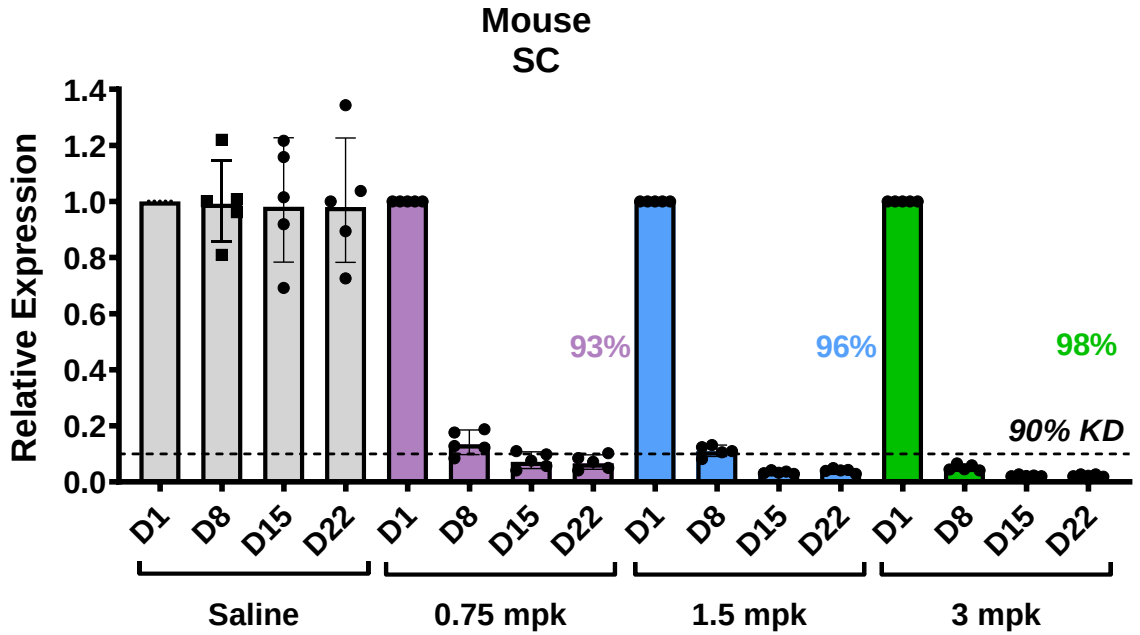
Platform Achieves Deep Serum Protein Knockdown in Mouse

Tissue Adipoq mRNA Expression



- Assessed mRNA gene KD in two different adipose tissues
- Achieved ≥ 80% gene KD in both tissues across dose range at 3 weeks post-dose

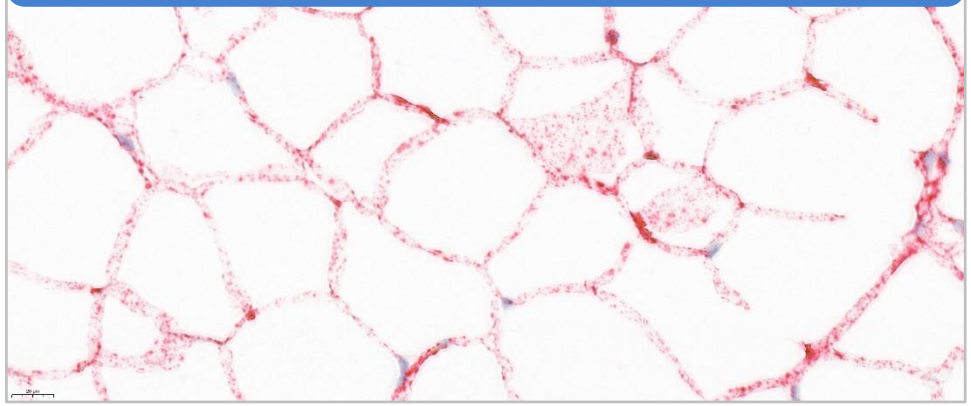
Serum Adipoq Protein Expression



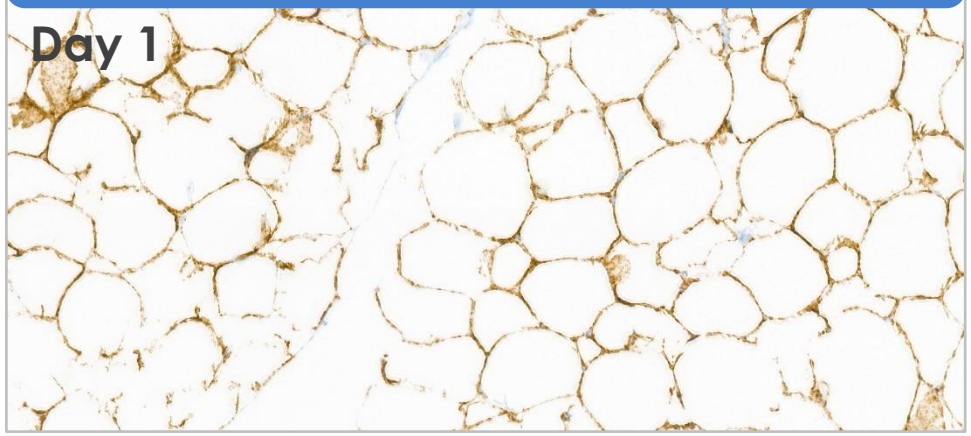
- ≥ 90% serum protein knockdown achieved in same dose range
- Corroborates with gene KD

Platform Targets Mouse Adipocytes

miRNAscope



RNAscope

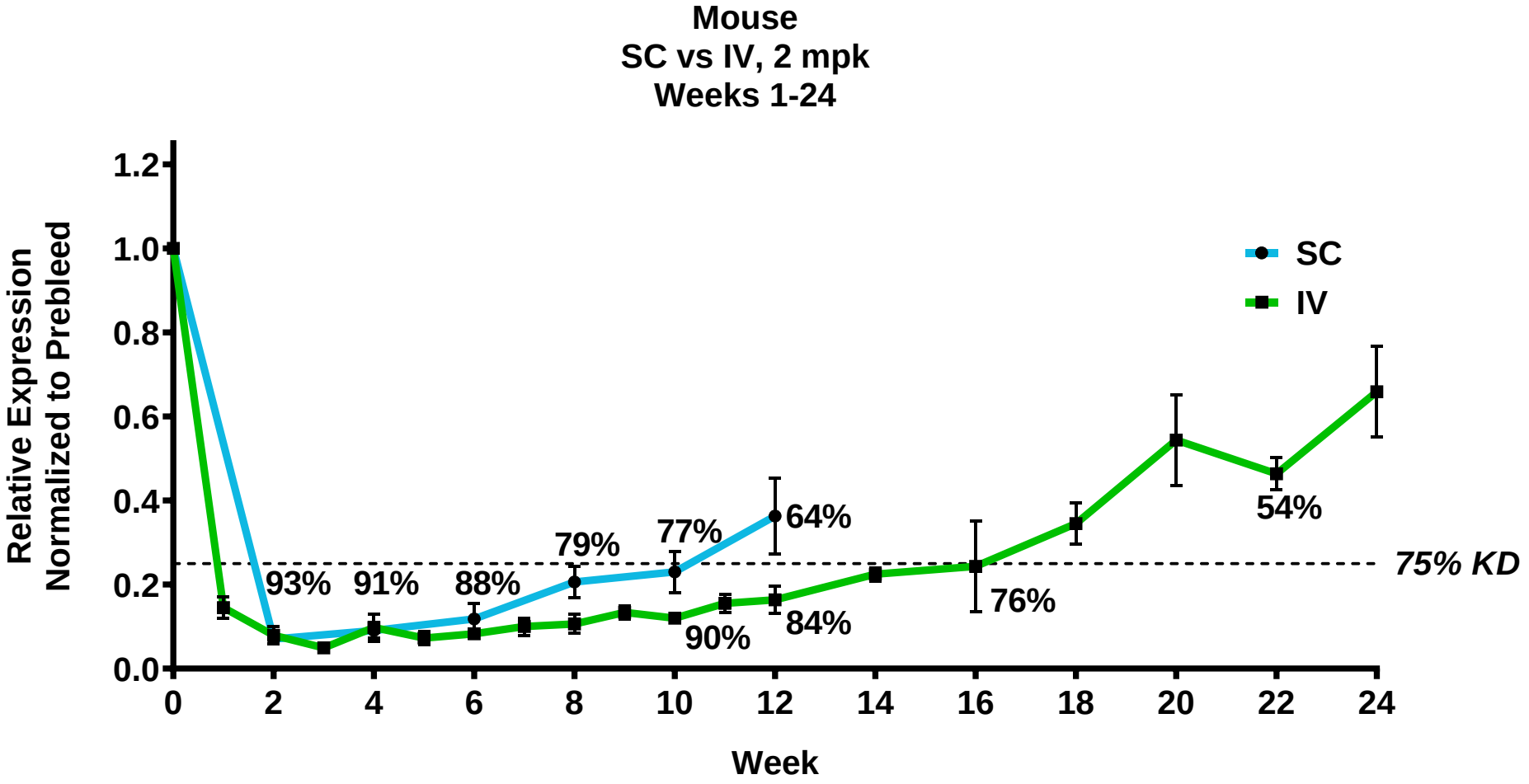


3 mpk dose (SC)

- Tissue-staining to confirm siRNA delivery and depletion of target mRNA in adipocytes
- Mice dosed with adipose platform at 3 mpk (SC), D15 harvest
- **miRNA visualization of trigger confirms delivery to adipocytes**
- **RNAscope confirms Adiponectin mRNA depletion**

Platform Achieves Deep & Durable Knockdown via Single 2 mpk Dose in Mouse

Serum Adipoq Protein Expression



SC Dosing

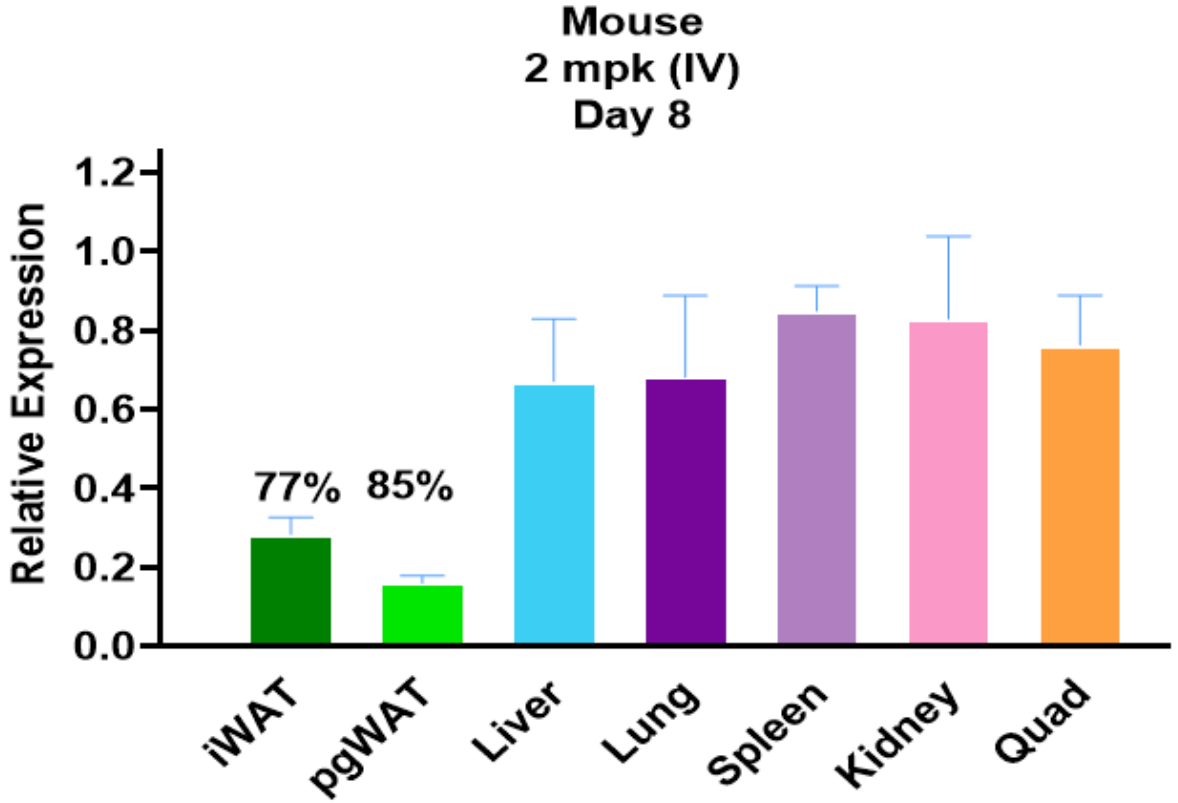
- ~90% serum Adipoq protein KD maintained through week 6
- ≥ 75% KD maintained through week 10

IV Dosing

- ~90% serum Adipoq protein KD maintained through week 10
- ≥ 75% KD maintained through week 16

Platform Demonstrates Functional Tissue Selectivity in Mouse

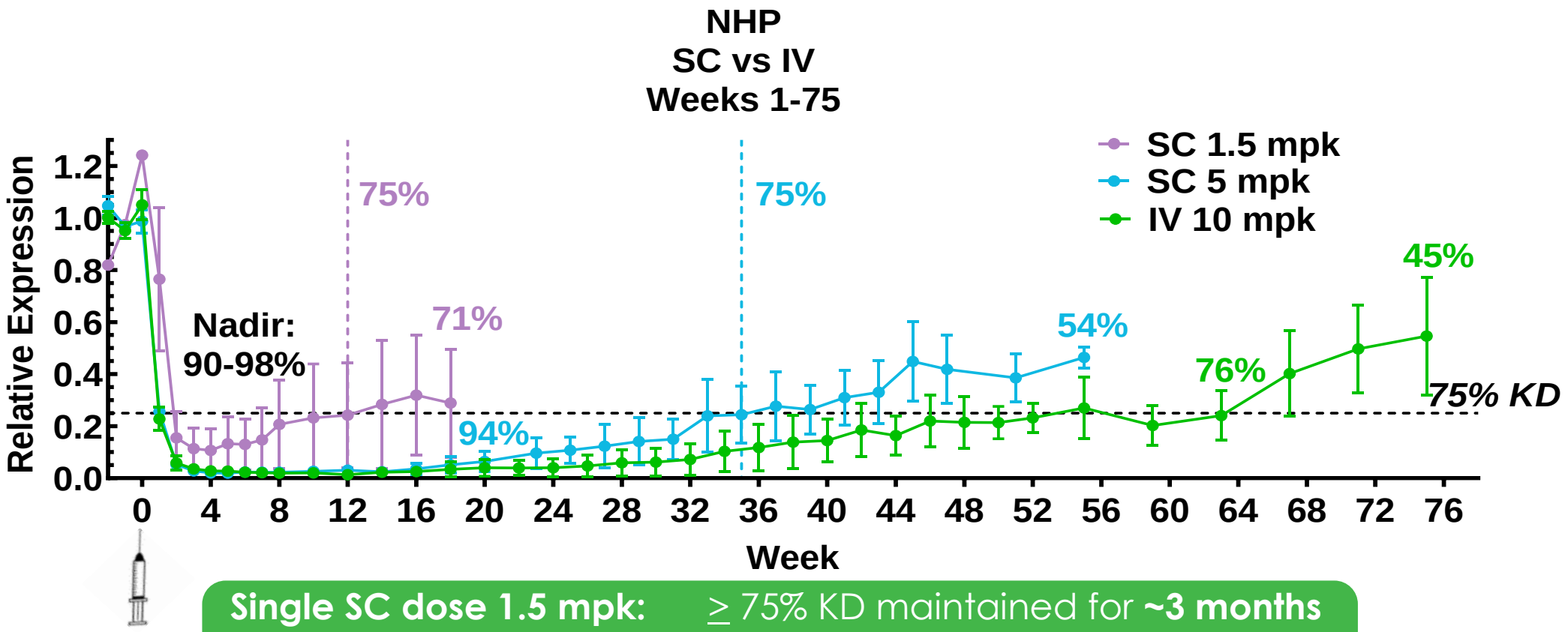
Tissue SOD1 mRNA Expression



Despite delivery to peripheral tissue, significant KD observed selectively in adipose tissues

Platform Achieves Deep and Durable Knockdown via Single Dose in NHP

Serum Adipoq Protein Expression



Single SC dose 1.5 mpk: ≥ 75% KD maintained for **~3 months**
Single SC dose 5 mpk: ≥ 75% KD maintained for **~9 months**
Single IV dose 10 mpk: ≥ 75% KD maintained for **~16 months**

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Adipose Platform Demonstrates Good Safety Profile

- Non-GLP exploratory tox study in rat:
  - Day 1, Day 15 SC dose up to 120 mpk
  - Necropsy at Day 16 and Day 29
- No mortality
- No noteworthy observations or body weight changes
- Minimal findings in clinical chemistry, hematology, and coagulation
- Histopathology: no adverse drug-related findings at Day 16 and Day 29 necropsies

Obesity Programs Webinar – August 14, 2024

ARO-ALK7 Program – Preclinical Data

Erik Bush, PhD
Senior Vice President of Biology

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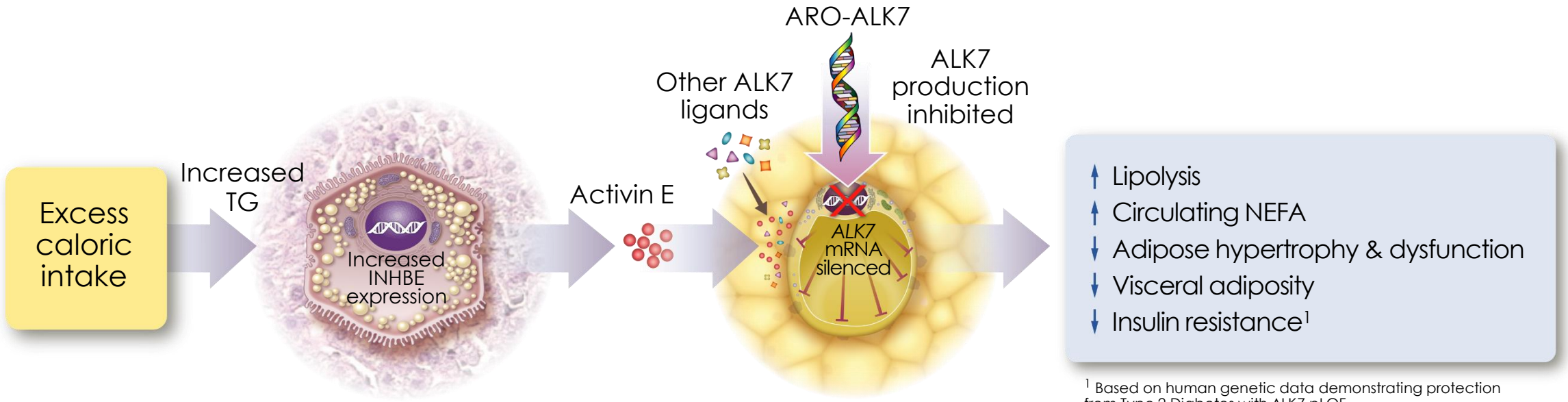
Activin receptor-like kinase 7 (ALK7, *ACVR1C*) is a genetically validated adipose target



[1] Based on human genetic data demonstrating protection from Type 2 Diabetes with ALK7 pLOF

- 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

Emdin et al, *Diabetes* 2019; 68(1):226-234. DOI: 10.2337/DB18-0857

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

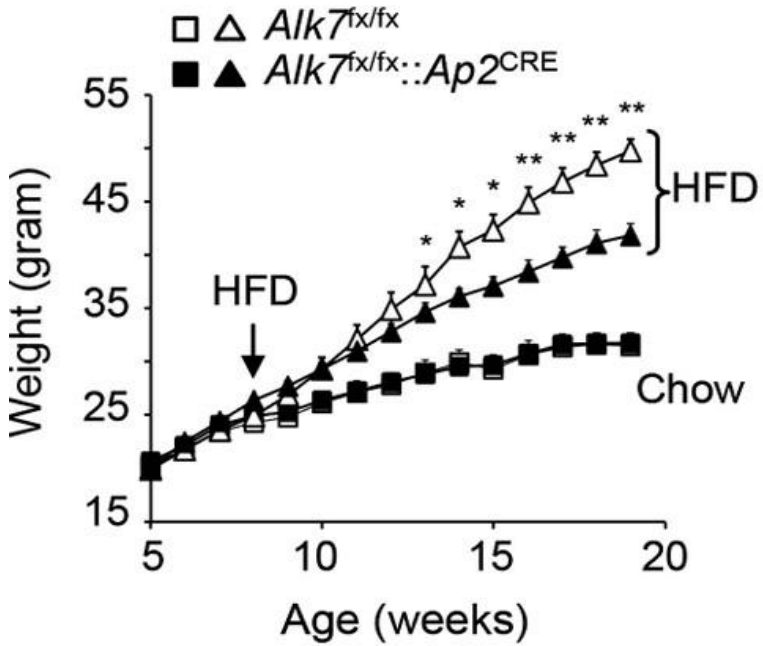
Table 2—Association of variants in *ACVR1C* with WHRadjBMI and with type 2 diabetes

Variant	Minor allele frequency (%)	WHRadjBMI		Type 2 diabetes	
		β (95% CI)	*P* value	OR (95% CI)	*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}

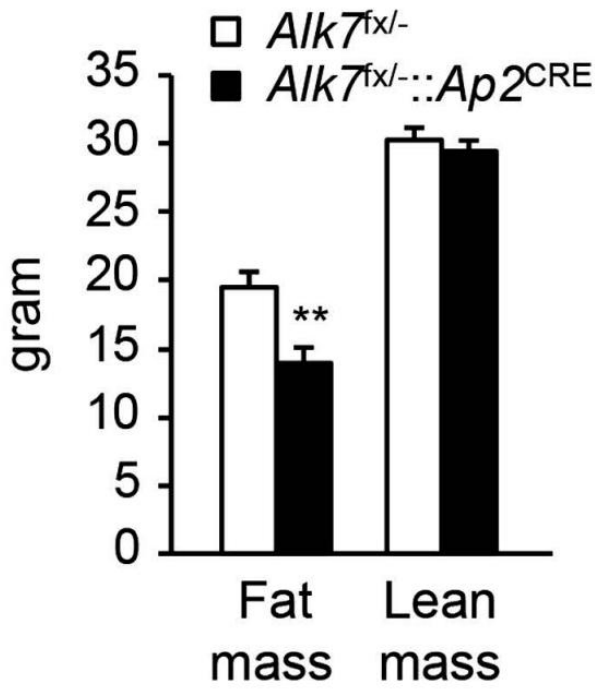
Estimates for WHRadjBMI were derived through linear regression analysis in UK Biobank. Estimates for type 2 diabetes were derived through meta-analysis of UK Biobank and the DIAGRAM ExTexT2D Consortium.

Adipose-specific *ALK7* Knockout Mice Data Exhibit Reduced Body Weight Gain and Fat Accumulation

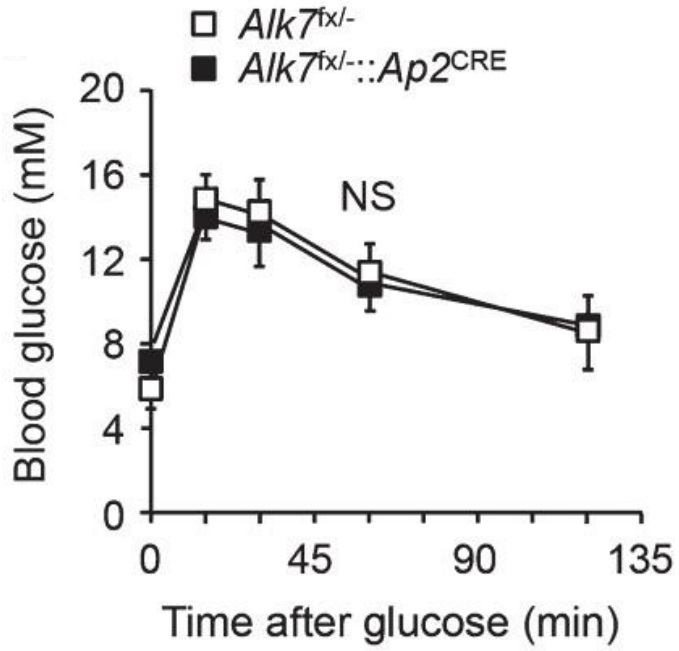
Body Weight



Body Composition (MRI)



Oral Glucose Tolerance Test



Guo et al, eLife 2014;3:e03245. DOI: 10.7554/eLife.03245

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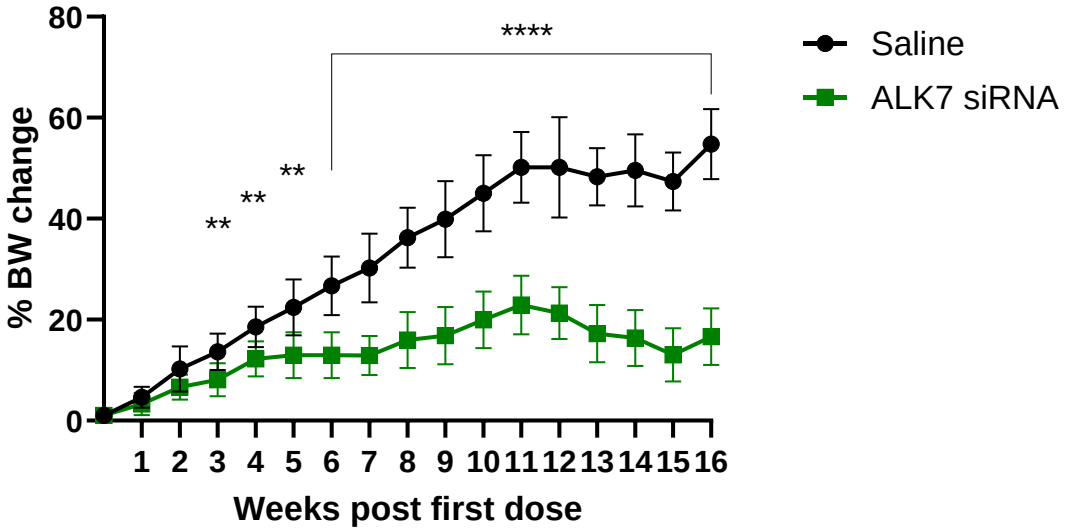
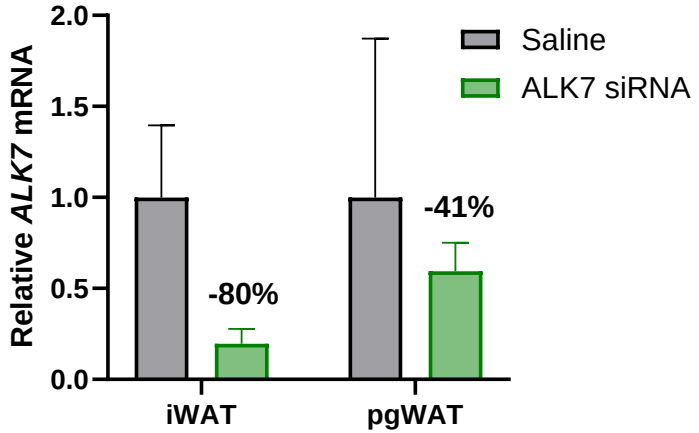
Adipose *ALK7* Silencing Limits Weight Gain in a Mouse Model of Diet-induced Obesity (DIO)

% Body Weight Change

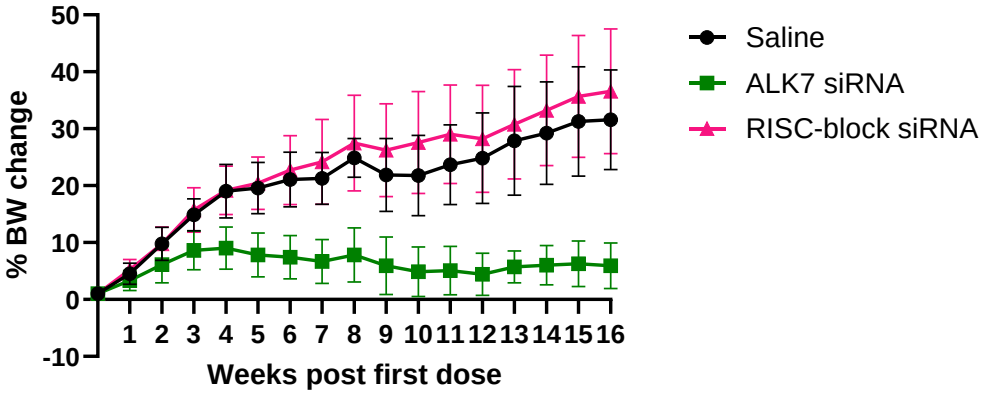


- Mice on a high-fat diet treated with an *ALK7* siRNA exhibit a 39% suppression in BW gain relative to controls
- Weekly 3 mg/kg SC dosing silenced ~80% *ALK7* mRNA in iWAT and ~40% in pgWAT
- Mice treated with control RISC loading blocked version of the *ALK7* siRNA were not protected from BW gain

WAT *ALK7* mRNA expression

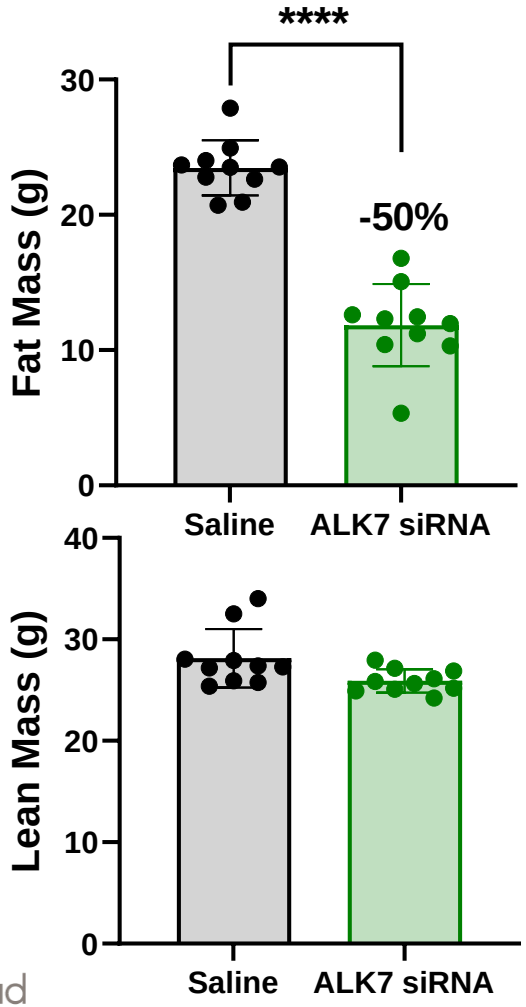


% Body Weight Change

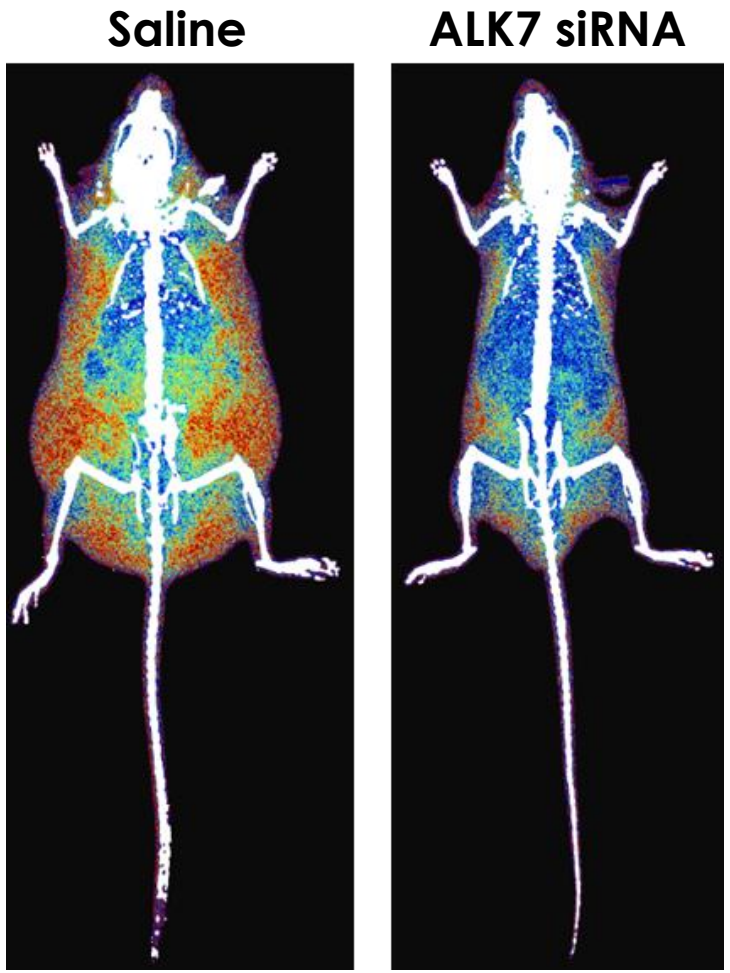


Adipose *ALK7* Silencing Reduces Fat Mass and Preserves Lean Mass in DIO Mouse Model

Body Composition



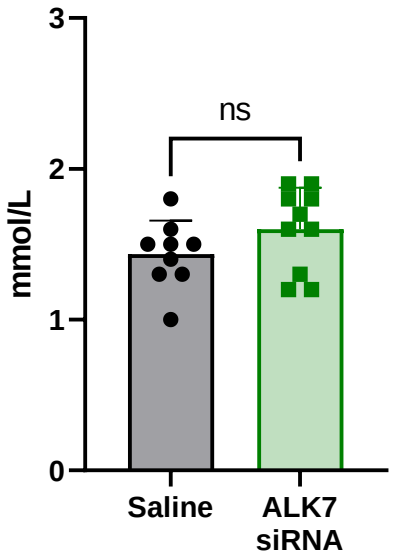
DEXA images



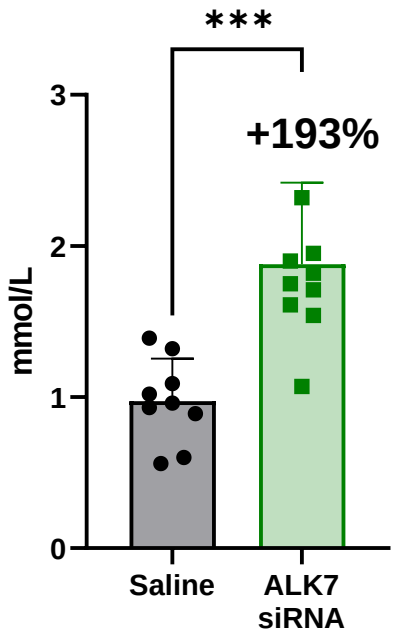
Adipose *ALK7* Silencing in DIO Mice May Enhance Catecholamine Sensitivity, Increasing Lipid Mobilization and Oxidation

Mice Treated With a Beta-3 Adrenergic Agonist to Stimulate Lipolysis

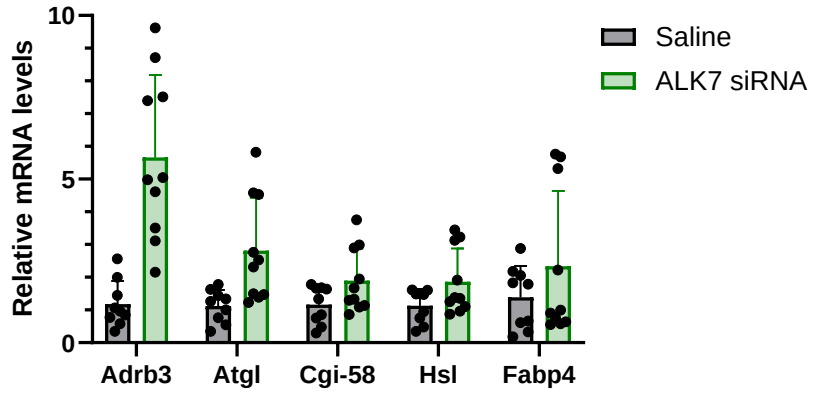
NEFA



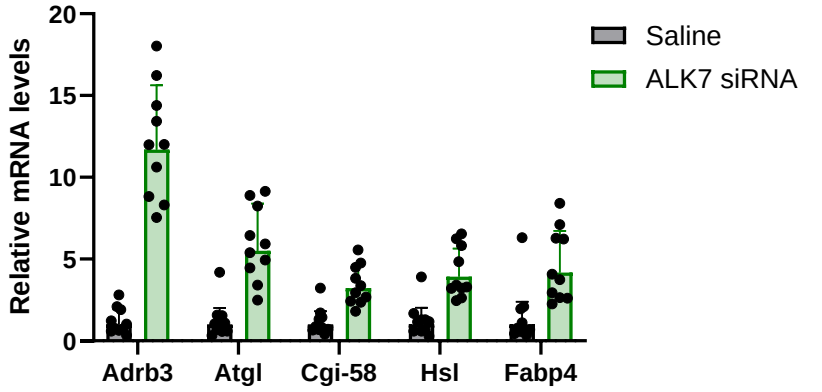
B-hydroxybutyrate



Lipolytic genes in iWAT

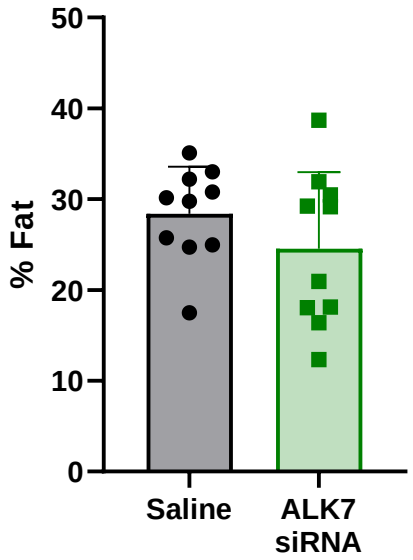


Lipolytic genes in pgWAT

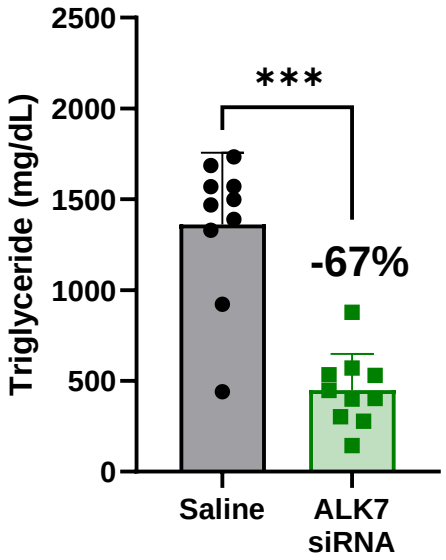


Increased Lipid Mobilization in *ALK7*-silenced DIO Mice is Not Associated With Liver Steatosis

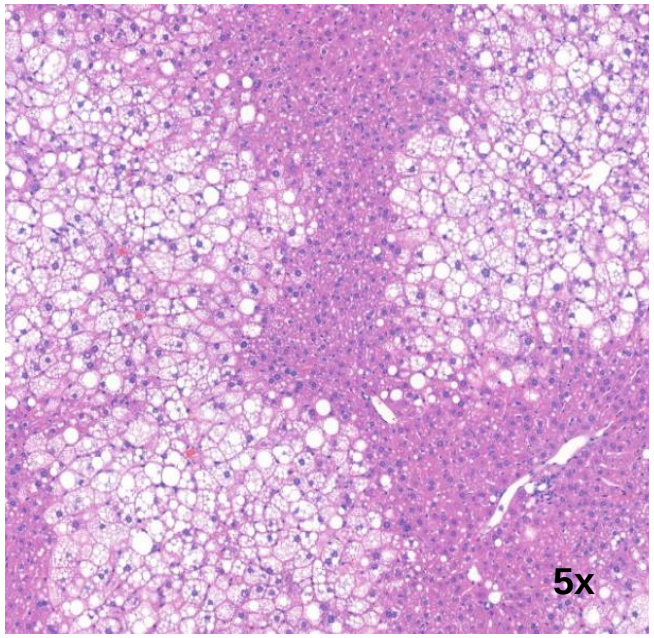
Liver Fat Composition (DEXA)



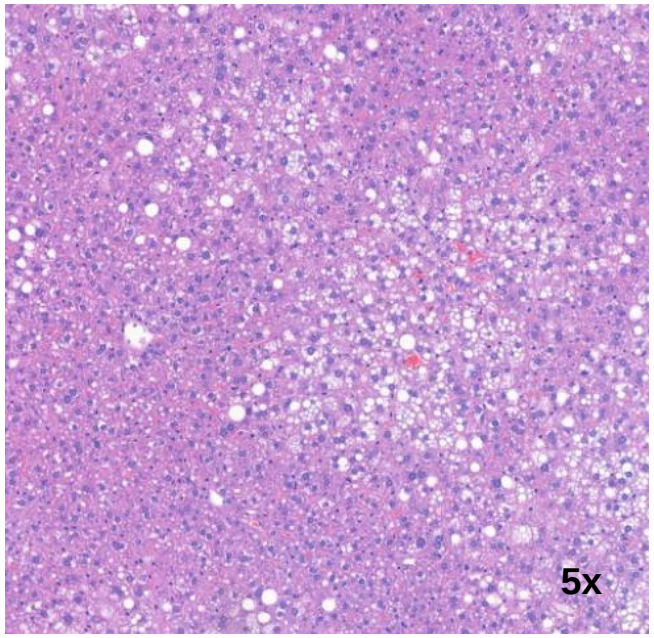
Liver Triglycerides



Saline



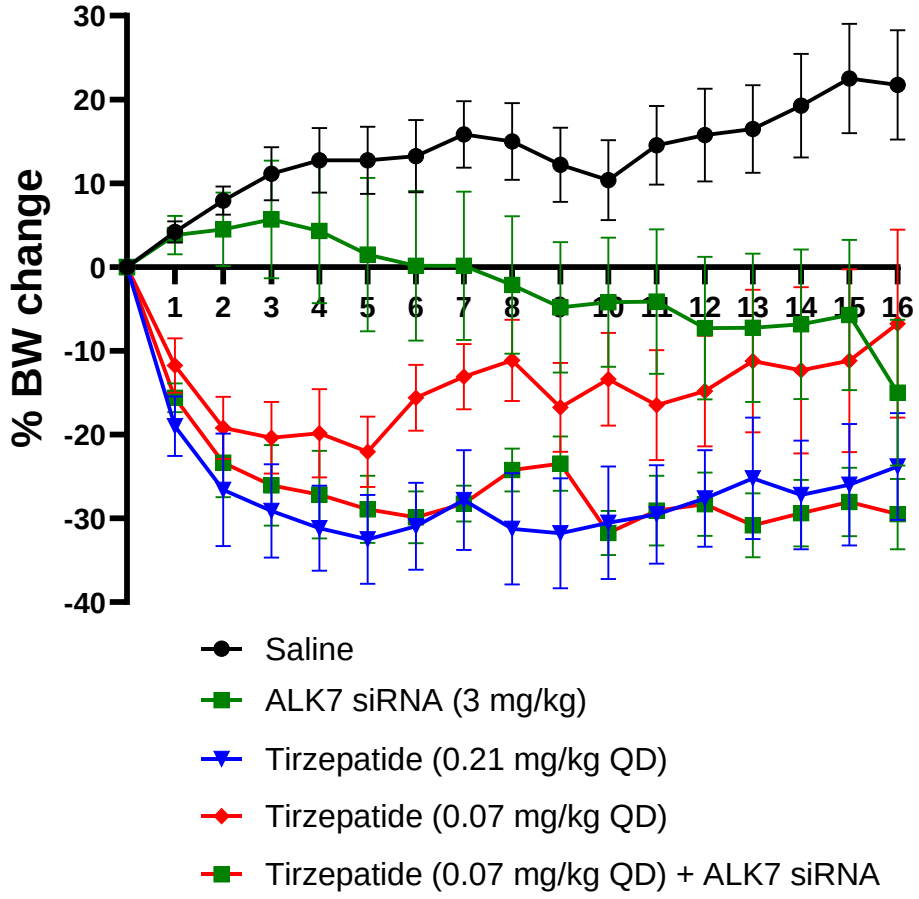
ALK7 siRNA



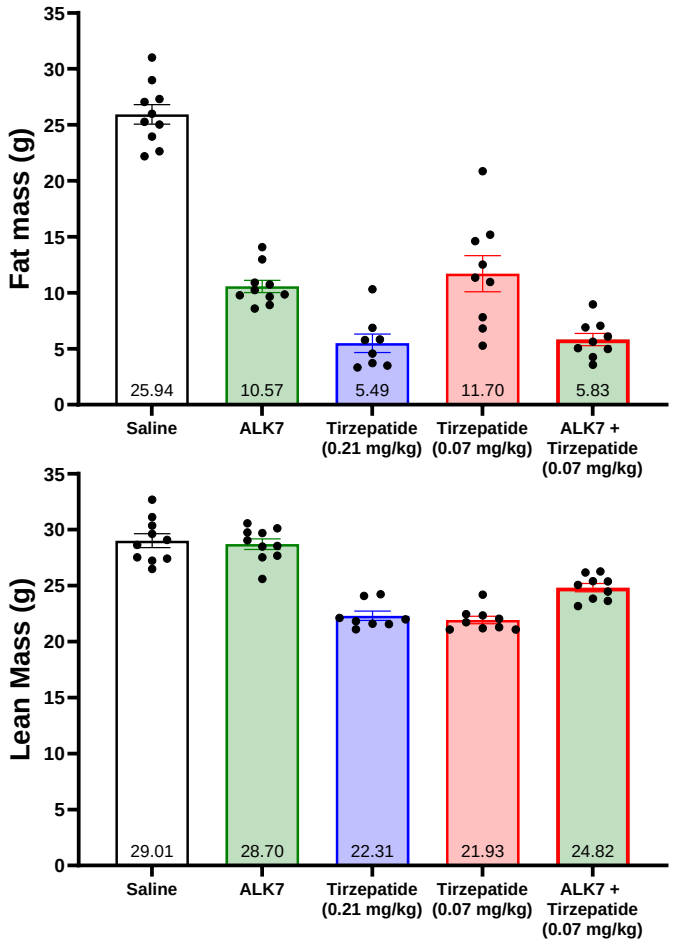
H&E shows less liver fat accumulation with adipose *ALK7* silencing relative to saline controls

ALK7 siRNA Plus Tirzepatide Improves Weight Loss and Body Composition in Mouse DIO Model

Body Weight Change



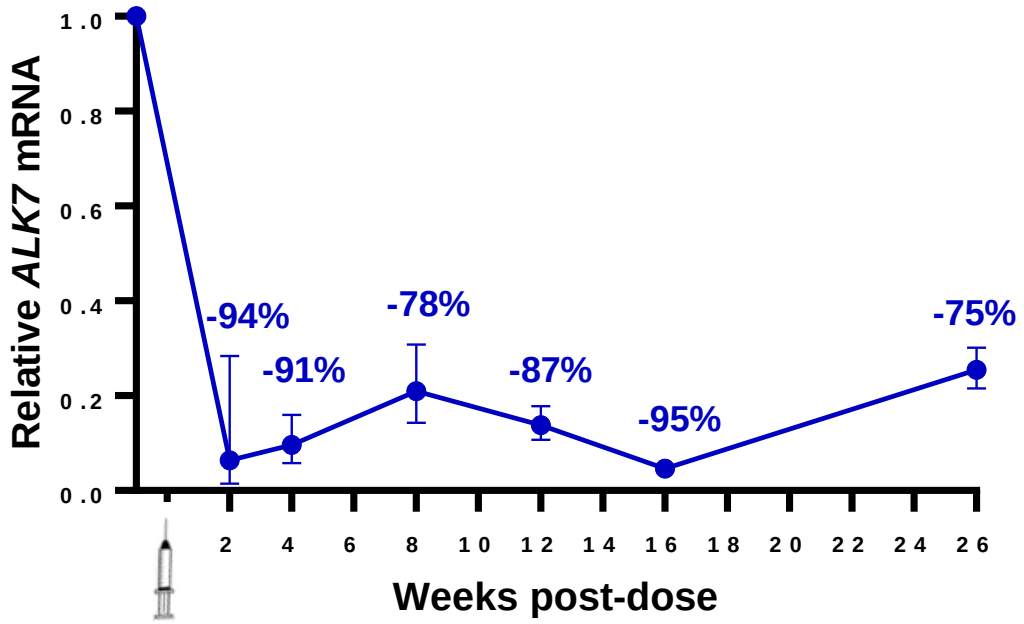
Body Composition



ARO-ALK7 Effectively and Durably Silences Adipose *ALK7* mRNA Expression in Lean Non-human Primates

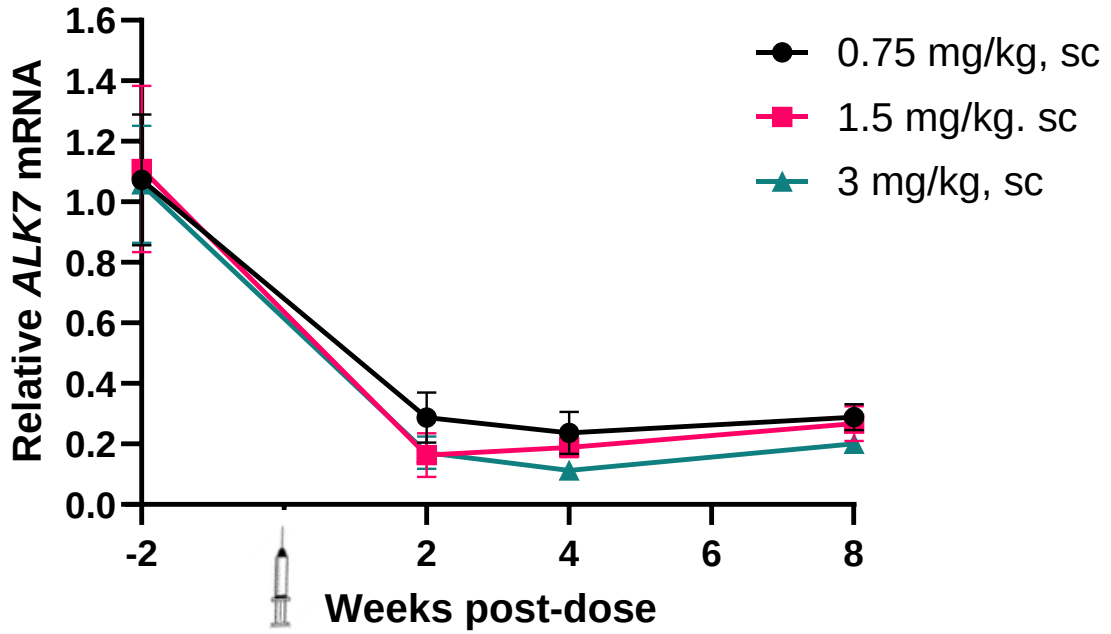
Cyno WAT *ALK7* mRNA Expression

ARO-ALK7 (3 mg/kg, sc)



Cyno WAT *ALK7* mRNA Expression

ARO-ALK7 Dose-response



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ARO-INHBE and ARO-ALK7 – Clinical Trial Designs and Status

James Hamilton, MD, MBA
Chief of Discovery & Translational Medicine

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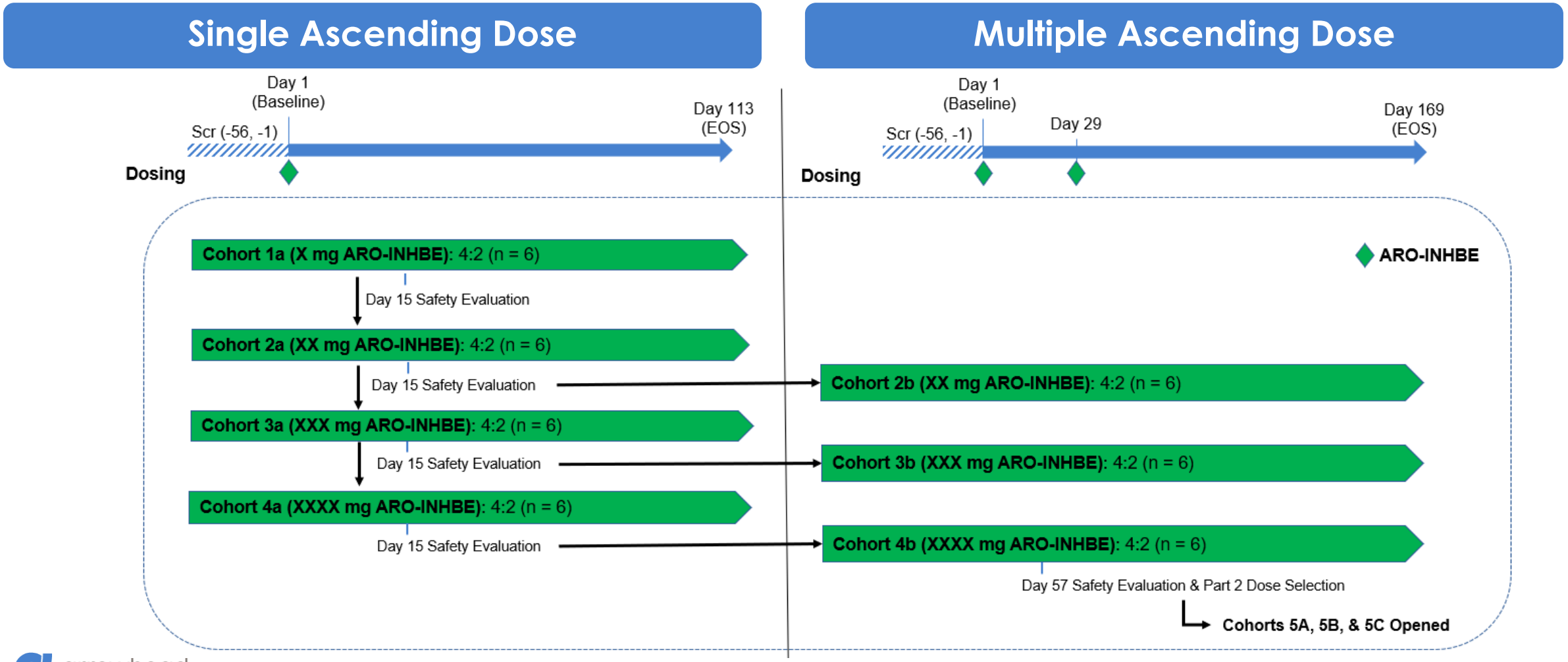
Phase 1/2a Study of ARO-INHBE in Volunteers With Obesity With and Without Type 2 Diabetes Mellitus

Part 1: Randomized, double-blind, placebo-controlled cohorts to evaluate single- and multiple-ascending doses of ARO-INHBE in volunteers with obesity.



Phase 1/2a Study of ARO-ALK7 in Volunteers with Obesity With and Without Type 2 Diabetes Mellitus

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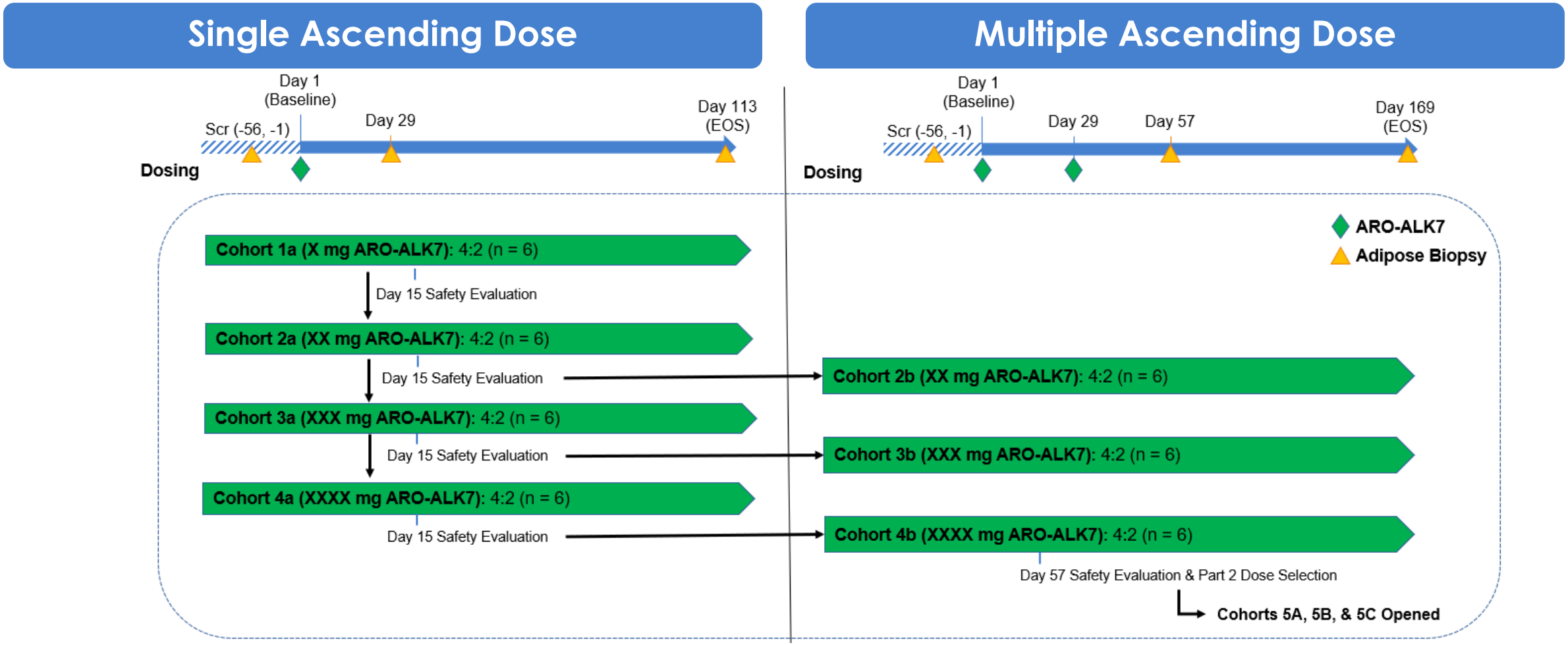
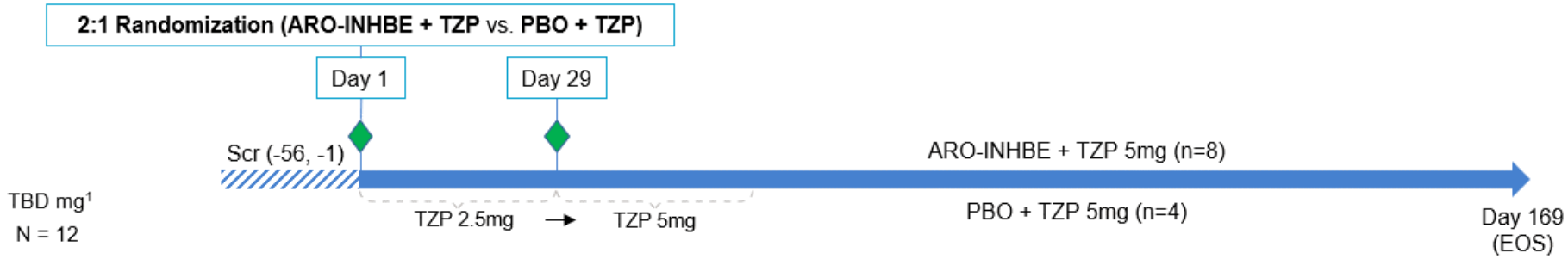


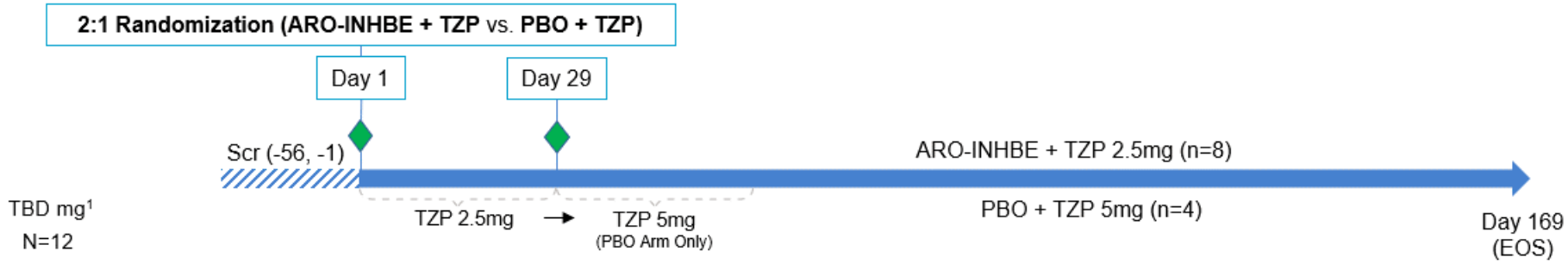
Phase 1/2a Study of ARO-INHBE in Volunteers With Obesity With and Without Type 2 Diabetes Mellitus

Part 2: Randomized, double-blind, placebo-controlled cohorts evaluating ARO-INHBE in combination with a GLP-1/GIP agonist.

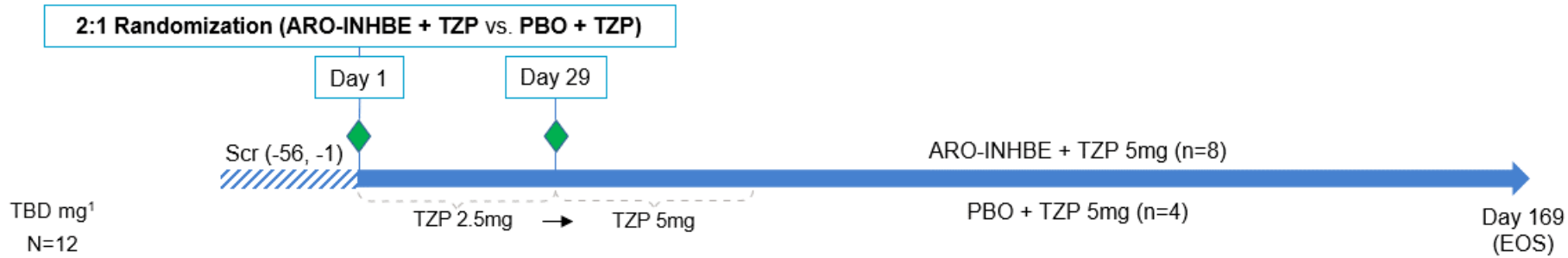
Obesity: Cohort 5A



Obesity: Cohort 5B



Obesity + T2DM: Cohort 5C



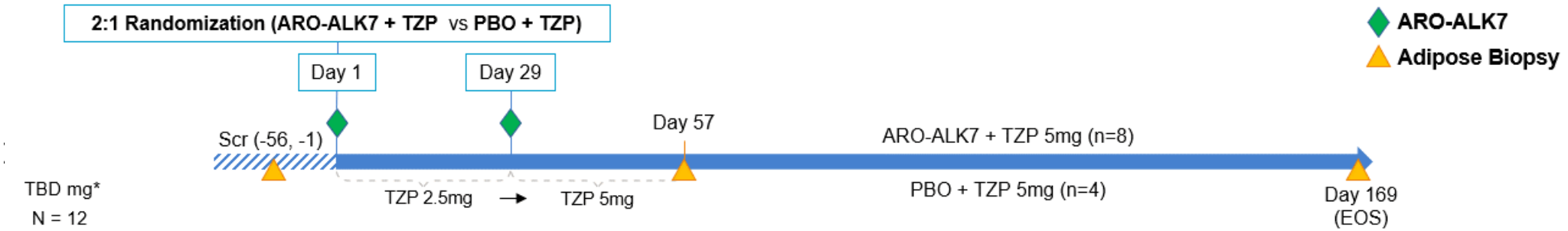
Abbreviations: PBO – placebo; TZP – tirzepatide

[1] Dose in Part 2 of the study to be determined based on safety and PD data from Part 1 of the study.

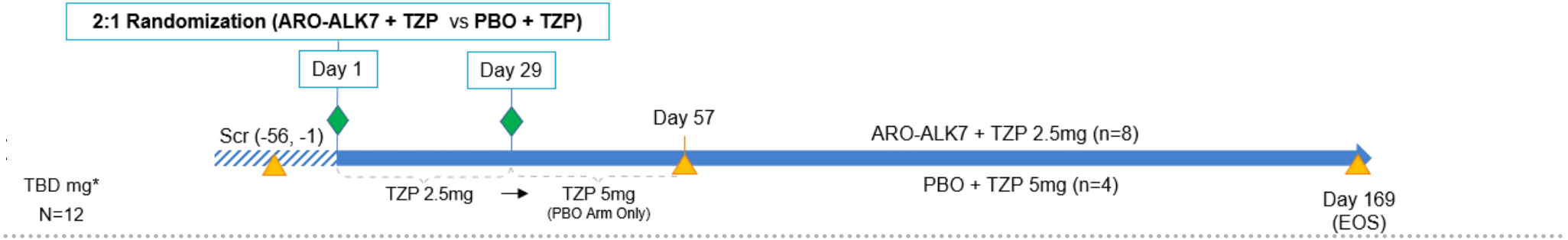
Phase 1/2a Study of ARO-ALK7 in Volunteers With Obesity With and Without Type 2 Diabetes Mellitus

Part 2: Randomized, double-blind, placebo-controlled cohorts evaluating ARO-ALK7 in combination with a GLP-1/GIP agonist.

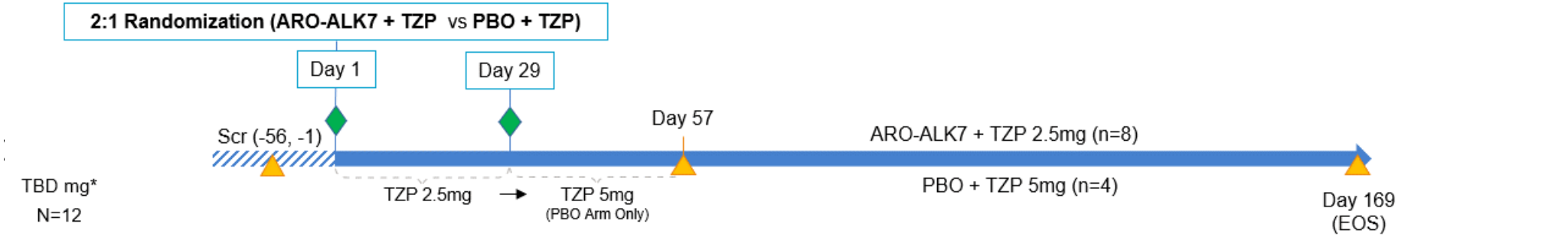
Obesity: Cohort 5A



Obesity: Cohort 5B



Obesity + T2DM: Cohort 5C



Abbreviations: PBO – placebo; TZP – tirzepatide

[1] Dose in Part 2 of the study to be determined based on safety and PD data from Part 1 of the study.

Key Endpoints

1° Safety

2° Pharmacokinetics

Exploratory

- **Serum Activin E** (ARO-INHBE only)
- **Adipose Expression of ALK7** (ARO-ALK7 only)
- 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

Obesity Webinar – August 14, 2024

Takeaways and Our Take on the Obesity Market and Opportunity

Vince Anzalone, CFA
Vice President, Finance and IR

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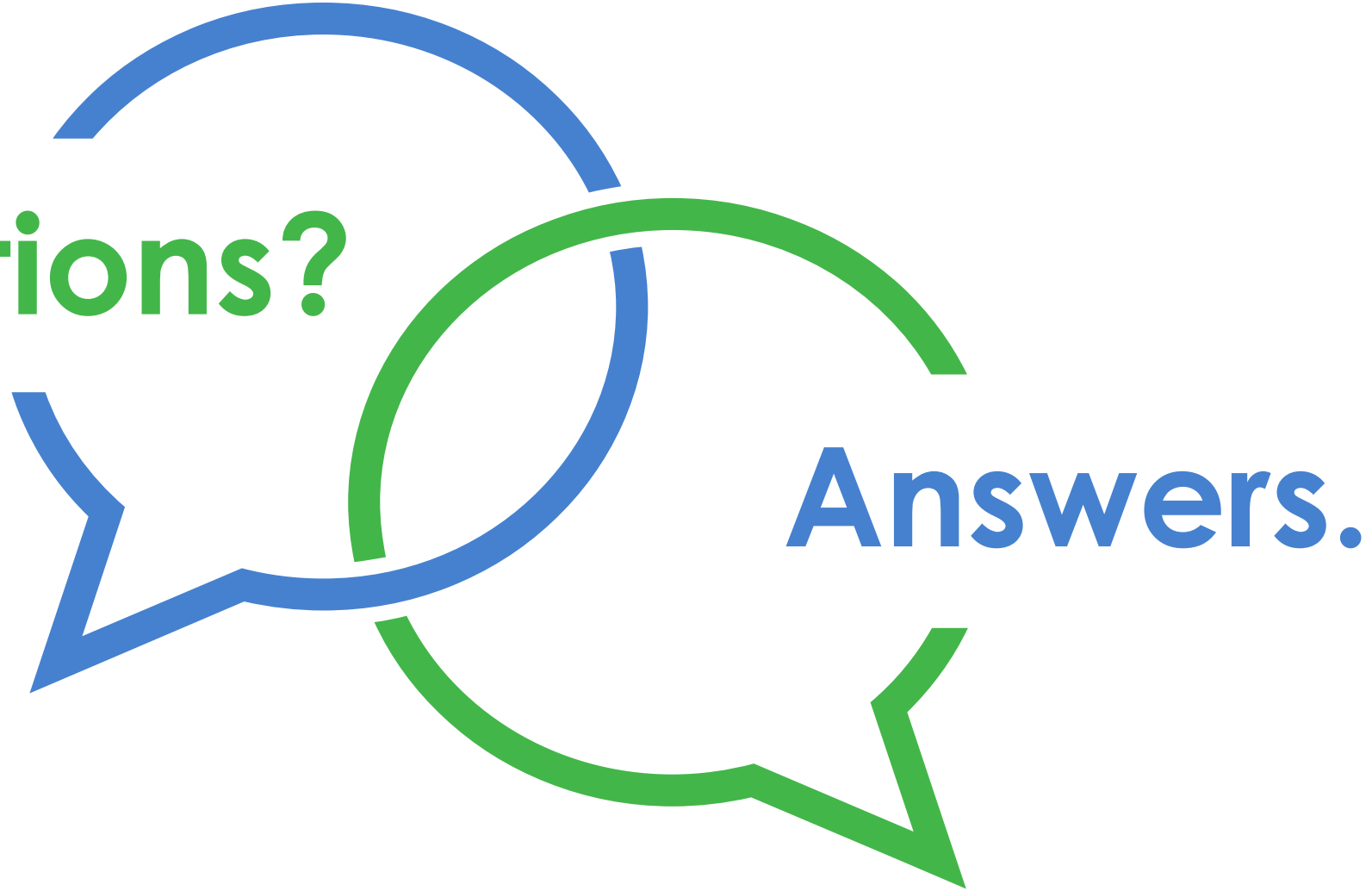
Takeaways

- Obesity increases risk of many diseases including diabetes, heart disease, stroke, and more and reducing fat mass may improve patient outcomes dramatically
- This is not a market driven by aesthetics, rather by health outcomes and payors agree
- New therapies have made a big impact, but opportunities clearly exist for:
  - Novel new mechanisms
  - Therapies that better maintain lean mass and improve body composition
  - Therapies that potentially reduce gastrointestinal adverse events
- Genetics and biology support the Activin E ligand and ALK7 receptor pathway
- ARO-INHBE and ARO-ALK7 are highly active and show promising preclinical results
- We believe we are first-in-class and best-in-class with both targets
- CTAs planned before end of year 2024

Questions?



Answers.