



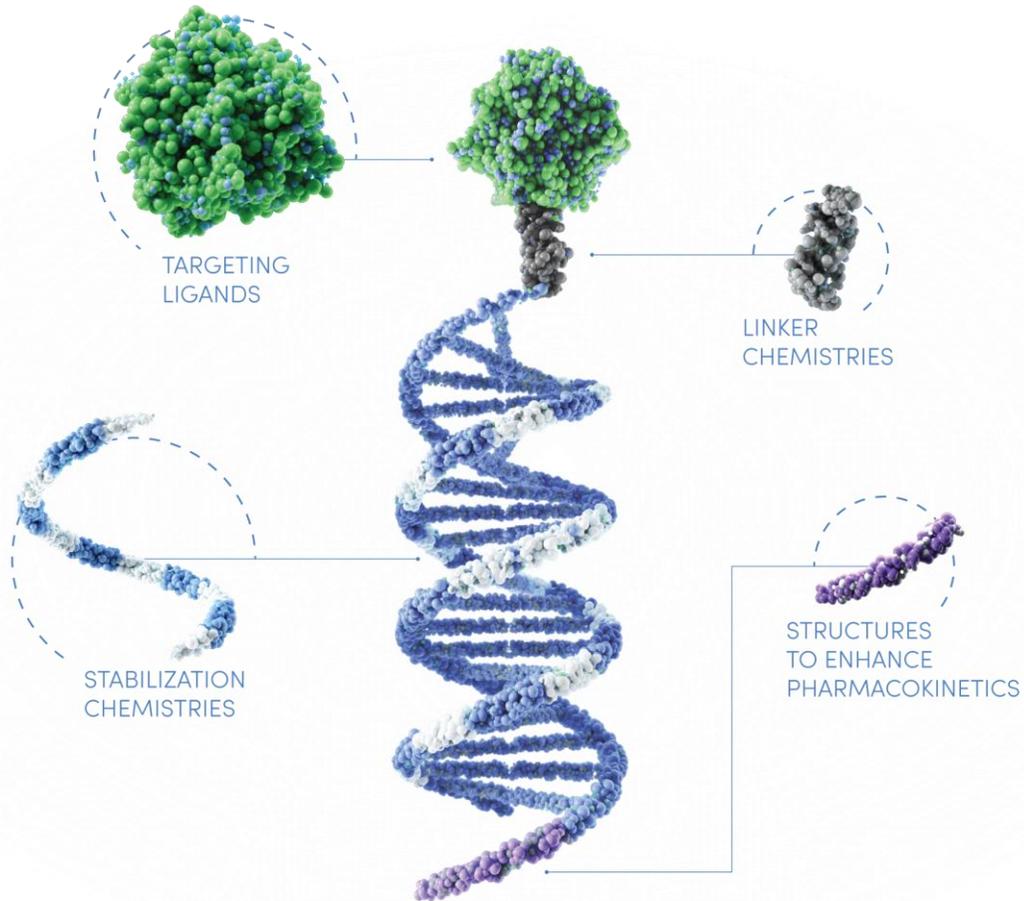
RNA Leaders Congress Targeting Obesity with RNAi-based Therapies

March 6, 2025

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.

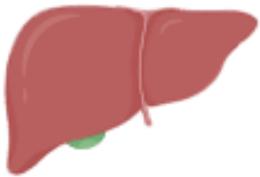
TRiM™ Platform: Targeted RNAi Molecule



- Rules and algorithms to optimize RNAi trigger sequence selection and chemical modification patterns
- Maximize activity, minimize off-target risk, and disallow miRNA homology
- More focus on **extra-hepatic delivery**, leading to a library of **PK/PD enhancers**, **linker chemistries**, and **targeting ligands** to facilitate extra-hepatic delivery

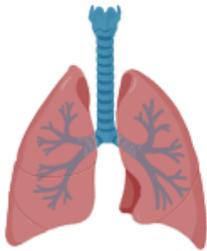
TRiM™ Platforms Drive Robust Pipeline for Multiple Tissue Types

Liver



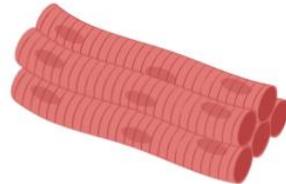
Strong clinical validation

Lung



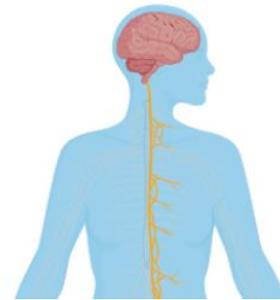
Deep lung clinical validation (RAGE)

Skeletal Muscle



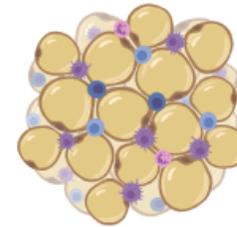
Early clinical stage

CNS



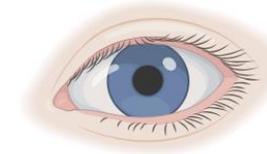
Early clinical stage

Adipose



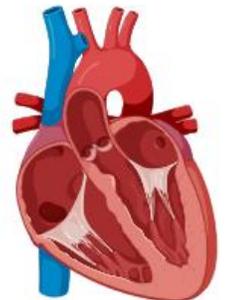
Preclinical Stage
FIH Q2, 25

Ocular



Preclinical Stage

Cardio-myocyte



Preclinical Stage

- TRiM™ technology enables oligonucleotide delivery to liver and six extrahepatic tissues

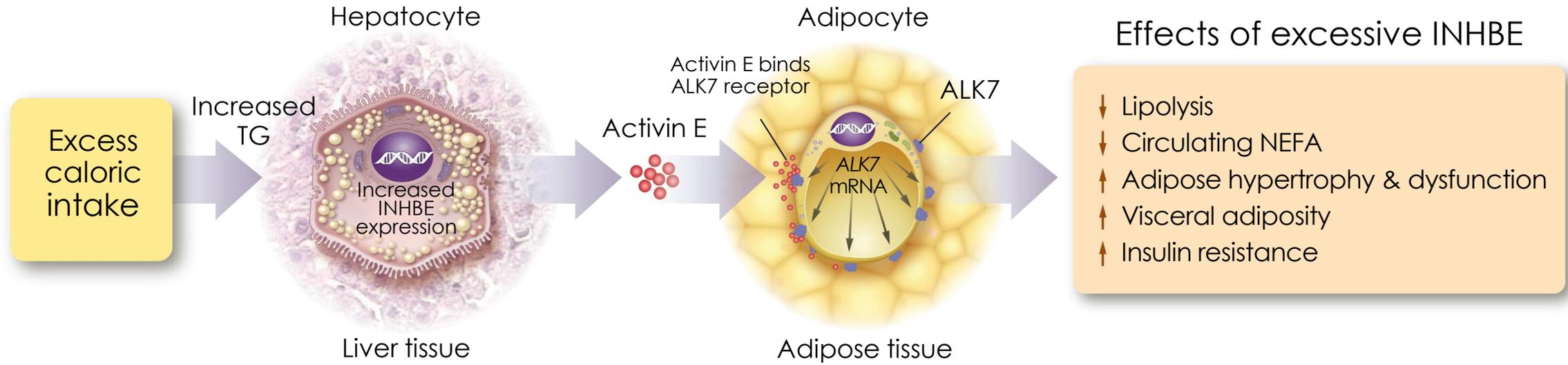
TRiM Platform has enabled 16 unique molecular entities in ongoing clinical trials

Therapeutic Area		Pre-clinical	Phase 1	Phase 2	Phase 3	Product Rights
Cardiometabolic	Plzasiran FCS/SHTG/ASCVD	[Green bar]				[Arrowhead logo]
	Zodasiran Dyslipidemia	[Green bar]				[Arrowhead logo]
	Olpasiran ASCVD	[Green bar]				AMGEN
	GSK4532990 MASH	[Green bar]				gsk
	ARO-PNPLA3 MASH	[Green bar]				[Arrowhead logo]
	ARO-INHBE Obesity	[Green bar]				[Arrowhead logo]
Pulmonary	ARO-RAGE Inflammatory Lung Diseases	[Blue bar]				[Arrowhead logo]
	ARO-MUC5AC Muco-Obstructive Lung Diseases	[Blue bar]				[Arrowhead logo]
	ARO-MMP7 Idiopathic Pulmonary Fibrosis	[Blue bar]				[Arrowhead logo]
Liver	Fazirsiran Alpha-1 Liver Disease	[Green bar]				[Arrowhead logo] Takeda
	Daplusiran/Tomligisiran Hepatitis B Virus	[Green bar]				gsk
Neuromuscular	ARO-DUX4 FSHD	[Orange bar]				[Arrowhead logo]
	ARO-DM1 Myotonic Dystrophy Type 1	[Orange bar]				[Arrowhead logo]
	ARO-ATXN2 Spinocerebellar Ataxia 2	[Dark Orange bar]				[Arrowhead logo]
Other	ARO-C3 Complement Mediated Disease	[Green bar]				[Arrowhead logo]
	ARO-CFB Complement Mediated Disease	[Green bar]				[Arrowhead logo]

ARO-INHBE Program Preclinical data



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

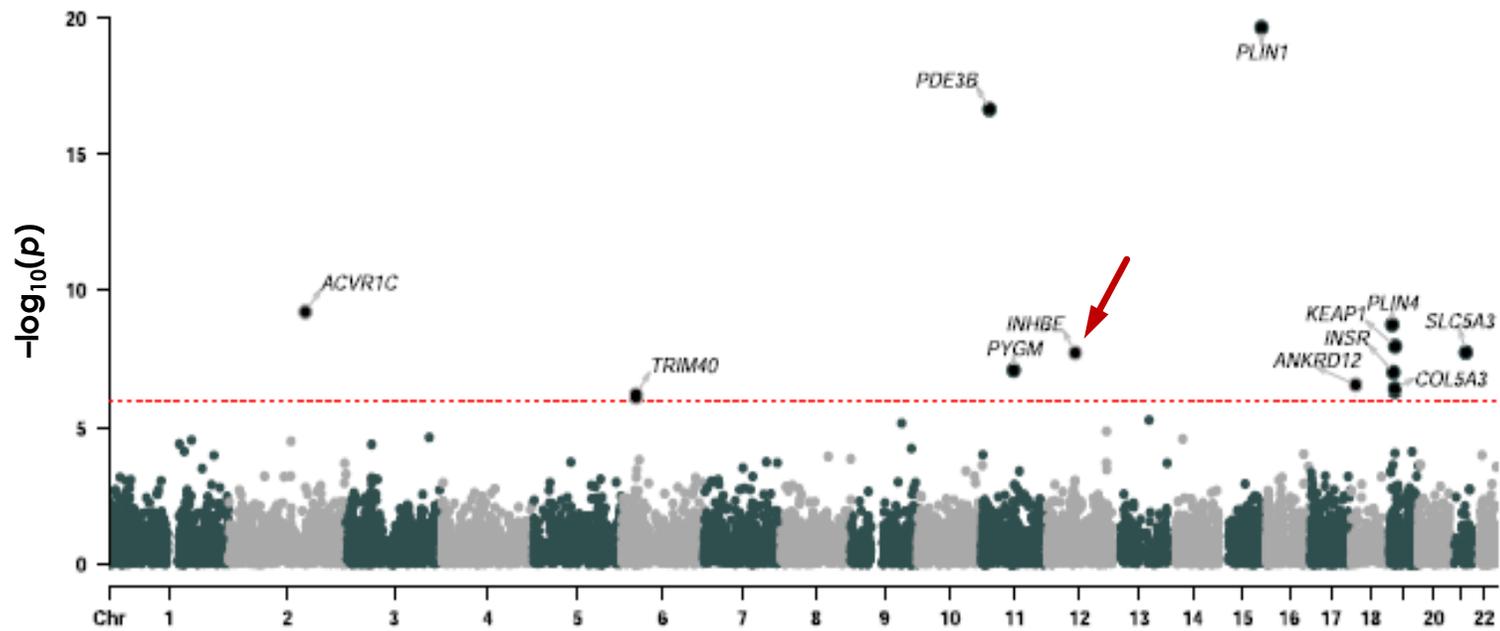


- Inhibin subunit beta E (*INHBE*) is primarily expressed in hepatocytes
- Activin E (dimeric *INHBE* protein) is potent hepatokine secreted by the liver
- Circulating Activin E promotes adipose storage of fats by suppressing lipolysis in adipose tissue

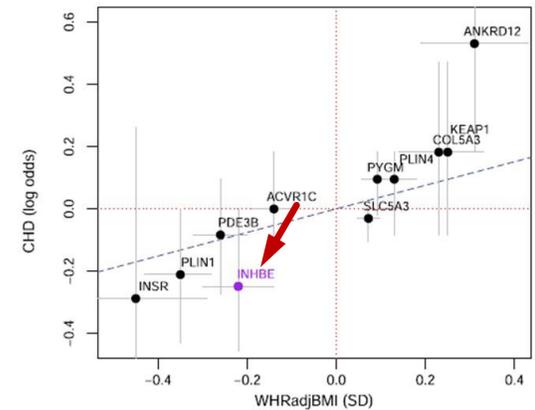
pLOF Variants of INHBE are Associated with Reduced Abdominal Fat and Lower Risk of Coronary Heart Disease and type 2 Diabetes

Human Genome-wide Association Study

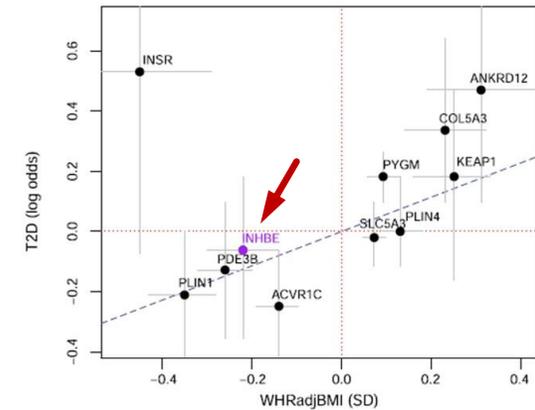
Waist-to-Hip Ratio Adjusted for BMI



CHD Risk



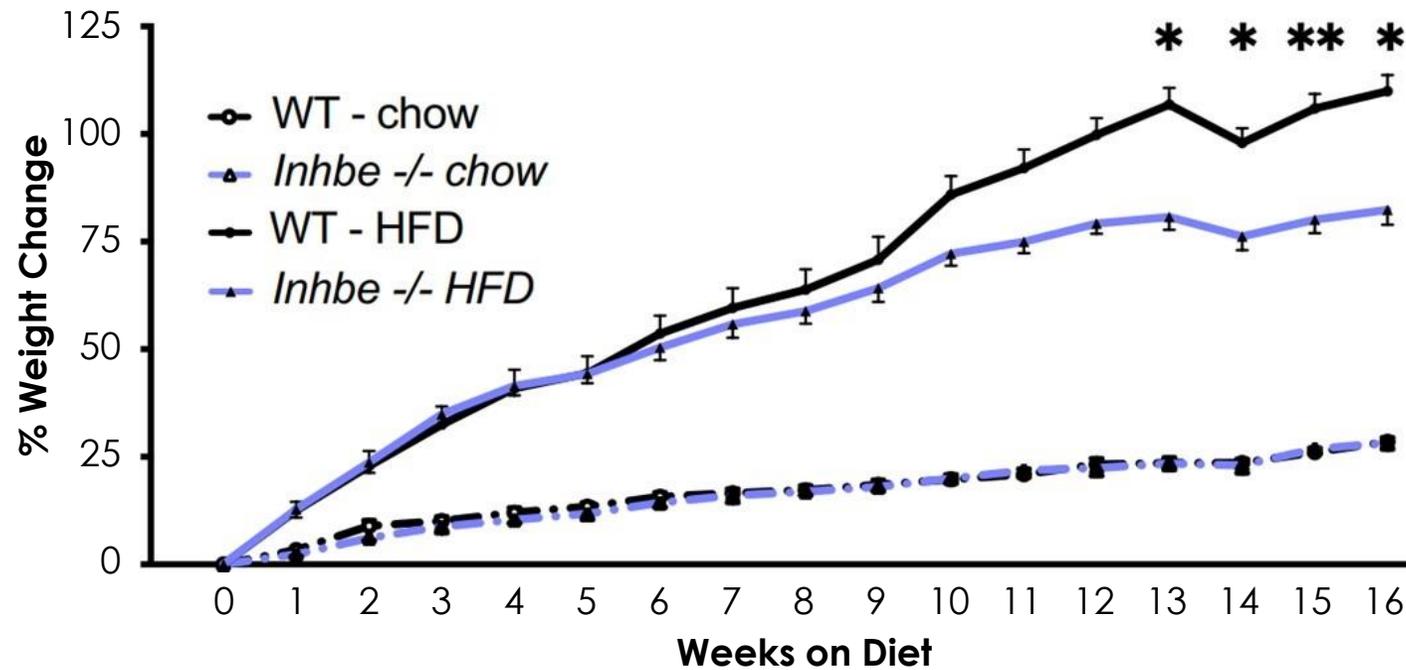
T2D Risk



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

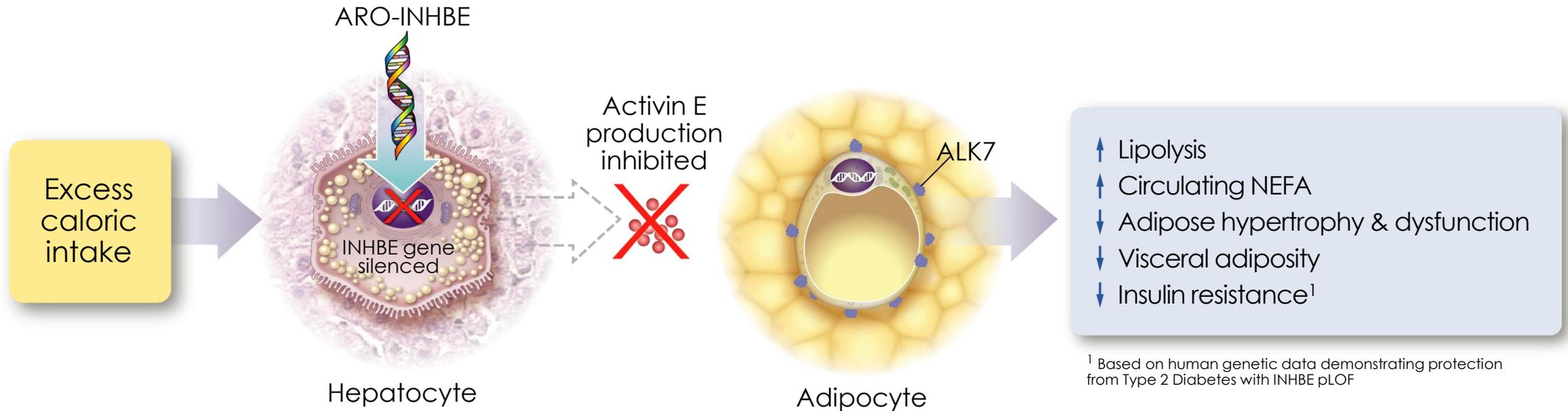
INHBE Knockout Mice on a High-fat Diet Exhibit Reduced Body Weight and Increased Adipose Lipolysis

Body Weight Gain



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

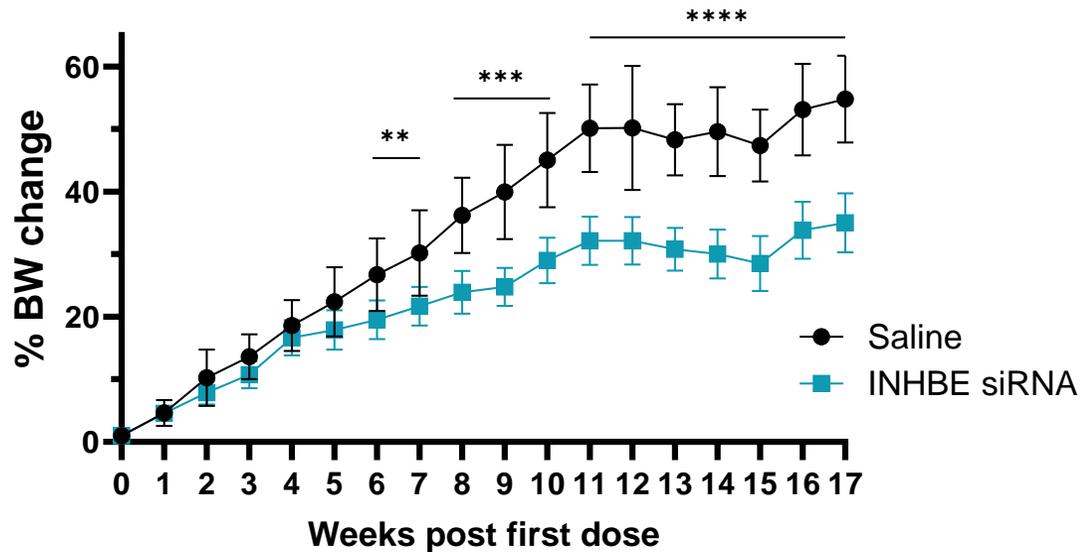
Silencing Hepatic *INHBE* May Inhibit Maladaptive Activin E – ALK7 Signaling and Improve Adipose Dysfunction in Obesity



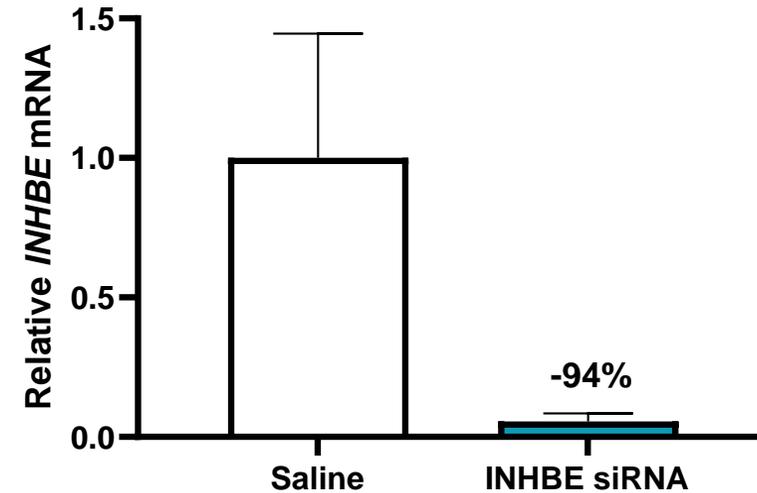
*Based on human genetic data demonstrating protection from Type 2 Diabetes with *INHBE* pLOF.

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

Body Weight Change



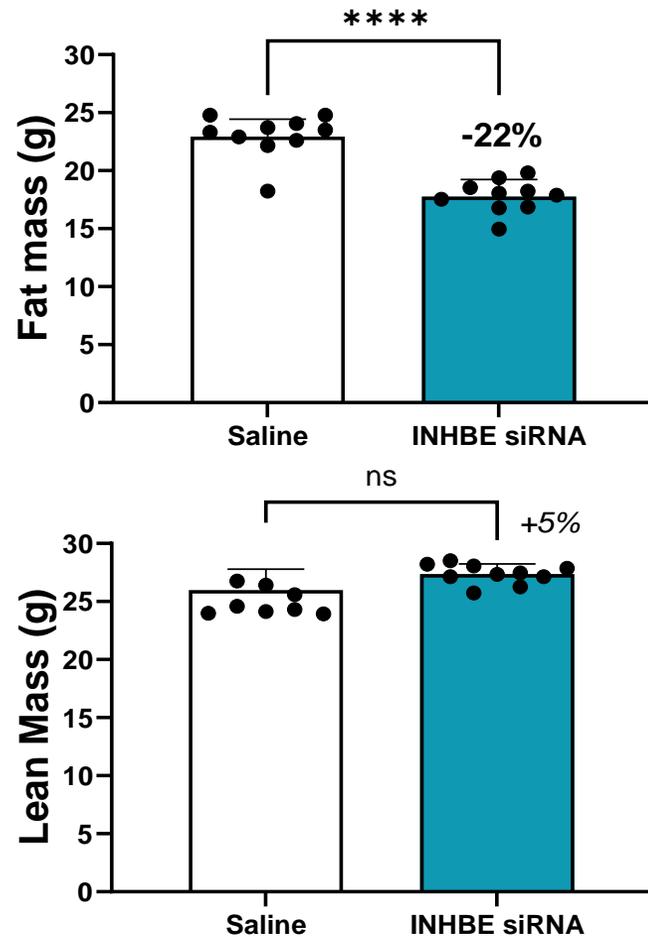
Liver *INHBE* mRNA Expression



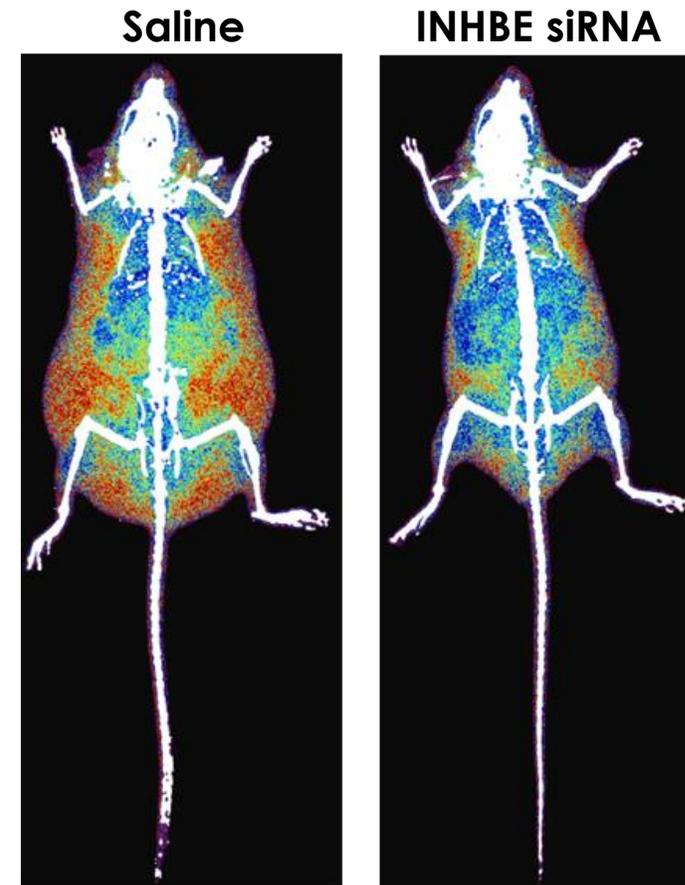
- Mice on a high calorie diet treated with an *INHBE* siRNA exhibit a **19% suppression** in BW gain relative to vehicle controls
- Mice treated with control RISC loading blocked version of the *INHBE* siRNA are not protected from BW gain

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

Body Composition

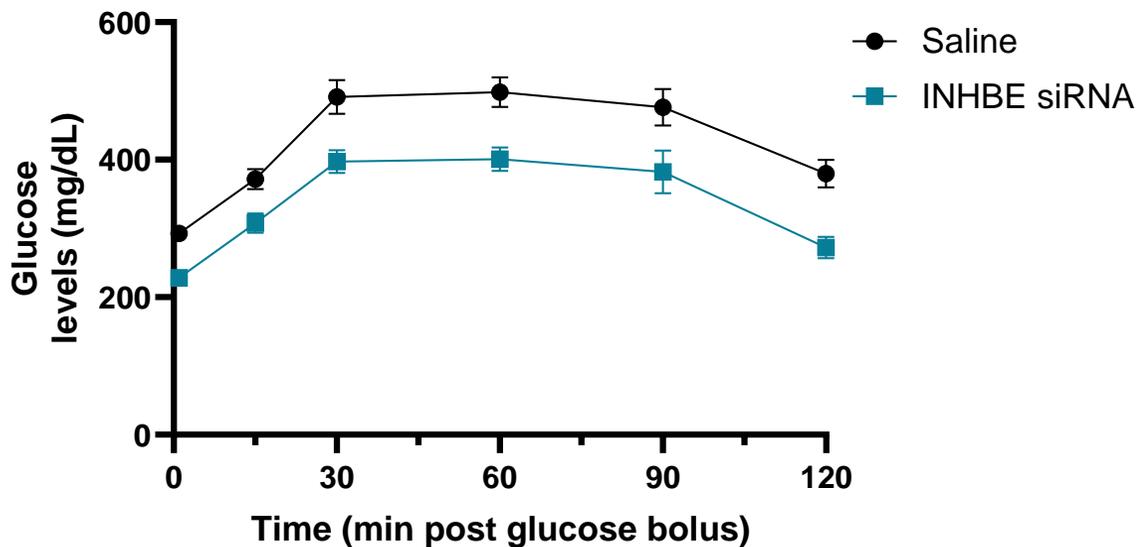


DEXA Images

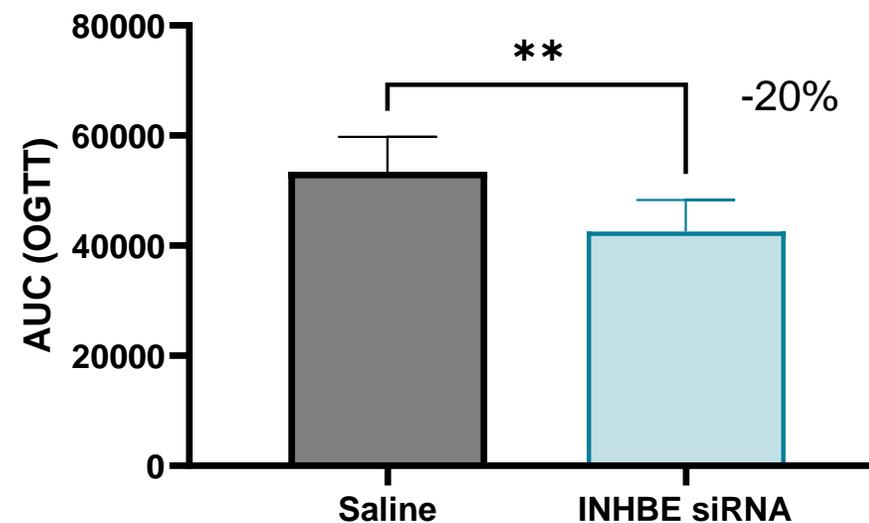


Trend to Improved Glycemic Control in DIO Mice with *INHBE* Silencing

Oral Glucose Tolerance Test



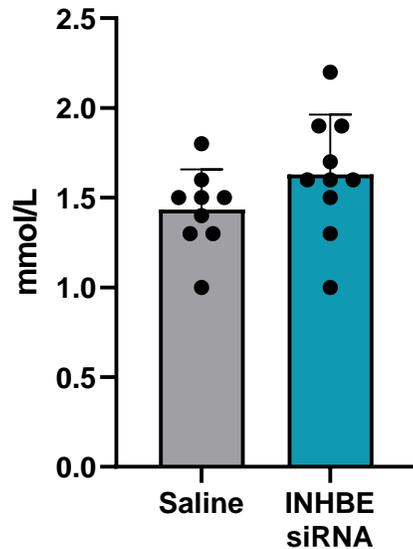
Glucose AUC



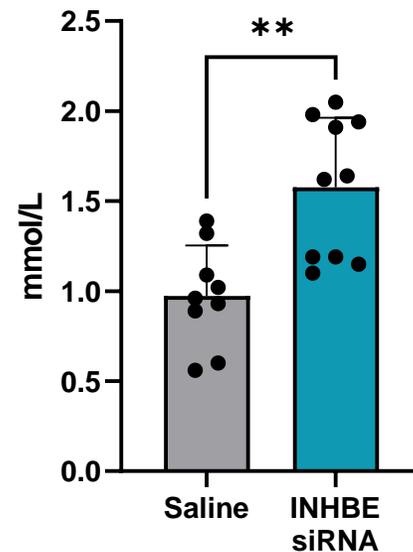
Hepatic *INHBE* Silencing in DIO Mice May Enhance Catecholamine Sensitivity, Increasing Lipid Mobilization and Oxidation

Mice Treated with a Beta 3 Adrenergic Agonist to Stimulate Lipolysis

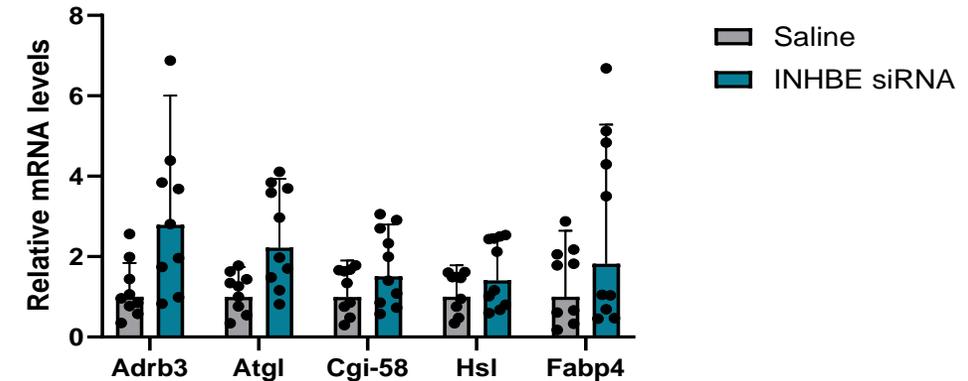
NEFA



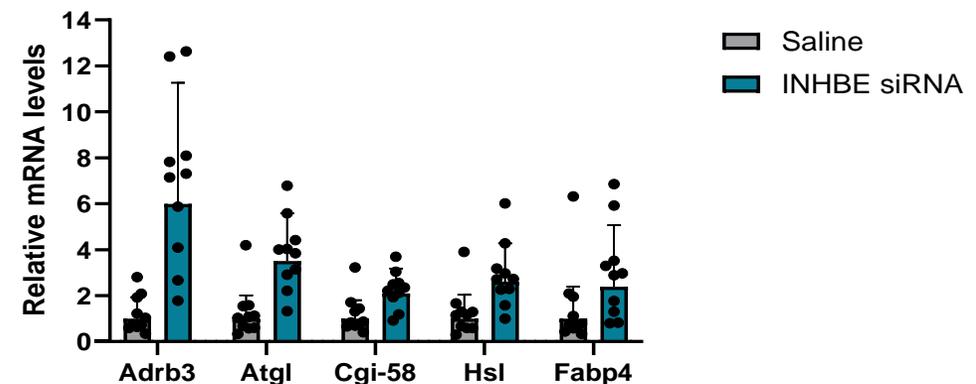
β -hydroxybutyrate



Lipolytic genes in iWAT

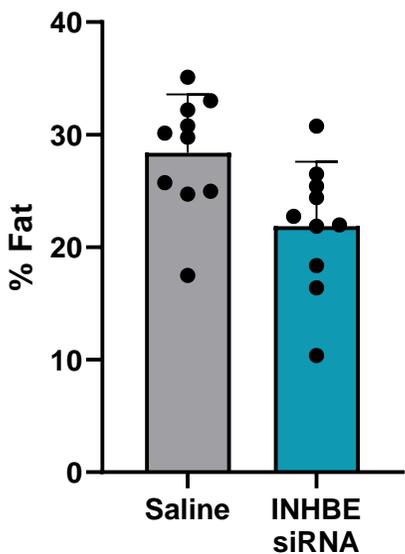


Lipolytic genes in pgWAT

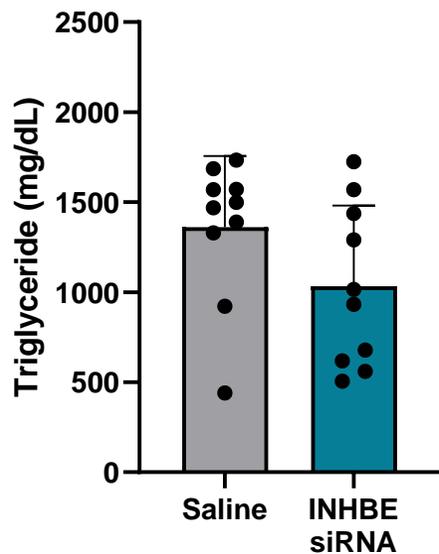


Increased Lipid mobilization in *INHBE*-silenced DIO Mice is not Associated With Liver Steatosis

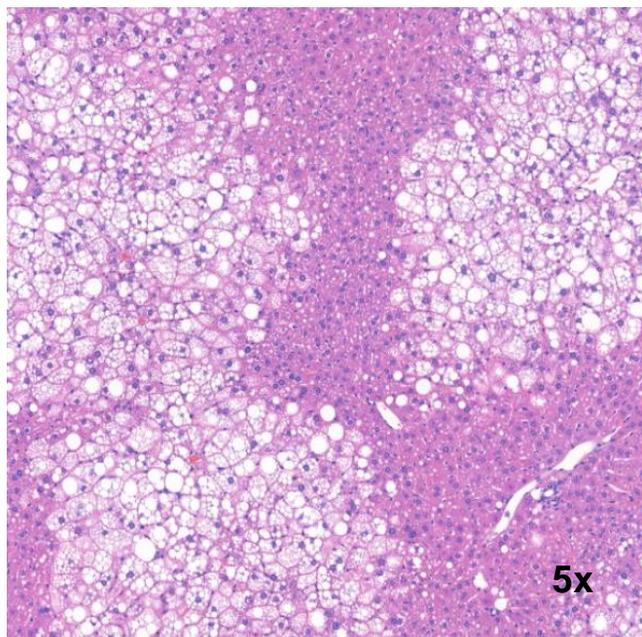
Liver Fat Composition (DEXA)



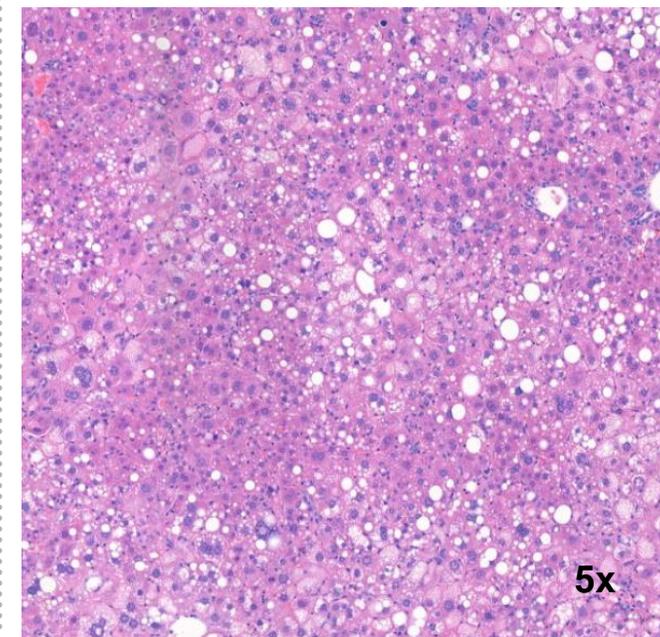
Liver Triglycerides



Saline



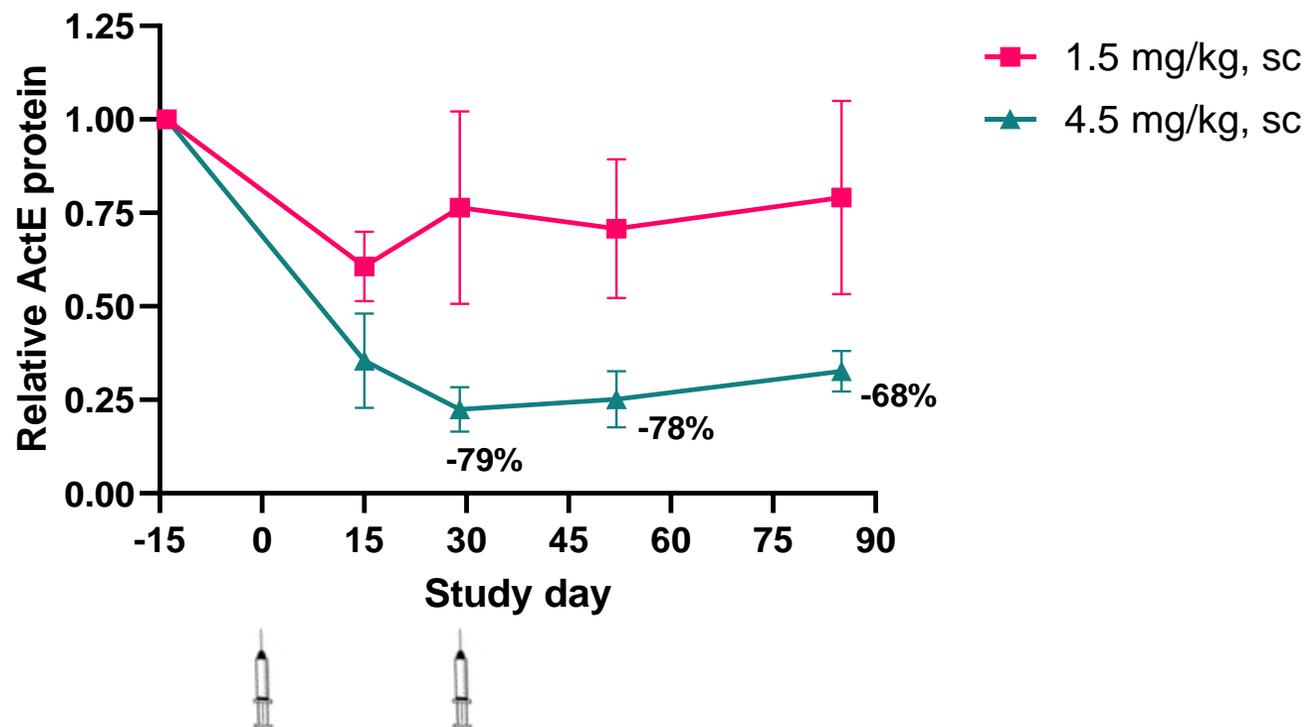
INHBE siRNA



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

Cyno Serum Activin E Protein Expression ARO-INHBE

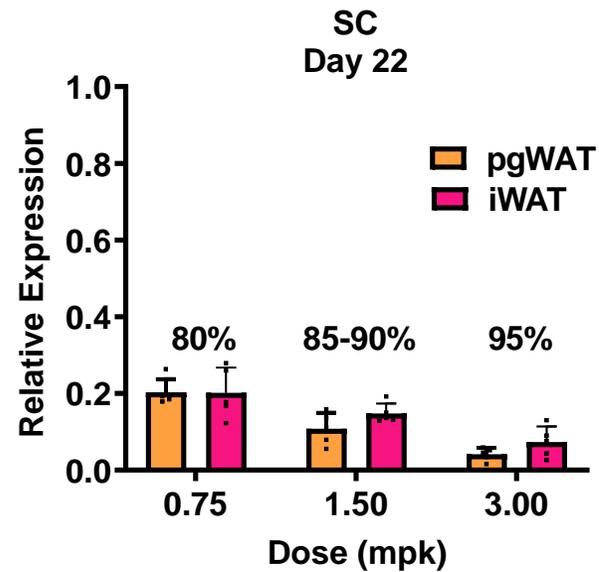


TRiM™ Platform for Adipose Delivery

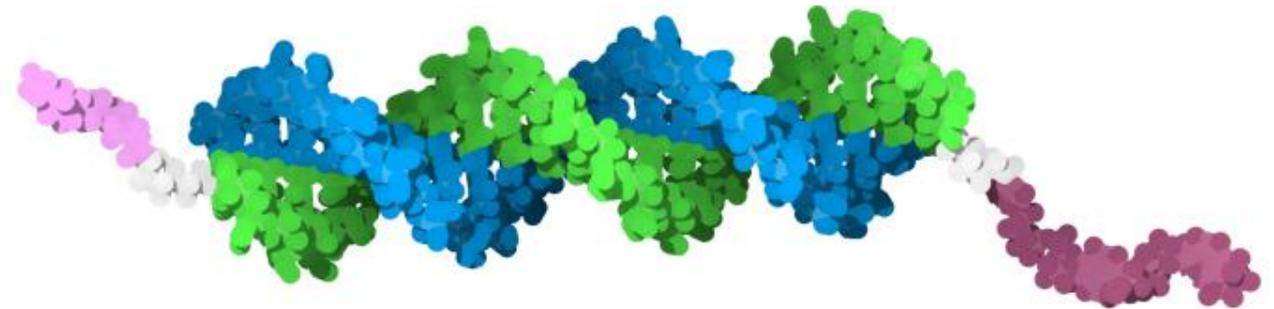


TRiM™ Adipose Platform Achieves Deep Gene Knockdown in Mouse

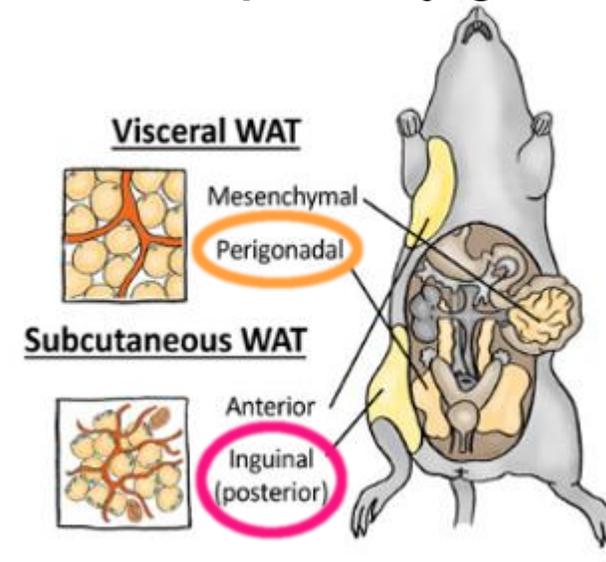
Tissue Adipoq mRNA Expression



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



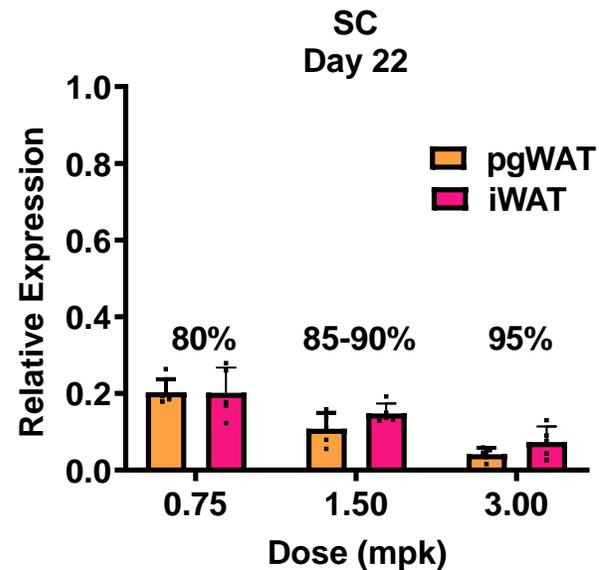
Dual Lipid Conjugate



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

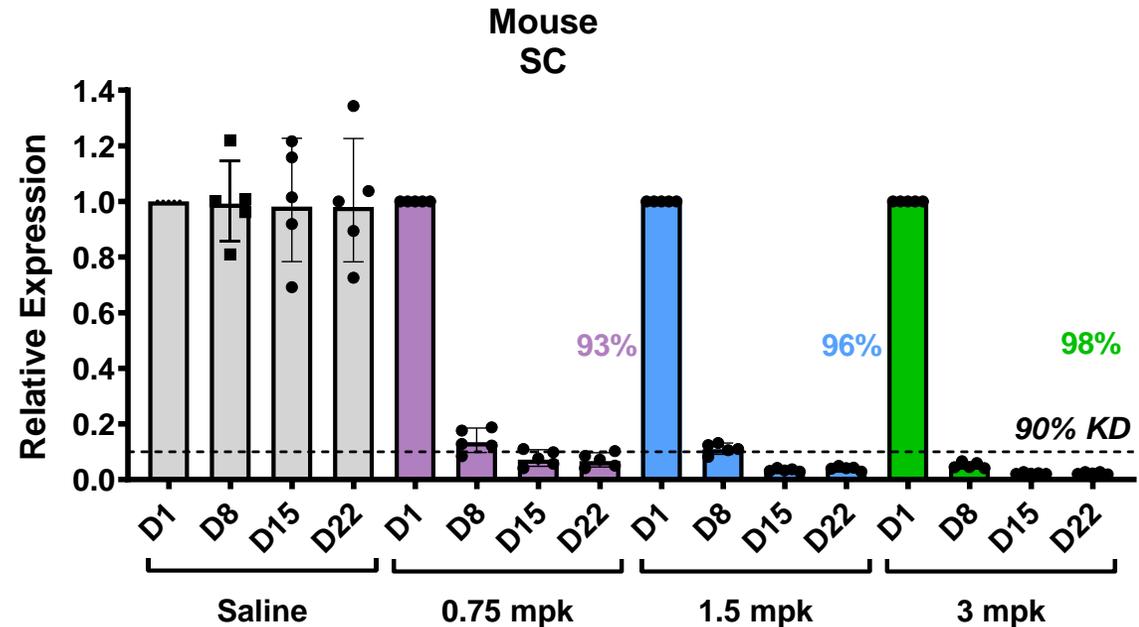
Platform Achieves Deep Serum Protein Knockdown in Mouse

Tissue Adipoq mRNA Expression



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

Serum Adipoq Protein Expression

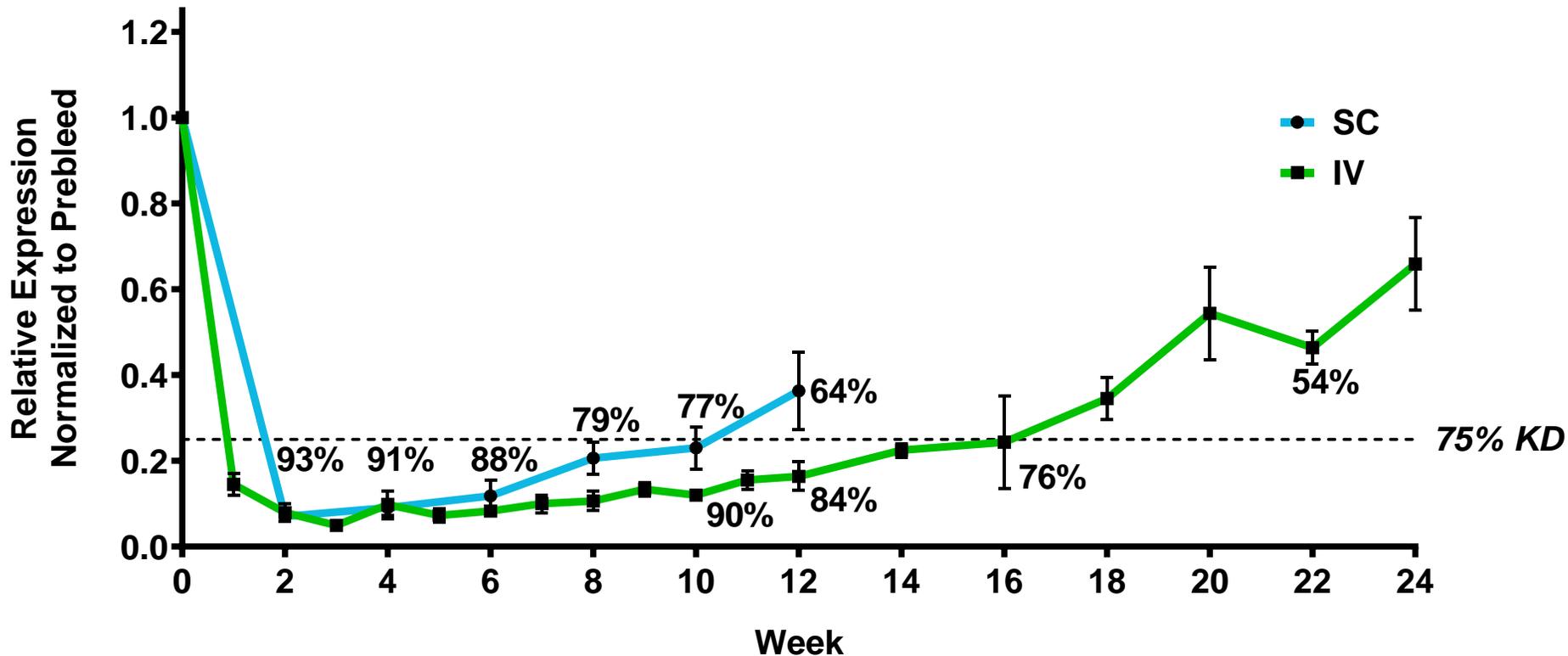


- $\geq 90\%$ serum protein knockdown achieved in same dose range
- Corroborates with gene KD

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

Serum Adipoq Protein Expression

Mouse
SC vs IV, 2 mpk
Weeks 1-24



SC Dosing

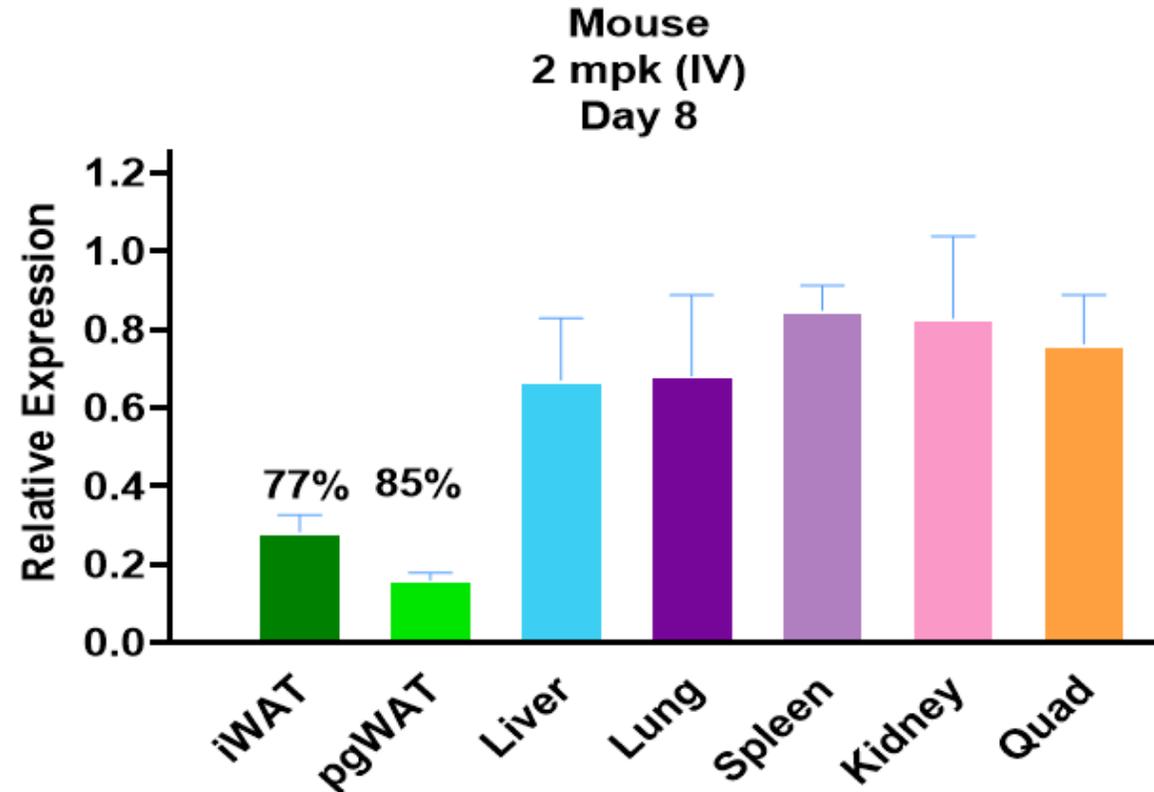
- ~90% serum Adipoq protein KD maintained through week 6
- $\geq 75\%$ KD maintained through week 10

IV Dosing

- ~90% serum Adipoq protein KD maintained through week 10
- $\geq 75\%$ KD maintained through week 16

Platform Demonstrates Functional Tissue Selectivity in Mouse

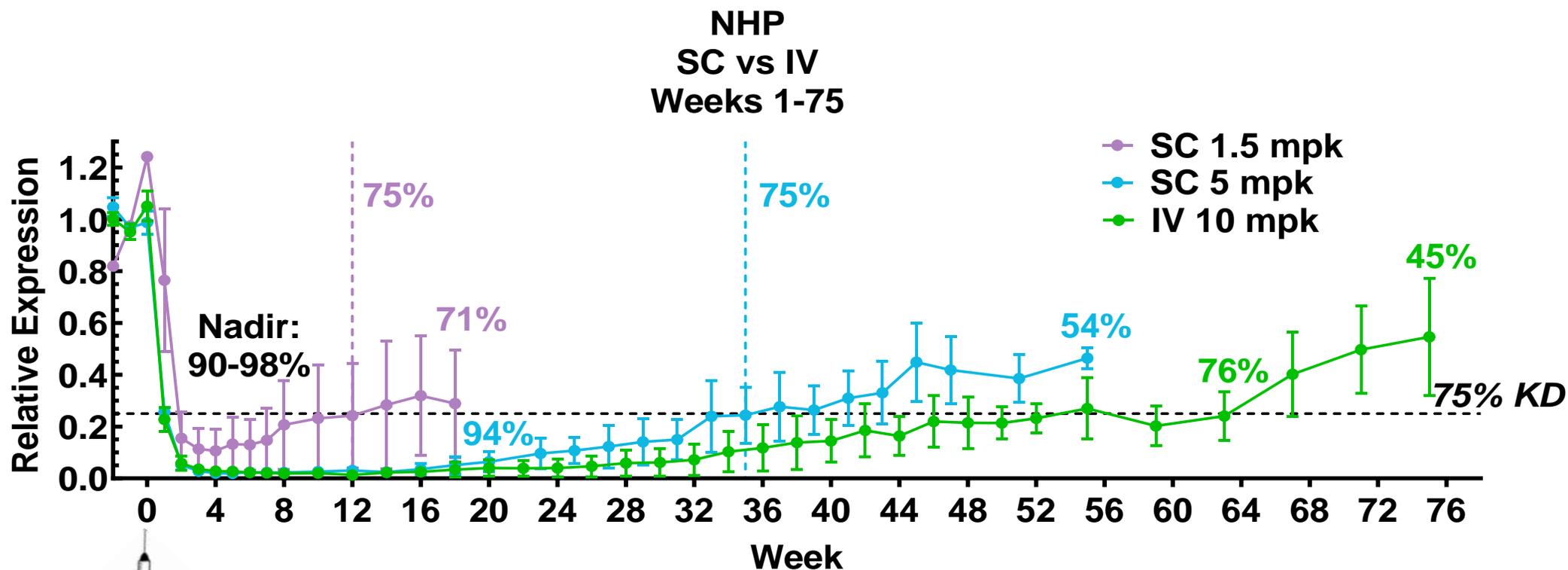
Tissue SOD1 mRNA Expression



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: $\geq 75\%$ KD maintained for ~3 months
Single SC dose 5 mpk: $\geq 75\%$ KD maintained for ~9 months
Single IV dose 10 mpk: $\geq 75\%$ KD maintained for ~16 months

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

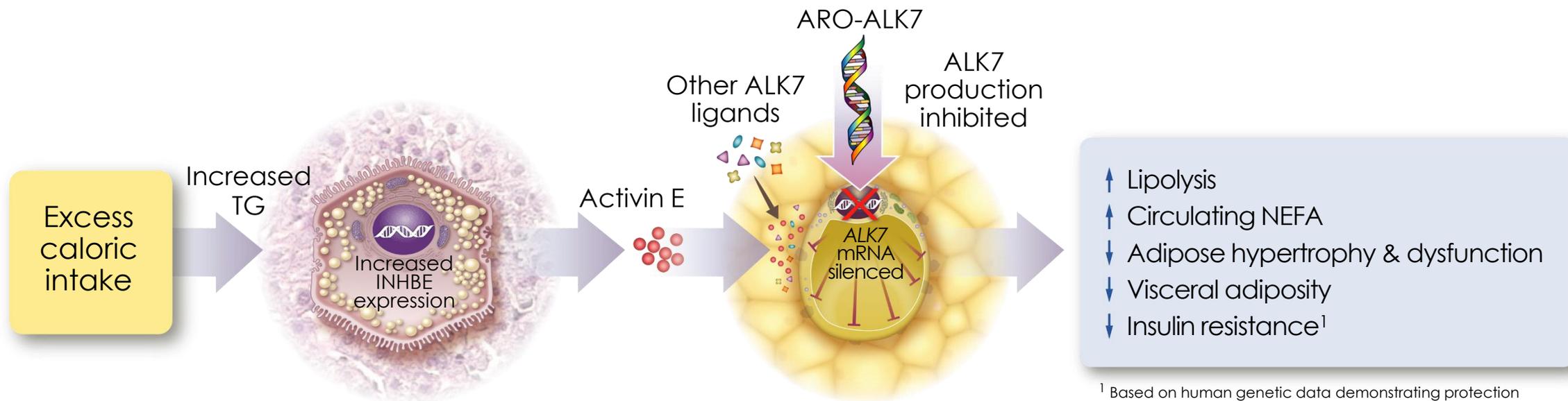
 Minimal findings in clinical chemistry, hematology, and coagulation

 Histopathology: no adverse drug-related findings at Day 16 and Day 29 necropsies

ARO-ALK7 Program Preclinical Data



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

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

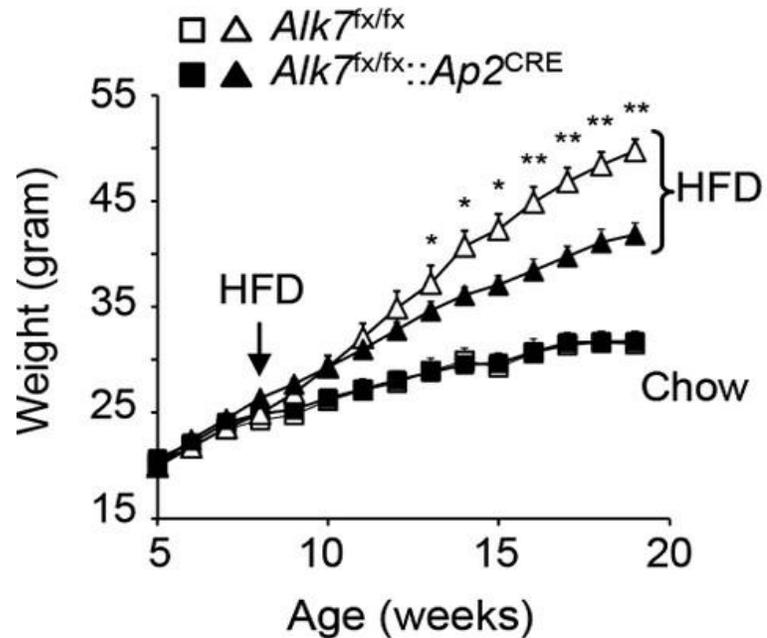
Variant	Minor allele frequency (%)	WHRadjBMI		Type 2 diabetes	
		β (95% CI)	P value	OR (95% CI)	P value
Asn150His	1.1	-0.089 (-0.11, -0.067)	3.4×10^{-17}	0.88 (0.83, 0.94)	8.7×10^{-5}
Ile195Thr	0.2	-0.15 (-0.09, 0.19)	1.0×10^{-9}	0.79 (0.67, 0.93)	0.005
Ile482Val	7.2	-0.019 (-0.01, -0.027)	1.6×10^{-5}	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.

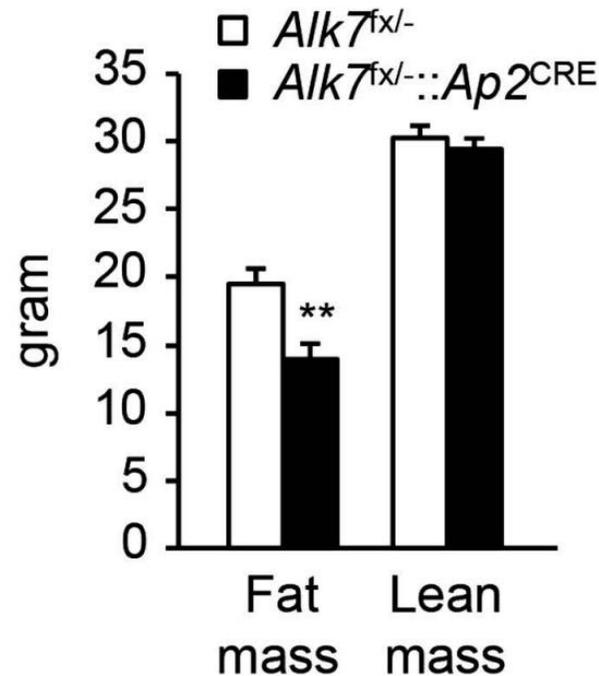
Emdin et al, *Diabetes* 2019; 68(1):226-234. DOI: 10.2337/DB18-0857

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

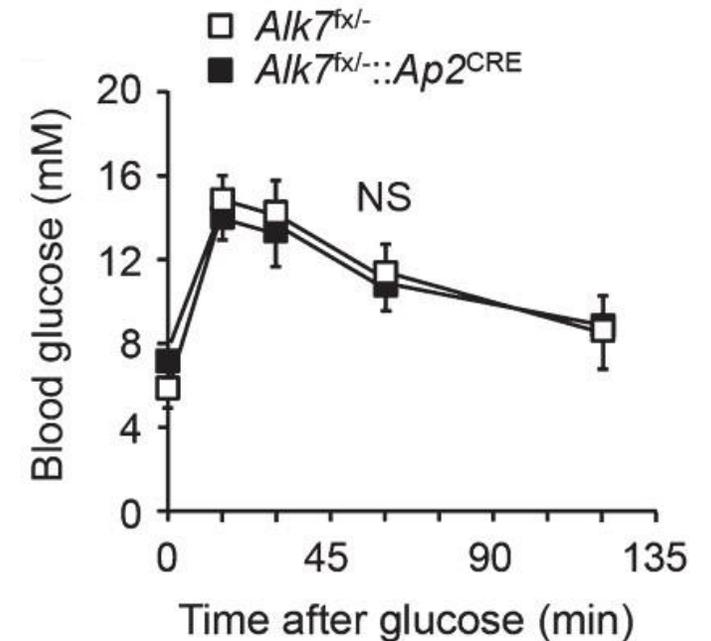
Body Weight



Body Composition (MRI)



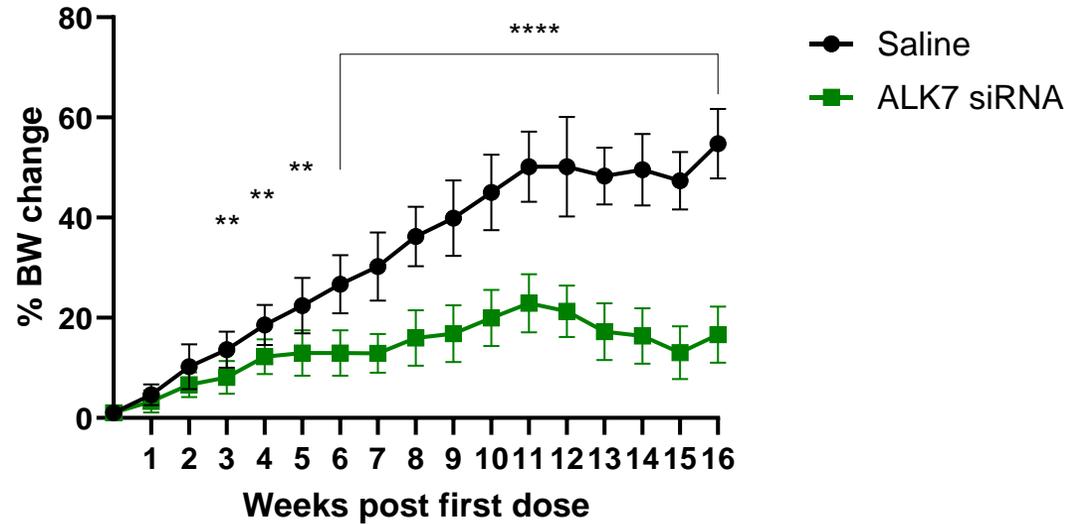
Oral Glucose Tolerance Test



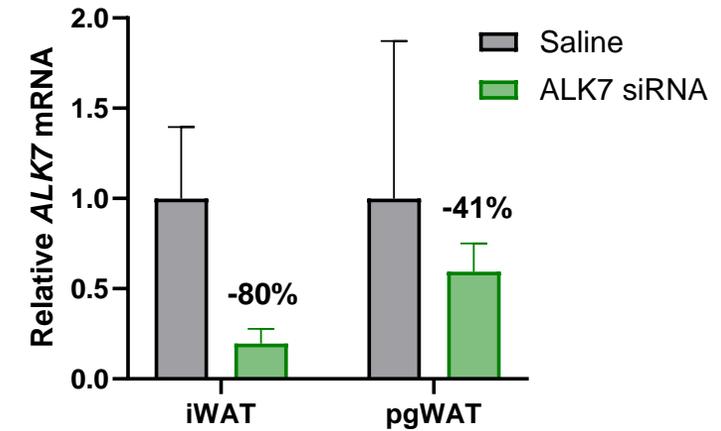
Guo et al, eLife 2014;3:e03245. DOI: 10.7554/eLife.03245

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

% Body Weight Change



WAT *ALK7* mRNA expression



Mice on a high-fat diet treated with an *ALK7* siRNA exhibit a 39% suppression in BW gain relative to controls

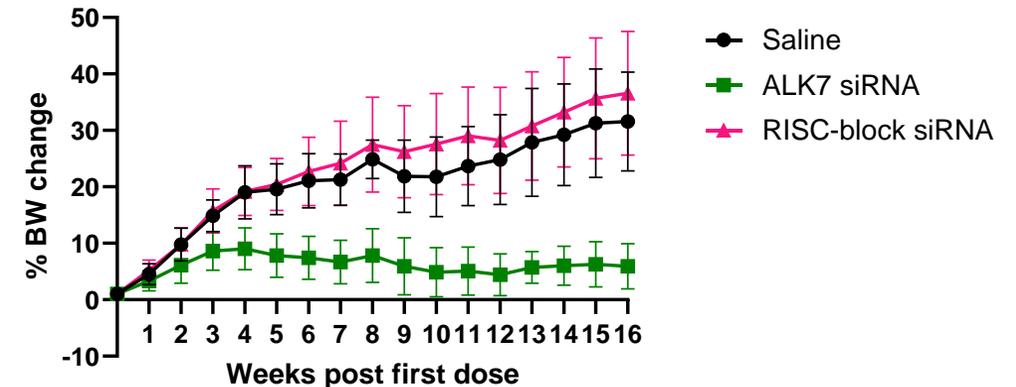


Weekly 3 mg/kg SC dosing silenced ~80% *ALK7* mRNA in iWAT and ~40% in pgWAT



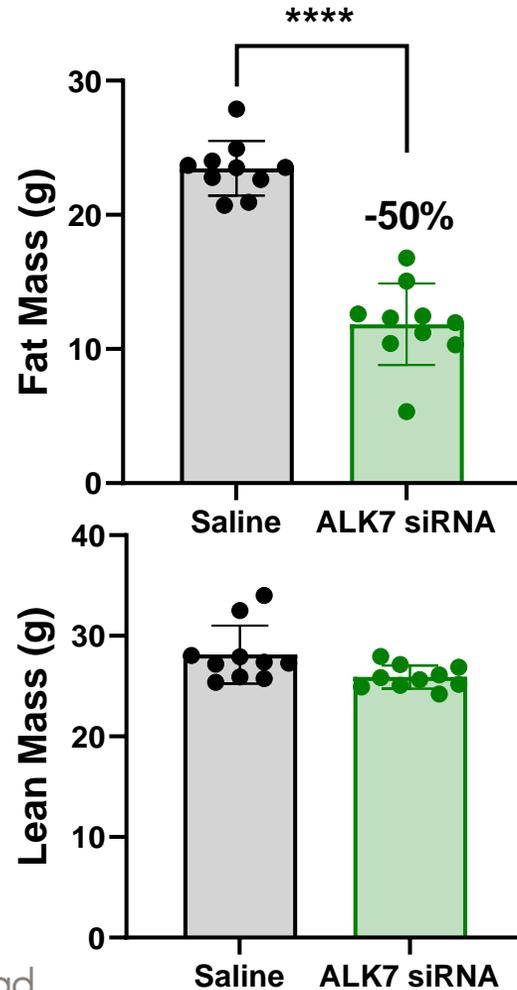
Mice treated with control RISC loading blocked version of the *ALK7* siRNA were not protected from BW gain

% Body Weight Change

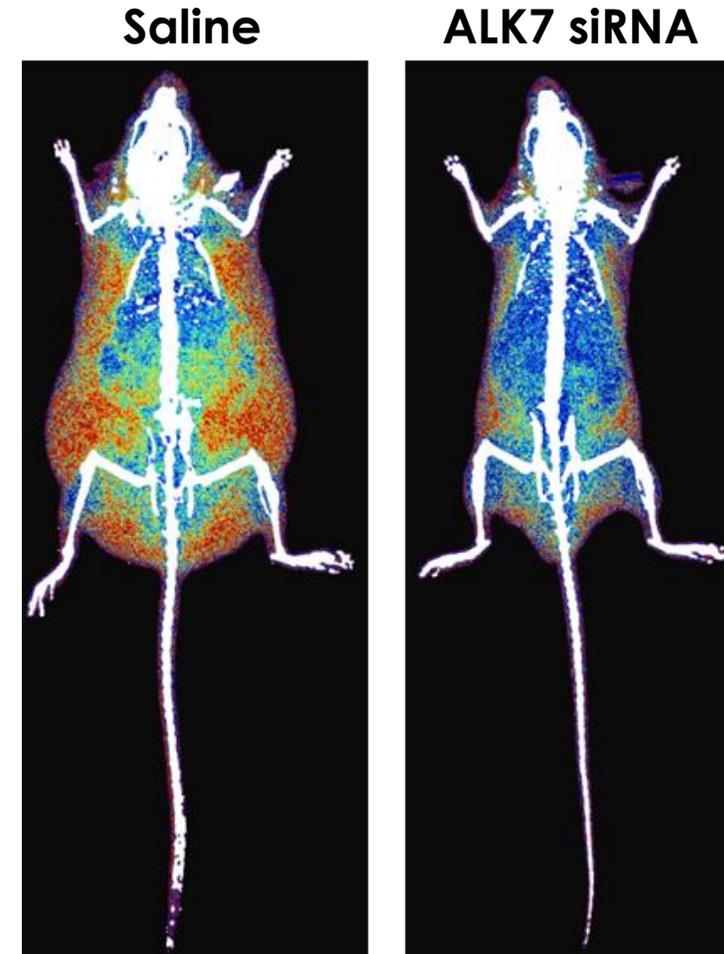


Adipose ALK7 Silencing Reduces Fat Mass and Preserves Lean Mass in DIO Mouse Model

Body Composition



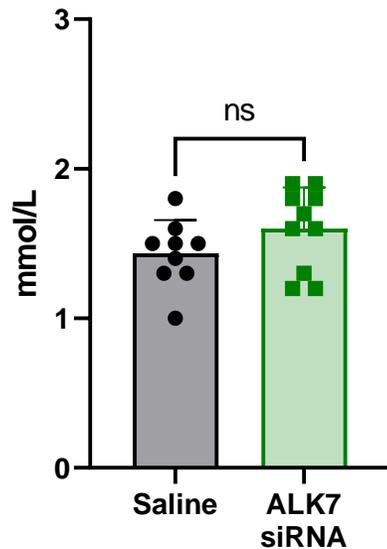
DEXA images



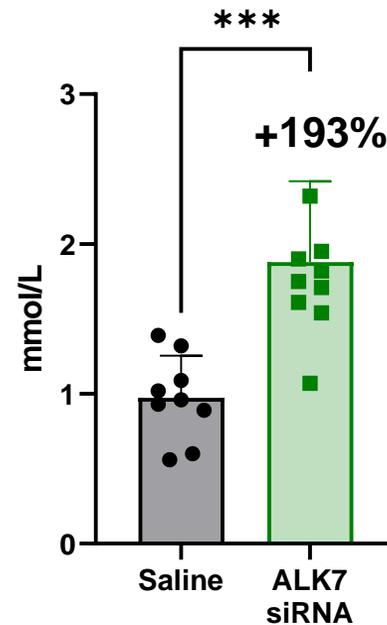
Adipose *ALK7* Silencing in DIO Mice May Enhance Catecholamine Sensitivity, Increasing Lipid Mobilization and Oxidation

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

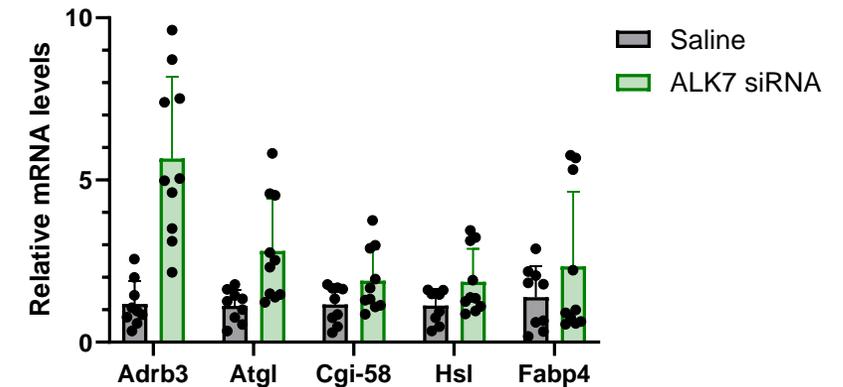
NEFA



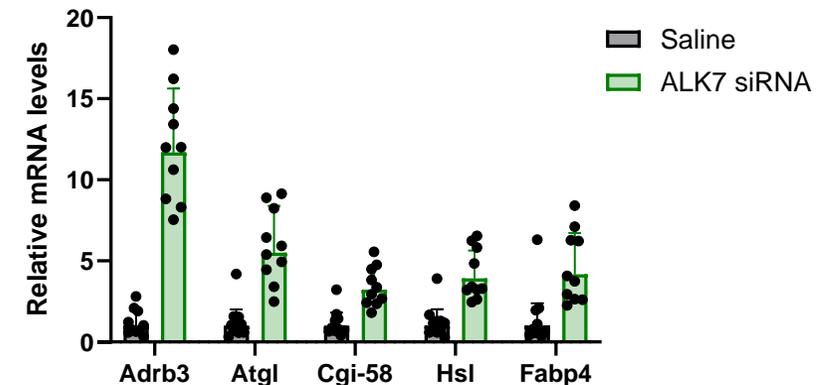
B-hydroxybutyrate



Lipolytic genes in iWAT

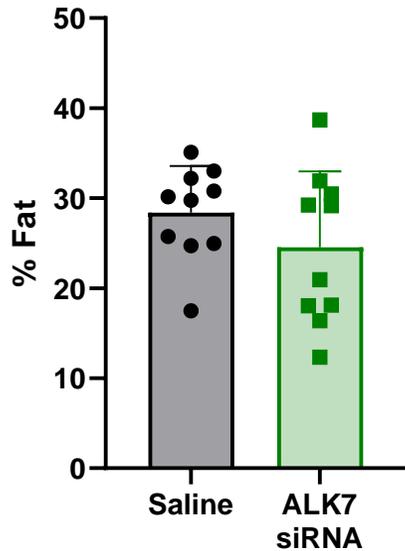


Lipolytic genes in pgWAT

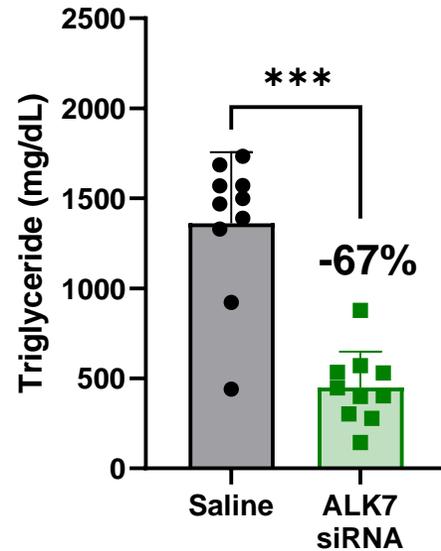


Increased Lipid Mobilization in *ALK7*-silenced DIO Mice is Not Associated With Liver Steatosis

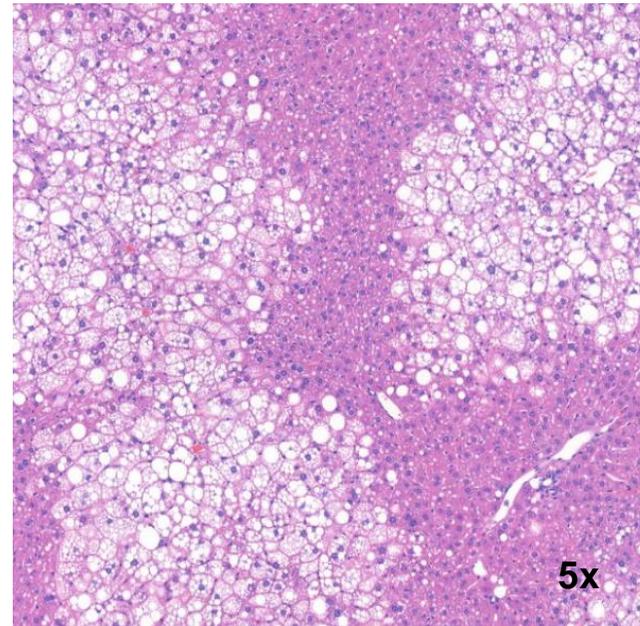
Liver Fat Composition (DEXA)



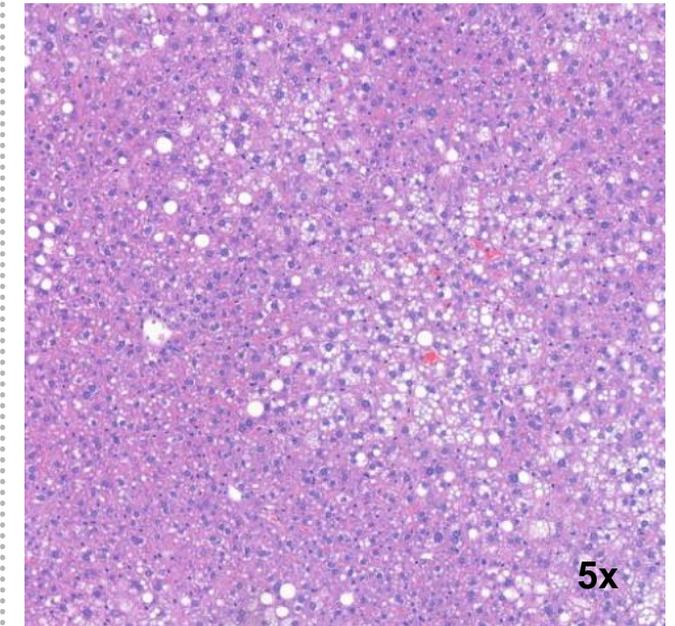
Liver Triglycerides



Saline



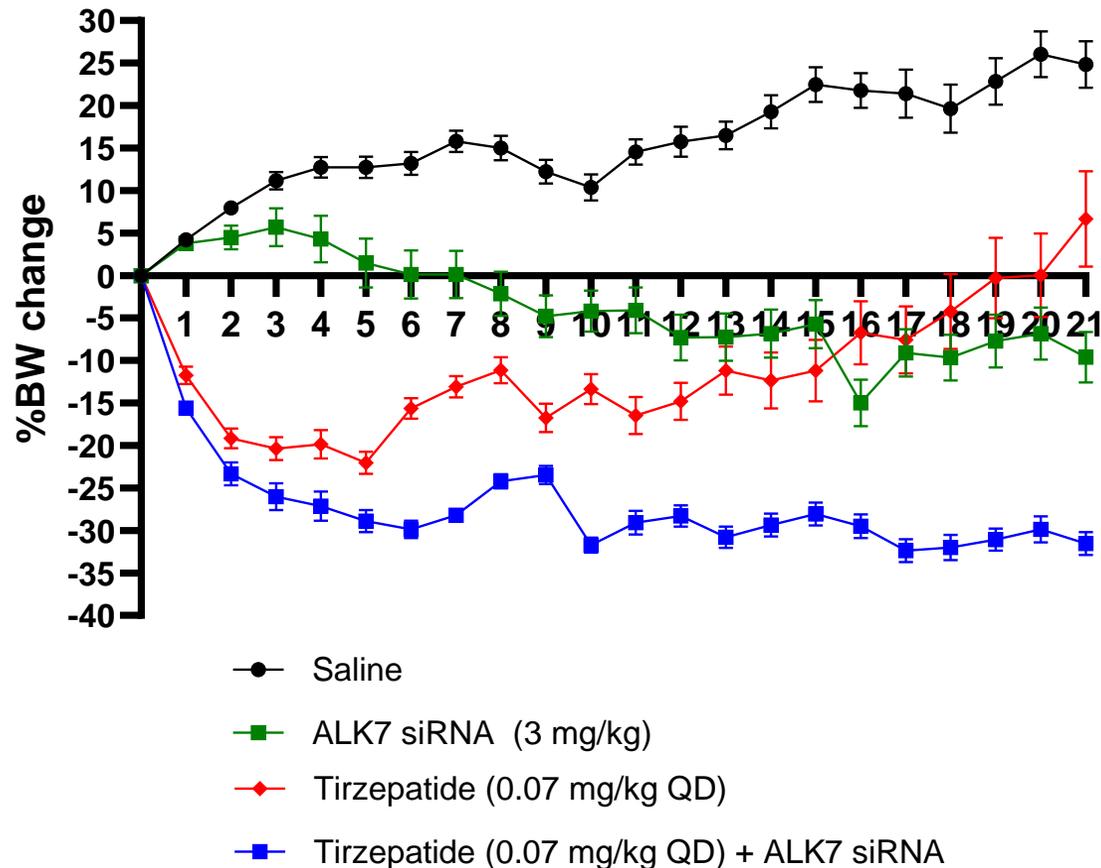
ALK7 siRNA



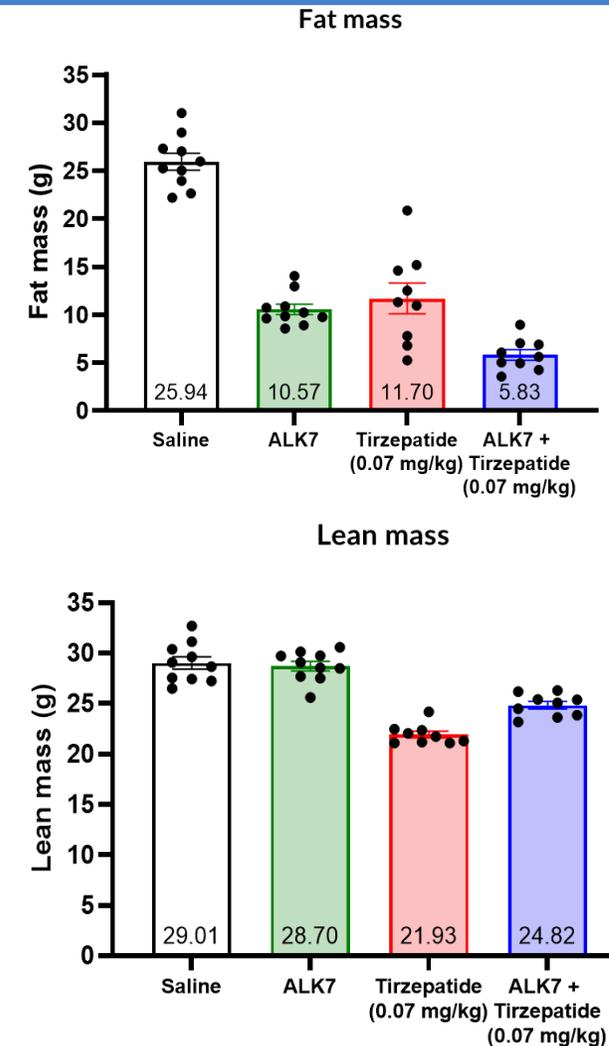
H&E shows less liver fat accumulation with adipose *ALK7* silencing relative to saline controls

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

Body Weight Change

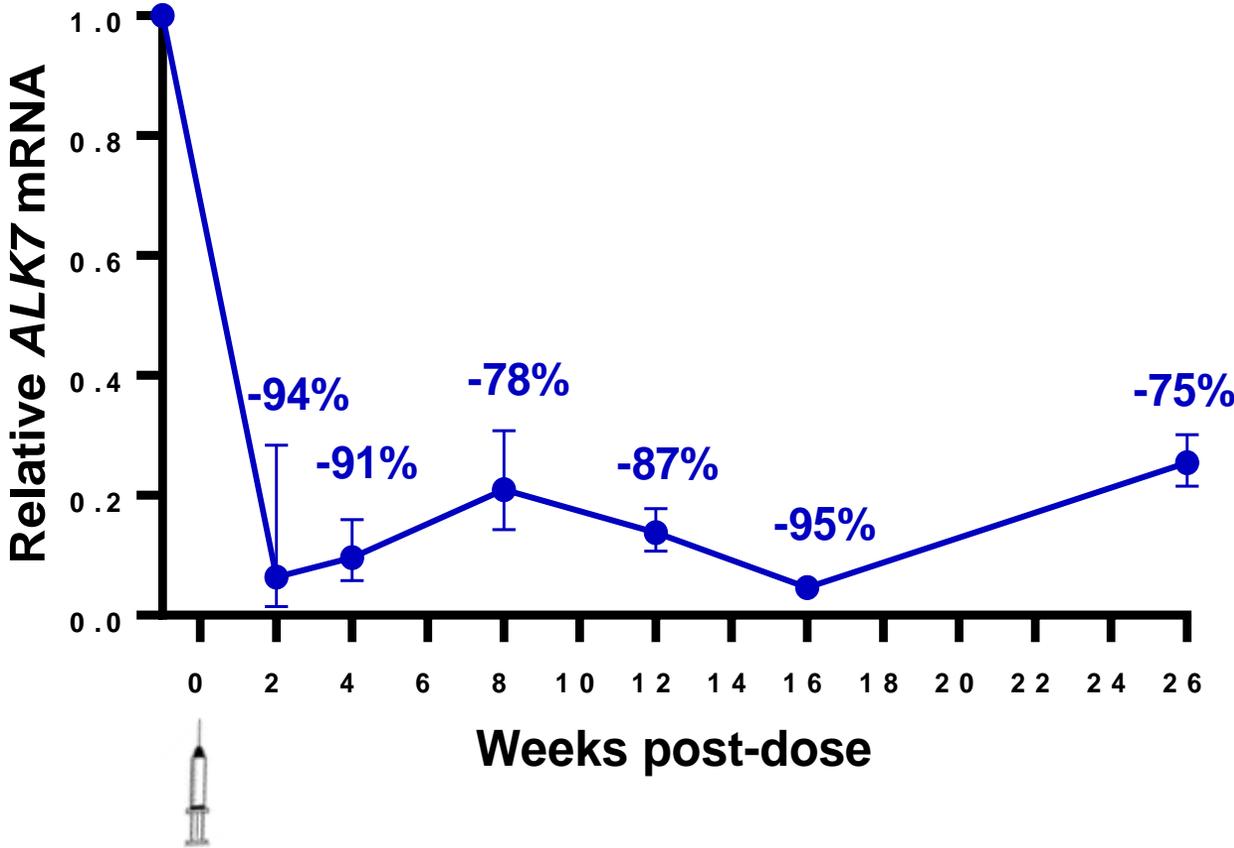


Body Composition



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)



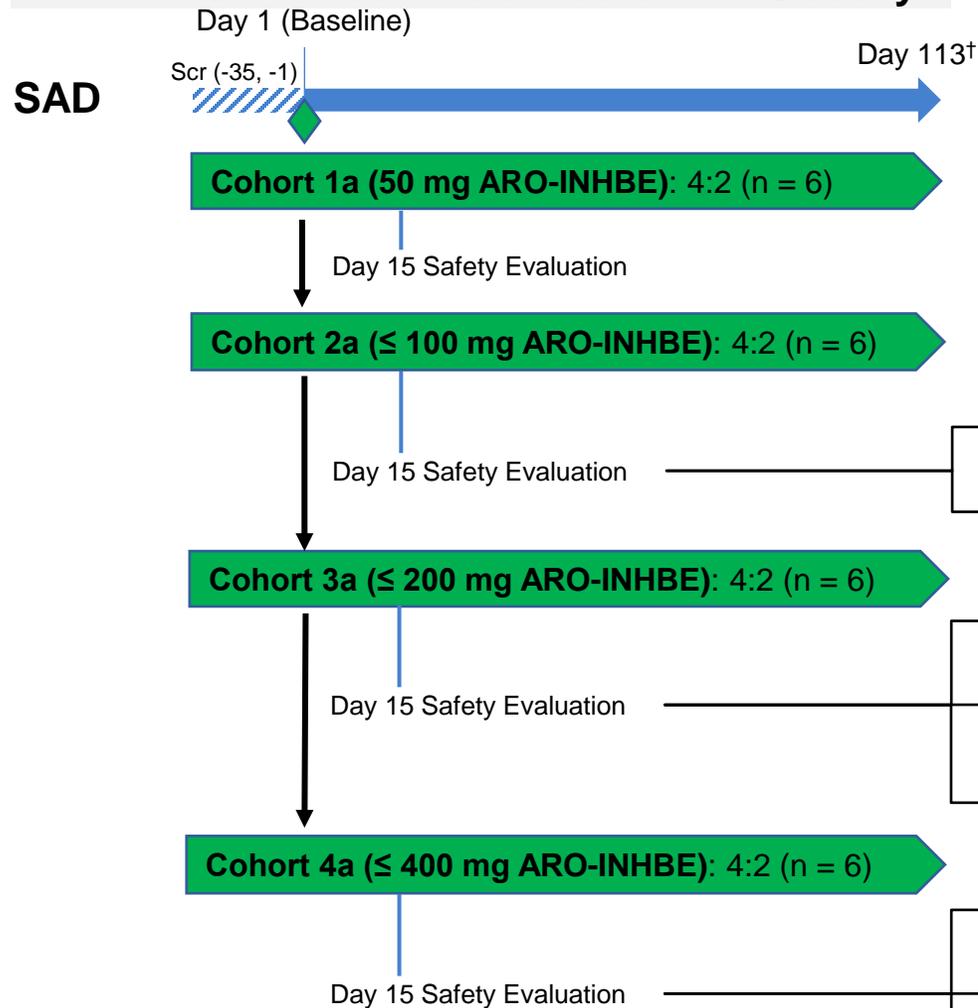
ARO-INHBE and ARO-ALK7 – Clinical Trial Designs and Status



ARO-INHBE Integrated Study Design (Part 1A/1B/2)

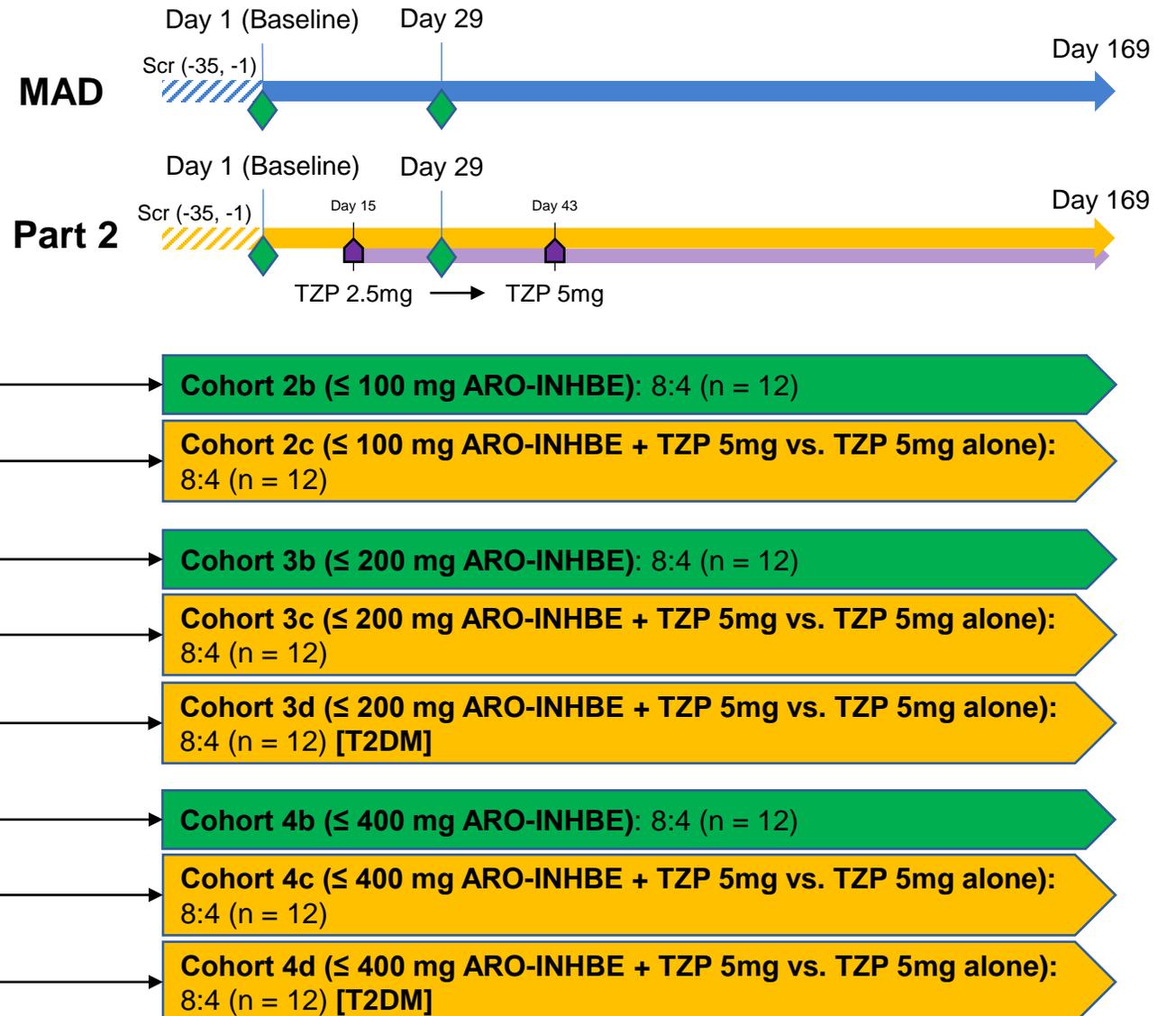
◆ ARO-INHBE
 ▲ Tirzepatide

Part 1A SAD: Adult Volunteers with Obesity



Part 1B MAD: Adult Volunteers with Obesity without T2DM

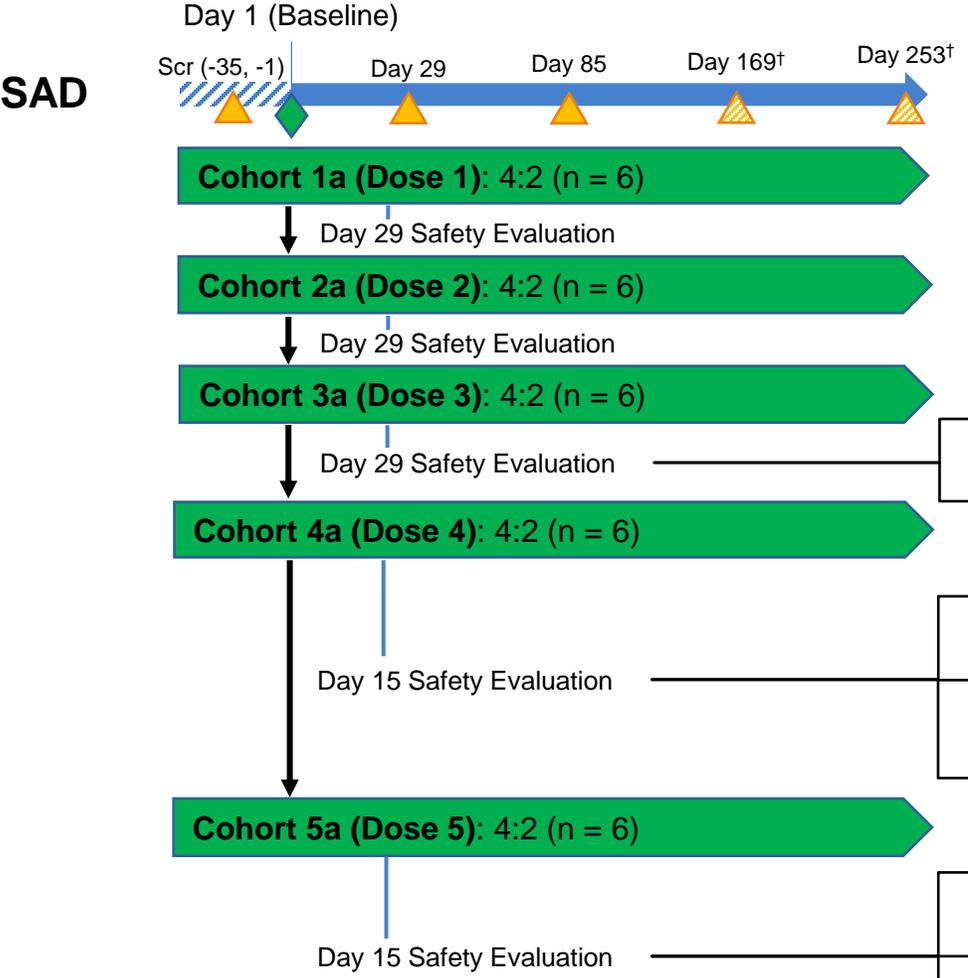
Part 2: Combination Treatment Patients Obesity with/without T2DM



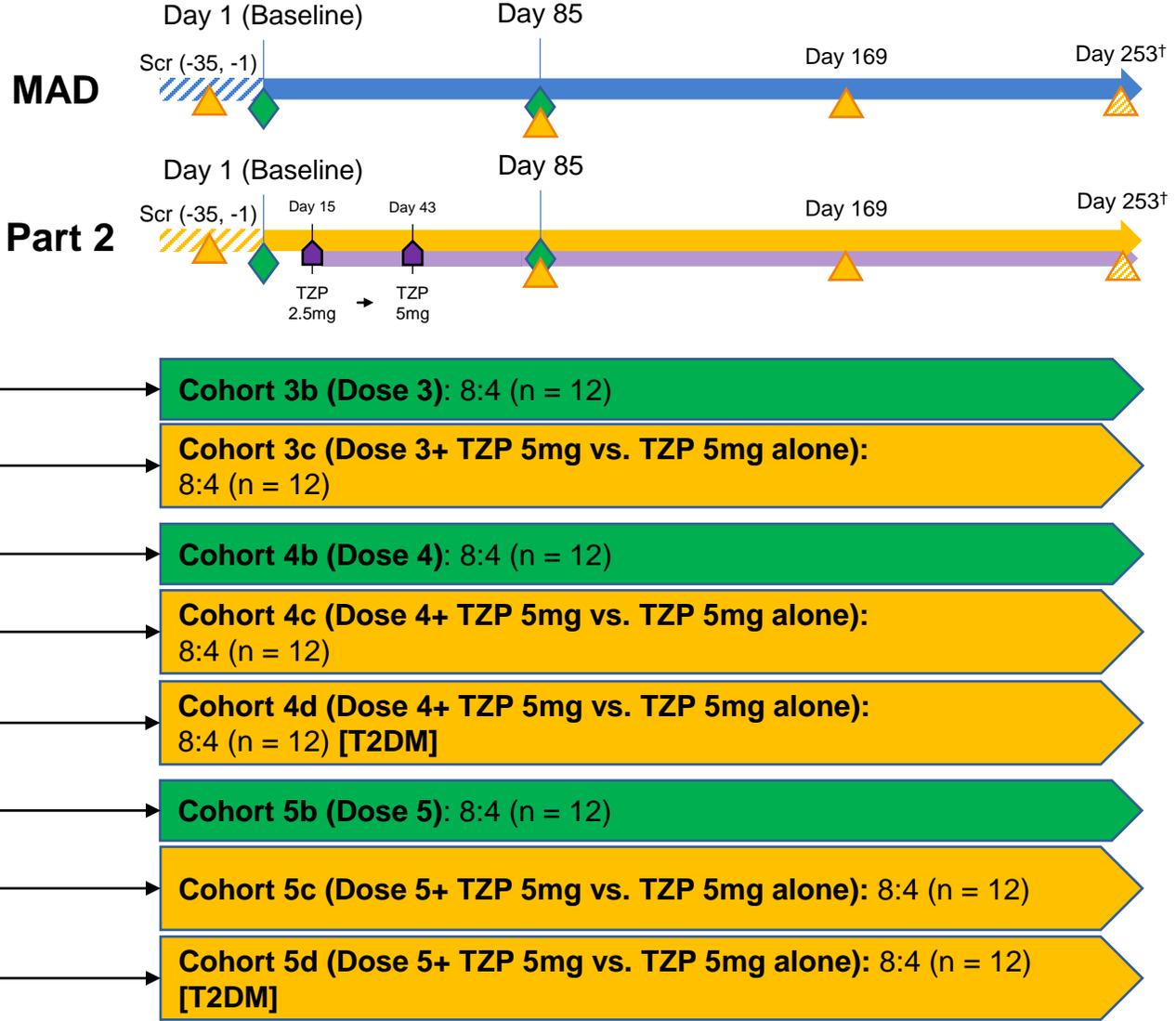
ARO-ALK7 Integrated Study Design (Part 1A/1B/2)

◆ ARO-ALK7 ■ Tirzepatide
▲ Adipose Aspiration

Part 1A SAD: Adult Volunteers with Obesity without T2DM



Part 1B MAD: Adult Volunteers with Obesity without T2DM Part 2: Combination Treatment Patients Obesity with/without T2DM



Key Endpoints

1° Safety

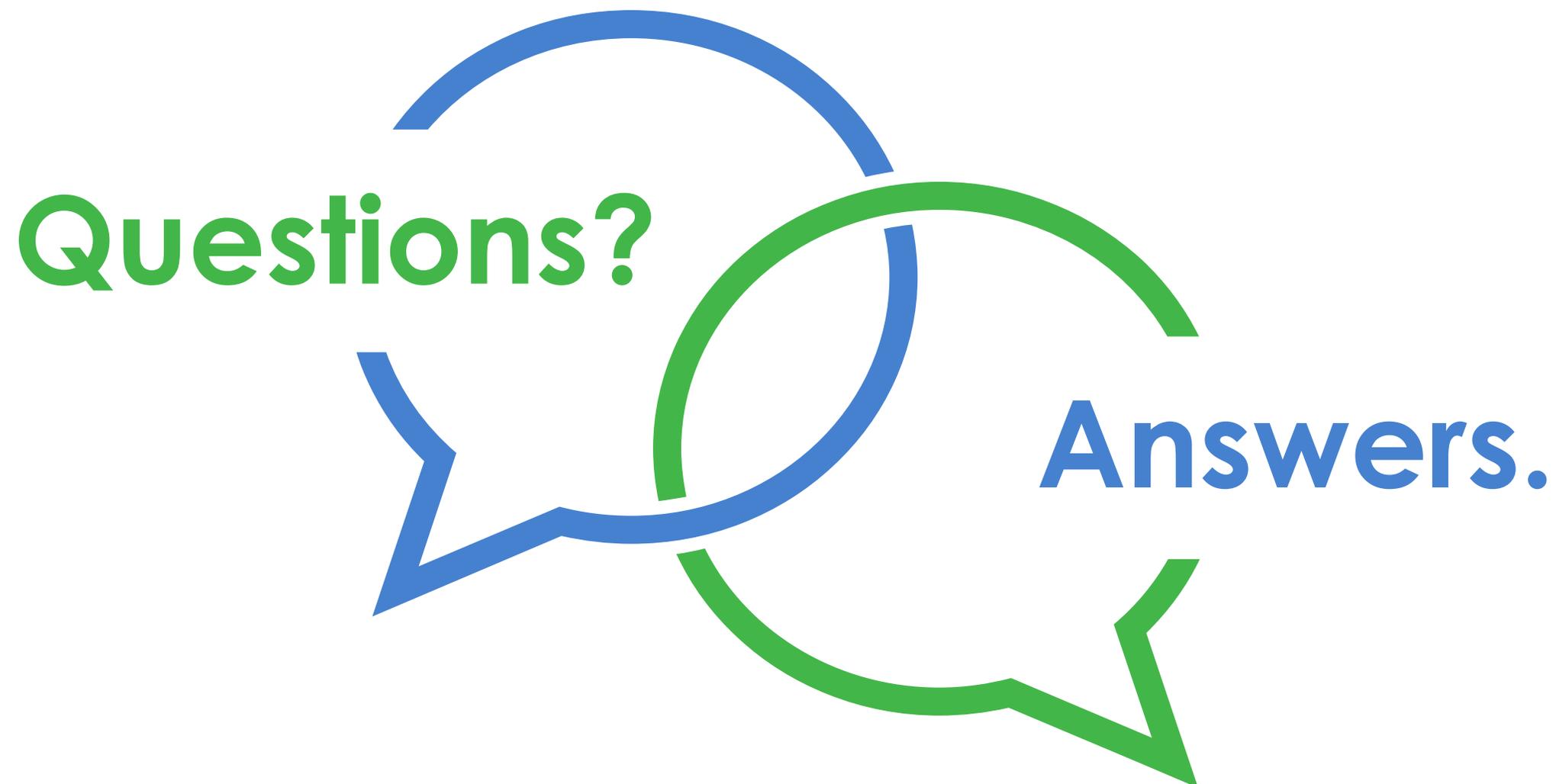
2° Pharmacokinetics



Exploratory

- INHBE SAD, MAD and combo data by YE 2025
- ALK7 initial SAD data by YE 2025

- **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



Questions?

Answers.