Elevated Activin E Levels Correlate with Insulin Resistance and Metabolic Dysfunction in Non-Human Primates and Adult Patients with Obesity and Type 2 Diabetes

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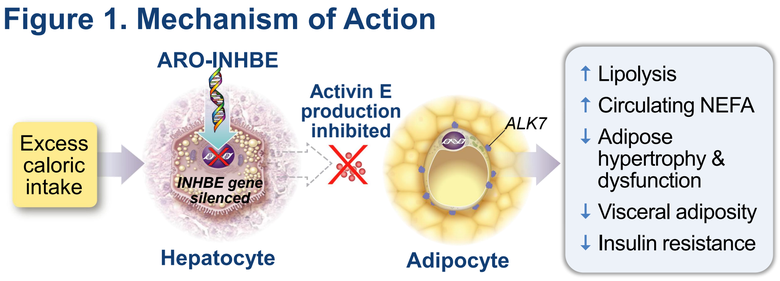
INTRODUCTION

- Incretin-based therapies promote weight loss and improve metabolic outcomes, but dose-dependent gastrointestinal adverse events, lean mass loss, and attenuated efficacy in individuals with diabetes highlight the need for therapies with novel mechanisms of action[1,2]
- The Inhibin subunit beta E (INHBE) gene is primarily expressed in hepatocytes, where it encodes for Activin E (dimeric INHBE protein), a hepatokine that is secreted in the blood and believed to promote fat storage in adipocytes via the ALK7 receptor[3]
- Predicted loss-of-function variants in INHBE are associated with a favorable metabolic profile and reduced cardiometabolic risk, including lower risk of Type 2 diabetes mellitus (T2DM)[3,4]
- ARO-INHBE is an investigational small interfering RNA (siRNA) designed to silence hepatic INHBE mRNA expression (**Figure 1**) and may represent a therapeutic strategy for targeting obesity and adipose dysfunction[5]

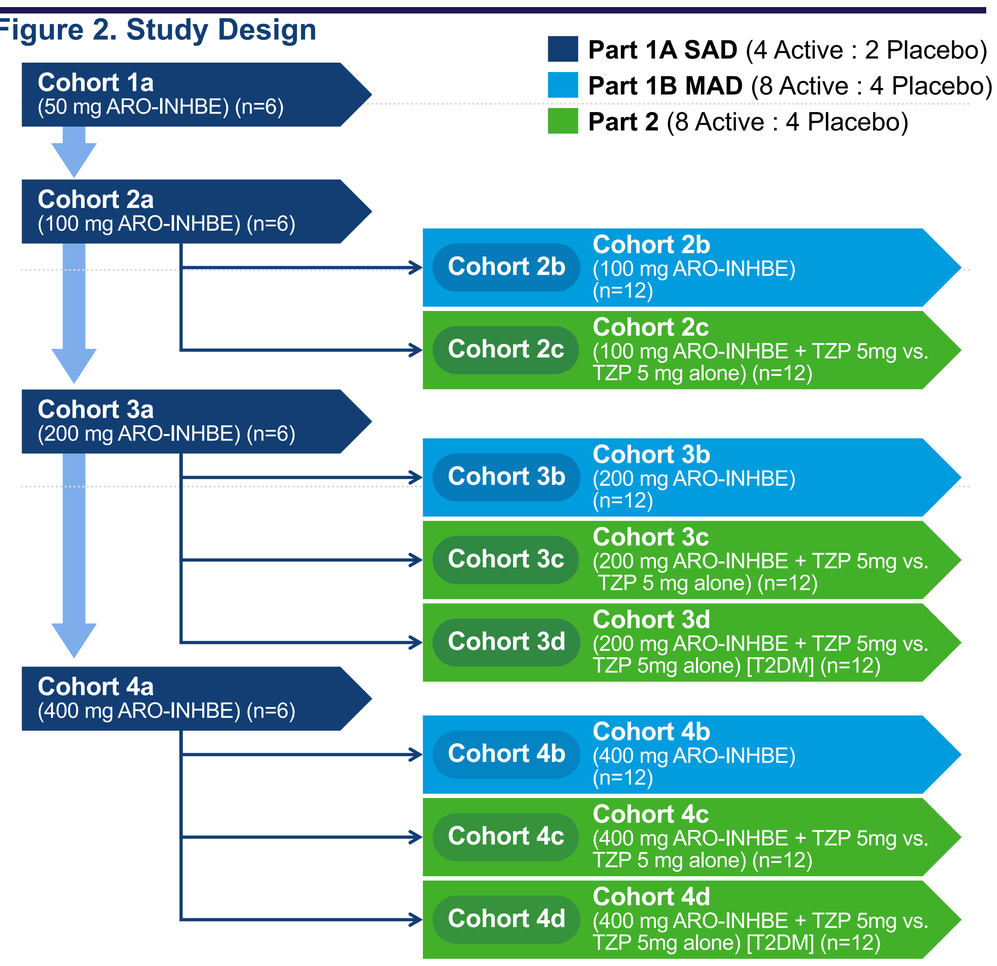
Figure 1. Mechanism of Action



METHODS

- Preclinical studies evaluated levels of circulating Activin E in non-human primates (NHPs) with and without T2DM
- ARO-INHBE-1001 is an ongoing Ph1/2a study evaluating the safety, tolerability, pharmacokinetics, and pharmacodynamics of subcutaneously administered ARO-INHBE:
  - Part 1A and Part 1B enrolled adult participants with obesity (BMI: 30–50 kg/m^2) who received single or multiple ascending doses of ARO-INHBE
  - Part 2 enrolled adult participants with obesity, with T2DM (HbA1c: 6.7–9.5%) or without T2DM (HbA1c <6.5%), who were randomized to receive multiple doses of ARO-INHBE concurrently with low-dose tirzepatide or tirzepatide alone
- Associations between Activin E levels and Clinical Characteristics at Baseline were evaluated using Pearson Correlation coefficient values (r)
- Baseline was defined as the last measurement obtained before the first dose of study drug; where not available or measurement error was likely, the preceding (Screening) value was used

Figure 2. Study Design



MAD, multiple ascending dose; SAD, single ascending dose; T2DM, type 2 diabetes mellitus; TZP, tirzepatide

RESULTS

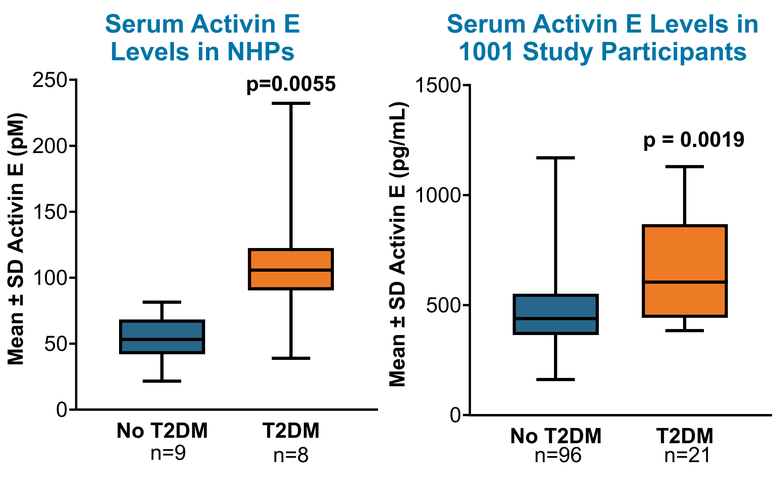
- Mean weight (103.7 vs 104.2 kg) and BMI (36.8 vs 37.0 kg/m^2) were similar between groups (**Table 1**)
- Participants with obesity and T2DM had higher mean liver fat content, visceral fat content, HbA1c, and Activin E levels compared to participants with obesity alone

Table 1. Baseline Demographic and Clinical Characteristics of AROINHBE-1001 Participants

	Participants with Obesity and T2DM (N=21)	Participants with Obesity (N=96)
Age, mean (SD), year	51.3 (7.7)	43.5 (11.4)
Sex, Female, n (%)	11 (52.4)	66 (68.8)
Race, n (%)		
White	12 (57.1)	62 (64.6)
Native Hawaiian or Pacific Islander	5 (23.8)	23 (24.0)
Asian	2 (9.5)	12 (12.5)
Other	3 (14.3)	8 (8.3)
Black or African American	0 (0)	2 (2.1)
Weight, mean (SD), kg	103.7 (17.8)	104.2 (15.6)
BMI, mean (SD), kg/m^2	36.8 (6.1)	37.0 (4.8)
Liver fat content, mean (SD), %	17.7 (9.6)	6.9 (5.5)
Visceral adipose tissue, mean (SD), L	6.8 (2.6)	4.7 (1.8)
HbA1c, mean (SD), %	7.4 (0.7)	5.4 (0.4)
Activin E, mean (SD), pg/mL	661.6 (234.1)	474.4 (171.0)

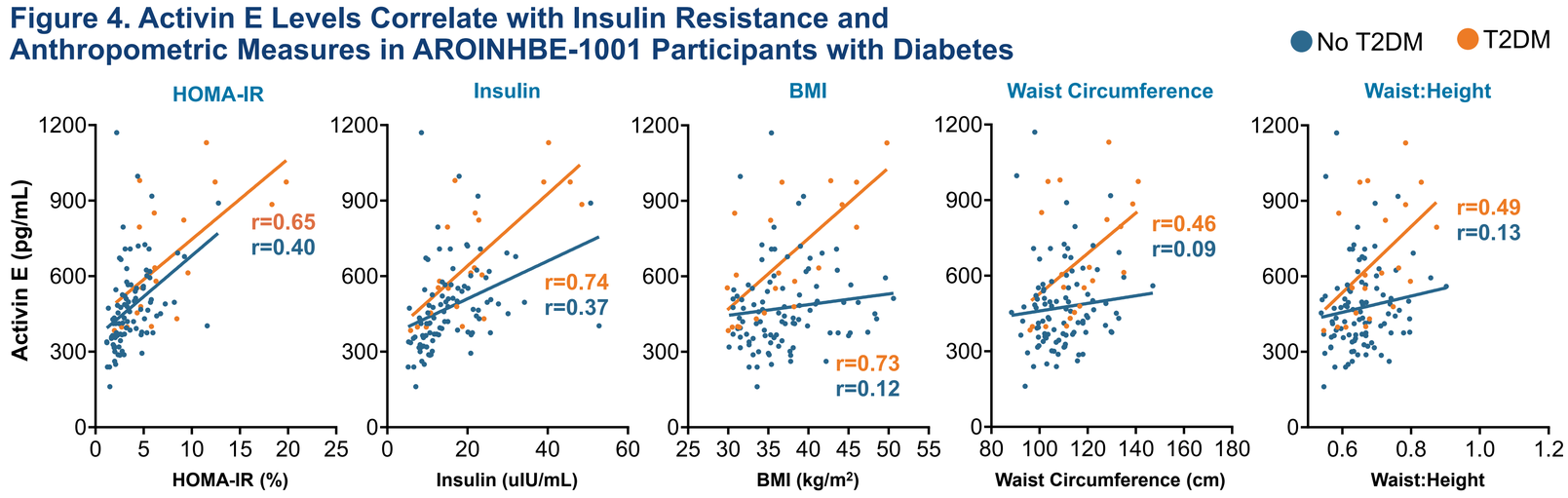
SD, standard deviation; BMI, body mass index; T2DM, type 2 diabetes mellitus.
Note: Patient may report more than one race; percentages may total over 100%.

Figure 3. Serum Activin E levels Are Elevated in Non-Human Primates with Diabetes and AROINHBE-1001 Study Participants



- In NHPs with T2DM, mean ± SD Activin E levels were 113.3 ± 51.1 pM (mean ± SD HbA1c of 9.0 ± 2.3%) compared to 53.7 ± 17.4 pM in NHPs without T2DM (p=0.0055) (**Figure 3**)
- Similarly, in participants with obesity and T2DM in AROINHBE-1001, baseline mean ± SD Activin E levels were 661.6 ± 234.1 vs 474.4 ± 171.0 pg/mL in participants with obesity alone (p=0.0019) (**Figure 3**)

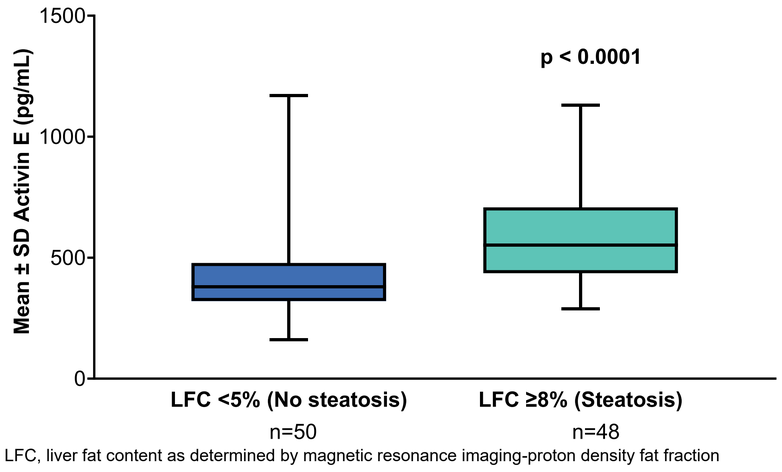
Figure 4. Activin E Levels Correlate with Insulin Resistance and Anthropometric Measures in AROINHBE-1001 Participants with Diabetes



BMI, body mass index; HOMA-IR, homeostatic model assessment for insulin resistance

- In ARO-INHBE-1001, baseline serum Activin E levels were observed to be correlated with insulin resistance (assessed with HOMA-IR) and insulin, irrespective of T2DM status
- Baseline serum Activin E levels were more strongly correlated with anthropometric measures (BMI, waist circumference, and weight:height ratio) in participants with obesity and T2DM than participants with obesity alone

Figure 5. Activin E Levels Correlate with Hepatic Steatosis



LFC, liver fat content as determined by magnetic resonance imaging-proton density fat fraction

- In ARO-INHBE-1001, baseline mean ± SD Activin E levels were significantly higher in individuals with clinically significant hepatic steatosis (599.5 ± 202.5 pg/mL) versus those without steatosis (421.2 ± 170.0 pg/mL)

CONCLUSIONS

- Activin E levels are elevated in T2DM and associated with obesity, insulin resistance, and hepatic steatosis
- These findings support dysregulation of the INHBE/Activin E pathway as a feature of the metabolic syndrome and provide a mechanistic rationale for targeting INHBE with ARO-INHBE in people with obesity and insulin resistance
- Directly targeting adipose fat storage via hepatic Activin E may complement existing incretin-based approaches for weight management
- The AROINHBE-1001 study is ongoing

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DISCLOSURES

R Murphy reports speaking honoraria from Lilly, Novo Nordisk, Boehringer Ingelheim; advisory board input to Abbot Diabetes Care, Dexcom, Lilly; and consultancy for NZ Clinical Trials. **G Shekhtman**, **M Ngai**, **E Garcia-Medel**, **B Tomasini-Johansson**, **R Fu**, **ZM Ding**, and **J Hamilton** are current employees of Arrowhead Pharmaceuticals.

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