# ARO-INHBE Demonstrates Clinically Meaningful Reductions in Liver Fat as Monotherapy and in Combination with Low-dose Tirzepatide in Adults with Obesity

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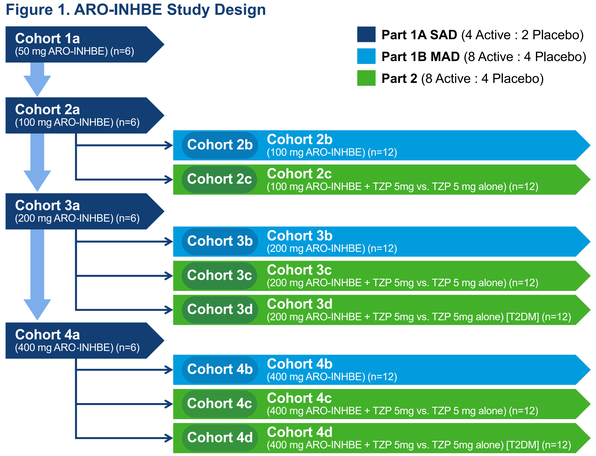
## INTRODUCTION

- Excess hepatic fat is highly prevalent in obesity and type 2 diabetes mellitus (T2DM), contributing to the development of metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH)[1]
- Inhibin subunit beta E (INHBE) 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[2]
- Predicted loss-of-function variants in INHBE are associated with a favorable cardiometabolic profile and reduced cardiometabolic risk, including reduced visceral fat and lower risk of Type 2 Diabetes Mellitus (T2DM)[2,3]
- ARO-INHBE is an investigational small interfering RNA (siRNA) designed to silence hepatic INHBE expression, which is predicted to decrease adipose hypertrophy, reduce visceral adiposity, and improve insulin sensitivity[4]

## METHODS

- ARO-INHBE-1001 (NCT06700538) is a Ph1/2a study to evaluate safety, tolerability, PK, and PD of ARO-INHBE in adults with obesity (BMI: 30–50 kg/m$^2$), with and without T2DM (**Figure 1**)
  - Part 1A and Part 1B evaluated ascending doses of ARO-INHBE (50 mg, 100 mg, 200 mg, and 400 mg) administered subcutaneously (SC) as a single dose on Day 1 or multiple doses on Day 1 and 29, compared with placebo in adults with obesity
  - Part 2 evaluated multiple doses of ARO-INHBE (100 mg, 200 mg, and 400 mg), or matched placebo, administered SC on Day 1 and 29 with concomitant initiation of tirzepatide in adults with obesity, with T2DM (HbA1c: 6.7–9.5%) or without T2DM (HbA1c <6.5%)
    - 2.5 mg SC tirzepatide was administered weekly (Day 15–42) and then escalated to 5 mg SC weekly (Day 43–169)
- The Primary Endpoint was the incidence, frequency, and severity of treatment-emergent adverse events (TEAEs)
- Exploratory Endpoints included percent change from baseline in serum activin E, body composition by MRI, liver steatosis by magnetic resonance imaging proton density fat fraction (MRI-PDFF), and biochemical parameters
- All analyses are based on data available as of March 3, 2026

### Figure 1. ARO-INHBE Study Design




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

## RESULTS

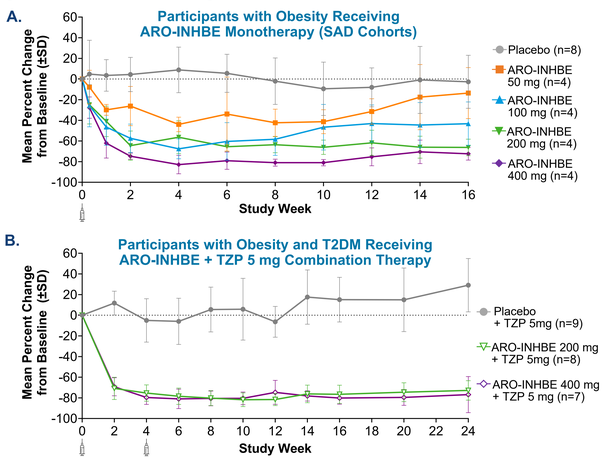
### Table 1. Baseline Demographic and Clinical Characteristics

| | ARO-INHBE Monotherapy* | ARO-INHBE + Tirzepatide 5mg Combination Therapy | |
|---|---|---|---|
| | Participants with Obesity (n=61) | Participants with Obesity and T2DM (n=25) | Participants with Obesity (n=36) |
| **Age, mean (SD), years** | 42.2 (10.5) | 51.8 (7.9) | 45.9 (12.4) |
| **Sex, Female, n (%)** | 38 (62.3) | 13 (52.0) | 28 (77.8) |
| **Race†** | | | |
| White, n (%) | 36 (59.0) | 14 (56.0) | 26 (72.2) |
| Native Hawaiian or Pacific Islander, n (%) | 20 (32.8) | 5 (20.0) | 4 (11.1) |
| Asian, n (%) | 8 (13.1) | 4 (16.0) | 4 (11.1) |
| Other, n (%) | 4 (6.6) | 3 (12.0) | 4 (11.1) |
| Black or African American, n (%) | 1 (1.6) | 0 (0) | 1 (2.8) |
| **Weight, mean (SD), kg** | 104 (14.6) | 102 (17.5) | 104 (17.3) |
| **BMI, mean (SD), kg/m$^2$** | 36.3 (4.5) | 36.4 (5.7) | 37.9 (5.2) |
| **Liver fat content, mean (SD), %** | 7.3 (5.9) | 16.9 (9.1) | 6.3 (4.7) |
| **Visceral adipose tissue, mean (SD), L** | 4.8 (1.7) | 6.6 (2.5) | 4.7 (1.9) |
| **Alanine aminotransferase, mean (SD), U/L** | 24.3 (14.4) | 30.6 (13.2) | 19.6 (11.7) |
| **HbA1c, mean (SD), %** | 5.4 (0.4) | 7.4 (0.7) | 5.4 (0.4) |
| **Serum activin E, mean (SD), pg/mL** | 488.2 (183.8) | 681.6 (251.4) | 451.5 (146.8) |

*Includes single ascending dose (SAD) and multiple ascending dose (MAD) cohorts; †Patients could report ≥1 race; percentages may total >100%.
SD, standard deviation; BMI, body mass index; T2DM, Type 2 Diabetes mellitus.

- In participants with obesity, dose-dependent reductions in Activin E were observed following a single administration of ARO-INHBE, with a mean maximum reduction of 85.3% achieved with ARO-INHBE 400 mg and persistent effect beyond 3 months (**Figure 2A**)
- Similar reductions were observed in participants with obesity and T2DM receiving two doses of ARO-INHBE (either 200 mg or 400 mg) in combination with tirzepatide 5 mg, with persistent effect through Week 24 (**Figure 2B**)
- No Activin E reductions were observed with TZP alone (**Figure 2B**)

### Figure 2. Mean Percent Change from Baseline in Activin E




- Participants with obesity and baseline LFC ≥8% receiving ≥200mg ARO-INHBE monotherapy (n=10; baseline LFC 14.5±5.1%) had a placebo-adjusted post-dose LFC reduction of 44% (t-test: p < 0.01) (**Figure 3A**)
- ARO-INHBE + tirzepatide 5 mg combination therapy resulted in enhanced reductions in visceral adipose tissue and LFC compared to tirzepatide alone in participants with obesity with or without T2DM (**Figure 3B–E**)

### Figure 3. Visceral Adiposity and Liver Fat Changes from Baseline

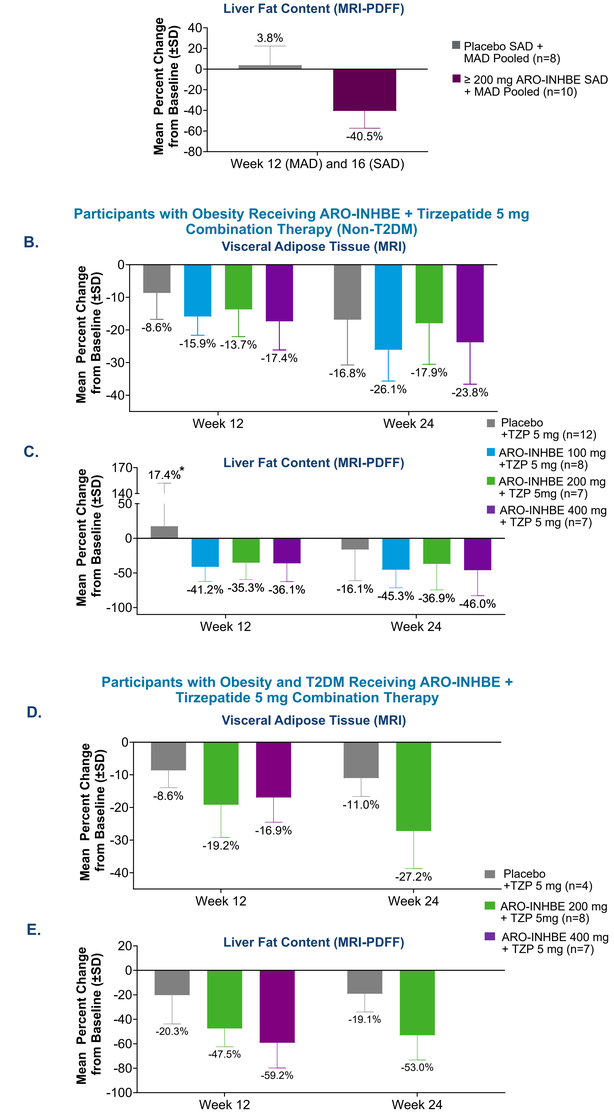



*Fig 3C: Mean percent change in LFC at Week 12 in the Placebo + 5 mg TZP cohort affected by a single outlier value.

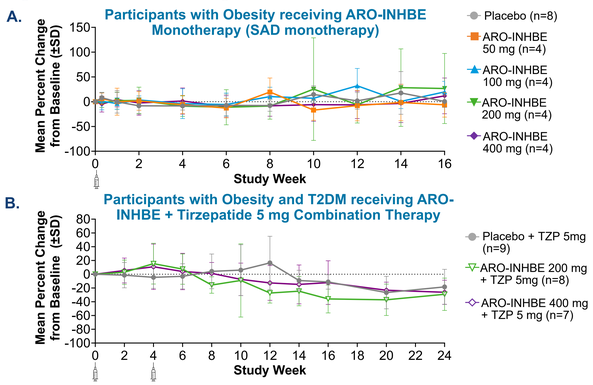
Fig 3D-E: ARO-INHBE 400 mg + 5 mg TZP data not yet available for Week 24.

Sample sizes in the figure legends reflect the number of evaluable participants at the last available time point.

MAD, Multiple Ascending Dose; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; SAD, Single Ascending Dose; T2DM, Type 2 Diabetes Mellitus; TZP, Tirzepatide.

- No pattern of adverse alanine aminotransferase (ALT) changes were observed with ARO-INHBE monotherapy versus placebo (**Figure 4A**) or with ARO-INHBE + tirzepatide 5 mg combination therapy versus tirzepatide alone (**Figure 4B**)

### Figure 4. Mean Percent Change in ALT from Baseline




- 91% of study participants reported a TEAE (**Table 2**); there were no drug-related SAEs, most TEAEs were mild, and no TEAEs led to study or study drug discontinuation
- No adverse laboratory trends (including HbA1c, ALT, and lipids) were observed

### Table 2. Most Common (>10%) TEAEs by Preferred Term, n (%)

| | ARO-INHBE Monotherapy* | ARO-INHBE + Tirzepatide 5mg Combination Therapy | |
|---|---|---|---|
| | Participants with Obesity (n=61) | Participants with Obesity and T2DM (n=25) | Participants with Obesity (n=36) |
| Any TEAEs | 53 (86.9%) | 22 (88.0%) | 36 (100.0%) |
| Upper respiratory tract infection | 20 (32.8%) | 10 (40.0%) | 11 (30.6%) |
| Headache | 20 (32.8%) | 4 (16.0%) | 11 (30.6%) |
| Nausea | 4 (6.6%) | 10 (40.0%) | 17 (47.2%) |
| Injection site erythema | 7 (11.5%) | 4 (16.0%) | 12 (33.3%) |
| Diarrhea | 3 (4.9%) | 9 (36.0%) | 11 (30.6%) |
| Decreased appetite | 0 (0.0%) | 6 (24.0%) | 15 (41.7%) |
| Constipation | 3 (4.9%) | 3 (12.0%) | 9 (25.0%) |

*Includes SAD and MAD cohorts; TEAEs with overall incidence >10% across all treatment groups were included.
TEAE, treatment-emergent adverse events.

## CONCLUSIONS

- RNAi-mediated silencing of INHBE with ARO-INHBE was well-tolerated and produced meaningful reductions in LFC as monotherapy or combination therapy with low-dose tirzepatide in individuals with obesity with and without T2DM
- Longer exposure to INHBE silencing resulted in continued improvements in visceral fat and liver fat from Week 12 to Week 24
- Targeting Activin E may represent a novel therapeutic strategy for MASH and obesity-related metabolic dysfunction and may complement existing incretin-based approaches
- The AROINHBE-1001 study is ongoing, and a Phase 2 study is planned

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