PO4.016 ASC47, a Muscle-Preserving Weight Loss Drug Candidate in Healthy Participants: A First-in-human Single Ascending Dose Study

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OBJECTIVES

The first-in-human (FIH) study of ASC47, a thyroid hormone receptor-β (THR-β) agonist prodrug, designed to evaluate the safety, tolerability and pharmacokinetics of ASC47 as a single-agent therapy in healthy participants and participants with obesity.

CASE

From July 11, 2024 to March 06, 2025, 28 participants were randomized as part of a Phase I study (Table 1). Healthy volunteers were randomized to receive ASC47 at doses of 10 mg (n=4), 30 mg (n=4), 90 mg (n=6), or placebo (n=6). Participants with obesity were randomized to receive 90 mg ASC47 (n=6) or placebo (n=2). All participants were included in the intention-to-treat analysis.

Table 1 Cumulative Exposures in ASC47 Clinical Studies by Age, Sex, and Racial Group

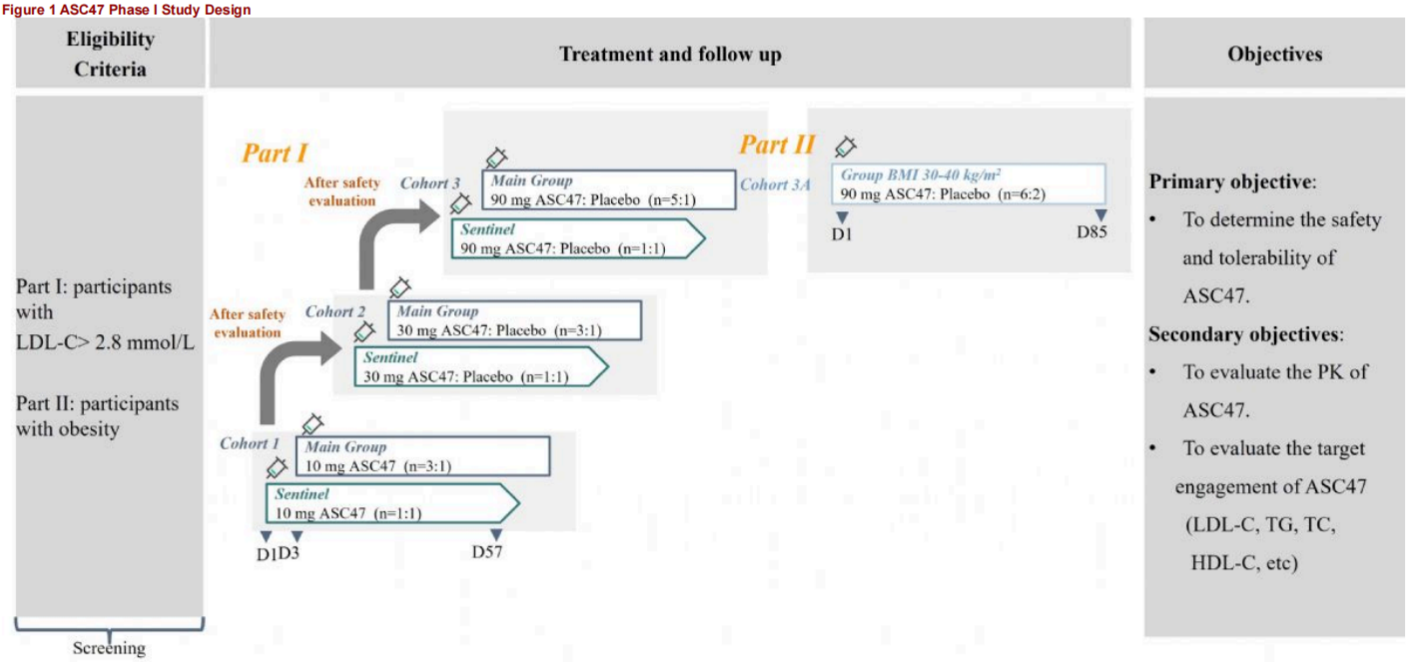
	Cohort 1 10 mg ASC47/placebo (n=6, HV)	Cohort 2 30 mg ASC47/placebo (n=6, HV)	Cohort 3 90 mg ASC47/placebo (n=8, HV)	Cohort 3A 90 mg ASC47/placebo (n=8, OB)	Overall
Sex					
Female	1 (16.7%)	1 (83.3%)	5 (62.5%)	3 (37.5%)	10 (35.7%)
Male	5 (83.3%)	5 (16.7%)	3 (37.5%)	5 (62.5%)	18 (64.3%)
Age					
<18	0	0	0	0	0
18-65	6 (100.0%)	6 (100.0%)	8 (100.0%)	8 (100.0%)	28 (100.0%)
>65	0	0	0	0	0
Race					
White	2 (83.3%)	3 (50.0%)	6 (75.0%)	4 (50.0%)	15 (53.6%)
Asian	1 (16.7%)	2 (33.3%)	1 (12.5%)	1 (12.5%)	5 (17.8%)
American Indian or Alaska	1 (16.7%)	0	0	0	1 (3.6%)
Black	0	0	1 (12.5%)	0	1 (3.6%)
Native Hawaiian or other Pacific Islander	1 (16.7%)	0	0	1 (12.5%)	2 (7.1%)
Other	0	1 (16.7%)	0	2 (25.0%)	3 (10.7%)
Unknown	1 (16.7%)	0	0	0	1 (3.6%)

Data collected up to March 06, 2025. HV= healthy volunteers. OB= participants with obesity.

MATERIALS-METHODS

This is a Phase I, randomized, double-blind, placebo-controlled study evaluating the safety, tolerability, and pharmacokinetics of a single subcutaneous dose of ASC47 (10 mg, 30 mg, or 90 mg) compared to placebo. Healthy participants with low-density lipoprotein cholesterol (LDL-C) > 2.8 mmol/L and participants with obesity (body mass index ≥ 30 kg/m²) were enrolled (Figure 1). The study consisted of three periods: a screening period (up to 28 days), a treatment period (single dose administration), and a follow-up period (56 days for healthy participants and 70 days for those with obesity). The trial is registered at ClinicalTrials.gov (Identifier: NCT06427590).

Figure 1 ASC47 Phase I Study Design



RESULTS

ASC47 injection demonstrated a half-life of up to 26 days and 40 days, respectively, in Phase Ib single subcutaneous injection studies in healthy subjects with elevated LDL-C and patients with obesity (Table 2).

Single subcutaneous injections of ASC47 in healthy subjects with elevated LDL-C (10 mg, 30 mg, and 90 mg) and in patients with obesity (90 mg) demonstrated clinically meaningful, placebo-adjusted reductions in low-density lipoprotein cholesterol (LDL-C) of up to 22% and total cholesterol (TC) of up to 16%, indicating effective target engagement in humans (Figure 2 and Figure 3).

In patients with obesity, ASC47 (90 mg) also showed a weight loss signal, with placebo-adjusted mean reductions of 0.2% at Day 29, 1.0% at Day 43, and a peak of 1.7% at Day 50.

No serious adverse events (SAEs) or discontinuations due to adverse events (AEs) occurred. Drug-related gastrointestinal AEs occurred only in the high-dose (90 mg) group, all of which were mild (Table 3). The majority of other AEs were mild (Grade 1), with no observed increases in heart rate or abnormal liver enzyme changes (Figure 4).

Table 2 ASC47 Demonstrated a Superior and Dose-Proportional PK Profile in Humans

Dose	10 mg ASC47 Injection	30 mg ASC47 Injection	90 mg ASC47 Injection	90 mg ASC47 Injection
Population (n)	Healthy participants (n=4)	Healthy participants (n=4)	Healthy participants (n=6)	Participants with obesity (n=6)
ASC47 concentration (mg/mL)	100	300	300	300
T1/2 (hr)	284.29±139.72	625.07±219.21	436.77±74.58	949.00±302.82
Tmax (hr)	258.00±136.29	276.00±124.71	204.00±84.17	260.00±95.30

Cmax (ng/mL)	6.54±2.08	7.46±2.20	35.79±25.92	20.46±11.45
AUC0-inf (h*ng/mL)	3744.27±1737.29	5748.37±1272.63	19469.17±9525.47	18240.83±11044.39

Follow-up duration was 57 days (1,344 hours) for Cohorts 1-3 and 85 days (2,016 hours) for Cohort 3A.

Figure 2 Mean Change from Baseline in in Low-Density Lipoprotein Cholesterol (LDL-C) by Cohort

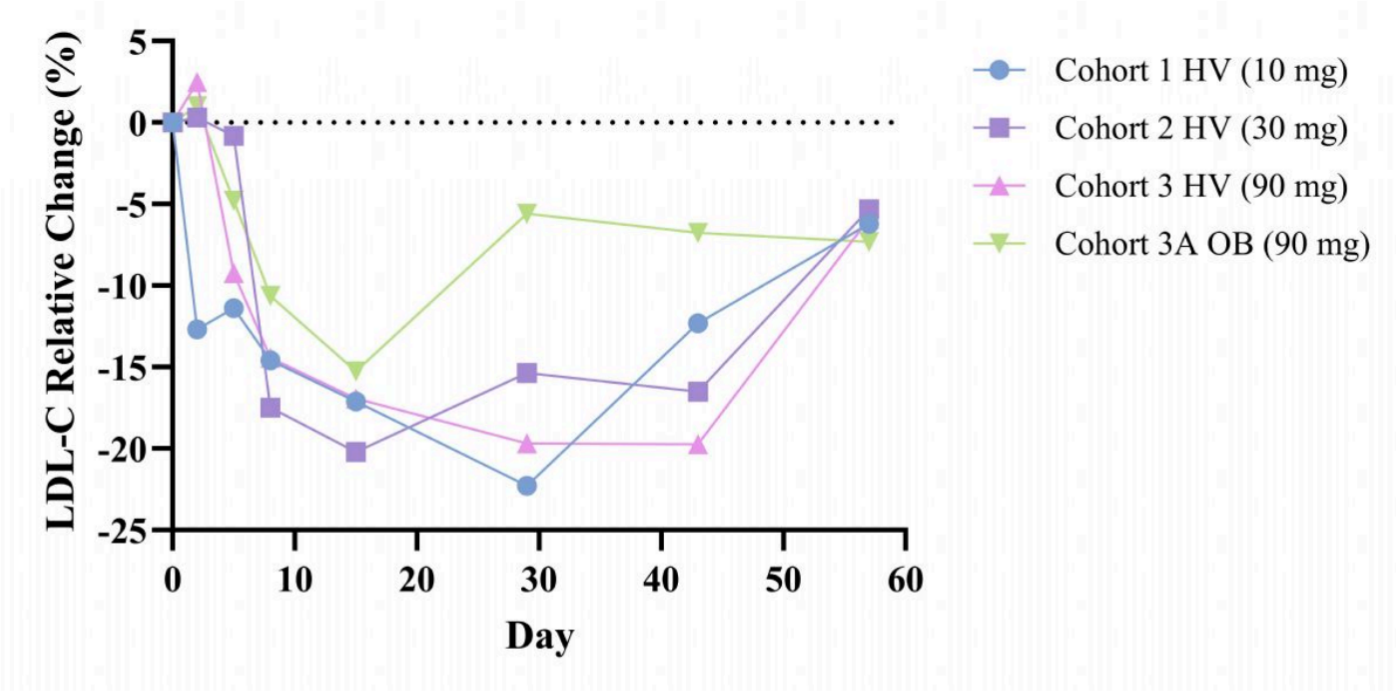


Figure 3 Mean Change from Baseline in Total Cholesterol (TC) by Cohort

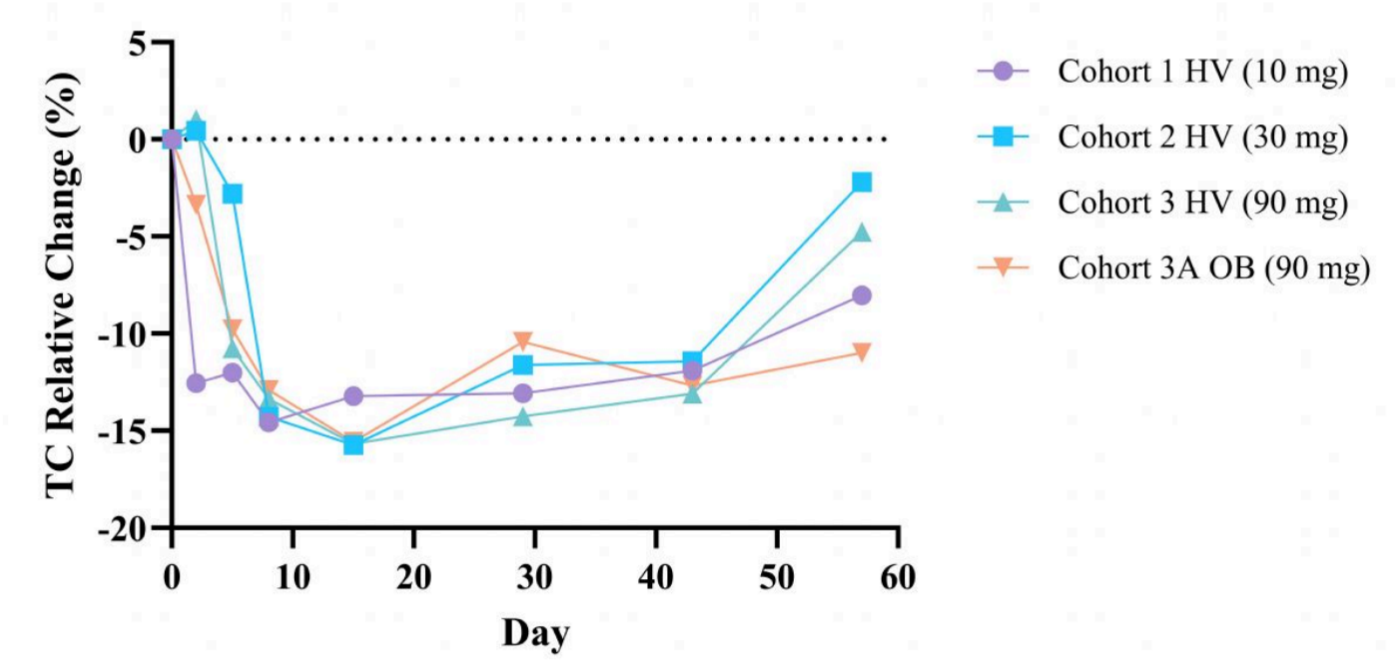
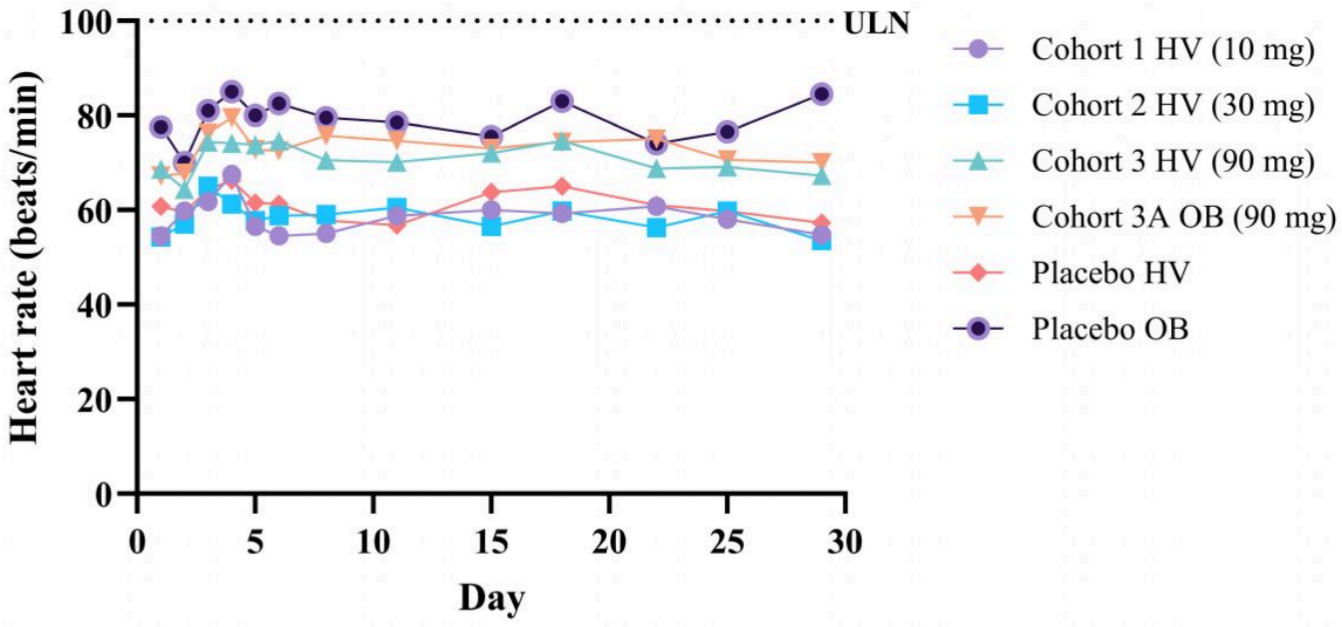


Table 3 Overall Summary of Gastrointestinal (GI)-Related Treatment-Emergent Adverse Events (TEAEs) Related to the Study Drug by Cohort

MedDRA Preferred Term	Placebo (n=8)	Cohort 1 10 mg ASC47 (n=4, HV)	Cohort 2 30 mg ASC47 (n=4, HV)	Cohort 3 90 mg ASC47 (n=6, HV)	Cohort 3A 90 mg ASC47 (n=6, OB)
Diarrhoea	0	0	0	0	2 (33.3%)
Nausea	0	0	0	1 (16.7%)	0
Vomiting	0	0	0	0	0
Constipation	0	0	0	0	0

HV=healthy volunteers; OB=participants with obesity.
All GI-related AEs were mild (Grade 1).
Coding using Medical Dictionary for Regulatory Activities Version 27.1.
Data collected up to March 06, 2025.

Figure 4 Mean Heart Rate from Week 1 to Week 4 by Cohort



ULN=the upper limit of the normal (100 beats/min).

DISCUSSION

AC47 single subcutaneous injection (90 mg) in participants with obesity demonstrated a weight loss signal, consistent with the speed of weight loss anticipated given ASC47's mechanism of action. One of the key mechanisms for ASC47 is through UCP-1-mediated thermogenesis which results in a slower rate of weight loss with the added benefit of muscle preservation, compared to incretin drugs. This slower rate of weight loss was seen in diet-induced obese (DIO) mouse models of ASC47 compared to incretin drugs. Muscle preservation of ASC47 treatment was also observed in DIO mouse models.

CONCLUSIONS

ASC47 demonstrated promising weight loss effects in patients with obesity, consistent with its mechanism of action through UCP-1-mediated thermogenesis. The slower, sustained weight loss observed with ASC47, along with muscle preservation, differentiates it from incretin-based therapies. Furthermore, ASC47 single subcutaneous injection demonstrated good tolerability up to the 90 mg dose, with no serious adverse events or significant safety concerns. These findings suggest that ASC47 could offer a novel and effective approach for weight management, with the potential for improved metabolic outcomes, long-term weight control, and muscle preservation.