ASC47 in Combination with Semaglutide Demonstrated Up to 111.8% Greater Relative Weight Loss in Participants with Obesity Compared to Semaglutide Monotherapy

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Introduction

ASC47 is a first-in-class, adipose-targeted, once-monthly subcutaneously injected, muscle-preserving weight loss drug candidate for the treatment of obesity. ASC47 is a new molecular entity as well as a potent and selective small molecule thyroid hormone receptor beta (THR-β) agonist discovered and developed in-house at Ascletis. ASC47 possesses unique and differentiated properties, in combination with ultra-long-acting subcutaneous (SQ) injection administration, enabling adipose targeting, resulting in dose-dependent high drug concentrations in the adipose tissue. The ASC47 first-in-human single ascending dose monotherapy study demonstrated that ASC47 was safe and well tolerated with a dose-dependent pharmacokinetic profile and a half-life of up to 40 days. We report here the first combination study of ASC47 and semaglutide in participants with obesity (NCT06972992).

Methods

ASC47-103 study, conducted in the U.S., was a randomized, double-blind, placebo-controlled study evaluating the safety, tolerability and efficacy of a single-dose, ultra-long-acting subcutaneously administered ASC47 in combination with four weekly doses of 0.5 mg semaglutide in participants with obesity, compared to volume-matched placebo in combination with four weekly doses of 0.5 mg semaglutide. The treatment duration was four weeks and the follow-up period was six weeks. The study, conducted in the U.S., enrolled 28 participants with obesity. Study objectives included evaluations of safety, tolerability, pharmacokinetics, and weight loss of three different single doses (10 mg, 30 mg and 60 mg) of ASC47 in combination with four weekly doses of 0.5 mg semaglutide. The effect on fat and lean mass was not an objective of this study given the short treatment duration (28 days). Study design is shown in Figure 1.

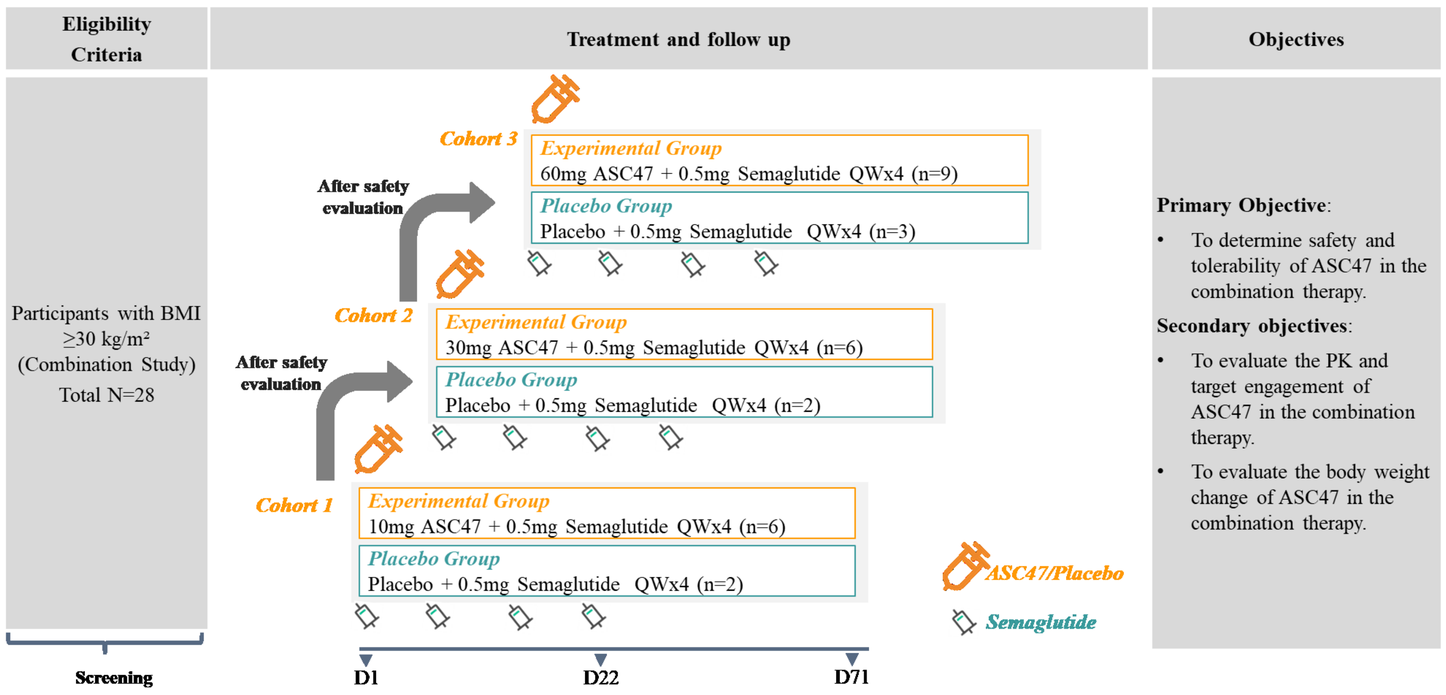

Figure 1. ASC47-103 Study Design

Results

- On day 29, a single SQ dose of 30 mg ASC47 in combination with four weekly doses of 0.5 mg semaglutide demonstrated a 111.8% greater relative reduction in body weight compared to four weekly doses of 0.5 mg semaglutide monotherapy.
- The gastrointestinal (GI) tolerability of ASC47 in combination with semaglutide was significantly better than semaglutide monotherapy (Table 1).
- The incidence of vomiting was 6.7% in the ASC47 in combination with semaglutide group compared to 57.1% in the semaglutide monotherapy group.

Table 1. The GI tolerability of ASC47 in combination with semaglutide was improved compared to semaglutide monotherapy

Category	30 mg ASC47 + 0.5 mg semaglutide (N=6) n (%)	60 mg ASC47 + 0.5 mg semaglutide (N=9) n (%)	30 mg/60 mg ASC47 + 0.5 mg semaglutide (N=15) n (%)	Placebo + 0.5 mg semaglutide (N=7) n (%)
Number of participants reporting at least one TEAE	6 (100.0%)	9 (100.0%)	15 (100.0%)	7 (100.0%)
Number of participants reporting SAEs	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Overall discontinuation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number of participants reporting TEAEs by severity				
Grade 1	6 (100.0%)	4 (44.4%)	10 (66.7%)	6 (85.7%)
Grade 2	0 (0.0%)	5 (55.6%)	5 (33.3%)	1 (14.3%)
Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Common GI-related TEAEs				
Vomiting	1 (16.7%)	0 (0.0%)	1 (6.7%)	4 (57.1%)
Nausea	3 (50.0%)	1 (11.1%)	4 (26.7%)	3 (42.9%)
Diarrhea	0 (0.0%)	1 (11.1%)	1 (6.7%)	2 (28.6%)
Constipation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Thyroid-related TEAEs				
Hypothyroidism	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hyperthyroidism	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Conclusions

- **ASC47 demonstrated strong synergy when combined with semaglutide and GI tolerability was significantly improved compared to semaglutide monotherapy.**
- **Based on these promising clinical data, further investigations of ASC47 in combination with incretin drugs are warranted.**