Ascletis Pharma Inc.
歌禮製藥有限公司
(incorporated in the Cayman Islands with limited liability)
(Stock Code: 1672)

VOLUNTARY ANNOUNCEMENT

ASCLETIS ANNOUNCES ASC47 IN COMBINATION WITH SEMAGLUTIDE DEMONSTRATED UP TO 56.2% GREATER RELATIVE REDUCTION IN BODY WEIGHT IN PARTICIPANTS WITH OBESITY COMPARED TO SEMAGLUTIDE MONOTHERAPY

- *The gastrointestinal (GI) tolerability of ASC47 in combination with semaglutide was significantly better than placebo in combination with semaglutide (semaglutide monotherapy). The incidence of vomiting was 6.7% in ASC47 in combination with semaglutide group compared to 57.1% in the semaglutide monotherapy group.*

- *Ultra-long-acting subcutaneous (SQ) depot formulation of ASC47 demonstrated a lower rebound effect after treatment discontinuation compared to the semaglutide monotherapy group, supporting the potential use of once-monthly ASC47 as a maintenance therapy.*

This announcement is made by Ascletis Pharma Inc. (the "**Company**" or "**Ascletis**", together with its subsidiaries, the "**Group**") on a voluntary basis for the purpose of keeping the shareholders of the Company and potential investors abreast of the latest business development of the Group.

The board (the "**Board**") of directors (the "**Directors**") of the Company announces that ASC47, a muscle-preserving weight loss drug candidate, in combination with semaglutide, demonstrated up to 56.2% greater relative reduction in body weight on day 29 in participants with obesity (body mass index ≥ 30 kg/m^2) compared to placebo in combination with semaglutide (semaglutide monotherapy).

ASC47-103 study (NCT06972992), 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, assessment of weight losses 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).

On day 29, a single SQ dose of 30 mg ASC47 in combination with four weekly doses of 0.5 mg semaglutide (N=6) demonstrated a 56.2% greater relative reduction in body weight compared to four weekly doses of 0.5 mg semaglutide monotherapy (N=7), and a single SQ dose of 60 mg ASC47 in combination with four weekly doses of 0.5 mg semaglutide (N=9) demonstrated a 15.1% greater relative reduction in body weight compared to four weekly doses of 0.5 mg semaglutide monotherapy (N=7). In a pooled patient analysis of both cohorts, ASC47 in combination with semaglutide (N=15) demonstrated a 31.6% greater relative reduction in body weight compared to semaglutide monotherapy (N=7). On day 29, four weekly doses of semaglutide monotherapy demonstrated a 2.5% reduction in body weight from baseline, consistent with the reported data in the literature. The 10 mg dose of ASC47 in combination with semaglutide did not show any additional decrease in body weight compared to semaglutide monotherapy. Target engagement to thyroid hormone receptor beta (THRβ) at the 10 mg dose of ASC47 as measured by sex hormone binding globulin (SHBG) was below the threshold required for clinical effect. However, both 30 mg and 60 mg ASC47 demonstrated significant target engagement to THRβ by the measurement of SHBG.

On day 29, there were significant reductions in low-density lipoprotein cholesterol (LDL-C) in 30 mg and 60 mg ASC47 group compared to semaglutide monotherapy group. 10 mg ASC47 group did not show significant reduction in LDL-C compared to semaglutide monotherapy group, suggesting again that the 10 mg dose of ASC47 was below the threshold required for clinical effect.

These topline clinical data are consistent with the results of animal studies previously conducted and reported by Ascletis in its announcement dated December 18, 2024. In a head-to-head diet-induced obese (DIO) mouse study, a single dose of 3 mg/kg ASC47 (human equivalent dose of approximately 25 mg for 100 kg humans based on the body surface area conversion) in combination with semaglutide demonstrated a 56.7% greater relative reduction in body weight compared to semaglutide monotherapy. The combination efficacy of a single dose of 9 mg/kg ASC47 (human equivalent dose of approximately 75 mg for 100 kg humans based on the body surface area conversion) in combination with semaglutide was less than the combination efficacy observed in 3 mg/kg ASC47 with semaglutide.

In the ASC47-103 study, ultra-long-acting SQ depot formulation of ASC47 demonstrated an observed half-life of up to 30 days. As a result, ASC47 significantly reduced body weight rebound after treatment discontinuation. On day 57 (4 weeks after treatment discontinuation), 30 mg ASC47 group (N=6) demonstrated a 157.1% greater relative reduction in body weight compared to the semaglutide monotherapy group (N=7), and 60 mg ASC47 group (N=9) demonstrated a 110.4% greater relative reduction in body weight compared to the semaglutide monotherapy group (N=7). In a pooled patient analysis of both cohorts, ASC47 group (N=15) demonstrated a 129.9% greater relative reduction in body weight compared to the semaglutide monotherapy group (N=7). As expected, in the semaglutide monotherapy group, weight loss from baseline observed on day 29 (2.5%) rebounded 68% to only 0.8% four weeks after patients came off semaglutide treatment. These topline data support the potential use of once-monthly ASC47 monotherapy as a maintenance therapy.

The pharmacokinetic profiles of semaglutide and ASC47 in combination were consistent with those observed in their respective monotherapies (semaglutide in this study and ASC47 in a previous study). These topline data suggest that dose adjustments are not necessary when co-administered.

ASC47 in combination with semaglutide was safe and well tolerated. Table 1 summarizes the treatment-emergent adverse event (TEAE) profile of ASC47 in combination with semaglutide compared to semaglutide monotherapy. The gastrointestinal (GI) tolerability of ASC47 in combination with semaglutide was significantly improved compared to semaglutide monotherapy. The incidence of vomiting was 6.7% in ASC47 in combination with semaglutide group compared to 57.1% in the semaglutide monotherapy group. Results of all thyroid function tests including thyroid stimulating hormone (TSH), free triiodothyronine (FT3), total triiodothyronine (TT3), free thyroxine (FT4) and total thyroxine (TT4) were within normal limits and no thyroid-related TEAEs were reported. All telemetry assessments and ECGs were within normal limits. No heart rate and QTc increases were observed.

In the current study, there were no titrations for semaglutide. The incidence rates of GI-related TEAEs of semaglutide monotherapy in the study are consistent with those reported in the literature in the absence of titration.

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%)	8 (88.9%)	14 (93.3%)	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 (66.6%)	6 (85.7%)
Grade 2	0 (0.0%)	4 (44.4%)	4 (26.7%)	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%)

Notes: TEAE(s): treatment-emergent adverse event(s); SAEs: serious adverse events; GI: gastrointestinal.

"As the first study to evaluate an adipose targeted THRβ agonist in combination with an incretin drug in participants with obesity, we're very encouraged that the addition of ASC47, an adipose-targeting THRβ agonist, to an incretin regimen led to a significant synergy in terms of body weight reduction, yielding up to an additional 56.2% increase in efficacy, and a substantial improvement in GI tolerability," said Jinzi Jason Wu, Ph.D., Founder, Chairman of the Board and chief executive officer of Ascletis, "This study provides important proof-of-concept data that will further inform our Phase IIb combination study designs for multiple metabolic diseases such as obesity and metabolic dysfunction-associated steatohepatitis (MASH)."

Pending on the consultation with the U.S. Food and Drug Administration and other regulatory agencies, the Phase IIb combination studies may include once-monthly subcutaneously administered ASC47 (30 mg and 60 mg) in combination with ASC35, a once-monthly subcutaneously administered GLP-1 receptor (GLP-1R)/GIP-receptor (GIPR) peptide agonist, and once-daily oral version of ASC47 in combination with once-daily oral ASC30.

ASC35 is an in-house discovered and developed GLP-1R/GIPR peptide agonist. The pharmacokinetic data in non-human primates (NHP) predict ASC35 has much longer observed half-life in humans than tirzepatide, supporting once-monthly SQ dosing. Furthermore, the DIO mouse model demonstrated that ASC35 reduced more body weight than tirzepatide. More ASC35-related data will be released in the near future.

About ASC47-103 Study

The ASC47-103 study, conducted in the U.S., is a randomized, double-blind, placebo-controlled clinical study designed to evaluate the safety, tolerability and efficacy of single-dose, ultra-long-acting subcutaneously administered ASC47 in combination with semaglutide in participants with obesity (body mass index ≥ 30 kg/m^2). The ASC47-103 study consists of three cohorts: Cohort 1 participants receive a single dose of 10 mg ASC47 (N=6), or volume-matched placebo (N=2) via SQ injection, and four doses of semaglutide (0.5 mg, once-weekly) via SQ injection. Cohort 2 participants receive a single dose of 30 mg ASC47 (N=6), or volume-matched placebo (N=2) via SQ injection, and four doses of semaglutide (0.5 mg, once-weekly) via SQ injection. Cohort 3 participants receive a single dose of 60 mg ASC47 (N=9), or volume-matched placebo (N=3) via SQ injection, and four doses of semaglutide (0.5 mg, once-weekly) via SQ injection. The treatment duration was four weeks and the follow-up period was six weeks.

Cautionary Statement required by Rule 18A.05 of the Rules Governing the Listing of Securities on The Stock Exchange of Hong Kong Limited: We cannot guarantee that we will be able to ultimately develop, manufacture and/or commercialize ASC47, ASC30 and/or ASC35 successfully.

By order of the Board
Ascletis Pharma Inc.
歌禮製藥有限公司
Jinzi Jason WU
Chairman

Hong Kong
September 22, 2025

As at the date of this announcement, the Board comprises Dr. Jinzi Jason WU and Mrs. Judy Hejingdao WU, as executive Directors; and Dr. Yizhen WEI, Mr. Jiong GU and Ms. Lin HUA, as independent non-executive Directors.