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, A MUSCLE-PRESERVING WEIGHT LOSS DRUG CANDIDATE FOR TREATMENT OF OBESITY, IN COMBINATION WITH SEMAGLUTIDE, DEMONSTRATED SUPERIOR WEIGHT LOSS TO SEMAGLUTIDE MONOTHERAPY IN A PRECLINICAL MODEL

- *In a head-to-head diet-induced obese (DIO) mouse study, ASC47 low dose combination 1 (ASC47, 3 mg/kg, subcutaneous (SQ), once every four weeks plus semaglutide, 30 nmol/kg, SQ, once daily), demonstrated superior weight loss compared to semaglutide monotherapy (30 nmol/kg, SQ, once daily), showing an average total body weight reduction of 36.2% compared to 23.1%, a 56.7% greater reduction in body weight compared to semaglutide monotherapy.*

- *Human equivalent dose of ASC47 low dose 1 (3 mg/kg, SQ, once every four weeks) in mice is estimated to be approximately 20 mg based on the body surface area conversion. Interim data from a Phase I single ascending dose (SAD) study in Australia in subjects with elevated low-density lipoprotein cholesterol (LDL-C) showed that ASC47, via SQ injection, demonstrated a good tolerability profile up to 90 mg. The Australian SAD study is still ongoing with higher doses of ASC47.*

- *ASC47 low dose combinations with semaglutide restored the body composition of obese mice to the level of healthy non-obese mice. At the end of treatment, the percentage of total muscle mass over the total body weight of obese mice treated with ASC47 low dose combination treatments (68.8%) was similar to healthy non-obese mice (66.0%), indicating healthy weight loss. Semaglutide monotherapy was unable to restore body composition to healthy levels.*

- *ASC47 low dose combination treatments were well tolerated in obese mice and exhibited a statistically significant reduction in levels of liver enzymes such as alanine aminotransferase (ALT) compared to vehicle treatment in obese mice.*

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 encouraging efficacy results from its study in diet-induced obese (DIO) mice combining ASC47, a first-in-class muscle-preserving weight loss drug candidate for the treatment of obesity, with semaglutide.

ASC47 is an adipose-targeted, once-monthly subcutaneously (SQ) injected thyroid hormone receptor beta (THRβ) selective small molecule agonist, discovered and developed in-house at Ascletis. ASC47 possesses unique and differentiated properties to enable adipose targeting, resulting in dose-dependent high drug concentrations in the adipose tissue.

Interim data from a Phase I single ascending dose (SAD) study in Australia in subjects with elevated low-density lipoprotein cholesterol (LDL-C) (NCT06427590) showed that ASC47, via SQ injection, demonstrated a half-life of 21 days. Further, ASC47 demonstrated a good tolerability profile up to 90 mg with no serious adverse events (SAEs) and no discontinuations due to adverse events (AEs). The majority of AEs were mild (grade 1). There were no gastrointestinal or cardiac AEs reported, as well as no abnormal liver enzymes reported (Link). The Australian SAD study is still ongoing with higher doses of ASC47.

In previous preclinical studies, ASC47 regular dose (45 mg/kg, SQ, once every two weeks) monotherapy demonstrated total body weight reduction of 24.6%, similar to semaglutide monotherapy (23.1%, 30 nmol/kg, SQ, once daily). ASC47 regular dose increased total muscle mass by 5.8%, compared to a decline in total muscle mass of 9.3 % for semaglutide (Link).

Detailed Preclinical Data of ASC47 Low Dose Combinations

The objective of the head-to-head ASC47 low dose combination DIO mouse study was to compare ASC47 low doses (3 mg/kg or 9 mg/kg) and low frequency (SQ, once every four weeks) combined with semaglutide (30 nmol/kg, SQ, once daily) against semaglutide monotherapy (30 nmol/kg, SQ, once daily). ASC47 low dose combination 1 (ASC47, 3 mg/kg, SQ, once every four weeks plus semaglutide, 30 nmol/kg, SQ, once daily) treatment was superior to semaglutide monotherapy (30 nmol/kg, SQ, once daily), showing an average total body weight reduction of 36.2% compared to 23.1%, achieving 56.7% more relative weight loss compared to semaglutide monotherapy (Table 1).

Table 1. ASC47 low dose combination treatments demonstrated superior weight loss to semaglutide monotherapy

Group	Dosing	Total body weight change from baseline	Total muscle mass/total body weight	Cumulative caloric intake (kCal)
Healthy non-obese mice	Vehicle	+8.53%	66.0%	308
Obese mice	Vehicle	+8.53%	46.6%	378
Obese mice treated with ASC47 low dose 1	ASC47, 3 mg/kg SQ, Q4W	+5.54%	48.6%	388
Obese mice treated with ASC47 low dose 2	ASC47, 9 mg/kg SQ, Q4W	-1.55%	52.1%	348
Obese mice treated with semaglutide	Semaglutide, 30 nmol/kg SQ, QD	-23.1%	57.2%	211
Obese mice treated with ASC47 low dose combination 1	ASC47, 3 mg/kg SQ, Q4W + semaglutide, 30 nmol/kg SQ, QD	-36.2% (p<0.0001 vs semaglutide monotherapy)	68.8% (p=0.0001 vs semaglutide monotherapy)	251 (p=0.0385 vs semaglutide monotherapy)
Obese mice treated with ASC47 low dose combination 2	ASC47, 9 mg/kg SQ, Q4W + semaglutide, 30 nmol/kg SQ, QD	-35.9% (p<0.0001 vs semaglutide monotherapy)	68.8% (p=0.0001 vs semaglutide monotherapy)	267 (p=0.001 vs semaglutide monotherapy)

Note: Treatment duration: 28 days; Obese mice: diet-induced obese mice; SQ: subcutaneous; QD: once daily; Q4W: once every four weeks

Human equivalent dose of ASC47 low dose 1 (3 mg/kg, SQ, once every four weeks) in mice is estimated to be approximately 20 mg based on the body surface area conversion. Interim data from a Phase I single ascending dose (SAD) study in Australia in subjects with elevated LDL-C showed that ASC47, via SQ injection, demonstrated a good tolerability profile up to 90 mg. The Australian SAD study is still ongoing with higher doses of ASC47.

ASC47 low dose combinations with semaglutide restored the body composition of obese mice to the level of healthy non-obese mice. At the end of treatment, the percentage of total muscle mass over the total body weight of obese mice treated with ASC47 low dose combination treatments (68.8%) was similar to healthy non-obese mice (66.0%), indicating healthy weight loss. Semaglutide monotherapy was unable to restore body composition to healthy levels (Table 1).

Cumulative caloric intake of obese mice with ASC47 low dose combination treatments at the end of treatment was statistically higher than that of obese mice with semaglutide monotherapy treatment (Table 1), suggesting that ASC47 has different mechanisms of action from incretin-based drugs.

ASC47 low dose combination treatments were well tolerated in obese mice and exhibited a statistically significant reduction in levels of liver enzymes such as alanine aminotransferase (ALT) compared to vehicle treatment in obese mice (Table 2).

Table 2. ASC47 low dose combination treatments demonstrated statistically significant ALT reduction compared to vehicle treatment in obese mice

Group	Dosing	ALT (U/L)
Healthy non-obese mice	Vehicle	31.5
Obese mice	Vehicle	234
Obese mice treated with ASC47 low dose 1	ASC47, 3 mg/kg SQ, Q4W	182
Obese mice treated with ASC47 low dose 2	ASC47, 9 mg/kg SQ, Q4W	159
Obese mice treated with semaglutide	Semaglutide, 30 nmol/kg SQ, QD	32.9 (p<0.0001 vs vehicle treated obese mice; no significant changes vs healthy non-obese mice)
Obese mice treated with ASC47 low dose combination 1	ASC47, 3 mg/kg SQ, Q4W + semaglutide, 30 nmol/kg SQ, QD	54.1 (p<0.0001 vs vehicle treated obese mice; no significant changes vs healthy non-obese mice and semaglutide monotherapy treated obese mice)
Obese mice treated with ASC47 low dose combination 2	ASC47, 9 mg/kg SQ, Q4W + semaglutide, 30 nmol/kg SQ, QD	70.0 (p<0.0001 vs vehicle treated obese mice; no significant changes vs healthy non-obese mice and semaglutide monotherapy treated obese mice)

Note: Treatment duration: 28 days; Obese mice: diet-induced obese mice; SQ: subcutaneous; QD: once daily; Q4W: once every four weeks

Both ASC47 low doses statistically and significantly reduced fasting blood glucose, cholesterol and LDL-C compared to vehicle treated obese mice (Table 3).

Table 3. ASC47 low dose treatments demonstrated statistically significant decreases in fasting blood glucose, cholesterol and LDL-C compared to vehicle treated obese mice

Group	Dosing	Fasting blood glucose (mmoL/L)	Cholesterol (mmoL/L)	LDL-C (mmoL/L)
Healthy non-obese mice	Vehicle	7.5	3.53	0.50
Obese mice	Vehicle	9.2	6.98	1.41
Obese mice treated with ASC47 low dose 1	ASC47, 3 mg/kg SQ, Q4W	6.9 (p=0.0017 vs vehicle treated obese mice; no significant changes vs semaglutide monotherapy treated obese mice)	4.08 (p<0.0001 vs vehicle treated obese mice; no significant changes vs semaglutide monotherapy treated obese mice)	0.58 (p<0.0001 vs vehicle treated obese mice; no significant changes vs semaglutide monotherapy treated obese mice)
Obese mice treated with ASC47 low dose 2	ASC47, 9 mg/kg SQ, Q4W	5.7 (p<0.0001 vs vehicle treated obese mice; no significant changes vs semaglutide monotherapy treated obese mice)	3.32 (p<0.0001 vs vehicle treated obese mice; no significant changes vs semaglutide monotherapy treated obese mice)	0.44 (p<0.0001 vs vehicle treated obese mice; no significant changes vs semaglutide monotherapy treated obese mice)
Obese mice treated with semaglutide	Semaglutide, 30 nmol/kg SQ, QD	6.4 (p=0.0001 vs vehicle treated obese mice)	3.90 (p<0.0001 vs vehicle treated obese mice)	0.61 (p<0.0001 vs vehicle treated obese mice)

Note: Treatment duration: 28 days; Obese mice: diet-induced obese mice; SQ: subcutaneous; QD: once daily; Q4W: once every four weeks

In obese mice, ASC47 low dose combination treatments reduced statistically and significantly more fasting blood glucose, cholesterol and LDL-C than semaglutide monotherapy treated obese mice (Table 4).

Table 4. ASC47 low dose combination treatments demonstrated superior fasting blood glucose, cholesterol and LDL-C reductions compared to semaglutide monotherapy

Group	Dosing	Fasting blood glucose (mmoL/L)	Cholesterol (mmoL/L)	LDL-C (mmoL/L)
Obese mice treated with ASC47 low dose combination 1	ASC47, 3 mg/kg SQ, Q4W + semaglutide, 30 nmol/kg SQ, QD	5.3 (p=0.0024 vs semaglutide monotherapy)	2.65 (p=0.0003 vs semaglutide monotherapy)	0.35 (p=0.0045 vs semaglutide monotherapy)
Obese mice treated with ASC47 low dose combination 2	ASC47, 9 mg/kg SQ, Q4W + semaglutide, 30 nmol/kg SQ, QD	4.7 (p<0.0001 vs semaglutide monotherapy)	2.57 (p=0.0002 vs semaglutide monotherapy)	0.36 (p=0.0055 vs semaglutide monotherapy)
Obese mice treated with semaglutide	Semaglutide, 30 nmol/kg SQ, QD	6.4	3.90	0.61

Note: Treatment duration: 28 days; Obese mice: diet-induced obese mice; SQ: subcutaneous; QD: once daily; Q4W: once every four weeks

Ascletis Obesity Portfolio

ASC47 is an adipose-targeted, once-monthly subcutaneously injected THRβ selective small molecule agonist. Interim data from a Phase I single ascending dose (SAD) study in Australia in subjects with elevated low-density lipoprotein cholesterol (LDL-C) (NCT06427590) have been released. ASC47 is currently in the clinical trials of patients with obesity in Australia, with topline data of Phase IIa study expected in the second quarter of 2025. In addition to ASC47, Ascletis is also developing ASC30, a GLP-1 receptor (GLP-1R) biased small molecule that can be dosed once daily orally or once monthly subcutaneously. Both ASC30 once-daily oral tablet (NCT06680440) and ASC30 once-monthly SQ injection (NCT06679959) are currently in Phase Ib clinical trials in the U.S. for the treatment of obesity, with topline data expected in the first quarter of 2025.

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 and/or ASC30 successfully.

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

Hangzhou, the People's Republic of China
December 18, 2024

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.