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 POSITIVE RESULTS FROM U.S. PHASE IA SINGLE ASCENDING DOSE STUDY OF SMALL MOLECULE ORAL GLP-1R AGONIST ASC30 AND PROVIDES PROGRAM UPDATE

- *ASC30 oral tablet demonstrated dose-proportional pharmacokinetic (PK) properties and a long half-life ($t_{1/2}$) up to 60 hours in the single ascending dose (SAD) study of patients with obesity, supporting once-daily or less frequent oral dosing.*

- *ASC30 oral tablet was generally safe and well tolerated. All adverse events (AEs) were mild (grade 1) or moderate (grade 2), and most of the AEs were gastrointestinal (GI)-related. There were no grade 3 or higher AEs as well as no serious AEs (SAEs). Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and other liver enzymes were in normal ranges.*

- *ASC30 oral tablet is stable at room temperature. Relative oral bioavailability of ASC30 tablet is 99% in animal models.*

- *Data from the animal models utilizing a new tablet formulation of ASC30 support up to once-weekly oral dosing.*

- *Topline results, including weight loss, safety and PK, from the U.S. Phase Ib multiple ascending dose (MAD) study of ASC30 oral tablet, once-daily, in obese patients are expected by the end of March 2025.*

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 positive topline results from its U.S. single ascending dose (SAD) study (NCT06680440) of ASC30 oral tablet in patients with obesity (body mass index (BMI): 30-40 kg/m^2). The SAD study consists of five cohorts (2 mg, 5 mg, 10 mg, 20 mg and 40 mg) with a total of 40 patients with obesity under fasting conditions.

ASC30 oral tablet demonstrated dose-proportional pharmacokinetic (PK) properties and a long half-life ($t_{1/2}$) up to 60 hours in the SAD study of patients with obesity, supporting once-daily or less frequent oral dosing. Cross-trial comparison indicates that in humans, drug exposure (area under the curve, "**AUC**") of 5 mg ASC30 single dose is 2.2-fold of that of 6 mg orforglipron single dose[1]. ASC30 oral tablet demonstrated superior PK properties (including a longer $t_{1/2}$ and higher AUC) to other small molecule oral GLP-1 receptor (GLP-1R) agonists in development[1-3], suggesting ASC30 oral tablet has the potential to be a best-in-class small molecule GLP-1R agonist to treat obesity.

In Cohort 5, 40 mg ASC30 oral tablet single dose was given orally to patients with obesity under both fasting and fed conditions. The data indicated that ASC30 oral tablet's PK properties including AUC and $t_{1/2}$ were essentially identical in the absence or presence of food, suggesting that ASC30 oral tablet can offer patient-friendly, once-daily oral dosing without food and water restrictions.

ASC30 oral tablet was generally safe and well tolerated in the Phase Ia SAD study. All adverse events (AEs) were mild (grade 1) or moderate (grade 2), and most of the AEs were gastrointestinal (GI)-related. There were no grade 3 or higher AEs, as well as no serious AEs (SAEs). GI-related safety profiles of ASC30 oral tablet were consistent with or better than other small molecule oral GLP-1R agonists in development[1, 3, 4] (Table 1). Furthermore, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and other liver enzymes were in normal ranges.

Table 1. All GI-related AEs of ASC30 oral tablet were mild (grade 1) or moderate (grade 2)

TEAE, n (%)	Placebo (N=10)	Cohort 1 2 mg ASC30 (N=6)	Cohort 2 5 mg ASC30 (N=6)	Cohort 3 10 mg ASC30 (N=6)	Cohort 4 20 mg ASC30 (N=6)	Cohort 5 40 mg ASC30 (N=6)
GI-related TEAE	1 (10.0)	0	1 (16.7)	4 (66.7)	5 (83.3)	6 (100.0)
Diarrhea	0	0	1 (16.7)	0	0	0
Constipation	1 (10.0)	0	0	0	1 (16.7)	1 (16.7)
Vomiting	0	0	0	2 (33.3)	5 (83.3)	5 (83.3)
Nausea	1 (10.0)	0	1 (16.7)	3 (50.0)	5 (83.3)	6 (100.0)

TEAE: Treatment-Emergent Adverse Event; GI: Gastrointestinal; n: Number of patients who had GI-related TEAE in each dose level; N: Number of patients who received the study drug.

ASC30 oral tablet formulation, which is stable at room temperature, was developed using Ascletis' proprietary technology and has a relative oral bioavailability of 99% at steady state in animal models. Data from the animal models utilizing a new tablet formulation (stable at room temperature) of ASC30 support up to once-weekly oral dosing.

ASC30 was discovered and developed in-house at Ascletis as a GLP-1R biased small molecule agonist without β-arrestin recruitment. ASC30 has unique and differentiated properties that enable the administration of one small molecule as both a once-monthly subcutaneous injection and a once-daily oral tablet. ASC30 has two- to three-fold better *in vitro* potency against GLP-1R when compared head-to-head with orforglipron. In the intravenous glucose tolerant test (IVGTT) in non-human primates (NHPs), ASC30 (1.5 mg/kg dose) stimulated statistically and significantly more insulin secretion when compared head-to-head with orforglipron (6 mg/kg dose).

ASC30 is the first and only small molecule GLP-1R biased agonist that can be dosed once monthly subcutaneously and once daily orally for the treatment of obesity. ASC30 oral tablet has the potential to be a best-in-class GLP-1R small molecule agonist given its PK and safety profiles as well as potency against GLP-1R.

ASC30 Oral Tablet U.S. Phase Ib MAD Study Update

The ASC30 oral tablet MAD study consists of 3 cohorts with weekly titrations in which patients with obesity are treated for 28 days with ASC30 oral tablet once daily or placebo. Cohort 1 (2 mg, 5 mg, 10 mg and 20 mg) has been completed. Cohort 2 (2 mg, 10 mg, 20 mg and 40 mg) and Cohort 3 (5 mg, 15 mg, 30 mg and 60 mg) are expected to be completed in late February and March 2025, respectively. Topline results from the MAD study, including weight loss, safety and PK, are expected by the end of March 2025.

ASC30 Oral Tablet U.S. Phase Ia and Ib Clinical Studies for the Treatment of Obesity

The Phase Ia study of ASC30 oral tablet once-daily is a randomized, double-blind, placebo-controlled, single ascending dose (5 cohorts) study to evaluate the safety, tolerability, and PK of ASC30 oral tablet in patients with obesity (BMI: 30-40 kg/m^2).

The Phase Ib study of ASC30 oral tablet once-daily is a randomized, double-blind, placebo-controlled, multiple ascending dose (3 cohorts, weekly titration, once-daily treatment for 28 days) study to evaluate the safety, tolerability, PK and efficacy of ASC30 in patients with obesity (BMI: 30-40 kg/m^2).

About ASC30

ASC30 is an investigational GLP-1R biased small molecule agonist and has unique and differentiated properties that enable the same small molecule for both subcutaneous injection and oral tablet administrations. ASC30 is a new molecular entity (NME), with U.S. and global compound patent protection until 2044.

References

1. Diabetes Obes Metab. 2023; 25:2634-2641.

2. Obesity 2024: Volume 32, Issue S1, Poster 342.

3. Obesity 2024: Volume 32, Issue S1, Poster 219.

4. Diabetes 2023: Volume 72, Issue Supplement_1, Poster 754.

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 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
January 21, 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.