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 DOSING OF THE FIRST PATIENT IN PHASE II CLINICAL TRIAL OF THRβ AGONIST ASC41 FOR 52-WEEK TREATMENT OF LIVER BIOPSY-PROVEN NASH

- *ASC41 is ranking first in China and third in the world in terms of clinical progress as a thyroid hormone receptor β (THRβ) agonist drug candidate for non-alcoholic steatohepatitis (NASH). ASC41 Phase II clinical trial is currently the most advanced 52-week Phase II clinical trial which is initiated by a China biotech company with enrollment of liver biopsy-proven NASH patients*

- *The Phase II clinical trial will enroll approximately 180 liver biopsy-proven NASH patients to be randomized into two treatment arms and one placebo control arm at the ratio of 1:1:1 with oral administration of ASC41 (2 mg or 4 mg) or placebo once daily for 52 weeks. The enrollment is expected to be completed in the third quarter of 2023*

- *The primary endpoint of the Phase II clinical trial is non-alcoholic fatty liver disease (NAFLD) activity score (NAS) improvement ≥2 points (improvement in inflammation or ballooning) and no worsening of fibrosis*

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 of directors (the "**Board**") of the Company announces dosing of the first patient in the 52-week Phase II clinical trial of thyroid hormone receptor β (THRβ) agonist ASC41 for treatment of liver biopsy-proven non-alcoholic steatohepatitis (NASH) patients. ASC41 Phase II clinical trial is currently the most advanced 52-week Phase II clinical trial which is initiated by China biotech company with enrollment of liver biopsy-proven NASH patients.

The randomized, double-blind, placebo-controlled and multi-center Phase II clinical trial intends to evaluate the safety and efficacy of ASC41 for treatment of liver biopsy-proven NASH patients, and will enroll approximately 180 liver biopsy-proven NASH patients to be randomized into two treatment arms and one placebo control arm at the ratio of 1:1:1 with oral administration of ASC41 (2 mg or 4 mg) or placebo once daily for 52 weeks. The enrollment is expected to be completed in the third quarter of 2023.

ASC41 is a liver-targeted prodrug, and its active metabolite is a selective THRβ agonist. THRβ is highly expressed in the liver, and THRβ agonists have demonstrated to be active in reducing low density lipoprotein (LDL), triglyceride (TG) and hepatic steatosis in humans. By promoting fatty acid breakdown and stimulating mitochondrial biogenesis, THRβ helps to reduce lipotoxicity and improve liver function, thereby reducing liver fat.

In January 2021, Ascletis announced the completion of a randomized, double-blind, placebo controlled single- and multiple-ascending dose Phase I clinical trial in 65 subjects with elevated low-density lipoprotein cholesterol (LDL-C) (>110 mg/dL), in which subjects demonstrated clinically meaningful and statistically significant reduction in LDL-C and TG compared with placebo after 14 days treatment of once daily oral dosing of ASC41 tablet. At a very low dose of 1 mg, placebo-adjusted relative TG reduction from baseline was 39% (P=0.002) (https://www1.hkexnews.hk/listedco/listconews/sehk/2021/0112/2021011200141.pdf). Compared with THRβ agonist Resmetirom (MGL-3196), ASC41 has higher potency and requires lower dosage (1 mg) to reach over 30% relative TG reduction as placebo-adjusted.

In February 2021, Ascletis announced positive clinical results in overweight and obese subjects for ASC41. Preliminary data suggested that over 28 days of oral dosing of ASC41, subjects demonstrated sustainable, clinically meaningful and statistically significant reduction in LDL-C, TG and total cholesterol (TC), compared with placebo. High-density lipoprotein cholesterol (HDL-C) remained relatively unchanged (https://www1.hkexnews.hk/listedco/listconews/sehk/2021/0221/2021022100037.pdf).

In September 2021, Ascletis completed the U.S. Phase I trial of drug-drug interactions in healthy subjects and pharmacokinetics (PK) in patients with non-alcoholic fatty liver disease (NAFLD) for ASC41 oral tablets. ASC41 is mainly metabolized by CYP3A4 to form an active metabolite ASC41-A, a selective THRβ agonist. This clinical study results demonstrated that clinically significant drug-drug interactions would be unlikely between ASC41/ASC41-A and antidepressants (selective-serotonin/serotonin-norepinephrine reuptake inhibitors (SSRIs/SNRIs), most of them are mild/moderate CYP3A4 inhibitors), which are commonly used in NASH patient population. It also revealed that the PK of ASC41/ASC41-A in healthy volunteers was not significantly different from that in patients with NAFLD (https://www1.hkexnews.hk/listedco/listconews/sehk/2021/0908/2021090800123.pdf).

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 commercialize ASC41 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
October 5, 2022

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.