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 24 HEALTHY SUBJECTS OF THE FIRST 3 COHORTS IN MULTIPLE-DOSE ESCALATION PHASE I CLINICAL TRIAL OF ORAL RDRP INHIBITOR ASC10 FOR COVID-19

- *The multiple-dose escalation Phase I clinical trial will enroll 72 healthy subjects including 60 subjects in 6 dose escalation cohorts and 12 subjects in food effect trial. The enrollment is expected to be completed in the fourth quarter of 2022*

- *ASC10 is an oral double prodrug. After oral administration, both ASC10 and single prodrug molnupiravir are rapidly and completely converted in vivo into the same active metabolite ASC10-A*

- *ASC10-A has broad spectrum of antiviral activity against Omicron variants including the most spreading variant BA.5 and the emerging variant BA.2.75*[2]

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 24 healthy subjects of the first 3 cohorts in multiple-dose escalation Phase I clinical trial of oral RNA-dependent RNA polymerase (RdRp) inhibitor ASC10 for COVID-19 at the National Medical Center for Infectious Diseases, the First Affiliated Hospital, School of Medicine, Zhejiang University.

The multiple-dose escalation Phase I clinical trial will enroll 72 healthy subjects including 60 subjects in 6 dose escalation cohorts and 12 subjects in food effect trial. The enrollment is expected to be completed in the fourth quarter of 2022. 60 healthy subjects will be randomized into 6 cohorts to receive escalated multiple doses of ASC10 tablets of 50 mg, 100 mg, 200 mg, 400 mg, 600 mg and 800 mg twice daily (BID) or matching placebo for 5.5 days in a double-blind, placebo-controlled manner to evaluate the safety, tolerability, and pharmacokinetics (PK) of ASC10 tablets. Another 12 subjects will be randomized to receive two single 800 mg doses (fed or fasted) to evaluate the food effect on PK of ASC10 tablets in healthy subjects.

Ascletis is China's first biotech company which has obtained Investigational New Drug (IND) approvals of an oral RdRp inhibitor from both the U.S. Food and Drug Administration ("**FDA**") and China National Medical Products Administration ("**NMPA**"). On August 3, 2022, Ascletis announced that FDA had approved the IND application for ASC10 to conduct the Phase Ib clinical trial in mild-to-moderate COVID-19 patients (https://www1.hkexnews.hk/listedco/listconews/sehk/2022/0803/2022080300885.pdf). On August 22, 2022, Ascletis announced that China NMPA had approved the IND application of ASC10 to conduct Phase I clinical trial in healthy subjects (https://www1.hkexnews.hk/listedco/listconews/sehk/2022/0822/2022082200059.pdf). Ascletis is actively communicating with regulatory authorities to explore the possibility of further accelerating the clinical development of ASC10.

ASC10 is an oral double prodrug which has a new and differentiated chemical structure from the single prodrug molnupiravir. After oral administration, both ASC10 and molnupiravir are rapidly and completely converted *in vivo* into the same active metabolite ASC10-A, also known as β-D-N4-hydroxycytidine (NHC). ASC10 was discovered and developed in-house. Ascletis has filed multiple patent applications for ASC10 and its use globally. ASC10 oral tablet formulation for the clinical study was developed with in-house proprietary technology of Ascletis.

By applying a double prodrug strategy, ASC10's permeability in Caco-2 cells (human colorectal adenocarcinoma cells) and active metabolite exposure in monkeys reached 3.2-fold and 2.1-fold of molnupiravir's, respectively. In the SARS-CoV-2 infected mouse models, ASC10 at 240 mg/kg twice daily led to a 4.0 log reduction in viral titer in lungs, equivalent to molnupiravir at 500 mg/kg twice daily[1]. Studies demonstrated[2,3] that ASC10-A (also known as EIDD-1931) has potent cellular antiviral activity against Omicron variants (BA.1 EC_{50}=0.3 μM; BA.2 EC_{50}=0.25 μM; BA.5 EC_{50}=0.23 μM; BA.2.75 EC_{50}=0.90 μM), Delta variant (EC_{50}=0.5 μM) and wild-type virus (EC_{50}=0.7 μM). It also suggested that there were no drug-drug interactions between ASC10 and other common medicines.

[1] Wahl, et al., Nature. 2021 March; 591(7850): 451-457.

[2] Takashita E, Yamayoshi S, Fukushi S, et al. Efficacy of Antiviral Agents against the Omicron Subvariant BA.2.75. N Engl J Med. 2022; 387(13): 1236-1238.

[3] In-house studies.

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 ASC10 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 10, 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.