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

VOLUNTARY ANNOUNCEMENT

GANNEX ANNOUNCES POSITIVE INTERIM RESULTS FROM 52-WEEK PHASE II CLINICAL TRIAL OF ONCE-DAILY ASC41 TABLET IN PATIENTS WITH BIOPSY-CONFIRMED NON-ALCOHOLIC STEATOHEPATITIS

- *Up to 68.2% mean relative reduction in liver fat content from baseline in biopsy-confirmed non-alcoholic steatohepatitis (NASH) patients receiving 12-week treatment of ASC41 tablet*

- *At Week 12, up to 93.3% patients achieved at least a 30% relative reduction in liver fat content from baseline*

- *At Week 12, placebo-adjusted mean relative reductions in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) from baseline were up to 37.8% and 41.5%, respectively*

- *At Week 12, placebo-adjusted mean relative reductions from baseline in low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC) and triglyceride (TG) were up to 27.7%, 23.4% and 46.5%, respectively*

- *Adverse events (AEs), including gastrointestinal (GI)-related AEs, were similar among patients receiving ASC41 tablet treatment versus placebo*

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 positive interim results from the 52-week Phase II clinical trial of thyroid hormone receptor β (THRβ) agonist ASC41 tablet for treatment of patients with biopsy-confirmed non-alcoholic steatohepatitis (NASH). ASC41 tablet is a drug candidate of Gannex Pharma Co., Ltd. (甘萊製藥有限公司, "**Gannex**"), a wholly-owned subsidiary of the Company. ASC41 is liver-targeting and highly THRβ-selective. Once-daily ASC41 tablet was developed by using Ascletis' proprietary formulation technology. The patent of ASC41 tablet formulation has been granted in the U.S.

This randomized, double-blind, placebo-controlled and multi-center Phase II clinical trial (ClinicalTrials.gov: NCT05462353) is being conducted in China and expected to enroll approximately 180 liver biopsy-confirmed NASH patients to be randomized into two treatment cohorts of ASC41 tablet (2 mg or 4 mg), once-daily and one placebo control cohort at the ratio of 1:1:1 for 52-week treatment and 4-week follow-up. The pre-specified interim analysis was conducted when 42 enrolled patients completed 12-week treatment of ASC41 tablet or placebo.

Interim results:

Reduction in Liver Fat Content from Baseline at Week 12

Patients receiving ASC41 tablet treatment achieved statistically significant reductions in liver fat content, as assessed by magnetic resonance imaging, proton density fat fraction (MRI-PDFF), relative to placebo (Table 1). Up to 93.3% patients receiving ASC41 tablet treatment experienced at least a 30% relative reduction from baseline in liver fat content, a level of reduction which is associated, especially for THRβ agonist class, with higher likelihood of histologic improvement in NASH.

Table 1. Reduction in Liver Fat Content at Week 12 Assessed by MRI-PDFF

	Placebo (n = 14)	ASC41 Tablet	
		2 mg, QD (n = 13)	4 mg, QD (n = 15)
Mean baseline liver fat content	18.2%	17.8%	18.9%
Mean relative change in liver fat content from baseline	-13.1%	-55.0% (p = 0.0001 vs placebo)	-68.2% (p < 0.0001 vs placebo)
Median relative change in liver fat content from baseline	-5.8%	-48.8%	-70.1%
Percentage of patients achieving ≥ 30% relative reduction in liver fat content from baseline	21.4%	92.3% (p = 0.0002 vs placebo)	93.3% (p < 0.0001 vs placebo)

Reduction in Liver Inflammatory Biomarkers from Baseline at Week 12

Mean alanine aminotransferase (ALT) and aspartate aminotransferase (AST) at baseline ranged from 65.9 to 84.8 U/L and 44.2 to 53.8 U/L, respectively, across ASC41 tablet and placebo cohorts. At Week 12, placebo-adjusted mean absolute reductions in ALT and AST from baseline were up to 34.2 U/L and 21.4 U/L, respectively. At Week 12, placebo-adjusted mean relative reductions in ALT and AST from baseline were up to 37.8% and 41.5%, respectively. Furthermore, placebo-adjusted percentage of patients achieving mean ALT decrease > 17 U/L was up to 51.9%. All above ALT and AST changes of ASC41 tablet cohorts were statistically significant versus the placebo cohort.

ALT and AST are important biomarkers for assessing hepatic injury and malfunction. Decline in serum ALT in NASH patients is associated with improvement in liver histology. Statistically significant and clinical meaningful reductions in ALT and AST in patients receiving ASC41 tablet treatment versus placebo notably differentiate ASC41 tablet from other THRβ agonists currently at clinical or registration stages.

Reduction in Lipids from Baseline at Week 12

Consistent with prior studies, patients receiving ASC41 tablet treatment demonstrated statistically significant and clinical meaningful placebo-adjusted mean reductions from baseline in low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC) and triglycerides (TG) up to 27.7%, 23.4% and 46.5%, respectively (Table 2). High-density lipoprotein cholesterol (HDL-C) remained unchanged from baseline among the cohorts receiving ASC41 tablet treatment or placebo. Statistically significant placebo-adjusted mean reduction in lipoprotein (a) (Lp(a)) was also observed in patients receiving ASC41 tablet treatment. Reductions in these lipids improve a patient's overall cardiometabolic profile and may reduce the risk of cardiovascular-related events.

Table 2. Reduction in Lipids from Baseline at Week 12

	Placebo (n = 14)	**ASC41 Tablet**	
		2 mg, QD (n = 13)	**4 mg, QD (n = 15)**
LDL-C, mean change from baseline	4.3%	-19.4% (p = 0.0002 vs placebo)	-23.4% (p < 0.0001 vs placebo)
TC, mean change from baseline	3.4%	-16.8% (p < 0.0001 vs placebo)	-20.0% (p < 0.0001 vs placebo)
TG, mean change from baseline	3.9%	-30.6% (p = 0.0001 vs placebo)	-42.6% (p < 0.0001 vs placebo)

Safety and Tolerability

ASC41 tablet showed promising safety and tolerability. ASC41 tablet was generally well tolerated, with adverse events (AEs) being grade 1 in majority across all cohorts, including the placebo cohort (Table 3). Among patients receiving ASC41 tablet treatment, only two patients (2/28, 7.1%) reported drug-related grade 2 treatment emergent adverse events (TEAEs). No drug-related grade 3 or higher TEAEs were observed in patients receiving ASC41 tablet treatment. Only one patient (1/28, 3.6%) among all patients receiving ASC41 tablet treatment discontinued from the study due to one grade-1 drug-related TEAE. No treatment-related serious adverse event (SAE) was reported in any patients receiving ASC41 tablet treatment or placebo. As in prior studies, ASC41 tablet demonstrated excellent gastrointestinal (GI) tolerability. Rates of nausea, vomiting, diarrhea, abdominal distension, abdominal pain (upper), constipation, dyspepsia and frequent bowel movements were low among patients receiving ASC41 tablet treatment (Table 3). Levels of thyroid axis hormones, including thyroid stimulating hormone (TSH), free triiodothyronine (fT3) and free thyroxine (fT4) were relatively unchanged from baseline among the cohorts receiving ASC41 tablet treatment versus the placebo. Changes in vital signs and electrocardiogram (ECG) were similar among patients receiving ASC41 tablet treatment versus the placebo.

Table 3. Safety and Tolerability Data

	Placebo (n = 14)	ASC41 Tablet	
		2 mg, QD (n = 13)	4 mg, QD (n = 15)
TEAEs [1] Number of subjects (%)	13(92.9%)	13(100%)	15(100%)
Drug-related TEAEs [2]	6(42.9%)	7(53.9%)	7(46.7%)
Grade 1	6(42.9%)	7(53.9%)	7(46.7%)
Drug-related GI AEs	2(14.3%)	3(23.1%)	1(6.7%)
Nausea	0(0.0%)	0(0.0%)	0(0.0%)
Vomiting	0(0.0%)	0(0.0%)	0(0.0%)
Diarrhea	1(7.1%)	3(23.1%)	1(6.7%)
Abdominal distension	1(7.1%)	0(0.0%)	0(0.0%)
Abdominal pain (upper)	0(0.0%)	0(0.0%)	0(0.0%)
Constipation	0(0.0%)	0(0.0%)	0(0.0%)
Dyspepsia	0(0.0%)	0(0.0%)	0(0.0%)
Frequent bowel movements	0(0.0%)	0(0.0%)	0(0.0%)

Notes:

Study safety population, defined as all patients who were randomized and received at least one dose of study drug.

[1] Data as of November 22, 2023.

[2] Deemed by investigator as possibly, probably, or definitely related to study drug.

Study Design

The randomized, double-blind, placebo-controlled and multi-center Phase II clinical trial intends to evaluate the efficacy and safety of ASC41 tablet for treatment of liver biopsy-confirmed NASH patients. Enrollment included patients with at least 7.5% liver fat content at baseline as measured by MRI-PDFF, as well as F2 and F3 liver fibrosis. The study allows up to 15% of enrolled patients to have F1 liver fibrosis. Approximately 180 patients will be enrolled and randomized into two treatment cohorts and one placebo control cohort at the ratio of 1:1:1 with oral administration of ASC41 tablet (2 mg or 4 mg) or placebo once daily for 52 weeks plus 4-week follow-up. Two liver biopsies will be performed at baseline and the end of 52-week treatment. MRI-PDFF will be performed at baseline, Week 12 and Week 52. The pre-specified interim analysis will be conducted after approximately 45 enrolled patients complete 12-week treatment of ASC41 tablet or placebo.

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
January 2, 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.