亞盛醫藥
Ascentage Pharma

ASCENTAGE PHARMA GROUP INTERNATIONAL
亞盛醫藥集團

(Incorporated in the Cayman Islands with limited liability)

(Stock Code: 6855)

VOLUNTARY ANNOUNCEMENT

ASCENTAGE PHARMA RELEASES PHASE I RESULTS OF IAP ANTAGONIST APG-1387 IN AN ORAL REPORT AT THE AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES ANNUAL MEETING SHOWING POTENTIAL FOR FUNCTIONALLY CURING CHRONIC HEPATITIS B

Ascentage Pharma Group International (the "**Company**" or "**Ascentage Pharma**") is pleased to announce that it has released results from a Phase I study of the investigational inhibitor of apoptosis protein (IAP) antagonist APG-1387 in Chinese patients with chronic hepatitis B (CHB), in an oral presentation at the 73rd American Association for the Study of Liver Diseases Annual Meeting (AASLD 2022). This is the world's first clinical study reporting favorable safety and preliminary efficacy of an IAP inhibitor for the treatment of patients with CHB.

Data from this clinical study suggest that APG-1387 has anti-hepatitis B virus (HBV) activity at doses of 12 mg and 30 mg, and synergistic effects when combined with sequential nucleos(t)ide analogue (NA) treatment. These data provide additional rationale for the continued development of APG-1387 in combination with other agents for the functional cure of CHB.

HBV infection is a global public health threat. The World Health Organization (WHO) estimates that approximately 300 million people worldwide are living with hepatitis B and 1.1 million deaths occur annually due to hepatitis B, hepatitis C, and their effects including liver cancer, cirrhosis, and other conditions caused by chronic viral hepatitis[1].

In China, the surface antigen of the hepatitis B virus (HBsAg) is present in 5%-6% of the population, and there are approximately 70 million patients with chronic HBV infections the country, of whom 20-30 million have CHB[2]. A total of 77% of liver cirrhosis cases and 84% of all primary hepatocellular carcinoma cases are associated with HBV infections[3]. Current guidelines recommend entecavir, tenofovir, tenofovir alafenamide, and long-acting interferon as standard anti-HBV treatments. However, only a small percentage of the patients who receive long-term treatment with these therapies can achieve HBsAg negativity and continued immune response after treatment. Majority of the patients require prolonged or even lifetime treatment, thus presenting an enormous unmet medical need for safe and effective therapies that can minimize the risk of disease progression and achieve functional cure with a relatively short duration of treatment.

Discovered and developed by Ascentage Pharma with global intellectual property rights, APG-1387 is a potent and highly selective next-generation IAP antagonist that has already shown anti-HBV potential in preclinical studies. Currently, the drug candidate is being evaluated in a Phase II study for the treatment of patients with CHB in China. AGP-1387 can induce apoptosis (programmed death in diseased cells) and confer immune modulation in HBV-infected liver cells, and has the potential as a novel therapeutic for the functional cure of CHB.

Details of the oral presentation on APG-1387 at AASLD 2022 are as follows:

First-in-Human Study of APG-1387, Targeting Inhibitor of Apoptosis Proteins, For the Treatment of Patients with Chronic Hepatitis B

- Abstract number: 32

- Session: Session 2 – Novel Therapies for the Functional Cure of CHB and CHC

Highlights:

- Investigational agent APG-1387 is a bivalent antagonist of IAPs that may enhance HBV-specific T-cell response and induce apoptosis of hepatocytes expressing HBV antigen.

- This study is the first to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of APG-1387 in Chinese patients with CHB.

- Treatment-naïve patients received 4 weekly doses of APG-1387 intravenously at escalating dose levels (7, 12, 20, and 30 mg), followed by a 12-week observation period. Nucleos(t)ide analogue (NA) treatment was initiated per clinical guidelines during follow-up.

- A total of 49 patients were enrolled, with a median age of 31 years, including 33 males and 29 patients who were HBeAg positive. Median (range) HBV DNA and HBsAg levels at baseline were 7.07 (4.59-8.87) log10 IU/mL and 3.91 (2.64-5.27) log10 IU/mL, respectively. During the observation period, 14 patients received NA and were classified as the sequential NA group, while the remaining 35 patients were classified as the monotherapy group; there were no significant differences in baseline characteristics between the two groups.

- PK analysis indicated a dose-proportional increase in plasma exposure from 7 to 30 mg. The mean terminal half-life ranged from 3.01 hours to 5.17 hours and no drug accumulation was observed after multiple dosing.

- A total of 30 patients experienced adverse events (AEs) considered to be related to the study treatment; the most prevalent AEs were transient alanine transaminase (ALT)/aspartate transaminase (AST) elevation (9/49 18.4%) and reversible Bell's palsy (7/49 14.3%).

- Results of virological response:

  - On Day 28, HBV DNA, HBsAg, and HBeAg decreased significantly from baseline in the 12 mg and 30 mg groups, with median (range) decreases of -0.38 (-2.02 to 0.09) and -0.38 (-1.13 to 0.39) log10 IU/mL, -0.14 (-0.71 to 0.14) and -0.04 (-0.79 to 0.09) log10 IU/mL, and -0.06 (-0.41 to 0.01) and-0.04 (-0.42 to 0.03) log10 signal to cut-off (S/CO), respectively.

  - On Day 112, median (range) decreases from baseline in HBV DNA, HBsAg, and HBeAg were -0.18 (-3.16 to 0.81) and -4.69 (-6.46 to -2.51) log10 IU/mL, 0.02 (-1.06 to 0.38) and 0.02 (-1.06 to 0.38) log10 IU/mL, and -0.03 (-2.34 to 0.10) and -1.73 (-2.49 to -0.04) log10 S/CO in monotherapy and sequential NA groups, respectively.

  - On Day 112, HBV DNA, HBsAg, and HBeAg decreased to a significantly greater amount in the sequential group than in the monotherapy group. ($p < 0.05$).

  - Multiple regression analysis showed that baseline HBeAg positivity, ALT flare, and sequential NA treatment were independent factors for HBsAg > 0.5 log10 IU/mL.

- IL-12 increased in a dose-dependent manner, and the other cytokines, including IFN-γ, IL-2Rα, and MCP-1, increased at 24 hours after the first dose of APG-1387, suggesting an immunomodulatory function for APG-1387.

Conclusions:

- APG-1387 treatment in patients with CHB is generally safe and tolerable.

- Exposure (AUC and Cmax) increased dose proportionally over the range from 7 to 30 mg, and no significant accumulation was seen after multiple dosing.

- APG-1387 showed significant anti-HBV effect at doses of 12 and 30 mg, and sustained antiviral effect after discontinuation, including even a synergistic effect when combined with sequential NA treatment.

- After treatment with APG-1387, the study observed increases in apoptotic biomarkers M30/M65 and cytokines such as IL-12 and IFN-γ, suggesting that APG-1387 has dual mechanisms of inducing apoptosis and immune modulation.

- These preliminary safety and efficacy data support continued development of APG-1387 in combination with other agents towards a functional cure of chronic HBV infection. A Phase II study of APG-1387 in combination with entecavir is ongoing (NCT04568265).

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 obtain further approval for, or ultimately market, APG-1387 successfully.

By order of the Board
Ascentage Pharma Group International
Dr. Yang Dajun
Chairman and Executive Director

Suzhou, People's Republic of China, November 7, 2022

As at the date of this announcement, the Board of Directors of the Company comprises Dr. Yang Dajun as Chairman and executive Director, Dr. Wang Shaomeng and Dr. Lu Simon Dazhong as non-executive Directors, and Mr. Ye Changqing, Dr. Yin Zheng, Mr. Ren Wei and Dr. David Sidransky as independent non-executive Directors.

References:

1. WHO Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021. Available at: https://www.who.int/publications/i/item/9789240027077

2. Liu, J., et al., Countdown to 2030: eliminating hepatitis B disease, China. Bull World Health Organ, 2019. 97(3): p. 230-238.

3. Chinese Society of Infectious Diseases and Chinese Society of Hepatology, Chinese Medical Association, Guidelines for the Prevention and Treatment of Chronic Hepatitis B (2019 version). Chin J Clin Infect Dis, 2019. 12(6): p. 401-428