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 Announces Preclinical Data Demonstrating Olverembatinib's Therapeutic Potential in Treating COVID-19 Published in EMBO Molecular Medicine

Ascentage Pharma Group International (the "**Company**" or "**Ascentage Pharma**") is pleased to announce that a new preclinical study, conducted by the researchers from Fred Hutchinson Cancer Center, Seattle, suggests the therapeutic potential of olverembatinib (HQP1351) in inhibiting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) omicron-mediated cytokine release. Results from this study were published today in the internationally renowned journal EMBO Molecular Medicine. Olverembatinib is approved for commercialization in China for tyrosine kinase inhibitor (TKI)-resistant chronic phase chronic myeloid leukemia (CML-CP) or accelerated-phase CML (CML-AP) harboring the T315I mutation.

Dr. Taran Gujral ("**Dr. Gujral**"), systems biologist at the Fred Hutchinson Cancer Research Center, University of Washington, is the corresponding author of this paper titled *Olverembatinib inhibits SARS-CoV-2-Omicron variant-mediated cytokine release in human peripheral blood mononuclear cells*[1].

Although most patients with COVID-19 only develop mild to moderate symptoms, 15% to 20% of patients still face hyper-inflammation induced by a massive release of cytokine also known as 'cytokine storm', which ultimately leads to alveolar damage and respiratory failure. Therefore, it has become an imperative to identify alternative therapies that can effectively inhibit the cytokine release in patients with moderate to severe COVID-19.

Dr. Gujral's research team found that the N-terminus domain (NTD) of the SARS-CoV-2 virus' spike protein can mediate the release of inflammatory cytokines in monocytes and peripheral blood mononuclear cells (PBMCs). Using an artificial intelligence screening platform, Dr. Gujral's team established that several protein kinases, including JAK1, EPHA7, IRAK1, MAPK12, and MAP3K3, are essential for the SARS-CoV-2-mediated cytokine release, and based on these key protein kinase inhibitor, they subsequently identified Ponatinib as a potent inhibitor of SARS-Cov-2-NTD mediated cytokine release[2].

In the current study, Dr. Gujral's team observed that the NTD of the SARS-CoV-2-Omicron variant can also promote the release of various cytokines, including IL-1β , IL-6, and the tumor necrosis factor (TNF-α), in PBMCs. A point to note is that olverembatinib treatment showed the highest suppression of the Omicron-NTD-mediated cytokine release, in a comparison between olverembatinib, ponatinib, and baricitinib.

Olverembatinib inhibited seven Omicron-NTD-mediated cytokines (GM-CSF, IL-1β , IL-10, IL-6, IL-8, CCL-2, and TNF-α), with a EC_{50} (concentration required to inhibit 50% of the Omicron-NTD-mediated cytokine release) between 7.7 and 56 nM, demonstrating a broader inhibition scope than that of baricitinib, a drug approved by the US FDA for the treatment of COVID-19[3] and the clinical option recommended by the WHO. A point to note is that Olverembatinib completely shuts down Omicron-NTD mediated cytokine storm in PBMCs from all 9 COVID-19 patients.

This study discovered that the NTD of SARS-CoV-2 and many of its variants can stimulate multiple downstream kinases (JAK1, EPHA7, IRAK1, MAPK12, and MAP3K8), leading to the hyper-inflammation induced by massive cytokine production. Olverembatinib blocks the activity of several kinases essential for cytokine signalling, thereby dampening the Omicron-NTD-mediated cytokine release in PBMCs and reducing inflammations. This indicates that agents targeting multiple kinases essential for SARS-CoV-2 and variant mediated cytokine release, such as olverembatinib, may represent a new therapeutic option for treating moderate to severe COVID-19 patients.

About olverembatinib

Olverembatinib is a novel type I drug developed by Ascentage Pharma which is an orally active, third-generation BCR-ABL inhibitor, and it has recently received approval in China for the treatment of adult patients with tyrosine kinase inhibitor (TKI)-resistant chronic phase chronic myeloid leukemia (CML-CP) or accelerated-phase CML (CML-AP) harboring the T315I mutation. Currently, olverembatinib is being evaluated in multiple clinical studies for the treatment of CML, acute lymphocytic leukemia (ALL), and gastrointestinal stromal tumor (GIST) in regions including the US and China.

About Ascentage Pharma

Ascentage Pharma is a China-based, globally focused, clinical-stage biotechnology company engaged in developing novel therapies for cancers, CHB (Chronic hepatitis B), and age-related diseases. On October 28, 2019, Ascentage Pharma became listed on the Main Board of The Stock Exchange of Hong Kong Limited with the stock code: 6855.HK.

Ascentage Pharma has its own platform for developing therapeutics that inhibit protein-protein interactions to restore apoptosis or programmed cell death. The Company has built a pipeline of eight type I small molecule clinical drug candidates which have entered the clinical development stage, including novel, highly potent Bcl-2, and dual Bcl-2/Bcl-xL inhibitors, as well as candidates aimed at IAP and MDM2-p53 pathways, and next-generation tyrosine kinase inhibitors (TKIs). Ascentage Pharma is also the only company in the world with active clinical programs targeting all three known classes of key apoptosis regulators. The Company is conducting more than 50 Phase I/II clinical trials in China, the US, Australia and Europe. Olverembatinib, the Company's core drug candidate developed for the treatment of drug-resistant chronic myeloid leukemia (CML), was granted Priority Review status and a Breakthrough Therapy Designation (BTD) by the Center for Drug Evaluation (CDE) of China National Medical Products Administration (NMPA), and is already approved for the indication. In addition, Olverembatinib has also been granted an Orphan Drug Designation (ODD) and a Fast Track Designation (FTD) by the US FDA, and an Orphan Designation by the EU. As at the date of this announcement, Ascentage Pharma has obtained a total of 15 ODDs from the US FDA and 1 ODD from the EU for four of the Company's investigational drug candidates. The Company has been designated for multiple major national R&D projects in China, including five Major New Drug Development Projects, one Enterprise Innovative Drug Incubator Base status, four Innovative Drug Research and Development Programs, and one Major Project for the Prevention and Treatment of Infectious Diseases.

Leveraging its robust research and development capabilities, Ascentage Pharma has built a portfolio of global intellectual property rights, and entered into global partnerships with numerous leading biotechnology and pharmaceutical companies and research institutes such as UNITY Biotechnology, MD Anderson Cancer Center, Mayo Clinic, Dana-Farber Cancer Institute, MSD, AstraZeneca and Pfizer. The Company has built a global and talented team with experience in the research and development of innovative drugs and clinical development, and is setting up its commercial manufacturing and sales and marketing teams with high standards. Ascentage Pharma aims to continuously strengthen its research and development capabilities and accelerate the clinical development progress of its product pipeline to fulfil its mission of 'addressing unmet clinical needs of patients in China and around the world' for the benefit of more patients.

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

Suzhou, People's Republic of China, May 18, 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, Dr. Tian Yuan, Dr. Lu Simon Dazhong and Mr. Liu Qian as non-executive Directors, and Mr. Ye Changqing, Dr. Yin Zheng, Mr. Ren Wei and Dr. David Sidransky as independent non-executive Directors.

Reference

1. Chan M, Holland EC, Gujral T. Olverembatinib inhibits SARS-CoV-2-Omicron variant-mediated cytokine release in human peripheral blood mononuclear cells. EMBO Mol Med. 2022 May 17;e15919.

2. Chan M, Vijay S, McNevin J, McElrath MJ, Holland EC, Gujral TS (2021) Machine learning identifies molecular regulators and therapeutics for targeting SARS-CoV2-induced cytokine release. Molecular systems biology 17: e10426

3. Favalli EG, Biggioggero M, Maioli G, Caporali R (2020) Baricitinib for COVID-19: a suitable treatment? The Lancet Infectious Diseases 20: 1012-1013