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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 Presents Results of Six Studies of Three Novel Drug Candidates under Development (Olverembatinib, APG-2575, and APG-1252) at the 63rd American Society of Hematology (ASH) Annual Meeting

Ascentage Pharma Group International (the "**Company**" or "**Ascentage Pharma**") is pleased to announce that it has released the updated data from six studies of the company's three novel drug candidates (olverembatinib, APG-2575, and APG-1252) at the 63rd American Society of Hematology (ASH) Annual Meeting. Prof. Qian Jiang, MD and Prof. Xiaojun Huang, MD from the Hematology Department of Peking University People's Hospital are the principal investigators of the studies of the class I novel drug candidate olverembatinib, of which one study was reported by Prof. Jiang in an oral presentation. This is the fourth consecutive year in which studies of olverembatinib were selected for oral presentation by the ASH Annual Meeting, demonstrating strong recognition of the drug candidate's promising efficacy and safety by the international hematology community.

The ASH Annual Meeting is one of the largest academic gatherings of the international hematology field, bringing together the latest and most cutting-edge research and other scientific and clinical developments in hematology. This year, abstracts from six studies of the company's drug candidates under development (olverembatinib, APG-2575, and APG-1252) were selected for presentations at the ASH Annual Meeting.

Among which, olverembatinib is a class I novel drug developed by Ascentage Pharma which recently received approval in November 2021 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, thus making olverembatinib the first China-approved third-generation BCR-ABL inhibitor targeting drug-resistant CML.

These results include data from two clinical studies of the company's novel Bcl-2-selective inhibitor lisaftoclax (APG-2575) and one preclinical study of its dual Bcl-2/Bcl-xL inhibitor pelcitoclax (APG-1252) that were released in poster presentations at the meeting.

It is worth highlighting that the multicenter, open-label Phase I study of APG-2575 in patients with hematologic malignancies has demonstrated favorable tolerability of APG-2575, without evidence of tumor lysis syndrome (TLS). As of data cutoff on July 27, 2021, 9 of the 25 patients who had received at least one tumor evaluation (of 31 enrolled patients) achieved complete responses (CR) or partial responses (PR). At doses ≥ 200 mg, all 6 patients with chronic lymphocytic lymphoma (CLL) achieved objective responses, including 1 with CR and 5 with PR.

The abstracts on olverembatinib presented at the 2021 ASH Annual Meeting are as follows:

Updated Safety and Efficacy Results of Phase 1 Study of Olverembatinib (HQP1351), a Novel Third-Generation BCR-ABL Tyrosine Kinase Inhibitor (TKI), in Patients with TKI-Resistant Chronic Myeloid Leukemia (CML)

- Format: Oral Presentation
- Abstract: 311
- Session: 632. Chronic Myeloid Leukemia: Clinical and Epidemiological: Mechanisms of resistance and expanded therapies
- Highlights
  - ➢ This Chinese, open-label, multicenter, Phase I trial evaluated the safety and efficacy of olverembatinib in adults with CML-CP or CML-AP. Eligible patients had CML-CP or CML-AP resistant or intolerant to first-and second-generation TKIs. Olverembatinib was orally administered once every other day (QOD) in 28-day cycles and at 11 dose cohorts ranging from 1 to 60 mg. This study reports data on patients with long-term follow-up.
  - ➢ From October 26, 2016, through September 27, 2021 (data cutoff), 101 patients with CML-CP (n=86) or CML-AP (n=15) were enrolled and treated with olverembatinib. 71 (70.3%) of those patients were male, at a median age of 40 (20–64) years, and the median (range) interval from diagnosis to initial olverembatinib treatment was 6.0 (0.3–15.2) years. In all, 84 (83.2%) patients received ≥ 2 prior lines of TKI-therapies, and 63 (62.4%) harbored the T315I mutation. At baseline, compound mutations were detected in 11 (10.9%) patients, of whom 7 (63.6%) had the BCR-ABL1^{T315I} genotype. A total of 20 (19.8%) patients had 2 (n=13) or ≥ 3 (n=7) mutations. The median follow-up was 39 (1.2–

58.6) months. As of the data cut-off date, 77 (77%) of 101 patients continued on the treatment, 24 patients discontinued the treatment of which 9 (9%) discontinued due to disease progression, 6 (6%) due to adverse events (AEs), 4 (4%) due to investigator-confirmed treatment failure, 4 (4%) due to withdrawal, and 1 (1%) case of death.

- Of evaluable patients with CML-CP who did not show any response at baseline, 100% had complete hematologic responses (CHR), 70% had complete cytogenetic responses (CCyR), and 55% had major molecular responses (MMR).

  — Among evaluable patients with CML-CP who only harbored the T315I mutation, 100% had CHR, 90% had MCyR, 84% had CCyR, 78% had MMR, 68% had MMR 4.0, and 58% had MR 4.5.

  — Among evaluable patients with CML-CP harboring the T315I and compound mutations, 100% had CHR, 64% had MCyR, 55% had CCyR, 58% had MMR, and 25% each for MMR 4.0 and MR 4.5.

  — Among evaluable patients with CML-CP harboring other mutations, 100% had CHR, 89% had MCyR, 67% had CCyR, 64% had MMR, 46% had MMR 4.0, and 27% had MR 4.5.

  — Among evaluable patients with CML-CP who did not harbor any mutation, 100% had CHR, 64% had MCyR, 55% had CCyR, 9% had MMR, and 5% had MMR 4.0.

- Of evaluable patients with CML-AP who did not show any response at baseline, 92% had CHR, and 43% had each CCyR and MMR.

  — Among evaluable patients with CML-AP who only harbored the T315I mutation, 67% had CHR, 60% had each CCyR, MMR, and MMR 4.0, and 40% had MR 4.5.

  — Among evaluable patients with CML-AP who harbored the T315I and other compound mutations, 100% had CHR, 60% had each CCyR, MMR, MMR 4.0 and MR 4.5.

  — Among evaluable patients with CML-AP who harbored other mutations, 100% had CHR, and none had achieved CCyR or MR.

  — Among evaluable patients with CML-AP who did not harbor any mutation, 100% had CHR, and none had achieved CCyR or MR.

- As of the data cut-off date, the progression-free survival (PFS) rates in patients with CML-CP and CML-AP were 92.7% (84.5%-96.7%) and 56.3% (27.2%-77.6%), and the overall survival (OS) rates were 94.1% (86.4%) and 71.4% (40.6%-88.2%), respectively.

  Olverembatinib demonstrated favorable tolerability and durable antitumor activity in patients with CML, including those with the T315I and compound mutations. Responses were durable and unaffected by baseline BCR-ABL1 mutational status.

- Most treatment-related AEs (TRAEs) were grade 1 or 2.

  — The most common nonhematologic AE (mostly grade 1 or 2) was skin hyperpigmentation (86.1%). Grade ≥ 3 nonhematologic AEs included hypertriglyceridemia (10.9%), pyrexia (6.9%), and proteinuria (5.0%).

  — The most common hematologic TRAEs included thrombocytopenia (77.2), of which 51.5% were grade ≥ 3; leukopenia (23%), of which 21% were grade ≥ 3; and anemia (46%), of which 17% were grade ≥ 3.

  All patients who experienced these AEs have recovered after temporary discontinuation, dose adjustments or intervention treatments.

- Conclusions: Olverembatinib was well-tolerated and exhibited durable and potent activity in patients TKI-resistant CML-CP or CML-AP.

Updated Results of Pivotal Phase 2 Trials of Olverembatinib (HQP1351) in Patients (Pts) with Tyrosine Kinase Inhibitor (TKI)-Resistant BCR-ABL1T315I-Mutated Chronic-and Accelerated-Phase Chronic Myeloid Leukemia (CML-CP and CML-AP)

- Format: Poster Presentation
- Abstract: 3598
- Session: 632. Chronic Myeloid Leukemia: Clinical and Epidemiological: Poster III
- Highlights:

  - HQP1351-CC201 and HQP1351-CC202 are Chinese open, single-arm, multicenter pivotal Phase II trials evaluating the safety and efficacy of olverembatinib in adults with TKI-resistant (BCR-ABL1T315I-mutated) CML-CP and CML-CP, respectively. Olverembatinib was administered at 40 mg orally QOD for 28-day cycles.

- As of the data cutoff on September 30, 2021, HQP1351-CC201 had enrolled 41 patients with CML-CP, of whom 32 (78%) completed ≥ 12 cycles. After ≥ 12 treatment cycles in patients without responses at baseline, 100% patients experienced CHR; 81 % MCyR; 68% CCyR; and 56% MMR. As of the data cutoff date, the PFS and OS rates in patients with CML-CP were 91.9% (76.9%-97.3%) and 95% (81.5%-98.7%), respectively.

- As of the data cutoff on September 30, 2021, HQP1351-CC202 had enrolled 23 patients with CML-CP, of whom 14 (61%) had completed≥ 12 cycles. After ≥ 12 treatment cycles in patients without responses at baseline, 74% experienced major hematologic responses (MaHR); 70% CHR; 52% MCyR; 52% CCyR; and 48% MMR. As of the data cutoff date, the PFS and OS rates in patients with CML-AP were 61.8% (37.6%-78.9%) and 69.1% (45.8%-83.9%), respectively.

- In HQP1351-CC201, the most frequent grade 3–4 TRAE was thrombocytopenia (48.8%), and no treatment-related deaths occurred.

- In HQP1351-CC202, the most frequent grade 3–4 TRAE was thrombocytopenia (56.5%).

- Conclusions: Olverembatinib was efficacious and well tolerated when administered as monotherapy in patients with TKI-resistant CML-CP or CML-AP and the BCR-ABL1^{T315I} mutation.

Trial in Progress: Phase 1b Bridging Study of the Pharmacokinetic (PK), Safety, and Efficacy of Orally Administered Olverembatinib (HQP1351) in Patients with Refractory Chronic Myeloid Leukemia (CML) and Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph^+ ALL)

- Format: Poster Presentation

- Abstract: 2551

- Session: 632. Chronic Myeloid Leukemia: Clinical and Epidemiological: Poster II

- Highlights

  - This open-label bridging trial in the US is evaluating the PK, efficacy, and safety of olverembatinib administered orally QOD in adults who have CML-CP, CML-AP or blast-phase CML (CML-BP) and Ph^+ ALL.

  - This study is currently recruiting patients, with enrolled individuals being allocated to three dose cohorts: 30, 40, or 50 mg QOD orally. Endpoints of this study include PK, antitumor activity, and safety.

A Phase 1 Study to Evaluate the Safety, Pharmacokinetics (PK) and Pharmacodynamics (PD) of Lisaftoclax (APG-2575), a Novel BCL-2 Inhibitor (BCL-2i), in Patients (pts) with Certain Relapsed or Refractory (R/R) Hematologic Malignancies (HMs)

- Format: Poster Presentation
- Abstract: 3730
- Session: 642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological: Poster III
- Highlights:
  - This Chinese, multicenter, open-label, single-agent, Phase I trial is designed to evaluate the safety (including dose-limiting toxicity DLT and maximum tolerated dose MTD), PK/PD, and preliminary efficacy of lisaftoclax in adults with R/R chronic lymphocytic leukemia (CLL) or non-Hodgkin's lymphoma (NHL).
  - As of July 27, 2021, 31 patients had been enrolled and treated with lisaftoclax at doses ranging from 20 to 800 mg. Patients had a median (range) of 4 (1–14) prior lines of treatment and diagnoses of CLL/SLL (n=9), mantle cell lymphoma (MCL; n=6), marginal zone lymphoma (MZL; n=3), follicular lymphoma (n=8), diffuse large B-cell lymphoma (n=2), lymphoplasmacytic lymphoma/ Waldenstrom macroglobulinemia (n=1), angioimmunoblastic T-cell lymphoma (n=1), or mycosis fungoides (MF; n=1). DLT, MTD, and laboratory/clinical tumor lysis syndrome (TLS) had not been observed. 600 mg was selected as the recommended Phase II dose (RP2D).
  - Lisaftoclax was generally well tolerated. Treatment-related adverse events (TRAEs) reported in 28 patients were mostly grade 1 or 2. Any grade TRAEs in > 10% of patients included thrombocytopenia (34.4%), anemia (28.1%), neutropenia (21.9%), leukopenia (21.9%), diarrhea (15.6%), hyperuricemia (15.6%), hyperphosphatemia (12.5%), and hypertriglyceridemia (12.5%). Grade 3–4 TRAEs were reported in 7 patients, including thrombocytopenia (18.8%), neutropenia (12.5%), leukopenia (9.4%), and anemia (6.3%). Serious TRAEs occurred in 1 patient and included anemia and thrombocytopenia (3.1% each).

- Among the 25 patients who had received at least one tumor evaluation, 9 achieved CR or PR, with a median time to response of 2 cycles. The highest response rates were seen in patients with CLL/SLL (66.7%). Overall Response was observed in all 6 patients with CLL received lisaftoclax at doses ≥ 200 mg, including 1 CR and 5 PR. 2 (66.7%) patients with MZL and 1 (25%) with MCL had achieved PR. In 1 patient with MF, skin tumor shrinkage was observed after 1 lisaftoclax treatment cycle. Favorable absolute lymphocyte count (ALC) profiles included reductions at lisaftoclax doses as low as 100 mg/day.

- The preliminary PK profile showed that exposures increased with lisaftoclax doses from 20 to 800 mg, with an average half-life of 4 to 6 hours. On BH3 profiling, lisaftoclax rapidly triggered changes in BCL-2 complex in patients with CLL/SLL, which were consistent with rapid clinical reductions in ALCs.

- Conclusions: Orally-administered Lisaftoclax was well tolerated up to 800 mg/day. No TLS was observed, even with the daily ramp-up schedule. Compared to venetoclax, lisaftoclax did not show any significant new or unmanageable TRAE. Therefore, lisaftoclax has the potential has a safe and effective treatment for patients with R/R HMs.

Trial in Progress: Phase 1b Study of Lisaftoclax (APG-2575) As a Single Agent or Combined with Other Therapeutic Agents in Patients with Relapsed and/or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (R/R CLL/SLL)

- Format: Poster Presentation

- Abstract: 1554

- Session: 642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological: Poster I

- Highlights:

  - This is a global, open-label, multicenter, two-part Phase Ib dose escalation and dose expansion study designed to assess the safety and tolerability of lisaftoclax (Part 1) and lisaftoclax combinations (Part 2).

  - In a standard "3+3" dose escalation design (Part 1), lisaftoclax is being administered orally once daily in a 28-day cycle at 3 dose levels 400,600, and 800 mg) in parallel. To lower the risk of TLS, lisaftoclax was administered with a daily dose ramp-up.

- Part 2 includes a further standard 3+3 dose escalation of lisaftoclax combined with rituximab, or acalabrutinib (in separate cohorts), with a further planned dose expansion at RP2D of these combination regimens.

- As of July 19, 2021, 71 patients have been enrolled (of 144 planned).

The abstract on pelcitoclax presented at the 2021 ASH Annual Meeting is as follows:

Antitumor Activity of Dual BCL-2/BCL-Xl Inhibitor Pelcitoclax (APG-1252) in Natural Killer/T-Cell Lymphoma (NK/TCL)

- Format: Poster Presentation

- Abstract: 2062

- Session: 203. Lymphocytes and Acquired or Congenital Immunodeficiency Disorders: Poster II

- Highlights:

  - This study evaluated the potential antitumor effect of pelcitoclax in preclinical models of NK/TCL. Cell-based antiproliferation studies showed activity of pelcitoclax and its more potent metabolite APG-1252-M1 toward NK/TCL cell lines that overexpressed BCL-xL. Half-maximal inhibitory concentrations (IC) for pelcitoclax in SNK-1, SNK-6, and SNK-8 (EBV-positive NK/TCL) cell lines were 2.652 ± 2.606 μM, 1.568 ± 1.109 μM, and 0.557 ± 0.383μM, respectively. Corresponding values for APG-1252-M1 were 0.133 ± 0.056 μM, 0.064 ±0.014 μM, and 0.020 ± 0.008 μM, respectively.

  - Mechanistic studies demonstrated that pelcitoclax and the APG-1252-M1 metabolite disrupted the complex of BCL-xL/BCL-2-associated X protein (Bax) and BCL-xL/BCL-2 homologous antagonist killer protein (Bak) in SNK-6 cells, thereby liberating these proapoptotic proteins and further activating downstream apoptosis pathways by cleaving poly-ADP ribose polymerase-1 (PARP-1) and caspase-3. In an SNK-6xenograft model, administration of pelcitoclax at 65 mg/kg and 100 mg/kg either twice or once weekly resulted in significant antitumor effects, with tumor growth rate (T/C%) values ranging from 13.7% to 30.7%.

- Furthermore, the combination of pelcitoclax with histone deacetylase (HDAC) inhibitor chidamide or DDGP (dexamethasone, cisplatin, gemcitabine, and pegaspargase) chemotherapy demonstrated synergistic effects. Pharmacokinetic assessment in mice showed that pelcitoclax had a long half-life in plasma (127 hours) and tumor tissues (25.2hours), justifying intermittent dosing schedules used in vivo. Importantly, the transformation of pelcitoclax to APG-1252-M1 was 16 times higher in tumor tissues compared to plasma (22% vs. 1.3%) after administration of pelcitoclax, thereby suggesting that pelcitoclax can reduce platelet toxicity caused by APG-1252-M1 in plasma.

- Conclusion: Pelcitoclax has promising antitumor effects in NK/TCL, either as a single agent or in combination with an HDAC inhibitor or chemotherapy. These findings provide evidence to further evaluate APG-1252 as a potential treatment for NK/TCL.

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 40 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 12 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, and AstraZeneca. 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.

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 olverembatinib will ultimately be successfully developed and marketed, and we cannot guarantee that we will be able to obtain further approval for, or ultimately market APG-2575, APG-1252 successfully.

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

Suzhou, People's Republic of China, December 14, 2021

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.