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 Delivers Oral Report on the Chinese and US Studies of Olverembatinib (HQP1351) at 2022 ASH Annual Meeting

Ascentage Pharma Group International (the "**Company**" or "**Ascentage Pharma**") is pleased to announce that it has delivered three oral presentations on Chinese and US studies of the Company's type 1 novel drug candidate olverembatinib (HQP1351) at the American Society of Hematology (ASH) 64th Annual Meeting and Exposition held in New Orleans, Louisiana, US. The oral presentations of Chinese studies featured key registration Phase II results and 5-year follow-up data of olverembatinib. Prof. Xiaojun Huang and Prof. Qian Jiang from the Hematology Department of Peking University People's Hospital are the principal investigators of these studies. Meanwhile, it has released preliminary results of olverembatinib (HQP1351) in patients with chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) in an oral presentation, marking the first data readout from an overseas study.

The ASH Annual Meeting is one of the largest gatherings of the international hematology field, featuring world-class advances on cutting-edge scientific and clinical research in hematology. Ascentage Pharma had results from 5 of its clinical trials selected for 4 oral presentations at this year's ASH Annual Meeting. In addition, multiple key product candidates of the Company have been selected for 4 poster presentations at ASH 2022 (with 3 poster presentations being research conducted by independent investigators based on real word evidence).

The oral presentation of the US clinical research of olverembatinib (HQP1351) at ASH 2022 are as follows:

Updated Results of Pivotal Phase 2 Trials of Olverembatinib (HQP1351) in Patients (Pts) with Tyrosine Kinase Inhibitor (TKI)-Resistant Chronic – and Accelerated-Phase Chronic Myeloid Leukemia (CML-CP and CML-AP) with T315I Mutation

- Format: Oral Presentation
- Abstract ID: #170698
- Session: 632. Chronic Myeloid Leukemia: Clinical and Epidemiological: Novel Therapies

- Time: Saturday, December 10, 2022, 10:30 AM, Eastern Time/Saturday, December 10, 2022, 11:30 PM, Beijing Time

- Highlights:

  - The T315I mutation can confer a high degree of resistance to many first- and second-generation TKIs. Olverembatinib is a novel, orally active, third-generation BCR-ABL1 TKI. These Phase II pivotal trials, HQP1351-CC-201 and HQP1351-CC-202, conducted based on favorable Phase I trial results, showed that olverembatinib was efficacious and well tolerated in patients with TKI-resistant CML-CP and CML-AP with the BCR-ABL1^{T315I} genotype.

  - **The HQP1351-CC-201 Study (in patients with CML-CP)**

    As of the cutoff date of September 30, 2022, 41 patients were enrolled, of whom 21 (51%) were male, with a median age of 47 (range, 22-70) years. The median interval from CML diagnosis to first olverembatinib dose was 5.3 (range, 0.6-23.2) years, and 32 (78%) patients had received ≥ 2 prior TKIs. The median treatment duration was 38 (range, 3-41) months, and Sanger sequencing detected 37 (90%) patients with the T315I mutation alone and 4 (10%) with T315I and compound mutations.

    Preliminary efficacy: 100% of patients with CML-CP achieved complete hematologic response (CHR) (31/31, 10 others had CHR at baseline), 83% (34/41) patients had a MCyR, 73% (30/41) had a complete cytogenetic response (CCyR), 59% (24/41) had a MMR, and 54% (22/41) had a molecular response 4.0 (MR$^{4.0}$). The 36-month cumulative rates of MCyR, CCyR, MMR, MR$^{4.0}$, and MR$^{4.5}$ were 80% (64%, 90%), 71% (54%, 83%), 59% (42%, 72%), 51% (35%, 66%), and 51% (35%, 66%), respectively. The rates of continued MCyR, CCyR, and MMR at 36 months were 80% (61%, 91%), 81% (60%, 92%), and 85% (61%, 95%), respectively. The progression-free survival (PFS) rate at 36 months was 92% (77%, 97%) and the overall survival (OS) rate was 95% (82%, 99%). A total of 2 patients withdrew because of progressive disease (PD), 3 failed treatments, 4 had intolerances, 3 withdrew consent, and 2 discontinued for other reasons.

    Safety: Frequent hematologic TRAEs (all grades; grade 3/4; SAEs) included thrombocytopenia (71%; 49%; 7%), anemia (71%; 32%; 2%), leukopenia (51%; 15%; 0), and neutropenia (41%; 22%; 0). Common nonhematologic TRAEs (all grades; grade 3/4) included skin pigmentation (56%; 0%) and elevations in creatine kinase (56%; 20%), alanine transaminase (ALT, 44%; 2%) and aspartate aminotransferase (AST, 37%; 0) levels.

  - **The HQP-1351-CC-202 Study (in patients with CML-AP)**

    As of the cutoff date of September 30, 2022, 23 patients were enrolled, of whom 18 (78%) were male, with a median age of 41 (range, 21-74) years. The median interval from CML diagnosis to first olverembatinib dose was 5.0 (range, 0.4-10.2) years, and 19 (83%) patients had received ≥ 2 prior TKIs. The median treatment duration was 20 (range, 1-41) months. The Sanger sequencing detected 19 (83%) patients with the T315I mutation alone and 4 (17%) with T315I and compound mutations.

Preliminary efficacy: 74% (17/23) of patients with CML-AP achieved CHR. The 36-month cumulative rates of MCyR, CCyR, MMR, $MR^{4.0}$, and $MR^{4.5}$ were 52% (30%, 71%), 52% (29%, 71%), 48% (25%, 68%), 35% (16%, 55%), and 35% (16%, 55%), respectively. The rates of continued MCyR, CCyR, and MMR at 36 months were 81% (44%, 95%), 66% (32%, 86%), and 22% (4%, 50%), respectively. The PFS rate at 36 months was 62% (38%, 79%) and the OS rate was 70% (47%, 84%). A total of 5 patients withdrew because of PDs, 2 failed treatments, 4 experienced intolerances, 1 died, and 1 other discontinued for other reasons.

Safety: Common hematologic TRAEs (all grades; grade 3/4; SAEs) included thrombocytopenia (78%; 57%; 17%), anemia (70%; 35%; 13%), leukopenia (57%; 30%; 0), and neutropenia (26%; 26%; 0). Common nonhematologic AEs included skin pigmentation (70%), hypocalcemia (52%), proteinuria (57%), hypertriglyceridemia (61%), hyperphosphatemia (48%), hyperuricemia (26%), and arthralgia (35%), of which most were grade 1/2.

➢ Conclusions: Olverembatinib was efficacious and well tolerated in patients with TKI-resistant CML-CP and CML-AP with the BCR-ABL1^{T315I} genotype. These results are consistent with the safety and efficacy profiles observed in the T315I mutant cohort in the Phase I study. Based on the results of these pivotal trials, the Center for Drug Evaluation (CDE) of the China National Medical Products Administration (NMPA) granted conditional approval for olverembatinib in November 2021.

A Five-Year Follow-up on Safety and Efficacy of Olverembatinib (HQP1351), a Novel Third-Generation BCR-ABL Tyrosine Kinase Inhibitor (TKI) in Patients with TKI-Resistant Chronic Myeloid Leukemia (CML) in China

- Format: Oral Presentation

- Abstract ID: #170868

- Session: 632. Chronic Myeloid Leukemia: Clinical and Epidemiological: Novel Therapies

- Time: Saturday, December 10, 2022, 10:00 AM, Eastern Time/Saturday, December 10, 2022, 11:00 PM, Beijing Time

- Highlights

  - This open-label, multicenter Phase I study assessed a 5-year follow-up on the safety and efficacy of olverembatinib in adult patients with CML-CP or CML-AP resistant or intolerant to first- or second-generation TKIs. Patients evaluated in the study were orally administered olverembatinib every other day (QOD) in 28-day cycles in 11 dose cohorts ranging from 1 to 60 mg. From October 26, 2016, to September 30, 2022 (data cutoff date), 101 patients with CML-CP (n = 86) and CML-AP (n = 15) were enrolled and treated with olverembatinib. The median treatment duration was 50 months. A total of 71 (70%) patients were male, with a median age of 40 (range, 20-64) years and a median interval from diagnosis to initial olverembatinib treatment of 6.0 (range, 0.3-15) years. A total of 84 (83%) patients received ≥ 2 lines of TKI therapy, and 63 (62%) had T315I mutations. At baseline, compound mutations were detected in 12 (12%) patients, of whom 8 (67%) had the BCR-ABL1^{T315I} genotype. A total of 20 (20%) patients had 2 (n = 13) or ≥ 3 (n = 7) mutations. As of the data cutoff date, 71 (70%) of the 101 patients continued treatment and 30 (23 with CML-CP and 7 with CML-AP) discontinued because of PD, intolerance, or other reasons.

  - Long-term efficacy: In efficacy-evaluable patients with CML-CP (≥ 30 mg dose cohort), the cumulative rate of MCyR, CCyR, MMR, MR$^{4.0}$, and MR$^{4.5}$ at 48 months were 80% (69%, 87%), 71% (60%, 80%), 55% (44%, 65%), 45% (34%, 55%), and 39% (28%, 49%), respectively; and rates of continued MCyR, CCyR, and MMR at 48 months were 75% (63%, 84%), 66% (52%, 77%), and 75% (60%, 86%), respectively. At 48 months, the PFS rate was 88.6 (79.2%, 93.9%).

    In efficacy-evaluable patients with CML-AP (≥ 30mg dose cohort), cumulative rates of MCyR, CCyR, MMR, MR$^{4.0}$, and MR$^{4.5}$ at 48 months were each 40% (15%, 64%); and the rates of continued MCyR, CCyR, and MMR at 48 months were each 83% (27%, 98%). At 48 months, the PFS rate was 50% (22.9%, 72.2%).

    Olverembatinib showed potent activity in patients with CML who harbored compound mutations. In efficacy-evaluable patients with CML-CP with compound mutations, cumulative rates of MCyR, CCyR, MMR, MR$^{4.0}$, and MR$^{4.5}$ at 48 months were 64%, 55%, 58%, 33%, and 25%, respectively; while in the efficacy-evaluable patients with CML-AP who harbored compound mutations, cumulative rates of MCyR, CCyR, MMR, MR$^{4.0}$, and MR$^{4.5}$ at 48 months were each 60% (all in patients receiving ≥ 30 mg).

  - Safety data from the 5-year follow-up: the incidence of hematologic TRAEs such as thrombocytopenia, leukopenia, and anemia, decreased as treatment proceeded over time. The incidence of grade 3/4 thrombocytopenia was associated with BCR-ABL1 mutation status and the interval from CML diagnosis to the first olverembatinib dose. The incidence of nonhematologic TRAEs such as skin pigmentation, hypertriglyceridemia, and proteinuria remained relatively unchanged with longer durations of treatment. Incidences of grade 3/4 cardiovascular events (CVEs) such as hypertension (4%), pulmonary arterial hypertension (1%), tricuspid valve insufficiency (1%), acute coronary syndrome (1%), arrhythmia (1%), coronary arteriosclerosis (1%), atrial fibrillation (1%), cerebral infarction (1%), lacunar infarction (1%), and myocardial damage (1%) did not notably increase as the treatment proceeded over time.

- Conclusions: The 5-year follow-up results of this first-in-human trial show that the response to olverembatinib in patients with TKI-resistant CML-CP and CML-AP improved with longer duration of treatment. The safety of olverembatinib was largely consistent with previously reported results, and the incidences of most TRAEs decreased over time.

Olverembatinib (HQP1351) Overcomes Ponatinib Resistance in Patients with Heavily Pretreated/Refractory Chronic Myeloid Leukemia (CML) and Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL)

- Format: Oral Presentation
- Abstract: #162387
- Session: 632. Chronic Myeloid Leukemia: Clinical and Epidemiological: Novel Agents
- Time: Saturday, December 10, 2022, 10:15 AM (Eastern Time)/Saturday, December 10, 2022, 11:15 PM (Beijing Time)
- Highlights
  - Olverembatinib is a novel third-generation BCR-ABL1 TKI with antitumor activity against CML and Ph+ ALL and a favorable safety profile.
  - This multicenter, open-label, randomized trial is the first to report on the safety, efficacy, and pharmacokinetics (PK) of olverembatinib in patients with CML and Ph+ ALL outside China, who were intolerant or resistant to at least 2 BCR-ABL1 inhibitors, including ponatinib and asciminib, except for those whose disease harbors the T315I mutation, for whom the number of prior lines of therapy was not limited. Study participants were randomized in a ratio of 3:3:2 to receive olverembatinib 30, 40, or 50 mg QOD in 28-day cycles.
  - As of Dec 5, 2022, a total of 51 patients have been enrolled, including 38 with CML-CP, and 13 with CML-AP, CML blast phase (-BP), or Ph+ ALL. The median treatment duration was 32.4 (range, 0-119) weeks. 54.9% (28/51) of patients were men, and the median age was 51 (range, 21-79). In all, 7 (13.7%), 14 (27.5%), and 25 (49%) patients received 2, 3, and ≥ 4 prior lines of treatment, respectively. A total of 28 (54.9%) patients were pretreated with the third-generation TKI ponatinib, including 21 (75.0%) with resistance and 7 (25.0%) with intolerance; a total of 19 (37.3%) had T315I mutations; 28 (54.9%) had cardiovascular diseases at baseline, and 18 (35.3%) had hypertension.
  - PK analysis indicated a dose-proportional increase in olverembatinib plasma exposure from 30 to 50 mg QOD and comparable plasma exposures between the Chinese and US CML populations.

- Safety: Olverembatinib was well tolerated. 34 patients experienced treatment related adverse events (TRAEs) of any grade, the incidence of which tended to be dose-dependent. Most of the nonhematologic TRAEs were grade 1/2. Common grade 3/4 nonhematologic TRAEs included thrombocytopenia (18.9%), neutropenia (16.2%), and decreased leukocyte counts (13.5%). 8 olverembatinib-related serious adverse events (SAEs) were observed in 6 patients, and none of these SAEs led to treatment discontinuation.

- Preliminary efficacy: Olverembatinib conferred potent antileukemic activity in patients with CML and Ph+ ALL. Of 23 efficacy-evaluable patients with CML-CP, 14/18 (77.8%) had a CCyR; 10/23 (43.5%) had a MMR. Olverembatinib was effective in patients with either the T315I-mutant (87.5%, CCyR; 55.6%, MMR) or T315I un-mutant (70.0%, CCyR; 35.7%, MMR), and its effectiveness was not compromised by prior use of ponatinib or asciminib. Among patients who were previously treated with ponatinib, 10/12 (83.3%) experienced CCyR and 6/14 (42.9%) experienced MMR. In particular, among patients with diseases resistant to ponatinib, 7/9 (77.8%) experienced CCyR, and 5/10 (50%) experienced MMR. In patients who were previously treated with asciminib, 1 experienced CCyR and MMR. In the 7 efficacy-evaluable patients with Ph+ leukemia in progressive phase (including CML-AP, CML-BP, and Ph+ ALL), 2 experienced CCyR and MMR. Both patients were resistant to ponatinib and neither harbored the T315I mutation. Of them, 1 patient with Ph+ ALL achieved CCyR after just one cycle of treatment with olverembatinib.

- Conclusions: Olverembatinib monotherapy is efficacious and well tolerated in patients with TKI-refractory CML and Ph+ ALL. Even in patients with CML who were ponatinib or asciminib resistant, or who had T315I mutations, olverembatinib also showed strong efficacy.

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

Suzhou, People's Republic of China, December 11, 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.