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 IS TO PRESENT FIVE STUDIES OF OLVEREMBATINIB, APG-2575, AND APG-115 AT THE AMERICAN SOCIETY OF HEMATOLOGY (ASH) ANNUAL MEETING, FOUR OF WHICH HAVE BEEN SELECTED FOR ORAL PRESENTATIONS

Ascentage Pharma Group International (the "**Company**" or "**Ascentage Pharma**") is pleased to announce that, five studies of Ascentage Pharma's three drug candidates (olverembatinib, lisaftoclax, alrizomadlin), have been selected for presentations, including four oral presentations. The updated results from three studies of the company's novel drug candidate, olverembatinib (HQP1351), have been selected for oral presentations. This is the fifth consecutive year in which studies of olverembatinib were selected for oral presentations at the ASH Annual Meeting, a growing recognition of the drug candidate's promising efficacy and safety by the international hematology community. Additionally, the initial results from a global Phase II study of the company's Bcl-2-selective inhibitor, lisaftoclax (APG-2575), as a monotherapy or in combination regimens for the treatment of relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (R/R CLL/SLL), have been selected for an oral presentation. In this presentation, Ascentage Pharma will release the first data of lisaftoclax in combination with acalabrutinib (CALQUENCE®), a Bruton tyrosine kinase inhibitor (BTKi), or rituximab in patients with R/R CLL/SLL.

It is worth noting that these results selected for oral presentations at the ASH Annual Meeting also include the first batch of safety and efficacy data from the first US study of olverembatinib in patients with chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). These interim results suggest that olverembatinib has promising efficacy and is well tolerated in patients with drug-resistant CML and Ph+ ALL, and has shown promising efficacy in patients who were ponatinib or asciminib resistant. Overall, these interim results signal olverembatinib's potential as the world's first next-generation BCR-ABL inhibitor that could overcome resistance to ponatinib or asciminib.

Additionally, data selected for the other two oral presentations include the updated results from a Phase II pivotal study of olverembatinib in patients with tyrosine kinase inhibitor (TKI)-resistant CML harboring the T315 mutation and the five-year follow-up data from a Phase I study in Chinese patients with TKI-resistant CML. These results further validate the promising safety and efficacy of olverembatinib.

This study of lisaftoclax, to be reported in an oral presentation at the ASH Annual Meeting, showed the promising therapeutic potential of lisaftoclax either as a monotherapy or in combinations in patients with R/R CLL/SLL, demonstrating an interim objective response rate (ORR) of 98% with lisaftoclax plus acalabrutinib and 87% with lisaftoclax plus rituximab. In addition, results from the monotherapy cohort are comparable to prior studies, suggesting favorable safety and promising efficacy of lisaftoclax. The combination therapies, especially lisaftoclax plus acalabrutinib, showed high response rates. In terms of safety profiles, the combination therapies maintained low incidence of tumor lysis syndrome (TLS) and hematologic adverse events.

The ASH Annual Meeting is one of the largest gatherings of the international hematology field, bringing together the latest and most cutting-edge scientific and clinical research in hematology. The 64th ASH Annual Meeting will take place on December 11-14, 2022, both online and in-person in New Orleans, the United States.

Developed by Ascentage Pharma, olverembatinib is a potential best-in-class novel drug that has been designated a Major New Drug Project by China's Ministry of Science and Technology. As the first approved third-generation BCR-ABL inhibitor in China and the second in any country globally, olverembatinib is recommended by both the Guidelines of the Chinese Society of Clinical Oncology (CSCO) and the China Anti-Cancer Association's (CACA) Guidelines for the Holistic Integrative Management of Cancers, for the treatment of patients with TKI-resistant CML harboring the T315I mutation (while the CACA Guidelines also recommend olverembatinib for the treatment of patients with CML intolerant/resistant to at least two TKIs).

Drug Candidate	**Abstract Title**	**Abstract#**	**Format**
Olverembatinib	Olverembatinib (HQP1351) Overcomes Ponatinib Resistance in Patients with Heavily Pretreated/Refractory Chronic Myeloid Leukemia (CML) and Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL)	162387	Oral Presentation
	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	170698	Oral Presentation
	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	170868	Oral Presentation

Drug Candidate	Abstract Title	Abstract#	Format
APG-2575 Lisaftoclax	Lisaftoclax (APG-2575)Safety and Activity As Monotherapy or Combined with Acalabrutinib or Rituximab in Patients (pts) with Treatment-Naïve, Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (R/R CLL/SLL): Initial Data from a Phase 2 Global Study	160386	Oral Presentation
APG-115 Alrizomadlin	MDM2-p53 Inhibitor Alrizomadlin (APG-115) Enhances Antitumor Activity of Pomalidomide in Multiple Myeloma (MM)	162666	Poster Presentation

The abstracts of olverembatinib and Lisaftoclax(APG-2575) to be reported in oral presentations at this year's ASH Annual Meeting are as follows:

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 ID :162387
- Session: 632. Chronic Myeloid Leukemia: Clinical and Epidemiological: Novel Therapies
- 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 is 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.

- ➢ A total of 30 patients have been enrolled, including 23 with CML-CP, 4 with CML-AP, 2 with blast-phase CML (CML-BP), and 1 with Ph+ ALL. The median treatment duration was 4.8 (range, 0.03-21.29) months and the median interval from CML/Ph+ ALL diagnosis to receiving the olverembatinib treatment was 7.0 (range, 1.5-24.0) years. Half (15/30) of patients were men, and the median age was 47.0 (range, 21.0-74.0). In all, 1 (3.3%), 7 (23.3%), 8 (26.7%), and 9 (30.0%) patients received 2, 3, 4, and ≥ 5 prior TKIs, respectively. A total of 21 (70.0%) patients were pretreated with the third-generation TKI ponatinib, including 17 (81.0%) with resistance and 4 (19.0%) with intolerance; a total of 5 (16.7%) were pretreated with asciminib; 12 (40.0%) had T315I mutations; and 13 (43.3%) had hypertension.

- ➢ Safety: Olverembatinib was well tolerated. 22 (73.3%) 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 grade3/4 nonhematologic TRAEs included thrombocytopenia (7/30; 23.3%), neutropenia (5/30; 16.7%), and decreased leukocyte counts (4/30; 13.3%). Of all 30 patients, 11(36.7%) experienced serious adverse events (SAEs), of which 6 (20%) were considered olverembatinib-related and 1 (3.3%) led to treatment discontinuation. 1 patient with CML-AP from the 50 mg dose cohort died of progressive disease (PD).

- ➢ Preliminary efficacy: Olverembatinib conferred potent antileukemic activity in patients with CML and Ph+ ALL. Of 21 efficacy-evaluable patients, 17 were evaluable for cytogenetic response, of whom 10 (58.8%) had a complete cytogenetic response (CCyR); 9/21 (42.9%) patients had a major molecular response (MMR). Olverembatinib was effective in patients with either the T315I-mutant (62.5%, CCyR; 50%, MMR) or T315I un-mutant (55.6%, CCyR; 38.5%, MMR), and its effectiveness was not compromised by prior use of ponatinib or asciminib. Among patients with ponatinib-resistant disease, 5/9 (55.6%) experienced CCyR and 6/11 (54.5%) experienced MMR. 4 of 5 patients pretreated with asciminib showed response. PK analysis indicated a dose-proportional increase in olverembatinib plasma exposure from 30 to 50 mg QOD and comparable plasma exposures between Chinese and US CML populations.

- ➢ 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.

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} mutation.

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

  As of the cutoff date of April 30, 2022, 41 patients were enrolled, of whom 21 (51.2%) were male, with a median age of 47 (range, 22-70) years. The median interval from CML diagnosis to first olverembatinib dose was 5.31 (range, 0.6-23.2) years, and 32 (78.1%) patients had received ≥ 2 prior TKIs. The median treatment duration was 32.7 (range, 3.1-36.7) months.

  Preliminary efficacy: 100% of patients achieved complete hematologic response (CHR) (31/31, 10 others had CHR at baseline), 34/41 (82.9%) had a major cytogenetic response (MCyR), 29/41 (70.7%) CCyR, and 24/41 (58.5%) MMR. Median time to CHR was 1 (95% CI: 1.0-1.9) month, median time to MCyR was 2.8 (95% CI: 2.8-5.6) months, and median time to MMR was 6.5 (95% CI: 2.8 to not reached [NR]) months. At 36 months, the progression-free survival (PFS) rate was 86.3% (95% CI: 70.2%-94.1%) and the overall survival (OS) rate was 95.1% (95% CI: 81.9%-98.8%). A total of 5 patients withdrew because of PD, 4 intolerances, 3 consent withdrawals, and 2 for other reasons.

  Safety: Frequent TRAEs (all grades; grade 3-4; SAEs) included thrombocytopenia (70.7%; 48.8%; 7.3%), anemia (70.7%; 31.7%; 2.4%), leukopenia (51.2%; 14.6%; 0), and neutropenia (41.4%; 21.9%; 0). Common nonhematologic TRAEs (all grades; grade 3-4) included skin pigmentation (56.1%; 0%) and elevations in creatine kinase (56.1%; 19.5%), alanine transaminase (ALT, 43.9%; 2.4%) and aspartate aminotransferase (AST, 36.6%; 0) levels.

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

  As of the cutoff date of April 30,2022, 23 patients were enrolled, of whom 18 (78.3%) were male, with a median age of 41 (range, 21-74) years. The median interval from CML diagnosis to first olverembatinib dose was 4.96 (range, 0.4-10.2) years, and 19 (82.6%) patients had received ≥ 2 prior TKIs. The median treatment duration was 19.7 (range, 1.4-36.4) months.

  Preliminary efficacy: A total of 18 (78.3%) patients experienced a major hematologic response (MaHR) (73.9% CHR and 4.4% no evidence of leukemia [NEL]); 12 (52.2%) MCyR; 12 (52.2%) CCyR; and 11 (47.8%) MMR. The median time to MaHR was 2.8 (95% CI: 1.0-4.7) months, the median time to MCyR was 5.6 (95% CI: 2.00-NR) months, and the median time to MMR was 13.1 (95% CI: 5.6-22.4) months. At 36 months, the PFS rate was 57.1% (95% CI: 33.3%-75.1%) and the OS rate was 69.6% (95% CI: 46.6%-84.2%). 6 patients withdrew because of PD, 4 because of intolerances, and 1 for other reasons; two patients died.

Safety: Common TRAEs (all grades; grade 3-4; SAEs) included thrombocytopenia (78.3%; 56.5%; 17.4%), anemia (69.6%; 34.8%; 13.0%), leukopenia (56.5%; 30.4%; 0), and neutropenia (26.1%; 26.1%; 0). Common nonhematologic AEs included skin pigmentation (69.6%), hypocalcemia (52.2%), proteinuria (56.5%), hypertriglyceridemia (60.9%), hyperphosphatemia (47.8%), hyperuricemia (26.1%), and arthralgia (34.8%), 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} mutation. 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: Chronic Myeloid Leukemia: Clinical and Epidemiological: Mechanisms of Resistance and Emerging Therapies
- Time: Saturday, December 10, 2022, 10:00 AM, Eastern Time/Saturday, December 10, 2022, 11:00 PM, Beijing Time

- Highlights

  - ➢ This open-label, multi-center 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 QOD in 28-day cycles in 11 dose cohorts ranging from 1 to 60 mg.

  - ➢ From October 26, 2016, to April 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 44.7 (1.2-63.1) months. 71 (70.3%) 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, 0.3-15.2) years. A total of 84 (83.2%) patients received ≥2 lines of TKI therapy, and 63 (62.4%) had disease harboring the T315I mutation. At baseline, compound mutations were detected in 12 (11.9%) patients, of whom 8 (66.7%) harbored the BCR-ABL1^{T315I} mutation. A total of 20 (19.9%) patients had 2 (n = 13) or ≥ 3 (n = 7) mutations. As of the data cutoff date, 72 (71.3%) patients continued treatment and 28 (21 with CML-CP and 7 with CML-AP) discontinued because of disease progression, intolerance, or other reasons. The cumulative median drug exposure dose was 20,175 (range, 660-34,395) mg. Of the 101 patients, 79 (78.2%) were treated > 3 years, 21 (20.8%) > 4 years, and 3 (3.0%) > 5 years.

- ➢ Preliminary efficacy: Of the evaluable patients with CML-CP, 100% experienced CHR, 80% MCyR, 71.3% CCyR, and 55.3% MMR; Of the evaluable patients with CML-AP, 85.7% had CHR and 40% each for MCyR, CCyR, and MMR; Of evaluable patients with the T315I mutation, 100% of those with CML-CP experienced CHR, 83.7% MCyR, and 73.1% MMR and 80.0% with CML-AP had CHR and 54.5% each for MCyR and MMR. PFS at 48 months was 85.6% (95% CI: 70.6%-93.3%) in patients with CML-CP and 50.0% (95% CI: 22.9%-72.2%) in patients with CML-AP; In the 12 patients with compound mutations, next-generation sequencing confirmed that 7 (58.0%) experienced MMR and 3 (25.0%) MR4.5. At the last follow-up, 3 patients had progressed to CML-AP or CML-BP and died, and 7 remained on olverembatinib. One patient had an MMR and 2 each CHR, CCyR, or MR4.5.

- ➢ Safety: Most TRAEs were grade 1-2. The most frequent nonhematologic AE was, primarily, grade 1-2 skin hyperpigmentation (85.1%). Grade ≥ 3 nonhematologic AEs included hypertriglyceridemia (10.9%), pyrexia (6.9%), and proteinuria (6.9%). The common hematologic TRAE was thrombocytopenia, which was observed in 79 (78.2%) patients, including 52 (51.5% of total population) with grade ≥ 3 and 7 (6.9%) with SAEs. Leukopenia was grade ≥ 3 in 21 (20.8%) patients but not serious, while anemia was grade ≥ 3 in 17 (16.8%) and serious in 4 (4.0%).

- ➢ Conclusions: The 5-year follow-up results of this first-in-human trial show durable responses and good tolerance of olverembatinib in heavily pretreated patients with CML.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (R/R CLL/SLL): Initial Data from a Phase 2 Global Study

- Format: Oral Presentation
- Abstract ID :160386
- Session: 642. Chronic Myeloid Leukemia: Clinical and Epidemiological: Developmental Medicine and COVID-19
- Time: Monday, December 12, 2022, 5:15 PM, Eastern Time/Tuesday, December 13, 2022, 6:15 AM, Beijing Time

- Highlights

  - ➢ Lisaftoclax, a specific Bcl-2 inhibitor, is active in patients with R/R CLL/SLL, including patients whose disease harbored del(17p) and had progressive disease (PD) after BTKi therapies. This is the first report of lisaftoclax combined with acalabrutinib or rituximab in patients with CLL/SLL.

  - ➢ Patients with R/R CLL/SLL were treated daily with oral lisaftoclax (400, 600, and 800 mg) alone or combined with continuous acalabrutinib or rituximab for six 28-day cycles. Primary objectives were to determine the recommended Phase II dose (RP2D), safety, and efficacy, including ORRs of lisaftoclax alone and combined with acalabrutinib or rituximab. Patients underwent lisaftoclax daily ramp-up over 4 to 6 days, with the monitoring of TLS as follows: Day 1 (D1) 20 mg; D2 50 mg; D3 100 mg; D4 200 mg; and D5 400 mg. Dose ramp-up was followed by Cycle 1 Day 1 (C1D1) of lisaftoclax target doses of 400, 600, or 800 mg. Patients in the combination groups completed ramp-up, as well as an additional 7 days of lead-in of lisaftoclax at the target dose, before acalabrutinib or rituximab was added on C1D8, and then treated until PD or unacceptable toxicity was observed.

- As of July 4, 2022, 141 patients had been enrolled. The median age was 62 (range, 18-80) years; 98 (70%) were male; and the Eastern Cooperative Oncology Group (ECOG) score was 0-1 in 125 (89%) and 2 in 15 (11%). The median number of prior therapies was 2 (range, 1-15). A total of 17 (12%) patients had progressed on BTKi (n = 15) and/or after venetoclax (n = 3) therapy. In the combination cohorts (n = 95), 39 (41%) patients had the TP53 mutation or del(17p), 27 (28%) had del(11q), 36 (38%) had unmutated IGHV, 14 (15%) had mutated IGHV, and 47% were unknown. Median exposure to lisaftoclax was 10.0 (range, 0-30) cycles, including 16.5 in the lisaftoclax monotherapy group, 9.0 (1-15) in the rituximab, and 7.0 (0-18) in the acalabrutinib combination cohorts. 3 (2%) patients with bulky disease met the criteria for TLS (2 clinical/1 laboratory), and 2 of them fully recovered. No TLS was observed when acalabrutinib or rituximab was added to lisaftoclax on C1D8.

- Safety: Common (> 5%) adverse events (AEs) of any grade in all cohorts were: neutropenia (30% [26% grade 3/4]); COVID-19 infection (26%); anemia (24% [12% grade 3/4]), diarrhea (20%); thrombocytopenia (17% [5% grade 3/4]), hyperuricemia or pyrexia (9% each); nausea, headache, or fatigue (8% each); increased aspartate aminotransferase (AST) levels (7%); hyperphosphatemia (6%); and increased creatinine (6%). First onset of grade ≥ 3 cytopenias occurred during ramp-up or C1 and rarely after C2 (n = 3[2%]). Grade ≥ 3 neutropenia was manageable with growth factor support in 13% of patients. No discontinuations were due to lisaftoclax alone or combined with the other agents. No dose-limiting toxicities were observed. No drug-drug interactions were observed in either combination group.

- Preliminary efficacy: Rapid normalization of absolute lymphocyte counts occurred in 56% of patients at the end of daily ramp-up. ORRs were 65% (n = 43) in the monotherapy group and 98% (n = 53) and 87% (n = 23) in the acalabrutinib and rituximab cohorts, respectively.

- Conclusions: Initiated with a daily dose ramp-up, lisaftoclax alone or combined with acalabrutinib or rituximab had a manageable safety profile and favorable clinical activity in patients with treatment-naïve or R/R CLL/SLL.

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-2575 and APG-115 successfully.

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

Suzhou, People's Republic of China, November 3, 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.