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 to Present Results from Multiple Clinical Studies of olverembatinib, lisaftoclax, APG-5918 and APG-2449 at the 2024 American Society of Hematology (ASH) Annual Meeting, two of which have been selected for Oral Reports

Ascentage Pharma Group International (the "**Company**" or "**Ascentage Pharma**") is pleased to announce that results from multiple clinical and preclinical studies of the Company's four drug candidates (olverembatinib, lisaftoclax, APG-5918 and APG-2449) have been selected for presentations, including two Oral Reports, at the American Society of Hematology (ASH) Annual Meeting. The multiple studies of its novel investigational drug candidate, olverembatinib (HQP1351), have been selected for presentations, including an Oral Report, at the 66th American Society of Hematology (ASH) Annual Meeting. This is the seventh consecutive year for clinical data of olverembatinib to be selected for Oral Reports at the meeting, an achievement reflecting the strong recognition of olverembatinib's safety and efficacy profile by the international hematology community. The latest results from three clinical studies of one of the Company's key drug candidate, lisaftoclax (APG-2575), have been selected for presentations, including an Oral Report, at the 66th American Society of Hematology (ASH) Annual Meeting. This is the third consecutive year for clinical results of lisaftoclax to be selected by the ASH Annual Meeting.

Developed by Ascentage Pharma, olverembatinib is the first China-approved third-generation BCR: ABL inhibitor, currently being jointly commercialized in China by Ascentage Pharma and Innovent Biologics, Inc. At this year's ASH Annual Meeting, Ascentage Pharma will present an Oral Report featuring the latest clinical data of olverembatinib in the second-line treatment for patients with chronic-phase chronic myeloid leukemia (CP-CML), from a study led by Professor Weiming Li, the principal investigator from Wuhan Union Hospital. Furthermore, updated data from a global multicenter study of olverembatinib and an investigational clinical study of olverembatinib in combination with lisaftoclax (APG-2575), another one of Ascentage Pharma's lead drug candidates in investigation, in children with relapsed/refractory Philadelphia chromosome-positive acute lymphoblastic leukemia (R/R Ph+ ALL) will also be released in Poster Presentations at the meeting. Olverembatinib is a compound under study as an investigational drug and not yet approved in the United States.

Developed by Ascentage Pharma, lisaftoclax is a novel orally available Bcl-2 inhibitor with global potential and clinical benefits for an array of hematologic malignancies and solid tumors. At this year's ASH Annual Meeting, Ascentage Pharma will present an Oral Report featuring the latest results from a Phase I/II study of lisaftoclax in patients with relapsed/refractory multiple myeloma (R/R MM) or immunoglobulin light chain (AL) amyloidosis. Furthermore, the latest data of lisaftoclax combinations in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and myelodysplastic syndrome (MDS) will also be released in Poster Presentation at the meeting. Lisoftoclax is a compound under study as an investigational drug and not yet approved in the United States.

The ASH Annual Meeting is one of the largest gatherings of the international hematology community, bringing together the latest scientific research in the pathogenesis and clinical treatment of hematologic diseases. The 66th ASH Annual Meeting will take place from December 7, 2024 to December -10, 2024, local time, both online and in-person in San Diego, California (United States.

An overview of presentations featuring Ascentage Pharma's drug candidates at ASH 2024 are set out as follows:

Format	**Drug Candidate**	**Abstract title**	**Abstract#**
Oral Presentation	Olverembatinib (HQP1351)	Olverembatinib as Second-Line (2L) Therapy in Patients (pts) with Chronic Phase-Chronic Myeloid Leukemia (CP-CML)	480
	Lisaftoclax (APG-2575)	Lisaftoclax (APG-2575) Combined with Novel Therapeutic Regimens in Patients (pts) with Relapsed or Refractory Multiple Myeloma (R/R MM) or Immunoglobulin Light Chain (AL) Amyloidosis	1022
Poster Presentation	Olverembatinib (HQP1351)	Olverembatinib (HQP1351) Overcomes Resistance/Intolerance to Asciminib and Ponatinib in Patients (pts) with Heavily Pretreated Chronic-Phase Chronic Myeloid Leukemia (CP CML): A 1.5-Year Follow-up Update with Comprehensive Exposure-Response (E-R) Analyses	3151
	Lisaftoclax (APG-2575)	Lisaftoclax (APG-2575) Demonstrates Activity and Safety When Given with Accelerated Ramp-up and then Combined with Acalabrutinib or Rituximab in Patients (pts) with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL), Including Those with Prior Exposure to Venetoclax	4614

Format	Drug Candidate	Abstract title	Abstract#
	Lisaftoclax (APG-2575)	Lisaftoclax (APG-2575), a Novel BCL-2 Inhibitor, in Combination with Azacitidine in Treatment of Patients with Myelodysplastic Syndrome (MDS)	3202
	Olverembatinib + Lisaftoclax	Safety and Efficacy of Olverembatinib (HQP1351) Combined with Lisaftoclax (APG-2575) in Children and Adolescents with Relapsed/Refractory Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (R/R Ph+ ALL): First Report from a Phase 1 Study	1443
	Lisaftoclax + APG-2449	APG-2449, a Novel Focal Adhesion Kinase (FAK) Inhibitor, Exhibits Antileukemic Activity and Enhances Lisaftoclax (APG-2575)-Induced Apoptosis in Acute Myeloid Leukemia (AML)	4150
	APG-5918	Embryonic Ectoderm Development (EED) Inhibitor APG-5918 Demonstrates Robust Antitumor Activity in Preclinical Models of T-Cell Lymphomas (TCLs)	1415
Abstract only	Olverembatinib + Lisaftoclax	Olverembatinib (HQP1351) in Combination with Lisaftoclax Overcomes Venetoclax Resistance in Preclinical Model of Acute Myeloid Leukemia (AML)	5777

Major study abstracts on olverembatinib and lisaftoclax selected for presentations at the 2024 ASH Annual Meeting are as follows:

Oral Presentation

Olverembatinib as Second-Line (2L) Therapy in Patients (pts) with Chronic Phase-Chronic Myeloid Leukemia (CP-CML)

Format: Oral Presentation

Abstract number: 480

Session: 632. Chronic Myeloid Leukemia: Novel Molecules in Clinical Practice

Time: Sunday, December 8, 2024; 9:30 AM – 11:00 AM (United States western time)/Monday, December 9, 2024; 1:30 AM – 3:30 AM (Beijing time)

First Author: Professor Weiming Li, Department of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology

Highlights:

Background: Olverembatinib, a third-generation tyrosine kinase inhibitor (TKI), has demonstrated remarkable efficacy and a favorable safety profile in patients with CML resistant and/or intolerant to at least 2 TKIs or with the T315I mutation. The aim of this study was to assess the efficacy and safety of olverembatinib as a second-line treatment for patients with CP-CML without the T315I mutation.

Introduction: This is a single-arm, multicenter, open-label study designed to evaluate the efficacy, safety, and patients' quality of life of orally-administered olverembatinib (40 mg QOD) in patients with CP-CML who were resistant/intolerant to one prior line of TKIs (including imatinib, flumatinib, nilotinib, and dasatinib) without the T315I mutation.

Enrolled Patients and Study Methods: As of July 29, 2024, the study enrolled a total of 42 patients with non-T315I-mutant CML-CP. These patients received orally-administered olverembatinib every other day (QOD) in 28-day cycles.

Efficacy Results:

- As of July 29, 2024, 33 (78.6%) patients had at least one efficacy assessment, 28 (66.7%) had at least two, 23 (54.8%) had at least three. Three patients had not yet undergone their first efficacy assessment.

- At data cutoff, 75.0% (24/32) of patients achieved a complete cytogenetic response (CCyR) and 40.6% (13/32) achieved a major molecular response (MMR). The CCyR and MMR rates evaluated at the end of Cycles 6, 9, 12, and 18 were 53.4% and 28.6%, 64.8% and 32.5%, 69.1% and 32.5%, and 77.7% and 43.9%, respectively, suggesting that efficacy improved over time.

- In 32 efficacy-evaluable patients, 23 were pretreated with second-generation TKIs as first-line treatment, of whom 19 (82.68%) achieved CCyR, and 10 (43.5%) achieved MMR. In 9 patients who were pretreated with imatinib, 5 achieved CCyR (55.6%) and 3 achieved MMR (33.3%).

Safety Results: The median (range) treatment duration was 16.0 (1-18) months. A total of 37 (88.1%) patients experienced any-grade treatment-related adverse events (TRAEs), of whom 19 (45.2%) had grade ≥ 3 TRAEs and 5 (11.9%) had olverembatinib-related serious AEs (SAEs). Nonhematologic TRAEs included skin hyperpigmentation (38.1%), hyperuricemia (23.8%), and creatine phosphokinase increase (21.4%). Most of these TRAEs were grade 1 or 2. Grade ≥ 3 hematologic toxicities included platelet count decreased (38.1%), neutropenia (21.4%), and anemia (7.1%). Possibly olverembatinib-related any-grade cardiovascular events included hypertension (4.8%) and atrial tachycardia (2.4%), all of which were grade 1 or 2. Olverembatinib-related SAEs included platelet count decreased (7.1%), anemia, myelosuppression, and pyrexia (2.4% each). No deaths were reported.

Conclusions: Olverembatinib may provide an effective and safe treatment option for patients with second-line CP-CML, especially those who have failed on second-generation TKIs in the first-list setting.

Lisaftoclax (APG-2575) Combined with Novel Therapeutic Regimens in Patients (pts) with Relapsed or Refractory Multiple Myeloma (R/R MM) or Immunoglobulin Light Chain (AL) Amyloidosis

Format: Oral Presentation

Abstract number#: 1022

Session: 654. Multiple Myeloma: Pharmacologic Therapies: Into the Future: New Drugs and Combinations in Multiple Myeloma

Time: Monday, December 9, 2024, 4:45 PM (United States western time)/Tuesday, December 10, 8:45 AM (Beijing time)

First Author: Dr. Sikander Ailawadhi, Mayo Clinic

Highlights:

Background:

- MM is characterized by the proliferation of abnormal clonal plasma cells, causing destructive bone lesions, kidney injury, anemia, and hypercalcemia. The treatment of MM involves immunomodulatory agents, proteasome inhibitors, and anti-CD38 monoclonal antibodies to achieve disease remission.

- AL amyloidosis comprises disorders of abnormal extracellular deposition of misfolded proteins in various organs with resultant damage, and the key strategy of treatment is to prolong the time to or reverse organ dysfunction. However, many patients will relapse from the standard triplet or quadruplet therapies, necessitating additional treatments with novel mechanisms of action.

- Lisaftoclax is a novel investigational Bcl-2 inhibitor that has shown strong antitumor activity in earlier studies. Here, we report the clinical data of lisaftoclax combined with novel therapeutic regimens in patients with R/R MM or R/R AL amyloidosis.

Introduction: This is a multicenter, open-label Phase I/II study.

Enrolled Patients and Study Methods:

- Eligible patients had an ECOG performance status ≤ 2, ≥ 1 prior line of therapy, and adequate organ function. Patients with R/R AL amyloidosis had confirmed symptomatic organ involvement. Lisaftoclax was administered orally daily in repeated 28-day cycles. Pomalidomide, daratumumab, and lenalidomide were administered per label use. Dexamethasone 40 mg (20 mg, patients > 75 years old) was administered on days 1, 8, 15, and 22 of 28-day cycles.

- This study evaluated the safety and efficacy of lisaftoclax combined with pomalidomide and dexamethasone (Pd; Arm A) or daratumumab, lenalidomide, and dexamethasone (DRd; Arm B) in R/R MM and lisaftoclax combined with the Pd regimen in R/R AL amyloidosis (Arm C).

- As of May 29, 2024, 52 patients were enrolled, including 42 with R/R MM and 10 with AL amyloidosis. The median (range) age of all patients was 69.5 (24-88) years, of whom 63.5% were male and 63.5% were ≥ 65 years of age. The enrolled patients were heavily pretreated, with a median (range) number of prior therapy lines of 3 (1-19).

- In Arm A (n = 35), lisaftoclax was administered orally at dose assigned: 400mg (n = 3); 600 mg (n = 4); 800 mg (n = 15); 1,000 mg (n = 7); and 1,200 mg (n = 6). In Arm B (n = 7), all patients were treated with lisaftoclax 600 mg. In Arm C (n = 10), lisaftoclax was administered at 400 mg (n = 1); 600 mg (n = 4); 800 mg (n = 3); and 1,000 mg (n = 2).

Efficacy Results:

- In Arm A, out of 31 evaluable patients, 3 (9.7%) achieved complete remission (CR), 7 (22.6%) reached very good partial remission (VGPR), and 9 (29.0%) achieved partial response (PR). The overall response rate (ORR) was 61.3%(n = 19), and 10 (32.3%) achieved ≥ VGPR.

- In Arm B, of 4 evaluable patients, 2 (50%) achieved CR and 2 (50%) achieved ≥ VGPR.

- In Arm C, of 7 assessed patients, 1 (14.3%) achieved CR, 4 (57.1%) achieved VGPR, 1 (14.3%) achieved PR, and 5 (71.4%) achieved ≥ VGPR, for an ORR of 6 (85.7%); 2 patients had cardiac responses.

Safety Results: Among 49 patients in the safety population, 34 (69.4%) reported any-grade lisaftoclax treatment-related AEs (TRAEs; ≥ 5% incidence), including neutropenia (20.4%), thrombocytopenia (6.1%), leukopenia (10.2%), nausea (16.3%), abdominal distension (10.2%), diarrhea (12.2%), and constipation (8.2%). A total of 11 patients experienced grade ≥ 3 TRAEs, including neutropenia (14.3%) and febrile neutropenia (2%), and 3 patients experienced lisaftoclax-related serious AEs (1 each): febrile neutropenia, acute kidney injury, and diarrhea with electrolyte imbalance. In Arm B, 1 pt experienced a dose-limiting toxicity (prolonged QT interval). Pharmacokinetic analyses showed no drug-drug interaction (DDI) in all patients treated with lisaftoclax at all doses in combination with other therapeutic agents used in 3 arms.

Conclusions: These findings suggest that lisaftoclax improves the depth of response in patients with R/R MM or AL amyloidosis when combined with Pd or DRd. These combination therapies demonstrated a favorable safety profile with no DDIs, particularly in hematologic side effects.

Poster Presentations

Olverembatinib (HQP1351) Overcomes Resistance/Intolerance to Asciminib and Ponatinib in Patients (pts) with Heavily Pretreated Chronic-Phase Chronic Myeloid Leukemia (CP CML): A 1.5-Year Follow-up Update with Comprehensive Exposure-Response (E-R) Analyses

Format: Poster Presentation

Abstract number: 3151

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

Time: Sunday, December 8, 2024; 6:00 PM – 8:00 PM (United States western time)/Monday, December 9, 2024; 10:00 AM – 12:00 AM (Beijing time)

First Author: Dr. Elias Jabbour, Department of Leukemia, The University of Texas MD Anderson Cancer Center

Highlights:

Introduction: New treatment options are needed for patients with CP-CML resistant/intolerant to third-generation (3G) TKI ponatinib and/or asciminib, a specifically targeting the ABL myristoyl pocket (STAMP) inhibitor. Olverembatinib is a well-tolerated TKI with potential to overcome resistance. This update presents efficacy and safety data of olverembatinib in patients with heavily pretreated CP-CML.

Enrolled Patients and Study Methods:

- Adults with CP-CML previously treated with ≥2 TKIs and/or a STAMP inhibitor, adequate organ function, and no major molecular response (MMR) were eligible.

- As of July 28, 2024, 67 pts with CP-CML were enrolled; median (range) follow-up was 74.3 (0.1-217.1) weeks; median (range) age, 50 (21-80) years; and 38 (56.7%) were male.

- Patients were randomly allocated to receive olverembatinib at doses of 30, 40, or 50 mg orally every other day (QOD) in 28-day cycles, with stratification based on T315I mutation status. Comprehensive E-R analyses were performed.

Efficacy Results:

- No patient had efficacy at baseline, 35 of 60 (58.3%) evaluable patients achieved CCyR and 29/64 (45.3%) achieved MMR. At 12 months, the overall MMR rate was 61.4% (27/44). CCyR was achieved by 66.7% of patients with the T315I mutation vs 54.8% without it, and MMR was achieved by 50.0% vs 43.5%, respectively.

- Of 28 cytogenetic response-evaluable patients with ponatinib-failed CP-CML, 15 (53.6%) achieved CCyR. The CCyR rates in patients with prior ponatinib resistance and intolerance were 52.2% (12/23) and 75.0% (3/4), respectively. In the 30 molecular response-evaluable patients who were previously treated with ponatinib, 12 (40%) achieved MMR, including 47.8% (11/23) of those with prior resistance and 16.7% (1/6) with intolerance. No patient above had efficacy at baseline.

- In evaluable patients with asciminib treatment failure, 37.5% (6/16) achieved CCyR and 30% (6/20) achieved MMR, including a CCyR rate of 30.8% (4/13) and an MMR rate of 26.7% (4/15) in those with prior resistance, and a CCyR rate of 50.0% (1/2) and an MMR rate of 25.0% (1/4) in those with intolerance. No patient had efficacy at baseline.

- CCyR and MMR rates in patients previously treated with both ponatinib and asciminib were 30% and 25%, respectively. No patient had efficacy at baseline.

Safety Results: Among 66 dosed subjects, a total of 62 (93.9%) reported TEAEs of any grade, with 44 (66.7%) experiencing ≥G3 TEAEs. In addition, 60 (90.9%) patients reported TRAEs of any grade. Common TRAEs (≥20%) were elevated creatine phosphokinase (37.9%), thrombocytopenia (24.2%), and increased alanine transaminase (22.7%).

Conclusions: Olverembatinib was well tolerated and showed strong and durable antileukemic activity in patients with heavily pretreated CP-CML. The registrational study is recruiting.

Safety and Efficacy of Olverembatinib (HQP1351) Combined with Lisaftoclax (APG-2575) in Children and Adolescents with Relapsed/Refractory Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (R/R Ph+ ALL): First Report from a Phase 1 Study

Format: Poster Presentation

Abstract number: 1443

Session: 613. Acute Lymphoblastic Leukemias: Therapies Excluding Allogeneic Transplantation: Poster I

Time: Saturday, December 7, 2024; 5:30 PM – 7:30 PM (United States western time)/Sunday, December 8, 2024; 9:30 AM to 11:30 AM (Beijing time)

First Author: Professor Jingliao Zhang, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences

Highlights:

Background: Olverembatinib, a novel third-generation TKI, is well tolerated and exerts strong and durable antileukemic activity in patients with heavily pretreated CP-CML with or without the T315I mutation. Investigational lisaftoclax, a novel Bcl-2 inhibitor, has shown clinical antitumor benefits in patients with multiple hematologic malignancies. Currently, there are no effective treatment options available for pediatric patients with R/R Ph+ ALL. This study was designed to explore the safety, efficacy, and pharmacokinetic (PK) profile of olverembatinib alone or combined with lisaftoclax in children and adolescents with R/R Ph+ ALL.

Methods:

- **Methods:** This was an open-label, Phase Ib study that enrolled children and adolescents aged < 18 years with R/R Ph+ ALL resistant or intolerant to at least 1 tyrosine kinase inhibitor (TKI) (prior use of TKIs was not considered if patients had T315I mutation). Patients were required to have adequate Karnofsky/Lansky performance status score and organ function. Patients with symptomatic central nervous system disorders or significant bleeding, which were unrelated to Ph+ ALL, were excluded.

- Olverembatinib was administered orally at 40 mg adult equivalent dose (AED) every other day for 2 weeks (Days [D] 1-14), followed by same dose of olverembatinib in combination with lisaftoclax at an assigned dose of 200/400/600 mg (AED) daily (QD) on D13-42 (a 3-day dose ramp-up from D13-15 was needed). Dexamethasone at 6 mg/m^2/day was administered orally QD from D15-42. The primary endpoints included safety assessments, overall response rate (ORR), measurable residual disease (MRD) negativity rate, and PK characteristics of olverembatinib alone/in combination with lisaftoclax.

Patient Enrollment: From September 2022 to June 2024, a total of 10 patients were enrolled. The median (range) age was 13.0 (11-15) years, and 6 patients were male. The median (range) body weight was 49.85 (35.9-86.0) kg. Nine (90.0%) patients expressed the p190 transcript and 1 patient (10.0%) expressed the p210 transcript. Three patients harbored BCR-ABL1 mutations [2, T315I; 1, F317L (c.951C>A)] at baseline. After 1 patient discontinued from the trial because of seizure on D1 of Course 1 (C1D1), 9 eligible patients were included in the 3+3 dose escalation model (n = 6, R/R; n = 3, intolerant): 3 patients in each Arm (A, B, and C) at assigned lisaftoclax dose levels of 200, 400, and 600 mg (AED), respectively. These patients completed 42 days of treatment and were assessed for the primary endpoints.

Efficacy Results: Among 6 patients evaluable for morphologic responses, 2 patients achieved complete responses with incomplete count recovery (CRis), 2 achieved partial responses (PRs) at the end of olverembatinib monotherapy (EOM), resulting in an overall response rate (ORR) of 66.7%; and 5 (83.3%) patients achieved CRis at the end of olverembatinib and lisaftoclax combination course (EOC). In the 7 patients who were evaluable for molecular responses, 5 (71.4%) achieved MRD negativity, of which 1 was at EOM and 4 at EOC.

Safety Results: 6 of 10 patients experienced grade ≥ 3 hematologic treatment-emergent adverse events, including anemia (3/10), neutropenia (7/10), and thrombocytopenia (3/10); 1 patient had grade 3 alanine aminotransferase increase leading to treatment discontinuation, and 1 patient discontinued the trial after experiencing a seizure at C1D1.

PK Analyses: Preliminary PK analyses revealed similar PK characteristics and comparable exposure between pediatric and adult populations for olverembatinib and lisaftoclax. There was no significant accumulation after multiple doses, and no drug-drug interactions were observed between olverembatinib and lisaftoclax.

Conclusions: These preliminary data showed that olverembatinib in combination with lisaftoclax appears to be a safe and effective regimen in pediatric patients with R/R Ph+ ALL. This regimen resulted in a promising CR rate of 83.3% and MRD negativity rate of 71.4% without intensive chemotherapy or immunotherapy. The study is currently in the dose-expansion phase.

Lisaftoclax (APG-2575) Demonstrates Activity and Safety When Given With Accelerated Ramp-up and Then Combined With Acalabrutinib or Rituximab in Patients (pts) With Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL), Including Those With Prior Exposure to Venetoclax

Format: Poster Presentation

Abstract number#: 4614

Session: 642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological: Poster III

Time: Monday, December 9, 2024; 6:00 PM – 8:00 PM (United States western time)/Tuesday, December 10, 2024; 10:00 AM – 12:00 AM (Beijing time)

First Author: Dr. Matthew Davids, Department of Medical Oncology, Dana-Farber Cancer Institute

Highlights:

Background: Bcl-2 inhibition with venetoclax (ven) was a major advance in CLL treatment, but the 5-week dose ramp-up to mitigate the risk of tumor lysis syndrome and drug-drug interactions (DDIs) challenge treatment optimization. Lisaftoclax is an investigational, oral Bcl-2i with a short half-life, allowing it to be ramped-up on a daily schedule.

Introduction:

- We present updated clinical data of lisaftoclax alone or combined with acalabrutinib or rituximab in patients with treatment-naïve (TN; lisaftoclax-acalabrutinib arm), relapsed/refractory, or prior ven-treated CLL/SLL.

Enrolled Patients and Study Methods:

- From March 20, 2020, to June 27, 2024, 176 patients were enrolled: 46 in monotherapy and 39 and 91 in rituximab and acalabrutinib combination cohorts, respectively; 87.5% (154/176) of patients were R/R and 12.5% (22/176) were TN. The median (range) age was 63 (34-80) years; 67% were male; 25.6% had del(17p) and/or TP53 mutation; and 70.6% had unmutated IGHV.

- Median (range) duration of treatment with lisaftoclax was 16.5 (1-54; monotherapy), 24 (3-39; rituximab), and 27 (1-43; acalabrutinib) months. In R/R patients, the median (range) number of prior lines of therapy was 2 (1-15), and 14 (9%) patients had been treated with ven. Patients who had received prior treatment with ven had a median (range) age of 65 (51-78); 79% were male;

- Of evaluable patients, 50% had del(17p), 36% had TP53 mut, 64% had del(11q), 38% had complex karyotype (≥ 3 abnormalities), and 92% had unmutated IGHV; 57% were BTKi naïve; and the median (range) number of prior therapies was 3 (1-6).

- Patients were treated with a rapid 4 – to 6-day daily ramp-up of lisaftoclax from 20 mg to a target dose of 400, 600, or 800 mg, receiving daily oral lisaftoclax alone or, plus continuous acalabrutinib or 6 cycles of rituximab in 28-day cycles, starting on Cycle 1 Day 8 (C1D8) until disease progression, complete response by C24, or unacceptable toxicity. Blood samples were collected for pharmacokinetic (PK) and exposure-response (E-R) analyses.

Efficacy Results:

The ORR for lisaftoclax plus acalabrutinib in 87 patients was 96.6%, and the median duration of response (DOR; 95% CI, 23-NR) and median progression-free survival (PFS; 95% CI, 34-NR) were not reached. The 12 – and 18-month PFS rates were 89% and 86%, respectively.

Fourteen R/R CLL ven-exposed patients received lisaftoclax plus acalabrutinib:

- of whom 9 had progressed on ven, 3 relapsed after completing ven, and 2 discontinued due to ven intolerance. Median (range) duration of treatment was 16 (3-25) months. Safety profile was similar to that of other study cohorts.

- ORR was 85.7% (12/14) in the ven-exposed patients;

- ORR was 100% (8/8) in the ven-exposed but BTKi-naïve patients;
- ORR was 66.7% (4/6) in the ven – and BTKi-exposed patients
- The median DOR and PFS were not reached. The 12 – and 18-month PFS rates were 84% and 73%, respectively.

Safety Results:

- Incidence and severity of TEAEs were similar across cohorts.
- Common (>10%) any-grade TEAEs in all cohorts combined were neutropenia (59 [33.5%]), diarrhea (38 [21.6%]), anemia (27 [15.3%]), and thrombocytopenia (26 [14.8%]). Grade ≥ 3 TEAEs were neutropenia in 15 (32.6%), 10 (25.6%), and 22 (24%) patients and anemia in 10 (21.7%), 5 (12.8%), and 12 (13.2%) patients in monotherapy, rituximab, and acalabrutinib combination cohorts, respectively. Comprehensive E-R analyses indicated that lisaftoclax had similar systemic exposure as monotherapy or when combined with acalabrutinib or rituximab; lisaftoclax had no DDI when combined with acalabrutinib or rituximab.
- No discontinuations were attributed to lisaftoclax TRAEs. Forty-four (95.7%) patients in monotherapy discontinued treatment. Most discontinuations were due to progressive disease (n = 41 [23.3%]) and AEs (n = 13 [7.4%]); 9 (5.1%) patients withdrew consent; 7 (4%) achieved complete response or MRD negativity after ≥ 24 cycles; 5 (2.8%) died; and 18 (10.2%) discontinued for other reasons. Clinical (n = 2) and laboratory (n = 3) TLS was observed in 5 (2.8%) patients on lisaftoclax (by Howard/Cairo-Bishop criteria), with cases rapidly resolving to resume lisaftoclax safely.

Conclusions: Our data suggest that lisaftoclax combined with acalabrutinib is effective for patients with prior ven exposure, including those with progression on ven. In this updated analysis with longer follow-up, no DDIs or new safety findings were observed in TN or R/R CLL/SLL patients treated with lisaftoclax monotherapy or combinations. We continue to accrue patients with prior ven exposure to further evaluate this promising signal. A global registrational phase III study is recruiting.

Lisaftoclax (APG-2575), a Novel BCL-2 Inhibitor, in Combination with Azacitidine in Treatment of Patients with Myelodysplastic Syndrome (MDS)

Format: Poster Presentation

Abstract number#: 3202

Session: 637. Myelodysplastic Syndromes: Clinical and Epidemiological: Poster II

Time: Sunday, December 8, 2024, 6:00 PM – 8:00 PM (United States western time)/Monday, December 9, 2024; 10:00 AM – 12:00 AM (Beijing time)

First Author: Prof. Huafeng Wang, The First Affiliated Hospital, Zhejiang University School of Medicine

Highlights

Background: Hypomethylating agents (HMAs) remain the standard of care in higher-risk MDS. However, its clinical efficacy is limited, and patients who have failed or are resistant to HMAs have a poor prognosis, leaving those patients in desperate need for new therapeutic options.

Introduction: Preclinical data have shown that the novel investigational Bcl-2 inhibitor lisaftoclax combined with an HMA can synergistically induce apoptosis in cancer cells in AML and MDS. Reported here are the follow-up safety and efficacy data from a Phase Ib/II clinical trial evaluating lisaftoclax combined with azacitidine in adults (≥18 years) with MDS.

Enrolled Patients and Study Methods:

- This study enrolled patients with higher-risk MDS (IPSS-R score > 3.5; blasts > 5%), including those with treatment-naïve (TN) or relapsed or refractory (R/R) disease, were enrolled. Lisaftoclax at an assigned dose (400, 600, or 800 mg) was administered orally once daily from Days 1 to 14 and combined with azacitidine (75 mg/m^2/day) on Days 1 to 7 in repeated 28-day cycles. A daily ramp-up was used before the first cycle to prevent tumor lysis syndrome (TLS). The primary objectives of the study were to assess the efficacy and safety of the combination regimen in patients with MDS and establish the recommended Phase III dose for lisaftoclax. Complete response (CR) and marrow CR (mCR) rates were evaluated in accordance with 2006 International Working Group (IWG) criteria.

- As of July 1, 2024, a total of 49 patients were enrolled: 8 had R/R MDS (lisaftoclax 600 mg [n = 5] and 800 mg [n = 3]) and 41 had TN MDS (lisaftoclax 400 mg [n = 16], 600 mg [n = 23], and 800 mg [n = 2]). The median (range) age was 66 (22-83) years, and 55.1% of patients were male. IPSS-R risk categories were intermediate (12/49 [24.5%]), high (24/49 [49.0%]), and very high (13/49 [26.5%]). Among the 39 patients with genetic mutational profile data, 9 (23.1%) had TP53 mutations; 11 (28.2%) had TET2 mutations; 10 (25.6%) had ASXL1 mutations; and 10 (25.6%) had RUNX1 mutations. At baseline, 70.8% of patients reported grade ≥ 3 anemia; 54.2% had grade ≥ 3 neutropenia; and 45.8% had grade ≥ 3 thrombocytopenia.

Efficacy Results:

- Lisaftoclax dose reduction occurred in 4 (8.2%) patients. Neither 60-day mortality nor TLS was reported. In 8 patients with R/R MDS, the median (range) duration of treatment (DOT) was 3.2 (1.2-9.4) months. The overall response rate (ORR = CR [12.5%] + marrow CR [62.5%]) was 75.0% (95% CI, 34.9-96.8). In 40 efficacy-evaluable patients with TN MDS, the median DOT (range) was 4.5 (0.5-12.1) months; the ORR was 77.5% (95% CI, 61.5-89.2); and the CR rate was 25.0% per IWG 2006 criteria. Furthermore, the ORR and CR rate in 23 patients with TN MDS treated with lisaftoclax 600 mg combined with azacitidine were 73.9% and 30.4%, respectively; because these patients had a relatively longer median DOT (6.01 months), we conducted further analyses per IWG 2023 criteria. The composite CR rate (CR2023 = CR [52.2%] + CRL [17.4%]) was 69.6%, and the median time to CR (range) was 2.84 (1.1 ~ 8.7) months. Both the median progression-free survival and overall survival rates were not reached.

Safety Results:

- All patients treated with lisaftoclax combined with azacitidine reported treatment-emergent adverse events (TEAEs). Of these, 93.8% were grade ≥ 3 AEs and 35.4% were serious AEs. Common grade ≥ 3 nonhematologic TEAEs (≥ 10% incidence) included pneumonia (24.4%) and hypokalemia (10.2%). Common grade ≥ 3 hematologic TEAEs included leukocyte count decreased (75.5%), neutropenia (69.4%), thrombocytopenia (65.3%), anemia (24.5%), and febrile neutropenia (18.4%).

- Grade ≥ 3 infections were reported in 46.9% of patients, of which 26.5% were treatment-related. Treatment delays between cycles due to AEs occurred in 11 (22.4%) patients, with a median delay time (range) of 12 (1-63) days.

- A total of 95.9% of patients reported treatment-related adverse events (TRAEs), of which 87.8% were grade ≥ 3 AEs and 28.6% were serious AEs. Common grade ≥ 3 hematologic TRAEs included leukocyte count decreased (71.4%), neutropenia (65.3%), thrombocytopenia (65.3%), anemia (20.4%), and febrile neutropenia (12.2%).

Conclusions: The clinical data support an emerging role for lisaftoclax in combination with azacitidine for treatment of patients with higher-risk TN or R/R MDS. The combination therapy was efficacious and well tolerated, resulting in no 60-day mortality, few dose modifications, and low infection rates, supporting further clinical development of this combination in patients with higher-risk MDS.

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, APG-5918 and APG-2449 successfully.

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

Suzhou, People's Republic of China, November 6, 2024

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, Mr. Ren Wei and Dr. David Sidransky as independent non-executive Directors.