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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 Presentation Featuring Updated Data Demonstrating Promising Efficacy and Safety of APG-2575 in Patients with Relapsed or Refractory CLL/SLL; APG-115 Demonstrating Complete Response in Combination with Pembrolizumab in Patients with Advanced Melanoma Resistant or Refractory to Prior Immuno-Oncologic Drugs

Ascentage Pharma Group International (the “**Company**” or “**Ascentage Pharma**”) is pleased to announce that the Company released updated results from the first-in-human study of the Bcl-2 inhibitor Lisoftoclax (APG-2575) in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (R/R CLL/SLL) and other hematologic malignancies. The findings were reported in an oral presentation at the 57th American Society of Clinical Oncology (ASCO) Annual Meeting. Meanwhile, the Company released updated results by way of oral presentation from a Phase II study of the MDM2-p53 inhibitor Alrizomadlin (APG-115) in combination with pembrolizumab in patients with unresectable or metastatic melanoma or advanced solid tumors that have progressed on prior immuno-oncologic (I-O) drugs.

Ascentage Pharma’s clinical study results have been selected for presentations at the ASCO Annual Meeting for the fourth consecutive year. This year, results from four of its studies clinical studies were selected for presentations at the ASCO Annual Meeting, including two oral presentations. Updated data on APG-2575 have demonstrated favorable safety and efficacy, including an objective response rate (ORR) of 80% and a favorable tolerability profile, with manageable adverse events (AEs) in patients with R/R CLL/SLL. Moreover, no dose-limiting toxicity (DLT) was observed at the maximum tested dose of 1,200 mg. The maximum tolerated dose (MTD) has not been reached, and no laboratory or clinical tumor lysis syndrome (TLS) has been reported. The clinical study data from the on-going Phase

II study of APG-115 have demonstrated a favourable safety profile and meaningful clinical antitumor activity, including one patient with a complete response (CR), an objective response rate (ORR) of 24.1% and a disease control rate (DCR) of 55.2% in the PD-1/PD-L1 inhibitor-resistant melanoma cohort. In addition, partial responses (PRs) were reported in enrolled patients with other tumor types.

An overview of the four abstracts presented at the 2021 ASCO Annual Meeting:

Drug Candidate	Abstract Title	Abstract #	Format
Lisaftoclax (APG-2575)	First-in-human study of APG-2575, a novel Bcl-2 inhibitor, in patients with relapsed/refractory (R/R) CLL and other hematologic malignancies (HMs)	7502	Oral Presentation
Alrizomadlin (APG-115)	Preliminary results of a phase II study of APG-115, a novel, small-molecule MDM2 inhibitor, in combination with pembrolizumab in patients with unresectable or metastatic melanoma or advanced solid tumors that have failed immuno-oncologic drugs	2506	Oral Presentation
	A phase I/II trial of novel MDM2 inhibitor APG-115, with or without platinum chemotherapy, in patients with p53 wild-type salivary gland carcinoma	TPS6094	Poster Presentation
Pelcitoclax (APG-1252)	A multicenter phase Ib/II study of APG-1252 in combination with paclitaxel in patients with relapsed/refractory small-cell lung cancer (R/R SCLC)	TPS8589	Poster Presentation

Highlights of the oral presentation on APG-2575 at this year's ASCO Annual Meeting:

First-in-human study of APG-2575, a novel Bcl-2 inhibitor, in patients with relapsed/refractory (R/R) CLL and other hematologic malignancies (HMs)

Abstract: #7502

- This first-in-human global Phase I study assessed the safety, pharmacokinetics (PK), pharmacodynamics (PD), efficacy, and MTD/recommended Phase II dose (RP2D) of APG-2575 in patients with R/R CLL and other HMs. APG-2575 was orally administered once daily in a 28-day cycle. Patients with CLL or intermediate-high TLS risk were initiated on a daily ramp-up schedule until the dose assigned before the study cycles.
- As of April 15, 2021, 36 patients had been enrolled and treated with APG-2575 at doses ranging from 20 to 1,200 mg, with a median of 2 (range: 1–13) prior lines of treatment. These patients had been diagnosed with R/R CLL/SLL (n=15), multiple myeloma (MM, n=6), follicular lymphoma (FL, n=5), Waldenström macroglobulinemia (WM, n=5); and either acute myeloid leukemia (AML), mantle cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL), myelodysplastic syndromes (MDS), or hairy cell leukemia (HCL; n=1 each). These patients received a median of 6 cycles (range: 1–24) of treatment with APG-2575.
- APG-2575 was well tolerated, with manageable AEs. No DLT was observed even at the maximum dose of 1,200 mg. The MTD has not been reached, and no laboratory or clinical TLS has been reported. Hematologic treatment-related adverse events (TRAEs) of any grade in more than 10% patients included neutropenia and anemia, while nonhematologic TRAEs included fatigue, diarrhea, constipation, and nausea.
- In the 15 evaluable patients with R/R CLL/SLL, 7 (46.7%) each were assessed as Rai stage III-IV or intermediate-high per International Prognostic Index (IPI). Patients in this cohort received a median of 9 (range: 5–24) cycles of treatment, and 12 patients achieved partial responses (PRs), for an ORR of 80% and a median time to response of 2 (range: 2–8) treatment cycles.
- Among 21 patients with R/R non CLL/SLL, who received a median of 3 (range: 1–13) prior lines of treatment, 20 were evaluable. Of these individuals, 1 with t(11;14)-mutant MM achieved minor response (MR) after 2 treatment cycles. A total of 10 (50%) patients in this cohort achieved stable disease (SD) or deeper responses.

- The preliminary PK profile showed that exposures increased with APG-2575 at doses ranging from 20 to 1,200 mg (average half-life: 4–5 hours). On BH3 profiling, APG-2575 rapidly triggered changes in Bcl-2 complex in CLL/SLL patient samples, which were consistent with rapid clinical reductions in absolute lymphocyte counts (ALCs).
- In conclusion, efficacy and safety data showed that the Bcl-2 inhibitor APG-2575 offers a potential alternative treatment for patients with R/R CLL/SLL and other HMs, with a daily ramp-up schedule that may be more patient-friendly and a favorable preliminary safety profile.

Highlights of the oral presentation on APG-115 at this year’s ASCO Annual Meeting:

Preliminary results of a phase II study of alrizomadlin (APG-115), a novel, small-molecule MDM2 inhibitor, in combination with pembrolizumab in patients with unresectable or metastatic melanoma or advanced solid tumors that have failed immuno-oncologic drugs

Abstract: #2506

- This open-label, multicenter Phase II study in the US assessed the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity of APG-115 in combination with pembrolizumab in patients with advanced solid tumors.
- As of April 15, 2021, 102 patients had been enrolled in the Phase II part of the study and treated with APG-115 at the recommended Phase II dose (RP2D) of 150 mg every other day, in combination with pembrolizumab. This study has 6 cohorts, including patients with: PD-1/PD-L1 inhibitor-resistant melanoma, non-small cell lung cancer (NSCLC), and urothelial carcinoma; or malignant peripheral nerve sheath tumor (MPNST), liposarcoma, and ATM mutant solid tumors.
- Antitumor Effects:
 - In the PD-1/PD-L1 inhibitor-resistant melanoma cohort (n=29), there was 1 confirmed partial response (PR) out of 7 patients with uveal (ocular) melanoma; 2 PRs (1 confirmed + 1 unconfirmed) out of 5 patients with mucosal melanoma; and 1 complete response (CR, confirmed) and 3 PRs (2 confirmed + 1 unconfirmed) out of 15 patients with cutaneous melanoma. The ORR and DCR in the melanoma cohort were 24.1% (7/29) and 55.2% (16/29), respectively.
 - In the MPNST cohort (n=6), 1 PR (unconfirmed).

- In the liposarcoma cohort (n=16), 1 PR (unconfirmed) and 12 stable diseases (SDs), at a DCR of 81.2% (13/16).
- In the PD-1/PD-L1 inhibitor-resistant NSCLC (n=15) and urothelial carcinoma (n=8 evaluable) cohorts, 1 patient in each cohort achieved confirmed PR.
- Common treatment-related adverse events (TRAEs) observed in more than 10% of patients were nausea, thrombocytopenia, vomiting, fatigue, decreased appetite, diarrhea, neutropenia, and anemia.
- In conclusion, APG-115 combined with pembrolizumab is well tolerated, and did not exhibit any overlapping toxicity. These preliminary results have established proof of concept clinically that the combination regimen has antitumor activity in patients with IO relapsed/refractory metastatic melanoma, (including uveal melanoma, mucosal melanoma, or cutaneous melanoma). In addition, this combination therapy also showed promising antitumor activity in patients with MPNST or liposarcoma for which pembrolizumab has no approved indications.

About APG-2575

APG-2575 is a novel, orally administered small-molecule Bcl-2-selective inhibitor being developed by Ascentage Pharma. APG-2575 is designed to treat hematologic malignancies and solid tumors by selectively blocking antiapoptotic protein Bcl-2 to restore the normal apoptosis process in cancer cells. APG-2575 is the first China-developed Bcl-2 inhibitor entering clinical development in China. At present, APG-2575 has been cleared and approved to enter multiple Phase Ib/II studies in the US, China, and Australia, and is being developed globally for the treatment of multiple hematologic malignancies.

About APG-115

Being developed by Ascentage Pharma, APG-115 is an orally administered, selective, small-molecule inhibitor of the MDM2 protein. APG-115 has strong binding affinity to MDM2 and is designed to activate tumor suppression activity of p53 by blocking the MDM2-p53 protein-protein interaction. APG-115 is the first MDM2-p53 inhibitor entering clinical development in China and is currently being investigated in multiple studies in solid tumors and hematologic malignancies in China, Australia, and the US.

About APG-1252

APG-1252 is a Bcl-2/Bcl-xL dual inhibitor drug designed to restore apoptosis through selective inhibition of Bcl-2 and Bcl-xL proteins. Multiple Phase Ib/II studies of APG-1252 as a single agent or in combinations for the treatment of a range of advanced tumors, including small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), are being conducted in China, the US and Australia.

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 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 key apoptosis regulators. The Company is conducting more than 40 Phase I/II clinical trials in China, the US and Australia. HQP1351, the Company's core drug candidate developed for the treatment of drug-resistant chronic myeloid leukemia (CML), has been granted an Orphan Drug Designation (ODD) and a Fast Track Designation (FTD) by the US FDA, and a New Drug Application (NDA) for the drug candidate has been submitted and subsequently granted Priority Review by the Center for Drug Evaluation (CDE) in China. As at the date of this announcement, Ascentage Pharma has obtained a total of eleven ODDs from the US FDA for four of the Company's investigational drug candidates.

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-115 and 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, June 8, 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.