CStone Pharmaceuticals
基石藥業
(Incorporated in the Cayman Islands with limited liability)
(Stock Code: 2616)

(1) BUSINESS UPDATES; (2) INSIDE INFORMATION – KEY AUDIT FINDING; AND (3) UNUSUAL PRICE AND TRADING VOLUME MOVEMENTS

BUSINESS UPDATES

Cstone Announced the International Multi-Center Registration Trial of Anti-Pd-1 Antibody Nofazinlimab in Combination with Lenvatinib as First-Line Treatment for Patients with Advanced Hepatocellular Carcinoma Successfully Reached the Prespecified Enrollment Target

CStone Pharmaceuticals (the "**Company**" or "**CStone**", together with its subsidiaries, the "**Group**") is pleased to announce that the international multi-center phase III registrational trial of the anti-PD-1 antibody nofazinlimab (CS1003) in combination with lenvatinib as first-line treatment for patients with advanced hepatocellular carcinoma ("**HCC**"), CS1003-305, has successfully reached its prespecified enrollment target.

Dr. Jason Yang, Chief Medical Officer of CStone, said, "We are pleased that the CS1003-305 trial met the prespecified patient enrollment target ahead of schedule. It's our third large registrational trial which has recently achieved the prespecified enrollment target in high incidence gastrointestinal cancer, following the two ongoing studies of sugemalimab as first-line treatment of gastric cancer and esophageal squamous cell carcinoma. Early phase clinical trial results[1] showed that nofazinlimab in combination with lenvatinib shows promising anti-tumor activity and a manageable safety profile in Chinese patients with unresectable HCC as first-line treatment. Nofazinlimab was granted Orphan Drug Designation ("**ODD**") by the U.S. Food and Drug Administration ("**FDA**") in 2020. We look forward to bringing this promising treatment option to the patients with advanced HCC worldwide."

CS1003-305 is an international, multi-center, double-blind, randomized, phase III registrational clinical trial to evaluate the efficacy and safety of nofazilimab in combination with lenvatinib compared with placebo in combination with lenvatinib in subjects with no prior systemic treatment and with unresectable advanced HCC. The trial is conducted in 74 study sites globally including China, US, Spain, Italy, and Poland. The primary endpoints are overall survival ("**OS**") and progression-free survival ("**PFS**"). Dr. Jia Fan, academician of Chinese Academy of Sciences (CAS) and president of Zhongshan Hospital affiliated to Fudan University, is the global principal investigator for this trial.

The CS1003-305 trial design was based on the encouraging data from the CS1003-102 trial.

CS1003-102[1] (NCT03809767) is a phase Ia/Ib, open-label, dose-escalation and expansion study conducted in China, arm 5 of phase Ib part which aimed to evaluate the safety and efficacy of nofazinlimab in combination with lenvatinib as first-line treatment for patients with unresectable HCC (uHCC). The primary endpoint is objective response rate ("**ORR**") per RECIST V1.1 by investigators.

As of June 22, 2020, 20 patients were enrolled and received study treatment. The majority of patients were male (90%), had ECOG PS score 1 (75%), had BCLC stage C HCC (90%), and had HBV infection (65%).

Nofazinlimab in combination with lenvatinib showed promising efficacy and manageable safety profile:

- A total of 20 patients were enrolled for evaluating preliminary anti-tumor activity, and the ORR reached 40% (8/20).

- Median follow-up duration was 6.2 months, and median PFS was 8.4 months. Median OS and duration of response (DoR) were not reached as of the data cut-off date.

- A total of 20 patients were evaluable for safety assessment. The most common treatment-related adverse events ("**TRAEs**") of any grade were blood bilirubin increased, protein urine present, and proteinuria. 5 patients each had a grade 3 TRAE, including hypertension, bilirubin conjugated increased, diarrhea, diabetes mellitus, and hypophosphatemia. No patients experienced grade 4 and above any treatment-related adverse events.

About HCC

Liver cancer is a common malignant tumor of digestive system worldwide. According to GLOBOCAN 2020 (Global Cancer Incidence, Mortality and Prevalence) data of the International Agency for Research on Cancer (IARC), a specialized agency of the World Health Organization, global new cases of liver cancer is more than 900,000, and death cases are more than 830,000 per year. The number of death cases is close to the number of new cases. Liver cancer is the second leading cause of cancer-related death and its incidence is increasing globally[2]. HCC is the most common form of liver cancer and accounts for approximately 90% of cases[3]. Systemic antitumor therapy plays an important role in the treatment of advanced HCC. Despite the expanding implementation of surgical and locoregional therapies worldwide, estimates suggest that approximately 50-60% of patients with HCC will ultimately be treated with systemic therapies[2]. A median survival for symptomatic advanced-stage HCC cases treated with systemic therapies is approximately 1-1.5 years[3]. Poor prognosis of HCC is attributed primarily to tumor presentation at an advanced stage when there is no effective treatment to achieve the long term survival of patients.[4]

About nofazinlimab (CS1003)

Nofazinlimab is a humanized recombinant IgG4 monoclonal antibody targeting human programmed cell death protein 1 ("**PD-1**") being developed in solid tumors. Nofazinlimab shows comparable high binding affinities to the PD-1 of humans, cynomolgus monkey, and mouse, and can block the interaction of PD-1 with its ligands PD-L1 and PD-L2.

The U.S. FDA has granted nofazinlimab ODD in July 2020 for the treatment of patients with HCC.

CStone formed a strategic collaboration agreement with EQRx, under which EQRx licensed the exclusive rights to two immuno-oncology assets, sugemalimab and nofazinlimab, for development and commercialization outside Greater China. CStone retains rights to nofazinlimab in Greater China, where it can continue to pursue development as a monotherapy or as part of its combination strategy for this drug.

Reference:

1. Shen L et al, ESMO Congress 2020, Abstract 987P, A Phase 1b study of the PD-1 antagonist CS1003 plus lenvatinib (LEN) in Chinese patients (pts) with the first-line (1L) unresectable hepatocellular carcinoma (uHCC).

2. Llovet JM et al, Nat Rev Clin Oncol. 2022 Mar;19(3):151-172. Immunotherapies for hepatocellular carcinoma

3. Llovet JM et al, Nat Rev Dis Primers. 2021 Jan 21;7(1):6. Hepatocellular carcinoma.

4. Ahn JC et al, Hepatology. 2021 Jan;73(1):422-436. Detection of Circulating Tumor Cells and Their Implications as a Biomarker for Diagnosis, Prognostication, and Therapeutic Monitoring in Hepatocellular Carcinoma

About CStone

CStone is a biopharmaceutical company focused on research, development, and commercialization of innovative immuno-oncology and precision medicines to address the unmet medical needs of cancer patients in China and worldwide. Established in 2015, CStone has assembled a world-class management team with extensive experience in innovative drug development, clinical research, and commercialization. The company has built an oncology-focused pipeline of 15 drug candidates with a strategic emphasis on immuno-oncology combination therapies. Currently, CStone has received seven new drug application approvals for its four drugs. Multiple late-stage drug candidates are now under pivotal clinical trials or registration. CStone's vision is to become globally recognized as a world-renowned biopharmaceutical company by bringing innovative oncology therapies to cancer patients worldwide.

For more information about CStone, please visit: www.cstonepharma.com.

Cstone Announced Acceptance of New Drug Application for Pralsetinib for the Treatment of Ret Fusion-Positive Non-Small Cell Lung Cancer in Hong Kong, China

The Company is also pleased to announce that the new drug application ("**NDA**") for pralsetinib for the treatment of rearranged during transfection ("**RET**") fusion-positive locally advanced or metastatic non-small cell lung cancer ("**NSCLC**") has been accepted in Hong Kong, China.

Dr. Jason Yang, Chief Medical Officer of CStone, said, "We are very glad that the NDA of another innovative precision medicine, pralsetinib, is accepted for the treatment of advanced RET fusion-positive NSCLC, after AYVAKIT® (avapritinib) was approved for the treatment of unresectable or metastatic PDGFRA D842V mutant gastrointestinal stromal tumors in Hong Kong, China in December 2021. In the global phase 1/2 ARROW study, pralsetinib demonstrated durable clinical benefits and a generally well-tolerated safety profile in patients with RET fusion-positive locally advanced or metastatic NSCLC. We look forward to the potential approval of pralsetinib in Hong Kong, China to help benefit more patients as quickly as possible."

The NDA acceptance of pralsetinib in Hong Kong, China is based on results from the global phase I/II ARROW study. This trial is designed to evaluate the safety, tolerability, and efficacy of pralsetinib in patients with RET-fusion positive NSCLC, RET-mutant medullary thyroid cancer ("**MTC**"), and other advanced solid tumors with RET fusions.

Results from the ARROW trial in global patients with advanced RET fusion-positive NSCLC were presented at the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting in June 2021. As of a date cutoff date of November 6, 2020, pralsetinib showed durable clinical benefits in patients with RET fusion-positive NSCLC who had measurable disease at baseline and received a starting dose of 400 mg once daily.

- In 68 treatment-naïve patients, the ORR was 79 percent (95% CI: 68%, 88%). The complete response ("**CR**") rate was 6 percent, 10 percent of patients had complete regression of target tumors, and 74 percent of patients had a partial response ("**PR**"). The median duration of response ("**DOR**") was not reached (95% CI: 9.0 months, not reached).

- In 126 patients who previously received platinum-based chemotherapy, the ORR was 62 percent (95% CI: 53%, 70%). The CR rate was 4 percent, 12 percent of patients had complete regression of target tumors, and 58 percent of patients had a PR. The median DOR was 22.3 months (95% CI: 15.1 months, not reached).

- As of the data cutoff date, a total of 471 patients were enrolled across tumor types with a pralsetinib dose starting at 400 mg once daily. The most common treatment-related adverse events (AEs) reported by investigators were neutropenia, increased aspartate aminotransferase, anemia, decreased white blood cell count, increased alanine aminotransferase, hypertension, constipation and asthenia.

About RET fusion-positive NSCLC

In recent years, China has had rising lung cancer incidence. According to the latest estimates on the global burden of cancer released by International Agency for Research on Cancer (IARC), in 2020, an estimated 0.82 million new lung cancer cases and 0.71 million new lung cancer deaths occurred in China. Among all Chinese cancer patients, lung cancer is the leading cause of cancer-related deaths. NSCLC is the most common type of lung cancer.

In lung cancer, there are a number of somatic mutations, including EGFR, ALK, and ROS1, that can be targeted with approved therapies. RET fusions account for 1-2% of NSCLC patients, the majority of whom are non-smokers.

About Pralsetinib

Pralsetinib is a once-daily oral targeted therapy approved by the National Medical Products Administration of China under the brand name GAVRETO® for the treatment of adults with locally advanced or metastatic rearranged during transfection (RET) fusion-positive NSCLC after platinum-based chemotherapy, and for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant MTC who requires systemic therapy, and adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who requires systemic therapy and radioactive iodine-refractory (if radioactive iodine treatment is appropriate).

GAVRETO is approved by the U.S. FDA for the treatment of three indications: adult patients with metastatic RET fusion-positive NSCLC as detected by an FDA approved test, adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant MTC, and adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate). These indications are approved under accelerated approval based on ORR and DOR. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

The European Commission has granted conditional marketing authorization for GAVRETO as a monotherapy for the treatment of adult patients with RET fusion-positive advanced NSCLC not previously treated with a RET inhibitor.

Pralsetinib is not approved for the treatment of any other indication in China, the United States or Europe.

Pralsetinib is designed to selectively and potently target oncogenic RET alterations, including secondary RET mutations predicted to drive resistance to treatment. In preclinical studies, pralsetinib inhibited RET at lower concentrations than other pharmacologically relevant kinases, including VEGFR2, FGFR2, and JAK2.

Pralsetinib is a potent and selective RET inhibitor discovered by CStone's partner Blueprint Medicines Corporation (NASDAQ: BPMC) ("**Blueprint Medicines**"). CStone has an exclusive collaboration and license agreement with Blueprint Medicines for the development and commercialization of pralsetinib in Greater China, which encompasses Mainland China, Hong Kong, Macau and Taiwan.

Blueprint Medicines and Roche are co-developing GAVRETO globally (excluding Greater China) for the treatment of patients with RET-altered NSCLC, thyroid cancer, and other solid tumors. Blueprint Medicines and Genentech, a member of the Roche Group, are co-commercializing GAVRETO in the U.S., and Roche has exclusive commercialization rights for GAVRETO outside of the U.S. (excluding Greater China).

About CStone

For more information about CStone, please see above and visit: www.cstonepharma.com.

INSIDE INFORMATION – KEY AUDIT FINDING

This part of the announcement is made by the Company pursuant to Rule 13.09(2) of the Rules Governing the Listing of the Securities on The Stock Exchange of Hong Kong Limited (the "**Listing Rules**") and the inside information provision (as defined in the Listing Rules) under Part XIVA of the Securities and Futures Ordinance (Cap. 571 of the Laws of Hong Kong) (the "**SFO**").

The board of directors (the "**Board**") of the Company wishes to inform the Shareholders and potential investors that, recently, during the course of the audit process for the year ended December 31, 2021, it has been identified that funds of the Company amounting to approximately HK$227 million, were invested, in July 2021, in a segregated portfolio company registered in the Cayman Islands via a fund linked note issued by CMB International Global Products Limited (the "**Investment**"). The Company is working with the auditors to provide additional information with respect to the Investment, including as to its validity and recoverability. In line with the auditor's request, the Audit Committee is arranging to engage specialists to conduct an independent investigation into the Investment, with findings to be reported in the first place to the Audit Committee of the Board. The Board's intention is that, based on findings of the investigation, it will be possible to properly assess the fair value of the investment as at December 31, 2021.

The Company is still in the process of finalizing the annual results of the Group for the year ended December 31, 2021. This announcement is made based on, among other information, the Board's preliminary review and assessment of the Group's unaudited consolidated management accounts and information currently available to the Board. The information contained in this announcement may therefore be subject to adjustments as and when further and/or updated information is made available to the Board. Details of the Group's financial performance for the year ended December 31, 2021 will be disclosed in its annual results announcement. In the light of the fact that the investigation referred to above will take time to complete, it is likely that the finalization of the audited financial statements and the completion of the audit may take longer than the prescribed time frame.

The Board acknowledges that any delay in publishing the annual results will constitute a non-compliance with Rule 13.49(1) of the Listing Rules.

Unusual Price and Trading Volume Movements

The Board has noted recent unusual fluctions in the price and trading volume of the Company's shares at The Stock Exchange of Hong Kong Limited. Having made all such enquiries with respect to the Group as is reasonable in the circumstances, the Board confirms that (i) the operations of the Group remain normal, and the Group continues to carry on its business as usual, and (ii) save as described above, the Board is not aware of any information which must be announced to avoid a false market in the Company's securities or of any inside information that needs to be disclosed under Part XIVA of the SFO. The Board and the management of the Group are closely monitoring the situation and market development. The Company will make further announcement(s) in compliance with applicable laws and regulations in order to avoid a false market in its securities or if the Company becomes aware of any material developments with respect to its business, operational and/or financial conditions.

Shareholders and potential investors of the Company are advised to exercise due caution when dealing in the securities of the Company. When in doubt, Shareholders and potential investors of the Company are advised to seek advice from professional or financial advisers.

By Order of the Board
CStone Pharmaceuticals
Dr. Frank Ningjun Jiang
Chairman

Suzhou, the People's Republic of China, March 18, 2022

As at the date of this announcement, the board of directors of the Company comprises Dr. Frank Ningjun Jiang as Chairman and executive director, Dr. Wei Li, Mr. Kenneth Walton Hitchner III, Mr. Yanling Cao, Mr. Xianghong Lin and Mr. Edward Hu as non-executive directors, and Dr. Paul Herbert Chew, Mr. Ting Yuk Anthony Wu and Mr. Hongbin Sun as independent non-executive directors.