

## OPERATIONS REVIEW

### INNOVATION PLATFORM

The Chi-Med pipeline of drug candidates has been created and developed by the in-house research and development operation, known as the Innovation Platform, which was started in 2002. Since then, Chi-Med has assembled a team of over 290 scientists and staff (end 2014: 238) based in China, of which 183 had advanced technical degrees including 21 M.D.s and 48 doctorate degrees as of 31 January 2016. This fast growing team has created a large scale and fully-integrated drug discovery and development operation covering chemistry, biology, pharmacology, toxicology, chemistry and manufacturing controls for clinical and commercial supply, clinical and regulatory and other functions, which work seamlessly together.

Over the last decade, the core research and development philosophy has been to take a highly disciplined chemistry-focused approach to design uniquely selective small molecule tyrosine kinase inhibitors against 8 molecular targets, deliberately engineered to improve drug exposure and reduce known off-target toxicities. Accordingly, we believe these drug candidates, such as savolitinib (targeting c-Met), HMPL-523 (targeting Syk) and HMPL-453 (targeting FGFR1/2/3), have the potential to be global first-in-class therapies. In the cases of fruquintinib (targeting VEGFR 1/2/3), sulfatinib (targeting VEGFR/FGFR1), epitinib (targeting EGFR activating mutation with brain metastasis), theliatinib (targeting EGFR wild-type) and HMPL-689 (targeting PI3K $\delta$ ) we believe these drug candidates are sufficiently differentiated to be potential global best-in-class, next generation therapies.

In 2015, the revenue of the Innovation Platform grew significantly to \$52.0 million (2014: \$20.3m) and as a result, the net loss attributable to Chi-Med dropped 83% to \$3.8 million (2014: -\$22.2m) despite clinical trial spending during 2015, by Chi-Med and its partners, totaling approximately \$64.1 million (2014: \$45.5m). We significantly advanced the oncology and immunology pipeline of clinical drug candidates, managing 19 active clinical trials (2014: 16) with six more in late planning, either independently or in collaboration with our partners. A total of 677 new patients, 249 outside China and 428 inside China, were enrolled into these clinical trials in 2015, bringing the total number of patients enrolled to 2,130 since the Innovation Platform's inception.

### Product Pipeline Progress

**Important definitions:** Most of the drug candidates have been designed for either global first-in-class or best-in-class potential and many have Breakthrough Therapy designation potential. In this context, first-in-class potential means that a drug candidate has the chance to be the first drug approved worldwide against its specific novel molecular (kinase) target. The benefits of being first-in-class are significant, and include first mover advantage and becoming the established standard of care over which all future drug candidates, targeting the same target and indication, must prove clinical superiority. Best-in-class means that a drug candidate, against its specific already validated target, is clinically superior in terms of safety and/or efficacy to the first-in-class standard of care.

Breakthrough Therapy designation, established by the U.S. Congress in 2012, is assigned by the U.S. FDA to novel drug candidates which, in simple terms, meet the following three criteria: (1) treat rare, untreatable, life-threatening disease; (2) clear understanding of molecular pathways (e.g. kinase target) of the disease; and (3) unprecedented efficacy. Breakthrough Therapy designation can lead to expedited NDA approval and market launch based on Phase II data, with Phase III studies being confirmatory.

**Savolitinib (AZD6094):** Savolitinib is a potential global first-in-class inhibitor of c-Met, an enzyme which has been shown to function abnormally in many types of solid tumors. We developed savolitinib as a potent and highly selective oral inhibitor that was designed to address renal (kidney) toxicity, the primary issue that has prevented all other selective c-Met inhibitors from gaining regulatory approval. In Phase I/II clinical studies, savolitinib has shown promising signs of clinical efficacy, causing tumor size reduction in patients with c-Met gene amplification in PRCC, NSCLC, colorectal cancer and gastric cancer.

**Active savolitinib clinical studies** – We are currently testing savolitinib in partnership with AstraZeneca in nine parallel proof-of-concept studies, both as a monotherapy and in combination with other targeted therapies, such as Iressa® and Tagrisso® (both EGFR inhibitors developed by AstraZeneca), and chemotherapy (Taxotere®). We and AstraZeneca plan to start three further proof-of-concept studies in savolitinib in the first quarter of 2016, two of which are combinations with immunotherapies.

**Savolitinib – Kidney Cancer:** Our strategy is to use PRCC, which currently has no approved targeted treatments on the global market, as the first indication to submit savolitinib for approval. PRCC is a sub-type of kidney cancer which accounted for approximately 14% (Frost & Sullivan) of all new cases of kidney cancer globally in 2014. We hope that if results from our current Phase II study (Study 1) are consistent with our Phase I data, we could consider applying for Breakthrough Therapy designation.

*Study 1 – Phase II PRCC (first-line) savolitinib monotherapy – in the U.S., Canada and Europe.* A Phase II study is underway to study savolitinib monotherapy (600 mg once daily) in first-line PRCC. The global Phase II study, which completed enrollment of 109 patients in October 2015, is an open label study with ORR and PFS as the primary endpoints and Disease Control Rate (“DCR” – percentage of patients with tumor growth of <20% versus baseline) and Overall Survival as secondary end points. In addition, molecular analysis of patient tissue samples is being carried out in parallel with treatment to determine the c-Met gene amplification status of each PRCC patient. In our extended Australia Phase I study of savolitinib, in 8 PRCC patients, we reported 38% ORR (3/8) and 75% DCR (6/8) with PRCC patients with c-Met gene amplification (40-75% of PRCC patients) showing the greatest response (Frost & Sullivan).

We have observed to date in the Phase II study, as we did in the Australia Phase I study, clear efficacy of savolitinib among patients with high levels of c-Met gene amplification. We expect to publish the results of the Phase II study, subject to the maturity of median PFS data, at a scientific conference in 2016. In the first half of 2016, we plan to meet with the U.S. FDA to discuss and seek guidance on registration strategy.

*Study 2 – Phase Ib PRCC savolitinib (600 mg daily) combined with immunotherapy – in UK.* A Phase Ib study is now in final planning to evaluate the safety and efficacy in PRCC. This study is premised on the hypothesis that a savolitinib/immunotherapy combination, if tolerable, could benefit all PRCC patients, not only those patients with c-Met gene amplification. Enrollment for this study is targeted to start in the first quarter of 2016.

*Study 3 – Phase Ib clear cell renal cell carcinoma (“CCRCC”) (second-line), VEGFR tyrosine kinase inhibitor-refractory, savolitinib (600 mg daily) monotherapy – in U.K.* A Phase Ib study is now in final planning to evaluate efficacy among Sutent® refractory CCRCC patients, being those patients that have not responded, or stopped responding, to treatment with Sutent®. A majority of these patients are known to have high levels of c-Met over-expression and may benefit from exposure to a highly selective c-Met inhibitor. Enrollment for this study is targeted to start the first quarter of 2016.

*Study 4 – Phase Ib CCRCC (second-line), VEGFR tyrosine kinase inhibitor-refractory, savolitinib (600 mg daily) combined with immunotherapy – in U.K.* A Phase Ib study is now in final planning to evaluate the safety and efficacy of savolitinib in combination with immunotherapy with the hypothesis being that the tyrosine kinase inhibitor/immunotherapy combination, if tolerable, will be more effective in treating CCRCC by targeting the disease from multiple angles. Enrollment for this study is targeted to start in the first quarter of 2016.

**Savolitinib – Non-small Cell Lung Cancer:** In November 2015, AstraZeneca received U.S. FDA approval for Tagrisso®, a therapy for the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC who have progressed on or after EGFR tyrosine kinase inhibitor (“TKI”) therapy, namely Iressa® or Tarceva® (erlotinib). Tagrisso® was granted Breakthrough Therapy designation and expedited approval by the U.S. FDA and was one of fastest development programs ever recorded – from start of Phase I clinical trials to approval in just over two and a half years. Speed of development and approval of Tagrisso® was driven by the clearly defined molecular pathways (T790M), major unmet medical need (TKI resistant NSCLC), and high degree of efficacy (59% ORR). In NSCLC, beyond T790M, c-Met gene amplification is clearly one of the major molecular drivers of cancer cell proliferation and as such, in our view, represents an obvious area of Breakthrough Therapy potential in NSCLC. We, and our partner AstraZeneca, are conducting four clinical studies in NSCLC, all of which we believe will generate important proof-of-concept data in 2016:

*Study 5 – Phase Ib/II NSCLC (second-line), EGFR tyrosine kinase inhibitor-refractory, savolitinib (600 mg daily) combined with Tagrisso® – Global.* As a result of the encouraging Phase I dose finding study, named TATTON, published at ASCO in 2015, which showed 55% ORR (6/11) and 100% DCR (11/11) among Iressa® and Tarceva® refractory T790M+/- (which means the patient’s T790M status is known) patients, we have initiated a global Phase Ib/II expansion study. The Phase Ib/II study aims to recruit an additional approximately 25 c-Met gene amplified, T790M negative patients in any line of treatment. This is a patient population represents approximately 10% of all Iressa® and Tarceva® refractory patients (Frost & Sullivan).

*Study 6 – Phase Ib/II NSCLC (third-line), EGFR/T790M tyrosine kinase inhibitor-refractory, savolitinib (600 mg daily) combined with Tagrisso® (T790M inhibitor) – Global.* A second arm of the global Phase Ib/II study will evaluate the use of savolitinib in combination with Tagrisso® in about 20 c-Met gene amplified patients who have progressed following treatment with Tagrisso®. NSCLC tumors are shown to develop resistance to third generation EGFR tyrosine kinase inhibitors (Tagrisso®) and c-Met gene amplification is one of the major resistance mechanisms. No firm data exists on what proportion of these Tagrisso® resistant patients are c-Met gene amplified, but it is believed to be material, and now that Tagrisso® is approved and expected to be used broadly, the proportion and resulting market potential for savolitinib, as a combination therapy with Tagrisso® in this third-line setting, should soon emerge.

*Study 7 – Phase Ib/II NSCLC (second-line), EGFR tyrosine kinase inhibitor-refractory, savolitinib (600 mg daily) combined with Iressa® (EGFR inhibitor) – China.* A Phase Ib/II study is now underway in China to evaluate efficacy among about 30 Iressa® refractory NSCLC patients. According to Frost & Sullivan, between 15% and 20% of these patients are known to be c-Met gene amplified and could benefit from exposure to a highly selective c-Met inhibitor such as savolitinib.

*Study 8 – Phase Ib NSCLC (first-line), EGFR wild-type, c-Met over-expression – China.* A Phase Ib study of savolitinib (500 mg twice daily) in China has been underway since late 2014 in wild-type EGFR, c-Met over-expression, NSCLC patients. According to Frost & Sullivan, approximately 67% of first-line NSCLC patients have some level of c-Met over-expression. For this study, we are only selecting patients with a high degree of c-Met over-expression based on the hypothesis that patients may benefit if we are able to heavily inhibit c-Met with high doses of savolitinib. This study is ongoing.

**Savolitinib – Gastric Cancer:** Patient screening and enrollment for the following four gastric cancer studies has been underway in China since 2014.

*Study 9 – Phase Ib gastric cancer, savolitinib monotherapy, patients with c-Met gene amplification – China.* A Phase Ib study of savolitinib (500 mg twice daily) in China is ongoing and to date we have seen clear partial response efficacy among the approximately 10% of gastric cancer patients with high c-Met gene amplification.

*Study 10 – Phase Ib gastric cancer, savolitinib monotherapy, patients with c-Met over-expression – China.* A Phase Ib study of savolitinib (500 mg twice daily) in China is ongoing. In this study, 40% of the patients have some level c-Met over-expression.

*Studies 11 and 12 – Phase Ib gastric cancer, patients with c-Met gene amplification/overexpression, savolitinib combined with Taxotere® (docetaxel) – China.* The first section of these Phase Ib dose finding studies are underway to assess combinability in patients with c-Met gene amplification and/or c-Met over-expression.

**HMPL-523:** We believe HMPL-523 is a potential global first-in-class oral inhibitor of Syk, a key protein involved in B-cell signaling. We are developing HMPL-523 for use in immunology, rheumatoid arthritis and lupus, as well as hematological cancers such as lymphoma and leukemia. In the past year, HMPL-523 has emerged, in our view, as one of Chi-Med's highest potential drug candidates. This is as a result of the successful completion of our Phase I study in healthy volunteers as well as fast emerging and highly compelling clinical proof-of-concept data from entospletinib (Gilead), which has begun to validate Syk as an important target in hematological cancer, in addition to its already established importance as a target in immunology.

Modulation of the B-cell signaling pathway has been proven to significantly advance the treatment of certain chronic immune diseases, such as rheumatoid arthritis. To date, targeted therapies approved in this area include monoclonal antibody (“mAb”) anti-Tumor Necrosis Factor alpha (“TNF $\alpha$ ”) immune modulators as well as the small molecule Janus Tyrosine Kinase (“JAK”) inhibitor, Xeljanz® (tofacitinib). The performance of Enbrel®, Pfizer's anti-TNF $\alpha$  mAb, is generally seen as the gold standard among these approved therapies, with 24 week ACR20/50/70 improvements of 44%/36%/15% in methotrexate resistant, placebo adjusted, rheumatoid arthritis patients. As an example, an ACR20 of 44% means that over a 24 week period an additional 44% of patients, over and above the placebo arm, observed a 20% improvement in their rheumatoid arthritis symptoms, according to the measurement scale established by the American College of Rheumatology (“ACR”).

A small molecule drug candidate has important advantages over intravenous mAb immune modulators because oral small molecule compounds are more convenient to take and clear the system faster, thereby reducing the risk of infections from sustained suppression of the immune system. Xeljanz® was the first-in-class JAK inhibitor, however poor selectivity and resulting off-target toxicities have limited its usage. Most recently a group of more selective, and thereby cleaner, potential best-in-class JAK inhibitors have shown positive Phase II results in rheumatoid arthritis with baricitinib 4mg daily (Lilly/Incyte); GLPG0634 100mg twice daily (Gilead/Galapagos) and ABT-494 24mg daily (AbbVie) reporting 12 week ACR20/50/70 improvements of 30%/28%/14%; 35%/40%/23%; and 32%/24%/18% respectively.

Syk is the upstream kinase in the B-cell signaling pathway, a different and possibly complimentary molecular pathway to JAK, and has been clinically validated as an important target in rheumatoid arthritis. In 2010, fostamatinib 100mg twice daily (AstraZeneca/Rigel) reported exciting Phase II ACR20/50/70 clinical efficacy of 32%/24%/18% showing that a small molecule Syk inhibitor can deliver meaningful clinical benefit. Unfortunately, fostamatinib was not a selective Syk inhibitor as it potently inhibited multiple other kinases including FLT-3, Ret, KDR, FGFR, Lyn and JAK. We believe that this poor kinase selectivity led to off-target toxicity, with patients suffering diarrhea (19%) as well as hypertension, leading to 23% of patients having to receive anti-hypertensive therapy. After conducting global Phase III studies (OSKIRA 1/2/3) on fostamatinib, ultimately AstraZeneca decided not to proceed with regulatory filings because efficacy at the safe dose level, while statistically significant over the placebo, was not clinically meaningful relative to mAbs.

With respect to the treatment of hematological cancers, in recent years there have been major clinical successes and drug approvals of inhibitors targeting other kinases in the B-cell signaling pathway such as Bruton's tyrosine kinase, or BTK, and PI3K $\delta$ . While these inhibitors have been successful, resistance to these inhibitors can emerge over time, leading to loss in efficacy, and new targets in B-cell signaling such as Syk are potential solutions to this problem. In late 2015, Gilead published highly compelling Phase II results for entospletinib (GS-9973), a small molecule selective Syk inhibitor being developed only in hematological cancer, in which a Nodal Response Rate ("NRR") of 65% was observed in chronic lymphocytic leukemia ("CLL") and small lymphocytic lymphoma. Nodal response is defined as a >50% decrease from baseline in the sum of lymph node diameters. Importantly also, GS-9973 reported an NRR of 44.4% (4/9 patients) in an exploratory clinical study in CLL patients previously treated with the first-in-class BTK inhibitor, Imbruvica® (ibrutinib), and the first-in-class PI3K $\delta$  inhibitor, Zydelig® (idelalisib), thereby indicating that Syk inhibition has potential to overcome resistance to Imbruvica® and Zydelig®. TAK-659 (Takeda), also a selective Syk inhibitor, saw similar strong signals of efficacy in their TAK-659 Phase I dose escalation study in lymphoma, also published in late 2015.

**HMPL-523 clinical results published in 2015/2016** – During late 2015, we reported the top-line results our successful Phase I dose escalation study in healthy volunteers in Australia.

*Study 20 – Phase I study of HMPL-523 in healthy volunteers – Australia.* The first-in-human Phase I study of HMPL-523 was a dose-escalation study conducted to assess the safety, tolerability and pharmacokinetics of both single and repeat doses of HMPL-523 in healthy volunteers in Australia. The study began in June 2014, and completed ten single dose cohorts, with eight patients per cohort, from 5mg single dose through 800mg single dose. In mid-2015, the multiple ascending dose section of the Phase I study commenced in which HMPL-523 was administered once daily for 14 consecutive days. Four dose cohorts were completed in this section of the study, again with eight patients per cohort, from 200mg multiple dose through to 400mg multiple dose. At 400mg daily, HMPL-523 drug exposures are believed to be well above the predicted efficacious dose level and, consequently, there is no intention to escalate dosing further in healthy volunteers.

The preliminary safety profile of HMPL-523 was in-line with our expectations. No material off-target toxicities such as diarrhea and hypertension were observed with HMPL-523 in this study. Furthermore, HMPL-523 exhibited a linear human pharmacokinetic profile and a dose dependent suppression of human plasma B-cell activation. Full results of this Phase I study will be published in due course.

**Active HMPL-523 clinical studies** – We currently retain all rights to HMPL-523 worldwide. Now that a dose range for the further development of HMPL-523 in autoimmune disease has been established, we are planning Phase II proof-of-concept studies against multiple autoimmune diseases, such as rheumatoid arthritis and lupus. These studies are targeted to start in 2016. In addition, we have just begun dose escalation in the following Phase I study in hematological cancer patients:

*Study 21 – Phase I of HMPL-523 in second/third-line lymphoma/leukemia patients – Australia.* In January 2016, we began a Phase I, open-label, dose escalation study of HMPL-523 as monotherapy administered orally to relapsed and/or refractory B-cell non-Hodgkin's lymphoma or CLL patients who do not respond to, or are unable to tolerate, standard therapy or for whom there is no standard therapy. We are planning two stages for this study: a dose escalation stage and a dose-expansion stage. We believe this study could quickly provide clinical proof-of-concept that HMPL-523 is an effective Syk inhibitor and that, as has been shown with entospletinib and TAK-659, modulation of the B-cell signaling pathway through inhibition of Syk will provide patients with a highly meaningful clinical benefit.

**Fruquintinib:** Fruquintinib is a highly selective and potent oral inhibitor of VEGFR, a receptor tyrosine kinase which contributes to tumor angiogenesis, which we believe has the potential to be a global best-in-class VEGFR inhibitor for many types of solid tumors. Based on the pre-clinical and clinical data compiled so far, fruquintinib's kinase selectivity has been shown to reduce off-target toxicity. This allows for drug exposure, from a single 5mg oral dose, that is able to fully inhibit VEGFR for 24 hours a day and has potential for use in combination with other targeted therapies and chemotherapy in earlier lines of treatment with larger patient populations. We believe these are major points of differentiation compared to other less selective small molecule VEGFR inhibitors that have already been approved, such as Sutent®, Nexavar® (sorafenib) and Stivarga® (regorafenib).

**Fruquintinib clinical results published in 2015/2016** – During 2015 we reported the results of the two Phase II proof-of-concept studies detailed below for which Lilly paid us \$33.1 million in success-based proof-of-concept cash payments during the year:

*Phase II study of fruquintinib monotherapy in third-line colorectal cancer – China.* In August 2014, we completed enrollment for a Phase II double-blind, placebo-controlled, multi-center study in China in just over four months to test fruquintinib as monotherapy among third-line metastatic colorectal cancer patients, using the 5 mg daily, 3 weeks on/1 week off dose regimen. The goal of this study was to compare the PFS efficacy of fruquintinib versus placebo in metastatic colorectal cancer patients who failed at least two prior lines of treatment, including fluorouracil, oxaliplatin and irinotecan. A total of 71 patients were enrolled, with 47 in the fruquintinib arm and 24 in the placebo arm. Patient baseline characteristics were similar between the two treatment arms.

Fruquintinib demonstrated very strong anti-tumor activity in this study. Median PFS was 4.7 months in the fruquintinib arm compared to median PFS of 1.0 month in the placebo arm (hazard ratio = 0.30 (p<0.001)). The DCR in the fruquintinib arm was 68.1% compared with 20.8% in the placebo arm (p<0.001). Interim median Overall Survival rate, at the 6-month cut-off, was 7.6 months and 5.5 months in the fruquintinib arm and the placebo arm, respectively. In this study, fruquintinib has not shown any major unexpected safety issues and clearly met its primary endpoint of superiority in median PFS.

*Phase II study of fruquintinib monotherapy in third-line NSCLC – China.* In June 2014, we initiated a Phase II randomized, double-blind, placebo-controlled, multi-center study of fruquintinib versus placebo among patients with advanced non-squamous NSCLC who failed two lines of chemotherapy. By early March 2015, enrollment had been completed with a total of 91 patients randomized to 5 mg of fruquintinib orally once per day, on a 3 weeks on/1 week off regimen plus best supportive care, or placebo plus best supportive care at a 2:1 ratio.

In September 2015, we reported that fruquintinib had clearly met its primary endpoint of superior median PFS versus placebo in this study. Assessment of secondary efficacy endpoints, including ORR, DCR and Overall Survival rate is ongoing, with all appearing in line with expectations at the August 2015 five-month data cut-off. The adverse events demonstrated in this study were consistent with the known safety profile for fruquintinib with no major unexpected safety issues. We expect to report the full data for this study at a scientific conference in 2016.

**Active fruquintinib clinical studies** – In partnership with Lilly, on fruquintinib, in China we are currently enrolling Phase III registration studies in two indications; the FRESCO study on colorectal cancer; and the FALUCA study on NSCLC. We also expect to start a Phase II proof-of-concept study on gastric cancer in China in the second half of 2016.

*Study 14 – Phase III study in third-line colorectal cancer – China.* In December 2014, we initiated FRESCO, a randomized, double-blind, placebo-controlled, multi-center, Phase III registration study of fruquintinib as monotherapy targeted at treating patients with locally advanced or metastatic colorectal cancer who have

failed at least two prior systemic cancer therapies, including fluoropyrimidine, oxaliplatin and irinotecan. Patients are randomized at a two-to-one ratio to receive either 5 mg of fruquintinib orally once per day, on a 3 weeks on/1 week off cycle, plus best supportive care or placebo plus best supportive care. The primary endpoint is Overall Survival, with secondary endpoints including PFS, ORR, DCR and duration of response. We expect enrollment to be completed in Q2 2016 after which we plan to establish an Independent Data Monitoring Committee (“IDMC”) to conduct an interim analysis on FRESCO in Q4 2016. Our China FDA registration strategy will be determined based on the results of the IDMC.

*Study 15 – Phase III study in third-line non-small cell lung cancer – China.* In December 2015, we initiated FALUCA, a Phase III registration study for fruquintinib in third-line non-squamous NSCLC patients in China who have failed two prior systemic cancer therapies. Patients are randomized at a two-to-one ratio to receive either 5 mg of fruquintinib orally once per day, on a 3 weeks on/1 week off cycle, plus best supportive care or placebo plus best supportive care. The primary endpoint is Overall Survival, with secondary endpoints including PFS, ORR, DCR and duration of response.

*Study 16 – Phase Ib study of fruquintinib combined with Taxol® in second-line gastric cancer – China.* In early 2015, we began a Phase Ib dose finding study of fruquintinib in combination with Taxol® to determine the recommended Phase II dose. We have completed two dose cohorts, 2 mg daily and 3 mg daily (both 3 weeks on/1 week off) with both regimens being tolerable and showing encouraging preliminary response. We are currently in the final expansion phase of a 4 mg daily cohort which, if successful, is expected to deliver full 24 hours a day VEGFR inhibition through an oral dose in combination with chemotherapy (Taxol®). This is an outcome that we believe has never been achieved before with a small molecule VEGFR TKI. After the completion of this Phase Ib dose finding study we expect to initiate a second-line gastric cancer Phase II study in China in the second half of 2016. Positive proof-of-concept results in combination with Taxol® could lead to potential global development of fruquintinib in combination with chemotherapy in earlier line settings in many other solid tumor indications including, but not limited to, NSCLC, colorectal cancer and breast cancer.

**Sulfatinib:** Sulfatinib is an oral drug candidate that selectively inhibits the tyrosine kinase activity associated with VEGFR and FGFR1, a receptor for a protein which also plays a role in tumor growth.

**Sulfatinib clinical results published in 2015/2016** – During 2015, we released expanded Phase I clinical data indicating that sulfatinib has the highest ORR reported to date in patients with NET. An ORR of 44.4% was observed for sulfatinib in 18 evaluable NET patients, and importantly efficacy was observed across many NET sub-types including those originating in the thymus, pancreas and across the gastrointestinal tract. This compares favorably to less than 10% ORR for Sutent® and Afinitor®, the two targeted therapies that are approved for pancreatic NET patients only.

**Active sulfatinib clinical studies** – We currently retain all rights to sulfatinib worldwide. In 2015, we applied for and received clearance to proceed with both Phase I clinical trials in the U.S. and Phase III clinical trials in China. Sulfatinib is the first oncology candidate that we have taken through proof-of-concept in China and have expanded into global development ourselves.

*Study 17 – Phase Ib/II study in first-line NET – China.* In early 2015, we began a 30 patient, 300 mg sulfatinib daily, Phase Ib/II study in China in broad spectrum NET patients (pancreatic, gastrointestinal, liver, lymph and lung, among others) which, due to strong demand due to the major unmet medical need and clear efficacy of sulfatinib, was expanded and subsequently completed enrollment of 81 NET patients in December 2015. We expect to publish top-line results for this study during the course of 2016.

*Study 17a. – Phase III study in first-line extra-pancreatic NET – China.* In December 2015, we initiated SANET-ep, a Phase III sulfatinib registration trial in China in patients with extra-pancreatic NET (non-pancreatic). SANET-ep is a randomized, double-blind, placebo-controlled, multi-center registration study to treat pathologically low or intermediate grade NET patients whose disease has progressed, locally advanced or distant metastasized and for whom there is no effective therapy. Patients are being randomized at a 2:1 ratio to receive either 300 milligrams of sulfatinib orally once per day, or placebo, on a 28-day treatment cycle. The primary objective of this study is to evaluate the PFS of sulfatinib as compared to that of placebo, with secondary endpoints including ORR, DCR, time to response, duration of response, Overall Survival, safety and tolerability. We expect to enroll about 270 patients in SANET-ep.

*Study 17b. – Phase III study in first-line pancreatic NET – China.* In the first quarter 2016, we intend to initiate a second sulfatinib Phase III registration trial, SANET-p, in pancreatic NET patients. SANET-p

employs a similar treatment regimen and has primary and secondary endpoints similar to those for SANET-ep trial. We expect to enroll about 195 patients in SANET-p.

*Study 18 – Phase I monotherapy in advanced solid tumors – U.S.* A Phase I study in Caucasian patients also began in the U.S. in late 2015. This study will evaluate the safety, tolerability and pharmacokinetics of sulfatinib in advanced solid tumors to determine the maximum tolerated dose and/or recommended Phase II dose, dose-limiting toxicities, pharmacokinetics profile, and preliminary anti-tumor activity in Caucasian patients. Once we have established the recommended Phase II dose among Caucasian patients, we expect to start a U.S. Phase II study of sulfatinib in broad spectrum NET patients in the second half of 2016.

*Study 19 – Phase II sulfatinib monotherapy in second-line thyroid cancer – China.* In Q1 2016, we plan to begin enrollment in a Phase II study in China in approximately 50 patients to evaluate the safety, pharmacokinetics and efficacy of sulfatinib in patients with locally advanced or metastatic radioactive iodine-refractory differentiated thyroid cancer or medullary thyroid cancer into this study, with approximately 25 patients in each tumor type. We believe that sulfatinib's VEGFR/FGFR1 inhibition profile has strong potential in second-line thyroid cancer patients, particularly in China where there are few safe and effective treatment options for this patient population.

**Epitinib:** EGFR inhibitors have revolutionized the treatment of NSCLC with EGFR activating mutation. However, existing EGFR inhibitors such as Iressa® and Tarceva® cannot penetrate the blood-brain barrier effectively, leaving the >50% of patients that ultimately develop brain metastasis without an effective therapy. In contrast, epitinib is a potent and highly selective oral EGFR inhibitor designed to optimize brain penetration and has demonstrated brain penetration and efficacy in both pre-clinical and clinical studies. We therefore believe epitinib is well-positioned to address a major global unmet medical need and possibly be considered for Breakthrough Therapy designation.

**Epitinib clinical results published in 2015/2016** – During 2015, we completed a Phase I dose escalation study and identified a recommended dose for proof-of-concept studies. We subsequently began a Phase Ib proof-of-concept study in NSCLC patients with EGFR activating mutation and brain metastasis. We have announced that preliminary clinical results in tumor assessments in the first 14 patients treated in the Phase Ib (Study 22 below) have been highly encouraging, with early patient tumor assessments showing strong efficacy in both the lung and brain.

**Active epitinib clinical studies** – We currently retain all rights to epitinib worldwide. In late 2015, we also submitted our Phase III clinical trial application in China for which we hope to receive clearance by mid-2016. Upon clearance, and subject to continued positive Phase Ib results, we expect to initiate a Phase III trial in China.

*Study 22 – Phase Ib epitinib monotherapy in first-line EGFR activating mutation positive NSCLC with brain metastasis – China.* We are conducting a Phase Ib proof-of-concept study of epitinib in approximately 30 patients to establish activity in EGFR activating mutation positive NSCLC patients with tumors metastasized to the brain. Full results of this Phase Ib study are expected later in 2016.

**Theliatinib:** Theliatinib is a novel EGFR inhibitor designed to treat tumors with wild-type EGFR activation such as gene amplification or protein over-expression. The current EGFR inhibitors such as Iressa® and Tarceva® are approved only for patients with EGFR activating mutation because they have limited binding affinity, and therefore response/efficacy, in cancers with wild-type EGFR. Theliatinib on the other hand has very strong binding affinity to the wild-type EGFR kinase and as such, in pre-clinical models, theliatinib has demonstrated 5- to 10-fold higher potency than Tarceva®.

**Active theliatinib clinical studies** – We currently retain all rights to theliatinib worldwide and are nearing completion of a Phase I dose escalation study.

*Study 23 – Phase I dose escalation – China.* We have completed 7 cohorts from 10mg daily through to 160mg daily. We have seen no dose limiting toxicities and intend to continue dose escalation. Once the Phase II dose is determined we intend to commence exploratory Phase Ib/II proof-of-concept studies in esophageal and head and neck cancers in 2016.

**HMPL-689:** There are multiple sub-families of PI3K kinases, and PI3K $\delta$  plays important roles in B-cell activation, development, survival and migration. PI3K $\delta$  is mainly expressed in circulating leukocytes and lymphoid tissues. PI3K $\delta$  is the central signaling enzyme that mediates the effects of multiple receptors on

B-cells. Aberrant B-cell function has also been observed in multiple autoimmune diseases and B-cell mediated malignancies. Therefore, PI3K $\delta$  is considered to be a promising target for drugs that aim to prevent or treat hematologic cancer, autoimmunity and transplant organ rejection and other related inflammation diseases.

HMPL-689 has been designed to be a second generation, potentially global best-in-class PI3K $\delta$  inhibitor in hematological cancer. It is intended to compete with Zydelig®, the first-in-class PI3K $\delta$  inhibitor, which was granted Breakthrough Therapy designation in 2013 and approved for the treatment of multiple types of non-Hodgkin's lymphoma in 2014. HMPL-689 is, in general, differentiated through high selectivity, particularly on a PI3K isoform level, sparing PI3K $\gamma$  and minimizing the risk of serious infection. HMPL-689 is over five-fold more potent than Zydelig® at the whole blood level and has favorable pharmacokinetic properties, with expected good human oral absorption, moderate tissue distribution and low clearance, making it suitable for once daily oral dosing. We also expect HMPL-689 will have a low risk of drug accumulation and drug-drug interaction issues. As a result, HMPL-689 is expected to provide improved target coverage and robust efficacy at much lower doses than Zydelig® and as such reduce compound related toxicities.

*Study 24 – Phase I of HMPL-689 in second/third-line hematological cancers (lymphoma/leukemia) – Australia.* In 2016, we plan to initiate a first-in-human Phase I dose escalation study of HMPL-689 in patients with hematologic malignancies in Australia. Subject to success in Phase I we will look to develop HMPL-689 both as a monotherapy and potentially in combination with other B-cell mediators such as HMPL-523.

**HMPL-453:** FGFRs belong to a sub-family of receptor tyrosine kinases whose activation through the phosphorylation of various downstream molecules ultimately leads to increased cell proliferation, migration and survival. FGF/FGFR signaling regulates a wide range of basic biological processes, including tissue development, angiogenesis, and tissue regeneration. Aberrant activation in FGF/FGFR signaling through mutations, fusion and gene amplification has been found to be a driving force in many types of cancer, including NSCLC, gastric, breast, cholangiocarcinoma and bladder.

Currently, FGFR mAbs, FGF ligand traps and small molecule FGFR inhibitors are being evaluated in early clinical studies. BGJ-398 (Novartis), AZD4547 (AstraZeneca) and JNJ-42756493 (Janssen) are the leading selective FGFR inhibitors, and their early clinical trials provided substantial proof-of-concept with regard to anti-tumor efficacy and pharmacodynamic markers of effective FGFR pathway inhibition. However, there are still many challenges in the development of FGFR-directed therapies. Uncertainties include the screening and stratifying of patients who are most likely to benefit from FGFR targeted therapy. Intra-tumor heterogeneity observed in FGFR amplified cancer may compromise the anti-tumor activity. In addition, the low frequency of specific FGFR molecular aberrance in each cancer type may hinder clinical trial enrollment.

HMPL-453 is a highly selective and potent, small molecule that targets FGFR 1/2/3. HMPL-453 exhibited strong anti-tumor activity that correlated with target inhibition in tumor models with abnormal FGFR activation. HMPL-453 has good pharmacokinetic properties characterized by rapid absorption following oral dosing, good bioavailability, moderate tissue distribution and moderate clearance in all pre-clinical animal species. HMPL-453 was found to have low likelihood of drug-to-drug interaction issues. We intend to start Phase I clinical trials in China, as well as possibly in Australia, in 2016.

**HMPL-004:** Since the result of our interim analysis of the Phase III registration study in ulcerative colitis (NATRUL-3) was published in August 2014, we have been working closely with Nestlé Health Science SA, our partner in the Nutrition Science Partners JV, to improve the chance of clinical success for HMPL-004. We now have a better understanding, in the context of HMPL-004, of the clinical importance of concomitant use of 5-ASAs; the definition of 5-ASA resistance and importantly biomarker analysis.

The remaining major issue with HMPL-004, which is a botanical substance, is the high pill burden and resulting compliance challenges of the 2,400mg daily HMPL-004 dose. In 2015, a team of about 30 research staff focused on optimizing HMPL-004 formulation, by adding several steps to the extraction process and thereby increasing the concentration of the key bioactive ingredients. The new enriched formulation of HMPL-004 that has been created, named HM004-6599, is now over 70% diterpenoids as compared to the original formulation which comprised approximately 15% diterpenoids. In extensive pre-clinical in-vitro and in-vivo models HM004-6599 has now been shown to demonstrate superior inhibition of NF- $\kappa$ B activation, pro-inflammatory cytokine IL-1 $\beta$  production and TNF- $\alpha$  dependent chemokine production including CCL-20. Given the enrichment, the predicted human efficacious dose of HM004-6599 could be as low as 400-500mg daily versus 2,400mg daily usage of HMPL-004. We now intend to progress

HM004-6599 through IND enabling drug safety and manufacturing processes and target to re-start clinical trials in 2017.

In parallel with the work being conducted on HM004-6599 we have expanded our joint research activities with Nestlé Health Science S.A., expecting to fund a team of 45 research staff in 2016 and working on creating a pipeline of multiple highly enriched botanical drug candidates in the immunology/inflammation arena of gastrointestinal disease.

**Discovery programs:** Our fully integrated discovery teams in oncology and immunology continued to make substantial progress during the period. We staff and resource our discovery team with the objective of producing one or two new internally discovered drug candidates per year. In addition to the drug candidates against 8 molecular targets that are either in clinical development or are expected to start clinical development in 2016, we have compounds against two further targets (one novel and one validated) that should reach candidate nomination in 2016 as well discovery programs against five further novel molecular targets that could reach candidate nomination over the next few years.

## **COMMERCIAL PLATFORM**

Since 2001, we have also developed a profitable Commercial Platform, with the key element being our Prescription Drugs business which has a commercial network of over 1,900 medical sales representatives covering over 16,500 hospitals in about 300 cities and towns in China. We operate our Prescription Drugs business through our JVs, SHPL and Hutchison Sinopharm, in which we nominate management and run the day-to-day operations. The second, less core, element of our Commercial Platform is our Consumer Health business which focuses primarily on the manufacture, marketing and distribution of over-the-counter (“OTC”) pharmaceutical products in China.

We intend to leverage this Commercial Platform, particularly our established Prescription Drugs business, to support the launch of products from our Innovation Platform if they are approved for use in China. Outside of China, we intend to commercialize our products in the U.S., Europe and other major markets either on our own or through partnerships with leading global pharmaceutical companies.

In 2015, sales of the Commercial Platform subsidiaries and JVs grew by 11% to \$518.9 million (2014: \$465.4m) and consolidated net profit attributable to Chi-Med from continuing operations increased by 10% to \$25.2 million (2014: \$22.8m), including non-recurring one-time costs of \$1.7 million associated with relocation to our new factories (\$0.4 million) and the take-back of commercial rights of certain products (\$1.3 million).

### **Prescription Drugs business:**

Sales of the subsidiaries and JVs in our Prescription Drugs business (SHPL and Hutchison Sinopharm) grew by 40% to \$286.6 million (2014: \$204.9m) and consolidated net profit attributable to Chi-Med increased by 20% to \$15.9 million (2014: \$13.2m) representing 63% of our Commercial Platform net profit.

**SHPL:** Our primarily own-brand Prescription Drugs business continues to perform very well, with 2015 sales up 17% to \$181.1 million (2014: \$154.7m). Our proprietary prescription cardiovascular drug SXBXP, which represented 88% of SHPL sales in 2015, grew 15% to \$159.3 million (2014: \$138.8m) as we continued to make progress through geographic and sales channel expansion and gaining market share in its mature markets. Within the coronary heart disease market in China, in 2015 SXBXP had approximately 12.1% market share, and market leadership in Shanghai with approximately 35.3% market share, among oral Chinese patented drugs (Frost & Sullivan).

Since its launch in 1983, the proprietary status of SXBXP has been supported by a combination of regulatory protection and in recent years the grant of State Secrecy protection which expires in December 2016. In July 2015, we were granted a 20-year invention patent covering SXBXP formulation from the China State Patent Office which will now secure our proprietary position on SXBXP in China through 2029. Furthermore, in 2015 we began to phase-in a 22% price increase on SXBXP, from its early 2015 level of RMB 2.7/day to RMB 3.3/day. This increase will bring SXBXP closer in-line with the 2014 Low Price Drug List policy which allows for maximum daily pricing for such products at RMB 5.0/day.

The SHPL commercial team now has about 1,900 medical sales representatives covering all regions of China, including about 1,800 cardiovascular and 100 central nervous system personnel. In 2015, for the first

time since its inception in 2001, SHPL began to expand into commercialization of third party prescription drug products. Fee for service income of \$5.1 million was earned during 2015 (2014: nil) from detailing Concor® (cardiovascular, Merck Serono) in certain provinces in China and Seroquel® (psychiatric disorders, AstraZeneca) across all China. The gross margins earned on this third party business are meaningful and while 2015 was a period of start-up and investment, we expect these activities to become an important net profit contributor for SHPL.

In 2016 we plan to transition production of SHPL's own-brand products, including SXBXP, to our new 78,000 sqm factory in Feng Pu district, 40 kilometers south of Shanghai. The transition, including the re-location of approximately 500 full time staff and the attainment of Good Manufacturing Practice ("GMP") certification on the new facility, while in parallel maintaining record production despite operating at full capacity in the old site, has required major coordination.

**Hutchison Sinopharm:** Our third-party prescription drugs commercialization business, Hutchison Sinopharm, is making very good progress with sales of \$105.5 million (2014: \$50.2m) as we report our first full year of operations versus less than nine months in 2014. The majority of the legacy business of Hutchison Sinopharm is to provide low-margin logistics and distribution services, primarily in Shanghai municipality, to third-party pharmaceutical companies.

The core strategic focus of Hutchison Sinopharm is now to rapidly expand/evolve its team of over 90 commercial staff (2014: 50), into a higher margin full-service third-party prescription drugs commercialization company in China. This will allow Hutchison Sinopharm to complete more commercial deals, similar to the exclusive China commercialization deal on Seroquel® with AstraZeneca that was signed in early 2015. In 2015, Seroquel® had approximately 47% market share (Frost & Sullivan) of the Chinese market for schizophrenia and bipolar drugs and accounted for \$21.1 million (2014: nil) of the sales of Hutchison Sinopharm between April and December 2015.

#### **Consumer Health business:**

Sales from continuing operations of the subsidiaries and JVs in our Consumer Health business (HBYS, Hutchison Hain Organic Holdings Limited ("HHO"), Hutchison Healthcare Limited ("HHL") and Hutchison Consumer Products Limited ("HCPL")) fell by 11% to \$232.3 million (2014: \$260.5m); and consolidated net profit attributable to Chi-Med from continuing operations fell by 4% to \$9.3 million (2014: \$9.6m) due mainly to a non-recurring one-time cost of \$1.3 million resulting from our decision to take-back commercial rights on all HHL's Zhi Ling Tong infant nutrition products from our former exclusive distributor.

**HBYS:** Our OTC drugs business in China is navigating a complex transition in both pricing and manufacturing strategy. As a result, HBYS sales fell 13% to \$211.6 million (2014: \$243.7m) while net profit attributable to Chi-Med grew 3% to \$8.6 million (2014: \$8.3m). HBYS is the market leader in China for its two core generic OTC drug sub-categories, with market share of approximately 32.5% for Fu Fang Dan Shen ("FFDS") tablets (angina) and 51.1% for Banlangen granules (anti-viral) in 2015 (Frost & Sullivan).

In 2015, HBYS entered a period of transition in which key raw material costs dropped dramatically, thereby improving our profitability. At the same time, we have been capacity constrained as we encounter tightening of supply by our contract manufacturers ahead of the start-up of our new GMP factory in Bozhou, Anhui province. Our strategy to manage this temporary supply tightness has been to keep prices high on key products such as FFDS. As a result, while FFDS gross margin increased to 62% (2014: 49%) overall sales fell by -21% to \$60.2 million (2014: \$76.3m).

While our pricing strategy has helped ease supply pressure in the short term, we remain focused on bringing on line the first phase of our 230,000 sqm Bozhou factory in late 2016. This will provide >50% increases in formulation (tablets and granules) capacity and, most importantly, it should address our main production bottle-neck - extraction - by adding 8,000 tons of new extraction capacity (>250% increase). The transition to Bozhou is highly complex due to the fact it is over 1,400 kilometers away from our Guangzhou base. We will however benefit in the mid- to long-term from cost efficiencies, by establishing this operation in central China, in terms of lower people and operating costs as well as close proximity to the source of key raw materials. We believe these cost efficiencies will contribute to materially increasing baseline HBYS gross margins, which were 43% in 2015 (2014: 40%), in future periods.

In July 2015, HBYS agreed to inject up to \$9.0 million into a new JV with Guangdong Lai Da Pharmaceutical Company Limited (“Lai Da”) for a 70% share in the new JV. Lai Da, for its 30% share, has contributed a portfolio of 31 drug products, with some being higher margin proprietary prescription drugs.

**HHO:** The performance of HHO, our natural and organic products venture with The Hain Celestial Group, Inc. (“Hain”), during 2015 continued to be strong with sales from continuing operations growing by 48% to \$17.0 million (2014: \$11.5m) and net profit attributable to Chi-Med of \$0.7 million (2014: \$0.3m). We believe the demand for high quality health-oriented consumer products is increasing and HHO is the exclusive regional distributor/marketer of a range of over 30 Hain brands of organic and natural products in nine countries/territories in Asia. In mid-2015 we re-entered the China market with the Earth’s Best® brand, Hain’s market leading U.S. organic infant formula brand.

**HHL and HCPL:** The sales in our smaller consumer businesses HHL and HCPL fell by 27% to \$3.6 million (2014: \$4.9m) with net loss attributable to Chi-Med of -\$0.1 million (2014: net profit \$1.1m). Our key product, Zhi Ling Tong, a supplement brand for babies and pregnant mothers, remains popular within its obstetrics and gynecology hospital, mother/baby and drug store commercial channels. In late 2015, we took the decision to terminate the commercial agreement on Zhi Ling Tong with our exclusive China distributor of almost ten years, thereby incurring one-time non-cash expenses of \$1.3 million. Under our direct control, we believe sales of Zhi Ling Tong in 2016 should grow rapidly and rapidly offset this cost of transition.

**Property compensation:** As previously reported both Commercial Platform JVs, SHPL and HBYS, are well advanced in the process of approximately tripling capacity through the construction of two major new GMP factories. The estimated total planned capital expenditures on these new factories are \$140 million. In 2015, capital expenditures were \$64.8 million and total aggregate capital expenditure, as at 31 December 2015, on the two new factories was \$125.4 million, or 90% of the planned total expenditure. We have funded this capital expenditure during the last two years mostly with the cash reserves held in our JVs as well as bank borrowing of \$26.5 million as at 31 December 2015.

In late 2015, we announced that SHPL had signed a land deal for the surrender of its 36-year land-use rights on its old 58,000 sqm factory site back to the Shanghai government in return for \$105 million in compensation. This will result in a substantial gain in 2016, for both SHPL and Chi-Med, given that the total net book value of the land and fixed assets at the old site was \$12.7 million as at 31 December 2015. In December 2015, SHPL received a first installment payment of \$31.1 million in cash with the balance of approximately \$73.9 million expected to be received in 2016. Furthermore, as a result of the deal, SHPL is also likely to receive approximately \$15.0 million in additional subsidies over the next five years.

Recently, the Guangzhou government has issued their new urban redevelopment policy. Under this new policy, we estimate that HBYS compensation, based solely on precedent land auctions in the immediate vicinity, for surrender of the remaining 38-year land-use rights on our two plots of land in Guangzhou, Plot 1 (59,400 sqm) and Plot 2 (26,700 sqm), could be similar on a compensation per square metre basis, to that paid to SHPL above. For reference, the aggregate net book value, as at 31 December 2015, for the land and fixed assets in Plot 1 and Plot 2 was \$24.0 million. While precedent land auctions are for indication only, and the outcome and timing of any deal remain uncertain and are not fully within our control, we are working towards agreeing on a compensation deal for Plot 2 in late 2016 or 2017.

## Summary

As a result of over a decade of total focus on investing in innovation, we now believe that Chi-Med is within reach of our primary objective of becoming a leading global biopharmaceutical company based in China.

Referencing our global biotech peers, clinical and regulatory success during 2016 and 2017 in just one of our novel global first-in-class drug candidates, savolitinib and HMPL-523, could provide the catalyst to achieve this. And, beyond these global first-in-class drug candidates, we have our broad clinical pipeline of possible best-in-class compounds – fruquintinib and sulfatinib are now both in Phase III registration studies in China and epitinib is expected to start its first Phase III registration study in 2016. We believe all this is set to create substantial shareholder value by providing great benefits to patients.

Our research team, the largest of its type in China, continues to produce global innovations in oncology and immunology with as many as half a dozen drug candidates against novel molecular targets expected to reach the clinic in the next five years.

A solid foundation of Chi-Med's business continues to be our increasingly cash generative Commercial Platform, with the Prescription Drugs business in China being the strategic core. We expect this cash flow will continue to help sustain Chi-Med's continuous investment in innovation in the future. Now looking forward to the next two to three years, a second benefit of this deep commercial capability is set to emerge – the ability to use our commercial team to launch our un-partnered innovative products in China ourselves and thereby maximize the economic benefits to Chi-Med.

Achieving our ambitious objectives requires that we continue to move fast, and execute effectively, on all aspects of our business. We are confident we are well positioned to do this in 2016 and beyond.

**Christian Hogg**  
**Chief Executive Officer, 29 February 2016**

**Important information**

*This announcement, which includes the appendices to it, does not constitute a registration statement on Form F-1 and does not constitute or form, and will not form, part of any offer or invitation to sell or issue, or the solicitation of an offer to purchase or acquire, any of the Ordinary Shares or ADSs or any other securities in the United States or in any other jurisdiction. Securities may not be offered or sold in the United States absent registration or an exemption from registration under the United States Securities Act of 1933, as amended ("U.S. Securities Act"). Any potential public offering of securities to be made in the United States will be made by means of a Form F-1 Registration Statement that has been declared effective by the SEC. The Form F-1 Registration Statement contains detailed information about the issuer and its management and financial statements. This announcement is being issued pursuant to and in accordance with Rule 135e under the U.S. Securities Act.*

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