HUTCHISON CHINA MEDITECH LTD

Hutchison China MediTech Limited ("Chi-Med")

(AIM: HCM)

Presentations of volitinib and epitinib data at the 2014 AACR Annual Meeting

London: Friday, 4 April 2014: Chi-Med today announces that data from certain preclinical and clinical studies by Hutchison MediPharma Limited ("HMP"), its majority owned R&D company, will be presented at the 105th Annual Meeting of the American Association for Cancer Research ("AACR") to be held in San Diego, California, USA from 5 to 9 April 2014. These presentations will include additional data on volitinib (HMPL-504/AZD6094) and epitinib (HMPL-813), two novel and highly selective small molecule drugs discovered by HMP. Presentations on volitinib were prepared jointly with HMP's collaboration partner AstraZeneca AB (publ) ("AstraZeneca").

AACR is the world's first and largest professional organisation dedicated to advancing cancer research and its mission to prevent and cure cancer. AACR membership includes more than 34,000 laboratory, translational and clinical researchers; population scientists; other health care professionals; and cancer advocates residing in more than 90 countries. AACR marshals the full spectrum of expertise of the cancer community to accelerate progress in the prevention, biology, diagnosis and treatment of cancer by annually convening more than 20 conferences and educational workshops, the largest of which is the AACR Annual Meeting with more than 18,000 attendees.

HMP will have one oral presentation encompassing the substantial research and early clinical evaluation of volitinib, as well as two poster presentations focused specifically on c-Met models in preclinical studies of volitinib, and on epidermal growth factor receptor ("EGFR") inhibition in oesophagus cancer.

1st Session:	New Drugs on the Horizon
Date:	Sunday, 6 April 2014
Presentation Title:	Discovery, preclinical and early clinical evaluation of volitinib: A potent and selective c-Met kinase inhibitor
2nd Session:	Kinase Inhibitors
Date:	Monday, 7 April 2014
Presentation Title:	A study on EGFR gene amplification and protein expression in Chinese oesophagus cancer patients and anti-tumour activity of an EGFR inhibitor epitinib in patient derived oesophagus cancer models
3rd Session:	Preclinical Studies in Model Organisms
Date:	Tuesday, 8 April 2014
Presentation Title:	Targeting MET in preclinical models to support the clinical development of volitinib in non-small cell lung cancer ("NSCLC")

Presentations will be made available at http://chi-med.com/eng/irinfo/presentations.htm. Further information about the 2014 AACR Annual Meeting and the abstracts are available in Notes to Editors and at http://www.aacr.org.

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Enquiries

Chi-Med	Telephone:	+852 2121 8200
Christian Hogg, CEO		
Panmure Gordon (UK) Limited	Telephone:	+44 20 7886 2500
Richard Gray		
Andrew Potts		
Citigate Dewe Rogerson	Telephone:	+44 20 7638 9571
Anthony Carlisle	Mobile:	+44 7973 611 888
David Dible	Mobile:	+44 7967 566 919

Notes to Editors

AACR 2014 Presentation Abstracts

Discovery, preclinical and early clinical evaluation of volitinib: A potent and selective c-Met kinase inhibitor

Aberrant activation of c-Met signalling pathway has been identified to drive tumour growth/invasion and be involved in drug resistance. Targeting c-Met pathway represents a compelling opportunity to new anti-cancer therapies. Volitinib (HMPL-504/AZD6094) is a potent small molecule c-Met kinase inhibitor with IC_{50}s in low nanomolar range at enzyme and cell levels. It was found to be highly selective in a screen against a broad panel of kinases. Volitinib has favourable pharmacokinetic properties and demonstrated strong anti-tumour activity in various human xenograft models harbouring c-Met gene amplification and/or protein over-expression. Strong pharmacokinetic/pharmacodynamic and target/tumour growth inhibition relationship was observed in the anti-tumour efficacy studies. In preclinical safety evaluation, volitinib was found to have favourable safety profile with large predicted safety margins. Volitinib is currently in Phase I clinical development. Detailed results on chemistry structure-activity relationship, including the chemical structure of volitinib and the strategy to address renal toxicity seen with other c-Met inhibitors, *in vitro* and *in vivo* evaluation including pharmacokinetic/pharmacodynamic correlation, pharmacokinetic and drug metabolism characterisation, and non-clinical safety evaluation will be presented.

A study on EGFR gene amplification and protein expression in Chinese oesophagus cancer patients and anti-tumour effect of an EGFR inhibitor in patient-derived oesophagus cancer models

Oesophagus cancer is the fifth most common malignancy and the fourth leading cause of cancer mortality in China. According to Chinese cancer registry annual report in 2012, oesophagus cancer accounts for nearly 1 in 10 of all cancer deaths. Despite the fact that much progress has been made in diagnosis and systemic chemotherapy regimens, the overall prognosis of oesophagus cancer is disappointing. The 5-year survival rate, all stages included, is around 15-25%. There remains a significant unmet medical need for oesophagus cancer treatment.

EGFR expression was reported in 30-90% oesophagus cancers and over-expression of EGFR was found to be associated with poorer survival. Unlike colon cancer, K-ras mutation was less frequently found in oesophagus cancer (5-10%), suggesting EGFR pathway blockade might bring therapeutic benefit to those patients with EGFR activation or over-expression. In this study, as of November 2013, 35 surgical oesophagus tumour samples were collected from a local hospital in Shanghai. 31 of the 35 samples were identified as squamous cell carcinoma. EGFR gene amplification, protein expression and K-ras mutation were studied. In addition, 9 patient derived oesophagus cancer xenograft models ("PDX") were developed and anti-tumour effect of a novel and highly potent EGFR inhibitor was evaluated in 6 PDX models.

Positive EGFR protein expression was found in 66% (23/35) of oesophagus cancer samples. EGFR gene amplifications were observed in 9% patients (3/35). In 9 established PDX models, 7 of them showed EGFR expression and 2 with EGFR gene amplification. No K-ras mutation was observed in the 9 models. A novel and highly potent EGFR inhibitor ("EGFRi"), developed by HMP and currently being evaluated in phase I clinical trials in China, demonstrated potent anti-tumour activity in several PDX models with tumour growth inhibition in a range of 70% to >100%. One PDX model with EGFR gene amplification and over-expression exhibited the highest sensitivity to EGFRi with remarkable tumour regression. EGFR signalling transduction was evaluated and the EGFRi inhibited phosphorylation of EGFR and downstream signalling molecules AKT and ERK.

In conclusion, EGFR expression and/or gene amplification was frequently found in Chinese oesophagus cancer. EGFR inhibition resulted in potent anti-tumour effect in multiple patient derived oesophagus cancer models carrying EGFR amplifications or high expression, suggesting the potential benefit that anti-EGFR agents might bring to oesophagus cancer patients with abnormal EGFR activation.

Targeting MET in preclinical models to support the clinical development of volitinib in NSCLC

MET is a transmembrane tyrosine kinase receptor that is deregulated (gene amplification, mutation and over-expression) across multiple cancer types. Signalling through MET is normally activated through interactions with its specific ligand, hepatocyte growth factor ("HGF"). Aberrant MET/HGF activation can stimulate tumour growth, promote angiogenesis, induce metastasis and may contribute to resistance mechanisms in several tumour types. Several non-selective MET inhibitors have entered clinical development; results have been mixed based on potency, selectivity, and/or patient selection. Volitinib is a potent (IC_{50} 4 nM) and selective (>650 fold selectivity over 265 kinases), small molecule inhibitor of MET. Recent evaluation of volitinib across a panel of cancer cell lines demonstrated selectivity for MET-driven disease, with MET amplified cell lines being most sensitive (IC50s of 1nM) and also suggesting limited off target activity. Volitinib resistant cell lines with MET amplification were identified and used to better understand the relationship of concurrent mutations with response. In addition to cancer cell line selectivity, we are analysing preclinical models of NSCLC that are representative of key patient segments, namely MET amplification and over-expression. In newly diagnosed NSCLC adenocarcinomas, focal MET amplification events represent ~3% of the population while over-expression of MET (without gene amplification) is observed in the majority of patients. In preclinical models, focal Met amplification in EBC-1 and NCI-H1993 caused significant tumour growth inhibition, confirming sensitivity to volitinib. Given the prevalence of over-expression in NSCLC, however, we sought to build a platform of evidence for the therapeutic use of volitinib in preclinical models lacking amplification of the MET gene. Using a patient-derived xenograft model (PDX) of EGFR wild-type ("WT"), KRAS WT and metastatic NSCLC disease (HLXF-036LN), we demonstrate that volitinib induces tumour regression as monotherapy and has added therapeutic benefit when used in combination with taxotere. In addition, we show robust efficacy effects for additional preclinical models, LG0567, LG0645 and Calu-3, for either volitinib alone or in combination with taxotere. In parallel pharmacodynamic studies, we demonstrate that volitinib inhibits p-MET and downstream signalling in each model. Together, using an integrated platform of molecular characterization and MET FISH and IHC scores, corresponding anti-tumour responses to volitinib are being evaluated for several patient segments. We are using these studies to inform the design of patient selection criteria for upcoming clinical trials in NSCLC.

About the c-Met signal pathway

The c-Met (also known as HGFR) signalling pathway has specific roles particularly in normal mammalian growth and development. However, this key pathway has been shown to function abnormally in a range of different cancers. Aberrant pathway activation can lead to uncontrolled tumour cell growth, invasion and survival. There are four different mechanisms of c-Met pathway activation: c-Met gene amplification, HGF/c-Met over-expression, mutation, and cross talk with other receptors. c-Met gene amplification is more prevalent in stomach, head & neck and colon cancers; whereas c-Met over-expression is found in many solid tumours, including lung, stomach, head & neck, colon, and oesophagus cancers. Moreover, many of these tumours are of relevance to the Asian population, such as lung, stomach, and oesophagus cancers (with EGFR mutations).

The estimated incidence of lung cancer worldwide was over 1.6 million in 2008, with over 520,000 cases in China. Lung cancer is the most common cancer both worldwide and in China.

About volitinib

Volitinib (HMPL-504/AZD6094) is a potent and highly selective small molecule inhibitor of the c-Met receptor with opportunities in lung, gastric, renal and other cancers. It has been demonstrated to inhibit the growth of tumours in a series of preclinical disease models, especially for those tumours with aberrant c-Met signalling such as gene amplification or c-Met over-expression. In addition, these biomarkers provide the potential to explore patient selection strategies in later stage clinical trials. In December 2011, HMP signed a global licensing deal with AstraZeneca on volitinib and then followed up with the start of Phase I study in Australia in February 2012. In June 2013 HMP initiated a Phase I study of volitinib in Asian patients in China.

To date, volitinib has demonstrated good safety and tolerability and favourable pharmacokinetic properties in late stage cancer patients. It has shown encouraging anti-tumour activity in several tumour-types, in particular in relation to papillary renal cell carcinoma ("PRCC"), a form of kidney cancer for which there is no specifically approved therapy on the global market. PRCC represents about 10-15% of all new cases of kidney cancer. Mutation leading to aberrant activation of the c-Met signalling pathway has been well documented in PRCC and effective inhibition of c-Met has been considered a potential treatment pathway for PRCC.

The results from the Phase I studies are planned to be released at the 50th annual meeting of the American Society of Clinical Oncology which will be held from 30 May to 3 June 2014 in Chicago, Illinois, USA. Phase II proof-of-concept studies on several tumour-types with c-Met amplification, mutation, or over-expression are being planned to start in 2014.

About oesophagus cancer

Oesophagus cancer is the fifth most common malignancy and the fourth leading cause of cancer mortality in China, accounting for nearly one in ten of all cancer deaths. Despite the fact that much progress has been made in diagnosis and systemic chemotherapy regimens, the overall prognosis of oesophagus cancer is disappointing. The 5-year survival rate, all stages included, is around 15-25%. There remains a significant unmet medical need for oesophagus cancer treatment.

About epitinib

Epitinib (HMPL-813) is a highly potent inhibitor of the EGFR tyrosine kinase involved in tumour growth, invasion and migration designed to maximise penetration of the drug into the brain. Epitinib has good kinase selectivity and demonstrated a broad spectrum of anti-tumour activity via oral dosing in multiple xenografts in preclinical studies. In preclinical studies, epitinib demonstrated excellent brain penetration and good efficacy in orthotopic brain tumour models and reached drug concentrations in the brain tissue that are expected to result in robust efficacy when given orally at doses well below toxic levels. The Phase I clinical trial started in China in mid-2011 showed it was well tolerated with excellent pharmacokinetic properties. It demonstrated the anti-tumour activity expected from EGFR inhibitors and partial response among patients with NSCLC with EGFR-activating mutation.

About HMP

HMP is a novel drug R&D company focusing on discovering, developing and commercialising innovative therapeutics in oncology and autoimmune diseases. With a team of around 200 scientists and staff, its pipeline is comprised of novel oral compounds for cancer and inflammation in development in North America, Europe, Australia and Greater China.

HMP is majority owned by Chi-Med. For more information, please visit: www.hmplglobal.com.

About Chi-Med

Chi-Med is a China-based healthcare group focused on researching, developing, manufacturing and selling pharmaceuticals and health-related consumer products. Its China Healthcare Division manufactures, markets and distributes prescription and over-the-counter pharmaceuticals in China. Its Drug R&D Division focuses on discovering and developing innovative therapeutics in oncology and autoimmune diseases. Its emerging Consumer Products Division focuses on organic and natural consumer products in Asia.

Chi-Med (LSE:HCM) is majority owned by the multinational conglomerate Hutchison Whampoa Limited (SEHK:13). For more information, please visit: www.chi-med.com.