

# R&D briefing Hutchison Medi Pharma (HMP)

Wednesday, 9 October 2013

9:30 am to 1 pm

The Brewery, 52 Chiswell Street London, EC1Y 4SD, United Kingdom



HUTCHISON CHINA MEDITECH LIMITED



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## Agenda

Buffet lunch

12:50

TOPIC **SPEAKER** Introduction Mr Christian Hogg, Chief Executive Officer 09:30 **Oncology in China** 09:45 Dr Andrew Mortlock, Vice President of Oncology Projects, AstraZeneca 10:15 China Oncology Market Clinical Pipeline Dr Hua Mu, Chief Medical Officer 10:55 *Coffee break* 11:05 **Global Market Clinical Pipeline** Dr Hua Mu, Chief Medical Officer **Discovery Research &** Dr Weiguo Su, Chief Scientific Officer 11:25 **Pre-clinical Development Funding R&D** Mr Christian Hogg, Chief Executive Officer 11:50 Mr Christian Hogg, Chief Executive Officer 12:10 Wrap up 12:25 Q&A



# Introduction

Christian Hogg Chief Executive Officer

### HMP highlights

The premier novel drug R&D Company in China Rich and unique pipeline in oncology and immunology

Strategic collaborations with Large pharma & healthcare companies Strong R&D leadership



# A world class operation based in China, with a global outlook on drug R&D

Focused on the discovery & development of innovative medicines for patients globally in oncology & immunology

- Established in 2002
- Dedicated state-of-the-art R&D facility in Shanghai
  - GMP facilities at other locations
- ~200 well-trained scientists & staff
- 6 clinical programmes + 4 pre-clinical candidates









## HMP's 3-legged innovative R&D strategy

#### Botanical drugs against multiple targets

- Platform specifically created to follow FDA's Botanical Drug Guidance (2004)
- New source for drugs
- JV with Nestlé, including HMPL-004 in phase III globally for inflammatory bowel disease

#### Small molecule drugs against validated targets

- Targets proven in the global market, but unmet needs in China market
- Identifying global potential through rapid China POC
- Encouraging phase I results with selective VEGFR inhibitor Fruquintinib

#### • Small molecule drugs against *novel* targets

- With best in class or first in class potential
- Co-development with global partners
- Landmark AstraZeneca partnership for selective c-Met inhibitor Volitinib



## Strong leadership team with global R&D experience



- Management team comprised mainly of returnees with average 20 years in multinational pharma & biotech
- All scientific leadership have participated in the discovery & development of blockbusters
  - e.g. Abraxane<sup>™</sup>, Avastin<sup>™</sup>,
    Exubera<sup>™</sup>, Incivek<sup>™</sup>, Sutent<sup>™</sup>,
    Trovan<sup>™</sup>, Zithromax<sup>™</sup>



**Oncology in China** 

9 October 2013

Dr Andrew Mortlock VP Oncology Projects AstraZeneca, Alderley Park, UK



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# **Oncology in China**

- Oncology and the unmet medical need in China
- Lung cancer how genomics crosses national boundaries
- c-Met a strategic priority for AstraZeneca
- Volitinib an insider's view of the AstraZeneca / Hutchison MediPharma collaboration
- AstraZeneca in China



# **Cancer - a huge issue for China**

An aging population, environmental factors (particularly air pollution and smoking) contribute to major rises in cancer incidence in China

#### Table 1: Mortality Rates of Top-10 Malignant Cancers in China

	Mortality (1/100,000 persons)				
Cancer	1973-75	1990-92	2004-05		
Lung cancer	7.09	17.54	30.83		
Liver cancer	12.54	20.37	26.26		
Gastric cancer	19.54	25.16	24.71		
Esophageal cancer	18.83	17.38	15.21		
Colorectal cancer	4.60	5.30	7.25		
Leukemia	2.72	3.64	3.84		
Brain tumor	NA	NA	3.13		
Breast cancer	1.65	1.72	2.90		
Pancreatic cancer	NA	NA	2.62		
Bone cancer	NA	NA	1.70		
All malignant cancers	83.65	108.26	134.80		

Note: NA = not available Source: PRC Ministry of Health In the past 30 years, death rate due to lung cancer increased by 465 percent and has become the most deadly cancer in China.

Cancer, the number one cause of death in urban China, accounts for 25% of deaths.

In rural areas, it is the second cause of death (after cerebrovascular disease), responsible for 21 percent of deaths.





# **Key Facts about Lung Cancer**

Lung cancer is the most common cancer worldwide with an estimated 1.6 million new cases and 1.4 million deaths per year





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# **NSCLC Incidence and Mortality**

NSCLC is one of the 'big four' most common cancers in the developed world and is by far the leading cause of cancer related death

#### **NSCLC** Incidence and Mortality in the US, EU5 and Japan



**GLOBOCAN 2008 (IARC)** 



# Lung Cancer Risk factors and Smoking

Smoking is the most common risk factor for lung cancer in both men and women, causing at least 85% of cases

- ~20% of smokers develop lung cancer, with duration of smoking the most important factor
  - The risk of developing lung cancer from smoking 20 cigarettes a day for 40 years is about eight times the risk from smoking 40 cigarettes a day for 20 years.
- Smoking triggers DNA mutations in the cells of the lung endothelium, impairs mucociliary clearance in the lungs and lowers immunological
  - The particulate phase of tobacco (the tar) contains 55 carcinogens.

#### Lifestyle

- Smoking
- Prior lung disease e.g. TB, asthma, pneumonia
- Age
- Diet high fat, cholesterol, alcohol
- Obesity

#### Genetic

- Family history
- Race / ethnicity
- Genetics? (area of current research activity)

#### Environmental

- Air pollution
- Radon-222
- Asbestos
- Occupational carcinogens (e.g. silicon, chromium, nickel)
  - **Passive smoking**

## **Incidence Trends**

Aging populations in the US, EU and Japan and high levels of smoking in China influence the upward NSCLC trends





- Tobacco smoking is the most common risk factor for NSCLC, thought to cause at least 85% of cases.
- In much of the developed world smoking is declining (currently ~20-30% of the population smoke), influenced by public health initiatives, changes in statute and in deemed social norms.
- HOWEVER, the number of incident cases continues to increase, albeit at a slower rate, due to an aging population which outweighs the effect of reduced smoking.
- It is estimated that 64% of NSCLC incident cases in 2008 occurred in males, although over the next 10 years it is forecast that the annual increase in males will be lower than in females.



#### China

- Smoking rates amongst Chinese men remain high (~50-65%), although rates amongst women are low (~5%).
- The use of solid fuel in the home and workplaces is an important additional risk factor.
- Whilst the crude incidence of NSCLC in China is lower than in the US, EU5 and Japan, age standardized rates are similar.
- China is has the fastest growth in incidence.



# **Genetic Segmentation, key to new treatments**

Reliable prognostic testing will fragment the commercial opportunity in NSCLC – brand positioning will be primarily clinically defined



- The segmentation of NSCLC into molecular subtypes will continue with increasingly smaller segments being defined, leading to more personalized treatment approaches.
- Based on the response rates achieved with EGFR, ALK and ROS1 drugs, it is likely other drugs will show high response rates in small patient populations.
- Approaches to target genetic resistance will increase, particularly in EGFR and ALK segments.



# **EGFR** mutations are more common in SE Asia

# Molecular lesions are similar in the two populations but incidences vary considerably



## What are EGFR Mutations?

~17% of NSCLC tumours have EGFR mutations – they are more common in females, never-smokers and patients of Asian origin

- Binding of EGF to the receptor on the tumour cell surface activates an intracellular signalling cascade, which is important in tumour development and survival.
- EGFR gene mutations can cause the EGFR to be permanently activated (i.e. in the absence of EGF).
- Several EFGR mutations have been identified, all somatic, but the most common (85-90% of all known EGFR mutations), are frame deletions in exon 19 or a specific missense mutation in exon 21 (L858R) of the tyrosine kinase domain.
- Exon 19 and 21 mutations strongly correlate with sensitivity to the reversible TKIs erlotinib and gefitinib, however, introduction of an additional EFGR mutation, T790M, has been shown to confer resistance to erlotinib and gefitinib but not to irreversible inhibitors.
- Patients with non-squamous NSCLC are routinely tested for EGFR mutations.







http://www.iressa.com/product-information/



# **Resistance to current EGFR TKIs**

# Median time of current EGFR TKIs is 10-12 months with half of patients progressing due to T790M mutations in EGFR

- 30% of pts have T790M positive cells detectable <u>before 1<sup>st</sup> line</u> <u>treatment</u>
- Different clonal populations in tumours may be, in part, responsible for resistance
- Treatment of heterogenous tumours with drugs active against both EGFRm+ and T790M in 1<sup>st</sup> line may prevent emergence of T790M-mediated resistance





# AZD9291 – Leading 3<sup>rd</sup> Generation EGFR TKI

Aging populations in the US, EU and Japan and high levels of smoking in China influence the upward NSCLC trends



- AZD9291 is an irreversible inhibitor selective for EGFRM and T790M
- AZD9291 targets both the activating mutant, EGFRm+ and the resistance mutation, T790M, whilst maintaining a margin to activity versus wild type EGFR
- AZD9291 entered Phase I clinical trials in March 2013

 Preliminary Phase I data on AZD9291 was reported at the ECCO / ESMO meeting in Amsterdam in September 2013



# c-MET – a key pathway in cancer

C-Met and its ligand HGF amplification and over-expression may allow for a practical patient selection approach



- Aberrant HGF/Met pathway activation leads to uncontrolled tumor cell growth, invasion and survival
- There are four different mechanisms of Met pathway activation:
  - Met gene amplification
  - HGF/Met over-expression
  - Mutation
  - Cross talk with other receptors

Novel therapeutic inhibitors of the cmet signaling pathway in cancer Joseph Paul Eder et al, Clin Cancer Res 2009; 15:2207-2214



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# **C-Met involvement in Multiple Tumor Types**

# c-Met and HGF are deregulated in a variety of tumour types, including many of relevance to the Asian population

- Met gene amplification mainly in stomach, head & neck and colon cancers
- Met over-expression found in many solid tumors, including stomach, lung, head & neck, colon, esophagus, etc
- Many of these tumors have high preference in Asia population, such as stomach, esophagus, and lung (with EGFR mutation)
- Clear advantage to expedite in Asia

	c-Met			New Cases (2008)		
Indication	Amplifi- cation	Mutation	Over- Expression	Global	China	
Stomach	10%	1%	41%	989,598	464,439	
Lung	4%	8%	67%	1,608,823	522,050	
Head & Neck	(11%)	27%	46%	653,199	76,370	
Melanoma				197,402	3,825	
Colon	10%		65%	1,233,711	221,313	
Multiple Myeloma				102,762	5,909	
Ovarian	4%	4%	33%	225,484	28,739	
Kidney (PRCC)		100%		30,150	3,612	
Kidney (Others)		13%	79%	271,348	32,508	
Esophagus	4%		92%	482,239	259,235	
Total				5,794,716	1,618,000	



# **c-MET Pathway inhibitors**

Selective small molecule c-Met inhibitors are following anti-bodies and non-selective first generation compounds



# Volitinib – the c-Met inhibitor of choice!

Volitinib is a highly selective small molecule inhibitor of the c-met receptor with opportunities in lung, gastric, renal and other cancers

- Potent, selective cMet inhibitor
- Inhibits in vitro growth of cMet amplified gastric and lung cell lines
- Inhibits in vitro growth of HGF-stimulated cell lines
- Induces regressions in cMet-amplified gastric xenografts, inhibits the growth of cMet-expressing lung xenografts
- Good oral bioavailability in rat and dog, with a relatively short half life (1-3 hrs)
- Mild and reversible toxicities associated with the stomach, kidney and heart
- FTIH initiated 2/2012 with PK data from cohort 1 available



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# **Tap Local Innovation**

#### **AZ-Hutchison Global Collaboration was signed in December 2011**



AstraZeneca and Hutchison Medi Pharma Enter into Global Collaboration to Co-Develop and Commercialize Novel Cancer Therapy

Shanghai: Wednesday, December 21, 2011: AstraZeneca and Hutchison MediPharma Limited ("HMP"), an R&D company majority owned by Chi-Med, today announce that they have entered into a global licensing, co-development, and commercialization agreement for Volitinib (HMPL-504), a novel targeted therapy and a highly selective inhibitor of the c-Met receptor tyrosine kinase for the treatment of cancer. Volitinib, which will imminently enter Phase I testing, has been discovered and developed in China by HMP.



- China-based innovative company
- Research and initial clinical work performed primarily in China
- Global licensing, co-development, and commercial agreement for Volitinib (novel c-Met inhibitor for cancer, currently in Phase I)
- Upfront payment plus potential milestones



# **Benefits of working with Hutchison MediPharma**

Novel partnership provides AZ development experience with HMP's knowledge of Chinese clinical practice and ways of working

- Experience of regulatory framework, notably the 'green path'
- Experience of working with key thought leaders in major Asian cancers, e.g, gastric cancer
- Well-developed network of relationships with innovative China-based contract research organisations
- Diversity of thought and approach in the cross-functional team, building an innovative and accelerated plan for Volitinib







# Significant investment in basic science in China

Bio-medical identified as one of seven emerging pillar industries, backed by increased government funding



In its 12<sup>th</sup> Five Year Plan (2011-2015), China's government aims to:

- Almost double government funding in biomedical R&D innovation from the 11th plan
- Launch 20+ innovative drugs fueled by significant investment over the last 5-year plan
- Become the 2nd largest pharma market globally, eclipsing Japan

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# **Innovation Center China Unique advantages**



Focusing on diseases important to Asia





Deep expertise in Translational Science to generate clear target





Lean and flexible model leveraging local capabilities

External innovation



Access to increasing innovation in China Asia





High caliber of talent with solid experience

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## AstraZeneca Innovation Center China New vision and mission

#### Vision

Deliver innovative medicines addressing unmet medical needs in Asia

#### **Mission**

1 Deliver candidate drugs and ultimately, clinical proof of concepts and valuable medicines

2 Maximize commercial potential of in-line products

**3** Provide strong Translational Science support



# HMP's clinical development pipeline

Dr Hua Mu Chief Medical Officer

#### Outline

#### Overview of HMP's clinical pipeline

- Oncology
- Immunology/inflammation

#### China-centered development

- Complex regulatory environment in China
- China-based development (fruquintinib, sulfatinib, epitinib, theliatinib)

#### Global development

- China-Australia in parallel development (volitinib)
- US/EU centered development: HMPL-004



#### HMP's clinical development pipeline

PROGRAM	TARGET / indication	LEAD	CANDIDATE	PRE-CLINICAL	PHASE I	PHASE II	PHASE III
HMPL-004	Ulcerative colitis						•
HMPL-004	Crohn's disease						Health Science
FRUQUINTINIB (HMPL-013)	<b>VEGFR</b> CRC, gastric, lung, other						Lilly
SULFATINIB (HMPL-012)	VEGFR/FGFR HCC, breast						
EPITINIB (HMPL-813)	EGFR NSCLC brain mets, GBM						
THELIATINIB (HMPL-309)	EGFR wild-type NSCLC						
VOLITINIB (HMPL-504)	<b>Selective C-Met</b> gastric, lung, kidney					AstraZ	eneca

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Oncology

Inflammation & Immunology



#### Our compounds target the largest tumour types in China



Source: 2012 Chinese cancer registry annual report

#### China regulatory environment

#### **China Regulatory Complexity**

- Comprehensive data package requirement and lengthy review/approval process for IND
- Clinical trial authorization (CTA) only for specific development phase (i.e., need a new CTA application for further development)
- Implications:
  - Much longer time and greater uncertainty to initiate a clinical program and advance to subsequent stages
- Special Review Process ("Green Channel")
  - Aimed to promote development of innovative drugs
  - Effective on January 7, 2009



## Regulatory review time of CTA

COUNTRY	CTA REVIEW TIME	SPECIAL REQUIREMENTS FOR CTA
US/EU	IND/CTA 30 days Multinational studies 60 days	Technical documentation and study protocol
Japan	30 days	Clinical Trial Notification form + study protocol, IC and CRF
Korea	3-4 months	Technical documentation and study protocol
Taiwan	3-4 months	Technical documentation and study protocol
China	9-15 months	Full Dossier (CMC, pre-clinical and clinical reports) required for CTA

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## China FDA's Special Review Process ("Green Channel") *Effective on January 7, 2009*

#### Green Channel Benefits

- Have priority in review and approval process
- Have additional communications with the CDE
  - Pre-IND meeting/regular communication meetings
  - Allowed to submit new data/documents in conjunction with a panel meeting/communication meeting
- HMP has been very successful in exploring & leveraging this mechanism


#### Two types of oncology development strategies

#### **China-based development**

- For drugs targeting validated pathways
  - VEGFR and VEGFR/FGFR inhibitors
  - EGFR inhibitors
- Pursue fast-to-market development in China
- Explore product differentiation (POC) for global potential

#### **China-Australia in parallel development**

- For drugs targeting novel pathways
  - c-Met inhibitor
- Leverage China/Australia complementarity to pursue expedited development in China and globally



### VEGFR and VEGFR/FGFR Inhibitors Fruquintinib and Sulfatinib

#### Angiogenesis inhibitors

- Angiogenesis is the growth of blood vessels (to feed tumours)
  - VEGFR is a key player in tumour angio- and lymphangiogenesis, a validated target for cancer
- Market for anti-angiogenesis drugs (VEGFR inhibitors) over \$10 billion
  - Small molecule inhibitors sales
     2012: \$1.2b Sutent<sup>™</sup>, \$1.0b
     Nexavar<sup>™</sup>
  - MAb inhibitors sales 2012:
    \$6.1b Avastin<sup>™</sup>





## Fruquintinib: a highly differentiated VEGFR inhibitor (HMPL-013)

	Sunitinib	Sorafenib	Axitinib	Cediranib	Tivozanib	Apatinib	Regorafenib	Fruquintinib
Kinase profile	VEGFR1,2,3 , PDGFRb, FLT3, CSF- 1R, c-Kit, Ret	RAF, VEGFR2, PDGFRb, Flt3, c-Kit, FGFR1	VEGFR1,2, PDGFR, CSF-1R, c- Kit, FGFR1	VEGFR1,2,3 , PDGFRa, PDGFRb, c- Kit, FGFR1	VEGFR1,2,3 , PDGFRa, PDGFRb, c- Kit, Tie2, EphB2	VEGFR1,2, PDGFRb, c- Kit, Ret, c- SRC	VEGFR1,2,3 , Raf, Ret, c- Kit, PDGFR	VEGFR1,2,3
Efficacy	22 pts	45 pts	36 pts	63 pts	37 eval. pts	37 pts	53 pts:	34 eval. pts
in Ph I (PR, SD, PD etc.)	PR: 4/22 (18%)	PR: 1 (2%)	PR: 3 (8%)	PR: 2 (3%)	PR: 1 (2.7%)	PR: 7 (18.9%)	PR: 3 (6%)	PR: 13 (38%)
	DCR: 27%	DCR: 58%		DCR: 38%	DCR: 51%	DCR: 84%	DCR: 66%	DCR: 82%

- Very potent and selective kinase profile
- Sustained target inhibition
- Excellent PK properties



## Fruquintinib: a highly differentiated VEGFR inhibitor: a potent and selective kinase profile







#### Fruquintinib development plan





#### Fruquintinib development overview

#### IND/Phase I CTA approval through Green Channel

- Phase I initiated in Q1 2011, completed in Q3 2012
  - At Fudan University Cancer Center in Shanghai
  - Enrolled 40 patients with late stage solid tumours
  - Very good results: acceptable safety, good PK, and promising efficacy
- Phase Ib/II initiated in December 2012
- Phase II and Phase III CTA approval granted by CFDA in July 2013
- Randomised Phase II ST#1 to start Q1 2014
- Randomised Phase II ST#2 & ST#3 to start during 2014



#### Fruquintinib Phase Ia study

#### Study design

• Phase I, dose-escalation (3+3) to evaluate safety, maximum tolerated dose (MTD), pharmacokinetics (PK), and preliminary efficacy

#### **Study status**

- Study initiation date: Q1 2011
- Data cut-off: Oct. 31, 2012
  - 40 patients with advanced solid tumours enrolled and treated at 5 fruquintinib doses given once daily continuously (QD) and 2 doses given once daily 3wks on and1 wk off (3/1 wk)
- 4 mg QD and 6 mg 3/1wk were identified as MTD, respectively



#### Fruquintinib Phase Ia study

#### **Study summary**

- Fruquintinib was well tolerated up to 4mg QD or 6mg 3/1 wk
   4mg QD and 5mg 3/1 wk were recommended Phase II doses
- Toxicity profile similar to / better than other VEGFR inhibitors
- PK data suggest a good dose proportionality in exposure over the tested doses without marked accumulation
- Promising preliminary clinical efficacy observed in patients with various heavily pre-treated advanced cancers, including partial response in colorectal, lung, gastric, breast, and other tumour types



#### Phase I study: baseline demographics

Characteristics (N=40)	
Median age: year (range)	56 (18-70)
Gender (male : female)	18:22
ECOG PS (0/1)	10/30
Primary tumour type, n	
CRC	12
Breast	8
NSCLC	7
Thyroid	3
Gastric	2
Others	8
Prior treatment	
Surgery	38
Radiation	20
Systemic regimens	
≤2	8
≥3	32

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#### Fruquintinib efficacy in Phase I trial

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Population	Patients No.	No. of PR	No. of SD	ORR	DCR
ITT	40	13	15	32.5%	70.0%
Evaluable pts	34	13	15	38.2%	82.4%
CRC	10	3	6	30.0%	90.0%
NSCLC	6	4	1	66.7%	83.3%
ВС	7	2	5	28.6%	100.0%
GC	2	1	0	50.0%	50.0%
Other	9	3	3	33.3%	66.7%



## Waterfall plot of best response (tumour size change from baseline) in evaluable patients (n=34)



\*\*: overall PD (non-target lesion, new lesion appeared)

\*\*\*: overall PD ( PR on D49 assessment was not confirmed 4wks later)



#### Phase Ib/II study status

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- Study initiation date: Dec 28, 2012
- Two study centers in China
- Two-stage design
  - A. Randomized 2-arm: QD vs. 3/1 wk → regimen selection: drop "the loser" or pick "the winner"
  - B. Single-arm Phase II (selected regimen)
- Stage A completed; optimal regimen has been determined
- Stage B with selected regimen to start in October 2013



#### First solid tumour randomized Phase II study

#### Study design

• A randomized, double blind, placebo-control phase II study: Fruquintinib + Best Supportive Care (BSC) vs. placebo + BSC

#### **Study plan and current status**

- Investigators' meeting completed
- First patient in: 2014
- Data read-out: 2015



#### Sulfatinib: a VEGFR/FGFR1 dual inhibitor

VEGFR is a key player in tumour angio- and lymph-angiogenesis, a validated target for cancer

**Blood Vessel** VEGF Production Grow th Tumor Tumor Growth

FGFR1 is amplified in a number of tumours, e.g., roughly 10% of breast tumours have FGFR1 amplification leading to Tamoxifen-resistance

#### Sulfatinib Phase I study summary

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#### **Study Status**

- Initiated in Q2 2010
- Patients enrolled in seven QD dose cohorts of 50 to 300 mg and two BID dose cohorts of 125 and 150 mg

#### **Preliminary data**

- Safe and well tolerated
  - Few serious adverse events (SAEs)
  - No unexpected adverse events
- Preliminary efficacy
  - 1 PR was observed in a liver cancer patient
  - Stable disease (SD) was observed in multiple tumour types



### EGFR inhibitors Epitinib and Theliatinib

#### Background to Epitinib & Theliatinib development

- Next generation EGFR inhibitors, similar in MOA to gefitinib and erlotinib
- Current EGF/EGFR inhibitors have low brain membrane penetration and poor efficacy on brain cancer
  - EGFR-activating mutations in 30-40% of glioblastoma patients (most common malignant primary brain tumours)
- Current EGF/EGFR inhibitors do not perform well on wild-type EGF
  - Majority of tumours grow without EGFR-activating mutations, i.e. due to normal EGFR activity (also known as wild-type EGFR)



#### Epitinib (HMPL-813) Phase I clinical trial progress

## Small molecule EGFR inhibitor with greater brain penetration and potential to target brain metastases and primary GBM with EGFR mutation

- Phase I study initiated in Q4 2011
- 25 patients with advanced solid tumours have been enrolled and treated in 6 dose cohorts
- MTD has not been identified, dose escalation is ongoing
- Safe and well tolerated
- Good PK properties: dose proportionality in exposure without marked accumulation; higher drug exposures achieved
- Preliminary efficacy including confirmed PR observed



#### Theliatinib (HMPL-309) Phase I clinical trial progress

Small molecule EGFR inhibitor with high potency and slow off rate targeting wild type EGFR activation in NSCLC and potentially other tumour types

- First patient was enrolled in Q4 2012
- Three dose cohorts completed, fourth cohort is ongoing

#### **Preliminary results**

- Safe and well tolerated
- Good PK properties
- No DLT, MTD not reached



# Volitinib (HMPL-504) clinical progress and status

#### Volitinib, a novel compound

- A highly selective small molecule inhibitor of c-Met kinase
- New chemical entity with strong global IP position discovered and developed by HMP
- Potent in vivo target inhibition and anti-tumour activity with good PK/PD correlation
- Good pre-clinical safety profile and PK properties
- Landmark partnership with AstraZeneca to co-develop and commercialize globally
  - A. HMP continues to lead development in China and Australia
  - B. AstraZeneca will lead development for rest of world



#### Volitinib's unique development strategy

#### Parallel China-Australia development

- Simultaneous CTA submission in China and Australia
- Quick initiation of multi-centre first-in-human Phase I trial in Australia
- Proactive discussion with China FDA on development plan through formal scientific advisory meeting
- China IND/CTA approval through Special Review Process ("Green Channel")
- Significant translational science effort to support patient population selection



#### Volitinib's unique development strategy (continued)

#### Parallel China-Australia development (cont'd)

- Leverage China / Australia complementarity to pursue accelerated clinical development
  - a) Mitigate regulatory and operational risks
  - b) Accelerated China Phase I studies based on Australian clinical data/experience
  - c) Leverage China advantages for quick POC
  - d) Clinical data from both Chinese and Caucasian patients to support global development



#### Volitinib's China-Australia complementarity in clinical trials

#### China-Australian complementarity in clinical trials

	CHINA	AUSTRALIA
Patient pools	Huge	Limited
Standard of Care	Sometimes different from US and Europe	Usually same as US and Europe
Start-up timelines	Slow	Fast
Costs	Low	High
Ethnicity	Chinese	Primarily Caucasian
Data acceptance by FDA and EMA	Variable	Good



#### Volitinib Australia Phase I study update

#### Study status

- 5 dose cohorts completed
- Dose escalation ongoing

#### Preliminary data

- Good safety and tolerability and PK profile
  - No significant or unexpected safety signals
- Preliminary efficacy including partial response (PR), minor response (MR), and durable stable disease (SD) observed in multiple tumour types



#### Volitinib China Phase I study update

#### Study status

- First patient enrolled in June 2013
- Per agreement with China FDA, started at a higher dose
  - Tumour type enrichment guided by Australia preliminary findings
  - Efficiency in speed and cost
- First dose cohort completed
- Dose escalation ongoing

#### Preliminary Data

- Good safety and tolerability
- PK data is consistent with Australia Phase I data



#### HMPL-004 A novel oral therapy in Phase III for ulcerative colitis

## HMPL-004 is a first-in-class oral therapy for inflammatory bowel disease

Significant potential	<ul> <li>Significant unmet medical need in IBD</li> <li>US\$1+ billion global opportunity</li> <li>Eranchisa potential in other GLand autoimmuna diseases</li> </ul>
	• Franchise potential in other Grand autoinfindure diseases
Unique	<ul> <li>Novel MOA to provide a new effective treatment option</li> </ul>
profile for an	<ul> <li>Clear differentiation from existing therapies</li> </ul>
unmet	Superior safety profile supports long-term maintenance use
medical need	Convenient oral dosing
Late stage	<ul> <li>Three global phase II trials completed</li> </ul>
development	<ul> <li>Global registration Phase III began in April 2013</li> </ul>
Maior barriers	<ul> <li>&gt;30 patents &amp; patent applications worldwide</li> </ul>
to entry /	<ul> <li>Natural multi-component products very difficult to copy</li> </ul>
exclusivity	<ul> <li>Proprietary process and manufacturing know-how</li> </ul>



#### HMPL-004 mechanism of action



- HMPL-004 targets multiple cellular pathways including NF-kB activation, leading to inhibition of production of multiple pro-inflammatory cytokines including TNFa, IL-1b, and IL-6
  - Combination of systemic and local anti-inflammatory effects



#### HMPL-004's successful global Phase IIb UC trial

- Significantly improved clinical response, clinical remission, and mucosal healing
- Excellent safety profile
- Clearly demonstrated dose response



- · Randomized, double-blind, placebo-controlled multicenter trial in mild to moderate active UC
- 3 arms: 1,800 mg/day, 1,200 mg/day, & Placebo. 8 weeks treatment.
- 224 patients at 50 centers in US and Europe



## HMPL-004's successful global Phase IIb UC trial: safety evaluation comparison

	Placebo (N=75)	HMPL-004 1,200 mg (N=75)	HMPL-004 1,800 mg (N=74)
No. of pts who had AEs	45 (60%)	45 (60.0%)	39 (52.7%)
No. of AEs	111	109	108
No. of pts who had "related" AEs	18 (24.0%)	29 (38.7%)	22 (29.7%)
No. of pts who had "severe" AEs	3 (4.7%)	1 (1.3%)	2 (2.7%)
No. of pts who had a SAE with outcome death	0	0	0
No. of pts withdrawn due to AEs	3 (4.0%)	7 (9.3%)	6 (8.1%)
No. of pts with SAEs	2 (2.7%)	2 (2.7%)	2 (2.7%)

- No "life-threatening" AEs assessed by the investigators
- No "related" SAEs assessed by the investigators



## HMPL-004 combines the strengths of market leading therapies

	5-ASAs	HMPL-004	Biologics
MOA	Non-selective – multiple targets: COX, LO, PPARγ, etc	Inhibition of pro- inflammatory cytokines	Anti-TNF
Route of admin	Oral, local	Oral	Injectible
Clinical response	40%~60%	~70% (Phase II data)	~70%
Maintenance efficacy	Varies	Good potential	Good
Side-effects	Minor	Minor	Infection risks with black box warning

### HMPL-004 offers a potential oral, effective, and safe treatment option for IBD patients



#### HMPL-004 ulcerative colitis (UC) global Phase III trial

 UC trial is named NATRUL: <u>Natural Andrographis-based Treatment for</u> the <u>Remission of UL</u>cerative colitis

NATRUL-3	<ul> <li>First 8-week induction study</li> <li>In UC patients with inadequate response to mesalamine</li> </ul>
NATRUL-4	<ul> <li>52-week maintenance therapy</li> <li>Patients who have achieved clinical response or remission from NATRUL-3 or NATRUL-5</li> </ul>
NATRUL-5	<ul> <li>Second 8-week induction study to fulfil regulatory requirements</li> <li>Protocol similar to NATRUL-3</li> </ul>



#### NATRUL-3 investigators' kick-off meetings

- Completed in the US & Europe
- Well attended
- Procedures & protocols well received
- A lot of enthusiasm among investigators for a new, natural and safe therapy for IBD





















#### Summary of HMPL-004

- UC ongoing
- Enrolment on track
- CD expected to start next year




## Discovery Research & Pre-clinical Development Strategy

Dr Weiguo Su Chief Scientific Officer

### NME success rates by phase and overall: 2004-2008



Black numerals refer to number of NME entries required in each phase to obtain 1 Approval; figures in red boxes are success rates for each phase



Source: PBF R&D General Metrics 2008; copyright © KMR Group, Inc.

### Level of target validation vs. success rate



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## HMP: innovative drug R&D strategy

#### Botanical drugs against multiple targets

- Platform specifically created to follow FDA's Botanical Drug Guidance (2004)
- New source for drugs
- Reverse pharmacology for improved success rate and speed (Quadrant 4)
- Small molecule drugs against validated targets
  - Targets proven in the global market (Quadrant 3) with good success rate
  - Major unmet needs in China market with global potential through rapid China POC
- Small molecule drugs against novel targets
  - With first/best in class potential, high risk Quadrant 1/2 targets
  - Risk mitigation through co-development with global partners



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## Botanicals positioned as the newer source of novel drugs

#### FDA new guidelines for botanical drug registration was established in 2004



[1] IMS Health data; [2] US FDA publications; [3] Investigational New Drug ("IND"); [4] Veregen™ is the first prescription botanical (herbal) drug approved by FDA under the "new" drug amendments of 1962 that required drugs to be proven both safe and effective prior to being marketed in the US – an extract of green tea for use in women's health.



### Overview of botanical drug discovery process



## Botanical compound library

#### • Library

- >1,200 medicinal plants
- 50,000 extracts and fractions
- 1500 purified natural products and/or derivatives

#### Expertise in natural product chemistry

- Sourcing/selection of plants with human use history and GAP plantation
- Extraction/fractionation method development/optimization
- Natural product isolation & structural identification
- Fingerprinting and mass balance
- IP generation/management







# Drug supply chain: from GAP plantation sites to GMP manufacturing





**GMP EXTRACTION** 



GMP FORMULATION



# The Discovery of HMPL-004: targeting anti-inflammation



- Over 40 plants were selected based on reported human use and/or anti-inflammation activity
- Over 1,000 extracts/fractions derived from these 40 plants were screened
- Bio-assay/clinical indication selection focuses on novel indications: NF-kB activation



## Building a botanical drug development pipeline with NSP

HMPL-004 in global Phase III development for UC and CD

#### Ongoing research

- GI therapeutic area
- Additional INDs in the next few years, targeting major commercial opportunities for global markets

#### Risk mitigated through partnership with NSP



## Positioned to become a strong leader in botanical drug R&D

#### Taking advantage of the new FDA guidelines for botanical drug development

- Major opportunity particularly for chronic diseases such as GI disorders
- Reverse biology for better success rate

#### Over 10 years of investment in botanical drug R & D infrastructure

- Wealth of information on human use knowledge of TCM, including a large database of herbs with information on chemical components, clinical indications, and drug safety
- Proprietary botanical drug R&D platform including natural product chemistry with the largest botanical sample library, disease-relevant assays and animal models and IP management
- Supply chain from GAP plantation sites to drug products with extensive experience in quality control and deep understanding regulatory requirement
- Extensive experience with regulatory agencies for botanical drug development



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### Focused on major medical/patient needs in China

- Unmet patient needs due to Big Pharma pricing/affordability in China created a major market opportunity
  - Due to the high pricing, novel therapies are not covered by medical insurance in China
  - Only ~5% of Chinese patients have access to novel therapies due to affordability
  - Early success of Icotinib, third oral EGFR inhibitor for NSCLC, supports this approach
- Major unmet medical needs for China-specific diseases, such as cancers of liver, stomach, esophagus, etc.
  - Large pharmas paid little attention due to limited commercial potential
  - Opportunity growing rapidly due to large patient population and increasing buying power
- If strong differentiation is demonstrated in POC, the product potential can be expanded to global market



## Conmana<sup>®</sup> (icotinib) development and commercial success

- Proven target for EGFR positive NSCLC by Iressa® (gefitinib) & Tarceva® (erlotinib)
  - The two drugs combined only treat <10% of eligible patients in China
- Conmana<sup>®</sup>, a close cousin of Tarceva<sup>®</sup>, completed clinical development in China in just over five years
- Conmana<sup>®</sup> demonstrated equivalent safety and efficacy to Iressa<sup>®</sup> in clinical trials



Tarceva® (erlotinib)

Conmana® (icotinib)



## Continue to invest in validated targets to capitalize on the unique opportunity

#### **Opportunity driven**

- Fast follow-on of proven/approved targets, for China market
  - Global potential if proven differentiated in clinical trials
- Only those targets with a major China opportunity
- Technically feasible



## HMP: innovative drug R&D strategy

#### Botanical drugs against multiple targets

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- New source for drugs
- Reverse pharmacology for improved success rate and speed (Quadrant 4)

#### Small molecule drugs against validated targets

- Targets proven in the global market (Quadrant 3) with good success rate
- Major unmet needs in China market with global potential through rapid China POC

#### Small molecule drugs against novel targets

- With first/best in class potential, high risk Quadrant 1/2 targets
- Risk mitigation through co-development with global partners

## Targeting first/best in class novel therapies

- Efficient speed and cost to reach human POC in China
  - Large naïve patient population for rapid enrolment
  - Supportive government policies for innovation
  - Strong interest from research and clinical community for novel targets
- Building a productive collaboration network for genetic and epigenetic studies
  - New target identification
  - Target validation



## Novel candidates in partnership with large pharma: Sharing risk and success

- Volitinib for cancer with AstraZeneca
  - Selective oral c-Met kinase inhibitor discovered by HMP
  - Global development in collaboration with AstraZeneca for multiple cancers
- Inflammation candidate with Janssen
  - Novel kinase inhibitor discovered by HMP in collaboration with Janssen
  - Janssen responsible for global development







## Syk inhibitor HMPL-523 for inflammation and oncology

- Syk plays key roles in the pathogenesis of rheumatoid arthritis, lupus, allergic asthma, and B cell malignancies
- Fostamatinib Phase II data provided target validation for RA
- HMPL-523 has much improved kinase selectivity and pharmacokinetic properties critical for maximizing the therapeutic effect
- Completed GLP toxicity evaluations; IND preparation in progress
- Will be seeking global partners





## HM5022523 in vivo Efficacy in rCIA Therapeutic Model *Paw volume*





## HM5022523 in vivo Efficacy in rCIA Therapeutic Model *Ankle histopathology score*



NORMAL ANKLE

**VEHICLE (DISEASE CONTROL)** 

HM5022523, 10 MPK, QD

HM5007535, 10 MPK, BID

#### Histopathology of hind paw sections in CIA rat





## Aberrant FGF/FGFR signaling in cancer

#### Gene amplification

- FGFR1 (lung and breast cancer, major unmet needs in Lung SCC and TN BC)
- FGFR2 (gastric cancer, no targeted therapies available)
- Activating mutation: FGFR3 (bladder cancer)
- Translocation: FGFR3 (multiple myeloma)





# HMPL-453: a potent and selective oral, small molecule FGFR inhibitor targeting FGFR 1, 2 & 3



- Lead FGFR compounds from AstraZeneca and Novartis in Phase I or II
- HMPL-453 is positioned to be First-in-class in China with potential for multiple major tumour types
- Potential for best-in-class
- Preparing for GLP toxicity studies
- Will be seeking partners



PROGRAM	TARGET / indication	LEAD	CANDIDATE	PRE-CLINICAL	PHASE I	PHASE II	PHASE III
HMPL-004	Ulcerative colitis						••••
HMPL-004	Crohn's disease						Nestle Health Science
FRUQUINTINIB (HMPL-013)	<b>VEGFR</b> CRC, gastric, lung, other						Lilly
SULFATINIB (HMPL-012)	VEGFR/FGFR HCC, breast						
EPITINIB (HMPL-813)	EGFR NSCLC brain mets, GBM						
THELIATINIB (HMPL-309)	EGFR wild-type NSCLC						
VOLITINIB (HMPL-504)	<b>Selective C-Met</b> gastric, lung, kidney					AstraZ	eneca
HMPL-523	<b>Syk</b> RA, MS, Lupus; (pot. Lymphoma, CLL)						
HMPL-453	<b>Selective FGFR</b> Lung SCC, Breast, Gastric, Bladder, MM					Onco	ology
R&D collaboration	Novel Inflammation Target <sup>[1]</sup>					Inflamn Immu	nation & nology

[1] Novel – means target link to disease not yet proven in-man;

Other Acronyms: HCC -- Hepatocellular carcinoma or liver cancer; CRC -- Colorectal cancer or colon cancer; NSCLC -- Non small cell lung cancer; RCC -- Renal cell carcinoma or kidney cancer; GBM -- Glioblastoma or brain cancer.

Hutchison Medi Phorma

	PROGRAM	TARGET / indication	LEAD	CANDIDATE	PRE-CLINICAL	PHASE I	PHASE II	PHASE III
	HMPL-004	Ulcerative colitis						• <b>•</b>
П	HMPL-004	Crohn's disease						Nestlé <mark>Health</mark> Science
	FRUQUINTINIB	VEGER CRC gastric lung other						Lilly
	Innov	ative botanical drugs	s for glo	bal mar	ket			
	(HMPL-012)	VEGER/FGER FICE, Diedst						
		EGFR NSCLC brain mets, GBM						
		EGFR wild-type NSCLC						
		<b>Selective C-Met</b> gastric, lung, kidney					AstraZ	eneca
		<b>Selective FGFR</b> Lung SCC, Breast, Gastric, Bladder, MM					Oncc	ology
							Inflamm Immur	nation & nology

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PROGRAM	TARGET / indication	LEAD	CANDIDATE	PRE-CLINICAL	PHASE I	PHASE II	PHASE III
Validated	targets for China ma	arket wi	t <mark>h pote</mark> n	tial for			
global ma	rket if differentiated						Health Science
FRUQUINTINIB (HMPL-013)	<b>VEGFR</b> CRC, gastric, lung, other						Lilly
SULFATINIB (HMPL-012)	VEGFR/FGFR HCC, breast						
EPITINIB (HMPL-813)	EGFR NSCLC brain mets, GBM						
THELIATINIB (HMPL-309)	EGFR wild-type NSCLC						
VOLITINIB (HMPL-504)	<b>Selective C-Met</b> gastric, lung, kidney					AstraZ	eneca
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PROGRAM	TARGET / indication	LEAD	CANDIDATE	PRE-CLINICAL	PHASE I	PHASE II	PHASE III
							Nestle Health Science
FRUQUINTINIB (HMPL-013)	<b>VEGFR</b> CRC, gastric, lung, other						Lilly
	VEGFR/FGFR HCC, breast						
Nov risk	el targets with first-i mitigation through p	n-class p partners	ootentia hip	l;			
(HMPL-309)							
VOLITINIB (HMPL-504)	<b>Selective C-Met</b> gastric, lung, kidney					AstraZ	eneca
HMPL-523	<b>Syk</b> RA, MS, Lupus; (pot. Lymphoma, CLL)						
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R&D collaboration	Novel Inflammation Target <sup>[1]</sup>					Inflamm Immur	nation & nology

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## HMP development pipeline: by quadrants



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## Funding Research & Development

Christian Hogg Chief Executive Officer

### China's leading oncology & immunology pipeline: *Risk will be well balanced through deals with major partners*

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### A proven track record of productivity & innovation



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#### **VOLITINIB PARTNERSHIP**

DEVELOPMENT PLAN	China	<b>Rest of World</b>
Clinical Development	HMP	AZ
Development Costs	HMP/AZ	AZ
FINANCIAL CONSIDERATION		Global
Upfront cash payment		US\$20 million
Development milestones		Up to US\$120 million
Commercial Milestones		Undisclosed
Royalty on Net Sales		Up to double digit

- First China clinical stage novel product to be partnered with a global pharma
- Parallel China and global development
- 2012 BayHelix/Elsevier Alliance of the Year; Scrip Licensing Deal 2012 Shortlist



#### Nestlé – the world's leading nutrition, health & wellness company

- ~US\$220 billion market cap; 300,000 employees
- Established Nestlé Health Science in 2011, focusing on developing science-based personalised nutrition to prevent & treat increasingly prevalent health conditions that are placing an unsustainable burden on healthcare

#### • HMP and Nestlé established a 50:50 equity joint venture

- Fund HMPL-004 Phase III and marketing & sales
- Botanical R&D in GI

#### HMP brings its botanical R&D platform

- New discovery research & FDA clinical expertise
- Nestlé brings nutritional sciences, diagnostics & commercial capabilities
  - Prometheus leader in IBD diagnostics

#### Funded primarily through Nestlé's initial investment and milestones



- Fruquintinib licensing, co-development, and commercialization in China
- Future development of Fruquintinib in China
  - Carried out by HMP
  - Costs will be shared between HMP and Lilly
- Financial terms
  - Up to US\$86.5 million in upfront, development and approval milestones
  - Tiered royalties starting in the mid-teens percentage of net sales
- Collaboration with Lilly will allow development across various tumour types in China and at a far greater speed
- Shared commitment to the medical needs of oncology patients in China



## HMP Group has secured ~US\$100 million in external funding and support since 2010

#### FUNDS FROM EXTERNAL SOURCES, 2010-2013

(US\$ in millions)


Wrap-up and Q&A

## Plans for 2014/15

#### Rapidly progress clinical portfolio

- HMPL-004 execute the NATRUL Phase III registration trials at speed
- Fruquintinib initiate Phase II/III studies in China
- Volitinib complete Phase I and initiate Phase II studies in multiple tumour types
- Sulfatinib complete China Phase I and submit CFDA Phase II/III Clinical Trial Approval
- Epitinib/Theliatinib complete China Phase I and prioritise/partner
- Finance HMP clinical portfolio through further licensing collaborations
  - Epitinib/Theliatinib (if differentiated from gefitinib/erlotinib)
  - Syk and Selective FGFR all attractive to global partners over next one to two years
- Discovery operation efficiency
  - Strategic research collaborations (e.g. Janssen/Nestlé) to help support discovery
  - Internal HMP discovery team to produce 1+ IND per year



## HMP, China's premier novel drug R&D company

### Tangible attributes

- Pipeline
  - Right place
  - Risk balance
- Strong leadership
- Evolving, integrated platform
  - Discovery  $\Rightarrow$  development  $\Rightarrow$  manufacturing  $\Rightarrow$  commercial

### Intangible attributes

- 1<sup>st</sup> mover advantage
- Partner of choice
- Strategic collaborations
- Stability



# Thank you

Hutchison MediPharma Ltd Building 4, 720 Cailun Road, Zhangjiang Hi-tech Park, Shanghai, 201203 China

Tel: +86 21 5079 0088 www.hmplglobal.com

