EDISON

Hutchison China MediTech

Focus shifts to R&D pipeline

H114 results and R&D update

Pharma & biotech

Hutchison China MediTech's H114 results highlighted that the investment case is increasingly centred on its R&D unit, Hutchison MediPharma. Its lead compound, HMPL-004, is approaching an interim analysis on 12 August in a Phase III trial for ulcerative colitis (UC). This could trigger a milestone payment from its partner, Nestlé, and the initiation of new Phase III trials in UC and Crohn's disease. Its broad portfolio of small molecule tyrosine kinase inhibitors for oncology is also advancing well. Meanwhile, the China Healthcare division maintains its strong growth with operating profit up 18.1% in H114. We increase our valuation to £11.54/share.

Year end	Revenue ($m)	PBT* ($m)	EPS* (c)	DPS (c)	P/E (x)	Yield (%)
12/12	22.4	1.9	1.7	0.0	N/A	N/A
12/13	46.0	11.0	17.0	0.0	N/A	N/A
12/14e	80.6	7.8	5.8	0.0	N/A	N/A
12/15e	102.0	16.7	17.4	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding intangible amortisation, exceptional items and share-based payments. Historic figures reflect the changes due to IFRS 11.

MediPharma set to deliver a stream of product news

Hutchison MediPharma is the R&D unit that discovers and develops innovative drugs for both the global and domestic Chinese markets. It has already struck a number of collaborations (including with Nestlé, Janssen, Lilly and AstraZeneca) and now has seven products in the clinic, in the fields of oncology and auto-immune diseases. Steady newsflow on the pipeline is expected, including Phase II data, over the next 12-18 months.

HMPL-004 approaching important interim analysis

On 12 August, an independent data monitoring committee (DMC) will conduct an interim analysis to review data from c 147 of 420 patients in the Phase III NATRUL-3 trial in UC. There are three likely outcomes of the analysis: 1) Further investment in JV by partner Nestlé is triggered and new Phase III trials start in UC and Crohn's disease; 2) no extra investment and new trials may start; or 3) no extra investment and HMPL-004 programme is stopped. No data are expected to be reported.

China Healthcare division maintains strong growth

Although attention is moving away from the China Healthcare division, which sells traditional Chinese medicine (TCM) products, it is still maintaining its strong growth and remains an important value driver. In H114, its sales increased by 15.0% to $261.7m and operating profit rose by 18.1% to $45.1m.

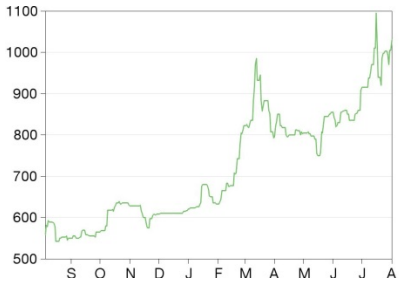
Valuation: $1.0bn (1,154p/share), ex property windfall

We raise our valuation by $230m to $1,021m. The increase is primarily due to advances made by MediPharma. Our indicative valuation would be $1,130m (1,278p per share) if the interim analysis of the HMPL-004 Phase III trial leads to new Phase III trials in UC and Crohn's disease. Other important catalysts over the next year are clinical data on the oncology assets, fruquintinib and volitinib.

4 August 2014

Price	**1,030p**
Market cap	**£545m**
	$1.70/£
Net cash ($m) at 30 June 2014	1.1
Shares in issue	52.9m
Free float	29.6%
Code	HCM
Primary exchange	AIM
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	12.6	28.0	91.5
Rel (local)	14.8	30.6	90.6
52-week high/low	1,095p		536p

Business description

Hutchison China MediTech is a primarily China-based healthcare group focused on researching, developing and selling pharmaceuticals and health-oriented consumer products.

Next events

HMPL-004 interim analysis	12 August 2014
Complete enrolment of fruquintinib Phase II trial	Q314
Phase I data on HMPL-523	Q414

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Edison profile page

Update: R&D is coming to the fore

Hutchison China MediTech's H114 results again demonstrated the financial strength of its business model with profits from its China Healthcare division more than offsetting the losses from its MediPharma R&D unit. This led to the net profit from continuing operations increasing by 19% to $5.6m. The interim results also showed that the investment case, which used to be largely supported by the China Healthcare division, now hinges more on MediPharma's pipeline following recent advances. Consequently, we are taking this opportunity to provide a thorough review of the pipeline to highlight its breadth and the progress achieved across a number of projects. An important catalyst is on 12 August, when the outcome of the interim analysis of data from the Phase III trial in ulcerative colitis (UC) with HMPL-004 should be announced.

Hutchison China MediTech is a holding company with three distinct business units:

- **Hutchison MediPharma**, which is the research and development unit. It researches synthetic and botanical drugs for both the global and domestic Chinese markets. MediPharma is 87.8% owned by Hutchison China MediTech, with Mitsui (a specialist venture fund) owning 12.2% of the equity following a $12.5m investment in late-2010.
- **China Healthcare**, which comprises the traditional Chinese medicine (TCM) operations in China and taps into the growth potential of the domestic Chinese healthcare market. Demand is set to climb not only because of the well-documented demographics but also because of supportive government policies. Over the past 12 years, Chi-Med has built a broad OTC and Rx (prescription-only drugs) TCM distribution network.
- **Consumer Products**, which is developing a range of healthy living products across Asia. This division targets the wider trends towards healthier living that are in place across Asia and looks to exploit the synergies with the Hutchison Whampoa retail structure. The strategy is to initially test market various product ranges in Hong Kong before implementing a phased roll-out into mainland China.

Hutchison MediPharma has good near-term drivers

Hutchison MediPharma is entering a particularly interesting period as a number of projects are approaching key points in the development process, where success should result in material value creation. The progress being achieved across a broad front would suggest further partnerships and collaborations are likely over the coming 18 months. As an example, AstraZeneca licensed Volitinib while it was still at the pre-clinical stage in a deal worth up to $120m in development fees (of which $20m was upfront) and up to double-digit royalties on net sales.

Sustained effort over the past five years, with almost $200m invested, has resulted in the building of a high-grade drug discovery and development operation at the Zhang Jiang High Tech Park in Shanghai, with proven discovery and screening platforms. This taps into the wealth of talent and opportunities that are presenting in China, capitalising on the cost efficiencies and speed benefits associated with performing R&D there. The attraction of China as a research base is confirmed by the sizeable R&D units set up by many multi-national pharmaceutical companies, with Eli Lilly, Roche and Novartis having established laboratories in Zhang Jiang. Incidentally, MediPharma was one of the first tenants, in 2002, in what has become the centre of the Chinese biotech industry.

The goal is to develop highly selective small molecules and to exploit the receptive environment in China for high technology drug programmes by progressing compounds through the pre-clinical phase to identify attractive lead compounds rapidly. The emphasis on speed, but with high quality, is maintained once in the clinical phases, with compounds expected to undergo the proof of concept studies (Phase II trials) primarily in China before a decision to either partner (locally or

globally) or initiate further trials is made. These early clinical trials are performed to Western standards and generate high-quality data that allow a go or no-go decision to be made quickly and, more importantly, relatively cheaply.

Exhibit 1: Hutchison MediPharma's key revenue opportunities

Project/partner	Indication	Status/notes
Small-molecule validated target	**Mechanism**	
Fruquintinib (HMPL-013)/**Lilly**	VEGFR inhibitor	Fruquintinib is an oral small molecule that is highly selective for VEGFR 1, 2 & 3 and shows high potency at low doses. Encouraging results from Phase I studies in breast, colorectal, gastric and non-small cell lung cancer (NSCLC). Overall response rate of 38% (46% in 4mg/day group) compares well with current VEGFR inhibitors. Progression free survival in NSCLC was 5.9 months and in colorectal cancer 6.0 months. A 70 patient Phase II study in colorectal cancer (advanced or metastatic) started in April 2014 and a 90 patient Phase II study in non-squamous NSCLC started in June 2014. Top-line results from these Chinese trials are expected in mid- to late-2015. If the Phase II/III programme confirms activity, it will be developed for global markets. In Oct 2013 Eli Lilly signed a deal to co-fund development for the Chinese market; this is worth up to $86.5m in upfront fees and milestones, with tiered royalties (initially mid-teens) on net sales and Lilly also has an option on the global product rights.
Sulfatinib (HMPL-012)	VEGFR/FGFR	Sulfatinib is an oral small molecule that selectively inhibits VEGFR and FGFR (fibroblast growth factor receptors). Pre-clinical results show a higher potency that existing VEGF drugs, with promising activity in hepatocellular carcinoma, as well as colorectal and breast cancer. Phase I results confirmed preliminary anti-tumour activity, especially in neuroendocrine tumours, and showed it was well tolerated up to 300mg daily. Expected to progress to Phase II/III in China during 2014.
Epitinib (HMPL-813)	EGFR	Epitinib is a highly potent oral small molecule inhibitor of EGFR. Results from a Phase I study in 19 patients with NSCLC or breast cancer showed it was well tolerated at doses of up to 160mg daily. Unlike currently available EGFR inhibitors, epitinib can cross the blood-brain barrier and reach effective concentrations. 30-40% of glioblastoma have EGFR-activating mutations. The continuing Phase I studies will examine glioblastoma patients (both primary and secondary). Initial results could be available by end-2014, with a positive outcome suggesting a global clinical programme.
Theliatinib (HMPL-309)	Wild-type EGFR	Theliatinib is an oral small molecule EGFR inhibitor that has shown potent preclinical activity against tumours with EGFR-activating mutations and those without (known as wild-type). Clinical activity against wild-type tumours could address a significant cancer population. A Phase I study is underway in China, with results due in 2015. A positive outcome would suggest global development.
Small-molecule novel target		
AZD 6094 (HMPL-504 Volitinib)/**AstraZeneca**	Selective c-Met	Volitinib is an oral small molecule that targets the c-Met signalling pathway (also known as hepatocyte growth factor receptor HGFR). ArQule's tivantinib and Amgen's rilotumumab are the most advanced products in development against this novel target. In March 2014 Roche's MetMab (onartuzumab) failed the key Phase III METLung trial despite the positive results in the earlier OAM4558g study. Volitinib has very promising preclinical data and is in Phase I (in Australia) with results presented at ASCO 2014. A Phase I/II trial started in China in June 2013 ($5m milestone). A global open-label Phase II study was started in May 2014 in papillary renal cell carcinoma (PRCC). c-Met is a partial driver of tumour growth, suggesting that adding volitinib to other therapies could add benefit. AstraZeneca paid an initial $20m in December 2011 for volitinib, with up to $120m in development milestones, unspecified commercial milestones and double-digit royalties on sales. AstraZeneca will fund global development and share costs for development in the Chinese market.
HMPL-523	SYK	SYK (spleen tyrosine kinase) is involved in activating signals within B-cells and its suppression might modulate autoimmune diseases. HMPL-523 is the lead candidate in a preclinical inflammation programme evaluating it in rheumatoid arthritis (RA), multiple sclerosis and lupus. It may also have utility in certain cancer types. A Phase I dose-escalation safety study started in June 2014, with initial results expected as early as end-2014. Fostamatinib (AZ's first-in-class compound) reported disappointing results in pivotal RA Phase III trials in June 2013, but HMPL-523 is a more selective SYK inhibitor.
HMPL-453	Selective FGFR	The FGF signalling pathway is increasingly implicated in tumour genesis and drug resistance. A number of small molecule FGFR inhibitors are in early-stage development with greater selectively being the goal. AstraZeneca is working in this field with AZ4547 (which enters Phase III for gastric cancer in 2014), although the evidence and commercial potential is rated as low.
Janssen collaboration	Novel inflammation target	The collaboration was initiated in June 2010 in inflammation and immunology. A $6m development milestone was triggered in Oct 2013, with up to additional $90.6m milestones payable (plus royalties) on successful progress to commercialisation.
Botanicals multi-target		
HMPL-004/Nestlé Health Sciences (NSP)	Ulcerative colitis and Crohn's disease	HMPL-004 is andrographolide, an oral anti-inflammatory derived from a herb used extensively in China. Identified through targeted screening, it works on a number of inflammatory pathways (both cytokine- and interleukin-mediated). Global Phase III registration trials (NATRUL 3, 4, & 5) for UC underway. NATRUL 3 compares 1,800mg/day and 2,400mg/day vs placebo in 420 patients, with first results expected Q215. The Crohn's programme will start if NATRUL 3 is successful. Nutrition Science Partners (NSP) is a 50:50 JV with Nestlé, funded by the initial capital injection and milestones on development progress. The initial focus is on developing botanically-sourced products for gastro-intestinal indications, with possible expansion into metabolic disease and brain health. Interim analysis for NATRUL 3 on 12 August could trigger a milestone and initiation of NATRUL-5 and Phase III studies in Crohn's disease.

Source: Hutchison China MediTech, Edison Investment Research

Exhibit 1 details Hutchison MediPharma's major pipeline opportunities. The portfolio can be considered as segmented into three main research areas: Botanicals (multi-target) and the two small molecule programmes (addressing both validated and novel targets).

Hutchison MediPharma is developing novel drugs using a three-stranded approach:

- compounds that address a validated pathway but are not sufficiently differentiated or superior to current class leaders are developed, at a lower cost, for the domestic Chinese market (eg fruquintinib with Eli Lilly);
- compounds that are either first-in-class or best-in-class are to be developed in collaboration with a multinational partner to target global markets (eg AZD6094/volitinib with AstraZeneca and Janssen collaboration); and
- botanical products, which exploit the rich source of pharmacologically active compounds provided by TCM, that target global markets (eg the Nutrition Science Partners joint venture with Nestlé Health Science).

Hutchison MediPharma is well placed to do so, having an established network of contract research organisations (CROs) to draw on as well as relationships with local key opinion leaders. Additionally, the experience of the domestic regulatory framework, particularly in using China FDA's Special Review Process[1] (the green channel), will be useful in pursuing development of both validated target compounds (pursuing a fast-to-market development in China) and novel target compounds (where the use of Australian and Chinese clinical trial centres accelerates progress).

This approach has generated a number of drug candidates that address both existing, well validated targets (which is typically associated with a lower clinical risk) and more novel targets (where the as yet unproven nature of the mechanism means the clinical risk is higher). The aim is to generate compounds that are either best-in-class or first-in-class, with compounds that are suitably well-differentiated licensed out for global development with a partner, with Hutchison MediPharma likely seeking to retain co-development rights for the Chinese market.

Hutchison MediPharma can also exploit compounds that demonstrate only equivalence to the existing globally-marketed compounds by developing these for the domestic Chinese market. Hence, the strategy is that compounds that are well differentiated from existing or known compounds will be partnered for global development with Hutchison MediPharma potentially retaining Chinese rights. However, compounds that are safe and effective but not sufficiently commercially differentiated to justify the costs of a global programme will be developed at low cost for the domestic market.

Small-molecule validated target portfolio

Tyrosine kinases are an attractive drug research area since they play important roles in the modulation of growth factor signalling, being involved in tumour cell growth and proliferation, creating apoptosis resistance, and promoting angiogenesis and metastasis. Tyrosine kinase signalling pathways normally prevent deregulated proliferation and contribute to sensitivity towards apoptotic stimuli. The more that is known about the intricacies of cellular signalling, the more that aberrant activation of tyrosine kinases are implicated in a plethora of cancers, resulting in their complex oncogenic signalling becoming a compelling target for cancer therapy.

Different approaches (such as monoclonal antibodies, antisense, peptide drugs, as well as small molecules) have been explored with varying degrees of success. A number of small molecule

[1] The China Food and Drug Administration (CFDA), formerly known as the SFDA, introduced a Special Review Programme in January 2009 to accelerate development times for novel agents addressing domestic medical needs. Known as the green channel or path, it aims to shorten the historically long and complex (and opaque) approval process, with greater communication and priority reviews.

tyrosine kinase inhibitors have been commercially rewarding globally; for instance, Novartis's Gleevec (imatinib), Roche's Tarceva (erlotinib), Bayer's Nexavar (sorafenib) and Pfizer's Sutent (sunitinib) are posting sales of over $1bn pa. Although an increasingly competitive field, advances in the understanding of tumour biochemistries still create exciting opportunities for novel inhibitors.

Hutchison MediPharma has five tyrosine kinase inhibitors that are effectively second-generation compounds in that they target known validated pathways but have the potential to offer additional benefits. The clinical programmes have been designed to rapidly characterise the compounds' activity profiles and so assess whether they are sufficiently differentiated from current and known near-future products to warrant global development.

Fruquintinib (HMPL-0013) differs from existing VEGFR inhibitors by targeting specifically for VEGFR 1, 2 and 3[2]; other products targeting these receptors also bind to several other proteins. The 40-patient Phase I study, completed in Q312 at Fudan University, Shanghai, shows that it is very potent, with good pharmacokinetic (PK) properties and sustained inhibition of the target kinases. A Phase Ib/II study was initiated in December 2012, with a two-stage design to select the best dosing regimen, and has resulted in 5mg on a three weeks on/one week off regimen being used in trials going forward.

The data guided the format of the Phase II proof-of-concept programmes, with a 70 patient study in advanced or metastatic colorectal cancer (CRC) and a 90 patient Phase II study in non-squamous NSCLC underway (started in April and June 2014 respectively). The primary endpoint is progression free survival (PFS), with secondary endpoints including disease control rate, overall response rate, overall survival and safety. The data read-out from these Chinese trials is expected in mid- to late-2015, which should determine fruquintinib's future development route globally. Before the completion of these trials, a Phase III study in CRC should start in Q414.

Exhibit 2: Fruquintinib compared to selected VEGFR inhibitors

Compound	Name	Company	Status	Efficacy profile in Phase I studies
Fruquintinib	HMPL-013	Hutchison MediPharma	Ph Ib/II	34 patients, PR (Partial Response):13 (38%); DCR (Disease Control Rate) 82%
Sunitinib	Sutent	Pfizer	Marketed	22 patients, PR: 4 (18%); DCR 27%
Sorafenib	Nexavar	Bayer/Onyx	Marketed	45 patients, PR 1 (2%); DCR 58%
Axitinib	Inlyta	Pfizer	Marketed	35 patients, PR 3 (8%)
Tivozanib	AV-951	AVEO/Astellas	Phase III	37 patients, PR 1 (2.7%); DCR 51%
Apatanib	YN968D1	Jiangsu Hengrui	Phase III	37 patients, PR 7 (18.9%); DCR 83.7%
Regorafenib	Stivarga	Bayer	Marketed	53 patients, PR 3 (6%); DCR 66%

Source: Hutchison MediPharma, Edison Investment Research. Note: DCR (disease control rate) is the sum of complete responses (CR) + partial responses (PR) + stable disease (SD).

Lung cancer is the most common form of cancer in China, with over 715,000 cases diagnosed in 2012 (which compares with about 220,000 new cases annually in the US), and accounts for 18.7% incidence among all cancer patients. Colorectal cancer is the third most common cancer in China, with around 390,000 cases diagnosed in 2012 and an incidence of 10.2%.

Fruquintinib's development in China will be co-funded by Lilly, with the clinical phases carried out by Hutchison MediPharma and the costs shared. In a deal agreed in October 2013, Lilly will pay up to $86.5m in upfront fees, development and approval milestones with tiered royalties (initially mid-teens) on net sales. If the Phase II data are very positive, we would expect Lilly to exercise its option for the global development rights.

Sulfatinib (HMPL-012) is a dual inhibitor of VEGFR and FGFR1 that first entered clinical trials in Q210 but variability in the pharmacokinetic profile meant the dose escalation programme was placed on hold. A new study with an improved formulation started enrolment in March 2013, with two dose cohorts (200mg and 300mg). Results from this trial presented at ASCO showed that

[2] VEGF 1 is critical for endothelial cell survival and vessel morphogenesis; VEGF 2 is the predominant receptor for cell proliferation and migration; VEGF 3 promotes endothelial sprouting and vascular network formation.

sulfatinib has significant potential in neuroendocrine tumours (n=11; ORR: 33%; DCR: 100%). Sulfatinib is expected to progress into proof of concept Phase II trials in China in late 2014.

Over-expression of FGFR1 is seen in a number of solid tumours (including breast, lung and prostate cancer) and is shown to lead to stimulation of intracellular signalling pathways that control cell proliferation, cell differentiation, cell migration, cell survival and cell shape. Aberrant activation of FGFR has been shown to result in poor patient prognosis, with data suggesting it is the strongest independent predictor of poor outcome in breast cancer. It is thought that FGF/FGFR signalling may serve as an escape pathway in tumours that are being treated with inhibitors of other cellular signalling components, such as VEGFR, hence its importance as a clinical target.

FGFR inhibitors under development include dovitinib (Novartis, Phase III), brivanib (BMS, Phase III), AZD4575 (AstraZeneca, Phase II), BGJ398 (Novartis, Phase I), LY2874455 (Lilly, Phase I), ARQ 087 (ArQule, Phase I) and JNJ-42756493 (Otsuka/J&J, Phase I). The pathway has not been without its issues, with brivanib failing a major hepatocellular carcinoma study in August 2013.

Epitinib (HMPL-813) and **Theliatinib** (HMPL-309) are next-generation EGFR inhibitors, with similar modes of action to gefitinib (Iressa) and erlotinib (Tarceva).

Epitinib differs from existing EGFR inhibitors through its greater brain penetration, offering the potential to target brain cancers (both primary and metastases). EGFR is activated in around 30-40% of glioblastoma patients, with a notably poor prognosis. The current EGFR inhibitors have a limited ability to cross the blood-brain barrier and the low resultant brain concentrations are seen as a key determinant of the disappointing clinical results (although alternative reasons are postulated).

A Phase I study was initiated in Q411 enrolling 25 patients with various advanced solid tumours and treating in six dose cohorts rising from 20mg to 200mg daily. The initial results show an encouraging activity profile, with good pharmacokinetics. A Phase Ib in brain metastases in China is ongoing.

Many solid tumours grow without EGF activating mutations and, understandably, current EGFR inhibitors do not perform well against such wild-type EGF. In contrast, Theliatinib has shown a high potency in a number of animal models. A Phase I trial started in Q412, with an initial four dose cohorts (10mg to 60mg daily). The pharmacokinetics are good, no unexpected side effects have been seen and the MTD has yet to be reached.

Both these compounds will be undergoing Phase II proof of concept trials in China to determine if they are sufficiently differentiated from existing EGFR inhibitors to warrant the initiation of a global development programme. However, even if not differentiated development for the Chinese market may be commercially worthwhile.

The oncology opportunities in China are large; the Chinese Ministry of Health reports that the cancer mortality rate has increased by 80% over the past 30 years and that around 1.8m people are dying annually (compared to around 0.6m in the US, according to the American Cancer Society). Yet, despite their proven efficacies, the newer classes of oncolytics are hampered by their high prices, since few patients in China have their drug costs fully reimbursed. For instance, the established EGFR inhibitors (Tarceva, Iressa and Erbitux) are posting sales of around $35-70m pa and cost $2,600 to $13,700 per month (close to their US prices).

Local Chinese companies have begun to exploit this by entering the market with ‘me-too’ EGFR products (these are different molecules but their mode of action, efficacy and safety profile is very similar to the originator product). Such undifferentiated products can be developed locally at lower cost (the clinical programmes can be completed for around $30-50m) and priced with the domestic market in mind rather than having to work within a global pricing regime. The leading example is Zhejiang Beta Pharma’s Conmana (icotinib), launched in Q212, which is similar to Iressa (gefitinib) and priced at around a 30% discount to it.

Small-molecule novel target portfolio

Hutchison MediPharma's novel target portfolio currently has two compounds in clinical development and two more completing their pre-clinical phases. These compounds have the potential to be first in their class; hence the higher inherent clinical risks are mitigated through development partnerships. Volitinib is a good example of the clinical route that is likely to be followed, with the first human study performed in Australia (on a mainly Caucasian patient pool) and the experience being used to direct the larger, later phases in China.

Volitinib (AZD 6094, HMPL-504) is a highly selective inhibitor of c-Met, a membrane receptor that is essential for embryonic development and other growth related functions such as wound healing; therefore, its activation is normally regulated. Hepatocyte growth factor (HGF) is the only known ligand of the Met receptor, and upon HGF stimulation, Met induces several biological responses that collectively give rise to tissue/vascular growth. Met is deregulated in many types of cancer, including stomach, colon, lung, head & neck, and kidney, and its activation in cancer triggers a signalling cascade that is associated with tumour growth, angiogenesis and metastasis. Inhibition of c-Met activity is shown to lead to increased apoptosis, decreased proliferation and suppressed growth.

Volitinib is undergoing studies in the US, Australia and China, with the rapid start-up times for initiating human trials in Australia being complemented by the large patient pools and low costs associated with China. The knowledge gained in Australia is used to guide the Chinese study designs and also helps accelerate Chinese regulatory approvals. The initial results from the Phase I study were presented at ASCO 2014. A total of 35 patients had been enrolled by April 2014, showing volitinib was well tolerated at doses up to 800mg daily or 400mg twice daily (bid). The maximum tolerated dose (MTD) has yet to be determined for the bid dosing schedule. The preliminary evidence shows no unexpected toxicities and there are early signs of efficacy (partial or minor responses) in multiple tumour types in patients with evidence of dysregulated c-Met signalling. The Chinese Phase I trial started at the higher dose in June 2013, with dose escalation still underway.

The value of c-Met was called into question when Roche announced in March 2014 that MetMAb (onartuzumab) had failed to show any benefit over placebo when used in combination with Tarceva (an EGFR inhibitor) in NSCLC patients with high c-Met expression, leading to Roche discontinuing the programme. The detailed data, presented at ASCO 2014, offered no explanations for the discrepancy between the positive results seen at Phase II and those in the METLung Phase III study. The c-Met pathway is one of the most frequently dysregulated pathways in human cancers and the scientific rationale of its inhibition is compelling. The METLung results raise questions as to whether the lack of effect is related to the study, the cancer type or the drug type. The continuing studies with other c-Met inhibitors in a number of cancer targets should help clarify the likely place and utility of c-Met in oncology treatment.

Given the attractiveness of the HGF/c-Met pathway as an oncology target, several companies are developing drugs with various approaches, including large molecule competitors to HGF or c-Met; antibodies against HGF or c-Met; and small molecular inhibitors of c-Met activation. The most advanced oral c-Met inhibitor is ArQule's tivantinib, which is in Phase III for hepatocellular carcinoma (HCC). Exelixis' cabozantinib, a dual inhibitor of c-Met and VEGFR, is in late-stage clinical development and has demonstrated single agent activity in a variety of cancer types, including RCC, HCC, CRPC and medullary thyroid carcinoma (MTC). Also Amgen has a HGF antibody, rilotumumab, in Phase III for gastric cancer.

AstraZeneca licensed volitinib in December 2011 (at the pre-Phase I stage) and has paid Hutchison MediPharma $20m in upfront fees, with up to $120m in development milestones. The commercial milestones have not been disclosed but royalties on net sales are up to double digits. Hutchison

MediPharma will use its relationships to develop volitinib in China, with the costs being shared, while AstraZeneca assumes all responsibility for ex-China development.

The data from the Phase I trial was sufficiently promising that AstraZeneca is hoping to get an accelerated route to market via FDA breakthrough designation in papillary renal cell carcinoma (pRCC) on the back of the current Phase II. There was an overall response rate of 50% among the six patients with pRCC in the Phase I trial. If this level of response is repeated in the Phase II trial, volitinib could reach the market in 2016. AstraZeneca should also start a Phase I trial with volitinib in combination with AZD9291 in NSCLC. AZD9291 has shown very impressive activity in NSCLC patients with the T790M EGFR mutation and this could lead to volitinib receiving breakthrough designation in this indication too.

HMPL-523 is a Syk inhibitor that is being evaluated by Hutchison MediPharma for inflammation and oncology. The non-receptor spleen tyrosine kinase (Syk) is a key mediator of signal transduction in a variety of cell types, including B lymphocytes, and is implicated in different human diseases such as allergy, asthma and other inflammatory and/or autoimmune disorders. B lymphocytes play a key role in inflammatory diseases and Syk is an essential element of the signalling pathway, hence an attractive target for areas as diverse as immunology and cancers.

The appeal of such a small molecule approach is as a possible oral alternative to injectable drugs such as AbbVie's Humira (adalimumab). Although AstraZeneca returned the rights for the leading Syk fostamatinib to Rigel in June 2013 (following disappointing pivotal Phase III results), the trial programme did provide validation that Syk might be a target for rheumatoid arthritis (RA). HMPL-523 has better kinase selectivity and an improved pharmacokinetic profile, which should translate into a superior efficacy and safety profile.

HMPL-523 started Phase I studies in June 2014, with initial results expected as early as the end of the year if the dose-escalation proceeds as suggested by the pre-clinical programme. This showed a reversal in the progression of joint inflammation and bone erosion in animal models, with evidence of a favourable potency and toxicity profile. If the early trials prove successful we expect HMPL-523 to be licensed out for global development.

HMPL-453 is a potent and selective oral FGFR inhibitor that targets FGFR 1, 2 and 3. Fibroblast growth factor receptors (FGFRs) play an important role in embryonic development, angiogenesis, wound healing, cell proliferation and differentiation. The fibroblast growth factor (FGF) and its receptor (FGFR) provide another pathway that seems critical to monitoring angiogenesis. Activation of FGFRs has an essential role in regulating cell survival, proliferation, migration and differentiation and so they represent an important target for cancer therapeutics. The leading compounds, from AstraZeneca and Novartis, are currently in Phase I and II and HMPL-453 has the potential to be the best-in-class compound. The pre-clinical dossier will be completed and then we expect Hutchison MediPharma to seek partners for clinical development.

Also within the inflammation field, Hutchison MediPharma is progressing a novel compound (the target is undisclosed) into pre-clinical development. This was discovered by Hutchison MediPharma as part of a research programme with Janssen (part of Johnson & Johnson) that was initiated in 2008. This generated a $6m milestone in October 2013, with up to $90.5m in further development and approval milestones and (undisclosed) royalties on net sales expected.

Botanicals multi-target programmes

Hutchison MediPharma's third strand in its R&D strategy is developing botanically-derived drugs that benefit from the long history of using herbal products in traditional Chinese medicine (TCM) combined with the FDA's Botanical Drug Guidance (established in 2004). These operations are the subject of an extensive 50:50 joint venture (known as Nutrition Science Partners) created with Nestlé Health Science in November 2012.

The purpose of Nutrition Science Partners (NSP) is to develop and commercialise novel medicines and nutritional products derived from botanical plant origins. NSP will focus initially on gastrointestinal indications, but may in the future expand into the metabolic disease and brain health areas. Hutchison MediPharma contributes HMPL-004 together with the extensive botanical library and related assets for gastro-intestinal indications and the well-established botanical R&D platform, while Nestlé Health Science funds (through the initial capital investment and further milestone payments) the extensive Phase III trials required for the approvals of HMPL-004. The partners will share any future revenues.

HMPL-004 is a novel oral anti-inflammatory mixture containing andrographolide, derived from a well-known Chinese remedy that was identified through targeted screening. The mode of action is through multiple pathways (including cytokine- and interleukin-mediated) that have both systemic and local anti-inflammatory effects. The very promising Phase IIb results in ulcerative colitis will now be evaluated in the global NATRUL Phase III trial programme, which forms the basis of the regulatory filing dossier.

The NATRUL (**N**atural **A**ndrographis-based **T**reatment for the **R**emission of **UL**cerative colitis) programme started in April 2013 and consists of three related trials: NATRUL-3 is an eight-week induction study evaluating patients who are inadequately controlled on mesalamine; NATRUL-5 is also an induction study with a similar protocol; and NATRUL-4 is a 52-week maintenance study for those patients who have achieved clinical response or remission in NATRUL-3 and -5.

Ulcerative colitis (UC) is a form of inflammatory bowel disease (IBD), classified as an autoimmune disease, characterised by T-cells infiltrating the colon. Average prevalence rates, from published epidemiology studies from the US and Europe, are approximately 200 cases per 100,000 individuals. This suggests a total patient population in the region of 1.6m. Crohn's disease (CD) is similar to UC and slightly more severe and less prevalent (~800,000 individuals), but it is less well treated and a less competitive market.

Exhibit 3: Pipeline of selected treatments for mild-to-moderate ulcerative colitis

Product	Company	Product type	Comment
HMPL-004	Hutchison China MediTech/Nestlé (NSP)	Cytokine (TNF-α/IL-1β/IL-6) inhibitor	2x Phase III NATRUL studies (n=420 + n=460) in mild-to-moderate UC (Mayo score 4-10; endoscopy subscore 2-3) patients taking mesalamine. Remission (Mayo score <2, no individual sub-score >1, rectal bleeding score = 0, endoscopy score = 0-1) assessed at week 8. Two dosing regimens: 1,800mg (600mg tablet 3x daily) and 2,400mg (2x400mg tablets 3x daily).
Etrolizumab (RG7413)	Roche	Anti-integrin beta (7) MAb	124-pt Phase II study (EUCALYPTUS) complete: 20.5% (at 100mg) and 10.3% (at 300mg) patients achieved clinical remission at week 10% vs 0% on placebo (p=0.004 and 0.049 respectively).
VB-201	VBL Therapeutics	TLR2 & TLR4 antagonist	110-pt Phase II study in mild to moderate UC, 80mg twice daily for 24 weeks. Clinical remission assessed at weeks 12 and 24.
Anrukinzumab (IMA-638)	Pfizer	Anti-IL-13 MAb	84-pt Phase IIa biomarker-based study complete (no results). 200-400mg IV (one-hour infusion), assessing mechanism (YKL 40) and pharmacodynamics (faecal calprotectin, lactoferrin, hs-CRP) biomarkers at week 14.
GLPG0974	Galapagos	Free fatty acid receptor 2 (FFAR2) inhibitor	45-pt Phase IIa proof-of-concept study in mild-to-moderate UC, dosed 200mg, twice daily, for 1 month.
GWP42003	GW Pharma	Cannabidiol (CBD)	62-pt Phase IIa in mild to moderate UC, dosed 150-250mg twice daily (1-5 capsules), for 10 weeks. Remission (Mayo ≤2, no subscore >1) at week 10.
Telotristat etiprate	Lexicon Pharmaceuticals	Tryptophan hydroxylase inhibitor	60-pt Phase IIa study in mild-to-moderate UC patients on 5-ASA.
AJM300	Ajinomoto	Alpha 4 integrin antag	Jul 2013: Phase II study ongoing.

Source: Edison Investment Research, clinicaltrials.gov

Treatment of UC ranges from anti-inflammatory agents such as aminosalicylates, particularly mesalamine (5-aminosalicylic acid, or 5-ASA), and corticosteroids, to immunosuppressive drugs (eg azathioprine) and anti-TNF antibodies such as Remicade, Humira and Simponi. Actavis's mesalamine product, Asacol, achieved ~$800m of sales in 2012, while sales of Humira for UC are expected to reach $500m by 2018 (EvaluatePharma). Newer agents such as vedolizumab (Takeda's Entyvio), tofacitinib (Pfizer's Xeljanz) and HMPL-004 are expected to grow the market, which Decision Resources estimates will increase from $2.1bn in 2012 to $3.6bn by 2022.

The HMPL-004 programme is approaching an important milestone on 12 August with the interim analysis from the NATRUL-3 Phase III study in UC. An independent data monitoring committee (DMC) will review the data from about 147 of the targeted 420 patients to be recruited. No clinical data are expected to be released; however, there are essentially three outcomes from the review:

- Best case scenario: a further investment in the JV by Nestlé is triggered and the NATRUL-5 Phase III study in UC and one in Crohn's disease are initiated.
- Mid case scenario: no further investment is triggered, and both new trials might only be started after completion of the NATRUL-3 study in H215.
- Worst case scenario: development of HMPL-004 is terminated if the DMC judges the trial to be futile with no sign of efficacy.

Financials

The H114 showed continued strong growth (note, JVs are equity accounted and no longer consolidated proportionately because of IFRS 11). Group revenues increased by 73% to $30.3m mainly because of Hutchison Sinopharm, which was formed in April 2014 and generated $12.8m in sales. MediPharma had sales of $9.9m ($10.5m in H113) from milestones and service fees and the consumer division produced revenues of $6.4m ($5.9m in H113). China Healthcare's sales (excluded from group revenues) grew by 15.0% to $261.7m.

The operating profit was $8.1m in H114, 9.4% growth, including the after-tax profits of $17.3m from China Healthcare, which increased by 20.1%. Total spending by MediPharma, including its contribution to the Phase III trials with HMPL-004, was only $16.2m, even though it has seven products in clinical development. This demonstrates the cost benefits of drug development in China and the tight cost control at MediPharma.

The company remains in a strong financial position with a group net cash position at H114 of $1.1m ($4.6m at FY13) and a gross cash position of $59.4m. Its share of the net cash held in its JVs was $45.8m at H114.

For 2014, we expect group revenues to be $80.6m, boosted by the sales of the newly-formed Hutchison Sinopharm (this 51% joint venture is consolidated) and MediPharma revenues of $22.0m. We forecast China Healthcare sales to rise by 14.9% to $490m. We expect operating profit to be $8.2m, with China Healthcare's profit contribution of $21.7m effectively offset by the increased R&D spend in MediPharma, with a reported pre-tax profit of $6.4m and attributable net profit of $1.8m. For 2015, we forecast group revenues to rise to $102.0m, with operating profit doubling to $16.8m and reported pre-tax profit similarly rising to $15.3m. We forecast attributable net profit to increase to $8.4m.

Valuation

We value Hutchison China MediTech using a sum-of-the-parts method (Exhibit 4):

- China Healthcare is generating sales and profits so earnings-based metrics are appropriate. This currently contributes the largest element and is valued using peers quoted on the Chinese stock exchanges (picking a group of comparator companies that are mid-sized TCM players with a similar geographic sales base). This results in a value of $505.4m (571.1p a share).
- The Consumer Products business is still small and its relative size means its contribution is not yet material, so a sales-based measure is suitable and gives $35.6m (40.2p a share).

- The MediPharma drug discovery and development unit is a classic emerging pharmaceutical play and is valued using a discounted cash flow, with the rNPV of the individual clinical projects (adjusted for the success probabilities) summed and netted against the costs of the operation.

Exhibit 4: Sum-of-the-parts valuation

Business unit	Method	Value ($m)	Value per share (p)
Hutchison MediPharma	rNPV	487.1	550.5
China Healthcare	P/E multiple	505.4	571.1
Consumer Products	Sales multiple	35.6	40.2
Net (debt)/cash and cash equivalents		(7.3)	(8.2)
Hutchison China MediTech total		1,020.7	1,153.6

Source: Edison Investment Research. Note: US$1.7/£.

The net debt forecast (at group level IFRS 11) for December 2014 is $7.3m (8.2p a share), which means our sum-of-the-parts valuation is $1,021m (1,154p a share). Our previous valuation was $791m (932p a share).

Looking at Hutchison MediPharma, our DCF calculation of the clinical projects gives a value of $300.4m (equivalent to 354p a share). Previously the clinical stage of HMPL-004 meant it carried the most value within our model. However, as Exhibit 5 shows, the tyrosine kinase inhibitors are progressing quickly through the clinical stages and that results in volitinib now becoming the more valuable asset.

Progress so far has resulted in us increasing our success probabilities for a number of programmes. We had also been conservative with the rate of sales growth, assuming peak sales were achieved after nine years; we have shortened this to six years, which is a more standard timeframe for products to reach peak sales. The most significant specific changes have been the raising of fruquintinib's probability from 18% to 35% to reflect the start of Phase II clinical studies, rNPV grown from $30.3m to $70.6m (35.7p a share to 79.8p a share), and similarly the initiation of Phase II trials and broadening of potential indications for volitinib, raising the probability from 18% to 35%, while rNPV has grown from $77.4m to $193.2m (91.2p a share to 218.5p a share).

Exhibit 5: Hutchison MediPharma DCF valuation

	Launch timings	Peak sales ($m)	Success probability	rNPV ($m)	rNPV (p/share)
HMPL-004	2017	500	64%	109.7	124.0
volitinib (HMPL-504)	2017/8	1,250	35%	193.4	218.5
fruquitinib (HMPL-013)	2017	450	35%	70.6	79.8
sulfatinib (HMPL-012)	2016	600	25%	63.3	71.5
epitinib (HMPL-813)	2017	350	12%	18.0	20.4
theliatinib (HMPL-309)	2017	350	5%	7.5	8.5
HMPL-518	2018	300	2%	1.4	1.5
HMPL-523	2018	1000	9%	25.5	28.8
				489.4	**553.0**
R&D+G&A costs				(2.3)	(2.5)
MediPharma Total				**487.1**	**550.5**

Source: Edison Investment Research

There is further upside potential if there are positive results from clinical trials or development programmes are expanded. Assuming even modest success within this element of the development pipeline could see a material uplift in our rNPV valuation, which in turn would directly affect our Hutchison China MediTech value. For example, our current valuation of HMPL-004 conservatively forecasts sales of $500m from UC. If the interim analysis leads to the initiation of Phase III trials in Crohn's disease, we anticipate increasing our estimated peak sales for HMPL-004 to $1bn and its value to $219.4m; this would result in our valuation increasing to $1,131m (1,278p a share). Similarly in FY15, data on HMPL-004, volitinib and fruquintinib could materially affect our valuation.

Importantly, we have not included the expected windfall profits from the appreciation in property values as China Healthcare relocates its existing production facilities into purpose built modern

plants of the outskirts of Guangzhou and Shanghai. Clearly such profits are difficult to forecast with any confidence. However, we conservatively believe they could amount to around $120m to $150m over the next five years.

Exhibit 6: Financial summary

US$000s	2012	2013	2014e	2015e	2016e
Year end December	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS					
Revenue	22,367	45,970	80,620	102,028	116,263
Cost of Sales	(12,754)	(22,208)	(56,384)	(76,902)	(89,070)
Gross Profit	9,613	23,762	24,236	25,126	27,194
R&D	(11,900)	(12,237)	(12,100)	(14,100)	(24,500)
S,G&A	(13,578)	(11,312)	(12,816)	(12,980)	(13,592)
Share of JV associates	17,147	10,900	8,142	18,709	30,783
EBITDA	4,561	13,481	9,602	18,155	21,284
Operating Profit (before amort. and except.)	3,061	12,518	8,202	16,755	19,884
Intangible Amortisation	(1,500)	(963)	(1,400)	(1,400)	(1,400)
Exceptionals	11,476	0	0	0	0
Operating Profit	13,037	11,555	6,802	15,355	18,484
Net Interest	(1,160)	(1,485)	(378)	(82)	(191)
Profit Before Tax (norm)	1,901	11,033	7,824	16,673	19,693
Profit Before Tax (FRS 3)	11,877	10,070	6,424	15,273	18,293
Tax	(1,116)	(1,050)	(1,600)	(1,600)	(2,000)
Discontinued operations	(7,221)	(1,978)	0	0	0
Minority interests	98	(1,127)	(3,000)	(5,300)	(6,800)
Net income (norm)	883	8,856	3,224	9,773	10,893
Net income (FRS 3)	3,638	5,915	1,824	8,373	9,493
Average Number of Shares Outstanding (m)	51.9	52.1	55.2	56.2	57.2
EPS - normalised (c)	1.7	17.0	5.8	17.4	19.0
EPS- normalised fully diluted (c)	1.7	17.0	5.8	17.4	19.0
EPS - IFRS (c)	7.0	11.4	3.3	14.9	16.6
Dividend per share (c)	0.0	0.0	0.0	0.0	0.0
Gross Margin (%)	43.0	51.7	30.1	24.6	23.4
EBITDA Margin (%)	20.4	29.3	11.9	17.8	18.3
Operating Margin (before GW and except.) (%)	13.7	27.2	10.2	16.4	17.1
BALANCE SHEET					
Fixed Assets	115,142	118,633	121,000	132,065	152,342
Intangible Assets	400	407	407	407	407
Tangible Assets	4,842	6,536	7,761	9,117	10,611
Investments including JV	109,900	111,690	112,832	122,541	141,324
Current Assets	44,600	67,034	67,891	70,949	66,090
Stocks	1,600	1,420	2,420	3,420	2,584
Debtors	11,100	16,766	19,248	21,033	19,197
Cash	30,800	46,863	44,239	44,511	42,323
Other	1,100	1,985	1,985	1,985	1,985
Current Liabilities	(35,607)	(78,434)	(49,945)	(50,345)	(49,545)
Creditors	(3,183)	(4,163)	(4,163)	(4,163)	(4,163)
Short term borrowings	(10,892)	(51,508)	(24,608)	(24,608)	(24,608)
Other	(21,532)	(22,763)	(21,174)	(21,574)	(20,774)
Long Term Liabilities	(53,510)	(18,363)	(48,263)	(53,563)	(60,363)
Long term borrowings	(26,923)	0	(26,900)	(26,900)	(26,900)
Other long term liabilities	(26,587)	(18,363)	(21,363)	(26,663)	(33,463)
Net Assets	70,625	88,870	90,683	99,107	108,524
CASH FLOW					
Operating Cash Flow	(10,207)	4,071	1,601	2,579	(254)
Net Interest	(800)	0	0	2,000	1,960
Tax	(400)	(1,181)	(1,600)	(1,600)	(2,000)
Capex	(4,600)	(2,500)	(2,625)	(2,756)	(2,894)
Acquisitions/disposals	(6,500)	0	0	0	0
Financing	600	7	0	0	0
Dividends	0	0	0	0	0
Other	2,000	2,000	0	50	1,000
Net Cash Flow	(19,907)	2,397	(2,624)	273	(2,188)
Opening net debt/(cash)	(12,769)	7,015	4,645	7,269	6,997
HP finance leases initiated	0	0	0	0	0
Other	123	(27)	0	0	0
Closing net debt/(cash)	7,015	4,645	7,269	6,997	9,185

Source: Hutchison China MediTech, Edison Investment Research. Note: The historic figures have been restated to reflect the changes due to the introduction of IFRS 11 on jointly controlled entities (JCEs). This means JCEs are no longer consolidated proportionately, with attributable profit only now shown on the P&L and JCE assets now effectively off balance sheet.

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