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Hutchison China MediTech

ASCO update

ASCO data set up fruquintinib for China launch

Pharma & biotech

At ASCO, Hutchison China MediTech (HCM) presented detailed Phase III trial results for one of its leading assets, fruquintinib (third-line colorectal cancer). Full data from the China-based FRESCO study demonstrated statistically meaningful improvements in both overall and progression-free survival while reinforcing the safety profile of the drug (no liver toxicity). This is the first full Phase III data readout from HCM and further validates its strategy of creating next-generation selective tyrosine kinase inhibitors (TKIs). HCM's (together with partner Lilly) NDA to the China FDA has been accepted (Lilly will pay HCM a $4.5m milestone payment) with a launch potentially now in 2018. We maintain our valuation of $2.7bn.

Year end	Revenue ($m)	Net profit* ($m)	EPS* (c)	DPS (c)	P/E (x)	Yield (%)
12/15	178.2	8.0	14.6	0.0	267	N/A
12/16	216.1	11.7	19.6	0.0	199	N/A
12/17e	234.2	(21.1)	(34.9)	0.0	N/A	N/A
12/18e	262.5	(9.7)	(16.0)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding amortisation of acquired intangibles, exceptional items and share-based payments.

Fruquintinib: FRESCO data shine bright

At ASCO, HCM presented the full data package (Abstract 3508) from FRESCO, its Phase III, 416-patient trial evaluating fruquintinib (a selective inhibitor of VEGFR 1, 2 and 3) in patients with metastatic colorectal cancer (positive top-line data announced in March). It met all primary and secondary endpoints; notably, median overall survival was 9.30 months in the fruquintinib group vs 6.57 months in the placebo group, a clinically significant achievement in this hard-to-treat patient population. Data demonstrate that it has a narrow serious side effect profile, notably no reported liver toxicity, a major advantage over available TKIs such as Bayer's Stivarga, which has a black box warning for liver toxicity. The most common serious AE reported on fruquintinib included clinically manageable hypertension.

Other assets highlighted at ASCO

Presentations from three collaborator-led trials with savolitinib (c-Met inhibitor) continued to reinforce its applicability in c-Met-driven cancers. In an AZN-led trial (Abstract 9020) tracking the response of osimertinib (Tagrisso) resistant NSCLC patients, 30% of resistant patients were c-Met-driven and 3/3 patients had a partial response when treated with savolitinib + EGFR TKI. Additional presentations included the initiation of an NIH/NCI-funded Phase II study (Abstract TPS4599) and an update on the VIKTORY trial (Abstract 4020). Also, promising preliminary results of a Phase II trial testing sulfatinib in selected thyroid cancers demonstrated that 4/17 efficacy-evaluable patients had confirmed partial responses.

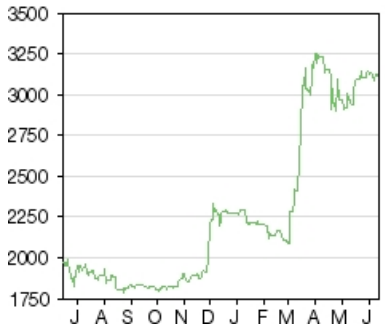
Valuation: $2.7bn (£36.1/share, $22.6/ADS)

Our SOTP valuation remains unchanged at $2.7bn (£36.1/share). IP is valued at $1,948.6m and placing the commercial platform's (CP) 2016e share of net profit on a 23.6x rating gives $788.8m (1,040p/share). Adding December 2016 net cash and netting out unallocated costs results in a value of $2.7bn. Please see our recent note Future stars are aligning for a detailed description of valuation and financials.

13 June 2017

Price	**3,117.50p**
Market cap	**£1,893m**
	US$1.25/£
Net cash ($m) at 31 December 2016	56.9
Shares in issue	60.7m
Free float	39.6%
Code	HCM
Primary exchange	AIM
Secondary exchange	NASDAQ

Share price performance



%	1m	3m	12m
Abs	6.0	29.2	58.9
Rel (local)	5.2	25.9	30.4
52-week high/low	3252.5p		1787.5p

Business description

Hutchison China MediTech (Chi-Med; HCM) is an innovative China-based biopharmaceutical company targeting the global market for novel, highly selective oral oncology, and immunology drugs. Its established China Healthcare business is growing ahead of the market.

Next events

Savolitinib PRCC OS data	H217
Savolitinib NSLC pivotal decision	H217
Fruquintinib China NDA CRC decision	2018

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Edison profile page

FRESCO positive efficacy, favourable safety

HCM and partner Lilly are developing fruquintinib as a potential best-in-class drug for it to compete in the global setting. In our view, FRESCO underpins the hypothesis that fruquintinib's safety and efficacy profile could enable it to be positioned as best in class in China. Its profile internationally will be determined by global Phase III trials; however, data from FRESCO bode well.

Full data were presented at ASCO from HCM's first pivotal Phase III trial (FRESCO), a China-based study, which evaluated fruquintinib, a VEGFR 1/2/3 inhibitor in third-line colorectal cancer patients. Colorectal cancer is believed to be one of the five most common cancers in both Chinese men and women, with an estimated 191.0 thousand deaths in China in 2015 (incidence of 376.3 thousand in 2015). Most Chinese CRC patients are treated with chemotherapy and few targeted therapies are approved, with limited salvage treatments in third line and above. If approved, fruquintinib could capture a significant portion of the market in these patients.

The FRESCO study randomised 416 patients (519 screened) 2:1 into fruquintinib (+ best standard of care [BSC] [n=278]) and placebo (+ BSC [N=138]) arms with an 80% powering to detect a hazard ratio of 0.7 (corresponding to a median OS improvement from 6.3 to nine months). Inclusion criteria included a range of factors, but notably patients had to have been diagnosed with metastatic stage IV colorectal cancer, have failed on two prior treatments (with fluoropyrimidine, oxaliplatin and irinotecan) and were allowed to have prior anti-VEGF or anti-EGFR targeted therapy. Eastern Cooperative Oncology Group (ECOG) status, a measure of patient health, demonstrated that 72.3% (n=201) of fruquintinib patients had an ECOG status of 1 and 27.7% had a status of ECOG 0 (placebo; ECOG 1:73.2% [n=101], ECOG 0:26.8% [n=37]). ECOG 0 patients are asymptomatic and ECOG 1 patients are symptomatic and restricted in strenuous physical activity, but can perform the majority of normal day-to-day functions (ECOG scale goes up to 5, which is death).

Positive efficacy in difficult patient population

Both overall survival and progression-free survival (PFS) (Exhibits 1 and 2) demonstrated statistical significance over placebo, a notable clinical achievement when considering the difficult patient population in which fruquintinib was tested. Key points include:

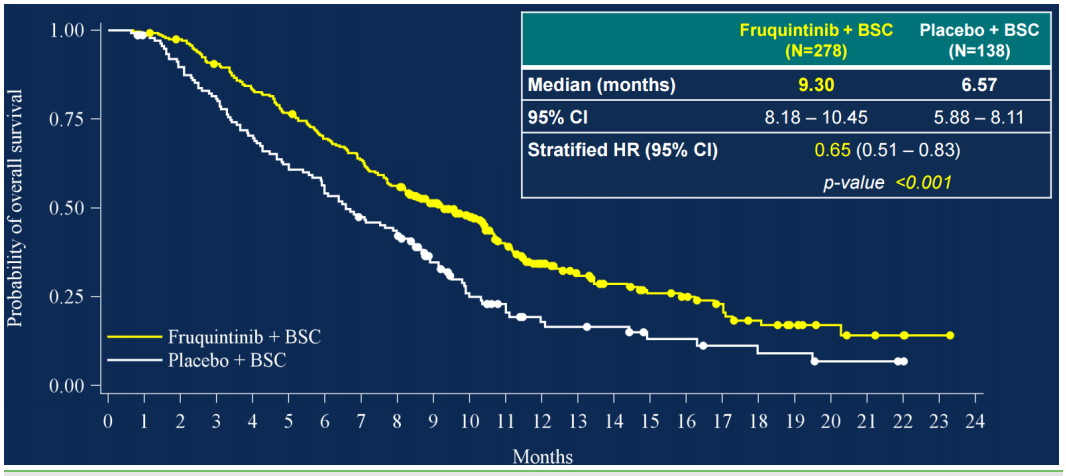
- Positive hazard ratio of 0.65 (95% CI: 0.51-0.83).
- Median overall survival (OS) of 9.30 months in the fruquintinib group (95% CI 8.18-10.45) vs 6.57 months in the placebo group (95% CI 5.88-8.11) (p-value < 0.001).
- Median progression-free survival (PFS) was 3.71 months (95% CI 3.65-4.63) vs 1.84 (95% CI 1.81-1.84) for placebo with a hazard ratio of 0.26 (95% CI 0.21-0.34) (p-value <0.001).
- The majority of responses in the treatment arm were stabilisation of disease at 57.6% (n=160). Comparatively, 12.3% of placebo patients (n=17) had stabilised disease, with the majority (71%, n=98) having progressive disease.
- One and 12 patients in the fruquintinib arm had a complete response and partial response respectively, while no patients experienced either in the placebo arm.
- Disease control rate (CR+ PR + SD, ≥ 8 weeks after randomisation, p<0.001) of 62.2% (n=173) vs 12.3% (n=17) was demonstrated.

These data compare favourably to both pivotal data from an international trial (CORRECT) with Bayer's Stivarga (regorafenib) (a multi-kinase inhibitor targeting VEGFR 1,2 and 3, which is approved and sold in multiple countries) and to a subgroup analysis focused on Chinese patients from an Asian study (CONCUR). Both trials were in patients with previously treated metastatic colorectal cancer. Median overall survival on Stivarga in the CORRECT study was 6.4 months (95%

CI, 5.8-7.3) versus 5.0 months (95% CI, 4.4-5.5) on placebo with a 0.77 hazard ratio (95% CI, 0.64-0.94). PFS was 2.0 months (95% CI, 1.9-2.3) vs 1.7 months on placebo (95% CI, 1.7-1.8).

Subgroup analysis of the CONCUR trial focused on Chinese patients (n=172, 112 on Stivarga, 60 on placebo). ECOG status of 1 was demonstrated in 72% of patients (n=81) and 0 in 28% of patients (31). OS in this Chinese patient subgroup was 8.4 months for Stivarga (vs 6.2 months on placebo, no CI given) with a hazard ratio of 0.56 (95% CI, 0.39-0.80). Median PFS was two months vs 1.7 on placebo (no CI given) with a hazard ratio of 0.32 (95% CI, 0.22-0.47).

Exhibit 1: FRESCO overall survival

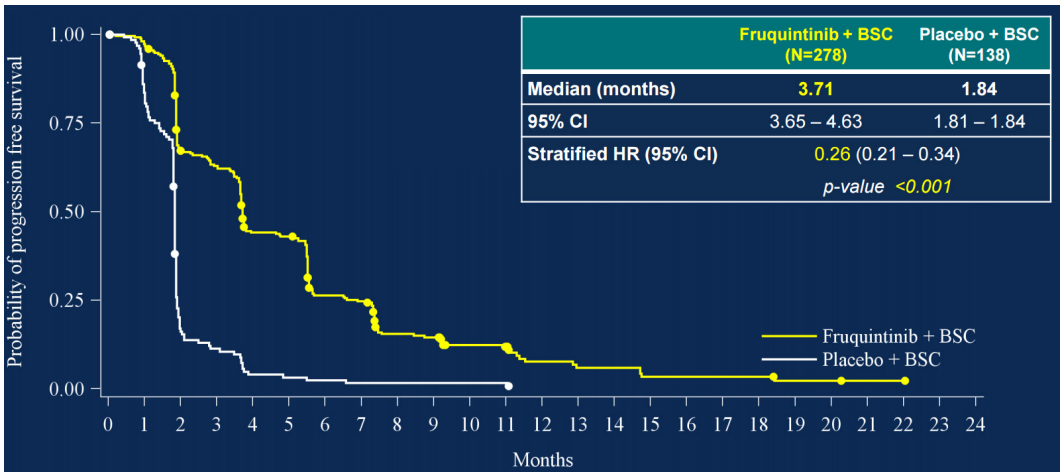


Source: Hutchison China MediTech

Favourable efficacy and safety in comparison to competition

Safety will be a key differentiator for fruquintinib as it looks to position itself in the Chinese market as a best-in-class product. Grade 3 and above adverse events (AEs) occurred in 61.1% (n=170) of patients receiving fruquintinib versus 19.7% (n=27) of patients in the placebo arm. Dose interruptions, a key indicator of tolerability, were 35.3% (n=98) in the fruquintinib arm and 10.2% (n=14) in the placebo arm, while treatment discontinuation occurred 15.1% (n=42) and 5.8% (n=8) in each arm respectively. The most common grade 3-5 adverse events were hypertension (21.2%, n=59), palmar-plantar erythrodysaesthesia/hand-foot syndrome (HFSR/PPE) (10.8%, n=30) and proteinuria (3.2%, n=9). All other grade 3-5 AEs occurred at a frequency below 3%, further reinforcing the selective nature of fruquintinib.

Exhibit 2: Progression-free survival



Source: Hutchison China MediTech

Due to varying patient demographics and standards of care, trial comparisons, while useful, can be complicated. Dose interruptions can be a key indicator for tolerability and can negatively affect the anti-angiogenic mode of action of VEGFR inhibitors.

In the CORRECT trial testing Stivarga (regorafenib), it was reported that 61% of patients receiving Stivarga required a dose interruption. Similar results occurred in the CONCUR trial, which demonstrated that 68.8% of patients had a dose interruption. In the CORRECT and CONCUR trials, treatment discontinuation occurred in 8.2% and 14% of the patients respectively.

In the CORRECT trial the most common grade ≥3 AEs were HFSR/PPE (17% vs 0% placebo), fatigue (15% vs 9% placebo), pain (9% vs 7% placebo), infection (9% vs 6% placebo), hypertension (8% vs <1% placebo), diarrhoea (8% vs 2% placebo), rash (6% vs >1% placebo) and mucositis (4% vs 0% placebo). All other grade ≥ 3 AEs occurred below 3%. Stivarga also contains a black box warning for fatal hepatotoxicity (liver damage), which occurred in 1.6% of the metastatic CRC patient population (vs 0.4% on placebo).

In the Chinese patient subgroup analysis of the CONCUR trial, grade 3,4 and 5 AEs occurred in 52% (n=58), 8% (n=9) and 10% (n=11) of patients on Stivarga and 35% (n=21), 2% (n=1) and 10% (n=6) on placebo, respectively.

Fruquintinib China sales possible in 2018

We believe that fruquintinib demonstrates comparable if not better efficacy than that of Stivarga, caveated by the fact that direct comparisons should be made cautiously. While severe side effects are apparent, mainly in the form of hypertension, these are manageable (eg hypertension controlling medication like beta blockers/ACE inhibitors and topical lotions for HFSR/PPE) and are a result of VEGFR inhibition. The lack of reported hepatotoxicity and a narrower side effect profile than Stivarga indicates that the majority of side effects are target based. We believe that this more controlled safety profile may be a key driver of sales. HCM has recently announced that the China FDA has accepted its new drug application (NDA) for fruquintinib in advanced CRC patients. This has triggered a milestone payment of RMB30.8m ($4.5m) to HCM from its partner Lilly. If approved, we anticipate a potential launch in China in 2018, where HCM's partner Lilly will be responsible for sales and marketing.

US bridging studies in Caucasians to start in 2017

In the US, a Phase I bridging study in Caucasian patients will initiate in 2017. This study should determine the dose required to take fruquintinib into US Phase II/II studies across its differing indications in preparation for a US NDA submission. Contingent on strong proof-of concept (POC) and Phase III results in fruquintinib clinical trials in China, Eli Lilly may exercise its option (once it receives the Phase III NSCLC data) to co-develop fruquintinib globally under the terms of the 2013 licence agreement. We expect fruquintinib to enter US Phase II/III trials regardless of whether Lilly exercises its option. We expect additional indications post the bridging study to be determined by a range of factors including combination potential and achievable market.

Savolitinib – patient selection drives efficacy

Presentations at ASCO from three collaborator trials utilising savolitinib (c-Met inhibitor) further reinforce its applicability in treating c-Met-driven patients. In an AstraZeneca (AZN) led trial (Abstract 9020), which tracked the response of osimertinib (Tagrisso) resistant NSCLC patients, 30% (7/23) of resistant patients were c-Met-driven (the largest driver of resistance and a significant new market opportunity); 3/3 of patients treated had a partial response when treated with savolitinib + EGFR TKI. Additional presentations included the initiation of an NIH/NCI-funded Phase II study

(Abstract TPS4599), which is looking to compare sunitinib with three MET-directed therapies (including savolitinib) in PRCC. An update on the VIKTORY trial (Abstract 4020), testing savolitinib in preselected MET amp/overexpressed patients, was presented.

- In an AstraZeneca-led trial (Massachusetts General Hospital Cancer Center), 23 patients who acquired resistance to osimertinib were tested to determine the mechanisms at play. Patients were tested with tumour biopsy and/or plasma circulating tumour biopsies. Tumour biopsies were analysed by next-generation sequencing (NGS) and fluorescence in situ hybridization (FISH) for MET and EGFR amplification. Plasma ctDNA was analysed by NGS. Tissue biopsies demonstrated that six patients had MET amplification, with a further one identified from plasma ctDNA. This was the most prevalent resistant mechanism to osimertinib occurring in 30% (7/23) of patients. Three of the MET-amplified patients were treated with savolitinib and an EGFR TKI; all three achieved a RECIST partial response to the combination.
- PAPMET, the Phase II NIH/NCI-funded trial, has enrolled 36 patients to date (target = 180). The study has four arms that aim to compare sunitinib (Pfizer, targets multiple receptor tyrosine kinases including PDGFRs and VEGFRs), cabozantinib (Exelixis, c-Met and VEGR2 inhibitor), crizotinib (Pfizer, ALK, ROS1 and c-Met inhibitor) and savolitinib in treating patients with metastatic papillary renal cell carcinoma (PRCC). Patients must have historically confirmed and measurable PRCC, received 0-1 lines of prior therapy, but no prior therapy with sunitinib. In addition to measuring the primary endpoint of PFS, secondary endpoints include overall survival, response rate, adverse events and an exploratory evaluation of MET mutational status and expression. We expect this to further highlight savolitinib's suitability in c-MET-driven PRCC. While no timelines have been given, we anticipate that enrolment will complete in 2018, with initial data in late 2018/early 2019.
- Updated results were provided on the multi-arm VIKTORY trial. The trial is a biomarker-based umbrella trial in gastric cancer with nine arms. Two of the arms aim to treat MET overexpressed or amplified patients with savolitinib, either as a monotherapy or in combination with docetaxel. As of the data presentation, four patients have been enrolled to be treated with the monotherapy and 19 in combination.

Phase II overall survival data on savolitinib in c-Met-driven PRCC later this year could support a US NDA application under breakthrough therapy designation, with potential to be HCM's first internationally launched asset (we expect launch in the US in 2018 by partner AstraZeneca, which we assume will be under breakthrough therapy designation). Additionally, positive data from the ongoing multi-arm TATTON trial in second-line, EGFR-mutant lung cancer with savolitinib in combination with osimertinib (Tagrisso) could support a US NDA under breakthrough therapy designation for lung cancer. We anticipate the initiation of Phase III trials in PRCC and potentially NSLC (if a pivotal decision is made) in H217

Sulfatinib

A Phase II multi-centre trial of sulfatinib (VEGFR 1, 2 & 3, FGFR1, CSF-1R inhibitor) in advanced medullary thyroid cancer (MTC) and radioiodine-refractory differentiated thyroid cancer (DTC) is ongoing. As of 31 March 2017, a total of 20 patients have been enrolled and treated (total enrolment expected 30-50 patients). 16 of these patients are evaluable for efficacy evaluation, four (25%) of whom had confirmed partial response (PR) and the other 12 had stable disease (SD) including two unconfirmed PR. Objective response rates (include complete response and PR) in the MTC and DTC groups were 16.7% (n=1/6) and 33.3% (n=3/10) respectively. All 20 patients experienced at least one adverse event (AE) with 11 (55%) patients experiencing a grade 3 or above treatment-related AE; the most common grade $\geq$3 AEs were hypertension (20%) and proteinuria (20%) irrespective of causality. Three patients experienced a serious treatment-related AE, but there were no deaths due to treatment. Nine patients (45%) had a dose reduction and 15

patients (75%) had a dose interruption. Based on these promising initial data, we expect the trial to continue as planned with further data readouts in 2018.

Sulfatinib is currently in six ongoing trials: two Phase III registration trials (pancreatic NET and extra[non]-pancreatic NET), three Phase II trials (biliary tract carcinoma and thyroid cancer) and one Phase I crossover study in the US. A Phase II US study in NET is expected to initiate by year-end 2017. PFS data (top-line) from the China Phase III registration trials (SANET-p and SANET-ep) are anticipated in 2018. Positive data could lead to a China FDA filing in 2018/19. Sulfatinib is an unpartnered asset and HCM could reap the full economic benefit by launching this asset through its extensive manufacturing and distribution prescription drug business in China.

Exhibit 3: Financial summary

	2014	2015	2016	2017e	2018e	2019e
December	US GAAP	US GAAP	US GAAP	US GAAP	US GAAP	US GAAP
PROFIT & LOSS						
Revenue	87,329	178,203	216,080	234,199	262,526	304,619
Cost of Sales	(58,849)	(110,777)	(156,328)	(158,810)	(161,601)	(171,066)
Gross Profit	28,480	67,426	59,752	75,389	100,925	133,554
Research and development	(29,914)	(47,368)	(66,871)	(85,000)	(89,500)	(100,000)
Other overheads	(16,825)	(29,829)	(39,578)	(42,699)	(46,858)	(49,946)
EBITDA	(16,994)	(7,756)	(44,264)	(48,575)	(30,933)	(11,062)
Operating Profit (before amort. and except.)	(18,259)	(9,771)	(46,697)	(52,310)	(35,433)	(16,392)
Intangible Amortisation	0	0	0	0	0	0
Operating Profit	(18,259)	(9,771)	(46,697)	(52,310)	(35,433)	(16,392)
Net Interest	(957)	(953)	(1,129)	(1,500)	(1,500)	(659)
Exceptionals	0	0	0	0	0	0
Profit Before Tax (norm)	(19,957)	(10,540)	(47,356)	(53,810)	(36,933)	(17,051)
Profit Before Tax (reported)	(19,957)	(10,540)	(47,356)	(53,810)	(36,933)	(17,051)
Tax	(1,343)	(1,605)	(4,331)	(3,229)	(3,000)	(3,410)
Equity investments, after tax	15,180	22,572	66,244	41,900	35,150	26,100
Profit After Tax (norm)	(6,120)	10,427	14,557	(15,138)	(4,783)	5,638
Profit After Tax (reported)	(6,120)	10,427	14,557	(15,138)	(4,783)	5,638
Minority	(3,220)	(2,434)	(2,859)	(6,000)	(4,900)	(3,700)
Discontinued operations	2,034	0	0	0	0	0
Net profit (norm)	(9,340)	7,993	11,698	(21,138)	(9,683)	1,938
Net profit (reported)	(7,306)	7,993	11,698	(21,138)	(9,683)	1,938
Average Number of Shares Outstanding (m)	52.6	54.7	59.7	60.6	60.6	60.6
EPS - normalised (c)	(17.8)	14.6	19.6	(34.9)	(16.0)	3.2
EPS - normalised and fully diluted (c)	(17.8)	14.6	19.5	(34.9)	(16.0)	3.2
EPS - (reported) (c)	(13.9)	14.6	19.6	(34.9)	(16.0)	3.2
Average number of ADS outstanding (m)	105.1	109.3	119.4	121.3	121.3	121.3
Earnings per ADS - normalised ($)	(0.09)	0.07	0.10	(0.17)	(0.08)	0.02
Earnings per ADS ($)	(0.07)	0.07	0.10	(0.17)	(0.08)	0.02
BALANCE SHEET						
Fixed Assets	120,992	140,087	175,057	173,222	183,872	184,642
Intangible Assets	4,096	3,903	3,606	3,419	3,194	2,928
Tangible Assets	7,482	8,507	9,954	16,406	22,131	27,067
Investments	109,414	127,677	161,497	153,397	158,547	154,647
Current Assets	89,842	89,675	167,380	149,834	135,700	142,406
Stocks	4,405	9,555	12,822	12,000	14,000	14,060
Debtors	27,924	38,628	49,349	51,838	76,659	93,231
Cash	38,941	31,949	79,431	60,218	33,533	23,607
St investments	12,179	0	24,270	24,270	10,000	10,000
Other	6,393	9,543	1,508	1,508	1,508	1,508
Current Liabilities	(75,299)	(81,062)	(95,119)	(91,581)	(95,581)	(99,418)
Creditors	(20,427)	(24,086)	(35,538)	(32,000)	(36,000)	(39,837)
Short term borrowings	(26,282)	(23,077)	(19,957)	(19,957)	(19,957)	(19,957)
Other	(28,590)	(33,899)	(39,624)	(39,624)	(39,624)	(39,624)
Long Term Liabilities	(37,584)	(46,415)	(43,258)	(43,258)	(43,258)	(43,258)
Long term borrowings	(26,923)	(26,923)	(26,830)	(26,830)	(26,830)	(26,830)
Other long term liabilities	(10,661)	(19,492)	(16,428)	(16,428)	(16,428)	(16,428)
Net Assets	97,951	102,285	204,060	188,217	180,733	184,372
Minority	(17,764)	(18,921)	(19,790)	(25,790)	(30,690)	(34,390)
Shareholder equity	80,187	83,364	184,270	162,427	150,043	149,982
CASH FLOW						
Operating Cash Flow	8,359	(9,385)	(9,569)	(8,508)	(28,254)	2,073
Net Interest	0	0	0	0	0	0
Tax	0	0	0	0	0	0
Capex	(3,729)	(3,324)	(4,327)	(10,000)	(10,000)	(10,000)
Acquisitions/disposals	689	0	0	0	0	0
Dividends	(1,179)	(590)	(564)	(700)	(2,700)	(2,000)
Equity financing and capital movements	5,860	(1,676)	97,076	0	0	0
Other	(12,179)	12,179	(29,270)	0	14,270	0
Net Cash Flow	(2,179)	(2,796)	53,346	(19,208)	(26,684)	(9,927)
Opening net debt/(cash and ST investments)	4,645	2,085	18,051	(56,914)	(37,701)	3,254
Increase/(decrease) in ST investments	12,179	(12,179)	24,270	0	(14,270)	0
Other	(7,440)	(991)	(2,651)	(5)	0	0
Closing net debt/(cash and ST investments)	2,085	18,051	(56,914)	(37,701)	3,254	13,180

Source: Hutchison China MediTech reports, Edison Investment Research. Note: Equity investments after tax include the net profit contribution from JVs.

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