Wilex

Second positive result

Edison investment research

Doubling PF survival

Biotech & pharma

The new data on HER2 negative breast cancer reinforces the 2010 positive findings in pancreatic cancer. In the sub-group of 95 patients who had received prior adjuvant chemotherapy, Mesupron plus Xeloda (capecitabine) gave 8.3 month progression free survival vs 4.3 months on capecitabine alone. Although not statistically powered, this is a positive trend. Together, these results could allow partnering by mid 2013 and the development of a Phase II/III programme, probably in the adjuvant setting. Data from the ARISER Rencarex study is due Q412.

Year end	Revenue (€m)	PBT* (€m)	EPS* (c)	DPS (c)	P/E (x)	Yield (%)
11/10	1.3	(22.5)	(134.4)	0.0	N/A	N/A
11/11	11.7	(13.6)	(65.8)	0.0	N/A	N/A
11/12e	15.7	(11.8)	(48.5)	0.0	N/A	N/A
11/13e	9.2	(12.4)	(50.1)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding intangible amortisation and exceptional items.

Mesupron extends progression-free survival

Mesupron is an oral inhibitor of the urokinase-type Plasminogen Activator (uPA) system. The uPA system produces active proteases on the surface of tumour cells, which facilitates cancer metastasis and tumour invasion. The efficacy indicated in high-risk patients who had received prior chemotherapy is promising for any subsequent statistically powered Phase II/III studies. The trial opens the way to a partnering deal probably in H113. Edison expects possible launch from 2017.

More news in H2

On 25 July, the FDA Oncologic Drugs Advisory Committee will meet to discuss imaging for clear-cell renal cell carcinoma. This should provide general advice on whether an imaging test provides useful clinical information. This advice could impact the development strategy for Redectane. Data on Rencarex is due in Q412. Avoiding an ARISER trial interim analysis makes statistical success easier to achieve as the threshold will be higher. Assuming success, an H113 filing is possible.

Valuation: Priced in data

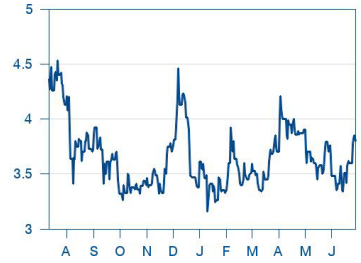
Edison's indicative valuation for Wilex is €207m, or €7.35/share. The indicative value has moved back slightly due to currency effects and an adjustment to the Mesupron launch expectation. Edison's valuation already used a high Phase II probability of 35% overall success so this has not been adjusted until the development pathway is clearer, probably not until a partner is signed. Edison assumes that Mesupron accounts for nearly 38% of expected risk-adjusted royalties; 60% if no risk adjustment is applied. In addition, the value of technology (like ADC: delivery of cytotoxic drugs by antibodies) is not included but could be significant if these products enter development. Wilex also sells cancer biomarker products.

29 June 2012

Price	€3.80
Market cap	€94m

Shares in issue	24.8m
Free float	54%
Code	WL6
Primary exchange	FRA
Other exchanges	N/A

Share price performance



%	1m	3m	12m
Abs	2.6	(1.3)	(5.2)
Rel (local)	5.5	12.3	10.5
52-week high/low		€4.48	€3.13

Business description

Wilex develops therapeutic and diagnostic products for cancer. Lead development programmes are Redectane (pre-registration), Rencarex (Phase III for adjuvant treatment of renal cancer) and Mesupron (Phase II for pancreatic and breast cancers).

Next events

25 July	FDA ODAC
July	Q2 results
Q412	ARISER data

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Edison profile page

Lowered portfolio risks

Wilex has three clinical lead projects plus a Phase I candidate. There are also two earlier stage oral candidates licensed from UCB and two research monoclonal leads. There are two revenue-earning businesses. These are shown in Exhibit 1.

Exhibit 1: Wilex portfolio

Product	Indication	Licensee(s)	Notes
Redectane (^{124}I-girentuximab) Monoclonal binding CAIX antigen	Pre-surgical detection of clear-cell renal cell carcinoma	Ion Beam Applications (w/w). 45% royalty on ex-factory sales (20% on sales <€7m) and certain undisclosed milestones; c 13% of US revenues and c 12% of ex-US revenues payable to g250 originators.	Pre-registration; US filing possible in 2012, but requirement for an outcomes study would likely delay this to 2014. FDA advisory committee on 25 July 2012; the subsequent FDA response will clarify if additional trials are required. The 226-pt Phase III study showed 87% specificity and 86% sensitivity.
	Clear-cell Renal Carcinoma	Early Detection Of Response to Sutent (sunitinib, Pfizer). (This an academic study not run by Wilex.)	To assess therapeutic response to sunitinib before CT scanning can detect any tumour shrinkage. Phase I, 25 pt, started April 2012; data due Q214.
Rencarex (girentuximab) Monoclonal binding CAIXantigen	Adjuvant therapy for non-metastatic clear cell renal cell carcinoma	Prometheus (Nestlé) (US) paid $19m up front and will either pay $20m cash or assign EU rights to an undisclosed marketed oncology drug. Edison has assumed up to $106m in milestones plus royalties (note: 10% of royalties due to G250 originators). Esteve holds southern EU rights. No northern EU partner.	864-pt ARISER (50mg followed by 20mg once weekly for 25 weeks) vs placebo as adjuvant therapy after recovery from surgery. Primary endpoint: disease-free survival determined by CT imaging. US fast-track status. Final data (with no interim penalty) expected in Q412, with potential filing in H113.
Mesupron (upamostat) Oral small molecule uPA inhibitor	Breast cancer	None – available for partnering. Primary endpoint reported June 2012 was progression-free survival.	132-pt Phase II trial ± capecitabine in HER2-negative metastatic breast cancer. Progression-Free Survival showed a clear trend response (8.3 vs 4.3mth median PFS) in the 95 patient subgroup who received prior chemotherapy. Overall Survival data due in H113.
	Pancreatic cancer	Data published 2010.	Phase II in 95 pts found PFS rate increased by 66% from 16.2% on gemcitabine alone to 22.5% of 200mg Mesupron and 26.9% on 400mg Mesupron.
WX-554 Oral MEK inhibitor.	Solid tumours	UCB (w/w) buyback/co-development options.	Ph I single-dose study showed dose-dependent MEK inhibition[i] A 50 patient dose escalation study Ph I/IIa started in April 2012; data due Q4/13- Q114.
WX-037 Oral PI3K inhibitor	Solid tumours	UCB (w/w, option)	Preclinical. Targets the PI3 kinase pathway[ii].Strong area of pharmaceutical development interest.
MAb projects	Cancer	UCB (w/w, option)	Research MAbs to two undisclosed targets.
ADC Technology	Cancer, inflammatory and autoimmune	Research contracts	Acquired as part of Heidelberg Pharma. Develops antibody drug conjugates (ADC) to target and kill cancer cells. Also has a range of preclinical disease models for use in development projects.
Oncogene Science	Biomarker tests	A brand name of Wilex Inc.	Sells the only FDA-cleared ELISA assay measuring blood HER2/neu level for therapy monitoring

Source: Edison

Science background on Mesupron: Why it works

Mesupron inhibits urokinase-type Plasminogen Activator (uPA), a key enzyme in the activation of proteases, which enables tumour invasion into surrounding tissues and also facilitates metastasis, Exhibit 2.[1] [2] A detailed summary of the technical characteristics of Mesupron is given in Exhibit 3.

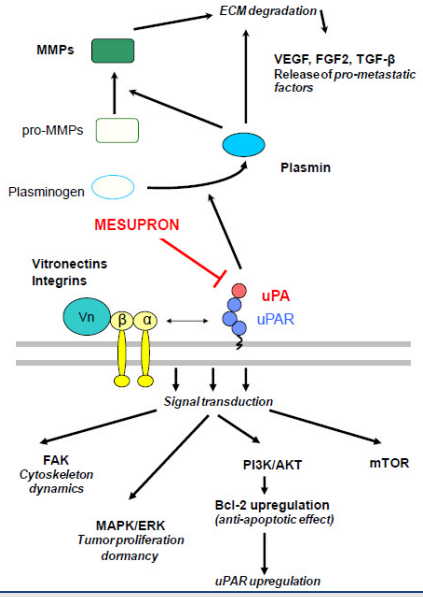
The Mesupron data released on 15 June 2012 supports the pancreatic cancer data released in June 2010. As predicted from the preclinical R&D, Mesupron appears to slow tumour growth and invasion rates. This enables it to act alongside cytotoxic drugs. Mesupron does not directly kill cancer cells. As the mechanisms of action are different, there should be little additive toxicity in combination therapy and this was confirmed in both the breast and pancreatic studies.

[i] MEK drives a key intracellular amplification signalling system leading to cell division.
[ii] PI3k is a receptor-activated membrane-bound kinase. It promotes cell growth and protects against apoptosis.

Mesupron's mechanism of action

uPA is released by cells and is captured by the uPA receptor (uPAR), Exhibit 2. Once captured, it can be activated by Plasmin. uPAR tends to be on the leading edge of cells so active uPA localises at the tumour invasive margin. The uPA-uPAR complex also recruits growth factors to stimulate growth. There is a natural inhibitor: Plasminogen Activator Inhibitor (PAI). This has three forms with PAI-1 being the most important. All bind to uPA and block its action; they also cause the internalisation and destruction of the uPA-PAI complex with recycling of uPAR. WX-UK1, the active metabolite of Mesupron, blocks uPA activity but it is unknown if it causes internalisation and also the degradation of the complex. Active uPA cleaves inactive plasminogen to form active plasmin, which can then activate more uPA: Plasmin is the active enzyme that degrades the long protein fibres of connective tissue like collagen. Plasmin also activates proteases called matrix metalloproteinases (MMPs) like collagenase.

Exhibit 2: Mechanism of action of Mesupron



Source: Wilex

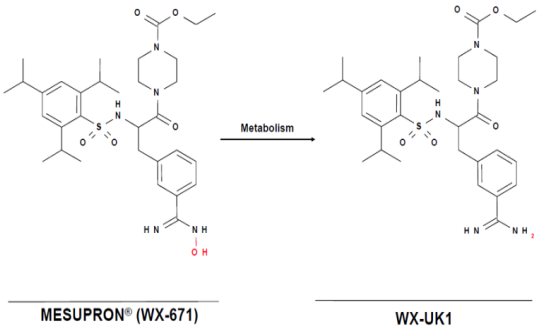
Clinical validation of uPA

The uPA system was clinically validated as a prognostic factor for newly diagnosed, node-negative breast cancer progression by an 8,000 patient pooled data analysis.[3] The concentration of uPA in the tumours of intermediate risk patients is a guide to whether chemotherapy, with serious side effects, is justified. Low-risk patients will not be offered chemotherapy and high-risk patients (assessed on clinical factors and HER2 status) will receive it anyway.

The uPA test as recommended by ASCO in 2007 uses an ELISA format as histopathology is not validated or reliable enough.[4] A clinical cut off of 3ng/mg protein is used since patients above this have a high progression risk; note that PAI-1 is also measured as high levels (14ng/g) tissue) indicate high risk. The hazard ratio (HR) on 10-year follow-up for all patients was 3.2; this means there is over a threefold higher risk of progression with high uPA tumours; PAI-1 was also identified as a high risk biomarker (HR 2.8). This method classifies 35-55% of patients as low risk whereas clinical factors alone give 20-40% as low risk. A large prospective study in 4,149 patients (NNBC3-Europe) is now underway and should report initial findings in 2012.[5]

The strong validation of uPA as a clinical biomarker in breast cancer is an indication of uPA's importance. It also gives a validated and commercially available companion diagnostic test if this is required. So far, patient uPA status has not been determined in Wilex's studies.

Exhibit 3: Mesupron data sheet

Mesupron	Mesupron is an orally available prodrug. Once absorbed into the blood from the intestine, it is chemically reduced (loses an oxygen atom) to the active form: WX-UK1. Mesupron itself is metabolised within 3-4 hours and is undetectable in plasma after 24 hours. Mesupron does not accumulate on repeat dosing.
Conversion of Mesupron to active WX-UK1 form	
Tissue retention 15 fold higher than plasma	WX-UK1 is retained in tissue and tumour at 15 fold the concentration detected in plasma. In both tissue and tumour 24 hours after dosing the mean of 11 samples (estimated by Edison) was 670ng./g.[6] There was no difference seen between the 200mg and 400mg doses although the study was not powered enough for this to be certain.
Dose	The evidence indicates that 200mg may be an adequate dose although 400mg gave superior trend results in the pancreatic study and the breast study tested only a 200mg dose.
Inhibitory effect	WX-UK1 has a Ki of 410nM[iii] against uPA.[7] To block uPA action, the drug needs to be taken daily. The 24 hr trough concentration in a head and neck cancer study had a mean of c 670ng/g (1,090nM) giving about 70% inhibition as a baseline, but with a wide range in the 11 observed patients. WX-UK1 also inhibits plasmin and thrombin at Ki's of 390nM and 490nM. Inhibition of plasmin may be a big advantage for the drug since it is a highly active component of the proteolytic system that itself activates uPA (see Exhibit 2 and "Mesupron's mechanism of action?"). Thrombin inhibition is weaker and no side effects are noted.

Source: Edison Investment Research, Wilex data, references as cited

Breast cancer results

The breast cancer trial was in HER2-negative metastatic breast cancer patients who had received first line chemotherapy.[iv] The comparison drug, capecitabine, is given on a three-week cycle: two weeks of therapy with seven days' recovery.[v] Treatment is given until disease progression. In the double blind study, capecitabine was given in combination with placebo in the one arm and 200mg Mesupron in the other arm. As expected, there were no drug interactions and no increase in toxicity.

The result overall was relatively unspectacular as progression free survival (PFS), the primary endpoint, only rose from 7.5 months to 8.3 months. The more interesting analysis is the 95 patient subgroup who had received prior chemotherapy where median PFS on the combination was 8.3 months up from 4.3 months on capecitabine alone. The increased difference was not due to a change in the combination median survival but arose because in the subgroup the capecitabine-only median PFS survival dropped from 7.5 to 4.3. This difference might be because the proportions of patients in the overall trial who had received prior adjuvant chemotherapy (and had a worse prognosis) were different, Exhibit 4. Exhibit 5 shows the Kaplan-Meier curve for this group as assessed by a blinded readout of

[iii] Ki is an absolute measure of the inhibition of an enzyme by a drug; for WX-UK1, 410nM. Normally chemists aim for a low, ideally single-digit Ki in the nM range. On these standards, WX-UK1 is a less potent drug than normal but it has clinical activity while more potent and selective compounds failed. Note that Ki gives a 50% inhibition. To get 90% inhibition, one needs tenfold the Ki as it is a logarithmic scale.
[iv] If HER2 is present (about 30% of diagnosed cases) a treatment schedule using Herceptin would be indicated.
[v] Capecitabine is a 5-fluorouracil prodrug normally given in combination with docetaxel after patients have failed other treatments.

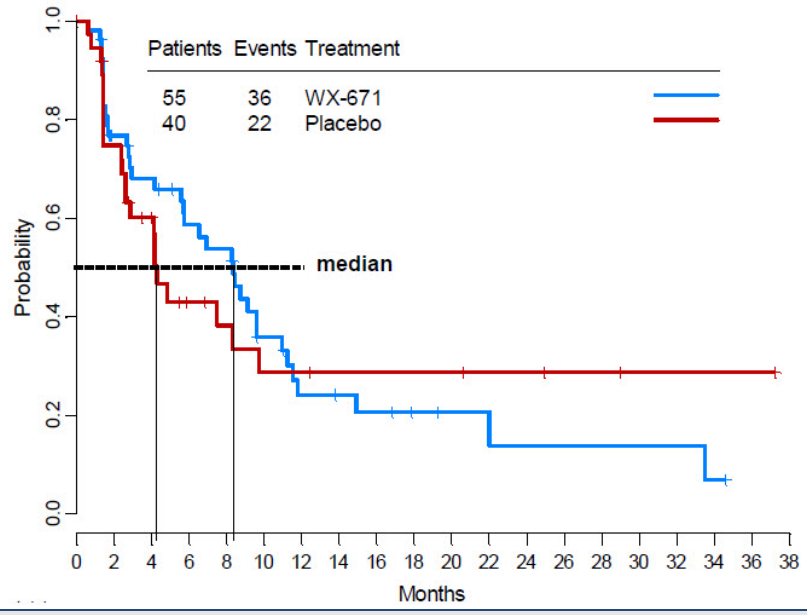
the CT scan data. Physicians with direct patient contact generally rated the patients worse than this central read out putting the Mesupron PFS value as 7.0 months vs 4.2 months on capecitabine alone.

Exhibit 4: Phase II Mesupron data

		Capacitebine only	Mesupron plus capecitabine
All patients (132 patients, 66 per arm)	% prior chemotherapy	61%	83%
	Median PFS (mths)	7.5	8.3
	Observed tumour response %	9%	17%
Subgroup of patients with prior chemotherapy only	% prior chemotherapy	100% (40 patients)	100% (55 patients)
	Median PFS (mths)	4.3	8.3

Source: Wilex

Exhibit 5: Kaplan-Meier PFS response in the prior chemotherapy subgroup



Source: Wilex

Pancreatic trial support

The breast data supports the earlier pancreatic cancer results, Exhibit 6, reported at ASCO in 2010.

Exhibit 6: Phase II pancreatic data

Therapy	Response	PFS*	overall 12 month survival	Median survival
Gemcitabine only	15.4%	16.2%	33.9%	9.9 months
Mesupron 200mg	21.4%	22.5%	40.7%	9.7 months
Mesupron 400mg	35.5%	26.9%	50.6%	12.5 months

Source: ASCO 2010

The 95 patients with non-metastatic but inoperable cancer[vi] were randomised to gemcitabine or gemcitabine plus Mesupron either 200mg or 400mg daily. Patients were followed until cancer progression. The trial was not statistically powered, but there clearly appears to be a substantial Mesupron effect.

[vi] The patient survival was generally better than typically seen for pancreatic cancer (c six month or less median survival being typical) since these were advanced but non-metastatic patients.

Other cancers

The uPA system is known to operate in numerous solid tumour types as a general invasive mechanism. Significant off-label experimental use could be expected if Mesupron receives approval for a major tumour type like HER2-negative breast cancer. This potential off-label or approved extended use is not valued in the Edison model,

Sensitivities

Following good indicative data, the development path of Mesupron needs to be clarified. The data above is from two non-statistically powered trials so these results could be by chance. The fact that there are two separate cancers showing the same trends indicates that this is real but it needs to be formally established. Wilex does not have the financial resources to run a powered Phase II/III study, which would need at least 300 patients and be expensive due to the use of capecitabine in both arms; this would cost about $25,000 per patient alone or $7.5m. By comparison with the Clovis LEAP study, the cost could be up to $50m. Hence, a partner is needed but may not be signed until H113 with work resuming H213. This makes a 2015 launch window, as previously assumed, look unrealistic and this has been adjusted to 2017. Again by comparison to the Clovis LEAP study, the lack of powered Phase II data may not preclude running a potentially pivotal Phase II, but any such trial may need to be at 90% power to minimise risks and use a high p value threshold to gain FDA approval.

The outcome of the Phase III ARISER study of Rencarex, likely to be known by the end of 2012, is a key sensitivity to the current investment case. The FDA has agreed a protocol amendment so it will accept the data without the planned interim analysis and at a higher statistical threshold since there is no interim statistical penalty. Rencarex is expected to have a late 2014 launch and this seems feasible at this time, assuming FDA submission by Prometheus before mid 2013. A centralised EMA submission also needs to be made; the CHMP assessment process runs to a rigid 210 day timetable, but with several clock stop periods. National stages and formal approval by the Commission then takes several more months. The role of Esteve, the South Europe licensee for Rencarex, in this is unclear. There is no Northern Europe partner but possibly Wilex could sell direct. This may link to the option of acquiring a marketed product from Prometheus, which might create a marketing infrastructure. No decision has been announced on whether Wilex will claim the $20m cash from Prometheus (US partner for Rencarex) or take the undisclosed product. If the cash is not taken, additional capital will be needed, but cash flow from the product would be generated.

The FDA Oncology Drugs Advisory Committee meets on 25 July to discuss and provide general advice on “the extent to which, if any, the pre-surgical identification of clear cell carcinoma of the kidney using an imaging test provides useful clinical information”. This is not specifically about Redectane, but it might enable the FDA to clarify any advice it gives for Redectane’s final development track. Edison continues to expect that a further Phase III trial may be needed to link Redectane imaging to clinical outcomes. It is possible that the advisory meeting advice could cause Edison to reassess the success probability of Redectane; this is currently at a near certain 90% probability. An investigator study in association with Sutent is underway to monitor tumour responses.

Valuation

The assumed risk-adjusted probability of success for Mesupron was set at 35% in the most recent Edison valuation (March). As the current data relates to exploratory studies, this seems realistic and hence the indicative valuation of €0.35 at the current exchange rate is unchanged by the new data.

Edison's indicative valuation for Wilex with the revised Mesupron launch date is €207m (€7.35/share). The Edison model assumes Mesupron accounts for nearly 37% of expected risk-adjusted royalties. The indicative value assumes that after tax cash flows above minimal administration cost of $2m annually are paid as dividends. This method leaves no residual value, assets or costs at the end of the forecast period (2024). In 2024, royalty revenues are expected (risk-adjusted) to be $119m.

Financials

2011 sales comprised revenue from the three divisions – therapeutics, diagnostics and customer-specific research – and included partial recognition of a $19m up-front payment from Prometheus plus a $2.5m milestone. The upfront payment is being booked over an undisclosed period to the end of Rencarex's development. R&D expenditure was €15.6m. R&D reimbursed by Prometheus is included in sales revenues and then fully deducted as a cost of sale; this reduces the R&D expenditure.

Wilex has guided to 2012 group revenue of €14-16m. This assumes recognition of $20m from Prometheus spread over three years: €5.3m per year at current exchange rates. However, the timing of any payment is unclear and Wilex may choose instead to gain an EU-marketed cancer product to market direct. This would give an infrastructure for direct northern EU Rencarex sales, although these are unlikely until 2015. If the product is taken, Wilex will need to cover the $20m from other sources which should include product cash flows. R&D expenditure is expected to be €15-17m.

Wilex had gross cash of €7.9m as of Q1 FY12 (February) after raising €9.9m gross through the issue of 3.2m new shares priced at €3.10 in a rights issue. Expenditure is $1.7m per month giving cash until mid Q3 (July 2012). The company believes it has funding sources to cover the gap to Rencarex data in Q4.

Edison's financial model to the end of fiscal 2013 is summarised in Exhibit 7. A reduction in R&D to €10m in 2013 has been assumed as current studies wind down. A further €15m funding requirement in 2013 has been factored in as an increase in long-term debt. A shareholder loan provided by Dievini Hopp and UCB amounting to €10m is unsecured and is classified on the balance sheet as a current liability. The model excludes possible (undisclosed) milestone payments from Esteve Rencarex, and Ion Beam Applications (on Redectane).

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Exhibit 7: Financial summary

€'000s	2010	2011	2012e	2013e
Year end 30 November	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS				
Revenue	**1,314**	**11,713**	**15,693**	**9,227**
Cost of sales	0	(4,165)	(6,103)	(6,408)
Gross profit	1,314	7,548	9,590	2,819
R&D expenditure	(19,704)	(15,641)	(16,000)	(10,000)
Administrative costs	(4,722)	(5,290)	(5,000)	(5,250)
Operating profit	(23,112)	(13,383)	(11,884)	(12,431)
Intangible amortisation	(133)	(268)	(350)	(250)
Exceptionals	0	0	0	0
Share-based payment	(470)	(97)	(450)	(450)
EBITDA	**(22,425)**	**(12,762)**	**(10,834)**	**(11,631)**
Operating profit (before GW and except)	(22,509)	(13,018)	(11,084)	(11,731)
Net interest	20	(541)	(700)	(700)
Profit before tax (norm)	**(22,489)**	**(13,559)**	**(11,784)**	**(12,431)**
Profit before tax (FRS 3)	**(23,092)**	**(13,924)**	**(12,584)**	**(13,131)**
Tax	(6)	(2)	(2)	(2)
Profit after tax (norm)	(22,486)	(13,608)	(11,768)	(12,432)
Profit after tax (FRS 3)	(23,099)	(13,926)	(12,586)	(13,132)
Average number of shares outstanding (m)	16.7	20.7	24.3	24.8
EPS - normalised (c)	(134.4)	(65.8)	(48.5)	(50.1)
EPS - FRS 3 (c)	(138.0)	(67.3)	(51.8)	(52.9)
Dividend per share (c)	0.0	0.0	0.0	0.0
BALANCE SHEET				
Fixed assets	**2,192**	**12,818**	**12,308**	**12,073**
Intangible assets & goodwill	1,166	10,467	10,123	9,879
Tangible assets	864	2,074	1,923	1,931
Other non-current assets	162	277	262	262
Current assets	**3,399**	**7,997**	**7,928**	**5,693**
Stocks	166	515	519	519
Debtors	1,290	4,061	4,250	4,500
Cash	1,943	3,421	3,159	674
Investments and other	0	0	0	0
Current liabilities	**(6,504)**	**(20,205)**	**(17,088)**	**(17,488)**
Trade accounts payable	(2,040)	(1,412)	(1,800)	(2,200)
Liabilities from leasing agreements	(58)	(252)	0	0
Short-term borrowings	0	(10,548)	(10,100)	(10,100)
Deferred revenue and other current liabilities	(4,406)	(7,993)	(5,188)	(5,188)
Long-term liabilities	**(382)**	**(5,132)**	**(5,432)**	**(15,244)**
Pension provisions	(24)	(25)	(25)	(25)
Liabilities from leasing agreements	(82)	(218)	(218)	(218)
Long-term borrowings	0	0	0	(15,000)
Deferred revenue and other long-term liabilities	(276)	(4,888)	(5,188)	0
Net assets	**(1,295)**	**(4,523)**	**(2,284)**	**(14,966)**
CASH FLOW				
Operating cash flow	**(19,253)**	**(8,982)**	**(8,789)**	**(16,669)**
Net interest	20	(18)	(700)	(700)
Tax	(6)	1	(2)	(2)
Capex	(46)	(281)	(99)	(108)
Expenditure on intangibles	(4)	(22)	(6)	(6)
Capitalisation of product development spend	0	0	0	0
Acquisitions/disposals	(426)	885	0	0
Financing	18,279	(73)	9,782	0
Dividends	0	0	0	0
Net cash flow	(1,436)	(8,489)	186	(17,485)
Opening net debt/(cash)	**(3,411)**	**(1,943)**	**7,128**	**6,941**
HP finance leases initiated	(38)	(106)	0	0
Other	6	-476	0	0
Closing net debt/(cash)	**(1,943)**	**7,128**	**6,941**	**24,426**

Source: Edison Investment Research. Note: 2012 and 2013 revenues include a $20m 2012 cash milestone deferred over three years at €5.2m recognised per year.

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