

OSE Immunotherapeutics

R&D update

Encouraging data from novel preclinical projects

OSE has a well-balanced R&D pipeline in terms of technology and asset stage (from discovery to Phase III). At the American Association of Cancer Research (AACR) Virtual Annual Meeting II in late June, OSE announced new data from its two more interesting preclinical programmes. C-type lectin receptor (CLEC-1) is a newly disclosed myeloid checkpoint target that tumour cells use to inhibit myeloid cells phagocytosis, a 'don't eat me' signal. Anti-CLEC-1 antibodies restored the phagocytosis function of macrophages and dendritic cells (a similar effect to SIRPα/CD47 axis inhibition). New data from OSE's bispecifics platform BiCKI were also presented, including with its first drug candidate BiCKI IL-7, an anti-PD-1 antibody fused with IL-7 interleukin. Our valuation is €230m or €15.3/share.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/18	24.5	4.8	0.38	0.0	15.6	N/A
12/19	26.0	(1.2)	(0.30)	0.0	N/A	N/A
12/20e	0.0	(22.9)	(1.53)	0.0	N/A	N/A
12/21e	0.0	(23.1)	(1.55)	0.0	N/A	N/A

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

CLEC-1: Novel myeloid checkpoint target for cancer

With its academic collaborators OSE found that CLEC-1 acts as a myeloid checkpoint. Myeloid checkpoint inhibitors (CPIs) are believed to work in a similar way to T-cell CPIs, but instead they inhibit the checkpoints between tumour cells and myeloid cells. Anti-CLEC-1 antibodies developed by OSE restored the phagocytosis function of macrophages and dendritic cells, which recognise the cancer cells as foreign, then attack and digest cancer cells leading to presentation of cancer antigens on the surface, which stimulates the immune system. This effect is similar to SIRPα/CD47 axis inhibition. OSE already has a SIRPα antagonist in Phase I, OSE-172, which is licensed to Boehringer Ingelheim (BI) for up to €1.1bn in potential milestones plus royalties.

BiCKI: Data with first drug candidate

Another major new data presentation at the AACR was from OSE's Bispecific Antibody Checkpoint Inhibitor (BiCKI) platform. CPIs have become a standard of care in many cancers, but resistance remains a significant issue. With its first drug candidate from this platform, a proprietary Anti-PD-1 antibody fused with IL-7 mutein, OSE expects to address the primary and secondary resistance to CPIs seen in many patients, which limits the use of CPIs.

Valuation: €230m or €15.3/share

Our valuation of OSE is unchanged at €230m or €15.3/share. We do not yet include any assets from BiCKI platform, as the research is still at an early, preclinical stage. However, OSE is developing this platform relatively quickly, so we will review potential assets once the platform has matured. In May 2020, OSE signed a €7m loan agreement with a consortium of banks, 90% guaranteed by the French government. This has extended the cash runway until Q321.

Pharma & biotech

8 July 2020

Price €5.92

Market cap €89m

Gross cash (€m) at end-FY19 (government debt not included) 25.8

Shares in issue 15.0m

Free float 25%

Code OSE

Primary exchange Euronext Paris

Secondary exchange N/A

Share price performance



% 1m 3m 12m

Abs 2.1 39.3 73.1

Rel (local) 5.3 22.5 92.0

52-week high/low €7.48 €2.99

Business description

OSE Immunotherapeutics is an immunotherapy company based in Nantes and Paris, France, and listed on the Euronext Paris exchange. It is developing immunotherapies for the treatment of solid tumours and autoimmune diseases and has established several partnerships with large pharma companies.

Next events

Update on Tedopi development/partnering 2020

Initiation of Phase II trials with OSE-127 2020

Update on BiCKI platform 2020

Update on COVID-19 project 2020

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Novel myeloid checkpoint target for cancer immunotherapy discovered

OSE's new preclinical [data](#) describing the discovery of a novel myeloid immune checkpoint target for cancer immunotherapy were accepted for poster and oral presentations at AACR Virtual Annual Meeting II, 22–24 June 2020. In collaboration with researchers at the Center for Research in Transplantation and Immunology, Nantes University Hospital, OSE found that CLEC-1 acts as myeloid checkpoint.

Hematopoietic stem cells are able to differentiate into cells of two primary lineages, lymphoid and myeloid. Cells of the lymphoid lineage include B cells, T cells and natural killer cells. Cells of the myeloid lineage include megakaryocytes, erythrocytes, granulocytes, dendritic cells and macrophages. Although the research is still early, myeloid CPIs are believed to work in a similar way as T cell CPIs, but instead of T cells such drugs inhibit the checkpoints between tumour cells and myeloid cells.

With its collaborators OSE found that tumour cells inhibit myeloid cell phagocytosis through CLEC-1. In other words, CLEC-1 acts as a 'don't eat me' signal. Anti-CLEC-1 antibodies developed by OSE restored the phagocytosis function of macrophages and dendritic cells, which recognise the cancer cells as foreign then attack and digest them. This leads to the presentation of cancer antigens on the cell surface, which stimulates the immune system. Mice that were genetically engineered to be CLEC-1 deficient were able to eradicate tumour cells more effectively. A synergy with chemotherapy in CLEC-1-deficient mice was also observed.

OSE already has an asset in Phase I stage, OSE-172, which is a first-in-class signal regulatory peptide alpha (SIRP α) antagonist. OSE-172 binds to SIRP α on myeloid cells, which inhibits the SIRP α /CD47 interaction (CD47 is found on the surface of cancer cells). CD47 also acts as a 'don't eat me' signal to macrophages of the immune system. When the SIRP α /CD47 axis is blocked, the expectation is, as with CLEC-1, the myeloid cells recognise the cancer cells as foreign so they attack and digest them. Phagocytosis leads to cancer-antigen presentation on the cell surface, which stimulates the cancer-specific immune system. OSE licensed OSE-172 to BI in April 2018; this is the company's largest deal with €1.1bn potential development, regulatory and sales milestones plus low double-digit royalties.

No myeloid checkpoint inhibitors have been approved yet. Most advanced projects are in early- to mid-clinical stages and target the SIRP α /CD47 axis, primarily CD47 (present in tumour cells). In our [initiation report](#) (December 2018), we identified US-based biotech Forty Seven as the leader in the myeloid CPI space with the anti-CD47 antibody magrolimab targeting myelodysplastic syndrome (MDS), acute myeloid leukaemia (AML) and diffuse large B-cell lymphoma. As [reported](#) in March 2020, Gilead Sciences agreed to acquire Forty Seven for \$4.9bn and completed this in April. Promising results from just a Phase Ib study with magrolimab in MDS and AML patients were sufficient to convince Gilead to pay the hefty premium (92% to share price before the deal).

So, myeloid checkpoint inhibition is increasingly attracting attention after T-cell CPIs became the mainstay treatment in many oncological indications. OSE has now identified a second potential myeloid checkpoint target. Although the data presented at the AACR are still early, it is cutting-edge research enabled by OSE's extended network with academic research groups.

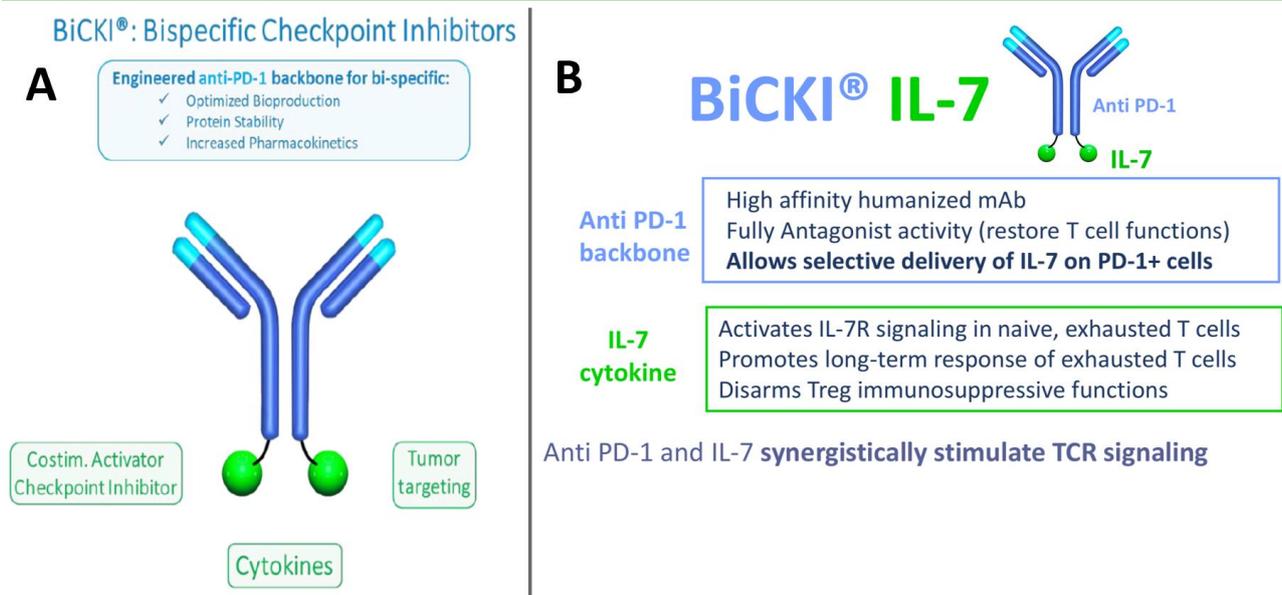
BiCKI: Bispecific platform update at AACR

Another major new data presentation at the AACR was from OSE's BiCKI platform. OSE revealed the platform in March 2019 and we reviewed it in our September 2019 [report](#). At the AACR last month, OSE presented [two posters](#): one focusing on the development of the platform itself, and a second on with new preclinical data with the first potential asset from this platform.

BiCKI is a bispecific/fusion antibody platform (Exhibit 1A) that consists of:

- **A humanised high-affinity anti-PD-1 monoclonal antibody.** OSE has developed its own anti-PD-1 antibody that forms the 'backbone' of the bispecifics. This is an IgG antibody (OSE-279) in that it has a normal structure with heavy and light chains, where the Fab region binds to the PD-1 receptor on T-cells. OSE chose it due to its good yield in terms of manufacturing and productivity.
- **Engineered proteins attached to the Fc region.** The silent Fc region of the antibody (the base of the heavy chains) is the effector part of the molecule. It determines what effect the antibody has once it has bound to the antigen, which is usually an immune response. OSE plans to engineer different proteins for the Fc region, eg IL-7, through protein fusion to target novel receptors.

Exhibit 1: BiCKI platform (A) and BiCKI IL-7 mechanism of action (B)



Source: OSE

CPIs have become a standard of care for many cancers. Although in some patients CPIs are remarkably effective, a significant percentage (depending on the cancer type) of patients either do not respond to treatment (primary resistance) or develop resistance after an initial period or response (secondary resistance). OSE hopes that anti-PD-1 bispecifics will help overcome the resistance (primary and secondary) to anti-PD-1 drugs by selecting targets that are involved in different stages of the immunity cycle. In particular, OSE is looking for targets that have synergistic potential.

BiCKI IL-7: First potential bispecific drug candidate

Persisting antigenic stimulation, such as in chronic infections and cancer, can lead to T cell exhaustion, a state of functional impairment, high expression of inhibitory receptors including Programmed Death-1 (PD-1) and defective immune memory ([Wherry and Kurachi, 2015](#)). This

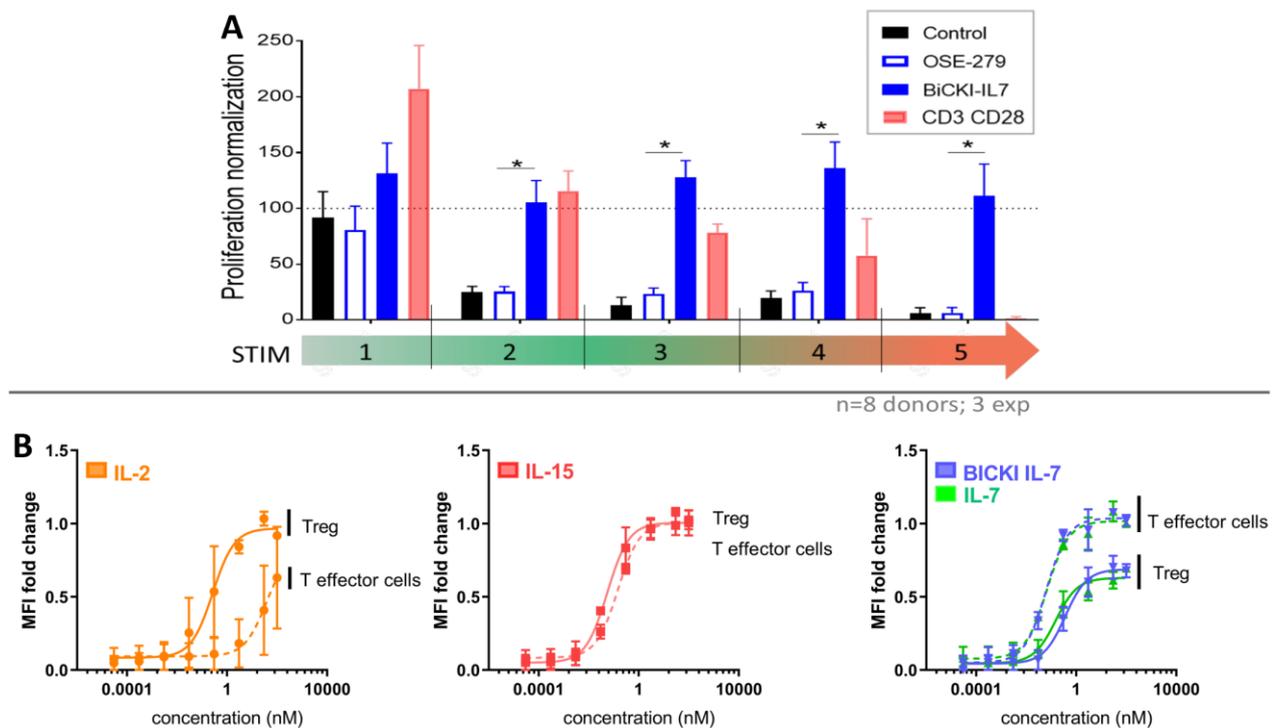
dampens the immune response. Blocking the PD-1:PD-L1 pathway can reinvigorate exhausted CD8+ T cells, improving viral and tumour control. This strategy has now been proven with the advent of CPIs; however, the primary and secondary resistance rates are high, as mentioned above.

OSE's first candidate based on this platform is BiCKI IL-7 (Exhibit 1B). IL-7 is a cytokine that controls the proliferation, apoptosis and activation of CD4+ and CD8+ T cells in humans. IL-7 receptor expression is reduced in exhausted T cells. In an in vitro chronic antigenic stimulation model, OSE has demonstrated that BiCKI IL-7 reinvigorated exhausted T cells (Exhibit 2A).

Another reason why OSE chose the combination of BiCKI and IL-7 was that IL-7 is a good target for stimulating effector (CD8+, CD4+) T cell function over regulatory T cells (Tregs). Tregs are known to contribute to the dampening of the anti-tumour immune response. This is because effector T cells express high levels of IL-7 receptors, while Tregs express low levels. As a result, BiCKI IL-7 tilts the balance towards effector T-cells over Tregs (Exhibit 2B).

OSE also showed that the advantage of the bispecific drug (over a combination of two drugs, anti-PD-1 with IL-7) is that BiCKI IL-7 synergistically increases T-cell receptor signalling and hence antigen-specific T cell responses.

Exhibit 2: BiCKI IL-7 reinvigorates exhausted T cells (A) and tilts balance towards effector T-cells over Tregs (B)



Source: OSE.

Large biotech/pharma are getting in early on bispecifics

The bispecifics field is a relatively new area but is receiving growing attention. Three bispecific antibodies have been approved (they do not target checkpoint receptors): Blincyto (blinatumomab, Amgen), Hemlibra (emicizumab, Roche) and Removab (catumaxomab, Fresenius, now withdrawn) but there are many more in [clinical stages](#). There are a few companies trying to use bispecifics to target multiple checkpoints with the aim of further reducing any T-cell inhibition by tumour cells and promoting T-cell activation.

Most of the programmes are still early to mid-stage so existing deals involve bispecific platforms or very early-stage assets (Exhibit 3). These deals achieved between \$45–150m in upfront payments

and \$180–1,700m in milestone payments (for the platform plus existing programmes), depending on the number of candidates included in the deal. As there is an appetite for bispecifics platforms and bispecific candidates from pharma, OSE's decision to invest in BiCKI seems well founded.

Exhibit 3: Selected bispecifics deals

Date	Licensor	Licensee	Product	Pharmacological class / Target	Indications included	Upfront (\$m)	Milestones (\$m)
08/03/2019	Xencor	Genentech (Roche)	XmAb24306	IL-15 and IL-15 receptor alpha (IL-15RA) bispecific MAb	Autoimmune disease and cancer	120	160
11/02/2019	TeneoOne	AbbVie	TNB-383B	Anti-B cell maturation antigen (BCMA) and CD3 bispecific MAb	Multiple myeloma	90	N/A
20/12/2018	Agenus	Gilead Sciences	AGEN1423 + option on four other programmes	Undisclosed bispecific MAb mechanism	Cancer indications	150 (including 30 equity)	1,700
27/11/2018	Zymeworks	BeiGene	ZW25, ZW49	HER2	Cancer indications	40	390
27/11/2018	Zymeworks	BeiGene	Azymetric and EFECT platforms	Bispecific platform	Cancer indications	20	702
23/10/2018	Zymeworks	LEO Pharma	Azymetric and EFECT platforms (two assets)	Cytokine-receptor pathways	Dermatology	5	475
13/11/2017	Zymeworks	J&J	Azymetric and EFECT platforms	Bispecific platform	Not disclosed	50	282 R&D 1,120 commercial
03/10/2017	CytomX Therapeutics	Amgen	CytomX Probody T-cell engaging bispecific + up to three additional undisclosed targets	Anti-EGFR and CD3 bispecific MAb N/A	Cancer indications Not disclosed	60 (including 20 equity) Up to 950 in additional upfront and milestones	455
04/06/2017	F-star	Merck KGaA	FS118 + option on 4 other programmes	Anti-LAG 3 and PD-1 bispecific MAb	Cancer indications	€115	€1,000
28/06/2016	Xencor	Novartis	XmAb14045 XmAb 13676	Anti-CD3 and IL-3 alpha/CD123 bispecific MAb Anti-CD3 and CD20 bispecific MAb	Acute myeloid leukaemia B-cell malignancies	150	N/A
16/09/2015	Xencor	Amgen	AMG 424 + 5 other programs	Anti-CD3 and CD38 bispecific MAb	Multiple myeloma + other cancer /immune disorders	45	1,700

Source: Edison Investment Research, EvaluatePharma, company press releases.

Clinical programme update and upcoming newsflow

Our up-to-date review of the developments with OSE's clinical-stage assets can be found in the [reports](#) published in March and April 2020.

- Tedopi neoepitope vaccine.** On 1 April 2020, OSE announced the primary endpoint was met in the predefined step one analysis of the Phase III Atalante 1 trial with its cancer vaccine Tedopi in HLA-A2 positive, non-small cell lung cancer (NSCLC) patients after they failed CPIs (anti-PD-1 or anti-PD-L1). The patients (n=99) were randomised and received treatment at least 12 months before step one analysis. The 12-month survival rate in the Tedopi arm was 46% (29 out of 63; CI 33–59%), well above the predefined futility threshold of 25%, so a statistically strong result. Due to the COVID-19 pandemic, OSE has decided to terminate enrolment into step two of the trial, as NSCLC patients are vulnerable to coronavirus infections and there was therefore a substantial risk of data loss. OSE will focus on regulatory interactions and partnering discussions given the availability of new data. An investigator-led Phase II trial in pancreatic cancer is ongoing.
- BI 765063, antagonist of SIRP α .** A Phase I study in solid tumours is ongoing in partnership with BI. First results are expected in H121. OSE has received a total of €30m in licence payments from BI. Up to €1.1bn is still potentially due plus royalties on sales.
- OSE-127, anti-IL-7R α antibody.** Following a positive Phase I in Q419, two Phase II trials with OSE-127 are planned to start in 2020 in ulcerative colitis (sponsored by OSE) and Sjögren's syndrome (sponsored by Servier), although the ongoing pandemic may affect the start dates. A €5m milestone payment from partner Servier is expected as soon as the first patient is recruited to the Phase II trial. OSE has a two-step option agreement with Servier. So far, the

company has received in total €20.3m. Up to €252m in milestone payments is still potentially due plus royalties.

- **FR104, CD28 antagonist.** Phase II-ready asset for autoimmune diseases or transplantation.
- **CoVepiT.** This new project was announced in May 2020, with a potentially prophylactic vaccine against the pandemic virus SARS-CoV-2. OSE is using its expertise in the selection and optimisation of peptides and their GMP formulation. Specifically, OSE is using its Memopi optimisation technology (Phase III stage Tedopi vaccine, a combination of antitumor neo-epitopes). After scanning of thousands of potential neo-epitopes, OSE selected four major proteins of coronaviruses with high potential for immunogenicity. First preclinical results from the CoVepiT project are expected in H220. If positive, it could allow the start of a clinical trial by end-2020.

Exhibit 4: OSE's R&D pipeline

PROGRAM	Indication	Pre-Clinical	Phase 1	Phase 2	Phase 3
IMMUNO-ONCOLOGY					
Tedopi® Neoepitopes	NSCLC				Positive Step-1 results Primary endpoint met
Tedopi®	Advanced pancreatic cancer			Combo with PD1 Opdivo® Ongoing	 
BI 765063 (OSE-172) SIRPα-CD-47	Various cancers		Ongoing		
BiCKI® Bispecific anti-PD-1 & Innovative Targets	Various cancers	2020			
AUTO-IMMUNE DISEASES					
FR104 CD28	Autoimmune diseases & Transplantation			Phase 2 planning ongoing	
OSE-127 IL-7R	Ulcerative Colitis Sjögren's syndrome		Positive Phase 1 Results Q4 2019	2020	
PROPHYLACTIC VACCINE PROGRAM					
CoVepiT Optimized Neoepitopes of SARS-CoV-2	COVID-19 vaccine	2020	Expected before end of 2020		

Source: OSE

Valuation

Our valuation of OSE is unchanged at €230m or €15.3/share. OSE will report H120 financial results in September 2020. In May 2020, OSE signed a €7m loan agreement with a consortium of banks, 90% guaranteed by the French government as support during the ongoing COVID-19 pandemic. According to OSE, this has extended the cash runway until Q321. The initial maturity period is 12 months, which OSE can extend for another five years.

We do not yet include any assets from the BiCKI platform, as the research is at an early, preclinical stage. However, OSE is developing this platform relatively quickly, so we will review potential assets once the platform has matured.

Exhibit 5: Sum-of-the-parts OSE valuation

Product	Launch	Peak sales (\$m)	Unrisked NPV (€m)	Unrisked NPV/share (€)	Probability (%)	rNPV (€m)	rNPV/share (€)
Tedopi – NSCLC	2023	657	291.9	19.5	25%	69.4	4.6
OSE-127 - ulcerative colitis	2027	843	184.0	12.3	15%	37.3	2.5
OSE-172 - multiple cancer indications (TNBC)	2027	1,801	273.1	18.2	10%	38.7	2.6
FR104 - rheumatoid arthritis	2026	1,056	242.9	16.2	15%	58.5	3.9
FY19e cash*			25.8	1.7	100%	25.8	1.7
Valuation			1,017.7	67.8		229.7	15.3

Source: Edison Investment Research. Note: WACC = 12.5% for product valuations. Note: *OSE's debt, not shown above, consists of government loans, which are typically repayable on commercial success only.

Exhibit 6: Financial summary

	€'000s	2018	2019	2020e	2021e
		IFRS	IFRS	IFRS	IFRS
December					
PROFIT & LOSS					
Revenue		24,456	25,952	0	0
Cost of Sales		0	0	0	0
Gross Profit		24,456	25,952	0	0
Research and development		(15,057)	(21,655)	(17,000)	(17,000)
EBITDA		4,963	(897)	(22,838)	(23,026)
Operating Profit (before amort. and except.)		4,847	(1,220)	(22,939)	(23,117)
Intangible Amortisation		0	(251)	0	0
Exceptionals		0	0	0	0
Other		0	0	0	0
Operating Profit		4,847	(1,471)	(22,939)	(23,117)
Net Interest		0	8	(6)	(12)
Profit Before Tax (norm)		4,847	(1,212)	(22,945)	(23,129)
Profit Before Tax (reported)		4,847	(1,463)	(22,945)	(23,129)
Tax		783	(3,188)	0	0
Profit After Tax (norm)		5,630	(4,400)	(22,945)	(23,129)
Profit After Tax (reported)		5,630	(4,651)	(22,945)	(23,129)
Average Number of Shares Outstanding (m)		14.6	14.9	15.0	15.0
EPS - normalised (€)		0.38	(0.30)	(1.53)	(1.55)
EPS - normalised fully diluted (€)		0.36	(0.30)	(1.53)	(1.55)
EPS - reported (€)		0.38	(0.31)	(1.53)	(1.55)
Dividend per share (€)		0.0	0.0	0.0	0.0
Gross Margin (%)		100.0	100.0	N/A	N/A
EBITDA Margin (%)		20.3	N/A	N/A	N/A
Operating Margin (before GW and except.) (%)		19.8	N/A	N/A	N/A
BALANCE SHEET					
Fixed Assets		53,879	55,871	55,770	55,679
Intangible Assets		52,600	52,600	52,600	52,600
Tangible Assets		904	1,009	908	817
Investments		375	2,262	2,262	2,262
Current Assets		14,687	26,589	12,256	2,747
Stocks		0	0	0	0
Debtors		2,253	747	747	747
Cash		9,573	25,842	11,509	2,000
Other		2,861	0	0	0
Current Liabilities		(9,075)	(14,330)	(14,330)	(14,330)
Creditors		(8,447)	(13,782)	(13,782)	(13,782)
Short term borrowings		(628)	(548)	(548)	(548)
Long Term Liabilities		(6,075)	(16,067)	(23,067)	(35,085)
Long term borrowings		(3,832)	(9,211)	(16,211)	(28,229)
Other long term liabilities		(2,243)	(6,856)	(6,856)	(6,856)
Net Assets		53,416	52,063	30,629	9,011
CASH FLOW					
Operating Cash Flow		1,860	5,989	(21,327)	(21,515)
Net Interest		0	0	(6)	(12)
Tax		(783)	3,148	0	0
Capex		(593)	0	0	0
Acquisitions/disposals		0	0	0	0
Financing		(37)	0	0	0
Other		(95)	2,288	0	0
Dividends		0	0	0	0
Net Cash Flow		352	11,425	(21,333)	(21,527)
Opening net debt/(cash)		(4,761)	(5,113)	(16,083)	5,250
HP finance leases initiated		0	0	0	0
Other		(0)	(455)	0	0
Closing net debt/(cash)		(5,113)	(16,083)	5,250	26,777

Source: Company data, Edison Investment Research

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