EDISON

Onconova Therapeutics

Clinical update

New insight into rigosertib mechanism of action

Pharma & biotech

New insights into the mechanism of action (MoA) of rigosertib help to explain certain phenotypic phenomena and provide an answer to previous mechanistic questions. The evidence supports a new MoA hypothesis and could open up some new indications for future development. While a new insight into the MoA will have little impact on the important outcome of the ONTIME Phase III trial, it indicates that the drug could be effective in several other indications. Our valuation remains unchanged at $476m given the early nature of these findings.

Year end	Revenue ($m)	PBT* ($m)	EPS* ($)	DPS ($)	P/E (x)	Yield (%)
12/11	1.5	(27.6)	(14.8)	0.0	N/A	N/A
12/12	46.2	(30.3)	(15.5)	0.0	N/A	N/A
12/13e	3.3	(68.5)	(8.9)	0.0	N/A	N/A
12/14e	50.0	(48.9)	(2.3)	0.0	N/A	N/A

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

Rigosertib's new MoA

Several new lines of evidence suggest that rigosertib binds to the Ras-binding domain (RBD) of Raf, a protein involved in the development of many types of cancer. This inhibits Raf kinase activation by preventing Ras from binding to the RBD, in turn shutting down signal transduction cascades downstream of Ras-Raf. As Ras-Raf is required for polo-like kinase-1 (PLK1) activation, rigosertib's new MoA provides a molecular explanation of the X-shaped chromosomal spindle in rigosertib-treated cells, which is also a hallmark of PLK1 inhibition. This MoA also sets a firmer foundation of rigosertib's role in PI3K inhibition, because PI3K requires the association with Ras for activation.

Rigosertib may have broader indication

While the new MoA is unlikely to change the near-term development strategy, which remains focused on MDS, it could help Onconova and its partners refine a long-term clinical development strategy, since Ras is one of the most frequently mutated genes in many types of cancer. We envision rigosertib being developed for Ras-driven cancers, such as pancreatic, colon and lung cancer, using molecular tools to select patients that may derive the most benefit from a Ras-inhibiting compound.

Valuation: Unchanged at $476m

Our risk-adjusted DCF valuation remains unchanged at $476m, or $22.3 per basic share ($20.7/share, fully diluted). Top-line results from ONTIME, which are due in Q1, are the next major valuation inflection point, which if positive would add significant value to our model.

10 February 2014

Price	**US$15.08**
Market cap	**US$323m**

Net cash ($m) as at December 2013e	99
Shares in issue	21.4m
Free float	21%
Code	ONTX
Primary exchange	NASDAQ
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	33.2	13.8	N/A
Rel (local)	36.2	10.7	N/A
52-week high/low	US$29.4	US$11.2	

Business description

Onconova Therapeutics is a clinical-stage bio-pharmaceutical company focused on developing novel small molecule drug candidates to treat cancer. Its lead drug candidate, rigosertib, is partnered with Baxter (Europe) and SymBio (Japan/Korea) and is in a Phase III trial for higher-risk MDS (IV form), and in Phase II for lower-risk MDS (oral form).

Next events

Rigosertib Phase III MDS top-line data	Q114
Rigosertib NDS filing	H214
Rigosertib (oral) MDS reg. path decision	2014

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Onconova datasheet

Exhibit 1: Onconova pipeline summary

Drug	Indication	Status	Notes
Rigosertib	Higher-risk MDS after HMA (IV)	Phase III top-line results Q114	Licensed to **Baxter** (total earnable payments of $600m) for Europe, and **SymBio** (total earnable payments of $50m) for Japan/Korea. Onconova retains all rights elsewhere (including in the US). Temple University is entitled to 25% of sub-licence fees from Baxter and SymBio and a low single-digit royalty on net sales.
	Lower-risk MDS (oral)	Phase II final results at ASH	
	Refractory head and neck cancer (oral)	Phase II single arm, first phase of 20 pts results: 2014	
ON 013105	Refractory lymphoma, solid tumours	Phase I (solid tumour)	Specific inhibitor of PLK2. Studies could resume in Q114.
Recilisib	Acute radiation syndrome	Phase I ongoing	Collaboration with the US Department of Defence for radiation-induced cytopenia. Expected to be licensed out early.

Source: Edison Investment Research. Notes: Only clinical-stage assets shown.

Exhibit 2: Ongoing rigosertib clinical trials

Trial name	Patients	Treatment	Details
ONTIME (04-21)	MDS, Vidaza or Dacogen failure	Rig (CI, 3-d Q2W for eight cycles or Q4W after eight cycles) plus BSC vs BSC alone	290-pt Phase III, primary endpoint: OS. Start: Nov 2010; results: Q114.
ONTARGET (09-05)	MDS, TD, low, Int-1 or trisomy 8 Int-2	Oral, 560mg bid for two weeks Q3W	60-pt Phase II, single arm, primary endpoint: units of blood cell transfusions at week eight. Start: May 2012, results: Oct 2014.
09-08	MDS, AML and CML	Oral, various doses bid for three weeks Q4W; plus Vidaza	40-pt Phase I/II, primary endpoints: safety. Trial start: Aug 2013. Results: Aug 2015.
09-09	Squamous cell carcinoma, refractory	Oral, 560mg bid for two weeks Q3W	80-pt Phase II, primary endpoint: ORR; trial start: March 2013. Results: Sept 2015.
09-07	MDS, transfusion dependent, low, Int-1	Oral, 560mg bid for two weeks Q3W	40 pt Phase II, primary endpoints: HI. Trial start: July 2013. Results: June 2015.
04-24 (ONTIME)	MDS, failure after Vidaza or Dacogen, excess blasts	CI, 1,800mg/m^2 for three days Q2W (eight cycles) or Q4W (after eight cycles)	90 pt Phase IIIB, primary endpoint: relationship btw Bm response and survival. Start: Aug 2013. Results Dec 2015.

Source: Edison Investment Research, Clinicaltrials.gov

Exhibit 3: Competitive environment: approved or developmental drugs for lower- and higher-risk MDS

Drug	Company	MoA	Main indication	Status	Route of admin.	Selected relevant data in higher and lower-risk MDS	Reference
Vidaza (azacitidine)	Celgene	HMA	High risk MDS	Approved in all major countries	IV and SC		N/A
Dacogen (decitabine)	Eisai/Astex	HMA	High risk MDS; elderly AML	Approved in US for MDS, EU for elderly AML	IV	Phase I, n=36 Int-2/high MDS failed Vidaza, 7/36 (19.4%) ORR, incl. 3mCR and 2SD, med. OS 7.3 months	ASH 2013 Abs# 2796
Revlimid	Celgene	IMiDs	Low risk, 5q-; MM	Approved worldwide	Oral	Phase II plus pred., n=25 low/Int-1, non-5q- MDS, 5/23 (22%) RBC TI	ASH 2013 Abs# 1506
SGI-110	Otsuka/ Astex	HMA	New or ref. MDS, AML	Phase II	SC	n=93, 74 AML, 19 MDS, 2 CR, 1CRp and 2CRi in AML; 2mCR, 3 HI-E, 1 HI-N and 1 HI-P in MDS (prior HMA)	ASH 2013 Abs# 1548
ARRY-614	Array Biopharma	p38 MAPK and Tie2 inhibitor	Low/Int-1 MDS	Phase I	Oral, qd or bid	n=62, 12/54 evaluable and 9/31 on drug >16 weeks had HI	ASH 2013 Abs# 387
Sapacitabine	Cyclacel Pharma	Nucleoside analogue	Elderly MDS ref. to HMA	Phase II randomised	Oral, qd or bid	n=63; 2 CR, 2 CRp, and 5 major HI; med. OS 8.6-9.7 months	ASH 2013 Abs# 2752
Clolar (clofarabine)	Sanofi/ Genzyme	Second-gen nucleoside analogue	rr ALL, AML etc	Approved for rr ALL	IV daily x5	Phase II w/ cytarabine, n=29, 8/24 (33%) CR/CRp/mCR, 4/24 (17%) had SD, med. OS 4.8 months	ASH 2013 Abs# 1525
Pracinostat (SB939)	MEI Pharma	HDAC inhibitor	New AML and MDS	Phase II	Oral, thrice weekly (TIW)	In pilot Phase II, MDS, w/aza, 7/9 (CR+CRi+PR) incl 7 CR	ASH 2012 ABS# 3821
Telintra (TLK199)	Telik	Glutathione S-transferase Inh.	Lower risk MDS	Phase II	Oral	n=38 low/Int-1 MDS, 11 of 38 (29%) had HI-E; 3 of 11 (27%) had TI	Cancer. 2012, 118:2138-2147
Oral azacitidine (CC-486)	Celgene	HMA	Maintenance Rx in AMLw/ CR	Phase III	Oral	n=53 low/Int-1 MDS; 18/53 (34%) ORR, 13/53 (24.5%) HI, 12/30 (40%) TI>56 d, 7/30 (23.3%) TI>84 d	ASH 2012 Abs# 424
Mocetinostat	Mirati Therapeutics	HDAC inhibitor	Int-2/high MDS	Phase I/II	Oral	n=66 AML and MDS, w/aza., 22 MDS (13/22 (59%, CR+CRi), 6/17 (35%) TI	ASH 2013 Abs# 1550
Vosaroxin	Sunesis Pharm.	Nucleoside analogue	AML or MDS	Phase I/II	IV	Data in MDS pending	N/A

Source: Edison Investment Research. Note: IMiDs = immunomodulatory drugs.

Update: A brand new MoA for rigosertib

New insights into the MoA of rigosertib help to explain certain phenotypic phenomena and provide a new hypothesis for some previous mechanistic questions. In this report we detail some of the evidence that supports this new MoA hypothesis and assert that it could open up some new indications for future development such as pancreatic, colon and lung cancer with molecular tools used to select patients that may derive the most benefit.

Rigosertib was established to be a dual inhibitor of the pathways of polo-like kinase 1 (PLK1) and phosphatidylinositol-3 kinase (PI3K), two kinases involved in the development of many cancers. However, the exact target had been elusive up to now. Recent work conducted by Onconova's scientific founder, Dr E Premkumar Reddy, professor of the Mount Sinai School of Medicine, details of which were presented in a recent webcast, has shown that rigosertib binds to the RBD of Raf. Raf is a protein implicated in the development of various cancers, including melanoma and pancreatic cancer.

Dr Reddy has further shown that rigosertib's binding to the RBD of Raf inactivates Raf and down-regulates several of Raf's downstream signal transduction cascades such as PLK1, providing a molecular mechanism for rigosertib's inhibition of the PLK1. These new findings also indicate that rigosertib binds to the RBD of PI3K and explains how it inhibits the PI3K pathway. As RBD exists in many oncogenes, such as RAF, MEKK and p120GAP, and Ras was frequently mutated in many types of cancer, this new MoA suggests rigosertib could have much broader activity than was previously thought.

Early findings and proposals of MoA

Rigosertib (ON 01910) was discovered in the early 2000s through a series cell-based assays, in which it was shown to inhibit the growth of cancer cells, but not normal ones. Further experimental work revealed that rigosertib arrests cancer cells at the G2/M cell cycle phase, causing DNA destruction, a hallmark of programmed cell death (also referred to as apoptosis).

Rigosertib treated cells form a typical X-shaped chromosomal spindle, a phenomenon known to be a consequence of PLK1 inhibition. As a result, rigosertib was earlier considered to be a PLK1 inhibitor. However, in vitro inhibition of PLK1 phosphorylation was never established, suggesting rigosertib interferes with the PLK1 pathway differently to most other kinase inhibitors, which typically bind to the kinase's ATP pocket, also referred to as the catalytic domain. Rigosertib does inhibit the phosphorylation of another kinase, PI3K, albeit with an IC_{50} in the micromolar (μM) range,[1] suggesting it is a PI3K inhibitor.

One early finding suggested rigosertib is unlikely to be an ATP-competitive, catalytic domain-binding inhibitor because no resistant cell lines could be generated through a series of pass-through assays. Such assays would typically result in resistant cell lines against ATP-competitive, catalytic domain-binding inhibitors because mutations at the kinase catalytic domain could render an inhibitor ineffective. This suggested rigosertib might be an allosteric inhibitor of the kinase, ie it binds to a region outside the catalytic domain. However, the exact target protein and the precise location within the protein to which rigosertib binds remained elusive.

The breakthrough

The recent breakthrough is evidence that rigosertib binds physically to the protein Raf (A-, B- and C-Raf) in a cell lysate "pull-down" experiment. In this study, rigosertib was chemically linked to biotin and used to "fish" proteins inside cells that may bind to rigosertib. Raf was the prominent

[1] Most other PI3K inhibitors have a stronger binding affinity to the enzyme with IC_{50} in the nano- to pico-molar range, or nM to pM.

signal transduction protein that was “pulled down” by rigosertib; other proteins were those involved in transportation, such as various subtypes of heat shock proteins (HSP). However, in vitro kinase assays showed that rigosertib **does not** inhibit the kinase activity of any of the Raf subtypes, suggesting rigosertib’s physical interaction with Raf falls outside the kinase catalytic domain.

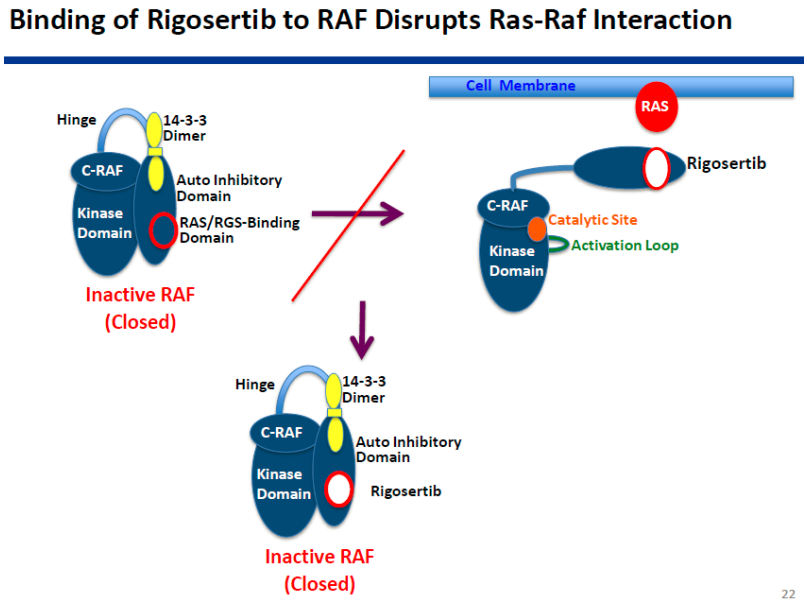
A key experiment that pinpointed the location of rigosertib’s binding to Raf was done with the so-called differential scanning fluorimetry (DSF), a time-saving and convenient technique that analyses binding of small molecules to proteins based on thermodynamic changes (shifts) of proteins before and after they are bound to a molecule.

Traditional small molecule protein-binding assays involve radio-labelling of the small molecule, which can be expensive and tedious to perform. The most stringent assay of small molecule protein-binding is ligand protein co-crystallography, which can be technically demanding. With DSF, rigosertib was found to bind to the N-terminal end, but not the C-terminal end of Raf. Raf’s C-terminal end contains the kinase catalytic domain, whereas the N-terminal end has the Ras-binding domain.

Although the kinase catalytic domain is where the kinase activation or inhibition takes place, the binding of Ras to the RBD regulates the activation or the inhibition of the kinase in cells. This explains the dilemma that rigosertib binds to Raf and inhibits its kinase activity in cells, but not in vitro, because rigosertib achieves this through disruption of Ras binding to RBD of Raf inside cells, but is incapable of inhibiting Raf kinase in vitro because Ras is not present in vitro (Exhibit 4).

An indirect line of evidence that also supported this hypothesis is the finding by an independent group[2] that Raf is involved in PLK1 activation. As noted above, rigosertib treatment causes the X-shaped chromosomal spindle that is the hallmark of PLK1 inhibition, despite the compound never having been found to directly inhibit PLK1. As Raf is required for PLK1 activation and rigosertib inhibits Raf by preventing Ras binding to the RBD of Raf, there is finally a molecular explanation of rigosertib’s effect on PLK1.

Exhibit 4: Proposed mechanism of action for rigosertib



Source: Modified from Varga et al. FEBS J 2010; 277(21):4376-82.

[2] A Mielgo et al., Nature Medicine, 2011, 17:1641-1645.

The evidence

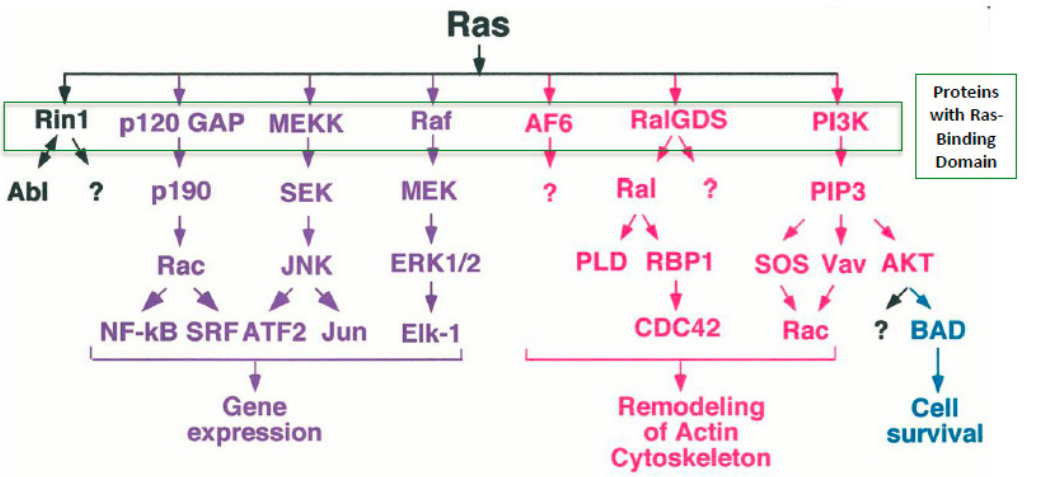
Dr Reddy's lab has recently conducted a series of supporting experiments that showed rigosertib binds to the RBD of Raf and, as a result, inhibits Raf's kinase activity. They have shown that rigosertib 1) binds to the RBD of all subtypes of Raf; 2) interferes with the binding of active Ras with the RBD domain of Raf; 3) blocks growth factor-induced Raf activation; 4) inhibits growth factor-induced Raf heterodimerisation with downstream kinases such as MEK and PLK1; and 5) binds to the RBD domain of other oncogenes, such as RalGDS. Planned additional experiments that could further strengthen this hypothesis include rigosertib's binding to more RBD-containing proteins (Exhibit 5) such as PI3K, MEKK, p120GAP, Rin1 and AF6, in thermal shift assay, rigosertib-Raf co-crystallography and rigosertib's anti-tumour assay in Ras-driven animal models.

The implications

Rigosertib's new proposed MoA (Exhibit 4) helps explain the drug's many observed phenotypic phenomena, such as inhibition of many different kinases inside cells but not in in vitro assays, the inability of generating resistant cell lines and the lack of myelosuppression in humans. Furthermore, it could prove to be a breakthrough in the search for an anti-Ras drug. As one of the most frequently mutated and well-studied oncogenes, Ras proves to be one of the most difficult drug targets because it is not a kinase itself. Traditional drug screening assays are mostly kinase based, which screen thousands to millions of compounds that modulate kinase activity in vitro. As such, approaches focusing on Ras downstream kinases such as RAF and MEK have led to the discovery and eventual approval of drugs such as Tafinlar (dabrafenib, GSK), Zelboraf (vemurafenib, Roche) and Mekinist (trametinib, GSK) for melanoma with a specific mutation in the Raf gene.

A compound that truly inhibits Ras activity in cells could be widely applicable since Ras was found to be mutated or over-expressed in more than 80% of all tumour samples tested (Exhibit 6, overleaf). The evidence provided by Dr Reddy suggests rigosertib could be just such a compound. Most importantly, this new MoA could help Onconova and its partners speed up the development of rigosertib by focusing on Ras-driving cancers and using molecular tools to select patients who will derive the most benefit from the drug. While we recognise that the new MoA has very little impact on the outcome of the upcoming Phase III results of ONTIME, we feel more confident about the drug's usefulness outside the currently pursued indications.

Exhibit 5: Ras signals through multiple effectors



Source: AB Vojtek and CJ Der J. Biol. Chem. 1998: 273:19925-19928

Exhibit 6: Distribution and frequency of Ras mutations in human cancer

Tumour type	Frequency of mutation		
	H-Ras	N-Ras	K-Ras
Biliary tract adenocarcinoma	0%	2%	**35%**
Bladder transitional cell carcinoma	**12%**	2%	4%
Colon adenocarcinoma	0%	2%	**36%**
Colon adenoma	0%	0%	**22%**
AML (acute myelogenous leukaemia)	0%	**12%**	4%
CMML (chronic myelomonocytic leukaemia)	1%	**15%**	**11%**
JMML (juvenile myelomonocytic myeloid leukaemia)	0%	**19%**	7%
Lymphoma	0%	**10%**	7%
Liver-hepatocellular carcinoma	0%	4%	4%
Lung-large cell carcinoma	4%	4%	**21%**
Lung-non-small cell carcinoma	0%	1%	**16%**
Lung-squamous cell carcinoma	1%	0%	6%
Pancreatic ductal adenocarcinoma	0%	1%	**69%**
Pancreatic endocrine tumour	0%	**75%**	1%
Prostate adenocarcinoma	6%	2%	8%
Malignant melanoma	1%	**20%**	2%
Malignant fibrous histiocytoma-pleomorphic sarcoma (soft tissue)	**15%**	2%	**16%**
Testis seminoma	**17%**	0%	0%
Thyroid-anaplastic carcinoma	4%	**17%**	9%
Thyroid-hurthle cell carcinoma	**16%**	4%	0%

Source: A Fernandez-Medarde and E Santos Genes & Cancer 2011, 2:344-358

Sensitivities

The investment case rests on the successful execution of the clinical trials of rigosertib, including the pivotal Phase III ONTIME and the Phase II lower-risk MDS trial, together with support from partners Baxter and SymBio. The key risk to our investment thesis is a negative outcome of the pivotal ONTIME Phase III trial and any subsequent decisions by the partners, particularly Baxter. Onconova is well financed with sufficient cash to last into 2015, but a negative ONTIME outcome could force the company to raise additional funds to support operations beyond 2015. A positive ONTIME outcome would greatly improve financial strength, as Onconova would trigger up to $100m milestone payments from its two partners.

Valuation

We have valued Onconova based on a DCF model that examines revenues, possible milestone payments and royalties over rigosertib's lifecycle (from approval to patent expiry in 2026/27) based on forecast sales in second-line, higher-risk and first-line, lower-risk MDS, with success probabilities of 65% and 35% applied to these two indications. This approach yields an intrinsic value of $476m, equivalent to $22.3 per share (basic) or $20.7 per share (fully diluted).

Financials

Onconova has guided to ending 2013 with of $98m of cash (our model suggests $99m), which should be sufficient to support operations into 2015 without including any milestone payments from partners. We estimate cash utilisation will be c $39m in 2014 and that Onconova will end the year with cash of $59m, assuming a risk-adjusted $50m rigosertib milestone payment (net of $25m paid to Temple University). Our model, which remains unchanged, is shown in Exhibit 7.

Exhibit 7: Financial summary

$m	2011	2012	2013e	2014e
Year end 31 December	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS				
Revenue	1.5	46.2	3.3	50.0
Cost of Sales	0.0	0.0	0.0	0.0
Gross Profit	1.5	46.2	3.3	50.0
EBITDA	(27.9)	(44.7)	(77.8)	(58.5)
Operating Profit (before amort. and except.)	(27.6)	(22.3)	(69.0)	(50.1)
Intangible Amortisation	0.0	0.0	0.0	0.0
Exceptionals	1.3	0.4	(0.1)	(0.1)
Other	0.0	0.6	0.5	1.2
Operating Profit	(26.3)	(21.3)	(68.5)	(49.0)
Net Interest	(0.0)	(8.6)	0.0	0.0
Profit Before Tax (norm)	(27.6)	(30.3)	(68.5)	(48.9)
Profit Before Tax (FRS 3)	(26.3)	(29.9)	(68.5)	(49.0)
Tax	0.0	0.0	0.4	0.0
Profit After Tax (norm)	(27.6)	(30.3)	(68.1)	(48.9)
Profit After Tax (FRS 3)	(26.3)	(29.9)	(68.1)	(49.0)
Average Number of Shares Outstanding (m)	2.14	2.21	7.97	22.00
EPS - normalised ($)	(14.79)	(15.51)	(8.86)	(2.34)
EPS - normalised fully diluted ($)	(14.79)	(15.51)	(8.86)	(2.34)
EPS - (IFRS) ($)	(12.30)	(13.55)	(8.54)	(2.23)
Dividend per share (c)	0.0	0.0	0.0	0.0
Gross Margin (%)	100.0	100.0	100.0	100.0
EBITDA Margin (%)	(1877.3)	(96.7)	(2339.8)	(117.1)
Operating Margin (before GW and except.) (%)	(1854.3)	(48.2)	(2075.9)	(100.2)
BALANCE SHEET				
Fixed Assets	0.6	0.6	(0.1)	1.3
Intangible Assets	0.0	0.0	0.0	0.0
Tangible Assets	0.6	0.6	(0.1)	1.3
Investments	0.0	0.0	0.0	0.0
Current Assets	3.8	83.3	105.9	59.0
Inventory	0.0	0.0	0.0	0.0
Accounts receivable, net	0.0	0.0	0.0	0.0
Cash and cash equivalents	2.7	81.5	99.0	59.0
Other	1.1	1.7	6.8	0.0
Current Liabilities	(12.1)	(25.4)	(17.4)	(21.2)
Creditors	(12.1)	(25.4)	(17.4)	(21.2)
Short term borrowings	0.0	0.0	0.0	0.0
Long Term Liabilities	(10.8)	(15.5)	(14.1)	(14.1)
Deferred revenue, long term	(10.7)	(15.4)	(14.0)	(14.0)
Other long term liabilities	(0.1)	(0.0)	(0.0)	(0.0)
Net Assets	(18.4)	43.0	74.3	25.0
CASH FLOW				
Operating Cash Flow	(14.2)	1.6	(62.5)	(39.3)
Net Interest	(0.0)	0.0	0.0	0.0
Tax	0.0	0.0	0.0	0.0
Capex	(0.2)	(0.3)	(0.6)	(0.3)
Acquisitions/disposals	0.0	0.0	0.0	0.0
Financing	9.8	77.5	79.7	0.5
Dividends	0.0	0.0	0.0	0.0
Net Cash Flow	(4.6)	78.8	16.5	(39.0)
Opening net debt/(cash)	(7.3)	(2.7)	(81.5)	(99.0)
HP finance leases initiated	0.0	0.0	0.0	0.0
Other	0.0	0.0	1.0	(1.0)
Closing net debt/(cash)	(2.7)	(81.5)	(99.0)	(59.0)

Source: Edison Investment Research, Onconova accounts

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