EDISON

Context Therapeutics

R&D update

R&D webinar highlights CTIM-76's potential

Pharma and biotech

Context Therapeutics' April R&D webinar included takeaways from its poster presentation on CTIM-76 preclinical data at the AACR Annual Meeting in April 2023. The presentation highlighted the development of Context's CLDN6 program and rationale for selecting CTIM-76 (a CLDN6xCD3 targeting bispecific antibody) as its new lead candidate (following the recent discontinuation of the ONA-XR program). We remind readers that while the therapeutic benefits of targeting CLDN6 (expressed on a variety of malignant tumor cells but rarely in healthy tissue) are well recognized, development hitherto has been hampered by a lack of selectivity and off target toxicities. Preclinical data presented by Context suggest that CTIM-76 selectively binds to CLDN6 with a potentially beneficial safety profile. The latest Phase I data in solid tumors from BioNTech's CLDN6 CAR-T asset BNT211 (33% overall response rate, ORR; n=21) highlight the potential of a CLDN6-targeting therapy and are an encouraging read-across for this asset class, including CTIM-76.

Year end	Revenue ($m)	PBT* ($m)	EPS* ($)	Operating cash flow ($m)	P/E (x)	Yield (%)
12/21	0.0	(10.6)	(3.74)	(10.5)	N/A	N/A
12/22	0.0	(14.8)	(0.93)	(15.4)	N/A	N/A

Note: *PBT and EPS are normalized, excluding exceptional items.

CTIM-76 preclinical data encouraging

As part of its 17 April R&D webinar, Context presented the development pathway for its CLDN6 program and the rationale for selecting CTIM-76 as its lead candidate. The preclinical in vitro data presented highlighted CTIM-76's high selectivity and specificity for CLDN6 and maximal T-cell induced lysis at low doses (vs other tested bispecific formats), without resulting in excessive cytokine production (suggesting a broad therapeutic window). Although early in its development journey, we believe CTIM-76's competitive edge could come from its superior selectivity for CLND6 (>1,000x CLDN9) and ease of administration (vs CAR-Ts for example). Investigational new drug (IND) enabling studies are ongoing, with IND filing planned for Q124. We expect the initial clinical focus to be on ovarian and testicular cancer, given the high CLDN6 expression in these tumors.

CLDN6's potential as a target externally validated

Encouraging Phase I/II follow-up data presented by category leader BioNTech on its CLDN6 CAR-T asset BNT211 in solid tumors in September 2022 (ORR of 33% for the 21-patient cohort and a higher 57% for a subset (n=7) of testicular cancer patients) provide early validation for CLDN6 as a promising target in certain malignant tumors. Market interest in the category has been growing, reflected in the April 2023 $158m Series B financing received by TORL BioTherapeutics for its claudin programs, which include TORL-1-23, an antibody drug conjugate (ADC) targeting CLDN6, currently in Phase I clinical trials.

Valuation: Under review

Following Context's decision (March 2023) to cease development of ONA-XR and focus its resources on CTIM-76, we have placed our estimates and valuation under review. We will present our revised forecasts and valuation in due course.

19 April 2023

Price	**$0.65**
Market cap	**$10.4m**
Net cash ($m) at 31 December 2022	35.5
Shares in issue	15.97m
Free float	91%
Code	CNTX
Primary exchange	Nasdaq
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	6.7	(3.2)	(59.3)
Rel (local)	0.6	(8.4)	(56.9)
52-week high/low		$2.34	$0.56

Business description

Context Therapeutics is a clinical-stage biopharma company developing therapeutics for solid tumors. Following a strategic pivot, the core pipeline focus will be on CTIM-76, a selective Claudin 6 (CLDN6) x CD3 bispecific antibody for CLDN6 positive tumors, which is in preclinical development with plans for an IND application filing in Q124.

Next events

Q123 results	May 2023
CTIM-76 IND filing	Q124

Analysts

Dr. Adam McCarter +44 (0)20 3077 5700

Jyoti Prakash, CFA +44 (0)20 3077 5700

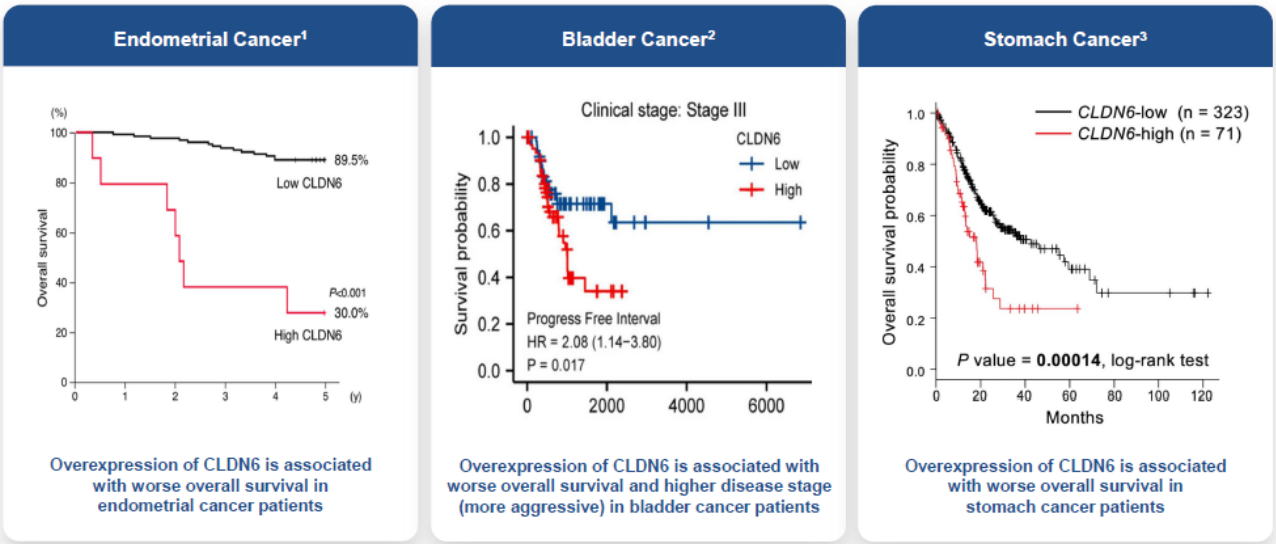
heathcare@edisongroup.com

Edison profile page

CLDN6: An exciting therapeutic target

CLDN6 is a member of the claudin family of tight junction proteins (27 members exist in humans), which play an important role in cell polarity, permeability and adhesion, and participate in the regulation of cell proliferation and differentiation. A unique aspect of CLDN6 is that it has been found to be upregulated in several malignant tumors such as endometrial, ovarian, lung and gastric cancers, but is rarely expressed in adult healthy tissue. However, expression appears to be heterogeneous across cancer subtypes and seems directly related to tumor grade (the higher the grade, the higher the CLDN6 enrichment). According to data presented by Context in its R&D webinar, CLDN6 expression can range from 2% to 95% across indications, with testicular and ovarian cancer reported to have the highest expression (95% and 54–55%, respectively). Importantly, studies have indicated that a higher level of CLDN6 expression leads to poorer prognosis in terms of overall survival and progression-free survival (Exhibit 1). A 2020 study assessing CLDN6 expression in endometrial cancer tissue resected from patients concluded that the five-year survival rate in the high CLDN6 expression group was 30%, compared to 90% for the low expression group. This makes CLDN6 an attractive therapeutic target for these indications, in our view.

Exhibit 1: High CLDN6 expression associated with poorer prognosis across a range of cancers



Source: Context Therapeutics R&D webinar presentation, April 2023. Notes: 1. Kojima, Cancers, 2020; 2. Zhang, Front. Cell Dev. Biol., 2021; 3. Kohmoto, Gastric Cancer, 2020

While several pharmaceutical companies are developing CLDN6-targeting antibodies, most candidates are in early-stage clinical or preclinical development (Exhibit 2). Historically, development has been hampered by challenges in accurate selectivity due to CLDN6's close resemblance to other claudins (such as CLDN9, CLDN4 and CLDN6), which are present in healthy cells. In particular, CLDN9, which differs from CLDN6 by only three amino acids in the extracellular domain, is crucial to maintaining normal hearing and a healthy gut, highlighting the importance of accurate targeting.

Exhibit 2: Ongoing Claudin 6 development programs

Company	Program name	Antibody format	Development phase	Indications	Comments
BioNTech	BNT211	CLDN6 CAR-T +CARVac	Phase I/II	Relapsed or refractory advanced solid tumors	Initial data presented in April 2022 (American Association for Cancer Research (AACR)), with an update in September 2022 (ESMO). Received priority medicines (PRIME) designation from the EMA in June 2022 for testicular cancer.
BioNTech	BNT142	CLDN6xCD3 mRNA encoded bispecific antibody	Phase I	Multiple solid tumors	Initiated Phase I development in mid-2022.
Amgen	AMG794	CLDN6xCD3 bispecific T-cell engager (BiTE)	Phase I	Non-small cell lung cancer, epithelial ovarian cancer	Candidate first presented in April 2022 (AACR); Phase I development initiated in Q123
Guangzhou Medical University	N/D	CLDN6-CAR-NK	Phase I	Ovarian cancer, testicular cancer, endometrial cancer	Engineered to express IL7/CCL19 and/or SCFVs against PD1/CTLA4/Lag3. Initiated Phase I trials in June 2022.
Daiichi	DS-9606a	CLDN6 + CLDN9 antibody drug conjugate	Phase I	Advanced solid tumors	Phase I trials initiated in mid-2022.
Chugai	SAIL66	CLDN6xCD3 bispecific antibody	Phase I	Advanced solid tumors	Phase I trials initiated in February 2023
TORL BioTherapeutics	TORL-1-23	CLDN6 antibody drug conjugate	Phase I	Advanced solid tumors, ovarian cancer, endometrial cancer, non-small cell lung cancer	Phase I trial initiated in November 2021. Received $158m in Series B financing in April 2023 to advance development pipeline.
Preclinical					
Context Therapeutics	CTIM-76	CLDN6xCD3 bispecific antibody	Preclinical	Ovarian cancer, testicular cancer	IND submission planned for Q124.
Xencor	N/D	CLDN6xCD3 bispecific antibody	Preclinical	Ovarian cancer	Reported positive preclinical data at AACR conference in April 2021; IND filing expected in 2023.
I-Mab	TJ-C64B	CLDN6x4IBB bispecific antibody	Preclinical	Ovarian cancer, other CLDN6 expressing tumors	Initial data presented April 2021 (AACR). IND filing expected in H223.

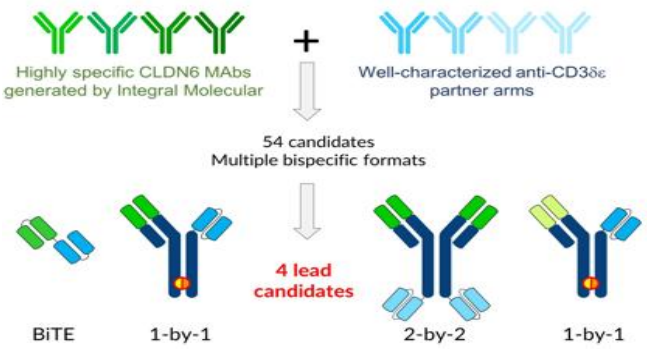
Source: Context Therapeutics, ClinicalTrials.gov, Edison Investment Research

CTIM-76: Shortlisted as clinical candidate for its high CLDN6 selectivity, potency and safety profile

Strong potency and safety…

As previously noted, Context's partner Integral Molecular had tested a library of 54 CLDN6xCD3 bispecific formats and combinations with high CLDN6 specificity, of which four lead candidates were shortlisted for further testing, comprising two one-by-one formats, including CTIM-76 (one binding site each with CLDN6 and CD3), one two-by-two format (two binding sites each with CLDN6 and CD3) and one BiTE platform developed by Amgen (one binding site each with CLDN6 and CD3 but without the typical IgG scaffold), see Exhibit 3.

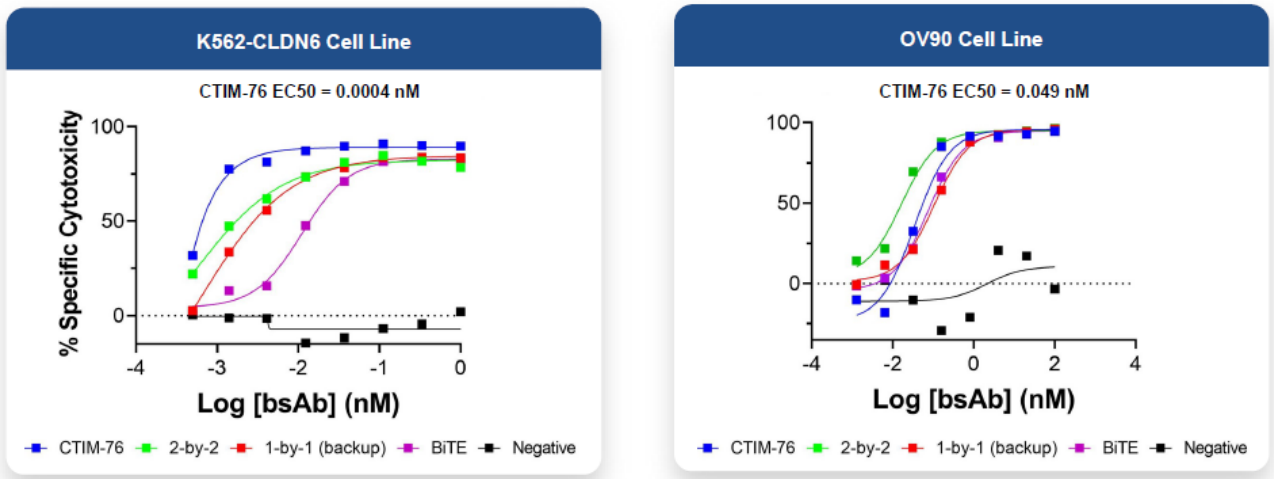
Exhibit 3: Integral Molecular CLND6 candidate selection process



Source: Context Therapeutics R&D webinar presentation, April 2023

CTIM-76 was selected as the final candidate for future development, based on higher potency and lower levels of cytokine release versus other tested bispecific constructs. CTIM-76 demonstrated higher or similar activity versus the other bispecific formats in both high CLDN6 expressing (K562 CLDN6) and medium CLDN6 expressing (OV90) cell lines (Exhibit 4).

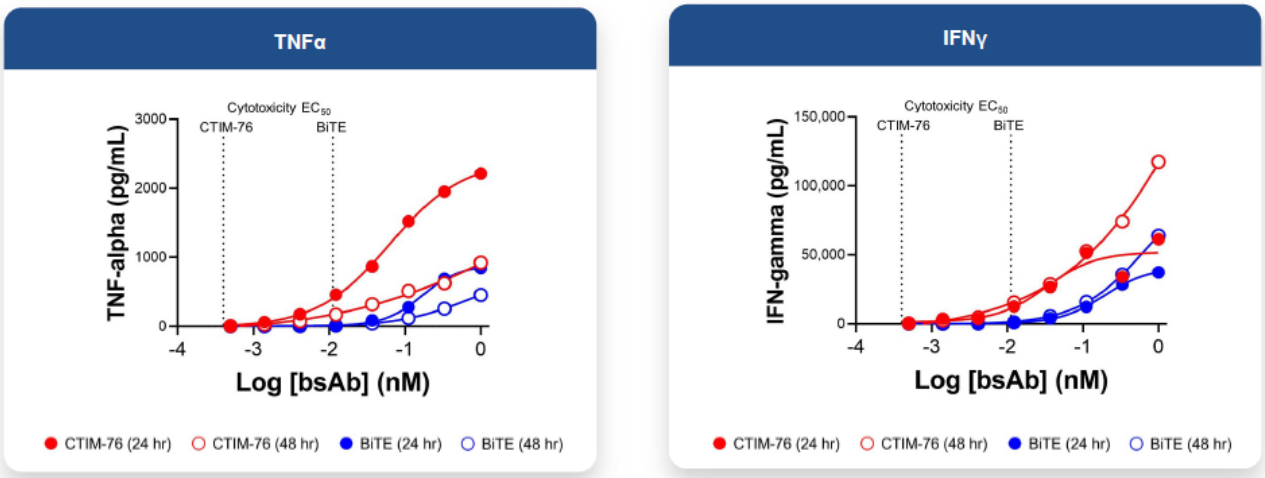
Exhibit 4: CTIM-76 demonstrated higher potency in cell death assays



Source: Context Therapeutics R&D webinar presentation, April 2023

Importantly, data presented by Context demonstrated that this level of activity can be achieved at extremely low concentrations (picomolar) based on CNDL6 expression levels (tEC$_{50}$ value of 0.0004nM for the high CNDL6 expressing line). This meant that in a cytokine release profiling test (Exhibit 5), CTIM-76 was able to induce cytotoxic T-cell activation without drastically increasing cytokine production compared to a BiTE molecule with identical binder arms, indicating a potentially broad therapeutic window. Cytokine release syndrome (CRS) is an adverse side-effect experienced in some patients in response to immunotherapy. Therefore, in our view, the lower selected therapeutic dose may potentially reduce the risk of CRS, although this will need to be confirmed in clinical trials.

Exhibit 5: CTIM-76 offers a broad therapeutic window

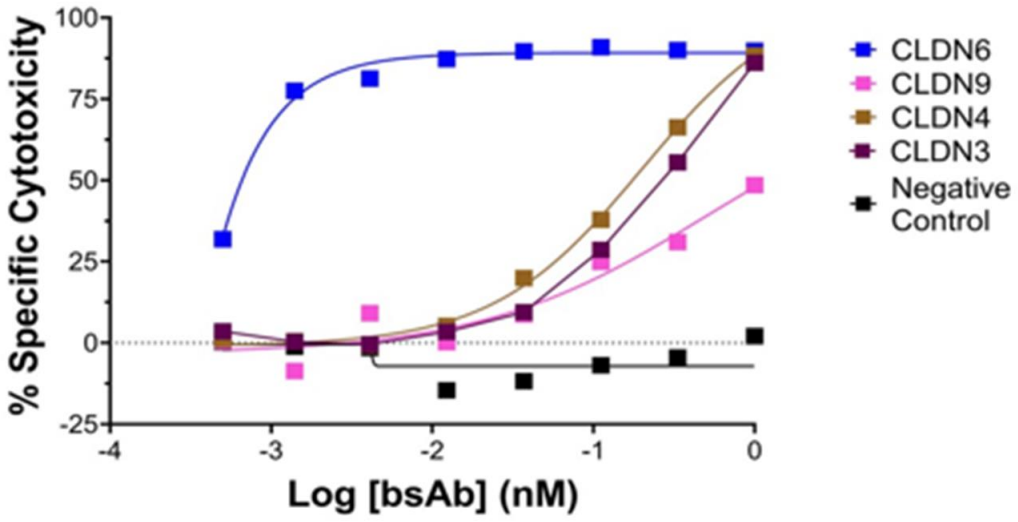


Source: Context Therapeutics R&D webinar presentation, April 2023

…combined with class-leading CLDN6 specificity

As highlighted previously, development of CLDN6-targeting therapies has been hampered due to CLDN6's strong resemblance to other claudins, resulting in off-target effects and toxicities (Astellas' ASAP1650/Ganymed's IMAB027 is a case in point where Phase II development was terminated due to the drug's high affinity for CLDN9). In contrast, CTIM-76 has shown meaningfully high specificity and cytotoxicity for CLDN6 at various doses in cell lines expressing different claudins (Exhibit 6). Management had earlier indicated that CTIM-76 is more than 1,000x more selective for CLDN6 than CLDN9. To our knowledge, this is higher than other drugs under development and should provide Context with a key competitive advantage if the results are reproduced in larger studies.

Exhibit 6: CTIM-76 cytotoxicity strongly preferential for CLDN6



Source: Context Therapeutics R&D webinar presentation, April 2023

Growing market interest in CLDN6's commercial potential

In September 2022, BioNTech, which we believe is the current leader in this category, presented encouraging follow-up data on its CLDN6 CAR-T asset BNT211 from its ongoing Phase I/II study, in patients with relapsed or refractory advanced solid tumors. Data were presented for 21 evaluable patients (testicular, ovarian and endometrial, as well as sarcoma, fallopian tube and gastric cancer),

who were treated across two dose levels (dose 1: $1x10^7$ CAR-T cells, n=7; and dose 2: $1x10^8$ CAR-T cells, n=15) alone or combined with CARVac (a vaccine designed to enhance T-cell activity and persistence through periodic infusions following CAR-T treatment). The overall response rate (ORR) for the cohort was 33%, with a disease control rate (DCR) of 67%, with one complete response, six partial responses and seven patients with stable disease. The results in patients with testicular cancer treated with dose 2 following lymphodepletion (n=7) were even more pronounced: an ORR of 57% and DCR of 85%, with one complete response, three partial responses and two with stable disease. More importantly, adverse events, including CRS and dose-limiting toxicities were manageable, a key issue in the development of this class of therapeutics in the past. We believe that the promising efficacy data, particularly in patients with testicular cancer (and an acceptable safety profile) presented by BioNTech have increased market interest in this novel therapeutic target, which bodes well for new and potentially improved assets under development. Context asserts that CTIM-76's easier manufacturability and administration versus CAR-Ts also offers a competitive advantage.

A key indicator of rising market interest in CLDN6 was the recent $158m fund-raising by TORL BioTherapeutics to advance its development pipeline, including the Phase I asset TORL-1-23, an ADC targeting CLDN6. Interestingly, Bristol Myers Squibb is one of the investors in the Series B financing, potentially indicating big pharma interest in the target.

CTIM-76 development pathway

Context has initiated IND-enabling studies with CTIM-76 and has indicated that it is on track for an IND application in Q124. Lonza is undertaking manufacturing of the drug substance and drug product following an agreement signed in November 2022. While target indications for clinical studies have not been officially communicated, we expect the initial areas of interest will be ovarian cancer, testicular cancer and non-small cell lung cancer, all indications with high CLDN6 prevalence (Exhibit 7). We note that there are more clinically advanced CLDN6xCD3 bispecific antibodies in development, notably BioNTech's BNT142 and Amgen's AMG 794, which are currently undergoing Phase I studies. However, Context argues that the structure and design of its candidate allows superior activity and binding to CLDN6 (more than 1,000x versus c 7x and c 630x for BNT142 and AMG 794, respectively) which, if proved in clinical studies, could offer market differentiation.

Exhibit 7: Potential target indications for CTIM-76

Initial indications of interest based on:
- CLDN6 prevalence
- Patient population size
- Observed clinical responses
- Eligibility for Orphan Designation

Selected Cancer indications	Incidence	R/R Incidence	CLDN6 Positive	Patient Population Based on R/R Incidence
Testicular	9,910	400	95%	380
Ovarian	19,900	12,800	54-55%	6,982
NSCLC	201,229	110,653	6-50%	35,221

Source: Context Therapeutics R&D webinar presentation, April 2023

The discontinuation of the ONA-XR program, as per management guidance should allow Context to extend its cash runway late FY24 (FY22 cash burn of $14.2m; y/e cash balance of $35.5m), which we expect to be sufficient to initiate the Phase I clinical trial for CTIM-76. However, additional funding would be required to progress the asset further through the clinic and management has communicated that it will explore all options, including external fund raising, partnership(s) or asset sale.

Valuation

Our forecast and valuation for Context are currently on hold, following the company's recent decision to cease development of its ONA-XR program and focus exclusively on CTIM-76. We will present our revised forecasts and valuation in due course.

Exhibit 8: Financial summary

$000s	2020	2021	2022
31-December	US GAAP	US GAAP	US GAAP
INCOME STATEMENT			
Revenue	0	0	0
Cost of Sales	0	0	0
Gross Profit	0	0	0
Research and Development Expenses	(1,642)	(6,893)	(7,591)
Sales, General and Administrative Expenses	(931)	(3,633)	(7,790)
EBITDA	(2,572)	(10,526)	(15,381)
Operating profit (before amort. and excepts.)	(2,572)	(10,526)	(15,381)
Amortisation of acquired intangibles	0	0	0
Exceptionals	0	0	0
Share-based payments	0	0	0
Reported operating profit	(2,572)	(10,526)	(15,381)
Net Interest	(661)	(64)	547
Joint ventures & associates (post tax)	0	0	0
Exceptionals	9,878	133	(2)
Profit Before Tax (norm)	(3,233)	(10,590)	(14,834)
Profit Before Tax (reported)	6,644	(10,457)	(14,836)
Reported tax	0	0	0
Profit After Tax (norm)	(3,233)	(10,590)	(14,834)
Profit After Tax (reported)	6,644	(10,457)	(14,836)
Minority interests	0	0	0
Discontinued operations	0	0	0
Net income (normalised)	(3,233)	(10,590)	(14,834)
Net income (reported)	6,644	(10,457)	(14,836)
Average Number of Shares Outstanding (m)	0	3	16
EPS - basic normalised ($)	(9.28)	(3.74)	(0.93)
EPS - normalised fully diluted ($)	(9.28)	(3.74)	(0.93)
EPS - basic reported ($)	19.07	(3.69)	(0.93)
Dividend ($)	0	0	0
BALANCE SHEET			
Fixed Assets	118	0	112
Intangible Assets	0	0	0
Tangible Assets	0	0	0
Investments & other	118	0	112
Current Assets	350	51,306	37,854
Stocks	0	0	0
Debtors	0	0	0
Cash & cash equivalents	341	49,686	35,497
Other	9	1,620	2,356
Current Liabilities	(9,548)	(3,033)	(3,208)
Creditors	(2,708)	(1,826)	(936)
Tax and social security	0	0	0
Short term borrowings	(5,884)	0	0
Other	(956)	(1,207)	(2,271)
Long Term Liabilities	(69)	0	102
Long term borrowings	(69)	0	102
Other long-term liabilities	0	0	0
Net Assets	(9,150)	48,272	34,860
Convertible preferred stock	(7,771)	0	0
Minority interests	0	0	0
Shareholders' equity	(16,921)	48,272	34,860
CASH FLOW			
Operating Cash Flow	(2,572)	(10,526)	(15,381)
Working capital	1,318	(2,225)	(278)
Exceptional & other	219	3,951	2,031
Tax	0	0	0
Net operating cash flow	(1,035)	(8,799)	(13,628)
Capex	0	(250)	(537)
Acquisitions/disposals	0	0	0
Net interest	0	0	0
Equity financing	0	58,394	0
Dividends	0	0	0
Other	0	0	0
Net Cash Flow	(1,035)	49,345	(14,165)
Opening net debt/(cash)	21,742	13,384	(49,686)
FX	0	0	0
Other non-cash movements	9,393	13,725	0
Closing net debt/(cash)	13,384	(49,686)	(35,521)

Source: Company reports, Edison Investment Research

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London | New York | Frankfurt
20 Red Lion Street
London, WC1R 4PS
United Kingdom