EDISON

Context Therapeutics

Pipeline update

CTIM-76 selected as clinical CLDN6 candidate

Pharma & biotech

In an encouraging pipeline development, Context Therapeutics has announced the selection of a final clinical candidate for its second R&D program, a CLDN6xCD3 bispecific antibody. The nominated candidate CTIM-76, which was introduced at the recent R&D webinar, was selected from partner Integral Molecular's CLDN6xCD3 library for its high CLDN6 binding and specificity and strong safety profile to date (low immunogenicity risk) at the selected dose. We reiterate that the therapeutic benefits of targeting CLDN6 (expressed on a variety of malignant tumor cells but rarely in healthy tissue) are well recognized, although development has been challenged by a lack of selectivity. Context asserts that its CLDN6 candidate has superior selectivity and activity, presenting a compelling upside case, provided there is successful clinical progression.

Year end	Revenue ($m)	PBT* ($m)	EPS* ($)	DPS ($)	P/E (x)	Yield (%)
12/20	0.0	(3.2)	(9.28)	0.0	N/A	N/A
12/21	0.0	(10.6)	(3.74)	0.0	N/A	N/A
12/22e	0.0	(18.1)	(1.13)	0.0	N/A	N/A
12/23e	0.0	(27.4)	(1.72)	0.0	N/A	N/A

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

CLDN6: A promising therapeutic target

CLDN6, a protein coding gene and part of the claudin family of tight junction proteins, is enriched in several malignant tumors such as ovarian, lung and gastric cancers, but is rarely expressed in adult healthy tissue. However, development against this target has been stymied by challenges in accurate selectivity due to CLDN6's structural similarity to other claudins such as CLDN9 and CLDN4, both of which are also expressed in healthy tissue. Although several candidates are under development, Context argues, based on preclinical data, that its bispecific antibody displays superior CLDN6 selectivity and activity compared to competitors.

CTIM-76 claims higher selectivity and safety

Encouraging Phase I/II follow-up data presented by category leader BioNTech on its CLDN6 CAR-T asset BNT211 has established proof of concept for CLDN6 as an effective target in certain malignant tumors. As part of its R&D webinar, Context presented compelling pre-clinical data on the high selectivity and specificity of its selected CLDN6xCD3 candidate CTIM-76 for CLDN6 and well as maximal T-cell induced lysis at the selected dose, without resulting in excessive cytokine production (demonstrating high efficacy and safety). Context has commenced IND-enabling studies and we expect the initial clinical focus to be on ovarian and testicular cancer, given the high CLDN6 expression in these tumors and clinical PoC via BNT211.

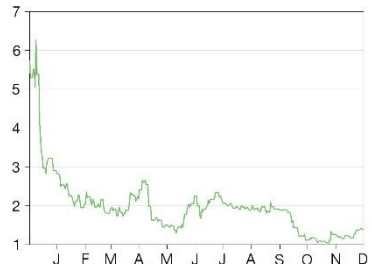
Valuation: Maintained at $146.5m or $9.18/basic share

Although we view the CLDN6 candidate finalization as a positive step, we await the selection of a target indication and initiation of clinical trials to incorporate the program in our valuation. We keep our valuation at $146.5m ($9.18 per basic share) but note the upside potential on CTIM-76's transition to the clinic, anticipated in 2024.

2 December 2022

Price	**$1.4**
Market cap	**$22m**
Net cash ($m) at 30 September 2022	39.4
Shares in issue	15.97m
Free float	67%
Code	CNTX
Primary exchange	Nasdaq
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	10.4	(27.0)	(80.7)
Rel (local)	4.4	(28.9)	(78.7)
52-week high/low		$6.3	$1.0

Business description

Context Therapeutics is a clinical-stage women's oncology company. Lead candidate ONA-XR is a 'full progesterone receptor antagonist currently being evaluated in three Phase II and one Phase Ib/II clinical trial in hormone-driven breast, endometrial and ovarian cancer. The other asset is a bi-specific monoclonal antibody, CLDN6xCD3, with the selected candidate CTIM-76 undergoing IND-enabling studies (IND submission is planned for Q124).

Next events

Phase II readout in HR+/HER2- mBC (ONA-XR+fulvestrant)	December 2022
Updated data from the Phase II trial in endometrial cancer	Mid-2023
ELONA trial Phase Ib data	Q423

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CLDN6: An exciting therapeutic target

CLDN6 is a member of the claudin family of tight junction proteins (27 members 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, the 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 December 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. 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 stood at 30%, compared to 90% for the low expression group. This makes CLDN6 an attractive therapeutic target for these indications, in our view.

While several pharmaceutical companies are developing CLDN6 targeting antibodies, most candidates are in early-stage clinical or preclinical development (Exhibit 1). Historically, development has been hampered by challenges in accurate selectivity due to CLDN6's close resemblance to other claudins, 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 1: Ongoing Claudin-6 development programs

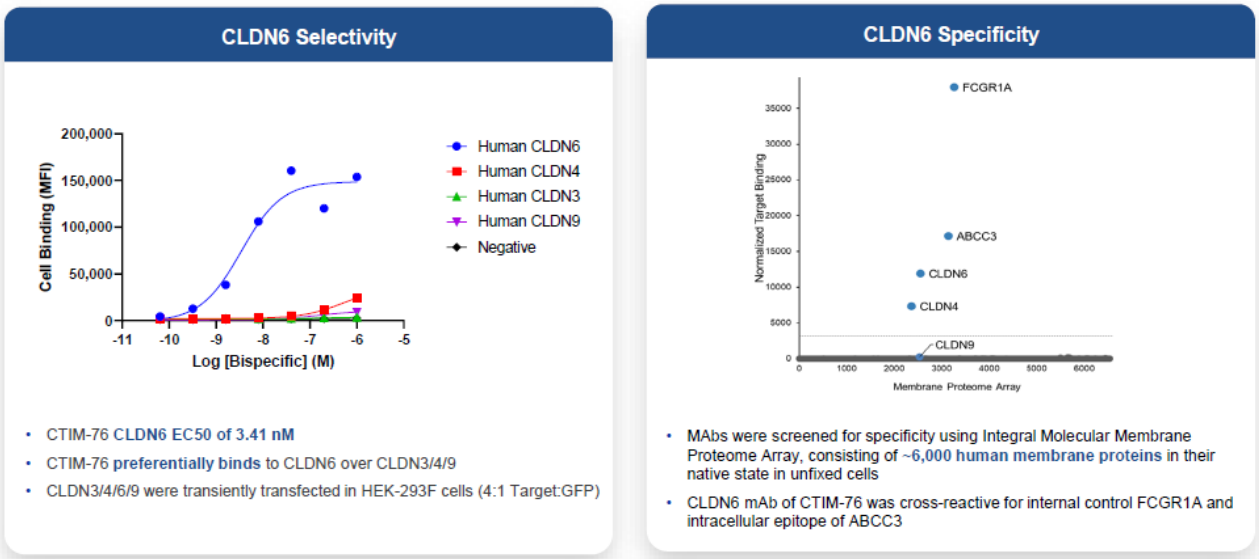
Company	Program name	Antibody format	Development phase	Indications	Comments
BioNTech	BNT211	CLDN6 CAR-T	Phase I/II	Relapsed or refractory advanced solid tumors	Initial data presented in April 2022 (American Association for Cancer Research (AACR)), with an update in September 2022 (ESMO). Received Priority Medicines (PRIME) designation from 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); expected to initiate Phase I development in December 2022.
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 + DXd antibody drug conjugate	Phase I	Advanced solid tumors	Phase I trials initiated in mid-2022.
Preclinical					
Context Therapeutics	CTIM-76	CLDN6xCD3 bispecific antibody	Preclinical	Gynecological cancers	IND submission planned for Q124.
Xencor	N/D	CLDN6Xcd3 bispecific antibody	Preclinical	Ovarian cancer	Reported positive preclinical data at AACR conference in April 2021; timeline for clinical progression not disclosed.
I-Mab	TJ-C64B	CLDN6X4IBB bispecific antibody	Preclinical	Ovarian cancer, other CLDN6 expressing tumors	Initial data presented April 2021 (AACR). IND filing is expected in H223.

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

CTIM-76: Selected for its high CLDN6 selectivity and strong safety profile

In its April 2022 R&D webinar, Context had indicated that partner Integral Molecular had tested a library of 54 CLDN6xCD3 combinations, of which 12 candidates were shortlisted for further testing at that time. Of these, CTIM-76 has now been selected as the final candidate for future development, with in-vitro data presented by the company highlighting the significantly higher selectivity and specificity of CTIM-76 for CLDN6 over other claudins (Exhibit 2).

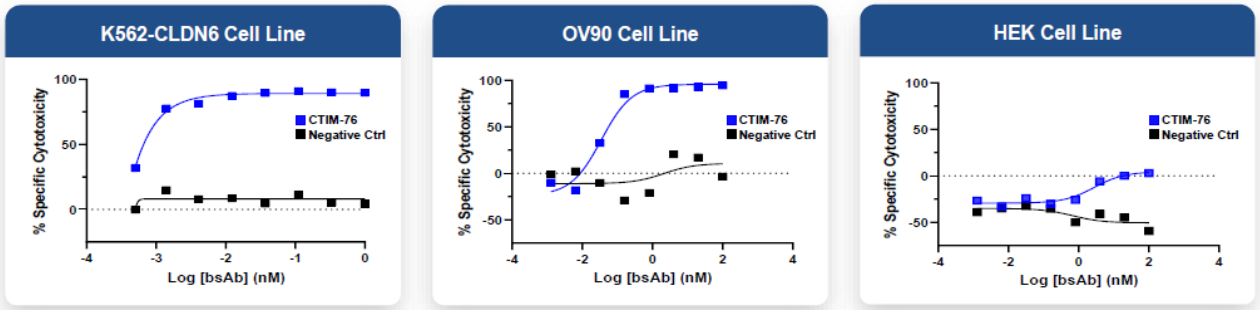
Exhibit 2: CTIM-76's selectivity and specificity for CLDN6



Source: Context Therapeutics R&D webinar presentation, December 2022

Data presented by the company also highlighted that T-cell mediated tumor destruction (lysis), which underscores the mechanism of action for Context's bispecific antibody (BsAb), could be achieved at extremely low concentrations (picomolar) on cells where CLDN6 is highly expressed; that is, the higher the CLDN6 expression, the higher the effectiveness of the cytotoxic T-cell response. For the high CLDN6 expressing K562 cell line, the EC_{50} value stood at 0.0004nM versus 2.79nM for the low CLDN6 expressing HEK cell line, representing a potentially broad and differentiating therapeutic window for CTIM-76 (Exhibit 3).

Exhibit 3: T-cell mediated lysis is directly linked to CLDN expression

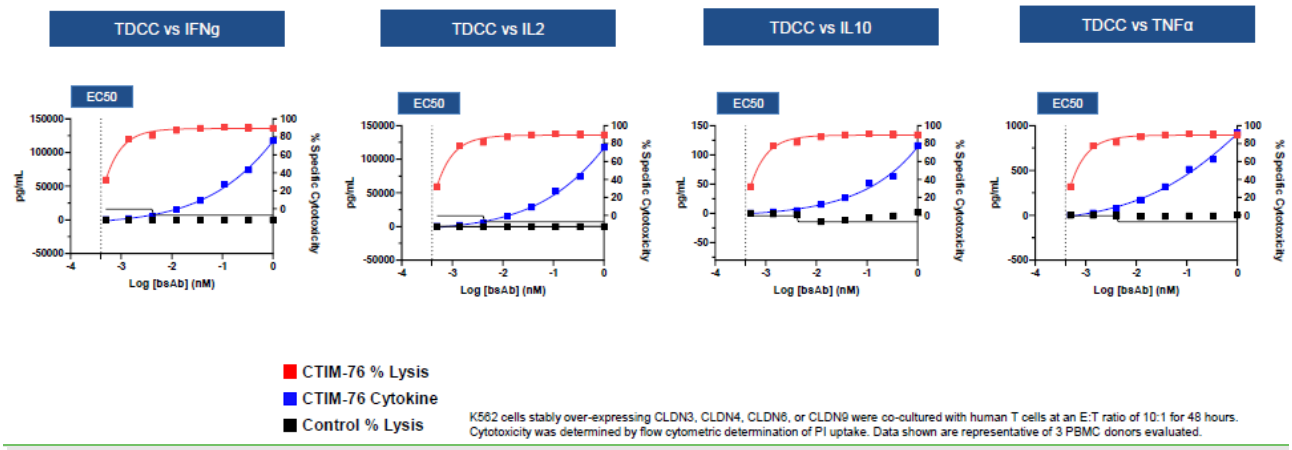


	K562-CLDN6	OV90	HEK
CLDN6 Expression	High	Medium	Low
CTIM-76 (EC50)	0.0004 nM	0.049 nM	2.79 nM

Source: Context Therapeutics R&D webinar presentation, December 2022

Importantly, testing CTIM-76 against the high CLDN6 expressing cell line (K562) showed that the drug could induce cytotoxic T-cell activation without drastically increasing cytokine production. Cytokine release syndrome (CRS) is an adverse side-effect experienced in some patients in response to immunotherapy, so, in our view, the lower selected therapeutic dose provides encouraging signs for CTIM-76's potential safety profile in the clinic (Exhibit 4). Similar observations were made (cytotoxic T-cell activation and cell lysis without drastically increasing cytokines) in the OV90 cell line (medium CLDN6 expression) at the selected dose (EC_{50}=0.049nM).

Exhibit 4: Comparison of T-cell dependent cytotoxicity (TDCC) to cytokine production in K562 cell line



Source: Context Therapeutics R&D webinar presentation, December 2022

BioNTech's BNT211 Phase I data establishes PoC

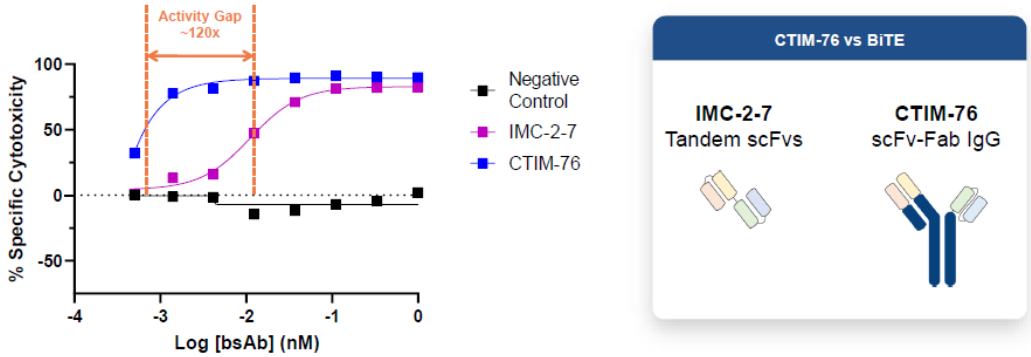
In September 2022, BioNTech, the current leader in this category, in our view, presented encouraging follow-up data on its CLDN6 CAR-T asset BNT211 from its ongoing Phase I/II study, in patients with relapsed or refractory advanced solid tumors. The data was presented for 21 evaluable patients (testicular, 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 objective 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 a DCR of 85%, with one complete response, three partial responses and two with stable disease. We see these early results as providing proof of concept for CLDN6 targeting therapeutics.

CTIM-76 promises higher activity than benchmark BiTE BsAb

We note that there are a handful of CLDN6 targeting BsAbs in development, notably BioNTech's BNT142 and Amgen's AMG794, which are currently undergoing Phase I studies (the latter is expected to start enrolment imminently). However, Context argues that the structure and design of its candidate allows superior activity and binding to CLDN6, which, if proved in clinical studies, could offer market differentiation. A head-to-head comparison with a bi-specific T-cell engager (BiTE) antibody (IMC-2-7) shows that CTIM-76 is able to induce a similar cytotoxic T-cell response at much lower dose concentrations than IMC-2-7, suggesting higher efficacy and potentially improved safety (Exhibit 5).

Exhibit 5: Benchmarking CTIM-76 against a BiTE candidate



Source: Context Therapeutics R&D webinar presentation, December 2022

Context has initiated Investigational New Drug (IND) enabling studies with CTIM-76 and the company plans to file an IND application in Q124. While the company has not disclosed a target indication for clinical studies, initial areas of interest include testicular cancer, ovarian cancer, non-small cell lung cancer and malignant rhabdoid, all indications with high CLDN6 prevalence (Exhibit 6). We expect Context to focus on the former two indications, although there will be further clarity as the drug approaches the clinic.

Exhibit 6: Potential target indications for CTIM-76

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
Malignant Rhabdoid	50	500	29-44%	183
Gastric	26,380	11,090	13-55%	3,771
Breast	290,600	43,800	2-41%	9,417
Endometrial	65,900	12,500	20-31%	3,188
Glioma	19,000	10,000	21%	2,100
Bladder	81,180	17,100	2-8%	855
SCLC	35,511	19,527	2%	391

Source: Context Therapeutics R&D webinar presentation, December 2022

Valuation

Our investment case remains unchanged following the selection of CTIM-76 as the company's CLDN6xCD3 candidate, given the early-stage nature of the data presented, although we note the potential for uplift as the drug transitions to the clinic.

Exhibit 7: Context Therapeutics valuation (risk-adjusted NPV)

Program	Indication	Status	Probability of success	Launch year	Peak sales ($m)	Economics	Risked NPV ($m)
ONA-XR	Second-line HR+/HER2- mBC (in combination with fulvestrant)	Phase II	15%	2026	498	US (fully owned) Europe (out-licensed)	41.4
	First-line escalation therapy for HR+/HER2- mBC (ctDNA+)	Phase Ib	7.5%	2027	222	US (fully owned) Europe (out-licensed)	7.4
	Second-third line HR+/HER2- mBC (in combination with elacestrant)	Phase Ib/II	10%	2028	374	US (fully owned) Europe (out-licensed)	17.5
	Recurrent PR+ endometrial cancer	Phase II	10%	2027	583	US (fully owned) Europe (out-licensed)	29.1
	Advanced GCT of the ovary	Phase II	10%	2027	292	US (fully owned) Europe (out-licensed)	11.9
Net cash (at the end of Q322) $m							39.4
Total firm value							**146.5**
Total basic shares (m)							16.0
Value per basic share ($)							**9.18**
Total diluted shares (m)							1.9
Value per diluted share ($)							8.18

Source: Edison Investment Research

Exhibit 8: Financial summary

$000s	2020	2021	2022e	2023e	2024e
Year end 31 December	US GAAP	US GAAP	US GAAP	US GAAP	US GAAP
INCOME STATEMENT					
Revenue	0	0	0	0	0
Cost of Sales	0	0	0	0	0
Gross Profit	0	0	0	0	0
Research and Development Expenses	(1,642)	(6,893)	(9,718)	(14,881)	(20,289)
Sales, General and Administrative Expenses	(931)	(3,633)	(8,356)	(12,534)	(13,787)
EBITDA	(2,572)	(10,526)	(18,074)	(27,415)	(34,076)
Operating profit (before amort. and excepts.)	(2,572)	(10,526)	(18,074)	(27,415)	(34,076)
Amortization of acquired intangibles	0	0	0	0	0
Exceptionals	0	0	0	0	0
Share-based payments	0	0	0	0	0
Reported operating profit	(2,572)	(10,526)	(18,074)	(27,415)	(34,076)
Net Interest	(661)	(64)	0	0	0
Joint ventures & associates (post tax)	0	0	0	0	0
Exceptionals	9,878	133	0	0	0
Profit Before Tax (norm)	(3,233)	(10,590)	(18,074)	(27,415)	(34,076)
Profit Before Tax (reported)	6,644	(10,457)	(18,074)	(27,415)	(34,076)
Reported tax	0	0	0	0	0
Profit After Tax (norm)	(3,233)	(10,590)	(18,074)	(27,415)	(34,076)
Profit After Tax (reported)	6,644	(10,457)	(18,074)	(27,415)	(34,076)
Minority interests	0	0	0	0	0
Discontinued operations	0	0	0	0	0
Net income (normalized)	(3,233)	(10,590)	(18,074)	(27,415)	(34,076)
Net income (reported)	6,644	(10,457)	(18,074)	(27,415)	(34,076)
Average Number of Shares Outstanding (m)	0	3	16	16	16
EPS - basic normalized ($)	(9.28)	(3.74)	(1.13)	(1.72)	(2.13)
EPS - normalized fully diluted (c)	(928.15)	(373.72)	(113.20)	(171.71)	(213.43)
EPS - basic reported ($)	19.07	(3.69)	(1.13)	(1.72)	(2.13)
Dividend ($)	0	0	0	0	0
BALANCE SHEET					
Fixed Assets	118	0	0	0	0
Intangible Assets	0	0	0	0	0
Tangible Assets	0	0	0	0	0
Investments & other	118	0	0	0	0
Current Assets	350	51,306	35,407	8,629	4,106
Stocks	0	0	0	0	0
Debtors	0	0	0	0	0
Cash & cash equivalents	341	49,686	34,759	7,980	3,458
Other	9	1,620	648	648	648
Current Liabilities	(9,548)	(3,033)	(5,209)	(5,845)	(5,398)
Creditors	(2,708)	(1,826)	(3,136)	(3,330)	(2,897)
Tax and social security	0	0	0	0	0
Short term borrowings	(5,884)	0	0	0	0
Other	(956)	(1,207)	(2,073)	(2,515)	(2,501)
Long Term Liabilities	(69)	0	0	0	(30,000)
Long term borrowings	(69)	0	0	0	(30,000)
Other long-term liabilities	0	0	0	0	0
Net Assets	(9,150)	48,272	30,198	2,784	(31,292)
Convertible preferred stock	(7,771)	0	0	0	0
Minority interests	0	0	0	0	0
Shareholders' equity	(16,921)	48,272	30,198	2,784	(31,292)
CASH FLOW					
Operating Cash Flow	(2,572)	(10,526)	(18,074)	(27,415)	(34,076)
Working capital	1,318	(2,225)	3,147	636	(447)
Exceptional & other	219	3,951	0	0	0
Tax	0	0	0	0	0
Net operating cash flow	(1,035)	(8,799)	(14,926)	(26,779)	(34,522)
Capex	0	(250)	0	0	0
Acquisitions/disposals	0	0	0	0	0
Net interest	0	0	0	0	0
Equity financing	0	58,394	0	0	0
Dividends	0	0	0	0	0
Other	0	0	0	0	0
Net Cash Flow	(1,035)	49,345	(14,926)	(26,779)	(34,522)
Opening net debt/(cash)	21,742	13,384	(49,686)	(34,759)	(7,980)
FX	0	0	0	0	0
Other non-cash movements	9,393	13,725	0	0	0
Closing net debt/(cash)	13,384	(49,686)	(34,759)	(7,980)	26,542

Source: Company reports, Edison Investment Research

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