EDISON

Kazia Therapeutics

Pipeline update

New indications for GDC-0084

Pharma & biotech

Kazia has added two further indications to the development programme for its brain-penetrant PI3K inhibitor GDC-0084 through collaborations with prestigious US-based cancer centres. The collaborations further validate the potential of GDC-0084, which was in-licensed from Genentech in 2016. Importantly, the two additional indications will provide alternative pathways to a potential first marketing approval for GDC-0084, increasing the overall likelihood of success. Kazia's ongoing Phase IIa study of GDC-0084 in glioblastoma (GBM) is expected to report first data in early 2019. Kazia raised A$3.4m through a recent share placement and has a share purchase plan (SPP) underway to raise additional funds. We increase our valuation range to between A$83m and A$139m.

Year end	Revenue (A$m)	PBT* (A$m)	EPS* (c)	DPS* (c)	P/E (x)	Yield (%)
06/17	8.6	(10.9)	(22.8)	0.0	N/A	N/A
06/18	13.0	(6.3)	(12.5)	0.0	N/A	N/A
06/19e	3.1	(11.9)	(21.9)	0.0	N/A	N/A
06/20e	12.3	(3.2)	(5.3)	0.0	N/A	N/A

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

Breast cancer brain metastases with Dana-Farber

The first collaboration is with the Dana-Farber Cancer Institute to investigate GDC-0084 in combination with Herceptin in women with HER2-positive breast cancer who have developed brain metastases. We had already included this potential indication in our valuation model for GDC-0084, so we are pleased to see that a trial will soon be underway. Genentech showed that GDC-0084 improves survival in this indication in animal studies, and a successful Phase III study for Novartis's BYL719 validates targeting PI3K in breast cancer.

DIPG childhood brain cancer with St Jude

The second collaboration is with St Jude Children's Research Hospital in a Phase I study of GDC-0084 in the aggressive childhood brain cancer diffuse intrinsic pontine glioma (DIPG). Although the number of patients with this disease is small, the fact that there are no approved treatments for this aggressive cancer could open up pathways to an accelerated approval or Breakthrough Designation. Approval could also earn a valuable FDA paediatric priority review voucher.

Cantrixil Phase I identifies MTD

The Cantrixil Phase I study has determined the maximum tolerated dose (MTD) in ovarian cancer to be 5mg/kg. A 12-patient cohort at the MTD is currently being recruited, with updated preliminary efficacy data expected to read out in Q319.

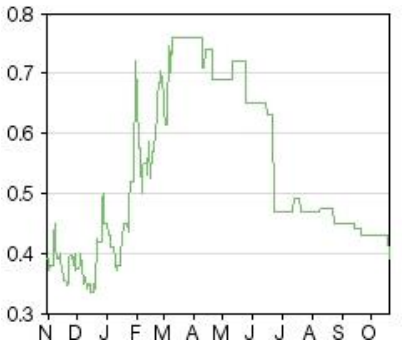
Valuation range: A$83–139m; SPP underway

We increase our indicative valuation range to A$83–139m or A$1.38–2.31 per share (vs A$73–133m, A$1.46–2.65 per share), under either post-Phase III approval or accelerated approval scenarios for GDC-0084. The changes reflect the addition of the DIPG indication, a modest increase in forecast peak sales for breast cancer brain metastases, and dilution from shares issued for the capital raise.

29 October 2018

Price	**A$0.38**
Market cap	**A$22m**
	A$/US$0.76
Net cash (A$m) at 30 June 2018	6.0
Shares in issue	57.3m
Free float	90%
Code	KZAX
Primary exchange	ASX
Secondary exchange	NASDAQ

Share price performance



%	1m	3m	12m
Abs	(10.5)	(22.2)	(6.1)
Rel (local)	(6.7)	(18.2)	(7.4)
52-week high/low	A$0.78		A$0.34

Business description

Kazia Therapeutics is an ASX- and NASDAQ-listed biotechnology company. It is developing the PI3K/mTOR inhibitor GDC-0084 for brain cancer and Cantrixil for ovarian cancer. GDC-0084 was in-licensed from Genentech in 2016.

Next events

GDC-0084 safety and dosing data	Q219
Cantrixil Phase I preliminary efficacy data	Q319
GDC-0084 Phase IIa preliminary efficacy	Q419

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Edison profile page

Collaborations expand development pipeline

Kazia has two company-sponsored trials underway: a Phase IIa study of GDC-0084 in glioblastoma and a Phase I trial of Cantrixil in ovarian cancer. The two new collaborative investigator-sponsored studies will allow it to explore the efficacy of GDC-0084 in two additional indications at a minimal cost to the company.

The collaborations provide validation from prestigious US-based research institutions of the potential of GDC-0084 to provide significant benefit to patients with a range of brain cancers. In particular, the Dana-Farber collaboration validates our decision to include an HER2+ breast cancer brain metastasis indication in our valuation model for GDC-0084. One or our reasons for doing this was that Genentech had shown that GDC-0084 alone and in combination therapy improved survival in a mouse model of HER2+ breast cancer, as described below.

Importantly, the two additional indications will provide alternative potential pathways to a first marketing approval for GDC-0084, increasing the overall chances of success for the development programme.

Placement completed, SPP underway

Kazia raised A$3.4m (before costs) through a private placement in October, and is currently undertaking a share purchase plan to raise additional funds from existing investors. No target has been set for the amount of funds to be raised by the SPP, but the maximum that could be raised under ASX listing rules is A$6.5m. For valuation purposes, we assume that the SPP will raise A$1m (before costs).

The funds raised would support operations to CY H219 and the anticipated readout of preliminary efficacy data from the ongoing GDC-0084 and Cantrixil clinical studies.

Collaboration with Dana-Farber in breast cancer brain metastases

Kazia announced on 22 October that it had entered into a collaboration with the Dana-Farber Cancer Institute (DFCI) in the US to investigate GDC-0084 in patients with HER2+ breast cancer that has spread to the brain (breast cancer brain metastases or BCBM).

DFCI will conduct an open-label Phase II trial of GDC-0084 in combination with Herceptin (trastuzumab) in HER2+ BCBM. Herceptin is a monoclonal antibody (mAb) drug that blocks HER2 activation and is approved for treating HER+ breast cancer. The study is expected to recruit between 22 and 49 patients and to take up to three years to complete. Recruitment is expected to commence in Q418 or Q119.

The Principal Investigator is Dr Jose Pablo Leone, an oncologist at DFCI who has published extensively on BCBM. The investigator-initiated study will be managed by DFCI, with Kazia providing support including study drug and a financial grant.

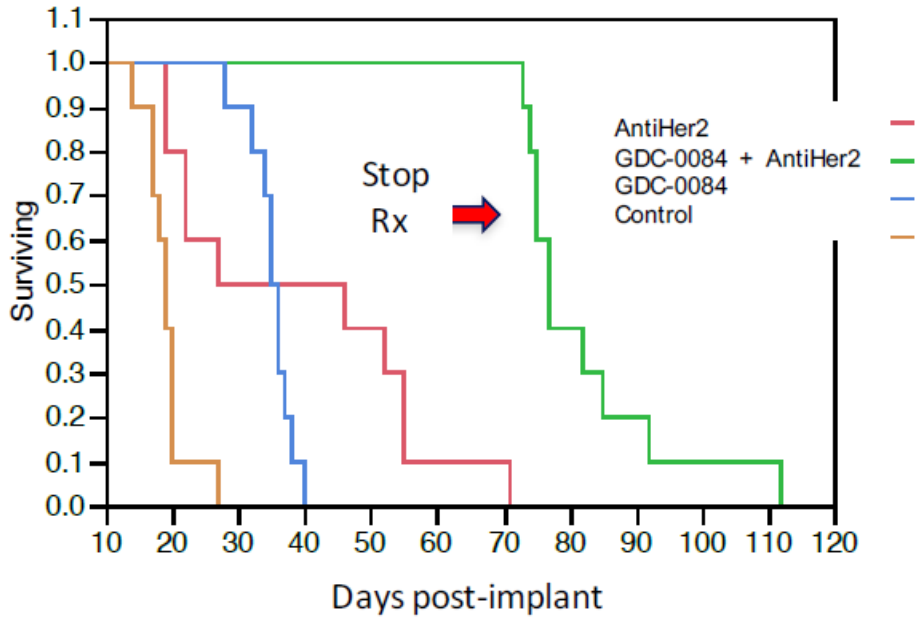
Genentech animal models showed BCBM survival benefit

Although Kazia is initially developing GDC-0084 in GBM, it also has the potential to treat brain metastases for a range for different cancers. Brain metastases are quite common, but there are few drugs available to treat them. Lung, breast and melanoma represent the majority of brain metastases.

Genentech has conducted preclinical studies showing that GDC-0084 improves survival in mouse models of brain metastases in HER2+ breast cancer, as shown in Exhibit 1. While anti HER2 monoclonal antibody drugs like Herceptin do not cross the intact blood brain barrier in a healthy brain, they can enter brain tissue if the blood brain barrier is disrupted by a tumour or radiation therapy.

HER2 signalling acts via the PI3K pathway, so combining GDC-0084 with Herceptin in HER2+ breast cancer blocks the growth-promoting signal in two places. This may explain the synergistic benefit of combining the two therapies seen in the Genentech preclinical study.

Exhibit 1: GDC-0084 improves survival in intracranial model of metastatic breast cancer as a single agent and in combination with an anti-HER2 antibody



Source: Internal company documents. Note: AntiHer2 indicates an anti-HER2 monoclonal antibody comparable to Herceptin.

BYL719 Phase III success validates PI3K in breast cancer

Novartis announced in August that its PI3K inhibitor BYL719 had met the primary endpoint of delaying disease progression in a Phase III study in breast cancer patients. The study treated patients with hormone receptor-positive, HER2-negative breast cancer carrying mutations in the PIK3CA gene with BYL719 plus hormone therapy. Detailed data released at the European Society for Medical Oncology (ESMO) conference in October showed that median progression-free survival was 12 months for the combination therapy, almost double the 5.7 months for hormone therapy alone. Side effects were described as predictable and manageable; the most common serious adverse event was hyperglycaemia experienced by 37% of subjects. Novartis estimates that ~40% of patients with hormone receptor-positive breast cancer carry PIK3CA mutations.[1]

The success of BYL719 validates the PI3K pathway as a target of therapy in breast cancer, and supports Kazia's strategy of targeting breast cancer brain metastases with its brain-penetrant PI3K inhibitor.

BYL719 was not designed to cross the blood-brain barrier, and the clinicaltrials.gov website does not contain any record of trials of the drug that target BCBM, so we do not expect it to be a direct competitor to GDC-0084 in this indication.

1 https://resource.globenewswire.com/Resource/Download/f65ae368-3f13-4aad-991a-f05db127c43d

Assessing the revenue opportunity from brain metastases

With a Phase II trial in BCBM expected to commence in the next few months, we thought it would be useful to detail our methodology for estimating the market opportunity in this indication. Our assumptions are unchanged from our previous reports, except that we have updated the incidence of breast cancer in the US to reflect the latest estimate from the National Cancer Institute.

There are forecast to be 266,000 new cases of breast cancer in the US in 2018,[2] and 37% of breast cancers are HER2+.[3] Pestalozzi et al[4] reviewed a number of studies of patients with early breast cancer who were followed up in trials of adjuvant chemotherapy or hormone therapy following surgical resection of their tumour. Their analysis of 9,500 patients enrolled in nine separate studies found that 6.8% of patients with HER2+ tumours developed brain metastases within 10 years of initial diagnosis. Combining these two factors, we estimate that 2.5% of all breast cancer patients would develop HER2+ brain metastases, equivalent to 6,650 women each year in the US. We assume that 50% of these patients would be treated with GDC-0084 at peak uptake. As mentioned above, we had already included potential sales for the treatment of HER2+ breast cancer brain metastases in our valuation model of GDC-0084.

Collaborating with St Jude in childhood brain cancer

On 3 October Kazia announced a collaboration with St Jude Children's Research Hospital in the US to investigate GDC-0084 in the aggressive childhood brain cancer known as diffuse intrinsic pontine glioma (DIPG).

St Jude will conduct an investigator-initiated Phase I trial of GDC-0084 in up to 41 children with newly diagnosed DIPG and other diffuse midline gliomas (brain cancers). The trial (clinicaltrials.gov identifier NCT03696355) is already recruiting patients and is expected to take up to three years to achieve full recruitment.

DIPG is an aggressive but rare brain tumour primarily affecting children, with a median survival after diagnosis of only nine months.[5] The current standard of care is radiotherapy, but the disease typically recurs after treatment. There are no approved drug treatments and no existing drug therapy has shown significant benefit in this disease to date. DIPG disease causes 250-300 deaths each year in the US.[6]

Given the small patient population, the potential sales in this indication are modest (we model peak sales of US$45m). We note that St Jude plans to recruit patients with other diffuse midline gliomas in addition to DIPG, which may expand the addressable market somewhat. We will review our estimate of the addressable market if additional information becomes available.

The unmet medical need for effective treatments for DIPG could potentially provide an alternative fast-to-market opportunity for GDC-0084 in this condition via Breakthrough Designation or Accelerated Approval pathways.

In our view, the key value of the DIPG project is that it offers an alternative pathway to an initial market approval for GDC-0084 in an indication with a very high unmet medical need.

2 https://seer.cancer.gov/statfacts/html/breast.html

3 Barker et al. *Clinical pharmacology & Therapeutics* 86 (1): 97-100, 2009. Supplementary Table 1.

4 Pestalozzi et al. *Annals of Oncology* 17: 935–944, 2006

5 Grasso et al, Nature Medicine 2015; 21 (6), 555–559.

6 ASMB Today, June/July 2015 issue.

A priority review voucher could potentially boost DIPG value

Under FDA rules, companies that develop a drug or biologic for a rare paediatric disease may qualify for a voucher, which can be redeemed for a priority review to shave four months off the FDA review period for any drug. If Kazia gains FDA approval for GDC-0084, we would expect it to receive a priority review voucher provided the programme is still in operation at that time.

Priority review vouchers can be sold to other companies, with the highest price paid for a voucher being US$350m by AbbVie in 2015. Spark Therapeutics sold a voucher to Jazz Pharmaceuticals for US$110m in April 2018.

We do not include any contribution from the sale of a priority review voucher in our valuation of the DIPG indication, but note that it could, in theory, add considerable value to the programme.

Maximum tolerated dose identified for Cantrixil

In early October, the Phase I study of Cantrixil determined the maximum tolerated dose (MTD) for the drug in ovarian cancer patients to be 5mg/kg. The MTD is towards the upper end of the dose range proposed for the study, and preclinical data suggest that this dose should be sufficient to detect the potential therapeutic effects of Cantrixil.

Eleven patients have been treated in the dose escalation study. The most common side effects have been abdominal pain, fatigue and vomiting.

Part B of the study is recruiting a further 12 patients at the MTD to further explore safety and preliminary efficacy of Cantrixil. The study is expected to conclude in H219.

This recent update did not release any new preliminary efficacy data. The company had previously reported that three of the first five patients who were evaluable for efficacy had achieved stable disease after two cycles of Cantrixil monotherapy. One of the three subsequently went on to achieve a partial response after being treated with Cantrixil in combination with chemotherapy.

Valuation

We have revised our valuation of Kazia to reflect the recent placement, which raised A$3.4m (before costs) through the issue of 8.9m shares at A$0.38 per share. We assume that the ongoing share purchase plan will raise a further A$1m at the same share price. We have added a DIPG indication for GDC-0084, and increased the addressable market for breast cancer brain metastases to reflect the latest incidence data, which results in a modest increase in peak sales.

Our base case valuation, which models a GDC-0084 market launch in 2026 following completion of a Phase III trial, has increased to A$83m (previously A$73m). Our valuation is equivalent to A$1.38/share undiluted (vs A$1.46/share) and A$1.33/share after diluting for options and convertible notes. Kazia is also listed on NASDAQ under the code KZIA, with each NASDAQ-listed ADR representing 10 ordinary shares. Our undiluted base case valuation equals US$10.51 per ADR at current exchange rates.

Our base case valuation assumes a 40% likelihood that GDC-0084 is out-licensed to a marketing partner in 2021 after reporting positive PFS data from the Phase II trial, in a deal that includes US$20m upfront and US$120m in clinical and regulatory milestone payments. We also assume that Kazia pays a royalty of 10% of net sales to Genentech and that global sales for GBM reach US$1,050m in 2030.

Exhibit 2 shows our base case market assumptions for GDC-0084 and Cantrixil and the contribution of product royalties and milestone payments to the rNPV, which have not changed

since our last note. We have offset the risk-adjusted trial cost against milestone revenue for each drug, rather than against royalty revenue. This understates the contribution of the milestone payments to the rNPV and overstates the contribution of royalties.

Exhibit 2: Kazia base case valuation (assumes confirmatory GDC-0084 pivotal trial required)

	Likelihood (%)	rNPV (A$m)	rNPV/ share (A$)	Assumptions
GDC-0084; GBM	25%	17.0	$0.28	Global peak sales* of US$1,050m from GBM (11,500 US cases/year, 61% unmethylated MGMT** promoter, 80% penetration); pricing of US$50k. Global sales 2x US sales; launch 2026; assumes receives 15% royalty on sales, pays away 10% of royalty to Genentech.
GDC-0084; brain metastases in HER2+ breast cancer	20%	7.2	$0.12	Global peak sales of US$600m (233,000 US breast cancer cases/year, 37% HER2+, 7% develop brain metastases, 50% penetration); pricing of US$50k. Global sales 2x US sales; launch 2026; assumes receives 15% royalty on sales, pays away 10% of royalty to Genentech.
GDC-0084; DIPG	20%	0.5	$0.01	Global peak sales of US$45m (275 US DIPG cases/year, 80% penetration); pricing of US$50k. Global sales 2x US sales; launch 2026; assumes receives 15% royalty on sales, pays away 10% of royalty to Genentech.
Ovarian and other abdominal cancers: Cantrixil	10%	27.4	$0.46	Global peak sales of US$680m from ovarian cancer (14,300 US deaths/year, 30% penetration) and bowel cancer (50,300 US deaths, 25% develop malignant ascites, 20% penetration); pricing of US$50k. Global sales 2x US sales; launch 2025; assumes receives 15% royalty on sales, pays away 5% of revenue to Yale.
GDC-0084 milestones		20.4	$0.34	Assumes potential licensing upfronts and milestones total US$140m (US$127m net of payments to Glioblast and Genentech; US$38m after risk adjustment).
Cantrixil milestones		18.3	$0.31	Assumes potential licensing upfronts and milestones total US$140m (US$23m after risk adjustment); assumes 5% of upfront and milestone payment paid away to Yale.
SG&A		(12.3)	($0.21)	
Portfolio total		**78.5**	**$1.31**	
Noxopharm shares market value		3.6	$0.06	
Net cash at end FY19e		0.8	$0.01	
Enterprise total		**82.9**	**$1.38**	

Source: Edison Investment Research. Note: *Peak sales in actual dollars in forecast year. ** MGMT = methylguanine-DNA methyltransferase gene. We assume that the addressable markets grow at 4% per year. Launch dates listed are calendar years (in some cases the launch will be in the financial year following the calendar year stated).

We have also valued Kazia under an alternative accelerated approval scenario for GDC-0084, which assumes a market launch in 2023, and that Kazia receives a higher 20% royalty rate and a larger US$40m upfront payment because the data are ready for filing, with other deal terms the same as for the post-Phase III approval base case scenario. Exhibit 3 shows that accelerated approval for GDC-0084 would increase our valuation for Kazia to A$139m (previously A$133m) or A$2.31/share (undiluted).

Exhibit 3: Kazia valuation in GDC-0084 accelerated approval scenario

	Likelihood (%)	rNPV (A$m)	rNPV/ share (A$)	Assumptions
GDC-0084 – GBM	25%	56.8	$0.95	As per Exhibit 2, except 2023 launch (vs 2026) and 20% gross royalty on sales (vs 15%).
GDC-0084 – brain metastases in HER2+ breast cancer	20%	14.3	$0.24	As per Exhibit 2, except 20% gross royalty on sales (vs 15%).
GDC-0084; DIPG	20%	1.1	$0.02	As per Exhibit 2, except 20% gross royalty on sales (vs 15%).
GDC-0084 milestones		28.6	$0.48	Assumes potential licensing upfronts and milestones total US$160m (US$147m net of payments to Glioblast and Genentech; US$48m after risk adjustment). Milestones received earlier than base case (final milestone in 2023 vs 2026).
GDC-0084 total		**100.8**	**$1.68**	
Remainder of portfolio		33.4	$0.56	
Portfolio total		**134.2**	**$2.24**	
Noxopharm shares market value		3.6	$0.06	
Net cash at end FY19e		0.8	$0.01	
Enterprise total		**138.6**	**$2.31**	

Source: Edison Investment Research. Note: Launch dates listed are calendar years.

Financials

We have revised our near-term expenditure forecasts downwards to reflect the later start of the GDC-0084 Phase IIb, as indicated in the July shareholder update. We now forecast R&D expenditure to be A$9.2m in FY19 and A$9.5m in FY20. Note that we include unrisked clinical trial costs in our financial forecasts to show the potential funding requirement if the clinical trial programme is conducted in line with our expectations (trial costs risk-adjusted for NPV calculation).

Kazia had A$6.0m cash at 30 June 2018 and has subsequently raised A$3.4m (before costs) through a share placement. We assume that the share purchase plan that is currently underway will raise a further A$1m (before costs). Kazia has an available-for-sale shareholding in Noxopharm, which has a current market value of A$3.6m. We expect the available funds, including the potential sale of the Noxopharm shareholding, to be sufficient to support operations into CY H219, by which time preliminary efficacy data from the Cantrixil Phase I and GDC-0084 Phase IIa studies are expected to read out. However, if is there is any slippage on the timelines, funds may need to be raised in H2 CY19 before the GDC-0084 Phase IIa trial reads out.

We estimate that Kazia will need additional funds in the order of A$15–20m to finance the GDC-0084 Phase IIb GBM study.

Exhibit 4: Financial summary

A$'000s	2016	2017	2018	2019e	2020e
Year end 30 June	AASB	AASB	AASB	AASB	AASB
PROFIT & LOSS					
Sales, royalties, milestones	0	0	0	0	9,250
Other (includes R&D tax rebate)	3,665	8,563	12,989	3,074	3,019
Revenue	3,665	8,563	12,989	3,074	12,269
R&D expenses	(9,894)	(11,136)	(9,774)	(9,207)	(9,463)
SG&A expenses	(4,343)	(7,580)	(8,132)	(4,342)	(4,668)
Other	0	0	0	0	0
EBITDA	(10,572)	(10,153)	(4,917)	(10,475)	(1,862)
Operating Profit (before GW and except.)	(10,671)	(10,271)	(5,127)	(10,475)	(1,882)
Intangible Amortisation	(1,320)	(82)	(1,336)	(1,458)	(1,312)
Exceptionals	(569)	0	0	0	0
Operating Profit	(12,560)	(10,353)	(6,464)	(11,933)	(3,195)
Net Interest	406	(516)	119	60	8
Profit Before Tax (norm)	(11,586)	(10,869)	(6,344)	(11,874)	(3,187)
Profit Before Tax (reported)	(12,154)	(10,869)	(6,344)	(11,874)	(3,187)
Tax benefit	0	199	305	0	0
Profit After Tax (norm)	(11,586)	(10,670)	(6,039)	(11,874)	(3,187)
Profit After Tax (reported)	(12,154)	(10,670)	(6,039)	(11,874)	(3,187)
Average Number of Shares Outstanding (m)	42.7	46.8	48.4	54.2	59.9
EPS - normalised (c)	(28.44)	(22.81)	(12.48)	(21.92)	(5.32)
EPS - diluted	(28.44)	(22.81)	(12.48)	(21.92)	(5.32)
Dividend per share (A$)	0.0	0.0	0.0	0.0	0.0
BALANCE SHEET					
Fixed Assets	1,427	16,430	18,915	17,557	16,325
Intangible Assets	822	15,918	14,579	13,121	11,809
Tangible Assets	592	490	1	101	181
Investments	13	22	4,335	4,335	4,335
Current Assets	34,090	19,480	9,260	4,789	5,446
Stocks	0	0	0	0	0
Debtors	199	4,263	2,535	3,250	3,189
Cash	33,453	14,455	5,956	772	1,488
Other	438	763	768	768	768
Current Liabilities	(1,432)	(5,384)	(3,888)	(5,334)	(5,510)
Creditors	(1,300)	(1,873)	(2,067)	(3,513)	(3,689)
Short term borrowings	0	0	0	0	0
Other	(132)	(3,512)	(1,821)	(1,821)	(1,821)
Long Term Liabilities	(154)	(5,188)	(5,046)	(5,046)	(7,046)
Long term borrowings	0	0	0	0	(2,000)
Other long term liabilities	(154)	(5,188)	(5,046)	(5,046)	(5,046)
Net Assets	33,931	25,338	19,242	11,967	9,215
CASH FLOW					
Operating Cash Flow	(12,383)	(11,683)	(8,780)	(9,324)	(1,191)
Net Interest	405	248	119	60	8
Tax	0	0	0	0	0
Capex	(525)	(20)	0	(100)	(100)
Acquisitions/disposals	3	(7,097)	150	0	0
Equity Financing	782	(18)	0	4,180	0
Dividends	0	0	0	0	0
Other	0	0	0	0	0
Net Cash Flow	(11,719)	(18,570)	(8,511)	(5,185)	(1,283)
Opening net debt/(cash)	(44,371)	(33,453)	(14,455)	(5,956)	(772)
HP finance leases initiated	0	0	0	0	0
Other	800	(429)	13	0	0
Closing net debt/(cash)	(33,453)	(14,455)	(5,956)	(772)	512

Source: Kazia Therapeutics accounts, Edison Investment Research

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