

Kazia Therapeutics

GDC-0084 – encouraging initial efficacy

GDC-0084 trial update

Pharma & biotech

25 November 2019

Price **A\$0.44**

Market cap **A\$32m**

US\$0.68/A\$

Cash (A\$m) at 30 June 2019 5.4

Shares in issue (after share issue Oct 2019) 72.17m

Free float 91%

Code KZA

Primary exchange ASX

Secondary exchange Nasdaq

Share price performance



% 1m 3m 12m

Abs (12.0) 18.9 18.9

Rel (local) (12.5) (15.0) 0.7

52-week high/low A\$0.58 A\$0.32

Business description

Kazia Therapeutics is an ASX- and Nasdaq-listed biotechnology company. It is developing the PI3K/mTOR inhibitor GDC-0084 for drug-resistant brain cancer and Cantrixil for ovarian cancer.

Next events

Cantrixil Phase I preliminary efficacy data Q419

Interim FY20 results Q120

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[Edison profile page](#)

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Kazia Therapeutics has presented very encouraging initial efficacy data from the dose-ranging stage of its current Phase II trial. The data are sufficient to give Kazia confidence that it can run a large, and potentially pivotal, study starting by mid-CY20. Promising Cantrixil interim data were released in September. FY19 results showed cash of A\$5.4m now boosted by a A\$3.8m net placing. Our indicative value remains at A\$137m adjusted to A\$1.91/share post-placing (about US\$13/ ADR).

Year end	Revenue (A\$m)	PBT* (A\$m)	EPS* (c)	DPS (c)	P/E (x)	Yield (%)
06/18	2.9	(11.0)	(22.2)	0.0	N/A	N/A
06/19	1.5	(7.7)	(12.9)	0.0	N/A	N/A
06/20e	1.5	(8.7)	(12.6)	0.0	N/A	N/A
06/21e	1.5	(11.1)	(17.9)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding exceptionals and share-based payments.

Possibility of a potentially pivotal study from H120

Kazia presented a [poster](#) on the Phase IIa ([NCT03522298](#)) GDC-0084 dose ranging results at the annual meeting of the Society for Neuro-Oncology (SNO), held from 20–24 November 2019. GDC-0084 at a 60mg dose shows a very encouraging survival profile in eight Stage 1 evaluable patients with median progression-free survival (PFS) of 8.4 months. All these patients are resistant to standard TMZ chemotherapy. As six of the eight patients were alive at the data point, median overall survival (OS) could not be determined. Interestingly, two of these patients were disease free after more than 15 months. Published clinical studies indicate comparison values for PFS of 5.9 months and OS of 12.7 months in this patient population. Kazia is recruiting a Stage 2, 20-patient expansion cohort to look at efficacy and activity so further data should be available during 2020.

The current data are probably enough for Kazia to be confident that it can start a potentially pivotal randomised study during H120 – noting that the design needs to be finalised with input from clinicians and regulators. We assume that this single trial might be adequate for FDA approval in 2024 as patients resistant to the current standard therapy, temozolomide, have no other options available.

Cantrixil efficacy indications possible by late 2019

Cantrixil is in a small Phase I study with results now likely in H120. Interim data from [September](#) in nine patients showed two (22%) 'partial responses'. The median PFS was 5.5 months, which compares favourably to historical controls of 3.4 months. Cantrixil, an intra-peritoneal injection of a novel cytotoxic agent, could become a standard treatment for third-line ovarian cancer patients who now have few therapy alternatives and very poor prognosis.

Valuation: Core scenario value of A\$137m

Kazia is aiming for a 2024 GDC-0084 US launch. Kazia had A\$5.4m cash at 30 June 2019 and raised A\$4m gross (A\$3.8m) net in October from issuing 10m shares at A\$0.40 each. We estimate ~A\$15–20m will be needed to fully fund the GDC-0084 potentially pivotal study now expected to start in 2020. A deal after good overall Phase IIa data might be possible. Progression of Cantrixil is assumed to require a partner. We maintain our value of A\$137m adjusted to A\$1.91/share to account for the 72m shares in issue (formerly A\$2.20/share at 62m shares).

Two novel anti-cancer drugs

Kazia Therapeutics is an Australian biotechnology company focused on oncology drug development, listed on both the ASX (KZA) and Nasdaq (KZIA). It has two products in development: GDC-0084 for brain tumours (glioblastoma) and Cantrixil for refractory ovarian cancer. This note focuses only on GDC-0084 as important new clinical data have been presented.

Exhibit 1: EdisonTV interview with Kazia's CEO

 EDISON TV

James Garner
CEO, Kazia Therapeutics



Kazia's leading product, GDC-0084, is in development for glioblastoma and could enable successful treatment of this aggressive and largely incurable brain cancer. What is unique about the product?

Source: Kazia, Edison Investment Research

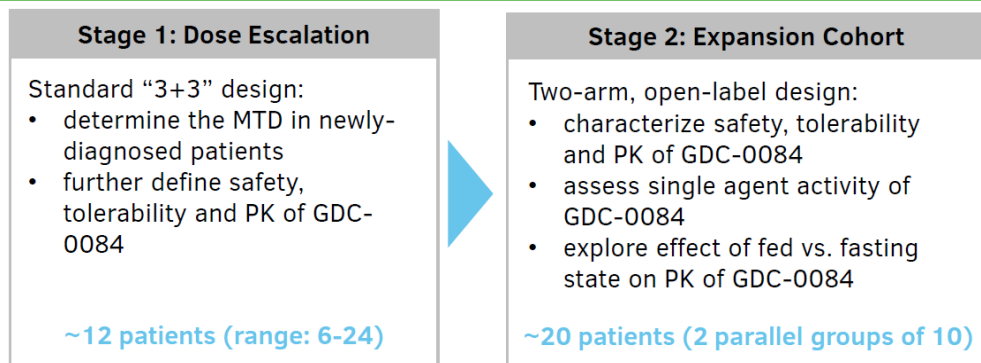
Very promising Phase I data show good survival

Kazia presented a [poster](#) on the Phase IIa ([NCT03522298](#))¹GDC-0084 dose and initial cohort expansion results at the annual meeting of the Society for Neuro-Oncology (SNO), held from 20–24 November 2019. These data are from the first stage of the study, which was dose ranging and found a maximum tolerated dose of 60mg as opposed to 45mg determined by Genentech in the original Phase I study.² Patients take GDC-0084 daily as 4, 15mg capsules in one dose in the morning.

¹ This record states that 66 patients will be required but most of these were contingency to the Stage 1 dose-ranging element and in fact this resolved with nine patients. The 20-patient continuation study is now running as planned.

² A higher dose of 75mg showed limiting toxicities of mucositis (inflamed lining of the mouth) and hyperglycaemia – high blood sugar. Both are known toxicities of this class of drug. Mucositis can be managed by steroid mouthwashes and hyperglycaemia resolved by standard diabetic control strategies.

Exhibit 2: Design of overall Phase II study



Source: Kazia [poster](#)

The data presented here are from Stage 1 ([September poster](#)). Patients all had surgical tumour debulking and combined radiation and temozolomide (TMZ) therapy using the Stupp regimen ([Stupp et al, 2005](#)).³ Stage 2, involving about 20 patients, is recruiting. Data on PFS and OS from the Stage 2, cohort, plus information on the activity of GDC-0084 if taken with food (currently it is taken before food), will be available in 2020. The extent of patient survival governs the time taken to read out data: longer survival means longer to read out.

Results so far

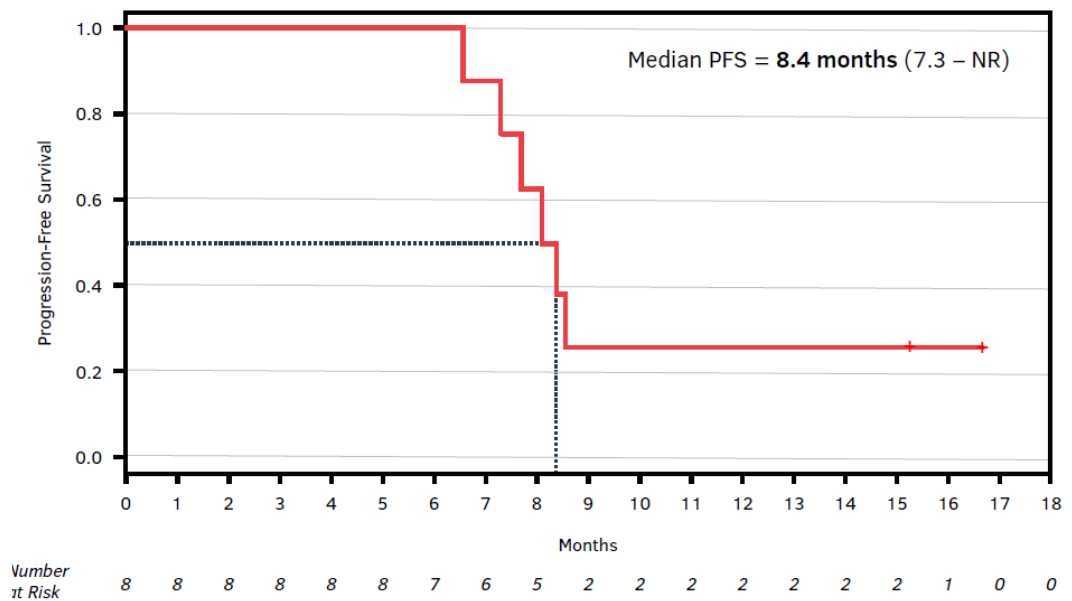
These results show a very encouraging survival profile in eight evaluable patients (out of nine) with median PFS of 8.4 months (Exhibit 3). All these patients are effectively resistant to standard TMZ chemotherapy as they produce the enzyme O⁶-methylguanine-DNA methyltransferase (MGMT) because they have an unmethylated MGMT gene promoter. MGMT repairs the DNA damage done by TMZ making patients resistant to that treatment ([Jiapaer et al, 2018](#)); about 61% of glioblastoma patients are TMZ refractory. If GDC-0084 can retard brain tumour growth in TMZ refractory patients, it could find a widespread, standard role.

In a large study, [Hegi et al \(2005\)](#) looked at TMZ resistance due to MGMT. Patients with the active form of the gene could repair TMZ damage and had a median PFS of 5.9 months. Patients with a deactivated MGMT gene did not repair the TMZ damage to their DNA so their tumour cells had a greater response to the drug and the patients showed a longer median PFS of 10.3 months.

³ Introduced in 2005, the Stupp regimen is now the standard of care in glioblastoma. It involves firstly surgical tumour debulking and secondly combined radiation and TMZ therapy (an alkylating agent) followed, third stage, by six cycles (each of one month) of adjuvant TMZ. The Stupp regimen gives two-year survival rates of 26.5% as against 10.4 months with radiotherapy alone – these patients were not stratified for TMZ resistance.

In the Kazia study, the third TMZ monotherapy phase is replaced by GDC-0084 monotherapy as, since these patients have the MGMT resistance profile, they are unlikely to benefit from TMZ monotherapy.

Exhibit 3: Progression-free survival from Stage 1



Source: Kazia [poster](#)

The small number of patients in the Stage 1 part of the GDC-0084 Phase IIa study means that the median PFS cannot be contrasted reliably to previously published figures. Clearly, these early data look better than the 5.9 months in TMZ-resistant patients but as yet are below the 10.3 months for TMZ-susceptible patients with methylated, MGMT promoter [Hegi et al \(2005\)](#). The data are very encouraging and merit a full comparison study. Stage 2 will yield more robust data.

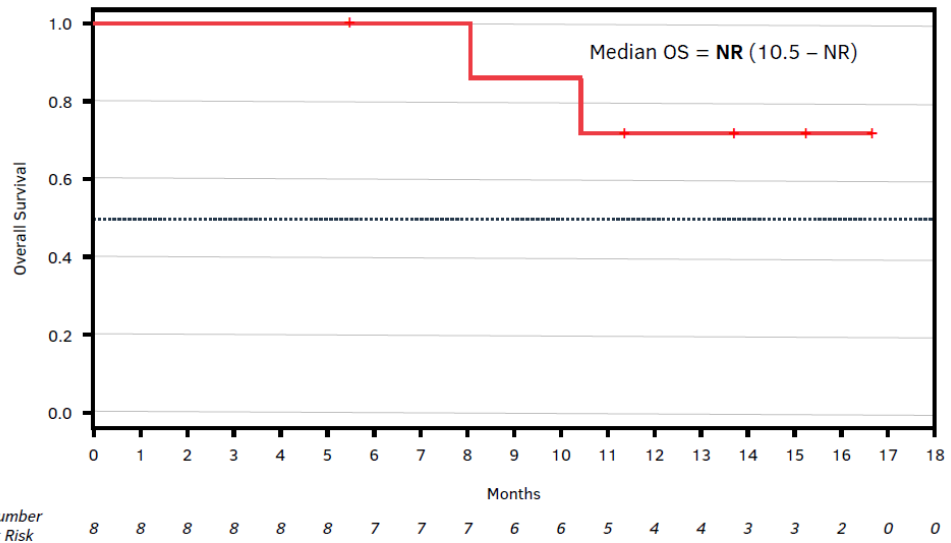
The important aspect for patients and their families – we need to remember that all these cold statistics have tragic individual stories behind them – is survival and quality of life. The Kaplan Meier OS curve (Exhibit 4) shows good survival in this small group with two deaths of eight cases reported. Of these, the two longest survivors were disease free after more than 15 months. As glioblastoma is retarded by GDC-0084 not killed by it, at least directly, this implies possible longer-term chronic use for a proportion of patients; if correct, this is commercially important as it might generate a large base of daily users by keeping them alive.

The OS curve (Exhibit 4) does not reach the 50% probability level, it sticks at 71%, so median survival cannot be determined. In their larger study, Hegi et al found that active MGMT gene patients, as studied here, had a medium overall survival of 12.7 months. Again however, the Stage 1 cohort is small so firm conclusions cannot be drawn.

There are many factors behind overall cancer survival, not just MGMT. For example, younger patients survive better than older ones. However, the median age for any brain cancer is 59 ([SEER](#)) and the Stage 1 cohort contained 55% of patients less than 59 years old so the sample does not seem skewed; in fact there was one patient in his 80s. Another key factor is the tumour size before surgery: under 42mm has a better prognosis than over 42mm; the tumour sizes of the patients in the study are not available. The [EORTC website](#) has a detailed consideration of such factors. There are also other mutations that have an impact on survival outcomes;⁴ these are more common in younger patients and were not controlled in this study.

⁴ The American Brain Tumor Association [notes](#) that: 'For patients with IDH mutant glioblastoma, the prognosis is significantly better (median survival of 27 – 31 months) compared to IDH wild type glioblastoma (median survival 11-13 months) after diagnosis.'

Exhibit 4: Overall survival from Stage 1



Source: Kazia [poster](#)

Conclusion

The crucial aspect of this result is that it enables Kazia to progress into a pivotal trial with a higher level of confidence. The current Phase IIa Stage 2 cohort will provide useful additional data. The Stage 1 data itself, while encouraging, has no randomised comparison group as a control – it was dose ranging – and, as management notes, historical controls are not necessarily a good guide to the outcome in such small patient groups.

Nonetheless, given the recurrent and aggressive nature of glioblastoma and the selection of patients who are more resistant to TMZ (due to the unmethylated MGMT promoter) as part of study inclusion criteria, we are impressed by the outcome so far.

Next step: Randomised pivotal study

The trial now being planned to start in H120 will compare GDC-0084 to adjuvant TMZ therapy and could be pivotal. This is planned by Kazia to be a randomised, two-arm study with 228 patients. The study will compare maintenance therapy with GDC-0084 vs standard-of-care TMZ. Patients will first undergo surgery to remove the bulk of the tumour followed by a radiation therapy combined with TMZ (Stupp regimen). Patients will be then randomised to receive maintenance therapy with either GDC-0084 or TMZ. TMZ is normally given for only six months due to toxicity.

The primary endpoint is likely to be either progression-free survival or overall survival. The average of five literature median PFS and OS values in GBM patients with an unmethylated MGMT promoter is PFS of 5.2 months and an OS of 13.8 months ([June 2019 note](#)).

Normally, the FDA requires two pivotal studies. In a small indication like glioblastoma, which is poorly controlled by current therapies and has short survival times, one well-run trial could be enough for approval if the data are robust and the product has a safe profile.

Other GDC-0084 trials

Kazia is also evaluating, using a series of alliances, the use of GDC-0084 in metastatic brain cancer and childhood disease, Exhibit 5. This spreads the clinical and financial risks, but such third-party studies can become prolonged.

Exhibit 5: GDC-0084 trials

Indication	Phase	Size	NCT	Sponsor	Next steps	Data
Newly diagnosed GBM (open label dose and efficacy)	II	29 adjusted, from 66	NCT03522298 (record Sept 2018)	Kazia	MTD determined at 60mg. Now entered a 20-patient dose expansion phase with data in late 2019. Adjuvant treatment given after surgery and radiotherapy with the cell killing agent temozolomide (TMZ) in TMZ resistant patients.	Q419
Genetic testing in brain metastases	II	150	NCT03994796	ACTO** Genentech NCI	This is a three-arm study testing three targeted therapies, CGC-0084 among them. Endpoint will be objective response rate. Due to start in H2 CY19 but not yet recruiting.	Q321
Breast cancer brain metastases (open label parallel assignment)	II	47	NCT03765983	Dana-Faber	A daily 45mg dose of GDC-0084 given with Trastuzumab every three weeks. The trial has two arms, one without surgical resection, the other with pre-surgical therapy followed by resection. Progress update H2 CY19.	Q421
DIPG* Children (open label paediatric)	I	41	NCT03696355	St Jude	GDC-0084 will be given 8–12 weeks after radiotherapy. Initial dose escalation completed to 27 mg/m ² . Cohort expansion underway.	Q121
PI3K-mutated brain metastases	I	18–30	TBA	MSK	In combination with radiation therapy. There will be an initial dose escalation followed by a cohort expansion	H221

Source: Edison Investment Research. Note: *DIPG = diffuse intrinsic pontine glioma. **Alliance for Clinical Trials in Oncology.

Some of these are structured as initially dose ranging with an ‘expansion’ cohort. One study ([NCT03765983](#)) is in breast cancer metastases combined with Herceptin but at a lower 45mg dose than the 60mg now used by Kazia. The Memorial Sloan Kettering (MSK) sponsored academic study, is a combination with radiotherapy. Radiotherapy is standard in brain tumour surgery. However, 30–50% of patients still progress.

The St Jude paediatric trial ([NCT03696355](#)) uses GDC-0084 two to three months after radiotherapy; this trial has [completed](#) dose escalation and has a maximum tolerated dose of 27mg/m². For example, a 20kg child has a [body surface area](#) of 0.7m² so the dose would be 18.9mg compared to the 60mg adult dose.

PI3K products from other companies

Outside brain cancers, other companies are developing PI3K inhibitors ([Zhao et al, 2017](#)). No other PI3K inhibitor can penetrate the brain, so only GDC-0084 could be used for brain cancers, but the class as a whole has shown anti-cancer efficacy. For example, [Aliqopa](#) (copanlisib, Bayer) is approved as an *iv* infusion for the treatment of adult relapsed follicular lymphoma and [Zydeliq](#) (idelalisib, Gilead) is approved as an oral treatment for chronic lymphocytic leukaemia (CLL) and follicular lymphoma. [Copiktra](#) (duvelisib, Verastem) was approved in October 2018 again for leukaemia (CLL) and some lymphomas. In 2019, the FDA approved [Piqray](#) (alpelisib, Novartis) as an oral combination therapy with fulvestrant for metastatic breast cancer therapy for patients with the PI3KCA mutation. This is the same mutation as in the Kazia-MSK trial. The approval was based on a progression-free survival of 11 months vs 5.7 months on fulvestrant alone. In glioblastoma, Roche/Genentech has a Phase I PI3K pathway inhibitor ([Ipatasertib](#)⁵) in a combination dose and safety trial ([NCT03673787](#), data, if released, Q121). No other PI3K inhibitor brain cancer studies are in progress according to the clinicaltrials.gov database.

⁵ Ipatasertib (GDC-0068) inhibits Protein Kinase B (also called Akt), a key signalling enzyme downstream of PI3K that is activated by the phosphorylated lipids (such as phosphatidylinositol (3,4,5)-trisphosphate) created by PI3K. Ipatasertib should have similar biochemical effects to GDC-0084 although clinical profiles will differ.

Valuation: Retained at A\$137m

Our assigned clinical probability of success for GDC-0084 is 25%. We have retained this because the Stage 1 data, although highly encouraging, are based on too few patients to be conclusive. The further patients in the expansion cohort will firm up the results. Our base case valuation of A\$137m assumes a GDC-0084 market launch in 2024 following a single pivotal study. This scenario also assumes that GDC-0084 is out-licensed to a marketing partner in 2023 -24. In this scenario, global sales for GBM reach US\$1,050m in 2030. Please see [earlier notes](#) for detailed assumptions. This base case is now equivalent to A\$1.91/share (A\$1.81/share including dilution) after the share placement in October increased shares in issue from 62m to 72m. Kazia is also listed on Nasdaq under the code KZIA, with each Nasdaq-listed ADR representing 10 ordinary shares.

There is an alternative scenario of a GDC-0084 launch in 2026 rather than 2024 if a further pivotal study is needed for FDA approval. On revised assumptions, this scenario valuation becomes A\$86m or A\$1.19/share (undiluted).

Financials: Cash following A\$3.8m net placing

Kazia had A\$5.4m cash on 30 June 2019, Exhibit 6. The operational FY19 cash use was A\$6.8m after R&D tax rebates of A\$1.4m. We still project higher cash costs in FY20 and FY21 as a pivotal trial is being planned and will need to be funded. Currently, Kazia does not have partnering income but good follow-on data from Stage 2 of the current trial could enable a deal.

In late October, Kazia completed a A\$4m funding, A\$3.8m net, by issuing 10 million new shares at A\$0.40 each. We estimate Kazia might spend A\$15–20m from mid-CY20 onwards to finance the large GDC-0084 study planned to start probably, in H1CY20 - although most clinical costs will occur from H2 CY20. Following the equity raise in October 2019, we have assumed long-term debt of a minimum A\$11m in FY21 in our forecasts (formerly A\$15m), but this could be from a mix of equity, partnering or grants. We have not assumed funding for a Phase II Cantrixil study.

Exhibit 6: Financial summary

	A\$000s	2018	2019	2020e	2021e
Year end 30 June		AASB	AASB	AASB	AASB
PROFIT & LOSS					
Sales, royalties, milestones		693	34	0	0
Other (includes R&D tax rebate)		2,200	1,431	1,500	1,500
Revenue		2,893	1,465	1,500	1,500
R&D expenses		(9,774)	(6,476)	(7,200)	(9,100)
SG&A expenses		(4,051)	(2,594)	(3,000)	(3,500)
Other		0	0	0	0
EBITDA		(10,932)	(7,604)	(8,700)	(11,100)
Operating Profit (before amort. and except.)		(11,142)	(7,711)	(8,700)	(11,100)
Intangible Amortisation		(1,336)	(1,084)	(1,000)	(1,000)
Exceptionals		8,411	0	0	0
Operating Profit		(6,687)	(10,568)	(9,700)	(12,100)
Net Interest		119	0	0	0
Profit Before Tax (norm)		(11,023)	(7,711)	(8,700)	(11,100)
Profit Before Tax (reported)		(6,344)	(10,568)	(9,700)	(12,100)
Tax benefit		305	298	0	0
Profit After Tax (norm)		(10,718)	(7,413)	(8,700)	(11,100)
Profit After Tax (reported)		(6,039)	(10,270)	(9,700)	(12,100)
Average Number of Shares Outstanding (m)		48.4	57.5	68.9	72.2
EPS - normalised (c)		(22.2)	(12.9)	(12.6)	(17.9)
EPS - diluted (c)		(21.1)	(12.4)	(12.2)	(14.9)
EPS reported (c)		(12.5)	(17.9)	(14.1)	(16.8)
Dividend per share (c)		0.0	0.0	0.0	0.0
BALANCE SHEET					
Fixed Assets		18,915	13,662	12,662	11,662
Intangible Assets		14,579	13,494	12,494	11,494
Tangible Assets		1	0	0	0
Investments		4,335	168	168	168
Current Assets		9,260	7,514	3,814	3,714
Stocks		0	0	0	0
Debtors		2,535	1,711	1,711	1,711
Cash		5,956	5,433	533	433
Other		768	370	370	370
Current Liabilities		(3,888)	(1,900)	(1,900)	(1,900)
Creditors		(2,067)	(1,764)	(1,764)	(1,764)
Short term borrowings		0	0	0	0
Other		(1,821)	(136)	(136)	(136)
Long Term Liabilities		(5,046)	(5,081)	(10,081)	(21,081)
Long term borrowings		0	0	0	(11,000)
Other long-term liabilities		(5,046)	(5,081)	(5,081)	(5,081)
Net Assets		19,242	14,195	4,495	(7,605)
CASH FLOW					
Operating Cash Flow		(8,780)	(6,714)	(8,700)	(11,100)
Net Interest		119	0	0	0
Tax		0	0	0	0
Capex		0	0	0	0
Acquisitions/disposals		150	2,359	0	0
Equity Financing		0	3,816	4000	0
Dividends		0	0	0	0
Other		0	0	-200	11,000
Net Cash Flow		(8,511)	(539)	(3,900)	(100)
Opening net debt/(cash)		(14,455)	(5,956)	(5,433)	(533)
HP finance leases initiated		0	0	0	0
Other		13	16	0	(11,000)
Closing net debt/(cash)		(5,956)	(5,433)	(533)	10,567

Source: Kazia Therapeutics accounts, Edison Investment Research

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