Circadian Technologies

Interim results; new structure

Edison investment research

Divine prospects

Pharma & biotech

Circadian has reorganised into three subsidiary operating companies: Ceres Oncology, Opthea and Precision Diagnostics, each of which could attract private funding. The Ceres investment case is the potential of VGX-100 (completing Phase I) to reduce secondary lymphoedema, a side effect of major breast cancer surgery. This may start Phase II in Q413. The major market is the potential of VGX-100 in combination with Avastin in solid tumours. This requires a partnering deal, assumed in 2014. Opthea is developing VGX-300 (preclinical), which may be used in combination with Lucentis or Eylea in wet AMD. Precision is developing a speciality diagnostic business. The Imclone-partnered IMC-3C5 could produce Phase I data in H213.

Year end	Revenue (A$m)	PBT* (A$m)	EPS* (c)	DPS (c)	P/E (x)	Yield (%)
06/11	0.45	(10.1)	(20.9)	0.0	N/A	N/A
06/12	0.51	(7.50)	(10.2)	0.0	N/A	N/A
06/13e	0.60	(8.07)	(16.6)	0.0	N/A	N/A
06/14e	0.65	(8.95)	(18.5)	0.0	N/A	N/A

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

Ceres: Secondary lymphoedema and Avastin combination

Ceres Oncology is the cancer company in the new Circadian structure developing VGX-100, a monoclonal antibody against VGF-C. Preclinical data in combination with Avastin in cancer models are strong and the Phase I dose escalation study has gone well, but validation depends on future Phase II studies. An orphan indication, secondary lymphoedema after breast cancer surgery, may start a Phase II trial in Q413. The lymphoedema indication has a fast read-out and can be run by Circadian. A solid tumour Phase II trial would require a partner, expected in 2014.

Opthea and Precision: Interesting, but early

Opthea is focused on VGX-300, a preclinical VEGF-C and-D trap fusion protein for wet age-related macular degeneration (AMD), the serious condition of retinal bleeding causing blindness. Its market may be similar to that of Eylea (Regeneron/Bayer), which has sales of nearly US$1bn after a year. The market, including Lucentis (Roche) grew to $2.6bn in 2012. VGX-300 needs funding or a deal to progress. Precision sells niche diagnostics that need validation and FDA approvals before gaining wider sales.

Valuation: Based on a 2014 deal

Ceres Oncology has cash to run a short Phase II trial in lymphoedema and to start a recurrent glioblastoma multiforme (GBM) trial. However, GBM completion and starting a major metastatic colorectal cancer (mCRC) Phase II trial requires a partner or substantial fund-raising. The value scenario is a mid-2014 deal on VGX-100 worth US$20m+ upfront with no dilutive external funding. All VGX-100 indications would be included at a high 20% royalty. Opthea has been valued on the basis of a 2014 deal at 50% probability with a 25% external investor equity stake. This gives a total NPV of A$1.93 share, but investors need to be aware of the risk of delays to deals. This makes the risk of additional dilution (amount, price and timing) hard to quantify.

5 March 2013

Price	A$0.28
Market cap	A$14m

Shares in issue	48.5m
Free float	69%
Code	CIR
Net cash (A$m)	12.2
Primary exchange	ASX
Other exchanges	OTCQX

Share price performance

%	1m	3m	12m
Abs	(8.2)	(21.1)	(47.7)
Rel (local)	(10.0)	(29.2)	(54.6)
52-week high/low		A$0.56	A$0.26

Business description

Circadian's focus is on its VEGF-C portfolio, which is now restructured into three businesses. In Ceres, an anti-VEGF-C antibody (VGX-100) will complete Phase I by Q213; a Phase II in secondary lymphoedema treatment after breast cancer surgery is planned to start in H213. Opthea is seeking funding or a deal to develop VGX-300 in wet AMD. Precision supplies niche diagnostic tests in the US and Australia. Circadian's receptor-blocking antibody (IMC-3C5) is in Phase I trials with ImClone (Lilly), with data maybe mid-2013.

Next events

VGX-100 dose data	Q213
Final results	August 2013
Lymphoedema Phase II start	Q413

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Investment summary: Divine prospects

Circadian has three development companies: Ceres Oncology, Opthea (ophthalmic indications) and Precision Diagnostics. It is intended that each subsidiary is separately funded via deals or equity to increase investment flexibility. Ceres can develop the secondary lymphoedema indication for VGX-100 though Phase II, but Phase II studies in solid tumours alongside Avastin (bevacizumab, Roche) need a partner. Opthea is developing a preclinical soluble VEGF C and D receptor trap, VGX-300, for wet AMD. This needs partnering or substantive funding. Precision provides some revenues from its niche diagnostics, reagent sales and test licensing. Circadian's Vegenics subsidiary has licensed a receptor fusion protein, IMC-3C5, to ImClone (Lilly). The Phase I trial may report data around mid-2013. Circadian retains stakes in two quoted companies (worth A$2.7m). It invested A$0.31m in Syngene, a private company in January 2012 in a funding to purchase a A$0.5m peptide stabilisation technology. This gave a 51% equity holding, so Syngene accounts are consolidated.

Sensitivities: Uncertainties over efficacy and funding

The VGX-100 lymphoedema indication offers a faster route to market, but the rationale has to be clinically verified in Phase II and the high price postulated ($20,000) requires excellent, but unproven, efficacy. The two solid tumour VGX-100 Phase II studies planned need partnering as Circadian cannot guarantee to fund the trials to completion. The first, in recurrent GBM, meets a major need as Avastin does not prolong survival. It is a highly risky first indication, with data unlikely before H115. The bigger market is mCRC, but this needs a bigger Phase II. Accordingly, investors have to assume a Ceres deal in 2014 and price in the dilution if this does not happen. Opthea's candidate, VGX-300, may be attractive now to big pharma as the therapy should be synergistic with both Eylea and Lucentis in the growing $2.6bn wet AMD market. If no deal is available, a private funding is likely. Patents and patent extensions provide good cover with minimal risks of generic completion until 2030, the forecast period. Precision has speciality diagnostics that may have limited immediate revenue impact.

Valuation: Dependant on a 2014 deal and future cash needs

The core value scenario is a mid-2014, US$20m+ upfront VGX-100 deal with no dilutive external funding. It is assumed that all VGX-100 indications are included at a high 20% royalty. Opthea has been valued on the basis of a 2014 deal at 50% probability with a 25% external investor equity stake. This gives a total NPV of A$1.93 a share before new investment. However, the mix of private subsidiary dilution on unknown terms plus uncertainty on deals means the impact on the publicly quoted share value is impossible to assess.

Financials: Cash though FY14

Circadian has indicated that its total annual cash burn will be A$7-8m in both FY13 and FY14. The Phase II lymphoedema trial might cost A$2m, but each VGX-100 Phase II in a solid tumour could cost A$5m, so these will need separate funding or a partner. R&D in H113 was A$1.9m. Edison estimates that R&D (excluding IP) will be about A$4m in FY13 and FY14 before Ceres and Opthea conclude partnering deals. At the interim stage, administration costs were level at A$2m plus A$0.27m in IP costs. Cash on 31 December 2012 was A$12.12m after an H113 operational cash burn of A$4.32m. On the assumptions above, Edison projects that Circadian has cash though FY14, but FY14 funding will be required; this might be through private deals in Ceres and Opthea. Circadian could sell its equity in two ASX-quoted biotech companies; these were valued at A$2.7m on 31 December 2012.

Outlook: Deals set to validate VEGF-C portfolio

Circadian's investment case rests on its position in anti-VEGF-C therapies. The focus is on the lead anti-VEGF-C therapeutic monoclonal antibody VGX-100 and the soluble VEGFR-3 molecule VGX-300. Preclinical data indicates that anti-VEGF-C therapies might potentiate the efficacy of current anti-angiogenic therapy with Avastin in solid tumours and that of Lucentis or Eylea in wet AMD. VGX-100 is completing its Phase I dose escalation study with and without Avastin. Ceres then plans to run a Phase II trial in secondary lymphoedema. This should have a fast read-out to confirm efficacy. Opthea needs either private finding or a deal to develop VGX-300 for wet AMD. Precision Diagnostics products provide near- to medium-term revenue opportunities.

The A and C of VEGF

All tissues need a supply of oxygen and nutrients delivered by the blood via the circulatory system and a drainage system to remove excess fluids, the lymphatic system. If either one is not functioning, signals are sent out to encourage the development of new vessels. There are various types of Vascular-Endothelial Growth Factors (VEGF), which bind to different receptors (VEGFR).

Exhibit 1: VEGF types and receptors

VEFG ligand	Receptor	Effects
VEGF-A	VEGFR2	VEGF-A binding to VEGFR2 causes new blood vessel formation: angiogenesis. This mechanism creates the blood supply for tumour and natural tissue growth. The therapeutic monoclonal Avastin (bevacizumab) binds and neutralises VEGF-A to block angiogenesis.
VEGF-C	VEFGR2 and VEGFR3	VEGF-C binds both VEGF2 and VEGFR3. VEGRF3 causes lymphangiogenesis (the formation of new lymph vessels). However, VEGF-C also stimulates blood vessel growth by binding VEGFR2 so is a possible resistance route against Avastin. Combining VGX-100 with Avastin may be synergistic.
VEGF-D	VEGFR3	VEGF-D's action and role is less well-characterised than VEGF-C. It may stimulate lymphangiogenesis.

Source: Edison Investment Research

Ceres Oncology

Ceres[i] Oncology is focused on the development of VGX-100, an anti-VEGF-C monoclonal antibody (see Exhibit 2). VGX-100 was developed by Human Genome Sciences; there is a net royalty estimated at 5.5%.[ii] An anti-VEGF-D candidate has been mothballed. VGX-100 is in a Phase I dose escalation study, due to complete in H113.[1] The likely single-agent dose will be 20mg/kg or 30mg/kg, but the combination may be 10mg/kg of Avastin plus 10mg/kg or 20mg/kg of VGX-100.

Ceres is planning two possible Phase II indications: firstly, as a potential treatment for secondary lymphoedema, a side effect of breast cancer surgery; and secondly, as a co-therapy for sold cancers with Avastin (bevacizumab, Roche) with or without additional chemotherapy. The probable Phase II solid tumour indications are recurrent GBM and mCRC.

VGX-100 composition of matter patents run until mid-2022 and extensions of up to five years are available, with data exclusivity of 12 years in the US and 10 years in the EU. Circadian also owns broad method-of-use patents covering biological inhibitors of the VEGF-C/D/VEGFR3 pathway, which run until mid-2033. Circadian has a strong patent position covering VEGF-C and D, so could gain licensing fees.

i Ceres is the ancient Roman fertility and grain goddess, typically shown seated with a flaming torch.
ii VGX-100 patents are now held by Teva. Human Genome Sciences transferred them to its subsidiary Cogenesys Inc, which was subsequently acquired by Teva. The patents are exclusively licensed to Circadian.

Exhibit 2: Ceres Oncology VGX-100 portfolio

Cancer	Stage	Mechanism
Recurrent GBM and mCRC	Phase I Initial data released Feb 2012	Monoclonal antibody against VEGF-C. In Phase I dose study. One arm is dose escalation of VGX-100 alone to either 20mg/kg or 30mg/kg. The second arm is a dose escalation in combination with Avastin. This runs to 10mg/kg to avoid excess toxicity. So far 16 patients have been dosed with VGX-100 alone with no toxicity reported. In the combination arm, the nine patients to date showed one instance of hypertension in a patient with a clinical history. Patients have a variety of solid tumours and efficacy indications are not expected. The next stage is planned as a 2013 Phase II GBM study with a possible 2014 trial in mCRC in 2014.
Breast	Lymphoedema	A complication of major breast cancer surgery where the arm swells unpredictably. There is a theory that VEGF-C drives the movement of excess fluid interstitial tissues.
Other	Preclinical	There seems to be a potential synergy with various tyrosine kinase inhibitors currently used for renal cancer. Potential indications may be prostate, CRC and ovarian.

Source: Edison Investment Research

Secondary lymphoedema: A new VGX-100 indication

Secondary lymphoedema is a chronic, progressive and often debilitating condition that occurs when high pressure, excessive fluid accumulates in tissue (see Exhibit 3). It is a well-known complication of breast cancer surgery where the adjacent (ipsilateral) arm swells (it can be in both arms). An anti-VEGF-C approach is potentially a promising drug treatment. Increased levels of VEGF-C have been found in lymphoedema patient samples and, in a small pilot study, inhibiting its receptor with Votrient reduced interstitial fluid pressure by 76% within a day. The effect on arm fluid volume after four weeks was modest, but the treatment was limited by significant toxicities. However, while these data are indicative, they cannot be deemed conclusive. In addition, preclinical data have shown variable results.

Potential development of VGX-100 in lymphoedema

Lymphoedema is a major unmet clinical need. Ceres Oncology Pty, a 100%-owned subsidiary of Circadian, intends to run a Phase II proof-of-concept study of VGX-100 in secondary lymphoedema following breast cancer surgery starting Q313. This may involve up to 20-30 patients at two dose levels of VGX-100 in an open-label study. The end points may be response (at least a 25% decrease in excess arm volume after four weeks) plus other measurements including changes in interstitial pressure and tissue fluid volume. If the Phase II proof-of-concept trial starts in Q313, data may be available during H114. This could enable a Phase III study to commence from late-2014. FDA agreement to the Phase III design and end points would be needed.

An orphan market

There are about 220,000 breast cancer cases per year in the US. Of these, 60% have no detectable lymph node spread, so are at low risk of lymphoedema. The incidence of lymphoedema is not well studied and that the numbers will vary with country and local surgical practise. Another 33% have lymph involvement but no metastasis. These would be the target group: about 75,000 cases per year. Lymphoedema does not necessarily occur immediately, although 80% of the more serious cases do occur within a year, so based on the number of patients who have had major surgery in the previous three years, the potential patient pool may be up to 215,000. There could be 6,000 severe cases within a year of surgery.[iii] In addition, there may be a prevalence of 37,000-less severe cases.[iv] Realistically, half these may be eligible for treatment: 18,000. Exhibit 3 notes that rates of up to 54% have been reported in a survey so numbers and use may be higher than used in projections.

iii Based on 75,000 at-risk patients and a 10% clinical incidence (7,500) with 80% of these within one year (6,000), of whom 50% (3,000) are diagnosed within six months of surgery.

iv Based on a rolling three-year population (215,000) and 20% prevalence so 43,000 cases less those immediate one-year cases implying 37,000. The condition may occur for 5-10 years post-surgery but data are lacking.

Exhibit 3: Secondary lymphoedema associated with breast cancer

Definition	Tissue oedema occurs when there is an imbalance between inward flow from the vasculature and outflow either to the circulation (veins) or lymph. The simplest measurement is of arm circumference. If the affected arm is swollen by 2cm or greater than the contralateral arm, lymphoedema may be diagnosed.
Lymphatic anatomy and breast cancer surgery	Lymph from the arm drains through the auxiliary lymph nodes. These are separate to the nodes draining the breast, although in very close proximity. Modern breast cancer surgery uses sentinel lymph node biopsy (SLNB) to check for metastatic tumours. To find the sentinel node for a tumour, a blue dye is injected at the tumour site and the dye traces back to the first lymph node. This is then sampled for any tumour cells. More radical surgery may involve auxiliary node dissection (ALND) combined with SLNB or removal of all lymph nodes.
Primary	This can affect any area and may be due to lymphatic malformation. It has no obvious direct cause such as surgery.
Secondary	This is the result of anatomical obstruction or disruption of the lymphatic system after surgery or due to disease.
Overall Incidence and prevalence	The National Cancer Institute cites 13-54% of patients suffer some swelling, a wide range. Higher levels are from a questionnaire survey by Paskett [2]who found 54% had arm and/or hand swelling with 32% reporting persistent effects within two years of surgery; note cases were not clinically verified. A study by Hayes *et al* in 211[3] cases found that 33% of patients developed lymphoedema up to 18 months after surgery. About 10% developed it within six months. Most were transitory, with only 40% having it for more than three months in the 18-month period. Of these, 63% developed it within six months, but these were often intermittent. A 251-patient study by Clark *et al* in a single hospital[4] found that 20% of patients developed lymphoedema within three years of surgery. Only 10% of patients had lymphoedema diagnosed during the study period. The remaining 10% were diagnosed at the one-off three-year follow-up and otherwise would not have recognised the condition. Of the patients recognised before the three-year follow-up, about 50% developed the condition within six months of surgery and 80% of this group did so within a year of surgery. A Brazilian study[5] found 20% of patients with lymphoedema and identified radiotherapy as a risk factor alongside obesity. Many of these patients had extensive surgery. Limiting surgery has reduced the lymphoedema rate.
Comparison of SLNB vs AND	A five-year study by McLaughlin et al (2008) in 936 patients compared SLNB relative to ALND.[6] In theory, SLNB should not affect auxiliary lymph drainage so a lower lymphoedema incidence would be expected. Patients with SLNB only had a 5% lymphoedema rate compared to 16% of patients who had also ALND. This difference was highly significant. Across reported studies, patients with SLNB only had a 0 to 7% risk of lymphoedema.
Risk factors	Risk factors are not consistent. Being over 50 may triple the odds, as does a sedentary lifestyle. Extensive surgery carries a 5.9-fold odds risk. Chemotherapy reduces the odds to 0.4. A BMI over 26 doubles the risk; Paskett found an odds ratio of 2.24 for obese patients. Radiotherapy is associated with lymphoedema, but more modern targeting may have reduced this. McLaughlin found that weight and BMI correlated as did infection and injury.[6].
Interstitial hypothesis and VEGF-C	VEGF-C might have a role in the pathophysiology of lymphoedema via reduced lymph velocity.[7] This causes a reduction in the movement of interstitial fluid, which triggers cells in the arm to produce VEGF-C. The effect of this is claimed to be on the blood vessels via VEGF-C binding to VEGFR2 since fluid is moving to and from blood vessels, but less so into the lymph. To stimulate the lymph, VEGF-C needs to bind VEGFR3 in lymph vessels. The effect is to cause an increased rate of fluid filtration bringing fluid, but not protein, into the tissues and causing swelling. The higher interstitial pressure leads to a greater fluid velocity into lymphatic vessels and this reduced VEGF-C production. So in the development of lymphoedema, VEGF-C levels will be high but then fall once the selling is stable. Reduction of VEGF-C or blocking of VEGFR2 should lead to a lower velocity reducing pressure and so reducing swelling.
VEGF-C and preclinical models	Various studies looked at VEGF-C administration in animal models of lymphoedema. These observe that exogenous VEGF-C, in some cases used with transplanted stem cells,[8] helps to rebuild the lymphatic system and reverse lymphoedema through lymphangiogenesis. Direct delivery of VEGF-C to excised node sites reduced lymphoedema.[9] If this is true in humans (animal modes track acute swelling), blocking VEGF-C would be counterproductive. A detailed 2006 study found that lymphatic hyperplasia with excess VEGF-C produced poorly functioning vessels.[10] In this case, reducing VEGF-C levels might help, although this was not tested.
Use of kinase inhibitors in lymphoedema	The VEGF inhibitor pazopanib (Votrient, GSK) has been tested for use in lymphoedema in a tiny 10-patient study. This showed that VEGFR inhibition cut interstitial fluid pressure by 76% within 24 hours with some reduction in tissue fluid volume. Five patients has a >25% reduction in arm volume after four weeks.[11] This shows that VEGF has a role in sustaining lymphoedema. The pazopanib toxicity was not acceptable and development has not continued.
Use of Avastin in lymphoedema	A 2009 study assayed VEGF-C levels in retrospective clinical samples from 16 patients with chronic lymphoedema against 31 matched controls.[12] The patients had increased VEGF-C (6,895pg/ml vs 5,349pg/ml, a 28% increased level). This is interesting, but may be cause or effect. Taken with the pazopanib data above, some role is indicated. A clinical study in 12 patients then administered bevacizumab (Avastin) to neutralise VEGF-A (not VEGF-C). Within 24 hours, the average level of interstitial fluid dropped by 42%. The trial was too small for significance, but two patients showed a 25% or greater reduction in excess arm volume after three weeks.

Source: Edison Investment Research from literature sources as cited

Lymphoedema is debilitating and a concern for all breast cancer patients that can persist and become debilitating irrespective of whether the cancer is cured. However, it is not life threatening so cancer-type pricing may be difficult. If an average course was US$20,000, the price targeted by circadian management based on initial market research, and 25-33% of the 24,000 eligible patients received treatment, the US market may be at about US$200m per year. Adding Europe and leading Asian-Pacific countries implies about US$250m global sales. Edison notes that the price and market share assumptions rely on a high level of efficacy.

Risk and value

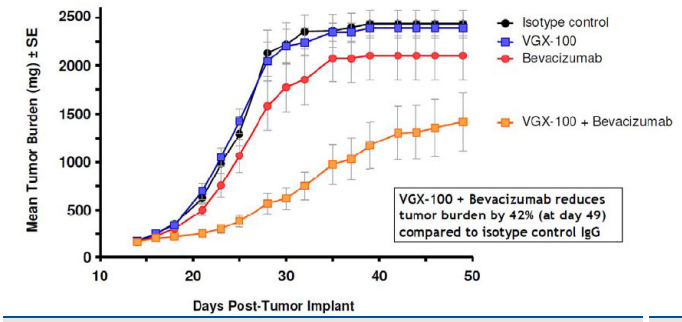
At this stage, lymphoedema is an interesting but unproven idea. Edison has used a 20% risk adjustment. This reflects the limited and indirect clinical data while acknowledging that there is a biological logic to target VEGF-C and that the proposed dose level of VGX-100 has been shown to be safe and tolerable in the ongoing solid tumour Phase I study. As the same product and dose may be used to treat solid tumours, this indication will have to be bundled with solid tumour indications for partnering. The Phase II lymphoedema data will be important in securing a good overall licensing deal.

VGX-100 to treat solid cancers

Preclinical data

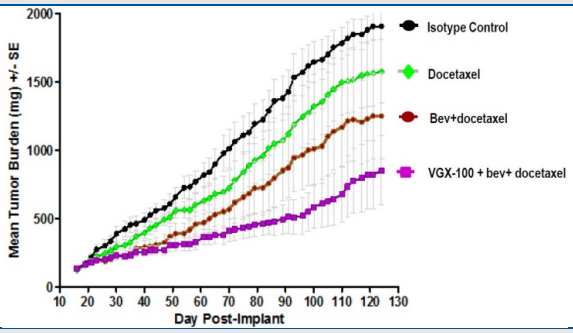
Preclinical data is available on the combination of VGX-100 with other agents: glioblastoma with Avastin (Exhibit 4), ovarian with Avastin and docetaxel (Exhibit 5) colorectal (CRC) with a tyrosine kinase (pazopanib) inhibitor combination (Exhibit 6) and prostate with Avastin and docetaxel (Exhibit 7).

Exhibit 4: Glioblastoma preclinical data



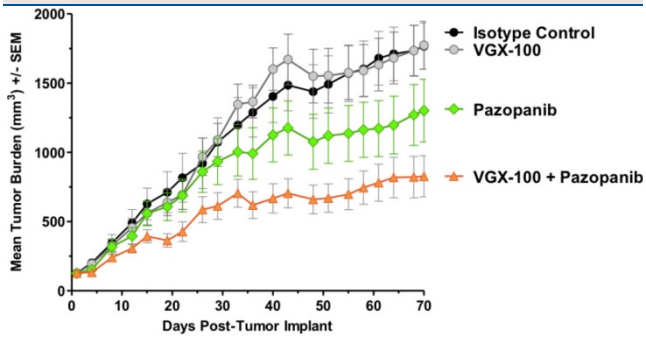
Source: Circadian Technologies

Exhibit 5: Ovarian preclinical model



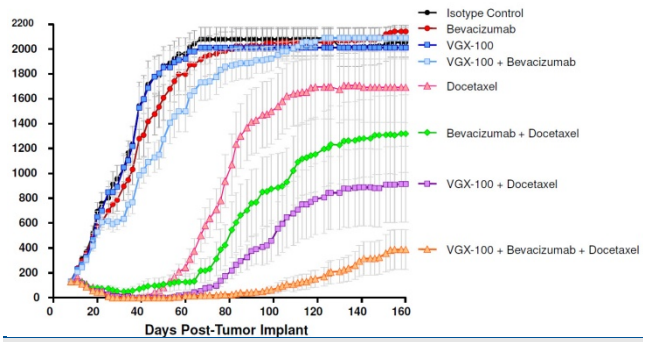
Source: Circadian Technologies

Exhibit 6: Colorectal preclinical data



Source: Circadian, Poster at EORTC-NCI-AACR November 2012

Exhibit 7: Prostate preclinical data



Source: Circadian, Poster at EORTC-NCI-AACR November 2012

Preclinical data from November 2012 shows that VGX-100 generates improved response rates with tyrosine kinase inhibitors; VEGFR-2 and VEGFR-3 are inhibited by these drugs. In a model of CRC, VGX-100 combinations with sorafenib (Nexavar, Bayer/Onyx, US$1bn 2012 sales), sunitinib (Sutent, Pfizer, US$1.2bn 2012 sales) and pazopanib (Votrient, GSK see Exhibit 5, fast-growing due to 2011 launch annualised c US$350m) have been tested. These preclinical models show single-agent efficacy and synergy with VGX-100. However, these kinase inhibitors are not indicated for GBM or mCRC.

Glioblastoma

Glioblastomas are highly vascularised and have been a consistent target for anti-angiogenic therapy. The VGX-100 dose in the GBM preclinical model was 40mg/kg: twice the expected human dose. A

critique of these models is that because the tumours grow so fast, vascular growth may respond quickly, whereas in the clinical situation, some patients have tumours that may be slower-growing and less susceptible to therapy.

Avastin is used as a single agent for relapsed GBM. A 25.9% objective response with a 4.2-month duration was seen in 85 patients treated with Avastin 10mg/kg every two weeks as a single agent. There was no evidence of any survival advantage. GBM escape mechanisms are poorly understood.[13] Gliomas can rebound if Avastin therapy is stopped.[14] Some reports suggest that Avastin encourages invasive tumour spread;[15] VEGF-C agents might retard this, depending on mechanism. The current plan is to initiate a Phase II in recurrent GBM in Q413, this will require a deal, hard in the short timescale, or private funding into Ceres. Marketing could start in 2018.

The standard US rate of new malignant central nervous system tumours is around 6.5 per 100,000 of the adult population: c 17-20,000 cases per year. GBM accounts for 54% of all malignant brain tumours with c 9,500 new cases per year.[16] Survival of GBM patients is low: 65% of patients die within a year and nearly 90% die within two years. The main treatment for primary GBM is radiotherapy with Temodar (temozolomide, Merck & Co) following surgery. In newly-diagnosed GBM, Temodar increased median survival from 12.1 to 14. 6 months: a 2.5-month benefit over radiation alone. Temodar lost patent exclusivity in the EU in 2009. In the first nine months of 2012, sales were US$699m; about US$1bn annualised. The US patent and exclusivity expire in February 2014 and a generic will enter the US market in August 2013. Other GBM therapies have a modest survival impact, eg Eisai's Gliadel (carmustine wafer) showed a 2.2-month survival benefit.

It has been hard for new therapies to show survival gains in GBM. A 500-patient Phase III with Cilengitide (Merck KGaA) failed to show efficacy when data reported in February 2013. NorthWest has an autologous cancer vaccine (CVax-L) in Phase III that may produce mid-2013 data. Celldex has an immunotherapy, rindopepimut, in Phase III with a 2016 possible data date.

Colorectal cancer

In mCRC, Avastin is indicated for first- or second-line treatment of patients at 5mg in combination with IFL (5-Fluorouracil and Leucovin) or 10mg/kg doses with FOLFOX-4 (oxaliplatin, leucovorin, and 5-fluorouracil). A mCRC study with VGX-100 may start in 2014. A small lead-in combination dose-ranging study may be required given the toxicity of the chemotherapy used. Assuming partnering in 2014, a mCRC indication could be approved by 2019. There is evidence for VEGF-C role.[17]

Zaltrap (ziv-aflibercept, Sanofi, a VEGFR1+2 mimic) in combination with FOLFIRI has been approved in mCRC for oxaliplatin-refractory patients. This binds VEGF-A, and PlGF (placental growth factor), but does not appear to offer much gain over Avastin. Avastin becomes generic in July 2019 in the US (2022, EU) and biosimilar versions may appear, although this is still very uncertain for many products.

Opthea

Opthea is developing VGX-300. This project is preclinical with a possible Phase I start in 2014. It is structured as a separate business that is seeking 'Series A' investment to fund a Phase II proof-of-concept study. VGX-300 is a soluble VEGFR-3 receptor that will be injected directly into the vitreous humour of the eye in wet AMD, a common condition where blood vessels grow through the retina and bleed into the vitreous humour. This obscures the vision and damages the retina. About 70% of patients respond to Lucentis (ranibizumab, Roche), but only 30% show a sustained improvement in vision. VGX-300 traps and neutralises both VEGF-C and D. In this respect, it is similar to Eylea (afilbercept, Regeneron), which is a recombinant protein with two binding regions. It binds VEGF-A (via

a VEGFR2 site) and PlGF and VEGF-A and B (at a VEGFR1 site). Lucentis binds only VEGF-A. The VGX-300 patent runs until 2025 in the US and 2021 in the EU. Patent extensions of up to five years are available plus data exclusivity. Additional patents have recently been filed, which may provide coverage until at least 2034.

The market for VGX-300 is considerable. Eylea was launched in the US in November 2011 and had US sales of $838m in 2012. Eylea has an eight-week dose interval rather than the 28 days of Lucentis. Lucentis 2012 sales were CHF1.48bn (US$1.6bn). With broad spectrum anti-VEGF activity, VGX-300 may take a significant share of the market. However, the preclinical data package is currently being generated and the need for investment and a Phase I deal to fund extensive studies means that shareholder returns may be diluted depending on when a deal is done and the financing terms obtained. Ideally, a single major partner invests alongside Circadian and develops VGX-300.

A dry eye and corneal graft indications are possible for VGX-100 but need a topical formulation. These are valued at a 5% risk adjustment as no topical formulation is currently planned.

Precision Diagnostics

Precision has two main products: a VEGF-D test and a proprietary software algorithm to predict the tissue origin of Cancer of Unknown Primary (CUP). The VEGF-D test (Exhibit 8) is used to diagnose a rare lung cancer (LAM). This test is available through the University of Cincinnati Children's hospital.

Exhibit 8: Lymphangioleimyomatosis

Definition	Lymphangioleimyomatosis (LAM) is a very rare disease of child-bearing women where muscle cells migrate into lung tissue and form cysts. Over a long period, this degrades lung function. There is no effective treatment. The disease is linked to the genetic condition tuberous sclerosis complex (TSC), treated with Votubia (everolimus, Novartis).
Incidence	The US prevalence of TSC is perhaps c 25,000. About 40% of adult pre-menopausal women with TSC develop LAM. On a US population incidence of 1:12,500, there are c 25,000 TSC cases. Assuming 50% female and with 34% of adult women showing the disease,[18] the prevalence might be c 4,000. This is c 50 new TSC associated cases per year in the US plus presumably c 250 spontaneous mutation cases: in total, 300 new US cases per year.[19]
Clinical basis	VEGF-D levels are elevated in LAM, but this alone is not diagnostic since there is a high-range overlap between normal and disease patients.[20] The tests help with diagnosis and could be used for disease progression monitoring.
Role of VEGF-D test	LAM is screened by expensive CT scanning so a reliable diagnostic screen could be widely used. Long term, the test could be used in diagnosing lung diseases and in cancer monitoring, but there is no clinical evidence yet to support this.
Value	Circadian estimates that the market may be up to 25,000 tests at $300 per screening test. Of this, Circadian might gain A$75 per test: A$1.5-2m revenues. However, routine screening needs FDA regulatory approval and a CE mark.

Source: Edison Investment Research, plus literature sources

The CUP test (Exhibit 9) enables a genetic assignment of a primary origin to help in selecting treatment options. This will be marketed in Australia, New Zealand, Malaysia and Singapore by Heathscope from Q213 with possible international sales by Circadian or its partners from 2014-15 after FDA approval and CE marking. There is also a VEGF-C test as a possible marker for cancer progression. Circadian has a deal with Bio-Rad for global distribution of VEGF-C and D research use assays.

Vegenics: IMC-3C5 – solid refractory cancers of any type

VGX-300 is a monoclonal antibody that blocks the VEGFR-3 receptor. It has been partnered by ImClone, now owned by Lilly, and accounts for most of Circadian reported revenues. Circadian will receive milestones and a double-digit royalty. IMC-3C5 is in a Phase I dose-escalation study (NCT01288989) in 40 advanced solid tumour patients. The study should report in Q313. The VEGFR-3 pathway is involved in tumour angiogenesis and lympangiogenesis. The current Phase I is not likely to yield meaningful efficacy data, so the question of whether this antibody retards tumour progression will remain unclear until Phase II data, probably not before 2016. The product has been given a nominal US$1bn market potential on the basis that Lilly will seek that level of sales. It has a Phase I probability

of 15%, as it is unclear how it fits into the partner portfolio. Some data were reported at ASCO. Vegenics was created by Circadian and became a fully owned subsidiary in August 2008.

Exhibit 9: CUP test data file

Incidence	About 3-5% of cancers (typically 10-18 per 100,000) have no apparent primary tissue source. CUP rates have fallen in the EU from about 18/100,000 in 1994 to about 11/100,000 in 2009. Rates increase dramatically with age.
Survival	As cancer therapies are based on the tumour type, knowing the tissue origin is necessary for optimal treatment. However, median survival is only three to four months with less than 25% of patients alive after a year and five-year survival of 10%. In most cases, intervention is harmful with no therapeutic gain.
Potential test numbers	In the US, there may be about 4-50,000 cases per year out of about 1.5m total cancer diagnoses. This puts the realistic world market for a CUP test at up to150,000 tests. Realistically, actual use will be much lower. The current market is via Healthscope in Australia (3-4,000 cases, NZ (800 cases), Singapore, 1,000 cases and Malaysia (5,000 possible on population grounds but much less in practise).
Status	The CUP test, branded CUPGUIDE is in Beta-stage testing in Australia by Healthscope. It might be commercially available from March 2013 on submission of validated data for peer-review publication. Circadian intends to apply for US approval by the 510(k) route and gain an EU CE mark, probably over 2014-15.
Performance	After three iterations of the software, the primary tumour was correctly identified in 98.5% of samples across 15 tumour types. This shows the test could be very powerful in identifying unknown tumour types.
HealthScope	Healthscope Pathology, part of the ASX-listed Healthscope hospital and healthcare group currently operates over 60 laboratories and 300+ patient centres in Australia and internationally in New Zealand, Singapore and Malaysia.
Pricing and royalty	The price is A$1,200-1,600 including the RNA testing done by Healthscope. Circadian gets about 6% royalty or A$90 per test. Assuming a 20% penetration 5% Malaysia, the Healthscope royalties might be A$100-200,000.
How does it work?	The software uses genetic test data and applies iterative analyses based on pattern identification. The algorithm was devised by National ICT Australia The software has shown a specificity of 98.5% across 15 tumour types showing that the test could be very powerful in identifying unknown tumour types.

Source: Edison Investment Research, based on Circadian and Healthscope company information and published cancer statistics

Sensitivities: Uncertainties over efficacy and funding

The VGX-100 lymphoedema indication offers a faster route to market, but the rationale has to be clinically verified in Phase II and the high price relies on excellent, but unproven, efficacy. The two planned solid tumour VGX-100 Phase II studies need a partner as Circadian cannot guarantee to be able to fund the trials to completion. The first indication, in recurrent GBM, meets a major need as Avastin does not prolong survival. It is a highly risky first indication with data unlikely before H115. The bigger market is mCRC but this needs a bigger Phase II. Accordingly, investors have to assume a Ceres deal or funding in 2014 and price in the risk and dilution if this does not happen; a combination of the two is likely. Opthea's development of VGX-300 may be attractive now to big pharma as the therapy should be synergistic with both Eylea and Lucentis in the growing $2.6bn wet AMD market. If no deal is available, a private funding is likely. Patents and patent extensions provide good cover with minimal risks of generic completion until 2030, the forecast period. Precision has speciality diagnostics that may have limited immediate revenue impact.

Valuation: Dependant on a 2014 deal and future cash needs

The core value scenario is mid-2014, US$20m+ upfront VGX-100 deal with no dilutive external funding. It is assumed that all VGX-100 indications are included at a high 20% royalty. Opthea has been valued on the basis of a 2014 deal at 50% probability with a 25% external investor equity stake. This gives a total NPV of A$1.93 share.

The uncertainty lies in the mix and timing of deals, private equity and public equity. Public shareholders risk significant loss of potential future value if core subsidiaries like Ceres and Opthea take in private investors. A typical structure might be a convertible preference loan with warrants which might be significantly dilutive on maturity. Edison cannot predict the timing and form of any such investment.

Exhibit 10: Valuation summary

	Indication	Probability	Royalty	NPV (A$m)
Ceres	VGX-100 partnering	50%		34.53
	VGX-100 in glioblastoma	20%	20%	43.78
	VGX-100 with Avastin in mCRC	20%	20%	56.62
	VGX-100 Lymphoedema	20%	20%	46.13
	IMC-3C5 (Imclone partnered)	15%	5%	23.76
Opthea	VGX-300 Wet AMD	10%	15%	12.55
	Corneal grafts	10%	15%	2.00
Precision	Diagnostics (CUP, LAM)	N/A	N/A	4.64
Total risk-adjusted revenues				221.50
Royalties to third parties				(47)
Net revenues				175
Continuing value @ 15-fold multiple				73
Net cash flows				20
Total value				93.69
Undiluted NPV per share (48.5m)				A$1.93

Source: Edison Investment Research

Financials: Cash until FY15

Circadian has indicated that its total annual cash burn will be A$7-8m in both FY13 and FY14. The Phase II lymphoedema trial might cost A$2m, but each VGX-100 Phase II in a solid tumour could cost A$5m so these will need separate funding or a partner. R&D in H113 was A$1.9m. Edison estimates that R&D (excluding IP) will be about A$4m in FY13 and FY14 before Ceres and Opthea conclude partnering deals. At the interim stage, administration costs were level at A$2m plus A$0.27m in IP costs. Cash on 31 December 2012 was A$12.12m after an H113 operational cash burn of A$4.32m. On the assumptions above, Edison projects that Circadian has cash though FY14 but FY14 funding will be required; this might be through private deals in Ceres and Opthea. Circadian could sell its equity in two ASX-quoted biotech companies; these were valued at A$2.7m on 31 December 2012.

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Exhibit 11: Financial summary

A$'000s	2011	2012	2013e	2014e
Year end 30 June	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS				
Revenue	446	510	600	650
Cost of Sales	0	0	0	0
Gross Profit	446	510	600	650
EBITDA	(11,459)	(8,418)	(8,365)	(8,815)
Operating Profit (before amort and except)	(11,487)	(8,450)	(8,400)	(8,850)
Intangible Amortisation	0	0	0	0
Exceptionals	(611)	0	0	0
Other	(333)	0	0	0
Operating Profit	(12,432)	(8,450)	(8,400)	(8,850)
Net Interest	1,388	976	329	(100)
Profit Before Tax (norm)	(10,099)	(7,474)	(8,071)	(8,950)
Profit Before Tax (FRS 3)	(11,043)	(7,474)	(8,071)	(8,950)
Tax	778	2,402	0	0
Profit After Tax (norm)	(9,654)	(4,906)	(8,071)	(8,950)
Profit After Tax (FRS 3)	(10,265)	(5,072)	(8,071)	(8,950)
Average Number of Shares Outstanding (m)	46.2	46.5	48.5	48.5
EPS - normalised (c)	(20.9)	(10.2)	(16.6)	(18.5)
EPS - normalised fully diluted (c)	(20.9)	(10.2)	(16.6)	(18.5)
EPS - (IFRS) (c)	(22.2)	(10.9)	(16.6)	(18.5)
Dividend per share (c)	0.0	0.0	0.0	1.0
Gross Margin (%)	100.0	100.0	100.0	100.0
EBITDA Margin (%)	N/A	N/A	N/A	N/A
Operating Margin (before GW and except) (%)	N/A	N/A	N/A	N/A
BALANCE SHEET				
Fixed Assets	2,109	4,435	4,435	4,435
Intangible Assets	189	677	677	677
Tangible Assets	98	107	107	107
Investments	1,822	3,652	3,652	3,652
Current Assets	22,393	18,170	10,099	1,747
Stocks	0	0	0	0
Debtors	289	1,731	1,731	1,731
Cash	22,104	16,439	8,368	16
Other	0	0	0	0
Current Liabilities	(2,436)	(2,125)	(2,125)	(2,674)
Creditors	(2,436)	(2,125)	(2,125)	(2,674)
Short term borrowings	0	0	0	0
Long Term Liabilities	(242)	(283)	(283)	(283)
Long term borrowings	0	0	0	0
Other long term liabilities	(242)	(283)	(283)	(283)
Net Assets	21,824	20,197	12,126	3,226
CASH FLOW				
Operating Cash Flow	(11,400)	(9,338)	(8,365)	(8,266)
Net Interest	1,396	976	329	(100)
Tax	588	(43)	0	0
Capex	(77)	(38)	(35)	(35)
Acquisitions/disposals	0	441	0	0
Financing	15	1,022	0	0
Dividends	0	0	0	0
Net Cash Flow	(9,477)	(6,981)	(8,071)	(8,402)
Opening net debt/(cash)	(31,855)	(22,104)	(16,439)	(8,368)
HP finance leases initiated	0	0	0	0
Other	(274)	1,316	0	50
Closing net debt/(cash)	(22,104)	(16,439)	(8,368)	(16)

Source: Circadian Technologies, Edison Investment Research. Note: The financial summary places interest as a cash flow item not as revenue as shown in the Australian accounts. A VGX-100 deal at 50% probability is included in the indicative valuation. Opthea is assumed to attract separate equity or loan funding with 25% dilution plus a deal.

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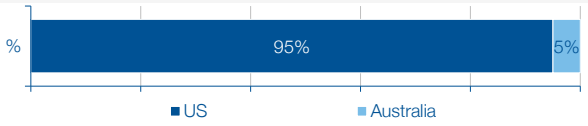
Revenue by geography



CAGR metrics		Profitability metrics		Balance sheet metrics		Sensitivities evaluation	
EPS 2010-14e	N/A	ROCE 13e	N/A	Gearing 13e	N/A	Litigation/regulatory	●
EPS 2012-14e	N/A	Avg ROCE 2010-14e	N/A	Interest cover 13e	N/A	Pensions	○
EBITDA 2010-14e	N/A	ROE 13e	N/A	CA/CL 13e	N/A	Currency	●
EBITDA 2012-14e	N/A	Gross margin 13e	N/A	Stock days 13e	N/A	Stock overhang	◖
Sales 2010-14e	N/A	Operating margin 13e	N/A	Debtor days 13e	N/A	Interest rates	○
Sales 2012-14e	N/A	Gr mgn / Op mgn 13e	N/A	Creditor days 13e	N/A	Oil/commodity prices	○

Management team

CEO: Robert Klupacs

Mr Klupacs joined Circadian in 2005, becoming managing director in 2008. Previously, he was CEO of ES Cell International, a human stem cell company, and COO of the Monash Institute of Reproduction and Development. He has a BSc in Pharmacology and is a registered patent attorney.

Director clinical research: Dr Ian Leitch

Dr Leitch joined Circadian in September 2011. Before joining Circadian, he was involved in developing novel therapeutics at Amgen and previously at Miravant. He has a PhD from the Department of Pharmacology at Monash University.

CEO Opthea: Dr Megan Baldwin

Megan joined Circadian in 2008 and was appointed CEO of Opthea Pty Ltd in November 2012. Prior to joining Circadian, she was employed at Genentech. She holds a PhD in Medicine from the University of Melbourne after doctoral studies at the Ludwig Institute for Cancer Research. Her research speciality was angiogenesis.

CFO Mr Steven Zammit

Steven Zammit joined Circadian on February 25 2013.
.He was most recently CFO of the Oliver Hume Real Estate Group and prior to that was with ASX listed Molopo Energy Limited. He is a CPA with a Business Degree from RMIT and a Masters of Banking and Finance from Monash University.

Principal shareholders	(%)
Packer & Co	15.31
Licentia	6.48
Ludwig Institute for Cancer Research	6.43

Companies named in this report

Imclone, Regeneron, Pfizer, Roche, Bayer, GSK, Merck