CEO on H1 Results & Outlook

Open Briefing interview with CEO & MD Robert Klupacs

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Circadian Technologies Limited (ASX:CIR, OTCQX:CKDXY) is an Australian biotechnology company developing biologics-based therapies for the treatment of cancer, eye disease and other serious human illnesses. Circadian owns a portfolio of products and intellectual property related to Vascular Endothelial Growth Factors (VEGFs), a class of proteins that play a critical role in regulating blood and lymphatic vessels.

In this Open Briefing®, Robert discusses:

- Outlook for cash burn
- Trial design targets key value inflection points in oncology, eye disease in short term
- Partnering prospects and strategy

Record of interview:

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Circadian Technologies Limited (ASX: CIR; OTCQX:CKDXY) reported net operating cash outflow of $4.32 million for the first half ended 31 December 2012, compared with outflow of $3.87 million in the previous corresponding period. This primarily reflected increased spending on R&D relating to the ongoing Phase I VGX-100 trial in cancer patients. What is the outlook for cash burn for the current year ending 30 June 2013?

CEO & MD Robert Klupacs
We still expect our total cash burn for 2012/13 to be between $7 million and $8 million on an annualised basis. The final amount for the year will depend on the timing of the completion of our current Phase I VGX-100 trial and how aggressive we are with our studies and development activities in the Opthea business.

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Cash stood at $12.12 million as at 31 December 2012, down from $16.44 million six months earlier. Given your objective of demonstrating clinical proof of principle for your assets in Phase II studies, are you adequately funded to progress towards this objective in the short to medium term?

CEO & MD Robert Klupacs
As we noted in our half year report, any decision to proceed with major Phase II or IND enabling studies will be made in the context of having appropriate levels of finance in the company, or the ability to raise additional finance to fund the studies and meet study end-points. If need be, we still have the option to defer the time frame of some of the studies while financing is finalised. Notwithstanding, based on our current thinking around probable Phase II study designs, we think we can achieve our objective with the $12 million we have available, as well as some of the liquid assets we have.

Large Phase II studies particularly in solid tumours conducted by biologics companies like us can cost upwards of $5 million each, which would entail additional funding. However, Ceres Oncology has an opportunity to complete a Phase II clinical proof of concept study of VGX-100 in cancer related lymphedema in up to 30 patients for an estimated cost of less than $2

million. To date Ceres Oncology (our 100 percent owned subsidiary) has successfully managed the ongoing Phase I clinical study within the projected timelines and budget, and that would also be the expectation for the Phase II clinical program.

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Ceres Oncology expects to complete its Phase I trial of VGX-100 in April, and to publish the results in the September quarter. As you've just mentioned, you are considering plans to undertake Phase II studies of the compound in lymphedema as well as conducting a Phase II study of VGX-100 in combination with Avastin® as a treatment for recurrent glioblastoma. What is the rationale for selecting these two indications for the crucial Phase II trials of VGX-100?

CEO & MD Robert Klupacs
The cancer related lymphedema indication has been on the radar for Ceres Oncology since the American Society of Clinical Oncology (ASCO) meeting in Chicago in early June last year, where we were able to review emerging data and have discussions with leading breast cancer clinicians who had showed that VEGF-C appears to be upregulated in women with breast cancer related lymphedema. These clinicians have published pilot clinical results with small molecule inhibition of the receptors of VEGF-C reporting promising efficacy in the disease, however ongoing development of this small molecule approach is limited by unacceptable toxicities due to the known non-selective nature of this small molecule therapy.

Ceres Oncology is developing VGX-100, which is a molecularly targeted fully human monoclonal antibody therapy for VEGF-C which has shown favourable safety/tolerability in animal toxicology studies and the ongoing Phase I oncology clinical study.

The feedback from key breast cancer opinion leaders is that VGX-100 would be expected to be a better candidate if the safety profile we're seeing in our current Phase I study is maintained in the cancer related lymphedema patient population. Based on the clinical measures of response in lymphedema, it appears that if VGX-100 demonstrates efficacy, the effects will be seen relatively quickly. Therefore the time lines for a Phase II study would be much shorter than that expected for a solid tumour study.

A Phase II lymphedema study would use VGX-100 as a single agent, which also offers advantages over a combination study with Avastin® and/or chemotherapy in solid tumours. Ceres Oncology estimates that the study could be completed in 12 months or less based on expected robust patient recruitment to the study due to limited treatment options.

Breast cancer related lymphedema is estimated to cost the US healthcare system US$1 billion to US$2 billion per annum based on the need for continuous physical and compression therapy, and the impact of the disease on patients' ability to work. It's a disease with significant physical, functional and quality of life issues for affected patients. Given that it's likely around one in four women with prior breast cancer surgery are likely to develop related lymphedema, there is a major unmet clinical need.

In recurrent glioblastoma multiforme ("brain cancer"), which is a highly angiogenic tumor type, Avastin® is approved as a single agent treatment but it has only demonstrated modest survival benefit. Some leading neuro-oncologists believe that this is due to the tumour adapting to the therapy by stimulating the release of other pro-angiogenic factors as an escape mechanism. VEGF-C is another major player in the ongoing angiogenesis process of the disease. We have shown in other cancer types that VEGF-C levels increase as patients treated with Avastin® disease becomes worse. Therefore combining Avastin® with VGX-100 in patients who have failed first-line therapy is a very promising approach for Ceres Oncology.

Recurrent glioblastoma is a very aggressive cancer, so if a significant effect on progression free survival can be shown in patients receiving VGX-100 combination therapy it would represent a real benefit in this disease. Ceres Oncology estimates that it could complete

such a study over an 18 to 24 month period, however the cost of the study would require additional funding.

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Opthea, your wholly owned subsidiary focused on developing VGX-300 for eye disease applications, has commenced pre-clinical studies of VGX-300 for the treatment of "sub-responding" wet age related macular degeneration (AMD). You expect IND-enabling studies to commence in the second half of calendar 2013. What is the potential market for VGX-300 in this indication and how does it compare with that for VGX-100 in "front of eye" diseases, which you've previously flagged as a development target?

CEO & MD Robert Klupacs
Treatments for wet AMD that are currently available include the recently launched Eylea®, which was developed by Regeneron Pharmaceuticals and Bayer and is already generating greater than US$800 million of annual sales, and Lucentis®, developed by Genentech (now Roche), which has annual sales of about US$1.5 billion worldwide. Both drugs target VEGF-A and sales are forecast to grow significantly over the next couple of years.

While these drugs have revolutionised the way wet AMD can now be treated and maintain vision in many patients, only 40 to 50 percent of those who take the drugs targeting VEGF-A will actually experience an improvement in their vision. Given that wet AMD is a disease characterised by aberrant angiogenesis, and we know that VEGF-C can potently stimulate this process, we strongly believe that the combination of our drug VGX-300 with the existing therapies will lead to vision gain in those wet AMD patients who are currently experiencing no vision gain with these therapies. If we can demonstrate this clinically, the commercial opportunity for Opthea with VGX-300 is very significant, particularly in light of the commercial success of Lucentis® and Eylea®, and given that the incidence of wet AMD is increasing every year due to the aging population worldwide.

Front of the eye disease offers much more discrete market segments. The biggest market opportunity in front of the eye disease is dry eye disease. While we think the data we have is very promising in this setting, we recognise that in order to move forward in this indication we'll likely need to develop a topical formulation. This will require significant financial investment and development time. Consequently, we have de-prioritised the activities for corneal disease to allow focus on the VGX-300 development program for wet AMD.

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Precision Diagnostics, the wholly owned subsidiary developing your diagnostic and reagent products, expects sales revenue to start flowing in the current half year from licensee Healthscope's CUPGUIDE test for cancer of unknown primary (CUP). The test was released by Healthscope in September 2012 in Australia, New Zealand, Singapore and Malaysia. What indications have you seen of the potential sales of CUPGUIDE in these markets? What is your strategy for the test in other markets?

CEO & MD Robert Klupacs
The feedback from Healthscope is that the key oncologists are very supportive; they are starting to order the tests but there's still going to be some lead time before sales really start to rise as a result of key opinion leader endorsements. This financial year, volume sales are expected to be in the hundreds, but Healthscope is targeting sales of 1,000 to 3,000 tests per annum in its region in the next 18 to 36 months. At around $1,500 per test, that's annual sales of up to $5 million, of which we get a large percentage in royalties.

We're looking at various models for the commercialisation of CUPGUIDE for the rest of the world. Our current preferred course is to partner with specialist pathology providers that already have their own molecular diagnostics and dedicated sales teams. We're looking to have discrete partnerships in the US, Canada and two or three major markets in Europe. We'd expect any licensing deals to include an upfront component, product development milestones and royalties on sales, but we will also look at arrangements where we might

support local trials for regulatory and re-imbursement approval in return for higher royalties on sales.

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Royalty and license fees totalled $0.28 million in the first half, up from $0.24 million in the previous corresponding period. ImClone, licensee of a VEGFR-3 therapeutic antibody, expects to complete its Phase I trial of the drug in the current half year, and Ark Therapeutics, licensee of VEGF-D gene therapy products, commenced Phase II studies in October. What implications do these developments have for your royalty and license fee income over the next six to 12 months?

CEO & MD Robert Klupacs
The developments won't have a huge impact on us over the next six to 12 months because most of our income from these deals is in the form of annual fees; it's only at certain later development stages that big milestone payments would occur.

However we expect our total royalties to continue to increase as a result of CUPGUIDE commercialisation, as well as increasing royalties from the increasing number of licensees we have or will sign up in the research reagents market segment.

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Circadian's "available for sale" financial assets were valued at $2.70 million as at 31 December 2012, down from $3.65 million six months earlier. Holdings in Antisense Therapeutics Limited and Optiscan Imaging Limited account for the majority of the assets. How does maintaining these holdings fit with your strategy of separating the business into three clear streams? Have your intentions with regard to these investments changed?

CEO & MD Robert Klupacs
Circadian is a drug development company and as we discussed earlier, implementation of a drug development strategy requires significant amounts of investment to bring projects to value inflexion points. One dilemma we face is that, partly because of these holdings, investors still perceive us to be an incubator fund, which is a business model we moved away from more than five years ago, and continue to value us based on our cash and investments in listed companies rather than our intellectual property.

Our core business is developing intellectual property, not investing in ASX listed companies, but we'll continue to hold these remaining investments until we can realise appropriate shareholder value: the holdings are non-core and at some point will be divested to release cash for our core business. At present, however, we believe the true value of Antisense and Optiscan is yet to be reflected in their market prices. We're expecting this to change in the short to medium term because published statements by both companies indicate that they are nearing major value accretion events.

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Balance sheet improvements through grants, partnership income and/or capital raisings are among the developments you expect over the next six to 12 months. In which areas are such developments likely? How has your restructuring of the business positioned it in relation to improving the balance sheet?

CEO & MD Robert Klupacs
We believe there's a real possibility of a partnering opportunity for Ceres Oncology in the next 12 months. From discussions we've had with major pharmaceutical companies, a key data outcome will be demonstrating an acceptable safety profile of VGX-100 when used in combination with Avastin®.

There are also opportunities for Ceres Oncology to attract grant funding for the cancer related lymphedema clinical study given the underserved patient population and major unmet need.

In the eye disease area, we've been very encouraged by the strong level of interest shown by the major pharmaceutical companies and speciality ophthalmology companies in VGX-300 and their knowledge of our program. There's no doubt that the success of Eylea® in the AMD segment over the last 12 months has really opened the eyes (sorry!) of many of the players who aren't in the ophthalmology space, as well as existing speciality ophthamology players. The fact that we have a drug that's very similar to Eylea®, and in combination with Eylea® could knock down all the members of the VEGF family of proteins, is quite a compelling story. Back of the eye disease is a very hot area at the moment and given there's not a huge amount of opportunity for big pharma to get into the space, we believe there's a possibility of a pre-clinical partnering opportunity for Opthea in this setting. That's a possibility that probably didn't exist six months ago. That it does now is at least partially due to our ability to offer a very focused story via our dedicated eye disease subsidiary Opthea.

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Thank you Robert.

For more information about Circadian Technologies, visit www.circadian.com or call Robert Klupacs on (+61 3) 9826 0399.

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