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CEO on VGX-100 clinical development plans

Open Briefing with CEO & MD Robert Klupacs

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In this Open Briefing®, CEO & MD Robert Klupacs discusses

- **Planned IND filing for VGX-100 in the US**
- **Implications of recent data indicating biomarker status of Circadian proteins**
- **Strategy for generating shareholder value**

Open Briefing interview:

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Circadian Technologies (ASX: CIR) recently announced it aims to file an investigational new drug (IND) application with the US Food and Drug Administration (FDA) in Q4 2011 to enable it to commence Phase I clinical trials of its lead molecule VGX-100 (a vascular endothelial growth factor C (VEGF-C) inhibitor) in cancer patients. Could you outline the design of the trials, end points and anticipated time lines?

MD & CEO Robert Klupacs
The first Phase I studies will be 'dose escalation' studies designed to assess safety and to find the optimal dose for Phase 2 studies. These will involve enrolling an initial group of patients who will be subjected to a low dosage of VGX-100. If we find that dosage is well tolerated, we then increase the dosage in subsequent groups until we identify a maximum tolerated dose.

There are two arms to these trials: the first will test VGX-100 alone and the second will combine it with Avastin, a widely used anti-cancer drug antibody to a related target VEGF-A. The two arms of the trials will be run concurrently and should take about 12 months to complete.

The primary end point of the trial is safety: we're looking to identify a well tolerated dose that we can use in our Phase II study. However, the trial has been designed so that if there are signs of patients responding positively, they'll remain on the drug as long as it's having an effect.

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In April, Circadian's licensee, ImClone Systems (a wholly owned subsidiary of Eli Lilly and Company) commenced Phase I clinical trials of the anti-body IMC-3C5 focused on blocking the VEGFR-3 receptor. Are there any commercial or clinical synergies between these trials and Circadian's VGX-100 trials?

MD & CEO Robert Klupacs
Even though IMC-3C5 and VGX-100 are different antibodies targeting different parts in the VEGF-C/VEGFR-3 axis, the results from the IMC-3C5 trials could assist us in VGX-100 development, because both drugs act, albeit differently, on the same pathways. For example, the information around the biomarkers identified in the IMC-3C5 trials, and their effects on other proteins expressed in the blood of the patients treated with it, could potentially have relevance for our own studies.

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A recent study by The University of Texas MD Anderson Cancer Center on colorectal cancer patients found that resistance to treatment with Avastin was associated with raised levels of plasma VEGF-C concentrations. What are the implications of this data for the use of Circadian's VGX-100 in combination with Avastin?

MD & CEO Robert Klupacs
This data is very significant. This points to VEGF-C as a mechanism of tumour "escape" from Avastin and provides further evidence for the concept of combining VGX-100 with Avastin to improve patient outcomes with anti-angiogenic therapy. Avastin has the ability to inhibit cancer disease progression, but doesn't always have an overall effect on improving survival. We believe this is because Avastin, which exerts its effects by blocking VEGF-A, ultimately causes the tumour to adapt by turning on other angiogenic proteins, such as VEGF-C, to continue the tumor growth and metastatic spread. We believe that by adding VGX-100 to Avastin to also block VEGF-C as well as VEGF-A, tumour growth can be inhibited for much longer, resulting in a more positive effect on the survival of cancer patients than Avastin alone. We are confirming the MD Anderson findings in larger studies.

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The scientists who conducted the study said it "provides further rationale for the development of VEGF-C and/or VEGF-D based biomarker tests to monitor cancer therapy." What further work would need to be done to enable you to begin marketing these biomarker tests and what is the potential market for them?

MD & CEO Robert Klupacs
To bring these VEGF-C and VEGF-D biomarkers to commercialisation will require much larger clinical samples. Fortunately, much of this work is now possible because clinicians around the world now routinely collect tissue and blood samples for biomarker analysis. We have commenced collaborations with a number of these groups to assess VEGF-C and VEGF-D levels in patients undergoing various cancer therapies. This is important information to register VEGF-C and VEGF-D biomarker kits with the FDA or European authorities for routine clinical use.

We think the potential market is considerable, given the prospect of not only identifying patients who may specifically respond to a VEGF-C inhibitor such as VGX-100, but also because such tests could be used to identify patients who aren't responding, or who are

unlikely to respond, to chemotherapy drug regimes. Given the costs of some of these therapies, as well as the need to start patients on other therapies as soon as possible if they are unlikely to respond, such tests are likely to be of significant value as well as be used in high numbers.

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Are there any similar biomarkers currently in use?

MD & CEO Robert Klupacs
The concept of measuring proteins or hormones for an indication of how a drug is working is quite common but there is a real need to find more predictive biomarkers of drug response. One of the best examples is the breast cancer drug, Herceptin. This drug works much better in patients who are positive for the biomarker human epidermal growth factor receptor 2 (HER2). In most countries of the world now, the drug is only prescribed if the patient is found to be HER-2 positive based on a biomarker companion diagnostic.

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You announced recently that you will also be developing VGX-100 as a new therapeutic for diseases of the cornea ("front of the eye"). What is the rationale for this decision, and what is the anticipated time line for clinical development?

MD & CEO Robert Klupacs
We believe the VEGF-C blockade can have a number of clinical applications. The work we've done to date in developing VGX-100 in cancer can be leveraged to support development in non-cancer indications. We've had, and continue to have, a program of work internally and externally looking to identify other potential therapeutic uses.

The front of the eye disease setting is an area of high prospects for VGX-100 for a number of reasons. Firstly, we have pre-clinical data that indicates VGX-100 is effective in this indication as a single agent, which is important, as this makes for an easier development path. Secondly, there is a large body of scientific data that has emerged over the last five or six years, that heavily implicates the lymphatic system in diseases of the front of the eye. Given that the blockade of VEGF-C appears to be one of the best approaches to inhibit lymphatic system growth, we have a major competitive edge as one of the few players in the world developing an anti-lymphatic therapy.

Thirdly, until now there has been a relatively unmet clinical need for front of the eye disease treatment. Therefore, we think it may be possible to do smaller trials and move more quickly toward registration. Finally, the ultimate cost to perform registrational clinical trials may be significantly less than many other conditions because, given cornea response is easily measurable, the clinical trials can be more quantitative. We hope to start clinical trials of VGX-100 in this setting by late 2012 or early 2013.

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Circadian had cash and listed investments totalling $27.3 million as at 31 December 2010. How are you placed to fund your development pipeline, including completion of VGX-100 Phase I trials?

MD & CEO Robert Klupacs
The cash and investments we have on hand are sufficient for us to complete our Phase I studies. We think the Phase 1 studies that we are going to do combining VGX-100 with Avastin will generate significant value for us.

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In the second half of 2011 Circadian will have two clinical development molecules. What is your strategy to maximise the commercial potential of your IP portfolio and grow shareholder value?

MD & CEO Robert Klupacs
Clinical proof of principle is the major value accretion point for a company like ours. So we're doing everything we can to get to that point.

We're looking to take our lead compound as far as we can to generate the maximum value for shareholders. We've had significant interest from international pharmaceutical companies and while we think gaining clinical proof of principle, before partnering would drive the highest value deal, shareholder value can also be driven by doing the right type of partnering deal before that, as long as we can maintain involvement through some type of co-development arrangement.

We'll also continue to look to drive shareholder value by seeking opportunities for our IP in indications outside cancer and eye disease and for other attributes of our compounds that could also be developed clinically.

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Thank you Robert.
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