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CEO on IND status for VGX-100

Open Briefing with CEO & MD Robert Klupacs

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

- **Clinical and commercial implications of IND status for VGX-100**
- **Design, end points and time lines of Phase I trials**
- **Outlook and value points for Circadian shareholders**

Open Briefing interview:

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Circadian Technologies Limited (ASX:CIR, OTCQX:CKDXY) announced that its 100% owned subsidiary, Vegenics Pty Ltd, has received clearance from the US Food and Drug Administration (FDA) following its investigational new drug (IND) application to initiate clinical trials of VGX-100. What are the clinical development and commercial implications of achieving IND status for VGX-100?

CEO & MD Robert Klupacs
From a clinical development point of view, the FDA's acceptance of our IND and Phase I clinical trial protocol is an endorsement of the suitability of the data we have been generating to undertake clinical trials. As a result, we can begin the clinical development of VGX-100 in the US.

From a commercial perspective, the clearance of the IND process with the FDA enables us to embark on the significantly value adding steps of generating clinical data, which should significantly help us with our interactions with potential partners. While it is a more expensive and time consuming process to file an IND with the FDA, rather than the slightly less rigorous requirements under the Australian Clinical Trials Notification scheme for smaller early phase Australian studies, major pharmaceutical companies looking at companies of our size to partner with, value a body of clinical data generated under the most stringent and internationally recognised regulatory standards.

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Will you test VGX-100 as a monotherapy as well as in combination with Avastin®? What is the design and what are the end points and anticipated time lines of the trials?

CEO & MD Robert Klupacs
The Phase I trial will ultimately have two arms running in parallel: the first arm to initiate will test VGX-100 as a monotherapy, the second will test VGX-100 in combination with Avastin®. While we hope to see an effective response in patients, the purpose of this study is to establish the safety profile of VGX-100 and establish the highest dose that is well tolerated for use in Phase II trials.

Our therapeutic approach is based on the blockade of new blood vessel (angiogenesis) and lymphatic vessel (lymphangiogenesis) growth. While Avastin® is currently the leading anti-angiogenic drug, we have data in animal models demonstrating that combining Avastin® with VGX-100 can have a more marked effect on tumour growth and prevent tumour spread. To test this combination in larger Phase II and III trials that are designed to test the efficacy of the agent, we first have to show that VGX-100 has an acceptable safety profile.

The VGX-100 alone arm of the Phase I trial will be initiated first. Once we've shown that certain doses of VGX-100 are well tolerated as a single agent, we will then combine it with Avastin® in the second arm of the study. In parallel, we will continue to dose groups of patients with higher doses of VGX-100 as a single-agent and in combination with Avastin®.

The trial design is a standard 'three plus three design' which involves dosing groups of three patients. It is an ascending dose study where we continue to increase the doses in those groups until we see a maximum tolerated dose or reach the highest dose level.

We're targeting completion of the trial by the second half of 2012.

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What is the patient selection process for the trials?

CEO & MD Robert Klupacs
Patients to be included in the study will be late stage cancer patients with a range of solid tumours who have progressed despite standard treatments. Patients who are particularly unwell or have other concurrent diseases will be excluded from the study.

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How will the results inform the design of further trials and the ongoing development of VGX-100?

CEO & MD Robert Klupacs
Phase I studies are designed to identify a suitable dose to take into Phase II. These studies will also help us to understand the pharmacokinetics and safety profile of VGX-100 and will be very important in informing the design of Phase II and Phase III studies. Phase I studies are also required to be completed prior to initiating larger Phase II and III studies. We have identified glioblastoma and metastatic colorectal cancer as our first Phase II trial indications.

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What is the expected cost of the Phase I trial? Is Circadian adequately funded to complete Phase I?

CEO & MD Robert Klupacs
The total cost of the Phase I study, including the direct patient costs and the clinician costs, is

expected to be about $1.5 -2 million. The figure could be a little less as we have been conservative in our budget estimates. We're comfortably funded to complete these Phase I trials.

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What are your licensing plans for VGX-100?

CEO & MD Robert Klupacs
The concept of blocking VEGF-C has picked up the interest of potential partners, who are interested to see clinical data, particularly from a safety perspective, and ultimately direct clinical proof of principle.

Our preference would be a co-development arrangement. To do that, we need to generate clinical data. We are seeking to co-develop general or specific oncology applications, with Circadian retaining rights for non-oncology applications.

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What implications would successful VGX-100 Phase I trials have for the remainder of Circadian's VEGF-C and VEGF-D IP portfolio?

CEO & MD Robert Klupacs
These studies won't have direct implication for the VEGF-D portfolio but are important for our VEGF-C/VGX-100 portfolio. Successfully administering the VGX-100 molecule to patients and demonstrating safety, particularly in combination with other agents, is important for both extending our IP coverage for oncology applications and for developing companion diagnostics to measure VEGF-C levels.

If VGX-100 can be shown to be well tolerated in the cancer setting, it will also be important for accelerating the development of VGX-100 in non-cancer indications.

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You also recently published results of a collaboration with Harvard that showed VGX-100 had significant effects in treating dry eye disease in animal models. What are your plans for VGX-100 in dry eye disease and/or other ocular disease areas?

CEO & MD Robert Klupacs
The VEGF-C/VEGF-D/VEGFR-3 pathway is very important for the growth of blood and lymphatic vessels, and both processes are involved in front-of-the-eye, or corneal disease. An agent that can block this pathway, such as VGX-100, could significantly inhibit corneal disease. This is a new treatment paradigm and given our agents targeting this pathway and strong IP position, we have a unique advantage.

The treatment of dry eye disease represents the largest market opportunity for corneal disease: it affects over 5 million people in the US each year and sufferers are relatively poorly served by the treatments currently available. However, we recognise that dry eye disease is one of the most difficult corneal diseases to develop a treatment for, so we're also working on treatments for two niche front-of-the-eye conditions: corneal allograft rejection post corneal transplant; and corneal neovascularisation where blood vessels grow into the eye, often due to an injury or other diseases of the eye.

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Healthscope Limited, Circadian's licensee and development partner for its "Cancers of Unknown Primaries" (CUP) diagnostic technology, has completed development and validation of a commercial test candidate. Commercial beta testing of the diagnostic is expected to be completed in early 2012. What must the beta tests demonstrate before the CUP diagnostic is commercially validated?

CEO & MD Robert Klupacs
We're seeking to validate the results we've seen to date in a "real-life" setting outside the Healthsope-Peter MacCallum-National ICT Australia data pool. We'll draw on a larger group of doctors with access to CUP patients who have previously undergone pathology tests to see whether their results are confirmed by our test.

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What will be the value inflection points for Circadian shareholders over the next 12 to 18 months?

CEO & MD Robert Klupacs
This is a very interesting time for us given we're starting clinical trials on VGX-100 before the end of this year and have significant new opportunities, not just in oncology, but also in ophthalmology and diagnostics.

The launch of the CUP test by Healthscope in the next few months will be an important value inflection point, as will the completion by our licensee Eli Lilly of its Phase I studies for IMC-3C5 in the second half of 2012. Another major value accretion point will be the initial results of our VGX-100 Phase I studies, which we expect to announce before the end of 2012.

Meanwhile, we also see some potential positive developments for our VEGF-D diagnostic that's already on the market: we expect to expand its license territories and will look for a significant uplift in revenues from that.

In addition, we expect our ongoing work in the ophthalmology area to generate further progress scientifically, technically and in terms of product development.

As we've previously flagged, there has been interest in our VEGF-C, VEGF-D and VEGFR-3 portfolio from international pharmaceutical and diagnostic companies, not just in the oncology applications but also in the ophthalmology and diagnostic applications. While there are no guarantees, we're pretty confident we'll have a significant licensing or partnership deal in place in at least one of those areas within the next 12 to 18 months.

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Thank you Robert.

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

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