VGX-300 Potential in AMD

Open Briefing interview with Dr Megan Baldwin, CEO of Circadian's wholly owned subsidiary Opthea, and Circadian 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 diseases 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 supply.

In this Open Briefing®, Megan and Robert discuss:

- Latest data showing VGX-300 as a potential treatment for AMD
- Potential market and development strategy
- Circadian development priorities and funding adequacy

Record of interview:

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Circadian Technologies Limited (ASX: CIR; OTCQX: CKDXY) recently announced that its collaborator Dr. Kameran Lashkari of the Schepens Eye Research Institute at Harvard Medical School had presented data at the annual Association for Research in Vision and Ophthalmology (ARVO) conference showing a link between Vascular Endothelial Growth Factor C (VEGF-C) levels and age-related macular degeneration (AMD), and that animal models had confirmed VGX-300, the VEGF-C inhibitor being developed by Opthea, Circadian's wholly owned subsidiary, as a potential new therapy in "wet" AMD. What are the implications of this new data for the development of VGX-300?

CEO Opthea, Dr Megan Baldwin
The data we presented at the ARVO meeting strongly implicates VEGF-C in the development and progression of wet AMD, and that indicates that VGX-300 has the potential to make a very big difference in patients who have the disease and aren't effectively responding to existing therapies that selectively target VEGF-A. Given we've demonstrated comparable activity to EYLEA®, one of the AMD treatments currently on the market, in a mouse model of wet AMD, the data indicates VGX-300 is a compelling candidate to move forward into clinical development. Importantly, this new data has generated significant enquiries from third parties who have expressed interest in partnering and/or investing in the program.

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How does the action of VGX-300 differ from existing AMD treatments such as EYLEA®, and what will be your clinical trial approach?

CEO Opthea, Dr Megan Baldwin
VGX-300 has a novel mechanism of action. Currently there are only two targeted therapies approved for the treatment of wet AMD: EYLEA® and Lucentis® which both block the activity of VEGF-A without blocking the activity of VEGF-C or VEGF-D. Like VEGF-A, both VEGF-C and VEGF-D can promote blood vessel growth and vascular leakage, which are two processes critical to wet AMD progression. It follows therefore that by blocking these

factors, VGX-300 may have an important impact on the disease, and that combined inhibition of all three VEGF targets has the potential to improve patient response by more effectively inhibiting the pathways involved in wet AMD progression.

Our initial clinical development strategy will be to target sub-responding patients who don't experience a gain in vision following treatment with EYLEA® or Lucentis®. These account for 40 to 50 percent of the patient population taking these existing therapies. This clinical strategy offers a means of selecting patients who stand to gain most from combination therapy, thereby improving the probability of demonstrating efficacy in a clinical program.

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What is the potential market for VGX-300 as a treatment for AMD?

CEO Opthea, Dr Megan Baldwin
The wet AMD market is estimated to be approximately US$5 billion per annum in the US alone. Wet AMD typically affects individuals aged 50 years or older and is the leading cause of blindness in the developed world. As such, the market is extremely large and it's potentially particularly large for VGX-300 as we're not seeking to replace existing treatments but to be complementary to the existing and emerging therapies for this disease.

The size of the wet AMD market is demonstrated by the sales figures for Lucentis® and EYLEA®. Lucentis® is a blockbuster drug with US$3 billion worth of sales in 2011. Sales of EYLEA®, first marketed in November 2011 for the treatment of wet AMD, were in excess of US$800 million in 2012 and are forecast to reach US$1.3 billion in 2013.

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What level of pre-clinical testing has been conducted on VGX-300, and what further work must be completed before you can take the drug into clinical trials?

CEO Opthea, Dr Megan Baldwin
We continue to generate pre-clinical proof of concept data in our own laboratory and in collaboration with internationally renowned research groups in various labs around the world. We're currently manufacturing VGX-300 that meets the specifications required for clinical use and we need to complete this manufacturing process, as well as complete safety/toxicology testing following local ocular administration in animals, prior to initiating clinical trials. Our program is progressing well and we're currently on track to file an investigational new drug (IND) application with the FDA and subsequently initiate a Phase I clinical trial in the second half of calendar 2014.

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What is the expected cost of the VGX-300 clinical trials and what potential is there for partnering the development of the drug?

CEO Opthea, Dr Megan Baldwin
Following the completion of our pre-clinical work, an investment of A$3 million to A$5 million would be sufficient for the VGX-300 program to reach a clinical proof of concept stage. This would cover the completion of a Phase I clinical trial as well as a randomised, controlled Phase II clinical study of approximately 200 wet AMD patients.

The generation of proof of concept data would be a significant value accretion point for the program and would pave the way for a partnership or licensing deal with a larger pharma or biotechnology company that could take the molecule forward in its development. While this proof of concept data usually comes from Phase II studies, given we'll be conducting our Phase I studies in patients with wet AMD, it's possible we'll see a clinical effect in this earlier trial.

That said, our discussions to date with third parties have confirmed that ophthalmology is an emerging, large market for targeted therapies, and that there is an appetite for investment in

a pre-clinical stage program. As such, we continue to explore the potential for an early stage deal.

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What is the expected time line for getting a drug such as VGX-300 to market?

CEO Opthea, Dr Megan Baldwin
Allowing for completion of Phase I, II and III clinical studies, filing for registration approval and regulatory review times, the expected time frame to get a drug such as VGX-300 onto the market is around seven to 10 years from today. Based on that assumption, an estimated launch date of 2020/2021is feasible.

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Circadian had cash of $12.12 million as at 31 December 2012, down from $16.44 million six months earlier. What are your immediate portfolio development priorities and are you adequately funded to progress them?

CEO & MD Circadian, Robert Klupacs
We have three immediate priorities at Circadian. As we've just discussed, the priority for the eye program being developed by Opthea is to continue to progress the necessary studies for an IND application, including manufacture and safety analysis, with the aim of getting VGX-300 into clinical trials in the second half of 2014.

The remaining priorities relate to our VGX-100 program, a human antibody against VEGF-C, which is being developed within our wholly owned cancer-focused subsidiary Ceres Oncology. The first of these priorities is to complete the ongoing Phase I study of VGX-100 in patients with advanced solid tumours. The second priority is to move VGX-100 into Phase II studies, particularly in breast cancer related lymphedema, an area of great unmet clinical need affecting 10 to 40 percent of patients who have been treated for breast cancer. We aim to start that study in the fourth quarter of 2013 and to have interim data available by the end of the second quarter 2014.

In respect to the adequacy of our funding, as well as the cash you mentioned, we also have our continued holdings in Antisense and Optiscan, which together are worth over A$2 million today. We believe we have sufficient capital to undertake the work required to achieve our three immediate priorities. At some point in the future we'll need to partner or to raise money by alternative means, but in the short term we're funded to achieve the milestones I've just outlined.

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Thank you Megan and Robert.

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

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