circadian

Shareholder Newsletter

APRIL 2015

LETTER FROM THE CEO

2015 is shaping up to be a landmark year for Circadian Technologies and our novel lead molecule OPT-302. As we move towards the initiation of a clinical trial in the United States, the ophthalmology community is increasingly focused on the potential for OPT-302 to tackle the devastating vision loss associated with wet AMD.

A lot has happened since I was appointed CEO in February 2014. The restructuring of Circadian to focus on our wet AMD asset has clearly won support from our growing cohort of institutional and sophisticated investors. Our capital raising in November earned A$17.4 million – nearly twice the company's market cap at that time– not only validated this new focus, but secured sufficient capital to cover our development and operating costs for the next three years.

Despite this vote of confidence – and the clinical potential of OPT-302- Circadian remains a significantly undervalued company.

When you consider that wet AMD is a growing and a very large market opportunity and that OPT-302 targets the same, as well as neighbouring pathways to the existing blockbuster drugs for the disease, we are very excited to be on the cusp of initiating clinical studies with the potential to improve outcomes for patients with wet AMD.

I encourage all Circadian shareholders to read the articles in this newsletter – articles that I believe show the remarkable potential of OPT-302 for the treatment of eye disease. Additional information is available on our websites: www.circadian.com.au and www.opthea.com. The websites describe the science that has attracted the interest and support of some of the best ophthalmologists and retinal clinicians in the world.

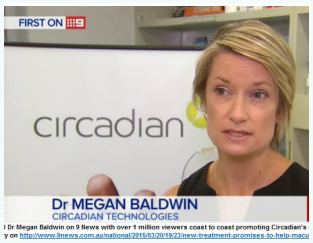
I look forward to updating you on our further progress in the busy and exciting year that lies ahead.

Dr Megan Baldwin

Chief Executive Officer
Circadian Technologies Ltd

IN THE NEWS

Circadian CEO Megan Baldwin features on national prime time business live TV on the Janine Perrett program on Sky Business News



National Nine News, March 20, 2015

US TRIALS HOLD VITAL KEY TO SUCCESS FOR OPT-302

The beginning of Phase 1 clinical trials in the United States in mid-2015 will be a defining milestone on the road to commercialising OPT-302 for the treatment of wet age-related macular degeneration (wet AMD).

Holding the trials in the US offers several potential benefits for Circadian, including compliance with the world's toughest drug regulator, the US Food and Drug Administration (FDA), and providing the company with a vital foothold in the world's largest medical market – a market where 1.75 million people suffer from wet AMD, and another 200,000 cases are diagnosed each year.

Circadian aims to begin its Phase 1 trial by July of this year. Patient cohorts will be given escalating doses of OPT-302 in combination with the standard anti-VEGF-A therapy Lucentis® over a 3 month period. At the maximum tolerated dose or highest dose tested, some patients will receive combination therapy and others will receive OPT-302 alone. The primary endpoint in the study will therefore be an assessment of the safety and tolerability of OPT-302 alone and in combination with Lucentis®, with a number of measures of clinical efficacy investigated concurrently with the primary evaluation of safety.

Primary data results for the Phase 1 study are expected by April next year. Following that analysis, the company intends to initiate a Phase 2 trial. It is anticipated that the Phase 2 study will be a randomized, controlled trial to evaluate the efficacy and safety of OPT-302 given in combination with Lucentis®, compared to Lucentis® monotherapy, for the treatment of patients with wet AMD. One of the very appealing aspects of the trial design is that at the end of the dosing period, patients who exhibit a sub-response to Lucentis® monotherapy will be offered OPT-302 in combination as a 'rescue' therapy. This trial design thereby allows the efficacy of OPT-302 to be tested in two patient populations, those that are previously untreated (treatment naïve) and those that are sub-responsive to Lucentis®.

PRECLINICAL DATA

OPT-302 has compelling preclinical credentials. We have demonstrated the ability of OPT-302 to block two of the key proteins that are involved in inducing blood vessels to grow and leak. These proteins are named VEGF-C and VEGF-D and belong to the same family of molecules as VEGF-A. VEGF-A is the target of the therapies currently on the market to treat wet AMD. When these proteins are overexpressed in a region of the back of the eye called the choroid, they cause the blood vessels to grow abnormally and into the overlying retinal tissue. These abnormal blood vessels are often leaky and cause damage to the retina and scarring, leading to a loss of vision in patients with wet AMD.

At present, there are three major drugs used clinically for the treatment of wet AMD and all block VEGF-A, but not VEGF-C or VEGF-D. Despite the current therapies improving vision in many patients with the disease, there remains a significant need to develop new therapies that can more effectively manage wet AMD progression and improve vision, particularly in those patients who experience limited visual improvement on the existing therapies.

> "In just over two years' time, the company will have randomised Phase 2 data on the efficacy of its OPT-302 against Lucentis®, when used in combination. If that data is clearly positive and clinically meaningful, then Circadian will have a very valuable asset in its possession"
>
> Bioshares, February 13 2015

Preclinical studies in mice with wet AMD have demonstrated that OPT-302 can reduce wet AMD lesion size and vessel leakage to a comparable extent as the marketed agent Eylea® (Regeneron/ Bayer). Used together in the same model, the two therapies more effectively inhibited wet AMD lesions than using either agent alone – raising solid prospects for combined therapy that more effectively blocks a pathway involved in the disease progression. This strategy to target VEGF-C/-D as well as VEGF-A directly targets mechanisms of resistance to the current VEGF-A therapies that are on the market.

Circadian is currently completing a series of animal studies to assess the safety and tolerability of OPT-302 when it is administered into the circulation and into the eye, as required for an Investigational New Drug (IND) application for clinical testing in the US. As well as vital safety tests, the IND includes quality testing of our single-use vials of OPT-302 produced by Patheon Biologics (formerly DSM Pharmaceutical Products).

While wet AMD remains our current focus, Circadian recognises that OPT-302 has the potential to be an effective treatment for a number of other ocular conditions including diabetic macular oedema, diabetic retinopathy and retinal vascular occlusion.

WORLD-LEADING OPHTHALMOLOGISTS JOIN CIRCADIAN'S ADVISORY BOARD

As we move towards initiating human trials in the United States, Circadian is pleased to have enlisted a group of advisors that reads like a Who's Who of the ophthalmic therapeutics industry.

The four founding members of our Clinical Advisory Board (CAB) are all internationally recognised clinicians and eye disease specialists, who have been involved in the development of a number of leading ophthalmic drugs including Macugen®, Fovista®, Eylea® and Lucentis®.

They include: Dr Pravin Dugel, a Clinical Professor at the University of Southern California; Dr Mark Gillies, Professor of Clinical Ophthalmology at the University of Sydney; Dr Peter Campochiaro, Professor of Opthalmology and Neuroscience at the Johns Hopkins Wilmer Eye Institute; and Dr Kameran Lashkari, Associate Professor at the Schepens Eye Research Institute at the Massachusetts Eye and Ear Infirmary.

Circadian has also enlisted the advisory services of a number of other leading ophthalmologists on both sides of the Pacific including: Dr Emmett Cunningham, Chairman of the Ophthalmology Innovation Summit in San Francisco; Dr Denis O'Shaughnessy, formerly of Eyetech and Senior Vice President of Clinical Affairs at Oraya Therapeutics; Dr David Worsley, retinal ophthalmologist at New Zealand's Hamilton Eye Clinic; and Dr Robert Finger, Retinal Ophthalmologist at the Royal Victorian Eye and Ear Hospital and Centre for Eye Research Australia.

The impressive scientific, clinical and regulatory credentials of these individuals not only confirm the widely recognised potential of OPT-302, but will ensure that Circadian receives strategic advice of the highest calibre as we advance towards FDA approval and commercialisation.

The four members of the CAB and ophthalmology advisors are currently working closely with our senior managers and clinical development team as we gear up for clinical trials, as well as providing longer term strategic advice on the clinical development strategy for OPT-302.

A WEALTH OF EXPERTISE:

CIRCADIAN'S FOUNDING CLINICAL ADVISORS

Dr Pravin Dugel is Managing Partner of Retinal Consultants of Arizona and a Founding Member of the Spectra Eye Institute. He is also Clinical Professor at the Department of Ophthalmology at the Keck School of Medicine, University of Southern California. Dr Dugel is globally recognised as a clinical researcher, having served as Principal Investigator for over 50 multicentre clinical trials for emerging and FDA-approved therapies for wet AMD including Fovista®, Lucentis® and Eylea®. The Becker Institute recently named him "one of the best 35 ophthalmologists in the United States".

Prof Mark Gillies is a retinal clinician with a distinguished 25-year history in the research of retinal disease. The first Australian ophthalmologist to be awarded a PhD, he studied in Boston and London before joining the University of Sydney's Save Sight Institute, where he leads the Macular Research Group. He has been a scientific advisor to the Macular Photocoagulation Study Group, the world's leading investigator-initiated study group for retinal diseases, and is currently Scientific Manager of the MacTel Project, an international project to identify a cure for Macular Telangiectasia Type 2.

Dr Peter Campochiaro is the George S. and Dolores Dor Eccles Professor of Ophthalmology and Neuroscience at the John Hopkins Wilmer Eye Institute. A highly respected clinical researcher with a particular expertise in ocular neovascularisation and vascular leakage, his laboratory research group helped to demonstrate the importance of the vascular endothelial growth factor (VEGF) pathway in retinal and choroidal vascular diseases. As a clinician he has had significant experience in many of the clinical studies evaluating anti-VEGF-A therapies including Lucentis® and Eylea®.

Dr Kameran Lashkari holds several academic positions including Clinical Assistant Scientist at the Schepens Eye Research Institute and Clinical Instructor of Ophthalmology at Harvard Medical School. He has completed a research fellowship at the Schepens Institute and medical and surgical fellowships in vitreoretinal disease at Harvard Medical School and the Massachusetts Eye and Ear Infirmary, where he serves as Assistant in Ophthalmology. He is currently conducting research into the pathophysiology of AMD including the response of patients with wet AMD to anti-VEGF therapy.

OPT-302 SHOWS ITS POTENTIAL AT LEADING 2015 CONFERENCES

The compelling clinical potential of OPT-302 will be put on show at some of the world's leading ophthalmology events over the coming months.

On April 11-12, our advisor and collaborator at Harvard Medical School, Dr Kameran Lashkari, will present a poster on our preclinical findings with respect to VEGF-C and D at the Angiogenesis Foundation's World Congress of Angiogenesis in Boston.

The following month, Dr Megan Baldwin will attend and Dr Lashkari will present more detailed preclinical data in a verbal presentation at the Association for Research in Vision and Ophthalmology's (ARVO) Annual Meeting – the largest gathering of eye and vision researchers in the world.

Held this year from May 3-7 at the Colorado Convention Center in Denver, the ARVO conference is an opportunity to update the global ophthalmology community on our OPT-302 program.

Two weeks later on May 19, Dr Megan Baldwin will attend the leading regional biotech event, Asia Biotech Invest 2015 in Hong Kong, where she will have an opportunity to present OPT-302 to some of the world's leading biotech investors.

USA PATENT FOR OPT-302 SECURED UNTIL JUNE 2026

Circadian holds extensive worldwide intellectual property patents in respect of VEGF-C and VEGF-D, as well as the VEGFR-3 receptor.

On 27 January, our global patent portfolio was greatly strengthened when we were granted a patent in the United States protecting compositions containing soluble VEGFR-3 fusion proteins, which include OPT-302.

The US Patent Office also approved our application for a substantial patent term adjustment, which extends this patent by 1,980 days, to 22 June 2026.

The equivalent patent case has already been granted in Europe, Japan, Canada and Australia.

Circadian also has a further patent family under application, which has the potential to extend the patent protection for OPT-302 out to 2034.

CONFERENCE LINKS:

http://angioworldcongress.com/
http://www.arvo.org/Annual_Meeting/
http://asiabiotechinvest.com/

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