ASX and Media Release
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Circadian Commences Wet AMD OPT-302 Clinical Trial

- **Institutional Review Board approves the Phase 1 clinical study and the investigators at each of the five clinical sites**
- **Initiation of the clinical sites in the US completed**
- **Clinical sites begin patient recruitment and screening**

Melbourne, Australia – Circadian Technologies Limited (ASX:CIR, OTCQX:CKDXY) has commenced its Phase 1 study of OPT-302 in patients with wet age-related macular degeneration (wet AMD) following receipt of Institutional Review Board (IRB) approval and initiation of the five clinical trial sites in the US. The trial is under an investigational new drug (IND) authorisation received from the US Food and Drug Administration (FDA) mid-June.

The first-in-human multi-centre dose-escalation clinical trial will investigate OPT-302 administered either alone or in combination with ranibizumab (Lucentis™) on a monthly basis for three months by ocular injection. The trial will be conducted in wet AMD patients who have either not been treated previously (treatment naïve patients) or who have demonstrated a sub-optimal response to prior anti-VEGF-A therapy. Endpoints of the study include assessment of the safety of OPT-302 and preliminary measures of clinical efficacy, including evaluation of visual acuity using eye charts as well as changes in wet AMD lesions using optical coherence tomography and fluorescein angiography. Analysis of data from the dose escalation cohorts in the clinical trial is anticipated in the first quarter of 2016.

Following IRB approval in the US for the Phase 1 study and the clinical investigators conducting the trial, the five sites have begun recruitment activities for patient screening and enrolment. The trial sites are strategically spread throughout North America in geographic regions of large patient populations with retinal diseases including wet AMD. The clinical investigators and site staff are highly experienced in ophthalmic clinical trials and provided key contributions to the clinical development of marketed wet AMD therapies including Lucentis™ and Eylea™.

Dr Megan Baldwin, Circadian's CEO and Managing Director said "We are delighted to begin the first clinical investigation of OPT-302 in patients with wet AMD. Many patients respond sub-optimally to existing treatments so there is great need for novel therapies to improve outcomes for wet AMD patients. IRB approval and commencement of patient recruitment and screening for this clinical program is an important step in the development of OPT-302 for the management of this disease."

Dr Ian Leitch, Director of Clinical Research at Circadian commented "Our clinical investigators and site staff are eager to begin the clinical evaluation of OPT-302 in their patients with wet AMD. Given the breadth of experience of our investigators in advancing new treatments in ophthalmology we look forward to their continued valuable clinical insights throughout the OPT-302 Phase 1 study."

Wet AMD is the leading cause of blindness in the elderly in the western world and is caused by excessive growth and leakage of blood vessels at the back of the eye that leads to chronic and often rapid loss of vision. Existing therapies for the disease are limited and target VEGF-A, but not VEGF-C or VEGF-D. Approximately half of these patients experience sub-optimal vision improvement following treatment. OPT-302 blocks VEGF-C and VEGF-D, which cause blood vessels to grow and leak. In preclinical models of wet AMD OPT-302 demonstrates significant activity as a monotherapy and additive activity when used in combination with existing agents that block VEGF-A.

The trial is being conducted via Circadian's wholly owned subsidiary Opthea Pty Ltd. The Clinical Trial Summary is part of this ASX Announcement as Appendix A.

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About Circadian Technologies Limited

Circadian (ASX:CIR; OTCQX:CKDXY) is a biologics drug developer focusing on ophthalmic disease therapies. It controls exclusive worldwide rights to a significant intellectual property portfolio around Vascular Endothelial Growth Factor (VEGF)-C, VEGF-D and VEGFR-3. The applications for the VEGF technology, which functions in regulating blood and lymphatic vessel growth, are substantial and broad. Circadian's internal product development programs are primarily focused on developing OPT-302 (formerly VGX-300, soluble VEGFR-3) for 'back of the eye' disease such as wet age-related macular degeneration (wet AMD). Circadian has also licensed rights to some parts of its intellectual property portfolio for the development of other products to ImClone Systems, a wholly-owned subsidiary of Eli Lilly and Company, including IMC-3C5, a monoclonal antibody targeting VEGFR-3.

About Wet AMD

Wet (neovascular) age-related macular degeneration, or wet AMD, is a disease characterised by the loss of vision of the middle of the visual field caused by degeneration of the central portion of the retina (the macula). Abnormal growth of blood vessels below the retina, and the leakage of fluid and protein from the vessels, causes retinal degeneration and leads to severe and rapid loss of vision.

Wet AMD typically affects individuals aged 50 years or older, and is the leading cause of blindness in the developed world. The prevalence of AMD is increasing annually as the population ages. Sales of the drug Lucentis™ (Roche/Novartis), which targets VEGF-A but not VEGF-C, were over $US4BN in 2014. Sales of EYLEA™ (Regeneron/Bayer), which also targets VEGF-A but not VEGF-C first marketed in November 2011 for the treatment of wet AMD, were over $US1.8BN in 2014. Approximately half of the people receiving Lucentis™/EYLEA™ are classified as non-responders or 'poor' responders and experience no significant gain in vision and/or have persistent retinal vascular leakage. There is great opportunity to improve patient responses by targeting more than one factor involved in disease progression. Existing therapies, such as Lucentis™/EYLEA™, target VEGF-A that promotes blood vessel growth and leakage through its receptor VEGFR-2. VEGF-C can also induce angiogenesis and vessel leakage through the same receptor as well as through an independent pathway. Combined inhibition of VEGF-A and VEGF-C, has the potential to improve patient response by more effective inhibition of the pathways involved in disease progression.

Inherent risks of Investment in Biotechnology Companies

There are a number of inherent risks associated with the development of pharmaceutical products to a marketable stage. The lengthy clinical trial process is designed to assess the safety and efficacy of a drug prior to commercialisation and a significant proportion of drugs fail one or both of these criteria. Other risks include uncertainty of patent protection and proprietary rights, whether patent applications and issued patents will offer adequate protection to enable product development, the obtaining of necessary drug regulatory authority approvals and difficulties caused by the rapid advancements in technology. Companies such as Circadian are dependent on the success of their research and development projects and on the ability to attract funding to support these activities. Investment in research and development projects cannot be assessed on the same fundamentals as trading and manufacturing enterprises. Thus investment in companies specialising in drug development must be regarded as highly speculative. Circadian strongly recommends that professional investment advice be sought prior to such investments.

Forward-looking statements

Certain statements in this ASX announcement may contain forward-looking statements regarding Company business and the therapeutic and commercial potential of its technologies and products in development. Any statement describing Company goals, expectations, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those risks or uncertainties inherent in the process of developing technology and in the process of discovering, developing and commercialising drugs that can be proven to be safe and effective for use as human therapeutics, and in the endeavour of building a business around such products and services. Circadian undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events, or otherwise. Actual results could differ materially from those discussed in this ASX announcement.

APPENDIX A - CLINICAL TRIAL SUMMMARY

Protocol Number	OPT-302-1001
Title	A Phase 1 Dose Escalation Study Evaluating the Safety, Pharmacokinetics and Pharmacodynamics of OPT-302 in combination with Ranibizumab in subjects with wet AMD
Sponsor	Opthea Pty Ltd
Indication	Neovascular (wet) age-related macular degeneration (AMD)
Study Phase	1
Primary Objective	To evaluate the safety OPT-302 administered by intravitreal (IVT) injection in combination with IVT ranibizumab (Lucentis™) in subjects with wet AMD
Key Secondary Objective(s)	To assess: • Mean change in best-corrected visual acuity from baseline • Mean change in choroidal neovascular (CNV) lesion area from baseline (measured by fluorescein angiogram) • Mean change in central retinal thickness from baseline (measured by spectral domain optical coherence tomography [SD-OCT]) • Pharmacokinetics (PK) of OPT-302
Study Design	First-in-human, multi-centre, sequential dose escalation study evaluating OPT-302 either alone or in combination with ranibizumab in subjects with wet AMD
Clinical Trial Investigators and Sites	5 sites in the USA
Key Eligibility Criteria	Subjects ≥ 50 years of either gender, with active CNV secondary to AMD confirmed by fluorescein angiography, who are either treatment naïve or have received prior intravitreal anti-VEGF-A therapy (previously treated) with evidence of sub-optimal response to treatment and the need for additional treatment
Clinical Parameters	The following clinical parameters will be evaluated: • Best corrected visual acuity • Fluorescein angiography and fundus photography • Spectral domain optical coherence tomography (SD-OCT) • Slit lamp ophthalmic examination • Fundus ocular examination • Eye intraocular pressure (IOP)
Safety Assessments	Systemic and ocular safety will be evaluated by assessing: • ECG • Vital signs • Patient blood sample laboratory analyses • Adverse events