ASX and Media release

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Completion milestone reached in Phase 1b oncology study of VGX-100 with Avastin®

- **Phase 1b dose ranging study successfully completes enrolment and the required 28 day safety review in 24 patients treated with combination VGX-100 and bevacizumab (Avastin®)**
- **The combination of VGX-100 and bevacizumab (Avastin®) was safe and well tolerated**
- **Result follows positive Phase 1a trial data of single agent VGX-100 and supports progressing VGX-100 to Phase 2 clinical studies as a combination therapy with bevacizumab**

Ceres Oncology Pty Ltd, a clinical stage biotechnology company and wholly owned subsidiary of Circadian Technologies Limited (ASX: CIR, OTCQX:CKDXY), has today announced the successful completion of patient enrolment and the 28 day safety review in its First-in-Human Phase 1a /1b clinical Study of VGX-100 as a novel cancer therapy.

The Phase 1b arm of the study is now fully enrolled with 24 patients who have advanced solid tumours, and all have completed the 28 day safety review of VGX-100 in combination with bevacizumab (Avastin®) at ascending doses.

The combination of VGX-100 and bevacizumab (Avastin®) was safe and well tolerated.

This positive Phase 1b result follows the successful Phase 1a arm of the trial (VGX-100 single agent dose escalation) and provides further support for Ceres Oncology to advance VGX-100 towards a Phase 2 clinical program.

A Phase 2 clinical trial is being planned for patients with relapsed brain tumours called recurrent Glioblastoma Multiforme (rGBM) of VGX-100 in combination with bevacizumab and is expected to commence in mid 2014.

As previously announced, a Phase 2 clinical trial in patients with breast cancer related lymphedema is expected to commence Q1 2014.

“It is encouraging that VGX-100 has shown an excellent safety profile when used in combination with Avastin and further Phase 2 clinical investigation is warranted in patients with solid tumors,” said Dr Jayesh Desai, Medical Oncologist at Royal Melbourne Hospital and medical monitor for the VGX-100 Phase 1 studies.

“We are grateful to the dedicated efforts of the principal investigators Dr Gerald Falchook at MD Anderson (Texas, USA) and Dr Lee Rosen at UCLA (Santa Monica, USA) as well as their clinical research teams, the patients and their families who have all contributed to the success of the Phase 1 clinical program.”

VGX-100 is a novel fully human monoclonal antibody that selectively inhibits vascular endothelial growth factor C (VEGF-C), which is a member of the VEGF family of secreted glycoproteins that are key mediators of tumor related angiogenesis, lymphangiogenesis and vascular permeability.

In several nonclinical animal models of human cancer, VGX-100 effectively inhibited tumor growth when administered as a monotherapy and increased the efficacy of bevacizumab (Avastin®) and/or standard chemotherapy. Avastin® is sold by Roche and is approved for a number of solid tumor indications including rGBM. It generates sales in excess of US$6 Billion a year but is limited by tumour escape and relapse due to up-regulation of pro-angiogenic factors including VEGF-C.

The Phase 1 oncology clinical trial, run under an Investigational New Drug (IND) program with the Food and Drug Administration (FDA), was conducted at 2 major sites in the USA as a dose escalation study of VGX-100 alone or in combination with bevacizimab (Avastin®).

The trial enrolled 43 patients with advanced or metastatic solid tumors;

- 19 patients received weekly intravenous (IV) administration of single agent VGX-100 at doses ranging from 1 – 30 mg/kg (Phase 1a);
- Another 24 patients received weekly IV dosing of VGX-100 (2.5 – 20 mg/kg) in combination with bevacizumab (5 or 10 mg/kg) given IV every two weeks.

The primary objective of the clinical study was to establish the safety profile of VGX-100 while secondary objectives include determination of anti-tumour activity, biomarker levels and pharmacokinetics of VGX-100 alone and in combination with bevacizumab. Subjects continued to receive study drugs VGX-100 weekly +/- bevacizumab every two weeks beyond the 28 day safety review period, until disease progression or if any other reason for study withdrawal was determined. Additional information of the clinical study (NCT01514123) can be found at www.clinicaltrials.gov.

VGX-100 was safe and well tolerated by all 43 patients and the only dose limiting toxicity was transient Grade 3 hypertension observed in one subject at the lowest dose level combination of VGX-100 (2.5 mg/kg) with bevacizumab (5 mg/kg).

A Maximum Tolerated Dose (MTD) was not reached with either single agent VGX-100 (highest dose tested: 30 mg/kg) or the combination of VGX-100 with bevacizumab (highest dose tested: VGX-100 at 20 mg/kg + bevacizumab at 10 mg/kg).

Preliminary study results showed that the VGX-100 pharmacokinetic (PK) parameters (C_{max} and AUC) increased linearly with the dose, the half-life is consistent with once weekly dosing and the PK profile for VGX-100 appears to be similar with and without co-administration of bevacizumab.

These results show that VGX-100, at well-tolerated doses, achieves concentrations in the blood that are anticipated to effectively inhibit circulating VEGF-C and support further development for the treatment of solid tumors including rGBM as well as Breast Cancer Related Lymphedema.

Additional detailed evaluation of VGX-100 alone or in combination with bevacizumab is ongoing with primary analysis of all patient data expected in early 2014 followed by presentation of the results at a major medical oncology conference later in the year.

"We are extremely proud to have reached this major development milestone of completing all patient enrolment in our Phase 1 clinical cancer studies and look forward to the progression of the VGX-100 clinical program into Phase 2," said Robert Klupacs, CEO of Circadian Technologies Limited.

"We are committed to providing novel therapeutic options for patients suffering from cancer, and believe that targeting VEGF-C with our lead antibody VGX-100 in combination with approved therapies such as Avastin® may lead to improved clinical outcomes."

Circadian controls exclusive worldwide rights to an extensive intellectual property portfolio enabling it to commercially develop antibodies targeting VEGF-C. In addition, Circadian recently created a 100% owned subsidiary company, Ceres Oncology Pty Ltd, to specifically focus on the development of VGX-100 in cancer related indications.

VGX-100 was rated by the leading pharmaceutical market research group, Windhover Conferences, a division of Elsevier Business Intelligence, as one of the Top 10 Oncology Projects to Watch in 2013.

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About Ceres Oncology Pty Ltd

Ceres Oncology Pty Ltd is a 100% owned subsidiary of Circadian Technologies Limited based in Melbourne, Australia. Ceres is developing VGX-100, which is a fully human monoclonal antibody that specifically and potently blocks the activity of vascular endothelial growth factor C (VEGF-C) which is involved in tumour angiogenesis (blood vessel growth), lymphangiogenesis (lymphatic vessel growth) and vascular leakage. By targeting and inhibiting the effects of VEGF-C, VGX-100 may have a broad utility in a range of oncology related disease states characterised by aberrant blood and/or lymphatic vessel growth, vascular leakage or edema, and/or inflammation, including solid tumours and lymphedema.

About Circadian Technologies Limited

Circadian (ASX:CIR; OTCQX:CKDXY)) is a biologics drug developer focusing on cancer, cancer related and ophthalmic disease therapies. It controls exclusive worldwide rights to a significant intellectual property portfolio around Vascular Endothelial Growth Factor (VEGF)-C and –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 VGX-100 (a human antibody against VEGF-C) as a treatment for lymphedema resulting from breast cancer treatment and solid tumours, in particular glioblastoma multiforme and metastatic colorectal cancer through its subsidiary Ceres Oncology, as well as developing VGX-300 (soluble VEGFR-3) for 'back of the eye' disease such as "wet" Age Related Macular Degeneration through its subsidiary Opthea. 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 the anti-lymphatic antibody-based drug IMC-3C5 targeting VEGFR-3.

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.