

ASX and Media release

30 Oct 2013

## Opthea Signs Manufacturing Agreement for Lead Product

**Circadian Technologies (ASX:CIR; OTCQX:CKDXY), through its 100% owned subsidiary Opthea Pty Ltd, today announced that it has signed an agreement with DSM Pharmaceutical Products, the custom manufacturing and technology business of Royal DSM (NYSEW, Euronext: DSM KON).**

The contract covers process development and cGMP manufacture by DSM for Opthea's lead molecule, a soluble form of human VEGFR-3 in development for the treatment of "wet" (neovascular) age-related macular degeneration (wet AMD).

The agreement represents a significant milestone in the development of OPT-302, previously named VGX-300, which is on-track to initiate a Phase I clinical trial by early 2015.

**A copy of the joint Opthea/DSM press release is attached.**

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### **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 and colorectal cancer, as well as developing OPT-302 (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.

## About Opthea Pty Ltd

Opthea Pty Ltd is a private, 100% owned subsidiary of Circadian Technologies Limited based in Melbourne, Australia. Opthea is developing novel biologic inhibitors of VEGF-C driven angiogenesis (blood vessel growth), lymphangiogenesis (lymphatic vessel growth) and vascular leakage for the treatment of ophthalmic diseases.

Opthea's compounds have broad utility in a range of eye diseases characterised by aberrant blood and/or lymphatic vessel growth, vascular leakage or edema, and inflammation, including wet AMD, diabetic macula edema, corneal neovascularisation and transplantation, and dry eye disease.

Opthea's lead compound, OPT-302, is a soluble receptor that specifically and potently blocks the activity of two members of the vascular endothelial growth factor family, namely VEGF-C and VEGF-D that are involved in the progression of both retinal and corneal diseases. Opthea's lead program is the development of OPT-302 for the treatment of "wet" (neovascular) age-related macular degeneration (wet AMD).

## About "wet" AMD

"Wet" (neovascular) age-related macular degeneration, or wet AMD, is a disease characterised by the loss of vision in 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. Sales of the drug Lucentis® (Roche), which targets VEGF-A but not VEGF-C, were over \$US3B in 2012. 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 \$US838M in 2012 and are forecast to reach \$1.3BN in 2013. Approximately half of the people receiving Lucentis®/Eylea® are classified as non-responders or 'poor' responders and experience no 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. 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.

A preclinical model of "wet" AMD has demonstrated that VEGF-C blockade can significantly inhibit disease progression and that low levels of VEGF-C during development affects formation of the retinal vessels. Like VEGF-A, VEGF-C can also induce vessel permeability that leads to vascular fluid and protein leakage. Inflammatory cytokines associated with wet AMD upregulate VEGF-C levels, and increased levels of the receptors for VEGF-C are detected in AMD tissue. VEGF-C is strongly implicated in the progression of wet AMD.

### **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.



## Press Release

Parsippany (USA), October 30, 2013

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# DSM and Opthea Sign Agreement to Manufacture Opthea's Lead Product for Eye Disease

DSM Pharmaceutical Products, the custom manufacturing and technology business of Royal DSM (NYSE, Euronext: DSM KON), announced today that it has signed an agreement with Opthea Pty Ltd of Melbourne, Australia.

The contract covers process development and cGMP manufacture by DSM for Opthea's lead molecule, a soluble form of human VEGFR-3 that blocks the activity of both VEGF-C and VEGF-D which promote blood and lymphatic vessel formation and are involved in the progression of eye diseases.

This project represents an agreement for process development at DSM Biologics Groningen facility and manufacture at the newly established cGMP facility in Brisbane, Australia. Opthea, a private 100% owned subsidiary of Circadian Technologies Limited (ASX: CIR; OTCQX: CKDXY), is developing its lead molecule OPT-302, previously known as VGX-300, initially for the treatment of "wet" (neovascular) age-related macular degeneration (wet AMD).

"Wet" (neovascular) age-related macular degeneration, or wet AMD, is a disease characterised by the loss of vision in 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, cause retinal degeneration and leads to severe and rapid loss of vision.

Dr. Megan Baldwin, CEO of Opthea said *"We are pleased to announce our manufacturing agreement with DSM and to have the opportunity to work with their highly experienced and internationally recognized team. Opthea is excited to be able to progress our manufacturing program in a new state-of-the-art facility within Australia and looks forward to further building on our strong relationship with DSM."*

Manja Bouman, President of DSM Biologics, commented *"We are honored to be working with an innovative company such as Opthea, and apply our expertise to help them bring this novel biologic treatment to patients in need. We look forward to working together with our partner on this exciting project and support them in their further development of this important drug."*

Queensland Minister for Science and Innovation Ian Walker has welcomed the deal signed by DSM Biologics and Melbourne-based Opthea today.

*"This is good news for Queensland and the deal is evidence of the growing reputation at a national and international level of the DSM facility with its experienced team, state-of-the-art equipment, its excellent manufacturing capability and its value for money proposition. These kinds of partnerships will be vital to the growth of this industry in Queensland,"* Mr Walker said.

### Forward-looking statements

This press release may contain forward-looking statements with respect to DSM's future (financial) performance and position. Such statements are based on current expectations, estimates and projections of DSM and information currently available to the company. DSM cautions readers that such statements involve certain risks and uncertainties that are difficult to predict and therefore it should be understood that many factors can cause actual performance and position to differ materially from these statements. DSM has no obligation to update the statements contained in this press release, unless required by law. The English language version of the press release is leading.



DSM Biologics, a business unit of DSM Pharmaceutical Products, focuses on optimizing mammalian-based biopharmaceutical manufacturing through its unique set of technologies and expertise. In addition to an R&D and manufacturing site in Groningen, The Netherlands, DSM has opened operations in Brisbane, Australia, with the support of the Government of Queensland and the Commonwealth of Australia. The Brisbane facility is DSM's blueprint for its 'biologics plant of the future' for the production of biopharmaceuticals. DSM's proprietary technologies drive down cost, processing times and capital requirements to meet market demand for developing affordable lifesaving medications.

Financial terms were not disclosed.

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For more information, please visit Opthea's website at [www.opthea.com](http://www.opthea.com)

#### **DSM - Bright Science. Brighter Living.™**

Royal DSM is a global science-based company active in health, nutrition and materials. By connecting its unique competences in Life Sciences and Materials Sciences DSM is driving economic prosperity, environmental progress and social advances to create sustainable value for all stakeholders. DSM delivers innovative solutions that nourish, protect and improve performance in global markets such as food and dietary supplements, personal care, feed, pharmaceuticals, medical devices, automotive, paints, electrical and electronics, life protection, alternative energy and bio-based materials. DSM's 23,000 employees deliver annual net sales of about € 9 billion. The company is listed on NYSE Euronext. More information can be found at [www.dsmbiologics.com](http://www.dsmbiologics.com) and [www.dsm.com](http://www.dsm.com).

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