ASX and Media Release
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# Opthea Chairman's Address to the 2018 AGM

**Melbourne, Australia; 29 November 2018 – Opthea Limited (ASX:OPT)**

Good morning. On behalf of all the Directors, I am pleased to welcome you to the 2018 Annual General Meeting of Opthea Limited. Thank you all for your attendance.

As Chairman, it is my pleasure to update you on our progress over the past 12 months and to share with you our enthusiasm to progress our lead drug candidate, OPT-302, through clinical development in two of the leading causes of blindness in both the elderly and diabetic populations.

When I addressed this forum in November of 2017, the company had completed an over-subscribed A$45m equity capital raising on the back of positive outcomes in the company's first in human Phase 1/2a clinical trial of OPT-302 in wet AMD patients. At that time, we were well advanced in regulatory interactions and our plans to initiate a larger, randomised controlled Phase 2b clinical study to investigate whether addition of OPT-302 to standard of care anti-VEGF-A therapy over a 6-month period improves visual acuity in patients with the highly debilitating retinal disease, wet AMD.

Fast forward 12 months, and I am pleased to have this opportunity today to reflect on what has been an extremely productive year at Opthea.

The Company not only initiated the Phase 2b study, recruiting patients from 113 clinical sites across 10 countries, including the United States, Israel and eight countries in Europe, but also completed enrolment months ahead of the projected timelines. This is positive news for a number of reasons.

Firstly, and perhaps most importantly, it demonstrates the need for new therapies to address the significant unmet medical need that remains for wet AMD patients despite the availability of standard of care anti-VEGF-A therapy. It also speaks to the motivation and commitment of patients and study investigators to advance innovative, promising new treatments such as OPT-302. And finally, it reflects the capability of the Opthea team to execute a multi-centre, international clinical program in a cost-effective and efficient manner. As a result of this dedication, we have brought forward the anticipated date for reporting of primary outcomes from the study to the fourth quarter of calendar year 2019.

Together with the progress of our Phase 2b wet AMD trial, we diversified our clinical development program through the initiation of a Phase 1b/2a clinical study in patients with persistent diabetic macular edema, or DME, despite prior standard of care treatment. The decision to expand our program into the diabetic population was based on sound scientific rationale for targeting VEGF-C/D in this population and reflects the growing prevalence of diabetes worldwide and the significant market opportunity given the large number of DME patients who respond sub-optimally to selective anti-VEGF-A therapy.

We have already made progress with this trial, having reported week 12 outcomes from the 9 patients enrolled in the Phase 1b dose escalation cohorts. Importantly, the outcomes from the Phase 1b trial demonstrated a favourable safety profile of OPT-302 when administered in combination with the VEGF-A inhibitor aflibercept (Eylea®). We have now demonstrated a favourable safety profile of OPT-302 administered in combination with the two standard of care

therapies, Lucentis® and Eylea®, that are approved for the treatment of wet AMD and DME. Our data from the Phase 1b dose escalation study in DME also provided evidence of clinical activity of OPT-302 to improve visual acuity and anatomical measures in DME patients. Opthea's CEO, Dr Megan Baldwin, will provide an update on the recently reported DME data at the conclusion of today's AGM.

Financially, Opthea is well positioned to execute our clinical development program with a strong cash position, bolstered recently by receipt of A$12.0 million research and development (R&D) tax credit from the Australian Taxation Office for R&D costs incurred in the 2017/2018 financial year, and proceeds from the exercise of quoted options issued in November 2014.

The options, issued to investors who participated in the Company's 2014 capital raising of A$17.4m, were exercisable at A$0.27 by November 25 2018. In what is a strong display of investor support and company performance since 2014, over 99% of option holders took up the opportunity to convert their options to ordinary shares, generating proceeds in excess of A$13.3m which will also be fully reinvested into completing both clinical trials.

Finally, I would like to emphasise the enthusiasm and commitment of your Board and Opthea's management team to advance OPT-302 and return value to shareholders. We have made great progress this year and 2019 promises to be a busy and important year for the company with the anticipated read-out pf primary data from Opthea's Phase 2 trials in wet AMD and DME before the end of 2019.

On behalf of myself, and my fellow directors Michael and Megan, thank you to our shareholders for your continued support. Thank-you also to the dedicated management team at Opthea, who continue to advance OPT-302 through development with professionalism and loyalty. Together the Board and the management team look forward to a productive and successful 2019.

**About OPT-302**

OPT-302 is a soluble form of vascular endothelial growth factor receptor 3 (VEGFR-3) or 'Trap' molecule that blocks the activity of two proteins (VEGF-C and VEGF-D) that cause blood vessels to grow and leak, processes which contribute to the pathophysiology of retinal diseases. Opthea is developing OPT-302 for use in combination with inhibitors of VEGF-A (eg. Lucentis®/Eylea®). Combination therapy of OPT-302 and a VEGF-A inhibitor achieves more complete blockade of members of the VEGF family, blocks mechanisms contributing to sub-optimal response to selective VEGF-A inhibitors and has the potential to improve vision outcomes by more completely inhibiting the pathways involved in disease progression.

Opthea has completed a Phase 1/2a clinical trial in the US investigating OPT-302 wet AMD patients as a monotherapy and in combination with Lucentis®. The trial was conducted under an FDA approved IND at 14 US clinical sites. The purpose of the trial was to evaluate the safety, pharmacokinetics (PK) and pharmacodynamics of OPT-302 administered as monthly intravitreal injections for 3 months with and without Lucentis® in patients with wet age related macular degeneration (AMD). Of the 51 patients enrolled, 25 were treatment naïve and 26 had received prior intravitreal anti-VEGF-A therapy.

Further details on Opthea's clinical trials can be found at www.clinicaltrials.gov, clinical trial identifiers: NCT02543229 (Phase 1/2a wet AMD); NCT03345082 (Phase 2b wet AMD) and NCT03397264 (Phase 1b/2a DME). Additional information on Opthea's technology and clinical trials can found on Opthea's website www.opthea.com.

**About Wet AMD and DME**

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 is the leading cause of blindness in the developed world in individuals aged 50 years or older. The prevalence of AMD is increasing annually as the population ages. Without treatment, wet AMD patients often experience a chronic, rapid decline in visual acuity and increase in retinal fluid.

DME is the leading cause of blindness in diabetics and is estimated to affect approximately 2 million people globally[1,2,3]. Chronically elevated blood glucose levels in Type 1 and Type 2 diabetics can lead to inflammation, vascular dysfunction and hypoxia, causing upregulation of members of the VEGF family of growth factors. VEGFs, including VEGF-A and VEGF-C, stimulate vascular permeability or vascular leakage, leading to fluid accumulation in the macula at the back of the eye and retinal thickening which affects vision. Existing standard of care treatments for DME are limited and include inhibitors of VEGF-A (Lucentis®, Eylea®), steroids and laser therapy. Despite these treatments, many patients remain refractory and have a sub-optimal response to therapy with persistent fluid and impaired vision. OPT-302 blocks VEGF-C and VEGF-D, which cause vessels to grow and leak. Used in combination with a VEGF-A inhibitor, OPT-302 has the potential to improve clinical outcomes in DME patients.

Existing standard of care treatments for DME and wet AMD include agents that inhibit VEGF-A, but not VEGF-C or VEGF-D. Sales of the drug Lucentis® (Roche/Novartis), which targets VEGF-A, were over $US3.4BN in 2017. Sales of Eylea® (Regeneron/Bayer), which also targets VEGF-A but not VEGF-C/-D were over $US5.9BN in 2017. Many patients receiving Lucentis®/Eylea® are classified as non-responders or 'poor' responders and do not experience a 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® and 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/-D, has the potential to improve patient response by more effective inhibition of the pathways involved in disease progression.

**About Opthea Limited**

Opthea (ASX:OPT) 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. Opthea's intellectual property is held within its wholly-owned subsidiary Vegenics Pty Ltd. The applications for the VEGF technology, which functions in regulating blood and lymphatic vessel growth, are substantial and broad. Opthea's product development programs are 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) and Diabetic Macular Edema (DME).

**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 Opthea 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. Opthea 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. Opthea 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.


1 Ding J, Wong TY. Current epidemiology of diabetic retinopathy and diabetic macular edema. *Curr Diab Rep.* 12: 346-354, 2012.

2 Lee R, Wong TY, Sabanayagam C. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. *Eye and Vision.* 2:17, 2015.

3 Managing Diabetic Eye Disease in Clinical Practice. Singh RP (ed). Springer International Publishing 2015.



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