ASX and Media Release
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Opthea Reports Positive Three-Month Data from Phase 1b Dose Escalation Study for OPT-302 in Diabetic Macular Edema

Melbourne, Australia; October 26 2018 – Opthea Limited (ASX:OPT), a clinical-stage biopharmaceutical company developing innovative biologic therapies to treat retinal diseases, today announced positive data from the Phase 1b dose escalation study of OPT-302 for patients with diabetic macular edema (DME). The study evaluated three escalating dose levels of OPT-302 (0.3, 1.0 or 2.0 mg), a novel VEGF-C/D 'Trap' therapy, in combination with aflibercept (Eylea®, 2.0 mg) administered once every 4 weeks for a total of 3 intravitreal injections in 9 patients with persistent central-involved DME despite sub-optimal responses to standard of care anti-VEGF-A therapy.

Eyes with persistent DME sub-responsive to multiple prior anti-VEGF-A injections demonstrated visual and anatomic improvement at 12 weeks following conversion to OPT-302 combination treatment. A dose-response relationship of increased gains in visual acuity (VA) was shown with ascending dose levels of OPT-302 combination treatment which also produced reductions in retinal swelling.

"Alternative approaches such as combination therapies are needed for treating patients with DME who have persistent macula swelling and vision loss despite treatment with standard of care" says David Boyer, MD, Clinical Professor of Ophthalmology at USC/Keck School of Medicine and principal investigator on the trial. "I am highly encouraged by the evidence of efficacy and continued favourable safety profile for OPT-302 combination therapy which has potential to benefit the many diabetic patients who have limited responses to anti-VEGF-A treatment".

Patients enrolled in the study had a history of diabetes with a mean duration of 14.1 years and persistent DME despite receiving a mean of 6.3 prior anti-VEGF-A injections. The mean change at week 12 from baseline in best corrected VA (BCVA) across all OPT-302 combination therapy dose groups was a gain of +7.7 letters (baseline of 65 letters) with a corresponding mean reduction in central subfield thickness (CST) of -71 µM (baseline of 434 µm). A dose-response relationship of improved visual acuity at all time-points from baseline to week 12 was demonstrated with ascending dose levels of combination treatment with BCVA gains of +3.0, +5.7 and +14.3 letters seen at 0.3 mg, 1.0 mg and 2.0 mg of OPT-302 respectively. A similar dose-response was observed in the proportion of patients gaining ≥ 5 letters in BCVA, with 33% (1/3), 67% (2/3) and 100% (3/3) of patients gaining 5 or more letters in each of the respective 0.3, 1.0 and 2.0 mg dose levels of OPT-302 in combination with aflibercept (2.0 mg).

Bilateral disease was present in 5 of the 9 patients with both eyes previously treated with anti-VEGF-A therapy for persistent DME (mean of 6 prior injections in both eyes) providing a within patient comparison of the study eye which received OPT-302 + aflibercept combination therapy and the fellow eye which continued on anti-VEGF-A monotherapy (alflibercept or ranibizumab). Combination therapy with OPT-302 + ranibizumab in the study eye had greater

improvements than the anti-VEGF-A monotherapy in the fellow eye for mean change from baseline to week 12 in BCVA of +10 letter gain (baseline of 63 letters) versus +2.6 letters (baseline of 73 letters) respectively and central subfield thickness reduction of -80 µm (baseline of 445 µm) versus -6 µm (baseline of 389 µm). In addition, 3/5 (60%) study eyes receiving OPT-302 combination therapy had a ≥ 50% reduction in excess foveal thickness, a measure of macular swelling, compared to 1/5 (20%) of fellow eyes that were administered anti-VEGF-A monotherapy.

The demonstration of a dose response relationship for OPT-302 combination treatment to improve visual acuity in patients with persistent DME in the Phase 1b study together with biological responses on anatomic measures in both DME and wet AMD lesions indicates that pan-VEGF (A, C and D) inhibition may offer benefits that exceed the inhibition of VEGF-A alone. OPT-302 combination therapy achieves more complete suppression of the VEGF/VEGFR pathway by blocking all members of the VEGF family of growth factors, including VEGF-A, VEGF-C and VEGF-D.

Dr Megan Baldwin, CEO and Managing Director of Opthea, commented "We are very encouraged by the results of this Phase 1b dose escalation study in patients with persistent DME. Together with previously reported results from our Phase 1/2a trial in wet AMD patients, we have now demonstrated a well-tolerated safety profile of OPT-302 in combination with aflibercept and ranibizumab (Lucentis®) and promising signs of clinical activity in both wet AMD and DME patients. Our data suggests that VEGF-C/D blockade may provide additional clinical benefit over standard of care anti-VEGF-A therapy. To that end, we look forward to reporting outcomes from our two international, multicentre Phase 2 trials that are currently ongoing and actively recruiting patients with newly diagnosed wet AMD and persistent DME despite prior anti-VEGF-A therapy."

OPT-302 + aflibercept intravitreal injections were well tolerated at all dose levels throughout week 12. No treatment-related ocular or systemic adverse events were observed throughout the week 12 timepoint, and the very few ocular events noted were mild and primarily related to the intravitreal injection procedure.

The Company's multi-centre Phase 2a randomised, controlled dose expansion trial is now actively recruiting patients with persistent DME. Patients in the Phase 2a study are randomised in a 2:1 ratio to receive either OPT-302 (2 mg) + aflibercept (2 mg) or aflibercept monotherapy by intravitreal injection once every 4 weeks for 3 doses. Enrolment in the Phase 2a trial is progressing at U.S. and Australian sites with primary data anticipated in 2H' 2019.

The Phase 1b DME study results were presented at the Ophthalmology Innovation Summit (OIS), held in conjunction with the annual meeting of the American Academy of Ophthalmology (AAO) in Chicago on Thursday, October 25th, 2018 (US Central Daylight Time). Additional meeting information is available at https://ois.net/ois-aao-2018/ and a copy of the OIS presentation is available on Opthea's website at www.opthea.com.

Additional information on Opthea's technology and clinical trials in wet AMD and diabetic macular edema (DME) can be found at www.opthea.com and ClinicalTrials.gov (ID#: NCT03345082 and ID#: NCT03397264, respectively).

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 DME and Wet AMD

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.
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.

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.

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2 Lee R, Wong TY, Sabanayagam C. *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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