ASX and Media Release
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Opthea Doses First Patient in Phase 2b Study of OPT-302 for Wet AMD

Melbourne, Australia; December 19 2017 – Opthea Limited (ASX:OPT), a developer of novel biologic therapies for the treatment of eye diseases, announced today the dosing of the first patient in the Company's Phase 2b trial of OPT-302 for wet AMD. The study is a randomised, controlled clinical trial of OPT-302, a novel VEGF-C/D 'Trap' therapy, in combination with ranibizumab (Lucentis®) for wet age-related macular degeneration (wet AMD) (ClinTrials.gov ID#: NCT03345082).

"The dosing of the first patient in this Phase 2b trial is clearly an important milestone for OPT-302's development, and we are delighted to clinically advance this novel VEGF-C/D inhibitor therapy which may offer patients improved outcomes when administered in combination with existing anti-VEGF-A agents," commented Dr Megan Baldwin, CEO and Managing Director of Opthea.

Opthea plans to enroll 351 patients at sites in the US, Europe and Israel. Patients will be randomised in a 1:1:1 ratio to each of three treatment groups to investigate the clinical efficacy and safety of OPT-302 administered at 0.5 mg or 2.0 mg in combination with Lucentis® (0.5 mg) compared to Lucentis® (0.5 mg) alone. Patients randomised to the Lucentis® alone group will also receive a sham injection to mask the patient to the treatment group. Treatments will be administered on a monthly basis for 6 months via intravitreal (ocular) injection.

The trial will be conducted in patients with wet AMD who have not received prior therapy (treatment naïve patients). The primary endpoint of the study is the mean change in best corrected visual acuity (BCVA) from baseline to week 24. A number of secondary endpoints will also be evaluated, including investigation of OPT-302 on anatomical parameters of the wet AMD lesion using imaging techniques such as optical coherence tomography and fluorescein angiography. Primary analysis of the data from the Phase 2b study is anticipated in early 2020.

"We are pleased to have a number of clinical sites in the US now actively recruiting patients for this Phase 2b study and look forward to commencing recruitment in Europe and Israel in the coming months. All of the trial investigators and site staff are highly experienced in ophthalmic clinical trials and are excited to commence the clinical evaluation of OPT-302 in this randomised, controlled study," commented Clare Price, Director of Clinical Development of Opthea.

The Phase 2b trial initiation follows successful completion and reporting of positive outcomes from the Phase 1/2A clinical trial of OPT-302 in 51 patients with wet AMD. The encouraging results from the Phase 1/2A study indicated that OPT-302 is well tolerated when administered as a monotherapy and in combination with Lucentis® and suggested that combined administration of OPT-302 + Lucentis® may lead to improved clinical outcomes over Lucentis® alone.

The Clinical Trial Summary is part of this ASX Announcement as Appendix A.

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 the Phase 1/2A trial can be found at: www.clinicaltrials.gov, Clinical trial identifier: NCT02543229. Details on the outcomes of the study can be found on the Opthea website: www.opthea.com

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 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. Sales of the drug Lucentis® (Roche/Novartis), which targets VEGF-A but not VEGF-C or VEGF-D, were over $US3.2BN in 2016. Sales of EYLEA® (Regeneron/Bayer), which also targets VEGF-A but not VEGF-C/-D first marketed in November 2011 for the treatment of wet AMD, were over $US5.4BN in 2016. Approximately half of the people 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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APPENDIX A - CLINICAL TRIAL SUMMMARY

Protocol Number	OPT-302-1002
Title	A dose-ranging study of intravitreal OPT-302 in combination with ranibizumab, compared with ranibizumab alone, in participants with neovascular age-related macular degeneration (wet AMD)
Sponsor	Opthea Limited
Indication	Neovascular (wet) age-related macular degeneration (AMD)
Study Phase	2b
Primary Objective	To determine the efficacy of two different doses of intravitreal OPT-302 when administered in combination with ranibizumab in participants with wet AMD
Primary Endpoint	Mean change from Baseline in Early Treatment Diabetic Retinopathy Study (ETDRS) best corrected visual acuity (BCVA) to Week 24
Secondary Endpoints	• The proportion of participants gaining 15 or more ETDRS BCVA letters from Baseline to the Week 24 Visit • Area under the ETDRS BCVA-over-time curve • Change in CST on SD-OCT from Baseline to Week 24 • Change in sub-retinal fluid on SD-OCT from Baseline to Week 24 • Presence or absence of intra-retinal fluid determined by the presence or absence of intra-retinal cysts on SD-OCT from Baseline to Week 24 • Proportion of participants losing 15 or more letters (on ETDRS BCVA chart) from Baseline to the Week 24 Visit • Incidence of ocular and non-ocular adverse events (AEs) • OPT-302 pharmacokinetic parameters • Participant incidence of ADA formation
Study Design	Multicentre, randomised, parallel-group, sham-controlled, double-masked, dose-ranging study
Investigational Product	OPT-302
Comparator	Ranibizumab (Lucentis®)
Control	Sham control
Study Arms	Three study arms, randomised in a 1:1:1 ratio (every 4 weeks for 6 treatment cycles via sequential intravitreal injection): • OPT-302 2 mg, with ranibizumab 0.5 mg, • OPT-302 0.5 mg, with ranibizumab 0.5 mg, • Sham intravitreal injection, with ranibizumab 0.5 mg
Clinical Trial Sites	Approximately 113 sites in USA, Europe and Israel
Key Eligibility Criteria	• Participants ≥ 50 years of either gender, with active CNV secondary to AMD confirmed by fluorescein angiography (FA), who are treatment naïve • An ETDRS BCVA score between 60 and 25 (inclusive) letters