ASX and Media Release
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Opthea Initiates OPT-302 Diabetic Macular Edema Clinical Trial

Melbourne, Australia; January 3 2018 – Opthea Limited (ASX:OPT), a late stage biopharmaceutical company developing novel biologic therapies to treat back-of-the-eye diseases, has commenced a Phase 1b/2a trial evaluating the safety and efficacy of OPT-302 in patients with center-involved diabetic macular edema (DME). Following submission of the study protocol to the Food and Drug Administration (FDA), and ethics approval by the central Institutional Review Board, clinical trial sites have been activated and are recruiting patients in the US. This marks the expansion of the clinical development program for OPT-302 into a second ocular indication and targets a severe complication of diabetes.

Dr Megan Baldwin, Opthea's CEO and Managing Director commented "We are delighted to advance and expand the clinical research program of OPT-302 into diabetic macular edema. Together with our Phase 2b clinical trial in wet AMD, this study will enable us to more broadly explore the therapeutic potential of OPT-302, which is well positioned as one of the few combination approaches in development that may address the unmet medical need for patients with these progressive, vision-threatening diseases."

Characterized by retinal thickening from leaky blood vessels, DME is the leading cause of blindness in diabetics and is estimated to affect over 2 million people globally[1,2,3]. Existing standard of care treatments for DME are limited and include inhibitors of VEGF-A, 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.

This multi-centre clinical trial to be conducted in the US and Australia is a two-part design consisting of a Phase 1b dose escalation of OPT-302 (0.3, 1 and 2 mg) used in combination with the VEGF-A inhibitor Eylea® (aflibercept, 2 mg), followed by a Phase 2a randomised, controlled dose expansion with treatment allocated in a 2:1 ratio to either OPT-302 with Eylea®, or Eylea® monotherapy. The trial will enrol ~117 patients with persistent central involved diabetic macular edema despite prior anti-VEGF-A therapy with each patient dosed on a monthly basis for 3 months via intravitreal (ocular) injection. The primary objectives are to evaluate the safety/tolerability and efficacy of OPT-302 by determination of the clinical response rate as defined by the proportion of patients receiving combination OPT-302 and Eylea® achieving a ≥ 5 letter gain in visual acuity (VA) compared to baseline at week 12. In addition, a number of secondary measures will be investigated, including changes in mean VA, diabetic retinopathy severity score, and anatomical parameters such as central subfield thickness (CST) and macular volume from baseline to week 12.

Primary analysis of data from the Phase 1b/2a clinical trial in DME is anticipated in 1H'2019.

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 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 $US3.2BN in 2016. Sales of Eylea® (Regeneron/Bayer), which also targets VEGF-A but not VEGF-C/-D were over $US5.4BN in 2016. 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 and leakage, 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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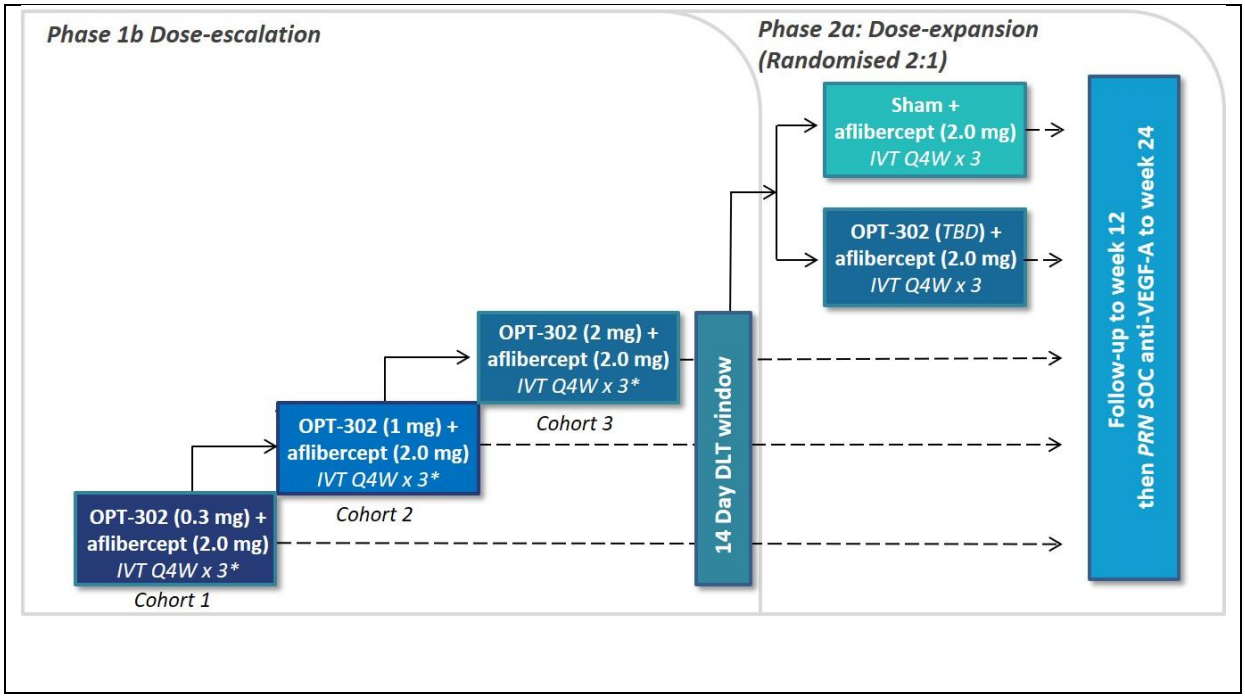
APPENDIX A - CLINICAL TRIAL SUMMMARY

Protocol Number	OPT-302-1003
Title	Phase 1b/2a study of OPT-302 in combination with aflibercept for persistent central-involved diabetic macular edema
Sponsor	Opthea Limited
Indication	Diabetic macular edema (DME)
Study Phase	1b/2a
Primary Endpoints	Phase 1b and Phase 2a: Safety: Subject incidence of adverse events, dose limiting toxicities and clinically significant changes in vital signs, ECGs and clinical laboratory tests Phase 2a: Efficacy: Response rate as defined by the proportion of participants receiving combination OPT-302 and aflibercept achieving at least a 5 letter gain in best corrected visual acuity (BCVA) compared to baseline at week 12 according to Early Treatment of Diabetic Retinopathy Study (ETDRS) criteria
Secondary Endpoint(s)	• Mean change in BCVA from baseline to week 12 using ETDRS criteria • Mean change from baseline to week 12 in central subfield thickness (CST) and macular volume on Spectral Domain Optical Coherence Tomography (SD-OCT) • Percent of eyes with ≥ 50% reduction in excess foveal thickness from baseline to week 12 on SD-OCT • Percent of eyes with CST < 300 µm on SD-OCT through week 12 • Percent of participants with a ≥ 2 step improvement from baseline to week 12 in ETDRS Diabetic Retinopathy Severity Score • The mean time to, and number of, retreatment injections of aflibercept anti-VEGF-A therapy based on protocol specified criteria during week 12 to week 24 follow-up • OPT-302 pharmacokinetics parameters • Incidence of anti-OPT-302 antibody formation

Study Design	Two part multi-centre study consisting of a Phase 1b open-label, sequential dose escalation followed by a Phase 2a randomized, controlled, dose expansion evaluating intravitreal OPT-302 in combination with aflibercept in patients with persistent central-involved DME
Investigational Product	OPT-302
Comparator	Aflibercept (Eylea®)
Control	Sham control
Dose Regimens	Phase 1b dose escalation: The dose regimens for the 3 sequential, escalating treatment cohorts in the Phase 1b are as follows: Cohort 1: OPT-302 0.3 mg and aflibercept 2 mg Cohort 2: OPT-302 1 mg and aflibercept 2 mg Cohort 3: OPT-302 2 mg and aflibercept 2 mg OPT-302 and aflibercept will be administered as separate intravitreal injections (each 0.05 mL) once every 4 weeks for 3 treatment cycles. Phase 2a dose expansion: At least 108 patients will be randomized in a 2:1 ratio between one of the following two treatment groups: Cohort 4: OPT-302 (*dose from Phase 1b*) and aflibercept 2 mg Cohort 5: Sham intravitreal injection and aflibercept 2 mg OPT-302 (or sham) and aflibercept will be administered as separate intravitreal injections (each 0.05 mL) every 4 weeks for 3 treatment cycles. Following the dosing period, in the Phase 1b and Phase 2a there will be a 4 week treatment free follow-up to week 12 and then a follow-up to week 24 during which the subject will receive as needed standard of care IVT aflibercept based on retreatment criteria for persistent DME if BCVA or CST worsens.
Clinical Trial Sites	Approximately 15-25 ophthalmology sites in the USA and Australia
Key Eligibility Criteria	• Males and females, ≥ 18 years of age • Diabetes mellitus (type 1 or type 2) • Edema that involves the center of the macula as confirmed by the reading center • Eyes with recurrent / persistent DME despite prior intravitreal anti-VEGF-A therapy with a suboptimal response • History of macular edema ≤ 12 months • An ETDRS BCVA letter score ≤ 73 and ≥ 24 (approximate Snellen equivalent 20/40 to 20/320), inclusive, in the study eye


Phase 1b Dose-escalation
Phase 2a: Dose-expansion
(Randomised 2:1)
OPT-302 (0.3 mg) + aflibercept (2.0 mg) IVT Q4W x 3*
Cohort 1
OPT-302 (1 mg) + aflibercept (2.0 mg) IVT Q4W x 3*
Cohort 2
OPT-302 (2 mg) + aflibercept (2.0 mg) IVT Q4W x 3*
Cohort 3
14 Day DLT window
Sham + aflibercept (2.0 mg) IVT Q4W x 3
OPT-302 (TBD) + aflibercept (2.0 mg) IVT Q4W x 3
Follow-up to week 12 then PRN SOC anti-VEGF-A to week 24