ASX and Media Release
26 July 2016

Opthea Reports Positive Data from wet AMD Clinical Trial

Company to Host Conference Call Today at 10:30AM Australian Eastern Daylight Time/8:30PM EDT

Melbourne, Australia, July 26 2016 – Opthea Limited (ASX:OPT)

- Phase 1 dose escalation study met primary objective demonstrating OPT-302 safety and tolerability as monotherapy and in combination with standard of care Lucentis®
- Changes in visual acuity (VA) and anatomic improvements on SD-OCT following the 3 month multiple dosing period demonstrate clinical activity of OPT-302 in both treatment naïve patients and prior treated patients
- Encouraging results suggest that combined inhibition of VEGF-C/D and VEGF-A may lead to improved outcomes over Lucentis® alone
- Results represent an important milestone for Opthea
- Opthea is actively accruing patients into Phase 2A dose expansion cohorts and planning for initiation of a randomised controlled Phase 2B clinical study in wet AMD patients in 2017

Opthea Limited (ASX:OPT), a developer of novel biologic therapies for the treatment of eye diseases, today announced positive data from its ongoing first-in-human clinical trial of OPT-302, a novel VEGF-C/D 'Trap' therapy for wet age-related macular degeneration (wet AMD). The Company will host a conference call and webcast at 10:30am Australian Eastern Daylight Time (8:30pm US EDT) today.

To access the live webcast, please visit the Presentations page of the Opthea website at **http://www.opthea.com/presentations/**. Alternatively, you may access the live conference call by dialling **(888) 576-4387** (U.S.) or **(719) 325-2244** (Australia & international) and using conference **ID 4334252**. An audio archive of the webcast will be available following the call at **http://www.opthea.com/presentations/**.

The study is being run under an Investigational New Drug (IND) program with the Food and Drug Administration (FDA) at 14 sites across the U.S. (ClinTrials.gov ID#: NCT02543229). The first-in-human trial of OPT-302 comprises two parts: a sequential dose escalation (Phase 1, 20 patients) and a randomised dose expansion study (Phase 2A, up to ~30 patients) in patients that have either not been treated previously (treatment naïve patients) or who have demonstrated a sub-optimal response to prior anti-VEGF-A therapy.

The Phase 1 dose escalation enrolled 20 patients (mean age 74.8 years) into three OPT-302 dose level groups (0.3, 1 or 2 mg) in combination with Lucentis® (0.5 mg) and an OPT-302 monotherapy group (2 mg). Patients received three intravitreal injections of OPT-302 either alone or in combination with Lucentis® at 4 week intervals, with a week 12 follow-up visit one month after the third dose. For patients who received OPT-302 monotherapy, Lucentis® rescue therapy was

provided at investigator discretion or if patients had a ≥5 letter decrease in vision and no reduction in central subfield thickness (CST) of at least 10% with presence of fluid. All cohorts enrolled 2 naïve patients and 3 patients who had received prior anti-VEGF-A therapy, with the exception of cohort 2 (OPT-302 1.0 mg + Lucentis®), which enrolled 5 previously treated patients.

The Phase 1 dose escalation study met its primary objective, with OPT-302 demonstrating safety and tolerability both as monotherapy and in combination with standard of care Lucentis®. Specifically, no dose limiting toxicities and no treatment-related serious adverse events were observed through week 12 of the study.

Secondary endpoints, which included changes from baseline in best corrected visual acuity and anatomic measures (central subfield thickness (CST)) on spectral domain-optical coherence tomography (SD-OCT) through week 12, demonstrated encouraging clinical activity of OPT-302 in both treatment naïve patients and those who showed a sub-optimal response to prior anti-VEGF-A therapy.

Overall, a majority of patients (16/19 evaluable at week 12) maintained or gained vision by week 12 compared to baseline and the other 3 patients that all received combination OPT-302 + Lucentis® therapy did not lose more than 3 letters (range -2 to -3 letters). The mean gain in visual acuity overall from baseline at week 12 in treatment naïve patients who received OPT-302 + Lucentis® was 16.5 letters (n=4) and 9.5 letters in the 2 mg OPT-302 + Lucentis® dose cohort (n=2). The mean visual acuity gain from baseline at week 12 in patients who showed a sub-optimal response to prior anti-VEGF-A therapy was 4 letters with combination OPT-302 + Lucentis® (n=10 evaluable patients; mean number of prior treatment injections = 10.5, range 3 – 55).

The mean central subfield thickness (CST), a measure of the average retinal thickness at the centre of the retina, decreased in all combination OPT-302 + Lucentis® treatment groups at week 12, with a mean reduction from baseline of 214 μM (42.7%) in treatment-naïve patients (n=4, mean baseline CST 501.7 μM) and 42 μM (10.8%) in patients who showed a sub-optimal response to prior anti-VEGF-A therapy (n=10 evaluable patients, mean baseline CST 394 μM).

In the OPT-302 monotherapy cohort, 3/5 patients (1 naïve and 2 prior treated) did not require rescue with anti-VEGF-A therapy. At week 12, in patients that did not undergo rescue, there was a mean visual acuity gain of 3.3 letters from baseline (range 2 to 6 letters) and a mean increase in CST of 18 μM.

Dr. Pravin Dugel, managing partner of Retinal Consultants of Arizona and clinical professor at the University of Southern California Eye Institute, Keck School of Medicine, and member of Opthea's Clinical Advisory Board, commented "Combination therapy with OPT-302 and standard of care Lucentis® is both feasible and well tolerated in patients who are either naïve to treatment or resistant to prior therapy. Although the preliminary clinical activity data to date is based on a small number of patients, the promising gains in vision and anatomic improvements on SD-OCT that have been observed suggest that combined inhibition of VEGF-C/D and VEGF-A may lead to improved outcomes over Lucentis® alone."

Data from the 20 patient Phase 1 dose-escalation study is planned to be presented at the EU Retina conference in September 2016.

Dr. Megan Baldwin, CEO and Managing Director of Opthea, stated "I am delighted that we have achieved the outcomes and expectations of this phase 1 dose escalation study and demonstrated the potential of OPT-302 to improve clinical outcomes for wet AMD patients."

"We are currently actively accruing up to ~30 additional patients into the Phase 2A dose expansion study cohorts. We look forward to monitoring the clinical outcomes to further build on our understanding of the mechanism of OPT-302, its safety profile and clinical activity, particularly in combination with Lucentis®."

Dr. Pravin Dugel concluded that “While we expect that the OPT-302 data will continue to evolve as more patients are enrolled in the Phase 2A trial, the early evidence of an additive benefit of OPT-302 observed in this study is very promising and warrants further investigation of OPT-302 in a large randomised controlled clinical study in wet AMD patients.”

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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. 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).

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 $US4.5BN in 2015. 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 $US2.6BN in 2015. 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 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. OPT-302 is currently being investigated in a Phase 1/2A clinical trial in wet AMD patients as a monotherapy and in combination with ranibizumab (Lucentis®). The trial is actively recruiting patients under an FDA approved IND at several US clinical sites. The purpose of the trial is 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). The study is being conducted in two parts: Part 1 (Phase 1) comprises an open label, sequential dose escalation that recruited 20 patients and Part 2 (Phase 2A) a randomized dose expansion that will recruit an additional ~30 patients and is aimed at further characterising the safety, pharmacokinetic profile and relationship between dose/PK and clinical activity of OPT-302 (+/- ranibizumab). Further details on the Phase 1/2A trial can be found at: www.clinicaltrials.gov, Clinical trial identifier: NCT02543229.

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.