ASX and Media Release
3 April 2017

Opthea Reports Positive Phase 1/2A Clinical Results for OPT-302 in wet AMD

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

Live webcast with presentation slides:
https://www.webcaster4.com/Webcast/Page/1668/20456 or
http://www.opthea.com/presentations/

Or dial: 1-800-094-765 (Australia)
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Conference ID 5945955

- Phase 1/2A trial met primary safety endpoint with OPT-302 well tolerated at all dose levels either alone or in combination with Lucentis® in 51 patients with wet AMD
- OPT-302 combination therapy showed improvements from baseline in visual acuity and retinal thickness in patients with wet AMD who were either treatment naïve or had received long term prior treatment with anti-VEGF-A
- Results suggest additive benefit of OPT-302 combination therapy with suppression of VEGF-C/D and VEGF-A
- OPT-302 monotherapy displayed evidence of clinical activity and visual acuity gains without background standard of care therapy through week 12 in patients not requiring rescue treatment with Lucentis®
- The data supports advancing OPT-302 to a Phase 2B randomised, controlled trial in wet AMD patients and investigation of OPT-302 in DME and prior treated patients in Phase 2A clinical trials which Opthea is planning to initiate in 2H 2017

Melbourne, Australia; 3 April 2017 – Opthea Limited (ASX:OPT), a developer of novel biologic therapies for the treatment of eye diseases, today announced positive results from its Phase 1/2A clinical trial of OPT-302, a novel VEGF-C/D 'Trap' therapy for wet age-related macular degeneration (wet AMD). The study has been conducted at 14 sites in the US (ClinTrials.gov ID#: NCT02543229) and run under an Investigational New Drug (IND) program with the Food and Drug Administration (FDA).

OPT-302 demonstrated clinical activity in all patient groups investigated, including naïve and prior-treated patients in both the monotherapy and combination OPT-302 + Lucentis® groups. Improvements in visual acuity (VA) and retinal swelling (central subfield thickness (CST) and sub-retinal fluid (SRF)) were observed suggesting additional clinical benefit with more complete suppression of VEGF-A and VEGF-C/D.

"We are excited by these promising results from the Phase 1/2A wet AMD clinical study with OPT-302" said Dr Megan Baldwin, CEO of Opthea. "This data warrants Opthea expanding its clinical

development program to progress OPT-302 as a novel combination therapy for the treatment of wet AMD as well as other eye diseases, including diabetic macular edema."

The Phase 1/2A study met its primary safety objective, with intravitreal injections of OPT-302 being well tolerated both as monotherapy and in combination with standard of care Lucentis®. No treatment related serious adverse events, systemic adverse events or dose limiting toxicities were observed.

“The results seen in Opthea’s Phase 1/2A trial are very encouraging," said 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, member of Opthea’s Clinical Advisory Board and study investigator. "The study has achieved both of its objectives by demonstrating a well-tolerated safety profile and clear signals of biological activity of OPT-302. The potential to treat patients with a combination therapy to provide additional clinical benefit over the current standard-of-care, and do it with a complementary mechanism of action, would be a significant advance in the treatment of retinal neovascular disease and beneficial for our patients."

Overall, 90% of patients (44/49) evaluable at week 12 maintained or improved VA at week 12, compared to baseline. Of the 49 patients, 100% had stabilization or improvement in visual acuity (defined as less than or equal to 15 letter loss on the ETDRS* eye chart).

In treatment naïve patients who received combination OPT-302 + Lucentis®, the mean change in VA from baseline at week 12 was +10.8 letters (n=18). The visual acuity improvements were seen as early as four weeks and continued to increase throughout the study to week 12. In addition, 33 percent of these treatment naïve patients showed BCVA gains of ≥ 15 letters (≥ 3 lines) on a standard eye-chart at week 12.

The mean change in VA from baseline at week 12 in previously treated patients with difficult to treat wet AMD was +4.9 letters (n=19 evaluable), despite long term prior treatment with anti-VEGF-A therapy (mean number of prior treatment injections = 17, range 3, 76).

The mean central subfield thickness (CST), a measure of the retinal thickness at the centre of the retina, decreased in all combination OPT-302 + Lucentis® treatment groups at week 12. The mean CST reduced to 283 μM at week 12 in treatment-naïve patients, which is approaching normal retinal thickness and represents a mean reduction of 119 μM from baseline (n=18, mean baseline CST 402 μM). In patients who showed a sub-optimal response to prior anti-VEGF-A therapy, mean CST decreased by -54 μM to 315 μM (n=19 evaluable, mean baseline CST 373 μM).

Reductions in sub-retinal fluid from baseline at week 12 were also observed in patients treated with combination OPT-302 + Lucentis®. In treatment naïve patients, mean SRF was reduced by 125 μM (83%), with 13/18 (72%) patients having complete (100%) resolution (n=18, baseline 142 μM). In those patients showing a sub-optimal response to prior anti-VEGF-A therapy, mean SRF decreased by 51% (-62 μM), with 3/19 (16%) patients having complete resolution of SRF and 9/19 (47%) patients having a >50% resolution of SRF at week 12 compared to baseline (n=19 evaluable, baseline 122 μM).

In patients receiving OPT-302 monotherapy, 7/13 patients (54%, 4 naïve and 3 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 change from baseline in VA of +5.6 letters (range 0 to 18), a mean decrease in CST of -15 μM (baseline 390 μM) and a reduction in mean sub-retinal fluid of -91μM (baseline 192 μM).

Dr Pravin Dugel concluded that, “The potential additive benefit of OPT-302 is very promising. The novel mechanism of action of OPT-302, together with the results of this Phase 1/2A clinical trial warrants further investigation of OPT-302 in patients with retinal neovascular diseases.”

An update on the Phase 1/2A wet AMD clinical trial with OPT-302 in wet AMD patients can be found on the company website: www.opthea.com

** ETDRS: Early Treatment of Diabetic Retinopathy Study*

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About the Phase 1/2A study of OPT-302 for Wet AMD

The Phase 1/2A trial recruited a total of 51 patients with wet AMD, who were either treatment naïve (n=25) or previously treated with prior intravitreal anti-VEGF-A therapy (n=26). Mean best corrected visual acuity (VA) was 59.4 letters at baseline. The study recruited a high proportion of heavily pre-treated patients (51%) and occult wet AMD lesions (73%) which are considered to be more difficult to treat with existing standard of care therapies.

The study had two parts: a sequential dose escalation (Phase 1) and a randomised dose expansion study (Phase 2A). The Phase 1 enrolled 20 patients into three ascending OPT-302 dose level cohorts (0.3, 1 and 2 mg) in combination with Lucentis® (0.5 mg), and an OPT-302 monotherapy group (2 mg). In the Phase 2A dose expansion, 31 subjects were randomised in a 3:1 ratio to two treatment cohorts with OPT-302 at 2 mg, either in combination with Lucentis® (n=23) or as monotherapy (n=8). Patients received three intravitreal injections of OPT-302 either alone or in combination with Lucentis® at 4 week intervals with a follow-up visit at week 12. For patients receiving OPT-302 monotherapy, Lucentis® rescue therapy was provided at investigator discretion or if there was a ≥ 5 letter decrease in VA and no reduction in central subfield thickness (CST) of at least 10% with presence of fluid.

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 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 has been investigated in a Phase 1/2A clinical trial in wet AMD patients as a monotherapy and in combination with ranibizumab (Lucentis®) (as referred to in this ASX announcement and the associated investor presentation). The trial is being conducted 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 recruited an additional 31 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.

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).

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.