ASX and Media Release

29 October 2019

Opthea First-in-Human Clinical Data for OPT-302 in wet AMD Published in Leading Ophthalmic Journal

Melbourne, Australia; 29 October 2019 – Opthea Limited (ASX:OPT), a clinical-stage biopharmaceutical company developing novel biologic therapies to treat back-of-the-eye diseases, today announced the publication of positive data from the first-in-human clinical trial of OPT-302, in patients with neovascular (wet) age-related macular degeneration (wet AMD). The successful trial results were published today in *Ophthalmology Retina,* a leading ophthalmic journal of the American Academy of Ophthalmology.

The publication provides detailed data of the first-in-human, dose escalation and expansion trial which evaluated the safety, pharmacokinetics and biological activity of repeated monthly intravitreal injections of OPT-302 alone or in combination with ranibizumab (Lucentis) in 51 patients with wet AMD who were either treatment naïve or had previously received anti-VEGF-A therapy.

"We are proud of the inclusion of the OPT-302 first-in-human study results in *Ophthalmology Retina*, which represents a valuable recognition of our work in a prestigious, peer-reviewed journal in the ophthalmic field" said Megan Baldwin, PhD, Opthea's CEO. "These important data provided the foundation for our Phase 2 development program, including the Phase 2b wet AMD study which reported superiority of OPT-302 combination therapy over ranibizumab for the primary endpoint of visual acuity gains at 6 months in treatment naïve patients, as well as the ongoing Phase 1b/2a trial evaluating OPT-302 combined with aflibercept (EYLEA) in the treatment of diabetic patients with persistent central involved macular edema. We are encouraged by the accumulating data with OPT-302 which may have the potential to bring enhanced responses and improved clinical benefit to patients suffering from retinal diseases who are in need of new treatment options."

In the paper, Dr Pravin Dugel, MD, Clinical Professor at the University of Southern California Roski Eye Institute, Keck School of Medicine and Managing Partner of Retinal Consultants of Arizona, and colleagues, summarize the study findings. "What is note-worthy about this study was the good tolerability and low systemic exposure of intravitreal OPT-302 combination therapy, with associated improvement in both visual function and lesion anatomical measures, despite most lesions being occult and more than half of the patients having persistent disease activity despite receiving previous regular standard of care anti-VEGF-A therapy" said Dr Dugel, retinal specialist and co-investigator on the study. "OPT-302 combination therapy may overcome an escape mechanism to VEGF-A suppression in the management of patients with wet AMD."

For a full discussion of the results from the first-in-human trial please refer to the published article in *Ophthalmology Retina* which is available online at https://www.ophthalmologyretina.org/inpress ahead of the future print edition which will be included in an upcoming issue of the Journal.

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 (e.g. Lucentis®/Eylea®). Combination therapy of OPT-302 and a VEGF-A inhibitor achieves more complete blockade of members of the VEGF family, blocking mechanisms contributing to sub-optimal responses to selective VEGF-A inhibitors and has the potential to improve vision outcomes by more completely inhibiting the pathways involved in disease progression.

About Wet AMD and DME

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.

Diabetic Macular Edema (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.

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 VEGF-C, VEGF-D and VEGFR-3. Opthea's intellectual property is held within its wholly-owned subsidiary Vegenics Pty Ltd. Opthea's product development programs are focused on developing OPT-302 for retinal diseases.

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. Therefore 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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