ASX and Media Release

21 August 2020

Opthea Completes Successful Meetings with FDA and EMA for OPT-302 Phase 3 Clinical Program in Wet AMD

- ***Regulatory engagement provides clear pathway through Phase 3 to support filing for marketing approvals in US and Europe***
- ***Regulatory agreement of using Lucentis® and Eylea® in combination with OPT-302 across two pivotal Phase 3 trials increases the potential multi-billion dollar market opportunity***
- ***Lucentis® and Eylea® had combined sales for retinal diseases of USD11.9BN in 2019***
- ***Company on-track to initiate Phase 3 trials in early 2021***

Melbourne, Australia; 21 August 2020 – Opthea Limited (ASX:OPT), a clinical-stage biopharmaceutical company developing a novel therapy to treat highly prevalent and progressive retinal diseases, is pleased to announce today that it has successfully completed End-of-Phase 2 meetings with the U.S. Food and Drug Administration (FDA), and a Scientific Advice meeting with the European Medicines Agency (EMA), to obtain guidance on the Phase 3 clinical development plans of OPT-302 as a treatment for neovascular (wet) age-related macular degeneration (wet AMD). The outcome of the meetings supports the progression of OPT-302 into Phase 3 and pre-commercial development. The company is on-track to initiate Phase 3 trials in early 2021.

The regulatory engagement conducted with the FDA and EMA covered key elements of the Phase 3 clinical studies and associated manufacturing processes for OPT-302 that will support the submission of a Biologics License Application in the US and Marketing Authorisation Application in Europe for the targeted wet AMD indication.

The FDA and EMA agreed on key aspects of the proposed Phase 3 clinical trial designs, including the conduct of two concurrent, global, multicenter, randomized, sham-controlled studies evaluating OPT-302 in combination with ranibizumab (Lucentis®) (Study OPT-302-1004, referred to as ShORe) or aflibercept (Eylea®) (Study OPT-302-1005, referred to as COAST). If successful, the investigation of OPT-302 in combination with two approved standard of care VEGF-A inhibitors could enable OPT-302 to be administered with either Eylea or Lucentis which had combined sales for retinal diseases of USD$11.9 billion in 2019. Furthermore, each trial will compare the clinical efficacy of OPT-302 administered in combination with a VEGF-A inhibitor on an every 4-week and every 8-week dosing regimen in order to understand the durability of OPT-302 treatment effect with less frequent dosing.

In the Study of OPT-302 in combination with Ranibizumab (ShORe), treatment-naïve patients with wet AMD will be randomized to one of three treatment arms to receive standard of care 0.5 mg ranibizumab every four weeks in combination with either 2.0 mg OPT-302 on a standard every four weeks dosing regimen or 2.0 mg OPT-302 on an extended every eight weeks dosing regimen after three monthly initiating doses, or with sham injections every four weeks.

In COAST, Combination OPT-302 with Aflibercept STudy, treatment-naïve patients with wet AMD will be randomized to one of three treatment arms to receive standard of care 2.0 mg aflibercept on its every eight-week dosing regimen, after three monthly initiating doses, in combination with either 2.0 mg OPT-

302 on a standard every four weeks dosing regimen or 2.0 mg OPT-302 on an extended every eight weeks dosing regimen after three monthly initiating doses, or with sham injections every four weeks.

Each trial is expected to enroll at least 900 patients worldwide. The primary endpoint is mean change in visual acuity from baseline to week 52 for OPT-302 and anti-VEGF-A combination therapy compared to anti-VEGF-A monotherapy, with the Company intending to submit Biologics License and Marketing Authorisation Applications with the FDA and EMA respectively following completion of this primary efficacy phase of the trials. Each patient will continue to be treated for a further year to evaluate safety and tolerability over a two-year period.

These two OPT-302 Phase 3 trials build upon and maintain key features for consistency with the Company's positive Phase 2b clinical trial of OPT-302, while evaluating the administration of OPT-302 combination therapy over a longer treatment period and in a greater number of patients. In addition, the Phase 3 trials are optimized based on Phase 2b outcomes to maximize probability of success and commercial opportunity. Analysis of the Phase 2b trial demonstrated that OPT-302 combination therapy increased visual acuity by a further +5.7 letters over Lucentis monotherapy in wet AMD patients with minimally classic and occult lesions, representing the majority (~80%) of wet AMD patients. Based on these positive data, primary analysis of the primary endpoint of the Phase 3 trials will be first conducted in patients with minimally classic and occult lesions administered OPT-302 every 4 weeks, followed by analysis on the every 8 week dosing groups and total patient population.

"We are very pleased with the valuable guidance received from the FDA and EMA which provides clear direction as we advance our Phase 3 registration program towards bringing OPT-302 to market" said Dr Megan Baldwin, Chief Executive Officer of Opthea. "We remain focused on further demonstrating, in our Phase 3 program, the potential of OPT-302 combination therapy as a novel and transformative treatment for wet AMD patients suffering vision loss."

"The analysis approach for our Phase 3 clinical trials allows the initial analysis of outcomes to be evaluated in the patient group which, based on data from our Phase 2b trial, would be expected to have the best response to OPT-302 combination therapy. Further pre-specified statistical analyses also allow us to evaluate the primary endpoint in the total patient population including minimally classic, occult and predominantly classic lesions, which maximizes the commercial opportunity for OPT-302" commented Dr Baldwin. "We believe this approach achieves the highest probability of success for our Phase 3 program and commercialization strategy."

The planning for the pivotal Phase 3 studies is well advanced including the manufacturing of OPT-302 drug product to be used in the trials. Importantly, there are now well-defined regulatory pathways in place to advance the Phase 3 program development of OPT-302 in the treatment of wet AMD in support of future registration filings for marketing approval and commercial launch in the U.S. and Europe.

Additional information on Opthea's technology and clinical trials can be found at www.opthea.com.

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 wet age-related macular degeneration (wet AMD) and diabetic macular edema (DME). 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.

Opthea has reported outcomes from an international, multi-centre, prospective, sham-controlled, double-masked, superiority study that enrolled 366 treatment-naïve patients with wet AMD. Participants in the study were randomized in a 1:1:1 ratio to receive one of the following treatment regimens administered once every 4 weeks for 24 weeks (six treatments in total): OPT-302 (0.5 mg) in combination with ranibizumab (Lucentis®) (0.5 mg); OPT-302 (2.0 mg) in combination with ranibizumab (0.5 mg); or sham in combination with ranibizumab (0.5 mg). The study met the primary endpoint demonstrating superior vision gains in participants who received OPT-302 (2.0 mg) in combination with ranibizumab at week 24. Opthea is also investigating OPT-302 in a Phase 2a clinical trial in patients with persistent,

centre-involved DME. Further details on the Company's clinical trials can be found at: www.clinicaltrials.gov, Clinical trial identifiers: NCT02543229, NCT03345082 and NCT03397264.

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.

Authorised for release to ASX by Megan Baldwin, CEO & Managing Director

Company & Media Enquiries:

Megan Baldwin, PhD
CEO & Managing Director
Opthea Limited
Tel: +61 (0) 447 788 674
megan.baldwin@opthea.com

Join our email database to receive program updates:

Tel: +61 (0) 3 9826 0399
info@opthea.com
www.opthea.com

Australia:
Rudi Michelson
Monsoon Communications
Tel: +61 (0) 3 9620 3333

U.S.A. & International:
Jason Wong
Blueprint Life Science Group
Tel: +1 415 375 3340, Ext 4
Jwong@bplifescience.com