ASX and Media Release

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Opthea Treats First Patient in Phase 3 Pivotal Trials of OPT-302 in Wet AMD

Melbourne, Australia; 15 March 2021 – Opthea Limited (ASX:OPT; Nasdaq:OPT), a clinical stage biopharmaceutical company developing a novel therapy to treat highly prevalent and progressive retinal diseases, is pleased to announce that the first patient has been treated in the Phase 3 pivotal clinical program of the Company's first-in-class VEGF-C/D 'trap' inhibitor, OPT-302, in participants with treatment-naïve wet (neovascular) age-related macular degeneration (AMD). The first patient was enrolled by Dr Allen Hu, MD, Cumberland Valley Retina Consultants, Hagerstown, Maryland, USA.

"Dosing the first patient in our OPT-302 Phase 3 pivotal clinical program in wet AMD marks a very important achievement for Opthea in accelerating the development of this novel VEGF-C/D inhibitor therapy towards market registration" commented Dr Megan Baldwin, Chief Executive Officer of Opthea. "We are now looking forward to quickly ramping up enrolment to meet the interest from participating clinical sites and retinal specialists. OPT-302, which has shown promising efficacy and favorable safety profiles in trials to date, is an important new treatment option which may offer patients improved outcomes when administered in combination with VEGF-A inhibitors."

Opthea is conducting two concurrent global, multi-center, randomized, double-masked, sham-controlled Phase 3 trials known as **ShORe** *(**S**tudy of **O**PT-302 in combination with **R**anibizumab)* and **COAST** *(**C**ombination **O**PT-302 with **A**flibercept **St**udy)*. Both clinical studies will enroll ~990 treatment-naive patients each and assess the efficacy and safety of intravitreal 2.0 mg OPT-302 in combination with 0.5 mg ranibizumab (Lucentis®) or 2.0 mg aflibercept (Eylea®), compared to ranibizumab or aflibercept monotherapy, respectively.

The primary endpoint of the ShORe and COAST studies is the mean change in Best Corrected Visual Acuity from baseline to week 52 for OPT-302 combination therapy compared to anti-VEGF-A monotherapy. Each patient will also continue to be treated for a further year to evaluate extended safety and tolerability over a two-year period. A number of secondary endpoints will also be evaluated, including other key measures of visual function, as well as anatomical changes in the wet AMD lesions assessed by optical coherence tomography (OCT) and fluorescein angiography imaging. In addition, extended durability of the OPT-302 treatment effect on clinical outcomes with less frequent every eight-weekly dosing will be compared with OPT-302 administered on an every four-weekly dosing regimen, in combination with each VEGF-A inhibitor.

The initiation of the Phase 3 pivotal clinical program follows the reporting of positive outcomes from the Phase 2b clinical trial of OPT-302 in 366 patients with wet AMD. The results from the Phase 2b study demonstrated a statistically significant superior mean gain in visual acuity in patients treated with OPT-302 combination therapy compared to ranibizumab monotherapy at week 24. The ShORe and COAST Phase 3 trials build upon and maintain key features of the successful Phase 2b wet AMD clinical trial, whilst also evaluating the administration of OPT-302 in combination with ranibizumab and aflibercept over a longer treatment period and in a greater number of patients.

Opthea anticipates reporting top-line data in 2023, with the Company intending to submit Biologics License and Marketing Authorisation Applications with the FDA and EMA respectively following completion of the 12-month primary efficacy phase of the trials.

Additional information on Opthea's technology and clinical trials can be found at www.opthea.com and at ClinicalTrials.gov (ShORe trial, ID#: NCT04757610; COAST trial, ID#: NCT04757636). Summaries of the ShORe and COAST Phase 3 Clinical Trials are included below.

CLINICAL TRIAL SUMMARIES

Protocol Number	OPT-302-1004
Study Title	A Phase 3 study of intravitreal OPT-302 in combination with ranibizumab, compared with ranibizumab alone, in participants with neovascular age-related macular degeneration (AMD)
Study Name	ShORe – Study of OPT-302 in combination with Ranibizumab in neovascular AMD
Sponsor	Opthea Limited
Indication	Neovascular (wet) age-related macular degeneration (AMD)
Study Phase	3
Primary Objective	To determine the efficacy of intravitreal 2.0 mg OPT-302 when administered in combination with intravitreal 0.5 mg ranibizumab, in participants with neovascular AMD
Primary Endpoint	Mean change from Baseline to Week 52 in Early Treatment Diabetic Retinopathy Study (ETDRS) best corrected visual acuity (BCVA) letters
Secondary Endpoints	• Proportion of participants gaining 10 or more ETDRS BCVA letters from Baseline to Week 52 • Proportion of participants gaining 15 or more ETDRS BCVA letters from Baseline to Week 52 • Proportion of participants with absence of both SRF and IR cysts by spectral domain optical coherence tomography (SD-OCT) at Week 52 • Change in CNV area by fluorescein angiography (FA) from Baseline to Week 52 • Change in CST by SD-OCT from Baseline to Week 52 • Change in the NEI VFQ-25 composite score from Baseline to Week 52 • Incidence of ocular and non-ocular treatment-emergent adverse events • Proportion of participants losing 15 or more ETDRS BCVA letters from Baseline to Week 52 • Participant incidence of ADA formation • OPT-302 pharmacokinetic parameters
Study Design	Phase 3, multicentre, randomised, parallel-group, sham-controlled, double-masked, superiority study
Investigational Product	2.0 mg OPT-302 intravitreal injection
Co-administered anti-VEGF-A therapy	0.5 mg ranibizumab intravitreal injection
Control	Sham intravitreal injection
Study Arms	Three study arms, randomised in a 1:1:1 ratio: • Standard Dosing: 2.0 mg OPT-302 (50 µl) intravitreal injection with 0.5 mg ranibizumab (50 µl) intravitreal injection, both administered 4-weekly (q4w) • Extended Dosing: 2.0 mg OPT-302 (50 µl) intravitreal injection (3 doses at 4-weekly intervals, and then 8-weekly [q4w x 3 then q8w]) with sham injection at visits when OPT-302 is not administered, with 0.5 mg ranibizumab (50 µl) intravitreal injection 4-weekly (q4w) • Control Sham intravitreal injection with 0.5 mg ranibizumab (50 µl) intravitreal injection, both administered 4-weekly (q4w)
Key Eligibility Criteria	• Participants ≥ 50 years of either gender, with active CNV secondary to AMD confirmed by fluorescein angiography (FA), who are treatment naïve • An ETDRS BCVA score between 60 and 25 (inclusive) letters

Protocol Number	OPT-302-1005
Study Title	A Phase 3 study of intravitreal OPT-302 in combination with aflibercept, compared with aflibercept alone, in participants with neovascular age-related macular degeneration (AMD)
Study Name	COAST – Combination OPT-302 with Aflibercept STudy in neovascular AMD
Sponsor	Opthea Limited
Indication	Neovascular (wet) age-related macular degeneration (AMD)
Study Phase	3
Primary Objective	To determine the efficacy of intravitreal 2.0 mg OPT-302 when administered in combination with intravitreal 2.0 mg aflibercept, in participants with neovascular AMD
Primary Endpoint	Mean change from Baseline to Week 52 in Early Treatment Diabetic Retinopathy Study (ETDRS) best corrected visual acuity (BCVA) letters
Secondary Endpoints	• Proportion of participants gaining 10 or more ETDRS BCVA letters from Baseline to Week 52 • Proportion of participants gaining 15 or more ETDRS BCVA letters from Baseline to Week 52 • Proportion of participants with absence of both SRF and IR cysts by spectral domain optical coherence tomography (SD-OCT) at Week 52 • Change in CNV area by fluorescein angiography (FA) from Baseline to Week 52 • Change in CST by SD-OCT from Baseline to Week 52 • Change in the NEI VFQ-25 composite score from Baseline to Week 52 • Incidence of ocular and non-ocular treatment-emergent adverse events • Proportion of participants losing 15 or more ETDRS BCVA letters from Baseline to Week 52 • Participant incidence of ADA formation • OPT-302 pharmacokinetic parameters
Study Design	Phase 3, multicentre, randomised, parallel-group, sham-controlled, double-masked, superiority study
Investigational Product	2.0 mg OPT-302 intravitreal injection
Co-administered anti-VEGF-A therapy	2.0 mg aflibercept intravitreal injection
Control	Sham intravitreal injection
Study Arms	Three study arms, randomised in a 1:1:1 ratio: • Standard Dosing: 2.0 mg OPT-302 (50 µl) intravitreal injection at 4-weekly intervals (q4w), with 2.0 mg aflibercept (50 µl) intravitreal injection (3 doses at 4-weekly intervals, and then 8-weekly [q4w x 3 then q8w]). • Extended Dosing: 2.0 mg OPT-302 (50 µl) intravitreal injection (q4w x 3 then q8w) with sham injection at visits when OPT-302 is not administered, with 2.0 mg aflibercept (50 µl) intravitreal injection (q4w x 3 then q8w). • Control Sham intravitreal injection 4-weekly, with 2.0 mg aflibercept (50 µl) intravitreal injection (q4w x 3 then q8w)
Key Eligibility Criteria	• Participants ≥ 50 years of either gender, with active CNV secondaryto AMD confirmed by fluorescein angiography (FA), who are treatment naïve • An ETDRS BCVA score between 60 and 25 (inclusive) letters

About Opthea

Opthea (ASX:OPT; Nasdaq:OPT) is a biopharmaceutical company developing a novel therapy to address the unmet need in the treatment of highly prevalent and progressive retinal diseases, including wet age-related macular degeneration (wet AMD) and diabetic macular edema (DME). Opthea's lead product candidate OPT-302 is being developed for use in combination with anti-VEGF-A monotherapies to achieve broader inhibition of the VEGF family, with the goal of improving overall efficacy and demonstrating superior vision gains over that which can be achieved by inhibiting VEGF-A alone.

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 commercialization 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 specializing 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 announcement may contain forward-looking statements, including within the meaning of the U.S. Private Securities Litigation Reform Act of 1995. Any statement describing Company goals, expectations, intentions or beliefs is a forward-looking statement and should be considered an at risk statement, including, but not limited to, the continuation of patient recruitment for Opthea's pivotal Phase 3 clinical trials of OPT-302 in wet AMD. Such statements are based on Opthea's current plans, objectives, estimates, expectations and intentions and are subject to certain risks and uncertainties, including risks and uncertainties associated with clinical trials and product development and the impact of general economic, industry or political conditions in Australia, the United States or internationally. These and other risks and uncertainties are described more fully in the section titled "Risk Factors" in the final prospectus filed with the SEC on October 19, 2020. The Company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events, or otherwise, except as required under applicable law. You should not place undue reliance on these forward-looking statements as predictions of future events, which statements apply only as of the date of this announcement. Actual results could differ materially from those discussed in this ASX announcement.

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