Opthea Reports Positive Phase 2a Trial Results of OPT-302 in Diabetic Macular Edema

June 9, 2020

- ***Primary endpoint of response with OPT-302 + Eylea® (aflibercept) achieved: 52.8% of refractory DME patients gained ≥ 5 letters of visual acuity at week 12 following OPT-302 combination therapy***
- ***Co-primary safety endpoint met: OPT-302 combination therapy was well tolerated with similar safety profile to Eylea***
- ***Totality of functional and anatomical endpoints warrant further investigation of OPT-302 combination therapy for DME***

Company to Host Conference Call Today at 9:00 AM AEST (Wed, 10th June Aust.)
7:00PM EDT (Tues, 9th June U.S.)
-Dial-in details posted at end of release-

MELBOURNE, Australia, June 09, 2020 (GLOBE NEWSWIRE) -- Opthea Limited (ASX:OPT), a developer of novel biologic therapies for the treatment of eye diseases, today announced positive topline results of its Phase 2a trial evaluating safety and efficacy of OPT-302 administered with Eylea® (aflibercept) in treatment refractory patients with persistent diabetic macula edema (DME).

The trial met the prespecified primary efficacy endpoint with 52.8% of patients (95% CI 41-64%) achieving ≥ 5 letters gain in Best Corrected Visual Acuity (BCVA) at week 12. The co-primary endpoint of safety was also met with 2.0 mg OPT-302 in combination with 2.0 mg Eylea being well tolerated with a similar safety profile to the Eylea + sham (control) group.

"These Phase 2a data are very promising given that dual-targeted inhibition of VEGF-C/-D and VEGF-A with OPT-302 combination therapy demonstrated biological activity across multiple vision and anatomical endpoints which may lead to improved outcomes in the management of DME," said David Boyer, MD, Senior Partner Retina Vitreous Associates Medical Group, Los Angeles, and Clinical Professor at the University of Southern California Roski Eye Institute, Keck School of Medicine, and study investigator on the trial.

"These results show the potential of OPT-302 combination therapy for people living with diabetic macular edema, a leading cause of vision loss in working-age adults. With limited treatment options currently available and many patients who do not adequately respond to anti-VEGF-A therapies, there remains a significant unmet need for more efficacious and durable therapies for DME. If we could add a treatment such as OPT-302 to potentially improve vision in this population of hard to treat patients, this would be significant", added Dr Boyer.

The Phase 2a trial is a randomized, double-masked, sham-controlled, proof-of-concept clinical trial conducted at 53 sites in the United States, Israel, Australia and Latvia. The trial recruited a total of 144 participants, with 115 of the 144 patients conforming sufficiently with the trial protocol and included in the Per Protocol population. All participants enrolled into the trial were diagnosed with persistent DME despite regular intravitreal administration of prior anti-VEGF-A monotherapy. Eligible participants had a BCVA in the study eye of 20/40 to 20/320 Snellen equivalent and central subfield thickness (CST) of ≥ 320 µm. Participants were randomized in a 2:1 ratio to receive either OPT-302 (2.0 mg) + Eylea (2.0 mg) or sham + Eylea (2.0 mg). Study treatments were administered by intravitreal (ocular) injection once every 4 weeks with a total of 3 doses and study outcomes were assessed from baseline through week 12.

The trial was statistically designed with a prespecified primary efficacy endpoint of ≥ 5 letter vision gain that represents a clinically relevant improvement in previously treated patients, and a treatment response rate of ≥38%, based on previously published studies that show limited ability to achieve a further 5 letter or more improvement following an initial loading dose period and ongoing anti-VEGF-A monotherapy. [1-5]

Key secondary endpoints of visual function, anatomic changes and diabetic retinopathy severity score (DRSS) were assessed for the OPT-302 combination therapy and Eylea control group. The trial was not powered to detect differences between the treatment groups, however these analyses provide insight into directional changes and totality of responses with OPT-302 combination therapy.

Mean change in BCVA at week 12 compared to baseline was 5.9 letters for OPT-302 combination therapy and was similar in the Eylea control group at 6.1 letters. 52% of patients in the OPT-302 combination and 60% of patients in the Eylea control group gained ≥5 letters, however a higher proportion of patients gained ≥10 and ≥15 letters of vision following OPT-302 combination treatment compared to Eylea control. The proportion of patients gaining ≥10 letters from baseline to week 12 was 26.7% in the OPT-302 combination group and 22.5% in the Eylea control. In addition, 12% of patients in the OPT-302 combination group and 7.5% of patients in the Eylea control group had ≥15 letter gains respectively. The percentage of patients who lost 5 or more letters was 2.7% in the OPT-302 combination therapy group, and 5% in the Eylea control group.

An exploratory subgroup analysis was conducted in patients with a prior anti-VEGF-A treatment history of only receiving previous Eylea to assess the effects of OPT-302 combination therapy following the most optimal first-line standard of care used to achieve maximal VEGF-A inhibition. In this subgroup, the mean change in BCVA at week 12 compared to baseline was 8.6 letters for OPT-302 + Eylea and 5.0 letters in patients who continued on Eylea monotherapy. The proportion of patients in the subgroup gaining ≥10 and ≥15 letters from baseline to week 12 was 50% and 16.7% in the OPT-302 combination group respectively and 0% for both parameters in the Eylea control. The percentage of patients losing 1 or more letters from baseline to week 12 was 8.3% in the OPT-302 + Eylea group, and 12.5% for the Eylea control.

Retinal thickness measured by CST on spectral domain optical coherence tomography (SD-OCT), was reduced by -52.16 µm, from 436 µm at

baseline to 384 µm at week 12 following OPT-302 combination therapy. The mean CST was reduced by -34.92 µm, from 422 µm at baseline to 389 µm at week 12 in the Eylea control group.

The proportion of patients with ≥ 1 step improvement in DRSS was 21.4% with OPT-302 combination therapy and 17.5% in the Eylea control group. The proportion of patients who had a severity score of between 47 and 53, representing moderately-severe to severe non-proliferative diabetic retinopathy (NPDR), was 65.3% at baseline and 54.8% following OPT-302 combination therapy to week 12, whereas there was no change in the Eylea monotherapy group with 60% of patients having moderately-severe to severe NPDR at baseline and week 12.

These secondary analyses were conducted in all evaluable patients in the Per Protocol population. Similar outcomes were also observed in the Intent to Treat Population.

"We believe that the results of this Phase 2a DME trial, together with the positive outcomes of the Company's Phase 2b trial with OPT-302 in wet AMD, further validate Opthea's approach to target VEGF-C and VEGF-D to address the substantial unmet medical need for patients with these retinal eye diseases despite the availability of selective inhibitors of VEGF-A " commented Arshad Khanani, M.D., M.A., Director of Clinical Research at Sierra Eye Associates, Reno, Nevada, and study investigator on the trial.

The tolerability of OPT-302 combination therapy was consistent with Eylea standard of care in DME patients, and there were no observed safety concerns, consistent with previous experience with OPT-302 in Phase 1/2a and Phase 2b clinical trials in wet AMD [6,7]. No ocular serious adverse events were reported and the incidence of intra-ocular inflammation in the study eye was low, occurring in one patient in each treatment group, and the events were manageable and resolved.

"I am very encouraged and hopeful for the potential of OPT-302 combination therapy to provide physicians with further treatment options for our patients. The well tolerated safety profile that we have consistently observed with this molecule is encouraging and the biological activity observed in this trial, in patients that are very difficult to treat and with different prior-treatment histories, bodes well for the further clinical development of OPT-302," added Dr. Khanani.

This Phase 2a trial is ongoing with the final participants due to complete the long-term week 24 follow-up visit later this month. It is anticipated that additional exploratory analyses and the final outcomes for longer term safety and treatment durability will be available in the second half of calendar year 2020. In addition to the ongoing Phase 2a DME trial, Opthea continues to undertake planning for its Phase 3 program in wet AMD, including regulatory engagement in the US and Europe, and to progress its manufacturing of OPT-302 for Phase 3 clinical trials.

"These positive topline Phase 2a results in a second disease indication of DME, build on our extensive prior clinical studies in wet AMD which demonstrated superiority in visual improvement with OPT-302 combination therapy compared to anti-VEGF-A monotherapy standard of care. The intent of this proof-of-concept study was to generate directional information on the safety, tolerability and therapeutic potential of OPT-302 combination therapy for DME. This trial was conducted in a difficult to treat refractory DME patient population, and these early results support further later stage clinical investigation of OPT-302 in a larger population of patients with DME. We greatly appreciate and thank the patients, investigators and site staff who participated in this study and look forward to presenting the study results at major medical conferences in the coming months," commented Dr. Megan Baldwin, CEO and Managing Director, Opthea Limited.

The Phase 2a DME trial results including primary and secondary outcomes, will be presented by Dr. David Boyer, MD at:

- The American Society of Retina Specialists (ASRS) Annual Meeting 2020, July 24-28th and
- The American Academy of Ophthalmology, Retina Sub-specialty Day 2020, November 13th.

1. Gonzalez VH, et al. Am J Ophthalmol 2016; 172:72-79.
2. Wells JA, et al. Ophthalmology. 2016; 123(6): 1351-1359.
3. Chatziralli I, et al. Eye. 2017; 31: 1594-1599.
4. Maturi RK, et al. JAMA Ophthalmology. 2018; 136: 29-38.
5. Spooner K, et al, Clin Ophthalmol. 2017; 11: 161-177.
6. Dugel, PD, et al, Ophthalmology Retina 2020.
7 Jackson, TJ, Euretina 2020

Conference call details:

Opthea Limited will hold a conference call to discuss the above results and welcomes participation from interested parties.

Conference ID **10007552**

Pre-registration (preferred option)

Participants can pre-register by navigating to:
https://s1.c-conf.com/DiamondPass/10007552-invite.html

Registered participants will receive their dial in number upon registration to enter the call automatically on the day.

Dial-in directly (toll free)

Australia
Wednesday 10th June, 2020
9.00 am (Australian Eastern Standard Time)

Australia Toll Free: 1800 455 963
Sydney: 02 9007 8048

USA

Tuesday 9th June, 2020
7.00 pm (Eastern Daylight Time)

USA/Canada Toll Free: 1855 624 0077

Dial-in direct numbers (toll free)			
Australia:	1800 455 963	Japan:	0066 3386 8000
Sydney:	02 9007 8048	Malaysia:	1800 816 441
New Zealand:	0800 452 795	Singapore:	800 101 2702
China:	10800 140 1776	South Africa:	0800 984 013
France:	0800 913 734	Spain:	900 823 322
Germany:	0800 183 0918	Switzerland:	0800 802 498
Hong Kong:	800 968 273	Taiwan:	0080 112 7377
India:	0008 0010 08070	UAE:	8000 3570 2706
Indonesia:	007 803 321 8057	UK:	0800 051 1453
Ireland:	1800 948 607	USA/Canada	1 855 624 0077
Other International (metered): +61 7 3145 4005			

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 also 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 every 4 weeks for 24 weeks: 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 on a monthly basis over 6 months. 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.

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