January 25, 2023

Ocuphire Announces Topline Results from ZETA-1 Phase 2 Trial of Oral APX3330 in Diabetic Retinopathy and Plans for End-of-Phase 2 Meeting with FDA

Oral APX3330 Achieved Statistical Significance on a Key Pre-specified Secondary Endpoint of Preventing Clinically Meaningful Progression of Diabetic Retinopathy (DR) after 24 Weeks of Treatment

Oral APX3330 Demonstrated Favorable Safety and Tolerability Allowing for a Potential Attractive Non-Invasive Option for Protection of Vision in Both Eyes in DR Patients

Conference Call and Webcast Today at 4:30pm ET

FARMINGTON HILLS, Mich., Jan. 25, 2023 (GLOBE NEWSWIRE) -- Ocuphire Pharma, Inc. (Nasdaq: OCUP), a clinical-stage ophthalmic biopharmaceutical company focused on developing and commercializing therapies for the treatment of refractive and retinal eye disorders, today announced topline efficacy and safety results from its ZETA-1 Phase 2 trial evaluating oral APX3330 for the treatment of diabetic retinopathy (DR).

“Our goals in this initial retina Phase 2 trial were to explore multiple endpoints to evaluate the potential for APX3330 as the first oral drug to safely benefit diabetic patients with eye disease,” said Mina Sooch, MBA, founder and CEO of Ocuphire Pharma. “Although we did not meet the primary endpoint (a precedented endpoint for local administration of anti-VEGF intravitreal injections), we are pleased that the ZETA-1 results on key pre-specified endpoints demonstrated positive outcomes with a favorable systemic and ocular safety profile that support our plans to move forward to an End-of-Phase 2 meeting with the FDA. Given the systemic delivery of APX3330, it is important to evaluate its effect on both eyes. APX3330 achieved statistical significance on a key pre-specified secondary endpoint – binocular 3-step or more worsening of DRSS (diabetic retinopathy severity score) – a clinically meaningful outcome that demonstrates the ability to slow the worsening of this progressive disease and is a potential Phase 3 registration endpoint. With the financial strength provided by our recent global Nyxol® license agreement, we have considerable flexibility to design and initiate the pivotal stage of the APX3330 program. We thank the study participants, clinical investigators and their site staffs for participating in the trial.”

Peter K. Kaiser, MD, Professor of Ophthalmology at the Cole Eye Institute of the Cleveland Clinic Foundation commented, “The diabetes epidemic, and the associated increase in the number DR patients, has become a major burden on the healthcare system. Diabetic patients with non-proliferative retinopathy currently have limited treatment options to prevent progression of retinopathy and loss of vision. The current treatment paradigm is for

physicians to wait and monitor early-stage DR patients, with anti-VEGF or steroid injectable therapy or laser treatment reserved for patients who advance to proliferative DR or DME. I am very encouraged by the data from ZETA-1 showing that APX3330 can potentially slow disease progression. In diabetic patients, APX3330 has demonstrated a favorable safety profile and has the advantage of being an oral agent treating both eyes at once. If these results are confirmed in Phase 3 and APX3330 is subsequently approved, healthcare providers would have an important new primary preventative therapeutic option that could be used in a large number of patients who are earlier in the course of disease. This would potentially reduce the number of patients who experience devastating vision loss."

Summary of ZETA-1 Phase 2 Topline Data

ZETA-1 was a randomized, double-masked, placebo-controlled Phase 2 trial designed to evaluate the efficacy and safety of APX3330 in diabetic retinopathy patients. ZETA-1 was conducted at 25 U.S. sites and enrolled 103 patients with at least one eye meeting criteria for moderately severe to severe non-proliferative DR (NPDR) or mild proliferative diabetic retinopathy (mild PDR). The ETDRS diabetic retinopathy severity scale (DRSS) is a categorical tool for clinical trials that contains 10 discreet steps, from no retinopathy to severe proliferative retinopathy, derived from the grading of fundus photographs for each eye at a central reading center. Each patient's study eye had a baseline DRSS step of 5, 6 or 7. The patients were randomized to receive 600 mg APX3330 or placebo daily (BID) over 24 weeks. Primary and secondary endpoints evaluated +/- 1, 2, 3, and 4 step improvement and worsening in DRSS at week 12 and week 24, change in best-corrected visual acuity (BCVA), change in central subfield thickness (CST) and safety and tolerability. Patient demographics and baseline characteristics were well-balanced across both treatment groups.

In the ZETA-1 Phase 2 trial, APX3330 did not meet the primary endpoint (% of patients with a ≥ 2-step improvement in DRSS at week 24 in the study eye). Given the oral systemic delivery of APX3330, however, it is important to evaluate the effect on both eyes. A potential Phase 3 registration primary endpoint is a ≥ 3-step worsening of DRSS as a composite of both eyes (binocular). This secondary endpoint was pre-specified and evaluated in the ZETA-1 trial. APX3330 demonstrated statistically significant reduction of disease progression at 24 weeks: No (0%) APX3330-treated patients had a binocular ≥ 3-step worsening of DRSS from baseline compared with 16% for placebo-treated patients (p=0.04). This endpoint is the planned Phase 3 primary endpoint for future registration trials that will be confirmed at the EOP2 meeting with the FDA.

Additional efficacy endpoints were directionally favorable to support the effect of APX3330 in slowing the progression of DR and preserving vision. Visual acuity was stable with APX3330 and a trend was seen with fewer APX3330 treated patients losing 5 or more letters of distance vision compared to placebo patients (6% vs 19%, p=0.07). APX3330 showed a favorable safety and tolerability profile. Treatment-related adverse events were uncommon, and most were mild in severity. There were no treatment-related serious adverse events. No changes were observed in liver, kidney, or heart function as well as complete blood count and comprehensive metabolic panel.

Further analysis of the trial data is ongoing and detailed results will be presented at multiple medical meetings and submitted for peer review publication in 2023, including Angiogenesis, Exudation and Degeneration, February 10-11, 2023, and The Macula Society Annual Meeting, February 15–18, 2023. For more information on the ZETA-1 trial, please visit

www.clinicaltrials.gov (NCT04692688).

About Diabetic Retinopathy and Disease Progression

Diabetes is the leading cause of blindness among adults age 20 to 74. DR is the most common diabetic complication that affects the eyes and is manifested when chronically elevated blood sugar levels cause damage to blood vessels in the retina. DR affects over 8 million patients in the U.S. and 93 million patients worldwide. This problem is expected to worsen as the number of individuals at risk of developing diabetes is projected to increase by 55% by 2035. In countries such as India and China, where the prevalence of diabetes and diabetic eye is high and access to retina specialists is challenging, an oral treatment option would be ideal.

The increasing prevalence of diabetes globally and the concomitant increase in vision loss as a consequence of DR have increased the need for early intervention to protect the retina from the damaging effects of diabetes and reduce the likelihood of vision loss. The ETDRS diabetic retinopathy severity score (DRSS) is an accepted surrogate for assessing the severity of DR because it is well established that progression on this 10-point scale correlates with the loss of vision due to proliferative DR and DME.[1],[2] Although anti-VEGF biologics have been approved for the treatment of DR, they are generally not used for patients with background disease prior to loss of vision due to the need for frequent office visits for intravitreal injection. A safe and convenient oral treatment that slows or prevents worsening of DRSS would be a significant advance in treatment options in the quest to reduce the vision loss associated with diabetic eye disease.

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[1] Ip MS, Zhang J, Ehrlich JS. The Clinical Importance of Changes in Diabetic Retinopathy Severity Score. Ophthalmology. 2017 May;124(5):596-603. doi:10.1016/j.ophtha.2017.01.003. Epub 2017 Mar 8. PMID: 28284785.

[2] Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS report number 12. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology. 1991 May;98(5 Suppl):823-33. PMID: 2062515.

About APX3330

APX3330 is a first-in-class, small molecule, oral inhibitor of the transcription factor regulator Ref-1 (reduction-oxidation effector factor-1). With a novel dual mechanism of action, APX3330 blocks the downstream pathways regulated by Ref-1 – including those involving angiogenesis (VEGF) and inflammation (NFkB) – to decrease abnormal activation of both angiogenesis, and of inflammatory pathways that are implicated across several ocular diseases, including DR, DME, and age-related macular degeneration (AMD). APX3330 has shown a favorable safety and tolerability profile in 12 clinical trials conducted in healthy, hepatitis, cancer, and diabetic subjects.

Conference Call and Webcast Details:
Date: January 25, 2023
Time: 4:30 PM ET
Dial-in information: 1-877-407-4018 (US); 1-201-689-8471 (International)
Passcode: 13736027

Webcast link

A link to the webcast can also be found on the “News and Media” section of Ocuphire’s corporate website at https://www.ocuphire.com/news-media/events.

About Ocuphire Pharma

Ocuphire is a publicly traded (Nasdaq: OCUP), clinical-stage, ophthalmic biopharmaceutical company focused on developing and commercializing small-molecule therapies for the treatment of refractive and retinal eye disorders.

The Company has a previously disclosed partnership to develop and commercialize Nyxol® eye drops as a preservative-free eye drop formulation of phentolamine mesylate, a non-selective alpha-1 and alpha-2 adrenergic antagonist designed to reduce pupil size by uniquely blocking the alpha-1 receptors found only on the iris dilator muscle without affecting the ciliary muscle. Nyxol has been studied in a total of 12 clinical trials (3 Phase 1, 5 Phase 2, 4 Phase 3) across three indications, including single-use for reversal of pharmacologically-induced mydriasis (RM), and once-daily for treatment of presbyopia and dim light or night vision disturbances (NVD), pending regulatory approvals. Nyxol has submitted an NDA for the first indication RM under the 505(b)(2) pathway and is currently in Phase 3 for presbyopia and NVD.

The Company’s late-stage product candidate APX3330 is an oral tablet designed to inhibit angiogenesis and inflammation pathways relevant to retinal and choroidal vascular diseases, such as diabetic retinopathy (DR) and diabetic macular edema (DME). APX3330 has been studied in 12 Phase 1 and 2 trials.

For more information, visit www.ocuphire.com

Forward Looking Statements

Statements contained in this press release regarding matters that are not historical facts are “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995. Such statements include, but are not limited to, statements concerning the success and timing of planned future clinical trials for APX3330, timing and occurrence of an End-of-Phase 2 meeting with the FDA, the potential of a Phase 3 registration path for APX3330, the success and timing of planned regulatory filings, business strategy, cash runway, scalability, the potential for APX3330 to be the first line of therapy for DR patients, and the potential market opportunity for the slowing of DR progression. These forward-looking statements are based upon Ocuphire’s current expectations and involve assumptions that may never materialize or may prove to be incorrect. Actual results and the timing of events could differ materially from those anticipated in such forward-looking statements as a result of various risks and uncertainties, including, without limitation: (i) the success and timing of regulatory submissions and pre-clinical and clinical trials, including enrollment and data readouts; (ii) regulatory requirements or developments; (iii) changes to clinical trial designs and regulatory pathways; (iv) changes in capital resource requirements; (v) risks related to the inability of Ocuphire to obtain sufficient additional capital to continue to advance its product candidates and its preclinical programs; (vi) legislative, regulatory, political and economic developments, (vii) changes in market opportunities, (viii) the effects of COVID-19 on clinical programs and business operations, (ix) risks that the Nyxol

partnership may not facilitate the commercialization or market acceptance of Ocuphire's product candidates; (x) the success and timing of commercialization of any of Ocuphire's product candidates and (xi) the maintenance of Ocuphire's intellectual property rights. The foregoing review of important factors that could cause actual events to differ from expectations should not be construed as exhaustive and should be read in conjunction with statements that are included herein and elsewhere, including the risk factors detailed in documents that have been and may be filed by Ocuphire from time to time with the SEC. All forward-looking statements contained in this press release speak only as of the date on which they were made. Ocuphire undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made.

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