July 22, 2021

Ocuphire Announces Publication in the Journal of Cellular Signaling Featuring its Oral Ref-1 Inhibitor APX3330 in Phase 2 Trial for the Treatment of Retinal Disease

Highlights Favorable Safety Profile of the Oral New Chemical Entity APX3330 and Its Novel Anti-Angiogenic and Anti-Inflammatory Mechanism of Action Properties Relevant to a Broad Range of Retinal Diseases

Phase 2 Data from ZETA-1 Trial in Diabetic Retinopathy Expected in 2022

FARMINGTON HILLS, Mich., July 22, 2021 (GLOBE NEWSWIRE) -- Ocuphire Pharma, Inc. (Nasdaq: OCUP), a clinical-stage ophthalmic biopharmaceutical company focused on developing and commercializing therapies for the treatment of several eye disorders, today announced the publication of a commentary article in the *Journal of Cellular Signaling* featuring its Ref-1 Inhibitor, APX3330, for the treatment of retinal disease. The article is titled "**APE1/Ref-1 as a Novel Target for Retinal Disease**".

The *Journal of Cellular Signaling* is an open-access peer reviewed journal which features articles on latest research findings and perspectives on cellular and molecular signaling – an essential process that orchestrates and integrates various biological functions through multiple signaling cascades and effector molecules. The article can be accessed online at the following link: Welcome to Scientific Archives | APE1/Ref-1 as a Novel Target for Retinal Diseases.

"We have now published over 21 peer-reviewed articles on APX3330 and over 70 articles on the APE1/Ref-1 target in various journals, with 5 publications specifically related to retinal disease," said Mark R. Kelley, PhD, Professor in the Department of Pediatrics and Glick Eye Center at Indiana University School of Medicine and member of Ocuphire's Medical Advisory Board. "This published commentary article discusses the comprehensive data on both Ref-1 as a novel retina target as well as our oral inhibitor, APX3330, predicted to reach human retinal concentrations several-fold greater than the dose required to show efficacy in mice. APX3330 simultaneously blocks key pathways involved in angiogenesis and inflammation processes, thereby conferring protection to the retina. APX3330 represents the Ref-1 program's lead compound, with pipeline candidates APX2009 and APX2014 that could be formulated for intravitreal sustained release delivery."

Highlights from the APE1/Ref-1 Review Article:

- *Ref-1 protein regulates multiple transcription factors regulating inflammation and angiogenesis.*

- *As a Ref-1 inhibitor, APX3330 decreases both abnormal angiogenesis and inflammation by blocking activation of HIF-1a, which then leads to reduced VEGF signaling and lower production of pro-inflammatory cytokines such as NF-kB, TNF-alpha, and STAT3.*
- *At the 300 mg oral twice per day dose being used in the ongoing Phase 2 clinical trial in patients with diabetic retinopathy (DR), APX3330 is expected to reach several-fold higher retinal Cmax, and many-fold concentrations above 15.4 ug/ml retinal AUC, than the efficacious dose of oral gavage 25 mg/kg twice per day given to mice in the L-CNV model of retinal disease.*
- *In five Phase 2 studies involving over 300 patients, APX3330 given oral (systemically) was well tolerated with no significant safety issues identified. No AE was observed in ≥ 5% of patients treated with APX3330. Mild rash and mild diarrhea were observed in 1% of APX3330 treated patients and were thought to be possibly drug-related.*
- *Ocuphire is presently recruiting for ZETA-1 Phase 2 clinical trial, which will enroll subjects across 20 U.S. sites with the primary endpoint of the percentage of subjects with >2-step improvement on the Diabetic Retinopathy Severity Scale score.*

The primary endpoint for the ZETA-1 trial is the Early Treatment Diabetic Retinopathy Score (ETDRS) diabetic retinopathy severity score (DRSS). This score is based on vascular abnormalities in retinal photographs, and a 2-step or more improvement in this score is the accepted regulatory endpoint for the treatment of DR. In the PANORAMA study which examined the effect of the anti-VEGF drug EYLEA® on DRSS, this primary endpoint was met with significantly more patients responding to treatment compared to placebo after 24 weeks of 2mg dosing intravitreal every 16 weeks. In the mouse L-CNV model, the efficacy of oral APX3330 was similar to EYLEA intravitreal injections. Taken together with the other safety, PK, and preclinical data, this provides a strong rationale for pursuing diabetic retinopathy in the ZETA-1 trial. Visual function and central retinal thickness will also be measured given the expected efficacy in treatment of diabetic macular edema (DME).

“With its dual mechanism of action targeting pathogenic inflammation downstream to Ref-1, we believe APX3330 could represent an important new therapeutic approach in addressing a number of ocular conditions, including as a single agent for diabetic retinopathy and as an adjunctive therapy to anti-VEGF in diabetic macular edema, wet age-related macular degeneration, and other retinal diseases,” said Mina Sooch, MBA, President and CEO of Ocuphire Pharma. “We are fortunate to build on the past 11 Phase 1 and 2 clinical trials studying inflammation in liver diseases by Eisai and angiogenesis in oncology by Apexian. As our clinical program surrounding Ref-1 inhibition continues to mature, we expect APX3330 to generate more attention ahead of our Phase 2 data readout in diabetic retinopathy anticipated next year.”

The progressive pathogenesis of retinal and choroidal disease often involves vascular leakage, retinal ischemia, and the release of vasoproliferative growth factors and inflammatory mediators. Earlier treatment options to prevent or delay irreversible vision loss for patients with diabetic eye disease are critical. Although biologic therapies such as Eylea (which are injections directly into the eye) have been approved in the field, the invasive nature of treatment leads to a reluctance by physicians to adopt bi-monthly chronic injection regimens during the early stages of disease progression. Today, diabetic retinopathy remains closely monitored by retinal specialists but largely untreated. An alternative (oral)

treatment modality presents immense potential to be used as monotherapy for non-proliferative or early proliferative stages of diabetic retinopathy.

“As an oral tablet with a favorable safety profile demonstrated in the early clinical trials, APX3330 could offer a convenient solution for a large and growing global population of diabetes-related retinal diseases,” said Dr. Peter Kaiser, Professor of Ophthalmology at the Cole Eye Institute, Cleveland Clinic. “More importantly, APX3330 has the potential to reduce the burden of intravitreal injections on the patients.”

About Diabetic Retinopathy

Diabetes is the leading cause of blindness among adults aged 20 – 74. In the United States alone, over 7 million patients suffer from diabetic retinopathy (DR), a complication of diabetes in which chronically elevated blood sugar levels cause damage to blood vessels in the retina. An additional 750,000 patients suffer from diabetic macular edema (DME), one of the most common complications of diabetic retinopathy where the macula swells from fluid leaked from damaged blood vessels. The disease progression of both DR and DME involves abnormal vessel proliferation and inflammation. Thus, current approved treatments for DR and DME encompass an over $10 billion global market and involve administering anti-VEGF injections (such as EYLEA® by Regeneron, Lucentis® by Genentech, and Avastin® by Genentech) to decrease vessel formation or steroids (such as OZURDEX® by Abbvie/Allergan) to decrease inflammation into eyes with advanced retinal disease. ZETA-1 is investigating the potential of APX3330 to offer an innovative and conveniently administered oral treatment for diabetic retinopathy that addresses both of these disease pathways.

About Ocuphire Pharma

Ocuphire is a publicly traded (NASDAQ: OCUP), clinical-stage ophthalmic biopharmaceutical company focused on developing and commercializing therapies for the treatment of several eye disorders. Ocuphire’s pipeline currently includes two small-molecule product candidates targeting front and back of the eye indications. The company’s lead product candidate, Nyxol® (0.75% phentolamine ophthalmic solution) Eye Drops, is a once-daily preservative-free eye drop formulation of phentolamine mesylate, a non-selective alpha-1 and alpha-2 adrenergic antagonist designed to reduce pupil size, and is being developed for several indications, including dim light or night vision disturbances (NVD), reversal of pharmacologically-induced mydriasis (RM), and presbyopia, and has been studied in 9 clinical trials including the recently completed Phase 3 trial in RM and Phase 2 trial in presbyopia. Ocuphire reported positive topline data in March 2021 for MIRA-2, a Phase 3 FDA registration study for treatment of RM. Ocuphire also reported positive top-line data in June 2021 for VEGA-1, a Phase 2 trial for the treatment of presbyopia. Nyxol is also currently in Phase 3 clinical development for NVD. Ocuphire’s second 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) and has been studied in 11 Phase 1 and 2 trials. APX3330 is currently enrolling subjects in a Phase 2 clinical trial in subjects with DR/DME. As part of its strategy, Ocuphire will continue to explore opportunities to acquire additional ophthalmic assets and to seek strategic partners for late-stage development, regulatory preparation, and commercialization of drugs in key global markets. Please visit www.clinicaltrials.gov to learn

more about Ocuphire's completed Phase 2 trials, recently completed Phase 3 registration trial in RM (NCT04620213), recently completed Phase 2 trial in presbyopia (NCT04675151), ongoing Phase 3 registration trial in NVD (NCT04638660), and Phase 2 trial in DR/DME (NCT04692688). For more information, please 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 expected timing of the Phase 2 ZETA-1 clinical trial in diabetic retinopathy, the potential formulation of APX2009 and APX2014, and the ability of APX3330 to represent an important new therapeutic approach in addressing a number of ocular conditions. 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) the success and timing of commercialization of any of Ocuphire's product candidates and (x) 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.

Ocuphire Contacts

Mina Sooch, President & CEO
Ocuphire Pharma, Inc.
ir@ocuphire.com
www.ocuphire.com

Corey Davis, Ph.D.
LifeSci Advisors
cdavis@lifesciadvisors.com

Ocuphire PHARMA

Source: Ocuphire Pharma