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Ocuphire Announces Publications Featuring the Ref-1 Protein, a Transcription Factor Regulator, as a Novel Therapeutic Target for the Treatment of Neovascular Retinal Diseases

New Review Publications Underscore the Role of the APE1/Ref-1 Protein in Multiple Pro-angiogenic Pathways Associated with Neovascular Eye Disease Including Diabetic Retinal Diseases and Age-Related Macular Degeneration

Ocuphire's Phase 2 ZETA-1Trial Evaluating APX3330 (an Oral Ref-1 Inhibitor) for the Treatment of Diabetic Retinopathy is Currently Recruiting with Data Expected in 2022

FARMINGTON HILLS, Mich., Oct. 07, 2021 (GLOBE NEWSWIRE) -- Ocuphire Pharma, Inc. (Nasdaq: OCUP), a clinical-stage ophthalmic biopharmaceutical company focused on developing and commercializing therapies for refractive and retinal eye disorders, today announced the publication of a review article titled "**Inhibition of APE1/Ref-1 for Neovascular Eye Disease: From Biology to Therapy**" within the Special Issue "Advances in Molecular Activity of Potential Drugs" of the *International Journal of Molecular Sciences*. APE1/Ref-1 was also featured as a potential therapeutic target for the treatment of age-related macular degeneration in a second published review article titled **"Potential Therapeutic Candidates for Age-Related Macular Degeneration (AMD)"** in *Cells* September 2021 issue. Ocuphire is developing a novel oral Ref-1 inhibitor, APX3330, for the treatment of retinal disease. APX3330 is currently being evaluated in an ongoing, randomized, placebo-controlled, double-masked, multi-center Phase 2 trial (ZETA-1) in the U.S. for the treatment of diabetic retinopathy with data expected in 2022.

The *International Journal of Molecular Sciences* is an international, peer-reviewed, open access journal providing an advanced forum for biochemistry, molecular and cell biology, molecular biophysics, molecular medicine, and all aspects of molecular research in chemistry. The article by researchers at the Indiana University School of Medicine can be accessed online at the following link: Inhibition of APE1/Ref-1 for Neovascular Eye Disease: From Biology to Therapy

"There are over 70 published articles on the APE1/Ref-1 target across multiple diseases, along with 10 peer-reviewed articles focused on how novel inhibitors of APE1/Ref-1 such as APX3330 may have the potential to improve disease outcomes for retinal patients," said Mark R. Kelley, PhD, Professor in the Department of Pediatrics and Glick Eye Institute at Indiana University School of Medicine and member of Ocuphire's Medical Advisory Board. "The article also describes how patients taking the currently approved pharmacological

treatments for retinal and choroidal neovascularization, including intravitreally administered biologic therapies targeting the vascular endothelial growth factor (VEGF) signaling pathway, may experience worsened eye disease, indicating that multiple pathways are involved in ocular angiogenesis. Therefore, the development of novel therapeutics, such as oral therapies, that inhibit APE1/Ref-1 protein, deactivating pro-angiogenic and pro-inflammatory pathways, could represent a promising approach towards treating neovascular eye disease, especially in diabetic retinopathy."

Highlights from the Review Article in *International Journal of Molecular Sciences*:

- Details the role of how APE1/Ref-1 protein and its transcription factors impact multiple pro-angiogenic pathways, including angiogenesis, inflammation, oxidative stress, and cell-cycle control in neovascular eye disease
- Explains the significance of APE1/Ref-1 activation across several ocular diseases, including age-related macular degeneration (AMD), diabetic retinopathy (RD), diabetic macular edema (DME), and retinopathy of prematurity (ROP)
- Provides rationale for developing novel therapeutic agents that target transcription factors of APE1/Ref-1 as a therapeutic approach in neovascular eye disease, highlighting Ocuphire's drug candidate, APX3330, as the first such inhibitor advanced to clinical trials
- Describes the critical binding specificity of APX3330 to block the downstream transcription factors of APE1/Ref-1, including NF-kB, HIF1 (which regulates VEGF) and STAT3
- Describes shortcomings associated with current injectable therapeutics for the treatment of neovascular eye disease, including the anti-VEGF biologics

In addition to the IJMS article described above, a review article titled "**Potential Therapeutic Candidates for Age-Related Macular Degeneration**" by Dr. Sonali Nashine at the Gavin Herbert Eye Institute at UC Irvine, was recently published in the journal *Cells*, noting the potential of APX3330 (referred to as "E3330") for the treatment of age-related macular degeneration (AMD). Because APE1/Ref-1 has been shown to contribute to retinal angiogenesis, the authors conclude that APE1/Ref-1 inhibitors such as APX3330 could inhibit the abnormal blood vessel formation seen in AMD by reducing retinal endothelial cell proliferation, migration, and tube formation. The article can be accessed online at the following link: Potential Therapeutic Candidates for Age-Related Macular Degeneration (AMD)

Cells is an international, peer-reviewed, open access, journal of cell biology, molecular biology, and biophysics, published monthly online by MDPI. The Spanish Society for Biochemistry and Molecular Biology (SEBBM), Signal Transduction Society (STS), Nordic Autophagy Society (NAS) and others are affiliated with *Cells.*

Mina Sooch, MBA, President and CEO of Ocuphire Pharma commented, "It is encouraging to see the growing body of scientific literature highlighting that multiple pro-angiogenic pathways are implicated across vascular eye disease, including diabetic retinopathy and diabetic macular edema. Earlier treatment options to prevent or delay irreversible vision loss for patients with diabetic eye diseases are critical. Specifically, diabetic retinopathy remains closely monitored by retinal specialists but largely untreated. By targeting pathogenic

inflammation downstream to Ref-1, we believe that APX3330 could represent an important new therapeutic approach addressing vascular retinal disease as a single agent for diabetic retinopathy and as an adjunctive therapy to anti-VEGF injection in diabetic macular edema and wet age-related macular degeneration. We look forward to the results of our well-controlled Phase 2 clinical trial in diabetic retinopathy anticipated in 2022."

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 Allergan) to decrease inflammation in 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 refractive and retinal 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® eye drops (0.75% phentolamine ophthalmic solution), 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 top-line 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. 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.

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