

## **Sirolimus and mTOR Inhibition for the Treatment of Wet AMD**

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Sirolimus, formerly known as rapamycin, and related derivatives have become the topic of intense research in the oncology community due to its ability to inhibit the mammalian target of rapamycin (mTOR). Through inhibition of mTOR, sirolimus demonstrates a broad spectrum of action of interest in retinal diseases, including inhibition of inflammation, proliferation, angiogenesis, vascular permeability, and fibrosis. Utilizing the favorable physiochemical properties of sirolimus, an ocular safe formulation has been developed (Perceiva™, MacuSight, Inc., Union City, CA, USA) which when administered by minimally invasive subconjunctival injection provides transscleral delivery to the retina/choroid tissues and sustained drug levels for 60 to 90 days. Two multi-center, open-label Phase 1 dose escalation studies have been conducted; one among 50 patients with chronic, recurrent diabetic macular edema (DME) and the second among 30 patients with newly diagnosed neovascular age-related macular degeneration (nvAMD). The safety profile was excellent, with no dose limiting toxicities, ocular inflammation, or increase in intraocular pressure observed. Additionally, clear, temporally-related improvements in visual acuity and retinal thickness reduction were observed in both studies. As a result, development of this product has progressed and is currently being evaluated in multiple Phase 2 clinical trials including: a dose-ranging, placebo controlled trial of 131 patients for DME; a small, monotherapy trial among 20 nvAMD patients, and a dose-ranging placebo-controlled combination trial among 62 nvAMD patients evaluating the use of sirolimus in combination with ranibizumab. All three trials have been fully-enrolled and trial designs and baseline demographic data will be presented.