

# APX3330 for the Treatment of Diabetic Retinopathy

Timothy W Corson

Department of Pharmacology and Toxicology; Department of Ophthalmology, Indiana University School of Medicine, Indianapolis, IN, USA



## Timothy W Corson

Timothy W Corson is professor and chair of the Department of Pharmacology and Toxicology and a member of the Eugene and Marilyn Glick Eye Institute, Department of Ophthalmology, Indiana University School of Medicine. He holds BSc, MSc and PhD degrees from the University of Toronto, and completed a postdoctoral fellowship in chemical biology at Yale University before establishing his group at Indiana University. His laboratory focuses on chemical biology approaches to identify targets for drug development in neovascular eye diseases and ocular tumors, with a special interest in the biology and preclinical assessment of Ref-1 inhibitors for ocular disease. He has published over 80 papers and filed 11 patents, and he has been invited to speak at institutions and conferences globally. His laboratory is currently supported by grants from the National Institutes of Health, the Reeves Foundation, the Retina Research Foundation and industry.

## Keywords

Angiogenesis, APX3330, clinical trial, diabetic macular oedema, diabetic retinopathy, inflammation, Ref-1

**Disclosures:** Timothy W Corson has received National Institutes of Health funding to research Ref-1 in eye disease and is an inventor on a related patent licensed to Ocuphire.

**Compliance with ethics:** This article is an interview and did not involve any studies with human or animal subjects performed by the author.

**Data availability:** Data sharing is not applicable to this article as no datasets were generated or analysed during the writing of this article.

**Authorship:** The named author meets the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, takes responsibility for the integrity of the work as a whole, and has given final approval for the version to be published.

**Access:** This article is freely accessible at touchOPHTHALMOLOGY.com. ©Touch Medical Media 2023.

**Received:** 14 March 2023

**Published online:** 24 April 2023

**Citation:** touchREVIEWS in Ophthalmology. 2023;17(1):Online ahead of journal publication

**Corresponding author:** Timothy W Corson, Department of Pharmacology and Toxicology, Department of Ophthalmology, Indiana University School of Medicine, Indianapolis, IN 46202, USA. E: tcorson@iu.edu

**Support:** No funding was received in the publication of this article.

Identifying treatments that prevent diabetic retinopathy progression is a priority in current research. Patients with non-proliferative retinopathy currently have limited treatment options to prevent the progression of retinopathy and loss of vision, and therapies such as anti-vascular endothelial growth factor (VEGF) therapy, steroid injectable therapy and laser treatment are reserved for patients who advance to proliferative diabetic retinopathy or diabetic macular oedema (DMO). The ZETA-1 phase IIb trial (ClinicalTrials.gov identifier: NCT04692688) was designed to evaluate the efficacy and safety of APX3330 in patients with diabetic retinopathy.<sup>1</sup> Although the trial did not meet its primary endpoint, APX3330 demonstrated a favourable safety and tolerability profile, and achieved statistical significance in a key prespecified secondary endpoint of preventing clinically meaningful progression of diabetic retinopathy.<sup>2</sup>

In this expert interview, Timothy W Corson describes the mechanism of action of APX3330, the ZETA-1 study and its findings, and highlights future directions in the development of APX3330.

## Q. What are the limitations of current therapeutic options for diabetic retinopathy?

There are currently no approved, specific therapies for mild-to-moderate diabetic retinopathy; management of systemic disease (glycaemic control) is the best option. For the advanced, proliferative form of diabetic retinopathy and for DMO, anti-VEGF biologicals have proven highly effective.<sup>3</sup> However, all the existing agents are biologicals that must be injected intravitreally and as frequently as monthly in some cases. This presents a considerable burden to patients in terms of cost and time for clinic visits, as well as the discomfort of this procedure and risk of rare but serious complications such as endophthalmitis. Our work and that from other groups has unsurprisingly revealed that, for these reasons, the vast majority of patients would prefer a topical or systemic therapy alternative to these intravitreal injections, if one were available.<sup>4,5</sup>

## Q. What is APX3330 and what is its mechanism of action?

APX3330 is a small molecule inhibitor of a protein known as redox factor 1/apurinic-apyrimidinic endonuclease 1 (Ref-1/APE1). This protein has two names because it has two functions.<sup>6</sup> One function is involved in DNA damage repair as an apurinic-apyrimidinic endonuclease. The other function, Ref-1, is crucial for reduction–oxidation (redox) regulation of various transcription factors. APX3330 specifically blocks this redox function. Ref-1 activity normally leads to activation of many transcription factors, including nuclear factor kappa B (NF- $\kappa$ B), hypoxia-inducible factor 1 alpha (HIF-1 $\alpha$ ) and others that are important for promoting inflammation and cell growth. By acting on the Ref-1 signalling nexus, APX3330 can therefore induce anti-inflammatory, anti-angiogenic and anti-proliferative effects mediated through multiple pathways, including VEGF signalling. Given this, APX3330 has shown preclinical efficacy in a number of inflammatory, neovascular and oncological disease models. In humans, it has shown good safety profiles across several studies, as well as promising efficacy in a phase I oncology trial.<sup>7,8</sup>

### Q. Could you provide a brief overview of the ZETA-1 phase II trial, including its rationale, design and eligibility criteria?

ZETA-1 was designed to assess the efficacy of APX3330 in diabetic retinopathy and DMO.<sup>1</sup> Ocuphire Pharma, Inc. (Farmington Hills, MI, USA) launched the ZETA-1 trial based on the strong preclinical data from our group and others, which implicated Ref-1 in regulating neovascularization in the eye across multiple models, as well as the excellent safety profile of oral APX3330 in humans and the unmet need in diabetic retinopathy treatment.<sup>9,10</sup> ZETA-1 was a placebo-controlled, double-masked, randomized phase IIb trial comparing 600 mg APX3330 daily (split across two doses) with placebo over 24 weeks. A total of 103 patients were enrolled at 25 US sites. Major inclusion criteria were males or females  $\geq 18$  years of age with a diagnosis of moderately severe to severe non-proliferative diabetic retinopathy or mild proliferative diabetic retinopathy, with or without non-central DMO in the study eye. Central DMO was allowed in the fellow eye. Best corrected visual acuity had to be 20/63 or better in the study eye with a Diabetic Retinopathy Severity Scale (DRSS) score of 47, 53 or 61. Patients had to be free of: photocoagulation in the past year (with no pan-retinal photocoagulation ever), anti-VEGF injections or intraocular steroids within 6 months, fluocinolone implant in the past 3 years, and significant other ocular or systemic disease or glycated haemoglobin of  $\geq 12\%$ .

### Q. What were the primary and secondary endpoints and how well were they achieved?

The primary endpoint was the percentage of patients with an improvement of  $\geq 2$  steps in the DRSS score in the study eye at week 24. This endpoint was not met, with 8% of both drug and placebo groups showing an improvement of  $\geq 2$  steps. However, a prespecified secondary endpoint of DRSS worsening across both eyes was met, with 16% of patients on placebo showing a worsening of  $\geq 3$  DRSS steps compared with none of the patients on APX3330 worsening by this much at 24 weeks ( $p=0.04$ ). Such binocular assessment is feasible for a systemic agent such as

APX3330 in a way that is not relevant for precedent intravitreal injections of anti-VEGF agents. In another secondary endpoint, there was a trend ( $p=0.07$ ) towards fewer patients in the APX3330 group losing  $\geq 5$  letters of vision (6% versus 19% in the placebo group). In addition, the safety profile of APX3330 was excellent and consistent with previous trials for other indications. Treatment-related adverse events were seen in 14 patients on APX3330 and 17 on placebo, with none involving liver, heart, kidney, brain, lung or vital signs. Finally, 88% of patients completed the trial, with only four of the withdrawals being due to adverse events (two APX3330, two placebo).

### Q. Are there any plans for further studies of APX3330 in diabetic retinopathy or other indications?

Based on the ZETA-1 findings, Ocuphire reports that they intend to meet with the United States Food and Drug Administration to discuss moving the programme forward for diabetic retinopathy. A longer, larger phase III trial may bring the potential effects of APX3330 into sharper focus. In addition, preclinical data suggest that APX3330 may have utility in other neovascular eye diseases, such as neovascular age-related macular degeneration, as well as other non-ocular indications. The excellent safety findings underscore the potential of this drug for exploration in other conditions.

### Q. Where do you see APX3330 sitting in the treatment paradigm for diabetic retinopathy?

If eventually approved, APX3330 would be a very appealing, first-line oral agent for the non-invasive prevention of progression and vision loss due to non-proliferative diabetic retinopathy, given the dearth of such agents currently. In DMO and proliferative diabetic retinopathy, APX3330 could be a powerful adjunct to reduce the frequency of intravitreal anti-VEGF therapies, or even potentially replace them in some patients. The ease of delivery of an oral agent would also increase access to vision-saving therapy in low-resource settings. □

- ClinicalTrials.gov. Study of the Safety and Efficacy of APX3330 in Diabetic Retinopathy (ZETA-1). ClinicalTrials.gov Identifier: NCT04692688. Available at: <https://clinicaltrials.gov/ct2/show/NCT04692688> (accessed date: 8 March 2023)
- Hutton D. Ocuphire Pharma's ZETA-1 phase 2 trial of diabetic retinopathy candidate offers mixed results. 2023. Available at: [www.opthalmologytimes.com/view/ocuphire-pharma-s-zeta-1-phase-2-trial-of-diabetic-retinopathy-candidate-offers-mixed-results](http://www.opthalmologytimes.com/view/ocuphire-pharma-s-zeta-1-phase-2-trial-of-diabetic-retinopathy-candidate-offers-mixed-results) (accessed date: 8 March 2023)
- Uludag G, Hassan M, Matsumiya W, et al. Efficacy and safety of intravitreal anti-VEGF therapy in diabetic retinopathy: What we have learned and what should we learn further? *Expert Opin Biol Ther.* 2022;22:1275–91. DOI: 10.1080/14712598.2022.2100694
- Jacobs B, Palmer N, Shetty T, et al. Patient preferences in retinal drug delivery. *Sci Rep.* 2021;11:18996. DOI: 10.1038/s41598-021-98568-7
- Polat O, Inan S, Özcan S, et al. Factors affecting compliance to intravitreal anti-vascular endothelial growth factor therapy in patients with age-related macular degeneration. *Turk J Ophthalmol.* 2017;47:205–10. DOI: 10.4274/tjo.28003
- Hartman GD, Lambert-Cheatham NA, Kelley MR, Corson TW. Inhibition of APE1/Ref-1 for neovascular eye diseases: From biology to therapy. *Int J Mol Sci.* 2021;22:10279. DOI: 10.3390/ijms221910279
- Shah F, Logsdon D, Messmann RA, et al. Exploiting the Ref-1-APE1 node in cancer signaling and other diseases: From bench to clinic. *NPJ Precis Oncol.* 2017;1:19. DOI: 10.1038/s41698-017-0023-0
- Shahda S, Lakhani NJ, O'Neil B, et al. A phase I study of the APE1 protein inhibitor APX3330 in patients with advanced solid tumors. *JCO.* 2019;37:3097–3097. DOI: 10.1200/JCO.2019.37.15\_suppl.3097
- Sardar Pasha SPB, Sishtia K, Sulaiman RS, et al. Ref-1/APE1 inhibition with novel small molecules blocks ocular neovascularization. *J Pharmacol Exp Ther.* 2018;367:108–18. DOI: 10.1124/jpet.118.248088
- Jiang A, Gao H, Kelley MR, Qiao X. Inhibition of APE1/Ref-1 redox activity with APX3330 blocks retinal angiogenesis in vitro and in vivo. *Vision Res.* 2011;51:93–100. DOI: 10.1016/j.visres.2010.10.008