Long-term safety of repeated intravitreal axitinib implant administrations in non-human primates

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PURPOSE

The safety of repeat dosing is crucial for chronic retinal vascular conditions as they often necessitate prolonged treatment regimens.[1,2] The intravitreal (IVT) axitinib hydrogel implant (OTX-TKI) is an investigational therapy being evaluated in neovascular age-related macular degeneration (nAMD) and diabetic retinopathy. OTX-TKI is designed to continuously control disease activity by sustained release of a potent tyrosine kinase inhibitor for 9-12 months. Reported here is OTX-TKI, which has the same hydrogel and active ingredient as the subsequent optimized OTX-TKI.

This study aimed to investigate the preclinical safety of OTX-TKI when administered repeatedly every 6 months in non-human primates (NHPs)

METHODS

Twelve cynomolgus monkeys were administered into the right eye two 700-µg OTX-TKI initially, followed by one 700-µg OTX-TKI at 6 and 12 months. Hydrogel vehicle was injected in the other eyes.

The 18-month study evaluating safety and toxicity included assessments of mortality, clinical signs, body weights, ophthalmic evaluations, intraocular pressure (IOP) measurements, ocular scoring (inflammation [IOI] scoring), optical coherence tomography (OCT), confocal scanning laser ophthalmoscopy (cSLO), electroretinography (ERG), bioanalysis, and clinical pathology.

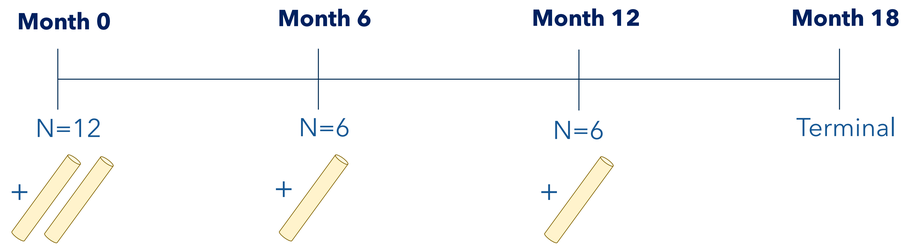

Figure 1. Eighteen-month repeat dose safety and efficacy study design in NHPs (N=12 eyes). OTX-TKI implants were administered at month 0 (2 implants), month 6 (1 implant), and month 12 (1 implant).

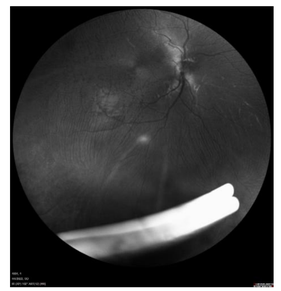

Figure 2. cSLO image showing the state of two IVT implants at month 5 in NHP.

Figure 3. IVT injection of OTX-TKI. Image shown is for illustrative purposes only.

RESULTS

Repeat dosing with OTX-TKI was generally well tolerated through 18 months

Safety of OTX-TKI was found to be similar to that of the hydrogel vehicle

- Ophthalmic assessments showed no clinically significant changes in IOP, cSLO, OCT, or ERG following repeat dosing every 6 months. Ocular exams up to month 18 were unremarkable and showed no inflammation
- No systemic effects related to OTX-TKI or its repeated dosing were observed
- Plasma samples revealed minimal to no systemic axitinib exposure over the study duration
- Implant bioresorption at ~5-6 months in NHPs is equivalent to ~8-9 months in humans

CONCLUSIONS

These findings reinforce the sustained release of axitinib from an IVT hydrogel implant, OTX-TKI, as a potential therapeutic option for the treatment of retinal vascular diseases

- Repeated IVT dosing of OTX-TKI in NHPs was generally well tolerated over an 18-month period with no inflammation and no IOP elevations, supporting the favorable safety profile of repeat doses of OTX-TKI every 6 months in NHPs (~8-9 months in humans)
- This study established the no-observed-adverse-effect-level (NOAEL) for OTX-TKI at a higher dose (two 700-µg implants [1400-µg])
- An optimized OTX-TKI is also being investigated using the same hydrogel with a more soluble form of axitinib

Support: Ocular Therapeutix. **Acknowledgments:** Writing and editorial assistance provided by i2Vision, funded by Ocular Therapeutix. **Study Disclosures:** The following presentation discusses an investigational drug, OTX-TKI, in development. OTX-TKI's efficacy and safety profiles have not been established, and it has not been approved for marketing by the FDA. This study was conducted in accordance with the U.S. Department of Health and Human Services, Food and Drug Administration, United States Code of Federal Regulations, Title 21, Part 58: Good Laboratory Practice for Nonclinical Laboratory Studies, and as accepted by Regulatory Authorities throughout the European Union (OECD Principles of Good Laboratory Practice), Japan (MHLW), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement. **Author Disclosures**: **Chintan Patel**: Code E (Employment): Ocular Therapeutix | **Madhoosudan Patil**: Code E (Employment): Ocular Therapeutix | **Erica Kahn**: Code E (Employment): OcularTherapeutix | **Joe Iacona**: Code E (Employment): Ocular Therapeutix | **Daniel Domingues**: Code E (Employment): Ocular Therapeutix | **Alyssa Whalen**: Code E (Employment): Ocular Therapeutix | **Charles Blizzard**: Code E (Employment): Ocular Therapeutix | **Olivia Sherman**: Code E (Employment): Ocular Therapeutix | **Mark Ransbottom**: Code E (Employment): Ocular Therapeutix | **Dinesh Haswani**: Code E (Employment): Ocular Therapeutix | **Rabia Gurses Ozden**: Code E (Employment): Ocular Therapeutix; Code C (Consultant/Contractor): Adverum | **Peter Jarrett**: Code E (Employment): Ocular Therapeutix. **References: 1.** Holz FG, et al. *Eye (Lond).* 2016;30:1063-1071. **2.** Holz FG, et al. *Br J Ophthalmol.* 2016;100:1623-1628.