A Pharmacokinetic and Tolerability Study of a Novel Hydrogel-based Axitinib Intravitreal Implant (OTX-TKI) in Non-Human Primates

Erica Kahn; Chintan Patel, PhD; Megan Priem; Joseph Iacona; Andrew Vanslette; Erik Wong; Charles D. Blizzard; Peter K. Jarrett, PhD; Rabia Gurses-Ozden, MD; Michael H. Goldstein, MD

BACKGROUND

- Current anti-VEGF therapy for neovascular retinal diseases is rapidly cleared from the vitreous necessitating injections up to every 1-2 months[1,2]
- Neovascular retinal diseases including wet AMD may be responsive to tyrosine kinase inhibitors (TKIs) which have a broader anti-angiogenic profile than current standard-of-care anti-VEGF agents[3,4] (**Figure 1**)
- OTX-TKI is a novel, hydrogel-based, biodegradable, sustained-release implant (**Figure 2**):
  - Designed to deliver the potent tyrosine kinase inhibitor, axitinib, for up to 6-9 months
  - Biodegrades completely and is cleared from the vitreous
  - Small implant with minimal to no visual impact but still allows for physician monitoring
- Previous studies have evaluated the tolerability and pharmacokinetics (PK) of OTX-TKI in rabbit models.[5-7] In this study, we report the tolerability and PK of OTX-TKI in non-human primates.

Figure 1. Tyrosine Kinase Inhibitors Mechanism of Action

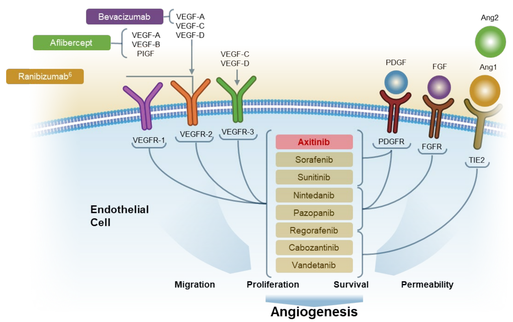
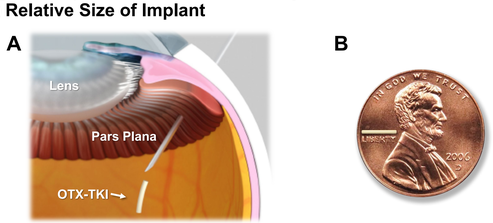


Figure 2. A) Schematic of OTX-TKI Injected into the Vitreous and B) Relative Size of Implant



STUDY OBJECTIVE

To characterize the ocular distribution and tolerability of axitinib from OTX-TKI implant following a single intravitreal injection in non-human primates

METHODS

Study Design

- OTX-TKI implant(s) with different doses of axitinib were injected intravitreally into both eyes of cynomolgus monkeys on Day 0 (**Table 1**)

Table 1. Treatment Groups

Group	Treatment (OU)	Number of Animals
1	3 x 200 µg OTX-TKI implant	N=8
2	300 µg OTX-TKI implant	N=8
3	600 µg OTX-TKI implant	N=8

- Experimental doses were selected to study the effects of dose and number of implants on axitinib distribution
  - Group 2 dose represents 1X human equivalent dose when normalized to vitreous volume in monkeys
  - Total dose of Groups 1 and 3 represent 2X human equivalent dose

Pharmacokinetics Assessments

- Subsets of eyes were enucleated at 3, 6, 9 and 12 months to collect retina, choroid/retinal pigment epithelium (RPE), vitreous humor and aqueous humor samples and analyzed for axitinib content
- Plasma samples were collected to measure systemic exposure to axitinib
- Implant was monitored via confocal scanning laser ophthalmoscopy (cSLO)

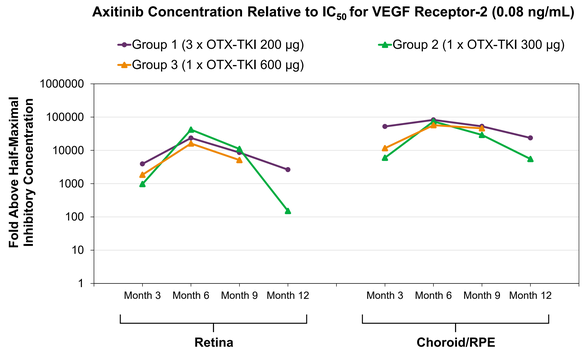
Tolerability Assessments

- Ophthalmic exams were performed via indirect ophthalmoscopy and slit-lamp biomicroscopy
- Intraocular pressure (IOP) was measured by rebound tonometry

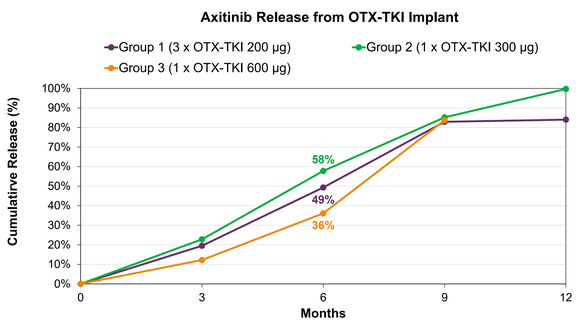
RESULTS

Ocular Pharmacokinetics

- Median axitinib concentrations in the retina and choroid/RPE were substantially greater than the inhibitory concentration (IC_{50}) of VEGF receptor-2 (0.08 ng/mL) from after Month 3
- In all groups, median axitinib levels were greatest at Month 6 (>16,000 x IC_{50}) and then decreased afterwards
  - Choroid/RPE axitinib levels were higher than those detected in the retina as seen with previous studies[8] and likely due to melanin binding
  - Drug distribution in retina and choroid/RPE was higher in Group 1 at Month 3, but comparable between all groups at Month 6 and 9



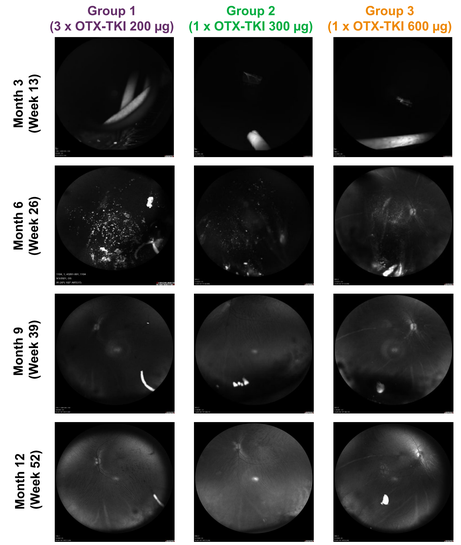
- By Month 6, Groups 1 and 2 implants released ~50% and Group 3 implants released 35% of the dose in the vitreous



- At Month 9, daily release rates were similar for Groups 1 and 3 (1.8 µg/day)
- Plasma samples showed axitinib levels were below the lower limit of quantification (LLOQ=0.1 ng/mL) up to Month 3, then slightly above LLOQ (0.1 – 0.2 ng/mL) in Month 6 samples and returned to below LLOQ at Month 9 indicating minimal systemic exposure to axitinib

Implant Degradation

- Hydrogel degradation was observed at approximately 5 to 6 months with released axitinib particles visible in the vitreous at Month 9 and localized at Month 12
- Appreciable clearance of axitinib between Month 6 and 12 was observed in all groups



Ocular Examination Findings and Intraocular Pressure

- No abnormal ophthalmoscopy findings, significant inflammatory response to OTX-TKI or clinically significant elevation in mean IOP was observed
- Transient and mild posterior inflammation was observed in Group 2 eyes at Week 6 and considered to be procedure-related

CONCLUSIONS

- **Axitinib levels capable of inhibiting VEGF receptors in target retina tissue were achieved with all OTX-TKI groups through 9 months in non-human primates**
- **Implants degraded at 5-6 months, and axitinib particles quickly cleared the vitreous from 6-12 months and steadily cleared the retina/choroid/RPE from 6-12 months**
- **No significant inflammation related to OTX-TKI was observed**
- **OTX-TKI is currently being investigated in humans for the treatment of wet AMD in a U.S.-based Phase 1b clinical trial.**

Disclosures: All authors are employees of Ocular Therapeutix, Inc. | This poster presentation discusses an investigational product, OTX-TKI. Its efficacy and safety profile have not been established and it has not been approved by the FDA. **|** This study was funded by Ocular Therapeutix, Inc.

Abbreviations: AMD, age-related macular degeneration; VEGF, vascular endothelial growth factor

References: 1. EYLEA (aflibercept) [prescribing information]. Tarrytown, NY: Regeneron Pharmaceutical, Inc.; 2021. **2.** LUCENTIS (ranibizumab) [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2018. **3.** Zhao Y, et al. *Oncologist*. 2015;20(6):660-673. **4.** Gross-Goupil M, et al. *Clin Med Insights Oncol*. 2013;7:269-277. **5.** Jarrett PK, et al. *Invest Ophthalmol Vis Sci*. 2017;58(8):1956. **6.** Jarrett T, et al. *Invest Ophthalmol Vis Sci*. 2017;58(8):1984. **7.** Jarrett PK, et al. *Invest Ophthalmol Vis Sci*. 2019;60(9):372. **8.** Huang WC, et al. *Trans Vis Sci Tech*. 2021;10(14):23.

Presented at the Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting in Denver, CO on May 2, 2022