Optimized pharmacokinetic profile of intravitreal axitinib implant (AXPAXLI™): a comparison of first- and second-generation implants

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Poster #B0300

PURPOSE

The intravitreal (IVT) axitinib implant (OTX-TKI) is designed to deliver axitinib for 9-12 months using a bioresorbable hydrogel platform. Neovascular age-related macular degeneration (nAMD) clinical studies using the 600-µg OTX-TKI* showed evidence of biological activity with no drug-related ocular or systemic serious adverse events.[1,2]

An optimized OTX-TKI† was developed to improve synchronization of total drug release with the durability of the hydrogel while increasing daily dose delivery.

Two preclinical studies were designed to assess the intraocular pharmacokinetics of the optimized OTX-TKI

METHODS

In the **first study, Cynomolgus monkeys** received one 300-µg optimized OTX-TKI (n=6) via IVT injection. Bioanalysis was performed at 3, 6, and 9 months. The results were compared with a prior study in which monkeys received either three 200-µg or one 600-µg OTX-TKI (n=4 per timepoint).[3]

In the **second study, Dutch-Belted rabbits** received one 300-µg (n=10) or 600 µg (n=10) optimized OTX-TKI. Animals from each group were sacrificed at 6 (n=3), 13 (n=3), and 24 weeks (n=4) for analysis. The results were compared with a prior study using OTX-TKI.

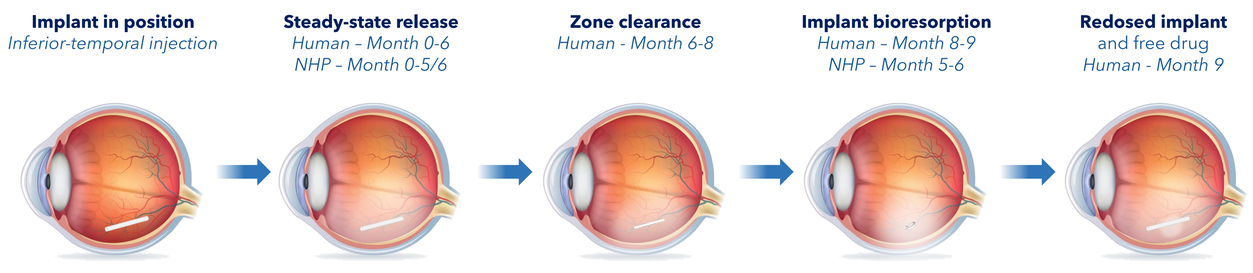

Image shown is for illustrative purposes only. Drawings show the implant behavior over time. As drug is depleted, a peripheral clear zone develops and grows inward. Hydrogel remains intact until final resorption event, which occurs over a span of about 3-4 weeks. In humans, the resorption occurs 8-9 months after implantation.

RESULTS

CYNOMOLGUS MONKEY

- Optimized OTX-TKI rapidly achieved higher initial axitinib concentrations in monkey target tissues and maintained steady-state concentrations after hydrogel bioresorption (6 months) better than OTX-TKI
- Consistency was achieved in axitinib concentrations at month 6 across retina and choroid (Chr)/retinal pigment epithelium (RPE) tissues

DUTCH-BELTED RABBIT

- Findings in rabbits were similar, with both optimized OTX-TKI groups achieving consistent axitinib levels in the retina and Chr/RPE through 6 months
- Chr/RPE axitinib concentration trends were generally similar between optimized OTX-TKI–treated rabbit and monkey groups

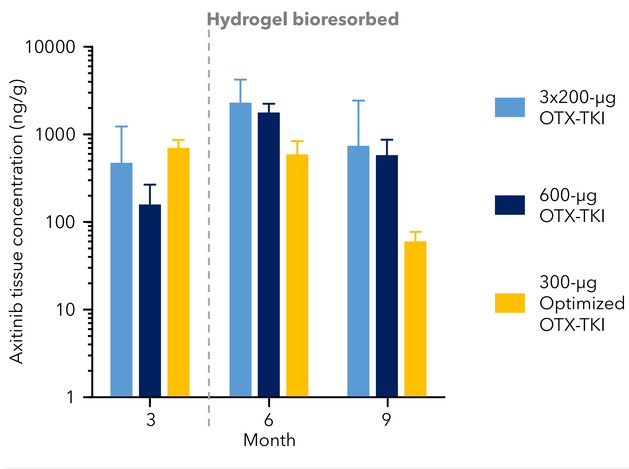

Figure 1. Retina tissue concentrations of axitinib in non-human primates (NHPs). Optimized OTX-TKI is bioresorbed ~5-6 months (in NHPs). Geometric mean ± geometric SD.

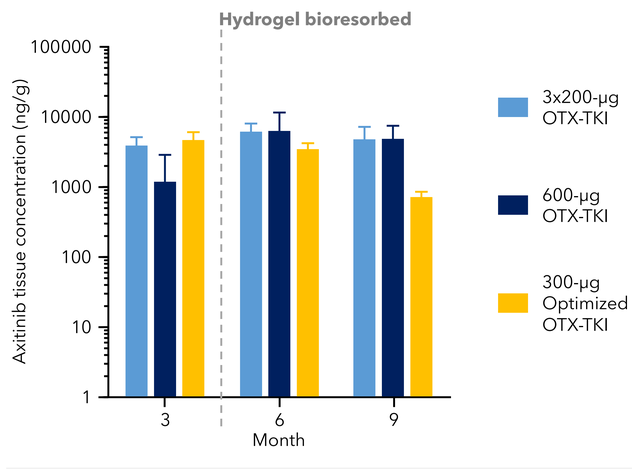

Figure 2. Chr/RPE tissue concentrations of axitinib in NHPs. Optimized OTX-TKI is bioresorbed ~5-6 months (in NHPs). Geometric mean ± geometric SD.

CONCLUSIONS

Results highlight the promising pharmacokinetic profile of optimized OTX-TKI in treating retinal vascular diseases

OPTIMIZED OTX-TKI

- Rapidly achieved higher initial axitinib concentrations in the target tissues, suggesting a potential earlier onset of action
- Maintained steady-state concentrations better than OTX-TKI due to drug left behind following hydrogel bioresorption at 6 months
- These findings, along with the rapid decrease in axitinib levels following hydrogel bioresorption (~8-9 months in humans), indicate improved synchronization of drug release with hydrogel durability, in addition to maintaining the daily dose delivered that may support evidence of biological activity in nAMD

*"OTX-TKI" refers to first-generation implant

†"Optimized OTX-TKI" refers to second-generation implant

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. The 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.

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References: 1. Moshfeghi AA, et al. *Invest Ophthalmol Vis Sci.* 2023;64(8):936.
2. Wong JG, et al. *Invest Ophthalmol Vis Sci.* 2021;62(8):218.
3. Kahn E, et al. *Invest Ophthalmol Vis Sci.* 2022;63(7):297 – F0100.