Evaluating Safety, Tolerability and Biological Activity of OTX-TKI, a Hydrogel-Based, Sustained-Release Intravitreal Axitinib Implant, in Subjects with Neovascular Age-Related Macular Degeneration

Interim Analysis of a Phase 1 Clinical Trial

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American Academy of Ophthalmology Annual Meeting | November 13-15, 2020 | Virtual

FINANCIAL DISCLOSURES: Clinical trial Sponsor: Ocular Therapeutix, Inc.
Boyer DS (presenting author) is a member of the Data and Safety Monitoring Committee for the on-going OTX-TKI clinical trial
J Wong, A Chang, R Guymer, S Wickremasinghe are investigators in the on-going clinical trial sponsored by Ocular Therapeutix, Inc.
MH Goldstein, A Gibson, JL Metzinger, S Vantipalli, N Bell are employees of Ocular Therapeutix, Inc. & AA Moshfeghi is a consultant for Ocular Therapeutix, Inc.

UNMET NEED IN RETINAL DISEASE

Problem with Immediate-Release Injections

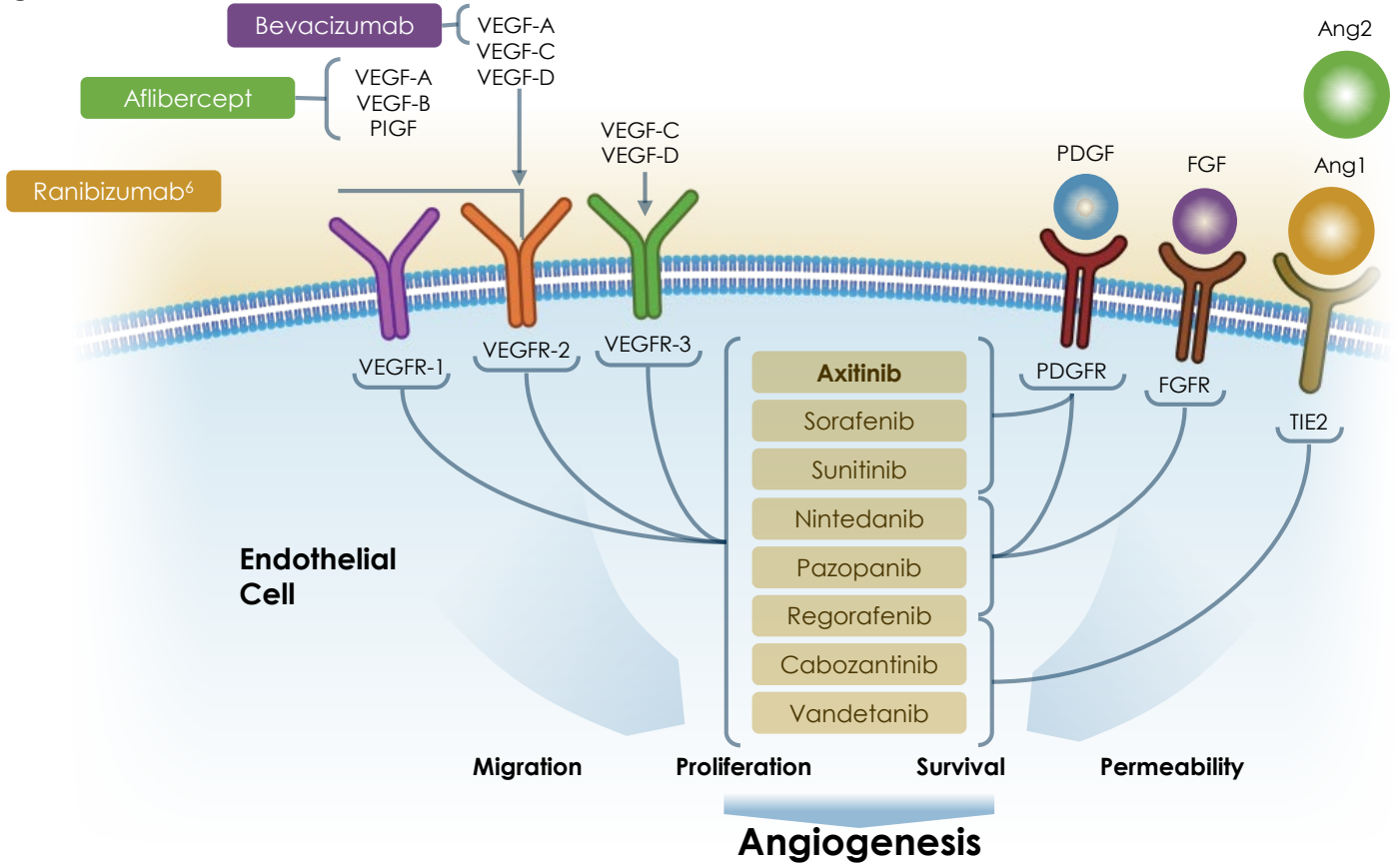
- Repeated intravitreal anti-VEGF injections are necessary to reach and maintain effective concentrations due to rapid vitreous clearance[1-3]
- Multiple visits and injections challenging for patients/families, 98% of retina specialists prefer treat and extend (TAE) paradigm[3]

Tyrosine Kinase Inhibitors Act Directly on VEGF Receptors[5]

- Axitinib targets VEGFR-1, 2, 3 and PDGFR signaling
- Axitinib acts intracellularly and interferes with cellular signaling through inhibition of the receptor tyrosine kinases, potentially varying the "time to biological onset of action" based on intracellular vs extracellular MOA of anti-VEGF
- Axitinib is more potent compared to other TKIs (e.g., sunitinib, sorafenib and pazopanib)[6] and has greater biocompatibility with ocular cell lines[7]

A New Therapy is Needed

- **New Mechanism of Action**
  TKIs act directly on VEGF receptors
- **Longer Duration of Action**
  TKIs are potent small molecules

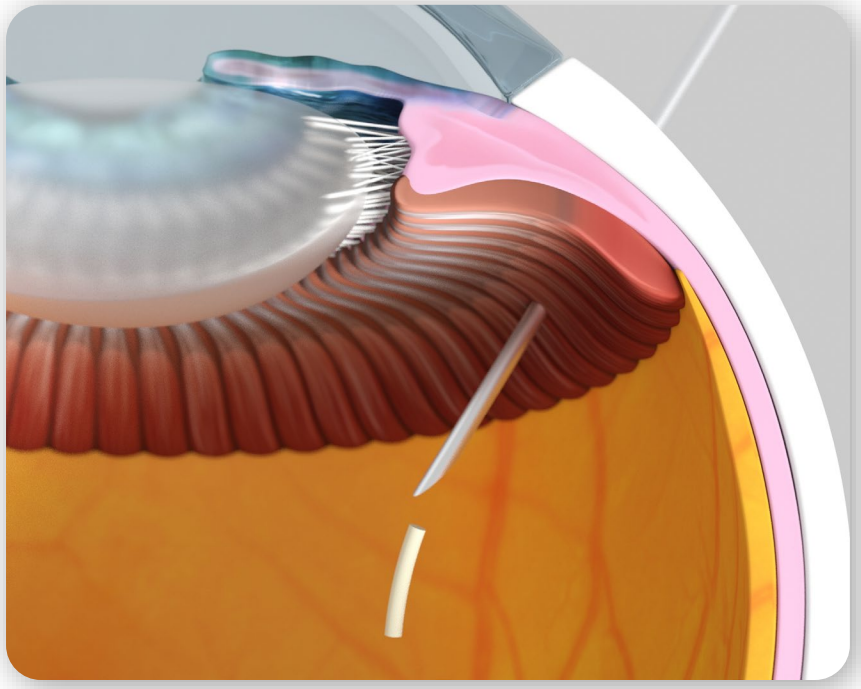


1. Bochot A, Fattal E. Liposomes for intravitreal drug delivery: a state of the art. *J Control Release*. 2012;161(2):628-634.
2. EYLEA Full Prescribing information 2019 https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125387lbl.pdf. Accessed July 20, 2020.
3. Lucentis Full Prescribing Information 2019 https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125156s111lbl.pdf. Accessed July 20, 2020.
4. Boyle J, Vukicevic M, Koklanis K, Itsiopoulos C, Rees G. Experiences of patients undergoing repeated intravitreal anti-vascular endothelial growth factor injections for neovascular age-related macular degeneration. *Psychol Health Med*. 2018;23(2):127-140.
5. Zhao Y, Adjei AA. Targeting Angiogenesis in Cancer Therapy: Moving Beyond Vascular Endothelial Growth Factor. *Oncologist*. 2015;20(6):660-673.
6. Gross-Goupil M, François L, Quivy A, Ravaud A. Axitinib: A Review of its Safety and Efficacy in the Treatment of Adults with Advanced Renal Cell Carcinoma. Clin Med Insights Oncol. 2013;7:269-277.
7. Thiele S, Liegl RG, König S, et al. Multikinase Inhibitors as a New Approach in Neovascular Age-Related Macular Degeneration (AMD) Treatment: In Vitro Safety Evaluations of Axitinib, Pazopanib and Sorafenib for Intraocular Use. Klin Monbl Augenheilkd. 2013;230(03):247-254.

OTX-TKI (Tyrosine Kinase Inhibitor Implant)
For Intravitreal Injection

Hydrogel Implant incorporates axitinib, a small molecule tyrosine kinase inhibitor, delivered by intravitreal injection

- Polyethylene glycol-based hydrogel fiber containing TKI biodegrades via ester hydrolysis in the presence of water
- Goal of sustained TKI release for 4 to 6+ months
- Hydrogel degrades; cleared from the vitreous
- Potential for broader anti-angiogenic profile Vs anti-VEGF
- Goal of longer duration with sustained delivery without surgical intervention
- Small fiber (minimal/no visual impact; product can be monitored by physician)
- Preservative-free
- Systemic TKI efficacy established in oncology

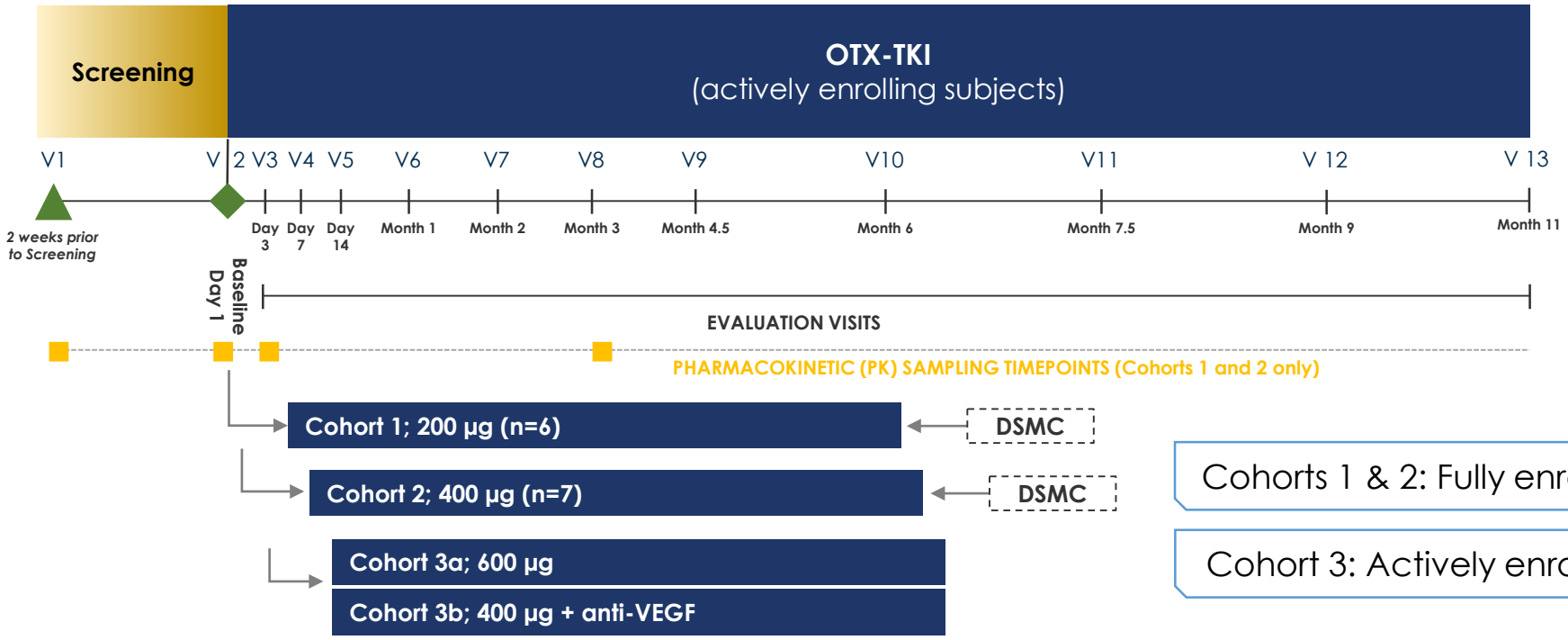


OTX-TKI Phase 1 Study

DESIGN
- Open-label, dose-escalation, feasibility study
- 5 sites in Australia
- 9-month study
- One eye per patient treated
- Key Inclusion criteria:
  - Active primary sub foveal neovascularization (SFNV) secondary to AMD – previously treated or naïve subjects but with retinal fluid present

OBJECTIVES
- Safety, tolerability, and biological activity
- Safety evaluations at all visits; mean change in central subfield thickness (CSFT) measured by SD-OCT, BCVA, and clinically-significant leakage on FA and/or OCT-A at 6 months

Question:
Does axitinib (a tyrosine kinase inhibitor; TKI) injected into the eye have biological activity?



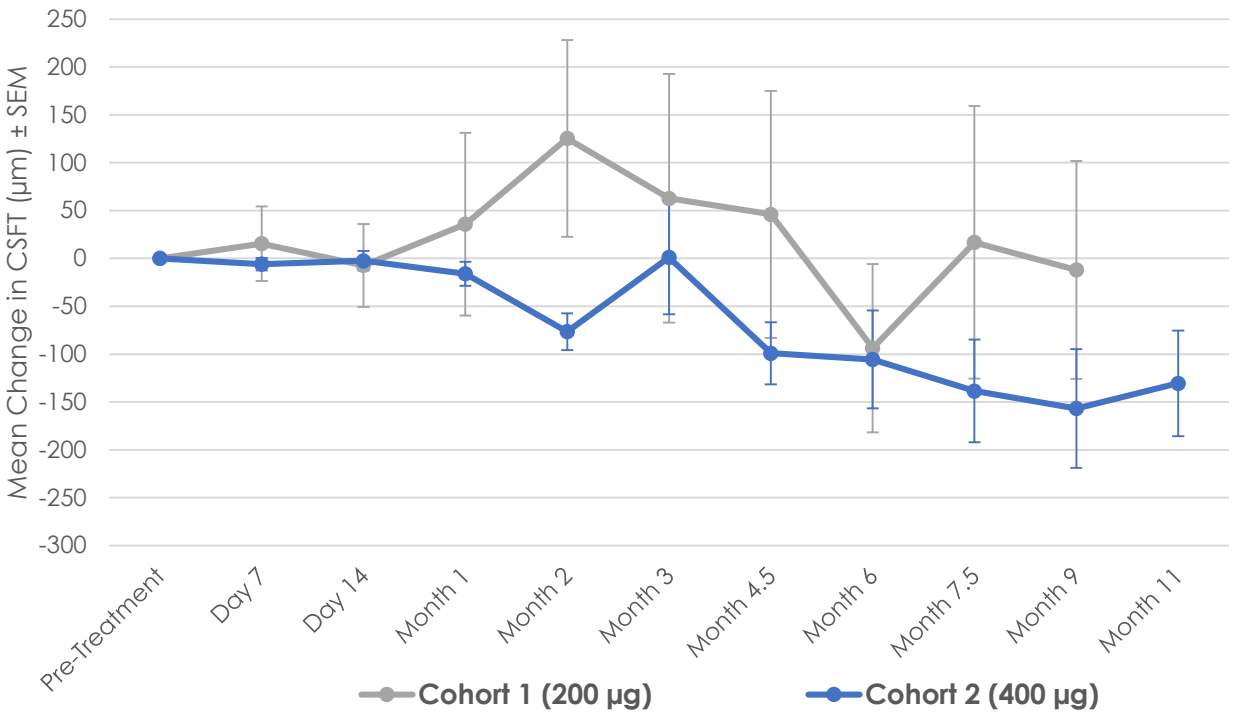
Cohorts 1 & 2: Fully enrolled

Cohort 3: Actively enrolling

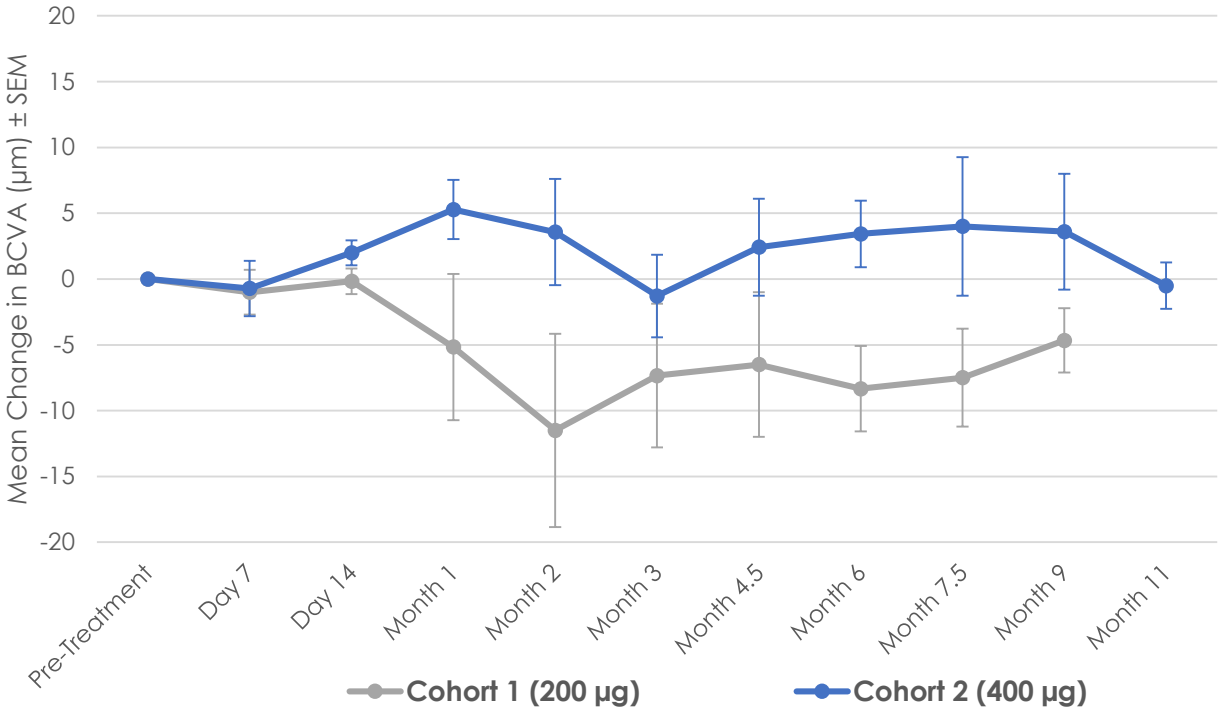
*NOTE: Interim review, unmonitored data; Data cut on October 23rd 2020

Cohort 1 & 2: MEAN CHANGE IN CENTRAL SUBFIELD THICKNESS VALUES & BEST CORRECTED VISUAL ACUITY

CSFT



BCVA

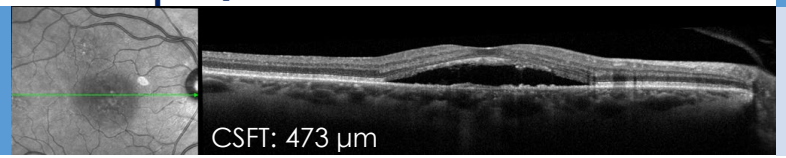
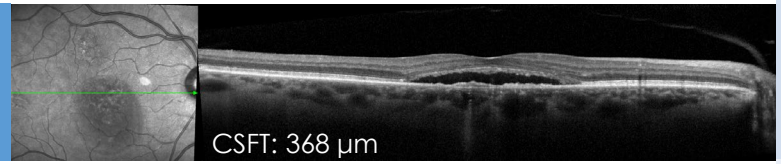
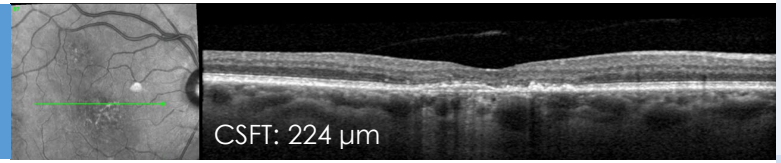
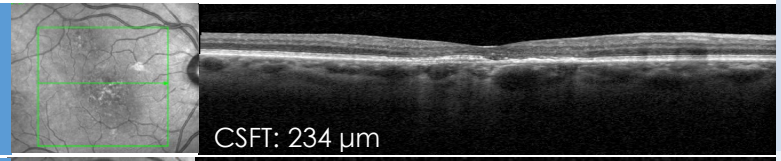
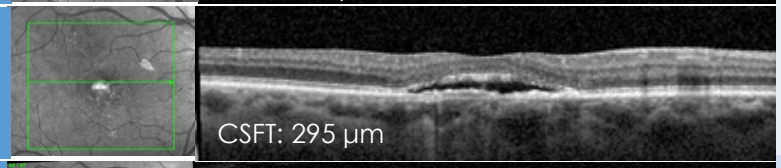
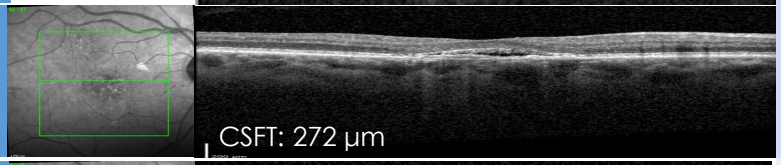
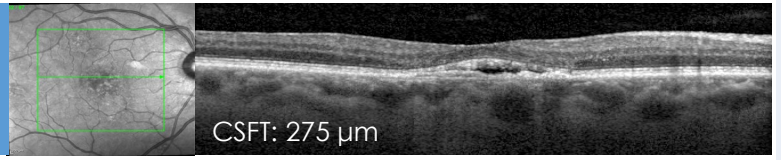


Cohort 1: n=6 until Month 9
Cohort 2: n=7 until Month 6; n=5 for Months 7.5 & 9; n=2 for Month 11

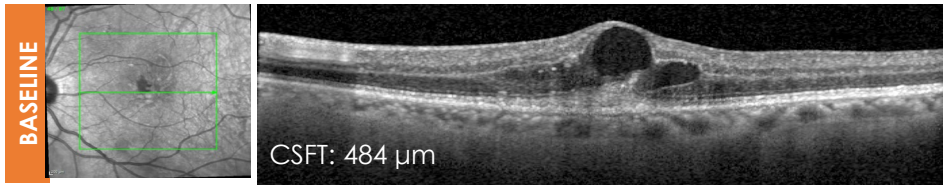
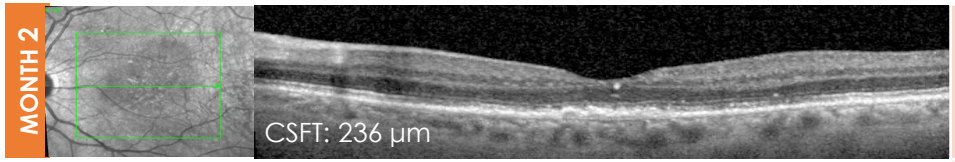
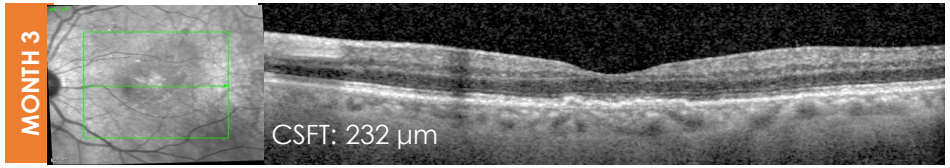
*All BCVA and CSFT values compared to Baseline visit
NOTE: Interim review, unmonitored data; Data cut on October 23rd, 2020 (Cohorts 1 & 2 only)

COHORT 2 (400 µg) & 3a (600 µg): SD-OCT EVALUATION

Cohort 2: Subject 1 (OD): History of Aflibercept Q4 Weeks for 16 months

		BCVA
BASELINE		-0.04 (20/18)
MONTH 2		-0.06 (20/17)
MONTH 4.5		0.30 (20/40)
MONTH 6		-0.08 (20/17)
MONTH 7.5		-0.08 (20/17)
MONTH 9		-0.06 (20/17)
MONTH 11		0.02 (20/21)

Cohort 3a: Subject 1 (OS): Treatment Naïve Subject

		BCVA
BASELINE		0.58 (20/76)
MONTH 2		0.22 (20/33)
MONTH 3		0.24 (20/40)

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COHORTS 1-2: SAFETY OVERVIEW

- No subjects had IOP elevation
- No subjects needed ocular steroids

Adverse Events

Number of subjects with:	Cohort 1 200 µg n=6	Cohort 2 400 µg n=7	Total n=13
Adverse Events (AEs)	14	17	31
Ocular AEs	12	12	24
Serious Ocular AEs	0	0	0
By severity			
Mild	12	14	26
Moderate	2	3	5
Severe	0	0	0
Treatment-related Ocular AEs	1	2	3

Percentage of Subjects Without Needing Rescue Medications

Cohorts	At 3 months % (n/N)	At 6 months % (n/N)	At 7.5 months % (n/N)	At 9 months % (n/N)
Cohort 1 (200 µg)	66.7 (4/6)	50 (3/6)	50 (3/6)	50 (3/6)
Cohort 2 (400 µg)	71.4 (5/7)	57.1 (4/7)	42.9 (3/7)	20 (1/5)*

Pharmacokinetics

Plasma concentrations of axitinib were below the limit of quantification of assay (BLQ) <0.1 ng/ml at all sampled timepoints in all subjects in Cohorts 1 & 2

* Only 5 of 7 subjects reached 9 months in the study
NOTE: Interim review, unmonitored data; Data cut on October 23rd, 2020, (Cohorts 1 & 2 only)

OTX-TKI CONCLUSIONS:

- **OTX-TKI was generally well tolerated**
  To date, observed to have a favorable safety profile, with no ocular serious adverse events; No measurable systemic exposure to axitinib observed in Cohorts 1-2
- **Preliminary biological signal of clinically-meaningful decrease in retinal fluid**
  Some subjects showed a decrease in intraretinal or subretinal fluid by 2 months in 400 µg Cohort 2 and 600 µg Cohort 3
- **Therapy durability suggests extended duration of action**
  In the 400 µg Cohort 2, several subjects demonstrated durability of therapy for up to 6 months and one subject demonstrated durability to 11 months
- **Consistent bio-resorption observed**
  Implant biodegraded in all subjects in Cohort 1 by 9-10.5 months
- **Implant location observation suggests limited movement**
  Implant was able to be adequately monitored

Study is ongoing; Next steps

- **Continued long-term evaluation of OTX-TKI cohorts:** Need to establish durability of treatment
- **New high-dose 600 µg Cohort 3 currently enrolling:** Evaluate tolerability with a higher dose & explore OTX-TKI with an initial anti-VEGF injection

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