Phase 1 Trial of a Novel, Hydrogel-based, Intravitreal Axitinib Implant for the Treatment of Neovascular Age-related Macular Degeneration

Andrew A. Moshfeghi, MD; James G. Wong, MBBS; Andrew A. Chang, MBBS, PhD; Robyn H. Guymer, MBBS, PhD; Sanjeewa S. Wickremasinghe, MBBS; Erin Reilly, MPH; Matthew Cheung, PharmD; Michael H. Goldstein, MD

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Financial Disclosures:
- Sponsorship of clinical trial: Ocular Therapeutix, Inc.
- Moshfeghi AA (presenting author) is a consultant for Ocular Therapeutix, Inc.
- Wong JG, Chang A, Guymer RH and Wickremasinghe S are investigators in the clinical trial.
- Goldstein MH, Cheung M & Reilly E are employees of Ocular Therapeutix, Inc.

Tyrosine Kinase Inhibitors in AMD

Tyrosine Kinase Inhibitors (TKI) Act Directly on VEGF Receptors

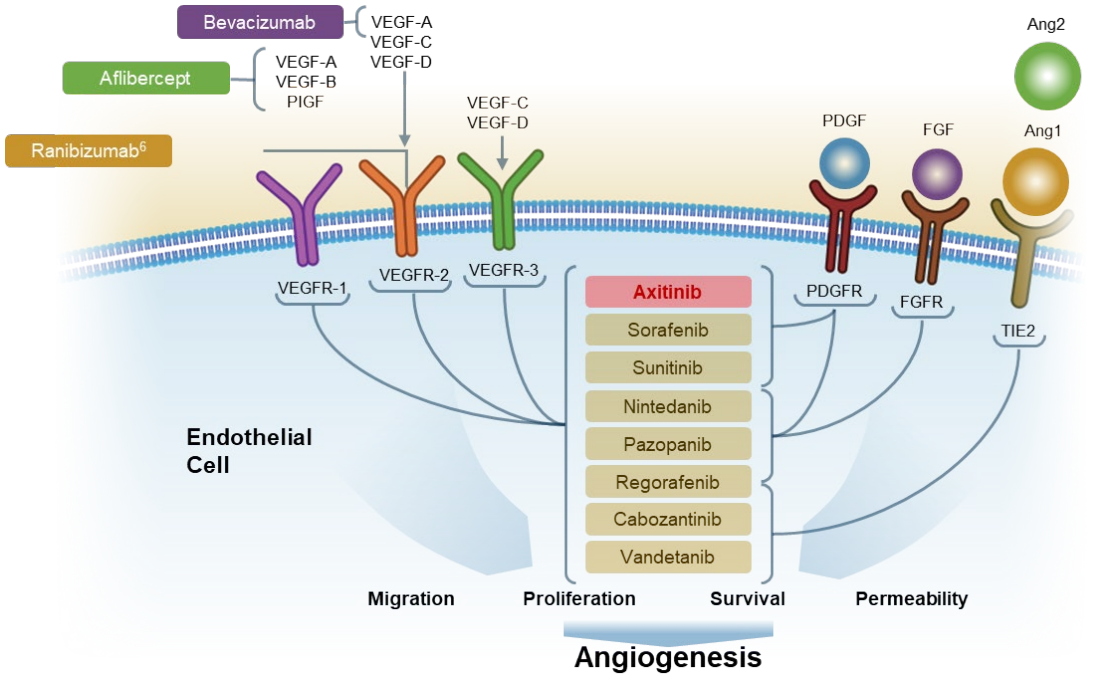
- Axitinib is a small molecule multi-receptor tyrosine kinase inhibitor, potent and highly selective inhibitor of VEGFR-1, 2, 3 and PDGFR signaling[1,2]
- Axitinib acts intracellularly and interferes with cellular signaling through inhibition of the receptor tyrosine kinases[2]
- Lower doses of axitinib (at nanomolar concentrations) exhibit high potency and selectivity compared to other TKIs (e.g., sunitinib, sorafenib and pazopanib)[2]

Inhibitory Concentrations (IC50 in nmol) for Multitargeted TKIs[2]

Drug	VEGFR-1	VEGFR-2	VEGFR-3	PDGFR α	PDGFR β
Axitinib	**0.1**	**0.2**	**0.1-0.3**	**5**	**1.6**
Pazopanib	10	30	47	71	84
Sunitinib	10	10	10	5-10	10
Sorafenib	--	90	20	50-60	50-60

- Lower doses of axitinib may minimize the TKI class-related adverse events resulting from systemic drug concentrations[3]
- Axitinib has low water solubility[4] compared to other TKIs (e.g., sunitinib, pazopanib, nintedanib),[5-7] allowing for controlled drug release

Tyrosine Kinase Inhibitor Targets



References: 1. Zhao Y, Adjei AA. *Oncologist*. 2015;20(6):660-673. **2.** Gross-Goupil M, François L, Quivy A, Ravaud A. Clin Med Insights Oncol. 2013;7:269-277. (Table adapted from manuscript) **3.** Giddabasappa A, Lalwani K, Norberg R, et al.. Experimental Eye Research. 2016;145:373-379. doi:10.1016/j.exer.2016.02.010. **4.** PubChem. Axitinib. Accessed October 15, 2021. https://pubchem.ncbi.nlm.nih.gov/compound/6450551. **5.** PubChem. Sunitinib. Accessed October 15, 2021. https://pubchem.ncbi.nlm.nih.gov/compound/5329102. **6.** PubChem. Pazopanib. Accessed October 15, 2021. https://pubchem.ncbi.nlm.nih.gov/compound/10113978. **7.** PubChem. Nintedanib. Accessed October 15, 2021. https://pubchem.ncbi.nlm.nih.gov/compound/135423438

Abbreviations: AMD, age-related macular degeneration; Ang, angiopoietin; FGFR, fibroblast growth factor receptor; PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endotheliall growth factor receptor

OTX-TKI (Axitinib Intravitreal Implant)
for Intravitreal Injection

Sustained-release

- Goal of longer duration without need for surgical intervention
- Goal of sustained release for 6 to 9 months

Intravitreal TKI Delivery

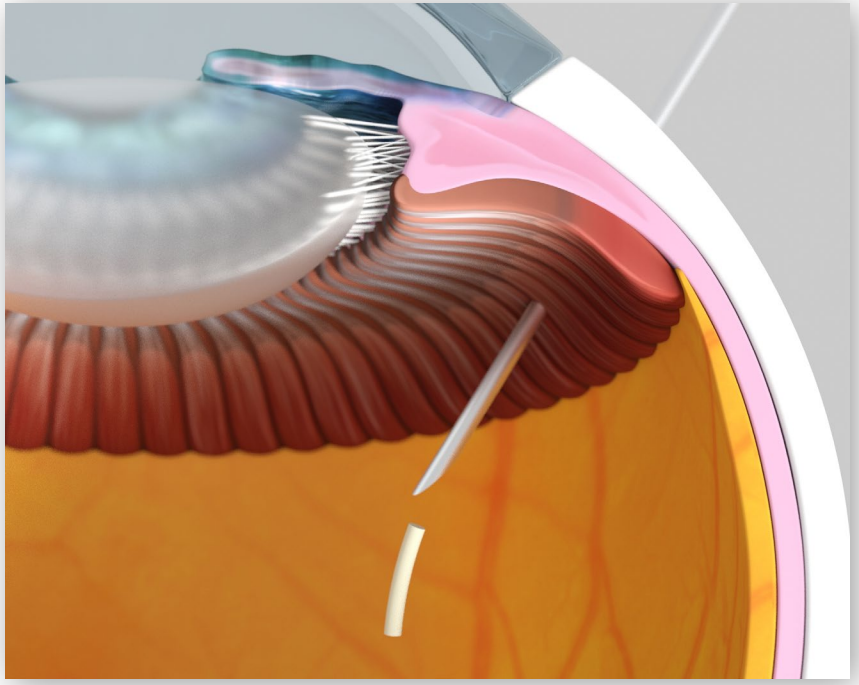
- Potential for broader anti-angiogenic profile compared to anti-VEGF agents
- Systemic TKI efficacy established in oncology

Biodegradable

- Polyethylene glycol-based hydrogel fiber containing TKI biodegrades via ester hydrolysis in the presence of water and is cleared from the vitreous

Other Product Attributes

- Small fiber means minimal to no visual impact but still allows physician monitoring
- Free of antimicrobial preservatives



Hydrogel implant incorporates axitinib delivered via an intravitreal injection

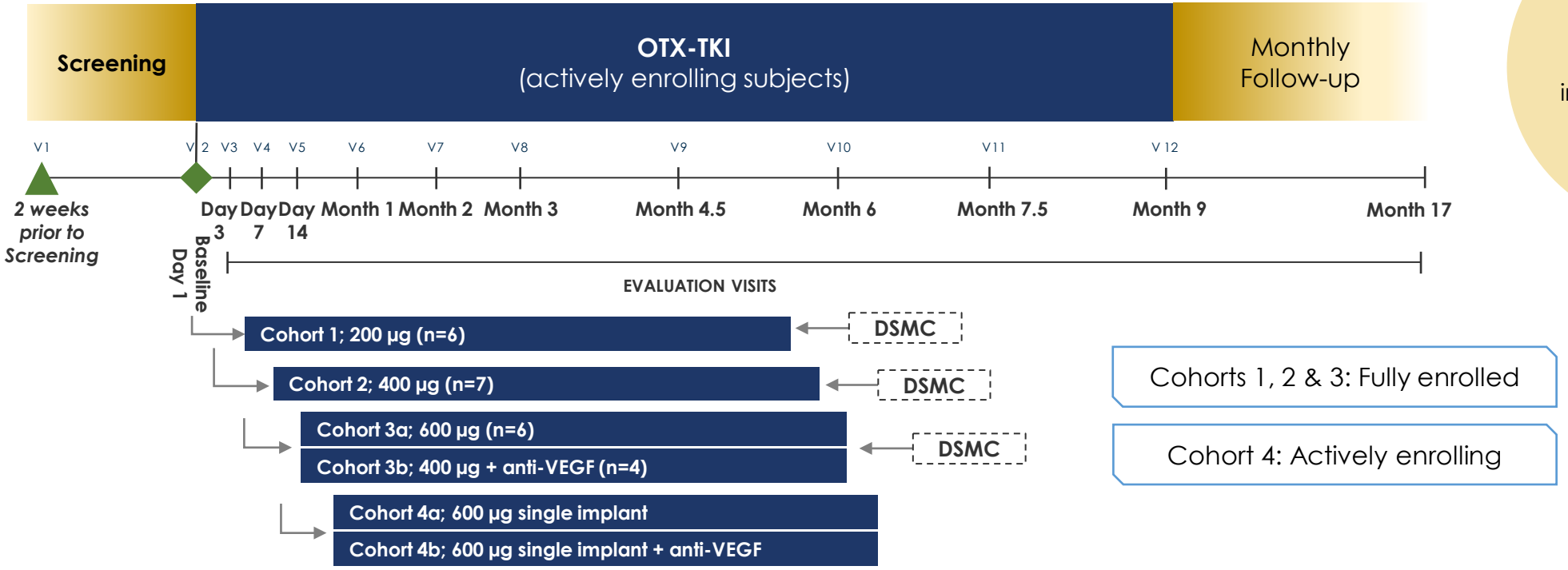
Study Objective and Design

Design

- Open-label, dose-escalation, feasibility study
- 5 sites in Australia
- 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



Question:

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

Cohorts 1, 2 & 3: Fully enrolled

Cohort 4: Actively enrolling

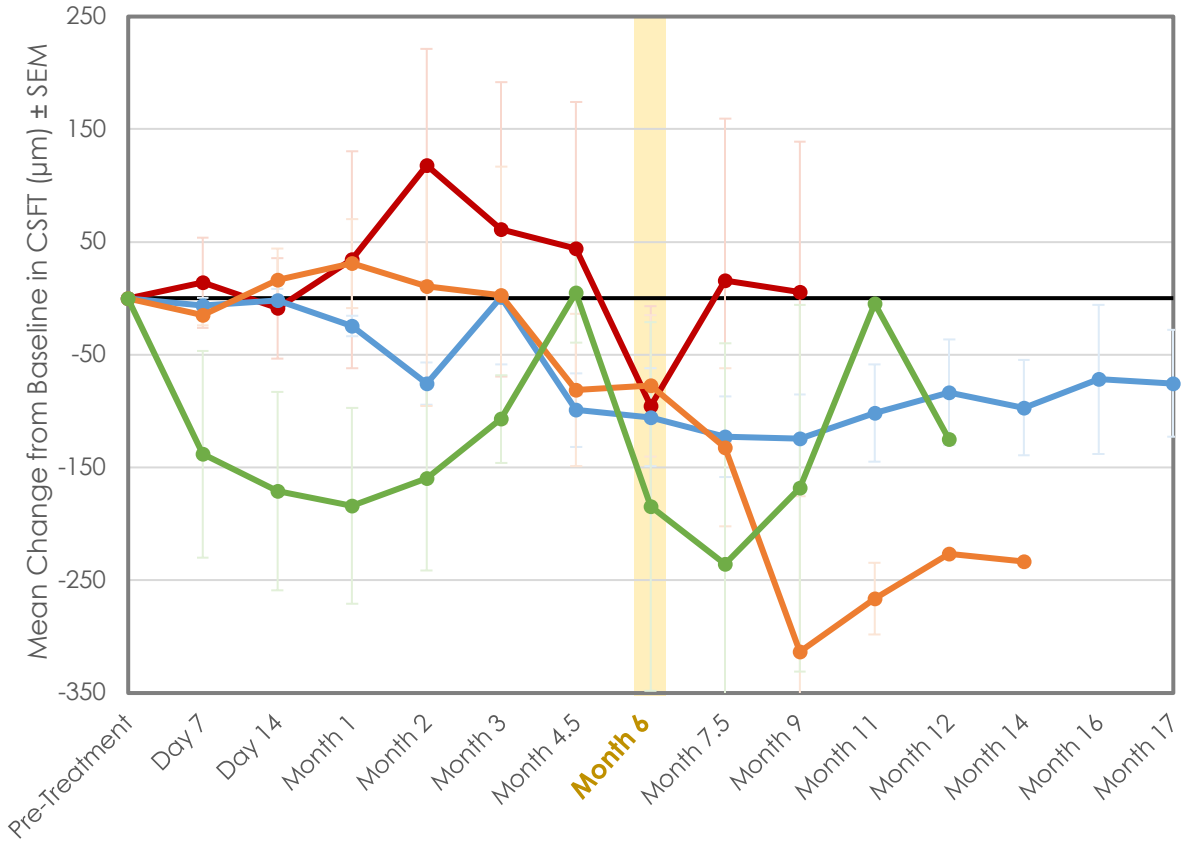
*NOTE: Interim review, unmonitored data; Data cut off October 15, 2021

Baseline Demographics

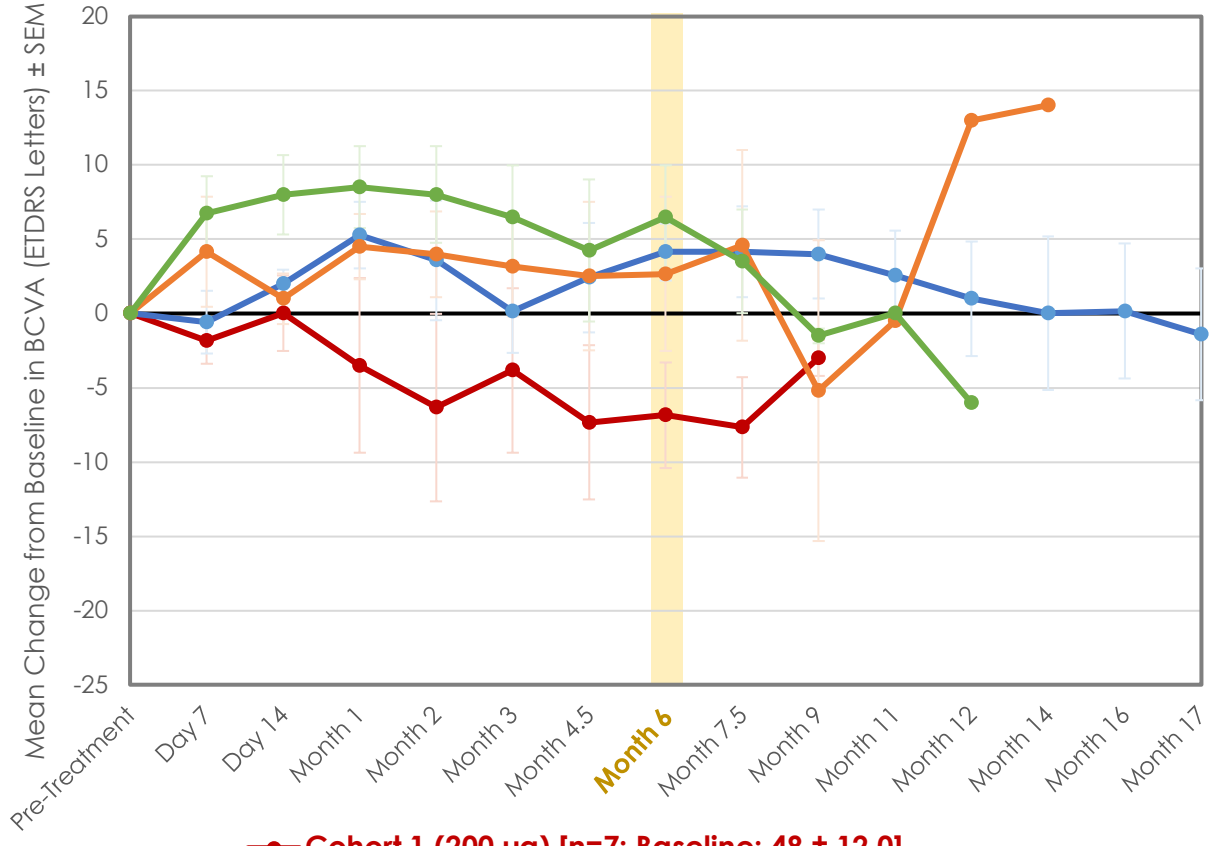
	Cohort 1 OTX-TKI 200µg (n=6)	Cohort 2 OTX-TKI 400µg (n=7)	Cohort 3a OTX-TKI 600µg (n=6)	Cohort 3b OTX-TKI 400µg + Anti-VEGF (n=4)	Total (n=23)
Age, years Mean (SD)	75.8 (3.7)	74.7 (5.4)	77.3 (5.4)	78.3 (8.1)	76.2 (5.3)
Sex, n (%) Male Female	5 (83.3%) 1 (16.7%)	4 (57.1%) 3 (42.9%)	5 (83.3%) 1 (16.7%)	3 (75.0%) 1 (25.0%)	17 (73.9%) 6 (26.1%)
BCVA, ETDRS Letters (Snellen equivalent) Mean ± SEM	48 (20/110) ± 12.0	62 (20/63) ± 8.5	46 (20/125) ± 6.4	47 (20/125) ± 11.8	51 (20/100) ± 4.7
CSFT, µm Mean ± SEM	680 ± 159	450 ± 29	521 ± 68	435 ± 58	526 ± 49

Abbreviations: anti-VEGF, anti-vascular endotheliall growth factor receptor; BCVA, best corrected visual acuity; CSFT, central subfield foveal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; SD, standard deviation; SEM, standard error of mean

Interim Results: Mean Change in CSFT & BCVA in Cohorts 1-3



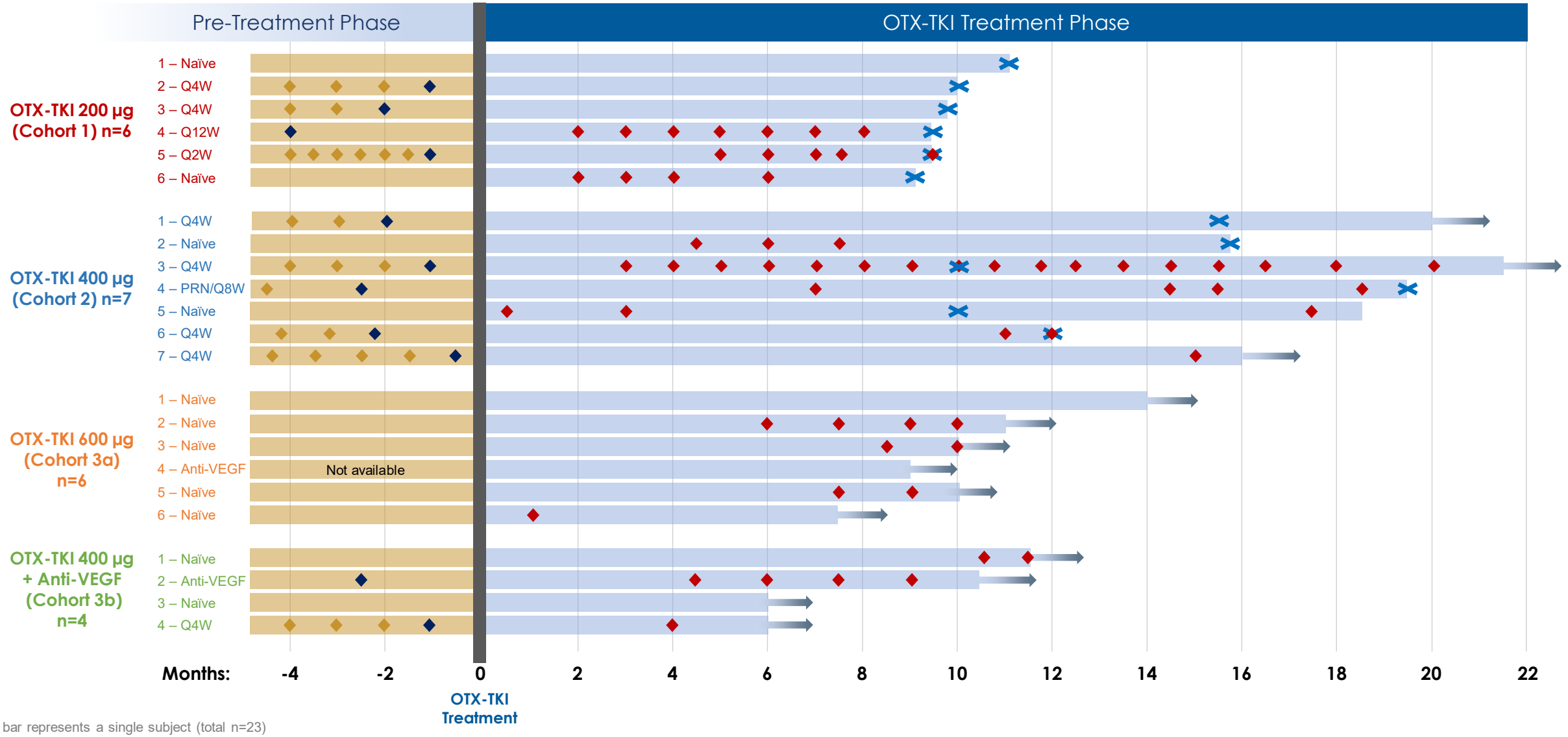
Cohort 1 (200 µg) [n=6; Baseline: 680 ± 159 µm]
Cohort 2 (400 µg) [n=7; Baseline: 450 ± 29 µm]
Cohort 3a (600 µg) [n=6; Baseline: 521 ± 68 µm]
Cohort 3b (400 µg + Anti-VEGF) [n=4; Baseline: 435 ± 58 µm]



Cohort 1 (200 µg) [n=7; Baseline: 48 ± 12.0]
Cohort 2 (400 µg) [n=7; Baseline: 62 ± 8.5]
Cohort 3a (600 µg) [n=6; Baseline: 46 ± 6.4]
Cohort 3b (400 µg + Anti-VEGF) [n=4; Baseline: 47 ± 11.8]

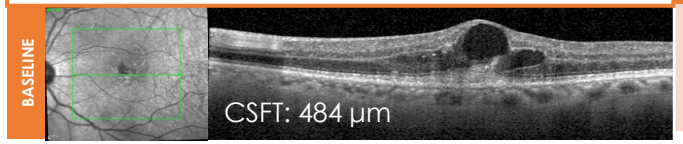
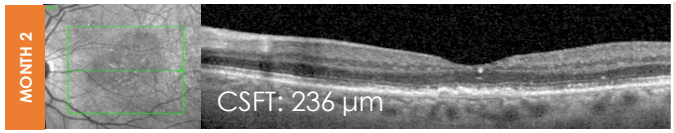
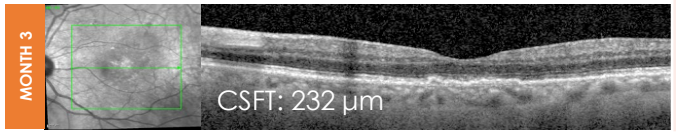
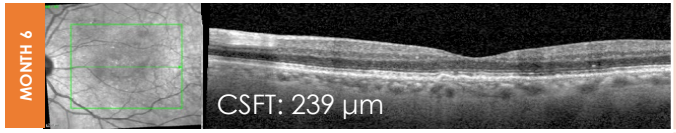
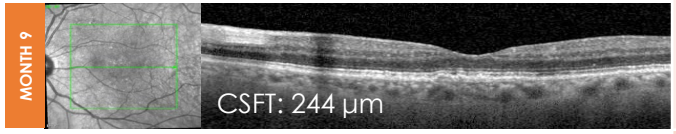
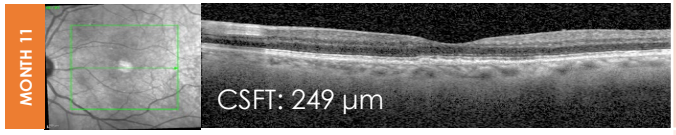
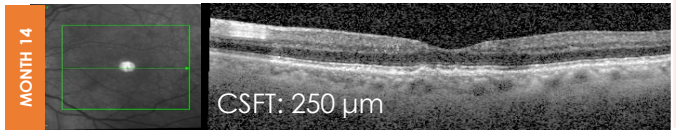
Cohort 1: n=6 until Month 9; Cohort 2: n=7 until Month 12, n=6 for Month 14 and 16, n=4 for Month 17
Cohort 3a: n=6 until Month 7.5, n=3 for Month 9, n=2 for Month 11, n=1 for Month 12 and 14; Cohort 3b: n=4 until Month 4.5; n=2 for Month 6, 7.5 and 9, n=1 for Month 11 and 12
All BCVA and CSFT values compared to baseline visit; NOTE: Interim review, unmonitored data; Data cut off October 15, 2021

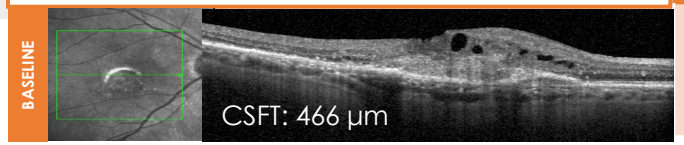
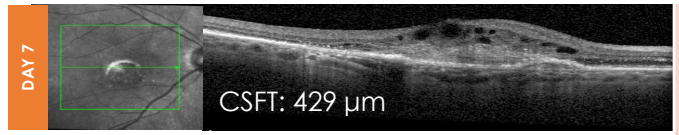
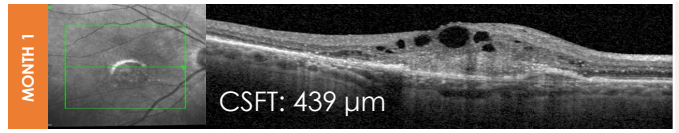
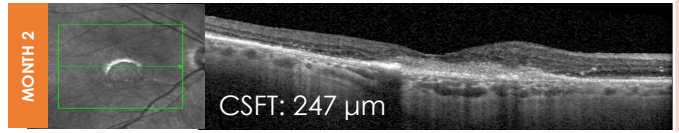
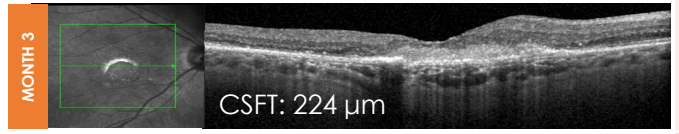
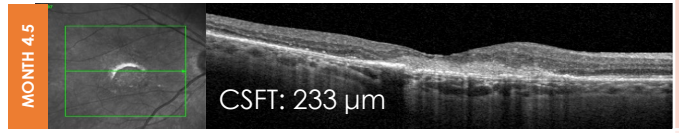
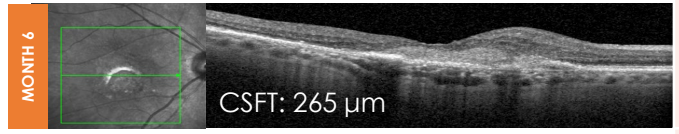
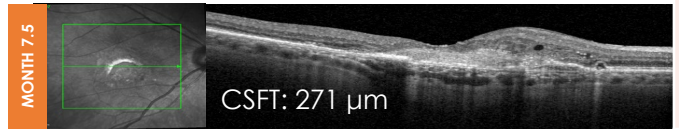
Durability Assessment



Each bar represents a single subject (total n=23)
NOTE: Interim review, unmonitored data; Data cut off October 15, 2021

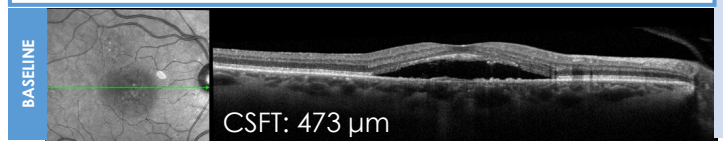
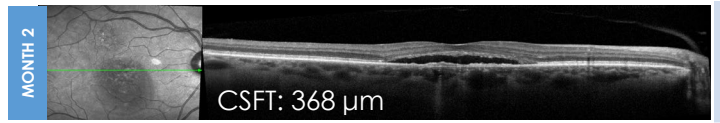
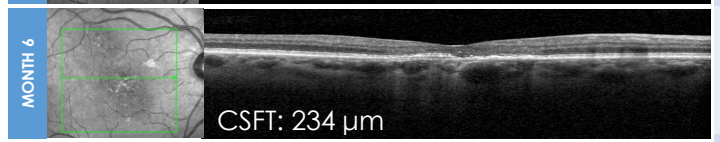
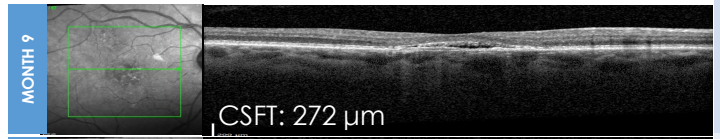
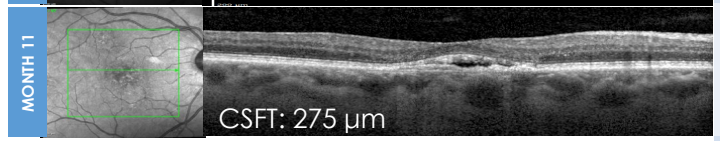
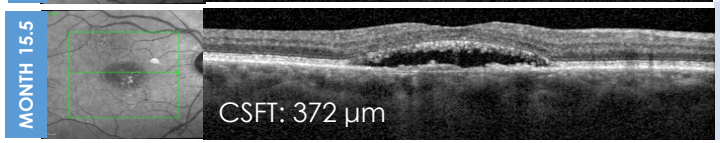
SD-OCT Evaluation: Cohort 3

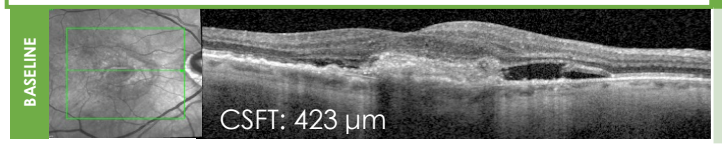
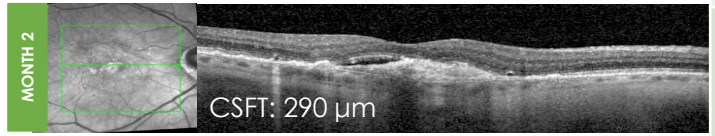
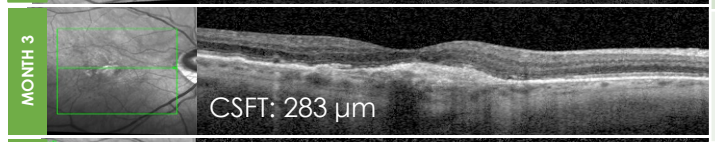
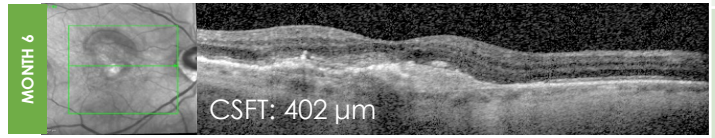
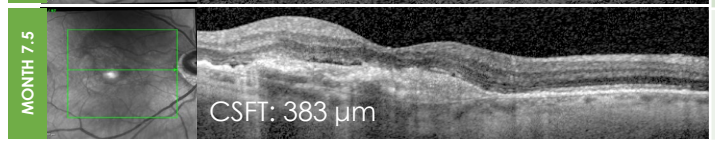
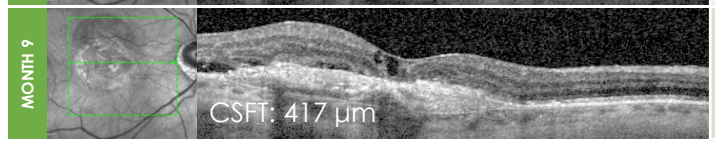
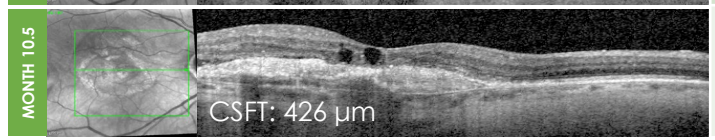
Cohort 3a (600µg): Subject 1 (OS): Treatment Naïve Subject	BCVA
	56 (20/80)
	74 (20/30)
	73 (20/40)
	80 (20/25)
	81 (20/25)
	76 (20/30)
	70 (20/40)

Cohort 3a (600µg): Subject 6 (OD): Treatment Naïve Subject	BCVA	
	28 (20/320)	
	30 (20/250)	
	28 (20/320)	Received anti-VEGF at Month 1
	30 (20/252)	
	31 (20/250)	
	30 (20/250)	
	27 (20/320)	
	40 (20/160)	

NOTE: Interim review, unmonitored data; Data cut off October 15, 2021.

SD-OCT Evaluation: Cohort 2 and 3

Cohort 2 (400µg): Subject 1 (OD): History of Aflibercept Q4 Weeks for 16 months	**BCVA**
	87 (20/18)
	88 (20/17)
	89 (20/17)
	88 (20/17)
	84 (20/21)
	90 (20/16)

Cohort 3b (400µg + Anti-VEGF): Subject 1 (OD): Treatment Naïve Subject	**BCVA**	
	39 (20/160)	
	54 (20/80)	
	52 (20/100)	
	52 (20/100)	
	46 (20/125)	
	38 (20/200)	
	35 (20/200)	**Received anti-VEGF at Month 10.5 & 11.5**

*NOTE: Interim review, unmonitored data; Data cut off October 15, 2021.

Safety and Tolerability Summary

Number of Adverse Events	Cohort 1 200 µg (n=6)	Cohort 2* 400 µg (n=7)	Cohort 3a* 600 µg (n=6)	Cohort 3b* 400 µg + Anti-VEGF (n=4)	Total (n=23)
Adverse Events (AEs)	14	27	31	13	85
Suspected Relationship to Study Product	1	2	3	3	9
Suspected Relationship to Injection Procedure	1	5	10	4	20
Ocular AEs	12	18	23	11	64
Ocular AEs (Study Eye)	6	15	20	9	50
Serious Ocular AEs	0	0	0	0	0
Serious Non-ocular AEs†	1	0	1	0	2
AEs by Severity					
Mild	12	20	25	12	69
Moderate	2	7	5	1	15
Severe	0	0	1‡	0	1

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, 3a and 3b

*Follow-up ongoing

† Serious non-ocular AEs: atrial fibrillation (Cohort 1) and ureterovesical stone (Cohort 3a)

‡ Severe AE: ureterovesical stone

NOTE: Interim review, unmonitored data; Data cut off October 15, 2021

Ocular Adverse Events

Most Common Ocular Adverse Events (>2 subjects) in the Study Eye*

Number of AEs Reported in the Study Eye	Cohort 1 200 µg (n=6)	Cohort 2† 400 µg (n=7)	Cohort 3a† 600 µg (n=6)	Cohort 3b† 400 µg + Anti-VEGF (n=4)	Total (n=23)
Subconjunctival hemorrhage	1	2	6	1	10
Eye pain	0	2	2	0	4
OTX-TKI implant affecting vision	0	1	3	0	4

- **No IOP elevations were reported**
- **Uveitis was reported in one subject (Cohort 3b) which resolved with treatment**

* All other ocular AEs in the study eye were reported in ≤2 subjects
† Follow-up ongoing
NOTE: Interim review, unmonitored data; Data cut off October 15, 2021

Duration of Effect

OVER 50% OF SUBJECTS DID NOT RECEIVE ANTI-VEGF THERAPY OUT TO 6 MONTHS

Percentage of Subjects Without Needing Anti-VEGF Injections

Extended Follow-up

Cohorts	At 1 months % (n/N)	At 3 months % (n/N)	At 6 months % (n/N)	At 7.5 months % (n/N)	At 9 months % (n/N)	At 12 months % (n/N)	At 14 months % (n/N)	At 17 months % (n/N)
Cohort 1 (200 µg)	**100** (6/6)	**66.7** (4/6)	**50** (3/6)	**50** (3/6)	**50** (3/6)	NA	NA	NA
Cohort 2 (400 µg)*	**85.7** (6/7)	**71.4** (5/7)	**57.1** (4/7)	**42.9**(3/7)	**42.9** (3/7)	**28.6**(2/7)	**28.6** (2/7)	**25** (1/4)*
Cohort 3a (600 µg)*	**83.3** (5/6)	**83.3** (5/6)	**66.6** (4/6)	**66.6** (4/6)	**40** (2/5)*	**100** (1/1)*	**100** (1/1)*	TBD
Cohort 3b (400 µg + anti-VEGF)*	**100** (4/4)	**100** (4/4)	**50** (2/4)	**50** (1/2)*	**50** (1/2)*	TBD	TBD	TBD

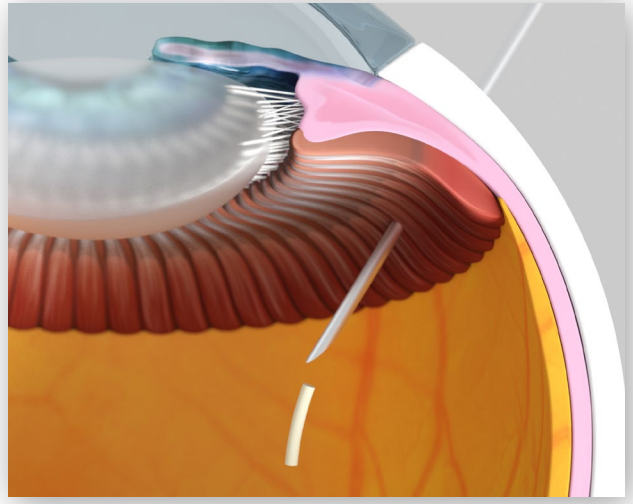
*Follow-up ongoing
NOTE: Interim review, unmonitored data; Data cut off October 15, 2021

Conclusions To Date

- **OTX-TKI was generally well tolerated**
  - To date, observed to have a favorable safety profile, with no ocular serious adverse events in treatment naïve & previously treated wet AMD patients
  - No measurable systemic exposure to axitinib observed in Cohort 1, 2, 3a and 3b
- **Preliminary biological signal of clinically-meaningful decrease in retinal fluid**
  - Some subjects showed a decrease in intraretinal or subretinal fluid by 2 months in Cohorts 2 (400 µg) & 3a (600 µg)
  - Combination of OTX-TKI + Anti-VEGF (Cohort 3b) showed a decrease in intraretinal or subretinal fluid as early as a week after treatment in two subjects
- **Therapy durability suggests extended duration of action (follow-up ongoing)**
  - Over 50% of subjects demonstrated durability of 6 months or longer
- **Consistent bio-resorption observed**
  - Implant biodegraded in subjects in Cohort 1 by 9-10.5 months
- **Implant location observation suggests limited movement**
  - Implant was able to be adequately monitored

UNMET NEED

Longer Duration of Action
&
Novel Mechanism of Action



OTX-TKI is being evaluated in an ongoing Phase 1b, U.S.-based, prospective, randomized, controlled, multicenter trial

NOTE: Interim review, unmonitored data; Data cut off October 15, 2021