Intravitreal Hydrogel-Based Axitinib Implant (OTX-TKI) for the Treatment of Neovascular AMD

A Phase 1 Trial Update

Andrew A. Moshfeghi

University of Southern California Roski Eye Institute

Clinical Trial Investigators: James G. Wong, Andrew A. Chang, Robyn H. Guymer, Sanjeewa S. Wickremasinghe, Alan Luckie, Mark Gillies

Angiogenesis, Exudation and Degeneration Symposium | February 11-12, 2022 | Virtual

Disclosures

Study Disclosures

- Sponsorship for the clinical trial: Ocular Therapeutix, Inc.
- The presentation discusses an investigational product, OTX-TIC. Its efficacy and safety profile has not been established and it has not been approved by the FDA

Presenter Financial Disclosures

- Consulting: Allergan, Genentech, Graybug, Novartis, Ocular Therapeutix, Placid0, Pr3vent, Regeneron, REGENXBIO
- Research Grants: Genentech, Novartis, Regeneron
- Equity Interests: OptiSTENT, Ocular Therapeutix, Placid0, Pr3vent

Take Home Points

Based on Phase I trial data currently available*

- OTX-TKI (Axitinib Intravitreal Implant) has been generally well tolerated and observed to have a favorable safety profile, with no ocular serious adverse events to date in all cohorts [Cohort 1(200 µg), Cohort 2(400 µg), Cohort 3a (600 µg) and Cohort 3b (400 µg + Anti-VEGF)]
- Preliminary biological signal of clinically-meaningful decrease in retinal fluid observed by 2 months in Cohorts 2 (400 µg) & 3a (600 µg), and as early as a week in Cohort 3b (400 µg + Anti-VEGF)
- Over 60% of all subjects showed durability of 6 months or longer including over 80% in Cohort 3a (600 µg)
  - Approximately 50% of all subjects showed durability of 7.5 months or longer

*NOTE: Interim review, unmonitored data; Data cut off January 11, 2022

Problems with Immediate-release Injections

Unmet Need in Retinal Disease

- Therapeutic challenges associated with current therapies include
  - Rapid clearance of VEGF inhibitors, requiring repeated injections every 1-2 months to maintain effective concentrations
  - Over time, repeated intravitreal injections can lead to infection, retinal detachment, elevated intraocular pressure and poor patient tolerance[1-3]
  - Even with flexible regimens (e.g., PRN and T&E protocols), multiple visits and injections challenging for patients/families leading to patient nonadherence and nonpersistence[4-5]
- To address these challenges, alternate therapies are being investigated that can provide
  - Novel Mechanism of Action
  - Longer Duration of Action

References: 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.** Okada M, Mitchell P, Finger RP, et al. Nonadherence or Nonpersistence to Intravitreal Injection Therapy for Neovascular Age-Related Macular Degeneration. Ophthalmology. 2021;128(2):234-247.

Tyrosine Kinase Inhibitors in AMD

Tyrosine Kinase Inhibitors (TKI) Act Directly on VEGF Receptors

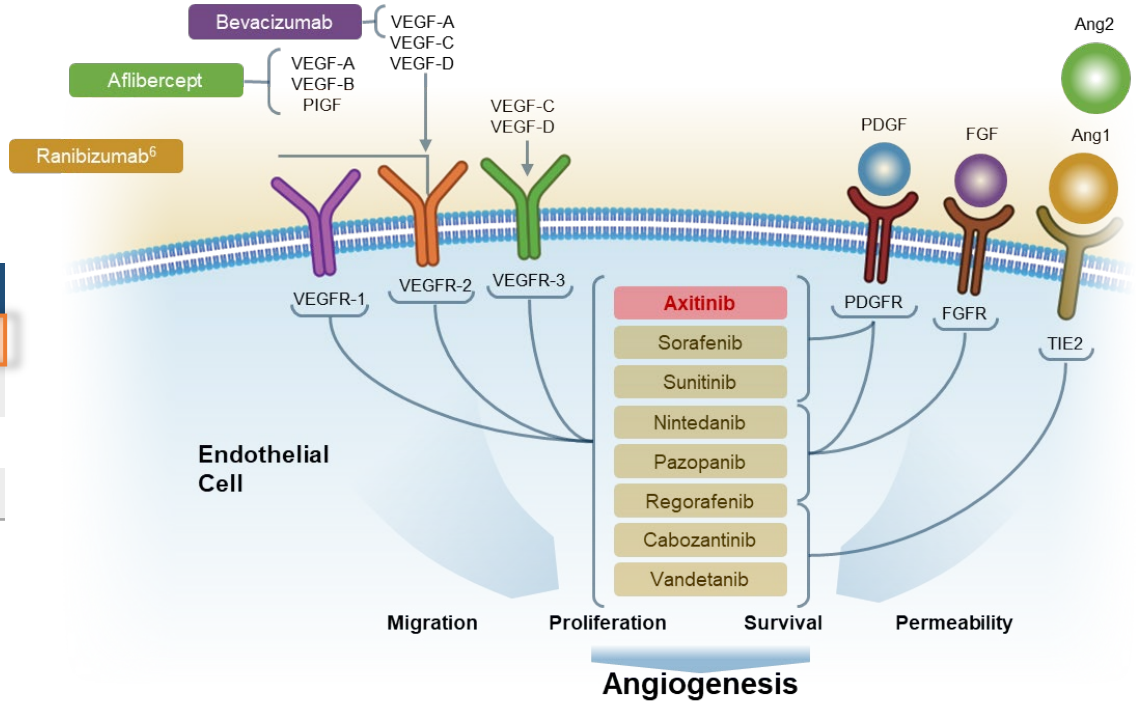
- Axitinib is a small molecule multi-receptor tyrosine kinase inhibitor, potent and highly selective inhibitor of VEGFR-1, 2, 3 and PDGFR signaling[1,2]
- Axitinib acts intracellularly and interferes with cellular signaling through inhibition of the receptor tyrosine kinases[2]
- Lower doses of axitinib (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

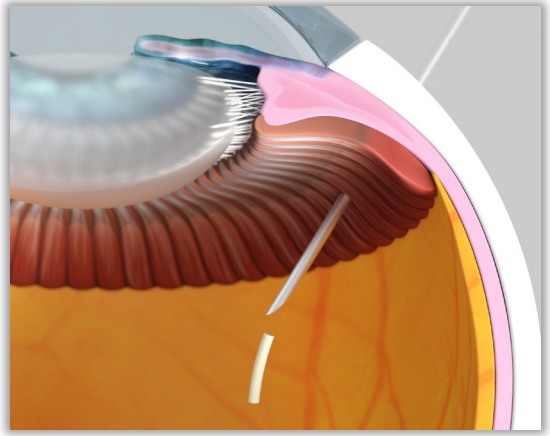
OTX-TKI (Axitinib Intravitreal Implant)
for Intravitreal Injection

Polyethylene glycol (PEG)-based Hydrogel Platform

- **Completely biodegrades** via ester hydrolysis
- **Biocompatible** with low potential for inflammation
- Engineered to deliver drug in days or months

Axitinib (Active Ingredient)

- Potential for **broader anti-angiogenic profile** compared to anti-VEGF agents
- **Highly potent** compared to other TKIs
- Systemic TKI efficacy established in oncology



OTX-TKI, a novel hydrogel-based, biodegradable, sustained-release axitinib implant

- Goal of delivering axitinib for **6 to 9 months** at near **zero-order kinetics**
- **Biodegrades completely** and is cleared from the vitreous
- **Small fiber** with minimal to no visual impact but still allows for physician monitoring
- Free of antimicrobial preservatives

OTX-TKI Phase 1 Study in Australia

Study Design

Status

- Cohorts 1, 2, 3a & 3b are fully enrolled
- Cohort 4a and 4b are actively enrolling

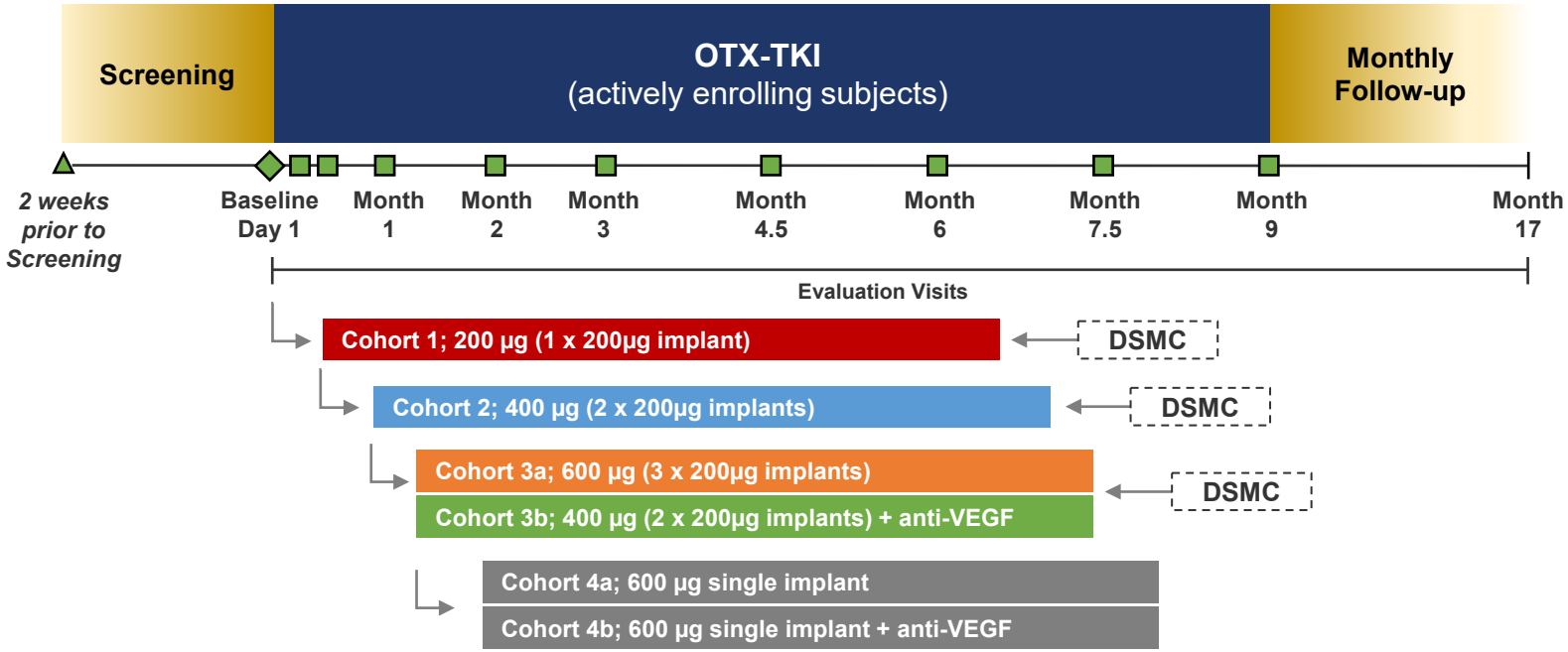
Key Inclusion Criteria

- Active primary sub foveal neovascularization secondary to AMD
- Previously treated or naïve subjects
- **Presence of retinal fluid**

Objectives

- Safety and tolerability
- Biological activity - mean change in central subfield thickness measured by SD-OCT, BCVA, and clinically-significant leakage on FA and/or OCT-A

Open-label, Dose Escalation, Feasibility Trial



Question:

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

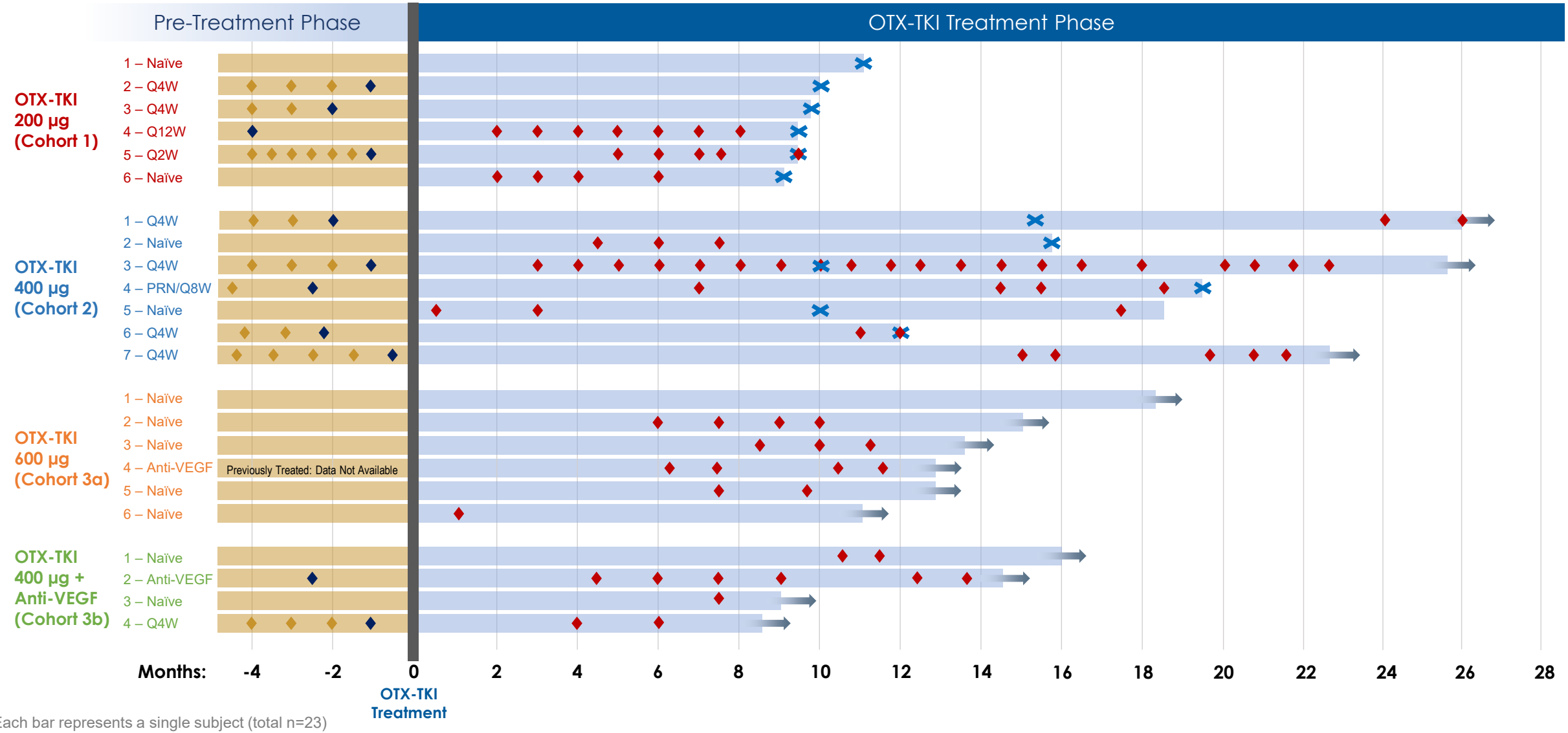
NOTE: Interim review, unmonitored data; Data cut off January 11, 2022

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)	All Subjects (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	5 (83.3%)	4 (57.1%)	5 (83.3%)	3 (75.0%)	17 (73.9%)
Female	1 (16.7%)	3 (42.9%)	1 (16.7%)	1 (25.0%)	6 (26.1%)
History of Treatment with anti-VEGF, n (%)					
Previously treated	4 (66.7%)	5 (71.4%)	1 (16.7%)	2 (50.0%)	11 (47.8%)
Treatment naïve	2 (33.3%)	2 (28.6%)	5 (83.3%)	2 (50.0%)	12 (52.2%)
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

NOTE: Interim review, unmonitored data; Data cut off January 11, 2022

Durability Assessment



Each bar represents a single subject (total n=23)
NOTE: Interim review, unmonitored data; Data cut off January 11, 2022

Duration of Effect

Over 60% of all subjects showed durability of 6 months or longer and approximately 50% of subjects showed durability of 7.5 months or longer

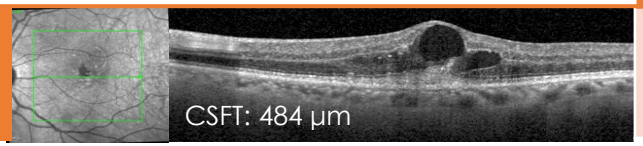
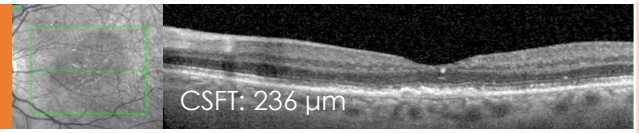
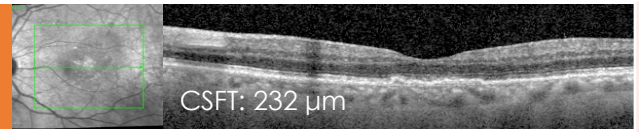
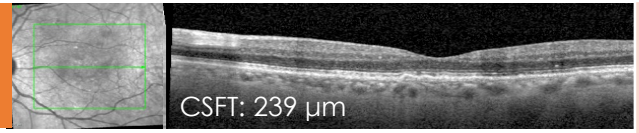
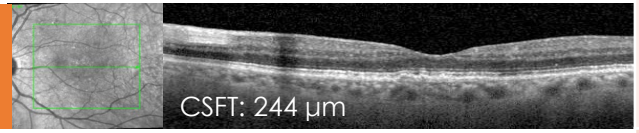
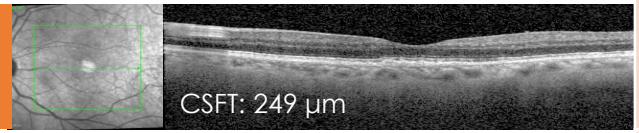
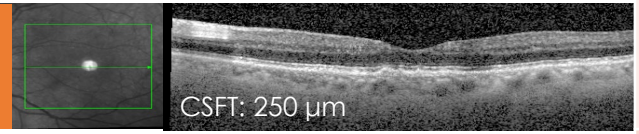
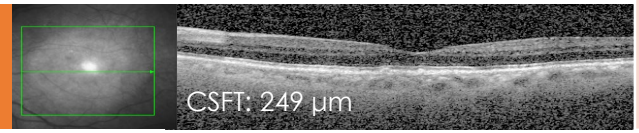
	Month 1 % (n/N)	Month 3 % (n/N)	Month 6 % (n/N)	Month 7.5 % (n/N)	Month 9 % (n/N)	Month 12 % (n/N)	Month 14 % (n/N)	Month 17 % (n/N)
Cohort 1 (200 µg)	**100%** (6/6)	**67%** (4/6)	**50%** (3/6)	**50%** (3/6)	**50%** (3/6)	NA	NA	NA
Cohort 2 (400 µg)	**86%** (6/7)	**71%** (5/7)	**57%** (4/7)	**43%** (3/7)	**43%** (3/7)	**29%** (2/7)	**29%** (2/7)	**14%** (1/5)
Cohort 3a (600 µg)	**100%** (6/6)	**83%** (5/6)	**83%** (5/6)	**50%** (3/6)	**17%** (1/6)	**20%** (1/5)*	**50%** (1/2)*	**100%** (1/1)*
Cohort 3b (400 µg + anti-VEGF)	**100%** (4/4)	**100%** (4/4)	**50%** (2/4)	**50%** (2/4)	**33%** (1/3)*	**0%** (0/2)*	**0%** (0/2)*	TBD
All Cohorts (Pooled)	**96%** (22/23)	**78%** (18/23)	**61%** (14/23)	**48%** (11/23)	**36%** (8/22)*	**21%** (3/14)*	**27%** (3/11)*	**33%** (2/6)*

Rescue Criterion:

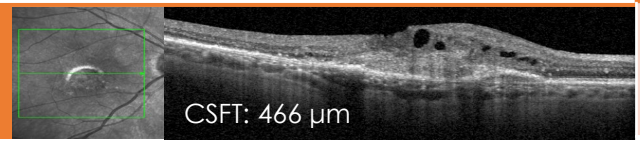
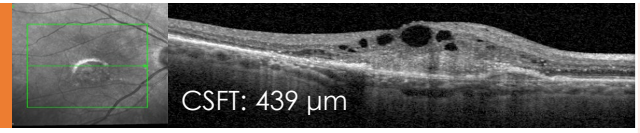
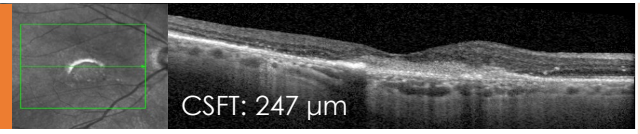
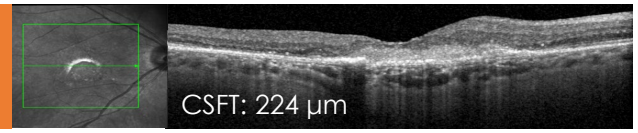
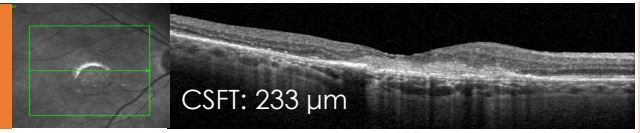
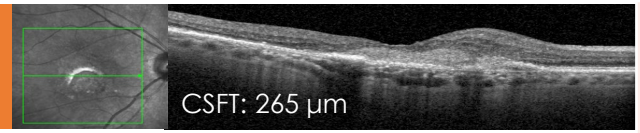
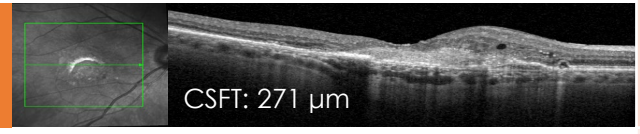
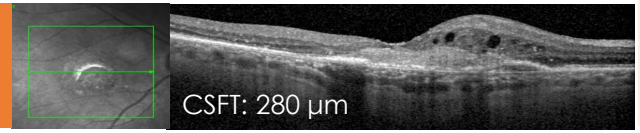
- If needed, any subject in any treatment arm may receive rescue therapy (i.e., anti-VEGF) at the Investigator's discretion
- The following criteria used to identify subjects who will likely require rescue therapy:
  - i. Loss of ≥ 15 letters from best previous BCVA due to AMD, with current BCVA not better than baseline; or
  - ii. Loss of ≥ 10 letters on 2 consecutive visits from best previous BCVA due to AMD, with current BCVA score not better than baseline
  - iii. Evidence of worsening disease activity manifest by greater than 75 microns CSFT from previous best value

If subjects received rescue anti-VEGF therapy at a study visit, they were counted as rescued at the following study visit in the table above.
* Follow-up is ongoing
NOTE: Interim review, unmonitored data; Data cut off January 11, 2022

SD-OCT Evaluation: Cohort 3

Cohort 3a (600µg): Subject 1 (OS): Treatment Naïve Subject		BCVA
Baseline		56 (20/80)
Month 2		74 (20/30)
Month 3		73 (20/40)
Month 6		80 (20/25)
Month 9		81 (20/25)
Month 11		76 (20/30)
Month 14		70 (20/40)
Month 15		60 (20/63)

Month 6

Cohort 3a (600µg): Subject 6 (OD): Treatment Naïve Subject		BCVA	
Baseline		28 (20/320)	
Month 1		28 (20/320)	
Month 2		30 (20/252)	Received anti-VEGF at Month 1
Month 3		31 (20/250)	
Month 4.5		30 (20/250)	
Month 6		27 (20/320)	
Month 7.5		40 (20/160)	
Month 10		41 (20/160)	

Month 6

NOTE: Interim review, unmonitored data; Data cut off January 11, 2022

SD-OCT Evaluation: Cohort 2 and 3

Cohort 2 (400µg): Subject 1 (OD): History of Aflibercept Q4 Weeks for 16 months		BCVA	
Baseline	CSFT: 473 µm	87 (20/18)	
Month 2	CSFT: 368 µm	88 (20/20)	
Month 3	CSFT: 337 µm	88 (20/20)	
Month 6	CSFT: 234 µm	89 (20/17)	
Month 9	CSFT: 272 µm	88 (20/20)	
Month 15.5	CSFT: 372 µm	90 (20/15)	OTX-TKI Implants No Longer Visualized at Month 15.5

Month 6

Cohort 3b (400µg + Anti-VEGF): Subject 1 (OD): Treatment Naïve Subject		BCVA	
Baseline	CSFT: 423 µm	39 (20/160)	
Month 2	CSFT: 290 µm	54 (20/80)	
Month 3	CSFT: 283 µm	52 (20/100)	
Month 6	CSFT: 402 µm	52 (20/100)	
Month 7.5	CSFT: 383 µm	46 (20/125)	
Month 9	CSFT: 417 µm	38 (20/200)	
Month 10.5	CSFT: 426 µm	35 (20/200)	Received anti-VEGF at Month 10.5

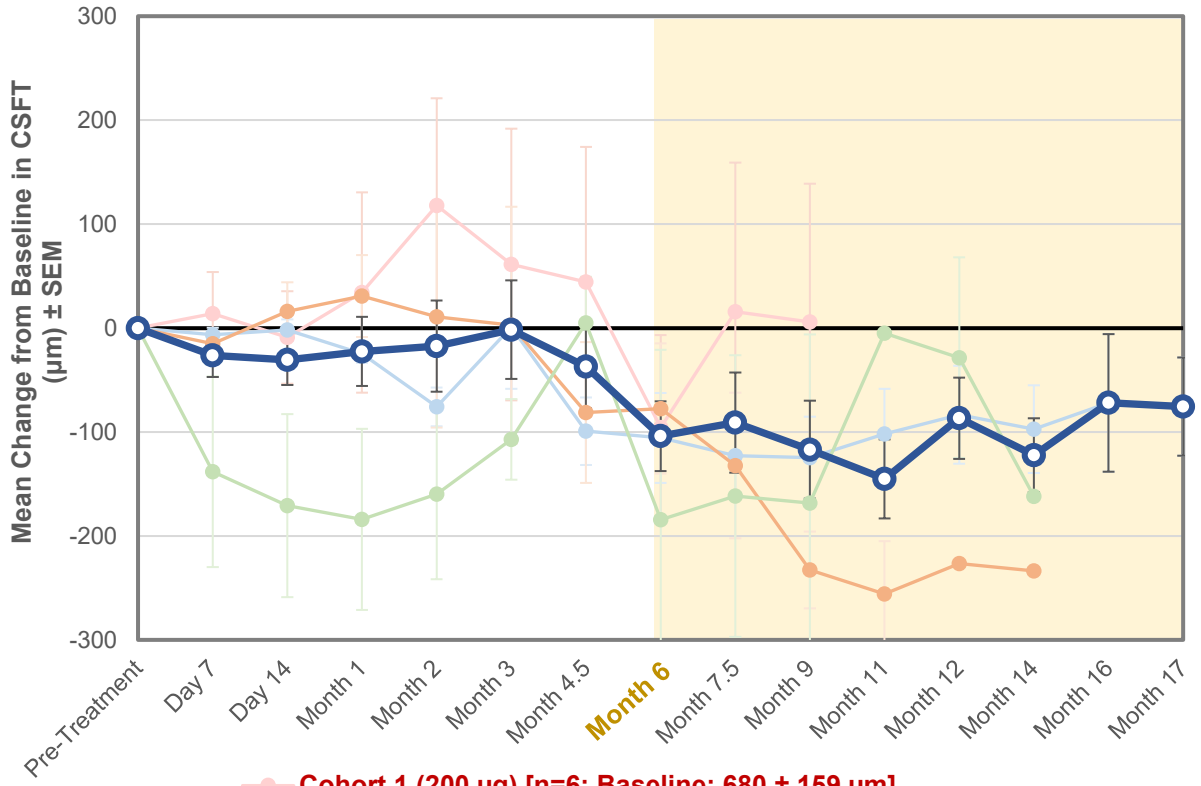
Month 6

NOTE: Interim review, unmonitored data; Data cut off January 11, 2022

Interim Results for All Subjects: Central Subfield Thickness and Visual Acuity

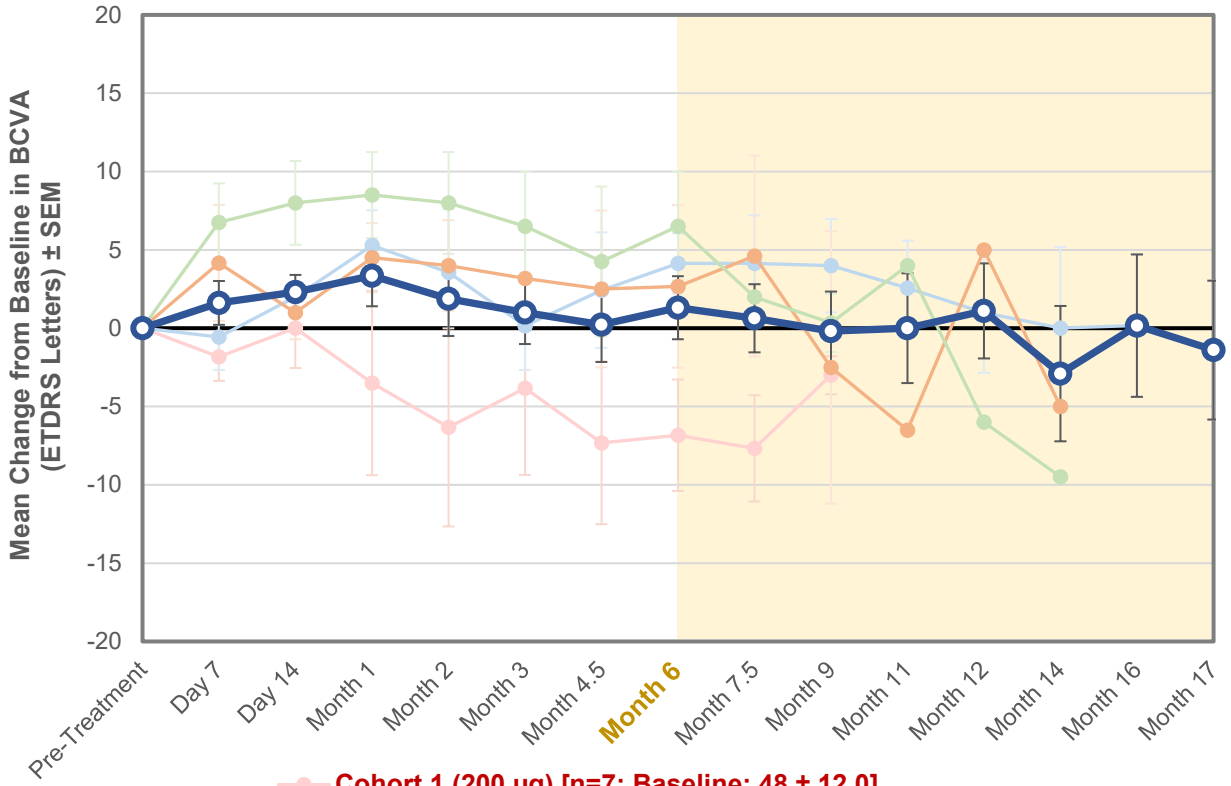
Effective control of retinal fluid and vision demonstrating sustained activity over time

Change from Baseline in CSFT



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]
All Cohorts (Pooled) [n=23; Baseline: 526.3 ± 48.9 µm)

Change from Baseline in BCVA



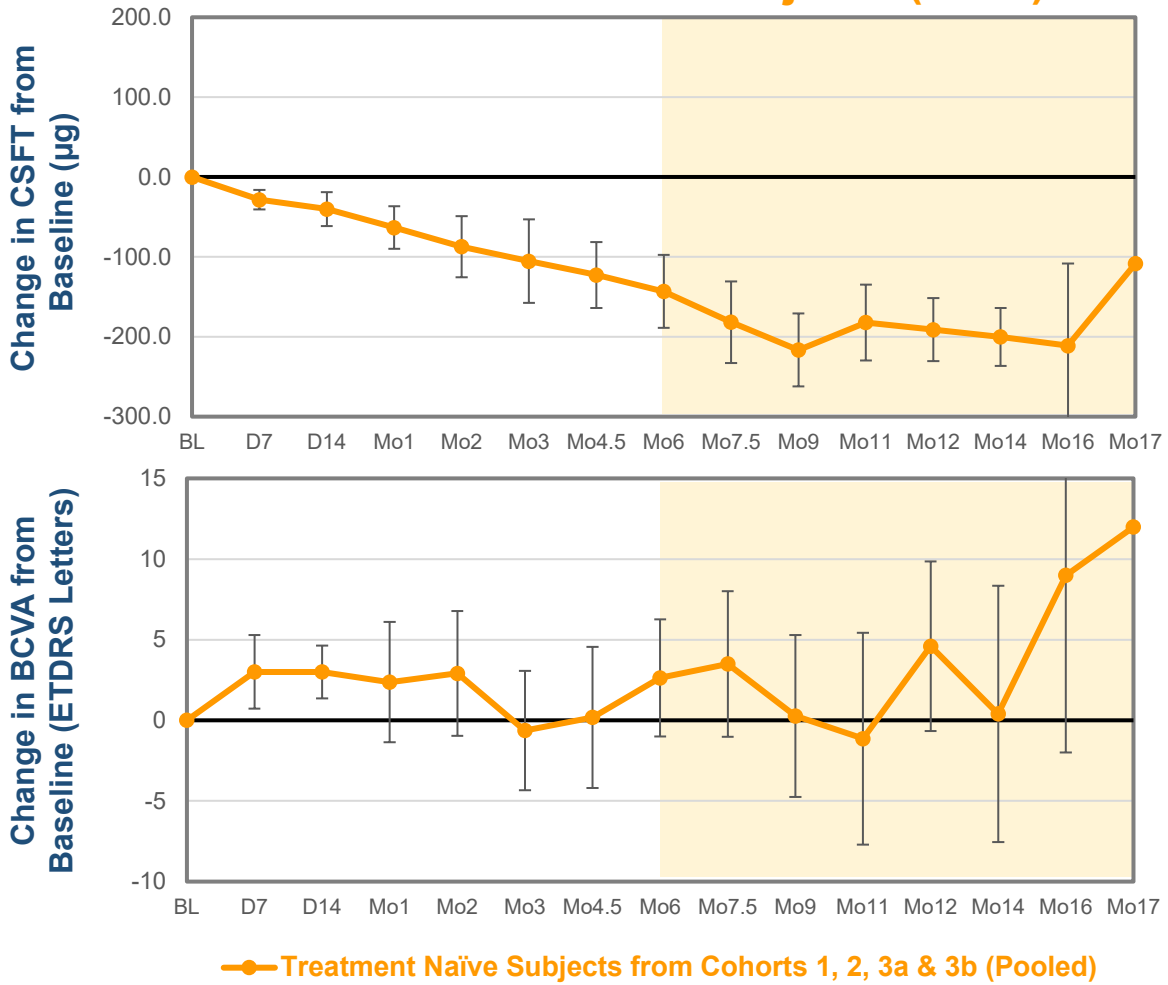
Cohort 1 (200 µg) [n=7; Baseline: 48 ± 12.0]
Cohort 2 (400 µg) [n=7; Baseline: 62 ± 8.5]
Cohort 3a (600 µg) [n=6; Baseline: 46 ± 6.4]
Cohort 3b (400 µg + Anti-VEGF) [n=4; Baseline: 47 ± 11.8]
All Cohorts (Pooled) [n=23; Baseline: 51.3 ± 4.7]

Cohort 1: n=6 until Month 9; Cohort 2: n=7 until Month 12, n=6 for Month 14, n=5 for Month 16 and 17
Cohort 3a: n=6 until Month 11, n=5 for Month 12, n=2 for Month 14, n=1 for Month 16 and 17; Cohort 3b: n=4 until Month 7.5; n=3 for Month 9, n=2 for Month 11 to 14; n=1 for Month 16
All BCVA and CSFT values compared to baseline visit; NOTE: Interim review, unmonitored data; Data cut off January 11, 2022

Interim Results for All Subjects: Central Subfield Thickness and Visual Acuity

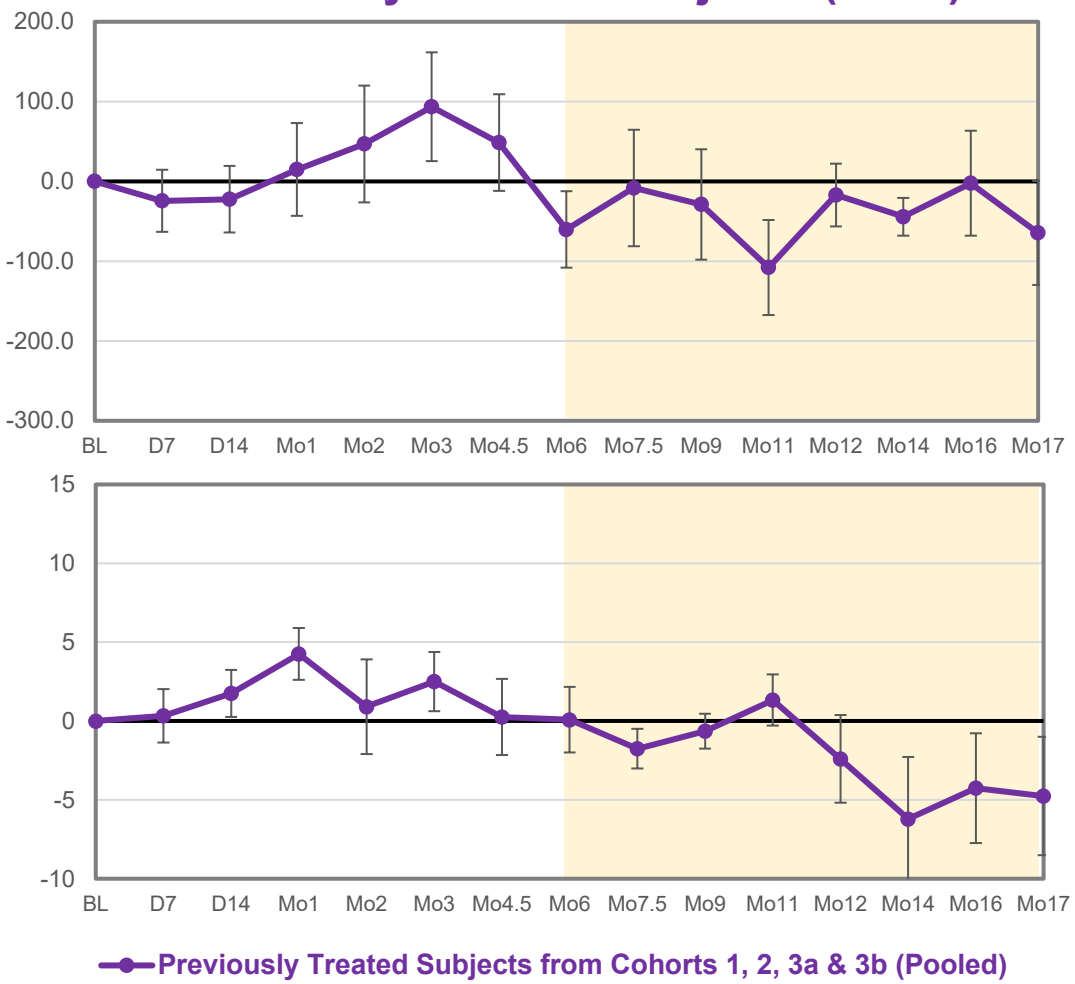
Evidence of biological activity with axitinib in treatment naïve subjects

Treatment Naïve Subjects (n=11)



Treatment Naïve Subjects from Cohorts 1, 2, 3a & 3b (Pooled)

Previously Treated Subjects (n=12)



Previously Treated Subjects from Cohorts 1, 2, 3a & 3b (Pooled)

All BCVA and CSFT values compared to baseline visit. Baseline CSFT and BCVA ± SEM for treatment naïve subjects was 571 ± 88.7 µm and 46 ± 5.6 letters, respectively. Baseline CSFT and BCVA ± SEM for previously treated subjects was 485 ± 47.6 µm and 57 ± 7.4 letters, respectively.
NOTE: Interim review, unmonitored data; Data cut off January 11, 2022

Safety and Tolerability

OTX-TKI has been generally well tolerated and observed to have a favorable safety profile

- ***No ocular serious adverse events (SAEs) reported***
- ***No reports of significant adverse events such as:***
  - No endophthalmitis
  - No retinal detachment
  - No implant migration into the anterior chamber
  - No elevated IOP
  - No retinal vasculitis

Number of AEs Reported in the Study Eye	Cohort 1 200 µg (1 x 200µg implant) n=6	Cohort 2† 400 µg (2 x 200µg implants) n=7	Cohort 3a† 600 µg (3 x 200µg implants) n=6	Cohort 3b† 400 µg + anti-VEGF (2 x 200µg implants) n=4	Total n=23
Vitreous floaters	0	1	0	1	2
Endophthalmitis	0	0	0	0	0
Retinal detachment	0	0	0	0	0
Implant migration into AC	0	0	0	0	0
Elevated IOP	0	0	0	0	0
Ocular inflammation	0	0	0	1	1
Subconjunctival hemorrhage	1	3	5	3	12
Eye pain	0	2	2	0	4
Pigmented keratic precipitates	3	0	0	0	3

AEs in > 2 subjects

† Follow-up is ongoing

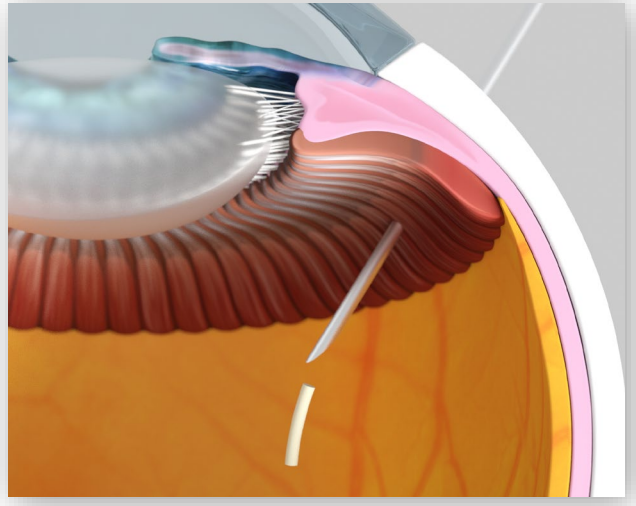
NOTE: Interim review, unmonitored data; Data cut off January 11, 2022

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 60% of all subjects showed durability of 6 months or longer (including over 80% in the 600 µg group) and approximately 50% of subjects showed durability of 7.5 months or longer
- **Consistent bio-resorption observed**
  - Implant biodegraded in Cohort 1 (single implant) 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 January 11, 2022

OTX-TKI Phase 1b Study in the US

Prospective, multi-center, double-masked, parallel-group study

Status

- Actively enrolling

Key Inclusion Criteria

- Active primary sub foveal neovascularization secondary to AMD
- **No active fluid**

Objectives

- Safety, tolerability, durability and biological activity
- BCVA, mean change in central subfield thickness (CSFT) measured by SD-OCT and safety evaluations at all visits

Key Differences in Study Design:

	US Phase 1b Study	Australia Phase 1 Study
Inclusion Criteria	**No active fluid**	Presence of retinal fluid
OTX-TKI Implant	**One 0.6 mg (600 µg) single implant**	Cohorts 1-3 used one to three 0.2 mg (200 µg) implants to achieve different dose levels (0.2, 0.4 and 0.6 mg)
Anti-VEGF Induction	**Yes, all subjects**	Only in Cohort 3b and 4b