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

A Phase 1 Trial Update

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Disclosures

Study Disclosures

- Sponsorship for the clinical trial: Ocular Therapeutix, Inc.

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)
- Therapy durability of 10 months observed in 400 µg Cohort 2 in some patients and one subject in 600 µg Cohort 3a demonstrated durability of therapy for up to 6 months (follow-up ongoing)

*NOTE: Interim review, unmonitored data; Data cut on January 29, 2021

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

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 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) exhibits high potency and selectivity compared to other TKIs (e.g., sunitinib, sorafenib and pazopanib)[2]
  - Inhibitory concentrations (IC50 in nmol) for targets with multitargeted TKIs (table below)[2]

Drug	VEGFR1	VEGFR2	VEGFR3	PDGFR α	PDGFR β
Axitinib	**0.1**	**0.2**	**0.1-0.3**	**5**	**1.6**
Paxopanib	10	30	47	71	84
Sunitinib	10	10	10	5-10	10
Sorafenib	Not available	90	20	50-60	50-60

- Lower doses of Axitinib may minimize the TKI class-related adverse events resulting from systemic drug concentrations[3]

1. Zhao Y, Adjei AA. Targeting Angiogenesis in Cancer Therapy: Moving Beyond Vascular Endothelial Growth Factor. *Oncologist*. 2015;20(6):660-673.
2. 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. (Table adapted from manuscript)
3. Giddabasappa A, Lalwani K, Norberg R, et al. Axitinib inhibits retinal and choroidal neovascularization in in vitro and in vivo models. Experimental Eye Research. 2016;145:373-379. doi:10.1016/j.exer.2016.02.010

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

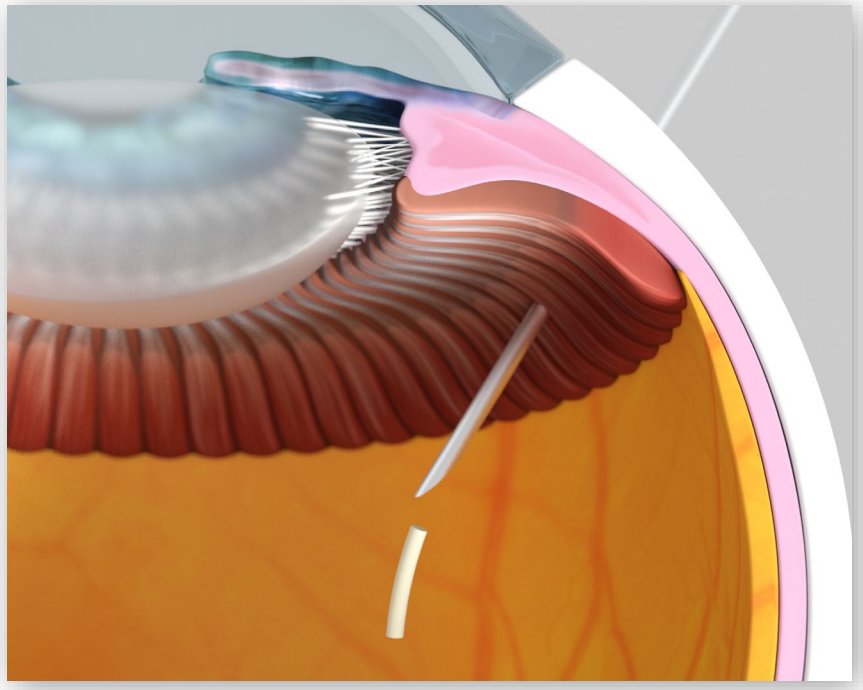
BIODEGRADABLE

- 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 Design

DESIGN

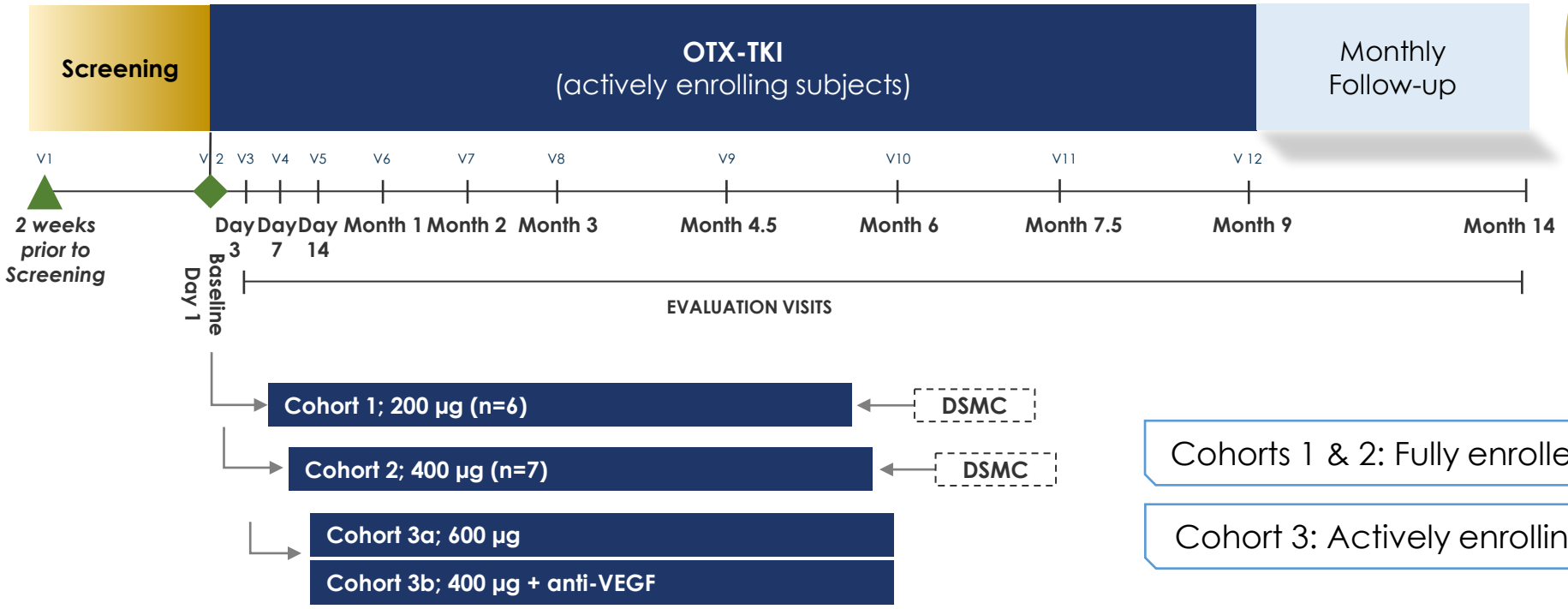
- Open-label, dose-escalation, feasibility study
- 5 sites in Australia
- One eye per patient treated
- Key Inclusion criteria:
  - Active primary sub foveal neovascularization (SFNV) secondary to AMD – previously treated or naïve subjects but with retinal fluid present

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: Fully enrolled

Cohort 3: Actively enrolling

*NOTE: Interim review, unmonitored data; Data cut on January 29th, 2021

Subject Demographics

Age, Mean ± SD
76 ± 4.6 years

Prior Treatment, n (%)
14 (70%) Prior Anti-VEGF Therapy
6 (30%) Treatment Naïve

Sex, n (%)
14 (70%) Males
6 (30%) Females

Baseline CSFT, Mean ± SE
554 ± 237 µm
Cohort 1 (n=6): 680 ± 159 µm
Cohort 2 (n=7): 450 ± 29 µm
Cohort 3 (n=7): 526 ± 60 µm

Time from Diagnosis to OTX-TKI Injection, Mean ± SD
1.9 ± 2.9 years

Mean Baseline BCVA (Snellen equivalent), Mean ± SE
0.68 (20/96) ± 0.47
Cohort 1 (n=6): 0.73 ± 0.26
Cohort 2 (n=7): 0.47 ± 0.17
Cohort 3 (n=7): 0.85 ± 0.35

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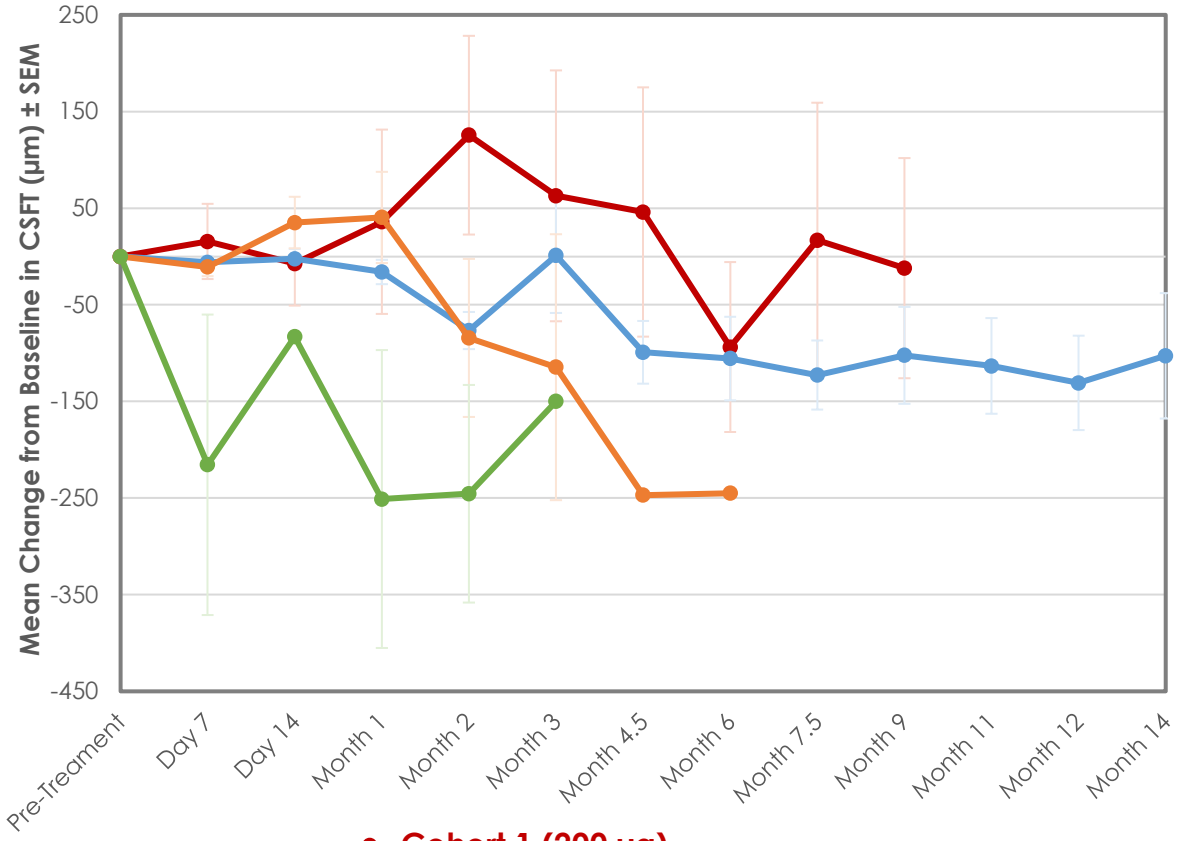
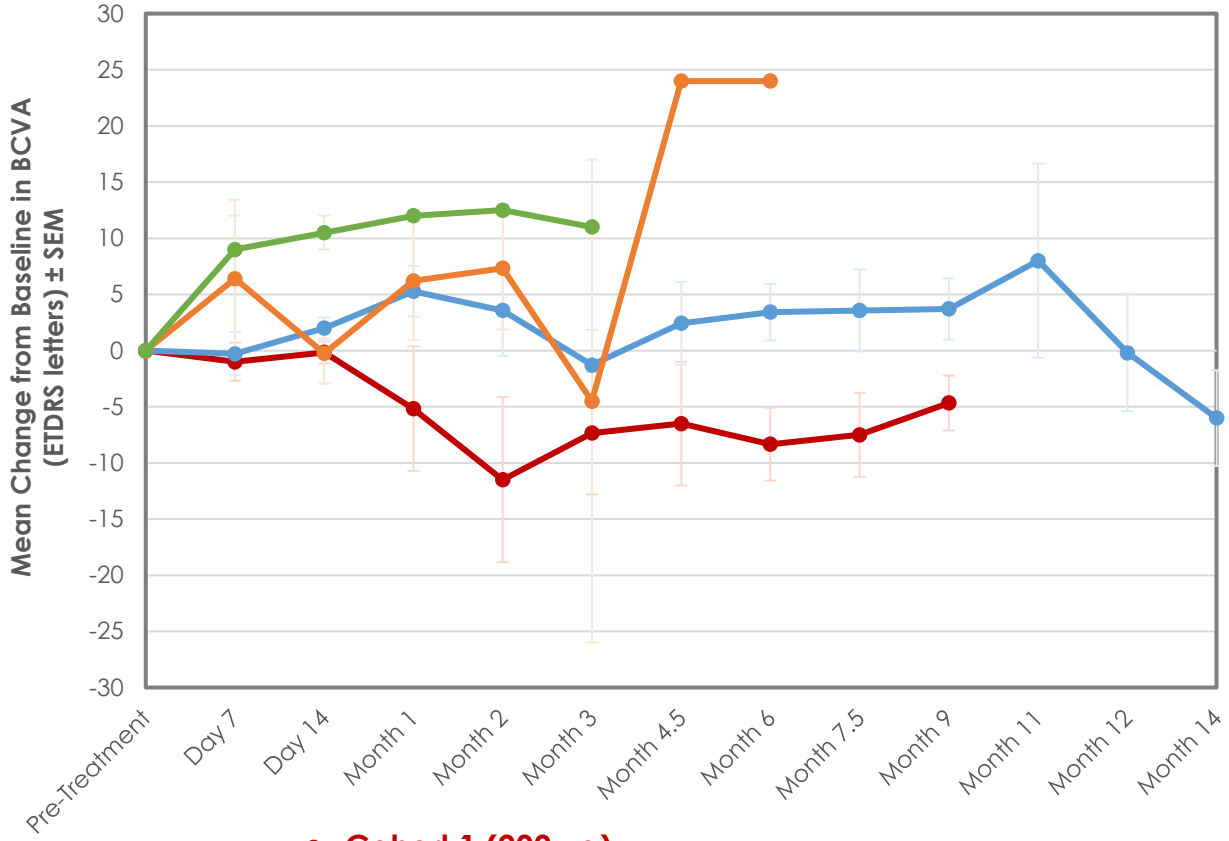
All Cohorts: Mean Change in CSFT and BCVA

Change from Baseline in CSFT



Change from Baseline in BCVA



Cohort 1: n=6 until Month 9; Cohort 2: n=7 until Month 9; n=6 for Month 11; n=6 for Month 12; n=4 for Month 14
Cohort 3a: n=5 until Month 1; n=3 for Month 2; n=2 for Month 3; n=1 for Months 4.5 & 6; Cohort 3b: n=2 until Month 2; n=1 until Month 3
*All BCVA and CSFT values compared to Baseline visit; NOTE: Interim review, unmonitored data; Data cut on January 29, 2021

SD-OCT Evaluation

Cohort 2 (400µg): Subject 1 (OD): History of Aflibercept Q4 Weeks for 16 months

		BCVA
BASELINE	CSFT: 473 µm	-0.04 (20/18)
MONTH 2	CSFT: 368 µm	-0.06 (20/17)
MONTH 3	CSFT: 337 µm	-0.06 (20/17)
MONTH 6	CSFT: 234 µm	-0.08 (20/17)
MONTH 9	CSFT: 272 µm	-0.06 (20/17)
MONTH 11	CSFT: 275 µm	0.02 (20/21)
MONTH 13.5	CSFT: 375 µm	-0.12 (20/15)

Cohort 3a (600µg): Subject 1 (OS): Treatment Naïve Subject

		BCVA
BASELINE	CSFT: 484 µm	0.58 (20/76)
MONTH 2	CSFT: 236 µm	0.22 (20/33)
MONTH 3	CSFT: 232 µm	0.24 (20/40)
MONTH 4.5	CSFT: 237 µm	0.1 (20/25)
MONTH 6	CSFT: 239 µm	0.1 (20/25)

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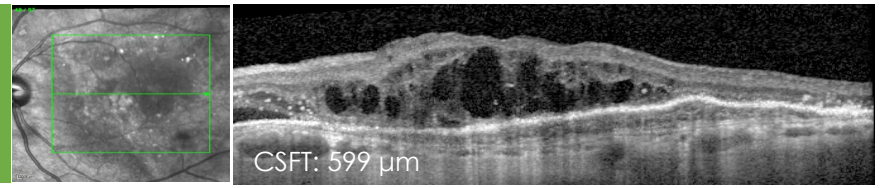
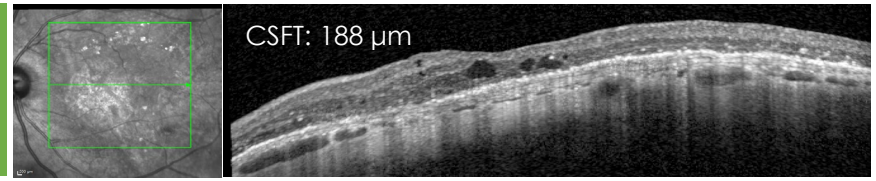
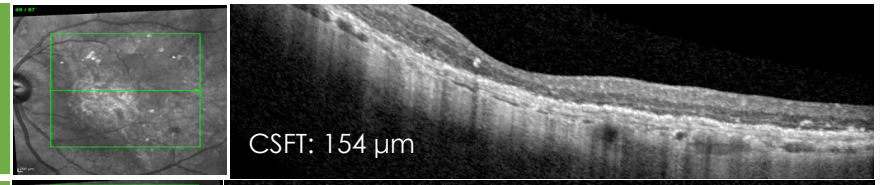
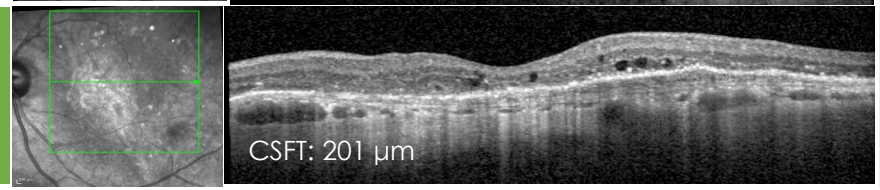
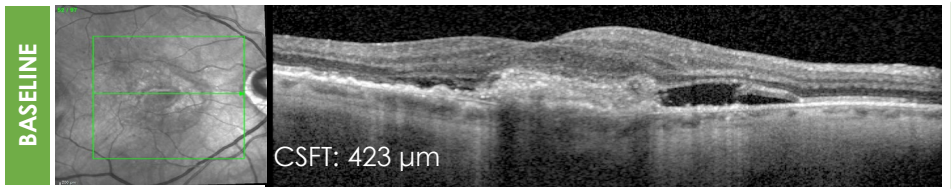
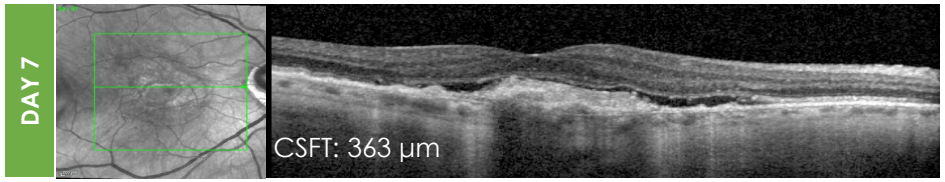
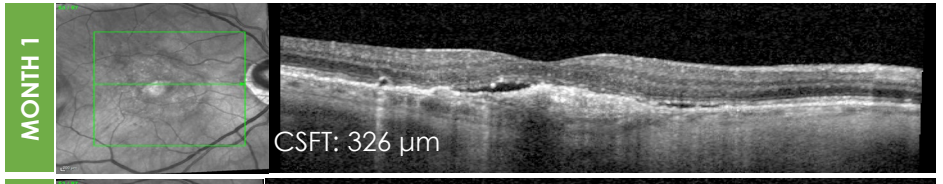
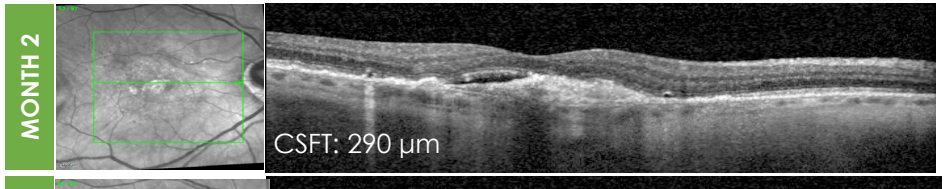
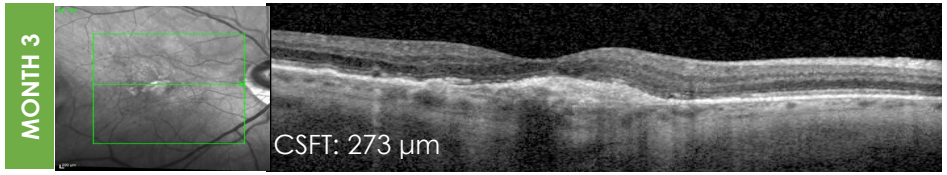
SD-OCT Evaluation (Cont.)

Cohort 3b (400µg + Anti-VEGF): Subject 2 (OS): History of Anti-VEGF therapy ~Q7 Weeks for 7 Months

		BCVA
BASELINE		1.34 (20/438)
DAY 7		1.1 (20/252)
MONTH 1		1.1 (20/252)
MONTH 2		1.1 (20/252)

Cohort 3b (400µg + Anti-VEGF): Subject 1 (OD): Treatment Naïve Subject

		BCVA
BASELINE		0.88 (20/152)
DAY 7		0.76 (20/115)
MONTH 1		0.64 (20/87)
MONTH 2		0.62 (20/83)
MONTH 3		0.66 (20/91)

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Overview of Safety and Tolerability

No subjects had IOP elevation, and no subject needed ocular steroids

Number of subjects with:	Cohort 1 200 µg n=6	Cohort 2* 400 µg n=7	Cohort 3a* 600 µg n=5	Cohort 3b* 400 µg + Anti-VEGF n=2	Total n=20
Adverse Events (AEs)	14	20	8	3	45
Ocular AEs	12	13	7	2	34
Ocular AEs (Study Eye)	7	11	5	2	25
Serious Ocular AEs	0	0	0	0	0
By severity					
Mild	12	16	8	3	39
Moderate	2	4	0	0	6
Severe	0	0	0	0	0
Treatment-related Ocular AEs	1	2	0	0	3

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

* Follow-up ongoing
NOTE: Interim review, unmonitored data; Data cut on January 29, 2021

Duration of Effect

Percentage of Subjects Without Needing Rescue Medications

Extended Follow-up

Cohorts	At 3 months % (n/N)	At 6 months % (n/N)	At 7.5 months % (n/N)	At 9 months % (n/N)	At 11 months % (n/N)	At 13.5 months % (n/N)
Cohort 1 (200 µg)	**66.7** (4/6)	**50** (3/6)	**50** (3/6)	**50** (3/6)	NA	NA
Cohort 2 (400 µg)*	**71.4** (5/7)	**57.1** (4/7)	**42.9**(3/7)	**42.9** (3/7)	**33.3**(2/6)*	**25** (1/4)*
Cohort 3a (600 µg)*	**100** (2/2)	**100** (1/1)	TBD	TBD	TBD	TBD
Cohort 3b (400 µg + anti-VEGF)*	**100** (1/1)	TBD	TBD	TBD	TBD	TBD

*Follow-up ongoing

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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 Cohorts 2 (400 µg) & 3a (600 µg)
  - Combination of OTX-TKI + Anti-VEGF (Cohort 3b) showed a decrease in intraretinal or subretinal fluid immediately, as early as a week after treatment in two subjects
- **Therapy durability suggests extended duration of action (follow-up ongoing)**
  - Cohort 2 (400 µg): Several subjects demonstrated durability of therapy for up to 10 months and one subject demonstrated durability to 13.5 months
  - Cohort 3a (600 µg): One subject demonstrates durability of therapy for up to 6 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

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