Phase 1 Study of an Intravitreal Axitinib Hydrogel-based Implant for the Treatment of Neovascular Age-Related Macular Degeneration (nAMD)

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Financial Disclosures

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

Unmet Need in Neovascular AMD Treatment

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]

UNMET NEED

Longer Duration of Action
&
Novel Mechanism of Action

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[6,7]
- Axitinib acts intracellularly and interferes with cellular signaling through inhibition of the receptor tyrosine kinases[7]
- Lower doses of Axitinib (at nanomolar concentrations) exhibits high potency and selectivity compared to other TKIs (e.g., sunitinib, sorafenib and pazopanib)[7]
- Lower doses of Axitinib may minimize the TKI class-related adverse events resulting from systemic drug concentrations[8]
- Axitinib has low water solubility[9] compared to other TKIs (e.g., sunitinib, pazopanib, nintedanib),[10-12] allowing for controlled drug release

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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

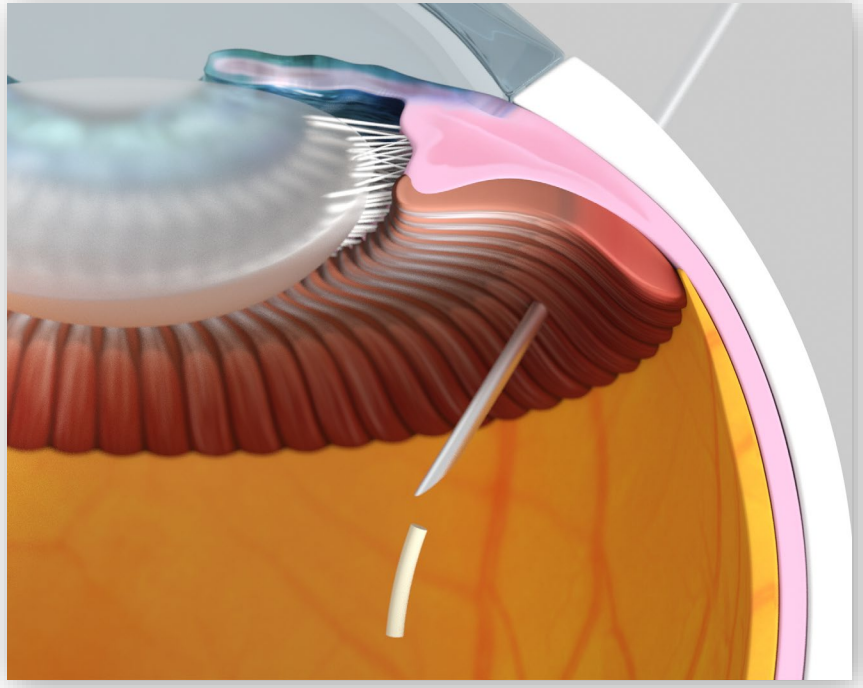
- Potential for broader anti-angiogenic profile compared to anti-VEGF agents
- Systemic TKI efficacy established in oncology

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

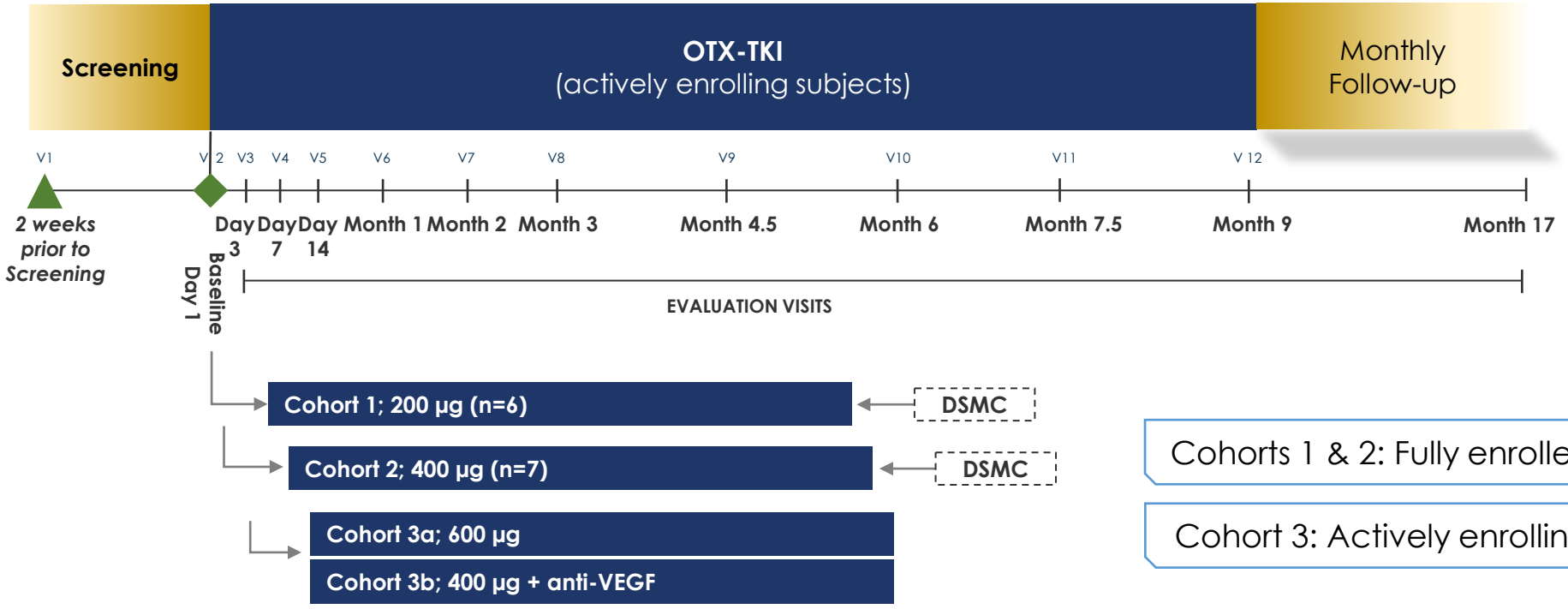
- Open-label, dose-escalation, feasibility study
- 5 sites in Australia
- One eye per patient treated
- Key Inclusion criteria:
  - Active primary sub foveal neovascularization (SFNV) secondary to AMD – previously treated or naïve subjects but with retinal fluid present

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?



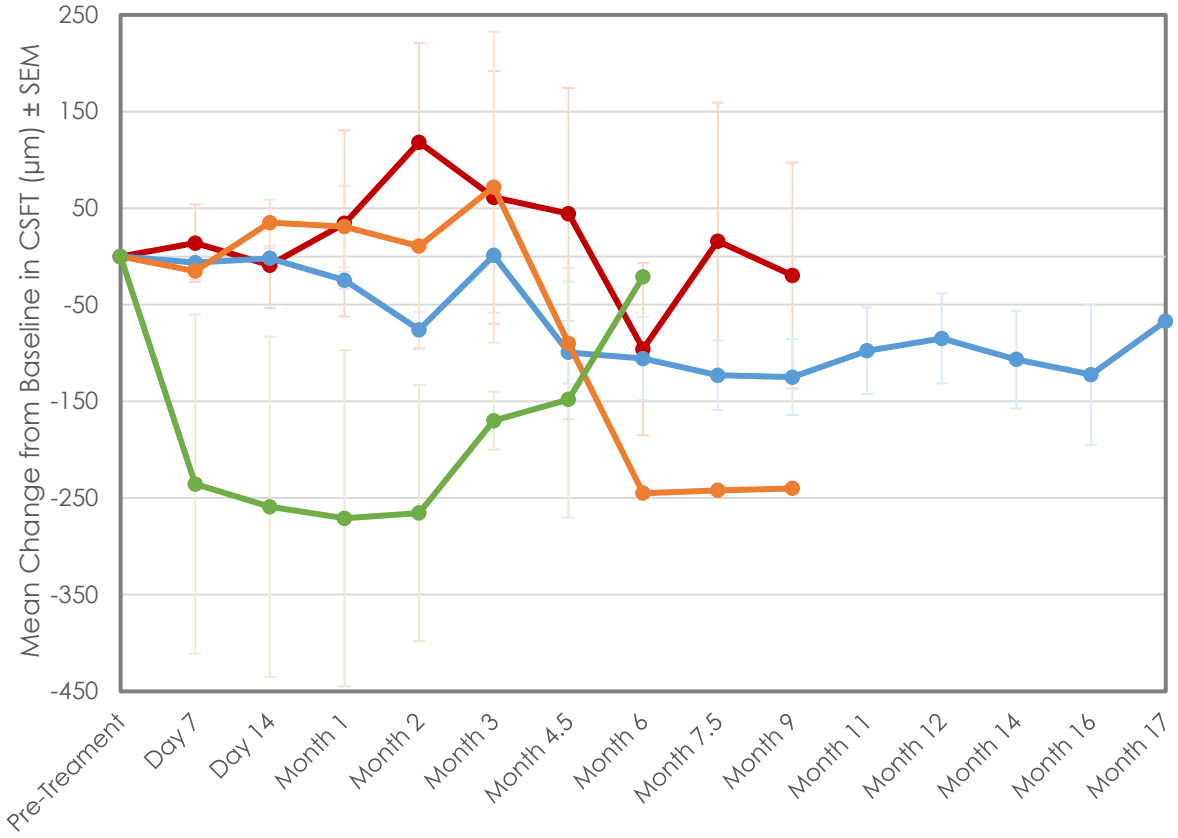
Cohorts 1 & 2: Fully enrolled

Cohort 3: Actively enrolling

*NOTE: Interim review, unmonitored data; Data cut on April 12th, 2021

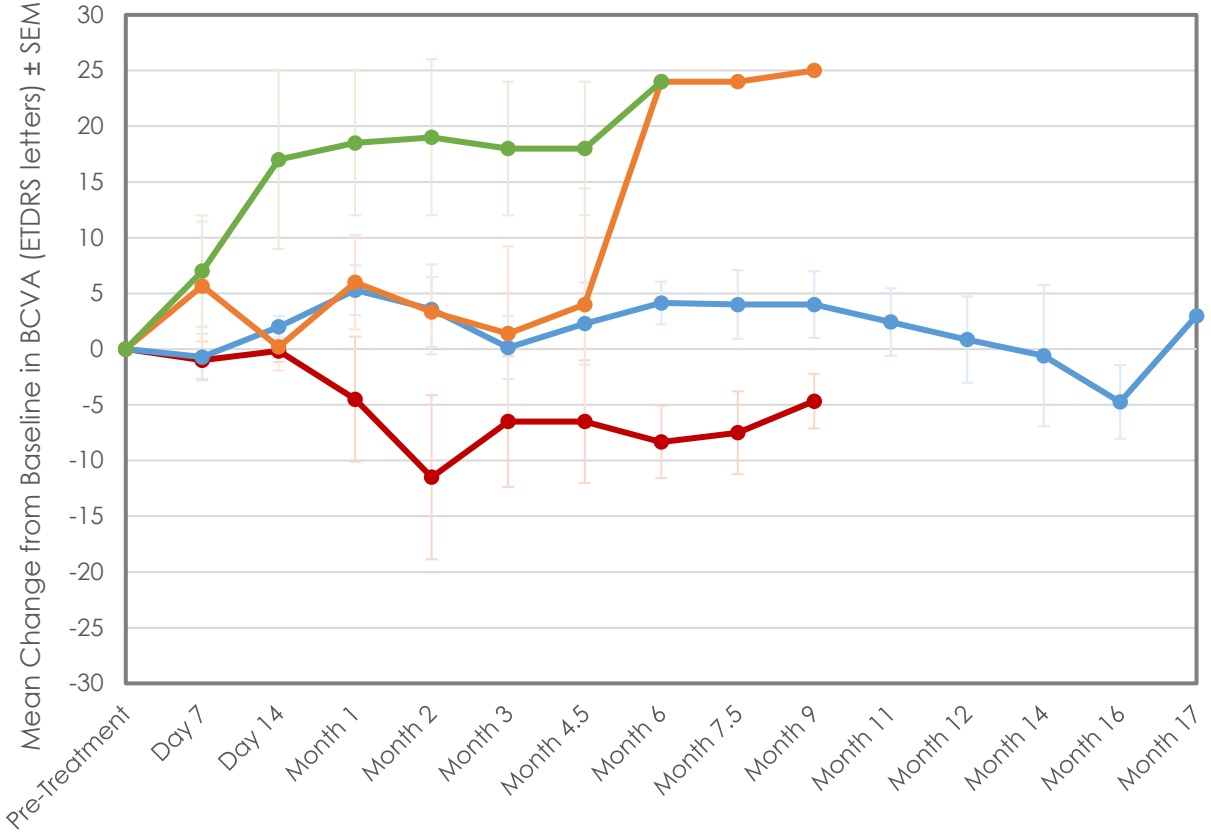
Interim Results: Mean Change in CSFT & BCVA in All Cohorts

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=2; Baseline: 511 ± 88 µm]

CHANGE FROM BASELINE IN BCVA



Cohort 1 (200 µg) [n=7; Baseline: 48 ± 13]
Cohort 2 (400 µg) [n=6; Baseline: 62 ± 8.5]
Cohort 3a (600 µg) [n=6; Baseline: 44 ± 6.8]
Cohort 3b (400 µg + Anti-VEGF) [n=2; Baseline: 23 ± 5]

Cohort 1: n=6 until Month 9; Cohort 2: n=7 until Month 12, n=5 for Month 14, n=4 for Month 16 & n=1 for Month 17
Cohort 3a: n=6 until Month 2, n=4 for Months 3; n=3 for Month 4.5 & n=1 until Month 9; Cohort 3b: n=2 until Month 4.5; n=1 for Month 6
*All BCVA and CSFT values compared to Baseline visit; NOTE: Interim review, unmonitored data; Data cut on April 12th, 2021

SD-OCT Evaluation: Cohort 3

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)
MONTH 7.5	CSFT: 242 µm	0.1 (20/25)
MONTH 9	CSFT: 244 µm	0.08 (20/24)

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

		BCVA
BASELINE	CSFT: 423 µm	1.14 (20/252)
DAY 7	CSFT: 363 µm	1.1 (20/252)
MONTH 1	CSFT: 326 µm	0.64 (20/87)
MONTH 2	CSFT: 290 µm	0.62 (20/83)
MONTH 3	CSFT: 283 µm	0.66 (20/91)
MONTH 4.5	CSFT: 397 µm	0.66 (20/91)
MONTH 6	CSFT: 402 µm	0.66 (20/91)

NOTE: Interim review, unmonitored data; Data cut on April 12th, 2021

SD-OCT Evaluation: Cohort 2

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 2 (400µg): Subject 2 (OS): Treatment Naïve Subject

		BCVA
BASELINE	CSFT: 513 µm	1.40 @ 1m (20/502)
MONTH 2	CSFT: 348 µm	1.40 @ 1m (20/502)
MONTH 3	CSFT: 316 µm	1.48 @ 1m (20/604) **Rescued at Month 4.5**
MONTH 6	CSFT: 236 µm	1.34 @ 1m (20/438) **Rescued at Month 6 & 7.5**
MONTH 9	CSFT: 194 µm	1.44 @ 1m (20/551)
MONTH 11	CSFT: 212 µm	1.44 @ 1m (20/551)
MONTH 16	CSFT: 199 µm	1.44 @ 1m (20/551)

*NOTE: Interim review, unmonitored data; Data cut on April 12th, 2021; BCVA presented in logMAR format with Snellen equivalent in parenthesis

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=6	Cohort 3b* 400 µg + Anti-VEGF n=2	Total n=21
Adverse Events (AEs)	14	24	16	3	57
Suspected Relationship to Study Product	1	2	1	0	4
Suspected Relationship to Injection Procedure	1	4	10	2	17
Ocular AEs	12	16	13	2	43
Ocular AEs (Study Eye)	7	14	11	2	34
Serious Ocular AEs	0	0	0	0	0
By severity					
Mild	12	19	15	3	49
Moderate	2	5	1	0	8
Severe	0	0	0	0	0

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 April 12th 2021

Duration of Effect

OVER 50% OF SUBJECTS DID NOT RECEIVE RESCUE THERAPY OUT TO 6 MONTHS

Percentage of Subjects Without Needing Rescue Medications | **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)	**20** (1/5)*	**50** (1/1)*
Cohort 3a (600 µg)*	**83.3** (5/6)	**100** (4/4)*	**100** (1/1)*	**100** (1/1)*	**100** (1/1)*	TBD	TBD	TBD
Cohort 3b (400 µg + anti-VEGF)*	**100** (2/2)*	**100** (2/2)*	**50** (1/2)*	TBD	TBD	TBD	TBD	TBD

*Follow-up ongoing

*NOTE: Interim review, unmonitored data; Data cut on April 12th, 2021

Conclusions

- **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 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 12 months
  - Cohort 3: One subject demonstrates durability of therapy for up to 9 months in the 600 µg group & up to 6 months in the OTX-TKI + Anti-VEGF group
- **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

*NOTE: Interim review, unmonitored data; Data cut on April 12th, 2021