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Safety and Efficacy of OTX-TKI, a Novel Tyrosine Kinase Inhibitor Hydrogel Intravitreal Implant

Phase 1 Trial Interim Review

ANNUAL VIT BUCKLE SOCIETY MEETING | APRIL 2020

ROBERT L. AVERY, MD

Safety and Efficacy of OTX-TKI, a Novel Tyrosine Kinase Inhibitor Hydrogel Intravitreal Implant

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Unmet Need in Retinal Disease

Problem with Immediate-Release Injections

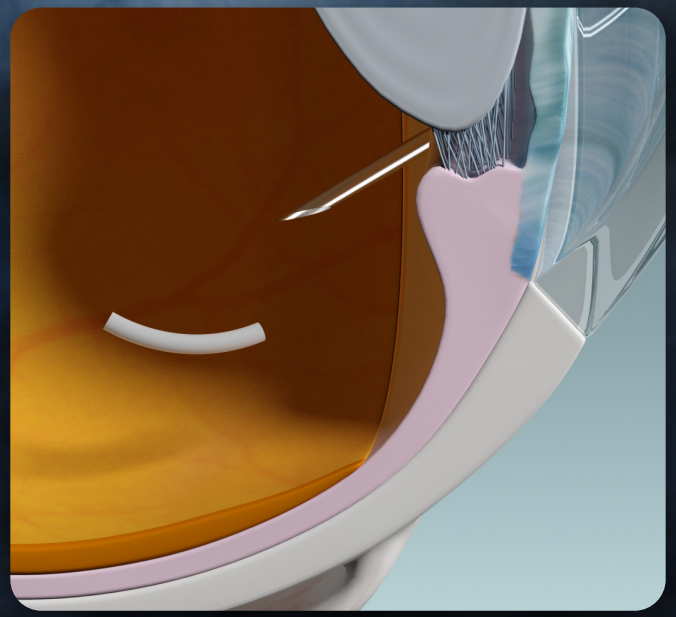
- Repeated intravitreal injections due to rapid vitreous clearance may cause side effects such as endophthalmitis, damage to the lens, and retinal detachment[1]
- Patient complaints include discomfort, eye pain, decreased vision, increased photosensitivity, and floaters[1]

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

- Polyethylene glycol-based hydrogel fiber containing TKI that biodegrades via ester hydrolysis in the presence of water
  - Targeting sustained TKI release for 3 to 6+ months
  - Hydrogel degrades and is cleared from the vitreous
- Broader anti-angiogenic profile than anti-VEGF alone and longer duration with sustained delivery
- Small fiber (27-30G needle) with minimal/no visual impact; product can be monitored by physician
- Preservative-free
- Systemic TKI efficacy established in oncology
- Different target than traditional VEGF therapies

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.

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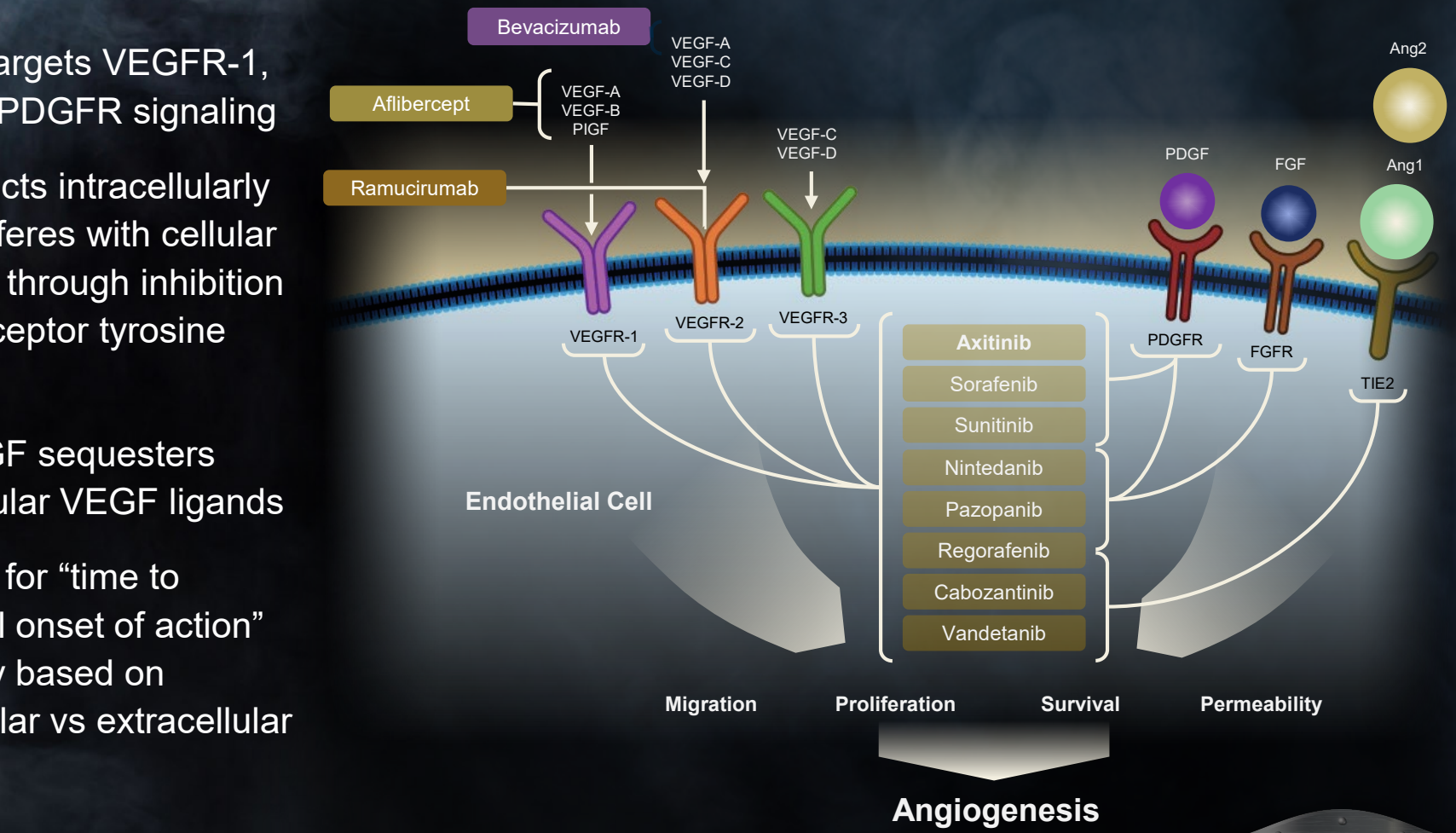
Tyrosine Kinase Inhibitors Act Directly on VEGF Receptors

- Axitinib targets VEGFR-1, 2, 3 and PDGFR signaling
- Axitinib acts intracellularly and interferes with cellular signaling through inhibition of the receptor tyrosine kinases
- Anti-VEGF sequesters extracellular VEGF ligands
- Potential for “time to biological onset of action” variability based on intracellular vs extracellular MOA



1. Zhao Y, Adjei AA. Targeting Angiogenesis in Cancer Therapy: Moving Beyond Vascular Endothelial Growth Factor. Oncologist. 2015;20(6):660-673. doi: 10.1634%2Ftheoncologist.2014-0465

OTX-TKI Phase 1 Study

DESIGN

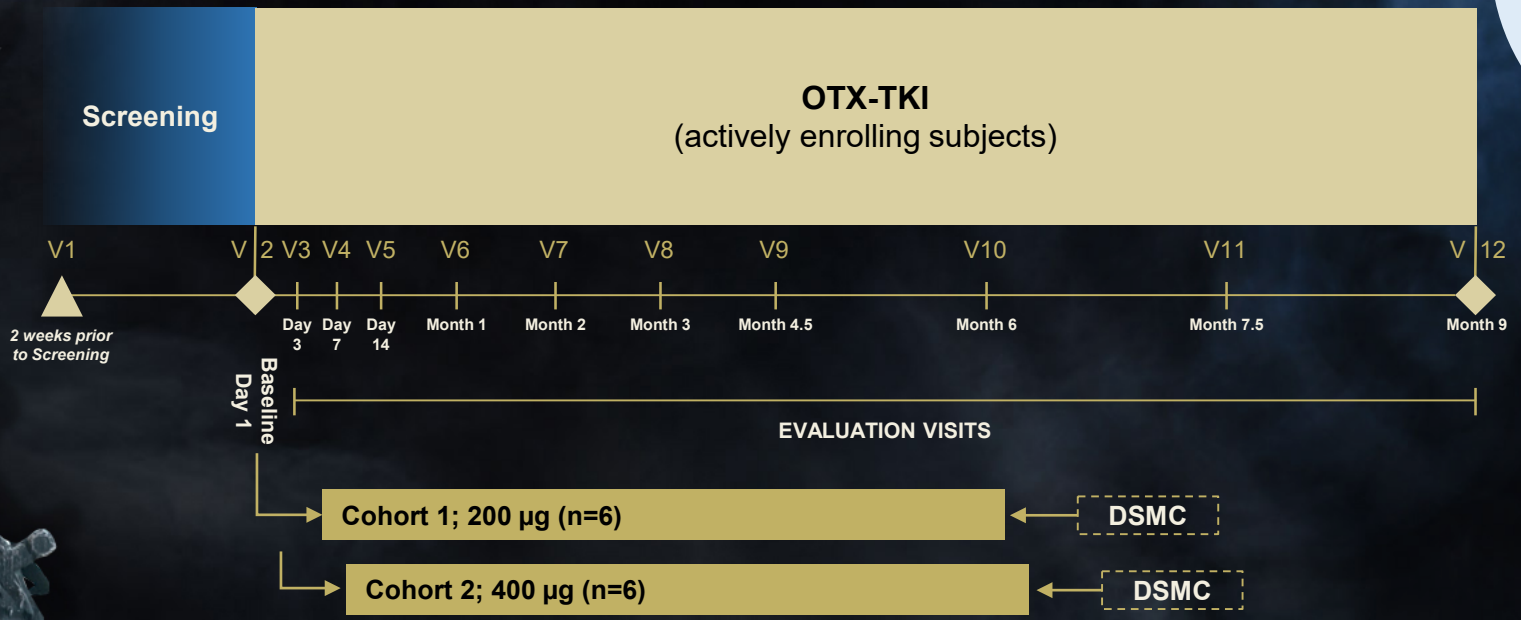
- Open-label, dose-escalation, feasibility study
- 5 sites in Australia
- 9-month study
- One eye per patient treated
- Key Inclusion criteria:
  - Active primary sub foveal neovascularization (SFNV) secondary to AMD – previously treated or naïve subjects but with retinal fluid present

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

Research Question:

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



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Cohort 1 & 2: Safety Overview

Total Adverse Events

Number of subjects with:	OTX-TKI 200 µg N=6	OTX-TKI 400 µg N=6	Total (N=12)
Adverse Events (AEs)	17	14	31
Ocular AEs	15	10	25
Serious Ocular AEs	0	0	0
By severity			
Mild	14	12	26
Moderate	3	2	5
Severe	0	0	0
Treatment-related AEs	2	1	3
Opacities around OTX-TKI implant	1	0	1
Tiny pigmented Keratic Precipitates*	1	0	1
Foreign material (fiber and reflective particles)	0	1	1

*Event did not require treatment

Interim look; Unmonitored data.

Cohort 1 & 2: Safety Overview

Ocular Adverse Events (Study Eye)

***To date, no iritis, vitritis, or retinitis has been observed in any subject**

No steroid treatment has been required

Number of subjects with:	OTX-TKI 200 µg N=6	OTX-TKI 400 µg N=6	Total (N=12)
Tiny pigmented Keratic Precipitates	3	0	3
Subconjunctival hemorrhage following injection	1	2	3
Subretinal hemorrhage	2	0	2
Pain following injection	0	2	2
Progressive/increased subretinal fluid	1	0	1
Discomfort/difficulty opening eyes upon waking	1	0	1
Dry eyes	1	0	1
Opacities around OTX-TKI implant	1	0	1
Visual distortion	0	1	1
Increased geographic atrophy	0	1	1
Vitreous floaters	0	1	1
Foreign material (fiber and reflective particles)	0	1	1

Interim look; Unmonitored data.

Cohort 1: SD-OCT Evaluation

Treatment Naïve Subject (OS)

		BCVA
BASELINE	CSFT: 1242 µm	1.14 @ 1m (20/276)
MONTH 2	CSFT: 997 µm	1.10 @ 1m (20/252)
MONTH 4.5	CSFT: 975 µm	1.04 @ 1m (20/219)
MONTH 6	CSFT: 947 µm	1.10 @ 1m (20/252)
MONTH 9	CSFT: 933 µm	1.12 @ 1m (20/264)

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Cohort 2: SD-OCT Evaluation

Subject 1: History of EYLEA Q4 Weeks (OD)

		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 4.5	CSFT: 224 µm	0.30 (20/40)
MONTH 5	CSFT: 225 µm	-0.02 (20/19)

Subject 2: Treatment Naïve Subject (OS)

		BCVA
BASELINE	CSFT: 513 µm	1.40 @ 1m (20/502)
MONTH 2	CSFT: 343 µm	1.40 @ 1m (20/502)
MONTH 3	CSFT: 316 µm	1.48 @ 1m (20/604)
MONTH 4.5	CSFT: 354 µm	1.36 @ 1m (20/458)

Cohort 2: SD-OCT Evaluation Continued

History of EYLEA Q4 Weeks (OS)

		BCVA	
BASELINE	CSFT: 448 µm	0.28 (20/38)	
MONTH 1	CSFT: 457 µm	0.26 (20/36)	
MONTH 2	CSFT: 383 µm	0.62 (20/83)	
MONTH 3	CSFT: 550 µm	0.54 (20/69)	Received rescue therapy (EYLEA)

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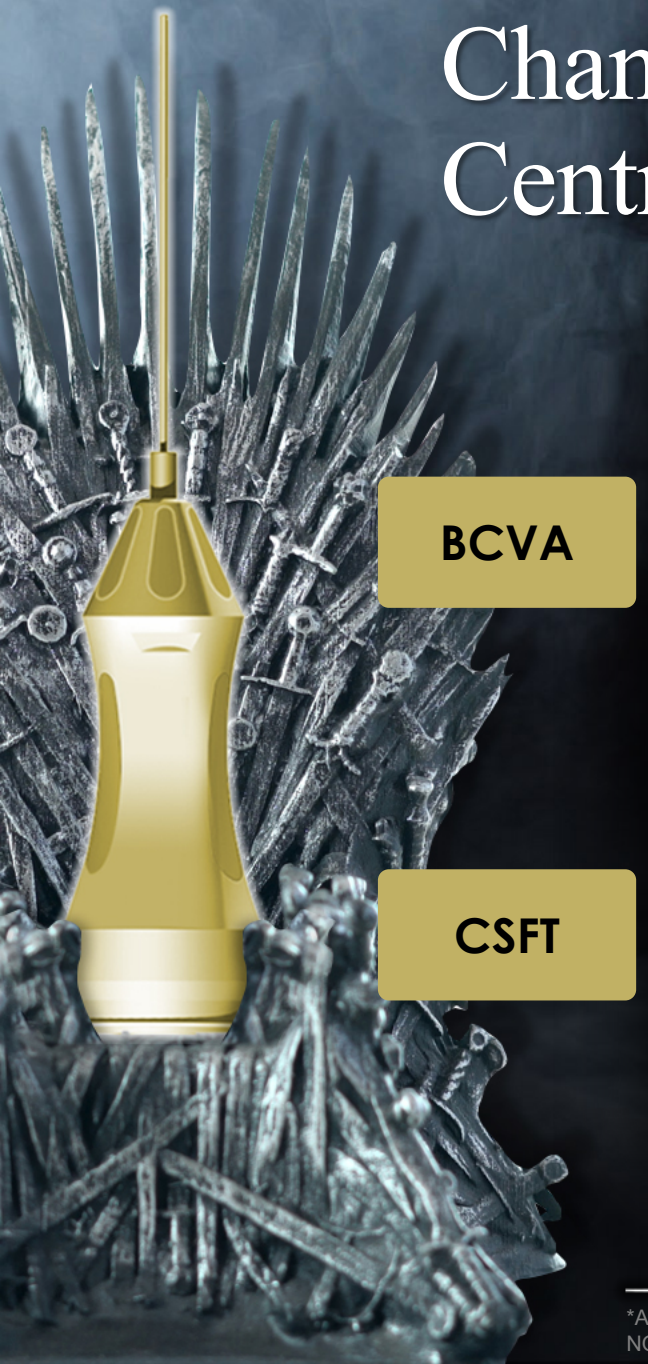
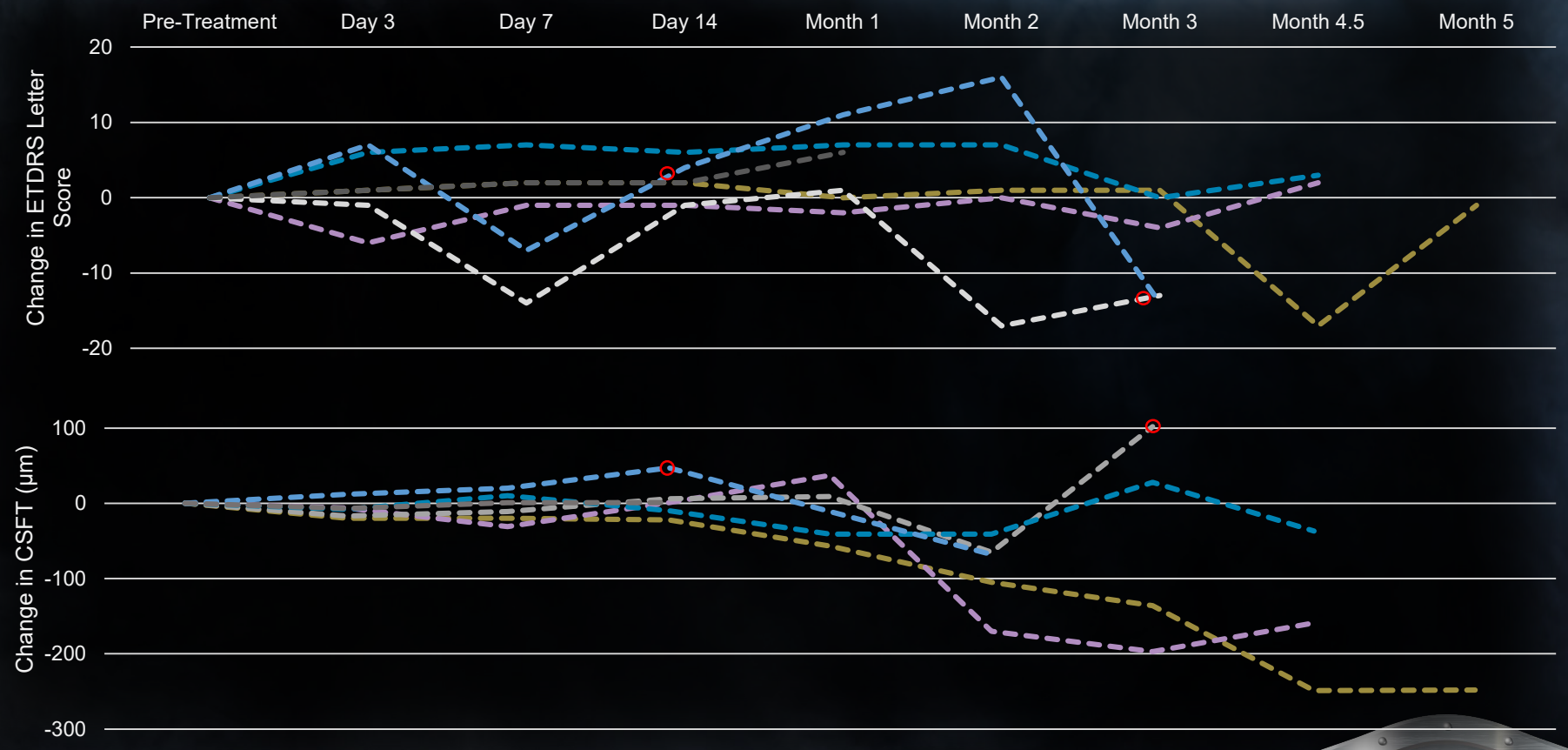
Change in Best Corrected Visual Acuity and Central Subfield Thickness Values: Cohort 2



BCVA

CSFT



○ Denotes administration of rescue therapy

*All BCVA and CSFT values compared to Baseline visit
NOTE: Interim review, unmonitored data

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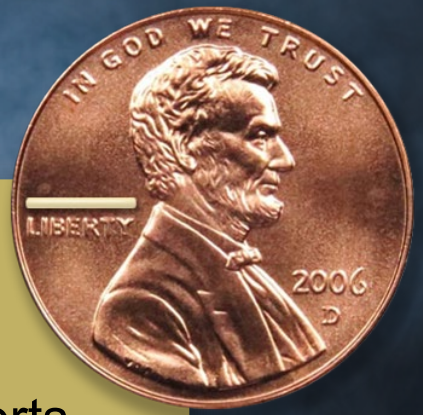
OTX-TKI Conclusions: To be Confirmed

- **OTX-TKI was generally well tolerated**
  To date, observed to have a favorable safety profile in both cohorts
- **Preliminary biological signal of clinically-meaningful decrease in retinal fluid**
  Some subjects showed a decrease in intraretinal or subretinal fluid by 2 months
- **Therapy durability suggests extended duration of action**
  In the higher dose cohort, several subjects demonstrated durability of therapy for up to 4.5 months. Patients still being followed in cohort 2, to be further determined
- **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;
continued long-term evaluation of both cohorts

- Need to establish durability of treatment
- Identify Maximum Tolerated Dose (MTD)
- Understand utility of OTX-TKI with anti-VEGF injection

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