Update on a Hydrogel-Based Intravitreal Axitinib Implant (OTX-TKI) for the Treatment of Neovascular Age-related Macular Degeneration

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Angiogenesis, Exudation, and Degeneration Meeting
Virtual | February 11, 2023

Disclosures

Financial Disclosures (Andrew A. Moshfeghi):

- Consultant: Ocular Therapeutix, Alimera, Allergan, Regeneron, Regenxbio, Genentech/Roche, Novartis, Pr3vent, Placid0, Valitor, SciNeuro, OcuTerra, Waldo
- Individual Stocks and stock options: Ocular Therapeutix, Valitor, Pr3vent, Placid0 (ended), Waldo
- Ownership Interest: Pr3vent, Placid0 (ended), Waldo, OptiSTENT (ended)
- Researcher: Regeneron, Genentech/Roche, Novartis

Study and Product Disclosures:

- The following presentation discusses an investigational drug, OTX-TKI, in development. OTX-TKI's efficacy and safety profiles have not been established, and it has not been approved for marketing by the U.S. Food and Drug Administration (FDA) or any other healthy agency
- Funding was provided by Ocular Therapeutix for the study

Take Home Points

OTX-TKI	• OTX-TKI is hydrogel delivery of axitinib, a potent tyrosine kinase inhibitor selectively targeting all VEGF and PDGF receptors
Study Design	• Multicenter, randomized, double-masked trial comparing single OTX-TKI implant to aflibercept Q8W in previously-treated wet AMD patients with controlled retinal fluid
Safety Analysis	• Up to 10 months, OTX-TKI was generally well-tolerated with no elevated IOP, retinal detachment, retinal vasculitis, or implant migration into the anterior chamber adverse events reported
Efficacy Analysis	• Vision and OCT CSFT with OTX-TKI were comparable to aflibercept Q8W up to 10 months
Durability	• 73% of subjects were rescue-free up to 10 months following a single OTX-TKI implant injection • 92% reduction in anti-VEGF treatment burden in OTX-TKI patients up to 10 months
Next Steps	• Study is ongoing and follow-up will continue through Month 12 per protocol • Phase 1 study evaluating OTX-TKI in subjects with Diabetic Retinopathy - initiated in December 2022

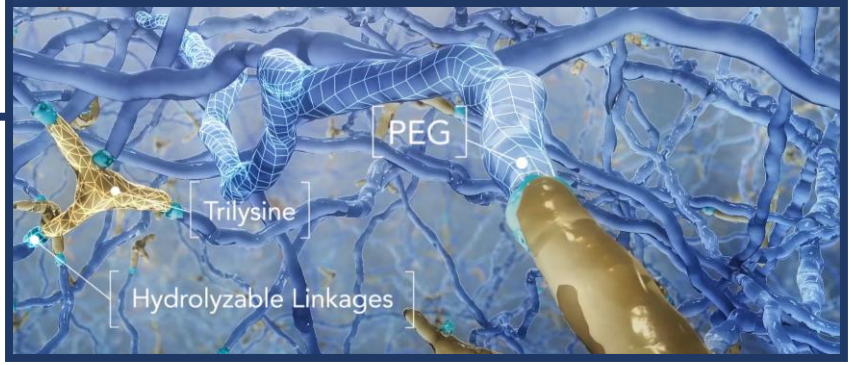
Interim review: data cut off December 12, 2022
CSFT=central subfoveal thickness; IOP=intraocular pressure; PDGF=platelet-derived growth factor; VEGF=vascular endothelial growth factor

OTX-TKI: Hydrogel Delivery of Axitinib

HYDROGEL DELIVERY PLATFORM

BIORESORBABLE, TARGETED, SUSTAINED DRUG DELIVERY

OTX's proprietary bioresorbable polymer matrix, a polyethylene glycol (PEG) hydrogel is a versatile platform for localized sustained drug delivery



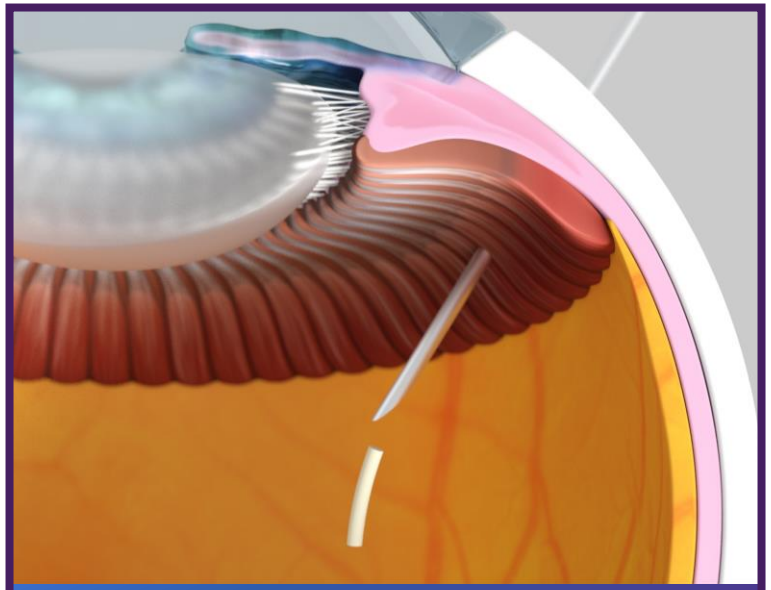
AXITINIB

MULTI-TARGET TYROSINE KINASE INHIBITOR FOR RETINAL VASCULAR DISEASES

Axitinib is a highly selective inhibitor of all VEGF and PDGF receptors with high affinity and low solubility compared to other ocular TKIs[1]

Drug	Inhibitory Concentrations for VEGFR2/KDR (IC_{50} in nM) (lower values indicate higher affinity)
Axitinib[2]	**0.2**
Sunitinib[3]	43
Vorolanib[3]	52

OTX-TKI: AXITINIB IN A HYDROGEL INTRAVITREAL IMPLANT



- Single implant
- Completely bioresorbable
- Target release for 6-12 months
- Administered by a 25G or smaller needle

References: 1. Zhao Y, et al. *Oncologist*. 2015;20(6):660-673. **2.** Gross-Goupil M, et al. *Clin Med Insights Oncol.* 2013;7:269-277. **3.** Eyepoint Pharmaceuticals, Inc. Form 8-K. Published online September 15, 2020. Accessed August 24, 2022. https://sec.report/Document/0001564590-20-043596/

KDR=kinase insert domain receptor; PDGF=platelet-derived growth factor; VEGF=vascular endothelial growth factor

U.S. Wet AMD Phase 1 Study Design

Multicenter, Randomized, Double-masked Trial

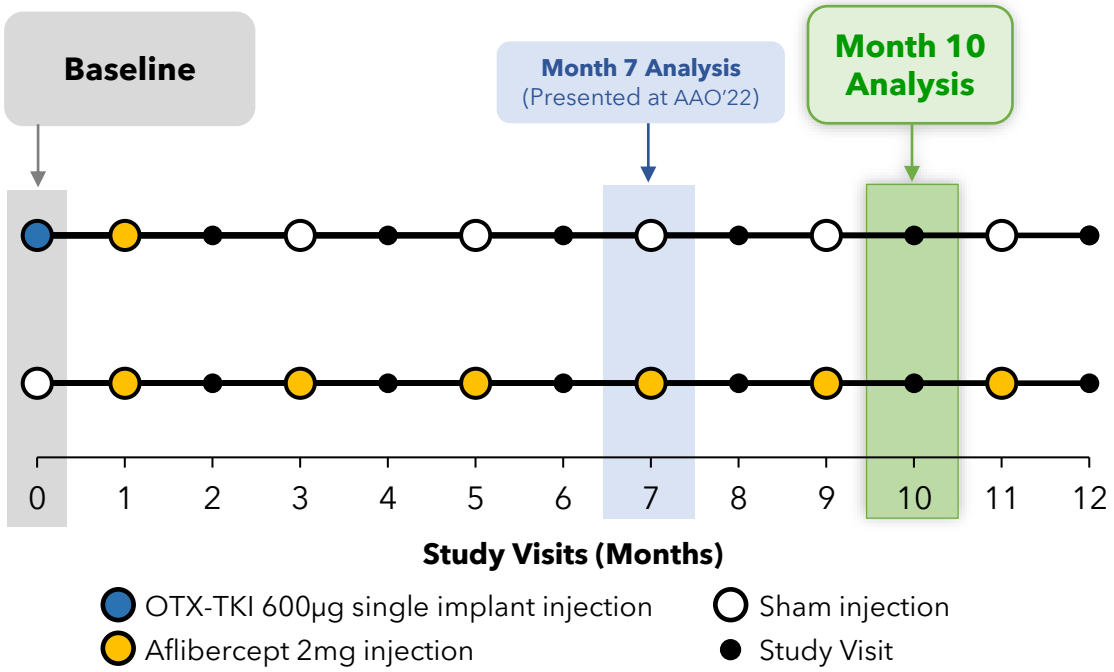
Screening

Key Inclusion Criteria

- Sub foveal neovascularization secondary to AMD
- **Controlled fluid**
- **Previously treated with anti-VEGF injections**

Randomization 3:1
OTX-TKI:Aflibercept

- **OTX-TKI Arm**
- **Aflibercept Arm**



Rescue Anti-VEGF Injection Criteria:

- Loss of ≥10 letters from best previous BCVA due to AMD with current BCVA worse than baseline, or
- Evidence of ≥75µm CSFT increase from previous best value and ≥5 letters loss from best previous BCVA, or
- New macular hemorrhage

AAO=American Academy of Ophthalmology; AMD=age-related macular degeneration; BCVA=best corrected visual acuity; BL=baseline; CSFT=central subfield thickness; AMD=age-related macular degeneration; VEGF=vascular endothelial growth factor

Baseline Characteristics

Baseline Characteristic	OTX-TKI (N=16)†	Aflibercept (N=5)
Mean (SD) Age, Years	76 (8)	84 (8)
Male, n (%) **Female, n (%)**	8 (50) 8 (50)	3 (60) 2 (40)
Mean (SD) Months since wet AMD diagnosis	18 (12)	18 (12)
Mean (SD) Number of anti-VEGF Injections within 12 Months Prior to baseline*	8 (3)	8 (4)
Mean (SD) BCVA in ETDRS Letters	70.9 (17.7)	73.8 (9.0)
Mean (SD) CSFT, µm	273.8 (43.0)	240.6 (29.6)

*Annualized data

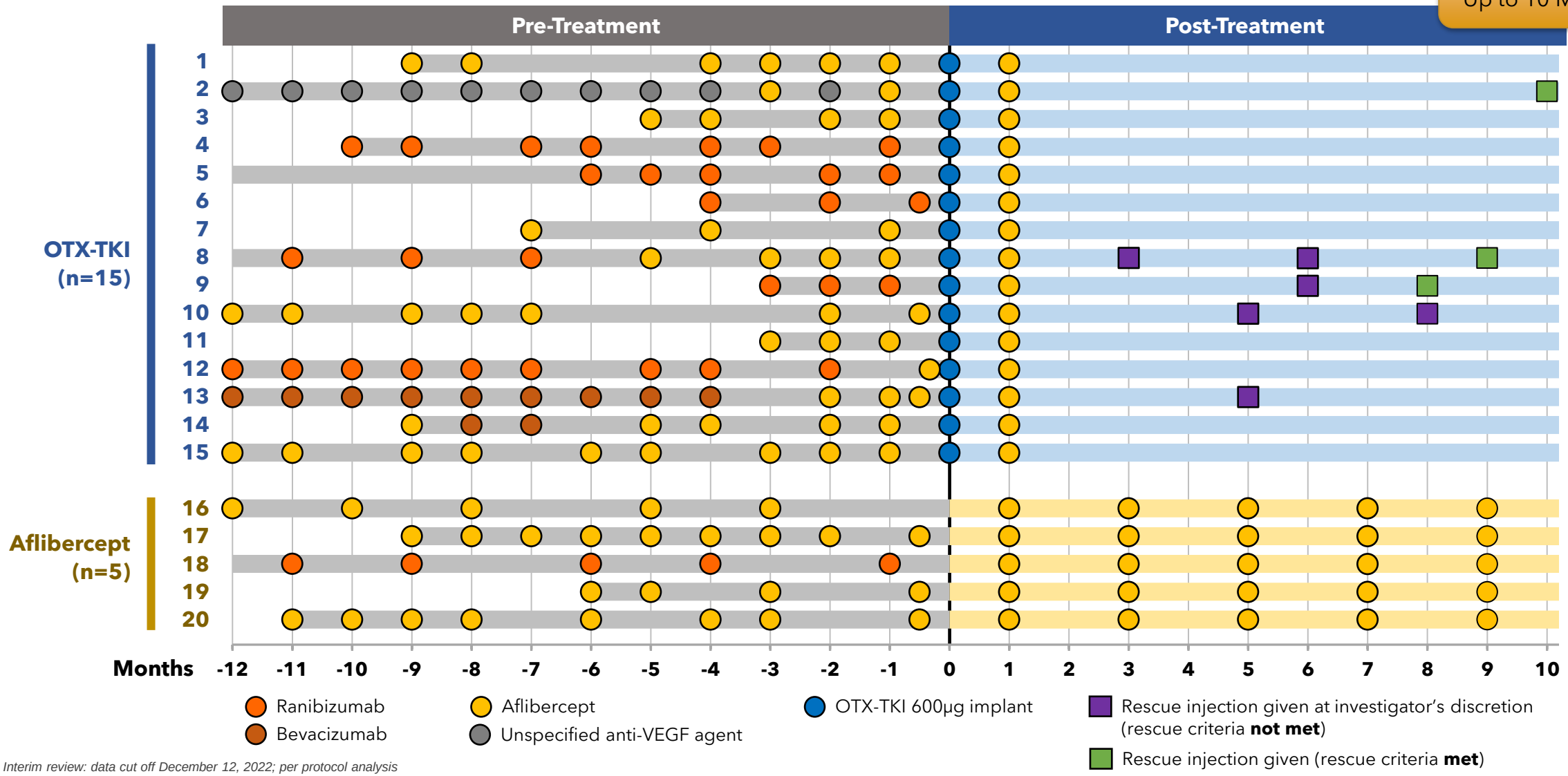
† Includes one subject not treated per protocol who has been removed from efficacy analysis as subject incorrectly received aflibercept instead of sham injection at Month 3 and 5 visits

Interim review: data cut off December 12, 2022

BCVA=best corrected visual acuity; CSFT=central subfield thickness; ETDRS=Early Treatment Diabetic Retinopathy Study; AMD=age-related macular degeneration; SD=standard deviation; VEGF=vascular endothelial growth factor

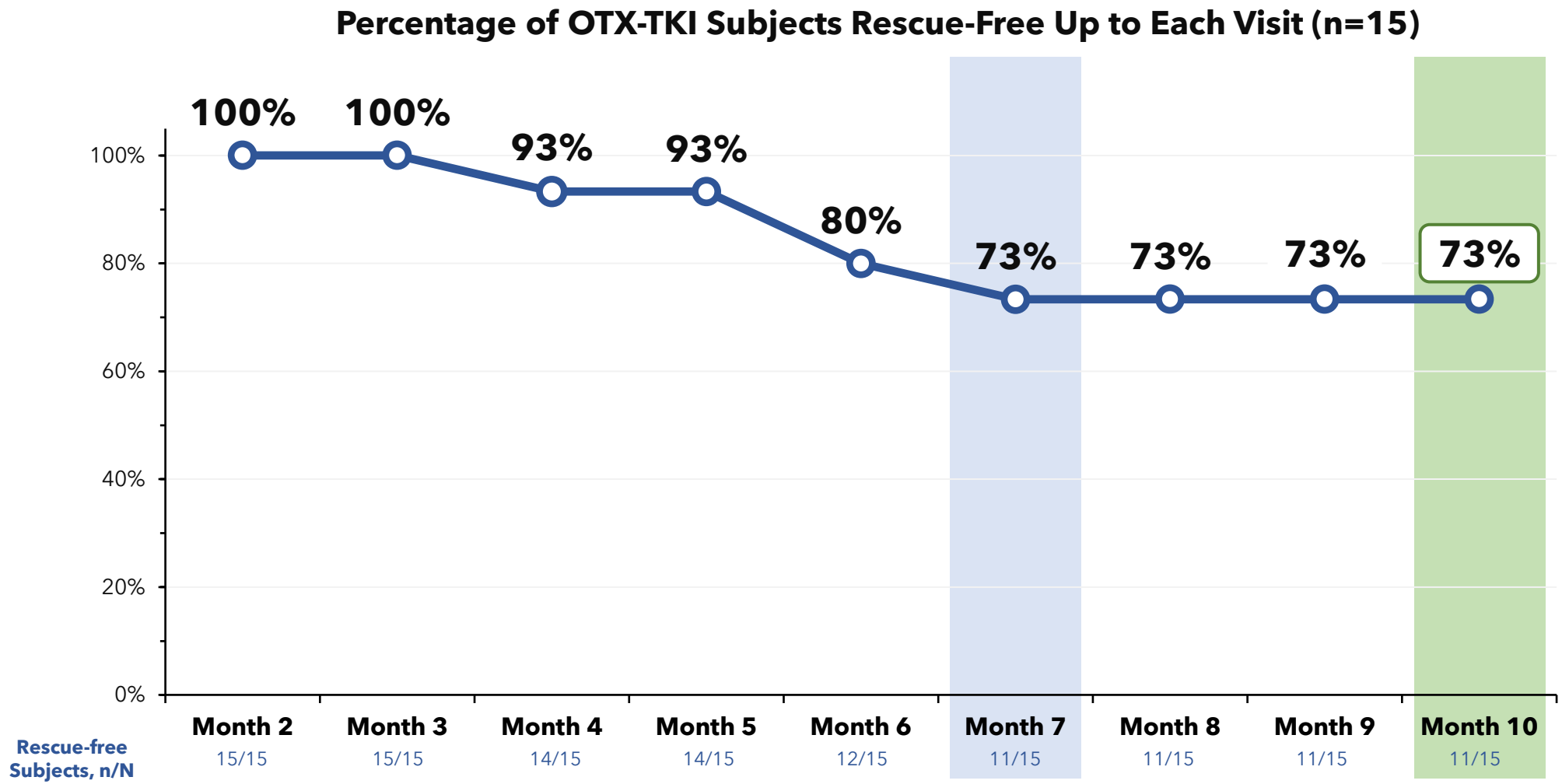
Reduction in Anti-VEGF Injections Following OTX-TKI Up to Month 10

Treatment Reduction
Up to 10 Months: 92%



Interim review: data cut off December 12, 2022; per protocol analysis
Reduction in treatment burden calculation includes all rescue injections up to Month 10
Sham injection was given at Month 0 in the Aflibercept Arm and at Month 3, 5, 7 and 9 in the OTX-TKI Arm (not shown).

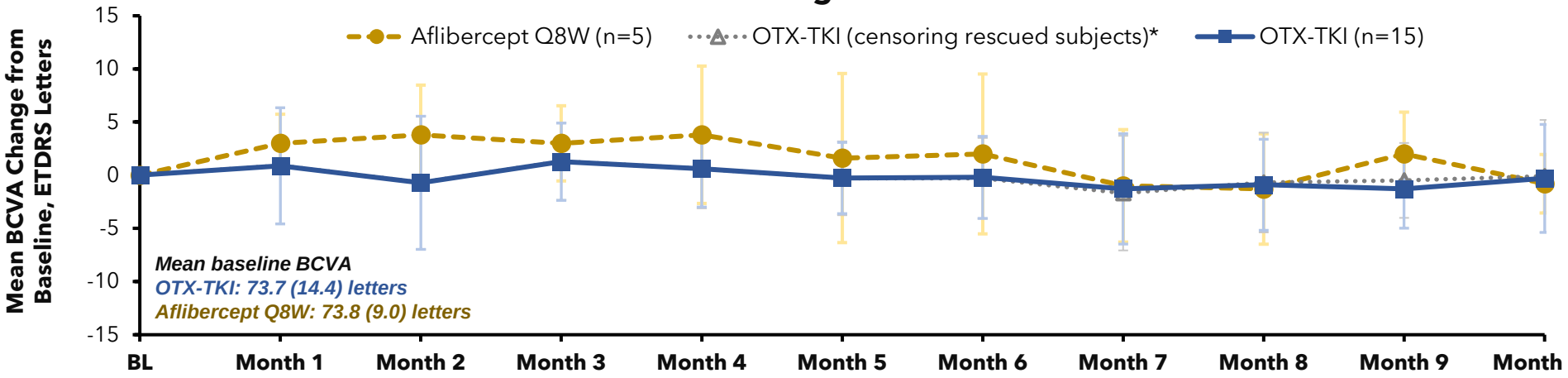
OTX-TKI Demonstrated Extended Duration of Action with 73% of Subjects Rescue-Free Up to 10 months



Interim review: data cut off December 12, 2022
Rescue-free rate calculations: If subjects received rescue anti-VEGF therapy at a study visit, those were reflected to the count at the following study visit in the graph above

Vision and CSFT with OTX-TKI were Comparable to Aflibercept Q8W Up to Month 10

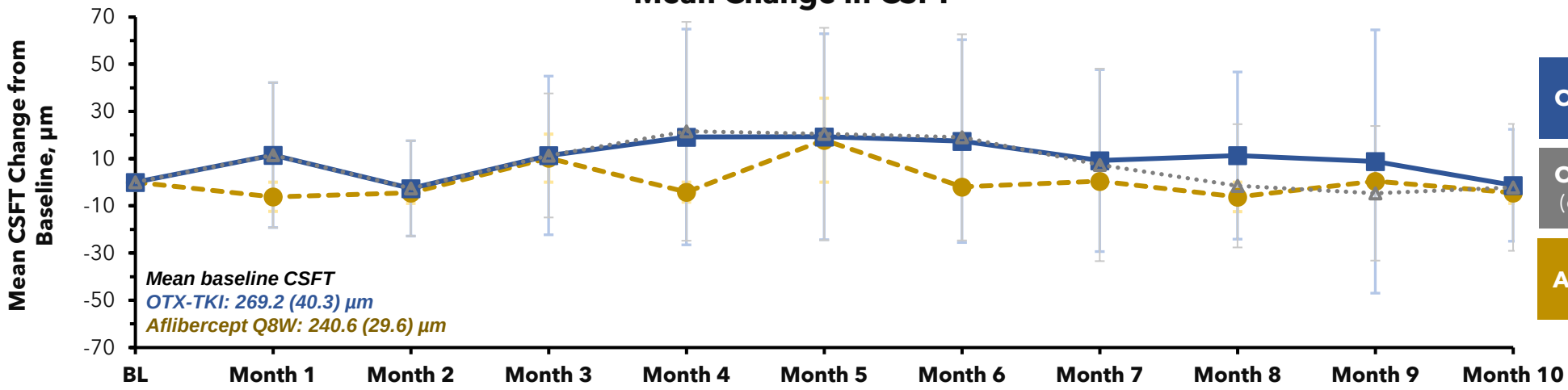
Mean Change in BCVA



Mean (SD) change in BCVA from baseline to Month 10:

- **OTX-TKI: -0.3 (5.1) letters**
- **OTX-TKI: -0.1 (5.3) letters** (censoring rescued subjects)
- **Aflibercept Q8W: -0.8 (2.8) letters**

Mean Change in CSFT



Mean (SD) change in CSFT from baseline to Month 10:

- **OTX-TKI: -1.3 (23.7) µm**
- **OTX-TKI: -2.1 (26.9) µm** (censoring rescued subjects)
- **Aflibercept Q8W: -4.5 (4.4) µm**

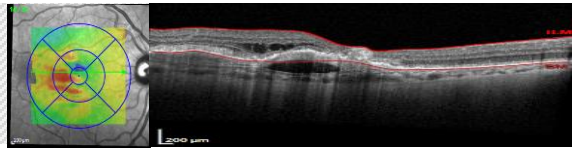
Interim review: data cut off December 12, 2022
Error bars represent standard deviation; n=14 in OTX-TKI arm at Months 2 and 7 due to missed visits
**Sample size for OTX-TKI (censoring rescued subjects): n=15 at Baseline and Months 1 and 3; n=14 at Month 2 (missed visit) and Months 4 and 5; n=12 at Month 6 and n=11 at Month 7, 8, 9, and 10*
BCVA=best corrected visual acuity; BL=baseline; CSFT=central subfield thickness; ETDRS=Early Treatment Diabetic Retinopathy Study

OTX-TKI Case Study 1: Patient 12

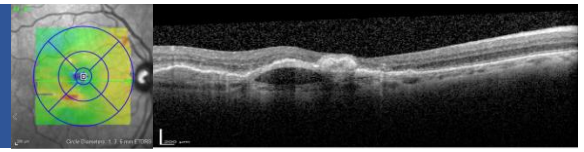
60-year-old male with anti-VEGF Q4-8W prior to study and rescue-free through Month 10

Patient received SOC wet AMD therapy prior to study

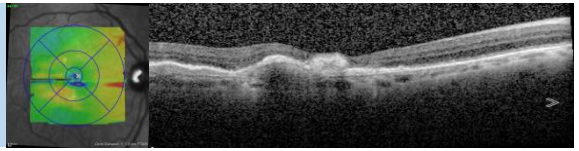
Historical OCT
(~1 month prior to baseline)
CSFT: 277 µm



Baseline
CSFT: 278 µm
BCVA: 54 letters



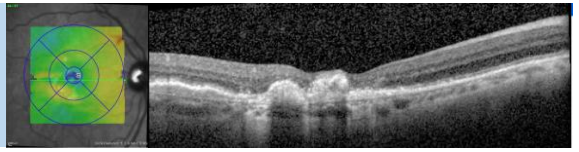
Month 1
CSFT change: -47 µm
BCVA change: +2 letters



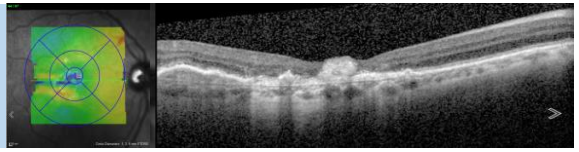
Month 2

Missed visit

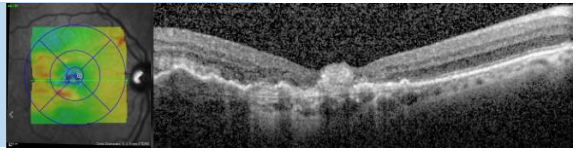
Month 3
CSFT change: -72 µm
BCVA change: +4 letters



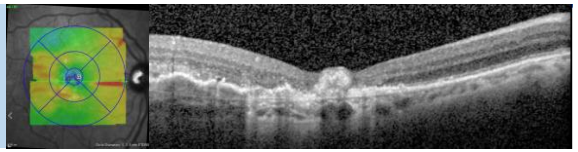
Month 4
CSFT change: -68 µm
BCVA change: +5 letters



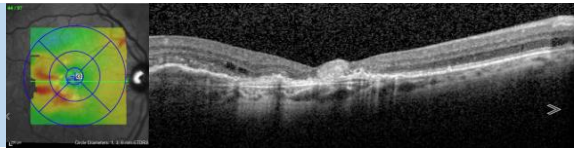
Month 5
CSFT change: -66 µm
BCVA change: +5 letters



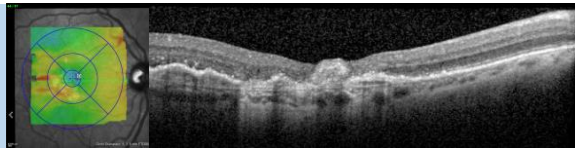
Month 6
CSFT change: -55 µm
BCVA change: +3 letters



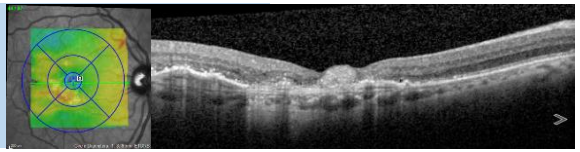
Month 7
CSFT change: -54 µm
BCVA change: +4 letters



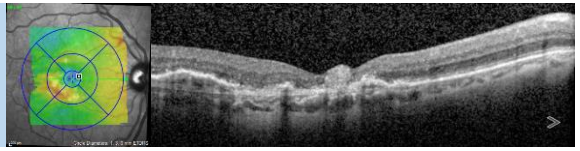
Month 8
CSFT change: -51 µm
BCVA change: +4 letters

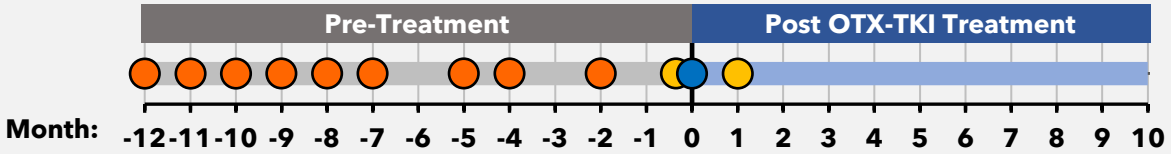


Month 9
CSFT change: -61 µm
BCVA change: +5 letters



Month 10
CSFT change: -51 µm
BCVA change: +8 letters





- Ranibizumab
- Aflibercept
- OTX-TKI 600µg implant
- Rescue injection given at investigator's discretion (criteria not met)
- Rescue injection given per rescue criteria

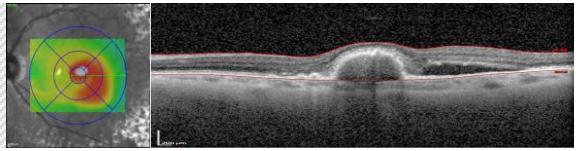
Patient received study-mandated aflibercept injection at Month 1; All changes in CSFT and BCVA are relative to baseline visit

OTX-TKI Case Study 2: Patient 15

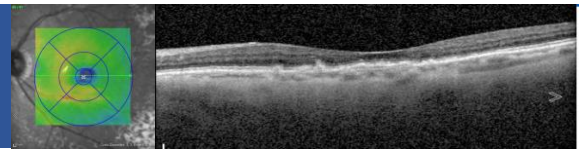
80-year-old female with aflibercept Q4-8W prior to study and rescue-free through Month 10

Patient received SOC wet AMD therapy prior to study

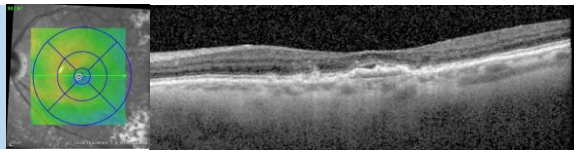
Historical OCT
(~21 months prior to baseline)
CSFT: 456 µm



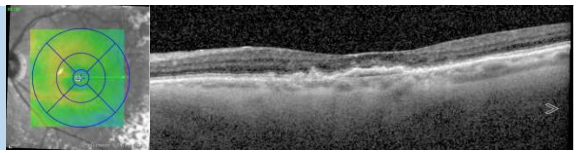
Baseline
CSFT: 183 µm
BCVA: 59 letters



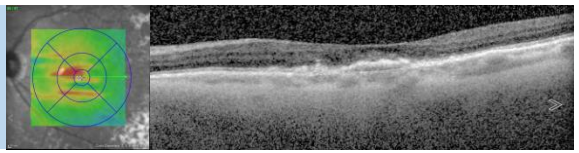
Month 1
CSFT change: +46 µm
BCVA change: 0 letters



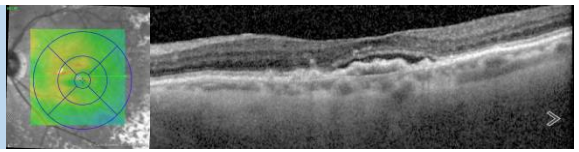
Month 2
CSFT change: +54 µm
BCVA change: +1 letter



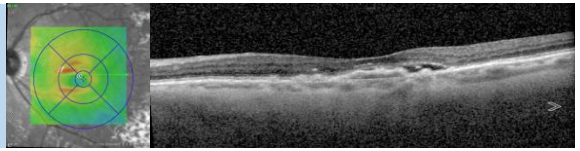
Month 3
CSFT change: +47 µm
BCVA change: -4 letters



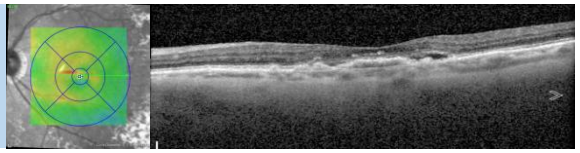
Month 4
CSFT change: +82 µm
BCVA change: +2 letters



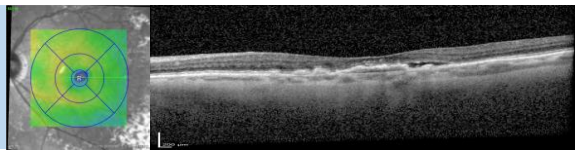
Month 5
CSFT change: +62 µm
BCVA change: -3 letters



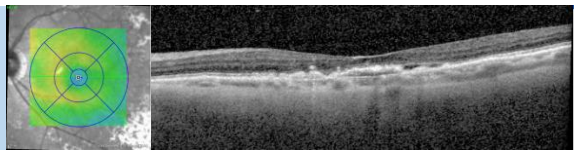
Month 6
CSFT change: +60 µm
BCVA change: -1 letter



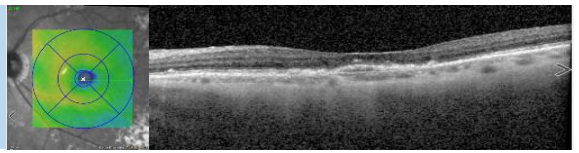
Month 7
CSFT change: +9 µm
BCVA change: -2 letters



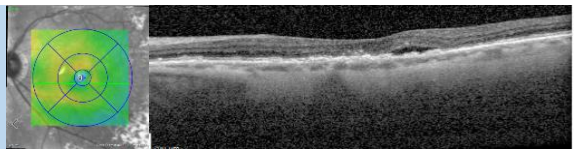
Month 8
CSFT change: +32 µm
BCVA change: +1 letter

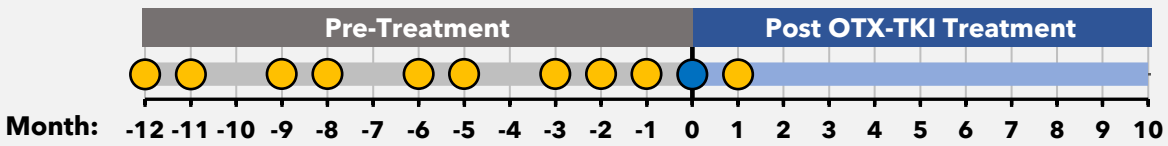


Month 9
CSFT change: -6 µm
BCVA change: 0 letters



Month 10
CSFT change: +53 µm
BCVA change: -1 letter





Aflibercept
OTX-TKI 600µg implant
Rescue injection given at investigator's discretion (criteria not met)
Rescue injection given per rescue criteria

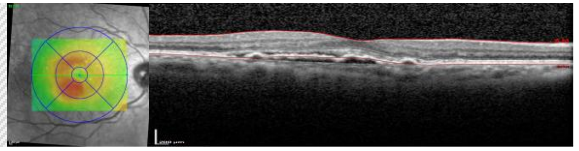
Patient received study-mandated aflibercept injection at Month 1; All changes in CSFT and BCVA are relative to baseline visit

OTX-TKI Case Study 3: Patient 14

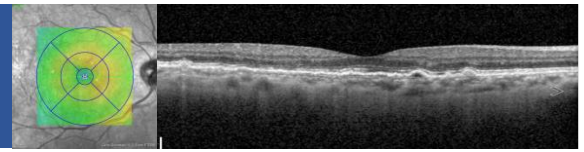
65-year-old female with anti-VEGF Q4-8W prior to study and rescue-free through Month 10

Received aflibercept

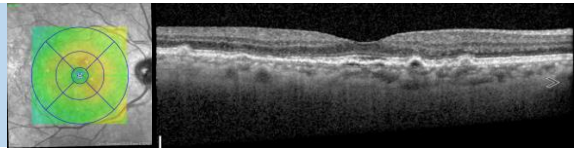
Historical OCT
(~4 months prior to baseline)
CSFT: 311 µm



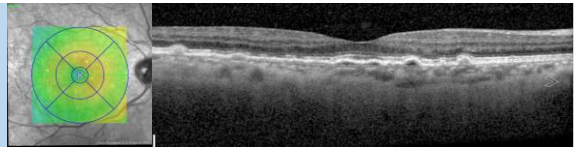
Baseline
CSFT: 243 µm
BCVA: 78 letters



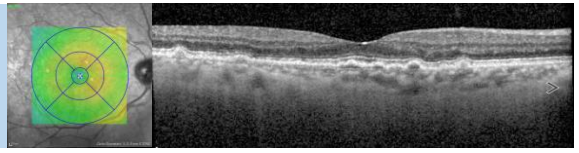
Month 1
CSFT change: +3 µm
BCVA change: +2 letters



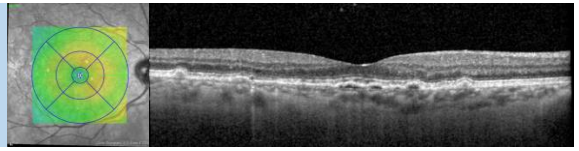
Month 2
CSFT change: +3 µm
BCVA change: -3 letters



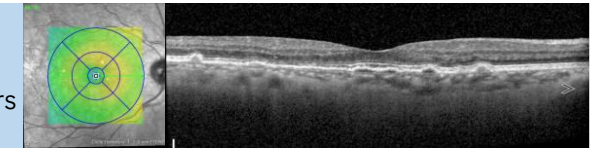
Month 3
CSFT change: +1 µm
BCVA change: +2 letters



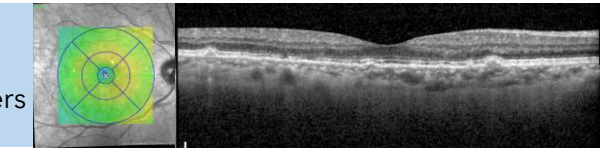
Month 4
CSFT change: 0 µm
BCVA change: +1 letter



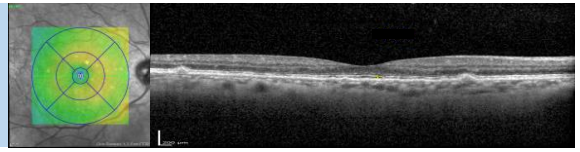
Month 5
CSFT change: -5 µm
BCVA change: +2 letters



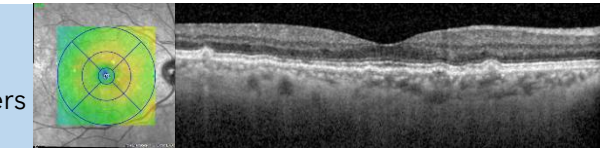
Month 6
CSFT change: -10 µm
BCVA change: +4 letters



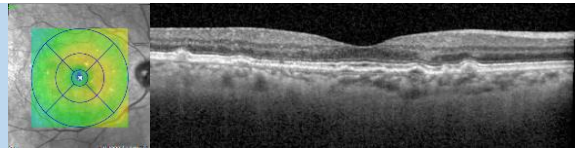
Month 7
CSFT change: -10 µm
BCVA change: +1 letter



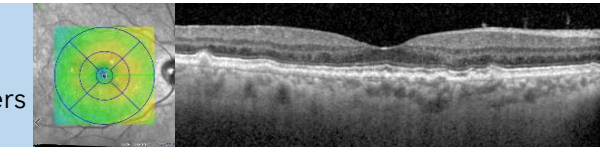
Month 8
CSFT change: -9 µm
BCVA change: +4 letters

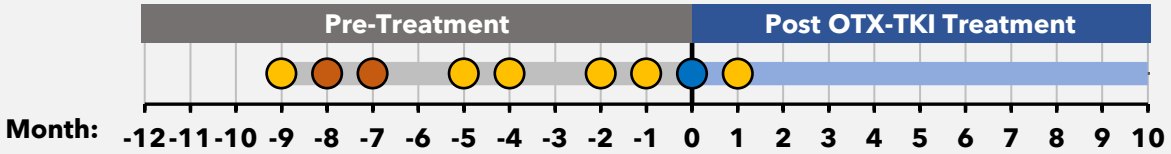


Month 9
CSFT change: -12 µm
BCVA change: 0 letters



Month 10
CSFT change: -6 µm
BCVA change: +2 letters





- Bevacizumab
- Aflibercept
- OTX-TKI 600µg implant
- Rescue injection given at investigator's discretion (criteria not met)
- Rescue injection given per rescue criteria

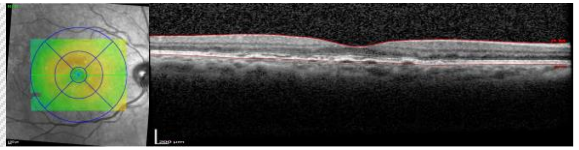
Patient received study-mandated aflibercept injection at Month 1; All changes in CSFT and BCVA are relative to baseline visit

OTX-TKI Case Study 3: Patient 14

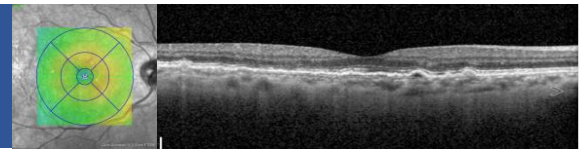
65-year-old female with anti-VEGF Q4-8W prior to study and rescue-free through Month 10

Received aflibercept

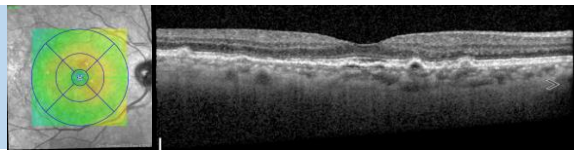
Historical OCT
(~2 months prior to baseline)
CSFT: 259 µm



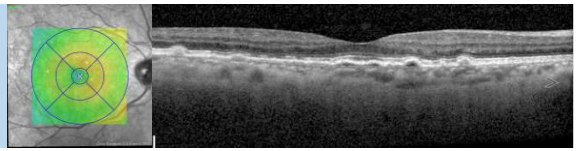
Baseline
CSFT: 243 µm
BCVA: 78 letters



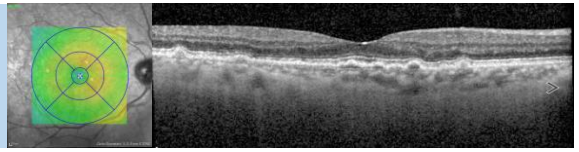
Month 1
CSFT change: +3 µm
BCVA change: +2 letters



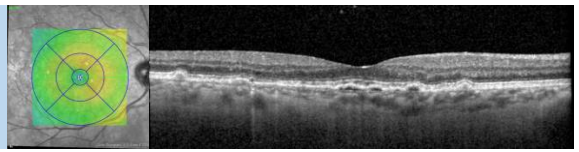
Month 2
CSFT change: +3 µm
BCVA change: -3 letters



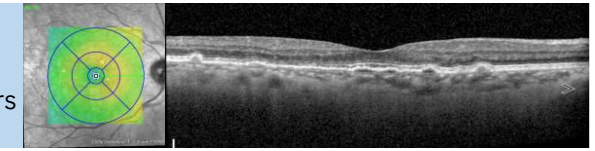
Month 3
CSFT change: +1 µm
BCVA change: +2 letters



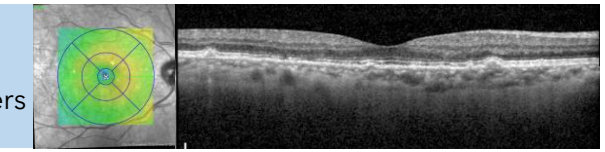
Month 4
CSFT change: 0 µm
BCVA change: +1 letter



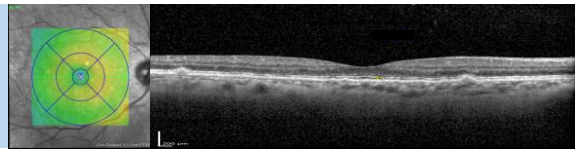
Month 5
CSFT change: -5 µm
BCVA change: +2 letters



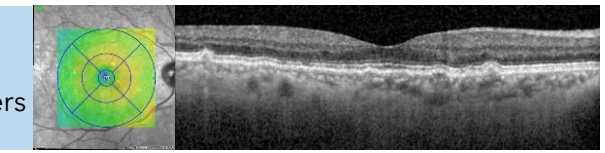
Month 6
CSFT change: -10 µm
BCVA change: +4 letters



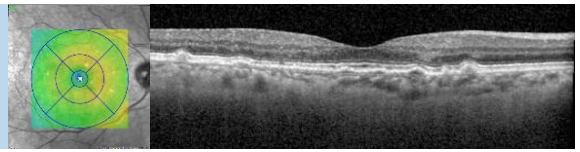
Month 7
CSFT change: -10 µm
BCVA change: +1 letter



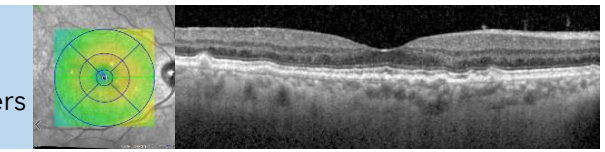
Month 8
CSFT change: -9 µm
BCVA change: +4 letters

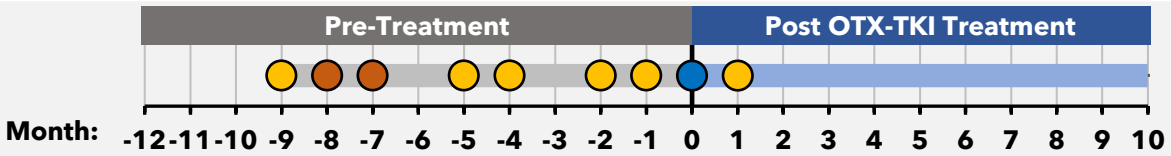


Month 9
CSFT change: -12 µm
BCVA change: 0 letters



Month 10
CSFT change: -6 µm
BCVA change: +2 letters





Bevacizumab
Aflibercept
OTX-TKI 600µg implant
Rescue injection given at investigator's discretion (criteria not met)
Rescue injection given per rescue criteria

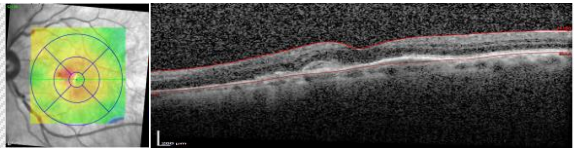
Patient received study-mandated aflibercept injection at Month 1; All changes in CSFT and BCVA are relative to baseline visit

OTX-TKI Case Study 4: Patient 5

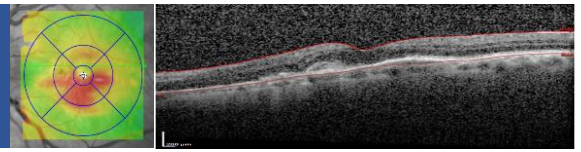
68-year-old female with ranibizumab Q4-8W prior to study and rescue-free through Month 10

Received ranibizumab

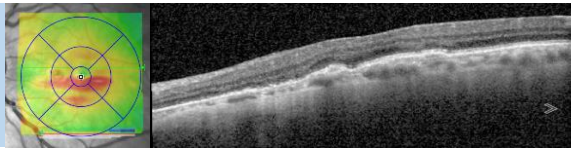
Historical OCT
(~6 months prior to baseline)
CSFT: 332 µm



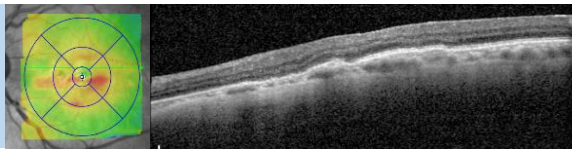
Baseline
CSFT: 331 µm
BCVA: 81 letters



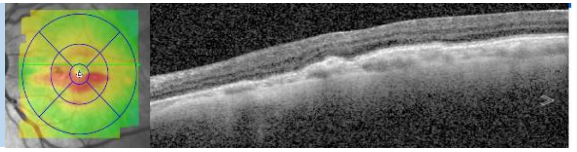
Month 1
CSFT change: -15 µm
BCVA change: -4 letters



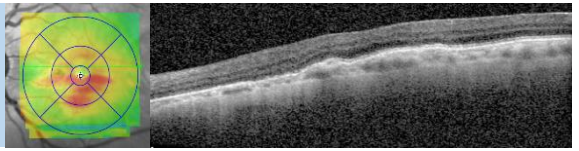
Month 2
CSFT change: -31 µm
BCVA change: +3 letters



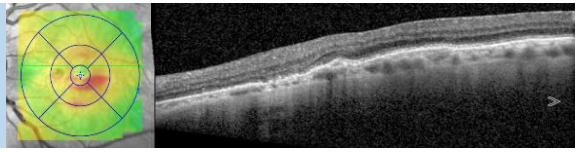
Month 3
CSFT change: -6 µm
BCVA change: +1 letter



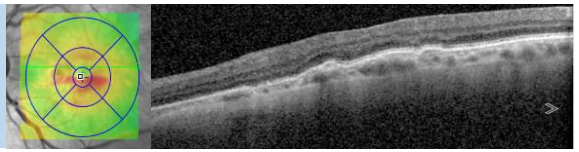
Month 4
CSFT change: -2 µm
BCVA change: +2 letters



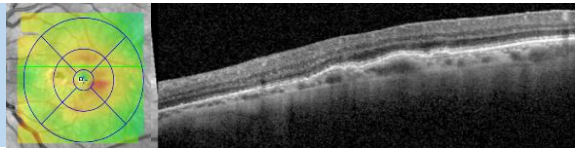
Month 5
CSFT change: -19 µm
BCVA change: -1 letter



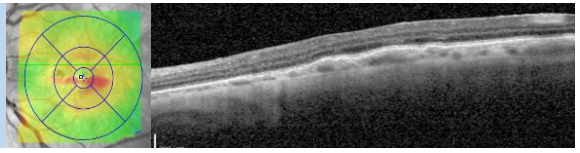
Month 6
CSFT change: -17 µm
BCVA change: 0 letters



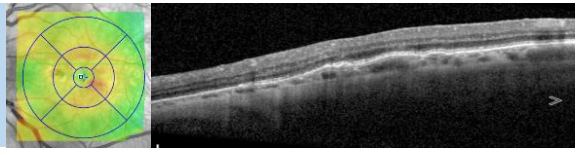
Month 7
CSFT change: -20 µm
BCVA change: 0 letters



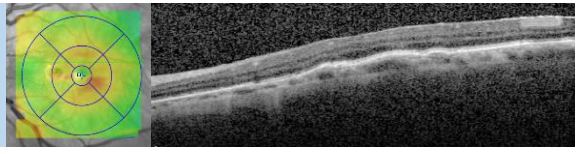
Month 8
CSFT change: -33 µm
BCVA change: -1 letter

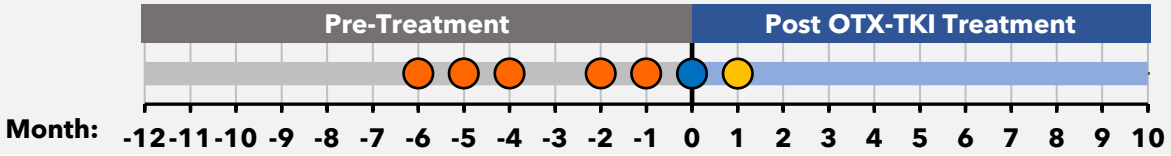


Month 9
CSFT change: -30 µm
BCVA change: -1 letter



Month 10
CSFT change: -26 µm
BCVA change: +2 letters





- Ranibizumab
- Aflibercept
- OTX-TKI 600µg implant
- Rescue injection given at investigator's discretion (criteria not met)
- Rescue injection given per rescue criteria

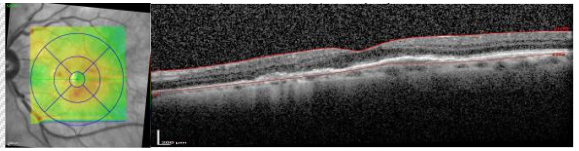
Patient received study-mandated aflibercept injection at Month 1; All changes in CSFT and BCVA are relative to baseline visit

OTX-TKI Case Study 4: Patient 5

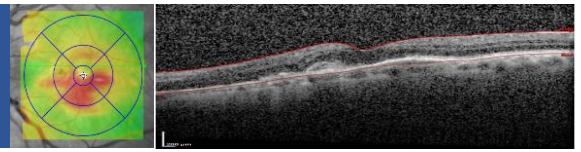
68-year-old female with ranibizumab Q4-8W prior to study and rescue-free through Month 10

Received ranibizumab

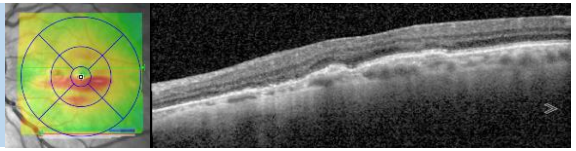
Historical OCT
(~2 months prior to baseline)
CSFT: 302 µm



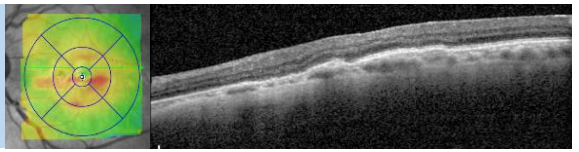
Baseline
CSFT: 331 µm
BCVA: 81 letters



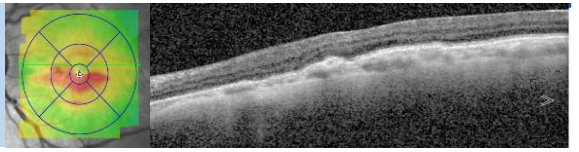
Month 1
CSFT change: -15 µm
BCVA change: -4 letters



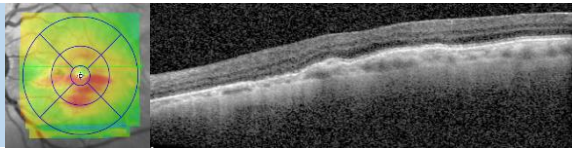
Month 2
CSFT change: -31 µm
BCVA change: +3 letters



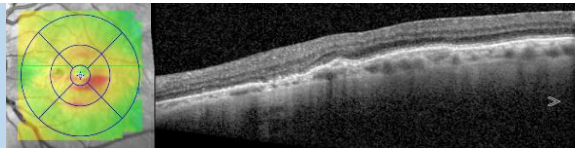
Month 3
CSFT change: -6 µm
BCVA change: +1 letter



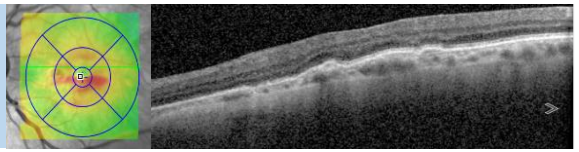
Month 4
CSFT change: -2 µm
BCVA change: +2 letters



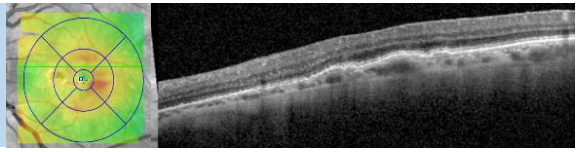
Month 5
CSFT change: -19 µm
BCVA change: -1 letter



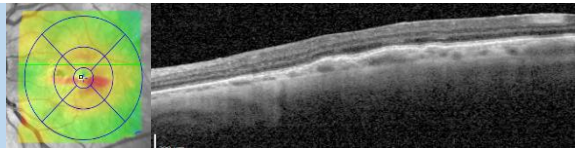
Month 6
CSFT change: -17 µm
BCVA change: 0 letters



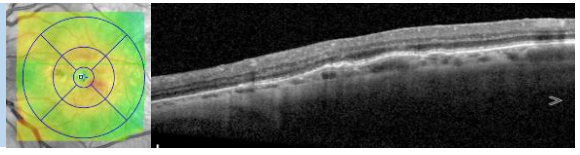
Month 7
CSFT change: -20 µm
BCVA change: 0 letters



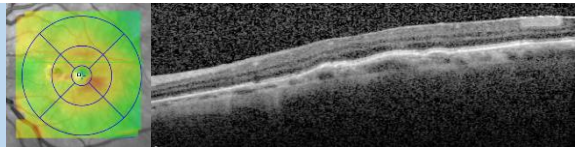
Month 8
CSFT change: -33 µm
BCVA change: -1 letter

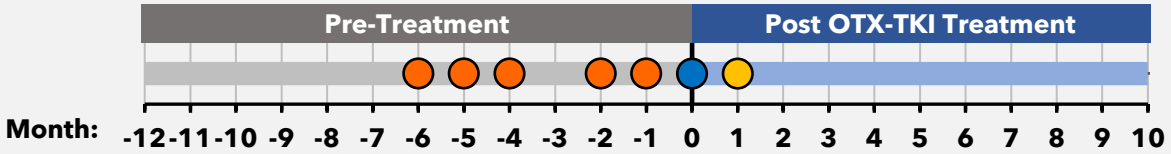


Month 9
CSFT change: -30 µm
BCVA change: -1 letter



Month 10
CSFT change: -26 µm
BCVA change: +2 letters





- Ranibizumab
- Aflibercept
- OTX-TKI 600µg implant
- Rescue injection given at investigator's discretion (criteria not met)
- Rescue injection given per rescue criteria

Patient received study-mandated aflibercept injection at Month 1; All changes in CSFT and BCVA are relative to baseline visit

Safety Summary Up to Month 10: OTK-TKI was generally well tolerated with a favorable safety profile

- No reports of drug-related ocular or systemic SAEs in either arm
- One event of acute endophthalmitis in OTX-TKI arm which occurred following mandated aflibercept injection at Month 1
  - Reported as moderate
  - Injection procedure related
  - Unrelated to the study drug
  - Resolved after intravitreal antibiotic injection, with vision returning to baseline
- All events were mild except
  - Acute endophthalmitis SAE (moderate and resolved) and worsening of cataract (moderate) in OTX-TKI arm
  - Elevated IOP in aflibercept arm (moderate and resolved)

Subjects with Adverse Events in the Study Eye	OTX-TKI n=16	Aflibercept n=5
Elevated IOP	0	1**
Retinal detachment	0	0
Retinal vasculitis	0	0
Implant migration into the anterior chamber	0	NA
Acute Endophthalmitis	1*	0
Subjects with Ocular Adverse Events Reported by Severity		
Ocular AEs	16	3
Mild	14	2
Moderate	2*	1**
Severe	0	0
Serious AEs	1*	0

*Moderate and serious ocular AE in OTX-TKI arm was Acute Endophthalmitis 6 days after mandated aflibercept injection at Month 1
**Moderate AE in Aflibercept arm was Elevated Intraocular pressure

Interim review: data cut off December 12, 2022
IOP=intraocular pressure; SAE=serious adverse event

Interim Results Up to Month 10 Demonstrated OTX-TKI Had Extended Durability in Patients with wet AMD in U.S. Phase 1 Trial

Phase 1 randomized, controlled US clinical trial in previously treated wet AMD patients with a single OTX-TKI implant showed safety, tolerability, and biological activity comparable to aflibercept administered every 2 months in this 10-month interim analysis

Safety

- OTX-TKI was generally well tolerated with a favorable safety profile
- No reports of drug-related ocular or systemic SAEs in either arm
- No reported adverse events such as elevated IOP, retinal detachment, retinal vasculitis, or implant migration into the anterior chamber in the OTX-TKI arm
- No subject drop-outs in either arm

Efficacy

- 80% of subjects were rescue-free up to 6 months & 73% of subjects were rescue-free up to 10 months following a single OTX-TKI implant injection
- At 10 months, vision (-0.3 letters) and CSFT (-1.3 µm) were stable with OTX-TKI and comparable to aflibercept Q8W (-0.8 letter; -4.5 µm)
- Clinically meaningful reduction in treatment burden observed up to 10 months post-treatment with OTX-TKI

Next Steps:

- Study is ongoing and follow-up will continue through Month 12 per protocol
- Phase 1 study evaluating OTX-TKI in subjects with Diabetic Retinopathy - initiated in December 2022

Interim review: data cut off December 12, 2022; Conclusions based on limited number of subjects OTX-TKI: n=16 and Aflibercept: n=5

Acknowledgements

Thank you to the investigators, study team and patients for their participation in the clinical study:

- **Stephen Couvillion, MD** (Bakersfield, CA)
- **David Eichenbaum, MD** (St. Petersburg, FL)
- **Arshad Khanani, MD** (Reno, NV)
- **Nathan Steinle, MD** (Santa Barbara, CA)
- **Charles Wykoff, MD, PhD** (Houston, TX)
- **Samantha Xavier, MD** (Altamonte Springs, FL)