U.S. Phase 1 Study of Intravitreal Axitinib Implant (OTX-TKI) for Neovascular Age-related Macular Degeneration

Andrew A. Moshfeghi, MD[1]; Arshad M. Khanani, MD[2]; David A. Eichenbaum, MD[3]; Charles C. Wykoff, MD, PhD[4]; Stephen Couvillion, MD[5]; Samantha Xavier, MD[6]; Nathan Steinle, MD[5]; Peter K. Kaiser, MD[7]; Rabia Gurses-Ozden, MD[8]

[1]Keck School of Medicine, USC Roski Eye Institute, University of Southern California, Los Angeles, CA; [2]Sierra Eye Associates, Reno, NV; [3]Retina Vitreous Associates of Florida, St Petersburg, FL; [4]Retina Consultants of Texas, Houston, TX; [5]California Retina Consultants, Santa Barbara, CA; [6]Florida Eye Clinic, Altamonte Springs, FL; [7]Cleveland Clinic Cole Eye Institute, Cleveland, OH; [8]Ocular Therapeutix, Bedford, MA

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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:

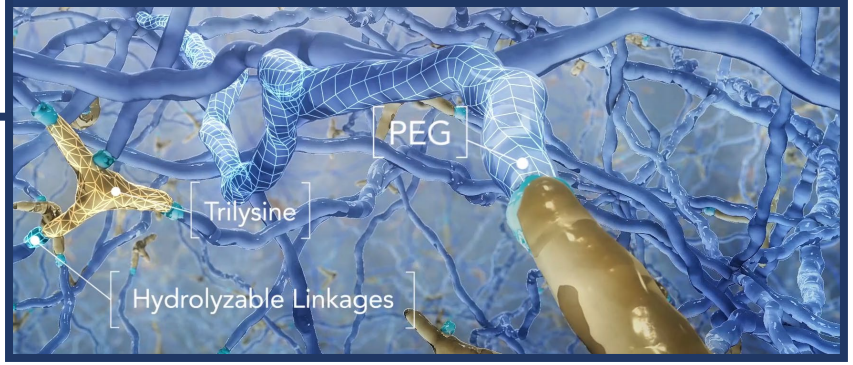
- The following presentation discusses an investigational drug, OTX-TKI, in development. OTX-TKI's efficacy and safety profiles have not been established, and it has not been approved for marketing by the U.S. Food and Drug Administration (FDA) or any other health agency
- Funding was provided by Ocular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

OTX-TKI Implant: Hydrogel Delivery of Axitinib

HYDROGEL DELIVERY PLATFORM

BIORESORBABLE, TARGETED, SUSTAINED DRUG DELIVERY

OTX's proprietary bioresorbable polymer matrix, hydrogel is a versatile platform for localized sustained drug delivery



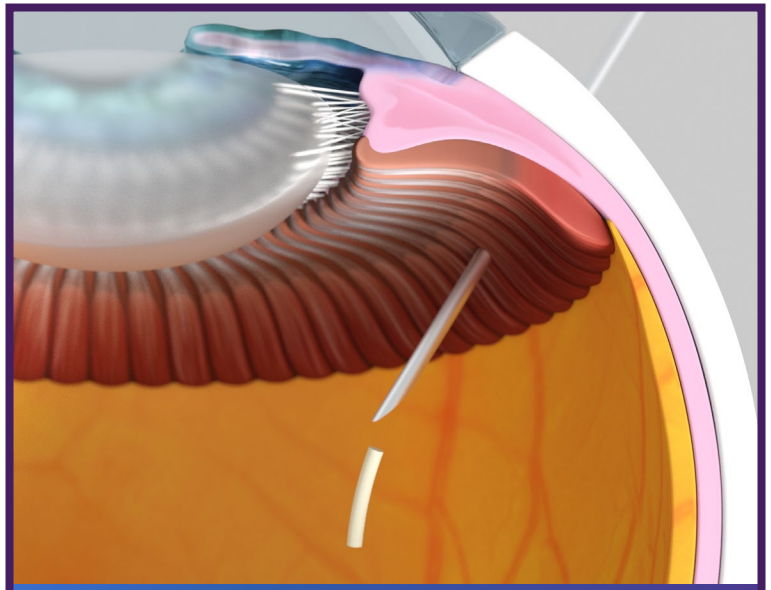
AXITINIB

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 INTRAVITREAL IMPLANT: AXITINIB IN HYDROGEL

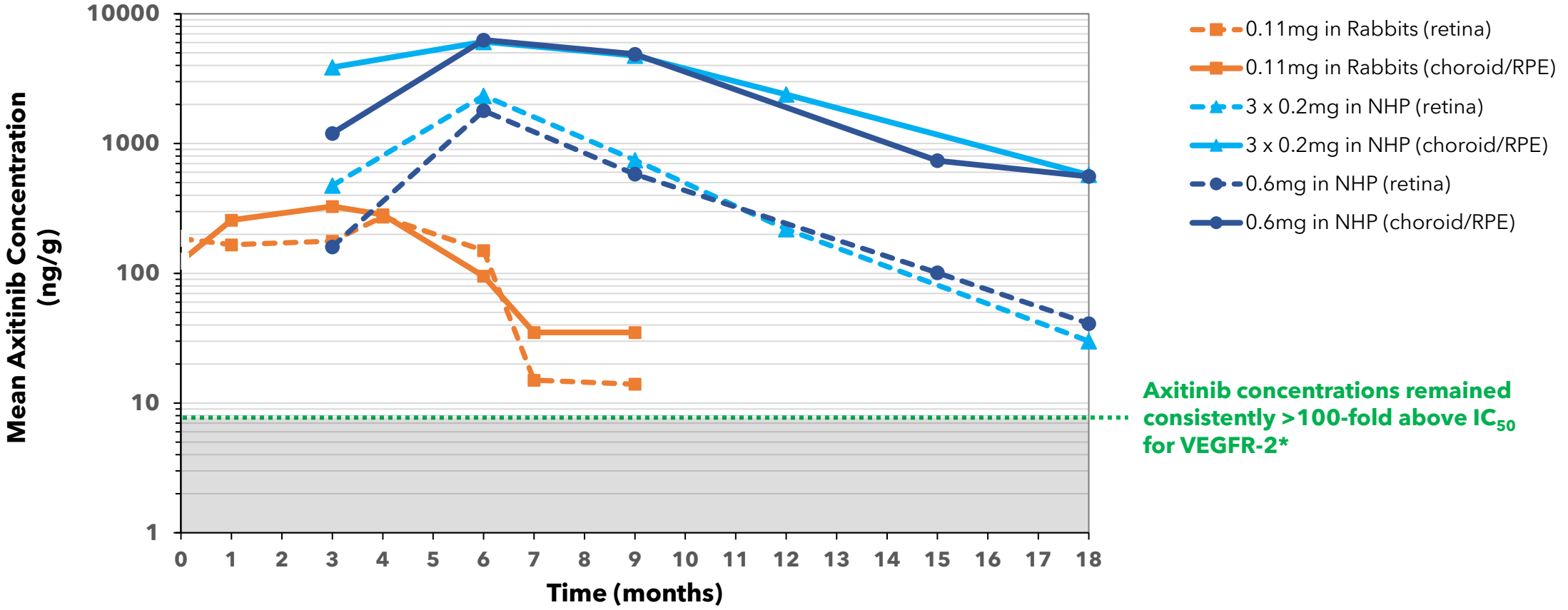


- Single implant
- Completely bioresorbable
- Target release for 6-12 months
- Administered by a 25G or smaller needle

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.** Liang C, et al. *Mol Ther Oncolytics*. 2022;24:577-584.
KDR=kinase insert domain receptor; PDGF=platelet-derived growth factor; VEGF=vascular endothelial growth factor

Preclinical Pharmacokinetic Studies Demonstrate OTX-TKI Provides Rapid and Sustained Release of Axitinib at Levels 100-Fold Above VEGFR-2 IC_{50} in Targeted Tissues

Pharmacokinetic Concentrations of Axitinib Demonstrate Excellent Drug Exposure in the Retina and Choroid in Preclinical Studies



First data point in rabbit study is at Day 1. Data points in the NHP studies were at Months 3, 6, 9, 12, 15 and 18.

* IC_{50} = 0.2nM = 0.07ng/mL.[1] Assumes tissue density of 1 g/mL.

Reference: 1. Huang WC, et al. *Transl Vis Sci Technol*. 2021;10(14):23.

U.S. Wet AMD Phase 1 Study Design

Multicenter, Randomized, Double-masked Trial

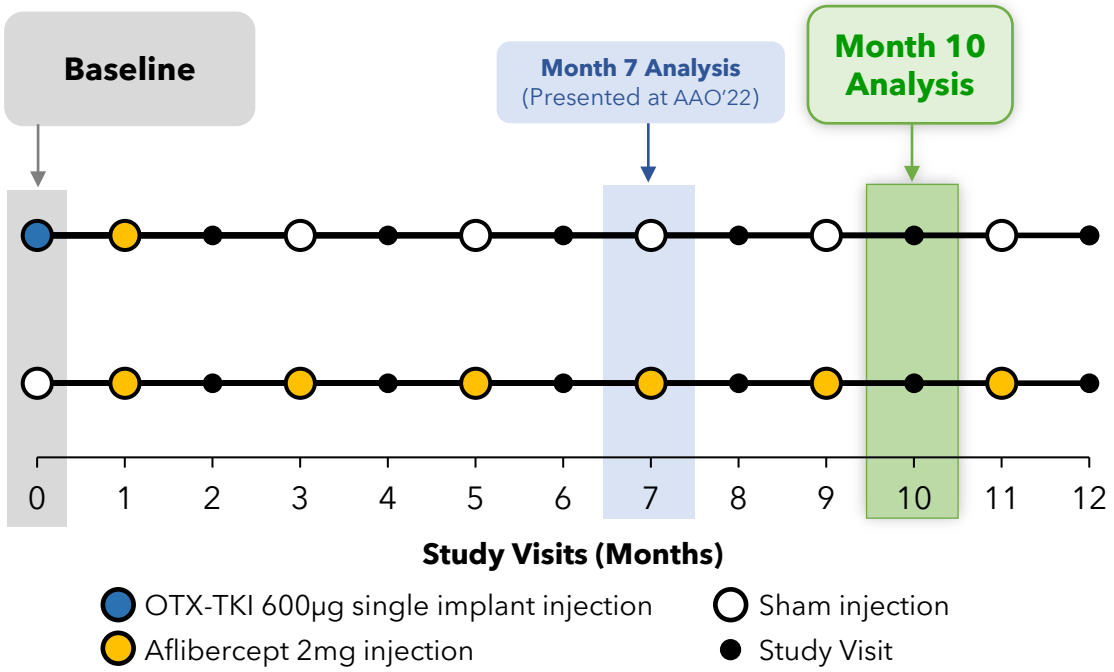
Screening

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 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

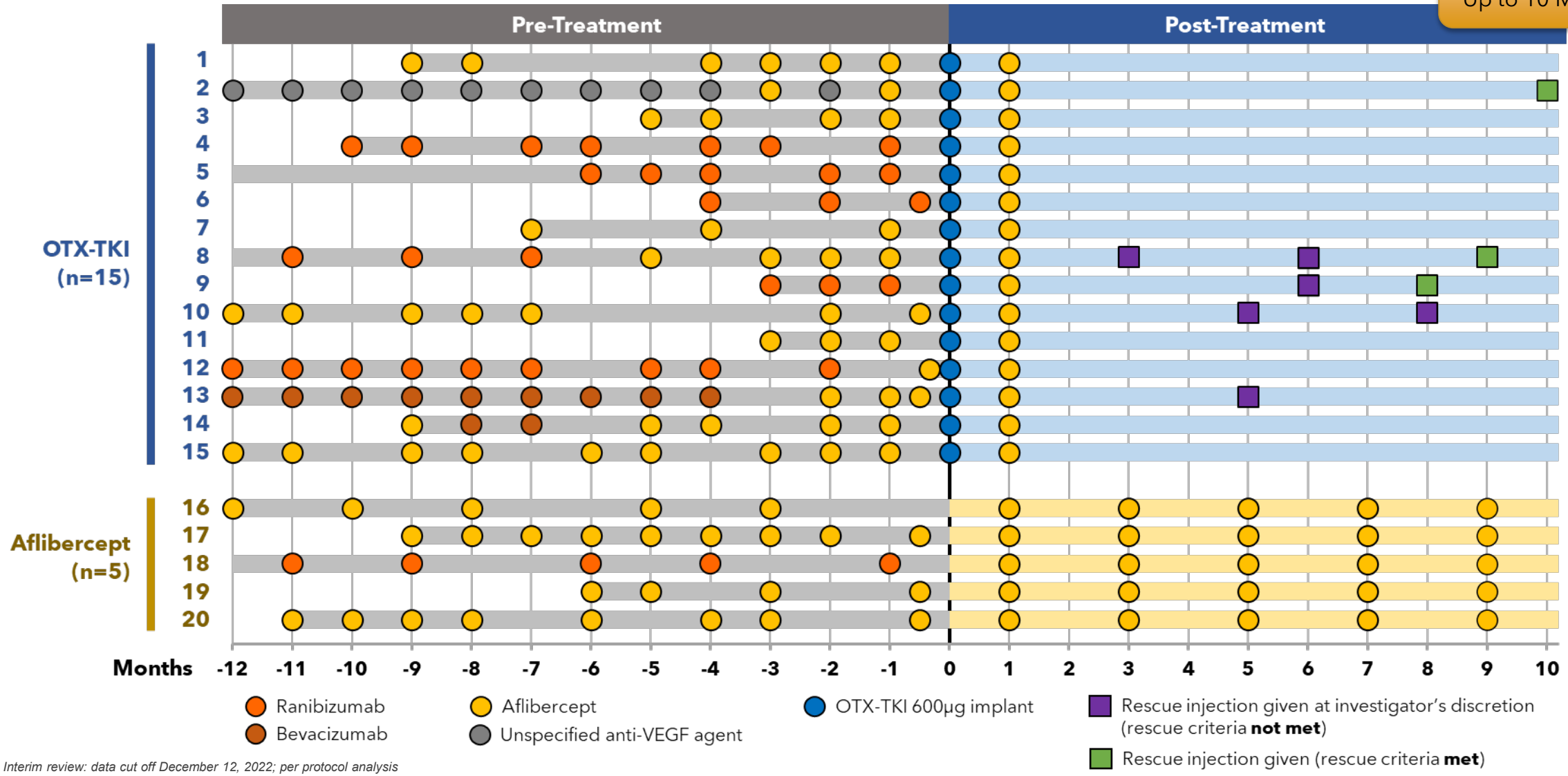
† Includes one subject not treated per protocol who has been removed from efficacy analysis as subject incorrectly received aflibercept instead of sham injection at Month 3 and 5 visits

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

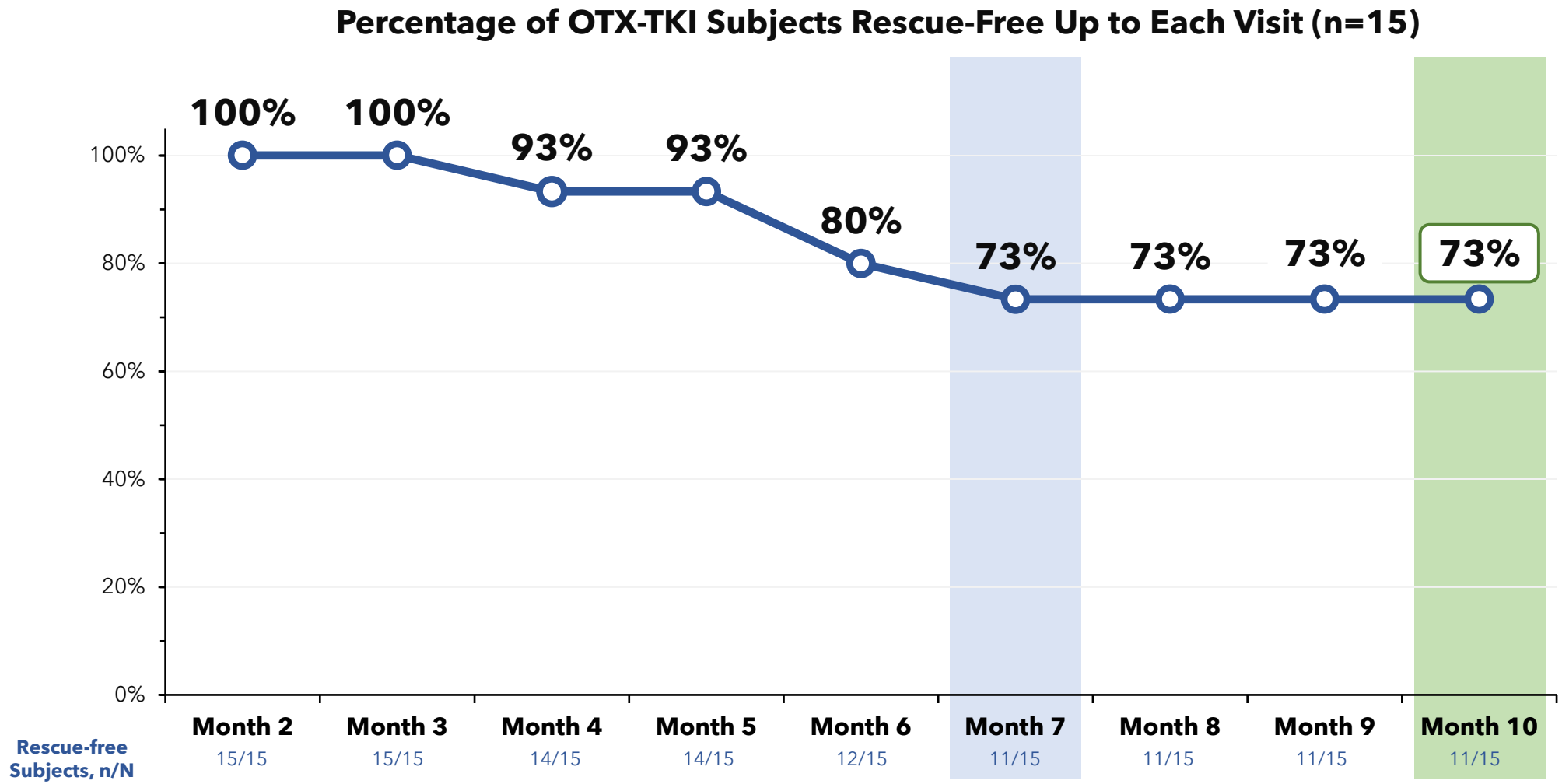
Reduction in Anti-VEGF Injections Following OTX-TKI Up to Month 10

Treatment Reduction
Up to 10 Months: 92%



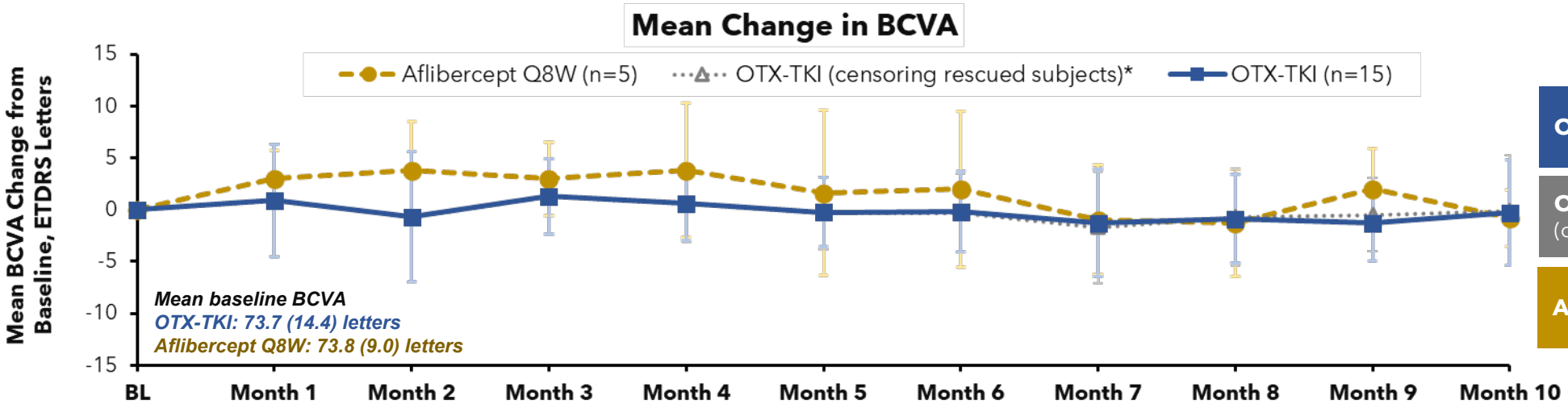
Interim review: data cut off December 12, 2022; per protocol analysis
Reduction in treatment burden calculation includes all rescue injections up to Month 10
Sham injection was given at Month 0 in the Aflibercept Arm and at Month 3, 5, 7 and 9 in the OTX-TKI Arm (not shown).

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



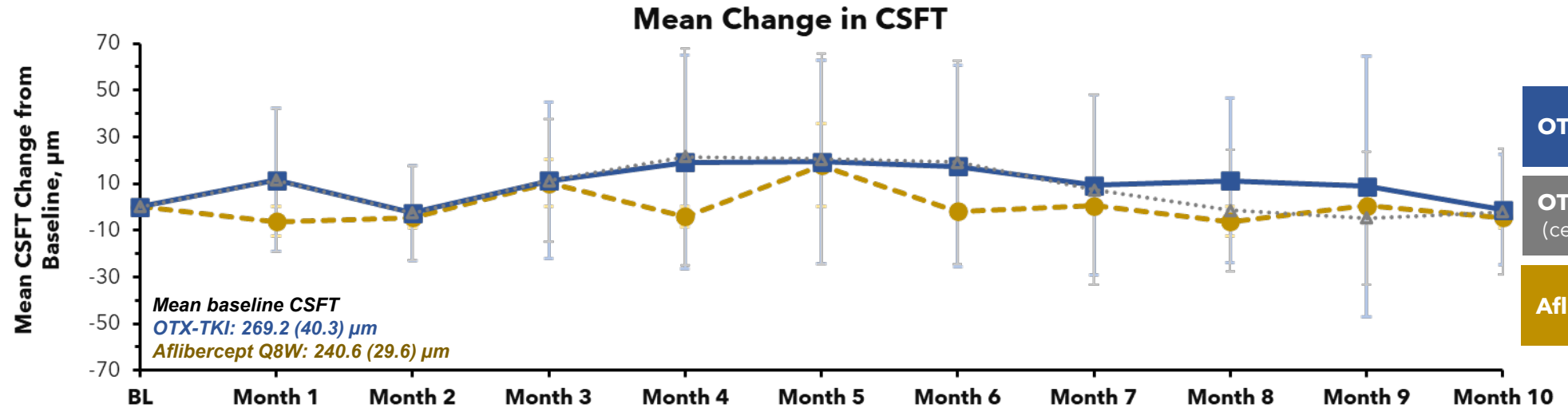
Interim review: data cut off December 12, 2022
Rescue-free rate calculations: If subjects received rescue anti-VEGF therapy at a study visit, those were reflected to the count at the following study visit in the graph above

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



Mean (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 (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**

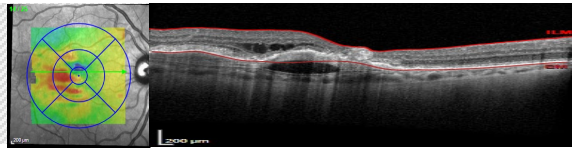
Interim review: data cut off December 12, 2022
Error bars represent standard deviation; n=14 in OTX-TKI arm at Months 2 and 7 due to missed visits
**Sample size for OTX-TKI (censoring rescued subjects): n=15 at Baseline and Months 1 and 3; n=14 at Month 2 (missed visit) and Months 4 and 5; n=12 at Month 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

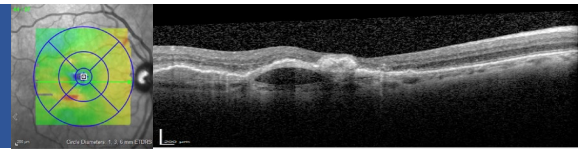
60-year-old male with anti-VEGF Q4-8W prior to study and rescue-free through Month 10

Patient received SOC wet AMD therapy prior to study

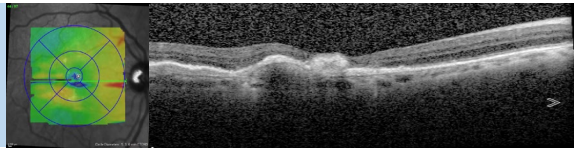
Historical OCT
(~1 month prior to baseline)
CSFT: 277 µm



Baseline
CSFT: 278 µm
BCVA: 54 letters



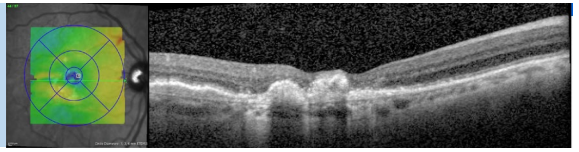
Month 1
CSFT change: -47 µm
BCVA change: +2 letters



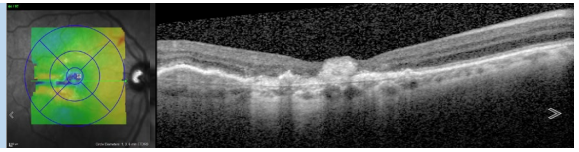
Month 2

Missed visit

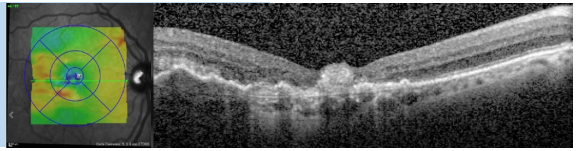
Month 3
CSFT change: -72 µm
BCVA change: +4 letters



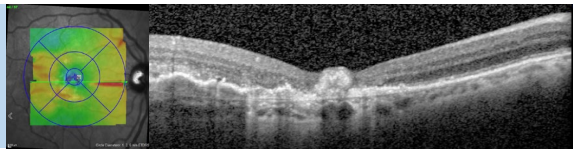
Month 4
CSFT change: -68 µm
BCVA change: +5 letters



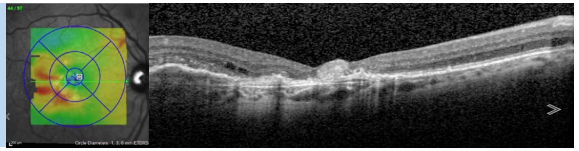
Month 5
CSFT change: -66 µm
BCVA change: +5 letters



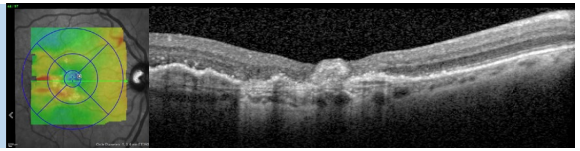
Month 6
CSFT change: -55 µm
BCVA change: +3 letters



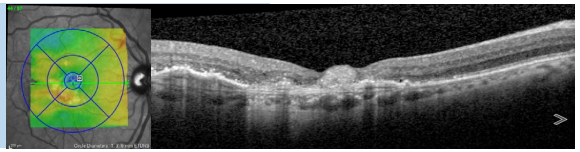
Month 7
CSFT change: -54 µm
BCVA change: +4 letters



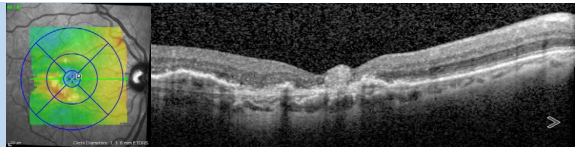
Month 8
CSFT change: -51 µm
BCVA change: +4 letters

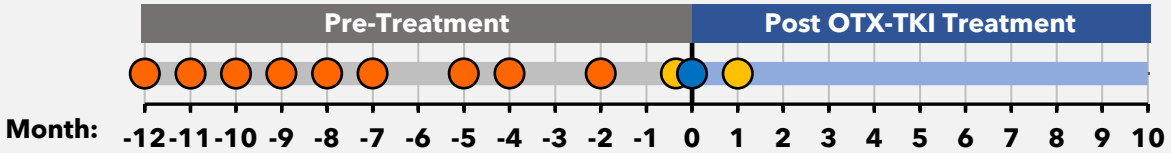


Month 9
CSFT change: -61 µm
BCVA change: +5 letters



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

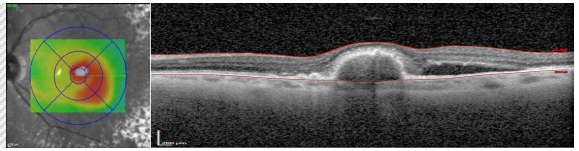
Patient received study-mandated aflibercept injection at Month 1; All changes in CSFT and BCVA are relative to baseline visit

OTX-TKI Case Study 2: Patient 15

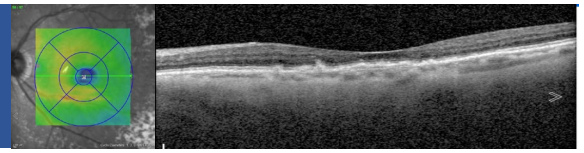
80-year-old female with aflibercept Q4-8W prior to study and rescue-free through Month 10

Patient received SOC wet AMD therapy prior to study

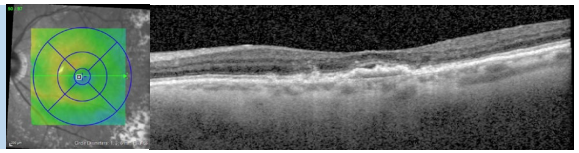
Historical OCT
(~21 months prior to baseline)
CSFT: 456 µm



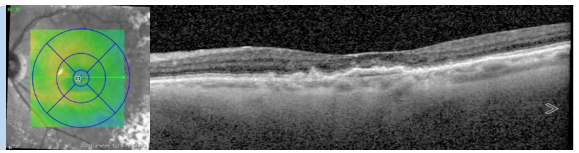
Baseline
CSFT: 183 µm
BCVA: 59 letters



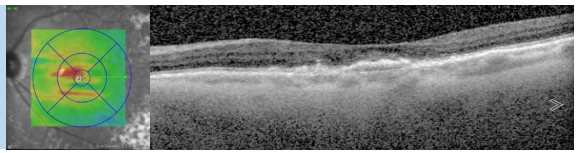
Month 1
CSFT change: +46 µm
BCVA change: 0 letters



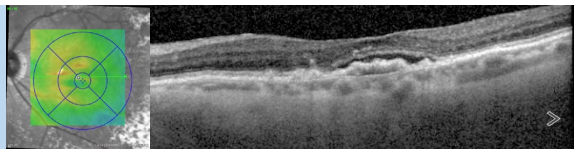
Month 2
CSFT change: +54 µm
BCVA change: +1 letter



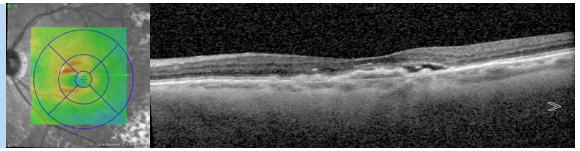
Month 3
CSFT change: +47 µm
BCVA change: -4 letters



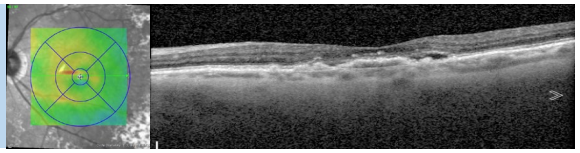
Month 4
CSFT change: +82 µm
BCVA change: +2 letters



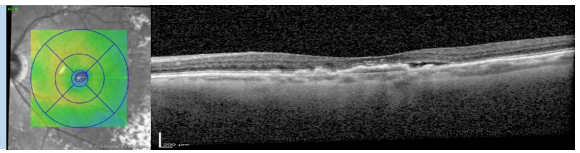
Month 5
CSFT change: +62 µm
BCVA change: -3 letters



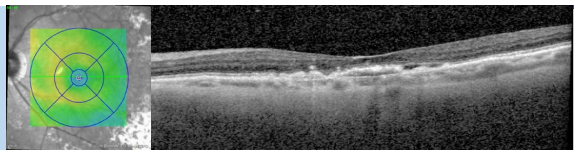
Month 6
CSFT change: +60 µm
BCVA change: -1 letter



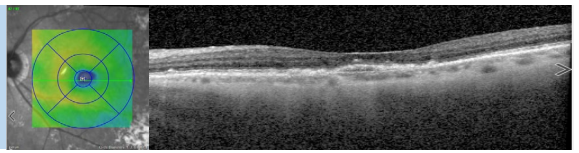
Month 7
CSFT change: +9 µm
BCVA change: -2 letters



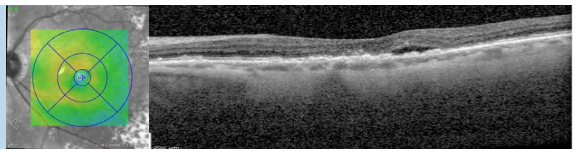
Month 8
CSFT change: +32 µm
BCVA change: +1 letter

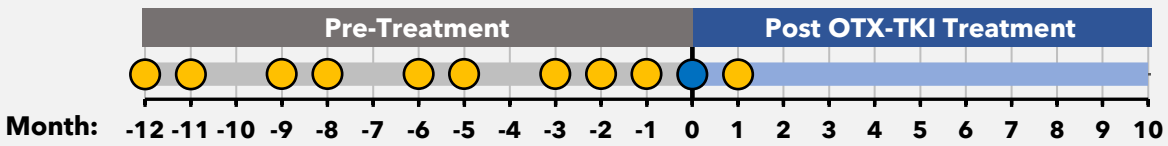


Month 9
CSFT change: -6 µm
BCVA change: 0 letters



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

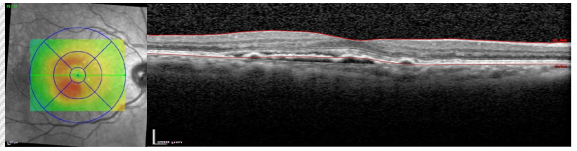
Patient received study-mandated aflibercept injection at Month 1; All changes in CSFT and BCVA are relative to baseline visit

OTX-TKI Case Study 3: Patient 14

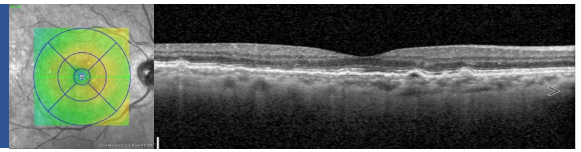
65-year-old female with anti-VEGF Q4-8W prior to study and rescue-free through Month 10

Received aflibercept

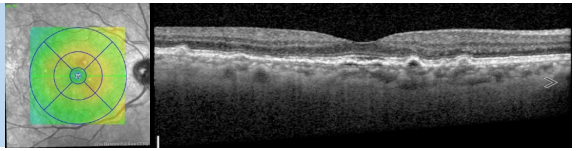
Historical OCT
(~4 months prior to baseline)
CSFT: 311 µm



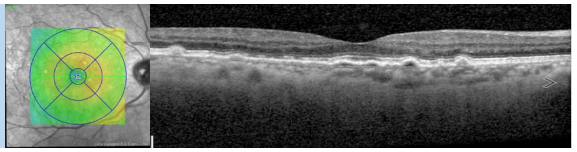
Baseline
CSFT: 243 µm
BCVA: 78 letters



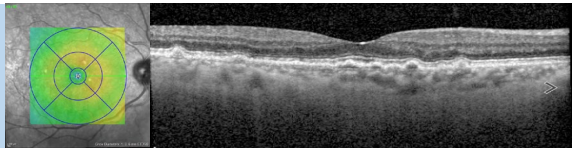
Month 1
CSFT change: +3 µm
BCVA change: +2 letters



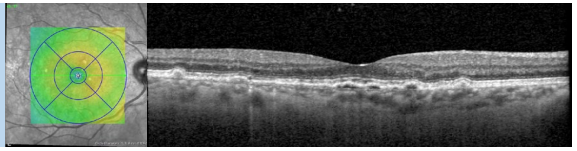
Month 2
CSFT change: +3 µm
BCVA change: -3 letters



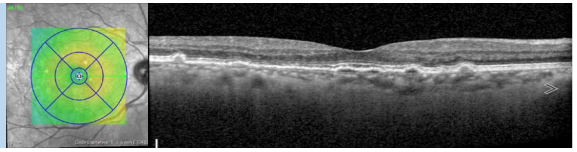
Month 3
CSFT change: +1 µm
BCVA change: +2 letters



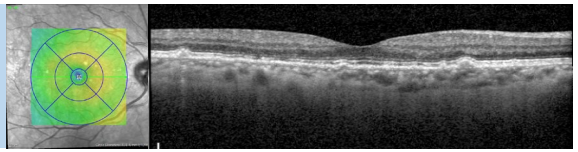
Month 4
CSFT change: 0 µm
BCVA change: +1 letter



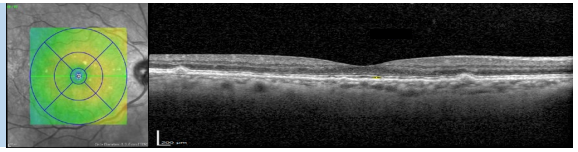
Month 5
CSFT change: -5 µm
BCVA change: +2 letters



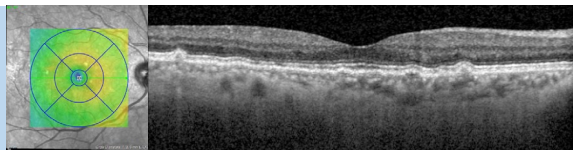
Month 6
CSFT change: -10 µm
BCVA change: +4 letters



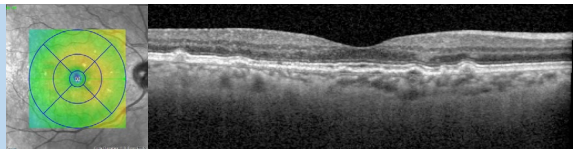
Month 7
CSFT change: -10 µm
BCVA change: +1 letter



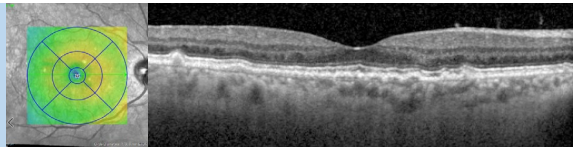
Month 8
CSFT change: -9 µm
BCVA change: +4 letters

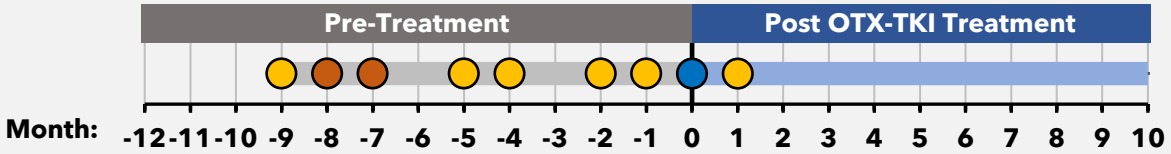


Month 9
CSFT change: -12 µm
BCVA change: 0 letters



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

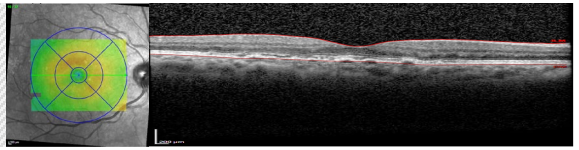
Patient received study-mandated aflibercept injection at Month 1; All changes in CSFT and BCVA are relative to baseline visit

OTX-TKI Case Study 3: Patient 14

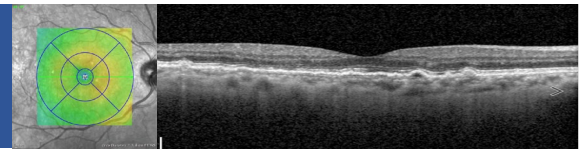
65-year-old female with anti-VEGF Q4-8W prior to study and rescue-free through Month 10

Received aflibercept

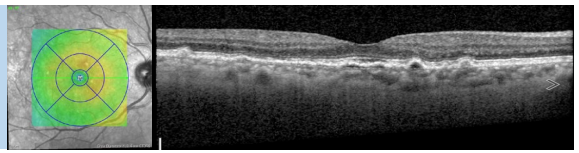
Historical OCT
(~2 months prior to baseline)
CSFT: 259 µm



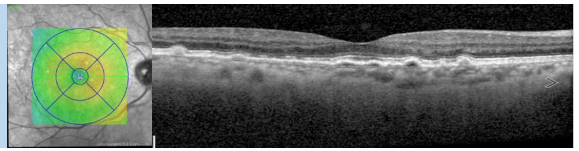
Baseline
CSFT: 243 µm
BCVA: 78 letters



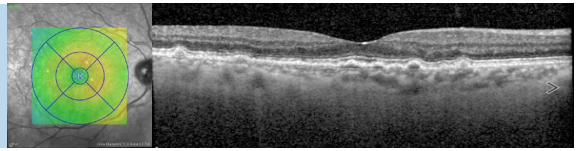
Month 1
CSFT change: +3 µm
BCVA change: +2 letters



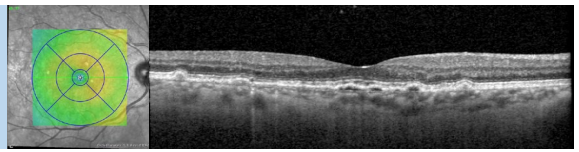
Month 2
CSFT change: +3 µm
BCVA change: -3 letters



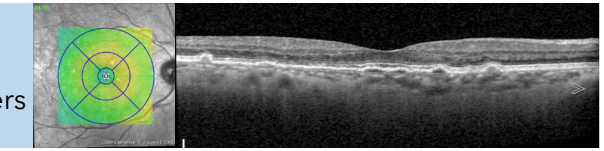
Month 3
CSFT change: +1 µm
BCVA change: +2 letters



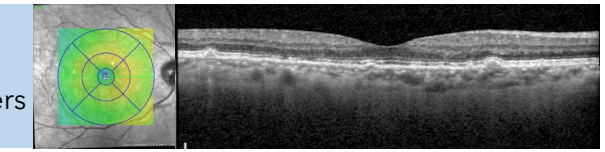
Month 4
CSFT change: 0 µm
BCVA change: +1 letter



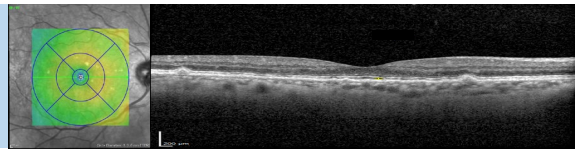
Month 5
CSFT change: -5 µm
BCVA change: +2 letters



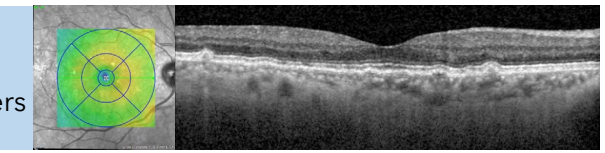
Month 6
CSFT change: -10 µm
BCVA change: +4 letters



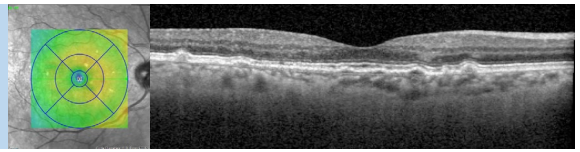
Month 7
CSFT change: -10 µm
BCVA change: +1 letter



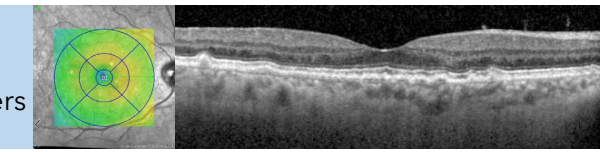
Month 8
CSFT change: -9 µm
BCVA change: +4 letters

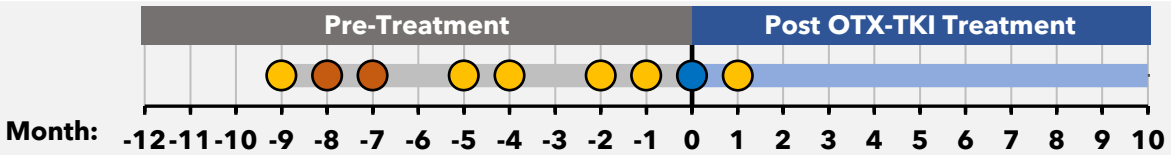


Month 9
CSFT change: -12 µm
BCVA change: 0 letters



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

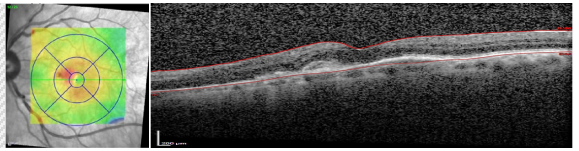
Patient received study-mandated aflibercept injection at Month 1; All changes in CSFT and BCVA are relative to baseline visit

OTX-TKI Case Study 4: Patient 5

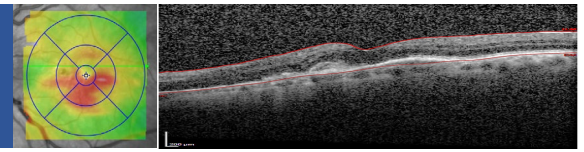
68-year-old female with ranibizumab Q4-8W prior to study and rescue-free through Month 10

Received ranibizumab

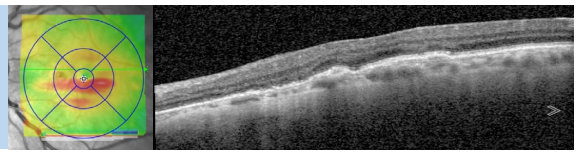
Historical OCT
(~6 months prior to baseline)
CSFT: 332 µm



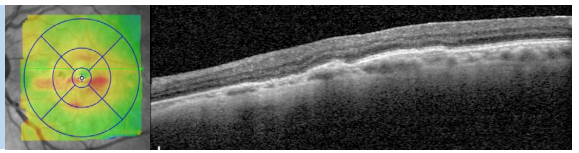
Baseline
CSFT: 331 µm
BCVA: 81 letters



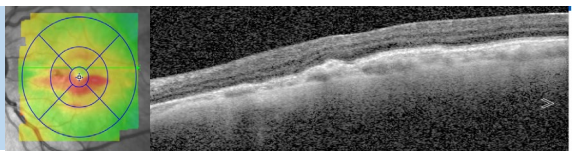
Month 1
CSFT change: -15 µm
BCVA change: -4 letters



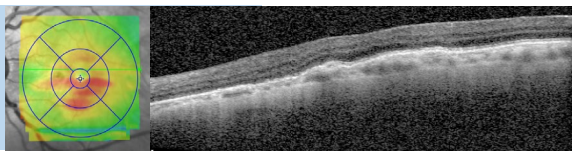
Month 2
CSFT change: -31 µm
BCVA change: +3 letters



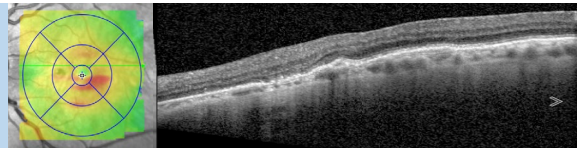
Month 3
CSFT change: -6 µm
BCVA change: +1 letter



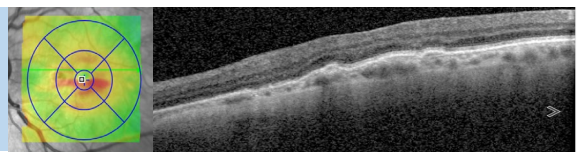
Month 4
CSFT change: -2 µm
BCVA change: +2 letters



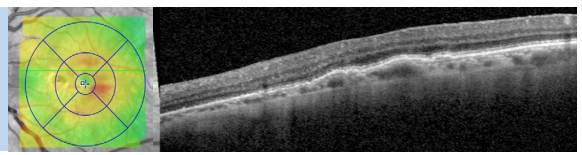
Month 5
CSFT change: -19 µm
BCVA change: -1 letter



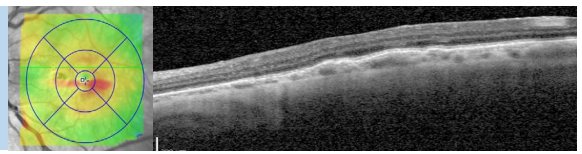
Month 6
CSFT change: -17 µm
BCVA change: 0 letters



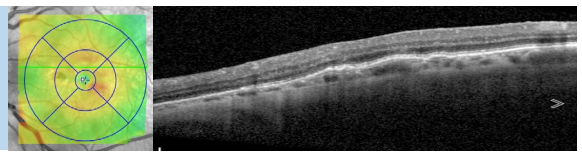
Month 7
CSFT change: -20 µm
BCVA change: 0 letters



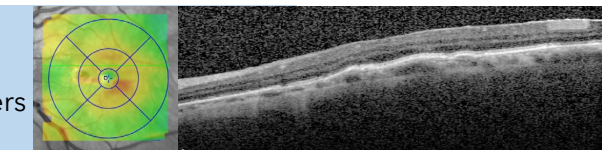
Month 8
CSFT change: -33 µm
BCVA change: -1 letter

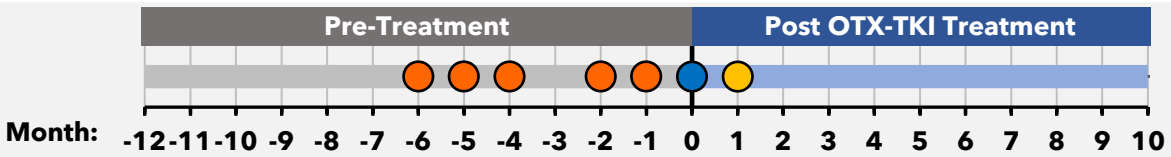


Month 9
CSFT change: -30 µm
BCVA change: -1 letter



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

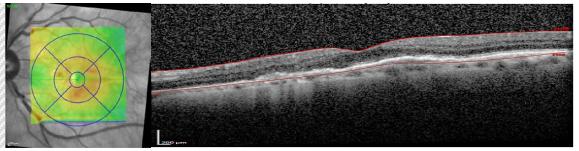
Patient received study-mandated aflibercept injection at Month 1; All changes in CSFT and BCVA are relative to baseline visit

OTX-TKI Case Study 4: Patient 5

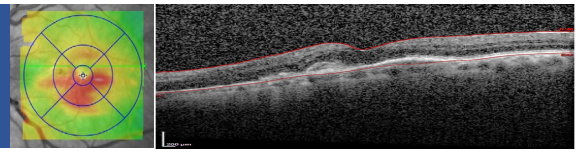
68-year-old female with ranibizumab Q4-8W prior to study and rescue-free through Month 10

Received ranibizumab

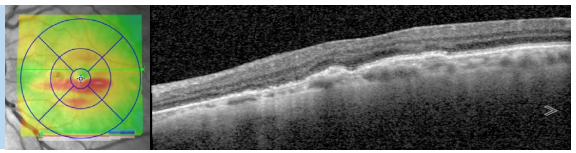
Historical OCT
(~2 months prior to baseline)
CSFT: 302 µm



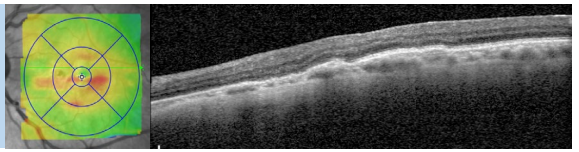
Baseline
CSFT: 331 µm
BCVA: 81 letters



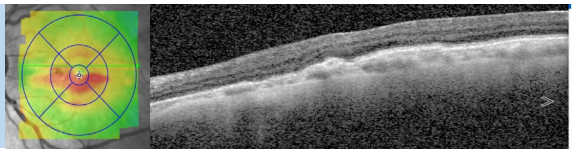
Month 1
CSFT change: -15 µm
BCVA change: -4 letters



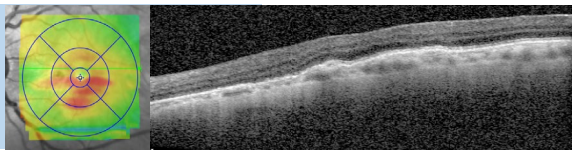
Month 2
CSFT change: -31 µm
BCVA change: +3 letters



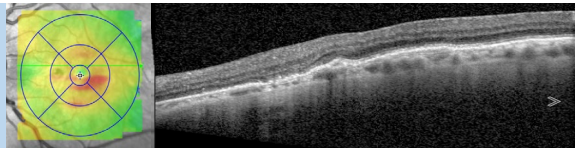
Month 3
CSFT change: -6 µm
BCVA change: +1 letter



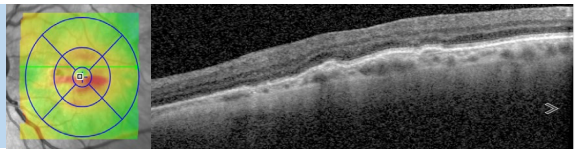
Month 4
CSFT change: -2 µm
BCVA change: +2 letters



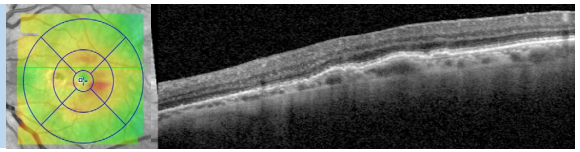
Month 5
CSFT change: -19 µm
BCVA change: -1 letter



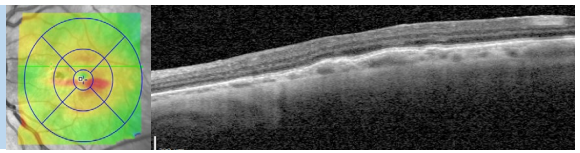
Month 6
CSFT change: -17 µm
BCVA change: 0 letters



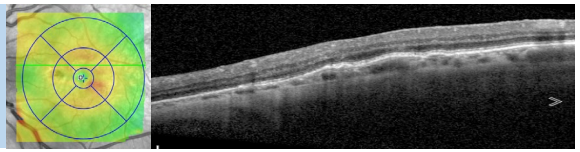
Month 7
CSFT change: -20 µm
BCVA change: 0 letters



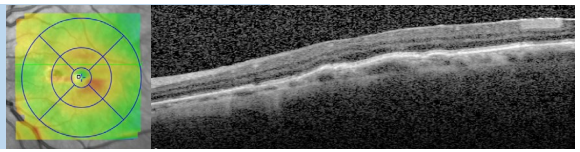
Month 8
CSFT change: -33 µm
BCVA change: -1 letter

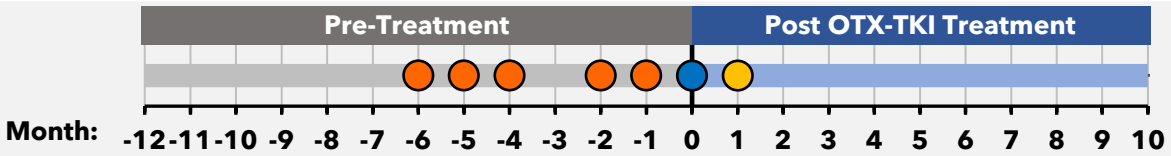


Month 9
CSFT change: -30 µm
BCVA change: -1 letter



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





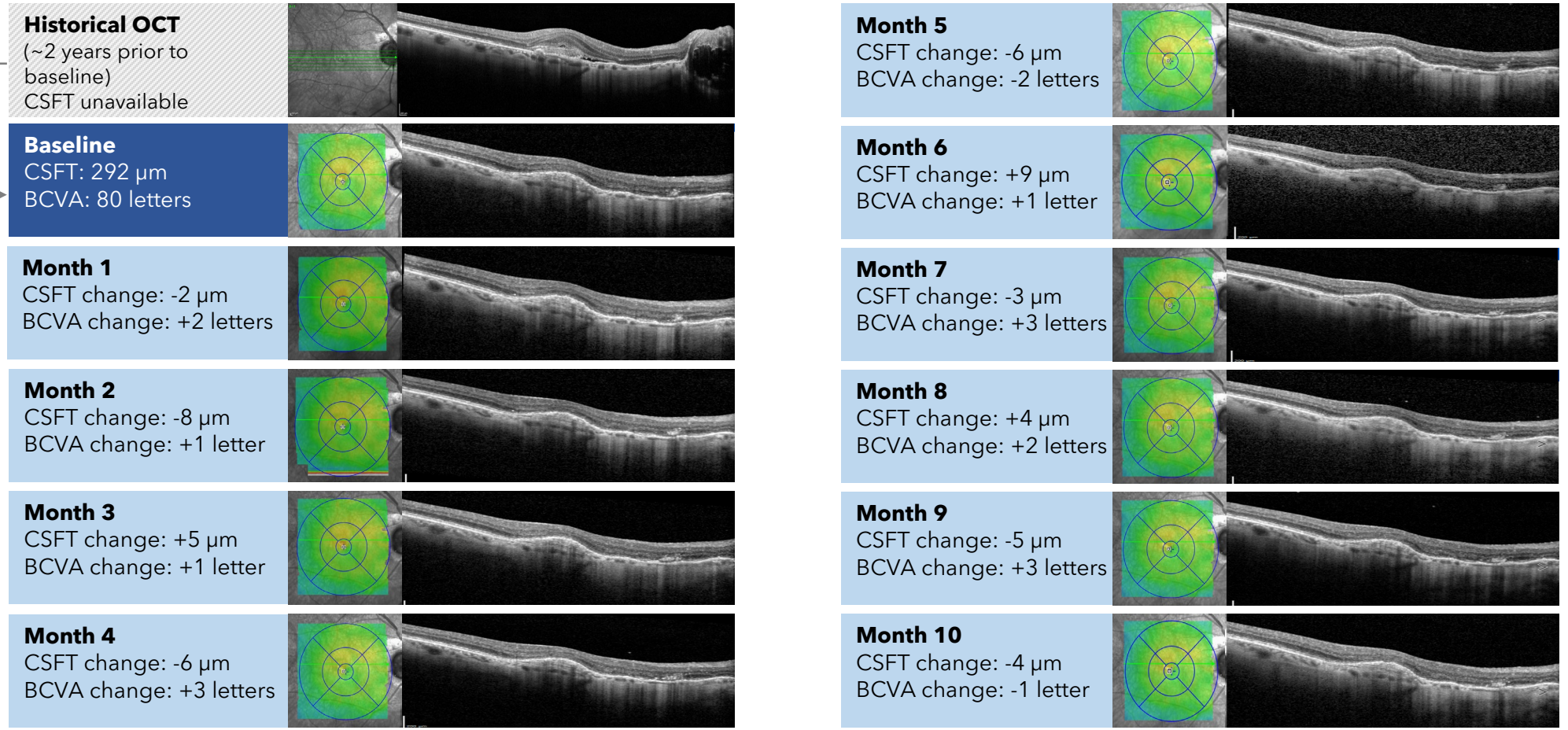
Ranibizumab
Aflibercept
OTX-TKI 600µg implant
Rescue injection given at investigator's discretion (criteria not met)
Rescue injection given per rescue criteria

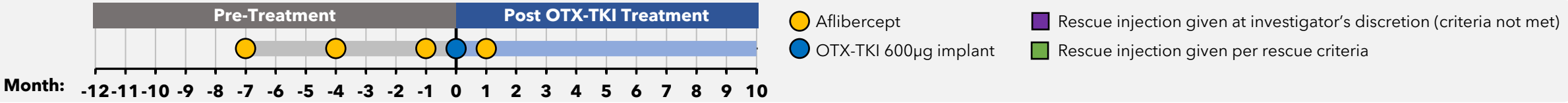
Patient received study-mandated aflibercept injection at Month 1; All changes in CSFT and BCVA are relative to baseline visit

OTX-TKI Case Study 5: Patient 7

75-year-old female with aflibercept Q12W prior to study and rescue-free through Month 10

Patient received SOC nAMD therapy prior to study





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

Safety Summary[1]: OTK-TKI was generally well tolerated

- 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

[1]*Interim review: data cut off December 12, 2022: includes n=4 subjects in the OTX-TKI arm past Month 12*
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

- Preclinical pharmacokinetic studies demonstrate OTX-TKI provides rapid and sustained-release of axitinib at levels 100-fold above IC_{50} in targeted tissues, providing excellent drug exposure in the retina and choroid

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
- 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

Implant Resorption

- Interim data suggests OTX-TKI 0.6mg hydrogel implant bioresorbs at an average of ~9 months

Next Steps:

- Study is ongoing and follow-up will continue through Month 12 per protocol
- Preparing for wet AMD pivotal trial initiation

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