OTX-TKI, Sustained-Release Axitinib Hydrogel Implant, for Neovascular Age-Related Macular Degeneration

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Disclosures

Financial Disclosures (Robert L. Avery)

Consultant

4DMT, Adverum, Alcon, Alimera, Allergan, Amgen, Apellis, Asclepix, Aviceda, Bausch + Lomb, Cardinal Health, Clearside, Coherus, Eyepoint Pharma, ForwardVue, Genentech, Glaukos, InFocus Captial Partners, Iridex, Imprimis, Ingenia, Kriya, KYS Vision, Notal Vision, Novartis, Nvasc, Ocular Therapeutix, Ocuterra, Outlook, Pr3vent AI, Pulsmedica, RegenXbio, Replenish, ReVana Therapeutics, Santen, Tenpoint Therapeutics, Vial, Visionary Ventures

Equity

Abbvie, Adverum, Alcon, Aldeyra, Apellis, Aviceda, Eyepoint Pharma, ForwardVue, Ingenia, Iveric, Kodiak, KYS Vision, Novartis, Nvasc, Outlook, ReVana Therapeutics, Regeneron, Replenish, Revana, Verana Health

Study and Product Disclosures

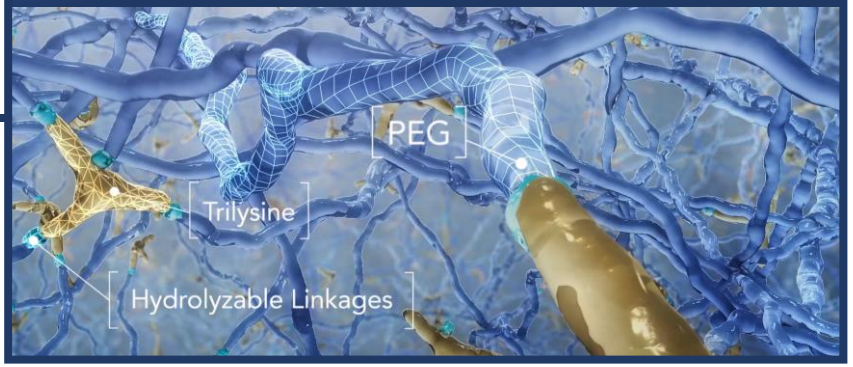
- The following presentation discusses an investigation drug, OTX-TKI, in development. OTX-TKI's efficacy and safety profiles have not been established, and it has not been approved for marketing by the U.S. Food and Drug Administration (FDA) or any other health agency
- Ocular Therapeutix sponsored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

OTX-TKI Implant: Axitinib Delivered Using Elutyx™ Technology

ELUTYX TECHNOLOGY

BIORESORBABLE, TARGETED, SUSTAINED DRUG DELIVERY

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



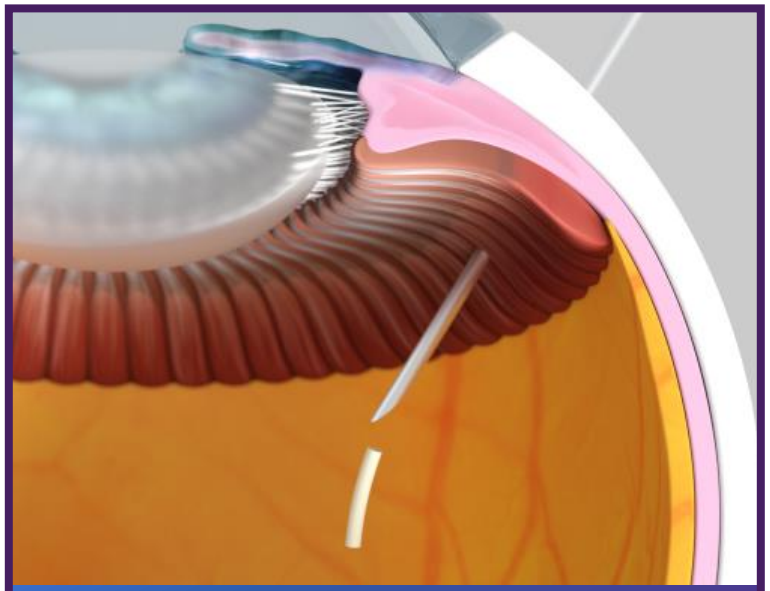
AXITINIB

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 DELIVERED USING ELUTYX TECHNOLOGY

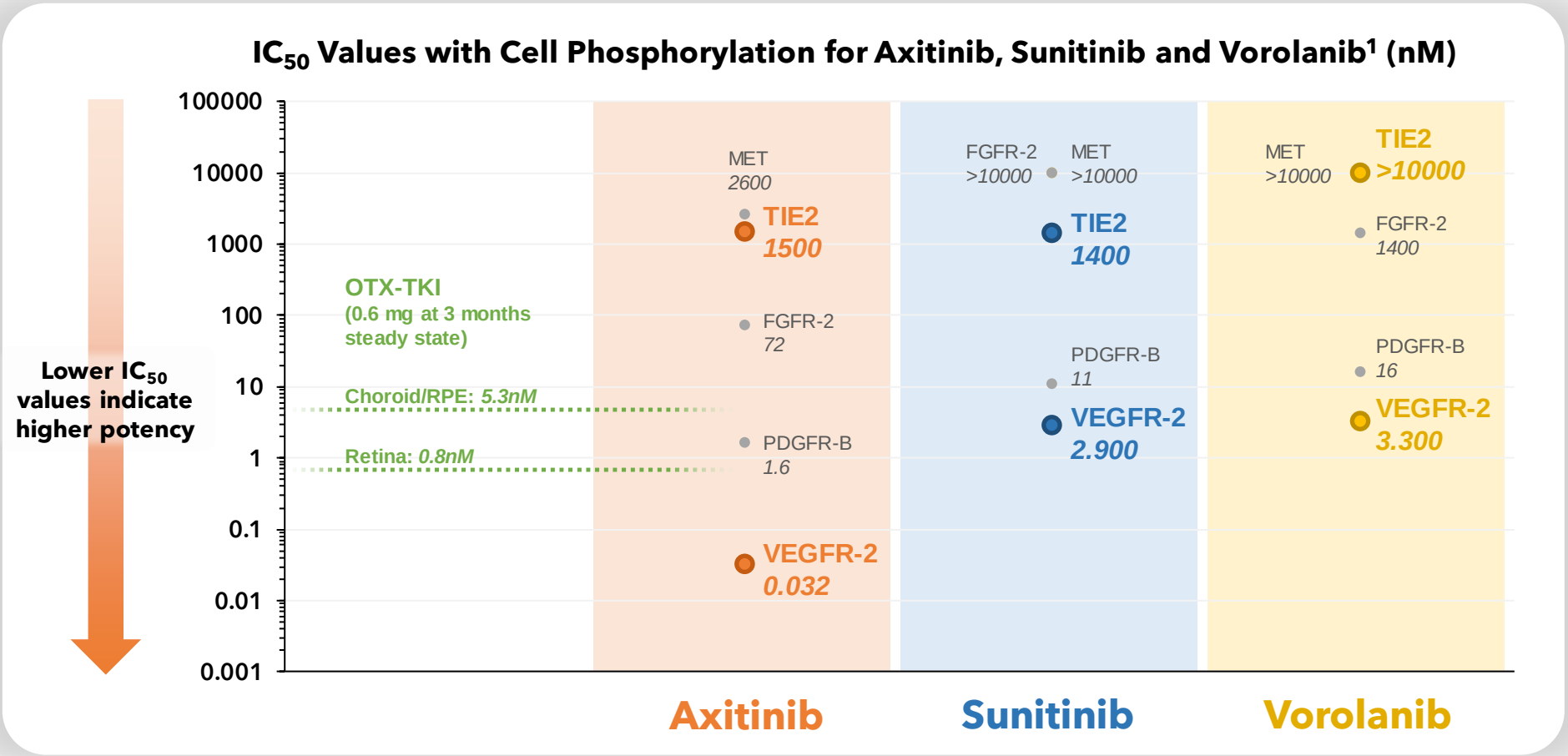


- Single implant
- Administered by a 25G needle
- Target release for 9-12 months
- Completely bioresorbable

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

Axitinib Has Highest Potency for VEGFR-2

- **Over 100 X potent for VEGFR-2 compared to Vorolanib and 90 X potent for VEGFR-2 compared to Sunitinib**
- **No TIE2 inhibition at clinically relevant tissue concentrations***



***following extensive protein and melanin binding in ocular tissues**

References: 1. Unpublished data; Data on File. In vitro cell-based assays used to characterize IC50 values of axitinib for receptors VEGFR-2 (using HUVECs), PDGFR-Beta (in murine fibroblast cells), and a non-target receptor TIE2 (utilizing CHO cells).

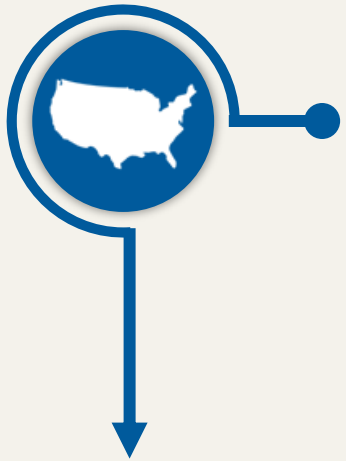
Abbreviations: CHO=Chinese Hamster Ovary; FGFR=fibroplast growth factor receptor; HUVEC=Human Umbilical Vein Endothelial Cells; MET=Mesenchymal-Epithelial Transition; PDGFR=platelet-derived growth factor receptor; TIE2=Tyrosine Kinase with Immunoglobulin-like and EGF-like domains 2; VEGFR=vascular endothelial growth factor receptor

OTX-TKI Clinical Development Program

Australia
Phase 1 Trial

Open-Label, Dose Escalation Trial*

- 29 subjects dosed with OTX-TKI
- To evaluate the safety and biological activity of OTX-TKI in treatment naïve or previously treated active wet AMD subjects
- Demonstrated potential as a durable sustained-release monotherapy in subjects with pre-existing fluid



U.S.
Phase 1 Trial

Randomized, Controlled Trial*

- 16 subjects dosed with OTX-TKI
- To evaluate the safety and biological activity of OTX-TKI in previously treated controlled wet AMD subjects compared to aflibercept Q8W
- Shows potential as a durable sustained-release maintenance therapy in subjects with controlled retinal fluid

* Safety follow-up is ongoing
Australia Phase 1 Trial Protocol CLN-Protocol-0046 (NCT03630315)
US Phase 1 Trial Protocol OTX-TKI-2020-101 (NCT04989699)

OTX-TKI Wet AMD Dose-Escalation Clinical Trial in Australia

Research Question: Does axitinib (tyrosine kinase inhibitor) have biological activity in wet AMD subjects with retinal fluid when administered intravitreally?

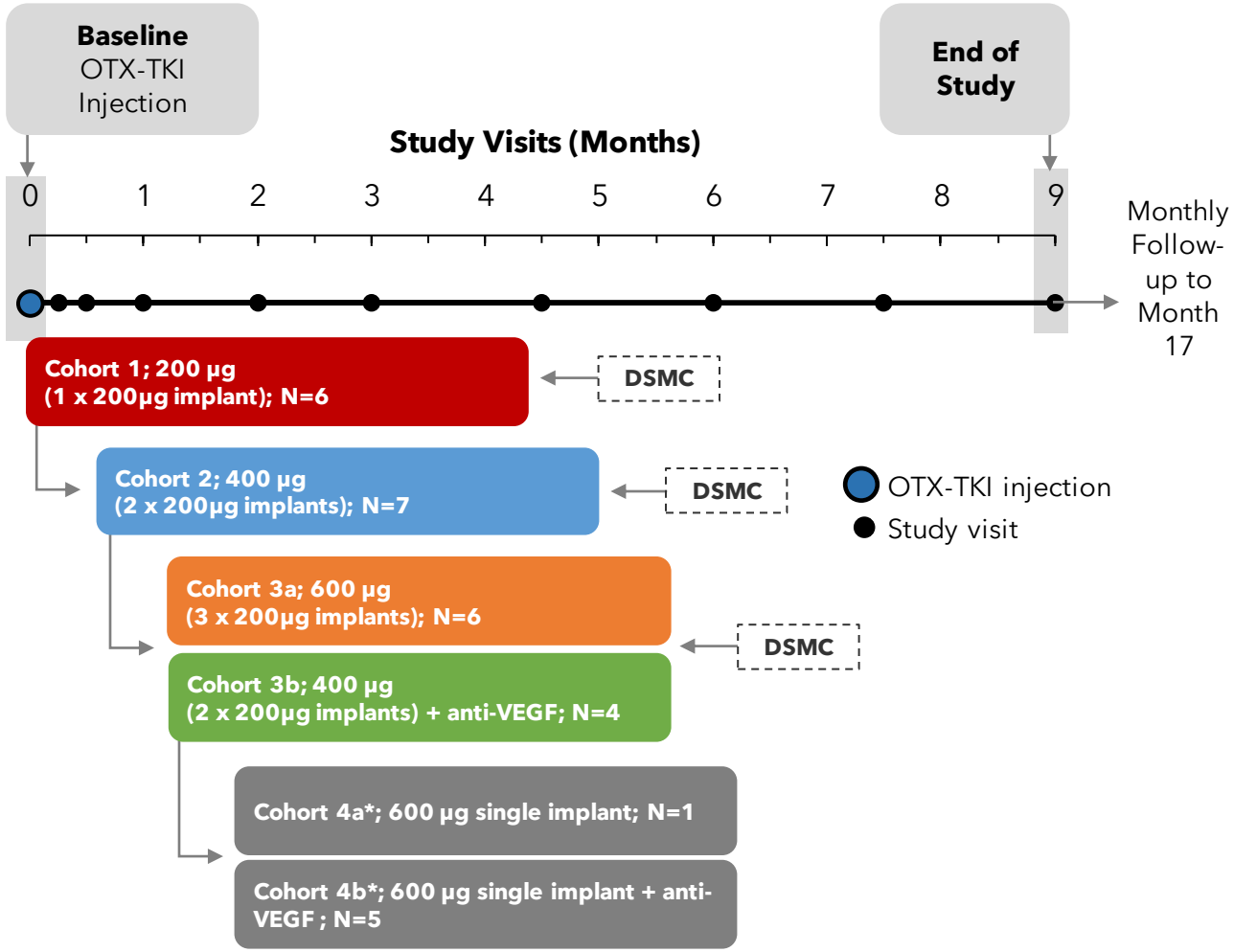
Open-label, Dose Escalation, Feasibility Trial

Objectives

- Safety and tolerability
- Biological activity: mean change in central subfield thickness measured by SD-OCT, BCVA, and clinically-significant leakage on FA and/or OCT-A

Key Inclusion Criteria

- Active primary sub foveal neovascularization secondary to AMD
- **Previously treated or treatment naïve subjects**
- **Presence of retinal fluid**

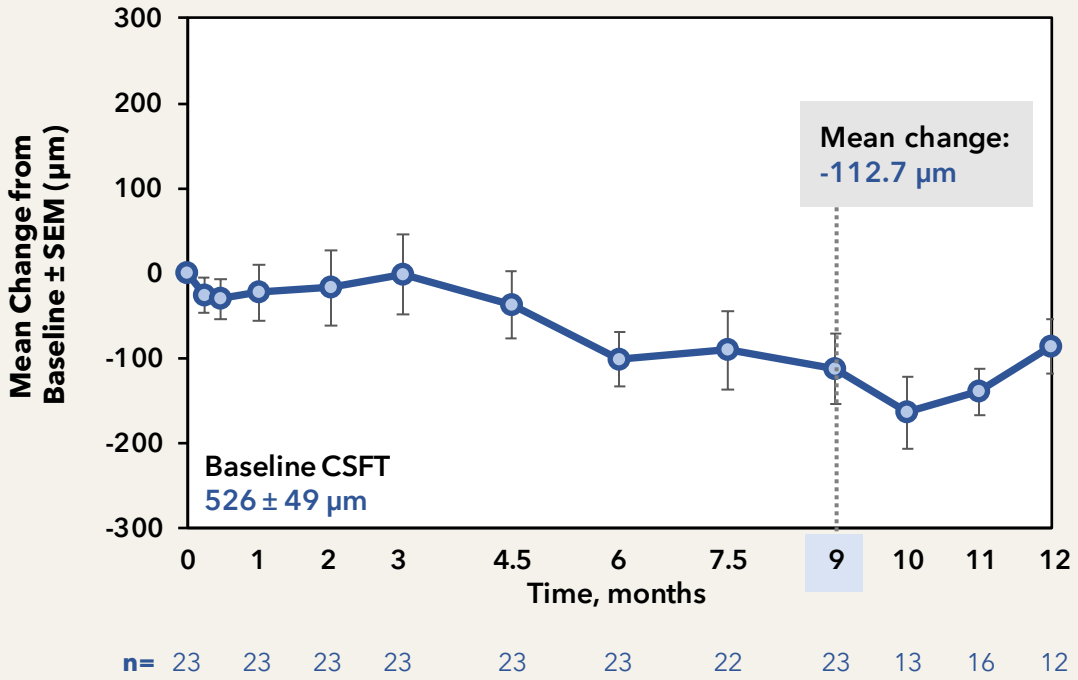


* Follow-up is ongoing

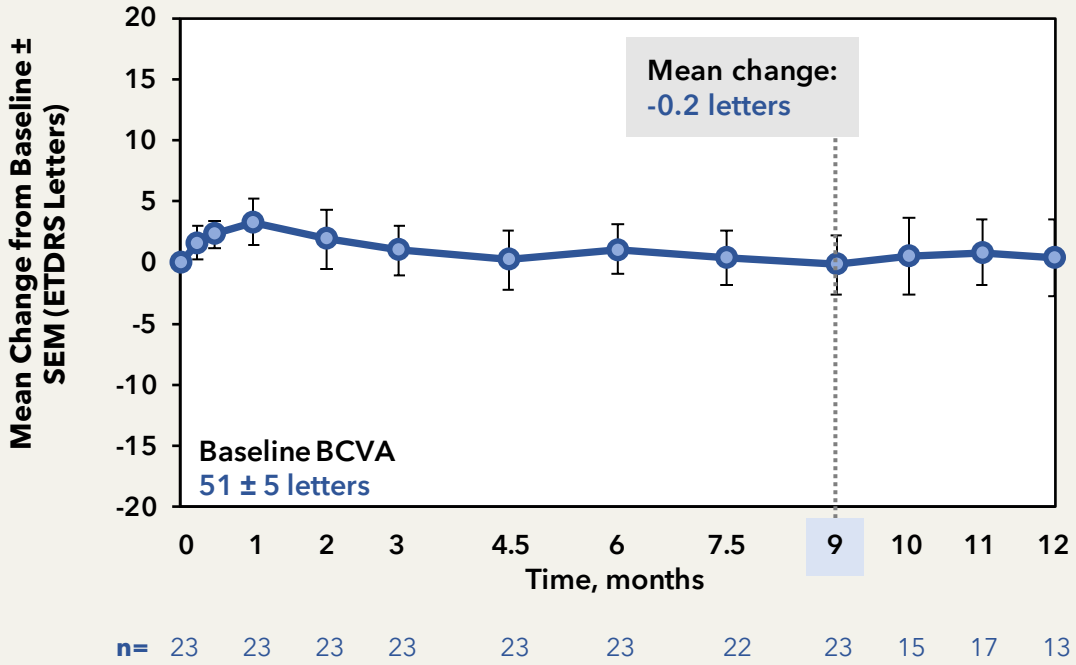
Abbreviations: AMD=age-related macular degeneration; BCVA=best corrected visual acuity; DSMC=data and safety monitoring committee; FA=fluorescein angiography; OCT-A,=ptical coherence tomography angiography; SD-OCT=spectral domain optical coherence tomography

OTX-TKI Data Suggest Control of Retinal Fluid and Vision Over Time

Central Subfield Thickness (CSFT)



Best Corrected Visual Acuity (BCVA)

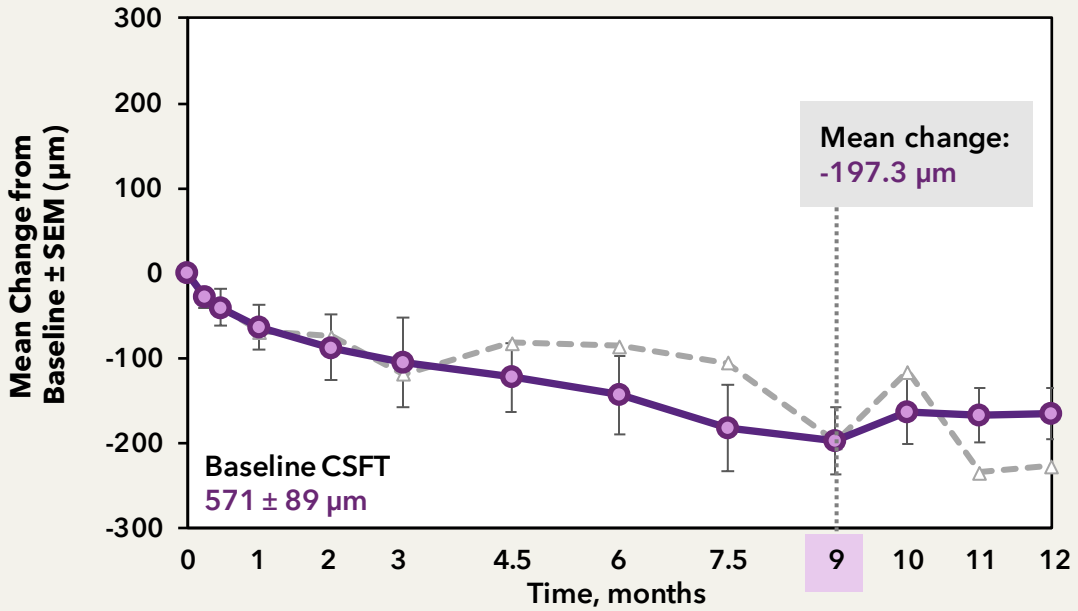


Cohorts 1-3 Subjects (Pooled; N=23)

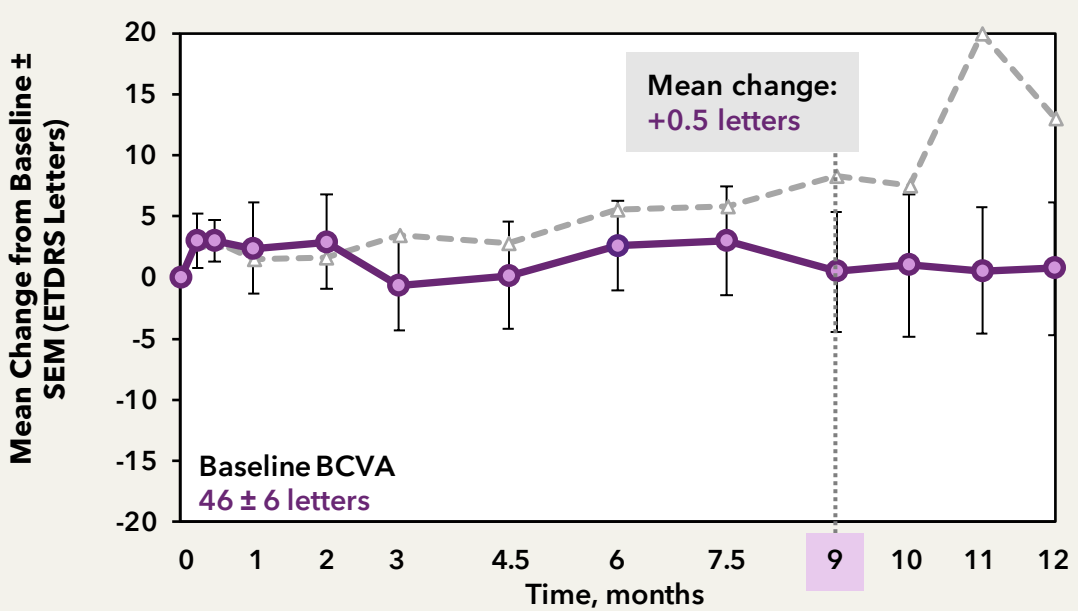
Note: Interim review, unmonitored data; Data cut off August 5, 2022

Post Hoc Analysis: Evidence of Biological Activity Observed After Single Treatment with OTX-TKI in Treatment Naïve Subjects

Central Subfield Thickness (CSFT)



Best Corrected Visual Acuity (BCVA)



Treatment-Naive Subjects (n=11) Treatment-Naive Subjects* (after removing rescue subjects)

Note: Interim review, unmonitored data; Data cut off August 5, 2022
Number of treatment-naïve subjects in each cohort. Cohort 1 (n=2), Cohort 2 (n=2), Cohort 3a (n=5), and Cohort 3b (n=2)

Safety and Tolerability*

No serious ocular adverse events reported

No reports of significant adverse events:

- No endophthalmitis
- No retinal detachment
- No implant migration into the anterior chamber
- No elevated IOP
- No retinal vasculitis

Adverse Events in the Study Eye, n	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=4)	Total (n=23)
Vitreous floaters	0	1	0	2	3
Endophthalmitis	0	0	0	0	0
Retinal detachment	0	0	0	0	0
Implant migration into AC	0	0	0	0	0
Elevated IOP	0	0	0	0	0
Ocular inflammation	0	0	0	1	1
Ocular Adverse Events in the Study Eye Reported by Maximum Severity, n					
Ocular AEs	4	7	6	3	20
Mild	4	4	3	2	13
Moderate	0	3	2	1	6
Severe	0	0	1[a]	0	1[a]
Serious AEs	0	0	0	0	0

[a] Severe ocular AE in Cohort 3a was worsening of cataract
Note: A subject is counted once for the most severe event if the subject reported one or more events.

*Follow-up is ongoing
Note: Interim review, unmonitored data; Data cut off August 5, 2022

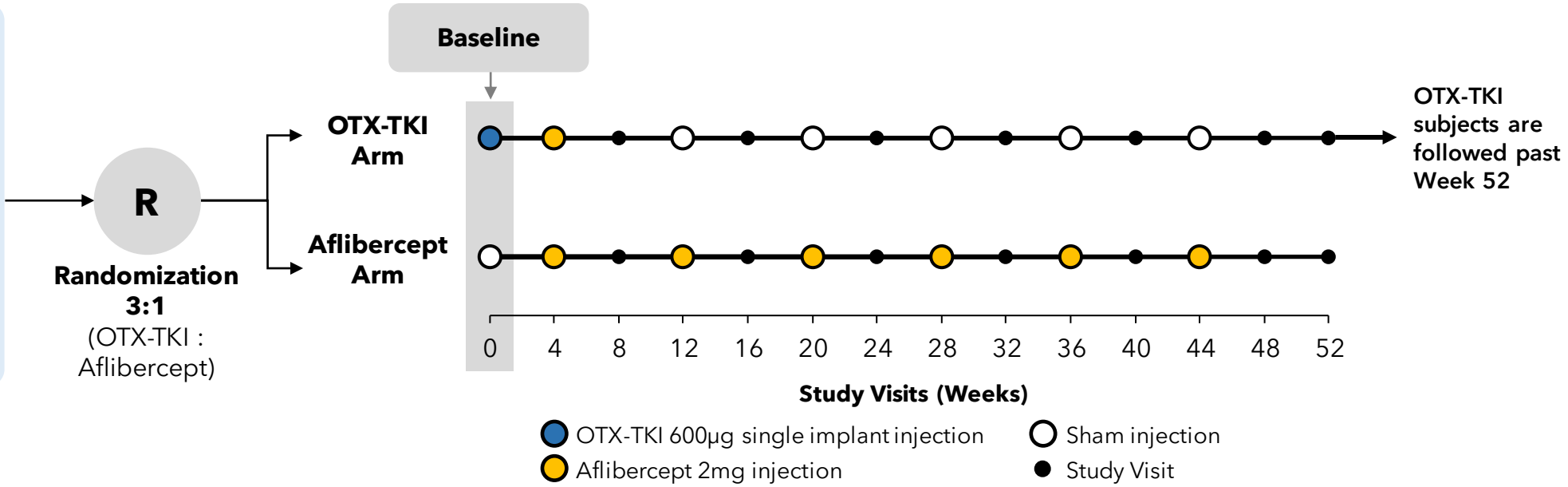
OTX-TKI U.S.-based Wet AMD Clinical Trial Design

Multicenter, Randomized, Double-masked Trial

Screening

Key Inclusion Criteria

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



Supplemental Anti-VEGF Injection Criteria:

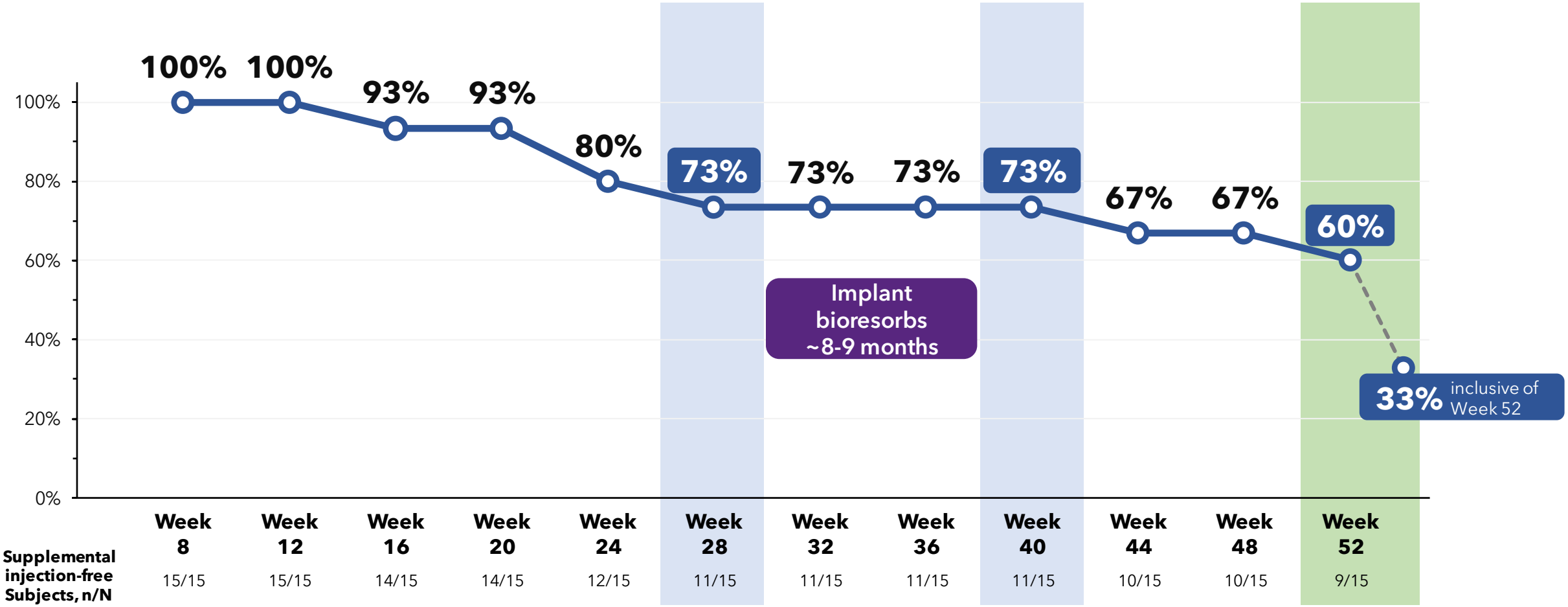
- Loss of ≥10 letters from best previous BCVA with current BCVA worse than baseline, or
- Evidence of ≥75µm CSFT increase from previous best value and ≥5 letters loss from best previous BCVA, or
- New macular hemorrhage

Abbreviations: AMD=age-related macular degeneration; BCVA=best corrected visual acuity; BL=baseline; CSFT=central subfield thick ness; AMD=age-related macular degeneration; VEGF=vascular endothelial growth factor

OTX-TKI Data Suggest Extended Duration of Action

60% were supplemental injection-free up to 12 months; 4 additional subjects received supplemental injections at 12 months

Percentage of OTX-TKI Subjects Supplemental Injection-Free Up to Each Visit (n=15)

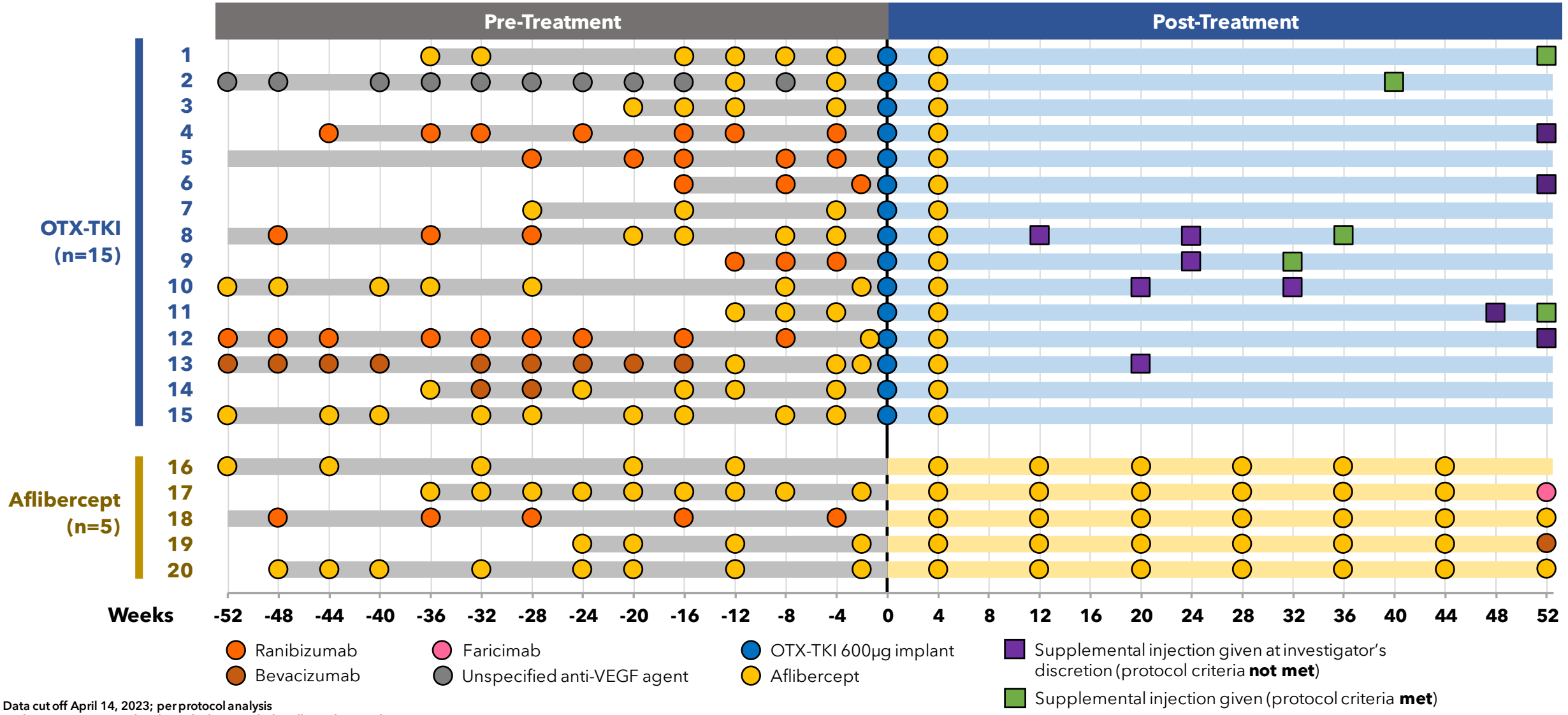


	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Supplemental injection-free Subjects, n/N	15/15	15/15	14/15	14/15	12/15	11/15	11/15	11/15	11/15	10/15	10/15	9/15

Data cut off April 14, 2023
Supplemental injection-free rate calculations: If subjects received supplemental anti-VEGF therapy at a study visit, those were reflected to count at the following study visit in the graph above
Percentages presented in the graph above represent supplemental injection-free rates up to each study visit, except for the 33% at Week 52 which includes supplemental injections given at the Week 52 study visit

Reduction in Anti-VEGF Injections Following OTX-TKI at 12 Months

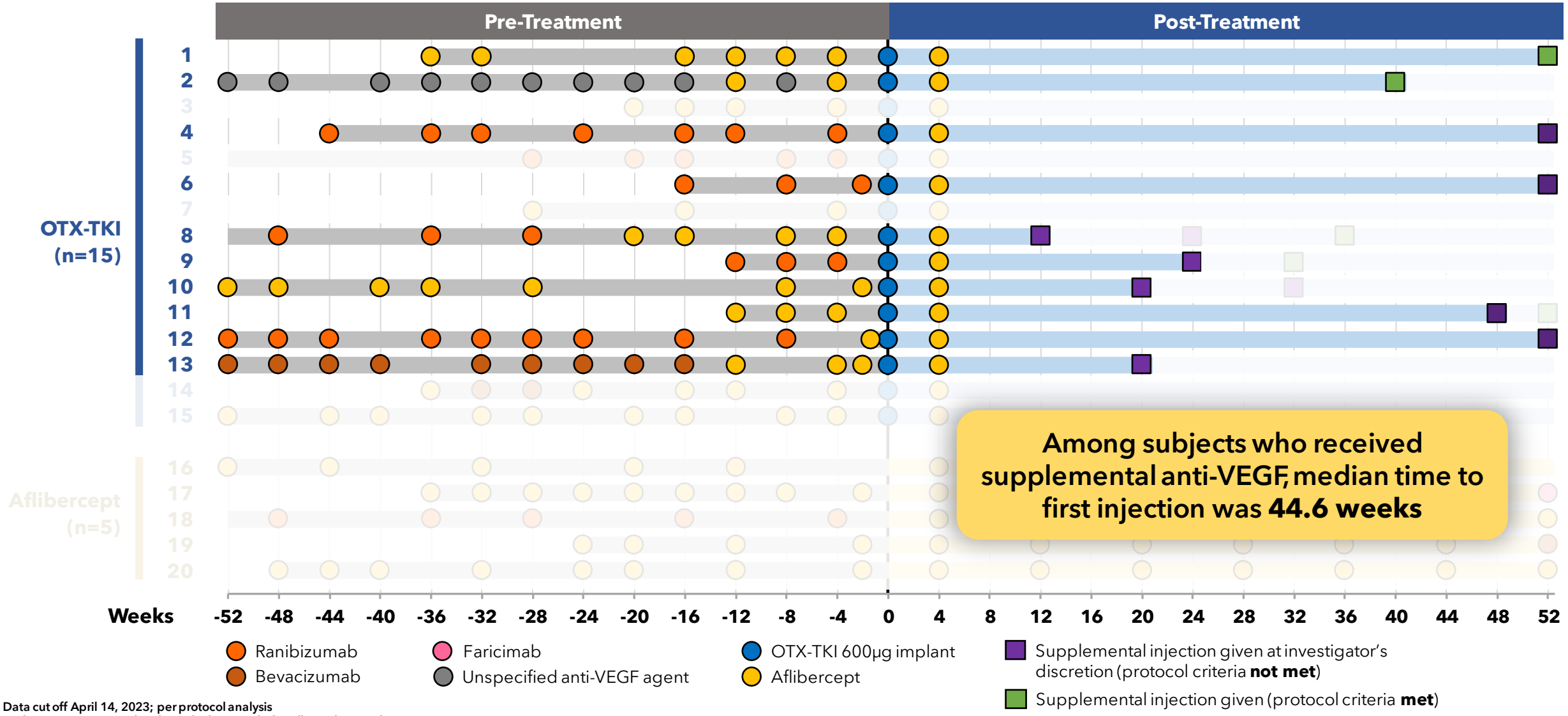
89% reduction in treatment burden with OTX-TKI at 12 months



Data cut off April 14, 2023; per protocol analysis
Reduction in treatment burden calculation includes all supplemental injections
Sham injection was given at Week 0 in the Aflibercept Arm and at Weeks 12, 20, 28, 36 and 44 in the OTX-TKI Arm (not shown). At Week 52, subjects in the aflibercept group were treated with wet AMD standard of care at the investigator's discretion.

Reduction in Anti-VEGF Injections Following OTX-TKI at 12 Months

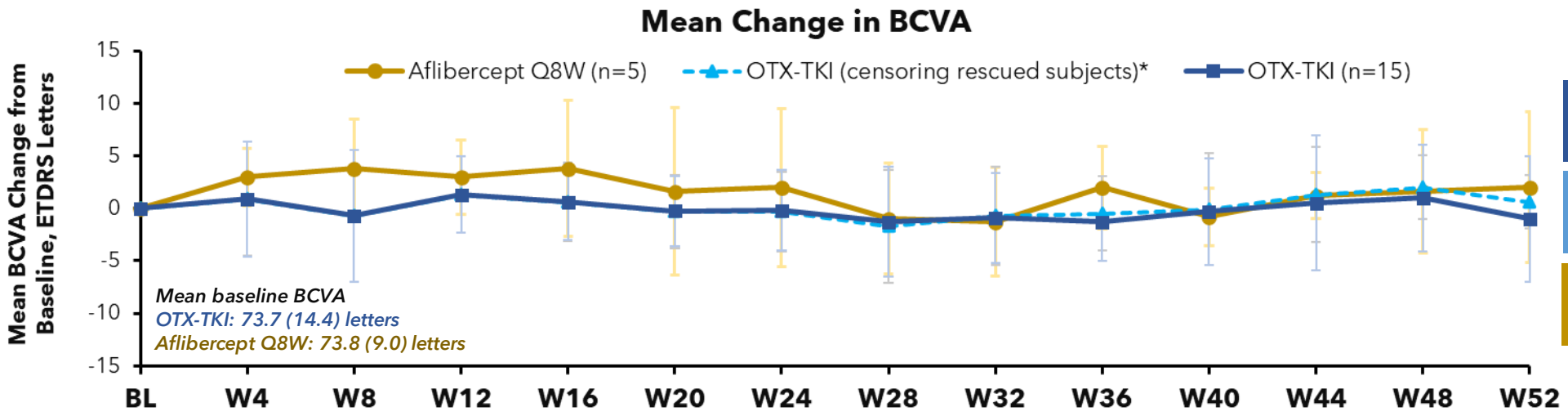
89% reduction in treatment burden with OTX-TKI at 12 months



Among subjects who received supplemental anti-VEGF, median time to first injection was 44.6 weeks

Data cut off April 14, 2023; per protocol analysis
Reduction in treatment burden calculation includes all supplemental injections
Sham injection was given at Week 0 in the Aflibercept Arm and at Weeks 12, 20, 28, 36 and 44 in the OTX-TKI Arm (not shown). At Week 52, subjects in the aflibercept group were treated with wet AMD standard of care at the investigator's discretion.

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

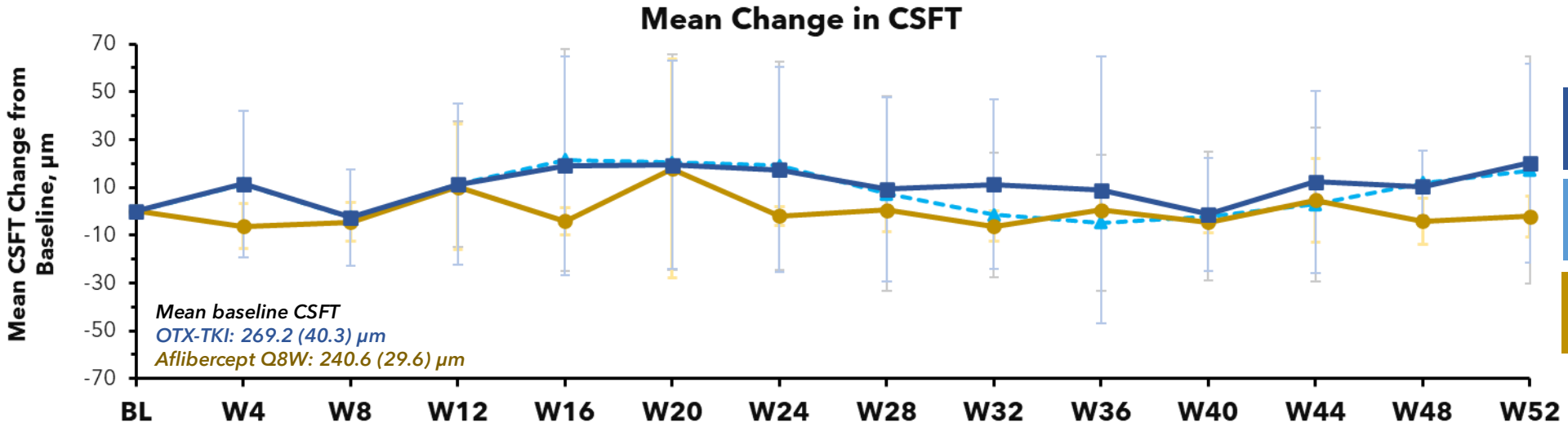


Mean (SD) change in BCVA from baseline to Week 52:

OTX-TKI: -1.0 (6.0) letters

OTX-TKI: +0.6 (2.6) letters (censoring subjects who received supplemental injections)

Aflibercept Q8W: +2.0 (7.2) letters



Mean (SD) change in CSFT from baseline to Week 52:

OTX-TKI: +20.2 (41.6) µm

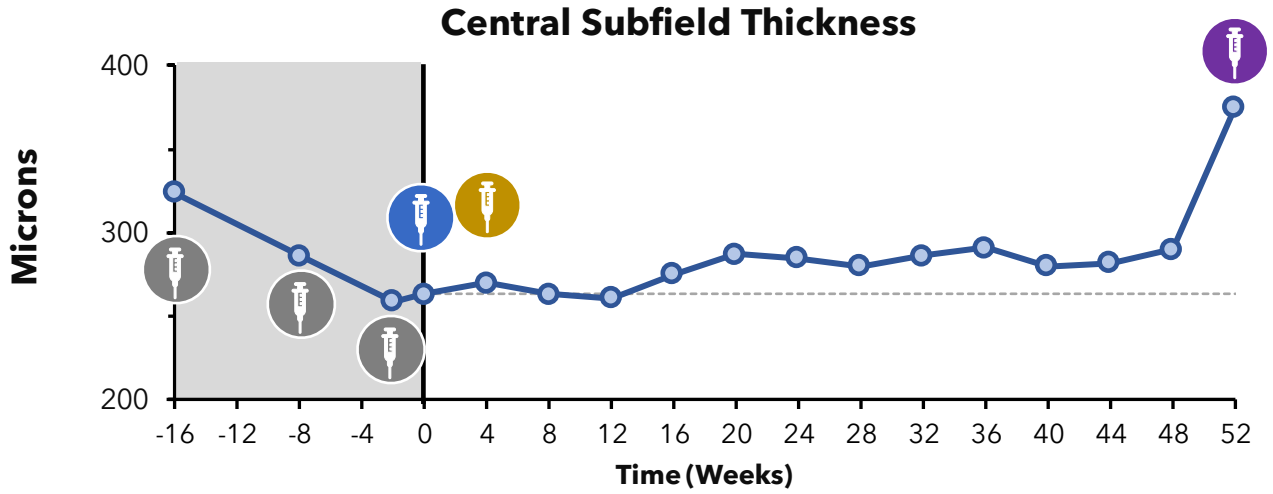
OTX-TKI: +17.2 (47.6) µm (censoring subjects who received supplemental injections)

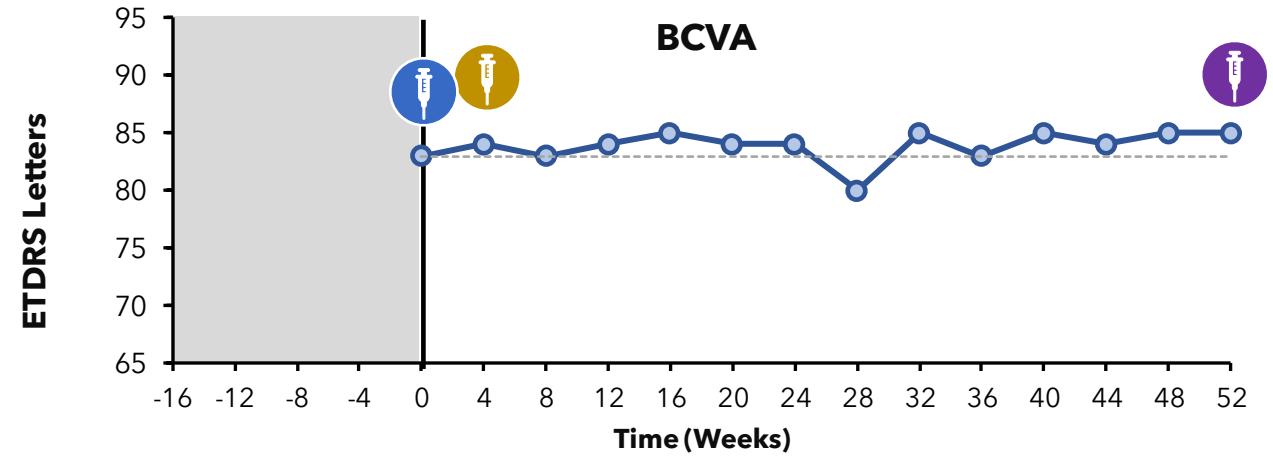
Aflibercept Q8W: -2.2 (8.5) µm

Data cut off April 14, 2023
Error bars represent standard deviation; n=14 in OTX-TKI arm at Weeks 8, 28, 40 and 48 due to missed visits
*Sample size for OTX-TKI (censoring subjects who received supplemental therapy): n=15 at Baseline and Weeks 4 and 12; n=14 at Week 8 (missed visit) and Weeks 16 and 20; n=12 at Week 24 and n=11 at Weeks 28, 32, 36 and 40; n=10 at Week 44; n=9 at Weeks 48 and 52
Abbreviations: BCVA=best corrected visual acuity; BL=baseline; CSFT=central subfield thickness; ETDRS=Early Treatment Diabetic Retinopathy Study; W, week

OTX-TKI-Treated Subject 6

81-year-old female with anti-VEGF Q8W prior to study and supplemental injection-free up to 1 year





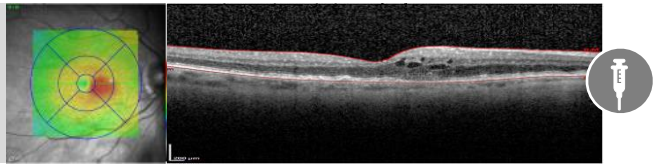
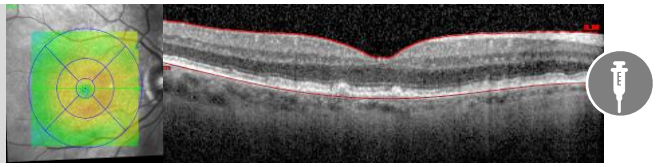
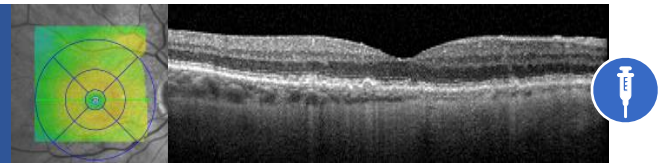
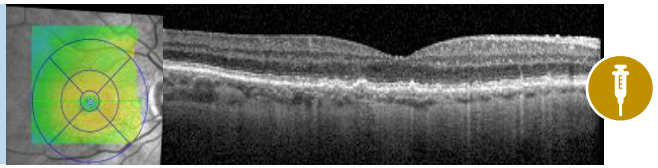
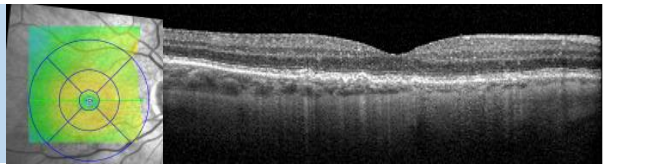
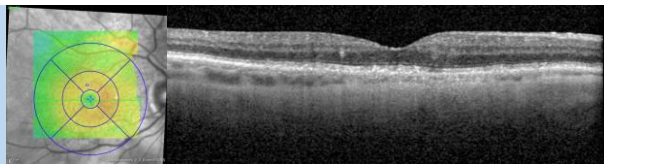
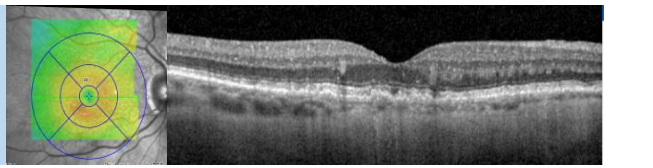
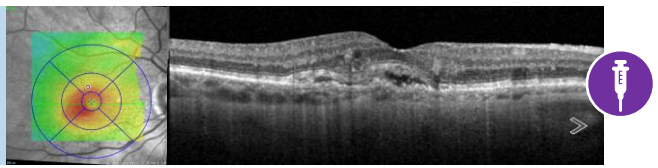
anti-VEGF injection

OTX-TKI administration

study-mandated aflibercept

supplemental injection given at investigator's discretion

Data cut off April 14, 2023

-16 Weeks	**CSFT:** 324 µm **BCVA:** Not available	
-8 Weeks	**CSFT:** 286 µm **BCVA:** Not available	
Baseline	**CSFT:** 263 µm **BCVA:** 83 letters	
Week 4	**CSFT Δ:** +7 µm **BCVA Δ:** +1 letter	
Week 8	**CSFT Δ:** 0 µm **BCVA Δ:** 0 letters	
Week 24	**CSFT Δ:** +22 µm **BCVA Δ:** +1 letter	
Week 48	**CSFT Δ:** +27 µm **BCVA Δ:** +2 letters	
Week 52	**CSFT Δ:** +112 µm **BCVA Δ:** +2 letters	

Safety Summary*

- 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, n (%)	OTX-TKI n=16	Aflibercept n=5
Elevated IOP	2 (12.5)	1 (20.0)**
Retinal detachment	0	0
Retinal vasculitis	0	0
Implant migration into the anterior chamber	0	NA
Acute endophthalmitis	1 (6.25)*	0
Subjects with Ocular Adverse Events in the Study Eye Reported by Maximum Severity, n (%)		
Ocular AEs	16 (100.0)	3 (60.0)
Mild	14 (87.5)	2 (40.0)
Moderate	2 (12.5)*	1 (20.0)**
Severe	0	0
Serious AEs	1 (6.25)*	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
Note: A subject is counted once for the most severe event if the subject reported one or more events.

*** Safety follow-up is ongoing**
Data cut off April 14, 2023
Abbreviations: IOP=intraocular pressure; SAE=serious adverse event

Summary of OTX-TKI Interim Data in Wet AMD

AUS TRIAL

- OTX-TKI in active wet AMD showed potential to stabilize or improve vision and potential to control retinal fluid for at least 6 months with an effect more pronounced in treatment naïve subjects

US TRIAL

- OTX-TKI showed potential to maintain vision and CSFT comparable to aflibercept Q8W with 89% reduction in treatment burden over a 12-month period
- Safety data* showed OTX-TKI was generally well-tolerated
- Implant bioresorption and axitinib elution were consistent with previous clinical data, potentially allowing a window for redosing
- Pharmacodynamic effects observed in this trial support the characteristics of a potential treatment for wet AMD with durability between 9-12 months with a single injection

SOL

- SOL: OTX-TKI pivotal clinical trial in wet AMD initiated
- Planned to enroll 300 evaluable wet AMD subjects who are treatment naïve in the study eye

* Safety follow-up is ongoing
AUS Trial: interim review, unmonitored data. Data cut August 5, 2022
US Trial: interim review. Data cut April 14, 2023. Conclusions based on limited number of subjects OTX-TKI: n=16 and Aflibercept: n=5