Safety and Efficacy of OTX-TKI in Moderately Severe to Severe NPDR: One Year Results from the HELIOS Phase 1 Trial

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Disclosures

FINANCIAL DISCLOSURES (DENNIS M. MARCUS)

Consultant: 4D Molecular Therapeutics, Annexon, Apellis, Clearside, Coherus, Genentech/Roche, Regenex Bio, Regeneron ,Vial, Vantage Biosciences.

Research Grants: Alexion Pharmaceuticals , Annexon, Apellis Pharmaceuticals , Aviceda Therapeutics, Carnegen Co ltd, Clearside Biomedical, Genentech/Roche, Gyroscope Therapeutics, Hoffman Roche, Ionis Pharmaceuticals, Iveric Bio, Kodiak Sciences, Kyowa Kirin, National Eye Institute, Oculis, Ocular Therapeutics, Opthea Ltd, Regenxbio, Rezolute Biotech, Shanghai Hengenix Bio.

STUDY AND PRODUCT DISCLOSURES

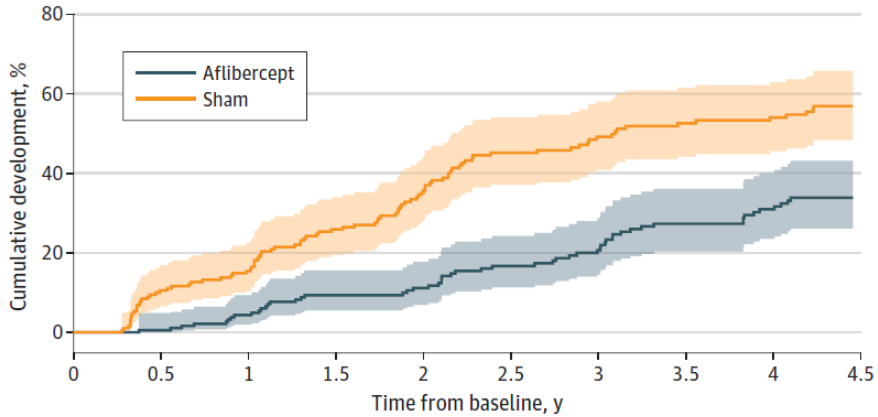
The following presentation discusses an investigational drug, OTX-TKI (also referred to as AXPAXLI™), in development. OTX-TKI's efficacy and safety profiles have not been established, and it has not been approved for marketing by the U.S. Food and Drug Administration (FDA) or any other health agency.

Ocular Therapeutix sponsored this clinical trial.

Diabetic Retinopathy is Chronic, Progressive, and Burdensome Earlier Treatment to Prevent Progression is Needed

- Efficacy of anti-VEGF therapy and **need for proactive treatment of NPDR established** in PANORAMA and Protocol W studies[1,2]
- Despite this, **<1% of NPDR patients are treated** with anti-VEGF therapy and majority of retina specialists (62.7%) **do not recommend treating NPDR** patients without DME[3-5]
- Due to the **unsustainable treatment burden** of frequent injections and **worse outcomes in eyes that had interrupted or reduced treatment** compared to those never treated at all[5]

Cumulative Development of PDR or CI-DME with Vision Loss[1]



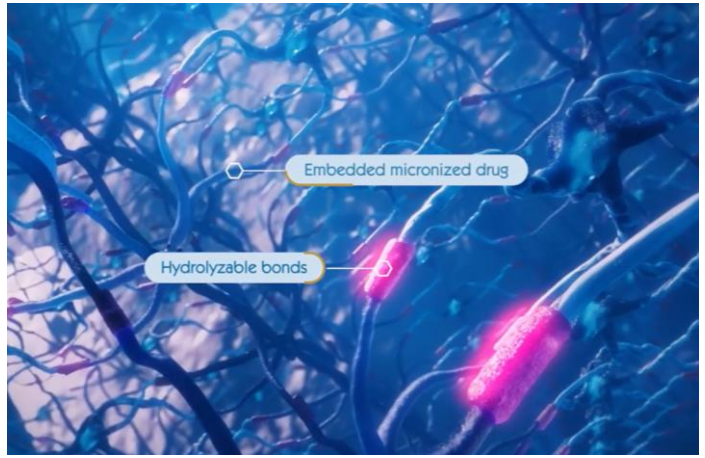
Early intervention with 3 aflibercept loading doses followed by Q16W, prevents progression to severe or vision-threatening disease

There is an unmet need for early intervention with a longer lasting treatment option

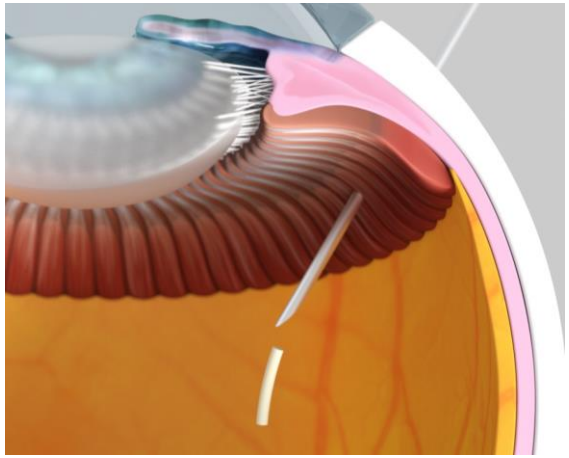
Abbreviations: CI-DME (center-involved diabetic macular edema); DR (diabetic retinopathy); NPDR (non-proliferative DR); PDR (proliferative DR); VEGF (vascular endothelial growth factor);

References: 1. Maturi RK, et al. *JAMA*. 2023;329(5):376-385. **2.** Brown DM, Wykoff CC, Boyer D, et al. *JAMA Ophthalmol*. 2021;139(9):946-955. **3.** Market Scope. 2022 Retinal Pharmaceuticals Market Report: Global Analysis for 2021 to 2027. Published August 2022. **4.** Market Scope. US Retina Quarterly Update: O2 2022 Analysis of Historical Trends and Latest Developments. Published August 2022 **5.** Hahn P, Garg SJ, eds. 2023 Global Trends in Retina Survey. Chicago, IL. American Society of Retina Specialists; 2023. **6**. Goldberg RA, Hill L, Davis T, et al. *BMJ Open Ophthalmol*. 2022;7(1):e001007.

OTX-TKI: Sustained-release Axitinib in Hydrogel



Drug	Inhibitory Concentrations for VEGFR2/KDR (Kinase Domain Receptor) in nM (lower Inhibitory Concentration-50 values indicate higher affinity)
Axitinib[5]	**0.2**
Sunitinib[6]	40
Vorolanib[6]	64



ELUTYX TECHNOLOGY

Bioresorbable, Targeted, Sustained Drug Delivery

- Proprietary bioresorbable polymer matrix is a hydrogel-based, versatile, biocompatible platform for localized sustained drug delivery

AXITINIB

Multi-target Tyrosine Kinase Inhibitor

- ~100X more potent for VEGFR-2 compared to sunitinib and vorolanib[1-3]
- Highly selective for all VEGF receptors[4-6] with no TIE2 inhibition at physiologic tissue concentrations[1]

OTX-TKI

Single Intravitreal Bioresorbable Implant

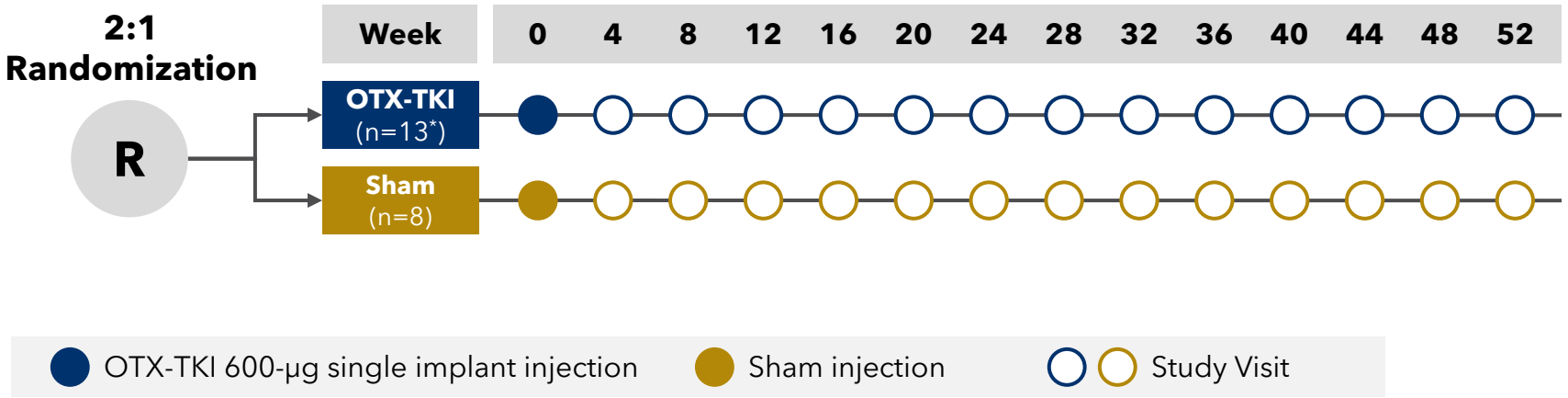
- Sustained axitinib release allowing a redosing interval for 6-12 months
- Administered by a 25G needle
- Patent coverage through 2044[7]

Abbreviations: IC (inhibitory concentration); KDR (kinase domain receptor); TIE2 (Tyrosine kinase with immunoglobulin-like and EGF-like domains-2); TKI (Tyrosine kinase inhibitor); VEGF (Vascular endothelial growth factor [receptor]).

References: 1. Unpublished data; Data on File. **2.** Hu-Lowe DD, et al. Clin Cancer Res. 2008;14(22):7272-7283. **3.** McTigue M, et al. Proc Natl Acad Sci U S A. 2012;109(45):18281-18289. **4.** Zhao Y, et al. Oncologist. 2015;20(6):660-673. **5.** Gross-Goupil M, et al. Clin Med Insights Oncol. 2013;7:269-277. **6.** Liang C, et al. Mol Ther Oncolytics. 2022;24:577-584. **7.** Blizzard CD, et al. US Patent: Ocular implant containing a tyrosine kinase inhibitor. Published online September 13, 2022. Accessed September 26, 2022.

HELIOS Phase 1 Study of OTX-TKI in NPDR

HELIOS



Multicenter, double-masked, randomized, parallel group study of OTX-TKI in patients with moderately severe to severe NPDR without CI-DME (as assessed by the investigator)

STUDY OUTCOMES

PRIMARY: Safety and tolerability of OTX-TKI

SECONDARY: DRSS changes, rescue therapy, BCVA, and CSFT changes

*14 patients enrolled in OTX-TKI treatment arm, with 1 patient death unrelated to treatment.

Abbreviations: BCVA (Best-corrected visual acuity); CI-DME (Center-involved diabetic macular edema); CSFT (Central subfield thickness); DRSS (Diabetic retinopathy severity scale); NPDR (Non-proliferative diabetic retinopathy).

Baseline Characteristics

Characteristic	OTX-TKI (N=14)	Sham (N=8)
Age, mean, years	53.7 (14.7)	64.0 (7.1)
Sex, n (%) Female Male	 5 (35.7) 9 (64.3)	 5 (62.5) 3 (37.5)
DRSS, n (%) Level 47 (Moderately severe NPDR) Level 53 (Severe NPDR)	 0 14 (100)	 2 (25.0) 6 (75.0)
BCVA, mean (SD), ETDRS letters Approximate Snellen equivalent	 82.9 (5.2) 20/25	 84.5 (5.2) 20/20
CSFT, mean (SD), μm	268.7 (21.5)	283.0 (32.1)

Abbreviations: BCVA (Best-corrected visual acuity); CSFT (Central subfield thickness); DRSS (Diabetic retinopathy severity scale); ETDRS (Early Treatment Diabetic Retinopathy Study); NPDR (Non-proliferative diabetic retinopathy); SD (standard deviation)

HELIOS Safety Overview at Week 48

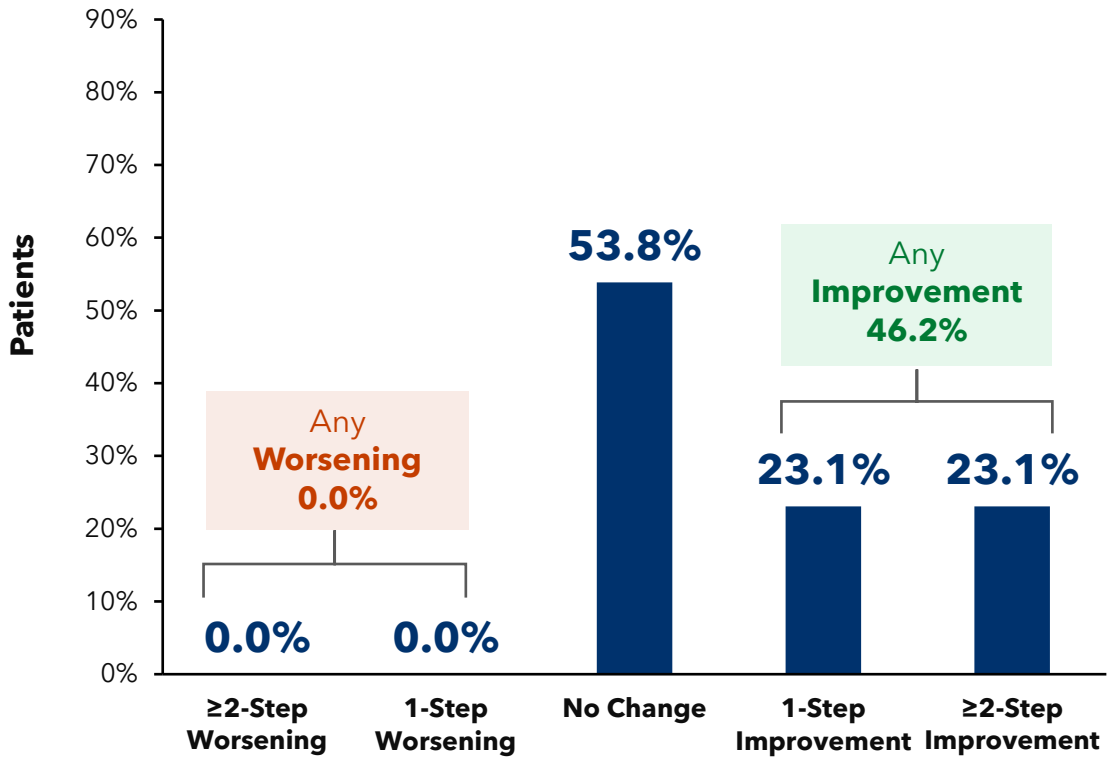
OTX-TKI was generally well tolerated, with no ocular SAEs reported

- OTX-TKI was generally well tolerated
- All AEs were mild and balanced across the two arms, with no moderate or severe AEs reported in either arm
- No ocular SAEs reported in either arm
- No treatment- or injection procedure-related intraocular inflammation, iritis, vitritis, or vasculitis
- No subjects in either arm received rescue medication

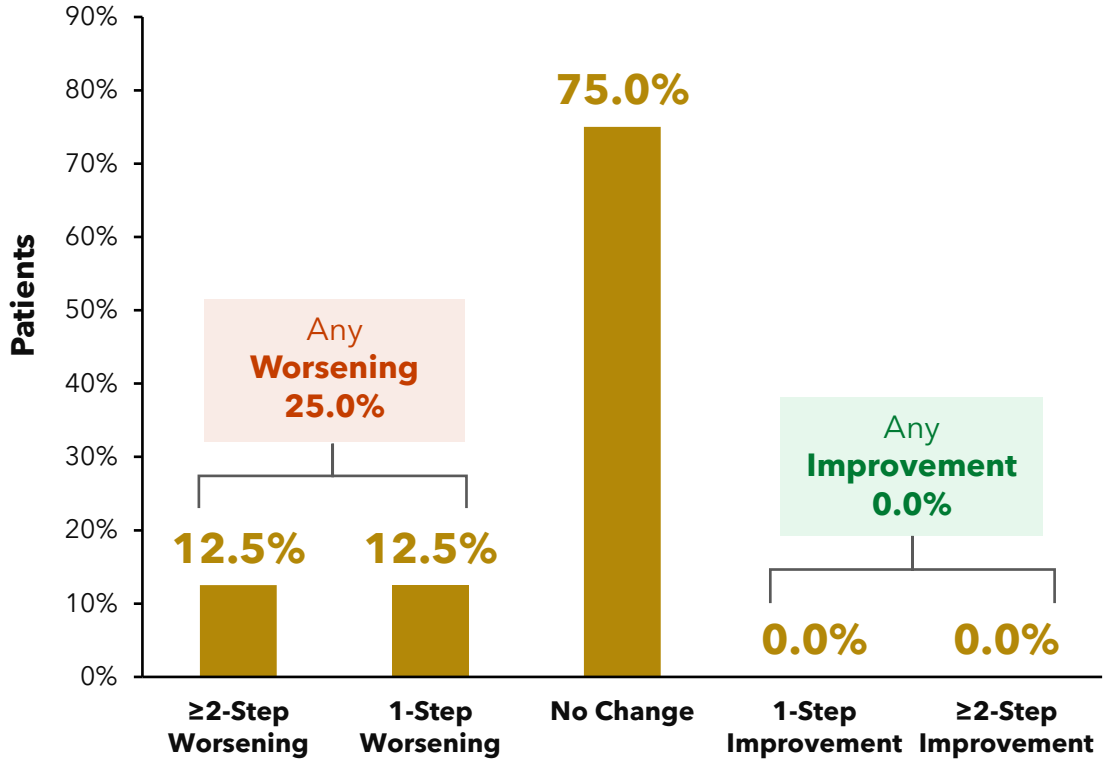
Abbreviations: AE (adverse event); SAE (serious AE).

DRSS Changes at Week 48:
23.1% in OTX-TKI arm had a ≥2-step DRSS improvement vs 0% in sham

OTX-TKI (n=13)
Change in DRSS From Baseline to Week 48

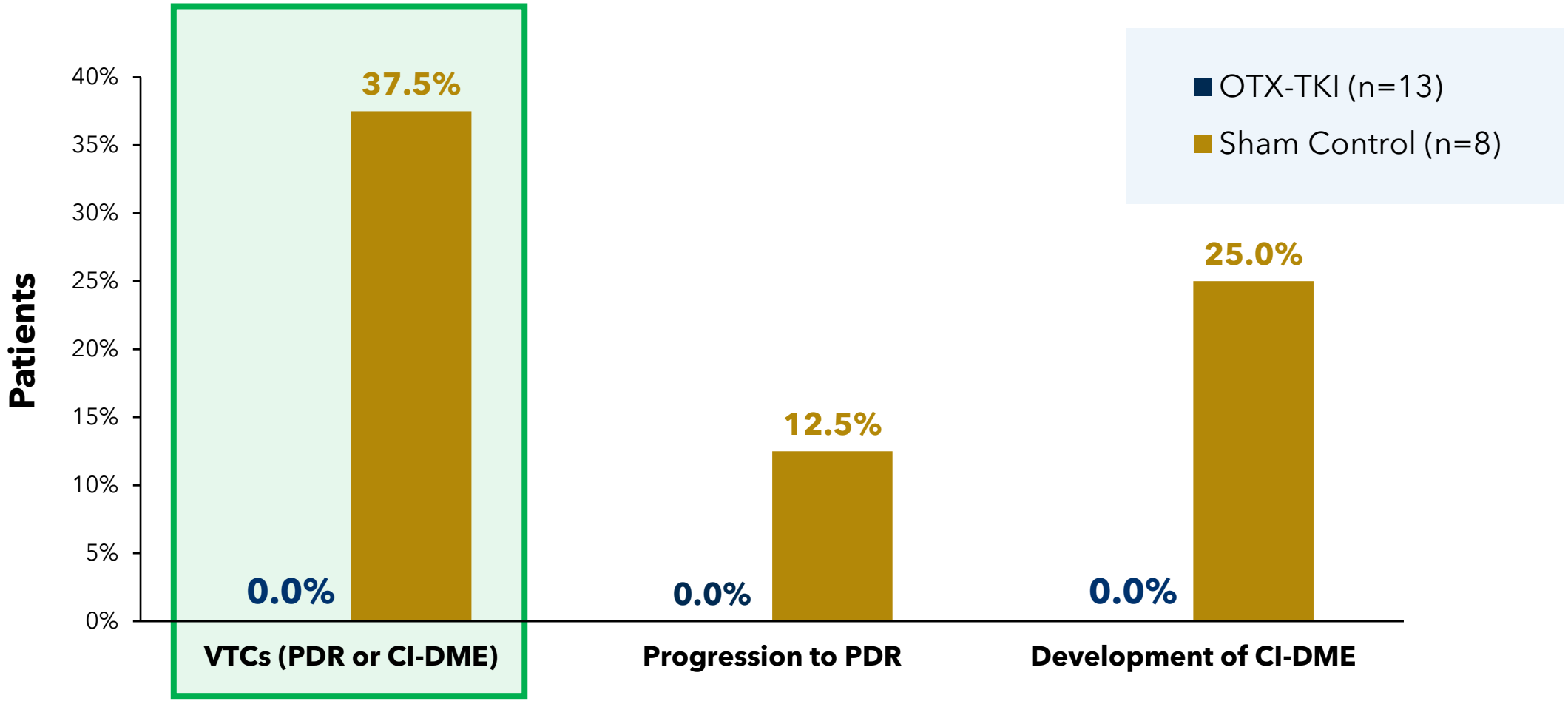


Sham Control (n=8)
Change in DRSS From Baseline to Week 48



Abbreviations: DRSS (Diabetic retinopathy severity scale).

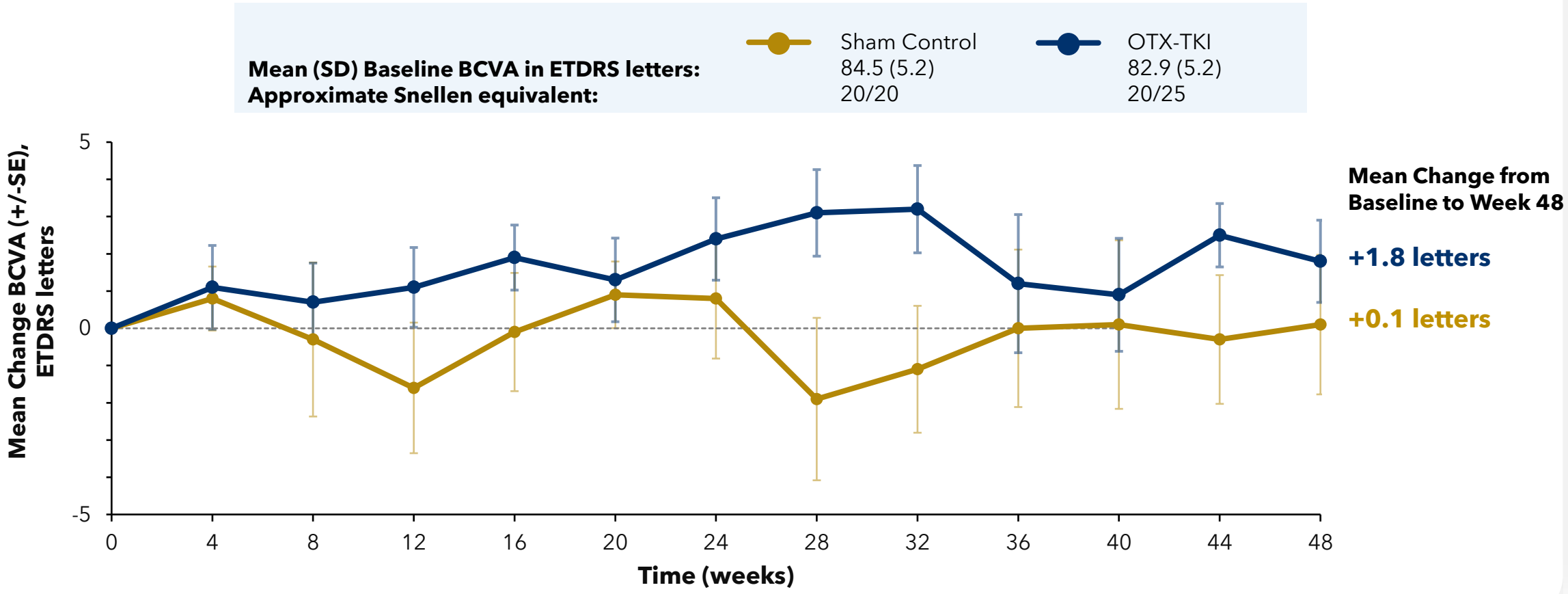
Vision-Threatening Complications (VTCs) at Week 48:
0% in OTX-TKI arm developed PDR or CI-DME vs 37.5% in sham



Abbreviations: CI-DME (Center-involved diabetic macular edema); PDR (Proliferative diabetic retinopathy); VTC (vision-threatening complications [includes PDR or CI-DME])

Mean BCVA Change from Baseline Over Time:
OTX-TKI-treated patients demonstrated stable vision through 48 weeks

MEAN BCVA CHANGE FROM BASELINE



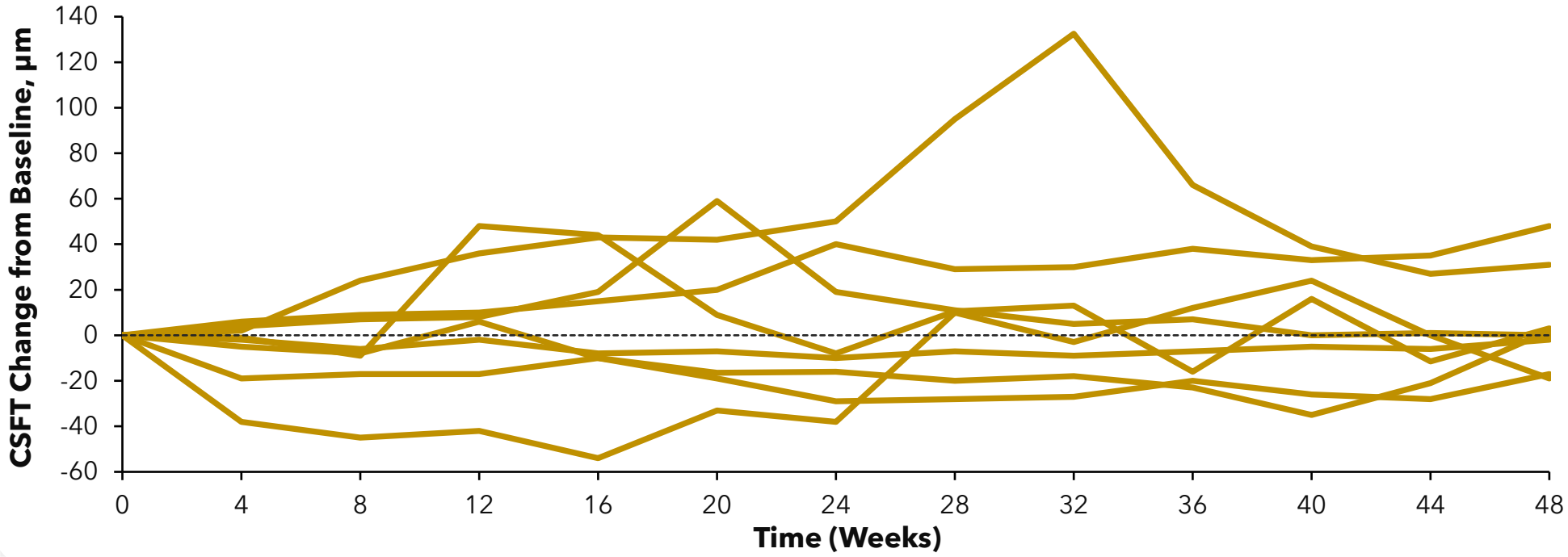
Error bars represent standard error.
Abbreviations: BCVA (Best-corrected visual acuity); ETDRS (Early Treatment Diabetic Retinopathy Study); SD (standard deviation)

CSFT Change from Baseline Over Time:
Highly variable CSFT fluctuations observed in sham control patients

CSFT CHANGE OVER TIME FROM BASELINE

Mean (SD) Baseline CSFT:

Sham Control
283.0 (32.1)



Mean Change from Baseline to Week 48

+5.75 µm

Abbreviations: CSFT (central subfield thickness); SD (standard deviation)

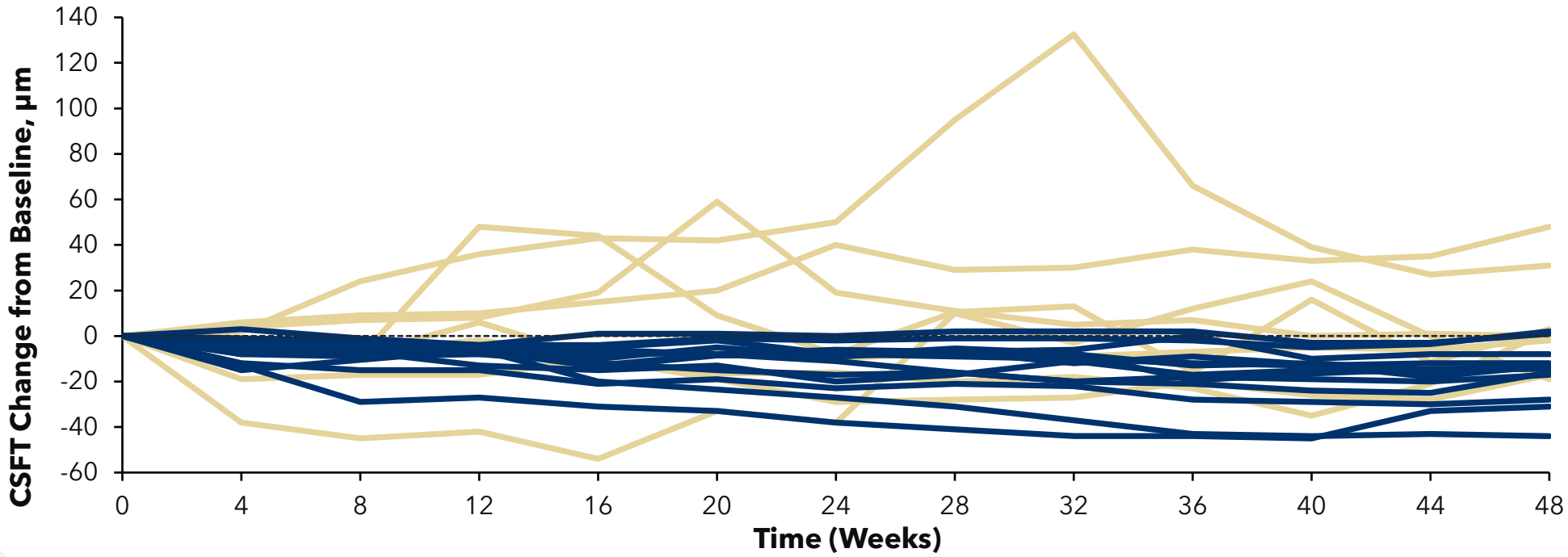
CSFT Change from Baseline Over Time:
Single OTX-TKI injection showed durable and consistent fluid suppression for 48 weeks

CSFT CHANGE OVER TIME FROM BASELINE

Mean (SD) Baseline CSFT:

Sham Control
283.0 (32.1)

OTX-TKI
268.7 (21.5)



Mean Change from Baseline to Week 48

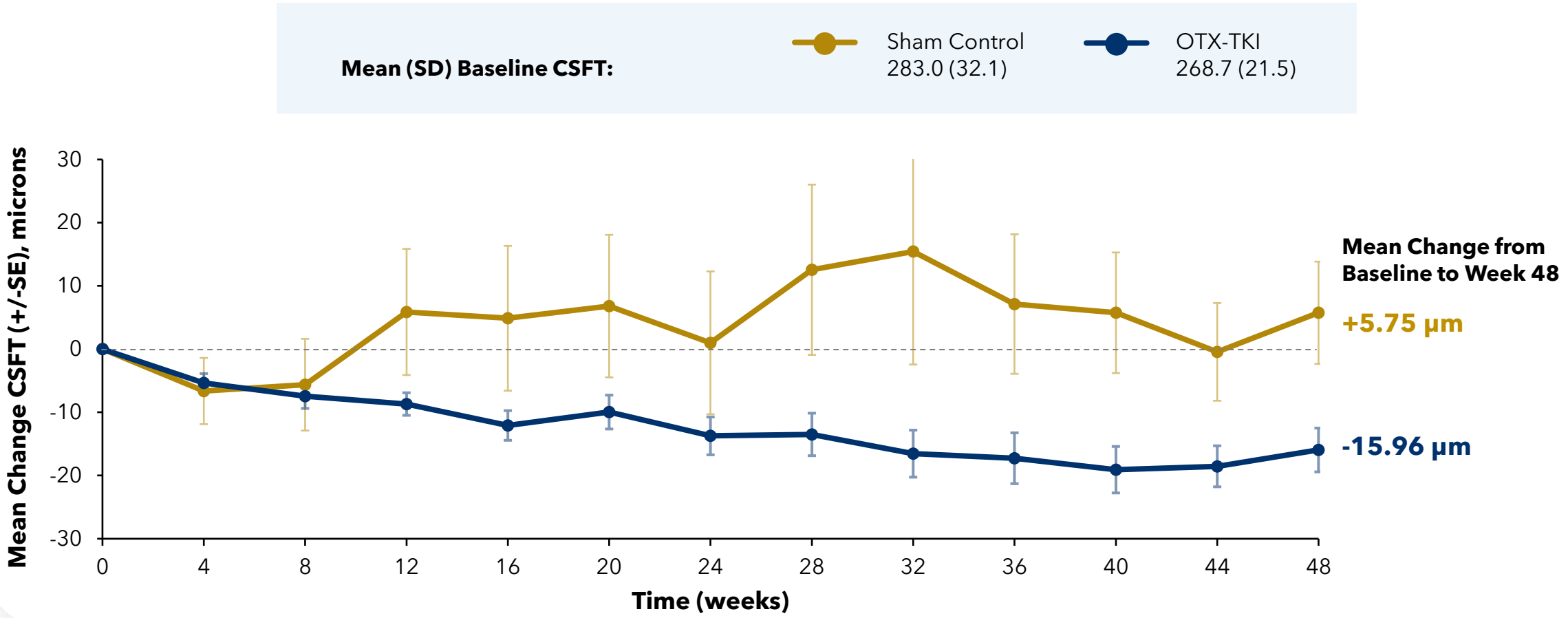
+5.75 µm

-15.96 µm

Abbreviations: CSFT (central subfield thickness); SD (standard deviation)

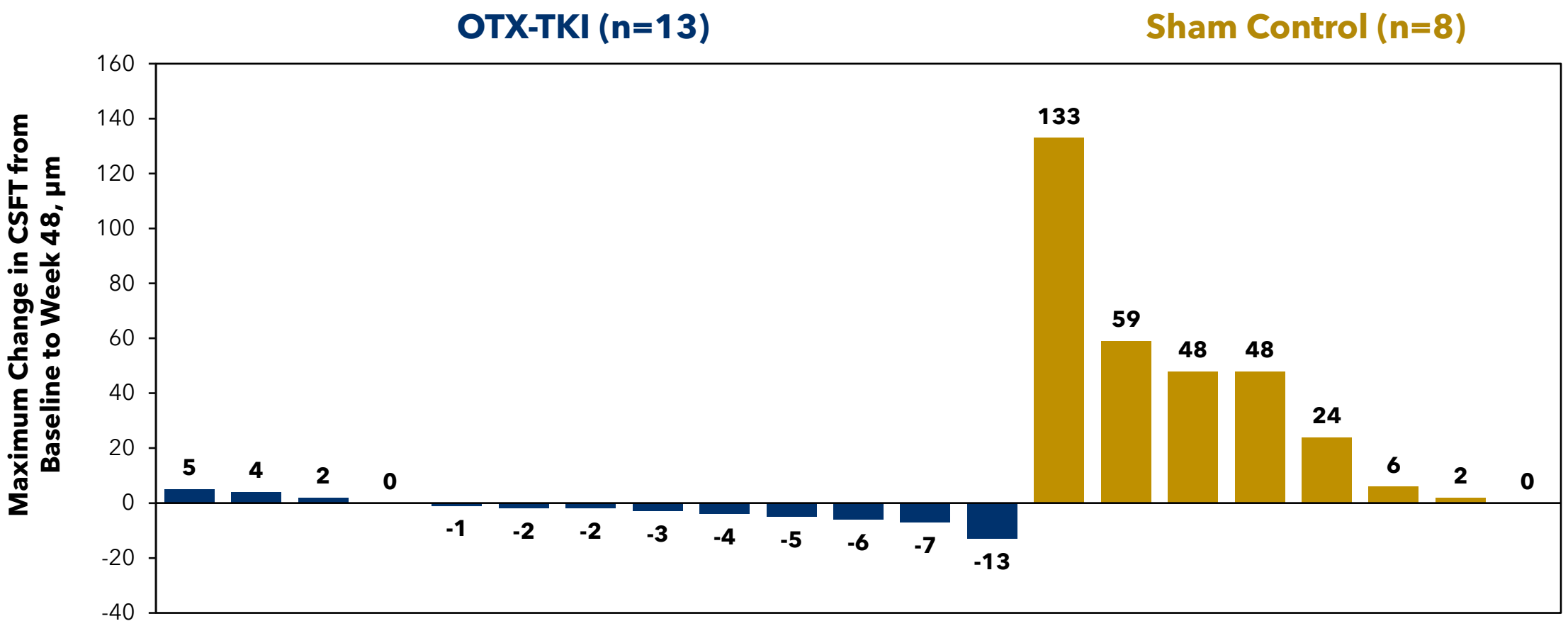
Mean CSFT Change from Baseline Over Time:
Strong trend towards consistent CSFT reduction observed with OTX-TKI

MEAN CSFT CHANGE OVER TIME FROM BASELINE



Error bars represent standard error.
Abbreviations : CSFT (Central subfield thickness); SE (standard error)

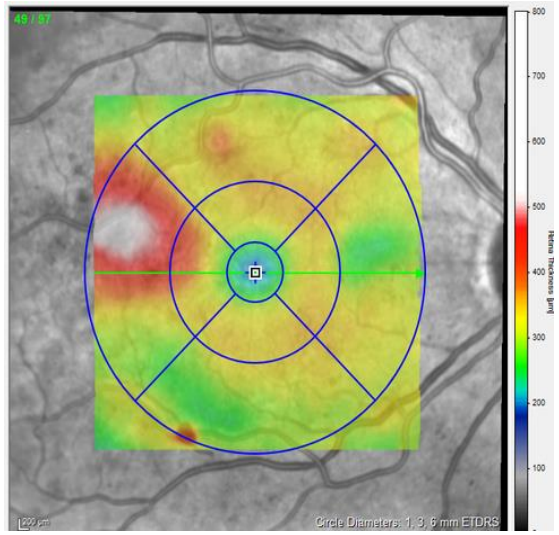
Maximum CSFT Change from Baseline to Week 48:
More stable fluid control indicated in OTX-TKI-treated patients



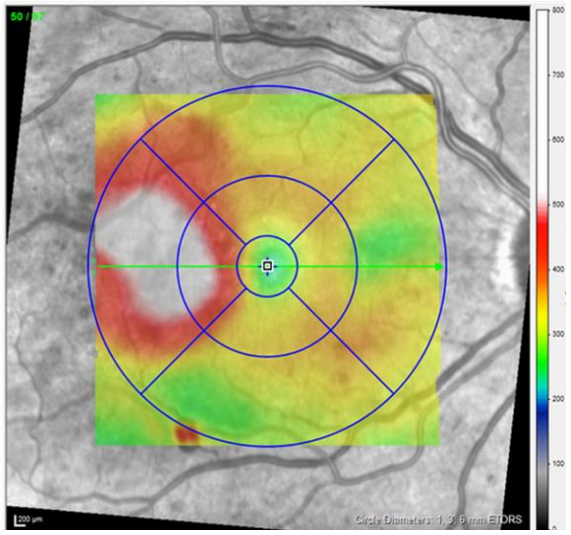
Each bar represents the change in CSFT for an individual patient. Patients are ordered from left to right by the magnitude of CSFT change.
Abbreviations: CSFT (central subfield thickness)

DME Changes from Baseline to Week 48: Sham vs OTX-TKI

Sham Control: Patient 11-002

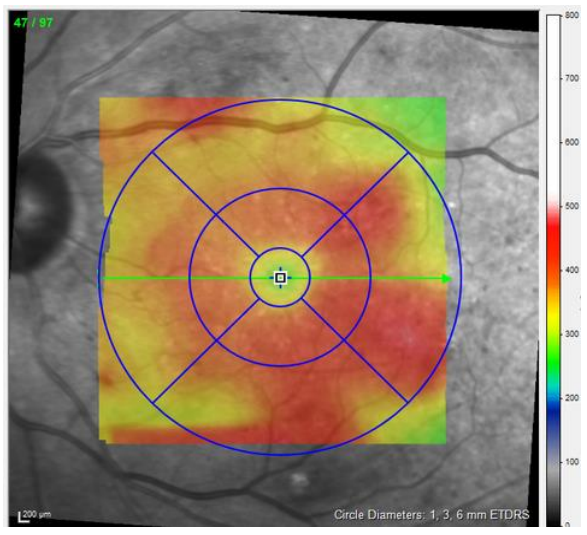


BASELINE
Volume = 9.35 mm^3

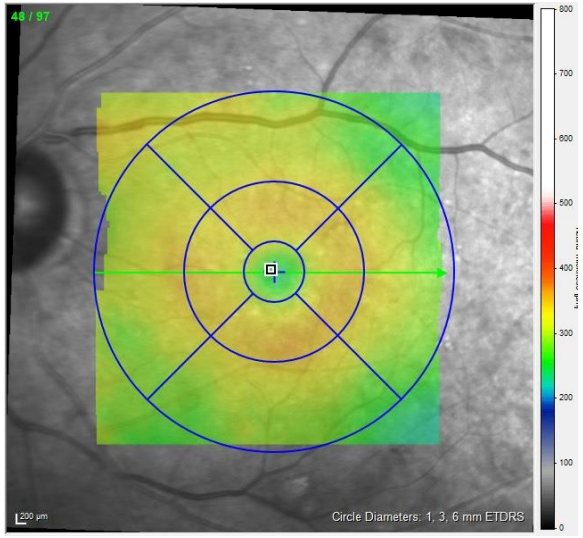


WEEK 48
Volume = 10.24 mm^3

OTX-TKI: Patient 11-008



BASELINE
Volume = 10.79 mm^3



WEEK 48
Volume = 8.76 mm^3

Abbreviations: DME (diabetic macular edema)

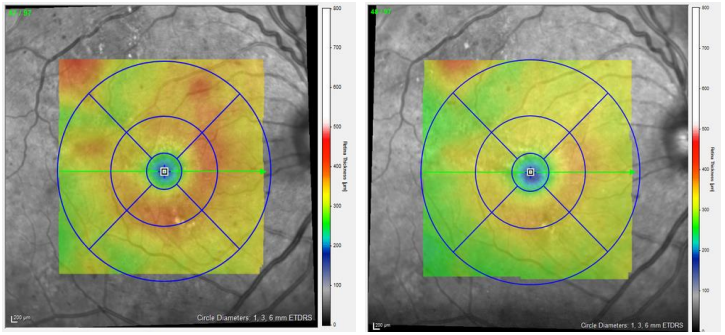
Improvement in DME in Patients Receiving OTX-TKI

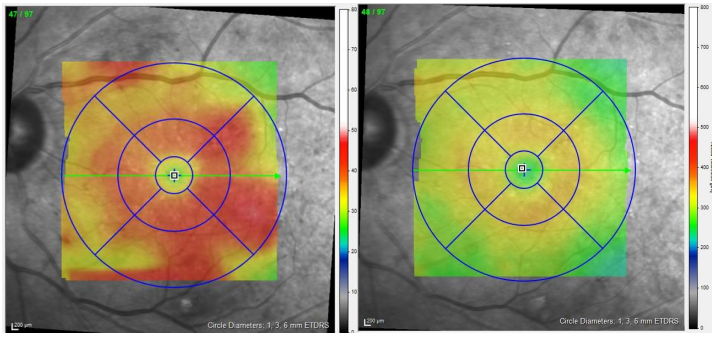
Patient 11-007
Baseline Vol. = 9.39 mm^3
Week 48 Vol.= 8.75 mm^3

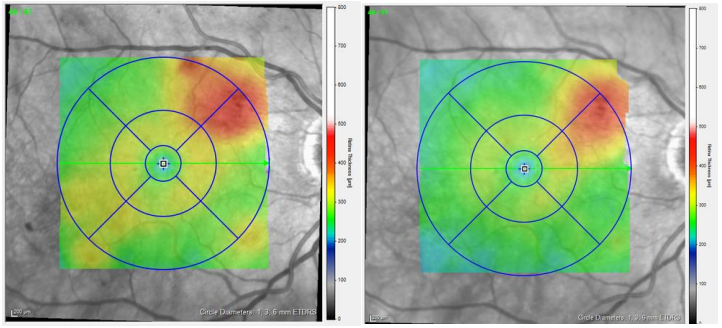
Patient 11-008
Baseline Vol. = 10.79 mm^3
Week 48 Vol. = 8.76 mm^3

Patient 13-001
Baseline Vol. = 8.60 mm^3
Week 48 Vol. = 7.90 mm^3

BASELINE **WEEK 48**





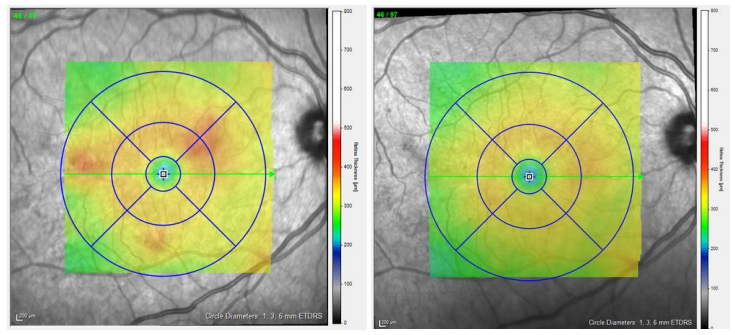


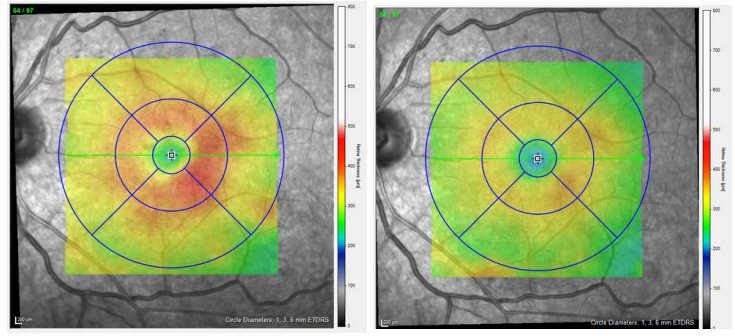
Patient 15-004
Baseline Vol. = 9.25 mm^3
Week 48 Vol. = 8.87 mm^3

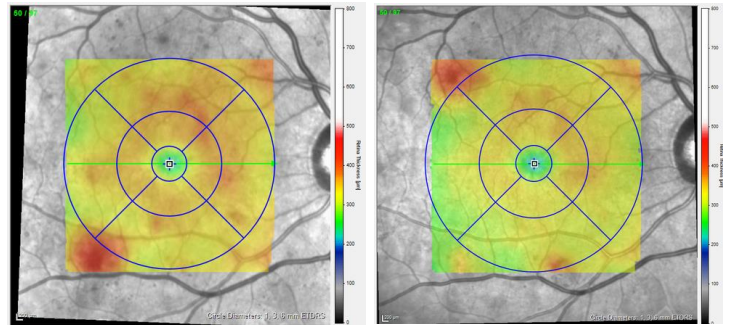
Patient 16-005
Baseline Vol. = 9.46 mm^3
Week 48 Vol. = 8.51 mm^3

Patient 16-006
Baseline Vol. = 9.59 mm^3
Week 48 Vol. = 9.01 mm^3

BASELINE **WEEK 48**

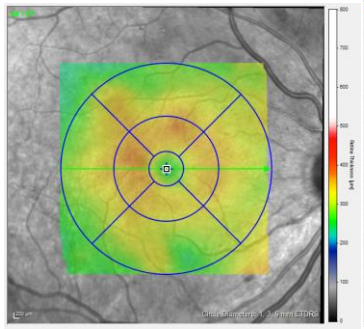
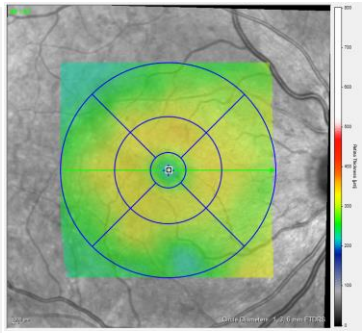
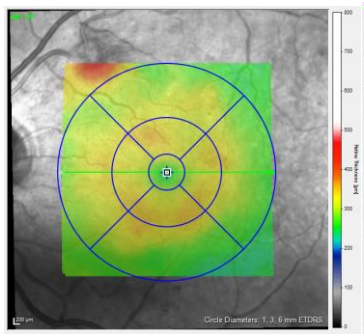
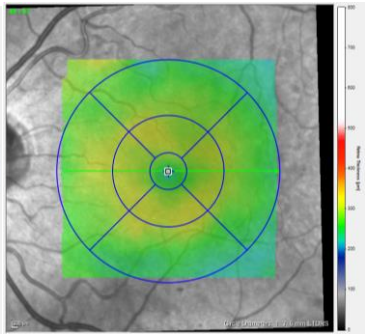






Abbreviations: DME (diabetic macular edema); Vol. (volume)

Improvement in DME in Patients Receiving OTX-TKI

	BASELINE	WEEK 48
Patient 12-002 Baseline Vol. = 8.93 mm^3 Week 48 Vol. = 8.23 mm^3		
Patient 16-009 Baseline Vol. = 8.56 mm^3 Week 48 Vol. = 7.85 mm^3		

Abbreviations: DME (diabetic macular edema); Vol. (volume)

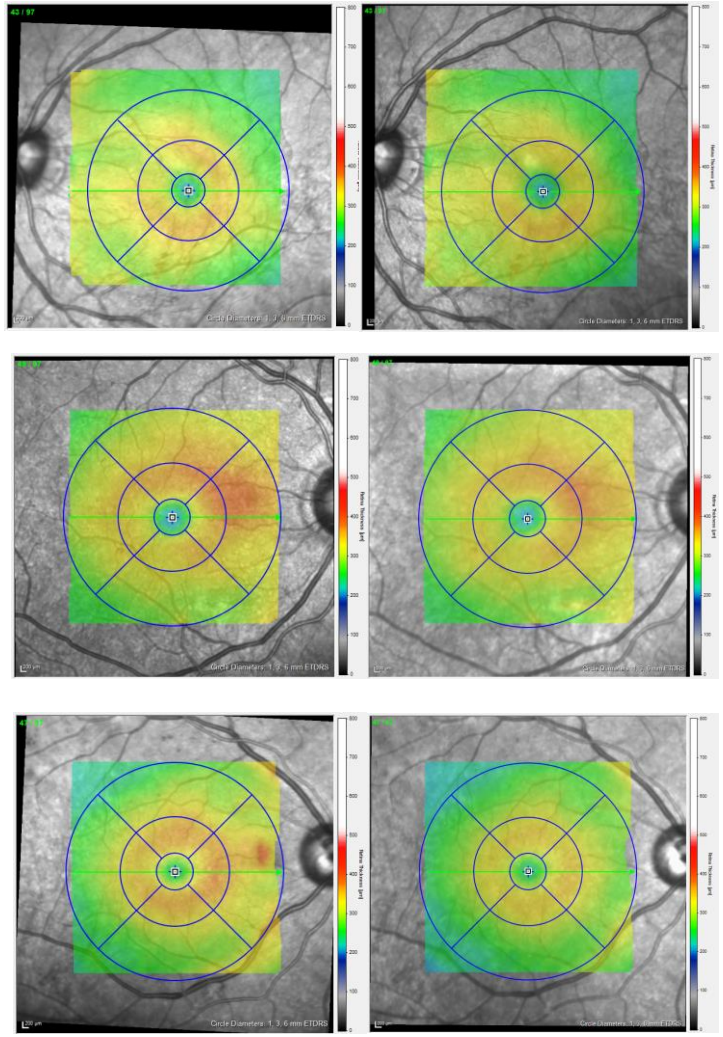
OTX-TKI-treated Patients without Initial DME Remained DME-Free Through Week 48

Patient 10-004
Baseline Vol. = 8.59 mm^3
Week 48 Vol. = 8.44 mm^3

Patient 11-004
Baseline Vol. = 9.19 mm^3
Week 48 Vol. = 8.99 mm^3

Patient 11-011
Baseline Vol. = 8.68 mm^3
Week 48 Vol. = 8.11 mm^3

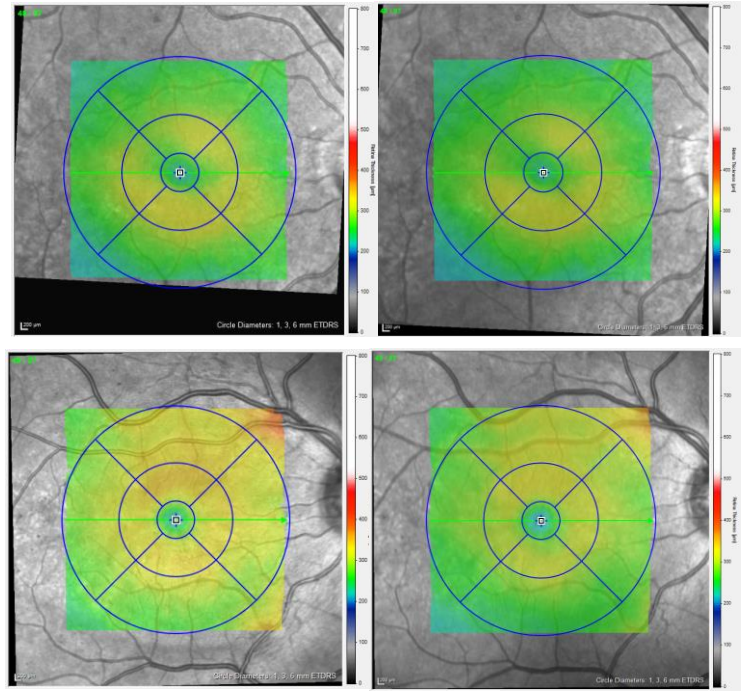
BASELINE WEEK 48



Patient 11-013
Baseline Vol. = 7.82 mm^3
Week 48 Vol. = 7.69 mm^3

Patient 16-003
Baseline Vol. = 8.74 mm^3
Week 48 Vol. = 8.14 mm^3

BASELINE WEEK 48



Abbreviations: DME (diabetic macular edema); Vol. (volume)

HELIOS Phase 1 Summary

OTX-TKI demonstrated DRSS stability or improvement with durability through 48 weeks

23.1% of patients in the OTX-TKI arm demonstrated a ≥2-step DRSS improvement, and 46.2% of patients demonstrated a 1- or ≥2-step DRSS improvement at 48 weeks

No subjects in the OTX-TKI arm experienced worsening in DRSS at 48 weeks

No OTX-TKI patients developed PDR or CI-DME through Week 48

37.5% in the sham control arm developed PDR or CI-DME through Week 48

A single OTX-TKI injection showed durable fluid suppression and more stable fluid control through Week 48

OTX-TKI was generally well tolerated with no incidence of treatment or injection procedure-related intraocular inflammation, iritis, vitritis, or vasculitis

Abbreviations: DRSS (Diabetic retinopathy severity scale); PDR (Proliferative diabetic retinopathy); CI-DME (Center-involved diabetic macular edema).

Thank you.