Safety and Efficacy of OTX-TKI for Diabetic Retinopathy: HELIOS Phase 1 Study

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Disclosures and Disclaimers

PRESENTER DISCLOSURES (DILSHER S. DHOOT, MD)

Consultant/Advisor: Alcon Pharmaceuticals; Alimera Sciences, Inc.; Allergan; Annexon; Apellis Pharmaceuticals, Inc.; Bayer Healthcare Pharmaceuticals, Inc.; Biocryst; Coherus; EyePoint Pharmaceuticals; Genentech; IvericBio; Novartis; Ocular Therapeutix; Optos, Inc.; Outlook Therapeutics; Oxular; Regeneron; REGENXBIO; Roche; Santen, Inc.

Grant: Ocular Therapeutix, Inc.

STUDY 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

ACKNOWLEDGEMENTS

OCT Analysis based on the findings of Justis P. Ehlers, MD (2025)

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]

- **Unsustainable treatment burden** of frequent injections and **worse outcomes in eyes that had interrupted or reduced treatment** compared to those never treated at all[6]

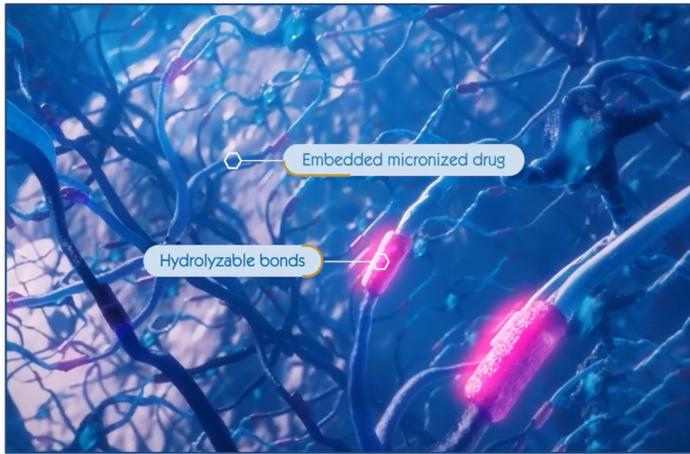**Cumulative Development of PDR or CI-DME with Vision Loss[1]**
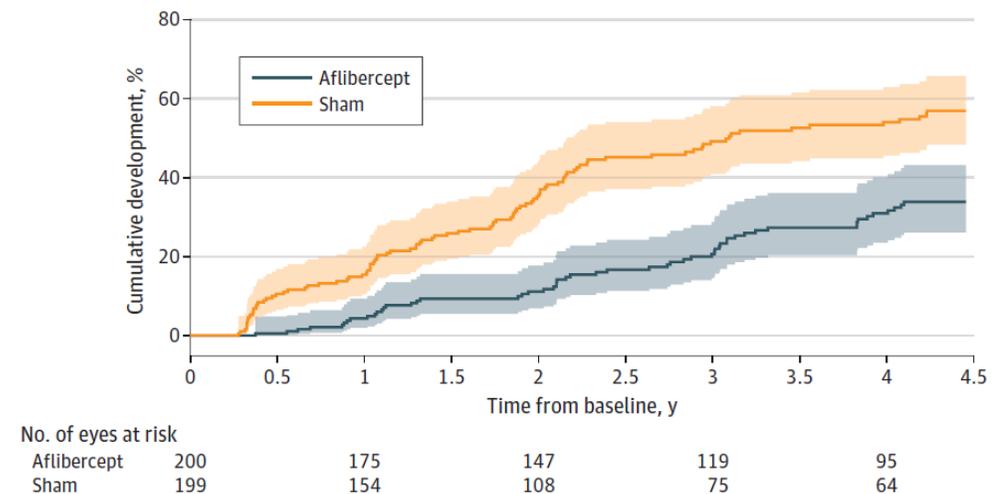
Early intervention with 3 aflibercept loading doses followed by Q16W, prevents progression to severe or vision-threatening disease

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 in 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

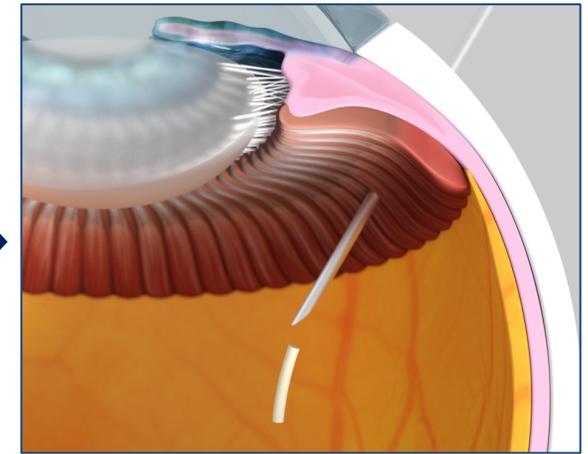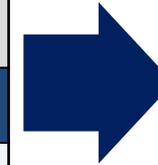- Proprietary bioresorbable hydrogel-based formulation technology for localized sustained drug delivery

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

Intravitreal Bioresorbable Hydrogel Injection

- Sustained axitinib release allowing a redosing interval for 6-12 months
- Administered by a 25G needle
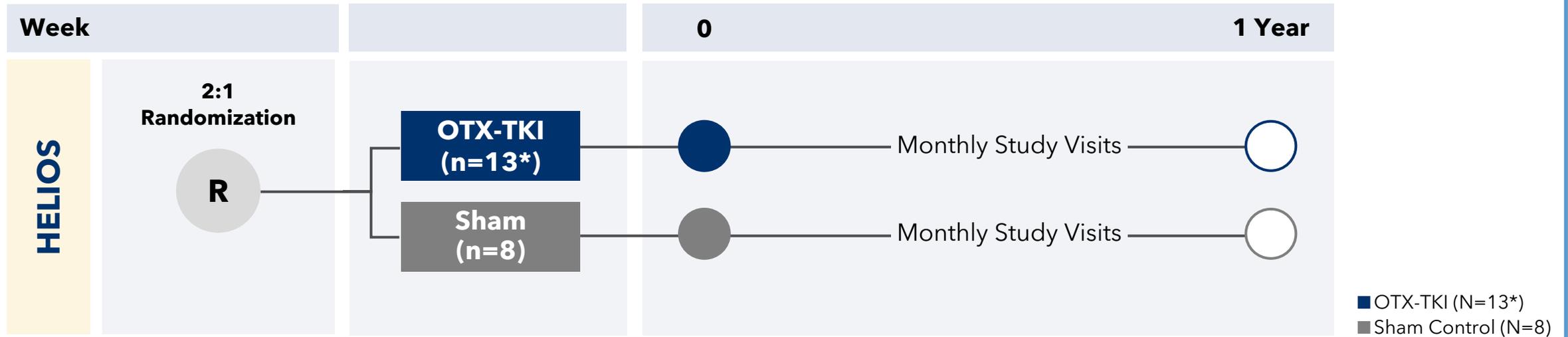- Patent coverage through 2041[7]

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

DESIGN

Multi-center, double-masked, randomized, parallel group study of OTX-TKI in moderate-severe to severe NPDR without CI-DME.

TRIAL SCHEMATIC

Week		0	1 Year

HELIOS

2:1 Randomization

R

OTX-TKI (n=13*) — ● — Monthly Study Visits — ○

Sham (n=8) — ● — Monthly Study Visits — ○

■ OTX-TKI (N=13*)
■ Sham Control (N=8)

STUDY OUTCOMES

PRIMARY: Safety and tolerability of OTX-TKI

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

*14 were enrolled, with one patient death unrelated to treatment prior to week 24 visit
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	5 (35.7)	5 (62.5)
Male	9 (64.3)	3 (37.5)
DRSS, n (%)		
Level 47 (Moderately severe NPDR)	0	2 (25.0)
Level 53 (Severe NPDR)	14 (100)	6 (75.0)
BCVA, mean (SD),		
ETDRS letters	82.9 (5.2)	84.5 (5.2)
Approximate Snellen equivalent	20/25	20/20
CSFT, mean (SD), µm	268.7 (21.5)	283.0 (32.1)

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)

Phase 1 Study Demonstrates at Week 48, more OTX-TKI Patients had DRSS Improvement and Did Not Develop Vision-Threatening Complications Compared to Sham

Safety Summary

- 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

Change in DRSS from Baseline to Week 48

	≥2-Step Worsening	1-Step Worsening	No Change	1-Step Improvement	≥2-Step Improvement
OTX-TKI	0.0%	0.0%	53.8%	23.1%	23.1%
Sham Control	12.5%	12.5%	75.0%	0.0%	0.0%
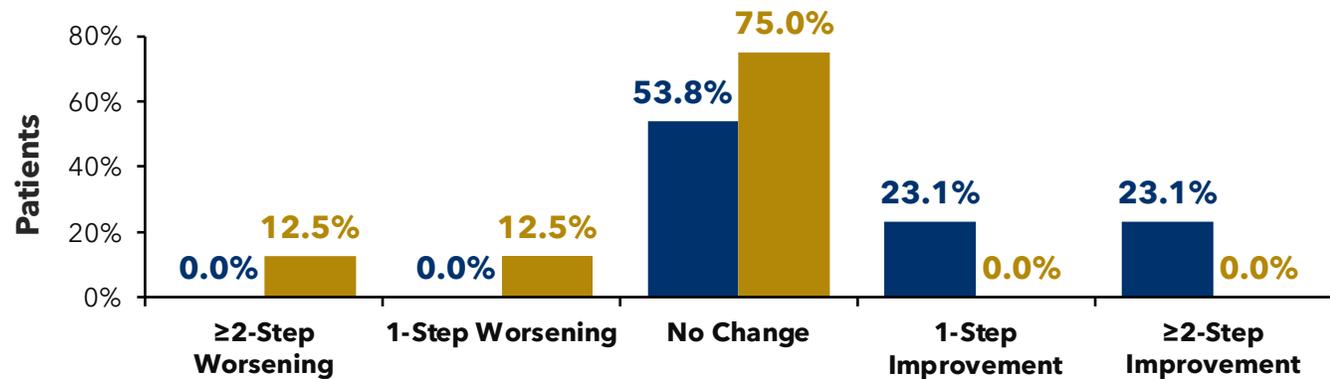
Vision-Threatening Complications (VTCs) at Week 48:

	Progression to PDR	Development of CI-DME	VTCs (PDR or CI-DME)
OTX-TKI	0.0%	0.0%	0.0%
Sham Control	12.5%	25.0%	37.5%

■ OTX-TKI (n=13*)   ■ Sham Control (n=8)

Mean BCVA from Baseline Over Time:

OTX-TKI-treated patients demonstrated stable vision through 48 weeks

MEAN BCVA CHANGE FROM BASELINE
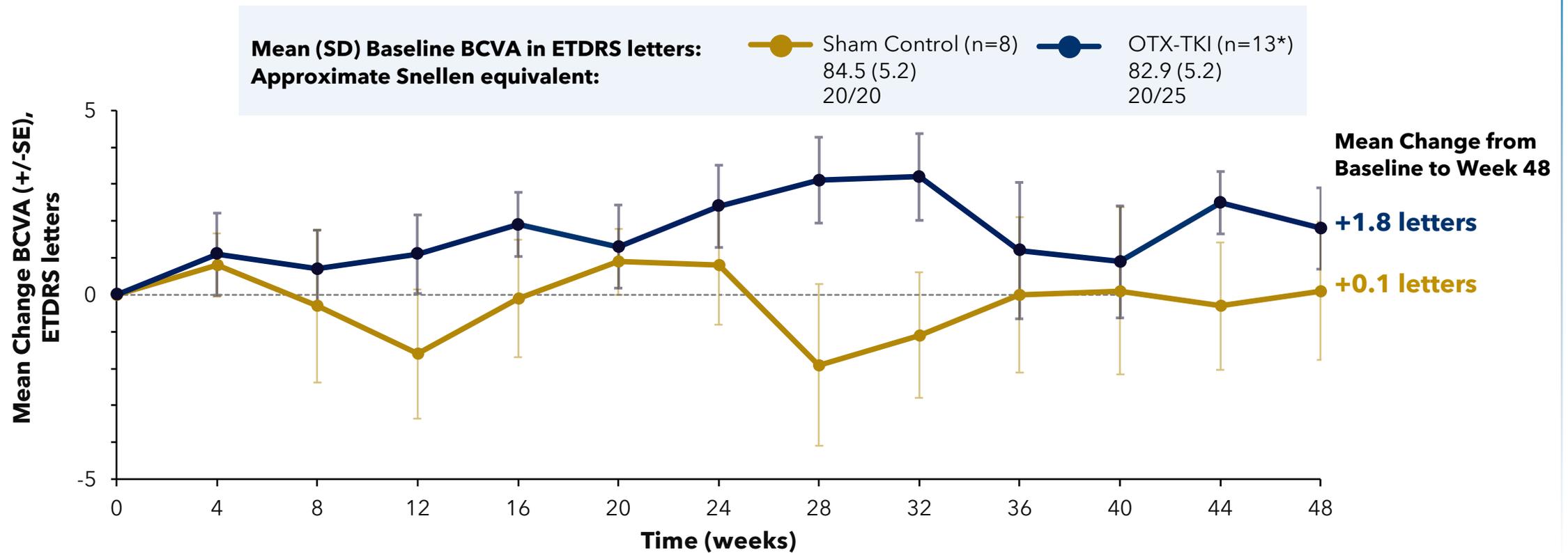
*14 were enrolled, with one patient death unrelated to treatment prior to week 24 visit
Error bars represent standard error.
BCVA (Best-corrected visual acuity); ETDRS (Early Treatment Diabetic Retinopathy Study); SD (standard deviation)
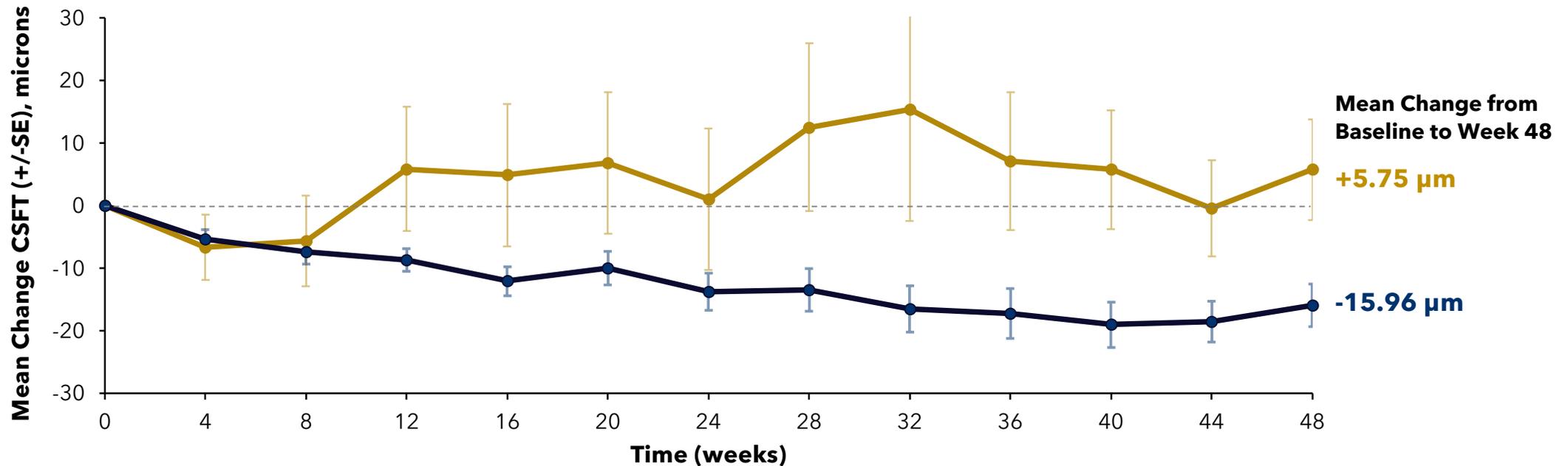
Mean CSFT Change from Baseline Over Time:

Strong trend towards consistent CSFT reduction observed with OTX-TKI

MEAN CSFT CHANGE OVER TIME FROM BASELINE

Mean (SD) Baseline CSFT:
Sham Control (n=8) 283.0 (32.1)
OTX-TKI (n=13*) 268.7 (21.5)

Mean Change from Baseline to Week 48
+5.75 μm
-15.96 μm

*14 were enrolled, with one patient death unrelated to treatment prior to week 24 visit
Error bars represent standard error.
CSFT (Central subfield thickness); SE (standard error)

Improvement in DME in Patients Receiving OTX-TKI

Patient 11-007
Baseline Vol. = 9.39 mm^3
Week 48 Vol.= 8.75 mm^3
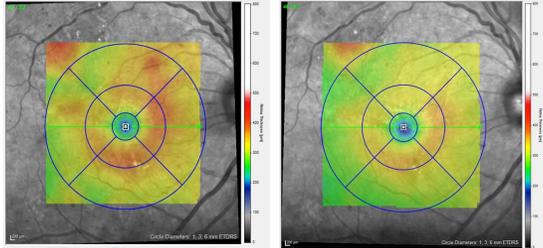
Patient 11-008
Baseline Vol. = 10.79 mm^3
Week 48 Vol. = 8.76 mm^3

Patient 13-001
Baseline Vol. = 8.60 mm^3
Week 48 Vol. = 7.90 mm^3
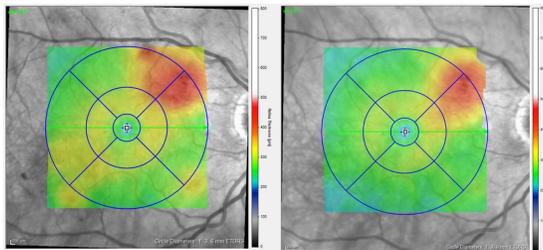
Patient 15-004
Baseline Vol. = 9.25 mm^3
Week 48 Vol. = 8.87 mm^3

Patient 16-005
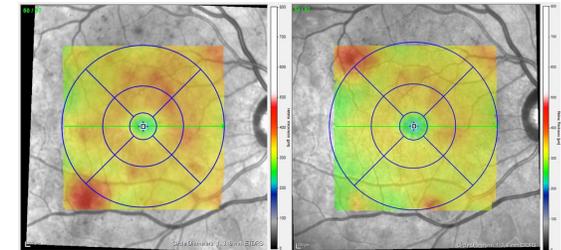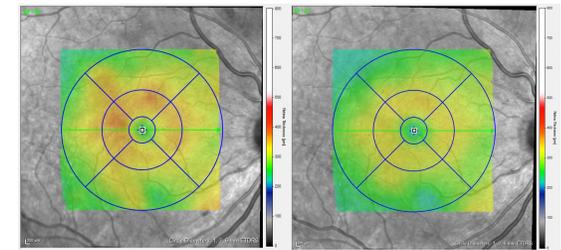Baseline Vol. = 9.46 mm^3
Week 48 Vol. = 8.51 mm^3
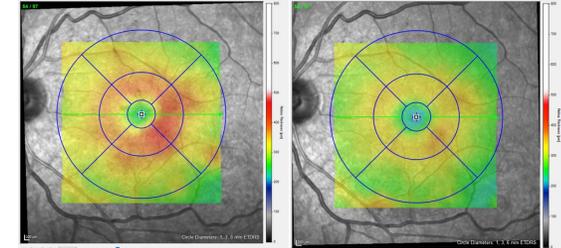
Patient 16-006
Baseline Vol. = 9.59 mm^3
Week 48 Vol. = 9.01 mm^3
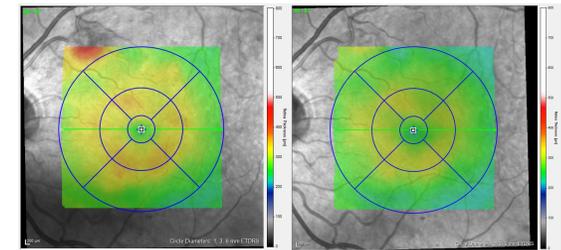
Patient 12-002
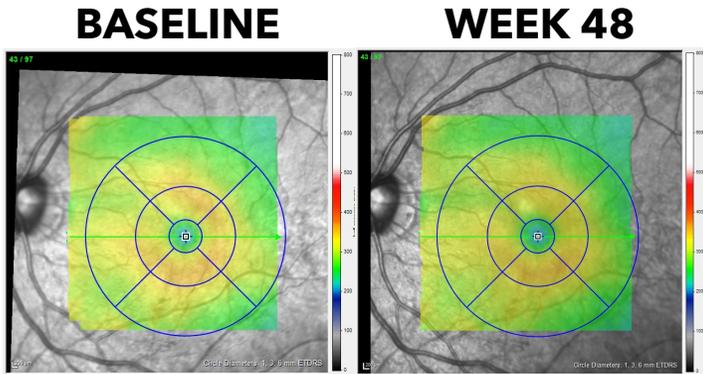Baseline Vol. = 8.93 mm^3
Week 48 Vol. = 8.23 mm^3

Patient 16-009
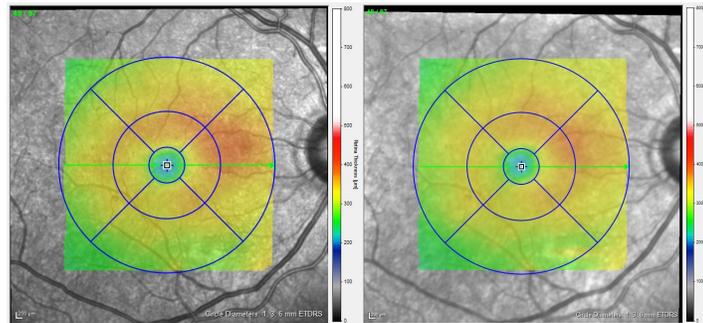Baseline Vol. = 8.56 mm^3
Week 48 Vol. = 7.85 mm^3

BASELINE WEEK 48 BASELINE WEEK 48

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

OTX-TKI Treated Patients Without Initial DME Remained DME-Free at Week 48

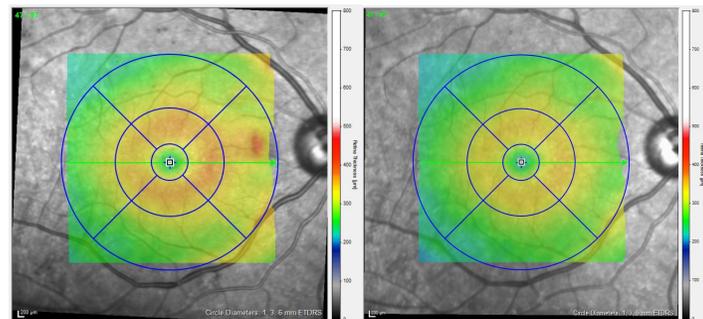**BASELINE**   **WEEK 48**

BASELINE   **WEEK 48**

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

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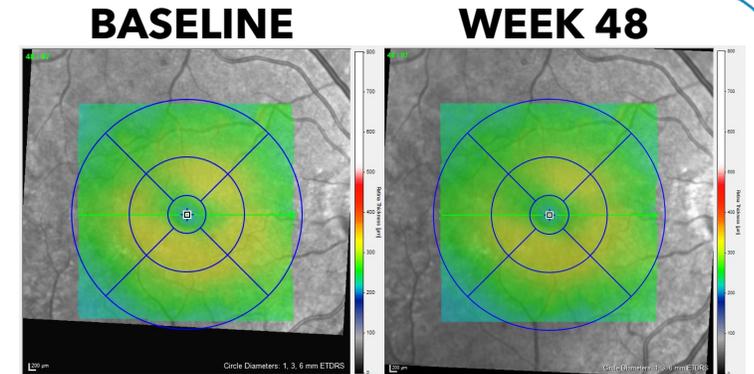Baseline Vol. = 7.82 mm^3
Week 48 Vol. = 7.69 mm^3

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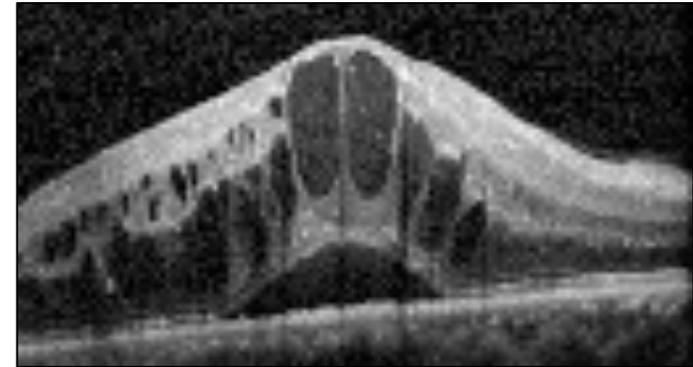Week 48 Vol. = 8.99 mm^3

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

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

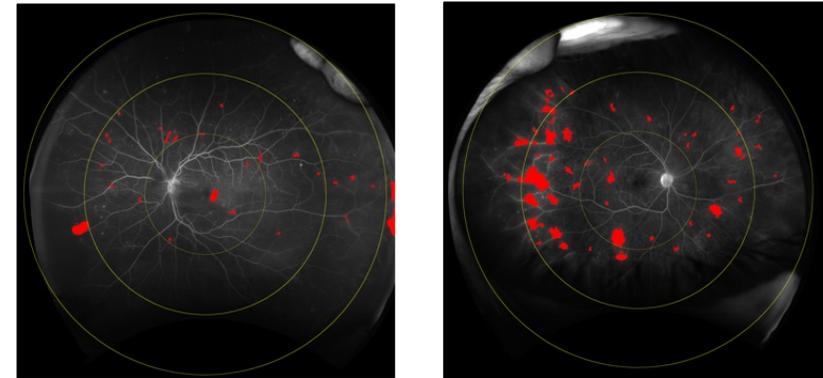Abbreviations: DME (diabetic macular edema); Vol. (volume)

Acknowledgement

OCT and Leakage analyses based on the findings of Justis P. Ehlers, MD and his Cole Eye research team

- Masked longitudinal assessment of quantitative leakage on UWFA images and advanced OCT feature analysis were conducted using a **machine-learning augmented feature and extraction** platform performed by certified readers with correction, as needed

- Leakage index was calculated as the proportion of retinal leakage (i.e., hyperfluorescence) within the analyzable retina area

Example of OCT scan

Examples of ultra-widefield fluorescein angiography imaging

Reference: Ehlers JP, Clark J, Uchida A, et al. Longitudinal Higher-Order OCT Assessment of Quantitative Fluid Dynamics and the Total Retinal Fluid Index in Neovascular AMD. Transl Vis Sci Technol. 2021;10(3):29.

OTX-TKI Patients Consistently Had Greater Reductions From Baseline in Retinal Volume Compared to Sham

Retinal Volume (mm³)

Baseline mean
OTX-TKI, 10.94 mm³
Sham, 10.26 mm³

Mean Change from
Baseline at Week 48
OTX-TKI, -0.92 mm³
Sham, -0.16 mm³

Mean Change from Baseline (mm³)

Study Timepoint (Weeks)

Sham (N=8)   OTX-TKI (N=14*)
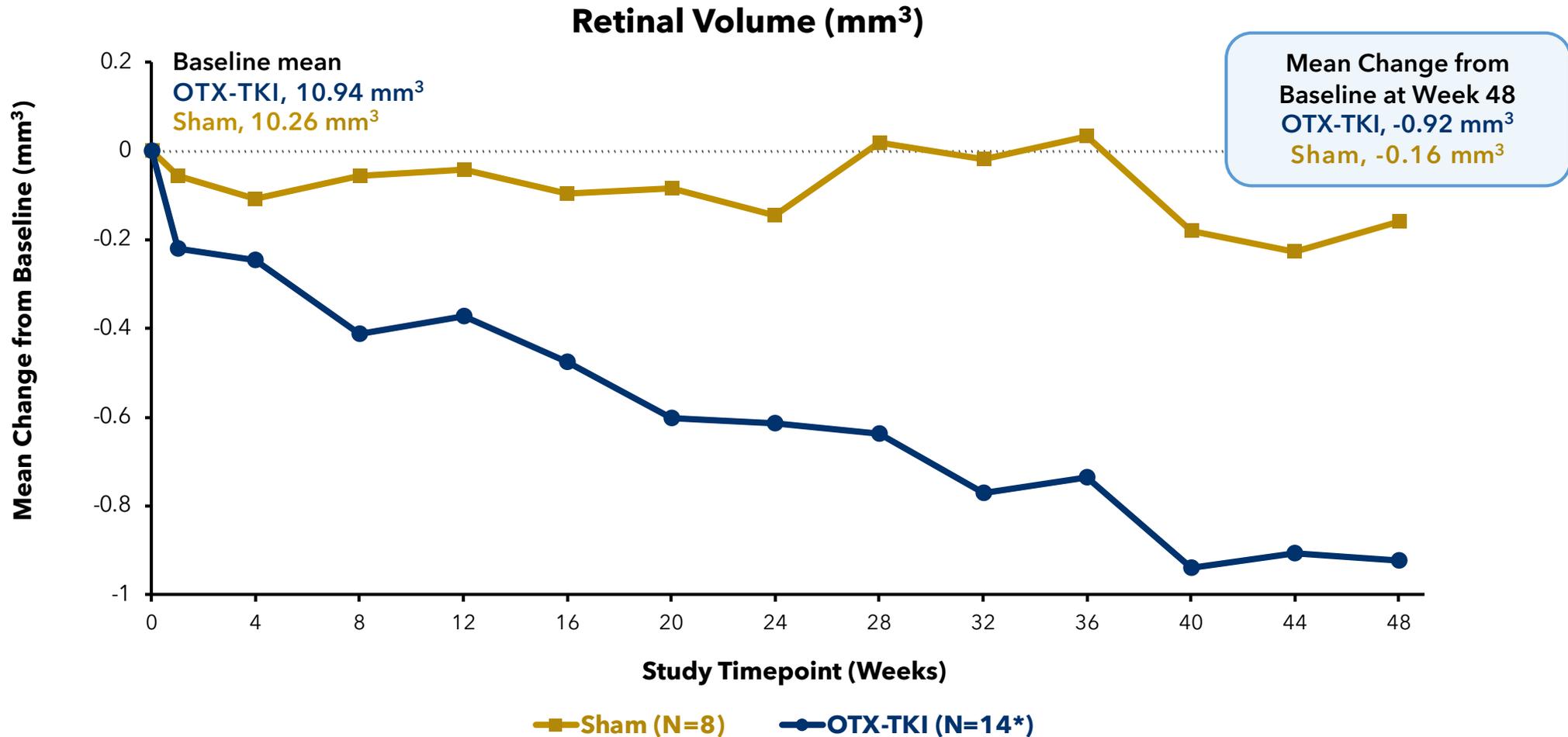
*14 were enrolled, with one death unrelated to treatment prior to week 24 visit.

OTX-TKI Provides a Durable Reduction in Total Retinal Vascular Leakage Over One Year Compared to Sham

Total Leakage Area

Screening mean
OTX-TKI, 45.1 mm^2
Sham, 21.5 mm^2

Sham: 15.5 (Week 24), 17.8 (End of Study)
OTX-TKI: -18.0 (Week 24), -19.2 (End of Study)

Y-axis: Mean Change from Screening (mm^2)
X-axis: Study Timepoint — Screening, Week 24, End of Study

Sham (N=8)   OTX-TKI (N=14*)

Total Leakage Index

Screening mean
OTX-TKI, 7.4%
Sham, 3.6%

Sham: 2.9 (Week 24), 3.5 (End of Study)
OTX-TKI: -2.8 (Week 24), -3.0 (End of Study)

Y-axis: Mean Change from Screening (%)
X-axis: Study Timepoint — Week 24, End of Study

Sham (N=8)   OTX-TKI (N=14*)

*14 were enrolled, with one patient death unrelated to treatment prior to week 24 visit
Total leakage area = panretinal (total leakage for the entire retina)

HELIOS Phase 1 Summary

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

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

Consistent improvement in fluid metrics and retinal leakage was observed in OTX-TKI–treated patients compared to sham

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

Thank you.