Learnings from the Phase 1 AXPAXLI HELIOS Diabetic Retinopathy Study

DILSHER DHOOT, MD

CALIFORNIA RETINA CONSULTANTS, BAKERSFIELD, CA

On behalf of the HELIOS investigators

Disclosures

FINANCIAL DISCLOSURES (DILSHER S. DHOOT)

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.

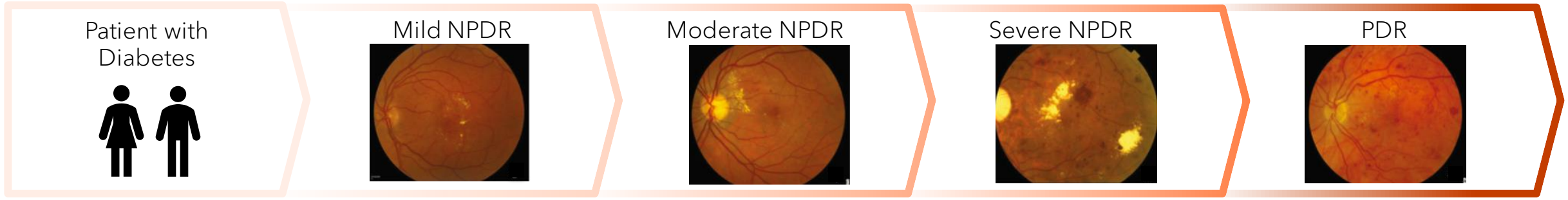
Grant: Ocular Therapeutix, Inc.

STUDY AND PRODUCT DISCLOSURES

The following presentation discusses an investigational drug, AXPAXLI (also referred to as OTX-TKI), in development. AXPAXLI'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

DR is Chronic, Progressive and Burdensome, with a Need for Earlier Treatment to Prevent Progression



Risk of Progression to PDR (1 year)

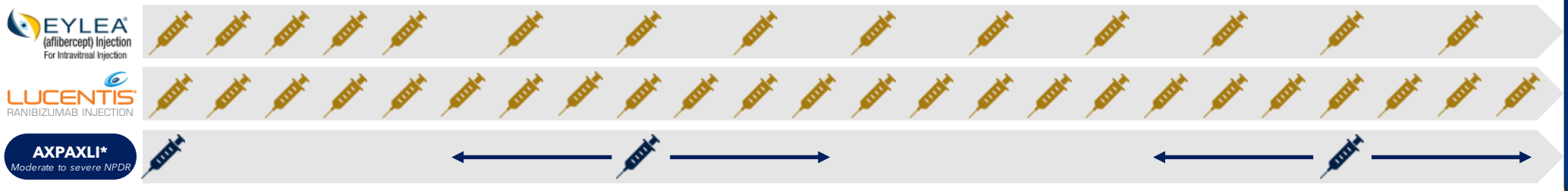
5% → 12-27% → ~52-75%

Patient Journey Overview

- One of most **common, severe diabetes complications**; **leading cause of blindness** in working-age population
- Diabetic patients often screened for DR, referred to **ophthalmologists**
- **No established standard of care** for NPDR (mainly observation), but **earlier intervention could treat NPDR and prevent progression** to severe/vision-threatening disease
  - Anti-VEGFs approved in NPDR, but <1% of NPDR patients are treated with anti-VEGF therapy because, among other reasons, they require frequent injections

Current Approved Treatments and Planned AXPAXLI Position for Moderate to Severe NPDR

24 Month Treatment Regimens:



*per planned protocol dosing

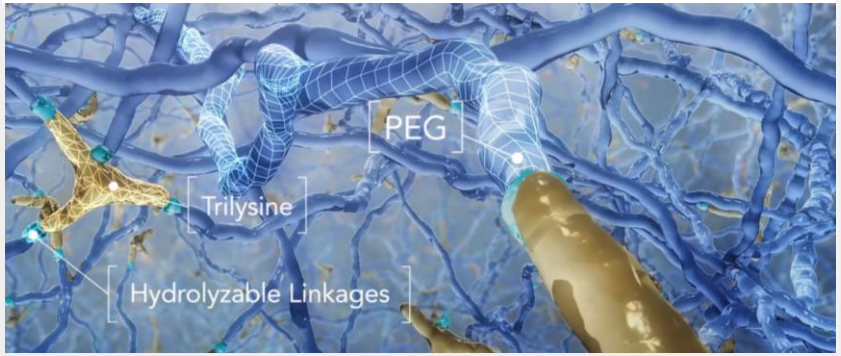
References: Eye care of the patient with diabetes mellitus. American Optometric Association, Second Edition; Market Scope - 2022 Retinal Pharmaceuticals Market Report, Global Analysis 2021-2027; Market Scope Q2-2022 US Retina Quarterly Update; AAO DR Preferred Practice Pattern; *JAMA Ophthalmol*. 2021;139(9):946-955 (PANORAMA); Arcadu F, et al. *NPJ Digit Med*. 2019;2:92.

AXPAXLI: Sustained-Release Axitinib in Hydrogel

ELUTYX TECHNOLOGY

Bioresorbable, Targeted, Sustained Drug Delivery

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



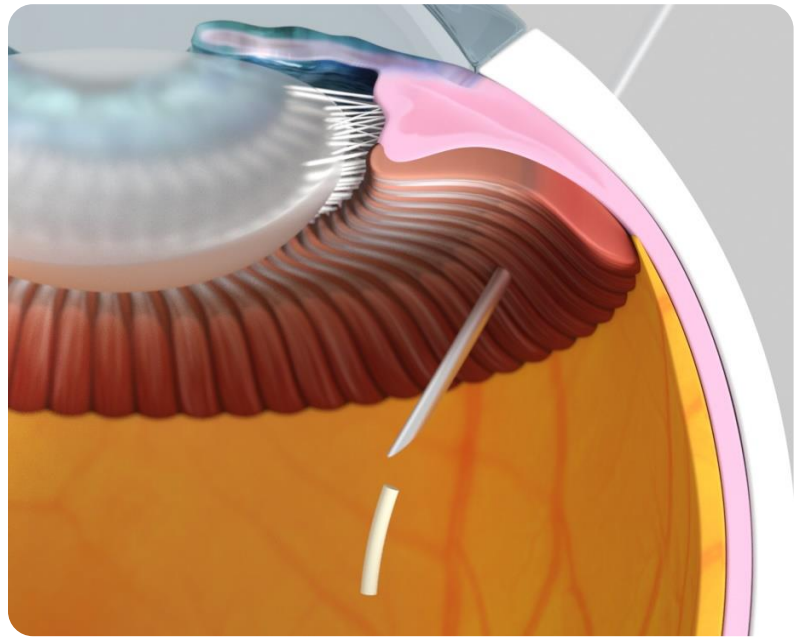
AXITINIB

Multi-target Tyrosine Kinase Inhibitor

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]	40
Vorolanib[3]	64

AXPAXLI (axitinib intravitreal implant)



- Completely bioresorbable over 9-12 months
- Administered by a 25G needle
- Covered by a US patent that expires 2041[4]

Abbreviations: KDR (Kinase insert domain receptor); PDGF (Platelet-derived growth factor); PEG (Polyethylene glycol); TKI (Tyrosine kinase inhbitor); VEGF (Vascular endothelial growth factor [receptor]).

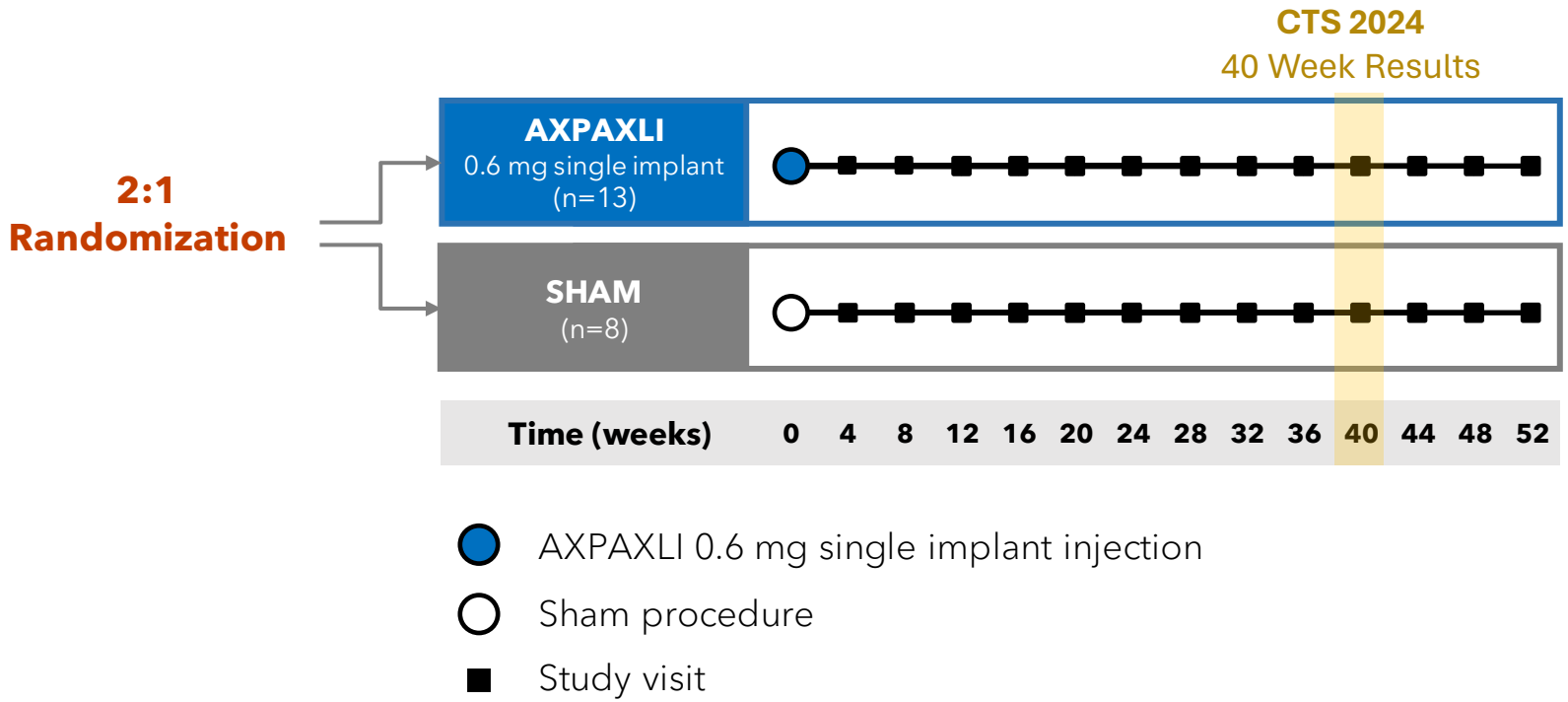
References: 1. Zhao Y, et al. *Oncologist*. 2015;20(6):660-673. **2.** Gross-Goupil M, et al. *Clin Med Insights Oncol*. 2013;7:269-277. **3.** Liang C, et al. *Mol Ther Oncolytics*. 2022;24:577-584. **4.** Blizzard CD, et al. US Patent: Ocular implant containing a tyrosine kinase inhibitor. Published online September 13, 2022. Accessed May 30, 2024.

CLINICAL TRIALS at the SUMMIT

HELIOS: Phase 1 Study of AXPAXLI in NPDR without CI-DME

HELIOS

Multicenter, double-masked, randomized, parallel group study of AXPAXLI in patients with moderately severe to severe NPDR without DME



STUDY OUTCOMES

Primary outcomes:

Safety and tolerability of AXPAXLI

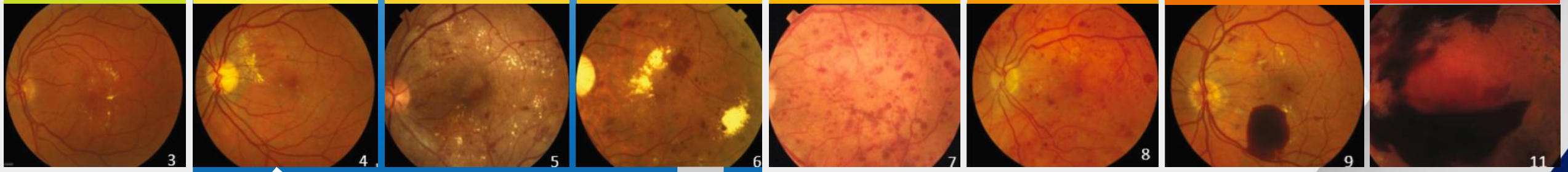
Secondary outcomes:

DRSS changes, rescue therapy, BCVA and CSFT changes

Abbreviations: NPDR (non-proliferative diabetic retinopathy); DME (diabetic macular edema); CI-DME (center-involved DME); DRSS (Diabetic Retinopathy Severity Scale); BCVA (best corrected visual acuity); CSFT (central subfield thickness)

Diabetic Retinopathy Severity Scale (DRSS)

35	43	47	53	60, 61	65	71-75	81-85
Mild NPDR	Moderate NPDR	Moderately Severe NPDR	Severe NPDR	Mild PDR	Moderate PDR	High-risk PDR	Advanced PDR



Example of a 2-step improvement

Abbreviations: DR (diabetic retinopathy); NPDR (nonproliferative DR); PDR (proliferative DR)

HELIOS: Key Eligibility Criteria

KEY INCLUSION CRITERIA

- Males or non-pregnant females ≥18 years of age
- Diabetic retinopathy secondary to diabetes mellitus type 1 or 2
- **Moderately severe to severe NPDR** (DRSS level 47 or 53 determined by a central reading center) in the study eye
- **BCVA ≥69 ETDRS letters** (Snellen equivalent ~20/40 or better) in the study eye

KEY EXCLUSION CRITERIA

- **DME within 6 months involving center of macula**; or DME threatening the center (within 200 microns) of the macula in the study eye
- OCT CSFT ≥320 µm in the study eye
- Any neovascular growth (including ASNV), vitreous hemorrhage, or tractional retinal detachment in the study eye
- Chronic or recurrent uveitis, or ongoing ocular infection or inflammation in the study eye
- Prior treatments in the study eye:
  - Systemic or **ocular anti-VEGF treatment in the prior 12 months**
  - Intraocular steroid injections within 4 months, dexamethasone intravitreal implant within 12 months, fluocinolone acetonide intravitreal implant at any time
  - Grid or focal laser photocoagulation within 500 microns of foveal center or PRP at any time
- Screening hemoglobin A1c >12.0%
- History of other clinically significant ocular or systemic disease per Investigator's discretion

Abbreviations: NPDR (nonproliferative diabetic retinopathy); DRSS (Diabetic Retinopathy Severity Scale); BCVA (best corrected visual acuity); ETDRS (Early Treatment Diabetic Retinopathy Study); DME (diabetic macular edema); OCT (optical coherence tomography); CSFT (central subfield thickness); ASNV (anterior segment neovascularization); PRP (panretinal photocoagulation)

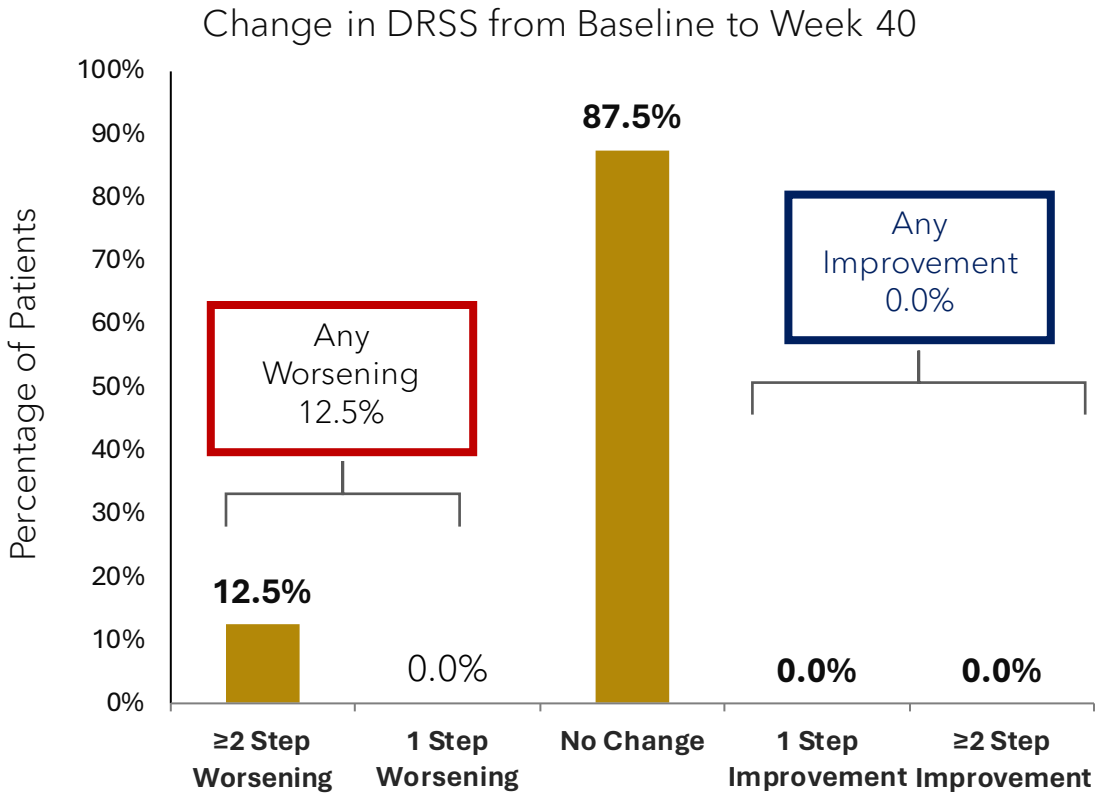
Safety Overview at 40 Weeks

- AXPAXLI was generally well tolerated
- No ocular SAEs reported in either arm
- All AEs were mild and balanced across the two arms, with no moderate or severe AEs reported in either arm
- AXPAXLI injection did not result in any reported intraocular inflammation, iritis, vitritis, or vasculitis
- No subjects in either arm received supplemental injections

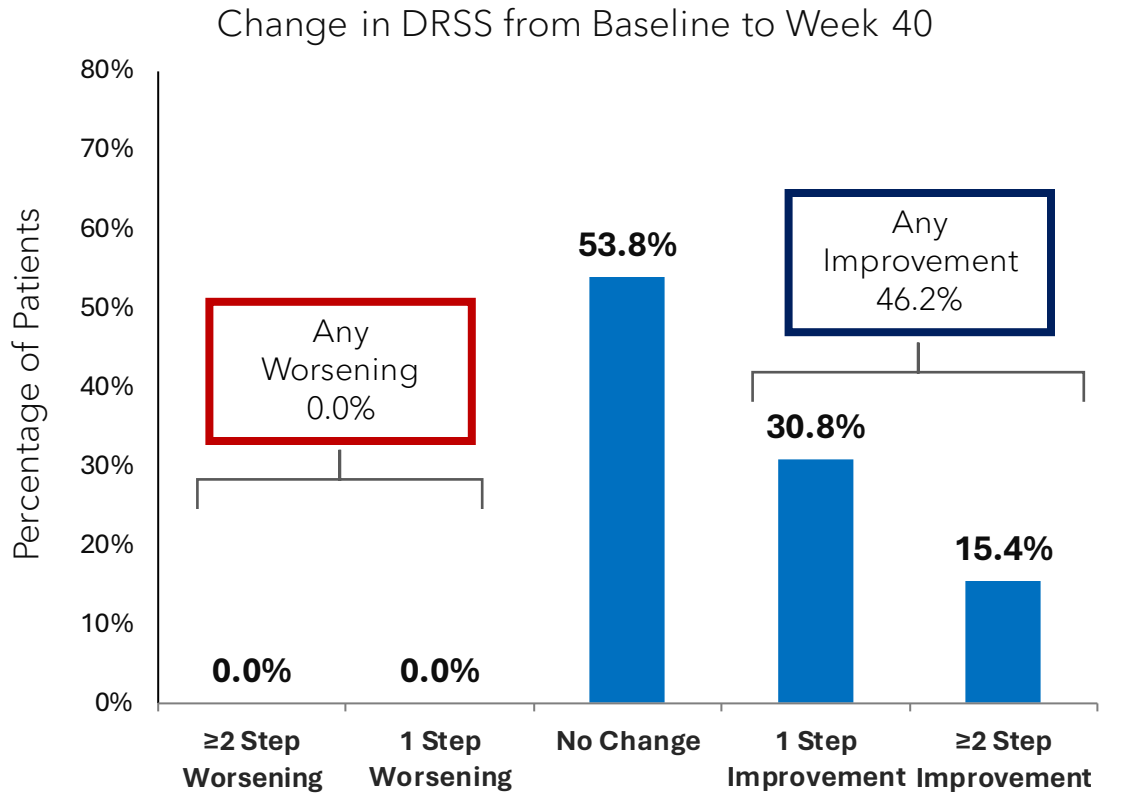
Datacut: March 21, 2024
Abbreviations: AE (adverse event); SAE (serious AE);

46.2% of Patients Demonstrated a 1- or 2-step DRSS Improvement at 40 Weeks in the AXPAXLI Arm*

Sham Arm (N=8)

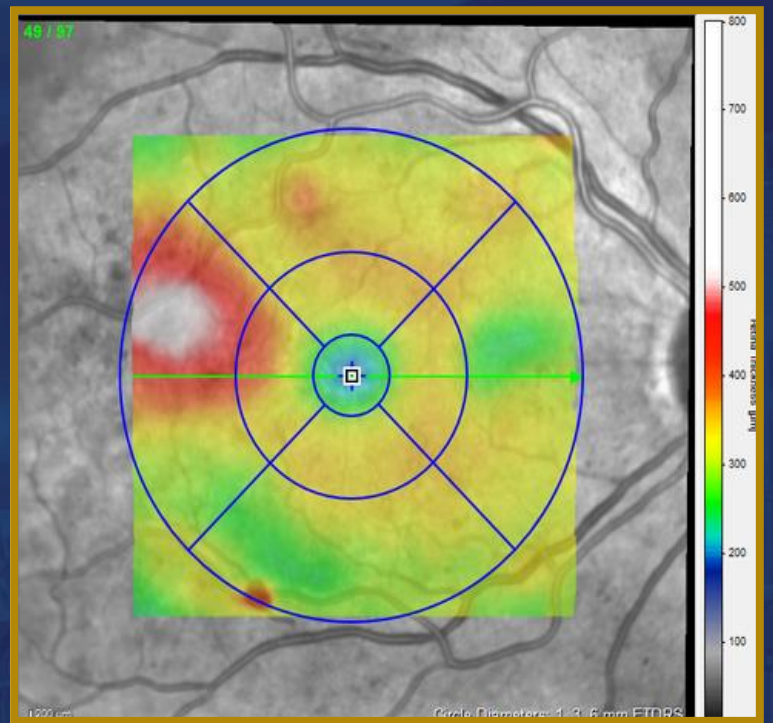


AXPAXLI Arm (N=13)

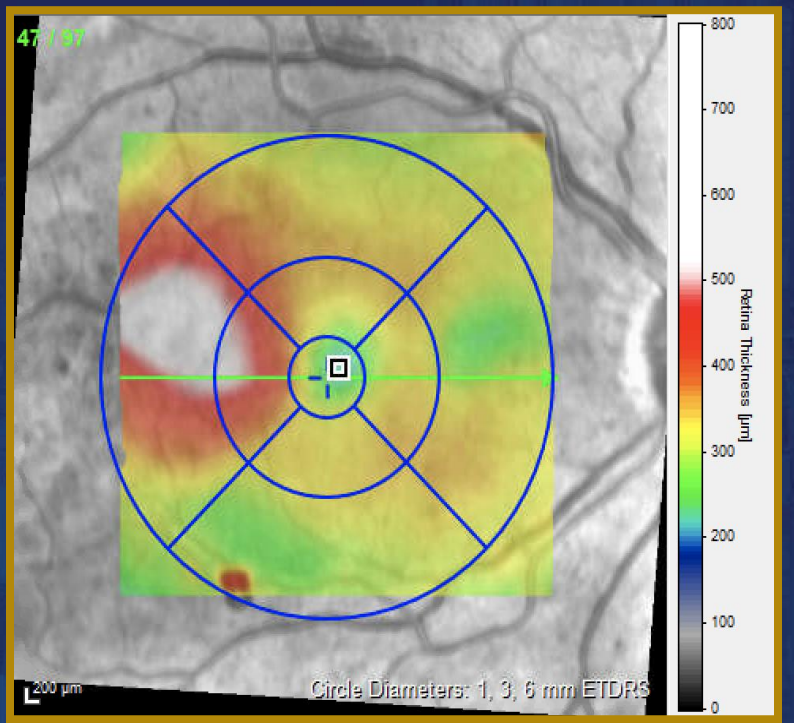


***Datacut:** March 21, 2024
Abbreviations: DRSS (Diabetic Retinopathy Severity Scale)

Worsening of Diabetic Macular Edema in a Subject from the Sham Arm



BASELINE
CSFT = 237 µm

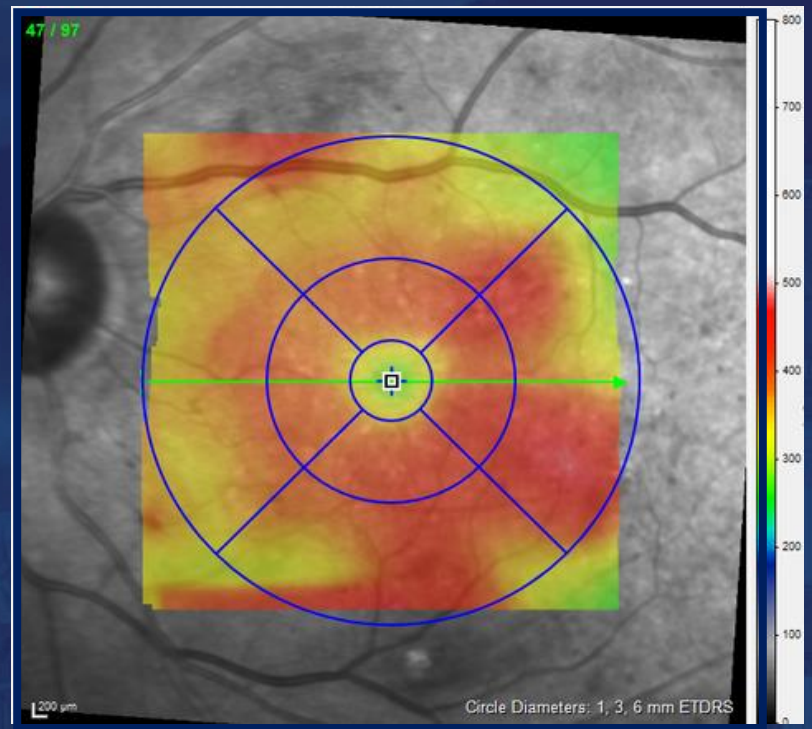


WEEK 40
CSFT = 270 µm

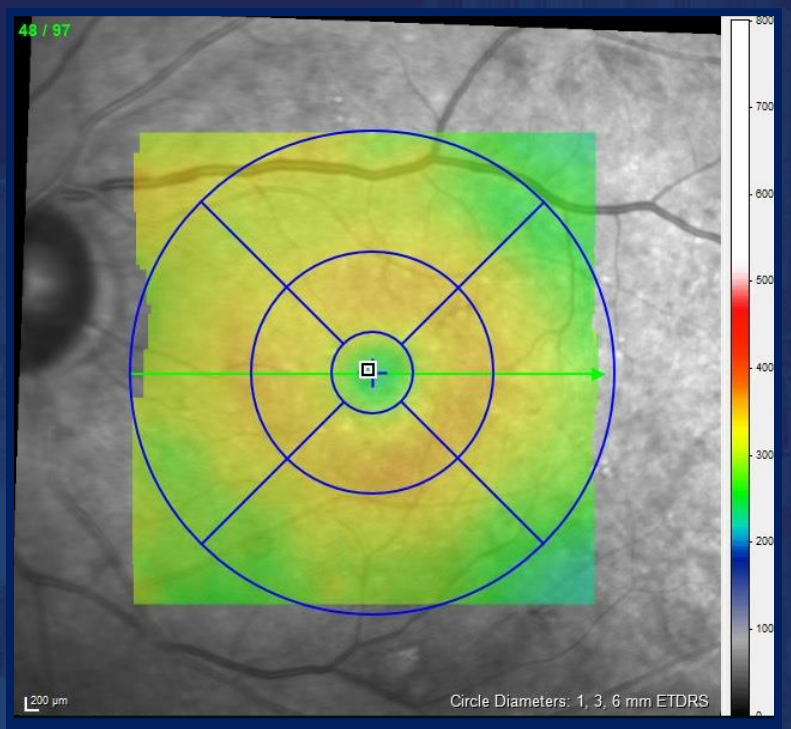
Subject in Sham Arm Developed CI-DME

Datacut: March 21, 2024
Abbreviations: CSFT (central subfield thickness); CI-DME (center-involved diabetic macular edema)

Regression of Diabetic Macular Edema in a Subject Receiving AXPAXLI



BASELINE
CSFT = 320 µm



WEEK 40
CSFT = 275 µm

Subject treated with AXPAXLI demonstrating regression at 40 weeks

Datacut: March 21, 2024
Abbreviations: CSFT (central subfield thickness)

Summary

AXPAXLI was generally well-tolerated

- Did not result in any reported incidence of IOIs, iritis, vitritis, or vasculitis
- No ocular SAEs reported
- No ocular severe AEs reported

AXPAXLI demonstrated DRSS stability or improvement with durability through 40 weeks

- 46.2% of patients demonstrated a 1- or 2-step DRSS improvement at 40 weeks in the AXPAXLI arm versus 0% in sham arm
- No subjects in the AXPAXLI arm experienced worsening in DRSS at 40 weeks versus 12.5% in sham arm

Datacut: March 21, 2024
Abbreviations: DRSS (Diabetic Retinopathy Severity Scale); IOI (intraocular inflammation); AE (adverse event); SAE (serious AE)

Thank You to the investigators in the HELIOS trial

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