Phase 1/2 Clinical Trial of Intravitreal 4D-150 in Patients with Wet Age-Related Macular Degeneration

PRISM

Interim Safety & Efficacy Data

May 2023

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Key Takeaways:
Intravitreal 4D-150 PRISM Phase 1 Dose Exploration Results

- **Routine intravitreal** injection
- **Well-tolerated & no significant safety signals or inflammation**
- **High clinical activity in advanced patients**
- Phase 2 enrollment **ahead of schedule**

Data Summary

Phase 1 Patient Population (N=15)

- Dose Cohorts: 3E10 (**high**; n=5) vs 6E9 & 1E10 (**lower doses**; n=10 total)
- **Advanced, high-need patients: top ~15%** anti-VEGF utilization (IRIS)

Safety

- **No Grade ≥1 inflammation** (up to 64 weeks f/u)

Clinical Activity

- **High** Dose Phase 2 BCVA-Eligible (36 weeks; n=4):
  - **4 of 4 (100%) Injection-Free**
  - **Mean CST meaningfully improved (-74 µm)**
- **Lower** Doses (24 weeks; n=10):
  - **75% reduction anti-VEGF injection frequency**
  - **7 of 10 (70%) ≤1 Injection** (4 of 10 or 40% Injection-Free)

PRISM Status & Next Steps

- **Phase 2 enrollment >50%; expect completion in Q3** (updated from Q4)
  - BCVA threshold raised for Phase 2: 25–78 → **34–83** ETDRS letters

Pipeline: Large Market Ophthalmology Portfolio

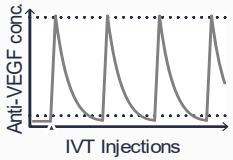
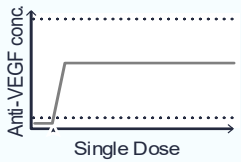
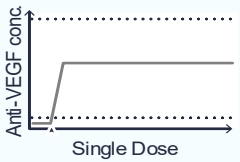
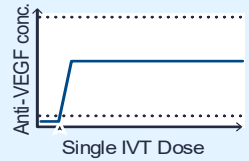
THREE LARGE & SUSTAINABLE PATIENT POPULATIONS

VECTOR *Delivery*	PRODUCT CANDIDATE	INDICATION	EPIDEMIOLOGY (PREVALENCE)	RESEARCH CANDIDATE	IND-ENABLING	PHASE 1 / 2	PHASE 3	PRODUCT RIGHTS
R100 *Intravitreal* 	**OPHTHALMOLOGY**							
	4D-150	**Wet AMD**	*~3M U.S./EUMM*					4DMT
		Diabetic Macular Edema	*~1.2M U.S.*					4DMT
	4D-125	XLRP	*~24K U.S./EUMM*					4DMT
	4D-110	CHM	*~13K U.S./EUMM*					4DMT
	4D-175	**Geographic Atrophy**	*~1M U.S.*					4DMT
A101 *Aerosol* 	**PULMONOLOGY**							
	4D-710	CF Lung Disease (modulator-ineligible)	*~6K U.S.*					4DMT
		CF Lung Disease (modulator-eligible)	*~34K U.S.*					4DMT
	4D-725	A1AT Deficiency Lung Disease	*~200K U.S./EUMM*					4DMT
C102 *IV* 	**CARDIOLOGY**							
	4D-310*	Fabry Disease Cardiomyopathy	*~50-70K U.S./EUMM*					4DMT

*Currently on clinical hold.

4D-150 is Highly Differentiated vs Eylea & AAV Competitors

POTENTIAL ADVANTAGES COMPARED TO ESTABLISHED & DEVELOPMENT-STAGE THERAPIES

Product Design		Eylea™	RGX-314 (subretinal)	RGX-314 (suprachoroidal)	ADVM-022 (IVT)	4D-150[1] (IVT)
Administration & PK	Illustrative Pharmacokinetics			*Not available*		
	Single dose	–	+	+	+	+
	IVT injection	+	–	–	+	+
Anti-VEGF Inhibition	VEGF-A	+	+	+	+	+
	VEGF-B	+	–	–	+	+
	PlGF (placental GF)	+	–	–	+	+
	VEGF-C	–	–	–	–	+
Safety Results To Date	No hypotony	+	+	+	–	+
	No significant uveitis	+	+	–*	–	+
	Primate evolved/optimized vector	NA	–	–	–	+
	Low-dose AAV	NA	–	–	–	+

For illustrative purposes only, no head-to-head comparison conducted. *Mild to moderate uveitis observed without steroids, steroid regimen currently being studied. 1. Based on interim clinical results from Phase 1/2 trial with data cutoff of April 3, 2023.

Goals: Intravitreal 4D-150 PRISM Phase 1 Dose Exploration Stage

ALL GOALS ACHIEVED

- ✓ **Determine safety & tolerability**
- ✓ **Demonstrate clinical activity**
  - First-in-human trial; severe disease patients
  - Phase 2 & 3 determine efficacy in broader patient population
- ✓ **Demonstrate dose-response**
- ✓ **Select Ph 2 randomized stage doses**
- ▪ **ALL goals achieved**

4D-150 Phase 1 Dose Exploration in Wet AMD Patients (N=15)

Interim Clinical Data (Data Cutoff: April 3, 2023)

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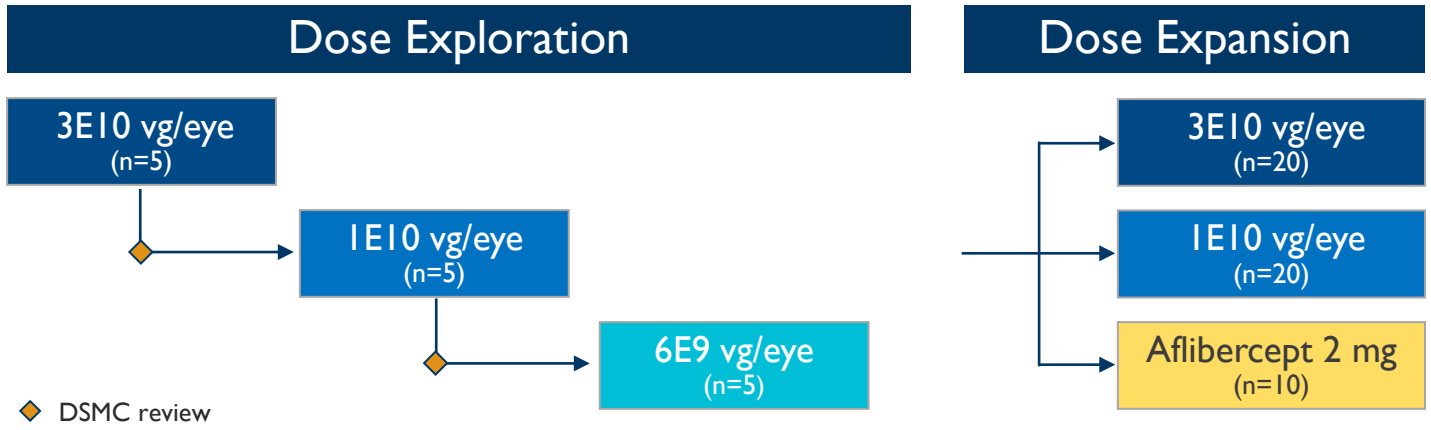
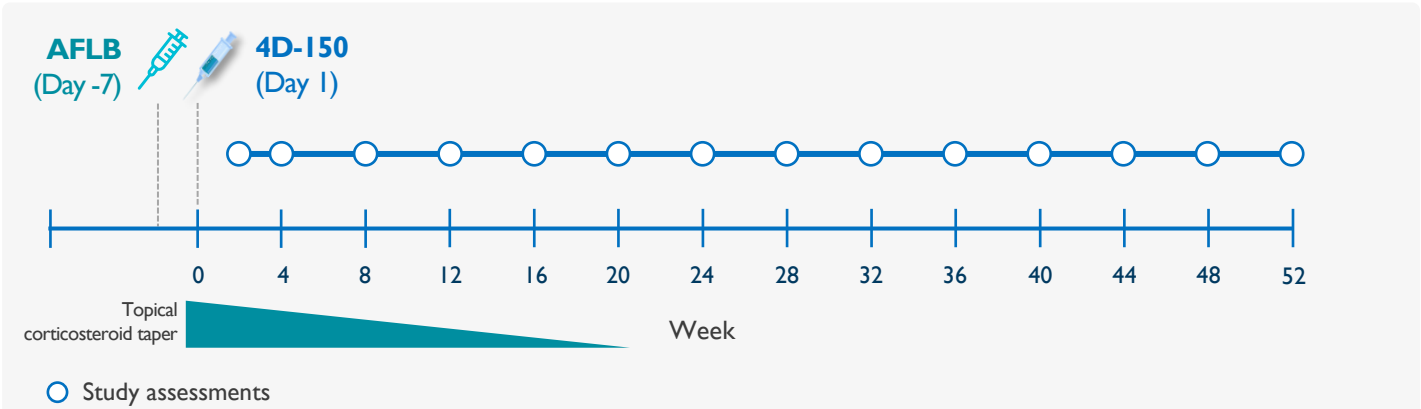
4D-150 Phase 1/2 Clinical Trial Design

OBJECTIVE: EVALUATE SAFETY, TOLERABILITY & CLINICAL ACTIVITY IN ANTI-VEGF-DEPENDENT PATIENTS

Study Design





*Dose exploration phase. †Sentinel subject. AMD, age-related macular degeneration; BCVA, Best-Corrected visual acuity; CNV, choroidal neovascularization; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; TEAE, treatment emergent adverse event; SAE, serious adverse event; VEGF, vascular endothelial growth factor.

Key Inclusion Criteria*

- CNV secondary to AMD
- Anti-VEGF injections last 12 months: ≥6 & responsive
- **Ph 1: 25–78 ETDRS letters†**
- **Ph 2: 34–83 ETDRS letters**

Primary Endpoint

- Incidence & severity of TEAEs & SAEs

Key Secondary Endpoints

- BCVA & CST: change from pre-treatment
- Aflibercept supplemental injections:
  - Key Criteria: CST (OCT) increase ≥75 microns, BCVA worsened ≥10 letters attributed to observed intraret or subret fluid, or new retinal hemorrhage
  - % requiring supplemental aflibercept
  - Annualized anti-VEGF injection rate: % change

Interim Safety Summary: All Patients 24-64 Weeks

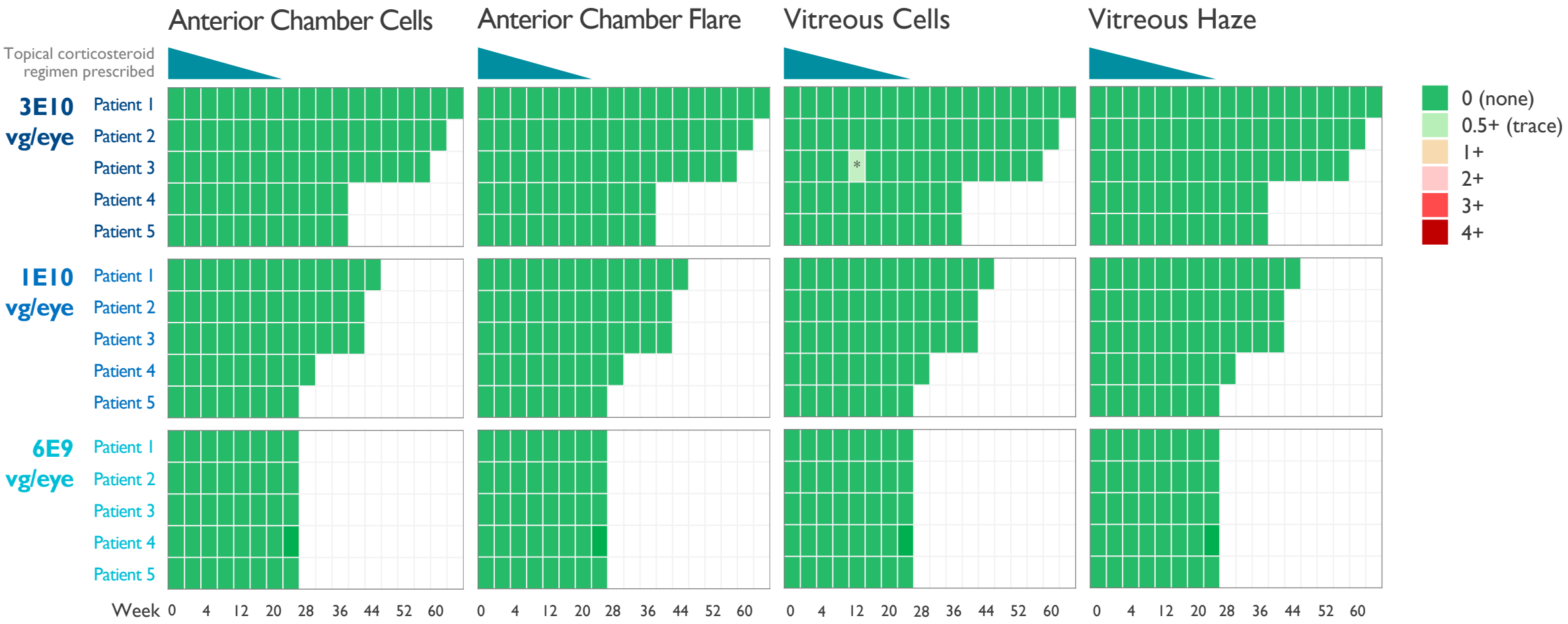
ALL DOSES WELL-TOLERATED WITH NO GRADE ≥1 INFLAMMATION OR HYPOTONY

- No DLTs
- No 4D-150-related SAEs
- **No inflammation Grade ≥1**
- **No significant 4D-150-related adverse events:**
  - No hypotony, no endophthalmitis, no retinal vasculitis, no choroidal effusions, no retinal artery occlusion

Data cutoff date, April 3, 2023. DLT, dose-limiting toxicity; SAE, serious adverse event.

Ophthalmic Exams for Inflammation: 99.8% Assessments Normal

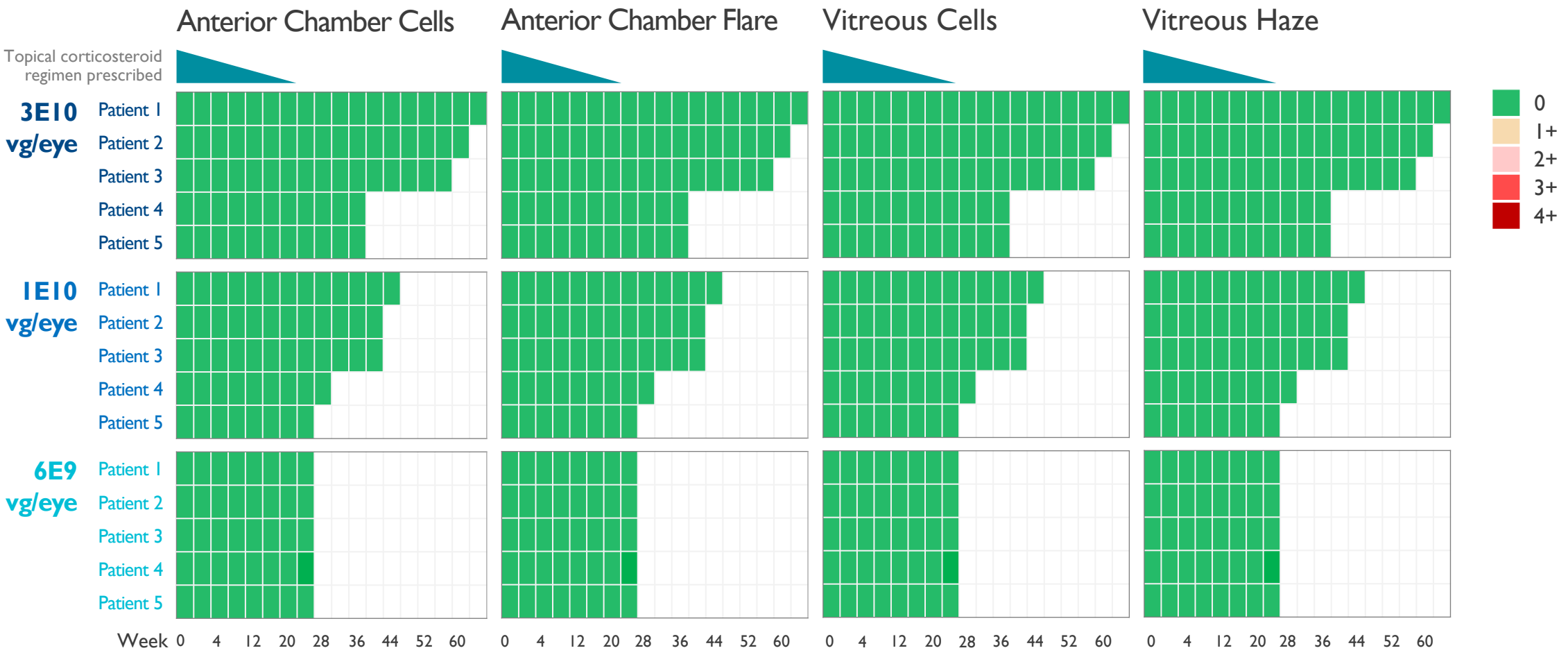
SUN & NEI SCORES FOR WBC, FLARE & HAZE (24-64 WEEKS); 667 OF 668 (99.8%) ASSESSMENTS NORMAL



Data cutoff date, April 3, 2023. Protocol-mandated 20-week prophylactic steroid eyedrop taper completed in all but one participant (patient 1, 3E10 vg/eye).
*Trace mixed pigmented and unpigmented cells. NEI, National Eye Institute; SUN, Standardization of Uveitis Nomenclature; WBC, white blood cells.

No Grade ≥1 Inflammation Episodes (n=668 Evaluations)

100% OF 668 ASSESSMENTS NEGATIVE FOR GRADE 1 OR HIGHER INFLAMMATION



Data cutoff date, April 3, 2023. Protocol-mandated 20-week prophylactic steroid eyedrop taper completed in all but one participant (Patient 1, 3E10 vg/eye).

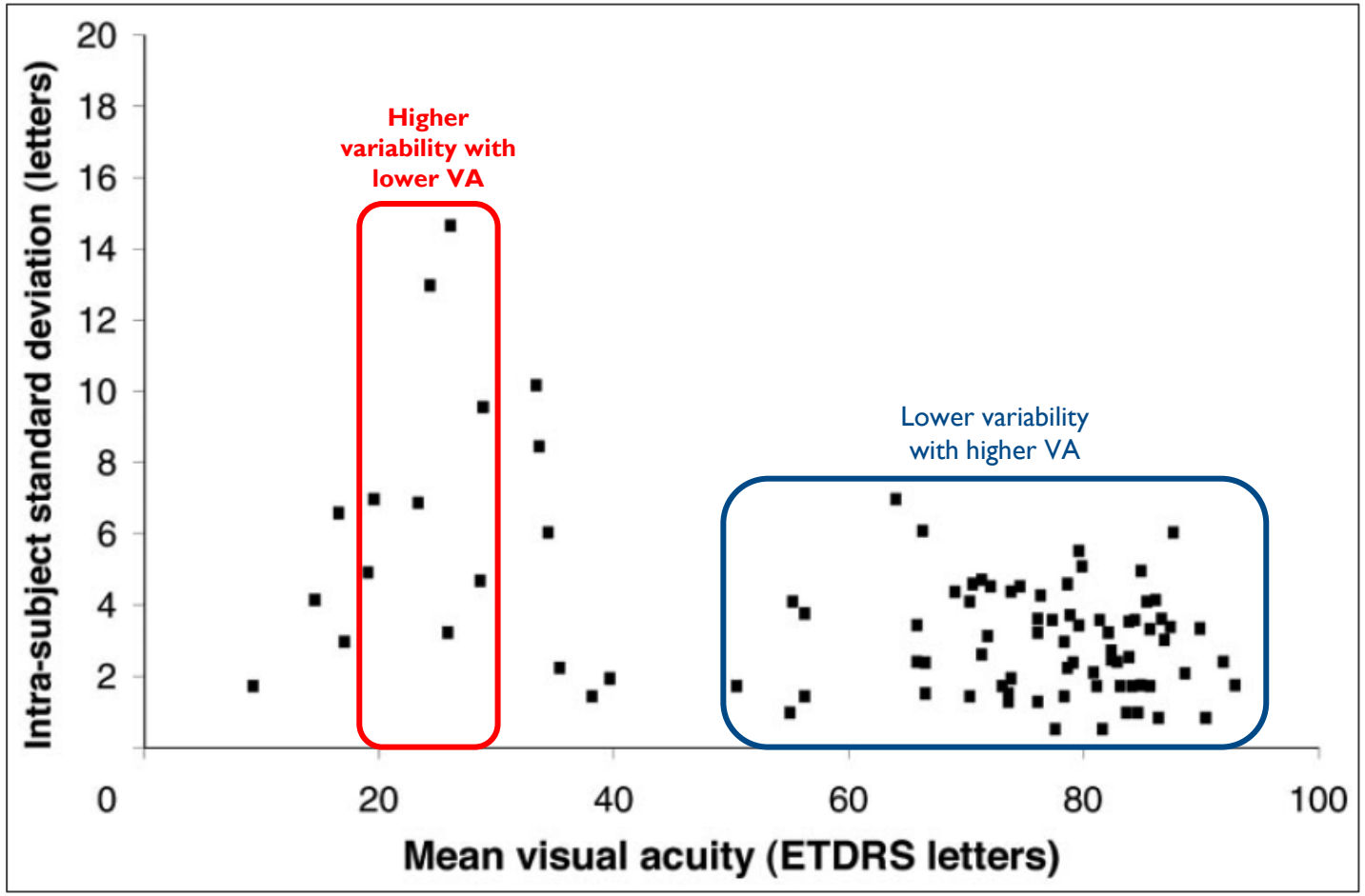
BCVA Intra-Patient Variability in Context: Rationale for BCVA Supplemental Injection Criteria

Individual Patients' SD vs. Mean Visual Acuity (n=90)[1]

Visual Acuity is Highly Variable in Late-Stage AMD[1]

Test/Re-Test BCVA:

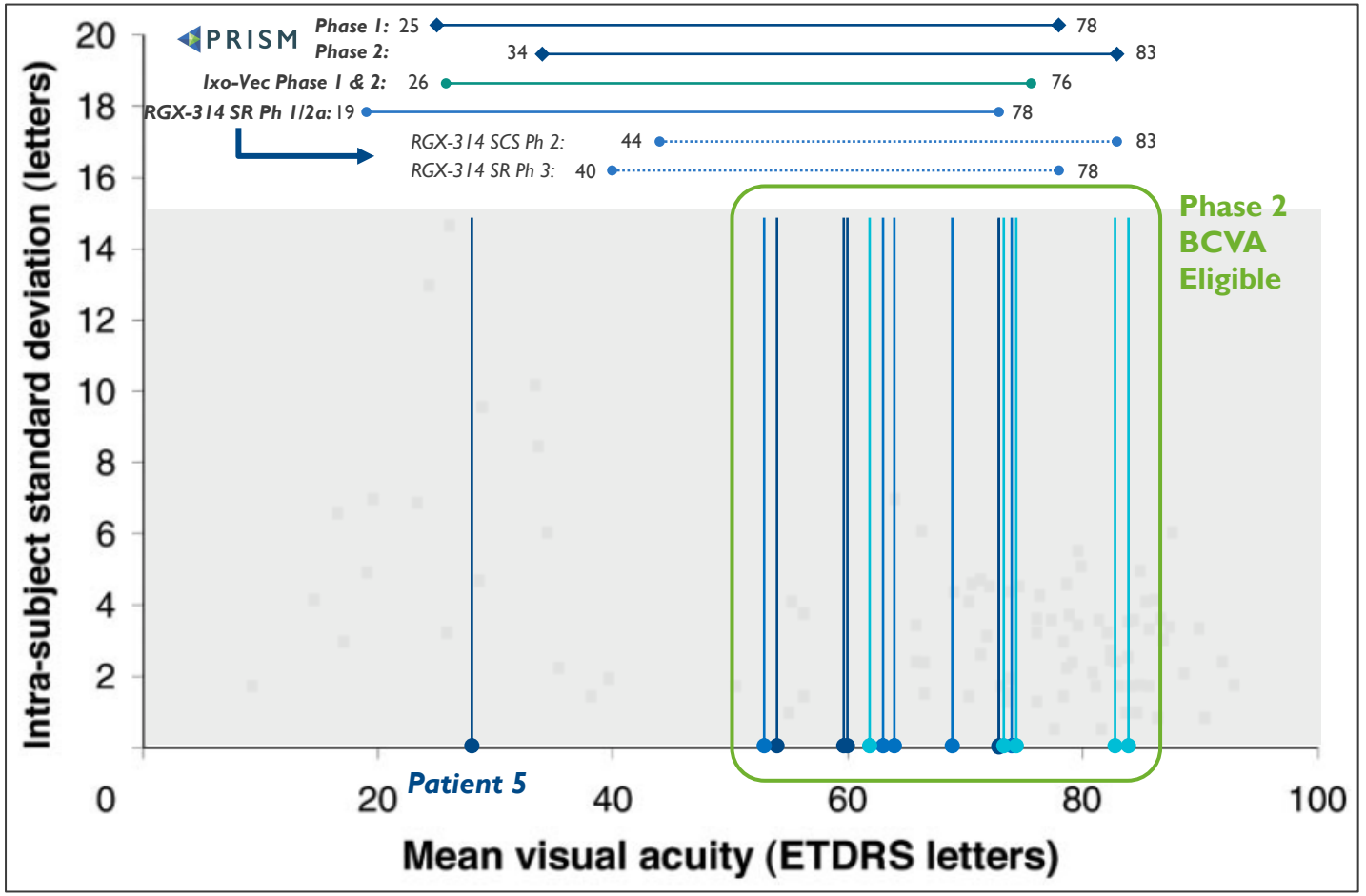
- **Variability 17 letters (+/-8.5)** in advanced AMD (vs **5 in normal**)[1]
- **Higher variability in low BCVA patients (e.g., pt 5)**



1. Patel, Praveen J et al. *Investigative ophthalmology & visual science* vol. 49,10 (2008): 4347-52. BCVA, Best-Corrected visual acuity; SD, Standard Deviation.

14 of 15 PRISM Patients in Typical Phase 2/3 Range; 1 Extreme Outlier (Low)

Individual PRISM Phase 1 Patients' Baseline Visual Acuity and Selected GT Trial Enrollment Criteria



Gene Therapy Trial Inclusion Criteria (BCVA)

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Phase 1 Treated Patients:

- 3E10 vg/eye
- 1E10 vg/eye
- 6E9 vg/eye

1. Patel, Praveen J et al. *Investigative ophthalmology & visual science* vol. 49,10 (2008): 4347-52. BCVA, Best-Corrected visual acuity; SD, Standard Deviation.

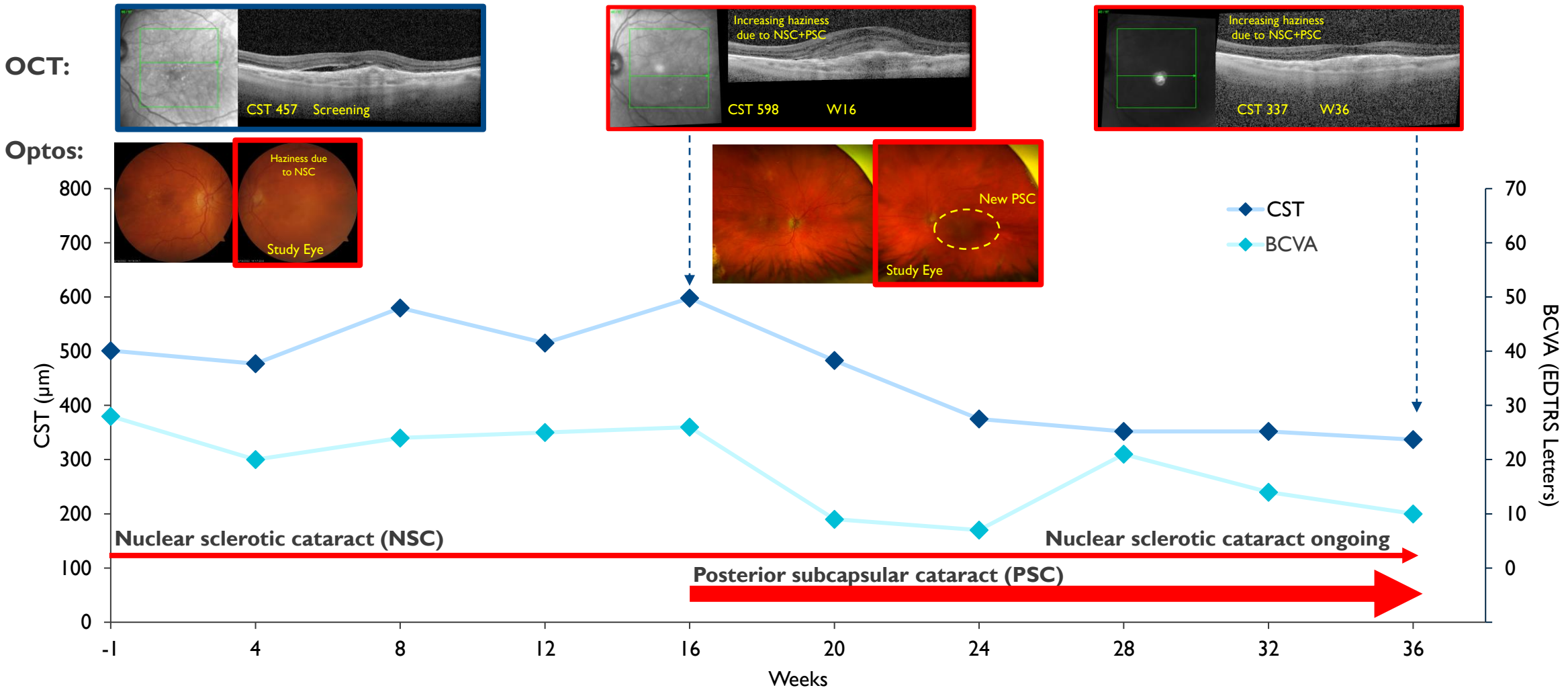
Interim Efficacy Data Analysis: 3E10 High Dose Patients

HIGH ANTI-VEGF NEED PATIENTS; ONE TOO ADVANCED FOR PHASE 2 OR PLANNED 3 ELIGIBILITY

- All patients advanced & high anti-VEGF need (mean annualized injections 11; up to 13)
- **4 of 5 patients Phase 2 BCVA-eligible: range 52-73**
- **Patient 5 not Phase 2 BCVA-eligible: 28 letters** (extreme outlier)
  - **Treatment eye pre-study history:**
    - Legally blind; BCVA highly variable (~20/400 or ~21 letters to "counting fingers at 4 feet" or 0 letters)
    - Cataract & glaucoma both eyes
  - **Treated eye on trial: multiple wAMD-independent factors affecting BCVA**
    - Cataract (not 4D-150-related) – NSC (nuclear sclerotic) at baseline, development of PSC (posterior subcapsular) at week 16
    - Continued BCVA highly variable; ~15 letter swings up & down on consecutive visits
  - **No evidence of toxicity**
    - Clinically (per investigator)
    - Imaging: Independent assessments including by central reading center (OCT, fluorescein angiography)

VEGF, vascular endothelial growth factor; BCVA, Best-Corrected visual acuity; CST, Central Subfield Thickness.

3E10 vg/eye Cohort Patient 5 Response Not Evaluable Due to Progressive Cataract



Interim Efficacy Data: 3E10 High Dose Patients Ph 2 Eligible BCVA

100% INJECTION-FREE (4 OF 4) IN PATIENTS WITH PHASE 2 ELIGIBLE BCVA

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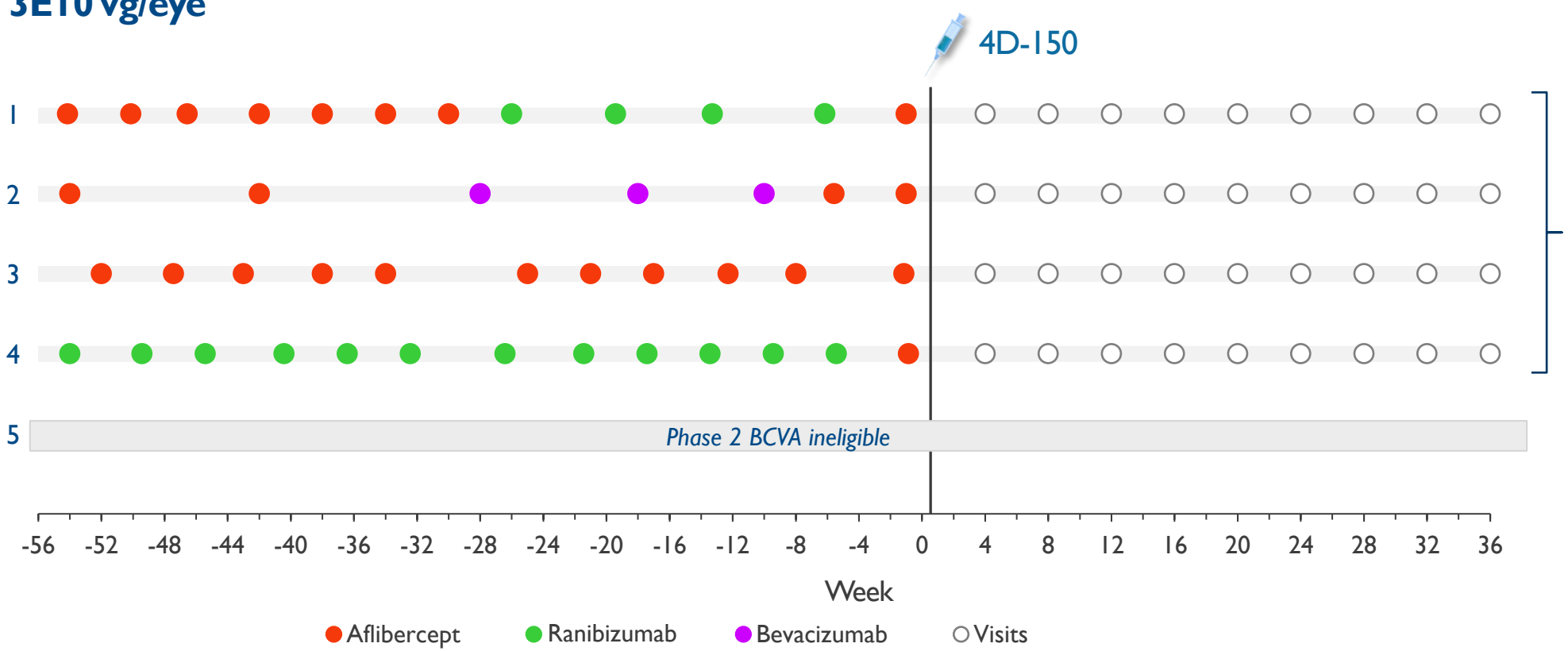
- Follow-up 36 weeks (n=4)
- **All advanced & high anti-VEGF need** (mean annualized injection freq 10; max 13)
- **100% of patients anti-VEGF injection-free (4 of 4)**
- **Mean CST improved: 74 µm**
- **BCVA maintained: +5, +1, 0 & -3***

Data cutoff date, April 3, 2023. *Last evaluable timepoint. VEGF, vascular endothelial growth factor; BCVA, Best-Corrected visual acuity; CST, Central Subfield Thickness.

Anti-VEGF Injection Data: 3E10 High Dose Cohort Ph 2 Eligible BCVA

4 OF 4 INJECTION-FREE PATIENTS AT 36 WEEKS



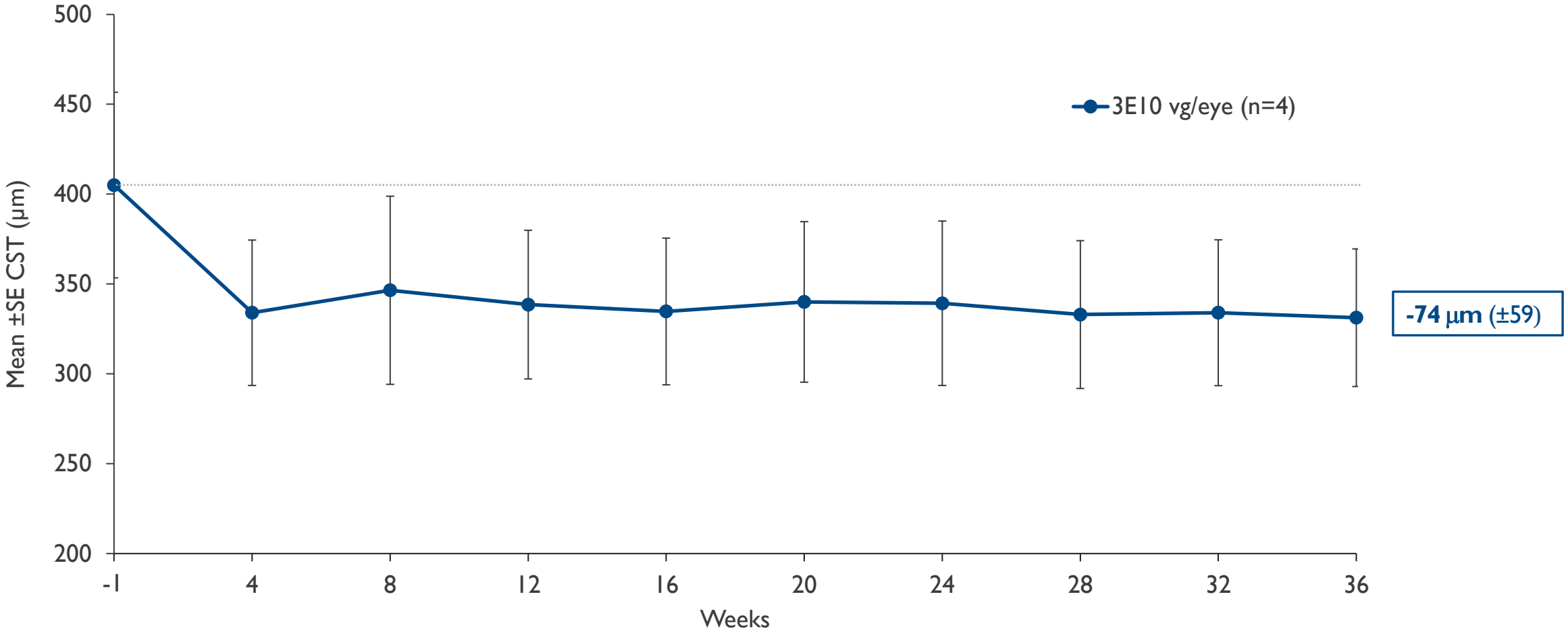
Durable Injection-Free:

100% (4 of 4)

Data cutoff, April 3, 2023. VEGF, vascular endothelial growth factor.

Mean CST Improved Overall Through 36 Weeks: 3E10 Injection-Free

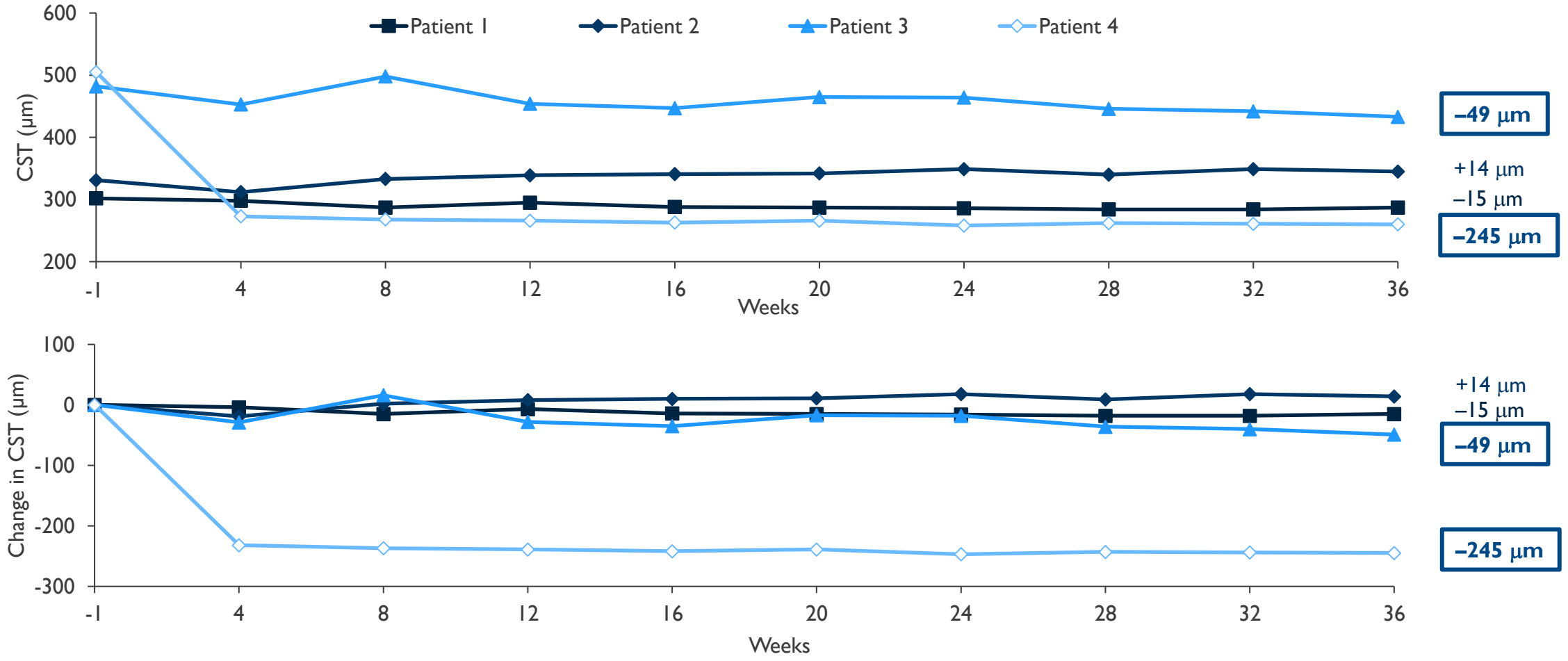
MEAN IMPROVEMENT OVER TIME IN ADVANCED PATIENTS WHO WERE INJECTION-FREE



Data cutoff date, April 3, 2023. CST, Central Subfield Thickness; SE, standard error.

CST Improved or Stable Through 36 Weeks: 3E10 Injection-Free

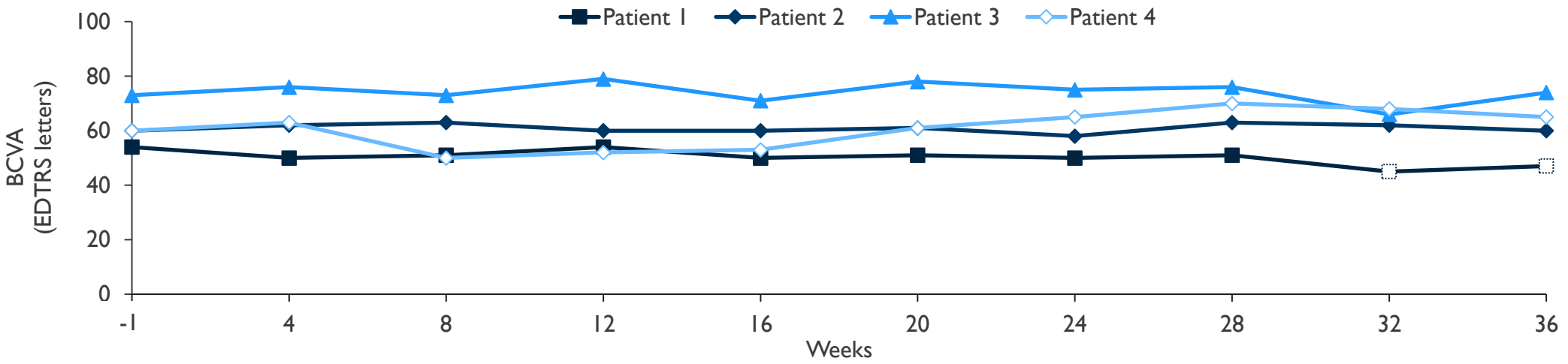
IMPROVEMENT OR MAINTENANCE OVER TIME IN ADVANCED PATIENTS WHO WERE INJECTION-FREE



Data cutoff date, April 3, 2023. CST, Central Subfield Thickness.

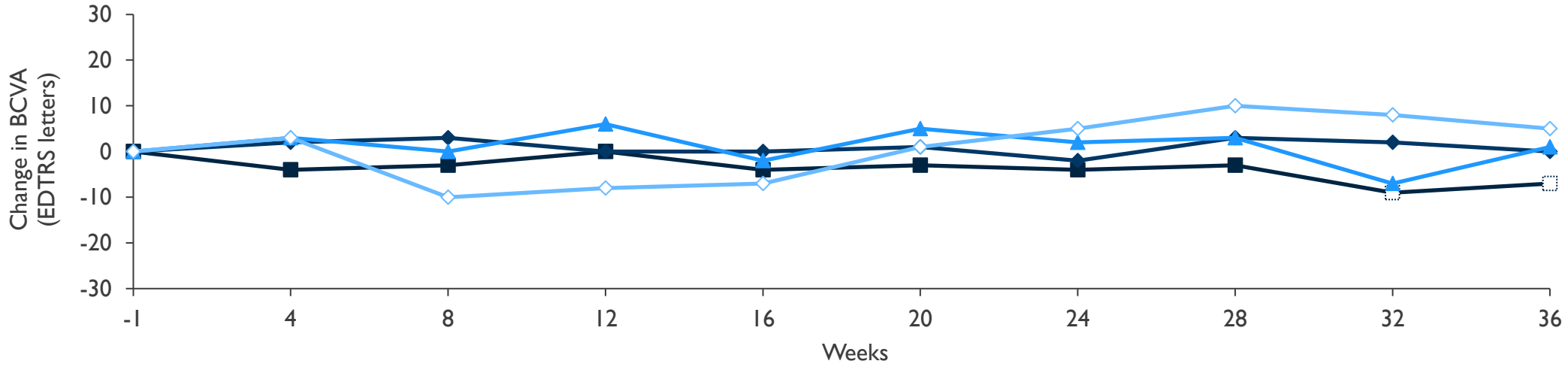
BCVA Maintained Through 36 Weeks: 3E10 Injection-Free

MAINTENANCE OVER TIME IN ADVANCED PATIENTS WHO WERE INJECTION-FREE



+1 letters
+5 letters
0 letters
-3 letters
(wk 28 pre-cataract*)

Cataract – BCVA back to baseline after removal (-7 to 0)*



+5 letters
+1 letters
0 letters
-3 letters
(wk 28 pre-cataract*)

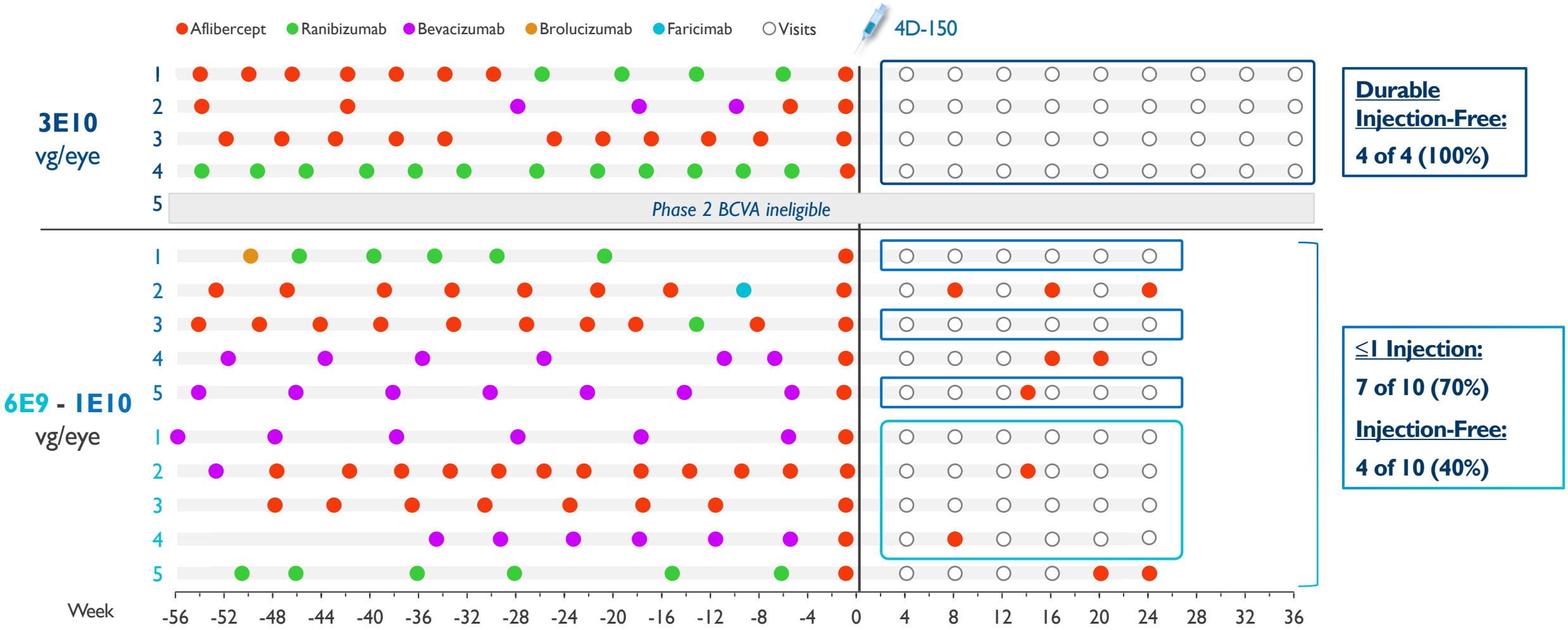
Cataract – BCVA back to baseline after removal (-7 to 0)*

Data cutoff date, April 3, 2023.

*Worsening cataract removed at 53 weeks; wk 36 with cataract -7 from baseline; BCVA zero change from baseline post-removal of cataract; BCVA, Best-Corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study.

Anti-VEGF Injections at 24-36 Weeks: Ph2 BCVA-Eligible

4 OF 4 (100%) INJECTION-FREE AT HIGHEST DOSE (3E10) IN HEAVILY ANTI-VEGF DEPENDENT PATIENTS



Durable Injection-Free:

4 of 4 (100%)

≤1 Injection:

7 of 10 (70%)

Injection-Free:

4 of 10 (40%)

Data cutoff date, April 3, 2023. VEGF, vascular endothelial growth factor; BCVA, Best-Corrected visual acuity. Anti-VEGF injection criteria: Loss of ≥10 letters from baseline in BCVA attributable to intraretinal or subretinal fluid; increase in CST >75 µm from baseline, confirmed by central reading center; presence of new vision-threatening hemorrhage due to wet AMD as determined by investigator.

Clinical Activity at 24 Weeks (Ph 2 BCVA-Eligible): High & Lower Doses Active

DOSE RESPONSE; 3E10 DOSE GROUP: MOST SEVERE DISEASE & 100% INJECTION-FREE

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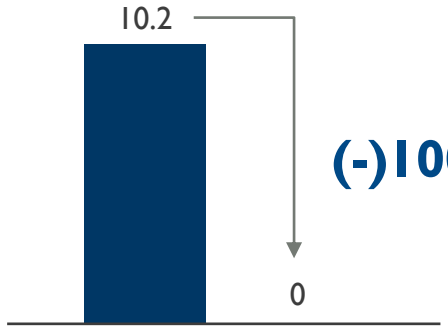
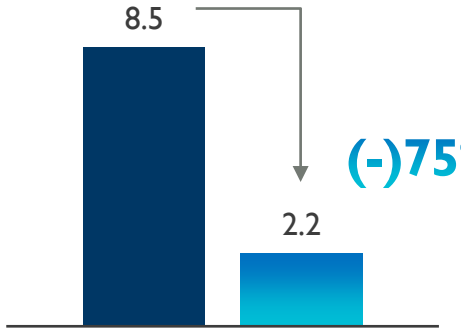
4D-150 Dose	Disease Severity (*Pre 4D-150*)			*Post 4D-150*			
				Anti-VEGF Injections		Mean Annualized Anti-VEGF Injection Rate	Mean Change in CST (μm)
	BCVA*	CST (μm)*	Anti-VEGF Inj†	Inj-Free	≤1 Injections		
3E10 vg/eye (n=4)	62	405	10	**100%** (4 of 4)	**100%** (4 of 4)	 **(-)100%**	**-74**
1E10 & 6E9 vg/eye (n=10)	70	377	9	**40%** (4 of 10)	**70%** (7 of 10)	 **(-)75%**	+21

Data cutoff, April 3, 2023. *Mean value. †Mean annualized anti-VEGF injection rate prior to administration of 4D-150. BCVA, best corrected visual acuity; CST, central subfield thickness; VEGF, vascular endothelial growth factor.

Data Summary

Phase 1 Patient Population (N=15)	▪ Dose Cohorts: 3E10 (**high**; n=5) vs 6E9 & 1E10 (**lower doses**; n=10 total) ▪ **Advanced, high-need patients: top ~15%** anti-VEGF utilization (IRIS)
Safety	▪ **No Grade ≥1 inflammation** (up to 64 weeks f/u)
Clinical Activity	▪ **High** Dose Phase 2 BCVA-Eligible (36 weeks; n=4): ○ **4 of 4 (100%) Injection-Free** ○ **Mean CST meaningfully improved (-74 µm)** ▪ **Lower** Doses (24 weeks; n=10): ○ **75% reduction anti-VEGF injection frequency** ○ **7 of 10 (70%) ≤1 Injection** (4 of 10 or 40% Injection-Free)
PRISM Status & Next Steps	▪ **Phase 2 enrollment >50%; expect completion in Q3** (updated from Q4) ○ BCVA threshold raised for Phase 2: 25–78 → **34–83** ETDRS letters

Key Takeaways:
Intravitreal 4D-150 PRISM Phase 1 Dose Exploration Results

- **Routine intravitreal** injection
- **Well-tolerated & no significant safety signals or inflammation**
- **High clinical activity in advanced patients**
- Phase 2 enrollment **ahead of schedule**

4D-150 Clinical Development: Planned Next Steps

WET AMD & DIABETIC MACULAR EDEMA

PRISM

Phase 2 Cohorts: Wet AMD

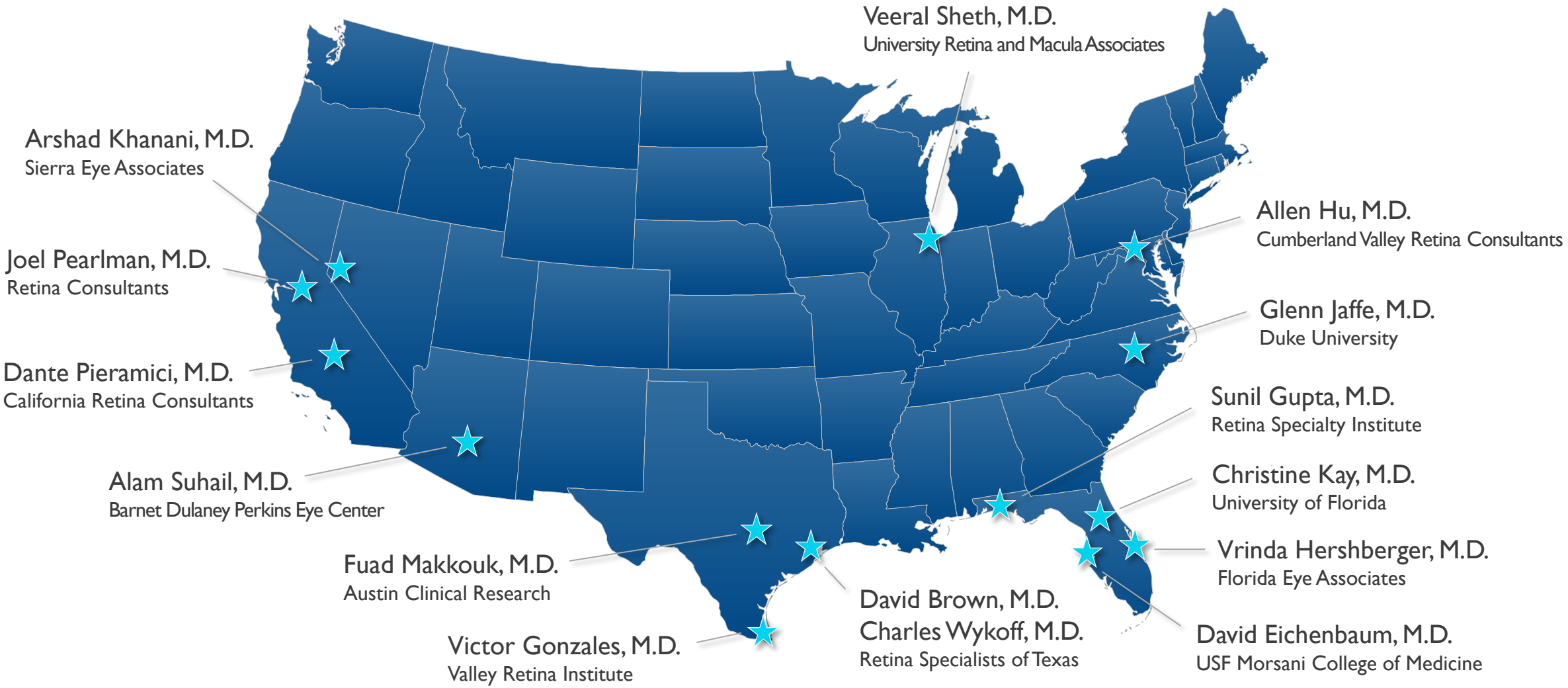
- **Complete randomized Phase 2 Dose Expansion** (N=50): target **Q3**
  - **>50% enrolled**; 3E10 vg/eye, 1E10 vg/eye, aflibercept 2 mg (2:2:1)
- **Phase 2 clinical data release:** target **H1 2024**
- **Phase 3 discussion with FDA:** target **Q4 2023**

ASPECTRA

Phase 2 Study: DME

- **IND open for** randomized Phase 2 trial (N=54)
- First patient enrolled: targeted for **Q3 2023**
- Initial Phase 2 data: targeted for **2024**

Acknowledgments



THANK YOU

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