Results of the Phase 2 BEHOLD Trial of UBX1325, A Novel Investigational Senolytic Agent for Diabetic Macular Edema

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Dr. Bhisitkul's Financial Disclosures

- Genentech/Roche (F)
- NGM Bio (F)
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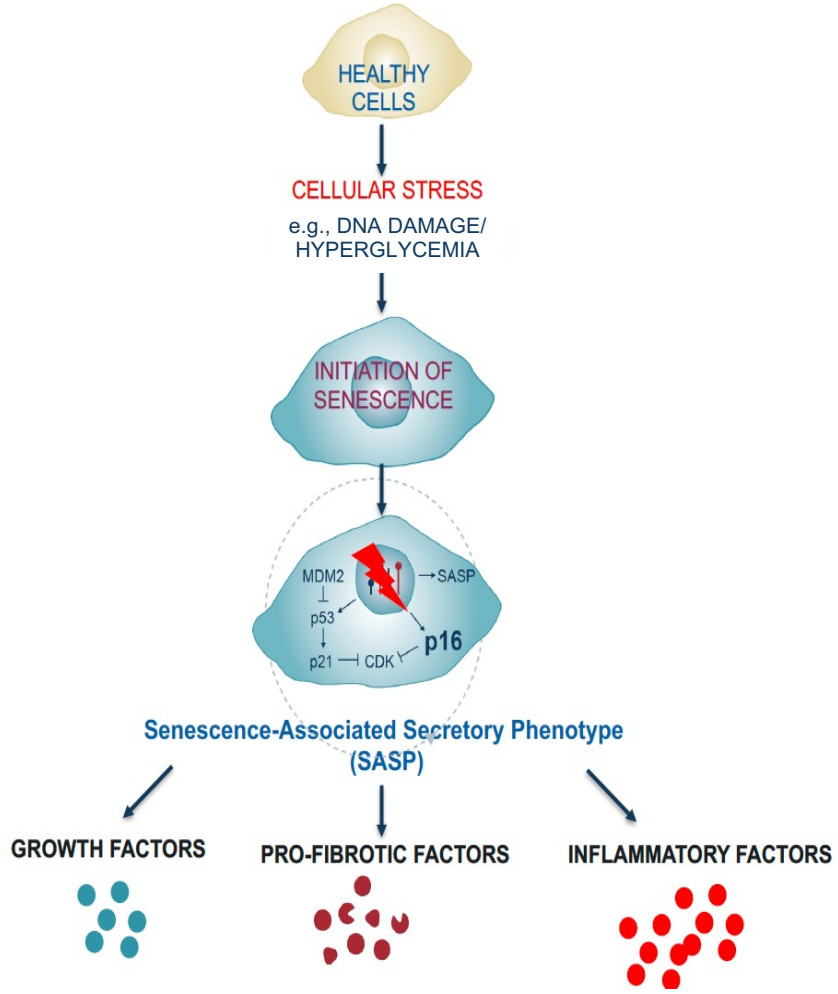
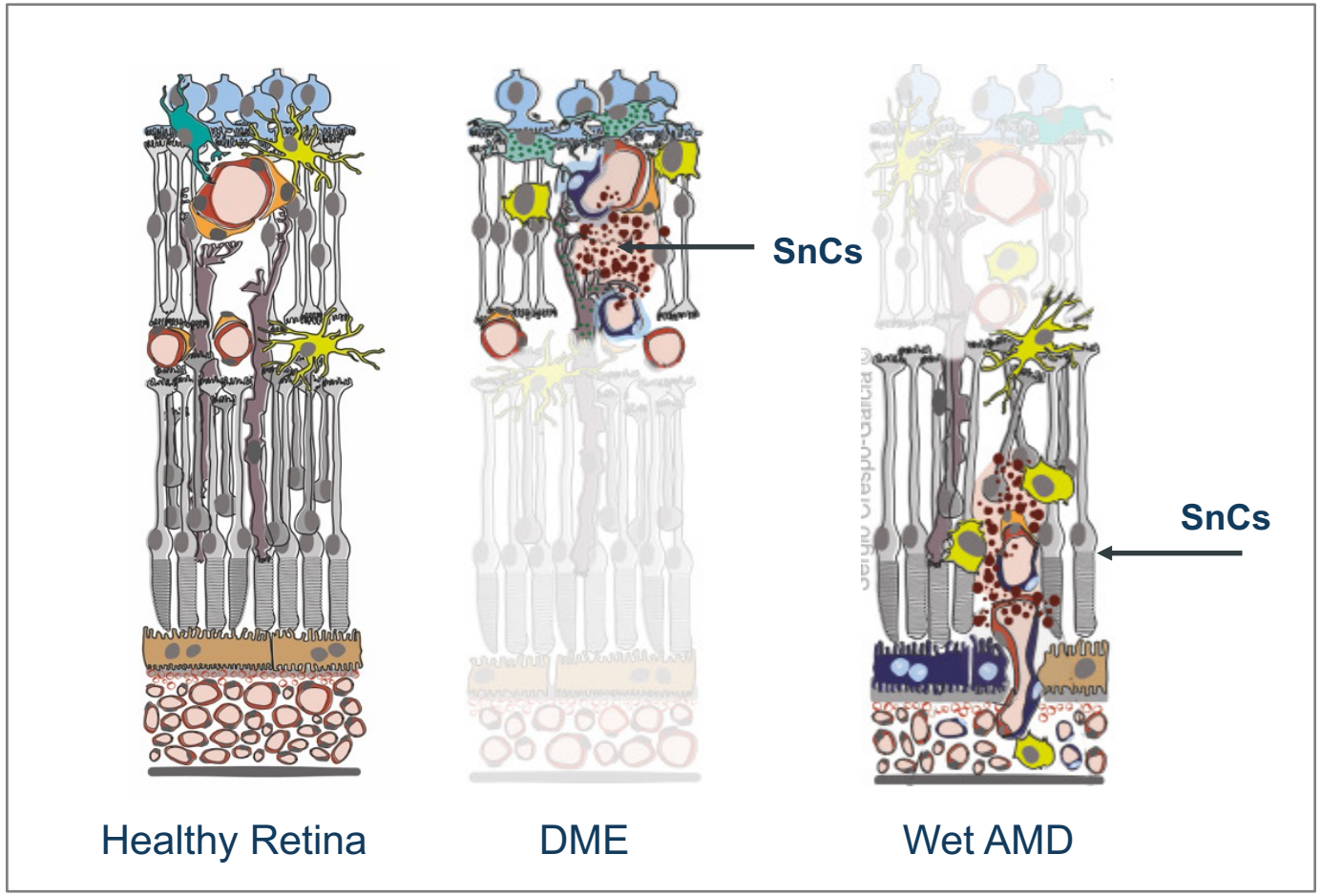
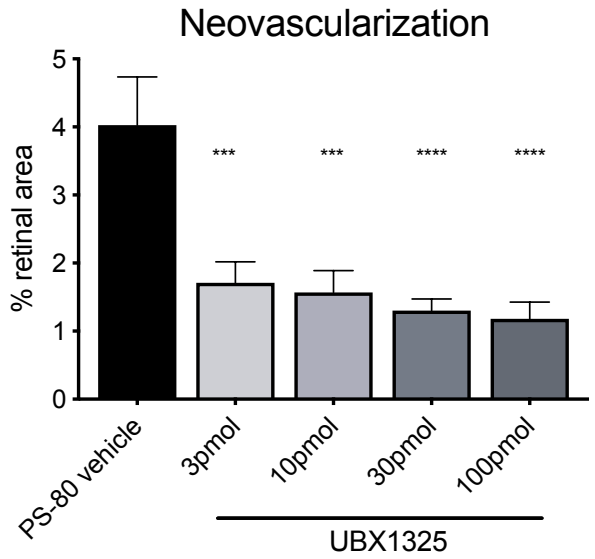
- RegenXBio (F)
- Rezolute, Inc (C)
- RIBOMIC, Inc (C)
- Unity Biotechnology (C)
- Visgenx (C)

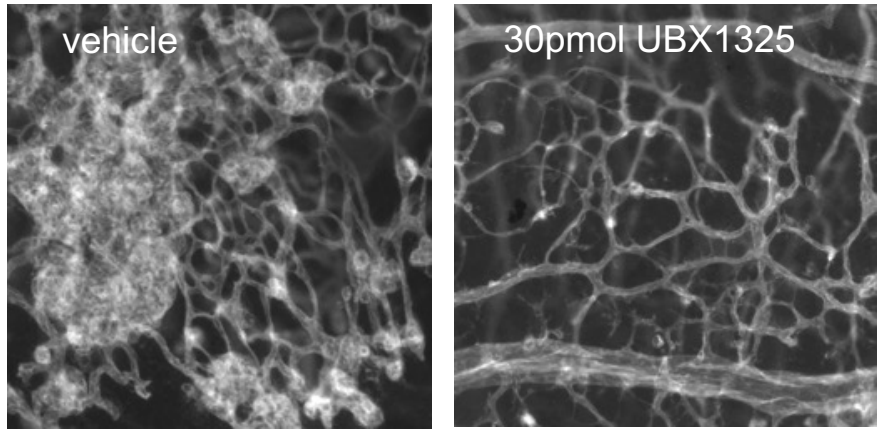
Senescent Cells Accumulate in Areas of Disease Activity in DME and Wet AMD, Releasing Mediators that Drive Pathology

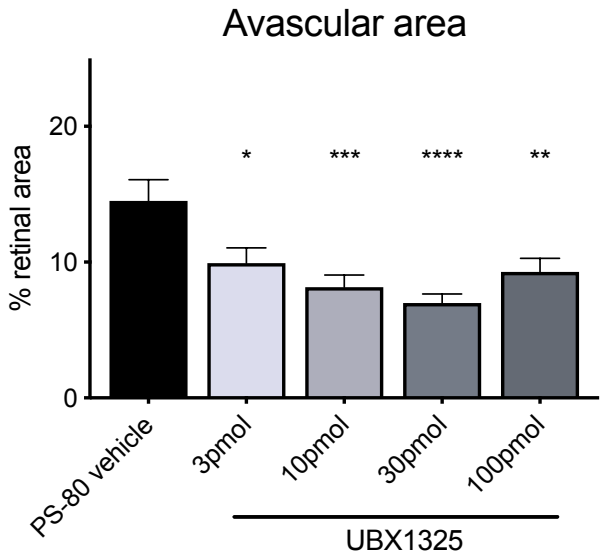


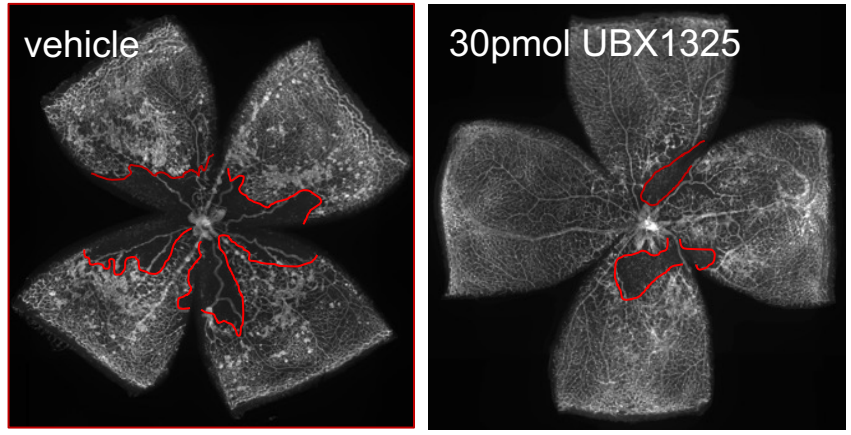


UBX1325 Improves Retinal Vasculature in Mouse OIR





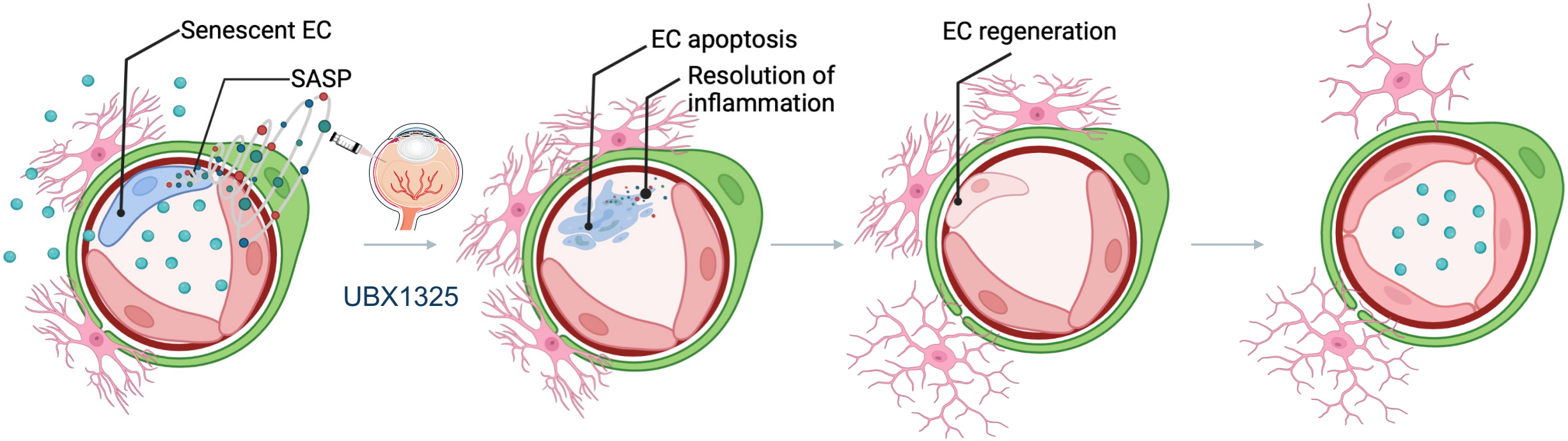




IVT UBX1325 decreases both neovascular and avascular areas in mouse OIR

Proposed Mechanism of Action for UBX1325

Diabetic blood vessel | **Vessel remodeling** | **Repaired blood vessel**

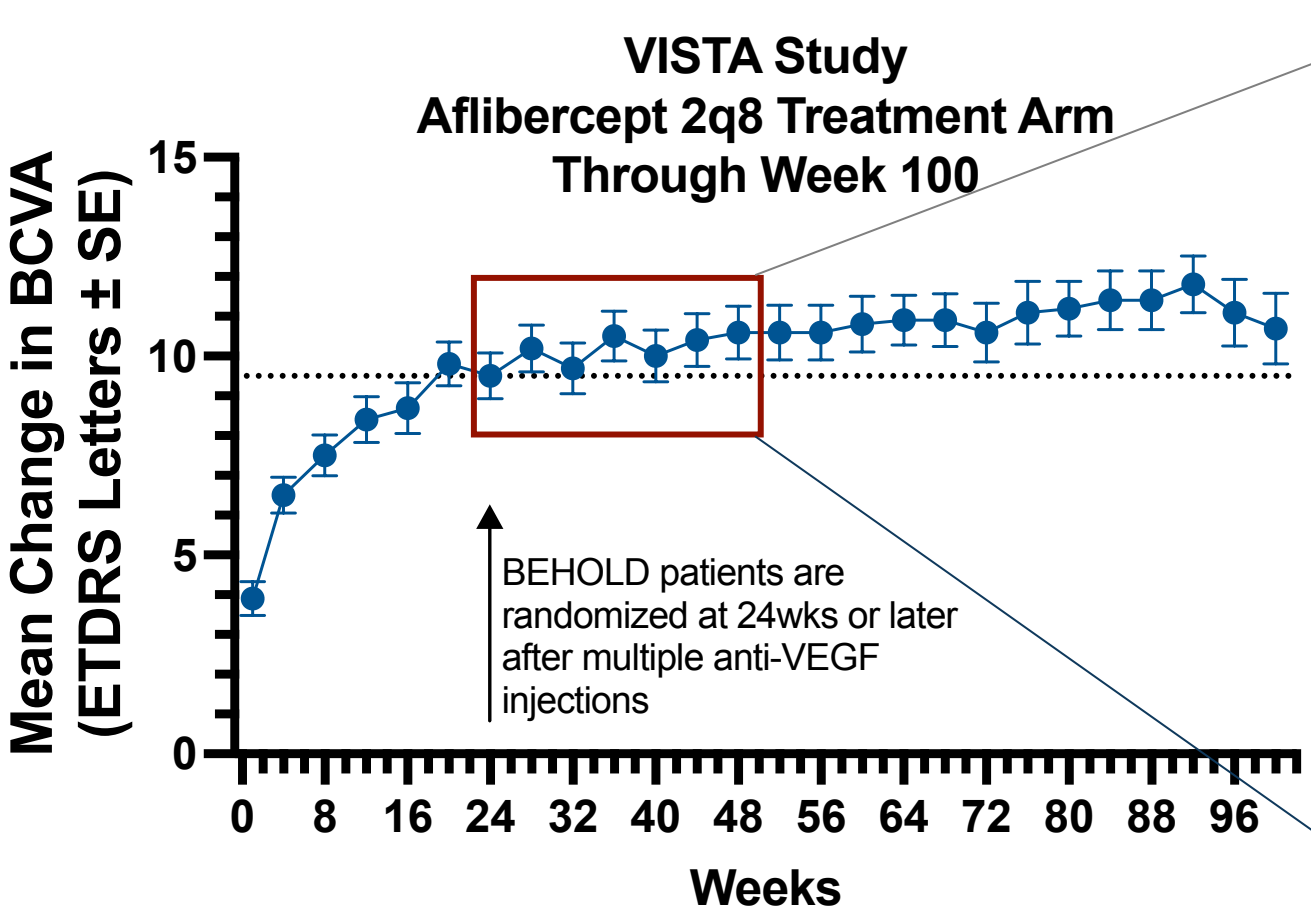


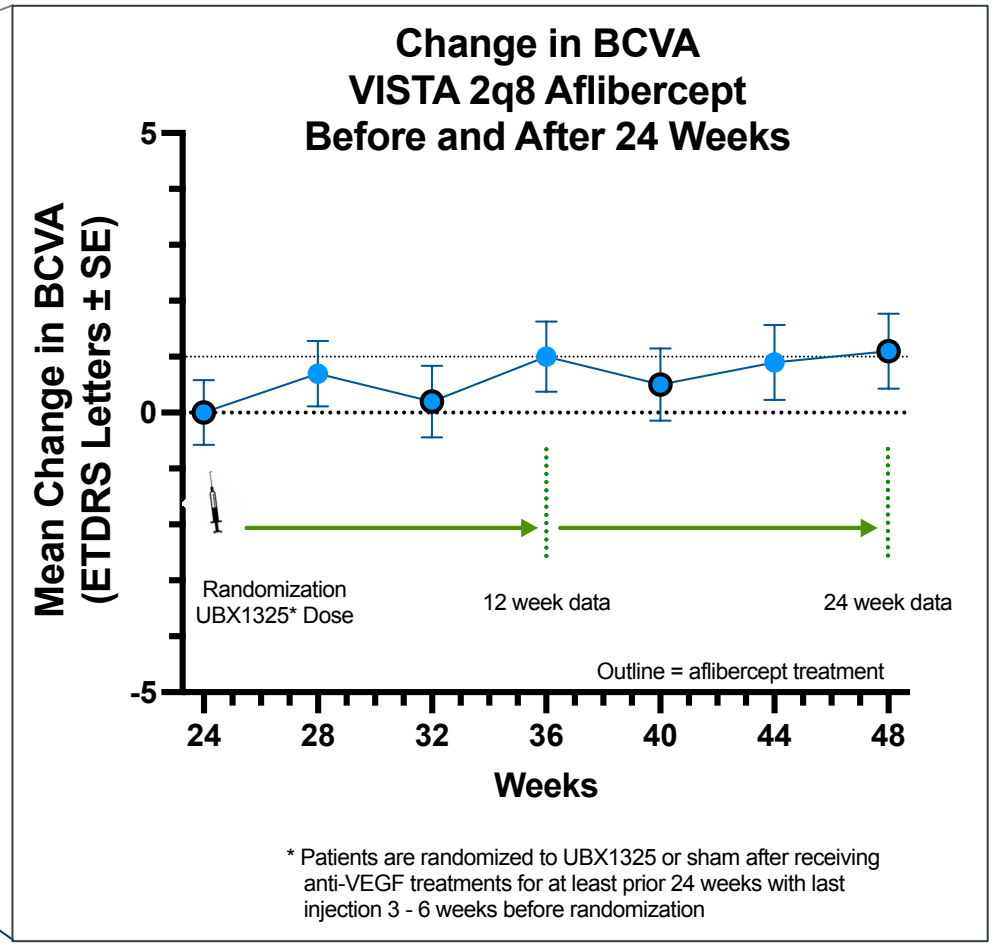
Senescent (Sn) ECs accumulate in diabetic retinas in areas of disease activity

- UBX1325 selectively triggers cell death of Sn ECs
- UBX1325 reduces retinal inflammation and vascular leakage

Preclinical data predicts progressive disease modification through vascular remodeling

Context for DME Data: Majority of Anti-VEGF BCVA Benefit is in First Six Months After Which Gains Are Limited To ~One or Fewer Letters



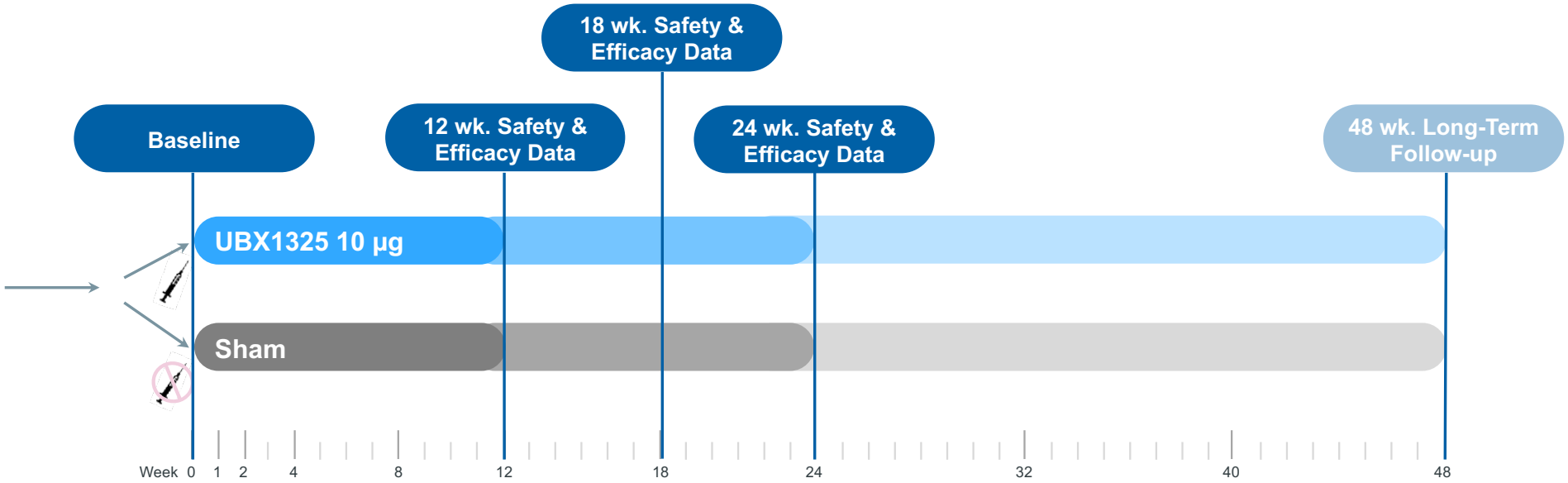


Aflibercept DME BLA 125387 Suppl 48, 25 Mar 2015

BEHOLD Study Design, Patient Population, and Endpoints

Key Inclusion Criteria

- Individuals with **Diabetic Macular Edema** (with moderate diabetic proliferative retinopathy or better)
- **CST** ≥300 µm and **BCVA** 73 – 20 ETDRS letters
- **Currently anti-VEGF** treated (≥2 injections over last 6 months, last 3-6 weeks prior to randomization)
  - Average previous anti-VEGF injections = ~4 over preceding 6 months in both groups



	UBX	Sham	Total
Total Enrolled	32	33	65
Withdrawal, out-of-window visit at Wk24, lost to f/u	4	2	6
24-week analysis set	28	31	59

= UBX1325 injection

= Sham injection

Endpoints

- Safety and tolerability
- BCVA change from baseline
- Durability of response
- Sub- and intra-retinal fluid, CST changes
- Proportion of UBX1325 patients requiring 2 or more rescue treatments
- Changes in retinal vasculature (FA, OCTA)

Summary of Treatment Emergent Adverse Events

	Sham (%) (N = 33)	UBX1325 10 µg (%) (N = 32)	Overall (%) (N = 65)
Subjects with at least one TEAE	28 (84.8)	24 (75.0)	52 (80.0)
Related TEAE	3 (9.1)	6 (18.8)	9 (13.8)
Grade ≥3 TEAE	4 (12.1)	3 (9.4)	7 (10.8)
Serious TEAE	3 (9.1)*	4 (12.5)*	7 (10.8)
Ocular TEAE for Study Eye	23 (69.7)	19 (59.4)	42 (64.6)
Treatment-related Ocular TEAE for Study Eye	3 (9.1)**	6 (18.8)**	9 (13.8)
TEAE leading to death	0	0	0
Intraocular inflammation, endophthalmitis, retinal artery occlusion, or vasculitis	**0**	**0**	**0**

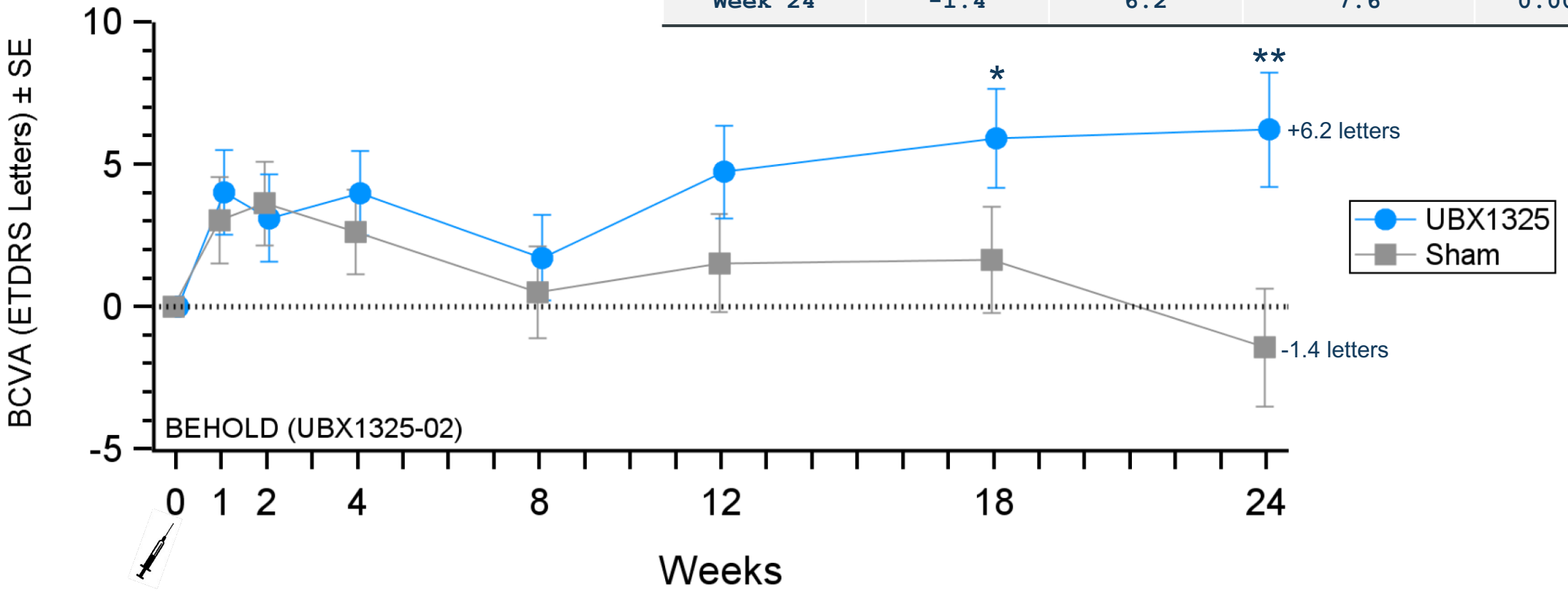
* Unrelated or likely unrelated to treatment

** 2/3 Sham and 5/6 UBX Most likely attributable to procedure: Conjunctival hemorrhage, eye irritation, conjunctival hyperemia All mild – moderate, resolved without further intervention

UBX1325 Was Well Tolerated With Favorable Safety Profile After a Single IVT Injection

BEHOLD: 24-Week BCVA Change from Baseline†
Patients Treated With a Single Injection of UBX1325 Gained 6.2-letter at 24 Weeks

	Sham	UBX1325	Difference	P-Value
Week 18	1.7	5.9	4.3	0.0943*
Week 24	-1.4	6.2	7.6	0.0084**

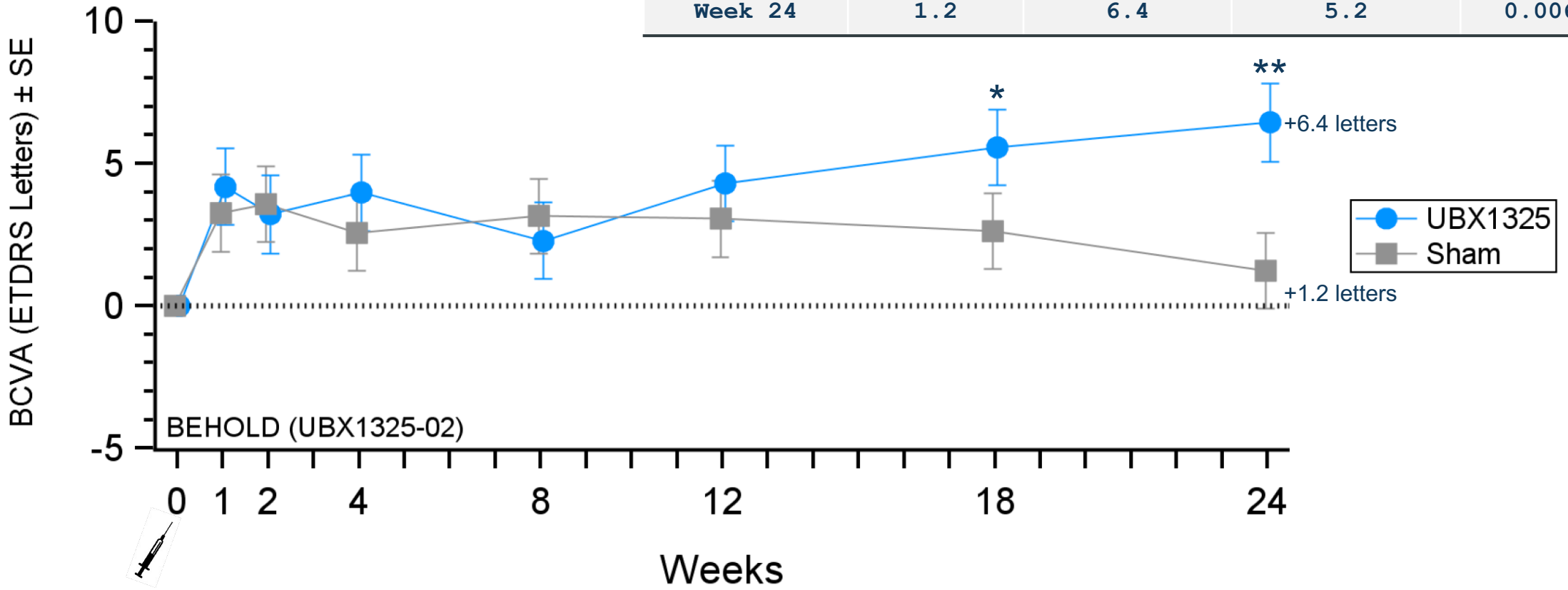


UBX1325 Led To A Sustained Improvement In BCVA Through 24 Weeks

† MMRM Analysis

BEHOLD: 24-Week BCVA Change from Baseline† Including Post-Rescue Data

	Sham	UBX1325	Difference	P-Value
Week 18	2.6	5.6	3.0	0.1160*
Week 24	1.2	6.4	5.2	0.0068**

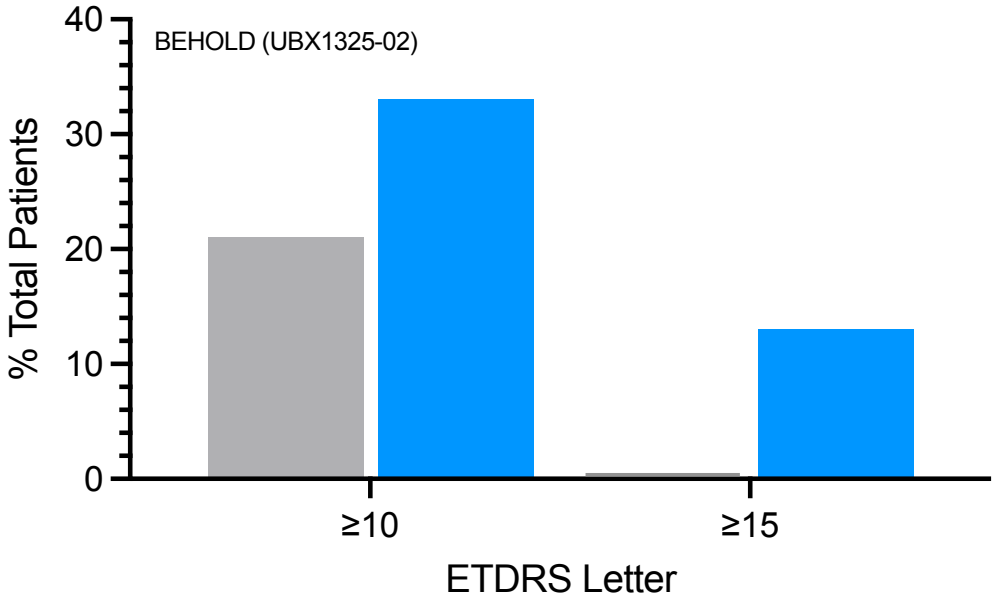


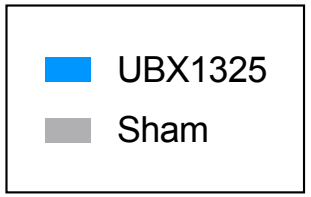
UBX1325 with As-Needed anti-VEGF Rescue Outperformed Sham with As-Needed Rescue Through 24 Weeks††

† MMRM Analysis
†† More rescues in Sham vs. UBX arms

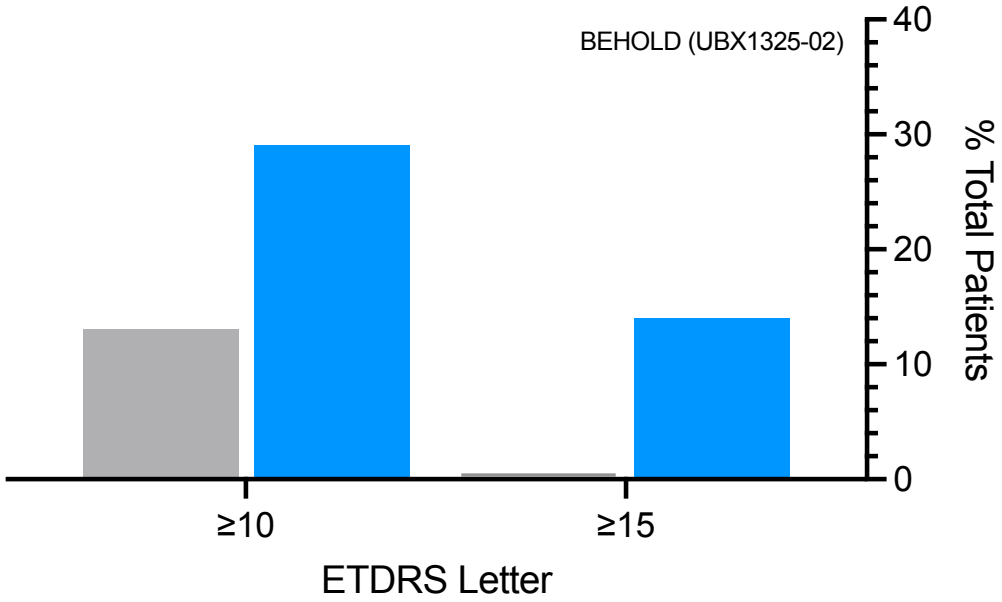
Greater Proportion of Patients in UBX1325 Arm Had Larger Visual Acuity Gains Compared to Sham at 24 Weeks

Gains in BCVA without Rescue





Gains in BCVA w/ Rescue



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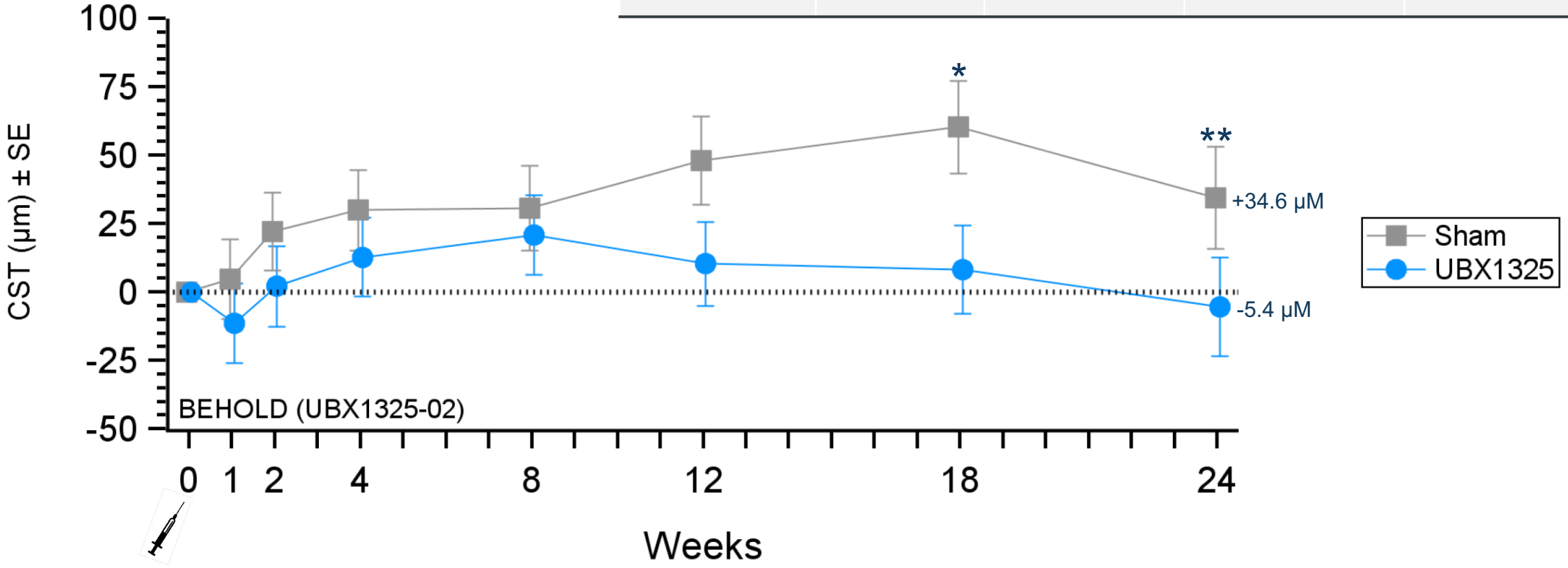
EFFICACY RESULTS: CST

Patients Treated With a Single Injection of UBX1325 Maintained CST at 24 Weeks

	Sham	UBX1325	Difference	P-Value
Week 18	60.3	8.2	-52.1	0.0278*
Week 24	34.6	-5.4	-40.0	0.1244**

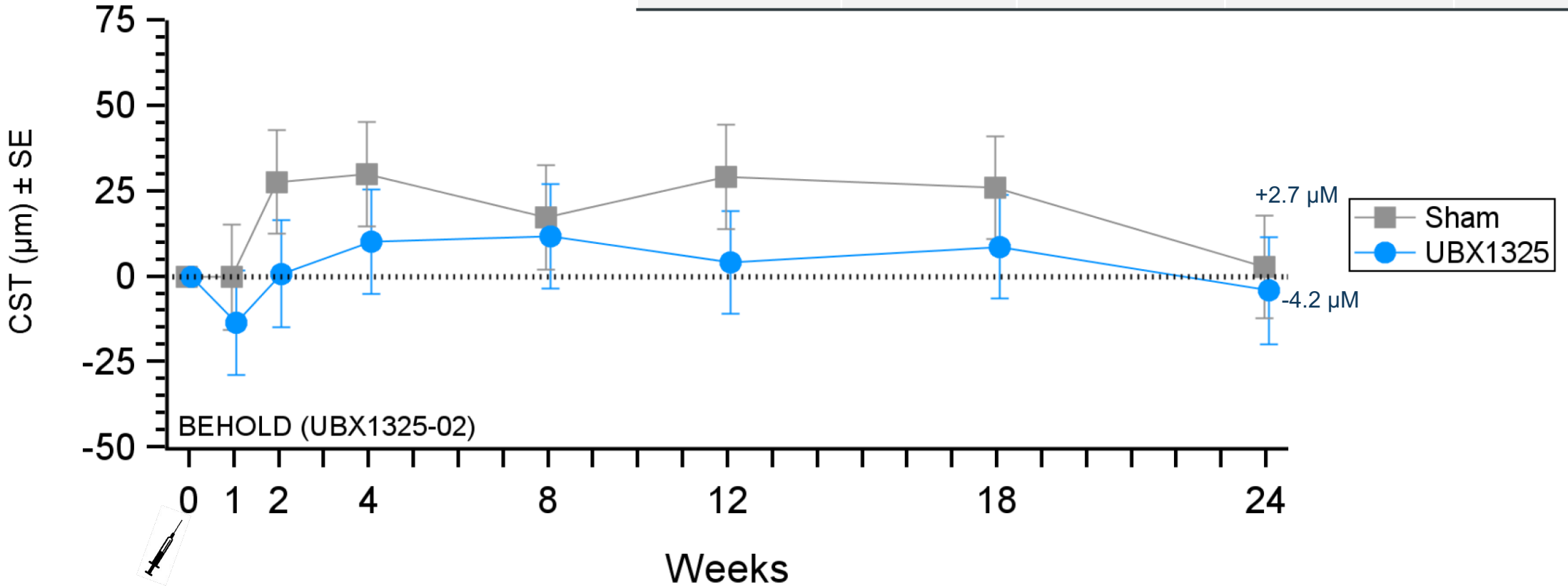


UBX1325 Stabilized the Retina Compared to Sham-Treatment

† MMRM Analysis

BEHOLD: 24-Week CST Change from Baseline† Including Post-rescue Data

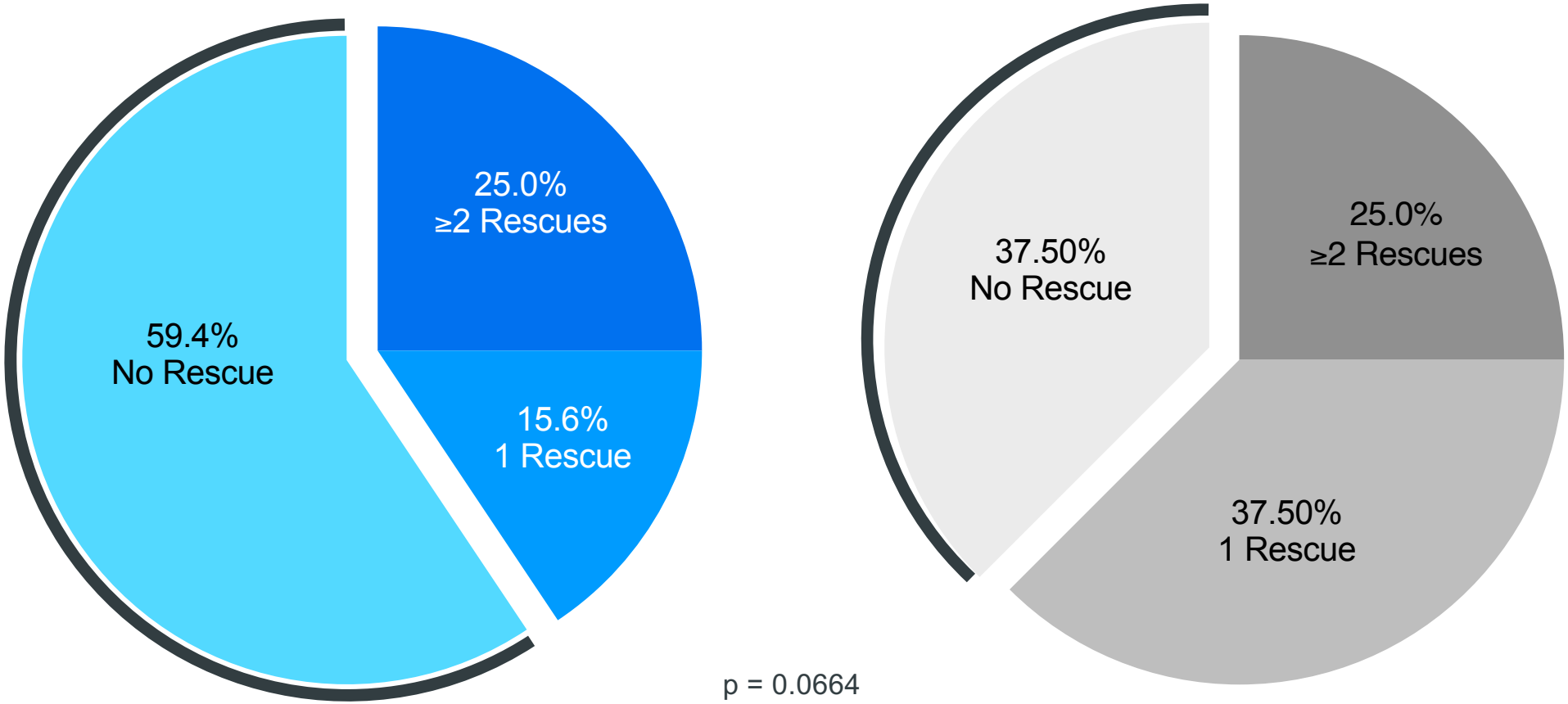
	Sham	UBX1325	Difference	P-Value
Week 18	26.0	8.7	-17.3	0.4179
Week 24	2.7	-4.2	-6.9	0.7522



Adding anti-VEGF rescue data improved CST in sham arm but not in UBX1325 arm††

† MMRM Analysis
†† More rescues in Sham vs. UBX arms

Majority of Patients on UBX1325 Were Rescue-free for 6 Months



p = 0.0664
No rescue: UBX vs Sham

n = 32

UBX1325

n = 32

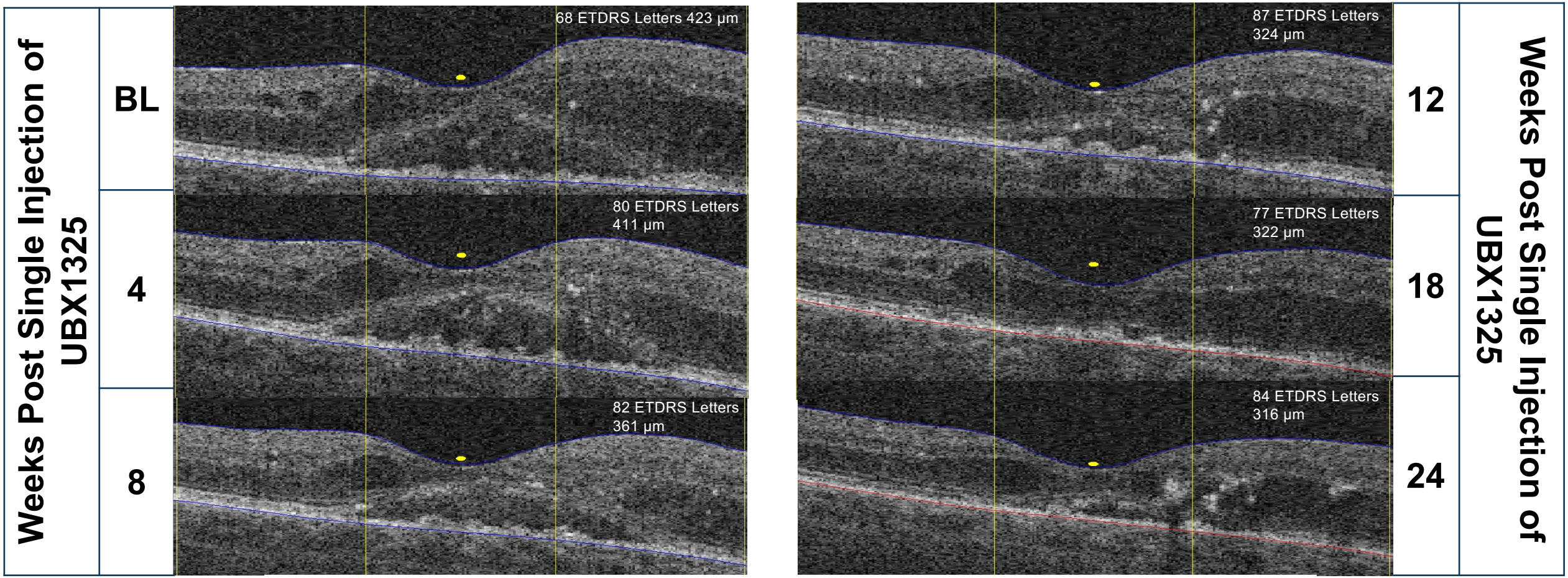
Sham

Rescue Eligibility Criteria (<u>Either</u> Triggers Rescue):

- Decrease in BCVA of -10 ETDRS letters from the highest value (peak)
- Increase in CST of +75µm from baseline

OCT Images

PATIENT A: Treated with a Single Injection of UBX1325 Without Rescue

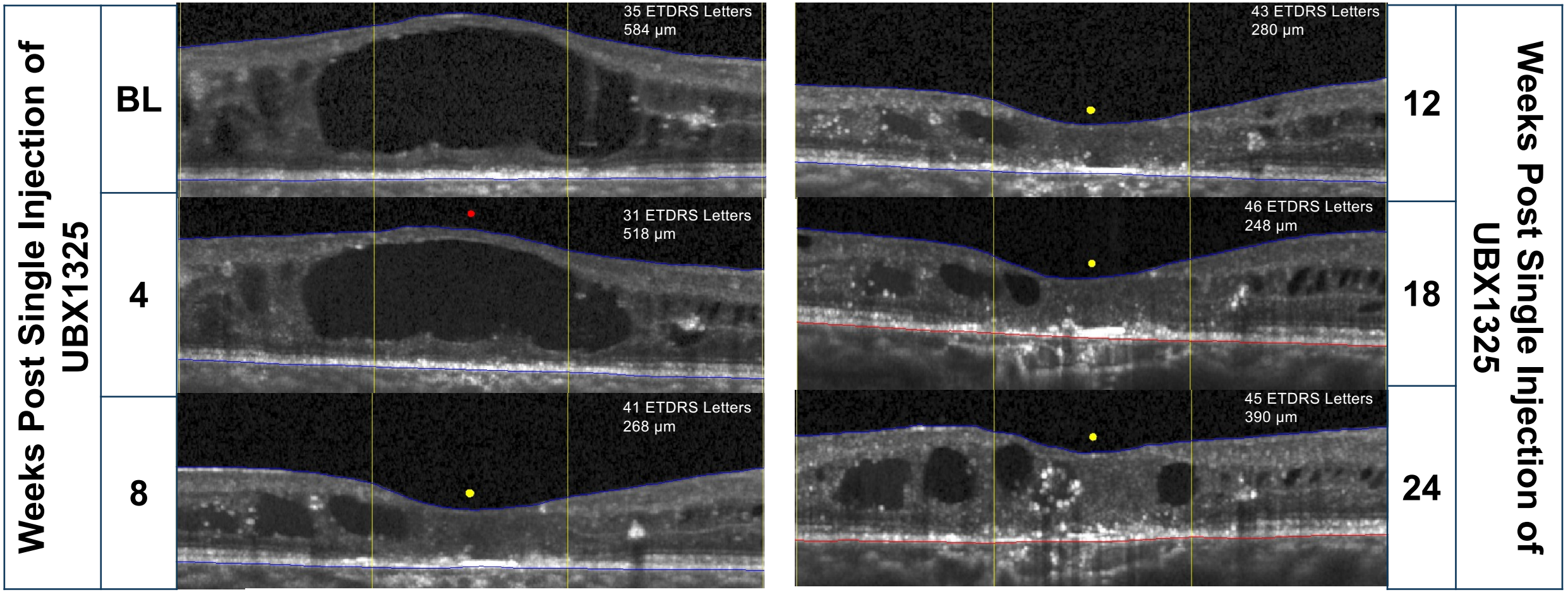


	CFBL	Week 12	Week 18	Week 24
BCVA (ETDRS letters)		+19	+9	+16
CST (µm)		-99	-101	-107

Tx History: aflibercept x5/6 mo. w/ last 4 weeks prior to randomization

Source: Duke Reading Center Images assessed by an independent unmasked image reader

PATIENT B: Treated with a Single Injection of UBX1325 Without Rescue



CFBL	Week 12	Week 18	Week 24
BCVA (ETDRS letters)	+8	+11	+10
CST (µm)	-304	-336	-194

Tx History: bevacizumab x4 doses/6 mo. w/ last 3 wks prior to randomization

Source: Duke Reading Center Images assessed by an independent unmasked image reader

Key Takeaways: BEHOLD Phase 2 Study in Patients with DME

UBX1325, A Novel Investigational Agent in Patients with DME

- Was well tolerated with a favorable safety profile and no intraocular inflammation
- Improved BCVA that was durable through 24 weeks
- Majority of UBX-treated patients required no rescue through 24 weeks
- Maintained retinal structure vs. sham-treated subjects

UBX1325 is currently also being evaluated in a Phase 2 study in nAMD