Effect of Patient Baseline Characteristics on Response to UBX1325, a Novel Senolytic Candidate For Patients With DME: BEHOLD Phase 2 Study 48 weeks follow-up

Dante Pieramici[1], Sharon Klier[2], Josh Rathmell[3], Craig Mallinckrodt[4], Przemyslaw Sapieha[2], Jamie Dananberg[2] and Anirvan Ghosh[2]

[1]California Retina Consultants, Santa Barbara, CA. [2]UNITY Biotechnology, South San Francisco, CA. [3]Cencora PharmaLex. [4]Pentara Corporation, South Millcreek, UT.

B0103

BACKGROUND

Diabetic retinopathy (DR) is amongst the earliest and most prevalent complications of diabetes[1]. Throughout all severity levels of DR, diabetic macular edema (DME) represents the leading cause of loss of vision[2] and requires frequent intravitreal (IVT) injections to manage symptoms of disease.

PURPOSE

Senescence is implicated in vascular pathology of DME. We explored the contribution of cellular senescence to disease progression and tested the effects of a single IVT injection of a novel senolytic small molecule inhibitor of anti-apoptotic protein BCL-xL, UBX1325, in patients with DME previously treated with Anti-VEGF.

METHODOLOGY

The BEHOLD study was a Phase 2, prospective, multicenter (23 sites), randomized, double-masked, sham-controlled study to assess the safety, tolerability, and evidence of activity of a single IVT injection of 10μg of UBX1325 in patients with DME who had visual acuity deficit and macular edema despite frequent anti-VEGF treatment. A total of 65 patients were randomized 1:1 into either UBX1325 (N=32) or sham (N=33) study arms. All patients were followed for approximately 48 weeks. Primary endpoints were ocular and systemic safety and tolerability with secondary objectives to assess biological activity through changes from baseline in Best Corrected Visual Acuity (BCVA) using Early Treatment of Diabetic Retinopathy Study (ETDRS) letters, Central Subfield Thickness (CST), changes in retinal edema, and rates of anti-VEGF rescue.

Table 1: Summary of Treatment-Emergent Adverse Events

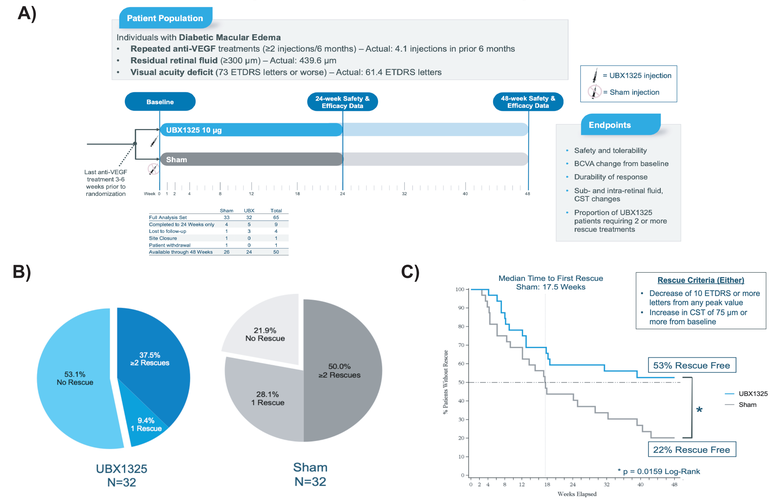
	Sham (%) (N = 33)	UBX1325 10 μg (%) (N = 32)	Overall (%) (N = 65)
Subjects with at least one TEAE	31 (93.9)	26 (81.3)	57 (87.7)
Related TEAE	3 (9.1)	6 (18.8)	9 (13.8)
Grade ≥3 TEAE	4 (12.1)	5 (15.6)	9 (13.8)
Serious TEAE*	3 (9.1)	5 (15.6)	8 (12.3)
Ocular TEAE for Study Eye	28 (84.8)	23 (71.9)	51 (78.5)
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 study drug (as reported by medical monitor assessment)

** Likely procedural related; In UBX group (5/6) and Sham-group (2/3) described as conjunctival hemorrhage, eye irritation, conjunctival hyperemia
One event within Sham-group: DME;
One event within UBX-group: anterior chamber pigmentation
All mild – moderate, resolved without further intervention

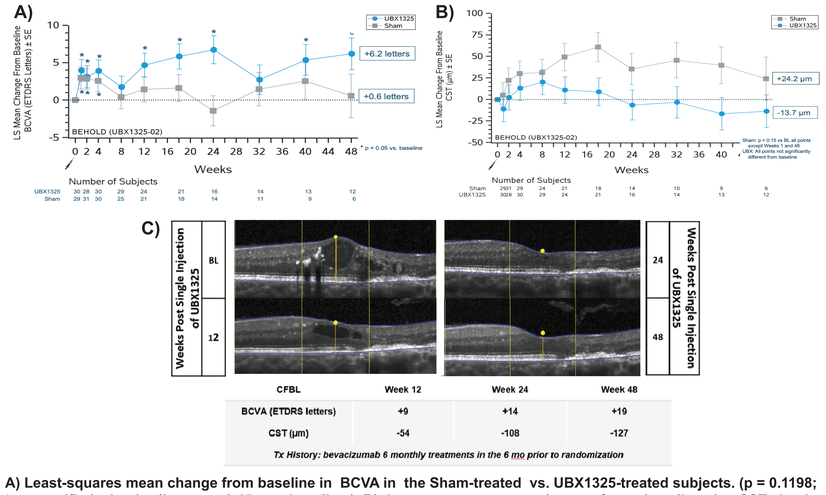
RESULTS

Figure 1: Patients on UBX1325 have significantly reduced need for anti-VEGF rescue compared to sham-treated patients.



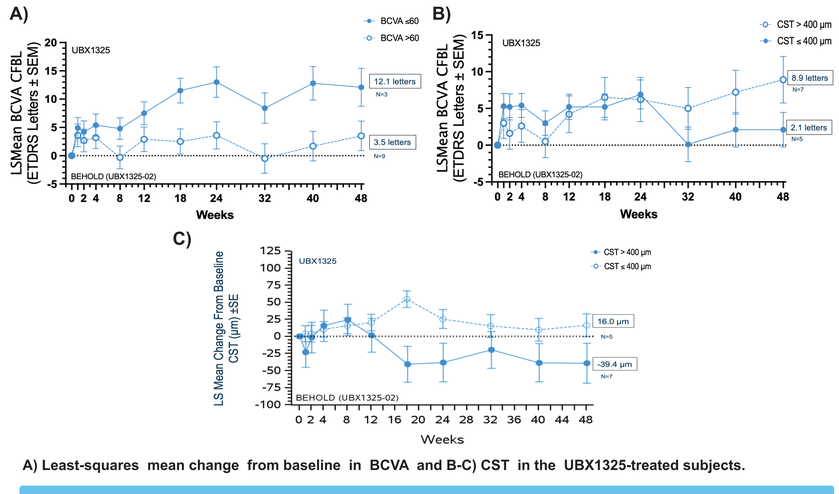
A) Diagram depicts design of the BEHOLD phase 2 study. Patients enrolled in the study were randomized to receive a sham-injection procedure or a single IVT injection of UBX1325 10μg. A total of 50 patients completed all 48 weeks of the trial. The last anti-VEGF treatment was 3-6 weeks prior to randomization. B) Pie charts depict proportion of subjects who required anti-VEGF rescue from baseline to week 48. There was a statistically significant difference in the use of rescue medications in the Sham-treated vs. UBX1325-treated subjects (15 vs. 25 subjects with ≥1 rescue treatment, p=0.0096). C) Kaplan Meier curves depict the time to first rescue in both UBX1325 and sham arms. (*=p=0.0159 based on Log-Rank analysis).

Figure 2: UBX1325 leads to significant improvement in best corrected visual acuity (BCVA) and stabilization of Central Subfield Thickness through 48 weeks.



A) Least-squares mean change from baseline in BCVA in the Sham-treated vs. UBX1325-treated subjects. (p = 0.1198; 'prespecified sig:p). (* = p < 0.15 vs. baseline.) B) Least-squares mean change from baseline in CST in the Sham-treated vs. UBX1325-treated subjects. All points in sham-treated group were statistically significant vs baseline (p < 0.15) except weeks 1 and 48. Change in CST in UBX-treated patients was not significantly different from baseline signifying stabilization. (* = p < 0.15 vs. baseline.) C) OCT images of a patient randomized to receive a single UBX1325 accross 4 study visits at baseline (BL), week 12, week 24 and week 48 (end of study). Yellow lines mark the centerpoint thickness measurement made by a reader during thegrading visits.

Figure 3: Mean Changes in Best Corrected Visual Acuity in Subgroup Analyses.



A) Least-squares mean change from baseline in BCVA and B-C) CST in the UBX1325-treated subjects.

CONCLUSION

The BEHOLD study highlights a role of cellular senescence in DR and more specifically supports development of senolytic drugs such as UBX1325 for DME treatment in a population previously treated with anti-VEGF. Given that cellular senescence may be a convergent mechanism for other diseases of the aging eye, senolytic drugs may be aspirational treatments for ocular diseases where cellular senescence has been identified such as glaucoma[3] and diabetic retinopathy[4,5] and potentially dry macular degeneration.

DISCLOSURES

This work was supported by UNITY Biotechnology.

REFERENCES

1.Stitt, Alan W et al. "The progress in understanding and treatment of diabetic retinopathy." Progress in retinal and eye research vol. 51 (2016): 156-86.

2.Lee, Ryan et al. "Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss." Eye and vision (London, England) vol. 2 17. 30 Sep. 2015.

3.Skowronska-Krawczyk, Dorota et al. "P16INK4a Upregulation Mediated by SIX6 Defines Retinal Ganglion Cell Pathogenesis in Glaucoma." Molecular cell vol. 59,6 (2015): 931-40.

4.Oubaha, Malika et al. "Senescence-associated secretory phenotype contributes to pathological angiogenesis in retinopathy." Science translational medicine vol. 8,362 (2016):362ra144.

5.Bertelli, Pietro Maria et al. "Long term high glucose exposure induces premature senescence in retinal endothelial cells." Frontiers in physiology vol. 13 929118. 26 Aug. 2022.

Clinical Trials.gov identifier: NCT04857996

CONTACT INFORMATION
Sharon.klier@unitybiotechnology.com