7/30/2023

48-Week End of Study Results From BEHOLD Phase 2 Study of UBX1325 in Patients With DME
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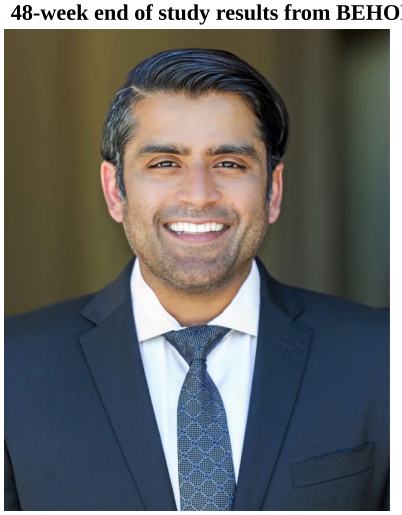

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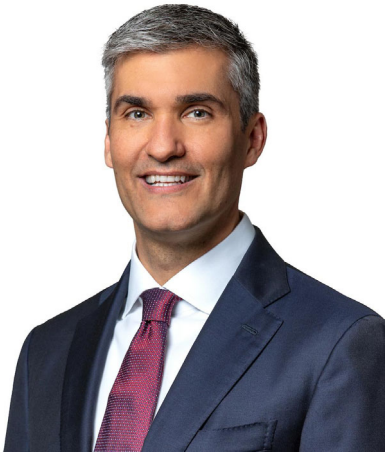
Objective: To assess the safety, tolerability, and evidence of activity of a single intravitreal injection ofUBX1325 in patients with DME
Purpose: Cellular senescence is implicated in vascular pathology of DME, and preclinical data in mouse models of retinopathy support a potential therapeutic rationale for UBX1325. This Ph 2 study tests the safety and efficacy and evidence of biological activity of a single IVT injection of UBX1325, a senolytic BCL-xL inhibitor, in patients with long-standing DME.
Methods: This study is prospective, multicenter, randomized, double-masked of UBX1325 vs. sham. The study (NCT04857996) is conducted in 23 sites in the US and Canada, enrolled patients ≥18 years with DME, BCVA 73 - 20 ETDRS letters and residual retinal fluid, plus previous treatment with at least 2 anti-VEGF injections in the preceding 6 months (last anti-VEGF 3-6 weeks prior to randomization). 65 patients were randomized 1:1 to receive either a single injection of UBX1325 10 µg IVT or sham and followed for 48 weeks. Patients could be rescued with anti-VEGF based on prespecified criteria or investigator discretion. Primary endpoint is ocular and systemic safety and tolerability of a single IVT injection of UBX1325. The secondary and exploratory endpoints include change in BCVA, CST, number of anti-VEGF rescue treatments received during the study period, retinal fluid, leakage and capillary nonperfusion. Analyses conducted used MMRM with values reported as least square mean (LSM).
Results: UBX1325-treated patients had a significant improvement in BCVA of +6.2 ETDRS letters from baseline (p = 0.0037) representing a difference of +5.6 ETDRS letters compared to sham (p = 0.1198) at 48 weeks. Close to 60% of UBX1325-treated patients gained 5 or more letters from baseline compared to less than 20% of sham-treated patients. Retinal structure was maintained in UBX1325-treated patients with a central subfield thickness (CST) of -16.6 µm from baseline at 40 weeks representing a treatment difference compared to sham of -56.3 µm (p = 0.0479) and a CST of -13.7 µm from baseline at 48 weeks representing a treatment difference compared to sham of -37.9 µm (p = 0.2289). 53.1% of UBX1325-treated patients did not require anti-VEGF rescue for at least 48 weeks compared to only 21.9% of patients in the sham arm (p = 0.0096). Data assessed through 48 weeks showed no events of IOI and AEs occurring at higher rates vs. sham were largely attributable to IVT procedure.
Conclusion: This data represents the potential proof-of-concept for the safety, tolerability and efficacy of UBX1325 in patients with DME who have residual visual acuity deficits and macular edema after being on anti-VEGF therapy for at least 6 months. UBX1325 is a novel senolytic agent that is being investigated for the treatment of DME and may represent a future treatment option for patients.

IRB APPROVAL Yes

7/30/2023

Tarcocimab Tedromer (KSI-301) Anti-VEGF Antibody Biopolymer Conjugate for DME: First-Time Efficacy, Durability and Safety Results of the GLEAM and GLIMMER Phase 3 studies

Tarcocimab Tedromer (KSI-301) Anti-VEGF Antibody Biopolymer Conjugate for DME: First-Time Efficacy, Durability and Safety Results of the GLEAM and GLIMMER Phase 3 studies



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Objective: GLEAM and GLIMMER are prospective, global Phase 3 studies designed to show that tarcocimab tedromer (tarcocimab; KSI-301) is non-inferior to aflibercept while meaningfully reducing treatment burden in patients with Diabetic Macular Edema (DME).
Purpose: A substantial need remains for therapeutics that maximize efficacy while reducing treatment burden in the management of retinal vascular diseases. Specifically, outcomes during DME management in routine practice are often suboptimal, due at least in part to the need for frequent repeat dosing with current generation anti-vascular endothelial growth factor (VEGF) pharmaceuticals. Tarcocimab tedromer (tarcocimab; KSI-301) is an antibody biopolymer conjugate designed to provide potent and long-lasting VEGF inhibition, with the potential to meaningfully reduce the treatment burden. In the GLEAM and GLIMMER Phase 3 studies, tarcocimab is being evaluated on a flexible dosing regimen with treatment intervals as infrequent as every 6 months after only three loading doses.
Methods: Two identically designed, prospective, double-masked, global, multi-center clinical trials in which treatment-naïve patients with DME were randomized 1:1 to receive tarcocimab 5 mg on an individualized dosing regimen every 8 to 24 weeks after 3 loading doses or aflibercept 2 mg every 8 weeks after 5 loading doses. A best-corrected visual acuity (BCVA) of 78 to 25 letters using Early Treatment Diabetic Retinopathy Study (ETDRS) charts (~20/25 to 20/320 Snellen equivalent) and a central subfield thickness of at least 320 microns on optical coherence tomography were required at baseline. The primary efficacy endpoint is the mean change from baseline in BCVA at 1 year.
Results: In total, 917 subjects were treated across 141 sites in the United States, Europe, and Israel. Mean age was 61.8 years; 63% were male. At baseline, mean BCVA was 65.3 ETDRS letters; mean baseline central subfield thickness was 469.5 µm. The primary efficacy, safety and durability results will be presented for the first time at the ASRS meeting.
Conclusion: Outcomes from the randomized, prospective, global, phase 3 GLEAM and GLIMMER trials involving over 900 patients in which tarcocimab tedromer was compared to aflibercept will provide important insight into the potential role of tarcocimab as a durable anti-VEGF treatment option for patients with DME.

IRB APPROVAL Yes

7/30/2023

Efficacy and Safety of CT-P42 Compared to Reference Aflibercept (AFL) in Diabetic Macular Edema (DME): 24-Week Results From the Phase 3 CT-P42 3.1 Study

Efficacy and Safety of CT-P42 compared to Reference Aflibercept (AFL) in Diabetic Macular Edema (DME): 24-Week Results from the Phase 3 CT-P42 3.1 Study.

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Objective: To demonstrate the therapeutic similarity of CT-P42 compared to Reference AFL in Patients with DME.

Purpose: CT-P42 is a proposed biosimilar to Reference AFL. This trial (NCT04739306) is to evaluate efficacy and safety of CT-P42 compared to Reference AFL in DME patients.

Methods: CT-P42 3.1 Study is an ongoing, randomized, double-masked, active-controlled Phase 3 Study. Patients with DME, who had central subfield retinal thickness of ≥350 μm, BCVA score of 73 to 34 letters in the study eye, were randomly assigned in a 1:1 ratio to receive 2mg/0.05 mL of CT-P42 or Reference AFL via intravitreal injection. The primary endpoint was the mean change from baseline at Week 8 in Best Corrected Visual Acuity (BCVA) using the Early Treatment of Diabetic Retinopathy Study chart to detect clinical difference between treatments on the steep part of response curve if such were to exist.

Results: A total of 348 patients were randomized (CT-P42: 173, Reference AFL: 175). The baseline characteristics were well balanced. The primary endpoint was met by demonstrating the mean change from baseline at Week 8 was similar between the groups and the 95% confidence interval (CI) for the estimate of treatment difference was entirely within the predefined equivalence margin of ±3 letters (95% CI: [-0.73, 1.88] for the Full analysis set and [-0.90, 1.66] for the Per-protocol set) (Table 1). Other secondary efficacy endpoints also showed similar results between the treatment groups up to Week 24. CT-P42 demonstrated a well-tolerated safety profile which was similar to that of Reference AFL up to Week 24. Treatment-emergent adverse events (TEAEs) were reported for 87 (50.3%) and 94 (53.7%) patients in the CT-P42 and the Reference AFL, respectively. With regards to adverse events of special interest, the proportion of patients who experienced at least 1 TEAE classified as arterial thromboembolism among the groups was same (CT-P42: 3 [1.7%], Reference AFL: 3 [1.7%]). There were no notable differences in TEAE related to injection procedure among the groups (CT-P42: 8 [4.6%], Reference AFL: 14 [8.0%]).

Conclusion: The results demonstrated that CT-P42 was therapeutically equivalent to reference AFL as measured by the mean change from baseline in BCVA at Week 8 in patients with DME. Comparable secondary efficacy results up to Week 24 supported the similarity of CT-P42 and Reference AFL. CT-P42 was also well tolerated with a safety profile comparable to that of Reference AFL.

IRB APPROVAL Yes

Table 1. Statistical Analysis of Mean Change from Baseline in BCVA at Week 8 (ANCOVA)

Analysis Set	Treatment	n	Least Squares Mean (Standard Error)	Estimate of Treatment Difference in LS Means (CT-P42 – Reference AFL)	90% CI	95% CI
Full Analysis Set (FAS)	CT-P42	169	9.43 (0.798)	0.58	(-0.52, 1.67)	(-0.73, 1.88)
	Reference AFL	172	8.85 (0.775)			
Per-protocol (PP) Set	CT-P42	165	9.22 (0.837)	0.38	(-0.70, 1.45)	(-0.90, 1.66)
	Reference AFL	167	8.84 (0.840)			

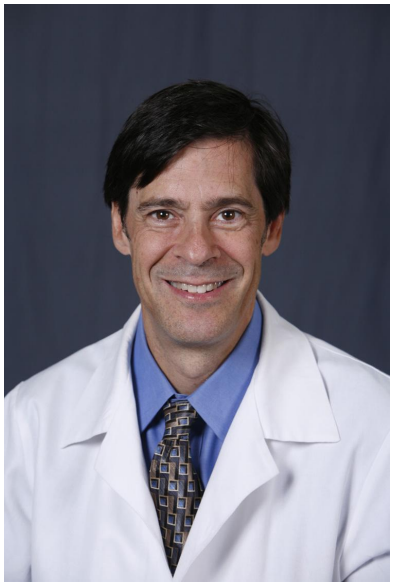
Covariates: baseline BCVA and country
Abbreviations: ANCOVA, analysis of covariance; LS, least squares; n, number of patients with BCVA score at Week 8

Statistical Analysis of Mean Change in Baseline in BCVA to Week 8 (ANCOVA)

7/30/2023

Impact of Faricimab vs Aflibercept on Epiretinal Membrane Formation Over 2 Years in Eyes With DME in the YOSEMITE/RHINE Phase 3 Trials

Impact of Faricimab vs Aflibercept on Epiretinal Membrane Formation Over 2 Years in Eyes with DME in the YOSEMITE/RHINE Phase 3 Trials



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- Peter Westenskow, PhD
- Jeffrey Willis, MD, PhD

Objective: To investigate differences in incidence of epiretinal membranes (ERMs) between faricimab and aflibercept using pooled YOSEMITE/RHINE trial data.

Purpose: We conducted a novel post-hoc analysis to compare incidence of ERM formation in eyes with diabetic macular edema (DME) treated with faricimab vs aflibercept over 2 years. We describe the impact of ERMs on BCVA, anatomy and treatment intervals.

Methods: YOSEMITE/RHINE (NCT03622580/03622593) were randomized, double-masked, active comparator–controlled, phase 3 trials designed to assess efficacy, durability, and safety of faricimab in patients with DME. Patients were randomized 1:1:1 to faricimab 6.0 mg every 8 weeks (Q8W) after 6 initial Q4W doses, faricimab 6.0 mg treat-and-extend (T&E) after 4 initial Q4W doses, or aflibercept 2.0 mg Q8W after 5 initial Q4W doses. The protocol-driven T&E algorithm allowed dosing intervals to be extended to Q16W, maintained, or reduced to Q4W based on visual acuity and anatomic criteria. Presence of ERMs was an exclusion criterion for both trials. Masked, independent ERM grading (defined prior to study start as significant distortion of macular architecture in the central 1 mm of OCT images) was conducted at the Central Reading Centers (Duke and Vienna) at baseline and weeks 16, 48, 52, 56, 92, 96, and 100. The intent-to treat population included eyes with no baseline ERM.

Results: Over 2 years, ERMs developed in 23/619 (3.7%), 31/618 (5.0%) and 45/604 (7.5%) of faricimab Q8W, T&E, and aflibercept Q8W eyes, respectively. Risk of ERM formation was lower for faricimab Q8W vs aflibercept (HR 0.48; 95% CI 0.29, 0.80; nominal P=0.0039). The corresponding data for T&E patients vs aflibercept were HR 0.65 (95% CI 0.41, 1.03; nominal P=0.0644). Using a treatment agnostic approach, at year 2, eyes that developed ERMs during the study tended to have worse BCVA and CST outcomes than those that did not develop ERMs. Similarly, eyes that developed ERMs also tended to have higher rates of intra- (63/83; 75.9% vs 649/1336; 48.6%) and sub-retinal fluid (9/85; 10.6% vs 47/1372; 3.4%) at 2 years than those without ERM. Among faricimab-treated eyes in the T&E arm, dosing was extended to Q16W in a larger proportion of eyes without ERMs (332/516; 64.3%) than those with ERMs (7/28; 25%).

Conclusion: For the first time, we have demonstrated a potential anti-fibrotic effect of faricimab vs aflibercept in an analysis of pooled YOSEMITE/RHINE trial data from eyes with DME. ERMs were associated with numerically worse visual acuity, worse anatomic outcomes, and a lower rate of dose extension to Q16W.

IRB APPROVAL Yes

7/30/2023

Phase 3 Randomized Studies of Efficacy and Safety of Revakinagene Taroretcel Producing Ciliary Neurotrophic Factor (CNTF) in Macular Telangiectasia Type 2

Phase 3 Randomized Studies of Efficacy and Safety of Revakinagene Taroretcel Producing Ciliary Neurotrophic Factor (CNTF) in Macular Telangiectasia Type 2

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- Martin Friedlander, MD, PhD

Objective:

To determine whether revakinagene taroretcel (NT-501) slowed the rate of disease progression among participants with macular telangiectasia type 2 (MacTel) as compared with sham treatment.

Purpose: MacTel is a neurodegenerative disease resulting in photoreceptor atrophy and loss of vision. There is currently no proven treatment. NT-501 is a first-in-class encapsulated cell therapy inserted surgically into the vitreous that produces sustained levels of ciliary neurotrophic factor (CNTF). Efficacy and safety of NT-501 were evaluated for treatment of MacTel.

Methods: Methods: NTMT-03-A and NTMT-03-B were identically designed, phase 3, multicenter, randomized, sham-controlled clinical trials. Participants diagnosed with MacTel with ellipsoid zone (EZ; inner segment/outer segment [IS/OS]) loss between 0.16 and 2.00 mm^2 were randomized 1:1 to NT-501 or sham treatment in the study eye (120 participants in NTMT-03-A and 119 in NTMT-03-B were included). The evaluators and participants were masked to the treatment assignments, and the ophthalmologists and clinic coordinators were unmasked. The primary endpoint was rate of change in EZ (IS/OS) area loss from baseline through month 24. Secondary safety endpoints were the proportion of participants with a ≥15-letter best corrected visual acuity loss on the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart and proportion of participants with ≥1 treatment-emergent serious adverse event (SAE).

Results: Results: Rate of EZ IS/OS area loss from baseline through month 24 was 56.4% lower in the NT-501 vs sham groups in NTMT-03-A (NT-501, 0.074 mm^2 [95% CI, 0.049-0.099]; sham, 0.170 mm^2 [0.145-0.195]; $P<0.0001$) and 29.2% lower in NTMT-03-B (NT-501, 0.116 mm^2 [0.088-0.144]; sham, 0.164 mm^2 [0.134-0.193]; $P=0.0210$). The proportion of participants with a decrease of ≥15 ETDRS letters was comparable between treatment groups in both NTMT-03-A (NT-501, 13.8% [8/58]; sham, 8.8% [5/57]; $P=0.558$) and NTMT-03-B (NT-501, 3.4% [2/59]; sham, 5.6% [3/54]; $P=0.669$). Ocular SAEs were low but higher in the NT-501 vs sham groups in NTMT-03-A (NT-501, 5.2% [3/58]; sham, 1.8% [1/57]) and NTMT-03-B (NT-501, 6.8% [4/59]; sham, 0) and predominantly transient and related to surgical complications.
Conclusion: Treatment with NT-501 significantly reduced anatomical disease progression through 24 months in both phase 3 studies. Treatment-related SAEs were uncommon and predominantly transient and related to surgical complications. These findings demonstrate that intravitreal delivery of CNTF via encapsulated cell therapy NT-501 is safe and effective for the treatment of MacTel.

IRB APPROVAL Yes