8/01/2023 12:00 am

Diabetic Retinopathy Symposium 4

ZETA-1 Phase 2 Trial Efficacy Results for APX3330: a Novel, Oral Ref-1 Inhibitor for the Treatment of Diabetic Retinopathy

- David Lally, MD
- Mitchell Brigell, PhD
- Jay Pepose, MD, PhD
- Mark Kelley, PhD
- Stephanie Kaiser
- Louis Haddad, MS
- Mina Sooch, MBA
- Peter Kaiser, MD FASRS
- David Boyer, MD

Objective: To evaluate the efficacy of APX3330, an oral, novel, small molecule inhibitor of Ref-1, a transcription factor regulator of both angiogenic and inflammatory signaling pathways relevant to diabetic retinal disease.
Purpose: To evaluate the efficacy of APX3330, an oral, novel, small molecule inhibitor of Ref-1, a transcription factor regulator of both angiogenic and inflammatory signaling pathways relevant to diabetic retinal disease.
Methods: ZETA-1 is a multi-center, placebo-controlled, double-masked Phase 2 trial which was randomized 1:1 to receive BID 600 mg APX3330 or placebo. Study eye eligibility criteria included moderate to severe non-proliferative DR or mild proliferative DR corresponding to reading center confirmed diabetic retinopathy severity scale (DRSS) scores of 47, 53, or 61, BCVA of 20/63 or better and absence of center-involved DME and no treatment for DR/DME within the past 6 months. The fellow eye criteria included any DRSS score and may have center-involved DME. The primary efficacy endpoint is percent of subjects with a ≥ 2 step improvement on the DRSS in the study eye at week 24 compared to baseline. Secondary endpoints include monocular and binocular ≥ 1, 2, 3, or 4 DRSS worsening or improvement, central subfield thickness (CST), BCVA, and other safety assessments.
Results: 103 DR subjects were enrolled in ZETA-1 with an average patient age of 56 years and 90% of patients having a baseline DRSS of 47 or 53; mean baseline CST in the study eye is 270 µm. Although the primary endpoint was not met with 8% of study eyes showing ≥ 2 step DRSS improvement in each treatment group, APX3330 showed a statistically significant binocular ≥ 3 step worsening after 24 weeks; 16% of placebo subjects worsened compared to 0% of APX3330 subjects (p=0.04). Additionally, APXX3330 subjects maintained their good vision compared to placebo (19% placebo vs. 5% APX3330 lost 5 or more letters of BCVA; p=0.07). Oral APX3330 showed a favorable ocular and systemic safety profile.
Conclusion: After 24 weeks of treatment, the primary endpoint was not met, but APX3300 did prevent ≥ 3 step worsening in binocular DRSS compared to placebo. Consideration of a binocular treatment effect is key for a systemically delivered drug that treats both eyes. It has been well established, starting with the ETDRS study, that progression of DRSS is associated with an increased risk for vision loss; thus, prevention of DRSS worsening should reduce the incidence of visual complications of DR. The efficacy data of APX3330 combined with its safety profile as an oral treatment warrants further clinical development.

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ZETA-1 Phase 2 Trial Safety and Tolerability Results for APX3330: a New Oral Ref-1 Inhibitor for the Treatment of Diabetic Retinopathy

- Daniel Su, MD
- Jay Pepose, MD, PhD
- Mark Kelley, PhD
- Audrey Lazar
- Louis Haddad, MS
- Mina Sooch, MBA
- Mitchell Brigell, PhD
- Peter Kaiser, MD FASRS
- David Boyer, MD

Objective: Can APX3330, a novel oral medication, be administered in patients with diabetic retinopathy with an acceptable safety profile?
Purpose: To evaluate the safety of APX3330, an oral, novel, small molecule inhibitor of Ref-1, a transcription factor regulator of both angiogenic and inflammatory signaling pathways relevant to diabetic eye disease.

Methods: ZETA-1 is a multi-center, randomized, placebo-controlled, double-masked Phase 2b clinical trial. Subjects with at least one eye with DR graded as moderate to severe non-proliferative diabetic retinopathy (NPDR) or mild PDR corresponding to reading center-confirmed diabetic retinopathy severity scale (DRSS) scores of 47, 53, or 61 were randomized 1:1 to receive BID 600 mg APX3330 or placebo. Safety measures included adverse events (AE)s, vital signs, labs, physical exam, and ocular examination. Central DME in the study eye was excluded but allowed in the fellow eye.

Results: 103 DR subjects were enrolled in ZETA-1 with an average patient age of 56 years and 90% of patients having a baseline DRSS of 47 or 53; mean baseline CST in the study eye is 270 µm. APX3330 showed a favorable safety profile. 14 treatment-emergent serious AEs were considered unrelated to the study medication, 11 in the placebo group and 3 in the APX3330 group. Two subjects in each group withdrew due to an AE. Of these, one placebo subject had worsening DME that was considered treatment-related. Overall, there were 211 AEs (91 APX3330, 120 placebo) in 64 subjects (29 APX3330, 35 placebo). Only 31 of these AEs were considered drug-related (14 APX3330, 17 placebo). All treatment-related AEs were mild or moderate in severity. Oral APX3330 showed a statistically significant reduction of disease progression: No (0%) APX3330-treated patients had a binocular ≥ 3-step worsening of DRSS from baseline compared with 16% for placebo-treated patients (p=0.04). Additionally, APXX3330 subjects maintained their baseline visual acuity compared to placebo (19% placebo vs. 5% APX3330 lost 5 or more letters of BCVA; p=0.07). There were no treatment-related serious adverse events. No changes were observed in liver, kidney, or heart function as well as complete blood count and comprehensive metabolic panel.

Conclusion: After 24 weeks of treatment, APX3330 in DR subjects demonstrated a favorable systemic and ocular safety profile. These safety findings in diabetic subjects are consistent with prior trial data in healthy, hepatic, and cancer subjects. Based on its safety and efficacy, APX3330 has the potential to be an oral treatment option for DR patients.

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Diabetic Retinopathy Symposium 4

Suprachoroidal Delivery of RGX-314 Gene Therapy for Diabetic Retinopathy: The Phase II ALTITUDE Study

- Dilsher Dhoot, MD

Objective: To evaluate the safety, tolerability, and efficacy of RGX-314 by suprachoroidal delivery in patients with Diabetic Retinopathy (DR) without Center-Involved Diabetic Macular Edema (CI-DME).

Purpose: In eyes with severe non-proliferative DR (NPDR), anti-VEGF therapy by repeated intravitreal bolus injections has been demonstrated to improve DR severity scores (DRSS) and reduce the development of vision threatening complications. RGX-314 is a gene therapy that utilizes an AAV8 vector to deliver a transgene for a soluble anti-VEGF fab designed to provide continuous anti-VEGF therapy following a single treatment. ALTITUDE is evaluating RGX-314 delivered into the suprachoroidal space (SCS) through an in-office procedure.

Methods: ALTITUDE is a controlled, open-label, randomized, dose-escalation trial evaluating the efficacy, safety and tolerability of suprachoroidal delivery of RGX-314 using the SCS Microinjector® in patients with a DR diagnosis of moderately severe or severe nonproliferative DR (NPDR) or mild proliferative DR (PDR). Enrollment is complete for Cohorts 1-3 with Cohort 1 evaluating RGX-314 at a dose of $2.5x10^{11}$ genomic copies per eye (GC/eye), Cohorts 2 and 3 evaluating RGX-314 at an increased dose level of $5x10^{11}$ GC/eye and Cohort 3 evaluating RGX-314 in patients who are NAb positive. ALTITUDE is currently enrolling an additional dose ($1x10^{12}$ GC/eye) with short-course, ocular steroids following RGX-314, and the two Cohorts (4 and 5) will be stratified by DRSS levels (NPDR and PDR). The primary outcome is the proportion of eyes a with 2-step improvement in DR severity scale score at 48 weeks. Secondary outcomes include safety as well as development and intervention for DR-related complications.

Results: As of October 17th, 2022, RGX-314 was well tolerated in 50 patients in Cohort 1-3 (Dose 1: $2.5x10^{11}$ GC/eye; n=15 and Dose 2: $5.0x10^{11}$ GC/eye; n=35). No cases of chorioretinal vasculitis, occlusion, or hypotony were observed. There were three cases of mild intraocular inflammation through 6 months which resolved with topical corticosteroids. Through the 6-month timepoint, 20% of patients (D1: 40%; D2: 11%) achieved a >2-step improvement vs. 10% in control, 54% of patients (D1: 60%; D2: 51%) achieved any DRSS improvement vs. 20% in control, and 0% percent of patients (D1: 0%; D2: 0%) worsened >2 steps vs. 20% in control.

Conclusion: A one time, in-office injection of RGX-314 gene therapy for the treatment of diabetic retinopathy could potentially provide long-lasting improvement in DR severity and reduce risk of vision threatening complications.

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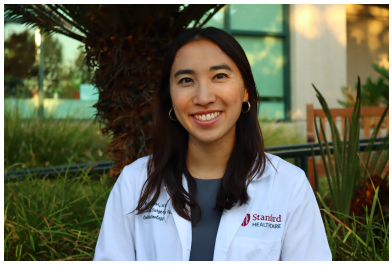
Progression to Pars Plana Vitrectomy After Monotherapy With Panretinal Photocoagulation or Anti-VEGF injections in Proliferative Diabetic Retinopathy



- Karen Wai, MD
- Aneesha Ahluwalia
- Cassie Ludwig, MD, MS
- Ravi Parikh, MD
- Ehsan Rahimy, MD
- Prithvi Mruthyunjaya, MD, MHS

Objective: In patients with proliferative diabetic retinopathy (PDR), does the rate of pars plana vitrectomy (PPV) differ for patients who are treated with pan-retinal photocoagulation (PRP) monotherapy compared to those treated with anti-vascular endothelial growth factors (anti-VEGF) injection monotherapy?
Purpose: PDR is a leading cause of blindness within the diabetic population, and treatment options can include PRP or anti-VEGF injections. We aim to compare the rate of PPV after monotherapy treatment with PRP or anti-VEGF injections in patients with PDR.
Methods: A retrospective cohort study was conducted using TriNetX (Cambridge, MA, USA), a federated electronic health records research network comprising of multiple large health organizations within the United States. Patients with newly diagnosed PDR were identified by ICD 9 or 10 code. PDR patients were stratified by monotherapy treatment with anti-VEGF agents or PRP using CPT code. Patients were excluded from their cohort if they received a combination of PRP treatment and anti-VEGF injections. Cohorts were matched for age, gender, race, and baseline HbA1c level. The primary outcome was need for pars plana vitrectomy (PPV) as determined by CPT code. One, three, and five year outcomes after either anti-VEGF agent use or PRP were compared between cohorts after propensity score matching using logistic regression.
Results: A total of 22400 patients were included in the analysis after propensity score matching with 11200 PDR patients in each of the PRP and anti-VEGF group cohorts. After matching, 50.7% vs 52.0% of patients were male, the average age was 63.3 years vs 63.8 years, and the average HbA1c was 11.9% vs 11.9% in the PRP and anti-VEGF groups, respectively. At baseline, 6.5% vs 8.5% had diabetic macular edema in the PRP and anti-VEGF groups, respectively. There were increased rates of PPV in the PRP group relative to the anti-VEGF group at one year (11.9% vs 7.8%, $p<0.01$), three years (15.1% vs 9.7%, $p<0.01$), and five years (16.2% vs. 10.3%, $p<0.01$].
Conclusion: Within a large and diverse real-world database, higher rates of PPV were seen in PDR patients treated solely with PRP compared to anti-VEGF agents. These finding align with those of the DRCR Protocol S trial, which compared ranibizumab treatment with PRP and found that monotherapy treatment with ranibizumab led to fewer vitrectomy procedures. Within clinical practice, the treatment for eyes with PDR should be ultimately guided by careful consideration of risks and benefits of each therapy as well as consideration of patient compliance.

IRB APPROVAL No - no IRB