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

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Disclosures

- Daniel Su: None
- Jay Stuart Pepose: Code C (Consultant/Contractor) Ocuphire , Code I (Personal Financial Interest) Ocuphire, Code O (Owner) Pepose Vision Institute
- Mark R. Kelley: Code C (Consultant/Contractor) Ocuphire, Code I (Personal Financial Interest) Ocuphire, Code E (Employment) Indiana University
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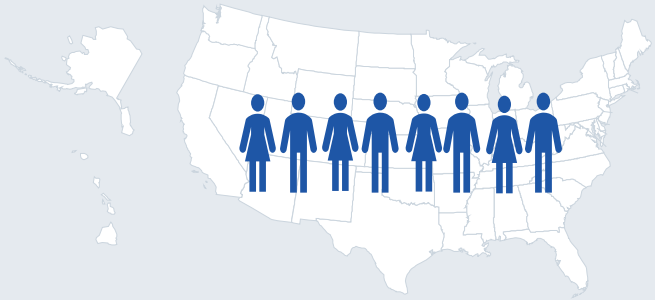
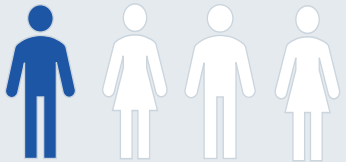
Diabetic Retinopathy At a Glance

Larger Disease to Manage with Growing Diabetes Epidemic



There are **8M** adults in the U.S. with DR[1]

DR/DME affects about **1 in 4** people with type 1 and type 2 diabetes



DR is the **leading cause of blindness** among working-age adults

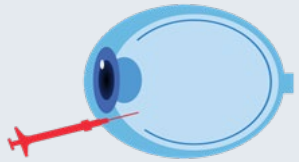
If untreated, DR can **rob people of their vision** prematurely[2,3]

The number of people with DR expected to increase more than **14M** by 2050

56% of patients reported anxiety related to anti-VEGF treatment

$13B (2020)

Global **Intravitreal Injection** Revenues

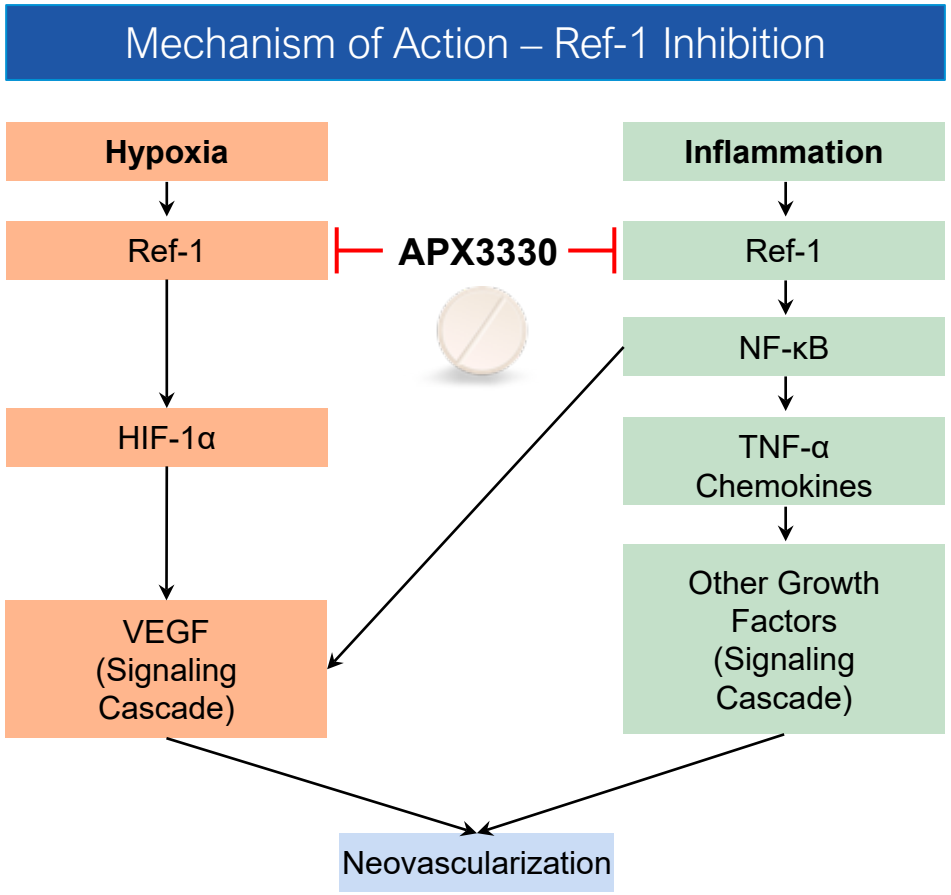


Majority of patients with mild to moderate DR are **not treated with anti-VEGF due to injection fear and burden**

Source:
1. American Diabetes Association; International Diabetes Federation; Healthline;
2. Das UN. DME, retinopathy and age-related macular degeneration as inflammatory conditions. Arch Med Sci. 2016;12(5):1142-1157. doi:10.5114/aoms.2016.61918
3. Patient survey adapted from Lions International Foundation and International Diabetes Foundation-Europe; Meltzer 2000

APX3330 History and Ref-1 Inhibition Mechanism

Ref-1 Involved in Key Pathways that Contribute to Diabetic Retinopathy and DME



- Ref-1 (reduction-oxidation effector factor-1) is a novel target discovered by Dr. Mark R. Kelley at Indiana University School of Medicine
- APX3330 is a small molecule oral drug candidate and a first-in-class inhibitor of Ref-1
- APX3330 previously developed for multiple hepatic inflammatory indications and later for advanced solid tumors in **11 Phase 1 and 2 trials**
  - Similar oncology origin as approved anti-VEGFs
- **MOA uniquely decreases both abnormal angiogenesis and inflammation by blocking pathways downstream of Ref-1**
- Extensively studied in over **20 in-vitro and animal studies** with favorable efficacy and safety

Logsdon et al (2018), Li et al (2014).

APX3330: Drug Development History and Patents

Significant Preclinical & Clinical Data Supporting Human Safety, MOA, and PK

APX3330
New Chemical Entity

12
Phase 1 & Phase 2 Trials

>375
Subjects Dosed

Exposure in Humans
365
Days

Patents to
2034+

☑ Preclinical Efficacy & Toxicology Package

☑ APX3330 IND

☑ 6 Phase 1 Trials

☑ 5 Phase 2 Trials

◉ Phase 2 Trials

☐ Phase 3 Registration

☐ NDA Filing

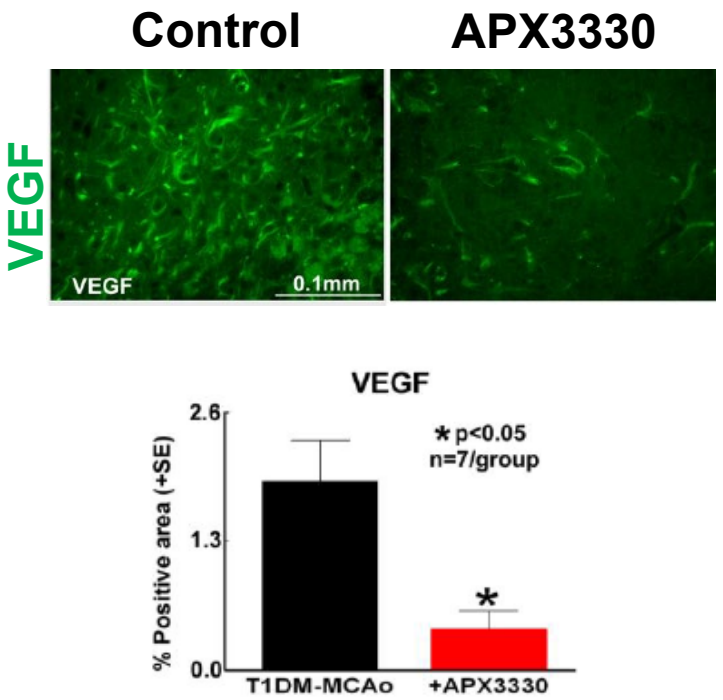
Studied in inflammation/hepatitis & cancer patients
(*Studied by Eisai & Apexian, respectively***)**

Focus on Ophthalmology

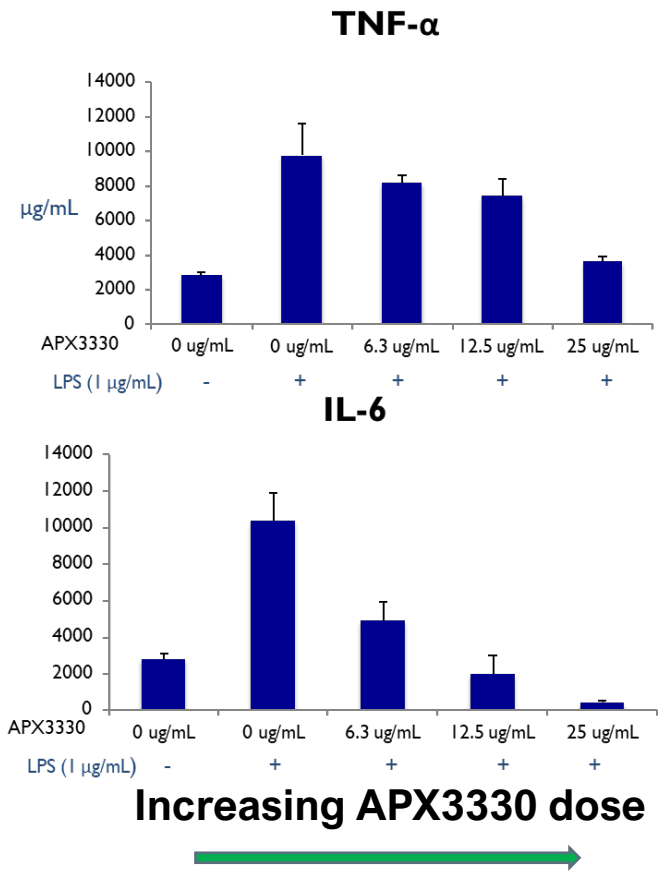
In-vitro Validation of Mechanism of Action

APX3330 Reduces VEGF levels and Inflammatory Cytokines; Provides Neuronal Protection

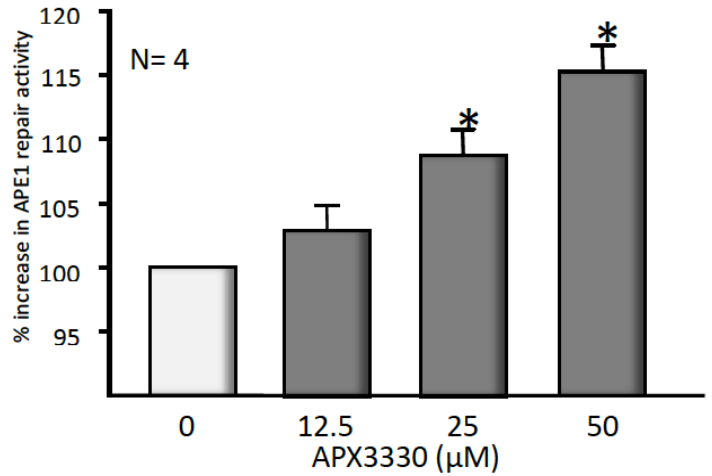
APX3330 reduces VEGF protein expression in preclinical stroke model



APX3330 reduces pro-inflammatory cytokines in LPS stimulated macrophages



APX3330 increases DNA oxidative repair and neuronal protection



APX3330 enhances Ref-1 endonuclease activity in dorsal root ganglion neurons

-Tao Yan *et al.* APX3330 Promotes Neurorestorative effects after stroke in type one diabetic rats. Aging and Disease. Vol 9, Oct 2018

-Apurinic/Apyrimidinic endonuclease 1 regulates inflammatory response in macrophages. Jedinak A, Dudhgaonkar S, Kelley MR, Sliva D. Anticancer Res. 2011 Feb;31(2):379-85. PMID: 21378315

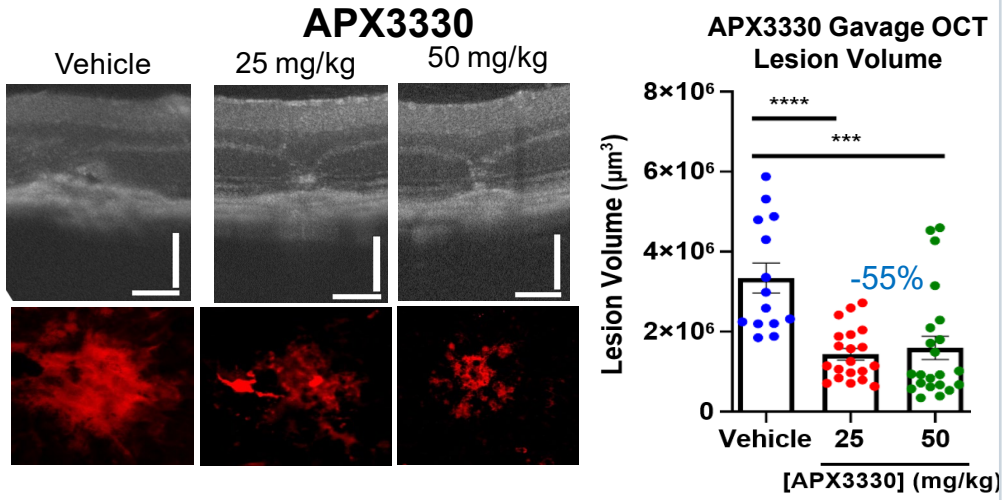
-Fehrenbacher, J. C., Guo, C., Kelley, M. R. & Vasko, M. R. DNA damage mediates changes in neuronal sensitivity induced by the inflammatory mediators, MCP-1 and LPS, and can be reversed by enhancing the DNA repair function of APE1. Neuroscience 366, 23-35, doi:10.1016/j.neuroscience.2017.09.039 (2017).

Preclinical Data: Oral APX3330 Blocks Neovascularization

Lesion Volume Decrease with Oral APX3330 in Murine Laser CNV Model Similar to EYLEA® Data

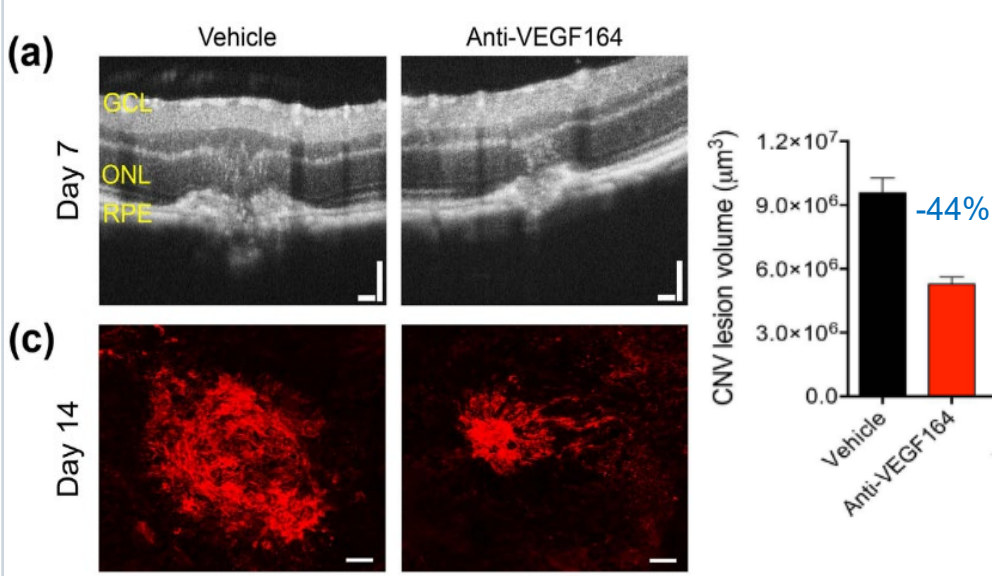
L-CNV Mouse Retina Model

Lesion Size and Corresponding Fluorescent Stains in L-CNV Models Treated with APX3330 at 25 mg/kg oral gavage



Silva et al, 2021

L-CNV Mouse Retina Model



- ✓ **Efficacy was also seen after single <u>intravitreal</u> injection of 20µM APX3330 in mouse L-CNV model****
- ✓ **Efficacy was also seen after dosing <u>intraperitoneal</u> injection of 50 mg/kg twice daily, 5 days on/2 days off, for 2 weeks in mouse L-CNV model*****
- ✓ **Efficacy was also seen after single <u>intravitreal</u> injection of 20µM APX3330 in Vldlr $^{-/-}$ mice model******

- Silva et al. ARVO 2021 Annual Meeting
- *Published data on EYLEA. This study was performed independently from APX3330 study and is a cross-study comparison.
- **Li 2014; *** Pasha 2018; ****Jiang 2011 (*Vldlr* $^{-/-}$: Very Low-Density Lipoprotein receptor knock-out mice)

Phase 2 ZETA-1 Trial of Oral AP3330 in Subjects With Diabetic Retinopathy

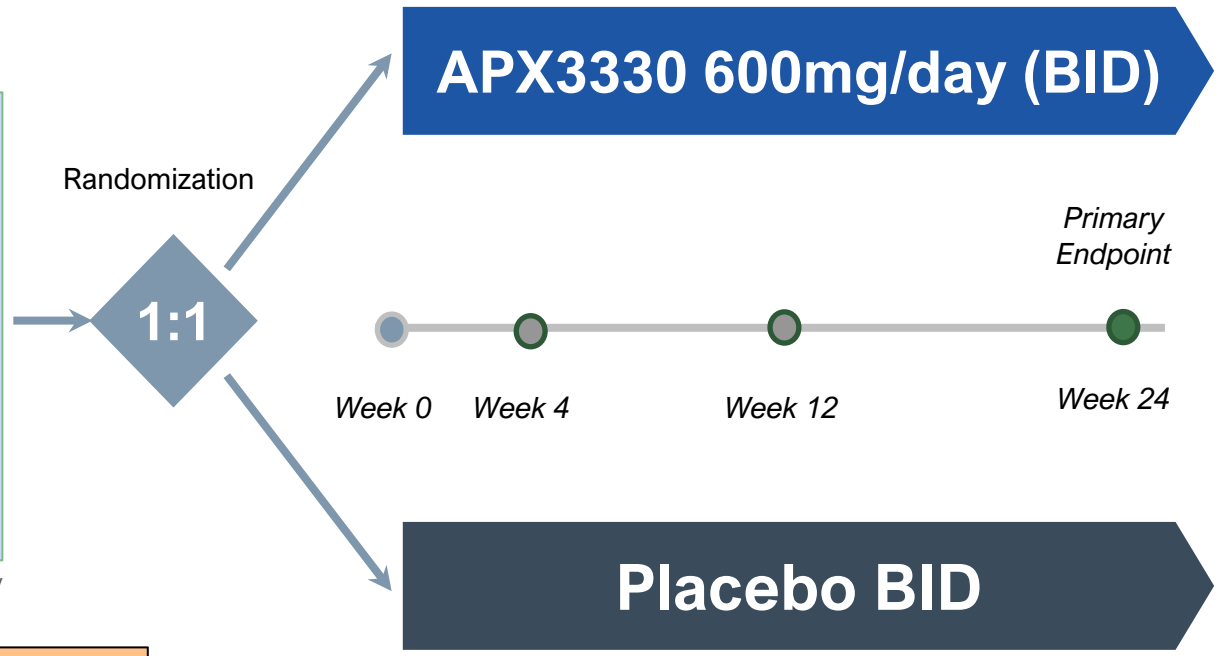
Randomized, Double-Masked, Placebo-Controlled 24-Week Trial

ZETA-1

25 US sites

90-100 participants with moderately severe to severe NPDR or mild PDR (DRSS 47, 53, 61)

NPDR = non-proliferative diabetic retinopathy
PDR = proliferative diabetic retinopathy



Eligibility Criteria:

Key Inclusion – Study Eye
- ≥ 18 years of age
- DRSS 47, 53, or 61
  - Noncentral DME is permitted in study eye
- ETDRS BCVA ≥ 60 Letters (20/63)

Key Exclusion – Study Eye
- OCT CST >320 μm^2
  - Center involved DME allowed in fellow eye
- Anti-VEGF within past 6 months[3]
- HbA1c ≥ 12.0%

103 Subjects Enrolled (FPFV Apr 2021 to LPLV Aug 2022)
Top Line Announced in Early 2023

Endpoints

Primary: % subjects with ≥ 2 step improvement on DRSS (Diabetic Retinopathy Severity Scale) at week 24

Secondary:
- DRSS worsening ≥1, ≥2, ≥3*, ≥4
- DRSS improvement ≥1, ≥2, ≥3*, ≥4
- Progression to vision threatening complications
- Central subfield thickness (CST)
- Best Corrected Distance Visual Acuity (BCDVA)
- Rescue subjects
- DME fellow eye status
- Safety and tolerability

Exploratory:
- Labs / PK

**Potential Phase 3 approvable endpoints*

1. By Central Reading Center
2. Center-Involved DME in Fellow Eye is Acceptable
3. Includes Systemic or IVT VEGF

www.clinicaltrials.gov (NCT04692688); Eylea® is registered trademark of Regeneron

ZETA-1: Baseline Demographics and Systemic Characteristics

Well-Balanced Across Arms

Demographics

	APX3330 n=51	Placebo n=52
Age (years) mean (range)	54.3 (26-81)	58.3 (24-78)
Sex: Male n (%)	24 (47%)	26 (50%)
Race: White n (%)	40 (78%)	41 (79%)
Ethnicity: Hispanic or Latino n (%)	28 (55%)	23 (44%)
Diabetes Status (years) mean (range)	15 (0-36)	16 (0-58)
Systolic Blood Pressure (mmHg) mean	136	139
Diastolic Blood Pressure (mmHg) mean	82	80
Heart Rate (beats/min) mean	78	76
Hemoglobin A1C (%) mean	8.4	8.3
Body Mass Index (kg/m^2) mean	31	31

DRSS Scores

	APX3330 n=51	Placebo n=52
DRSS Score – Study Eye		
47 (Moderately severe to severe NPDR)	22 (43%)	18 (35%)
53 (Moderately severe to severe NPDR)	25 (49%)	28 (54%)
61 (Mild proliferative diabetic retinopathy)	4 (8%)	6 (12%)
DRSS Score – Fellow Eye		
43 or Lower (Mild to moderate NDPR or better)	**14 (31%)**	**12 (24%)**
47 (Moderately severe to severe NPDR)	13 (29%)	19 (39%)
53 (Moderately severe to severe NPDR)	12 (27%)	9 (19%)
61 (Mild proliferative diabetic retinopathy)	1 (2%)	4 (8%)
65 or Higher (Moderate to severe prolif. DR)	**5 (11%)**	**5 (10%)**

Note: 15 fellow eyes were CST>320 microns (center-involved DME eyes)

Key Visual Metrics

	APX3330 n=51	Placebo n=52	Total n=103
BCVA Study Eye *Letters (mean)*	**81**	**78**	**80 (20/25 Snellen)**
BCVA Fellow Eye *Letters (mean)*	76	77	77 (20/32 Snellen)
OCT CST Study Eye *(µm)*	**270**	**271**	**271**
OCT CST Fellow Eye *(µm)*	292	286	289
Intraretinal Fluid in the Center of SE	Y – 21 N – 26	Y – 12 N – 31	Y – 33 N – 57
Intraretinal Fluid at the Foveal Center of SE	Y – 1 N – 20	Y – 1 N – 41	Y – 2 N – 61
Intraocular Pressure in Study Eye (mmHg)	15	16	15

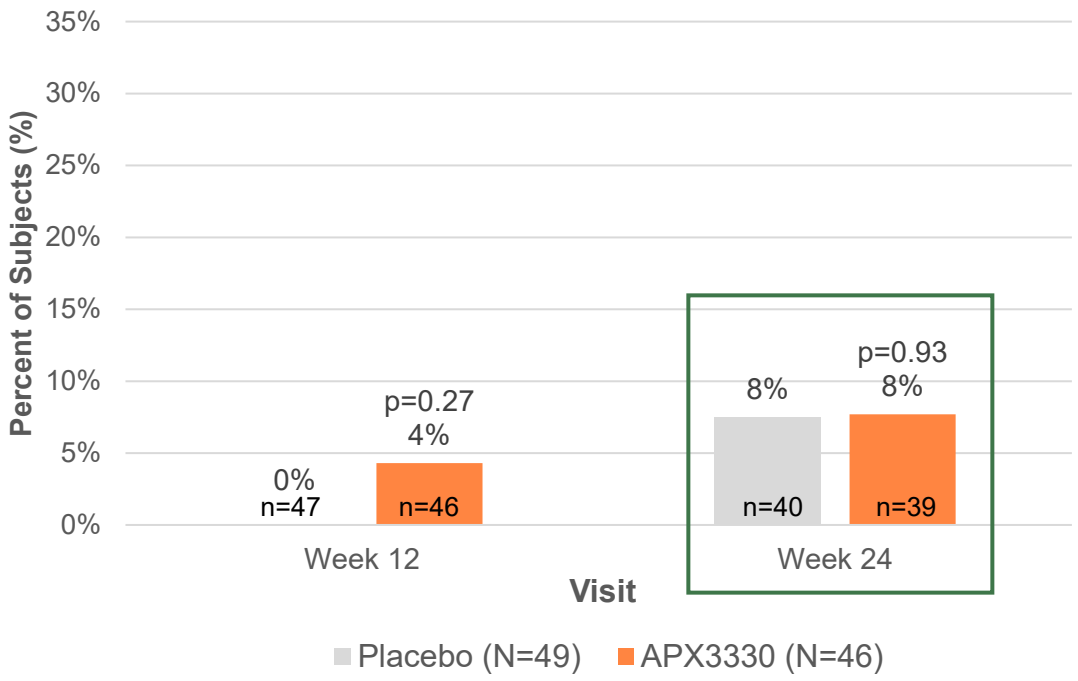
Good Visual Acuity Fluid Below 320µm

Source: ZETA-1 Clinical Trial

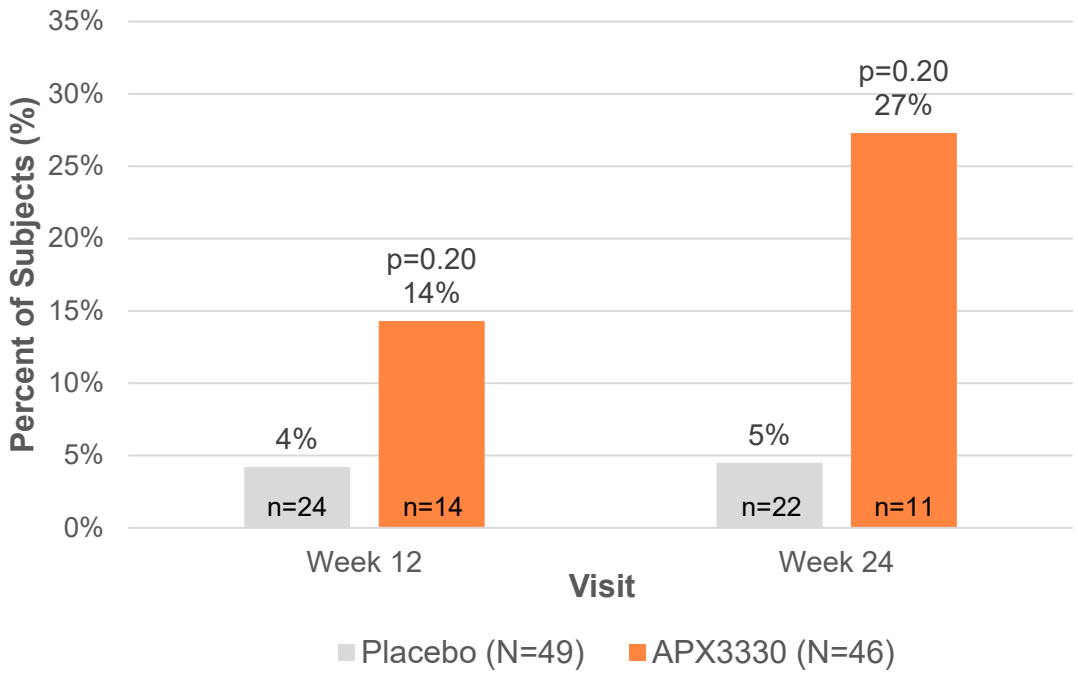
Percent of Subjects With ≥ 2-Step Improvement in DRSS From Baseline

ZETA-1 Did Not Meet the Week 24 Phase 2 Primary Endpoint (based on Anti-VEGF Precedence for DR)

Percent of Subjects With ≥ 2-step Improvement in DRSS From Baseline by Visit (mITT) – **Study Eye**



Percent of Subjects With ≥ 2-step Improvement in DRSS From Baseline by Visit (mITT) – **Qualified Fellow Eye**

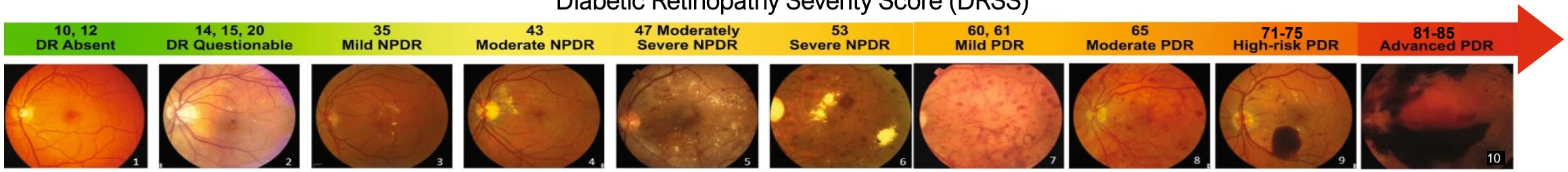


Source: ZETA-1 Clinical Trial
Note: Large "N" indicates total number of participants within each arm for the mITT population. Small "n" indicates total number of evaluable eyes for each respective endpoint and arm.
Note: Images from Central Reading Center will be reviewed prior to EOP2 FDA meeting

Clinically Meaningful Registration Endpoints in DR

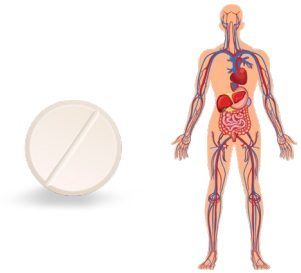
Systemic Drugs Should Evaluate DRSS Change in Both Eyes; To Be Formally Confirmed at EOP2 FDA Meeting

Diabetic Retinopathy Severity Score (DRSS)



DRSS established as surrogate endpoint for DR

FDA accepts improvement OR worsening (prevention of progression) in DR as endpoints[1]



Systemic Drugs

Recent preliminary discussions with FDA indicate binocular ≥ 3-step DRSS worsening (i.e., sum of right and left eye change in DRSS) could be acceptable for registration

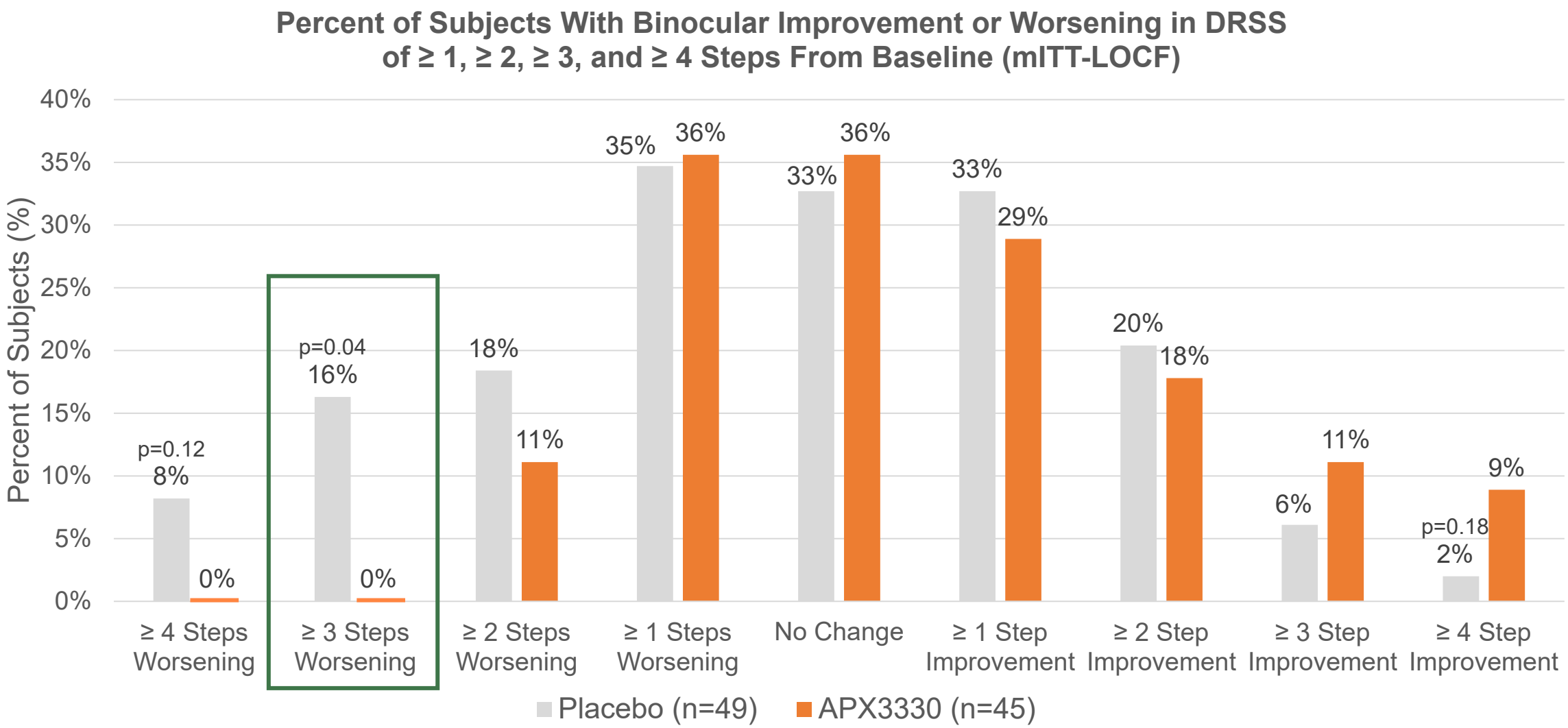
➢ *Distinct from historical anti-VEGF IVT endpoint precedent due to systemic delivery*

Source: ZETA-1 Clinical trial

1. Nair P, Aiello LP, Gardner TW, Jampol LM, Ferris FL III. Report From the NEI/FDA Diabetic Retinopathy Clinical Trial Design and Endpoints Workshop. Invest Ophthalmol Vis Sci. 2016 Oct 1;57(13):5127-5142. doi: 10.1167/iovs.16-20356. PMID: 27699406; PMCID: PMC6016432.

Percent of Subjects with Binocular Improvement or Worsening in DRSS at Wk 24

APX3330 Demonstrated Statistical Efficacy on the Planned Phase 3 Registration Endpoint

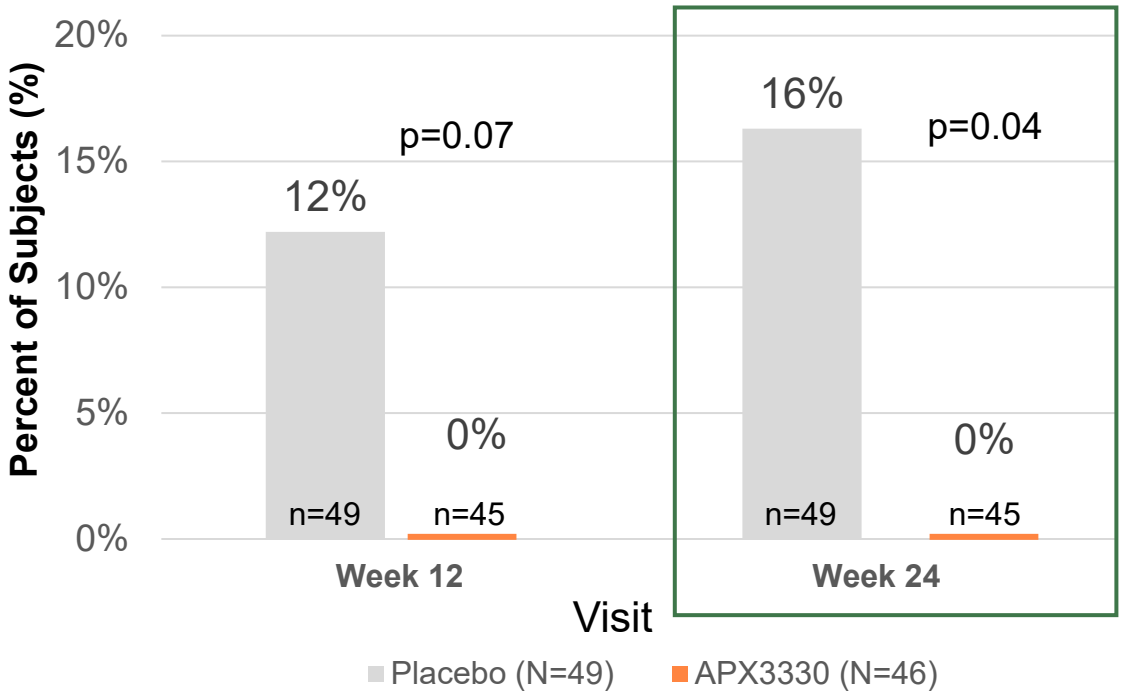


Source: ZETA-1 Clinical Trial; p values shown if p<0.20

% of Subjects With Binocular ≥ 3-Step Worsening in DRSS and Worsening of BCVA

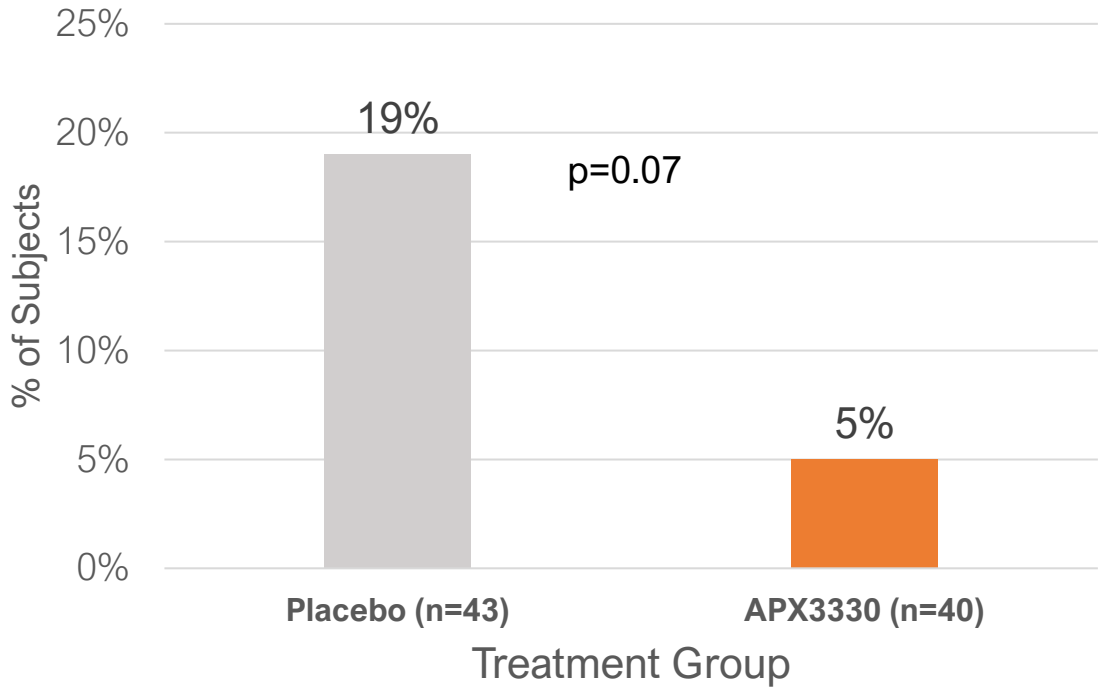
APX3330 Prevented Progression of Structural Retinal Abnormalities and Reduced Worsening of Visual Function

Percent of Subjects With Worsening in DRSS of ≥3 Steps From Baseline by Visit Binocular Eyes (mITT-LOCF)



Based on extrapolation from ZETA-1 and Rise/Ride extension trials[1], estimated **~25% of untreated patients may progress by ≥ 3 steps in binocular DRSS over 1 year**

Percentage of Subjects with ≥ 5 Letters of BCVA Lost at Week 24 (Safety Population)



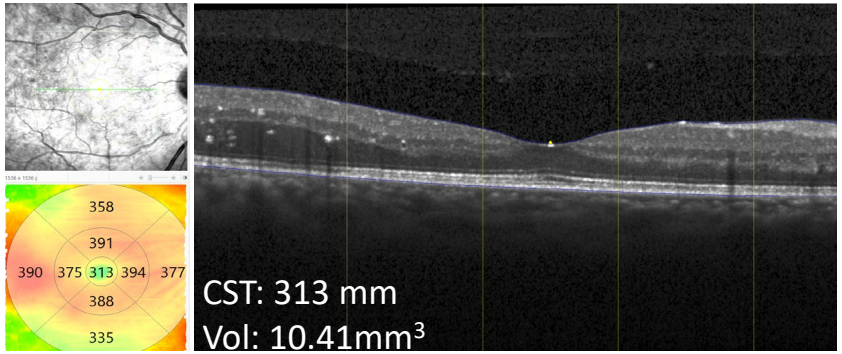
BCVA data shows **function followed structure with fewer APX3330 treated subjects losing visual acuity** compared to placebo at week 24

Source: ZETA-1 Clinical Trial; [1] Sun JK, Evidence for DR Progression and Regression from Clinical Trials. Presented at NDI/FDA DR Clinical Trials Design and Endpoints Workshop, June 26, 2015.
Note: Images from Central Reading Center will be reviewed prior to EOP2 FDA meeting
Note: Large "N" indicates total number of participants within each arm for the mITT-LOCF population. Small "n" indicates total number of evaluable eyes for each respective endpoint and arm.

ZETA-1 Trial: Placebo Subject 02-010 45 yr-old White Male (Study Eye-OD)

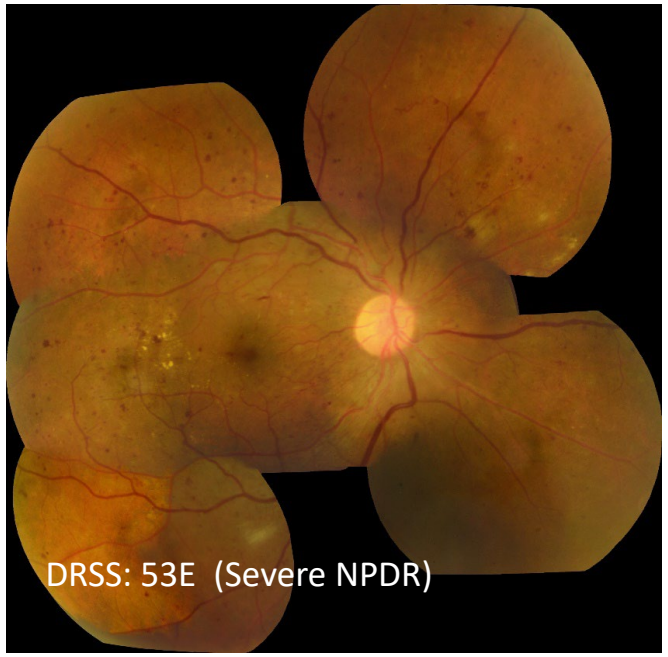
At Week 24, Placebo Eye Progressed from NPDR to PDR, CST Increased by 318 mm, BCVA Loss of 14 Letters

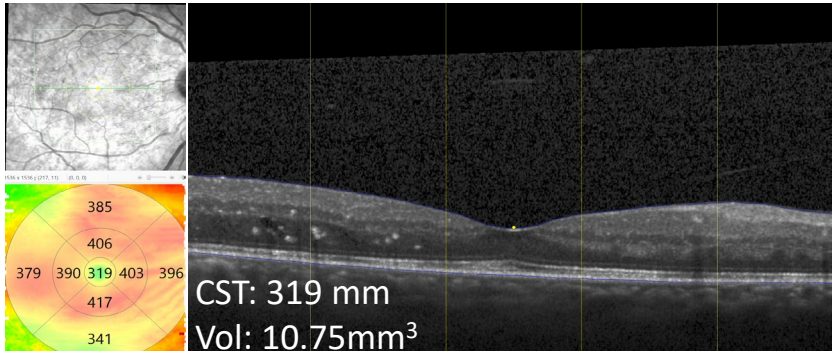
Screening



BCVA: 82 Letters

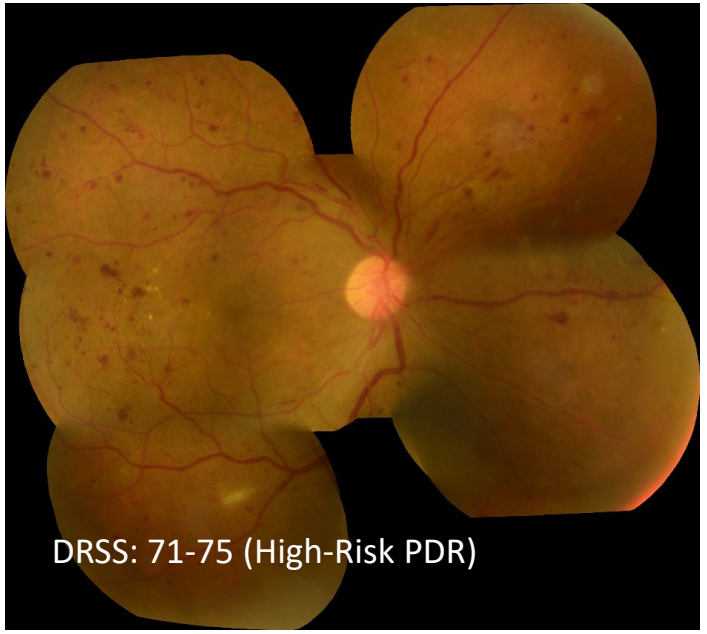
Week 12

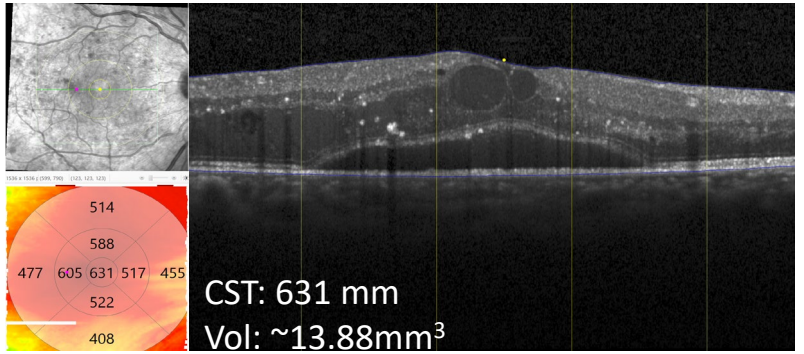




BCVA: 82 Letters

Week 24





BCVA: 68 Letters

ZETA-1 Treatment Emergent Adverse Events

Oral APX3330 Showed a Favorable Safety Profile; Consistent with That Seen in Prior Trials

	APX3330 (n=51)	Placebo (n=52)	Total (n=103)
Total AEs	91	120	211
# of Subjects with AEs	29 (57%)	35 (67%)	64 (62%)
Treatment Related AEs	**14 (45%)**	**17 (55%)**	**31 (30%)**
Serious AEs	3 (3%)	11 (9%)	14 (7%)
Subjects Withdrawals Due to AEs	2 (4%)	1 (2%)	3 (3%)
Deaths	0 (0%)	1 (2%)	1 (1%)
AEs in >5% of Subjects			
Diabetic Retinal Edema	**2 (4%)**	**5 (10%)**	**7 (7%)**
Diabetic Retinopathy	**1 (2%)**	**6 (12%)**	**7 (7%)**
Vitreous detachment	0 (0%)	3 (6%)	3 (3%)
Cataract	3 (6%)	1 (2%)	4 (4%)
Pruritus	**6 (12%)**	**1 (2%)**	**7 (7%)**
Rash	**3 (6%)**	**1 (2%)**	**4 (4%)**
COVID-19	1 (2%)	5 (10%)	6 (6%)

| Eye disorders |

APX3330 SAEs: Dyskinesia, TIA, Chest pain
Placebo SAEs: Vertigo, Asthenia, Multiple organ dysfunction, Bradycardia, CAD
AEs → Withdrawal APX3330: Presyncope, Dyspnea; **Placebo:** DME (both eyes)

- **Limited AEs, most mild in severity**
- Few serious treatment-related AEs, all unrelated to study medication
- No ocular AEs other than expected DR progression
- No effect of APX3330 on clinical labs
- **No adverse effects on heart, kidney, liver, CNS, GI**
- No effect on vital signs (HR, BP)
- **Patients continued routine medications to manage their diabetes comorbidities**

Summary

- APX3330 first-in-class oral drug that inhibits Ref-1 which reduces VEGF and inflammatory cytokines to normal physiological levels
- Potential approvable endpoint for systemic (oral) drugs for DR treatment
  - Binocular ≥ 3-step worsening of DRSS
- Prevention of worsening is a clinically meaningful registration endpoint that was met in ZETA-1: *No subjects treated with APX3330 had a binocular ≥ 3-step DRSS worsening from baseline compared with 16% for placebo (p=0.04) after 24 weeks of treatment*
- APX3330 demonstrated favorable safety & tolerability in diabetic patients
- An EOP2 meeting with FDA is planned to advance to Phase 3 registration trials

We thank all the ZETA-1 study participants, investigators and their staff !!!