The 46th Annual

Macula Society Meeting

February 15-18 Fontainebleau - Miami, FL

David Boyer, MD, Caroline Baumal, MD, Mitchell Brigell, PhD, David Brown, MD, Jeffery Heier, MD, Peter Kaiser, MD, David Lally, MD, Eliot Lazar, MD, Anat Lowenstein, MD, PhD, Jay Pepose, MD, PhD, Daniel Su, MD, Christina Weng, MD, Charlie Wykoff, MD, PhD for the ZETA-1 study team

Rishi P. Singh, MD
Staff Physician and President, Cleveland Clinic Florida

Stuart,FL

Safety and Efficacy of an Oral Therapeutic APX3330 from ZETA-1 Phase 2 Trial in Patients with Diabetic Retinopathy

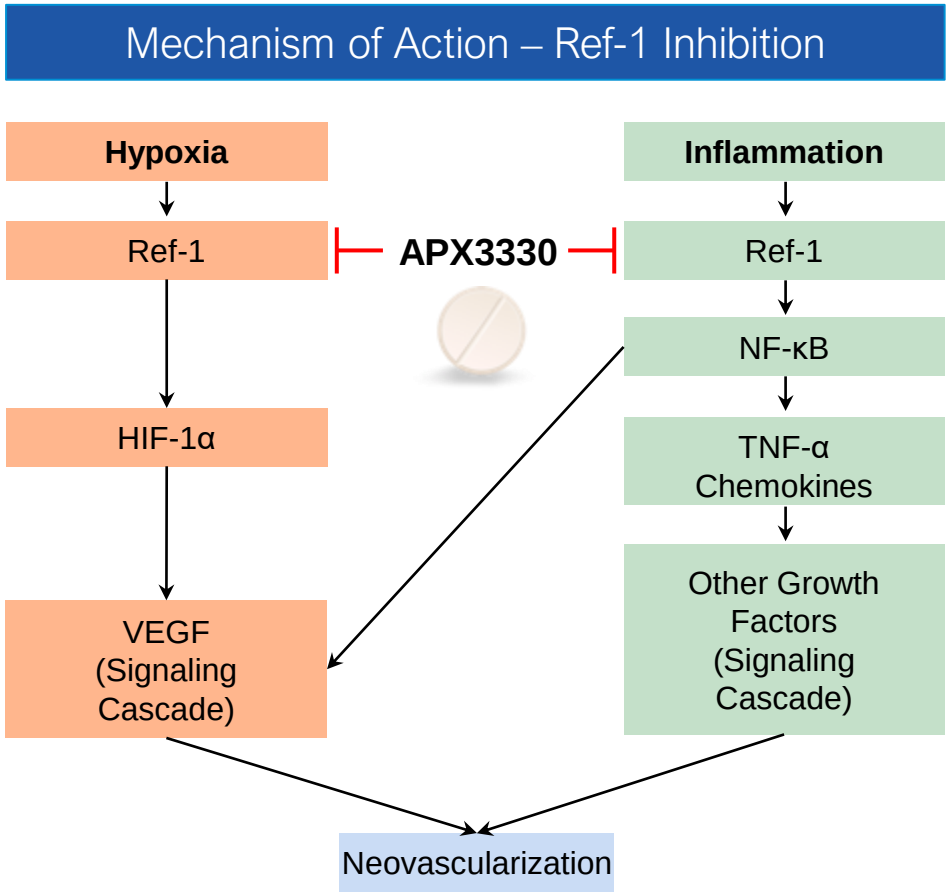
February 17, 2023

Disclosures

- Consultant: Regeneron, Alcon, Genentech, Bausch and Lomb, Ocuphire, Asclepix, Gyroscope, Apellis, Iveric

APX3330 History and Ref-1 Inhibition Mechanism

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



- APX3330 is a **small molecule oral drug** candidate and a first-in-class inhibitor of Ref-1 (reduction-oxidation effector factor-1)
- Novel MOA **reduces both VEGF and inflammatory cytokines to normal levels** by blocking HIF1α and NF-κB
- Extensively studied in **over 20 in-vitro and animal studies** with favorable efficacy and safety
- APX3330 previously developed by Eisai for multiple hepatic indications and later by Apexian for advanced solid tumors in **11 Phase 1 and 2 trials**

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

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

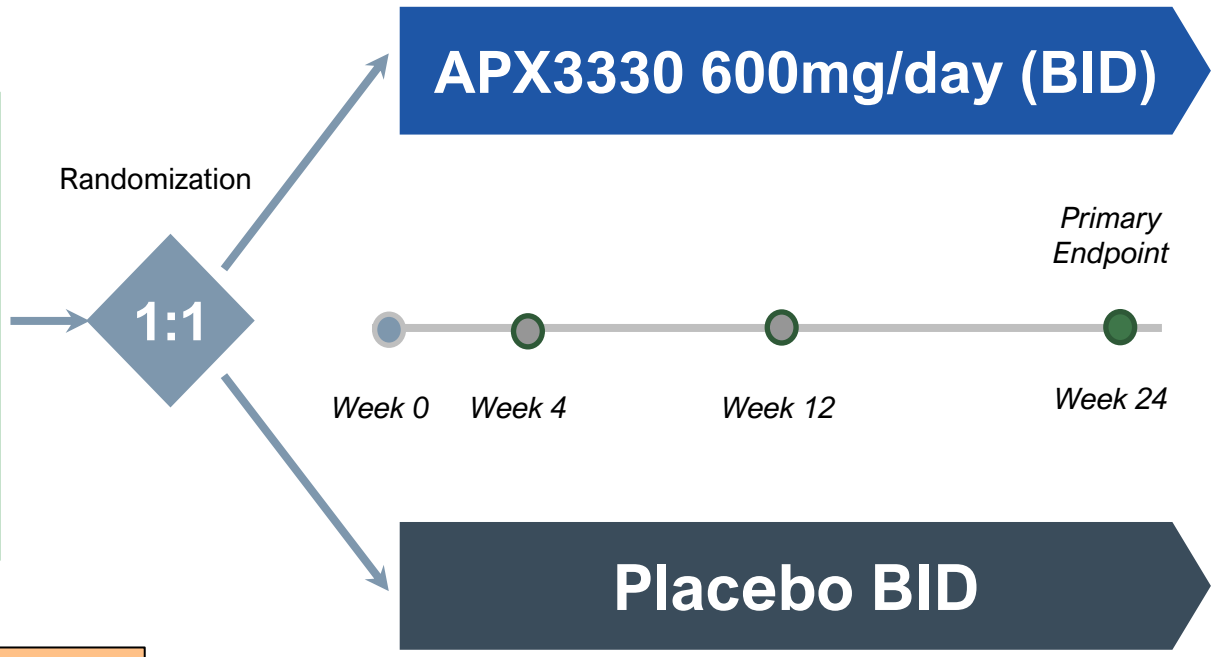
Randomized, Double-Masked, Placebo-Controlled 24-Week Trial

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

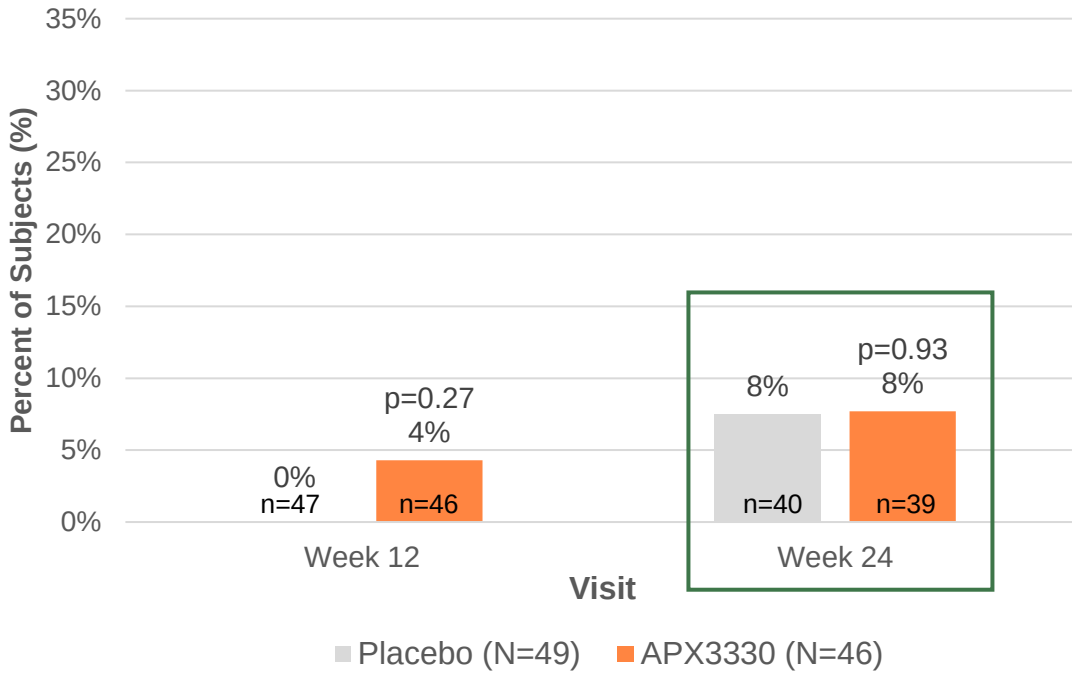
Good Visual Acuity Fluid Below 320µm

Source: ZETA-1 Clinical Trial

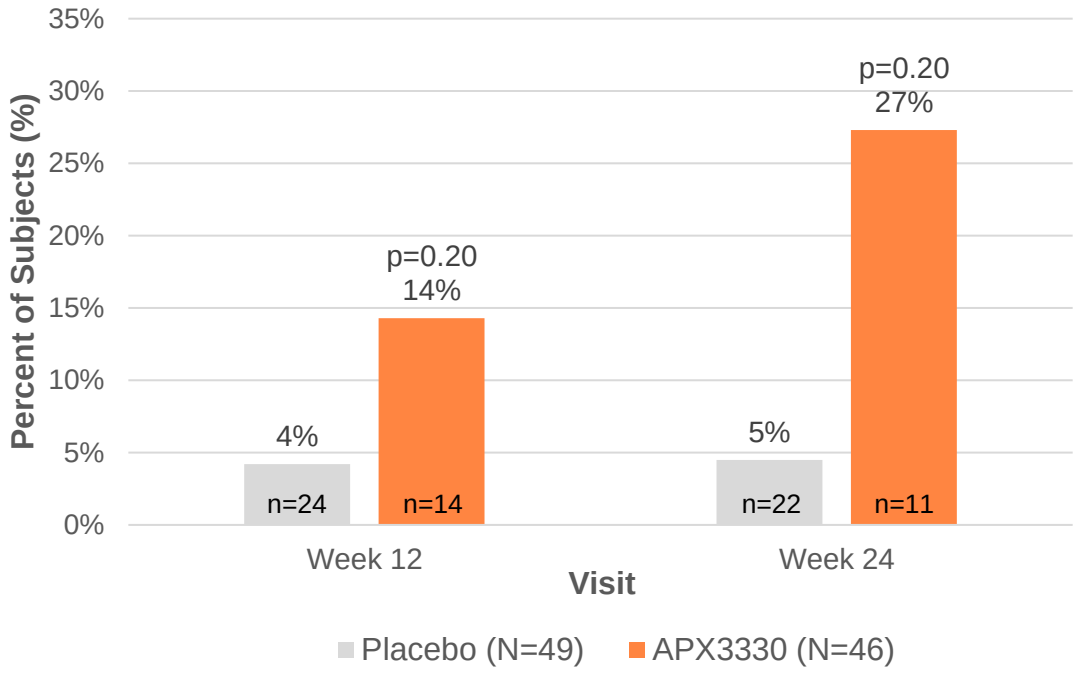
Percent of Subjects With ≥ 2-Step Improvement in DRSS From Baseline

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**



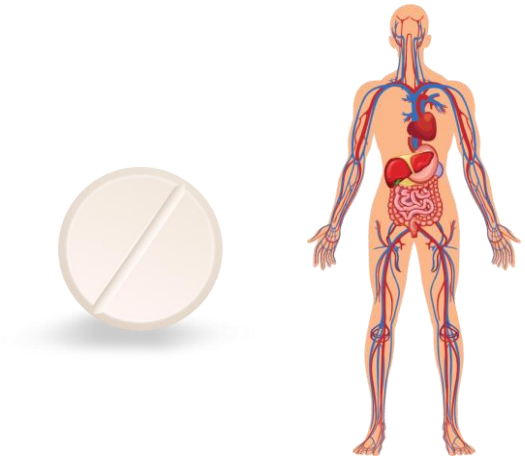
Source: ZETA-1 Clinical Trial
Note: Large "N" indicates total number of participants within each arm for the mITT population. Small "n" indicates total number of evaluable eyes for each respective endpoint and arm.
Note: Images from Central Reading Center will be reviewed prior to EOP2 FDA meeting

Clinically Meaningful Registration Endpoints in DR

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

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

DRSS established as surrogate endpoint for DR



Systemic Drugs

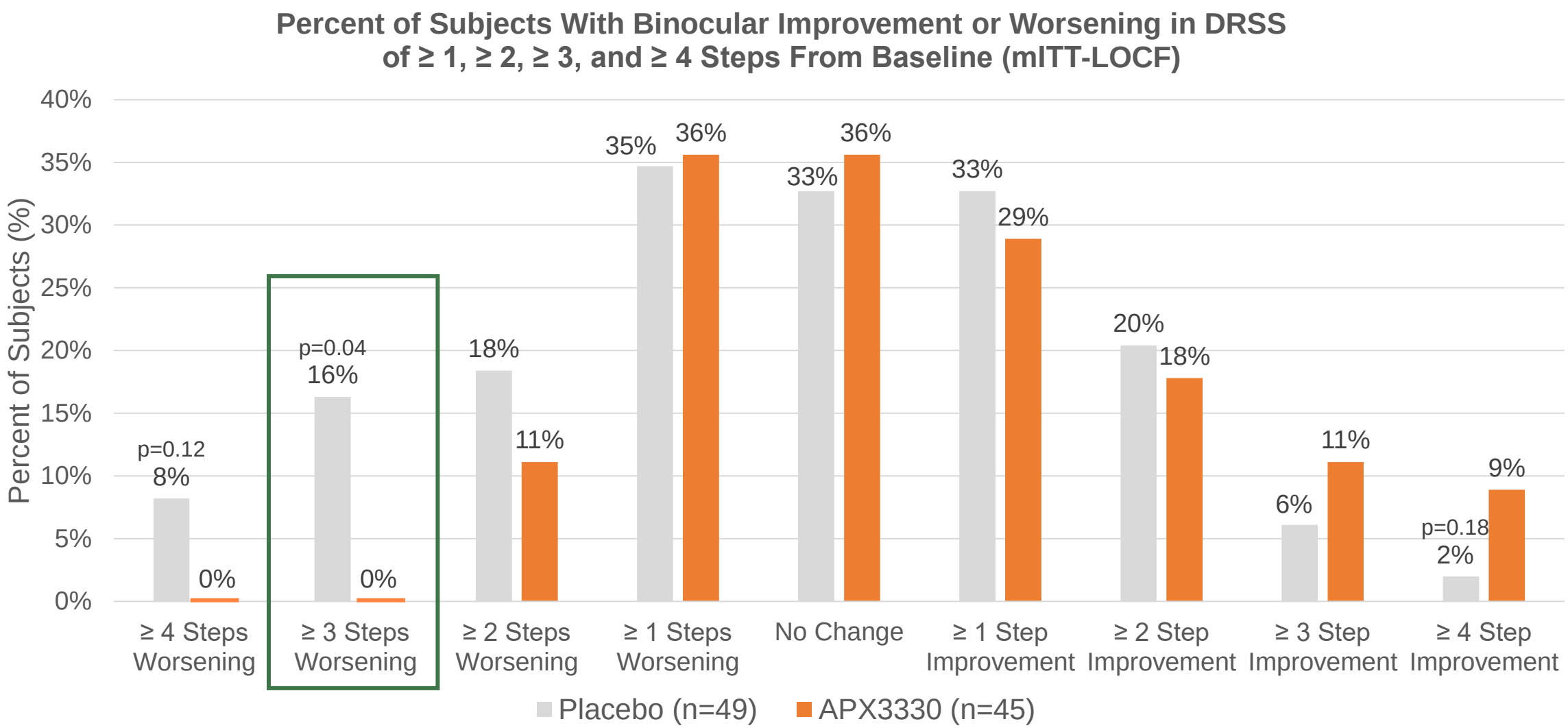
Recent preliminary discussions with FDA indicate binocular ≥ 3-step DRSS worsening (i.e., sum of right and left eye change in DRSS) could be acceptable for registration

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

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.
Source: ZETA-1 Clinical trial

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

APX3330 Demonstrated Statistical Efficacy on the Planned Phase 3 Registration Endpoint

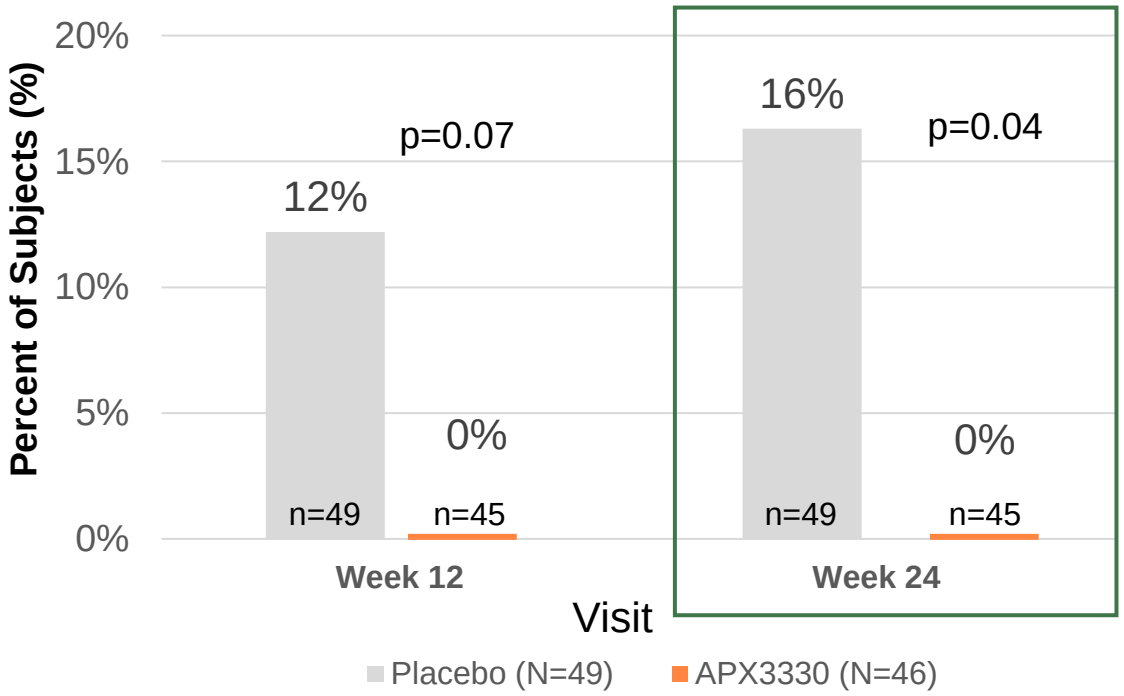


Source: ZETA-1 Clinical Trial; p values shown if p<0.20

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

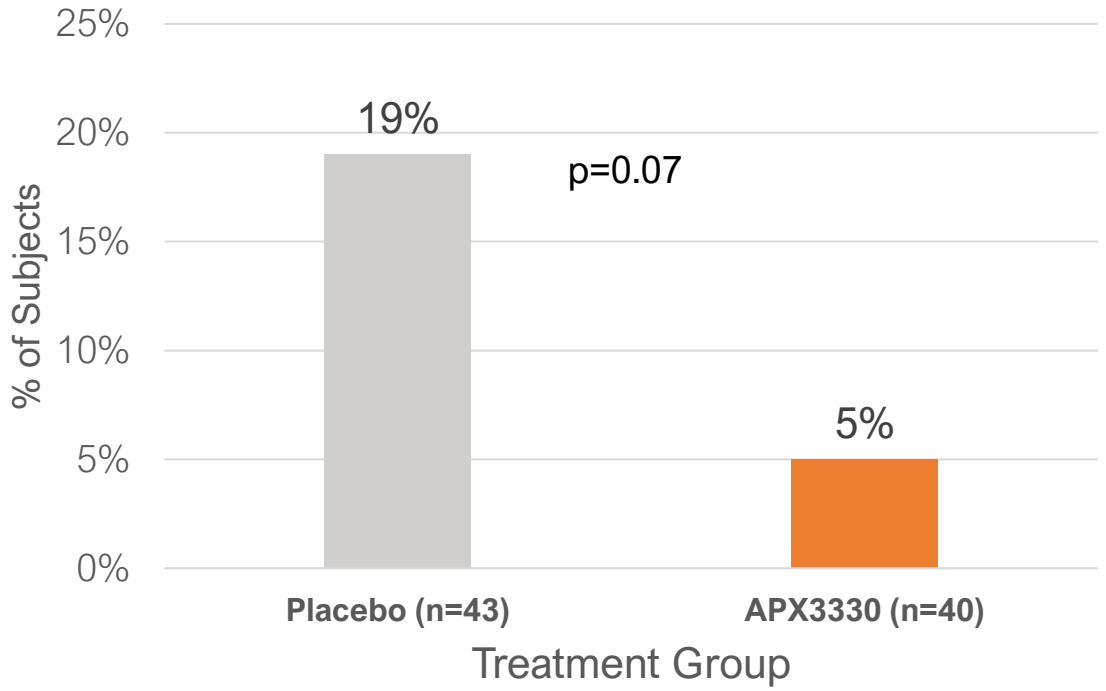
APX3330 Prevented Progression of Structural Retinal Abnormalities and Reduced Worsening of Visual Function

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 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			
Eye disorders			
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%)

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

APX3330 Safety Profile:

- **Limited AEs, most mild in severity**
- AEs similar to or less than placebo (except for pruritis/rash)
- Few serious treatment-related AEs, all unrelated to study medication
- No ocular AEs other than expected DR progression
- No effect 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 !!!