WOMEN IN OPHTHALMOLOGY
EMPOWERING ASPIRATIONS

Presenter:
Priya Vakharia, MD

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

WIO 2023

Disclosures

Priya Vakharia, MD

Consultant: Ocuphire

Equity options:

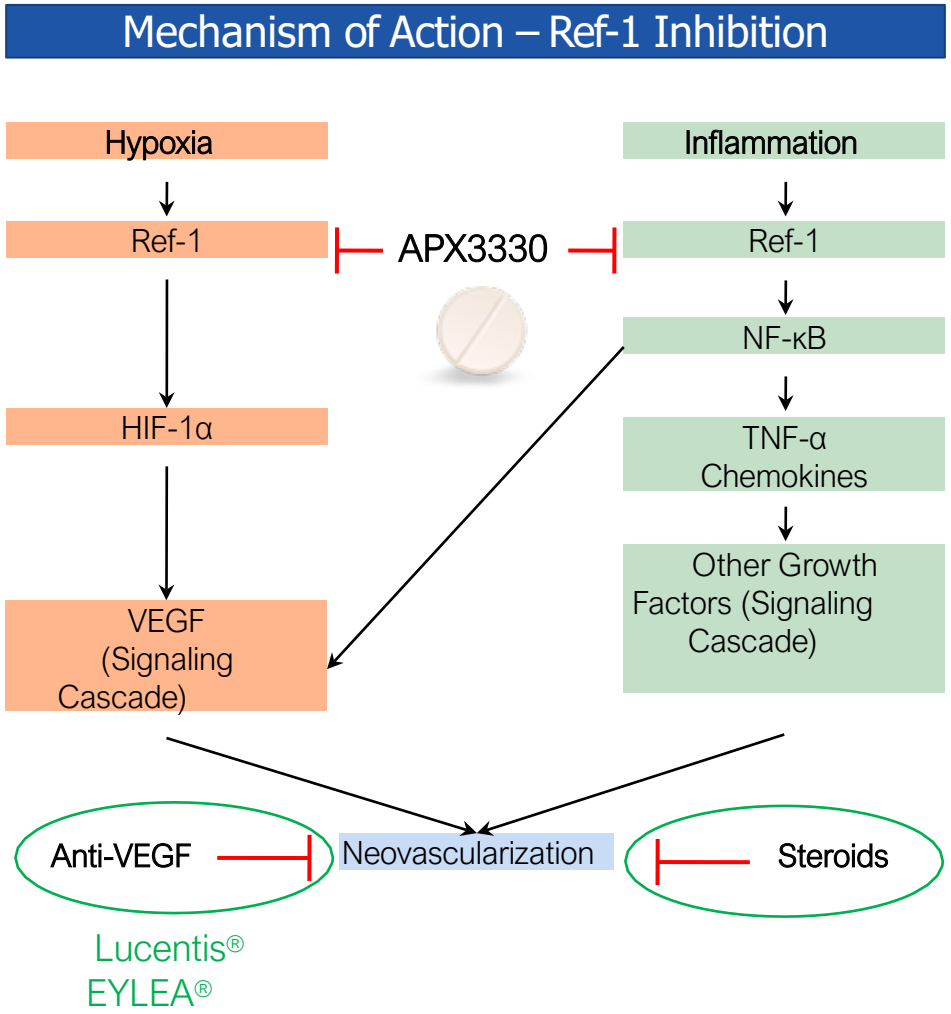
Grants:

Speaker:

All relevant financial relationships have been mitigated.

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), a novel target for retinal diseases, is a transcription factor regulator of angiogenesis (VEGF) and inflammation (NFkB)
- **Unique dual MOA decreases abnormal angiogenesis and inflammation**
- **Anti-VEGF injections *do not* target inflammation**
- Previously developed by Eisai for hepatic inflammatory indications and by Apexian for solid tumors in **11 Phase 1 and 2 trials**
- Extensively studied in over **20 in-vitro and animal studies** with favorable efficacy and safety

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

Eligibility Criteria

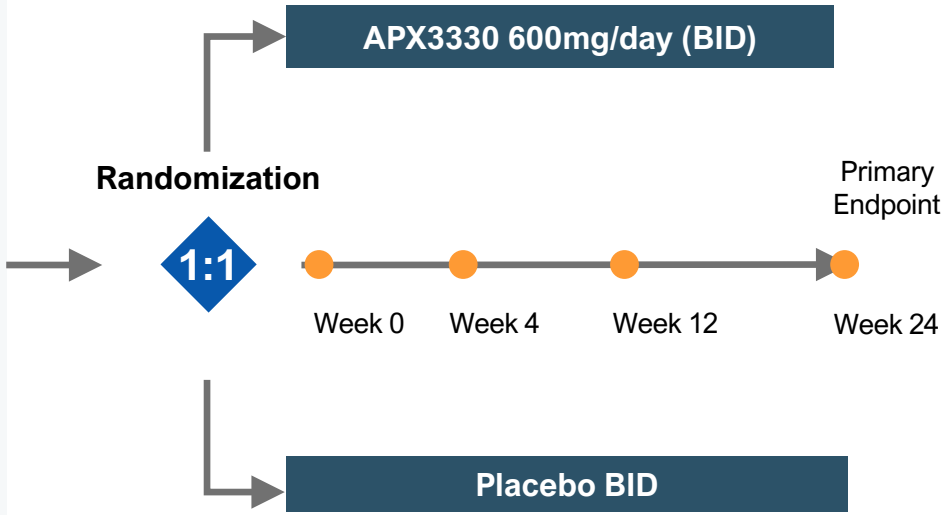
- 25 US sites
- N = 90-100 participants with moderately severe to severe NPDR or mild PDR (DRSS 47, 53, 61)

Key inclusion:

- ≥ 18 years of age
- DRSS 47, 53, or 61
  - Noncentral DME permitted
- ETDRS BCVA ≥ 60 letters (20/63)

Key exclusion:

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



Endpoints

Primary:

- % subjects with ≥ 2 step improvement on DRSS (Diabetic Retinopathy Severity Scale[1]) at week 24

Secondary:

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

Exploratory:

- Inflammatory cytokines

103 subjects enrolled (FPFV Apr 2021 to LPLV Aug 2022)
Topline announced in early 2023

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

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	77	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

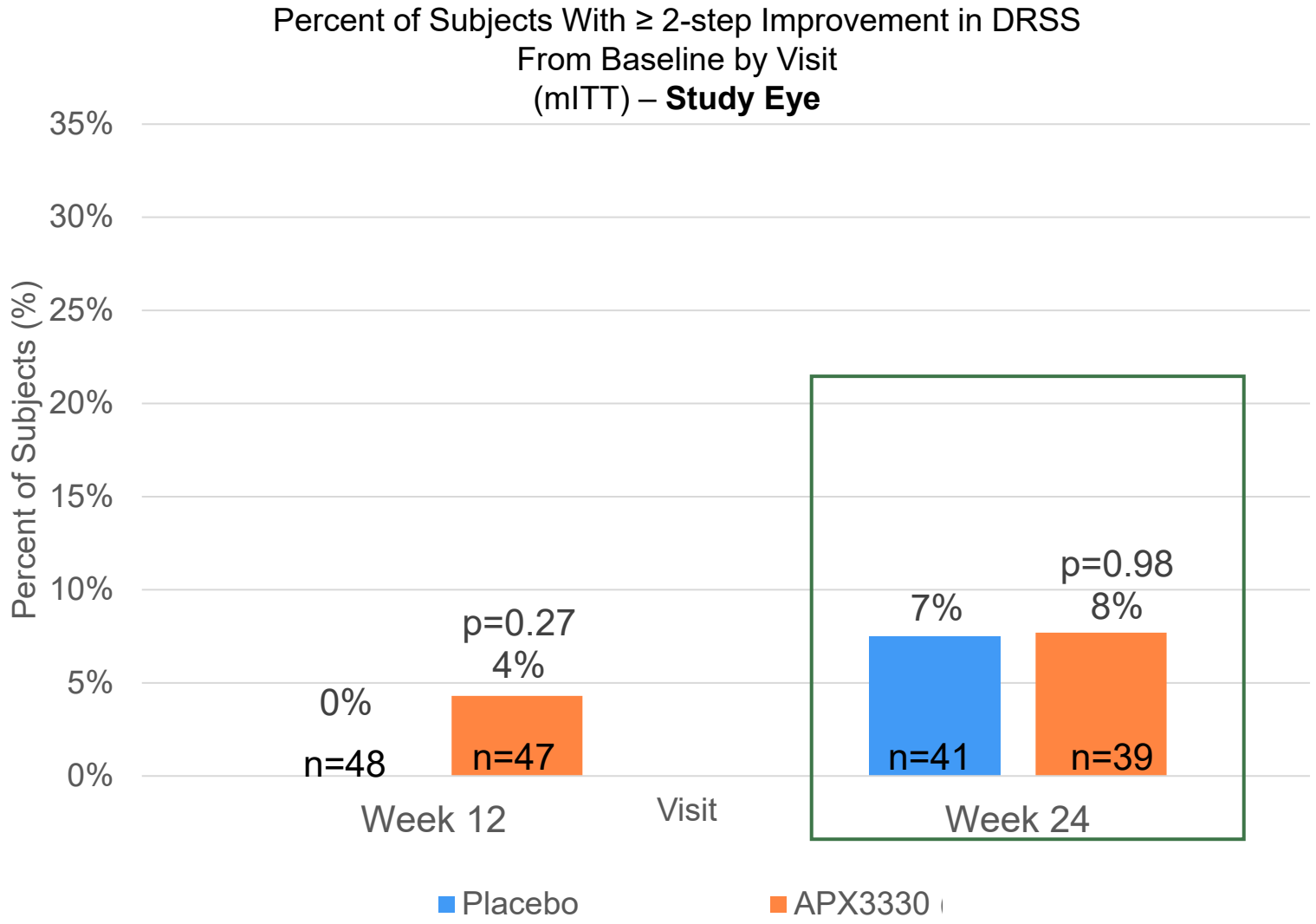
	APX3330 n=51	Placebo n=52	Total n=103
BCVA Study Eye *Letters (mean)*	**81**	**78**	**80 (20/25 Snellen)**
BCVA Fellow Eye *Letters (mean)*	76	77	77 (20/32 Snellen)
OCT CST Study Eye *(µm)*	**270**	**271**	**271**
OCT CST Fellow Eye *(µm)*	292	286	289
Intraretinal Fluid in the Center of SE	Y – 21 N – 26	Y – 12 N – 31	Y – 33 N – 57
Intraretinal Fluid at the Foveal Center of SE	Y – 1 N – 20	Y – 1 N – 11	Y – 2 N – 31
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)



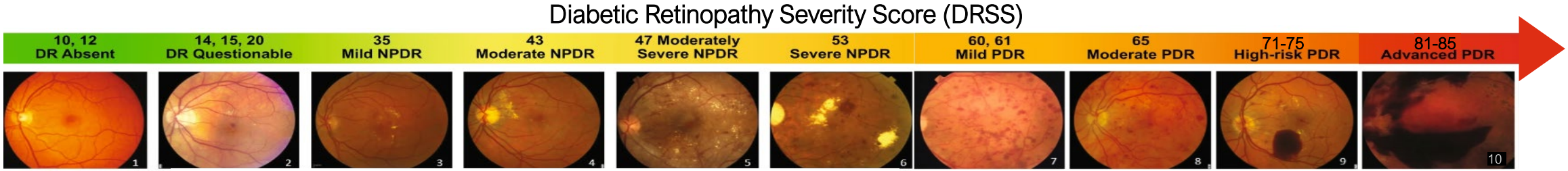
Source: ZETA-1 Clinical Trial

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

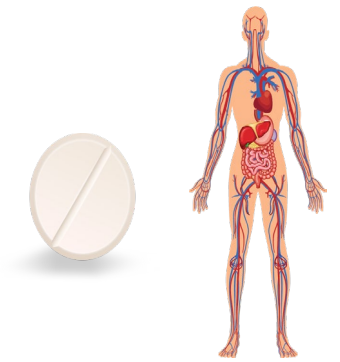


Research Opportunities

Report From the NEI/FDA Diabetic Retinopathy Clinical Trial Design and Endpoints Workshop

Prashant Nair,[1] Lloyd Paul Aiello,[2] Thomas W. Gardner,[3] Lee M. Jampol,[4] and Frederick L. Ferris III[5]

[1]Washington, DC, United States
[2]Joslin Diabetes Center, Boston, Massachusetts, United States
[3]University of Michigan, Ann Arbor, Michigan, United States
[4]Northwestern University, Chicago, Illinois, United States
[5]National Eye Institute, Bethesda, Maryland, United States



Systemic Drugs

- "Dr. Chambers reminded the gathering that the FDA is willing to consider both prevention and regression of DR as potential outcome measures…."
- " The anatomic endpoints that the FDA considers acceptable final-not surrogate-endpoints of drug trials are improvement of DR; prevention of DR progression…"

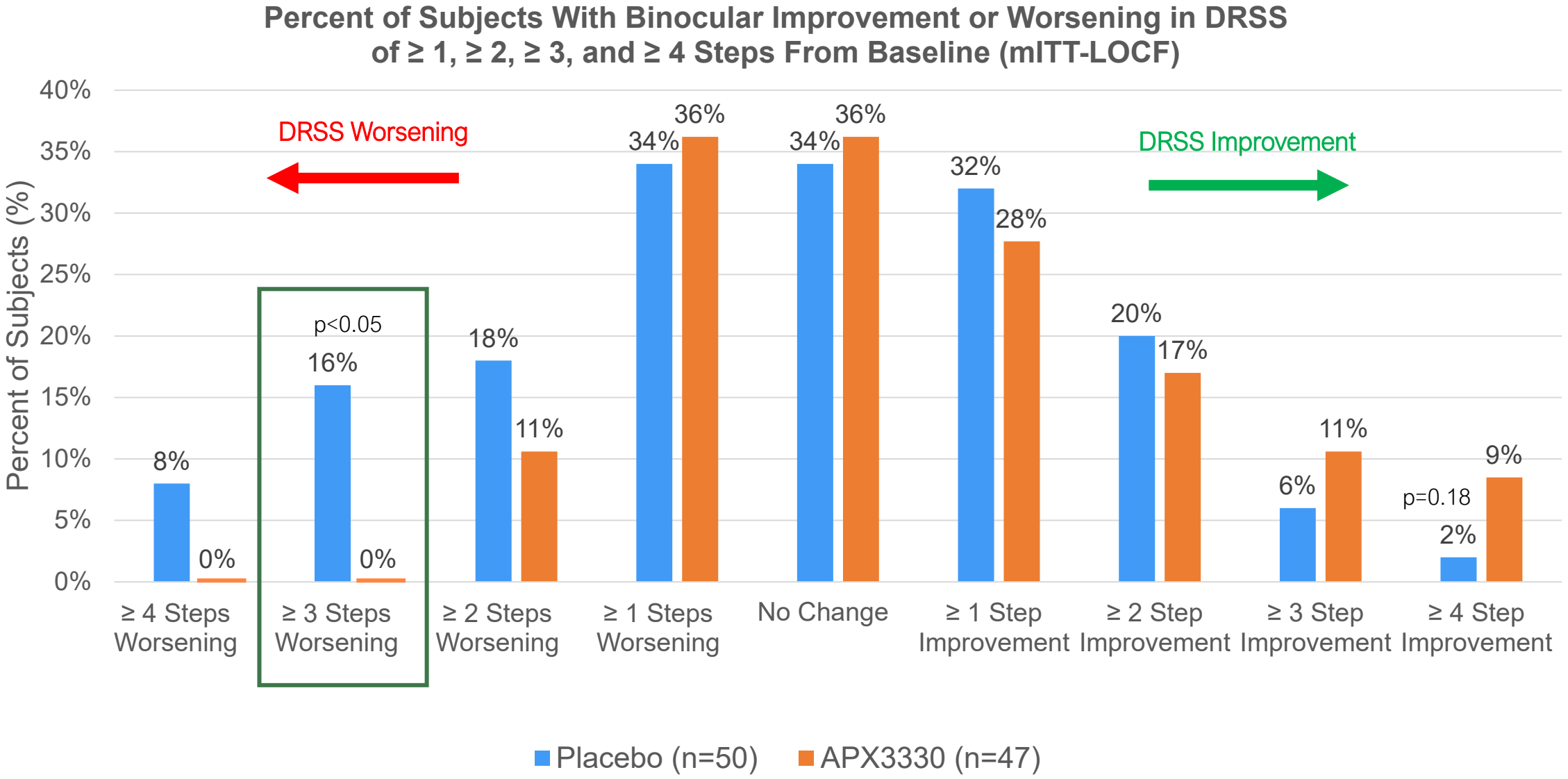
- End-of-Phase 2 meeting with FDA in 2H 2023 to align on binocular ≥ 3-step DRSS worsening (i.e., sum of right and left eye change in DRSS) as an acceptable primary endpoint for registration.
- This endpoint is distinct from historical anti-VEGF IVT precedent due to different delivery

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

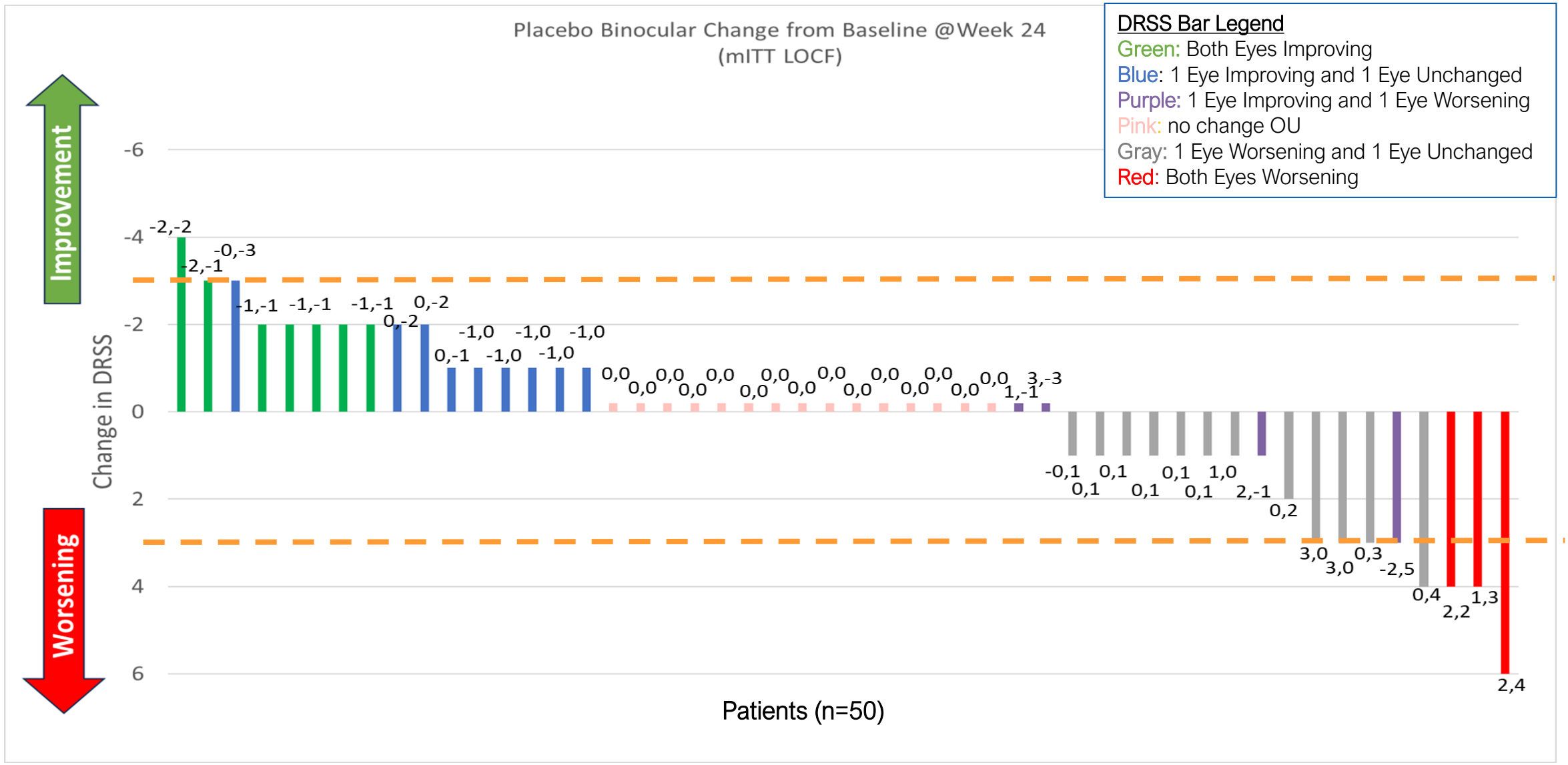
APX3330 Demonstrated Statistical Efficacy on the Pre-Specified, Planned Phase 3 Registration Endpoint



Source: ZETA-1 Clinical Trial; p values shown if p<0.20
Table 14.2.2.7, March 2023

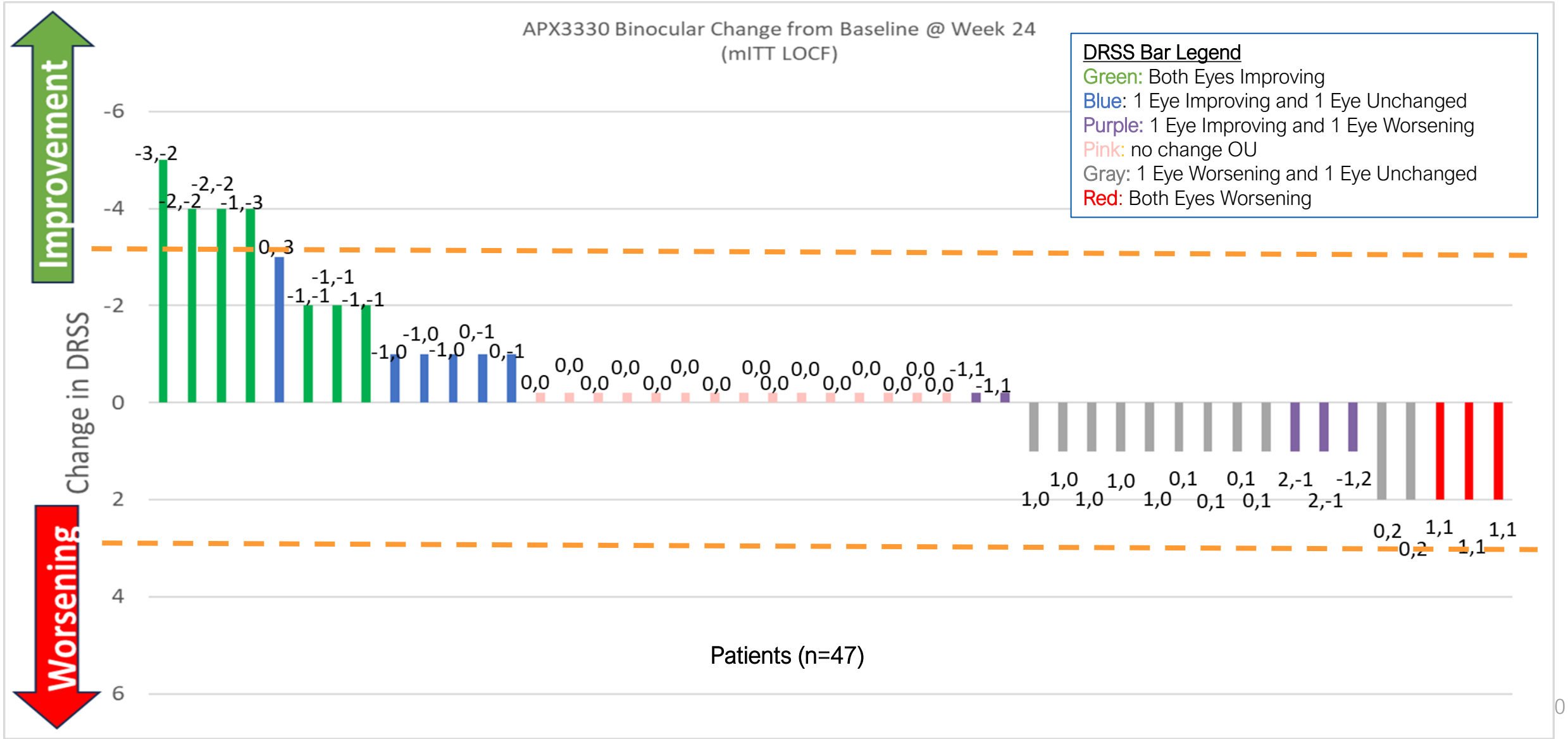
Change in DRSS Score by Patient by Eyes

16% Patients in Placebo Treatment Group had Binocular 3-Step Worsening



Change in DRSS Score by Patient by Eyes

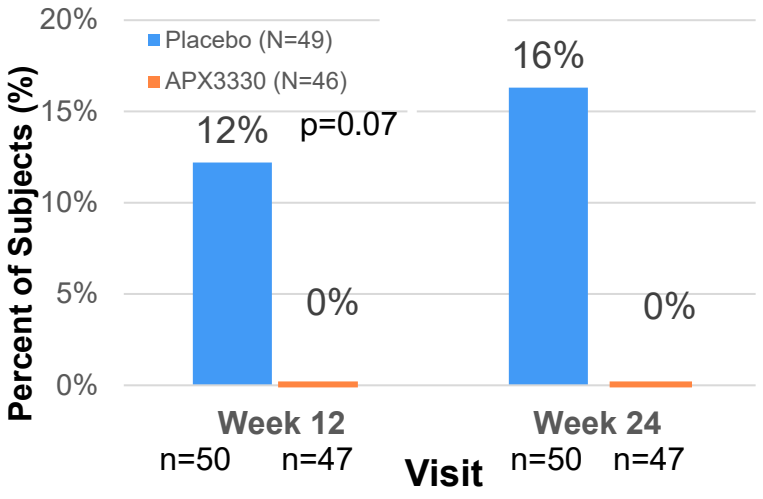
0% Patients in APX3330 Treatment Group had Binocular 3-Step Worsening



% of Subjects With Binocular ≥ 3-Step Worsening in DRSS and Progression to PDR

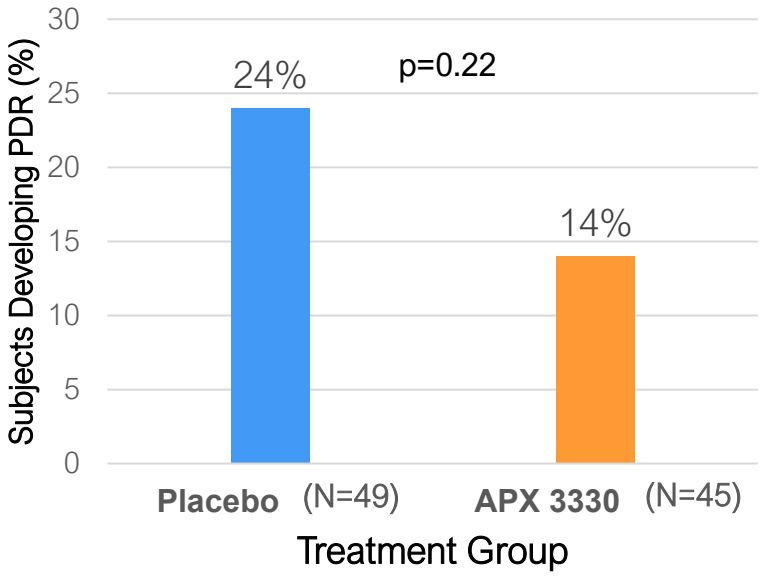
APX3330 Prevented Progression of Structural Retinal Abnormalities

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



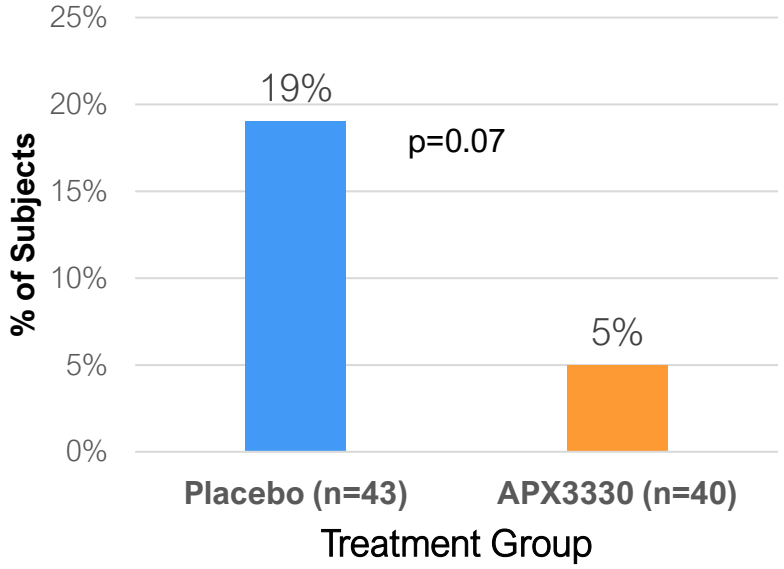
It is estimated ~25% of untreated patients may progress by ≥ 3 steps in binocular DRSS over 1 year[1]

Percentage of Subjects Developing PDR (mITT Population) at week 24



APX3330 reduced the percentage of subjects who developed PDR over the course of 24 weeks

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



BCVA data shows **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.

Summary of Efficacy

- APX3330 is a 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 or improvement of DRSS score*
- Prevention of worsening is a clinically meaningful endpoint
  - *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*
- **End-of-Phase 2 meeting is confirmed with FDA for 4Q 2023 to agree on registration endpoint and study parameters for Phase 3**

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