Bascom Palmer Eye Institute
UNIVERSITY OF MIAMI HEALTH SYSTEM

Angiogenesis, Exudation, and Degeneration 2023

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Efficacy and Safety Data for APX3330, a Novel Oral Drug Candidate for DR/DME from the ZETA-1 Phase 2b Trial

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Disclosures

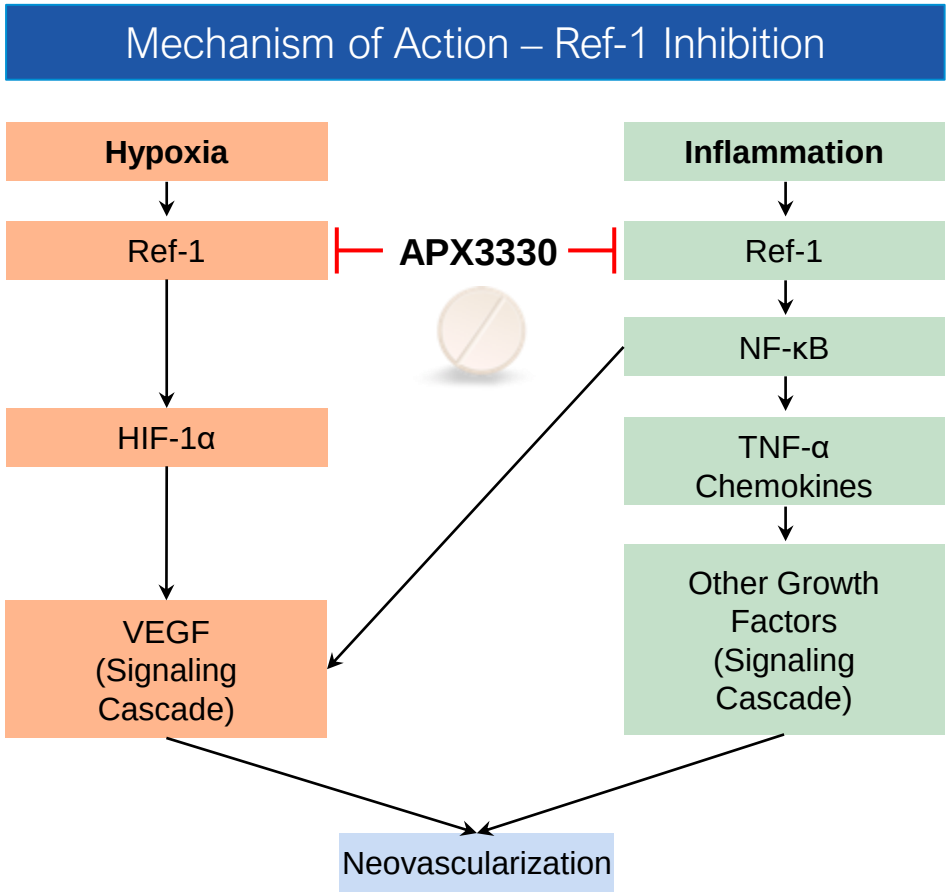
- Aerie, AffaMed Therapeutics, Allegro, Allergan, Allgenesis, Alnylam Pharmaceuticals, Alzheon, Annexon Biosciences, AsclepiX, Aviceda, Bayer, Bausch and Lomb, Biogen Idec, Bionic Vision Technologies, Boerenger Ingelheim, Carl Zeiss Meditec, Clearside Biomedical, DelSiTech, Dompe, DTx Pharma, Duet Therapeutics, Eyepoint, Eyevensys, Galecto Biotech, Galimedix, Gemini Therapeutics, Glaukos, Innovent, iRenix, IvericBio, jCyte, Kanaph Therapeutics, Kanghong, Kera Therapeutics, Kodiak, Kriya Therapeutics, LensGen, Nanoscope Therapeutics, Novartis , Ocugenix, Oculis, Ocuphire, OcuTerra Therapeutics, Omeros, Oxurion, Palatin, Regeneron, RegenxBio, Retinal Sciences, Retrope, Roivant, Samsung Bioepis, SGN Nanopharma Inc., Stealth Biotherapeutics, Stuart, Sustained Nano Systems, Takeda, Théa, 2020 Onsite

Take Home Messages

- APX3330 is a first-in-class oral drug being developed for DR
- APX3330 targets Ref-1 which plays a role in signaling under both ischemic and inflammatory conditions, both of which are relevant to DR
- Potential approvable endpoint for systemic (oral) drugs for DR treatment
  - Binocular ≥ 3-step improvement or prevention of worsening of DRSS
    - In contrast to IVTs, systemic drugs treat both eyes, and thus, the response of both eyes needs to be considered
    - Prevention of worsening is a clinically meaningful endpoint
- APX3330 demonstrated efficacy and favorable safety & tolerability in patients with diabetic retinopathy
- Results from ZETA-1 Phase 2 trial in DR and EOP2 FDA meeting guidance will inform the design of Phase 3 registration trials

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 and Ocuphire's Scientific Advisor for APX program
- APX3330 is a small molecule **oral drug candidate** and a first-in-class inhibitor of Ref-1
- **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
- APX3330 previously developed by Eisai for multiple hepatic inflammatory indications and later by Apexian for advanced solid tumors in **11 Phase 1 and 2 trials**

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

Key Eligibility Criteria in ZETA-1

Oral Medication Provides Binocular Treatment; DME Allowed in Fellow Eye

Inclusion	Exclusion
• Males or non-pregnant females ≥ 18 years of age • At least one eye with DR **DRSS 47, 53, or 61, confirmed by a central reading center)** in which PRP and intravitreal injections of an anti-VEGF agent can be safely deferred for ≥ 6 months in the opinion of the Investigator • **BCVA assessed by ETDRS protocol letters score of ≥ 60 letters (Snellen equivalent 20/63 or better) in the study eye** • Body mass index (BMI) between 18 and 40 kg/m^2, inclusive	• Retinopathy from causes other than diabetes in study eye • Presence of **center involved diabetic macular edema (DME) defined as a central subfield thickness (CST) ≥ 320 µm on SD-OCT** – **Center involved DME in the fellow eye is allowed** • Prior treatment in study eye with focal/grid laser photocoagulation within the past year, PRP at any time, **systemic or intravitreal anti-VEGF agents within last 6 months in study eye** • Intraocular steroids including triamcinolone and dexamethasone implant within the last 6 months • Fluocinolone implant within the last 3 years • HbA1c ≥ 12.0% • Clinically significant systemic disease (e.g., uncontrolled diabetes, myasthenia gravis, cancer, hepatic, renal, endocrine, or cardio-vascular disorders) that might interfere as deemed by Investigator

Source: ZETA-1 Clinical trial

DR/DME ZETA-1 Phase 2 Design

Randomized, Double-Masked, Placebo-Controlled 24-Week Trial (Similar To Eylea® Phase 3 DR Trial)

ZETA-1

25 US sites

90-100 participants with moderately severe-to-severe NPDR or mild PDR

Noncentral DME is permitted in study eye and central DME allowed in fellow eye

Eligibility Screening

1:1

Randomization

APX3330 600mg/day (BID)

Placebo BID

Primary Endpoint

Week 0 *Week 4* *Week 12* *Week 24*

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

103 Subjects Enrolled (FPFV Apr 2021- 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*
- DRSS improvement ≥1, ≥2, ≥3*
- 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*

NPDR = non-proliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy
ZETA-1 Clinical Trial is Sponsored by Ocuphire Pharma; Eylea® is registered trademark of Regeneron

ZETA-1: Baseline Demographics and Systemic Characteristics

Well-Balanced Across Arms

	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 (%) **African American** n (%) **Asian** n (%) **Other** n (%)	40 (78%) 5 (10%) 3 (6%) 3 (6%)	41 (79%) 6 (12%) 1 (2%) 0 (0%)
Ethnicity: Hispanic or Latino n (%)	28 (55%)	23 (44%)
Time (Years) Since Onset of Diabetes: Mean	15	16
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

Source: ZETA-1 Clinical Trial

ZETA-1: Baseline Ophthalmologic Characteristics

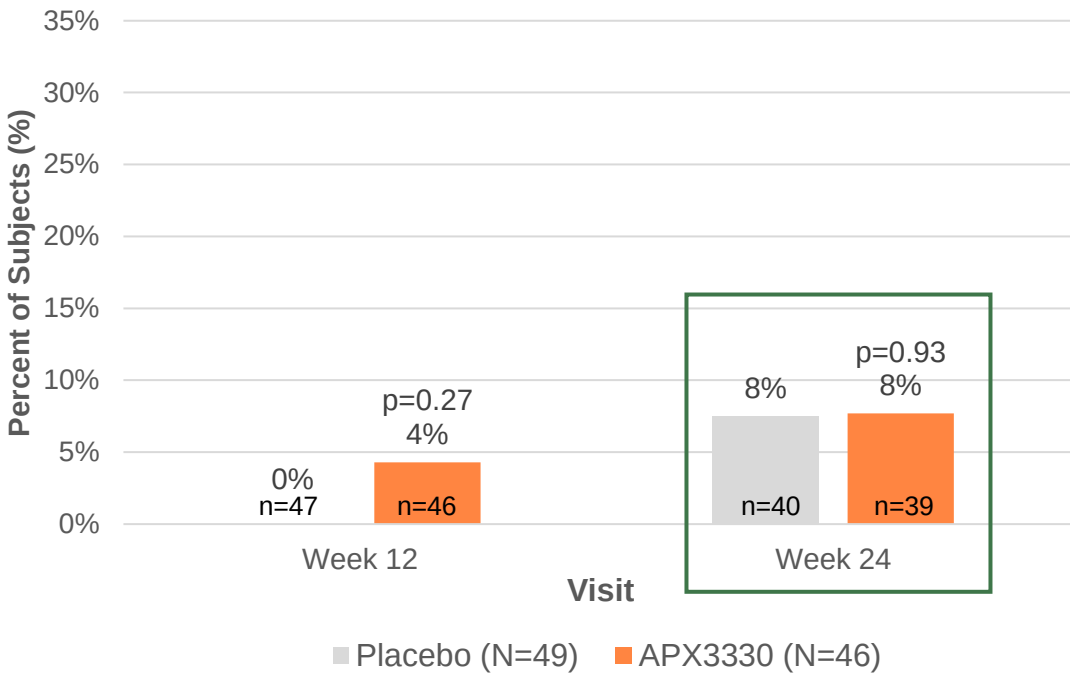
Well-Balanced Across Arms

	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%)**
BCVA letters in Study Eye Letters Read (mean)	**81**	**78**
BCVA letters in Fellow Eye *Letters Read (mean)*	76	77
OCT Central Subfield Thickness in Study Eye (µm)	**270**	**271**
OCT Central Subfield Thickness in Fellow Eye (µm)	292	286
Intraocular Pressure in Study Eye (mmHg)	15	16

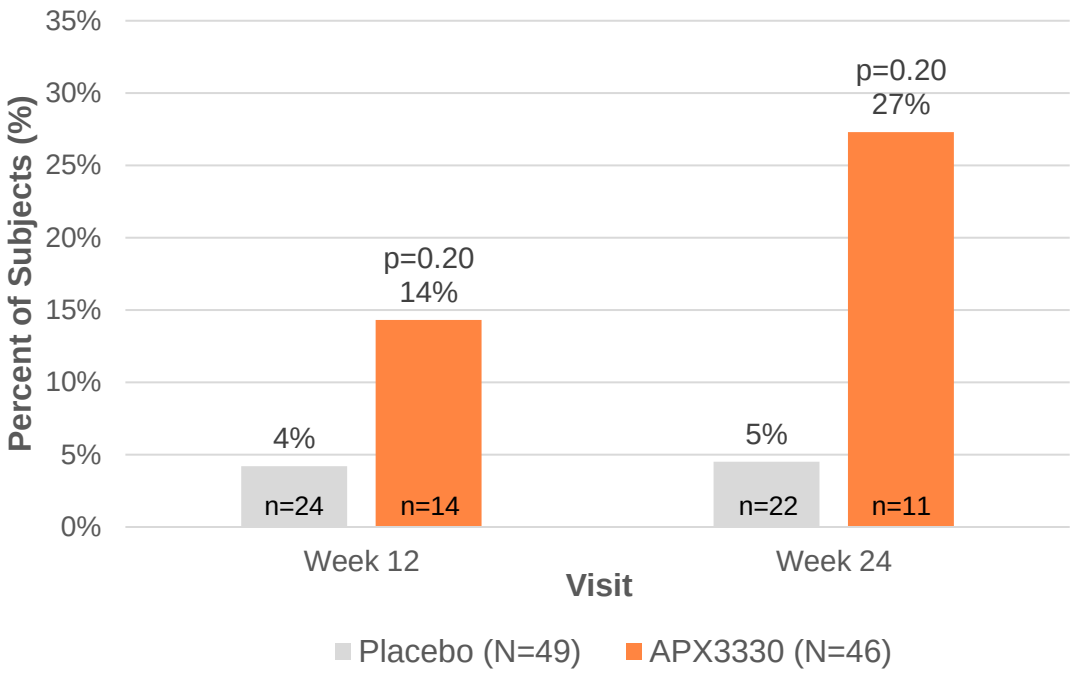
Percent of Subjects With ≥ 2-Step Improvement in DRSS in Study/Fellow Eye

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.

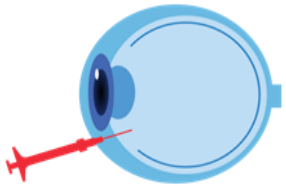
Note: Images from Central Reading Center will be reviewed prior to EOP2 FDA meeting

Clinically Meaningful Registration Endpoints in DR

Systemic Drugs Should Evaluate DRSS Change in Both Eyes

FDA accepts improvement OR worsening (prevention of progression)* of the disease AND DRSS is an established surrogate endpoint for DR

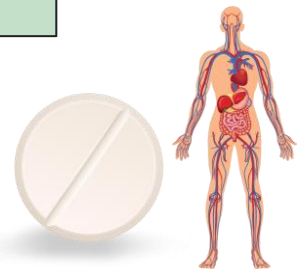
Local Drugs (Intravitreal Injections)



Precedent approvable endpoint for locally-delivered drugs (Non-Systemic) in DR:

- ≥ 2-step DRSS improvement in **study eye**
  - Aflibercept (PANORAMA trial)
  - Ranibizumab (RISE/RIDE/DRCR trials)

Systemic Drugs



Potential approvable endpoints for systemic drug in DR (to be confirmed at the EOP2 FDA meeting) include:

- ≥ 3-step **binocular** DRSS improvement
- ≥ 3-step **binocular** DRSS worsening

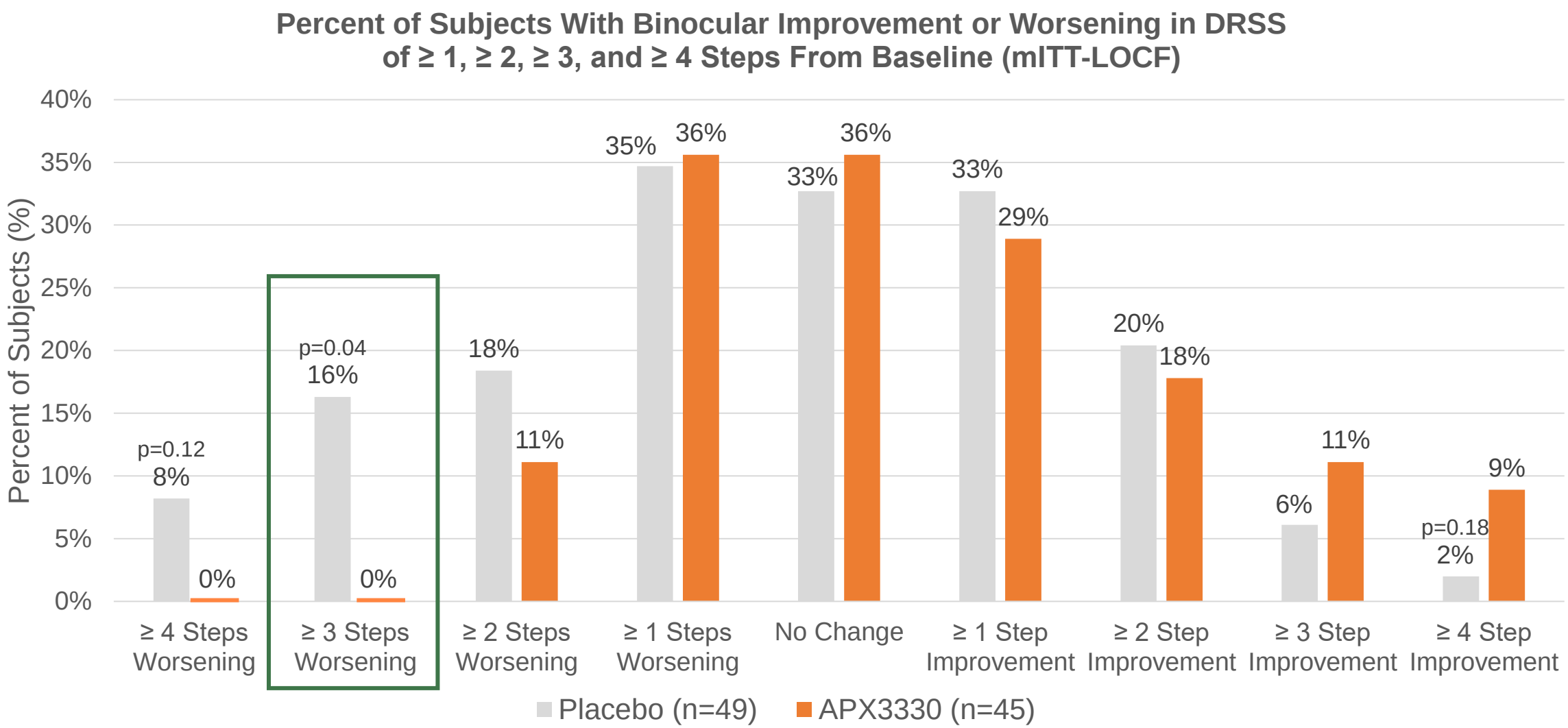
Recent preliminary discussions with FDA indicate binocular ≥ 3-step worsening in DRSS (i.e.,. sum of right and left eye change in DRSS) could be acceptable for registration; this endpoint is distinct from historical anti-VEGF IVT precedent due to different delivery

*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; Eylea® is registered trademark of Regeneron; Lucentis® is registered trademark of Roche/Genentech

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

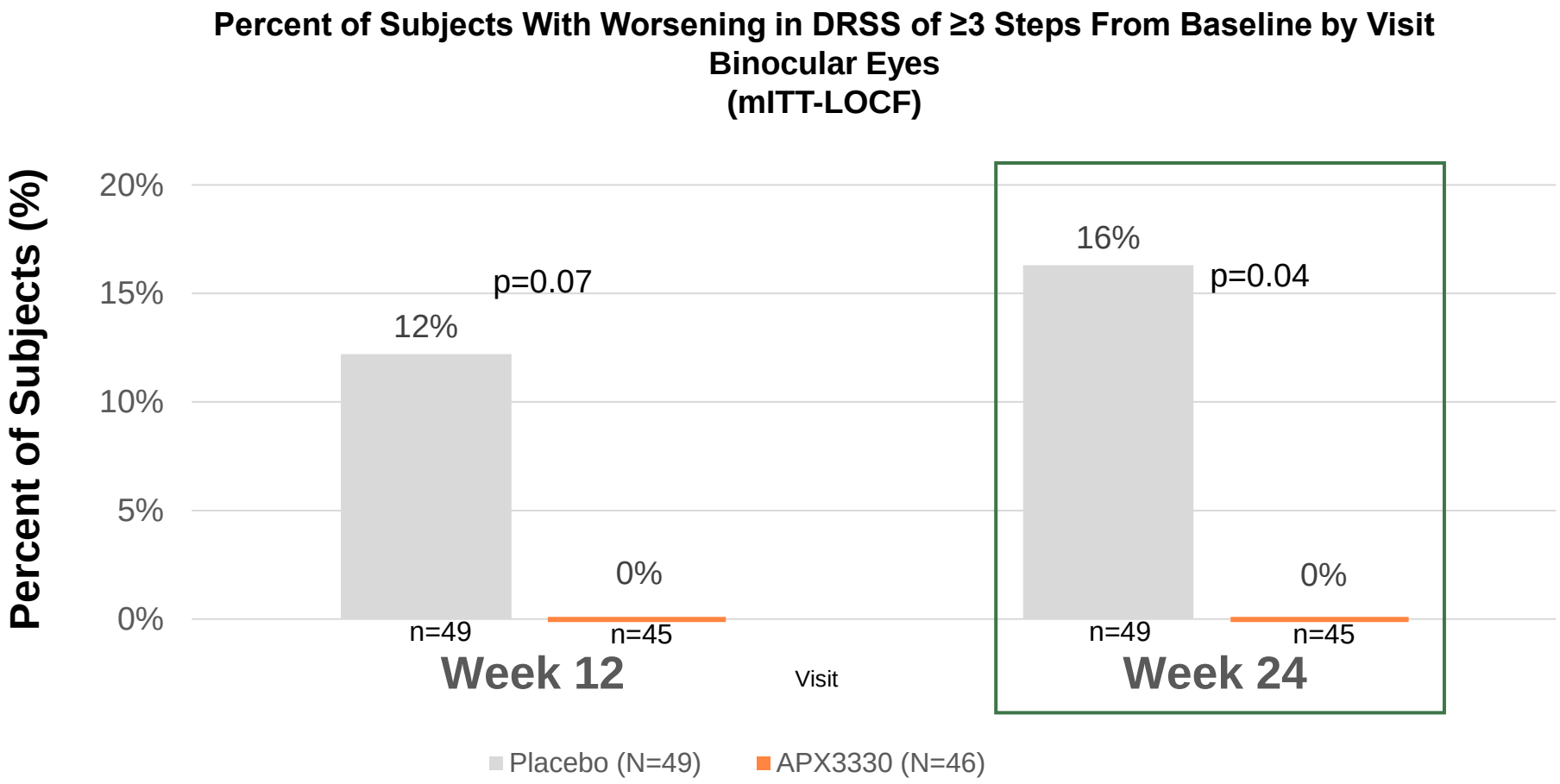
APX3330 Demonstrated Statistical Efficacy for the New Phase 3 Registration Endpoint



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

Percent of Subjects With Binocular ≥ 3-Step Worsening in DRSS

Selected Primary Registration Endpoint for Planned Phase 3, To Be Formally Confirmed at EOP2 FDA Meeting

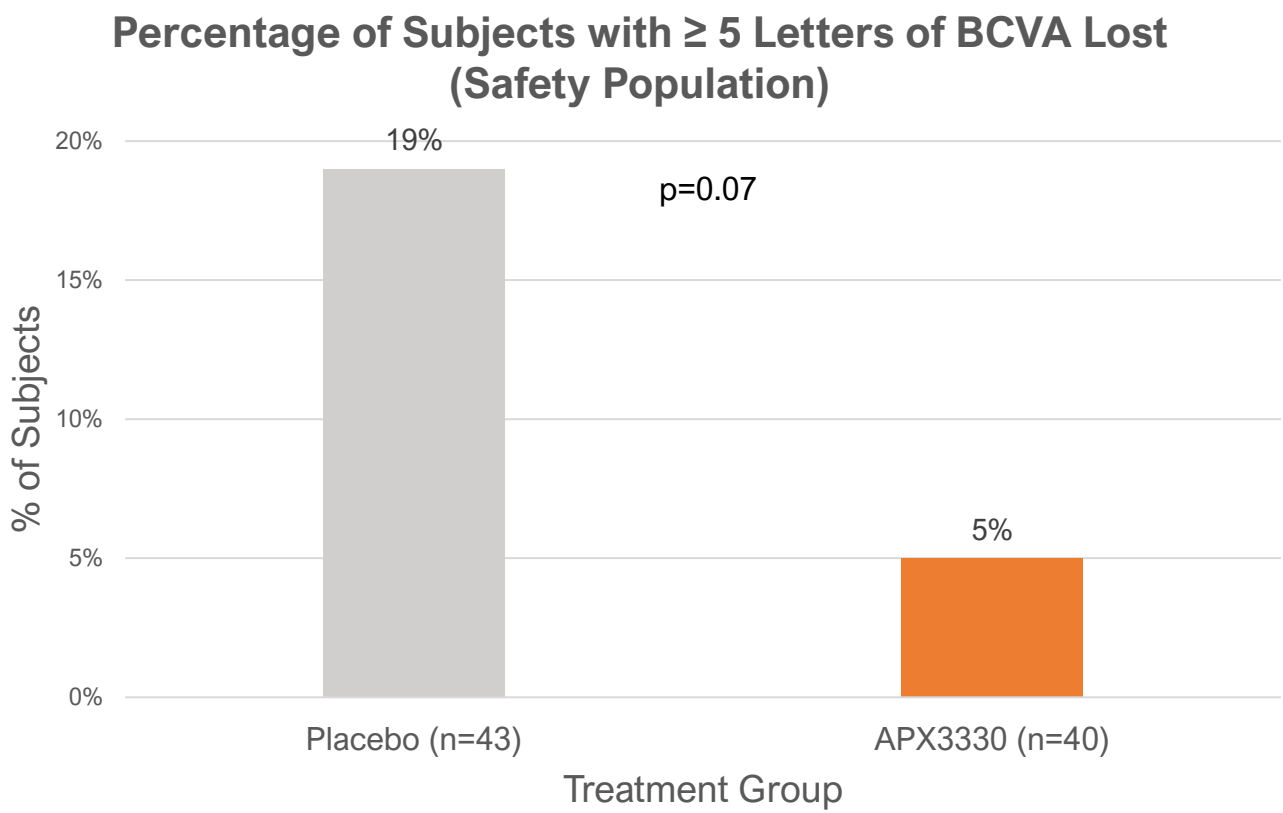


Based on extrapolation from ZETA-1, ~25% of patients may progress by ≥ 3 steps in binocular DRSS over 1 year if untreated

Source: ZETA-1 Clinical Trial
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.

Percentage of Subjects Losing ≥ 5 Letters BCVA from Baseline

Fewer APX3330 Treated Subjects Had a Decrease in BCVA At Week 24



Source: ZETA-1 Clinical Trial
Note: Images from Central Reading Center will be reviewed prior to EOP2 FDA meeting

ZETA-1 Overall Safety Findings

During the 24-Week Trial, Patients Continued Routine Medications to Manage Their Diabetes Comorbidities

103
Subjects Enrolled

91
Subjects completed thru week 24

211 Treatment Emergent AEs (64 Subjects)
91 (29 Subjects) APX3330, 120 (35 Subjects) Placebo

31
Treatment-Related AEs (in 21 Subjects)

APX3330
14 AEs in 10 subjects
(10 mild, 4 moderate, 0 severe)

Placebo
17 AEs in 11 subjects
(8 mild, 9 moderate, 0 severe)

4
withdrew due to an AE
2 APX, 2 PBO

5
lost to follow-up
2 APX, 3 PBO

3
withdrew consent or site closure
2 APX, 1 PBO

0
Treatment-Related AEs involving liver, heart, kidney, brain, lung, or vital signs

14 SAEs (in 11 Subjects)

3 unrelated SAEs in APX3330

11 unrelated SAEs in Placebo

Oral APX3330 safety profile consistent with that seen in prior trials

ZETA-1 Clinical Trial Safety Population (subject to final review)

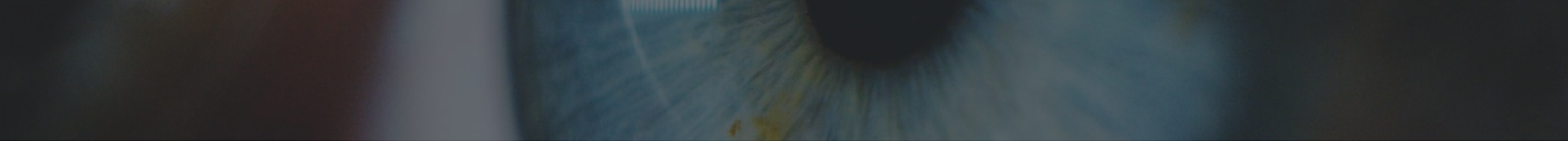
Summary

Key Takeaways

- APX3330 is the most advanced oral program in development for diabetic eye disease
- Recent preliminary discussions with FDA indicate prevention of ≥ 3-step worsening in binocular DRSS could be acceptable for registration for oral (systemic) drugs in DR
- ZETA-1 Phase 2 trial demonstrated a statistically significant reduction in the percentage of patients who lost ≥ 3-steps of binocular DRSS after 24 weeks of treatment (this potential Phase 3 registration endpoint):
  - 0% APX3330-treated patients had a binocular ≥ 3-step worsening of DRSS from baseline compared with 16% for placebo-treated patients (p=0.04)
- APX3330 demonstrated favorable safety and tolerability profile in diabetic patients
- Planning for EOP2 FDA meeting for APX3330 in DR indication to advance into Phase 3 trials

Goal

To have a clinically meaningful impact on ***preventing progression of DR*** to reduce likelihood of vision loss in diabetic retinopathy patients



Thank you to all the ZETA-1 study participants, investigators and their study staff

The Sponsor of ZETA-1 Clinical Trial is Ocuphire Pharma, Inc.
www.clinicaltrials.gov (NCT04692688)