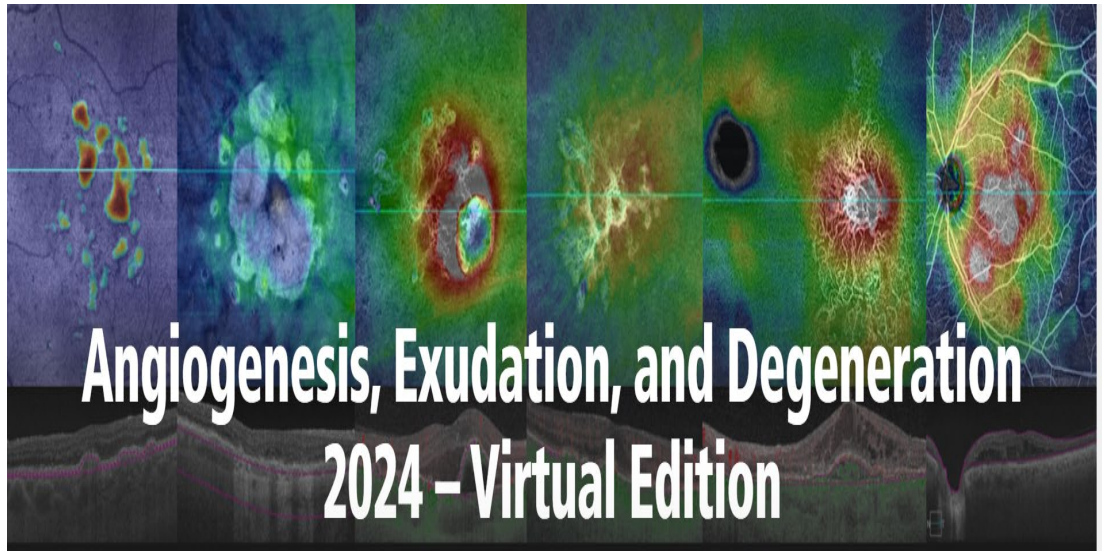

February 3rd, 2024

APX3330 Oral Treatment to Slow the Progression of Diabetic Retinopathy Using a Binocular DRSS Severity Scale as the Endpoint

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Disclosures

Speaker: Alimera, Apellis, Genentech, and IvericBio

Consultant: Genentech, Novartis, Alimera, EyePoint, IvericBio, Graybug, Apellis, Regeneron, Vial, **Ocuphire**, Unity

Contracted research: 4D Molecular Therapeutics, Abbie, Adverum Biotechnologies, Alimera Sciences, Allergan, Ashvattha Therapeutics, Chengdu Kanghong, Eyepoint Pharmaceuticals, Genentech, Gyroscope Therapeutics, i-Lumen Scientific, Ionis, IvericBio, Janssen Pharmaceuticals, NGM Biopharmaceuticals, Novartis, Ocular Therapeutix, OcuTerra, Olix, Opthea, Outlook, Oxurion, Recens Medical, Regeneron Pharmaceuticals, RegenXBio, RevOpsis, Roche, SalutarisMD, SamChungDang, Santen, Unity Biotechnology, Vanotech

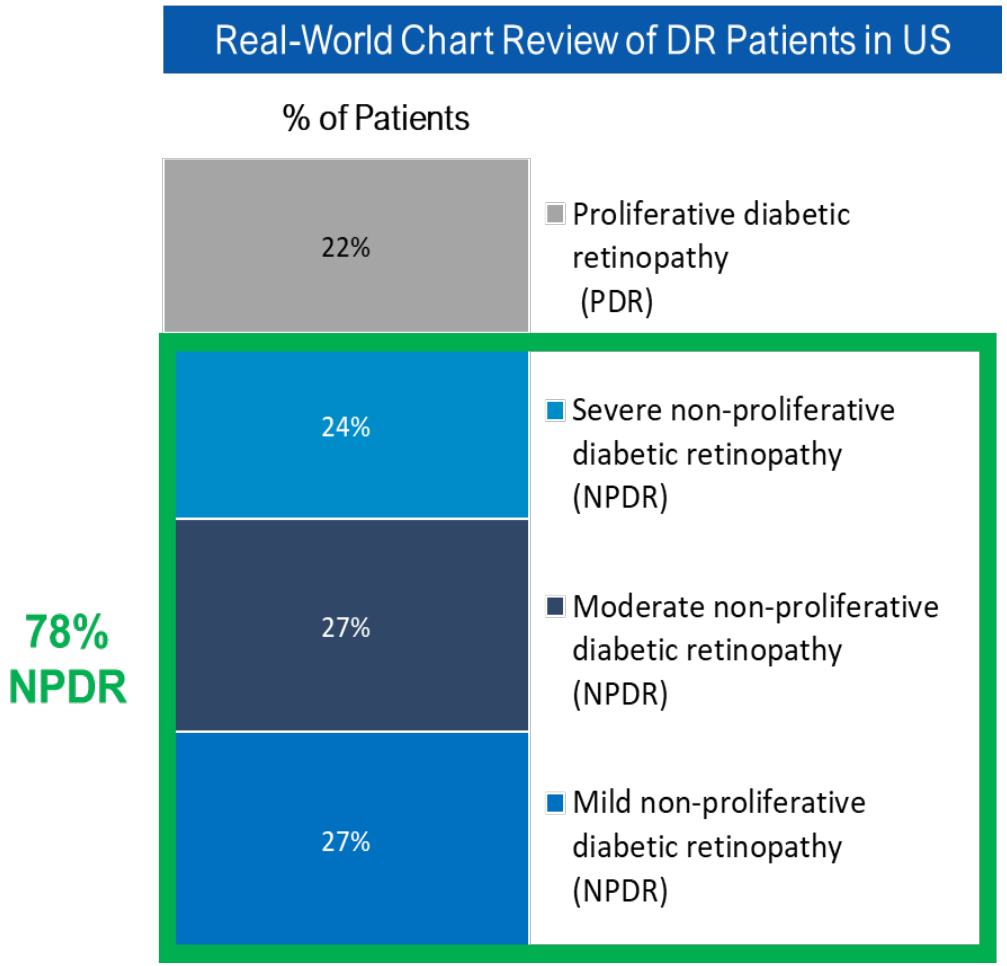
Background & Objectives

- Oral APX3330 is a small molecule REF-1 inhibitor that is being developed for the treatment of diabetic retinopathy

- Objectives:
  - To review the MOA of APX3330
  - Review Person-Level Scale – a new registration endpoint for oral therapies in retina
  - Update on plans for the Phase 3 program following an End of Phase 2 meeting with FDA

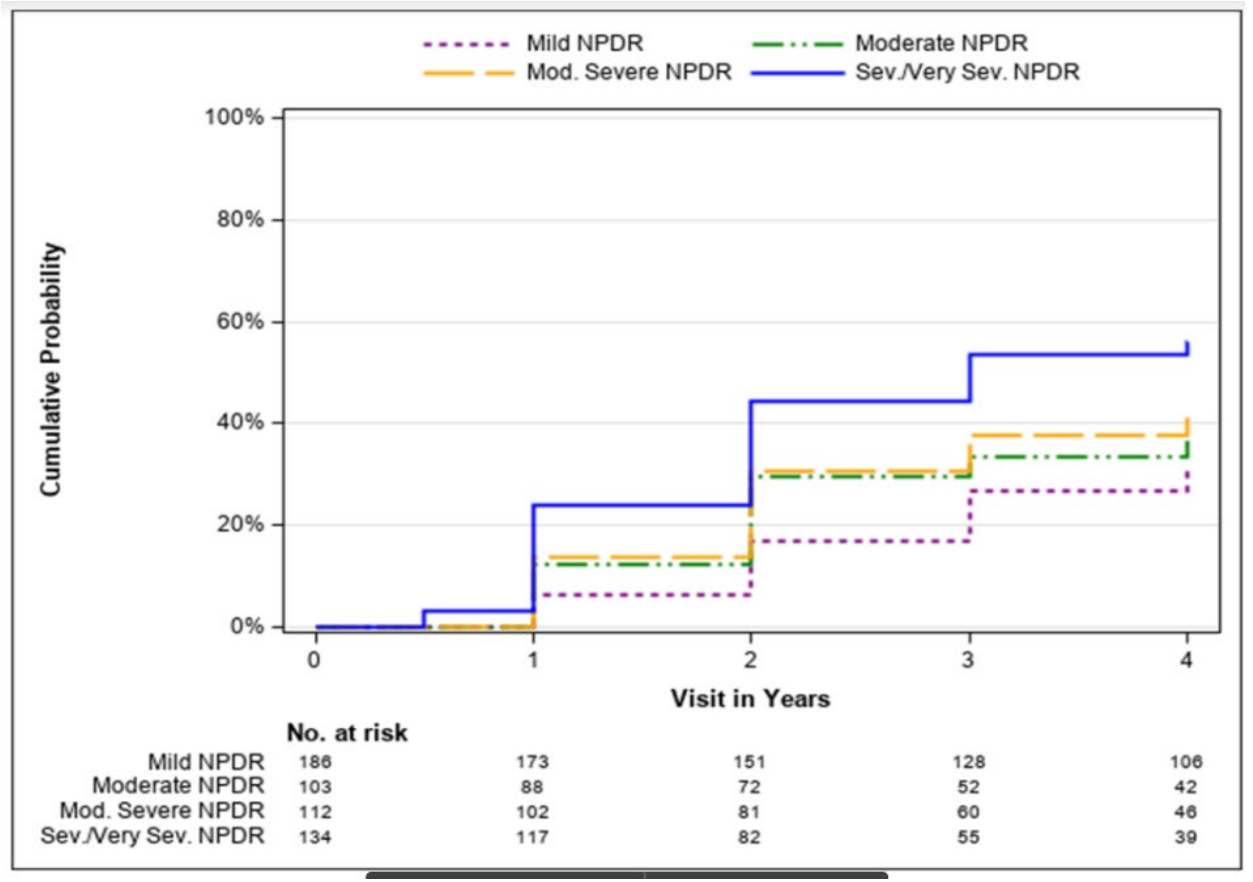
Early Intervention in NPDR Remains a High Unmet Need

Majority of DR is Non-Proliferative With a High Likelihood of Progression to PDR Over Time



American Diabetes Association; International Diabetes Federation; Healthline; *Ocuphire internal analysis and assumptions; Spherix Global Insights

DRCRNet Protocol AA
Progression to VTC Depends on DR Severity

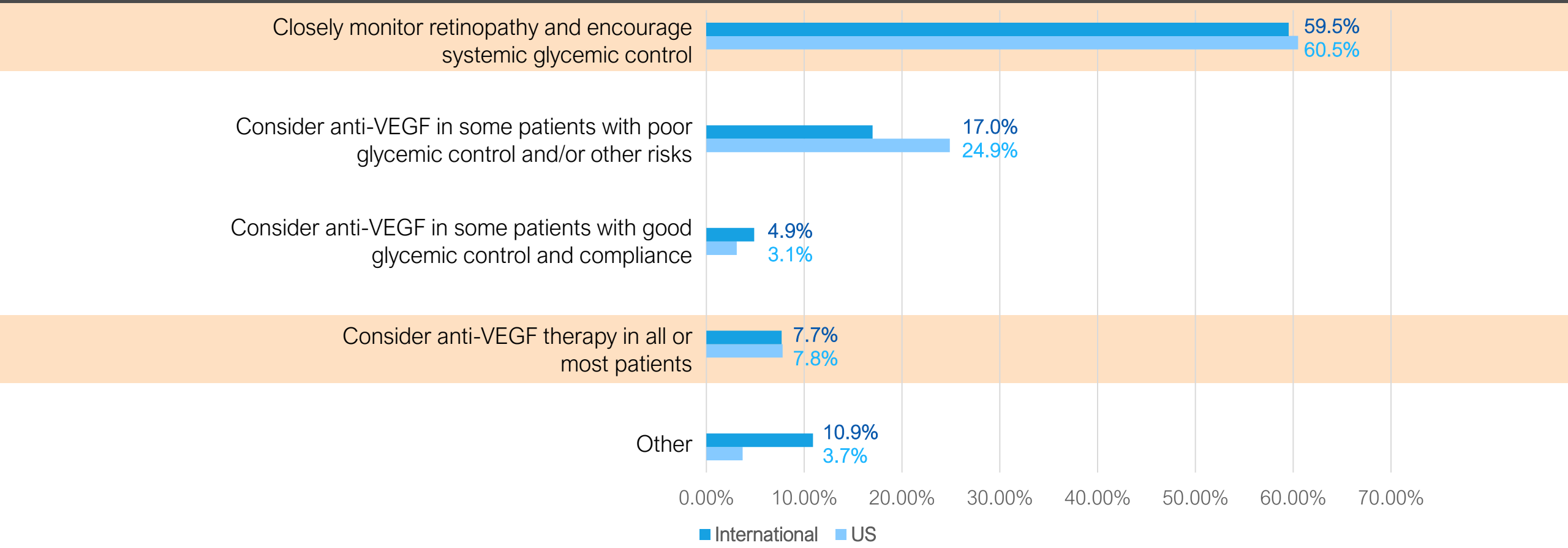


Source: DRCRNet Protocol AA

Majority of Physicians Use a "Wait and Monitor" Approach for NPDR

NPDR Patients Are Not Treated Proactively and Anti-VEGF Use is Limited

How do physicians treat patients with severe NPDR without DME?

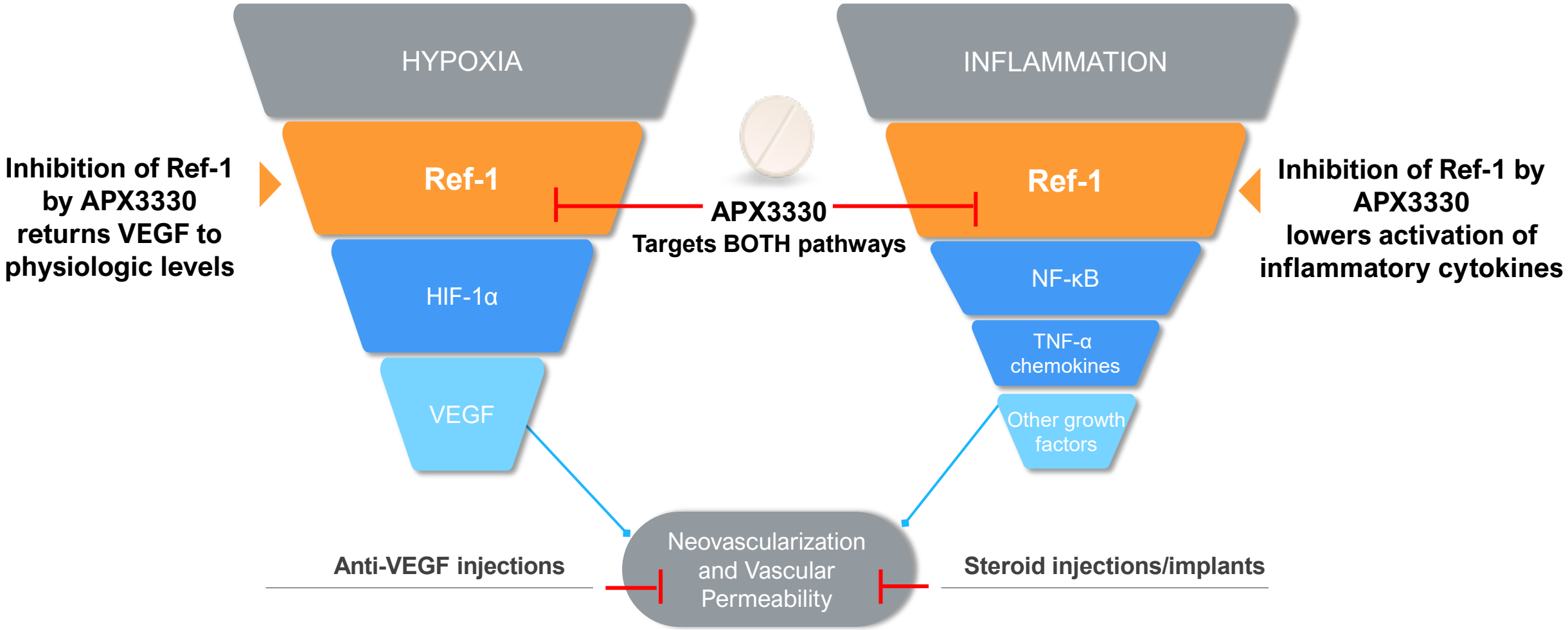


Source: ASRS 2021 Preferences and Trends (PAT) Survey

APX3330 History and Ref-1 Inhibition Mechanism

Ref-1 Involved in Key Pathways that are Upregulated in Diabetic Retinopathy and DME

Ref-1 regulates transcription factors involved in angiogenesis and inflammation



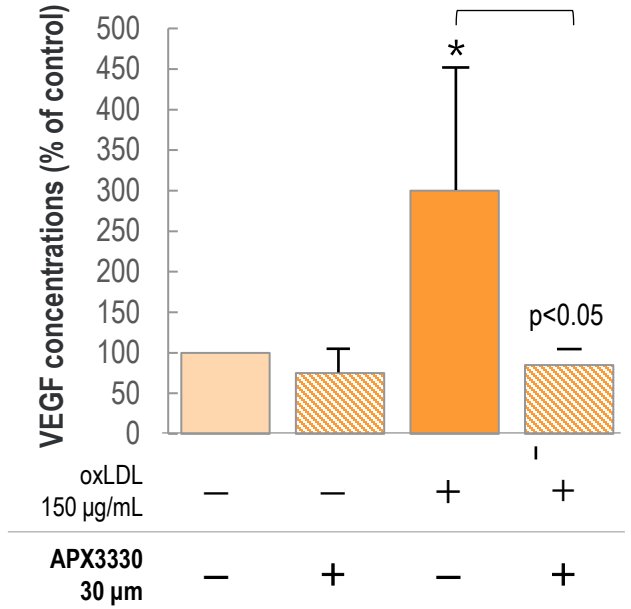
Inhibition of Ref-1 by APX3330 returns VEGF to physiologic levels

Inhibition of Ref-1 by APX3330 lowers activation of inflammatory cytokines

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

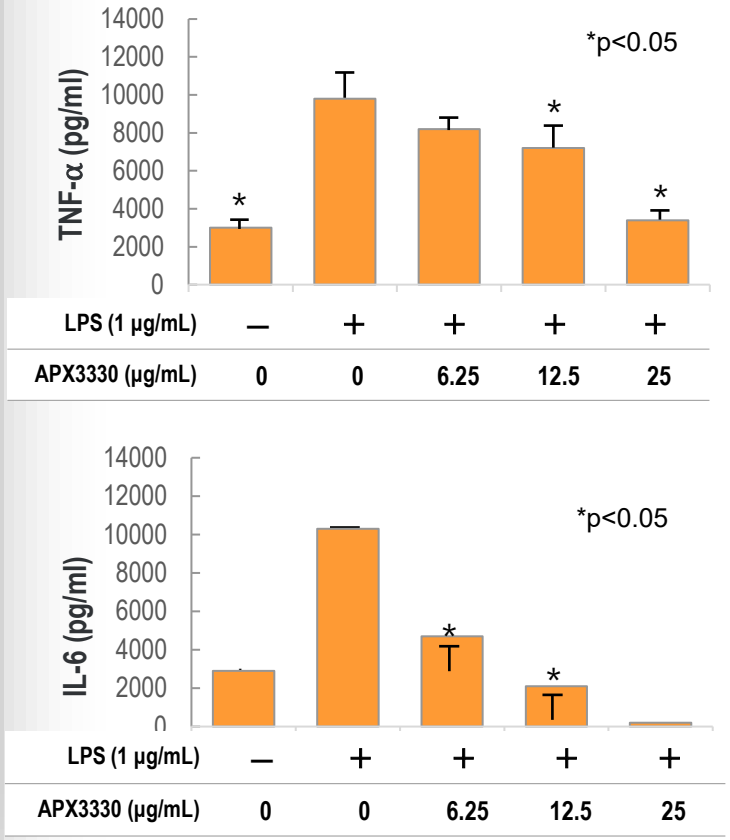
In vitro validation of APX3330 MOA

AXP3330 restores physiologic VEGF levels[1]

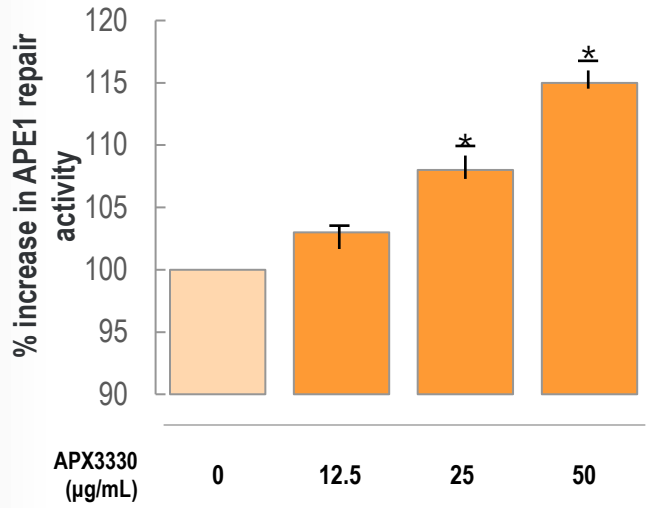


APX3330 significantly inhibited the overproduction of VEGF in ARPE-19 cells, protecting from oxidative stress

APX3330 reduces pro-inflammatory cytokines (in macrophages)[2]



APX3330 increases DNA oxidative repair and neuronal protection[3]



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

APE-1, apyrimidinic endonuclease 1; LPS, lipopolysaccharide; oxLDL, oxidized low density lipoprotein, TNF-α, tumor necrosis factor-alpha; IL-6, interleukin 6; VEGF, vascular endothelial growth factor.

1. Li Y, et al. *Redox Biology 2.* 2014;485-494. 2. Jedinak A, et al. *Anticancer Research.* 2011;379-386. 3. Fehrenbacher JC, et al. *Neuroscience.* 2017;16:23-35.

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

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

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

Eligibility Criteria

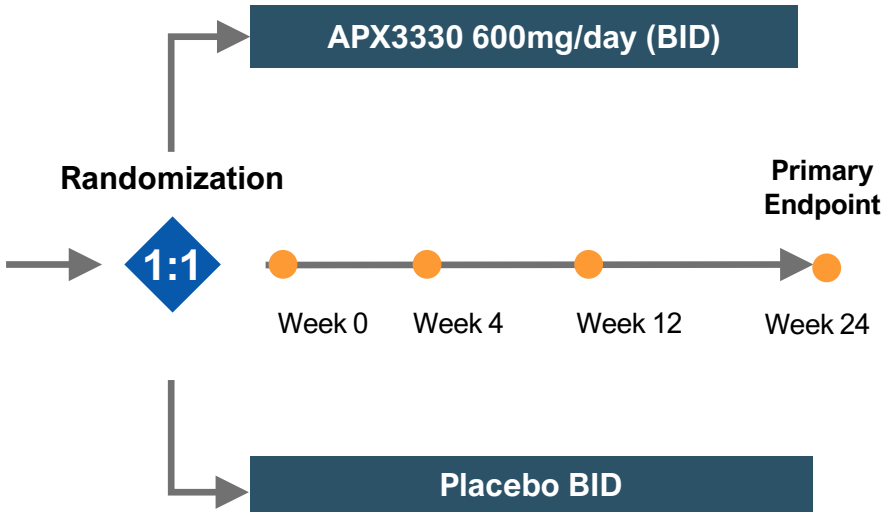
- 25 US sites
- N = 103 participants with moderately severe to severe NPDR or mild PDR (DRSS 47, 53, 61)

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 Visual Acuity (BCVA)
- DME fellow eye status
- Safety and tolerability

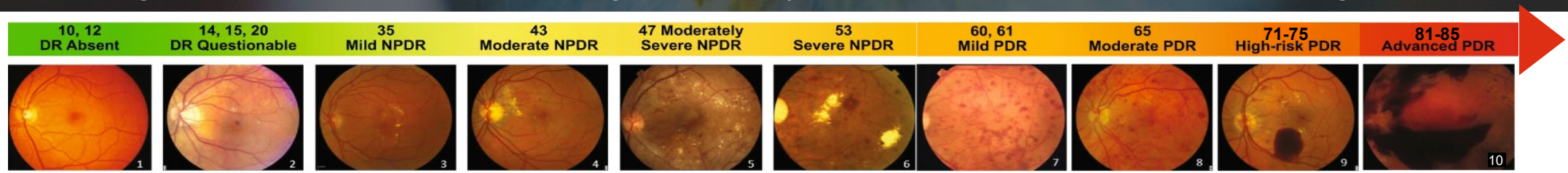
Exploratory:

- Inflammatory cytokines

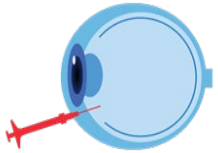
1. By Central Reading Center 2. Center-Involved DME in Fellow Eye is Acceptable 3. Includes Systemic or IVT VEGF
www.clinicaltrials.gov (NCT04692688);
NPDR = non-proliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy;

Clinically Meaningful Registration Endpoints in DR

*Systemic Drugs Should Evaluate DRSS Change in **Both** Eyes; Confirmed at EOP2 FDA Meeting - **November 2023***



FDA accepts improvement OR worsening (prevention of progression)[1] of the disease AND progression along DRSS is an established surrogate endpoint for increased risk of sight threatening disease

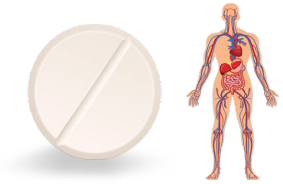


Local Drugs (Intravitreal Injections)

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

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

Systemic Drugs



Approvable endpoints for systemic drug in DR include either:

- ≥ 3-step DRSS improvement on a binocular person-level scale
- ≥ 3-step DRSS worsening on a binocular person-level scale

This endpoint is distinct from historical anti-VEGF IVT precedent due to different 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.

FDA Accepts the Binocular DRSS Person-Level Scale For Phase 3 APX3330 in DR

DRSS is a Validated Surrogate Endpoint; Person-Level Scale is used in the Landmark ACCORD Study

Level (worse eye/better eye)	Description	Scale Step
10/10	No DR	1
20/<20 20/20	Microaneurysms only, one or both eyes	2-3
35/<35 35/35	Mild NPDR, one or both eyes	4–5
43/<43 43/43	Moderate NPDR, one or both eyes	6-7
47/<47	Moderately severe NPDR, one eye	8
47/47	Moderately severe NPDR, both eyes	9
53/<53	Severe or very severe NPDR, one eye	10
53/53	Severe or very severe NPDR, both eyes	11
60 or 61/<60	Mild PDR and/or SPC, one eye	12
60 or 61/60 or 61	Mild PDR and/or SPC, both eyes	13
65/<65 65/65	Moderate PDR, one or both eyes	14-15
71+/<71 71+/71+	High risk PDR, one or both eyes	16-17+

In the binocular Person-Level Scale, the worse eye is weighted instead of calculating the sum of both eyes

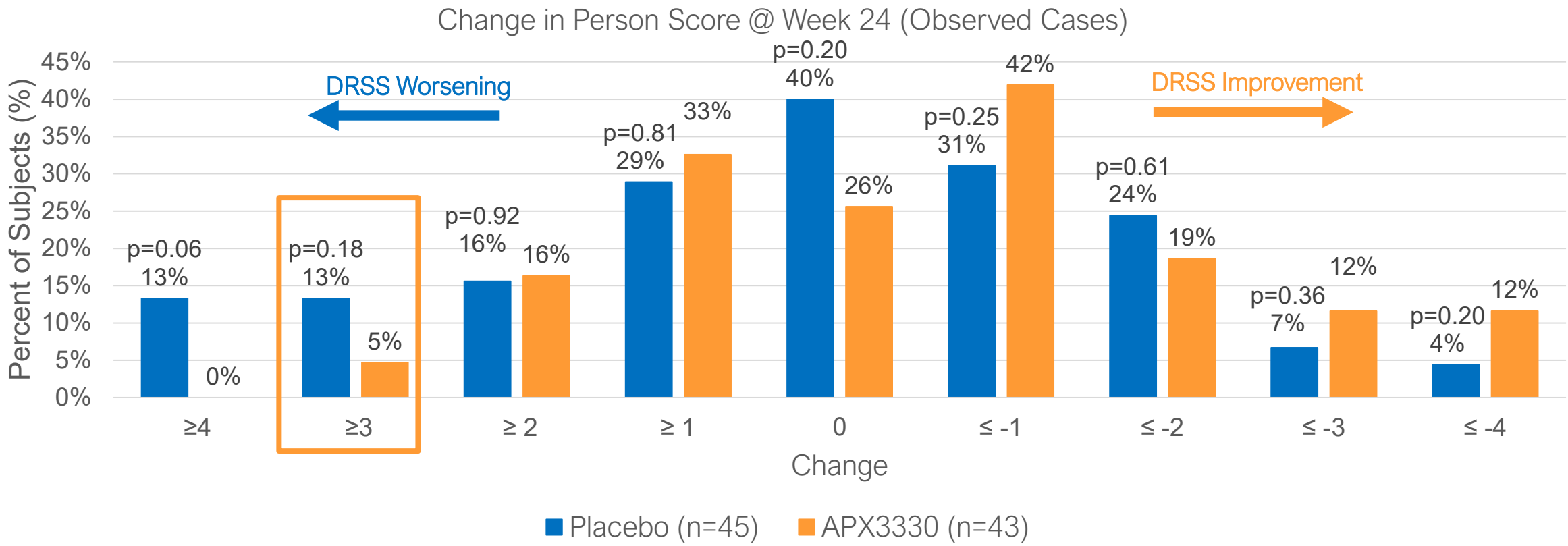
A 3-step change on this scale is considered clinically meaningful by FDA

Baseline 47,43 = Step 8

Final 53,53 = Step 11 **(3-step change)**

DR, Diabetic Retinopathy; FDA, Food and Drug Administration; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; Scars of photocoagulation (SPC),; US, United States; VEGF, vascular endothelial growth factor.

ZETA-1: Percent of Subjects with Improvement or Worsening in DRSS at Week 24 on the Binocular Person-Level Scale (Observed Cases)

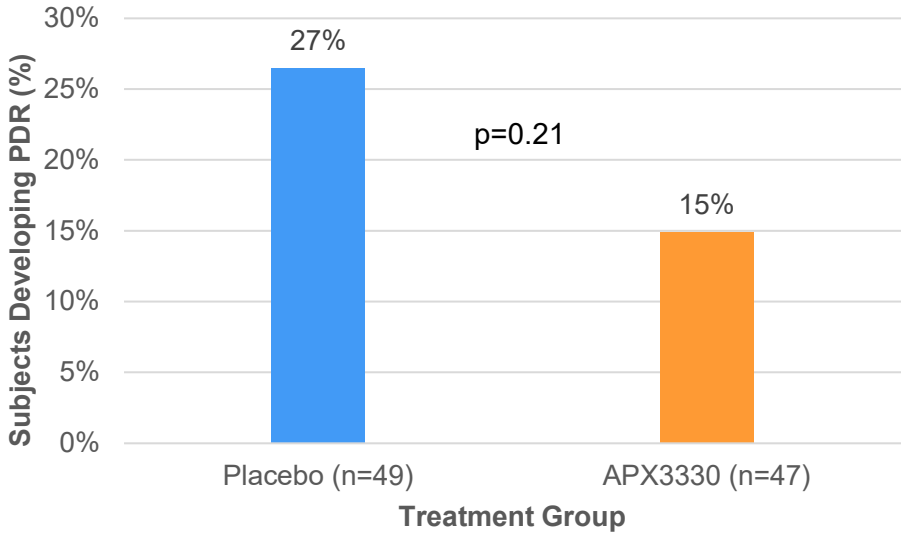


Source: Zeta 1 Table 14.2.2.9.2

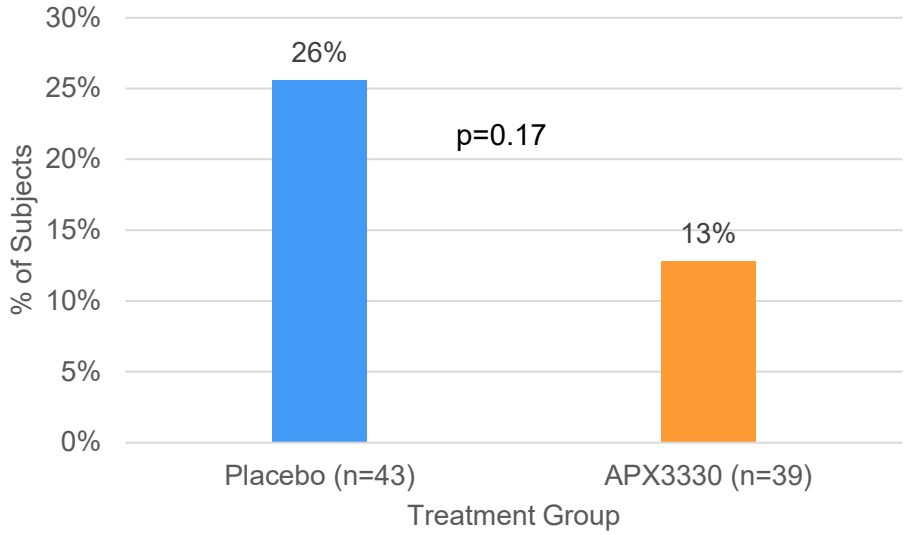
ZETA 1: APX3330 Reduced % of Subjects Developing PDR and % Losing BCVA

APX3330 Prevented Progression of Structural Retinal Abnormalities

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



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



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

Fewer APX3330-treated subjects lost visual acuity compared to placebo at week 24

ZETA-1 Clinical Trial.
Source: Table 14.2.6.7.2; Table 14.3.6.5

ZETA-1: Treatment Emergent Adverse Events

Oral APX3330 Showed a Favorable Safety and Tolerability Profile Consistent with Prior Trials

	Placebo (n=52)	**APX3330 (n=51)**
Total AEs	120	91
#of Subjects with AEs	35 (67%)	29 (57%)
Treatment-related AEs	17 (14%)	14 (15%)
Serious AEs	11 (9%)	3 (3%)
Subjects Withdrawals Due to AEs	1 (2%)	2 (4%)
Deaths	1 (2%)	0 (0%)
AEs in >5% of Subjects*		
Diabetic Retinal Edema	5 (10%)	2 (4%)
Diabetic Retinopathy	6 (12%)	1 (2%)
Vitreous detachment	3 (6%)	0 (0%)
Cataract	1 (2%)	3 (6%)
Pruritus	1 (2%)	6 (12%)
Rash	1 (2%)	3 (6%)
COVID-19	5 (10%)	1 (2%)

| *Eye disorders* |

APX3330 Safety Profile

- Limited AEs, most mild in severity
  - Pruritis: Mild and resolved without APX3330 dose de-escalation or discontinuation
- AEs similar to or less than placebo
- Few serious treatment-related AEs, all unrelated to study medication
- **Patients continued routine medications to manage their diabetes comorbidities**

- APX3330 SAEs: Dyskinesia, TIA, Chest pain
- Placebo SAEs: Vertigo, Asthenia, Multiple organ dysfunction, Bradycardia, CAD, Cholelithiasis, COVID-19 pneumonia, Cellulitis, Respiratory failure, Skin ulcer, Peripheral embolism
- AEs → Withdrawal APX3330: Presyncope, Dyspnea; Placebo: DME (both eyes)
- *Preferred Term within Organ Class

APX3330 - Key Takeaways

- NPDR without DME is generally not treated with anti-VEGF therapies approved for DR
  - Standard of care watch-and-monitor; Treat with anti-VEGF and/or laser when develop sight threatening disease
- Oral APX3330 demonstrated favorable safety & tolerability in diabetic patients[1]
- End-of-Phase 2 meeting with FDA confirmed registration endpoint of reducing the incidence of ≥ 3-step worsening on 17-step binocular Person-level Scale over 48-weeks compared to placebo
- Company plans to submit a Special Protocol Assessment (SPA) in anticipation of initiating phase 3 trials
- **Oral APX3330 has the potential to provide a non-invasive treatment for NPDR patients with good visual acuity, slowing progression to visual threatening complications**

1 ZETA-1 Phase 2 Trial