Ocuphire PHARMA

Restore Vision & Clarity

November 2023

# Ocuphire Corporate Presentation

# Disclosures and Forward-Looking Statements

This presentation contains “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995. Such statements include, but are not limited to, statements concerning the success and timing of planned regulatory filings and approvals, pre-commercial activities, commercialization strategy and timelines, business strategy, product labels, cash runway, scalability, future clinical trials in presbyopia (P), dim light/night vision disturbance (DLD) and diabetic retinopathy (DR) / diabetic macular edema (DME), including the potential for Phentolamine Ophthalmic Solution (POS) to be a “best in class” presbyopia drop, and timing of planned future clinical trials for APX3330, APX2009 and APX2014, the advancement to Phase 3 registration path for APX3330, FDA agreement on Special Protocol Assessment, the success and timing of planned regulatory filings, business strategy, cash runway, scalability, the potential for APX3330 to be the most advanced and the first line of therapy for DR patients, and the potential market opportunity for and the ability of APX3330 to slow DR progression. These forward-looking statements are based upon the Company’s current expectations and involve assumptions that may never materialize or may prove to be incorrect. Actual results and the timing of events could differ materially from those anticipated in such forward-looking statements as a result of various risks and uncertainties, including, without limitation: (i) the success, costs, and timing of regulatory submissions and pre-clinical and clinical trials, including enrollment and data readouts; (ii) regulatory requirements or developments; (iii) changes to clinical trial designs and regulatory pathways; (iv) changes in capital resource requirements; (v) risks related to the inability of Ocuphire to obtain sufficient additional capital to continue to advance its product candidates and its preclinical programs; (vi) legislative, regulatory, political and economic developments, (vii) changes in market opportunities, (viii) risks that the partnership with Viatris may not facilitate the commercialization or market acceptance of Ocuphire’s product candidates; (ix) the success and timing of commercialization of any of Ocuphire’s product candidates, including the scalability of Ocuphire’s product candidates and (x) the maintenance of Ocuphire’s intellectual property rights. The foregoing review of important factors that could cause actual events to differ from expectations should not be construed as exhaustive and should be read in conjunction with statements that are included herein and elsewhere, including the risk factors detailed in documents that have been and may be filed by the Company from time to time with the SEC. All forward-looking statements contained in this presentation speak only as of the date on which they were made. The Company undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made.

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# Ocuphire Pipeline

| Product Candidate | Indication | Pre-clinical | Phase 1 | Phase 2 | Phase 3 | Regulatory Approval | Upcoming Milestones |
|---|---|---|---|---|---|---|---|
| **APX3330**<br>**Oral Pill** | **Diabetic Retinopathy (DR)** | | | | SPA Submission | | ☑ EOP2 Mtg October 2023<br>❑ Special Protocol Assessment (SPA) Submission |
| **APX3330**<br>**Local Delivery** | **Retina** | | | | | | ❑ Select retinal drug delivery technology |
| **APX2009 and APX2014**<br>**Local Delivery** | **Retina** | | | | | | ❑ Select retinal drug delivery technology |
| **Phentolamine Ophthalmic Solution 0.75%**<br>**Eyedrops** | **Pharmacologically-Induced Mydriasis** | Partnered with Viatris | | | | | ☑ **APPROVED (*RYZUMVI™*) *Sept 2023*** |
| | **Presbyopia (P)** | | | | | | ❑ VEGA-2 Phase 3 Topline Data Q4 2023 |
| | **Dim Light or Night Vision Disturbances (DLD)** | | | | | | ☑ SPA Submitted<br>❑ LYNX-2 2nd Phase 3 trial (n=150+) |

# Management Team with Decades of Drug Development Experience

**George Magrath, MD, MBA**
CEO

MUSC Medical University of South Carolina · The Citadel · Lexitas · Johns Hopkins University · Hovione · Edison

**Ronil Patel, MTech, MS**
SVP, Operations and BD

Florida Tech · Betaliq · Revitalid · PointGuard Partners LLC · Oculos Integrated Insight.

**Charlie Hoffmann, MBA**
SVP, Corporate Development

Tuck School of Business at Dartmouth · Ocularis Pharma · Prudential · SynDevRx · Goldman Sachs

**Amy Rabourn, CPA**
SVP, Finance

Michigan Ross · Gemphire Therapeutics · Pfizer · NeuroBo Pharmaceuticals · pwc

**Drey Coleman**
VP, Clinical Operations

Oculos Integrated Insight. · SIRION Therapeutics · UCF

**Mitch Brigell, PhD**
Head, Clinical Development and Strategy

Kansas State University · aerpio · Pfizer · Novartis

**Barbara Withers, PhD**
VP, Clinical and Regulatory Strategy

Wayne State University School of Medicine · aerpio · UBC · Pfizer

**Bindu Manne**
Head, Market Development and Commercialization

UNC Pembroke · Takeda · Shire · Merck · Ocular Therapeutix · equinox · ThromboGenics

**Chris Ernst**
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Northern Kentucky · aerpio · Akebia Therapeutics · MEDPACE

**Laura Gambino**
Director, Project Management

Eastern Michigan University · aerpio · Akebia Therapeutics · Pfizer

**Daniela Oniciu, PhD**
Global Head, R&D, Chemistry and Product Development

UF University of Florida · Gemphire Therapeutics · Esperion · Cerenis Therapeutics · Pfizer

# Corporate Highlights

## Late-Stage Clinical Candidate for Retinal Diseases Represents Multi-Billion Dollar Opportunity

**APX3330:** *Paradigm Changing, Non-invasive, Safe Oral Tablet for millions of NPDR patients that are currently left untreated*

- *Ref-1, a novel, dual target (angiogenesis and inflammation) for retinal diseases*
- *ZETA-1 Phase 2 showed APX3330 prevented or slowed progression of Diabetic Retinopathy (DR)*
- *Successful EOP2 meeting with the FDA and a Special Protocol Assessment (SPA) to be submitted*

## Phentolamine Ophthalmic Solution 0.75% (POS) for Refractive Disorders

- Global license agreement with Viatris to fund all development and commercialization for phentolamine indications:
  - ***RYZUMVI™ (Phentolamine Ophthalmic Solution) 0.75% for the treatment of pharmacologically-induced mydriasis received FDA approval in September 2023***
    - *Approval triggered $10M milestone payment*
  - ***Presbyopia*** *and* ***Dim Light Disturbances*** *currently in Phase 3*

Experienced Retina Drug Development Team to Advance APX3330 into Phase 3

# Diabetic Retinopathy Market and Unmet Need

# Diabetic Eye Disease is a Common Cause of Blindness

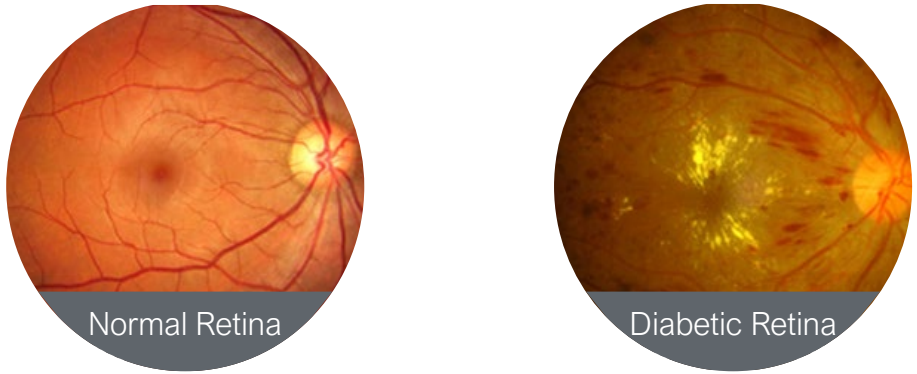
*Diabetes and Diabetic Retinopathy (DR)*

Diabetes Mellitus is a group of diseases characterized by high blood glucose levels. Diabetes results from defects in the body's ability to produce and/or use insulin

**Type 1 diabetes (T1D):** The body produces very little or no insulin, which means that patients need daily insulin injections to maintain blood glucose levels

**Type 2 diabetes (T2D):** The most common form of diabetes - either the body does not produce enough insulin, or resists insulin

Diabetic retinopathy (DR) occurs when fluctuations or instability in blood glucose levels damages blood vessels in the retina




## Two Types of DR

**Non-Proliferative Diabetic Retinopathy (NPDR)** – most common form of DR – early stages of edema and exudates, blurred central vision

**Proliferative Diabetic Retinopathy (PDR)** – later stage of DR, marked by abnormal blood vessels and scar tissue on retina

Diabetic Macular Edema (DME) can occur at any stage of DR

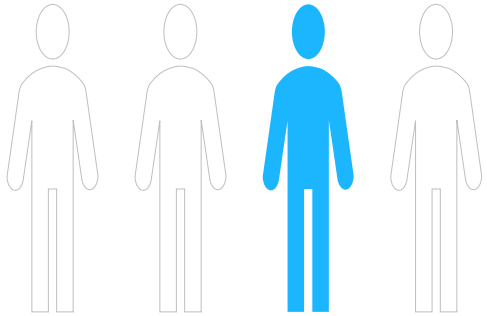
https://webeye.ophth.uiowa.edu/eyeforum/tutorials/diabetic-retinopathy-med-students/Classification.htm
https://www.mayoclinic.org/diseases-conditions/type-1-diabetes/symptoms-causes/syc-20353011
https://www.mayoclinic.org/diseases-conditions/type-2-diabetes/symptoms-causes/syc-20351193

# Diabetic Retinopathy at a Glance

*Current Treatment Landscape Demonstrates Need for Non-Invasive Therapies*

There are ~8M adults in the U.S. with NPDR

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

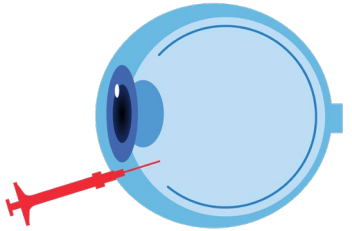


DR is the leading cause of blindness among working-age adults with the median age of onset at 45 – 50 years

Physicians have no non-invasive options for NPDR with current standard being wait-and-monitor

Prevention of Progression is favored by payors with chronic diseases such as diabetes which is the primary driver of increased healthcare costs

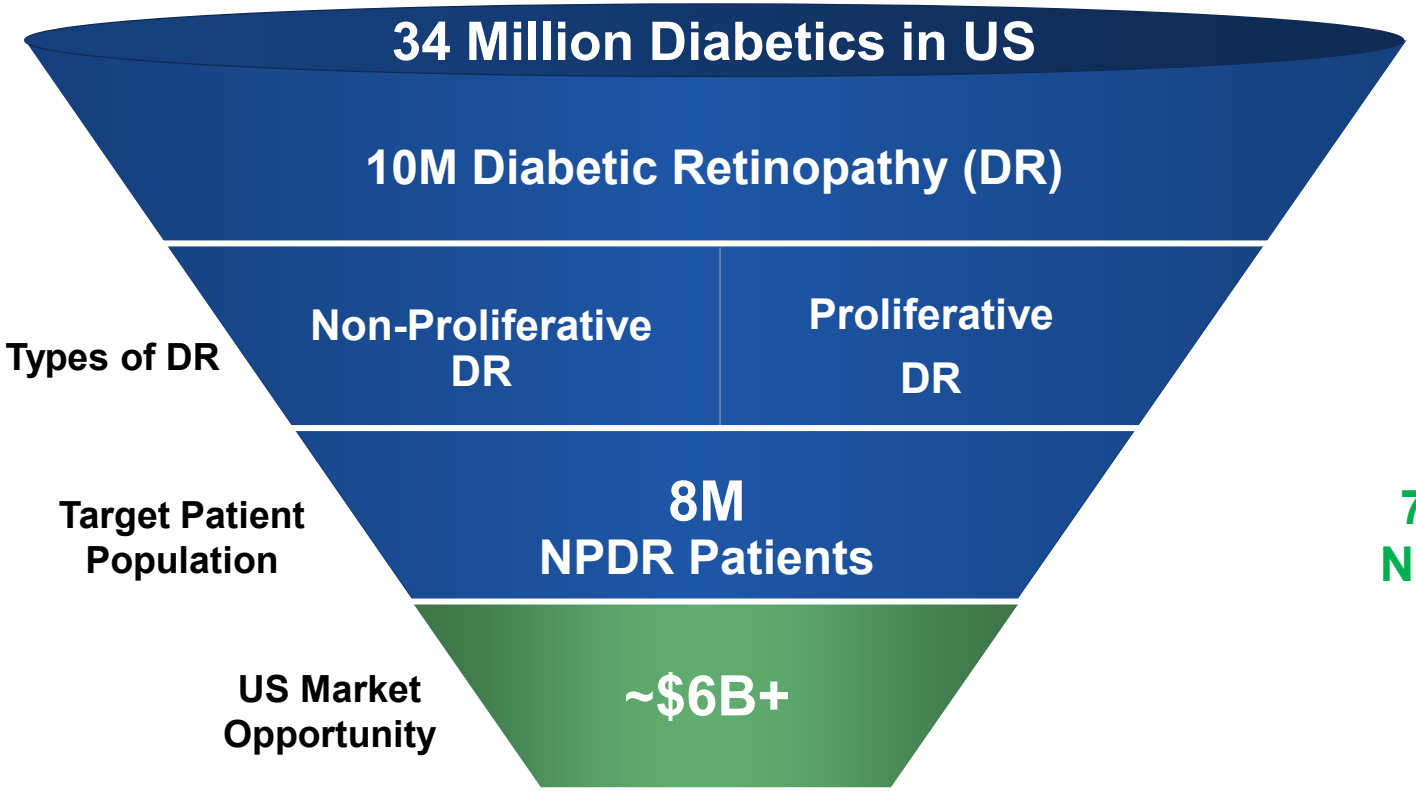
Majority of moderate to severe patients with DR are not treated with anti-VEGF due to injection burden and no benefit to visual acuity



American Diabetes Association; International Diabetes Federation; Healthline; *Ocuphire internal analysis and assumptions
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
Patient survey adapted from Lions International Foundation and International Diabetes Foundation-Europe; Meltzer 2000
Guidehouse Triangulation of Global Data, Market Scope and Investor Forecasts (2020) AMD = Age-Related Macular Degeneration; DME = Diabetic Macular Edema ; BRVO = Branch Retinal Vein Occlusion
National Center for Chronic Disease Prevention & Health Promotion. Health & economic costs of chronic diseases. Atlanta (GA): Centers for Disease Control & Prevention, US Department of Health and Human Services; 2018
Four-Year Visual Outcomes in a Randomized Trial of Intravitreous Aflibercept for Prevention of Vision Threatening Complications of Diabetic Retinopathy (Protocol W).” JAMA. February 7, 2023

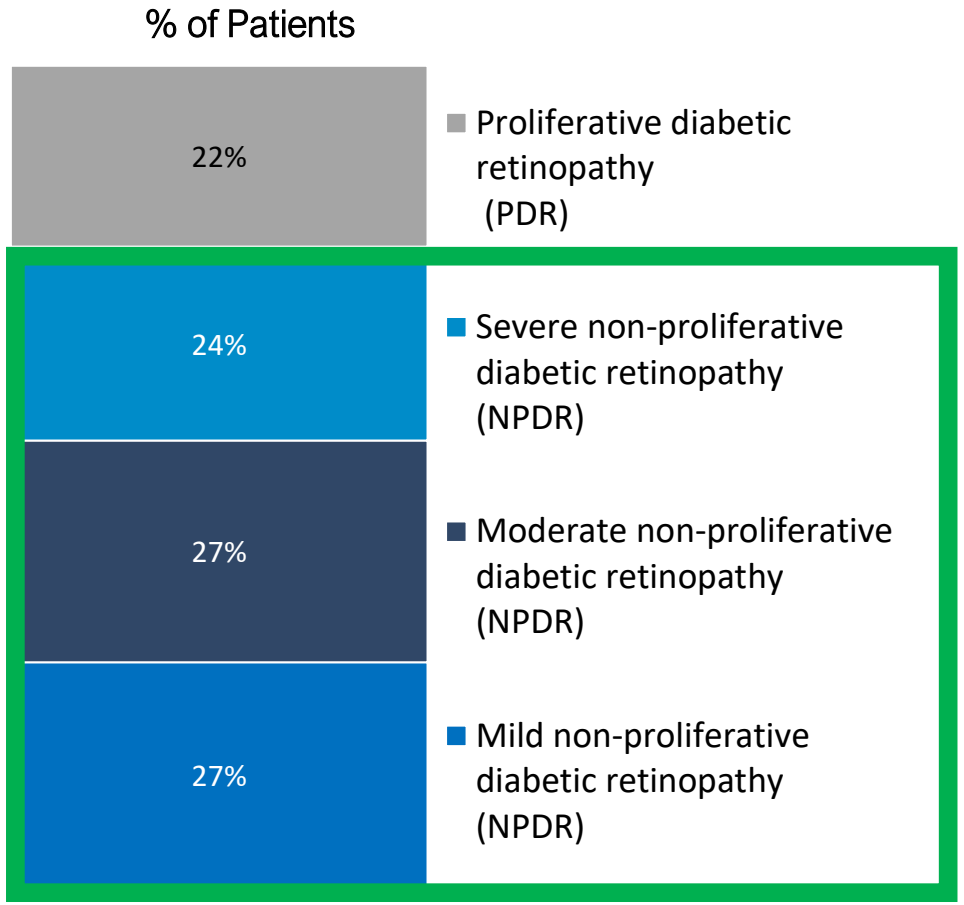
# U.S Diabetic Retinopathy Market

*Majority of the DR Patients are NPDR Severity → Target Population for APX3330*




78% NPDR

## Real-World Chart Review of DR Patients in US

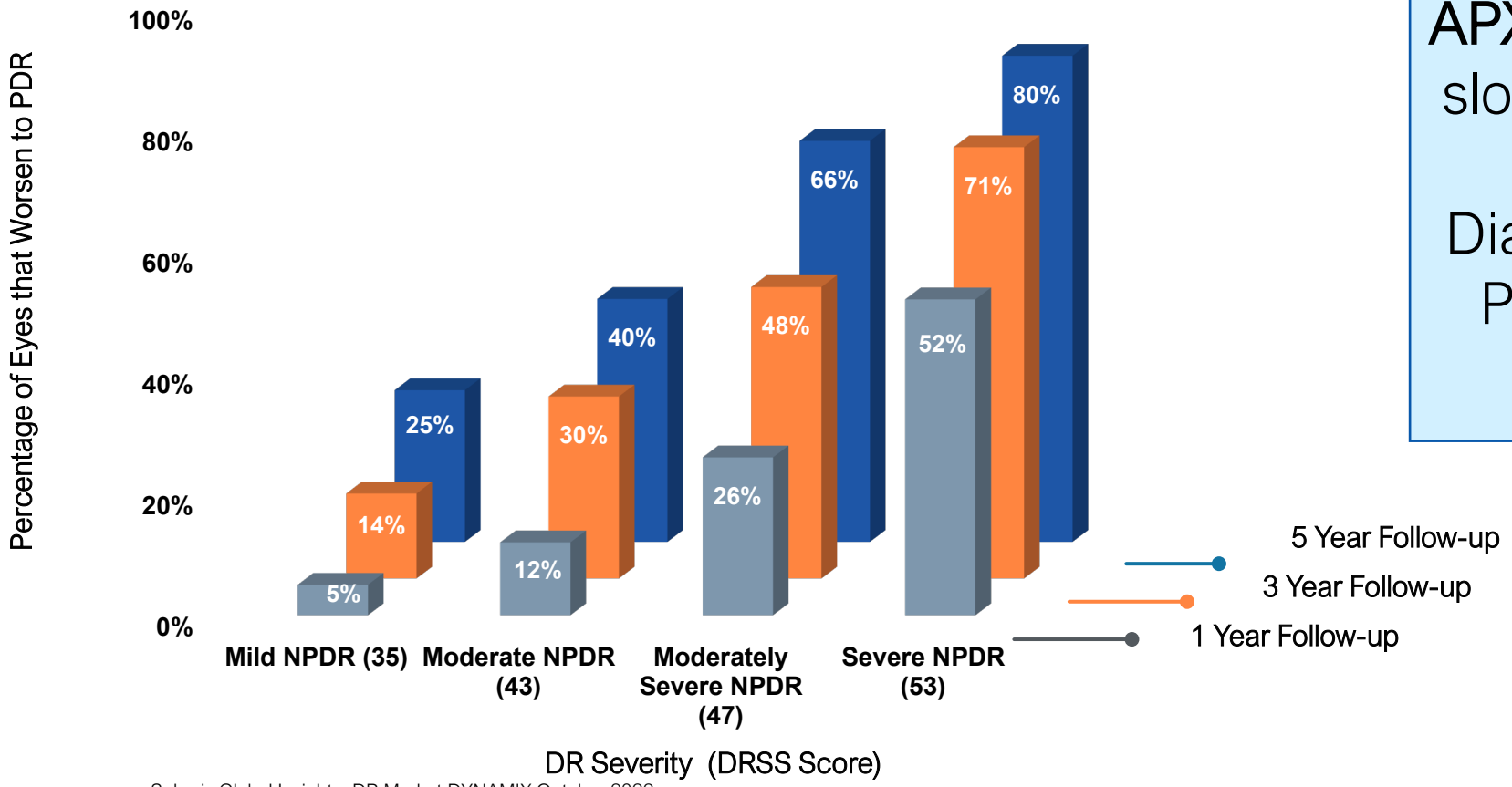



American Diabetes Association; International Diabetes Federation; Healthline; *Ocuphire internal analysis and assumptions; Spherix Global Insights
Patient survey adapted from Lions International Foundation and International Diabetes Foundation-Europe; Meltzer 2000
Estimates are provided by the National Eye Institute, FactSheet, Global Data, and Research and Markets. Estimated values are rounded.
Estimated prevalence in the U.S.; DME- Diabetic Macular Edema; Age-related Macular Degeneration; Geographic Atrophy; Retinal Vein Occlusion

# Progression of DR Severity Measured up to 5 Years

*NPDR Patients are Rarely Treated with anti-VEGF Intravitreal Injections Due to Treatment Burden*

**Regardless of severity, all eyes worsen over time**




Early Intervention with **APX3330** can potentially slow the **progression** of Non-Proliferative Diabetic Retinopathy to Proliferative Diabetic Retinopathy


Spherix Global Insights: DR Market DYNAMIX October 2022

Early treatment diabetic retinopathy study research group. ophthalmology. 1991;98(5 suppl):823-33.

Diabetes control and complications trial research group. N Engl J Med. 1993;329(14):997-86.

Fathy C, Patel S, Sternberg P Jr, Kohanim S. Disparities in adherence to screening guidelines for diabetic retinopathy in the United States: a comprehensive review and guide for future directions. *Semin Ophthalmol*. 2016;31(4):364–377. doi: 10.3109/08820538.2016.1154170

# Diabetic Retinopathy Treatment Landscape

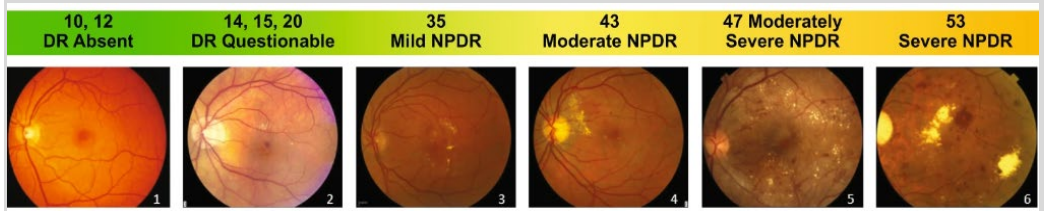
# Current Standard of Care Based on Severity

*Currently, There Are No Non-Invasive Treatments Approved for Early Intervention or Slowing the Progression*

2021 ASRS PAT Survey

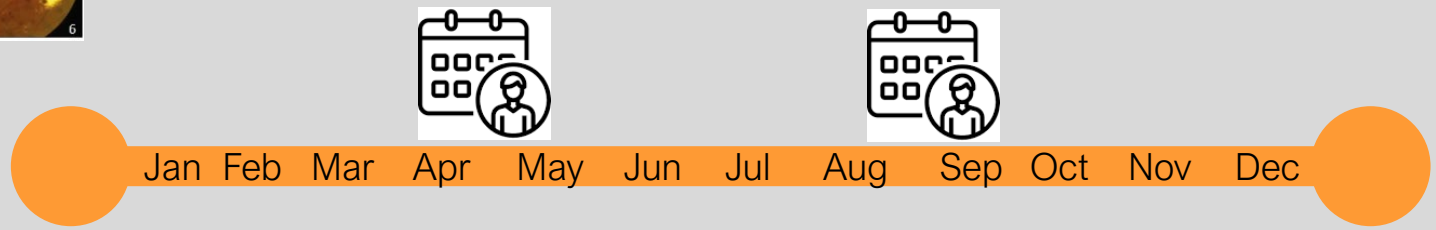
Closely monitor retinopathy and encourage systemic glycemic control


## Mild to Moderate NPDR

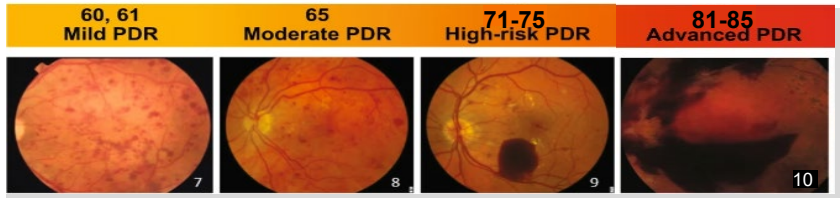



NPDR patients are monitored for progression requiring visits to the office every 4-6 months

### Wait and Monitor for Progression

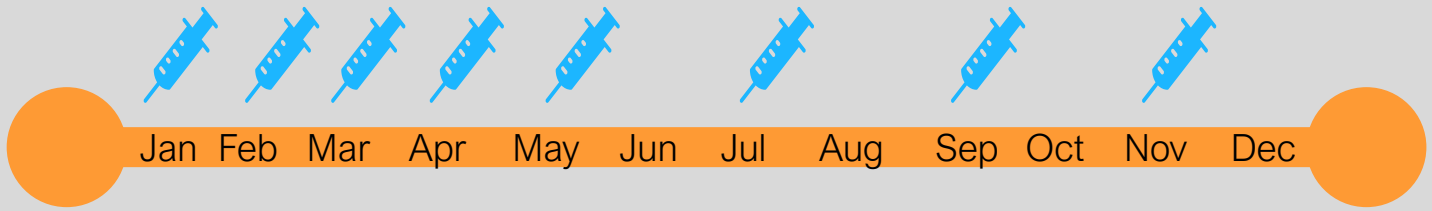



## PDR




Gold standard Eylea® and Lucentis® injections are effective treatments in the first year for PDR

### Anti-VEGF Injections



# Landscape of Investigational Non-Invasive Therapies for Diabetic Retinopathy

*Ocuphire's APX3330 is the Most Advanced Oral Drug Candidate*

| Company | Drug | Target/MOA | Indication | Route of Administration | Phase 1 | Phase 2 | Phase 3 | Primary Endpoint/ Secondary Endpoints |
|---|---|---|---|---|---|---|---|---|
| Ocuphire Pharma | APX3330 | Ref-1 inhibitor (Anti-angiogenesis & Anti-inflammatory) | DR | Oral | ✓ | ✓ 2022 | | 2020: 2-step DRSS @wk24 |
| Roche | RG7774 | CB2 receptor (cannabinoid) | DR | Oral | ✓ | X 2023 | | 2020: 2-step DRSS @wk36 |
| Bayer | BAY1101042 | Guanylate Cyclase activator | DR | Oral | ✓ | ◌ | | 2021: 2-step DRSS @wk24 |
| Valo | OPL-0401 | ROCK 1/2 inhibitor | DR | Oral | ✓ | ◌ | | 2021: 2-step DRSS @wk24 |
| Vantage Biosciences | VX-01 | AOC-3 inhibitor | DR | Oral | ✓ | ◌ | | 2022: Not Disclosed |
| OcuTerra Therapeutics | OTT166 | Integrin inhibitor | DR | Eyedrop | ✓ | ◌ | | 2022: 2-step DRSS @wk24 |

*Note: Two Tyrosine Kinase and a Plasma Kallikrein Inhibitors failed as orals in Phase 2 due to dose limiting adverse events (e.g., liver and cardiovascular)*

| ✓ *Completed* | ◌ *Ongoing* | × *Discontinued* |
|---|---|---|

**APX3330 is the ONLY candidate with validated retinal pathways of angiogenesis and inflammation.**

**Human exposure** >10,000 subject days of systemic exposure at 600mg/day dose and a **favorable safety and tolerability profile.**

# Landscape of Invasive Therapies (IVT/Suprachoroidal) for Diabetic Retinopathy

*Eylea®/Lucentis® Approved, But Not Used in Patients with NPDR; Rarely Used in Mild PDR*

| Company | Drug | Target/MOA | Route of Administration | Phase 1 | Phase 2 | Phase 3 | Commercial |
|---|---|---|---|---|---|---|---|
| REGENERON | Eylea® (aflibercept) | VEGF-A/B; PIGF | Intravitreal | ✓ | ✓ | ✓ | ✓*1 |
| Roche | Lucentis® (ranibizumab) | VEGF-A | Intravitreal | ✓ | ✓ | ✓ | ✓*2 |
| KODIAK | KSI-301 (Tarcocimab) | VEGF | Intravitreal | ✓ | N/A | ◌ | |
| EyePoint Pharmaceuticals | EYP-1901 | Voloronib* (TKI) | Intravitreal | ✓ | ◌ | | |
| Boehringer Ingelheim | BI 764524 | Anti-Sema3A Ischemia modulator | Intravitreal | ✓ | ◌ | | |
| Ocular Therapeutix | OTX-TKI | Axitinib* (TKI) | Intravitreal | ✓ | ◌ | | |
| REGENXBIO | RGX-314 | AAV8-VEGF | Suprachoroidal (Gene Therapy) | ✓ | ✓ | | |

* Failed as oral/systemic treatments in retina due to dose limiting toxicity

✓ *Completed* ◌ *Ongoing* X *Discontinued*

*Trials to Support Approval
[1] Panorama Clinical Trial
[2] Protocol I & T and Rise & Ride

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Company websites and www.clinicaltrials.gov (as of October 31, 2023)
Eylea® is trademark of Regeneron and Lucentis® is trademark of Genentech

# APX3330 Background

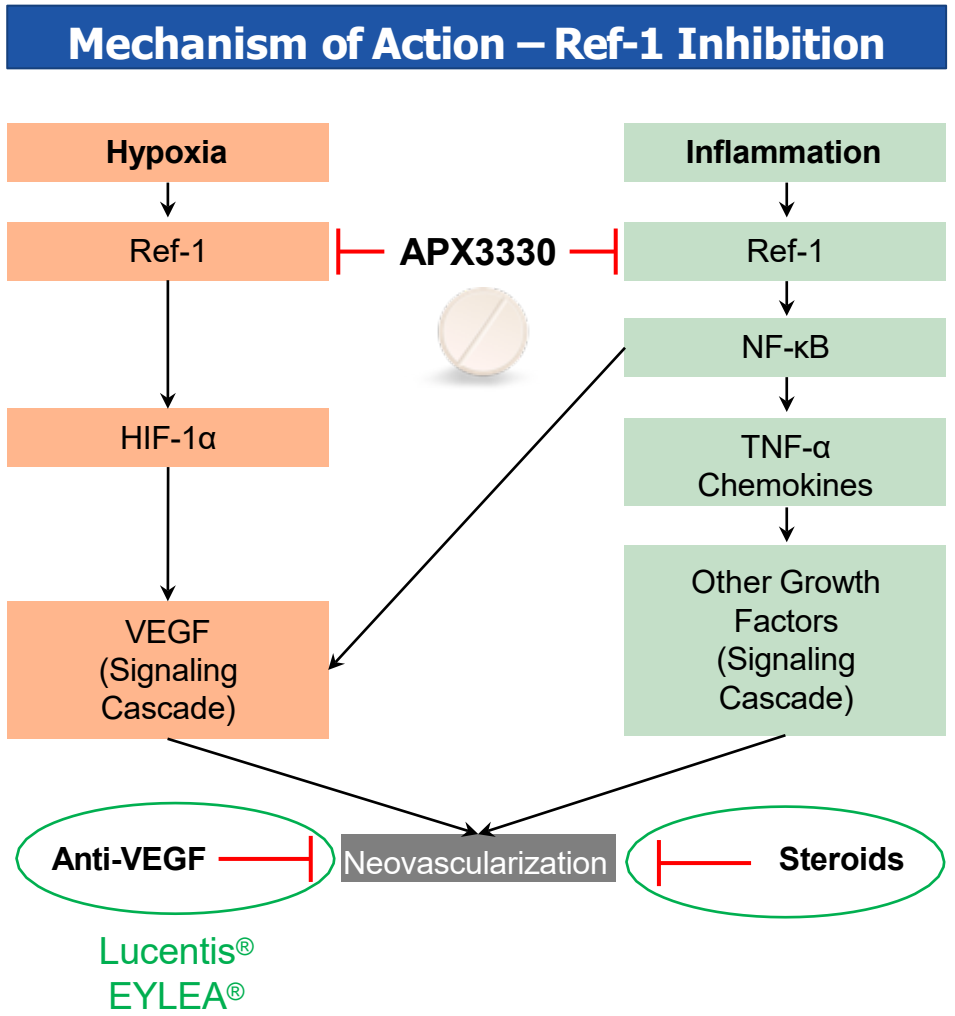
# APX3330 - Mechanism of Action Targeting Ref-1 Inhibition

*Ref-1 Involved in Key Pathways that Contribute to Diabetic Retinopathy and Diabetic Macular Edema*

**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 MOA decreases abnormal angiogenesis and inflammation**
  - APX3330 does not deplete the VEGF levels but rather normalizes VEGF levels to physiologic levels
- **Anti-VEGF injections *do not* target inflammation**




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

Exposure in Humans
**>10,000**
Subject Days at 600mg/day

Patents to
**2035+**

| ☑ | ☑ | ☑ | ☑ | ☑ | ☐ | ☐ |
|---|---|---|---|---|---|---|
| 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**

- 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 results

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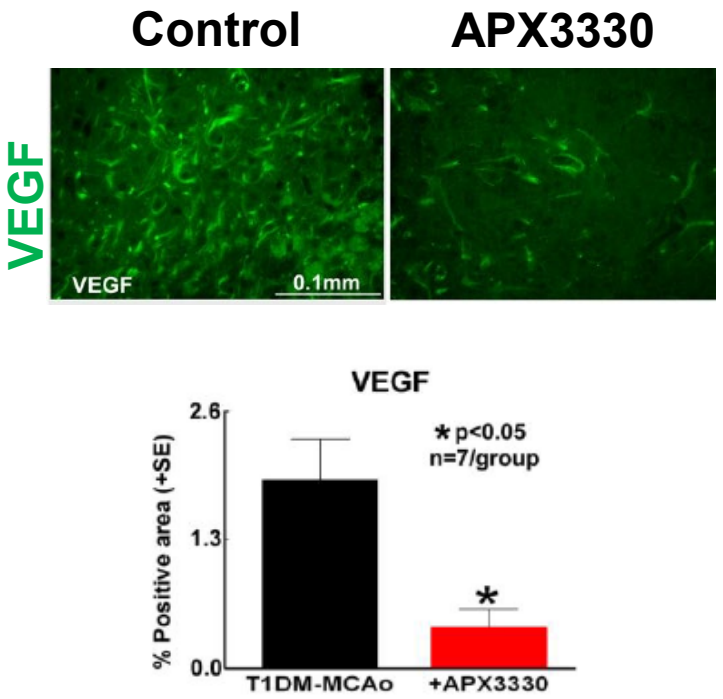
Includes ZETA-1 trial

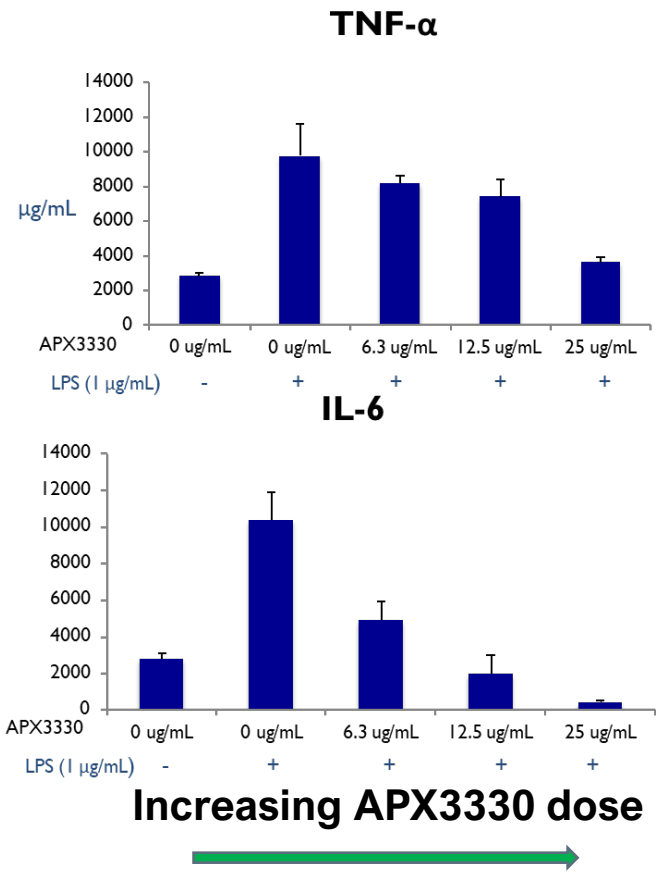
# In-vitro Validation of Mechanism of Action

*APX3330 Reduces VEGF levels and Inflammatory Cytokines; Provides Neuronal Protection*

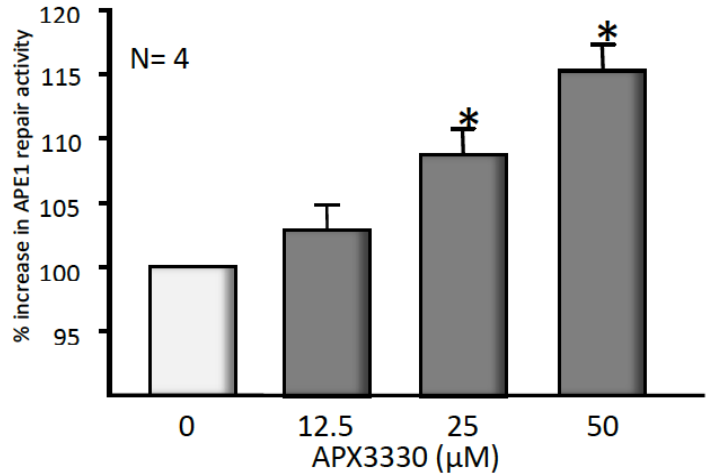
## APX3330 reduces VEGF protein expression in preclinical stroke model




## 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*

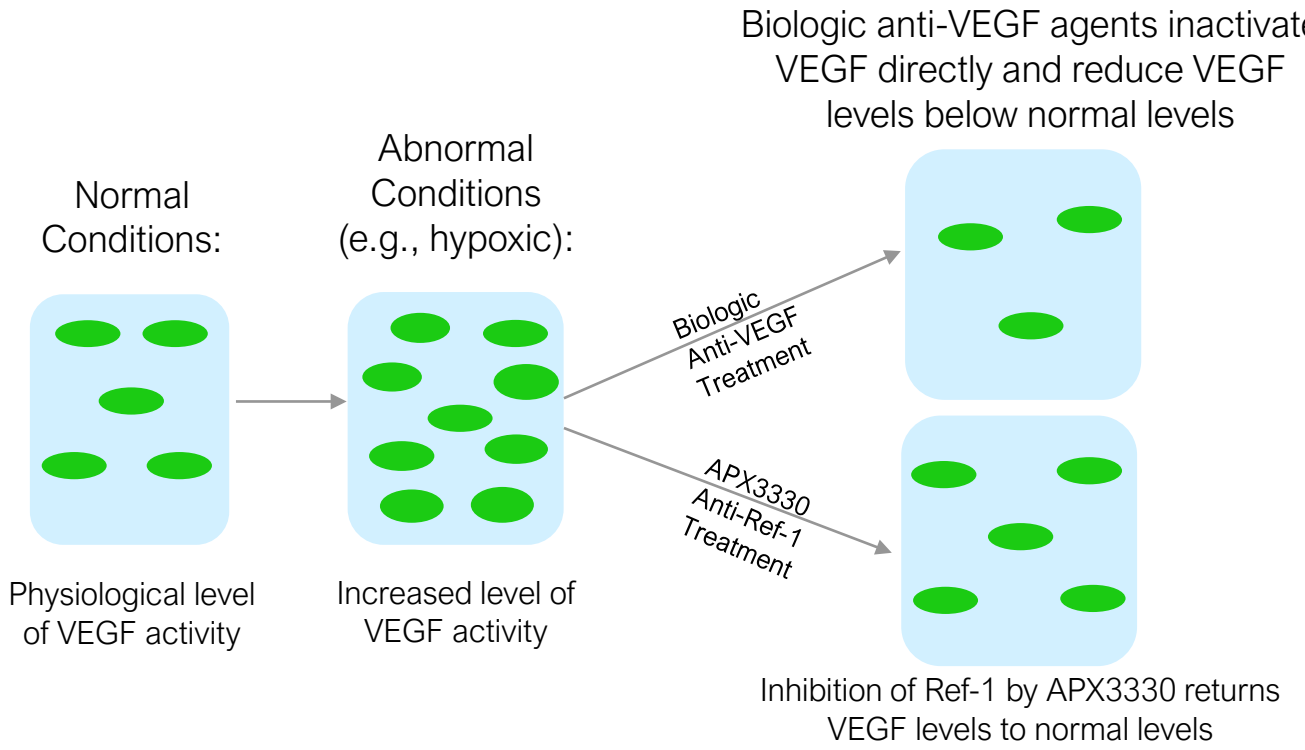

Tao Yan *et al.* APX3330 Promotes Neurorestorative effects after stroke in type one diabetic rats. Aging and Disease. Vol 9, Oct 2018

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

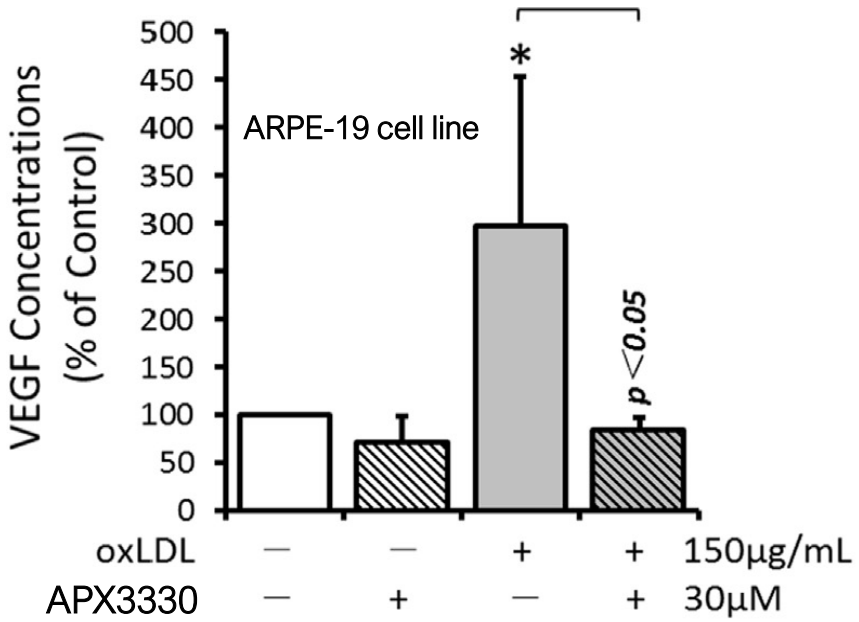
Fehrenbacher, J. C., Guo, C., Kelley, M. R. & Vasko, M. R. DNA damage mediates changes in neuronal sensitivity induced by the inflammatory mediators, MCP-1 and LPS, and can be reversed by enhancing the DNA repair function of APE1. Neuroscience 366, 23-35, doi:10.1016/j.neuroscience.2017.09.039 (2017)

# APX3330 VEGF Effects in Normal Cells

*APX3330 Restores Normal Levels Unlike Biologic Anti-VEGFs that Reduce VEGF Below Normal*




APX3330 prevents VEGF overproduction in ARPE-19 cells




- VEGF is a growth factor that is necessary for normal function of multiple cell types including vascular endothelium and neurons ➔ By returning VEGF levels to normal, APX3330 can reduce neovascularization, vascular leakage and the inflammatory response without adverse systemic effects
- The safety profile of APX3330 to date has not shown any of the adverse effects that has been seen with systemic administration of anti-VEGF biologics such as cardiovascular pathology, hypertension, arteriothrombotic events, or renal dysfunction

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Kamba 2007; Girardi 2010; Li 2014
APX3330 Investigator Brochure

# APX3330 ZETA-1 Clinical Trial

# ZETA-1: Phase 2 Trial of Oral APX3330 in Subjects With Diabetic Retinopathy

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

## Eligibility Criteria

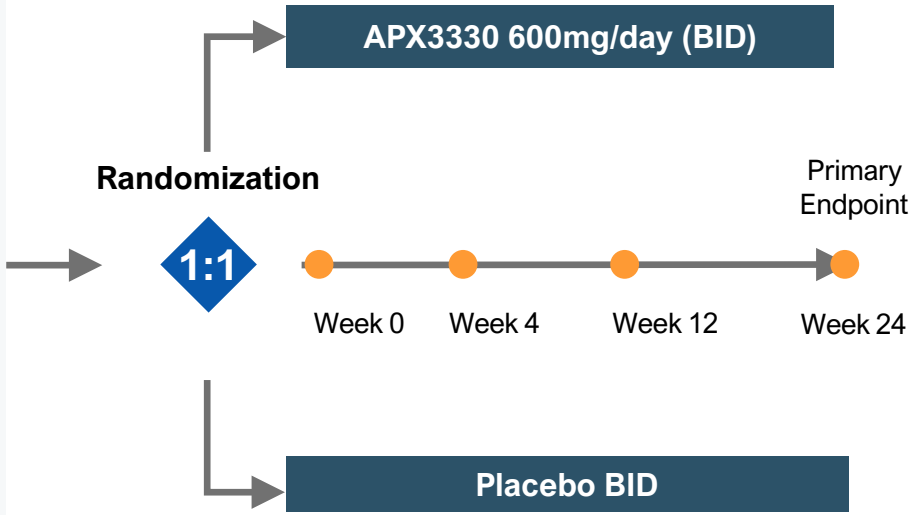
- 25 US sites
- N = 103 participants with moderately severe to severe NPDR or mild PDR (DRSS 47, 53, 61)

### Key inclusion:

- ≥ 18 years of age
- DRSS 47, 53, or 61
  - Noncentral DME permitted[2]
- 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 data announced in January 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*

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# 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=49 | 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)** | **15 (31%)** | **13 (25%)** |
| 47 (Moderately severe to severe NPDR) | 15 (31%) | 20 (38%) |
| 53 (Moderately severe to severe NPDR) | 12 (25%) | 10 (19%) |
| 61 (Mild proliferative diabetic retinopathy) | 1 (2%) | 4 (8%) |
| **65 or Higher (Moderate to severe prolif. DR)** | **6 (12%)** | **5 (10%)** |

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

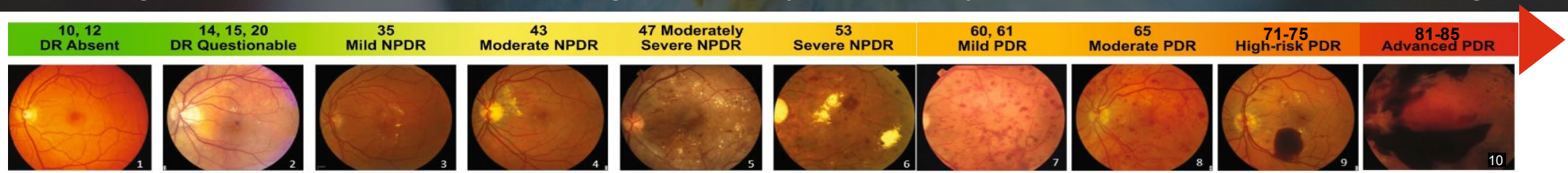
## Key Visual Metrics

| | 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 |

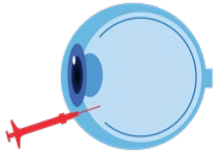
Good Visual Acuity / Fluid Below 320µm

# Clinically Meaningful Registration Endpoints in DR

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




FDA accepts improvement OR worsening (slowing or prevention of progression)[1] of the disease AND DRSS is an established surrogate endpoint for DR

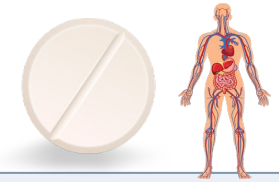


## Local Drugs (Intravitreal Injections)

Precedent approvable endpoint for locally-delivered drugs (non-systemic) in DR:

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

## Systemic Drugs



Approvable endpoints for systemic drug in DR include either:

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

**For oral administration, the binocular DRSS endpoint is distinct from 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.

# End-of-Phase 2 Meeting Outcome

# FDA Accepts the Binocular DRSS Person Scale For Phase 3 APX3330 DR Program

*DRSS is a Validated Surrogate Endpoint*

| 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 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

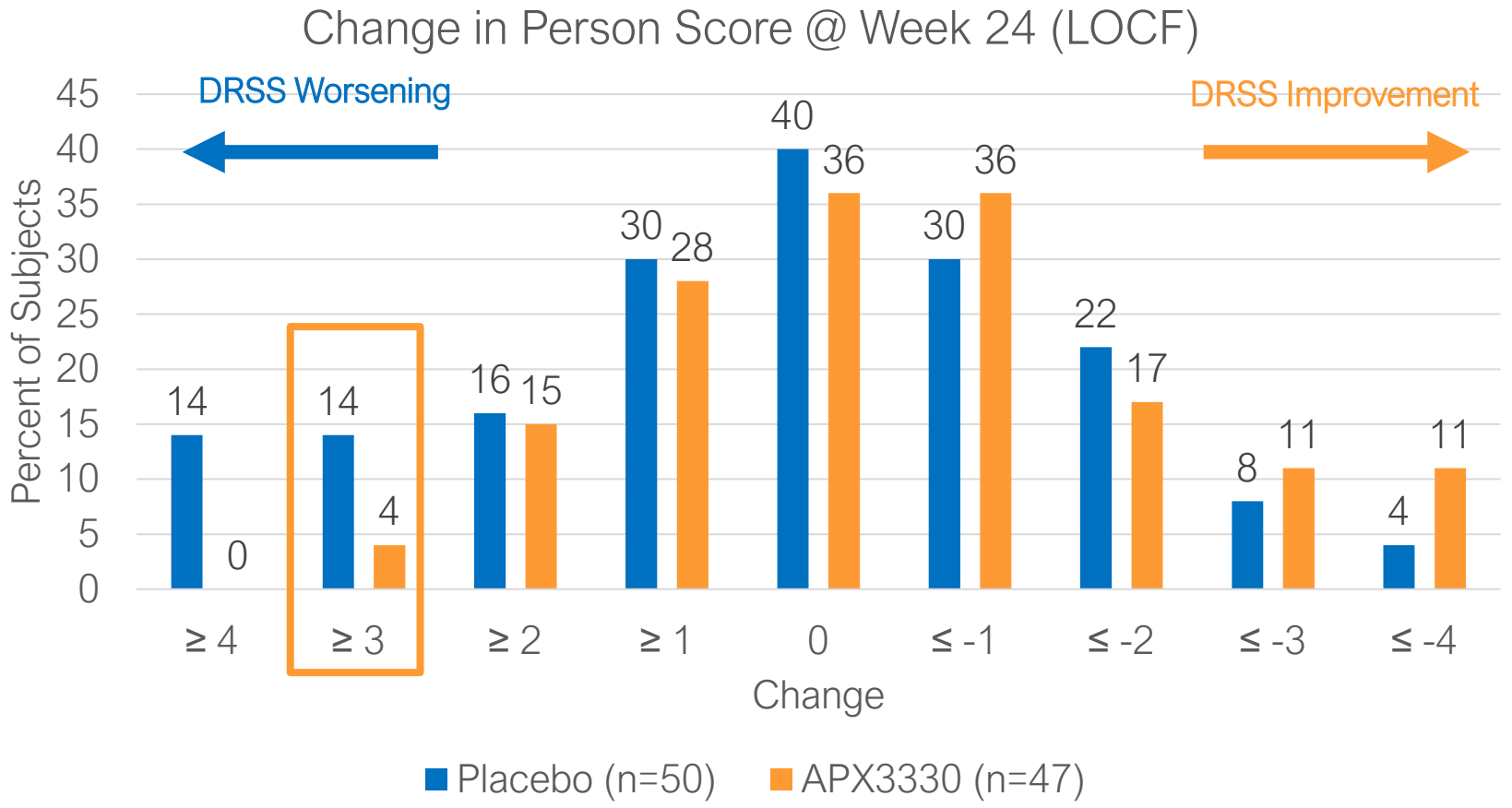
Final 47,47 = Step 9 (1-step change)

Final 53,43 = Step 10 (2-step change)

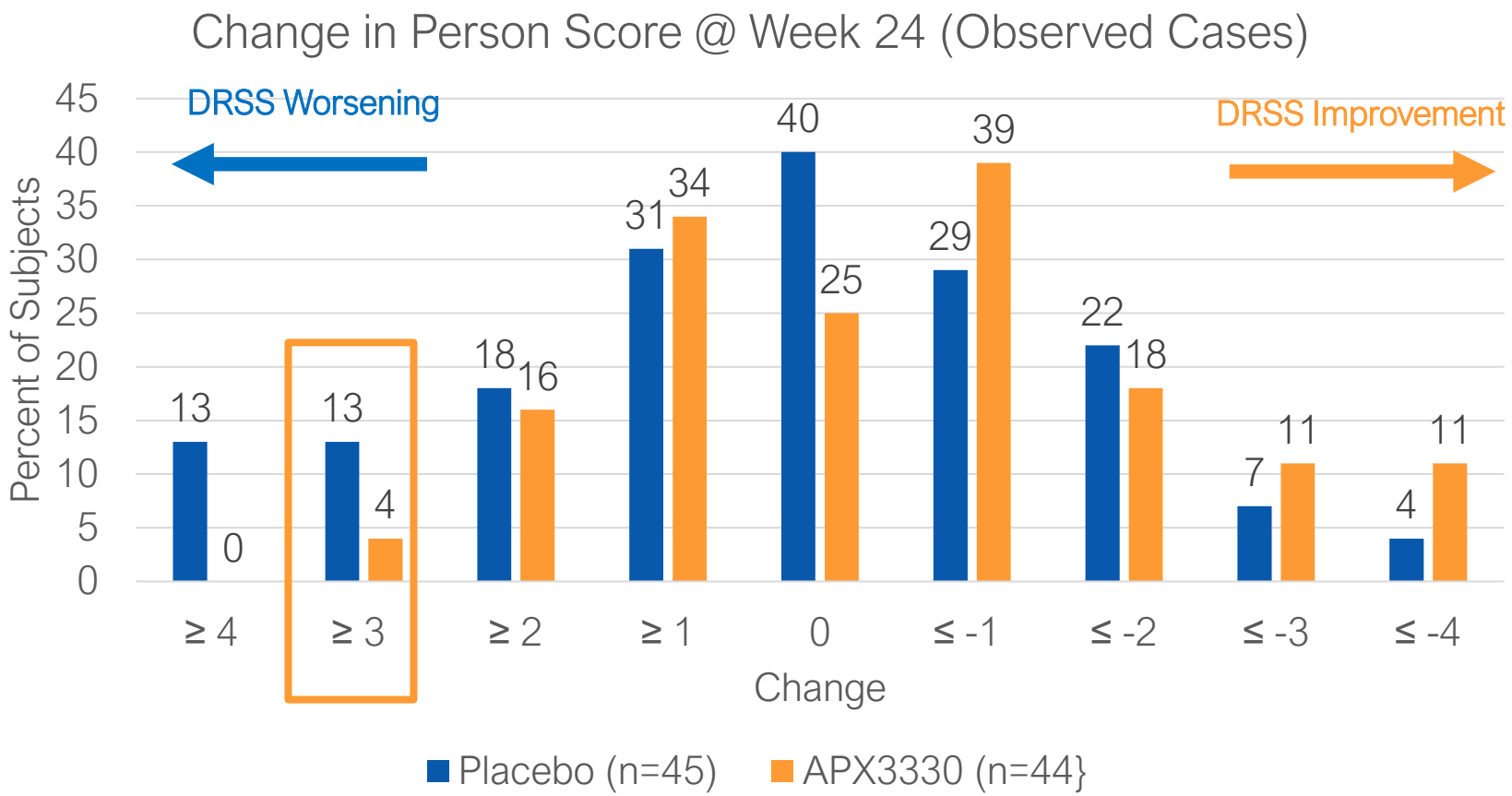
Final 61,43 = Step 12 (4-step change)

Final 61,53 = Step 12 (4-step change)

# ZETA-1: Percent of Subjects with Improvement or Worsening in DRSS at Wk 24 on the Binocular Person Scale (LOCF)

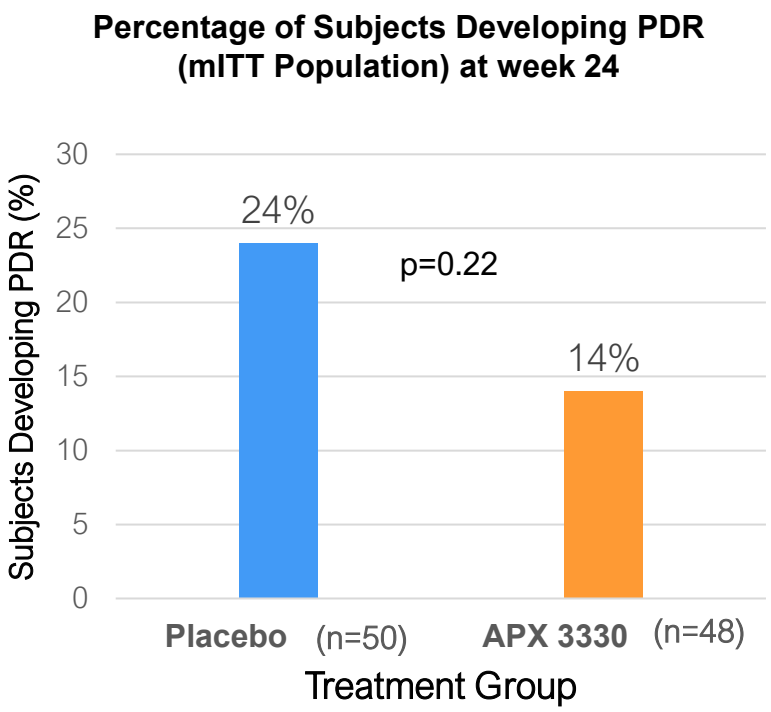


# ZETA-1: Percent of Subjects with Improvement or Worsening in DRSS at Wk 24 on the Binocular Person Scale (Observed Cases)

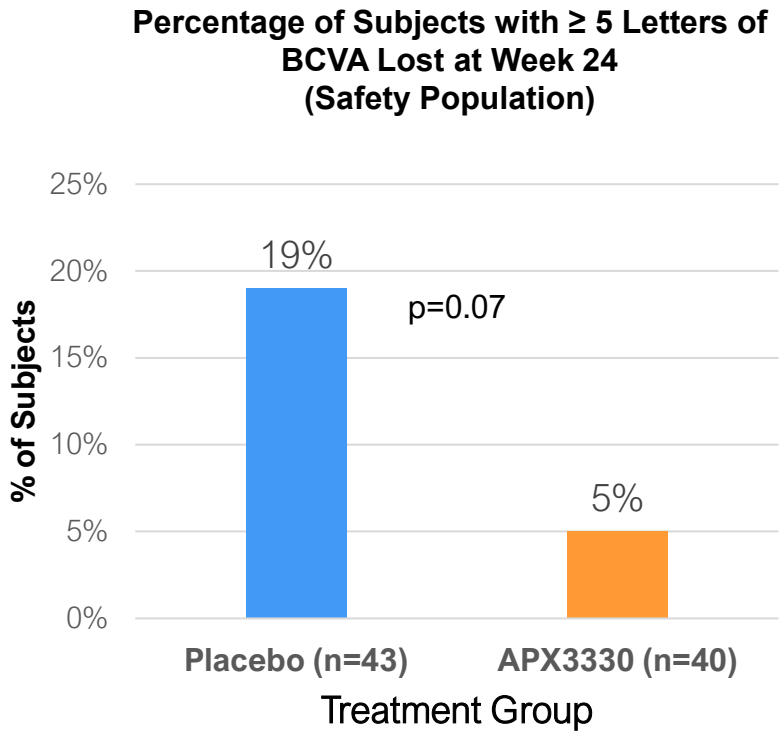


# APX3330 Reduced % of Subjects Developing PDR and % Losing BCVA

*APX3330 Prevented Progression of Structural Retinal Abnormalities*




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




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

ZETA-1 Clinical Trial.

# ZETA-1: Treatment of 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* | | |
| \| *Eye disorders* \| 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%) |

<u>APX3330 Safety Profile</u>:

- 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
- No ocular AEs other than expected DR progression
  - Lower incidence of clinical DR/DME worsening with APX3330
- **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 Summary

## APX3330 Milestones

- Successful EOP2 FDA meeting completed in October 2023; agreement that a 3-step change on the binocular person scale is an approvable registration endpoint
- Submit Special Protocol Assessment (SPA)
- Advance APX3330 into Phase 3 program with long-term exposure (up to 2 years)

**Our Goal for Patients**

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

# DR and APX3330 Key Takeaways

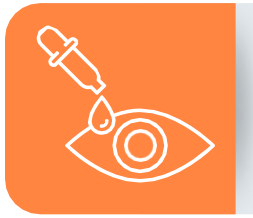
- DR is one of the largest markets in retina with 10M patients in US and over 100M worldwide
- Majority of the NPDR patients are not candidates for approved biologics treatments and are left untreated
- APX3330 first-in-class oral drug with unique MOA that inhibits Ref-1 which reduces VEGF and inflammatory cytokines to normal physiological levels
- Prevention of worsening is a clinically meaningful potential registration endpoint
- APX3330 demonstrated favorable safety and tolerability in diabetic patients
- **Successful EOP2 meeting with the FDA and a Special Protocol Assessment (SPA) to be submitted**
- APX3330 has the potential to be an early, non-invasive preventative treatment for the 8 million NPDR patients with the potential to treat other organs affected by diabetes (e.g., kidney disease, peripheral neuropathy)
- Broad prescriber base including general ophthalmology, optometry and primary care due to favorable safety

# Phentolamine Ophthalmic Solution 0.75%

# Global Partnership with Viatris for Phentolamine Ophthalmic Solution 0.75%

*Viatris Has Selected POS to be a Key Element of its Global Eye Care Division*

Partner for global commercialization



Fully funded development and commercialization costs for all 3 phentolamine indications

Allows Ocuphire to focus on APX3330 development

Strengthens cash position into 2025

- **$35 million upfront**
- **Fully funded development and commercialization for all 3 indications**
- **$130 million in regulatory and sales milestones**
  - First milestone payment of $10 million on FDA approval for pharmacologically-induced mydriasis indication
- **Tiered double digit royalties through 2040**

# Phentolamine Ophthalmic Solution 0.75%

## THREE INDICATIONS

NEW PARTNERSHIP WITH VIATRIS

VIATRIS™

## Treatment of Pharmacologically-Induced Mydriasis

APPROVED



**RYZUMVI™ (Phentolamine Ophthalmic Solution) 0.75% for the Treatment of Pharmacologically-Induced Mydriasis Produced by Adrenergic Agonists (e.g., Phenylephrine) or Parasympatholytic (e.g., Tropicamide) Agents**

## Presbyopia

1 **POS as a Single Drop**

2 **POS with LDP Adjunctive Therapy**


## Dim Light or Night Vision Disturbances (DLD)

# Summary of Phentolamine Ophthalmic Solution 0.75% Trial Results

*Comprehensive Body of Clinical Data Supporting Efficacy and Safety Across 3 Indications*

| Indication & Status | Primary Endpoint | Efficacy Data | Key Secondary Endpoint(s) | Safety & Tolerability |
|---|---|---|---|---|
| **Ryzumvi™**<br>**Approved September 2023** | Return to baseline pupil diameter at 90 minutes after dilation | **Met Phase 3 primary endpoint**<br>**MIRA-3**: 58% POS vs. 6% placebo<br>**MIRA-2**: 49% POS vs. 7% placebo (p<0.0001)<br>**MIRA-4**: 64% POS vs. 25% placebo | Efficacy across all mydriatic agents, iris color, 1 or 2 drops, and all ages (3-80) | • No headaches<br>• No blurry vision<br>• ~5% mild redness<br>• No change in IOP<br>• No SAEs<br>• Most AEs were mild |
| **Presbyopia (POS Alone)**<br>**Phase 3** | ≥3 line gain in near vision with loss of no more than 1 line in distance vision | **Met planned Phase 3 primary endpoint**<br>**VEGA-1**: 29% POS vs.12% placebo at 12 hrs post-POS dose (p=0.02) | Durable near vision (18 hrs)<br>Optimal pupil size<br>Pupillary light reflex | |
| **Presbyopia (POS + LDP)**<br>**Phase 3** | | **Met Phase 2 primary endpoint**<br>**Met planned Phase 3 primary endpoint**<br>**VEGA-1**: 61% combo post-LDP dose (30 min) + post-POS dose (12 hrs) vs. 14% placebo (p<0.0001) | Durable near vision gain<br>Optimal pupil size<br>Pupillary light reflex | |
| **DLD**<br>**2nd Phase 3** | ≥3 lines (eye test) of improvement in mesopic low contrast best-corrected distance visual acuity (mLCVA) | **Met Phase 3 primary endpoint**<br>**LYNX-1**: 13% POS vs. 3% placebo at Day 8 (p<0.05) and 21% in POS vs.3% placebo at Day 15 (p<0.01) | Improvement visual acuity measures (distance and near) in dim light conditions | |

# Corporate Highlights

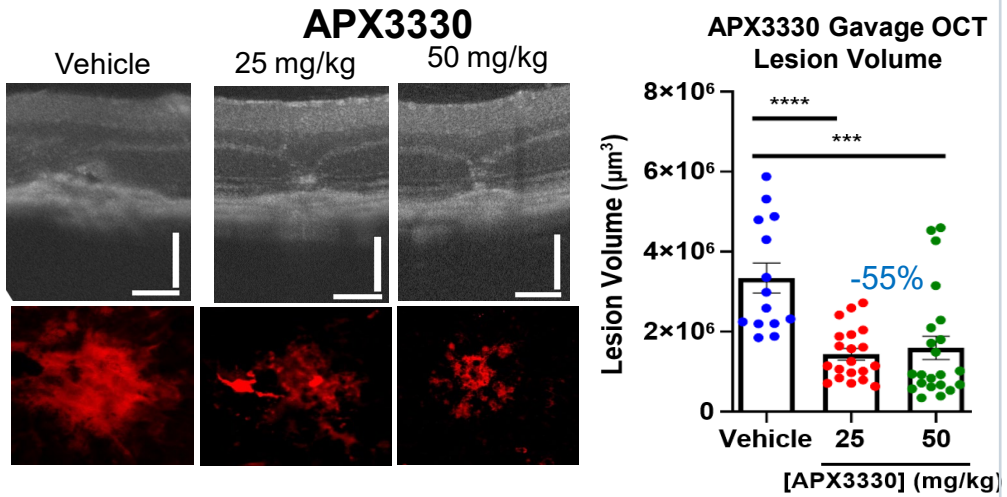
- ***Late-Stage Retinal Pipeline*** *Represents* ***Multi-Billion Dollar Opportunity*** *in Unmet NPDR Patients*
- ***APX3330 – Novel, Non-Invasive, Safe Oral Tablet*** *to Treat Diabetic Retinopathy*
- *APX Pipeline Driven by a* ***Paradigm Changing, Dual Target Ref-1 Platform*** *for Retinal Diseases*
- ***Global License Agreement with Viatris*** *to Fund Development and Commercialization of Phentolamine Ophthalmic Solution 0.75% for All Refractive Indications*
- ***Strong Financial Position*** *to Fund Operations into 2025*

# Preclinical Data: Oral APX3330 Blocks Neovascularization

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

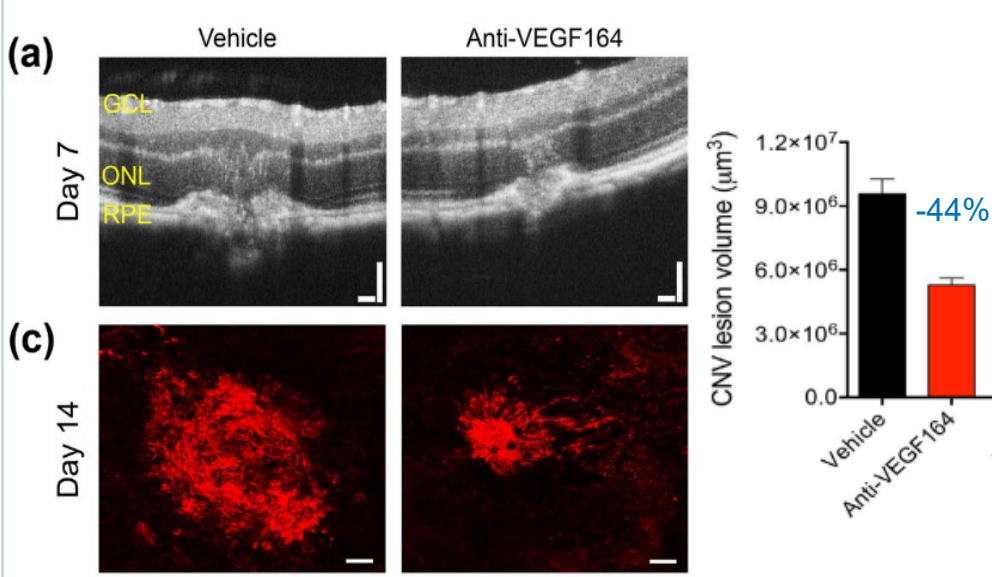
## L-CNV Mouse Retina Model

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******

Ocuphire PHARMA

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)

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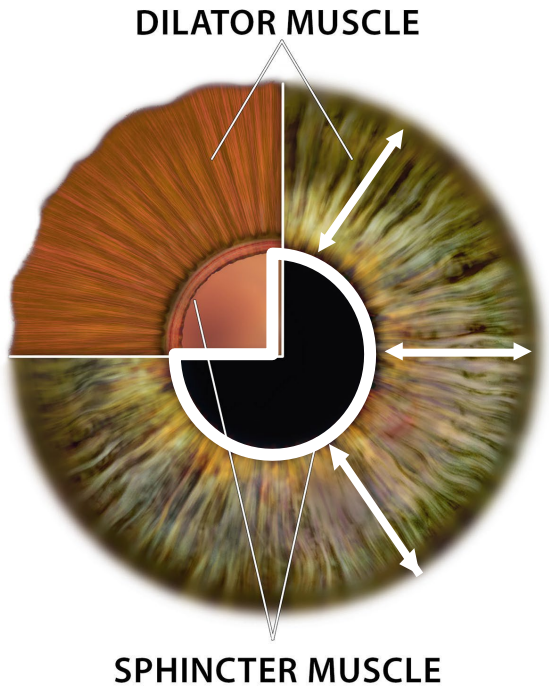
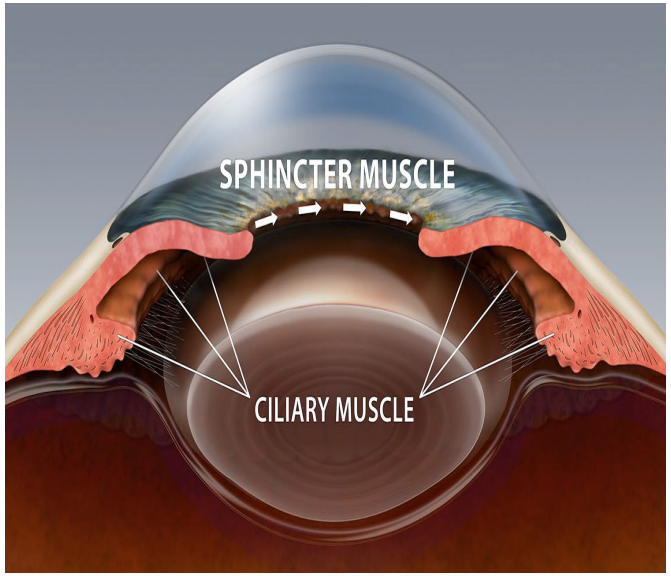
# Appendix

# Phentolamine Ophthalmic Solution 0.75%'s Differentiated MOA as an Alpha-1 Blocker

*No Engagement of Ciliary Muscle, No Headaches and Lower Risk of Retinal Detachment*

## Phentolamine is the Active Ingredient in POS: a non-selective α Antagonist



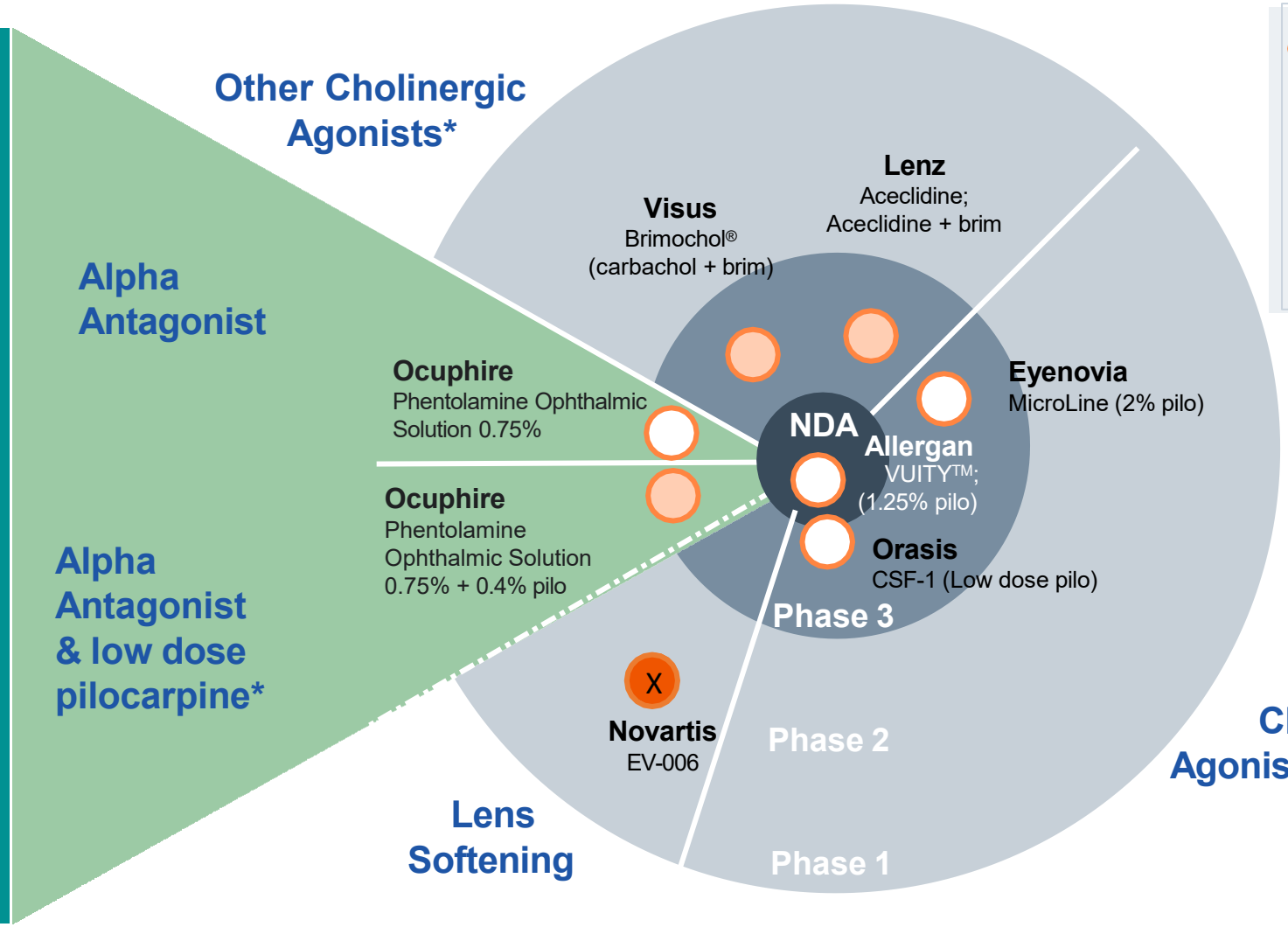

Phentolamine blocks α1 receptors on the **Iris Dilator Muscle up to 24 hours**

Decreases pupil size (moderately) **without affecting the iris sphincter or ciliary muscles**

**505(b)(2) Regulatory Pathway Supported by Prior Phentolamine Approvals in Non-Ophthalmic Indications**

# A New, Differentiated MOA and Combination Therapy Offers Tunability

- **POS's potential differentiation:**
  1) **New MOA class** (iris dilator muscle inhibitor)
  2) **Favorable safety and tolerability** (e.g.: no headaches, no accommodative spasm, no risk of retinal detachment)
  3) **24-hour durability**
  4) **Broad range of patients including high myopes**
  5) **Improvement in night vision disturbances**
- **POS+LDP may offer added efficacy and tunability**




** acts on sphincter and ciliary muscles in dose-dependent manner*

Corporate Websites as of October 31, 2023,
Grzybowski, A, Markeviciute A, Zemaitiene R. A Review of Pharmacological Presbyopia Treatment. 2020

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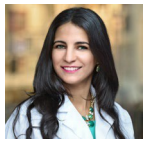

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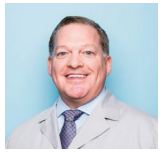

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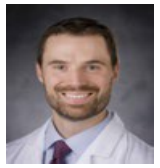

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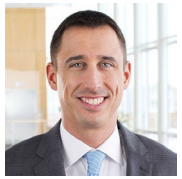

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