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 Ocphire 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 Ocphire’s product candidates; (ix) the success and timing of commercialization of any of Ocphire’s product candidates, including the scalability of Ocphire’s product candidates and (x) the maintenance of Ocphire’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

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

Partnered with Viatris
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
Diabetic Retinopathy at a Glance

Current Treatment Landscape Demonstrates Need for Non-Invasive Therapies

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

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

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
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

34 Million Diabetics in US

10M Diabetic Retinopathy (DR)

Types of DR

Non-Proliferative DR

Proliferative DR

Target Patient Population

8M NPDR Patients

US Market Opportunity

~$6B+

Real-World Chart Review of DR Patients in US

% of Patients

- 22% Proliferative diabetic retinopathy (PDR)
- 24% Severe non-proliferative diabetic retinopathy (NPDR)
- 27% Moderate non-proliferative diabetic retinopathy (NPDR)
- 27% Mild non-proliferative diabetic retinopathy (NPDR)

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

Spheres Global Insights: DR Market DYNAMIX October 2022
Early treatment diabetic retinopathy study research group, ophthalmology. 1991;98(5 suppl):823-33.
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

Wait and Monitor for Progression

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

PDR

Anti-VEGF Injections

Gold standard Eylea® and Lucentis® injections are effective treatments in the first year for PDR
**Landscape of Investigational Non-Invasive Therapies for Diabetic Retinopathy**

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

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

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).

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*

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug</th>
<th>Target/MOA</th>
<th>Route of Administration</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Commercial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>REGENERON</strong></td>
<td><strong>Eylea®</strong></td>
<td>VEGF-A/B; PIGF</td>
<td>Intravitreal</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓*¹</td>
</tr>
<tr>
<td>(aflibercept)</td>
<td><strong>Lucentis®</strong></td>
<td>VEGF-A</td>
<td>Intravitreal</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓*²</td>
</tr>
<tr>
<td><strong>Roche</strong></td>
<td><strong>KSI-301</strong></td>
<td>VEGF</td>
<td>Intravitreal</td>
<td>✓</td>
<td>N/A</td>
<td></td>
<td>○</td>
</tr>
<tr>
<td>(Tarcocimab)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>KODIAK</strong></td>
<td><strong>EYP-1901</strong></td>
<td>VEGF</td>
<td>Intravitreal</td>
<td>✓</td>
<td></td>
<td></td>
<td>○</td>
</tr>
<tr>
<td><strong>EyePoint</strong></td>
<td><strong>BI 764524</strong></td>
<td>Anti-Sema3A</td>
<td>Intravitreal</td>
<td>✓</td>
<td></td>
<td></td>
<td>○</td>
</tr>
<tr>
<td>Pharmaceuticals</td>
<td></td>
<td>Ischemia modulator</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boehringer Ingelheim</td>
<td><strong>OTX-TKI</strong></td>
<td>Axitinib* (TKI)</td>
<td>Intravitreal</td>
<td>✓</td>
<td></td>
<td></td>
<td>○</td>
</tr>
<tr>
<td><strong>Ocular</strong></td>
<td><strong>RGX-314</strong></td>
<td>AAV8-VEGF</td>
<td>Suprachoroidal (Gene Therapy)</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biologics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

Company websites and [www.clinicaltrials.gov](http://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 (NFκB)

**Mechanism of Action – Ref-1 Inhibition**

- **Hypoxia**
  - Ref-1
  - HIF-1α
  - VEGF (Signaling Cascade)

- **Inflammation**
  - APX3330
  - Ref-1
  - NF-κB
  - TNF-α
  - Chemokines
  - Other Growth Factors (Signaling Cascade)

**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

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+**

**APX3330 Preclinical Efficacy & Toxicology Package**

- **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

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**

**VEGF**

Control  APX3330

Increasing APX3330 dose

**VEGF**

% Positive area (±SE)

T1DM-MCAo  +APX3330

**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


**APX3330 VEGF Effects in Normal Cells**

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

- 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.

**Normal Conditions:**
- Physiological level of VEGF activity

**Abnormal Conditions (e.g., hypoxic):**
- Increased level of VEGF activity

**Biologic anti-VEGF agents inactivate VEGF directly and reduce VEGF levels below normal levels**

**Inhibition of Ref-1 by APX3330 returns VEGF levels to normal levels**

**APX3330 prevents VEGF overproduction in ARPE-19 cells**

- OxLDL: 0, 50, 100, 150 μg/mL, 30 μM
- APX3330: -, +

Graph showing VEGF Concentrations (% of Control) with significance level p < 0.05.
**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
- ETDRS BCVA ≥ 60 letters (20/63)

**Key exclusion:**
- OCT CST >320 µm²
- Center involved DME allowed in fellow eye
- Anti-VEGF within past 6 months
- HbA1c ≥ 12.0%

**Endpoints**

**Primary:**
- % subjects with ≥ 2 step improvement on DRSS (Diabetic Retinopathy Severity Scale) 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
### ZETA-1: Baseline Demographics and Systemic Characteristics

**Well-Balanced Across Arms**

### Demographics

<table>
<thead>
<tr>
<th>Demographic</th>
<th>APX3330 n=51</th>
<th>Placebo n=52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) mean (range)</td>
<td>54.3 (26-81)</td>
<td>58.3 (24-78)</td>
</tr>
<tr>
<td>Sex: Male n (%)</td>
<td>24 (47%)</td>
<td>26 (50%)</td>
</tr>
<tr>
<td>Race: White n (%)</td>
<td>40 (78%)</td>
<td>41 (79%)</td>
</tr>
<tr>
<td>Ethnicity: Hispanic or Latino n (%)</td>
<td>28 (55%)</td>
<td>23 (44%)</td>
</tr>
<tr>
<td>Diabetes Status (years) mean (range)</td>
<td>15 (0-36)</td>
<td>16 (0-58)</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg) mean</td>
<td>136</td>
<td>139</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg) mean</td>
<td>82</td>
<td>80</td>
</tr>
<tr>
<td>Heart Rate (beats/min) mean</td>
<td>77</td>
<td>76</td>
</tr>
<tr>
<td>Hemoglobin A1C (%) mean</td>
<td>8.4</td>
<td>8.3</td>
</tr>
<tr>
<td>Body Mass Index (kg/m^2) mean</td>
<td>31</td>
<td>31</td>
</tr>
</tbody>
</table>

### DRSS Scores

#### DRSS Score – Study Eye

<table>
<thead>
<tr>
<th>Score Description</th>
<th>APX3330 n=49</th>
<th>Placebo n=52</th>
</tr>
</thead>
<tbody>
<tr>
<td>47 (Moderately severe to severe NPDR)</td>
<td>22 (43%)</td>
<td>18 (35%)</td>
</tr>
<tr>
<td>53 (Moderately severe to severe NPDR)</td>
<td>25 (49%)</td>
<td>28 (54%)</td>
</tr>
<tr>
<td>61 (Mild proliferative diabetic retinopathy)</td>
<td>4 (8%)</td>
<td>6 (12%)</td>
</tr>
</tbody>
</table>

#### DRSS Score – Fellow Eye

<table>
<thead>
<tr>
<th>Score Description</th>
<th>APX3330 n=49</th>
<th>Placebo n=52</th>
</tr>
</thead>
<tbody>
<tr>
<td>43 or Lower (Mild to moderate NPDR or better)</td>
<td>15 (31%)</td>
<td>13 (25%)</td>
</tr>
<tr>
<td>47 (Moderately severe to severe NPDR)</td>
<td>15 (31%)</td>
<td>20 (38%)</td>
</tr>
<tr>
<td>53 (Moderately severe to severe NPDR)</td>
<td>12 (25%)</td>
<td>10 (19%)</td>
</tr>
<tr>
<td>61 (Mild proliferative diabetic retinopathy)</td>
<td>1 (2%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>65 or Higher (Moderate to severe prolif. DR)</td>
<td>6 (12%)</td>
<td>5 (10%)</td>
</tr>
</tbody>
</table>

### Key Visual Metrics

<table>
<thead>
<tr>
<th>Metric</th>
<th>APX3330 n=51</th>
<th>Placebo n=52</th>
<th>Total n=103</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCVA Study Eye Letters (mean)</td>
<td>81</td>
<td>78</td>
<td>80 (20/25 Snellen)</td>
</tr>
<tr>
<td>BCVA Fellow Eye Letters (mean)</td>
<td>76</td>
<td>77</td>
<td>77 (20/32 Snellen)</td>
</tr>
<tr>
<td>OCT CST Study Eye (µm)</td>
<td>270</td>
<td>271</td>
<td>271</td>
</tr>
<tr>
<td>OCT CST Fellow Eye (µm)</td>
<td>292</td>
<td>286</td>
<td>289</td>
</tr>
<tr>
<td>Intraretinal Fluid in the Center of SE</td>
<td>Y – 21 N – 26</td>
<td>Y – 12 N – 31</td>
<td>Y – 33 N – 57</td>
</tr>
<tr>
<td>Intraretinal Fluid at the Foveal Center of SE</td>
<td>Y – 1 N – 20</td>
<td>Y – 1 N – 11</td>
<td>Y – 2 N – 31</td>
</tr>
<tr>
<td>Intracocular Pressure in Study Eye (mmHg)</td>
<td>15</td>
<td>16</td>
<td>15</td>
</tr>
</tbody>
</table>

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

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

**Systemic Drugs**

Approvable endpoints for systemic drug in DR include either:

- \(\geq 3\)-step DRSS improvement on a binocular scale
- \(\geq 3\)-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

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**

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

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)

Change in Person Score @ Week 24 (LOCF)

Placebo (n=50)  APX3330 (n=47)

<table>
<thead>
<tr>
<th>Change</th>
<th>Placebo</th>
<th>APX3330</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 4</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>≥ 3</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>≥ 2</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>≥ 1</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>0</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>≤ -1</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>≤ -2</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>≤ -3</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>≤ -4</td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>
ZETA-1: Percent of Subjects with Improvement or Worsening in DRSS at Wk 24 on the Binocular Person Scale (Observed Cases)

Change in Person Score @ Week 24 (Observed Cases)

<table>
<thead>
<tr>
<th>Change</th>
<th>Placebo (n=45)</th>
<th>APX3330 (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 4</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>≥ 3</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>≥ 2</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>≥ 1</td>
<td>31</td>
<td>34</td>
</tr>
<tr>
<td>0</td>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td>≤ -1</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>≤ -2</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td>≤ -3</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>≤ -4</td>
<td>4</td>
<td>11</td>
</tr>
</tbody>
</table>

DRSS Improvement

DRSS Worsening
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: Treatment of Emergent Adverse Events**

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

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

**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
- 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

**AEs in >5% of Subjects***

- Diabetic Retinal Edema: 5 (10%) Placebo, 2 (4%) APX3330
- Diabetic Retinopathy: 6 (12%) Placebo, 1 (2%) APX3330
- Vitreous detachment: 3 (6%) Placebo, 0 (0%) APX3330
- Cataract: 1 (2%) Placebo, 3 (6%) APX3330
- Pruritus: 1 (2%) Placebo, 6 (12%) APX3330
- Rash: 1 (2%) Placebo, 3 (6%) APX3330
- COVID-19: 5 (10%) Placebo, 1 (2%) APX3330

---

*Preferred Term within Organ Class

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

- $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

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
Treatment of Pharmacologically-Induced Mydriasis

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

Phentolamine Ophthalmic Solution
0.75%

THREE INDICATIONS

Presbyopia

1. POS as a Single Drop
2. POS with LDP Adjunctive Therapy

Dim Light or Night Vision Disturbances (DLD)

NEW PARTNERSHIP WITH VIATRIS
## Summary of Phentolamine Ophthalmic Solution 0.75% Trial Results

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

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

- Efficacy was also seen after single intravitreal injection of 20µM APX3330 in mouse L-CNV model**
- Efficacy was also seen after dosing intraperitoneal 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 intravitreal injection of 20µM APX3330 in Vldlr \(-/-\) mice model****

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)
Phentolamine is the Active Ingredient in POS: a non-selective \( \alpha \) Antagonist

Phentolamine blocks \( \alpha_1 \) 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
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

Other Cholinergic Agonists*

Alpha Antagonist

Alpha Antagonist & low dose pilocarpine*

Lens Softening

Cholinergic Agonist* (pilocarpine)
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