Ocuphire KOL Event: APX3330

October 14, 2022
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## Ocuphire APX3330 KOL Event: Agenda & Speakers

<table>
<thead>
<tr>
<th>Speakers</th>
<th>Agenda</th>
<th>Time (EDT)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mina Sooch, MBA</strong>&lt;br&gt;President &amp; CEO and Founder</td>
<td>Introductions &amp; Company Overview</td>
<td>11:00 am – 11:10 am</td>
</tr>
<tr>
<td><strong>Caroline Baumal, MD</strong>&lt;br&gt;Tufts Medical Center</td>
<td>Disease of Diabetic Retinopathy</td>
<td>11:10 am – 11:20 am</td>
</tr>
<tr>
<td><strong>Peter Kaiser, MD</strong>&lt;br&gt;Cleveland Clinic Cole Eye Institute</td>
<td>Current DR/DME Treatment Landscape</td>
<td>11:20 am – 11:35 am</td>
</tr>
<tr>
<td><strong>David Lally, MD</strong>&lt;br&gt;New England Retina Consultants</td>
<td>APX3330, Paradigm-Shifting Oral Treatment Option</td>
<td>11:35 am – 11:50 am</td>
</tr>
<tr>
<td><strong>Caroline Baumal, MD</strong>&lt;br&gt;Tufts Medical Center</td>
<td>ZETA-1, Phase 2b Trial in Diabetic Retinopathy and Masked Safety Data</td>
<td>11:50 am – 12:00 pm</td>
</tr>
</tbody>
</table>
# Ocuphire APX3330 KOL Event: Agenda & Speakers

<table>
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<th>Time (EDT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peter Kaiser, MD</td>
<td>ZETA-1 Trial Design and Data Expectations</td>
<td>12:00 pm – 12:15 pm</td>
</tr>
<tr>
<td>Caroline Baumal, MD</td>
<td></td>
<td></td>
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<tr>
<td>David Lally, MD</td>
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</tr>
<tr>
<td></td>
<td>Q&amp;A</td>
<td>12:15 pm – 12:30 pm</td>
</tr>
<tr>
<td>Mina Sooch, MBA</td>
<td>Q&amp;A Closing Remarks</td>
<td></td>
</tr>
<tr>
<td>Mitch Brigell, PhD</td>
<td></td>
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<tr>
<td>Mark Kelley, PhD</td>
<td></td>
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</tr>
<tr>
<td>Peter Kaiser, MD</td>
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<tr>
<td>Caroline Baumal, MD</td>
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<tr>
<td>David Lally, MD</td>
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</tbody>
</table>
Company Overview

Presenter: Mina Sooch, CEO and Founder of Ocuphire Pharma

- Over 25 years of pharmaceutical and biotech experience as CEO, entrepreneur, venture capitalist, and strategy consultant
- Successful track record of hundreds of millions of capital raised for leading private/public biotech companies
- Experience across multiple diseases (cardiovascular, oncology, renal, NASH, CNS, etc.) prior to ophthalmology
- Recipient of numerous awards, including Deal Makers of the Year in 2016 and Alumni Commencement Speaker WSU College of Engineering in 2021
Upcoming Catalysts in 4Q22:

- Topline Results APX3330 ZETA-1 P2b trial for DR/DME
- NDA Filing for Nyxol for RM

Ocuphire Pharma
Nasdaq: OCUP

Founded in 2018, Acquired 2 Lead Assets for Front & Back of Eye Therapies with Novel MOAs & Patent Coverage to 2034+

- Nyxol eyedrops
  - Reversal of Mydriasis ("RM") – eye dilation
  - Presbyopia – age-related blurry near vision
  - Night Vision Disturbance ("NVD") – halos, glares, starbursts
- APX3330 oral tablets
  - Diabetic retinopathy ("DR") – diabetes-related retinal (eye) disease

Four Large Markets (~$20B US total) w/Unmet Needs and Limited to No Competition

Successful Execution of 5 Trials in last 2 Years with 6 Positive Phase 3 & Phase 2 Data Read-outs for Nyxol in RM, Presbyopia, and NVD

- Potential 2023 commercialization opportunities in RM
- Near-term initiation planned for Presbyopia VEGA Phase 3 program with Nyxol alone and Nyxol with 0.4% Low Dose Pilocarpine as adjunctive therapy
# Ocuphire Overview

*Two Late-Stage Clinical Assets Addressing Unmet Needs in Multiple Large Markets*

## Refractive

<table>
<thead>
<tr>
<th>Nyxol</th>
<th>APX3330</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novel α1/α2 Blocker 505(b)(2)</td>
<td>Oral REF-1 Inhibitor New Chemical Entity</td>
</tr>
<tr>
<td>NDA-Filing Ready</td>
<td>Phase 2b Data 4Q22</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>12 Completed Phase 1, Phase 2, and Phase 3 Trials</th>
<th>11 Completed Phase 1 and Phase 2 Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;650 Subjects Dosed</td>
<td>&gt;340 Subjects Dosed</td>
</tr>
<tr>
<td>Exposure in Humans 28 Days</td>
<td>Exposure in Humans 365 Days</td>
</tr>
<tr>
<td>Patent Coverage 2034+</td>
<td>Patent Coverage 2034+</td>
</tr>
</tbody>
</table>

### Prevalence (US) Development Milestone

| Reversal of Mydriasis | ~100 M | 2 Phase 3 Positive Data & Ped P3 |
| Presbyopia | ~128 M | Phase 2 Positive Data Single & Combo |
| Night Vision Disturbances | ~36 M | 1st Phase 3 Positive Data |

| Diabetic Retinopathy | ~8 M | Phase 2b Last Patient Last Visit Completed Aug 22 |
| Diabetic Macular Edema | ~2.4 M | |

Source: Eisai and Apexian Data; GlobalData Market Research Report, 2020; Company Estimates for US Market Size; Ocuphire internal estimates
Track Record of Achieving Milestones
Multiple Positive Data Readouts with Multiple Catalysts Ahead

2021 – 1H 2022

- **Positive** Nyxol Phase 3 Data for RM (MIRA-2)
- **Positive** Nyxol+LDP Phase 2 Data for Presbyopia (VEGA-1)
- **Positive** Nyxol Alone P2 Data for Presbyopia (VEGA-1)
- **Positive** Nyxol 2nd Phase 3 Data for RM (MIRA-3)
- **Positive** Nyxol Pediatric Data for RM (MIRA-4)
- **Positive** Nyxol Phase 3 Data for NVD (LYNX-1)

2H 2022 – 2023

- Submit Nyxol NDA for RM
- Report APX3330 Phase 2b Data for DR/DME (ZETA-1)
- Initiate VEGA Phase 3 Presbyopia Program
- Potential Nyxol Approval and Commercialization

Ongoing Partnering Discussions with Leading Ophthalmic Companies (including Europe and Asia)
Disease of Diabetic Retinopathy

Presented by: Caroline Baumal, MD

Caroline Baumal, MD
University of Toronto

- Professor of Ophthalmology at Tufts Medical Center
- Co-Director of the Retina Service and Medical Retina Fellowship at New England Eye Center
- Authored over 170 publications, 33 book chapters on retinal diseases, and edited the book Treatment of Diabetic Retinopathy
- Recognized by the American Society of Retinal Surgeons, The Retinal Hall of Fame and received such honors as the Donald J. Gass Beacon of Sight Award from the Florida Ophthalmologic Society and the ASRS Crystal Apple award from the Vit-Buckle Society.
Diabetic Eye Disease is 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
Diabetes is a Growing Global Health Epidemic

Diabetes Cost Burden Over $900 Billion Dollars in Worldwide Health Expenditure

Diabetic Patients Usually Present with Complex Co-Morbidities

Diabetic Patients are Young and Face Life-long Systemic and Ocular Complications


Patients with DME have an even greater risk of complications than diabetes patients without DME

DR is the most common cause of vision loss or blindness in working-age adults, usually affecting both eyes

DME is a vision threatening complication caused by DR where excess fluid leaks near fovea and triggers swelling of the macula

Treating DR leads to control of DME

Oral options have the potential to reach other vascular beds to treat kidney and neuropathic co-morbidities
Global Prevalence of Diabetes-Associated Retinal Disease

DR Affects 1 in 3 People with Diabetes; DME Affects 1 in 13 People with Diabetes


2. American Diabetes Association; American Journal of Managed Care, International Diabetes Federation; Healthline; Ocufize internal analysis and assumptions

*Global estimates are provided by the National Eye Institute, FactSheet, Global Data, Research and Markets, American Academy of Ophthalmology, and PLOS One
Diabetic Retinopathy Severity Scale (DRSS) was developed to differentiate proliferative DR (PDR) from non-proliferative DR (NPDR).
Early screening and treatment for DR can reduce vision loss by up to 94%.

Regardless of severity, all eyes worsen over time.

Vision Loss is #1 Concern of Diabetic Patients

Diabetic Retinopathy is a Progressive Vision-Threatening Disease

What are the top concerns for diabetic patients?

- **Vision Loss**: 40%
- **Amputation, Losing a Leg**: 38%
- **Cardiovascular/Heart Problems**: 35%
- **Other Eye Problems**: 35%
- **Foot Problems**: 30%
- **Kidney Problems**: 25%

Source: Patient survey adapted from Lions International Foundation and International Diabetes Foundation-Europe; Meltzer 2000

N=2702
Early Management of Diabetic Retinopathy
Poor Adherence to Medical Management and Lifestyle Options Worsen DR

Medical and lifestyle management is first line of treatment

- Control of Blood Sugar
- Control of Blood Pressure
- Smoking Cessation
- Control of Lipids

Majority of Physicians Use a “Wait and Monitor” Approach for DR Patients
Over 90% of DR Patients Are Not Treated Proactively and Anti-VEGF Use is Limited

How do physicians treat patients with severe NPDR without DME?

<table>
<thead>
<tr>
<th>Option</th>
<th>International</th>
<th>US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Closely monitor retinopathy and encourage systemic glycemic control</td>
<td>69.5%</td>
<td>60.5%</td>
</tr>
<tr>
<td>Consider anti-VEGF in some patients with poor glycemic control and/or other risks</td>
<td>17.0%</td>
<td>24.9%</td>
</tr>
<tr>
<td>Consider anti-VEGF in some patients with good glycemic control and compliance</td>
<td>4.9%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Consider anti-VEGF therapy in all or most patients</td>
<td>7.7%</td>
<td>7.8%</td>
</tr>
<tr>
<td>Other</td>
<td>10.9%</td>
<td>3.7%</td>
</tr>
</tbody>
</table>

Source: ASRS 2021 Preferences and Trends (PAT) Survey
Diabetic Retinopathy At a Glance
Current Treatment Landscape Demonstrates Need for Less Invasive Therapies

There are ~8M adults in the U.S. with DR¹

DR/DME affects about 1 in 4 people with type 1 and type 2 diabetes

DR is the leading cause of blindness among working-age adults

If untreated, DR can rob people of their vision prematurely²,³

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

56% of patients reported anxiety related to anti-VEGF treatment

$13B (2020)

Global Intravitreal Injection Revenues in AMD, DME and BRVO⁴

 Majority of moderate to severe patients with DR are not treated with anti-VEGF due to injection fear and burden

Source:
1. American Diabetes Association; International Diabetes Federation; Healthline; *Ocuphire internal analysis and assumptions;
3. Patient survey adapted from Lions International Foundation and International Diabetes Foundation – Europe; Meltzer 2000
4. 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
Current DR/DME Treatment Landscape

Presented by: Peter Kaiser, MD

- Chaney Family Endowed Chair in Ophthalmology Research, Professor of Ophthalmology, Cleveland Clinic Lerner College of Medicine and Cole Eye Institute
- Clinical research expert, serving as a Study Chairman of 5 major, multi-center, international trials, and principal investigator for numerous studies for AMD, DR, and other retinal disorders.
- Major contributions to medical literature having authored 7 textbooks, more than 250 peer-reviewed papers
- Recognized by American Academy of Ophthalmology and American Society of Retina Specialist with Senior Achievement Awards.
MOA focused on VEGF and local delivery have demonstrated efficacy for approved treatments, are the current standard of care, and have been highly effective for wAMD/DME. However, these therapies have limited use in DR.
Panorama Study Further Emphasizes Need for Proactive Treatment of NPDR

Eyes Treated with Aflibercept Showed a >2-step Improvement in DRSS Level at 24 and 52 Weeks

Population: Adults with severe NPDR w/o DME
- 225 Male; 177 Female
- Mean Age: 56 years (10.5)

Setting: Global, Multi-Center Study

Intervention: 402 Eyes randomized to 3 arms (1 eye per participant)
- IVT Aflibercept 2q16
  - 2 mg monthly x 3 doses then every 8 weeks x 1 dose, followed by every 16 weeks through week 100
- IVT Aflibercept 2q8 as needed
  - 2 mg monthly x 5 doses then every 8 weeks through week 52 then as needed through week 100
- IVT Sham
  - Observation with sham IV injections

Primary Endpoint:
- Proportion of participants with ≥2 step improvement in the DRSS scale at 24 and 52 weeks

Proportion of Eyes With ≥ 2-Step Improvement in DRSS Score From Baseline Through Week 100 (n = 133)

## AAO-Preferred Practice Pattern Reveals High Unmet Need in Mild, Moderate, and Severe NPDR Patients

Unmet Need Remains High in Mild, Moderate and Severe NPDR Patients

### Management Recommendations for Patients with Diabetes

<table>
<thead>
<tr>
<th>Severity of Retinopathy</th>
<th>Presence of Macular Edema</th>
<th>Follow-up (Months)</th>
<th>Panretinal Photocoagulation (Scatter) Laser</th>
<th>Focal and/or Grid Laser*</th>
<th>Intravitreal Anti-VEGF Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal or minimal NPDR</td>
<td>No</td>
<td>12</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Mild NPDR</td>
<td>No</td>
<td>12</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>NCI-DME</td>
<td>3-6</td>
<td>No</td>
<td>Sometimes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>CI-DME</td>
<td>1*</td>
<td>No</td>
<td>Rarely</td>
<td>Usually</td>
</tr>
<tr>
<td>Moderate NPDR</td>
<td>No</td>
<td>6-12t</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>NCI-DME</td>
<td>3-6</td>
<td>No</td>
<td>Sometimes</td>
<td>Rarely</td>
</tr>
<tr>
<td></td>
<td>CI-DME</td>
<td>1*</td>
<td>No</td>
<td>Rarely</td>
<td>Usually</td>
</tr>
<tr>
<td>Severe NPDR</td>
<td>No</td>
<td>3-4</td>
<td>Sometimes</td>
<td>No</td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td>NCI-DME</td>
<td>2-4</td>
<td>Sometimes</td>
<td>Sometimes</td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td>CI-DME</td>
<td>1*</td>
<td>Sometimes</td>
<td>Rarely</td>
<td>Usually</td>
</tr>
<tr>
<td>Non-high-risk PDR</td>
<td>No</td>
<td>3-4</td>
<td>Sometimes</td>
<td>No</td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td>NCI-DME</td>
<td>2-4</td>
<td>Sometimes</td>
<td>Sometimes</td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td>CI-DME</td>
<td>1*</td>
<td>Sometimes</td>
<td>Sometimes</td>
<td>Usually</td>
</tr>
<tr>
<td>High-risk PDR</td>
<td>No</td>
<td>2-4</td>
<td>Recommended</td>
<td>No</td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td>NCI-DME</td>
<td>2-4</td>
<td>Recommended</td>
<td>Sometimes</td>
<td>Sometimes</td>
</tr>
<tr>
<td></td>
<td>CI-DME</td>
<td>1*</td>
<td>Recommended</td>
<td>Sometimes</td>
<td>Usually</td>
</tr>
</tbody>
</table>

An oral option for DR strengthens treatment options across all stages. Physicians have limited non-invasive treatment options.

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Source: Diabetic Retinopathy Preferred Practice Pattern – AAO 2019; LTFU: Lost To Follow-up; IVT: Intravitreal Injections; PRP: Panretinal Photocoagulation
Current Conventional Treatment is Challenging for Patients
Access and Time Burden are Further Barriers for DR Patient Compliance

Patient-Reported Barriers to Follow-Up Treatment (N = 209)

<table>
<thead>
<tr>
<th>Reported Barriers</th>
<th>Adjusted Odds Ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long waiting times</td>
<td>1.22 (0.63-2.00)</td>
</tr>
<tr>
<td>Other medical or physical condition</td>
<td>1.91 (1.02-3.57)</td>
</tr>
<tr>
<td>Forgot to come</td>
<td>4.35 (2.14-8.86)</td>
</tr>
<tr>
<td>Unable to leave work responsibilities</td>
<td>1.15 (0.41-3.22)</td>
</tr>
<tr>
<td>Other incidental obligations</td>
<td>1.81 (0.59-5.51)</td>
</tr>
<tr>
<td>Lack of an escort</td>
<td>2.14 (0.60-7.58)</td>
</tr>
<tr>
<td>Unhappy with previous care</td>
<td>0.92 (0.27-3.12)</td>
</tr>
<tr>
<td>Financial cost</td>
<td>0.70 (0.20-2.41)</td>
</tr>
</tbody>
</table>

Office Visit Time Commitments
Mean: 90 min
Range: 13 - 261 min

DR patients are generally asymptomatic which contributes to poor adherence and compliance

* adjusted for age, gender, insurance type, severity of DR

Multiple Targets in DME/DR Treatment Landscape

Anti-VEGF Therapy is Mainstay, but Under/Non-Responders Remain, and Early Treatment is Limited

Available Commercialized Therapies:

**Anti-VEGF IVT:**
- Afibercept (Eylea®)
- Ranibizumab (Lucentis®)
- Bevacizumab (Avastin®)
- Faricimab (Vabysmo®)

**IVT Steroids:**
- Dexamethasone (Ozurdex®)

Emerging therapies that could shape industry:

- Longer Duration IVTs
- Extended Release
- Combination Therapies

Oral Therapies
- Topical
- Gene Therapies

https://www.reviewofophthalmology.com/article/a-peek-into-the-diabetic-retinopathy-pipeline
## Intravitreal Injections Landscape (DR patients)

*Eylea/Lucentis Approved, But Not Used in Patients with Mild NPDR and 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>REGENERON</td>
<td>Eylea (aflibercept)</td>
<td>VEGF-A/B; PIGF</td>
<td>Intravitreal</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓*¹</td>
</tr>
<tr>
<td>Roche</td>
<td>Lucentis (ranibizumab)</td>
<td>VEGF-A</td>
<td>Intravitreal</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓*²</td>
</tr>
<tr>
<td>KODIAK</td>
<td>KSI-301 (Tarcocimab)</td>
<td>VEGF</td>
<td>Intravitreal</td>
<td>✓</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EyePoint</td>
<td>EYP-1901</td>
<td>Voloronib (TKI)</td>
<td>Intravitreal</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boehringer Ingelheim</td>
<td>BI 764524</td>
<td>Anti-Sema3A Ischemia modulator</td>
<td>Intravitreal</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular</td>
<td>OTX-TKI</td>
<td>Axitinib (TKI)</td>
<td>Intravitreal</td>
<td>✓</td>
<td></td>
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</tr>
<tr>
<td>Regenxbio</td>
<td>RGX-314</td>
<td>AAV8-VEGF</td>
<td>Suprachoroidal (Gene Therapy)</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Company websites: www.clinicaltrials.gov

![Ocuhire logo](image-url)
## Topical Eyedrops in Clinical Development for DR/DME

*Inflammation MOAs in Phase 2 with Novel Eyedrops*

<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>Commercial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oculis</td>
<td>OCS-01</td>
<td>Steroid</td>
<td>DME</td>
<td>Eyedrop</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td></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></td>
</tr>
</tbody>
</table>

✔️ Completed  ○ Ongoing  ✗ Discontinued or Failed study

Company websites: [www.clinicaltrials.gov](http://www.clinicaltrials.gov)
### Oral Treatments in Clinical Development (DR)

**Most Drugs Target Only Inflammation**

<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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lilly</strong></td>
<td>LY333531</td>
<td>Protein Kinase C inhibitor</td>
<td>DR</td>
<td>Oral</td>
<td>✓</td>
<td>✓</td>
<td>X 2006</td>
</tr>
<tr>
<td><strong>Ocuphire</strong></td>
<td>APX3330</td>
<td>Ref-1 inhibitor (Anti-VEGF and Anti-inflammatory)</td>
<td>DR</td>
<td>Oral</td>
<td>✓</td>
<td>○</td>
<td></td>
</tr>
<tr>
<td><strong>ALKAHEST</strong></td>
<td>BAY1101042</td>
<td>Guanylate Cyclase activator</td>
<td>DR</td>
<td>Oral</td>
<td>✓</td>
<td>○</td>
<td></td>
</tr>
<tr>
<td><strong>Roche</strong></td>
<td>AKST4290</td>
<td>CCR3 Eotaxin inhibitor</td>
<td>DR</td>
<td>Oral</td>
<td>✓</td>
<td>○</td>
<td></td>
</tr>
<tr>
<td><strong>Boehringer</strong></td>
<td>RG7774</td>
<td>CB2 receptor (cannabinoid)</td>
<td>DR</td>
<td>Oral</td>
<td>✓</td>
<td>○</td>
<td></td>
</tr>
<tr>
<td><strong>Ingelheim</strong></td>
<td>BI 1467335</td>
<td>AOC3</td>
<td>DR</td>
<td>Oral</td>
<td>✓</td>
<td>○</td>
<td></td>
</tr>
<tr>
<td><strong>InflamX</strong></td>
<td>HCB 1019</td>
<td>Connexin 43 (inflammasome)</td>
<td>DR</td>
<td>Oral</td>
<td>✓</td>
<td>○</td>
<td></td>
</tr>
<tr>
<td><strong>Valo</strong></td>
<td>OPL-0401</td>
<td>ROCK 1/2 inhibitor</td>
<td>DR</td>
<td>Oral</td>
<td>✓</td>
<td>○</td>
<td></td>
</tr>
<tr>
<td><strong>REZDLUTE</strong></td>
<td>RZ402</td>
<td>Plasma Kallikrein</td>
<td>DME</td>
<td>Oral</td>
<td>✓</td>
<td>○</td>
<td></td>
</tr>
</tbody>
</table>

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

**Most Drugs Target Only Inflammation**

- ✓ Completed
- ○ Ongoing
- X Discontinued or Failed study
APX3330 is Different Than Past Oral Failures in Retina
APX3330 Targets Dual, Validated Retinal Disease Pathways with Favorable Human Safety Data

Phase 1

TKIs
- VEGF MOA
- Oral failed due to dose limiting organ toxicity (e.g., hepatic)

Phase 2

Plasma Kallikrein
- MOA targets inflammation
- Oral failed due to systemic toxicity (liver, cardiovascular monitoring)

Phase 3

Protein Kinase C
- VEGF MOA
- Phase 3 endpoint was visual acuity
- FDA requested more data for approval. Eli Lily did not pursue additional clinical trials

Approved

OTC Oral Successes
Nutritional Supplements: Ocuvite®, PreserVision, EyePromise, Oral Vit C & E, Zn, Cu, Lutein, Zeaxanthin®

Iptacopan
Oral Complement inhibitor for GA Safety in Ph2 PNH study:
- headache (31% of patients)
- abdominal discomfort (15%)
- blood alkaline phosphatase increase (15%)
- cough (15%), oropharyngeal pain (15%)
- pyrexia (raised body temperature; 15%), and
- upper respiratory infection (15%)

Eyeleaf® and Lucentis label AREDS & AREDS2 study
New MOAs/therapies are needed to:
• Provide non-invasive options for early disease management
• Decrease in Diabetic Retinopathy Severity Score (DRSS)
• Decrease in macular edema
• Reduce vision threatening complications (VTC)
• Improve in macular ischemia
• Improve compliance by longer acting drugs
• Manage inflammation
• Address non-responders

APX3330 offers:
• A novel, dual MOA
• A novel and non-invasive route, where oral medication allows for early intervention
APX3330: Paradigm Shift Oral Treatment Option

Presented by: David Lally, MD

- Director of the Retina Research Institute at New England Retina Consultants
- Retina Surgeon at Baystate Medical Center
- Assistant Professor of Ophthalmology at the University of Massachusetts Medical School-Baystate
- Published in over 25 peer-reviewed ophthalmic journals and delivered over 25 presentations at national meetings
- Active member of the American Society of Retina Specialists with the Fellow of the American Society of Retina Specialist (FASRS) award designation
APX3330 – Novel and Dual-Acting MOA in an Oral Pill

Ref-1 Involved in Multiple Key Pathways that Contribute to Diabetic Retinopathy and DME

Mechanism of Action – Ref-1 Inhibition

- Ref-1 (reduction-oxidation effector factor-1) is a novel target discovered by Dr. Mark R. Kelley at Indiana University School of Medicine
- APX3330 is a small molecule oral drug candidate and a first-in-class inhibitor of Ref-1
- APX3330 previously developed by Eisai for multiple hepatic inflammatory indications and later by Apexian for advanced solid tumors
  - Similar oncology origin as approved anti-VEGFs
- MOA uniquely decreases both abnormal angiogenesis and inflammation by blocking pathways downstream of Ref-1
In Vitro Validation of APX3330 Mechanism of Action

APX3330 Reduces VEGF levels and Inflammatory Cytokines; Provides Neuronal Protection

APX3330 reduces VEGF protein expression in preclinical stroke model

**Control**  
**APX3330**

APX3330 reduces pro-inflammatory cytokines in LPS stimulated macrophages

**TNF-α**

**IL-6**

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


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 in over 300 subjects has not shown any of the adverse effects that have been seen with systemic administration of anti-VEGF biologics such as cardiovascular pathology, hypertension, arteriothrombotic events, or renal dysfunction.

Kamba 2007; Girardi 2010; Li 2014; APX3330 Investigator Brochure
APX3330 Preclinical & IND-Enabling Studies
Completed Over 20 Preclinical Studies with Favorable Efficacy and Safety

Toxicology Studies
PK, Absorption, Distribution, & Excretion Studies
Safety Pharmacology Studies
Geno Tox, Repro Tox & Antigenicity Studies
Pharmacology Models of Retinal Disease Studies

Extensively Studied in Over 20 In-Vitro and Animal Studies with Favorable Efficacy and Safety
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

- Efficacy was also seen after single intravitreal injection of 20 µM 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 20 µM APX3330 in Vldlr-/- mice model

Silva et al, 2021

*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)
# Summary of APX3330 Prior Clinical Trials

Completed 11 Clinical Trials Across Healthy, Hepatic and Cancer Patients

Extensively Studied in 11 Clinical Trials across Phase 1 and Phase 2 by Eisai and Apexian

## Phase 1 Studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Patient Population</th>
<th>Treatment Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>APX_CLN_0001</td>
<td>Healthy Subjects</td>
<td>APX3330, Placebo</td>
</tr>
<tr>
<td>APX_CLN_0002</td>
<td>Healthy Subjects</td>
<td>APX3330, Placebo</td>
</tr>
<tr>
<td>APX_CLN_0003</td>
<td>Healthy Subjects</td>
<td>APX3330</td>
</tr>
<tr>
<td>APX_CLN_0004</td>
<td>Healthy Subjects</td>
<td>APX3330</td>
</tr>
<tr>
<td>APX_CLN_0008</td>
<td>Healthy Subjects</td>
<td>APX3330, Placebo</td>
</tr>
</tbody>
</table>

## Phase 2 Studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Patient Population</th>
<th>Treatment Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>APX_CLN_0005</td>
<td>Chronic Hep B</td>
<td>APX3330</td>
</tr>
<tr>
<td>APX_CLN_0006</td>
<td>Chronic Hep C</td>
<td>APX3330</td>
</tr>
<tr>
<td>APX_CLN_0007</td>
<td>Chronic Hep C</td>
<td>APX3330, Placebo</td>
</tr>
<tr>
<td>APX_CLN_0009</td>
<td>Acute severe hepatitis</td>
<td>APX3330</td>
</tr>
<tr>
<td>APX_CLN_0010</td>
<td>Alcoholic hepatitis</td>
<td>APX3330</td>
</tr>
<tr>
<td>APX_CLN_0011</td>
<td>Cancer (solid tumors)</td>
<td>APX3330</td>
</tr>
</tbody>
</table>
Phase 1 Clinical Trials: PK Data Supporting the ZETA-1 Trial
APX3330 has Oral Bioavailability and a Sustained PK Profile

**Favorable Oral Bioavailability**

**Sustained Pharmacokinetic Profile**
- $T_{\text{max}}$ 3–4 hours
- Linear dose-proportional PK
- Dose-proportional increase in $C_{\text{max}}$/AUC exposure
- Half-life elimination of 45 hours (steady state [SS] 5–6 days)
- Meals have no clinically meaningful impact on the PK of orally administered APX3330

**Sufficient APX3330 Exposure**
- Plasma levels observed after 120 and 240 mg/day dosing is multiple times higher than what was required for efficacy in preclinical studies
  - planned clinical dose is 600 mg/day
Safety Summary From Phase 1 and Phase 2 Trials
Low AEs Across 11 Trials, <5% Mild Drug Related AEs, Discontinuations Similar Across Arms

<table>
<thead>
<tr>
<th></th>
<th>APX3330 20-240 mg (N=236)</th>
<th>Placebo (N=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%) # events</td>
<td>n (%) # events</td>
</tr>
<tr>
<td>Any event</td>
<td>40 (16.9%) 52</td>
<td>11 (16.2%) 15</td>
</tr>
<tr>
<td>Mild or Moderate adverse Events</td>
<td>39 (16.5%) 50</td>
<td>9 (13.2%) 13</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>1 (0.4%) 2</td>
<td>2 (2.9%) 2</td>
</tr>
<tr>
<td>Adverse events leading to discontinuation</td>
<td>10 (4.3%) 16</td>
<td>5 (7.4%) 7</td>
</tr>
</tbody>
</table>

% = proportion of subjects relative to N, where n = number of subjects with an event and N = the number of subjects in the enrolled population.

Note: This table was generated by Eisai which has slightly different event and sample size counts than the Ocushare analysis. Ocushare will be creating an integrated safety database. The overall conclusions between the Eisai and Ocushare analyses are the same.

<table>
<thead>
<tr>
<th>Totals Across ALL Phase 1 and Phase 2 Studies (Among Healthy Subjects, Hepatitis Patients, and Oncology Patients)</th>
<th>APX3330</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea/Soft Stool (mild)</td>
<td>14/346 (4%)</td>
<td>2/95 (2%)</td>
</tr>
<tr>
<td>Rash/Pruritis (mild)</td>
<td>14/346 (4%)</td>
<td>1/95 (1%)</td>
</tr>
</tbody>
</table>

This includes over 2078 subject-days of exposure at doses ≥600mg and over 17,961 subject-days of exposure at doses <600mg.
ZETA-1 Phase 2b Trial in Diabetic Retinopathy

Presented by: David Lally, MD

David Lally, MD
Jefferson Medical College
ZETA-1 Phase 2b Design for DR/DME

Ongoing, Randomized, Double-Masked, Placebo-Controlled 24-Week Trial (Similar To Eylea P3 DR Trial)

25 US sites
90-100 participants with moderately severe to severe NPDR or mild PDR
Noncentral DME is permitted

Eligibility Screening
Randomization

1:1

Placebo BID

APX3330 600 mg/day (BID)

Primary:
- % of subjects with a ≥ 2 step improvement on the DRSS (Diabetic Retinopathy Severity Scale) score at week 24

Secondary:
- Central subfield thickness (CST)
- BCDVA (ETDRS)
- DRSS change at week 12
- Rescue subjects
- Safety and tolerability

Exploratory:
- Labs / PK

Enrollment of 103 DR Patients Completed (Apr 2021 to Mar 2022)
Top Line Data Expected in Q4 2022
### Key Eligibility Criteria in ZETA-1

**Oral Medication Provides Binocular Treatment; DME Allowed in Fellow Eye**

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Males or non-pregnant females ≥ 18 years of age</td>
<td>- Retinopathy from causes other than diabetes in study eye</td>
</tr>
<tr>
<td>- At least one eye with DR graded at least moderately severe to severe NPDR or mild PDR (corresponding to DRSS 47, 53, or 61, <strong>confirmed by a central reading center</strong>) in which PRP and intravitreal injections of an anti-VEGF agent can be safely deferred for ≥ 6 months in the opinion of the Investigator</td>
<td>- Presence of center involved diabetic macular edema (DME) defined as a central subfield thickness (CST) ≥ 320 μm on SD-OCT or the presence of intra- or subretinal fluid within the central subfield</td>
</tr>
<tr>
<td>- BCVA assessed by ETDRS protocol letters score of ≥ 60 letters (Snellen equivalent 20/63 or better) in the study eye</td>
<td>- Center involved DME in the fellow eye is allowed</td>
</tr>
<tr>
<td>- Body mass index (BMI) between 18 and 40 kg/m², inclusive</td>
<td>- 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</td>
</tr>
<tr>
<td></td>
<td>- Intraocular steroids including triamcinolone and dexamethasone implant within the last 6 months</td>
</tr>
<tr>
<td></td>
<td>- Fluocinolone implant within the last 3 years</td>
</tr>
<tr>
<td></td>
<td>- HbA1c ≥ 12.0%</td>
</tr>
<tr>
<td></td>
<td>- Clinically significant systemic disease (e.g., uncontrolled diabetes, myasthenia gravis, cancer, hepatic, renal, endocrine, or cardiovascular disorders) that might interfere as deemed by Investigator</td>
</tr>
</tbody>
</table>

Source: ZETA-1 trial
Why DRSS is an Important Endpoint?

**FDA Accepted Endpoint for EYLEA® in PANORAMA Pivotal DR Trial - 2 Step Improvement on the DRSS Score**

**Diabetic Retinopathy Severity Scale (DRSS)**

- **DRSS 35**
  - Mild NPDR
  - Visual symptoms mostly absent
  - Small bulges in blood vessels and intraretinal hemorrhages

- **DRSS 43**
  - Moderate NPDR
  - May experience visual symptoms
  - Spotted leaking of blood

- **DRSS 47**
  - Moderately Severe NPDR
  - May experience visual symptoms
  - Leaking of blood in retina, unevenly shaped veins

- **DRSS 53**
  - Severe NPDR
  - May experience visual symptoms
  - Widespread leaking of blood, more unevenly shaped veins

- **DRSS > 60**
  - PDR
  - Visual symptoms are usually present
  - Growth of new fragile blood vessels, in some cases leading to bleeding in the retina and center of the eye

**Example of 2-step improvement**
ZETA-1 Trial: Demographics and Masked Safety Data

Presented by: Caroline Baumal, MD

Caroline Baumal, MD
University of Toronto
## Baseline Characteristics for ZETA-1 Trial

### Typical Demographics for Diabetic Population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total N = 103</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years):</strong></td>
<td>56 (24-81)</td>
</tr>
<tr>
<td>Mean (range)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex:</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>50 (49%)</td>
</tr>
<tr>
<td>Female</td>
<td>53 (51%)</td>
</tr>
<tr>
<td><strong>Race:</strong></td>
<td></td>
</tr>
<tr>
<td>American Indian or Alaskan Native</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Asian</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>11 (11%)</td>
</tr>
<tr>
<td>White</td>
<td>81 (79%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (3%)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²):</strong></td>
<td>31 (21-40)</td>
</tr>
<tr>
<td>Mean (range)</td>
<td></td>
</tr>
<tr>
<td><strong>Systolic BP (mmHg):</strong></td>
<td>138 (100-180)</td>
</tr>
<tr>
<td>Mean (range)</td>
<td></td>
</tr>
<tr>
<td><strong>Diastolic BP (mmHg):</strong></td>
<td>80 (53-109)</td>
</tr>
<tr>
<td>Mean (range)</td>
<td></td>
</tr>
<tr>
<td><strong>Heart rate (BPM):</strong></td>
<td>77 (51-96)</td>
</tr>
<tr>
<td>Mean (range)</td>
<td></td>
</tr>
<tr>
<td><strong>Hemoglobin A1c:</strong></td>
<td>8.1 (5.3-12.3)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: ZETA-1 Demographics and Baseline Characteristics
## Baseline Characteristics for ZETA-1 Trial (Continued)

**DRSS Scores in Diabetic Study Population**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total N = 103</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Eye DRSS n(%)</strong></td>
<td></td>
</tr>
<tr>
<td>DRSS 47 (Moderately Severe NPDR)</td>
<td>39 (38%)</td>
</tr>
<tr>
<td>DRSS 53 (Severe NPDR)</td>
<td>53 (52%)</td>
</tr>
<tr>
<td>DRSS 61 (Mild PDR)</td>
<td>11 (11%)</td>
</tr>
<tr>
<td><strong>Fellow Eye DRSS n(%)</strong></td>
<td></td>
</tr>
<tr>
<td>DRSS 20-40 (Mild to Moderate NPDR)</td>
<td>29 (28%)</td>
</tr>
<tr>
<td>DRSS 47 (Moderately Severe NPDR)</td>
<td>34 (33%)</td>
</tr>
<tr>
<td>DRSS 53 (Severe NPDR)</td>
<td>22 (21%)</td>
</tr>
<tr>
<td>DRSS 61 (Mild PDR)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>DRSS 65-85 (Moderate to Severe PDR)</td>
<td>11 (11%)</td>
</tr>
<tr>
<td>Not Graded</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>

Note: 15 fellow eyes were CST>320 microns (center-involved DME eyes)
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total</th>
<th>N = 103</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Eye Screening CST (um):</td>
<td>mean</td>
<td>270</td>
</tr>
<tr>
<td></td>
<td>(range)</td>
<td>(203-319)</td>
</tr>
<tr>
<td>Fellow Eye Screening CST (um)*:</td>
<td>mean</td>
<td>289</td>
</tr>
<tr>
<td></td>
<td>(range)</td>
<td>(211-491)</td>
</tr>
<tr>
<td>Study Eye BCVA:</td>
<td>mean</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(range)</td>
<td></td>
</tr>
<tr>
<td>Study Eye BCVA:</td>
<td>Letters Read:</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>(range)</td>
<td>(60-93)</td>
</tr>
<tr>
<td>Study Eye BCVA:</td>
<td>Letters Read:</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>(range)</td>
<td>(0-91)</td>
</tr>
<tr>
<td>Fellow Eye BCVA:</td>
<td>Letters Read:</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>(range)</td>
<td>(0-91)</td>
</tr>
<tr>
<td>Fellow Eye BCVA:</td>
<td>Letters Read:</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>(range)</td>
<td>(0-91)</td>
</tr>
<tr>
<td>IOP Study Eye and Fellow Eye (mmHg):</td>
<td>mean</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>(range)</td>
<td>(8-22)</td>
</tr>
<tr>
<td>Diabetic Status (Years):</td>
<td>mean</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>(range)</td>
<td>(0-58)</td>
</tr>
<tr>
<td>Study Eye with anti-VEGF injections within 6 months prior to Screening</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Fellow Eye with anti-VEGF injections within 6 months prior to Screening</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

Source: ZETA-1 Demographics and Baseline Characteristics
* N=102 due to a fellow eye not being graded.
Comprehensive Laboratory Panels Collected in ZETA-1

Blood, Kidney, and Inflammatory Markers Evaluated

**Chemistry**
- Albumin
- Alanine aminotransferase (ALT)
- Alkaline Phosphatase
- Aspartate aminotransferase (AST)
- Blood Urea Nitrogen (BUN)
- Creatinine
- Glucose (Random)
- Sodium

**Test Panel Components**
- Total bilirubin
- Total protein

**Hematology**
- (CBC without Differential)
  - WBC
  - RBC
  - HGB (Hemoglobin)
  - HCT (Hematocrit)
  - Platelet Count
  - Calcium
  - Carbon Dioxide (Bicarbonate)
  - Chloride

**Cytokine Panel (Biomarker)**
- Interleukin-1 β (IL-1β)
- Interleukin-6 (IL-6)
- Interleukin-8 (IL-8)
- Tumor Necrosis Factor α (TNF-α)

**PK and Biomarkers**
- REF-1 ELISA 1
- Pharmacokinetics

**Kidney Function**
- eGFR
- Creatinine
Masked Safety Findings from Ongoing ZETA-1 Trial

Favorable Safety Profile (as of 9/15/2022) Observed with 600 mg Oral Daily Doses in Diabetic Subjects

1. 12 events in 8 subjects: diarrhea, worsening DME (OD and OS), pruritis, urticaria, blurry vision, decrease in hemoglobin level, ischemic diabetic maculopathy and central vision scotoma (in same subject), photophobia (OD and OS) and hypoaesthesia (in same subject)

2. Cellulitis (2 events in same subject), dyskinesia, transient ischemic event, COVID-19 and acute respiratory failure (same subject), progression of multivessel coronary artery disease, cholelithiasis, osteomyelitis, vertigo, chest pain, infection of toe and ulcer of toe and embolism (3 events in same subject), multi-system organ failure, worsening bradycardia

3. DME, Dyspnea, Pre-Syncope.

Note: ZETA-1 Interim Data as of database 9/15/22 with monitoring to be completed before final database lock; assumes 50% subjects on APX3330

Oral APX3330 safety profile consistent with that seen in prior trials

1. 12 events in 8 subjects: diarrhea, worsening DME (OD and OS), pruritis, urticaria, blurry vision, decrease in hemoglobin level, ischemic diabetic maculopathy and central vision scotoma (in same subject), photophobia (OD and OS) and hypoaesthesia (in same subject)

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Note: ZETA-1 Interim Data as of database 9/15/22 with monitoring to be completed before final database lock; assumes 50% subjects on APX3330
**APX3330 Product Candidate Profile for Multiple Retinal Indications**

*Oral, First-In-Class Ref-1 Inhibitor with Favorable Human Safety Data*

<table>
<thead>
<tr>
<th>Expected Efficacy Data</th>
<th>Favorable Safety Profile</th>
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| Novel MOA for treating retina  
↓ Inflammation  
↓ Abnormal Angiogenesis | ~10,000 Subject-exposure days* at ≥ 600 mg/day dose |
| Convenient Oral Dosing for Patient Compliance | **Few Systemic Adverse Effects**  
~ 5% Mild Diarrhea  
~ 5% Mild Skin Rash (reversible) |
| Allow Daily vs. Episodic Exposure  
Oral pill may reduce the burden of frequent anti-VEGF injections | **No Treatment-Related Organ Toxicity**  
(Liver, Cardiovascular {BP, HR}, Kidney, Neurologic, Pulmonary) |
|  | **No Ocular Effects**  
• No observed ocular AEs |

*11 completed Phase 1 and Phase 2 clinical trials by Eisai and Apexian; along with ongoing ZETA-1 trial by Ocuphire (*includes ~103 subject)*
ZETA-1 Trial Design and Data Expectations
APX3330 has the Potential to be First Line of Therapy for DR Patients

**Efficacy Signal**
Percent of patients on APX3330 with a ≥ 2 step improvement on the DRSS score at week 24 (and 52) compared to placebo in 2 well-controlled, multi-center clinical trials

**Safety**
Approval depends on a product’s benefit outweighing its risks in the intended population – this benefit should be evaluated in multi-center, 2-year clinical trials

**Non-Invasive Treatment Option**
FDA does not require comparative arm of approved anti-VEGF injections such as Eylea for DR

**Efficacy Signal**
- Clinically meaningful decrease in diabetic retinopathy severity with APX3330
- Early intervention with oral may reduce progression to vision threatening DR into DME

**Safety**
- No major organ toxicities
- Well-tolerated (e.g., AEs acceptable if mild and infrequent for oral)

**Non-Invasive Treatment Option**
- Eylea®, although approved, is currently not used as standard of care because of the treatment burden for asymptomatic DR patients
- Ability to be prescribed by all eye care doctors
- Oral option increases global access, especially in underserved regions
APX3330 is Positioned to Fulfill a Significant Unmet Need in Diabetic Eye Disease

- Favorable PK and safety data from clinical trials and overall masked safety data supports a potential oral treatment for diabetics with DR/DME.
- Dual mechanism of action may benefit inflammation from co-morbidities.
- DR/DME treatments are large attractive market opportunity.
- Oral therapeutic decreases burden of treatment (invasive intravitreal injections, time devoted to treatment, etc.) which may strengthen adherence and overall favorable outcomes.
- Oral therapeutic can be prescribed as early treatment option for diabetic patients who may otherwise fall under the “wait and see” treatment approach.
- Well-controlled, multi-center Phase 2b ZETA-1 for APX3330 topline results expected in 4Q22.