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 regulatory timelines, commercial timelines, cash runway, and future clinical trials in RM, presbyopia, NVD and DR/DME, including the potential for Nyxol to be a “best in class” presbyopia drop. 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 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) the effects of COVID-19 on clinical programs and business operations, (ix) the success and timing of commercialization of any 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 Investor R&D Day 1/31/22 Agenda & Speakers

<table>
<thead>
<tr>
<th>Speakers</th>
<th>Agenda</th>
<th>Time (EST)</th>
</tr>
</thead>
</table>
| Mina Sooch, MBA  
President & CEO and  
Founder | Introductions & Company Overview  
Closing Remarks | 10:00 am – 10:10 am  
12:10 pm – 12:15 pm |
| Peter Kaiser, MD  
David Boyer, MD | I. APX3330 DR/DME Program | 10:10 am – 10:50 am  
New Data |
| Mark Kelley, PhD  
Peter Kaiser, MD  
David Boyer, MD | II. Nyxol Reversal of Mydriasis Program | 10:50 am – 11:30 am |
| Paul Karpecki, OD  
Mitchell Jackson, MD  
Bindu Manne | III. Nyxol Presbyopia Program | 11:30 am – 12:10 pm  
New Data |
| Jay Pepose, MD, PhD  
James Katz, MD | | |

Corey Davis, LifeSci Advisors will moderate Q&A
Company Overview

Presenter: Mina Sooch, CEO, 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 raise and 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
Ocuphire Pharma
Restoring Vision and Clarity for Your Eyes, Today and Tomorrow
Ophthalmology – An Attractive Biotech Sector

Demographics, M&A, Regulatory Approvals and Efficient Trials Favor Ophthalmic Drugs

Deal Activity

- April 2021: Alcon/Simbrinza $355M
- September 2021: Regenxbio
- October 2021: Thea/Theraclear ~$2B
- December 2021: Thera/Theraclear ~$1B
- December 2021: Genentech/Lineage $670M

New Product Approvals

7 of 60 Total FDA Drug Approvals in 2021 Were Ophthalmic Drugs¹ and 1 in 2022

- Favorable Regulatory Environment
- Active M&A
- Aging Population
- Lower Cost, Quick Enrolling, Short Duration Clinical Trials

Deal Activity

- April 2021: Alcon/Simbrinza $355M
- September 2021: Regenxbio
- October 2021: Thea/Theraclear ~$2B
- December 2021: Thera/Theraclear ~$1B
- December 2021: Genentech/Lineage $670M

Source: 1. Endpoint Dec 29, 2021- Hitting a new record on drug approvals, the FDA offers a thumbs-up to another atopic dermatitis contender; OIS Year in Review 2021; Company press releases
Nyxol & APX3330: Drug Development History and Patents

Significant Preclinical & Clinical Data Supporting Human Safety, MOA, Efficacy, and PK

### Refractive

<table>
<thead>
<tr>
<th>Nyxol®</th>
<th>Novel α1/α2 Blocker 505(b)(2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>9</strong></td>
<td>Phase 1, Phase 2, and Phase 3 Trials</td>
</tr>
<tr>
<td>&gt;330</td>
<td>Subjects Dosed</td>
</tr>
<tr>
<td><strong>28</strong></td>
<td>Exposure in Humans 28 Days</td>
</tr>
<tr>
<td><strong>2034+</strong></td>
<td>Patent Coverage</td>
</tr>
</tbody>
</table>

### Retina

<table>
<thead>
<tr>
<th>APX3330</th>
<th>Oral REF-1 Inhibitor New Chemical Entity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>11</strong></td>
<td>Phase 1 &amp; Phase 2 Trials</td>
</tr>
<tr>
<td>&gt;340</td>
<td>Subjects Dosed</td>
</tr>
<tr>
<td><strong>365</strong></td>
<td>Exposure in Humans 365 Days</td>
</tr>
<tr>
<td><strong>2034+</strong></td>
<td>Patents to</td>
</tr>
</tbody>
</table>

- **Presbyopia**
- **Reversal of Mydriasis**
- **Night Vision Disturbances**
- **Diabetic Retinopathy**
- **Diabetic Macular Edema**

Source: Eisai and Apexian Data
# Ocuphire Pipeline & Clinical Milestones

*Multiple Phase 3 & Phase 2 Clinical Data Readouts Anticipated Over the Next Year*

<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>Anticipated Milestones</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.75% Nyxol® Eye Drop</td>
<td>Reversal of Mydriasis (RM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓ ✓</td>
<td>- MIRA-3 Phase 3 data expected in early 2022 (n=330)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- MIRA-4 Pediatric safety study data expected in early 2022 (n=20)</td>
</tr>
<tr>
<td>0.75% Nyxol® + Low-Dose 0.4% Pilocarpine Eye Drops</td>
<td>Presbyopia (P)</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td>- VEGA Phase 3 program planned to initiate in mid 2022</td>
</tr>
<tr>
<td>0.75% Nyxol® Eye Drop</td>
<td>Dim Light or Night Vision Disturbances (NVD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓ ✓</td>
<td>- LYNX-1 Phase 3 data expected in early 2022 (n=140)</td>
</tr>
<tr>
<td>APX3330 Oral Pill</td>
<td>Diabetic Retinopathy (DR)/ Macular Edema (DME)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓ ✓</td>
<td>- ZETA-1 Phase 2b data expected in 2H22 (n=90-100)</td>
</tr>
<tr>
<td>APX2009 (Intravitreal or Local Delivery)</td>
<td>DME or Wet Age-Related Macular Degeneration (wAMD)</td>
<td>✓ ✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Positive data readout Ongoing trial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Seeking partner funding for IND enabling studies and further development</td>
</tr>
</tbody>
</table>

Note: 0.75% Nyxol (Phentolamine Ophthalmic Solution) is the same as 1% Nyxol (Phentolamine Mesylate Ophthalmic Solution)
Differentiated, Late-Stage Pipeline for Front and Back of the Eye

- Nyxol with > 330 patients treated across 9 trials (505(b)(2) regulatory pathway)
- APX3330 with > 340 patients treated across 11 trials (NCE development pathway)
- Nyxol and APX3330 achieved promising clinical data and favorable safety profile across multiple Phase 1, 2, and 3 trials

Poised for Commercial Success in Multiple Large Unmet Markets

- Addressing 4 large markets with unmet needs: RM, Presbyopia, NVD, and DR/DME
- Successful trial execution with 2 recent positive Phase 3 and Phase 2 data read-outs for Nyxol in RM and Nyxol + LDP Presbyopia, respectively
- Stable, small-molecule drugs with commercial scalability
- Robust and growing IP portfolio: US and global issued thru 2034 for both assets as well as new 2039 Nyxol patent issued for presbyopia

Many Catalysts in 2022 with Track Record of Execution

- $24.5 million cash reported at 12-31-21 sufficient for operations into 2Q 2023
- Highly experienced management, Board and KOLs with broad ophthalmic and biotech drug development and commercialization success
- Lower-cost, fast-enrolling, shorter-duration clinical trials
- Favorable, precedent regulatory environment for ophthalmic drug approval
- Analyst coverage by Cantor, Canaccord, Jones Trading, Alliance Global, and HCW

A Look Ahead Into 2022:

- Nyxol MIRA-3 P3 trial for RM **EARLY 2022**
- Nyxol Pediatric trial for RM **EARLY 2022**
- Nyxol LYNX-1 P3 trial for NVD **EARLY 2022**
- APX3330 ZETA-1 P2b trial for DR/DME **2H22**
- NDA Filing for Nyxol for RM **LATE 2022**

RM = Reversal of Mydriasis
NVD = Night Vision Disturbances
DR/DME = Diabetic Retinopathy/Diabetic Macular Edema
I. APX3330 Program Update

Mark Kelley, PhD
Founder
Apexian/APX3330

Peter Kaiser, MD
Harvard Medical School

David Boyer, MD
Chicago Medical School
APX3330 Chemistry and MOA

Presented by: Mark Kelley, PhD

- Chief Scientific Officer and Founder of Apexian Pharmaceuticals
- Discovered and has developed the redox-specific inhibitors of Ref-1 for over 20 years
- Associate Director of Basic Science at Indiana University Simon Comprehensive Cancer Center
- Betty and Earl Herr Professor of Pediatric Oncology Research, Indiana University
- Fellow, American Association for the Advancement of Science
APX3330 History and Ref-1 Inhibition Mechanism

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

- Ref-1 (reduction-oxidation effector factor-1) is a novel target discovered by Dr. Mark R. Kelley at Indiana University School of Medicine
- 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

APX3330 reduces pro-inflammatory cytokines in LPS stimulated macrophages

APX3330 increases DNA oxidative repair and neuronal protection

- Tao Yan et al. APX3330 Promotes Neurorestorative effects after stroke in type one diabetic rats. Aging and Disease. Vol 9, Oct 2018
Abnormal Conditions (e.g., hypoxic):

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

Normal Conditions:

Physiological level of VEGF activity

Increased level of VEGF activity

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

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 in over 300 subjects 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.
APX3330 Preclinical & IND-Enabling Studies

Extensively Evaluated in Over 20 Studies by Large Japanese Pharma Eisai

- 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

✓ 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)
APX3330 Human PK and Safety Summary

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.
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

---

1. Apexian preclinical data (unpublished)
2. APX3330 Investigator Brochure
3. Eisai PK clinical data APX_CLN_0002
Phase 1/2 Clinical Trials: PK Data Supporting the ZETA-1 Trial
APX3330 Reaches the Retina via Oral Administration

Does oral administration of APX3330 reach the retina in sufficient concentration?

Orally administered, radiolabeled APX3330 reaches high levels in rat eye

25 mg/kg APX3330 oral gavage measured in mouse retina

Human clinical dose: 300 mg BID (600mg/day total)
Established PBPK model using human data predicts APX3330 reaches sufficient human retinal concentrations

APX3330 is orally bioavailable & detectable in mouse and rat retina
Preclinical PK and PBPK human modeling support 600 mg/day dosing for clinical development

---

1. Silva et al. Oral APX3330 treatment reduces L-CNV lesions in preclinical mouse model and confirms Phase 2 DR/DME clinical dose with sufficient distribution to human retina using PBPK modeling. Presented at the ARVO 2021 Annual Meeting
2. Eisai Preclinical Data
3. Apexian preclinical data
### Subject Exposure Across 11 Prior Clinical Trials

**Over 2000 Subject-Days of Exposure at ≥600 mg/day**

<table>
<thead>
<tr>
<th>11 Trials Prior to ZETA-1</th>
<th>≥600 mg/day APX3330</th>
<th>&lt;600 mg/day** APX3330</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Subjects</td>
<td>34* Subjects</td>
<td>328* Subjects</td>
</tr>
<tr>
<td>Subject-Days of Exposure</td>
<td>2078 Subject-days</td>
<td>17961 Subject-days</td>
</tr>
<tr>
<td>Subjects with ≥21 days of exposure</td>
<td>16 Subjects</td>
<td>245 Subjects</td>
</tr>
<tr>
<td>Subjects with &gt;300 days of exposure</td>
<td>3 Subjects</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*18 subjects in dose escalation trials received doses <600mg/day and ≥600mg/day and are included in both columns, resulting in greater than 340 subjects;

**Many of the subjects between 20-240
### Safety Summary From Phase 1 and Phase 2 Studies

#### Low AEs Across 11 Trials, <5% Mild Drug Related AEs, Discontinuations Similar Across Arms

#### Integrated Overall Summary of Adverse Events in Eisai Phase 2 Studies (Hepatitis)

<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 Ocuphire analysis. Ocuphire will be creating an integrated safety database. The overall conclusions between the Eisai and Ocuphire analyses are the same.

#### Totals Across ALL Phase 1 and Phase 2 Studies (Among Healthy Subjects, Hepatitis Patients, and Oncology Patients)

<table>
<thead>
<tr>
<th></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/Pruritus (mild)</td>
<td>14/346 (4%)</td>
<td>1/95 (1%)</td>
</tr>
</tbody>
</table>
### APX3330: Well-tolerated Oral Dose up to 600mg/day
#### Twice Daily Dosing

<table>
<thead>
<tr>
<th>Expected Efficacy Data</th>
<th>Favorable Safety Profile</th>
</tr>
</thead>
</table>
| Improving Eye Health in Diabetics  
↓ Inflammation  
↓ Abnormal Angiogenesis | Few Systemic Adverse Effects  
• < 5% Mild Gastrointestinal (diarrhea)  
• < 5% Mild Skin Rash (reversible)  
• No Significant Organ Toxicity:  
  • Liver  
  • Cardiovascular (BP, HR)  
  • Kidney  
  • Neurologic  
  • Pulmonary |
| Enhance Compliance & Exposure  
Oral pill may reduce the burden of frequent anti-VEGF injections | No Ocular Effects  
• No observed ocular AEs |
APX3330 Addressing Unmet Needs in Retina

Presented by: Peter Kaiser, MD
Clinical Unmet Need in Diabetic Retinal Diseases

Increasing Prevalence of DR with No Early Intervention Options

The Problem

• DR/DME are major causes of vision loss in working aged adults

• Diabetic population expected to increase dramatically worldwide

• Approved therapies for DR are effective but require IVT injection

• DR patients are not routinely treated with approved injectable anti-VEGF drugs until they develop center-involved DME or PDR
  – DR progresses resulting in vision loss

• Early, noninvasive intervention targeting DR represents a therapeutic unmet need

Growing Incidence of Diabetes and DR

<table>
<thead>
<tr>
<th></th>
<th>US</th>
<th>Worldwide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>34 M</td>
<td>&gt;450 M</td>
</tr>
<tr>
<td>DR</td>
<td>7 M</td>
<td>&gt;150 M</td>
</tr>
</tbody>
</table>

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

American Diabetes Association; International Diabetes Federation; Healthline
Diabetic Retinopathy is a Progressive, Vision Threatening Disease

Losing Vision is Diabetic Patients’ Top Concern

**What are the top concerns for diabetic patients?**

**Going Blind**
- Amputation, losing a leg: 38%
- Cardiovascular/heart problems: 35%

**Other Eye Problems**
- Foot problems: 30%
- Kidney problems: 25%

Percentage of respondents (N=2702)

Source: Patient survey adapted from Lions International Foundation and International Diabetes Foundation-Europe; Meltzer 2000
### Key Clinical Landscape in Diabetic Retinopathy (and DME)

**Intravitreal Injection the Focus for Drugs in Development; Ocuphire Pioneering an Oral Option**

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug</th>
<th>Target/MOA</th>
<th>Route of Administration</th>
<th>Pre-clinical</th>
<th>Ph1</th>
<th>Ph2</th>
<th>Ph3</th>
<th>Commercial</th>
<th>2021 Annual Sales (US/Ex-U.S.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regeneron/Bayer</td>
<td>Eylea (aflibercept)</td>
<td>VEGF-A/B; PIGF</td>
<td>Intravitreal (DR &amp; DME)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>~$6 B/ ~$4 B</td>
</tr>
<tr>
<td>Roche/Novartis</td>
<td>Lucentis (ranibizumab)</td>
<td>VEGF-A</td>
<td>Intravitreal (DR &amp; DME)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td><del>$1.5 B/</del>$2 B</td>
</tr>
<tr>
<td>Roche</td>
<td>Ranibizumab PDS</td>
<td>VEGF-A</td>
<td>Surgical/Refill (DME)</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Roche</td>
<td>Faricimab</td>
<td>VEGF-A x Ang2</td>
<td>Intravitreal (DME)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓ Oct 2021</td>
</tr>
<tr>
<td>Kodiak</td>
<td>KSI-301</td>
<td>VEGF</td>
<td>Intravitreal (DR &amp; DME)</td>
<td>✓</td>
<td>✓</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kalvista</td>
<td>KVD0001</td>
<td>Plasma Kallikrein</td>
<td>Intravitreal (DME)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
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<tr>
<td>Eli Lilly</td>
<td>LY333531</td>
<td>Protein Kinase C inhibitor</td>
<td>Oral (DR)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>X</td>
<td>2006</td>
</tr>
<tr>
<td>Ocuphire</td>
<td>APX3330</td>
<td>Ref-1 inhibitor</td>
<td>Oral (DR)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
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<td></td>
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<tr>
<td>Bayer</td>
<td>BAY1101042</td>
<td>Guanylate Cyclase activator</td>
<td>Oral (DR)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
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<tr>
<td>Alkahest</td>
<td>AKST4290</td>
<td>CCR3 Eotaxin inhibitor</td>
<td>Oral (DR)</td>
<td>✓</td>
<td>✓</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Roche</td>
<td>RG7774</td>
<td>CB2 Receptor</td>
<td>Oral (DR)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Boehringer Ing.</td>
<td>BI 1467335</td>
<td>AOC3</td>
<td>Oral (DR)</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>X</td>
<td>2021</td>
<td></td>
</tr>
<tr>
<td>Rezolute</td>
<td>RZ402</td>
<td>Plasma Kallikrein</td>
<td>Oral (DME)</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OcuNexus</td>
<td>HCB 1019</td>
<td>Connexin 43 (inflammasome)</td>
<td>Oral (DR)</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OcuTerra</td>
<td>OTT166</td>
<td>Integrin inhibitor</td>
<td>Eyedrop (DR)</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- ✓ Completed
- ◢ Recruiting
- X Discontinued/Failed study

Guggenheim report (2020); www.clinicaltrials.gov; Company websites

ORAL Rx
ZETA-1 Phase 2b Clinical Trial (APX3330 in DR)

Presented by: David Boyer, MD

- Board-certified Ophthalmologist specializing in treatment of retinal and vitreous diseases
- Widely-published author and internationally recognized lecturer on retinal research and innovative approaches
- Investigator in numerous innovative product retinal trials over the last 35 years

David Boyer, MD
Chicago Medical School
DR/DME ZETA-1 Phase 2b Design

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

ZETA-1

25 US sites

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

Noncentral DME is permitted

Eligibility Screening

Randomization

APX3330 600mg/day (BID)

Placebo BID

1:1

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

Phase 2b Initiated in April 2021

Top Line Expected in 2H22

NPDR = non-proliferative diabetic retinopathy (which includes non centrally involved diabetic macular edema)
PDR = proliferative diabetic retinopathy (which includes non centrally involved diabetic macular edema)
https://clinicaltrials.gov/ct2/show/NCT04692688?term=ZETA-1&draw=2&rank=1

28
Key Eligibility Criteria in ZETA-1

Inclusion

- Moderately-severe to severe NPDR or mild PDR in study eye as confirmed by reading center
- BCVA > 20/63 in study eye

Exclusion

- Retinopathy from causes other than diabetes in study eye
- Presence of center involved diabetic macular edema (DME) defined as a central subfield thickness (CST) ≥ 320 μm on SD-OCT or the presence of intra- or subretinal fluid within the central subfield
  - Center involved DME in the fellow eye is allowed
- Prior treatment in study eye with focal/grid laser photocoagulation within the past year, PRP at any time, systemic or intravitreal anti-VEGF agents within last 6 months in study eye
- HbA1c ≥ 12.0%
- Clinically significant systemic disease (e.g., uncontrolled diabetes, myasthenia gravis, cancer, hepatic, renal, endocrine, or cardiovascular disorders) that might interfere as deemed by Investigator
Why DRSS is an Important Endpoint?

Eylea® Panorama study

FDA Accepted Endpoint for EYLEA® in PANORAMA Pivotal DR Trial - 2 Step Improvement on the DRSS Score at Week 24

Diabetic Retinopathy Severity Scale (DRSS)

Non-proliferative disease

Proliferative disease

ETDRS Severity Level

Steps

Very Mild Mild Mod Sev. Very Sev. Mild Mod High Risk

Risk of vision-threatening events increases with worsening step progression

PANORAMA: Reduction of DRSS Significantly reduces the incidence of Vision Threatening DR

Proportion of Patients Developing a VTC or CI-DME through Week 100

Kaplan-Meier Analysis

VTC (PDR/ASNV) or CI-DME

VTC

CI-DME

VTC = Vision threatening complication defined as PDR/ASNV
CI-DME = center involved DME

*Nominal p < 0.001 vs. sham
Enrollment Update on ZETA-1

~70% Completion of Enrollment in 24-week Phase 2b Trial

April 2021: 68 Patients Enrolled

90-100 target
### Comparison of Subject Exposure Before and After ZETA-1

**Subject-Days of Exposure at 600 mg/day Substantially Increases Exposure Data**

<table>
<thead>
<tr>
<th></th>
<th>≥600 mg/day</th>
<th>&lt;600 mg/day**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prior to ZETA-1</td>
<td>To Date*</td>
</tr>
<tr>
<td><strong>Total Subjects</strong></td>
<td>34 Subjects</td>
<td>+34 Subjects</td>
</tr>
<tr>
<td><strong>Subject-Days of Exposure</strong></td>
<td>2078 Subject-days</td>
<td>+3727 Subject-days</td>
</tr>
<tr>
<td><strong>Subjects with ≥21 days of exposure</strong></td>
<td>16 Subjects</td>
<td>+27 Subjects</td>
</tr>
<tr>
<td><strong>Subjects with &gt;300 days of exposure</strong></td>
<td>3 Subjects</td>
<td>3 Subjects</td>
</tr>
</tbody>
</table>

*Assumed 50% of ZETA-1 patients are on active treatment

**Many of the subjects between 20-240 mg/day

---

*Interim Zeta-1 Data as of 01-12-22; *Eisai and Apexian Phase 1 and Phase 2 clinical trials (subject to final safety database)
Baseline Characteristics for ZETA-1 Trial (Interim)

Typical Demographics for Diabetic Population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total N = 68</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years):</strong> mean (range)</td>
<td>55 (24-81)</td>
</tr>
<tr>
<td><strong>Sex: Male n (%)</strong></td>
<td>34 (50%)</td>
</tr>
<tr>
<td><strong>Female n (%)</strong></td>
<td>34 (50%)</td>
</tr>
<tr>
<td><strong>Weight (kg):</strong> mean (range)</td>
<td>84 (54-123)</td>
</tr>
<tr>
<td><strong>BMI (kg/m(^2)):</strong> mean (Range)</td>
<td>30 (21-40)</td>
</tr>
<tr>
<td><strong>Systolic BP (mmHg):</strong> mean (range)</td>
<td>137 (100-172)</td>
</tr>
<tr>
<td><strong>Diastolic BP (mmHg):</strong> mean (range)</td>
<td>80 (53-104)</td>
</tr>
<tr>
<td><strong>Heart rate (BPM):</strong> mean (range)</td>
<td>76 (51-96)</td>
</tr>
</tbody>
</table>

Source: ZETA-1 Demographics and Baseline Characteristics
Masked Safety Findings from Ongoing ZETA-1 Trial

**Favorable Safety Profile (as of 1/12/2022) Observed with 600 mg Oral Daily Doses**

<table>
<thead>
<tr>
<th>APX3330 Masked Safety Data ZETA-1 Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>68</td>
</tr>
<tr>
<td>Randomized Subjects</td>
</tr>
<tr>
<td>&gt;3700</td>
</tr>
<tr>
<td>Subject-Days of Exposure (50% on APX3330)</td>
</tr>
<tr>
<td>28</td>
</tr>
<tr>
<td>Subjects with AEs (52 total events)</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>SAEs, all unrelated to study medication</td>
</tr>
</tbody>
</table>

- 52 TEAEs in 28 subjects
  - 6/52 AEs were considered probably or possibly related to study medication
    - 4 Mild (vertigo, rash, pruritus, frequent bowel movements); 2 moderate (DME*, diarrhea**)
    - 46/52 AEs were ‘not’ or ‘unlikely’ related (32 mild, 14 moderate)

- 6 SAEs in 6 subjects
  - None of these treatment emergent events were related to study medication
    - Cellulitis, dyskinesia, transient ischemic event, COVID-19, progression of multivessel coronary artery disease, cholecystitis

- Only 2 subjects have withdrawn from study due to AEs: vasovagal near syncope** considered unrelated to study medication and DME* possibly study medication related (APX3330 or placebo)

*same subject; **same subject
Note: ZETA-1 Interim Data as of database 1/12/22 with complete monitoring before final database lock

Source: ZETA-1 trial
Takeaways: Masked Interim Safety Findings from ZETA-1 Trial

- ~70% completion of enrollment in 24-week ZETA-1 Phase 2b Trial
- No major organ toxicities (liver, heart, kidney, brain, lung) or vital sign abnormalities (blood pressure or heart rate) were observed
- Incidence of mild rash and diarrhea in the diabetic patient population is lower than previously observed in hepatitis patients

Review of masked safety data for 600 mg/day daily dose is consistent with the favorable safety profile seen in previous studies with APX3330
Broad Opportunities to Treat Retinal Diseases with APX Platform

APX3330 May Treat Patients Across Retinal Diseases as Single Agent or Adjunctive Therapy

Potential Differentiated Solution

• Potential First Oral Rx for Retina Diseases
  – First-line earlier intervention for the diabetic eye
  – Add-on therapy to current anti-VEGF treatments to reduce intravitreal injection burden

• Proven Novel Mechanism
  – May decrease both inflammation and angiogenesis

• Convenient Daily Regimen

• Favorable Oral Safety Profile
  – As seen in 11 completed Phase 1 and Phase 2 clinical trials

• Improve Patient Compliance
  – Potentially alleviate the frequent burden of injections

Inflammatory component is common across these retina indications and potentially addressable by the MOA of Ref-1

Current anti-VEGF treatments

APX3330
APX2009
APX2014
APX3330 (Local Delivery)
Large Global/US Market Opportunity in Retinal Disease

Retinal US Markets Served by Anti-VEGF Injections Alone are Greater than $10B+ Today

**Global Disease Prevalence (Patients)**
- 113 M wAMD, RVO, DME combined
- 93 M DR
- 5 M GA
- 1 M Dry AMD

**Global Forecasted Disease Prevalence (5-10 years)**
- 130 M wAMD, RVO, DME* combined
- 110 M DR*
- 10 M GA
- 2 M Dry AMD

↑ Aging
↑ Access
↑ Diabetes
↑ New Rx Products

Anti-VEGF Injectable US Revenue
- $13 B US Revenues
- $20 B US Projected Revenue
- $5+B GA Revenues
- $10+B Oral Rx Revenues

4% CAGR

*As early intervention options and exams are performed, there may be less DME and more DR

Market Scope 2020
Tilahun M et. al, Prevalence of Diabetic Retinopathy and Its Associated Factors among Diabetic Patients at Debre Markos Referral Hospital, Northwest Ethiopia, 2019: Hospital-Based Cross-Sectional Study. Diabetes Metab Syndr Obes. 2020;13:2179-2187

Aging
Access
Diabetes
New Rx Products
What’s Important?

APX3330 has the Potential to be 1st 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 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 as demonstrated in, multi-center, 2 years clinical trial

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
FOR
DIABETIC
RETINOPATHY

Question & Answer
APX3330 is a **novel orally administered** drug initially being developed for DR/DME

**APX3330 targets Ref-1 which plays a role in signaling under both ischemic and inflammatory conditions**, both of which are relevant to diabetic eye disease; resulting in inhibiting clinically validated pathways downstream of Ref-1 (e.g., VEGF and inflammation)

**ZETA-1’s masked safety findings as of 01/12/2022 support favorable safety profile of APX3330 as an oral treatment option for DR** consistent with 11 prior Phase 1 and 2 clinical trials

APX3330 randomized, double-masked, placebo-controlled, multi-center ZETA-1 Phase 2b trial enrollment on track at **68 subjects (of 90-100 subjects) with results expected in second half of 2022**

Oral APX3330 has potential **utility as adjunctive treatment with anti-VEGF injections for other retinal vascular/inflammatory diseases** such as DME, GA, RVO and AMDs; future opportunities with APX2009/2014 pipeline locally or orally delivered
II. Nyxol Reversal of Mydriasis Overview

Paul Karpecki, OD
Indiana University

Mitchell Jackson, MD
University of Chicago

Bindu Manne
Head of Commercialization
Reversing Dilations: Addressing an Unmet Need with α1 Blocker Nyxol

Presented by: Paul Karpecki, OD

- Director of Cornea Services for Kentucky Eye Institute, Gaddie Eye Centers, Midwest Center for Sight
- Associate Professor at the Kentucky College of Optometry and Board Member of Optometry Giving Sight
- Medical Director for KEPLR Vision and Dry Eye Institutes of Kentucky and Indiana
- Chief Medical Editor for Review of Optometry, Chairman of the NTT Conferences

Paul Karpecki, OD
Indiana University
Problem: Dilated Eyes for Exams and Procedures

Patients Report Significant Side Effects after Dilated Eye Exam

The Problem
Pharmacologically-induced pupil dilation is a necessary tool for routine ophthalmoscopy…

…but there is 6 to 24 hours of impaired vision including:

- Inability to Focus
- Photophobia (sensitivity to light)
- Cycloplegia (loss of accommodation)
- Difficulty Reading and Driving
- Halos and Glare

Physician’s Use of Mydriatic Agents

<table>
<thead>
<tr>
<th>Mydriatic Agent</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tropicamide Alone</td>
<td>52%</td>
</tr>
<tr>
<td>Tropicamide and Phenylephrine</td>
<td>18%</td>
</tr>
<tr>
<td>Phenylephrine Alone</td>
<td>16%</td>
</tr>
<tr>
<td>Paremyd</td>
<td>9%</td>
</tr>
<tr>
<td>Cyclopentolate</td>
<td>5%</td>
</tr>
<tr>
<td>Tropicamide and Phenylephrine</td>
<td>18%</td>
</tr>
</tbody>
</table>

Note - Tropicamide and Cyclopentolate have same MOA

NO REVERSAL DROPS COMMERCIALLY AVAILABLE

1. GlobalData Market Research Survey; Oraverse and Regitine Label
Current Off-Label Landscape for RM

Physicians AVOID Use of Cholinergic Agonists (Pilocarpine) Due to the Risk on Ciliary Muscle

2 Classes of Mydriatic Agents

- Phenylephrine
  - (α1 agonist)
  - Sympathetic (primarily α1)
    - Innervation stimulates the iris dilator muscles

- Tropicamide
  - (anti-cholinergic)
  - Parasympathetic
    - Innervation stimulates the iris sphincter and ciliary muscle

Reversal via the Ciliary Muscle by Cholinergic Agonists* is Not a ‘Safe’ Option

- Induces accommodation spasm and reduction in distance vision\(^1\)
- Induced anterior shift of the lens can increase the risk of acute angle-closure glaucoma\(^1\)
- High incidence of brow ache and headache following installation\(^3\)
- Retinal tear has been reported in some patients\(^2\)

* Cholinergic Agonists include pilocarpine, carbachol, and aceclidine. Note, pilocarpine is rarely used off-label for RM given these safety concerns.

Nyxol\(^\text{®}\) is the only eye drop in clinical development for multiple indications that does not affect the ciliary muscle

1. Optician (2012)- Mydriatic Drugs: Practical Considerations
2. Pilocarpine FDA Label (2017)
Nyxol’s Differentiated MOA as an Alpha-1 Blocker

Phentolamine Mesylate Reformulated as a Proprietary Topical Eye Drop ➔ Nyxol

<table>
<thead>
<tr>
<th>Phentolamine Mesylate is the Active Ingredient in Nyxol: a Non-selective α1 &amp; α2 Antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blocking α1</strong></td>
</tr>
<tr>
<td>Reduces Pupil Size</td>
</tr>
</tbody>
</table>

- **Iris Dilator Muscle**
- **Iris Sphincter Muscle**

Nyxol blocks α1 receptors only found on the Iris Dilator Muscle

↓ Decreases Pupil Size (Moderate Miosis) without Affecting the Ciliary Muscle

- Phentolamine mesylate is approved for 2 indications:
  - Regitine® (Pheochromocytoma) – intravenous injection approved in 1952
  - OraVerse® (Reversal of oral anesthesia) – intramuscular injection approved in 2008

505(b)(2) Regulatory Approval Pathway
## Nyxol Product Candidate Profile

**Novel, Differentiated Alpha 1/2 Blocker Eye Drop for Refractive Indications**

<table>
<thead>
<tr>
<th>Effective</th>
<th>Favorable Safety Profile</th>
<th>Durable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nyxol Improves Vision by Decreasing Pupil Size (1 to 1.5mm)</strong></td>
<td><strong>No Systemic Effects</strong></td>
<td><strong>Effects Last ( \geq 24 ) Hours</strong></td>
</tr>
<tr>
<td>↑ Near &amp; Distance Visual Acuity</td>
<td><strong>Well-Tolerated Topical Effects</strong></td>
<td>Chronic daily dosing of Nyxol at bedtime reduced pupil size for up to 24 - 36 hours</td>
</tr>
<tr>
<td>↑ Contrast Sensitivity (night)</td>
<td><strong>IOP Unchanged or Decreased</strong></td>
<td>With nighttime use, patients wake up without eye redness</td>
</tr>
<tr>
<td><strong>Nyxol: 0.75% Phentolamine Ophthalmic Solution</strong></td>
<td><strong>No Headaches</strong></td>
<td></td>
</tr>
<tr>
<td>Preservative Free, EDTA Free, and Stable</td>
<td><strong>Favorable safety profile vs competitors</strong></td>
<td></td>
</tr>
</tbody>
</table>
Nyxol Clinical Data for Reversing Dilations

Presented by: Paul M. Karpecki, OD
MIRA Program Evaluating Nyxol for the Reversal of Mydriasis

Efficient Clinical Programs have Positioned Ocuphire to Target NDA Filing in Late 2022

2019
Phase 2b
n=32 crossover
Primary Endpoint Met ✓
Secondary Endpoints Met ✓

2021
Phase 3
n=185
Primary Endpoint Met ✓
Secondary Endpoints Met ✓

2022
Phase 3
n=330
Primary Endpoint Met ✓
Secondary Endpoints Met ✓

2022
Pediatric Safety
n=20

2022
NDA Submission

RM NDA Filing
MIRA-2/3 Phase 3 Registration Trial Design

Randomized, Double-Masked, Placebo-Controlled, Parallel, One-Day Trial

12 to 16 US sites
185 to 330 target healthy subjects

0.75% Nyxol

Mydriatic Agent A, B, or C

Mydriasis - 1 Hour

Treatment (Max Dilation)
0 min 1 Hr 2 Hr 3 Hr 4 Hr 6 Hr 24 Hr

Primary:
- % of subjects (study eye) returning to baseline (within 0.2 mm) photopic pupil diameter (PD) at 90 min

Secondary:
- % of subjects returning to baseline at 0min, 30min, 1h, 90 min 2h, 3h, 4h, 6h, 24h (overall, by mydriatic agent, by iris color)
- Mean change in pupil diameter at all timepoints
- Accommodation (Tropicamide/Paremyd)
- Visual acuity & discomfort w/ glare
- Pupillary light reflex
- Safety and tolerability (redness)

Enrollment MIRA-3 Started in 4Q21

Topline Results Expected in Early 2022

Endpoints

Mydriatic 3:1:1 – 2.5% phenylephrine (alpha-1 agonist), 1% tropicamide (cholinergic blocker), Paremyd® (combination)

Eligibility Screening
Randomization
# MIRA-2: Participant Characteristics

**MIRA-2 Study was Balanced Across Both Nyxol and Placebo Groups**

<table>
<thead>
<tr>
<th>MIRA-2 Phase 3 Trial</th>
<th>Nyxol n=94</th>
<th>Placebo n=91</th>
<th>Total n=185</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years): Median (Range)</strong></td>
<td>31 (12-70)</td>
<td>30 (13-73)</td>
<td>31 (12-73)</td>
</tr>
<tr>
<td><strong>Sex: Male n (%)</strong></td>
<td>36 (38%)</td>
<td>36 (40%)</td>
<td>72 (39%)</td>
</tr>
<tr>
<td><strong>Female n (%)</strong></td>
<td>58 (62%)</td>
<td>55 (60%)</td>
<td>113 (61%)</td>
</tr>
<tr>
<td><strong>Race: White n (%)</strong></td>
<td>70 (75%)</td>
<td>74 (81%)</td>
<td>144 (78%)</td>
</tr>
<tr>
<td><strong>African American n (%)</strong></td>
<td>17 (18%)</td>
<td>16 (18%)</td>
<td>33 (18%)</td>
</tr>
<tr>
<td><strong>Asian n (%)</strong></td>
<td>6 (6%)</td>
<td>3 (3%)</td>
<td>9 (5%)</td>
</tr>
<tr>
<td><strong>Other^ n (%)</strong></td>
<td>2 (2%)</td>
<td>1 (1%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>^includes American Indian or Alaska Native; Native Hawaiian or Other Pacific Islander</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dark Iris Color: n (%)</strong></td>
<td>49 (52%)</td>
<td>46 (51%)</td>
<td>95 (51%)</td>
</tr>
<tr>
<td><strong>Light Iris Color: n (%)</strong></td>
<td>45 (48%)</td>
<td>45 (50%)</td>
<td>90 (49%)</td>
</tr>
<tr>
<td><strong>Baseline Pupil Diameter Mean (mm)</strong></td>
<td>5.09</td>
<td>5.18</td>
<td>5.13</td>
</tr>
<tr>
<td><strong>Max Dilated Pupil Diameter Mean (mm)</strong></td>
<td>7.21</td>
<td>7.20</td>
<td>7.20</td>
</tr>
<tr>
<td><strong>Accommodation Median (diopters)</strong></td>
<td>7.28</td>
<td>7.41</td>
<td>7.41</td>
</tr>
</tbody>
</table>

Note: 14 pediatric subjects 12-17 years old were enrolled in the trial; Race is more than 100% given subjects could check more than one category.
MIRA-2: Phase 3 RM Trial Met Primary Endpoint

49% of Patients Returned to ≤ 0.2mm of Baseline at 90 Minutes

Nyxol Reduced More Subjects to Baseline Pupil Diameter (PD) at Every Timepoint

Source: MIRA-2 Trial Table 14.1.2.1, mITT Population (same as Safety Population)
*Data includes three of the most common mydriatics used in practice (Phenylephrine, Tropicamide, Paremyd)

Study Eye
Percent of Subjects Returning to ≤ 0.2 mm of Baseline PD

Time Post-Treatment with Nyxol/Placebo (Hours)

<table>
<thead>
<tr>
<th>Time (Hours)</th>
<th>Placebo n=91</th>
<th>Nyxol n=94</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>1</td>
<td>2%</td>
<td>28%</td>
</tr>
<tr>
<td>1.5</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>2</td>
<td>7%</td>
<td>49%</td>
</tr>
<tr>
<td>3</td>
<td>11%</td>
<td>59%</td>
</tr>
<tr>
<td>4</td>
<td>18%</td>
<td>80%</td>
</tr>
<tr>
<td>6</td>
<td>30%</td>
<td>82%</td>
</tr>
</tbody>
</table>

p<0.0001
MIRA-2: Study Eye and Non-Study Eye

Similar Rapid Return to Baseline Pupil Size Results with 1 or 2 Drops of Nyxol

1 or 2 Drops Nyxol Reduced More Subjects to Baseline Pupil Diameter (PD) at Every Timepoint

Study Eye (2 Drops)
Percent of Subjects Returning to ≤ 0.2 mm of Baseline PD

<table>
<thead>
<tr>
<th>Time Post-Treatment with Nyxol/Placebo (Hours)</th>
<th>Placebo n=91</th>
<th>Nyxol n=94</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>1</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>1.5</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>2</td>
<td>11%</td>
<td>18%</td>
</tr>
<tr>
<td>3</td>
<td>18%</td>
<td>30%</td>
</tr>
<tr>
<td>4</td>
<td>30%</td>
<td>45%</td>
</tr>
<tr>
<td>6</td>
<td>45%</td>
<td>90%</td>
</tr>
</tbody>
</table>

Non-Study Eye (1 Drop)
Percent of Subjects Returning to ≤ 0.2 mm of Baseline PD

<table>
<thead>
<tr>
<th>Time Post-Treatment with Nyxol/Placebo (Hours)</th>
<th>Placebo n=91</th>
<th>Nyxol n=94</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>1</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>1.5</td>
<td>6%</td>
<td>10%</td>
</tr>
<tr>
<td>2</td>
<td>10%</td>
<td>14%</td>
</tr>
<tr>
<td>3</td>
<td>14%</td>
<td>24%</td>
</tr>
<tr>
<td>4</td>
<td>24%</td>
<td>45%</td>
</tr>
<tr>
<td>6</td>
<td>45%</td>
<td>86%</td>
</tr>
</tbody>
</table>

Source: MIRA-2 Trial Table 14.1.2.1, mITT Population (same as Safety Population)
*Data includes three of the most common mydriatics used in practice (Phenylephrine, Tropicamide, Paremyd)
MIRA-2: Responders Returning to Baseline Pupil Size by Iris Color

Nyxol Works in Subjects with Both Light and Dark Irides, with a More Vigorous Response in Light Irides

**Nyxol Reverses Dilation in Light and Dark Irides**

**Light Irides (Study Eye)**
Percent of Subjects Returning to ≤ 0.2 mm of Baseline

<table>
<thead>
<tr>
<th>Time Post-Treatment with Nyxol/Placebo (Hours)</th>
<th>Placebo n=45</th>
<th>Nyxol n=45</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>1</td>
<td>0%</td>
<td>31%</td>
</tr>
<tr>
<td>1.5</td>
<td>2%</td>
<td>56%</td>
</tr>
<tr>
<td>2</td>
<td>7%</td>
<td>71%</td>
</tr>
<tr>
<td>3</td>
<td>13%</td>
<td>89%</td>
</tr>
<tr>
<td>4</td>
<td>24%</td>
<td>96%</td>
</tr>
<tr>
<td>6</td>
<td>49%</td>
<td>93%</td>
</tr>
</tbody>
</table>

**Dark Irides (Study Eye)**
Percent of Subjects Returning to ≤ 0.2 mm of Baseline

<table>
<thead>
<tr>
<th>Time Post-Treatment with Nyxol/Placebo (Hours)</th>
<th>Placebo n=46</th>
<th>Nyxol n=49</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>7%</td>
<td>2%</td>
</tr>
<tr>
<td>1</td>
<td>4%</td>
<td>25%</td>
</tr>
<tr>
<td>1.5</td>
<td>11%</td>
<td>43%</td>
</tr>
<tr>
<td>2</td>
<td>15%</td>
<td>47%</td>
</tr>
<tr>
<td>3</td>
<td>22%</td>
<td>71%</td>
</tr>
<tr>
<td>4</td>
<td>35%</td>
<td>69%</td>
</tr>
<tr>
<td>6</td>
<td>41%</td>
<td>88%</td>
</tr>
</tbody>
</table>

Source: MIRA-2 TLR table #14.2.1.6 (mITT)
*Data includes three of the most common mydriatics used in practice (Phenylephrine, Tropicamide, Paremyd)
MIRA-2: Mean Pupil Size Over Time After Maximum Pupil Dilation

Nyxol Treatment Significantly Reduced PD Starting at 1 Hour Post-Dose through 24 Hours

**MIRA-2 Phase 3 Trial**

**Nyxol Reduced PD Faster Across All Mydriatic Agents***

Study Eye
Mean Pupil Diameter

![Graph showing mean pupil size over time after treatment with Nyxol or placebo.](chart)

- **Max pupil dilation**
- **Treatment Administered**
- **Time Post-Treatment with Nyxol/Placebo (Hours):**
  - Mean Pupil Diameter (mm)
  - Nyxol n=94
  - Placebo n=91

Source: MIRA-2 TLR table #14.2.2.1 (mITT). Standard Error bars are shown.
*Data includes three of the most common mydriatics used in practice (Phenylephrine, Tropicamide, Paremyd)
MIRA-2: Mean Pupil Diameter Over Time by Mydriatic Agent

Nyxol Reduced Pupil Diameter with All Mydriatic Agents; More Rapidly with Phenylephrine as Expected

Source: MIRA-2 TLR table #14.2.2.3 (mITT). Standard Error bars are shown.

Phenylephrine (Study Eye)
Mean Pupil Diameter

Tropicamide or Paremyd (Study Eye)
Mean Pupil Diameter

Nyxol Reduced PD Faster Across All Mydriatic Agents
MIRA-2: Gain of Visual Function (Accommodation)

Nyxol Demonstrates a Faster Return to Baseline Accommodation

**Accommodation**

- **Definition:** Changing optical power to maintain a clear image or focus on an object as the distance varies
- Inhibition of the cholinergic system dilates the pupil (mydriasis) and relaxes the ciliary muscle, which adjusts the lens shape and thickness, worsening accommodation (cycloplegia) and causing latent refractive errors to manifest
- Mydriatic agents including Tropicamide and Paremyd inhibit the cholinergic system; not seen with Phenylephrine

**Nyxol**

- Nyxol, a non-selective, alpha-1 antagonist, constricts the pupil enhancing depth of focus by blocking unfocused peripheral light, independent of the ciliary muscle

**Note:** Worsening of accommodation was defined as an amplitude decrease of greater than 1 diopter

**Source:** MIRA-2 CSR table #14.2.3.2.1. PP population is the per protocol population.

MIRA-2: Safety Findings (After Dilation with Mydriatic Agent)

*Nyxol was Well Tolerated with a Favorable Safety Profile*

<table>
<thead>
<tr>
<th>Total Treatment Emergent Adverse Events (n)</th>
<th>Nyxol n=94</th>
<th>Placebo n=91</th>
<th>Total n=185</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Treatment Emergent Adverse Events (n)</td>
<td>113</td>
<td>31</td>
<td>144</td>
</tr>
<tr>
<td>TEAEs by Severity (n [%])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>47 (50%)</td>
<td>15 (17%)</td>
<td>62 (33%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>3 (3%)</td>
<td>0 (0%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

| AEs Occurring in ≥ 5% of subjects (n [%])  |            |              |             |
| Instillation Site Discomfort               | 36 (38%)   | 8 (9%)       | 44 (24%)    |
| Conjunctival Hyperemia                     | 12 (13%)   | 0 (0%)       | 12 (7%)     |

| Conjunctival Hyperemia (mean [SD])         |            |              |             |
| Baseline (-1 hour)                         | 0.7 (0.6)  | 0.7 (0.5)    | --          |
| 60 minutes after instillation of Nyxol     | 1.7 (0.5)  | 0.5 (0.5)    | --          |
| 4 Hours after instillation of Nyxol        | 1.2 (0.7)  | 0.5 (0.5)    | --          |

Conjunctival Hyperemia Grading Scale (CCLRU)

- None (0)
- Mild (+1)
- Moderate (+2)
- Severe (+3)

94% of the AEs in the Nyxol group were mild

Installation site discomfort was 97% mild; No burning, no stinging, no ptosis upon installation

From a baseline mean of 0.7, the mean hyperemia score increased by approximately 1.0 unit (on a 4-point scale) at 60 minutes post-dose and decreased steadily thereafter

There were no deaths, serious AEs, or withdrawals due to AEs
NDA Submission Targeted in Late 2022

Ongoing Activities Sets Ocuphire on Path to a Potential Regulatory Approval in 2023

**Target Label Indication**
The treatment of pharmacologically induced mydriasis produced by adrenergic (e.g., phenylephrine) or parasympatholytic (e.g., tropicamide) agents, or a combination thereof.

---

**Preservative-Free**
Single Unit Vial (5-pack)

**Nyxol®**

---

**Topline Results**
Expected in Early 2022

---

**P3 Clinical Trial**
Complete a 2nd Phase 3 trial in RM with ~330 subjects which also meets 24-hour safety population exposure

---

**Pediatric Safety**
Complete RM trial with 20 subjects ages 3 to 11 per agreed FDA initial pediatric plan

---

**Manufacturing**
Completed 3 registration batches; 1-year CMC stability for NDA

---

**Regulatory Approval**
Submit NDA by Late 2022
What’s Important?

Nyxol has the Potential to be the only FDA-Approved Treatment Option to Reverse Dilation

Efficacy Signal
- Compelling magnitude of response compared to placebo with statistical significance
- More rapid response with Nyxol vs. placebo
- Works in all iris colors
- Works across all commonly used mydriatic agents

Efficacy Signal
- Statistically significant percent of subjects on Nyxol compared to placebo returning to baseline (within 0.2 mm) photopic pupil diameter (PD) at 90 min demonstrated in 2 well-controlled, multi-center clinical trials
- Precedent set with RevEyes Approval

Safety
- Well-tolerated drop
- No significant ocular or systemic AEs or SAEs

Safety
- No systemic side-effects such BP, HR, headache
- Mild, transient hyperemia is acceptable and common in Rx drops

Label Expansion
- Opportunity to expand label with ongoing pediatric trial in kids 3 years and up given safety shown in dental reversal approval for phentolamine

Label Expansion
- Patients desire more rapid return to normal activities
- Patients actively asking for ‘reversal’ drops
- Patients want a comfortable experience post-dilation
- Patients more likely to maintain their annual exams if option to reverse dilation is presented

FDA Guidance

Physician/Patients

Patient Experience

Opportunity to expand label with ongoing pediatric trial in kids 3 years and up given safety shown in dental reversal approval for phentolamine

Opportunity to expand label with ongoing pediatric trial in kids 3 years and up given safety shown in dental reversal approval for phentolamine
RM Market Opportunity and Commercialization

Presented by: Mitchell Jackson, MD

- Founder and CEO of Jacksoneye in Illinois
- 29 years of experience as a Comprehensive Ophthalmologist
- 2021 - Best Cataract Surgeon in America
- 2021 - Top 50 Global Key Opinion Leaders (KOL)
Patients are Vocal About the Negative Effects of Mydriasis

“I hate having my eyes dilated” generated thousands of results on Google, Social Media and Patient Forums

“It takes all day or sometimes overnight to return to normal! I have too much to do!”

“I hate going to the eye doctor. Ruins my whole day.”

“I HATE having my eyes dilated. Every time=migraine”

“I have to visit my retina MD for my monthly injections, where I am dilated. Being dilated every month is a huge burden on my day.”

“Ever since I was a little kid, I have hated getting my eyes dilated. I hate trying to walk, let alone try to drive in the sun with dilated eyes.”

“I had a premium cataract procedure by my MD, and I was unable to see clearly for two days. My doctor said it was due to my dilation. I did not expect my dilation to last that long.”

Quotes are from anonymous patients.
# Importance of Dilations

**Dilated Eye Exam Remains the Recommended Standard of Care**

### Patient Types For Dilation
- Patients with or at-risk for glaucoma, diabetes, AMD, etc.
- Patients undergoing cataract evaluation
- Patients undergoing refractive evaluation (includes first or annual exams)
- Patients receiving anti-VEGF injections
- Anyone over the age of 60 or other risk populations

### Reasons Patients Decline
- Blurry vision
- Photophobia
- Headaches
- Loss of accommodation
- Allergic reactions
- Digital strain
- Phobia
- Lifestyle
- Work

### Non-Dilated Exam
- Ultra-Widefield Imaging (UWFI) Tool
- Barriers:
  - Capital Equipment Cost
  - Training time
  - Cost to patient $40-80
  - Not a replacement for a dilated exam
  - Dilated exam is standard of care

### Advocacy

- **$35 B+**
  - Societal cost of major visual disorders among U.S. residents aged 40+
- **63%**
  - of participants who had eye disease were not aware

Source: American Academy of Ophthalmology, Comprehensive Adult Medical Eye Evaluation Preferred Practice Pattern, 2020
Bottom-Up Calculation of Annual Dilated Eye Exams

~101 Million Annual Dilated Eye Exams are Performed in the US

<table>
<thead>
<tr>
<th>Providers</th>
<th>Number of Providers (X)</th>
<th>Average Number of Weekly Exams (Y)</th>
<th>Estimated % Patients Dilated (Z)</th>
<th>Total (X<em>Y</em>Z) * 48 wk/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optometrists</td>
<td>46,000</td>
<td>59</td>
<td>40%</td>
<td>~52 M</td>
</tr>
<tr>
<td>Ophthalmologists</td>
<td>18,000</td>
<td>88</td>
<td>50+%</td>
<td>~38M</td>
</tr>
<tr>
<td>Retina Specialists</td>
<td>3,000</td>
<td>150</td>
<td>50%</td>
<td>~11 M</td>
</tr>
</tbody>
</table>

Supply Side Validation: Based on the ~2 million total units of mydriatic agents sold in 2020, we calculated the total number of dilated eye exams to be ~125 million patients, consistent with demand side estimates.

*IQVIA 2020 sales data; KOL Interview; GlobalData market research; and AOA Excel and Jobson Medical Information
‘Bottom-Up Calculation’ assumes 48 total work weeks in a year Supply side validation assumed each unit (bottle) has ~10 mL fill volume and each patient gets 2-4 drops
GlobalData Market Research Survey

Market Research Methodology by GlobalData
Market Research Conducted in 2H 2020 for RM, Presbyopia, and Night Vision Disturbances

GlobalData conducted this research in 4 phases of primary research, which allowed us to inform the survey instruments for each audience as the project progressed.

1. Physician Perceptions
   - OBJECTIVE: Assess the competitive environment in each of the three indications from the perspective of treating physicians

2. Payer Perceptions
   - OBJECTIVE: Understand the assignment of coverage in pharmacy or vision plans

3. Patient Perceptions
   - OBJECTIVE: Understand patients' current unmet needs as well as their potential acceptance of or desire for Nyxol

4. Quantitative Physician Input
   - OBJECTIVE: Quantitatively assess the potential use of Nyxol in each of the three indications

>200 Total Patients Surveyed
- Reversal of mydriasis (N=190)
- Presbyopia (N=134)
- Dim Light Vision Disturbance (N=120)

120* Optometrists & Ophthalmologists Surveyed
(N=69 Optometrists; N=51 Ophthalmologists)
* Retina specialist were not surveyed
Reversal of Mydriasis (RM) Market Opportunity

With No Commercially Available Treatment, Nyxol may Achieve Significant Revenue Potential

GlobalData Market Research Findings

- **58%** physicians would start prescribing Nyxol within the 1st year
- **0** Current Commercially Available Treatments
- **81%** patients would be more likely to schedule yearly eye exams with a reversal drop
- **68%** physicians would be willing to use Nyxol even if patients had to still wear sunglasses within the 1st hour

- **101M** Annual Dilations
- **95%** of Dilating Drops Used by ECPs
- **80%** of Patients Likely to Request Drop
- **65%** Report Moderate to Severe Impact to Daily Function
- **Patient Willingness** to Pay $10 to $20+

-$500+M Estimated US RM Market Opportunity

Source: GlobalData Market Research Survey
### Problems with Rev Eyes

- 4 drops from a multiuse office bottle (added additional chair time)
- Significant Side-effects
  - Burning and stinging sensation
  - Ptosis
  - ‘beefy red eyes’
  - Nicknamed “Red-Eyes”
- Not an acceptable commercial formulation
- Burden of preparation given requirement to mix at physician office
  - Product stable for only 21 days
- Limited marketing effort
  - Years of being on-and-off the market given multiple pharma owners hindered uptake

### Nyxol Differentiation

- 1 to 2 drops for a rapid reversal from a single-unit vial
- No burning and stinging sensation
- No ptosis
- 94% of AEs were mild
- A hassle-free, room temperature shelf-stable, sterile, preservative-free, single-unit vial
- Experienced team committed to commercial success in RM
  - Expected growth in dilations due to an aging population and digital dependence

---

**Why 1990’s Rev-Eyes is Not a Benchmark for Nyxol Future RM Sales**

**Nyxol’s Broad Differentiation Addresses the Unmet Need for Reversal Drops in New Era**

---

**Safety**

**Efficacy**

**Stability**

**Commercialization**
RM Market Opportunity and Commercialization

Presented by: Bindu Manne

- 16 years of experience primarily in product launches (12+) across all ophthalmic specialists
- Dynamic experience ranging from sales, market development, professional and medical affairs
- **Ophthalmic World Leader:** Rising Star Award Recipient
- Non-Profit Board Member: Holland Foundation For Sight Restoration and Ophthalmic World Leaders
Perspective from Practice Administrators on Reversing Dilations

Leading Practice Administrators Confirm the ‘Market Need,’ and Value to Patient

• Anterior Segment Practice in Southeast
  – “We’ve explored and offered several options over the years to reverse mydriasis – both as a tool to elevate the patient experience and to reduce liability when a patient with poor accommodation walks out of my practice. We’ve used pharmacologic agents to reverse the effects of dilation in the past, but those products had significant limitations, and I would welcome a new option indicated for RM in my practice.” – Certified Ophthalmic Executive and CEO

• Multi-Specialty Practice, Midwest
  – “We call our patients guests so anything to enhance their experience is valuable for our practice. Pupil dilation is a perceived inconvenience – especially for the working-age population. They grab up our evening appointments typically, so they don’t have to go back to work while dilated. Having an option to reverse dilation is something we and our guests would enjoy.” – Certified Ophthalmic Executive and CEO

• Leading Academic Eye Center
  – “Patients have anxiety over dilation and if we could reduce that fear, help them regain accommodation faster, I would like to consider that option across all specialties.” – Head of Operations, Certified

Willingness to Implement:

~ We would be comfortable passing this cost to the patient as a premium to resume visual function faster.

~ Patients would be willing to pay for this benefit.
Pre-Commercial Activities in 2022
Activities Underway to Support Capital-Efficient Nyxol RM Commercial Launch

- **Market Development**: Engage leading Key Opinion Leaders and Professional Societies to establish our commitment to refractive and retinal disorders.

- **Physician Targeting**: Broad HCP opportunity with focus on early adopters to capture post-market data and patient experience.

<table>
<thead>
<tr>
<th>Eye Care Practitioners in U.S.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Ophthalmologists</td>
<td>18,000</td>
</tr>
<tr>
<td>Total Optometrists</td>
<td>46,000</td>
</tr>
<tr>
<td>Total Retina Specialists</td>
<td>3,000</td>
</tr>
</tbody>
</table>

- **Patient Journey**: Establish Ocuphire as a patient-centric company and leader in improving everyday vision through education to empower purchasing decisions.

- **Brand Awareness Across Eye Care Professionals**: Initiate branded and unbranded education for ophthalmologists, optometrists and practice professionals.
Go-To-Market Strategy for 2023
Nyxol as RM Allows Efficient Pharmaceutical Launch Across Eye Care Practices

Ocuphire Preferred Go-To Market Strategy for 2023

Partner with existing commercial sales and distribution players that have established ophthalmic products and relationships

An Efficient Launch…
* No approved drug/competition
* Routine part of practice
* Patients daily function impacted by eye dilations
### Practice Implementation Models

*Positive Feedback from Physicians on Integration of a Reversal Agent into Practice*

<table>
<thead>
<tr>
<th>Optometry</th>
<th>Ophthalmology</th>
<th>Retina</th>
</tr>
</thead>
</table>

- Adoption into practice requires no additional staff or patient training.
- Practices across all specialties expressed the positive impact on patient experience and adherence to dilated exams.
- Ophthalmology and Optometry practices would pass a nominal fee into their routine refraction and include it in their surgical pricing.
- Retina practices across academic centers favored offering to patients at no additional cost due to the volume of dilated exams and as a patient satisfaction service.
Nyxol® for Reversal of Mydriasis (RM)

QUESTION & ANSWER
**Summary of Nyxol Reversal of Mydriasis Program**

Nyxol, the first ophthalmic formulation of *phentolamine mesylate*, is a differentiated MOA uniquely suited for **reversal of pharmacologically-induced mydriasis**

In MIRA-1 and MIRA-2, **Nyxol met its primary endpoint of rapidly returning subjects** as well as many key secondary endpoints

Consistent with prior trials, Nyxol has demonstrated **favorable safety and tolerability with a MOA uniquely suited to avoid safety issues** associated with cholinergic drug (e.g. pilocarpine) reversal of dilations

MIRA-3 Phase 3 and MIRA-4 Pediatric Safety trials are **currently enrolling** patients at 15 sites in the US **with data expected in early 2022**

We anticipate the results of these trials will support an **NDA submission for Nyxol in late 2022**

Nyxol has the potential to be the **ONLY commercially-available, FDA-approved Rx treatment to reverse pupil dilation** in a growing $500+M US Market
III. Nyxol Presbyopia Program

Jay Pepose, MD, PhD
UCLA School of Medicine

James Katz, MD
University of Illinois, College of Medicine
Pupil Modulation Eye Drops for Presbyopia

Presented by: Jay Pepose, MD, PhD

- Founder and Medical Director of Pepose Vision Institute
- Founder of Midwest Vision Research Foundation
- Recognized Thought Leader in Ophthalmology
- 40 Years of Experience as a Treating Physician and Widely Published Researcher
The Time for Presbyopia Drops

Headlines from Academia and Industry Articles with an Early First Approval for Vuity™

“The correction of presbyopia remains ophthalmology’s ‘Holy Grail’…”

-OIS
What is the Optimal Pupil Size?

**Literature Highlights** New Drops to Treat Presbyopia Achieve Optimal Pupil Diameter of 2-3 mm

"A fixed 2- to 3-mm small pupil or a 30% pupil miosis can both produce near visual acuity gains without significant losses to distance acuity or image quality, and therefore can be considered as optimal for a presbyope experiencing a wide range of light levels."

- Optometry and Vision Science, November 2016

---

**Photopic Lighting** (100 - 1000 lux)
Natural Pupil Size ~ 4 mm

---

**Effect of Target Luminance on Optimum Pupil Diameter for Presbyopic Eyes**
Renfeng Xu*, Larry Thibos*, and Arthur Bradley*

---

"The impact of pupillary modulation on the functional depth of field differs among patients with refractive error versus those who are truly emmetropic."

- Cataract & Refractive Surgery Today (CSRT), January 2022

---

Source: Xu et al, OVS 2016; Pepose & Xu CSRT article 2022, Effect of Target Luminance on Optimum Pupil Diameter for Presbyopic Eyes
Nyxol with LDP as Adjunctive Therapy in Presbyopia

Presented by: Jay Pepose, MD, PhD
Nyxol® with Low-Dose Pilocarpine (LDP) as Adjunct Therapy

Moderate Action on Iris Dilator and Iris Sphincter Muscles for Near Vision Improvement

0.75% Nyxol

Iris Dilator
Muscle
Inhibition

• Phentolamine (alpha1/2 antagonist)
• Novel MOA on iris dilator with 24+ hour durability
• Moderate 1+mm pupil reduction
• No daytime redness
• Well-tolerated with no systemic effects
• Stable, preservative-free, single-use vial

Evening drop

0.4% LDP

Iris Sphincter
Muscle
Activation

• Pilocarpine (cholinergic agonist)
• Known MOA on sphincter (and ciliary) muscle as potent miotic at approved doses (1%, 2%, 4%)
• Low concentration avoids known safety issues:
  ➢ headache and browache
  ➢ redness
  ➢ accommodative spasm causing loss of distance vision especially at night

Pin-hole target is 2 to 3 mm with contributions from each MOA

Daytime drop

Source: 1) Nyxol® data from 9 completed trials; Pilocarpine Product label and Literature
VEGA-1: Presbyopia Phase 2 Trial Design

Randomized, Double-Masked, Placebo-Controlled, Multi-Center One-Week Trial

---

**Endpoints**

**Primary:** % of subjects with ≥ 3 lines of improvement in distance-corrected near visual acuity comparing Nyxol + LDP vs placebo alone at 1 hour

**Secondary:**
- % of subjects with ≥ 2 and ≥ 3 lines gained at time points from 30 min to 6 hours in photopic lighting comparing Nyxol + LDP vs placebo, Nyxol alone, and LDP alone
- % of subjects with ≥ 3 lines of near vision gain with less than 5 letters of distance loss
- Pupil diameter at time points
- Safety and tolerability

---

**Eligibility Criteria**

- Males or females ≥ 40 and ≤ 64 years of age
- BCDVA of 0.0 LogMAR (20/20 Snellen equivalent) or better in each eye under photopic conditions
- DCNVA of 0.4 LogMAR (20/50 Snellen equivalent) or worse in photopic conditions in each eye & binocularly

---

**Phase 2 Enrollment Completed Feb to May 2021 – 150 Subjects Reported Topline Results End of 2Q21**

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Clinical trial NCT#04675151. DCNVA = distance-corrected near visual acuity. BCDVA = best corrected distance visual acuity; *3-4 evenings; VEGA-1 Study Design
# VEGA-1: Demographics and Baseline Characteristics

_Treatment and Placebo Arms were Balanced in the VEGA-1 Phase 2 Clinical Trial_

<table>
<thead>
<tr>
<th></th>
<th>Placebo Alone N=43</th>
<th>Nyxol Alone N=30</th>
<th>LDP Alone N=31</th>
<th>Nyxol+LDP Combo N=43</th>
<th>Total N=147</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years): Median (Range)</strong></td>
<td>52 (42-62)</td>
<td>54 (41-60)</td>
<td>52 (44-64)</td>
<td>53 (43-63)</td>
<td>53 (41-64)</td>
</tr>
<tr>
<td><strong>Sex: Male n (%) Female n (%)</strong></td>
<td>15 (35%) 28 (65%)</td>
<td>7 (23%) 23 (77%)</td>
<td>13 (42%) 18 (58%)</td>
<td>5 (12%) 38 (88%)</td>
<td>40 (27%) 107 (73%)</td>
</tr>
<tr>
<td><em><em>Race: White n (%) Other</em> n (%)</em>*</td>
<td>37 (86%) 6 (14%)</td>
<td>26 (87%) 1 (3%)</td>
<td>28 (90%) 3 (10%)</td>
<td>40 (93%) 3 (7%)</td>
<td>131 (89%) 15 (11%)</td>
</tr>
<tr>
<td><strong>Dark Iris Color: n (%)</strong></td>
<td>18 (42%)</td>
<td>12 (40%)</td>
<td>12 (39%)</td>
<td>18 (42%)</td>
<td>60 (41%)</td>
</tr>
<tr>
<td><strong>Light Iris Color: n (%)</strong></td>
<td>25 (58%)</td>
<td>18 (60%)</td>
<td>19 (61%)</td>
<td>25.1 (58%)</td>
<td>87 (59%)</td>
</tr>
<tr>
<td><strong>Photopic DCNVA Mean Letters read-Binocular (Snellen Equiv.) 70 letters = 20/20</strong></td>
<td>46 (20/63)</td>
<td>45 (20/63)</td>
<td>48 (20/63)</td>
<td>46 (20/63)</td>
<td>46 (20/63)</td>
</tr>
<tr>
<td><strong>Photopic BCDVA Mean Letters read-Binocular (Snellen Equiv.) 55 letters = 20/20</strong></td>
<td>62 (20/15)</td>
<td>61 (20/15)</td>
<td>60 (20/15)</td>
<td>61 (20/15)</td>
<td>61 (20/15)</td>
</tr>
<tr>
<td><strong>Photopic Pupil Diameter Mean (mm)</strong></td>
<td>4.3</td>
<td>4.5</td>
<td>4.3</td>
<td>4.3</td>
<td>4.3</td>
</tr>
<tr>
<td><strong>Mesopic Pupil Diameter Mean (mm)</strong></td>
<td>5.1</td>
<td>5.0</td>
<td>5.0</td>
<td>5.1</td>
<td>5.1</td>
</tr>
</tbody>
</table>
VEGA-1: Nyxol+LDP Met Primary & Secondary Endpoints

61% Patients with Nyxol+LDP had ≥ 15 Letter Near Gain with Fast Onset & Durable Responses

**VEGA-1 Phase 2 Trial**

Percent of Subjects with ≥ 15 Letters Binocular Photopic DCNVA Improvement from Baseline

<table>
<thead>
<tr>
<th>Time (Hours)</th>
<th>Placebo (n=43)</th>
<th>Nyxol+LDP (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>16%</td>
<td>33%</td>
</tr>
<tr>
<td>0.5</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>28%</td>
<td>61%</td>
</tr>
<tr>
<td>2</td>
<td>16%</td>
<td>63%</td>
</tr>
<tr>
<td>3</td>
<td>21%</td>
<td>47%</td>
</tr>
<tr>
<td>4</td>
<td>21%</td>
<td>47%</td>
</tr>
<tr>
<td>6</td>
<td>19%</td>
<td>37%</td>
</tr>
</tbody>
</table>

**P**

Note: PP population differs from mITT by only one subject; results were essentially identical.

Source: VEGA-1 TLR Table 14.2.1.2 Percent of Subjects with Improvement From Baseline in Photopic DCNVA by Time Point (PP Population). 15 letters is 3 lines.
VEGA-1: Planned P3 Efficacy Endpoint Met by Nyxol+LDP

Pre-Specified Endpoints Demonstrate Superiority of Combo vs. Components & >10 Letter Near Gain

**VEGA-1 Phase 2 Trial**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=43)</th>
<th>Nyxol+LDP (n=43)</th>
<th>Nyxol (n=30)</th>
<th>LDP (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 15 Letter Gain In Near &amp; &lt; 5 Letter Loss In Distance at 30 Minutes</td>
<td>14%</td>
<td>61%</td>
<td>33%</td>
<td>26%</td>
</tr>
</tbody>
</table>

Nyxol + LDP combination achieved statistical superiority to LDP and Nyxol alone arms even with a small sample size.

77% of subjects achieved ≥ 10 letter improvement in DCNVA at 30 minutes (p=0.015 vs placebo) and similar trend at other timepoints.

Source: VEGA-1 TLR Table 14.2.2.2 Percent of Subjects with >= 15 Letters of Improvement in Photopic DCNVA and < 5 Letters of Loss in Photopic Binocular BCDVA by Time Point (PP Population); Table 14.2.1.2 Percent of Subjects With Improvement From Baseline in Photopic DCNVA by Time Point (PP Population)
**VEGA-1: Improvement in Functional Near Vision**

Nyxol+LDP had a Rapid Improvement in Near Vision to 20/32 for many Patients

### VEGA-1 Phase 2 Trial

#### Binocular Photopic DCNVA

Nyxol + LDP

---

**Improvement in Snellen Equivalent**

- **84%** 20/40 or Better Near Vision
- **68%** 20/32 or Better Near Vision

---

<table>
<thead>
<tr>
<th>Snellen Acuity</th>
<th>Percent of Subjects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20/15</td>
<td>7%</td>
</tr>
<tr>
<td>20/20</td>
<td>0%</td>
</tr>
<tr>
<td>20/25</td>
<td>0%</td>
</tr>
<tr>
<td>20/32</td>
<td>23%</td>
</tr>
<tr>
<td>20/40</td>
<td>26%</td>
</tr>
<tr>
<td>20/63</td>
<td>33%</td>
</tr>
<tr>
<td>20/80</td>
<td>40%</td>
</tr>
<tr>
<td>20/100</td>
<td>23%</td>
</tr>
</tbody>
</table>

---

**Source:** VEGA-1 TLR Table 14.2.24.1 Percent of Subjects with Photopic DCNVA by Time Point (PP Population)
VEGA-1: Mean Pupil Diameter Over Time

Achieved Optimal Pupil Size in Nyxol+LDP (& Nyxol) Consistent with 3-line Near Vision Gain

VEGA-1 Phase 2 Trial

Best Eye (PP Population)
Mean Photopic Pupil Diameter

**p<0.01
***p<0.0001

Placebo (n=43)
Nyxol-LDP (n=43)
Nyxol (n=30)
Placebo + LDP (n=31)

Source: VEGA-1 TLR Table 14.2.12.1 Observed Values and Change from Baseline in Photopic Pupil Diameter by Time Point (PP Population)
% of Subjects With Improvement or Loss From Baseline in Photopic and Mesopic BCDVA at 1 Hour

**VEGA-1 Phase 2 Trial**

**Percent of Subjects With Improvement or Loss From Baseline in Photopic BCDVA at 1 hour**

- **Placebo (n=43)**: 9%, 20%, 19%
- **Nyxol+LDP (n=43)**: 28%, 72%, 77%
- **Nyxol (n=30)**: 91%, 72%, 74%
- **LDP (n=31)**: 0%, 3%, 7%

**Percent of Subjects With Improvement or Loss From Baseline in Mesopic BCDVA at 1 Hour**

- **Placebo (n=43)**: 9%, 23%, 27%
- **Nyxol+LDP (n=43)**: 39%, 72%, 73%
- **Nyxol (n=30)**: 55%, 7%, 7%
- **LDP (n=31)**: 7%, 5%, 0%

Source: VEGA-1 TLR Table 14.2.8.1 and 14.2.10.1 Percent of Subjects With Improvement or Loss From Baseline in Photopic and Mesopic BCDVA by Time Point (PP)
**VEGA-1: Safety Findings Across All Arms**

*NyxoL+LDP Combination (& NyxoL Alone) was Well Tolerated with a Favorable Safety Profile*

<table>
<thead>
<tr>
<th></th>
<th>Placebo Alone n=45</th>
<th>NyxoL Alone n=30</th>
<th>LDP Alone n=31</th>
<th>NyxoL+LDP n=44</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Treatment Emergent Adverse Events (n)</strong></td>
<td>4</td>
<td>18</td>
<td>13</td>
<td>50</td>
</tr>
<tr>
<td><strong>TEAEs by Severity (n [%])</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1 (2.2%)</td>
<td>6 (20%)</td>
<td>6 (19.4%)</td>
<td>13 (29.5%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 (2.2%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (2.3%)</td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (2.3%)</td>
</tr>
<tr>
<td><strong>AEs Occurring in ≥ 5% of subjects (n [%])</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Instillation Site Pain (Mild)</td>
<td>1 (2.2%)</td>
<td>3 (10%)</td>
<td>0 (0%)</td>
<td>4 (9.1%)</td>
</tr>
<tr>
<td>Instillation Site Erythema (Mild)</td>
<td>0 (0%)</td>
<td>3 (10%)</td>
<td>2 (6.5%)</td>
<td>5 (11.4%)</td>
</tr>
<tr>
<td>Conjunctival Hyperemia (Mild)</td>
<td>0 (0%)</td>
<td>2 (6.7%)</td>
<td>0 (0%)</td>
<td>2 (4.5%)</td>
</tr>
<tr>
<td>Eye Disorders (Mild)</td>
<td>1 (2.2%)</td>
<td>2 (6.7%)</td>
<td>4 (12.9%)</td>
<td>5 (11.4%)</td>
</tr>
</tbody>
</table>

• No deaths, no serious AEs
• Almost all AEs were mild
• 0% headaches or brow aches reported for NyxoL+LDP arm; headaches not reported in NyxoL trials
• ~5% mild, transient conjunctival hyperemia AEs in NyxoL+LDP arm
• Distance vision: 0% NyxoL + LDP arm had > 5 letter distance loss in photopic lighting (5% in mesopic)
• No change in IOP

Source: VEGA-1 TLR Table 14.3.1.1 Overall Summary of Treatment Emergent Adverse Events (TEAE) (Safety Population) 
Table 14.3.1.3 Treatment-Emergent Adverse Events (TEAE) by System Organ Class, Preferred Term, and Severity (Safety Population)
What’s Important?
*Nyxol+LDP has the Potential to be “Best in Class” Presbyopia Eyedrop*

**Efficacy Signal**
Percent of subjects with ≥3-line improvement in near vision with less than 5 letters of distance loss in Nyxol+LDP combo compared to Nyxol alone and LDP alone as demonstrated in 2 well-controlled, multi-center clinical trials.

**Safety**
No loss of distance (included in efficacy)
Maintain night distance vision
Well-tolerated

**Broad Label Opportunity**
For Vuity™, FDA did not limit the use of the product to clinical trial parameters such as:
- age
- lighting conditions (photopic or mesopic)
- monocular or binocular
- phakic status

**FDA Guidance**
- Achieve “functional near vision” and intermediate vision
- Achieve optimal pupil size
- Durability
- Dynamic/responsive pupil

**Physician/Patients**
- No loss of distance vision
- No headaches or brow aches
- Reliable night distance vision
- No stinging or burning
- Minimal redness

**Patient Experience**
- Tunability - ability to customize treatment based on patient’s lifestyle needs
- Favorable tolerability for continued use and Rx refills
Nyxol Alone in Presbyopia

Presented by: James Katz, MD

- President of the Midwest Center for Sight
- Board-certified Ophthalmologist with specialties in Cornea, Cataract, and Refractive Surgery
- Well-Published in Distinguished Ophthalmologic Journals With Over 50 Publications and Over 300 Presentations
VEGA-1 Study Design Assessed Nyxol Alone Efficacy

Nyxol as Single Drop vs. Placebo Met Pre-Specified Endpoints in the Trial

**VEGA-1 Phase 2 Trial**

**Visit 1**
- Screening/Baseline
- Nyxol (N=43)
- Nyxol (N=30)
- Placebo (N=31)
- Placebo (N=43)

**Visit 2** (Day 5)
- LDP Drop
- Nyxol + LDP (N=43)
- Nyxol (N=30)
- Placebo (N=31)
- Placebo (N=43)

17 US sites
150 Presbyopic patients

*N=73
*N=74

0.75% Nyxol

Nyxol or Placebo

- 4 days
- ~8PM Evening Dosing
- 12 Hrs

Primary Endpoint

30min 1 Hr 2 Hr 3 Hr 4 Hr 6 Hr

18 Hrs Post-dose

Nyxol alone evaluated 12 hours post dosing

*3-4 daily evening doses and then visit 2 on Day 5
Source: VEGA-1 Study Design
VEGA-1: Nyxol Meets Planned P3 Efficacy Endpoint at 12 Hours

Nyxol as a Single Drop Provides a Statistical 3 Line or More Gain Compared to Placebo

Source: VEGA-1 TLR Table 14.2.1.7 Percent of Subjects with Improvement in Photopic DCNVA at 0 Minutes for Nyxol and Placebo Treated Subjects (PP Population)

Nyxol showed promising ≥15 letter near vision gain at 12 hours
VEGA-1 Phase 2 Trial

Percent ofSubjects with ≥10 Letters Binocular Photopic DCNVA Improvement from Baseline

- Placebo (n=74)
- Nyxol (n=73)

p=0.005

53%

28%

NyxoI showed promising ≥10 letter near vision gain at 12 hours

Source: VEGA-1 TLR Table 14.2.1.7 Percent of Subjects with Improvement in Photopic DCNVA at 0 Minutes for Nyxol and Placebo Treated Subjects (PP Population)
VEGA-1: Improvement in Functional Near Vision

Nyxol Single Drop Significantly Improves Functional Near Visual Acuity

VEGA-1 Phase 2 Trial

Table 14.2.24.1 Percent of Subjects with Photopic DCNVA by Time Point (PP Population)

<table>
<thead>
<tr>
<th>Snellen Acuity</th>
<th>Baseline</th>
<th>12 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>20/15</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td>20/20</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td>20/25</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>20/32</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>20/40</td>
<td>0%</td>
<td>12%</td>
</tr>
<tr>
<td>20/50</td>
<td>0%</td>
<td>16%</td>
</tr>
<tr>
<td>20/63</td>
<td>36%</td>
<td>23%</td>
</tr>
<tr>
<td>20/80</td>
<td>34%</td>
<td>15%</td>
</tr>
<tr>
<td>20/100</td>
<td>19%</td>
<td>11%</td>
</tr>
</tbody>
</table>

Nyxol Single Drop Significantly Improves Functional Near Visual Acuity

Baseline Inclusion: Photopic DCNVA of 20/50 or worse

Source: VEGA-1 TLR Table 14.2.24.1 Percent of Subjects with Photopic DCNVA by Time Point (PP Population)
# VEGA-1: Functional Vision Durability

*Single Drop of Nyxol has Durable Response for 18 Hours*

---

**Nyxol as a Single Drop**

<table>
<thead>
<tr>
<th>Time Point (Hrs post Nyxol dose)</th>
<th>% of Subjects</th>
<th>Statistics vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects achieving <strong>3-line gain</strong> in photopic, binocular DCNVA (N= 30)</td>
<td>12.5</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>37%</td>
</tr>
<tr>
<td>Subjects achieving <strong>20/40 or better</strong> in photopic, binocular DCNVA (N= 30)</td>
<td>18</td>
<td>60%</td>
</tr>
</tbody>
</table>

* *Trend toward statistical significance even in smaller Nyxol arm from time 0 to time 6 hrs (n=30); larger sample size for all arms planned in Phase 3 program*
VEGA-1(Post-Hoc): Efficacy Across Presbyopia Ages

Nyxol Highest Efficacy in Young Presbyopes as Expected; Also Efficacy Seen in Older Presbyopes

VEGA-1 Phase 2 Trial

Percent of Subjects With 15 Letter Improvement From Baseline in Photopic DCNVA at 0 Minutes for Nyxol and Placebo Treated Subjects by Age Group 40-54 yrs and 55-64 yrs

- Nyxol demonstrated efficacy in 55 to 64 age group and efficacy seen at 12 hours

Note: Trend toward statistical significance p=0.15 in age 40-54; larger sample size for all arms planned in Phase 3 program

Source: VEGA-1 TLR Table 14.2.1.7.1 & 14.2.1.7.2 Percent of Subjects with Improvement in Photopic DCNVA by Age Group (PP Population)
Presbyopia Drops: Ocuphire Next Steps and Competitive Landscape

Presented by: Jay Pepose, MD, PhD
Two Treatment Options for Spectrum of Presbyopic Patients

Two NDA Submissions Targeted in 2023: Nyxol Alone and Nyxol+LDP

Pursuing Product Labels for 1 Drop and 2 Drop Options for the Treatment of Presbyopia

Nyxol as a Single Agent for Presbyopia
Single Durable Drop

Nyxol with LDP as Adjunctive Therapy for Presbyopia
Two Drops Tunable Option

Initiating VEGA Phase 3 Program in Mid-2022 for Both Labels
Potential ‘Best in Class’ Presbyopia Drop(s)

*Nyxol and Nyxol+LDP Combination Data Differentiates on Efficacy, Safety, and Durability*

<table>
<thead>
<tr>
<th>Product Attributes*</th>
<th>VUITY™</th>
<th>Nyxol</th>
<th>Nyxol+LDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Efficacy (3 Line Gain in DCNVA - Primary Endpoint Responders)*</td>
<td>26-31% (3 hours)</td>
<td>30% (12 hours)</td>
<td>~61% (1 hour)</td>
</tr>
<tr>
<td>2) Safety: Loss of Distance in Mesopic</td>
<td>No Significant Loss</td>
<td>No Significant Loss</td>
<td>No Significant Loss</td>
</tr>
<tr>
<td>3) Tolerability: Headaches and Conjunctival Hyperemia</td>
<td>&gt;5% Headaches &gt;5% redness</td>
<td>No Headaches &gt;5% mild redness</td>
<td>No Headaches ~5% mild redness</td>
</tr>
<tr>
<td>4) Durability (% responders at the longest timepoint)</td>
<td>18% at 6 hours</td>
<td>37% at 18 hours</td>
<td>37% at 6 hours</td>
</tr>
</tbody>
</table>

Caveats of cross-trial comparisons for VUITY™ and Nyxol/LDP. Differences include age, severity of near vision loss, lighting conditions, doses, timing, and # of patients.

Placebo Adjusted Values for Vuity were 15-23% in Gemini1 & 2; Placebo Adjusted Nyxol was 16% and Nyxol+LDP was 33% (all stat significant).
Source: Nyxol Data: ASCRS (July 2021) Abstract# 76645 (Phase 2) and VEGA-1; Abstract 74336 (Phase 3). VUITY™ Data FDA Label and AAO 2021 Presentation.
Presbyopia Eye Drops Competitive Landscape

Validation of Pupil Modulating Drops Achieving Pin-Hole Effect & Efficacy, Many with Pilocarpine

- **Phase 1**
  - Orasis (CSF-1; low dose pilo)
  - Visus (Brimonucle®; brimonidine + carbachol)

- **Phase 2**
  - Ocuphire (0.75% Nyxol + 0.4% pilo)
  - Novartis (EV-06)

- **Phase 3**
  - Allergan (VUITY™; 1.25% pilo)
  - Orasis (CSF-1; low dose pilo)

- **Other Cholinergic Agonists**
  - Efenovia (MicroLine; 2% pilo)
  - Lenz (PRX-100; aceclidine)

- **Alpha Antagonist & Pilocarpine**
  - Ocuphire (0.75% Nyxol)

- **Alpha 1 Antagonist**
  - Lenz (PRX-100; aceclidine)

- **Cholinergic Agonist** (pilocarpine)
  - Allergan (VUITY™; 1.25% pilo)
  - Orasis (CSF-1; low dose pilo)

- **Alpha Antagonist & Pilocarpine**
  - Ocuphire (0.75% Nyxol)

Nyxol is differentiated as a new MOA class using the iris dilator muscle to reach an optimal pupil size.

*Cholinergic Agonist* (pilocarpine)* act on sphincter and ciliary muscles in dose-dependent manner.

Corporate Websites, Grzybowsk, A, Markevicu A, Zemaitiene R. A Review of Pharmacological Presbyopia Treatment. 2020
Large and Growing Presbyopia Market

Presented by: James Katz, MD
Presbyopia is a Burgeoning Opportunity

One of the Largest Disease Segments, Increasing Spend from Global Reading Glasses Market

The Problem

- Lens loses ability to change shape when viewing objects up close as we age
- Dependence on reading glasses for intermittent and prolonged use, but unable to see near and far at the same time
- Aesthetics and inconvenience

100% of adults over the age of 40 years are at risk of developing presbyopia

Presbyopess (US)
\(~128\,M\)

Global Reading Glasses Market (USD Billion), 2019 & 2027

- 2019: $36 B
- 2027: $56 B

Key Findings from GlobalData Market Research on Presbyopia

Insights Very Consistent with Other Competitors Market Research Surveys

<table>
<thead>
<tr>
<th>120+ Million</th>
<th>90%</th>
<th>70%</th>
<th>40%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presbyopia patients in the US</td>
<td>presbyopia patients wear reading glasses ≥ once per day</td>
<td>patients would consider an eye drop as an alternative to reading glasses</td>
<td>patients have asked their physicians about alternatives to reading glasses</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>51%</th>
<th>67%</th>
<th>70%</th>
</tr>
</thead>
<tbody>
<tr>
<td>physicians would offer eye drops as a first-line presbyopia treatment</td>
<td>physicians indicated interest in Nyxol+LDP</td>
<td>patients considered the 2 drops/bottle dosing to be moderately-to-very convenient</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>≥ $50/mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Willing to Pay</td>
</tr>
<tr>
<td>Vuity™ is priced at $79 for a 30-day supply</td>
</tr>
</tbody>
</table>

Physician Perspective
N=120

Patient Perspective
n=134

GlobalData Market Research Survey
Presbyopia Market Segments

Tens of Millions of Likely Early Users → Emmetropes, Hyperopes, and Pseudophakes

~128M Presbyopes in the US

- Emmetropes
  - Naturally occurring clear vision
  - No refractive error/post-LASIK

- Hyperopes
  - Poor near vision (starting at age 40)

- Pseudophakes
  - Cataract surgery for artificial lens (monofocal, multifocal IOLs)

- Myopes
  - Poor distance vision

66 M

14 M

9 M

39 M

~44 M Patients Likely To Be Early Users of Presbyopia Eyedrops

Assume 50% use eye drops*


Vuity™ is the First FDA-Approved Eyedrop for Presbyopia

Approval Sets the Stage for Market Development by Large Pharma to Build a Large Market

FDA Approval of Vuity™ positive for the presbyopia space

Opportunities for new entrants with differentiated product attributes in a newly established segment with physicians and patients/consumers

~44 M Patients Likely To Be Early Users of Presbyopia Eyedrops

3-6 refills per year assumed

Private Cash Pay (Vuity™ fill List Price)

~$10B - $20B Estimated US Presbyopia Market Opportunity

~2 Billion Presbyopes Globally for Even Larger Market Potential

# Summary of Nyxol and Nyxol+LDP Presbyopia Program

<table>
<thead>
<tr>
<th><strong>Nyxol as a single drop is differentiated as a new MOA class</strong> working on the iris dilator muscles; <strong>Nyxol with LDP as adjunct therapy uniquely offers pupil ‘tunability’</strong> depending on patient lifestyle</th>
</tr>
</thead>
</table>
| **In VEGA-1 trial:**  
  - Nyxol+LDP met its primary efficacy endpoint ≥ 15 letter near visual acuity gain.  
  - **Nyxol as a single drop met efficacy endpoints at 12 hours and 18 hours** |
| **Consistent with prior trials across other indications, Nyxol, dosed alone or with LDP, has demonstrated favorable safety and tolerability** |
| **VEGA Phase 3 program** planned for Nyxol and Nyxol+LDP for the treatment of presbyopia **to initiate mid-2022** |
| **Potential NDA submissions for presbyopia in 2023**  
  - **Nyxol as a single drop**  
  - **Nyxol with LDP as adjunct therapy** |
| **Presbyopia drops projected to be one of the largest $10+B new segments** in Ophthalmology |
Closing Remarks

Mina Sooch, CEO, Founder of Ocufhite Pharma
Ocuphire Management Team
Decades of Biotech and Drug Development Experience

Charlie Hoffmann, MBA
VP Corporate Development and Operations
Tuck School of Business at Dartmouth

Mina Sooch, MBA
President & CEO and Founder

Amy Rabourn, CPA
VP, Finance

Drey Coleman
VP, Clinical Operations

Roni Patel, MS
Senior Director BD and Market Strategy

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

Mitch Brigell, PhD
Head, Clinical Development and Strategy

Barbara Withers, PhD
VP, Clinical and Regulatory Strategy

Bindu Manne
Head, Market Development and Commercialization

Chris Ernst
Global Head, QA and Manufacturing

Laura Gambino
Director, Project Management

Drey Coleman
VP, Clinical Operations
Ocuphire's World-Class Medical Advisory Board

Fortunate for the Insights of Leading KOLs & Drug Candidate Co-Founders

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- Mark Kelley, PhD, Indiana University Co-Founder Apexian/APX3330
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- Mark Kelley, PhD, Indiana University Co-Founder Apexian/APX3330
- Eliot Lazar, MD, Georgetown University
- Ed Holland, MD, Loyola University Chicago
- Marguerite McDonald, MD, Columbia University
- James Katz, MD, University of Illinois
- Jay Pepose, MD, PhD, UCLA School of Medicine

Refractive Specialist
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- Mitch Jackson, MD, University of Chicago
- Thomas Samuelson, MD, University of Minnesota

Retinal Specialist
- Jeffrey Heier, MD, Boston University
- Peter Kaiser, MD, Harvard Medical School
- David Brown, MD, Baylor University

Optometry
- Paul Karpecki, OD, Indiana University
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Ocuphire Board of Directors

Seasoned Directors with Decades of Drug Development, M&A/Financings, & Ophthalmology

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Board Director

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Thanks To Our Network of Partners

A Strong Foundation has been Built to Efficiently Grow and Deliver Our Vision for Patients…

- 4+ Stats/Labs
- 50+ Clinical Investigators
- 4+ CMC Consultants
- 2 Pre-Clin/Tox CROs
- 2 Clinical CROs
- 26 Global API Mfrs
- 5 MD Interns
- 3 Global API Mfrs
- 18 Medical Advisors
- 6 Final Product/ Packaging Mfr
- 5+ Reg/Preclin Consultants
- 10+ Patent/Profess. Advisors
- 6+ Medical Advisors
- 5 Refractive Patients
- 5 Retina Patients

OCUPHIRE Team (15+)
Track Record of Achieving Milestones ➔ Exciting 2022 News Cadence

Multiple Late-Stage Data Catalysts Expected in 2022 for Potential First NDA Approval in 2023

2021

☑ Report Positive Phase 3 Data for RM (MIRA-2)
☑ Report Positive Nyxol+LDP Phase 2 Data for Presbyopia (VEGA-1)
☑ New Patent Claims for Presbyopia
☑ ASCRS 2021 Presentation for MIRA-2 & VEGA-1
☑ Manufacture 3xRegistration Batches for Nyxol Blow-Fill-Seal (BFS) Eye Drops
☑ Initiate 2nd Phase 3 RM AND Pediatric RM trial

2022

☑ Report Positive Nyxol Alone Phase 2 Data for Presbyopia
☑ Report 2nd Phase 3 Data for RM (MIRA-3)
☑ Report Pediatric Data in RM (MIRA-4)
☑ Report Phase 3 Data for NVD (LYNX-1)
☑ Submit Nyxol NDA for RM
☑ Report Phase 2 Data for DR/DME (ZETA-1)
☑ Initiate VEGA Phase 3 Presbyopia Program

Ongoing Partnering Discussions with Leading Ophthalmic Companies (including European and Asian Players)
Overall Highlights from Ocuphire Investor R&D Day

**Nyxol®**

Nyxol® eye drops, as a platform, is uniquely positioned to address growing markets in refractive disorders.

Nyxol, if approved in 2023, would be the only Rx drop for reversing dilations and positively impact the patient experience in an eye care practice.

Nyxol represents a novel class with a differentiated MOA and potential as a convenient single evening drop with efficacy at 12 hours (and 18 hours) in the large presbyopia market.

Ocuphire plans to pursue both Nyxol as a single agent and with low dose pilocarpine as adjunctive therapy to treat a breadth of presbyopia patient types ➔ more details to follow.

**APX3330**

The well-controlled, multi-center Phase 2b ZETA-1 for APX3330 is ~70% enrolled.

APX3330 new interim masked safety data support favorable safety profile as a potential oral treatment for diabetics with DR/DME.

APX3330 oral with dual MOA targeting VEGF and inflammation may be well-suited to reduce treatment burden and/or improve outcomes adjunctive to traditional anti-VEGF intravitreal injections across retinal diseases.
Thank You for Joining Us

Click Here for the Recorded Event

Ocuphire Pharma Investor R&D Day

January 31, 2022