

UNITED STATES  
SECURITIES AND EXCHANGE COMMISSION  
WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 OR 15(d) of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): October 14, 2022

**Ocuphire Pharma, Inc.**

(Exact name of registrant as specified in its charter)

**Delaware**

(State or other jurisdiction of incorporation)

**001-34079**

(Commission File Number)

**11-3516358**

(IRS Employer Identification No.)

**37000 Grand River Avenue, Suite 120 Farmington Hills, MI 48335**

(Address of principal executive offices and zip code)

**248-681-9815**

(Registrant's telephone number including area code)

(Registrant's former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

- Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
- Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
- Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
- Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

**Title of each class**

Common Stock, par value \$0.0001 per share

**Trading Symbol(s)**

OCUP

**Name of each exchange on which registered**

The Nasdaq Stock Market LLC

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging Growth Company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

**Item 7.01 Regulation FD Disclosure.**

On October 14, 2022, Ocuphire Pharma, Inc. (the “Company”) will present new data and updates on its APX3330 clinical program. A copy of this presentation is furnished herewith as Exhibit 99.1 to this Current Report on Form 8-K (this “Report”) and is incorporated by reference herein.

The information in this Report, including Exhibit 99.1 hereto, is furnished pursuant to Item 7.01 and shall not be deemed “filed” for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the “Exchange Act”), or otherwise subject to the liabilities of that Section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such a filing. The Company’s submission of this Report shall not be deemed an admission as to the materiality of any information required to be disclosed solely to satisfy the requirements of Regulation FD.

Exhibit 99.1 hereto contains forward-looking statements within the meaning of the federal securities laws. These forward looking statements are based on current expectations and are not guarantees of future performance. Further, the forward-looking statements are subject to the limitations listed in Exhibit 99.1 and in the other reports of the Company filed with the Securities and Exchange Commission, including that actual events or results may differ materially from those in the forward-looking statements.

**Item 9.01 Financial Statements and Exhibits.****(d) Exhibits**

<b>Exhibit No.</b>	<b>Description</b>
<a href="#">99.1</a>	Corporate Presentation, dated October 14, 2022
104	Cover Page Interactive Data File (embedded with Inline XBRL document).

**SIGNATURE**

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the Registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Dated: October 14, 2022

**OCUPHIRE PHARMA, INC.**

By: /s/ Mina Sooch  
Mina Sooch  
Chief Executive Officer

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Restore Vision & Clarity



## Ocuphire KOL Event: APX3330

October 14, 2022

## Disclosures and Forward-Looking Statements



















This presentation contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Such statements include, but are not limited to, statements concerning the success and timing of planned regulatory filings, including planned NDA filings, pre-commercial activities, commercialization strategy and timelines, business strategy, product labels, cash runway, scalability, future clinical trials in reversal of mydriasis (RM), presbyopia (P), dim light/night vision disturbance (NVD) and diabetic retinopathy (DR)/diabetic macular edema (DME), and the potential market opportunity in DR/DME. These forward-looking statements are based upon the Company's current expectations and involve assumptions that may never materialize or may prove to be incorrect. Actual results and the timing of events could differ materially from those anticipated in such forward-looking statements as a result of various risks and uncertainties, including, without limitation: (i) the success, costs, and timing of regulatory submissions and preclinical 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, including the scalability of Ocuphire's product candidates, and (x) the maintenance of Ocuphire's intellectual property rights. The foregoing review of important factors that could cause actual events to differ from expectations should not be construed as exhaustive and should be read in conjunction with statements that are included herein and elsewhere, including the risk factors detailed in documents that have been and may be filed by the Company from time to time with the SEC. All forward-looking statements contained in this presentation speak only as of the date on which they were made. The Company undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made.

The Company makes no representation or warranty, express or implied, as to the accuracy or completeness of the information contained in or incorporated by reference into this presentation. Nothing contained in or incorporated by reference into this presentation is, or shall be relied upon as, a promise or representation by the Company as to the past or future. The Company assumes no responsibility for the accuracy or completeness of any such information. This presentation also contains estimates and other statistical data made by independent parties and by us relating to market shares and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. The trademarks included herein are the property of the owners thereof and are used for reference purposes only. Such use should not be construed as an endorsement of such products.

# Ocuphire APX3330 KOL Event: Agenda & Speakers

Speakers	Agenda	Time (EDT)
 <p><b>Mina Sooch, MBA</b> President &amp; CEO and Founder </p>	<b>Introductions &amp; Company Overview</b>	11:00 am – 11:10 am
 <p><b>Caroline Bauml, MD</b> </p>	<b>Disease of Diabetic Retinopathy</b>	11:10 am – 11:20 am
 <p><b>Peter Kaiser, MD</b>  Cleveland Clinic Cole Eye Institute</p>	<b>Current DR/DME Treatment Landscape</b>	11:20 am – 11:35 am
 <p><b>David Lally, MD</b> </p>	<b>APX3330, Paradigm-Shifting Oral Treatment Option</b>	11:35 am – 11:50 am
 <p><b>Caroline Bauml, MD</b> </p>	<b>ZETA-1, Phase 2b Trial in Diabetic Retinopathy and Masked Safety Data</b>	11:50 am – 12:00 pm

# Ocuphire APX3330 KOL Event: Agenda & Speakers

Speakers			Agenda	Time (EDT)
 <b>Peter Kaiser, MD</b>  <small>Cleveland Clinic Cole Eye Institute</small>	 <b>Caroline Bauml, MD</b>  <small>Tufts Medical Center</small>	 <b>David Lally, MD</b>  <small>NEW ENGLAND RETINA CONSULTANTS</small>	<b>ZETA-1 Trial Design and Data Expectations</b>	12:00 pm – 12:15 pm
 <b>Mina Sooch, MBA</b> <small>President, CEO, and Founder</small> 	 <b>Mitch Brigell, PhD</b> <small>Head, Clinical Strategy</small> 	 <b>Mark Kelley, PhD</b> <small>APX Program Scientific Advisor</small> 	<b>Q&amp;A Closing Remarks</b>  <small>Q&amp;A Moderator: Corey Davis, PhD</small> 	12:15 pm – 12:30 pm
 <b>Peter Kaiser, MD</b>  <small>Cleveland Clinic Cole Eye Institute</small>	 <b>Caroline Bauml, MD</b>  <small>Tufts Medical Center</small>	 <b>David Lally, MD</b>  <small>NEW ENGLAND RETINA CONSULTANTS</small>		



## Company Overview

**Presenter: Mina Sooch, CEO and Founder of Ocuphire Pharma**



Mina Sooch, MBA  
Harvard University

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



# Ocuphire Pharma

Nasdaq: OCUP

## Upcoming Catalysts in 4Q22:

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

P = Presbyopia  
RM = Reversal of Mydriasis  
NVD = Night Vision Disturbances  
DR/DME = Diabetic Retinopathy/Diabetic Macular Edema



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

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

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

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

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

# Ocuphire Overview

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



## Refractive

Nyxol

Novel  $\alpha 1 / \alpha 2$  Blocker  
505(b)(2)

NDA-Filing Ready

12 Completed Phase 1, Phase 2, and Phase 3 Trials	>650 Subjects Dosed	Exposure in Humans 28 Days	Patent Coverage 2034+
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	Prevalence (US)	Development Milestone
 Reversal of Mydriasis	~100 M	2 Phase 3 Positive Data & Ped P3
 Presbyopia	~128 M	Phase 2 Positive Data Single & Combo
 Night Vision Disturbances	~36 M	1 <sup>st</sup> Phase 3 Positive Data





## Retina

APX3330

Oral REF-1 Inhibitor  
New Chemical Entity

Phase 2b Data 4Q22

11 Completed Phase 1 and Phase 2 Trials	>340 Subjects Dosed	Exposure in Humans 365 Days	Patent Coverage 2034+
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	Prevalence (US)	Development Milestone
 Diabetic Retinopathy	~8 M	Phase 2b Last Patient Last Visit Completed Aug 22
 Diabetic Macular Edema	~2.4 M	



Source: Eisai and Apexian Data; GlobalData Market Research Report, 2020; Company Estimates for US Market Size; Ocuphire internal estimates

# Track Record of Achieving Milestones

Multiple Positive Data Readouts with Multiple Catalysts Ahead

2021 – 1H 2022

2H 2022 – 2023

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

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

Ongoing Partnering Discussions with Leading Ophthalmic Companies (including Europe and Asia)



## Disease of Diabetic Retinopathy

Presented by: **Caroline Baumal, MD**



**Tufts** Medical  
Center

Caroline Baumal, MD  
University of Toronto

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

# Diabetic Eye Disease is Common Cause of Blindness

## Diabetes and Diabetic Retinopathy (DR)

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

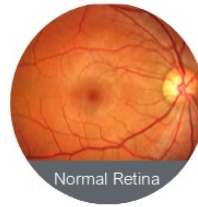


**Type 1 diabetes (T1D):** The body produces very little or no insulin, which means that patients need daily insulin injections to maintain blood glucose levels

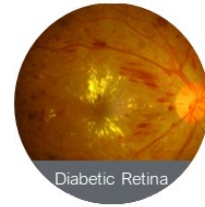


**Type 2 diabetes (T2D):** The most common form of diabetes - either the body does not produce enough insulin, or resists insulin

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



Normal Retina



Diabetic Retina

### Two Types of DR

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

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

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

# Diabetes is a Growing Global Health Epidemic

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

## North America & Caribbean (NAC)

2045	63 million	↑ 24% increase
2030	57 million	
2021	51 million	

## South & Central America (SACA)

2045	49 million	↑ 50% increase
2030	40 million	
2021	32 million	

## Africa (AFR)

2045	55 million	↑ 134% increase
2030	33 million	
2021	24 million	



## World

2045	783 million	↑ 46% increase
2030	643 million	
2021	537 million	

## Europe (EUR)

2045	69 million	↑ 13% increase
2030	67 million	
2021	61 million	

## Western Pacific (WP)

2045	260 million	↑ 27% increase
2030	238 million	
2021	206 million	

## South-East Asia (SEA)

2045	152 million	↑ 68% increase
2030	113 million	
2021	90 million	

## Middle East & North Africa (MENA)

2045	136 million	↑ 87% increase
2030	95 million	
2021	73 million	

# Diabetic Patients Usually Present with Complex Co-Morbidities

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

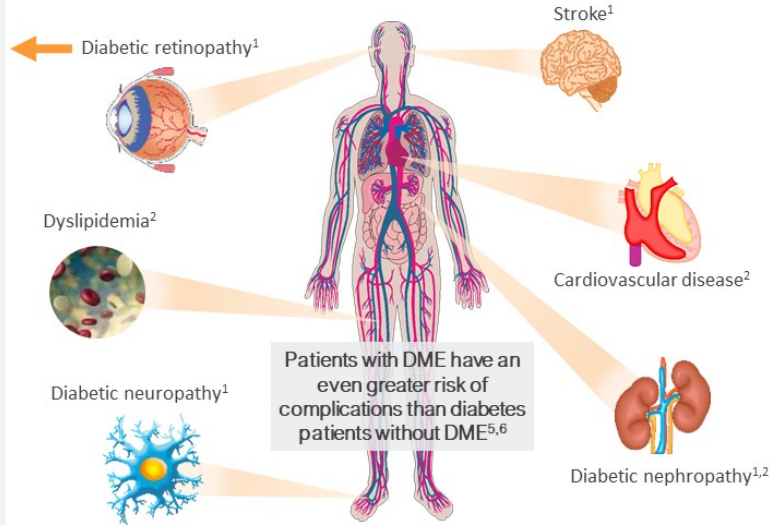
DR is the most common cause of vision loss or blindness in working-age adults, usually affecting both eyes



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



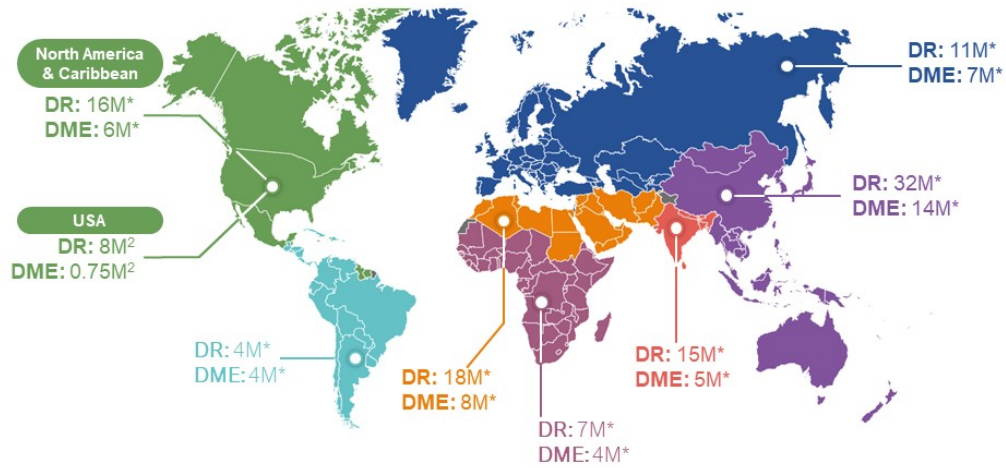
Treating DR leads to control of DME



Oral options have the potential to reach other vascular beds to treat kidney and neuropathic co-morbidities

# Global Prevalence of Diabetes-Associated Retinal Disease

DR Affects 1 in 3 People with Diabetes; DME Affects 1 in 13 People with Diabetes<sup>1</sup>

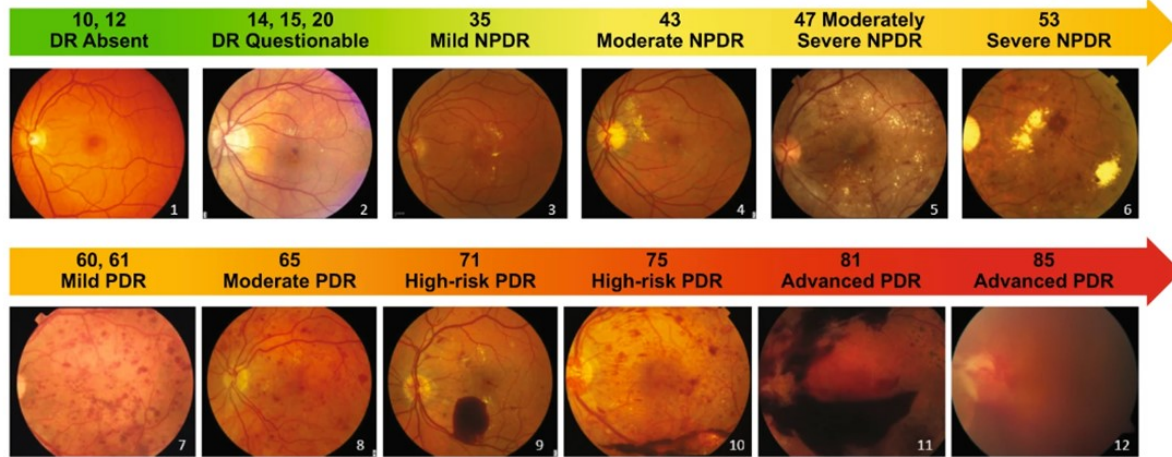




# Measuring the Severity of Diabetic Retinopathy

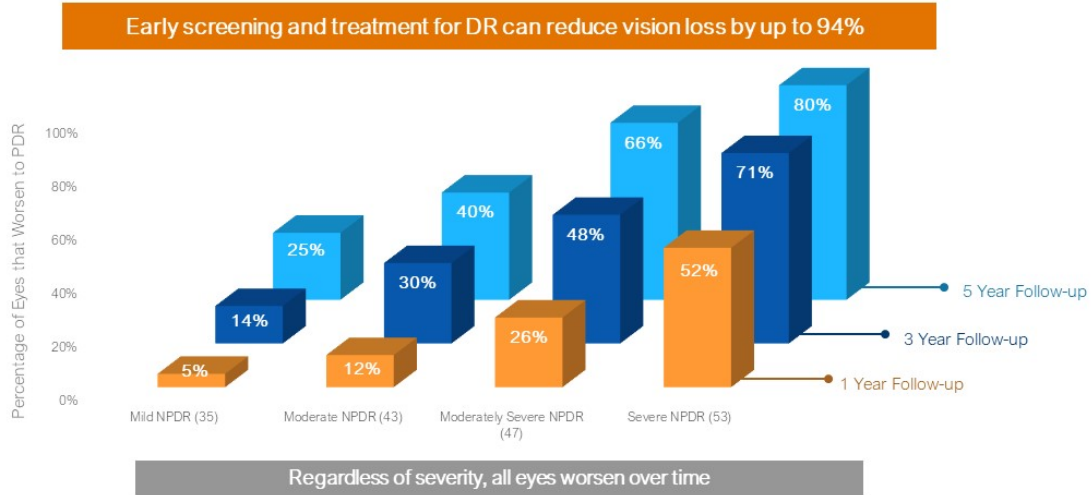
DRSS is Regularly Used For FDA Approvals; Not As Widely Used in Everyday Practice

Diabetic Retinopathy Severity Scale (DRSS) was developed to differentiate proliferative DR (PDR) from non-proliferative DR (NPDR)



# DRSS Predicts Vision-Threatening Complications (PDR/DME)

Percent of Eyes Progress to PDR at 1-Year, 3-Year, and 5-Year Visits by Baseline DR Severity

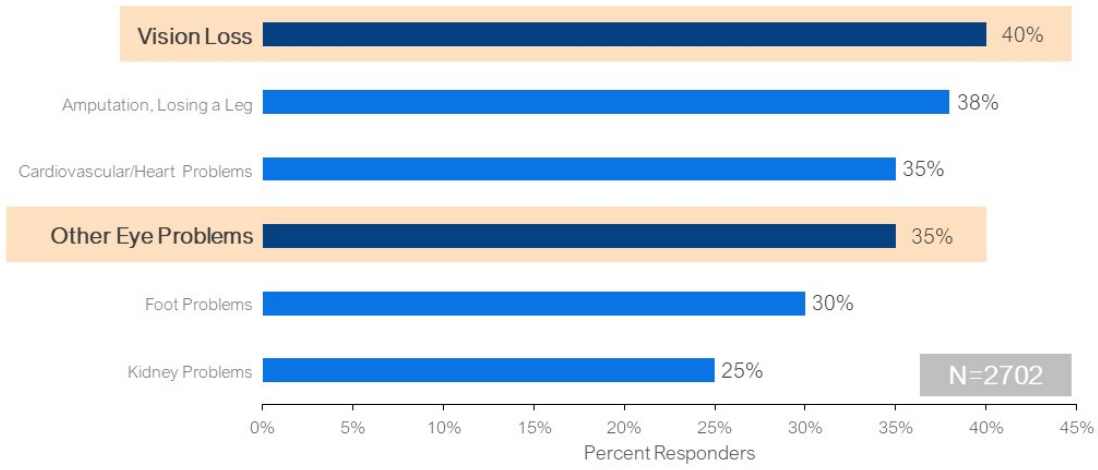


1. Early treatment diabetic retinopathy study research group. *ophthalmology*. 1991;98(5 suppl):823-33.
2. Diabetes control and complications trial research group. *N Engl J Med*. 1993;329(14):977-86.
3. Fathy C, Patel S, Sternberg P Jr, Kohanim S. Disparities in adherence to screening guidelines for diabetic retinopathy in the United States: a comprehensive review and guide for future directions. *Semin Ophthalmol*. 2016;31(4):364-377. doi: 10.3109/08820538.2016.1154170

# Vision Loss is #1 Concern of Diabetic Patients

Diabetic Retinopathy is a Progressive Vision-Threatening Disease

## What are the top concerns for diabetic patients?



# Early Management of Diabetic Retinopathy

*Poor Adherence to Medical Management and Lifestyle Options Worsen DR*

Medical and lifestyle management is first line of treatment

Control of Blood Sugar



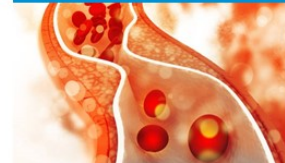
Control of Blood Pressure



Smoking Cessation



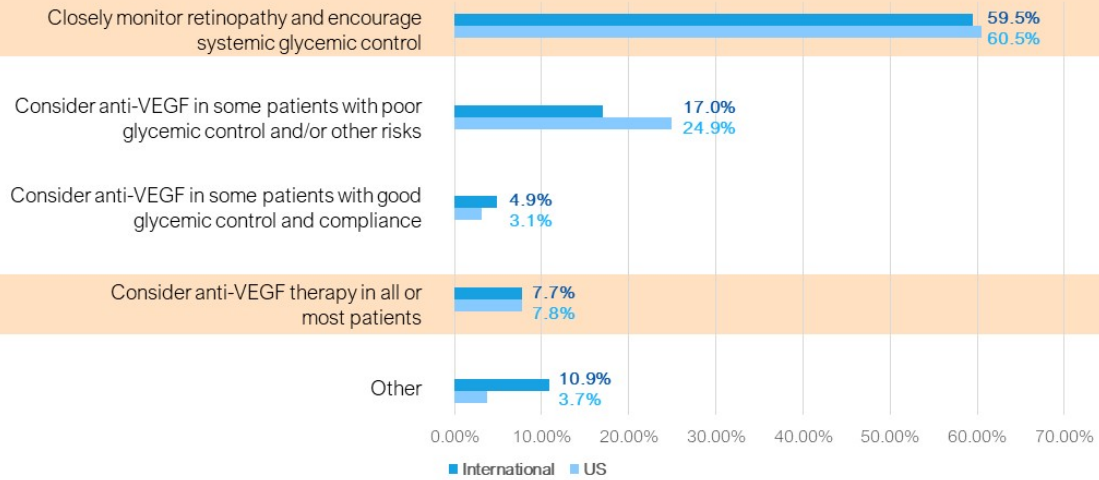
Control of Lipids



# Majority of Physicians Use a “Wait and Monitor” Approach for DR Patients

Over 90% of DR Patients Are Not Treated Proactively and Anti-VEGF Use is Limited

## How do physicians treat patients with severe NPDR without DME?



# Diabetic Retinopathy At a Glance

Current Treatment Landscape Demonstrates Need for Less Invasive Therapies



There are ~8M adults in the U.S. with DR<sup>1</sup>

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



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



If untreated, DR can **rob people of their vision** prematurely<sup>2,3</sup>

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

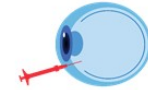


**56%** of patients reported anxiety related to anti-VEGF treatment

**\$13B**  
(2020)

Global **Intravitreal Injection** Revenues in AMD, DME and BRVO<sup>4</sup>

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



Sources:

1. American Diabetes Association; International Diabetes Federation; Healthline; \*Ocuphire internal analysis and assumptions;

2. Das UN. DME, retinopathy and age-related macular degeneration as inflammatory conditions. Arch Med Sci. 2016;12(5):1142-1157. doi:10.5114/aoms.2016.61918

3. Patient survey adapted from Lions International Foundation and International Diabetes Foundation-Europe; Meltzer 2000

4. Guidehouse Triangulation of Global Data, Market Scope and Investor Forecasts (2020) AMD = Age-Related Macular Degeneration; DME = Diabetic Macular Edema ; BRVO = Branch Retinal Vein Occlusion

## Current DR/DME Treatment Landscape

Presented by: Peter Kaiser, MD

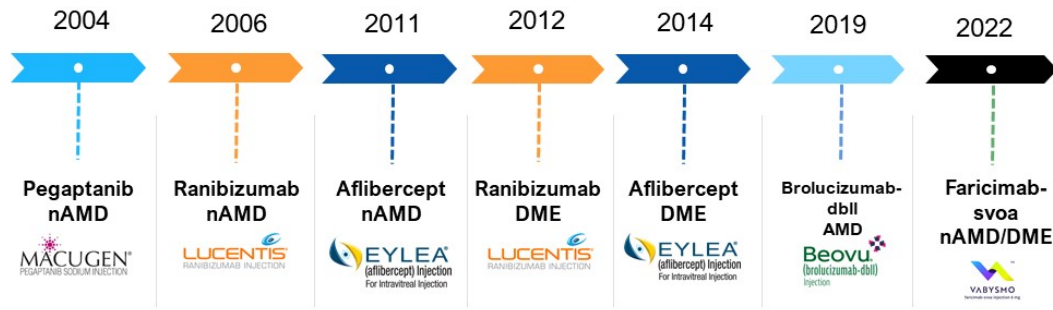


Peter Kaiser, MD  
Harvard Medical School

- 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.

# IVT Anti-VEGF Therapies are Standard of Care for AMD/DME

Anti-VEGF Therapies Over the Decades; Limited Use in DR Patients



MOA focused on VEGF and local delivery have demonstrated efficacy for approved treatments, are the current standard of care, and have been highly effective for wAMD/DME. However, these therapies have limited use in DR

**EYLEA<sup>®</sup>**  
(aflibercept) Injection  
For Intravitreal Injection

**LUCENTIS**  
RANIBIZUMAB INJECTION

**\$9b+**  
2021 Revenue

**\$2b+**  
2021 Revenue



# Panorama Study Further Emphasizes Need for Proactive Treatment of NPDR

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

**Population:** Adults with severe NPDR w/o DME

- 225 Male; 177 Female
- Mean Age: 56 years (10.5)

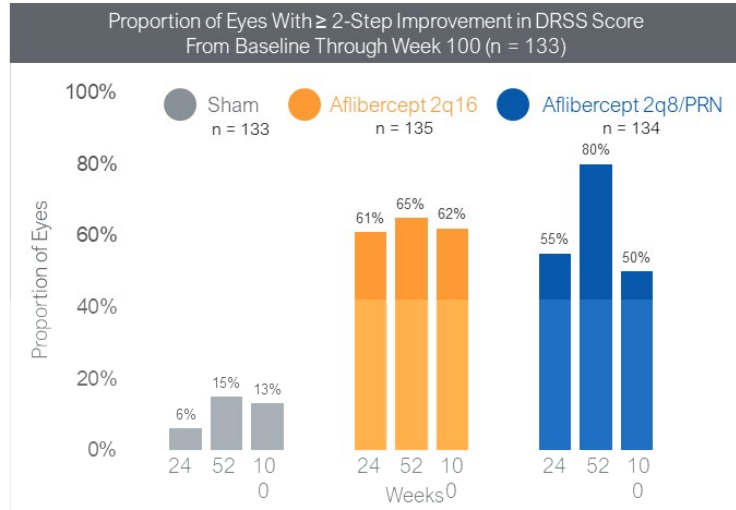
**Setting:** Global, Multi-Center Study

**Intervention:** 402 Eyes randomized to 3 arms (1 eye per participant)

- IVT Aflibercept 2q16
  - 2 mg monthly x 3 doses then every 8 weeks x 1 dose, followed by every 16 weeks through week 100
- IVT Aflibercept 2q8 as needed
  - 2 mg monthly x 5 doses then every 8 weeks through week 52 then as needed through week 100
- IVT Sham
  - Observation with sham IV injections

**Primary Endpoint:**

- Proportion of participants with  $\geq 2$  step improvement in the DRSS scale at 24 and 52 weeks



Brown DM, Wyckoff CC, Boyer D, Heier JS, Clark WL, Emanuele A, Higgins PM, Singer M, Weinreich DM, Yancopoulos GD, Berliner AJ, Chu K, Reed K, Cheng Y, Vitti R. Evaluation of Intravitreal Aflibercept for the Treatment of Severe Nonproliferative Diabetic Retinopathy: Results From the PANORAMA Randomized Clinical Trial. JAMA Ophthalmol. 2021 Sep 1;139(9):946-955. doi: 10.1001/jamaophthol.2021.2809. PMID: 34351414; PMCID: PMC8343518.

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

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

Management Recommendations for Patients with Diabetes

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

An oral option for DR strengthens treatment options across all stages

Physicians have limited non-invasive treatment options

# Current Conventional Treatment is Challenging for Patients

Access and Time Burden are Further Barriers for DR Patient Compliance

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

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

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



### Office Visit Time Commitments

Mean: 90 min

Range: 13 - 261 min

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

# Multiple Targets in DME/DR Treatment Landscape

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

## Available Commercialized Therapies:

### Anti-VEGF IVT:

Aflibercept (Eylea®)  
Ranibizumab (Lucentis®)  
Bevacizumab (Avastin®)

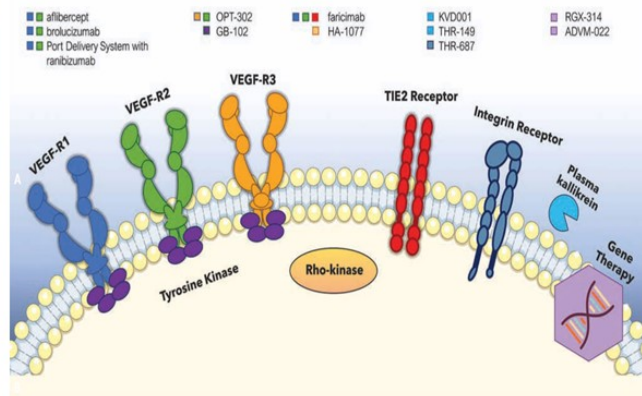
### IVT Steroids:

Dexamethasone (Ozurdex®)

## Emerging therapies that could shape industry:







Longer Duration IVTs  
Extended Release  
Combination Therapies

Oral Therapies  
Topical  
Gene Therapies



# Intravitreal Injections Landscape (DR patients)



Eylea/Lucentis Approved, But Not Used in Patients with Mild NPDR and Mild PDR

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

\*Trials to Support Approval  
<sup>1</sup>Panorama Clinical Trial  
<sup>2</sup>Protocol I & T and Rise & Ride

# Topical Eyedrops in Clinical Development for DR/DME


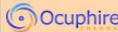








Inflammation MOAs in Phase 2 with Novel Eyedrops

Company	Drug	Target/MOA	Indication	Route of Administration	Phase 1	Phase 2	Phase 3	Commercial
 Oculis	OCS-01	Steroid	DME	Eyedrop	✓	✓		
 OCUTERRA THERAPEUTICS	OTT 166	Integrin inhibitor	DR	Eyedrop	✓	○		

✓ Completed   ○ Ongoing   X Discontinued or Failed study

# Oral Treatments in Clinical Development (DR)

Most Drugs Target Only Inflammation

Company	Drug	Target/MOA	Indication	Route of Administration	Phase 1	Phase 2	Phase 3
 Lilly	LY333531	Protein Kinase C inhibitor	DR	Oral	✓	✓	X 2006
 Ocuphire	APX3330	Ref-1 inhibitor (Anti-VEGF and Anti-inflammatory)	DR	Oral	✓	○	
 Bayer	BAY1101042	Guanylate Cyclase activator	DR	Oral	✓	○	
 ALKAHEST	AKST4290	CCR3 Eotaxin inhibitor	DR	Oral	✓	○	
 Roche	RG7774	CB2 receptor (cannabinoid)	DR	Oral	✓	○	
 Boehringer Ingelheim	BI 1467335	AOC3	DR	Oral	✓	X 2021	
 InflamX	HCB 1019 (Xiflam)	Connexin 43 (inflammasome)	DR	Oral	✓	○	
Valo	OPL-0401	ROCK 1/2 inhibitor	DR	Oral	✓	○	
 REZOLUTE	RZ402	Plasma Kallikrein	DME	Oral	✓		
 NOVARTIS	GT005	Increasing production of CFI protein (anti-inflammatory)	GA	Oral	✓	○	
 THE CURACLE	CU06-RE	Endothelial dysfunction blocker	wAMD	Oral	✓		

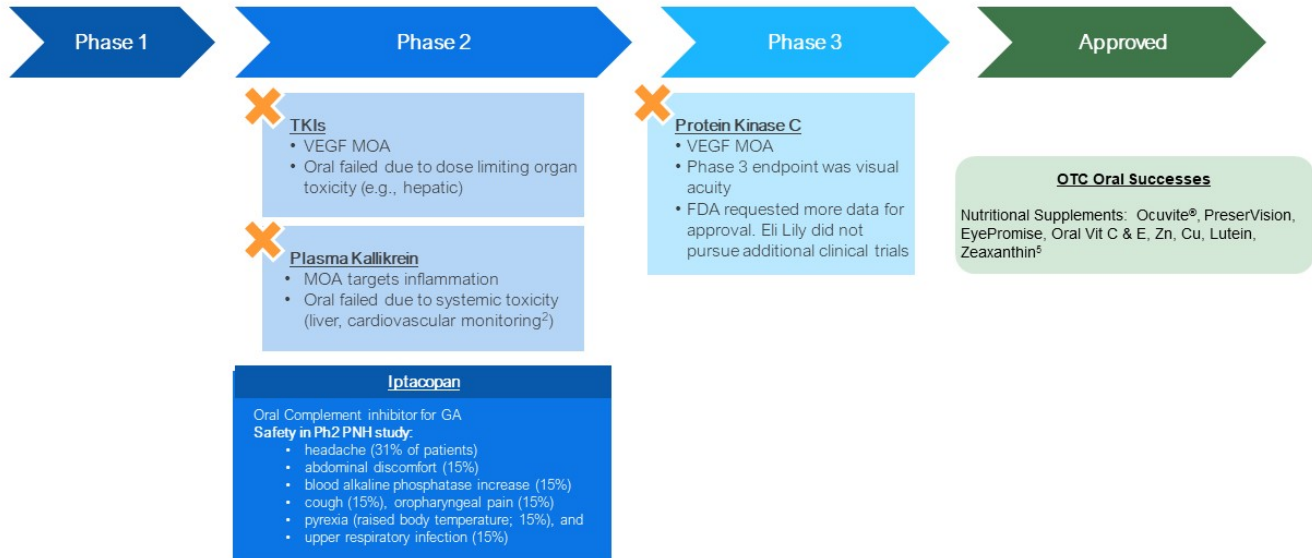


Company websites: [www.clinicaltrials.gov](http://www.clinicaltrials.gov)  
Most Drugs Target Only Inflammation

✓ Completed ○ Ongoing X Discontinued or Failed study

# APX3330 is Different Than Past Oral Failures in Retina

APX3330 Targets Dual, Validated Retinal Disease Pathways with Favorable Human Safety Data





## Opportunities for New Therapies in Retina

*Unmet Needs in Retina Especially in NPDR*

### New MOAs/therapies are needed to:

- Provide non-invasive options for early disease management
- Decrease in Diabetic Retinopathy Severity Score (DRSS)
- Decrease in macular edema
- Reduce vision threatening complications (VTC)
- Improve in macular ischemia
- Improve compliance by longer acting drugs
- Manage inflammation
- Address non-responders

### APX3330 offers:

- A novel, dual MOA
- A novel and non-invasive route, where oral medication allows for early intervention

## APX3330: Paradigm Shift Oral Treatment Option

Presented by: David Lally, MD

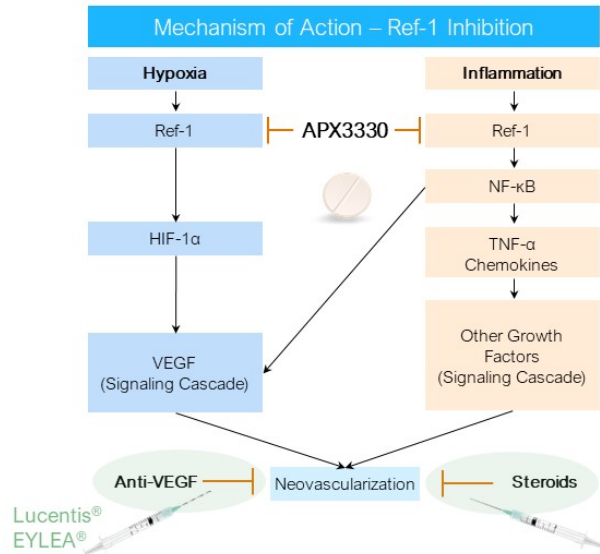


David Lally, MD  
Jefferson Medical College

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

# APX3330 – Novel and Dual-Acting MOA in an Oral Pill

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

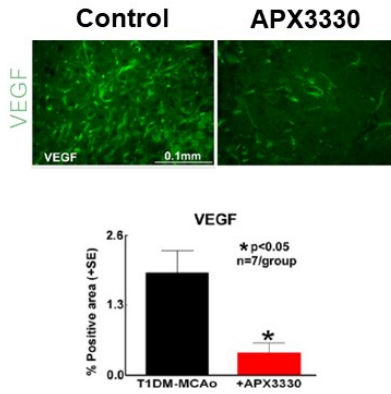


- Ref-1 (reduction-oxidation effector factor-1) is a novel target discovered by Dr. Mark R. Kelley at Indiana University School of Medicine
- APX3330 is a small molecule oral drug candidate and a first-in-class inhibitor of Ref-1
- APX3330 previously developed by Eisai for multiple hepatic inflammatory 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

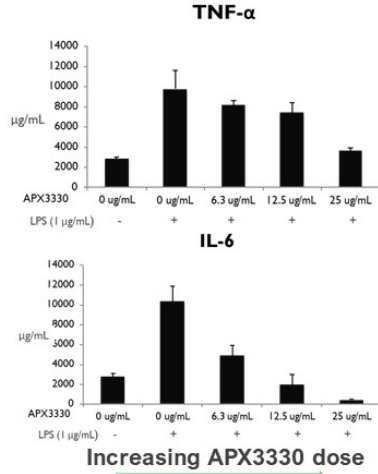
# In Vitro Validation of APX3330 Mechanism of Action

APX3330 Reduces VEGF levels and Inflammatory Cytokines; Provides Neuronal Protection

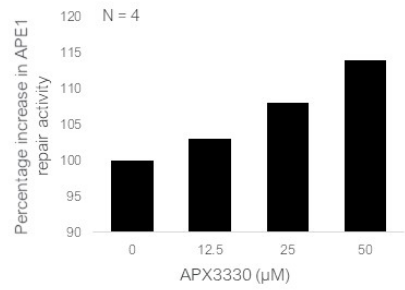
APX3330 reduces VEGF protein expression in preclinical stroke model



APX3330 reduces pro-inflammatory cytokines in LPS stimulated macrophages



APX3330 increases DNA oxidative repair and neuronal protection

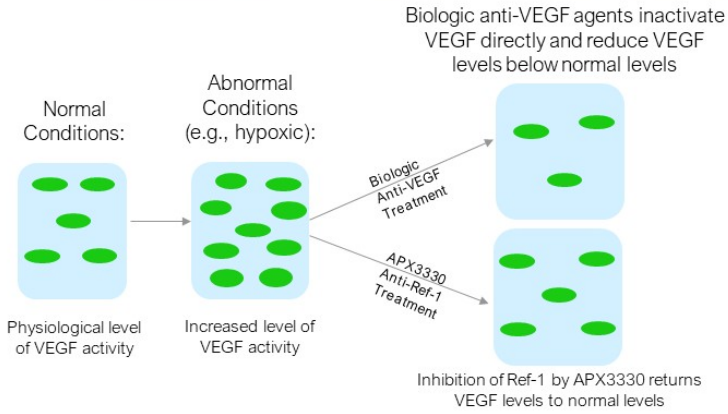


APX3330 enhances Ref-1 endonuclease activity in dorsal root ganglion neurons

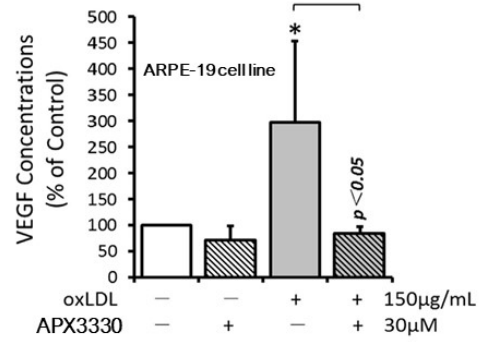
Tao Yan et al. APX3330 Promotes Neurorestorative effects after stroke in type one diabetic rats. Aging and Disease, Vol 9, Oct 2018  
 Apurinic/Apyrimidinic endonuclease 1 regulates inflammatory response in macrophages. Jedinak A, Dudhgaonkar S, Kelley MR, Silva D. Anticancer Res, 2011 Feb;31(2):379-85, PMID: 21378315  
 Fehrenbacher, J. C., Guo, C., Kelley, M. R., & Vasko, M. R. DNA damage mediates changes in neuronal sensitivity induced by the inflammatory mediators, MCP-1 and LPS, and can be reversed by enhancing the DNA repair function of APE1. Neuroscience 366, 23-35, doi:10.1016/j.neuroscience.2017.09.039 (2017).

# APX3330 VEGF Effects in Normal Cells

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



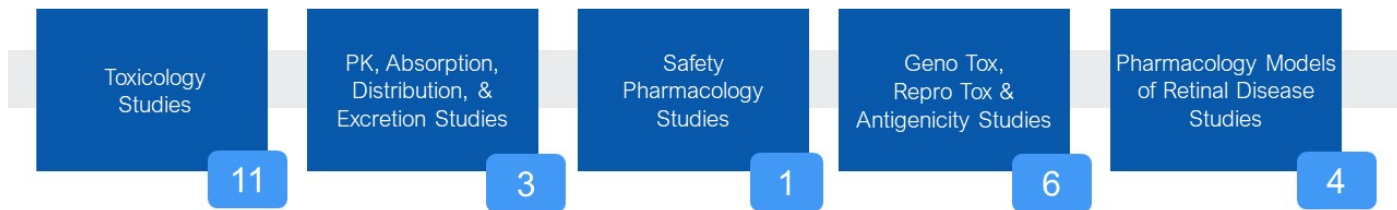
APX3330 prevents VEGF overproduction in ARPE-19 cells



- VEGF is a growth factor that is necessary for normal function of multiple cell types including vascular endothelium and neurons → By returning VEGF levels to normal, APX3330 can reduce neovascularization, vascular leakage and the inflammatory response without adverse systemic effects
- The safety profile of APX3330 to date 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

Completed Over 20 Clinical Trials Across Healthy, Hepatic and Cancer Patients



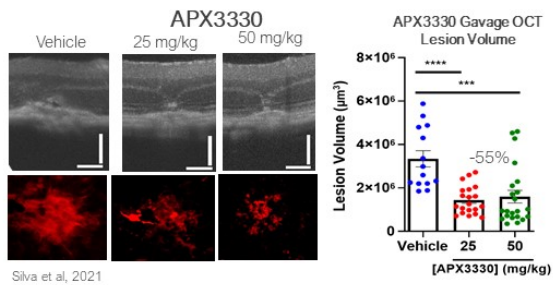
Extensively Studied in Over 20 In-Vitro and Animal Studies with Favorable Efficacy and Safety

# Preclinical Data: Oral APX3330 Blocks Neovascularization

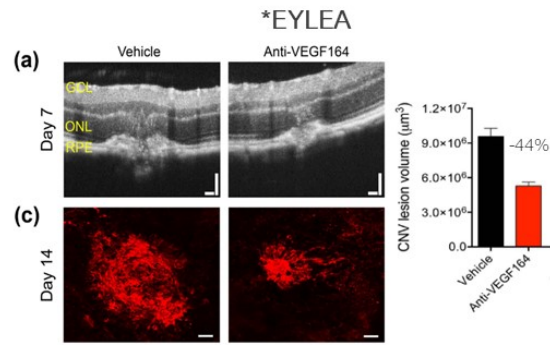
Lesion Volume Decrease with Oral APX3330 in Murine Laser CNV Model Similar to EYLEA® Data

## L-CNV Mouse Retina Model

Lesion Size and Corresponding Fluorescent Stains in L-CNV Models Treated with APX3330 at 25 mg/kg oral gavage



## L-CNV Mouse Retina Model



- ✓ Efficacy was also seen after single intravitreal injection of 20 μM APX3330 in mouse L-CNV model\*\*
- ✓ Efficacy was also seen after dosing intraperitoneal injection of 50 mg/kg twice daily, 5 days on/2 days off, for 2 weeks in mouse L-CNV model\*\*\*
- ✓ Efficacy was also seen after single intravitreal injection of 20 μM APX3330 in Vldlr<sup>-/-</sup> mice model\*\*\*\*

# Summary of APX3330 Prior Clinical Trials

Completed 11 Clinical Trials Across Healthy, Hepatic and Cancer Patients

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

## Phase 1 Studies

5

Phase 1		
Study ID	Patient Population	Treatment Groups
APX_CLN_0001	Healthy Subjects	APX3330, Placebo
APX_CLN_0002	Healthy Subjects	APX3330, Placebo
APX_CLN_0003	Healthy Subjects	APX3330
APX_CLN_0004	Healthy Subjects	APX3330
APX_CLN_0008	Healthy Subjects	APX3330, Placebo

## Phase 2 Studies

6

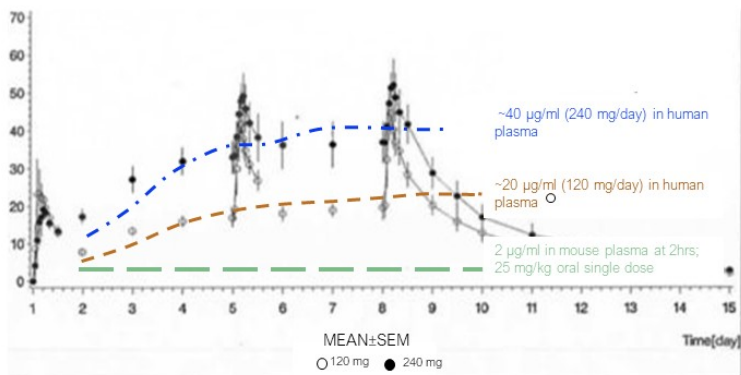
Phase 2		
Study ID	Patient Population	Treatment Groups
APX_CLN_0005	Chronic Hep B	APX3330
APX_CLN_0006	Chronic Hep C	APX3330
APX_CLN_0007	Chronic Hep C	APX3330, Placebo
APX_CLN_0009	Acute severe hepatitis	APX3330
APX_CLN_0010	Alcoholic hepatitis	APX3330
APX_CLN_0011	Cancer (solid tumors)	APX3330



# Phase 1 Clinical Trials: PK Data Supporting the ZETA-1 Trial

APX3330 has Oral Bioavailability and a Sustained PK Profile

Plasma concentration of APX3330<sup>2</sup>



## Favorable Oral Bioavailability

### Sustained Pharmacokinetic Profile

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

### Sufficient APX3330 Exposure

- Plasma levels observed after 120 and 240 mg/day dosing is multiple times higher than what was required for efficacy in preclinical studies → planned clinical dose is 600 mg/day

## Safety Summary From Phase 1 and Phase 2 Trials

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

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

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

% = 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)

	APX3330	Placebo
Diarrhea/Soft Stool (mild)	14/346 (4%)	2/95 (2%)
Rash/Pruritis (mild)	14/346 (4%)	1/95 (1%)

*This includes over 2078 subject-days of exposure at doses  $\geq 600$ mg and over 17,961 subject-days of exposure at doses <600mg.*

## ZETA-1 Phase 2b Trial in Diabetic Retinopathy

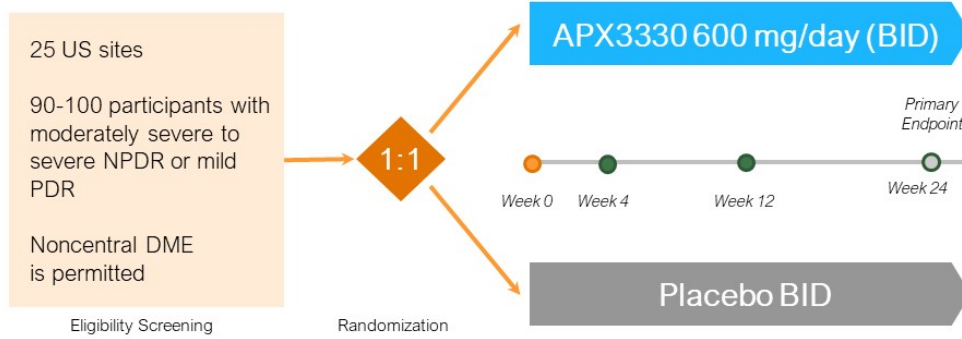
Presented by: David Lally, MD



David Lally, MD  
Jefferson Medical College

# ZETA-1 Phase 2b Design for DR/DME

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



## Endpoints

**Primary:** % of subjects with a  $\geq 2$  step improvement on the DRSS (Diabetic Retinopathy Severity Scale) score at week 24

### Secondary:

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

### Exploratory:

- Labs / PK

Enrollment of 103 DR Patients Completed (Apr 2021 to Mar 2022)

Top Line Data Expected in Q4 2022



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)  
ZETA-1 Clinical Trial is Sponsored by Ocuphire Pharma <https://clinicaltrials.gov/ct2/show/NCT04692688?term=ZETA-1&draw=2&rank=1>

# Key Eligibility Criteria in ZETA-1

Oral Medication Provides Binocular Treatment; DME Allowed in Fellow Eye

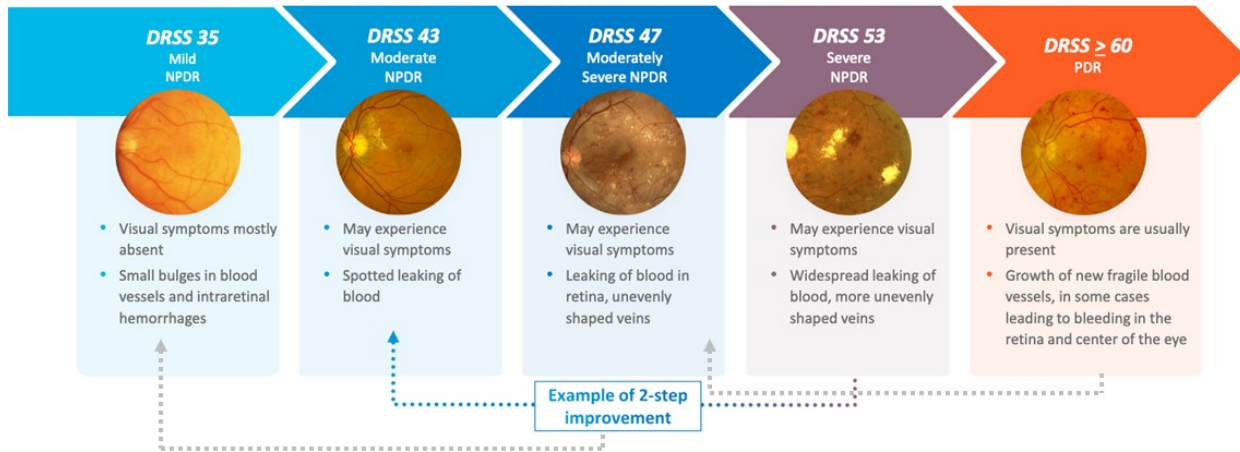
Inclusion	Exclusion
<ul style="list-style-type: none"><li>• Males or non-pregnant females <math>\geq 18</math> years of age</li><li>• At least one eye with DR graded at least moderately severe to severe NPDR or mild PDR (corresponding to DRSS 47, 53, or 61, confirmed by a central reading center) in which PRP and intravitreal injections of an anti-VEGF agent can be safely deferred for <math>\geq 6</math> months in the opinion of the Investigator</li><li>• BCVA assessed by ETDRS protocol letters score of <math>\geq 60</math> letters (Snellen equivalent 20/63 or better) in the study eye</li><li>• Body mass index (BMI) between 18 and 40 kg/m<sup>2</sup>, inclusive</li></ul>	<ul style="list-style-type: none"><li>• Retinopathy from causes other than diabetes in study eye</li><li>• Presence of center involved diabetic macular edema (DME) defined as a central subfield thickness (CST) <math>\geq 320</math> <math>\mu\text{m}</math> on SD-OCT or the presence of intra- or subretinal fluid within the central subfield<ul style="list-style-type: none"><li>– Center involved DME in the fellow eye is allowed</li></ul></li><li>• 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</li><li>• Intraocular steroids including triamcinolone and dexamethasone implant within the last 6 months</li><li>• Fluocinolone implant within the last 3 years</li><li>• HbA1c <math>\geq 12.0\%</math></li><li>• Clinically significant systemic disease (e.g., uncontrolled diabetes, myasthenia gravis, cancer, hepatic, renal, endocrine, or cardiovascular disorders) that might interfere as deemed by Investigator</li></ul>

# Why DRSS is an Important Endpoint?

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

## Diabetic Retinopathy Severity Scale (DRSS)

▶ INCREASING RISK OF DEVELOPING VISION THREATENING COMPLICATIONS ▶



## ZETA-1 Trial: Demographics and Masked Safety Data

Presented by: Caroline Bauml, MD



**Tufts** Medical Center

Caroline Bauml, MD  
University of Toronto

# Baseline Characteristics for ZETA-1 Trial

Typical Demographics for Diabetic Population

Parameter		Total N = 103
<b>Age (years):</b>	mean (range)	56 (24-81)
<b>Sex: n (%)</b>	Male	50 (49%)
	Female	53 (51%)
<b>Race: n (%)</b>	American Indian or Alaskan Native	4 (4%)
	Asian	4 (4%)
	Black or African American	11 (11%)
	White	81 (79%)
	Other	3 (3%)
<b>BMI (kg/m<sup>2</sup>):</b>	mean (range)	31 (21-40)
<b>Systolic BP (mmHg):</b>	mean (range)	138 (100-180)
<b>Diastolic BP (mmHg):</b>	mean (range)	80 (53-109)
<b>Heart rate (BPM):</b>	mean (range)	77 (51-96)
<b>Hemoglobin A1c:</b>		8.1 (5.3-12.3)



## Baseline Characteristics for ZETA-1 Trial (Continued)

DRSS Scores in Diabetic Study Population

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

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

## Baseline Characteristics for ZETA-1 Trial (Continued)

Key Visual Metrics in Diabetic Study Population

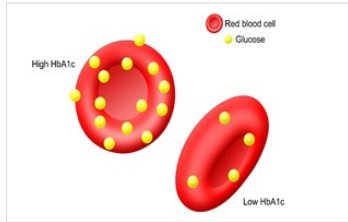
Parameter		Total N = 103	
<b>Study Eye Screening CST (um):</b>	mean (range)	270 (203-319)	
<b>Fellow Eye Screening CST (um)*:</b>	mean (range)	289 (211-491)	
<b>Study Eye BCVA:</b>	mean (range)	Letters Read: 80 (60-93)	Snellen Equivalent: 20/25 (20/63-20/15)
<b>Fellow Eye BCVA:</b>	mean (range)	Letters Read: 77 (0-91)	Snellen Equivalent: 20/32 (20/1000-20/15)
<b>IOP Study Eye and Fellow Eye (mmHg):</b>	mean (range)	15 (8-22)	
<b>Diabetic Status (Years):</b>	mean (range)	16 (0-58)	
<b>Study Eye with anti-VEGF injections within 6 months prior to Screening</b>		None	
<b>Fellow Eye with anti-VEGF injections within 6 months prior to Screening</b>		15	



Source: ZETA-1 Demographics and Baseline Characteristics  
\* N=102 due to a fellow eye not being graded.

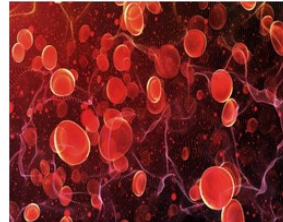
# Comprehensive Laboratory Panels Collected in ZETA-1

Blood, Kidney, and Inflammatory Markers Evaluated



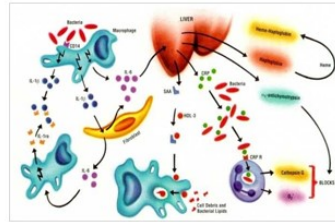
## Chemistry

Albumin  
 Alanine aminotransferase (ALT)  
 Alkaline Phosphatase  
 Aspartate aminotransferase (AST)  
 Blood Urea Nitrogen (BUN)  
 Creatinine  
 Glucose (Random)  
 Sodium  
**Total bilirubin**  
**Total protein**



## Test Panel Components Hematology (CBC without Differential)

WBC  
 RBC  
 HGB (Hemoglobin)  
 HCT (Hematocrit)  
 Platelet Count  
 Calcium  
 Carbon Dioxide (Bicarbonate)  
 Chloride



## Cytokine Panel (Biomarker)

Interleukin-1  $\beta$  (IL-1 $\beta$ )  
 Interleukin-6 (IL-6)  
 Interleukin-8 (IL-8)  
 Tumor Necrosis Factor  $\alpha$  (TNF- $\alpha$ )

## PK and Biomarkers

REF-1 ELISA 1  
 Pharmacokinetics

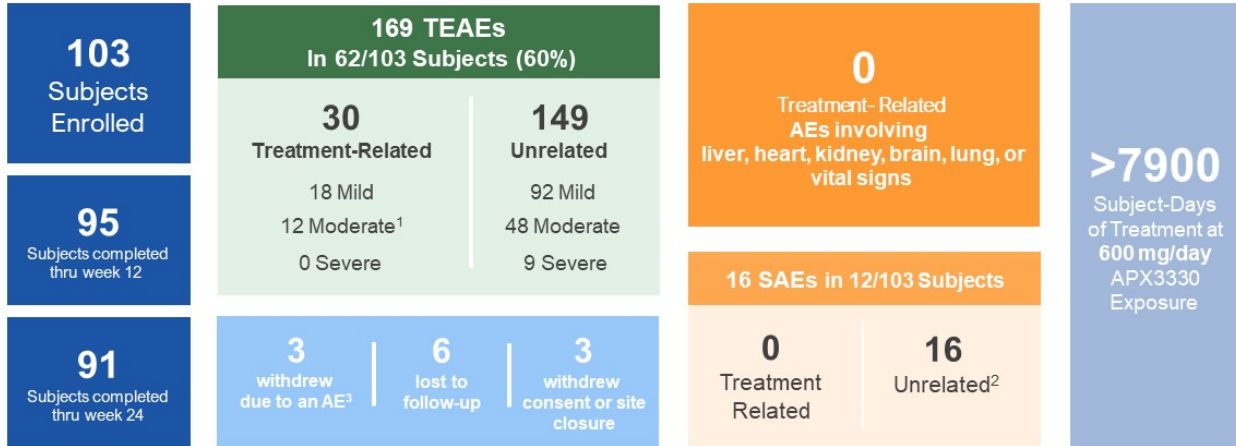


## Kidney Function

eGFR  
 Creatinine

# Masked Safety Findings from Ongoing ZETA-1 Trial

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



**Oral APX3330 safety profile consistent with that seen in prior trials**

1. 12 events in 8 subjects: diarrhea, worsening DME (OD and OS), pruritis, urticaria, blurry vision, decrease in hemoglobin level, ischemic diabetic maculopathy and central vision scotoma (in same subject), photophobia (OD and OS) and hypoaesthesia (in same subject)  
 2. Cellulitis (2 events in same subject), dyskinesia, transient ischemic event, COVID-19 and acute respiratory failure (same subject), progression of multivessel coronary artery disease, cholelithiasis, osteomyelitis, vertigo, chest pain, infection of toe and ulcer of toe and embolism (3 events in same subject), multi-system organ failure, worsening bradycardia  
 3. DME, Dyspnea, Pre-Syncope  
 Note: ZETA-1 Interim Data as of database 9/15/22 with monitoring to be completed before final database lock; assumes 50% subjects on APX3330

# APX3330 Product Candidate Profile for Multiple Retinal Indications

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



APX3330: Well-tolerated Oral Dose up to 600 mg/day | Twice Daily Dosing

## Expected Efficacy Data

Novel MOA for treating retina

- ↓ Inflammation
- ↓ Abnormal Angiogenesis

Convenient Oral Dosing for Patient Compliance

Allow Daily vs. Episodic Exposure  
Oral pill may reduce the burden of frequent anti-VEGF injections



## Favorable Safety Profile

~10,000 Subject-exposure days\* at  $\geq 600$  mg/day dose

Few Systemic Adverse Effects

- ~ 5% Mild Diarrhea
- ~ 5% Mild Skin Rash (reversible)

No Treatment-Related Organ Toxicity  
(Liver, Cardiovascular {BP, HR}, Kidney, Neurologic, Pulmonary)

No Ocular Effects

- No observed ocular AEs



## ZETA-1 Trial Design and Data Expectations



# APX3330 has the Potential to be First Line of Therapy for DR Patients

## Efficacy Signal

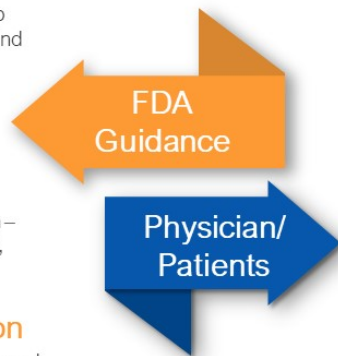
Percent of patients on APX3330 with a  $\geq 2$  step improvement on the DRSS score at week 24 (and 52) compared to placebo in 2 well-controlled, multi-center clinical trials

## Safety

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

## Non-Invasive Treatment Option

FDA does not require comparative arm of approved anti-VEGF injections such as Eylea for DR



## Efficacy Signal

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

## Safety

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

## Non-Invasive Treatment Option

- Eylea<sup>®</sup>, although approved, is currently not used as standard of care because of the treatment burden for asymptomatic DR patients
- Ability to be prescribed by all eye care doctors
- Oral option increases global access, especially in underserved regions

## APX3330 is Positioned to Fulfill a Significant Unmet Need in Diabetic Eye Disease



Favorable PK and safety data from clinical trials and overall masked safety data supports a potential oral treatment for diabetics with DR/DME



Dual mechanism of action may benefit inflammation from co-morbidities



DR/DME treatments are large attractive market opportunity



Oral therapeutic decreases burden of treatment (invasive intravitreal injections, time devoted to treatment, etc.) which may strengthen adherence and overall favorable outcomes



Oral therapeutic can be prescribed as early treatment option for diabetic patients who may otherwise fall under the "wait and see" treatment approach

Well-controlled, multi-center Phase 2b ZETA-1 for APX3330 topline results expected in 4Q22



