Ocuphire PHARMA

Restore Vision & Clarity

Ocuphire KOL Event: APX3330

October 14, 2022

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Ocuphire APX3330 KOL Event: Agenda & Speakers

Speakers	Agenda	Time (EDT)
 Mina Sooch, MBA *President & CEO and Founder* Ocuphire Pharma	Introductions & Company Overview	11:00 am – 11:10 am
 Caroline Baumal, MD Tufts Medical Center	Disease of Diabetic Retinopathy	11:10 am – 11:20 am
 Peter Kaiser, MD Cleveland Clinic Cole Eye Institute	Current DR/DME Treatment Landscape	11:20 am – 11:35 am
 David Lally, MD New England Retina Consultants	APX3330, Paradigm-Shifting Oral Treatment Option	11:35 am – 11:50 am
 Caroline Baumal, MD Tufts Medical Center	ZETA-1, Phase 2b Trial in Diabetic Retinopathy and Masked Safety Data	11:50 am – 12:00 pm

Ocuphire APX3330 KOL Event: Agenda & Speakers

Speakers	Agenda	Time (EDT)
 Peter Kaiser, MD — Cleveland Clinic Cole Eye Institute  Caroline Baumal, MD — Tufts Medical Center  David Lally, MD — New England Retina Consultants	ZETA-1 Trial Design and Data Expectations	12:00 pm – 12:15 pm
 Mina Sooch, MBA, *President, CEO, and Founder* — Ocuphire  Mitch Brigell, PhD, *Head, Clinical Strategy* — Ocuphire  Mark Kelley, PhD, *APX Program Scientific Advisor* — Ocuphire  Peter Kaiser, MD — Cleveland Clinic Cole Eye Institute  Caroline Baumal, MD — Tufts Medical Center  David Lally, MD — New England Retina Consultants	Q&A Closing Remarks *Q&A Moderator: Corey Davis, PhD* — LifeSci	12:15 pm – 12:30 pm

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

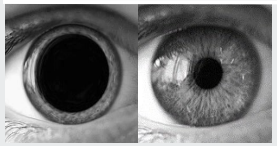
Ocuphire Overview

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

Refractive

Nyxol — *Novel α1/ α2 Blocker 505(b)(2)* — *NDA-Filing Ready*

12	>650	Exposure in Humans 28	Patent Coverage 2034+
Completed Phase 1, Phase 2, and Phase 3 Trials	Subjects Dosed	Days	

		Prevalence (US)	Development Milestone
	Reversal of Mydriasis	~100 M	2 Phase 3 Positive Data & Ped P3
	Presbyopia	~128 M	Phase 2 Positive Data Single & Combo
	Night Vision Disturbances	~36 M	1st Phase 3 Positive Data

Retina

APX3330 — *Oral REF-1 Inhibitor New Chemical Entity* — *Phase 2b Data 4Q22*

11	>340	Exposure in Humans 365	Patent Coverage 2034+
Completed Phase 1 and Phase 2 Trials	Subjects Dosed	Days	

		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

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

2H 2022 – 2023

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

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

Disease of Diabetic Retinopathy

Presented by: Caroline Baumal, MD

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

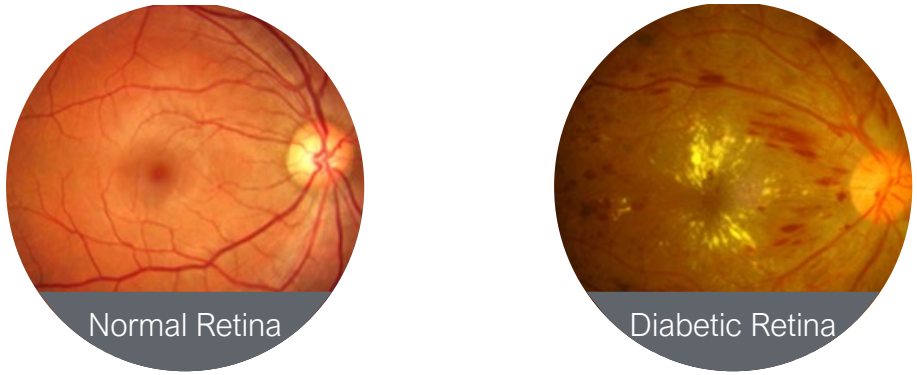
Diabetes and Diabetic Retinopathy (DR)

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



Two Types of DR

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

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

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

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

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
2030	57 million
2021	51 million

24% increase

South & Central America (SACA)

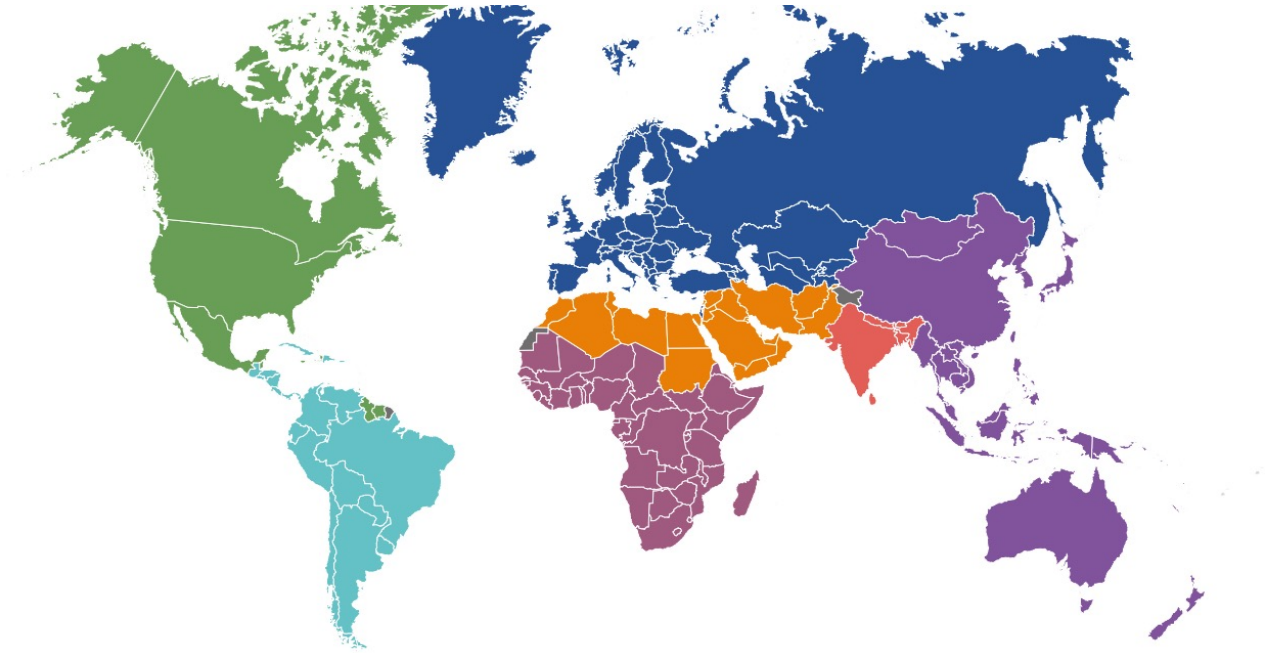
2045	49 million
2030	40 million
2021	32 million

50% increase

Africa (AFR)

2045	55 million
2030	33 million
2021	24 million

134% increase



World

2045	783 million
2030	643 million
2021	537 million

46% increase

Europe (EUR)

2045	69 million
2030	67 million
2021	61 million

13% increase

Western Pacific (WP)

2045	260 million
2030	238 million
2021	206 million

27% increase

South-East Asia (SEA)

2045	152 million
2030	113 million
2021	90 million

68% increase

Middle East & North Africa (MENA)

2045	136 million
2030	95 million
2021	73 million

87% increase

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Source: International Diabetes Federation, Diabetes Atlas 10th Edition, 2021, https://diabetesatlas.org/atlas

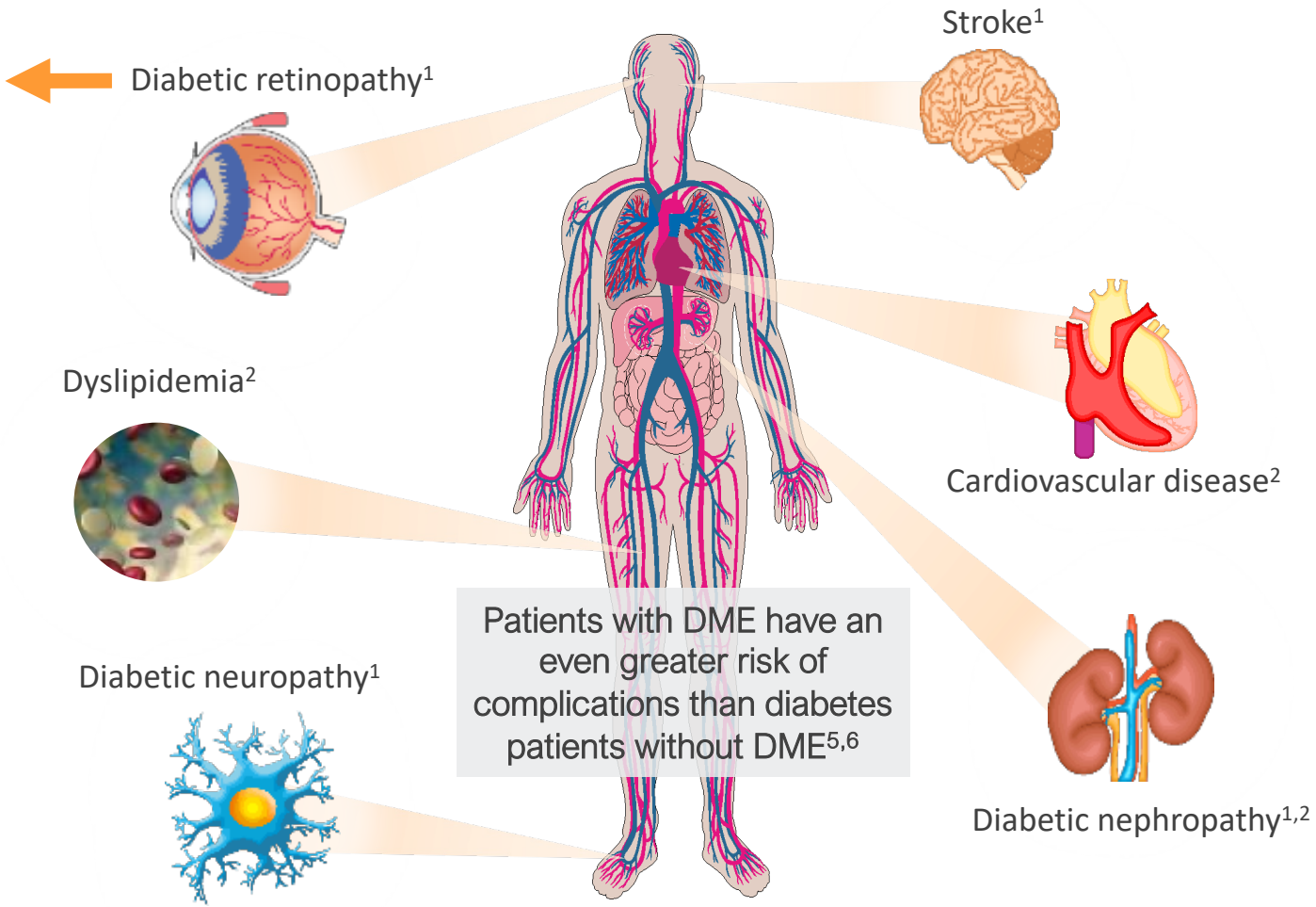
Diabetic Patients Usually Present with Complex Co-Morbidities

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

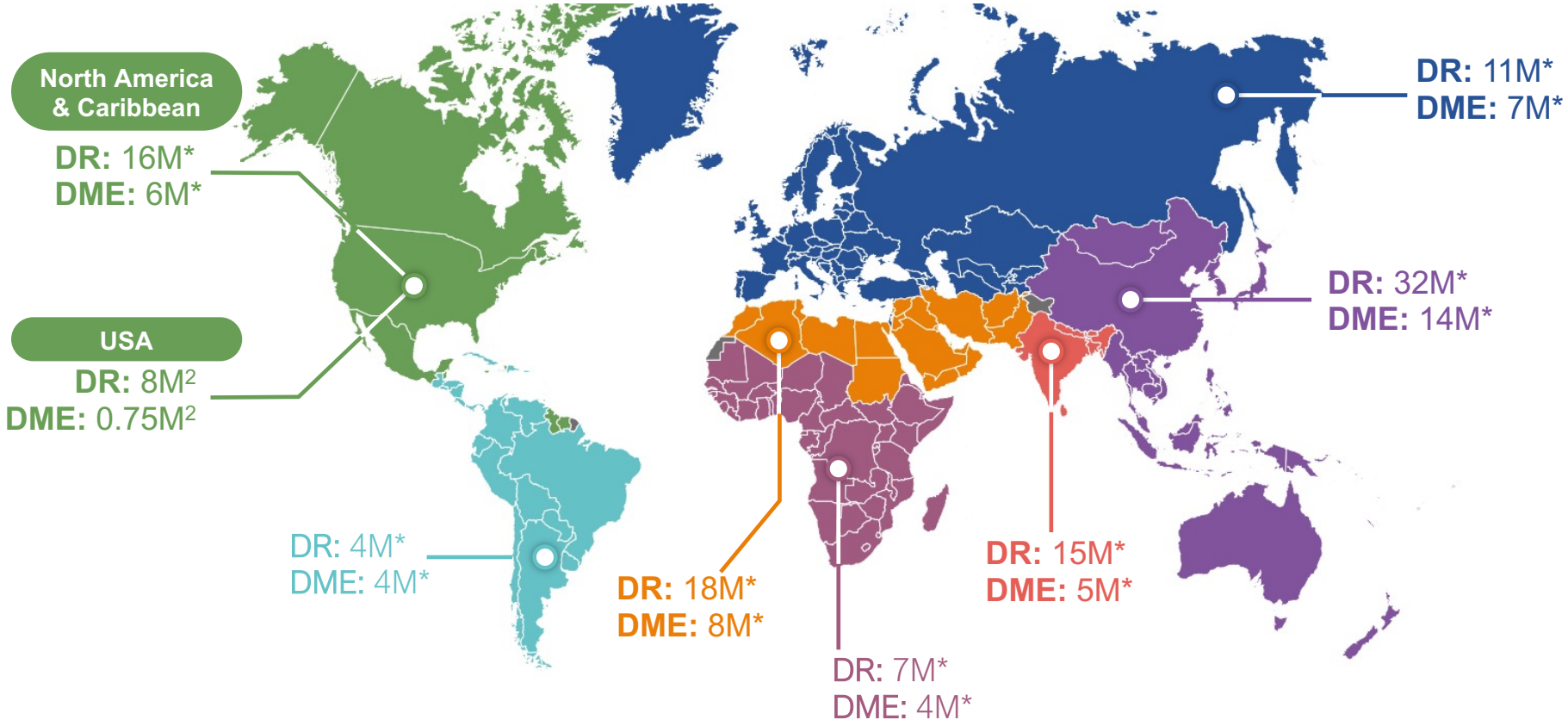


Oral options have the potential to reach other vascular beds to treat kidney and neuropathic co-morbidities

1. Petrella RJ, et al. J Ophthalmol 2012;159167; 2. International Diabetes Federation, Diabetes Atlas 6th Edition, http://www.idf.org/diabetesatlas;
3. National Diabetes Fact Sheet, 2011 http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf; 4. Rodbard HW, et al. Endocr Pract 2007;13:4-69; 5. Wong TY, et al. JAMA 2002;288:67-74; 6. Nguyen-Khoa B, et al. BMC Ophthalmol 2012;12:11

Global Prevalence of Diabetes-Associated Retinal Disease

DR Affects 1 in 3 People with Diabetes; DME Affects 1 in 13 People with Diabetes1



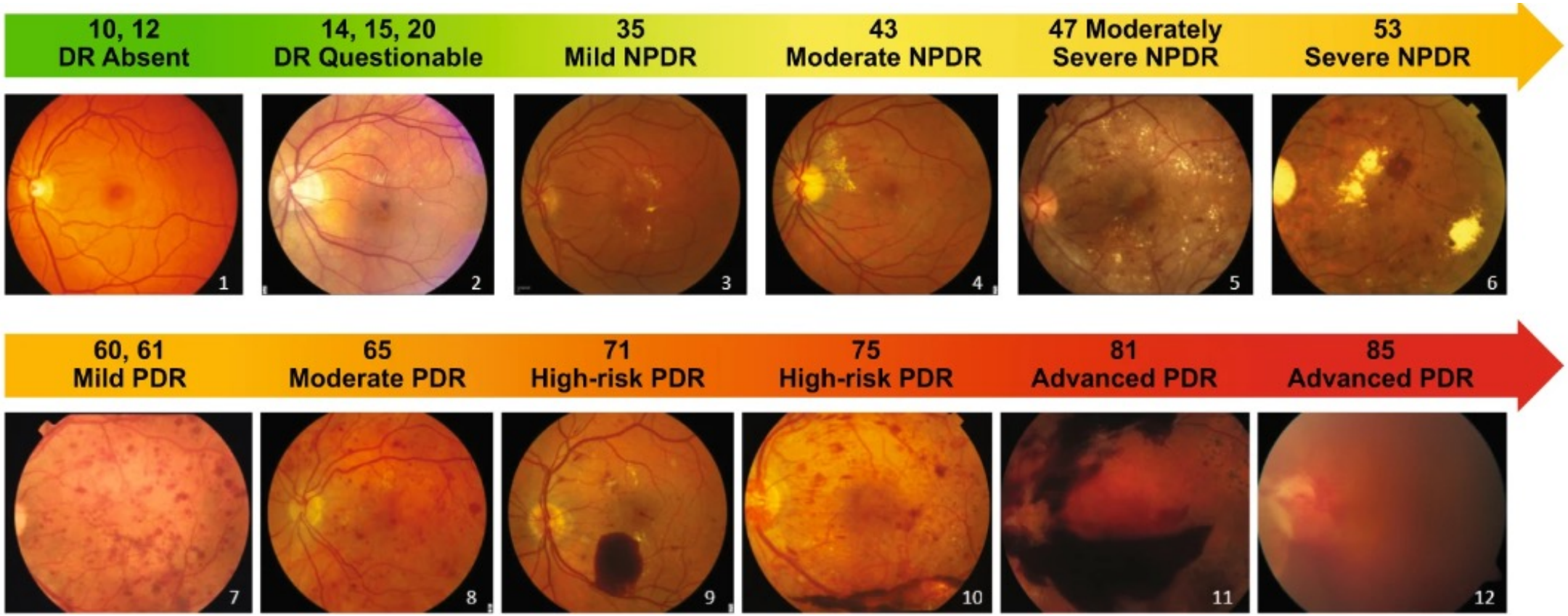
*Global estimates are provided by the National Eye Institute, FactSheet, Global Data, Research and Markets, American Academy of Ophthalmology, and PLOS One

1. Holekamp N. M. (2016). Overview of diabetic macular edema. The American journal of managed care, 22(10 Suppl), s284–s291.
2. American Diabetes Association; American Journal of Managed Care, International Diabetes Federation; Healthline; Ocuphire internal analysis and assumptions

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)

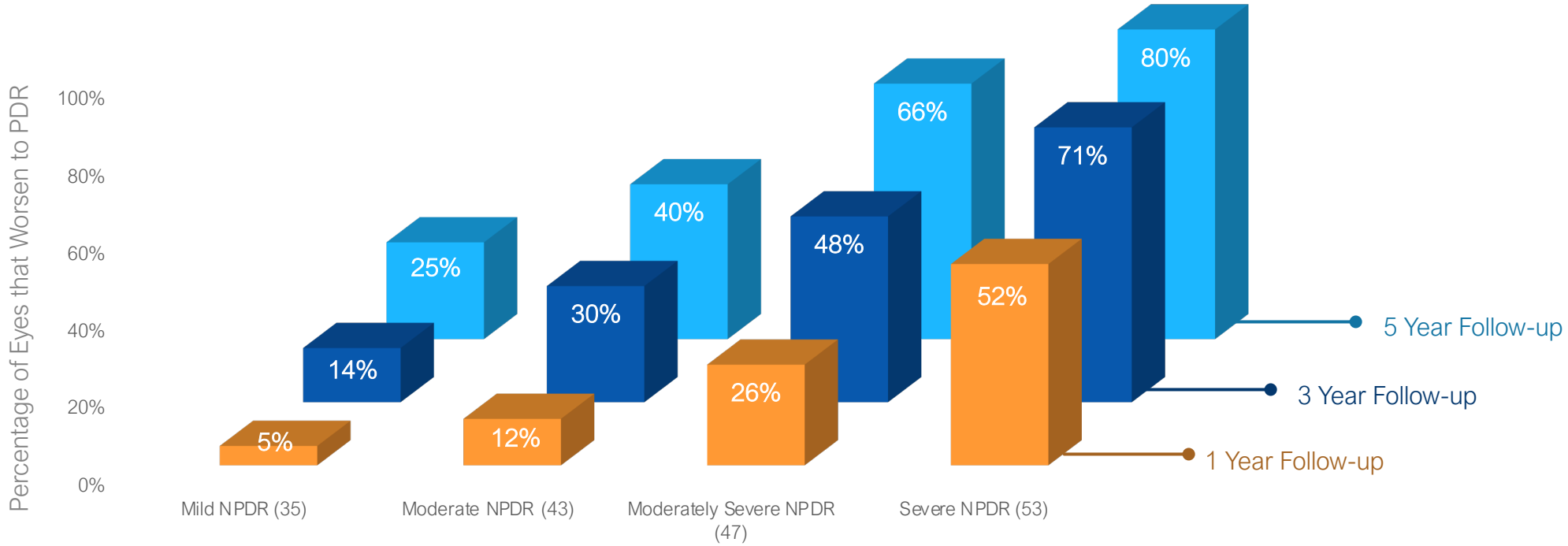


Arcadu, F., Benmansour, F., Maunz, A. et al. Deep learning algorithm predicts diabetic retinopathy progression in individual patients. npj Digit. Med. 2, 92 (2019). https://doi.org/10.1038/s41746-019-0172-3.

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

Early screening and treatment for DR can reduce vision loss by up to 94%



Regardless of severity, all eyes worsen over time

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):997-86.
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

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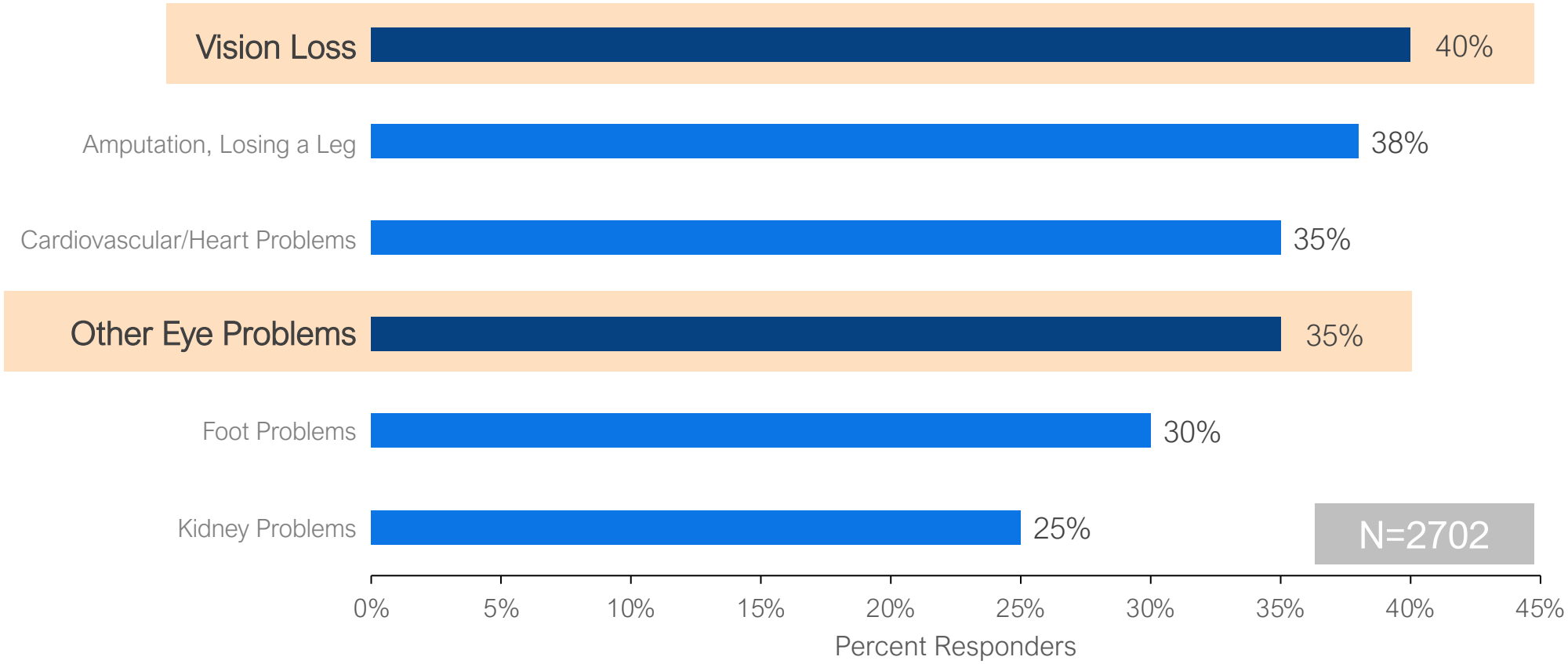
Vision Loss is #1 Concern of Diabetic Patients

Diabetic Retinopathy is a Progressive Vision-Threatening Disease

What are the top concerns for diabetic patients?



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

Early Management of Diabetic Retinopathy

Poor Adherence to Medical Management and Lifestyle Options Worsen DR

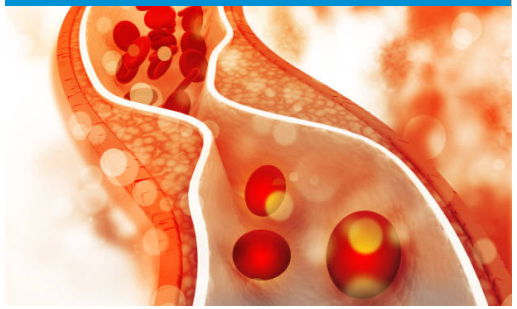
Medical and lifestyle management is first line of treatment

Control of Blood Sugar

Control of Blood Pressure

Smoking Cessation

Control of Lipids

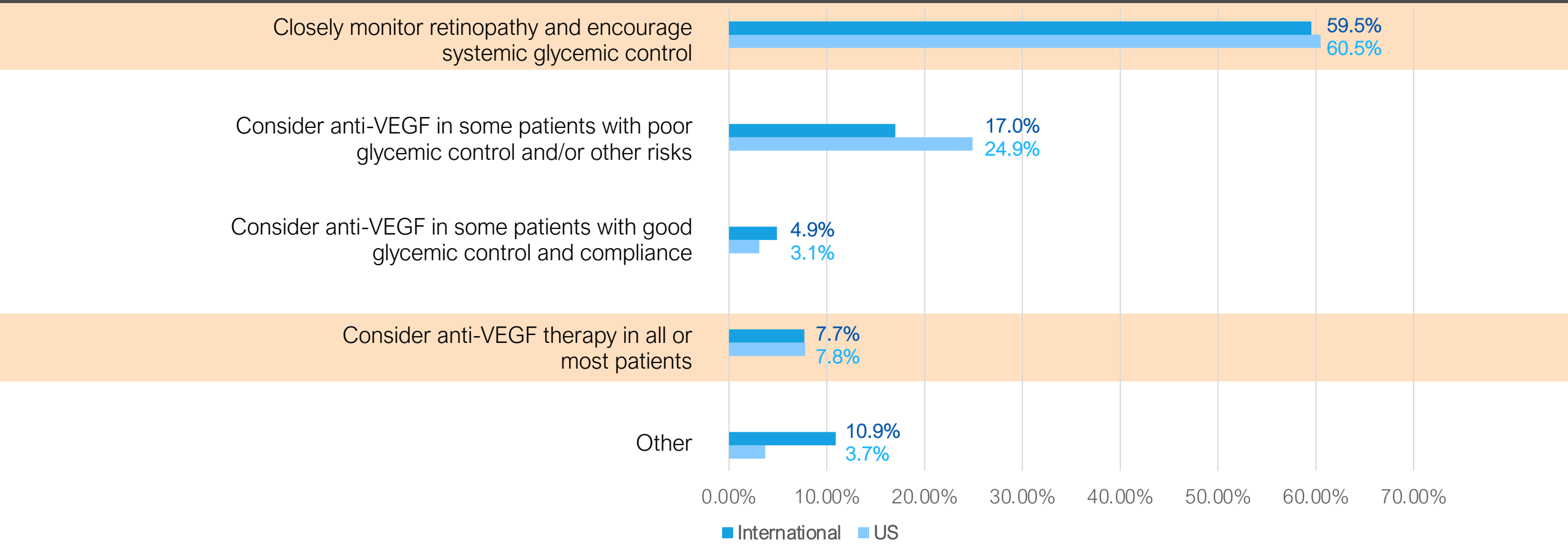


Source: Zhang X et al. Cell Biosci. 2014;14:4:27

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?



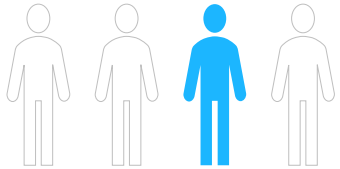
Source: ASRS 2021 Preferences and Trends (PAT) Survey

Diabetic Retinopathy At a Glance

Current Treatment Landscape Demonstrates Need for Less Invasive Therapies

There are ~8M adults in the U.S. with DR[1]

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[2,3]

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

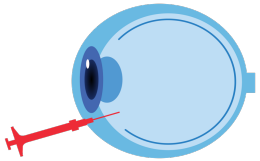
56% of patients reported anxiety related to anti-VEGF treatment

$13B

(2020)

Global Intravitreal Injection Revenues in AMD, DME and BRVO[4]

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



Source:

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

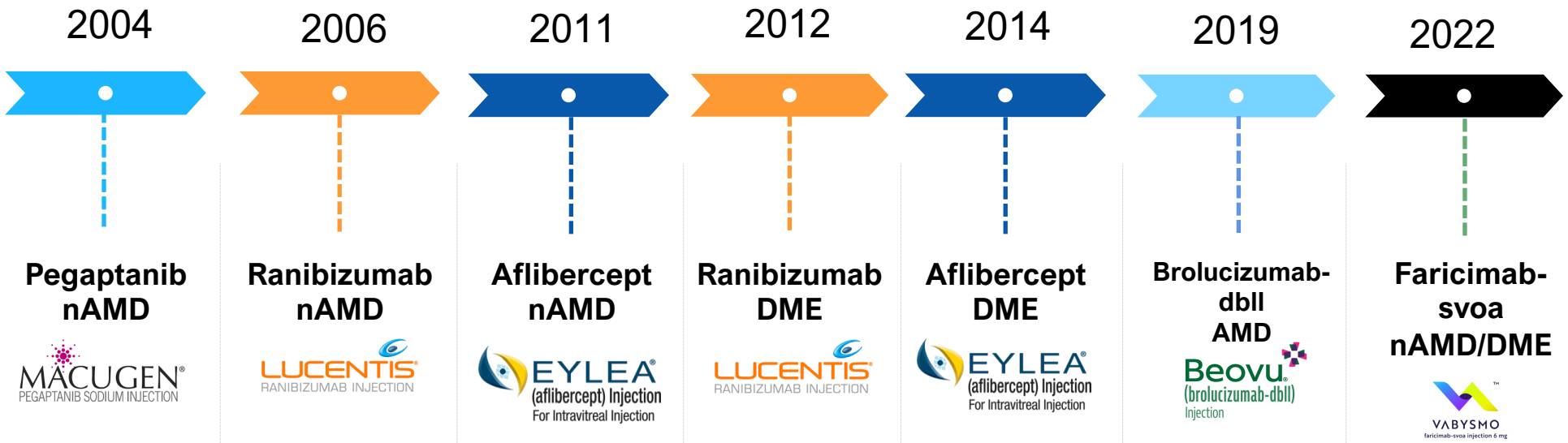
Cleveland Clinic
Cole Eye Institute

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® (aflibercept) Injection For Intravitreal Injection

$9b+
2021 Revenue

LUCENTIS® RANIBIZUMAB INJECTION

$2b+
2021 Revenue

Source: Company websites

Panorama Study Further Emphasizes Need for Proactive Treatment of NPDR

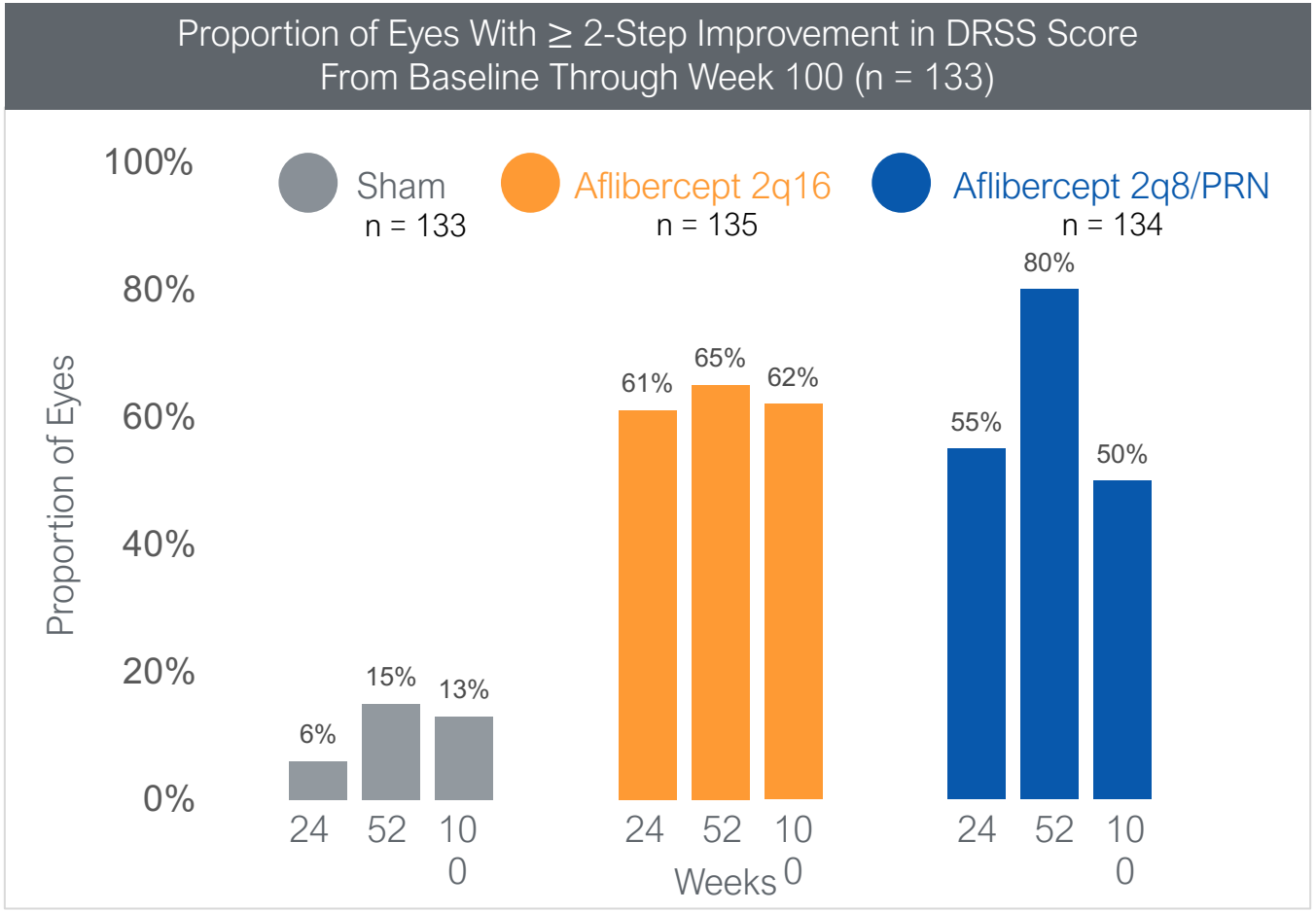
Eyes Treated with Aflibercept Showed a >2-step Improvement in DRSS Level at 24 and 52 Weeks

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

Setting: Global, Multi-Center Study

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

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



Brown DM, Wykoff CC, Boyer D, Heier JS, Clark WL, Emanuelli 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/jamaophthalmol.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[1,2]
	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

Source: Diabetic Retinopathy Preferred Practice Pattern – AAO 2019; LTFU: Lost To Follow-up; IVT: Intravitreal Injections; PRP: Panretinal Photocoagulation

Current Conventional Treatment is Challenging for Patients

Access and Time Burden are Further Barriers for DR Patient Compliance

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

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

Lu AJ, et al. Analysis of patient-reported barriers to diabetic retinopathy follow-up. Ophthalmic Surg Lasers Imaging Retina. 2019;50(2):99-105.
Prenner J et al. Am J Ophthalmol, 2015;160(4):725-731.e1.

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®)

Faricimab (Vabysmo®)

IVT Steroids:

Dexamethasone (Ozurdex®)

Emerging therapies that could shape industry:

Longer Duration IVTs

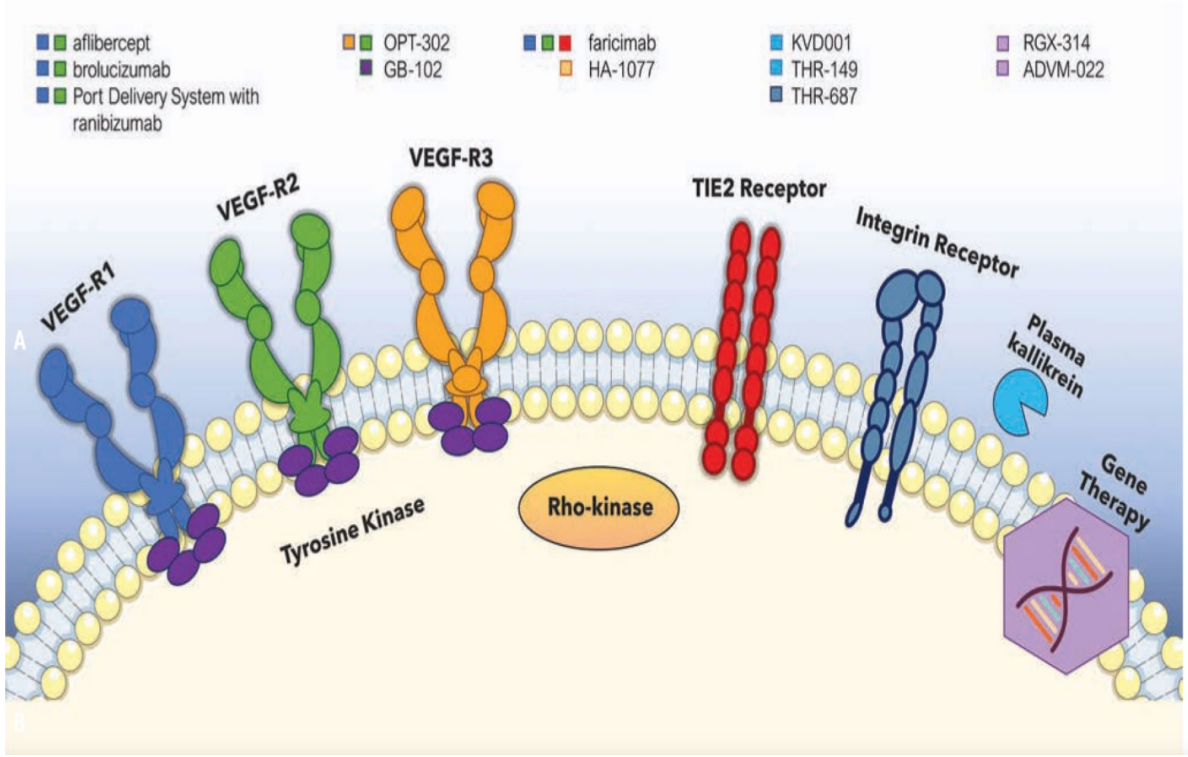
Extended Release

Combination Therapies

Oral Therapies

Topical

Gene Therapies



https://www.reviewofophthalmology.com/article/a-peek-into-the-diabetic-retinopathy-pipeline

Intravitreal Injections Landscape (DR patients)

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

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

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

Company websites; www.clinicaltrials.gov

✓ Completed ◌ Ongoing X Discontinued or Failed study

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	OTT166	Integrin inhibitor	DR	Eyedrop	✓	◌		

✓ Completed ◌ Ongoing X Discontinued or Failed study

Company websites; www.clinicaltrials.gov

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 PHARMA	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	
InflammX	HCB 1019 (Xiflam)	Connexin 43 (inflammasome)	DR	Oral	✓	○	
Valo	OPL-0401	ROCK 1/2 inhibitor	DR	Oral	✓	○	
REZOLUTE	RZ402	Plasma Kallikrein	DME	Oral	✓		

Company websites; www.clinicaltrials.gov
Most Drugs Target Only Inflammation

✓ *Completed* ○ *Ongoing* X *Discontinued or Failed study*

APX3330 is Different Than Past Oral Failures in Retina

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

Phase 1 | Phase 2 | Phase 3 | Approved

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

Plasma Kallikrein
- MOA targets inflammation
- Oral failed due to systemic toxicity (liver, cardiovascular monitoring[2])

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

Iptacopan

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

OTC Oral Successes

Nutritional Supplements: Ocuvite®, PreserVision, EyePromise, Oral Vit C & E, Zn, Cu, Lutein, Zeaxanthin[5]

Bhatwadekar 2020 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7265898/pdf/nihms-1594067.pdf
Bryant 2009 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4905712/pdf/nihms786745.pdf
Eylea® and Lucentis label ARED & AREDS2 study

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

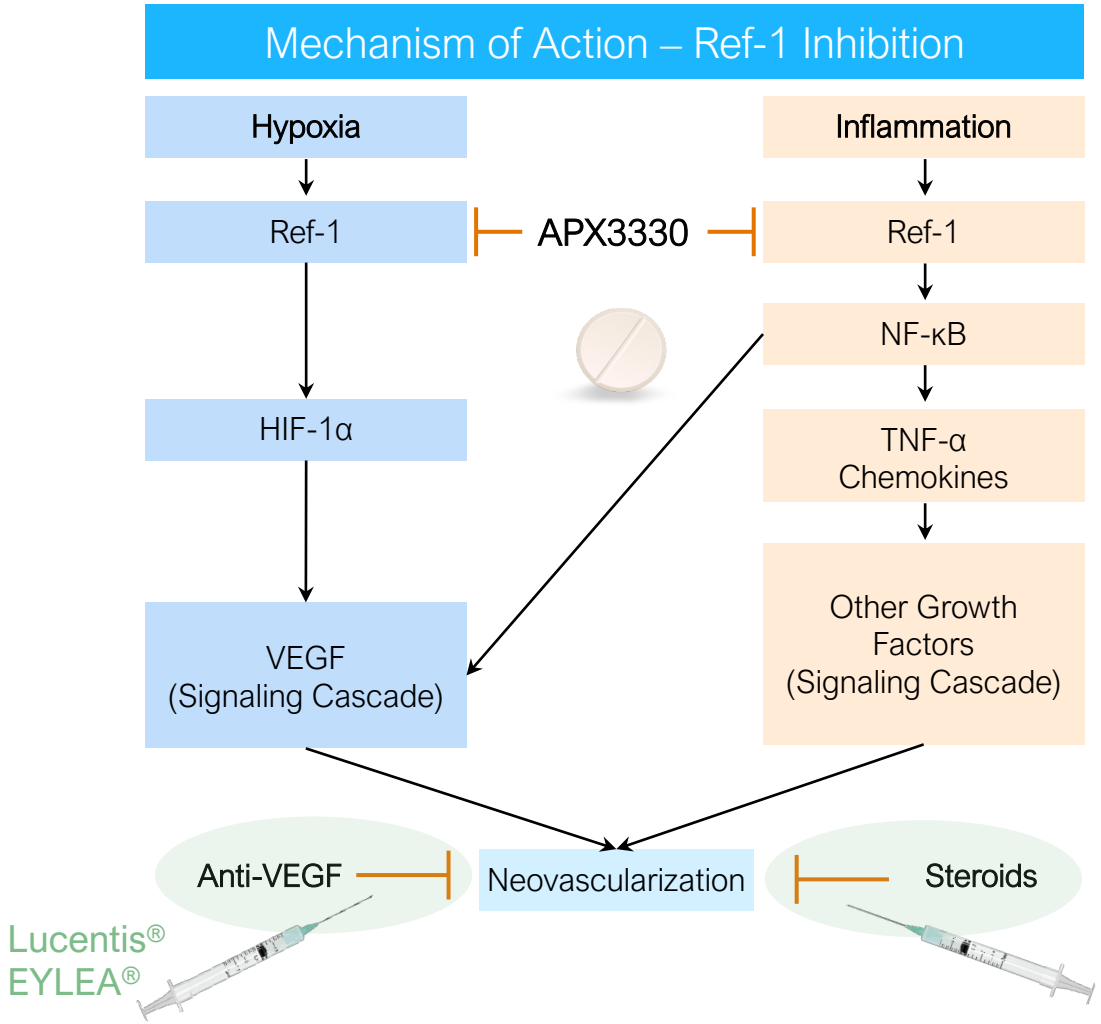
New England Retina Consultants

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



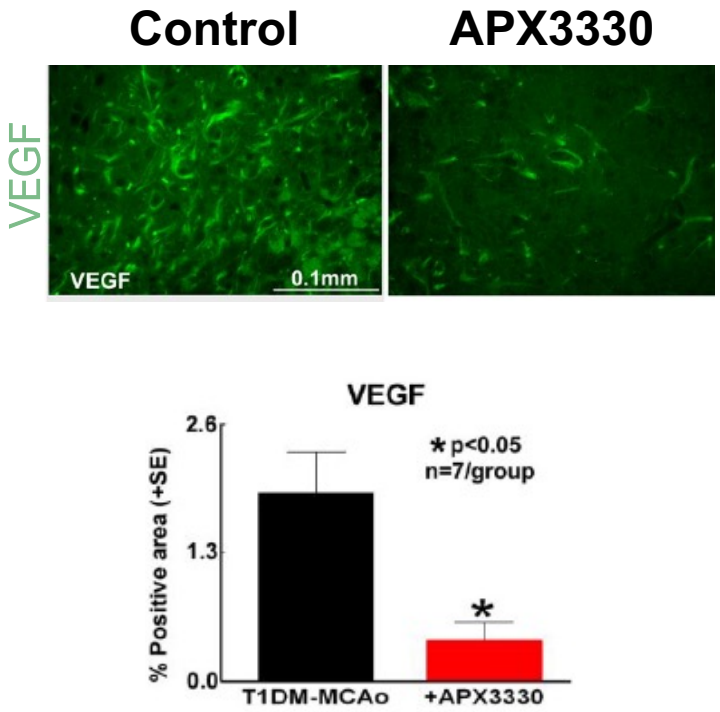
- Ref-1 (reduction-oxidation effector factor-1) is a novel target discovered by Dr. Mark R. Kelley at Indiana University School of Medicine
- APX3330 is a small molecule oral drug candidate and a first-in-class inhibitor of Ref-1
- APX3330 previously developed by Eisai for multiple hepatic inflammatory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

Logsdon et al (2018), Li et al (2014).
Rangasamy S, McGuire PG, Das A. Middle East Afr J Ophthalmol 2012;19:52–59; Sohn HJ et al. Am J Ophthalmol 2011;152:686–694.

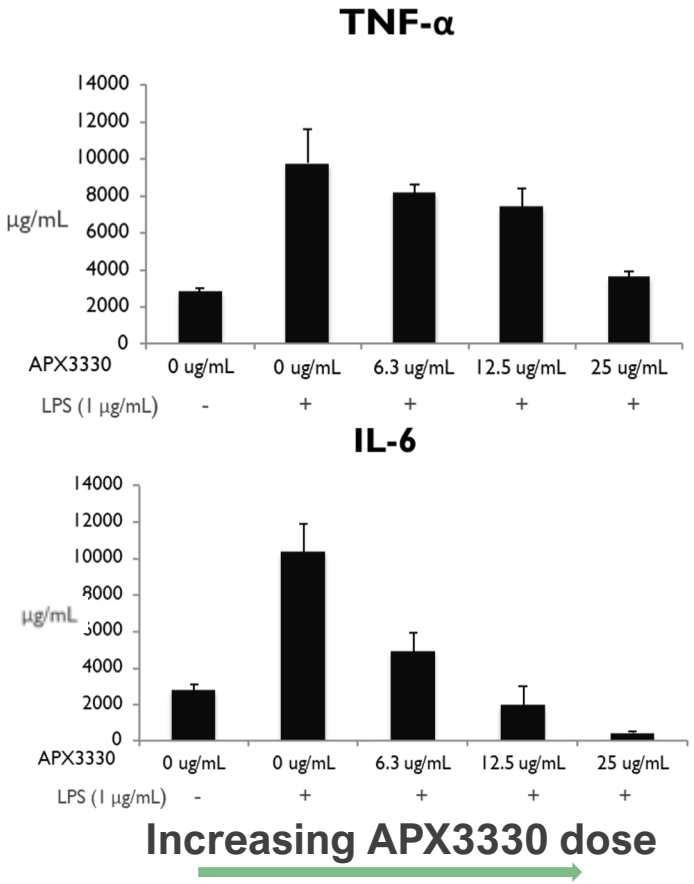
In Vitro Validation of APX3330 Mechanism of Action

APX3330 Reduces VEGF levels and Inflammatory Cytokines; Provides Neuronal Protection

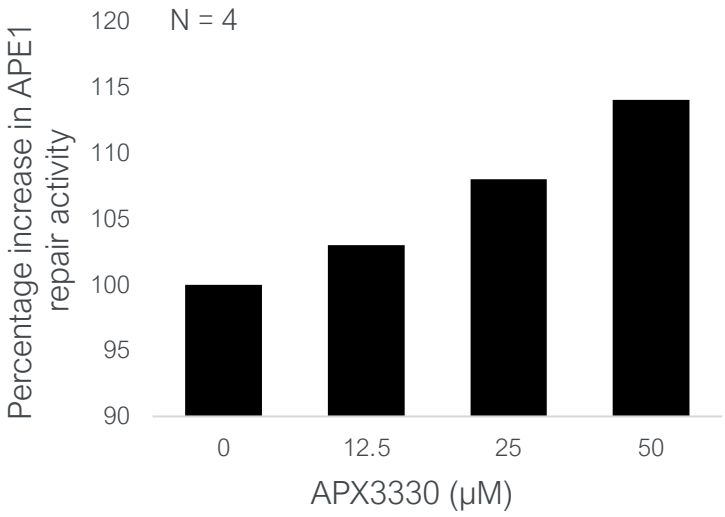
APX3330 reduces VEGF protein expression in preclinical stroke model



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

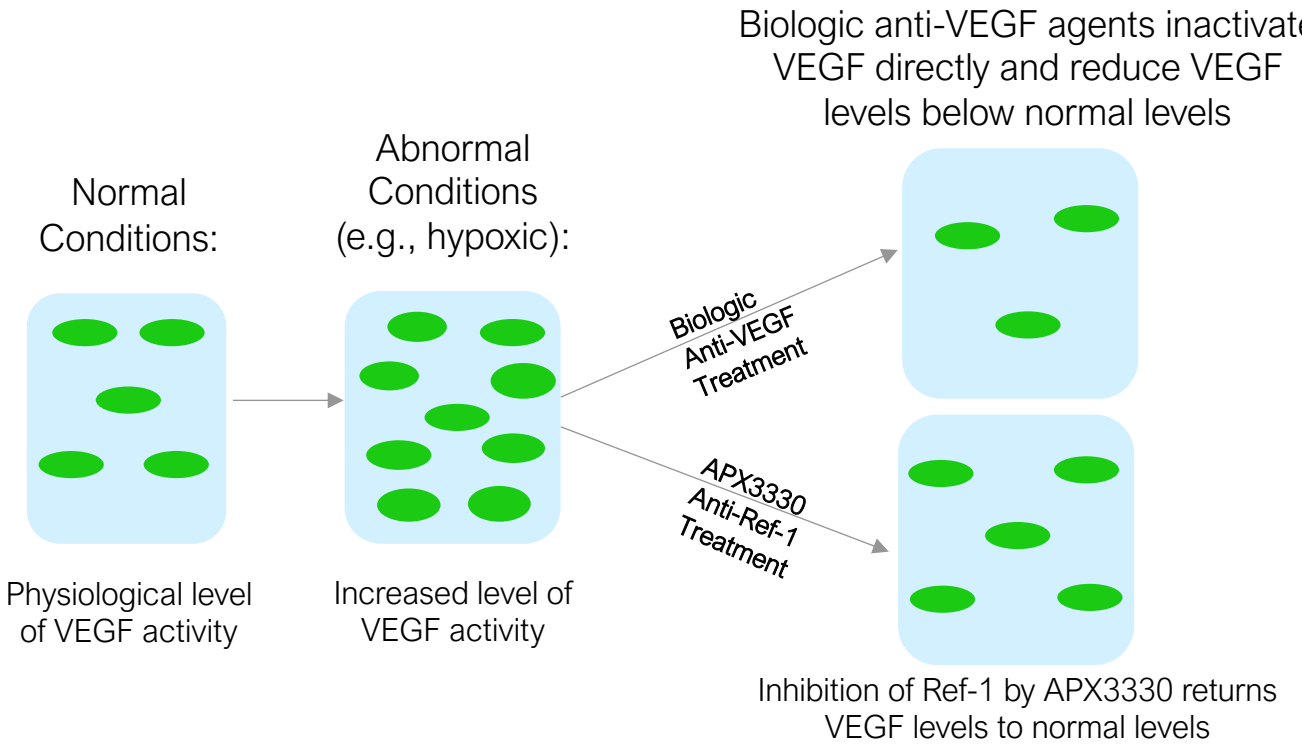
Tao Yan et al. APX3330 Promotes Neurorestorative effects after stroke in type one diabetic rats. Aging and Disease. Vol 9, Oct 2018

Apurinic/Apyrimidinic endonuclease 1 regulates inflammatory response in macrophages. Jedinak A, Dudhgaonkar S, Kelley MR, Sliva D. Anticancer Res. 2011 Feb;31(2):379-85. PMID: 21378315

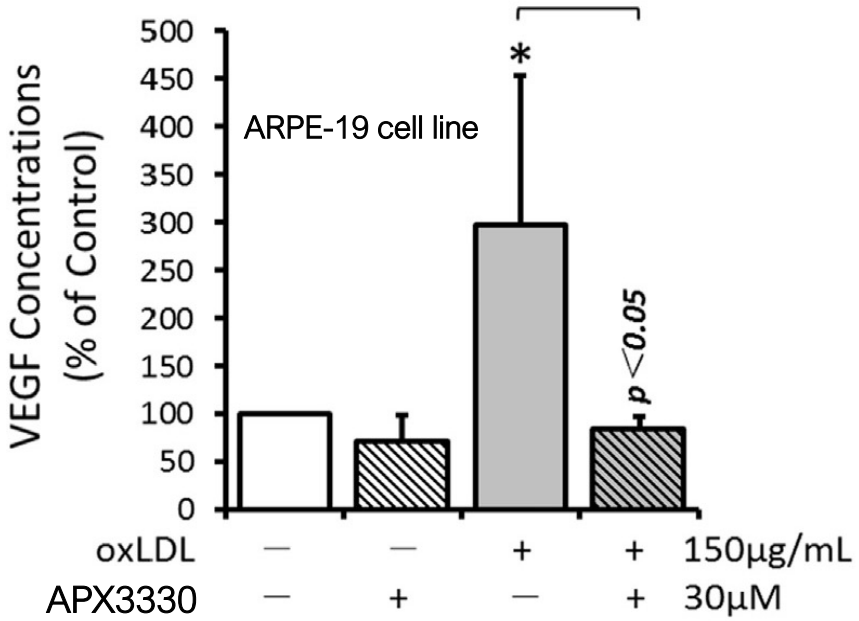
Fehrenbacher, J. C., Guo, C., Kelley, M. R. & Vasko, M. R. DNA damage mediates changes in neuronal sensitivity induced by the inflammatory mediators, MCP-1 and LPS, and can be reversed by enhancing the DNA repair function of APE1. Neuroscience 366, 23-35, doi:10.1016/j.neuroscience.2017.09.039 (2017).

APX3330 VEGF Effects in Normal Cells

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



APX3330 prevents VEGF overproduction in ARPE-19 cells



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

Kamba 2007; Girardi 2010; Li 2014; APX3330 Investigator Brochure

APX3330 Preclinical & IND-Enabling Studies

Completed Over 20 Preclinical Studies with Favorable Efficacy and Safety

Toxicology Studies	PK, Absorption, Distribution, & Excretion Studies	Safety Pharmacology Studies	Geno Tox, Repro Tox & Antigenicity Studies	Pharmacology Models of Retinal Disease Studies
11	3	1	6	4

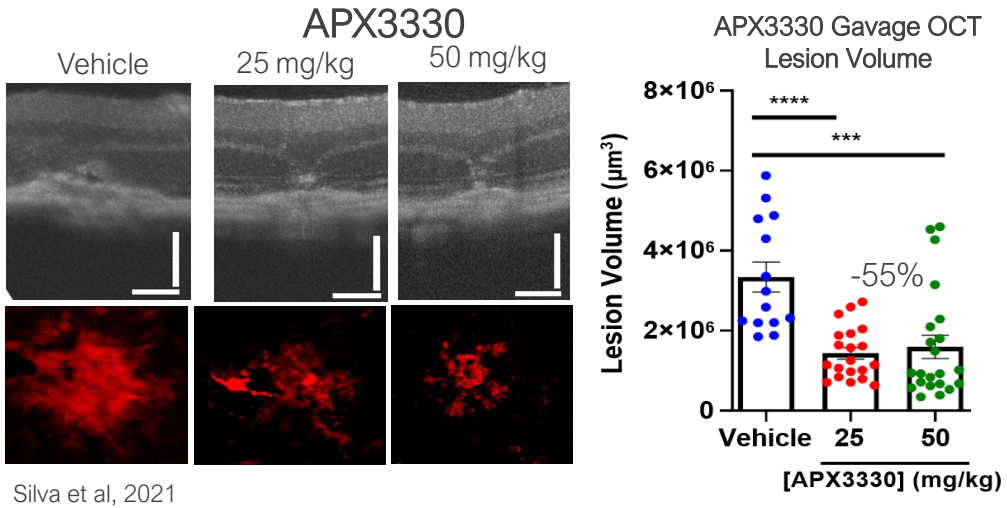
Extensively Studied in Over 20 In-Vitro and Animal Studies with Favorable Efficacy and Safety

Preclinical Data: Oral APX3330 Blocks Neovascularization

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

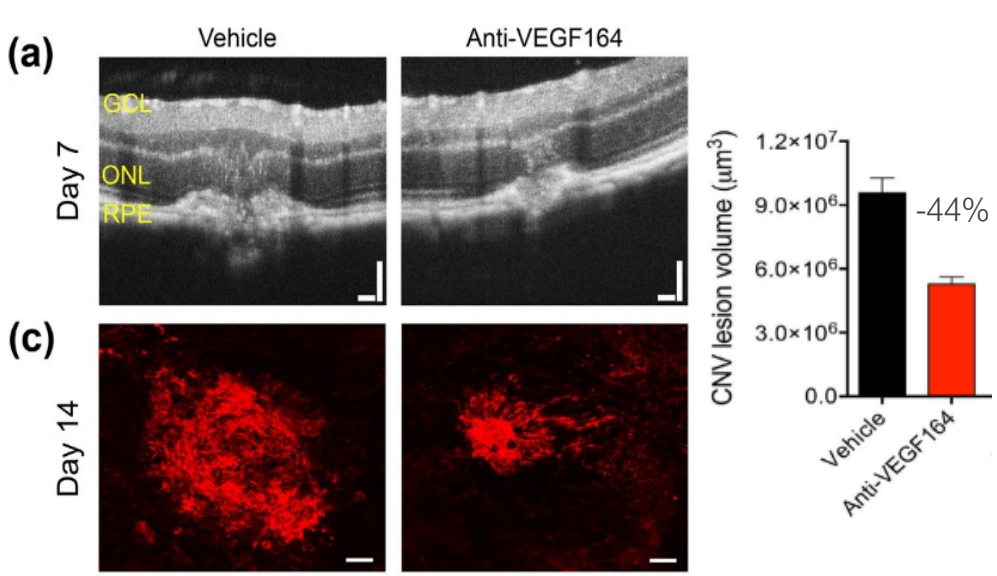
L-CNV Mouse Retina Model

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



Silva et al, 2021

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 $^{-/-}$ 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)

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

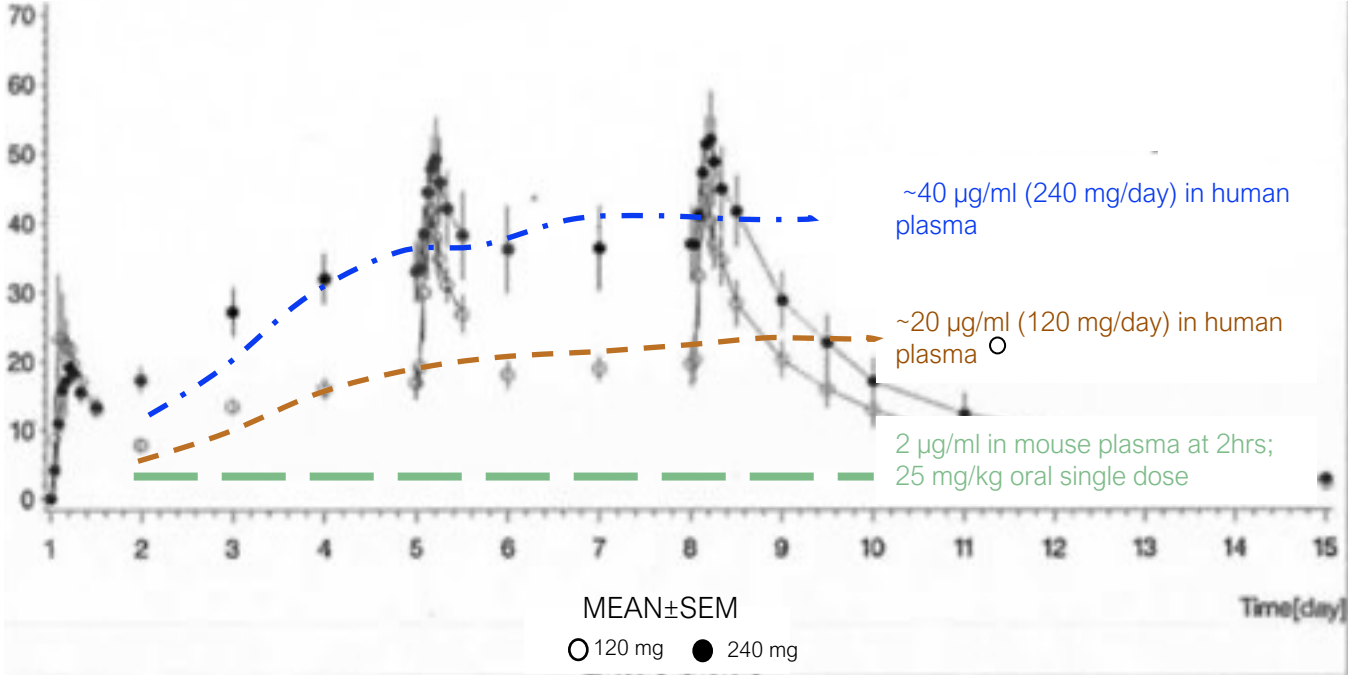
Phase 2 Studies 6

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[2]



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

Apexian preclinical data (unpublished)
APX3330 Investigator Brochure
Eisai PK clinical data APX_CLN_0002

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 **≥600mg** and over **17,961** subject-days of exposure at doses **<600mg**.*

ZETA-1 Phase 2b Trial in Diabetic Retinopathy

Presented by: David Lally, MD

David Lally, MD
Jefferson Medical College

ZETA-1 Phase 2b Design for DR/DME

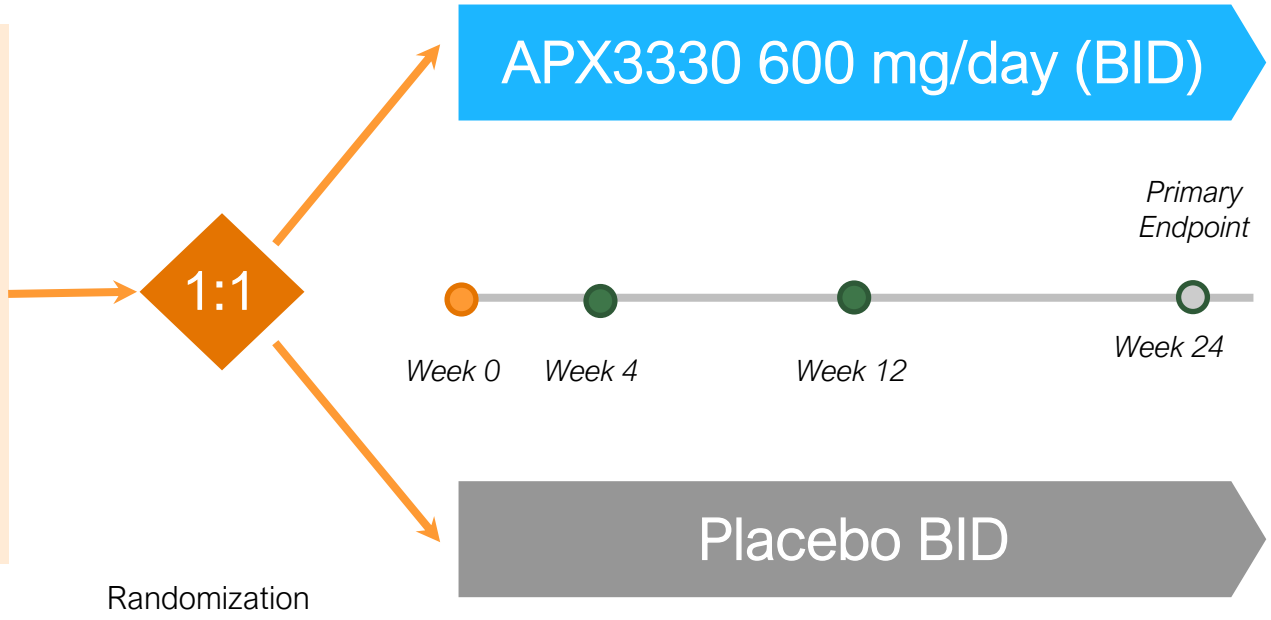
Ongoing, Randomized, Double-Masked, Placebo-Controlled 24-Week Trial (Similar To Eylea P3 DR Trial)

25 US sites

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

Noncentral DME is permitted

Eligibility Screening



Randomization

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

Top Line Data Expected in Q4 2022

Endpoints

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

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

- Males or non-pregnant females ≥ 18 years of age
- 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 ≥ 6 months in the opinion of the Investigator
- **BCVA assessed by ETDRS protocol letters score of ≥ 60 letters (Snellen equivalent 20/63 or better) in the study eye**
- Body mass index (BMI) between 18 and 40 kg/m^2, inclusive

Exclusion

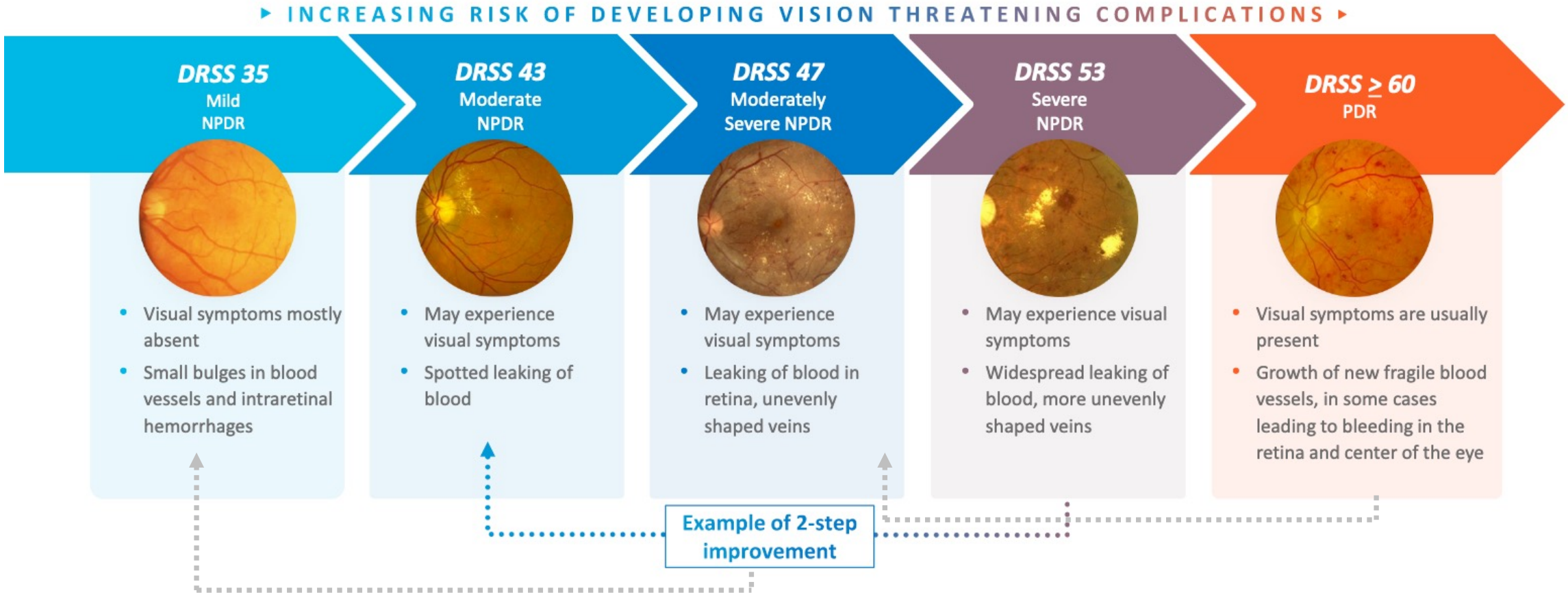
- Retinopathy from causes other than diabetes in study eye
- Presence of **center involved diabetic macular edema (DME) defined as a central subfield thickness (CST) ≥ 320 µm** on SD-OCT or the presence of intra- or subretinal fluid within the central subfield
  - **Center involved DME in the fellow 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**
- Intraocular steroids including triamcinolone and dexamethasone implant within the last 6 months
- Fluocinolone implant within the last 3 years
- HbA1c ≥ 12.0%
- Clinically significant systemic disease (e.g., uncontrolled diabetes, myasthenia gravis, cancer, hepatic, renal, endocrine, or cardio-vascular disorders) that might interfere as deemed by Investigator

Source: ZETA-1 trial

Why DRSS is an Important Endpoint?

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

Diabetic Retinopathy Severity Scale (DRSS)



ZETA-1 Trial: Demographics and Masked Safety Data

Presented by: Caroline Baumal, MD

Tufts Medical Center

Caroline Baumal, MD
University of Toronto

Baseline Characteristics for ZETA-1 Trial

Typical Demographics for Diabetic Population

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

Source: ZETA-1 Demographics and Baseline Characteristics

Baseline Characteristics for ZETA-1 Trial (Continued)

DRSS Scores in Diabetic Study Population

Parameter	Total N = 103	
Study Eye DRSS n(%)	DRSS 47 (Moderately Severe NPDR)	39 (38%)
	DRSS 53 (Severe NPDR)	53 (52%)
	DRSS 61 (Mild PDR)	11 (11%)
Fellow Eye DRSS n(%)	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%)
	Not Graded	2 (2%)

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

Baseline Characteristics for ZETA-1 Trial (Continued)

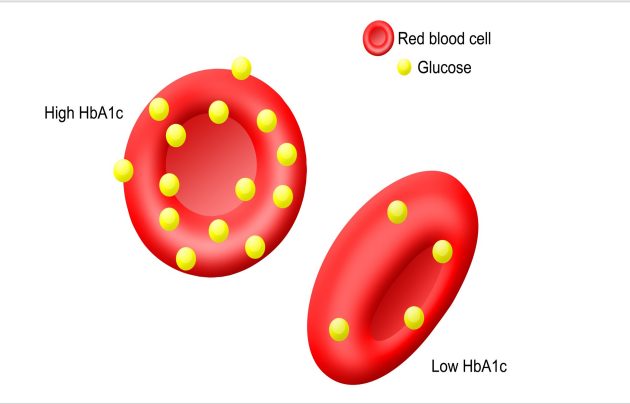
Key Visual Metrics in Diabetic Study Population

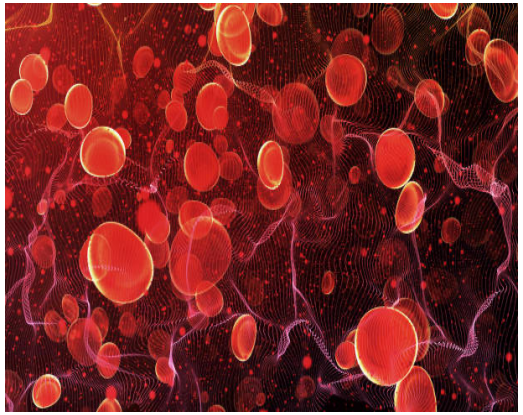
Parameter		Total N = 103	
Study Eye Screening CST (um):	mean (range)	270 (203-319)	
Fellow Eye Screening CST (um)*:	mean (range)	289 (211-491)	
Study Eye BCVA:	mean (range)	Letters Read: 80 (60-93)	Snellen Equivalent: 20/25 (20/63-20/15)
Fellow Eye BCVA:	mean (range)	Letters Read: 77 (0-91)	Snellen Equivalent: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

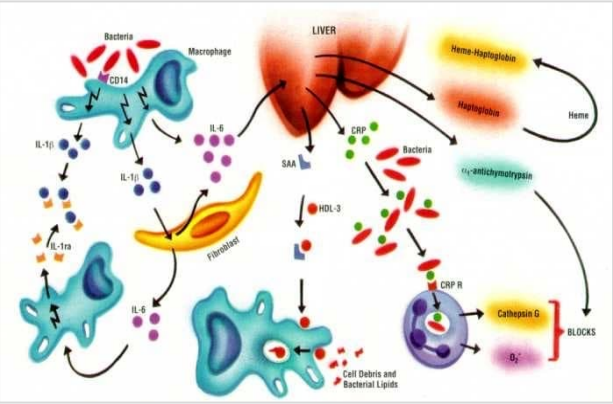
Source: ZETA-1 Demographics and Baseline Characteristics
* N=102 due to a fellow eye not being graded.

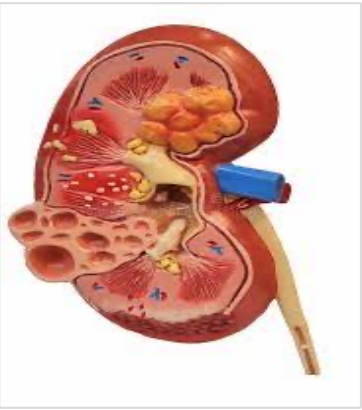
Comprehensive Laboratory Panels Collected in ZETA-1

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 ß (IL-1ß)
- Interleukin-6 (IL-6)
- Interleukin-8 (IL-8)
- Tumor Necrosis Factor α (TNF-α)

PK and Biomarkers

- REF-1 ELISA 1
- Pharmacokinetics

Kidney Function

- eGFR
- Creatinine

Masked Safety Findings from Ongoing ZETA-1 Trial

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

103
Subjects Enrolled

95
Subjects completed thru week 12

91
Subjects completed thru week 24

169 TEAEs
In 62/103 Subjects (60%)

30 Treatment-Related	**149** Unrelated
18 Mild	92 Mild
12 Moderate[1]	48 Moderate
0 Severe	9 Severe

3 withdrew due to an AE[3]

6 lost to follow-up

3 withdrew consent or site closure

0
Treatment- Related **AEs involving liver, heart, kidney, brain, lung, or vital signs**

16 SAEs in 12/103 Subjects

0 Treatment Related	**16** Unrelated[2]

>7900
Subject-Days of Treatment at **600 mg/day** APX3330 Exposure

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 ≥ 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

*11 completed Phase 1 and Phase 2 clinical trials by Eisai and Apexian; along with ongoing ZETA-1 trial by Ocuphire (*includes ~103 subject)

ZETA-1 Trial Design and Data Expectations

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

Efficacy Signal

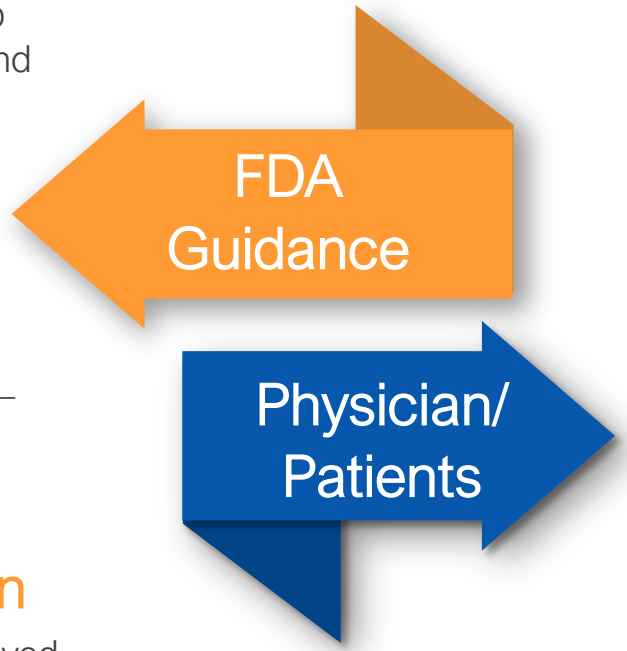
Percent of patients on APX3330 with a ≥ 2 step improvement on the DRSS score at week 24 (and 52) compared to placebo in 2 well-controlled, multi-center clinical trials

Safety

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

Non-Invasive Treatment Option

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



Efficacy Signal

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

Safety

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

Non-Invasive Treatment Option

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

Ocuphire PHARMA

Eylea® label; APX3330 Investigator Brochure, ZETA-1 clinical trial

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