AMERICAN ACADEMY OF OPHTHALMOLOGY®

Favorable Safety and Tolerability Profile of Oral APX3330 Drives Dosing Strategy for Ongoing Phase 2 Trial for DR/DME

Abstract # PO332

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Disclosures

Ocuphire Pharma (consultant)

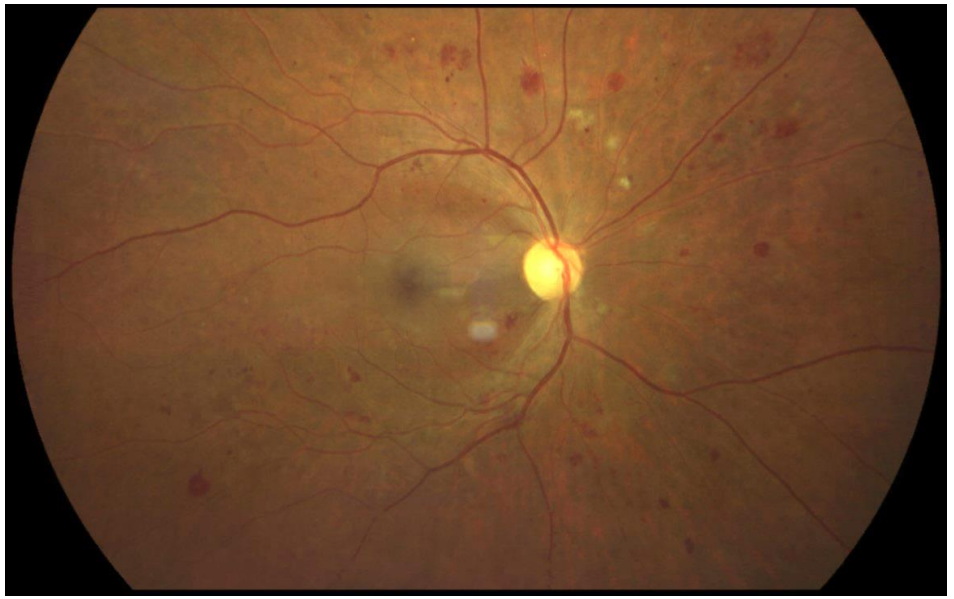
Alimera Sciences (consultant)

Iveric Bio (consultant)

Clinical unmet need in diabetic retinal diseases

The Problem

- DR/DME are major causes of vision loss in working aged adults
- Diabetic population expected to increase dramatically worldwide
- Approved therapies for DR are effective but require IVT injection
- **Early, noninvasive intervention targeting DR represents a therapeutic unmet need**



Worldwide incidence of diabetes and DR	
Diabetes	~450M currently ~700M by 2045
DR	>150M + with DR

Wong, TY et al (2020)

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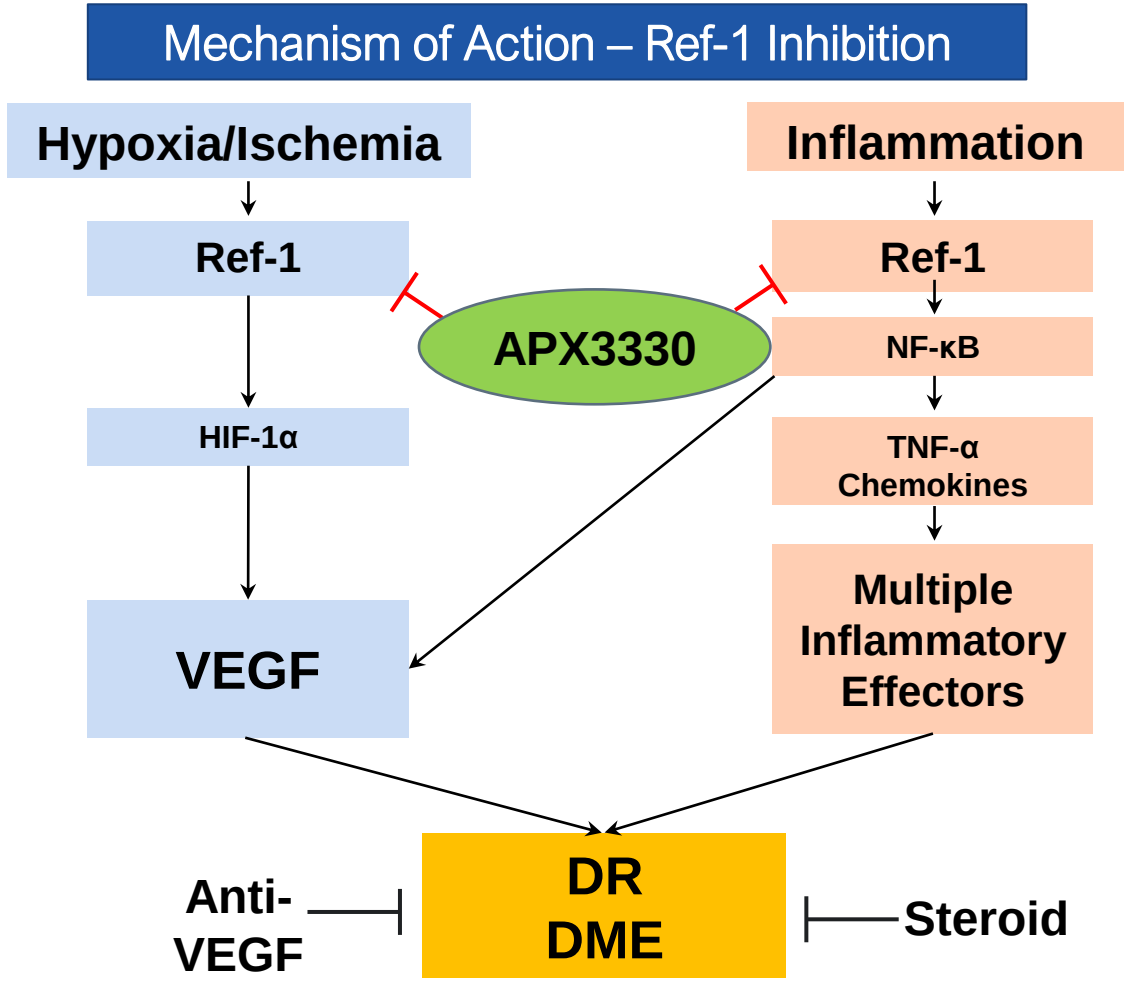
APX3330 target Ref-1 is involved in key DR pathways

- **APX3330 is a first in class small molecule oral inhibitor of Ref-1 (reduction-oxidation effector factor-1)**
- Ref-1 is activated early under both hypoxic and inflammatory conditions
- APX3330 inhibits Ref-1 thus blocking both VEGF and inflammatory cytokine expression
- APX3330 targets two major pathobiologic pathways driving DR



Logsdon et al (2018), Li et al (2014)

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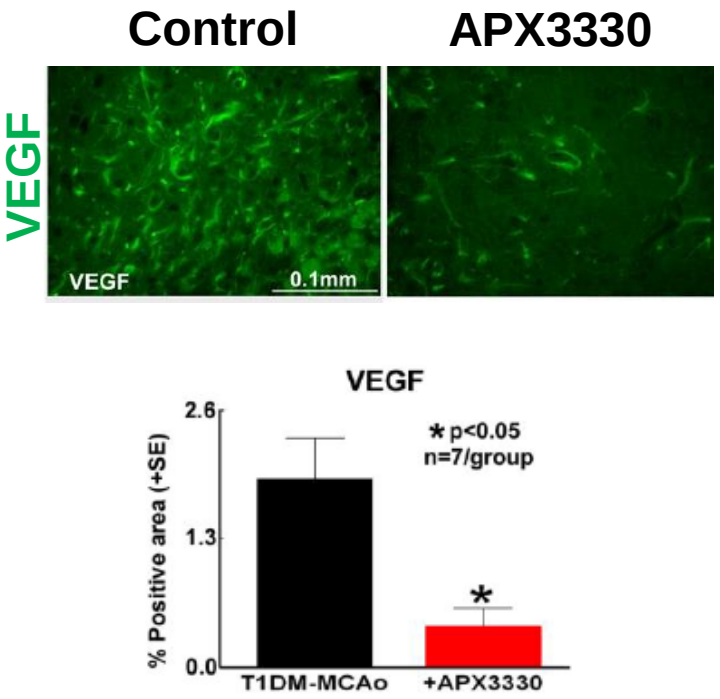
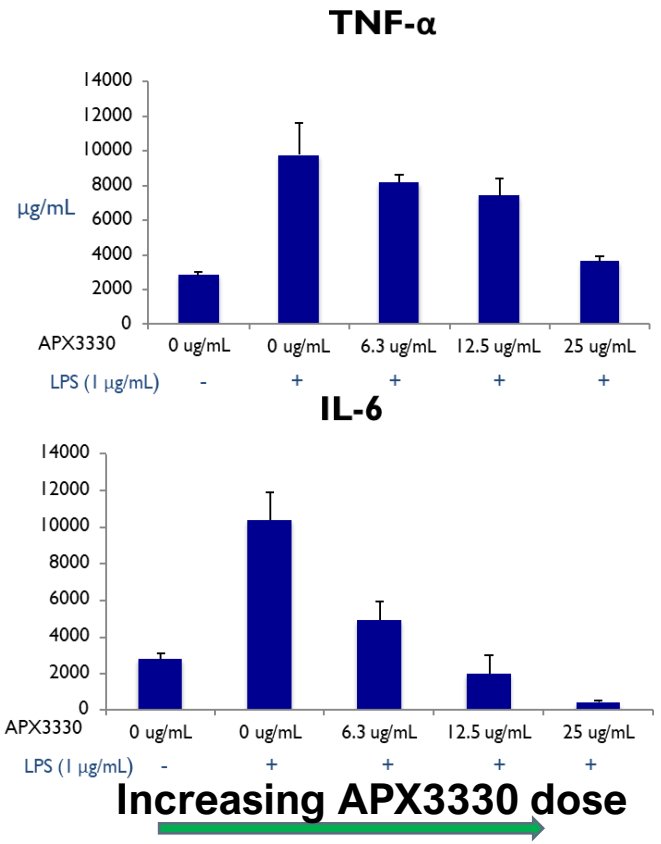
APX3330 down-regulates VEGF and inflammatory cytokines; without negatively affecting normal cells

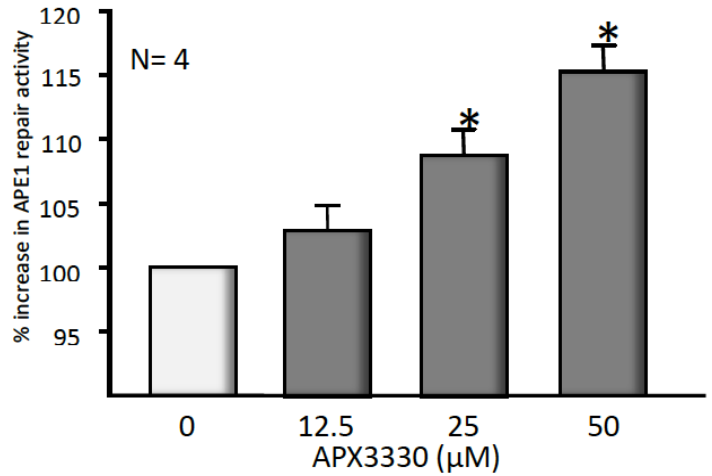
APX3330 reduces VEGF protein expression in preclinical stroke model



APX3330 reduces pro-inflammatory cytokines in LPS stimulated macrophages



APX3330 increases DNA repair in neurons



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).

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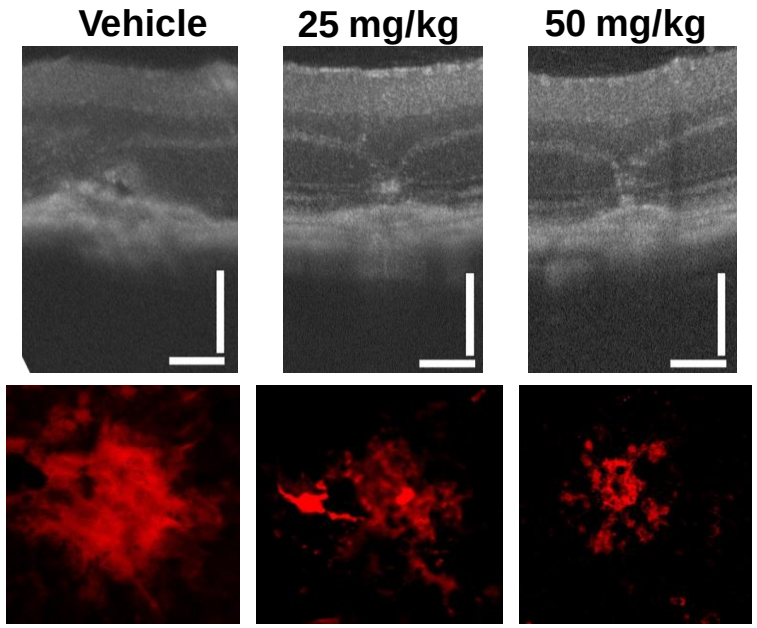
Oral APX3330 reduces CNV lesion size

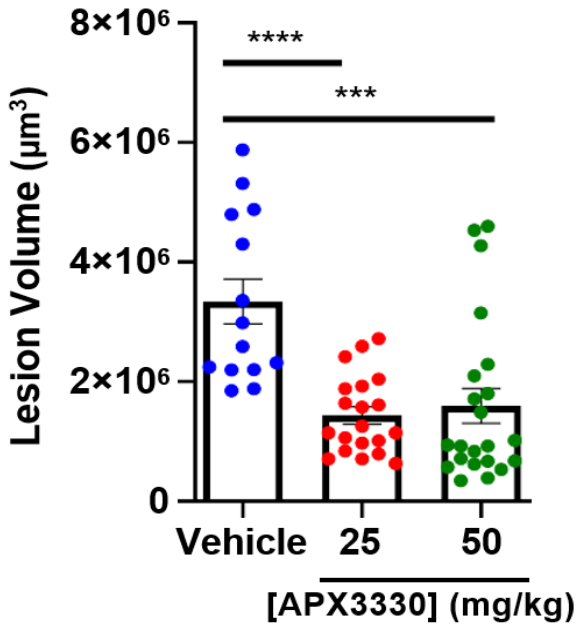
Mouse Laser CNV Model

OCT and histology of CNV lesions



Silva et al, 2021

OCT lesion volume



APX3330 is orally bioavailable and reaches the retina at therapeutic levels

Preclinical PK and human modeling support 600 mg/day dosing for clinical development

Mouse

Retinal levels in mice exceed IC50 and show efficacy in laser CNV model

Rat

Orally administered, radiolabeled APX3330 reaches high levels in rat eye

Human

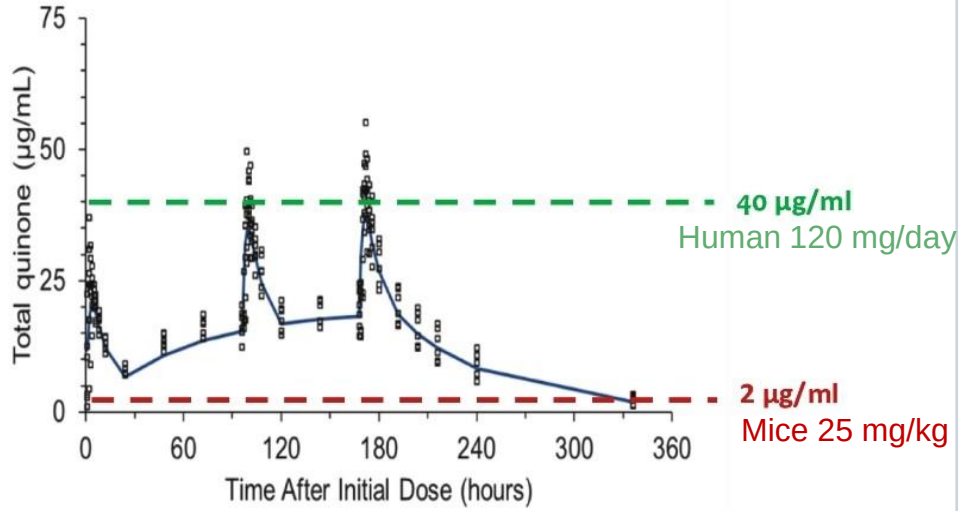
Human clinical dose: 300 mg BID

Established PBPK model predicts APX3330 reaches sufficient human retinal concentrations

Phase 1 PK Clinical Data

Human Drug Exposure Multiple Times Higher than Mouse Efficacious Levels

Human Pharmacokinetics of APX3330 at 120 mg/day



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

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APX3330 was well tolerated in phase 1 and 2 studies

APX3330: 600mg Oral Dose

Prior clinical experience

- **11 phase 1 and 2 clinical studies**
- **> 340 subjects**
- **Doses ranging up to 720 mg/day**
- **Dosing over 1 year**
- **Biological activity in cancer and hepatitis patients**

Safety data

Few Systemic Adverse Effects

- < 5% Mild Gastrointestinal (diarrhea)
- < 5% Mild Skin Rash (reversible)
- No significant neurologic, cardiovascular, hepatic, or pulmonary toxicities

No Ocular Adverse Events

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ZETA-1 phase 2b trial design in DR patients

Ongoing, Randomized, Double-Masked, Placebo-Controlled 24-Week Trial

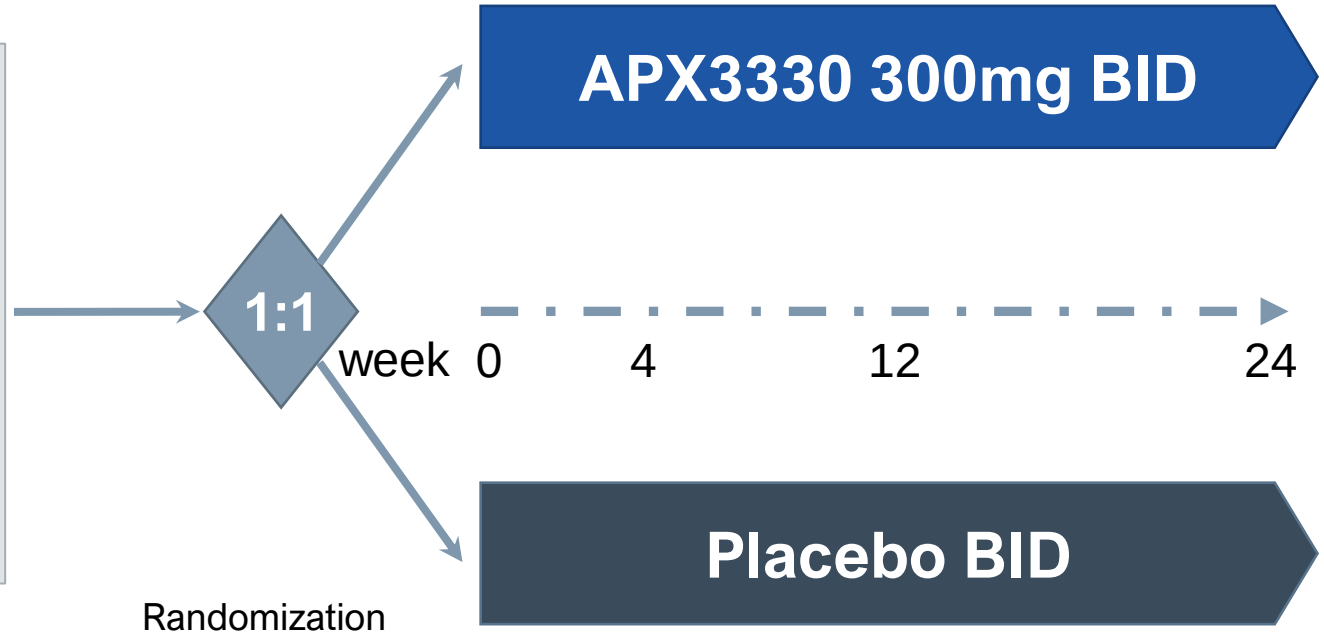
ZETA-1

25 US sites

~100 participants with moderate-to-severe NPDR or mild PDR

Noncentral DME is permitted

Eligibility Screening



Randomization

Endpoints

Primary: % of subjects with a ≥ 2 step improvement on the DRSS at week 24

Secondary:

- **Central subfield thickness (CST)**
- **BCVA**
- **Safety and tolerability**
- **Rescue subjects**

Exploratory:

- **Labs / PK**

Trial Results Expected in 2022

ZETA-1 Clinical Trial Sponsor is Ocuphire Pharma

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Take home messages

- **Early, noninvasive intervention targeting DR represents a therapeutic unmet need**
- **APX3330 targets Ref-1 which plays a role in signaling under both ischemic and inflammatory conditions, both of which are relevant to DR**
- **APX3330 is an orally administered drug being developed for DR with supportive preclinical data including in L-CNV mice model**
- **APX3330 has demonstrated good safety and tolerability across 11 prior Phase 1 and 2 clinical trials**
  - **No adverse effects seen with APX3330 compared to systemic administration of anti-VEGF biologics such as cardiovascular pathology, hypertension, arteriothrombotic events, or renal dysfunction**
- **ZETA-1 Phase 2b clinical trial of APX3330 in participants with clinically significant DR results expected in 2022**
- **APX3330 has potential utility as adjunct therapy for other retinal vascular diseases**

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