



**Presenter:
Daniel Su, MD**

**ZETA-1 Phase 2 Trial Safety and Tolerability results
for APX3330: a Novel, Oral Ref-1 Inhibitor for the Treatment of
Diabetic Retinopathy**

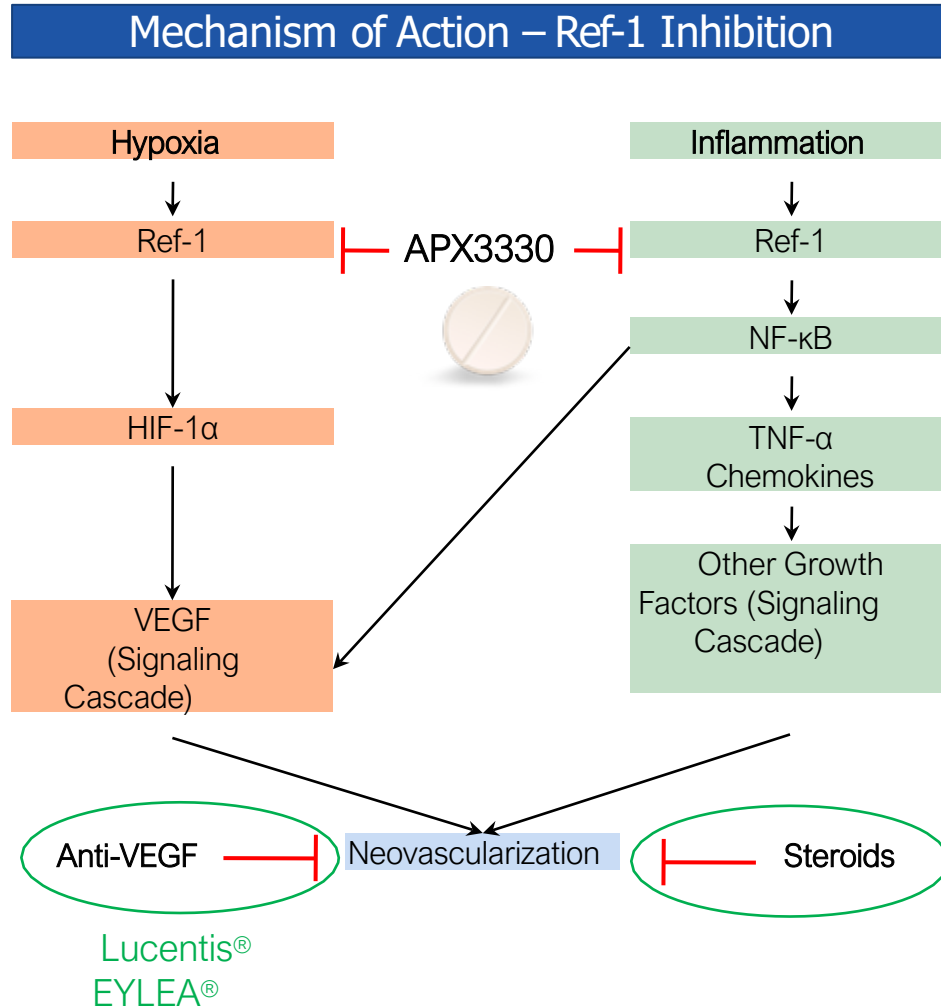
July 28 - August 1, 2023

Disclosures

- Medical Advisor to OcuPhire
- Investigator

APX3330 History and Ref-1 Inhibition Mechanism

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

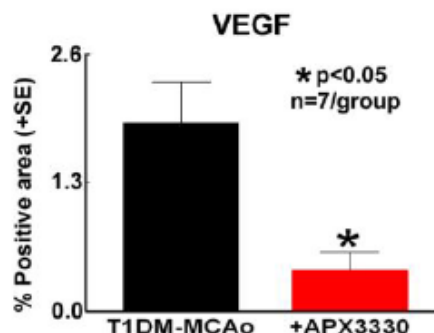
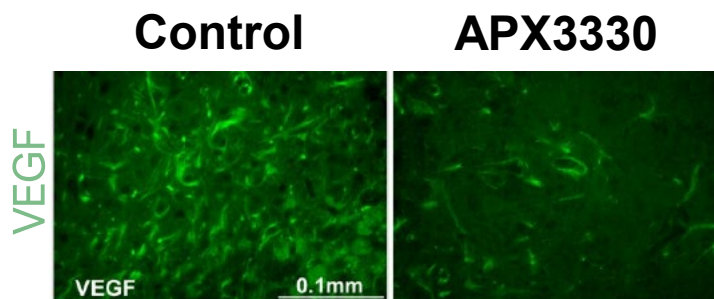


- Ref-1 (reduction-oxidation effector factor-1), a novel target for retinal diseases, is a transcription factor regulator of angiogenesis (VEGF) and inflammation (NFκB)
- Unique dual MOA decreases abnormal angiogenesis and inflammation
- Anti-VEGF injections *do not* target inflammation
- Previously developed by Eisai for hepatic inflammatory indications and by Apexian for solid tumors in **11 Phase 1 and 2 trials**
- Extensively studied in over **20 in-vitro and animal studies** with favorable efficacy and safety

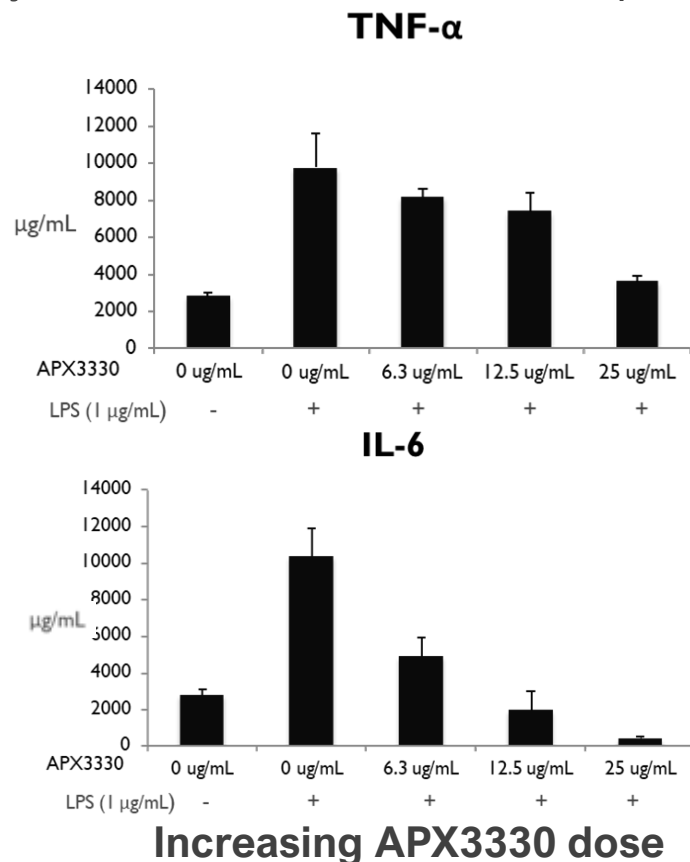
In Vitro Validation of APX3330 Mechanism of Action

APX3330 Reduces VEGF levels and Inflammatory Cytokines; Provides Neuronal Protection

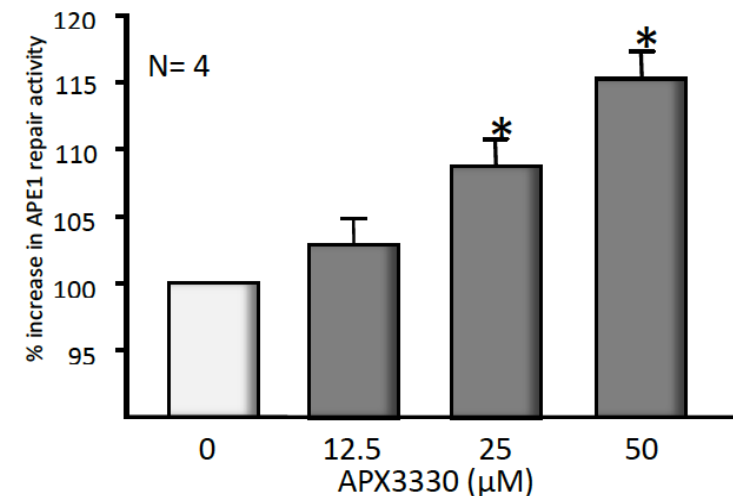
APX3330 reduces VEGF protein expression in preclinical stroke model



APX3330 reduces pro-inflammatory cytokines in LPS stimulated macrophages



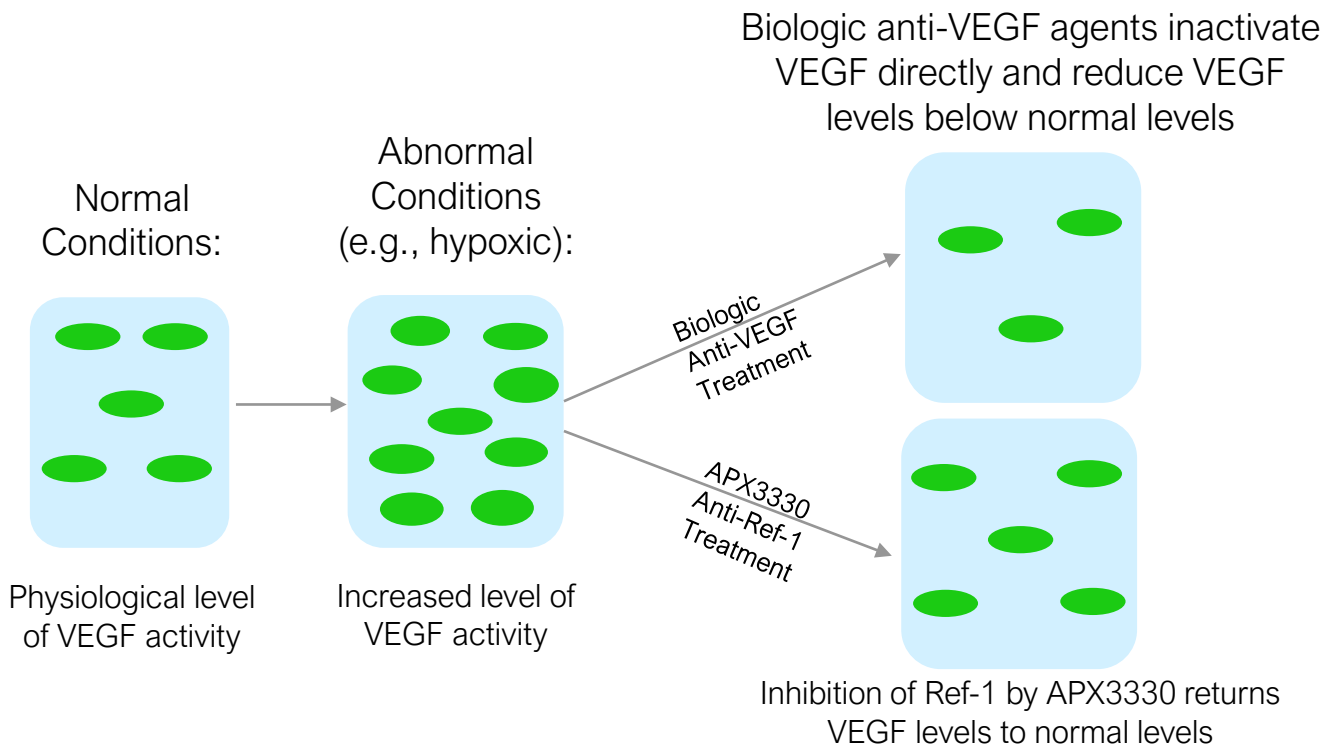
APX3330 increases DNA oxidative repair and neuronal protection



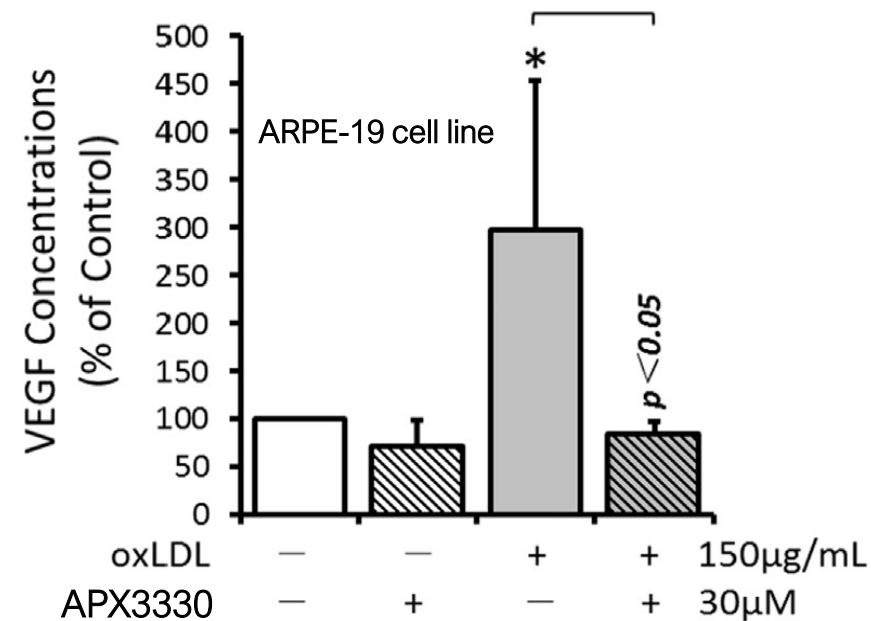
APX3330 enhances Ref-1 endonuclease activity in dorsal root ganglion neurons

APX3330 VEGF Effects in Normal Cells

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



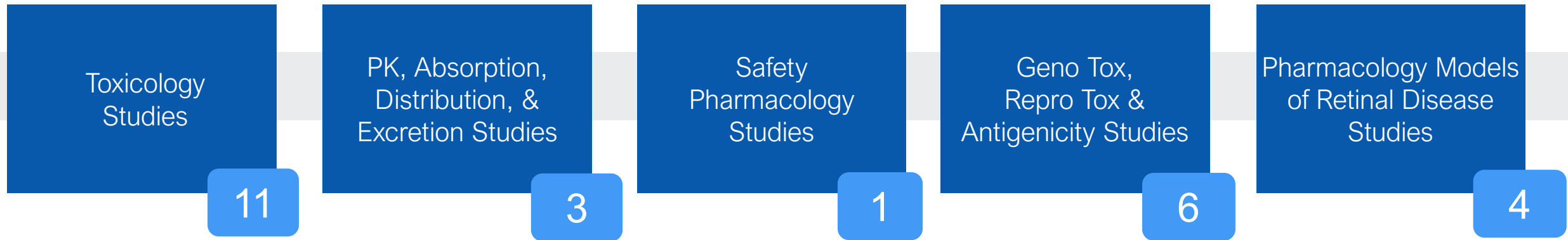
APX3330 prevents VEGF overproduction in ARPE-19 cells



- 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 Preclinical Studies with Favorable Efficacy and Safety



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

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

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Phase 1	
Patient Population	Treatment Groups
Healthy Subjects	APX3330, Placebo
Healthy Subjects	APX3330, Placebo
Healthy Subjects	APX3330
Healthy Subjects	APX3330
Healthy Subjects	APX3330, Placebo

Phase 2 Studies

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Phase 2	
Patient Population	Treatment Groups
Chronic Hep B	APX3330
Chronic Hep C	APX3330
Chronic Hep C	APX3330, Placebo
Acute severe hepatitis	APX3330
Alcoholic hepatitis	APX3330
Cancer (solid tumors)	APX3330

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.

Phase 2 ZETA-1 Trial of Oral AP3330 in Subjects With Diabetic Retinopathy

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

Eligibility Criteria

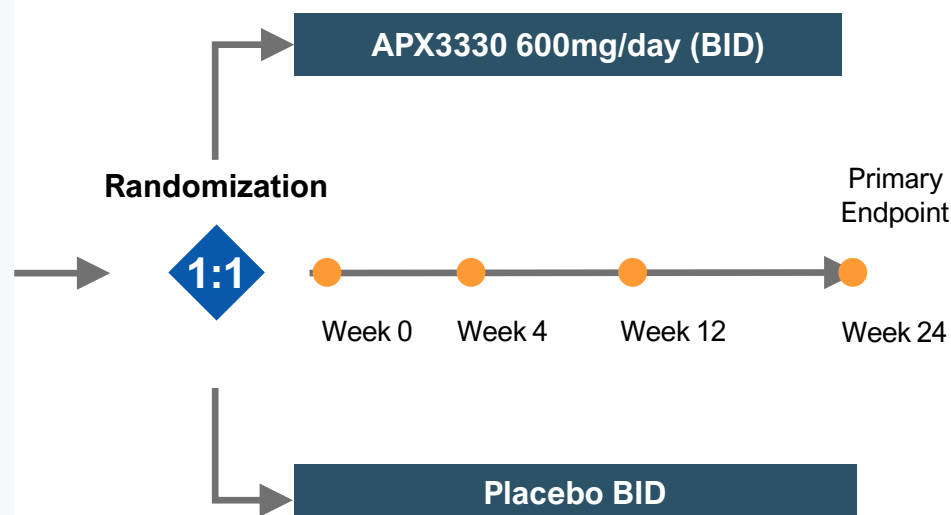
- 25 US sites
- N = 90-100 participants with moderately severe to severe NPDR or mild PDR (DRSS 47, 53, 61)

Key inclusion:

- ≥ 18 years of age
- DRSS 47, 53, or 61
 - Noncentral DME permitted
- ETDRS BCVA ≥ 60 letters (20/63)

Key exclusion:

- OCT CST >320 μm^2
- Center involved DME allowed in fellow eye
- Anti-VEGF within past 6 months³
- HbA1c ≥ 12.0%



Endpoints

Primary:

- % subjects with ≥ 2 step improvement on DRSS (Diabetic Retinopathy Severity Scale¹) at week 24

Secondary:

- DRSS improvement ≥1, ≥2, ≥3, ≥4 study eye, fellow eye, binocular
- DRSS worsening ≥1, ≥2, ≥3, ≥4, study eye, fellow eye, binocular
- Progression to vision threatening complications
- Central subfield thickness (CST)
- Best Corrected Distance Visual Acuity (BCDVA)
- DME fellow eye status
- Safety and tolerability

Exploratory:

- Inflammatory cytokines

103 subjects enrolled (FPFV Apr 2021 to LPLV Aug 2022)
Topline announced in early 2023

1. By Central Reading Center

2. Center-Involved DME in Fellow Eye is Acceptable

3. Includes Systemic or IVT VEGF

www.clinicaltrials.gov (NCT04692688); Eylea® is registered trademark of Regeneron

NPDR = non-proliferative diabetic retinopathy PDR = proliferative diabetic retinopathy

ZETA-1: Treatment Emergent Adverse Events

Oral APX3330 Showed a Favorable Safety and Tolerability Profile Consistent with Prior Trials

	Placebo (n=52)	APX3330 (n=51)
Total AEs	120	91
#of Subjects with AEs	35 (67%)	29 (57%)
Treatment-related AEs	17 (14%)	14 (15%)
Serious AEs	11 (9%)	3 (3%)
Subjects Withdrawals Due to AEs	1 (2%)	2 (4%)
Deaths	1 (2%)	0 (0%)
AEs in >5% of Subjects*		
Diabetic Retinal Edema	5 (10%)	2 (4%)
Diabetic Retinopathy	6 (12%)	1 (2%)
Vitreous detachment	3 (6%)	0 (0%)
Cataract	1 (2%)	3 (6%)
Pruritus	1 (2%)	6 (12%)
Rash	1 (2%)	3 (6%)
COVID-19	5 (10%)	1 (2%)

| Eye disorders |

APX3330 Safety Profile:

- Limited AEs, most mild in severity
 - Pruritis: Mild and resolved without APX3330 dose de-escalation or discontinuation
- AEs similar to or less than placebo
- Few serious treatment-related AEs, all unrelated to study medication
- No ocular AEs other than expected DR progression
 - Lower incidence of clinical DR/DME worsening with APX3330
- **Patients continued routine medications to manage their diabetes comorbidities**

APX3330 SAEs: Dyskinesia, TIA, Chest pain

Placebo SAEs: Vertigo, Asthenia, Multiple organ dysfunction, Bradycardia, CAD, Cholelithiasis, COVID-19 pneumonia, Cellulitis, Respiratory failure, Skin ulcer, Peripheral embolism

AEs → Withdrawal APX3330: Presyncope, Dyspnea; Placebo: DME (both eyes)

*Preferred Term within Organ Class

of Subjects With Treatment Emergent Adverse Events By System Organ Class I

Safety Population

System Organ Class Preferred Term	APX3330 (N=51) n (%)	Placebo (N=52) n (%)	Total (N=103) n (%)
Eye disorders	9 (17.6)	15 (28.8)	24 (23.3)
Diabetic retinal oedema	2 (3.9)	5 (9.6)	7 (6.8)
Diabetic retinopathy	1 (2.0)	6 (11.5)	7 (6.8)
Vitreous haemorrhage	1 (2.0)	2 (3.8)	3 (2.9)
Infections and infestations	8 (15.7)	11 (21.2)	19 (18.4)
Skin and subcutaneous tissue disorders	8 (15.7)	4 (7.7)	12 (11.7)
Pruritus	6 (11.8)	1 (1.9)	7 (6.8)
Rash	3 (5.9)	1 (1.9)	4 (3.9)
Gastrointestinal disorders	6 (11.8)	5 (9.6)	11 (10.7)
Diarrhoea	1 (2.0)	2 (3.8)	3 (2.9)
Nervous system disorders	6 (11.8)	8 (15.4)	14 (13.6)
Investigations	5 (9.8)	5 (9.6)	10 (9.7)
Musculoskeletal and connective tissue disorders	5 (9.8)	2 (3.8)	7 (6.8)
General disorders and administration site conditions	3 (5.9)	3 (5.8)	6 (5.8)

of Subjects With Treatment Emergent Adverse Events By System Organ Class II

Safety Population

System Organ Class Preferred Term	APX3330 (N=51) n (%)	Placebo (N=52) n (%)	Total (N=103) n (%)
Respiratory, thoracic and mediastinal disorders	3 (5.9)	3 (5.8)	6 (5.8)
Metabolism and nutrition disorders	2 (3.9)	3 (5.8)	5 (4.9)
Ear and labyrinth disorders	1 (2.0)	2 (3.8)	3 (2.9)
Immune system disorders	1 (2.0)	0	1 (1.0)
Psychiatric disorders	1 (2.0)	1 (1.9)	2 (1.9)
Renal and urinary disorders	1 (2.0)	1 (1.9)	2 (1.9)
Vascular disorders	1 (2.0)	5 (9.6)	6 (5.8)
Blood and lymphatic system disorders	0	1 (1.9)	1 (1.0)
Cardiac disorders	0	2 (3.8)	2 (1.9)
Hepatobiliary disorders	0	1 (1.9)	1 (1.0)
Injury, poisoning and procedural complications	0	1 (1.9)	1 (1.0)

Summary of Safety and Tolerability

- APX3330 is a first-in-class dual mechanism oral drug that inhibits Ref-1 which reduces VEGF and inflammatory cytokines to normal physiological levels
- Robust pre-clinical evaluation in over 20 studies
- Favorable safety and tolerability in hepatic inflammation and cancer indications
- Safety and tolerability in ZETA-1 trial was consistent with historic safety in hepatic and cancer indications
- Low incidence of overall AEs in APX3330 treated group as well as low incidence of clinical worsening of DR and DME
 - Pruritis was the most common AE which was mild and did not require dose de-escalation or discontinuation of APX3330
- **End-of-Phase 2 meeting is confirmed with FDA for 4Q 2023 to agree on registration endpoint and study parameters for Phase 3**