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

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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

<table>
<thead>
<tr>
<th>Worldwide incidence of diabetes and DR</th>
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<tr>
<td>Diabetes</td>
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<tr>
<td>DR</td>
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Wong, TY et al (2020)
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

**Mechanism of Action – Ref-1 Inhibition**

- **Hypoxia/Ischemia**
  - Ref-1
  - HIF-1α
  - VEGF

- **Inflammation**
  - Ref-1
  - NF-κB
  - TNF-α
  - Chemokines
  - Multiple Inflammatory Effectors

- **Anti-VEGF**
- **DR DME**
- **Steroid**

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

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

Oral APX3330 reduces CNV lesion size

Mouse Laser CNV Model

OCT and histology of CNV lesions

Silva et al, 2021

OCT lesion volume

Silva et al, 2021
APX3330 is orally bioavailable and reaches the retina at therapeutic levels

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

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

Orally administered, radiolabeled APX3330 reaches high levels in rat eye

**Human clinical dose: 300 mg BID**

Established PBPK model predicts APX3330 reaches sufficient human retinal concentrations

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**Phase 1 PK Clinical Data**

**Human Drug Exposure Multiple Times Higher than Mouse Efficacious Levels**

Human Pharmacokinetics of APX3330 at 120 mg/day

- 40 μg/ml Human 120 mg/day
- 2 μg/ml Mice 25 mg/kg

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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
APX3330 was well tolerated in phase 1 and 2 studies

**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**
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

1:1

Week 0 4 12 24

**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

**APX3330 300mg BID**

**Placebo BID**

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