Oral APX3330 treatment reduces L-CNVC lesions in preclinical mouse model and confirms Phase 2 DR/DME clinical dose with sufficient distribution to human retina using PBPK modeling.

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Presenter Disclosure

• I have no actual or potential conflict of interest in relation to this presentation.
APX3330

- Small molecule, first-in-class therapy targeting the APE1/Ref-1 protein
- Oral anti-cancer and anti-retinal disease agent
- Demonstrates pre-clinically, single agent activity against a number of tumors and efficacy in diseases like diabetic retinopathy, diabetic macular edema, wet age-related macular degeneration, and inflammatory bowel disease
- Confirmed safety in over 300 patients in 11 Phase I/II clinical studies
Mechanism Of Action

**Inactive State**
- Inactive, oxidized TFs
  - e.g., NFκB, HIF-1α, STAT3

**Active State**
- Active, reduced TFs
  - e.g., NFκB, HIF-1α, STAT3

Ref-1

APX3330

IL-6, TNFα, and other inflammatory cytokines

NF-κB

HIF1α

VEGF

STAT3

Angiogenesis

Inflammatory cytokines
Purpose

1. To determine the efficacy of oral administration of APX3330 to reduce lesion size in a laser-induced choroidal neovascularization (L-CNV) mouse model;

2. To develop a physiological-based pharmacokinetic (PBPK) model for retinal delivery of APX3330 to confirm dosing for a Phase 2 trial.
Laser-induced CNV Mouse Model

- Female (7-8 w) C57BL/67 mice (n=15) → laser treatment

- APX3330 twice-daily gavages for 2w
  - Group 1: Vehicle (n=5)
  - Group 2: 25 mg/kg (n=5)
  - Group 3: 50 mg/kg (n=5)

- Optical coherence tomography (OCT), fundoscopy, and 3-dimensional quantification of agglutinin stained CNV.
Oral APX3330 Effectively Treats a Laser-Induced CNV Model – OCT Images

A) Representative OCT images of lesions imaged 14 days post-laser. Scale bars = 100 µm.

B) Representative confocal images of agglutinin-stained choroidal flat mounts following enucleation 14 days post-laser.
Oral APX3330 Effectively Treats a Laser-Induced CNV Model – Lesion Volume

**RESULTS**

OCT Lesion Volume

Confocal Lesion Volume

**Results**

***, P=0.0002; ****, P<0.0001
Purpose

1. To determine the efficacy of oral administration of APX3330 to reduce lesion size in a laser-induced choroidal neovascularization (L-CNV) mouse model;

2. To develop a physiological-based pharmacokinetic (PBPK) model for retinal delivery of APX3330 to confirm dosing for a Phase 2 trial.
Building blocks of a PBPK model

Organism properties
- Organ volumes
- Surface areas
- Tissue composition
- Blood flow rates
- Expression levels

Drug properties
- Lipophilicity (logP, logD, logMA)
- Molecular Weight
- pKa/pKb

Drug biological properties
- Fu
- Partition coefficients
- Permeability
- active processes (Km, Vmax, Kd)

Study protocol and formulation properties
- Formulation (empirical or mechanistic dissolution function)
- Administration protocol (dose and dosing regimen)
- Special events (food intake, exercise, EHC)

Source: Kuepfer, CPT:PSP 2016
PBPK Model

- APX3330 physicochemical properties \(\rightarrow\) ADMET Predictor™ 9.5

- Development and validation of a human full PBPK model for plasma concentrations profiles after single oral doses of 60, 180 and 240 mg \(\rightarrow\) GastroPlus™ 9.6

- Simulation for human retinal exposure of different oral posology \(\rightarrow\) OCAT™ model within GastroPlus™ 9.6

Source: SimulationPlus-GastroPlus user guide
PBPK Model Could Predict Plasma Concentration of Oral APX3330

APX3330 180 mg QD

Model Average Fold Error

\[ AFE = 10^{ \frac{1}{\pi} \sum \log \left( \frac{\text{predicted}}{\text{observed}} \right) } = 0.98 \]
PBPK Model Could Predict Retinal Exposure of Oral APX3330

<table>
<thead>
<tr>
<th>Posology</th>
<th>Retinal Predicted $AUC_{0-24h}$</th>
<th>Retinal Predicted $AUC_{0-\infty}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mg TID</td>
<td>30.1 $\mu$g h/mL</td>
<td>13.5 $\mu$g h/mL</td>
</tr>
<tr>
<td>240 mg BID</td>
<td>21.8 $\mu$g h/mL</td>
<td>12.3 $\mu$g h/mL</td>
</tr>
<tr>
<td><strong>300 mg BID</strong></td>
<td><strong>27.4 $\mu$g h/mL</strong></td>
<td><strong>15.4 $\mu$g h/mL</strong></td>
</tr>
<tr>
<td>480 mg QD</td>
<td>22.8 $\mu$g h/mL</td>
<td>16.5 $\mu$g h/mL</td>
</tr>
<tr>
<td>600 mg QD</td>
<td>28.6 $\mu$g h/mL</td>
<td>20.7 $\mu$g h/mL</td>
</tr>
</tbody>
</table>

At 25 mg/kg oral dosing in the mouse L-CNV model, we observed 32-176 ng/g in the retina $\rightarrow$ **0.176 $\mu$g/mL**

Source: SimulationPlus-GastroPlus user guide
Conclusions

- Oral administration of APX3330 safely and effectively reduced neovascularization in an L-CNV preclinical model;

- The PBPK model resulted in important insights into delivery of orally administered APX3330 to the human retina with predicted levels significantly higher than observed and required for efficacy in preclinical studies;

- These findings confirm the 300 mg dose BID for APX3330 for a Phase 2 trial DR/DME trial*.

*registered on clinicaltrials.gov (NCT 04692688) by Sponsor Ocushine Pharma