Efficacy of APX001 in Treatment of *Candida* Endophthalmitis and Hematogenous Meningoencephalitis in the Non-neutropenic Rabbit Model

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Female New Zealand white rabbits weighing 2.8 to 3.6 kg at the time of inoculation were used in this study.

Atraumatic vascular access was established in each rabbit by the surgical placement of a Silastic tunneled central venous catheter.
Organism and Inoculation

- *Candida albicans* - isolate NIH-8621 (ATCC-MYA1237)
- The inoculum was administered intravenously in $1 \times 10^6$ concentration of *C. albicans* blastoconidia in 5 ml
- Antifungal therapy - therapy was initiated 48 h after inoculation and continued throughout the course of the experiments for 7 days
Antifungal therapy was initiated 48 h after inoculation and continued throughout the course of the experiment for 7 days.
Antifungal activity was determined by quantitative clearance of *C. albicans* from tissues
- Cerebrum
- Cerebellum
- Spinal cord
- Cerebrospinal fluid (CSF)
- Meninges
- Vitreous humor

Representative sections were weighed, homogenized, diluted, and plated. CFU/g for each organ and CFU/ml for CSF and vitreous humor were counted after 24 h, and log CFU/g or log CFU/ml was calculated.

(1→3)-β-D-glucan levels in CSF and serum detected by *Limulus* amebocyte lysate assay
Pharmacokinetics of APX001A in Plasma, Tissues, and Fluids in Infected Rabbits

- The plasma pharmacokinetics samples for APX001A were collected from three rabbits in APX25 group, and six rabbits in APX50 and APX100 groups.

- Plasma sampling was performed on day 6 of antifungal therapy. Blood samples were drawn pre-dose and at 1, 2, 4, 6, 8, and 12 h post-dosing.

- Plasma samples for tissue/plasma ratio calculations were obtained on day 7 of antifungal therapy, 1 hour after last dose, at the end of experiment.

- Tissue samples for APX001A concentrations were collected 1 hour after last dose of therapy.

- Concentrations of APX001A were analyzed by LC-MS/MS Method (Triple Quadrupole MS (API 4000), Applied Biosystems, Inc.), by QPS (Newark, DE).
Comparisons between study groups were performed by analysis of variance (ANOVA) with Bonferroni’s correction for multiple comparisons or the Mann-Whitney U-test, as appropriate.
Plasma Pharmacokinetics of APX001A after Multiple Dosing of APX001 PO

APX001A Plasma Mean Concentrations after Multiple Dosing

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>AUC_{o-168} (µg hr/mL)</th>
<th>C_{max} (µg/mL)</th>
<th>CL (mL/hr/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>3.96 ± 0.41</td>
<td>15.78 ± 3.12</td>
<td>1.54 ± 0.34</td>
</tr>
<tr>
<td>50</td>
<td>4.14 ± 1.11</td>
<td>30.79 ± 5.01</td>
<td>1.48 ± 0.28</td>
</tr>
<tr>
<td>100</td>
<td>11.46 ± 1.12</td>
<td>95.91 ± 14.56</td>
<td>0.79 ± 0.18</td>
</tr>
</tbody>
</table>
APX001A Tissue Concentrations and Tissue/Plasma Concentration Ratios

**CSF**

- **Plasma ug/mL**
- **CSF ug/mL**

**Aqueous humor**

- **Plasma ug/mL**
- **Aqueous humor ug/mL**

<table>
<thead>
<tr>
<th>Liquid/Plasma concentrations ratio</th>
<th>APX 25 mg/kg</th>
<th>APX 50 mg/kg</th>
<th>APX 100 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Aqueous humor</td>
<td>0.52</td>
<td>0.25</td>
<td>0.19</td>
</tr>
</tbody>
</table>
APX001 Therapeutic Response in Eye, CSF, and Meninges: CFU Reduction

*\(p<0.05\); †\(<0.01\) in comparison to Untreated Controls
APX001A Tissue Concentrations and Tissue/Plasma Concentration Ratios

<table>
<thead>
<tr>
<th>Tissue/Plasma concentrations ratio</th>
<th>APX 25 mg/kg</th>
<th>APX 50 mg/kg</th>
<th>APX 100 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrum</td>
<td>0.99</td>
<td>0.80</td>
<td>0.98</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>1.03</td>
<td>1.13</td>
<td>1.02</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>1.35</td>
<td>1.13</td>
<td>1.20</td>
</tr>
</tbody>
</table>
APX001 Therapeutic Response in Brain and Spinal Cord: CFU Reduction

*C < 0.05; † < 0.01 in comparison to Untreated Controls
Serum (1→3)-β-D-glucan Levels

*p<0.05; †p<0.01; decrease of serum (1→3)-β-D-glucan levels in rabbits treated with APX25, APX50, APX100, or DAMB in comparison to that of untreated controls

*p<0.05; decrease of CSF (1→3)-β-D-glucan levels in rabbits treated with APX50, APX100, or DAMB in comparison to that of untreated controls
Conclusions

- APX001A demonstrated high level penetration into infected tissues of the eye and brain.

- Rabbits treated with APX25, APX50, and APX100 demonstrated significant dose dependent antifungal activity in treatment of experimental *Candida* endophthalmitis and hematogeneous *Candida* meningoencephalitis.

- These results were comparable in activity to those of rabbits treated with humanized dose of DAmB.

- These findings provide an experimental foundation for APX001 in treatment of *Candida* endophthalmitis and HCME during the course of clinical trials of candidemia and invasive candidiasis.
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