In Vitro and In Vivo Activity of Manogepix, a Novel Antifungal with Activity against Aspergillus and Rare Molds

Hubbard MD, 1 Ibrahim AS, 2 Gebremariam T, 3 Anes DR, 4 Bilen PA, 5 Shaw KJ, 6 Hodges MR

JMI Laboratories, North Liberty, Iowa; 2The Lundquist Institute at Harbor-UCLA Medical Center, Torrance, CA; 3University of Wisconsin, Madison, WI; 4Amplyx Pharmaceuticals, San Diego, CA; 5Hearts Consulting Group, San Diego, CA.

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Introduction

The increasing global emergence of resistance to available classes of antifungal therapy has major clinical implications for the treatment of Aspergillus spp. and rare molds. Despite current antifungal therapy, mortality rates are high and new treatments are needed.

Manogepix (FMGX, APX001A), a novel, first-in-class antifungal agent with broad spectrum of activity, including Aspergillus and rare molds.

Manogepix acts as a hydrogenperoxide mimetic which is rapidly and completely metabolized by systemic aldehyde dehydrogenases to the active moiety, manogepix.

Manogepix targets the highly conserved fungal enzyme Gwt1, which catalyzes a key step in GP-degrading pathways.


Materials and Methods

• The in vitro activity of manogepix and comparator agents was determined against 570 recent (2017–2018) mould isolates collected worldwide in the EDFY surveillance program and included Aspergillus spp., Fusarium spp., unidentified filamentous species complex, Scedosporium spp. and other rare molds.

• Isolate identifications were confirmed using matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF) and molecular methods (as necessary).

• Both minimum inhibitory concentration (MIC) and minimum fungicidal concentration (MFC) values were determined for species where ≤ 10 isolates were available, and median effective concentration (MEC) values were determined for species with ≥10 isolates available.

• Quality control was performed as recommended in CLSI guidelines (CLSI M27-A3 [2017]) and CLSI (2017).

• Recently published (CLSI M60 [2018]) epidemiologic cutoff values (ECVs) were applied to manogepix (see available).

• In the in vitro efficacy of manogepix was evaluated in a highly immunocompromised mouse model of invasive fungal infection (IR).

• Male ICR mice were immunosuppressed with cyclophosphamide (200 mg/kg) and continuous acetate (550 mg/kg) on days 2 and 3, relative to infection.

• Immunocompromised mice were infected with Aspergillus fumigatus, a strain susceptible to FMGX, in an intrahemorrhage chamber by aerosolizing 12 mL of a 3.4 x 10⁶/mL suspension of conidia with a small particle nebulizer driven by compressed air.

• To extend the halflife of FMGX, mice were administered 50 mg of the cytochrome P450 inhibitor 4-aminopyridine (APX) 2 h prior to manogepix administration. Treatment with placebo (isotonic control, FMGX 7.8 mg/kg in 5 mL 0.9% DC, PO) doses which give rise to exposures in mice that are similar to exposures achieved clinically, or posaconazole (30 mg/kg, OD or 30 mg/kg, BD [equivalent to 6 times the humanized dose]) 12 h in postinfection and continued daily.

• To evaluate the consequences of manogepix treatment, conidial burdens were determined by conidial equivalent (CE) using qPCR, white GM, which was determined using the Platelab® Aspergillus panDNA.

• Pharmacokinetic/Pharmacodynamic (PK/PD) target determinations were evaluated.

• As a fungicidal isolates were chosen, including three isolates with Gwt1 mutations and one laboratory isolate with an F41C mutation.

• Dose-response experiments were performed with the use of a fungicidal isolates in the invasive pulmonary aspergillosis model.

• Six dose levels consisting of 5, 10, 24, 64, and 128 mg/kg/3 h were administered by the oral route with the duration of treatment of 9 h. ABT was used in this in vivo study since manogepix was administered every 3 h.

• The PK/PD relationships were examined utilizing the plasma free drug concentrations from pharmacokinetic studies.

• Treatment results and associated PK/PD indices AUC/MIC, Cₘ₉₀/MIC, and T>MIC were modeled to Hill equation and PK/PD target studies.

• Correlation between efficacy and AUC/MIC was analyzed by nonlinear regression PK/PD target analyses.

• Static and ED₅₀ targets were determined.

Results

In vitro evaluation:

• Manogepix demonstrated potent in vitro activity (MIC₅₀ [0.008-0.015 mg/L]) against all Aspergillus spp. isolates included the pan–aminocaproic–transpeptidase and IgGase enzyme complexes.

• A total of 2.6% (9/350) of Aspergillus spp. (MIC₅₀/₉₀, ≥0.008 mg/L) were resistant to voriconazole.

• Manogepix demonstrated notable activity against Fusarium spp. (MIC₅₀ ≤0.015 mg/L), Gibberella fujikuroi (MIC₅₀ ≤0.008 mg/L), and Sordaria spp. (MIC₅₀ ≤0.008 mg/L).

• Non–conjugated humanized doses of manogepix were highly active in vivo against Aspergillus spp.

• The PK/PD target exposure derived should be useful for designing optimized drug-dosing regimens for confirmatory clinical development of this promising antifungal.

Conclusions

• Manogepix demonstrated potent in vitro activity against Aspergillus spp., Fusarium spp., Gibberella fujikuroi species complex, Sordaria spp. and rare mold isolates.

• Manogepix demonstrated potent in vivo efficacy in a highly immunocompromised mouse model of invasive aspergillosis.

• The PK/PD evaluation demonstrated that manogepix has concentration-dependent, in vivo efficacy against Aspergillus spp. resistant, and echinocandin-resistant A fumigatus.

• The AUC/MIC ratios were highly associated with efficacy in vivo.

• The PK/PD target exposure derived should be useful for designing optimized drug-dosing regimens for confirmatory clinical development of this promising antifungal.

• The in vivo data supports the continued clinical evaluation of the novel antifungal agent, manogepix, in the treatment of invasive aspergillosis and rare mold infections.

Table 1: in vitro activity of manogepix and comparators against recent (2017–2018) mould isolates collected worldwide

<table>
<thead>
<tr>
<th>Organism (Site)</th>
<th>Clinical MEC (mg/L)</th>
<th>Clinical MIC (mg/L)</th>
<th>T10</th>
<th>T50</th>
<th>T90</th>
<th>T95</th>
<th>Range</th>
<th>ECV</th>
<th>UNIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillus spp. (570)</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manogepix</td>
<td>0.008 - 0.015</td>
<td>0.008 - 0.015</td>
<td>6</td>
<td>12</td>
<td>24</td>
<td>64</td>
<td>-</td>
<td>0.015</td>
<td>mg/L</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>0.25 - &gt;8</td>
<td>0.25 - &gt;8</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>10</td>
<td>-</td>
<td>0.5</td>
<td>mg/L</td>
</tr>
<tr>
<td>Micafungin</td>
<td>0.015 - 0.06</td>
<td>0.015 - 0.06</td>
<td>6</td>
<td>12</td>
<td>24</td>
<td>64</td>
<td>-</td>
<td>0.06</td>
<td>mg/L</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>0.015 - 2</td>
<td>0.015 - 2</td>
<td>6</td>
<td>12</td>
<td>24</td>
<td>64</td>
<td>-</td>
<td>2</td>
<td>mg/L</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>0.015 - 0.03</td>
<td>0.015 - 0.03</td>
<td>12</td>
<td>30</td>
<td>60</td>
<td>120</td>
<td>-</td>
<td>0.03</td>
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<tr>
<td>Posaconazole</td>
<td>&gt;8 - &gt;8</td>
<td>&gt;8 - &gt;8</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>10</td>
<td>-</td>
<td>&gt;8</td>
<td>mg/L</td>
</tr>
</tbody>
</table>

Figure 1: Manogepix (FMGX) protects mice from IPA

Figure 2: In vivo PK/PD of APX001 against Aspergillus spp.