APX001 a broad spectrum, novel mechanism of action, antifungal agent with potential to treat severe fungal infections

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October, 2017

Dr. Michael Hodges MD, Chief Medical Office, Amplyx Pharmaceuticals, Inc.
Disclosures

• Background
  – Licensed British Medical Doctor, board certified in internal medicine

• Previous positions
  – MRC/INSERM HIV clinical trials
  – Pfizer, Inc. HIV antivirals, azithromycin, fluconazole, voriconazole and anidulafungin
  – Santaris Pharma HCV miravirsen
  – Consultancy antifungal drug development
  – Non-executive director of F2G Ltd.

• Current position
  – Chief Medical Officer for Amplyx Pharmaceuticals FTE
  – Scientific Advisory Boards Exicure Inc. and Arcturus Therapeutics Inc.
Invasive Fungal Infections (IFIs)
High Medical Need Remains

- Almost 3% of US adults are immunosuppressed (CDC data, 2013)
  - 90% of IFIs occur in immunosuppressed individuals
- Over 600,000 cases of target fungal infections annually worldwide

<table>
<thead>
<tr>
<th>Invasive Fungal Infection</th>
<th>Worldwide Incidence</th>
<th>Mortality Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidiasis</td>
<td>&gt;400,000</td>
<td>46-75</td>
</tr>
<tr>
<td>Aspergillosis</td>
<td>&gt;200,000</td>
<td>30-95</td>
</tr>
<tr>
<td>Rare Molds</td>
<td>~20-30,000</td>
<td>30-90</td>
</tr>
</tbody>
</table>

- Increasing incidence of invasive candidiasis and invasive aspergillosis reported in several western countries

www.bccresearch.com;
Stanzani 2007 Therapeutics and Clinical Risk Management
Brown 2012 Science and Translational Medicine
Ramana KV 2013 Am Jrl Inf Dies and Microbiol
Harpaz R 2016 JAMA
Need for new antifungal drugs

Drug resistance

Emerging pathogens

Drug toxicity

High mortality

Novel targets

Improved efficacy

Oral agents

Improved Safety

With permission Jeniel Nett, MD PhD IDWeek 2017
Antifungal Drug Pipeline

- Antifungal Pipeline a Reality Check
- Sertraline
- Tamoxifen
- Cloudbreak molecule
- APX001
- Aminocandins
- NIKKOMYCN Z
- SCY078
- Echinocandins
- Icofungipen
- Sordarins
- Endoplasmic reticulum
- Pdk1 inhibitors (e.g. UCN-01)
- AR-12
- Mohangamide A
- Mohangamide B
- F901318
- Pentamidine
- Icofungipen
- Endoplasmic reticulum
- MGCD290
- Rifampin
- 5-flucytosine
- AR-12
- Mohangamide A
- Mohangamide B
- F901318
- Pentamidine
- Mitochondria
- Stress response
- Calcineurin inhibitors (e.g. tacrolimus)
- HOG pathway inhibitors (e.g. fludioxonil, ambruticins)
- Hsp90 inhibitors (e.g. efungumab and geldanamycin)
- Trehalose inhibitors
- Ergosterol, 1,6-β-glucans, 1,3-β-glucans, UDP-glucose, Chitin, Mannoproteins PMN, 1,3-β-glucan synthase
- Calcineurin inhibitors (e.g. tacrolimus)
- Hsp90 inhibitors (e.g. efungumab and geldanamycin)
- Trehalose inhibitors
- Pdk1 inhibitors (e.g. UCN-01)
Antifungal Drug Pipeline
Drugs that target the cell wall

- Numerous molecules can be attacked by antifungals, including fungus-specific components of the cell wall or cell membrane
- Three classes of approved drug (red)

Courtesy of John Perfect 2017 NRDD
Antifungal Pipeline a Reality Check
APX001 Key Characteristics

- **First in class novel mechanism of action – inhibition of Gwt1**
- Broad spectrum yeasts and molds – including resistant isolates
- Oral & IV formulations – 1 hr infusions
- Excellent PK profile – once day dosing with low variability
- Safe and well tolerated over 14-days in healthy volunteers
- Low DDI liability

Gwt1 GPI-anchored wall transfer protein 1

> 99% plasma protein bound
APX001A Mechanism of Action

- GPI-anchored proteins (e.g. mannoproteins) provide cell wall integrity, are involved in membrane homeostasis, promote adhesion, pathogenicity and immune evasion
- Gwt1 is essential for the conversion of glucosaminyl phosphatidylinositol glucosaminyl(acyl)phosphatidylinositol, an essential/early step in GPI synthesis
- APX001A is a potent inhibitor of fungal Gwt1 and has no activity vs. related mammalian PIG-W protein

Inhibiting GPI Anchor Biosynthesis in Fungi Stresses the Endoplasmic Reticulum and Enhances Virulence
The diameter of yeast-like cells treated with 4X MIC APX001A increases over time.

By 24 hr, Sytox Green stain confirms cell death.
Fungal Cytological Profiling *Candida albicans*

Changes in Cell Wall Content

- Data supports similar changes in cell wall content as those seen with echinocandins, however additional ER stress response is observed following exposure to APX001A
  - Build up of chitin in cell wall, depletion of mannan, failure to bud and enlargement of cells over time
APX001 Key Characteristics

- First in class novel mechanism of action – inhibition of Gwt1
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1 Gwt1 GPI-anchored wall transfer protein 1
In vitro Activity

- APX001A has low MICs against most strains tested, including strains resistant to existing treatments
- APX001A is broadly active against Candida spp. (MIC$_{90}$ ≤0.06 µg/mL)
  - Significant activity vs C. auris (MIC$_{90}$ 0.03 µg/mL) - APX001A is the most microbiologically active drug tested
  - Higher MICs against C. krusei
- APX001A is broadly active against Aspergillus spp. (MEC$_{90}$ ≤0.06 µg/mL)
- APX001A is broadly active against the rare hard-to-treat molds
  - Good activity against Scedosporium spp. and Fusarium spp.
  - Higher MICs against Mucoromycotina
- Activity against resistant organisms (no cross-resistance)
- Synergy *in vitro* and *in vivo*, long PAFE, biofilm prevention
- Low frequency of resistance similar to echinocandins
**In vivo Activity**

- APX001 has demonstrated activity, both survival and/or decreased fungal burden (kidney, lung, spleen and brain) in a number of immunocompromised (5-FU and CPA) and immunocompetent murine animal models of invasive infection\(^1\) including both pulmonary and disseminated models
  - *Candida albicans*, *C. tropicalis*, *C. glabrata*, *C. auris* [5FU & CPA]
  - *Aspergillus fumigatus*, *A. flavus* [5FU]
  - Rare molds including *Fusarium solani*, *Scedosporium prolificans*, *Rhizopus oryzae* [5FU & CPA]
  - *Cryptococcus neoformans* [CPA]
  - *Coccidioides immitis* [immunocompetent]
- Efficacy driven by AUC/MIC

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5-FU 5-Fluorouracil; CPA cyclophosphamide
\(^1\) In addition non invasive VVC and OPC animal models
Candida auris - an Emerging Infection

- Is this a fungal superbug?
  - Often multidrug-resistant
  - Nosocomial transmission leading outbreaks in healthcare settings
  - Echinocandin resistance can occur rapidly whilst on treatment
  - Difficult to eradicate from hospital settings
### APX001A Activity Against C. auris

<table>
<thead>
<tr>
<th></th>
<th>APX001A</th>
<th>5FC</th>
<th>AMB</th>
<th>AFG</th>
<th>CAS</th>
<th>FLC</th>
<th>FLC</th>
<th>ITC</th>
<th>MFG</th>
<th>POSA</th>
<th>VRC</th>
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<tbody>
<tr>
<td>24h</td>
<td>50%</td>
<td>50%</td>
<td>100%</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
</tr>
</tbody>
</table>

**Range**
- APX001A: 0.002-0.063
- 5FC: 0.5-1
- AMB: 2-4
- AFG: 0.125-0.25
- CAS: 0.25-1
- FLC: 1->64
- ITC: 12->64
- MFG: 0.063-1
- POSA: 0.25-2
- VRC: 0.063-2

**MIC50**
- APX001A: 0.008
- 5FC: 0.5
- AMB: 4
- AFG: 0.125
- CAS: 0.5
- FLC: 16
- ITC: >64
- MFG: 0.5
- POSA: 1
- VRC: 0.25

**MIC90**
- APX001A: 0.008
- 5FC: 1
- AMB: 1
- AFG: 0.25
- CAS: 1.0
- FLC: >64
- ITC: >64
- MFG: 1
- POSA: 1
- VRC: 0.5

- **CLSI M27-A3 methodology**
- **C. auris** MIC evaluation (n=16)
  - Diverse panel (Germany, Japan, SK and India)
  - APX001A most active agent MIC\(_{50}\) 10x lower than AFG
Disseminated C. auris Mouse model
Survival

- All treatments significant improvements in survival
- APX001 all 3 dose levels significant improvement in survival vs AFG

Larkin 2017 IDWeek
Evaluation of the In Vitro and In Vivo Antifungal Activity of APX001A/APX001 Against Candida auris
Disseminated C. auris Mouse model
CFU 48-hrs

- Initiated study examining tissue burden after 48 hrs
  - Reduction in kidney and lung burden equivalent to AFG observed
  - Significant reduction in brain CFU for APX (AFG no effect)
APX001 Key Characteristics

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- Excellent PK profile – once day dosing with low variability
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- Low DDI liability

1 Gwt1 GPI-anchored wall transfer protein 1
**APX001 Early Clinical Development Plan**

**Phase 1 program**

<table>
<thead>
<tr>
<th>APX001</th>
<th>Phase</th>
<th>Population &amp; Outcomes</th>
<th>n</th>
<th>Route</th>
<th>Comparator</th>
<th>Objective</th>
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<tbody>
<tr>
<td>101</td>
<td>1</td>
<td>Healthy Volunteers</td>
<td>120</td>
<td>IV</td>
<td>Placebo</td>
<td>Safety and PK</td>
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<tr>
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<td>• SAD and MAD</td>
<td></td>
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<td></td>
<td></td>
<td>• Decreased infusion times</td>
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<td></td>
<td></td>
<td>• Loading dose</td>
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</tr>
<tr>
<td>102</td>
<td>1</td>
<td>Healthy Volunteers</td>
<td>46</td>
<td>oral</td>
<td>Placebo</td>
<td>Safety and PK</td>
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<tr>
<td></td>
<td></td>
<td>• SAD and MAD</td>
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<td></td>
<td></td>
<td>• Food effect</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>• DDI “Cocktail” cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>103</td>
<td>1b</td>
<td>AML patients</td>
<td>20</td>
<td>IV &amp;</td>
<td>none</td>
<td>Safety and PK</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Multiple doses in target patient</td>
<td></td>
<td>oral</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>population</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• APX001 in combo with SOC chemo &amp;</td>
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<tr>
<td></td>
<td></td>
<td>azole prophylaxis</td>
<td></td>
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<td></td>
<td></td>
<td>• Supports APX001 low DDI liability</td>
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</tbody>
</table>
APX001-101 IV Phase 1 Study schematic

- Sentinel dosing was included in all cohorts
- The Safety Review Committee (SRC) evaluated sentinel subjects’ safety data prior to continued dosing in each cohort
- The SRC evaluated safety and PK data prior to dose escalations

**Double-blind, Placebo-controlled, Single Ascending Dose**
- IV Dose 1 - IV Dose 2
- IV Dose 3 - IV Dose 4
- IV Dose 5 - IV Dose 6
- Cohorts 1-6: n=8/cohort

**Double-blind, Placebo-controlled, Multiple Ascending Dose**
- IV Dose 1
- IV Dose 2
- IV Dose 3
- IV Dose 4
- Cohorts 7-10: n=8/cohort

**Double-blind, Placebo-controlled, Single Dose, Decreased Infusion Times**
- Dose 1, 3-hr IV
- Dose 1, 2-hr IV
- Dose 1, 1-hr IV
- Dose 1, 0.5-hr IV
- Cohorts 11a-11d: n=8/cohort

**Double-blind, Placebo-controlled, Loading Dose**
- Cohort 12: n=8
- IV Load
- IV Maintenance

SAD 10-350 mg
MAD 50-600 mg od x 14d
SD 1000 mg
Load 1000 mg bid -> 600 mg od x7d
APX001-101 IV Phase 1
SAD PK

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>C max (µg/mL)</th>
<th>AUC (0-24) (µg.hr/mL)</th>
<th>AUC (inf) (µg.hr/mL)</th>
<th>T ½ (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.16</td>
<td>1.54</td>
<td>4.05</td>
<td>39.2</td>
</tr>
<tr>
<td>30</td>
<td>0.48</td>
<td>4.33</td>
<td>14.13</td>
<td>50.8</td>
</tr>
<tr>
<td>100</td>
<td>1.44</td>
<td>14.36</td>
<td>50.37</td>
<td>52.5</td>
</tr>
<tr>
<td>200</td>
<td>2.41</td>
<td>20.75</td>
<td>83.17</td>
<td>67.0</td>
</tr>
<tr>
<td>275</td>
<td>3.96</td>
<td>37.07</td>
<td>119.74</td>
<td>48.6</td>
</tr>
<tr>
<td>350</td>
<td>4.33</td>
<td>38.17</td>
<td>173.42</td>
<td>74.9</td>
</tr>
</tbody>
</table>
• 50, 150, 300 and 600 mg PO x 14 days
• AUCs\(_{(0-24)}\) attain current targets for \textit{Candida}, \textit{Aspergillus}, \textit{Fusarium}, \textit{Scedosporium} and Mucorales
**APX001-101 IV Phase 1**

**Loading Dose PK**

- Target AUC for efficacy achieved on Day 1 using a well tolerated loading dose regimen
  - **Day 1**: 2 x 1000 mg, 2-hr infusion AM & PM
  - **Day 2 to 7**: 600 mg, 1-hr infusion AM only

---

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>1,000 mg / 2 hr at 0 &amp; 9 hr</th>
<th>600 mg / 1 hr QD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 4</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>11.0 (6)</td>
<td>1.00 (5)</td>
</tr>
<tr>
<td>AUC(0-24) (hr×ng/mL)</td>
<td>[11.0 – 11.1]</td>
<td>[1.00 – 1.00]</td>
</tr>
<tr>
<td>λz (1/hr)</td>
<td>‑</td>
<td>‑</td>
</tr>
<tr>
<td>t½ (hr)</td>
<td>‑</td>
<td>‑</td>
</tr>
<tr>
<td>CL</td>
<td>‑</td>
<td>‑</td>
</tr>
<tr>
<td>(mL/hr)</td>
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<tr>
<td>(mL/hr/kg)</td>
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<td>‑</td>
</tr>
<tr>
<td>Vz</td>
<td>‑</td>
<td>‑</td>
</tr>
<tr>
<td>(L)</td>
<td>‑</td>
<td>‑</td>
</tr>
<tr>
<td>(L/kg)</td>
<td>‑</td>
<td>‑</td>
</tr>
</tbody>
</table>

*Geometric mean [geometric %CV] (N) except Tmax for which the median (N) [Range] is reported.
APX001-102 Oral Phase 1
Study schematic

- Sentinel dosing was included in all cohorts
- The Safety Review Committee (SRC) evaluated sentinel subjects’ safety data prior to continued dosing in each cohort
- The SRC evaluated safety and PK data prior to dose escalations
**APX001-102 Oral Phase 1 SAD PK**

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Administration Route</th>
<th>PK Parameters: APX001A</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C-max (µg/mL)</td>
</tr>
<tr>
<td>200</td>
<td>IV 3hr</td>
<td>2.64</td>
</tr>
<tr>
<td>100</td>
<td>PO</td>
<td>1.30</td>
</tr>
<tr>
<td>300</td>
<td>PO</td>
<td>3.75</td>
</tr>
<tr>
<td>400</td>
<td>PO</td>
<td>4.25</td>
</tr>
<tr>
<td>500</td>
<td>PO</td>
<td>6.53</td>
</tr>
</tbody>
</table>

Hodges 2017 IDWeek
Phase 1 Study to Assess Safety, Tolerability and PK of Single and Multiple Oral Doses of APX001 and to Investigate the Effect of Food on APX001A Bioavailability
APX001-102 Oral Phase 1
Food Effect

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Period</th>
<th>C-max (µg/mL)</th>
<th>AUC(0-24) (hr.µg/mL)</th>
<th>AUC(Inf) (hr.µg/mL)</th>
<th>T ½ (hr)</th>
<th>T-max (hr)</th>
<th>F (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>PO fasted</td>
<td>4.25</td>
<td>30.18</td>
<td>175.1</td>
<td>67.2</td>
<td>2.5</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>400</td>
<td>PO fed</td>
<td>4.52</td>
<td>32.33</td>
<td>190.0</td>
<td>67.6</td>
<td>3.78</td>
<td>&gt;90%</td>
</tr>
</tbody>
</table>

Mean plasma concentrations 400 mg PO under fasted and fed conditions
APX001-102 Oral Phase 1
MAD PK

- 500 mg, 1000 mg tablets and 500 mg oral solution x 14 days
- AUCs\(_{(0-24)}\) attain current targets for *Candida, Aspergillus, Fusarium, Scedosporium* and Mucorales

Hodges 2017 IDWeek
Phase 1 Study to Assess Safety, Tolerability and PK of Single and Multiple Oral Doses of APX001 and to Investigate the Effect of Food on APX001A Bioavailability
Phase 1 Studies Summary
Safety and PK Profile

- APX001 IV 1-hr infusion and oral 14-days safe, well tolerated and exceeded target exposures for efficacy against *Candida*, *Aspergillus* and the rare molds
  - No DLTs and the MTD was not determined/reached in these studies i.e. we could have dose escalated further
- Loading dose achieves target AUCs within 24 hrs
- Oral bioavailability 90% “switch with confidence”
- PK linear, dose proportional with low variability
- Half-life ~2 days, no food effect, no clinically significant DDI data interactions
### Defining the Medical Need

**High unmet medical need populations**

<table>
<thead>
<tr>
<th>Infection</th>
<th>Unmet Need</th>
<th>1st Line Treatment</th>
<th>Current Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive Mucor</td>
<td>+++</td>
<td>Azoles or AmB 1st line</td>
<td>Limited efficacious options, resistance, toxicity and high mortality</td>
</tr>
<tr>
<td>Invasive Fusarium</td>
<td>+++</td>
<td>Azoles 1st line: need for better tolerated drug with no DDIs</td>
<td>Emerging resistance, and high mortality</td>
</tr>
<tr>
<td>Invasive Scedosporium</td>
<td>+++</td>
<td>Candins 1st line: need for IV/Oral option</td>
<td></td>
</tr>
<tr>
<td>Invasive Aspergilosis</td>
<td>++</td>
<td>No 1st line treatment; Azoles are contraindicated</td>
<td></td>
</tr>
<tr>
<td>Invasive Candidiasis</td>
<td>++</td>
<td>No 1st line treatment; Azoles are contraindicated</td>
<td></td>
</tr>
<tr>
<td>Prophylaxis w/Azole contraindication e.g. ALL</td>
<td>++</td>
<td>No 1st line treatment; Azoles are contraindicated</td>
<td></td>
</tr>
</tbody>
</table>
**APX001-201 Phase 2 Candidemia**

<table>
<thead>
<tr>
<th><strong>APX001-201 Candidemia</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Objectives</strong></td>
</tr>
<tr>
<td><strong>Design</strong></td>
</tr>
<tr>
<td><strong>Patients</strong></td>
</tr>
<tr>
<td><strong>Regimen</strong></td>
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<tr>
<td><strong>Primary endpoint</strong></td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
</tr>
<tr>
<td><strong>Countries</strong></td>
</tr>
</tbody>
</table>

- Proof of concept in Candidemia
- Patients where there is a potential advantage of APX001 over SOC e.g. resistance, early switch to oral, safety/toleration
APX001 - Summary

• Broad spectrum activity with IV & oral formulations
  – Once-daily first line monotherapy (potential for combination)
  – Potential to treat established IFIs plus preemptive and prophylaxis

• Excellent Phase 1 safety and PK profile
  – Target AUCs achieved with no clinically significant safety signals

• Conduct trials in high unmet medical need populations
  – Immunosuppressed patients with hematologic malignancies with invasive fungal infections
  – Resistant fungal pathogens
  – Populations where standard of care may not be appropriate
APX001 Key Characteristics

- First in class novel mechanism of action – inhibition of Gwt1
- Broad spectrum yeasts and molds – including resistant isolates
- Oral & IV formulations – 1 hr infusions
- Excellent PK profile – once day dosing with low variability
- Safe and well tolerated over 14-days in healthy volunteers
- Low DDI liability

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<tr>
<td>Invasive Fusarium</td>
<td>+++</td>
<td>Azoles 1st line: need better tolerated &amp; no DDIs</td>
<td>Emerging resistance, and high mortality</td>
</tr>
<tr>
<td>Invasive Scedosporium</td>
<td>+++</td>
<td>Candins 1st line: need for IV/Oral option</td>
<td></td>
</tr>
<tr>
<td>Invasive Aspergilosis</td>
<td>++</td>
<td>No 1st line treatment; Azoles problematic</td>
<td>Significant breakthrough fungal infections</td>
</tr>
<tr>
<td>Invasive Candidiasis</td>
<td>++</td>
<td>No 1st line treatment; Azoles problematic</td>
<td></td>
</tr>
<tr>
<td>Prophylaxis w/Azole contraindication e.g. ALL</td>
<td>++</td>
<td>No 1st line treatment; Azoles problematic</td>
<td></td>
</tr>
</tbody>
</table>

1 Gwt1 GPI-anchored wall transfer protein 1
APX001A

C. krusei

- Decrease in colony size with increasing APX001A concentration
- 50% growth inhibition in microtiter at 16 µg/mL
**In vivo Animal Model Data**

*Candida, Aspergillus*

Disseminated Fluconazole-Resistant *C. albicans*

![Graph showing survival over days after infection for different APX001 dosages and VRCZ 10 mg/kg.](image)

- **Neutropenic model:** APX001A PO TID, VRCZ PO TID, 3 days

Pulmonary *A. fumigatus*

![Graph showing survival over days after infection for different APX001 dosages.](image)

- **Neutropenic model:** APX001 IP TID for 6 days

Hata et al. AAC 2011, ICAAC 2011 F1-1377
In vivo Animal Model Data
Scedosporium and Fusarium

Disseminated *Fusarium solani*

Pulmonary *Scedosporium prolificans*

**Neutropenic model:**
APX001 IP TID, L-AMB IP QD for 5 days

Hata et al. *ICAAC 2011* F1-1377
Hata et al. *unpublished. Study report W-20160050*
Efficacy of APX001 antifungal against Pulmonary Mucormycosis: *Rhizopus delemar*

- APX001 (oral) BID vs LAmB (IV) QD

**Survival**

*P <0.05 vs. placebo; **P <0.03 vs. placebo, 40 or 120 mg/kg dose

**Lung CFU**

*P <0.05 vs. placebo

**Brain CFU**

*P <0.05 vs. placebo; **P <0.05 vs all other treatment

*Rhizopus delemar*

**MIC (μg/mL)**

- APX001A 0.25
- PSCZ 1
- AMB (0.25)
Efficacy of APX001
Cryptococcus neoformans Disseminated Infection Model

- APX001 mono and combination treatment reduced brain & lung CFUs
  - APX001 MTD: mice tolerated BID PO dosing of 390mg/kg (600 mg/kg/day APX001A) for 3 days (no observable adverse effects, no weight loss)
  - C. neoformans strain H99 via tail vein injection (MIC 1 µg/mL)
  - Treatment starting 1 hr of infection for 6 days, sacrifice on day 7; assess brain and lung CFU

\[ \text{AVG Log}_{10} \text{CFU/g} \]

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Brain</th>
<th>Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>8</td>
<td>6</td>
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<tr>
<td>APX001 390 mg/kg PO TID</td>
<td><strong>7</strong></td>
<td><strong>5</strong></td>
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<tr>
<td>FCZ 80 mg/kg IP QD</td>
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<td><strong>5</strong></td>
</tr>
<tr>
<td>APX+FCN</td>
<td><strong>7</strong></td>
<td><strong>5</strong></td>
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</tbody>
</table>

*P < 0.05
** P < 0.0001
Act was designed to provide pharmaceutical and biotechnology companies with incentives to develop new innovative antibiotics for the treatment of life-threatening infectious diseases caused by drug resistant pathogens

- Pathogens are identified as qualified infectious disease product (QIDP)
- Five years of exclusivity in addition to Hatch-Waxman, orphan drug, or pediatric exclusivity for a total of 12.5 years
- Fast-track status and priority review of designated products
- Four fungal pathogens are currently listed:
  - Aspergillus spp.
  - Candida spp.
  - Coccidioides spp.
  - Cryptococcus spp.
Bacterial Cytological Profiling

*C. albicans* – DAPI (DNA, blue) and FM 4-64 (membranes, red) 24 hr drug exposure
# APX001-101 Safety

## APX001-101 Most Frequent Treatment Emergent Adverse Events N=120

<table>
<thead>
<tr>
<th>Adverse Event System Organ Class Preferred Term</th>
<th>Single Dose 3-hr IV</th>
<th>Single Dose, 2 – 0.5-hr IV</th>
<th>Multiple Dose 3-hr IV</th>
<th>Loading Dose 1000 mg BID 2-hr IV Day 1, 600 mg QD 1-hr IV Days 2-7</th>
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</thead>
<tbody>
<tr>
<td>Placebo N=12</td>
<td>Placebo N=8</td>
<td>1000 mg 2 hr IV N=6</td>
<td>1000 mg 0.5 hr IV N=6</td>
<td>Placebo N=8</td>
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<tr>
<td>10-1000 mg N=42</td>
<td>1000 mg 1hr IV N=6</td>
<td>1000 mg 0.5 hr IV N=6</td>
<td></td>
<td>50-600 mg N=24</td>
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<tr>
<td><strong>n</strong></td>
<td><strong>%</strong></td>
<td><strong>n</strong></td>
<td><strong>%</strong></td>
<td><strong>n</strong></td>
</tr>
<tr>
<td>Headache</td>
<td>1 8%</td>
<td>5 83%</td>
<td>4 67%</td>
<td>1 17%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0 0%</td>
<td>2 33%</td>
<td>2 33%</td>
<td>5 83%</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 8%</td>
<td>2 25%</td>
<td>2 33%</td>
<td>2 33%</td>
</tr>
<tr>
<td>Vomitting</td>
<td>0 0%</td>
<td>0 0%</td>
<td>0 0%</td>
<td>0 0%</td>
</tr>
<tr>
<td>General Disorders †</td>
<td>Fatigue</td>
<td>2 17%</td>
<td>0 0%</td>
<td>2 33%</td>
</tr>
</tbody>
</table>

In the multiple-dose cohorts, adverse events AEs related to the site of infusion were reported by subjects in both placebo and APX001 groups. In the pooled multiple-dose placebo group, 80% of subjects reported AEs related to the site of infusion. In the pooled multiple-dose APX001 group, 67% of subjects reported AEs related to the site of infusion. These adverse events were classified by the investigator as not or unlikely related to study drug.

- APX001 safe and well tolerated – no DLTs and the MTD not reached
- AEs were mostly mild, transient, resolved with out intervention and did not cause subject to stop dosing
## APX001-102 Safety

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo N=2</th>
<th>100 - 500 mg N=6</th>
<th>Placebo N=2</th>
<th>400 mg Fasted N=8</th>
<th>400 mg Fed N=8</th>
<th>Placebo N=4</th>
<th>500 &amp; 1000 mg N=12</th>
<th>APX001 500 mg N=12</th>
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<tbody>
<tr>
<td>System Organ Class Preferred Term</td>
<td>Single Dose</td>
<td>Single Dose, Fasted: Fed</td>
<td>Multiple Dose</td>
<td>Oral Solution</td>
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<tr>
<td>CNS Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
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<td>1</td>
<td>17%</td>
<td>4</td>
<td>50%</td>
<td>2</td>
<td>25%</td>
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<tr>
<td>Dizziness</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
<td>1</td>
<td>13%</td>
<td>1</td>
<td>13%</td>
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<tr>
<td>GI Disorders</td>
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<tr>
<td>Nausea</td>
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<td>0%</td>
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<td>0%</td>
<td>5</td>
<td>63%</td>
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<tr>
<td>Vomitting</td>
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<td>0%</td>
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<td>0%</td>
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<tr>
<td>General Disorders</td>
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<td>0%</td>
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<td>0%</td>
<td>0</td>
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</tr>
</tbody>
</table>

- APX001 safe and well tolerated – no DLTs and the MTD not reached
- AEs were mostly mild, transient, resolved with out intervention and did not cause subject to stop dosing
APX001-101 IV Phase 1
Objectives

- First-In-Human, randomized, double-blind, placebo-controlled single ascending dose (SAD) and multiple ascending dose (MAD) escalation study in healthy volunteers
- Different dosing regimens were also evaluated
  - Decreased infusion times
  - Loading dose
- Objectives included
  - evaluation of safety, tolerability, and PK of single and multiple doses of APX001 administered by intravenous (IV) infusion in healthy volunteers
  - exploration of APX001 dose and dose regimen required to attain APX001A target plasma exposures (AUC$_{24}$) required for clinical efficacy against *Candida*, *Aspergillus* and the hard-to-treat rare molds (*Scedosporium*, *Fusarium* and Mucorales) IFIs
APX001-102 Oral Phase 1
Objectives

• Double-blind, placebo-controlled, randomized study in healthy volunteers

• Objectives included
  – evaluation of safety, tolerability, PK of single and multiple doses of APX001
  – Assessment of bioavailability of single doses of APX001 administered IV and orally
  – determine the effect of food on the PK of APX001 and APX001A following a single oral dose of administration APX001
  – evaluate the effect, if any, of APX001 on the PK of CYP isoenzyme substrates following repeated oral administration of APX001
Phase 1 - PK Profile

- Pharmacokinetic parameters are linear and dose proportional
- Low variability in PK parameters between patients
- Half-life ~2 days
- Oral bioavailability ~90%
- No food effect
- No clinically significant DDI data interactions
- Target exposures for efficacy against *Candida* and *Aspergillus* as well as the high MIC pathogens exceeded at doses that are safe and well tolerated
- After a single dose drug levels were above the MIC of *Candida* and *Aspergillus* for one week
- A twice daily loading dose achieves target exposure for efficacy against *Candida* and *Aspergillus* as well as the high MIC pathogens within 24 hours
Phase 1 – Safety Profile

- All single and multiple IV 3-hr infusions and oral doses of APX001 were well tolerated
  - Most were mild and did not require treatment
- Faster infusions (SD 0.5 hours and MD 1-hour) also well tolerated
- Loading dose 1000 mg over 2-hr infusions twice daily well tolerated
- There were no severe AE or SAEs reported and there were no withdrawals due to treatment related AEs
- No AEs or laboratory safety tests results met any of the *a priori* rules that prevented dose escalation
- No DLTs were observed and the MTD was not determined/reached in these studies
  - We could have dose escalated further
### APX001A Activity Against C. auris

- **C. auris** MIC evaluation (n=16)
  - Diverse panel (worldwide isolation)

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<thead>
<tr>
<th>C. auris Strain #</th>
<th>APX001A</th>
<th>5FC</th>
<th>AMB</th>
<th>ANID</th>
<th>CAS</th>
<th>MICA</th>
<th>FLU</th>
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