Rezafungin PK/PD in a Mouse Model of *Pneumocystis* Pneumonia

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Rezafungin

A Better Echinocandin
A Better Antifungal

- Increased stability
  - Reduced toxic degradation products
  - Prolonged PK half-life; higher “front-loaded” peak with less frequent dosing

Rezafungin is currently in Phase 3 Treatment and Phase 3 Prophylaxis is Coming Soon

Treatment of Candidemia and Invasive Candidiasis

Up to 4 weeks: 400 mg rezafungin in Week 1, followed by 200 mg once-weekly (QW)

Versus

Once-daily (QD) caspofungin

Prevention of Invasive Fungal Infections, including *Candida*, *Aspergillus*, and *Pneumocystis*

13 weeks: 400 mg rezafungin in Week 1, followed by 200 mg QW

Versus QD standard of care azole: fluconazole w/ optional posaconazole (+GVHD)

AND

QD trimethoprim sulfamethoxazole (TMP/SMX)

Novel Echinocandin

Novel Prophylaxis: One drug for all antifungal including *Pneumocystis*
Pneumocystis Prophylaxis Mouse Model

Infection:
- 2 x 10⁶/50 μl, P. murina
- Intra-nasally (2d post-i.s.)

Immunosuppression:
- Dexamethasone (4 μg/L) in acidified drinking water (sulfuric acid; 1mL/L); i.s. continued through 6 wk

Treatment:
- 10% DMSO/1% Tween/PBS IP/mg/kg = Negative Control
- 6 wk

Microscopic enumeration:
- log transformed, Kruskall-Wallis, Dunn’s post test for multiple comparisons (GraphPadPrismv.6).

Extract lungs
Homogenize
Mince

<table>
<thead>
<tr>
<th>Grp</th>
<th>Drug</th>
<th>Dose</th>
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<tbody>
<tr>
<td>1</td>
<td>Neg. control</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>RZF</td>
<td>20 mg/kg 3x/wk</td>
</tr>
<tr>
<td>3</td>
<td>RZF</td>
<td>20 mg/kg 1x/wk</td>
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<tr>
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<td>7</td>
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<tr>
<td>8</td>
<td>TMP/SMX</td>
<td>50/250 mg/kg 3x/wk</td>
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</tbody>
</table>

10 animals in each group

RZF = Rezafungin

Cushion & Ashbaugh ASH 2016
Univ. of Cincinnati, Cincinnati VAMC, CERV
Rezafungin Efficacy in Pneumocystis Prophylaxis Mouse Model
Equivalent Efficacy to TMP/SMX Demonstrated

- Cysts /Asci containing 1,3-β-D-glucan synthase- (R panels) are more sensitive to rezafungin
- Formation of Nuclei (L panels) reduced to a lesser extent
- Efficacy comparable to TMP/SMX treatment dose (50/250 mg/kg) at doses much lower than required for Candida or Aspergillus models
- Selected least sensitive (nuclei) data for PK/PD analysis

Study 2 Included PK Study in Infected Animals

- Blood samples for plasma collection from male *Pneumocystis murina*-infected C3H/HeN mice; 3/time point/dose (via cardiac puncture) at 1, 3, 6, 12, 24, 48, and 72 hours following single intraperitoneal (IP) dose (0.5 or 5 mg/kg)
- Analyzed by liquid chromatography with tandem mass spectrometric detection (LC-MS/MS)
- PK and PK/PD using Phoenix WinNonlin and Prism
  - 2-compartment modeling with simulation of various dosing regimens, eg 5 mg/kg 1x, 2x, or 7x/wk

- Once-weekly
- Twice-weekly
- Daily

- Calculated PK parameters were fit to individual and mean PD data from study 1 and 2, and combined
Rezafungin PK/PD in *Pneumocystis* Prophylaxis Mouse Model

AUC and Dose response curves versus nuclei were similar due to linear kinetics and low variability of the drug.
Trough concentrations selected for determining antifungal dose requirements for prophylaxis [note: minimum dose from *Aspergillus* study results*]

- Both studies showed similar concentration response curves although control growth varied by ~ 1-Log
- Evaluation of apparent outliers provided insights on efficacy and its relationship to the shape of the exposure curve

* Flanagan et al, EBMT 2019
Rezafungin PK/PD in *Pneumocystis* Prophylaxis Mouse Model Trough Concentrations

- Within studies, at similar or higher trough, lower efficacy was observed
- Drivers of efficacy: higher Cmax and Dose/AUC
- Trough remains important, but as seen in dose fractionation study “exposure shape matters”*
  - Efficacy was greater with front-loaded exposure from a single dose VS. the same dose divided into multiple, repeated administrations
- Clinical doses of RZF are once weekly

*Lakota et al AAC 2017*
Key Results and Conclusions

• Dosing with higher doses/ less frequently appears to be beneficial for prophylaxis of *Pneumocystis* infections, as has been demonstrated for treatment in mouse model of disseminated candidiasis.

• Once-weekly doses below 50 mg in humans are expected to be efficacious for prevention of *Pneumocystis* infections.

• These studies give confidence that prevention of *Pneumocystis* infections (in addition to *Candida* and *Aspergillus*) can be included with a single antifungal agent in upcoming Phase 3 rezafungin prophylaxis trial with 400 mg first dose, followed by 200 mg once weekly.
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