Analysis of Efficacy from STRIVE Phase 2 Trial of Rezafungin Treatment of Candidemia and/or Invasive Candidiasis: Outcomes During Initial Days of Treatment

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Treatment of Candidemia
‘Hit Early, Hit Hard’

• Hit Early
  – Delayed treatment predicts mortality (OR=1.42, \( p<0.05 \))\(^1\)

• Hit Hard
  – Guidelines recommend 1st-line treatment with echinocandins\(^2,3\)
  – Echinocandins significantly decrease mortality (27% vs 36% for azole- or polyene-based regimens; \( p<0.0001 \))\(^4\)

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• Is This Enough?\(^5,6\)
  – Current doses defined before modern PK/PD era
  – Increasing echinocandin MICs (\( FKS \) mutations)
  – Evidence of inadequate drug exposure in critically ill, moderate-severe hepatic impairment, obesity, ECMO, burn

\(^1\) Ostrosky-Zeichner, et al. *Med Mycology* 2011;49
\(^3\) Cornely, et al. *Clin Microbio Infect* 2012;18
\(^4\) Andes, et al. *Clin Infect Dis* 2012;54
\(^5\) Pea and Lewis. *J Antimicrob Chemother* 2018;73.
Front-Loading and Exposure Shape for Antifungal Efficacy

High drug exposure early in therapy...

...greater fungal killing vs lower exposures repeated over time

Simulated dose fractionation of rezafungin in healthy mice, total dose 2 mg/kg

Fungal burden in neutropenic mice following *Candida albicans* infection and 2 mg/kg rezafungin

**Trial Design and Subanalysis**

**mITT N=183**

**REZAFUNGIN once-weekly**
400/400 mg (N=76) or 400/200 mg (N=46)

**CASPOFUNGIN once-daily**
70/50 mg (N=61) with optional oral Fluco step-down 800/400 mg

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**Primary endpoint:**
Overall Response (Mycological & clinical response)

**Overall Response (Mycological & clinical response)**

**Mycological and clinical response (IC only)**
All cause mortality

**Mycological and clinical response**

**End of Follow Up Period**

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**Subanalysis of Efficacy During Initial Days of Treatment in Patients with Candidemia**

- Time to negative blood culture
- % of patients with negative blood culture at 24 and 48 hours
- Outcomes at Day 5
  - Mycological cure
  - Overall success

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mITT: microbiological intent-to-treat (all randomized subjects who receive any amount of study drug who had documented *Candida* infection

**Time to Negative Blood Culture**

**mITT:** All randomized patients who received study drug and had documented *Candida* infection

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Pooled rezafungin vs Caspofungin

\[ p=0.0016 \text{ posthoc log-rank test} \]

- Rezafungin efficacy early in treatment course suggests clinical effect of high, front-loaded plasma drug exposure
**Time to Negative Blood Culture**

**mITT:** All randomized patients who received study drug and had documented *Candida* infection

**mITT2:** Patients in mITT with positive blood culture within 12h before and 72h after enrollment

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- Rezafungin efficacy early in treatment course suggests clinical effect of high, front-loaded plasma drug exposure

- More pronounced effect in mITT2 suggests patients with infection at the time of treatment initiation may be more likely to benefit from potential clinical effect of front-loaded exposure

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Pooled rezafungin vs Caspofungin

\[ p<0.0001 \text{ posthoc log-rank test} \]
Efficacy In Initial Days of Treatment
Patients with Candidemia Only

mITT
All randomized patients who received study drug and had documented Candida infection

Efficacy In Initial Days of Treatment
Patients with Candidemia Only

Day 1
Negative Blood Culture
At 24 hours
74.7%
84.5%
Percent of Patients (n/N)
Pooled Rezafungin (71/96) Caspofungin (32/49)

At 48 hours
53.3%
64.4%

Percent of Patients (n/N)
Pooled Rezafungin (80/93) Caspofungin (32/49)

Day 5
Efficacy Endpoints at Day 5
Percent of Patients (n)
Mycological Cure
73.1%
73.1%
Percent of Patients (n)
Pooled Rezafungin (68) Caspofungin (28)
64.5%
64.5%
Percent of Patients (n)
Pooled Rezafungin (60) Caspofungin (25)
Overall Success
58.3%
52.1%

Percent of Patients (n)
Pooled Rezafungin (N=93) Caspofungin (N=48)
Efficacy In Initial Days of Treatment
Patients with Candidemia Only

mITT
All randomized patients who received study drug and had documented Candida infection

mITT2
Patients in mITT with positive blood culture within 12h before and 72h after enrollment
Conclusions

• Rezafungin, a novel echinocandin in clinical development, demonstrates high plasma drug exposure following front-loaded, once-weekly dosing

• In the STRIVE Phase 2 trial, rezafungin demonstrated high rates of early treatment efficacy in patients with candidemia

• Rezafungin efficacy was more pronounced among patients with ongoing active infection

• Ongoing Phase 3 treatment trial (ReSTORE; NCT03667690) will provide further data regarding rezafungin efficacy and the potential clinical benefit and effect of front-loaded pharmacometrics