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Integrated Analysis of Efficacy and ICU Length of Stay Data from Phase 2 and Phase 3 Trials of Rezafungin for the Treatment of Invasive Candidiasis and/or Candidemia

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INTRODUCTION AND OBJECTIVES

- Candidemia (bloodstream candida infection) and invasive candidiasis (IC; the deep-seated candida infection) remain significant causes of morbidity and mortality. Associated health economic burden is largely due to prolonged hospital and intensive care unit (ICU) stays, contributing more than half of the total costs.[1]
- Rezafungin is a once-weekly (QWk) echinocandin antifungal agent that offers prolonged half-life and high front-loaded plasma exposures.[2–4]
- The current post-hoc analysis aimed to examine outcomes regarding mortality, early indicators of treatment efficacy and length of stay (LoS) in the ICU with rezafungin therapy using data from the integrated Phase 2 and Phase 3 clinical trials, STRIVE (NCT02734862) and ReSTORE (NCT03667690).[5,6]

METHODS

STRIVE and ReSTORE clinical study designs

- STRIVE comprised a global, Phase 2, prospective, multicenter, double-blind, comparator study. Overall, 183 adults with candidemia and/or IC were randomised to receive QWk rezafungin 400/400 mg (n=76), QWk rezafungin 400/200 mg (n=46), or caspofungin once-daily (QD) standard dose (n=61) for ≤4 weeks.
- ReSTORE was a global, double-blind, double-dummy, randomised, controlled, Phase 3 non-inferiority trial. Adults with candidemia and/or IC (modified intention-to-treat population) were randomised to receive QWk rezafungin 400/200 mg (n=93) or QD caspofungin (n = 94). The ReSTORE trial was conducted almost entirely during the COVID-19 pandemic.

Integrated analysis methodology

- The current analysis compared treatment outcomes for patients treated with rezafungin (QWk 400/200 mg) or caspofungin (QD standard dose) using the microbiological/modified intention-to-treat population (mITT).
- STRIVE and ReSTORE had similar study designs, which enabled integrated analysis of efficacy data. Where efficacy outcome measures/definitions differed between studies additional post-hoc analyses were used to incorporate those STRIVE participants receiving the same rezafungin QWk 400/200 mg dose used in the ReSTORE study.
- Integrated primary endpoint was all-cause mortality (ACM) rate through Day 30, defined as subjects known to be deceased or with unknown survival status. Secondary efficacy and exploratory endpoints included mycological response on Day 5 and ICU LoS.
  - Subgroup analyses per final diagnosis (candidemia only vs invasive candidiasis) were planned for primary and secondary endpoints, hence the Day 5 mycological responses in subset of patients with candidemia only were available for integration.
- The Statistical Analysis Plan (SAP) for the STRIVE and ReSTORE trials stipulated that ICU LoS outcomes should be reported for survivors only.
  - To account for observed imbalance between groups regarding the proportion of patients receiving mechanical ventilation (MV), a generalised linear model (log-link, gamma distribution) analysis was undertaken with MV as a binary covariate in the total ICU subset, including non-survivors.

RESULTS

- The integrated analysis included 294 patients; 139 from rezafungin treatment arms and 155 patients from caspofungin arms across the STRIVE and ReSTORE trials.
- Overall, 215 patients (73%) were diagnosed with candidemia only; 100 in rezafungin arms and 115 in caspofungin arms.
- Treatment groups were well balanced at baseline, with the exception of those receiving MV (rezafungin: 12.2%; caspofungin: 21.9%). However, the distribution of APACHE II scores and absolute neutrophil counts were comparable between the groups.

Primary efficacy endpoint: ACM at Day 30

- Analysis of integrated data from the STRIVE and ReSTORE trials showed that Day 30 ACM was 18.7% and 19.4% for the rezafungin and caspofungin groups, respectively (Table 1).
- The treatment difference (95% confidence interval [CI]) between arms was -1.5 (-10.7, 7.7) and demonstrated non-inferiority.

Secondary efficacy endpoint: Day 5 mycological eradication (candidemia-only)

- Patients with a candidemia diagnosis demonstrated Day 5 mycological eradication rates of 80.0% with rezafungin treatment and 67.8% with caspofungin (Table 2).
- The treatment difference (95% CI) was 12.9 (1.5, 24.3), which was statistically significant.

Table 1. Day 30 ACM (mITT population)

Outcome	Rezafungin (n=139)	Caspofungin (n=155)	Treatment difference (95% CI)
ACM (Day 30) %(n)	18.7 (26)	19.4 (30)	-1.5 (-10.7, 7.7)

Abbreviations: ACM, all-cause mortality; CI, confidence interval; mITT, microbiological/modified intention-to-treat population.

Table 2. Day 5 mycological eradication (mITT population, candidemia-only subset)

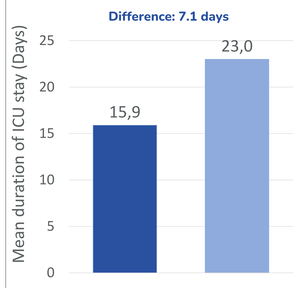
Outcome	Rezafungin (n=100)	Caspofungin (n=115)	Treatment difference (95% CI)
Mycological eradication (Day 5), %(n)	80.0 (80)	67.8 (78)	12.9 (1.5, 24.3)

Abbreviations: CI, confidence interval, mITT, microbiological/modified intention-to-treat population.

ICU LoS analysis

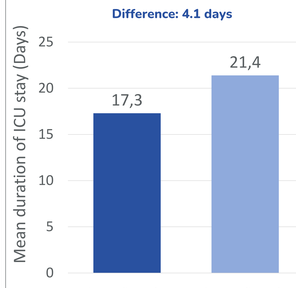
- Of the 294 patients included in the integrated analysis, 126 (43%) required ICU admission; 55 were treated with rezafungin and 71 received caspofungin therapy.
- Overall, 35 patients in the rezafungin arm and 53 in the caspofungin arm were discharged from ICU (survivors – as per the SAP)
  - For survivors, mean ICU LoS was 15.9 days in rezafungin and 23.0 days in caspofungin groups (difference in ICU LoS (95% CI): 7.1 days (-0.8, 19.2); Figure 1).
- Mean LoS in the ICU after adjustment for MV was 17.3 (rezafungin) and 21.4 (caspofungin) days (Figure 2). The difference in adjusted ICU LoS (95% CI) was 4.1 days (-1.9,12.5).

Figure 1. Mean ICU LoS; survivors only



Abbreviations: ICU, intensive care unit; LoS, length of stay

Figure 2. Mean ICU LoS; adjusted, all ICU patients



CONCLUSIONS

Pooled data from two RCTs demonstrated rezafungin efficacy and non-inferior to caspofungin with higher mycological eradication with rezafungin on Day 5.

Rezafungin showed a trend for improvements in ICU LoS for actual and adjusted analyses, but no conclusions can be made and further studies are warranted.

References

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Disclosures

Inga Bielicka, Sara Dickerson, Nick Manamley are employees of Mundipharma. Anita Das and Taylor Sandison are employees of Cidara Therapeutics. The STRIVE study was funded by Cidara Therapeutics. Mundipharma holds exclusive rights to develop and market rezafungin in all markets except the US and Japan, where Cidara retains the rights.

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