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Analysis of Safety from STRIVE Phase 2 Trial of Rezafungin Treatment of Candidemia and/or Invasive Candidiasis: Assessment of Adverse Events and Laboratory Values

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INTRODUCTION

- The overall safety and tolerability of echinocandins has been established since their introduction over 20 years ago. However, hepatic toxicity has been reported with caspofungin and the other approved echinocandins[1,2]
- Patients requiring antifungal treatment are often critically ill or have comorbidities that may affect hepatic function[3,4]
- Rezafungin (RZF) is a novel next-generation echinocandin in Phase 3 development for treatment of candidemia and invasive candidiasis (IC) [ReSTORE; NCT03667690]
- Non-clinical data did not show adverse hepatic effects, and Phase 1 trials did not demonstrate liver function abnormalities[5,6]
- STRIVE (Phase 2; NCT02734862) compared the safety and efficacy of RZF with caspofungin (CAS) in patients with candidemia and/or IC (Table 1). The trial met its primary objectives and demonstrated a positive risk/benefit profile for rezafungin[7]
- This sub-analysis of STRIVE evaluated additional safety endpoints, including liver function tests

METHODS

- Adults (aged >18 y) were randomized to receive RZF or CAS
- Safety was evaluated by treatment-emergent adverse event (TEAEs) data and laboratory chemistry values

Table 1. Description of Treatment groups in STRIVE

Group	Dose Regimen	Dose Schedule
RZF Group 1	IV rezafungin 400 mg QWk	On Days 1 and 8
RZF Group 2[a]	IV rezafungin 400 mg on Week 1, followed by 200 mg QWk[a]	Optional dose(s) on Day 15 (and on Day 22 for IC)
CAS	IV caspofungin 70 mg on Day 1, followed by 50 mg QD (w/optional step-down to oral fluconazole)	Once daily for up to 21 days for candidemia or 28 days for IC ± candidemia

[a]Rezafungin dosing in ongoing Phase 3 trials.

RESULTS

- High rates of TEAEs were observed in all treatment groups, reflecting the high underlying medical acuity of the trial population (Table 2)
- Rates of TEAEs leading to study drug discontinuation were 5.2% for RZF (RZF groups pooled) and 5.9% in the CAS group (Table 2)
- Overall, no concerning trends between groups or between treatments (RZF groups pooled versus caspofungin) were observed in the occurrence of TEAEs or in lab chemistry values with a post-baseline increase of ≥2 toxicity grades (Table 3)
- There were no other substantial post-baseline changes or unexpected findings in lab chemistry values or hematology test results

Table 2. Summary of TEAE Data from the STRIVE Trial (Safety Population)

Parameter % (n)	RZF Group 1 (N=81)	RZF Group 2 (N=53)	RZF Pooled (N=134)	CAS (N=68)
≥1 TEAE	87.7 (71)	92.5 (49)	89.6 (120)	80.9 (55)
Study drug–related TEAE	8.6 (7)	11.3 (6)	9.7 (13)	13.2 (9)
Serious TEAE (SAE)	43.2 (35)	52.8 (28)	47.0 (63)	42.6 (29)
SAE leading to death	17.3 (14)	11.3 (6)	14.9 (20)	22.1 (15)
TEAE leading to study drug D/C	7.4 (6)	1.9 (1)	5.2 (7)	5.9 (4)

D/C=discontinuation; TEAE=treatment-emergent adverse event.

Table 3. Selected Laboratory Parameters with Post-Baseline Increases of ≥2 Grades (Safety Population)

Parameters % (n/N1)	RZF Group 1 (N=81)	RZF Group 2 (N=53)	RZF Pooled (N=134)	CAS (N=68)
ALT	6.7 (5/75)	4.1 (2/49)	5.6 (7/124)	6.3 (4/64)
AST	9.5 (7/74)	6.3 (3/48)	8.2 (10/122)	12.5 (8/64)
ALKP	5.6 (4/71)	13.3 (6/45)	8.6 (10/116)	8.6 (5/58)
Direct bilirubin	8.5 (4/47)	9.4 (3/32)	8.9 (7/79)	10.8 (4/37)
Total bilirubin	8.2 (6/73)	2.1 (1/48)	5.8 (7/121)	7.7 (5/65)
Creatinine	7.9 (6/76)	2.1 (1/48)	5.6 (7/124)	7.6 (5/66)

ALKP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; N1=number of subjects with a baseline and post-baseline value.

CONCLUSIONS

- This sub-analysis of the STRIVE Phase 2 trial of rezafungin further demonstrates the comparable safety between rezafungin and caspofungin treatment in patients with candidemia and/or IC
- No concerning trends between groups or between treatments were observed in the occurrence of TEAEs or laboratory values evaluated
- The relatively short duration of treatment (2-4 weeks) may have lessened the ability to detect possible differences in hepatic toxicity between caspofungin and rezafungin
- The ongoing Phase 3 treatment trial (ReSTORE; NCT03667690) will provide further data on rezafungin safety and contribute to the evidence of safety in the echinocandin class of antifungals

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