

Rezafungin (Once Weekly) versus Standard Antimicrobial Regimen (Daily) for Antifungal Prophylaxis in Allogeneic Hematopoietic Stem Cell Transplantation: ReSPECT, a Multicenter, Randomized, Double-Blind, Phase 3 Study

(LB-2201.3)

Johan Maertens¹; Drew Winston²; Shariq Haider³; Francisco Javier López-Jiménez⁴; Matthias Breugelmans⁵; Hosnieh Fathi⁵; Yuri Martina⁵; Federica Sorá⁶

1. University Hospitals Leuven, Belgium; 2. UCLA Medical Center, University of California, USA; 3. Juravinski Hospital and Cancer Center, McMaster University, Canada; 4. Hospital Universitario Ramon y Cajal, IRYCIS, University of Alcalá Henares, Madrid, Spain; 5. Mundipharma Research Ltd, Cambridge, UK; 6. University Cattolica del Sacro Cuore and Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy



Disclosures

Shariq Haider reports:

- Research / clinical trial funding from AVIR Pharmaceuticals and Cidara Therapeutics
- Consulting fees from Merck
- Honoraria from AVIR Pharmaceuticals

All relevant financial disclosures have been mitigated

- Antifungal prophylaxis is standard of care for allo-HSCT recipients to prevent life-threatening IFD
- Daily azole + TMP/SMX is the cornerstone of current antifungal prophylaxis
 - Complicated by drug toxicities, DDIs, TDM, antifungal resistance, and challenges of daily oral administration, which can result in treatment interruption or suboptimal exposure^{1–3}
- Rezafungin is a next-generation echinocandin
 - PK profile enables high front-loaded dosing and once-weekly IV administration⁴
 - Broad antifungal activity: range of *Candida* spp., *Aspergillus* spp. (including azole-resistant strains), and *Pneumocystis jirovecii*⁵
 - Indicated to treat invasive candidiasis (and candidemia in US) since 2023⁶

Allo-HSCT, allogeneic hematopoietic stem cell transplantation; DDI, drug–drug interactions; IFD, invasive fungal disease; PK, pharmacokinetic; TDM, therapeutic drug monitoring; TMP/SMX, trimethoprim/sulfamethoxazole

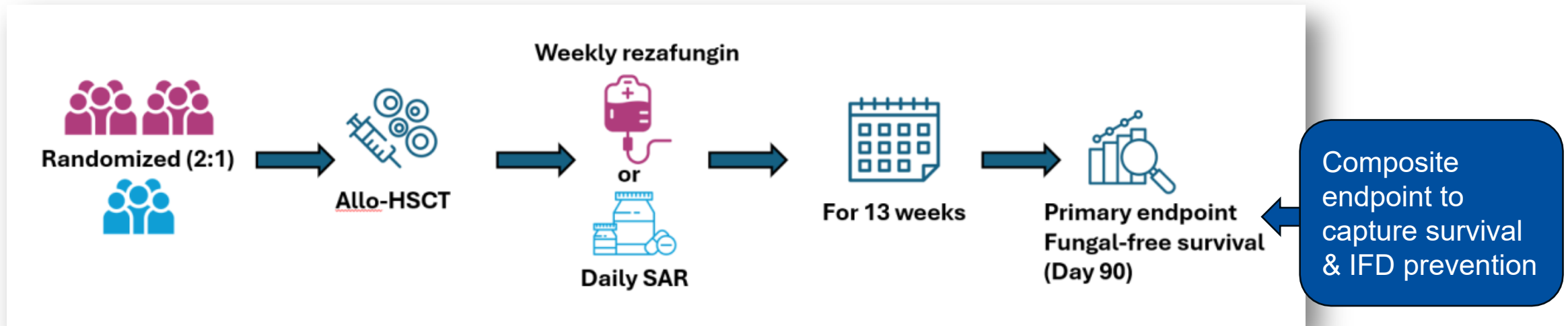
1. Lewis et al. *J Antimicrob Chemother.* 2024;79:1203-1217; 2. McCreary et al. *Pharmacotherapy.* 2023;43:1043-1050; 3. Benitez & Carver. *Drugs.* 2019;79:833-853; 4. Andes et al. *J Antimicrob Chemother.* 2025;80:18-28; 5. Hoenigl, et al. *Drugs.* 2021;81:1703-1729; 6. Syed. *Drugs* 2023;83:833–840.

ReSPECT overview

- ReSPECT is a Phase 3, multicenter, double-blind, double-dummy RCT (NCT 04368559)

Aim: evaluate the efficacy and safety of antifungal prophylaxis with once-weekly IV rezafungin vs daily oral SAR (azole + TMP/SMX) in allo-HSCT recipients

- Adults undergoing allo-HSCT received once-weekly rezafungin (IV) or daily oral SAR (azole + TMP/SMX) on Day 0 (± 2 days)^a after cell transplantation for 13 weeks



^aTMP/SMX initiated after neutrophil and platelet engraftment and by Day 30 (≤ 3 days after neutrophil and platelet engraftment) or Day 40 if engraftment not achieved by Day 30

Allo-HSCT, allogeneic hematopoietic stem cell transplantation; IFD, invasive fungal disease; RCT, randomized controlled trial; SAR, standard antimicrobial regimen; TMP/SMX, trimethoprim/sulfamethoxazole

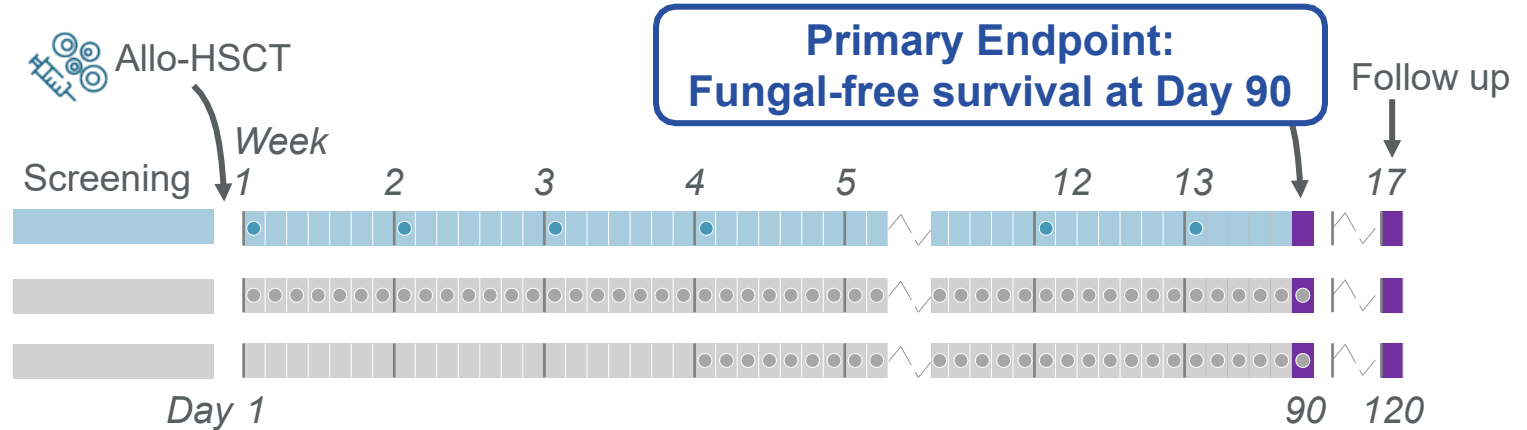
ReSPECT Study Design

Rezafungin (n=400)

Rezafungin QW (IV)^a

Azole placebo QD (capsule)

TMP/SMX placebo QD^c



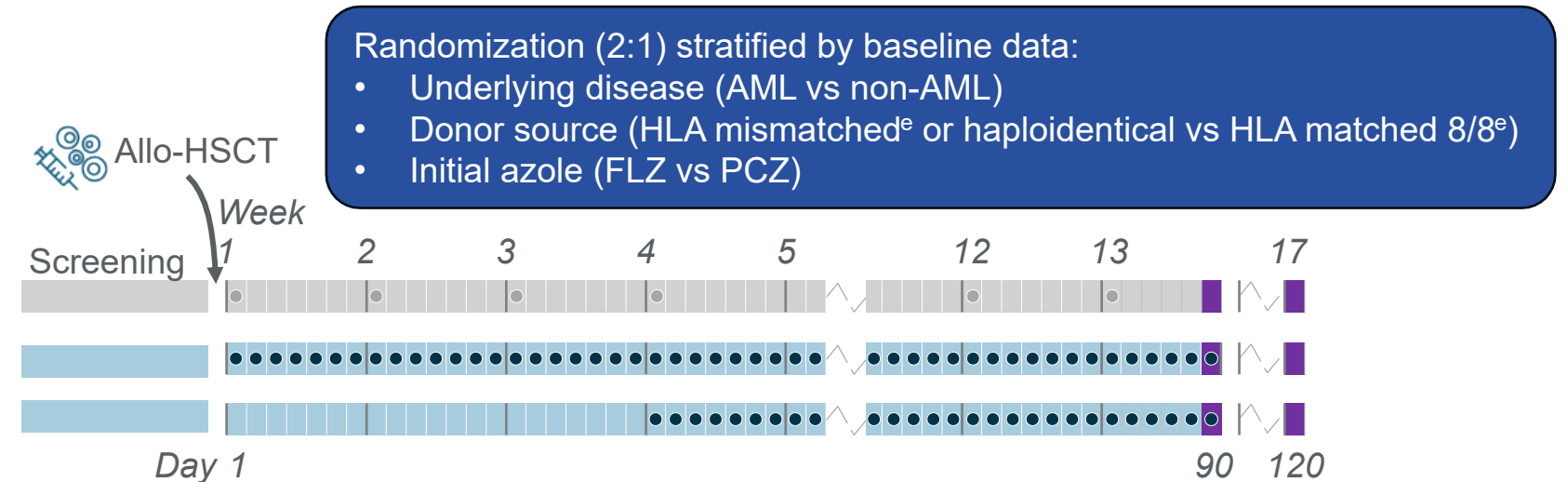
Permanent switch of FLZ to PCZ permitted for significant acute GvHD^d

SAR (n=200)

Rezafungin placebo QW (IV)^a

FLZ or PCZ QD (capsule)^b

TMP/SMX QD^c



^a400 mg Week 1 and 200 mg subsequent weeks, initiated after stem cell infusion; ^bFLZ 400 mg QD or PCZ Day 1 300 mg BID then 300 mg QD, initiated after stem cell infusion; ^cTMP 80 mg/SMX 400 mg, initiated after engraftment and by Day ≤40; ^dGrade ≥2 requiring additional immunosuppressive therapy;

^eRelated or unrelated

Allo-HSCT, allogeneic hematopoietic stem cell transplantation; AML, acute myeloid leukemia; FLZ, fluconazole; GvDH, graft versus host disease; HLA, human leukocyte antigen; PCZ, posaconazole; QD, once daily; QW, once weekly; SAR, standard antimicrobial regimen; TMP/SMX, trimethoprim/sulfamethoxazole

Endpoints^b

1^o

Primary endpoint

Fungal-free survival at Day 90^a

2^o

Key secondary endpoints

- Discontinuation due to toxicity or intolerance at Day 90^a
- Incidence of IFD at Day 90^a
- Invasive candidiasis-free survival at Day 90^a
- FFS in patients with/without clinically significant GvHD at Day 90^a
- Time to IFD or death
- Overall & IFD-related mortality



Safety^c

- TEAEs, SAEs, laboratory values and vital signs

Composite endpoint:

- **Survival**, and
- **No proven or probable IFD** (per 2020 modification of EORTC-MSGERC criteria), and
- **No non-study drug systemic antifungal therapy for >10 days (cumulative)**

Statistical analysis

- *Non-inferiority*: 95% CI lower limit of treatment difference (rezafungin minus SAR) > -12.5%
- *Superiority*: treatment difference $p < 0.05$ (CMH test)

^a±7 days; ^bIndependent external Data Review Committee adjudicated determination of IFD and IFD-attributable mortality in a blinded manner;

^cIndependent Data Safety Monitoring Board regularly reviewed unblinded safety data prepared by an independent statistician

CI, confidence interval; CMH, Cochran-Mantel-Haenszel; EORTC-MSGERC, European Organization for Research and Treatment of Cancer Mycoses Study Group Education and Research Consortium; FFS, fungal-free survival; GvHD, graft versus host disease; IFD, invasive fungal disease; SAE, serious adverse event; SAR, standard antimicrobial regimen; TEAE, treatment-emergent adverse event

ReSPECT: Key enrolment criteria



Key inclusion criteria^a



- ≥18 years of age
- Scheduled for allo-HSCT^b
- Receiving myeloablative or reduced intensity conditioning
- Adequate renal & hepatic function prior to conditioning
- Protocol-permitted diagnosis (includes acute leukemia,^c MDS, lymphoma,^d aplastic anemia, myelofibrosis, CLL, CML, drepanocytosis, RBC aplasia, & MM)
- Negative *Platelia galactomannan* EIA and β-D-glucan assays ≤15 days prior to transplant



Key exclusion criteria^a



- AML not in morphological remission
- Chemotherapy-resistant lymphoma
- Suspected / diagnosed IFD ≤4 weeks of randomization
- Positive *Toxoplasma* IgM ≤6 weeks of randomization
- Suspected or documented PCP ≤2 y of screening
- Reduced lung function or cardiac abnormalities^f
- Prior allo-HSCT
- Ataxia, tremor, or neuropathy (current: Grade ≥2; prior: Grade ≥3)
- Planned receipt of cord blood for transplantation

^aFull enrolment criteria available at <https://clinicaltrials.gov/study/NCT04368559>; ^bHLA matched or mismatched or haploidentical; ^cIn first or second remission; ^dChemosensitive; ^eSymptomatic heart failure or with altered LVEF, history of QT interval prolongation, or co-administration of drugs metabolized by CYP3A4 that may cause QT prolongation

Allo-HSCT, allogeneic hematopoietic stem cell transplantation; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; EIA, enzyme immunoassay; HLA, human leukocyte antigen; IFD, invasive fungal disease; MDS, myelodysplastic syndrome; MM, multiple myeloma; RBC, red blood cell; PCP, *Pneumocystis pneumonia*

Baseline characteristics

ITT population	Rezafungin QW (N=402)	SAR ^b QD (N=200)
Age in years, mean (SD)	55.0 (14.1)	54.4 (14.5)
Male, n (%)	259 (64.4)	117 (58.5)
Normal renal function (eCrCl ≥90 mL/min), n(%)	300 (74.6)	154 (77.0)
Sorrer Score ≥3	126 (31.3)	57 (28.4)
Frequent underlying diseases		
AML	162 (40.3)	80 (40.0)
MDS	87 (21.6)	38 (19.0)
ALL	59 (14.7)	30 (15.0)
Allo-HSCT characteristics^c		
HLA matched (related or unrelated)	232 (57.7)	132 (66.0)
HLA mismatched (related or unrelated)	66 (16.4)	26 (13.0)
Haploidentical	102 (25.4)	41 (20.5)
Peripheral blood stem cells	384 (95.5)	189 (94.5)
Reduced intensity conditioning	208 (51.7)	107 (53.5)

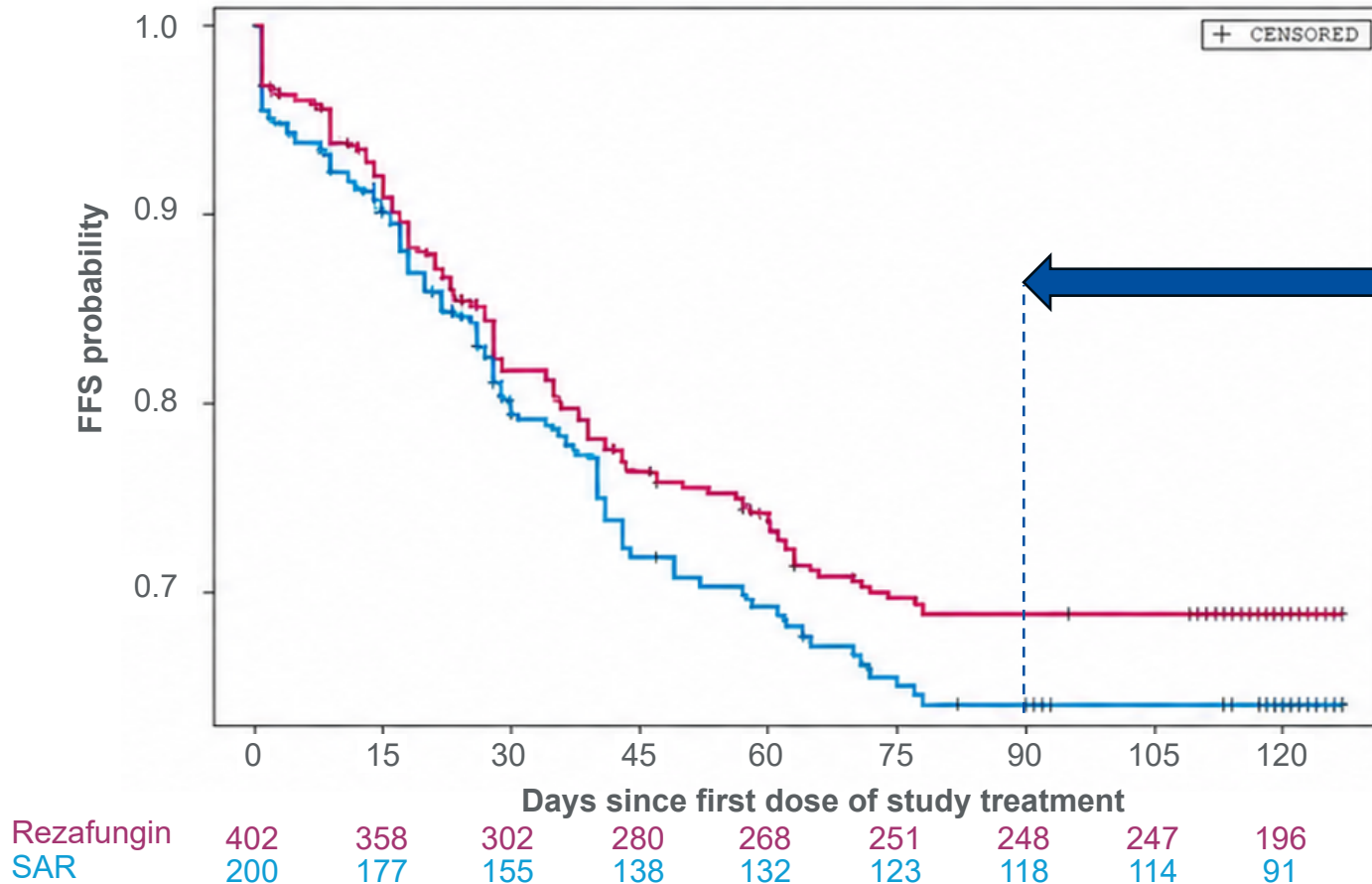
- FLZ n=172, PCZ n=25^a
- Permanent switch from FLZ to PCZ permitted for significant, acute GvHD^d: n=20

^aDifferences in n values reflect patients randomized but not treated with study medication; ^bFLZ or PCZ plus trimethoprim/sulfamethoxazole;

^cThree patients did not undergo transplantation (rezafungin n=2, SAR n=1); ^dGrade ≥2 requiring additional immunosuppressive therapy
 allo-HSCT, allogeneic hematopoietic stem cell transplantation; AML, acute myeloid leukemia; eCrCl, estimated creatinine clearance; FLZ, fluconazole;
 HLA, human leukocyte antigen; ITT, intent-to-treat; MDS, myelodysplastic syndrome; PCZ, posaconazole; QD, once daily; QW, once weekly;
 SAR, standard antimicrobial regimen

Primary endpoint: FFS (Day 90)

Primary endpoint was met: FFS (Day 90) with rezafungin was non-inferior to SAR (ITT population)



Rezafungin QW (N=402)	SAR ^a QD (N=200)
60.7%	59.0%
Difference 1.6% (95% CI -6.2, 9.3) ^b	
Non-inferiority $P=0.0002$	

- Non-inferiority margin for rezafungin vs SAR was achieved:
 - Lower limit of difference 95% CI > -12.5%
- Primary endpoint supported by 6 pre-specified sensitivity analyses^c

^aFLZ or PCZ plus trimethoprim/sulfamethoxazole; ^bCI adjusted for randomization stratification factors (underlying disease [AML vs non-AML], donor source [HLA mismatched or haploidentical vs HLA matched], and initial SAR azole); ^cExplored handling of indeterminate FFS (including imputed using data through Day 120), definitions of IFD, impact of stratification factors, and non-study-drug systemic antifungal therapy use for >10 days
CI, confidence interval; FFS, fungal-free survival; HLA, human leukocyte antigen; IFD, invasive fungal disease; ITT, intent-to-treat; SAR, standard antimicrobial regimen

FFS (Day 90): key drivers

- **Most FFS ‘failures’ at Day 90 were due to use of non-study systemic antifungal drugs for >10 days (cumulative)**
 - Numerically lower with rezafungin 27.4% vs SAR^a 32.5%
- Other FFS failures (rezafungin, SAR) were due to death (4.5%, 5.5%), proven/probable IFD (3.5%, 4.5%), and indeterminate FFS^b (10.0%, SAR 6.0%)
- bIFI due to key fungal spp. were comparable across the rezafungin and SAR cohorts

Proven or probable bIFI by Day 90 (ITT population)

bIFI species, n (%)	Rezafungin QW (N=402)	SAR ^a QD (N=200)
<i>Candida</i> spp.	5 (1.2)	2 (1.0)
<i>Aspergillus</i> spp.	8 (2.0)	6 (3.0)
<i>Pneumocystis jirovecii</i>	1 (0.2)	0
Other yeast or mold ^c	1 (0.2)	1 (0.5)

^aFluconazole or posaconazole plus trimethoprim/sulfamethoxazole; ^bInsufficient data to assess FFS status ^c*Geotrichum clavatum* and unspecified *Magnusiomyces* (n=1, rezafungin) and *Fusarium keratoplasticum* (n=1, SAR)
 allo-HSCT, allogeneic haematopoietic stem cell transplantation; bIFI, breakthrough IFI; IFD, invasive fungal disease; FFS, fungal-free survival; ITT, intent-to-treat; QD, once daily; QW, once weekly; SAR, standard antimicrobial regimen

Safety overview (safety population)

Safety population n (%)	Rezafungin QW (N=397)	SAR ^a QD (N=197)
TEAE	396 (99.7)	197 (100)
Study drug-related ^b TEAE	62 (15.6)	37 (18.8)
TEAE leading to study discontinuation	37 (9.3)	29 (14.7)
TEAE leading to study drug dose reduction/interruption/withdrawal	123 (31.0)	94 (47.7)
Grade 4/5 TEAE	114 (28.7)	70 (35.5)
SAE	262 (66.0)	133 (67.5)
Study drug-related ^a SAE	13 (3.3)	4 (2.0)

Acute kidney injury^c was the most frequent of these events:

- Rezafungin 5.5% vs SAR 10.2%

^aFluconazole or posaconazole plus trimethoprim/sulfamethoxazole; ^bRelated to any study drug (rezafungin/placebo, azole/placebo, or TMP/SMX or placebo); ^cNCI CTCAE v5.0 preferred term defined as acute loss of renal function (within 2 weeks)

QD, once daily; QW, once weekly; SAE, serious adverse event; SOC, system organ class; TEAE, treatment-emergent adverse event

Frequent TEAEs^a (safety population)

n (%)	Rezafungin QW (N=397)	SAR ^b QD (N=197)
Diarrhea	230 (57.9)	117 (59.4)
Pyrexia	188 (47.4)	90 (45.7)
Mucosal inflammation	148 (37.3)	65 (33.0)
Nausea	137 (34.5)	57 (28.9)
Febrile neutropenia	118 (29.7)	62 (31.5)
Vomiting	106 (26.7)	52 (26.4)
Headache	110 (27.7)	46 (23.4)
Acute GvHD (skin)	101 (25.4)	51 (25.9)
Peripheral edema	91 (22.9)	55 (27.9)
Acute kidney injury ^c	68 (17.1)	51 (25.9)

Liver enzyme elevations were comparable across treatment groups (no confirmed Hy's Law cases)

Acute kidney injury^c had largest difference for rezafungin vs SAR

^a≥25% in rezafungin or SAR cohort; ^bfluconazole or posaconazole plus trimethoprim/sulfamethoxazole; ^cNCI CTCAE v5.0 preferred term defined as

acute loss of renal function (within 2 weeks)

GvHD; graft versus host disease; QD, once daily; QW, once weekly; SAR, standard antimicrobial regimen; TEAE, treatment-emergent adverse event

ReSPECT supports using rezafungin for antifungal prophylaxis in allo-HSCT recipients

- **FFS (Day 90) was non-inferior with once-weekly rezafungin (IV) vs daily SAR (oral azole + TMP/SMX) for IFD prophylaxis: 60.7% vs 59.0%** (difference 1.6% [95% CI -6.2, 9.3], $P=0.0002^a$)
 - Incidence of bIFI with *Candida* spp., *Aspergillus* spp., and *Pneumocystis jirovecii* was low and comparable across treatment groups, and aligned with the anticipated reduction of bIFD with SAR prophylaxis
 - Most FFS ‘failures’ were due to use of non-study systemic antifungal drugs
- **Safety profile of rezafungin was consistent with the licensed indication for invasive candidiasis**
 - No new safety signals identified in allo-HSCT recipients
 - Rezafungin had fewer TEAEs leading to dose reduction/interruption/withdrawal vs SAR (31.0% vs 47.7%)
 - Rezafungin had a favorable renal safety profile compared with SAR
- **Rezafungin can provide sustained antifungal coverage and has the potential for a simpler antifungal prophylaxis regimen vs daily oral azole + TMP/SMX**
 - Single agent with once-weekly, non-oral dosing schedule

^aP value for on-inferiority; Allo-HSCT, allogeneic hematopoietic stem cell transplantation; bIFD, breakthrough invasive fungal disease; Allo-HSCT, allogeneic hematopoietic stem cell transplantation; bIFI, breakthrough invasive fungal infection; CI, confidence interval; FFS, fungal-free survival; SAR, standard antimicrobial regimen; TEAE, treatment-emergent adverse event; TMP/SMX, trimethoprim/sulfamethoxazole



Acknowledgements

- The authors thank the patients, study investigators, and study site personnel who participated in ReSPECT
- ReSPECT was sponsored by Mundipharma Research Ltd
- Statistical analysis was performed by MMS Holdings, Inc., funded by Mundipharma Research Ltd
- Medical writing support (Siân Marshall, SIANTIFIX Ltd, Cambridge UK) was funded by Mundipharma Research Ltd

BACK-UP

(to support Q on indeterminant FFS & other sensitivity analyses)

Pre-planned sensitivity analyses of Day 90 FFS (ITT population)

Participants with FFS, n (%)	Rezafungin QW N=402	SAR ^a QD N=200	Difference %, 95% CI	P value ^b
ITT population (primary analysis)	244 (60.7)	118 (59.0)	1.6 (-6.2, 9.3)	0.0002
Pre-planned sensitivity analyses				
Multiple imputation for indeterminate results ^c	244 (60.7)	118 (59.0)	5.1 (-3.0, 13.3)	<0.0001
Without stratification factors	244 (60.7)	118 (59.0)	1.7 (-6.5, 10.1)	0.0004
IFD definition: adapted from 2020 EORTC-MSGERC Guidelines	244 (60.7)	118 (59.0)	1.6 (-6.2, 9.3)	0.0004
IFD definition: adapted from 2009 EORTC-MSGERC Guidelines	245 (60.9)	118 (59.0)	1.8 (-6.0, 9.6)	0.0003
Imputed using data through Day 120 ^d	247 (61.4)	118 (59.0)	2.5 (-5.3, 10.3)	0.0002
Non-study systemic antifungal therapy ignored	310 (77.1)	155 (77.5)	0.8 (-6.2, 7.7)	0.0004

- Six sensitivity analyses explored handling of indeterminate FFS, definitions of IFD, impact of stratification factors, and non-study-drug systemic antifungal therapy use for >10 days
 - All supported the primary endpoint of non-inferiority

^aFluconazole or posaconazole plus trimethoprim/sulfamethoxazole; ^bFor non-inferiority; ^cInstead of imputing indeterminate outcome as FFS failure;

^dParticipants with missing data at Day 90 who were alive and had no IFD from Day 90–120 considered to have FFS at Day 90

EORTC-MSGERC, European Organisation for Research and Treatment of Cancer - Mycoses Study Group Education and Research Consortium;

FFS, fungal-free survival; ITT, intent-to-treat; QD, once daily; QW, once weekly; SAR, standard antimicrobial regimen