# Melinta Therapeutics

# Administration of Rezafungin

ICD-10 Coordination and Maintenance Committee Meeting
March 7, 2023

**Rezafungin is an investigational antifungal therapy that has not been approved by any regulatory authority. The safety and effectiveness of rezafungin has not yet been established.**

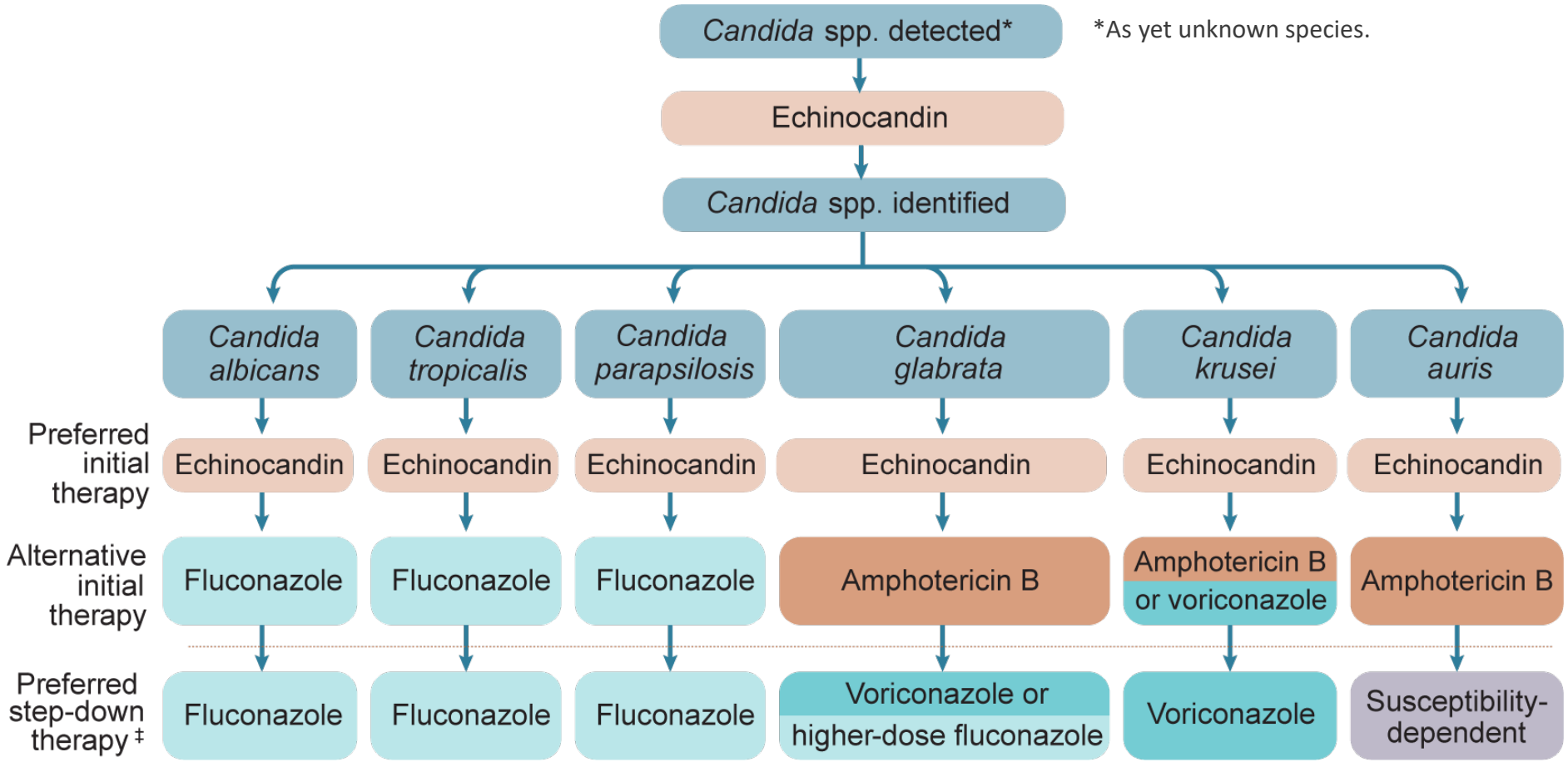
# Rezafungin

## A Novel Long-Acting Echinocandin With Distinctive Properties

| Properties | Evidence |
|---|---|
| Long-acting PK | Once-weekly dosing as in Phase 3 clinical trials[1,2] |
| Front-loaded plasma drug exposure | Efficacy: Shorter time to negative blood culture[3,4] |
| Broad-spectrum activity | Efficacy vs *Candida*, *Aspergillus*, and *Pneumocystis* spp.[5,6] |
| Observed absence of toxic degradation products | Safety: Lack of hepatotoxicity[7] |
| No clinically relevant DDIs and favorable hepatic and renal safety | Compatibility with other medications[8-10] |

1. ReSTORE CSR; 2. ClinicalTrials.gov. NCT04368559. Accessed October 24, 2022. https://clinicaltrials.gov/ct2/show/NCT04368559; 3. Lakota EA et al. *Antimicrob Agents Chemother*. 2017;61:e00758-17; 4. Soriano A et al. Presented at: European Congress of Clinical Microbiology and Infectious Diseases, Lisbon, Portugal, 23-26 April 2022. Abstract no. 04673; 5. Pfaller MA et al. *Antimicrob Agents Chemother*. 2020: AAC.00099-20; 6. Cushion MT, Ashbaugh A. *J Fungi (Basel)*. 2021;7:747; 7. Ong V et al. Poster presented at: Infectious Diseases Week 2020. Poster 1286; 8. Ong V et al. Poster presented at: European Society for Blood and Marrow Transplantation, Lisbon, Portugal, 18-21 March 2018. Poster no. B196; 9. Flanagan S et al. Poster presented at: 10th Annual Congress on Trends in Medical Mycology (TIMM), Aberdeen, Scotland, October 8-11 2021. Poster no. P335; 10. Sandison T et al. Presented at: The 22nd Symposium of the International Immunocompromised Host Society (ICHS)/Annual Congress of the Swiss Society for Allergology and Immunology (SSAI) Joint Congress, Basel, Switzerland, September 8-11, 2022. Poster P13.

# Algorithm for the Management of Invasive Candidiasis – Echinocandins as First-Line




‡Step-down therapy to fluconazole is usually based on documented susceptible MIC to fluconazole (<2 µg/ml for *C. albicans, C. parapsilosis,* and *C. tropicalis* and <32 µg/ml for *C. glabrata*) and clinical stabilization of the patient. Higher-dose fluconazole consists of 12 mg/kg per day.

1. Pappas, P., et al. *Nat Rev Dis Primers* 4, 18026 (2018).

# Rezafungin: Development Program

| | PHASE 2 Dose Finding Study | PHASE 3 Treatment Trial |
|---|---|---|
| | STRIVE [1] | ReSTORE [2] |
| **Potential Indication** | Support Phase 3:<br><br>Treatment of invasive candidiasis and candidemia | Treatment of invasive candidiasis & candidemia |
| **Trial Size** | mITT N=183<br>(Not Powered for Inferential Statistical Analysis) | 187 patients in mITT<br>(20% nonferiority margin) |
| **Trial Status** | Complete | Complete* |

**FDA Filing Status**

NDA Submitted: 09/30/2022
QIDP designation: 06/27/2017
Action Date (PDUFA): 3/22/2023

[a]Study sites in China are still recruiting patients for submission of rezafungin to the Center for Drug Evaluation in China.
IFD, invasive fungal disease; mITT, modified intent-to-treat population.


1. Thompson, et al. *Clin Infect Dis*. 2020, ciaa1380, https://doi.org/10.1093/cid/ciaa1380. ,
2. Thompson GR III, et al. 2022 ECCMID LB0244.
3. Clinicaltrials.gov NCT04368559 accessed 20 April 2022.

# Rezafungin Phase 3 Treatment Trial: ReSTORE

## Primary Endpoints: Global Cure at Day 14 and All-Cause Mortality at Day 30 (mITT Population)

### Rezafungin was noninferior to caspofungin for both primary endpoints

#### All-cause mortality at Day 30 (–2 days)

| Endpoint | Proportion of Patients, % (n) Rezafungin 400/200 mg weekly n=93 | Proportion of Patients, % (n) Caspofungin 70/50 mg daily n=94 |
|---|---|---|
| **ACM at Day 30** | 23.7 (22) | 21.3 (20) |
| **Difference (95% CI)** | 2.4 (–9.7, 14.4) | |
| **Known deceased** | 20.4 (19) | 18.1 (17) |
| **Unknown survival** | 3.2 (3) | 3.2 (3) |
| **Alive** | 76.3 (71) | 78.7 (74) |

Noninferiority (NI) achieved; upper bound of 95% CI was within the 20% NI margin.

#### Global response at Day 14 (±1 day)

| Endpoint | Proportion of Patients, % (n) Rezafungin 400/200 mg weekly n=93 | **Proportion of Patients, % (n)** Caspofungin 70/50 mg daily n=94 |
|---|---|---|
| **Global Cure[a] at Day 14** | 59.1 (55) | 60.6 (57) |
| **Difference (95% CI)[b]** | –1.1 (–14.9 to 12.7) | |
| **Failure** | 30.1 (28) | 30.9 (29) |
| **Indeterminate** | 10.8 (10) | 8.5 (8) |

NI achieved; lower bound of 95% CI was within 20% NI margin.
[a]Defined as 1) clinical cure as assessed by the investigator; 2) radiological cure for those patients with IC documented by radiologic/imaging evidence at baseline; and 3) mycological eradication, as confirmed by an independent DRC.
[b]Adjusted for the two randomization strata and APACHE II score/ANC at screening.

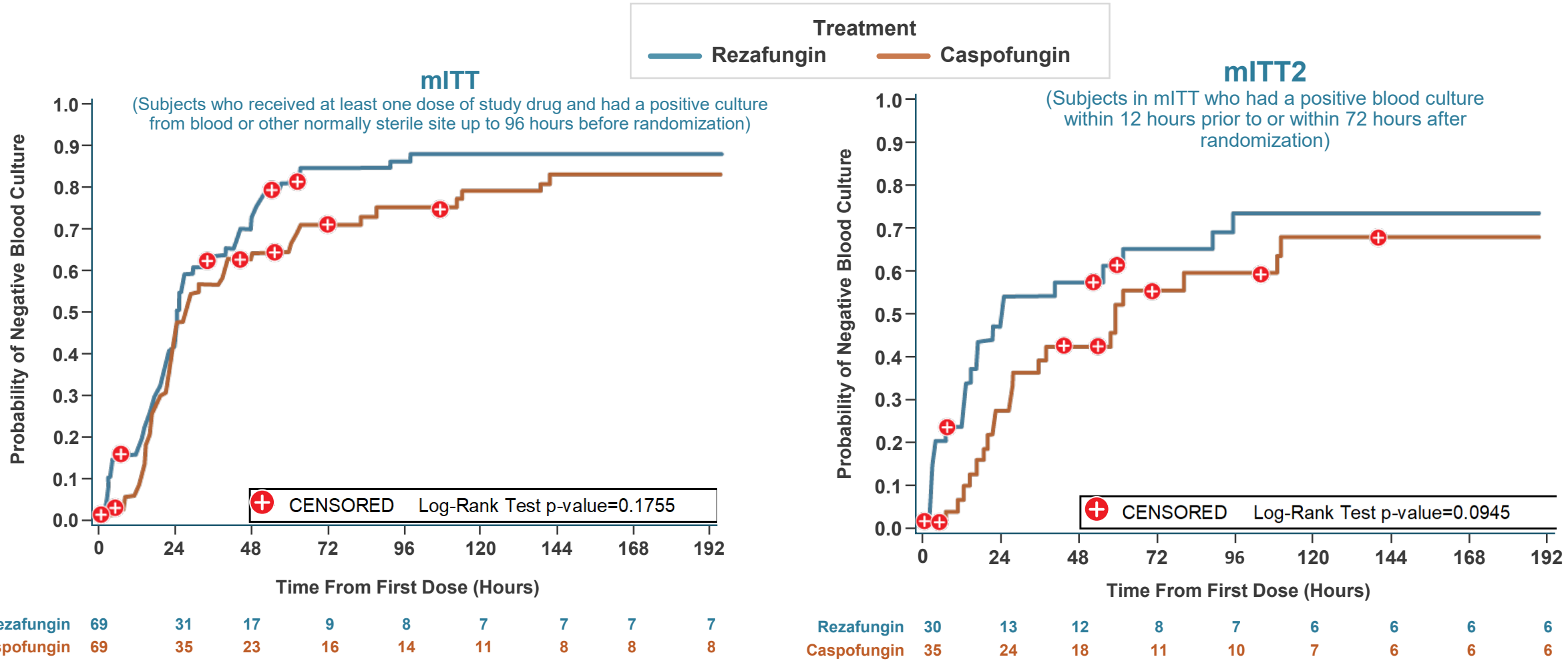
ACM: all-cause mortality; ANC: absolute neutrophil count; APACHE II: Acute Physiology and Chronic Health Evaluation II; CI: confidence interval; DRC: data review committee; NI: noninferiority.

1. ReSTORE CSR.

# Rezafungin Phase 3 Treatment Trial: ReSTORE

## Faster Time to Negative Blood Culture (mITT and mITT2 Populations)

### A trend toward shorter time to negative blood culture was observed for rezafungin



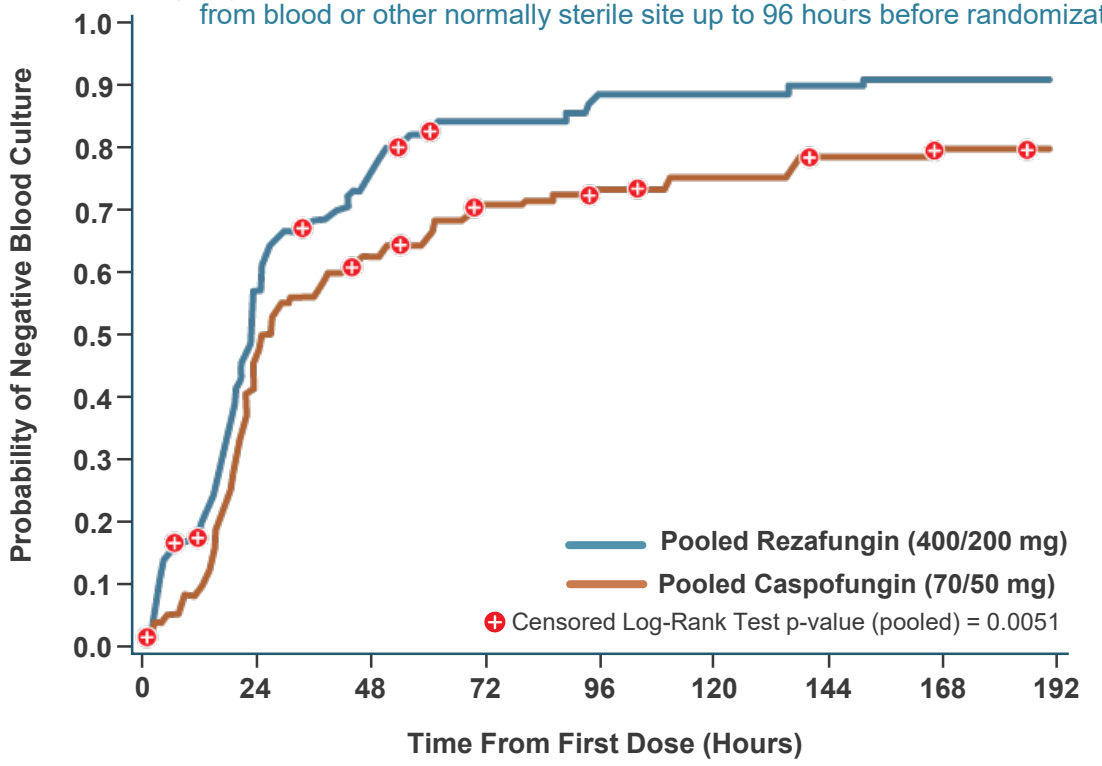

mITT: modified intent-to-treat; mITT2: patients with a positive blood culture proximal to randomization.

1. ReSTORE CSR.

# Rezafungin: STRIVE and ReSTORE Pooled Analysis
## Faster Time to Negative Blood Culture (mITT and mITT2 Populations)

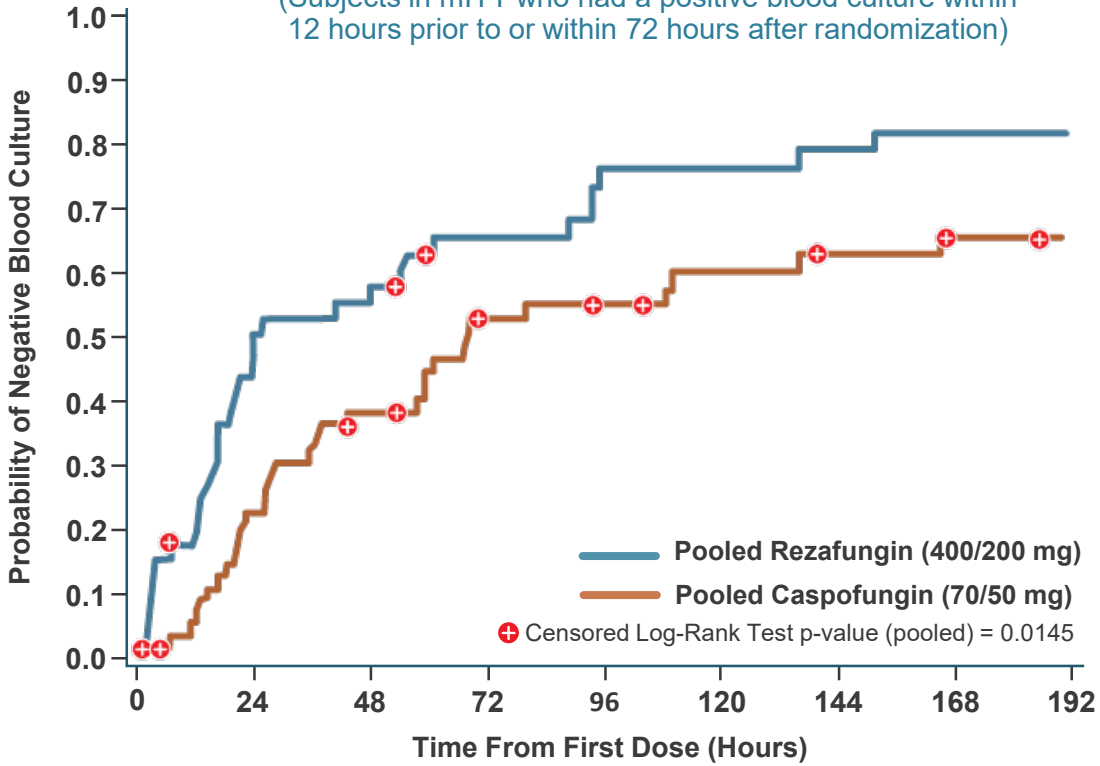
### Significant differences in time to negative blood culture

#### mITT
(Subjects who received at least one dose of study drug and had a positive culture from blood or other normally sterile site up to 96 hours before randomization)




| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Rezafungin | 109 | 42 | 23 | 13 | 10 | 9 | 8 | 7 | 7 |
| Caspofungin | 122 | 59 | 42 | 30 | 27 | 23 | 19 | 19 | 16 |

#### mITT2[a]
(Subjects in mITT who had a positive blood culture within 12 hours prior to or within 72 hours after randomization)




| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Rezafungin | 42 | 20 | 18 | 12 | 9 | 8 | 7 | 6 | 6 |
| Caspofungin | 53 | 39 | 30 | 20 | 18 | 15 | 13 | 13 | 10 |

*P*-values for the pooled groups is from a stratified log-rank test with Study ID and part as a stratum.
mITT: modified intent-to-treat; mITT2: patients with a positive blood culture proximal to randomization. [a]Positive culture from blood drawn within 12 hours prior to randomization or within 72 hours after randomization.
1. Soriano A et al. Presented at ECCMID 2022. Abstract no. 04673.

# Rezafungin Phase 3 Treatment Trial: ReSTORE

## TEAEs >5% by Treatment in the Safety Population

| TEAEs | Rezafungin 400/200 mg weekly (N=98), n (%) | Caspofungin 70/50 mg daily (N=98), n (%) |
|---|---|---|
| **Blood and lymphatic system disorders** | 15 (15.3) | 22 (22.4) |
| Anemia | 9 (9.2) | 9 (9.2) |
| **Cardiac disorders** | 16 (16.3) | 10 (10.2) |
| **Eye disorders** | 5 (5.1) | 1 (1.0) |
| **Gastrointestinal disorders** | 36 (36.7) | 29 (29.6) |
| Diarrhea | 6 (6.1) | 7 (7.1) |
| Vomiting | 6 (6.1) | 2 (2.0) |
| Abdominal pain | 5 (5.1) | 4 (4.1) |
| Constipation | 5 (5.1) | 3 (3.1) |
| Nausea | 5 (5.1) | 2 (2.0) |
| **General disorders and administration site conditions** | 29 (29.6) | 24 (24.5) |
| Pyrexia | 14 (14.3) | 5 (5.1) |
| Multiple organ dysfunction syndrome | 5 (5.1) | 2 (2.0) |
| **Hepatobiliary disorders** | 9 (9.2) | 10 (10.2) |
| **Infections and infestations** | 50 (51.0) | 48 (49.0) |
| Pneumonia | 10 (10.2) | 3 (3.1) |
| Septic shock | 10 (10.2) | 9 (9.2) |
| Sepsis | 6 (6.1) | 4 (4.1) |
| Bacteremia | 5 (5.1) | 3 (3.1) |

| TEAEs | Rezafungin 400/200 mg weekly (N=98), n (%) | Caspofungin 70/50 mg daily (N=98), n (%) |
|---|---|---|
| **Injury, poisoning, and procedural complications** | 11 (11.2) | 5 (5.1) |
| **Investigations** | 14 (14.3) | 13 (13.3) |
| **Metabolism and nutrition disorders** | 32 (32.7) | 31 (31.6) |
| Hypokalemia | 13 (13.3) | 9 (9.2) |
| Hypomagnesemia | 7 (7.1) | 3 (3.1) |
| Hypophosphatemia | 5 (5.1) | 4 (4.1) |
| Hyperkalemia | 2 (2.0) | 6 (6.1) |
| **Neoplasms benign, malignant, and unspecified*** | 6 (6.1) | 3 (3.1) |
| **Nervous system disorders** | 12 (12.2) | 11 (11.2) |
| **Psychiatric disorders** | 8 (8.2) | 9 (9.2) |
| **Renal and urinary disorders** | 11 (11.2) | 15 (15.3) |
| Acute kidney injury | 3 (3.1) | 8 (8.2) |
| **Respiratory, thoracic, and mediastinal disorders** | 22 (22.4) | 16 (16.3) |
| **Skin and subcutaneous tissue disorders** | 7 (7.1) | 11 (11.2) |
| **Vascular disorders** | 15 (15.3) | 16 (16.3) |
| Hypotension | 5 (5.1) | 6 (6.1) |

*Including cysts and polyps
TEAE: treatment-emergent adverse event.
1. ReSTORE CSR.

# Key Points – Phase 3 Randomized Controlled Trial (ReSTORE)

- Rezafungin QW was noninferior to caspofungin QD for both primary endpoints
  - ACM at Day 30: 23.7% vs 21.3% (2.4; 95% CI, -9.7, 14.4)
  - Global response at Day 14: 59.1% vs 60.6% (-1.1; 95% CI, -14.9, 12.7)
- Global cure and mycological eradication rates generally favored rezafungin at Days 5, 14, and 30
- A trend toward a shorter time to negative blood culture was observed for rezafungin
- Rezafungin was generally well tolerated, with a safety profile similar to caspofungin

ACM: all-cause mortality; QD: once daily QW: once weekly.

# Key Points – Phase 2 Randomized Controlled Trial (STRIVE)

- Overall cure rates were 60.5% for rezafungin 400 mg QW, 76.1% for rezafungin 400/200 mg QW, and 67.2% for caspofungin QD
- Investigator-assessed clinical cure rates were 69.7%, 80.4%, and 70.5%, respectively
- 30-day all-cause mortality was 15.8%, 4.4%, and 13.1%, respectively
- Candidemia was cleared in 19.5 and 22.8 hours in rezafungin and caspofungin patients, respectively
- No concerning safety trends were observed
- Rezafungin was associated with a shorter time to negative blood culture vs. caspofungin (*P*=0.02)

QD: once daily QW: once weekly.

# Code Request

**Administration Description**

Rezafungin is an antifungal drug being developed to treat invasive candidiasis and candidemia which is a life-threatening infection associated with high mortality and morbidity. Patients are frequently immunocompromised with significant underlying conditions and includes hematological malignancy patients and surgical patients, especially those admitted to the intensive care unit. Patients may be treated for multiple weeks and treatment needs to continue for 14 days following the last positive culture. The loading dose of 400 mg is administered over a one-hour long intravenous infusion on day 1 and then a maintenance dose of 200 mg on day 8 and once weekly thereafter.

**Documentation**

The administration of rezafungin will be documented either as a pharmacy order or infusion center order if administered as outpatient. The clinical documentation of the administration of rezafungin will likely be in the inpatient or outpatient's medical record. Melinta expects a patient’s medical record to include notes from the physician and nursing staff that describe the suspected infection and documentations including blood or specimen culture and laboratory tests such as susceptibility, at the treating healthcare provider’s discretion.

# Thank You