FDA Introductory Comments

NDA 217417 Rezafungin
Antimicrobial Drugs Advisory Committee Meeting
January 24, 2023

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OID/OND/CDER/FDA

Introduction

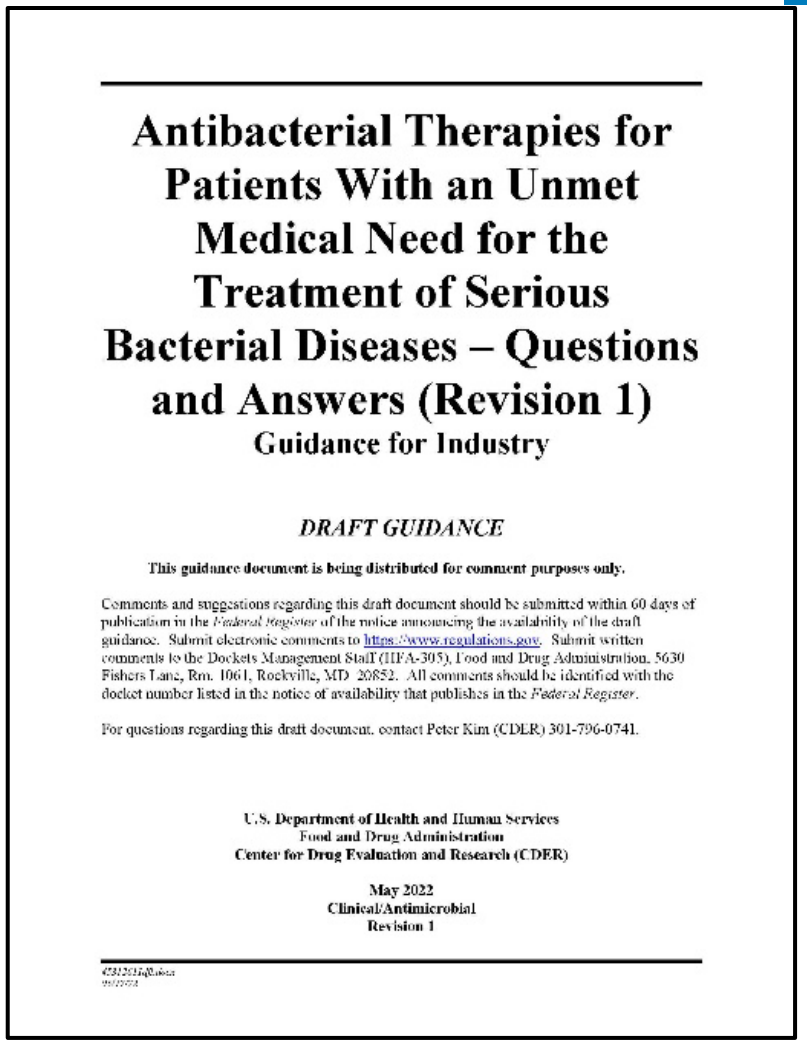
- The Applicant, Cidara Therapeutics, Inc., has submitted NDA 217417 for rezafungin for injection.
  - Rezafungin is a member of the echinocandin class of antifungals
- The proposed indication is treatment of candidemia and invasive candidiasis (IC) in patients 18 years of age and older.
- The proposed dosing regimen is once weekly administration by IV infusion, with an initial 400 mg loading dose followed by 200 mg once weekly thereafter.

Development Program

- Rezafungin has been granted Orphan Drug, Qualified Infectious Disease Product, and Fast Track designations for the treatment of candidemia/IC caused by susceptible *Candida* species.
- The NDA contains clinical data from:
  - One adequate and well-controlled phase 3 non-inferiority trial in adults with candidemia/IC
  - One exploratory dose-finding phase 2 study enrolling a similar population with candidemia/IC
  - Integrated phase 2/3 safety database consisting of 151 patients with candidemia/IC receiving the proposed rezafungin clinical dosing regimen, as well as an additional 81 patients with candidemia/IC receiving a higher rezafungin dose, for up to 28 days.

Drugs To Treat Serious Diseases In Patients With An Unmet Need

- For antibacterial drugs with the potential to treat serious infections in patients with few or no available treatments, FDA may consider a more flexible development program.
- This is aligned with 21 CFR part 312, subpart E (further discussion follows).
- We believe it may be appropriate to utilize a flexible development program in the antifungal space for select products, but we seek the committee's input.



Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases – Questions and Answers (Revision 1)

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Peter Kim (CDER) 301-796-0741.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2022
Clinical/Antimicrobial
Revision 1

Drugs To Treat Serious Diseases In Patients With An Unmet Need

21 CFR part 312, subpart E:

"The Food and Drug Administration (FDA) has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness. These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely debilitating illnesses, than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated."

Drugs To Treat Serious Diseases In Patients With An Unmet Need

- There must be adequate data to demonstrate the drug is safe and effective and the statutory standards for approval are met:
  - A drug's effectiveness must be established by substantial evidence defined as:
    - "evidence consisting of adequate and well-controlled investigations, including clinical investigations, . . ." [The United States Federal Food, Drug, and Cosmetic 505(d) 21 USC 355(d)]
    - Interpretated generally as requiring two adequate and well-controlled (A&WC) trials, each convincing on its own.
  - The Food and Drug Administration Modernization Act amended the provision to add that FDA may consider "data from one A&WC clinical investigation and confirmatory evidence".

Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (Draft, December 2019): https://www.fda.gov/media/133660/download

Adequate and Well-Controlled Trials

- The purpose of these trials is to distinguish the effect of the drug from other influences (spontaneous change, placebo effect, observational biases).

- 21 CFR 314.126 describes the trial design elements intended to minimize bias and permit a valid comparison with a control to assess the drug's effect.

Characteristics of Adequate and Well-Controlled Trials

1	Clear statement of objectives and proposed methods of analysis
2	Permits valid comparison with a control to provide quantitative assessment of drug effect
3	Method of selecting subjects provides assurance they have disease being studied – or evidence of susceptibility and exposure to disease to be prevented
4	Method of assignment to study arm minimizes bias and is intended to ensure comparability between groups
5	Measures to minimize bias on the part of subject, observers, analysts of the data
6	Method of assessing treatment response is well-defined and reliable
7	Analysis of the results is adequate to assess the drug's effects – analytic methods used, comparability of test and control groups, effects of any interim analyses

21 CFR 314.126

Considerations for Flexible Development Programs

- If the flexible development program involves smaller, shorter, or fewer clinical trials:
  - There may be less clinical safety data; and nonclinical toxicology studies may play a greater role in safety evaluations.
  - There may be smaller sample sizes and greater uncertainty in efficacy trials leading to greater reliance on nonclinical data such as activity of the drug at therapeutically relevant exposures in vitro and in animal models.

Labeling Considerations

- For anti-infective drugs developed under a flexible program:
  - The labeling should include the known risks and benefits as well as a description of the limitations of the data available to support approval.
  - The indication should identify the approved patient population for which FDA has determined the benefits of the drug outweigh the risks so that the healthcare community is informed of how to use the drug appropriately.
- Example wording for an indication based on use of a flexible development program for patients with a serious infection in the setting of limited or no alternative treatment options, what we will refer to as a “limited use indication”:
  - *Drug-X* is indicated for the treatment of *Infection-Y* in patients who have limited or no alternative treatment options. Approval of this indication is based on limited clinical safety and efficacy data.

Overview of the Day

- Presentations by the Applicant, Cidara Therapeutics, Inc.
- Presentations by FDA
  - Efficacy assessment by Dr. Xianbin Li
  - Nonclinical safety assessment by Dr. Owen McMaster
  - Clinical safety assessment by Dr. Shrimant Mishra
  - Clinical microbiology assessment by Dr. Jalal Sheikh
  - Clinical pharmacology assessment by Dr. Timothy Bensman
  - Summary comments by Dr. Heidi Smith
- Lunch
- Open public hearing
- Committee discussion
- Question to the Committee

Efficacy Assessment

NDA 217417 Rezafungin

Xianbin Li, Ph.D.
Statistical Reviewer, FDA/CDER/OTS/OB/DBIV

Proposed Indication and Efficacy Studies Reviewed

Proposed indication:

- Treatment of candidemia/invasive candidiasis (IC) in patients ≥18 years of age

Reviewed Studies:

- One phase 2 exploratory dose-finding trial (STRIVE)
- One phase 3 noninferiority trial (ReSTORE)

Both trials were multicenter, randomized, double-blind, active-controlled.

Phase 2 Trial: Design

- Primary objectives:
  - Safety and tolerability of rezafungin in the Safety Population
  - Overall success at Day 14 of study treatment in the microbiological ITT Population (mITT)
- The study had multiple parts:
  - Initially 1:1:1 randomization to high-dose rezafungin, low-dose rezafungin, or caspofungin group (Part A).
    - High-dose rezafungin: 400 mg on Day 1 and Day 8; optional 400 mg dose on Day 15 and Day 22
    - Low-dose rezafungin: 400 mg on Day 1, 200 mg on Day 8; optional 200 mg dose on Day 15 and Day 22
    - Caspofungin: 70 mg loading dose on Day 1 and then 50 mg/day up to a maximum of 28 days. After 3 days of IV therapy, subjects could be switched to oral stepdown therapy (fluconazole)
  - Prior to initiation of the phase 3 trial in order to increase numbers for the overall safety database, Part B was added via two protocol amendments using a 2:1 randomization ratio to rezafungin (high-dose, later changed to low-dose group) and caspofungin group.

Phase 2 Trial: Interim Analyses

- Two unblinded efficacy reviews:
  - One for selected efficacy and safety data on the first 70 subjects enrolled in Part A.
  - One for all parameters on all 107 subjects enrolled in Part A.
- Multiplicity was not addressed for this trial with a descriptive interpretation.

Phase 2 Trial: Analyses

- The primary efficacy outcome was overall response at Day 14 (resolution of signs of the disease and mycological eradication).
- Analyses were descriptive.
  - Only an exact 2-sided 95% confidence interval (CI) for the estimated overall success rate in each treatment group was planned.
- Mortality through Day 30 and the follow-up visit (Days 45-59) was an additional efficacy endpoint.

Phase 2 Trial: Day 30 All-Cause Mortality

	Rezafungin 400/400 mg N=76	Rezafungin 400/200 mg N=46	Caspofungin N=61
Deceased	18 (23.7%)	4 (8.7%)	10 (16.4%)
Known Death	12 (15.8%)	2 (4.3%)	8/23 (13.1%)
Unknown survival status	6 (7.9%)	2 (4.3%)	2 (3.3%)
Difference (95% CI) Reza-caspo	6.7% (-7.1%, 20.5%)	-7.0% (-21.2%, 7.3%)	

Phase 2 Trial: Mycological Eradication by Part

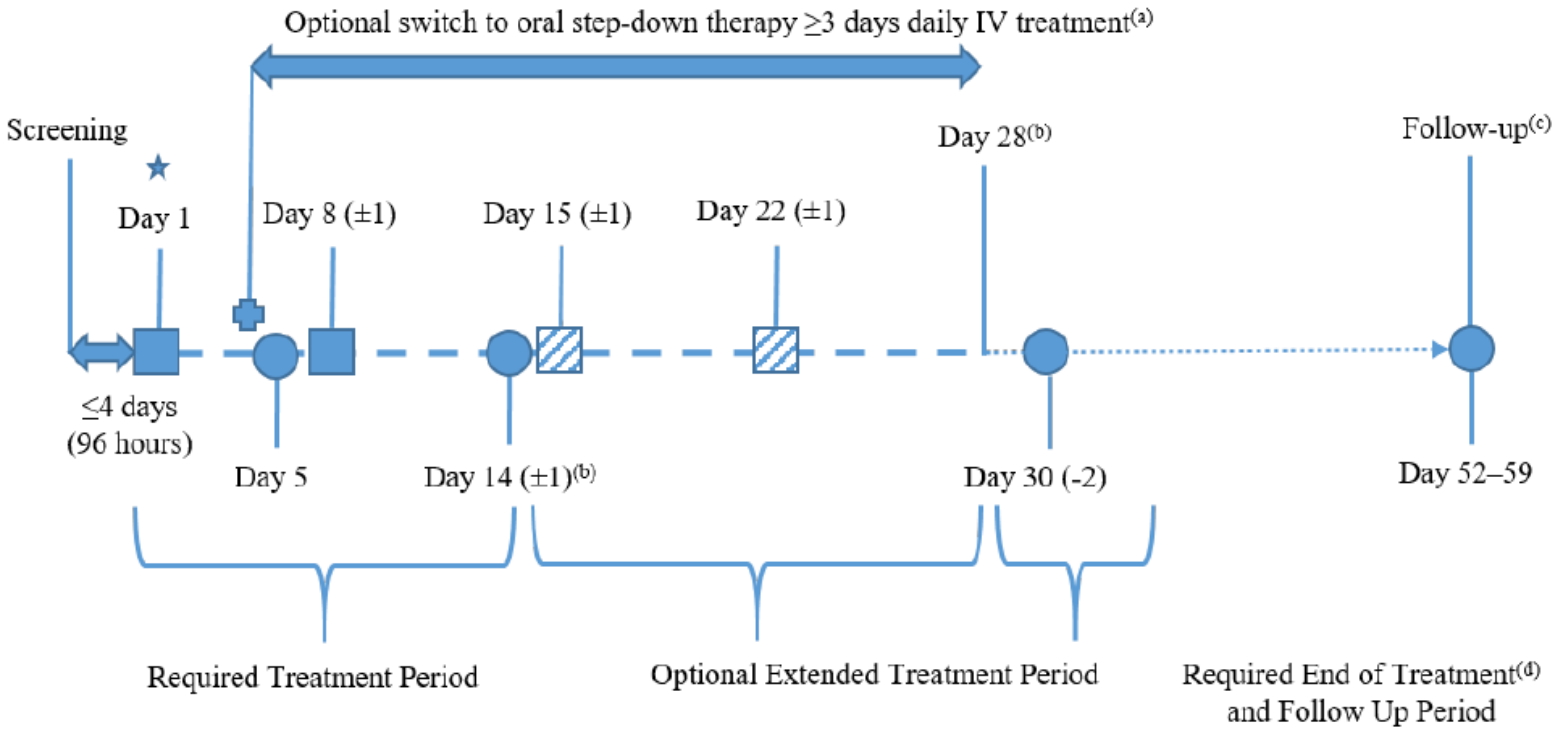
Day	Part	Rezafungin 400/400 mg	Rezafungin 400/200 mg	Caspofungin
5*	A	29/33 (87.9%)	24/31 (77.4%)	20/28 (71.4%)
	B1	25/43 (58.1%)	-	17/23 (73.9%)
	B2	-	14/15 (93.3%)	5/10 (50%)
	All	**54/76 (71.1%)**	**38/46 (82.6%)**	42/61 (68.9%)
14	A	25/33 (75.8%)	24/31 (77.4%)	20/28 (71.4%)
	B1	29/43 (67.4%)	-	18/23 (78.3%)
	B2	-	13/15 (86.7%)	6/10 (60%)
	All	**54/76 (71.1%)**	**37/46 (80.4%)**	44/61 (72.1%)

* Both rezafungin groups had received a single 400 mg dose by this assessment timepoint

Phase 2 Trial Conclusions

- The study provided initial evidence suggesting efficacy to allow for further study of rezafungin in a pivotal study.
- Caution is needed when interpreting the results from this exploratory study due to:
  - Lack of inferential testing
  - Multiple amendments and interim analyses with no multiplicity adjustment
  - The differences observed between the 2 rezafungin groups at Day 5 when both groups had received the same dose

Phase 3 Trial Diagram



Phase 3 Trial Design

- **Treatment groups**
  - Rezafungin: same dose as the low-dose group in phase 2 trial
  - Caspofungin: same as in the phase 2 trial
- **Randomization:** 1:1 by randomization strata (diagnosis, APACHE II score and ANC)
- **mITT Population**: Randomized subjects who received any amount of study drug and had documented *Candida* infection from a baseline specimen. This population was used for the primary efficacy analysis.

APACHE II = acute physiology and chronic health evaluation II; ANC = absolute neutrophil count

Phase 3 Trial Endpoints

- Primary efficacy endpoint: Day 30 all-cause mortality (ACM), assessed using a 20% noninferiority margin (NI) margin
- Secondary efficacy endpoints:
  - Global response (cure, failure, indeterminate)
  - Mycological response (eradication, failure, indeterminate)
  - Clinical response (cure, failure, indeterminate)
  - Radiological response (for subjects with IC)

Noninferiority Margin for Day-30 ACM

- A justification of the NI margin was conducted by the Applicant and the FDA.
  - The FDA determined that the treatment effect of an echinocandin-based regimen (M1) was at least 31%. Derived using:
    - An estimate of the Day-30 ACM rate for no treatment/inadequate treatment determined based on a literature search that identified clinical studies or other historical evidence on the effect of no treatment or inadequate treatment in patients with candidemia and invasive candidiasis.
    - An estimate of the Day-30 ACM rate for treatment with an echinocandin-based regimen determined based on the 4 contemporary clinical trials that were conducted in support of the approvals of caspofungin, anidulafungin, and micafungin.
  - Noting the importance of preserving the treatment effect for an endpoint of ACM from a clinical perspective, a 10% NI margin was recommended for a pivotal phase 3 trial. However, a wider NI margin of 20% could be considered to obtain a limited use indication.

Phase 3 Trial: Subject Disposition

Parameter, n(%)	Rezafungin 400/200 mg	Caspofungin
ITT population	100 (100.0)	99 (100.0)
mITT population	93 (93.0)	94 (94.9)
Discontinuation from study	41 (41.0)	40 (40.4)
Death	22 (22.0)	21 (21.2)
Discontinuation of treatment	34 (34.0)	28 (28.3)
Adverse event	8 (8.0)	7 (7.1)
Death	8 (8.0)	8 (8.1)

Phase 3 Trial: Demographics and Clinical Factors

Parameter, n(%)	Rezafungin 400/200 mg (N = 93)	Caspofungin (N = 94)
Age, mean (SD)	59.5 (15.80)	62.0 (14.57)
Sex, male (%)	67 (67.0)	56 (56.6)
Diagnosis		
Candidemia only	73 (73.0)	68 (68.7)
Invasive candidiasis	27 (27.0)	31 (31.3)
APACHE II/ANC (cells/μL)		
APACHE II ≥20 or ANC<500	22 (22.0)	21 (21.2)
APACHE II <20 and ANC≥500	75 (75.0)	78 (78.8)

APACHE II = acute physiology and chronic health evaluation II; ANC = absolute neutrophil count

Phase 3 Trial: Primary Efficacy Endpoint: Day 30 All-Cause Mortality in the mITT Population

	Rezafungin 400/200 mg (N = 93)	Caspofungin (N = 94)
Deceased	22 (23.7%)	20 (21.3%)
Known Death	19	17
Unknown Survival Status	3	3
Survived	71	74
Difference (95% CI)	2.4% (-9.7%, 14.4%)	

Phase 3 Trial: Global Response

Cure	Rezafungin 400/200 mg (N = 93)	Caspofungin (N = 94)	Diff (95% CI)
Day 5	52 (55.9%)	49 (52.1%)	3.8 (-10.5, 17.9)
Day 14	55 (59.1%)	57 (60.6%)	-1.5 (-15.4, 12.5)
Day 30	46 (49.5%)	46 (48.9%)	0.5 (-13.7, 14.7)
EOT*	56 (60.2%)	59 (62.8%)	-2.6 (-16.4, 11.4)
Follow-up (Days 52–59)	42 (45.2%)	39 (41.5%)	3.7 (-10.5, 17.7)

*EOT (End of Treatment) was to occur within 2 days of the last dose and could be before Day 30, not a fixed timepoint for all subjects

Phase 3 Trial: Mycological Response

Eradication	Rezafungin 400/200 mg (N = 93)	Caspofungin (N = 94)	Diff (95% CI)
Day 5	**64 (68.8%)**	**58 (61.7%)**	7.1 (-6.6%, 20.6%)
Day 14	63 (67.7%)	62 (66.0%)	1.8 (-11.7%, 15.2%)
Day 30	56 (60.2%)	53 (56.4%)	3.8 (-10.3%, 17.8%)
EOT*	63 (67.7%)	63 (67.0%)	0.7 (-12.7%, 14.1%)
Follow-up (Days 52–59)	48 (51.6%)	49 (52.1%)	-0.5 (-14.7%, 13.7%)

*EOT was to occur within 2 days of the last dose and could be before Day 30, not a fixed timepoint for all subjects

Phase 3 Trial: Clinical Response

Cure	Rezafungin 400/200 mg (N = 93)	Caspofungin (N = 94)	Diff (95% CI)
Day 5	**59 (63.4%)**	**70 (74.5%)**	-11.0% (-24.0%, 2.3%)
Day 14	62 (66.7%)	63 (67.0%)	-0.4% (-13.8%, 13.1%)
Day 30	51 (54.8%)	52 (55.3%)	-0.5% (-14.6%, 13.7%)
EOT*	65 (69.9%)	64 (68.1%)	1.8% (-11.5%, 15.0%)
Follow-up (Days 52–59)	46 (49.5%)	44 (46.8%)	2.7% (-11.6%, 16.8%)

*EOT was to occur within 2 days of the last dose and could be before Day 30, not a fixed timepoint for all subjects

Phase 3 Trial Conclusions

- The trial demonstrated noninferiority of rezafungin to caspofungin with respect to Day 30 ACM, using a 20% NI margin.
- It provided evidence for efficacy to support an indication with a limited use statement.

Pooling of Phase 2 and 3 Trials

- Applicant does not propose a limited use indication.
- The results of the phase 2 and 3 studies pooled:
  - The upper bound of the 95% CI for the difference in Day 30 ACM analysis of the pooled phase 2 and phase 3 studies conducted for the Integrated Summary of Efficacy was 7.7%
    - Difference -1.5% and 95% CI (-10.7%, 7.7%)
- Due to the issues with the phase 2 trial mentioned before, we do not consider that the pooled results are sufficient for claiming a 10% NI margin was met.

Statistical Issues with Pooling Phase 2 and 3 Trials

Potential for inflating the estimate of the treatment effect

- The primary assessment was not prespecified to be based on the integrated results.
  - Need for supportive evidence given a single phase 3 trial

Potential for the phase 2 trial to overestimate the efficacy of low-dose rezafungin selected for further development because the observed differences from high-dose rezafungin were possibly due to chance

- Observed differences between rezafungin groups seen at Day 5 when no difference would be expected from the pharmacological and clinical perspective
- From adaptive design guidance*: “For trials intended to provide substantial evidence of effectiveness, statistical hypothesis testing methods should account for the adaptive selection of a best dose or doses from among the multiple doses evaluated in the trial.”

*FDA, Adaptive Designs for Clinical Trials of Drugs and Biologics. https://www.fda.gov/media/78495/download

Efficacy Summary

- We do not agree with pooling the phase 2 and 3 trials as the primary assessment of efficacy in support of the indication claim.
- Primary assessment of efficacy is based on the results of the phase 3 study. The phase 2 study provides supportive evidence.
- The phase 3 study was designed with and met a 20% NI margin which was determined to be an acceptable margin from a clinical standpoint to support a limited use indication. The study did not meet a 10% NI margin.

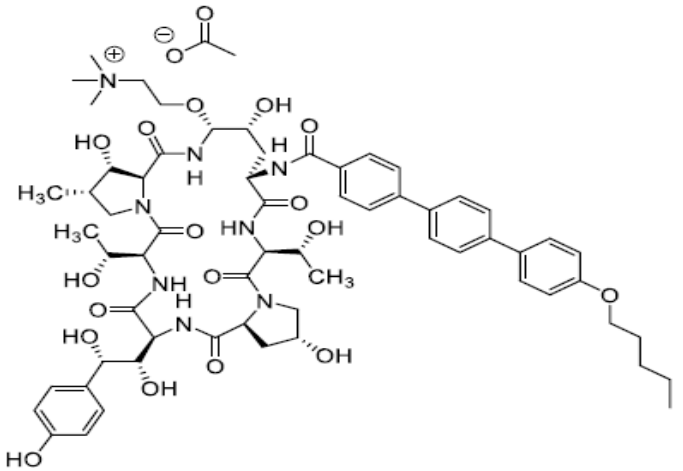
Rezafungin Tremors

Owen McMaster, Ph.D.

Pharmacology/Toxicology Reviewer DPTID/OID/OND/CDER/FDA

Rezafungin

- A semi-synthetic echinocandin synthesized from ERAXIS® (anidulafungin)
- ERAXIS® (anidulafungin) is associated with tremor in pediatric patients
- CANCIDAS® (caspofungin acetate) lists tremor among adverse reactions
- Cationic amphiphilic drug (CAD)
- Phospholipidosis-concentrically lamellated accumulations of osmiophilic membranous/lipid rich material. Considered nonadverse



Rezafungin Pharmacokinetics in Monkey

- Slow Plasma Elimination: Plasma $T_{½}$: 39 to 59 hours
- Highest exposure observed in spinal nerve dorsal root ganglia, (44,605 µg equiv•h/g) compared to liver (39,575 µg equiv•h/g), or blood (3,184 µg equiv•h/g)*
- Elimination of radioactivity from tissues was very slow.
- Spinal nerve $T_{½}$ estimated to be 874 hr

*NC-162 Pharmacokinetics: Excretion Mass Balance, Pharmacokinetics, and Tissue Distribution by Quantitative Whole-Body Autoradiography in Monkey

Tremors in Pivotal Monkey Studies

- NC-118: A 3-Month Once Every 3 Days Intravenous Infusion Toxicity and Toxicokinetic Study of CD101 in Cynomolgus Monkeys with a 4-Week Recovery Period

- NC-154: A 13-week Investigative Repeat-dose Intravenous (20-Minute) Infusion Neurotoxicity Study of CD101 in Female Cynomolgus Monkeys with a 13-Week Recovery Period

- NC-190: A 26-Week Once Weekly Intravenous Infusion Toxicity and Toxicokinetic Study of Rezafungin in Mature Cynomolgus Monkeys with a 52-Week Recovery Period

Definitions

- **Tremors:** involuntary twitching or trembling of muscles characterized by small contractions of localized area of the body which may be continuous or intermittent.
- **Intention tremors:** tremors that were more pronounced when movements are initiated.
- Cidara does not consider tremors to be adverse
- **Cidara Proposed Prescribing Information:**

  13.2 Animal Toxicology and/or Pharmacology

  No adverse findings occurred in monkeys after either 4 or 13 weeks of dosing at 30 mg/kg administered every 3 days (9 times the clinical AUC exposure)

NC-118: A 3-Month Once Every 3 Days Intravenous Infusion Toxicity and Toxicokinetic Study of CD101 in Cynomolgus Monkeys with a 4-Week Recovery Period

- Cynomolgus monkeys, *Macaca fascicularis*; of Chinese origin, 2 to 4 years old
- Sexual maturity is reached at four years of age for the female and six years of age for the male
- Rezafungin doses 0, 3, 10, 30, 60 mg/kg
- 60 mg/kg was about 16 times the clinical dose based on AUC comparisons
- 3 monkeys/sex (plus 2 recovery animals/sex at 0, 30 and 60 mg/kg)
- Due to an increased incidence of neurobehavioral-related findings in the Group 5 females as well as the declining condition of several animals within the group, dosing was terminated early (after 7 weeks of dosing) and early primary necropsy was scheduled on Day 49

Study 118: Tremors

- Tremors were typically seen during or around the time of infusion
- Tremors were seen in the 3 mg/kg/dose group (female on Day 84)
- Tremors were seen in a 10 mg/kg/dose female on Day 70
- Tremors in the 30 mg/kg/dose group began on Day 48
- Tremors in the 60 mg/kg/dose group occurred as early as Day 35, continuing throughout the dosing period
- Recovery animals: Intention tremors were observed on 2 occasions in a single 60/45 mg/kg/dose group female during the second and third week of the recovery period

Report Title: A 3-Month Once Every 3 Days Intravenous Infusion Toxicity and Toxicokinetic Study of CD101 in Cynomolgus Monkeys with a 4-Week Recovery Period

Test article: Rezafungin (CD101, Biafungin, SP-3025)

Dose (mg/kg)	0 (Control)		3		10		30		60/45[a]	
Number of animals	**M:5**	**F:5**	**M:3**	**F:3**	**M:3**	**F:3**	**M:5**	**F:5**	**M:5**	**F:5**
Clinical observations										
Intention tremors										
Prior to infusion	0	0	0	0	0	0	0	3	4	5
1 to 2 hours post infusion	0	0	0	0	0	0	1	3	4	5
3 to 4 hours post infusion	0	0	0	0	0	0	0	2	4	5
Non-dosing day	0	0	0	0	0	0	2	0	4	4
Unscheduled observation	0	0	0	0	0	0	0	0	1	0
At physical examination	0	0	0	0	0	0	2	1	4	4
Tremors										
Prior to infusion	0	0	0	0	0	0	0	0	1	0
Immediately post infusion	0	0	0	0	0	0	1	4	3	5
1 to 2 hours post infusion	0	0	0	0	0	0	0	1	0	4
3 to 4 hours post infusion	0	0	0	0	0	0	0	1	2	1
Non-dosing day	0	0	0	0	0	0	0	0	2	0
Unscheduled observation	0	0	1	1	0	0	0	0	4	2
At physical examination	0	0	0	0	0	1	0	2	0	2

NC-118: Axonal Degeneration, Hyperplasia, Demyelination

- Severe axonal degeneration of multiple fascicles in the right sciatic nerve at the terminal necropsy in one male at 60/45 mg/kg. After recovery, one 60/45 mg/kg male had moderate axonal degeneration in the left sural nerve.
- Increased cellularity/hyperplasia of Schwann cells in some sensory ganglia and peripheral nerves of a few animals at 30 mg/kg/dose groups and all animals at 60/45 mg/kg. Schwann cell hyperplasia persisted through the recovery necropsy. Schwann cell hyperplasia is a common, very prominent feature of nerve fiber degeneration
- Demyelination (mild to moderate severity) at ≥ 30 mg/kg at the end of dosing and in recovery animals. Electron microscopy confirmed thinning, loss, and splitting of the compact myelin sheath, at the 30 and 60/45 mg/kg/dose groups but with higher incidence and severity in the 60/45 mg/kg/dose group.
- Minimal to marked intracytoplasmic inclusions in the peripheral nerves at all doses was considered evidence of nonadverse phospholipidosis

13 Week Female Cynomolgus Monkey Study with 13 Week Recovery Period (Study NC-154)

- More detailed neurobehavioral assessments such as measures of nerve conduction velocity
- 30 mg/kg rezafungin (9 times the clinical exposure based on AUC)
- Females only. More sensitive in the previous 13-week toxicity study.
- Juvenile (3- to 5-year-old) Cynomolgus monkeys. Sexual maturity is reached at four years of age for the female

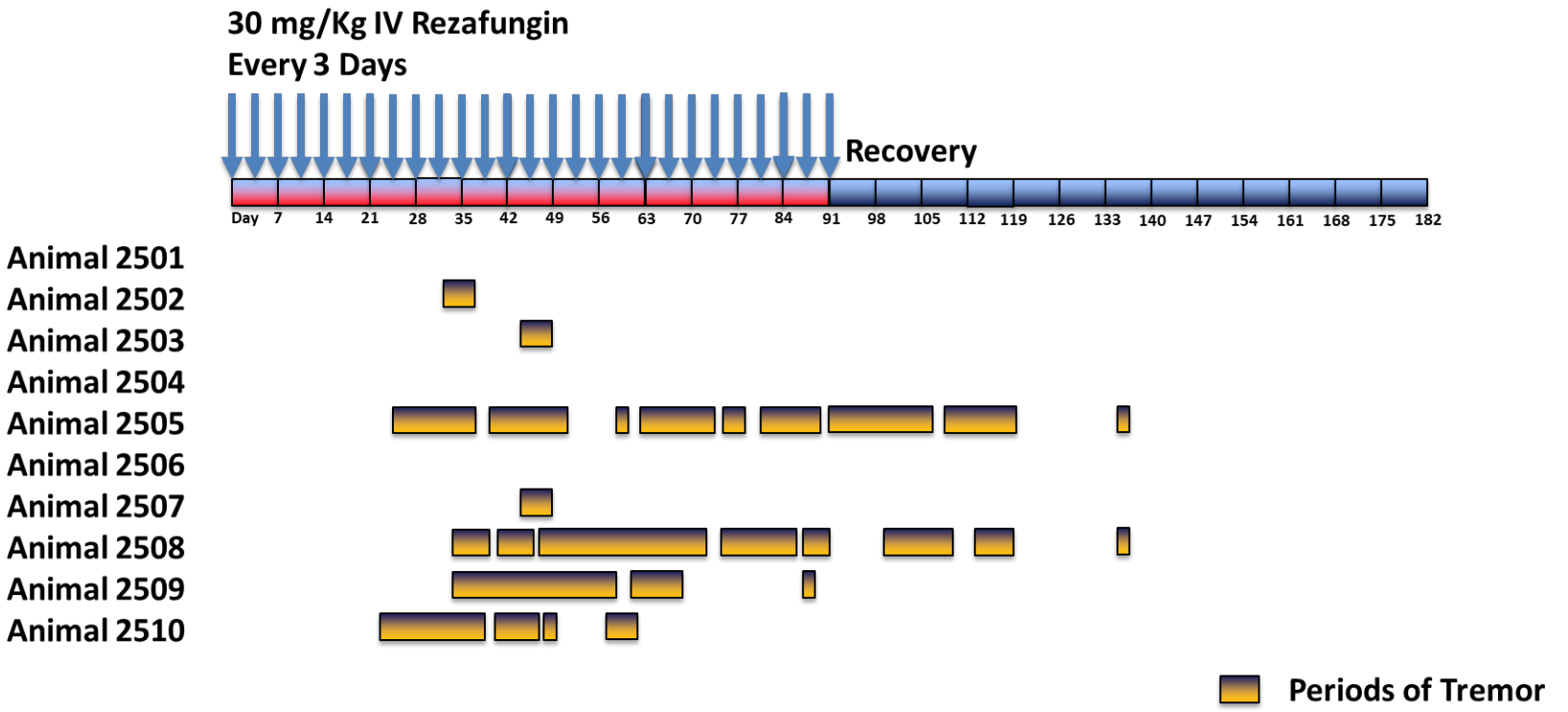
13 Week Female Cynomolgus Monkey Study with 13 Week Recovery Period (Study NC-154)

Text Table 1
Experimental Design

Group Number	Treatment	Dose Level[a] (mg/kg/dose)	Concentration (mg/mL)	Dose Volume[b] (mL/kg)	Number of Animals[c]
					Females
1	Vehicle	0	0	5	6
2	CD101	30	6.0	5	10

[a] Corrected for purity/potency based on potency of 86.7%; thus, the correction factor was 1.15.
[b] Five animals from Group 2 and 3 animals from Group 1 were assigned to the terminal necropsy. The remaining 5 animals from Group 2 and 3 animals from Group 1 were assigned to 93 days of recovery.
[c] The dose volume was consistent with previous study.[1]

13 Week Female Cynomolgus Monkey Study with 13 Week Recovery Period (Study NC-154)



NC-154: Necropsy Findings in Animal 2505

- Schwann Cell Proliferation
- Axonal Degeneration and Regeneration
- Vacuolated Histiocytes
- Decreased Myelin Sheath
- Inclusions in Schwann cells, did not reverse during the 13-week recovery period

Summary NC-154

- Tremors began on Day 22, persisted 44 days after the end of dosing (Day 134)
- In female animal 2505, in a portion of the sciatic nerve and essentially the entire tibial, sural, and medial plantar nerves (all branches of the sciatic nerve) there was demyelination, axonal degeneration, vacuolated histiocytes, axonal regeneration, Schwann cell proliferation
- Nonadverse Findings
- Inclusions in Schwann cells (in the dorsal and ventral spinal nerve roots, the trigeminal nerve, the sciatic, tibial, sural, and/or medial plantar nerves, and nerves serving the sympathetic ganglia) in the terminal necropsy and recovery animals.
- This finding did not reverse during the 13-week recovery period.

NC-190: A 26-Week Once Weekly Intravenous Infusion Toxicity and Toxicokinetic Study of Rezafungin in Mature Cynomolgus Monkeys with a 52-Week Recovery Period

- Once weekly dosing
- 0, 5, 15, 30 mg/kg (up to 9 times clinical exposure)
- 26 weeks dosing
- Adult cynomolgus monkeys (6-10 years old)
- 6/sex
- Blinded evaluations of clinical signs
- Assess toxicokinetics of weekly dosing
- Nerve conduction evaluations
- 52-week reversibility period

NC-190: Tremors in All Study Groups

Dose Level (mg/kg)	Sex	Involvement	Total	Mean	Comment
0	M	5 of 6	59	11.8	The signs were observed generally while the monkeys were being dosed, and they were dosed once weekly. There were, thus, 26 opportunities to observe tremors.
	F	2 of 6	12	6	
5	M	5 of 6	41	8.2	
	F	4 of 6	16	4	
15	M	5 of 6	30	6.0	
	F	2 of 6	8	4	
30	M	6 of 6	67	11.2	
	F	4 of 6	20	5	

M = male; F = female
Involvement = number of monkeys within a group displaying the sign at least once during the 26-week dosing period.
Mean = the number of occurrences divided by the number of monkeys for which the sign was recorded.

Tremor Severity

- *Minimal:*
- Barely perceptible, no impact to quality of life (able to grasp and manipulate food normally, has normal locomotion and gait, exhibits normal posture)
  - *Observed in all study groups , including controls*
- *Moderate:*
- Easily perceptible, no impact to quality of life (able to grasp and manipulate food normally, has normal locomotion and gait, exhibits normal posture)
  - *Observed once in one 5 mg/kg monkey. Day 69, M9016*
  - *Observed on 8 occasions in one 15 mg/kg animal beginning Days 63-133, M9002*
- *Severe:*
- Overtly perceptible, affects quality of life (impacts ability to grasp or manipulate food or impairs ability to move normally, or affects posture)
  - *30 mg/kg animal, Day 152, M9017. Missed his mouth a couple of times with treats.*

NC-190 Findings

- Main study animals
- Increased incidence of moderate tremors in rezafungin-treated animals
- Minimal axonal degeneration in the medial plantar nerve of 30 mg/kg group male
- Recovery Evaluations
  - Minimal axonal degeneration observed in the sural nerve of a 5 mg/kg female and the medial plantar nerve of a 30 mg/kg female after
- Phospholipidosis
- Phospholipidosis (lysosomes filled with lipid/membranous material) in the dorsal spinal nerve root, peripheral nerves, sympathetic nerves and/or trigeminal nerve of 5, 15, and 30 mg/kg groups males and females at the end of dosing and in some recovery animals

Increased incidence of moderate tremors in rezafungin-treated animals

Tremors, Adverse or Nonadverse?

- NC-190 confirmed drug-related increase in moderate tremors after weekly rezafungin
- Cidara does not consider these tremors to be adverse, since tremors “did not interfere with daily activities”
- FDA takes the position that tremors are adverse at any treatment dose unless a known mode of action determines the observation irrelevant
- In one monkey tremors were so severe, he missed his mouth on several occasions. Interfering with daily activities.

Rezafungin Summary

- Rezafungin is an echinocandin synthesized from anidulafungin, which lists tremors among potential adverse effects in its prescribing information.
- Tremors were increased in rezafungin-treated juvenile monkeys, as early as Day 22 following every-3-day dosing
- In 13-week, every 3-day dosing monkey studies, tremors persisted up to 44 days after the end of dosing
- In a blinded, follow-up, 6-month, study of weekly rezafungin in adult monkeys, a drug-related increase in moderate and severe tremors was observed
- Rezafungin dosing was also associated with histopathological evidence of axonal degeneration, demyelination and Schwann cell proliferation
- Rezafungin administration is consistently associated with dose-related neurotoxicity, including tremors in monkeys

Clinical Safety Assessment

NDA 217417 Rezafungin

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Medical Officer, DAI/OND/CDER/FDA

Clinical Safety Database

- Eight Phase 1 studies
- Phase 2 and Phase 3 studies (formed Integrated Summary of Safety [ISS])
  - 232 rezafungin treated patients
    - **151 rezafungin subjects at proposed dose (400mg/200mg)**
    - Median duration 14 days; Maximum 28 days
    - An additional 81 patients studied at 400mg/400mg dose
- Expanded access patients
- Ongoing studies
  - Phase 3 Prophylaxis study (13 weeks treatment); Phase 3 Extension of IC/Candidemia study (China)

Overview of Adverse Events (AE), ISS

Event Category	Reza (400/200 mg) N=151 n (%)	Caspo N=166 n (%)	Reza (400/200 mg) vs. Caspo Risk Difference (%) (95% CI)
Any AE	138 (91.4)	138 (83.1)	8.3 (1.0, 15.5)[a]
Severe and worse	75 (49.7)	85 (51.2)	-1.5 (-12.6, 9.5)
Moderate	38 (25.2)	30 (18.1)	7.1 (-2.0, 16.2)
Mild	25 (16.6)	23 (13.9)	2.7 (-5.2, 10.6)
Serious Adverse Event (SAE)	83 (55.0)	81 (48.8)	6.2 (-4.8, 17.2)
SAEs with fatal outcome	35 (23.2)	40 (24.1)	-0.9 (-10.3, 8.4)
AE leading to permanent discontinuation of study drug	14 (9.3)	15 (9.0)	0.2 (-6.1, 6.6)

Deaths, ISS

- Septic shock, multiple organ dysfunction syndrome, sepsis most common etiologies in rezafungin arm
- Case narratives examined- no death could reasonably be attributed to rezafungin
  - Significant comorbidities and coinfections; palliative care
- Similar findings with SAEs overall in rezafungin arm

Treatment Emergent Adverse Events (TEAE), ISS

- TEAEs occurring in the rezafungin arm at ≥ 10% incidence in rezafungin arm: hypokalemia (14.6%), pyrexia (11.9%), and diarrhea (11.3%)
- Pyrexia and vomiting occurred in the rezafungin arm at a rate at least 5% greater than in the caspofungin arm

Adverse Events of Special Interest

- Phototoxicity
  - Erythema with UV light exposure
- Infusion Reactions
  - Known class reaction
  - Warmth, nausea, abdominal discomfort, chest tightness/dyspnea
  - Occasional treatment discontinuations
- Neurotoxicity (including tremors and peripheral neuropathy)

Neurotoxicity

- In the ISS dataset, the incidence of AEs in the *nervous system disorders* system organ class between the rezafungin arm (22 of 151; 14.6%) and the caspofungin arm (20 of 166; 12.0%) was similar.
- An imbalance in the incidence of tremors was noted, with a higher incidence in the rezafungin arm
  - 4 cases rezafungin arm vs. 0 cases caspofungin arm
- Other neurological AESIs occurred at similar rates in both treatment arms.
- 400mg/400mg arm no cases of tremor, ataxia, or peripheral neuropathy

Tremors

- Listed as Adverse Reaction in caspofungin and anidulafungin labeling
- 4 cases noted in the rezafungin arm in the ISS dataset; none in caspofungin arm
- Generally had alternative plausible etiologies
  - Electrolyte disturbance
  - Neurologic comorbidities

Tremors – Clinical Cases

- 84 y/o female developed mild rest and intention tremors in upper extremities 3 days after second weekly infusion. Continued with 2 more weekly infusions. Tremors resolved approximately 1 month later without specific therapy.
- 67 y/o male with Parkinson's Disease and acute right-sided CVA developed mild tremors of both upper extremities along with left eye deviation, left facial twitching 12 days after last (second) infusion. Resolved the next day.
- 77 y/o female developed mild tremors of both hands 13 days after last (second) weekly infusion. Intention tremor with application of eye makeup and resolved 1 month later. Had concomitant hypokalemia and both tremors and hypokalemia (treated with spironolactone) resolved at the same time.
- 28 y/o female with tremors of hands and feet 4 days after last (second) infusion. Resolved two days later without specific treatment. Had concomitant hypocalcemia and given calcium gluconate on day tremors resolved.

Clinical Safety Conclusions

- While the size of the safety database is modest, the safety findings are consistent with the expectations for the echinocandin class in this patient population
- Assessment of neurotoxicity potential ongoing
- Current safety assessment covers up to 4 weeks of drug exposure only
  - Chronic exposure (up to 13 weeks) being evaluated in ongoing prophylaxis study

Assessment of Rezafungin's Antimicrobial Activity Relative to the FDA-Approved Echinocandins: NDA 217417

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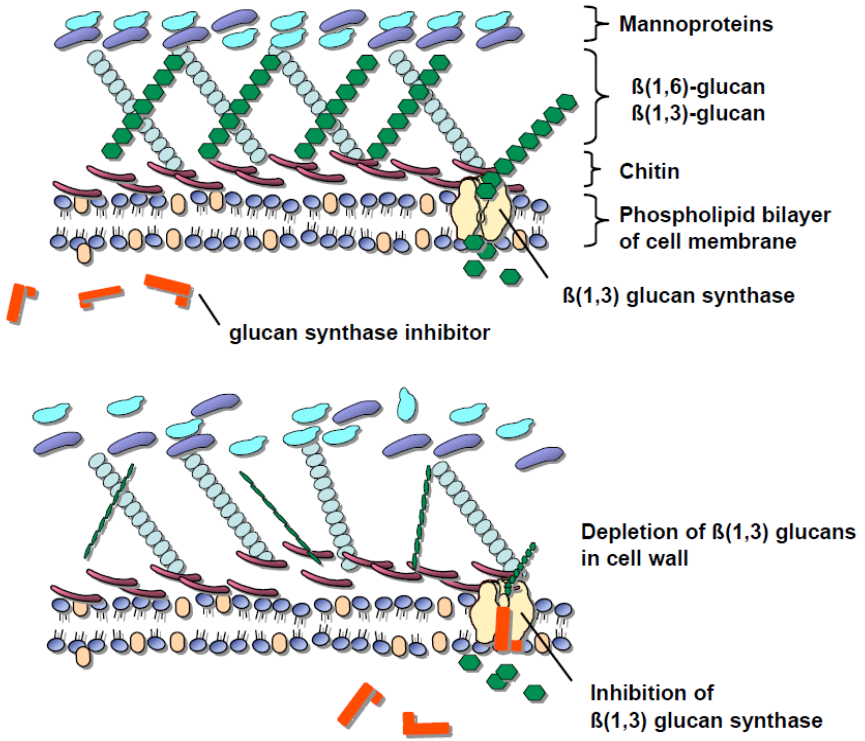
Echinocandins: Mechanisms of Action (MOA), and Resistance Mechanism

Echinocandins MOA



Echinocandin Resistance

- Mutations in *fks1*, *fks2*, *fks3*
- Mutations happen in the highly conserved 'hot spot' regions (HS1 and HS2) of *fks1* and *fks2*
- HS regions are only 8-9 aa long located in different positions of FKS1 and FKS2 proteins

Rezafungin: microbiology

- Rezafungin is a 2nd generation echinocandin drug and a structural analogue of anidulafungin.
- The structural modification provides rezafungin improved chemical stability to host degradation pathways and increases $t_{1/2}$ life that allows weekly dosing.
- Similar to other echinocandins, rezafungin demonstrates in vitro and in vivo activity against most *Candida* species including *C. auris* and some filamentous fungal species.

In vitro MIC90 values: Rezafungin and other echinocandins

MIC90 values (mcg/mL) of *Candida* spp. isolates from 2018-2020 Surveillance Studies						CDC Study[a]
Echinocandin Drugs	*C. albicans* (n=943)	*C. glabrata* (n=407)	*C. tropicalis* (n=244)	*C. parapsilosis* (n=356)	*C. krusei* (n=147)	*C. auris* (n=100)
Rezafungin	0.06	0.06	0.06	2	0.06	0.5
Anidulafungin	0.06	0.12	0.06	4	0.06	2
Caspofungin	0.03	0.06	0.06	0.5	0.25	0.5
Micafungin	0.03	0.03	0.06	1	0.12	2

Source: NDA-217417; Appendix 1 - Ad hoc analyses susceptibility value source data for rezafungin and comparator echinocandins vs. primary yeast and mold species, Summary of Clinical Pharmacology, 2.4.2.4 Special Studies
MIC, Minimum Inhibitory Concentration
[a]Clinical isolates collected by the CDC, representing each of the 4 known clades of C. auris, including 8 isolates with elevated MICs to one or more echinocandins.

- **Overall, rezafungin's in vitro MIC90 values are comparable to other FDA-approved echinocandins against targeted *Candida* species.**

In vitro MIC data against isolates of *Candida* spp. with *fks*-mutations

In vitro MICs (mcg/mL) of *Candida* spp. isolates with fks-mutations (n=27)										
Echinocandin Drugs	**0.06**	**0.12**	**0.25**	**0.50**	**1.0**	**2.0**	**4.0**	**8.0**	**16**	**Total**
Rezafungin	2	3	11	4	6	1	x	x	x	27
Anidulafungin	1	3	10	3	6	3	1	x	x	27
Caspofungin	0	1	4	9	7	4	x	1	1	27

Source: NDA-217417; Table 23 (p95 of 294), 2.7.2 Summary of Clinical Pharmacology, 2.4.2.4 Special Studies

- **Rezafungin had similar in vitro activity against isolates with *fks*-mutations compared to anidulafungin**
- **Rezafungin has better activity against isolates with *fks*-mutations compared to caspofungin**

Data from other in vitro studies

- Against azole-resistant isolates, rezafungin exhibited in vitro activities similar to other echinocandins. Against fluconazole-nonsusceptible isolates, MIC_{90} values were: 0.5, 0.5, 1.0, and 0.03 µg/mL for rezafungin, anidulafungin, caspofungin, and micafungin, respectively.

- The spontaneous mutation frequencies for rezafungin against *Candida* spp. appear comparable to other echinocandins, ranging from 1.35×10^{-8} to 3.86×10^{-9}.

- Rezafungin demonstrated fungicidal activity (3-log kill from the baseline inoculum) at 4-fold or higher MICs at 24hrs for most isolates tested (47/49); comparable to other echinocandins.

In vivo Activities in Disseminated Candidiasis Mouse Model

- **In vivo studies were conducted in disseminated candidiasis mouse model with *C. albicans* isolates to evaluate the activity of rezafungin.**
- **Rezafungin administration was compared to either untreated control, anidulafungin, micafungin, fluconazole, or amphotericin B.**
- **Rezafungin demonstrated better in vivo activity compared to fluconazole.**
- **Overall, similar in vivo activities were observed when rezafungin was compared to either anidulafungin (NC-035, -040, and -042) or micafungin (NC-128 and -130) at comparable doses.**
- **Rezafungin demonstrated better activity compared to micafungin in three in vivo studies (NC-056, -087, and -088) when administered at higher doses.**

Clinical Microbiology Highlights of Rezafungin Clinical Program

- The Applicant conducted a single Phase 2 study (STRIVE) and a single Phase 3 study (ReSTORE) for the treatment of Candidemia and Invasive Candidiasis (C/IC) in adult patients using rezafungin as the study drug and caspofungin as the comparator.

- For efficacy and safety analyses, individual and pooled data were presented from both Phase 2 and Phase 3 studies.

- The evaluation of mycological eradication at Day 5, Day 14, and Day 30 was conducted as clinical efficacy secondary endpoints in both studies.

- For clinical microbiology analysis, Day 14 pooled data were primarily used for mycological response, mycological eradication by baseline MIC values of the clinical isolates, and for the breakpoints (BPs) determination.

Clinical Microbiology Highlights from Clinical Studies – 1

Table: Summary of baseline Predominant *Candida* spp. isolated from mITT-population in both treatment arms (pooled data from STRIVE and ReSTORE studies)

Predominant *Candida* spp.	Overall n (n/N [%])	
	Rezafungin 400/200 mg (N=139)	Caspofungin 70/50 mg (N=155)
C. albicans	58 (41.7)	69 (44.5)
C. glabrata	38 (27.3)	35 (22.6)
C. tropicalis	27 (19.4)	22 (14.2)
C. parapsilosis	14 (10.1)	27 (17.4)
C. krusei	5 (3.6)	3 (1.9)

- ***C. albicans*** **were isolated at the highest frequency at baseline followed by** ***C. glabrata*****,** ***C. tropicalis*****, and** ***C. parapsilosis*****.**

Clinical Microbiology Highlights from Clinical Studies – 2

Table: Summary of per-pathogen 14-Day Mycological Response of Predominant *Candida* spp. from mITT population of both treatment arms

Predominant *Candida* spp.	14-Day Mycological Response (Pooled – n/N1 [%])		Rezafungin MIC90 (mcg/mL)
	Rezafungin 400/200 mg (N=139)	Caspofungin 70/50 mg (N=155)	Against baseline isolates from both arms
C. albicans	39/58 (67.2)	46/69 (66.7)	≤0.06 (N=127)
C. glabrata	32/38 (84.2)	22/35 (62.9)	≤0.12 (N=73)
C. tropicalis	20/27 (74.1)	14/22 (63.6)	≤0.12 (N=49)
C. parapsilosis	11/14 (78.6)	19/27 (70.4)	≤2.0 (N=41)
C. krusei	2/5 (40.0)	3/3 (100)	NA (N=8)

Preliminary Conclusions of Clinical Microbiology Review

- **Overall, rezafungin demonstrated similar in vitro activity against most *Candida* species compared to other echinocandin drugs.**
- **Limited in vitro data suggest that against *fks* mutations (n=27), rezafungin appears to demonstrate slightly better activity compared to caspofungin, but this activity is comparable to anidulafungin.**
- **Similar in vivo activity was observed in murine animal models compared to other echinocandin comparators, e.g., micafungin and anidulafungin.**
- **When compared to other echinocandins, rezafungin has similar activity against both azole-resistant and -susceptible isolates.**
- **Similar mutation frequencies were observed compared to other echinocandins.**

Clinical Pharmacology Assessment

NDA 217417 Rezafungin

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Clinical Pharmacology Considerations

Applicant's postulated advantages of rezafungin compared to FDA-approved antifungals:

1. Probability of target attainment (PTA) with non-clinical PK-PD
   - *Underdosing concern with FDA-approved echinocandins for Candida species*
   - *Rezafungin may be able to treat infections caused by Candida spp. that have higher MIC values compared to caspofungin, micafungin, and anidulafungin*
2. Tissue penetration
3. Drug-drug interaction (DDI) risks

PTA with Non-Clinical PK-PD (1)

For FDA approved echinocandins:

- FDA/CLSI current breakpoints are informed by publicly reported clinical success rates against *C. albicans* and *C. glabrata* §
- PTA under-predicts clinical success

Drug	MIC [mg/L]	Clinical Success	PTA#
Caspofungin	*C. albicans* 0.25	91% (21/23)	36%
Anidulafungin	*C. albicans* 0.03	91% (10/11)	53%
	C. albicans 0.06	87% (6/7)	1%
	C. glabrata 0.06	87% (20/23)	54%
Micafungin	*C. albicans* 0.03	79% (135/170)	10%

Note: No micafungin & caspofungin comparisons could be made against *C. glabrata* as the number of patients with isolates at MIC's with PTA <90% rare.
CLSI = Clinical & laboratory Standards Institute

Sources: § PMID 21353623 | #https://doi.org/10.1093/ofid/ofx163.687

PTA with Non-Clinical PK-PD (2)

For rezafungin:

- Review of Applicant's rezafungin PTA findings is ongoing
- Postulated improvement in PTA (compared to caspofungin) up to MICs of 0.5 mg/L (*C. albicans*) or 8 mg/L (*C. glabrata*), however, rezafungin's clinical program does not afford a determination of concordance between PTA & clinical outcome at these MICs

Maximum MIC (mg/L) for Study Drug Received by Baseline Candida Species (Number of Patients in mITT Population) With Available Data on Mycological Response at Day 14[§]		
Candida Species	**Rezafungin (Total N=137)**	**Caspofungin (Total N=157)**
Candida albicans	0.12 (n=8)	0.12 (n=2)
Candida glabrata	0.5 (n=1)	0.12 (n=2)

Source: [§] Briefing document, Table 15 (pg. 28)

Clinical Pharmacology Considerations

Applicant's postulated pharmacological advantages of rezafungin compared to FDA-approved antifungals:

1. Probability of target attainment (PTA) with non-clinical PK-PD
2. Tissue penetration

— *Substantially improved distribution to infected tissues in a nonclinical invasive candidiasis mouse model, increasing the likelihood of achieving the required PK-PD target at the site of infection compared to other echinocandins*

3. Drug-drug interaction (DDI) risks

Tissue Penetration

- At the doses (5 mg/kg intraperitoneally) associated with approximate humanized systemic drug concentrations, rezafungin did not appear to show better tissue penetration compared to micafungin in a murine intra-abdominal candidiasis study [#]
- Anidulafungin showed greater drug penetration (in rat liver, kidney, and lung) than micafungin or rezafungin as reported in a single-dose rat echinocandin PK and tissue distribution review[$]
- No tissue penetration information available for more exclusive sites (e.g., brain, eye, prostate)
- Available clinical data did not suggest better tissue penetration given no substantial difference in Day 30 all-cause mortality rates observed between rezafungin and caspofungin*

Source: FDA Briefing document: [#]Page 28, [$]PMID: 28137817, *Table 3, 9 (p. 14, 19)

Clinical Pharmacology Considerations

Applicant's postulated pharmacological advantages of rezafungin compared to FDA-approved antifungals:

1. Probability of target attainment (PTA) with non-clinical PK-PD
2. Tissue penetration
3. Drug-drug interaction (DDI) risks

   —*Rezafungin has shown low potential for interactions with other drugs.*

DDI Risks

- Rezafungin DDI studies show no/low DDI risks §
  - Minimal cytochrome P450 (CYP) metabolism & not a substrate of drug transporters
  - No clinically meaningful CYP enzyme or drug transporters inhibition/induction
- Azoles: Frequent and varying degree of DDI risks
  - All azole drugs are both victims and perpetrators of PK DDIs via CYP enzymes
  - Dose adjustments / increased monitoring recommended
- Echinocandins: Generally low/no DDI risks except for caspofungin
  - For caspofungin, an alternative dosing regimen recommended when administered concomitantly with drugs that are CYP enzyme inducers.

Source: § Based on summary information in Briefing document Pages 37-39

Preliminary Conclusions

PTA with non-clinical PK-PD: Clinical significance of postulated improvement in rezafungin PTA compared to FDA-approved echinocandins is unknown

Tissue Penetration: There is insufficient evidence to demonstrate that rezafungin achieves better tissue penetration or activity at the site of infection than FDA approved echinocandins

Drug-Drug Interaction Risks: Rezafungin has a low DDI risk potential that is more favorable than currently FDA approved azoles and caspofungin

Summary Comments

NDA 217417 Rezafungin
Antimicrobial Drugs Advisory Committee Meeting
January 24, 2023

Heidi Smith, MD, PhD
Clinical Team Leader, Division of Anti-Infectives
OID/OND/CDER/FDA

Efficacy Assessment

- 10% NI margin for a Day 30 ACM endpoint recommended to support candidemia/IC treatment indication without a limited use statement
  - Preserves approximately two-thirds of the estimated echinocandin treatment effect on mortality endpoint in patients with candidemia/IC
- Efficacy data from a single rezafungin phase 3 NI trial
  - Primary endpoint of Day 30 ACM was within a 20% NI margin but did not meet a 10% NI margin
- Phase 2 exploratory dose-ranging study provides supportive evidence of effectiveness

Safety Assessment

- Nonclinical studies of rezafungin in nonhuman primates identified drug-related neurotoxicity
  - Findings in sub-chronic dosing studies included tremors (typically developing after Day 35)
  - Histopathologic changes included axonal degeneration and demyelination
- Clinical safety database included 151 patients with candidemia/IC receiving proposed rezafungin clinical dose and 81 patients receiving a higher dose for up to 28 days
  - Higher incidence of tremors in the rezafungin arm; all were mild and reversible
  - Otherwise, safety findings consistent overall with FDA-approved echinocandins

Clinical Microbiology/Clinical Pharmacology

- Rezafungin is primary distinguished from FDA-approved echinocandins by an extended half-life supporting once weekly dosing
  - Microbiological activity against *Candida* spp. in vitro is comparable
  - In vivo activity in murine models of candidemia/IC is similar
- Clinical significance of postulated improvement in rezafungin PTA compared to FDA-approved echinocandins is unknown
- Insufficient evidence to demonstrate that rezafungin achieves better tissue penetration or activity at the site of infection than FDA-approved echinocandins
- Rezafungin has a low DDI risk potential

Points to Consider

- The Applicant is seeking approval of rezafungin for the treatment of candidemia/IC based on:
  - Single phase 3 adequate and well-controlled NI study meeting the pre-specified 20% NI margin [treatment difference (rezafungin − caspofungin) of 2.4% (95% CI -9.7%, 14.4%)] for Day 30 all-cause mortality
  - Supportive evidence provided by a phase 2 dose-ranging study
  - Integrated safety dataset from phase 2 and 3 studies consisting of 151 subjects with candidemia/IC receiving the proposed rezafungin clinical dosing and an additional 81 subjects receiving a higher rezafungin dose for up to 28 days

Charge to the Committee

Voting Question

Is the overall benefit-risk assessment favorable for the use of rezafungin for treatment of candidemia/IC in adults with limited or no alternative treatment options?

- If yes, it would help us to understand the context of use for rezafungin, that is, the clinical scenario(s) in which rezafungin fulfills an unmet need.
- If no, please comment on the additional information that would be needed for the benefit-risk assessment to be favorable for the use of rezafungin in this/these population(s).


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