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The latest developments from US FDA drug, biologic, and medical device advisory committee meetings.

January 24, 2023
Meeting Begin Time: 9:05 a.m. | **End Time:** 3:56 p.m.

Today's Headline: Support for Limited Use of Cidara's Rezafungin to Treat Candidemia and Invasive Candidiasis

IN THIS ISSUE

Antimicrobial Drugs Advisory Committee Meeting

AdComm Profiles and Voting Histories—Drugs/Biologics (IDRAC 175864)

Subject: New drug application (NDA) 217417: Rezzayo (rezafungin) lyophilized powder for injection, submitted by Cidara Therapeutics, Inc, for the treatment of candidemia and invasive candidiasis (IC) in adults.

Announced in the Federal Register
November 25, 2022 (IDRAC 356015)
(Volume 87, Number 226)

Decision/Voting

The Antimicrobial Drugs Advisory Committee (AMDAC) solidly agreed that the benefits of Rezzayo (rezafungin), submitted by Cidara Therapeutics, Inc, outweigh the risks for adults with candidemia and invasive candidiasis (IC) who have limited or no alternative treatments. Although panelists had reservations about the supporting data for rezafungin, they noted that the drug would be a beneficial option for this patient population.

FDA Question(s) to the Committee	Vote		Comments
	Yes	No	
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?	**14**	1	
NOTE: The FDA is not obligated to follow the voting recommendation of the advisory committee, but it may do so once all information is considered.			

The AMDAC reviewed data from 2 studies that the sponsor submitted in support of the new drug application (IDRAC 34571) (NDA) for rezafungin—a phase 3 study, ReSTORE, and a phase 2 study, STRIVE. An echinocandin, rezafungin was developed under a flexible drug development program to support an indication with a limitations-of-use (LOU) statement (see *Regulatory Issues*). In addition to assessing the overall benefit-risk of rezafungin, the FDA asked for input from the panel on the potential content of the LOU statement, including which populations would benefit from the drug.

The FDA and the sponsor agreed that under this program, a wider noninferiority (NI) margin of 20% could be used for the all-cause mortality (ACM) primary endpoint from ReSTORE. Several panel members expressed concern that the NI margin was too wide for the ACM primary

endpoint. A panelist commented that it seemed inappropriate for a "serious outcome" such as ACM to have a "generous" NI margin. In addition, the broad margin allowed for the sponsor to include efficacy data from a smaller sample size. As a result, the 95% confidence interval (CI) with respect to ACM was also large, creating uncertainty among the panel about the effectiveness of rezafungin. The FDA and the sponsor noted that the smaller sample size was due to enrollment challenges for the clinical studies, and it may take more time to acquire a larger sample size.

Despite these concerns, almost every panel member voted to support rezafungin with an LOU statement. It was a "challenging" decision for several members, but they agreed that this treatment could benefit certain groups of patients. For example, patients who need prolonged therapy could benefit from weekly doses of rezafungin instead of daily doses of other echinocandins. Having a weekly dose could help these patients to be discharged and leave the hospital between treatments, some panelists highlighted. Furthermore, a majority of panelists were reassured that the safety profile for rezafungin was mostly consistent with that of other echinocandins. They noted that echinocandins are a well-studied drug class with a known mechanism of action.

Panelists who voted "yes" clarified that they supported an indication in patients with limited to no alternative treatments for candidemia and IC, but there were no clinical data for this specific group of patients. They encouraged the sponsor to collect more data in this population and other groups that were unrepresented/underrepresented in the clinical studies, including children, adolescents, pregnant women, and racially and ethnically diverse individuals. These panel members also had reservations about supporting an approval for rezafungin without an LOU statement. Approval without such a statement would require a bigger sample size to address the large 95% CI. In addition, more information would be needed to understand the neurotoxicity signal found in nonhuman primate studies and clinical studies during drug development (see *Clinical Issues*).

The panel member who voted "no" acknowledged the sponsor's challenges with enrolling participants but did not think the evidence met the clinical trial approval criteria the FDA highlighted in the Event Materials (IDRAC 358812). In particular, she noted that the pooled analyses were not prespecified and could not be used to support efficacy. Although the sponsor's evidence is "growing" and appears to be leaning "in their favor," standards should still "be maintained," she remarked.

Background Information

During this meeting, the Antimicrobial Drugs Advisory Committee (AMDAC) was convened to discuss new drug application (IDRAC 34571) (NDA) 217417 for Rezzayo (rezafungin [ATC: J02AX08]) lyophilized powder for injection, submitted by Cidara Therapeutics, Inc (Cidara), for the treatment of candidemia and invasive candidiasis (IC) in adults. Rezafungin, an echinocandin, exhibits fungicidal activity against many *Candida* species (spp.) by inhibiting synthesis of β-(1,3)-D-glucan, a polysaccharide component of the cell wall of some pathogenic fungi.

IC is a fungal infection caused by *Candida* yeast, and it can affect the blood, heart, brain, eyes, bones, or other parts of the body. The most common form of IC is a *Candida* bloodstream infection, which is also known as candidemia. According to the Centers for Disease Control and Prevention (CDC), approximately (~) 25,000 cases of candidemia occur each year in the US. Because candidemia accounts for a portion of all IC, the CDC notes that the total number of cases for IC may be twice as high. Most people who develop IC already have other medical conditions and are usually treated with antifungal medications, including echinocandins. Echinocandins are typically used as first-line therapies against IC and candidemia except for infections in the central nervous system, eye, or urinary tract. After treatment with echinocandins, most patients transition to oral azole antifungals once they are clinically stable.

Cidara included data from a single adequate and well-controlled (A&WC) phase 3 noninferiority (NI) study, ReSTORE, and an exploratory dose-finding phase 2 study, STRIVE, to support NDA 217417. As noted in the Event Materials (IDRAC 358812), the FDA agreed that the sponsor could submit data from a single phase 2 study and a single phase 3 study to support the approval of rezafungin within a flexible drug development program. A flexible development program can help to facilitate drug development for diseases with unmet need. A drug

approved under a flexible program must include a limitations-of-use (LOU) statement in its label. The label should include descriptions of the limitations of the data used to support approval. A description of the target population (e.g., patients who have limited or no alternative treatment options) for the drug must also be included.

As part of the flexible program, the FDA informed the sponsor that a wider NI margin in the phase 3 study could be used to support a limited-use indication. In its review, the agency stated that ReSTORE did meet the agreed primary endpoint for the LOU statement. However, the sponsor proposed to combine efficacy data from ReSTORE and STRIVE to support the approval of rezafungin without an LOU statement. The FDA disagreed with this proposal, noting that an integrated analysis was not prespecified, and pooled results had "potentially inflated the estimate of the treatment effect" for rezafungin.

Moreover, the FDA expressed concern over a neurotoxicity signal identified in nonhuman primate (NHP) studies. Compared to control animals, those treated with rezafungin had an increase in drug-related tremors. These trials also showed an imbalance in the occurrence of tremor in the rezafungin treatment arm compared to the echinocandin comparator arm. The other 3 FDA-approved echinocandins (see *Market Issues*) have similar safety profiles to rezafungin, but they do not have warning statements related to neurotoxicity, the agency noted.

Given these issues, the FDA stated that the data did not show rezafungin was safer, had improved activity against *Candida* spp., or provided greater tissue penetration compared to other echinocandins. However, the agency acknowledged that rezafungin has a longer half-life than the other products and could be a potential therapeutic option for patients with limited or no alternative treatments. During today's meeting, panelists considered the overall benefit-risk profile of rezafungin and assessed whether it would be a viable treatment option for this population.

Proposed Indication

- *Rezzayo (rezafungin) for the treatment of candidemia and IC in patients aged ≥18 years.*

Proposed Dose

- *Rezafungin lyophilized powder for injection at a loading intravenous (IV) dose of 400 mg in week 1, followed by a 200 mg IV dose once weekly (QW) thereafter.*

Regulatory History

2015	The sponsor and the FDA participated in a pre–investigational new drug application (IND) meeting to discuss the development of rezafungin [Draft Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products, December-2017 (IDRAC 267090); Guidance Bulletin (IDRAC 268263)].
May 11, 2015	The sponsor announced that the FDA designated rezafungin as a qualified infectious disease product (IDRAC 269067) (QIDP) and granted it fast track status (IDRAC 37909) for candidemia and IC.
February 8, 2016	The FDA granted rezafungin orphan drug designation (IDRAC 37910) for the treatment of candidemia and IC infections caused by susceptible *Candida* spp.
April 2018	The sponsor informed the FDA about the neurological adverse events (AEs) identified in a 13-week repeat-dose study of rezafungin in NHP studies.
May 2018	The sponsor agreed to follow safety measures proposed by the FDA to mitigate the risk of neurotoxicity in ReSTORE.
July 2018	The FDA and the sponsor agreed on the study design for ReSTORE at an end-of-phase 2 meeting (IDRAC 268263).
September 10, 2018	The FDA granted rezafungin QIDP and fast track designations for the prevention of invasive fungal infections in adults undergoing allogeneic hematopoietic stem cell transplantation (HSCT).
May 2021	The sponsor submitted interim findings from a toxicology study in

	NHPs and a summary of neurologic AEs from ReSTORE to the FDA.
June 2021	The FDA and the sponsor discussed the clinical data needed to support the rezafungin NDA. The FDA recommended increasing the size of the safety database, but the sponsor cited difficulties in enrolling more subjects.
September 2021	The FDA and the sponsor participated in a Type C meeting (IDRAC 268263) and reached an agreement on integrating the safety and efficacy data of STRIVE and ReSTORE for the NDA.
2022	During a pre-NDA meeting (IDRAC 268263) with the sponsor, the agency agreed that it was "reasonable" to proceed with the rezafungin NDA.
July 22, 2022	The sponsor submitted NDA 217417 for rezafungin to the FDA and entered into a license agreement with Melinta Therapeutics LLC to commercialize rezafungin in the US [Application Format, Content and Submission (IDRAC 34571)].
September 2022	The sponsor submitted a final report of the 26-week NHP study to the NDA.
September 20, 2022	The sponsor announced in a press release that the FDA accepted NDA 217417 for filing and granted it priority review (IDRAC 37909).
March 22, 2023	The anticipated Prescription Drug User Fee Act (IDRAC 9046) (PDUFA) target action date for NDA 217417, according to the sponsor.

Regulatory Issues

The Guidance for Industry: Qualified Infectious Disease Product Designation—Questions and Answers, May-2021 (IDRAC 329687) [Guidance Bulletin (IDRAC 269067)] explains the FDA's implementation of Title VIII of the Food and Drug Administration Safety and Innovation Act (IDRAC 146311) (FDASIA), also known as Generating Antibiotic Incentives Now (GAIN). Under GAIN, sponsors can qualify for a 5-year exclusivity extension for certain antibacterial and antifungal products that have been granted QIDP designation and are approved under section 505 of the Federal Food, Drug, and Cosmetic Act (IDRAC 17027) (FD&C Act). Antimicrobial products with QIDP designation are intended to treat serious or life-threatening infections. The FDA is required to give priority review to the first application submitted for a specific product with QIDP designation, and sponsors can also request fast track designation for their QIDP-designated products.

Under the FD&C Act, sponsors must provide "substantial evidence" through A&WC clinical studies to establish the effectiveness of a new drug. Generally, the FDA requires 2 AW&C trials to demonstrate a drug's effectiveness. However, under some circumstances (e.g., a flexible drug development program), a single A&WC study with confirmatory evidence may be sufficient for supporting effectiveness [Draft Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, December-2019 (IDRAC 304030].

The flexible program for rezafungin was based on the FDA's Draft Guidance for Industry: Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases – Questions and Answers (Revision 1), May-2022 (IDRAC 347790), which explains possible development programs for antibacterial drugs. Flexible drug development programs are used to address an unmet medical need for serious bacterial infections. Sponsors must still demonstrate that their products are safe and effective, but they can conduct smaller and fewer clinical trials through these programs. The guidance includes suggestions for clinical trial design, statistical approaches, and safety considerations for a flexible development program.

According to the FDA, a clinical trial with an adaptive design can be changed after its initiation with "prospectively planned modifications" [Guidance for Industry: Adaptive Designs for Clinical Trials of Drugs and Biologics, November-2019 (IDRAC 303151); Guidance Bulletin (IDRAC 104462)]. Compared to non-adaptive designs, adaptive designs can provide various advantages. For example, an adaptive design can increase the chance of detecting whether a treatment has "a true drug effect" by providing greater statistical power. However, some

adaptive design features can "lead to statistical bias" when estimating treatment effects. Some methods can reduce or remove bias, but they should be prospectively planned before the trial begins.

The FDA previously held a workshop on the development of new antifungal drugs to address unmet medical need [FDA Workshop Bulletin, 04-August-2020 (IDRAC 318641)]. Some regulatory considerations for drugs intended to treat candidemia and IC include using an NI trial design and endpoints such as all-cause mortality (ACM) at a fixed time point. NI trials are usually conducted when a superiority study cannot be used. Instead of showing that a new drug is superior or equivalent to an existing treatment, an NI trial is intended to demonstrate that a new product is "not materially worse than the control" [Guidance for Industry: Non-Inferiority Clinical Trials to Establish Effectiveness (Final), November-2016 (IDRAC 235135); Guidance Bulletin (IDRAC 104461)].

Clinical Issues

The sponsor submitted data from 2 studies to support NDA 217417: ReSTORE and STRIVE. The FDA focused primarily on the phase 3 study, ReSTORE, as the basis for reviewing the approvability of rezafungin. Data from STRIVE, a phase 2 study, were submitted as supportive evidence. Both trials were conducted in adult participants aged ≥18 years with ≥1 attributable systemic sign of candidemia and/or IC. Table 1 and the Event Materials (IDRAC 358812) include additional information on ReSTORE and STRIVE.

Table 1. Rezafungin Clinical Program

Trial	Design	Regimen	No. Patients	Primary Endpoint
STRIVE	Exploratory, multicenter, randomized, double-blind phase 2 study	Part A, 1:1:1 randomization[1]: 1. **rezafungin 400/400 mg:** rezafungin 400 mg IV on day 1 and day 8; optional 400 mg on day 15; optional 400 mg on day 22 for subjects with IC 2. **rezafungin 400/200 mg:** rezafungin 400 mg IV on day 1 and 200 mg on day 8; optional 200 mg on day 15; optional 200 mg on day 22 for subjects with IC 3. **caspofungin 70/50 mg:** caspofungin 70 mg IV on day 1, then 50 mg QD for 14 days; optional 50 mg QD on days 15-21; optional 50 mg QD on days 22-28 for subjects with IC	107	Overall response at day 14, defined as resolution of attributable systemic signs of candidemia and/or IC that were present at baseline
		Part B, 2:1 randomization[1]: rezafungin[2] or caspofungin 70/50 mg	100	
ReSTORE	International, multicenter, randomized, double-blind, double-dummy phase 3 study	1:1 randomization: rezafungin 400 mg IV single dose in week 1, followed by 200 mg QW for a total of 2-4 doses ***or*** caspofungin 70 mg IV loading dose on day 1, then caspofungin 50 mg QD up to 28 days[3]	199	ACM at day 30

QD = once daily
[1]Subjects in all treatment groups could receive oral stepdown therapy after ≥3 days of IV therapy. Oral step-down: oral placebo (saline; rezafungin groups) or oral fluconazole 800 mg on the first day, followed by 400 mg/day thereafter.
[2]Under protocol amendment 5, subjects were enrolled into part B and were randomized to rezafungin 400/400 mg every week or caspofungin. After a complete review of unblinded part A data, amendment 6 defined part B treatment as rezafungin 400/200 mg or caspofungin. Subjects enrolled under amendment 5 continued receiving their originally assigned study drug regardless of subsequent approval of amendment 6.
[3]After ≥3 days (or the minimum duration of IV therapy advised by the site's national/regional/local guidelines, whichever was greater) of caspofungin treatment, subjects who met the stepdown therapy eligibility criteria could be switched to oral fluconazole at a dose of 6 mg/kg administered QD (rounded to the nearest 200 mg increment) with a maximum daily dose of 800 mg (e.g., a subject weighing 73 kg would receive fluconazole 400 mg dose [2 capsules, 200 mg each] based on a 6 mg/kg target dose [73 kg × 6 mg/kg = 438 mg]).

Safety

The FDA evaluated safety through the integrated summary of safety (ISS) for rezafungin, which included data from both ReSTORE and STRIVE. The ISS pooled results from 151 subjects who received the proposed dose of rezafungin (400 mg loading dose, followed by 200 mg QW) and 166 subjects who received caspofungin. Overall, participants in the rezafungin arm experienced slightly higher rates of treatment-emergent AEs (TEAEs) and serious AEs (SAEs). The most common TEAEs (≥10% frequency) in the rezafungin arm were hypokalemia (14.6%), pyrexia (11.9%), and diarrhea (11.3%). Both treatment arms had similar rates of treatment discontinuations due to TEAEs. The sponsor also monitored the following AEs of special interest (AESIs): phototoxicity, infusion-related reactions, and neurotoxicity. More information on neurotoxicity is described below.

Neurotoxicity signal. As mentioned previously, the FDA noted its concern about a neurotoxicity safety signal identified in NHP studies during rezafungin drug development. During a 3-month study, cynomolgus monkeys that received ≥30 mg/kg rezafungin showed signs of neurotoxic effects (e.g., tremors, hypercellularity in Schwann cells, axonal degeneration). Additional NHP studies, including a 13-week follow-up study in female primates and a 6-month follow-up study in 6- to 10-year-old monkeys, confirmed the presence of tremors and other neurotoxicity signals after treatment with rezafungin.

Due to the neurotoxicity signal, the sponsor changed the eligibility criteria for its phase 3 clinical studies. Participants who were at an increased risk for neurologic AEs (e.g., had a history of tremor or neuropathy) were excluded. In addition, subjects were monitored for signs of ataxia, tremor, and peripheral neuropathy. These neurological AEs were considered AESIs for phase 2 and 3 studies. The incidence of AEs related to nervous system disorders in the ISS was similar between the rezafungin (14.6%) and caspofungin (12.0%) arms. However, a higher incidence of tremors occurred in the rezafungin arm (4 tremors) compared to the caspofungin arm (0 cases). Because tremor is listed as an adverse reaction in the labels of other echinocandins, a relationship between rezafungin and tremor development "cannot be dismissed," the FDA noted.

Efficacy

STRIVE. The efficacy analysis from STRIVE showed that the rezafungin 400/200 mg arm had a higher overall response of success at day 14 compared to the rezafungin 400/400 mg and caspofungin arms. The FDA highlighted that the rezafungin 400/200 mg group also showed a much greater proportion of success than the rezafungin 400/400 mg on day 5 but noted that this could have been due to chance. Table 2 includes the efficacy results for STRIVE.

Table 2. Efficacy Results From STRIVE

Visit	Response	Statistic	Rezafungin 400/400 mg n = 76	Rezafungin 400/200 mg n =46	Caspofungin n = 61
Day 5	Success	n (%) 95% CI	42 (55.3) 43.4, 66.7	34 (73.9) 58.9, 85.7	34 (55.7) 42.4, 68.5
	Failure/indeterminate	n (%)	34 (44.7)	12 (26.1)	27 (44.3)
	Failure	n (%)	24 (31.6)	10 (21.7)	24 (39.3)
	Indeterminate	n (%)	10 (13.2)	2 (4.3)	3 (4.9)
Day 14	Success	n (%)	46 (60.5)	35 (76.1)	41 (67.2)

		95% CI	48.6, 71.6	61.2, 87.4	54.0, 78.7
	Failure/indeterminate	n (%)	30 (39.5)	11 (23.9)	20 (32.8)
	Failure	n (%)	20 (26.3)	8 (17.4)	17 (27.9)
	Indeterminate	n (%)	10 (13.2)	3 (6.5)	3 (4.9)
CI = confidence interval					

ReSTORE. For ReSTORE, the ACM by day 30 achieved NI with a 20% NI margin. However, the study did not meet a 10% NI margin; the upper limit of the 95% CI for the difference in mortality rates was at a margin of 14.4%. Table 3 summarizes the primary efficacy results from ReSTORE.

Table 3. Efficacy Results From ReSTORE

Characteristic, n (%)	Rezafungin 400/200 mg n = 93	Caspofungin n = 94	Difference (%) (95% CI)
Deceased	22 (23.7)	20 (21.3)	2.4 (-9.7, 14.4)
Known deceased	19 (20.4)	17 (18.1)	
Unknown survival status	3 (3.2)	3 (3.2)	
Alive	71 (76.3)	74 (78.7)	

FDA review of efficacy. Under the flexible development program for rezafungin, the FDA stated that it would consider a wider NI margin (20%) with respect to ACM at day 30 to support a limited-use indication for candidemia and/or IC. For an indication without an LOU statement, the agency recommended that the NI margin for ACM at day 30 should be 10%. ReSTORE achieved a 20% NI margin, but it did not meet the 10% NI margin, even at the upper limit of the 95% CI for the difference in day 30 ACM rates. As a result, ReSTORE could be used to support a limited-use indication, the FDA noted.

However, the sponsor submitted its marketing application for an indication without an LOU statement. By pooling the results from STRIVE and ReSTORE, the sponsor stated that the upper limit of the 95% CI for the difference in day 30 ACM rates would be <10%. The FDA found several issues with this proposal. As stated before, the primary assessment was not prespecified to be an integrated analysis. Without prespecification, the pooled results could inflate the estimate of the treatment effect. Furthermore, in STRIVE, the rezafungin 400/200 mg arm had a higher proportion of subjects with mycological eradication (82.6%) than the rezafungin 400/400 mg arm (71.7%) for week 1. Because both treatment arms had the same dose of rezafungin at week 1, there should not be a difference at this timepoint, the FDA stated. This difference could contribute to the overestimation of the treatment effect.

The agency also did not consider STRIVE an A&WC study. An A&WC study should include hypotheses that are predefined. However, the STRIVE study report stated that it was an "exploratory study" and "no inferential statistical analyses were conducted." Additionally, STRIVE was changed from an exploratory study to an adaptive study after protocol amendments were made. The sponsor terminated the rezafungin 400/200 mg treatment arm for part B initially but added it back after an unblinded analysis of part A. Based on the FDA's guidance on adaptive design (see *Regulatory Issues*), a trial with an adaptive design that is intended to provide "substantial evidence of effectiveness" should utilize "statistical hypothesis testing methods" for the "adaptive selection of a best dose."

Rezafungin activity relative to other echinocandins. There are currently 3 echinocandin antifungals approved by the FDA for candidemia and IC (see *Market Issues*). To compare the activity between rezafungin and the other echinocandins, the sponsor submitted *in vitro* minimum inhibitory concentration (MIC) data against *Candida* spp. and *in vivo* data from mouse studies. Overall, rezafungin had similar *in vitro* and *in vivo* activity against all *Candida* spp. compared to the other echinocandins. The sponsor claimed that rezafungin had better *in vitro* activity against echinocandin-resistant isolates than the other FDA-approved products. However, rezafungin was only better than caspofungin against the isolates, the FDA noted. The sponsor did not provide MIC data for micafungin, and rezafungin showed similar activity to anidulafungin. Similarly, rezafungin did not demonstrate a greater treatment effect in the *in vivo* studies.

The sponsor also stated that rezafungin had greater tissue penetration than the other echinocandins, but the FDA did not agree with this conclusion. Results from a nonclinical mouse study showed that rezafungin (20 mg/kg) had greater absolute concentrations in the liver than micafungin (5 mg/kg), but the study did not compare rezafungin to the other echinocandins. Moreover, a published systemic review of echinocandin tissue distribution studies in rats suggested that anidulafungin had greater tissue penetration than micafungin and rezafungin. As a result, it is unclear whether rezafungin can achieve better tissue penetration than all the approved echinocandins, the agency noted.

Medical Issues

Candida normally lives inside the body and on the skin, but in certain patients, *Candida* can cause IC by infecting various parts of the body. Candidemia, a *Candida* bloodstream infection, is the most common type of IC. According to the CDC, there are several risk factors for developing IC, including diabetes, kidney failure, spending time in the intensive care unit, and having a central venous catheter. Common symptoms for IC are fever and chills. High rates of morbidity and mortality are associated with invasive *Candida* infections. The CDC estimates that the in-hospital all-cause (crude) mortality of people with candidemia is ~25%.

Various *Candida* spp. are becoming more drug resistant against first- and second-line antifungal medications, including echinocandins. IC infections are usually caused by *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei*. There is growing concern for *C. auris*, an emerging, multidrug-resistant fungus that has caused outbreaks in healthcare settings.

Pharmacology Issues

Rezafungin has improved molecular stability and biological properties compared to other echinocandins primarily because of a choline moiety on the cyclic hexapeptide ring, according to the sponsor. With improved stability, rezafungin has a longer half-life than other echinocandins.

Patients with IC and candidemia have a higher chance of experiencing harmful drug-drug interactions (DDIs) when transitioning from echinocandins to oral azoles. The sponsor conducted studies to determine the DDI potential of rezafungin and found that it underwent minimal cytochrome P450 (CYP)–mediated metabolism. It also did not inhibit or induce major drug-metabolizing enzymes or drug transporters, including CYP3A4 and/or P-glycoprotein. Compared to azoles, rezafungin has a lower DDI potential, according to the FDA.

Market Issues

If the FDA approves Rezzayo (rezafungin), from Cidara Therapeutics, Inc, it will be the first new echinocandin approved in over a decade. Rezafungin would also be a second-generation echinocandin, with greater stability and a longer half-life, according to the sponsor. Echinocandins currently available in the US to treat candidemia and IC, shown in Table 4, require daily IV dosing; dosing with rezafungin would be once weekly.

Table 4. FDA-Approved Echinocandins for Candidemia and IC
(ATC: J02AX)

Trade Name	Generic Name	Company
Cancidas (IDRAC 337897)	caspofungin acetate	Merck Sharp and Dohme Corp
Eraxis (IDRAC 319025)	anidulafungin	Vicuron Holdings LLC
Mycamine (IDRAC 304258)	micafungin sodium	Astellas US Pharma, Inc

In August 2022, the European Medicines Agency (EMA) accepted a marketing authorization application (MAA) for rezafungin for the treatment of adult patients with IC [Marketing Authorization Procedures: Review, Communication, and Approval (European Union) (IDRAC 14888)].

The sponsor is also investigating rezafungin for the prevention of invasive fungal infections in adults undergoing allogeneic HSCT. In September 2018, the FDA granted QIDP and fast track designations to rezafungin for this indication. Cidara is recruiting participants for a randomized, double-blind, multicenter, prospective phase 3 study to evaluate the efficacy and safety of IV rezafungin for the prevention of invasive fungal diseases in subjects undergoing allogeneic

blood and marrow transplantation. The ~462 participants receive either an oral or IV azole antifungal (i.e., active comparator) or IV rezafungin. The primary outcome measures are the number and percentage of subjects who are fungal free and survive by day 90. The sponsor started the study in May 2020, and it is projected to complete in August 2024.

In the Pipeline

SCYNEXIS, Inc, is recruiting ~220 participants for a multicenter, randomized, double-blind phase 3 study to investigate ibrexafungerp [Brexafemme (IDRAC 356467)], a glucan synthase inhibitor. Ibrexafungerp was previously approved to treat vulvovaginal candidiasis and reduce the incidence of recurrent vulvovaginal candidiasis. Participants with candidemia and/or IC are randomized to receive an IV echinocandin and oral ibrexafungerp or an IV echinocandin and oral fluconazole. The primary outcome measure is 30-day ACM. Begun in August 2022, the study is estimated to complete in February 2024.

In a double-blind, 2-arm phase 3 study, Pfizer Inc is planning to evaluate the safety and effectiveness of fosmanogepix in ~450 participants with candidemia or IC. Fosmanogepix is a first-in-class antifungal agent that targets glycosylphosphatidylinositol-anchored wall protein transfer 1 (Gwt1), a fungal enzyme that is important for fungal cell growth. Two-thirds of all participants will receive placebo or IV fosmanogepix with the option of changing to oral fosmanogepix, and one-third will be given placebo or IV caspofungin with the option of switching to oral fluconazole. The primary outcome measure is the proportion of participants who are living by day 30. The study is anticipated to start in February 2023 and complete in February 2026.

Additional *Cortellis RI* Resources Briefing Information

Event Materials (IDRAC 358812)

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