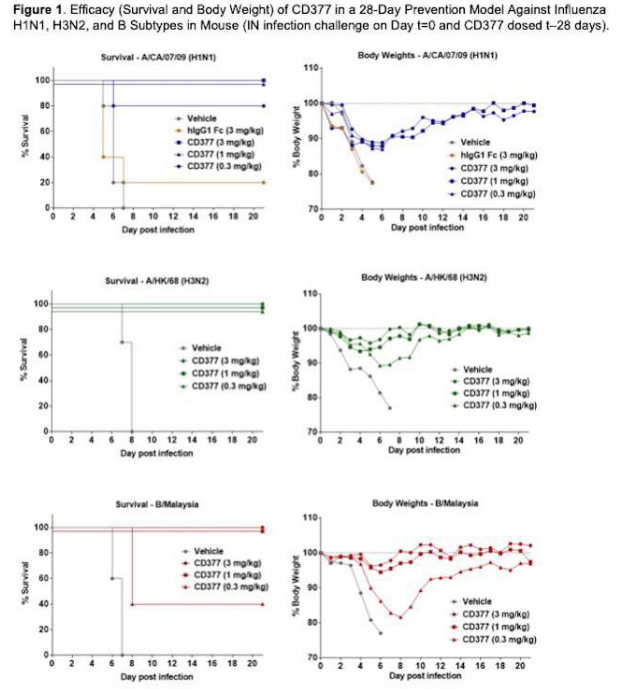
Figure 1. Efficacy (Survival and Body Weight) of CD377 in a 28-Day Prevention Model Against Influenza H1N1, H3N2, and B Subtypes in Mouse (IN infection challenge on Day t=0 and CD377 dosed t–28 days).



Conclusion. The stability and safety of CD377, together with its long half-life and efficacy with a single dose, support the potential of CD377 as a long-acting, novel AVC for the prevention and treatment of influenza.

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1284. Outcomes by Baseline Pathogens and Susceptibility in the STRIVE Phase 2 Trial of Once-Weekly Rezafungin for Treatment of Candidemia and Invasive Candidiasis Compared with Caspofungin

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Session: P-58. Novel Agents

Background. Rezafungin (RZF) is a novel echinocandin in Phase 3 development for treatment of candidemia and invasive candidiasis (IC) and for prevention of invasive fungal disease caused by *Candida*, *Aspergillus*, and *Pneumocystis* in blood and marrow transplant recipients. This analysis of the completed Phase 2 STRIVE trial (NCT02734862) of RZF treatment was conducted to evaluate outcomes based on baseline pathogen and susceptibility.

Methods. In STRIVE, adults (≥ 18 y) with systemic signs and mycological evidence of candidemia and/or IC were randomized to either RZF once weekly or caspofungin (CAS) once daily for ≥ 14 days (Fig. 1). The primary efficacy endpoint was Overall Response (resolution of clinical signs of infection + mycological eradication) at Day 14. For this analysis, outcomes by treatment group were stratified by *Candida* species and by its in vitro susceptibility (CLSI broth microdilution MIC values; M27-Ed4).

Figure 1. Treatment Groups of the Phase 2 STRIVE Trial

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Treatment Group	Dose Regimen
RZF Group 1	IV rezafungin 400 mg QWk
RZF Group 2	IV rezafungin 400 mg on Week 1, followed by 200 mg QWk
CAS	IV caspofungin 70 mg on Day 1, followed by 50 mg QD (with optional step-down to oral fluconazole)

CAS=caspofungin; RZF=rezafungin; QD=once daily; QWk=once weekly.

Results: A total of 196 *Candida* isolates were recovered from 183 patients across all treatment groups (Fig. 2). *C. albicans* was the most common species, followed by *C. glabrata*, *C. parapsilosis*, and *C. tropicalis;* non-*albicans Candida* comprised 54% of all baseline isolates (Fig. 2). Among all clinical isolates, MIC distributions and ranges for RZF were generally lower than or comparable to those for CAS (Table 1). The rate of Overall Response (as defined above) against *C. parapsilosis* was lower for CAS than for RZF (Table 2). Overall, outcomes by *Candida* species and MIC did not appear to be affected by MIC values for either RZF or CAS (Table 1).

Figure 2. Candida Species Distribution and MIC ranges in the Phase 2 STRIVE Trial (mITT)

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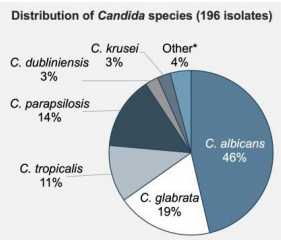

*Other: *C. fermentati, C. intermedia, C. kefyr, C. metapsilosis, C. rugosa, C. utilis* (n=1 each), and *C. guilliermondii* (n=2)

mITT=microbiological intent-to-treat population

Candida species	MIC Range, µg/mL (no. of isolates) RZF (pooled) once weekly N=122	MIC Range, µg/mL (no. of isolates) CAS once daily N=61
C. albicans	≤0.008–0.25 (87)	0.03–0.5 (89)
C. glabrata	0.03–0.25 (37)	0.12–1 (37)
C. parapsilosis	0.5–2 (28)	0.06–1 (28)
C. tropicalis	0.016–0.25 (22)	0.03–0.5 (22)

Table 1. Overall Response Rates (%) for Most Frequently Isolated Candida Species at Baseline by Treatment Group and MIC Values (mITT)

Table 1. Overall Response Rates (%) for Most Frequently Isolated *Candida* Species at Baseline by Treatment Group and MIC Values (mITT)

Organism Treatment Group (no. of isolates)	Rate of Overall Response, n/N (%)[a] ≤0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4
C. albicans										
RZF Group 1 (38)	1/3 (33.3)	6/15 (40)	2/7 (28.6)	6/8 (75.0)	1/2 (50)					
RZF Group 2 (19)	3/3 (100)	8/9 (88.9)	2/3 (66.7)	0/2 (0)	1/2 (50)					
CAS (33)			0/1 (0)	6/6 (100)	12/20 (60)	4/4 (100)	2/2 (100)			
C. glabrata										
RZF Group 1 (13)				6/6 (100)	5/6 (83.3)	1/1 (100)				
RZF Group 2 (14)				5/7 (71.4)	5/5 (100)	1/2 (50)				
CAS (10)					1/1 (100)	4/6 (66.7)	2/3 (66.7)			
C. parapsilosis										
RZF Group 1 (10)							2/3 (66.7)	1/2 (50)	3/5 (60)	
RZF Group 2 (7)							1/1 (100)	2/2 (100)	3/4 (75)	
CAS (11)				0/1 (0)			1/1 (100)	3/9 (33.3)		
C. tropicalis										
RZF Group 1 (9)		1/1 (100)	1/3 (33.3)	1/2 (50)	1/1 (100)	0/2 (0)				
RZF Group 2 (7)			3/3 (100)	2/3 (66.7)	0/1 (0)					
CAS (6)					1/1 (100)	3/4 (75)	1/1 (100)			

[a]Numerator: the number of patients who demonstrated overall response; denominator: the number of patients whose isolate(s) had the MIC value (µg/mL) indicated by column header. Not all isolates had MIC data.

Table 2. Overall Response Rates (%) for Most Frequently Isolated Candida Species at Baseline by Treatment Group (mITT)

Table 2. Overall Response Rates (%) for Most Frequently Isolated *Candida* Species at Baseline by Treatment Group (mITT)

Candida species MIC, μg/mL[a] (no. of isolates)	Overall Response, n/N (%)		
	Rezafungin 400 mg/400 mg QWk	Rezafungin 400 mg/200 mg QWk	Caspofungin 70 mg/50 mg QD
C. albicans	19/38 (50)	14/19 (73.7)	25/34 (73.5)
MIC_{90} (89[b])	0.06		0.25
C. glabrata	12/13 (92.3)	11/14 (78.6)	7/10 (70)
MIC_{90} (37)	0.25		0.5
C. parapsilosis	6/10 (60)	6/7 (85.7)	4/11 (36.4)
MIC_{90} (28)	2		1
C. tropicalis	4/9 (44.4)	5/7 (71.4)	5/6 (83.3)
MIC_{90} (22)	0.12		0.5

[a]Not all isolates had MIC data.
[b]MIC_{90} of rezafungin against *C. albicans* based on 87 isolates.

Conclusion: This analysis demonstrated RZF efficacy across multiple *Candida* species. RZF outcomes were similar to or better than those for CAS regardless of species identified. There was no clear correlation between increased MICs and clinical outcomes although, based on MICs, all isolates exhibited a wild-type in vitro susceptibility profile. These findings from STRIVE, together with future analyses from the ongoing Phase 3 trial of RZF treatment of candidemia and IC (ReSTORE; NCT03667690), will further our understanding of the relationships between MIC values and clinical outcomes in patients with candidemia or IC.

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1285. Outcomes in Patients with Gram-Negative Bacteremia from Phase 2 and Phase 3 Clinical Trials of Cefiderocol, a Novel Siderophore Cephalosporin

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Session: P-58. Novel Agents

Background. Cefiderocol (CFDC) is the first siderophore cephalosporin approved (US and EU) for a broad range of infections caused by Gram-negative (GN) bacteria, including carbapenem-resistant Enterobacterales (ENT) and non-fermenters (NFs). Bacteremia is a serious manifestation of GN infection and understanding how well an antibiotic works to clear the bacteremia is an important part of drug evaluation.

Methods. All completed clinical studies for CFDC development were used to identify patients with GN bacteremia. Information collected included the primary infection site, species identification and antibiotic susceptibility, post randomization blood cultures and clinical and bacteremia outcome. In patients with missing data (blood cultures) clinical response of cure was used to impute microbiological eradication. Indeterminate responses resulted from a combination of missing data and clinical failure, including death prior to test of cure (TOC).

Results. Three clinical studies randomized 900 patients (CFDC 552; comparators 348) of whom 84 (CFDC 52; comparators 32) had GN bacteremia at baseline (Table). Bacteremia rate by study was CREDIBLE-CR 25.3%, APEKS-cUTI 6.2%, APEKS-NP 6.0%. *Escherichia coli* (29), *Klebsiella pneumoniae* (23) and *Acinetobacter* spp (21) were most frequent species. Sources included urinary tract (31), lung (22), unknown (10), IV line (8), intraabdominal (6), or other (7). Persistence of bacteremia at TOC was seen in 2/52 (3.8%) CFDC and 2/32 (6.2%) control patients (Table), usually due to lack of source control. Clinical outcomes varied by study and infection source and were often confounded (indeterminate response). Eradication in patients with ENT at TOC was determined for 27/39 (69%) for CFDC and 16/23 (70%) for controls, and for 9/16 (56%) for CFDC and 10/11 (91%) for controls in patients with NFs, respectively.

Table. Clinical and bacteremia microbiological outcomes per patient at TOC.

Table. Clinical and bacteremia microbiological outcomes per patient at TOC.

		CREDIBLE-CR (Phase 3; NCT02714595)		APEKS-NP (Phase 3; NCT03032380)		APEKS-cUTI (Phase 2; NCT02321800)	
		CFDC (N=25)	BAT (N=13)	CFDC (N=8)	MEM (N=10)	CFDC (N=19)	I/C (N=9)
Clinical outcome, n (%)	Clinical cure	10 (40)	6 (46)	1 (13)	5 (50)	15 (79)	6 (67)
	Clinical failure	10 (40)	6 (46)	4 (50)	4 (40)	1 (5)	1 (11)
	Indeterminate	5 (20)	1 (8)	3 (38)	1 (10)	3 (16)	2 (22)
Bacteremia outcome, n (%)	Eradication	16 (64)	11 (85)	1 (13)	6 (60)	17 (89)	7 (78)
	Persistence	2 (8)	1 (8)	0	0	0	1 (6)
	Indeterminate	7 (28)	1 (8)	7 (88)	4 (40)	2 (11)	1 (16)

CFDC, cefiderocol; I/C, imipenem/cilastatin; MEM, meropenem; TOC, test of cure.
CREDIBLE-CR: adult patients with nosocomial pneumonia (NP), bloodstream infection/sepsis, or complicated urinary tract infection (cUTI) caused by carbapenem-resistant Gram-negative pathogens received CFDC or best available therapy (BAT).
APEKS-NP: adult patients with NP received CFDC or high-dose, extended-infusion meropenem (2 g, q8h, 3-h infusion).
APEKS-cUTI: adult patients with cUTI received CFDC or high-dose imipenem-cilastatin (1 g/1 g, three-times daily, 1 h infusion).
CFDC was given at 2 g, q8h, infused over 1 (APEKS-cUTI) or 3 (APEKS-NP, CREDIBLE-CR) hours with dose adjustment based on renal function. All treatments were given for 7–14 days (extendable to 21 days).

Conclusion. Post-treatment negative blood cultures were inconsistently collected, especially in APEKS-NP and -cUTI, however, negative blood cultures on therapy without recurrence was seen in 96% of CFDC patients with sufficient information. A dedicated clinical trial in GN bacteremia (GAME CHANGER; NCT03869437) is ongoing and will better delineate microbiological outcomes.

Disclosures. **David Paterson**, **Accelerate** (Speaker's Bureau)**BioMerieux** (Speaker's Bureau)**BioMerieux** (Advisor or Review Panel member)**Entasis** (Advisor or Review Panel member)**Merck** (Advisor or Review Panel member)**Merck** (Grant/Research Support)**Merck** (Speaker's Bureau)**Pfizer** (Speaker's Bureau)**Shionogi & Co., Ltd.** (Grant/Research Support)**VenatoRx** (Advisor or Review Panel member) **Masahiro Kinoshita, MPharm**, **Shionogi & Co., Ltd.** (Employee) **Kiichiro Toyoizumi, PhD**, **Shionogi & Co., Ltd.** (Employee) **Yuko Matsunaga, MD**, **Shionogi Inc.** (Employee) **Roger Echols, MD**, **Shionogi Inc.** (Consultant)

1286. Pharmacokinetics, Excretion, and Mass Balance of [^{14}C]-Rezafungin Following Intravenous (IV) Administration in Healthy Adults

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Session: P-58. Novel Agents

Background. Rezafungin is a once-weekly novel echinocandin antifungal currently in Phase 3 development for treatment of candidemia and invasive candidiasis (ReSTORE) and for prevention of invasive fungal disease caused by *Candida*, *Aspergillus*, and *Pneumocystis* in blood and marrow transplant recipients (ReSPECT). Nonclinical ADME studies in rats and monkeys show rezafungin is primarily excreted unchanged in feces, with urine as a minor route. This study was conducted to characterize the routes of elimination of [^{14}C]-rezafungin and the pharmacokinetics of total radioactivity and plasma rezafungin in humans.

Methods. Nine healthy male subjects received a single IV 400-mg rezafungin infusion containing 200 μCi of [^{14}C]-rezafungin. Serial blood samples, urine, and feces were collected at specified times over 60 days; subjects were initially confined in the clinical research unit (CRU) for 17 days postdose and returned for two follow-up visits (days 29 and 60). During the period of time subjects were away from the CRU, recovery of radioactivity was estimated by linear interpolation.

Results. Rezafungin exhibited a long plasma half-life and was mainly excreted in feces unchanged. Cumulative recovery of radioactivity from excreta collected through the first 17 days was 52% (38% in feces, 14% in urine), reinforcing the slow overall elimination of rezafungin. Overall recovery of the administered dose by day 60 was estimated to be 88.3% (65.6% in feces, 22.7% in urine) (Figure 1). Mean blood/plasma concentration ratios ranged from 0.860 to 1.02 through the last collection time point (day 60), which indicated low association of radioactivity with blood cells. Rezafungin was the predominant compound measured in plasma and feces across all collected time points. In the urine, as observed in rat and monkey metabolite profiling studies, low level, inactive, oxidative metabolites were identified as 2-, 3-, 4-hydroxylpentyl rezafungin, and despentyl-rezafungin