Table. Activity of cefiderocol and comparators against non-fermenting Gram-negative bacilli											
	N	MIC_{90}[a] (μg/mL)									
		CFDC	FEP	CZA	C/T	CIP	CST	MEM	MVB[b]	ATM/AVI[b]	SXT[a,b]
Non-fermenters	12293	1	64	64	64	>8	2	>64	64	>8	-
P. aeruginosa	6213	0.5	16	8	2	>8	2	16	8	>8	NT
CarbNS *P. aeruginosa*	1416	1	64	64	>64	>8	2	64	8	>8	NT
A. baumannii complex	4185	2	>64	>64	>64	>8	2	>64	>64	>8	NT
CarbNS *A. baumannii* complex	2274	2	>64	>64	>64	>8	>8	>64	>64	>8	NT
S. maltophilia	1565	0.5	>64	>64	>64	8	>8	>64	8	8	1
B. cepacia complex	265	0..25	>64	8	32	>8	>8	16	8	8	NT
CarbNS *B. cepacia* complex	80	2	>64	16	>64	>8	>8	16	8	8	NT
[a]MVB, ATM/AVI, SXT were only included in SIDERO-WT-2018; [b]SXT was only tested against *S. maltophilia*; NT not tested.											

Disclosures: Yuuta Ukai, MSc, Shionogi & Co., Ltd. (Employee) Rio Nakamura, BSc, Shionogi & Co., Ltd. (Employee) Merime Oota, BSc, Shionogi & Co., Ltd. (Employee) Roger Echols, MD, Shionogi Inc. (Consultant) Miki Takemura, MSc, Shionogi & Co., Ltd. (Employee) Yoshinori Yamano, PhD, Shionogi & Co., Ltd. (Employee) Daniel F. Sahm, PhD, IHMA (Employee)Pfizer, Inc. (Consultant)Shionogi & Co., Ltd. (Independent Contractor)

165. Cefiderocol Treatment for Serious Infections Caused by Carbapenem-resistant Bacteria: Post-hoc Analysis of Outcomes by Pathogen in the CREDIBLE-CR Study

Yuko Matsunaga, MD[1]; Mari Ariyasu, BPharm[2]; Miki Takemura, MSc[2]; Yoshinori Yamano, PhD[2]; Kiichiro Toyoizumi, PhD[3]; Masahiro Kinoshita, MPharm[2]; Roger Echols, MD[4]; Tsutae Den Nagata, MD[2]; [1]Shionogi Inc., Florham Park, New Jersey; [2]Shionogi & Co., Ltd., Osaka, Osaka, Japan; [3]Shionogi Inc, Florham Park, New Jersey; [4]Infectious Disease Drug Development Consulting LLC, Easton, Connecticut

Session: O-32. Novel agents

Background: The efficacy and safety of cefiderocol (CFDC), a novel siderophore cephalosporin, for the treatment of serious infections due to carbapenem-resistant (CR) Gram-negative pathogens was assessed in the CREDIBLE-CR study. The current analysis evaluated clinical and microbiological outcomes by baseline CR pathogen.

Methods: An open-label, prospective, randomised 2:1, Phase 3 study (CREDIBLE-CR; NCT02714595) was conducted in adult patients with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia, bloodstream infections or sepsis, and complicated urinary tract infections caused by CR Gram-negative pathogens. Patients received either intravenous (IV) CFDC 2g, q8h, 3-h infusion, or IV best available therapy (BAT: up to 3 drugs in combination), for 7–14 days (extendable to 21 days). Clinical and microbiological outcomes were assessed in the CR microbiological intent-to-treat (CR-MITT) population by CR pathogen, baseline MIC and by mechanism of carbapenem resistance at test of cure (TOC). Only summary statistics were collected.

Results: In the CR-MITT population (CFDC N=80; BAT N=38), *Acinetobacter baumannii* (46.3% and 44.7%), *Klebsiella pneumoniae* (33.8% and 31.5%), and *Pseudomonas aeruginosa* (15% and 26%) were the most frequent pathogens in CFDC and BAT arms, respectively. For all CR pathogens, clinical cure rates were achieved in 52.5% in the CFDC arm and 50.0% in the BAT arm at TOC; rates were similar between treatment arms by baseline CR pathogen (Table 1). Numerically higher clinical cure and microbiological outcomes were observed with CFDC for Enterobacterales (Table 1), especially against NDM-producing bacteria or those with porin-channel mutations (Table 1). CFDC MIC values ranged between ≤0.03 and 4 μg/mL, except for one pathogen (Table 2). Microbiological outcomes for CR *A. baumannii*, CR *K. pneumoniae*, and CR *P. aeruginosa* at TOC by baseline MICs of ≤4 μg/mL ranged between 0–40%, 0–100%, and 0–100%, respectively; at MIC ≤4 μg/mL, clinical and microbiological outcomes were equal (Table 2).

Table 1. Clinical and microbiological outcomes by most frequent baseline CR pathogens and CR mechanisms at test of cure (all infection sites) in the carbapenem-resistant microbiological intent-to-treat* population.

	Clinical cure rate		Microbiological eradication rate	
	Cefiderocol, (N=80) n/N (%)	BAT, (N=38) n/N (%)	Cefiderocol, (N=80) n/N (%)	BAT, (N=38) n/N (%)
Overall by patient	42/80 (52.5)	19/38 (50.0)	25/80 (31.3)	9/38 (23.7)
All non-fermenters	22/49 (44.9)	13/25 (52.0)	11/49 (22.4)	6/25 (24.0)
Enterobacterales	19/29 (65.5)	5/11 (45.5)	14/29 (48.3)	2/11 (18.2)
Mixed	1/2 (50.0)	1/2 (50.0)	0/2 (0)	1/2 (50.0)
Acinetobacter baumannii	18/37 (48.6)	9/17 (52.9)	10/37 (27.0)	5/17 (29.4)
Klebsiella pneumoniae	17/27 (63.0)	7/12 (58.3)	13/27 (48.1)	3/12 (25.0)
Pseudomonas aeruginosa	7/12 (58.3)	5/10 (50.0)	1/12 (8.3)	2/10 (20.0)
Resistance mechanisms				
NDM-producer (Enterobacterales)	6/8 (75.0)	0/4 (0)	5/8 (62.5)	0/4 (0)
KPC-producer (Enterobacterales)	8/14 (57.1)	4/7 (57.1)	5/14 (35.7)	2/7 (28.6)
Porin channel mutation (Enterobacterales)	10/15 (66.7)	5/9 (55.6)	7/15 (46.7)	1/9 (11.1)
MBL-producer** (non-fermenters or Enterobacterales)	12/16 (75.0)	2/7 (28.6)	7/16 (43.8)	1/7 (14.3)
OXA-producer (non-fermenters)	15/36 (41.7)	9/17 (52.9)	9/36 (25.0)	5/17 (29.4)

*CR status confirmed by central laboratory; **Includes IMP-, NDM-, VIM-producers; IMP: imipenemase metallo-β-lactamase; KPC: *Klebsiella pneumoniae* carbapenemase; MBL: metallo-β-lactamase; NDM: New Delhi metallo-β-lactamase; OXA: oxacillinase; VIM: Verona integron-encoded metallo-β-lactamase.

Table 2. Clinical cure and microbiological eradication rates by CR pathogen in the CR-Micro-ITT population in CFDC arm

	CR *A. baumannii* (N=37), n/N (%)		CR *K. pneumoniae* (N=27), n/N (%)		CR *P. aeruginosa* (N=12), n/N (%)	
	Clinical	Microbiological	Clinical	Microbiological	Clinical	Microbiological
Overall by pathogen	18/37 (48.6%)	10/37 (27.0%)	17/27 (63.0%)	13/27 (48.1%)	7/12 (58.3%)	1/12 (8.3%)
Cefiderocol MIC at baseline, μg/mL						
≤0.03	–	–	–	–	–	–
0.06	3/5 (60.0)	2/5 (40.0)	0/1 (0.0)	0/1 (0.0)	–	–
0.12	2/7 (28.6)	2/7 (28.6)	3/3 (100.0)	1/3 (33.3)	1/3 (33.3)	0/3 (0.0)
0.25	6/11 (54.5)	3/11 (27.3)	5/7 (71.4)	2/7 (28.6)	2/2 (100.0)	0/2 (0.0)
0.5	1/4 (25.0)	1/4 (25.0)	2/2 (100.0)	2/2 (100.0)	1/3 (33.3)	0/3 (0.0)
1	2/6 (33.3)	1/6 (16.7)	3/5 (60.0)	3/5 (60.0)	1/2 (50.0)	0/2 (0.0)
2	1/1 (100.0)	0/1 (0.0)	2/5 (40.0)	2/5 (40.0)	1/1 (100.0)	0/1 (0.0)
4	0/1 (0.0)	0/1 (0.0)	3/4 (75.0)	3/4 (75.0)	1/1 (100.0)	1/1 (100.0)
8	–	–	–	–	–	–
16	0/1 (0.0)	0/1 (0.0)	–	–	–	–
32	–	–	–	–	–	–
≥64	–	–	–	–	–	–
Unknown	1/1 (100)	1/1 (100)	–	–	–	–

Conclusion: CFDC, via a novel mechanism of entry and its stability against β-lactamases, was effective against serious infections caused by CR pathogens with various resistance mechanisms or baseline MIC values.

Disclosures: Yuko Matsunaga, MD, Shionogi Inc. (Employee) Mari Ariyasu, BPharm, Shionogi & Co., Ltd. (Employee) Miki Takemura, MSc, Shionogi & Co., Ltd. (Employee) Yoshinori Yamano, PhD, Shionogi & Co., Ltd. (Employee) Kiichiro Toyoizumi, PhD, Shionogi & Co., Ltd. (Employee) Masahiro Kinoshita, MPharm, Shionogi & Co., Ltd. (Employee) Roger Echols, MD, Shionogi Inc. (Consultant) Tsutae Den Nagata, MD, Shionogi & Co., Ltd. (Employee)

166. Activity of a Novel β-lactamase Inhibitor QPX7728 Combined With β-lactams Against st258 *klebsiella Pneumoniae* and st131 *escherchia Coli* Isolates Producing β-lactamases

Mariana Castanheira, PhD[1]; Jill Lindley[1]; Timothy B. Doyle[1]; Andrew P. Davis, BS[1]; Olga Lomovskaya, PhD[2]; [1]JMI Laboratories, North Liberty, Iowa; [2]Qpex Biopharma, San Diego, California

Session: O-32. Novel agents

Background: ST258 *K. pneumoniae* and ST131 *E. coli* clones are considered vectors for the global spread of multidrug resistance. We evaluated the activity of β-lactams in combination with QPX7728, a novel β-lactamase inhibitor active against all β-lactamase classes, against a collection of 210 isolates belonging to these clones collected from a worldwide surveillance study.

Methods: A total of 118 ST258 *K. pneumoniae* and 92 ST131 *E. coli* (single loci variant also included) were susceptibility tested by reference broth microdilution against various β-lactams ± QPX7728 and comparator agents. All isolates were screened for β-lactamases using whole genome sequencing analysis.

Results: All β-lactam agents had limited activity against 118 ST258 *K. pneumoniae* (1.7–7.6% susceptible). Among these, 104 carried carbapenemase-encoding genes: 66 KPC variants, 20 NDM and 17 OXA-48-like. One isolate carried 2 carbapenemases. The addition of QPX7728 at 4 mg/L or 8 mg/L lowered the MICs for cefepime ($MIC_{50/90}$, 0.25/1 mg/L and $MIC_{50/90}$, 0.12/0.5 mg/L), ceftolozane ($MIC_{50/90}$, 0.5/ > 32 mg/L and $MIC_{50/90}$, 0.25/16 mg/L), ertapenem ($MIC_{50/90}$, 0.12/2 mg/L and $MIC_{50/90}$, 0.06/0.5 mg/L), and meropenem ($MIC_{50/90}$, 0.06/0.5 mg/L and $MIC_{50/90}$, 0.03/0.12 mg/L; Table). QPX7728 at 4 mg/L reduced the ceftibuten ($MIC_{50/90}$, 0.25/8 mg/L) or tebipenem ($MIC_{50/90}$, 0.12/2 mg/L) MICs for ST258 isolates. *E. coli* ST131 carried mainly CTX-M variant (85 isolates), but 6 isolates harbored carbapenemases. Carbapenems were the only β-lactams displaying > 80.0% activity against ST131 *E. coli*, followed by piperacillin-tazobactam (79.3% susceptible). Only 5.4%and 41.3% ST131 isolates were susceptible to cefepime and ceftibuten, respectively. MIC_{50}/MIC_{90} values for these agents with QPX7728 were ≤ 0.015/≤ 0.015 mg/L for cefepime and ≤ 0.015/0.06 mg/L for ceftolozane with the inhibitor at 8 mg/L and ≤ 0.015/0.03 mg/L for ceftibuten with the inhibitor at 4 mg/L.

Conclusion: QPX7728 lowered the MICs for all agents tested to clinically achievable levels when tested against isolates multidrug resistant belonging to important clones responsible to the dissemination of KPC, CTX variants, and metallo-β-lactamases. The development of this broad β-lactamase inhibitor should be pursued.

Table 1

Agent/combination	ST258 *K. pneumoniae*			ST131 *E. coli*		
	MIC_{50}	MIC_{90}	% inhibited at 4 mg/L[a]	MIC_{50}	MIC_{90}	% inhibited at 4 mg/L[a]
Cefepime	>32	>32	4.2	32	32	15.2
Cefepime + QPX7728 at fixed 8 mg/L	0.12	0.5	99.2	≤0.015	≤0.015	100.0
Ceftolozane	>32	>32	2.5	16	>32	27.2
Ceftolozane + QPX7728 at fixed 8 mg/L	0.25	16	82.2	≤0.015	0.06	100.0
Ertapenem	>32	>32	5.1	0.03	0.5	94.6
Ertapenem + QPX7728 at fixed 8 mg/L	0.06	0.5	100.0	≤0.015	≤0.015	100.0
Meropenem	>32	>32	13.6	0.03	0.12	97.8
Meropenem + QPX7728 at fixed 8 mg/L	0.03	0.12	100.0	≤0.015	≤0.015	100.0
Ceftibuten	>32	>32	4.2	16	32	40.2
Ceftibuten + QPX7728 at fixed 4 mg/L	0.25	8	89.0	≤0.015	0.03	100.0
Tebipenem	4	32	52.5	1	8	95.7
Tebipenem + QPX7728 at fixed 4 mg/L	0.12	2	94.9	0.12	0.5	100.0
[a] 4 mg/L was used for comparison purposes only						

Disclosures: Mariana Castanheira, PhD, 1928 Diagnostics (Research Grant or Support)A. Menarini Industrie Farmaceutiche Riunite S.R.L. (Research Grant or Support)