

Outcomes with Cefiderocol Treatment in Patients with Bacteraemia Enrolled into Prospective Phase 2 and Phase 3 Randomised Clinical Studies

David L Paterson,¹ Masahiro Kinoshita,² Takamichi Baba,² Roger Echols,³ Simon Portsmouth⁴

¹ Centre for Clinical Research, Faculty of Medicine, The University of Queensland, Royal Brisbane and Women's Hospital Campus, Brisbane, Australia

² Shionogi & Co., Ltd., Osaka, Japan

³ Infectious Disease Drug Development Consulting, LLC, Easton, CT, USA

⁴ Shionogi Inc., Florham Park, NJ, USA

Corresponding author:

Simon Portsmouth

Shionogi Inc., 300 Campus Park, Florham Park, NJ 07932, USA

Email: Simon.Portsmouth@shionogi.com

Supplementary Table S1 Clinical and microbiological bacteraemia outcomes at end of treatment and test of cure by patient in the three studies (intention-to-treat population)

	APEKS-cUTI		APEKS-NP		CREDIBLE-CR	
	Cefiderocol (N = 19)	Imipenem/ cilastatin (N = 9)	Cefiderocol (N = 8)	Meropenem (N = 10)	Cefiderocol (N = 25)	BAT (N = 13)
EOT						
Bacteraemia outcome, n (%)						
Eradication	17 (89.5)	8 (88.9)	3 (37.5)	7 (70.0)	15 (60.0)	6 (46.2)
<i>Eradication</i>	5 (26.3)	2 (22.2)	1 (12.5)	2 (20.0)	11 (44.0)	6 (46.2)
<i>Presumed eradication</i>	12 (63.2)	6 (66.7)	2 (25.0)	5 (50.0)	4 (16.0)	0
Persistence	0	1 (11.1) ^a	0	0	0	0
Recurrence	0	0	1 (12.5) ^b	0	0	0
Indeterminate	2 (10.5)	0	4 (50.0)	3 (30.0)	10 (40.0)	7 (53.8)
Clinical outcome, n (%)						
Cure	17 (89.5)	8 (88.9)	4 (50.0)	6 (60.0)	16 (64.0)	7 (53.8)
Failure	1 (5.3)	0	3 (37.5)	3 (30.0)	7 (28.0)	6 (46.2)
Indeterminate	1 (5.3)	1 (11.1)	1 (12.5)	1 (10.0)	2 (8.0)	0
TOC						
Bacteraemia outcome, n (%)						
Eradication	15 (78.9)	6 (66.7)	1 (12.5)	5 (50.0)	11 (44.0)	6 (46.2)
<i>Eradication (true)</i>	1 (5.3)	0	0	1 (10.0)	10 (40.0)	4 (30.8)
<i>Presumed eradication</i>	14 (73.7)	6 (66.7)	1 (12.5)	4 (40.0)	1 (4.0)	2 (15.4)
Persistence	0	0	0	0	0	0
Recurrence	0	0	0	0	1 (4.0) ^c	0
Indeterminate	4 (21.1)	3 (33.3)	7 (87.5)	5 (50.0)	13 (52.0)	7 (53.8)
Clinical outcome, n (%)						
Cure	15 (78.9)	6 (66.7)	1 (12.5)	5 (50.0)	10 (40.0)	6 (46.2)
Failure	1 (5.3)	2 (22.2)	4 (50.0)	4 (40.0)	10 (40.0)	6 (46.2)
Indeterminate	3 (15.8)	1 (11.1)	3 (37.5)	1 (10.0)	5 (20.0)	1 (7.7)

BAT best available therapy, CR carbapenem-resistant, EA early assessment, EOT end of treatment, ITT intention-to-treat, TOC test of cure

^aEarly EOT assessment on Day 2 following an adverse event

^b*B. cenocepacia* isolate

^cCR *E. coli* as a result of inadequate source control; this recurrence was due to CR *E. coli* and probably occurred as a result of inadequate source control in a patient whose drainage was left in place following surgery for cancer up to the TOC visit; blood samples at EA and EOT were negative

Supplementary Table S2 Clinical and microbiological outcomes at early assessment, end of treatment and test of cure by pathogen for Enterobacterales and *Acinetobacter* spp. in the three studies (intention-to-treat population)

	APEKS-cUTI		APEKS-NP		CREDIBLE-CR	
	Cefiderocol (N = 19)	Imipenem/ cilastatin (N = 9)	Cefiderocol (N = 8)	Meropenem (N = 10)	Cefiderocol (N = 25)	BAT (N = 13)
Enterobacterales	N' = 18	N' = 8	N' = 6	N' = 8	N' = 15	N' = 7
EA						
Bacteraemia outcome, n (%)						
Eradication	18 (100)	6 (75.0)	3 (50.0)	8 (100)	11 (73.3)	4 (57.1)
<i>Eradication</i>	14 (77.8)	5 (62.5)	2 (33.3)	6 (75.0)	9 (60.0)	4 (57.1)
<i>Presumed eradication</i>	4 (22.2)	1 (12.5)	1 (16.7)	2 (25.0)	2 (13.3)	0
Persistence	0	1 (12.5)	1 (16.7)	0	1 (6.7)	2 (28.6)
Indeterminate	0	1 (12.5)	2 (33.3)	0	3 (20.0)	1 (14.3)
Clinical outcome, n (%)						
Cure	18 (100)	6 (75.0)	4 (66.7)	7 (87.5)	12 (80.0)	2 (28.6)
Failure	0	2 (25.0)	1 (16.7)	1 (12.5)	2 (13.3)	5 (71.4)
Indeterminate	0	0	1 (16.7)	0	1 (6.7)	0
EOT						
Bacteraemia outcome, n (%)						
Eradication	16 (88.9)	7 (87.5)	3 (50.0)	6 (75.0)	10 (66.7)	4 (57.1)
<i>Eradication</i>	5 (27.8)	2 (25.0)	1 (16.7)	2 (25.0)	8 (53.3)	4 (57.1)
<i>Presumed eradication</i>	11 (61.1)	5 (62.5)	2 (33.3)	4 (50.0)	2 (13.3)	0
Persistence	0	1 (12.5) ^a	0	0	0	0
Recurrence	0	0	0	0	0	0
Indeterminate	2 (11.1)	0	3 (50.0)	2 (25.0)	5 (33.3)	3 (42.9)
Clinical outcome, n (%)						
Cure	16 (88.9)	7 (87.5)	3 (50.0)	5 (62.5)	10 (66.7)	4 (57.1)
Failure	1 (5.6)	0	3 (50.0)	2 (25.0)	3 (20.0)	3 (42.9)
Indeterminate	1 (5.6)	1 (12.5)	0	1 (12.5)	2 (13.3)	0
TOC						
Bacteraemia outcome, n (%)						
Eradication	14 (77.8)	5 (62.5)	1 (16.7)	4 (50.0)	7 (46.7)	3 (42.9)
<i>Eradication</i>	1 (5.6)	0	0	1 (12.5)	6 (40.0)	3 (42.9)

<i>Presumed eradication</i>	13 (72.2)	5 (62.5)	1 (16.7)	3 (37.5)	1 (6.7)	0
Persistence	0	0	0	0	0	0
Recurrence	0	0	0	0	1 (6.7) ^b	0
Indeterminate	4 (22.2)	3 (37.5)	5 (83.3)	4 (50.0)	7 (46.7)	4 (57.1)
Clinical outcome, n (%)						
Cure	14 (77.8)	5 (62.5)	1 (16.7)	4 (50.0)	8 (53.3)	3 (42.9)
Failure	1 (5.6)	2 (25.0)	3 (50.0)	3 (37.5)	4 (26.7)	3 (42.9)
Indeterminate	3 (16.7)	1 (12.5)	2 (33.3)	1 (12.5)	3 (20.0)	1 (14.3)
<i>Acinetobacter</i> spp	N' = 0	N' = 1	N' = 2	N' = 0	N' = 12	N' = 6
EA						
Bacteraemia outcome, n (%)						
Eradication	0	1 (100)	0	0	9 (75.0)	4 (66.7)
<i>Eradication</i>	0	1 (100)	0	0	9 (75.0)	4 (66.7)
<i>Presumed eradication</i>	0	0	0	0	0	0
Persistence	0	0	0	0	1 (8.3)	1 (16.7)
Indeterminate	0	0	2 (100)	0	2 (16.7)	1 (16.7)
Clinical outcome, n (%)						
Cure	0	1 (100)	0	0	6 (50.0)	1 (16.7)
Failure	0	0	1 (50.0)	0	5 (41.7)	4 (66.7)
Indeterminate	0	0	1 (50.0)	0	1 (8.3)	1 (16.7)
EOT						
Bacteraemia outcome, n (%)						
Eradication	0	1 (100)	0	0	7 (58.3)	3 (50.0)
<i>Eradication</i>	0	0	0	0	5 (41.7)	3 (50.0)
<i>Presumed eradication</i>	0	1 (100)	0	0	2 (16.7)	0
Persistence	0	0	0	0	0	0
Recurrence	0	0	0	0	0	0
Indeterminate	0	0	2 (100)	0	5 (41.7)	3 (50.0)
Clinical outcome, n (%)						
Cure	0	1 (100)	0	0	8 (66.7)	3 (50.0)
Failure	0	0	1 (50.0)	0	4 (33.3)	3 (50.0)
Indeterminate	0	0	1 (50.0)	0	0	0
TOC						
Bacteraemia outcome, n (%)						

Eradication	0	1 (100)	0	0	6 (50.0)	3 (50.0)
<i>Eradication</i>	0	0	0	0	6 (50.0)	2 (33.3)
<i>Presumed eradication</i>	0	1 (100)	0	0	0	1 (16.7)
Persistence	0	0	0	0	0	0
Recurrence	0	0	0	0	0	0
Indeterminate	0	0	2 (100)	0	6 (50.0)	3 (50.0)
Clinical outcome, n (%)						
Cure	0	1 (100)	0	0	4 (33.3)	3 (50.0)
Failure	0	0	1 (50.0)	0	6 (50.0)	3 (50.0)
Indeterminate	0	0	1 (50.0)	0	2 (16.7)	0

BAT best available therapy, CR carbapenem resistant, EA early assessment, EOT end of treatment, TOC test of cure

N', total number of isolates of a given species

^aEarly EOT assessment on Day 2 following an adverse event

^bCR *E. coli* as a result of inadequate source control; this recurrence was due to CR *E. coli* and probably occurred as a result of inadequate source control in a patient whose drainage was left in place following surgery for cancer up to the TOC visit; blood samples at EA and EOT were negative

Supplementary Table S3 Clinical and microbiological outcomes at early assessment, end of treatment and test of cure by pathogen for carbapenem-resistant Enterobacterales and *Acinetobacter* spp. in CREDIBLE-CR (intention-to-treat population)

	CR Enterobacterales		CR <i>Acinetobacter</i> spp	
	Cefiderocol (N = 25) N' = 12	BAT (N = 13) N' = 6	Cefiderocol (N = 25) N' = 10	BAT (N = 13) N' = 6
EA				
Bacteraemia outcome, n (%)				
Eradication	9 (75.0)	3 (50.0)	7 (70.0)	4 (66.7)
<i>Eradication</i>	7 (58.3)	3 (50.0)	7 (70.0)	4 (66.7)
<i>Presumed eradication</i>	2 (16.7)	0	0	0
Persistence	1 (8.3)	2 (33.3)	1 (10.0)	1 (16.7)
Indeterminate	2 (16.7)	1 (16.7)	2 (20.0)	1 (16.7)
Clinical outcome, n (%)				
Cure	10 (83.3)	2 (33.3)	5 (50.0)	1 (16.7)
Failure	1 (8.3)	4 (66.7)	4 (40.0)	4 (66.7)
Indeterminate	1 (8.3)	0	1 (10.0)	1 (16.7)
EOT				
Bacteraemia outcome, n (%)				
Eradication	8 (66.7)	3 (50.0)	5 (50.0)	3 (50.0)
<i>Eradication</i>	6 (50.0)	3 (50.0)	4 (40.0)	3 (50.0)
<i>Presumed eradication</i>	2 (16.7)	0	1 (10.0)	0
Persistence	0	0	0	0
Recurrence	0	0	0	0
Indeterminate	4 (33.3)	3 (50.0)	5 (50.0)	3 (50.0)
Clinical outcome, n (%)				
Cure	8 (66.7)	3 (50.0)	6 (60.0)	3 (50.0)
Failure	3 (25.0)	3 (50.0)	4 (40.0)	3 (50.0)
Indeterminate	1 (8.3)	0	0	0
TOC				
Bacteraemia outcome, n (%)				
Eradication	5 (41.7)	2 (33.3)	4 (40.0)	3 (50.0)
<i>Eradication</i>	4 (33.3)	2 (33.3)	4 (40.0)	2 (33.3)
<i>Presumed eradication</i>	1 (8.3)	0	0	1 (16.7)

Persistence	0	0	0	0
Recurrence	1 (8.3) ^a	0	0	0
Indeterminate	6 (50.0)	4 (66.7)	6 (60.0)	3 (50.0)
Clinical outcome, <i>n</i> (%)				
Cure	6 (50.0)	2 (33.3)	2 (20.0)	3 (50.0)
Failure	4 (33.3)	3 (50.0)	6 (60.0)	3 (50.0)
Indeterminate	2 (16.7)	1 (16.7)	2 (20.0)	0

EA early assessment, *BAT* best available therapy, *CR* carbapenem-resistant, *EOT* end of treatment, *ITT* intention-to-treat, *TOC* test of cure

N', total number of isolates of a given species

^aCR *E. coli* as a result of inadequate source control; this recurrence was due to CR *E. coli* and probably occurred as a result of inadequate source control in a patient whose drainage was left in place following surgery for cancer up to the TOC visit; blood samples at EA and EOT were negative

Supplementary Table S4 Characteristics of baseline pathogens isolated from blood and study drug minimum inhibitory concentrations in the three studies

APEKS-cUTI					
Pt	Arm	Diagnosis	Bacteria from blood (MIC of study drug, µg/mL)	Molecular information for bacteria from urine	Eradication at study visits
1	Cefiderocol	cUTI	<i>E. coli</i> (MIC=2)	CTX-M-15, OXA-1, TEM-1	EA, EOT, TOC
2	Cefiderocol	cUTI	<i>E. coli</i> (MIC=2)	CTX-M-15	EA, EOT, TOC
3	Cefiderocol	cUTI	<i>E. coli</i> (MIC=2)	CTX-M-15, OXA-1	EA, EOT
4	Cefiderocol	cUTI	<i>E. coli</i> (MIC=0.25)	CTX-M-27	EA, EOT
1	Imipenem-cilastatin	cUTI	<i>E. coli</i> (MIC=0.12)	CTX-M-15, OXA-1, TEM-1	EOT
2	Imipenem-cilastatin	cUTI	<i>A. baumannii</i> complex (MIC=8)	OXA-23	EA, EOT, TOC
APEKS-NP					
Pt	Arm	Diagnosis	Bacteria from blood (cefiderocol MIC, µg/mL)	Molecular information for bacteria from respiratory sample	
1	Cefiderocol	HAP	<i>K. pneumoniae</i> (MIC=2)	CTX-M-15, NDM-1, SHV-OSBL, TEM-OSBL	EA
2	Cefiderocol	HAP	<i>A. baumannii</i> (MIC=0.5)	GES-type	–
CREDIBLE-CR					
Pt	Arm	Diagnosis	Bacteria from blood (cefiderocol MIC, µg/mL)	Molecular information	
1	Cefiderocol	Sepsis	<i>K. pneumoniae</i> (MIC=1)	NDM-1, CMY-6	EA, EOT, TOC
2	Cefiderocol	cUTI	<i>K. pneumoniae</i> (MIC=0.12)	SHV-OSBL, OXA-48, CTX-M-15	EA
3	Cefiderocol	Sepsis	<i>K. pneumoniae</i> (MIC=2)	OXA-48, SHV-OSBL, TEM-OSBL	–
4	Cefiderocol	BSI	<i>A. baumannii</i> (MIC=0.12)	OXA-23	EA
5	Cefiderocol	BSI	<i>A. baumannii</i> (MIC=0.12)	OXA-23	EA
6	Cefiderocol	BSI	<i>A. baumannii</i> (MIC=0.12)	OXA-23	–
7	Cefiderocol	BSI	<i>A. baumannii</i> (MIC=0.06)	OXA-72	–
8	Cefiderocol	BSI	<i>K. pneumoniae</i> (MIC=0.25) <i>A. baumannii</i> (MIC=0.25) <i>E. coli</i> (MIC=0.5)	No carbapenemase producer OXA-23 No carbapenemase producer	EA, EOT, TOC
9	Cefiderocol	BSI	<i>E. coli</i> (MIC=0.5)	NDM-5	EA, EOT

10	Cefiderocol	BSI	<i>A. baumannii</i> (MIC=0.5)	OXA-23	EA, EOT
11	Cefiderocol	BSI	<i>A. baumannii</i> (MIC=0.5)	OXA-23	EA, EOT, TOC
12	Cefiderocol	cUTI	<i>E. coli</i> (MIC=32)	TEM-OSBL, CTX-M-15, NDM-5	EOT, TOC
13	Cefiderocol	VAP	<i>A. baumannii</i> (MIC=0.5)	OXA-23	–
14	Cefiderocol	BSI	<i>A. radioresistens</i> (MIC≤0.03)	No carbapenemase producer	EA, EOT, TOC
15	Cefiderocol	BSI	<i>K. pneumoniae</i> (MIC=2)	SHV-OSBL, KPC-3	–
16	Cefiderocol	BSI	<i>K. pneumoniae</i> (MIC=0.25)	SHV-OSBL, KPC-3	EA, EOT
17	Cefiderocol	BSI	<i>A. baumannii</i> (MIC=0.12)	OXA-23	EA, EOT, TOC
18	Cefiderocol	BSI	<i>K. pneumoniae</i> (MIC=2)	KPC-3	EA, EOT
19	Cefiderocol	BSI	<i>K. pneumoniae</i> (MIC=2)	SHV-OSBL, KPC-3	EA, EOT, TOC
20	Cefiderocol	BSI	<i>A. baumannii</i> (MIC missing)	Missing	EA, EOT, TOC
21	Cefiderocol	BSI	<i>A. baumannii</i> (MIC=4)	NDM-1, OXA-23	EA, EOT, TOC
22	Cefiderocol	VAP	<i>K. oxytoca</i> (MIC≤0.03)	No carbapenemase producer	–
23	Cefiderocol	cUTI	<i>K. pneumoniae</i> (MIC=0.25)	KPC-2, SHV-OSBL, TEM-OSBL	EA, EOT, TOC
24	Cefiderocol	BSI	<i>K. pneumoniae</i> (MIC=1)	No carbapenemase producer/SHV-OSBL, TEM-OSBL, CTX-M-14, DHA-1	EA
25	Cefiderocol	BSI	<i>K. pneumoniae</i> (MIC=1)	SHV-OSBL, OXA-232, NDM-1, CTX-M-15	EA, EOT, TOC
1	Ceftazidime-avibactam, gentamicin	Sepsis	<i>K. pneumoniae</i> (MIC n/a)	KPC-3, SHV-OSBL, TEM-OSBL	EA, EOT, TOC
2	Ceftolozane-tazobactam, colistin	BSI	<i>P. aeruginosa</i> (MIC n/a)	No carbapenemase producer/PDC-37	EA
3	Cefepime, colistin, tigecycline	BSI	<i>A. baumannii</i> (MIC n/a) <i>P. stuartii</i> (MIC n/a)	OXA-23 No carbapenemase producer	EA, EOT, TOC
4	Ampicillin-sulbactam, colistin	VAP	<i>A. baumannii</i> (MIC n/a)	OXA-23	EA, EOT
5	Colistin, imipenem-cilastatin	BSI	<i>K. pneumoniae</i> (MIC n/a)	SHV-OSBL, OXA-48, CTX-M-15	EA,
6	Cefoperazone-sulbactam, colistin	Sepsis	<i>A. baumannii</i> (MIC n/a)	OXA-23	EA, EOT, TOC
7	Gentamicin	BSI	<i>K. pneumoniae</i> (MIC n/a)	No carbapenemase producer/SHV-OSBL, CTX-M-15	EOT, TOC
8	Ampicillin-sulbactam, colistin	BSI	<i>A. baumannii</i> (MIC n/a)	OXA-23	–

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9	Colistin, fosfomycin	BSI	<i>K. pneumoniae</i> (MIC n/a)	SHV-OSBL, VEB-1, NDM-1, KPC-2, CTX-M-15	EA, EOT
10	Colistin, tigecycline	BSI	<i>A. baumannii</i> (MIC n/a)	OXA-23	EA
11	Colistin, tigecycline	VAP	<i>K. pneumoniae</i> (MIC n/a)	CTX-M-15, NDM-1, OXA-244, SHV-OSBL	–
12	Ceftazidime, ciprofloxacin	BSI	<i>P. aeruginosa</i> (MIC n/a)	No carbapenemase producer/PDC-31	EA
13	Colistin, ertapenem	Sepsis	<i>A. baumannii</i> (MIC n/a) <i>M. morganii</i> (MIC n/a)	OXA-23 No carbapenemase-producer	–

BSI bloodstream infection, *CMY* cephamycin-hydrolysing beta-lactamase, *cUTI* complicated urinary tract infection, *CTX-M* cefotaxime-hydrolysing beta-lactamase, *DHA* Dhahran Hospital in Saudi Arabia beta-lactamase, *EA* early assessment, *EOT* end of treatment, *GES* Guiana extended-spectrum beta-lactamase, *HAP* hospital-acquired infection, *KPC* *Klebsiella pneumoniae* carbapenemase, *MIC* minimum inhibitory concentration, *n/a* not available, *NDM* New Delhi metallo-beta-lactamase, *OSBL* original-spectrum beta-lactamase, *OXA* oxacillinase, *PDC* *Pseudomonas*-derived cephalosporinase, *Pt* patient, *SHV* sulfhydryl variant of TEM extended-spectrum beta-lactamase, *TEM* Temoneira extended-spectrum beta-lactamase, *TOC* test of cure, *VAP* ventilator-associated pneumonia, *VEB* Vietnamese extended-spectrum beta-lactamase, –, no eradication.

Supplementary Table S5 Day-14 and Day-28 all-cause mortality rates in the three studies (intention-to-treat population)

	APEKS-cUTI		APEKS-NP		CREDIBLE-CR	
	Cefiderocol (N = 19)	Imipenem/cilastatin (N = 9)	Cefiderocol (N = 8)	Meropenem (N = 10)	Cefiderocol (N = 25)	BAT (N = 13)
Day-14 ACM, n (%)	1 (5.3)	0 (0)	4 (50.0)	2 (20.0)	7 (28.0)	1 (7.7)
Day-28 ACM, n (%)	1 (5.3)	0 (0)	4 (50.0)	3 (30.0)	8 (32.0)	4 (30.8)

ACM all-cause mortality, BAT best available therapy