FDA Introductory Comments

NDA 209445: Cefiderocol

Antimicrobial Drugs Advisory Committee Meeting

October 16, 2019

Edward Weinstein, MD, PhD

Clinical Team Leader, Division of Anti-Infective Products

FDA

Introduction

- NDA 209445: Cefiderocol for injection
- Applicant: Shionogi Inc.
- Qualified Infectious Disease Product (QIDP) designation for:
  - Complicated Urinary Tract Infections (cUTI)
  - Hospital-Acquired Bacterial Pneumonia (HABP), Ventilator-Associated Bacterial Pneumonia (VABP)
  - Bloodstream infections (BSI)
- NDA granted priority review as the product has QIDP designation

Proposed Indication

- As a single agent in patients aged 18 years or older for the treatment of complicated urinary tract infections (cUTIs), including pyelonephritis, caused by the following susceptible Gram-negative microorganism(s): *Escherichia coli* (including with concurrent bacteremia), *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Citrobacter freundii* complex, *Enterobacter cloacae* complex, *Morganella morganii*, and *Serratia marcescens*

As only limited clinical safety and efficacy data for cefiderocol are currently available, cefiderocol should be reserved for use in patients who have limited or no alternative treatment options

Proposed Dosing Regimen

Renal Function Category	Dose
Augmented renal clearance (CrCl ≥ 120 mL/min)	2 gm IV every 6 hours
Normal renal function (CrCl 90 to < 120 mL/min) or Mild renal impairment (CrCl 60 to < 90)	2 gm IV every 8 hours
Moderate renal impairment (CrCl 30 to < 60 mL/min)	1.5 gm IV every 8 hours
Severe renal impairment (CrCl 15 to < 30 mL/min)	1 gm IV every 8 hours
ESRD (CrCl < 15 mL/min) or intermittent HD	0.75 gm IV every 12 hours

CrCl = creatinine clearance estimated by Cockcroft-Gault equation; ESRD = end stage renal disease; HD = hemodialysis; IV = intravenous

Development Program

- Six phase 1 studies including a lung penetration study, a thorough QT study and a renal impairment study
- Two active-controlled clinical trials in adult patients
  - cUTI trial compared cefiderocol to imipenem/cilastatin in patients with carbapenem-susceptible Gram-negative pathogens
  - The CREDIBLE-CR trial compared cefiderocol to the best available therapy in patients infected with carbapenem-resistant pathogens across body sites
    - CREDIBLE-CR completed enrollment during the review cycle. No clinical study report submitted.
- One phase 3 trial in adults with nosocomial pneumonia* due to carbapenem-susceptible Gram-negative pathogens (APEKS-NP)
  - Recently completed enrollment. Only summary mortality data submitted.

* Hospital-Acquired Bacterial Pneumonia (HABP), Ventilator-Associated Bacterial Pneumonia (VABP), and Healthcare-Associated Bacterial Pneumonia (HCABP)

cUTI Trial

- 2:1 Randomized, double-blinded noninferiority (NI) trial comparing cefiderocol to imipenem/cilastatin for 7 to 14 days of treatment
- Trial design generally consistent with the FDA cUTI guidance
- No IV to oral antibacterial therapy switch was permitted
  - Dose adjustments based upon creatinine clearance
- Primary endpoint: Composite of microbiologic eradication and clinical cure rate in the microbiological intent-to-treat (Micro-ITT) population at the test of cure (TOC) visit occurring 7 +/- 2 days after the last dose of study drug
- Given the potential of cefiderocol to address an unmet clinical need, the Agency agreed that a single clinical trial would provide sufficient evidence of efficacy for a limited use cUTI indication
  - Pre-specified non-inferiority margin of 15%

cUTI Trial Results at TOC

(Micro-ITT Population)

Study Endpoint	Cefiderocol N/n (%)	Imipenem/Cilastatin N/n (%)	Treatment Difference (95% CI)[a]
Composite Response	183/252 (72.6%)	65/119 (54.6%)	18.6 (8.2, 28.9)
Microbiologic Response	184/252 (73.0%)	67/119 (56.3%)	17.3 (6.9, 27.6)
Clinical Response	226/252 (89.7%)	104/119 (87.4%)	2.4 (-4.7, 9.4)

CI = confidence interval; Micro-ITT = microbiological intent-to-treat; TOC = Test of Cure

[a] The treatment difference and 95% CI were based on the Cochran-Mantel-Haenzel method

CREDIBLE-CR Trial

- 2:1 Randomized, open-label trial comparing cefiderocol to best available therapy (BAT) across body sites for the treatment of carbapenem-resistant Gram negative pathogens.
  - No formal hypothesis testing was prespecified.
  - A colistin-based regimen was used as BAT in the majority of subjects.
- Cefiderocol dosing regimen was same as in cUTI trial, except infusion time was 3h
  - 7 to 14 days of treatment but permitted an extension of up to 21 days of treatment.
- Primary endpoints:
  - Pneumonia or BSI/sepsis: clinical outcome at the test of cure visit.
  - cUTI: Microbiological outcome at the test of cure .

CREDIBLE-CR Trial Mortality Data

	Cefiderocol	BAT	Difference	95% CI
Overall				
Day 14	19/101 (18.8%)	6/49 (12.2%)	6.6%	-5.4% to 18.5%
Day 28	25/101 (24.8%)	9/49 (18.4%)	6.4%	-7.3% to 20.1%
Day 49	34/101 (33.7%)	10/49 (20.4%)	13.3%	-1.3% to 27.8%
cUTI Subset				
Day 14	3/26 (11.5%)	2/10 (20.0%)	-8.5%	-36.1% to 19.2%
Day 28	4/26 (15.4%)	2/10 (20.0%)	-4.6%	-33.0% to 23.8%
Day 49	4/26 (15.4%)	2/10 (20.0%)	-4.6%	-33.0% to 23.8%

Safety Assessment

- Safety assessment will present the trials separately
  - There are substantial differences between the trials, such as the type and severity of infection, duration of treatment, patient population, multiple comparators in the BAT regimen and use of concomitant medications
- Safety of cefiderocol in the cUTI trial was consistent with the cephalosporin class; potential safety signals included reduced seizure threshold, hepatotoxicity, *C. difficile* colitis, and hypersensitivity reactions.

Outline for the Day

- Presentations by the Applicant
- Presentations by the FDA
  - **Microbiology** by Kalavati Suvarna, PhD
  - **cUTI and CREDIBLE-CR Trials Presented Individually**
    - **Efficacy** by Daniel Rubin, PhD
    - **Safety** by Shabnam Naseer, DO, MS
- Clarifying Questions
- Lunch
- Open Public Hearing
- Questions to the committee

Question 1

- Please discuss your evaluation of the mortality imbalance observed in the CREDIBLE-CR study with respect to the overall risk benefit assessment for cefiderocol and provide recommendations for labeling and/or the need for additional studies.

Question 2

Has the Applicant provided substantial evidence of the efficacy and sufficient evidence of the safety of cefiderocol for the treatment of complicated urinary tract infections (cUTI) including pyelonephritis in patients with limited or no alternative treatment options?

a. If yes, please provide any recommendations concerning labeling.
b. If no, what additional studies/analyses are needed?

Clinical Microbiology Considerations

Cefiderocol

Antimicrobial Drugs Advisory Committee Meeting

October 16, 2019

Kalavati Suvarna, PhD

Clinical Microbiology Reviewer

Division of Anti-infective Products

Office of Antimicrobial Products, CDER, FDA

Outline

- Background
- *In vitro* susceptibility test method
- *In vitro* activity assessments:
  - Minimum inhibitory concentration (MICs) for target Gram-negative pathogens
  - Time kill studies
- Pharmacodynamic studies:
  - *In vitro* - chemostat
  - *In vivo* - neutropenic thigh model
- Resistance
- Summary

Background

- Cefiderocol can chelate iron and use the bacterial iron transport system to enhance entry into the periplasmic space of Gram-negative aerobic bacteria
- **Mechanism of action: Inhibition of peptidoglycan synthesis by binding to penicillin binding proteins (PBPs)**

Binding To Penicillin Binding Proteins (PBPs)

	Cefiderocol IC_{50} (mcg/mL)[a]			
	E. coli NIHJ JC-2	*K. pneumoniae* SR22291	*P. aeruginosa* ATCC 27853	*A. baumannii* ATCC 17978
PBP1	NT	NT	NT	1.05
PBP1a	3.8	2.8	0.85	NT
PBP1b	3.37	3.5	>4	NT
PBP2	2.12	0.063	>4	2.31
PBP3	0.04	0.062	0.06	0.67
PBP4	NC[b]	0.28	>4	NT
PBP5/6	NC[c]	>4	>4	NT

a The drug concentration of cefiderocol required to inhibit the binding of [14C]-penicillin G binding to a PBP by 50% for each strain
b Percent of inhibition of cefiderocol for PBP4 is 63% at 4 mcg/mL and 31% at 0.063 mcg/mL
c Percent of inhibition of cefiderocol for PBP5/6 is 55% at 4 mcg/mL and 7% at 0.063 mcg/mL; NT = not tested
Source: Studies EB-103-N, EB-126-N, and EB-200-N

In Vitro Susceptibility Method

- Cefiderocol MICs in cation-adjusted Mueller-Hinton Broth (CAMHB) were 2-4 fold higher than in iron depleted media (ID-CAMHB) against Enterobacteriaceae and non-fermenters

- ID-CAMHB is being used for the broth microdilution susceptibility test method

- Total iron in ID-CAMHB is 0.02 mcg/mL (sufficient for bacterial growth; similar to concentration of non-transferrin bound iron in healthy human serum)

In Vitro Activity Against Target Bacteria

Gram-negative bacteria (no. of isolates)	**Cefiderocol MIC_{90}** (MIC Range) **in mcg/mL**
Enterobacteriaceae (n = 17,847)	**1.0** (≤ 0.002 to >128)
Meropenem non-susceptible (n = 1,021)	4.0 (0.004 to 32)
Non-fermenters	
***Pseudomonas aeruginosa* (n = 4942)**	**0.5** (≤ 0.002 to 8)
Meropenem non-susceptible (n =1154)	1.0 (≤ 0.002 to 8)
MDR *P. aeruginosa* (n = 262)	1.0 ~~2.0~~ (0.002 to 32.0)
***Acinetobacter baumannii* (n = 2896)**	**2.0** (≤ 0.002 to >256)
Meropenem non-susceptible (n =1891)	2.0 (≤ 0.002 to >256)
MDR *A. baumannii* (n = 368)	8.0 (0.015 to >256)
***Stenotrophomonas maltophilia* (n = 1173)**	**0.25** (≤ 0.002 to 64)
Meropenem non-susceptible (n =1155)	0.25 (≤ 0.002 to 64)
MDR *S. maltophilia* (n = 218)	0.25 (0.015 to 2.0 ~~>256~~)

Meropenem non-susceptible was defined as meropenem MIC ≥ 2 mcg/mL for Enterobacteriaceae and ≥ 4 mcg/mL for non-fermenters. MDR = multidrug resistant non-fermenter (resistant to meropenem (MIC ≥ 4 mcg/mL), amikacin (MIC ≥ 64 mcg/mL) and ciprofloxacin (MIC ≥ 4 mcg/mL)). Errors in the briefing document are shown as strikethrough and the correct number is reflected in red
Source: Study EB-344-N and Study EF-115N

Degradation By β-lactamases

- MICs of cefiderocol in the presence of β-lactamase inhibitors [avibactam (AVI), clavulanic acid (CVA), and dipicolinic acid (DPA)] were measured for several clinical isolates
- AVI and CVA inhibits serine type β-lactamases
- DPA inhibits metallo type β-lactamases

Degradation By β-lactamases

- Baseline cefiderocol MICs for 74 isolates (Enterobacteriaceae and non-fermenters) tested ranged from 2 to >32 mcg/mL
- Addition of AVI lowered the cefiderocol MICs by ≥8 fold in 47/74 (63.5%) isolates
- Addition of AVI and DPA lowered the cefiderocol MICs by ≥8 fold in 64/74 (86.5%)
- Cefiderocol can be hydrolyzed by serine and metallo-type β-lactamases

In Vitro Assessments

- **Time kill studies (Enterobacteriaceae and Non-fermenters)**
  - Regrowth is observed after initial 2-3 $\log_{10}$ kill at 8 hours at concentrations greater than or equal to cefiderocol MICs
  - Cefiderocol concentrations 2-16x MIC were required to achieve sustained killing of Enterobacteriaceae over 24 hours
  - No sustained killing was observed for non-fermenters at 16x MIC although cefiderocol MICs for the strains tested were low (0.015-0.06 mcg/mL)

- ***In vitro* pharmacodynamic (chemostat) studies**
  - Risk of resistance development
  - Simulated exposures based on humanized cefiderocol dosing of 2 gm every 8 hours administered as 3 hour infusion
  - Regrowth was observed after 8 hours for Enterobacteriaceae and non-fermenters
  - Regrowth was sometimes to the same level as unexposed controls

Neutropenic Thigh Infection Model

Bacteria Group or Species	MIC range (mcg/mL)	Range of mean absolute growth or reduction in log_{10}CFU* relative to starting inoculum at 24 hours	
		Control	Cefiderocol
Enterobacteriaceae (n = 39)	0.12 to >64	1.24 to 3.89	1.82 to -2.96
A. baumannii (n = 35)	0.12 to >256	1.01 to 3.63	2.51 to -2.49
P. aeruginosa (n = 21)	0.25 to 8	2.60 to 4.28	2.56 to -2.42

Simulated human dose (2gm every 8 hours as 3 hour infusion)
Endpoint: ≥ 1-log_{10} reduction at 24 hours
* CFU = colony forming units

Source: Study report EF-231-R


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ADMINISTRATION

Efficacy Assessment of Cefiderocol for the Treatment of cUTI

Antimicrobial Drugs Advisory Committee Meeting

October 16, 2019

Daniel Rubin, PhD

Biometrics Reviewer, Division of Biometrics IV, Office of Biostatistics, Office of Translational Sciences, CDER, FDA

Outline

- Study design of the cUTI trial
- Efficacy results
- Efficacy summary

Study Design

- Randomized, double-blind, active-controlled, multinational

- Intravenous cefiderocol 2 grams every 8 hours for 7-14 days

  versus

  Intravenous imipenem/cilastatin 1 gram every 8 hours for 7-14 days

- No oral step down therapy

Study Design

- Inclusion/exclusion criteria:
  - Adults ≥18 years old
  - Diagnosis of cUTI with or without pyelonephritis based on complications, signs/symptoms, and urinalysis evidence of pyuria
  - Uncomplicated pyelonephritis limited to ≤30% of study population
  - Patients excluded for suspected imipenem/cilastatin resistance

Study Design

- Composite primary efficacy endpoint at the Test of Cure visit 7±2 days after the end of treatment:
  - Eradication: Pathogen at study entry reduced to $<10^4$ CFUs/mL
  - Clinical cure: Sufficient resolution or improvement of symptoms
- Primary analysis population:
  - Micro-ITT Population of randomized patients who received any dose of study drug with a baseline Gram-negative uropathogen on blood culture or urine culture ($\geq 10^5$ CFUs/mL)
- Designed with planned testing for a 15% noninferiority margin

Composite Clinical and Microbiological Response at Test of Cure by subgroup (Micro-ITT)

	Cefiderocol	Imipenem/Cilastatin	Difference	95% CI
Age group				
<65 years	ô ó l í í ï	~ï ô ó ñX ðì •	~ 17.7 X	ï 2.5 to 33.0
H ò ñ	õÇ ò l í ïÇõ •	~ï ò lõ òX ñí •	~ 18.3 X	ô 3.9 to 32.7
Gender				
Male	ô ð l í í õ	~î ñ l øX ôõ •	~ 18.5 X	í 2.2 to 34.8
Female	õ õ l í ï ï	~ð óì ð øX íð •	~ 18.1 X	ï 4.4 to 31.8
Clinical Diagnosis				
cUTI with Pyelonephritis	ð ð l ò ñ	~ í òï ó øX õó •	~ 22.9 X	ô 1.5 to 44.2
cUTI without Pyelonephritis	ô ñ l í î î	~î ôõ ð øX ñó •	~ 18.8 X	õ 3.2 to 34.3
Uncomplicated Pyelonephritis	ñ ð l ò ñ	~ î ôð ï l Xï ñ •	~ 14.5 X	ò 3.4 to 32.4
Baseline pathogen				
Escherichia coli	í í ï l í ñ î	ð ñô lð óX õï •	~ 17.4ó X	ì 4.4 to 30.3
Klebsiella pneumoniae	ï ò l ð ô	~ íó î ñl X ñ •	~ 27.0 X	ì 3.9 to 50.1
Proteus mirabilis	í ï l í ó	~ ó ìò l Xï ñ •~	ì X ì •	
Pseudomonas aeruginosa	ôX	ï l ñ ~ ò ì X ì •		

Source: Statistical reviewer

Microbiological Outcome (Micro-ITT)

	Cefiderocol (n = 252)	Imipenem/Cilastatin (n = 119)	Difference	95% CI
Early Assessment				
Eradication	232 (92.1)	109 (90.8)	1.3	-4.8 to 7.4
Failure	14 (5.6)	7 (5.9)		
Indeterminate	6 (2.4)	4 (3.4)		
End of Treatment				
Eradication	244 (96.8)	114 (95.8)	1.1	-3.0 to 5.3
Failure	3 (1.2)	3 (2.5)		
Indeterminate	5 (2.0)	2 (1.7)		
Test of Cure				
Eradication	184 (73.0)	67 (56.3)	17.3	6.9 to 27.6
Failure	53 (21.0)	44 (37.0)		
Indeterminate	15 (6.0)	8 (6.7)		
Follow-up Visit				
Sustained Eradication	144 (57.1)	52 (43.7)	13.9	3.2 to 24.6
Failure	84 (33.3)	42 (35.3)		
Indeterminate	24 (9.5)	25 (21.0)		

Source: 1409R2121 Clinic Study Report Amendment 2, Table 11-8

Clinical Outcome (Micro-ITT)

	Cefiderocol (n = 252)	Imipenem/Cilastatin (n = 119)	Difference	95% CI
Early Assessment				
Clinical Cure	228 (90.5)	108 (90.8)	-0.3	-6.6 to 6.1
Clinical Failure	23 (9.1)	10 (8.4)		
Indeterminate	1 (0.4)	1 (0.8)		
End of Treatment				
Clinical Cure	247 (98.0)	118 (99.2)	-1.1	-3.4 to 1.3
Clinical Failure	4 (1.6)	0 (0.0)		
Indeterminate	1 (0.4)	1 (0.8)		
Test of Cure				
Clinical Cure	226 (89.7)	104 (87.4)	2.4	-4.7 to 9.4
Clinical Failure	14 (5.6)	8 (6.7)		
Indeterminate	12 (4.8)	7 (5.9)		
Follow-up				
Sustained Cure	205 (81.3)	86 (72.3)	9.0	-0.4 to 18.4
Clinical Failure	19 (7.5)	13 (10.9)		
Clinical Relapse	12 (4.8)	12 (10.1)		
Indeterminate	16 (6.3)	8 (6.7)		

Source: 1409R2121 Clinical Study Report Amendment 2, Table 11-10

Urinary Symptoms

- Symptoms evaluated included feeling feverish, chills, malaise, urinary frequency, urinary urgency, dysuria, incontinence, cloudy or urine color change, nausea, vomiting, pain above the pubic bone, abdominal pain, flank pain, and back pain

- Symptoms were measured as none, mild, moderate, or severe

- Each symptom was absent in ≥90% of patients in each treatment group in the Micro-ITT population at the Test of Cure visit (with missing values excluded), and there were no notable differences in symptom resolution rates between the cefiderocol and imipenem/cilastatin groups

Efficacy Summary

- Cefiderocol was superior to imipenem/cilastatin for the primary analysis of composite Clinical and Microbiological Outcome at the Test of Cure visit
- Results for the composite endpoint were consistent across subgroups
- Results were driven by higher microbiological eradication for cefiderocol
- Clinical cure rates and symptoms were similar between treatment groups

Clinical Assessment and Safety of Cefiderocol for the Treatment of cUTI

Antimicrobial Drugs Advisory Committee Meeting
October 16, 2019

Shabnam Naseer, DO, MS
Clinical Reviewer, Division of Anti-Infective Products,
Office of Antimicrobial Products, CDER, FDA

Outline

- Safety Population and Exposure
- Safety Results
- Increases in MIC to Study Drugs
- Summary

Overview of Safety Population

Trials	Cefiderocol N = 761	Comparator N = 367	Total N = 1128
Phase 1	212	20	232
cUTI †	**300**	**148**	**448**
CREDIBLE-CR††	**101**	**49**	**150**
APEKS-NP†:	148	150	298
Overall Exposed to Cefiderocol: 761 **Subjects Exposed to Proposed Dose, Duration, and cUTI Indication: 326**			

† Enrolled patients with carbapenem-susceptible pathogens, comparator was a carbapenem

†† Enrolled patients with carbapenem-resistant pathogens, comparator was BAT

Outline

- Safety Population and Exposure
- Safety Results
- Increases in MIC to Study Drugs
- Summary

Summary of Treatment-Emergent Adverse Events (TEAEs)

Number of Subjects with	Cefiderocol (N=300) n (%)	IMP (N=148) n (%)
Any TEAE	122 (40.7)	76 (51.4)
Any SAE	14 (4.7)	12 (8.1)
TEAE leading to death	1 (0.3)	0
TEAE leading to discontinuation	5 (1.7)	3 (2.0)
Severe TEAE	6 (2.0)	5 (3.4)

TEAE = adverse event reported after initial dose up to 28 days after last dose of study drug
SAEs = Serious Adverse Events defined as resulting in death, life-threatening condition, hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, other medically important condition
Severe = causes interruption of daily activities or has a clinically significant effect

Cardiac Evaluation

- Standardized MedDRA query (SMQ) for cardiac arrhythmias
  - 3 patients (1%) in cefiderocol vs. 0 in IMP group
    - 2 patients had sinus bradycardia on electrocardiogram (ECG)
      - Not receiving confounding medications
      - No further complications
    - 1 patient had new onset atrial fibrillation and dyspnea on Day 1
      - No prior cardiac history
      - Required medical management (amiodarone)
      - Cefiderocol withdrawn on Day 6 due to pneumonia; cardiac failure
- No clinically significant effect of cefiderocol on QT interval (thorough QT/QTc Study)

Treatment Discontinuations due to TEAE

Adverse Event	Cefiderocol (N=300) n (%)	IMP (N=148) n (%)
Any Discontinuation	**5 (1.7)**	**3 (2.0)**
Cardio-respiratory arrest	1 (0.3)*	0
Cardiac failure	0	1 (0.7)
Diarrhea	1 (0.3)†	0
Drug hypersensitivity	1 (0.3) †	0
Pneumonia	1 (0.3)	0
Abscess	0	1 (0.7)
Hepatic enzyme increased	1 (0.3) †	0
Hematocrit decreased	0	1 (0.7)

*Discontinuation due to death

† considered treatment-related per investigator

Cefiderocol Discontinuation for Hepatic TEAE

- 32 year old female with no prior medical history, normal baseline liver tests, and acute uncomplicated pyelonephritis
  - Concomitant medications: levonorgestrel, acetaminophen (day 2), drotaverine (day 1-16), metamizole (day 1-8), mometasone nasal spray
  - Day 4: AST >5x ULN, ALT >4x ULN, GGT >4x ULN, TB normal
  - Day 8: Cefiderocol discontinued due to liver event
  - Day 9: PT and INR just above 1x ULN; other liver tests decreased
  - Day 17: AST, ALT, PT, INR resolved

Abbreviations: AST = aspartate aminotransferase, ALT =alanine aminotransferase, GGT = gamma-glutamyl transferase, TB = total bilirubin, PT = prothrombin time, INR = International normalized ratio, ULN = upper limit of normal

SAEs in ≥ 2 Patients in Any Treatment Group

Adverse Event	Cefiderocol (N=300) n (%)	IMP (N=148) n (%)
Any SAE	**14 (4.7)**	**12 (8.1)**
Cardiac failure (includes acute cardiac failure)	2 (0.7)	1 (0.7)
Anemia (includes hemorrhagic anemia, low hematocrit)	2 (0.7)	1 (0.7)
C.difficile colitis	1 (0.3)	2 (1.4)

SAEs by Baseline Characteristics

	Cefiderocol N=300 n (%)	IMP N=148 n (%)
Patients with SAEs (total)	**14 (4.7)**	**12 (8.1)**
Age Group, n/N (%)		
Age < 65 years	5/142 (3.5)	9/70 (12.9)
Age ≥ 65 years	9/158 (5.7)	3/78 (3.8)
Gender, n/N (%)		
Female	6/163 (3.7)	5/82 (6.1)
Male	8/137 (5.8)	7/66 (10.6)
Creatinine Clearance Group, n/N (%)		
> 80 (normal)	4/152 (2.6)	6/63 (9.5)
> 50-80 (mild)	4/89 (4.5)	4/50 (8.0)
30-50 (moderate)	4/49 (8.2)	2/28 (7.1)
< 30 (severe)	2/8 (25.0)	0/7 (0)

TEAEs with Incidence ≥ 2% in Cefiderocol Group

Adverse Event	Cefiderocol (N=300) n (%)	IMP (N=148) n (%)
Any TEAE	**122 (40.7)**	**76 (51.4)**
Diarrhea	13 (4.3)	9 (6.1)
Hypertension	13 (4.3)	7 (4.7)
Infusion site reactions[a]	11 (3.7)	7 (4.7)
Constipation	10 (3.3)	6 (4.1)
Rash[b]	9 (3.0)	1 (0.7)
Elevated liver laboratory tests[c]	7 (2.3)	1 (0.7)
Headache	7 (2.3)	8 (5.4)
Nausea	7 (2.3)	6 (4.1)
Cough	7 (2.3)	1 (0.7)
Candidiasis[d]	6 (2.0)	4 (2.7)
Hypokalaemia[e]	6 (2.0)	4 (2.7)
Vomiting	6 (2.0)	2 (1.4)

[a] infusion site erythema, inflammation, pain, or pruritis, injection site pain or phlebitis; [b] erythema, skin irritation, rash, rash macular, or rash maculo-papular; [c] AST, ALT, ALP, GGT or hepatic enzyme increased; [d] oral or vulvovaginal candidiasis, candiduria; [e] blood potassium decreased

TEAEs by Baseline Characteristics

	Cefiderocol N=300 n (%)	IMP N=148 n (%)
Patients with TEAEs (total)	**122 (40.7)**	**76 (51.4)**
Age Group, n/N (%)		
Age < 65 years	62/142 (43.7)	31/70 (44.3)
Age ≥ 65 years	60/158 (38.0)	45/78 (57.7)
Gender, n/N (%)		
Female	76/163 (46.6)	49/82 (59.8)
Male	46/137 (33.6)	27/66 (40.9)
Creatinine Clearance Group, n/N (%)		
> 80 (normal)	62/152 (40.8)	26/63 (41.3)
> 50-80 (mild)	35/89 (39.3)	27/50 (54.0)
30-50 (moderate)	22/49 (44.9)	18/28 (64.3)
< 30 (severe)	3/8 (37.5)	5/7 (71.4)

Adverse Events of Special Interest (Hepatobiliary)

	Cefiderocol N=300	IMP N=148
High Level Group Term	**n (%)**	**n (%)**
Gallbladder Disorders†	5 (1.7)	0
Maximum Post-Baseline Increase		
AST or ALT > 3x ULN	4 (1.3)	1 (0.7)
AST or ALT > 5x ULN	2 (0.7)	1 (0.7)

†cholecystitis, cholecystitis chronic, cholelithiasis, gallbladder pain; 4/5 patients with no prior history of gall-bladder disorders

Other Adverse Events of Special Interest

- Lowering of Seizure Threshold
  - 1 (0.3%) vs. 0 in cefiderocol and IMP, respectively
    - Patient in cefiderocol group had history of seizure and was not receiving anti-seizure medications
    - Study drug was continued without further seizure activity
- No significant worsening in post-baseline renal or hematological laboratory changes

Outline

- Safety Population and Exposure
- Safety Results
- Increases in MIC to Study Drugs
- Summary

Increases in MIC to Study Drugs

- 4-fold increase is a change in MIC that might indicate resistance has occurred or may be emerging
- MIC increased in 10 patients: 7 (2.3%) patients in cefiderocol and 3 (2.0%) in IMP group after starting study drug
  - Most often noted in the Enterobacteriaceae group (*E.coli*, Enterobacter spp.)
  - Composite outcome at follow-up (FUP) visit was failure for 9/10 patients

Increases in MIC to Study Drugs

#	Pathogen	MIC increase/ Study visit	Composite Outcome at TOC	Composite Outcome at FUP
Cefiderocol				
1	*E. coli*	0.03 to 0.25/FUP	Response	Failure
2	*E. cloacae complex*	0.12 to 0.5/TOC	Failure	Failure
3	*E. coli*	0.25 to 1.0/FUP	Response	Response
4	*P. aeruginosa*	0.03 to 8.0/FUP	Response	Failure, re-infection with new *P.aeruginosa* strain
5	*E. coli*	0.03 to 0.12/TOC	Failure	Failure
6	*P. mirabilis*	0.06 to 0.5/TOC	Failure	Failure
7	*E. aerogenes*	0.015 to 0.12/FUP	Response	Failure
IMP				
1	*E. coli*	0.12 to 0.5/FUP	Response	Failure
2	*E. coli*	0.12 to 0.5/FUP	Indeterminate	Failure
3	*P. aeruginosa*	1 to >8/TOC	Failure	Failure

Outline

- Safety Population and Exposure
- Safety Results
- Increases in MIC to Study Drugs
- Summary

Summary of Clinical Assessment

- The frequency of TEAEs, SAEs, and discontinuations due to TEAEs were greater in the IMP group as compared to cefiderocol group
  - There was 1 death in the cefiderocol group which appeared unrelated to study drug
  - The most common TEAEs in the cefiderocol group were diarrhea, infusion site reactions, elevated liver tests, and rash
- Increases in MIC to study drugs occurred at similar frequency in both treatment groups
- Overall safety findings consistent with cephalosporin class
  - Hypersensitivity reactions, hepatotoxicity, seizure, *C. difficile* colitis


FDA
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ADMINISTRATION

Statistical Assessment of the Study in Carbapenem-Resistant Organisms (CREDIBLE-CR)

Antimicrobial Drugs Advisory Committee Meeting

October 16, 2019

Daniel Rubin, PhD

Biometrics Reviewer, Division of Biometrics IV, Office of Biostatistics, Office of Translational Sciences, CDER, FDA

Outline

- Design of the CREDIBLE-CR Trial
- Efficacy results
- Statistical considerations in the assessment of mortality

Study Timeline

- September 2016: First patient randomized
- December 2018: The NDA was submitted while this study was still ongoing, and included an interim study summary for the first 70 patients
- March 2019: All 150 patients enrolled
- August 2019: Summary and datasets submitted for the completed study

Study Design

- Randomized, open-label, active-controlled, multinational

- Intravenous cefiderocol 2 grams every 8 hours for 7-14 days

  versus

  Investigator chosen best available therapy (BAT) for 7-14 days

- Descriptively analyzed without formal statistical hypothesis testing

Inclusion/Exclusion Criteria

- Suspected carbapenem-resistant Gram-negative infections

- Three infection types:
  - Hospital-acquired, ventilator-associated, or healthcare-associated bacterial pneumonia (HABP/VABP/HCABP)
  - Bloodstream infections or sepsis (BSI/sepsis)
  - Complicated urinary tract infections (cUTI)

- Potentially effective prior antibacterial therapy was allowed for ≤36 hours for HABP/VABP/HCABP and BSI/sepsis and ≤24 hours for cUTI

Endpoints and Analysis Populations

- Primary efficacy endpoint:
  - HABP/VABP/HCABP and BSI/sepsis: Clinical Outcome at the Test of Cure (TOC) visit 7±2 days after the end of therapy, with cure requiring resolution or substantial improvement of disease
  - cUTI: Microbiological Outcome at the TOC visit
- Primary efficacy analysis population:
  - Carbapenem-Resistant Microbiological Intent to Treat (CR mITT) Population of patients with baseline carbapenem-resistant Gram-negative pathogens
- Safety Population:
  - All 150 randomized and treated patients

Regulatory History

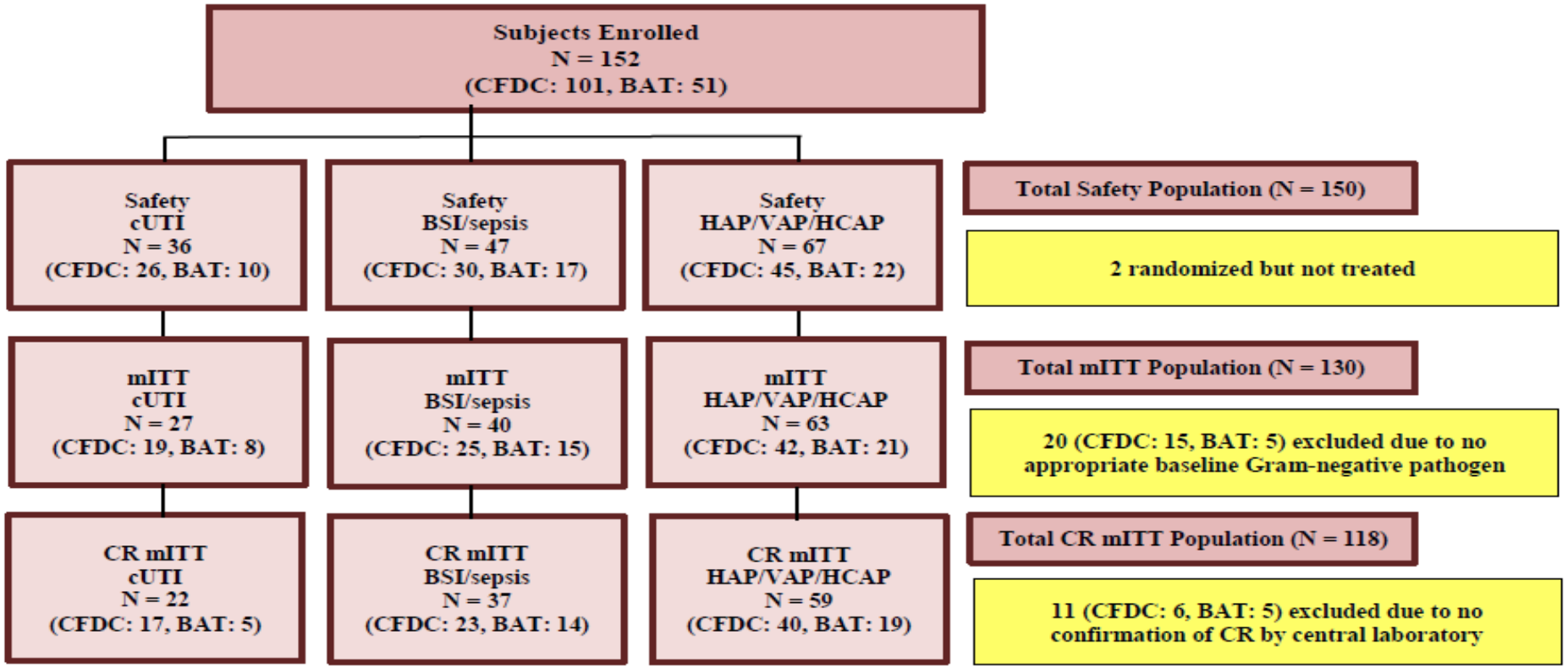
- FDA did not agree at the design stage that this trial was an adequate and well-controlled study

- Limitations:
  - Relatively small sample size of 150 total patients
  - Descriptive analysis
  - Combining of cUTI with different and more serious infection types
  - Open-label assessment of the subjective Clinical Outcome primary endpoint
  - The applicant's continuous monitoring of unblinded results by treatment group

- The applicant first alerted FDA of a mortality imbalance in the then ongoing study of 6/25 (24.0%) for cefiderocol versus 0/13 (0.0%) for BAT

- An independent data safety monitoring board was convened, at each meeting the board recommended continuation, and the study enrolled to the planned sample size of 150 patients

Patient Disposition



Source: CREDIBLE-CR Final Study Summary, Figure 1

Baseline Demographics (Safety Population)

	Cefiderocol (n = 101)	BAT (n = 49)
Age		
<65 years	37 (36.6)	27 (55.1)
≥65 years	64 (63.4)	22 (44.9)
Gender		
Male	66 (65.3)	35 (71.4)
Female	35 (34.7)	14 (28.6)
Race		
White	63 (62.4)	32 (65.3)
Asian	29 (28.7)	14 (28.6)
Other	9 (8.9)	3 (6.1)
Region		
North America	6 (5.9)	3 (6.1)
South America	9 (8.9)	4 (8.2)
Europe	57 (56.4)	28 (57.1)
Asia-Pacific	29 (28.7)	14 (28.6)

Source: CREDIBLE-CR Final Study Summary, Table 1

Baseline Characteristics (Safety Population)

	Cefiderocol (n = 101)	BAT (n = 49)
Clinical diagnosis		
HABP/VABP/HCABP	45 (44.6)	22 (44.9)
BSI/sepsis	30 (29.7)	17 (34.7)
cUTI	26 (25.7)	10 (20.4)
APACHE II score		
≤15	55 (54.5)	27 (55.1)
≥16	46 (45.5)	22 (44.9)
Baseline pathogen		
Acinetobacter baumannii	39 (38.6)	17 (34.7)
Klebsiella pneumoniae	34 (33.7)	16 (32.7)
Pseudomonas aeruginosa	17 (16.8)	12 (24.5)
Stenotrophomonas maltophilia	5 (5.0)	0 (0.0)
Creatinine clearance (mL/min)		
<30 (severe)	20 (19.8)	7 (14.3)
30 to 50 (moderate)	23 (22.8)	8 (16.3)
>50 to 80 (mild)	20 (19.8)	12 (24.5)
>80 to <120 (normal)	18 (17.8)	10 (20.4)
≥120 (augmented)	20 (19.8)	12 (24.5)

Source: CREDIBLE-CR Final Study Summary, Table 1

Initial Gram-negative Therapy (Safety Population)

- Cefiderocol group:
  - 86/101 (85.1%) with cefiderocol monotherapy
  - 15/101 (14.9%) with cefiderocol plus adjunctive therapy, including tigecycline, fosfomycin, amikacin, and quinolones

- BAT group:
  - 30/49 (61.2%) with colistin based regimens
  - 19/49 (38.8%) with non-colistin based regimens, including ceftazidime-avibactam, tigecycline, aminoglycosides, quinolones, and doripenem

Efficacy Results at TOC (CR mITT Population)

Clinical Cure	Cefiderocol	BAT	Difference	95% CI
Entire CR mITT	42/80 (52.5)	19/38 (50.0)	2.5	-16.8 to 21.8
HABP/VABP/HCABP	20/40 (50.0)	10/19 (52.6)	-2.6	
BSI/sepsis	10/23 (43.5)	6/14 (42.9)	0.6	
cUTI	12/17 (70.6)	3/5 (60.0)	10.6	
Microbiologic Eradication*	**Cefiderocol**	**BAT**	**Difference**	**95% CI**
Entire CR mITT	25/80 (31.2)	9/38 (23.7)	7.6	-9.3 to 24.5
HABP/VABP/HCABP	9/40 (18.0)	4/19 (21.1)	1.4	
BSI/sepsis	7/23 (30.4)	4/14 (28.6)	1.9	
cUTI	9/17 (52.9)	1/5 (20.0)	32.9	

Source: CREDIBLE-CR Final Study Summary, Tables 7 and 13
*Includes presumed eradication

Mortality Assessment

- Secondary objectives included assessment of Day 14 and Day 28 all-cause mortality, and all patients had complete data for these endpoints

- Mortality was captured through the End of Study visit 28 ± 3 days after the end of 7-14 days of therapy, or later to follow up a serious adverse event

- All recorded deaths through the End of Study visit occurred by Day 49

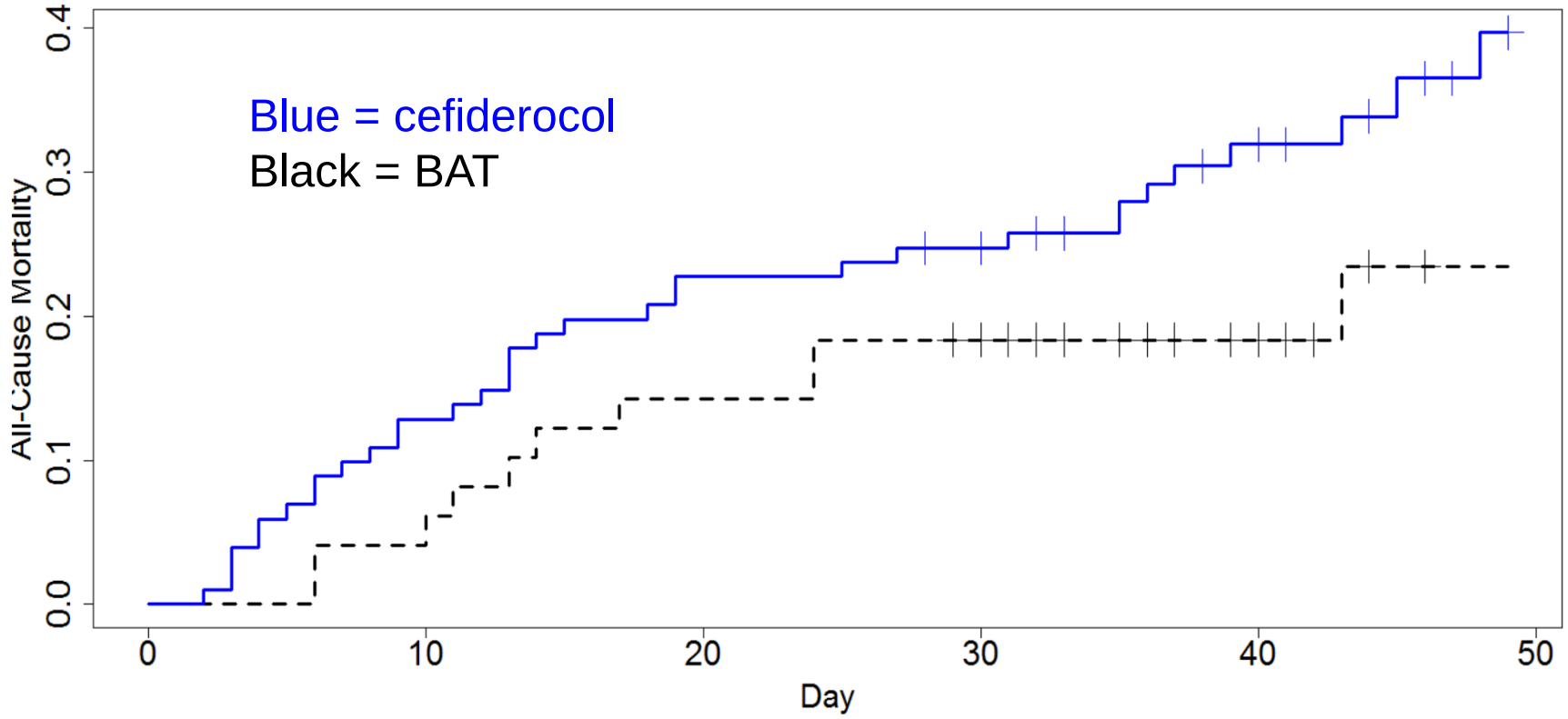
Censored Mortality Status by Timepoint (Safety Population)

Timepoint	Cefiderocol censored (n = 101)	BAT censored (n = 49)	Total censored (n = 150)
Day 28	0 (0.0)	0 (0.0)	0 (0.0)
Day 35	7 (6.9)	6 (12.2)	13 (8.7)
Day 42	35 (34.7)	20 (40.8)	55 (36.7)
Day 49	48 (47.5)	27 (55.1)	75 (50.0)

Source: Statistical reviewer

Time-to-death Through Day 49 (Safety Population)

Hazard ratio	95% CI	Two-sided p-value
1.77	0.87 to 3.57	0.11



Source: Statistical reviewer

All-cause Mortality Results (Safety Population)

Timepoint	Cefiderocol (n = 101)	BAT (n = 49)	Difference	95% CI
Day 14	19 (18.8)	6 (12.2)	6.6	-5.4 to 18.5
Day 28	25 (24.8)	9 (18.4)	6.4	-7.3 to 20.1
Day 49*	34 (33.7)	10 (20.4)	13.3	-1.3 to 27.8

*Censored outcome at Day 49 was imputed as survival for 75 patients

Source: Statistical reviewer and CREDIBLE-CR Final Study Summary, Table 21

Day 28 all-cause Mortality by Clinical Diagnosis (Safety Population)

	Cefiderocol	BAT	Difference	95% CI
HABP/VABP/HCABP	14/45 (31.1)	4/22 (18.2)	12.9	-8.1 to 34.0
BSI/Sepsis	7/30 (23.3)	3/17 (17.6)	5.7	-17.9 to 29.3
cUTI	4/26 (15.4)	2/10 (20.0)	-4.6	-33.0 to 22.8

Source: Statistical reviewer

Day 28 all-cause Mortality by Subgroup (Safety Population)

	Cefiderocol	BAT	Difference	95% CI
Age				
<65 years	7/37 (18.9)	3/27 (11.1)	7.8	-9.5 to 25.1
≥65 years	18/64 (28.1)	6/22 (27.3%)	0.9	-20.8 to 22.5
Gender				
Male	15/66 (22.7)	7/35 (20.0)	2.7	-13.9 to 19.4
Female	10/35 (28.6)	2/14 (14.3)	14.3	-9.4 to 37.9
Region				
North America	0/6 (0.0)	0/3 (0.0)	0.0	
South America	0/9 (0.0)	0/4 (0.0)	0.0	
Europe	14/57 (24.6)	6/28 (21.4)	3.1	-15.7 to 22.0
Asia-Pacific	11/29 (37.9%)	3/14 (21.4)	16.5	-11.3 to 44.3

Source: Statistical reviewer

Day 28 all-cause Mortality by Subgroup (Safety Population)

	Cefiderocol	BAT	Difference	95% CI
APACHE II score				
≤15	11/55 (20.0)	5/27 (18.5)	1.5	-16.6 to 19.5
≥16	14/46 (30.4)	4/22 (18.2)	12.3	-8.6 to 33.1
Baseline pathogen				
Acinetobacter baumannii	14/39 (35.9)	3/17 (17.6)	18.3	-5.3 to 41.8
Klebsiella pneumoniae	4/34 (11.8)	4/16 (25.0)	-13.2	-37.1 to 10.6
Pseudomonas aeruginosa	4/17 (23.5)	2/12 (16.7)	6.9	-22.3 to 36.0
Stenotrophomonas maltophilia	4/5 (80.0)	0/0		
Creatinine clearance (mL/min)				
<30 (severe)	5/20 (25.0)	2/7 (28.6)	-3.6	
30 to 50 (moderate)	7/23 (30.4)	2/8 (25.0)	5.4	
>50 to 80 (mild)	7/20 (35.0)	2/12 (16.7)	18.3	-11.4 to 48.0
>80 to <120 (normal)	4/18 (22.2)	1/10 (10.0)	12.2	-14.5 to 39.0
>120 (augmented)	2/20 (10.0)	2/12 (16.7)	-6.7	-31.5 to 18.2

Source: Statistical reviewer

Statistical Considerations

- There were numerical trends toward higher mortality for cefiderocol

- The difference in mortality rates was not large enough to provide statistically conclusive evidence of increased cefiderocol mortality, but did prompt additional clinical evaluation

Clinical Assessment of the CREDIBLE-CR Study

Antimicrobial Drugs Advisory Committee Meeting
October 16, 2019

Shabnam Naseer, DO, MS
Clinical Reviewer, Division of Anti-Infective Products,
Office of Antimicrobial Products, CDER, FDA

Outline

- Exposure to Study Drug
- Safety Overview
- Analysis of Mortality
- Increases in MIC to Study Drugs
- Other Safety Events
- Summary

CREDIBLE-CR*Study: Exposure (Safety Population)

	Cefiderocol N = 101	BAT† N = 49
Overall Mean, Median (days)	11.5, 11.0	11.9, 12.0
HABP/VABP/HCABP or BSI/Sepsis, n	**75**	**39**
Mean (days)	11.5	12.9
Median (days)	11.0	13.0
cUTI, n‡	**26**	**10**
Mean (days)	11.5	7.6
Median (days)	10.5	6.5

*study enrolled patients with carbapenem-resistant pathogens

† 1-3 antibacterial drugs targeting carbapenem-resistant Gram-negative bacteria, 61% colistin-based

‡ 7 vs. 0 patients received ≥ 14 days of treatment in cefiderocol and BAT groups, respectively

Outline

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Summary of Treatment-Emergent Adverse Events (TEAE)*

Type of TEAE	Cefiderocol (N=101) n (%)	BAT (N=49) n (%)
Any TEAE	92 (91.1)	47 (95.9)
Any SAE**	50 (49.5)	23 (46.9)
Any Fatal SAE	34 (33.7)	9 (18.4)
Any TEAE leading to discontinuation	10 (9.9)	3 (6.1)
Severe TEAE†	43 (42.6)	22 (44.9)

*TEAE - occurring after first dose of study drug up to 28 days after end of treatment +/- 3 Days

**SAEs – serious adverse event resulting in death, life-threatening condition, hospitalization or prolongation of existing hospitalization, persistent/significant disability, congenital anomaly, other medically important condition

† Severe TEAE - causes interruption of daily activities or has clinically significant effect

Outline

- Exposure to Study Drug
- Safety Overview
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Deaths by Study Day

	Cefiderocol (N = 101)				BAT (N = 49)			
Study Day	**< 15**	**15 - 30**	**>30-49**	**Total**	**< 15**	**15 - 30**	**>30-49**	**Total**
Deaths n (%)	19 (18.8)	6 (5.9)	9 (8.9)	**34 (33.7)**	6 (12.2)	3 (6.1)	1 (2.0)*	**10 (20.4)**

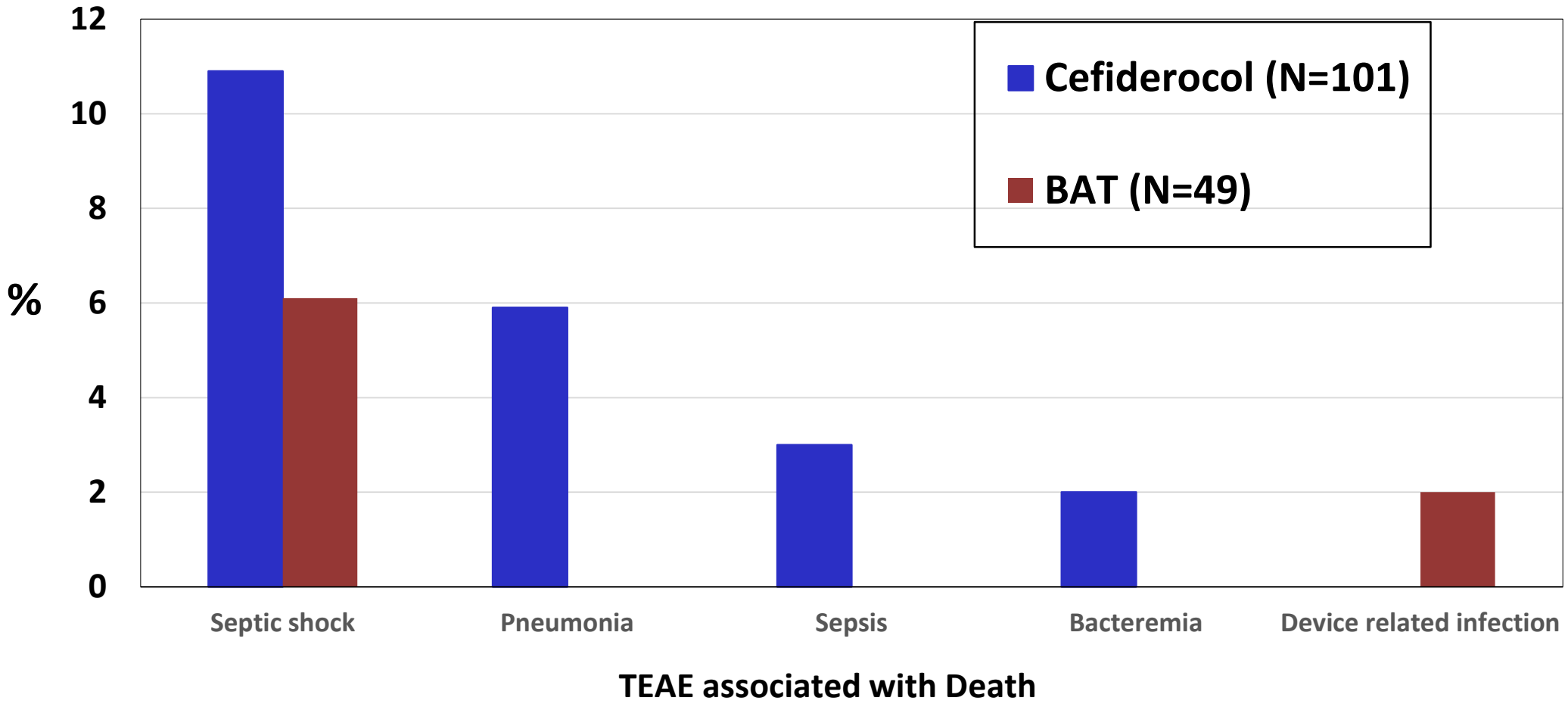
* 1 death past 30 days in which TEAE leading to death was unknown

Most Common TEAEs leading to Death

	Cefiderocol (N=101)				BAT (N=49)			
Study Day	< 15	15 - 30	> 30-49	**Total**	< 15	15 - 30	> 30-49*	**Total**
Infections & Infestations System Organ Class	12 (11.9)	3 (3.0)	6 (5.9)	**21 (20.8)**	2 (4.1)	1 (2.0)	N/A	**3 (6.1)**

* 1 death past 30 days in which TEAE leading to death was unknown

Infection-Related TEAEs leading to Death



Other TEAEs Leading to Death

TEAE leading to Death	Cefiderocol (N=101) n (%)	BAT (N=49) n (%)
Cardiac arrest	4 (4.0)	2 (4.1)
Respiratory failure/acute respiratory failure/ respiratory arrest/obstructive airways disorder	3 (3.0)	2 (4.1)
Oliguria/anuria/acute kidney injury	3 (3.0)	1 (2.0)
Multi-organ failure	2 (2.0)	2 (4.1)
Shock/hypotension	1 (1.0)	0
Cardiac failure congestive	1 (1.0)	0
Chronic hepatic failure/hepatic failure	2 (2.0)	0
Hyponatremia	1 (1.0)	0
Lung neoplasm malignant	1 (1.0)	0
Myocardial infarction	1 (1.0)	0
Sudden death	1 (1.0)	0
General physical health deterioration	0	1 (2.0)
Bradycardia	0	1 (2.0)
Metabolic acidosis	0	1 (2.0)

Adjudication Committee

Sponsor appointed 3 experts in medicine, infectious disease, and intensive care to adjudicate 43 deaths (34 cefiderocol, 9 BAT)

- Reviewed narratives and classified cause of death with blinding
- First categorized death as *directly related* or *unrelated* to the original gram-negative infection for which the patient was randomized into study
- Next, voted on subcategories
  - For death directly related to the original gram-negative infection, was there failure of the study drug treatment?
  - For death unrelated to the original gram-negative infection, was death likely due to patient's underlying comorbidity, other infection, or a drug-related adverse event?

Results of Adjudication Committee

Cause of Death	Cefiderocol (N = 101) n (%)	BAT (N = 49) n (%)	Difference (%)
Overall Mortality	34 (33.7)	9 (18.4)	15.3
***Directly related* to original Gram-negative infection**			
Failure of study drug treatment	16 (15.8)	4 (8.2)	7.7
No failure of study drug treatment	1 (1.0)	1 (2.0)	-1.0
No unanimous vote	1 (1.0)	0	1.0
***Unrelated* to original Gram-negative infection**			
Underlying comorbidity	10 (9.9)	2 (4.1)	5.8
Other infection	4 (4.0)	2 (4.1)	-0.1
No unanimous vote	2 (2.0)	0	2.0

Deaths due to Treatment Failures

Parameter	Cefiderocol (N = 101) n (%)	BAT (N = 49) n (%)
Failure of study drug treatment	**16 (15.8)**	**4 (8.2)**
Timing of Death		
< Day 15	11 (10.9)	1 (2.1)
Day 15-30	3 (3.0)	3 (6.1)
≥ Day 30	2 (2.0)	0
Baseline Pathogen		
A. baumannii or A. nosocomialis	9 (8.9)	1 (2.1)
Mixed (≥ 2 pathogens)	4 (4.0)*	0
P. aeruginosa	0	1 (2.1)
S. maltophilia	1 (1.0)	0
Enterobacteriaceae (*K. pneumoniae* or *E. cloacae*)	2 (2.0)	2 (4.1)

*Mixed: 1) *A. baumannii* and *S. maltophilia* 2) *A. baumannii, K. pneumoniae, P. aeruginosa* 3) *A. baumannii, E.coli, K. pneumoniae* 4) *A. baumannii, P. aeruginosa*

Deaths due to Treatment Failures (continued)

Parameter	Cefiderocol (N = 101) n (%)	BAT (N = 49) n (%)
Failure of study drug treatment	**16 (15.8)**	**4 (8.2)**
APACHE II Score*		
≥ 16	11 (10.9)	3 (6.1)
≤ 15	5 (5.0)	1 (2.1)
Mean	19	19
Baseline Clinical Diagnosis Group		
HABP/VABP	13 (12.9)	2 (4.1)
BSI	2 (2.0)	2 (4.1)
cUTI	1 (1.0)	0

* Acute Physiology and Chronic Health Evaluation II includes 12 variables that provide a measure of severity of disease. An increasing score correlates with subsequent risk of death in patients admitted to an intensive care unit.

Deaths in the cUTI Subgroup

- 6 deaths: 4 (4.0%) in cefiderocol and 2 (4.0%) in BAT group
- Cefiderocol: 1 death adjudicated as treatment failure
  - 92 year old male with COPD, CR *K. pneumoniae* cUTI, APACHE 11, SOFA 1
  - Nausea, vomiting on Day 3 followed by refractory shock
  - Family withdrew consent and patient died on Day 4
- BAT: no deaths adjudicated as treatment failure

Outline

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Increases in MIC to Study Drugs (CRmITT Population)

- 4 fold increase may indicate that resistance has occurred or may be emerging
- Cefiderocol: 15/80 (18.8%) patients
  - 9 had fatal outcome, 6 survived (2 failure, 4 cure)
- BAT: 5/38 (13.1%) patients
  - MIC increased to specific components in BAT
  - 2 had fatal outcome, 3 survived (all had failure)

MIC Increase to Cefiderocol & Death

Patient #	Dx	Pathogen	MIC at baseline	MIC (Study Day)	Outcome by TOC	Day of Death	TEAE leading to Death
1	VABP	*A. baumannii*	0.25	1.0 (Day 3)	Death	9	Non-resolved sepsis
2	VABP	*A. baumannii*†	1.0	8 (Day 10)	Death	24	Non-resolved sepsis
3	VABP	*S. maltophilia*†	0.06	0.25 (Day 8)	Death	8	Septic shock, hepatic failure
4	HABP	*A. baumannii*†	1.0	4.0 (Day 11)	Death	13	Aggravated pneumonia
		P. aeruginosa	0.25	2.0 (Day 11)			
5	VABP	*S. maltophilia*	0.06	0.25 (Day 14)	Death	15	Septic shock, cardiac arrest
6	Sepsis (VABP)	*A. baumannii*	2	>64 (Day 16)	Cure	27	Obstructive airways disorder
7	VABP	*A. baumannii*	0.25	4.0 (Day 14)	Failure*	39	Septic shock
8	VABP	*A. baumannii*†	1.0	8.0 (Day 15)	Failure*	45	Septic shock
9	HABP	*K. pneumoniae*†	0.25	2 (Day 23)	Failure*	31	Septic shock

Red = death directly related to original infection with study treatment failure † more than 1 pathogen at baseline (other pathogens without 4-fold MIC increase) * Treatment with rescue antibacterial drugs

MIC Increase to BAT & Death

Patient #	Dx	Pathogen	MIC at baseline	MIC (Study Day)	Study Drug	Outcome by TOC	Day of Death	Fatal PT
1	BSI	*K. pneumoniae*	≤ 0.5	> 8 (Day 13)	colistin	Death	17	Septic shock
2	VABP	*K. pneumoniae*	≤ 0.5	8 (Day 13)	colistin	Failure*	25	Cardiopulmonary arrest
			1	> 4 (Day 13)	tigecycline			

Red = death directly related to original infection with study treatment failure

* Treatment with rescue antibacterial drugs

Outline

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Treatment Discontinuations due to TEAEs

TEAE	Cefiderocol N = 101 n (%)	BAT N = 49 n (%)
Any Discontinuation	**10 (9.9)**	**3 (6.1)**
Septic shock	4 (4.0)	0
Transaminases increased	2 (2.0) *	0
Cardiac arrest	1 (1.0)	0
Drug eruption	1 (1.0)	0
Hyponatraemia	1 (1.0)	0
Pyrexia	1 (1.0)	0
Respiratory failure	1 (1.0)	0
Anaphylactic reaction	0	1 (2.0)
Endocarditis	0	1 (2.0)
Status epilepticus	0	1 (2.0)

*Includes one patient with AST and ALT increased (not considered treatment-related per investigator)

TEAE ≥ 10% in either Treatment Group

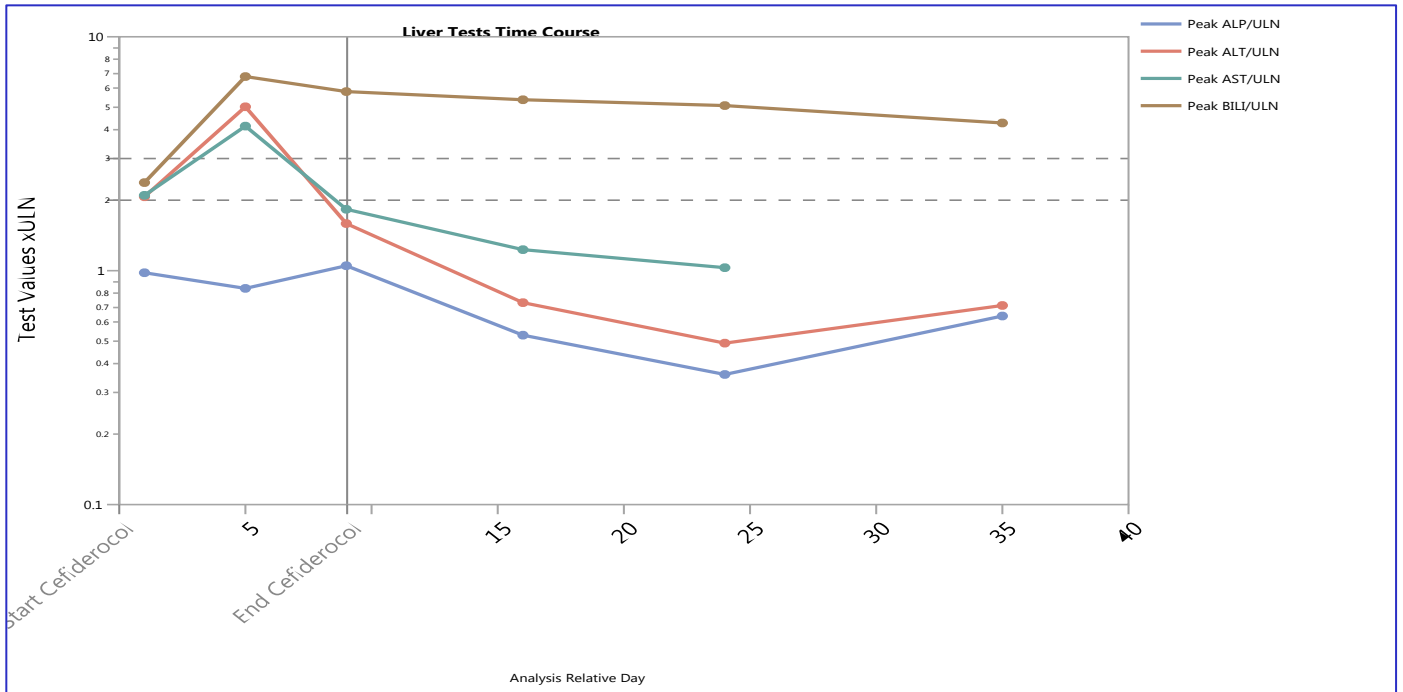
TEAE	Cefiderocol (N=101) n (%)	BAT (N=49) n (%)
Subjects with any TEAE	**92 (91.1)**	**47 (95.9)**
Diarrhea	19 (18.8)	6 (12.2)
Elevated liver tests*	18 (17.8)	6 (12.2)
Pyrexia	14 (13.9)	6 (12.2)
Septic shock	13 (12.9)	7 (14.3)
Vomiting	13 (12.9)	7 (14.3)
Acute kidney injury*	13 (12.9)	8 (16.3)
Hypokalemia*	10 (9.9)	7 (14.3)
Hyperkalemia*	5 (4.9)	6 (12.2)
Thrombocytopenia*	6 (5.9)	6 (12.2)

*Elevated liver tests: ALT, AST increased, hepatic enzyme increased, hepatic function abnormal, liver function abnormal, transaminases increased; Acute kidney injury: blood creatinine increased, renal failure, renal function test abnormal, renal impairment, renal injury; Hypokalemia: blood potassium decreased; Hyperkalemia: blood potassium increased; Thrombocytopenia: platelet count decreased

Biochemical Criteria for Hy's Law in Cefiderocol group

46 year old male with diabetes mellitus, Down syndrome, chronic hepatitis B infection diagnosed 12 years prior to study

- Admission for asthmatic crisis requiring mechanical ventilation
- CR *K. oxytoca* HABP treated with cefiderocol on Day 1-8
- Day 4: ALT >3x ULN, TB >2x ULN and ALP <2x ULN



Outline

- Exposure to Study Drug
- Safety Overview
- Analysis of Mortality
- Increases in MIC to Study Drugs
- Other Safety events
- Summary

Summary

- Mortality analysis shows imbalance of deaths disfavoring cefiderocol
- Cause of mortality imbalance is uncertain
  - No deaths attributed to a specific drug-related adverse event
  - Greater number of deaths in cefiderocol group related to treatment failure and increases in MIC
    - Often involved Acinetobacter species and HABP/VABP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Summary Comments

NDA 209445: Cefiderocol

Antimicrobial Drugs Advisory Committee Meeting

October 16, 2019

Edward Weinstein, MD, PhD

Clinical Team Leader, Division of Anti-Infective Products

FDA

Data Presented

- Nonclinical data: *in vitro* antimicrobial activity and animal models of infection
- Clinical data package
  - a randomized, active controlled noninferiority trial in cUTI comparing cefiderocol to imipenem-cilastatin (IMP)
  - a descriptive study (CREDIBLE-CR) comparing cefiderocol to best available therapy (BAT) in patients with infections due to carbapenem-resistant organisms
- A clinical trial in patients with nosocomial pneumonia* was completed during the NDA review. The trial results have not been reviewed by the Agency.

* Hospital-Acquired Bacterial Pneumonia (HABP), Ventilator-Associated Bacterial Pneumonia (VABP), and Healthcare-Associated Bacterial Pneumonia (HCABP)

Summary of cUTI Trial

- Clinical and microbiologic success rates at the test of cure visit were 183/252 (72.6%) in the cefiderocol group and 65/119 (54.6%) in the IMP group; difference in success rates of 18.6% [95% CI, 8.2% to 28.9%]
  - Clinical response rates were similar between the treatment groups
  - The difference in overall response was driven by the microbiologic success component of the composite endpoint
- The safety profile was consistent with a cephalosporin-class antibacterial drug
  - The safety database was relatively small (300 subjects)
  - Adverse Events included hypersensitivity reactions, *C. difficile* colitis, seizure, and hepatobiliary adverse events
  - There was 1 death in the cefiderocol group that appeared to be unrelated to the drug. No deaths occurred in the IMP group.

Summary of CREDIBLE-CR

- Trial enrolled patients across body sites with carbapenem-resistant Gram-negative organisms
  - BAT regimens were 1 to 3 drugs, the majority were colistin-based
  - Descriptive study with no pre-specified hypothesis testing
- All-cause mortality was higher in the cefiderocol group compared to the BAT group
  - Mortality imbalance disfavoring cefiderocol occurred in the pneumonia and BSI/sepsis subgroups, but not in cUTI
  - An independent adjudication committee determined that infection-related death with treatment failure was more frequent in the cefiderocol group than in the BAT group but also noted an imbalance in death due to underlying co-morbidities
  - Pharmacokinetic exposure-response analysis did not show an association between cefiderocol exposure and the risk of mortality
  - The most frequent treatment emergent adverse events (TEAEs) that led to death in the cefiderocol group were generally infection-related, such as septic shock, pneumonia, sepsis, and bacteremia
  - Hepatic TEAEs occurred more frequently in cefiderocol-treated patients than BAT-treated patients

Points for Consideration

- The cUTI trial indicated statistical superiority of cefiderocol compared to IMP, primarily due to differences in microbiologic success rates
  - Clinical cure rates were comparable, so the clinical relevance of the microbiologic superiority is uncertain
  - Microbiological failures generally did not require retreatment or rescue therapy

Points for Consideration

- There was no specific reason identified for the observed mortality imbalance in the CREDIBLE-CR study
  - Some of the deaths were related to progression of infection and/or lack of clinical response
  - Some deaths were associated with infections due to non-fermenting Gram-negative organisms such as *A. baumannii*, *S. maltophilia*, and *P. aeruginosa*
  - MIC increases to cefiderocol were observed both *in vitro* and within the clinical data
    - There was at least a 4-fold increase in cefiderocol MIC, including eight deaths that involved carbapenem-resistant non-fermenters
  - It is unclear whether the difference in mortality truly reflects a deficit in the activity of cefiderocol in critically ill patients or is a chance finding
  - A mortality imbalance was not observed in the cUTI subgroup of the trial, but this subgroup was less severely ill than subjects with pneumonia or BSI/sepsis

BACK-UP SLIDES SHOWN

CREDIBLE-CR Day 49 All-Cause Mortality by Clinical Diagnosis and Baseline Pathogen (Safety Population)

Summary of Day 49 All-Cause Mortality by Clinical Diagnosis and Baseline Pathogen in the Credible-CR Trial (Safety Population)

		Cefiderocol	BAT
HABP/VABP/HCABP	*A. baumannii*	4/11 (36.4%)	0/6 (0.0%)
	K. pneumoniae	13/27 (48.1%)	2/10 (20.0%)
	P. aeruginosa	3/10 (30.0%)	2/7 (28.6%)
	S. maltophilia	4/5 (80.0%)	0/0
BSI/Sepsis	*A. baumannii*	1/2 (50.0%)	1/4 (25.0%)
	K. pneumoniae	6/11 (54.5%)	2/7 (28.6%)
	P. aeruginosa	4/11 (36.4%)	1/4 (25.0%)
	S. maltophilia	0/0	0/0
cUTI	*A. baumannii*	1/4 (25.0%)	1/2 (50.0%)
	K. pneumoniae	0/1 (0%)	0/0
	P. aeruginosa	1/13 (7.7%)	1/5 (20.0%)
	S. maltophilia	0/0	0/0

Source: Statistical reviewer

CREDIBLE-CR Joint Distribution of Day 49 All-Cause Mortality and Clinical Outcome (Safety Population)

Day 49 ACM, Clinical Outcome	Cefiderocol (n = 101)	BAT (n = 49)
Survival, Clinical Cure	52 (51.5%)	27 (55.1%)
Survival, Indeterminate	4 (4.0%)	4 (8.2%)
Survival, Clinical Failure	11 (10.9%)	8 (16.3%)
Death	34 (33.7%)	10 (20.4%)

Source: Statistical reviewer