CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

209445Orig1s002

Trade Name:	FETROJA for injection, 1 gram per vial
Generic or Proper Name:	cefiderocol
Sponsor:	Shionogi, Inc.
Approval Date:	September 25, 2020
Indication:	This Prior Approval supplemental new drug application provides for the use of FETROJA in patients 18 years of age and older for the treatment of Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP) caused by the following susceptible Gram-negative microorganisms: Acinetobacter baumannii complex, Escherichia coli, Enterobacter cloacae complex, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Serratia marcescens.

CENTER FOR DRUG EVALUATION AND RESEARCH

209445Orig1s002

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Officer/Employee List	
Multidiscipline Review(s) • **Summary Review** • **Office Director** • **Cross Discipline Team Leader** • **Clinical** • **Non-Clinical** • **Statistical** • **Clinical Pharmacology**	**X**
Product Quality Review(s)	
Clinical Microbiology / Virology Review(s)	
Other Reviews	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209445Orig1s002

APPROVAL LETTER

NDA 209445/S-002

SUPPLEMENT APPROVAL

Shionogi, Inc.
Attention: Priyanka Kamath, MS
Senior Manager, US Regulatory Affairs
300 Campus Drive
Florham Park, NJ 07932

Dear Ms. Kamath:

Please refer to your supplemental new drug application (sNDA) dated and received March 27, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for FETROJA (cefiderocol) for injection, 1 gram per vial.

This Prior Approval supplemental new drug application provides for the use of FETROJA in patients 18 years of age and older for the treatment of Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP) caused by the following susceptible Gram-negative microorganisms: *Acinetobacter baumannii* complex, *Escherichia coli, Enterobacter cloacae* complex, *Klebsiella pneumoniae, Pseudomonas aeruginosa, and Serratia marcescens*.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at

FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]
The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric studies from birth to less than 18 years of age because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. These required studies are listed below:

3940-1 Conduct an open-label, randomized, multicenter, active-controlled trial to evaluate the pharmacokinetics, safety and tolerability of FETROJA (cefiderocol) in children from 3 months to less than 18 years of age with complicated Urinary Tract Infections (cUTI) and HABP/VABP.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The dose for this study for children 3 months to less than 18 years of age will be determined by the data from a single-dose, non-comparative study assessing the pharmacokinetics of FETROJA (cefiderocol) in pediatric patients from 3 months to less than 12 years of age with suspected or confirmed Gram-negative infections.

The timetable you submitted on September 22, 2020, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	01/2021
Study Completion:	12/2023
Final Report Submission:	04/2024

3940-2 Conduct an open-label, single arm, non-comparative study to evaluate the pharmacokinetics, safety and tolerability of multiple doses of FETROJA (cefiderocol) in children from birth to less than 3 months of age with suspected or confirmed Gram-negative infections. The dose for this study will be determined by the data from a single-dose, non-comparative study assessing the pharmacokinetics of FETROJA (cefiderocol) in pediatric patients from birth to less than 3 months of age with suspected or confirmed Gram-negative infections.

The timetable you submitted on September 22, 2020, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	06/2022
Study Completion:	08/2024
Final Report Submission:	01/2025

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 116787, with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

These PMRs replace PMR 3744-1 and PMR 3744-2, listed in the November 14, 2019, approval letter. We remind you that there are other postmarketing requirements listed in the November 14, 2019, approval letter that are still open.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infectives
Office of Infectious Diseases
Center for Drug Evaluation and Research

ENCLOSURE:

- Content of Labeling
  - Prescribing Information

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUMATHI NAMBIAR
09/25/2020 05:55:24 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209445Orig1s002

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FETROJA® safely and effectively. See full prescribing information for FETROJA.

FETROJA (cefiderocol) for injection, for intravenous use
Initial U.S. Approval: 2019

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	9/2020
Dosage and Administration (2)	9/2020
Warnings and Precautions (5)	9/2020

----------INDICATIONS AND USAGE----------

FETROJA is a cephalosporin antibacterial indicated in patients 18 years of age or older for the treatment of the following infections caused by susceptible Gram-negative microorganisms:

- Complicated Urinary Tract Infections (cUTI), including Pyelonephritis (1.1)
- Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP) (1.2)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of FETROJA and other antibacterial drugs, FETROJA should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. (1.3)

----------DOSAGE AND ADMINISTRATION----------

- Administer 2 grams of FETROJA for injection every 8 hours by intravenous (IV) infusion over 3 hours in patients with creatinine clearance (CLcr) 60 to 119 mL/min. (2 1)
- Dose adjustments are required for patients with CLcr less than 60 mL/min, (including patients receiving intermittent hemodialysis (HD) or continuous renal replacement therapy (CRRT)), and for patients with CLcr 120 mL/min or greater. (2.2)
- See full prescribing information for instructions on preparation of FETROJA doses. (2.3)
- See full prescribing information for drug compatibilities. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

For injection: 1 gram of cefiderocol as a lyophilized powder for reconstitution in single-dose vials. (3)

----------CONTRAINDICATIONS----------

FETROJA is contraindicated in patients with a known history of severe hypersensitivity to cefiderocol and other beta-lactam antibacterial drugs or other components of FETROJA. (4)

----------WARNINGS AND PRECAUTIONS----------

- Increase in All-Cause Mortality in Patients with Carbapenem-Resistant Gram-Negative Bacterial Infections: An increase in all-cause mortality was observed in FETROJA-treated patients compared to those treated with best available therapy (BAT). Closely monitor the clinical response to therapy in patients with cUTI and HABP/VABP. (5.1)
- Hypersensitivity Reactions: Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam antibacterial drugs. Hypersensitivity was observed with FETROJA. Cross-hypersensitivity may occur in patients with a history of penicillin allergy. If an allergic reaction occurs, discontinue FETROJA. (5.2)
- *Clostridioides difficile*-Associated Diarrhea (CDAD): CDAD has been reported with nearly all systemic antibacterial agents, including FETROJA. Evaluate if diarrhea occurs. (5.3)
- Seizures and Other Central Nervous System (CNS) Adverse Reactions: CNS adverse reactions such as seizures have been reported with FETROJA. If focal tremors, myoclonus, or seizures occur, evaluate patients to determine whether FETROJA should be discontinued. (5.4)

----------ADVERSE REACTIONS----------

- cUTI: The most frequently occurring adverse reactions in greater than or equal to 2% of cUTI patients treated with FETROJA were diarrhea, infusion site reactions, constipation, rash, candidiasis, cough, elevations in liver tests, headache, hypokalemia, nausea, and vomiting. (6.1)
- HABP/VABP: The most frequently occurring adverse reactions in greater than or equal to 4% of HABP/VABP patients treated with FETROJA were elevations in liver tests, hypokalemia, diarrhea, hypomagnesemia, and atrial fibrillation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Shionogi Inc. at 1-800-849-9707 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Use alternate testing methods to confirm positive results of dipstick tests (urine protein, ketones, or occult blood). (7.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 9/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Complicated Urinary Tract Infections (cUTIs), Including Pyelonephritis

FETROJA® is indicated in patients 18 years of age or older for the treatment of complicated urinary tract infections (cUTIs), including pyelonephritis caused by the following susceptible Gram-negative microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Enterobacter cloacae* complex *[see Clinical Studies (14.1)]*.

1.2 Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP)

FETROJA is indicated in patients 18 years of age or older for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia, caused by the following susceptible Gram-negative microorganisms: *Acinetobacter baumannii* complex, *Escherichia coli*, *Enterobacter cloacae* complex, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Serratia marcescens [see Clinical Studies (14.2)]*.

1.3 Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of FETROJA and other antibacterial drugs, FETROJA should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of FETROJA is 2 grams administered every 8 hours by intravenous (IV) infusion over 3 hours in adults with a creatinine clearance (CLcr) of 60 to 119 mL/min.

Dosage adjustment of FETROJA is recommended for patients with CLcr less than 60 mL/min, including patients receiving intermittent hemodialysis (HD) or continuous renal replacement therapy (CRRT), and for patients with CLcr 120 mL/min or greater *[see Dosage and Administration (2.2)]*. The recommended duration of treatment with FETROJA is 7 to 14 days. The duration of therapy should be guided by the patient's clinical status.

2.2 Dosage Adjustments in Patients with CLcr Less Than 60 mL/min (Including Patients Undergoing Intermittent HD or CRRT), and CLcr 120 mL/min or Greater

Dosage Adjustments in Patients with CLcr Less Than 60 mL/min Including Patients Receiving Intermittent HD

Dosage adjustment of FETROJA is recommended in patients with CLcr less than 60 mL/min (Table 1). For patients undergoing intermittent HD, start the dosing of FETROJA immediately after the completion of HD. For patients with fluctuating renal function, monitor CLcr and adjust dosage accordingly.

Table 1 Recommended Dosage of FETROJA for Patients with CLcr Less Than 60 mL/min Including Patients Receiving Intermittent HD

Estimated Creatinine Clearance (CLcr)[a]	Dose	Frequency	Infusion Time
CLcr 30 to 59 mL/min	1.5 grams	Every 8 hours	3 hours
CLcr 15 to 29 mL/min	1 gram	Every 8 hours	3 hours
CLcr less than 15 mL/min, with or without intermittent HD[b]	0.75 grams	Every 12 hours	3 hours

HD = hemodialysis.

[a] CLcr = creatinine clearance estimated by Cockcroft-Gault equation.

[b] Cefiderocol is removed by HD; administer FETROJA immediately after HD for patients receiving intermittent HD.

Dosage Adjustments in Patients Receiving CRRT

For patients receiving CRRT, including continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD) and continuous venovenous hemodiafiltration (CVVHDF), the dosage of FETROJA should be based on the effluent flow rate in CRRT (see Table 2). These recommendations are intended to provide initial dosing in patients receiving CRRT. Dosing regimens may need to be tailored based on residual renal function and patient's clinical status *[see Use in Specific Populations (8.6)]*.

Table 2 Recommended Dosage of FETROJA for Patients Receiving CRRT

Effluent Flow Rate[a]	Recommended Dosage of FETROJA
2 L/hr or less	1.5 grams every 12 hours
2.1 to 3 L/hr	2 grams every 12 hours
3.1 to 4 L/hr	1.5 grams every 8 hours
4.1 L/hr or greater	2 grams every 8 hours

CRRT = continuous renal replacement therapy.

[a] Ultrafiltrate flow rate for CVVH, dialysis flow rate for CVVHD, ultrafiltrate flow rate plus dialysis flow rate for CVVHDF.

Dosage Adjustments in Patients with CLcr 120 mL/min or Greater

For patients with CLcr greater than or equal to 120 mL/min, FETROJA 2 grams administered every 6 hours by IV infusion over 3 hours is recommended *[see Use in Specific Populations (8.6)]*.

2.3 Preparation of FETROJA Solution for Administration

FETROJA is supplied as a sterile, lyophilized powder that must be reconstituted and subsequently diluted using aseptic technique prior to intravenous infusion.

Preparation of Doses

Reconstitute the powder for injection in the FETROJA vial with 10 mL of either 0.9% sodium chloride injection, USP or 5% dextrose injection, USP and gently shake to dissolve. Allow the vial(s) to stand until the foaming generated on the surface has disappeared (typically within 2 minutes). The final volume of the reconstituted solution will be approximately 11.2 mL. The reconstituted solution is for intravenous infusion only after dilution in an appropriate infusion solution.

To prepare the required doses, withdraw the appropriate volume of reconstituted solution from the vial according to Table 3 below. Add the withdrawn volume to a 100 mL infusion bag containing 0.9% sodium chloride injection, USP or 5% dextrose injection, USP *[see Dosage and Administration (2.4)]*.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. FETROJA infusions are clear, colorless solutions. Discard any unused FETROJA solution in the vial (see Table 3).

Table 3 Preparation of FETROJA Doses

FETROJA Dose	Number of 1-gram FETROJA Vials to be Reconstituted	Volume to Withdraw from Reconstituted Vial(s)	Total Volume of FETROJA Reconstituted Solution for Further Dilution into a 100 mL Infusion Bag
2 grams	2 vials	11.2 mL (entire contents) of each vial	22.4 mL
1.5 grams	2 vials	11.2 mL (entire contents) of first vial AND 5.6 mL from second vial	16.8 mL
1 gram	1 vial	11.2 mL (entire contents)	11.2 mL
0.75 gram	1 vial	8.4 mL	8.4 mL

2.4 Drug Compatibility

FETROJA solution for administration is compatible with:

- 0.9% sodium chloride injection, USP
- 5% dextrose injection, USP

The compatibility of FETROJA solution for administration with solutions containing other drugs or other diluents has not been established.

2.5 Storage of Reconstituted Solutions

Reconstituted FETROJA

Upon reconstitution with the appropriate diluent, the reconstituted FETROJA solution in the vial should be immediately transferred and diluted into the infusion bag. Reconstituted FETROJA can be stored for up to 1 hour at room temperature in the vial. Discard any unused reconstituted solution.

Diluted FETROJA Infusion Solution

The diluted FETROJA infusion solution in the infusion bag is stable for up to 6 hours at room temperature.

The diluted FETROJA infusion solution in the infusion bag may also be refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours, protected from light; and then the infusion should be completed within 6 hours at room temperature.

3 DOSAGE FORMS AND STRENGTHS

FETROJA 1 gram for injection is supplied as a white to off-white, sterile, lyophilized powder for reconstitution in single-dose, clear glass vials; each vial contains 1 gram of cefiderocol.

4 CONTRAINDICATIONS

FETROJA is contraindicated in patients with a known history of severe hypersensitivity to cefiderocol or other beta-lactam antibacterial drugs, or any other component of FETROJA *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Increase in All-Cause Mortality in Patients with Carbapenem-Resistant Gram-Negative Bacterial Infections

An increase in all-cause mortality was observed in patients treated with FETROJA as compared to best available therapy (BAT) in a multinational, randomized, open-label trial in critically ill patients with carbapenem-resistant Gram-negative bacterial infections (NCT02714595). Patients with nosocomial pneumonia, bloodstream infections, sepsis, or cUTI were included in the trial. BAT regimens varied according to local practices and consisted of 1 to 3 antibacterial drugs with activity against Gram-negative bacteria. Most of the BAT regimens contained colistin.

The increase in all-cause mortality occurred in patients treated for nosocomial pneumonia, bloodstream infections, or sepsis. The 28-Day all-cause mortality was higher in patients treated with FETROJA than in patients treated with BAT [25/101 (24.8%) vs. 9/49 (18.4%), treatment difference 6.4%, 95% CI (-8.6, 19.2)]. All-cause mortality remained higher in patients treated with FETROJA than in patients treated with BAT through Day 49 [34/101 (33.7%) vs. 10/49 (20.4%), treatment difference 13.3%, 95% CI (-2.5, 26.9)]. Generally, deaths were in patients with infections caused by Gram-negative organisms, including non-fermenters such as *Acinetobacter baumannii* complex, *Stenotrophomonas maltophilia*, and *Pseudomonas aeruginosa*, and were the result of worsening or complications of infection, or underlying comorbidities. The cause of the increase in mortality has not been established.

Closely monitor the clinical response to therapy in patients with cUTI and HABP/VABP.

5.2 Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported in patients receiving beta-lactam antibacterial drugs. Hypersensitivity was observed in FETROJA-treated patients in clinical trials *[see Adverse Reactions (6.1)]*. These reactions are more likely to occur in individuals with a history of beta-lactam hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe reactions when treated with cephalosporins.

Before therapy with FETROJA is instituted, inquire about previous hypersensitivity reactions to cephalosporins, penicillins, or other beta-lactam antibacterial drugs. Discontinue FETROJA if an allergic reaction occurs.

5.3 *Clostridioides difficile*-associated Diarrhea (CDAD)

Clostridioides difficile-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial agents, including FETROJA. CDAD may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *C. difficile*.

C. difficile produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, antibacterial drugs not directed against *C. difficile* may need to be discontinued. Manage fluid and electrolyte levels as appropriate, supplement protein intake, monitor antibacterial treatment of *C. difficile*, and institute surgical evaluation as clinically indicated.

5.4 Seizures and Other Central Nervous System (CNS) Adverse Reactions

Cephalosporins, including FETROJA, have been implicated in triggering seizures *[see Adverse Reactions (6.1)]*. Nonconvulsive status epilepticus (NCSE), encephalopathy, coma, asterixis, neuromuscular excitability, and myoclonia have been reported with cephalosporins particularly in patients with a history of epilepsy and/or when recommended dosages of cephalosporins were exceeded due to renal impairment. Adjust FETROJA dosing based on creatinine clearance *[see Dosage and Administration (2.2)]*. Anticonvulsant therapy should be continued in patients with known seizure disorders. If CNS adverse reactions including seizures occur, patients should undergo a neurological evaluation to determine whether FETROJA should be discontinued.

5.5 Development of Drug-Resistant Bacteria

Prescribing FETROJA in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria *[see Indications and Usage (1.3)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described in greater detail in the Warnings and Precautions section:

- Increase in All-Cause Mortality in Patients with Carbapenem-Resistant Gram-Negative Bacterial Infections *[see Warnings and Precautions (5.1)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.2)]*
- *Clostridioides difficile*-Associated Diarrhea (CDAD) *[see Warnings and Precautions (5.3)]*
- Seizures and Other Central Nervous System Adverse Reactions *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Complicated Urinary Tract Infections (cUTIs), Including Pyelonephritis

FETROJA was evaluated in an active-controlled, randomized clinical trial in patients with cUTI, including pyelonephritis (Trial 1). In this trial, 300 patients received FETROJA 2 grams every 8 hours infused over 1 hour (or a renally-adjusted dose), and 148 patients were treated with imipenem/cilastatin 1 gram/1 gram every 8 hours infused over 1 hour (or a renally-adjusted dose). The median age of treated patients across treatment arms was 65 years (range 18 to 93 years), with approximately 53% of patients aged greater than or equal to 65. Approximately 96% of patients were White, most were from Europe, and 55% were female. Patients across treatment arms received treatment for a median duration of 9 days.

Serious Adverse Reactions and Adverse Reactions Leading to Discontinuation

In Trial 1, a total of 14/300 (4.7%) cUTI patients treated with FETROJA and 12/148 (8.1%) of cUTI patients treated with imipenem/cilastatin experienced serious adverse reactions. One death (0.3%) occurred in 300 patients treated with FETROJA as compared to none treated with imipenem/cilastatin. Discontinuation of treatment due to any adverse reaction occurred in 5/300 (1.7%) of patients treated with FETROJA and 3/148 (2.0%) of patients treated with imipenem/cilastatin. Specific adverse reactions leading to treatment discontinuation in patients who received FETROJA included diarrhea (0.3%), drug hypersensitivity (0.3%), and increased hepatic enzymes (0.3%).

Common Adverse Reactions

Table 4 lists the most common selected adverse reactions occurring in ≥ 2% of cUTI patients receiving FETROJA in Trial 1.

Table 4 Selected Adverse Reactions Occurring in ≥ 2% of cUTI Patients Receiving FETROJA in Trial 1

Adverse Reaction	FETROJA[a] (N = 300)	Imipenem/Cilastatin[b] (N = 148)
Diarrhea	4%	6%
Infusion site reactions[c]	4%	5%
Constipation	3%	4%
Rash[d]	3%	< 1%
Candidiasis[e]	2%	3%
Cough	2%	< 1%
Elevations in liver tests[f]	2%	< 1%
Headache	2%	5%
Hypokalemia[g]	2%	3%
Nausea	2%	4%
Vomiting	2%	1%

cUTI = complicated urinary tract infection.

[a] 2 grams IV over 1 hour every 8 hours (with dosing adjustment based on renal function).

[b] 1 gram IV over 1 hour every 8 hours (with dosing adjustment based on renal function and body weight).

[c] Infusion site reactions include infusion site erythema, inflammation, pain, pruritis, injection site pain, and phlebitis.

[d] Rash includes rash macular, rash maculopapular, erythema, skin irritation.

[e] Candidiasis includes oral or vulvovaginal candidiasis, candiduria.

[f] Elevations in liver tests include alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, blood alkaline phosphatase, hepatic enzyme increased.

[g] Hypokalemia includes blood potassium decreased.

Other Adverse Reactions of FETROJA in the cUTI Patients (Trial 1)

The following selected adverse reactions were reported in FETROJA-treated cUTI patients at a rate of less than 2% in Trial 1:

Blood and lymphatic disorders: thrombocytosis

Cardiac disorders: congestive heart failure, bradycardia, atrial fibrillation

Gastrointestinal disorders: abdominal pain, dry mouth, stomatitis

General system disorders: pyrexia, peripheral edema

Hepatobiliary disorders: cholelithiasis, cholecystitis, gallbladder pain

Immune system disorders: drug hypersensitivity

Infections and infestations: *C. difficile* infection

Laboratory investigations: prolonged prothrombin time (PT) and prothrombin time international normalized ratio (PT-INR), red blood cells urine positive, creatine phosphokinase increase

Metabolism and nutrition disorders: decreased appetite, hypocalcemia, fluid overload

Nervous system disorders: dysgeusia, seizure

Respiratory, thoracic, and mediastinal disorders: dyspnea, pleural effusion

Skin and subcutaneous tissue disorders: pruritis

Psychiatric disorders: insomnia, restlessness

Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP)

FETROJA was evaluated in an active-controlled clinical trial in patients with HABP/VABP (Trial 2). In this trial, 148 patients received FETROJA 2 grams every 8 hours infused over 3 hours, and 150 patients received meropenem 2 grams every 8 hours infused over 3 hours. Doses of study treatments were adjusted based on renal function. The median age was 67 years, approximately 59% of patients were 65 years of age and older, 69% were male, and 68% were White. Overall, approximately 60% were ventilated at randomization, including 41% with VABP and 14% with ventilated HABP. The mean Acute Physiology And Chronic Health Evaluation (APACHE II) score was 16. All patients received empiric treatment for Gram-positive organisms with linezolid for at least 5 days.

Serious Adverse Reactions and Adverse Reactions Leading to Discontinuation

In Trial 2, serious adverse reactions occurred in 54/148 (36.5%) HABP/VABP patients treated with FETROJA and 45/150 (30%) of HABP/VABP patients treated with meropenem. Adverse reactions leading to death were reported in 39/148 (26.4%) patients treated with FETROJA and 35/150 (23.3%) patients treated with meropenem. Adverse reactions leading to discontinuation of treatment occurred in 12/148 (8.1%) of patients treated with FETROJA and 14/150 (9.3%) of patients treated with meropenem. The most common adverse reactions leading to discontinuation in both treatment groups were elevated liver tests.

Common Adverse Reactions

Table 5 lists the most common selected adverse reactions occurring in ≥ 4% of patients receiving FETROJA in the HABP/VABP trial.

Table 5 Selected Adverse Reactions Occurring in ≥ 4% of HABP/VABP Patients Receiving FETROJA in Trial 2

Adverse Reaction	**FETROJA[a] N = 148**	**Meropenem[b] N = 150**
Elevations in liver tests[c]	16%	16%
Hypokalemia[d]	11%	15%
Diarrhea	9%	9%
Hypomagnesemia	5%	< 1%
Atrial fibrillation	5%	3%

HABP/VABP = hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia.

[a] 2 grams IV over 3 hours every 8 hours (with dosing adjustment based on renal function).

[b] 2 grams IV over 3 hours every 8 hours (with dosing adjustment based on renal function).

[c] Elevations in liver tests include the following terms: aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyl transferase increased, liver function test increased, liver function test abnormal, hepatic enzyme increased, transaminases increased, hypertransaminesemia.

[d] Hypokalemia includes blood potassium decreased.

Other Adverse Reactions of FETROJA in HABP/VABP Patients in Trial 2

The following selected adverse reactions were reported in FETROJA-treated HABP/VABP patients at a rate of less than 4% in Trial 2:

Blood and lymphatic disorders: thrombocytopenia, thrombocytosis

Cardiac disorders: myocardial infarction, atrial flutter

Gastrointestinal disorders: nausea, vomiting, abdominal pain

Hepatobiliary disorders: cholecystitis, cholestasis

Infections and infestations: *C. difficile* infection, oral candidiasis

Laboratory investigations: prolonged prothrombin time (PT) and prothrombin time international normalized ratio (PT-INR), and activated partial thromboplastin time (aPTT)

Metabolism and nutrition disorders: hypocalcemia, hyperkalemia

Nervous system disorders: seizure

Renal and genitourinary disorders: acute interstitial nephritis

Respiratory, thoracic, and mediastinal disorders: cough

Skin and subcutaneous tissue disorders: rash including rash erythematous

7 DRUG INTERACTIONS

7.1 Drug/Laboratory Test Interactions

Cefiderocol may result in false-positive results in dipstick tests (urine protein, ketones, or occult blood). Use alternate clinical laboratory methods of testing to confirm positive tests.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on FETROJA use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

Available data from published prospective cohort studies, case series, and case reports over several decades with cephalosporin use in pregnant women have not established drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes *(see Data)*.

Developmental toxicity studies with cefiderocol administered during organogenesis to rats and mice showed no evidence of embryo-fetal toxicity, including drug-induced fetal malformations, at doses providing exposure levels 0.9 (rats) or 1.3 times (mice) higher than the average observed in patients receiving the maximum recommended daily dose.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

While available studies cannot definitively establish the absence of risk, published data from prospective cohort studies, case series, and case reports over several decades have not identified an association with cephalosporin use during pregnancy and major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Available studies have methodologic limitations, including small sample size, retrospective data collection, and inconsistent comparator groups.

Animal Data

Developmental toxicity was not observed in rats at intravenous doses of up to 1000 mg/kg/day or mice at subcutaneous doses of up to 2000 mg/kg/day given during the period of organogenesis (gestation days 6-17 in rats and 6-15 in mice). No treatment-related malformations or reductions in fetal viability were observed. Mean plasma exposure (AUC) at these doses was approximately 0.9 times (rats) and 1.3 times (mice) the daily mean plasma exposure in patients that received 2 grams of cefiderocol infused intravenously every 8 hours.

In a pre- and postnatal development study, cefiderocol was administered intravenously at doses up to 1000 mg/kg/day to rats from Day 6 of pregnancy until weaning. No adverse effects on parturition, maternal function, or pre- and postnatal development and viability of the pups were observed.

In pregnant rats, cefiderocol-derived radioactivity was shown to cross the placenta, but the amount detected in fetuses was a small percentage (< 0.5%) of the dose.

8.2 Lactation

Risk Summary

It is not known whether cefiderocol is excreted into human milk; however, cefiderocol-derived radioactivity was detected in the milk of lactating rats that received the drug intravenously. When a drug is present in animal milk, it is likely that the drug will be present in human milk. No information is available on the effects of FETROJA on the breastfed infant or on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for FETROJA and any potential adverse effects on the breastfed child from FETROJA or from the underlying maternal condition.

Data

Cefiderocol-derived radioactivity was detected in milk following intravenous administration to lactating rats. The peak level in rat milk was approximately 6% of the peak plasma level.

8.4 Pediatric Use

Safety and effectiveness of FETROJA in pediatric patients younger than 18 years of age have not been established.

8.5 Geriatric Use

cUTI

Of the 300 patients treated with FETROJA in the cUTI trial, 158 (52.7%) were 65 years of age and older, and 67 (22.3%) were 75 years of age and older. No overall differences in safety or efficacy were observed between these patients and younger patients.

HABP/VABP

Of the 148 patients treated with FETROJA in the HABP/VABP trial, 83 (56.1%) were 65 years of age and older, and 40 (27%) were 75 years of age and older.

The incidence of adverse reactions in patients treated with FETROJA was similar in patients under 65 years of age as compared to older patients (65 years of age and older and 75 years of age and older). The incidence of adverse reactions in older patients (65 years of age and older and 75 years of age and older) was also similar between treatment groups.

Clinical cure rates at the Test-of-Cure (TOC) visit in FETROJA-treated adult patients younger than 65 years of age, 65 years of age to younger than 75 years of age and 75 years of age and older were 60%, 77.5% and 60% respectively. In comparison, the clinical cure rates at the TOC visit in the meropenem-treated patients for each of these subgroups were 65.5%, 64.4% and 70.5%, respectively. The observed all-cause mortality rates at Day 14 in the FETROJA-treated patients for each of these subgroups were 12.3%, 7.5% and 17.5%, respectively. In comparison, in the meropenem-treated patients for each of these subgroups, they were 10.3%, 17.8% and 9.1%, respectively.

cUTI and HABP/VABP

FETROJA is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. No dosage adjustment is required based on age. Dosage adjustment for elderly patients should be based on renal function *[see Dosage and Administration (2.2), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

Patients with CLcr 60 to 89 mL/min

No dosage adjustment of FETROJA is recommended in patients with CLcr 60 to 89 mL/min.

Patients with CLcr Less Than 60 mL/min Including Patients Receiving Intermittent HD

Dose adjustment is required in patients with CLcr less than 60 mL/min, and in patients who are receiving HD. In patients requiring HD, complete HD at the latest possible time before the start of cefiderocol dosing *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*. Monitor renal function regularly and adjust the dosage of FETROJA accordingly as renal function may change during the course of therapy.

Patients Receiving CRRT

A total of 16 patients treated with FETROJA received CRRT in clinical trials. Dosage adjustment of FETROJA is required in patients receiving CRRT including CVVH, CVVHD and CVVHDF. Dosage of FETROJA should be based on the effluent flow rate in patients receiving CRRT *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*. While on CRRT, a patient's residual renal function may change. Improvements or reductions in residual renal function may warrant a change in FETROJA dosage.

Patients with CLcr 120 mL/min or greater

CLcr 120 mL/min or greater may be seen in seriously ill patients, who are receiving intravenous fluid resuscitation. Dosage adjustment of FETROJA is required in patients with CLcr 120 mL/min or greater *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*. Monitor renal function regularly and adjust the dosage of FETROJA accordingly as renal function may change during the course of therapy.

8.7 Hepatic Impairment

The effects of hepatic impairment on the pharmacokinetics of cefiderocol have not been evaluated. Hepatic impairment is not expected to alter the elimination of cefiderocol as hepatic metabolism/excretion represents a minor pathway of elimination for cefiderocol. Dosage adjustments are not necessary in patients with impaired hepatic function.

10 OVERDOSAGE

There is no information on clinical signs and symptoms associated with an overdose of FETROJA. Patients who receive doses greater than the recommended dose regimen and have unexpected adverse reactions possibly associated with FETROJA should be carefully observed and given supportive treatment, and discontinuation or interruption of treatment should be considered.

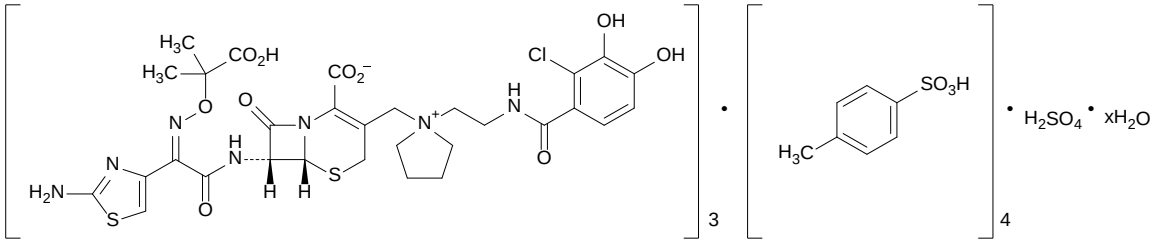
Approximately 60% of cefiderocol is removed by a 3- to 4-hour hemodialysis session *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

FETROJA is a cephalosporin antibacterial drug product consisting of cefiderocol sulfate tosylate for intravenous infusion. Cefiderocol functions as a siderophore *[see Microbiology (12.4)]*.

The chemical name of cefiderocol sulfate tosylate is Tris[(6*R*,7*R*)-7-[(2*Z*)-2-(2-amino-1,3-thiazol-4-yl)-2-{[(2-carboxypropan-2-yl)oxy]imino}acetamido]-3-({1-[2-(2-chloro-3,4-dihydroxybenzamido)ethyl]pyrrolidin-1-ium-1-yl}methyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate] tetrakis(4-methylbenzenesulfonate) monosulfate hydrate, and the molecular weight is 3043.50 (anhydrous). The molecular formula is $3C_{30}H_{34}ClN_7O_{10}S_2 \bullet 4C_7H_8O_3S \bullet H_2SO_4 \bullet xH_2O$.

Figure 1 Chemical Structure of Cefiderocol Sulfate Tosylate



FETROJA for injection is a white to off-white, sterile, lyophilized powder formulated with 1 gram of cefiderocol (equivalent to 1.6 grams of cefiderocol sulfate tosylate), sucrose (900 mg), sodium chloride (216 mg), and sodium hydroxide to adjust pH. The sodium content is approximately 176 mg/vial. The pH of the reconstituted solution of 1 gram cefiderocol (1 vial) dissolved in 10 mL water is 5.2 to 5.8.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

FETROJA is an antibacterial drug *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

The percent time of dosing interval that unbound plasma concentrations of cefiderocol exceed the minimum inhibitory concentration (MIC) against the infecting organism best correlates with antibacterial activity in neutropenic murine thigh and lung infection models with *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *A. baumannii*, and *S. maltophilia*. Compared to a 1-hour infusion, a 3-hour infusion increased the percent time of dosing interval that unbound plasma concentrations of cefiderocol exceed the MIC. The *in vivo* animal pneumonia

studies showed that the antibacterial activity of cefiderocol was greater at the human equivalent dosing regimen of 3-hour infusion compared to that of 1-hour infusion.

Cardiac Electrophysiology

At doses 1 and 2 times the maximum recommended dosage, FETROJA does not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

Cefiderocol exposures (C_{max} and daily AUC) in cUTI patients, HABP/VABP patients and healthy volunteers are summarized in Table 6. Cefiderocol C_{max} and AUC increased proportionally with dose.

Table 6 Cefiderocol Exposures Mean (±SD) in Patients and Healthy Volunteers with CLcr 60 mL/min or Greater

PK Parameters	cUTI Patients[a] (N = 21)	HABP/VABP Patients[a] (N = 146)	Healthy Volunteers[b] (N = 43)
C_{max} (mg/L)	115 (±57)	111 (±56)	91.4 (±17.9)
$AUC_{0\text{-}24\ hrs}$ (mg·hr/L)	1944 (±1097)	1773 (±990)	1175 (±203)

C_{max} = maximum concentration.

$AUC_{0\text{-}24\ hrs}$ = area under the concentration time curve from 0 to 24 hours.

[a] After multiple (every 8 hours) FETROJA 2-gram doses infused over 3 hours or adjusted based on renal function.

[b] After a single FETROJA 2-gram dose was infused over 3 hours.

Distribution

The geometric mean (±SD) cefiderocol volume of distribution was 18.0 (± 3.36) L. Plasma protein binding, primarily to albumin, of cefiderocol is 40% to 60%.

Following a FETROJA 2-gram dose (or renal function equivalent dose) at steady state in patients with pneumonia requiring mechanical ventilation with a 3-hour infusion, the cefiderocol concentrations in epithelial lining fluid ranged 3.1 to 20.7 mg/L and 7.2 to 15.9 mg/L at the end of infusion and at 2 hours after the end of infusion, respectively.

Elimination

Cefiderocol terminal elimination half-life is 2 to 3 hours. The geometric mean (± SD) cefiderocol clearance is estimated to be 5.18 (± 0.89) L/hr.

Metabolism

Cefiderocol is minimally metabolized [less than 10% of a single radiolabeled cefiderocol dose of 1 gram (0.5 times the approved recommended dosage) infused over 1 hour].

Excretion

Cefiderocol is primarily excreted by the kidneys. After a single radiolabeled cefiderocol 1-gram (0.5 times the approved recommended dosage) dose infused over 1 hour, 98.6% of the total radioactivity was excreted in urine (90.6% unchanged) and 2.8% in feces.

Specific Populations

No clinically significant differences in the pharmacokinetics of cefiderocol were observed based on age (18 to 93 years of age), sex, or race. The effect of hepatic impairment on the pharmacokinetics of cefiderocol was not evaluated.

Patients with Renal Impairment

Approximately 60% of cefiderocol was removed by a 3- to 4-hour hemodialysis session.

Cefiderocol AUC fold changes in subjects with renal impairment compared to subjects with CLcr 90 to 119 mL/min are summarized in Table 7.

Table 7 Effect of Renal Impairment on the AUC of Cefiderocol[a]

CLcr (mL/min)	**Cefiderocol AUC Geometric Mean Ratios (90% CI)[b]**
60 to 89 (N = 6)	1.37 (1.15, 1.62)
30 to 59 (N = 7)	2.35 (2.00, 2.77)
15 to 29 (N = 4)	3.21 (2.64, 3.91)
< 15 (N = 6)	4.69 (3.95, 5.56)

CI = confidence interval.

[a] After a single FETROJA 1-gram dose (0.5 times the approved recommended dosage).

[b] Compared to AUC in subjects with CLcr 90 to 119 mL/min (N = 12).

Patients Receiving CRRT

In an *in vitro* study, effluent flow rate was the major determinant of cefiderocol clearance by CRRT. Variables examined included effluent flow rate, CRRT mode (CVVH or CVVHD), filter type and point of dilution (pre- or post-filter dilution). The effluent flow rate-based dosing recommendations in Table 2 are predicted to provide cefiderocol exposures similar to those achieved with a dose of 2 grams given every 8 hours in patients not receiving CRRT *[see Dosage and Administration (2.2)]*.

Patients with CLcr 120 mL/min or Greater

Increased cefiderocol clearance has been observed in patients with CLcr 120 mL/min or greater. A FETROJA 2-gram dose every 6 hours infused over 3 hours provided cefiderocol exposures comparable to those in patients with CLcr 90 to 119 mL/min *[see Dosage and Administration (2.2)]*.

Drug Interaction Studies

Clinical Studies

No clinically significant differences in the pharmacokinetics of furosemide (an organic anion transporter [OAT]1 and OAT3 substrate), metformin (an organic cation transporter [OCT]1, OCT2, and multidrug and toxin extrusion [MATE]2-K substrate), and rosuvastatin (an organic anion transporting polypeptide [OATP]1B3 substrate) were observed when coadministered with cefiderocol.

In Vitro Studies Where Drug Interaction Potential Was Not Further Evaluated Clinically

Cytochrome P450 (CYP) Enzymes: Cefiderocol is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4. Cefiderocol is not an inducer of CYP1A2, CYP2B6, or CYP3A4.

Transporter Systems: Cefiderocol is not an inhibitor of OATP1B1, MATE1, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), or bile salt export pump transporters. Cefiderocol is not a substrate of OAT1, OAT3, OCT2, MATE1, MATE2-K, P-gp, or BCRP.

12.4 Microbiology

Mechanism of Action

FETROJA is a cephalosporin antibacterial with activity against Gram-negative aerobic bacteria. Cefiderocol functions as a siderophore and binds to extracellular free (ferric) iron. In addition to passive diffusion via porin

channels, cefiderocol is actively transported across the outer cell membrane of bacteria into the periplasmic space using the bacterial siderophore iron uptake mechanism. Cefiderocol exerts bactericidal action by inhibiting cell wall biosynthesis through binding to penicillin-binding proteins (PBPs).

Cefiderocol has no clinically relevant *in vitro* activity against most Gram-positive bacteria and anaerobic bacteria.

Resistance

In vitro, MIC increases that may result in resistance to cefiderocol in Gram-negative bacteria have been associated with a combination of multiple beta-lactamases, modifications of PBPs, and mutations of transcriptional regulators that impact siderophore expression.

Cefiderocol does not cause induction of AmpC beta-lactamase in *P. aeruginosa* and *E. cloacae*. The frequency of resistance development in Gram-negative bacteria including carbapenemase producers exposed to cefiderocol at 10x minimum inhibitory concentration (MIC) ranged from 10^{-6} to $< 10^{-8}$.

Cross-resistance with other classes of antibacterial drugs has not been identified; therefore, isolates resistant to other antibacterial drugs may be susceptible to cefiderocol.

Cefiderocol has shown *in vitro* activity against isolates of *S. maltophilia* and a subset of isolates of Enterobacterales and *P. aeruginosa* that are resistant to meropenem, ciprofloxacin, amikacin, cefepime, ceftazidime-avibactam, and ceftolozane/tazobactam. Cefiderocol has shown *in vitro* activity against subset of isolates of *A. baumannii* complex that are resistant to meropenem, ciprofloxacin, and amikacin. Cefiderocol is active against some colistin-resistant *E. coli* isolates containing *mcr-1*.

Cefiderocol demonstrated *in vitro* activity against a subgroup of Enterobacterales genetically confirmed to contain the following: ESBLs (TEM, SHV, CTX-M, oxacillinase [OXA]), AmpC, AmpC-type ESBL (CMY), serine-carbapenemases (such as KPC, OXA-48), and metallo-carbapenemases (such as NDM and VIM). Cefiderocol demonstrated *in vitro* activity against a subgroup of *P. aeruginosa* genetically confirmed to contain VIM, IMP, GES, AmpC and a subgroup of *A. baumannii* containing OXA-23, OXA-24/40, OXA-51, OXA-58 and AmpC. Cefiderocol is active *in vitro* against a subgroup of *S. maltophilia* containing metallo-carbapenemase (L1) and serine beta-lactamases (L2).

Cefiderocol maintained *in vitro* activity against *K. pneumoniae* in the presence of porin channel deletions (OmpK35/36), and against *P. aeruginosa* in the presence of porin channel deletions (OprD) and efflux pump up-regulation (MexAB-OprM, MexCD-OprJ, MexEF-OprN, and MexXY).

In vitro, the addition of the beta-lactamase inhibitors (such as avibactam, clavulanic acid, and dipicolinic acid) results in the lowering of MICs of some clinical isolates with relatively high MICs (range 2 to 256 mcg/mL) to cefiderocol.

Interaction with Other Antimicrobials

In vitro studies showed no antagonism between cefiderocol and amikacin, ceftazidime/avibactam, ceftolozane/tazobactam, ciprofloxacin, clindamycin, colistin, daptomycin, linezolid, meropenem, metronidazole, tigecycline, or vancomycin against strains of Enterobacterales, *P. aeruginosa*, and *A. baumannii*.

Activity against Bacteria in Animal Infection Models

In a neutropenic murine thigh infection model using a humanized dose (2 grams every 8 hours), cefiderocol demonstrated $1\log_{10}$ reduction in bacterial burden against most *E. coli, K. pneumoniae, A. baumannii, S. maltophilia,* and *P. aeruginosa* including some carbapenemase-producing (KPC, OXA-23, OXA-24/40, OXA-58) isolates with MICs of ≤ 4 mcg/mL to cefiderocol.

In an immunocompetent rat pneumonia model, reduction in bacterial counts in the lungs of animals infected with *K. pneumoniae* with MICs ≤ 8 mcg/mL, *A. baumannii* with MICs ≤ 2 mcg/mL, and *P. aeruginosa* with

MICs ≤ 1 mcg/mL including carbapenemase (KPC, NDM and IMP) producing isolates was observed using humanized cefiderocol drug exposure.

In an immunocompetent murine urinary tract infection model, cefiderocol reduced bacterial counts in the kidneys of mice infected with *E. coli, K. pneumoniae,* and *P. aeruginosa* isolates with MICs ≤ 1 mcg/mL. In an immunocompromised murine systemic infection model, cefiderocol increased survival in mice infected with *E. cloacae, S. maltophilia,* and *Burkholderia cepacia* isolates with MICs ≤ 0.5 mcg/mL compared to untreated mice. In an immunocompetent murine systemic infection model, cefiderocol increased survival in mice infected with *S. marcescens* and *P. aeruginosa* isolates with MICs ≤ 1 mcg/mL compared to untreated mice.

The clinical significance of the above findings in animal infection models is not known.

Antimicrobial Activity

FETROJA has been shown to be active against the following bacteria, both *in vitro* and in clinical infections *[see Indications and Usage (1)]*.

Complicated Urinary Tract Infections, Including Pyelonephritis

Gram-negative bacteria

Escherichia coli

Enterobacter cloacae complex

Klebsiella pneumoniae

Proteus mirabilis

Pseudomonas aeruginosa

Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP)

Gram-negative bacteria

Acinetobacter baumannii complex

Escherichia coli

Enterobacter cloacae complex

Klebsiella pneumoniae

Pseudomonas aeruginosa

Serratia marcescens

The following *in vitro* data are available, but their clinical significance is not known. At least 90% of the following bacteria exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for FETROJA against isolates of similar genus or organism group. However, the efficacy of FETROJA in treating clinical infections caused by these bacteria has not been established in adequate and well-controlled clinical trials.

Gram-negative bacteria

Achromobacter spp.

Burkholderia cepacia complex

Citrobacter freundii complex

Citrobacter koseri

Klebsiella aerogenes

Klebsiella oxytoca

Morganella morganii

Proteus vulgaris

Providencia rettgeri

Stenotrophomonas maltophilia

Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see https://www.fda.gov/STIC.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies in animals have not been conducted with cefiderocol.

Mutagenesis

Cefiderocol was negative for genotoxicity in a reverse mutation test with *S. typhimurium* and *E. coli* and did not induce mutations in V79 Chinese hamster lung cells. Cefiderocol was positive in a chromosomal aberration test in cultured TK6 human lymphoblasts and increased mutation frequency in L5178Y mouse lymphoma cells. Cefiderocol was negative in an *in vivo* rat micronucleus test and a rat comet assay at the highest doses of 2000 and 1500 mg/kg/day, respectively.

Impairment of Fertility

Cefiderocol did not affect fertility in adult male or female rats when administered intravenously at doses up to 1000 mg/kg/day. The AUC at this dose is approximately 0.9 times the mean daily cefiderocol exposure in patients who received the maximum recommended clinical dose of 2 grams every 8 hours.

14 CLINICAL STUDIES

14.1 Complicated Urinary Tract Infections, Including Pyelonephritis

A total of 448 adults hospitalized with cUTI (including pyelonephritis) were randomized in a 2:1 ratio and received study medications in a multinational, double-blind trial (Trial 1) (NCT02321800) comparing FETROJA 2 grams intravenously (IV) every 8 hours (infused over 1 hour) to imipenem/cilastatin 1gram/1gram IV every 8 hours (infused over 1 hour) for 7 to 14 days. No switch from IV to oral antibacterial therapy was permitted.

Efficacy was assessed as a composite of microbiological eradication and clinical cure at the Test of Cure (TOC) visit in the microbiological intent-to-treat (Micro-ITT) population, which included all patients who received at least a single dose of study medication and had at least one baseline Gram-negative uropathogen. Other efficacy endpoints included the microbiological eradication rate and the clinical response rate at TOC in the Micro-ITT population.

The Micro-ITT population consisted of 371 patients of whom 25% had cUTI with pyelonephritis, 48% had cUTI without pyelonephritis, and 27% had acute uncomplicated pyelonephritis. Complicating conditions included obstructive uropathy, catheterization, and renal stones. The median age was 66 years, with 24% of patients over the age of 75 years, and 55% of the population were female. The median duration of therapy in both treatment groups was 9 days (range: 1-14 days). Of the 371 patients, 32% had CLcr > 50-80 mL/min, 17% had CLcr 30-50 mL/min, and 3% had CLcr < 30 mL/min at baseline. Concomitant Gram-negative bacteremia

was identified in 7% of patients. In the Micro-ITT population, the most common baseline pathogens were *E. coli* and *K. pneumoniae*.

Table 8 provides the results of a composite of microbiological eradication (all Gram-negative uropathogens found at baseline at $\geq 10^5$ CFU/mL reduced to $< 10^4$ CFU/mL) and clinical response (resolution or improvement of cUTI symptoms and no new symptoms assessed by the investigator) at the TOC visit, 7 +/- 2 days after the last dose of study drug. The response rates for the composite endpoint of microbiological eradication and clinical response at the TOC visit were higher in the FETROJA arm compared with imipenem/cilastatin, as shown in Table 9. Clinical response rates at the TOC visit were similar between FETROJA and imipenem/cilastatin. Most patients with microbiological failure at the TOC visit in either treatment arm did not require further antibacterial drug treatment. Subgroup analyses examining composite outcomes by baseline pathogen are shown in Table 8 and demonstrated responses consistent with the overall population. Subgroup analyses examining outcomes by age, gender, and/or outcomes in patients with renal impairment, concomitant bacteremia, complicated UTI with or without pyelonephritis, or acute uncomplicated pyelonephritis demonstrated responses were consistent with the overall population.

Table 8 Composite, Microbiological, and Clinical Response Rates at the TOC Visit in cUTI Patients (Micro-ITT Population) in Trial 1

Study Endpoint	FETROJA n/N (%)	Imipenem/Cilastatin n/N (%)	Treatment Difference (95% CI)[a]
Composite response at TOC	183/252 (72.6%)	65/119 (54.6%)	18.6 (8.2, 28.9)
Microbiologic response TOC	184/252 (73.0%)	67/119 (56.3%)	17.3 (6.9, 27.6)
Clinical response TOC	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-Haenszel method.

Table 9 Composite Endpoint of Microbiological Eradication and Clinical Response at the TOC Visit in cUTI Patients (Micro-ITT Population) by Baseline Pathogen[a] Subgroups

Baseline Pathogen Subgroup	FETROJA n/N (%)	Imipenem/Cilastatin n/N (%)
Escherichia coli	113/152 (74.3)	45/79 (57.0)
Klebsiella pneumoniae	36/48 (75.0)	12/25 (48.0)
Proteus mirabilis	13/17 (76.5)	0/2 (0.0)
Pseudomonas aeruginosa	8/18 (44.4)	3/5 (60.0)
Enterobacter cloacae complex	8/13 (61.5)	3/3 (100.0)

[a] Patients may have had more than one pathogen in the baseline urine culture.

In the FETROJA treatment group, 61 (24.2%) bacterial isolates were ESBL producers compared with 32 (26.9%) in the imipenem/cilastatin group. The composite response rate of patients with these ESBL isolates at the TOC visit was consistent with the overall results.

14.2 Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP)

A total of 298 hospitalized adults with HABP/VABP received study medications in a multicenter, randomized, double-blind trial (Trial 2) (NCT03032380) comparing FETROJA 2 grams administered intravenously every 8 hours as a 3-hour infusion to meropenem (2 grams every 8 hours infused over 3 hours). Dosing was adjusted for renal function. Patients in both treatment arms received linezolid 600 mg every 12 hours for at least 5 days

for empiric treatment of Gram-positive organisms. The trial protocol permitted administration of potentially active prior antibacterial therapy for no more than 24 hours within 72 hours prior to randomization and disallowed systemic concomitant antibacterial therapy until the test-of-cure visit (TOC, 7 days after end of treatment). The analysis population was the modified intent-to-treat (mITT) population, which included all randomized patients who received study medication and had evidence of bacterial pneumonia, except those with only anaerobic or Gram-positive aerobic infections.

Of the 292 patients in the mITT population, the median age was 67 years, and 58% of the population was 65 years of age and older, with 29% of the population 75 years of age and older. The majority of patients were male (68%), White (69%), and were from Europe (67%). Approximately 4% (11/292) were from the United States. The median baseline APACHE II score was 15, and 29% of patients had a baseline APACHE II score of greater than or equal to 20. At randomization, 68% of patients were in the ICU, and 60% were mechanically ventilated. 60% of patients had CLcr less than or equal to 80 mL/min at baseline; among these, 34% had CLcr less than or equal to 50 mL/min, and 14% had a CLcr less than 30 mL/min. Augmented renal clearance (CLcr greater than 120 mL/min) was present in 16% of patients. Gram-negative bacteremia was present at baseline in 6% of patients. In both treatment groups, most patients (70%) received between 7 and 14 days of study medication and 18% between 15 and 21 days.

Table 10 shows the Day 14 and Day 28 all-cause mortality rates, as well as clinical cure at the TOC visit. FETROJA was noninferior to meropenem with regard to the primary efficacy endpoint (Day 14 all-cause mortality in the mITT population). Clinical cure was defined as resolution or substantial improvement in signs and symptoms associated with pneumonia, such that no additional antibacterial therapy was required for the treatment of the current infection through the TOC visit.

Table 10 All-cause Mortality and Clinical Cure at the TOC Visit in HABP/VABP Patients (mITT Population) in Trial 2

Endpoint	FETROJA n/N (%)	Meropenem n/N (%)	Treatment Difference[a] (95% CI)
Day 14 All-cause Mortality	18/145 (12.4)	18/147 (12.2)	0.2 (-7.2, 7.7)
Day 28 All-cause Mortality	32/145 (22.1)	31/147 (21.1)	1.1 (-8.2, 10.4)
Clinical Cure at TOC	94/145 (64.8)	98/147 (66.7)	-2.0 (-12.5, 8.5)

CI = confidence interval; TOC = Test of Cure.

[a] The adjusted treatment difference (FETROJA minus meropenem) and associated 95% CI were based on the Cochran-Mantel-Haenszel stratum-weighted method. Subjects with unknown survival status were considered deaths. For Day 14 All-cause Mortality, 1 meropenem subject had unknown status; for Day 28 All-cause Mortality, 1 meropenem subject and 2 FETROJA subjects had unknown status.

The Day 14 and Day 28 all-cause mortality rates by pathogen in patients in the mITT population who had a baseline LRT pathogen that was susceptible to meropenem are shown in Table 11; the clinical outcome at the TOC visit is shown in Table 12. There were 51 patients with *A. baumannii* complex at baseline, of which 17 (33.3%) patients had isolates susceptible to meropenem (MIC $\leq$ 8 mcg/mL, based on meropenem 2 grams every 8 hours). Among 51 patients with *A. baumannii* complex at baseline, all-cause mortality at Day 14 was 5/26 (19.2%) in FETROJA and 4/25 (16.0%) in the meropenem treatment group and at Day 28 was 9/26 (34.6%) in FETROJA and 6/25 (24.0%) in the meropenem treatment group. The clinical cure rates at the TOC visit were 14/26 (53.8%) in the FETROJA and 15/25 (60.0%) in the meropenem treatment group.

Table 11 All-cause Mortality by Baseline Pathogens Susceptible to Meropenem* in HABP/VABP Patients (mITT Population) in Trial 2

Baseline Pathogen	Day 14 All-cause Mortality		Day 28 All-cause Mortality	
	FETROJA n/N (%)	Meropenem n/N (%)	FETROJA n/N (%)	Meropenem n/N (%)
Klebsiella pneumoniae	4/38 (10.5)	4/36 (11.1)	8/38 (21.1)	9/36 (25.0)
Pseudomonas aeruginosa	2/20 (10.0)	4/17 (23.5)	2/20 (10.0)	5/17 (29.4)
Acinetobacter baumannii complex[a]	1/8 (12.5)	0/9 (0.0)	3/8 (37.5)	0/9 (0.0)
Escherichia coli	3/18 (16.7)	3/21 (14.3)	5/18 (27.8)	4/21 (19.0)
Other Enterobacterales[b]	2/16 (12.5)	2/14 (14.3)	4/16 (25.0)	3/14 (21.4)

Each cell excludes subjects in whom baseline pathogen had meropenem MIC > 8 mcg/mL or where MIC was unknown.
Subjects with unknown survival status were considered deaths.

* Susceptible defined as MIC of ≤ 8 mcg/mL to meropenem.

[a] Includes *A. baumannii, A. nosocomialis*, and *A. pittii.*

[b] Includes *Enterobacter cloacae* complex (*E. cloacae*, *E. asburiae* and *E. kobei*) and *Serratia marcescens*.

Table 12 Clinical Cure Rates by Baseline Pathogen Susceptible to Meropenem* at the TOC Visit in HABP/VABP (mITT Population) in Trial 2

Baseline Pathogen	Clinical Cure	
	FETROJA n/N (%)	Meropenem n/N (%)
Klebsiella pneumoniae	24/38 (63.2)	23/36 (63.9)
Pseudomonas aeruginosa	13/20 (65.0)	13/17 (76.5)
Acinetobacter baumannii complex[a]	6/8 (75.0)	7/9 (77.8)
Escherichia coli	12/18 (66.7)	13/21 (61.9)
Other Enterobacterales[b]	10/16 (62.5)	8/14 (57.1)

Each cell excludes subjects whose pathogen-specific meropenem MIC > 8 mcg/mL or where MIC was unknown.

* Susceptible defined as MIC of ≤ 8 mcg/mL to meropenem.

[a] Includes *A. baumannii, A.nosocomialis*, and *A. pittii.*

[b] Includes *Enterobacter cloacae* complex (*E. cloacae*, *E. asburiae* and *E. kobei*) and *Serratia marcescens*.

In the FETROJA treatment group, 45 (31%) patients had ESBL-producing bacterial isolates compared with 42 (28.6%) patients in the meropenem treatment group. All-cause mortality at Day 14 and Day 28 of patients with these ESBL-producing bacterial isolates was consistent with the overall results.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

FETROJA 1 gram (cefiderocol) for injection is supplied as a white to off-white sterile lyophilized powder for reconstitution in single-dose, clear glass vials (NDC 59630-266-01) sealed with a rubber stopper (not made with natural rubber latex) and an aluminum seal with flip-off cap. Each vial is supplied in cartons containing 10 single-dose vials.

NDC 59630-266-10 FETROJA (cefiderocol) 1 gram/vial, 10 vials/carton

16.2 Storage and Handling

FETROJA vials should be stored refrigerated at 2°C to 8°C (36°F to 46°F). Protect from light. Store in the carton until time of use. Store reconstituted solutions of FETROJA at room temperature *[see Dosage and Administration (2.5)]*.

17 PATIENT COUNSELING INFORMATION

Serious Allergic Reactions

Advise patients and their families that allergic reactions, including serious allergic reactions, could occur with FETROJA and that serious reactions require immediate treatment. Ask patients about any previous hypersensitivity reactions to FETROJA, other beta-lactams (including cephalosporins), or other allergens *[see Warnings and Precautions (5.2)]*.

Potentially Serious Diarrhea

Advise patients and their families that diarrhea is a common problem caused by antibacterial drugs, including FETROJA. Sometimes, frequent watery or bloody diarrhea may occur and may be a sign of a more serious intestinal infection. If severe watery or bloody diarrhea develops, tell patient to contact his or her healthcare provider *[see Warnings and Precautions (5.3)]*.

Seizures

Counsel patients on the implication of cephalosporins, including FETROJA, in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced and in patients with a history of epilepsy *[see Warnings and Precautions (5.4)]*.

Antibacterial Resistance

Patients should be counseled that antibacterial drugs including FETROJA should only be used to treat bacterial infections. They do not treat viral infections (e.g., influenza, common cold). When FETROJA is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by FETROJA or other antibacterial drugs in the future *[see Warnings and Precautions (5.5)]*.

Manufactured by
Shionogi & Co., Ltd.
Osaka 541-0045
Japan

Manufactured for
Shionogi Inc.
Florham Park, NJ
USA, 07932

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUMATHI NAMBIAR
09/25/2020 05:55:24 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209445Orig1s002

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	Efficacy Supplement
Application number(s)	NDA 209445/S-002
Priority or standard	Priority
Submit date(s)	3/27/2020
Received date(s)	3/27/2020
PDUFA goal date	9/27/2020
Division	Division of Anti-Infectives (DAI)
Review completion date	8/14/2020
Established name	Cefiderocol
Trade name	Fetroja
Pharmacologic class	Cephalosporin
Code name	S-649266
Applicant	Shionogi, Inc.
Dose form/formulation(s)	Intravenous
Dosing regimen	2 gm every 8 hours (2 vials of 1 gm every 8 hours)
Applicant proposed indication(s)/population(s)	FETROJA is indicated in patients 18 years of age or older for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia, caused by the following susceptible Gram-negative microorganisms: *Acinetobacter baumannii* complex, *Burkholderia cepacia* complex, (b) (4) *Escherichia coli*, *Enterobacter cloacae* complex, (b) (4), *Klebsiella pneumoniae*, (b) (4) *Pseudomonas aeruginosa*, *Serratia marcescens*, and (b) (4)
Proposed SNOMED indication	425464007: Hospital-acquired Bacterial pneumonia 429271009: Ventilator-associated Bacterial pneumonia
Regulatory action	Approval
Approved indication(s)/population(s) (if applicable)	FETROJA is indicated in patients 18 years of age or older for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia, caused by the following susceptible Gram-negative microorganisms: *Acinetobacter baumannii* complex, *Escherichia coli*, *Enterobacter cloacae complex*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Serratia marcescens*.
Approved SNOMED indication	425464007: Hospital-acquired Bacterial pneumonia 429271009: Ventilator-associated Bacterial pneumonia

Table of Contents

Table of Tables

Table of Figures

Glossary

ABG	arterial blood gas
ACC	Ambler class C
ACM	all-cause mortality
ACT	AmpC type
ADC	Acinetobacter-derived cephalosporinase
AE	adverse event
AKI	acute kidney injury
ALB	albumin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APACHE	Acute Physiology and Chronic Health Evaluation
APEKS-NP	*Acinetobacter baumannii, Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae,* and *Stenotrophomonas maltophilia* in Nosocomial Pneumonia
aPTT	activated partial thromboplastin time
AR	adverse reaction
ARDS	acute respiratory distress syndrome
ARLG	Antimicrobial Resistance Leadership Group
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUP	acute uncomplicated pyelonephritis
AZT	aztreonam
BAL	bronchoalveolar lavage
BILI	bilirubin
BSI	bloodstream infection
CAMHB	Cation Adjusted Mueller Hinton Broth
$C_{dialysate}$	concentration in dialysate
CHF	congestive heart failure
CI	confidence interval
CKD	chronic kidney disease
CLcr	creatinine clearance
CL_{CRRT}	clearance by ultrafiltration or dialysis of continuous renal replacement therapy
CL_{CVVH}	clearance by continuous venovenous hemofiltration
CL_{CVVHD}	clearance by continuous venovenous hemodialysis
$CL_{nonrenal}$	nonrenal clearance
CLSI	Clinical and Laboratory Standards Institute
CMC	chemistry, manufacturing, and controls
CMH	Cochran-Mantel-Haenszel
CMY	cephalosporinase
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
C_{post}	concentration from a postfilter sampling port
C_{pre}	concentration from an undiluted prefilter sampling port

CREDIBLE-CR	A Multicenter, Randomized, Open-label Clinical Study of S-649266 or Best Available Therapy for the Treatment of Severe Infections Caused by Carbapenem-Resistant Gram-Negative Pathogens
CRRT	continuous renal replacement therapy
CT	computed tomography
CTX-M	cefotaximase
C_{uf}	concentration in ultrafiltrate
CVA	cerebrovascular accident
CVVDF	continuous venovenous diafiltration
CVVH	continuous venovenous hemofiltration
CVVHD	continuous venovenous hemodialysis
CVVHDF	continuous venovenous hemodiafiltration
DAI	Division of Anti-Infectives
DHA	Dhahran Hospital
DM	diabetes mellitus
DSMB	Data Safety Monitoring Board
EA	early assessment
ECMO	extracorporeal membrane oxygenation
eGFR	estimated glomerular filtration rate
ELF	epithelial lining fluid
EOS	end of study
EOT	end of treatment
ESBL	extended-spectrum β-lactamase
ESRD	end-stage renal disease
FDA	Food and Drug Administration
FMQ	FDA Medical Dictionary for Regulatory Activities Query
FOX	cefoxitin
FU	follow-up
fu	free fraction of drug in plasma
GCP	good clinical practice
GES	Guiana extended-spectrum β-lactamase
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GIM	German imipenemase
HABP	hospital-acquired bacterial pneumonia
HAP	hospital-acquired pneumonia
HCABP	healthcare-associated bacterial pneumonia
HCAP	healthcare-associated pneumonia
HTN	hypertension
ID-CAMHB	Iron Depleted Cation Adjusted Mueller Hinton Broth
IMP	imipenemase metallo-β-lactamase
IND	investigational new drug
INR	international normalized ratio
IPM	imipenem
iPSP	initial pediatric study plan

ITT	intention-to-treat
IV	intravenous
KPC	*Klebsiella pneumoniae* carbapenemase
LFT	liver function test
LOE	lack of efficacy
Mex	multidrug efflux pump
MDR	multidrug-resistant
MI	myocardial infarction
MIC	minimum inhibitory concentration
MIC_{90}	minimum inhibitory concentration required to inhibit 90% of tested isolates
MIR	Miriam Hospital
mITT	modified intention-to-treat
MODS	multiple organ dysfunction syndrome
MOX	moxalactam
MRSA	methicillin-resistant *Staphylococcus aureus*
NDA	new drug application
NDM	New Delhi metallo-β-lactamase
NI	noninferiority
NP	nosocomial pneumonia
OBJ	objective function value
Opr	outer membrane porin
OXA	oxacillinase
pcVPC	prediction-corrected visual predictive check
PD	pharmacodynamics
PDC	*Pseudomonas*-derived cephalosporinase
PDUFA	Prescription Drug User Fee Act
PE	pulmonary embolism
PER	Pseudomonas extended resistance
PK	pharmacokinetics
PPK	population pharmacokinetics
PSP	pediatric study plan
PMR	postmarketing requirement
PT	preferred term
Q_b	blood flow rate
Q_d	dialysate flow rate
Q_E	effluent flow rate
Q_{rep}	prefilter replacement fluid rate
Q_{uf}	ultrafiltrate/replacement fluid flow rate
SA	saturation coefficient
SAE	serious adverse event
SC	sieving coefficient
SD	standard deviation
SHV	sulfhydryl variable
sNDA	supplemental new drug application
SOC	system organ class

SPM	São Paulo metallo-β-lactamase
TEAE	treatment-emergent adverse event
TEM	temoneira
TOC	test-of-cure
ULN	upper limit of normal
UTI	urinary tract infection
VABP	ventilator-associated bacterial pneumonia
VAP	ventilator-associated pneumonia
VIM	Verona integron-encoded metallo-β-lactamase
WBC	white blood cell
XDR	extensively drug-resistant

I. Executive Summary

1. Summary of Regulatory Action

Cefiderocol (FETROJA™) is approved for treatment of adults with complicated urinary tract infections (cUTI). This supplemental NDA (sNDA) proposes to add a second indication, treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) based upon APEKS-NP (NCT02321800), a double-blind, active-controlled, randomized, noninferiority trial conducted to compare Fetroja to meropenem. This sNDA was reviewed by a multidisciplinary review team. Each discipline has recommended approval of the sNDA, and I, the signatory authority for this application, concur with the recommendations.

In support of this indication, the APEKS-NP clinical trial met its primary endpoint of noninferiority of cefiderocol to meropenem for day 14 all-cause mortality (ACM) in the modified intent-to treat (mITT) population: day 14 ACM was 12.4% in the cefiderocol and 11.6% in the meropenem group for a treatment difference of 0.8 (95% confidence intervals, -6.6, 8.2). The secondary endpoints of day 28 all-cause mortality and clinical outcomes supported the finding of noninferiority (see benefit-risk assessment, below). The Statistical Review team concurs that appropriate statistical inference testing was conducted, and this single adequate and well-controlled trial provides substantial evidence of effectiveness of cefiderocol for the treatment of HABP/VABP due to the designated susceptible bacteria. Additional supportive information was provided from *in vitro* studies and animals models of infection.

The safety profile of cefiderocol was generally similar to meropenem in the APEKS-NP trial. The study population consisted of severely ill patients, and deaths occurred in approximately one-quarter of patients and serious adverse events in approximately one-third of patients in both treatment groups (see benefit-risk summary, and review Sections 7.6-7.7). The clinical review team recommends providing information on the adverse reactions (ARs) observed in the APEKS-NP trial in section 6 of labeling (Adverse Reactions) and routine postmarketing surveillance.

Notable labeling changes include dosing recommendations for patients undergoing continuous renal replacement therapy (CRRT; discussed in Sections 8.1, 14.1, and 11 of this review).

The current labeling contains a warning in section 5.1 describing an increase in all-cause mortality based upon observations in a randomized, open-label trial (CREDIBLE-CR) in patients with cUTI, nosocomial pneumonia, bloodstream infections, or sepsis due to carbapenem-resistant gram-negative bacteria. The cause of the increased mortality was not established, but some deaths were attributed to treatment failure or underlying conditions (Division of Anti-Infectives 2019). The current trial in HABP/VABP with carbapenem-susceptible organisms provides some reassuring safety data; however, the clinical review team recommends retaining the warning from the CREDIBLE-CR trial as the safety concern remains regarding the risk of mortality in patients with carbapenem-resistant infections.

The data from the APEKS-NP trial supports the safety and effectiveness of cefiderocol for the treatment of HABP/VABP and mutually supports the previous finding of safety and

effectiveness for the treatment of cUTI. In both trials, the 10% noninferiority margin recommended for a standard indication was met; therefore, the limited use statement in the product labeling is recommended to be removed.

The overall benefit-risk is favorable as summarized in the Benefit-Risk Assessment below. For detailed information supporting the basis for this approval, please refer to the detailed reviews included in this Interdisciplinary Assessment document and the separate Product Quality Review.

2. Benefit-Risk Assessment

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) are acute infections of the lung parenchyma that occur in hospitalized patients. • HABP is generally defined as occurring 48 hours or more after hospital admission and is not associated initially with mechanical ventilation. • Ventilated HABP (vHABP) is a subset of HABP in which patients with HABP require mechanical ventilation as part of their treatment. VABP is generally defined as occurring 48 hours or more after endotracheal intubation. • Both conditions are associated with acute respiratory symptoms and the presence of new or progressive infiltrates on chest radiograph. • The microbiology of HABP and VABP include gram-positive bacteria, such as *S. aureus*, and gram-negative bacteria, such as *P. aeruginosa, Acinetobacter spp.,* and Enterobacterales. Antibacterial resistance is commonly observed in bacterial isolates that cause HABP and VABP. • Mortality among patients with HABP and VABP has been reported to be 20 to 50% (Alp et al. 2004).	HABP and VABP are serious infections that cause significant morbidity and mortality in hospitalized patients.
Current Treatment Options	• The initial treatment of HABP/VABP is empiric as culture results are typically not initially available, but usually includes intravenous (IV) antibacterial drugs that cover *S. aureus* and *P. aeruginosa*. • The choice of antibacterial drugs depends on the local epidemiology and patient risk factors for resistant organisms. The antibacterial drug regimen is usually tailored after culture results are available. • FDA-approved antibacterial drugs with gram-negative coverage that are used for the treatment of HABP/VABP include β-lactam/β-lactam inhibitor combinations (ceftolozane/tazobactam, ceftazidime/avibactam, piperacillin-tazobactam), certain cephalosporins, fluoroquinolones, monobactams, aminoglycosides, and carbapenems.	There are several antibacterial drugs approved to treat HABP/VABP, but antimicrobial resistance and patient factors may limit their use.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The efficacy of cefiderocol in treatment of HABP/VABP was evaluated in a randomized clinical trial (APEKS-NP) that compared cefiderocol 2 grams IV every 8 hours with meropenem 2 grams IV every 8 hours. Linezolid was given to patients in both treatment groups for treatment of possible concomitant infection with gram-positive organisms. Of 300 patients, 148 and 152 were randomized to receive either cefiderocol or meropenem, respectively. There were no significant issues with trial design, conduct, or analysis. • The primary endpoint was all-cause mortality (ACM) at day 14. Secondary endpoints included ACM at day 28, clinical and microbiological outcome at the test-of-cure visit (TOC), which occurred about 7 days after the end of treatment. The mortality and clinical outcome endpoints are measures of clinical benefit (how a patients survives, feels, and functions). • ACM at day 14 and day 28 was 12.4% and 22.1% in the cefiderocol and 12.2% and 21.1% in the meropenem group respectively in the modified intention-to-treat (mITT) population. The results of ACM at day 14 met the threshold for noninferiority. • Clinical cure at TOC was 64.8% in the cefiderocol and 66.7% in the meropenem group. Microbiological cure at TOC was 47.6% in the cefiderocol and 48% in the meropenem group. • The results are similar between treatment groups across various patient subgroups and robust to sensitivity analyses. • To ensure that the efficacy results were not largely driven by meropenem-nonsusceptibility; i.e., by the possibility that a significant proportion of subjects in the meropenem arm were unlikely to benefit from meropenem, the key efficacy analyses were repeated by restricting them to patients where the isolate was susceptible to meropenem. The results corroborated the original results from the full mITT population. • As only 59% of the mITT population had subjects known to be susceptible to meropenem, the differences in efficacy in certain subgroups based on baseline pathogen were difficult to discern. • At baseline, 51 subjects were infected with *A. baumannii* complex however only 17 (33%) had meropenem-susceptible isolates . Of these 17 isolates, there were (<10) isolates in either treatment group. Generally, for inclusion of an organism in the indication, clinical data in the test arm on at least 10 isolates is	The submitted evidence showed noninferiority of cefiderocol to meropenem for ACM at day 14. A key secondary endpoint of microbiological cure did not demonstrate statistical significance, and other endpoints (day 28 and clinical cure) were considered exploratory. Day 28 ACM rates were similar across treatment groups and clinical cure rates slightly disfavored cefiderocol. The analysis of key endpoints when restricting to patients with meropenem susceptible pathogens (MIC $\leq$8 mcg/mL based on 2 g 3hour infusion) did not demonstrate significant differences between the treatment groups. The mortality and clinical cure endpoints were relatively similar in the overall subset of patients with *A. baumannii* complex (N=51) and a few subgroups with increasing MIC to meropenem trended favorably for cefiderocol. As this information reflects that cefiderocol likely has efficacy in treatment of patients with *A. baumannii* complex HABP/VABP, *A. baumannii* complex was included in the indication and List 1 in labeling. The table in the Clinical Studies section of the labeling will present the comparative results from patients with meropenem-susceptible *A.baumannii* complex at baseline and additional information on outcomes in patients with HABP/VABP due to *A. baumannii* complex will be described in this section so that the healthcare provider can take this information into consideration while making treatment decisions.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	expected. In these 51 patients, clinical cure rates, ACM at day 14 and 28 slightly disfavored cefiderocol, and the mortality imbalance in the CREDIBLE-CR trial in the subgroup of patients with *A. baumannii* also raised concerns about including this organism in the indication. • When all Acinetobacter isolates (N=53) were included in efficacy analysis, the ACM mortality at day 14 and 28 were similar between treatment groups. Moreover, in the subgroups of patients with MIC to meropenem ranging from >16 to >64 mcg/mL, day 14 ACM may have favored the cefiderocol group.	
Risk and Risk Management	• The safety database included 148 patients of which 97 received the proposed dose and duration of cefiderocol (7-14 days), 33 received >14 days, and 18 received <7 days of cefiderocol. Relative to recent HABP/VABP studies, this is a small safety database. Patient characteristics were adequately represented in terms of gender and age. Patients from the United States were underrepresented (4%) but significant regional differences in HABP/VABP trials are not anticipated. Approximately 50 percent were receiving mechanical ventilation at enrollment (VABP/vHABP). • The following adverse reactions (ARs) occurred in at least 4% of cefiderocol-treated patients: elevated liver tests, anemia, hypokalemia, diarrhea, hypomagnesemia, and atrial fibrillation. • Treatment-emergent adverse events (TEAEs) leading to death occurred in 26.4% [39/148] in the cefiderocol group and 23.3% [35/150] in the meropenem group (a risk difference of 3.1%). • While some deaths appeared to be related to lack of efficacy or an adverse reaction (AR), the majority in both treatment groups appeared to be related to underlying medical conditions or concurrent illness in a critically ill population. • A higher number of arterial thromboembolic events (e.g., myocardial infarction, intestinal infarction) were reported and proposed as ARs in labeling. • Seizures, *Clostridioides difficile*-associated diarrhea, and hypersensitivity reactions were reported and are already in current labeling.	There are limitations to the safety and causality assessment given the relative small size of the safety database and the complexity of patients' underlying comorbidities. The benefits and risk of cefiderocol have been communicated in labeling. Monitoring for TEAEs of special interest will continue in the postmarketing phase. No specific risk mitigation strategies are needed at this time.

Conclusions Regarding Benefit-Risk

In this sNDA, the Applicant is seeking an indication for the treatment of HABP/VABP. Bacterial infections of the lung parenchyma are serious, frequently life threatening infections that are often associated with antibacterial drug resistance, particularly when acquired in a healthcare setting. While there are multiple antibacterial drugs currently approved to treat HABP/VABP, antimicrobial resistance continues to evolve which may limit the utility of the current armamentarium. Cefiderocol is a modified cephalosporin that utilizes a siderophore-based entry mechanism into gram-negative bacterial cells; therefore, it may offer a treatment option for some patients with HABP/VABP.

The submitted evidence met the statutory standard for effectiveness. The APEKS-NP trial achieved the primary objective demonstrating that cefiderocol is noninferior to meropenem in the treatment of patients with HABP/VABP with respect to the primary endpoint of ACM at day 14 in the mITT population (cefiderocol 12.4%, meropenem 11.6% [difference 0.8%; 95% CI: - 6.6 to 8.2]). This conclusion was supported by the secondary endpoint assessments of ACM at day 28 (cefiderocol 21.0%, meropenem 20.5% [difference 0.5%; 95% CI: - 8.7 to 9.8]), and clinical cure, which assessed the resolution of signs and symptoms of disease. The favorable clinical response at the TOC visit in the mITT population was 64.8% and 66.7%, in the cefiderocol and meropenem groups, respectively (difference – 2.0%; 95% CI: - 12.5 to 8.5). Various sensitivity analyses of the primary endpoint produced similar conclusions as the primary analysis when accounting for potentially confounding factors, such as prior and concomitant antibacterial therapy as well as missing data (Sections 6.4.1 and 16). Subgroup analyses by subject demographics and disease characteristics were consistent with the primary results. Certain subgroup analyses of the micro-ITT population were limited by small sample sizes, such as analyses by baseline pathogen. Noninferiority was preserved in the subgroup of patients who strictly met the criteria for study inclusion as described by the FDA guidance *Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment* (June 2020). The main issue affecting interpretability were the criteria for meropenem susceptibility when utilizing a high dose, extended duration of infusion dosing regimen (Section 6.4.2). With a sensitivity analysis restricted to patients with meropenem susceptible pathogens, as defined by MIC ≤8 mcg/mL, there were no significant differences between the treatment groups (Section 6.4.2).

The safety database from the APEKS-NP trial included 148 patients of which 97 received the proposed dose and duration of cefiderocol. Patient demographic characteristics were balanced, and approximately 50% were mechanically ventilated at enrollment (VABP/ventilated HABP). Overall, safety profiles were similar between cefiderocol and meropenem. The most common TEAEs (greater than or equal to 4% incidence) experienced by patients in this trial were the following: elevated liver tests, anemia, hypokalemia, diarrhea, hypomagnesemia, and atrial fibrillation. TEAEs leading to death occurred in 26.4% [39/148] in the cefiderocol group and 23.3% [35/150] in the meropenem group (a risk difference of 3.1%). The majority of deaths in both treatment groups appeared to be related to underlying medical conditions or concurrent illness in a critically ill population. The reported adverse events in the HABP/VABP patient population were generally consistent with the known safety profile of cefiderocol observed in the trial for cUTI. Most adverse reactions (ARs), such as seizures, *Clostridioides difficile*-associated diarrhea, and hypersensitivity reactions are

already described in the current labeling. ARs added to the labeling include (b) (4) thromboembolic events (e.g., myocardial infarction,), (b) (4) and electrolyte abnormalities. There are limitations to the safety and causality assessment given the relative small size of the safety database and the complexity of patients' underlying comorbidities.

The overall benefit-risk assessment of cefiderocol for the treatment of HABP/VABP is favorable. A descriptive study (CREDIBLE-CR) raises concerns about the potential for a decrement in efficacy with cefiderocol in patients with HABP/VABP and bacteremia, particularly those caused by certain carbapenem-resistant, lactose non-fermenting Gram-negative bacteria such as *P. aeruginosa*, *A. baumannii* and *S. maltophilia*. The primary analysis population in the APEKS-NP trial was carbapenem-susceptible organisms due to the selection of meropenem as the comparator. The point estimate of 14- and 28-day mortality was lower for patients with *P. aeruginosa* at baseline who were treated with cefiderocol (Section 6.4.2, Table 17). The majority of subjects with *A. baumannii* at baseline were not included in the primary analysis due to carbapenem-resistance; however, an examination of patient outcomes regardless of susceptibility of the baseline pathogen across study endpoints and timepoints did not raise safety concerns (Sections 6.4.3, and 7.1). No deaths occured through day 28 in the small subgroup of patients who were treated with cefiderocol (n=5) with *A. baumannii* at baseline with a meropenem MIC >64 mcg/ml. While the data from APEKS-NP are reassuring, the current warning in labeling will be retained since the findings from CREDIBLE-CR trial are not fully explained, and APEKS-NP was not designed to assess carbapenem-resistant pathogens.

II. Interdisciplinary Assessment

3. Introduction

Cefiderocol (Fetroja) is a structurally modified cephalosporin antibacterial drug that utilizes a siderophore-based mechanism for bacterial cell entry. Cefiderocol was approved on November 14, 2019, for the treatment of complicated urinary tract infections (cUTI) including pyelonephritis due to susceptible gram-negative bacteria in adults with limited to no alternative treatment options.

The proposed indication is for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) caused by carbapenem-susceptible gram-negative bacteria in adults with limited or no alternative treatment options. The proposed dosing regimen is 2 grams by intravenous (IV) administration every 8 hours (with dosing adjustment for renal impairment) for 7 to 14 days. In hospitalized patients with pneumonia, gram-negative organisms can account for >60% of isolated bacteria, with one of the most frequently isolated pathogens being *Pseudomonas aeruginosa*. Other common gram-negative pathogens isolated in patients with HABP and VABP are *Escherichia coli, Klebsiella pneumoniae, Enterobacter spp.* and *Acinetobacter spp.*

Currently available treatment options for HABP/VABP due to gram-negative bacteria include carbapenems, β-lactam/β-lactamase inhibitor combinations, cephalosporins, fluoroquinolones, and aminoglycosides. The initial empiric treatment is guided by the patient's risk factors, local epidemiology, and antibacterial susceptibility patterns. Empiric treatment usually includes coverage for *Staphylococcus aureus*, *P. aeruginosa*, and other gram-negative bacilli. Definitive treatment follows based on the diagnostic workup and the clinical response to empiric treatment.

Cefiderocol was granted both fast track and Qualified Infectious Disease Product designation on August 18, 2015, for this indication. The supplemental new drug application (sNDA) contains results of the APEKS-NP trial (*Acinetobacter baumannii, Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae,* and *Stenotrophomonas maltophilia* in Nosocomial Pneumonia, ClinicalTrials.gov ID 1615R2132), a phase 3, multicenter, randomized, parallel-group, double-blind, active-controlled noninferiority (NI) trial comparing cefiderocol to meropenem for the treatment of HABP/VABP/HCABP. Linezolid was administered to subjects in both study arms to provide coverage for methicillin-resistant *S. aureus*. The primary endpoint of the study was all-cause mortality (ACM) at day 14 in the modified intention-to-treat (mITT) population.

The following review issues were identified and discussed in Sections 6.4 and 7.7.

- Confounding of treatment effect by prior and concomitant antibacterial drugs
- Inclusion of *Acinetobacter*, *S. maltophilia* and *Burkholderia cepacia* in List 1
- Sensitivity analysis excluding patients with meropenem-nonsusceptible pathogens
- Revisit breakpoints established by FDA for Enterobacteriaceae and *P. aeruginosa* and establish breakpoints for *A. baumannii* complex
- Mortality analysis
- Thromboembolic treatment-emergent adverse event (TEAE) analysis

- Potential for resistance development (increases in minimum inhibitory concentration [MIC] on therapy)

3.1. Approach to the Review

The original new drug application (NDA) submitted for the approval of cUTI, including pyelonephritis included six clinical pharmacology studies, a completed phase 2 cUTI trial, and a study summary and datasets from the CREDIBLE-CR trial (A Multicenter, Randomized, Open-label Clinical Study of S-649266 or Best Available Therapy for the Treatment of Severe Infections Caused by Carbapenem-Resistant Gram-Negative Pathogens, ClinicalTrials.gov ID 1424R2131). The CREDIBLE-CR trial results were analyzed during the review of the original NDA; the clinical study report, which was previously unavailable, has been submitted with the sNDA in response to a postmarketing requirement. In this sNDA review, the single trial in HABP/VABP (APEKS-NP) is reviewed in support of the efficacy and safety of cefiderocol in patients with HABP/VABP. Although the CREDIBLE-CR trial enrolled patients with this indication, the trial was primarily conducted to study carbapenem-resistant pathogens and had distinct features which precluded pooling of efficacy or safety results. At the pre-NDA stage, it was agreed with the Applicant that results of the APEKS-NP trial and the HABP/VABP subgroup of the CREDIBLE-CR trial would be analyzed separately.

Table 3 provides an overview of the clinical trials important to the review of cefiderocol efficacy and safety. CREDIBLE-CR trial information has been included here as information from patients receiving continuous renal replacement therapies (CRRTs) in this trial informed CRRT dosing in the labeling.

The review team's approach included identifying key benefit and risk issues at the pre-NDA meetings. The key benefit and risk issues are addressed in the Sections 6.4 and 7.7, respectively. Several information requests were also sent to the Applicant to supplement or clarify information contained in the sNDA.

Table 3. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations[a] for Cefiderocol

Trial Identifier	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Randomized[b]	Number of Centers and Countries
1615R2132 APEKS-NP NCT03032380	Adults with NP (HABP/VABP/HCABP) caused by a susceptible gram-negative pathogen who required hospitalization	Phase 3, MC, R, DB, AC, PG	Drug: Cefiderocol Dose: 2 g IV q8h Number treated: 148 Duration: 7-21 d	Primary: All-cause mortality at day 14 in mITT population Secondary: Microbiological and clinical outcomes at EA, EOT, TOC, FU, all-cause mortality at day 28 and EOS	Planned: 300 (150 in each treatment group) Actual: 300 subjects (148 in cefiderocol group, 152 in meropenem group)	Centers: 104 Countries: 17
1424R2131 CREDIBLE-CR NCT02714595	Adults with NP, BSI/sepsis, or cUTI caused by a carbapenem-resistant gram-negative pathogen	Phase 3, MC, R, OL, AC, PG	Drug: Cefiderocol Dose: 2 g IV q8h Number treated: 101 Duration: 7-21 d	Primary: Clinical outcome at TOC in patients with NP, BSI/sepsis; microbiological outcome at TOC in patients with cUTI Secondary: All-cause mortality at day 14, 28 for NP, BSI/sepsis; clinical and microbiological outcome at EA, EOT	Planned: 152 Actual: 150	Centers: 95 Countries: 16

Source: Reviewer
[a] Includes all submitted clinical trials, even if Not Reviewed in-depth, except for phase 1 and pharmacokinetic studies.
[b] If no randomization, then replace with "Actual Enrolled"
Abbreviations: AC, active-controlled; BSI, bloodstream infection; cUTI, complicated urinary tract infections; DB, double-blind; EA, early assessment; EOS, end of study; EOT, end of treatment; FU, follow-up; HABP, healthcare-acquired bacterial pneumonia; HCABP, healthcare-associated bacterial pneumonia; IV, intravenous; MC, multicenter; mITT, modified intention-to-treat; NP, nosocomial pneumonia; OL, open-label; PG, parallel group; q8h, every 8 hours; R, randomized; TOC, test-of-cure; VABP, ventilator-associated bacterial pneumonia

4. Patient Experience Data

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		
☐	Patient-reported outcome	6.3
☐	Observer-reported outcome	
☒	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Data Considered in the Assessment (but Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

Table 5. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class	Fetroja is a cephalosporin antibacterial drug product.
Mechanism of action	Fetroja is a cephalosporin antibacterial with activity against gram-negative aerobic bacteria. Cefiderocol functions as a siderophore and binds to extracellular free (ferric) iron. In addition to passive diffusion via porin channels, cefiderocol is actively transported across the outer cell membrane of bacteria into the periplasmic space using the bacterial siderophore iron uptake mechanism. Cefiderocol exerts bactericidal action by inhibiting cell wall biosynthesis through binding to penicillin-binding proteins (PBPs).
Active moieties	Cefiderocol
QT prolongation	At doses 1 and 2 times the maximum recommended dosage, Fetroja does not prolong the QT interval to any clinically relevant extent.
	General Information
Bioanalysis	Validated HPLC/MS/MS methods were used to determine the concentrations of cefiderocol in plasma and urine.
Healthy subjects versus patients	No clinically meaningful differences in cefiderocol PK were observed between patients with infection and healthy subjects.
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	**PK Parameters** / **cUTI Patients[a] N=238** / **HABP/VABP Patients[b] N=146** / **Healthy Volunteers[c] N=43** C_{max} (mg/L)[d]: 114 (41.5) / 99.7 (46.9) / 89.7 (21) $AUC_{0\text{-}24\ hrs}$ (mg·hr/L)[d]: 1062 (40.3) / 1560 (53.0) / 1158 (17203) [a] After multiple (every 8 hours) Fetroja 2-gram doses infused over 1 hour (1/3 of the recommended infusion duration) in cUTI patients with CLcr 60 mL/min or greater [b] After multiple (every 8 hours) Fetroja 2-gram doses infused over 3 hours or adjusted based on renal function [c] After a single Fetroja 2-gram dose was infused over 3 hours in healthy volunteers with CLcr 60 mL/min or greater [d] Mean (%CV) Abbreviations: AUC, area under the curve; CLcr, creatinine clearance; C_{max}, maximum plasma concentration; cUTI, complicated urinary tract infection; CV, coefficient of variation; HABP, hospital-acquired bacterial pneumonia; VABP, ventilator-associated bacterial pneumonia
Range of effective dose(s) or exposure	Cefiderocol PK/PD target was determined to be 75% $T_{Cf > MIC}/\tau$ for 1-log10 bacterial reduction based on a neutropenic murine thigh infection model. Compared to a 1-hour infusion, a 3-hour infusion increased the percent time of dosing interval that unbound plasma concentrations of cefiderocol exceed the MIC.
Maximally tolerated dose (MTD) or exposure	An MTD was not determined. The highest evaluated dose in humans was 4000 mg single dose (in a TQT trial).
Dose proportionality	The C_{max} and AUC of cefiderocol increased in a dose-proportional manner within the dose range from 100 to 4000 mg.
Accumulation	After administration of 2 g doses of cefiderocol q8h, no accumulation was observed for C_{max} or AUC.
Time to achieve steady-state	Steady state was attained within 1 day after the start of multiple dose administration.
Bridge between to-be marketed and clinical trial formulations	The to-be-marketed g/vial solution for infusion formulation was used in the pivotal clinical trials.

Characteristic	Drug Information
	Absorption
Bioavailability	Not relevant
T_{max}	Not relevant
Food effect (fed/fasted) geometric least square mean and 90% CI	Not relevant
	Distribution
Volume of distribution	Volume of distribution during the terminal phase (Vz) of cefiderocol was 18.0 L (18.1%) [geometric mean (%CV)].
Plasma protein binding	58%
Lung distribution	Following a Fetroja 2-gram dose at steady state (or renal function equivalent dose) in patients with pneumonia requiring mechanical ventilation with a 3-hour infusion, the cefiderocol concentrations in epithelial lining fluid (ELF) ranged 3.1 to 20.7 mg/L and 7.2 to 15.9 mg/L at the end of infusion and at 2 hours after the end of infusion, respectively.
Drug as substrate of transporters	Cefiderocol was not a substrate of OAT1, OAT3, OCT2, MATE1, MATE2-K, P-gp, or BCRP.
	Elimination
Mass balance results	Following IV administration of a single 1000 mg (approximately equivalent to 100 microCi =3.7 MBq) dose of [^{14}C]-cefiderocol infused over 1 hour, total radioactivity was primarily (geometric mean: 98.59%) excreted in urine, with a minor amount (geometric mean: 2.79%) excreted into feces. Unchanged cefiderocol (90.57% of administered dose) was the major radioactive component detected in urine. A total of 21 cefiderocol-related components (M1 – M21 determined to be metabolites, impurities or degradation products) were detected in plasma, urine or feces.
Clearance	5.18 (17.2%) L/hr [geometric mean (%CV)]
Half-life	2 to 3 hours
Metabolic pathway(s)	Metabolism of cefiderocol is minimal. The most predominant metabolite, pyrrolidine chlorobenzamide, which is a degradation product of cefiderocol, accounted for 4.7% of the plasma AUC for total radioactivity, while other minor metabolites accounted for <2% of the plasma AUC for total radioactivity.
Primary excretion pathways (% dose)	Cefiderocol is primarily eliminated by the kidneys. Approximately 90% of a cefiderocol dose is excreted unchanged in urine, with 2.8% of the administered dose excreted in feces.
	Intrinsic Factors and Specific Populations
Body weight	No clinically meaningful differences in cefiderocol PK based on body weight were observed.
Age	No clinically significant differences in the pharmacokinetics of cefiderocol were observed based on age (18 to 93 years of age).
Renal function	Cefiderocol exposures increased with reduced renal function. Dose adjustment is needed in patients with CLcr less than 60 mL/min. Dose adjustment is also needed in patients receiving continuous renal replacement therapy (CRRT). Increased cefiderocol clearance has been observed in patients with CLcr 120 mL/min or greater. Dose adjustment is needed in patients with CLcr 120 mL/min or greater.
Hepatic impairment	The effect of hepatic impairment on the pharmacokinetics of cefiderocol is not evaluated. However, hepatic impairment is not expected to alter the elimination of cefiderocol because cefiderocol is mainly excreted by the kidneys.

Characteristic	Drug Information
	Drug Interaction Liability (Drug as Perpetrator)
Inhibition/induction of metabolism	• No concentration- or no time-dependent inhibitions of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 by cefiderocol • No significant induction of CYP1A2, 2B6, and 3A4
Inhibition/induction of transporter systems	• No significant inhibitory effect on OATP1B1, MATE1, P-gp, BCRP, or BSEP. • In vitro study suggested potential for cefiderocol to inhibit OAT1, OAT3, OCT1, OCT2, OATP1B3, and MATE2-K transporters (IC_{50} values ranged from 141 to 4850 µmol/L). • The results from a clinical drug-drug interaction study indicate that cefiderocol had no clinically meaningful effects on the PK of furosemide (substrate for OAT1 and OAT3), metformin (for OCT1, OCT2, and MATE2-K), and rosuvastatin (for OATP1B3).

Abbreviations: AUC, area under the curve; BCRP, breast cancer resistance protein; BSEP, bile salt export pump; CL_{CR}, creatinine clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; CYP, cytochrome P450; HPLC/MS/MS, high-performance liquid chromatography-mass spectrometry; IC_{50}, half maximal inhibitory concentration; IV, intravenous; MATE, multidrug and toxin extrusion protein; MBq, megabecquerel; MIC, minimum inhibitory concentration; OAT, organic anion transporter; OCT, organic cation transporter; PD, pharmacodynamics; P-gp, P-glycoprotein; PK, pharmacokinetics; q8h, every 8 hours; TQT, thorough QT

5.1. Nonclinical Assessment of Potential Effectiveness

In Vitro Activity

Cefiderocol has in vitro activity against several gram-negative pathogens including Enterobacterales and nonfermenting bacteria such as *P. aeruginosa*, *A. baumannii*, and *S. maltophilia*. Cefiderocol does not have any clinically relevant activity against gram-positive bacteria and anaerobic bacteria. The cefiderocol MIC required to inhibit 90% of tested isolates (MIC_{90}) for Enterobacterales, *P. aeruginosa*, *A. baumannii* complex, *B. cepacia* complex, and *S. maltophilia* in surveillance studies were 1, 0.5, 2, 0.25, and 0.5 mcg/mL, respectively (see Section 18 Table 71). The cefiderocol MIC_{90} values against meropenem-resistant Enterobacterales and *A. baumannii* were four- or eight-fold higher than those of meropenem-susceptible isolates. On the other hand, the cefiderocol MIC_{90} values for meropenem-resistant *P. aeruginosa* were similar to those of the meropenem-susceptible isolates (see Section 18, Table 72).

Cefiderocol demonstrated in vitro activity against certain Enterobacteriaceae genetically confirmed to contain the following: extended-spectrum β-lactamases (ESBLs; temoneira [TEM], sulfhydryl variable [SHV], cefotaximase [CTX-M], oxacillinase [OXA]); AmpC; AmpC-type ESBL (CMY); serine carbapenemases (such as *K. pneumoniae* carbapenemase [KPC], OXA-48); and metallo-carbapenemases (such as New Delhi metallo-β-lactamase [NDM] and Verona integron-encoded metallo-β-lactamase [VIM]). Cefiderocol demonstrated in vitro activity against certain *P. aeruginosa* genetically confirmed to contain VIM, imipenemase metallo-β-lactamase (IMP), Guiana extended-spectrum β-lactamase (GES), and AmpC, and against certain *A. baumannii* containing OXA-23, OXA-24/40, OXA-51, OXA-58, and AmpC. Cefiderocol has demonstrated in vitro activity against some *K. pneumoniae* isolates with OmpK35/36 porin deletion and some isolates of *P. aeruginosa* with outer membrane porin D (OprD) deletion. The activity of cefiderocol against efflux pump overexpressing strains isolates other than the *P. aeruginosa* multidrug efflux pump AB (MexAB)-OprM, MexCD-OprJ, MexEF-OprN, and MexXY-OprM cannot be concluded from the data provided (see Section 18).

In Vivo Activity

In a neutropenic murine thigh infection model using a humanized dose (2 grams every 8 hours), cefiderocol demonstrated 1 $\log_{10}$ reduction in bacterial burden against most *E. coli, K. pneumoniae, A. baumannii,* and *P. aeruginosa*, including some carbapenemase-producing isolates with cefiderocol MICs of ≤4 mcg/mL and *S. maltophilia* isolates with cefiderocol MICs of ≤0.5 mcg/mL (see Section 18).

In an immunocompetent rat pneumonia model, reduction in bacterial counts in the lungs of animals infected with *K. pneumoniae* with cefiderocol MICs ≤8 mcg/mL, *P. aeruginosa* with cefiderocol MICs ≤1 mcg/mL, and *A. baumannii* with cefiderocol MICs ≤2 mcg/mL was observed using humanized cefiderocol dose.

In an immunocompetent murine urinary tract infection (UTI) model, cefiderocol reduced bacterial counts in the kidneys of mice infected with *E. coli, K. pneumoniae,* and *P. aeruginosa* isolates with MICs ≤1 mcg/mL. In an immunocompromised murine systemic infection model, cefiderocol increased survival in mice infected with *Enterobacter cloacae, S. maltophilia,* and *B. cepacia* isolates with MICs ≤0.5 mcg/mL compared to survival in untreated mice. In an immunocompetent murine systemic infection model, cefiderocol increased survival in mice infected with *Serratia marcescens* and *P. aeruginosa* isolates with MICs ≤1 mcg/mL compared to that in untreated mice.

6. Evidence of Benefit (Assessment of Efficacy)

6.1. Assessment of Dose and Potential Effectiveness

The following proposed dosing regimen of cefiderocol is acceptable for the general patient population with HABP/VABP:

- Cefiderocol 2 grams administered every 8 hours by intravenous (IV) infusion over 3 hours

The same dose regimen has been approved for the general patient population with cUTI including pyelonephritis.

The proposed dose regimen and the equivalent dose with adjustments for renal function [based on creatinine clearance (CLcr)] was evaluated in the Phase 3 trial APEKS-NP and compared to meropenem (2 grams every 8 hours infused over 3 hours). The APEKS-NP study met its primary endpoint by demonstrating that cefiderocol was noninferior to meropenem for the primary efficacy endpoint (Day 14 all-cause mortality in the mITT population) because the upper bound of the confidence interval of the difference in death rates at day 14 is less than the noninferiority margin (8.2% versus 12.5%).

Monte-Carlo simulations of cefiderocol PK at the proposed dosing regimens using the data from all clinical studies were performed to calculate the probability of PK/PD target attainments (PTA) with the target values of 75%, 90%, and 100% of time for which free drug concentration

in plasma exceeds MIC over dosing interval ($fT > MIC$) across an MIC range of 0.25 to 16 µg/mL. Monte-Carlo simulations were also performed to calculate PTA with free drug concentration in epithelial lining fluid (ELF) ($\%fT > MIC_{ELF}$). The results showed that PTA based on plasma concentrations (Table 6) and ELF concentrations (Table 7) were >90% at MIC of up to 4 µg/mL regardless of infection, suggesting that the proposed cefiderocol dosing regimen would provide adequate exposure of cefiderocol in patients with cUTI/AUP, BSI/sepsis, or HABP/VABP against bacteria with MIC ≤4 µg/mL.

Table 6. Overall Probability of Target Attainment (PTA) for 75%, 90%, and 100% *f*T > MIC in Plasma in Simulated Patients With Weighting for Distribution of CLcr in Phase 3 Studies

$\%fT_{>MIC}$ / $\%fT_{>MIC,ELF}$	PK variable	Infection disease	MIC (µg/mL)						
			0.25	0.5	1	2	4	8	16
75%	Plasma	HABP/VABP/HCABP	100	100	100	100	99.9	96.0	72.8
		BSI/sepsis	100	100	100	100	99.6	93.6	61.5
		cUTI/AUP[a]	100	100	100	100	100	98.1	79.9
90%	Plasma	HABP/VABP/HCABP	100	100	100	99.9	98.5	89.4	55.4
		BSI/sepsis	100	100	100	99.9	97.4	84.6	45.1
		cUTI/AUP[a]	100	100	100	100	99.4	94.2	69.4
100%	Plasma	HABP/VABP/HCABP	100	100	100	99.9	97.7	86.1	50.1
		BSI/sepsis	100	100	100	99.4	95.8	80.9	40.6
		cUTI/AUP[a]	100	100	100	100	98.9	92.9	64.8

AUP = acute uncomplicated pyelonephritis; BSI = bloodstream infection; cUTI = complicated urinary tract infection; ESRD = end-stage renal disease; HABP = hospital acquired bacterial pneumonia; HCABP = healthcare associated bacterial pneumonia; MIC = minimum inhibitory concentration; q6h = every 6 hours; q8h = every 8 hours; q12h = every 12 hours; VABP = ventilator-associated bacterial pneumonia
1000 simulated patients in each simulation scenario.

The simulations were performed using the final model. PK steady state was assumed. PTA is shown in percent (%).

Creatinine clearance for 1000 simulated patients was assumed according to the distribution of CrCl in the Phase 3 CREDIBLE-CR and APEKS-NP studies;

CrCl > 120 mL/min: 20.3%, CrCl 90 to < 120 mL/min: 15.0%, CrCl 60 to < 90 mL/min: 24.6%, CrCl 30 to < 60 mL/min: 32.6%, CrCl 15 to < 30 mL/min: 4.8%, CrCl 5 to < 15 mL/min: 2.7%.

Body weight was assumed to be log-normal distributed with mean of 72.6 kg and CV of 30%.

Albumin was assumed to be log-normal distributed with mean of 2.8 g/dL and CV of 30%.

a Simulated using the parameters for cUTI patients in the CREDIBLE-CR study.

Source: Adapted from Table 2.7.2-12 from 2.7.2 Summary of Clinical Pharmacology – HABP/VABP

Table 7. Overall PTA for 75%, 90%, and 100% *f*T > MIC_{ELF} in Epithelial Lining Fluid (ELF) in Simulated Patients With Weighting for Distribution of CLcr in Phase 3 Studies

Probability of target attainment for target $\%fT_{>MIC,ELF}$							
	MIC (µg/mL)						
Target	0.25	0.5	1	2	4	8	16
75% $fT_{>MIC,ELF}$	100	100	100	99.8	93.1	59.5	14.4
90% $fT_{>MIC,ELF}$	100	100	100	99.7	92.4	59.3	14.4
100% $fT_{>MIC,ELF}$	100	100	100	99.7	92.4	59.3	14.4

PK steady state was assumed. PTA is shown in percent (%).

1000 simulated patients in each simulation scenario.

Creatinine clearance for 1000 simulated patients was assumed according to the distribution of CrCL in the phase 3 CREDIBLE-CR and APEKS-NP studies;

CrCL ≥ 120 mL/min: 20.3%, CrCL 90 to < 120 mL/min: 15.0%, CrCL 60 to < 90 mL/min: 24.6%, CrCL 30 to < 60 mL/min: 32.6%, CrCL 15 to < 30 mL/min: 4.8%, CrCL 5 to < 15 mL/min: 2.7%.

Body weight was assumed to be log-normal distributed with mean of 72.6 kg and CV of 30%.

Albumin was assumed to be log-normal distributed with mean of 2.8 g/dL and CV of 30% .

Source: Table 4 from the Applicant's study report of s-649266-cpk-005

6.2. Design of Clinical Trials Intended to Demonstrate Benefit to Patients

6.2.1. Trial Design

Results from the APEKS-NP trial served as the basis of the benefit evaluation. This trial was largely designed in accordance with recommendations given in FDA's guidance for industry *Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment* (June 2020). The guidance states that randomized, double-blind, active-controlled, NI trials are appropriate for evaluating the efficacy and safety of an experimental treatment. Appropriate primary endpoints include ACM assessed at a fixed time point between day 14 and day 28 inclusive. For NI margins, the guidance set the M1 margin (i.e., improvement in survival rate due to use of the active control treatment instead of placebo) at 20% and recommended an M2 margin of 10% (i.e., the experimental treatment is considered noninferior to the active control if its survival rate is within 10% of the active control rate). As discussed below, the trial's main divergence from guidance recommendations consisted in setting the M2 margin at 12.5% rather than 10%.

The APEKS-NP trial was a phase 3, randomized, double-blind, multisite, NI trial with an experimental cefiderocol arm and an active control meropenem arm. Its principal aim with regard to efficacy was to evaluate whether cefiderocol is noninferior to meropenem as a treatment for nosocomial pneumonia (NP) caused by gram-negative bacteria. Both treatments were administered intravenously for an anticipated 7 to 14 days, with possible extension up to 21 days. Linezolid was administered in both arms to provide coverage of methicillin-resistant *S. aureus* and in the cefiderocol arm to provide coverage for gram-positive bacteria. Three hundred subjects were randomized (148 to cefiderocol, 152 to meropenem) at 77 sites. Randomization was stratified by infection type (HABP, VABP, and HCABP) and by Acute Physiology and Chronic Health Evaluation (APACHE) II score at baseline (≤15 versus ≥16)

The trial employed a group sequential design, with interim analyses planned for when about 50 and then 150 subjects had been randomized and completed treatment and follow-up. See Section 15 for additional details.

Clinical and microbiological outcomes were assessed at the following occasions:

- Early assessment (EA): day 3 or 4
- End of treatment (EOT): end of last infusion (same calendar day or +1 day)
- Test-of-cure (TOC): EOT +7 days (+/- 2 days)
- Follow-up (FU): EOT +14 days (+/- 3 days)

Further details are provided in Section 14.

6.2.2. Eligibility Criteria

Section 15 gives the full sets of inclusion and exclusion criteria.

Key inclusion criteria included: age 18 years or greater; diagnosis of HABP, VABP, or HCABP; chest X-ray showing the presence of new or progressive infiltrate(s) suggestive of bacterial pneumonia; and suspected gram-negative infection involving the lower respiratory tract.

Key exclusion criteria included: known or suspected community-acquired bacterial pneumonia, atypical pneumonia, viral pneumonia, or chemical pneumonia; hypersensitivity to cephalosporins or to carbapenems; gram-negative infection caused by carbapenem-resistant pathogen; and an APACHE II score >35.

6.2.3. Statistical Analysis Plan

The Applicant and the review division agreed on the APEKS-NP statistical analysis plan prior to the trial completion. Of particular note, in an April 25, 2016 letter to the Applicant, under IND 116787, the division wrote, "Your proposal to use a noninferiority (NI) margin of 12.5% will be adequate to support approval with a limited use statement." Note that this NI margin still maintained an appreciable proportion of the guidance's M1 value of 20%.

Efficacy Endpoints

- Primary: ACM at day 14 (since first administration of study drug).
- Key secondary:
  - Microbiological outcome at TOC: eradication of all baseline gram-negative pathogens versus persistence of any such pathogens. If it was not possible to obtain a clinical culture and the subject had a successful clinical outcome, then the response was presumed to be eradication. This was only defined for subjects with a gram-negative pathogen detected at baseline.
  - Clinical outcome at TOC: per investigator assessment, cure (resolution or substantial improvement in baseline signs and symptoms of pneumonia such that no antibacterial therapy needed) versus failure (persistence or worsening of baseline signs and symptoms and/or new signs/symptoms or death).
- Other secondary endpoints included: ACM at day 28 and end of study (EOS). Microbiological outcome and clinical outcome at EA, EOT, and FU.

Primary Population

The primary analysis population was the mITT population. The full intention-to-treat (ITT) population included all randomized subjects who received at least one dose of study drug (cefiderocol 148, meropenem 150, total 298). The mITT population included all ITT subjects who met either of the following (cefiderocol 145, meropenem 147, total 292, 98.0% of the ITT population):

- Evidence of a gram-negative infection of lower respiratory tract.
- Evidence of infection of lower respiratory tract but culture or other tests didn't provide a microbiological diagnosis.

Significance Levels for Testing

The two-sided alpha level used was 0.0496 and was adjusted for the two interim analyses that were conducted. The study did not stop early. Correspondingly, 95.04% (rather than 95%) confidence intervals (CIs) were reported.

Testing Noninferiority of Cefiderocol to Meropenem Regarding the Primary Endpoint

An NI margin of 12.5% was used. This meant that cefiderocol was considered noninferior to meropenem if the difference between its ACM rate at day 14 and the corresponding meropenem rate was less than 12.5%. Otherwise, cefiderocol was not considered noninferior to meropenem. The Cochran-Mantel-Haenszel stratum-weighted estimator (described in Section 15) was used to perform the test and construct CIs.

Testing and Analyzing Secondary Endpoints

If statistical significance was achieved for the primary NI test, then (i) the superiority of cefiderocol to meropenem regarding microbiological outcome at TOC was tested. If significant, then (ii) the superiority regarding clinical outcome at TOC was tested. Then, if significant, (iii) the superiority regarding ACM at day 14 was tested. If statistical significance was not achieved at this point in the testing sequence, all testing was halted and subsequent secondary efficacy analyses were considered exploratory.

Additional statistical details are provided in Section 16.

6.3. Results of Analyses of Clinical Trials/Studies Intended to Demonstrate Benefit to Patients

The following table examines between-arm balance on demographic and baseline clinical status characteristics in the ITT population. The ITT population was identical to the safety population and contained six more subjects than the mITT population (298 total subjects to 292 total subjects [cefiderocol 145, meropenem 147]; mITT population included 98.0% of the ITT population). The six subjects in the ITT population who were not in the mITT population did not have evidence of a lower respiratory tract infection. The table results were similar to results for the mITT population.

Table 8. Baseline Demographic and Clinical Characteristics, ITT Population, APEKS-NP Trial

Characteristic	Cefiderocol N=148	Meropenem N=150	Total N=298
Sex			
Male	101 (68.2)	104 (69.3)	205 (68.8)
Female	47 (31.8)	46 (30.7)	93 (31.2)
Age, years			
Mean (SD)	64.7 (14.5)	65.6 (15.1)	65.2 (14.8)
Median (min, max)	67.0 (18.0, 91.0)	68.0 (20.0, 94.0)	67.0 (18.0, 94.0)
Age group			
≥65 years	83 (56.1)	92 (61.3)	175 (58.7)
<65 years	65 (43.9)	58 (38.7)	123 (41.3)
<75 years	108 (73.0)	103 (68.7)	211 (70.8)
≥75 years	40 (27.0)	47 (31.3)	87 (29.2)
Ethnicity			
Not Hispanic or Latino	140 (94.6)	139 (92.7)	279 (93.6)
Not reported	4 (2.7)	8 (5.3)	12 (4.0)
Hispanic or Latino	4 (2.7)	3 (2.0)	7 (2.3)

Characteristic	Cefiderocol N=148	Meropenem N=150	Total N=298
Race			
White	102 (68.9)	100 (66.7)	202 (67.8)
Asian	44 (29.7)	44 (29.3)	88 (29.5)
Other	2 (1.4)	4 (2.7)	6 (2.0)
Black or African American	0	1 (0.7)	1 (0.3)
Region			
Europe	99 (66.9)	100 (66.7)	199 (66.8)
Asia-Pacific	43 (29.1)	44 (29.3)	87 (29.2)
North America	6 (4.1)	6 (4.0)	12 (4.0)
Clinical diagnosis as collected			
VABP	60 (40.5)	65 (43.3)	125 (41.9)
HABP	60 (40.5)	61 (40.7)	121 (40.6)
HCABP	28 (18.9)	24 (16.0)	52 (17.4)
Ventilation status at randomization			
Ventilated	91 (61.5)	87 (58.0)	178 (59.7)
Nonventilated	57 (38.5)	63 (42.0)	120 (40.3)
Ventilation status at randomization[a]			
Ventilated	91 (61.5)	87 (58.0)	178 (59.7)
VABP	59 (39.9)	64 (42.7)	123 (41.3)
HABP	22 (14.9)	21 (14)	43 (14.4)
HCABP	10 (6.8)	2 (1.3)	12 (4)
Nonventilated	57 (38.5)	63 (42.0)	120 (40.3)
HABP	38 (25.7)	40 (26.7)	78 (26.2)
HCABP	18 (12.2)	22 (14.7)	40 (13.4)
VABP	1 (0.7)	1 (0.7)	2 (0.7)
Creatinine clearance renal grading group			
>120 ml/min	22 (14.9)	26 (17.3)	48 (16.1)
>80-120 ml/min	33 (22.3)	35 (23.3)	68 (22.8)
>50-80 ml/min	44 (29.7)	37 (24.7)	81 (27.2)
30-50 ml/min	29 (19.6)	32 (21.3)	61 (20.5)
<30 ml/min	20 (13.5)	20 (13.3)	40 (13.4)
Creatinine clearance			
Mean (SD)	77.8 (55.1)	82.1 (56.2)	79.9 (55.6)
Median (min, max)	65.2 (4.7, 305.8)	68.9 (7.4, 281.2)	67.7 (4.7, 305.8)
Empiric treatment failure status			
Yes	49 (33.1)	48 (32.0)	97 (32.6)
No	99 (66.9)	102 (68.0)	201 (67.4)
Prior therapy			
Yes	107 (72.3)	103 (68.7)	210 (70.5)
No	41 (27.7)	47 (31.3)	88 (29.5)
CPIS category			
<6	74 (50.0)	91 (60.7)	165 (55.4)
6-7	60 (40.5)	40 (26.7)	100 (33.6)
7-9	12 (8.1)	16 (10.7)	28 (9.4)
>9	2 (1.4)	3 (2.0)	5 (1.7)
ICU admission flag			
Yes	103 (69.6)	99 (66.0)	202 (67.8)
No	45 (30.4)	51 (34.0)	96 (32.2)
Severity of disease			
Mild	4 (2.7)	7 (4.7)	11 (3.7)
Moderate	73 (49.3)	93 (62.0)	166 (55.7)
Severe	71 (48.0)	50 (33.3)	121 (40.6)

Characteristic	Cefiderocol N=148	Meropenem N=150	Total N=298
SOFA score (ventilated)			
Mean (SD)	6.1 (2.8)	6.3 (3.1)	6.2 (3.0)
Median (min, max)	6.0 (1,13)	6.0 (0,16)	
SOFA score (nonventilated)			
Mean (SD)	2.8 (2.5)	2.7 (2.5)	2.7 (2.78)
Median (min, max)	2 (0,12)	2 (0,7)	2 (0,12)
Total APACHE II score as collected			
Mean (SD)	16.1 (6.1)	16.3 (6.9)	16.2 (6.5)
Median (min, max)	15.0 (3.0, 34.0)	15.0 (4.0, 35.0)	15.0 (3.0, 35.0)

Source: adsl.xpt; Software: Python
All values are expressed as n (%) unless specified otherwise.
[a] Ventilation status by clinical diagnosis.
Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CPIS, clinical pulmonary infection score; HABP, hospital-acquired bacterial pneumonia; HCABP, healthcare-associated bacterial pneumonia; ICU, intensive care unit; ITT, intention-to-treat; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; VABP, ventilator-associated bacterial pneumonia

Table 9 examines between-arm balance on baseline microbiological characteristics in the ITT population. Again, results were similar for the mITT population.

Table 9. Baseline Microbiology Characteristics, ITT Population, APEKS-NP Trial

Characteristic	Cefiderocol N=148	Meropenem N=150	Total N=298
Baseline pathogen type			
Gram-negative pathogens	113 (76.4)	105 (70.0)	218 (73.2)
Mixed pathogens	11 (7.4)	22 (14.7)	33 (11.1)
Culture negative	12 (8.1)	8 (5.3)	20 (6.7)
No pathogen	3 (2.0)	5 (3.3)	8 (2.7)
No respiratory sample	3 (2.0)	4 (2.7)	7 (2.3)
Gram-positive pathogens	3 (2.0)	3 (2.0)	6 (2.0)
Fungal pathogens	1 (0.7)	1 (0.7)	2 (0.7)
Missing	2 (1.4)	2 (1.3)	4 (1.3)
Top 5 baseline gram-negative pathogens			
Klebsiella pneumoniae	48 (32.4)	44 (29.3)	92 (30.9)
Pseudomonas aeruginosa	24 (16.2)	24 (16.0)	48 (16.1)
Acinetobacter baumannii	23 (15.5)	24 (16.0)	47 (15.8)
Escherichia coli	19 (12.8)	22 (14.7)	41 (13.8)
Enterobacter cloacae	7 (4.7)	8 (5.3)	15 (5.0)
Baseline blood culture status			
Negative	124 (83.8)	118 (78.7)	242 (81.2)
Positive	13 (8.8)	16 (10.7)	124 (50.0)
Gram-negative	8 (5.4)	10 (6.7)	18 (6.0)
Gram-positive	5 (3.4)	6 (4.0)	11(3.7)
Blood culture not done	11 (7.4)	16 (10.7)	27 (9.1)
Baseline gram-negative pathogens number			
0	24 (16.2)	23 (15.3)	47 (15.8)
1	95 (64.2)	96 (64.0)	191 (64.1)
2	25 (16.9)	26 (17.3)	51 (17.1)
3	2 (1.4)	4 (2.7)	6 (2.0)
>3	2 (1.4)	1 (0.7)	3 (1.0)

Characteristic	Cefiderocol N=148	Meropenem N=150	Total N=298
Gram-negative bacteremia pathogens			
Klebsiella pneumoniae	3 (2.0)	4 (2.7)	7 (2.3)
Serratia marcescens	2 (1.4)	1 (0.7)	3 (1.0)
Burkholderia cenocepacia	1 (0.7)	1 (0.7)	2 (0.7)
Acinetobacter anitratus; Escherichia coli	1 (0.7)	0	1 (0.3)
Acinetobacter baumannii	1 (0.7)	0	1 (0.3)
Enterobacter cloacae	0	1	1 (0.3)
Escherichia coli	0	1 (0.7)	1 (0.3)
Providencia stuartii	0	1 (0.7)	1 (0.3)
Pseudomonas aeruginosa	0	1 (0.7)	1 (0.3)

Source: adsl.xpt; Software: Python
All values are expressed as n (%) unless specified otherwise.
Abbreviations: ITT, intention-to-treat

In addition to the baseline characteristics above, the frequency of underlying medical conditions were similar between the treatment groups, as noted in Table 10 below.

Table 10. Medical History in ≥10% of Patients in Either Treatment Group, ITT Population, APEKS-NP Trial

Dictionary-Derived Term	Cefiderocol N=148	Meropenem N=150
Anemia	28 (18.9)	27 (18.0)
Atrial fibrillation	33 (22.3)	40 (26.7)
Cardiac failure, chronic	14 (9.5)	17 (11.3)
Coronary artery disease	24 (16.2)	20 (13.3)
Myocardial ischemia	18 (12.2)	26 (17.3)
Pneumonia	16 (10.8)	22 (14.7)
Diabetes mellitus	22 (14.9)	21 (14.0)
Hypokalemia	28 (18.9)	25 (16.7)
Type 2 diabetes mellitus	23 (15.5)	14 (9.3)
Chronic kidney disease	19 (12.8)	17 (11.3)
Acute respiratory failure	18 (12.2)	15 (10.0)
Chronic obstructive pulmonary disease	41 (27.7)	31 (20.7)
Hypertension	96 (64.9)	103 (68.7)

Source: Reviewer Table, created in JMP Clinical
All values are expressed as n (%) unless specified otherwise
Abbreviations: ITT, intention-to-treat

The frequency of diabetes mellitus (DM) and type 2 diabetes mellitus was 30% and 23% in the cefiderocol and meropenem groups, respectively. Of note, tobacco use was reported in 1.4% and 2.7% in the cefiderocol and meropenem groups, respectively.

Of 357 patients screened, 57 were considered screening failures, and 300 were randomized. Two patients in the meropenem group were not treated, and thus, the total number of patients treated was 298 (n=148 in cefiderocol and 150 in the meropenem group). A slightly higher number of patients discontinued the study and received fewer than 7 days of study treatment in the cefiderocol group than in the meropenem group; the majority were due to deaths and treatment-emergent AEs (TEAEs).

Table 11. Patient Disposition, ITT Population, APEKS-NP Trial

Disposition Outcome	Cefiderocol N=148	Meropenem N=152	Total N=300
Subjects randomized	148 (100.0)	152 (100.0)	300 (100.0)
Subjects randomized but not treated	0	2 (1.3)	2 (0.7)
Subjects treated	148 (100.0)	150 (98.7)	298 (99.3)
Completed study	106 (71.6)	112 (73.7)	218 (72.7)
Discontinued study	42 (28.4)	40 (26.3)	82 (27.3)
Adverse event	0	1 (0.7)	1 (0.3)
Lack of efficacy	1 (0.7)	0	1 (0.3)
Withdrawal by subject	2 (1.4)	3 (2.0)	5 (1.7)
Protocol deviation	0	0	0
Recovery	0	1 (0.7)	1 (0.3)
Lost to follow-up	0	0	0
Death	39 (26.4)	34 (22.4)	73 (24.3)
Other	0	1 (0.7)	1 (0.3)
Received less than 7 days of study treatment	18 (12.2)	15 (9.9)	33 (11.0)
Adverse event	10 (55.6)	10 (66.7)	20 (6.7)
Lack of efficacy	2 (11.1)	1 (6.7)	3 (1.0)
Withdrawal by subject	1 (5.6)	0	1 (0.3)
Death	4 (22.2)	1 (6.7)	5 (1.6)
Meropenem resistant	0	2 (13.3)	3 (1.0)
Clinical cure	0	1 (6.7)	1 (0.3)
Palliative care	1 (3.6)	0	1 (0.3)

Source: Applicant
All values are expressed as n (%) unless specified otherwise
Abbreviation: ITT, intention-to-treat; N, number of subjects; n, number of subjects with at least one event.

Table 12 examines length of treatment in days in the mITT population. The intended length of treatment for both arms was 7 to 14 days, with treatment up to 21 days allowed if clinically indicated. In the meropenem arm, 73.5% of subjects received the intended duration of treatment, while 66.2% of subjects did in the cefiderocol arm. Somewhat larger proportions of subjects in the cefiderocol arm received less than the intended duration and received more than the intended duration than in the meropenem arm.

Table 12. Length of Treatment in Days in the mITT Population, APEKS-NP Trial

Length of Treatment	Cefiderocol	Meropenem
Median	10	9
<7 days	17 (11.7)	14 (9.5)
7-14 days	96 (66.2)	108 (73.5)
15-21 days	30 (20.7)	24 (16.3)
≥22 days	2 (1.4)	1 (0.7)

Source: adsl.xpt.
All values are expressed as n (%) unless specified otherwise
Notes. The mITT population included 292 subjects: the cefiderocol arm included 145 subjects and the meropenem arm included 147 subjects.
Abbreviations: mITT, modified intention-to-treat

Table 13 presents the analyses of ACM at day 14, the primary endpoint, and ACM at day 28. Because the upper bound of the CI for the difference in death rates at day 14 is less than the NI margin (8.2% versus 12.5%), the NI of cefiderocol to meropenem is demonstrated with respect to the primary endpoint. Note that the observed meropenem mortality rate of 11.6% at day 14 is close to the rate of 10% the Applicant assumed in its sample size calculations.

Table 13. All-Cause Mortality at Days 14 and 28 in the mITT Population, APEKS-NP Trial

Endpoint	Cefiderocol	Meropenem	Difference
ACM at day 14	18/145 (12.4)	17/146 (11.6)	0.8 (-6.6, 8.2)[a]
ACM at day 28	30/143 (21.0)	30/146 (20.5)	0.5 (-8.7, 9.8)

Source: adsl.xpt.
All values are expressed as n/N' (%) except those in Difference column, which are expressed as % (CI).
Notes. Estimates of difference in mortality rates and construction of confidence intervals derived from use of Cochran-Mantel-Haenszel (CMH) stratum-weighted estimator, with strata based on Apache II score at randomization (≤15 vs. ≥16). Per Applicant, subjects with unknown survival status are not included in analyses. 95.04% (rather than 95%) confidence intervals are reported, per adjustment in alpha level due to performance of multiple interim analyses.
The mITT population included 292 subjects: the cefiderocol arm included 145 subjects and the meropenem arm included 147 subjects.
[a] The null hypothesis that cefiderocol is inferior to meropenem (with respect to the 12.5 noninferiority margin) was rejected, 2-sided p =.002. No hypothesis tests were performed with respect to ACM at day 28.
Abbreviations: ACM, all-cause mortality; CI, confidence interval; mITT, modified intention-to-treat; n, number of subjects who died by the indicated timepoint; N', number of subjects with known survival status at the indicated timepoint

Sensitivity analyses of the ACM endpoints are presented in Section 16 and are consistent with the results presented so far. As also discussed in that section, the extent of missing data was negligible and had little impact on results. Section 16 also reports results of subgroup analyses of ACM at 14 days.

Table 14 presents the results of analyses of the two key secondary endpoints, microbiological outcome at TOC and clinical outcome at TOC. Microbiological outcome endpoints are only defined for subjects who had gram-negative pathogens detected at baseline. Of the 145 mITT subjects in the cefiderocol arm, 124 (85.5%) had such pathogens detected at baseline; of the 147 mITT subjects in the meropenem arm, 127 (86.4%) had such pathogens detected at baseline.

As discussed above, because cefiderocol NI was demonstrated with regard to the primary endpoint, the superiority/nonsuperiority of cefiderocol versus meropenem was tested with regard to the first key secondary endpoint, microbiological outcome at TOC. This test yielded a statistically nonsignificant result, which, per the Applicant's testing scheme, meant that no further hypothesis testing was to be conducted and all subsequent statistical analyses were to be considered exploratory in nature. The table shows that, for both key secondary endpoints, the treatment success rates for the two arms were similar, with slightly lower rates for cefiderocol.

Table 14. Key Secondary Endpoints at Test of Cure in the mITT Population, APEKS-NP Trial

Endpoint	Cefiderocol	Meropenem	Difference
Microbiological eradication	59/124 (47.6)	61/127 (48.0)	-1.4 (-13.5, 10.8)[a]
Clinical cure	94/145 (64.8)	98/147 (66.7)	-2.0 (-12.5, 8.5)

Source: adsl.xpt; admbo.xpt; adclo.xpt.
All values are expressed as n/N' (%) except those in the Difference column, which are expressed as % (CI).
Notes. The test-of-cure assessment occurred 7 days (+/- 2) after the end of treatment. Estimates of difference in mortality rates and construction of confidence intervals derived from use of Cochran-Mantel-Haenszel (CMH) stratum-weighted estimator, where subjects with unknown microbiological/clinical status are considered treatment failures. 95.04% (rather than 95%) confidence intervals are reported, due to adjustment in alpha level due to performance of multiple interim analyses.
The mITT population included 292 subjects: the cefiderocol arm included 145 subjects and the meropenem arm included 147 subjects.
Abbreviations: CI, confidence interval; mITT, modified intention-to-treat; n, number of subjects who were treatment successes; N', number of subjects in arm for whom the endpoint is defined;

See Section 16 for results of analyses of microbiological outcome and clinical outcome at other time points. These results and the subgroup analysis results are consistent with the results presented in this section.

6.4. Review Issues Relevant to the Evaluation of Benefit

6.4.1. Important Review Issue #1 Relevant to Benefit

Issue

Confounding of treatment effect by prior and concomitant antibacterial drugs

Background

Since there were a limited number of subjects in the APEKS-NP trial, the quality of clinical data was an important review issue. Patients who were included in the trial due to failed empiric therapy under criterion 9(b)(ii), or protocol violations resulting in the administration of prior and and/or concomitant gram-negative antibacterial therapy may have had the potential to reduce the assay sensitivity in this NI trial and artificially drive results in the two groups toward similar outcomes.

Assessment

The following sensitivity analyses were performed to isolate patient subpopulation(s) in the mITT population who would best demonstrate the treatment effect of cefiderocol relative to meropenem with minimal confounding: 1) subjects who received 24 hours or less of effective prior antibacterial therapy (during the previous 72 hours prior to randomization) and less than 72 hours of effective concomitant antibacterial therapy; 2) subjects who received 24 hours or less of effective prior antibacterial therapy (during the previous 72 hours prior to randomization); 3) subjects who received less than 72 hours of effective concomitant antibacterial therapy.

Potentially effective antibacterial therapy was defined as IV, oral, or inhaled therapy which had activity against gram-negative bacteria. If the pathogen was intrinsically resistant or resistant per the MIC or surrogate MIC, the patient was not excluded. If MIC results or the concomitant or prior antibacterial drug identification were not available, the pathogen was assumed to be susceptible. Patients were excluded if they had greater than or equal to 72 hours of concomitant antibacterial therapy from time to first dose of study drug up to but not including the day of TOC. This review was conducted by the Applicant upon request from the Division prior to NDA submission.

Table 15. Sensitivity Analysis of All-Cause Mortality at Day 14 After Start of Study Treatment Excluding Subjects With Potentially Effective Antibacterial Therapy[a]

Patients Who Did Not Receive the Following Potentially Effective Antibacterial Therapy	Cefiderocol N=145 n/N' (%)	Meropenem N=147 n/N' (%)	Treatment Comparison[b] Difference (%)	95% CI[c]
Prior or concomitant therapy	15/126 (11.9)	16/128 (12.5)	-0.4	(-8.3, 7.6)
Prior therapy	15/137 (10.9)	16/138 (11.6)	-0.5	(-7.9, 6.9)
Concomitant therapy	18/134 (13.4)	17/135 (12.6)	1.0	(-7.0, 8.9)

Source: Adapted from Applicant's response to IR dated February 24, 2020
Day 14 ACM = all-cause mortality at Day 14 since first infusion of study drug
[a] Effective prior antibacterial therapy include systemic antibacterial therapy which have activity for gram-negative bacteria and were given for >24 hours during the 72 hours prior to first dose of study drug and effective concomitant antibacterial therapy include systemic antibacterial therapy which has activity for gram-negative bacteria and were taken for >=72 hours any time after first infusion of study drug until TOC.
[b] Treatment difference (cefiderocol minus meropenem) is the adjusted estimate of the difference in the all-cause mortality rate at Day 14 between the 2 treatment arms based on Cochran-Mantel Haenszel weights using APACHE II score (≤15 and ≥16) as the stratification factor.
[c] The 95% CI (2-sided) is based on a stratified analysis using Cochran-Mantel Haenszel weights using APACHE II score (≤15 and ≥16) as the stratification factor. The CI is calculated using a normal approximation to the difference between 2 binomial proportions (Wald method).
Abbreviations: ACM, all-cause mortality; APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; N, number of subjects in the analysis set; n, number of subjects who died; N', number of subjects with known survival status; TOC, test of cure

Conclusions

As displayed in Table 15, these analyses are consistent with the overall study analyses. In the subgroups of patients who did not receive effective prior, concomitant, or either prior or concomitant antibacterial therapy, NI was demonstrated in day 14 ACM between the cefiderocol and meropenem groups.

6.4.2. Important Review Issue #2 Relevant to Benefit

Issue

Does meropenem nonsusceptibility contribute to the demonstration above that cefiderocol is noninferior to meropenem?

Discussion

In the preceding discussion of benefit, statistical analysis of the primary endpoint, ACM at 14 days, showed that cefiderocol is noninferior to meropenem with respect to this endpoint. In theory, this result could largely be driven by meropenem-nonsusceptibility, i.e., by the possibility that a significant proportion of subjects in the meropenem arm were unlikely to benefit from meropenem. This is concerning in an NI trial because it is important that the active control have its expected activity in order to make the NI conclusions meaningful. We examine this possibility by redoing key efficacy analyses with restrictions for subjects with baseline pathogens known to be susceptible to meropenem. Here, a subject is included in the analysis if, for all gram-negative pathogens detected at baseline, the baseline meropenem MIC is ≤8 mcg/mL. If the baseline meropenem MIC is greater than 8 mcg/mL or is missing for at least one gram-negative pathogen, then the subject is excluded from the analyses reported below.

Assessment

Of the 292 subjects in the mITT population, 172 (58.9%) were known to be susceptible to meropenem. The cefiderocol arm included 89 such subjects, and the meropenem arm included 83 subjects.

The following table (Table 16) presents the results of key efficacy analyses when restricted to subjects known to be susceptible to meropenem. The key takeaway is that the NI of cefiderocol to meropenem, with regard to the primary endpoint, is again demonstrated, as the relevant CI upper bound of 7.4% is less than the NI margin of 12.5%. For all three endpoints reported in the table, the estimated differences in rates slightly favor cefiderocol.

Table 16. Key Endpoint Analyses Restricted to Subjects With Known Meropenem Susceptibility, APEKS-NP Trial

Endpoint	Cefiderocol	Meropenem	Difference
ACM at day 14	9/89 (10.1)	10/82 (12.2)	-2.1 (-11.6, 7.4)
ACM at day 28	16/87 (18.4)	16/82 (19.5)	-1.1 (-13.0, 10.7)
Clinical outcome at TOC	60/89 (67.4)	53/83 (63.9)	3.6 (-10.7, 17.8)

Source: adsl.xpt, adclo.xpt, adms.xpt.
All values are expressed as n/N' (%) except those in the Difference column, which are expressed as % (CI).
Notes. Estimates of difference in mortality/clinical cure rates are equal to differences in rates per arm. Per Applicant, subjects with unknown survival status are not included in ACM analyses and subjects with indeterminate clinical outcome values are considered clinical failures. Wald confidence intervals are computed. 95.04% (rather than 95%) confidence intervals are reported, per adjustment in alpha level due to performance of multiple interim analyses.
Abbreviations: ACM, all-cause mortality; CI, confidence interval; n, number of subjects who died by/experienced clinical cure at the indicated timepoint; N', number of subjects with known survival status at the indicated timepoint (ACM rows), N', all subjects with known susceptibility (clinical outcome row); TOC, test-of-cure

The following tables (Table 17, Table 18) examine outcomes on three key endpoints by baseline pathogen. These tables also differ from the preceding table by restricting focus to subjects known to be susceptible for at least one baseline gram-negative pathogen rather than to subjects known to be susceptible to all of their baseline pathogens. Hence, the tables draw from a wider set of subjects than the preceding table. Each table row reports the outcomes of subjects known to be susceptible to the row's pathogen. The per-pathogen subsamples are not large, so strong signals would be hard to discern, but the tables provide no evidence of the inferiority of cefiderocol to meropenem with respect to the key endpoints.

Table 17. All-Cause Mortality by Baseline Pathogen, Restricted to Baseline Pathogens With Meropenem Susceptibility, APEKS-NP Trial

	Day 14 All-Cause Mortality		Day 28 All-Cause Mortality	
Baseline Group or Pathogen	Fetroja	Meropenem	Fetroja	Meropenem
Klebsiella pneumoniae	4/38 (10.5)	4/36 (11.1)	8/38 (21.1)	9/36 (25.0)
Pseudomonas aeruginosa	2/20 (10.0)	3/16 (18.8)	2/20 (10.0)	4/16 (25.0)
Acinetobacter baumannii complex	1/8 (12.5)	0/9 (0.0)	2/7 (28.6)	0/9 (0.0)
Escherichia coli	3/18 (16.7)	3/21 (14.3)	5/18 (27.8)	4/21 (19.0)
Enterobacter cloacae complex	1/9 (11.1)	2/10 (20.0)	2/9 (22.2)	3/10 (30.0)
Serratia marcescens	1/8 (12.5)	0/4 (0.0)	2/8 (25.0)	0/4 (0.0)
Proteus mirabilis	0/2 (0.0)	1/5 (20.0)	0/2 (0.0)	1/5 (20.0)

Source: adsl.xpt, adms.xpt.
All values are expressed as n/N' (%).
Note: Per Applicant, subjects with unknown survival status are excluded.
Abbreviations: n, number of subjects who died by the indicated timepoint; N', number of subjects known to be meropenem suscept ble for the pathogen and with known survival status at the indicated timepoint

See Section 16 for a sensitivity analysis that treats unknown survival status as death, as is done in the label.

Table 18. Clinical Outcome at Test of Cure by Baseline Pathogen, Restricted to Baseline Pathogens With Known Meropenem Susceptibility, APEKS-NP Trial

	Clinical Outcome at TOC	
Baseline Group or Pathogen	**Fetroja**	**Meropenem**
Klebsiella pneumoniae	24/38 (63.2)	23/36 (63.9)
Pseudomonas aeruginosa	13/20 (65.0)	13/17 (76.5)
Acinetobacter baumannii complex	6/8 (75.0)	7/9 (77.8)
Escherichia coli	12/18 (66.7)	13/21 (61.9)
Enterobacter cloacae complex	5/9 (55.6)	5/10 (50.0)
Serratia marcescens	5/8 (62.5)	3/4 (75.0)
Proteus mirabilis	1/2 (50.0)	1/5 (20.0)

Source: adsl.xpt, adclo.xpt, adms.xpt.
All values are expressed as n/N' (%).
Note: Per Applicant, subjects with indeterminate clinical outcome values are considered clinical failures.
Abbreviations: n, number of subjects who experienced clinical cure at test-of-cure visit; N, number of subjects known to be meropenem susceptible for the pathogen; TOC, test-of-cure

Conclusion

The results of analyses reported in the preceding three tables provide no evidence that the finding of cefiderocol NI to meropenem was driven by meropenem nonsusceptibility.

6.4.3. Important Review Issue #3 Relevant to Benefit

Issue

Inclusion of *Acinetobacter spp., S. maltophilia,* and *B. cepacia* in the indication and List 1 of the microbiology section of the labeling.

In addition to in vitro data, organisms included in this list must be relevant to HABP/VABP and be identified in sufficient numbers in the clinical trial for the HABP/VABP indication.

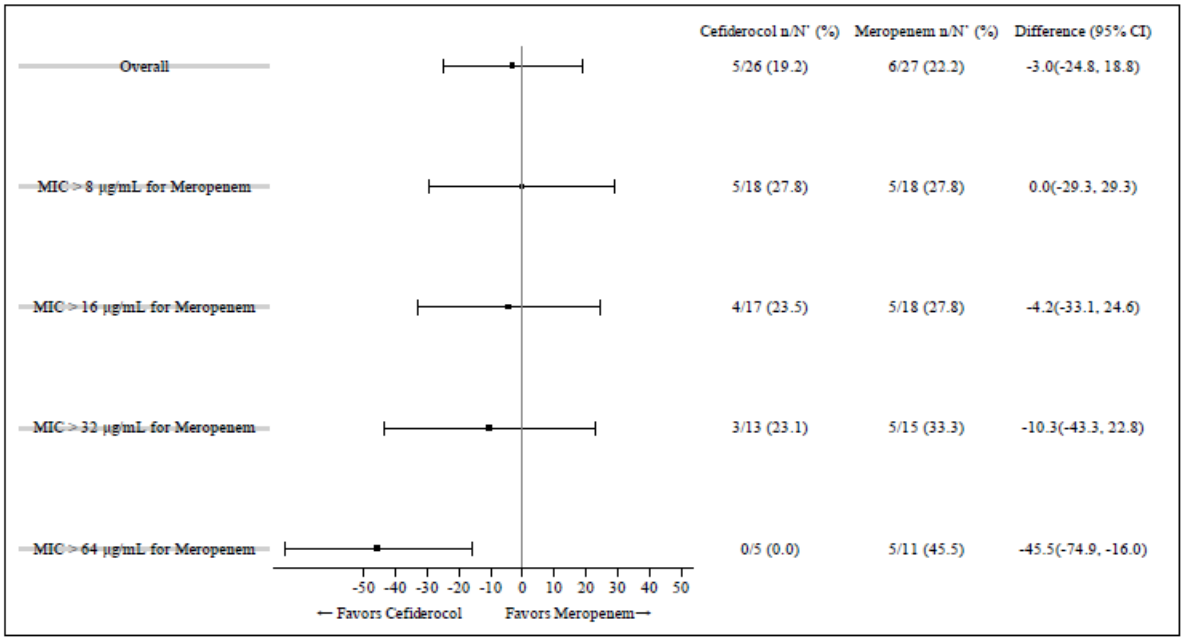
Inclusion of *A. baumannii* in labeling was a challenging issue. While *A. baumannii* was the third most common pathogen identified in the APEKS-NP study, approximately 66% of Acinetobacter isolates were meropenem non-susceptible (MIC >8 mcg/ml, based on the dose of 2 gram infused over 3 hours, every 8 hours). The APEKS-NP study was designed to exclude carbapenem-resistant pathogens since the comparator was meropenem. When excluding patients with meropenem nonsusceptible (MIC >8 mcg/ml) isolates or isolates with unknown susceptibility in both treatment arms, there were only eight patients in the cefiderocol and nine patients in the meropenem group. Generally, for inclusion of an organism in the indication, clinical data in the test arm on at least 10 isolates is expected. An additional concern was that in the subgroup of patients with *A. baumannii* complex at baseline, the mortality at day 14, 28 and clinical cure at TOC were numerically disfavorable in the cefiderocol group, as noted in Table 17 and Table 18. Similar findings were also seen in the subgroup of isolates that were not susceptible to meropenem, a subgroup where one would have expected the results to be in favor of cefiderocol.

There were 51 patients with *A. baumannii* complex at baseline, of which 17 (33.3%) patients had isolates susceptible to meropenem (MIC ≤8 mcg/mL, based on meropenem 2 grams every 8 hours). Among these 51 patients, all-cause mortality at day 14 was 5/26 (19.2%) in Fetroja and 4/25 (16.0%) in the meropenem treatment group and at day 28 was 9/26 (34.6%) in Fetroja and

6/25 (24.0%) in the meropenem treatment group. The clinical cure rates at the TOC visit were 14/26 (53.8%) in the Fetroja and 15/25 (60.0%) in the meropenem treatment group.

Figure 1 shows day 14 ACM in all patients with Acinetobacter infections including unspeciated Acinetobacter and *A. junii* and in subgroups of patients with increasing MIC to meropenem. In the subgroups of patients with MIC to meropenem ranging from >16 to >64 mcg/mL, day 14 ACM may have favored the cefiderocol group. No deaths occured through day 28 in the small subgroup of patients who were treated with cefiderocol (n=5) with *Acinetobacter spp.* at baseline with a meropenem MIC >64 mcg/ml. Further information on mortality by pathogen is provided in Section 7.7.

Figure 1. 14-Day ACM Among Subjects With Acinetobacter Infections at Baseline by MIC to Meropenem, APEKS-NP



All Acinetobacter infections including *Acinetobacter Junnii* and unspeciated *Acinetobacter*.

Source: Applicant's justification document for inclusion of *A. baumannii complex*

The data suggests a trend in 14-day ACM to favor cefiderocol as the MIC to meropenem increases. This is anticipated, since meropenem's activity against Acinetobacter is expected to be inversely proportional to the MIC. Figure 1 reflects that cefiderocol likely has efficacy in treatment of patients with Acinetobacter HABP/VABP. Taking into consideration all the available data on Acinetobacter HABP/VABP in the sNDA, *A. baumannii* complex was included in the indication and List 1 in labeling. While, it is difficult to draw any conclusions from these posthoc subgroup analysis of the overall population, it is important that the limitations of these data be communicated in labeling so that the healthcare provider can take this information into consideration, while making treatment decisions. Therefore, the table in the Clinical Studies section of the labeling will present the comparative study results from patients with meropenem-susceptible *A. baumannii* complex at baseline.

The secondary endpoints of the APEKS-NP trial were clinical and microbiological outcomes at TOC and other timepoints (EA, EOT, and FU) by baseline pathogen. The clinical cure rates and microbiological eradication rates are shown in Table 19. Microbiological eradication at TOC

with cefiderocol was 45.8% (22/48) for *K. pneumoniae*, 37.5% (9/24) for *P. aeruginosa*, 39.1% (9/23) for *A. baumannii*, and 52.6% (10/19) for *E. coli*. For meropenem, these values were 54.5% (24/44), 45.8% (11/24), 33.3% (8/24), and 50.0% (11/22), respectively. Microbiological eradication and clinical cure rates at TOC were generally similar with cefiderocol and high-dose/extended-infusion meropenem for the five most common baseline pathogens (*K. pneumoniae, P. aeruginosa, A. baumannii, E. coli,* and *E. cloacae*). However, meropenem is not indicated for HABP/VABP and Acinetobacter, *S. maltophilia*, *B. cepacia.* There are limited data (<10 subjects with microbiological and clinical outcome) on HABP/VABP subjects with the following baseline pathogens: *B. cepacia* complex, *Citrobacter koseri*, *E. cloacae* complex, *Klebsiella aerogenes, Klebsiella oxytoca, Proteus mirabilis, S. marcescens,* and *S. maltophilia.* However, based on available data and similarity in clinical outcomes of subjects with *E. cloacae* complex and *S. marcescens* to the subjects with pathogens from the order Enterobacterales, *E. cloacae* complex and *S. marcescens* were included in the indication and List 1.

Table 19. Summary of Clinical Cure and Microbiological Eradication Per Baseline Pathogen by Time Point -Modified Intention-to-Treat Population

	EA		EOT		TOC		FU	
Pathogen	**Clinical Cure**	**Micro Eradication**	**Clinical Cure**	**Micro Eradication**	**Clinical Cure**	**Micro Eradication**	**Sustained Clinical Cure**	**Sustained Micro Eradication**
Cefiderocol								
K. pneumoniae (n=48)	41 (85.4)	19 (39.6)	38 (79.2)	28 (58.3)	31 (64.6)	22 (45.8)	27 (56.3)	19 (39.6)
P. aeruginosa (n=24)	20 (83.3)	8 (33.3)	22 (91.7)	17 (70.8)	16 (66.7)	9 (37.5)	14 (58.3)	10 (41.7)
A. baumannii (n=23)	19 (82.6)	11 (47.8)	15 (65.2)	14 (60.9)	12 (52.2)	9 (39.1)	10 (43.5)	7 (30.4)
E. coli (n=19)	16 (84.2)	8 (42.1)	15 (78.9)	12 (63.2)	12 (63.2)	10 (52.6)	12 (63.2)	9 (47.4)
S. marcescens (n=8)	7 (87.5)	3 (37.5)	6 (75.0)	5 (62.5)	5 (62.5)	4 (50.0)	5 (62.5)	4 (50.0)
E. cloacae (n=7)	7 (100.0)	4 (57.1)	5 (71.4)	4 (57.1)	5 (71.4)	4 (57.1)	5 (71.4)	3 (42.9)
E. aerogenes (n=4)	1 (25.0)	1 (25.0)	2 (50.0)	2 (50.0)	1 (25.0)	1 (25.0)	1 (25.0)	1 (25.0)
H. influenzae (n=3)	3 (100.0)	3 (100.0)	3 (100.0)	2 (66.7)	2 (66.7)	2 (66.7)	2 (66.7)	2 (66.7)
M. catarrhalis (n=3)	3 (100.0)	2 (66.7)	3 (100.0)	3 (100.0)	3 (100.0)	2 (66.7)	3 (100.0)	1 (33.3)
P. mirabilis (n=2)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)
K. oxycota (n=2)	2 (100.0)	1 (50.0)	1 (50.0)	2 (100.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)
A. nosocomialis (n=2)	1 (50.0)	2 (100.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)
E. asburiae (n=2)	0	2 (100.0)	0	0	0	0	0	0
S. maltophilia (n=1)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)
C. koseri (n=1)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)
M. morganii (n=1)	0	1 (100.0)	0	0	0	0	0	0
C. freundii (n=1)	0	0	0	0	0	0	0	0
A. pittii (n=1)	0	1 (100.0)	0	1 (100.0)	1 (100.0)	1 (100.0)	0	1 (100.0)
B. cepacia (n=1)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)
H. parahaemolyticus (n=1)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)

Pathogen	EA		EOT		TOC		FU	
	Clinical Cure	Micro Eradication	Clinical Cure	Micro Eradication	Clinical Cure	Micro Eradication	Sustained Clinical Cure	Sustained Micro Eradication
Meropenem								
K. pneumoniae (n=44)	36 (81.8)	30 (68.2)	35 (79.5)	33 (75.0)	29 (65.9)	24 (54.5)	25 (56.8)	17 (38.6)
P. aeruginosa (n=24)	20 (83.3)	11 (45.8)	19 (79.2)	16 (66.7)	17 (70.8)	11 (45.8)	13 (54.2)	10 (41.8)
A. baumannii (n=24)	17 (70.8)	9 (37.5)	19 (79.2)	11 (45.8)	14 (58.3)	8 (33.3)	13 (54.2)	7 (20.2)
E. coli (n=22)	20 (90.9)	11 (50.0)	19 (86.4)	16 (72.7)	13 (59.1)	11(50.0)	11 (50.0)	9 (40.9)
S. marcescens (n=4)	3 (75.0)	2 (50.0)	3 (75.0)	2 (50.0)	3 (75.0)	2 (50.0)	3 (75.0)	2 (50.0)
E. cloacae (n=8)	5 (62.5)	6 (75.0)	7 (87.5)	8 (100.0)	4 (50.0)	3 (37.5)	4 (50.0)	3 (37.5)
E. aerogenes (n=1)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)
H. influenzae (n=5)	5 (100.0)	4 (80.0)	5 (100.0)	5 (100.0)	4 (80.0)	4 (80.0)	4 (80.0)	2 (40.0)
M. catarrhalis (n=2)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	0
P. mirabilis (n=6)	5 (83.3)	3 (50.0)	4 (66.7)	4 (66.7)	2 (33.3)	1 (16.7)	2 (33.3)	1 (16.7)
K. oxycota (n=3)	3 (100.0)	3 (100.0)	2(66.7)	3 (100.0)	2(66.7)	2(66.7)	1 (33.3)	2(66.7)
A. nosocomialis (n=1)	0	0	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	0	0
E. asburiae (n=1)	1 (100.0)	1 (100.0)	1 (100.0)	0	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)
S. maltophilia (n=3)	2 (66.7)	1 (33.3)	2 (66.7)	2 (66.7)	2 (66.7)	1 (33.3)	2 (66.7)	1 (33.3)
C. koseri (n=2)	2 (100.0)	1 (50.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)
M. morganii (n=2)	1 (50.0)	2 (100.0)	2 (100.0)	2 (100.0)	0	0	0	0
C. freundii (n=1)	1 (100.0)	0	1 (100.0)	0	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)
A. pittii (n=0)	0	0	0	0	0	0	0	0
B. cepacia (n=0)	0	0	0	0	0	0	0	0
H. parahaemolyticus (n=0)	0	0	0	0	0	0	0	0

Source: Table 14.2.8.1.1 and Table 14.2.9.1.1
All values are presented as n (%)
Abbreviations: EA, early assessment; EOT, end of therapy; FU, follow-up; TOC, test-of-cure

6.4.4. Important Review Issue #4 Relevant to Benefit

Issue

Revisit breakpoints established by FDA for Enterobacteriaceae and *P. aeruginosa* and establishbreakpoints for *A. baumannii* complex.

The currently approved FDA breakpoints are shown in Table 20.

Table 20. FDA-Identified Breakpoints

	MIC (mcg/mL)			Disk Diffusion (Sone Diameters in mm)		
Pathogen	**S**	**I**	**R**	**S**	**I**	**R**
Enterobacteriaceae[a]	≤2	4	≥8	≥18	14–17	≤13
Pseudomonas aeruginosa	≤1	2	≥4	≥25	19–24	≤18

Source: https://www.fda.gov/drugs/development-resources/cefiderocol-injection
[a] Includes *E. coli*, *K. pneumoniae*, *P. mirabilis*, and *E. cloacae* complex.
For disk diffusion, use paper disks impregnated with 30 mcg cefiderocol.
Abbreviations: I, intermediate; MIC, minimum inhibitory concentration; R, resistant; S, Susceptible

These breakpoints were established by taking into account the cefiderocol MIC distribution in surveillance and clinical studies, cefiderocol MIC_{90} values in surveillance studies, clinical cure rates by MIC of the baseline pathogen in the cUTI study, and pharmacokinetic-pharmacodynamic (PK-PD) target attainment analyses. The Applicant's proposed breakpoints are shown in Table 21. These breakpoints rely heavily on the animal data using simulated human dosing for PK/PD assessments to bridge the gap between data from surveillance and clinical studies and on the cefiderocol MIC_{90} values for carbapenem-resistant pathogens. These breakpoints were also tentatively proposed by the Clinical and Laboratory Standards Institute (CLSI) based on animal data.

Table 21. Applicant's Proposed Breakpoints

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)		
	S	**I**	**R**
Enterobacterales	≤4	8	≥16
Pseudomonas aeruginosa	≤4	8	≥16
Acinetobacter baumannii complex	≤4	8	≥16
The following breakpoints are based on in vitro MIC data and the efficacy of cefiderocol in treating clinical infections due to these bacteria has not been established in adequate and well-controlled clinical trials.			
Stenotrophomonas maltophilia	≤4	8	≥16

Source: Table 7 in section 2.7.2.4.Addendum-HABP/VABP of the Application
Abbreviations: I, intermediate; MIC, minimum inhibitory concentration; R, resistant; S, susceptible

The cefiderocol MIC_{90} values against Enterobacterales, *P. aeruginosa*, and *A. baumannii* complex in surveillance studies and the cefiderocol MIC_{90} values against meropenem-resistant Enterobacterales, *P. aeruginosa*, and *A. baumannii* complex using the updated surveillance study data are the same as those in the original NDA. For the APEKS-NP study, the clinical cure rates and microbiological eradication rates for subjects with baseline Enterobacterales at the cefiderocol MIC of 2 mcg/mL were 70% (7/10) and 40% (4/10), respectively. There are very limited data at MIC of 4 mcg/mL (clinical cure rate 50% (1/2) and no microbiological eradication). However, four subjects in the cUTI trial had isolates with cefiderocol MIC of 4

mcg/mL. All four subjects were clinically cured, and three out of the four subjects showed microbiological eradication.

In the case of *P. aeruginosa*, the cefiderocol MIC for the clinical isolates ranged from ≤0.03 to 1 mcg/mL (MIC_{90}=0.5 mcg/mL). There were two subjects with isolates at an MIC of 1 mcg/mL, and both were clinically cured with microbiological eradication in one subject. There were no data above an MIC of 1 mcg/mL. The Applicant stated that in addition to the APEKS-NP data, five subjects in the compassionate use program (three with cefiderocol MIC of 2 mcg/mL and two with cefiderocol MIC of 4 mcg/mL) responded to cefiderocol treatment. However, the compassionate use data were not considered in the assessment due to the open-label and uncontrolled nature of the data.

In the case of *A. baumannii*, the cefiderocol MIC for the clinical isolates ranged from ≤0.03 to >64 mcg/mL (MIC_{90}=2 mcg/mL). The cefiderocol MIC_{90} for *A. baumannii* complex in surveillance studies was 2 mcg/mL. There were two subjects with isolates at an MIC of 1 mcg/mL and both had a clinical cure with microbiological eradication in one subject. At an MIC of 2 mcg/ml, the clinical cure and microbiological eradication rates were 33.3% (1/3).

The combined data from the cUTI and HABP/VABP clinical studies support a change in MIC breakpoints for Enterobacterales but not *P. aeruginosa*. The cefiderocol susceptible breakpoint for *A. baumannii* can be set at ≤1 mcg/mL based on limited clinical data. The resistant breakpoint is set at ≥ 4 mcg/mL. No breakpoints are proposed for *S. maltophilia* as it is not indicated for HABP/VABP. The revised FDA identified breakpoints are shown in Table 22.

Table 22. Revised FDA Identified Breakpoints

	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
Pathogen	**S**	**I**	**R**	**S**	**I**	**R**
Enterobacterales[a,b]	≤4	8	≥ 16	≥16	9-15	≤8
Pseudomonas aeruginosa	≤1	2	≥ 4	≥22	13-21	≤12
Acinetobacter baumannii complex	≤1	2	≥ 4	≥19	12-18	≤11

[a]Clinical efficacy was shown for *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Enterobacter cloacae* complex in patients with complicated urinary tract infections (cUTI).
[b]Clinical efficacy was shown for *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae* complex, and *Serratia marcescens* in patients with hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) .
S = Susceptible; I = Intermediate; R = Resistant
For disk diffusion, use paper disks impregnated with 30 mcg cefiderocol.

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

No new safety concerns based on nonclinical data have been found. See review of NDA 209445 (Division of Anti-Infectives 2019) for information noted previously.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Potential risks based on β-lactam antibacterial class effects include rash/hypersensitivity reactions, *Clostridioides difficile*-associated diarrhea, hepatotoxicity, seizures and other central nervous system abnormalities, renal toxicity, and hematologic reactions (immune-mediated hemolytic anemia, hypothrombinemia). Additional safety concerns include other hematologic risks such as anemia, bleeding, coagulopathy, and thrombosis due to the iron-based mechanism of entry. Patients with TEAEs related these antibacterial class effects are noted in Section 7.6.5.

7.3. Potential Safety Concerns Identified Through Postmarket Experience

A search of the FDA Adverse Event Reporting System database yielded eight postmarketing reports of TEAEs associated with the use of cefiderocol. Five cases were from the United States, and the remaining were from foreign countries. Two resulted in death, one was life-threatening, and three had other outcomes. The individual preferred terms (PTs) were pyrexia (possible drug fever), PR prolongation and extrasystoles, cardiac arrest, seizure, chromaturia (asymptomatic blue to purplish discoloration of the urine), sepsis and multiple organ dysfunction syndrome (MODS) in two patients (both resulting in death), and acute kidney injury (AKI). In addition, there have been two 15-day safety reports of AKI due to suspected allergic interstitial nephritis associated with cefiderocol; one was submitted on June 10, 2019, prior to approval, and one was submitted on April 9, 2020. In both cases, peripheral eosinophilia occurred with a decline in renal function while on cefiderocol, but a renal biopsy was not performed for confirmatory evidence. In the first report, aztreonam was given concomitantly; however, the physician suspected cefiderocol rather than aztreonam due to timing of administration. Other confounders included colistin given for an unknown duration and a possible concomitant UTI. In the second report, there was no other confounding medication except for paracetamol, and the event of AKI was noted to be possibly related by the investigator. Confounders also included underhydration.

There were two cardiac events reported. One patient with a history of coronavirus disease 2019 (COVID-19) about 2 months prior to receiving cefiderocol developed PR prolongation with frequent extrasystoles. The PR prolongation resolved after discontinuation of cefiderocol and the investigator causality was related. Another patient with a history of ongoing COVID-19 pneumonia (onset unknown) developed cardiac arrest 2 days after receiving cefiderocol leading to treatment discontinuation. The investigator causality was related, and potential confounders were furosemide, propofol, and fentanyl.

Seizure occurred in one patient with no prior seizure history who was receiving CRRT for AKI. The seizure occurred 13 days after cefiderocol was started, leading to treatment discontinuation. Seizure is noted as a warning in cefiderocol labeling.

In addition, a 7-day report was submitted on January 13, 2020, for a patient who had developed mucormycosis requiring withdrawal of cefiderocol with an outcome of not recovered. The patient was an 18-year-old female with a history of cystic fibrosis who was treated with cefiderocol for *Achromobacter xylosoxidans* and *Haemophilus influenzae* pneumonia, and multi-organ dysfunction requiring extracorporeal membrane oxygenation (ECMO) in the compassionate use program. She also developed *A. xylosoxidans* bacteremia. She underwent left femoral artery ECMO decannulation with angioplasty with greater saphenous vein patch and lower extremity fasciotomy due to acute limb ischemia associated with common femoral artery thrombosis. The fasciotomy site grew a Mucor species for which she was given amphotericin. The attending physician discontinued cefiderocol due to the concern that cefiderocol may have acted as a xenosiderophore and promoted infection with Mucor species by increasing available free iron. Other risk factors for development of Mucor species included neutropenia, hyperglycemia, ischemic injury from ECMO and fasciotomy, steroids, and blood transfusion.

7.4. FDA Approach to the Safety Review

Data from the APEKS-NP trial is the focus of the safety review. Although the CREDIBLE-CR trial included subjects with NP, the data was not pooled for safety assessments given differences in study design and populations. The available data from the CREDIBLE-CR trial was assessed during the original NDA review, and the clinical study report submitted with this sNDA contains the same information as was previously reviewed. See original NDA for the review of the CREDIBLE-CR trial.

7.5. Adequacy of the Clinical Safety Database

The dosing, duration, and number of subjects in the safety database are sufficient to conduct a safety review for the HABP/VABP indication. A total of 97 of 148 (65.5%) patients in the cefiderocol arm and 110 of 150 (73.3%) patients in the meropenem arm received between 7 and 14 days of therapy, which is the proposed duration of treatment for the indication sought. Of note, more patients in the cefiderocol arm had a longer exposure to treatment (>14 days) than in the meropenem group. Per protocol, treatment duration may have been extended up to 21 days based on the investigator's clinical assessment of the patients. Two subjects in the cefiderocol group and one subject in the meropenem group were shown as having 22 days of exposure to study treatment due to how their infusion start and end times fell on calendar days. However, actual administration duration was 21 days for each of these three subjects.

Table 23. Duration of Exposure, Safety Population, APEKS-NP Trial

Variable	Cefiderocol N=148	Meropenem N=150	Total N=298
Duration of treatment (days)			
Mean (SD)	10.4 (4.1)	10.1 (4.0)	10.3 (4.1)
Median (min, max)	10.0 (2.0, 22.0)	8.5 (1.0, 22.0)	9.0 (1.0, 22.0)
Subjects treated, by duration, n (%)			
<7 days	18 (12.2)	15 (10.0)	33 (11.1)
7 to 14 days	97 (65.5)	110 (73.3)	207 (69.5)
>14 to 20 days	31 (20.9)	24 (16.0)	55 (18.5)
>21 days	2 (1.4)	1 (0.7)	3 (1.0)

Source: adex.xpt; Software: Python
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; SD, standard deviation

7.6. Safety Findings and Safety Concerns Based on Review of the Clinical Safety Database

7.6.1. Overall Adverse Event Summary

An overall summary of TEAEs is presented in Table 24. While TEAEs occurred at a similar frequency in both treatment groups, moderate or severe TEAEs and serious AEs (SAEs) with or without a fatal outcome occurred more frequently in the cefiderocol group (≥3%) than they did in the meropenem group. TEAEs leading to discontinuation of the study drug occurred at a similar frequency in both treatment groups. The TEAEs leading to interruption of the study drug in the cefiderocol group were cardiac arrest and cardiac failure (one patient each, both considered not related to study drug per the investigator and with fatal outcomes); and ear discomfort and headache (one patient, considered related to study drug per the investigator with outcome ‘resolved’). In the meropenem group, TEAEs leading to interruption of study drug were hemorrhagic shock (with a fatal outcome), renal impairment (outcome not resolved), and anuria (outcome not resolved). The TEAEs occurred in one patient each and were all considered not related per the investigator.

Table 24. Overview of Treatment-Emergent Adverse Events, Safety Population, APEKS-NP Trial

Event Category	Cefiderocol N=148	Meropenem N=150	Total N=298	Risk Difference
Any TEAE	130 (87.8)	129 (86.0)	259 (86.9)	1.8 (-5.8, 9.5)
Moderate or severe TEAEs	97 (65.5)	92 (61.3)	189 (63.4)	4.2 (-6.7, 15.1)
Any SAE	54 (36.5)	45 (30.0)	99 (33.2)	6.5 (-4.2, 17.2)
SAE with fatal outcome	39 (26.4)	35 (23.3)	74 (24.8)	3.1 (-6.7, 12.9)
TEAE leading to discontinuation of study drug	12 (8.1)	14 (9.3)	26 (8.7)	-1.2 (-7.6, 5.2)
TEAE leading to dose modification of study drug	3 (2.0)	3 (2.0)	6 (2.0)	0.0 (-3.2, 3.2)
TEAE leading to interruption of study drug	3 (2.0)	1 (0.7)	4 (1.3)	1.3 (-1.3, 3.9)
TEAE leading to reduction of study drug	0	2 (1.3)	2 (0.7)	-1.3 (-3.2, 0.5)
TEAE leading to delay of study drug	0	0	0	0.0 (0.0, 0.0)

Source: adae.xpt; Software: Python
All values are expressed as n (%) except those in the Risk Difference column. The Risk Difference column shows absolute difference (with 95% confidence interval) between cefiderocol and meropenem.
Treatment-emergent adverse events are defined as adverse events that started after the initial dose of study treatment or comparator and up to the EOS
The severity of an event was graded by the investigator or subinvestigator according to the following definitions: Mild: A finding or symptom is minor and does not interfere with usual daily activities; Moderate: The event causes discomfort and interferes with usual daily activity or affects clinical status; Severe: The event causes interruption of the subject's usual daily activities or has a clinically significant effect
Abbreviations: CI, confidence interval; EOS, end of study; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event; TEAE, treatment-emergent adverse event

7.6.2. Deaths

In the safety population (n=298), there were 74 treatment-emergent deaths, i.e., 74 patients died on or before the EOS, including one subject ((b) (6)), who had an ongoing SAE at the EOS visit and died the next day. TEAEs leading to death occurred in 26.4% (39/148) in the cefiderocol group and 23.3% (35/150) in the meropenem group (a risk difference of 3.0%). In addition, there were eight patients (three in the cefiderocol group and five in the meropenem group) who were reported as having died after the EOS through spontaneous reporting such as in response to an Electronic Data Capture query or in a FU liver event form.

None of the deaths in either treatment group were considered related to study treatment by either the sponsor or investigator. However, TEAEs leading to death were reported for one patient (sepsis secondary to HABP) in the cefiderocol group and two patients (Pseudomonas infection in one patient; disseminated intravascular coagulation and MODS, both related to a concomitant medication [linezolid]) in one patient in the meropenem group. Most often, the deaths occurred as a result of the underlying comorbidities and concurrent illness in this severely ill population with NP and were relatively similar between treatment groups. As the labeling for cefiderocol includes a mortality warning in patients with NP based on the results of the mortality imbalance in the CREDIBLE-CR trial, a detailed mortality analysis was performed for the APEKS-NP trial, and results are noted in Section 7.7.1.

7.6.3. Serious Adverse Events

SAEs occurred at a slightly higher frequency in the cefiderocol group, with a risk difference of 6.5%. The following table lists SAEs by system organ class (SOC). The SOCs with at least a 1% higher frequency of SAEs in the cefiderocol group were infections and infestations, respiratory, thoracic, and mediastinal and gastrointestinal (GI) disorders. The SAEs were further evaluated with the currently available FDA Medical Dictionary for Regulatory Activities Queries (FMQs)

as noted in Table 26. Of note, FMQs are currently in development and a complete listing of FMQs are not available at the time of this review [e.g., an FMQ related to cerebrovascular accident (CVA) has not yet been developed].

Pneumonia in the infections and infestations SOC and acute coronary syndrome in the cardiac disorders SOC were reported in a greater number of patients in the cefiderocol group. As grouped queries for all pneumonia-related TEAEs yielded even higher numbers of patients with pneumonia in both treatment groups, these were analyzed further and are discussed in Section 7.6.5. Other infectious and cardiac events are also discussed in this section. SAEs by other FMQs did not raise safety concerns.

Per the investigator, there were three patients in the cefiderocol group and five in the meropenem group with treatment-related SAEs. In the cefiderocol group, two patients had elevated liver tests which resolved and one patient had acute respiratory failure, pleural effusion, and sepsis secondary to HABP, which led to death. In the meropenem group, three subjects had treatment-related SAEs that were considered related to linezolid or other concomitant therapy (i.e., red blood cell transfusion). One patient had an SAE of Pseudomonas infection and hemorrhagic shock that led to death, and one patient had elevated liver tests that did not resolve by the EOS.

Additional SAEs in which contribution of cefiderocol could not be excluded are noted below. An additional five SAEs in the cefiderocol group appeared to be related to elevated liver tests. Case summaries for hepatic TEAEs are noted in Section 7.6.5.

- (b) (6) – Coagulopathy. 79-year-old male with hypertension (HTN) and DM with a baseline international normalized ratio (INR, normal range 0.8 to 1.2) of 1.5 and activated partial thromboplastin time (aPTT, normal range 25 to 43 seconds) of 28.2 seconds developed nonserious coagulopathy on day 5 with a prothrombin time of 29.1 seconds (normal range not provided) and aPTT >150 seconds. He had been receiving enoxaparin from day -9 until day 7. Cefiderocol was given until day 14. An SAE of coagulopathy occurred on day 12 (prothrombin time: 29 seconds, INR 2.2, aPTT 47.4 seconds). No bleeding events were reported. It cannot be fully excluded that cefiderocol increased the coagulation parameters, even after confounding medication (enoxaparin) was discontinued. He died due to cardiac arrest on day 14.
- (b) (6) – Thrombocytopenia. 75-year-old female with CKD, DM, and HTN developed thrombocytopenia from days 15 to 25. The baseline platelet count was 394×10^9/L (normal range 150 to 450) and decreased to 78×10^9/L on day 22. Cefiderocol was discontinued on day 16. The platelet count recovered to 585×10^9/L by day 27. No bleeding events were noted, but hematology was consulted and did not recommend medical intervention. It cannot be fully excluded that cefiderocol contributed to thrombocytopenia.
- (b) (6) – Stridor. 55-year-old female with asthma, chronic obstructive pulmonary disease (COPD), and depression developed a TEAE of HTN on day 7, which did not resolve. She developed dermatitis, which was treated with chloropyramine on day 20 and was resolved by day 26. Cefiderocol was discontinued on day 8. Whether events between the onsets of dermatitis and stridor occurred is unknown. On day 36, she developed an SAE of stridor for which she underwent balloon dilatation. No other etiology of stridor was given. However, due to the delayed onset of stridor (28 days after study drug discontinuation), causality to cefiderocol is less likely.

(b) (6) – Status epilepticus. 26-year-old male with chronic kidney disease (CKD) on hemodialysis, HTN, and history of typhoid fever developed hypocalcemia on day 3. The serum calcium was 1.7 mmol/L at baseline (normal range 2.12 to 2.5) and decreased to 1.3 mmol/mL on day 3. Hypocalcemia resolved on day 39 after treatment with calcium carbonate from days 12 to 27. Cefiderocol was discontinued on day 11. He also had TEAEs of coronary artery disease (CAD) and congestive heart failure (CHF). On day 33, he developed SAEs of acute respiratory failure, cardiorespiratory arrest, left ventricular dysfunction, and status epilepticus, for which he was given antiseizure medication. It cannot be fully excluded that cefiderocol contributed to hypocalcemia, hypocalcemia-triggered status epilepticus, or status epilepticus alone given risk for seizures with use of cefiderocol.

Table 25. Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, APEKS-NP Trial

System Organ Class Preferred Term	Cefiderocol N=148	Meropenem N=150	Total N=298	Risk Difference
Any SAE	54 (36.5)	45 (30.0)	99 (33.2)	6.5 (-4.2, 17.2)
Infections and infestations	17 (11.5)	14 (9.3)	31 (10.4)	2.2 (-4.8, 9.1)
Pneumonia	6 (4.1)	3 (2.0)	9 (3.0)	2.1 (-1.8, 5.9)
Septic shock	4 (2.7)	1 (0.7)	5 (1.7)	2.0 (-0.9, 5.0)
Sepsis	3 (2.0)	2 (1.3)	5 (1.7)	0.7 (-2.2, 3.6)
Bacteremia	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Bacterial sepsis	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Herpes zoster	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Lung infection	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Pneumonia bacterial	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Spinal cord infection	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Urinary tract infection	1 (0.7)	2 (1.3)	3 (1.0)	-0.6 (-2.9, 1.7)
Acinetobacter bacteremia	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Brain abscess	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Meningitis	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Meningoencephalitis bacterial	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Pneumonia necrotising	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Pseudomonas infection	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Septic encephalopathy	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Systemic candida	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Respiratory, thoracic and mediastinal disorders	17 (11.5)	15 (10.0)	32 (10.7)	1.5 (-5.5, 8.5)
Acute respiratory failure	6 (4.1)	1 (0.7)	7 (2.3)	3.4 (-0.0, 6.8)
Pulmonary edema	2 (1.4)	0	2 (0.7)	1.4 (-0.5, 3.2)
Pneumonia aspiration	3 (2.0)	2 (1.3)	5 (1.7)	0.7 (-2.2, 3.6)
Acute respiratory distress syndrome	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Pneumothorax spontaneous	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Pulmonary hypertension	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Stridor	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Pulmonary artery thrombosis	3 (2.0)	3 (2.0)	6 (2.0)	0.0 (-3.2, 3.2)
Pleural effusion	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.8, 1.9)
Pulmonary embolism	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.8, 1.9)
Respiratory failure	2 (1.4)	3 (2.0)	5 (1.7)	-0.6 (-3.6, 2.3)
Bronchopleural fistula	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Chronic obstructive pulmonary disease	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Pneumothorax	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Pulmonary congestion	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Respiratory distress	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)

System Organ Class Preferred Term	Cefiderocol N=148	Meropenem N=150	Total N=298	Risk Difference
Gastrointestinal disorders	4 (2.7)	2 (1.3)	6 (2.0)	1.4 (-1.8, 4.6)
Abdominal wall hematoma	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Gastric hemorrhage	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Intestinal infarction	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Intestinal ischemia	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Acute abdomen	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Gastrointestinal hemorrhage	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Cardiac disorders	16 (10.8)	15 (10.0)	31 (10.4)	0.8 (-6.1, 7.7)
Cardiac arrest	7 (4.7)	5 (3.3)	12 (4.0)	1.4 (-3.1, 5.9)
Acute myocardial infarction	2 (1.4)	0	2 (0.7)	1.4 (-0.5, 3.2)
Left ventricular dysfunction	2 (1.4)	0	2 (0.7)	1.4 (-0.5, 3.2)
Cardio-respiratory arrest	3 (2.0)	2 (1.3)	5 (1.7)	0.7 (-2.2, 3.6)
Myocardial infarction	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Cardiovascular insufficiency	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.8, 1.9)
Cardiac failure	2 (1.4)	3 (2.0)	5 (1.7)	-0.6 (-3.6, 2.3)
Cardiac failure congestive	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Cardiogenic shock	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Cardiopulmonary failure	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Cardiovascular disorder	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Cardiac failure acute	0	2 (1.3)	2 (0.7)	-1.3 (-3.2, 0.5)
General disorders and administration site conditions	7 (4.7)	6 (4.0)	13 (4.4)	0.7 (-3.9, 5.4)
General physical health deterioration	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Sudden death	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Multiple organ dysfunction syndrome	4 (2.7)	4 (2.7)	8 (2.7)	0.0 (-3.6, 3.7)
Death	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.8, 1.9)
SIRS	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Lung cancer metastatic	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Skin and subcutaneous tissue disorders	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Diabetic foot	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Surgical and medical procedures	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Leg amputation	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Injury, poisoning and procedural complications	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.8, 1.9)
Subarachnoid hemorrhage	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Splenic rupture	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Hepatobiliary disorders	1 (0.7)	2 (1.3)	3 (1.0)	-0.6 (-2.9, 1.7)
Hepatocellular injury	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Cholecystitis acute	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Hepatic function abnormal	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Metabolism and nutrition disorder	1 (0.7)	2 (1.3)	3 (1.0)	-0.6 (-2.9, 1.7)
Lactic acidosis	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Hyperkalemia	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Hypovolemia	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)

System Organ Class Preferred Term	Cefiderocol N=148	Meropenem N=150	Total N=298	Risk Difference
Nervous system disorders	9 (6.1)	11 (7.3)	20 (6.7)	-1.2 (-6.9, 4.5)
Cerebrovascular accident	2 (1.4)	1 (0.7)	3 (1.0)	0.7 (-1.6, 3.0)
Intracranial pressure increased	2 (1.4)	1 (0.7)	3 (1.0)	0.7 (-1.6, 3.0)
Autonomic nervous system imbalance	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Cerebral ischemia	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Hypoxic-ischemic encephalopathy	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Status epilepticus	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Stroke in evolution	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Metabolic encephalopathy	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.8, 1.9)
Brain injury	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Encephalopathy	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Lacunar stroke	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Brain edema	1 (0.7)	5 (3.3)	6 (2.0)	-2.6 (-5.8, 0.6)
Investigations	6 (4.1)	8 (5.3)	14 (4.7)	-1.2 (-6.0, 3.6)
Liver function test increased	2 (1.4)	0	2 (0.7)	1.4 (-0.5, 3.2)
Alanine aminotransferase increased	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Blood pressure increased	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Aspartate aminotransferase increased	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.8, 1.9)
Transaminases increased	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.8, 1.9)
Liver function test abnormal	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Hepatic enzyme increased	1 (0.7)	5 (3.3)	6 (2.0)	-2.6 (-5.8, 0.6)
Renal and urinary disorders	1 (0.7)	3 (2.0)	4 (1.3)	-1.3 (-3.9, 1.3)
Acute kidney injury	1 (0.7)	3 (2.0)	4 (1.3)	-1.3 (-3.9, 1.3)
Vascular disorders	1 (0.7)	3 (2.0)	4 (1.3)	-1.3 (-3.9, 1.3)
Peripheral vascular disorder	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Femoral artery embolism	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Hypotension	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Hypovolemic shock	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Shock hemorrhagic	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Blood and lymphatic system disorders	2 (1.4)	6 (4.0)	8 (2.7)	-2.6 (-6.3, 1.0)
Coagulopathy	1 (0.7)	2 (1.3)	3 (1.0)	-0.6 (-2.9, 1.7)
Thrombocytopenia	1 (0.7)	2 (1.3)	3 (1.0)	-0.6 (-2.9, 1.7)
Disseminated intravascular coagulation	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Hemorrhagic anemia	0	2 (1.3)	2 (0.7)	-1.3 (-3.2, 0.5)

Source: adae.xpt; Software: Python
All values are expressed as n (%) except those in the Risk Difference column. The Risk Difference column shows absolute difference (with 95% confidence interval) between cefiderocol and meropenem.
Treatment-emergent adverse are defined as the severity of an event was graded by the investigator or subinvestigator according to the following definitions: Mild: A finding or symptom is minor and does not interfere with usual daily activities; Moderate: The event causes discomfort and interferes
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event; SIRS, systemic inflammatory response syndrome

Table 26. Serious Adverse Events by FDA MedDRA Query (Narrow), Safety Population, APEKS-NP Trial

FMQ (Narrow) Preferred Term	Cefiderocol N=148	Meropenem N=150	Total N=298	Risk Difference
Pneumonia	10 (6.8)	6 (4.0)	16 (5.4)	2.8 (-2.4, 7.9)
Pneumonia	6 (4.1)	3 (2.0)	9 (3.0)	2.1 (-1.8, 5.9)
Pneumonia aspiration	3 (2.0)	2 (1.3)	5 (1.7)	0.7 (-2.2, 3.6)
Lung infection	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Pneumonia bacterial	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Pneumonia necrotising	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)

FMQ (Narrow) Preferred Term	Cefiderocol N=148	Meropenem N=150	Total N=298	Risk Difference
Acute coronary syndrome	3 (2.0)	0	3 (1.0)	2.0 (-0.2, 4.3)
Acute myocardial infarction	2 (1.4)	0	2 (0.7)	1.4 (-0.5, 3.2)
Myocardial infarction	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Systemic hypertension	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Blood pressure increased	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Malignancy	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Lung cancer metastatic	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Seizure	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Status epilepticus	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Hepatic injury	2 (1.4)	2 (1.3)	4 (1.3)	0.1 (-2.5, 2.7)
Alanine aminotransferase increased	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Hepatocellular injury	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Aspartate aminotransferase increased	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.8, 1.9)
Hepatic function abnormal	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Hemorrhage	3 (2.0)	3 (2.0)	6 (2.0)	0.0 (-3.2, 3.2)
Abdominal wall hematoma	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Gastric hemorrhage	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Subarachnoid hemorrhage	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Gastrointestinal hemorrhage	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Shock hemorrhagic	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Hemorrhagic anemia	0	2 (1.3)	2 (0.7)	-1.3 (-3.2, 0.5)
Thrombocytopenia	1 (0.7)	2 (1.3)	3 (1.0)	-0.6 (-2.9, 1.7)
Thrombocytopenia	1 (0.7)	2 (1.3)	3 (1.0)	-0.6 (-2.9, 1.7)
Abdominal pain	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Acute abdomen	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Cholecystitis	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Cholecystitis acute	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Dyspnea	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Respiratory distress	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Hypotension	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Hypotension	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Acute kidney injury	1 (0.7)	3 (2.0)	4 (1.3)	-1.3 (-3.9, 1.3)
Acute kidney injury	1 (0.7)	3 (2.0)	4 (1.3)	-1.3 (-3.9, 1.3)
Anemia	0	2 (1.3)	2 (0.7)	-1.3 (-3.2, 0.5)
Hemorrhagic anemia	0	2 (1.3)	2 (0.7)	-1.3 (-3.2, 0.5)

Source: adae.xpt; Software: Python
All values are expressed as n (%) except those in the Risk Difference column. The Risk Difference column shows absolute difference (with 95% confidence interval) between cefiderocol and meropenem.
Treatment-emergent adverse events are defined as adverse events that started after the initial dose of study treatment or comparator and up to the EOS
The severity of an event was graded by the investigator or subinvestigator according to the following definitions: Mild: A finding or symptom is minor and does not interfere with usual daily activities; Moderate: The event causes discomfort and interferes with usual daily activity or affects clinical
Abbreviations: CI, confidence interval; EOS, end of study; FMQ, FDA medDRA query; N, number of subjects in treatment arm; n, number of subjects with adverse event

7.6.4. Dropouts and/or Discontinuations Due to Adverse Events

Of all randomized patients in the trial, 28.4% (42/148) in the cefiderocol group and 26.3% (40/152) in the meropenem group discontinued the study. No patients in the cefiderocol group and one patient (471005) in the meropenem group discontinued the study, which was due to an SAE of abnormal hepatic function.

A similar number of patients in both treatment groups discontinued study treatment due to TEAEs, as noted in Table 27 below. A listing of each discontinuation and an assessment of relatedness to study drug by the investigator and reviewer is noted in Section 17, Table 69. The most common TEAE leading to discontinuation in both treatment groups involved hepatotoxicity (elevated liver tests). In the cefiderocol group, hepatic-related TEAEs that may have resulted in treatment discontinuation (reviewer assessment was 'related') included increases in aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased, and blood alkaline phosphatase (ALP) increased, abnormal liver function test (LFT) abnormal, increased LFT increased, and hepatic failure and in the meropenem group, hepatic-related TEAEs included increased hepatic enzyme increased. In the cefiderocol group, two additional TEAEs [(acute myocardial infarction ([MI]) and cerebrovascular accident (CVA)] may have resulted in treatment discontinuation. Also, in another patient, acute respiratory distress syndrome (ARDS), due to progression of the original NP may have resulted in treatment discontinuation and the need for rescue antibacterial drugs. In the meropenem group, systemic inflammatory response syndrome (SIRS), acute respiratory failure, and respiratory failure may have resulted in treatment discontinuation due to progression of the original NP. The other TEAEs leading to discontinuation appeared to be unrelated to treatment discontinuation.

Table 27. TEAEs by System Organ Class Leading to Discontinuation, Safety Population, APEKS-NP Trial

System Organ Class Preferred Term	Cefiderocol N=148	Meropenem N=150	Total N=298	Risk Difference
Any TEAE leading to discontinuation	12 (8.1)	14 (9.3)	26 (8.7)	-1.2 (-7.6, 5.2)
Investigations	5 (3.4)	5 (3.3)	10 (3.4)	0.1 (-4.0, 4.2)
Alanine aminotransferase increased	2 (1.4)	0	2 (0.7)	1.4 (-0.5, 3.2)
Aspartate aminotransferase increased	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Blood alkaline phosphatase increased	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Liver function test abnormal	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Liver function test increased	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Hepatic enzyme increased	0	5 (3.3)	5 (1.7)	-3.3 (-6.2, -0.5)
Nervous system disorders	4 (2.7)	1 (0.7)	5 (1.7)	2.0 (-0.9, 5.0)
Autonomic nervous system imbalance	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Cerebrovascular accident	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Stroke in evolution	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Brain oedema	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.8, 1.9)
Hepatobiliary	2 (1.4)	1 (0.7)	3 (1.0)	0.7 (-1.6, 3.0)
Hepatic failure	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Hepatocellular injury	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Hepatic function abnormal	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Gastrointestinal disorders	2 (1.4)	1 (0.7)	3 (1.0)	0.7 (-1.6, 3.0)
Gastric hemorrhage	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Intestinal infarction	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Upper gastrointestinal hemorrhage	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Cardiac disorders	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Acute myocardial infarction	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Metabolism and nutrition disorders	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Lactic acidosis	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)

System Organ Class Preferred Term	Cefiderocol N=148	Meropenem N=150	Total N=298	Risk Difference
Respiratory, thoracic and mediastinal disorders	1 (0.7)	2 (1.3)	3 (1.0)	-0.6 (-2.9, 1.7)
Acute respiratory distress syndrome	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Acute respiratory failure	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Pulmonary congestion	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Respiratory failure	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Infections and infestations	1 (0.7)	4 (2.7)	5 (1.7)	-2.0 (-4.9, 0.9)
Septic shock	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Acinetobacter infection	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Meningitis bacterial	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Sepsis	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Urinary tract infection	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Blood and lymphatic system disorders	0	2 (1.3)	2 (0.7)	-1.3 (-3.2, 0.5)
Disseminated intravascular coagulation	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Leukopenia	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
General disorders and administration site conditions	0	2 (1.3)	2 (0.7)	-1.3 (-3.2, 0.5)
Multiple organ dysfunction syndrome	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Systemic inflammatory response syndrome	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)

Source: adae.xpt; Software: Python
All values are expressed as n (%) except those in the Risk Difference column. The Rsk Difference column shows absolute difference (with 95% confidence interval) between total treatment and comparator.
Treatment-emergent adverse events defined as adverse events that started after the initial dose of study treatment or comparator and up to the EOS
Abbreviations: CI, confidence interval; EOS, end of study; N, number of subjects in treatment arm; n, number of subjects with adverse event; TEAE, treatment-emergent adverse event

7.6.5. Treatment-Emergent Adverse Events

TEAEs occurred in over 85% of patients in both treatment groups, with a risk difference of 1.8 (Table 28). In this table, grouped queries were created in which similar TEAEs were pooled to detect a safety signal. Individual PTs are listed under each grouped query term. The grouped queries demonstrating a frequency at least 2% higher in the cefiderocol group than in the meropenem group were UTI, arrhythmia, anemia, cardiac arrest, HTN, pleural effusion, hypomagnesemia, and hypoglycemia. For labeling, a higher cut-off of 4% rather than 2% was proposed due to a large number of TEAEs and for consistency with other recent antibacterial drug labels. Selected ARs in ≥4% of patients in the cefiderocol group were elevated liver tests, anemia, hypokalemia, diarrhea, hypomagnesemia, and atrial fibrillation. The reasons for selecting these ARs in labeling among all TEAEs occurring in at least 4% of patients are noted below.

Table 28. Grouped Queries by Preferred Term, Occurring in at Least 4% of Patients in Cefiderocol Arm, Safety Population, APEKS-NP Trial

Grouped Query Preferred Term	Cefiderocol N=148	Meropenem N=150	Total N=298	Risk Difference
Any TEAE	130 (87.8)	129 (86.0)	259 (86.9)	1.8 (-5.8, 9.5)
Elevated liver tests	24 (16.2)	25 (16.7)	49 (16.4)	-0.5 (-8.9, 8.0)
Aspartate aminotransferase increased	10 (6.8)	6 (4.0)	16 (5.4)	2.8 (-2.3, 7.9)
Alanine aminotransferase increased	9 (6.1)	6 (4.0)	15 (5.0)	2.1 (-2.9, 7.1)
Gamma-glutamyltransferase increased	5 (3.4)	2 (1.3)	7 (2.3)	2.1 (-1.3, 5.5)
Hepatic enzyme increased	4 (2.7)	10 (6.7)	14 (4.7)	-4.0 (-8.8, 0.8)
Transaminases increased	4 (2.7)	4 (2.7)	8 (2.7)	0.0 (-3.7, 3.7)
Liver function test increased	2 (1.4)	0	2 (0.7)	1.4 (-0.5, 3.3)
Blood alkaline phosphatase increased	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Liver function test abnormal	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Hypertransaminasemia	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Blood bilirubin increased	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Urinary tract infection (UTI)	25 (16.9)	18 (12.0)	43 (14.4)	4.9 (-3.1, 12.9)
UTI	23 (15.5)	16 (10.7)	39 (13.1)	4.8 (-2.8, 12.4)
Escherichia UTI	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Pyelonephritis	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Pyelonephritis chronic	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Cystitis	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
UTI bacterial	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Arrthymia	19 (12.8)	13 (8.7)	32 (10.7)	4.1 (-2.9, 11.1)
Atrial fibrillation	7 (4.7)	4 (2.7)	11 (3.7)	2.0 (-2.3, 6.3)
Bradycardia	3 (2.0)	2 (1.3)	5 (1.7)	0.7 (-2.2, 3.6)
Tachycardia	2 (1.4)	2 (1.3)	4 (1.3)	0.1 (-2.5, 2.7)
Ventricular extrasystoles	2 (1.4)	1 (0.7)	3 (1.0)	0.7 (-1.6, 3.0)
Sinus tachycardia	1 (0.7)	2 (1.3)	3 (1.0)	-0.6 (-2.9, 1.7)
Arrhythmia	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Atrial flutter	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Cardiovascular insufficiency	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Extrasystoles	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Supraventricular tachycardia	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Supraventricular extrasystoles	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Anemia	18 (12.2)	13 (8.7)	31 (10.4)	3.5 (-3.4, 10.4)
Anemia	12 (8.1)	12 (8.0)	24 (8.1)	0.1 (-6.1, 6.3)
Iron deficiency anemia	3 (2.0)	0	3 (1.0)	2.0 (-0.3, 4.3)
Anemia of chronic disease	2 (1.4)	0	2 (0.7)	1.4 (-0.5, 3.3)
Hemoglobin decreased	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Iron deficiency	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Normochromic normocytic anemia	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
RBC count decreased	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Nephrogenic anemia	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Hypokalemia	16 (10.8)	23 (15.3)	39 (13.1)	-4.5 (-12.1, 3.1)
Hypokalemia	16 (10.8)	23 (15.3)	39 (13.1)	-4.5 (-12.1, 3.1)
Blood potassium decreased	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Diarrhea	13 (8.8)	13 (8.7)	26 (8.7)	0.1 (-6.3, 6.5)
Diarrhea	13 (8.8)	13 (8.7)	26 (8.7)	0.1 (-6.3, 6.5)

Grouped Query Preferred Term	Cefiderocol N=148	Meropenem N=150	Total N=298	Risk Difference
Pneumonia	13 (8.8)	12 (8.0)	25 (8.4)	0.8 (-5.5, 7.1)
Pneumonia	11 (7.4)	8 (5.3)	19 (6.4)	2.1 (-3.4, 7.6)
Lung infection	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Pneumonia bacterial	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Acinetobacter infection	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Pneumonia necrotising	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Pseudomonas infection	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Cardiopulmonary failure	10 (6.8)	13 (8.7)	23 (7.7)	-1.9 (-8.0, 4.2)
Pulmonary edema	3 (2.0)	1 (0.7)	4 (1.3)	1.3 (-1.3, 3.9)
Cardiac failure	2 (1.4)	4 (2.7)	6 (2.0)	-1.3 (-4.5, 1.9)
Pulmonary congestion	2 (1.4)	3 (2.0)	5 (1.7)	-0.6 (-3.5, 2.3)
Ejection fraction decreased	2 (1.4)	0	2 (0.7)	1.4 (-0.5, 3.3)
Cardiac failure congestive	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Right ventricular failure	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Cardiac failure acute	0	2 (1.3)	2 (0.7)	-1.3 (-3.1, 0.5)
Acute pulmonary edema	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Cardiopulmonary failure	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Encephalopathy	10 (6.8)	10 (6.7)	20 (6.7)	0.1 (-5.6, 5.8)
Delirium	5 (3.4)	4 (2.7)	9 (3.0)	0.7 (-3.2, 4.6)
Confusional state	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Encephalopathy	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Metabolic encephalopathy	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Abnormal behaviour	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Hypoxic-ischemic encephalopathy	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Coma	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Disorientation	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Septic encephalopathy	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Cardiac arrest	10 (6.8)	7 (4.7)	17 (5.7)	2.1 (-3.2, 7.4)
Cardiac arrest	7 (4.7)	5 (3.3)	12 (4.0)	1.4 (-3.1, 5.9)
Cardio-respiratory arrest	3 (2.0)	2 (1.3)	5 (1.7)	0.7 (-2.2, 3.6)
Hypertension	10 (6.8)	7 (4.7)	17 (5.7)	2.1 (-3.2, 7.4)
Hypertension	5 (3.4)	7 (4.7)	12 (4.0)	-1.3 (-5.8, 3.2)
Blood pressure increased	2 (1.4)	0	2 (0.7)	1.4 (-0.5, 3.3)
Hypertensive crisis	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Essential hypertension	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Hypertensive heart disease	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Pleural effusion	10 (6.8)	6 (4.0)	16 (5.4)	2.8 (-2.3, 7.9)
Pleural effusion	10 (6.8)	6 (4.0)	16 (5.4)	2.8 (-2.3, 7.9)
Constipation	9 (6.1)	7 (4.7)	16 (5.4)	1.4 (-3.7, 6.5)
Constipation	7 (4.7)	6 (4.0)	13 (4.4)	0.7 (-3.9, 5.3)
Ileus paralytic	2 (1.4)	1 (0.7)	3 (1.0)	0.7 (-1.6, 3.0)
Respiratory failure	8 (5.4)	6 (4.0)	14 (4.7)	1.4 (-3.4, 6.2)
Acute respiratory failure	6 (4.1)	1 (0.7)	7 (2.3)	3.4 (-0.0, 6.8)
Respiratory failure	2 (1.4)	3 (2.0)	5 (1.7)	-0.6 (-3.5, 2.3)
Hypoxia	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Respiratory acidosis	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Respiratory distress	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Hypomagnesemia	8 (5.4)	1 (0.7)	9 (3.0)	4.7 (0.8, 8.6)
Hypomagnesemia	8 (5.4)	1 (0.7)	9 (3.0)	4.7 (0.8, 8.6)

Grouped Query Preferred Term	Cefiderocol N=148	Meropenem N=150	Total N=298	Risk Difference
Candidiasis	7 (4.7)	9 (6.0)	16 (5.4)	-1.3 (-6.4, 3.8)
UTI fungal	4 (2.7)	2 (1.3)	6 (2.0)	1.4 (-1.8, 4.6)
Oral candidiasis	2 (1.4)	0	2 (0.7)	1.4 (-0.5, 3.3)
Fungal sepsis	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Candida infection	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Dermatitis diaper	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Fungal infection	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Infectious disease carrier	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Intertrigo	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Skin Candida	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Systemic Candida	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Pyrexia	7 (4.7)	6 (4.0)	13 (4.4)	0.7 (-3.9, 5.3)
Pyrexia	5 (3.4)	5 (3.3)	10 (3.4)	0.1 (-4.0, 4.2)
Hyperthermia	2 (1.4)	1 (0.7)	3 (1.0)	0.7 (-1.6, 3.0)
Hypoalbuminemia	6 (4.1)	8 (5.3)	14 (4.7)	-1.2 (-6.0, 3.6)
Hypoalbuminemia	5 (3.4)	8 (5.3)	13 (4.4)	-1.9 (-6.5, 2.7)
Blood albumin decreased	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Tracheobronchitis	6 (4.1)	8 (5.3)	14 (4.7)	-1.2 (-6.0, 3.6)
Tracheobronchitis	2 (1.4)	4 (2.7)	6 (2.0)	-1.3 (-4.5, 1.9)
Bronchitis	2 (1.4)	3 (2.0)	5 (1.7)	-0.6 (-3.5, 2.3)
Bronchitis bacterial	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Respiratory tract infection	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Tracheitis	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Anxiety	6 (4.1)	5 (3.3)	11 (3.7)	0.8 (-3.5, 5.1)
Anxiety	3 (2.0)	0	3 (1.0)	2.0 (-0.3, 4.3)
Restlessness	2 (1.4)	2 (1.3)	4 (1.3)	0.1 (-2.5, 2.7)
Agitation	1 (0.7)	3 (2.0)	4 (1.3)	-1.3 (-3.9, 1.3)
Hypoglycemia	6 (4.1)	3 (2.0)	9 (3.0)	2.1 (-1.8, 6.0)
Hypoglycemia	6 (4.1)	3 (2.0)	9 (3.0)	2.1 (-1.8, 6.0)
Hyperinsulinemic hypoglycemia	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)

Source: adae.xpt; Software: Python
All values are expressed as n (%) except those in the Risk Difference column. The Risk Difference column shows absolute difference (with 95% confidence interval) between total treatment and comparator.
Treatment-emergent adverse events are defined as adverse events that started after the initial dose of study treatment or comparator and up to the EOS
Abbreviations: CI, confidence interval; EOS, end of study; N, number of subjects in treatment arm; n, number of subjects with adverse event; RBC, red blood cell; TEAE, treatment-emergent adverse event

Infections

Urinary Tract Infection

While commonly reported as TEAEs in this trial, UTI and pneumonia were not generally considered as selected ARs in labeling as the study drug would not be expected to directly cause the TEAE. UTI was the most frequently reported infection-related TEAE in both treatment groups and was higher in the cefiderocol group by approximately 5%. A total of 42 patients had UTI; 24/148 (16.2%) in the cefiderocol group had a PT of UTI or *E. coli* UTI and 18/150 (12%) in the meropenem group had a PT of UTI, cystitis, or UTI bacterial. The Applicant provided a rationale for increased UTI, which included having a high percentage of intubated patients (60% of the study population), patients admitted in the intensive care unit (68% of the study population), and a higher chance of having a urinary catheter in these populations. The Applicant was unable to explain the increased frequency in the cefiderocol group but pointed to the successful cUTI trial data as evidence of effectiveness of cefiderocol in treatment of cUTI.

To gain a better understanding of the causative pathogen and treatment for these UTIs, information requests were sent to the Applicant. After several attempts at obtaining details not clearly available in the datasets, the following information was reported. One patient ((b) (6)) in the cefiderocol group had a known causative bacterial uropathogen (*E. coli*, susceptibility unknown) at day 26, which was treated with imipenem (IPM) for 3 days. The patient had *P. aeruginosa* NP and completed cefiderocol treatment on day 15 with clinical cure and microbiological eradication; thus, this appeared to be a new infection. Upon review of the narratives, an additional patient ((b) (6)) in the cefiderocol group was found to have urine culture results (*C. albicans*, ESBL *K. pneumoniae*, and *P. aeruginosa*) and the UTI was treated with amikacin and ceftazidime on day 19 (7 days after discontinuation of cefiderocol). While this UTI occurred after the EOT, the same pathogens present in respiratory cultures at baseline (including ESBL *K. pneumoniae)* were present in the urine.

The remaining 40 patients did not have urine culture results. Five patients in each treatment group had a breakthrough infection (i.e., the UTI occurred before EOT). Of these five patients in each of the treatment groups, three in the cefiderocol group and four in the meropenem group were treated with nonstudy antibacterial drugs. In summary, most UTIs were new infections that occurred after the EOT. As the majority required antibacterial therapy, these were indicative of a suspected infection rather than colonization. No information about susceptibility is available to determine resistance to study drug. A sensitivity analysis excluding potentially effective concomitant antibacterial therapy (noted in Section 6.4) would be anticipated to account for antibacterial therapy given for these new infections.

Pneumonia

Pneumonia was reported in 13/148 (8.8%) and 12/150 (8.0%) patients in the cefiderocol and meropenem groups, respectively. With the exception of two patients in the cefiderocol group and one in the meropenem group, all of the other patients received additional antibacterial therapy for the pneumonia TEAE, indicative of suspected or confirmed infection rather than colonization. Except for one patient in the cefiderocol group, all of the pneumonia TEAEs began on or after EOT (i.e., new or recurrent infection rather than breakthrough infections). Five out of 13 patients in the cefiderocol group had at least one baseline nonfermenters (2 with *A. baumannii*, 2 with *P. aeruginosa*, and 1 with both *A. baumannii* and *K. pneumoniae*), and 2 out of 12 patients in the meropenem group had at least one baseline nonfermenter (2 with *P. aeruginosa*).

While the frequency of pneumonia was similar in both treatment groups, five patients in the cefiderocol group and one patient in the meropenem group had both recurrence of at least one of the baseline pathogens and required additional antibacterial therapy, as noted below. In addition, patient ((b) (6)) in the cefiderocol group described below had baseline *Acinetobacter nosocomialis* and *Acinetobacter spp*. in cultures taken 2 days before death but did not receive antibacterial drugs. Seven patients in the meropenem group were given rescue antibacterial drugs but did not have subsequent cultures.

Cefiderocol group:

- (b) (6) Pneumonia bacterial – 40-year-old male with history of HTN, hemorrhagic stroke status post decompressive craniotomy, and tracheostomy developed *A. baumannii* VABP. Cefiderocol was discontinued on day 15 due to increased ALT and AST and thrombocytosis. On day 20, a “sanitation” bronchoscopy was performed and he had an SAE of pneumonia bacterial on day 21 for which he received ciprofloxacin and

tigecycline. The bronchoalveolar lavage (BAL) culture showed *A. baumannii* and *K. pneumoniae*, susceptible to cefiderocol by CLSI criteria. The clinical outcome at TOC was failure. The SAE resolved on day 37 and patient survived at EOS.

- (b) (6) Lung infection – 80-year-old male with atrial fibrillation, alcoholism, and GI adenoma developed a *P. aeruginosa* HABP. Cefiderocol was completed on day 8 with a clinical cure. On day 20, an SAE of lung infection was treated with amikacin and piperacillin. *P. aeruginosa*, susceptible to cefiderocol by CLSI criteria, was noted in sputum culture. The clinical outcome at TOC was cure and relapse at FU. The SAE resolved on day 30 and the patient survived at EOS.
- (b) (6) Pneumonia – 77-year-old male with COPD, myocardial ischemia, and DM developed *Citrobacter freundii* and *Enterobacter aerogenes* VABP. Cefiderocol was discontinued on day 7. On day 15, an SAE of pneumonia aspiration due to methicillin-sensitive *S. aureus* was reported and treated with flucloxacillin. On day 26, another SAE of pneumonia was reported and treated with ciprofloxacin, amikacin, and meropenem. A tracheal aspirate revealed susceptible *E. aerogenes* and *E. coli*. On day 32, the patient had sudden death, which was considered probably related to the new episode of pneumonia and autopsy was not performed.
- (b) (6) Pneumonia – 40-year-old male with a cervical spinal cord injury secondary to a fracture developed *K. pneumoniae* and *P. aeruginosa* VABP. Cefiderocol was given until day 12. On day 19, SAEs of UTI and pneumonia occurred. The tracheal aspirate grew susceptible *P. aeruginosa*, which was treated with amikacin and ceftazidime. The SAE resolved on day 23 and the patient survived at EOS. The clinical outcome was cure at TOC and relapse at FU.
- (b) (6) Pneumonia – 64-year-old male with HTN, COPD, pulmonary mass developed an *A. baumannii, H. influenza, K. pneumoniae*, and *P. aeruginosa* HABP for which he was given cefiderocol until day 21. On day 21, he developed a pneumonia and a tracheal aspirate showed *A. baumannii* for which colistin was given. There was clinical failure at TOC and survival at EOS.
- (b) (6) Pneumonia – 91-year-old male with CKD, HTN, and Parkinson's disease developed an *A. nosocomialis* and *E. coli* HABP for which cefiderocol was given until day 16. At day 14, a tracheal aspirate grew *Acinetobacter spp*. and *E. coli* at the local lab, and he was a clinical failure on that day. On day 16, he developed severe pneumonia and cardiac failure and died due to septic shock and respiratory failure. The case report form mentions that the patient died due to infection at randomization.

Meropenem group:

- (b) (6) Pneumonia – 79-year-old male with HTN, MI, and cardiac failure developed *P. mirabilis* VABP for which meropenem was given until day 10. He had a mild pneumonia on day 16, which was treated with piperacillin-tazobactam. The tracheal aspirate grew susceptible *P. mirabilis, S. marcescens, and K. oxytoca*. There was clinical failure at TOC and relapse at FU.

Candidiasis

The overall frequency of candidiasis as a grouped query was slightly lower in the cefiderocol group, as noted in the table above. Candidiasis is expected to be a common AR in the study setting; the risk factors for invasive fungal disease in critically ill patients include sepsis, broad spectrum antibacterial drugs, central venous catheters, and mechanical ventilation (Muskett et al. 2011). Fungal UTI and oral candidiasis were proposed in ARs ≤4% in cefiderocol labeling. These TEAEs coincided with cefiderocol administration and required systemic antifungal treatment. However, the Applicant disagreed with adding fungal UTI as the etiology was likely due to routine urinary catheter placement in this population in an ICU setting. This was acceptable to the Division as the presence of urinary catheters in all patients with fungal UTI could not be excluded.

Cardiovascular and Pulmonary Disorders

Arrhythmia

As a grouped query, arrhythmias occurred at a higher frequency in the cefiderocol group than in the meropenem group. The FMQ for arrhythmias shows a similar frequency of events as the reviewer-generated grouped query. Of these arrhythmias, atrial fibrillation and bradycardia were proposed as labeled ARs, over 4% and under 4%, respectively. Both ARs were previously reported in the cUTI trial as well. While most patients in the cefiderocol group with either atrial fibrillation or flutter had a prior history, three did not. Patien (b) (6) was a 71-year-old male who developed atrial fibrillation on day 7 while on cefiderocol and required heparin followed by acenocoumarol from day 7 to 26. Patient (b) (6) was a 60-year-old female with myeloma, hypothyroidism, and asthma who developed atrial fibrillation on day 1 which resolved with amiodarone on day 2 while still receiving cefiderocol. Patient (b) (6) was a 57-year-old male with DM, obstructive sleep apnea and MI who developed atrial flutter on day 4 with delirium. He was given amiodarone on day 4 and also was discontinued from the study due to "withdrawal by subject." Patient (b) (6), as discussed in Section 7.7.2, had unexplained bradycardia. Also, there was a greater frequency of bradycardia in the cefiderocol group in the analyses of specific vital signs, as noted in the table below.

The Applicant disagreed with adding bradycardia, atrial fibrillation and flutter to labeling citing that there were no adverse findings in the TQT study and infection itself could lead to atrial fibrillation or flutter. The Division agreed with removal of bradycardia as the events were generally mild and likely confounded by concomitant medications.

Hypertension

The baseline frequency of HTN was over 60% in the study population. The majority of patients with TEAEs related to HTN had a prior history. Two patients ((b) (6)) who did not have a prior history of HTN in the cefiderocol group had a maximum postbaseline systolic blood pressure in the range of 160 to 180 mm Hg and a diastolic blood pressure in the range of 90 to 100 mm Hg. Both patients required antihypertensive medications. This TEAE was not considered an AR because alternative etiologies in a critically ill population (pain, procedures, concomitant medications) are possible. Changes in blood pressure are noted in the table below and appeared to be similar between treatment groups.

Table 29. Subjects With Vital Sign Predefined Category Outliers at Postbaseline Safety Population

Parameter (Unit) Category	Cefiderocol N=148	Meropenem N=150
Systolic blood pressure (mm Hg)		
Value ≥160 or INC ≥20	98 (66.2)	102 (68)
Value ≤90 or DEC ≥20	91 (61.5)	110 (73.3)
Diastolic blood pressure (mm Hg)		
Value ≥105 or INC ≥15	81 (54.7)	80 (53.3)
Value ≤50 or DEC ≥15	90 (60.8)	102 (68)
Pulse rate (bpm)		
Value ≥120 or INC ≥15	84 (56.8)	84 (56)
Value ≤50 or DEC ≥15	113 (76.4)	102 (68)

Source: advs.xpt; Software: R
All values are expressed as n (%).
Abbreviations: bpm, beats per minute; DEC, decrease; INC, increase

Thromboembolic Events

Thromboembolic events were also proposed as ARs under 4% and are discussed in Section 7.7.2. These include arterial thromboembolic events such as MI, CVA (primary SOC, nervous system disorders), and intestinal ischemia and infarction (primary SOC, GI disorders). The FMQ for acute coronary syndrome which contains the same PTs as the myocardial ischemia and infarction also shows a greater frequency in the cefiderocol group as well.

The Applicant disagreed with the inclusion of MI, intestinal ischemia, and CVA in labeling. For MI and intestinal ischemia, the Applicant stated that the TEAEs were not considered related to the drug by the investigators and that most patients had a cardiac history or other complex medical history. However, given the possible safety signal of arterial thromboembolic events and as certain patients did not have a significant prior history of similar events (patients (b) (6) and (b) (6)), drug-induced MI or intestinal ischemia could not be excluded. It was agreed that CVA could be removed as patient (b) (6) had evidence of pre-existing artherosclerosis of the carotid arteries which may have contributed to CVA more than a drug-related etiology.

Cardiac Arrest

Overall, the frequency of cardiac or cardio-respiratory arrest was higher in the cefiderocol group. However, review of the individual cases showed confounding underlying medical history including DM, HTN, atherosclerosis, cardiac failure, and CKD in which relatedness to study drug was difficult to attribute. In the patient ((b) (6)) noted above, the MI was the likely cause of cardiac arrest. Thus, the TEAEs of cardiac arrest were considered to be a consequence of certain events and not ARs, given the underlying severity of illness in the study population.

Cardiopulmonary Failure and Pleural Effusion

Cardiac and pulmonary failure TEAEs that appeared to be similar in pathogenesis were combined, and the frequency was greater in the meropenem group. Three patients (b) (6)) who did not have a prior history of cardiac failure developed pulmonary edema, but each had a history of CKD as a possible confounder. Several patients also had pleural effusion in both treatment groups. In the cefiderocol group, each of these patients had other predisposing conditions (e.g., recent surgery and bed-ridden state, cardiac failure, valvulopathy). One patient ((b) (6)) had SAEs of acute respiratory failure, pleural effusion, and sepsis secondary to HABP, which were considered related to cefiderocol. However, this pleural effusion was noted to be multiloculated on chest ultrasound and may have more of an empyema

rather than simple fluid overload given the recurrence of HABP and sepsis. Thus, these TEAEs were not proposed as ARs in labeling.

Respiratory Failure

The majority of patients with respiratory failure-related TEAEs had an alternative cause for respiratory failure such as fluid overload, worsening of the underlying pneumonia or a new infectious process such as aspiration pneumonia. Thus, this was not proposed as an AR in labeling.

Blood and Lymphatic Disorders

Anemia-related TEAEs were analyzed in detail given the siderophore-based mechanism of cefiderocol. At least 8 out of 18 patients in the cefiderocol group who developed anemia had no prior history of anemia. Although acute infection, blood draws for laboratory studies, or procedures can precipitate anemia, the frequency of anemia-related TEAEs were greater in the cefiderocol arm. There were no specific PTs suggestive of aplastic or hemolytic anemia, however, Coombs' tests, peripheral smears, reticulocyte counts and haptoglobin were not routinely performed. The possibility of immune-related anemia secondary to cefiderocol could not be fully excluded. A few patients with anemia without prior history may have had a positive dechallenge with cefiderocol ([(b) (6)]). A few patients without a prior history ([(b) (6)]) required treatment (i.e., iron or transfusion of blood products). Maximum postbaseline decreases in hemoglobin were overall slightly worse in the cefiderocol group, as noted in the table below (Table 30).

Table 30. Maximum Postbaseline Decreases in Hemoglobin, APEKS-NP Trial

Baseline Hemoglobin Grade[a] Postbaseline Hemoglobin Grade	Cefiderocol N=148	Meropenem N=150
Total subjects (any grade)	91 (61.5)	83 (55.3)
Grade 0		
Grade 1	25 (16.9)	21 (14)
Grade 2	8 (5.4)	11 (7.3)
Grade 3	4 (2.7)	1 (0.7)
Grade 1		
Grade 2	31 (20.9)	20 (13.3)
Grade 3	4 (2.7)	3 (2)
Grade 2		
Grade 3	10 (6.8)	13 (8.7)

Source: ad b.xpt; Software: R
All values are expressed as n (%).
Laboratory grades are based on CTCAE version 5.0.
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; LLN, lower limit of normal

Additional time trends for hemoglobin and hematocrit are shown in figures in Section 17.

The Applicant did not agree with including anemia in the cefiderocol labeling due to the lack of a plausible mechanism and the following specific reasons were cited: the life-span of the erythrocyte is 120 days, and short-term treatment with an iron-binding chelator would not impact erythropoiesis; the nonclinical studies did not show a propensity of cefiderocol to induce red blood cell hemolysis; the clinical studies did not reveal evidence of hemolysis, although no direct tests for hemolysis were performed; including anemia would give a misleading impression that cefiderocol has a direct effect on hematologic parameters. Thus, anemia was removed from the cefiderocol labeling but will continue to be monitored for in the post-marketing setting. One

reassurance that the degree of anemia is not significantly worse in the cefiderocol group as compared to meropenem is that a similar number of patients required blood transfusion, as noted in Table 41.

Thrombocytopenia and thrombocytosis were also noted as ARs. Patient (b) (6) had an SAE of thrombocytopenia as noted in Section 7.6.3. Thrombocytosis occurred in three patients ((b) (6)) that did not appear to have an alternative cause. Patient (b) (6) who had a peak platelet count of 526×10^9/L on day 10 seemed to have a positive dechallenge with cefiderocol.

Electrolyte Abnormalities

Theoretically, while siderophores have a preference for iron-binding, they can also chelate numerous other metals with variable affinities (Schalk et al. 2011). Thus, electrolyte disturbances involving cations were considered as potential ARs. Hypomagnesemia and hypokalemia occurred in ≥4% and hyperkalemia, hypocalcemia, and hyponatremia occurred in ≤4% of patients treated with cefiderocol; these were considered ARs if there was no alternative cause, if there were possible clinical consequences, or if grade 4 toxicity was present.

The PT of hypomagnesemia occurred much more frequently in the cefiderocol group, with a risk difference of 4.7. Eight patients with hypomagnesemia had mild changes in magnesium with grade 0 to 1 toxicity (below lower limit of normal to 0.5 mmol/L) using the Common Terminology Criteria for Adverse Event grading system (National Cancer Institute 2017). Upon examination of hypomagnesemia in laboratory findings, more patients with hypomagnesemia were identified, as noted in the table below. One patient ((b) (6)) had grade 4 hypomagnesemia on day 20 (decreased from 1.86 to 0.27 mmol/L) and normalized after discontinuation of cefiderocol. Except for fluconazole, no concomitant medications were given until day 24. About 10% or more patients in both treatment groups had TEAEs of hypokalemia. Upon examination of hypokalemia in laboratory findings, more patients in the cefiderocol had toxicity grades of 3 or 4 , as noted in the table below. Two patients ((b) (6)) had grade 4 hypokalemia and subsequent fatal cardiac events (cardiac arrest and MI), respectively.

A PT of hyperkalemia was noted in four patients in the cefiderocol group; one of these patients ((b) (6)) did not appear to have an alternative cause for hyperkalemia (increased potassium from 4.9 to 5.7 mmol/L) such as concomitant medications or CKD on day 4. A few patients in the cefiderocol group had grade 4 toxicity in laboratory findings for hypocalcemia and hyponatremia. Patient (b) (6) had an TEAE of hypocalcemia from day 3 to 38 with an eventual SAE of status epilepticus. Patient (b) (6) had an TEAE of hyponatremia without any apparent alternative cause.

Table 31. Laboratory Abnormalities for Electrolytes (CTCAE Version 5.0), Worsened Grade, Safety Population, APEKS-NP Trial

	Cefiderocol N=148			Meropenem N=150		
Parameter	**Any Grade**	**Grade 1-2**	**Grade 3-4**	**Any Grade**	**Grade 1-2**	**Grade 3-4**
Magnesium (mmol/L) - decreased	35 (23.6)	34 (23)	1 (0.7)	24 (16)	22 (14.7)	2 (1.3)
Calcium (mmol/L) - decreased	49 (33.1)	34 (23)	15 (10.1)	46 (30.7)	33 (22)	13 (8.7)
Potassium (mmol/L) - decreased	45 (30.4)	27 (18.2)	18 (12.2)	44 (29.3)	31 (20.7)	13 (8.7)
Potassium (mmol/L) - increased	22 (14.9)	18 (12.2)	4 (2.7)	21 (14)	18 (12)	3 (2)
Sodium (mmol/L) - decreased	41 (27.7)	37 (25)	4 (2.7)	55 (36.7)	47 (31.3)	8 (5.3)

Source: ad b.xpt; Software: R
All values are expressed as n (%).

Laboratory grades are based on CTCAE version 5.0.
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; LLN, lower limit of normal

The Applicant disagreed with inclusion of all of the electrolyte disturbances discussed above citing that there cannot be a chelating effect with cefiderocol for Mg^{2+} and Ca^{2+}based on non-clinical (spectrophotometry) studies, and that there were no notable changes from baseline for potassium or calcium. However, the Division proposed to retain these ARs as there were some grade 4 changes as noted in the table above. The difference in frequency of hypomagnesemia was particularly striking, and hypokalemia has been frequently labeled in other antibacterial drug labels. The following electrolyte abnormalities were included in labeling: hypomagnesemia, hypokalemia, hyperkalemia, and hypocalcemia.

Gastrointestinal Disorders

GI symptoms such as nausea, vomiting, diarrhea, and abdominal pain are often considered common ARs associated with antibacterial drugs. Of these symptoms, diarrhea occurred in ≥4% of patients in both treatment groups and was considered treatment-related by the investigator in a few patients in each group. Most TEAEs of diarrhea were mild to moderate and did not lead to treatment discontinuation. A slightly higher risk difference (≤2%) was noted in the cefiderocol group than in the meropenem group for nausea, abdominal pain and constipation, as noted in the table of FMQs below. Four patients (2.7%) in each treatment group developed *C. difficile* infection or colitis. All *C. difficile* infections resolved except for in one patient ((b) (6)) in the cefiderocol group, in which the outcome was unknown.

Hepatobiliary Disorders and Hepatic Investigations

The overall frequency of any hepatic TEAE, including those in the investigations and hepatobiliary SOC, was similar in both treatment groups. Clinically significant increases in liver tests in both treatment groups are noted in Section 18 (Table 69 of treatment discontinuations, and section on Hy's law). The Applicant did not identify any cases of Hy's law in either treatment group. Patients in the cefiderocol group who had SAEs, treatment discontinuations, or liver events considered related to study drug are summarized below. Specific hepatic TEAE occurring in the meropenem group are not discussed below as elevated liver tests are noted as ARs in meropenem labeling.

- (b) (6) had SAEs of LFT increase and hepatic enzyme increase, respectively. Both events met biochemical criteria for Hy's law but had confounding medical history as noted in Section 17.
- (b) (6) – 77-year-old male with a history of hepatomegaly had a moderate TEAE of hepatic failure and SAEs of AST (≥19x upper limit of normal [ULN]) and ALT (≥10x) increased (all with onset on day 5) for which cefiderocol was discontinued. The SAEs were assessed as related by the investigator and reviewer.
- (b) (6) – 61-year-old male with no relevant medical history had an SAE of LFT increase (increased AST ≥4x ULN) and prothrombin time-INR ≥1.5x ULN on day 4, which led to discontinuation of cefiderocol. The SAE was assessed as related to multiple organ failure by the investigator and related to both multiple organ failure and cefiderocol by the reviewer.
- (b) (6) – 65-year-old male with relevant medical history had an SAE of increased transaminases (AST ≥5x ULN and PT-INR ≥1.5x ULN) on day 15 which was considered

related per the investigator and the reviewer and resolved by day 29. The ultrasound showed diffuse hepatic parenchymal disease and acalculous cholecystitis and the gastroenterologist suspected drug-induced liver injury on top of chronic liver disease.

- (b) (6) – 83-year-old male with no relevant medical history had an SAE of hepatocellular injury on day 3 along with other SAEs of lactic acidosis, intestinal infarction, and septic shock that led to death. Due to many confounders, hepatocellular injury was difficult to attribute to cefiderocol alone.
- (b) (6) – 86-year-old male with no relevant medical history had a TEAE of LFT increase (AST ≥5x ULN and ALT increased ≥1.5x ULN) on day 4 for which cefiderocol was discontinued. Meropenem was started and the liver tests resolved by day 9.
- (b) (6) – 64-year-old male with no relevant medical history had a TEAE of blood ALP increase ≥10x ULN on day 3 that led to treatment discontinuation. The study drugs were withdrawn as a precautionary measure with a possible relationship to linezolid. Also on day 3, the patient had a moderate TEAE of cholecystitis. Meropenem was started. The TEAE did not resolve by the time of the patient death on day 8 due to myocardial infarction.
- (b) (6) – 52-year-old female with no relevant medical history had a TEAE of gamma-glutamyl transferase (GGT) increased on day 6 that was considered related to study treatment by the investigator. However, the GGT was elevated at baseline (89 U/L) and all subsequent GGT values available in the datasets were lower than at baseline.
- (b) (6) – 78-year-old male with no relevant medical history had a TEAE of ALT (≥5x ULN, AST ≥4x ULN) increase on day 6 and GGT (≥5x ULN) increase on day 13, which was considered related to cefiderocol by the investigator. Cefiderocol was discontinued due to ALT increased on day 5 and AST/ALT increase resolved on day 13.
- (b) (6) – 58-year-old male with no relevant medical history developed a TEAE of hypertransaminasemia on day 4 which included increased ALT (≥1.5x ULN) and GGT (≥1x ULN), which reached ≥15x ULN by day 22. No cause was identified for increased GGT after discontinuation of cefiderocol on day 15. Given the similarity to other PTs in the investigations SOC, hypertransaminasemia was included in elevated liver tests grouped query as noted in the table of TEAE ≥4% and was also added to labeling in section 6.

Table 32. Hepatic TEAEs, Safety Population, APEKS-NP Trial

System Organ Class Preferred Term	Cefiderocol N=148	Meropenem N=150
Any hepatic TEAE	29 (19.6)	30 (20.0)
Investigations	23 (15.5)	25 (16.7)
Aspartate aminotransferase increased	10 (6.8)	6 (4.0)
Alanine aminotransferase increased	9 (6.1)	6 (4.0)
Gamma-glutamyltransferase increased	5 (3.4)	2 (1.3)
Liver function test increased	2 (1.4)	0
Transaminases increased	4 (2.7)	4 (2.7)
Blood alkaline phosphatase increased	1 (0.7)	1 (0.7)
Liver function test abnormal	1 (0.7)	1 (0.7)
Blood bilirubin increased	0	1 (0.7)
Hepatic enzyme increased	4 (2.7)	10 (6.7)

System Organ Class Preferred Term	Cefiderocol N=148	Meropenem N=150
Hepatobiliary disorders	8 (5.4)	6 (4.0)
Cholestasis	2 (1.4)	0
Cholecystitis	2 (1.4)	1 (0.7)
Cholelithiasis	1 (0.7)	0
Hepatic failure	1 (0.7)	0
Hepatic vein dilatation	1 (0.7)	0
Hepatomegaly	1 (0.7)	0
Hypertransaminasemia	1 (0.7)	0
Cholecystitis acute	0	1 (0.7)
Hepatic cyst	0	1 (0.7)
Hepatic function abnormal	0	1 (0.7)
Hepatocellular injury	1 (0.7)	3 (2.0)

Source: adae.xpt; Software: R
All values are expressed as n (%).
Abbreviations: TEAE, treatment-emergent adverse event

In addition, the maximum increases liver test postbaseline are shown in the table below (Table 33).

Table 33. Maximum Increases in Liver Tests Postbaseline, Safety Population, APEKS-NP Trial (Unireview Table 59, Request 18)

Test	Baseline Value	Maximum Increase in Value	Cefiderocol N=148	Meropenem N=150
ALT (U/L)	≤ULN	>ULN	39 (26.4)	46 (30.7)
		>3x ULN	4 (2.7)	7 (4.7)
		>5x ULN	1 (0.7)	5 (3.3)
	ULN to ≤3x ULN	>3x ULN	4 (2.7)	6 (4)
		>5x ULN	6 (4.1)	6 (4)
AST (U/L)	≤ULN	>ULN	38 (25.7)	40 (26.7)
		>3x ULN	2 (1.4)	4 (2.7)
		>5x ULN	3 (2)	5 (3.3)
	ULN to ≤3x ULN	>3x ULN	5 (3.4)	8 (5.3)
		>5x ULN	4 (2.7)	7 (4.7)
ALP (U/L)	≤ULN	>ULN	35 (23.6)	44 (29.3)
		>3x ULN	0	1 (0.7)
	ULN to ≤3x ULN	>3x ULN	4 (2.7)	4 (2.7)
		>5x ULN	1 (0.7)	0
BILI (mcmol/L)	≤ULN	>ULN	11 (7.4)	17 (11.3)
		>1.5x ULN	3 (2)	10 (6.7)
		>3x ULN	1 (0.7)	1 (0.7)
	>ULN	>1.5x ULN	14 (9.5)	15 (10)
		>3x ULN	0	2 (1.3)
GGT (U/L)	≤ULN	>ULN	23 (15.5)	28 (18.7)
		>2.5x ULN	7 (4.7)	7 (4.7)
		>5x ULN	4 (2.7)	2 (1.3)
	ULN to ≤2.5x ULN	>2.5x ULN	13 (8.8)	14 (9.3)
		>5x ULN	5 (3.4)	3 (2)
	>2.5x ULN to ≤5x ULN	>5x ULN	4 (2.7)	5 (3.3)

Source: adae.xpt and adlb.xpt; Software: R
All values are expressed as n (%).
Laboratory grades are based on CTCAE version 5.0.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin; CTCAE, Common Terminology Criteria for Adverse Events; GGT, gamma glutamyl transferase; ULN, upper limit of normal

Gall bladder disorders (cholecystitis, cholelithiasis, gallbladder pain) had been previously reported in the cUTI trial and noted as ARs in labeling. A few patients had suspected cholecystitis ([redacted]) and cholestasis ([redacted]) in the cefiderocol group, and these ARs were proposed in labeling (frequency under 4%).

Coagulation Disorders and Iron Metabolism

Based on the cUTI trial, labeling includes increased prothrombin time and prothrombin time-INR. In this trial, routine measurements aPTT and prothrombin time-INR were conducted. Of the eight patients in the cefiderocol group with baseline prothrombin time-INR values of ≤1.5 that increased to >1.5, only two were not on anticoagulation. Both patients ([redacted]) had increased prothrombin time-INR at least 12 days after EOT with cefiderocol. Patients [redacted] (not on anticoagulation) and [redacted] (on heparin) in the cefiderocol group had an INR of 107 and 100, which was out of the normal reference range; these high values were isolated and other INR values 7 days before and after were within the normal range. It is unclear whether these INR values represent laboratory error. Patient [redacted] was a 75-year-old male with no relevant medical history completed cefiderocol on day 9 and developed a prothrombin time-INR of 100 and an aPTT of 38 on day 22. Confounding medications included antibacterial drugs a few days prior to enrollment and miconazole until day 3. No bleeding events were reported in these eight patients. The Applicant agreed with adding prolonged prothrombin time, prothrombin time-INR, and aPTT to the ARs section in labeling.

Table 34. Maximum Postbaseline Increase in PT-INR and aPTT, Safety Population, APEKS-NP Trial

Parameter Baseline Value	Maximum Increase in Value	Cefiderocol N=148	Meropenem N=150
PT-INR			
≤1.5	>1.5	8 (5.4)	6 (4)
≥1.5	>1.5	0 (0)	2 (1.3)
aPTT			
Any value	1-1.5 x ULN	39 (26.4)	37 (24.7)
	1.5-2 x ULN	15 (10.1)	13 (8.7)
	2-4 x ULN	7 (4.7)	15 (10)
	>=4 x ULN	2 (1.4)	2 (1.3)

Source: ad b.xpt; Software: R
All values are expressed as n (%).
Laboratory grades are based on CTCAE version 5.0.
Abbreviations: aPTT, activated partial thromboplastin time; CTCAE, Common Terminology Criteria for Adverse Events; PT-INR, prothrombin time-international normalized ratio; ULN, upper limit of normal

Specialized tests for iron metabolism (hepcidin, total iron-binding capacity, iron, and transferrin saturation were performed. Changes in these parameters over time from screening to TOC did not appear to be clinically relevant. Figures demonstrating these changes are noted in Section 17.

Nervous System Disorders

Three patients (2.0%) and two (1.3%) in the cefiderocol and meropenem groups, respectively had a seizure during the study. One patient ([redacted]) of the three in the cefiderocol group had status epilepticus, which was discussed in Section 7.6.3. The other two patients in the cefiderocol group did not have a history of seizures. One had a history of craniocerebral injury and subdural hematoma status post evacuation and developed seizures during treatment, and the other, who had a history of cerebrovascular disorder, cerebral atrophy, and hypocalcemia, developed

seizures 14 days after EOT. Seizure is proposed as an AR as it is associated with β-lactam therapy and was noted in both the cUTI and APEKS-NP trials. Dizziness, headache, and paresthesia are also listed as ARs under 4% in labeling as they were noted to be treatment-related by the investigator. The Applicant did not agree with adding headache as the investigator clarified that the event occurred due to malposition during prolonged infusion of study drug and there was no positive rechallenge.

Hypersensitivity Reactions

The grouped query for rash showed a similar frequency of rash-related TEAEs in both treatment groups (5 [3.4%] in the cefiderocol and 5 [3/3%] in the meropenem group). In the cefiderocol group, one patient each had dermatitis, dermatitis allergic, rash, rash erythematous, and skin irritation. One patient ((b) (6)) in the cefiderocol group had a treatment-related rash per the investigator which began on day 6 and resolved by day 11. There were three additional patients who had PTs (stridor, bronchospasm, and laryngeal edema) related to the hypersensitivity Standardised Medical Dictionary for Regulatory Activities Query.

- (b) (6) – 55-year-old female with a history of asthma and COPD who received cefiderocol until day 8. On days 5 and 7, she was treated with new medications for depression (clonazepam, escitalopram, piracetam) and HTN (amlodipine). Dermatitis developed on day 20 and resolved on day 26 after treatment with chloropyramine. On day 36, she developed an SAE of inspiratory stridor which resolved with tracheoscopy and balloon dilatation. Possible etiologies of dermatitis and stridor include delayed-type hypersensitivity reaction to cefiderocol or any of the other concomitant medication or perhaps a nondrug related reaction (e.g., due to an underlying medical condition such as asthma).
- (b) (6) – 82-year-old male with myasthenia gravis and interstitial lung disease who completed cefiderocol on day 22. Bronchospasm developed on day 43 and resolved by day 49 after treatment with salbutamol. The investigator did not consider the TEAE related to cefiderocol. The bronchospasm may have been related to the patient's underlying medical conditions.
- (b) (6) – 71-year-old female with asthma and CVA who completed cefiderocol on day 15. Laryngeal edema developed on day 13 and resolved by day 18 after treatment with dexamethasone. No etiology was given and the investigator did not consider the TEAE related to cefiderocol.

TEAEs were also evaluated using narrow FMQs. The frequencies of certain TEAEs were similar to the reviewer created grouped queries. A risk difference of ≥2% was noted for the following FMQs: anemia, arrythmia, acute coronary syndrome, hypoglycemia, and anxiety. Hypoglycemia was not considered an AR due to confounding by underlying medical history (e.g., DM) and concomitant medications. Anxiety and insomnia was also not considered ARs due to possible alternate etiologies and narratives describing details about TEAEs in the psychiatric disoders SOC were not available.

Table 35. FDA MedDRA Queries[a] by System Organ Class Occurring at Higher Frequency in Treatment Arm Than in Comparator Arm

System Organ Class FMQ (Narrow)	Cefiderocol N=148	Meropenem N=150	Total N=298	Risk Difference
Blood and lymphatic system disorders				
Anemia	18 (12.2)	15 (10.0)	33 (11.1)	2.2 (-5.0, 9.3)
Cardiac disorders				
Arrhythmia	18 (12.2)	12 (8.0)	30 (10.1)	4.2 (-2.7, 11.0)
Acute coronary syndrome	3 (2.0)	0	3 (1.0)	2.0 (-0.2, 4.3)
Myocardial infarction	3 (2.0)	0	3 (1.0)	2.0 (-0.2, 4.3)
Myocardial ischemia	3 (2.0)	0	3 (1.0)	2.0 (-0.2, 4.3)
Systemic hypertension	9 (6.1)	7 (4.7)	16 (5.4)	1.4 (-3.7, 6.5)
Endocrine disorders				
Hypoglycemia	6 (4.1)	3 (2.0)	9 (3.0)	2.1 (-1.8, 5.9)
Gastrointestinal disorders				
Nausea	4 (2.7)	2 (1.3)	6 (2.0)	1.4 (-1.8, 4.6)
Abdominal pain	3 (2.0)	1 (0.7)	4 (1.3)	1.4 (-1.3, 4.0)
Constipation	7 (4.7)	6 (4.0)	13 (4.4)	0.7 (-3.9, 5.4)
Diarrhea	13 (8.8)	13 (8.7)	26 (8.7)	0.1 (-6.3, 6.5)
General disorders and administration site conditions				
Fatigue	3 (2.0)	1 (0.7)	4 (1.3)	1.4 (-1.3, 4.0)
Pyrexia	7 (4.7)	6 (4.0)	13 (4.4)	0.7 (-3.9, 5.4)
Hepatobiliary disorders				
Hepatic injury	14 (9.5)	12 (8.0)	26 (8.7)	1.5 (-4.9, 7.9)
Hepatic failure	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Cholecystitis	2 (1.4)	2 (1.3)	4 (1.3)	0.0 (-2.6, 2.6)
Immune system disorders				
Angioedema	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Infections and infestations				
Pneumonia	15 (10.1)	14 (9.3)	29 (9.7)	0.8 (-5.9, 7.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Malignancy	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Nervous system disorders				
Paresthesia	2 (1.4)	0	2 (0.7)	1.4 (-0.5, 3.2)
Headache	3 (2.0)	1 (0.7)	4 (1.3)	1.4 (-1.3, 4.0)
Seizure	3 (2.0)	2 (1.3)	5 (1.7)	0.7 (-2.2, 3.6)
Dizziness	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Confusional state	6 (4.1)	6 (4.0)	12 (4.0)	0.1 (-4.4, 4.5)
Psychiatric disorders				
Anxiety	3 (2.0)	0	3 (1.0)	2.0 (-0.2, 4.3)
Insomnia	5 (3.4)	3 (2.0)	8 (2.7)	1.4 (-2.3, 5.1)
Depression	3 (2.0)	2 (1.3)	5 (1.7)	0.7 (-2.2, 3.6)
Psychosis	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Respiratory, thoracic and mediastinal disorders				
Cough	2 (1.4)	0	2 (0.7)	1.4 (-0.5, 3.2)
Bronchospasm	2 (1.4)	1 (0.7)	3 (1.0)	0.7 (-1.6, 3.0)

System Organ Class FMQ (Narrow)	Cefiderocol N=148	Meropenem N=150	Total N=298	Risk Difference
Skin and subcutaneous tissue disorders				
Erythema	2 (1.4)	0	2 (0.7)	1.4 (-0.5, 3.2)

Source: adae.xpt; Software: Python
All values are expressed as n (%) except those in the risk difference column. Risk difference column shows absolute difference (with 95% confidence interval) between total treatment and comparator.
Treatment-emergent adverse events defined as adverse events that started after the initial dose of study treatment or comparator and up to the EOS
The severity of an event was graded by the investigator or subinvestigator according to the following definitions: Mild: A finding or symptom is minor and does not interfere with usual daily activities; Moderate: The event causes discomfort and interferes with usual daily activity or affects clinical status; Severe: The event causes interruption of the subject's usual daily activities or has a clinically significant effect
Arrhythmia includes arrhythmia, atrial fibrillation, atrial flutter, bradycardia, extrasystoles, sinus tachycardia, supraventricular extrasystoles, supraventricular tachycardia, tachycardia, ventricular extrasystoles; Anemia includes anemia, anemia of chronic disease, hemoglobin decreased, hemorrhagic anemia, iron deficiency anemia, nephrogenic anemia, normochromic normocytic anemia; Hypoglycemia includes hyperinsulinaemic hypoglycemia, hypoglycemia; Acute coronary syndrome includes acute myocardial infarction, angina unstable, myocardial infarction; Myocardial infarction includes acute myocardial infarction, myocardial infarction; Myocardial ischemia includes acute myocardial infarction, angina unstable, myocardial infarction; Anxiety includes anxiety; Hepatic injury includes alanine aminotransferase increased, aspartate aminotransferase increased, cholestasis, hepatic failure, hepatic function abnormal, hepatocellular injury, hepatomegaly; Systemic hypertension includes blood pressure increased, essential hypertension, hypertension, hypertensive crisis; Insomnia includes insomnia; Nausea includes nausea; Paraesthesia includes hypoesthesia oral, paraesthesia; Cough includes cough, hemoptysis; Erythema includes palmar erythema, rash erythematous; Abdominal pain includes abdominal pain, abdominal pain upper, acute abdomen; Fatigue includes asthenia, fatigue, malaise; Headache includes headache; Pneumonia includes infectious pleural effusion, lung abscess, lung infection, pneumonia, pneumonia aspiration, pneumonia bacterial, pneumonia necrotising, pulmonary tuberculosis; Constipation includes constipation; Pyrexia includes hyperthermia, pyrexia; Seizure includes seizure, status epilepticus; Depression includes depressed mood, depression, persistent depressive disorder; Bronchospasm includes asthma, bronchial hyperreactivity, bronchospasm; Hepatic failure includes hepatic failure; Angioedema includes laryngeal edema; Malignancy includes lung cancer metastatic; Dizziness includes dizziness; Psychosis includes hallucination, visual; Diarrhea includes diarrhea; Confusional state includes confusional state, delirium, disorientation; Cholecystitis includes cholecystitis, cholecystitis acute, gallbladder empyema
Abbreviations: CI, confidence interval; EOS, end of study; FMQ, FDA medDRA query; N, number of subjects in treatment arm; n, number of subjects with adverse event

Other clinical safety assessments regarding iron metabolism, Hy's law screening, postbaseline changes in renal function, a full listing of TEAEs by PT and SOC, TEAEs by demographic subgroups, a listing of treatment discontinuations and deaths are noted in Section 17.

7.6.6. Laboratory Findings

See sections above for clinically significant laboratory findings.

7.7. Review Issues Relevant to the Evaluation of Risk

7.7.1. Important Risk Review Issue #1

Issue

Analysis of ACM.

Background

ACM was an important review issue as the CREDIBLE-CR trial reviewed in the original NDA showed an increased frequency in mortality in patients treated with NP as well as bloodstream infections (BSIs) and sepsis. Briefly, the greatest mortality imbalance disfavoring cefiderocol was noted in the NP subgroup at day 49 [19/45 (42.2%) in the cefiderocol, 4/22 (18.2%) in best available therapy treatment groups, difference 24.0, 95% CI 2.4 to 45.7]. Also, in the cefiderocol

group, the majority of deaths due to treatment failure, as determined by an external adjudication committee, occurred in patients who had a baseline clinical diagnosis of NP; 13 patients had a baseline clinical diagnosis of NP among 16 patients with treatment failure.

Thus, ACM was reviewed in the APEKS-NP trial to determine if there were any similarities to deaths that had occurred in the CREDIBLE-CR trial.

Assessment

The table below (Table 36) shows the number of deaths based on the study day on which the TEAE occurred and the corresponding SOC. The majority of deaths occurred before 14 days in the cefiderocol group and between 14 to 28 days in the meropenem group. There was no other consistent pattern among deaths based on study day. There was a slightly greater frequency of deaths related to the infections/infestations and GI disorders SOC in the cefiderocol group.

Table 36. TEAEs Leading to Deaths by System Organ Class, Safety Population, APEKS-NP Trial

	Cefiderocol N=148				Meropenem N=150			
Primary SOC	**<14 Days**	**14-28 Days**	**>28 Days**	**Total**	**<14 Days**	**14-28 Days**	**>28 Days**	**Total**
Number of deaths	18 (12.2)	13 (8.8)	8 (5.4)	39 (26.4)	14 (9.3)	16 (10.7)	5 (3.3)	35 (23.3)
Cardiac disorders	4 (2.7)	6 (4.1)	1 (0.7)	11 (7.4)	7 (4.7)	8 (5.3)	0	15 (10)
Infections and infestations	3 (2.0)	3 (2.0)	3 (2.0)	9 (6.1)	2 (1.3)	2 (1.3)	2 (1.3)	6 (4.0)
General disorders and administration site conditions	1 (0.7)	3 (2.0)	3 (2.0)	7 (4.7)	2 (1.3)	3 (2.0)	1 (0.7)	6 (4.0)
Respiratory, thoracic and mediastinal disorders	3 (2.0)	2 (1.4)	2 (1.4)	7 (4.7)	1 (0.7)	3 (2.0)	2 (1.3)	6 (4.0)
Nervous system disorders	5 (3.4)	0	0	5 (3.4)	4 (2.7)	3 (2.0)	1 (0.7)	8 (5.3)
Gastrointestinal disorders	3 (2.0)	0	0	3 (2.0)	0	1 (0.7)	0	1 (0.7)
Hepatobiliary disorders	1 (0.7)	0	0	1 (0.7)	0	0	0	0
Injury, poisoning and procedural complications	0	1 (0.7)	0	1 (0.7)	0	0	0	0
Investigations	1 (0.7)	0	0	1 (0.7)	1 (0.7)	0	0	1 (0.7)
Metabolism and nutrition disorders	1 (0.7)	0	0	1 (0.7)	0	1 (0.7)	0	1 (0.7)
Neoplasms benign, malignant and unspecified*	1 (0.7)	0	0	1 (0.7)	0	0	0	0
Vascular disorders	1 (0.7)	0	0	1 (0.7)	1 (0.7)	1 (0.7)	0	2 (1.3)
Blood and lymphatic system disorders	0	0	0	0	1 (0.7)	0	0	1 (0.7)

Source: adae.xpt; Software: R
All values are expressed as n (%).
* Neoplasms include cysts and polyps.
Abbreviations: SOC, system organ class; TEAE, treatment-emergent adverse event

Table 37 displays the TEAEs leading to death by PT. After grouping of similar terms, the top five most commonly reported PTs leading to death were CVA, intestinal ischemia or infarction, MI, septic shock, and pulmonary embolism (PE). Cerebrovascular accident, intestinal ischemia/infarction, MI and PE were considered as special events related to thrombosis and embolism and are discussed in Section 7.7.2. Infection and respiratory-related PTs (e.g., pneumonia, septic shock, sepsis, respiratory failure, ARDS, MODS) that could indicate progression of the original NP at randomization were evaluated to analyze differences between treatment groups. The majority of patients with these PTs appeared to have worsening of the underlying NP, which may have led to subsequent death. However, the frequency of these events appeared to be relatively similar between treatment groups.

Investigator and reviewer assessments of relatedness to study drug with reviewer comments for each individual patient are noted in Table 69, Section 17. The investigator assessed relatedness with a category of 'related' or 'not related.' The assessment of relatedness by the reviewer was categorized by 'related,' 'not related,' and 'indeterminate.' The relatedness to treatment was considered 'indeterminate' if there were several confounders or if the study drug had been discontinued too early to determine causality. If the death appeared to be related to the study drug, it was further categorized as a possible AR or due to lack of efficacy (LOE). Relatedness to study drug was attributed to LOE when there was evidence of clinical failure, when there was recurrence of the original pathogen(s), or when rescue antibacterial drugs were provided.

The reviewer's assessment of relatedness to study drug in the three categories discussed above showed similarities between treatment arms. In the cefiderocol group, 14 deaths were considered related to study drug (4 due to ARs, 9 due to LOE, 1 with both AR and LOE). In the meropenem group, 14 deaths were considered related to study drug (4 due to ARs, 10 due to LOE). The patients who experienced ARs in the cefiderocol group ([redacted] (b) (6)) are described in Section 7.7.2 as they had serious thromboembolic events. Patient [redacted] (b) (6) had unexpected unstable angina and MI during treatment, and this was confounded by a cardiac history. The patients who were considered to have had LOE contributing to death in both treatment groups usually had infection-related death (NP, sepsis, or septic shock due to the original baseline pathogen(s) or a complication of the underlying diagnosis (ARDS, multiorgan failure). Many of the deaths considered 'not related' were attributable to underlying comorbidities and to events preceding randomization. For instance, several patients in both treatment groups had CVA in the month prior to randomization, with subsequent cardiac-related deaths. The majority of poststroke deaths are attributed to neurological damage, and cardiovascular complications are the second leading cause of poststroke mortality (Chen et al. 2017).

Table 37. Deaths, Safety Population, APEKS-NP Trial

Preferred Term	Cefiderocol N=148	Meropenem N=150	Total N=298	Risk Difference
TEAE leading to death	39 (26.4)	35 (23.3)	74 (24.8)	3.1 (-6.7, 12.9)
Cerebrovascular accident[a]	2 (1.4)	0	2 (0.7)	1.4 (-0.5, 3.2)
Intestinal ischemia[b]	2 (1.4)	0	2 (0.7)	1.4 (-0.5, 3.2)
Myocardial infarction[b]	2 (1.4)	0	2 (0.7)	1.4 (-0.5, 3.2)
Septic shock	3 (2.0)	1 (0.7)	4 (1.3)	1.3 (-1.3, 3.9)
Pulmonary embolism[b]	3 (2.0)	2 (1.3)	5 (1.7)	0.7 (-2.2, 3.6)
Acute respiratory distress syndrome	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Autonomic nervous system imbalance	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Gastrointestinal hemorrhage	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)

Preferred Term	Cefiderocol N=148	Meropenem N=150	Total N=298	Risk Difference
Blood pressure increased	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Lactic acidosis	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Lung cancer metastatic	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Peripheral vascular disorder	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Subarachnoid hemorrhage	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Sudden death	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
General physical health deterioration	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Cardiac arrest[b]	6 (4.1)	6 (4.0)	12 (4.0)	0.1 (-4.4, 4.5)
Sepsis[b]	2 (1.4)	2 (1.3)	4 (1.3)	0.1 (-2.5, 2.7)
Multiple organ dysfunction syndrome	4 (2.7)	4 (2.7)	8 (2.7)	0.0 (-3.6, 3.7)
Pneumonia[b]	4 (2.7)	4 (2.7)	8 (2.7)	0.0 (-3.6, 3.7)
Cardiovascular insufficiency	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.8, 1.9)
Hepatoxicity[b]	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.8, 1.9)
Intracranial pressure increased	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.8, 1.9)
Respiratory failure[b]	2 (1.4)	3 (2.0)	5 (1.7)	-0.6 (-3.6, 2.3)
Acute abdomen	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Brain injury	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Bronchopleural fistula	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Cardiogenic shock	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Cardiovascular disorder	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Disseminated intravascular coagulation	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Encephalopathy	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Hypotension	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Hypovolemia	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Shock hemorrhagic	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Systemic inflammatory response syndrome	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Urinary tract infection	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Death (due to unknown cause)	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Brain edema	1 (0.7)	5 (3.3)	6 (2.0)	-2.6 (-5.8, 0.6)
Cardiopulmonary failure[b]	3 (2.0)	7 (4.7)	10 (3.4)	-2.7 (-6.8, 1.4)

Source: adae.xpt; Software: Python
All values in the cefiderocol and meropenem columns are expressed as n (%). Risk difference column shows absolute difference (with 95% confidence interval) between cefiderocol and meropenem.
Treatment-emergent adverse events are defined as adverse events that started after the initial dose of study treatment or comparator and up to the EOS
[a] Cerebrovascular accident includes cerebrovascular accident, stroke in evolution; Intestinal ischemia includes intestinal infarction, intestinal ischemia; Myocardial infarction includes acute myocardial infarction, myocardial infarction, Pulmonary embolism includes pulmonary embolism, pulmonary artery thrombosis; Cardiac arrest includes cardiac arrest, cardio-respiratory arrest; Pneumonia includes pneumonia (one patient had PT of pneumonia and death for which the verbatim term was death due to pneumonia), pneumonia necrotising, pseudomonal infection; Hepatoxicity includes hepatic enzyme increased, hepatocellular injury; Respiratory failure includes acute respiratory failure, respiratory failure; Cardiopulmonary failure includes cardiac failure, cardiac failure acute, cardiac failure congestive, cardiopulmonary failure, pulmonary edema
Abbreviations: CI, confidence interval; EOS, end of study; N, number of subjects in treatment arm; n, number of subjects with adverse event; TEAE, treatment-emergent adverse event

Mortality by Baseline Microbiological Characteristics

In patients with known MIC, whether the MIC was >8 mcg/mL for meropenem or <8 mcg/mL, the trend for ACM at the EOS was worse in the cefiderocol group as compared to the meropenem group. . Of the top five pathogens at baseline, subgroups with greater mortality in the cefiderocol group included those with *A. baumannii* and *E. coli* NP. Mortality in patients with baseline *A. baumannii* species was analyzed further.

Table 38. All-Cause Mortality at EOS by Meropenem Susceptibility and Baseline Pathogens, Safety Population

Characteristic	Cefiderocol N=148	Meropenem N=150	Risk Difference	95% CI
MIC >8 mcg/mL for meropenem[a]				
No	21/89 (23.6)	19/84 (22.6)	1.0	(-11.6, 13.5)
Yes	12/30 (40.0)	9/26 (34.6)	5.4	(-19.9, 30.7)
Top 5 pathogens				
Klebsiella pneumoniae	15/48 (31.3)	14/44 (31.8)	-0.6	(-19.6, 18.4)
Pseudomonas aeruginosa	4/24 (16.7)	7/24 (29.2)	-12.5	(-36.0, 11.0)
Acinetobacter baumannii	9/23 (39.1)	7/24 (29.2)	10.0	(-17.0, 37.0)
Escherichia coli	6/19 (31.6)	4/22 (18.2)	13.4	(-13.0, 39.8)
Enterobacter cloacae	0/7 (0.0)	2/8 (25.0)	-25.0	

Source: adsl.xpt; admbo.xpt.
All values in the cefiderocol and meropenem columns are expressed as n (%). Risk Difference column shows absolute difference between cefiderocol and meropenem. Confidence intervals for the risk difference, using Wald method, are computed when both arms contain at least 10 subjects in the subgroup. Subjects with unknown survival status at EOS are considered deaths.
[a] 63 subjects have missing MIC data
Abbreviations: CI, confidence interval;; EOS, end of study; MIC, minimum inhibitory concentration

In patients who had *A. baumannii* complex (includes *A. baumannii* and *A. nosocomialis*) at baseline, there was slightly greater mortality at all the time points in the cefiderocol group than in the meropenem group., as noted in Table 39. Of these patients who died by EOS, a similar number of patients in each treatment group had meropenem nonsusceptible *A. baumannii* complex.

Table 39. Mortality in Patients With Baseline *A. baumannii Complex* Species

All-Cause Mortality	Cefiderocol	Meropenem	Difference	(95% CI)
Day 14	5/26 (19.2)	4/25 (16.0)	3.2	(-17.7, 24.1)
Day 28[a]	9/26 (34.6)	6/25 (24.0)	10.6	(-14.2, 35.4)
EOS[a]	10/26[b] (38.5)	7/25[c] (28.0)	10.5	(-15.2, 36.1)

Source: adsl.xpt; admbo.xpt.
All values in the cefiderocol and meropenem columns are expressed as n/N (%). 26 subjects in the cefiderocol arm and 25 subjects in the meropenem arm were known to be infected at baseline with an *A. baumannii complex* species. Confidence intervals for the difference in mortality rates computed using the Wald method.
[a] One cefiderocol subject had unknown status at day 28 and at EOS and was considered as having an outcome of death.
[b] 6 meropenem nonsusceptible, 3 meropenem susceptible,1 unknown status.
[c] 7 meropenem nonsusceptible.
Abbreviations: CI, confidence interval; EOS, end of study

An additional sensitivity analysis was conducted in which clinical success was defined as clinical cure at TOC and survival at EOS. Clinical success occurred in 12/26 (46.2%) cefiderocol-treated patients and 13/25 (52.0%) meropenem-treated patients (difference: -5.8, 95% CI -33.2, 21.6). Overall outcomes in the patients with baseline *A. baumannii* complex appeared to be worse in patients treated with cefiderocol as compared to meropenem. However, mortality in this subset of patients in APEKS-NP trial is still within the range of mortality reported among patients with Acinetobacter infections in the ICU setting (approximately 25% in patients with susceptible strains and up to 70% in patients with carbapenem-resistant strains (Spellberg and Bonomo 2014).

Mortality by Subgroups

Several subgroups were examined based on demographic variables and clinical characteristics and are shown in the next table (Table 40). The following subgroups were associated with an absolute mortality rate that was 10% higher in the cefiderocol than in the meropenem group at

EOS: male gender, age ≥75 years, Asian race, Asia-Pacific region, creatinine clearance <30 mL/min, and empiric treatment status of 'yes.' Other TEAEs were also analyzed by demographic subgroups as noted in Section 17. Compared to Asian patients in the meropenem group, Asian patients in the cefiderocol group had a higher frequency of ventilation at randomization (43.9% versus 34.9%), clinical pulmonary infection score ≥6 (14.6% versus 9.3%), disease severity (41.5% versus 23.3%), intensive care unit admission (46.3% versus 32.6%), and *Acinetobacter spp.* at baseline (14.7% versus 8.6%). The mean and median APACHE II score, clinical pulmonary infection score, and Sequential Organ Failure Assessment score were similar among Asian patients in both groups. There are limitations of this subgroup analysis, including the inability to adjust for multiple variables.

Table 40. Summary of All-Cause Mortality at EOS by Subgroups of Safety Population

Characteristic	Cefiderocol N=148	Meropenem N=150	Risk Difference	95% CI
Demographic characteristics				
Gender				
Male	34/101 (33.7)	23/104 (22.1)	11.5	(-0.6, 23.7)
Female	8/47 (17.0)	12/46 (26.1)	-9.1	(-25.7, 7.6)
Age group				
<65 years	18/65 (27.7)	12/58 (20.7)	7.0	(-8.1, 22.1)
≥65 to <75 years	8/43 (18.6)	14/45 (31.1)	-12.5	(-30.3, 5.3)
≥75 years	16/40 (40.0)	9/47 (19.1)	20.9	(2.0, 39.7)
Race*				
White	29/102 (28.4)	28/100 (28.0)	0.4	(-12.0, 12.8)
Black or AA	0/0 (0.0)	0/1 (0.0)		
Asian	13/44 (29.5)	6/44 (13.6)	15.9	(-1.0, 32.8)
Other	0/2 (0.0)	1/4 (25.0)	-25.0	
Region				
North America	1/6 (16.7)	0/6 (0.0)	16.7	
Europe	29/99 (29.3)	29/100 (29.0)	0.3	(-12.3, 12.9)
Asia-Pacific	12/43 (27.9)	6/44 (13.6)	14.3	(-2.5, 31.1)
Hispanic/Latino[a]				
Hispanic/Latino	0/4 (0.0)	0/3 (0.0)	0.0	
Not Hispanic/Latino	41/140 (29.3)	34/139 (24.5)	4.8	(-5.6, 15.2)
Clinical characteristics				
Diagnosis at baseline				
HABP	19/60 (31.7)	15/61 (24.6)	7.1	(-8.9, 23.1)
VABP	18/60 (30.0)	18/65 (27.7)	2.3	(-13.6, 18.2)
HCABP	5/28 (17.9)	2/24 (8.3)	9.5	(-8.5, 27.5)
APACHE II score				
≤15	17/75 (22.7)	13/78 (16.7)	6.0	(-6.6, 18.6)
16-19	10/32 (31.3)	7/26 (26.9)	4.3	(-19.1, 27.8)
≥20	15/41 (36.6)	15/46 (32.6)	4.0	(-16.0, 24.0)
CPIS				
<6	17/74 (23.0)	19/91 (20.9)	2.1	(-10.6, 14.8)
6-7	20/60 (33.3)	8/40 (20.0)	13.3	(-3.9, 30.5)
8-9	5/12 (41.7)	6/16 (37.5)	4.2	(-32.5, 40.8)
>9	0/2 (0.0)	2/3 (66.7)	-66.7	
Bacteremia status				
No	37/135 (27.4)	30/134 (22.4)	5.0	(-5.3, 15.3)
Yes	5/13 (38.5)	5/16 (31.2)	7.2	(-27.6, 42.1)

Characteristic	Cefiderocol N=148	Meropenem N=150	Risk Difference	95% CI
Creatinine clearance				
>120 mL/min	4/22 (18.2)	4/26 (15.4)	2.8	(-18.5, 24.1)
>80-120 mL/min	11/33 (33.3)	7/35 (20.0)	13.3	(-7.5, 34.2)
>50-80 mL/min	11/44 (25.0)	6/37 (16.2)	8.8	(-8.7, 26.2)
30-50 mL/min	7/29 (24.1)	13/32 (40.6)	-16.5	(-39.6, 6.6)
<30 mL/min	9/20 (45.0)	5/20 (25.0)	20.0	(-8.9, 48.9)
MDRD-eGFR				
≥90	9/35 (25.7)	10/47 (21.3)	4.4	(-14.2, 23.1)
60 to <90	14/50 (28.0)	8/39 (20.5)	7.5	(-10.3, 25.2)
30 to <60	12/43 (27.9)	10/43 (23.3)	4.7	(-13.8, 23.1)
15 to <30	4/9 (44.4)	4/10 (40.0)	4.4	
<15	3/11 (27.3)	3/11 (27.3)	0	(-37.2, 37.2)
Empiric treatment failure status				
No	26/99 (26.3)	25/102 (24.5)	1.8	(-10.3, 13.8)
Yes	16/49 (32.7)	10/48 (20.8)	11.8	(-5.6, 29.3)
ICU admission				
No	6/45 (13.3)	5/51 (9.8)	3.5	(-9.3, 16.4)
Yes	36/103 (35.0)	30/99 (30.3)	4.6	(-8.3, 17.6)
Ventilation status				
No	10/57 (17.5)	9/63 (14.3)	3.3	(-9.9, 16.4)
Yes	32/91 (35.2)	26/87 (29.9)	5.3	(-8.5, 19.0)

Source: adsl.xpt.
All values in the cefiderocol and meropenem columns are expressed as n/N' (%) unless specified otherwise. Confidence intervals for the risk difference, using Wald method, are computed when both arms contain at least 10 subjects in the subgroup.
Note: Subjects with unknown EOS survival status are considered deaths
[*] 1 subject has unknown race
[a] 12 subjects have unknown status
Abbreviations: AA, African American; APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; CPIS, clinical pulmonary infection score; eGFR, estimated glomerular filtration rate; EOS, end of study; HABP, hospital-acquired bacterial pneumonia; HCABP, healthcare-associated bacterial pneumonia; ICU, intensive care unit; MDRD, Modification of Diet in Renal Disease; MIC, minimum inhibitory concentration; VABP, ventilator-associated bacterial pneumonia

Mortality by Blood Transfusion

As cefiderocol acts as a siderophore and there was theoretical concern of decreased uptake in bacterial cells in a state of iron excess, mortality was analyzed based on receipt of blood transfusion. There is no increased receipt of blood transfusions nor an increased risk of mortality in patients receiving blood transfusion in either treatment group.

Table 41. All-Cause Mortality by Receipt of Blood Transfusion

Receipt of Transfusion	Cefiderocol N=148 n/N' (%)	Meropenem N=150 n/N' (%)	Risk Difference
Blood transfusion	10/33 (30.3)	14/31 (45.2)	-14.9
No blood transfusion	29/115 (25.2)	21/119 (17.6)	7.6

Source: adsl.xpt and admh.xpt; Software: R
All values in the cefiderocol and meropenem columns are expressed as n/N' (%).

Conclusions

An analysis of mortality by the different parameters discussed above showed that overall mortality in patients was relatively similar in both treatment groups. There was a greater frequency of deaths due to thromboembolic events in the cefiderocol group, and this will be discussed further below. In patients with *Acinetobacter spp*. at baseline, there was also a slightly

higher increased mortality in the cefiderocol group; however, the actual number of deaths was similar, and the groups were relatively small.

7.7.2. Important Risk Review Issue #2

Issue

Increased frequency of serious thromboembolic events in the cefiderocol group

Background

A review of the fatal outcomes suggested a possible pattern of thromboembolic events. We therefore examined the safety population using a custom query and stratified the output on the basis of arterial and venous events. Since venous events may occur as a result of immobility due to hospitalization, arterial events were examined separately.

Assessment

Eleven (7.4%) patients in the cefiderocol group and three (2.0%) patients in the meropenem group had a thromboembolic TEAE considered related to arterial circulation. Of these 11, all but 2 were SAEs (1 developed nonserious unstable angina, but progressed to acute MI; 1 was a nonserious CVA). Of the 11, 9 had fatal outcomes by EOS. MI (including acute MI) and CVA (including cerebral ischemia and stroke in evolution) occurred in ≥2% of patients in the cefiderocol group whereas no patient had MI and 1.4% had CVA (including lacunar stroke) in the meropenem group.

Table 42. Thrombotic and Embolic TEAEs, APEKS-NP Trial

	Cefiderocol (N=148)		Meropenem (N=150)		RD Per
Preferred Term	Events	n (%)	Events	n (%)	Hundred
Arterial thrombosis	12	11 (7.4)	3	3 (2.0)	5.4
Acute myocardial infarction	2	2 (1.4)		0	1.4
Angina unstable	1	1 (0.7)		0	0.7
Cerebral ischemia	1	1 (0.7)		0	0.7
Cerebrovascular accident	3	3 (2.0)	1	1 (0.7)	1.3
Femoral artery embolism		0	1	1 (0.7)	-0.7
Intestinal infarction	1	1 (0.7)		0	0.7
Intestinal ischemia	1	1 (0.7)		0	0.7
Intracardiac thrombus	1	1 (0.7)		0	0.7
Lacunar stroke		0	1	1 (0.7)	-0.7
Myocardial infarction	1	1 (0.7)		0	0.7
Stroke in evolution	1	1 (0.7)		0	0.7
Venous thrombosis	8	5 (3.4)	6	6 (4.0)	-0.6
Deep vein thrombosis	1	1 (0.7)			0.7
Post thrombotic syndrome	1	1 (0.7)			0.7
Pulmonary artery thrombosis	3	3 (2.0)	3	3 (2.0)	0.0
Pulmonary embolism	1	1 (0.7)	2	2 (1.3)	-0.7
Venous thrombosis	2	1 (0.7)	1	1 (0.7)	0.0

Source: Reviewer Table, created in MAED.
Abbreviations: RD, risk difference; TEAE, treatment-emergent adverse event

While the majority of patients in both treatment groups had underlying comorbidities that would predispose them to thromboembolic events, some of the patients had either less confounding medical histories or the event of interest was more unexpected. These cases are noted below. Of note, none of the events were related to study drug per the investigator.

- (b) (6) – 59-year-old male with DM and HTN was diagnosed with a *P. aeruginosa* VABP and randomized to cefiderocol. He had had a prolonged hospitalization and pleural drainage on day 1 for hydropneumothorax. On day 5, he developed bradycardia (pulse 43 beats/minute), and SAEs of acute MI and cardiac arrest which resolved with medical management. The AST and ALT increased to ≥10x ULN and were attributed to cardiac arrest. Cefiderocol treatment was completed on day 8. The aPTT increased to 52 seconds. On day 9, he developed multiple organ dysfunction and died. Autopsy showed postinfarction cardiosclerosis, pneumonia, liver cirrhosis, and acute respiratory insufficiency.
- (b) (6) – 69-year-old female with obesity, CHF, and COPD developed a closed craniocerebral injury on day -16 and was randomized to cefiderocol for an *A. baumannii* HCABP on day 1. Six days after completion of cefiderocol treatment, she had an SAE of CVA which resolved with sequelae (regression of cognitive and motor impairment). Trauma as a cause of craniocerebral injury was not reported. Of note, the Applicant reported that the duplex scan at the time of craniocerebral injury had shown atherosclerotic disease of the carotid arteries. Given this pre-existing condition, CVA was considered to be less likely due to study treatment.
- (b) (6) – 73-year-old female with pulmonary tuberculosis 2 years prior and a neck mass s/p excision with lung metastasis was randomized to cefiderocol for *A. baumannii* VABP. On day -3, she received a blood transfusion for anemia and developed postprocedural hemorrhage on day 3. On days 4 and 5, the patient had severe hypokalemia (potassium decreased from 3.5 to 1.8 mg/dL) and mild chest pain which resolved the next day with potassium and tramadol, respectively. On day 14, an electrocardiogram showed anterior wall ischemia and ST depression, and an SAE of acute MI was reported on day 15. The hemoglobin decreased from 91 to 75 g/L and platelets decreased from 269 to 32×10^9/L. The aPTT increased to 48 from 25 at baseline. Cefiderocol was withdrawn the same day. On day 16, the patient had a cardiorespiratory arrest and the family withdrew care. She died on day 16 due to acute MI.
- (b) (6) – 84-year-old female with emphysema, intracranial aneurysm, and subarachnoid hemorrhage diagnosed 20 years ago was randomized to cefiderocol for *E.coli* VABP. On day 10, she had an SAE of intestinal ischemia. Cyanosis and coldness of the lower limbs were noted and CT confirmed intestinal ischemia, poor contrast enhancement of the small intestine, marked gas in the intestine, portal vein gas, and suspicion of GI necrosis. Due to the patient's age, she was monitored conservatively. On the same day, she developed hypotension and bradycardia and died due to intestinal ischemia. The last day of study drug was day 8.

The frequency of TEAEs related to venous circulation was similar in both groups. Four patients in each treatment group (2.7% in the cefiderocol and 2.6% in the meropenem group) had PE or pulmonary artery thrombosis (an essentially synonymous term). Risk factors for PE include prolonged immobilization, recent surgery, cancer, and recent CVA. The risk of deep vein thrombosis is elevated in the first 1 to 3 months after CVA, in part due to stroke-related immobility, and PE is the most common cause of death at its peak occurrence about 2 to 4 weeks after stroke onset (Kelly et al. 2001). Of these four patients in the cefiderocol group, three had had a CVA within the past month, and one had recent HTN-induced intracerebral hemorrhage.

Despite anticoagulation, all four had fatal outcomes that appeared to be related to the PE. In summary, venous thromboembolic events were more likely to be due to these alternate etiologies.

Conclusion

Due to the increased frequency and timing of these TEAEs in relationship to study drug administration, a drug-induced effect cannot be fully excluded. Given the potential safety risk of thromboembolic events in this trial, cefiderocol labeling will include individual PTs (MI and intestinal ischemia) at a frequency of ≤4% each. The Applicant justified the rationale for exclusion of CVA in labeling which was agreeable to the Divison (see Section 7.6.5). Routine postmarketing surveillance will be recommended to monitor for such events.

The approved labeling of meropenem (section 6, systemic ARs) mentions pulmonary embolus and MI.

7.7.3. Important Risk Review Issue #3

Issue

MIC increases during treatment.

Background

Resistance development during treatment could result in treatment failure. The relationship of a ≥ four-fold increase in MIC from baseline to treatment outcome was examined in the two treatment arms.

Assessment

A total of 19 subjects (9 in the cefiderocol arm and 10 in the meropenem arm) had isolates which showed a four-fold increase in MIC to the study drug (Table 43). In the cefiderocol arm, all except one subject had persistence of the baseline pathogen at TOC or had died. Three of the nine subjects with baseline *A. baumannii* or *K. pneumoniae* died and five subjects were clinical failures. One subject with *K. pneumoniae* developed resistance to cefiderocol (MIC >8 mcg/mL). Two subjects with *A. baumannii* had MIC increases and one subject died. In the meropenem arm, four had clinical failure at TOC and one died.

Four-fold increases in MIC with subsequent death were evaluated to determine clinical correlation; there were four and one patient in the cefiderocol and meropenem groups, respectively. Table 70 provides details for each patient. Of the four patients in the cefiderocol group, two involved treatment failure/lack of efficacy (patient (b) (6)). In both cases, there was a recurrence of pneumonia with at least one baseline pathogen (Enterobacterales) and treatment with rescue antibacterial drugs. Another patient ((b) (6)), had a sudden death with unknown cause and autopsy results were unavailable. The death was assessed as indeterminate due to very limited information leading up to the sudden death. Lastly, one patient ((b) (6)) had autopsy results showing no pneumonia but a hemorrhagic CVA and brain edema as a cause of death; this death was assessed as not related. In the meropenem group, patient (b) (6) had a recurrence of the baseline pathogen and was assessed as having had lack of efficacy, but treatment with rescue antibacterial drugs was not given.

Conclusion

A four-fold MIC increase was noted in a similar number of patients in both treatment groups. However, more patients in the cefiderocol group had an unfavorable outcome (i.e., clinical failure or death, 8/9 in the cefiderocol and 5/10 in the meropenem group). Among patients who had a four-fold MIC increase and death, two patients in the cefiderocol group and one in the meropenem group had death involving lack of efficacy for treatment of the baseline NP.

Table 43. Subjects With 4-Fold-Increase in Cefiderocol MIC During Treatment

USUBID	Treatment Arm	Baseline Pathogen	Pathogen With 4-Fold MIC Increase	MIC Increase(Specimen; Day)	Microbiological Outcome at TOC	Clinical Outcome at TOC
(b) (6)	Cefiderocol	*Acinetobacter baumannii*	*Acinetobacter baumannii*	0.25 to 1 (BAL; day 3)	Indeterminate	Indeterminate
	Cefiderocol	*Enterobacter aerogenes*	*Enterobacter aerogenes*	0.12 to 0.5 (sputum; day 3)	Indeterminate	Failure
	Cefiderocol	*Citrobacter freundii; Enterobacter aerogenes*	*Enterobacter aerogenes*	0.06 to 0.5 (sputum; day 3) 0.06 to 0.25 (Tracheal aspirate; day 15)	Persistence	Failure
	Cefiderocol	*Klebsiella pneumoniae*	*Klebsiella pneumoniae*	0.25 to 1 (Tracheal aspirate, day 17)	Persistence	Indeterminate
	Cefiderocol	*Klebsiella pneumoniae*	*Klebsiella pneumoniae*	≤0.03 to >8 (Tracheal aspirate; day 15)	Persistence	Cure
	Cefiderocol	*Enterobacter cloacae; Serratia marcescens*	*Enterobacter cloacae*	1 to 4 (Tracheal aspirate; day 11)	Persistence	Failure
			Serratia marcescens	0.06 to 0.25 (sputum; day 4)		
	Cefiderocol	*Acinetobacter baumannii*	*Acinetobacter baumannii*	0.12 to 2 (Tracheal aspirate; day 3, day 22 and day 31)	Persistence	Failure
	Cefiderocol	*Klebsiella pneumoniae*	*Klebsiella pneumoniae*	≤0.03 to 0.12 (Tracheal aspirate; day 15)	Persistence	Indeterminate
	Cefiderocol	*Klebsiella pneumoniae*	*Klebsiella pneumoniae*	0.06 to 0.25 (BAL; day 3)	Indeterminate	Failure
	Meropenem	*Acinetobacter baumannii; Klebsiella pneumoniae*	*Klebsiella pneumoniae*	2 to 8 (BAL; day 4)	Eradication	Failure
	Meropenem	*Pseudomonas aeruginosa*	*Pseudomonas aeruginosa*	0.12 to 64 (BAL; day 4)	Eradication	Failure
	Meropenem	*Acinetobacter baumannii*	*Acinetobacter baumannii*	1 to 64 (Tracheal aspirate; day 3)	Indeterminate	Failure
	Meropenem	*Acinetobacter baumannii*	*Acinetobacter baumannii*	1 to 32 (BAL; day 10) 1 to >64 (Tracheal aspirate; day 3)	Persistence	Cure
	Meropenem	*Pseudomonas aeruginosa*	*Pseudomonas aeruginosa*	0.25 to 4 (Tracheal aspirate; day 15 and day 22)	Indeterminate	Cure

USUBID	Treatment Arm	Baseline Pathogen	Pathogen With 4-Fold MIC Increase	MIC Increase(Specimen; Day)	Microbiological Outcome at TOC	Clinical Outcome at TOC
(b) (6)	Meropenem	*Klebsiella pneumoniae; Pseudomonas aeruginosa*	*Pseudomonas aeruginosa*	0.12 to 16 (Tracheal aspirate; day 11)	Indeterminate	Indeterminate
	Meropenem	*Klebsiella pneumoniae; Pseudomonas aeruginosa*	*Pseudomonas aeruginosa*	0.25 to 4 (Tracheal aspirate; day 15)	Persistence	Cure
	Meropenem	*Citrobacter freundii; Enterobacter asburiae*	*Citrobacter freundii*	≤0.03 to 0.12 (Tracheal aspirate; day 3)	Eradication	Cure
	Meropenem	*Acinetobacter baumannii*	*Acinetobacter baumannii*	0.12 to >64 (Tracheal aspirate; day 14 and day 21)	Persistence	Failure
	Meropenem	*Acinetobacter baumannii; Pseudomonas aeruginosa; Stenotrophomonas maltophilia*	*Acinetobacter baumannii*	0.12 to >64 (Sputum; day 8)	Persistence	Cure

Source: Reviewer analysis using MICROB.xpt
Subjects shown in red died; Bacteria in blue considered as colonizers;
Abbreviations: BAL, bronchoalveolar lavage; MIC, minimum inhibitory concentration; TOC, test-of-cure

7.7.4. Important Risk Review Issue #4

No further issues identified.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Renal function was identified to be the only intrinsic factor warranting dose adjustment. The clinical pharmacology review from the original NDA presented dose adjustments for patients with creatinine clearance (CLcr) <60 mL/min including end-stage renal disease (ESRD) patients with intermittent hemodialysis and for patients with CLcr ≥120 mL/min. In addition, we also recommended dose adjustment for patients receiving CRRT. However, it was determined not to include the dosage adjustment for patients receiving CRRT in the labeling at that time because it was agreed that CRRT would not be required in patients with the cUTI, the indication that Fetroja was being labeled for. In this submission, the Applicant included additional in vitro and clinical data that support the recommendation of dose adjustment for patients receiving CRRT. The current review focuses on dose adjustments in patients receiving CRRT based on additional data submitted in this sNDA.

Patients Receiving Continuous Renal Replacement Therapy

Critically ill patients with AKI may be required to receive CRRT including continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), or continuous venovenous hemodiafiltration (CVVHDF). Cefiderocol is supposed to be cleared by CRRT. Therefore, specific dose adjustment needs to be considered for patients receiving CRRT.

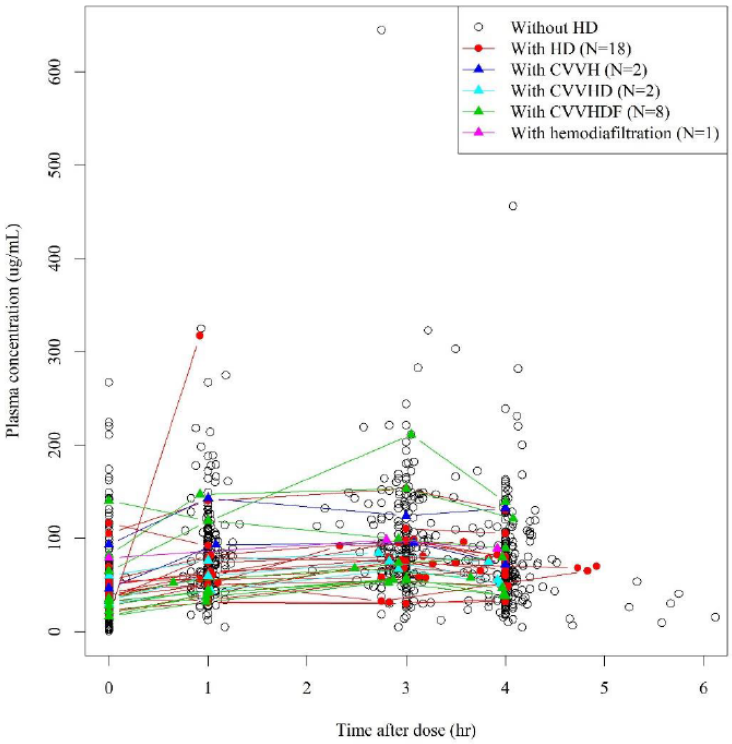
CRRT Dose Adjustment in Phase 2 and Phase 3 Studies

The Applicant adjusted cefiderocol dose at 1 g q12h, 1.5 g q12h, and 1.5 g q12h for patients receiving CVVH, CVVHD, and CVVHDF, respectively, in the CREDIBLE-CR and APEKS-NP trials. The rationale for this dose adjustment is described below.

For patients receiving CRRT, drug clearance (CL) is calculated by the equation $CL = CL_{nonrenal}+CL_{CRRT}$, where $CL_{nonrenal}$ is the remaining systemic clearance of cefiderocol in this patient population that is largely attributed from nonrenal CL, and CL_{CRRT} is the clearance by ultrafiltration or dialysis of CRRT.

When proposing the above mentioned CRRT-mode based dose adjustments, the Applicant estimated the CL_{CRRT} for cefiderocol by using the reported CL_{CRRT} of cefepime by CVVH or CVVHD/CVVHDF since the molecular weights of both drugs are in the similar scale (b) (4) [redacted] was corrected when estimating the CL_{CRRT} of cefepime by CVVH or CVVHD/CVVDF for cefiderocol. In the CREDIBLE-CR and APEKS-NP studies, observed cefiderocol concentration-time profiles were available from a total of 12 patients receiving CRRT who were treated with cefiderocol at the above-mentioned dose adjustments. As shown in Figure 2, the plasma cefiderocol concentrations from these patients were within the range of plasma concentrations for the patients without hemodialysis, CVVH, or CVVHDF.

Figure 2. Observed Plasma Cefiderocol Concentration Profiles for Patients With or Without Hemodialysis in CREDIBLE-CR and APEKS-NP Studies



Source: Figure 2.7.7-16 from 2.7.2 Summary of Clinical Pharmacology – HABP/VABP
Abbreviations: CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; HD, hemodialysis

Recommended Effluent Flow Rate (Q_E)-Based Dose Adjustments in Patients Receiving CRRT

The FDA's clinical pharmacology review team considers that it is not appropriate to recommend one fixed dose regimen for all patients requiring CRRT, either by CVVH or CVVHD/CVVHDF, as administered in CREDIBLE-CR and APEKS-NP studies because Q_E, that is presumed to determine CL_{CRRT} may vary among patients receiving CRRT. The review team conducted separate analyses and recommended a Q_E-based dose adjustment, as described below.

As stated above, CL of cefiderocol in patients receiving CRRT is calculated by the equation $CL = CL_{nonrenal}+CL_{CRRT}$. $CL_{nonrenal}$ of cefiderocol was estimated to be 1.14 L/h, which is the value in subjects with ESRD (study 1222R2113: PK study in subjects with renal impairments). CL_{CRRT} is estimated by the equation $CL_{CRRT} = Q_E \times SC$ or SA (Pistolesi et al. 2019). Q_E is determined by the CRRT conditions, such as ultrafiltration rate for CVVH, dialysis rate, and ultrafiltration rates for CVVHD and CVVHDF, pre- or postfilter replacement fluid flow rate, as well as other factors, such as patient's body weight. SC represents sieving coefficient for convective CRRT modality (e.g., CVVH) and SA represents saturation coefficient for diffusive CRRT modality (e.g., CVVHD). For drugs with molecular weight <1000 Da, it can be assumed that entire free drug can cross the membrane and SC can be approximated to free (i.e., unbound) fraction of drug in plasma (fu) (Pistolesi et al. 2019). Likewise, the SA value for drugs with molecular weight <500 Da is generally superimposable to fu (Pistolesi et al. 2019). Hence, CL_{CRRT} of cefiderocol can be calculated as $CL_{CRRT} = Q_E \times fu$, with fu =0.422 for cefiderocol, regardless of CRRT modality. Therefore, cefiderocol CL in patients receiving CRRT depends on patient's $CL_{nonrenal}$

and Q_E (i.e., $CL = CL_{nonrenal}+Q_E \times fu$). Because Q_E varies with prescriptions of CRRT in different clinical settings and different patient conditions, cefiderocol dosage in patients receiving CRRT is required to be adjusted as a function of Q_E under the assumption that $CL_{nonrenal}$ is not substantially changed in patients receiving CRRT. Therefore, the CRRT-mode based dose adjustments in phase 2 and phase 3 studies are not appropriate to accommodate the various clinical settings where Q_E varies substantially. Thus, we recommend a Q_E-based dose adjustment because Q_E is a net input for determining cefiderocol clearance by CRRT.

In addition, the Applicant conducted an in vitro CRRT study in order to identify CRRT features that could impact the clearance of cefiderocol by CRRT (refer to Section 14.1). These CRRT features include CRRT mode (CVVH versus CVVHD), filter type (b) (4), point of dilution (b) (4), and Q_E (2 versus 4 L/h). The results showed that CRRT mode, filter type, and point of dilution did not have significant effect on the clearance by CRRT. However, Q_E made a significant difference in the calculation of CL_{CRRT}. This confirms our recommendation of Q_E-based dose adjustment.

Cefiderocol dosing regimens in patients undergoing CRRT were then determined based on drug clearance estimated by $CL = CL_{nonrenal}+Q_E \times fu$. With a clinically relevant Q_E range (0.5 to 5 L/h), an average $CL_{nonrenal}$ value from patients with ESRD (i.e., 1.14 L/hr), and an unbound fraction in plasma of 0.422, cefiderocol daily doses were calculated for patients receiving CRRT (Table 44). These doses are expected to provide exposure comparable to the average daily area under the concentration-time curve (AUC, 1,560 mcg·hr/mL) obtained in patients with HABP/VABP from CREDIBLE-CR and APEKS-NP studies. Note that, in this analysis, we presumed that $CL_{nonrenal}$ is not substantially changed in patients receiving CRRT. In addition, we confirmed that the effect of % prefilter replacement fluid (b) (4) on cefiderocol CL is not clinically relevant in patients receiving CRRT (the data are not included).

Table 44. Determination of Cefiderocol Daily Doses for Patients Receiving CRRT According to Effluent Flow Rate (Q_E)

Q_E (L/hr)	0.5	1	2	3	4	5
CL_{CRRT} (L/hr)[a]	0.211	0.422	0.844	1.27	1.69	2.11
CL (L/hr)[b]	1.35	1.56	1.98	2.41	2.83	3.25
Darily dose (grams)[c]	2.11	2.44	3.10	3.75	4.41	5.07

Source: Clinical Pharmacology Review Team's assessments
[a] $CL_{CRRT} = Q_E \times fu$ (fu of cefiderocol =0.422)
[b] $CL = CL_{CRRT}+CL_{nonrenal}$ ($CL_{nonrenal}$ of cefiderocol =1.14 L/hr)
[c] Daily Dose = target daily AUC×CL (target daily AUC =1,560 mcg·hr/mL)
Abbreviations: CL, clearance; CRRT, Continuous Renal Replacement Therapy

Based on the results of above analyses, the Q_E- based cefiderocol dose regimens for patients receiving CRRT were recommended as shown in Table 45.

Table 45. Recommended Dose Regimens Adjusted Based on Effluent Flow Rates (Q_E) for Patients Receiving CRRT

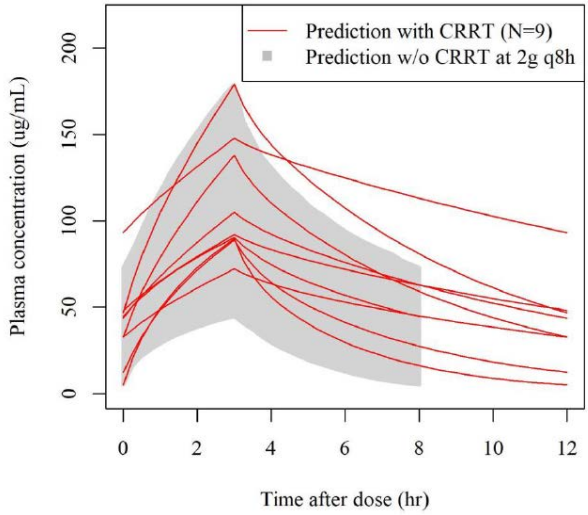
Q_E	Dose Regimens
2 L/hr or less	1.5 grams q12h
2.1 to 3 L/hr	2 grams q12h
3.1 to 4 L/hr	1.5 grams q8h
4.1 L/hr or greater	2 grams q8h

Source: Adapted from Table S1 in the Applicant's study report of s-649266-cpk-007-c
Abbreviations: CRRT, continuous renal replacement therapy; q8h, every 8 hours; q12h, every 12 hours

Prediction of Cefiderocol PK Profiles in Phase 3 CRRT Patients at the Recommended Q_E-Based Dosing Regimens

Of the 12 CRRT patients from phase 3 studies who provided observed PK data, records of Q_E were available from 9 patients. The Applicant predicted PK profiles of cefiderocol in nine patients at the dose regimens adjusted by their actual Q_E according to Table 45, using the post hoc PK parameters that were estimated from a population PK model developed with pooled PK data from phase 1, phase 2, and 3 studies (refer to Section 14.3). Predicted plasma concentrations in the nine patients receiving CRRT are presented in Figure 3 and are superposed with the prediction interval of plasma concentrations in patients not receiving CRRT who were dosed at 2 g every 8 hours. As shown in Figure 3, plasma concentrations of cefiderocol predicted at the recommended Q_E–based dose regimens (Table 45) in patients receiving CRRT were similar to those at 2 g q8h in patients not receiving CRRT. The predicted geometric means of C_{max} and daily AUC in patients receiving CRRT were 107 mcg/mL and 1553 mcg·hr/mL, respectively, which are similar to those from patients with HABP/VABP in phase 3 studies (geometric means C_{max} of 99.7 mcg/mL, daily AUC of 1560 mcg·hr/mL), demonstrating that the recommended Q_E–based dose regimens (Table 45) would provide adequate exposure of cefiderocol in patients receiving CRRT.

Figure 3. Predicted Plasma Concentrations in Patients Receiving CRRT at the Recommended Q_E-Based Dose Regimens and Prediction Interval of Plasma Concentrations for Patients Not Receiving CRRT at 2 g q8h



Source: Figure 1 from the Applicant's study report of s-649266-cpk-007-c
Abbreviations: CRRT, continuous renal replacement therapy; q8h, every 8 hours; q12h, every 12 hours

8.2. Drug Interactions

No updates on drug-drug interactions from the review of original NDA.

8.3. Pediatric Labeling / Plans for Pediatric Drug Development

The initial pediatric study plan (iPSP) was agreed to March 4, 2017, and the amended iPSP for the original NDA was issued by the Division on November 26, 2018. Two pediatric

Postmarketing Requirements (PMRs) were agreed to by the Applicant at the time of approval of the original NDA:

PMR 3744-1: Conduct an open-label randomized multicenter, active-controlled trial to evaluate the PK, safety, and tolerability of Fetroja (cefiderocol) in children from 3 months to less than 18 years of age with cUTI. The dose for this study for children 3 months to less than 18 years of age will be determined by the data from a single-dose, noncomparative study assessing the PK of Fetroja (cefiderocol) in pediatric patients from 3 months to less than 12 years of age with suspected or confirmed gram-negative infections.

Draft Protocol Submission: Submitted [December 5, 2018]
Final Protocol Submission: Submitted [July 26, 2019]
Study Completion: 12/2023
Final Report Submission: 04/2024 [from iPSP]

PMR 3744-2: Conduct an open-label, single arm noncomparative study to evaluate the PK, safety, and tolerability of multiple doses of Fetroja (cefiderocol) in children from birth to less than 3 months of age with suspected or confirmed cUTI. The dose for this study will be determined by the data from a single-dose, noncomparative study assessing the PK of Fetroja (cefiderocol) in pediatric patients from birth to less than 3 months of age with suspected or confirmed gram-negative infections.

Draft Protocol Submission: Submitted [Aug 29, 2019]
Final Protocol Submission: 06/2022
Study Completion: 08/2024
Final Report Submission: 01/2025 [from iPSP]

The following information was conveyed to the Applicant:

(b) (4)

(b) (4)

8.4. Pregnancy and Lactation

See the original review of NDA 209445 (Division of Anti-Infectives 2019). The Applicant did not submit additional nonclinical reproductive toxicology data in this amendment and none were necessary to support the proposed additional clinical indications. Minor changes (regarding exposure multiples) to section 8.1 in labeling were based on human PK data from a clinical study to support the new indication and not on new nonclinical or animal data.

9. Product Quality

The Applicant proposes to use the currently approved and marketed drug product, Fetroja for injection, for the proposed new indication. The drug product formulation remains the same as currently approved in the NDA. Hence, there is no new product quality (chemistry, manufacturing, and controls [CMC]) information associated with this sNDA.

9.1. Device or Combination Product Considerations

This section is not applicable to the sNDA.

10. Human Subjects Protections/Clinical Site and Other GCP Inspections/Financial Disclosure

Two clinical sites were chosen for inspection based upon their high enrollment (sites 466, Czech Republic and 422, Belgium). However, due to the COVID-19 pandemic and associated travel restrictions present during the review cycle, in-person inspections were unable to be completed. The Agency attempted to schedule off-site inspections, but because of the pandemic, these inspections were not able to be conducted. The health authorities of these chosen sites submitted a written justification of the infeasibility of remote inspections (limited resources due to COVID-19, disallowed remote source data verification). As a result, the Office of Scientific Investigations inquired with DAI whether this sNDA could be reviewed without inspections. DAI determined that as the clinical sites did not have any concerning safety or efficacy results, it would be acceptable to proceed with review of the application without inspection of the clinical sites. In addition, during review of the original NDA, four clinical sites were inspected and no major issues were noted.

11. Advisory Committee Summary

An advisory committee was not convened for this sNDA; however, CRRT dosing information is not available in any anti-infective product labeling. The scientific rationale for the addition of dosing recommendations for patients undergoing CRRT was presented at the CDER Medical Policy and Program Review Council on July 22, 2020 (see Sections 8.1 and 14.1 of this review). The Council provided a unanimous, positive opinion on the question of whether to include the dosing recommendations for the CRRT patient population in labeling.

III. Appendices

12. Summary of Regulatory History

The Applicant received marketing registration for Fetroja (cefiderocol) on November 14, 2019, for the indication of treatment of complicated urinary tract infections (cUTI), including pyelonephritis in patients 18 years of age or older who have limited or no alternative treatment options. The Applicant is now seeking approval to add the hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) indications to prescribing information.

Fetroja was granted both fast track and Qualified Infectious Disease Product designations on August 18, 2015, for the HABP/VABP indications. Therefore, this efficacy supplement is being reviewed on a priority review timeline. The supplemental new drug application (sNDA) was received on March 27, 2020, and has a PDUFA goal date of September 27, 2020.

The IND associated with this new drug application (NDA), IND 116787, was originally received on March 22, 2013, and was deemed safe to proceed on April 17, 2013. Like the original cUTI

marketing application, the study conducted in support of the HABP/VABP indications was also conducted under this IND. The sNDA submission contains results of the APEKS-NP (*Acinetobacter baumannii, Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae,* and *Stenotrophomonas maltophilia* in Nosocomial Pneumonia) trial, a phase 3, multicenter, randomized, parallel-group, double-blind, active-controlled noninferiority (NI) trial comparing cefiderocol to meropenem for the treatment of HABP/VABP.

The trial was completed in the fall of 2019, and the Applicant requested a type B pre-sNDA meeting to discuss their plans for submission of the efficacy supplement on December 13, 2019. The meeting was granted by DAI and took place on February 24, 2020. Several key points were discussed during the meeting, namely the clinical microbiology data needed to support the inclusion of *A. baumannii* in the first list of clinically relevant pathogens. Given the lack of gram-negative therapy and the use of monotherapy in the APEKS-NP trial, it was agreed that additional sensitivity analyses may be required to aid in ascertaining treatment effect based on potentially confounding factors.

In addition, during the pre-sNDA meeting, the Applicant informed the Division that they had in vitro minimum inhibitory concentration (MIC) data on less than 100 Achromobacter isolates but that this could be augmented with MIC values and outcome data from the compassionate use program, where Achromobacter was the third most frequent pathogen. It should be noted that postapproval, the Fetroja drug product was not readily commercially available due to manufacturing constraints, which were later resolved in February of 2020. This required care providers to obtain the drug through the compassionate use (i.e., emergency IND) program. The Division advised the Applicant to submit the compassionate use information in the sNDA but did note that the utility of this data will be limited due to being open-labeled and uncontrolled. The Applicant was also advised during the meeting that it would be necessary to provide a justification that pathogens proposed for inclusion in the second list (in vitro activity) in the **Microbiology (12.4)** subsection in the prescribing information are relevant to the HABP/VABP indication.

An additional key point of discussion during the pre-sNDA meeting involved the determination of the susceptibility test interpretive criteria (breakpoints) and the necessity to justify these values with both clinical and animal data. The Applicant indicated during the meeting that they utilized a significant amount of in vivo animal data in their analysis. In combination with human pharmacokinetics/pharmacodynamics (PK/PD) data from plasma and an epithelial lining fluid (ELF) study, they believe they can justify their desired MIC. The Division agreed to consider this information along with the totality of other data as part of the review.

The Division held an internal filing meeting for the sNDA on May 13, 2020, and the Applicant was informed on May 22, 2020, that their application would be reviewed under a priority review time frame. In addition, the Applicant was informed that no filing issues were identified and the application was filed on May 26, 2020. The PDUFA goal date is September 27, 2020.

13. Pharmacology Toxicology Assessments and Additional Information

See the original review of NDA 209445 (Division of Anti-Infectives 2019). The Applicant did not submit additional nonclinical pharmacology/toxicology data in this amendment and none were necessary to support the proposed additional clinical indications.

14. Clinical Pharmacology Assessment: Additional Information

14.1. In Vitro Studies

In Vitro CRRT Study (S-649266-CF-323-N)

The objectives of this study are to determine cefiderocol clearance for continuous renal replacement therapy (CRRT) using an in vitro model and to identify the CRRT operational settings that could impact the clearance of cefiderocol by CRRT.

In vitro CRRT was set up using a Prismaflex 7.2 control machine in continuous venovenous hemofiltration (CVVH) and continuous venovenous hemodialysis (CVVHD) modes. Bovine plasma containing potassium oxalate/sodium-fluoride was used as the vehicle in all experiments. The blood flow rate was fixed at 200 mL/min for all experiments. The study was designed to compare effect of CRRT mode (CVVH versus CVVHD), filter type (b) (4) , point of dilution (b) (4) and effluent flow rate ($Q_{E;}$ 2 versus 4 L/h) on the determination of sieving coefficient (SC), saturation coefficient (SA), and CL_{CRRT}. Cefiderocol was dosed to the CRRT in vitro model, which aimed to provide a mean AUC value comparable to that achieved in cUTI patients administered 2 g every 8 hours during the APEKS-cUTI trial. Serial undiluted prefilter plasma samples of cefiderocol at six time points were collected. Postfilter plasma and effluent samples of cefiderocol and urea were also collected at two time points. Table 46 summarizes all experimental conditions.

Table 46. Summary of In Vitro CRRT Experiments

CRRT mode	Filter type	Blood flow (mL/min)	Ultrafiltrate removal (L/h)	Countercurrent dialysis flow (L/h)	Replacement fluid (L/h)	Point of dilution
CVVH	(b) (4)	200	2	n/a	2	50% pre-filter 50% post-filter
			4		4	
		200	2	n/a	2	50% pre-filter 50% post-filter
			4		4	
CVVH		200	2	n/a	2	100% pre-filter
						100% post-filter
		200	2	n/a	2	100% pre-filter
						100% post-filter
CVVHD		200	n/a	2	n/a	n/a
				4		
		200	n/a	2	n/a	n/a
				4		

Source: Table 1 from the Applicant's study report of s-649266-cf-323-n
Abbreviations: (b) (4) CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; n/a, not applicable; (b) (4)

(b) (4)

Calculation results of cefiderocol CL_{CRRT} from CVVH or CVVHD modes are summarized in Table 47 and Table 48, repectively.

Table 47. Cefiderocol CL_{CRRT} During In Vitro CVVH as Determined by SC×Flow Rate[a]

	SC1	SC2	SC3	SC4	SC5	CL_{TM1} (L/h)	CL_{TM2} (L/h)	CL_{TM3} (L/h)	CL_{TM4} (L/h)	CL_{TM5} (L/h)
CVVH					HF1400					
2 L/h, 50/50%	1.01 ± 0.20	1.10 ± 0.22	1.00 ± 0.09	0.96 ± 0.09	1.00 ± 0.09	2.02 ± 0.40	2.19 ± 0.43	2.00 ± 0.19	1.92 ± 0.17	1.99 ± 0.17
2 L/h, 100/0%	0.81 ± 0.09	0.95 ± 0.11	0.84 ± 0.07	0.84 ± 0.07	0.91 ± 0.08	1.62 ± 0.19	1.89 ± 0.22	1.68 ± 0.15	1.68 ± 0.15	1.82 ± 0.16
2 L/h, 0/100%	1.01 ± 0.07	1.01 ± 0.07	1.08 ± 0.07	1.00 ± 0.07	1.00 ± 0.07	2.02 ± 0.15	2.02 ± 0.15	2.16 ± 0.15	2.01 ± 0.13	2.00 ± 0.13
4 L/h, 50/50%	1.11 ± 0.13	0.95 ± 0.12	1.14 ± 0.12	1.06 ± 0.11	0.98 ± 0.10	4.42 ± 0.54	3.79 ± 0.46	4.58 ± 0.48	4.24 ± 0.44	3.92 ± 0.41
CVVH					M150					
2 L/h, 50/50%	0.82 ± 0.17	0.88 ± 0.19	0.91 ±0.16	0.88 ± 0.15	0.92 ± 0.16	1.63 ± 0.34	1.77 ± 0.37	1.82 ± 0.31	1.76 ± 0.30	1.84 ± 0.31
2 L/h, 100/0%	0.74 ± 0.06	0.87 ± 0.07	0.81 ± 0.05	0.81 ± 0.05	0.88 ± 0.05	1.49 ± 0.12	1.73 ± 0.14	1.61 ± 0.10	1.61 ± 0.10	1.75 ± 0.10
2 L/h, 0/100%	0.94 ± 0.07	0.94 ± 0.07	1.02 ± 0.07	0.95 ± 0.07	0.95 ± 0.07	1.89 ± 0.13	1.89 ± 0.13	2.04 ± 0.14	1.89 ± 0.13	1.89 ± 0.13
4 L/h, 50/50%	0.92 ± 0.11	0.79 ± 0.09	0.95 ± 0.07	0.88 ± 0.06	0.82 ± 0.06	3.67 ± 0.42	3.14 ± 0.36	3.82 ± 0.26	3.53 ± 0.23	3.27 ± 0.22

Source: Table 4 from the Applicant's study report of s-649266-cf-323-n
SC1, SC2, SC3, SC5 and CL_{TM1}, CL_{TM2}, CL_{TM3}, CL_{TM4}, CL_{TM5} represent 5 approaches to calculate sieving coefficient and clearance by CRRT, respectively, based on point of dilution (predilution, postdilution, or both)
All values are presented as mean ± SD
[a] n=2 experiments in each mode, at each flow rate, point of dilution, and filter type (24 total experiments)
Abbreviations: CL_{TM}: transmembrane clearance, which is CRRT clearance determined from in vitro model; CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; SC, sieving coefficient; SD, standard deviation

Table 48. Cefiderocol CL_{CRRT} During In Vitro CVVHD as Determined by SA×Flow Rate[a]

CVVHD	SA1	SA2	CL_{TM1} (L/h)	CL_{TM2} (L/h)	SA1	SA2	CL_{TM1} (L/h)	CL_{TM2} (L/h)
Cefiderocol			HF1400				M150	
2 L/h	0.87 ± 0.03	0.93 ± 0.02	1.74 ± 0.06	1.86 ± 0.04	0.84 ± 0.02	0.90 ± 0.05	1.68 ± 0.04	1.79 ± 0.10
4 L/h	0.87 ± 0.07	0.94 ± 0.05	3.48 ± 0.27	3.79 ± 0.20	0.65 ± 0.03	0.67 ± 0.11	2.59 ± 0.13	2.68 ± 0.42

Source: Table 6 from the Applicant's study report of s-649266-cf-323-n
SA1, SA2 and CL_{TM1}, CL_{TM2} represent 2 approaches to calculate saturation coefficient and clearance by CRRT, respectively, based on point of dilution (predilution, postdilution, or both)
All values are presented as mean ± SD
[a] n=2 experiments in each mode, at each flow rate, point of dilution, and filter type (24 total experiments)
Abbreviations: CL_{TM}: transmembrane clearance, which is CRRT clearance determined from in vitro model; CRRT, continuous renal replacement therapy; CVVHD, continuous venovenous hemodialysis; SA, saturation coefficient; SD, standard deviation

The overall results of this study are summarized below:

- Overall mean (±SD) % adsorption of cefiderocol to the CRRT circuit across all experiments was 10.93±6.28%.
- The mean (±SD) protein binding of cefiderocol to bovine plasma was 36.1±0.04%.
- The point of dilution (pre-, postdilution or both) did not make significant difference in the calculation of CL_{CRRT}.
- There were no significant differences in the calculation of CL_{CRRT} by SC (or SA)×Q_E method and by AUC method.
- CRRT mode, filter type did not affect the calculation of CL_{CRRT} significantly.

- However, significant mean differences were observed in CL_{CRRT} calculated by SC/SA at 4 L/h versus 2 L/h in both CVVH ($P<0.001$) and CVVHD ($P<0.001$) modes, respectively. The significant differences in CL_{CRRT} was observed at flow rates of 4 L/h versus 2 L/h when used (b) (4) ($P<0.001$) and (b) (4) filters ($P<0.001$), respectively.
- A linear regression equation between CL_{CRRT} and flow rate (2 and 4 L/h) was established to be: CL_{CRRT} =0.600 L/h+(flow rate (L/h)×0.606)

We agree with the overall conclusions that CRRT mode, filter type, and point of dilution did not have significant effect on CL_{CRRT} while Q_E made significant difference in the calculation of CL_{CRRT}. However, we consider that the linear regression equation between CL_{CRRT} and flow rate is not appropriate to be used to calculate CL_{CRRT}. This is because that the relationship of CL_{CRRT} and Q_E was established only based on two flow rates (2 and 4 L/h), which is not adequate to precisely define a linear relationship. The additional caveat of this study is the use of bovine plasma as the matrix in the experiments. This could present differences in plasma protein binding, blood/plasma drug partitioning, etc., when compared to human blood.

14.2. In Vivo Studies

Intrapulmonary Pharmacokinetics Study in Ventilated Patients Being Treated for Pneumonia (Study R2117)

Study R2117 was an open-label, multicenter, single-arm, phase 1b study where the primary objective was to assess the concentration of cefiderocol in ELF at steady state in hospitalized subjects with known or suspected bacterial pneumonia on treatment with standard-of-care antibiotics and requiring mechanical ventilation, and to estimate the ratio of the concentration for cefiderocol in ELF relative to plasma in these subjects. Subjects meeting eligibility criteria received 2 g of cefiderocol (or renally adjusted doses) by intravenous (IV) administration over 3 hours q8h or q6h if they had augmented renal function.

Cefiderocol was to be administered for an expected minimum of three doses and up to a total of six doses in subjects with normal or augmented renal function and in subjects with mild or moderate renal impairment. For subjects with severe renal impairment a minimum of six doses up to a total of nine doses were expected. The ELF sample for determination of cefiderocol concentrations was to be collected by BAL procedure at 3, 5, or 7 hours post the start of infusion (depending on the ELF cefiderocol concentration data obtained); after administration of at least three doses of cefiderocol in subjects with normal or augmented renal function and in subjects with mild or moderate renal impairment; and after administration of at least six doses of cefiderocol in subjects with severe renal impairment.

Table 49 presents plasma and ELF concentrations of cefiderocol and ELF/plasma concentration ratios from study R2117. The ELF concentrations were 3.10 to 20.7 mcg/mL at the end of infusion and 7.19 to 15.9 mcg/mL at 2 hours after the end of infusion. The geometric mean ELF/free plasma ratio was 0.212 at the end of infusion and 0.547 at 2 hours after the end of infusion based on free drug in plasma using plasma protein unbound fraction of 0.422.

Table 49. Cefiderocol Concentrations in Plasma and ELF and ELF/Plasma Concentration Ratios From Study R2117

Time	Subject	Dose regimen	Plasma CFDC (µg/mL)	BAL CFDC (µg/mL)	Serum urea (mmol/L)	BAL urea (mmol/L)	ELF CFDC (µg/mL)	ELF/ total plasma ratio	ELF/ free plasma ratio
3 h (end of infusion)	(b) (6)	1.5 g q8h	69.1	0.529	38.91	3.15	6.53	0.0946	0.224
		1 g q8h	116	1.14	44.63	2.46	20.7	0.178	0.422
		1.5 g q8h	81.8	0.346	58.91	6.57	3.10	0.0379	0.0898
		2 g q8h	81.6	0.919	21.6	2.45	8.10	0.0993	0.235
5 h (2 h after the end of infusion)		2 g q6h	20.7	0.241	10.14	0.34	7.19	0.347	0.822
		2 g q8h	84.8	0.143	27.74	0.25	15.9	0.187	0.443
		2 g q6h	51.5	0.380	33.38	1.3	9.76	0.190	0.450

Source: Table 2.7.2-2 from 2.7.2 Summary of Clinical Pharmacology – HABP/VABP
Abbreviations: BAL, bronchoalveolar lavage; CFDC, cefiderocol; ELF, epithelial lining fluid; q8h, every 8 hours

14.3. Population PK Analyses

14.3.1. Review Summary

The Applicant's population pharmacokinetics (PPK) analysis for cefiderocol, which was to update a previously developed PPK model by including additional phase 3 data (APEKS-NP study, 1615R2132), is acceptable to support the current submission as outlined in Table 50. The Applicant's final PPK model adequately described the observed cefiderocol plasma concentrations. Parameter estimates for the final model were estimated with acceptable precision with relative standard error (<15%) for total clearance (CL), volume of distribution in central compartment (V1), volume of distribution in peripheral compartment (V2 and V3), the intercompartmental clearance (Q2 and Q3), and covariates (creatinine clearance [CLcr] and infection site on CL, body weight, albumin [ALB] and infection on V1, and body weight on V2). The shrinkages for interindividual variability on CL and V1 were <15%. The goodness-of-fit plots showed a good agreement between the observed and the individual predicted concentrations without any obvious bias over time or predicted concentrations. The prediction-corrected visual predictive check (pcVPC) plots showed a good agreement between the observed and the simulated concentrations. The Applicant's analyses were verified by the reviewer, with no significant discordance identified.

Cefiderocol is known to be substantially excreted by the kidney. The updated PPK model identified CLcr as the most significant covariate on the PK of cefiderocol and the influence of renal function on PK was shown in the box plots for Bayesian-estimated CL by study and renal function group (Figure 6). Per the current approved labeling, dose adjustments are recommended for patients with CLcr less than 60 mL/min and for patients with CLcr 120 mL/min or greater. The Applicant's analysis of cefiderocol C_{max} and daily AUC estimated by the updated PPK model at CLcr adjusted dose regimens in the renal function groups did not show notable change from the estimates from the previous model.

Based on Applicant's analysis of plasma cefiderocol concentrations, the dose for patients with intermittent hemodialysis, continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), continuous venovenous hemodiafiltration (CVVHDF), or

intermittent hemodiafiltration is reasonable since their minimum of plasma concentration (13.6 mcg/mL) was higher than the target MIC of 4 mcg/mL.

Table 50. Specific Comments on Applicant's Final Population PK model

Utility of the Final Model			Reviewer's Comments
Intrinsic and extrinsic factors	Intrinsic factor	Based on a population pharmacokinetic analysis, age, gender, race, AST, ALT, BILI and ventilation do not have a statistically meaningful effect on the pharmacokinetics of cefiderocol. Meanwhile, CLcr, albumin, body weight and infection (no infection, cUTI/AUP, cUTI, BSI/sepsis, HAP/VAP/HCAP) have a statistically significant effect on pharmacokinetics of cefiderocol.	The Applicant adequately performed covariates assessment and evaluated the impact of identified covariates on cefiderocol PK under forward inclusion and backward deletion criteria. Based on the estimated impacts, **the review agrees with the Applicant's conclusions**. Inclusion of covariates into the base model were determined with the significance level of 0.01 based on χ^2 test ($p<0.01$, a decrease in OBJ >6.64 for one degree of freedom). In the stepwise backward deletion, deletion of covariates from the full model was determined with the significance level of 0.001 based on χ^2 test ($p<0.001$, an increase in OBJ >10.83 for one degree of freedom) to construct a final model.
	Extrinsic factor		
Derive exposure metrics for Exposure-response analyses	C_{max}, AUC		The Applicant's final model is generally acceptable for generating exposure metrics for exposure-response analyses (Table 53).
Predict exposures at alternative dosing regimen	NA		NA

Source: Pharmacometric Review Team's assessments and applicant's S-649266-CPK-004 - Study Report (link).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the curve; AUP, acute uncomplicated pyelonephritis; BILI, bilirubin; BSI, bloodstream infection; cUTI, complicated urinary tract infection; C_{max}, maximum plasma concentration; CLcr, creatinine clearance; HAP, hospital-acquired pneumonia; HCAP, healthcare-associated pneumonia; NA, not applicable; OBJ, objective function value,;PK, pharmacokinetics; VAP, ventilator-associated pneumonia

Detailed statistical explanation of covariates was shown in Section 14.3.4.

14.3.2. Introduction

The primary objectives of the Applicant's analysis were to:

- Characterize the structural PK model and quantify the population variability in the PK parameters of cefiderocol.
- Describe the effects of intrinsic and/or extrinsic factors on cefiderocol exposure.
- Generate individual clearance estimates for patients in phase 1, 2 and 3 studies that can be used for subsequent exposure-response analyses

14.3.3. Model Development

Data

PPK models were developed by Applicant to describe the PK of cefiderocol (S-649266) using a total of 3855 plasma concentration data of cefiderocol from 641 subjects, from phase 1 single ascending dose/multiple ascending dose study (1203R2111) and the renal impairment study (1222R2113), the phase 2 APEKS-cUTI study (1409R2121), the phase 3 CREDIBLE-CR trial (1424R2131), and the APEKS-NP study (1615R2132). It included 92 subjects without infection, 326 patients with cUTI or acute uncomplicated pyelonephritis (AUP), 193 patients with either hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP)/healthcare-associated pneumonia (HCAP), and 30 patients with BSI/sepsis. The dosing regimen and PK sampling for the clinical studies included PPK analysis were summarized in Table 51 and demographic covariates for analysis were summarized in Table 52.

Table 51. Summary of Clinical Study Designs

Study	Dose Regimen	Plasma PK Sampling
Phase 1 SAD/MAD study for healthy subjects in Japan (Study No.1203R2111; PK Analysis Study No. S-649266-CB-063-N)	Part 1: Single cefiderocol 0.1-,0.25-, 0.5-, 1-, 2-g doses or matching placebo infused over 1 hour Part 2: Multiple cefiderocol 1- or 2-g doses, or matching placebo infused over 1 hour q8hr for 10 days	Part 1: Predose, 0.5, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36 and 48 hours from the start of the infusion Part 2: Day 1 (morning dose: first dose): predose, 0.5, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12 and 16 hours Days 2, 3, 5, 8 and 9 (each morning dose): predose Day 10 (morning dose: last dose): predose, 0.5, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36 and 48 hours from the start of the infusion
Phase 1 renal impairment study in U.S. (Study No. 1222R2113)	Single cefiderocol 1-g dose infused over 1 hour	Predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48 and 72 hours from the start of the infusion
Phase 2 APEKS-cUTI study for patients with cUTI and AUP (Study No. 1409R2121)	Cefiderocol 2-g doses infused over 1 hour q8hr with adjustments for creatinine clearance and body size	Just prior to the infusion of the dose, −0.25 to 0 hours at the end of infusion, and 1±0.5 hours after the end of infusion on Day 3
Phase 3 CREDIBLE-CR trial for patients with HAP/VAP/HCAP, BSI/sepsis, or cUTI (Study No. 1424R2131)	Cefiderocol 2-g doses infused over 3 hour q8hr with adjustments for eGFR and creatinine clearance	Just prior to the start of infusion, 1 hour after the start of infusion, at the end of infusion, and 1 hour after the end of infusion on Day 3. For patients with nonstable renal function resulting in a dosing adjustment, another PK sampling was performed within 24 to 72 hours after their dosing adjustment at the same timing on Day 3.

Study	Dose Regimen	Plasma PK Sampling
Phase 3 APEKS-NP study for patients with HAP/VAP/HCAP (Study No. 1615R2132)	Cefiderocol 2-g doses infused over 3 hour q8hr with adjustments for eGFR and creatinine clearance	Just prior to the start of infusion, 1 hour after the start of infusion, before the end of infusion, and 1 hour after the end of infusion on Day 3 or Day 4. For patients with nonstable renal function resulting in a dosing adjustment, another PK sampling was performed within 24 to 72 hours after their dosing adjustment at the same timing as above.

Source: Applicant's S-649266-CPK-004 - Study Report, Table T1 on Page 16 (link).
Abbreviations: AUP, acute uncomplicated pyelonephritis; BSI, bloodstream infection; cUTI, complicated urinary tract infection; eGFR, estimated glomerular filtration rate; HAP, hospital-acquired pneumonia; HCAP, healthcare-associated pneumonia; MAD, multiple ascending dose; OBJ: objective function value,;PK, pharmacokinetics; SAD, single ascending dose; VAP, ventilator-associated pneumonia

Table 52. Summary of Baseline Demographic Covariates for Analysis

(b) Overall

Study	Background characteristics	Mean (SD)	Median (range)
Overall	Body weight (kg)	75.3 (18.3)	72.6 (25.0 - 156.0)
	Age (years)	58.2 (18.2)	62.0 (18 - 93)
	eGFRadj (mL/min/1.73 m^2)	78.9 (41.5)	76.0 (4 - 507)
	eGFRabs (mL/min)	84.3 (45.0)	81.0 (4 - 533)
	CrCL (mL/min)	89.5 (50.9)	83.0 (5 - 540)
	Albumin (g/dL)	3.7 (0.8)	3.9 (1.2 - 5.3)
	Aspartate aminotransferase (U/L)	27.2 (25.2)	19.5 (3 - 367)
	Alanine aminotransferase (U/L)	25.9 (21.4)	18.0 (4 - 153)
	Total bilirubin (mg/dL)	0.75 (0.93)	0.59 (0.10 - 15.20)
	Sex (male : female) [a]	309 (59.9%) : 207 (40.1%)	
	Race (White : non-White) [a]	373 (72.3%) : 143 (27.7%)	
	(Asian : White : Black or African American : native American or Alaska native : the others) [a]	114 (22.1%) : 373 (72.3%) : 17 (3.3%) : 1 (0.2%) : 11 (2.1%)	
	Disease status (no infection : cUTI/AUP : HAP/VAP/HCAP : BSI/Sepsis) [a]	91 (17.6%) : 259 (50.2%) : 146 (28.3%) : 20 (3.9%)	

Source: Applicant's S-649266-CPK-004 - Study Report, on Page 43 (link).
[a] Number of subjects (percentage of all subjects)
Abbreviations: AUP, acute uncomplicated pyelonephritis; BSI, bloodstream infection; CrCL, creatinine clearance calculated by Cockcroft-Gault equation; cUTI, complicated urinary tract infection; eGFRabs, absolute estimated glomerular filtration rate; eGFRadj, body-surface-area-adjusted estimated glomerular filtration rate; HAP, hospital-acquired pneumonia; HCAP, healthcare-associated pneumonia; SD, standard deviation; VAP, ventilator-associated pneumonia

Base Model

The **base model** was a three-compartment PK model with infusion and first-order elimination from the central compartment for healthy subjects, subjects with various renal functions, and patients with HAP/VAP/HCAP, BSI/sepsis, or cUTI/AUP. The three-compartment model included the following parameters: CL, V1, V2, V3, Q2, and Q3.

Interindividual variability was modelled assuming a log-normal distribution for patient level random effects. The interindividual variability was considered for CL, V1, Q2, and V2 since the interindividual variability for V3 and Q3 was not estimable for the data in healthy volunteers and subjects with various renal functions. Furthermore, the data obtained with the sparse sampling in the phase 2 study (1409R2121) and phase 3 studies (1424R2131 and 1615R2132) were not expected to be informative for the interindividual variability relevant to the three compartmental parameters.

Intraindividual variability was tested as proportional or combination error model (the additive error + the proportional error model) on the dependent variable.

Model evaluation and selection were based on the point estimates of PK parameters, their respective relative standard errors and standard statistical criteria of goodness-of-fit, such as a decrease in the minimum objective function value, accuracy of parameter estimation (i.e., 95% CI excluding 0) by bootstrap, successful model convergence, and diagnostic plots (pcVPC).

Covariate Analysis

Covariate parameters, including CLcr, body weight, age, sex, ALB AST, ALT, bilirubin (BILI), race, infection, and ventilation were tested on CL, and body weight, age, sex, ALB, race, infection, and ventilation were tested as a covariate on V1. In addition body weight was tested as a covariate on other PK parameters (Q2 and V2).

Covariates (power model, piece-wise linear model, power + linear combination model, and multiplicative model) were assessed for covariates with forward selection criteria of the significant level of 0.01 based on χ^2 test ($p<0.01$, a decrease in OBJ >6.64 for one degree of freedom) and backward deletion criteria with the significance level of 0.001 based on χ^2 test ($p<0.001$, an increase in OBJ >10.83 for one degree of freedom)

14.3.4. Final Model

The parameter estimates for the final PPK model are listed in Table 53. The goodness-of-fit plots for the final covariate model for all data are shown in Figure 4. The pcVPC plot for the final covariate model with all data is shown in Figure 5. The structural model for the final PPK model was a three-compartmental model as parameterized with CL, V1, V2, V3, Q2, and Q3 for cefiderocol. An exponential error model was used for interindividual variability, and a proportional error model was used for intra-individual variability.

CLcr and infection site on CL, body weight, ALB, infection on V1, and body weight on V2 were identified as significant covariates and included in the final model:

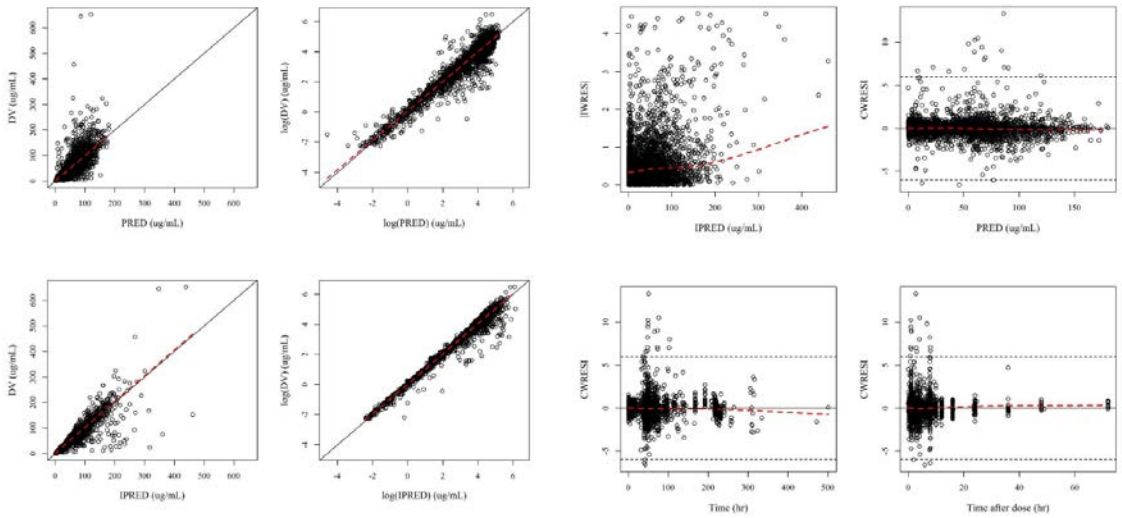
- CLcr was the most significant covariate on the PK of cefiderocol (see Section 14.3.5 for details)
- Infection with cUTI/AUP, BSI/sepsis, or HAP/VAP/HCAP was a significant covariate on CL and V1 in the final model. The final model suggested CL in patients with cUTI/AUP in the phase 2 study was 27% higher than that in subjects without infection. CL in patients were 13% lower for the cUTI in the CREDIBLE-CR trial, 8% higher for BSI/sepsis, or 2% lower for HAP/VAP/HCAP than that in subjects without infection. The final model also suggested V1 in patients with infection was 39% higher than that in subjects without infection.
- A negative correlation between ALB and V1 was observed. The median of ALB for patients in the CREDIBLE-CR and APEKS-NP studies were 2.7 and 3.0 g/dL, respectively, and lower than that for subjects in the phase 1 and phase 2 studies (4.2 g/dL).
- Body weight was a significant covariate on V1 and V2 with a power model with exponent of 0.58.

Table 53. Population Pharmacokinetic Parameter Estimates for the Final Model

Pharmacokinetic parameters	Units	Final model [a] Estimates	%RSE	Bootstrap estimates Median	Bootstrap estimates 95% CI (lower - upper)
CL	(L/hr)	4.04	1.8	4.04	3.89 - 4.20
V1	(L)	7.78	5.2	7.93	7.07 - 8.85
Q2	(L/hr)	6.19	5.7	5.97	4.57 - 7.24
V2	(L)	5.77	3.2	5.68	5.02 - 6.15
Q3	(L/hr)	0.127	14.1	0.119	0.0792 - 0.228
V3	(L)	0.798	6.4	0.772	0.621 - 1.09
Effect of CrCL on CL (CrCL cut-off value of 150 mL/min)		0.682	4.0	0.681	0.626 - 0.735
Effect of body weight on V1 and V2		0.580	12.2	0.571	0.433 - 0.725
Effect of infection with cUTI/AUP in phase 2 cUTI study on CL		1.27	3.1	1.27	1.20 - 1.35
Effect of infection with cUTI in phase 3 CREDIBLE-CR study on CL		0.872	6.4	0.869	0.769 - 1.01
Effect of infection with BSI/sepsis on CL		1.08	10.4	1.07	0.894 - 1.37
Effect of infection with HAP/VAP/HCAP on CL		0.981	4.1	0.978	0.893 - 1.07
Effect of albumin on V1		-0.617	10.9	-0.624	-0.985 - -0.244
Effect of infection on V1		1.39	6.7	1.36	1.22 - 1.54
Inter-individual variability (CV%) [sh_ηp]					
CL	%	37.5 [3.6]	10.4	37.0	32.9 - 40.7
V1	%	56.9 [13.6]	19.8	57.9	45.3 - 71.0
V2	%	33.6 [18.2]	35.0	35.5	19.7 - 50.2
Covariance between CL and V1		0.0886 (R = 0.415)	29.1	0.0807	0.0338 - 0.146
Covariance between CL and V2		0.0792 (R = 0.629)	33.2	0.0767	0.0187 - 0.140
Covariance between V1 and V2		0.150 (R = 0.784)	27.3	0.115	-0.0930 - 0.218
Intra-individual variability (CV%) [sh_ε]					
Proportional residual error	%	20.5 [13.2]	5.1	20.3	18.5 - 22.5

Source: Applicant's S-649266-CPK-004 - Study Report, Table 5 on page 48 (link).
[a] CrCL <150 mL/min; CL =4.04*(CrCL/83.0)$^{0.682}$ * (1.27 for patients with cUTI/AUP in phase 2 cUTI study) * (0.872 for patients with cUTI in phase 3 CREDIBLE-CR trial) * (1.08 for patients with BSI/sepsis) * (0.981 for patients with HAP/VAP/HCAP)
[a (cont.)] CrCL ≥150 mL/min; CL =4.04*(150/83.0)$^{0.682}$ * (1.27 for patients with cUTI/AUP in phase 2 cUTI study) * (0.872 for patients with cUTI in phase 3 CREDIBLE-CR trial) * (1.08 for patients with BSI/sepsis) * (0.981 for patients with HAP/VAP/HCAP)
V1=7.78 * (body weight/72.6)$^{0.580}$ * (a bumin/3.9)$^{-0.617}$ * (1.39 for patients with infection)
V2=5.77 * (body weight/72.6)$^{0.580}$
Abbreviations: AUP, acute uncomplicated pyelonephritis; BSI, bloodstream infection; CI, confidence interval; CrCL, creatinine clearance calculated by Cockcroft-Gault equation; cUTI, complicated urinary tract infection; CV, coefficient of variation; HAP, hospital-acquired pneumonia; HCAP, healthcare-associated pneumonia; sh_ηp, shrinkage in the standard deviation of interindividual variability parameters η; sh_ε, shrinkage in the standard deviation of intra-individual variability parameters ε; %RSE, relative standard error in percent; R, coefficient of correlation; VAP, ventilator-associated pneumonia

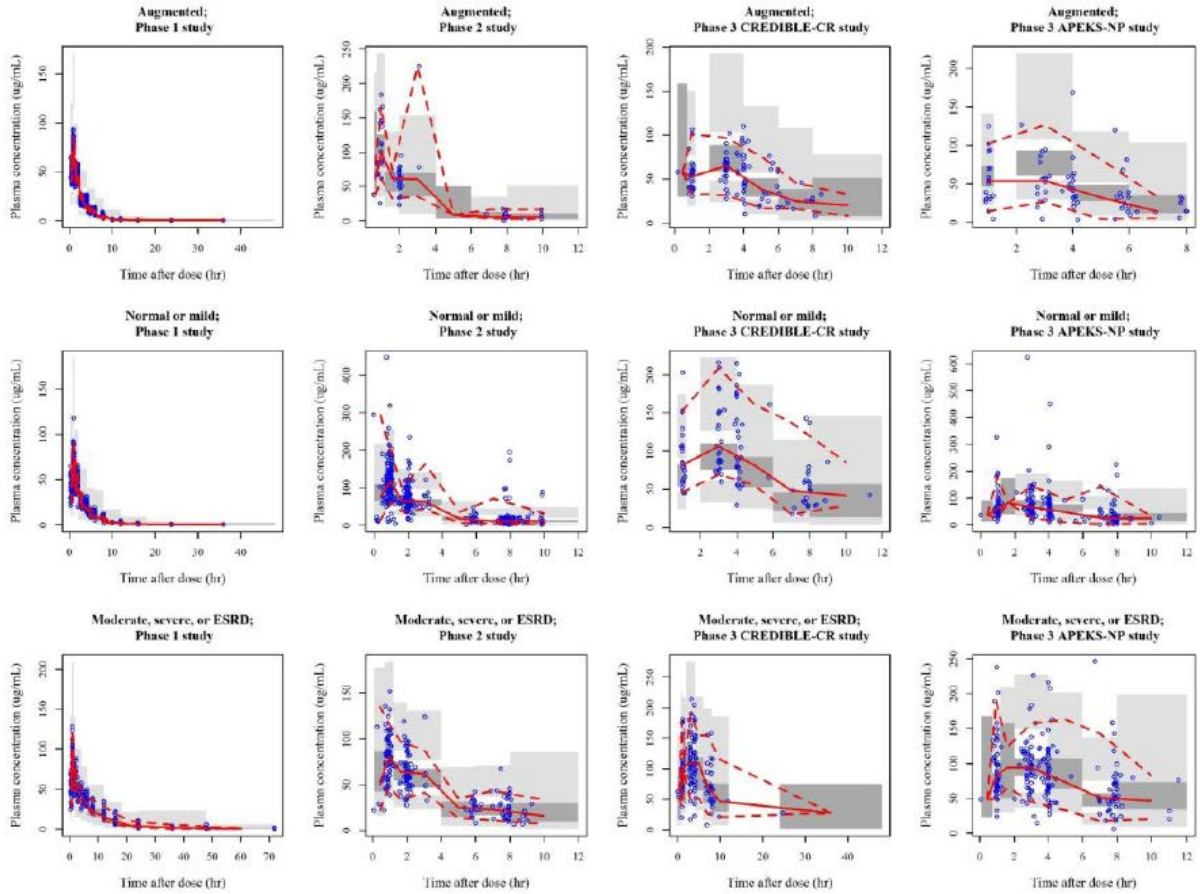
Figure 4. Goodness-of-Fit Plots for Final Covariate Model



Source: Applicant's S-649266-CPK-004 - Study Report, Figure 10 on Page 84-85(link).

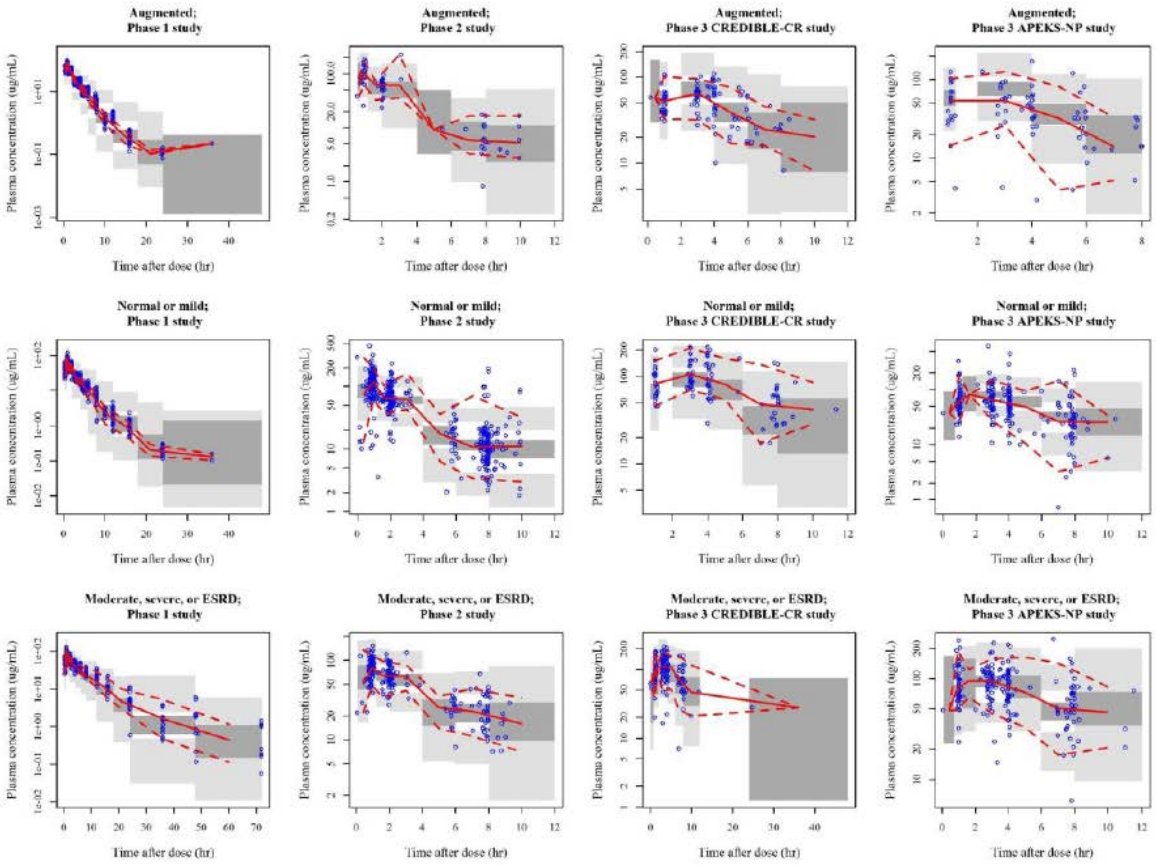
Figure 5. pcVPC Plots for Final Covariate Model

(a) Linear scale



(Figure 5 cont. on the next page)

(b) Semilog scale



Source: Applicant's S-649266-CPK-004 - Study Report, Figure 15 on Page 100-101 (link).
Solid line: observed median. Dashed line: observed 2.5th and 97.5th percentiles.
Dark grey shaded area: model predicted 95% CI of median.
Grey shaded area: model predicted 95% CIs of 2.5th and 97.5th percentiles. 500 simulations
Abbreviations: ESRD, end stage renal disease; pcVPC, prediction-corrected visual predictive check

14.3.5. Effect of Renal Function

Cefiderocol is known to be substantially excreted by the kidney. Similar to the previously developed model, the updated PPK model identified CLcr as the most significant covariate on the PK of cefiderocol, and time-varying CLcr was a better predictor than baseline CLcr in phase 3 studies. The influence of renal function to PK is shown in the box plots for Bayesian-estimated CL by study and renal function group (Figure 6). The daily AUC values at the dose regimen adjusted by CLcr (Table 54) were summarized by different renal function groups and study (Table 55). At the dose regimen adjusted by CLcr, the ratios of geometric mean daily AUC in the augmented or impaired renal function groups relative to the normal renal function group ranged from 0.92 to 1.44 in the APEKS-NP study and from 0.74 to 1.22 in the CREDIBLE-CR trial.

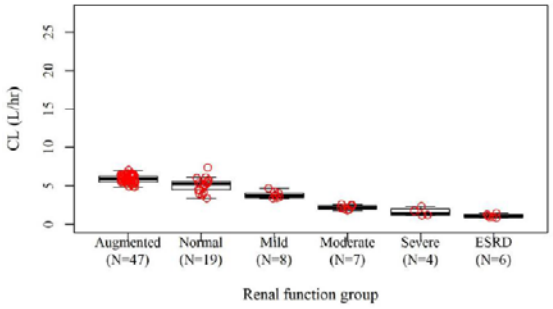
Table 54. Renal Function Groups and Adjusted Dose Regimens

Renal Function Group	CLcr (mL/min)	Dose Regimens With 3-hr Infusion
Augmented renal function	≥120	2 g q6hr
Normal renal function	90 to <120	2 g q8hr
Mild renal impairment	60 to <90	2 g q8hr
Moderate renal impairment	30 to <60	1.5 g q8hr
Severe renal impairment	15 to <30	1 g q8hr
ESRD	5 to <15	0.75 g q12hr

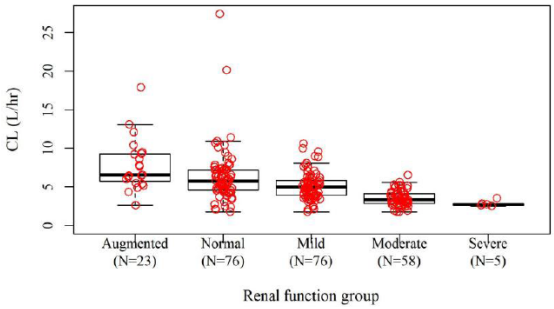
Source: Applicant's S-649266-CPK-004 - Study Report, Table T2 on Page 27 (link).
Abbreviations: CLcr, creatinine clearance; ESRD, end-stage of renal disease; q6hr, every 6 hours; q8hr, every 8 hours; q12hr, every 12 hours

Figure 6. Box Plots for Bayesian-Estimated CL by Study and Renal Function Group

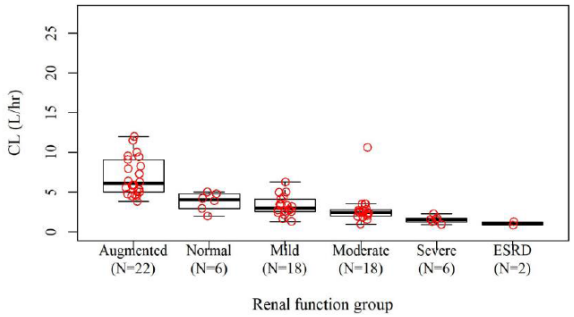
(a) Subjects without infection in the phase 1 studies



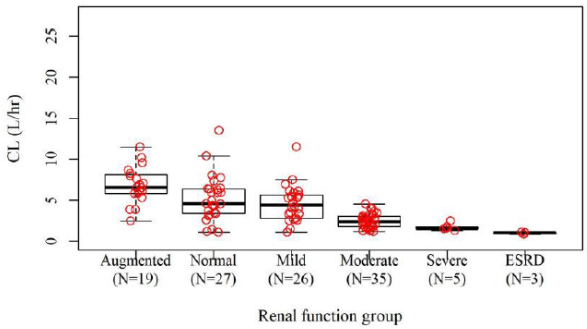
(b) Patients in the phase 2 study



(c) Patients in the CREDIBLE-CR study



(d) Patients in the APEKS-NP study



Source: Applicant's S-649266-CPK-004 - Study Report, Figure 17 on Page 102 (link).
Abbreviations: CL, clearance; ESRD, end-stage of renal disease;

Table 55. Summary of Post hoc Estimates of Daily AUC at CrCL-Adjusted Dose Regimens by Study and Renal Function Group for Patients With Infection

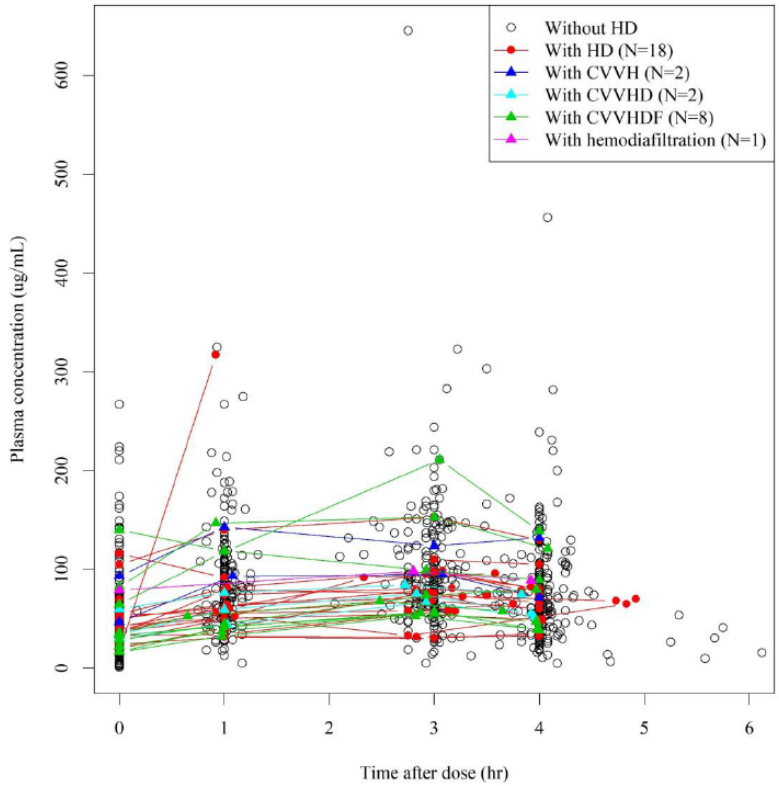
Subject Population	Sub-population	N	AUC (μg·hr/mL)[a]
Patients with cUTI/AUP in phase 2 study	Augmented (CrCL ≥ 120)	23	1111 (42.4)
	Normal (CrCL 90 to < 120)	76	1050 (47.7)
	Mild (CrCL 60 to < 90)	76	1238 (36.7)
	Moderate (CrCL 30 to < 60)	58	1325 (29.9)
	Severe (CrCL 15 to < 30)	5	1061 (13.6)
Patients with HAP/VAP/HCAP, BSI/sepsis, and cUTI in CREDIBLE-CR study	Augmented (CrCL ≥ 120)	22	1218 (34.5)
	Normal (CrCL 90 to < 120)	6	1650 (36.3)
	Mild (CrCL 60 to < 90)	18	1962 (40.9)
	Moderate (CrCL 30 to < 60)	18	1781 (49.8)
	Severe (CrCL 15 to < 30)	6	2007 (30.6)
	ESRD (CrCL < 15)	2	1444 (26.7)
Patients with HAP/VAP/HCAP in APEKS-NP study	Augmented (CrCL ≥ 120)	19	1238 (38.0)
	Normal (CrCL 90 to < 120)	27	1340 (65.9)
	Mild (CrCL 60 to < 90)	26	1463 (54.3)
	Moderate (CrCL 30 to < 60)	35	1934 (37.2)
	Severe (CrCL 15 to < 30)	5	1776 (24.9)
	ESRD (CrCL < 15)	3	1526 (14.8)

Source: Applicant's S-649266-CPK-004 - Study Report, Table 9 on Page 52 (link).
[a] Geometric mean (CV%)
Abbreviations: AUC, area under the curve; AUP, acute uncomplicated pyelonephritis; BSI, bloodstream infection; CrCL, creatinine clearance calculated by Cockcroft-Gault equation; cUTI, complicated urinary tract infection; CV, coefficient of variation; ESRD, end-stage renal disease; HAP, hospital-acquired pneumonia; HCAP, healthcare-associated pneumonia; VAP, ventilator-associated pneumonia

14.3.6. Comparison of Pharmacokinetics Between Patients With and Without Hemodialysis

The Applicant graphically evaluated the effect of intermittent hemodialysis, CVVH, CVVHD, CVVHDF and intermittent hemodiafiltration on the exposures of cefiderocol. As shown in Figure 7, the plasma cefiderocol concentrations for the patients with intermittent hemodialysis, CVVH, CVVHD, CVVHDF, or intermittent hemodiafiltration were within the range of plasma concentrations for the patients without these treatments. The Applicant reported that the minimum of plasma concentration of cefiderocol for the patients with hemodialysis was 13.6 mcg/mL (5.74 mcg/mL as free cefiderocol plasma concentration), which was higher than the target MIC of 4 mcg/mL. The study suggested that adequate exposure to cefiderocol was achieved at the selected dose regimen for the patients with intermittent hemodialysis, CVVH, CVVHD, CVVHDF, or intermittent hemodiafiltration.

Figure 7. Observed Plasma Cefiderocol Concentration Profiles for Patients With or Without Hemodialysis in CREDIBLE-CR Trial



Source: Applicant's S-649266-CPK-004 - Study Report, Figure 33 on Page 118 (link).
Abbreviations: CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; HD, hemodialysis.

15. Trial Design: Additional Information and Assessment

The following is the protocol synopsis dated February 22, 2019, as submitted in the complete study report dated January 24, 2020, for the APEKS-NP trial. Additional details and commentary on the trial design are provided after the synopsis.

Synopsis

Study title: A Multicenter, Randomized, Double-blind, Parallel-group, Clinical Study of S-649266 Compared with Meropenem for the Treatment of Hospital-acquired Bacterial Pneumonia, Ventilator-associated Bacterial Pneumonia, or Healthcare-associated Bacterial Pneumonia Caused by Gram-negative Pathogens

Study number: 1615R2132

Study phase: 3

Primary objective:

- To compare all-cause mortality (ACM) at day 14 of subjects who receive S-649266 with that of subjects who receive the comparator, meropenem, in adults with HABP,VABP, or healthcare-associated bacterial pneumonia (HCABP) caused by gram-negative pathogens

Secondary objectives:

Key secondary objectives:

- To compare the clinical outcome of treatment with S-649266 with that of meropenem in subjects at test-of-cure (TOC)[1]
- To compare the microbiologic outcome of treatment with S-649266 with that of meropenem at TOC
- To compare day 14 ACM of S-649266 with that of meropenem for superiority of S-649266

Other secondary objectives:

Efficacy:

- To compare the clinical outcome of treatment with S-649266 with that of meropenem in subjects at early assessment (EA),[2] end of treatment (EOT),[3] and follow-up (FU)
- To compare the microbiologic outcome of treatment with S-649266 with that of meropenem at EA, EOT, and FU
- To compare the ACM at day 28 of subjects treated with S-649266 with that of subjects treated with meropenem
- To compare the ACM during treatment and the FU period (until end of study [EOS])[4] of S 649266 with that of meropenem
- To compare the resource utilization required for the two study treatments for the study-qualifying infection. This endpoint will not be included in the clinical study report, but it will be analyzed based upon a separate analytical plan after the conclusion of the study

Safety:

- To assess the safety of S-649266

Study design:

This is a phase 3, multicenter (multinational), double-blind, parallel-group, randomized, active-controlled study in approximately 300 subjects with documented nosocomial pneumonia (NP) caused by gram-negative bacteria. Subjects meeting eligibility criteria and assessed by the investigator as requiring 7 to 14 days of IV treatment in the hospital will be randomized (1:1) to either S-649266, 2 g, administered intravenously over 3 hours every 8 hours (q8h), or to meropenem, 2 g, administered intravenously over 3 hours, q8h. Linezolid will be administered for at least 5 days to subjects in both arms to provide coverage for methicillin-resistant *Staphylococcus aureus* and to maintain the study blind and in the S-649266 arm to provide coverage for gram-positive bacteria.

[1] TOC is defined as end of treatment (EOT) + 7 days (±2 days).
[2] EA is defined as start of treatment +3 days to 4 days.
[3] EOT is defined as the last day of study treatment.
[4] EOS is defined as the last day of the study

Study population:

Subjects with documented NP caused by a suspected gram-negative pathogen(s) will be enrolled.

Key inclusion criteria:

Subjects who fulfill the following criteria at Screening will be included in the study:

- Subjects 18 years or older at the time of signing informed consent.
- Subjects who have provided written informed consent or their informed consent has been provided by a legally authorized representative (Note: Country-specific rules and local ethics committee approval for legally authorized representative informed consent will determine whether or not and how a subject unable to comprehend or sign the informed consent is allowed to be enrolled in the study).
- Subjects who meet the clinical diagnosis criteria for HABP/VABP/HCABP.
- All subjects must fulfill at least one of the following clinical criteria at screening:
  - New onset or worsening of pulmonary symptoms or signs, such as cough, dyspnea, tachypnea (e.g., respiratory rate >25 breaths/minute), expectorated sputum production, or requirement for mechanical ventilation.
  - Hypoxemia (e.g., a partial pressure of oxygen [PaO_2] <60 mm Hg while the subject is breathing room air, as determined by arterial blood gas [ABG], or worsening of the ratio of the PaO_2 to the fraction of inspired oxygen [PaO_2/FiO_2]).
  - Need for acute changes in the ventilator support system to enhance oxygenation, as determined by worsening oxygenation (ABG or PaO_2/FiO_2) or needed changes in the amount of positive end-expiratory pressure.
  - New onset of or increase in (quantity or characteristics) suctioned respiratory secretions, demonstrating evidence of inflammation and absence of contamination.
- All subjects must have at least one of the following signs:
  - Documented fever (i.e., core body temperature [tympanic, rectal, esophageal] ≥38°C [100.4°F], oral temperature ≥37.5°C, or axillary temperature ≥37°C).
  - Hypothermia (i.e., core body temperature [tympanic, rectal, esophageal] ≤35°C [95.0°F], oral temperature ≤35.5°C, and axillary temperature ≤36°C).
  - Leukocytosis with a total peripheral white blood cell (WBC) count ≥10,000 cells/mm^3.
  - Leukopenia with total peripheral WBC count ≤4500 cells/mm^3.
  - Greater than 15% immature neutrophils (bands) noted on peripheral blood smear.
- All subjects must have a chest radiograph during screening or have a previous chest radiograph within 48 hours prior to randomization showing the presence of new or progressive infiltrate(s) suggestive of bacterial pneumonia. A computed tomography (CT) scan in the same time window showing the same findings could also be acceptable.
- All subjects must have a suspected gram-negative infection involving the lower respiratory tract by one or more of the following:

  - Gram stain of lower respiratory secretions showing gram-negative bacteria, either alone or mixed with gram-positive bacteria at or within 72 hours prior to randomization.
  - Microbiologic culture of respiratory tract secretions within 72 hours prior to randomization identifying gram-negative aerobic bacteria.
  - Other diagnostic tests, including molecular tests, which provide evidence of gram-negative bacterial infection of the lower respiratory tract.
  - Pneumonia highly suspected to be due to gram-negative bacteria based on prior antibiotic use or local epidemiologic evidence of gram-negative infection outbreak.

- Subject is male (no contraception required) or female and meets one of the following criteria:
  - Surgically sterile (has had a hysterectomy and/or bilateral oophorectomy, or a bilateral salpingectomy or tubal ligation for the purpose of contraception for at least 6 weeks with appropriate documentation of such surgery).
  - Postmenopausal (defined as older than 45 years of age with cessation of regular menstrual periods for at least 6 months and a follicle-stimulating hormone level of >40 mIU/mL, or amenorrhea for at least 12 months).
  - Of childbearing potential and using combined (estrogen and progestogen) or progestogen-only hormonal contraception associated with inhibition of ovulation (including oral, intravaginal, injectable, implantable, and transdermal contraceptives), or an intrauterine device, or intrauterine hormone-releasing system for the entire duration of the study.
  - Of childbearing potential and practicing abstinence as a preferred and usual life style and agrees to continue practicing abstinence from screening for the entire duration of the study.
  - Of childbearing potential and whose sole heterosexual partner has been successfully vasectomized and agrees to not have other heterosexual partners for the entire duration of the study.
- Subjects who failed empiric therapy will be allowed in this study. However, confirmation of both clinical and microbiological failure is necessary.
  - Clinical failure: An investigator needs to confirm clinical failure of empiric treatment by clinically available information such as vital signs, physical examinations, laboratory data, and/or imaging.
  - Microbiological failure: Respiratory specimens from a subject need to meet either of the following:
    - The lower respiratory tract specimen taken at the time of or before empiric therapy shows that the pathogen cultured is a gram-negative aerobic bacteria, and the pathogens are resistant or intermediate to all the empiric antibiotics used.

- The pathogen from a specimen obtained after at least 2 calendar days of the empiric antibiotic regimen demonstrates that it is a gram-negative aerobe, or shown in Gram stain as gram-negative bacteria.

Exclusion criteria:

Subjects who meet any of the following criteria at screening will be excluded from the study:

- Subjects who have known or suspected community-acquired bacterial pneumonia, atypical pneumonia, viral pneumonia, or chemical pneumonia (including aspiration of gastric contents, inhalation injury).
- Subjects who have a history of any hypersensitivity to cephalosporins or to carbapenems, or severe hypersensitivity to any other type of β-lactams other than cephalosporins and carbapenems (e.g., penicillins, monobactams), or hypersensitivity to linezolid (Note: For β-lactams, a history of a mild rash followed by uneventful re-exposure is not a contraindication to enrollment).
- Subjects with a gram-negative infection caused by a carbapenem-resistant pathogen, if known at the time of randomization (Note: Subjects who have a carbapenem-resistant pathogen identified after randomization should be evaluated clinically before discontinuation of study treatment).
- Subjects with coinfection caused by invasive aspergillosis, mucormycosis, or other highly lethal mold.
- Subjects who have central nervous system infection (e.g., meningitis, brain abscess, shunt infection).
- Subjects with cystic fibrosis.
- Subjects in refractory septic shock, defined as persistent hypotension despite adequate fluid resuscitation or despite vasopressive therapy at the time of randomization.
- Subjects with neutropenia (i.e., polymorphonuclear neutrophils <500 cells/mcL).
- Female subjects who have a positive pregnancy test at screening, who are lactating, or who refuse to use one of the previously specified methods of contraception.
- Subjects with an APACHE II score of >35.
- Subjects who have received potentially effective antibiotic therapy for a continuous duration of more than 24 hours during the previous 72 hours prior to randomization (Note: Subjects failing empiric therapy as defined in inclusion criterion 9 may be eligible for inclusion).
- Subjects with any condition or circumstance that, in the opinion of the investigator, would compromise the safety of the subject or the quality of the study data.
- Subjects receiving peritoneal dialysis (hemofiltration and hemodialysis are permitted).
- Subjects requiring continued treatment with methotrexate, procainamide, probenecid, monoamine oxidase inhibitors, or valproic acid.

- Subjects who have received another investigational drug or device within 30 days prior to study entry.
- Subjects who have previously been randomized in this study or have previously received S-649266.
- Subjects with one or more of the following laboratory abnormalities in baseline specimens: AST, ALT, ALP, or total BILI level >3 times the upper limit of normal (ULN), platelet count <40,000/mcL
- Subjects with bronchiectasis with symptoms of persistent or recurrent bronchial infection related to irreversibly damaged and dilated bronchi; namely, subjects with clinical bronchiectasis.
- Subjects with lung abscesses.

Test drug, dose, and mode of administration:

S-649266 (cefiderocol), 2 g, is to be administered intravenously q8h as a 3-hour infusion in subjects with normal renal function. Dose adjustment for renal function or dialysis is required, and the dosages established by clinical testing are presented in the protocol. The solution volume for infusion must be at least 100 mL.

Control treatment, dose, and mode of administration:

The control population will be treated with meropenem. The dosing regimen will be 2 g as a 3-hour infusion q8h. Dosage adjustment for renal function is required. The solution volume for infusion must be at least 100 mL.

Concomitant linezolid treatment, dose, and mode of administration:

Linezolid 600 mg will be administered intravenously every 12 hours (q12h) over 30 minutes to 2 hours concomitantly to provide coverage for gram-positive bacteria in the S-649266 arm, to provide coverage for methicillin-resistant *S. aureus* (MRSA) in both study arms, and to maintain the study blind. Linezolid can be discontinued after 5 days if a subject's lower respiratory tract specimens do not provide evidence of gram-positive infection when appropriate lower respiratory tract specimens have been obtained, and the subject is not at high risk for MRSA infection (e.g., no prior known MRSA colonization in the lower airway, no prior MRSA pneumonia in the past 6 months, or low prevalence (<10% to 20%) of MRSA in the healthcare facility, etc.). If a subject's lower respiratory tract specimens demonstrate gram-positive infection, if respiratory specimens have not been obtained, or if a subject is at high risk for MRSA infection, then linezolid should be administered for the entire treatment period of 7 to 14 days along with S-649266 or meropenem.

Duration of treatment:

The treatment duration for S-649266 or meropenem is anticipated to be 7 to 14 days, which is consistent with published treatment guidelines for HABP/VABP/HCABP infections. Based on the investigator's clinical assessment of the subject and a clear reason being documented in the electronic case report form, treatment may be extended up to 21 days. All study treatments are to be administered in the hospital.

Prohibited concomitant therapy:

- Systemic antibiotics, other than linezolid, meropenem, and S-649266, are not permitted from randomization until TOC.
- Aerosolized antibiotics are not permitted from randomization until after TOC.
- Probenecid, methotrexate, procainamide, monoamine oxidase inhibitors, and valproic acid are not permitted from screening until EOT.

Efficacy assessment:

In addition to the 14-day ACM (primary efficacy endpoint), both clinical and microbiological outcomes will be assessed by the investigator at EA, EOT, TOC, and FU. If case study treatment duration is extended beyond 14 days, an additional clinical and microbiological outcome will be assessed on day 14.

Pharmacokinetic assessments:

All subjects will have blood drawn for sparse sampling of plasma concentrations of S-649266 for PK assessment. PK blood sampling will preferably be performed on day 3 or 4. The following is the schedule for the sampling time points:

(1) Just prior to the start of the 3-hour infusion
(2) 1 hour after the start of infusion
(3) Before the end of infusion
(4) 1 hour after the end of infusion

The actual sampling date and time will be recorded.

The PK sampling will be repeated when/if the drug dosage was changed due to changes in renal function determined at EA; this should occur 24 to 72 hours after the change in dosing regimen.

In the case of premature EOT, a single blood sampling should be performed, if possible, as soon as possible at EOT (within 24 hours), which is defined as receiving <7 days of IV treatment with either S-649266 or meropenem.

Safety assessments:

Subject safety will be assessed from the time of having signed informed consent to the end of the study by identifying TEAEs with the addition of physical and laboratory evaluations, which include multiple electrocardiograms obtained early in the treatment with study drug.

In case treatment duration is extended beyond 14 days, additional safety assessments will be conducted on day 14. Safety surveillance will extend up to 28 days after the last dose of the drug treatment.

Statistical methods:

For the primary efficacy endpoint, the adjusted estimates of the difference in the ACM at day 14 between S-649266 and meropenem will be presented along with 95% CIs based on a stratified analysis using Cochran-Mantel-Haenszel (CMH) weights. The CI will be two-sided. The CMH weights will be calculated with the stratification factor: APACHE II score (≤15 and ≤16).

Sample size:

The study design and the primary objective are based on a 12.5% NI margin to exclude the possibility that S-649266 is more than 12.5% inferior to meropenem for the endpoint of ACM at day 14.

A sample size of 244 evaluable subjects (122 evaluable subjects in the S-649266 group and 122 evaluable subjects in the meropenem group) is required to have 90% power with a one-sided significance level of 0.025 assuming a 10% ACM rate at day 14 in both groups with a 12.5% NI margin. It is further estimated that approximately 20% of randomized subjects will be nonevaluable, and therefore excluded from the primary population, because they have not received any doses of a study drug treatment, or because they had a bacterial pneumonia caused by anaerobic and/or gram-positive aerobic bacteria only. Therefore, it is expected that it will be necessary to randomize up to 300 subjects. The nonevaluable rate will be assessed based on a blinded estimate performed after approximately 150 subjects are enrolled, and the randomized population size may be adjusted to meet study requirements. Additionally, the Applicant will conduct a blinded evaluation of ACM after approximately 150 subjects are enrolled and may perform a blinded re-estimation of sample size if deemed necessary.

Stratification at randomization:

Randomization will be performed by the stratified randomization method using the infection diagnosis (HABP/VABP/HCABP) and APACHE II score (≤15 and ≤16) as allocation factors.

Safety and efficacy evaluation:

When approximately 50 and 150 subjects have completed treatment and the FU visit, an evaluation of safety and efficacy data will be performed by the Data Safety Monitoring Board (DSMB) according to the DSMB charter. After the review, the DSMB will communicate their recommendation(s) to the Applicant.

Number of study sites/countries:

It is estimated that approximately 135 study sites from around the world will participate in this clinical study.

Study duration:

Study duration for individual subjects: approximately 5 to 7 weeks

Planned duration of the study: approximately 26 months (24 months for enrollment and 5 to 7 weeks to complete the study)

Date of original (Version 1): August 2, 2016

Date of latest amendment: February 22, 2019

We now provide additional details and commentary on the trial design.

Changes to the Protocol and Statistical Analysis Plan

The first subject was recruited on October 24, 2017, and the final subject completed study participation on April 1, 2019. A number of changes were made to the protocol and statistical analysis plan after the initiation of the trial, with the final set of changes to both protocol and statistical analysis plan made on February 22, 2019. No important changes to either protocol nor

statistical analysis plan were made prior to this final set of changes, which occurred after both DSMB-conducted interim analyses. The major changes made in the final set were:

- Two-sided p-values were to be used for testing NI and superiority of the primary and key secondary endpoints.
- In prior versions of the protocol, the unblinded DSMB looked at efficacy and safety data were not considered interim analyses. In the final protocol, they were considered interim analyses, with an alpha spend of 0.0001 to be used to control alpha at each interim analysis. It appears that formal efficacy analyses were not conducted at the interim analyses.
- Clarification that systematic antibiotics for gram-negative infections, other than the two study drugs, were not permitted from randomization until the TOC visit.
- If a subject withdrew from the study, the investigator was to attempt to collect TEAE information through the planned EOS. In addition, major nonfatal TEAEs was to be evaluated at days 14 and 28.

Interim Analyses

As noted in the protocol synopsis, an independent DSMB was to perform unblinded reviews of safety and efficacy data, and results of the interim analyses were not to be shared with the Applicant. The DSMB could recommend continuing, stopping, or modifying the study. In addition, after about 150 subjects were enrolled: (i) the rate of subjects included in the modified intention-to-treat (mITT) population was to be assessed based on a blinded estimate, and (ii) a blinded estimation of the rate of ACM was to be performed. Either could lead to an adjustment in sample size.

Cochran-Mantel-Haenszel Stratum-Weighted Estimator

In analyzing binary endpoints ACM, microbiological outcome, and clinical outcome at different time points, the Applicant specified using the CMH stratum-weighted estimator to estimate between-arm differences in mortality/treatment success rates, to construct CIs, to and test hypotheses. This estimator estimates the difference in rates within predefined strata and then computes a weighted average of the strata-specific differences to obtain a population-wide estimate of the between-arm difference in rates. For ACM endpoints, two strata were specified, in terms of high versus low baseline APACHE II scores. For microbiological and clinical outcomes, six strata were specified by crossing high versus low baseline APACHE II scores with diagnosis at baseline (HABP, VABP, HCABP).

The CMH stratum-weighted estimator consistently estimates the population-level between-arm difference in rates and hence is a valid estimation method.

Handling Missing and Indeterminate Data

We discuss how missing and indeterminate data were handled with regard to the ACM, clinical outcome, and microbiological outcome endpoints.

- ACM at days 14/28: If a subject withdraws from the study prior to day 14/28, then, per the Applicant, ACM at that time point is considered missing and the subject is ignored in efficacy analyses of ACM at that time point. That is, per the Applicant, efficacy analyses of ACM are complete case analyses.

- Clinical outcome and microbiological outcome at EA/EOT/TOC: Per the Applicant, subjects lost to FU or who had missing or indeterminate outcomes were considered treatment failures.

Strictly speaking, values coded as "indeterminate" were not necessarily missing values. For example, subjects who died from causes other than pneumonia had postdeath clinical outcome values coded as "indeterminate." Given how indeterminate values were handled for clinical outcome, however, such subjects were treated as clinical failures.

The Applicant's analyses of ACM endpoints were not intention-to-treat (ITT) analyses as they only included subjects with complete data rather than including all subjects in the mITT population. ITT sensitivity analyses for these endpoints are presented in Section 16.

16. Efficacy Assessment Additional Information and Assessment

This section provides additional analyses of the key efficacy endpoints, including sensitivity analyses of the primary endpoint and subgroup analyses. The results reported here are consistent with the results reported in Section 6. In addition, missing and indeterminate data rates are examined and the results of interim analyses are discussed.

Missing and Indeterminate Data Rates

The following table presents the amount of missing or indeterminate data, by arm, for the key endpoints. The two ACM endpoints have negligible amounts of missing data in both arms. Almost one third of subjects had indeterminate values on microbiological outcome at TOC, with the indeterminate proportion roughly equal in the two arms. Rates of indeterminate values in clinical outcome at TOC were roughly half of those for microbiological outcome at TOC, with the cefiderocol arm having 4.4% more indeterminacy than the meropenem arm.

Table 56. Amount of Missing or Indeterminate Data in Key Endpoints in the mITT Population, APEKS-NP Trial

Endpoint	Cefiderocol	Meropenem
ACM at day 14	0/145 (0.0)	1/147 (0.7)
ACM at day 28	2/145 (1.4)	1/147 (0.7)
Microbiological outcome at TOC	39/124 (31.5)	39/127 (30.7)
Clinical outcome at TOC	24/145 (16.6)	18/147 (12.2)

Source: adsl.xpt.
All values are expressed as n/N' (%).
The cefiderocol arm included 145 subjects; the meropenem arm included 147 subjects.
Abbreviations: ACM, all-cause mortality; mITT, modified intention-to-treat; n, number of subjects with missing or indeterminate date; N', number of subjects for whom the endpoint is defined; TOC, test-of-cure

Interim Analyses' Results

Unblinded interim analyses of safety and efficacy data, to be conducted by the DSMB, were scheduled for when 50 and then 150 subjects had completed treatment and at FU. At the first interim analysis, the decision was made to continue the trial as planned but to hold a second interim analysis when 100 subjects had completed treatment and at FU. At this interim analysis, the decisions were made to again continue the trial as planned and to cancel the interim analysis at 150 subjects. A third interim analysis was conducted when all subjects had completed treatment and at FU, prior to the official conduct of efficacy and safety analyses. At each of the

three interim analyses, alpha =0.0001 was used for testing efficacy-related hypotheses. In addition, the blinded sample size re-estimation after recruitment of about 150 subjects led to the decision to maintain the planned sample size rather than increase it.

Use of standard methods of estimation and CI construction in trials with group sequential designs can lead to biased estimates and CIs that do not achieve their nominal coverage rates. We conducted a simulation study to examine whether standard methods sufficed for this trial. The study showed that standard point estimates were nearly unbiased and CIs achieved their nominal coverage rates. Therefore, special statistical methods for estimation and CI construction were not needed.

Additional Efficacy Results

Additional Analyses for All-Cause Mortality

We first present two sensitivity analyses that examine the consequences of handling unknown survival status differently than the Applicant did. The Applicant excluded subjects with unknown status from its ACM analyses, which were presented in Section 6. One alternative approach is the "worst-case" handling of missing endpoint data, which imputes values in a way that maximally disadvantages cefiderocol in its comparison with meropenem: missing values in the cefiderocol arm are imputed as treatment failures and missing values in the meropenem arm are imputed as treatment successes. Another alternative approach, more commonly used than excluding subjects, is to consider subjects with missing endpoint values as treatment failures (regardless of which arm they belong to). Note that both alternative approaches produce ITT analyses, as they include all subjects in the primary analysis population.

The following two tables present the results of analyses of ACM at 14 and 28 days using the alternative approaches to handling missing data described above. The key takeaway from these tables is that cefiderocol is noninferior to meropenem even using alternative missing data handling. The overall results presented are similar to the Applicant's complete case results, as would be expected given the paucity of unknown survival status.

Table 57. All-Cause Mortality at Days 14 and 28 in the mITT Population With "Worst-Case" Handling of Missing Data, APEKS-NP Trial

Endpoint	Cefiderocol	Meropenem	Difference % (CI)
ACM at day 14	18/145 (12.4)	17/147 (11.6)	0.9 (-6.5, 8.3)[a]
ACM at day 28	32/145 (22.1)	30/147 (20.4)	1.7 (-7.5, 11.0)

Source: adsl.xpt.
All values in the cefiderocol and meropenem columns are expressed as n/N' (%).
Estimates of difference in mortality rates and construction of confidence intervals derived from use of Cochran-Mantel-Haenszel (CMH) stratum-weighted estimator, with strata based on APACHE II score at randomization (<=15 vs. >=16). 95.04% (rather than 95%) confidence intervals are reported, per adjustment in alpha level due to performance of multiple interim analyses.
The cefiderocol arm included 145 subjects; the meropenem arm included 147 subjects. For ACM at day 14, 0 cefiderocol subjects and 1 meropenem subject had unknown survival status; for ACM at day 28, 2 cefiderocol subjects and 1 meropenem subject had unknown survival status.
[a] The null hypothesis that cefiderocol is inferior to meropenem (with respect to the 12.5 noninferiority margin) was rejected, 2-sided p =0.002. No hypothesis tests were performed with respect to ACM at day 28.
Abbreviations: ACM, all-cause mortality; APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; mITT, modified intention-to-treat; n, number of subjects who died by the indicated timepoint; N', number of subjects in the mITT population of treatment arm

Table 58. All-Cause Mortality at Days 14 and 28 in the mITT Population With Unknown Survival Status Treated as Death, APEKS-NP Trial

Endpoint	Cefiderocol	Meropenem	Difference % (CI)
ACM at day 14	18/145 (12.4)	18/147 (12.2)	0.2 (-7.2, 7.7)[a]
ACM at day 28	32/145 (22.1)	31/147 (21.1)	1.1 (-8.2, 10.4)

Source: adsl.xpt.
All values in the cefiderocol and meropenem columns are expressed as n/N' (%).
Estimates of difference in mortality rates and construction of confidence intervals derived from use of Cochran-Mantel-Haenszel (CMH) stratum-weighted estimator, with strata based on APACHE II score at randomization (<=15 vs. >=16). 95.04% (rather than 95%) confidence intervals are reported, per adjustment in alpha level due to performance of multiple interim analyses.
The cefiderocol arm included 145 subjects; the meropenem arm included 147 subjects. For ACM at day 14, 0 cefiderocol subjects and 1 meropenem subject had unknown survival status; for ACM at day 28, 2 cefiderocol subjects and 1 meropenem subject had unknown survival status.
[a] The null hypothesis that cefiderocol is inferior to meropenem (with respect to the 12.5 noninferiority margin) was rejected, 2-sided p =0.001. No hypothesis tests were performed with respect to ACM at day 28.
Abbreviations: ACM, all-cause mortality; APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; mITT, modified intention-to-treat; n, number of subjects who died by the indicated timepoint

The next table provides a sensitivity analysis for the "per pathogen" table presented in the discussion of important review issue #2 in Section 6.4.2. It examines ACM using the approach of considering subjects with unknown survival status as deaths rather than excluding them. The results are unchanged for most pathogens, given the paucity of unknown survival status, and overall remain consistent with the NI of cefiderocol to meropenem.

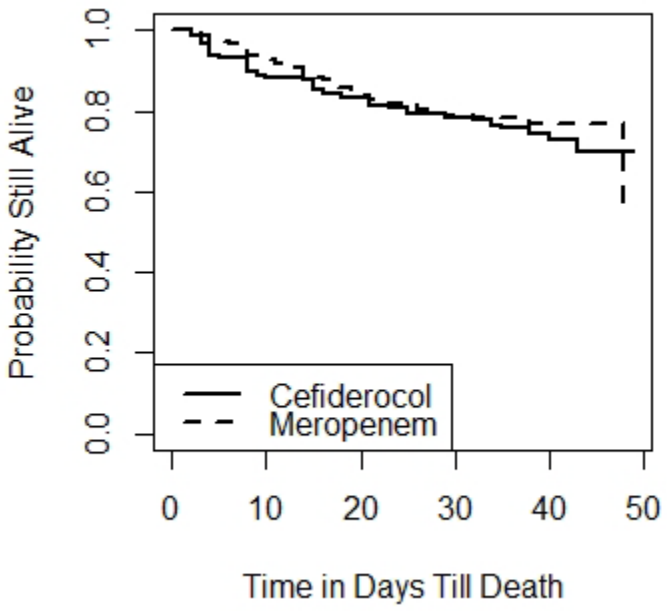
Table 59. All-Cause Mortality by Baseline Pathogens With Known Meropenem Susceptibility in mITT Population, Treating Unknown Survival Status as Death, APEKS-NP Trial

	Day 14 All-Cause Mortality		Day 28 All-Cause Mortality	
Baseline Group or Pathogen	**Fetroja**	**Meropenem**	**Fetroja**	**Meropenem**
Klebsiella pneumoniae	4/38 (10.5)	4/36 (11.1)	8/38 (21.1)	9/36 (25.0)
Pseudomonas aeruginosa	2/20 (10.0)	4/17 (23.5)	2/20 (10.0)	5/17 (29.4)
Acinetobacter baumannii complex	1/8 (12.5)	0/9 (0.0)	3/8 (37.5)	0/9 (0.0)
Escherichia coli	3/18 (16.7)	3/21/ (14.3)	5/18 (27.8)	4/21 (19.0)
Enterobacter cloacae complex	1/9 (11.1)	2/10 (20.0)	2/9 (22.2)	3/10 (30.0)
Serratia marcescens	1/8 (12.5)	0/4 (0.0)	2/8 (25.0)	0/4 (0.0)
Proteus mirabilis	0/2 (0.0)	1/5 (20.0)	0/2 (0.0)	1/5 (20.0)

Source: adsl.xpt, adms.xpt.
All values are expressed as n/N' (%).
The cefiderocol arm included 145 subjects; the meropenem arm included 147 subjects. For ACM at day 14, 0 cefiderocol subjects and 1 meropenem subject had unknown survival status; for ACM at day 28, 2 cefiderocol subjects and 1 meropenem subject had unknown survival status.
The label reported results for "Other Enterobacterales," which combines Enterobacter cloacae complex and Serratia marcescens. The results for ACM at Day 14 are Fetroja 2/16 (12.5), Meropenem 2/14 (14.3); the results for ACM at Day 28 are Fetroja 4/16 (25.0), Meropenem 3/14 (21.4).
Abbreviations: ACM, all-cause mortality; mITT, modified intention-to-treat; n, number of subjects who died by the indicated timepoint; N', number of subjects with the pathogen at baseline known to be meropenem suscept ble

The following figure provides estimated per-arm probabilities of survival over time, between initial receipt of study medication and EOS (EOT +28 days (+/-3 days)). The cefiderocol arm's estimated survival curve closely tracks but is slightly inferior to the meropenem arm's curve almost through day 40, after which limited data points lead to vague estimates of survival probability.

Figure 8. Kaplan-Meier Survival Curves in the mITT Population, APEKS-NP Trial



Source: adsl.xpt.
Abbreviations: mITT, modified intention-to-treat

Additional Analyses for Clinical Outcome

The following table presents clinical outcome cure rates at different time points. The cefiderocol cure rates are uniformly smaller than, but close to, the meropenem rates. All of the CIs for the difference in cure rates include zero, indicating that the data do not provide suggestive evidence of between-arm differences in rates.

Table 60. Clinical Outcome at Different Time Points in the mITT Population, APEKS-NP Trial

Time Point	Cefiderocol	Meropenem	Difference % (CI)
EA	120/145 (82.8)	122/147 (83.0)	-0.3 (-8.8, 8.2)
EOT	112/145 (77.2)	119/147 (81.0)	-3.8 (-12.9, 5.2)
TOC	94/145 (64.8)	98/147 (66.7)	-2.0 (-12.5, 8.5)

Source: adsl.xpt; adclo.xpt.
All values in the cefiderocol and meropenem columns are expressed as n/N' (%).
Estimates of difference in clinical cure rates and construction of confidence intervals derived from use of Cochran-Mantel-Haenszel (CMH) stratum-weighted estimator, where subjects with indeterminate clinical status are considered treatment failures. 95.04% (rather than 95%) confidence intervals are reported, due to adjustment in alpha level due to performance of multiple interim analyses.
The cefiderocol arm included 145 subjects; the meropenem arm included 147 subjects.
Abbreviations: CI, confidence interval; EA, early assessment occurring at day 3 or 4; EOT, end of treatment; TOC, test-of-cure assessment occurring 7 days (±2) after the end of treatment; mITT, modified intention-to-treat; n, number of subjects who were clinical cures; N', number of subjects in the mITT population of treatment arm

Additional Analyses for Microbiological Outcome

The microbiological outcome eradication rates at different time points are reported in the table below. Recall that these endpoints are only defined for subjects who had gram-negative pathogens detected at baseline. The EA results suggest that the meropenem eradication rate may be superior to the cefiderocol rate at this time point. At EOT and TOC, however, the two arms have similar eradication rates and both CIs for eradication rate differences include zero.

Table 61. Microbiological Outcome at Different Time Points in the mITT Population, APEKS-NP Trial

Time Point	Cefiderocol	Meropenem	Difference % (CI)
EA	52/124 (41.9)	68/127 (53.5)	-12.4 (-24.4, -0.4)
EOT	79/124 (63.7)	85/127 (66.9)	-3.8 (-15.5, 8.0)
TOC	59/124 (47.6)	61/127 (48.0)	-1.4 (-13.5, 10.8)

Source: adsl.xpt; admbo.xpt.
All values in the cefiderocol and meropenem columns are expressed as n/N' (%).
Estimates of difference in eradication rates and construction of confidence intervals derived from use of Cochran-Mantel-Haenszel (CMH) stratum-weighted estimator, where subjects with indeterminate microbiological status are considered treatment failures. 95.04% (rather than 95%) confidence intervals are reported, due to adjustment in alpha level due to performance of multiple interim analyses.
The cefiderocol arm included 124 subjects with gram-negative pathogens detected at baseline; the meropenem arm included 127 such subjects.
Abbreviations: CI, confidence interval; EA, early assessment occurring at day 3 or 4; EOT, end of treatment; TOC, test-of-cure assessment occurring 7 days (±2) after the end of treatment; mITT, modified intention-to-treat; n, number of subjects for whom all baseline gram-negative were eradicated clinical cures; N', number of subjects in the mITT population of treatment arm

Subgroup Analyses of All-Cause Mortality at Day 14

The following table (Table 62) presents the results of analyses of the primary endpoint for a variety of demographic and baseline health status subgroups. The reader is cautioned that these are exploratory analyses that generally have modest statistical power. Per the Applicant, CIs for the difference in death rates were only constructed when a subgroup contained at least 10 subjects per arm. All of the CIs include zero, meaning that they do not provide strong suggestions of between-arm differences in survival at day 14.

Table 62. All-Cause Mortality at Day 14 in mITT Subgroups, APEKS-NP Trial

Baseline Variable Subgroup	Cefiderocol	Meropenem	Difference % (CI)
Demographic characteristics			
Gender			
Male	14/99 (14.1)	10/100 (10.0)	4.1 (-4.9, 13.2)
Female	4/46 (8.7)	7/46 (15.2)	-6.5 (-19.7, 6.7)
Age group			
<65 years*	8/65 (12.3)	5/57 (8.8)	3.5 (-7.3, 14.4)
65≤to <75 years	3/40 (7.5)	8/45 (17.8)	-10.3 (-24.1, 3.6)
≥75 years	7/40 (17.5)	4/44 (9.1)	8.4 (-6.1, 23.0)
Race			
White	13/102 (12.7)	15/98 (15.3)	-2.6 (-12.2, 7.1)
Black or African American	0/0	0/1 (0.0)	
Asian	5/41 (12.2)	2/43 (4.7)	7.5 (-4.3, 19.4)
Other	0/2 (0.0)	0/3 (0.0)	0.0
Region			
North America	1/6 (16.7)	0/6 (0.0)	16.7
Europe	12/99 (12.1)	15/97 (15.5)	-3.3 (-13.0, 6.3)
Asia-Pacific	5/40 (12.5)	2/43 (4.7)	7.8 (-4.2, 19.9)
Hispanic/Latino?			
No	18/137 (13.1)	17/136 (12.5)	0.6 (-7.3, 8.6)
Yes	0/4 (0.0)	0/3 (0.0)	0.0
Baseline health status			
Diagnosis			
HABP	6/59 (10.2)	9/60 (15.0)	-4.8 (-16.7, 7.1)
VABP	9/59 (15.3)	8/63 (12.7)	2.6 (-9.8, 14.9)
HCABP	3/27 (11.1)	0/23 (0.0)	11.1 (-0.8, 23.0)
APACHE II score			
≤15	6/74 (8.1)	5/76 (6.6)	1.5 (-6.8, 9.9)

Baseline Variable Subgroup	Cefiderocol	Meropenem	Difference % (CI)
16-19	5/31 (16.1)	3/25 (12.0)	4.1 (-14.1, 22.3)
≥20	7/40 (17.5)	9/45 (20.0)	-2.5 (-19.1, 14.1)
CPIS			
<6	9/72 (12.5)	12/88 (13.6)	-1.1 (-11.6, 9.4)
6-7	6/59 (10.2)	2/40 (5.0)	5.2 (-5.1, 15.4)
8-9	3/12 (25.0)	2/15 (13.3)	11.7 (-18.3, 41.7)
>9	0/2 (0.0)	1/3 (33.3)	-33.3
Bacteremia?			
No	13/132 (9.8)	14/131 (10.7)	-0.8 (-8.2, 6.5)
Yes	5/13 (38.5)	3/15 (20.0)	18.5 (-14.9, 51.8)
Creatinine clearance			
>120 mL/min	3/22 (13.6)	2/25 (8.0)	5.6 (-12.2, 23.5)
>80-120 mL/min	4/33 (12.1)	3/35 (8.6)	3.55 (-11.0, 18.1)
>50-80 mL/min	3/43 (7.0)	2/35 (5.7)	1.262 (-9.6, 12.1)
30-50 mL/min	2/27 (7.4)	6/31 (19.4)	-11.9 (-29.0, 5.1)
<30 mL/min	6/20 (30.0)	4/20 (20.0)	10.0 (-16.7, 36.7)
MDRD-eGFR			
≥90	4/35 (11.4)	5/46 (10.9)	0.6 (-13.3, 14.4)
60 to <90	7/48 (14.6)	3/38 (7.9)	6.7 (-6.5, 19.9)
30 to <60	2/42 (4.8)	4/41 (9.8)	-5.0 (-16.1, 6.2)
15 to <30	3/9 (33.3)	3/10 (30.0)	3.3
<15	2/11 (18.2)	2/11 (18.2)	0.0 (-32.3, 32.3)
Empiric treatment failure?			
No	12/97 (12.4)	11/99 (11.1)	1.3 (-7.8, 10.3)
Yes	6/48 (12.5)	6/47 (12.8)	-0.3 (-13.7, 13.1)
Prior antibacterials?			
No	1/40 (2.5)	5/46 (10.9)	-8.4 (-18.6, 1.9)
Yes	17/105 (16.2)	12/100 (12.0)	4.2 (-5.3, 13.7)
ICU admission?			
No	3/43 (7.0)	1/50 (2.0)	5.0 (-3.6, 13.5)
Yes	15/102 (14.7)	16/96 (16.7)	-2.0 (-12.1, 8.2)
Ventilated?			
No	4/56 (7.1)	5/61 (8.2)	-1.1 (-10.7, 8.6)
Yes	14/89 (15.7)	12/85 (14.1)	1.6 (-9.0, 12.2)
Meropenem nonsusceptible?[a]			
No	9/84 (10.7)	9/79 (11.4)	-0.7 (-10.3, 9.0)
Yes	6/35 (17.1)	6/30 (20.0)	-2.9 (-21.9, 16.2)
Meropenem MIC >8?[b]			
No	9/89 (10.1)	10/83 (12.0)	-1.9 (-11.3, 7.5)
Yes	6/30 (20.0)	5/26 (19.2)	0.8 (-20.1, 21.6)
Top 5 gram-negative pathogens			
Klebsiella pneumoniae	5/48 (10.4)	5/44 (11.4)	-0.9 (-13.7, 11.8)
Pseudomonas aeruginosa	2/24 (8.3)	3/23 (13.0)	-4.7 (-22.4, 13.0)
Acinetobacter baumannii	5/23 (21.7)	4/24 (16.7)	5.1 (-17.5, 27.6)
Escherichia coli	4/19 (21.1)	3/22 (13.6)	7.4 (-15.9, 30.7)
Enterobacter cloacae	0/7 (0.0)	1/8 (12.5)	-12.5

Source: adsl.xpt; admbo.xpt.
All values in the cefiderocol and meropenem columns are expressed as n/N (%).

Estimates of difference in mortality rates are equal to the difference in the cefiderocol and meropenem arms' rates. Confidence intervals, using Wald method, are computed when both arms contain at least 10 subjects in the subgroup. Per Applicant, subjects with unknown survival status are not included in analyses. 95.04% (rather than 95%) confidence intervals are reported, per adjustment in alpha level due to performance of multiple interim analyses.
The cefiderocol arm included 145 subjects; the meropenem arm included 147 subjects; one meropenem subject and zero cefiderocol subjects had unknown survival status at day 14.
[*] The label reports age group mortality rates, treating unknown survival status as death. The only subject with unknown survival status was <65 years in the meropenem arm, so in the label that subgroup's arm is reported as 6/58 (10.3).
[a] Meropenem-nonsusceptibility based on CLSI. 63 subjects had unknown nonsusceptibility status and were not included in the subgroup analyses; these included the 41 members of the mITT population who did not have any gram-negative pathogens detected at baseline.
[b] 63 subjects had unknown status and were not included in the subgroup analyses; these included the 41 members of the mITT population who did not have any gram-negative pathogens detected at baseline.
Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; CLSI, Clinical and Laboratory Standards Institute; CPIS, clinical pulmonary infection score; eGFR, estimated glomerular filtration rate; HABP, hospital-acquired bacterial pneumonia; HCABP, healthcare-associated bacterial pneumonia; ICU, intensive care unit; MDRD, Modification of Diet in Renal Disease; MIC, minimum inhibitory concentration; mITT, modified intention-to-treat; n, number of subjects who died by day 14; N, number of subjects in subgroup with known survival status at day 14; VABP, ventilator-associated bacterial pneumonia

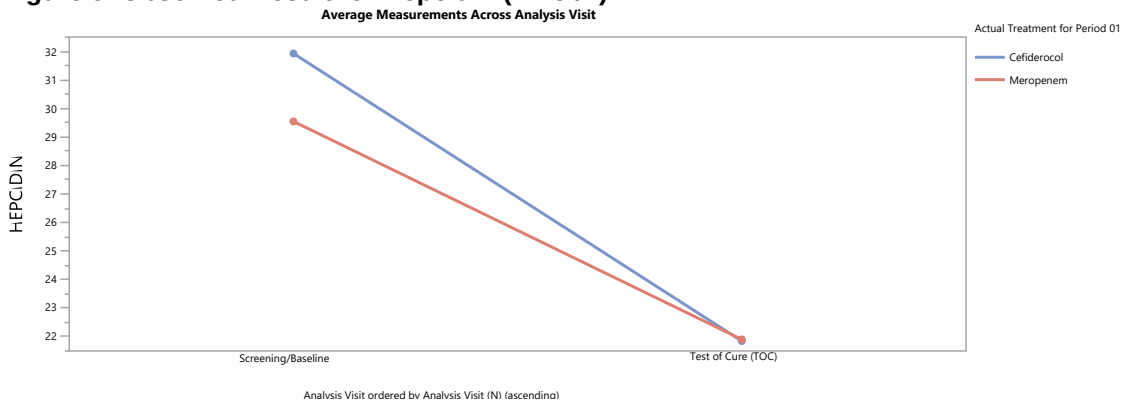
17. Clinical Safety Assessment Additional Information and Assessment

This section provides additional analysis on safety issues related to cefiderocol's mechanism of action and other class effects of β-lactam drugs. There is also a complete listing of treatment-emergent AE (TEAE) by system organ class (SOC) without any grouped queries, an analysis of TEAEs and serious AEs (SAEs) by demographic subgroups, and subject-level listings of discontinuations and deaths.

Time Trends for Iron Parameters

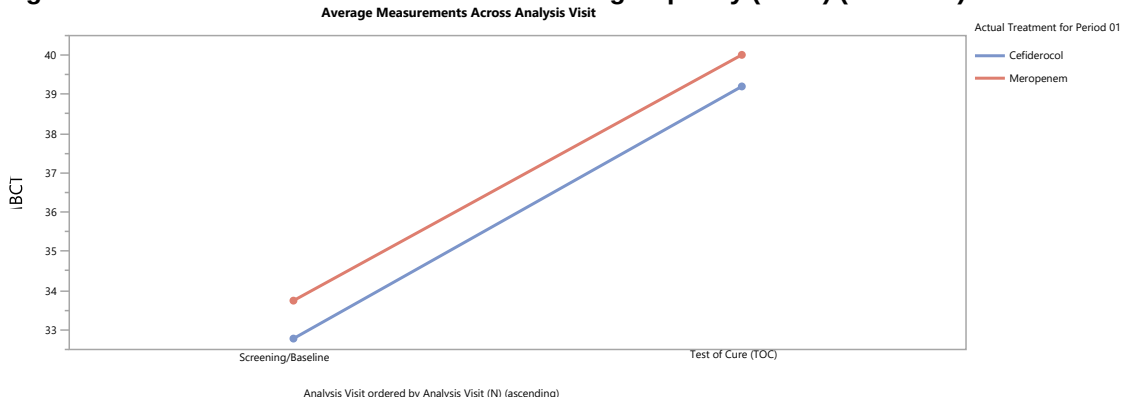
Given cefiderocol's siderophore-based mechanism of cell entry, iron parameters were measured. The values for hepcidin, total iron-binding capacity, iron, and transferrin saturation were analyzed over time from screening to TOC. Hepcidin is an acute phase reactant and normal values have not been established. The iron parameters trended in a linear fashion in both treatment groups and changes over time did not appear clinically significant. Hemoglobin and hematocrit declined more rapidly in the cefiderocol group as compared to the meropenem group by the EA and then remained low until the TOC. There was approximately a 1 g/dL decrease in hemoglobin and 2% decrease in hematocrit from baseline to TOC in the cefiderocol-treated patients. The hemoglobin and hematocrit appeared to be more stable in the meropenem group over time, but in both groups, these parameters improved by the FU visit. (b) (4)

Figure 9. Observed Result for Hepcidin (nmol/L)



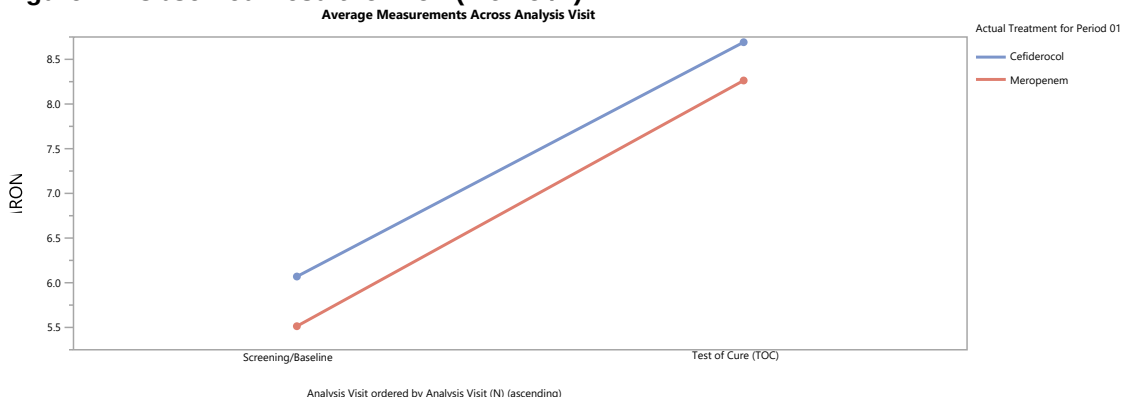
Source: Reviewer Figure, created in JMP Clinical

Figure 10. Observed Result for Total Iron Binding Capacity (TIBC) (mcmol/L)



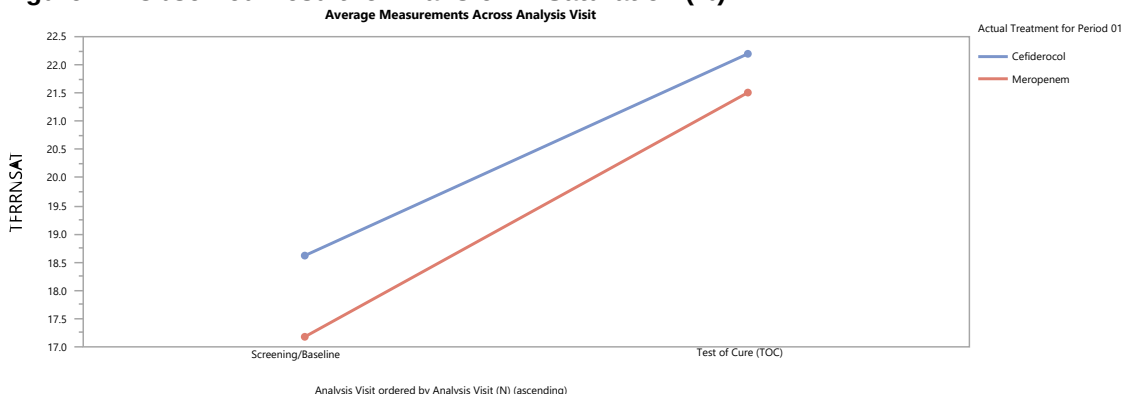
Source: Reviewer Figure, created in JMP clinical

Figure 11. Observed Result for Iron (mcmol/L)



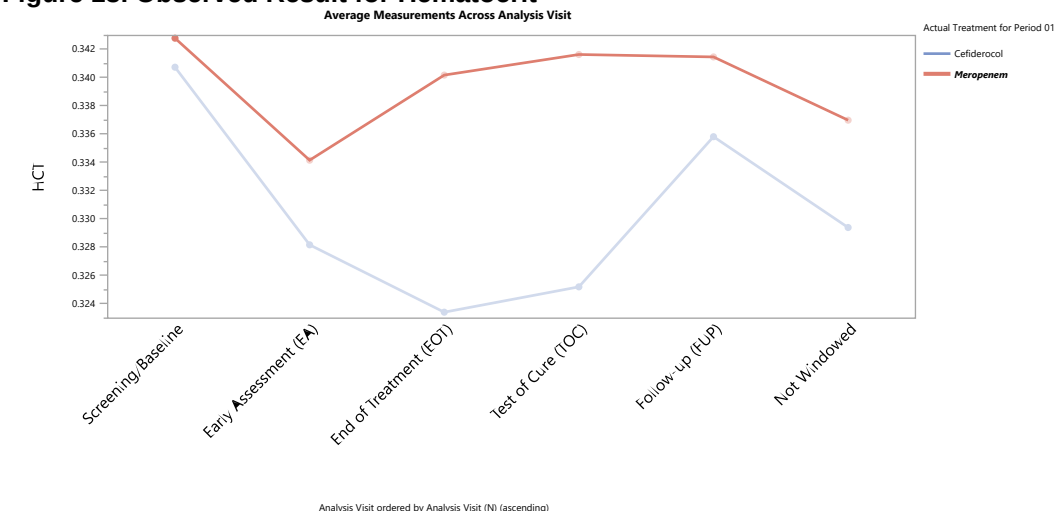
Source: Reviewer Figure, created in JMP clinical

Figure 12. Observed Result for Transferrin Saturation (%)



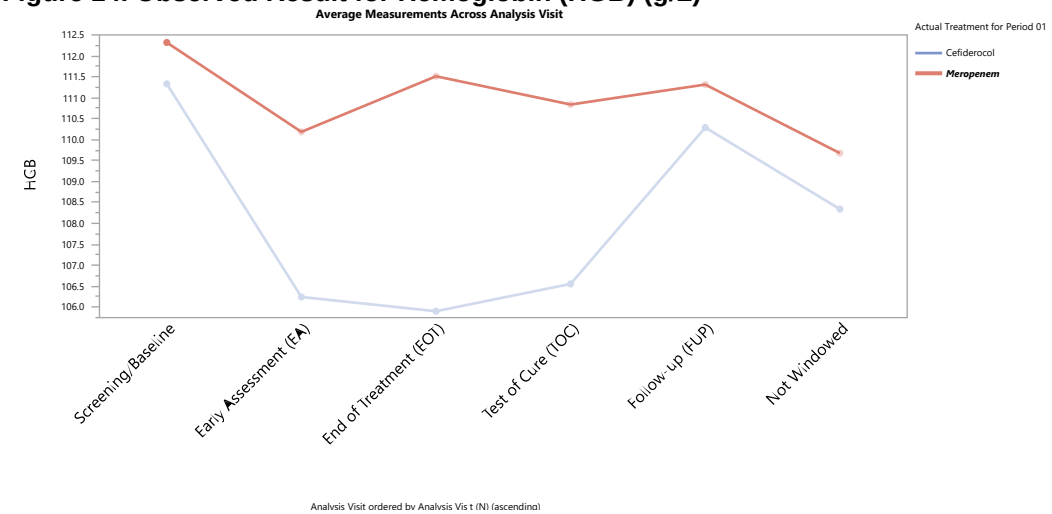
Source: Reviewer Figure, created in JMP Clinical

Figure 13. Observed Result for Hematocrit



Source: Reviewer Figure, created in JMP Clinical

Figure 14. Observed Result for Hemoglobin (HGB) (g/L)



Source: Reviewer Figure, created in JMP Clinical

Hy's Law Screening

Four patients in the meropenem and two patients in the cefiderocol group met biochemical criteria of Hy's law (AST or ALT ≥3x ULN, total BILI ≥2x ULN, and ALP <2x ULN), as shown in Figure 15. The two patients in the cefiderocol group are described further below. Neither patient had known chronic liver disease at the time of enrollment, but both had confounding medications and concurrent sepsis. Both had a fatal outcome.

- Patient (b) (6) – 81-year-old female with aortic valve replacement, atrial flutter s/p ablation, CHF, chronic obstructive pulmonary disease, hypertension (HTN), and hypercholesterolemia who was admitted since day -9 for *E. coli* urinary tract infection (UTI) and septic shock. The APACHE II score was 48, and she was randomized to cefiderocol for VABP. On day 2, SAEs of hepatic enzyme increased and septic shock occurred. Despite vasopressors, she died on day 3 due to septic shock and lactic acidosis which was considered related to CHF due to septic shock. Concomitant medications included amiodarone, heparin, insulin, levothyroxine, methylprednisolone, omeprazole, and propofol. The liver enzymes are noted below:

Table 63. Liver Enzymes for Hy's Law Screening for Patient (b) (6)

Day	AST (RR =0-40 IU/L)	ALT (RR =0-41 IU/L)	ALP (RR =35-130 IU/L)	GGT (RR =6-71 IU/L)	Total BILI (RR =0-1.2 mg/dL)	ALB (RR =34-48 g/L)
1	42 H	57 H	181 H	272 H	1.5 H	34 L
3	2544 H	2083 H	198 H	237 H	3.2 H	32 L

Source: Applicant's Narratives
Abbreviations: ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin; GGT, gamma-glutamyl transferase; RR, reference range, H, high, L, low

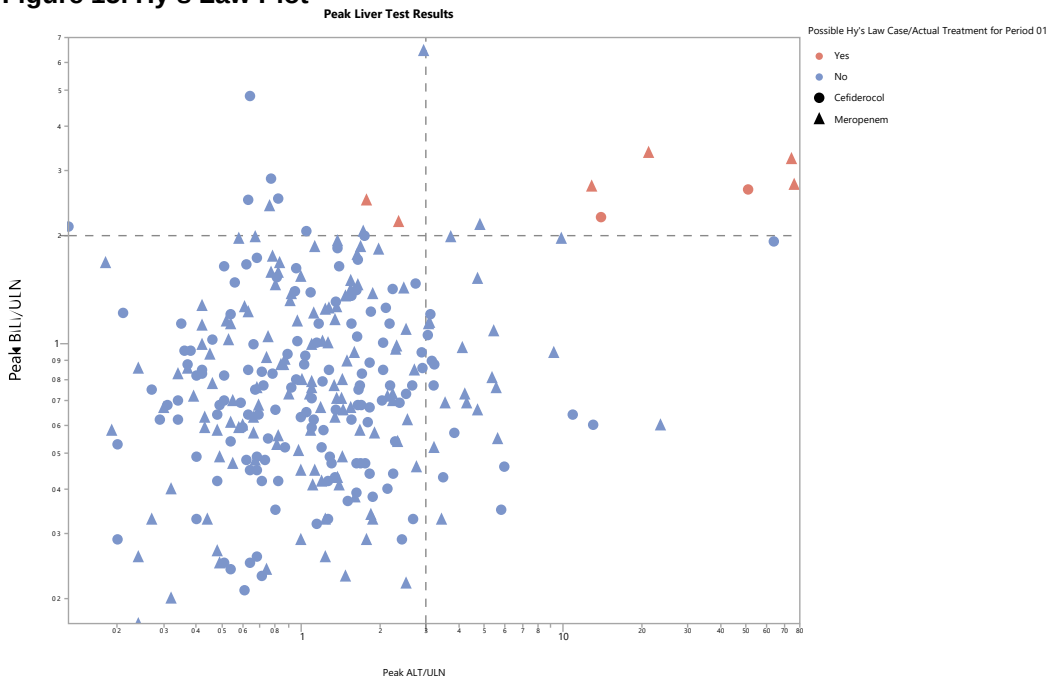
- Patient (b) (6) – 57-year-old male with DM and CVA with recent acute MI and coronary artery bypass. On day -14, he had atrial fibrillation and chronic CHF and 3 days later, multiple organ dysfunction syndrome (MODS), acute kidney injury (AKI), cardiac arrest, and ischemic hepatitis. He was randomized to cefiderocol for VABP. On day 6, he had a mild rash that resolved on day 11. On day 9, cefiderocol was discontinued due to bacteremia and clinical ineffectiveness of antibacterial therapy for NP. SAEs of liver function test (LFT) increased and sepsis occurred. On day 10, he had hemodiafiltration due to anuria and worsened encephalopathy. On day 15, he developed liver failure and died due to MODS. Concomitant medications included amiodarone, levofloxacin, omeprazole, dalteparin, caspofungin, and acetaminophen. The liver enzymes are below. The ALP criteria of Hy's Law was not met at the same time as the criteria for elevated AST/ALT and BILI.

Table 64. Liver Enzymes for Hy's Law Screening for Patient (b) (6)

Day	AST (RR =5-35 U/L)	ALT (RR =5-45 U/L)	ALP (RR =30-120 U/L)	GGT (RR =7-55 U/L)	Total BILI (RR =5-21 mcmol/L)	ALB (RR =35-52 g/L)	PT-INR (RR =0.85-1.25)
1	23 H	116 H	238 H	316 H	22 H	26 L	2.22 H
3	31.9 H	64.5 H	45 H	188.4 H	16.6 H	24 L	1.28 H
9	184 H	179 H	291 H	104 H	12 H	27 L	1.76 H
15	382 H	628 H	647 H	185 H	47 H	29 L	2.18 H

Source: Applicant's Narratives
Abbreviations: ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin; GGT, gamma-glutamyl transferase; PT-INR, prothrombin time-international normalized ratio; RR, reference range, H, high, L, low

Figure 15. Hy's Law Plot



Source: Reviewer Figure, created in JMP Clinical
Abbreviations: ALT, alanine aminotransferase; BILI, bilirubin; ULN, upper limit of normal

Although both patients had several comorbidities and concomitant medications, a possible increase in liver enzymes from cefiderocol is not fully excluded. Increased liver tests is a labeled AR. The patients in the meropenem group are not discussed as increased liver tests are labeled ARs for meropenem as well.

Renal Abnormalities

The frequency of any postbaseline worse stage of renal function by estimated glomerular filtration rate (eGFR) using the derived GFR was slightly higher in the cefiderocol group than in the meropenem group. Patients with normal GFR at baseline who developed stage 3 or higher postbaseline worst stage are described below. The first three cases listed had confounding medical history (DM, HTN, or renal failure) and medications. The fourth case may have been confounded by loss of volume from bleeding and concomitant medications. The last case was least confounded and may have had a positive dechallenge with cefiderocol, but a narrative was not available for detailed history and causality assessment could not be made. In all cases, eGFR was calculated in mL/min/1.73 m^2.

- (b) (6) – 82-year-old white male with a history of DM, HTN, and myasthenia gravis received cefiderocol until day 22 for VABP. The eGFR decreased gradually from 114 to 57 by day 36. TEAEs included edema, herpetic infection, diarrhea, and metabolic alkalosis. The patient also had a bladder operation (balloon placement) on day 13 (indication not provided). Confounding medications may have included acyclovir and furosemide.
- (b) (6) – 77-year-old white male with a history of DM, renal failure, and sepsis received cefiderocol until day 6 for HABP. The eGFR decreased from 101 to 46 at day 15, but improved to 121 by day 22. TEAEs included hypernatremia from day 7 to day 22. Confounding medications included furosemide until day 11 and amikacin from day 15 to day 16.
- (b) (6) – 63-year-old Asian female with a history of HTN and DM received cefiderocol until day 10 for a HCABP. The eGFR decreased from 93 to 59 at day 25 and increased to 67 by day 39. TEAEs included dyspnea, pyrexia, hemoptysis and hypokalemia.
- (b) (6) –73-year-old Asian female with a history of a neck mass with tumor extension pulmonary tuberculosis, and hypokalemia received cefiderocol for VABP until day 15. The eGFR declined sharply from 139 to 21 at day 14. Other TEAEs were postprocedural hemorrhage after tracheostomy, hypokalemia, gastroenteritis, chest pain, abnormal urinalysis, urine output decreased, and acute myocardial infarction (MI) on day 15 which led to death. At baseline, the urine contained 3+ blood and glucose, and on day 14, there was 2+ protein. The blood eosinophil count remained within the range of normal. Confounding medications included furosemide given to increase urine output.
- (b) (6) – 53-year-old white male with a history of amyotrophic lateral sclerosis and respiratory failure received cefiderocol until day 8 for VABP. The eGFR decreased from 225 to 3 on day 8, and then improved to 155 on day 21. No TEAEs were reported.

Table 65. eGFR Shift Table, Safety Population

Baseline GFR Category	Postbaseline Worst Stage	Cefiderocol N=148	Meropenem N=150
Total Subjects	**Any Worse Stage**	40 (27.0)	37 (24.7)
Stage 1: eGFR ≥90: Normal or high GFR	Stage 2: eGFR 60-89	5 (3.4)	11 (7.3)
	Stage 3a: eGFR 45-59	3 (2)	1 (0.7)
	Stage 4: eGFR 15-29	1 (0.7)	0
	Stage 5: eGFR <15	1 (0.7)	0
Stage 2: eGFR 60-89: Mild GFR	Stage 3a: eGFR 45-59	10 (6.8)	8 (5.3)
	Stage 3b: eGFR 30-44	1 (0.7)	2 (1.3)
	Stage 4: eGFR 15-29	1 (0.7)	2 (1.3)
	Stage 5: eGFR <15	1 (0.7)	0
Stage 3a: eGFR 45-59: Moderate GFR	Stage 3b: eGFR 30-44	5 (3.4)	4 (2.7)
	Stage 4: eGFR 15-29	3 (2)	2 (1.3)
Stage 3b: eGFR 30-44: Moderate GFR	Stage 4: eGFR 15-29	5 (3.4)	4 (2.7)
	Stage 5: eGFR <15	2 (1.4)	2 (1.3)
Stage 4: eGFR 15-29: Severe GFR	Stage 5: eGFR <15	2 (1.4)	1 (0.7)

Source: ad b.xpt; Software: R
All values are expressed as n (%).
Abbreviations: eGFR, estimated glomerular filtration rate

Adverse Events by System Organ Class and Preferred Term

A complete list of TEAEs by SOC and preferred term (PT) ordered by risk difference relative to treatment with cefiderocol (without reviewer grouped queries or FDA Medical Dictionary for Regulatory Activities Queries) is noted in the table below (Table 66).

Table 66. TEAEs by SOC and PT

System Organ Class Preferred Term	Cefiderocol N=148	Meropenem N=150	Total N=298	Risk Difference (95% CI)
Infections and infestations	60 (40.5)	53 (35.3)	113 (37.9)	5.2 (-5.8, 16.2)
Urinary tract infection	23 (15.5)	16 (10.7)	39 (13.1)	4.8 (-2.8, 12.4)
Pneumonia	11 (7.4)	8 (5.3)	19 (6.4)	2.1 (-3.4, 7.6)
Septic shock	5 (3.4)	2 (1.3)	7 (2.3)	2.1 (-1.3, 5.5)
Urinary tract infection fungal	4 (2.7)	2 (1.3)	6 (2.0)	1.4 (-1.8, 4.6)
Genitourinary tract infection	2 (1.4)	0	2 (0.7)	1.4 (-0.5, 3.3)
Oral candidiasis	2 (1.4)	0	2 (0.7)	1.4 (-0.5, 3.3)
Urethritis	2 (1.4)	0	2 (0.7)	1.4 (-0.5, 3.3)
Clostridium difficile infection	4 (2.7)	3 (2.0)	7 (2.3)	0.7 (-2.7, 4.1)
Sepsis	4 (2.7)	3 (2.0)	7 (2.3)	0.7 (-2.7, 4.1)
Ascariasis	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Bacteremia	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Bacterial sepsis	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Conjunctivitis	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Device related infection	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Ear infection	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Escherichia urinary tract infection	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Fungal sepsis	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Herpes zoster	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Lung infection	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Pyelonephritis	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Pyelonephritis chronic	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Respiratory tract infection	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Spinal cord infection	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Streptococcal bacteremia	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Tracheitis	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Sinusitis	2 (1.4)	2 (1.3)	4 (1.3)	0.1 (-2.5, 2.7)
Bronchitis bacterial	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Gastroenteritis	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Influenza	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Pneumonia bacterial	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Postoperative wound infection	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Pulmonary tuberculosis	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Bronchitis	2 (1.4)	3 (2.0)	5 (1.7)	-0.6 (-3.5, 2.3)
Acinetobacter bacteremia	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Acinetobacter infection	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Bacteriuria	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Brain abscess	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Candida infection	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Chronic sinusitis	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Clostridium difficile colitis	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Cystitis	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Fungal infection	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Gallbladder empyema	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Gangrene	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Infectious disease carrier	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Infectious pleural effusion	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)

System Organ Class Preferred Term	Cefiderocol N=148	Meropenem N=150	Total N=298	Risk Difference (95% CI)
Joint tuberculosis	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Liver abscess	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Meningitis	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Meningitis bacterial	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Meningoencephalitis bacterial	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Otitis media	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Pneumonia necrotising	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Pseudomonas infection	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Septic encephalopathy	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Skin candida	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Streptococcal sepsis	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Systemic candida	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Urinary tract infection bacterial	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Wound infection	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Tracheobronchitis	2 (1.4)	4 (2.7)	6 (2.0)	-1.3 (-4.5, 1.9)
Lung abscess	0	2 (1.3)	2 (0.7)	-1.3 (-3.1, 0.5)
Gastrointestinal disorders	41 (27.7)	36 (24.0)	77 (25.8)	3.7 (-6.2, 13.6)
Nausea	4 (2.7)	2 (1.3)	6 (2.0)	1.4 (-1.8, 4.6)
Abdominal pain	2 (1.4)	0	2 (0.7)	1.4 (-0.5, 3.3)
Constipation	7 (4.7)	6 (4.0)	13 (4.4)	0.7 (-3.9, 5.3)
Gastrointestinal hemorrhage	2 (1.4)	1 (0.7)	3 (1.0)	0.7 (-1.6, 3.0)
Ileus paralytic	2 (1.4)	1 (0.7)	3 (1.0)	0.7 (-1.6, 3.0)
Abdominal pain upper	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Abdominal wall hematoma	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Chronic gastritis	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Duodenitis	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Gastric hemorrhage	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Gastritis	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Hemorrhoids thrombosed	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Hypoesthesia oral	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Intestinal infarction	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Intestinal ischemia	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Intra-abdominal fluid collection	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Peptic ulcer	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Retroperitoneal hematoma	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Diarrhea	13 (8.8)	13 (8.7)	26 (8.7)	0.1 (-6.3, 6.5)
Flatulence	2 (1.4)	2 (1.3)	4 (1.3)	0.1 (-2.5, 2.7)
Upper gastrointestinal hemorrhage	2 (1.4)	2 (1.3)	4 (1.3)	0.1 (-2.5, 2.7)
Gastritis erosive	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Ascites	1 (0.7)	2 (1.3)	3 (1.0)	-0.6 (-2.9, 1.7)
Acute abdomen	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Duodenal ulcer	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Duodenal ulcer hemorrhage	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Dysphagia	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Gastroesophageal reflux disease	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Intestinal hemorrhage	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Mouth hemorrhage	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Pancreatitis acute	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Dyspepsia	0	2 (1.3)	2 (0.7)	-1.3 (-3.1, 0.5)
Hemorrhoids	0	2 (1.3)	2 (0.7)	-1.3 (-3.1, 0.5)
Vomiting	1 (0.7)	4 (2.7)	5 (1.7)	-2.0 (-4.9, 0.9)

System Organ Class Preferred Term	Cefiderocol N=148	Meropenem N=150	Total N=298	Risk Difference (95% CI)
Cardiac disorders	31 (20.9)	27 (18.0)	58 (19.5)	2.9 (-6.1, 11.9)
Atrial fibrillation	7 (4.7)	4 (2.7)	11 (3.7)	2.0 (-2.3, 6.3)
Left ventricular dysfunction	3 (2.0)	0	3 (1.0)	2.0 (-0.3, 4.3)
Cardiac arrest	7 (4.7)	5 (3.3)	12 (4.0)	1.4 (-3.1, 5.9)
Acute myocardial infarction	2 (1.4)	0	2 (0.7)	1.4 (-0.5, 3.3)
Tricuspid valve incompetence	2 (1.4)	0	2 (0.7)	1.4 (-0.5, 3.3)
Bradycardia	3 (2.0)	2 (1.3)	5 (1.7)	0.7 (-2.2, 3.6)
Cardio-respiratory arrest	3 (2.0)	2 (1.3)	5 (1.7)	0.7 (-2.2, 3.6)
Ventricular extrasystoles	2 (1.4)	1 (0.7)	3 (1.0)	0.7 (-1.6, 3.0)
Angina unstable	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Cardiac valve disease	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Coronary artery disease	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Dilatation atrial	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Dilatation ventricular	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Extrasystoles	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Hypertensive heart disease	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Intracardiac thrombus	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Myocardial infarction	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Pericardial disease	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Pericardial effusion	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Right atrial dilatation	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Right ventricular dilatation	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Right ventricular failure	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Supraventricular tachycardia	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Tachycardia	2 (1.4)	2 (1.3)	4 (1.3)	0.1 (-2.5, 2.7)
Arrhythmia	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Atrial flutter	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Cardiac failure congestive	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Cardiovascular insufficiency	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Sinus tachycardia	1 (0.7)	2 (1.3)	3 (1.0)	-0.6 (-2.9, 1.7)
Cardiogenic shock	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Cardiopulmonary failure	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Cardiovascular disorder	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Pericarditis	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Supraventricular extrasystoles	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Cardiac failure	2 (1.4)	4 (2.7)	6 (2.0)	-1.3 (-4.5, 1.9)
Cardiac failure acute	0	2 (1.3)	2 (0.7)	-1.3 (-3.1, 0.5)
Respiratory, thoracic and mediastinal disorders	37 (25.0)	34 (22.7)	71 (23.8)	2.3 (-7.4, 12.0)
Acute respiratory failure	6 (4.1)	1 (0.7)	7 (2.3)	3.4 (-0.0, 6.8)
Pleural effusion	10 (6.8)	6 (4.0)	16 (5.4)	2.8 (-2.3, 7.9)
Pulmonary hypertension	3 (2.0)	0	3 (1.0)	2.0 (-0.3, 4.3)
Pulmonary edema	3 (2.0)	1 (0.7)	4 (1.3)	1.3 (-1.3, 3.9)
Pneumonia aspiration	3 (2.0)	2 (1.3)	5 (1.7)	0.7 (-2.2, 3.6)
Asthma	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Bronchial secretion retention	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Bronchospasm	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Bullous lung disease	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Cough	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Dyspnea	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Hemoptysis	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Laryngeal edema	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Nasal dryness	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Pleurisy	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)

System Organ Class Preferred Term	Cefiderocol N=148	Meropenem N=150	Total N=298	Risk Difference (95% CI)
Pneumothorax spontaneous	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Stridor	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Tracheal ulcer	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Pulmonary artery thrombosis	3 (2.0)	3 (2.0)	6 (2.0)	0.0 (-3.2, 3.2)
Acute respiratory distress syndrome	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Atelectasis	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Pneumothorax	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Tachypnea	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Hydrothorax	5 (3.4)	6 (4.0)	11 (3.7)	-0.6 (-4.9, 3.7)
Pulmonary congestion	2 (1.4)	3 (2.0)	5 (1.7)	-0.6 (-3.5, 2.3)
Respiratory failure	2 (1.4)	3 (2.0)	5 (1.7)	-0.6 (-3.5, 2.3)
COPD	1 (0.7)	2 (1.3)	3 (1.0)	-0.6 (-2.9, 1.7)
Pulmonary embolism	1 (0.7)	2 (1.3)	3 (1.0)	-0.6 (-2.9, 1.7)
Acute pulmonary edema	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Bronchial hyperreactivity	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Bronchiectasis	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Bronchopleural fistula	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Emphysema	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Hypoxia	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Paranasal sinus hypersecretion	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Pleuritic pain	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Pneumomediastinum	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Respiratory acidosis	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Respiratory distress	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Epistaxis	0	2 (1.3)	2 (0.7)	-1.3 (-3.1, 0.5)
Investigations	32 (21.6)	29 (19.3)	61 (20.5)	2.3 (-6.9, 11.5)
Aspartate aminotransferase increased	10 (6.8)	6 (4.0)	16 (5.4)	2.8 (-2.3, 7.9)
Alanine aminotransferase increased	9 (6.1)	6 (4.0)	15 (5.0)	2.1 (-2.9, 7.1)
GGT increased	5 (3.4)	2 (1.3)	7 (2.3)	2.1 (-1.3, 5.5)
Amylase increased	3 (2.0)	0	3 (1.0)	2.0 (-0.3, 4.3)
Blood pressure increased	2 (1.4)	0	2 (0.7)	1.4 (-0.5, 3.3)
Ejection fraction decreased	2 (1.4)	0	2 (0.7)	1.4 (-0.5, 3.3)
Liver function test increased	2 (1.4)	0	2 (0.7)	1.4 (-0.5, 3.3)
Blood creatinine increased	2 (1.4)	1 (0.7)	3 (1.0)	0.7 (-1.6, 3.0)
Blood albumin decreased	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Hemoglobin decreased	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Protein total decreased	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Red blood cell count decreased	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Urine analysis abnormal	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Urine output decreased	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Transaminases increased	4 (2.7)	4 (2.7)	8 (2.7)	0.0 (-3.7, 3.7)
Blood alkaline phosphatase increased	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Blood lactate dehydrogenase increased	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Liver function test abnormal	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Blood bilirubin increased	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Blood glucose increased	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Blood potassium decreased	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Blood potassium increased	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Blood urea increased	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Mean arterial pressure decreased	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
C-reactive protein increased	0	2 (1.3)	2 (0.7)	-1.3 (-3.1, 0.5)
Hepatic enzyme increased	4 (2.7)	10 (6.7)	14 (4.7)	-4.0 (-8.8, 0.8)

System Organ Class Preferred Term	Cefiderocol N=148	Meropenem N=150	Total N=298	Risk Difference (95% CI)
General disorders and administration site conditions	22 (14.9)	19 (12.7)	41 (13.8)	2.2 (-5.6, 10.0)
Hyperthermia	2 (1.4)	1 (0.7)	3 (1.0)	0.7 (-1.6, 3.0)
Asthenia	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Calcinosis	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Chest pain	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
General physical health deterioration	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Inflammation	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Malaise	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Mucosal atrophy	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Pain	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Sudden death	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Pyrexia	5 (3.4)	5 (3.3)	10 (3.4)	0.1 (-4.0, 4.2)
Multiple organ dysfunction syndrome	4 (2.7)	4 (2.7)	8 (2.7)	0.0 (-3.7, 3.7)
Chest discomfort	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Death	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Fatigue	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Edema peripheral	2 (1.4)	3 (2.0)	5 (1.7)	-0.6 (-3.5, 2.3)
Catheter site hemorrhage	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Granuloma	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Injection site edema	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Edema	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
SIRS	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Hypothermia	0	2 (1.3)	2 (0.7)	-1.3 (-3.1, 0.5)
Nervous system disorders	20 (13.5)	17 (11.3)	37 (12.4)	2.2 (-5.3, 9.7)
Cerebrovascular accident	3 (2.0)	1 (0.7)	4 (1.3)	1.3 (-1.3, 3.9)
Headache	3 (2.0)	1 (0.7)	4 (1.3)	1.3 (-1.3, 3.9)
Intracranial pressure increased	2 (1.4)	1 (0.7)	3 (1.0)	0.7 (-1.6, 3.0)
Cerebral calcification	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Cerebral ischemia	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Dizziness	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Hypoxic-ischemic encephalopathy	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Neuromyopathy	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Paresthesia	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Status epilepticus	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Stroke in evolution	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
White matter lesion	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Seizure	2 (1.4)	2 (1.3)	4 (1.3)	0.1 (-2.5, 2.7)
Autonomic nervous system imbalance	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Encephalopathy	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Metabolic encephalopathy	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Brain injury	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Cerebral hematoma	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Coma	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
ICU-acquired weakness	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Lacunar stroke	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Paresis	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Brain edema	1 (0.7)	5 (3.3)	6 (2.0)	-2.6 (-5.8, 0.6)

System Organ Class Preferred Term	Cefiderocol N=148	Meropenem N=150	Total N=298	Risk Difference (95% CI)
Psychiatric disorders	17 (11.5)	14 (9.3)	31 (10.4)	2.2 (-4.7, 9.1)
Anxiety	3 (2.0)	0	3 (1.0)	2.0 (-0.3, 4.3)
Insomnia	5 (3.4)	3 (2.0)	8 (2.7)	1.4 (-2.3, 5.1)
Delirium	5 (3.4)	4 (2.7)	9 (3.0)	0.7 (-3.2, 4.6)
Depression	2 (1.4)	1 (0.7)	3 (1.0)	0.7 (-1.6, 3.0)
Abnormal behaviour	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Hallucination, visual	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Persistent depressive disorder	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Restlessness	2 (1.4)	2 (1.3)	4 (1.3)	0.1 (-2.5, 2.7)
Confusional state	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Depressed mood	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Disorientation	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Sleep disorder	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Agitation	1 (0.7)	3 (2.0)	4 (1.3)	-1.3 (-3.9, 1.3)
Injury, poisoning and procedural complications	6 (4.1)	3 (2.0)	9 (3.0)	2.1 (-1.8, 6.0)
Post procedural hemorrhage	3 (2.0)	1 (0.7)	4 (1.3)	1.3 (-1.3, 3.9)
Back injury	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Procedural pain	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Subarachnoid hemorrhage	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Laceration	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Splenic rupture	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Hepatobiliary disorders	8 (5.4)	6 (4.0)	14 (4.7)	1.4 (-3.4, 6.2)
Cholestasis	2 (1.4)	0	2 (0.7)	1.4 (-0.5, 3.3)
Cholecystitis	2 (1.4)	1 (0.7)	3 (1.0)	0.7 (-1.6, 3.0)
Cholelithiasis	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Hepatic failure	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Hepatic vein dilatation	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Hepatomegaly	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Hypertransaminasemia	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Cholecystitis acute	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Hepatic cyst	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Hepatic function abnormal	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Hepatocellular injury	1 (0.7)	3 (2.0)	4 (1.3)	-1.3 (-3.9, 1.3)
Musculoskeletal and connective tissue disorder	5 (3.4)	4 (2.7)	9 (3.0)	0.7 (-3.2, 4.6)
Gouty arthritis	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Muscle twitching	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Musculoskeletal stiffness	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Back pain	2 (1.4)	2 (1.3)	4 (1.3)	0.1 (-2.5, 2.7)
Osteoarthritis	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Costochondritis	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Musculoskeletal pain	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.4)	1 (0.7)	3 (1.0)	0.7 (-1.6, 3.0)
Lung cancer metastatic	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Prostatic adenoma	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Adrenal adenoma	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Surgical and medical procedures	2 (1.4)	1 (0.7)	3 (1.0)	0.7 (-1.6, 3.0)
Bladder operation	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Leg amputation	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Gastrostomy tube removal	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)

System Organ Class Preferred Term	Cefiderocol N=148	Meropenem N=150	Total N=298	Risk Difference (95% CI)
Endocrine disorders	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Hypothyroidism	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Adrenal insufficiency	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Blood and lymphatic system disorders	27 (18.2)	28 (18.7)	55 (18.5)	-0.5 (-9.3, 8.3)
Iron deficiency anemia	3 (2.0)	0	3 (1.0)	2.0 (-0.3, 4.3)
Anemia of chronic disease	2 (1.4)	0	2 (0.7)	1.4 (-0.5, 3.3)
Thrombocytosis	4 (2.7)	3 (2.0)	7 (2.3)	0.7 (-2.7, 4.1)
Lymphadenopathy	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Normochromic normocytic anemia	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Anemia	12 (8.1)	12 (8.0)	24 (8.1)	0.1 (-6.1, 6.3)
Leukocytosis	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Eosinophilia	1 (0.7)	2 (1.3)	3 (1.0)	-0.6 (-2.9, 1.7)
Disseminated intravascular coagulation	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Leukopenia	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Nephrogenic anemia	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Coagulopathy	1 (0.7)	3 (2.0)	4 (1.3)	-1.3 (-3.9, 1.3)
Hemorrhagic anemia	0	2 (1.3)	2 (0.7)	-1.3 (-3.1, 0.5)
Hypocoagulable state	0	2 (1.3)	2 (0.7)	-1.3 (-3.1, 0.5)
Thrombocytopenia	2 (1.4)	8 (5.3)	10 (3.4)	-3.9 (-7.9, 0.1)
Reproductive system and breast disorders	2 (1.4)	3 (2.0)	5 (1.7)	-0.6 (-3.5, 2.3)
Benign prostatic hyperplasia	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Prostatitis	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Scrotal swelling	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Scrotal ulcer	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Vulvovaginal pruritus	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Ear and labyrinth disorders	1 (0.7)	2 (1.3)	3 (1.0)	-0.6 (-2.9, 1.7)
Ear discomfort	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Hematotympanum	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Vestibular disorder	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Eye disorders	1 (0.7)	2 (1.3)	3 (1.0)	-0.6 (-2.9, 1.7)
Visual acuity reduced	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Amaurosis	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Cataract	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Macular degeneration	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Vision blurred	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Metabolism and nutrition disorders	43 (29.1)	47 (31.3)	90 (30.2)	-2.2 (-12.6, 8.2)
Hypomagnesemia	8 (5.4)	1 (0.7)	9 (3.0)	4.7 (0.8, 8.6)
Hypoglycemia	6 (4.1)	3 (2.0)	9 (3.0)	2.1 (-1.8, 6.0)
Hyperkalemia	4 (2.7)	1 (0.7)	5 (1.7)	2.0 (-0.9, 4.9)
Hypocalcemia	4 (2.7)	1 (0.7)	5 (1.7)	2.0 (-0.9, 4.9)
Hyperglycemia	4 (2.7)	2 (1.3)	6 (2.0)	1.4 (-1.8, 4.6)
Hypochloremia	2 (1.4)	0	2 (0.7)	1.4 (-0.5, 3.3)
Hyperuricemia	3 (2.0)	1 (0.7)	4 (1.3)	1.3 (-1.3, 3.9)
Hypernatremia	2 (1.4)	1 (0.7)	3 (1.0)	0.7 (-1.6, 3.0)
Diabetes mellitus	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Hypercholesterolemia	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Hyperinsulinemic hypoglycemia	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Iron deficiency	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Lactic acidosis	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Type 2 diabetes mellitus	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Hypophosphatemia	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Hypovolemia	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)

System Organ Class Preferred Term	Cefiderocol N=148	Meropenem N=150	Total N=298	Risk Difference (95% CI)
Hypoproteinemia	3 (2.0)	4 (2.7)	7 (2.3)	-0.7 (-4.1, 2.7)
Acidosis	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Cerebral salt-wasting syndrome	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Hyperphosphatemia	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Metabolic syndrome	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Gout	1 (0.7)	3 (2.0)	4 (1.3)	-1.3 (-3.9, 1.3)
Metabolic alkalosis	1 (0.7)	3 (2.0)	4 (1.3)	-1.3 (-3.9, 1.3)
Hypoalbuminemia	5 (3.4)	8 (5.3)	13 (4.4)	-1.9 (-6.5, 2.7)
Electrolyte imbalance	0	4 (2.7)	4 (1.3)	-2.7 (-5.3, -0.1)
Hyponatremia	4 (2.7)	10 (6.7)	14 (4.7)	-4.0 (-8.8, 0.8)
Hypokalemia	16 (10.8)	23 (15.3)	39 (13.1)	-4.5 (-12.1, 3.1)
Renal and urinary disorders	8 (5.4)	13 (8.7)	21 (7.0)	-3.3 (-9.1, 2.5)
Anuria	2 (1.4)	1 (0.7)	3 (1.0)	0.7 (-1.6, 3.0)
Hematuria	2 (1.4)	1 (0.7)	3 (1.0)	0.7 (-1.6, 3.0)
Cystitis hemorrhagic	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Leukocyturia	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Renal failure	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Renal impairment	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Urinary retention	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Dysuria	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Hemorrhage urinary tract	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Neurogenic bladder	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Polyuria	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Renal hematoma	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Renal tubular acidosis	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Acute kidney injury	1 (0.7)	3 (2.0)	4 (1.3)	-1.3 (-3.9, 1.3)
Vascular disorders	18 (12.2)	28 (18.7)	46 (15.4)	-6.5 (-14.7, 1.7)
Aortic arteriosclerosis	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Aortic dilatation	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Deep vein thrombosis	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Essential hypertension	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Peripheral vascular disorder	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Post thrombotic syndrome	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Hypertensive crisis	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Vasospasm	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Venous thrombosis	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Phlebitis	3 (2.0)	4 (2.7)	7 (2.3)	-0.7 (-4.1, 2.7)
Angiosclerosis	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Brachiocephalic vein thrombosis	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Femoral artery embolism	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Hemodynamic instability	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Hot flush	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Hypovolemic shock	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Lymphostasis	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Shock hemorrhagic	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Hypertension	5 (3.4)	7 (4.7)	12 (4.0)	-1.3 (-5.8, 3.2)
Hypotension	2 (1.4)	10 (6.7)	12 (4.0)	-5.3 (-9.7, -0.9)
Skin and subcutaneous tissue disorders	11 (7.4)	23 (15.3)	34 (11.4)	-7.9 (-15.0, -0.8)
Skin lesion	2 (1.4)	0	2 (0.7)	1.4 (-0.5, 3.3)
Dermatitis allergic	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Diabetic foot	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Palmar erythema	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Rash	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Rash erythematous	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)

System Organ Class Preferred Term	Cefiderocol N=148	Meropenem N=150	Total N=298	Risk Difference (95% CI)
Skin irritation	1 (0.7)	0	1 (0.3)	0.7 (-0.6, 2.0)
Dermatitis	1 (0.7)	1 (0.7)	2 (0.7)	0.0 (-1.9, 1.9)
Dermatitis atopic	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Dermatitis diaper	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Drug eruption	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Eczema	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Intertrigo	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Papule	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Pruritus	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Rash macular	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Skin maceration	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Subcutaneous emphysema	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Urticaria	0	1 (0.7)	1 (0.3)	-0.7 (-2.0, 0.6)
Skin necrosis	0	2 (1.3)	2 (0.7)	-1.3 (-3.1, 0.5)
Decubitus ulcer	4 (2.7)	10 (6.7)	14 (4.7)	-4.0 (-8.8, 0.8)

Source: adae.xpt; Software: Python
All values in the cefiderocol, meropenem, and total columns are expressed as n (%). Risk difference column shows absolute difference (with 95% confidence interval) between cefiderocol and meropenem.
Treatment-emergent adverse events are defined as adverse events that started after the initial dose of study treatment or comparator and up to the EOS
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; EOS, end of study; GGT, gamma-glutamyltransferase; ICU, intensive care unit; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SIRS, systemic inflammatory response syndrome; SOC, system organ class

Adverse Events Based on Demographic Subgroups

The overall incidence of TEAEs in younger (<65 years or <75 years of age) patients was similar to those in older (≥65 years or ≥75 years of age) patients in the cefiderocol group, and similar across patients in the same age subgroups in the meropenem arm. However, patients ≥75 years of age had a higher number of SAEs than those <75 years of age in the cefiderocol group and patients ≥75 years of age in the meropenem arm. Asians had a TEAE frequency similar to those of whites in the cefiderocol group and patients in the meropenem group. The number of SAEs was higher than those of whites in the cefiderocol group and Asians in the meropenem subgroups. The possible reasons for this differences was discussed in Section 7.7.1 (Mortality by Subgroups).

Table 67. TEAE incidence by Baseline Characteristics, Safety Population

	Cefiderocol N=148		Meropenem N=150	
Subgroup	**n (%)**	**N**	**n (%)**	**N**
Any TEAE	130 (87.8)	148	129 (86)	150
Sex				
Female	39 (83)	47	40 (87)	46
Male	91 (90.1)	101	89 (85.6)	104
Age Group				
<65 years	57 (87.7)	65	49 (84.5)	58
≥65 years	73 (88)	83	80 (87)	92
<75 years	95 (88)	108	88 (85.4)	103
≥75 years	35 (87.5)	40	41 (87.2)	47

	Cefiderocol N=148		Meropenem N=150	
Subgroup	**n (%)**	**N**	**n (%)**	**N**
Race				
Asian	38 (86.4)	44	38 (86.4)	44
Black or African American	0	0	1 (100)	1
Other	2 (100)	2	4 (100)	4
White	90 (88.2)	102	85 (85)	100
Missing	0	0	1 (100)	1
Ethnicity				
Hispanic or Latino	3 (75)	4	3 (100)	3
Not Hispanic or Latino	123 (87.9)	140	118 (84.9)	139
Not reported	4 (100)	4	8 (100)	8
Region				
Asia-Pacific	37 (86)	43	38 (86.4)	44
Europe	87 (87.9)	99	85 (85)	100
North America	6 (100)	6	6 (100)	6
BMI group				
<30 kg/m2	101 (85.6)	118	94 (85.5)	110
≥30 kg/m2	29 (96.7)	30	35 (87.5)	40
Creatine clearance group				
>80 (normal)	51 (92.7)	55	49 (80.3)	61
>50-80 (mild)	34 (77.3)	44	32 (86.5)	37
30-50 (moderate)	26 (89.7)	29	30 (93.8)	32
<30 (severe)	19 (95)	20	18 (90)	20

Source: adae.xpt; Software: R
Abbreviations: BMI, body mass index; TEAE, treatment-emergent adverse event

Table 68. SAE Incidence by Baseline Characteristics, Safety Population

	Cefiderocol N=148		Meropenem N=150	
Subgroup	**n (%)**	**N**	**n (%)**	**N**
Any SAE	54 (36.5)	148	46 (30.7)	150
Sex				
Female	16 (34)	47	16 (34.8)	46
Male	38 (37.6)	101	30 (28.8)	104
Age group				
<65 years	26 (40)	65	18 (31)	58
≥65 years	28 (33.7)	83	28 (30.4)	92
<75 years	36 (33.3)	108	34 (33)	103
≥75 years	18 (45)	40	12 (25.5)	47
Race				
Asian	18 (40.9)	44	11 (25)	44
White	36 (35.3)	102	35 (35)	100
Ethnicity				
Hispanic or Latino	1 (25)	4	0	3
Not Hispanic or Latino	51 (36.4)	140	46 (33.1)	139
Not reported	2 (50)	4	0	8
Region				
Asia-Pacific	18 (41.9)	43	11 (25)	44
Europe	35 (35.4)	99	33 (33)	100
North America	1 (16.7)	6	2 (33.3)	6
BMI group				
<30 kg/m2	44 (37.3)	118	35 (31.8)	110
≥30 kg/m2	10 (33.3)	30	11 (27.5)	40

	Cefiderocol N=148		Meropenem N=150	
Subgroup	**n (%)**	**N**	**n (%)**	**N**
Creatine clearance group				
>80 (normal)	22 (40)	55	16 (26.2)	61
>50-80 (mild)	13 (29.5)	44	7 (18.9)	37
30-50 (moderate)	9 (31)	29	14 (43.8)	32
<30 (severe)	10 (50)	20	9 (45)	20

Source: adae.xpt; Software: R
Abbreviations: BMI, body mass index; SAE, serious adverse event

Table 69. List of Treatment-Emergent Adverse Events Leading to Discontinuation, Safety Population, APEKS-NP Trial

Subject ID	Age, Sex	PT	VT	SAE[1]	Study Day of TEAE Onset	Duration (Days)		Assessment of Relatedness		If Related, Confounders for TEAE; If NR, other cause of TEAE
						TEAE	Ex	Invest.	Rev.	
Cefiderocol										
(b) (6)	64, M	Blood ALP increased (≥10x ULN)	Persistent elevated ALP	N	3		4	NR	R	Cholecystitis, linezolid, sepsis
	63, M	Brain edema	Cerebral edema	Y	8	1	8	NR	NR	Hemorrhagic CVA
	61, M	Stroke in evolution	Worsening of ischemic stroke	Y	3	2	4	NR	NR	Extension of first CVA prior to enrollment
		LFT increased (AST ≥4x ULN)	Elevation of liver markers	Y	4		4	NR	R	Sepsis, Amiodarone
	78, M	ALT increased (≥5x ULN)	ALT increasing	N	5	15	5	R	R	MOF, cipro, metamizole, propofol
	67, F	Gastric hemorrhage	Acute gastric hemorrhage	Y	2	1	2	NR	NR	Gastro-duodenitis, Crohn's disease, heparin
	83, M	Septic shock	Septic shock	Y	2	2	3	NR	NR	Drug DC due to death on Day 3, not one particular TEAE. Multiple causes of death
		Lactic acidosis	Lactic acidemia	Y	3	1	3	NR		
		Intestinal infarction	Mesenteric infarction	Y	3	1	3	NR		
		Hepatocellular injury (AST/ALT ≥20x ULN)	Hepatic cytolysis	Y	3	1	3	NR		
	86, M	LFT abnormal (AST ≥5x ULN)	Abnormal LFTs	N	4	5	4	NR	R	Atorvastatin, pantoprazole, nadroparin, furosemide

Subject ID	Age, Sex	PT	VT	SAE[1]	Study Day of TEAE Onset	Duration (Days)		Assessment of Relatedness		If Related, Confounders for TEAE; If NR, other cause of TEAE
						TEAE	Ex	Invest.	Rev.	
(b) (6)	77, M	ALT increased (≥10x ULN)	Elevation of ALT	Y	5	8	5	R	R	Hx of hepato-megaly, Ceftriaxone, enoxaparin, levofloxacin, propofol.
		Hepatic failure	Unspecified hepatic failure	N	5	8	5	R		
		AST increased	Elevation of AST till 1161 u/l >19 upper limit	Y	5	6	5	R		
	72, F	Autonomic NS imbalance	Dysautonomia	Y	2	3	4	NR	NR	Cerebrovascular bleeding due to ruptured carotid artery aneurysm
	73, F	Acute MI	Acute MI	Y	15	2	15	NR	R	No cardiac hx. Chest pain TEAE on days 5-14, treated with tramadol. Abn ECG day 14
	64, M	ARDS	ARDS	Y	2	3	4	NR	R	ARDS likely 2^{o} NP progression
	84, M	CVA	Stroke	Y	4	1	4	NR	R	Long-standing AF on bisoprolol, dalteparin, advanced age
Meropenem										
(b) (6)	68, M	Sepsis	Worsening of sepsis	Y	5	2	5	NR	NR	Sepsis may have been due to new infection
	46, M	Meningitis bacterial	2^{o} postoperative bacterial meningitis	N	5		6	NR	NR	Secondary meningitis from multiple brain surgeries
	38, F	Hepatic enzyme increased (AST ≥4x, TB ≥2x ULN)	Liver event (elevation of ALT, AST, bilirubin	Y	5		5	R	R	Metoclopramide

Subject ID	Age, Sex	PT	VT	SAE[1]	Study Day of TEAE Onset	Duration (Days)		Assessment of Relatedness		If Related, Confounders for TEAE; If NR, other cause of TEAE
						TEAE	Ex	Invest.	Rev.	
(b) (6)	69, M	Hepatic enzyme increased (AST/ALT ≥50x TB ≥3x ULN)	Elevation of liver enzymes >5x ULN	Y	4	5	4	NR	R	Hy's Law met on Day 8. Low cardiac output (per hepatologist, less likely to be drug-related)
	92, M	DIC	DIC	Y	6	4	6	R	R	Inv strongly believed due to linezolid. No other cause noted.
		MODS	MOF	Y	6	4	6	R		
	70, M	Hepatic enzyme increased (AST ≥15x, ALT ≥9x ULN)	Progression of liver enzymes elevation	N	3		3	NR	NR	Ongoing liver steatosis prior to Day 1; fluconazole, pantoprazole, paracetamol
	75, F	Hepatic enzyme increased (AST ≥30x, ALT ≥10x, TB ≥2x ULN	Liver enzymes elevation	Y	8		8	NR	R	CHF, congestive hepatopathy
	67, M	Hepatic enzyme increased (AST/ALT ≥50x, TB ≥2xULN)	Liver enzymes elevation	Y	3		3	NR	NR	Cardiac arrest, hypovolemic shock 1 day prior to increased liver enzymes, alcoholism
	35, M	Hepatic function abnormal (AST/ALT ≥20x, TB ≥2x ULN)	Abnormal liver function	Y	5	32	5	NR	R	AST/ALT ≥1-1.5x ULN at baseline, enoxaparin, paracetamol
	67, M	Brain edema	Worsening of cerebral edema	Y	3	1	3	NR	NR	SAH

Subject ID (b) (6)	Age, Sex	PT	VT	SAE[1]	Study Day of TEAE Onset	Duration (Days)		Assessment of Relatedness		If Related, Confounders for TEAE; If NR, other cause of TEAE
						TEAE	Ex	Invest.	Rev.	
	77, F	SIRS	SIRS	Y	7	1	7	NR	R	Drug DC in response to treatment failure
		Leukopenia	Leukocytopenia	N	7		7	NR		
	82, F	UTI	UTI	N	8	9	7	NR	NR	
		UGI hemorrhage	UGI bleeding	N	8	3	7	NR	NR	
		Pulmonary congestion	Pulmonary congestion	N	8	1	7	NR	NR	
		Acute respiratory failure	Acute respiratory failure 2^{o} to new onset HABP	Y	8	9	7	NR	R	Drug DC in response to treatment failure
	77, F	Respiratory failure	Progression of respiratory failure due to pneumonia	Y	3	1	3	NR	R	Drug DC due to treatment failure
	59, M	Acinetobacter infection	*Acinetobacter baumannii* pulmonary infection	N	11		11	NR	NR	New infection developed, associated with lung cancer and bronchopleural fistula

Source: adae.xpt; Software: Python, Patient narratives
[1] Serious adverse events classified by Applicant in [dataset]
Abbreviations: 2°, secondary; AF, atrial fibrillation; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; CVA, cerebrovascular accident; DC, discontinuation; DIC, disseminated intravascular coagulation; ECG, electrocardiogram; Ex, exposure; ID, identification; HABP, hospital-acquired bacterial pneumonia; LFT, liver function test; MI, myocardial infarction; MODS, multiple organ dysfunction syndrome; MOF, multiorgan failure; NR, not related; NS, nervous system; PT, preferred term; R, related; SAE, serious adverse event; SAH, subarachnoid hemorrhage; SIRS, systemic inflammatory response syndrome; TB, total bilirubin; TEAE, treatment-emergent adverse event; ULN, upper limit of normal; UGI, upper gastrointestinal; UTI, urinary tract infection; VT, verbatim term

Table 70. List of Deaths in Safety Population, APEKS-NP Trial

				Study Day		Duration (Days)		Assessment of Relatedness		
Subj ID	Age, Sex	Preferred Term	VT	Death	TEAE Onset	TEAE	Tx	Inv	Rev	MO Comment
Cefiderocol										
(b) (6)	64, M	Cardio-respiratory arrest	Cardiopulmonary collapse due to MI	8	8	1	4	NR	NR	Unlikely to survive at enrollment, too many concurrent illness, palliative care day 5
	46, M	MODS	Multisystem organ failure	34	34	1	22	NR	NR	Cure/micro eradication at TOC, autopsy: MOF, compartment sx
	18, F	General physical health deterioration	Worsening physical state due to main disease - polytrauma.	21	21	1	15	NR	NR	Worsening of polytrauma
	63, M	Brain edema	Cerebral edema	8	8	1	8	NR	NR	Autopsy: No pneumonia, Brain edema due to hemorrhagic CVA. Unknown significance of 4-fold MIC increase for *A. baumannii* in BAL culture on day 3.
	61, M	Stroke in evolution	Worsening of ischemic stroke	4	3	2	4	NR	I	Difficult to determine if MOF was due to stroke, original or new infectious process, no autopsy
	53, M	Cardiovascular insufficiency	Acute cardiovascular insufficiency	4	4	1	4	NR	NR	CVA day -15 may have predisposed to LBBB which caused acute cardiovascular insufficiency
	82, M	PA thrombosis	Thromboembolia of the PA	35	34	2	15	NR	NR	Recent CVA, age, immobility
	78, M	PA thrombosis	Thromboembolia of the PA	29	29	1	5	NR	NR	Recent CVA, age, immobility

Subj ID (b) (6)	Age, Sex	Preferred Term	VT	Study Day		Duration (Days)		Assessment of Relatedness		MO Comment
				Death	TEAE Onset	TEAE	Tx	Inv	Rev	
	67, F	Gastric hemorrhage	Acute gastric hemorrhage	2	2	1	2	NR	NR	Crohn's, gastroduodenitis, necrotizing colitis s/p jejunal tube exteriorization, colon resection on day -10
	87, F	MODS	MOF	34	27	8	13	NR	I	Difficult to determine if MOF was 2º ischemic stroke, CHF, original infection (had CF at TOC), super infections (UTI, *A. baumannii* in tracheal cx at day 13), given amikacin, tigecycline
	57, M	MODS	Worsening of MOF	15	15	1	9	NR	R	LOE: cefiderocol DC due to LOE, CF, *S. marcescens* bacteremia (from original NP), given ertapenem on day 9. Anuria, liver failure, MODS, sepsis on day 15; Autopsy: cardiopulmonary, endogenous intoxication with CHF
	66, M	Blood pressure increased	Increased blood pressure	8	7	2	8	NR	NR	Baseline SBP 197, not on medication. Subarachnoid hemorrhage due to PCA dissection on day -6
		ICP increased	Increased ICP	8	7	2	8	NR		
	83, M	Hepatocellular injury	Hepatic cytolysis	3	3	1	3	NR	NR	MOF (CAD, CABG, renal failure, ECMO) started prior to enrollment. Autopsy: cardiac arrest, mesenteric ischemia, hepatic failure, ARDS, *E. coli* bacteremia (original pathogen).
		Intestinal infarction	Mesenteric infarction	3	3	1	3	NR		
		Lactic acidosis	Lactic acidemia	3	3	1	3	NR		
		Septic shock	Septic shock	3	2	2	3	NR		

Subj ID	Age, Sex	Preferred Term	VT	Study Day		Duration (Days)		Assessment of Relatedness		MO Comment
				Death	TEAE Onset	TEAE	Tx	Inv	Rev	
(b) (6)	56, M	Lung cancer metastatic	Worsening metastatic lung cancer	3	3	1	2	NR	NR	Metastatic lung cancer, palliative care on day 2
	81, F	Septic shock	Refractory septic shock with lactic acidosis	3	2	2	3	NR	NR	Ongoing shock, UTI before randomization, APACHE II 48. Biochemical criteria met for Hy's law on day 3, likely due to sepsis
	77, M	Pneumonia	New episode of pneumonia	32	26	7	6	NR	R	LOE: Recurrence of *E. aerogenes* pneumonia (with 4-fold MIC increase in tracheal aspirate 0.06 to 0.25), new *E. coli* pneumonia, given meropenem. CF and micro persistence at TOC.
		Death due to pneumonia	Death probably related to new pneumonia	32	32	1	6	NR		
	84, F	Intestinal ischemia	Intestinal ischemia	10	10	1	8	NR	R	AR: unexplained cyanosis and coldness of lower limbs, CT confirmed intestinal ischemia on day 10. No autopsy.
	68, M	Pneumonia	Pneumonia	18	18	1	9	NR	R	LOE: Recurrence of *K. pneumoniae* NP, given imipenem. 4-fold MIC increase of *K. pneumoniae* in tracheal aspirate (0.25 to 1).
	86, M	Pneumonia	Broncho-pneumonia	21	17	5	4	NR	I	Received only 4 days of cefiderocol due to increased LFTs, then meropenem given until day 9.

Subj ID	Age, Sex	Preferred Term	VT	Study Day		Duration (Days)		Assessment of Relatedness		MO Comment
				Death	TEAE Onset	TEAE	Tx	Inv	Rev	
(b) (6)	59, M	MODS	Acute MOF	9	9	1	8	NR	R	AR: unexplained bradycardia, cardiac arrest, MI, confounded by DM, HTN, AKI. LOE: MOF due to original NP contributed to death
	78, M	Acute respiratory failure	Acute respiratory failure	8	8	1	7	NR	R	AR: unexpected unstable angina, MI during treatment; confounded by CAD, CVA
		MI	MI	8	8	1	7	NR		
		PVD	Peripheral circulation disorders	8	8	1	7	NR		
	79, M	Cardiac arrest	Cardiac arrest	14	14	1	14	NR	NR	Cardiac history, cause of death: pulmonary HTN, coagulopathy (2^{o} enoxaparin per Inv, but possibly related to cefiderocol as coagulopathy continued after stopping heparin)
	77, M	Cardiac arrest	Asystole	15	15	1	5	NR	NR	MI, TBI, intracerebral hemorrhages may have predisposed to cardiac arrest
	56, M	Cardiac arrest	Cardiac arrest	25	25	1	15	NR	R	LOE: Bilateral pneumonia developed day 11, CF day 15, meropenem, piperacillin-tazobactam given
	84, M	Cardiac arrest	Cardiac arrest, asystole	21	21	1	8	NR	NR	HTN, CHF; CVA on Day -19 may have predisposed to cardiac arrest

Subj ID	Age, Sex	Preferred Term	VT	Study Day		Duration (Days)		Assessment of Relatedness		MO Comment
				Death	TEAE Onset	TEAE	Tx	Inv	Rev	
(b) (6)	72, F	Autonomic NS imbalance	Dysautonomia	4	2	3	4	NR	NR	No autopsy. Death certificate: cerebrovascular disease, ruptured carotid artery aneurysm, HTN, HABP
	52, F	Cardiac failure	Severe decompensated heart failure 2^{o} to severe mitral stenosis	2	2	1	2	NR	NR	RHD, CHF, CKD, HTN
	85, M	Sepsis	Severe sepsis 2^{o} to HABP	38	34	5	11	R	R	LOE: Recurrence of original NP (*P. aeruginosa*) on day 25, rescue abx given for CF
	42, M	Pulmonary edema	Pulmonary edema	25	24	2	8	NR	NR	CC by TOC, CHF predominant cause at Day 24, NP on day 25 (no pathogen available)
	65, M	Cardio-respiratory arrest	Cardiopulmonary arrest	43	43	1	15	NR	NR	Too many confounders: pulmonary TB at day 26, Aspiration pneumonia, ARF on day 40
	66, M	PE	PE	5	5	1	5	NR	NR	Immobility, CVA may have predisposed to PE
	73, F	Acute MI	Acute MI	16	15	2	15	NR	R	AR: chest pain, hypokalemia on day 4 may have led to MI
	79, M	Septic shock	Septic shock	8	8	1	8	NR	R	LOE: due to original NP, confounded by candidemia

Subj ID	Age, Sex	Preferred Term	VT	Study Day		Duration (Days)		Assessment of Relatedness		MO Comment
				Death	TEAE Onset	TEAE	Tx	Inv	Rev	
(b) (6)	52, M	Acute respiratory failure	Acute respiratory failure 2º to central cause 2º to acute on top of subacute SAH	15	11	5	11	NR	I	Cause of respiratory failure unclear: CN NP at baseline, super infection with *A. baumannii* in tracheal aspirate on day 3, 6, 11, no rescue abx; worsening of SAH, seizure on day 11, palliative care on day 15
		SAH	Acute on top of subacute, progressive SAH	15	11	5	11	NR		
	64, M	ARDS	ARDS	4	2	3	4	NR	R	LOE: CF at day 3, worsening of VABP on chest x-ray, ARDS likely consequence of original VABP
	91, M	Cardiac failure	Heart failure with pulmonary edema	16	16	1	16	NR	R	LOE: CF at day 14 (EOT), *A pitti* and *E. coli* (tracheal aspirate). Baseline pathogen: *A. nosocomialis* and *E. coli*. CRF: subject died due to infection at randomization by day 28
		Pneumonia	Severe pneumonia	16	16	1	16	NR		
	64, M	Sepsis	Sepsis	40	40	1	15	NR	R	LOE: CF at TOC, 7 days after EOT, respiratory failure due to *P. aeruginosa* (tracheal aspirate), abx given. CN at baseline, but *P. aeruginosa* noted at day 3. Also had MSSA bacteremia, fungal sepsis, *C. difficile*. Autopsy: septicemia with MOF

Subj ID	Age, Sex	Preferred Term	VT	Study Day		Duration (Days)		Assessment of Relatedness		MO Comment
				Death	TEAE Onset	TEAE	Tx	Inv	Rev	
(b) (6)	64, M	Sudden death	Sudden death	23	23	1	14	NR	I	Day 14, ventricular extrasystoles, resolved same day; day 21, sudden death (unknown cause, no autopsy. Hx esophageal CA with liver mets
	84, M	CVA	Stroke	4	4	1	4	NR	R	AR: sudden CVA on treatment, confounded by cerebral arteriosclerosis, atrial fibrillation
Meropenem										
(b) (6)	53, F	Pneumonia necrotising	Necrotizing pneumonia	36	18	19	9	NR	R	LOE: Left-sided pneumonia persisted, CF at TOC, cefepime, piperacillin-tazobactam given. Confounded by necrotizing bowel, comfort care on day 35
	63, M	Cardiac failure acute	Acute heart failure due to acute MI	17	17	1	17	NR	NR	SAH on day -7 may have predisposed to MI with subsequent CHF. Cardiac arrest noted in labeling. Autopsy: SAH caused by tearing of saccular aneurysm and acute MI
		Brain edema	Cerebral edema 2º SAH after rupture of saccular aneurysm of cerebral vessels.	17	17	1	17	NR		
	62, M	Cardiac failure acute	Acute heart failure due to acute MI	4	4	1	4	NR	NR	Hemorrhagic CVA on day -12 may have predisposed to MI with subsequent CHF. Brain edema likely caused by CVA. No autopsy.
		Brain edema	Cerebral edema due to recurrent hemorrhagic stroke.	4	4	1	4	NR		

Subj ID	Age, Sex	Preferred Term	VT	Study Day		Duration (Days)		Assessment of Relatedness		MO Comment
				Death	TEAE Onset	TEAE	Tx	Inv	Rev	
(b) (6)	63, M	Brain edema	Cerebral edema 2º hemorrhagic stroke, recurrent intracerebral hematoma in the left hemisphere.	48	48	1	21	NR	I	Brain edema likely due to CVA. Clinical cure at TOC (Day 21). day 28, received TMP/SMX, cefoperazone, piperacillin for *A. baumannii*, *S. maltophilia*, *P. aeruginosa* tracheobronchitis and developed new *A. baumannii* bacteremia. Autopsy: original *K. pneumoniae* NP and new *P. aeruginosa* endobronchitis.
	68, F	Sepsis	Worsening of sepsis	6	5	2	5	NR	NR	Suspected cause of death*: A. baumannii* bacteremia probably due to infected hip phlegmon, cellulitis on day 3
	66, M	Death due to pneumonia	Death by unknown reason	26	26	1	17	NR	I	Found dead, unknown cause, no autopsy
	46, M	Cardiovascular insufficiency	Acute cardiovascular insufficiency	17	17	1	6	NR	NR	TBI, SDH day -5 may have predisposed to cardiac event. Meropenem DC day 8 due to secondary bacterial meningitis. Day 17, sharp “heart pain” and acute CV failure. Unclear if patient had an MI
	38, F	Cardiopulmonary failure	Increasing cardiopulmonary insufficiency	10	10	1	5	NR	NR	Meropenem DC day 5 due to hepatotoxicity. Day 10, cardiopulmonary failure occurred. Autopsy: cardiopulmonary failure

				Study Day		Duration (Days)		Assessment of Relatedness		
Subj ID	Age, Sex	Preferred Term	VT	Death	TEAE Onset	TEAE	Tx	Inv	Rev	MO Comment
(b) (6)	67, F	Brain edema	Cerebral edema	13	13	1	13	NR	NR	CVA on day 1 and secondary CVA on day 13 with brain edema causing asystole
	83, F	PA thrombosis	Thromboembolia of the PA	32	32	1	14	NR	R	AR: Drug-induced pulmonary embolism (labeled), confounded by CVA
	63, M	PA thrombosis	Thromboembolia of the PA	22	22	1	19	NR	R	AR: Drug-induced pulmonary embolism (labeled), confounded by CVA
	83, F	MODS	MOF	38	36	3	18	NR	R	LOE: MODS associated with relapse of NP and empyema (day 36, culture NA, but microbiological persistence *P. mirabilis* in day 18 tracheal aspirate, given cipro, doxycycline, meropenem
	81, F	Cardio-respiratory arrest	Cardiorespiratory arrest	19	16	4	8	NR	I	Meropenem DC day 8 due to CF, cipro, piperacillin-tazobactam given. Day 19, had cardiorespiratory arrest due to dyspnea thought to have started after AVR on day -11, and refusal to remain on ventilator
	69, F	Cardio-respiratory arrest	Cardiorespiratory arrest	7	7	1	7	NR	NR	Critical care myopathy since day -15, failed to wean off ventilator on day 4, died shortly after withdrawal of care day 7

Subj ID	Age, Sex	Preferred Term	VT	Study Day		Duration (Days)		Assessment of Relatedness		MO Comment
				Death	TEAE Onset	TEAE	Tx	Inv	Rev	
(b) (6)	63, M	Brain injury	Severe brain injury justifying therapeutic deescalation	8	8	1	8	NR	NR	Intraparenchymal hematoma with coma since day -4, worsened on day 8. Died shortly after de-escalation in care on day 8.
	69, M	Hepatic enzyme increased	Elevation of liver enzymes >5x ULN	8	4	5	4	NR	R	Biochemical criteria for Hy's law met on day 8. Meropenem DC on day 4 due to AST >10x ULN, ALT >5x ULN, given piperacillin-tazobactam. Confounders: low cardiac output (per hepatologist, less likely to be drug-related)
		Cardiogenic shock	Cardiogenic shock with MOF	8	5	4	4	NR		
	46, M	Shock hemorrhagic	Severe hemorrhagic shock	13	13	1	13	NR	R	LOE: 4-fold MIC increase, *P. aeruginosa* NP recurrence on day 11. Hemorrhagic shock considered to be related to low vitamin K 2º vancomycin (given for CNS endocarditis), meropenem
		Pseudomonas infection	Pseudomonas resistant to meropenem	13	11	3	13	R		
	73, M	Encephalopathy	Worsening of multifactorial encephalopathy	14	7	8	7	NR	NR	Encephalopathy since day -7. Meropenem DC on day 7 as NP considered cured. Day 7, worsening encephalopathy due to sepsis from new infection (IAI due to previous cholecystectomy or line infection). Withdrawal of care on day 7
	92, M	MODS	MOF	9	6	4	6	R	R	

Subj ID	Age, Sex	Preferred Term	VT	Study Day		Duration (Days)		Assessment of Relatedness		MO Comment
				Death	TEAE Onset	TEAE	Tx	Inv	Rev	
		DIC	DIC	9	6	4	6	R		AR: liver test elevation, decreased platelets (labeled ARs)
(b) (6)	70, M	Septic shock	Septic shock	21	21	1	3	NR	R	LOE: Tx ended on day 3 due to *K. pneumoniae* persistence, but meropenem (nonstudy drug given until day 12). Pneumonia and septic shock on day 19, given rescue abx
		Pneumonia	Suspected pneumonia	21	19	3	3	NR		
		Cardiac failure	Worsening cardiac failure	21	21	1	3	NR		
	75, F	Cardiac failure	Progression of cardiac failure	11	8	4	8	NR	NR	Meropenem DC due to increased LFTs on day 8. CHF on day 8. Died on day 11 due to CHF (hx of CHF, cardiomyopathy)
	67, M	Cardiovascular disorder	Progression of cardiovascular instability	4	2	3	3	NR	NR	Accidental fall with femoral fracture on day -12, s/p endoprosthesis complicated by femoral artery embolism and splenic rupture, coagulopathy on day 2. Early death on day 4 due to CHF, hemorrhagic shock
	67, M	Brain edema	Worsening of cerebral edema	3	3	1	3	NR	NR	SAH due to intracranial aneurysm and cerebral edema since day -4. Brain edema worsened on day 3. Died same day despite treatment with mannitol. No autopsy

Subj ID	Age, Sex	Preferred Term	VT	Study Day		Duration (Days)		Assessment of Relatedness		MO Comment
				Death	TEAE Onset	TEAE	Tx	Inv	Rev	
(b) (6)	70, M	Cardiac failure congestive	Worsening of congestive heart failure	19	19	1	10	NR	R	LOE: *K. oxytoca* (one of the baseline NP pathogens) persisted, pneumonia on day 18, ciprofloxacin given, CHF may have been precipitated by NP. Confounded by hx of CHF, ischemic cardiomyopathy
	69, F	Hypotension	Arterial hypotension caused by heart failure	28	28	1	15	NR	NR	Cardiac arrest likely precipitated by CVA on day -6
		Cardiac arrest	cardiac arrest	28	28	1	15	NR		
	80, M	Cardiac failure	Cardiovascular failure	17	17	1	15	NR	NR	Cardiac arrest and failure likely due to lacunar CVA on day 13. Hx of CVA, AF, CHF
		Cardiac arrest	Asystole	17	17	1	15	NR		
	77, F	Cardiac arrest	Heart asystole/cardiac arrest	7	7	1	7	NR	I	SIRS on day 7, colistin given. Appeared to be infectious, but no source identified. CF at EOT, possibly due to LOE. Also had hemorrhagic CVA on day -12 which may have predisposed to cardiac arrest
		SIRS	SIRS	7	7	1	7	NR		
	70, F	Cardiac arrest	Heart asystole/cardiac arrest	20	20	1	5	NR	R	LOE: meropenem discontinued day 5 due to CF/micro persistence, rescue abx given. Pneumonia and UTI on days 18 (*S. maltophilia* in tracheal cx). Cardiac arrest may have been precipitated by ICH.
		UTI	Aggravation of UTI	20	18	3	5	NR		
		Pneumonia	VABP relapse	20	18	3	5	NR		

Subj ID (b) (6)	Age, Sex	Preferred Term	VT	Study Day		Duration (Days)		Assessment of Relatedness		MO Comment
				Death	TEAE Onset	TEAE	Tx	Inv	Rev	
	55, M	ICP increased	Elevated intracerebral pressure	16	14	3	8	NR	NR	Neuroendocrine lung tumor with brain metastases stage IV likely contributed to respiratory failure with increased ICP pressure. Clinical cure noted at TOC
		Respiratory failure	Impending respiratory failure 2º to elevated intracerebral pressure 2º to brain metastasis	16	14	3	8	NR		
	49, F	Hypovolemia	Hypovolemia	22	21	2	7	NR	NR	Clinical cure and discharge on day 20, readmitted at OSH for acute abdomen 2º to ruptured tumor recently diagnosed
		Acute abdomen	Acute abdomen secondary to ruptured tumor	22	21	2	7	NR		
	71, M	MODS	MOD	14	14	1	7	NR	I	DC home on day 12, had clinical cure at EOT. Found dead in bed by wife on day 14. Death reported as due to MODS given hx of DM, CKD, cardiac arrhythmia
	72, M	MODS	MODS	26	26	1	15	NR	R	LOE: suspected pneumonia on day 24 (no pathogen), given rescue abx, MODs considered related to pneumonia and CHF
	79, M	Sepsis	Sepsis	29	25	5	10	NR	R	LOE: Pneumonia with *S. marcescens* on day 25, confounded by palliative care same day
		Respiratory failure	Impending respiratory failure	29	24	6	10	NR		

				Study Day		Duration (Days)		Assessment of Relatedness		
Subj ID	Age, Sex	Preferred Term	VT	Death	TEAE Onset	TEAE	Tx	Inv	Rev	MO Comment
(b) (6)	77, F	Respiratory failure	Progression of respiratory failure due to pneumonia	3	3	1	3	NR	R	Inv reported treatment failure (LOE) and colistin was started for NP. Respiratory failure was due to NP and patient withdrawn from study on day 3
	59, M	Bronchopleural fistula	Bronchial stump leak (insufficiency)	14	13	2	11	NR	NR	Had slow response to meropenem (persistent fevers), but *K. pneumoniae* NP eradicated. Hx of lung cancer s/p left pulmonectomy on day -20. *A. baumannii* pneumonia on day 11, colistin given. Death due to bronchopleural fistula, leak repair unsuccessful.

Source: adae.xpt; Software: Python, Patient narratives
Abbreviations: 2°, secondary; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; AR, adverse reaction; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; AVR, aortic valve replacement; BAL, bronchoalveolar lavage; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CF, cardiac failure; CHF, congestive heart failure; CKD, chronic kidney disease; CN, culture negative; CNS, central nervous system; CT, computed tomography; CVA, cerebrovascular accident; DC, discontinuation; DIC, disseminated intravascular coagulation; DM, diabetes mellitus; ECMO, extracorporeal membrane oxygenation; EOT, end of treatment; Ex, exposure; Hx, history of; I, intermediate; HTN, hypertension; IAI, intra-abdominal infection; ICP, intracranial pressure; ICH, International Conference on Harmonisation; ID, identification; IV, intravenous; LBBB, left bundle branch block; LFT, liver function test; LOE, lack of efficacy; MI, myocardial infarction; MIC, minimum inhibitory concentration; MO, medical officer; MODS, multiple organ dysfunction syndrome; MOF, multiorgan failure; NP, nosocomial pneumonia; NR, not related; NS, nervous system; OSH, outside hospital; PA, pulmonary artery; PCA, posterior cerebral artery; PVD, peripheral vascular disease; R, related; RHD, rheumatic heart disease; SAE, serious adverse event; SAH, subarachnoid hemorrhage; SBP, systolic blood pressure; SDH, subdural hematoma; SIRS, systemic inflammatory response syndrome; TB, total bilirubin; TBI, traumatic brain injury; TEAE, treatment-emergent adverse event; TMP, trimethoprim; TOC, test of cure; Tx, treatment; UGI, upper gastrointestinal; ULN, upper limit of normal; UTI, urinary tract infection; VT, verbatim term; VABP, ventilator-associated bacterial pneumonia

18. Mechanism of Action / Drug Resistance Additional Information and Assessment

The nonclinical microbiology assessments of the mechanism of action of cefiderocol and drug resistance to cefiderocol were previously described. See review for original NDA 209445 (Division of Anti-Infectives 2019).

The new studies included in the sNDA are updated surveillance data and molecular characterization of surveillance isolates, in vivo activity against (b) (4) and under iron overload condition, and data on activity against efflux pumps. The key findings are below.

In Vitro Activity

The in vitro susceptibility testing of 38,288 clinical isolates collected during the period 2014 to 2018 from North America and European countries to cefiderocol was conducted using Iron Depleted Cation Adjusted Muller Hinton Broth (ID-CAMHB) in surveillance studies. The cefiderocol MIC required to inhibit 90% of tested isolates (MIC_{90}) for Enterobacterales, *P. aeruginosa*, *A. baumannii* complex, *B. cepacia* complex, and *S. maltophilia* were 1, 0.5, 2, 0.25, and 0.5 mcg/mL, respectively (Table 71). The cefiderocol MIC_{90} values were 4, 2, and 1 mcg/mL against 814 meropenem-nonsusceptible (MEPM-NS, defined as meropenem MIC ≥2 mcg/mL for Enterobacterales and meropenem MIC ≥4 mcg/mL for *P. aeruginosa* and *A. baumannii*) Enterobacterales, (b) (4) MEPM-NS *A. baumannii*, and (b) (4) MEPM-NS *P. aeruginosa*, respectively (Table 72). The MIC_{90} values of cefiderocol for the multidrug-resistant (MDR, defined as nonsusceptible to the antimicrobial agent in three antimicrobial categories) and extensively drug-resistant (XDR, defined as nonsusceptible to the antimicrobial agent in four antimicrobial categories) subsets of Enterobacterales, *A. baumannii*, and *P. aeruginosa* were same as the MIC_{90}s for MEPM-NS isolates.

Table 71. In Vitro Activity of Cefiderocol Against Gram-Negative Pathogens

Pathogen (No. of Isolates)	MIC Range (mcg/mL)	MIC_{50} (mcg/mL)	MIC_{90} (mcg/mL)
Achromobacter spp. (27)[a]	<0.03-64	0.25	1
Acinetobacter baumannii complex (4185)	≤0.002->256	0.12	2
Burkholderia cepacia complex (265)	≤0.002-128	0.015	0.25
Burkholderia pseudomallei (271)	<0.03-32	0.06	1
Citrobacter freundii complex (1138)	≤0.002-8	0.06	0.5
Citrobacter koseri (670)	0.004-8	0.25	0.5
Enterobacter cloacae complex (2580)	≤0.002-128	0.25	1
Escherichia coli (6424)	≤0.002-32	0.12	1
Klebsiella aerogenes (1175)	≤0.002-8	0.12	0.5
Klebsiella oxytoca (1780)	≤0.002-4	0.06	0.25
Klebsiella pneumoniae (5798)	≤0.002-128	0.12	1
Morganella morganii (801)	≤0.002->256	0.12	0.25
Proteus mirabilis (924)	≤0.002->256	0.015	0.12
Proteus vulgaris (552)	≤0.002-0.5	0.015	0.12
Providencia rettgeri (378)	≤0.002->256	0.015	0.12
Pseudomonas aeruginosa (6213)	≤0.002-8	0.12	0.5
Serratia marcescens (3092)	≤0.002-128	0.12	0.5
Stenotrophomonas maltophilia (1565)	≤0.002-128	0.06	0.5

Source: Study Report: S-649266-EB-387-N Table 2; Report S-649266-EF-304-N; Study Report: S-649266-EF-312-N; compassionate use Table 15 in Addendum -HABP/VABP
[a] *Achromobacter* spp (n=11) from compassionate use patients
Abbreviations: MIC, minimum inhibitory concentration

Table 72. In Vitro Activity of Cefiderocol Against Resistant Gram-Negative Pathogens

Pathogen (No. of Isolates)	MIC Range (mcg/mL)	MIC_{50} (mcg/mL)	MIC_{90} (mcg/mL)
Enterobacterales (25995)	≤0.002->256	0.12	1
MEPM-S Enterobacterales (25181) [a]	≤0.002->256	NA	0.5
MEPM-NS Enterobacterales (814) [b]	0.004->256	1	4
MDR Enterobacterales (923)[c]	0.004->256	1	4
XDR Enterobacterales (204)[d]	0.008->256	1	4
Escherichia coli (6424)	≤0.002-32	0.12	1
MEPM-S *E. coli* (6391) [a]	≤0.002-8	NA	0.5
MEPM-NS *E. coli* (33) [b]	0.015-32	NA	4
Klebsiella pneumoniae (5798)	≤0.002-128	0.12	1
MEPM-S *K. pneumoniae* (5245) [a]	≤0.002-8	NA	1
MEPM-NS *K. pneumoniae* (553) [b]	0.008-128	NA	4
Klebsiella oxytoca (1780)	≤0.002-4	0.06	0.25
MEPM-S *K. oxytoca* (1764) [a]	≤0.002-4	NA	0.25
MEPM-NS *K. oxytoca* (16) [b]	0.03-4	NA	4
Enterobacter cloacae (2235)	≤0.002-128	0.25	1
MEPM-S *E. cloacae* (2163) [a]	≤0.002-128	NA	1
MEPM-NS *E. cloacae* (72) [b]	0.06-8	NA	4
Klebsiella aerogenes (1175)	≤0.002-8	0.12	0.5
MEPM-S *K. aerogenes* (1156) [a]	≤0.002-8	NA	0.5
MEPM-NS *K. aerogenes* (19) [b]	0.06-2	NA	1
Citrobacter freundii complex (1138)	≤0.002-8	0.06	0.5
MEPM-S *C. freundii* complex (1111) [a]	≤0.002-4	NA	0.5
MEPM-NS *C. freundii* complex (27) [b]	0.008-8	NA	2
Citrobacter koseri (668)	0.004-8	0.25	0.5
MEPM-S *C. koseri* (2) [a]	0.004-8	0.25	0.5
MEPM-NS *C. koseri* (2) [b]	0.25-4	NA	-

Pathogen (No. of Isolates)	MIC Range (mcg/mL)	MIC_{50} (mcg/mL)	MIC_{90} (mcg/mL)
Serratia marcescens (3092)	≤0.002-128	0.12	0.5
MEPM-S *S. marcescens* (3023) [a]	≤0.002-32	NA	0.25
MEPM-NS *S. marcescens* (69) [b]	0.008-128	NA	2
Nonfermenters			
Pseudomonas aeruginosa (6213)	≤0.002-8	0.12	0.5
MEPM-S *P. aeruginosa* (4797) [a]	≤0.002-8		0.5
MEPM-NS *P. aeruginosa* (1416) [b]	≤0.002-8	0.25	1
MDR *P. aeruginosa* (638)[c]	≤0.002-8	0.25	1
XDR *P. aeruginosa* (12)[d]	0.03-2	0.25	1
Acinetobacter baumannii (3583)	≤0.002->256	0.12	2
MEPM-S *A. baumannii* (1323) [a]	0.004->256	NA	0.5
MEPM-NS *A. baumannii* (2260) [b]	≤0.002->256	0.25	2
MDR *A. baumannii* (2154)[c]	≤0.002->256	0.25	2
XDR *A. baumannii* (302)[d]	0.03-64	0.25	2

Source: S-649266-EB-387-N, Table 2 and Response to FDA Information Request dated 29 May 2020 (eCTD 0067).
Nonsusceptible was defined using the following criteria:
For Enterobacterales: Meropenem MIC: ≥2 mcg/mL, Cefepime MIC: ≥4 mcg/mL, Ciprofloxacin MIC: ≥0.5 mcg/mL, Colistin MIC: ≥4 mcg/mL.
For *P. aeruginosa*: Meropenem MIC: ≥4 mcg/mL, Cefepime MIC: ≥16 mcg/mL, Ciprofloxacin MIC: ≥1 mcg/mL, Colistin MIC: ≥4 mcg/mL.
For *A. baumannii*: Meropenem MIC: ≥4 mcg/mL, Cefepime MIC: ≥16 mcg/mL, Ciprofloxacin MIC: ≥2 mcg/mL, Colistin MIC: ≥4 mcg/mL.
[a] MEPM-S strain was defined as the strains which show susceptible to MEPM. For Enterobacterales MEPM MIC: ≤1 mcg/mL. For *P. aeruginosa* and *Acinetobacter* spp. MEPM MIC: ≤2 mcg/mL
[b] MEPM-NS strain was defined as the strains which show nonsusceptible to MEPM.
[c] MDR strains was defined as the strains which shows nonsusceptible to the antimicrobial agent in 3 antimicrobial categories.
[d] XDR strains was defined as the strains which shows nonsusceptible to the antimicrobial agent in 4 antimicrobial categories.
Abbreviations: MIC, minimum inhibitory concentration; NA, not available

The percent susceptibility of surveillance isolates to cefiderocol was examined for isolates nonsusceptible to cefepime, ceftazidime-avibactam and ceftolozane-tazobactam in the SIDERO-WT study (Table 73). Cefiderocol is active in vitro against Enterobacterales and *P. aeruginosa* that are resistant to cefepime, ceftazidime-avibactam and ceftolozane-tazobactam. However, this activity would depend on the resistance mechanisms and β-lactamases present in the bacteria.

Table 73. Percentage (%) of Cefiderocol Susceptible Isolates Against Cefepime-, Ceftazidime-Avibactam-, and Ceftolozane/Tazobactam-Nonsusceptible Isolates From SIDERO-WT

Species (Number of Strains)	Percentage of Susceptible Strains (%) [a]								
	Cefiderocol			Cefepime	Ceftazidime -avibactam	Ceftolozane /tazobactam	Meropenem	Ciprofloxacin	Colistin
	MIC ≤ 1 µg/mL	MIC ≤ 2 µg/mL	MIC ≤ 4 µg/mL						
Cefepime NS Enterobacterales (N=3599)	77.68	91.16	98.97	-	94.38	58.71	79.43	14.86	93.51 (N=3348) [b]
Ceftazidime-avibactam NS Enterobacterales (N=209)	50.23	71.29	91.38	3.34	-	4.3	9.56	7.17	90.22 (N=174) [b]
Ceftolozane/tazobactam NS Enterobacterales (N=2167)	72.68	87.35	98.33	31.42	90.77	-	65.62	34.05	87.98 (N=1989) [b]
Cefepime NS *P. aeruginosa* (N=1075)	92.65	98.13	99.81	-	65.86	68.00	31.9	25.11	98.79
Ceftazidime-avibactam NS *P. aeruginosa* (N=391)	87.97	97.95	100	6.13	-	22.76	7.67	9.20	98.97
Ceftolozane/tazobactam NS *P. aeruginosa* (N=381)	88.18	97.37	99.73	9.71	20.73	-	9.71	7.61	97.63

Source: Table 23 section 2.7.2.4 addendum-HABP/VABP of the Application
Abbreviations: MIC, minimum inhibitory concentration

Of the studies providing external validations, cefiderocol MIC range of 0.03 to 4 mcg/mL were noted for 66 *S. maltophilia* isolates in the surveillance study from Canada (study S-649266-EF-311-N) although MIC_{90} values were similar to that observed in surveillance studies conducted in the United States and Europe. Additionally, cefiderocol MIC_{90} values for carbapenem-resistant isolates of Enterobacterales (n=305*), P. aeruginosa* (n=111) and *A. baumannii* (n=99) obtained from the Public Health England's Antimicrobial Resistance and Healthcare Associated Infections Reference Unit were 4, 8 and 16 mcg/mL, respectively (S-649266-EF-329-N).

Cefiderocol is active in vitro against *A. baumannii* complex, *B. cepacia* complex, *Citrobacter freundii* complex, *Citrobacter koseri, E. coli, E. cloacae* complex, *Klebsiella aerogenes, Klebsiella oxytoca, K. pneumoniae, Morganella morganii, Proteus mirabilis, Proteus vulgaris, Providencia rettgeri, P. aeruginosa, Serratia marcescens,* and *Stenotrophomonas maltophilia*. However, the MIC_{90} values maybe impacted by specific geographical locations. The cefiderocol MIC_{90} values against meropenem nonsusceptible Enterobacterales and *A. baumannii* isolates were four- or eight-fold fold higher compared to the MIC_{90} values for meropenem-susceptible isolates in the surveillance studies. Cross-resistance between cefiderocol and β-lactam is observed for isolates that are resistant to β-lactam and β-lactam/β-lactamase inhibitors based on the mechanism of action and mechanism of resistance.

Burkholderia. pseudomallei

B. pseudomallei is the causative agent of melioidosis, which is characterized by a variety of symptoms ranging from self-limiting abscess to sepsis and dissemination to the solid organs and brain. Melioidosis is endemic in Thailand and northern Australia and other tropical regions. The cefiderocol MIC_{90} against 271 *B. pseudomallei* isolates from Australia was 1 mcg/mL (cefiderocol MIC range ≤0.03 to 32 mcg/mL) (S-649266-EF-312-N).

Although infections with *B. pseudomallei* has been documented in military personnel from the United States and can result in environmentally acquired respiratory tract illness, the pathogen is not associated with HABP/VABP. Additionally, *B. pseudomallei* is classified by the Centers for Disease Control and Prevention as a category B bioterrorism agent and the activity of cefiderocol against *B. pseudomallei* will need to be ascertained in clinical trials. (b) (4)

Achromobacter spp.

Achromobacter species are commonly found in the environment and may colonize the human gastrointestinal (GI) tract. They are opportunistic pathogens and can cause respiratory tract infections and bacteremia in immunocompromised patients such as cancer patients, lung transplant patients, patients with cystic fibrosis, and patients with chronic renal failure. The cefiderocol MIC_{90} against 16 isolates of *Achromobacter* spp. was 1 mcg/mL (cefiderocol MIC range <0.03–16 mcg/mL). Data for 11 isolates from patient receiving compassionate use of cefiderocol was provided. Inclusion of these data results in a cefiderocol MIC range of <0.03 to 64 mcg/mL but does not impact the cefiderocol MIC_{90} values.

Based on data against *Achromobacter* species, it can be included in the second list of pathogens in the microbiology section of the labeling.

Resistance

The new information on the molecular characterization of gram-negative clinical isolates collected in the SIDERO-WT-2015 and -2016 studies is described in this section. To understand the potential mechanisms of resistance and activity against resistant bacteria, the presence of β-lactamase and carbapenemase in meropenem nonsusceptible isolates (meropenem MIC: ≥2 mcg/mL for Enterobacteriaceae and ≥4 mcg/mL for *P. aeruginosa* and *A. baumannii*) from the surveillance studies (SIDERO-WT-2015 and SIDERO-WT-2016) were examined using PCR and sequencing and the cefiderocol MICs determined for these isolates. Some of the isolates could carry more than one resistant determinants. Isolates could also carry nonenzymatic mechanism of resistance or enzymes that were not part of these screen (for example, the chromosomally coded β-lactamases common *to S. marcescens, E. cloacae, K. aerogenes*, and *K. oxytoca*). The results suggest that the presence of Pseudomonas extended resistant (PER) β-lactamase alone or along with oxacillinase (OXA)-23 group enzymes and New Delhi metallo-β-lactamase (NDM) enzymes in *A. baumannii* contributes to cefiderocol resistance (Table 75). Reduced susceptibility (or increase in MIC values) to cefiderocol was observed for *P. aeruginosa* containing NDM or PER β-lactamases; however, the number of isolates tested were small. Reduced susceptibility to cefiderocol was observed for Enterobacterales containing NDM carbapenemases (Table 74). In vitro, the addition of the β-lactamase inhibitors (such as avibactam, clavulanic acid, and dipicolinic acid) results in the lowering of MICs of some isolates with relatively high MICs (range 2 to 256 mcg/mL) to cefiderocol.

Table 74. In Vitro Activity of Cefiderocol Against Molecularly Characterized Meropenem Nonsusceptible Isolates of Enterobacterales From Surveillance Studies

Pathogen/Genotype	No of Isolates	MIC_{90} (mcg/mL)	MIC Range (mcg/mL)	% Isolates With Cefiderocol MIC ≤2 mcg/mL	% Isolates With Cefiderocol MIC ≤4 mcg/mL	Source Study Reference
Enterobacterales						
Enterobacterales VIM	45	4	0.12-4	88.9	100	S-649266-EB-385-N
Enterobacterales VIM	47	4	≤0.03-8	80.9	95.7	S-649266-EF-329-N
E. coli VIM	1	-	0.06	100	100	S-649266-EF-327-N
K. pneumoniae VIM	2	-	0.5	100	100	S-649266-EF-327-N
E. cloacae VIM	1	-	2	100	100	S-649266-EF-327-N
E. cloacae GIM	1	-	4	-	100	S-649266-EF-327-N
Enterobacterales NDM	33	4	0.25-8	57.6	94	S-649266-EB-385-N
Enterobacterales NDM	61	8	0.25-32	41.0	72.1	S-649266-EF-329-N
E. coli NDM	1	-	1	100	100	S-649266-EF-327-N
K. pneumoniae NDM	2	-	2-4	50	100	S-649266-EF-327-N
E. cloacae NDM	2	-	1-8	50	50	S-649266-EF-327-N
Enterobacterales KPC	160	4	0.015-4	79.4	100	S-649266-EB-385-N
Enterobacterales KPC	56	2	≤0.03-8	91.1	98.2	S-649266-EF-329-N
E. coli KPC-3	1	-	0.06	100	100	S-649266-EF-327-N
K. pneumoniae KPC-2	3	-	≤0.03-2	100	100	S-649266-EF-327-N
K. pneumoniae KPC-3	6	-	0.25-2	100	100	S-649266-EF-327-N
K. pneumoniae ST512/KPC-3	25	4	0.25-4	80	100	S-649266-EF-326-N
K. pneumoniae ST258/KPC-3	25	2	0.25-2	100	100	S-649266-EF-326-N
Enterobacterales OXA-48	143	4	0.015-8	79.7	98.6	S-649266-EB-385-N
Enterobacterales OXA-48	56	2	≤0.03-8	92.9	98.2	S-649266-EF-329-N
E. coli OXA-48	1	-	0.06	100	100	S-649266-EF-327-N
K. pneumoniae OXA-48	6	-	0.06-4	83.3	100	S-649266-EF-327-N
K. pneumoniae ST11/OXA-48 + CTX-M-15	25	2	≤0.03-4	96	100	S-649266-EF-326-N
K. pneumoniae ST15/OXA-48 + CTX-M-15	25	4	≤0.03-4	88	100	S-649266-EF-326-N
K. pneumoniae ST392/OXA-48 + CTX-M-15	4	-	0.06-1	100	100	S-649266-EF-326-N
K. pneumoniae ST147/OXA-48	3	-	0.06-0.5	100	100	S-649266-EF-326-N
E. cloacae OXA-48	1	-	0.5	100	100	S-649266-EF-327-N
E. coli OXA-162	1	-	0.5	100	100	S-649266-EF-327-N
K. pneumoniae OXA-162	1	-	16	0	0	S-649266-EF-327-N
Enterobacterales-ESBL+	17	4	≤0.03-8	Not available	90	S-649266-EF-327-N
E. coli ESBL+	29	1	≤0.03-2	100	100	S-649266-EF-311-N
K. pneumoniae ESBL+	11	4	≤0.03-4	81.8	100	S-649266-EF-311-N
K. pneumoniae ESBL+	13	2	≤0.03-2	100	100	S-649266-EF-326-N
Enterobacterales-ESBL+ porin loss	26	4	0.06-32	61.5	88.5	S-649266-EF-329-N

Pathogen/Genotype	No of Isolates	MIC_{90} (mcg/mL)	MIC Range (mcg/mL)	% Isolates With Cefiderocol MIC ≤2 mcg/mL	% Isolates With Cefiderocol MIC ≤4 mcg/mL	Source Study Reference
E. coli AmpC producing	6	-	≤0.03-2	100	100	S-649266-EF-311-N
Enterobacterales-AmpC + porin loss	25	2	0.06-2	100	100	S-649266-EF-329-N
Enterobacterales IMP	15	2	≤0.03-4	93.3	100	S-649266-EF-329-N
Enterobacterales GES, SME, IMI	19	1	0.06-2	100	100	S-649266-EF-329-N

Source: Study reports from which data was obtained is listed in the column source study reference
Genotypes in red shows reduced suscept bility to cefiderocol.
Abbreviations: CTX-M, cefotaximase; ESBL, extended-spectrum β-lactamase; GES, Guiana extended-spectrum β-lactamase; IMI, imipenemase; IMP, imipenemase metallo-β-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; MIC, minimum inhibitory concentration; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; SME, *Serratia marcescens* enzyme; VIM, Verona integron-encoded metallo-β-lactamase

Table 75. In Vitro Activity of Cefiderocol Against Molecularly Characterized Meropenem Nonsusceptible Isolates of *Pseudomonas aeruginosa* and *Acinetobacter spp*. From Surveillance Studies

Pathogen/Genotype	No of Isolates	MIC_{90} (mcg/mL)	MIC Range (mcg/mL)	% Isolates With Cefiderocol MIC ≤1mcg/mL	% Isolates With Cefiderocol MIC ≤2 mcg/mL	Source Study Reference
P. aeruginosa						
IMP	12	4	0.12-4	16.6	75	S-649266-EB-385-N
IMP	5	-	0.5-1	100	100	S-649266-EF-327-N
IMP	25	8	0.06-16	80	80	S-649266-EF-329-N
VIM, PER/VEB	1	-	1	100	100	S-649266-EB-385-N
VIM	108	1	0.008-4	94.9	99	S-649266-EB-385-N
VIM	10	8	0.25-8	60	90	S-649266-EF-327-N
VIM	30	1	≤0.03->128	90	93.3	S-649266-EF-329-N
GIM	1	-	2	0	100	S-649266-EF-327-N
NDM	2	-	2	0	100	S-649266-EF-327-N
NDM	11	16	1->128	18.2	45.5	S-649266-EF-329-N
GES	9	-	0.06-1	100	100	S-649266-EF-385-N
GES	20	2	0.06-4	85	90	S-649266-EF-329-N
PER	15	8	0.06-16	53.3	66.7	S-649266-EF-329-N
VEB	10	2	0.5-8	70	90	S-649266-EF-329-N
Acinetobacter spp.						
NDM	3	-	2-8	0	33.3	S-649266-EB-385-N
NDM	20	16	1-≥128	15	50	S-649266-EF-329-N
OXA-23, PER/VEB	18	>256	1->256	5.6	5.6	S-649266-EB-385-N
OXA-23	693	2	≤0.002->256	87.3	94.9	S-649266-EB-385-N
OXA-23	41	16	0.06-≥128	78	85.4	S-649266-EF-329-N
ST2/OXA-23	25	0.5	0.06-1	100	100	S-649266-EF-326-N

Pathogen/Genotype	No of Isolates	MIC_{90} (mcg/mL)	MIC Range (mcg/mL)	% Isolates With Cefiderocol MIC ≤1mcg/mL	% Isolates With Cefiderocol MIC ≤2 mcg/mL	Source Study Reference
OXA-23 like	4	-	0.06-0.25	100	100	S-649266-EF-327-N
OXA-24, PER/VEB	40	>256	0.12->256	2.5	5.0	S-649266-EB-385-N
OXA-24	222	2	0.03-8	81.1	92.4	S-649266-EB-385-N
ST2/OXA-24/40	25	16	0.5-16	32	52	S-649266-EF-326-N
OXA-24/40	9	-	0.25-4	66.7	88.9	S-649266-EF-329-N
OXA-24-like	3	-	0.06-0.25	100	100	S-649266-EF-327-N
OXA-51	19	0.5	0.06-16	94.7	94.7	S-649266-EF-329-N
OXA-58	49	2	0.06-4	87.8	97.9	S-649266-EB-385-N
OXA-58	10	0.25	0.06-≥128	90	90	S-649266-EF-329-N
ST2/OXA-58	25	0.5	0.06-0.5	100	100	S-649266-EF-326-N
ST745/OXA-58	5	-	0.06-0.25	100	100	S-649266-EF-326-N
PER/VEB	61[a]	>256	0.12->256	4.9	6.6	S-649266-EB-385-N

Source: Study reports from which data was obtained is listed in the column source study reference
[a] PER/VEB type positive carbapenem nonsusceptible *Acinetobacter spp*. including 58 carbapenemase-producing strains. Genotypes in red shows reduced susceptibility to cefiderocol.
Abbreviations: GES, Guiana extended-spectrum β-lactamase; GIM, Germany imipenemase; IMI, imipenemase; IMP, imipenemase metallo-β-lactamase; MIC, minimum inhibitory concentration; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; PER, Pseudomonas extended resistance; VEB, Vietnam extended-spectrum β-lactamase; VIM, Verona integron-encoded metallo-β-lactamase

Whole genome sequencing analyses were performed on 71 isolates (64 *A. baumannii*, 1 *A. nosocomialis*, 4 *K. pneumoniae*, 1 *P. mirabilis*, and 1 *Burkholderia multivorans*) with cefiderocol MICs ≥8 mcg/mL. Isolates with substitutions in the PBP1a protein, mutations or deletions in the *pir-A like* (ferrienterobactin receptor) and *piu-like* (iron carrier binding protein) genes or outer membrane porin D (*oprD)* gene were observed in addition to PER enzyme in *A. baumannii* isolates. The *K. pneumoniae* isolates carried OXA-48 or NDM-1 in addition to β-lactamases, variant *pbp3* gene, disruption in OmpK35, and/or extended-spectrum β-lactamase (ESBL) gene. The *P. mirabilis* contained a temoneira (TEM)-2 gene, mutation in the siderophore uptake gene (*cir-A like* gene) and variant *pbp3* gene. *B. multivorans* possessed an intrinsic PEN-A element, variations in *pbp2* and *pbp3* gene and mutation in the siderophore uptake gene (*fiu-like* gene).

In general, resistance to cefiderocol in gram-negative bacteria has been associated with the presence of β-lactamases including AmpC β-lactamase overproduction, modifications of penicillin binding proteins, and mutations of transcriptional regulators that impact siderophore or efflux pump expression. Clinical isolates may produce multiple β-lactamases, or a combination of resistant determinants (ESBL, carbapenemase, porin, AmpC) that contribute to increase in cefiderocol MIC.

In the original NDA, data to support the in vitro activity of cefiderocol against certain Enterobacterales genetically confirmed to contain the following: ESBLs (TEM, sulfhydryl variable [SHV], cefotaximase [CTX-M], OXA), AmpC, AmpC-type ESBL (CMY), serine-carbapenemases (such as *K. pneumoniae* carbapenemase [KPC], OXA-48), and metallo-carbapenemases (such as NDM and Verona integron-encoded metallo-β-lactamase [VIM]) was provided. Cefiderocol was also shown to be active in vitro against certain *P. aeruginosa* genetically confirmed to contain VIM, Guiana extended-spectrum β-lactamase (GES), AmpC and certain *A. baumannii* containing OXA-23, OXA-24/40, OXA-51, and OXA-58. Additionally, cefiderocol was shown to be active in vitro against some *K. pneumoniae* isolates with OmpK35/36 porin deletion and some isolates of *P. aeruginosa* with OprD porin deletion. The Applicant claims activity of cefiderocol against *P. aeruginosa* carrying imipenemase metallo-β-lactamase (IMP). The cefiderocol MICs against *P. aeruginosa* carrying IMP (n=42) were high and 64% isolates were susceptible at MIC of 1 mcg/mL.

S. maltophilia produces two β-lactamases, metallo-carbapenemase (L1) and serine β-lactamases (L2). The cefiderocol MICs ranged from ≤0.03 to 0.25 mcg/mL, with MIC_{90} value of 0.25 mcg/mL for 25 isolates of *S. maltophilia* (study report S-649266-EF-220-R). These isolates were from the external validation study (b) (4) for the testing Of Novel therApeUTics), supported by the (b) (4) and contained both L1 and L2 β-lactamases. All isolates were meropenem and cefepime resistant and 21 out of the 25 were ceftazidime-avibactam resistant.

The Applicant claims activity against *A. baumannii* containing AmpC and states that AmpC is produced by all *A. baumannii* isolates. No data was provided to support that cefiderocol does not induce AmpC β lactamases in *A. baumannii*. However, data on 34 clinical isolates containing AmpC with cefiderocol MIC range of 0.06 to >32 mcg/mL were provided. Whole genome sequencing of *A. baumannii* isolates with low susceptibility to cefiderocol revealed that all contained Acinetobacter-derived cephalosporinases (ADCs) genes which are variants of AmpC (study report S-649266-EB-331-N).

Activity of Cefiderocol Against Knock-Out Mutants, Porin Mutants and Efflux Pump Overproducers

The original NDA included the data shown in Table 76 and Table 77 to support the activity of cefiderocol against efflux pump overproducers. It should be noted that cefiderocol MIC for the parent PAO1 varied in the two studies as the CAMHB medium supplemented with apotransferrin (20 micromol/L) was used in the experiments used to generate results depicted in Table 76 and ID-CAMHB medium was used to generate results depicted in Table 74. The cefiderocol MICs against *P. aeruginosa* strains with knockout mutations, PW8599 (*piuA*), PW8601 (*piuC*), and SR-L00001 (*piuA* and *piuC*), were several fold higher (2 mcg/mL) than that against parent strain PAO1 (0.031 mcg/mL) (report S-649266-EB-191-N). As the four-fold increase observed for the knockout mutants in *ampD, mexF, mexR* and *nfxB* (0.125 mcg/mL) compared to the parent strain PAO1 (0.031 mcg/mL) were in the susceptible range (0.031 to 0.125 mcg/mL), the Applicant concludes that the cefiderocol activity was not affected by the mutations in *mexR* or *nfxB* (strain PW1777 or PW8753) and consequent overexpression of efflux pumps MexAB-OprM or MexCD-OprJ, respectively (Table 76). The Applicant states that the ceftazidime and cefepime MICs against the mutants of *mexR* (strain PW1777) or *ampD* (strain PW8615), which caused overproduction of efflux pump MexAB-OprM or AmpC, respectively were eight-fold higher (4 to 16 mcg/mL) compared to susceptible range (0.5 to 2 mcg/ml). The cefiderocol MICs against mutant strain OFR 504 which is deficient in MexA-MexB-OprM but was stated to overproduce OprJ was four-fold lower (≤0.031 mcg/mL) than parent PAO1 strain (0.125 mcg/mL) in these experiments (Table 77). OprJ may enhance the permeability of the *P. aeruginosa* outer membrane to cefiderocol as a porin. Due to the variability in cefiderocol MICs as a result of the different medium used in the two studies (MIC of 0.031 mcg/mL in Table 76 and 0.125 mcg/ml in Table 77), it is difficult to compare results across studies. Cefiderocol MIC against OprD deficient mutant was similar to that of the parent strain while that of imipenem (IPM) which uses porin to cross the outer membrane was eight-fold higher than the parent strain. In the case of efflux pump OprM overexpressing strain SO20, the MIC of aztreonam (AZT) which uses the OprM to discharge the drug was higher than the parent strain. However, MICs for ceftazidime, IPM, cefepime were not impacted in this OprM overproducing strain.

Table 76. Antibacterial Activity Against the Mutant Strains of *P. aeruginosa* PAO1 (EB-191-N)

Strain	Genotype	Phenotype	MIC (μg/mL) of			
			Cefiderocol	Ceftazidime	Cefepime	Meropenem
PAO1	–	Wild type	0.031	0.5	0.5	0.5
PW7590	*fecA*	Deficiency of iron transporter FecA	0.063	1	2	0.5
PW4366	*feuA* (*cirA*)	Deficiency of iron transporter FeuA	0.063	2	1	0.5
PW1861	*fiuA*	Deficiency of iron transporter FiuA	0.063	2	1	0.5
PW5144	*foxA* (*optS*)	Deficiency of iron transporter FoxA	0.125	2	1	0.5
PW8161	*fptA*	Deficiency of iron transporter FptA	0.125	2	2	0.5
PW5036	*fpvA*	Deficiency of iron transporter FpyA	0.063	2	2	0.5
PW8065	*fpvB*	Deficiency of iron transporter FpyB	0.063	2	2	0.5
PW5503	*pfeA*	Deficiency of iron transporter PfeA	0.063	1	1	0.25
PW3399	*pfuA*	Deficiency of iron transporter PfuB	0.063	2	1	0.5
PW2689	*pirA*	Deficiency of iron transporter PirA	0.063	2	1	0.5
PW8599	*piuA*	Deficiency of iron transporter PiuA	2	2	2	0.5
SR-L00001	*piuA* and *pirA*	Deficiency of iron transporters PiuA and PirA	2	2	2	0.5
PW8601	*piuC*	Deficiency of iron transporter PiuC	2	2	2	0.5
PW7952	*ampC*	Deficiency of AmpC	0.063	2	2	0.5
PW8615	*ampD*	Overproduction of AmpC	0.125	16	8	2
PW1781	*mexB*	Deficiency of efflux pump MexAB-OprM	0.031	0.5	0.5	0.063
PW8750	*mexD*	Deficiency od efflux pump MexCD-OprJ	0.063	2	1	0.5
PW5183	*mexF*	Deficiency of efflux pump MexEF-OprN	0.125	2	2	2
PW1777	*mexR*	Overproduction of MexAB-OprM	0.125	4	4	4
PW4498	*mexY*	Deficiency of efflux pump MexXY	0.063	1	1	0.5
PW8753	*nfxB*	Overproduction of efflux pump MexCD-OprJ	0.125	2	2	0.5
PW2742	*oprD*	Deficiency of porin OprD	0.063	2	2	2

Source: Study S-649266-EB-191-N
The shaded cells show the MIC values out of the susceptible range
Abbreviations: MIC, minimum inhibitory concentration

Table 77. Antibacterial Activity Against the Mutant Strains of *P. aeruginosa* PAO1 (EB-204-N)

Species	Strain	Character	S-649266	CAZ	IPM	CPFX	AZT
Pseudomonas aeruginosa	IPM46	ΔOprD	0.063	2	8	0.063	4
Pseudomonas aeruginosa	SO20	OprM high producer	0.125	4	0.5	0.5	32
Pseudomonas aeruginosa	YY165	*ΔmexB*	≤0.031	1	1	≤0.031	0.25
Pseudomonas aeruginosa	SLH910	*ΔmexB*, AmpC high producer	0.25	>32	1	≤0.031	>32
Pseudomonas aeruginosa	OFR504	*ΔmexB*, OprJ high producer	≤0.031	1	1	1	0.25
Pseudomonas aeruginosa	PAO4141	*blaJ* mutation (AmpC non producer)	≤0.031	1	0.125	0.125	4
Pseudomonas aeruginosa	AC2064	*ΔampC*	0.063	2	0.125	0.125	4
Pseudomonas aeruginosa	DAC27	*ΔoprD*, *ΔampC*	0.063	2	0.25	0.125	4
Pseudomonas aeruginosa	AC22mx	*ΔmexB*, *ΔampC*	≤0.031	0.5	0.125	≤0.031	0.25
Pseudomonas aeruginosa	PAO1 (TU)	Parent	0.125	2	1	0.125	4

Source: Study Report S-649266-EB-204-N Table 15.
Abbreviations: AZT, aztreonam; CAZ, ceftazidime; CPFX, ciprofloxacin; IPM, imipenem

The increase in MIC in relation to AmpC overexpression or MexAB-OprM or MexCD-OprJ efflux overexpression due to knockout of *ampD*, *mexR* or *nfxB* were four fold but within the susceptible range. The mutation of nfxB may suppress efflux system(s) other than MexAB-OprM and MexXY-OprM.

The new data in this submission included cefiderocol MICs for well characterized clinical isolates of *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* (study report S-649266-EF-313-N). In this study, correlation of cefiderocol MIC values to the presence of β-lactamases and genetic expression of *blaKPC*, *ompK35*, *ompK36* and *arcB* in 34 *K. pneumoniae* clinical isolates, the genetic expression of *ampC*, *oprD*, *mexA*, *mexC*, *mexE* and *mexX* in 33 *P. aeruginosa* clinical isolates, and the genetic expression of *ampC*, *oxa51*, *adeB*, and *abeM* in 34 *A. baumannii* clinical

isolates were analyzed using two-tailed student's t-test and multiple linear regression analysis. A p-value<0.05 in this analyses was considered significant. The cefiderocol MIC range for *K. pneumoniae* isolates containing the carbapenemase KPC was 0.06 to 0.5 mcg/mL (Table 78). The cefiderocol MIC range for *K. pneumoniae* isolates containing only an ESBL (*bla*SHV) was 0.25 to 4 mcg/mL. The one isolate in this group with a cefiderocol MIC of 4 mcg/mL also possessed an AmpC-type (ACT-1) enzyme. The authors conclude that there was no correlation between cefiderocol MICs and expression of the *bla*KPC, the efflux-related genes *marA*, *ramA*, *soxS*, and *acrB*, and the porin-related genes *ompK35* or *ompK36*.

Table 78. Antibacterial Activity of Cefiderocol and Expression Level of Resistance Related Genes in Clinical Isolates of *K. pneumoniae*

Strain	β-lactamase gene		Relative RNA expression level of							MIC of Cefiderocol (μg/mL)
	KPC	SHV ESBL	bla KPC	mar	sox	acrB	ram	ompK35	ompK36	
503	Yes	Yes	198.75	0.91	21.3	6.01	63.5	1.44	4.51	2
302		Yes		0.13	0.165	0.21	0.31	0.23	1.32	0.5
302	Yes	Yes	40	1.33	4.26	1.6	26.6	1.15	8.19	1
504		Yes		0.33	0.81	0.45	1.23	0.54	4.58	1
505				0.004	0.005	0.02	0.01	0.24	1.31	0.06
507	Yes		3.75	0.52	2.5	0.41	0.44	0.17	0.06	0.5
511		Yes		0.75	0	0.5	0	1.25	3.11	0.25
512		Yes		0.87	0	1.07	0	2.5	8.22	0.5
513	Yes	Yes	18.75	1.18	0	1.64	0	0.94	7.71	0.5
516	Yes		1	0.04	0.23	0.2	0.11	2.74	4.19	1
518		Yes		0.003	0.005	0.02	0.007	0.13	1.01	2
806		Yes		0.07	0.00005	0.11	0.0001	1.11	1.81	0.5
839	Yes	Yes	5	0.48	0	0.74	0	0.37	7.59	0.12
855	Yes	Yes	15	0.23	1.68	0.17	2.67	0.11	0.18	2
152				1.87	13.2	1.71	5.43	1.27	1.92	0.5
375				0.1	0.12	0.21	0.12	2.84	6.12	0.12
834	Yes	Yes	1.25	0.02	0.02	0.32	0.04	0.54	2.94	0.06
351		Yes		0.05	0.15	0.34	0.11	0.43	1.97	1
370				0.01	0.19	0.07	0.0003	1.88	0.86	0.5
417		Yes		0.9	6	1.24	52.3	0.28	1.36	0.25
420				0.73	0	0.41	0	1.45	3.03	0.12
528	Yes		22.5	0.5	0	0.56	0	0.16	3.28	1
850	Yes	Yes	2.5	0.007	0.01	0.04	0.008	0.08	0.004	4
107		Yes, +ACT-1		0.25	4.23	0.45	3.1	0.5	3.85	4
31	Yes	Yes	1	0.34	0.58	0.49	0.36	0.06	0.25	0.25
340				0.06	0.15	0.24	0.36	0.51	1.04	0.25
5				0.009	0.88	2.65	3.05	1.43	5.1	0.5
12				4.92	15.6	2.85	6.93	1.51	5.41	0.06
54				0.99	4.3	1.5	1.95	4.39	5.18	<0.03
9	Yes		1.1	0.01	0.04	0.05	0.79	0.49	1.7	1
522		Yes		0.007	0.001	0.003	0.03	0.18	0.88	1
307				0.02	0.19	0.38	0.38	0.02	1.41	0.25
555	Yes	Yes	5	1.78	0	1.21	0	1.8	4.47	0.5
822	Yes	Yes	1.1	0.92	0	0.52	0	1.58	5.7	0.25

Source: S-649266-EF-313-N
Abbreviations: MIC, minimum inhibitory concentration

P. aeruginosa isolates with increased *ampC* expression (>10 time control) had modestly higher cefiderocol MICs compared to isolates without increased expression of this enzyme (0.67±1.01 versus 0.27±0.23 mcg/mL, p =0.2) (Table 79). The presence of multiple resistant determinant expression results in higher cefiderocol MIC compared to isolates with high expression of single efflux, porin or *ampC* gene. The authors state that there was no correlation between cefiderocol MICs and expression of *ampC mexA*, *mexC*, *mexE*, *mexX*, and *oprD* in *P. aeruginosa*.

Table 79. Antibacterial Activity of Cefiderocol and Expression Level of Resistance Related Genes in Clinical Isolates of *P. aeruginosa*

Strain	Relative RNA expression level of						MIC of Cefiderocol (μg/mL)
	ampC	oprD	mexA	mexC	mexE	mexX	
311	1.36	1.79	1.67	0.767	1.22	6.64	0.25
322	2353	0.171	3.49	0.461	0.223	19.6	0.5
504	7.47	0.943	1.45	4.36	0.713	4.4	0.5
513	1469	0.464	3.12	2.02	0.6	42.6	0.5
537	376	0.135	0.872	0.196	0	87.7	1
104	0.412	10.1	2.22	16.1	0.546	16.2	0.12
119	2.67	1.23	2.41	2.21	0	5.7	0.25
504	1.8	0	1.81	1.83	0.648	5.69	0.12
510	2.62	0.813	0.97	2.69	0.395	5.03	0.12
519	2.08	0	1.04	1.03	0.228	34.6	1
521	3.75	0	1	1.65	0.667	1.13	0.5
506	65.5	0.164	0.721	0	0.009	0.951	4
501	928	0.0937	1.37	4.05	0.758	29.3	1
545	269	0.132	1.13	0.867	0.236	31.6	0.12
546	483	0.035	0.523	0.069	0.196	6.69	0.06
553	607	0.0954	0.411	0.0772	0	24.3	0.12
555	2.4	0	1.65	0.151	0	31.2	0.12
140	5.46	11.1	2.21	2.13	0.211	6.87	0.06
188	0.31	4.06	3.94	3.04	0.427	5.82	0.5
503	3.96	1.02	1.75	9.43	1.69	4.01	0.12
505	0.705	0.19	1.53	8.95	1.09	12.9	0.12
516	3.52	0	2.59	1.37	0.663	1.11	0.5
550	6.16	0.269	1.42	0	2.76	73.4	0.12
558	1.99	0.384	1.02	0.84	1.45	17.8	0.12
575	169	0.561	0.879	2.86	0.414	52.6	0.5
118	1.28	0.024	0.961	0.671	0	9.62	0.12
140	5.06	2.36	12.6	9.3	1.64	331	0.12
517	2.35	0.347	0.905	0.954	1.78	3.78	0.12
128	3.65	0	0.714	0.291	0.409	2.8	0.5
339	295	0.276	5.02	2.46	0.658	22.9	0.12
602	29.2	0.711	3.48	1.79	0.191	0.06	0.12
609	2646	0	1.93	0.173	0.05	29.4	0.12
311	974	0.705	2.83	0.171	0.0065	19	0.5

Source: S-649266-EF-313-N
Abbreviations: MIC, minimum inhibitory concentration

A. baumannii isolates containing an SHV ESBL had significantly higher cefiderocol MICs than isolates without ESBLs (8.04±11.58 versus 0.86±1.08 mcg/mL, p=0.02) (Table 80). The authors conclude that there was no correlation between cefiderocol MICs and expression of genes encoding *ampC*, *bla*OXA-51, and the efflux systems *adeB* and *abeM* in *A. baumannii* based on regression analysis (p=0.02).

Table 80. Antibacterial Activity of Cefiderocol and Expression Level of Resistance Related Genes in Clinical Isolates of *A. baumannii*

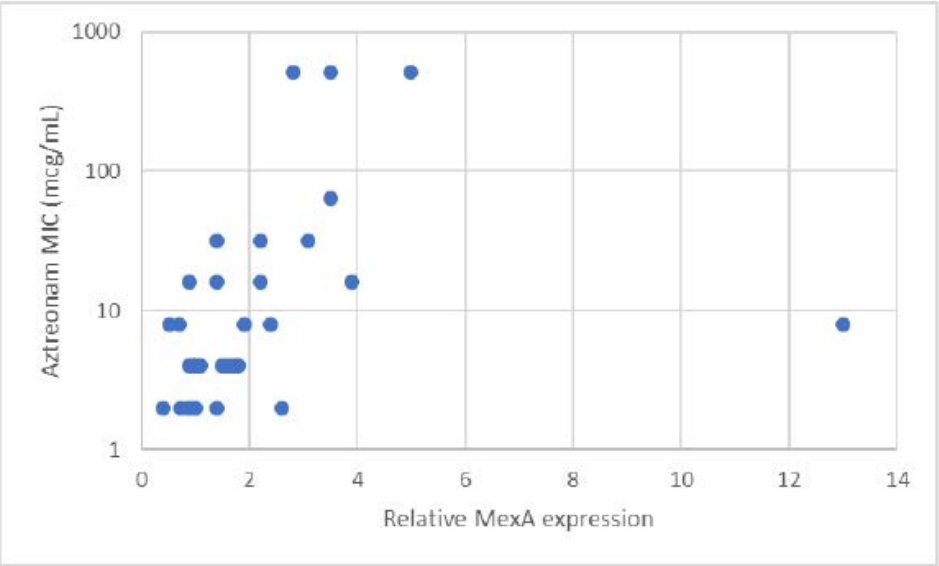
Strain	β-lactamase gene	Relative RNA expression level of						MIC of Cefiderocol (μg/mL)
	SHV ESBL	ampC	bla OXA-51	oprF	oprD	adeB	abeM	
123	Yes	17.6	405	1.8	1.94	0	0.78	0.12
142		7	163	1.3	1.8	0	1	0.12
301	Yes	114	46.7	5.9	2.14	6.3	7.2	2
335		17.3	109	4.2	2.2	28.8	3.2	2
503	Yes	53	302	4.4	2	2.6	3.6	32
308	Yes	14	58.6	2.2	4.56	2.2	1.8	4
101	Yes	35	160	1.4	1.57	1.5	2.7	0.5
501		18.3	2514	1.3	233	2.1	4.8	4
507	Yes	12.3	17.5	0.14	1.9	1.3	2.7	32
113	Yes	16	189	1.1	0.42	1.2	2.2	2
160		12	193	1.1	0.339	1.8	1.7	0.5
167		87	346	3	4.07	3.3	6.2	2
304		0.95	0.3	1.4	6.49	1	0.04	0.12
305		83	26.6	0.59	5.1	2	1.3	1
307	Yes	9.2	226	2.3	4.18	28.6	2	4
308	Yes	248	1313	0.86	2.39	1.1	1.9	4
316		270	60	0.59	9.3	0.03	1.5	0.12
320		9.2	446	1.5	26.8	2.3	3.6	1
322		10.4	388	2.5	2.3	4.4	8.5	1
343		0.25	36.2	1.5	9.6	3.2	2.4	0.12
349		0.28	29.4	2.1	2.82	2	0.01	0.12
357		0.19	61.5	2.2	0.4	4.9	2.3	2
328	Yes	169	404	3.8	2.39	3.4	0.92	32
340	Yes	0	6.25	3.4	3.2	4.2	1.6	4
348	Yes	401	23.1	10.6	1.84	14.3	2.1	1
504	Yes	44.4	2046	1.3	1.18	0.64	2	1
311		0.49	10.2	1.6	0.34	5.4	1.8	0.12
324		0.12	0.76	1.1	27	0.08	1.2	0.25
526	Yes	16.6	1320	1.2	57	2.5	1.6	8
37	Yes	4.9	26.1	6.4	6.13	1.4	1	4
309	Yes	75.7	30	1.8	3.69	27.3	4.2	2
310	Yes	5.2	296	0.5	9.18	0.67	1.1	4
541		0.12	9.8	0.53	1.3	1.2	1.5	0.06
22		0.18	119	0.71	0.36	1.3	1.6	0.12

Source: S-649266-EF-313-N
Abbreviations: MIC, minimum inhibitory concentration

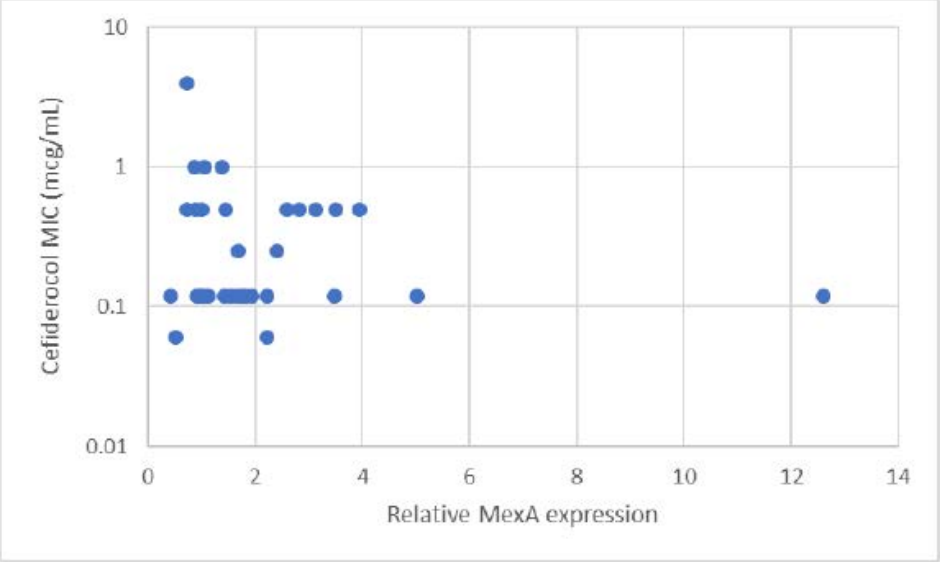
The Applicant further analyzed the relationship between AZT MIC and MexA expression level in *P. aeruginosa* using published data (Figure 16). The Applicant concluded that AZT MIC are high in the isolates which showed higher expression level of MexA while cefiderocol retained low MIC against these isolates and the efflux pump MexAB-OprM in *P. aeruginosa* does not contribute to MIC increases of cefiderocol.

Figure 16. Relationship Between the Expression Level of MexA and MIC of Aztreonam (A) or Cefiderocol (B) Against *P. aeruginosa*

A. Aztreonam



B. Cefiderocol



Source: Figure 17 in section 2.7.2.4 Addendum-HABP/VABP of the Application
Abbreviations: MIC, minimum inhibitory concentration

The authors and Applicant conclude that there is no significant correlation between cefiderocol MICs and the expression level of resistance determinants such as efflux pumps (AcrB of *K. pneumoniae*, and MexA, MexC, MexE and MexX of *P. aeruginosa*, and AdeB and AbeM of *A. baumannii*) and porins (OmpK35, OmpK36 of *K. pneumoniae*, and OprD of *P. aeruginosa*). Cefiderocol was shown to be active against *K. pneumoniae* with *ompK35/36* porin mutation and *P. aeruginosa* with *oprD* porin mutation previously (original NDA).

Both high and low levels of resistance are associated with overproduction of the pumps, with additional resistance mechanisms required for high-level resistance. The β-lactam resistance in clinical isolates of *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* is a result of the interplay between multiple resistance mechanisms. In *P. aeruginosa*, it is the result of interplay between diminished production of OprD, increased activity of AmpC, and several efflux systems. Simultaneous expression of more than one efflux systems can cause misinterpretation of the substrate specificity of each multidrug efflux system. Multiple-knockout experiments, use of isogenic strains, and direct measurements of efflux are necessary to elucidate the actual substrate specificities of the different efflux pumps. The multiple regression analyses performed by the authors do not address assumptions made regarding interactions between different resistant determinants as differences in presence of β-lactamases, membrane permeability impacting influx can confound the results. The analyses have limited sensitivity as only large changes in efflux can be detected in the presence of select β-lactamases and porin expression. Use of appropriate methodology is important to allow for drawing conclusions on efflux activity.

Cross-Resistance

Cross-resistance of cefiderocol with other classes of antibacterial drugs has not been identified; therefore, isolates resistant to other antibacterial drugs may be susceptible to cefiderocol. In the surveillance study conducted in 2018, 72 gram-negative isolates had cefiderocol MIC >4 mcg/mL(study report S-649266-EF-308-N). The cross-resistance between cefiderocol and cefepime or meropenem is observed for majority of the *A. baumannii* isolates (Table 81). In the case of Enterobacterales, cross-resistance between cefiderocol and cefepime, ceftazidime-avibactam, or ceftolozane-tazobactam was observed in approximately 40 to 50% isolates.

Table 81. In Vitro Activity of Cefiderocol and Comparators Against 72 Gram-Negative Clinical Isolates With Cefiderocol MICs of >4 mcg/mL Using CLSI Breakpoints

Organism (N) Compound	Breakpoint	%I	%R	MIC_{90}	MIC Range
A. baumannii (50)					
Cefiderocol	≤4 | 8 | ≥16	6.0	94.0	>256	8->256
Aztreonam-avibactam	No breakpoints	na	na	>8	8->8
Cefepime	≤8 | 16 | ≥32	0.0	98.0	>64	8->64
Ceftazidime-avibactam	No breakpoints	na	na	>64	16->64
Ceftolozane-tazobactam	No breakpoints	na	na	>64	≤0.06->64
Ciprofloxacin	≤1 | 2 | ≥4	0.0	98.0	>8	1->8
Colistin	≤2 | -- | ≥4	0.0	2.0	2	0.5->8
Meropenem	≤2 | 4 | ≥8	0.0	78.0	>64	0.5->64
Meropenem-vaborbactam	No breakpoints	na	na	>64	0.25->64
E. cloacae (2)					
Cefiderocol	≤4 | 8 | ≥16	100	0	--	8-8
Aztreonam-avibactam	No breakpoints	na	na	--	0.5->8
Cefepime	≤2 | 4-8 | ≥16	0	100	--	>64->64
Ceftazidime-avibactam	≤8 | -- | ≥16	0.0	50.0	--	4-16
Ceftolozane-tazobactam	≤2 | 4 | ≥8	0	100	--	32-32
Ciprofloxacin	≤0.25 | 0.5 | ≥1	0.0	50.0	--	0.25->8
Colistin	≤2 | -- | ≥4 (EUCAST)	0	0	--	0.5-1
Meropenem	≤1 | 2 | ≥4	0.0	50.0	--	≤0.06-32
Meropenem-vaborbactam	≤4 | 8 | ≥16	0.0	50.0	--	≤0.06-16
E. coli (2)					
Cefiderocol	≤4 | 8 | ≥16	50.0	50.0	--	8-32
Aztreonam-avibactam	No breakpoints	na	na	--	≤0.12-2
Cefepime	≤2 | 4-8 | ≥16	0	100	--	16->64

Organism (N) Compound	Breakpoint	%I	%R	MIC_{90}	MIC Range
Ceftazidime-avibactam	≤8 | -- | ≥16	0.0	50.0	--	0.25->64
Ceftolozane-tazobactam	≤2 | 4 | ≥8	0.0	50.0	--	0.5->64
Ciprofloxacin	≤0.25 | 0.5 | ≥1	0	100	--	8->8
Colistin	≤2 | -- | ≥4 (EUCAST)	0	0	--	≤0.25-0.5
Meropenem	≤1 | 2 | ≥4	0.0	50.0	--	≤0.06-64
Meropenem-vaborbactam	≤4 | 8 | ≥16	0.0	50.0	--	≤0.06-64
K. aerogenes (1)					
Cefiderocol	≤4 | 8 | ≥16	100	0	--	8-8
Aztreonam-avibactam	No breakpoints	na	na	--	≤0.12-≤0.12
Cefepime	≤2 | 4-8 | ≥16	0	0	--	0.25-0.25
Ceftazidime-avibactam	≤8 | -- | ≥16	0	0	--	0.5-0.5
Ceftolozane-tazobactam	≤2 | 4 | ≥8	100	0	--	4-4
Ciprofloxacin	≤0.25 | 0.5 | ≥1	0	0	--	≤0.12-≤0.12
Colistin	≤2 | -- | ≥4 (EUCAST)	0	0	--	0.5-0.5
Meropenem	≤1 | 2 | ≥4	0	0	--	≤0.06-≤0.06
Meropenem-vaborbactam	≤4 | 8 | ≥16	0	0	--	≤0.06-≤0.06
K. pneumoniae (5)					
Cefiderocol	≤4 | 8 | ≥16	60.0	40.0	--	8-128
Aztreonam-avibactam	No breakpoints	na	na	--	0.5-1
Cefepime	≤2 | 4-8 | ≥16	0	100	--	32->64
Ceftolozane-tazobactam	≤2 | 4 | ≥8	0	100	--	>64->64
Ciprofloxacin	≤0.25 | 0.5 | ≥1	0	100	--	>8->8
Colistin	≤2 | -- | ≥4 (EUCAST)	0.0	20.0	--	0.5-8
Meropenem	≤1 | 2 | ≥4	0	100	--	8->64
Meropenem-vaborbactam	≤4 | 8 | ≥16	0.0	80.0	--	4->64
P. mirabilis (2)					
Cefiderocol	≤4 | 8 | ≥16	0	100	--	128-256
Aztreonam-avibactam	No breakpoints	na	na	--	0.5->8
Cefepime	≤2 | 4-8 | ≥16	50.0	50.0	--	4->64
Ceftazidime-avibactam	≤8 | -- | ≥16	0.0	50.0	--	4-32
Ceftolozane-tazobactam	≤2 | 4 | ≥8	0	100	--	8-32
Ciprofloxacin	≤0.25 | 0.5 | ≥1	0.0	50.0	--	0.25->8
Colistin	≤2 | -- | ≥4 (EUCAST)	0	100	--	>8->8
Meropenem	≤1 | 2 | ≥4	0	0	--	≤0.06-0.25
Meropenem-vaborbactam	≤4 | 8 | ≥16	0	0	--	0.12-0.25
S. marcescens (2)					
Cefiderocol	≤4 | 8 | ≥16	50.0	50.0	--	8-128
Aztreonam-avibactam	No breakpoints	na	na	--	0.5-2
Cefepime	≤2 | 4-8 | ≥16	0	100	--	>64->64
Ceftazidime-avibactam	≤8 | -- | ≥16	0	100	--	>64->64
Ceftolozane-tazobactam	≤2 | 4 | ≥8	0	100	--	>64->64
Ciprofloxacin	≤0.25 | 0.5 | ≥1	100	0	--	0.5-0.5
Colistin	≤2 | -- | ≥4 (EUCAST)	0	100	--	>8->8
Meropenem	≤1 | 2 | ≥4	0	100	--	64->64
Meropenem-vaborbactam	≤4 | 8 | ≥16	0	100	--	64->64

Source: Study S-649266-EF-308-N Table 17.
$MIC_{90,}$ and Range in mcg/mL, avibactam and tazobactam tested at a fixed concentration of 4 mcg/mL
Vaborbactam tested at a fixed concentration of 8 mcg/mL
MIC_{90} not calculated for n ≤10.
Abbreviations: CLSI, Clinical and Laboratory Standards Institute; I, intermediate; MIC, minimum inhibitory concentration; na, no available breakpoints; R, resistant

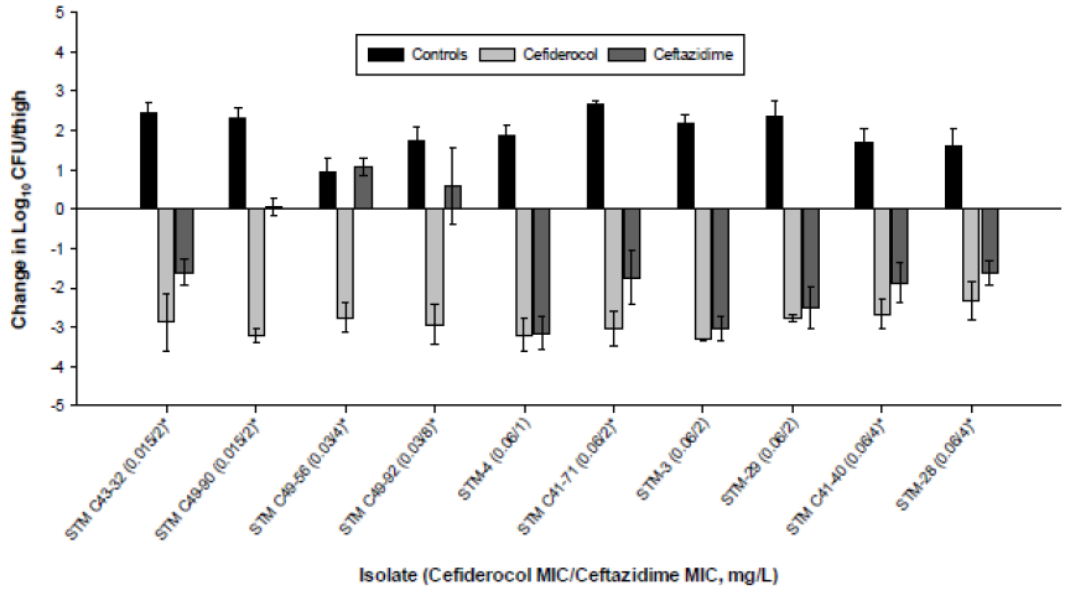
Enterobacter cloacae complex isolates (n=2) with amino acid deletion in the R2 loop of AmpC β-lactamase were concurrently resistant to ceftazidime-avibactam, cefepime and cefiderocol (Kawai et al. 2020; Shields et al. 2020).

In Vivo Activity

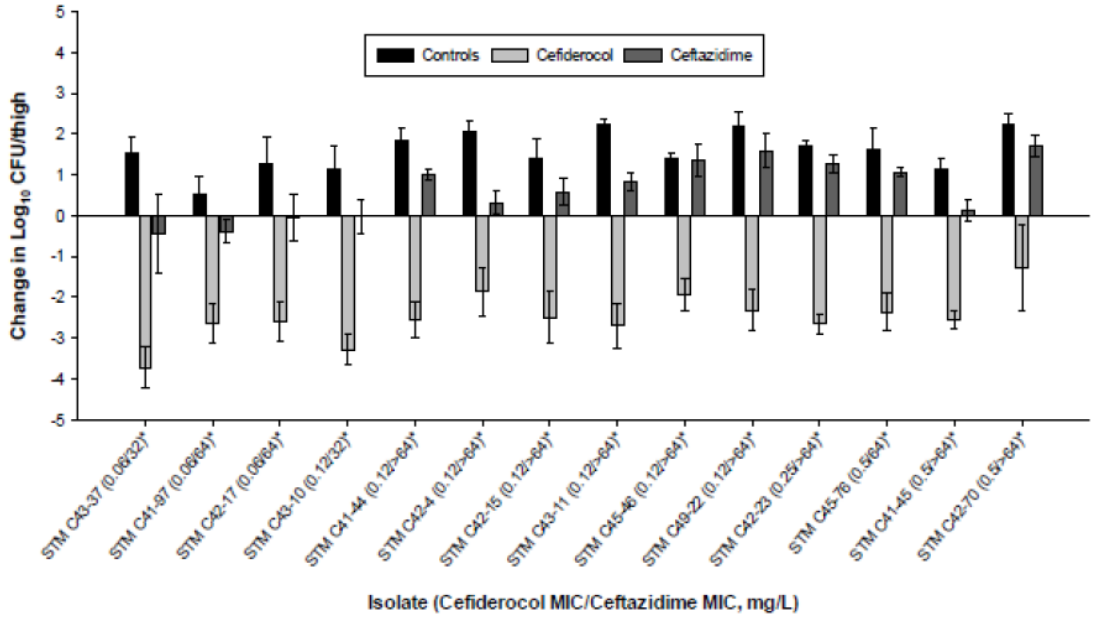
The activity of cefiderocol against 24 *S. maltophilia* (cefiderocol MIC range 0.015 to 0.5 mg/mL) was examined in the neutropenic murine thigh infection model (report S-649266-EF-353-R). The thighs of mice were inoculated with 10^8 CFU/mL and treatment with human simulated dose of cefiderocol (2 gm q8H 3-hour infusion) and ceftazidime (2 gm q8H 2-hour infusion) was initiated 2 hours postinfection. Bacterial reduction of ≥2 log-reduction was achieved in 21 isolates (87.5%) and ≥1 log-reduction was achieved in the remaining three isolates (12.5%) at 24 hours in cefiderocol treated mice (Figure 17).

Figure 17. Efficacy of 24 Hours of a Cefiderocol Human-Simulated Regimen (2 g q8h, 3-Hour Infusion) and a Ceftazidime Human-Simulated Regimen (2 g q8h, 2-Hour Infusion) Against Ceftazidime-Susceptible (A) and Ceftazidime-Resistant (B) *S. maltophilia* in Neutropenic Murine Thigh Infection Model

(A)



(B)

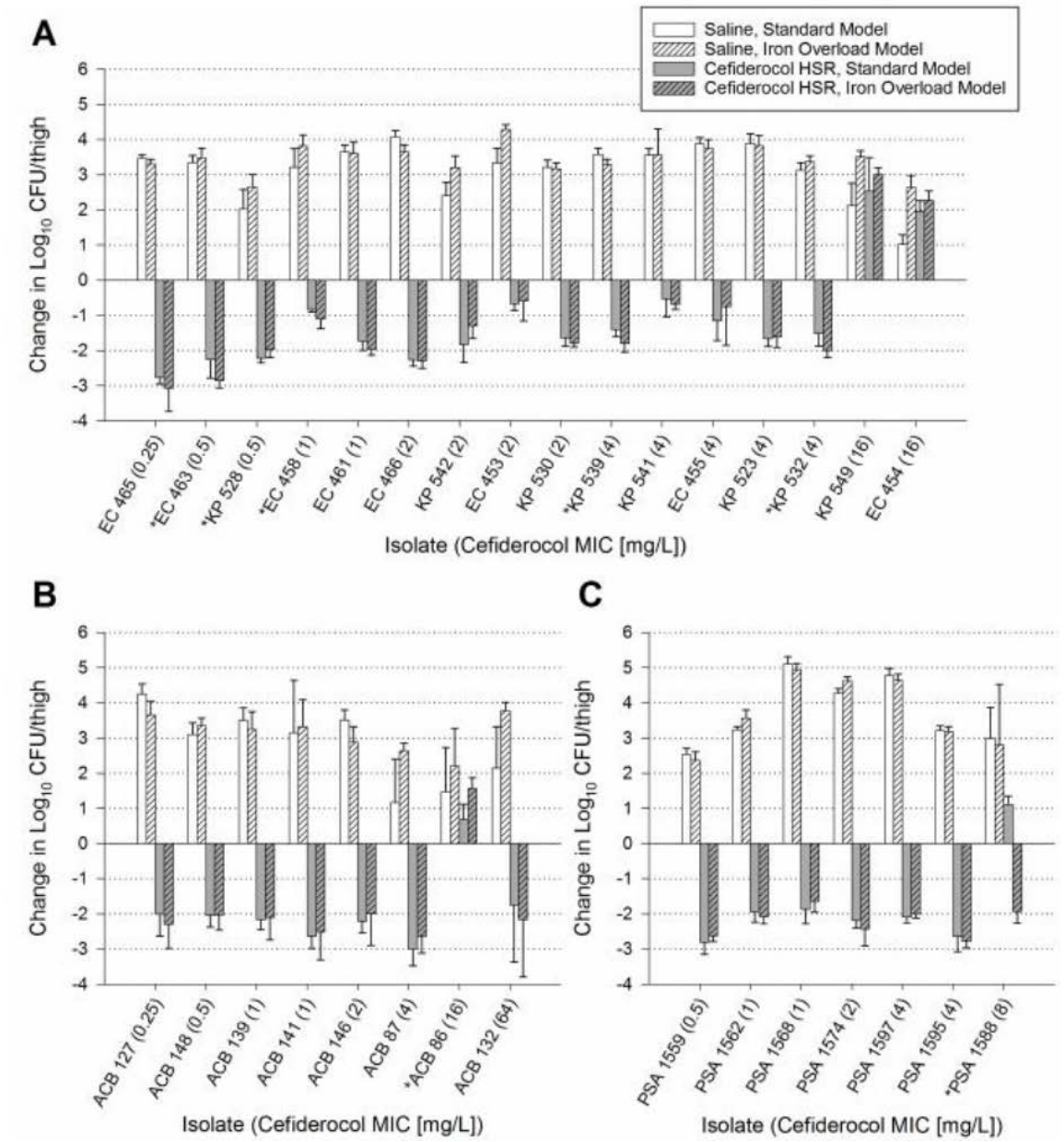


Source: S-649266-EF-353-R, Figure 2.
* Indicate statistically significant differences (p≤0.05) between cefiderocol and ceftazidime
Abbreviations: CFU, colony forming units; MIC, minimum inhibitory concentration; q8h, every 8 hours; STM, *S. maltophilia*

The activity of cefiderocol was examined in the iron overloaded murine thigh infection model to evaluate the effects of iron overload (report S-649266-EF-347-R). The neutropenic thigh

infection model were treated with iron dextran 100 mg/kg daily for 14 days to load iron. Mice were infected with 31 strains of gram-negative bacteria, including *E. coli, K. pneumoniae*, *P. aeruginosa*, and *A. baumannii* and treated with cefiderocol human-simulated regimen. For individual isolates treated with cefiderocol (Figure 18), significant differences in efficacy between models were observed in one *P. aeruginosa* strain PSA 1588, with growth in the standard model and killing in the iron overloaded model. Cefiderocol was active against gram negative bacteria in the presence of iron overload.

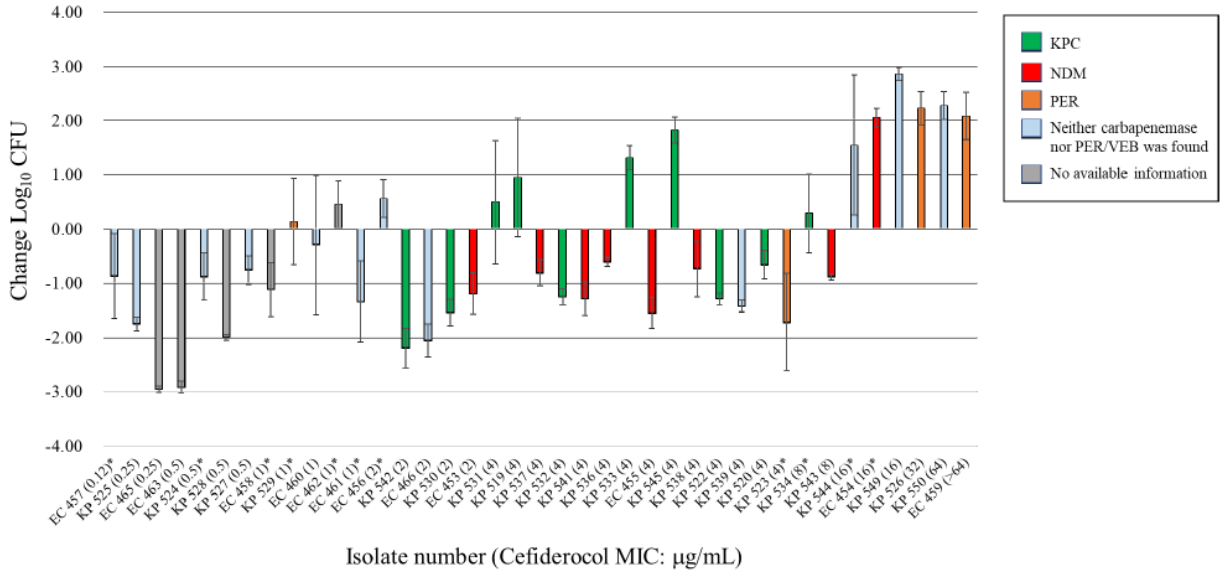
Figure 18. Efficacy of 24 Hours of a Cefiderocol Human-Simulated Regimen (HSR) (2 g q8h, 3-Hour Infusion) Against *E.coli* and *K. pneumoniae* (A), *A. baumannii* (B), and *P. aeruginosa* (C) in Standard and Iron Overloaded Murine Thigh Infection Models



Source: S-649266-EF-347-R, Figure 2.
* Isolates for which cefiderocol had a significantly different change in log10 CFU/thigh between standard and iron overloaded models
Abbreviations: CFU, colony forming unit; MIC, minimum inhibitory concentration; q8h, every 8 hours

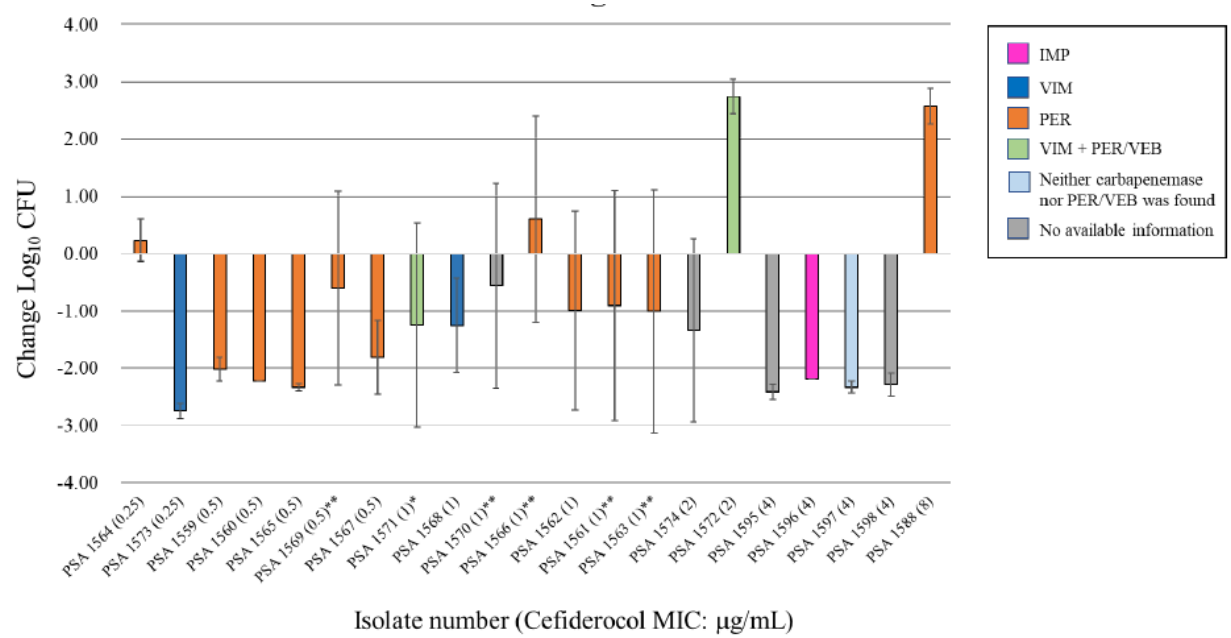
Data on molecular characterization of isolates previously tested in the murine neutropenic thigh model were included in this submission (report S-649266-EF-231-R amended). These data were also provided during labeling negotiations for the original NDA (Figure 19, Figure 20 and Figure 21).

Figure 19. Bacterial Reduction Against Each Isolate of Enterobacteriaceae in Murine Thigh Infection Models Under Humanized PK of Cefiderocol



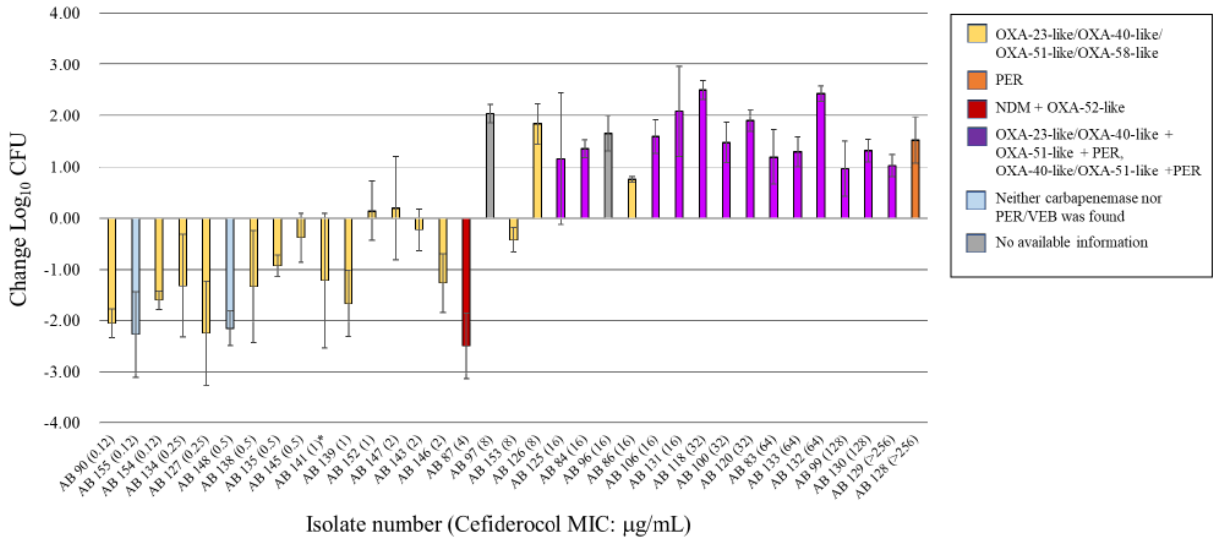
Source: Study Report S-649266-EF-231-R Appendix D.
Each * represents the number of times the isolate was repeated. All repeat data were averaged together.
EC 462 contained the cephalosporinase CMY-42 and EC 455 contained the cephalosporin CMY-2 in addition to NDM
Abbreviations: CFU, colony forming unit; MIC, minimum inhibitory concentration; PK, pharmacokinetics

Figure 20. Bacterial Reduction Against Each Isolate of *P. aeruginosa* in Murine Thigh Infection Models Under Humanized PK of Cefiderocol



Source: Study Report S-649266-EF-231-R Appendix F.
Each * represents the number of times the isolate was repeated. All repeat data were averaged together.
Abbreviations: CFU, colony forming unit; MIC, minimum inhibitory concentration; PK, pharmacokinetics

Figure 21. Bacterial Reduction Against Each Isolate of *A. baumannii* in Murine Thigh Infection Models Under Humanized PK of Cefiderocol



Source: Study Report S-649266-EF-231-R Appendix E.
Each * represents the number of times the isolate was repeated. All repeat data were averaged together.
Abbreviations: CFU, colony forming unit; MIC, minimum inhibitory concentration; PK, pharmacokinetics

The study shows that the human simulated cefiderocol dosing is active against Enterobacteriaceae, *A. baumannii*, and *P. aeruginosa* including some carbapenemase-producing isolates with cefiderocol MICs of ≤4 mcg/mL and *S. maltophilia* isolates with MICs ≤0.5 mcg/mL in the neutropenic thigh infection model. It should be noted that isolates with range of cefiderocol MIC were selected to assess the in vivo activity based on the PK-PD target attainment using the humanized dosing regimen. Discordance between in vitro and in vivo activity against metallo–β-lactamases has been reported previously (MacVane et al. 2014; Zmarlicka et al. 2015). The in vivo mouse model can overestimate the activity of the drug against bacteria containing metallo–β-lactamases as drugs without in vitro activity against metallo–β-lactamases are active in vivo. The in vivo data confirms the in vitro resistance observed in *A. baumannii* strains carrying the PER gene. There is minimum data available against other genotypes. Previous studies have shown regrowth of bacteria with increase in MIC in 3 of 15 isolates with cefiderocol MICs <8 mcg/mL with humanized dosing.

Key findings from data submitted in the original NDA include the following:

- In an immunocompetent rat pneumonia model, reduction in bacterial counts in the lungs of animals infected with *K. pneumoniae* with MICs ≤8 mcg/mL and *P. aeruginosa* with MICs ≤1mcg/mL was observed using humanized cefiderocol dose. The Applicant would like to claim activity of cefiderocol against *S. maltophilia* with MICs ≤0.5 mcg/mL and *A. baumannii* with MICs ≤2 mcg/mL in the immunocompetent rat infection model based on studies submitted in the original NDA summarized below:

Immunocompetent Rat Lung Infection Model

The activity of cefiderocol was evaluated against three *P. aeruginosa* (two MDR strain), five *A. baumannii* (two MDR strains, one OXA-23 strain), three NDM-1-producing *K. pneumoniae*, four KPC-producing *K. pneumoniae*, and two *S. maltophilia* strains in the immunocompetent rat

lung infection model [study reports 2014N197096_01, S-649266-EF-299-N, S-649266-EB-157-N and S-649266-EB-303-N]. Rats were infected via intratracheal instillation of bacteria in molten agar. The cefiderocol human plasma exposure profiles were simulated in these studies and treatment was initiated at 1-hour postinfection for mice infected with *A. baumannii* and *K. pneumoniae* and 2 hours postinfection for *P. aeruginosa*. Cefiderocol 2 g was administered intravenously thrice a day as a 1-hour or 3-hour infusion for 4 days. The bacterial burden in the lungs were measured at the EOT. These studies suggest that 3-hour infusion provides greater bacterial burden control than 1-hour infusion (Table 82). Although a >2 log reduction was observed in cefiderocol treated rats infected with *S. maltophilia*, very little growth/replication was observed in untreated control over the 96 hours of study duration (shaded cells, Table 71). Similar observations were made with some *A. baumannii* and *K. pneumoniae* strains (shaded cells, Table 82).

Table 82. Summary of in Vivo Efficacy Studies Using Immunocompetent Rat Lung Infection Model

Test Organisms	Resistance	Cefiderocol MIC (mcg/mL)	Result
P. aeruginosa ATCC 27853 (10^4 CFU/rat)	-	0.25	>3 $\log_{10}$ reduction in bacterial burden in the lungs. Activity was similar to ceftazidime.
P. aeruginosa SR27001 (10^4 CFU/rat)	MDRP (IMP-1); CAZ MIC >64 mcg/mL	1.0	3 $\log_{10}$ reduction in bacterial burden in the lungs. Activity was superior to ceftazidime.
P. aeruginosa SR24888 (10^5 CFU/rat)	MDRP (IMP-1) MEPM MIC >64 mcg/mL, colistin MIC 0.6 mcg/mL	0.25	3 $\log_{10}$ reduction in bacterial burden in the lungs. Activity was superior to meropenem and colistin.
A. baumannii 1484911 (10^6CFU/rat)	CC92; CAZ MIC >32 mcg/mL	0.25	~2 $\log_{10}$ reduction in bacterial burden in the lungs 3 -- and 1-hour infusions. Activity was superior to ceftazidime.
A. baumannii 1485176 (10^6 CFU/rat)	MDRA (CC92); CAZ and MEPM MIC ≥32mcg/mL	0.125	3 $\log_{10}$ reduction in bacterial burden in the lungs with 3- and 1-hour infusions. Activity was superior to ceftazidime. 2 untreated controls mice showed decrease in bacterial burden or no change in bacterial burden at 96 hours.
A. baumannii 1515988 (10^6 CFU/rat)	Ceftazidime resistant CAZ MIC >32 mcg/mL	0.125	≥3 $\log_{10}$ reduction in bacterial burden in the lungs with 3- and 1-hour infusions. Activity was superior to ceftazidime and similar to meropenem. 1 $\log_{10}$.growth of untreated controls at 96 hours. And no change in bacterial burden in 1 of 4 mice.
A. baumannii 1485247 (10^6 CFU/rat)	MDRA; CAZ MIC >32 mcg/mL and MEPM MIC 8 mcg/mL	2.0	3 $\log_{10}$ reduction in bacterial burden in the lungs with 3-hour infusion. Activity was superior to ceftazidime. 1 $\log_{10}$.growth of untreated controls at 96 hours.

Test Organisms	Resistance	Cefiderocol MIC (mcg/mL)	Result
A. baumannii Ab13 (10^5 CFU/rat)	MDRA, OXA-23 MEPM MIC 64 mcg/mL	0.125	2.5 log_{10} reduction in bacterial burden in the lungs. Activity was superior to meropenem
K. pneumoniae VA-384 (10^6 CFU/rat)	KPC-2 CAZ and MEPM MIC >32mcg/mL	0.25	3 log_{10} reduction with 3-hour infusion. No reduction with 1-hour infusion or meropenem. Bacterial growth in untreated controls was 0.5 log_{10} at 96 hours.
K. pneumoniae VA-361 (10^6 CFU/rat)	KPC-2 CAZ MIC >32 mcg/mL and MEPM MIC 16 mcg/mL	0.25	3 log_{10} reduction with 3-hour infusion. 1 log_{10} reduction with 1-hour infusion. No reduction with ceftazidime
K. pneumoniae K12 (10^6 CFU/rat)	NDM-1; CAZ and MEPM MIC >32mcg/mL	0.25	3 log_{10} reduction with 3 hour and 1-hour infusion. No reduction with ceftazidime
K. pneumoniae NCTC 13443 (10^6 CFU/rat)	NDM-1; CAZ and MEPM MIC >32mcg/mL	2.0	≥3 log_{10} reduction with 3-hour infusion. 1 log_{10} reduction with 1-hour infusion. No reduction with meropenem
K. pneumoniae VA-391 (10^6 CFU/rat)	KPC-3 CAZ MIC >32 mcg/mL and MEPM 16 mcg/mL	≤0.125	>3 log_{10} reduction with 3-hour infusion and 2 log_{10} reduction with 1-hour infusion. No reduction with ceftazidime. Bacterial growth in untreated controls was minimal at 96 hours.
K. pneumoniae OMA3 (10^5 CFU/rat)	NDM-1, CTX-M-15, carbapenem resistant MEPM MIC 64 mcg/mL	1.0	~2 log_{10} reduction with 1-hour infusion. Activity superior to meropenem and colistin
K. pneumoniae SR08651 (10^5 CFU/rat)	Carbapenem resistant, KPC, SHV MEPM MIC >64 mcg/mL	2.0	~2 log_{10} reduction with 1-hour infusion. Activity superior to meropenem and colistin
S. maltophilia 1373179 (6.6×10^5 CFU/rat)	-	-	Not interpretable; no increase in bacterial burden in the lungs of control rats.
S. maltophilia 1444466 (2.6×10^6 CFU/rat	MEPM MIC =64 mcg/mL	0.06	>2 log_{10} reduction observed with 3-hour infusion. No reduction with meropenem. However, <1 log_{10} increase in CFU/untreated controls mice was observed at 96 hours compared to start of treatment in 3 of 4 mice with data.

Test Organisms	Resistance	Cefiderocol MIC (mcg/mL)	Result
S. maltophilia 1476057 (3.3×10^6 CFU/rat	MEPM MIC =128 mcg/mL	0.5	>2 $\log_{10}$ reduction observed with 3-hour infusion. No reduction with meropenem. However, only 0.5$\log_{10}$ increase in CFU/untreated controls mice was observed at 96 hours compared to start of treatment.

Study Reports 2014N197096_01, S-649266-EF-299-N, S-649266-EB-157-N and S-649266-EB-303-N
Abbreviations: CAZ, ceftazidime; CFU, colony-forming unit; CTX-M, cefotaximase; IMP, imipenemase metallo-β-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; NDM-1, New Delhi metallo-beta-lactamase 1; MDRA, multidrug resistant *A. baumannii*; MDRP, multidrug resistant *P. aeruginosa*; MEPM, meropenem; MIC, minimum inhibitory concentration; SHV, sulfhydryl variable

It appears that some strains of *A. baumannii* and *K. pneumoniae* may not be fit for use in this model. Variability was observed in the 96-hour saline untreated controls, making it difficult to interpret the log reduction attributable to cefiderocol treatment. The 3-hour infusion of cefiderocol appears to have an effect on immunocompetent rats infected with *A. baumannii* strains. Several studies that used *S. maltophilia* to infect the lungs of mice or rats did not document significant increases in bacterial numbers postinoculation; rather, bacterial burden declined postinoculation (Di Bonaventura et al. 2010; Rouf et al. 2011). The role of the rat lung infection model for determination of activity against *S. maltophilia* is unclear:

- In an immunocompetent murine urinary tract infection model, cefiderocol reduced bacterial counts in the kidneys of mice infected with *E. coli*, *K. pneumoniae*, and *P. aeruginosa* isolates with MICs ≤1 mcg/mL.
- In an immunocompromised murine systemic infection model, cefiderocol increased survival in mice infected with *E. cloacae*, *S. maltophilia*, and *B. cepacia* isolates with MICs ≤0.5 mcg/mL compared to untreated mice. In an immunocompetent murine systemic infection model, cefiderocol increased survival in mice infected with *S. marcescens* and *P. aeruginosa* isolates with MICs ≤1 mcg/mL compared to untreated mice.

Clinical Study

Additional microbiological assessments conducted for the breakpoint determination include an assessment at TOC by baseline pathogen and cefiderocol MIC (Table 83).

Table 83. Summary of Clinical Cure and Microbiological Eradication at Test-of-Cure (TOC) Per Baseline Pathogen and Minimum Inhibitory Concentration Values in the Modified Intention-to-Treat Population

	Cefiderocol N=145		
Baseline Pathogen	**Cefiderocol MIC (mcg/mL)**	**Clinical Cure at TOC n/N' (%)**	**Microbiological Eradication at TOC n/N'(%)**
K. pneumoniae (n=48)	≤0.03	5/8 (62.5)	3/8 (37.5)
	0.06	1/3 (33.3)	1/3 (33.3)
	0.12	1/1 (100.0)	1/1 (100.0)
	0.25	3/6 (50.0)	3/6 (50.0)
	0.5	5/9 (55.6)	4/9 (44.4)
	1	9/9 (100.0)	7/9 (77.8)
	2	6/9 (66.7)	3/9 (33.3)
	4	1/2 (50.0)	0/2
MIC range	≤0.03 to 4	31/47(66)	22/47 (46.8)
MIC_{90}	2	-	-
E. coli (n=19)	≤0.03	4/5 (80.0)	3/5 (60.0)
	0.06	3/4 (75.0)	2/4 (50.0)
	0.12	2/2 (100.0)	2/2 (100.0)
	0.25	0/2	0/2
	0.5	1/4 (25.0)	1/4 (25.0)
	1	2/2 (100.0)	2/2 (100.0)
MIC range	≤0.03 to 1	12/19 (63.2)	10/19 (52.6)
MIC_{90}	0.5		
S. marcescens (n=8)	≤0.03	1/1 (100.0)	1/1 (100.0)
	0.06	0/1	0/1
	0.12	0/1	0/1
	0.25	4/4 (100.0)	3/4 (75.0)
	0.5	0/1	0/1
MIC range	≤0.03 to 0.5	5/8 (62.5)	4/8 (50.0)
MIC_{90}	0.25		
E. cloacae (n=7)	0.06	1/1 (100.0)	1/1 (100.0)
	0.5	2/3 (66.7)	2/3 (66.7)
	1	1/2 (50.0)	0/2
	2	1/1 (100.0)	1/1 (100.0)
MIC range	0.06 to 2	5/7 (71.4)	4/7 (57.1)
MIC_{90}	-		
E. aerogenes (n=4)	0.06	0/3	0/3
	1	1/1 (100.0)	1/1 (100.0)
MIC range	0.06 to 1	1/4 (25.0)	1/4 (25.0)
MIC_{90}	-		
M. catarrhalis (n=2)	≤0.03	1/1 (100.0)	0/1
	0.25	1/1 (100.0)	1/1 (100.0)
MIC range	≤0.03 to 0.25	2/2 (100.0)	1/2 (50.0)
MIC_{90}	-		
P. mirabilis (n=2)	≤0.03	1/2 (50.0)	1/2 (50.0)
K. oxycota (n=2)	≤0.03	1/1 (100.0)	1/1 (100.0)
	0.06	0/1	0/1
MIC range	≤0.03 to 0.06	1/2 (50.0)	1/2 (50.0)
MIC_{90}	-		

	Cefiderocol N=145		
Baseline Pathogen	**Cefiderocol MIC (mcg/mL)**	**Clinical Cure at TOC n/N' (%)**	**Microbiological Eradication at TOC n/N'(%)**
C. koseri (n=1)	0.5	1/1 (100.0)	1/1 (100.0)
C. fruendii (n=1)	0.5	0/1	0/1
M. morganii (n=1)	0.06	0/1	0/1
P. aeruginosa (n=24)	≤0.03	1/1 (100.0)	1/1 (100.0)
	0.06	2/3 (66.7)	2/3 (66.7)
	0.12	4/7 (57.1)	1/7 (14.3)
	0.25	5/7 (71.4)	2/7 (28.6)
	0.5	2/4 (50.0)	2/4 (50.0)
	1	2/2 (100.0)	1/2 (50.0)
MIC range	≤0.03 to 1	16/24 (66.7)	9/24 (37.5)
MIC_{90}	0.5	-	-
A. baumannii (n=23)	≤0.03	1/1 (100.0)	1/1 (100.0)
	0.12	1/4 (25.0)	1/4 (25.0)
	0.25	2/4 (50.0)	2/4 (50.0)
	0.5	4/6 (66.7)	2/6 (33.3)
	1	2/2 (100.0)	1/2 (50.0)
	2	1/3 (33.3)	1/3 (33.3)
	4	0/1	0/1
	>64	1/1 (100.0)	1/1 (100.0)
MIC range	≤0.03 to >64	12/22 (54.5)	9/22 (40.9)
MIC_{90}	2		
A. nososcomialis (n=2)	0.25	1/2 (50.0)	1/2 (50.0)
A. pitti (n=1)	0.5	1/1 (100.0)	1/1 (100.0)
S. maltophilia (n=1)	0.25	1/1 (100.0)	1/1 (100.0)
B. cepacia (n=1)	≤0.03	1/1 (100.0)	1/1 (100.0)

Source: Table 14.2.8.1.2 and Table 14.2.9.1.2 Study Report 1615R2132 Amendment 1.
Percentage is calculated using N'
Abbreviations: N, total number of subjects in mITT population; N', the number of baseline pathogens at the given MIC level; n, the number (%) of microbiological eradication at Test of Cure for the baseline pathogen at the given MIC level; MIC_{90}, minimum inh bitory concentration required to inh bit 90% of isolates; MIC, minimum inhibitory concentration; mITT, modified-intention-to-treat

The ACM by baseline resistant determinants in isolates that were meropenem resistant is shown in Table 84. Multiplex PCR with some sequencing was carried out using meropenem-resistant isolates collected in the APEKS-NP study. Enterobacterales isolates were screened for the presence of *bla* encoding ESBLs (TEM, SHV, five subtypes of CTX-Ms including CTX-M-1-group, CTX-M-2-group, CTX-M-8-group, CTX-M-9-group, and CTX-M-25-group, VEB, PER, GES), plasmid-encoded AmpC β-lactamases (ACC, ACT, CMY, DHA, FOX, MIR, MOX), and carbapenemases (KPC, OXA-48-like, IMP, VIM, NDM, SPM, and GIM). *P. aeruginosa* isolates were screened for the presence of *bla* encoding ESBLs, plasmid encoded AmpC β-lactamases and the chromosomally-encoded pseudomonal AmpC β-lactamase (PDC), and carbapenemases (KPC, OXA-24/40-like, IMP, VIM, NDM, SPM, and GIM). *Acinetobacter baumannii* isolates were screened for the presence of *bla* encoding ESBLs and carbapenemases (OXA-23-like, OXA-24/40-like, OXA-48-like, OXA-58-like, KPC, IMP, VIM, NDM, and SPM). The porin genes found in *K. pneumoniae* (*ompK35* and *ompK36*), *E. cloacae* (*ompF* and *ompC*), *P. aeruginosa* (*oprD*) and *A. baumannii* (*oprD* and *carO*) were amplified and sequenced. *P. aeruginosa mexB, mexD, mexF*, and *mexY* transcript (mRNA) levels were normalized to transcript levels of the ribosomal gene *rpsL*

and compared to transcript levels observed for the reference strain PAO 1. *A. baumannii oprD* and *carO* transcript levels were normalized to 16S RNA and compared to transcript levels observed for the reference strain ATCC 19606.

Table 84. Mortality in Meropenem Resistant Isolates by Baseline Resistant Determinants

Time Point Subgroup	Cefiderocol (N= 145) n/N' (%)	Meropenem (N= 147) n/N' (%)	I
Day 14 ACM			
OXA-48 Producing	1/4 (25.0)	0/1 (0.0)	
OXA other than OXA-48 Producing	4/16 (25.0)	5/17 (29.4)	
NDM-producing	0/6 (0.0)	0/1 (0.0)	
Metallo Beta Lactamase-producing	0/8 (0.0)	0/3 (0.0)	
Porin Channel Mutated	2/19 (10.5)	2/8 (25.0)	
ESBL Producing Overall	6/45 (13.3)	6/42 (14.3)	
ESBL Producing Enterobacteriaceae	5/36 (13.9)	3/25 (12.0)	
ESBL Producing Acinetobacter	2/10 (20.0)	3/16 (18.8)	
ESBL Producing Pseudomonas	0/1 (0.0)	1/3 (33.3)	
Day 28 ACM			
OXA-48 Producing	1/4 (25.0)	0/1 (0.0)	
OXA other than OXA-48 Producing	4/16 (25.0)	7/17 (41.2)	
NDM-producing	2/6 (33.3)	0/1 (0.0)	
Metallo Beta Lactamase-producing	2/8 (25.0)	1/3 (33.3)	
Porin Channel Mutated	2/19 (10.5)	3/8 (37.5)	
ESBL Producing Overall	11/45 (24.4)	11/42 (26.2)	
ESBL Producing Enterobacteriaceae	9/36 (25.0)	6/25 (24.0)	
ESBL Producing Acinetobacter	3/10 (30.0)	5/16 (31.3)	
ESBL Producing Pseudomonas	0/1 (0.0)	1/3 (33.3)	
EOS ACM			
OXA-48 Producing	3/4 (75.0)	0/1 (0.0)	
OXA other than OXA-48 Producing	5/16 (31.3)	8/17 (47.1)	
NDM-producing	3/6 (50.0)	0/1 (0.0)	
Metallo Beta Lactamase-producing	3/8 (37.5)	1/3 (33.3)	
Porin Channel Mutated	6/19 (31.6)	3/8 (37.5)	
ESBL Producing Overall	16/45 (35.6)	13/42 (31.0)	
ESBL Producing Enterobacteriaceae	13/36 (36.1)	7/25 (28.0)	
ESBL Producing Acinetobacter	4/10 (40.0)	6/16 (37.5)	
ESBL Producing Pseudomonas	1/1 (100.0)	1/3 (33.3)	

Source: Table 2.20.3 in ISS/ISE.
[a] Treatment difference (cefiderocol minus meropenem) is the estimate of the difference in the all-cause mortality rate at each timepoint between the 2 treatment arms.
Abbreviations: ACM, all-cause mortality; EOS, end of study; N', number of subjects with each baseline resistance mechanism and known survival outcome at each time point

19. Other Drug Development Considerations Additional Information

Not applicable.

20. Data Integrity-R Consults (OSI, Other Inspections)

Not applicable.

21. Labeling Summary of Considerations and Key Additional Information

21.1. Prescribing Information

Key modifications to the proposed labeling submitted on March 27, 2020, are described in Table 85. Consultations were obtained from the Office of Prescription Drug Promotion (OPDP) and the Division of Cardiorenal Products (DCRP) who provided recommendations on CRRT dosing information.

Table 85. Summary of Key Labeling Modifications

Section	Applicant's Modification Proposed in Labeling	Additions/Modifications/Conclusion/Rationale
Indications and Usage (1.1)	Applicant proposed removal of the limited use statement for the treatment of cUTI	Division agreed; efficacy has now been replicated in a second study, the NI margin met the more conservative and traditional 10% threshold and the cefiderocol safety database has increased.
Indications and Usage (1.2)	Applicant proposed following pathogens for the HABP/VABP indication: *A. baumannii complex,* (b) (6) *E. coli, E. cloacae complex,* (b) (6) *K. pneumoniae,* (b) (6) *P. aeruginosa, S. marcescens* (b) (6)	Division proposed removal of pathogens (b) (6) *A. baumannii complex* retained after discussions with Applicant. Agreement; justification for inclusion of *A. baumannii complex* is noted in section 6.4.3
Dosage and Administration (2.1 and 2.2)	Applicant proposed CRRT dosage recommendations and Division proposed revisions.	Division proposed revisions to the effluent flow rate based dosage in patients receiving CRRT. Division also proposed removal of ESRD from labeling as new terminology has been proposed. Agreement; the in vitro CRRT study and the observed PK data from patients who underwent CRRT in Phase 3 studies supported the effluent flow rate-based CRRT dose regimens (see section 8.1)

Section	Applicant's Modification Proposed in Labeling	Additions/Modifications/Conclusion/Rationale
5. Warnings and Precautions (5.1)	(b) (4)	Division did not accept this change as the description is relevant to the CREDIBLE-CR trial; *A. baumannii "complex"* added for consistency of the terminology and to include deaths due to *A. nosocomialis.*
		(b) (4)
6. Adverse Reactions (6.1)		(b) (4)
6. Adverse Reactions (6.1)	Applicant proposed the number of patients in the FETROJA and meropenem groups that had serious ARs and ARs leading to discontinuation.	Division added ARs leading to death and that the most common ARs leading to discontinuation in both treatment groups were elevated liver tests . Applicant agreed.
	(b) (4)	Division proposed a different incidence rate and additional adverse reactions as follows: anemia, hypokalemia, hypomagnesemia, and atrial fibrillation as selected ARs occurring in ≥4% (Table 5) and occurring in <4%: thrombo-cytopenia, thrombocytosis, bradycardia, myocardial infarction, atrial flutter, intestinal ischemia, abdominal pain, gastritis, chest pain, cholecystitis, cholelithiasis, fungal urinary tract infection, blood creatinine increased, prolonged prothrombin time, PT-INR, aPTT, hypocalcemia, hyponatremia, hyperkalemia, cerebrovascular accident, seizure, dizziness, paresthesia, headache, bronchospasm, stridor, dermatitis. *C.difficile* infection (b) (4) Elevations in liver tests and diarrhea were retained in Table 5. Applicant did not agree with any of the additions. Division agreed to remove anemia, bradycardia, gastritis, chest pain, fungal urinary tract infection, blood creatinine increased, cerebrovascular accident, headache, bronchospasm, stridor, dermatitis (see section 7.6.5 for rationale). Upon further review, blood creatinine increased was changed to acute kidney injury. Applicant agreed with retaining thrombocytosis, myocardial infarction, atrial flutter, abdominal pain, cholecystitis,

Section	Applicant's Modification Proposed in Labeling	Additions/Modifications/Conclusion/Rationale
		cholestatis, prolonged prothrombin time, PT-INR, aPTT, hypocalcemia, hyperkalemia and submitted a justification for removing thrombocytopenia, intestinal ischemia, hypomagnesemia, hyponatremia, dizziness, and acute kidney injury. Division agreed to remove intestinal ischemia, hyponatremia, paresthesia, and dizziness but retain the other ARs. (b) (4) Appliant proposed to change acute kidney injury to acute interstitial nephritis. Division agreed.
8. Use in Specific Populations (8.5)		Division proposed a description of the differences in safety and efficacy (incidence of ARs, mortality, and clinical cure) based on age group. Applicant agreed.
8. Use in Specific Populations (8.6) and 12. Clinical Pharmacology, (12.3)		Division proposed a adding labeling language on patients receiving CRRT to subsections 8.6 and 12.3. Applicant agreed.

Section	Applicant's Modification Proposed in Labeling	Additions/Modifications/Conclusion/Rationale
12. Clinical Pharmacology (12.4)	Applicant proposed removal of mutations of transcriptional regulators that impact expression of efflux pump and added maintenance of in vitro activity of cefiderocol against P. aeruginosa in the presence of efflux pump up-regulation (MexAB-OprM, MexCD-OprJ, MexEF-OprN, and MexXY), (b) (4)	Division agreed to the removal of mutations of transcriptional regulators that impact expression of efflux pump and addition of maintenance of in vitro activity of cefiderocol against P. aeruginosa in the presence of efflux pump up-regulation (MexAB-OprM, MexCD-OprJ, MexEF-OprN, and MexXY (b) (4)
	Applicant proposed several pathogens for the first and second list.	Applicant agreed to revisions to the pathogen in the first list. *A. baumanni complex* was retained in the first list based on additional data and further review by the division (see Section 6.4.3). *B. cepacia complex, C. koseri, K. aerogenes, K.oxytoca, and S. maltophilia* were moved to the second list. (b) (4) *was removed from the second list (see section 18).*
Clinical Studies (14.1)	Applicant proposed tables 11 and 12 (ACM and clinical cure by pathogen, respectively) based on susceptibility to both FETROJA and meropenem. For tables 10 and 11, the Applicant proposed the following pathogens: *K.pneumoniae, P. aeruginosa, Acinetobacter baumannii* complex and *Escherichia coli*	Division proposed modification of tables 11 and 12 (ACM and clinical cure by pathogen, respectively) based on susceptibility to meropene (b) (4) and added a comparative analysis of clinical outcomes in all 51 patients with *A. baumannii complex* in both treatment groups. For tables 10 and 11, the division added the following pathogens to the applicant's proposal: Other Enterobacterales (Includes *Enterobacter cloacae* complex (*E. cloacae*, *E. asburiae and E. kobei*) and *Serratia marcescens).* Applicant agreed.

Abbreviations: ACM, all-cause mortality; aPTT, activated partial thromboplastin time; AR, adverse reaction; CRRT, continuous renal replacement therapy; ESRD, end stage renal disease; MIC, minimum inhibitory concentration; PK, pharmacokinetic; PT, prothrombin time; PT-INR, prothrombin time-international normalized ratio

22. Postmarketing Requirements and Commitments

The following pediatric PMRs were proposed at the time of approval of cefiderocol for the HABP/VABP indication.

Conduct an open-label randomized multicenter, active-controlled trial to evaluate the pharmacokinetics, safety and tolerability of Fetroja (cefiderocol) in children from 3 months to less than 18 years of age with cUTI and HABP/VABP. The dose for this study for children 3

months to less than 18 years of age will be determined by the data from a single-dose, non-comparative study assessing the pharmacokinetics of FETROJA (cefiderocol) in pediatric patients from 3 months to less than 12 years of age with suspected or confirmed gram-negative infections.

Final Protocol Submission: 01/2021
Study Completion: 12/2023
Final Report Submission: 04/2024

Conduct an open-label, single arm non-comparative study to evaluate the pharmacokinetics, safety and tolerability of multiple doses of FETROJA (cefiderocol) in children from birth to less than 3 months of age with suspected or confirmed gram-negative infections. The dose for this study will be determined by the data from a single-dose, non-comparative study assessing the pharmacokinetics of FETROJA (cefiderocol) in pediatric patients from birth to less than 3 months of age with suspected or confirmed gram-negative infections.

Final Protocol Submission: 06/2022
Study Completion: 08/2024
Final Report Submission: 01/2025

(b) (4)

23. Financial Disclosure

Table 86. Covered Clinical Studies: APEKS-NP Trial

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of principal investigators identified: 116		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

An attachment to form 3455 was submitted for two subinvestigators for whom a financial disclosure statement could not be obtained. (b) (6) acted as a subinvestigator for the principal investigator (b) (6) acted as a subinvestigator for the principal investigator (b) (6) . During study close out activities, it was discovered that a financial disclosure statement from this subinvestigators could not be found. The study team had reached out to these subinvestigators to obtain a financial disclosure statement post hoc but have been unsuccessful. Therefore, it cannot be confirmed if these subinvestigators had financial interests or arrangements to disclose. In lieu of this confirmation, a form FDA 3455 has been completed, without any boxes checked for both of these subinvestigators. Shionogi confirms that they have not entered into a financial arrangement with these subinvestigators whereby the value of the compensation for conducting the study could be influenced by the outcome of the study. The principal investigators of the sites have also attested that they have entered into no such arrangement. Shionogi also confirms that no payments outside of those related to the APEKS-NP study have been made. This issue is unlikely to alter the results of the trial.

24. References

Alp, E, M Güven, O Yildiz, B Aygen, A Voss, and M Doganay, 2004, Incidence, risk factors and mortality of nosocomial pneumonia in intensive care units: a prospective study, Ann Clin Microbiol Antimicrob, 3:17.

Chen, Z, P Venkat, D Seyfried, M Chopp, T Yan, and J Chen, 2017, Brain-Heart Interaction: Cardiac Complications After Stroke, Circ Res, 121(4):451-468.

Di Bonaventura, G, A Pompilio, R Zappacosta, F Petrucci, E Fiscarelli, C Rossi, and R Piccolomini, 2010, Role of excessive inflammatory response to Stenotrophomonas maltophilia lung infection in DBA/2 mice and implications for cystic fibrosis, Infect Immun, 78(6):2466-2476.

Division of Anti-Infectives, 2019, Multi-Disciplinary Review and Evaluation: NDA 209445, Fetroja (cefiderocol), Food and Drug Administration.

Guidance for Industry, Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment (June 2020)

Kawai, A, CL McElheny, A Iovleva, EG Kline, N Sluis-Cremer, RK Shields, and Y Doi, 2020, Structural Basis of Reduced Susceptibility to Ceftazidime-Avibactam and Cefiderocol in *Enterobacter cloacae* Due to AmpC R2 Loop Deletion, Antimicrobial Agents and Chemotherapy, 64(7):e00198-00120.

Kelly, J, A Rudd, R Lewis, and BJ Hunt, 2001, Venous thromboembolism after acute stroke, Stroke, 32(1):262-267.

MacVane, SH, JL Crandon, WW Nichols, and DP Nicolau, 2014, Unexpected in vivo activity of ceftazidime alone and in combination with avibactam against New Delhi metallo-β-lactamase-producing Enterobacteriaceae in a murine thigh infection model, Antimicrobial agents and chemotherapy, 58(11):7007-7009.

Muskett, H, J Shahin, G Eyres, S Harvey, K Rowan, and D Harrison, 2011, Risk factors for invasive fungal disease in critically ill adult patients: a systematic review, Crit Care, 15(6):R287.

Pistolesi, V, S Morabito, F Di Mario, G Regolisti, C Cantarelli, and E Fiaccadori, 2019, A Guide to Understanding Antimicrobial Drug Dosing in Critically Ill Patients on Renal Replacement Therapy, Antimicrobial Agents and Chemotherapy, 63(8):e00583-00519.

Rouf, R, SM Karaba, J Dao, and NP Cianciotto, 2011, Stenotrophomonas maltophilia strains replicate and persist in the murine lung, but to significantly different degrees, Microbiology (Reading), 157(Pt 7):2133-2142.

Schalk, IJ, M Hannauer, and A Braud, 2011, New roles for bacterial siderophores in metal transport and tolerance, Environ Microbiol, 13(11):2844-2854.

Shields, RK, A Iovleva, EG Kline, A Kawai, CL McElheny, and Y Doi, 2020, Clinical evolution of AmpC-mediated ceftazidime-avibactam and cefiderocol resistance in Enterobacter cloacae complex following exposure to cefepime, Clin Infect Dis.

Spellberg, B and RA Bonomo, 2014, The deadly impact of extreme drug resistance in Acinetobacter baumannii, Critical care medicine, 42(5):1289-1291.

Zmarlicka, MT, MD Nailor, and DP Nicolau, 2015, Impact of the New Delhi metallo-beta-lactamase on beta-lactam antibiotics, Infection and drug resistance, 8:297-309.

25. Review Team Acknowledgements

Table 87. Reviewers of Interdisciplinary Assessment

Role	Name(s)
Regulatory Project Manager	J. Christopher Davi, MS
Chief, Project Management Staff	Maureen Dillon-Parker, MS, RAC
Clinical Pharmacology Reviewer(s)	Xiahou (Tracey) Wei, PhD
Clinical Pharmacology Team Leader(s)	Seong Jang, PhD
Pharmacometrics Reviewer(s)	Hezhen Wang, Ph.D.
Pharmacometrics Team Leader(s)	Justin Earp, Ph.D.
Clinical Reviewer	Shabnam Naseer, DO, MS
Clinical Team Leader/CDTL	Edward Weinstein, MD, PhD
Statistical Reviewer	Edward Bein, PhD
Statistical Team Leader	Karen Higgins, ScD
Clinical Microbiology Team Leader	Avery Goodwin, PhD
Clinical Microbiology Reviewer	Kalavati Suvarna, PhD
Associate Director for Labeling	Abimbola Adebowale, PhD
Division Director (DAI)/Signatory Authority	Sumathi Nambiar, MD, MPH

Table 88. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Ramesh Gopalaswamy, PhD
OPDP	David Foss, PharmD, BCPS, RAC
OSI	Cheryl A. Grandinetti, PharmD

OPQ, Office of Pharmaceutical Quality
OPDP, Office of Prescription Drug Promotion
OSI, Office of Scientific Investigations
ADL, Associate Director for Labeling

Table 89. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Cross-Disciplinary	J. Christopher Davi, MS	ORO/DRO-ID/DAI	12.0 ☒ Authored ☐ Approved
Project Manager	**Signature:** Joseph C. Davi -S Digitally signed by Joseph C. Davi -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Joseph C. Davi -S, 0.9.2342.19200300.100.1.1=1300232781 Date: 2020.09.25 12:00:49 -04'00'		
Chief, Regulatory Project Management Staff	Maureen Dillon-Parker, MS, RAC	ORO/DRO-ID/DAI	12.0 ☐ Authored ☒ Approved
Supervisor	**Signature:** Maureen P. Dillon Parker -S Digitally signed by Maureen P. Dillon Parker -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300042254, cn=Maureen P. Dillon Parker -S Date: 2020.09.25 12:21:51 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Xiaohui (Tracey) Wei, PhD	OCP/DIDP	5, 6.1, 8.1, 8.2, 14.1, 14.2 ☒ Authored ☐ Approved
Reviewer	**Signature:** Xiaohui Wei -S Digitally signed by Xiaohui Wei -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xiaohui Wei -S, 0.9.2342.19200300.100.1.1=2001735821 Date: 2020.09.25 09:24:21 -04'00'		
Clinical Pharmacology	Seong Jang, PhD	OCP/DIDP	5, 6.1, 8.1, 8.2, 14 ☐ Authored ☒ Approved
Team Leader	**Signature:** Seong H. Jang -S Digitally signed by Seong H. Jang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Seong H. Jang -S, 0.9.2342.19200300.100.1.1=1300193054 Date: 2020.09.25 09:29:01 -04'00'		
Pharmacometrics	Hezhen Wang, PhD	OCP/DPM	14.3 ☒ Authored ☐ Approved
Reviewer	**Signature:** Hezhen Wang -S (Affiliate) Digitally signed by Hezhen Wang -S (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002094069, cn=Hezhen Wang -S (Affiliate) Date: 2020.09.25 09:15:06 -04'00'		
Pharmacometrics	Justin Earp, PhD	OCP/DPM	14.3 ☐ Authored ☒ Approved
Team Leader	**Signature:** Justin C. Earp -S Digitally signed by Justin C. Earp -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Justin C. Earp -S, 0.9.2342.19200300.100.1.1=1300436664 Date: 2020.09.24 16:16:42 -04'00'		
Clinical	Shabnam Naseer, DO, MS	OID/DAI	2, 3, 4, 6.4.1, 6.4.3, 7, 8.3, 10, 17, 20, 21, 22, 23, 24 ☒ Authored ☐ Approved
Reviewer	**Signature:** Shabnam N. Naseer -S Digitally signed by Shabnam N. Naseer -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002304111, cn=Shabnam N. Naseer -S Date: 2020.09.25 09:07:37 -04'00'		
Clinical	Edward Weinstein, MD, PhD	OID/DAI	1, 2, 11 (Authored) 1-25 (Approved) ☒ Authored ☒ Approved
Cross-Disciplinary Team Lead	**Signature:** *{See appended electronic signature page}*		
Statistical	Edward Bein, PhD	OB/DBIV	6.2, 6.3, 6.4.2, 15, 16 ☒ Authored ☐ Approved
Reviewer	**Signature:** Edward D. Bein -S Digitally signed by Edward D. Bein -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Edward D. Bein -S, 0.9.2342.19200300.100.1.1=2002192594 Date: 2020.09.25 09:35:24 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Karen Higgins, ScD	OB/DBIV	6.2, 6.3,6.4.2, 15, 16 ☐ Authored ☒ Approved
Team Leader	**Signature:** Karen M. Higgins -S Digitally signed by Karen M. Higgins -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300117310, cn=Karen M. Higgins -S Date: 2020.09.24 16:14:10 -04'00'		
Clinical Microbiology	Kalavati Suvarna, PhD	OID/DAI	5.1, 6.4.3,6.4.4,7.7.3,18, 22 ☒ Authored ☐ Approved
Reviewer	**Signature:** Kalavati C. Suvarna -S Digitally signed by Kalavati C. Suvarna -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300171764, cn=Kalavati C. Suvarna -S Date: 2020.09.25 09:05:22 -04'00'		
Clinical Microbiology	Avery Goodwin, PhD	OID/DAI	5.1, 6.4.3,6.4.4,7.7.3,18, 22 ☐ Authored ☒ Approved
Team Leader	**Signature:** Avery C. Goodwin -S Digitally signed by Avery C. Goodwin -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300211785, cn=Avery C. Goodwin -S Date: 2020.09.24 16:59:52 -04'00'		
Associate Director for Labeling	Abimbola Adebowale, PhD	OID/DAI	21 ☐ Authored ☒ Approved
	Signature: Abimbola O. Adebowale -S Digitally signed by Abimbola O. Adebowale -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300141826, cn=Abimbola O. Adebowale -S Date: 2020.09.24 16:40:21 -04'00'		
Division Director	Sumathi Nambiar, MD, MPH	OID/DAI	Section I ☒ Authored ☒ Approved
	Signature: *{See Appended Electronic Signature Page}*		

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

EDWARD A WEINSTEIN
09/25/2020 02:26:03 PM

SUMATHI NAMBIAR
09/25/2020 05:23:29 PM