CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206494Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

Product Quality Microbiology Review

27 January 2015

NDA: 206-494/N-000

Drug Product Name
Proprietary: Avycaz™
Non-proprietary: ceftazidime-avibactam for injection

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
25 June 2014	25 June 2014	na	08 July 2014
18 August 2014	18 August 2014	na	na

Submission History (for 2nd Reviews or higher): NA

Applicant/Sponsor
Name: Cerexa, Inc.
Address: 2100 Franklin St., Suite 900
Oakland, CA 94612
Representative: Kristina Haeckl, RAC
Executive Director, Regulatory Affairs,
Telephone: 510-285-9482

Name of Reviewer: Robert J. Mello, Ph.D.

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original NDA

2. SUBMISSION PROVIDES FOR: Marketing Authorization

3. MANUFACTURING SITE: (drug product)

GlaxoSmithKline Manufacturing S.p.A.
Via Alessandro
Fleming 2 Verona
Verona 37135
Italy
(DUNS: 338773877)
(FEI: 3002807084)

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Injection, Intravenous, 2.5g (2.0g Ceftazidime + 0.5g Avibactam) packaged as a sterile powder in a 20 mL, clear, Type I glass vial having a (b) (4) rubber stopper (b) (4) and sealed with an aluminum flip-off overseal.

5. METHOD(S) OF STERILIZATION: (b) (4) powder filling of the drug product.

6. PHARMACOLOGICAL CATEGORY: anti-infective.

B. SUPPORTING/RELATED DOCUMENTS:

- The following IND applications were cross-referenced by the Applicant, Cerexa (a wholly owned subsidiary of Forest Laboratories, Inc.):
  - IND 101,307 (ceftazidime/avibactam [CAZ-AVI]) sponsored by Cerexa
  - IND (b) (4)
- Letter of Authorization (from (b) (4)) dated 26 January 2014, authorizing review of DMF (b) (4)
- Letter of Authorization (from (b) (4)) dated 10 February 2014, authorizing review of DMF (b) (4).
- Microbiology review of DMF (b) (4) dated 10 October 2014 ((b) (4)).

C. REMARKS: The ceftazidime pentahydrate plus ceftazidime pentahydrate/sodium carbonate blend (i.e., Ceftazidime for Injection) is an approved drug product (FORTAZ, NDA 50-578 approved July 1985). The sterile FORTAZ drug substance is manufactured at (b) (4). This manufacturing process and associated (b) (4) process validations have been previously reviewed and approved by microbiology in a series of previously approved NDA

supplements related to the drug substance [redacted] and the drug product (at the Verona, Italy site).

- Microbiology Review (V. Pawar) dated 05/24/2004 for NDA 50-578/SCM-047 (Ceftazidime for Injection) for the addition of the GSK Verona, Italy site (drug product). [redacted] process validations were reviewed and approved.
- Microbiology Review (A. Lolas) dated 10/03/2005 for NDA 50-578/SCS-049 (Ceftazidime for Injection) for manufacturing changes for the drug product at the GSK Verona, Italy site (drug product). [redacted] process validations were reviewed and approved.
- Microbiology Review (B. Riley) dated 03/15/2007 for NDA 50-578/SCP-052 (Ceftazidime for Injection) for the change in the [redacted] process and the container closure for the sterile drug substance the [redacted] site (drug substance). [redacted] process validations were reviewed and approved.
- Microbiology Review (J. Metcalfe) dated 07/15/2009 for NDA 50-578/SCS-056 (Fortaz, ceftazidime) for the addition of a [redacted] at the GSK [redacted] site (drug substance). Process validations were reviewed and approved.
- Microbiology Review (S. Donald) dated 08/02/2012 for NDA 50-558/S-071 (Cefuroxime injection, bundled supplement with NDA 50-578/S-058, Ceftazidime for Injection) for the addition of [redacted] for the drug product at the GSK Verona, Italy site (drug product).
- Microbiology Review (J. Cole) dated 05/13/2013 for NDA 50-558/S-072 (Cefuroxime injection, bundled supplement with NDA 50-578/S-059, Ceftazidime for Injection) for the addition of [redacted] for the drug product at the GSK Verona, Italy site (drug product).
- Establishment Inspection Report for GlaxoSmithKline Manufacturing S.p.A. Verona, Italy (EI dates 3/10-18/2014).

filename: N206494N000R1

Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommended for Approval

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The two drug substances are both produced via (b) (4) processing. The final drug product is manufactured via an (b) (4)
Finally, there are post-constitution hold times listed in the labelling for solutions of dextrose as well as lactated Ringer's solution.

B. Brief Description of Microbiology Deficiencies - None

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

D. Contains Potential Precedent Decision(s)- ☐ **Yes** ☒ **No**
(If yes, provide a brief description and a reference to the page where the precedent is discussed in depth)

III. Product Quality Microbiology Risk Assessment

A. Initial Product Quality Microbiology Risk Assessment

CQA	Risk Factor	Prob. of Occ. (O)	Modifier for O[3, 4, 5]	Severity of Effect (S)	Detect. (D)	Risk Priority Number[6] (RPN)	Additional Review Emphasis based on Risk (in addition to normal review process)
(b) (4)							

(b) (4)

B. Final Risk Assessment - The Applicant has demonstrated adequate controls over the (b) (4) manufacture of the 2 drug substances and the (b) (4) final drug product. There was also adequate primary container closure integrity study data supporting the sterility maintenance of the final packaged drug substances as well as the drug product. Post-constitution microbial challenge studies were performed and support the preparation and use hold times listed in the draft labelling.

III. Administrative: See last page for signatures

A. Reviewer's Signature _____

Robert J. Mello, Ph.D.
Senior Microbiology Reviewer

B. Endorsement Block _____

Neal J. Sweeney, Ph.D.
Senior Microbiology Reviewer

20 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Endorsement page:

Robert J. Mello, Ph.D.
Senior Microbiology Reviewer
OPQ/OPF/DMA

Robert J. Mello -A
Digitally signed by Robert J. Mello -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300369984, cn=Robert J. Mello -A
Date: 2015.02.03 07:54:05 -05'00'

Neal J. Sweeney, Ph.D.
Senior Microbiology Reviewer
OPQ/OPF/DMA

Neal J. Sweeney -A
Digitally signed by Neal J. Sweeney -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300109587, cn=Neal J. Sweeney -A
Date: 2015.02.03 08:26:50 -05'00'

DIVISION OF ANTI-INFECTIVE PRODUCTS CLINICAL MICROBIOLOGY REVIEW

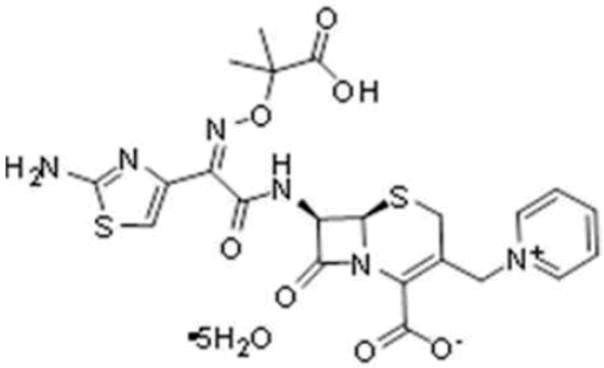
NDA: 206494 DATE REVIEW COMPLETED: 11-06-2014
Ceftazidime-avibactam

Date Company Submitted: 06/25/14
Date received by CDER: 06/25/14
Date Assigned: 06/25/14
Reviewer: Avery Goodwin, Ph.D.

NAME AND ADDRESS OF APPLICANT:
Cerexa Inc.
2100 Franklin St. Suite 900
Oakland, CA 94612
Tel No: 510-285-9200

CONTACT PERSON:
Kristina Haeckl, RAC, Executive Director,
Regulatory Affairs, Cerexa, Inc.
Tel No: 510-285-92208
Fax No: 510-285-9482
khaeckl@cerexa.com

DRUG PRODUCT NAMES:
Propriety Name: Not yet Assigned
Established Name: Ceftazidime/Avibactam
Ceftazidime pentahydrate
Chemical name: Pentahydrate of pyridinium, 1-[[7-[[(2-amino-4-thiazolyl)[(1-carboxy-1-methylethoxy) imino] acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl] methyl]-, hydroxide, inner salt, [6R-[6α,7β(Z)]]
Molecular weight: 636.6
Molecular Formula: $C_{22}H_{32}N_6O_{12}S_2$
Structural Formula:

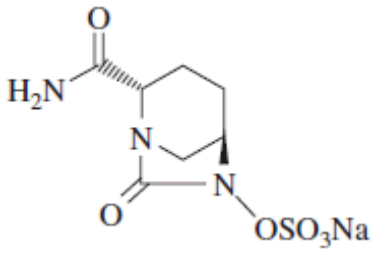


Avibactam: (formerly NXL 104 and AVE1330)
Chemical name: 1,6-Diazabicyclo [3.2.1] octane-2-carboxamide, 7-oxo-6-(sulfooxy)-, monosodium salt, (1R, 2S, 5R)-rel- (9CI)
Molecular Weight: 287
Molecular Formula**:** $C_7H_{10}N_3O_6SNa$
Structural Formula:

DIVISION OF ANTI-INFECTIVE PRODUCTS CLINICAL MICROBIOLOGY REVIEW

NDA: 206494 DATE REVIEW COMPLETED: 11-06-2014

Ceftazidime-avibactam



PROPOSED DOSAGE FORM AND STRENGTH:

The recommended dosage of CAZ-AVI is 2.5 g (2 g ceftazidime + 0.5 g avibactam) administered every 8 hours (q8h) by intravenous (IV) infusion over 2 hours for up to 14 days in patients ≥ 18 years of age.

PROPOSED INDICATION:

Complicated Intra-abdominal Infection (cIAI)

Complicated intra-abdominal infections (in combination with metronidazole) caused by *Escherichia coli* (including cases with concurrent bacteremia), *Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii, Enterobacter cloacae, Klebsiella oxytoca, Pseudomonas aeruginosa,* and *Pseudomonas stutzeri*; and polymicrobial infections caused by aerobic and anaerobic organisms including *Bacteroides* spp., (many strains of *Bacteroides fragilis* are resistant to TRADENAME).

Complicated Urinary Tract Infection (cUTI), including Acute Pyelonephritis (AP)

Complicated urinary tract infections, including acute pyelonephritis, caused by *Escherichia coli* (including cases with concurrent bacteremia), *Klebsiella pneumoniae*, *Citrobacter koseri*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Citrobacter freundii*, *Proteus* spp.*,* including *Proteus mirabilis* and indole-positive *Proteus,* and *Pseudomonas aeruginosa*.

SUMMARY AND RECOMMENDATIONS:

The data submitted by the Applicant supports the findings that ceftazidime-avibactam is efficacious against indicated, susceptible bacterial isolates associated with complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI), including acute pyelonephritis (AP). Please note that susceptibility interpretive criteria for *Enterobacteriaceae* and *Pseudomonas aeruginosa* are based on an IV dose of 2 grams ceftazidime + 0.5 gram avibactam every 8 hours in patients with normal renal function.

This Reviewer suggests removing the term "(b) (4)" from the first list since this may be misleading. Ceftazidime-avibactam is only active against serine β-lactamase including Class A, C and certain Class D β-lactamase. It is not active against Class B β-lactamase. Although the β-lactamase producing phenotype of the organism is important, from a clinical microbiology point of view, the MIC of the organism takes precedence. (b) (4)

Due to limited clinical experience at treating ceftazidime non-susceptible bacterial isolates, a section depicting the activity of CAZ-AVI against CAZ-non-susceptible (CAZ-NS) organisms in animal infection models is included

in section 12.4 of the label.

EXECUTIVE SUMMARY:

Antimicrobial Spectrum of Activity

Ceftazidime in combination with avibactam extends the in vitro and in vivo activity of ceftazidime against a number of clinically important gram-negative bacteria including *P. aeruginosa* and bacteria belonging to the family of *Enterobacteriaceae*. When used in combination, avibactam protects ceftazidime from degradation by serine β-lactamase enzymes and maintains the antibacterial activity of ceftazidime against isolates associated with multidrug resistance. Ceftazidime-avibactam (CAZ-AVI) is capable of overcoming some AmpC-mediated resistance in *P. aeruginosa,* reducing MIC90 levels to 4 mg/L for isolates from the United States. The MIC90 for all worldwide isolates ranged from 4-64 mg/L. Among the ceftazidime-nonsusceptible isolates from the United States, the MIC90 for ceftazidime-avibactam was 16 mg/L in one study and 8 mg/L in a second compared with > 8 and > 128 mg/L for meropenem and piperacillin-tazobactam, respectively. The ceftazidime-avibactam MIC90 values were 16 mg/L in Europe, 32 mg/L in Latin America, 8 mg/L in the Middle East and Africa and 64 mg/L in the Asia/Pacific region for the ceftazidime-non- susceptible subset. Against *Enterobacteriaceae,* CAZ-AVI demonstrates activity against some Class A, C and some Class D ESBL producing isolates. All *Enterobacteriaceae* demonstrated ceftazidime-avibactam MIC ≤ 4 mg/L.

Mechanism of Action

Ceftazidime is a semisynthetic, third-generation cephalosporin, β-lactam antibacterial drug that exerts its primary effect by inhibition of enzymes responsible for cell-wall synthesis. Mechanistically, its primary mode of action is the inhibition of bacterial cell wall synthesis. Ceftazidime shows high affinity for PBP3 of *P. aeruginosa* and *E. coli*, with IC_{50} values of 0.06-0.22 mg/L in competitive binding experiments. Ceftazidime also competes for binding to PBPs 1a and 1b, but with 2- to 84-fold lower affinity. Gram-negative bacteria form filaments when exposed to ceftazidime at concentrations similar to the IC_{50} for PBP3; however, upon exposure to higher concentrations, cell lysis occurs.

Avibactam is a diazabicyclooctanone, non-β-lactam β-lactamase inhibitor. Avibactam inhibits class A ESBLs and carbapenemases, class C β-lactamases and some class D oxacillinases and carbapenemases. It is hypothesized that the inhibition of β-lactamases by avibactam occurs when the inhibitor binds to the catalytic serine residue in the active site of the enzyme, giving rise to a highly stable carbamoyl linkage

Avibactam differs from other β-lactamase inhibitors such as clavulanic acid, sulbactam, and tazobactam in three key aspects. Structurally, avibactam is a [3,2,1]-diazabicyclooctanone derivative that employs a reactive urea rather than a β-lactam to inhibit serine β-lactamases. Second, the mechanism of avibactam inhibition of β-lactamases is covalent, but reversible, in contrast to clavulanic acid, sulbactam and tazobactam which are also covalent but irreversible. Third, avibactam has an expanded spectrum of β-lactamase inhibition compared to the other three molecules, which are largely limited to coverage of class A enzymes. Avibactam inhibits class A ESBLs, class A carbapenemases such as KPC-2, some class C enzymes of the AmpC family, and some class D OXA enzymes as demonstrated by IC50 studies.

Resistance Studies

Resistance to cephalosporins may be mediated through a variety of mechanisms including the alterations of PBPs, formation of cephalosporinases that inactivate the drug, a decrease in the ability of the drug to penetrate the cell wall and reach the drug target, or efflux of the drug thereby preventing the drug from reaching its target. In gram- negative organisms, the predominant mode of resistance is the production of β-lactamase hydrolyzing enzyme. In avibactam mutant selection studies, frequencies for stable mutants from *P. aeruginosa* and *Enterobacteriaceae* with ESBL, AmpC or KPC β-lactamases was assessed and ranged from 2.04×10^{-9} to 1.8×10^{-6}. Stable *E. coli* mutant had CTX-M-15 sequence change (Lys237Gln). Resistance to avibactam in *Enterobacter cloacae* was determined to be associated with amino acid deletion in AmpC, loss of OmpC and/or OmpF.

Bactericidal Activity

Studies were conducted to investigate the bactericidal activity of ceftazidime-avibactam against Gram-negative pathogens by determination of minimum bactericidal concentrations (MBCs) and by time-kill studies. Ceftazidime-avibactam demonstrated bactericidal activity based on MBC/MIC ratios of ≤ 4 in a single study against 20 *Pseudomonas aeruginosa* and 13 *Enterobacteriaceae*, including some isolates that produced a variety of β-lactamases. The MBCs for most isolates were within one dilution of the MIC and an MBC/MIC ratio of ≤ 4 was observed for all isolates. Ceftazidime-avibactam was bactericidal at low MIC within the first 6 hours and against all strains tested. Higher concentrations of ceftazidime-avibactam appear to have no effect on the speed of bacterial killing thereby suggesting that killing was not concentration dependent. Ceftazidime-avibactam demonstrated time-dependent killing. Maximal rates of killing were generally seen at greater than or equal to two-times the MIC, with bactericidal effects (≥ 3-log10 killing) occurring within 5 to 24 hours. The addition of avibactam to ceftazidime had no effect on the metallo-β-lactamase-producing and OXA-23-expressing *P. aeruginosa*. Against *Enterobacteriaceae*, at least a 3-log10 reduction in CFU/mL was observed at 6 hour. Bacterial killing was less pronounced against *P. aeruginosa* isolates, where a 1- to 2-log10 reduction in CFU/mL at 6 hours was observed.

Animal Studies

CAZ-AVI was studied in five animal models with infections caused by Class A and Class C serine β-*lactamase*-producing bacteria.

Murine Systemic Infection

In this model, separate experimental systemic infections induced by seven *Enterobacteriaceae* strains were established by intraperitoneal injection to obtain an inoculum between 10-100 times the lethal does. Mice were treated subcutaneously at 0 and 4 hours post infection with CAZ-AVI (4/1 w/w) and comparators (cefepime, piperacillin-tazobactam (8/l-w/w), co-amoxiclav (4/1 w/w). The activity of ceftazidime was restored when combined with avibactam against all 7 strains (ED_{50} range: 5 - 29 mg/kg for class A producers and ED_{50} range: <5 - <15 mg/kg for class C producers). Cefepime was active against 6 out of the 7 strains at levels similar

to CAZ/AVI. Piperacillin-tazobactam and co-amoxiclav were generally less effective than CAZ-AVI against class A producing strains and totally inactive against all AmpC producers.

Pneumonia Immune-compromised mice

CAZ-AVI (4/1 w/w) was compared to ceftazidime alone, ceftazidime-clavulanate (4/1 and 2/1-w/w), and imipenem, in a mouse model of pneumonia induced by *K. pneumoniae.* Pneumonia was induced by intranasal inoculation of mice with about 4 x 10^6 CFU of *K. pneumoniae* 283KB4 (AmpC DHA-2) or *K. pneumoniae* 283KB5 (AmpC LAT-4 + SHY-11). Mice were treated three times a day for 2 days, beginning 16-18 h after infection. Untreated animals developed bacteremic pneumonia and fatal disease within 2 to 4 days; the bacterial lung load 16-18 hours post infection was around 10^{11} CFU/g of lung tissue. Ceftazidime alone showed no activity. CAZ-AVI demonstrated a significant 5-6 $\log_{10}$ reduction in lung bacterial counts 48h after therapy initiation. Imipenem showed similar efficacy to CAZ-AVI.

Pyelonephritis Immune-compromised mice

CAZ-AVI was compared to ceftazidime alone, ceftazidime-clavulanate (4/1 -w/w), and imipenem, in a mouse model of pyelonephritis induced by ceftazidime-resistant *K. pneumoniae* (Class A + AmpC), *E. coli* (one Class A and one AmpC), *E. cloacae* (AmpC), *M. morganii* (AmpC), or *C. freundii* (AmpC). Pyelonephritis was induced by direct inoculation in the kidney with about 10^4 CFU of each bacterial strain. Mice were treated 4 times, at 4, 8, 24 and 32 hour after infection, with ceftazidime or imipenem alone at 10 or 25 mg/kg, or with ceftazidime-clavulanate or CAZ-AVI. The in vivo efficacy was monitored using bacterial kidney clearance; in untreated animals the bacterial load 48 hours post-infection were between the ranges of 10^5 - 10^7 CFU/kidney. Ceftazidime alone was ineffective against all 6 strains compared to the non-treated control group. In each case, the CAZ-AVI demonstrated efficacy with a significant 2.6-4.5 $\log_{10}$ reduction in kidney bacterial counts 48h after therapy initiation. Overall imipenem showed similar efficacy to CAZ-AVI, while the ceftazidime-clavulanate combination was active against one strain.

Meningitis Immune-competent Rabbit

CAZ-AVI was also evaluated in rabbits infected with 10^5 CFU of *K. pneumoniae* 283KB4 (AmpC DHA-2) by direct injection into the subarachnoid space. About 18 hours following the infection, the animals were treated at T_0 with intravenous injections of the CAZ/AVI (ceftazidime 150 mg/kg; ratio 4/1) or meropenem (125 mg/kg). The animals received a second injection of ceftazidime alone (150 mg/kg) or meropenem (125 mg/kg) alone, 4 hours later. Cerebrospinal fluid and blood were sampled from T_0 to 8 hours following initiation of antibacterial therapy and tested for CAZ-AVI and meropenem concentrations; in addition, bacterial titers were measured in cerebrospinal fluid. Bacterial titers in cerebrospinal fluid were significantly decreased following treatment with CAZ-AVI combination: > 5 log reduction at 8 hours after initiation of therapy. Meropenem decreased bacterial load to a lower extent than CAZ-AVI (statistical significance at $p < 0.05$). Ceftazidime alone was without clinically significant effect (0.10 $\log_{10}$ reduction in bacterial load, as compared with 0.47 $\log_{10}$ increase for untreated rabbits).

Murine Thigh infection

The efficacy of CAZ-AVI was evaluated in mouse neutropenic thigh infection model against *K. pneumoniae* (KPC; MIC ≥256 mg/L) and *P. aeruginosa*. For *K. pneumoniae* thigh infection was induced by the intramuscular injection of KPC-producing strain into the right thigh. Mice were treated 1.5 hour post-infection with either

CAZ alone or CAZ-AVI (4:1 w/w). After thighs were removed at 24 hours post-infection, a >2-$\log_{10}$ CFU reduction was observed for mice treated with CAZ-AVI (4:1 w/w) at doses of =128:32 mg/kg compared to CAZ doses of = 1,024 mg/kg which were unable to reduce the numbers of CFUs. For *P. aeruginosa,* thigh infection was induced by an inoculum of 10^8 CFU in non-neutropenic mice and 10^7 CFU in neutropenic animals. Human simulated CAZ-AVI therapy commenced 2 hours after infection. Human simulated dosage resulted in bacterial reductions of 0.3 to 1.95 $\log_{10}$ CFU, and 13 of 15 achieved a reduction of ≥ 0.75 $\log_{10}$ CFU in non-neutropenic mice which also included three animals in this group that had CAZ-AVI MICs of ≤16 mg/L. In the neutropenic study, CAZ-AVI treatment resulted in bacterial load reductions based on CAZ-AVI MIC; bacterial killing was observed for 16 of 17 isolates with CAZ-AVI MIC of ≤8mg/L and 5 of 8 isolates with CAZ-AVI MICs of ≤16 mg/L.

Clinical Trials

The safety and efficacy of ceftazidime-avibactam were evaluated in one Phase 2 clinical trial in individuals with complicated intra-abdominal infections (cIAI) (Report# NXL104/2002) and in one Phase 2 clinical trial in subjects with complicated urinary tract infections (cUTI) (Report# NXL104/2001). In addition to the Phase 2 studies, ceftazidime-avibactam is being evaluated in an ongoing open label, randomized, Phase 3 clinical trial versus best available therapy (BAT) for the treatment of cIAI or cUTI caused by ceftazidime-non-susceptible gram-negative organisms (Report# D4280C00006).

Based on the limited clinical trial data, PK/PD, and in vitro data, the microbiology reviewer supports the proposed ceftazidime-avibactam MIC interpretive criteria:

Proposed Susceptibility Interpretive Criteria for Ceftazidime and Avibactam				
Pathogen	***Minimum Inhibitory Concentration[a] (mg/L)***		***Disk Diffusion Zone Diameter (mm)***	
	S	*R*	*S*	*R*
Enterobacteriaceae[§]	≤ 8/4	≥ 16/4	≥ 21	≤ 20
Pseudomonas aeruginosa[§]	≤ 8/4	≥ 16/4	≥ 18	≤17

Scatter plots for ceftazidime-avibactam for the available 60 isolates of β-lactamase-producing *Enterobacteriaceae* (including *C. freundii, E. cloacae, E. coli, K. oxytoca, P. stuartii* and *P. mirabilis*) were analyzed. The isolates that resulted in failure of antibiotic treatment included *K. pneumoniae* (ARC3603 and 3800) and *E. coli* (ARC3535). The isolates expressed bla_{NDM-1} (either integrated into the bacterial chromosome or on a plasmid), a class B metallo-beta-lactamase, class A (TEM, SHV, VEB and CTX-M types) and class D (OXA-oxacillinases).

Although ceftazidime-avibactam demonstrates favorable activity in vitro, clinical efficacy in patients may not be guaranteed. A phenomenon that may reduce clinical effect against ESBL-producing bacteria, despite good in vitro activity, is the inoculum effect. This may occur when the minimum inhibitory concentration of the antibiotic rises with increasing size of the number of bacteria. The effect has been described for β-lactams and β-lactamase-inhibitor combination (eg, piperacillin-tazobactam), where the enhanced susceptibility rate of piperacillin/tazobactam correlated with increased consumption of this antibiotic. The error rates generated

using the PK/PD breakpoint of 8 mg/L were similar to those generated using the PK/PD breakpoint of 4 mg/L for ceftazidime.

INTRODUCTION AND BACKGROUND:

Cerexa Inc. submits the original NDA 206494 for ceftazidime (a third generation cephalosporin) in combination with avibactam (a non-β-lactam-β-lactamases inhibitor) for injection to the requirements of section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, Section 314.50 of the United States Code of Federal Regulations. The Applicant is seeking approval of ceftazidime-avibactam for the treatment of complicated intra-abdominal infection (cIAI); complicated urinary tract infection (cUTI), including acute pyelonephritis (AP). A limited use indication is being sought for aerobic gram-negative infections with limited treatment options.

The dosage regimen for ceftazidime-avibactam in the Phase 2 cUTI Study was 500 mg ceftazidime/125 mg avibactam as a 30 minute infusion IV administered q8h. The comparator agent was imipenem administered as 500 mg q6h. The dosage regimen for ceftazidime-avibactam in the Resistant Pathogen Study was 2000 mg ceftazidime/500 mg avibactam as 120 minute infusion administered q8h. In the Phase 2 cIAI study, the dose regimen in the Resistant Pathogen Study was ceftazidime 2000 mg plus avibactam 500 mg administered IV q8h over 120 minutes. Subjects who were randomized to receive ceftazidime-avibactam also received metronidazole 500 mg administered IV over 60 minutes. In the Resistant Pathogen Study the comparator was the best available therapy (BAT) where the subjects received doses based on the Investigator's standard of care and the local label recommendation.

The cephalosporins were first produced by fermentation of *Cephalosporium acremonium* in 1945; however, it was not until 1964 that the first cephalosporin was introduced for clinical use by Eli Lilly[1]. The mechanism of activity is similar to that of other β-lactam antibiotics. Cephalosporins act by binding to penicillin binding proteins (PBPs); thereby, interfering with bacterial transpeptidation and transglycosylation pathways. The net result is the inhibition of bacterial cell wall biosynthesis[2].

Cephalosporins are chemically engineered by various substitutions of the dihydrothiazine ring thereby creating novel compounds capable of inhibiting bacteria PBP's. Modifications to cephalosporins result in changes to the microbiologic and pharmacologic differences and serves as a basis for classification[3]. Ceftazidime is a third generation cephalosporin with activity against *P. aeruginosa* and *Enterobacteriaceae*. Like other cephalosporins, the structural backbone includes a β-lactam ring fused to sulfur containing 6-member dihydrothiazine ring[3,4].

The third generation cephalosporins were introduced in the early 1980's to combat β-lactamase-mediated bacterial resistance[4]. However, in 1983, plasmid encoded β-lactamases that could hydrolyze the extended-spectrum cephalosporins were identified[4,5]. These plasmid encoded β-lactamases conferred resistance to β-lactam antibiotics (such as penicillins and cephalosporins) by enzymatic cleavage of the β-lactam ring [4,5,6]. The enzymes that confer resistance to cephalosporins are generally chromosomal or plasmid mediated AmpC β-lactamases and/or extended-spectrum β-lactamases (ESBLs) that are expressed in *Enterobacteriaceae* and *Pseudomonas aeruginosa*[4,5]. Although ESBLs have been described in a range of *Enterobacteriaceae* and

Pseudomonadaceae from different parts of the world, they appear to be most often identified in *Klebsiella pneumoniae* and *Escherichia coli*[7].

There are two classification systems used to categorize β-lactamases; the Ambler classification and the Bush-Medeiros-Jacoby classification system[4,8]. For the purpose of this review, the Ambler classification will be used. The Ambler classification system divides the β-lactamases into four classes (A, B, C and D) based on amino acid sequences[4,8]. The majority of ESBLs identified in clinical isolates to date are classified as producers of class A enzymes of which there are three main groups: CTX-M, SHV or TEM type enzymes. Class A enzymes are capable of hydrolyzing third generation cephalosporins. The SHV and TEM type enzymes have evolved from substitutions of key amino acids from narrow-spectrum β-lactamases such as plasmid-mediated TEM-1, -2 and SHV-1[4,8,9]. Non-TEM and non-SHV class A cephalosporinases include but are not limited to VEB and the CTX-M enzymes. The CTX-M enzymes, having originated from *Kluyvera* spp., have extended spectrum activity and appear to be the most widespread cephalosporinases[4]. Additionally, CTX-M family of enzymes consists of non-homogenous group that are distinguished by the insertion of genetic mobilization units and diverged probably as a result of antimicrobial selective pressure. The CTX-M dissemination rates among gram-negative bacteria have been increasing among bacteria in Europe, Africa, Asia, South America and North America[4,10]. Other class A serine carbapenemases include the *K. pneumoniae* carbapenemases (KPCs) which are ESBLs that have the ability to hydrolyze a wide variety of β-lactams including penicillins, cephalosporins and carbapenems[11]. The Class B enzymes are referred to the metallo- β-lactamases which are capable of hydrolyzing cephalosporins and other member of the β-lactam class of drugs and include the New Delhi metallo- β-lactamases (NDM-1) found in *Enterobacteriaceae*[11]. The class C enzymes are either chromosomally or plasmid encoded cephalosporinases produced by *P. aeruginosa* and *Enterobacteriaceae* such as chromosomally AmpC β-lactamases and plasmid mediated AmpC (other AmpC like enzymes include variations of ACC, CMY, FOX and LAT enzymes)[4,6,12]. The class D enzymes are β-lactamases that are capable of hydrolyzing extended-spectrum cephalosporins (e.g., OXA-10, OXA-48) and carbapenems (e.g., OXA-23). Class D enzymes are typically found in non-fermenting bacteria such as *P. aeruginosa* and *Acinetobacter baumannii* and in *Enterobacteriaceae*[11]. The class A, C, and D enzymes are serine β-lactamases that uses an active site serine to hydrolyze the β-lactam ring while class B requires zinc; hence the metallo-protease designation.[8,11].

Avibactam is a novel non- β-lactam-β-lactamases reversible inhibitor of class A, class C and some class D β-lactamases (described above) and is capable of restoring susceptibility of some *Enterobacteriaceae* and *Pseudomonas aeruginosa* isolates to ceftazidime[13-15]. Inhibitors of class A β-lactamases, such as clavulanic acid, tazobactam and sulbactam binds irreversible to class A enzymes and have less of an effect against AmpC β-lactamases[16]. In many *Enterobacteriaceae*, AmpC expression is low but may be inducible in response to β-lactam exposure[16,17]. Avibactam demonstrates activity against *Enterobacteriaceae* with derepressed chromosomal and plasmid derived AmpC β-lactamases, a class C enzyme, as well as many known class A enzymes[14-17]. Data on the activity of avibactam against many extended-spectrum AmpC (ESAC) β-lactamase enzymes suggest that avibactam binding domain remains conserved and variations that are not in close proximity to the active site of the enzyme binding domain does not appear to affect activity[18]. However, published studies suggest that not all of the extended-spectrum class C β-lactamase enzymes are susceptible to inhibition to an equivalent extent. There are a number of different structural variations in some class C ESAC β-lactamases that are close to the avibactam binding site that do impair the activity of this inhibitor[18]. If Avibactam is approved, it will be the first β-lactamase inhibitor with activity against class C β-lactamases.

Resistance to avibactam exists in *Enterobacteriaceae* and non-fermenters. *Enterobacteriaceae* expressing metallo- β-lactamases such as NDM-1 along with other class A, class C and class D β-lactamases usually demonstrate higher MICs when tested against ceftazidime-avibactam[16,18].

ANTIMICROBIAL SPECTRUM OF ACTIVITY

The Applicant evaluated the in vitro activity of ceftazidime (a 3rd generation cephalosporin) in combination with avibactam (a non-β-lactam inhibitor of serine β-lactamases) against a number of clinically important gram-negative isolates. The data presented in this section includes the antibacterial spectrum of activity of ceftazidime-avibactam and other comparator agents against β-lactamase producing isolates of clinically important species of *Enterobacteriaceae* and *P. aeruginosa*.

The data presented in this review encompasses of more than 5700 isolates of *Enterobacteriaceae* including *E. coli*, *Klebsiella* spp. and *P. mirabilis* collected in the United States during 2012 (Table 1). Of those isolates, it was indicated that 701 met the CLSI criteria for ESBL phenotype, (MIC > 1 mg/L for aztreonam, ceftazidime and/or ceftriaxone). PCR data confirmed that CTX-M-15-like enzymes (303/701 isolates; 43.2%) were by far the most commonly identified class A β-lactamase in this study, followed by ESBL versions of SHV enzymes (176/701 isolates; 25.1%) and KPC enzymes (118/701 isolates; 16.8%).

Table 1: Occurrences of ESBL, acquired cephalosporinases (AmpC) and carbapenemase enzymes detected among 701 ESBL-phenotype-positive *Enterobacteriaceae* collected in USA hospitals by USA census regions.

Region (no. of isolates tested)	*No. of isolates (% of isolates tested by region) positive for:*[a]							
	CTX-M-15-like	*SHV ESBL*	*KPC*	*CTX-M-14-like*	*CMY-2-like*	*FOX*	*TEM ESBL*	*DHA*
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a Various isolates were positive for one or more tested β-lactamase encoding genes tested.
Source: Castanheira et al 2014.

The activity of the combination of ceftazidime with 4 mg/L avibactam against the 701 EBSL producing organisms identified above are shown in Table 2. The MIC_{90} values for ceftazidime-avibactam ranged from 0.25-2 mg/L against the confirmed β-lactamase producers. All isolates were inhibited by ≤ 4 mg/L ceftazidime-avibactam including KPC-producing isolates and isolates producing multiple enzyme types. The addition of avibactam to ceftazidime appears to have extended the activity of ceftazidime since the ceftazidime MIC_{90} values ranged from 16-> 32 against these same isolates.

Table 2. Activities of ceftazidime-avibactam and comparator antimicrobial agents when tested against 701 ESBL-phenotype-positive *Enterobacteriaceae* isolates collected from 72 hospitals located in the nine United States Census regions.

Isolate group (no. tested)/ Antimicrobial agent	*MIC_{50} (mg/L)*	*MIC_{90} (mg/L)*	*Range (mg/L)*	*CLSI[a]*	*EUCAST[a]*
				%S / %I / %R	*%S / %I / %R*
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Isolate group (no. tested)/ Antimicrobial agent	*MIC_{50} (mg/L)*	*MIC_{90} (mg/L)*	*Range (mg/L)*	*CLSI[a]*	*EUCAST[a]*
				%S / %I / %R	*%S / %I / %R*
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Isolate group (no. tested)/ Antimicrobial agent	*MIC_{50} (mg/L)*	*MIC_{90} (mg/L)*	*Range (mg/L)*	*CLSI[a]*	*EUCAST[a]*
				%S / %I / %R	*%S / %I / %R*
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a Criteria as published by the CLSI M100-S23, 2013 and EUCAST 2013.
b US-FDA breakpoints were applied (CLSI M100-S23, 2013).
c CTX-M-15-like producing isolates do not include KPC- or NDM-1-producing isolates.
d CTX-M-14-like producing isolates do not include CTX-M-15-like-producing isolates.
e SHV ESBL producing isolates do not include CTX-M-15-like-, CTX-M-14-like-, KPC- or NDM-1-producing isolates.
f CMY-2-like producing isolates do not include CTX-M-15-like-, CTX-M-14-like-, KPC- or NDM-1-producing producing isolates.
Source: Castanheira et al 2014.

Ceftazidime-avibactam is being developed to treat serious life threatening infections caused by *Enterobacteriaceae* and non-fermenters such as *Pseudomonas aeruginosa*. According to the Applicant, many of the isolates collected were resistant to ceftazidime and/or carbapenems, or to multiple antibacterial classes.

Activity against *Escherichia coli*

In another in vitro study, the activity of ceftazidime/avibactam was determined against 13126 isolates of *E. coli* from 17 separate studies and presented in Table 3. The ceftazidime-avibactam MIC90 values ranged from 0.12-0.5 mg/L across all studies compared to MIC90 values that ranged from 1-64 mg/L for ceftazidime alone. Against isolates from the United States, the MIC90 was 0.12 mg/L in three studies and 0.25 mg/L in two studies. Against European isolates it was reported that ceftazidime-avibactam MIC90 was 0.12 mg/L (2113 isolates tested) in one study and 0.25 mg/L in another (1481 isolates tested). It was noted that some isolates exhibited MIC values of up to 64 mg/L; and most of these high MIC isolates were found to be metallo-β-lactamase producers originating from specific countries within this region and for which avibactam is not predicted to have any effect on the ceftazidime MIC. A similar phenomenon was observed in the Asia-Pacific region where the MIC90 was 0.25 mg/L, but isolates with MIC values up to > 128 mg/L were found that produced metallo-β-lactamases. One exception was a single isolate from the Philippines with an elevated ceftazidime-avibactam MIC that was found to only produce a CTX-M-15 enzyme. However, the exact mechanism of resistance for this isolate is unknown.

Table 3. Summary of In Vitro Studies to Evaluate the Activity of Ceftazidime-Avibactam Against *E. coli*.

Test Method	*[N]*	*Ceftazidime MIC (mg/L)*			*Ceftazidime-avibactam MIC (mg/L)*			*Study*
		Range	*50%*	*90%*	*Range*	*50%*	*90%*	
CLSI Broth Microdilution (Frozen)	25	0.06-4	0.25	1	≤ 0.03-0.25	0.12	0.12	Study CAZ-AVI-M2-093 (USA 2013)
	26	≤ 0.06-64	0.25	16	≤ 0.06-0.25	0.25	0.25	Study CAZ-AVI-M2-109 (USA 2013)
	486	≤ 0.015-> 128	0.25	8	≤ 0.015 - 1	0.12	0.25	Study CAZ-AVI-M2-100 (USA 2012)
	1481	≤ 0.015-> 128	0.25	32	≤ 0.015 - 64	0.12	0.25	Study CAZ-AVI-M2-106 (Europe 2012)
	500	≤ 0.25-> 32	≤ 0.25	1	≤ 0.06-1	0.12	0.25	Study CAZ-AVI-M2-097 (Canada 2013)
	496	≤ 0.015-> 128	0.25	64	≤ 0.015 - 4	0.12	0.5	Study CAZ-AVI-M2-104 (Latin America 2012)
	779	≤ 0.015-> 128	0.25	64	≤ 0.015 - > 128	0.12	0.25	Study CAZ-AVI-M2-107 (Asia-Pacific 2012)
	25	0.06-> 128	1	64	0.06-0.5	0.12	0.5	Study CAZ-AVI-M2-108 (China 2013)
	100	≤ 0.06-> 128	0.25	16	≤ 0.06-0.5	≤ 0.06	0.25	Study CAZ104-M2-006-AAC11A3001 (Japan 2013)
	253	≤ 0.015-> 128	0.25	32	≤ 0.015 - 4	0.12	0.25	Study CAZ-AVI-M2-105 (Middle East and Africa)
CLSI Broth Microdilution (Dried)	2767	≤ 0.015-> 32	0.12	2	≤ 0.015-2	0.06	0.12	Study CAZ-AVI-M2-101 (USA 2012)
	718	≤ 0.015-> 32	0.12	2	≤ 0.03-1	0.06	0.12	Study CAZ-AVI-M2-098 (USA 2011)
	953	≤ 0.015-> 32	0.25	1	≤ 0.03-2	0.12	0.25	Study CAZ104-M2-005-09-NXL-02 (USA 2009)
	2113	≤ 0.06-> 32	0.12	16	≤ 0.03-2	0.06	0.12	Study CAZ-AVI-M2-088 (Europe 2011)
	1217	0.06-> 32	0.25	2	≤ 0.03-2	0.12	0.25	Study CAZ104-M2-005-09-NXL-02 (Europe 2009)
	517	≤ 0.03-> 32	0.25	32	≤ 0.03-2	0.06	0.25	Study CAZ-AVI-M2-091 (Latin America)
	670	≤ 0.03-> 32	1	> 32	≤ 0.03-> 32	0.12	0.25	Study CAZ-AVI-M2-090 (Asia-Pacific and South Africa 2011)

Against a global collection of *E. coli* collected during a 2012 surveillance program, the ceftazidime-avibactam MIC90 was 0.12 mcg/ml against all isolates tested. Ceftazidime-avibactam significantly lowered the MIC90 value against the 2012 surveillance *E. coli* isolates shown in Table 4.

Table 4. Activity of Ceftazidime-Avibactam and Comparators against *E. coli* from the 2012 Global Surveillance Program

Drug	*N*	*MIC Range (mg/L)*	*MIC_{50} (mg/L)*	*MIC_{90} (mg/L)*	*CLSI*			*EUCAST*		
					%Sus	*%Int*	*%Res*	*%Sus*	*%Int*	*%Res*
United States (Dried)[a]										
Ceftazidime-avibactam	2767	≤ 0.015 - 2	0.06	0.12	-	-	-	-	-	-
Ceftazidime	2767	≤ 0.015 - > 32	0.12	2	91.8	1.5	6.7	89.2	2.6	8.2
Gentamicin	2767	≤ 1 - > 8	≤ 1	> 8	87.3	0.5	12.2	86.3	1.0	12.7
Levofloxacin	2767	≤ 0.12 - > 4	≤ 0.12	> 4	70.7	0.5	28.8	70.3	0.4	29.3
Meropenem	2767	≤ 0.06 - 8	≤ 0.06	≤ 0.06	99.9	0.0	0.1	99.9	0.1	0.0
Piperacillin-tazobactam	2767	≤ 0.5 - > 64	2	8	95.2	2.0	2.8	92.4	2.8	4.8
United States (Frozen)[b]										
Ceftazidime-avibactam	486	≤ 0.015 - 1	0.12	0.25	-	-	-	-	-	-
Ceftazidime	486	≤ 0.015 - > 128	0.25	8	89.3	0.8	9.9	87.2	2.1	10.7
Amikacin	486	≤ 0.25 - 32	2	8	99.4	0.6	0.0	98.2	1.2	0.6
Levofloxacin	486	≤ 0.03 - > 4	0.06	> 4	71.2	0.4	28.4	71.0	0.2	28.8
Meropenem	486	≤ 0.004 - 0.12	0.03	0.03	100	0.0	0.0	100	0.0	0.0
Piperacillin-tazobactam	486	≤ 0.25 - > 128	2	8	94.0	4.5	1.4	92.0	2.1	6.0
Europe (Frozen)[c]										
Ceftazidime-avibactam	1481	≤ 0.015 - 64	0.12	0.25	-	-	-	-	-	-
Ceftazidime	1481	≤ 0.015 - > 128	0.25	32	85.2	1.7	13.2	81.1	3.4	14.9
Amikacin	1481	≤ 0.25 - > 32	2	8	98.0	0.7	1.2	94.0	4.1	2.0
Levofloxacin	1481	≤ 0.03 - > 4	0.06	> 4	72.1	1.4	26.5	71.5	0.6	27.9
Meropenem	1481	≤ 0.004 - > 8	0.03	0.03	99.8	0.1	0.1	99.9	0.1	0.1
Piperacillin-tazobactam	1481	≤ 0.25 - > 128	2	32	86.6	6.8	6.6	81.9	4.7	13.4

Drug	*N*	*MIC Range (mg/L)*	*MIC_{50} (mg/L)*	*MIC_{90} (mg/L)*	*CLSI*			*EUCAST*		
					%Sus	*%Int*	*%Res*	*%Sus*	*%Int*	*%Res*
Latin America (Frozen)[d]										
Ceftazidime-avibactam	496	≤ 0.015 - 4	0.12	0.5	-	-	-	-	-	-
Ceftazidime	496	≤ 0.015 - > 128	0.25	64	67.9	3.2	28.8	64.1	3.8	31.1
Amikacin	496	0.5 - > 32	2	8	98.2	1.2	0.6	91.1	6.7	1.8
Levofloxacin	496	≤ 0.03 - > 4	4	> 4	50.0	1.4	48.6	49.6	0.4	50.0
Meropenem	496	0.008 - 8	0.03	0.03	99.4	0.0	0.6	99.4	0.6	0.0
Piperacillin-tazobactam	496	≤ 0.25 - > 128	2	64	84.3	9.5	6.3	73.4	10.9	15.7
Middle East and Africa (Frozen)[e]										
Ceftazidime-avibactam	253	≤ 0.015 - 4	0.12	0.25	-	-	-	-	-	-
Ceftazidime	253	≤ 0.015 - > 128	0.25	32	81.0	1.6	17.4	77.1	4.0	19.0
Amikacin	253	0.5 - > 32	2	8	98.8	0.8	0.4	95.3	3.6	1.2
Levofloxacin	253	≤ 0.03 - > 4	0.25	> 4	66.0	1.2	32.8	66.0	0.0	34.0
Meropenem	253	0.015 - 8	0.03	0.03	99.6	0.0	0.4	99.6	0.4	0.0
Piperacillin-tazobactam	253	≤ 0.25 - > 128	2	64	81.8	11.1	7.1	79.5	2.4	18.2
Asia/Pacific Region (Frozen)[f]										
Ceftazidime-avibactam	779	≤ 0.015 - > 128	0.12	0.25	-	-	-	-	-	-
Ceftazidime	779	≤ 0.015 - > 128	0.25	64	70.2	2.7	27.1	63.4	6.8	29.8
Amikacin	779	0.5 - > 32	2	8	98.2	0.3	1.5	95.8	2.4	1.8
Levofloxacin	779	≤ 0.03 - > 4	2	> 4	50.8	1.2	48.0	49.8	1.0	49.2
Meropenem	779	≤ 0.004 - > 8	0.03	0.06	99.2	0.3	0.5	99.5	0.3	0.3
Piperacillin-tazobactam	779	≤ 0.25 - > 128	2	64	87.2	5.0	7.8	81.8	5.4	12.8

[a] Study CAZ-AVI-M2-101; [b] Study CAZ-AVI-M2-100; [c] Study CAZ-AVI-M2-106; [d] Study CAZ-AVI-M2-104; [e] Study CAZ-AVI-M2-105; [f] Study CAZ-AVI-M2-107

Table 5 shows the activity of ceftazidime-avibactam against the ESBL-phenotype subset. Rates of ceftazidime-non-susceptibility varied by region, with the lowest rates found in the United States and Europe and the highest rates found in Latin America, the Middle East, Africa and the Asia/Pacific regions. Ceftazidime-avibactam was consistently the most active agents tested against these isolates with significantly lower MIC90 values ranging from 0.25-1 mg/L.

Table 5. Activity of Ceftazidime-Avibactam and Comparators against ESBL-phenotype *E. coli* from the 2012 Global Surveillance Program

Drug	*N*	*MIC Range (mg/L)*	*MIC_{50} (mg/L)*	*MIC_{90} (mg/L)*	*CLSI*			*EUCAST*		
					%Sus	*%Int*	*%Res*	*%Sus*	*%Int*	*%Res*
United States (Dried)[a]										
Ceftazidime-avibactam	328	≤ 0.015 - 2	0.12	0.25	-	-	-	-	-	-
Ceftazidime	328	0.5 - > 32	16	> 32	30.8	12.8	56.4	9.1	21.7	69.2
Gentamicin	328	≤ 1 - > 8	2	> 8	64.8	0.3	34.9	62.7	2.1	35.2
Levofloxacin	328	≤ 0.12 - > 4	> 4	> 4	23.8	1.5	74.7	22.6	1.2	76.2
Meropenem	328	≤ 0.06 - 8	≤ 0.06	≤ 0.06	98.8	0.7	0.6	99.4	0.6	0.0
Piperacillin-tazobactam	328	1 - > 64	8	> 64	76.8	10.4	12.8	61.9	14.9	23.2
United States (Frozen)[b]										
Ceftazidime-avibactam	46	≤ 0.015 - 1	0.25	0.5	-	-	-	-	-	-
Ceftazidime	46	0.5 - > 128	32	128	23.9	6.5	69.6	8.7	15.2	76.1
Amikacin	46	1 - 32	4	16	93.5	6.5	0.0	84.8	8.7	6.5
Levofloxacin	46	≤ 0.03 - > 4	> 4	> 4	8.7	0.0	91.3	8.7	0.0	91.3
Meropenem	46	0.015 - 0.06	0.03	0.03	100	0.0	0.0	100	0.0	0.0
Piperacillin-tazobactam	46	1 - > 128	8	32	80.4	17.4	2.2	67.4	13.0	19.6
Europe (Frozen)[c]										
Ceftazidime-avibactam	235	≤ 0.015 - 8	0.12	0.5	-	-	-	-	-	-
Ceftazidime	235	0.25 - > 128	32	128	24.7	8.5	66.8	8.1	16.6	75.3
Amikacin	235	1 - > 32	8	16	93.6	2.6	3.8	76.6	17.0	6.4
Levofloxacin	235	≤ 0.03 - > 4	> 4	> 4	26.0	2.1	71.9	25.5	0.4	74.0
Meropenem	235	0.008 - 4	0.03	0.06	99.6	0.0	0.4	99.6	0.4	0.0
Piperacillin-tazobactam	235	0.5 - > 128	16	> 128	63.4	19.6	17.0	48.1	15.3	36.6

Drug	*N*	*MIC Range (mg/L)*	*MIC_{50} (mg/L)*	*MIC_{90} (mg/L)*	*CLSI*			*EUCAST*		
					%Sus	*%Int*	*%Res*	*%Sus*	*%Int*	*%Res*
Latin America (Frozen)[d]										
Ceftazidime-avibactam	161	≤ 0.015 - 4	0.25	0.5	-	-	-	-	-	-
Ceftazidime	161	0.5 - > 128	32	128	13.7	8.1	78.3	4.4	9.3	86.3
Amikacin	161	0.5 - > 32	8	16	96.9	2.5	0.6	80.1	16.8	3.1
Levofloxacin	161	≤ 0.03 - > 4	> 4	> 4	5.6	1.9	92.6	5.6	0.0	94.4
Meropenem	161	0.015 - 8	0.03	0.06	99.4	0.0	0.6	99.4	0.6	0.0
Piperacillin-tazobactam	161	1 - > 128	16	64	72.1	19.3	8.7	44.1	28.0	28.0
Middle East and Africa (Frozen)[e]										
Ceftazidime-avibactam	49	≤ 0.015 - 4	0.25	1	-	-	-	-	-	-
Ceftazidime	49	0.12 - > 128	32	128	20.4	8.2	71.4	8.2	12.2	79.6
Amikacin	49	0.5 - 32	4	8	98.0	2.0	0.0	95.9	2.0	2.0
Levofloxacin	49	≤ 0.03 - > 4	> 4	> 4	20.4	2.0	77.6	20.4	0.0	79.6
Meropenem	49	0.015 - 0.06	0.03	0.06	100	0.0	0.0	100	0.0	0.0
Piperacillin-tazobactam	49	0.5 - > 128	8	> 128	63.3	18.4	18.4	57.1	6.1	36.7
Asia/Pacific Region (Frozen)[f]										
Ceftazidime-avibactam	262	≤ 0.015 - 8	0.25	0.5	-	-	-	-	-	-
Ceftazidime	262	0.5 - > 128	16	128	26.3	7.6	66.0	10.7	15.7	73.7
Amikacin	262	0.5 - > 32	4	8	95.8	0.8	3.4	90.5	5.3	4.2
Levofloxacin	262	≤ 0.03 - > 4	> 4	> 4	18.7	0.8	80.5	17.9	0.8	81.3
Meropenem	262	0.008 - > 8	0.03	0.06	99.2	0.4	0.4	99.6	0.0	0.4
Piperacillin-tazobactam	262	≤ 0.25 - > 128	4	128	79.4	8.0	12.6	67.9	11.5	20.6

[a] Study CAZ-AVI-M2-101; [b] Study CAZ-AVI-M2-100; [c] Study CAZ-AVI-M2-106; [d] Study CAZ-AVI-M2-104; [e] Study CAZ-AVI-M2-105; [f] Study CAZ-AVI-M2-107

Activity against *Klebsiella* species

The Applicant determined the activity of ceftazidime-avibactam against 6,926 *K. pneumoniae*, 1,103 *K. oxytoca* and 1,156 non-speciated *Klebsiella* isolates from 17 separate studies. Tables 6 and 7 show the activity of ceftazidime-avibactam against all *Klebsiella pneumoniae* and *K. oxytoca*. Ceftazidime-avibactam significantly lowers the MIC90 values compared to ceftazidime alone.

Table 6: Summary of In Vitro Studies to Evaluate the Activity of Ceftazidime-Avibactam Against *K. pneumoniae.*

Test Method	*[N]*	*Ceftazidime MIC (mg/L)*			*Ceftazidime-avibactam MIC (mg/L)*			*Study*
		Range	*50%*	*90%*	*Range*	*50%*	*90%*	
CLSI Broth Microdilution (Frozen)	25	≤ 0.03-> 64	0.25	> 64	≤ 0.03-2	0.12	0.25	Study CAZ AVI M2 093 (USA 2013)
	27	≤ 0.06-64	0.25	32	≤ 0.06-2	0.12	0.5	Study CAZ AVI M2 109 (USA 2013)
	293	0.03-> 128	0.25	64	≤ 0.015-> 128	0.12	0.5	Study CAZ AVI M2 100 (USA 2012)
	933	≤0.015->128	0.5	>128	≤0.015->128	0.25	1	Study CAZ AVI M2 106 (Europe 2012)
	169	≤0.25->32	≤0.25	0.5	≤0.06-8	0.12	0.5	Study CAZ AVI M2 097 (Canada 2013)
	316	≤0.015->128	2	>128	≤0.015-4	0.25	1	Study CAZ AVI M2 104 (Latin America 2012)
	532	≤0.015->128	0.25	128	≤0.015->128	0.12	0.5	Study CAZ AVI M2 107 (Asia Pacific 2012)
	25	0.12->128	1	64	0.06-2	0.12	1	Study CAZ AVI M2 108 (China 2013)
	100	≤0.06-32	0.12	0.25	≤0.06-2	≤0.06	0.12	Study CAZ104 M2 006 AAC11A3001 (Japan 2013)
	165	0.03->128	2	64	0.03-4	0.12	0.5	Study CAZ AVI M2 105 (Middle East and Africa 2012)
CLSI Broth Microdilution (Dried)	1847	≤0.015->32	0.12	32	≤0.015->32	0.12	0.5	Study CAZ AVI M2 101 (USA 2012)
	818	≤0.015->32	0.12	>32	≤0.03-4	0.12	0.25	Study CAZ AVI M2 098 (USA 2011)
	858	0.03->32	2	>32	≤0.03->32	0.12	0.5	Study CAZ AVI M2 088 (Europe 2011)
	373	0.03->32	2	>32	≤0.03-4	0.12	0.5	Study CAZ AVI M2 091 (Latin America 2011)
	445	≤0.015->32	0.5	>32	≤0.03->32	0.12	0.5	Study CAZ AVI M2 090 (Asia Pacific and South Africa 2011)

Test Method	*[N]*	*Ceftazidime MIC (mg/L)*			*Ceftazidime-avibactam MIC (mg/L)*			*Study*
		Range	*50%*	*90%*	*Range*	*50%*	*90%*	
CLSI Broth Microdilution (Dried)	680	0.03-> 32	0.12	16	≤ 0.03-8	0.12	0.5	Study CAZ104-M2-005-09-NXL-02 (USA 2009)
	476	0.03-> 32	0.25	> 32	≤ 0.03-32	0.12	0.5	Study CAZ104-M2-005-09-NXL-02 (Europe 2009)

Table 7. Summary of In Vitro Studies to Evaluate the Activity of Ceftazidime-Avibactam Against *K. oxytoca*

Test Method	*[N]*	*Ceftazidime MIC (mg/L)*			*Ceftazidime-avibactam MIC (mg/L)*			*Study*
		Range	*50%*	*90%*	*Range*	*50%*	*90%*	
CLSI Broth Microdilution (Frozen)	25	≤ 0.03-2	0.06	0.25	≤ 0.03-0.5	0.06	0.25	Study CAZ AVI M2 093 (USA 2013)
	29	≤ 0.06-16	0.12	0.5	≤ 0.06-0.5	0.12	0.5	Study CAZ AVI M2 109 (USA 2013)
	50	≤ 0.25-1	≤ 0.25	0.5	≤ 0.06-0.5	0.12	0.5	Study CAZ AVI M2 097 (Canada 2013)
	25	0.06-4	0.25	2	0.06-0.5	0.25	0.5	Study CAZ AVI M2 108 (China 2013)
	50	≤ 0.06-> 128	0.12	2	≤ 0.06-64	≤ 0.06	0.5	Study CAZ104 M2 006 AAC11A3001 (Japan 2013)
CLSI Broth Microdilution (Dried)	442	≤ 0.03 - > 32	0.12	0.5	0.03 - 1	0.06	0.25	Study CAZ AVI M2 101 (USA 2012)
	244	≤ 0.03 - > 32	0.12	1	≤ 0.03 - 4	0.06	0.25	Study CAZ AVI M2 098 (USA 2011)
	160	≤ 0.03 - > 32	0.12	2	≤ 0.03 - > 32	0.12	0.5	Study CAZ AVI M2 088 (Europe 2011)
	40	≤ 0.03 - > 32	0.12	4	≤ 0.03 - 0.5	0.12	0.5	Study CAZ AVI M2 091 (Latin America 2011)
	38	0.06 - 32	0.12	2	≤ 0.03 - 1	0.06	0.25	Study CAZ AVI M2 090 (Asia Pacific and South Africa 2011)

The ceftazidime-avibactam MIC90 values ranged from 0.25 to 1 mg/L and the ceftazidime MIC90 values ranged from 0.12-> 128mg/L across all studies and for *K. pneumoniae*, *K. oxytoca* and *Klebsiella* spp. isolates. Against United States isolates, the MIC90 values were either 0.25 mg/L or 0.5 mg/L. Against isolates from Europe, the MIC90 values were 0.5 or 1 mg/L. There appear to be very little difference in ceftazidime-avibactam activity noted among the studies, with the exception of a few isolates with elevated ceftazidime-avibactam MIC values reported from various regions and/or in specific surveillance years.

The Applicant noted that isolates of *K. pneumoniae* from Greece were found to produce either VIM-1 or VIM-26 in combination with other β-lactamases, two isolates from Russia and two from the United States were found to produce NDM-1 and five isolates from the Philippines produced various metallo- β-lactamases. One *K. oxytoca from South Africa (VIM-1 producer)* was identified that produced a metallo-β-lactamase Five other high ceftazidime-avibactam MIC *K. oxytoca* were identified, including two from China that produced SHV-12 in combination with KPC-2, one isolate from the Philippines that produced a combination of SHV-12, TEM-1 and CTX-M-15 and one isolate from China with inconclusive results.

Table 8 shows additional in vitro data of ceftazidime-avibactam against a collection of *K. pneumoniae* isolates during a 2012 surveillance program. Table 9 shows the data for the subset with ESBL-phenotypes and Table 10 shows the activity against meropenem-non-susceptible subsets.

Table 8 Activity of Ceftazidime-Avibactam and Comparators against *K. pneumoniae* from the 2012 Global Surveillance Program

Drug	*N*	*MIC Range (mg/L)*	*MIC_{50} (mg/L)*	*MIC_{90} (mg/L)*	*CLSI*			*EUCAST*		
					%Sus	*%Int*	*%Res*	*%Sus*	*%Int*	*%Res*
United States (Dried)[a]										
Ceftazidime-avibactam	1847	≤ 0.015 - > 32	0.12	0.5	-	-	-	-	-	-
Ceftazidime	1847	≤ 0.015 - > 32	0.12	32	85.4	1.3	13.3	84.1	1.4	14.6
Gentamicin	1847	≤ 1 - > 8	≤ 1	2	91.7	1.7	6.6	90.1	1.7	8.3
Levofloxacin	1847	≤ 0.12 - > 4	≤ 0.12	> 4	86.1	1.5	12.4	85.0	1.1	13.9
Meropenem	1847	≤ 0.06 - > 8	≤ 0.06	≤ 0.06	93.8	0.1	6.1	93.9	1.5	4.6
Piperacillin-tazobactam	1847	≤ 0.5 - > 64	4	> 64	86.6	2.7	10.8	80.7	5.8	13.4
United States (Frozen)[b]										
Ceftazidime-avibactam	293	≤ 0.015 - > 128	0.12	0.5	-	-	-	-	-	-
Ceftazidime	293	0.03 - > 128	0.25	64	84.0	1.7	14.3	82.3	1.7	16.0
Amikacin	293	≤ 0.25 - > 32	1	4	96.9	2.4	0.7	93.2	3.8	3.1
Levofloxacin	293	≤ 0.03 - > 4	0.06	> 4	83.6	1.4	15.0	82.6	1.0	16.4
Meropenem	293	0.008 - > 8	0.03	0.06	94.9	0.7	4.4	95.6	1.0	3.4
Piperacillin-tazobactam	293	≤ 0.25 - > 128	4	128	86.4	2.7	10.9	78.2	8.2	13.7
Europe (Frozen)[c]										
Ceftazidime-avibactam	933	≤ 0.015 - > 128	0.25	1	-	-	-	-	-	-
Ceftazidime	933	≤ 0.015 - > 128	0.5	> 128	62.7	1.1	36.2	60.8	1.9	37.3
Amikacin	933	≤ 0.25 - > 32	2	16	92.2	4.5	3.3	87.9	4.3	7.8
Levofloxacin	933	≤ 0.03 - > 4	0.12	> 4	68.4	2.4	29.3	66.5	1.9	31.6
Meropenem	933	≤ 0.004 - > 8	0.03	0.5	91.2	0.4	8.4	91.6	1.7	6.7
Piperacillin-tazobactam	933	≤ 0.25 - > 128	4	> 128	65.6	9.4	25.0	58.6	7.0	34.4

Table 9. Activity of Ceftazidime-Avibactam and Comparators against ESBL-phenotype *K. pneumoniae* from the 2012 Global Surveillance Program

Drug	*N*	*MIC Range (mg/L)*	*MIC_{50} (mg/L)*	*MIC_{90} (mg/L)*	*CLSI*			*EUCAST*		
					%Sus	*%Int*	*%Res*	*%Sus*	*%Int*	*%Res*
United States (Dried)[a]										
Ceftazidime-avibactam	296	≤ 0.015 - > 32	0.5	1	-	-	-	-	-	-
Ceftazidime	296	1 - 32	> 32	> 32	8.8	8.1	83.1	1.0	7.8	91.2
Gentamicin	296	≤ 1 - > 8	4	> 8	51.4	10.8	37.8	42.6	8.8	48.6
Levofloxacin	296	≤ 0.12 - > 4	> 4	> 4	24.3	5.1	70.6	22.6	1.7	75.7
Meropenem	296	≤ 0.06 - > 8	≤ 0.06	> 8	61.1	1.1	37.8	62.2	9.1	28.7
Piperacillin-tazobactam	296	1 - > 64	> 64	> 64	24.4	11.9	63.7	17.3	7.1	75.6
United States (Frozen)[b]										
Ceftazidime-avibactam	38	0.06 - > 128	0.5	2	-	-	-	-	-	-
Ceftazidime	38	4 - > 128	128	> 128	7.9	5.3	86.8	0.0	7.9	92.1
Amikacin	38	0.5 - > 32	4	32	86.8	7.9	5.3	65.8	21.1	13.2
Levofloxacin	38	0.06 - > 4	> 4	> 4	26.3	0.0	73.7	23.7	2.6	73.7
Meropenem	38	0.015 - > 8	0.03	> 8	76.3	2.6	21.1	79.0	5.3	15.8
Piperacillin-tazobactam	38	4 - > 128	128	> 128	42.1	7.9	50.0	29.0	13.2	57.9
Europe (Frozen)[c]										
Ceftazidime-avibactam	297	≤ 0.015 - > 128	0.5	1	-	-	-	-	-	-
Ceftazidime	297	1 - > 128	128	> 128	3.7	2.4	93.9	0.7	3.0	96.3
Amikacin	297	0.5 - > 32	4	32	82.5	7.7	9.8	74.8	7.7	17.5
Levofloxacin	297	≤ 0.03 - > 4	> 4	> 4	29.6	3.7	66.7	25.9	3.7	70.4
Meropenem	297	≤ 0.004 - > 8	0.06	8	87.2	1.0	11.8	88.2	2.4	9.4
Piperacillin-tazobactam	297	0.5 - > 128	128	> 128	25.3	23.6	51.2	12.8	12.5	74.8
Latin America (Frozen)[d]										
Ceftazidime-avibactam	143	≤ 0.015 - 4	0.5	2	-	-	-	-	-	-
Ceftazidime	143	0.12 - > 128	64	> 128	7.7	5.6	86.7	2.8	4.9	92.3
Amikacin	143	0.5 - > 32	4	32	86.7	3.5	9.8	76.9	9.8	13.3
Levofloxacin	143	≤ 0.03 - > 4	> 4	> 4	40.6	1.4	58.0	37.8	2.8	59.4
Meropenem	143	0.008 - > 8	0.06	4	81.8	5.6	12.6	87.4	7.0	5.6
Piperacillin-tazobactam	143	1 - > 128	64	> 128	37.1	14.0	49.0	28.0	9.1	62.9
Middle East and Africa (Frozen)[e]										
Ceftazidime-avibactam	69	0.03 - 2	0.25	1	-	-	-	-	-	-
Ceftazidime	69	2 - > 128	32	> 128	8.7	4.4	87.0	0.0	8.7	91.3
Amikacin	69	0.5 - 32	4	16	97.1	2.9	0.0	89.9	7.3	2.9
Levofloxacin	69	0.06 - > 4	1	> 4	55.1	11.6	33.3	53.6	1.5	44.9
Meropenem	69	0.03 - > 8	0.06	0.06	98.6	0.0	1.5	98.6	0.0	1.5
Piperacillin-tazobactam	69	2 - > 128	16	> 128	55.1	21.7	23.2	42.0	13.0	44.9
Asia/Pacific Region (Frozen)[f]										
Ceftazidime-avibactam	152	≤ 0.015 - > 128	0.25	2	-	-	-	-	-	-
Ceftazidime	152	0.03 - > 128	64	> 128	21.1	2.0	77.0	7.9	13.2	79.0
Amikacin	152	0.5 - > 32	2	> 32	82.9	2.0	15.1	82.2	0.7	17.1
Levofloxacin	152	≤ 0.03 - > 4	4	> 4	46.7	5.9	47.4	42.8	4.0	53.3
Meropenem	152	0.015 - > 8	0.03	0.12	93.4	0.7	5.9	94.1	1.3	4.6
Piperacillin-tazobactam	152	0.5 - > 128	32	> 128	48.0	13.8	38.2	34.2	13.8	52.0

[a] Study CAZ-AVI-M2-101; [b] Study CAZ-AVI-M2-100; [c] Study CAZ-AVI-M2-106; [d] Study CAZ-AVI-M2-104; [e] Study CAZ-AVI-M2-105; [f] Study CAZ-AVI-M2-107

Table10. Activity of Ceftazidime-Avibactam and Comparators against meropenem-non-susceptible *K. pneumoniae* from the 2012 Global Surveillance Program

Drug	*N*	*MIC Range (mg/L)*	*MIC_{50} (mg/L)*	*MIC_{90} (mg/L)*	*CLSI*			*EUCAST*		
					%Sus	*%Int*	*%Res*	*%Sus*	*%Int*	*%Res*
United States (Dried)[a]										
Ceftazidime-avibactam	115	0.06 - > 32	0.5	2	-	-	-	-	-	-
Ceftazidime	115	16 - > 32	> 32	> 32	0.0	0.0	100	0.0	0.0	100
Gentamicin	115	≤ 1 - > 8	8	> 8	48.7	17.4	33.9	33.0	15.7	51.3
Levofloxacin	115	≤ 0.12 - > 4	> 4	> 4	7.0	1.7	91.3	5.2	1.8	93.0
Meropenem	115	2 - > 8	> 8	> 8	0.0	2.6	97.4	2.6	23.5	73.9
Piperacillin-tazobactam	115	> 64	> 64	> 64	0.0	0.0	100	0.0	0.0	100
United States (Frozen)[b]										
Ceftazidime-avibactam	15	0.5 - > 128	2	> 128	-	-	-	-	-	-
Ceftazidime	15	16 - > 128	> 128	> 128	0.0	0.0	100	0.0	0.0	100
Amikacin	15	1 - > 32	16	> 32	60.0	26.7	13.3	20.0	40.0	40.0
Levofloxacin	15	4 - > 4	> 4	> 4	0.0	6.7	93.3	0.0	0.0	100
Meropenem	15	2 - > 8	> 8	> 8	0.0	13.3	86.7	13.3	20.0	66.7
Piperacillin-tazobactam	15	128 - > 128	> 128	> 128	0.0	0.0	100	0.0	0.0	100
Europe (Frozen)[c]										
Ceftazidime-avibactam	82	0.12 - > 128	2	128	-	-	-	-	-	-
Ceftazidime	82	0.5 - > 128	> 128	> 128	3.7	0.0	96.3	3.7	0.0	96.3
Amikacin	82	1 - > 32	16	32	53.7	42.7	3.7	30.5	23.2	46.3
Levofloxacin	82	0.06 - > 4	> 4	> 4	13.4	0.0	86.6	11.0	2.4	86.6
Meropenem	82	2 - > 8	> 8	> 8	0.0	4.9	95.1	4.9	19.5	75.6
Piperacillin-tazobactam	82	2 - > 128	> 128	> 128	2.4	0.0	97.6	1.2	1.2	97.6
Latin America (Frozen)[d]										
Ceftazidime-avibactam	38	0.12 - 4	1	2	-	-	-	-	-	-
Ceftazidime	38	2 - > 128	128	> 128	5.3	5.3	89.5	0.0	5.3	94.7
Amikacin	38	0.5 - > 32	16	32	71.1	21.1	7.9	47.4	23.7	29.0
Levofloxacin	38	0.06 - > 4	> 4	> 4	13.2	0.0	86.8	13.2	0.0	86.8
Meropenem	38	2 - > 8	8	> 8	0.0	21.1	79.0	21.1	42.1	36.8
Piperacillin-tazobactam	38	8 - > 128	> 128	> 128	2.6	5.3	92.1	2.6	0.0	97.4
Middle East and Africa (Frozen)[e]										
Ceftazidime-avibactam	8	0.5 - 4	--	--	-	-	-	-	-	-
Ceftazidime	8	4 - > 128	--	--	12.5	0.0	87.5	0.0	12.5	87.5
Amikacin	8	2 - 32	--	--	50.0	50.0	0.0	37.5	12.5	50.0
Levofloxacin	8	0.12 - > 4	--	--	25.0	25.0	50.0	25.0	0.0	75.0
Meropenem	8	8 - > 8	--	--	0.0	0.0	100	0.0	37.5	62.5
Piperacillin-tazobactam	8	> 128 - > 128	--	--	0.0	0.0	100	0.0	0.0	100
Asia/Pacific Region (Frozen)[f]										
Ceftazidime-avibactam	14	0.12 - > 128	2	> 128	-	-	-	-	-	-
Ceftazidime	14	16 - > 128	> 128	> 128	0.0	0.0	100	0.0	0.0	100
Amikacin	14	0.5 - > 32	16	> 32	50.0	21.4	28.6	42.9	7.1	50.0
Levofloxacin	14	1 - > 4	4	> 4	42.9	7.1	50.0	42.9	0.0	57.1
Meropenem	14	2 - > 8	> 8	> 8	0.0	7.1	92.9	7.1	28.6	64.3
Piperacillin-tazobactam	14	16 - > 128	> 128	> 128	7.1	0.0	92.9	0.0	7.1	92.9

[a] Study CAZ-AVI-M2-101; [b] Study CAZ-AVI-M2-100; [c] Study CAZ-AVI-M2-106; [d] Study CAZ-AVI-M2-104; [e] Study CAZ-AVI-M2-105; [f] Study CAZ-AVI-M2-107

Activity against *Enterobacter* species

The in vitro activity of ceftazidime-avibactam was determined against 1216 *E. aerogenes* and 3040 *E. cloacae* United States and European isolates from 17 separate studies (Table 10 and 11).

Table 10. Summary of In Vitro Studies to Evaluate the Activity of Ceftazidime-Avibactam Against *E. aerogenes*

Test Method	*[N]*	*Ceftazidime MIC (mg/L)*			*Ceftazidime-avibactam MIC (mg/L)*			*Study*
		Range	*50%*	*90%*	*Range*	*50%*	*90%*	
CLSI Broth Microdilution (Frozen)	25	0.06-64	0.25	32	≤ 0.3-0.5	0.12	0.25	Study CAZ-AVI-M2-093 (USA 2013)
	31	0.12-128	0.25	64	0.12-2	0.25	1	Study CAZ-AVI-M2-109 (USA 2013)
	76	0.06 - 128	0.25	64	≤ 0.015-2	0.12	0.5	Study CAZ-AVI-M2-100 (USA 2012)
	161	0.12 - > 128	0.5	128	0.06 - 128	0.25	1	Study CAZ-AVI-M2-106 (Europe 2012)
	24	≤ 0.25-> 32	≤ 0.25	32	≤ 0.06-16	0.25	0.5	Study CAZ-AVI-M2-097 (Canada 2013)
	40	0.12 - 128	0.25	32	0.03 - 1	0.12	0.5	Study CAZ-AVI-M2-104 (Latin America 2012)
	97	0.06 - > 128	2	128	≤ 0.015-16	0.25	1	Study CAZ-AVI-M2-107 (Asia-Pacific 2012)
	26	0.06 - 128	0.5	64	0.06 - 0.5	0.25	0.5	Study CAZ-AVI-M2-108 (China 2013)
	50	0.12 - 64	0.25	0.5	≤ 0.06-0.5	0.12	0.25	Study CAZ104-M2-006-AAC11A3001 (Japan 2013)
	20	0.12 - 64	0.25	16	0.06 - 1	0.12	0.25	Study CAZ-AVI-M2-105 (Middle East and Africa 2012)
CLSI Broth Microdilution (Dried)	357	0.06-> 32	0.25	32	≤ 0.015 - 16	0.12	0.25	Study CAZ AVI M2 101 (USA 2012)
	143	0.03->32	0.25	16	≤0.03 - 1	0.12	0.25	Study CAZ-AVI-M2-098 (USA 2011)
	102	0.06-> 32	0.25	32	≤ 0.03 - 1	0.12	0.25	Study CAZ-AVI-M2-088 (Europe 2011)
	64	0.06-> 32	0.5	> 32	≤ 0.03 - 1	0.12	0.25	Study CAZ-AVI-M2-090 (Asia-Pacific and South Africa 2011)

Table 11. Summary of In Vitro Studies to Evaluate the Activity of Ceftazidime-Avibactam Against *E. cloacae*

Test Method	*[N]*	*Ceftazidime MIC (mg/L)*			*Ceftazidime-avibactam MIC (mg/L)*			*Study*
		Range	*50%*	*90%*	*Range*	*50%*	*90%*	
CLSI Broth Microdilution (Frozen)	25	0.06-> 128	0.5	> 128	≤ 0.03-4	0.25	1	Study CAZ-AVI-M2-093 (USA 2013)
	26	≤ 0.06-> 128	0.5	128	≤ 0.06-32	0.25	1	Study CAZ-AVI-M2-109 (USA 2013)
	87	0.12-> 128	0.5	128	0.06-1	0.25	1	Study CAZ-AVI-M2-100 (USA 2012)
	306	≤ 0.015-> 128	0.5	128	≤ 0.015-> 128	0.25	1	Study CAZ-AVI-M2-106 (Europe 2012)
	69	≤ 0.25-> 32	0.5	> 32	≤ 0.06-8	0.25	1	Study CAZ-AVI-M2-097 (Canada 2013)
	85	0.03-> 128	2	> 128	≤ 0.015-32	0.25	1	Study CAZ-AVI-M2-104 (Latin America 2012)
	125	0.06-> 128	1	> 128	≤ 0.015-> 128	0.25	1	Study CAZ-AVI-M2-107 (Asia-Pacific 2012)
	26	0.12-128	0.5	64	0.12-1	0.25	0.5	Study CAZ-AVI-M2-108 (China 2013)
	100	≤ 0.06-> 128	0.25	64	≤ 0.06-4	0.12	0.5	Study CAZ104-M2-006-AAC11A3001 (Japan 2013)
	42	0.12-> 128	0.5	64	≤ 0.015-2	0.25	0.5	Study CAZ-AVI-M2-105 (Middle East and Africa 2012)
CLSI Broth Microdilution (Dried)	951	0.03-> 32	0.25	> 32	≤ 0.015-4	0.12	0.5	Study CAZ AVI M2 101 (USA 2012)
	379	0.03-> 32	0.25	> 32	≤ 0.03-4	0.12	0.5	Study CAZ-AVI-M2-098 (USA 2011)
	428	0.06-> 32	0.25	> 32	≤ 0.03-> 32	0.12	0.5	Study CAZ-AVI-M2-088 (Europe 2011)
	172	0.06-> 32	2	> 32	≤ 0.03-> 32	0.25	1	Study CAZ-AVI-M2-091 (Latin America 2011)
	219	0.03-> 32	0.5	> 32	≤ 0.03-> 32	0.25	1	Study CAZ-AVI-M2-090 (Asia-Pacific and South Africa 2011)

The data indicate that the ceftazidime-avibactam MIC90 values ranged from 0.25-1 mg/L for both *Enterobacter* species. The MIC90 ranged from 0.25 to 1 mg/L against isolates from the United States and Europe. However, it was noted that MIC values as high as 128 mg/L were observed against a small subset of isolates. Additionally, higher MIC values were noted for *E. cloacae* isolates based on both the MIC90 values and the MIC ranges. There were minimal regional differences in ceftazidime-avibactam activity noted among the studies. In another study, the in vitro activity of ceftazidime-avibactam against *E. aerogenes* collected during the 2012 surveillance program is shown in Table 12.

Table 12. Activity of Ceftazidime-Avibactam and Comparators against *E. aerogenes* from the 2012 Global Surveillance Program

Drug	*N*	*MIC Range (mg/L)*	*MIC_{50} (mg/L)*	*MIC_{90} (mg/L)*	*CLSI*			*EUCAST*		
					%Sus	*%Int*	*%Res*	*%Sus*	*%Int*	*%Res*
United States (Dried)[a]										
Ceftazidime-avibactam	357	≤ 0.015 - 16	0.12	0.25	-	-	-	-	-	-
Ceftazidime	357	0.06-> 32	0.25	32	77.0	1.7	21.3	74.2	2.8	23.0
Gentamicin	357	≤ 1 - > 8	≤ 1	≤ 1	97.2	0.6	2.2	96.4	0.8	2.8
Levofloxacin	357	≤ 0.12 - > 4	≤ 0.12	0.25	96.9	1.1	2.0	95.5	1.4	3.1
Meropenem	357	≤ 0.06 - 4	≤ 0.06	≤ 0.06	99.4	0.3	0.3	99.7	0.3	0.0
Piperacillin-tazobactam	357	≤ 0.5 - 64	4	64	80.6	14.7	4.8	73.8	6.8	19.4
United States (Frozen)[b]										
Ceftazidime-avibactam	76	≤ 0.015 - 2	0.12	0.5	-	-	-	-	-	-
Ceftazidime	76	0.06 - 128	0.25	64	73.7	0.0	26.3	72.4	1.3	26.3
Amikacin	76	≤ 0.25 - 4	1	2	100	0.0	0.0	100	0.0	0.0
Levofloxacin	76	≤ 0.03 - > 4	0.06	0.25	97.4	0.0	2.6	96.1	1.3	2.6
Meropenem	76	0.008 - 1	0.06	0.12	100	0.0	0.0	100	0.0	0.0
Piperacillin-tazobactam	76	1 - 128	4	64	75.0	17.1	7.9	72.4	2.6	25.0
Europe (Frozen)[c]										
Ceftazidime-avibactam	161	0.06 - 128	0.25	1	-	-	-	-	-	-
Ceftazidime	161	0.12 - > 128	0.5	128	63.4	1.9	34.8	58.4	5.0	36.7
Amikacin	161	0.5 - 16	2	4	100	0.0	0.0	98.8	1.2	0.0
Levofloxacin	161	≤ 0.03 - > 4	0.06	4	89.4	1.2	9.3	86.3	3.1	10.6
Meropenem	161	0.03 - > 8	0.06	0.12	98.8	0.6	0.6	99.4	0.0	0.6
Piperacillin-tazobactam	161	1 - > 128	4	128	65.2	21.1	13.7	61.5	3.7	34.8

Drug	*N*	*MIC Range (mg/L)*	*MIC_{50} (mg/L)*	*MIC_{90} (mg/L)*	*CLSI*			*EUCAST*		
					%Sus	*%Int*	*%Res*	*%Sus*	*%Int*	*%Res*
Latin America (Frozen)[d]										
Ceftazidime-avibactam	40	0.03 - 1	0.12	0.5	-	-	-	-	-	-
Ceftazidime	40	0.12 - 128	0.25	32	80.0	0.0	20.0	77.5	2.5	20.0
Amikacin	40	0.5 - > 32	1	4	95.0	2.5	2.5	95.0	0.0	5.0
Levofloxacin	40	≤0.03- >4	0.06	1	92.5	0.0	7.5	90.0	2.5	7.5
Meropenem	40	0.03-1	0.06	0.12	100	0.0	0.0	100	0.0	0.0
Piperacillin-tazobactam	40	1->128	4	64	80.0	17.5	2.5	77.5	2.5	20.0
Middle East and Africa (Frozen)[e]										
Ceftazidime-avibactam	20	0.06 - 1	0.12	0.25	-	-	-	-	-	-
Ceftazidime	20	0.12 - 64	0.25	16	80.0	0.0	20.0	80.0	0.0	20.0
Amikacin	20	0.5 - 16	1	2	100	0.0	0.0	95.0	5.0	0.0
Levofloxacin	20	≤ 0.03 - 1	0.06	0.06	100	0.0	0.0	100	0.0	0.0
Meropenem	20	0.03 - 0.12	0.06	0.06	100	0.0	0.0	100	0.0	0.0
Piperacillin-tazobactam	20	2 - 128	4	32	85.0	10.0	5.0	80.0	5.0	15.0
Asia/Pacific Region (Frozen)[f]										
Ceftazidime-avibactam	97	≤ 0.015 - 16	0.25	1	-	-	-	-	-	-
Ceftazidime	97	0.06 - > 128	2	128	53.6	4.1	42.3	49.5	4.1	46.4
Amikacin	97	0.5 - 16	1	2	100	0.0	0.0	99.0	1.0	0.0
Levofloxacin	97	≤ 0.03 - > 4	0.06	2	91.8	4.1	4.1	88.7	3.1	8.3
Meropenem	97	0.015 - > 8	0.06	0.12	99.0	0.0	1.0	99.0	0.0	1.0
Piperacillin-tazobactam	97	1 - > 128	8	128	57.7	26.8	15.5	51.6	6.2	42.3

[a] Study CAZ-AVI-M2-101; [b] Study CAZ-AVI-M2-100; [c] Study CAZ-AVI-M2-106; [d] Study CAZ-AVI-M2-104; [e] Study CAZ-AVI-M2-105; [f] Study CAZ-AVI-M2-107

The data show that the MIC90 for ceftazidime-avibactam was generally lower than all the comparator agents except meropenem against *E. aerogenes*. Ceftazidime-avibactam demonstrated MIC90 values ranging from 0.5-2 mg/L against the ceftazidime-non-susceptible subset (Table 13). A large proportion of these isolates were non-susceptible to piperacillin-tazobactam, which suggests that the primary mechanism of resistance is overexpression of AmpC β-lactamase. The activity of ceftazidime-avibactam against these isolates highlights the activity of this combination against presumed AmpC overexpressing organisms.

Table 13. Activity of Ceftazidime-Avibactam and Comparators against ceftazidime-non-susceptible *E. aerogenes* from the 2012 Global Surveillance Program

Drug	*N*	*MIC Range (mg/L)*	*MIC_{50} (mg/L)*	*MIC_{90} (mg/L)*	*CLSI*			*EUCAST*		
					%Sus	*%Int*	*%Res*	*%Sus*	*%Int*	*%Res*
United States (Dried)[a]										
Ceftazidime-avibactam	82	≤ 0.015-16	0.25	0.5	-	-	-	-	-	-
Ceftazidime	82	8-> 32	32	> 32	0.0	7.3	92.7	0.0	0.0	100
Gentamicin	82	≤ 1-> 8	≤ 1	4	91.5	2.4	6.1	87.8	3.7	8.5
Levofloxacin	82	≤ 0.12-> 4	≤ 0.12	2	90.2	3.7	6.1	85.4	4.8	9.8
Meropenem	82	≤ 0.06-4	≤ 0.06	0.12	97.6	1.2	1.2	98.8	1.2	0.0
Piperacillin-tazobactam	82	1-> 64	64	> 64	22.0	57.3	20.7	11.0	11.0	78.0
United States (Frozen)[b]										
Ceftazidime-avibactam	20	0.12 - 1	0.5	0.5	-	-	-	-	-	-
Ceftazidime	20	16 - 128	32	128	0.0	0.0	100	0.0	0.0	100
Amikacin	20	1 - 4	1	2	100	0.0	0.0	100	0.0	0.0
Levofloxacin	20	≤ 0.03 - > 4	0.06	0.5	95.0	0.0	5.0	90.0	5.0	5.0
Meropenem	20	0.03 - 0.12	0.06	0.12	100	0.0	0.0	100	0.0	0.0
Piperacillin-tazobactam	20	2 - 128	64	128	5.0	65.0	30.0	5.0	0.0	95.0
Europe (Frozen)[c]										
Ceftazidime-avibactam	59	0.12 - 128	0.5	2	-	-	-	-	-	-
Ceftazidime	59	8 - > 128	64	> 128	0.0	5.1	94.9	0.0	0.0	100
Amikacin	59	0.5 - 16	2	8	100	0.0	0.0	96.6	3.4	0.0
Levofloxacin	59	≤ 0.03 - > 4	0.12	> 4	76.3	3.4	20.3	71.2	5.1	23.7
Meropenem	59	0.03 - > 8	0.06	0.25	96.6	1.7	1.7	98.3	0.0	1.7
Piperacillin-tazobactam	59	4 - > 128	64	128	10.2	52.5	37.3	5.1	5.1	89.8
Latin America (Frozen)[d]										
Ceftazidime-avibactam	8	0.25 - 1	--	--	-	-	-	-	-	-
Ceftazidime										
Amikacin	8	0.5 - > 32	--	--	87.5	0.0	12.5	87.5	0.0	12.5
Levofloxacin	8	0.06 - 2	--	--	100	0.0	0.0	87.5	12.5	0.0
Meropenem	8	0.03 - 0.12	--	--	100	0.0	0.0	100	0.0	0.0
Piperacillin-tazobactam	8	16 - > 128	--	--	12.5	75.0	12.5	0.0	12.5	87.5
Middle East and Africa (Frozen)[e]										
Ceftazidime-avibactam	4	0.25 - 1	--	--	-	-	-	-	-	-
Ceftazidime	4	16 - 64	--	--	0.0	0.0	100	0.0	0.0	100
Amikacin	4	0.5 - 16	--	--	100	0.0	0.0	75.0	25.0	0.0
Levofloxacin	4	0.06 - 1	--	--	100	0.0	0.0	100	0.0	0.0
Meropenem	4	0.06 - 0.12	--	--	100	0.0	0.0	100	0.0	0.0
Piperacillin-tazobactam	4	16 - 128	--	--	25.0	50.0	25.0	0.0	25.0	75.0
Asia/Pacific Region (Frozen)[f]										
Ceftazidime-avibactam	45	0.06 - 16	0.5	1	-	-	-	-	-	-
Ceftazidime	45	8 - > 128	64	> 128	0.0	8.9	91.1	0.0	0.0	100
Amikacin	45	0.5 - 16	1	4	100	0.0	0.0	97.8	2.2	0.0
Levofloxacin	45	≤ 0.03 - > 4	0.12	4	86.7	8.9	4.4	80.0	6.7	13.3
Meropenem	45	0.03 - > 8	0.12	0.12	97.8	0.0	2.2	97.8	0.0	2.2
Piperacillin-tazobactam	45	8 - > 128	64	> 128	11.1	55.6	33.3	2.2	8.9	88.9

[a] Study CAZ-AVI-M2-101; [b] Study CAZ-AVI-M2-100; [c] Study CAZ-AVI-M2-106; [d] Study CAZ-AVI-M2-104; [e] Study CAZ-AVI-M2-105; [f] Study CAZ-AVI-M2-107

The in vitro activity of ceftazidime-avibactam against additional *E. cloacae* collected during the 2012 surveillance program is shown in Table 14. Like above, the addition of avibactam to ceftazidime extended the activity of ceftazidime and produced lower MIC90 values against *E. cloacae*.

Table 14. Activity of Ceftazidime-Avibactam and Comparators against *E. cloacae* from the 2012 Global Surveillance Program

Drug	*N*	*MIC Range (mg/L)*	*MIC_{50} (mg/L)*	*MIC_{90} (mg/L)*	*CLSI*			*EUCAST*		
					%Sus	*%Int*	*%Res*	*%Sus*	*%Int*	*%Res*
United States (Dried)[a]										
Ceftazidime-avibactam	951	≤ 0.015-4	0.12	0.5	-	-	-	-	-	-
Ceftazidime	951	0.03-> 32	0.25	> 32	79.0	1.0	20.00	76.9	2.1	21.0
Gentamicin	951	≤ 1 - > 8	≤ 1	≤ 1	94.5	0.9	4.6	94.2	0.3	5.5
Levofloxacin	951	≤ 0.12 - > 4	≤ 0.12	0.5	94.1	2.0	3.9	92.5	1.6	5.9
Meropenem	951	≤ 0.06 - > 8	≤ 0.06	≤ 0.06	99.5	0.0	0.5	99.5	0.2	0.3
Piperacillin-tazobactam	951	≤ 0.5-> 64	2	64	85.0	7.1	7.9	80.9	4.1	15.0
United States (Frozen)[b]										
Ceftazidime-avibactam	87	0.06 - 1	0.25	1	-	-	-	-	-	-
Ceftazidime	87	0.12 - > 128	0.5	128	79.3	2.3	18.4	73.6	5.8	20.7
Amikacin	87	0.5 - > 32	1	2	98.9	0.0	1.2	98.9	0.0	1.2
Levofloxacin	87	≤ 0.03 - > 4	0.06	0.5	94.3	1.2	4.6	93.1	1.2	5.8
Meropenem	87	0.015 - 4	0.03	0.12	98.9	0.0	1.2	98.9	1.2	0.0
Piperacillin-tazobactam	87	≤ 0.25 - > 128	4	> 128	82.8	1.2	16.1	80.5	2.3	17.2
Europe (Frozen)[c]										
Ceftazidime-avibactam	306	≤ 0.015 - > 128	0.25	1	-	-	-	-	-	-
Ceftazidime	306	≤ 0.015 - > 128	0.5	128	67.7	1.6	30.7	64.4	3.3	32.4
Amikacin	306	0.5 - > 32	2	4	96.7	0.7	2.6	94.8	2.0	3.3
Levofloxacin	306	≤ 0.03 - > 4	0.06	2	92.8	2.0	5.2	88.2	4.6	7.2
Meropenem	306	0.015 - > 8	0.03	0.12	98.4	0.0	1.6	98.4	0.7	1.0
Piperacillin-tazobactam	306	≤ 0.25 - > 128	4	> 128	74.8	7.8	17.3	69.3	5.6	25.2
Latin America (Frozen)[d]										
Ceftazidime-avibactam	85	≤ 0.015 - 32	0.25	1	-	-	-	-	-	-
Ceftazidime	85	0.03 - > 128	2	> 128	52.9	1.2	45.9	48.2	4.7	47.1
Amikacin	85	0.5 - > 32	2	16	94.1	4.7	1.2	89.4	4.7	5.9
Levofloxacin	85	≤ 0.03 - > 4	0.06	> 4	76.5	1.2	22.4	74.1	2.4	23.5
Meropenem	85	0.008 - 0.5	0.06	0.12	100	0.0	0.0	100	0.0	0.0
Piperacillin-tazobactam	85	0.5 - > 128	4	> 128	67.1	15.3	17.7	62.4	4.7	32.9
Middle East and Africa (Frozen)[e]										
Ceftazidime-avibactam	42	≤ 0.015 - 2	0.25	0.5	-	-	-	-	-	-
Ceftazidime	42	0.12 - > 128	0.5	64	81.0	0.0	19.1	76.2	4.8	19.1
Amikacin	42	0.5 - > 32	1	4	97.6	0.0	2.4	95.2	2.4	2.4
Levofloxacin	42	≤ 0.03 - > 4	0.06	1	97.6	0.0	2.4	97.6	0.0	2.4
Meropenem	42	≤ 0.004 - 0.25	0.06	0.12	100	0.0	0.0	100	0.0	0.0
Piperacillin-tazobactam	42	≤ 0.25 - > 128	4	64	81.0	9.5	9.5	78.6	2.4	19.1
Asia/Pacific Region (Frozen)[f]										
Ceftazidime-avibactam	125	≤ 0.015 - > 128	0.25	1	-	-	-	-	-	-
Ceftazidime	125	0.06 - > 128	1	> 128	56.0	0.0	44.0	52.8	3.2	44.0
Amikacin	125	≤ 0.25 - > 32	1	8	97.6	0.0	2.4	93.6	4.0	2.4
Levofloxacin	125	≤ 0.03 - > 4	0.06	> 4	80.8	4.0	15.2	76.8	4.0	19.2
Meropenem	125	0.015 - > 8	0.06	0.25	96.0	0.8	3.2	96.8	2.4	0.8
Piperacillin-tazobactam	125	0.5 - > 128	4	> 128	63.2	11.2	25.6	58.4	4.8	36.8

[a] Study CAZ-AVI-M2-101; [b] Study CAZ-AVI-M2-100; [c] Study CAZ-AVI-M2-106; [d] Study CAZ-AVI-M2-104; [e] Study CAZ-AVI-M2-105; [f] Study CAZ-AVI-M2-107

The MIC90 for ceftazidime-avibactam was the same or lower than all the comparator agents except meropenem. Susceptibility values were generally high for the aminoglycosides, levofloxacin and meropenem. Ceftazidime-non-susceptibility values ranged from 19% to 47.1%. The ceftazidime-avibactam MIC90 values ranged from 1-2 mg/L against these isolates (Table 15), including against the presumed AmpC overexpressing isolates that were non-susceptible to piperacillin-tazobactam.

Table 15. Activity of Ceftazidime-Avibactam and Comparators against ceftazidime-non-susceptible *E. cloacae* from the 2012 Global Surveillance Program

Drug	*N*	*MIC Range (mg/L)*	*MIC_{50} (mg/L)*	*MIC_{90} (mg/L)*	*CLSI*			*EUCAST*		
					%Sus	*%Int*	*%Res*	*%Sus*	*%Int*	*%Res*
United States (Dried)[a]										
Ceftazidime-avibactam	200	≤ 0.015 - 4	0.5	1	-	-	-	-	-	-
Ceftazidime	200	8-> 32	> 32	> 32	0.0	5.0	95.0	0.0	0.0	100
Gentamicin	200	≤ 1 - > 8	≤ 1	> 8	77.4	3.5	19.1	76.4	1.0	22.6
Levofloxacin	200	≤ 0.12 - > 4	≤ 0.12	> 4	76.9	8.0	15.1	73.4	3.5	23.1
Meropenem	200	≤ 0.06 - > 8	≤ 0.06	0.25	97.5	0.0	2.5	97.5	1.0	1.5
Piperacillin-tazobactam	200	2-> 64	64	> 64	29.1	33.2	37.7	17.1	12.0	70.9
United States (Frozen)[b]										
Ceftazidime-avibactam	18	0.12 - 1	1	1	-	-	-	-	-	-
Ceftazidime	18	8 - > 128	128	> 128	0.0	11.1	88.9	0.0	0.0	100
Amikacin	18	1 - 2	1	2	100	0.0	0.0	100	0.0	0.0
Levofloxacin	18	≤ 0.03 - > 4	0.12	> 4	72.2	5.6	22.2	72.2	0.0	27.8
Meropenem	18	0.03 - 0.25	0.06	0.12	100	0.0	0.0	100	0.0	0.0
Piperacillin-tazobactam	18	4 - > 128	> 128	> 128	22.2	5.6	72.2	22.2	0.0	77.8
Europe (Frozen)[c]										
Ceftazidime-avibactam	99	0.12 - > 128	0.5	2	-	-	-	-	-	-
Ceftazidime	99	8 - > 128	128	> 128	0.0	5.1	95.0	0.0	0.0	100
Amikacin	99	0.5 - > 32	2	32	89.9	2.0	8.1	84.9	5.1	10.1
Levofloxacin	99	≤ 0.03 - > 4	0.5	> 4	81.8	3.0	15.2	68.7	13.1	18.2
Meropenem	99	0.03 - > 8	0.06	0.25	95.0	0.0	5.1	95.0	2.0	3.0
Piperacillin-tazobactam	99	2 - > 128	128	> 128	27.3	21.2	51.5	16.2	11.1	72.7
Drug	*N*	*MIC Range (mg/L)*	*MIC_{50} (mg/L)*	*MIC_{90} (mg/L)*	*CLSI*			*EUCAST*		
					%Sus	*%Int*	*%Res*	*%Sus*	*%Int*	*%Res*
Latin America (Frozen)[d]										
Ceftazidime-avibactam	40	0.12 - 32	0.5	2	-	-	-	-	-	-
Ceftazidime	40	8 - > 128	128	> 128	0.0	2.5	97.5	0.0	0.0	100
Amikacin	40	0.5 - > 32	4	32	87.5	10.0	2.5	77.5	10.0	12.5
Levofloxacin	40	0.06 - > 4	1	> 4	57.5	2.5	40.0	55.0	2.5	42.5
Meropenem	40	0.015 - 0.5	0.06	0.25	100	0.0	0.0	100	0.0	0.0
Piperacillin-tazobactam	40	2 - > 128	32	> 128	35.0	30.0	35.0	27.5	7.5	65.0
Middle East and Africa (Frozen)[e]										
Ceftazidime-avibactam	8	0.25 - 2	--	--	-	-	-	-	-	-
Ceftazidime	8	32 - > 128	--	--	0.0	0.0	100	0.0	0.0	100
Amikacin	8	0.5 - > 32	--	--	87.5	0.0	12.5	87.5	0.0	12.5
Levofloxacin	8	0.06 - > 4	--	--	87.5	0.0	12.5	87.5	0.0	12.5
Meropenem	8	≤ 0.004 - 0.25	--	--	100	0.0	0.0	100	0.0	0.0
Piperacillin-tazobactam	8	16 - > 128	--	--	12.5	37.5	50.0	0.0	12.5	87.5
Asia/Pacific Region (Frozen)[f]										
Ceftazidime-avibactam	55	0.12 - > 128	0.5	2	-	-	-	-	-	-
Ceftazidime	55	16 - > 128	128	> 128	0.0	0.0	100	0.0	0.0	100
Amikacin	55	0.5 - > 32	2	16	94.6	0.0	5.5	87.3	7.3	5.5
Levofloxacin	55	≤ 0.03 - > 4	1	> 4	63.6	5.5	30.9	54.6	9.1	36.4
Meropenem	55	0.015 - > 8	0.12	0.5	92.7	1.8	5.5	94.6	3.6	1.8
Piperacillin-tazobactam	55	4 - > 128	128	> 128	18.2	25.5	56.4	7.3	10.9	81.8

[a] Study CAZ-AVI-M2-101; [b] Study CAZ-AVI-M2-100; [c] Study CAZ-AVI-M2-106; [d] Study CAZ-AVI-M2-104; [e] Study CAZ-AVI-M2-105; [f] Study CAZ-AVI-M2-107

Activity against *Proteus* species

The in vitro activity of ceftazidime-avibactam was assessed against 2,419 *P. mirabilis* and 370 *P. vulgaris* isolates from 17 separate studies (16 and Table 17).

Table 16. Summary of In Vitro Studies to Evaluate the Activity of Ceftazidime-Avibactam Against *P. mirabilis*

Test Method	*[N]*	*Ceftazidime MIC (mg/L)*			*Ceftazidime-avibactam MIC (mg/L)*			*Study*
		Range	*50%*	*90%*	*Range*	*50%*	*90%*	
CLSI Broth Microdilution (Frozen)	25	≤ 0.03-2	≤ 0.03	0.06	≤ 0.03-0.12	≤ 0.03	≤ 0.03	Study CAZ-AVI-M2-093 (USA 2013)
	25	≤ 0.06-128	≤ 0.06	0.12	≤ 0.06-2	≤ 0.06	≤ 0.06	Study CAZ-AVI-M2-109 (USA 2013)
	97	≤ 0.0.15-2	0.06	0.12	≤ 0.015-0.12	0.03	0.06	Study CAZ-AVI-M2-100 (USA 2012)
	307	≤ 0.015->128	0.06	4	≤ 0.015-8	0.03	0.12	Study CAZ-AVI-M2-106 (Europe 2012)
	39	≤ 0.25-4	≤ 0.25	4	≤ 0.06-0.25	≤ 0.06	0.12	Study CAZ-AVI-M2-097 (Canada 2013)
	91	≤ 0.015-8	0.06	1	≤ 0.015-0.12	0.03	0.06	Study CAZ-AVI-M2-104 (Latin America 2012)
	137	≤ 0.015-> 128	0.06	0.12	≤ 0.015-4	0.03	0.06	Study CAZ-AVI-M2-107 (Asia-Pacific 2012)
	24	0.06-> 128	0.06	64	0.06-1	0.06	0.25	Study CAZ-AVI-M2-108 (China 2013)
	100	≤ 0.06-8	0.12	0.5	≤ 0.06-0.25	≤ 0.06	≤ 0.06	Study CAZ104-M2-006-AAC11A3001 (Japan 2013)
	44	≤ 0.015-32	0.06	1	≤ 0.015-0.06	0.03	0.06	Study CAZ-AVI-M2-105 (Middle East and Africa 2012)
CLSI Broth Microdilution (Dried)	683	0.03-8	0.06	0.12	≤ 0.015-0.5	0.03	0.06	Study CAZ AVI M2 101 (USA 2012)
	230	0.03-4	0.06	0.12	≤ 0.03-0.12	≤ 0.03	0.06	Study CAZ-AVI-M2-098 (USA 2011)
	118	0.03-8	0.06	0.12	≤ 0.03-0.25	0.06	0.12	Study CAZ104-M2-005-09-NXL-02 (USA 2009)
	270	≤ 0.015-> 32	0.06	1	≤ 0.03-2	≤ 0.03	0.06	Study CAZ-AVI-M2-088 (Europe 2011)
	116	0.03-32	0.06	1	≤ 0.03-0.25	0.06	0.12	Study CAZ104-M2-005-09-NXL-02 (Europe 2009)
	57	0.03-> 32	0.06	2	≤ 0.03-0.5	≤ 0.03	0.12	Study CAZ-AVI-M2-091 (Latin America 2011)
	56	0.03-> 32	0.06	0.25	≤ 0.03-1	≤ 0.03	0.06	Study CAZ-AVI-M2-090 (Asia-Pacific and South Africa 2011)

Table 17. Summary of In Vitro Studies to Evaluate the Activity of Ceftazidime-Avibactam Against *P. vulgaris*

Test Method	*[N]*	*Ceftazidime MIC (mg/L)*			*Ceftazidime-avibactam MIC (mg/L)*			*Study*
		Range	*50%*	*90%*	*Range*	*50%*	*90%*	
CLSI Broth Microdilution (Frozen)	25	≤ 0.03-0.5	0.06	0.25	≤ 0.03-0.06	≤ 0.03	0.06	Study CAZ-AVI-M2-093 (USA 2013)
	17	≤ 0.06-128	0.12	1	≤ 0.06-4	≤ 0.06	1	Study CAZ-AVI-M2-109 (USA 2013)
	21	≤ 0.015-16	0.06	0.25	≤ 0.015-2	0.03	0.12	Study CAZ-AVI-M2-100 (USA 2012)
	131	≤ 0.015-16	0.06	0.25	≤ 0.015-0.5	0.06	0.12	Study CAZ-AVI-M2-106 (Europe 2012)
	13	≤ 0.25-0.5	≤ 0.25	0.5	≤ 0.06-0.25	0.12	0.12	Study CAZ-AVI-M2-097 (Canada 2013)
	17	0.03-32	0.12	32	0.03-0.25	0.06	0.12	Study CAZ-AVI-M2-104 (Latin America 2012)
	61	≤ 0.015-1	0.06	0.12	≤ 0.015-0.25	0.03	0.06	Study CAZ-AVI-M2-107 (Asia-Pacific 2012)
	27	0.06-1	0.06	0.5	0.06-0.12	0.06	0.12	Study CAZ-AVI-M2-108 (China 2013)
	50	≤ 0.06-32	≤ 0.06	0.12	≤ 0.06-2	≤ 0.06	≤ 0.06	Study CAZ104-M2-006-AAC11A3001 (Japan 2013)
	8	≤ 0.015-0.12	-	-	≤ 0.015-0.06	-	-	Study CAZ-AVI-M2-105 (Middle East and Africa 2012)

Against *Proteus* species, ceftazidime-avibactam MIC90 values ranged from ≤ 0.03 to 1 mg/L. Against United States isolates, the MIC90 ranged from ≤ 0.03 to 1 mg/L and 0.06-0.12 mg/L for isolates from Europe. All isolates were inhibited by ≤ 4 mg/L ceftazidime-avibactam. A number of isolates from Europe and Asia-Pacific demonstrated ceftazidime MIC values ranging from 8-> 128 mg/L. There appear to be little regional differences in ceftazidime-avibactam activity noted among the studies. Ceftazidime-avibactam demonstrated robust activity against the *P. mirabilis* collected during the 2012 surveillance program shown in Table 18.

Table 18. Activity of Ceftazidime-Avibactam and Comparators against *P. mirabilis* from the 2012 Global Surveillance Program

Drug	*N*	*MIC Range (mg/L)*	*MIC_{50} (mg/L)*	*MIC_{90} (mg/L)*	*CLSI*			*EUCAST*		
					%Sus	*%Int*	*%Res*	*%Sus*	*%Int*	*%Res*
United States (Dried)[a]										
Ceftazidime-avibactam	683	≤ 0.015-0.5	0.03	0.06	-	-	-	-	-	-
Ceftazidime	683	0.03-8	0.06	0.12	99.1	0.9	0.0	97.4	1.6	0.9
Gentamicin	683	≤ 1-> 8	≤ 1	8	88.7	2.6	8.7	84.6	4.2	11.3
Levofloxacin	683	≤ 0.12-> 4	≤ 0.12	> 4	75.5	5.4	19.1	71.4	4.1	24.5
Meropenem	683	≤ 0.06-0.5	≤ 0.06	0.12	100	0.0	0.0	100	0.0	0.0
Piperacillin-tazobactam	683	≤ 0.5-> 64	≤ 0.5	1	99.7	0.2	0.1	99.6	0.2	0.3
United States (Frozen)[b]										
Ceftazidime-avibactam	97	≤ 0.015 - 0.12	0.03	0.06	-	-	-	-	-	-
Ceftazidime	97	≤ 0.015 - 2	0.06	0.12	100	0.0	0.0	96.9	3.1	0.0
Amikacin	97	1 - 16	4	8	100	0.0	0.0	97.9	2.1	0.0
Levofloxacin	97	≤ 0.03 - > 4	0.12	> 4	73.2	2.1	24.7	68.0	5.2	26.8
Meropenem	97	0.015 - 1	0.06	0.12	100	0.0	0.0	100	0.0	0.0
Piperacillin-tazobactam	97	≤ 0.25 - 2	≤ 0.25	1	100	0.0	0.0	100	0.0	0.0
Europe (Frozen)[c]										
Ceftazidime-avibactam	307	≤ 0.015 - 8	0.03	0.12	-	-	-	-	-	-
Ceftazidime	307	≤ 0.015 - > 128	0.06	4	91.2	3.9	4.9	89.3	2.0	8.8
Amikacin	307	0.5 - > 32	4	8	91.9	0.0	8.1	90.2	1.6	8.1
Levofloxacin	307	≤ 0.03 - > 4	0.12	> 4	81.1	3.9	15.0	74.9	6.2	18.9
Meropenem	307	≤ 0.004 - 4	0.12	0.25	99.7	0.0	0.3	99.7	0.3	0.0
Piperacillin-tazobactam	307	≤ 0.25 - > 128	0.5	2	97.1	1.0	2.0	96.1	1.0	2.9
Latin America (Frozen)[d]										
Ceftazidime-avibactam	91	≤ 0.015 - 0.12	0.03	0.06	-	-	-	-	-	-
Ceftazidime	91	≤ 0.015 - 8	0.06	1	98.9	1.1	0.0	92.3	6.6	1.1
Amikacin	91	≤ 0.25 - > 32	4	16	94.5	4.4	1.1	85.7	8.8	5.5
Levofloxacin	91	≤ 0.03 - > 4	0.06	> 4	73.6	1.1	25.3	70.3	3.3	26.4
Meropenem	91	0.03 - 1	0.06	0.12	100	0.0	0.0	100	0.0	0.0
Piperacillin-tazobactam	91	≤ 0.25 - 64	≤ 0.25	1	98.9	1.1	0.0	98.9	0.0	1.1
Middle East and Africa (Frozen)[e]										
Ceftazidime-avibactam	44	≤ 0.015 - 0.06	0.03	0.06	-	-	-	-	-	-
Ceftazidime	44	≤ 0.015 - 32	0.06	1	97.7	0.0	2.3	93.2	4.6	2.3
Amikacin	44	1 - 16	4	8	100	0.0	0.0	95.5	4.6	0.0
Levofloxacin	44	0.06 - > 4	0.06	> 4	75.0	6.8	18.2	75.0	0.0	25.0
Meropenem	44	0.03 - 0.25	0.06	0.12	100	0.0	0.0	100	0.0	0.0
Piperacillin-tazobactam	44	≤ 0.25 - 32	≤ 0.25	1	97.7	2.3	0.0	97.7	0.0	2.3
Asia/Pacific Region (Frozen)[f]										
Ceftazidime-avibactam	137	≤ 0.015 - 4	0.03	0.06	-	-	-	-	-	-
Ceftazidime	137	≤ 0.015 - > 128	0.06	0.12	95.6	0.7	3.7	94.2	1.5	4.4
Amikacin	137	≤ 0.25 - > 32	4	8	97.8	1.5	0.7	95.6	2.2	2.2
Levofloxacin	137	≤ 0.03 - > 4	0.12	> 4	78.1	3.7	18.3	69.3	8.8	21.9
Meropenem	137	0.03 - 0.25	0.06	0.12	100	0.0	0.0	100	0.0	0.0
Piperacillin-tazobactam	137	≤ 0.25 - 32	≤ 0.25	0.5	99.3	0.7	0.0	99.3	0.0	0.7

[a] Study CAZ-AVI-M2-101; [b] Study CAZ-AVI-M2-100; [c] Study CAZ-AVI-M2-106; [d] Study CAZ-AVI-M2-104; [e] Study CAZ-AVI-M2-105; [f] Study CAZ-AVI-M2-107

The MIC90 values for ceftazidime-avibactam were lower than all the comparator agents tested and were similar to meropenem. Susceptibility rates were > 90% for ceftazidime, the aminoglycosides, piperacillin-tazobactam and meropenem, but ranged from 73.2-81.1% for levofloxacin. Similar results were obtained for *P. vulgaris* isolates (Table 19).

Table 19. Activity of Ceftazidime-Avibactam and Comparators against *P. vulgaris* from the 2012 Global Surveillance Program

Drug	*N*	*MIC Range (mg/L)*	*MIC_{50} (mg/L)*	*MIC_{90} (mg/L)*	*CLSI*			*EUCAST*		
					%Sus	*%Int*	*%Res*	*%Sus*	*%Int*	*%Res*
United States (Dried)[a]										
Ceftazidime-avibactam	153	0.03-0.5	0.06	0.06	-	-	-	-	-	-
Ceftazidime	153	0.03-0.5	0.06	0.12	100	0.0	0.0	100	0.0	0.0
Gentamicin	153	≤ 1-8	≤ 1	2	98.7	1.3	0.0	94.7	4.0	1.3
Levofloxacin	153	≤ 0.12-> 4	≤ 0.12	≤ 0.12	98.7	0.6	0.7	98.7	0.0	1.3
Meropenem	153	≤ 0.06-0.12	≤ 0.06	0.12	100	0.0	0.0	100	0.0	0.0
Piperacillin-tazobactam	153	≤ 0.5-> 64	≤ 0.5	1	99.3	0.0	0.7	99.3	0.0	0.7
United States (Frozen)[b]										
Ceftazidime-avibactam	21	≤ 0.015 - 2	0.03	0.12	-	-	-	-	-	-
Ceftazidime	21	≤ 0.015 - 16	0.06	0.25	95.2	0.0	4.8	90.5	4.8	4.8
Amikacin	21	1 - 8	2	4	100	0.0	0.0	100	0.0	0.0
Levofloxacin	21	≤ 0.03 - > 4	0.06	0.25	90.5	0.0	9.5	90.5	0.0	9.5
Meropenem	21	0.06 - 0.12	0.12	0.12	100	0.0	0.0	100	0.0	0.0
Piperacillin-tazobactam	21	≤ 0.25 - 32	0.5	8	90.5	9.5	0.0	90.5	0.0	9.5
Europe (Frozen)[c]										
Ceftazidime-avibactam	131	≤ 0.015 - 0.5	0.06	0.12	-	-	-	-	-	-
Ceftazidime	131	≤ 0.015 - 16	0.06	0.25	97.7	1.5	0.8	97.7	0.0	2.3
Amikacin	131	0.5 - > 32	2	4	99.2	0.0	0.8	97.7	1.5	0.8
Levofloxacin	131	≤ 0.03 - > 4	0.06	0.25	96.2	2.3	1.5	94.7	1.5	3.8
Meropenem	131	0.015 - 1	0.06	0.25	100	0.0	0.0	100	0.0	0.0
Piperacillin-tazobactam	131	≤ 0.25 - 8	≤ 0.25	1	100	0.0	0.0	100	0.0	0.0

Drug	*N*	*MIC Range (mg/L)*	*MIC_{50} (mg/L)*	*MIC_{90} (mg/L)*	*CLSI*			*EUCAST*		
					%Sus	*%Int*	*%Res*	*%Sus*	*%Int*	*%Res*
Latin America (Frozen)[d]										
Ceftazidime-avibactam	17	0.03 - 0.25	0.06	0.12	-	-	-	-	-	-
Ceftazidime	17	0.03 - 32	0.12	32	88.2	0.0	11.8	88.2	0.0	11.8
Amikacin	17	1 - > 32	2	> 32	82.4	5.9	11.8	82.4	0.0	17.7
Levofloxacin	17	≤ 0.03 - > 4	0.06	2	94.1	0.0	5.9	88.2	5.9	5.9
Meropenem	17	0.03 - 0.12	0.06	0.12	100	0.0	0.0	100	0.0	0.0
Piperacillin-tazobactam	17	≤ 0.25 - 2	0.5	1	100	0.0	0.0	100	0.0	0.0
Middle East and Africa (Frozen)[e]										
Ceftazidime-avibactam	-	-	-	-	-	-	-	-	-	-
Ceftazidime	-	-	-	-	-	-	-	-	-	-
Amikacin	-	-	-	-	-	-	-	-	-	-
Levofloxacin	-	-	-	-	-	-	-	-	-	-
Meropenem	-	-	-	-	-	-	-	-	-	-
Piperacillin-tazobactam	-	-	-	-	-	-	-	-	-	-
Asia/Pacific Region (Frozen)[f]										
Ceftazidime-avibactam	61	≤ 0.015 - 0.25	0.03	0.06	-	-	-	-	-	-
Ceftazidime	61	≤ 0.015 - 1	0.06	0.12	100	0.0	0.0	100	0.0	0.0
Amikacin	61	≤ 0.25 - 8	2	4	100	0.0	0.0	100	0.0	0.0
Levofloxacin	61	≤ 0.03 - 4	0.06	0.25	98.4	1.6	0.0	95.1	3.3	1.6
Meropenem	61	0.03 - 0.25	0.06	0.12	100	0.0	0.0	100	0.0	0.0
Piperacillin-tazobactam	61	≤ 0.25 - 1	≤ 0.25	0.5	100	0.0	0.0	100	0.0	0.0

[a] Study CAZ-AVI-M2-101; [b] Study CAZ-AVI-M2-100; [c] Study CAZ-AVI-M2-106; [d] Study CAZ-AVI-M2-104; [e] Study CAZ-AVI-M2-105; [f] Study CAZ-AVI-M2-107

Activity against other *Enterobacteriaceae*

The Applicant also assessed the activity of ceftazidime-avibactam against an additional 5,462 representative isolates of *Enterobacteriaceae* species. Ceftazidime-avibactam MIC90 values ranged from 0.12 to 1 mg/L against 182 *Citrobacter freundii* (Table 20) and 176 *Citrobacter koseri* (Table 21) from five different studies.

Table 20. Summary of In Vitro Studies to Evaluate the Activity of Ceftazidime-Avibactam Against *Citrobacter freundii*

Test Method	*[N]*	*Ceftazidime MIC (mg/L)*			*Ceftazidime-avibactam MIC (mg/L)*			*Study*
		Range	*50%*	*90%*	*Range*	*50%*	*90%*	
CLSI Broth Microdilution (Frozen)	25	0.06-128	0.25	32	0.06-1	0.12	0.25	Study CAZ-AVI-M2-093 (USA 2013)
	22	0.25-> 128	0.5	128	≤ 0.06-1	0.25	0.5	Study CAZ-AVI-M2-109 (USA 2013)
	11	≤ 0.25-32	0.5	1	0.12-0.5	0.12	0.25	Study CAZ-AVI-M2-097 (Canada 2013)
	24	0.06-> 128	8	128	0.06-2	0.25	1	Study CAZ-AVI-M2-108 (China 2013)
	100	0.12-> 128	0.5	128	≤ 0.06-1	0.12	0.25	Study CAZ104-M2-006-AAC11A3001 (Japan 2013)

Table 21. Summary of In Vitro Studies to Evaluate the Activity of Ceftazidime-Avibactam Against *Citrobacter koseri*

Test Method	*[N]*	*Ceftazidime MIC (mg/L)*			*Ceftazidime-avibactam MIC (mg/L)*			*Study*
		Range	*50%*	*90%*	*Range*	*50%*	*90%*	
CLSI Broth Microdilution (Frozen)	25	0.06-2	0.12	1	≤ 0.63-0.25	0.06	0.12	Study CAZ-AVI-M2-093 (USA 2013)
	34	0.12-128	0.25	0.5	0.12-1	0.12	0.25	Study CAZ-AVI-M2-109 (USA 2013)
	40	≤ 0.25-> 32	≤ 0.25	1	≤ 0.06-1	0.12	0.25	Study CAZ-AVI-M2-097 (Canada 2013)
	27	0.06-64	0.12	0.5	0.06-0.5	0.12	0.25	Study CAZ-AVI-M2-108 (China 2013)
	50	0.12-> 128	0.12	8	≤ 0.06-0.5	≤ 0.06	0.25	Study CAZ104-M2-006-AAC11A3001 (Japan 2013)

All of these isolates were inhibited by ≤ 2 mg/L ceftazidime-avibactam, including against ceftazidime-non-susceptible isolates that had ceftazidime MIC values ranging from 8-> 128 mg/L. An additional 1,722 *Citrobacter* spp. isolates were collected as part of the 2012 global surveillance program and in six other surveillance studies conducted from 2009-11 (Table 22). The ceftazidime-avibactam MIC90 values ranged from 0.25-0.5 mg/L in these studies, including against ceftazidime-non-susceptible isolates (Table 22). Nearly all of the isolates were inhibited by ≤ 4 mg/mL ceftazidime-avibactam.

Table 22. Summary of In Vitro Studies to Evaluate the Activity of Ceftazidime-Avibactam Against *Citrobacter* spp.

Test Method	**[N]**	*Ceftazidime MIC (mg/L)*			*Ceftazidime-avibactam MIC (mg/L)*			**Study**
		Range	*50%*	*90%*	*Range*	*50%*	*90%*	
CLSI Broth Microdilution (Frozen)	83	0.03-> 128	0.5	64	0.03-4	0.12	0.5	Study CAZ-AVI-M2-100 (USA 2012)
	239	≤ 0.015-> 128	0.5	128	≤ 0.015-32	0.12	0.5	Study CAZ-AVI-M2-106 (Europe 2012)
	62	≤ 0.015-> 128	0.5	64	≤ 0.015-1	0.12	0.5	Study CAZ-AVI-M2-104 (Latin America 2012)
	145	0.06-> 128	0.5	128	≤ 0.01503-128	0.12	0.5	Study CAZ-AVI-M2-107 (Asia-Pacific 2012)
	33	0.12-128	0.12	1	0.03-0.5	0.06	0.25	Study CAZ-AVI-M2-105 (Middle East and Africa 2012)
CLSI Broth Microdilution (Dried)	371	0.03-> 32	0.25	16	≤ 0.015-16	0.12	0.25	Study CAZ AVI M2 101 (USA 2012)
	272	0.03-> 32	0.25	> 32	≤ 0.03-4	0.12	0.25	Study CAZ-AVI-M2-098 (USA 2011)
	63	0.06-> 32	0.25	32	0.06-2	0.12	0.5	Study CAZ104-M2-005-09-NXL-02 (USA 2009)
	200	0.06-> 32	0.25	> 32	≤ 0.03-4	0.12	0.25	Study CAZ-AVI-M2-088 (Europe 2011)
	57	0.06-> 32	0.25	32	≤ 0.03-2	0.12	0.5	Study CAZ104-M2-005-09-NXL-02 (Europe 2009)
	51	0.06-> 32	0.5	> 32	≤ 0.03-> 32	0.12	0.25	Study CAZ-AVI-M2-091 (Latin America 2011)
	146	0.06-32	0.5	> 32	≤ 0.03-> 32	0.12	0.5	Study CAZ-AVI-M2-090(Asia-Pacific and South Africa 2011)

Ceftazidime-avibactam activity was also evaluated against 1,304 *Morganella morganii* (Table 23) collected across 17 surveillance studies. Nearly all the isolates tested had MIC values of ≤ 4 mg/L (the exceptions included a few isolates from the United States and the Middle East/Africa in 2012 that tested with MIC values of 8 mg/L). The MIC90 values for ceftazidime-avibactam ranged from ≤ 0.06-0.25 mg/L, including against ceftazidime-non-susceptible isolates with MIC values between 8 and > 128 mg/L and MIC90 values ranging from 4-64 mg/L.

Table 23. Summary of In Vitro Studies to Evaluate the Activity of Ceftazidime-Avibactam Against *Morganella morganii*

Test Method	*[N]*	*Ceftazidime MIC (mg/L)*			*Ceftazidime-avibactam MIC (mg/L)*			*Study*
		Range	*50%*	*90%*	*Range*	*50%*	*90%*	
CLSI Broth Microdilution (Frozen)	25	≤ 0.03-64	0.25	64	≤ 0.03-2	≤ 0.03	0.25	Study CAZ-AVI-M2-093 (USA 2013)
	32	≤ 0.06-32	0.12	8	≤ 0.06-0.25	≤ 0.06	0.12	Study CAZ-AVI-M2-109 (USA 2013)
	38	0.06-64	0.25	4	≤ 0.015-0.25	0.06	0.12	Study CAZ-AVI-M2-100 (USA 2012)
	108	≤ 0.015-> 128	0.12	8	≤ 0.015-2	0.06	0.12	Study CAZ-AVI-M2-106 (Europe 2012)
	57	≤ 0.25-32	0.5	16	≤ 0.06-4	0.12	0.25	Study CAZ-AVI-M2-097 (Canada 2013)
	40	≤ 0.015-64	0.25	16	≤ 0.015-1	0.06	0.25	Study CAZ-AVI-M2-104 (Latin America 2012)
	63	0.03-> 128	0.12	16	≤ 0.015-1	0.06	0.25	Study CAZ-AVI-M2-107 (Asia-Pacific 2012)
	25	0.06-128	1	64	0.06-1	0.12	1	Study CAZ-AVI-M2-108 (China 2013)
	50	≤ 0.06-128	0.12	0.5	≤ 0.06-1	≤ 0.06	≤ 0.06	Study CAZ104-M2-006-AAC11A3001 (Japan 2013)
	20	0.03-16	0.25	1	≤ 0.015-8	0.06	0.12	Study CAZ-AVI-M2-105 (Middle East and Africa 2012)
CLSI Broth Microdilution (Dried)	295	0.03-> 32	0.12	16	≤ 0.015-8	0.06	0.12	Study CAZ AVI M2 101 (USA 2012)
	192	0.03-> 32	0.12	16	≤ 0.03-1	0.06	0.12	Study CAZ-AVI-M2-098 (USA 2011)
	165	0.03-> 32	0.12	16	≤ 0.03-0.5	≤ 0.03	0.12	Study CAZ-AVI-M2-088 (Europe 2011)
	61	0.03-> 32	0.25	16	≤ 0.03-0.5	0.06	0.25	Study CAZ-AVI-M2-091 (Latin America 2011)
	133	0.03-> 32	0.12	8	≤ 0.03-0.5	≤ 0.03	0.06	Study CAZ-AVI-M2-090 (Asia-Pacific and South Africa 2011)

Ceftazidime-avibactam combination extended the activity of ceftazidime against many *Enterobacteriaceae* isolates and similar results were obtained for 57 *Providencia rettgeri* (Table 24), 59 *Providencia stuartii* (Table 25), 360 *Providencia* spp. (Table 26) and 1,996 *Serratia marcescens* (Table 27), where MIC90 values ranged from ≤ 0.06-1 mg/L. However, in one study from the United States the MIC90 value for 25 isolates of *Providencia rettgeri* was 4 mg/L. Again, a small subset of isolates was obtained with MIC values above 4 mg/L, but in general the addition of 4 mg/L avibactam lowered the MIC of ceftazidime at or below the susceptible breakpoint for ceftazidime alone.

Table 24. Summary of In Vitro Studies to Evaluate the Activity of Ceftazidime-Avibactam Against *P. rettgeri*

Test Method	*[N]*	*Ceftazidime MIC (mg/L)*			*Ceftazidime-avibactam MIC (mg/L)*			*Study*
		Range	*50%*	*90%*	*Range*	*50%*	*90%*	
CLSI Broth Microdilution (Frozen)	25	≤ 0.03-> 128	0.06	128	≤ 0.06-> 32	≤ 0.06	4	Study CAZ-AVI-M2-093 (USA 2013)
	12	≤ 0.06-0.12	≤ 0.06	≤ 0.06	≤ 0.06-0.12	≤ 0.06	≤ 0.06	Study CAZ-AVI-M2-109 (USA 2013)
	8	≤ 0.25-≤ 0.25	-	-	≤ 0.06-1	-	-	Study CAZ-AVI-M2-097 (Canada 2013)
	12[a]	0.06-> 128	0.5	> 128	0.06-> 128	0.5	1	Study CAZ-AVI-M2-108 (China 2013)

a *Providencia* spp.

Table 25. Summary of In Vitro Studies to Evaluate the Activity of Ceftazidime-Avibactam Against *P. stuartii*

Test Method	*[N]*	*Ceftazidime MIC (mg/L)*			*Ceftazidime-avibactam MIC (mg/L)*			*Study*
		Range	*50%*	*90%*	*Range*	*50%*	*90%*	
CLSI Broth Microdilution (Frozen)	25	0.06-> 128	1	32	0.06-16	0.25	2	Study CAZ-AVI-M2-093 (USA 2013)
	30	≤ 0.06-64	0.25	2	≤ 0.06-2	0.25	0.5	Study CAZ-AVI-M2-109 (USA 2013)
	4	≤ 0.25-0.5	-	-	0.25-0.5	-	-	Study CAZ-AVI-M2-097 (Canada 2013)

Table 26. Summary of In Vitro Studies to Evaluate the Activity of Ceftazidime-Avibactam Against *Providencia* spp.

Test Method	*[N]*	*Ceftazidime MIC (mg/L)*			*Ceftazidime-avibactam MIC (mg/L)*			*Study*
		Range	*50%*	*90%*	*Range*	*50%*	*90%*	
CLSI Broth Microdilution (Frozen)	50	≤ 0.06-> 128	1	8	≤ 0.06-32	0.25	2	Study CAZ104-M2-006-AAC11A3001 (Japan 2013)
CLSI Broth Microdilution (Dried)	268	≤ 0.03-> 32	0.12	4	≤ 0.015-16	0.12	0.5	Study CAZ AVI M2 101 (USA 2012)
	28	≤ 0.03-> 32	0.12	16	≤ 0.03-> 32	0.12	1	Study CAZ-AVI-M2-088 (Europe 2011)
	8	≤ 0.03-16	0.12	-	≤ 0.03-0.25	0.12	-	Study CAZ-AVI-M2-091 (Latin America 2011)
	6	≤ 0.03-> 32	2	-	≤ 0.03-> 32	0.25	-	Study CAZ-AVI-M2-090 (Asia-Pacific and South Africa 2011)

Table 27. Summary of In Vitro Studies to Evaluate the Activity of Ceftazidime-Avibactam Against *S. marcescens*

Test Method	*[N]*	*Ceftazidime MIC (mg/L)*			*Ceftazidime-avibactam MIC (mg/L)*			*Study*
		Range	*50%*	*90%*	*Range*	*50%*	*90%*	
CLSI Broth Microdilution (Frozen)	25	0.06-0.25	0.12	0.25	≤ 0.03-0.25	0.12	0.25	Study CAZ-AVI-M2-093 (USA 2013)
	25	0.12-0.5	0.25	0.5	≤ 0.06-0.5	0.25	0.5	Study CAZ-AVI-M2-109 (USA 2013)
	32	0.12-> 128	0.25	0.5	0.03-1	0.12	0.25	Study CAZ-AVI-M2-100 (USA 2012)
	90	0.06-128	0.25	0.5	0.03-16	0.25	0.5	Study CAZ-AVI-M2-106 (Europe 2012)
	40	≤ 0.25-1	≤ 0.25	0.5	≤ 0.06-1	0.25	0.25	Study CAZ-AVI-M2-097 (Canada 2013)
	36	0.03-> 128	0.25	8	0.03-1	0.12	0.5	Study CAZ-AVI-M2-104 (Latin America 2012)
	46	0.06-> 128	0.12	1	0.03-> 128	0.12	0.5	Study CAZ-AVI-M2-107 (Asia-Pacific 2012)
	25	0.12-8	0.25	8	0.12-1	0.12	1	Study CAZ-AVI-M2-108 (China 2013)
	100	0.12-128	0.25	2	≤ 0.06-2	0.25	0.5	Study CAZ104-M2-006-AAC11A3001 (Japan 2013)
	10	0.12-0.25	0.12	0.25	0.06-0.25	0.12	0.12	Study CAZ-AVI-M2-105 (Middle East and Africa 2012)
CLSI Broth Microdilution (Dried)	506	0.03-> 32	0.25	0.5	0.03-16	0.12	0.5	Study CAZ AVI M2 101 (USA 2012)
	237	0.03-> 32	0.25	0.5	≤ 0.03-2	0.12	0.5	Study CAZ-AVI-M2-098 (USA 2011)
	163[a]	0.06-> 32	0.25	0.5	0.06-2	0.25	0.5	Study CAZ104-M2-005-09-NXL-02 (USA 2009)
	273	0.03-> 32	0.12	0.5	≤ 0.03-> 32	0.12	0.5	Study CAZ-AVI-M2-088 (Europe 2011)
	109[a]	0.03-32	0.12	1	0.06-8	0.25	0.5	Study CAZ104-M2-005-09-NXL-02 (Europe 2009)
	118	0.06-> 32	0.12	16	0.06-16	0.12	0.5	Study CAZ-AVI-M2-091 (Latin America 2011)
	161	0.06-> 32	0.25	0.5	0.06-> 32	0.12	0.5	Study CAZ-AVI-M2-090 (Asia-Pacific and South Africa 2011)

a *Serratia* spp.

Activity against *Pseudomonas aeruginosa*

The activity of ceftazidime-avibactam was assessed against 7,400 *P. aeruginosa* isolates from 17 separate studies. MIC90 values ranged from 4 to 8 mg/L across these studies with the exception of one surveillance study from Latin America where the reported MIC90 value was 16 mg/L (Table 28). The MIC values for ceftazidime-avibactam ranged up to 8 mg/L in one US study, but isolates with MIC values as high as > 32 mg/L were observed in three other US studies. In Europe, > 90% of isolates were inhibited by ≤ 8 mg/L ceftazidime-avibactam; however, some isolates were recovered with MIC values ≥ 128 mg/L. MIC values increased to > 16 mg/L for some isolates from China and Canada and up to > 128 mg/L among isolates from Japan, Latin America and the Asia/Pacific region. The data indicated that approximately 90% of all the isolates tested had ceftazidime-avibactam MIC values of ≤ 8 mg/L, including those highly resistant to ceftazidime.

Table 28. Summary of In Vitro Studies to Evaluate the Activity of Ceftazidime-Avibactam Against *P. aeruginosa*

Test Method	*[N]*	*Ceftazidime MIC (mg/L)*			*Ceftazidime-avibactam MIC (mg/L)*			*Study*
		Range	*50%*	*90%*	*Range*	*50%*	*90%*	
CLSI Broth Microdilution (Frozen)	25	1-128	2	8	1-8	1	8	Study CAZ-AVI-M2-093 (USA 2013)
	30	1-64	2	16	1-32	2	4	Study CAZ-AVI-M2-109 (USA 2013)
	240	0.5-> 128	2	32	0.5-64	2	4	Study CAZ-AVI-M2-100 (USA 2012)
	707	0.06-> 128	2	32	0.06-> 128	2	8	Study CAZ-AVI-M2-106 (Europe 2012)
	264	≤ 0.25-> 32	4	16	0.12-> 16	2	8	Study CAZ-AVI-M2-097 (Canada 2013)
	204	0.5-> 128	4	64	0.12-> 128	2	8	Study CAZ-AVI-M2-104 (Latin America 2012)
	317	0.5-> 128	2	32	0.12-> 128	2	4	Study CAZ-AVI-M2-107 (Asia-Pacific 2012)
	25	0.5-64	4	16	1-16	4	8	Study CAZ-AVI-M2-108 (China 2013)
	100	0.5-> 128	2	32	0.5-> 128	2	8	Study CAZ104-M2-006-AAC11A3001 (Japan 2013)
	90	1-64	2	16	0.5-64	2	8	Study CAZ-AVI-M2-105 (Middle East and Africa 2012)
CLSI Broth Microdilution (Dried)	1967	0.06-> 32	2	32	0.06-> 32	2	4	Study CAZ AVI M2 101 (USA 2012)
	213	0.5-> 32	2	32	0.25-> 32	2	8	Study CAZ-AVI-M2-098 (USA 2011)
	471	0.12-> 32	2	32	0.12-> 32	2	8	Study CAZ104-M2-005-09-NXL-02 (USA 2009)
	1137	0.25-> 32	4	>32	0.25-> 32	2	16	Study CAZ104-M2-005-09-NXL-02 (Europe 2009)
	517	0.25-> 32	4	> 32	0.25-> 32	2	16	Study CAZ-AVI-M2-091 (Latin America 2011)
	612	0.25-> 32	4	> 32	0.12-> 32	2	8	Study CAZ-AVI-M2-090 (Asia-Pacific and South Africa 2011)

The in vitro activities of ceftazidime-avibactam and comparators against *P. aeruginosa* collected during the 2012 surveillance program are shown in Table 29 (all isolates), Table 30 (ceftazidime-non-susceptible isolates) and Table 31 (meropenem-non-susceptible isolates). In the 2012 Global Surveillance Program a total of 1967 *P. aeruginosa* isolates were tested and the ceftazidime-avibactam MIC90 was reported as 4 mg/L.

Table 29. Activity of Ceftazidime-Avibactam and Comparators against *P. aeruginosa* from the 2012 Global Surveillance Program

Drug	*N*	*MIC Range (mg/L)*	*MIC_{50} (mg/L)*	*MIC_{90} (mg/L)*	*CLSI*			*EUCAST*		
					%Sus	*%Int*	*%Res*	*%Sus*	*%Int*	*%Res*
United States (Dried)[a]										
Ceftazidime-avibactam	1967	0.06-> 32	2	4	-	-	-	-	-	-
Ceftazidime	1967	0.06-> 32	2	32	83.2	3.8	13.0	83.2	0.0	16.8
Gentamicin	1967	≤ 1 - > 8	≤ 1	8	88.8	3.4	7.8	88.0	0.0	11.2
Levofloxacin	1967	≤ 0.12 - > 4	0.5	> 4	75.3	6.5	18.2	66.7	8.6	24.7
Meropenem	1967	≤ 0.06 - > 8	0.5	8	82.0	5.6	12.4	82.0	11.4	6.6
Piperacillin-tazobactam	1967	≤ 0.5 - > 64	8	> 64	78.3	8.9	12.8	78.3	0.0	21.7
United States (Frozen)[b]										
Ceftazidime-avibactam	240	0.5 - 64	2	4	-	-	-	-	-	-
Ceftazidime	240	0.5 - > 128	2	32	78.3	6.7	15.0	78.3	0.0	21.7
Amikacin	240	≤ 0.25 - > 32	4	8	95.4	1.3	3.3	92.1	3.3	4.6
Levofloxacin	240	≤ 0.03 - > 4	0.5	> 4	68.3	7.9	23.8	61.3	7.1	31.7
Meropenem	240	≤ 0.06 - > 8	0.5	8	73.8	10.0	16.3	73.8	16.7	9.6
Piperacillin-tazobactam	240	≤ 0.25 - > 128	8	128	72.5	12.1	15.4	72.5	0.0	27.5
Europe (Frozen)[c]										
Ceftazidime-avibactam	707	0.06 - > 128	2	8	-	-	-	-	-	-
Ceftazidime	707	0.06 - > 128	2	32	84.4	4.7	10.9	84.4	0.0	15.6
Amikacin	707	≤ 0.25 - > 32	4	16	92.2	2.6	5.2	88.5	3.7	7.8
Levofloxacin	707	≤ 0.03 - > 4	0.5	> 4	73.1	5.2	21.6	66.3	6.8	26.9
Meropenem	707	≤ 0.06 - > 8	0.5	> 8	77.7	6.2	16.1	77.7	12.0	10.3
Piperacillin-tazobactam	707	≤ 0.25 - > 128	8	128	78.9	10.2	10.9	78.9	0.0	21.1
Latin America (Frozen)[d]										
Ceftazidime-avibactam	204	0.12 - > 128	2	8	-	-	-	-	-	-
Ceftazidime	204	0.5 - > 128	4	64	73.5	4.9	21.6	73.5	0.0	26.5
Amikacin	204	≤ 0.25 - > 32	4	> 32	83.3	2.5	14.2	77.9	5.4	16.7
Levofloxacin	204	0.12 - > 4	1	> 4	63.7	4.9	31.4	53.4	10.3	36.3
Meropenem	204	≤ 0.06 - > 8	0.5	> 8	65.2	7.8	27.0	65.2	13.7	21.1
Piperacillin-tazobactam	204	0.5 - > 128	8	> 128	67.2	14.7	18.1	67.2	0.0	32.8
Middle East and Africa (Frozen)[e]										
Ceftazidime-avibactam	90	0.5 - 64	2	8	-	-	-	-	-	-
Ceftazidime	90	1 - 64	2	16	87.8	3.3	8.9	87.8	0.0	12.2
Amikacin	90	2 - > 32	4	8	96.7	1.1	2.2	90.0	6.7	3.3
Levofloxacin	90	0.12 - > 4	0.5	> 4	80.0	5.6	14.4	71.1	8.9	20.0
Meropenem	90	≤ 0.06 - > 8	0.5	8	75.6	7.8	16.7	75.6	16.7	7.8
Piperacillin-tazobactam	90	2 - > 128	8	64	76.7	13.3	10.0	76.7	0.0	23.3
Asia/Pacific Region (Frozen)[f]										
Ceftazidime-avibactam	317	0.12 - > 128	2	4	-	-	-	-	-	-
Ceftazidime	317	0.5 - > 128	2	32	85.5	3.2	11.4	85.5	0.0	14.5
Amikacin	317	0.5 - > 32	4	8	97.2	1.6	1.3	95.0	2.2	2.8
Levofloxacin	317	≤ 0.03 - > 4	0.5	> 4	79.5	3.8	16.7	70.7	8.8	20.5
Meropenem	317	≤ 0.06 - > 8	0.5	> 8	77.9	4.7	17.4	77.9	11.4	10.7
Piperacillin-tazobactam	317	≤ 0.25 - > 128	8	128	78.6	9.5	12.0	78.6	0.0	21.5

[a] Study CAZ-AVI-M2-101; [b] Study CAZ-AVI-M2-100; [c] Study CAZ-AVI-M2-106; [d] Study CAZ-AVI-M2-104; [e] Study CAZ-AVI-M2-105; [f] Study CAZ-AVI-M2-107

Table 30. Activity of Ceftazidime-Avibactam and Comparators against ceftazidime-non-susceptible *P. aeruginosa* from the 2012 Global Surveillance Program

Drug	*N*	*MIC Range (mg/L)*	*MIC_{50} (mg/L)*	*MIC_{90} (mg/L)*	*CLSI*			*EUCAST*		
					%Sus	*%Int*	*%Res*	*%Sus*	*%Int*	*%Res*
United States (Dried)[a]										
Ceftazidime-avibactam	330	0.5-> 32	4	16	-	-	-	-	-	-
Ceftazidime	330	16-> 32	32	> 32	0.0	22.7	77.3	0.0	0.0	100
Gentamicin	330	≤ 1 - > 8	2	> 8	67.3	6.3	26.4	67.3	0.0	32.7
Levofloxacin	330	≤ 0.12 - > 4	> 4	> 4	39.4	9.7	50.9	30.3	9.1	60.6
Meropenem	330	≤ 0.06 - > 8	4	> 8	45.3	9.4	45.3	45.3	28.6	26.1
Piperacillin-tazobactam	330	2-> 64	> 64	> 64	4.5	22.8	72.7	4.5	0.0	95.5
United States (Frozen)[b]										
Ceftazidime-avibactam	52	1 - 64	4	8	-	-	-	-	-	-
Ceftazidime	52	16 - > 128	32	64	0.0	30.8	69.2	0.0	0.0	100
Amikacin	52	0.5 - > 32	4	32	88.5	1.9	9.6	78.9	9.6	11.5
Levofloxacin	52	0.06 - > 4	> 4	> 4	34.6	9.6	55.8	23.1	11.5	65.4
Meropenem	52	0.25 - > 8	4	> 8	32.7	19.2	48.1	32.7	34.6	32.7
Piperacillin-tazobactam	52	8 - > 128	128	> 128	3.9	28.9	67.3	3.9	0.0	96.2
Europe (Frozen)[c]										
Ceftazidime-avibactam	110	1 - > 128	4	16	-	-	-	-	-	-
Ceftazidime	110	16 - > 128	32	64	0.0	30.0	70.0	0.0	0.0	100
Amikacin	110	1 - > 32	8	> 32	72.7	7.3	20.0	60.9	11.8	27.3
Levofloxacin	110	≤ 0.03 - > 4	> 4	> 4	36.4	8.2	55.5	28.2	8.2	63.6
Meropenem	110	0.25 - > 8	8	> 8	34.6	15.5	50.0	34.6	36.4	29.1
Piperacillin-tazobactam	110	4 - > 128	128	> 128	10.0	31.8	58.2	10.0	0.0	90.0
Latin America (Frozen)[d]										
Ceftazidime-avibactam	54	1 - > 128	8	32	-	-	-	-	-	-
Ceftazidime	54	16 - > 128	64	> 128	0.0	18.5	81.5	0.0	0.0	100
Amikacin	54	2 - > 32	16	> 32	61.1	7.4	31.5	44.4	16.7	38.9
Levofloxacin	54	0.25 - > 4	> 4	> 4	25.9	3.7	70.4	18.5	7.4	74.1
Meropenem	54	≤ 0.06 - > 8	> 8	> 8	25.9	13.0	61.1	25.9	18.5	55.6
Piperacillin-tazobactam	54	8 - > 128	128	> 128	9.3	29.6	61.1	9.3	0.0	90.7
Middle East and Africa (Frozen)[e]										
Ceftazidime-avibactam	11	1 - 64	4	8	-	-	-	-	-	-
Ceftazidime	11	16 - 64	32	64	0.0	27.3	72.7	0.0	0.0	100
Amikacin	11	2 - > 32	8	> 32	81.8	0.0	18.2	72.7	9.1	18.2
Levofloxacin	11	0.25 - > 4	4	> 4	36.4	18.2	45.5	27.3	9.1	63.6
Meropenem	11	0.12 - > 8	8	> 8	27.3	18.2	54.6	27.3	54.6	18.2
Piperacillin-tazobactam	11	32 - > 128	128	> 128	0.0	36.4	63.6	0.0	0.0	100
Asia/Pacific Region (Frozen)[f]										
Ceftazidime-avibactam	46	2 - > 128	4	64	-	-	-	-	-	-
Ceftazidime	46	16 - > 128	32	> 128	0.0	21.7	78.3	0.0	0.0	100
Amikacin	46	0.5 - > 32	4	32	89.1	4.4	6.5	82.6	6.5	10.9
Levofloxacin	46	0.12 - > 4	> 4	> 4	41.3	6.5	52.2	37.0	4.4	58.7
Meropenem	46	0.12 - > 8	8	> 8	34.8	4.4	60.9	34.8	21.7	43.5
Piperacillin-tazobactam	46	8 - > 128	128	> 128	8.7	19.6	71.7	8.7	0.0	91.3

[a] Study CAZ-AVI-M2-101; [b] Study CAZ-AVI-M2-100; [c] Study CAZ-AVI-M2-106; [d] Study CAZ-AVI-M2-104; [e] Study CAZ-AVI-M2-105; [f] Study CAZ-AVI-M2-107

Table 31. Activity of Ceftazidime-Avibactam and Comparators against meropenem-non-susceptible *P. aeruginosa* from the 2012 Global Surveillance Program

Drug	*N*	*MIC Range (mg/L)*	*MIC_{50} (mg/L)*	*MIC_{90} (mg/L)*	*CLSI*			*EUCAST*		
					%Sus	*%Int*	*%Res*	*%Sus*	*%Int*	*%Res*
United States (Dried)[a]										
Ceftazidime-avibactam	354	0.5-> 32	4	16	-	-	-	-	-	-
Ceftazidime	354	1-> 32	16	> 32	49.2	10.7	40.1	49.2	0.0	50.8
Gentamicin	354	≤ 1 - > 8	4	> 8	64.7	7.6	27.7	64.7	0.0	35.3
Levofloxacin	354	≤ 0.12 - > 4	> 4	> 4	33.6	8.2	58.2	21.8	11.8	66.4
Meropenem	354	4-> 8	8	> 8	0.0	31.4	68.6	0.0	63.3	36.7
Piperacillin-tazobactam	354	≤ 0.5 - > 64	64	> 64	36.4	23.2	40.4	36.4	0.0	63.6
United States (Frozen)[b]										
Ceftazidime-avibactam	63	1 - 64	4	8	-	-	-	-	-	-
Ceftazidime	63	1 - > 128	16	64	44.4	17.5	38.1	44.4	0.0	55.6
Amikacin	63	0.5 - > 32	8	32	87.3	3.2	9.5	77.8	9.5	12.7
Levofloxacin	63	0.12 - > 4	> 4	> 4	33.3	11.1	55.6	25.4	7.9	66.7
Meropenem	63	4 - > 8	8	> 8	0.0	38.1	61.9	0.0	63.5	36.5
Piperacillin-tazobactam	63	4 - > 128	64	> 128	31.8	25.4	42.9	31.8	0.0	68.3
Europe (Frozen)[c]										
Ceftazidime-avibactam	158	1 - > 128	4	8	-	-	-	-	-	-
Ceftazidime	158	1 - > 128	8	64	54.4	13.3	32.3	54.4	0.0	45.6
Amikacin	158	0.5 - > 32	8	> 32	73.4	8.2	18.4	64.6	8.9	26.6
Levofloxacin	158	≤ 0.03 - > 4	> 4	> 4	36.7	8.9	54.4	25.3	11.4	63.3
Meropenem	158	4 - > 8	8	> 8	0.0	27.9	72.2	0.0	53.8	46.2
Piperacillin-tazobactam	158	4 - > 128	32	> 128	37.3	29.8	32.9	37.3	0.0	62.7

Drug	*N*	*MIC Range (mg/L)*	*MIC_{50} (mg/L)*	*MIC_{90} (mg/L)*	*CLSI*			*EUCAST*		
					%Sus	*%Int*	*%Res*	*%Sus*	*%Int*	*%Res*
Latin America (Frozen)[d]										
Ceftazidime-avibactam	71	1 - > 128	4	32	-	-	-	-	-	-
Ceftazidime	71	2 - > 128	32	> 128	43.7	4.2	52.1	43.7	0.0	56.3
Amikacin	71	1 - > 32	16	> 32	60.6	5.6	33.8	47.9	12.7	39.4
Levofloxacin	71	0.25 - > 4	> 4	> 4	32.4	1.4	66.2	18.3	14.1	67.6
Meropenem	71	4 - > 8	> 8	> 8	0.0	22.5	77.5	0.0	39.4	60.6
Piperacillin-tazobactam	71	2 - > 128	64	> 128	29.6	28.2	42.3	29.6	0.0	70.4
Middle East and Africa (Frozen)[e]										
Ceftazidime-avibactam	22	1 - 64	4	8	-	-	-	-	-	-
Ceftazidime	22	2 - 64	8	64	63.6	13.6	22.7	63.6	0.0	36.4
Amikacin	22	2 - > 32	8	32	86.4	4.6	9.1	68.2	18.2	13.6
Levofloxacin	22	0.25 - > 4	2	> 4	59.1	0.0	40.9	36.4	22.7	40.9
Meropenem	22	4 - > 8	8	> 8	0.0	31.8	68.2	0.0	68.2	31.8
Piperacillin-tazobactam	22	4 - > 128	32	> 128	45.5	27.3	27.3	45.5	0.0	54.6
Asia/Pacific Region (Frozen)[f]										
Ceftazidime-avibactam	70	1 - > 128	4	64	-	-	-	-	-	-
Ceftazidime	70	1 - > 128	8	64	57.1	7.1	35.7	57.1	0.0	42.9
Amikacin	70	1 - > 32	4	32	88.6	5.7	5.7	80.0	8.6	11.4
Levofloxacin	70	0.25 - > 4	> 4	> 4	40.0	5.7	54.3	22.9	17.1	60.0
Meropenem	70	4 - > 8	8	> 8	0.0	21.4	78.6	0.0	51.4	48.6
Piperacillin-tazobactam	70	4 - > 128	32	> 128	40.0	25.7	34.3	40.0	0.0	60.0

[a] Study CAZ-AVI-M2-101; [b] Study CAZ-AVI-M2-100; [c] Study CAZ-AVI-M2-106; [d] Study CAZ-AVI-M2-104; [e] Study CAZ-AVI-M2-105; [f] Study CAZ-AVI-M2-107

The MIC90 for ceftazidime-avibactam among the *Pseudomonas aeruginosa* isolates from the United States was 4 mg/L; however, the MIC90 for all worldwide isolates range from 4-64 mg/L. The MIC90 for meropenem and piperacillin tazobactam is reported to be >8 mg/L. The majority of isolates tested were less susceptible to meropenem (65.2-82.0% susceptible) and piperacillin-tazobactam (67.2-78.9% susceptible). Among the ceftazidime-nonsusceptible isolates from the United States, the MIC90 for ceftazidime-avibactam was 16 mg/L in one study and 8 mg/L in a second compared with > 8 and > 128 mg/L for meropenem and piperacillin-tazobactam, respectively. The ceftazidime-avibactam MIC90 values were 16 mg/L in Europe, 32 mg/L in Latin America, 8 mg/L in the Middle East and Africa and 64 mg/L in the Asia/Pacific region for the ceftazidime-non-susceptible subset and similar results for the comparators were observed across these various regions. Similar results were obtained for the meropenem-non-susceptible subset of isolates where ceftazidime-avibactam was the most potent agent tested.

Activity against *Acinetobacter* species

The Applicant assessed the activity of ceftazidime-avibactam against 616 isolates of *Acinetobacter baumannii* from nine separate studies and additional 1,999 *Acinetobacter* isolates from an additional seven studies. MIC90 values ranged from 8 to > 128 mg/L across these studies. Although MIC values as low as ≤ 0.03 mg/L were observed against some isolates, in general ceftazidime-avibactam did not demonstrate any meaningful activity against the majority of the *Acinetobacter* species. The data are summarized in Table 32.

Table 32. Summary of In Vitro Studies to Evaluate the Activity of Ceftazidime-Avibactam Against *Acinetobacter baumannii*

Test Method	*[N]*	*Ceftazidime MIC (mg/L)*			*Ceftazidime-avibactam MIC (mg/L)*			*Study*
		Range	*50%*	*90%*	*Range*	*50%*	*90%*	
CLSI Broth Microdilution (Frozen)	25	2-> 128	16	> 128	2-> 128	16	>128	Study CAZ-AVI-M2-093 (USA 2013)
	28	0.5-> 128	128	> 128	0.25-> 128	32	> 128	Study CAZ-AVI-M2-109 (USA 2013)
	72	0.12-> 128	64	> 128	0.06-> 128	16	128	Study CAZ-AVI-M2-100 (USA 2012)
	256	0.015->128	128	>128	0.03->128	32	128	Study CAZ-AVI-M2-106 (Europe 2012)
	14	2->32	4	8	2->16	8	>16	Study CAZ-AVI-M2-097 (Canada 2013)
	67	1-> 128	128	> 128	0.25-> 128	32	128	Study CAZ-AVI-M2-104 (Latin America 2012)
	94	0.5-> 128	4	> 128	0.5-> 128	8	64	Study CAZ-AVI-M2-107 (Asia-Pacific 2012)
	28	2-> 128	8	> 128	1-> 128	8	32	Study CAZ-AVI-M2-108 (China 2013)
	100[a]	1-> 128	2	8	1-> 128	2	8	Study CAZ104-M2-006-AAC11A3001 (Japan 2013)
	32	4-> 128	64	> 128	4-> 128	32	128	Study CAZ-AVI-M2-105 (Middle East and Africa 2012)
CLSI Broth Microdilution (Dried)	321[a]	0.5->32	32	>32	0.25->32	16	>32	Study CAZ AVI M2 101 (USA 2012)
	118[a]	0.12-> 32	8	> 32	≤ 0.03-> 32	32	> 32	Study CAZ104-M2-005-09-NXL-02 (USA 2009)
	457[a]	0.5-> 32	> 32	> 32	0.25-> 32	16	> 32	Study CAZ-AVI-M2-088 (Europe 2011)
	193[a]	0.06-> 32	> 32	> 32	0.06-> 32	16	> 32	Study CAZ104-M2-005-09-NXL-02 (Europe 2009)
	448[a]	1-> 32	> 32	> 32	1-> 32	> 32	> 32	Study CAZ-AVI-M2-091 (Latin America 2011)
	362[a]	1-> 32	> 32	> 32	1-> 32	32	> 32	Study CAZ-AVI-M2-090 (Asia-Pacific and South Africa 2011)

a *Acinetobacter spp.*

Activity against *Haemophilus influenzae*

The in vitro activity of ceftazidime-avibactam was assessed against 1,067 isolates of *H. influenzae* during the 2012 global surveillance program (Table 33). *H. influenzae* isolates from all geographic regions had ceftazidime MIC90 values of ≤ 0.25 mg/L, including against ampicillin-non-susceptible isolates. Avibactam did not appear to either improve or compromise the activity of ceftazidime against these isolates.

Table 34. Activity of Ceftazidime-Avibactam and Comparators against *H. influenzae* from the 2012 Global Surveillance Program

Drug	*N*	*MIC Range (mg/L)*	*MIC_{50} (mg/L)*	*MIC_{90} (mg/L)*	*CLSI*			*EUCAST*		
					%Sus	*%Int*	*%Res*	*%Sus*	*%Int*	*%Res*
United States (Dried)[a]										
Ceftazidime-avibactam	902	≤ 0.015 - 0.25	≤ 0.015	0.03	-	-	-	-	-	-
Ceftazidime	902	≤ 0.015 - 1	0.06	0.12	100	0.0	0.0	-	-	-
Ampicillin	902	≤ 0.25 - > 8	≤ 0.25	> 8	75.8	0.8	23.4	75.8	0.0	24.2
Levofloxacin	902	≤ 0.12-1	≤ 0.12	≤ 0.12	100	-	-	100	0.0	0.0
Ceftriaxone	902	≤ 0.06-0.25	≤ 0.06	≤ 0.06	100	-	-	99.9	0.0	0.1
United States (Frozen)[b]										
Ceftazidime-avibactam	39	≤ 0.03 - 0.12	≤ 0.03	0.06	-	-	-	-	-	-
Ceftazidime	39	≤ 0.03 - 0.25	0.06	0.12	100	0.0	0.0	na	na	na
Ampicillin	39	0.12 - > 8	0.5	> 8	74.4	12.8	12.8	74.4	0.0	25.6
Levofloxacin	39	0.008 - 0.03	0.015	0.03	100	0.0	0.0	100	0.0	0.0
Ceftriaxone	39	≤ 0.03 - ≤ 0.03	≤ 0.03	≤ 0.03	100	0.0	0.0	100	0.0	0.0
Europe (Frozen)[c]										
Ceftazidime-avibactam	60	≤ 0.03 - 0.5	≤ 0.03	≤ 0.03	-	-	-	-	-	-
Ceftazidime	60	≤ 0.03 - 0.5	0.06	0.12	100	0.0	0.0	na	na	na
Ampicillin	60	0.12 - > 8	0.5	2	83.3	10.0	6.7	83.3	0.0	16.7
Levofloxacin	60	≤ 0.004 - 0.5	0.015	0.015	100	0.0	0.0	100	0.0	0.0
Ceftriaxone	60	≤ 0.03 - 0.06	≤ 0.03	≤ 0.03	100	0.0	0.0	100	0.0	0.0
Latin America (Frozen)[d]										
Ceftazidime-avibactam	13	≤ 0.03 - 0.12	≤ 0.03	≤ 0.03	-	-	-	-	-	-
Ceftazidime	13	≤ 0.03 - 0.25	0.12	0.12	100	0.0	0.0	na	na	na
Ampicillin	13	0.25 - > 8	0.5	> 8	76.9	0.0	23.1	76.9	0.0	23.1
Levofloxacin	13	0.008 - 0.03	0.015	0.015	100	0.0	0.0	100	0.0	0.0
Ceftriaxone	13	≤ 0.03 - ≤ 0.03	≤ 0.03	≤ 0.03	100	0.0	0.0	100	0.0	0.0

Drug	*N*	*MIC Range (mg/L)*	*MIC_{50} (mg/L)*	*MIC_{90} (mg/L)*	*CLSI*			*EUCAST*		
					%Sus	*%Int*	*%Res*	*%Sus*	*%Int*	*%Res*
Middle East and Africa (Frozen)[e]										
Ceftazidime-avibactam	13	≤ 0.03 - 0.06	≤ 0.03	0.06	-	-	-	-	-	-
Ceftazidime	13	0.06 - 0.12	0.12	0.12	100	0.0	0.0	na	na	na
Ampicillin	13	0.25 - > 8	0.5	> 8	76.9	7.7	15.4	76.9	0.0	23.1
Levofloxacin	13	≤ 0.004 - 0.015	0.015	0.015	100	0.0	0.0	100	0.0	0.0
Ceftriaxone	13	≤ 0.03 - ≤ 0.03	≤ 0.03	≤ 0.03	100	0.0	0.0	100	0.0	0.0
Asia/Pacific Region (Frozen)[f]										
Ceftazidime-avibactam	40	≤ 0.03 - 0.25	≤ 0.03	0.12	-	-	-	-	-	-
Ceftazidime	40	≤ 0.03 - 0.5	0.12	0.25	100	0.0	0.0	na	na	na
Ampicillin	40	0.12 - > 8	1	> 8	67.5	5.0	27.5	67.5	0.0	32.5
Levofloxacin	40	0.008 - 1	0.015	0.03	100	0.0	0.0	100	0.0	0.0
Ceftriaxone	40	≤ 0.03 - 0.25	≤ 0.03	0.06	100	0.0	0.0	95.0	0.0	5.0

[a] Study CAZ-AVI-M2-101; [b] Study CAZ-AVI-M2-100; [c] Study CAZ-AVI-M2-106; [d] Study CAZ-AVI-M2-104; [e] Study CAZ-AVI-M2-105; [f] Study CAZ-AVI-M2-107

Aerobic Gram-positive Organisms

The activity of ceftazidime-avibactam was evaluated against some gram-positive pathogens including *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Streptococcus agalactiae*. The data indicated that the MIC values appear similar to ceftazidime alone suggesting that the addition of avibactam did not affect the activity of ceftazidime. Moreover, avibactam also did not improve the activity of ceftazidime against methicillin-resistant *S. aureus* (MRSA) or penicillin-intermediate or penicillin-resistant *S. pneumoniae* (PISP/PRSP). For this reason, the Applicant summarized data for the methicillin-susceptible *S. aureus* and penicillin-susceptible *S. pneumoniae* only. However, additional information on the activity of ceftazidime-avibactam against MRSA and PISP/PRSP are available in the surveillance study reports.

Activity against *Staphylococcus aureus*:

Against 18,490 *Staphylococcus aureus* collected in the 2012 global surveillance program, [including 10,075 methicillin-resistant (MRSA) and 8,415 methicillin-susceptible (MSSA) isolates] the MIC90 for ceftazidime-avibactam was either 8 or 16 mg/L for the MSSA isolates and was similar across all geographic regions. The MIC90 of ceftazidime alone was either 8 or 16 mg/L.

Activity against *Streptococcus pneumoniae*

The in vitro activity of ceftazidime-avibactam and comparators against 3,606 clinical isolates of penicillin susceptible (MIC ≤ 2 mg/L) *S. pneumoniae* was determined.
The MIC90 for both ceftazidime and ceftazidime-avibactam was 8 mg/L across all geographic regions except for one United States study and in the Middle East/Africa region, where the MIC90 for ceftazidime alone was 16 mg/L.

Activity against *Streptococcus pyogenes*

MIC values for ceftazidime-avibactam and comparators against 1,271 *Streptococcus pyogenes* were determined. The MIC90 values for both ceftazidime and ceftazidime-avibactam were either 0.12 or 0.25 mg/L for all isolates across all geographic regions.

Activity against *Streptococcus agalactiae*

MIC values for ceftazidime-avibactam and comparators against 905 clinical isolates of *Streptococcus agalactiae* collected in the 2012 global surveillance were determined. The MIC90 values for both ceftazidime and ceftazidime-avibactam were either 0.5 or 1 mg/L for isolates from all geographic regions.

Evaluation of Ceftazidime-Avibactam Activity by Site of Infection

***Enterobacteriaceae* (by infection site)**

In another study, the Applicant analyzed the activity of ceftazidime-avibactam against isolates from the 2012 United States surveillance program by sites of infection. The susceptibility data was organized by species collected from patients with bloodstream infections (BSI), respiratory infections, intra-abdominal infections (IAI) or urinary tract infections (UTI). A total of 7,568 Gram-negative isolates were evaluated. Table 34 shows the activity of ceftazidime-avibactam across four infections sources against 5,605 *Enterobacteriaceae* isolates. The MIC90 values ranged from 0.12-0.25 mg/L for each infection site when looking at all *Enterobacteriaceae* combined. These data were very similar when looking at individual species of this group where the MIC90 values ranged from 0.06-1 mg/L.

Table 34. Activity of ceftazidime-avibactam and comparators against *Enterobacteriaceae* by Site of Infection from 2012 United States surveillance

Organism/ Antimicrobial Agent (no. tested)	*BSI*			*Pneumonia*			*IAI*			*UTI*		
	MIC (mg/L)		*%S/%I/ %R*	*MIC (mg/L)*		*%S/%I/ %R*	*MIC (mg/L)*		*%S/%I/ %R*	*MIC (mg/L)*		*%S/%I/ %R*
	MIC_{50}	MIC_{90}	CLSI[a]	MIC_{50}	MIC_{90}	CLSI[a]	MIC_{50}	MIC_{90}	CLSI[a]	MIC_{50}	MIC_{90}	CLSI[a]
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Organism/ Antimicrobial Agent (no. tested)	*BSI*			*Pneumonia*			*IAI*			*UTI*		
	MIC (mg/L)		*%S/%I/ %R*	*MIC (mg/L)*		*%S/%I/ %R*	*MIC (mg/L)*		*%S/%I/ %R*	*MIC (mg/L)*		*%S/%I/ %R*
	MIC_{50}	MIC_{90}	CLSI[a]	MIC_{50}	MIC_{90}	CLSI[a]	MIC_{50}	MIC_{90}	CLSI[a]	MIC_{50}	MIC_{90}	CLSI[a]

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Organism/ Antimicrobial Agent (no. tested)	*BSI*			*Pneumonia*			*IAI*			*UTI*		
	MIC (mg/L)		*%S/%I/ %R*	*MIC (mg/L)*		*%S/%I/ %R*	*MIC (mg/L)*		*%S/%I/ %R*	*MIC (mg/L)*		*%S/%I/ %R*
	MIC_{50}	MIC_{90}	CLSI[a]	MIC_{50}	MIC_{90}	CLSI[a]	MIC_{50}	MIC_{90}	CLSI[a]	MIC_{50}	MIC_{90}	CLSI[a]

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Organism/ Antimicrobial Agent (no. tested)	*BSI*			*Pneumonia*			*IAI*			*UTI*		
	MIC (mg/L)		*%S/%I/ %R*	*MIC (mg/L)*		*%S/%I/ %R*	*MIC (mg/L)*		*%S/%I/ %R*	*MIC (mg/L)*		*%S/%I/ %R*
	MIC[a]	MIC[a]	CLSI[a]	MIC[a]	MIC[a]	CLSI[a]	MIC[a]	MIC[a]	CLSI[a]	MIC[a]	MIC[a]	CLSI[a]

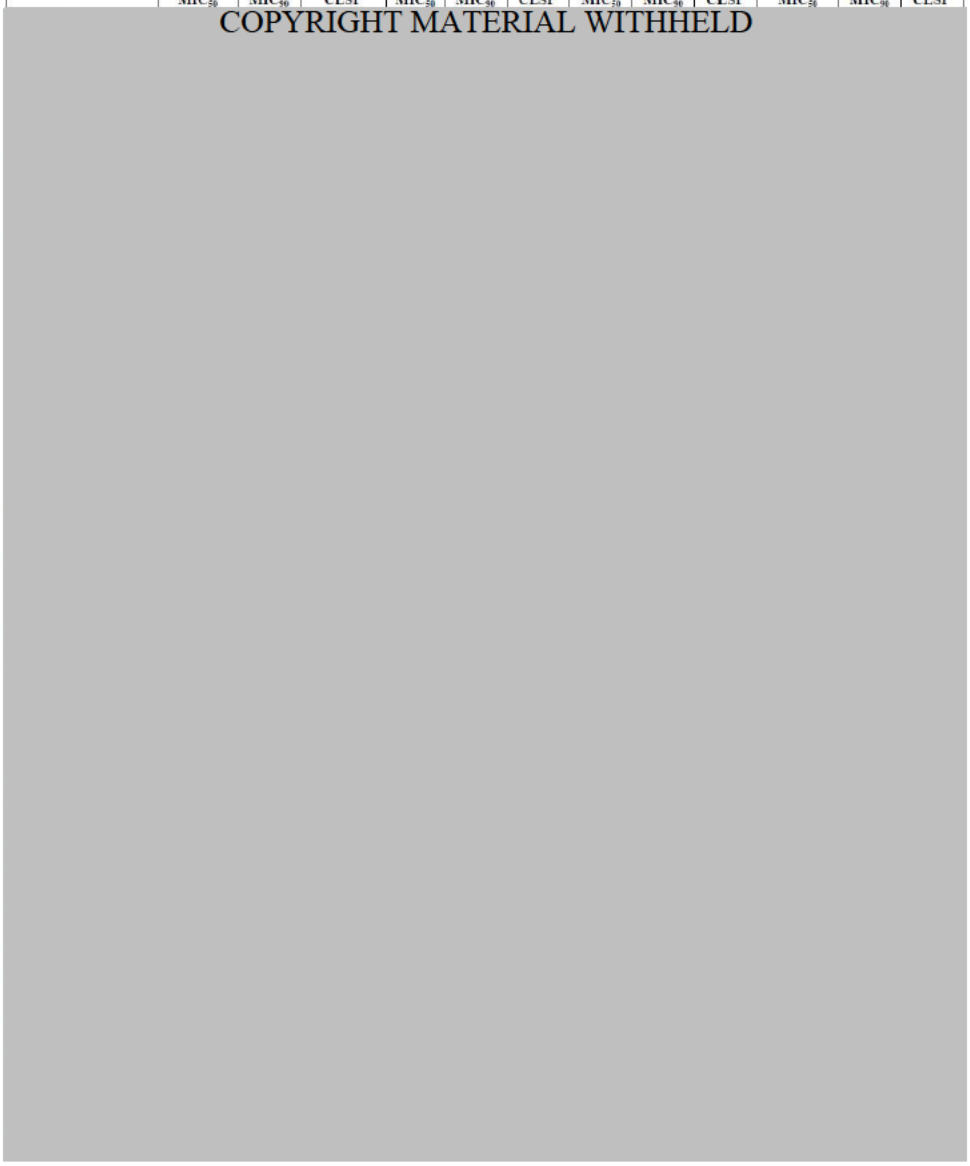
a Criteria as published by the CLSI.
b In the absence of CLSI breakpoint, USA-FDA breakpoints were applied when available.
c Susceptibility data not presented when number of isolates < 10.
Source: Flamm et al 2013

***P. aeruginosa, A. baumannii, H. influenzae* and *M. catarrhalis* (by infection site)**

In another study, the activity of ceftazidime-avibactam against non-*Enterobacteriaceae* was determined. Against *P. aeruginosa* isolates, the ceftazidime-avibactam MIC90 values ranged from 4-8 mg/L for all isolates and from 4-> 32 mg/L for ceftazidime-non-susceptible and meropenem-non-susceptible *P. aeruginosa* (Table 35). MIC90 values of 16 mg/L were only observed among a small number of IAI isolates. Against Acinetobacter spp., the addition of avibactam did not appear to improve the activity of ceftazidime against *Acinetobacter* spp. (MIC90 values ranged from 8-> 32 mg/L). All the isolates of *H. influenzae* and *M. catarrhalis* tested in this study were susceptible to ceftazidime and the addition of avibactam did not improve or compromise the activity of ceftazidime.

Table 35. Activity of ceftazidime-avibactam and comparators against *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Haemophilus influenzae*, and *Moraxella catarrhalis* by site of infection from 2012 United States surveillance

Organism/ Antimicrobial Agent (no. tested)	*BSI*			*Pneumonia*			*IAI*			*UTI*		
	MIC (mg/L)		*%S/%I/ %R*	*MIC (mg/L)*		*%S/%I/ %R*	*MIC (mg/L)*		*%S /%I/ %R*	*MIC (mg/L)*		*%S/%I/ %R*
	MIC_{50}	MIC_{90}	CLSI[a]	MIC_{50}	MIC_{90}	CLSI[a]	MIC_{50}	MIC_{90}	CLSI[a]	MIC_{50}	MIC_{90}	CLSI[a]



Organism/ Antimicrobial Agent (no. tested)	*BSI*			*Pneumonia*			*IAI*			*UTI*		
	MIC (mg/L)		*%S/%I/ %R*	*MIC (mg/L)*		*%S/%I/ %R*	*MIC (mg/L)*		*%S /%I/ %R*	*MIC (mg/L)*		*%S/%I/ %R*
	MIC_{50}	MIC_{90}	CLSI[a]	MIC_{50}	MIC_{90}	CLSI[a]	MIC_{50}	MIC_{90}	CLSI[a]	MIC_{50}	MIC_{90}	CLSI[a]

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a Criteria as published by the CLSI.
b TMP/SMX: trimethoprim/sulfamethoxazole.
c Susceptibility data not presented when number of isolates < 10.
Source: Flamm et al 2013.

Activity against Anaerobes

The in vitro activity of ceftazidime-avibactam was determined against clinically relevant anaerobic bacterial species in two separate studies (Study CAZ104-M2-008-NXL104-AP0020, Dubreuil et al 2012; Study CAZ104-M2-017-NXL104-AP0031, Citron et al 2011). In the first study, ceftazidime-avibactam was tested against 316 anaerobes isolated in 2008 including 225 *Bacteroides fragilis*, 78 clostridial isolates, and 51 gram-positive cocci. The overall MIC90 for ceftazidime-avibactam against the gram-negative anaerobes was 64 mg/L, including 32 mg/L for *B. fragilis*. The MIC90 for *Clostridium difficile* was 64 mg/L. The overall MIC90 for the other gram-positive cocci was 8 mg/L (Study CAZ104-M2-008-NXL104-AP0020). In the second study, ceftazidime-avibactam was tested against 407 anaerobe isolates with various levels of susceptibility to other β-lactam/β-lactamase inhibitor combinations (Table 36).

Table 36. Ceftazidime-avibactam susceptibilities of clinical isolates of anaerobic bacterial species

Organism	*N*	*CAZ-AVI MIC (mg/L)*			*Reference*
		Range	*MIC_{50}*	*MIC_{90}*	
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Organism	*N*	*CAZ-AVI MIC (mg/L)*			*Reference*
		Range	*MIC_{50}*	*MIC_{90}*	
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Ceftazidime-avibactam demonstrated limited activity against most of the species tested based on MIC90 values; however, activity was observed against some isolates from each species group. The most notable activity was against some *Prevotella* spp. isolates from Europe (MIC50 = 16 mg/L), *Prevotella-Porphyromonas* spp. isolates from the United States (MIC values ranging up to 8 mg/L and MIC90 of 4 mg/L was observed. Taken together, the data suggest that ceftazidime-avibactam is not active against most clinically relevant gram-negative and –positive anaerobic bacterial isolates. Although the data was not shown, the Applicant stated that many of the isolates were susceptible to metronidazole alone.

Activity against characterized β-lactamase-producing clinical isolates

The Applicant conducted a series of studies to evaluate the activity of ceftazidime-avibactam against isolates carrying a single class A, C or D β-lactamase. As indicated above, Class B metallo-β-lactamases are not inhibited by avibactam and were therefore not included in the summaries below. The activity of ceftazidime-avibactam was compared to ceftazidime alone, piperacillin-tazobactam and a carbapenem (either imipenem or meropenem). The data in the following Tables indicate that avibactam extended the activity of ceftazidime

against the Class A enzymes that were tested including representatives of the TEM, SHV, CTX-M, SME, GES, NMC, IMI, KPC, PER, VEB and BEL type β-lactamases. All but one isolate tested was inhibited by ≤ 4 mg/L ceftazidime-avibactam including organisms producing ESBL variants of TEM, SHV and CTX-M types and KPC carbapenemases. There was one *P. aeruginosa* VEB-1 producing isolate that had MIC values of 32 mg/L to both ceftazidime-avibactam and imipenem. However, in the same analysis, VEB-1 expressed in *E. coli* appeared susceptible to ceftazidime-avibactam. The data are summarized in Table 37 for Class A ESBL producing organisms and Table 38 for class A carbapenemase producing organisms.

Table 37. The activity of ceftazidime-avibactam and comparators against characterized clinical or laboratory isolates carrying (in addition to chromosomal *bla* genes) a single, class A extended-spectrum β-lactamase (ESBL) gene

Enzyme	*Organism*	*MIC (mg/L)*				*Reference*
		CAZ-AVI	*CAZ*	*PIP-TAZ*	*MER*	
TEM-2	*P. aeruginosa*	1	16	> 128	2	5
TEM-3	*E. coli*	0.25	64	4	≤ 0.015	2
TEM-3	*E. coli*	0.12	8	1	≤ 0.015	3
TEM-3	*K. pneumoniae*	1	128	8	0.06	2
TEM-6	*E. coli*	0.5	128	4	≤ 0.015	3
TEM-6	*K. pneumoniae*	0.5	128	16	0.03	3
TEM-9	*E. coli*	0.5	> 128	8	≤ 0.015	2
TEM-10	*E. coli*	0.5	256	2	0.015	1
TEM-10	*E. coli*	0.5	> 128	4	≤ 0.015	2
TEM-11	*K. pneumoniae*	4	> 128	8	0.06	2
TEM-12	*E. coli*	0.25	64	64	0.06	3
TEM-15	*E. coli*	0.5	16	2	0.03	1
TEM-17	*E. coli*	0.25	2	> 128	≤ 0.015	1
TEM-19	*E. coli*	0.25	0.5	4	0.03	1
TEM-25	*E. coli*	0.25	64	4	≤ 0.015	2
TEM-26	*E. coli*	1	> 128	2	0.03	1

Enzyme	*Organism*	*MIC (mg/L)*				*Reference*
		CAZ-AVI	*CAZ*	*PIP-TAZ*	*MER*	
TEM-28	*E. coli*	0.25	128	8	≤ 0.015	3
TEM-33	*E. coli*	0.12	0.25	128	≤ 0.015	2
TEM-34	*E. coli*	0.25	0.25	16	0.03	2
TEM-35	*E. coli*	0.25	0.5	128	≤ 0.015	2
TEM-36	*E. coli*	0.25	0.25	64	0.03	2
TEM-43	*E. coli*	1	128	8	0.06	3
TEM-71	*E. coli*	≤0.06	32	1	≤ 0.015	3
TEM-71	*K. pneumoniae*	2	128	32	2	3
TEM-191	*E. coli*	0.5	1	>128	0.03	1
SHV-2	*E. coli*	0.25	4	4	0.03	1
SHV-2	*K. pneumoniae*	1	64	> 128	1	3
SHV-2	*K. pneumoniae*	1	32	> 128	0.5	2
SHV-3	*K. pneumoniae*	2	> 128	> 128	2	3
SHV-3	*K. pneumoniae*	0.25	8	8	0.06	2
SHV-4	*K. pneumoniae*	1	> 128	> 128	0.5	3
SHV-5	*E. coli*	1	> 128	> 128	0.5	3
SHV-7	*E. coli*	1	> 128	> 128	0.03	1
SHV-8	*E. coli*	0.5	32	2	0.03	1
SHV-10	*E. coli*	0.25	0.5	> 128	≤ 0.015	1
SHV-14	*E. coli*	0.25	1	> 128	≤ 0.015	1
SHV-18	*K. pneumoniae*	0.5	> 128	8	0.03	3
SHV-26	*E. coli*	0.25	0.25	2	0.03	1
SHV-30	*E. coli*	0.25	4	2	0.03	1
SHV-49	*E. coli*	0.25	0.5	> 128	0.03	1
SHV-52	*E. coli*	2	128	8	0.03	2
SHV-84	*E. coli*	0.25	0.5	4	≤ 0.015	1
SHV-102	*E. coli*	0.5	16	> 128	0.03	1
SHV-106	*E. coli*	0.25	8	8	0.03	1
SHV-120	*E. coli*	0.5	8	> 128	0.03	1
SHV-129	*E. coli*	0.25	64	2	≤ 0.015	1
SHV-141	*E. coli*	1	1	2	≤ 0.015	1
SHV-154	*E. coli*	0.5	> 128	4	0.03	1
SHV-161	*E. coli*	0.25	2	> 128	0.03	1
CTX-M-2	*P. mirabilis*	0.12	1	1	0.12	2
CTX-M-8	*E. coli*	0.12	1	2	≤ 0.015	2
CTX-M-15	*P. mirabilis*	≤ 0.06	0.25	0.25	0.12	2
CTX-M-24	*E. coli*	0.12	2	2	≤ 0.015	2
CTX-M-27	*E. coli*	0.25	8	2	0.03	2
CTX-M-37	*E. coli*	0.25	1	2	≤ 0.015	2
CTX-M-44	*E. coli*	0.12	8	4	≤ 0.015	2
CTX-M-55	*E. coli*	0.5	128	16	0.03	2
CTX-M-101	*E. coli*	0.25	32	2	0.03	2
CTX-M-133	*E. coli*	0.5	4	128	0.03	2
PER-1	*E. coli*	0.5	> 512	0.5	0.25	4
PER-1	*P. aeruginosa*	4	128	16	4[a]	4
PER-1	*P. aeruginosa*	4	> 128	16	2	5
VEB-1	*E. coli*	1	> 512	4	0.5[b]	4
VEB-1	*P. aeruginosa*	32	> 512	16	32[b]	4
BEL-1	*E. coli*	0.5	8	16	0.5[b]	4

Abbreviations: CAZ = ceftazidime; AVI = avibactam; PIP-TAZ = piperacillin-tazobactam; MER = meropenem.

a Imipenem tested instead of meropenem.

Source: [1] CAZ-AVI-M2-099; [2] Study CAZ-AVI-M2-125; [3] Study CAZ-AVI-M2-121; [4] Study CAZ104-M2-026-NXL104-AP0001; [5] Mushtaq et al 2010; [6] Stachyra et al 2009

Table 38. The activity of ceftazidime-avibactam and comparators against characterized clinical or laboratory isolates carrying (in addition to chromosomal *bla* genes) a single, characterized class A carbapenemase gene

Enzyme	*Organism*	*MIC (mg/L)*				*Reference*
		CAZ-AVI	*CAZ*	*PIP-TAZ*	*MER*	
SME-1	*S. marcescens*	1	0.5	4	32	3
SME-2	*S. marcescens*	0.25	0.12	1	32	3
GES-2	*E. coli*	1	32	4	1[a]	4
GES-2	*P. aeruginosa*	4	32	64	32[a]	4
GES-3	*E. coli*	0.25	128	16	4[a]	4
GES-4	*E. coli*	1	128	2	1[a, b]	4
NMC-A	*E. cloacae*	0.12	0.25	1	128[a,	4
IMI-2	*E. asburiae*	0.25	0.25	2	> 512[a]	4
KPC-2	*K. pneumoniae*	0.5	128	> 512	32[a]	4
KPC-2	*K. pneumoniae*	0.5	512	1024	16[a]	6
KPC-3	*K. pneumoniae*	0.25	512	256	1[a]	6
KPC-5	*E. coli*	0.5	32	64	0.12	1
KPC-6	*E. coli*	0.5	32	64	0.12	1
KPC-8	*E. coli*	4	> 128	>128	0.5	1

Abbreviations: CAZ = ceftazidime; AVI = avibactam; PIP-TAZ = piperacillin-tazobactam; MER = meropenem.

a Represents data for imipenem

Source: [1] Study CAZ-AVI-M2-099; [3] Study CAZ-AVI-M2-121; [4] Study CAZ104-M2-026-NXL104-AP0001; [6] Stachyra et al 2009

In another study, avibactam extending the activity of ceftazidime against most isolates producing class C β-lactamases (Table 39). There were two isolates of *P. aeruginosa* (ceftazidime MIC values 32 and 128 mg/L) that demonstrated ceftazidime-avibactam MIC values of 8 mg/L. Twelve of the 25 characterized Class C β-lactamase-producing isolates were resistant to piperacillin-tazobactam (MIC values ≥ 128 mg/L). MIC values of meropenem were ≤ 1 mg/L except against two isolates: one AmpC producing *Pseudomonas aeruginosa* isolate against which the MIC was > 32 mg/L and one DHA-1 producing *Klebsiella pneumoniae* isolate against which the MIC was 16 mg/L.

Table 39. The activity of ceftazidime-avibactam and comparators against characterized clinical or laboratory isolates carrying (in addition to chromosomal *bla* genes) a single, characterized class C β-lactamase gene

Enzyme	*Organism*	*MIC (mg/L)*				*Reference*
		CAZ-AVI	*CAZ*	*PIP-TAZ*	*MER*	
AmpC	*E. cloacae*	1	> 128	> 128	0.12	2
AmpC	*E. cloacae*	2	> 128	> 128	0.06	2
AmpC	*E. coli*	1	128	> 128	0.25	2
AmpC	*E. cloacae*	1	2	8	0.25	3
AmpC	*E. cloacae*	2	> 128	> 128	0.25	3
AmpC	*C. freundii*	0.06	64	128	0.06	2
AmpC	*C. freundii*	0.12	64	64	0.03	3
AmpC	*P. aeruginosa*	2	16	64	0.25	2
AmpC	*P. aeruginosa*	8	128	>128	0.5	3
AmpC	*P. aeruginosa*	≤0.06	0.5	0.25	0.15	5
AmpC	*M. morganii*	0.25	32	32	0.03	3
CMY-2	*E. coli*	2	>128	>128	16	3
DHA-1	*K. pneumoniae*	0.25	64	4	0.015	3
FOX-4	*E. coli*	4	128	>128	1	1
FOX-5	*K. pneumoniae*	1	64	64	0.12	3
MOX-1	*K. pneumoniae*	2	>128	>128	1	2
MOX-2	*K. pneumoniae*	0.12	16	4	0.03	3
ACT-1	*E. coli*	0.5	>128	>128	0.03	3
CMY-2	*C. koseri*	2	16	64	0.25	2
CMY-8	*K. pneumoniae*	2	64	32	0.12	2
CMY-24	*E. coli*	0.5	64	8	0.03	2
CMY-32	*E. coli*	0.25	32	2	≤ 0.015	1
CMY-33	*E. coli*	0.5	4	4	≤ 0.015	1
S2	*S. marcescens*	0.25	≤ 0.06	2	0.03	3

Abbreviations: CAZ = ceftazidime; AVI = avibactam; PIP-TAZ = piperacillin-tazobactam; MER = meropenem.
Source: [1] Study CAZ-AVI-M2-099; [2] Study CAZ-AVI-M2-125; [5] Mushtaq et al 2010

Against non-fermenters (*P. aeruginosa* and *A. baumannii*) isolates producing Class D β-lactamase (OXA family of enzymes), ceftazidime-avibactam activity was variable. The presence of avibactam did not appear to improve the activity of ceftazidime against either susceptible or non-susceptible OXA-producing isolates, nor was any antagonism by avibactam observed. The data are summarized in Table 40.

Table 40. The activity of ceftazidime-avibactam and comparators against characterized clinical or laboratory isolates carrying (in addition to chromosomal *bla* genes) a single, characterized class D β-lactamase gene.

Enzyme	*Organism*	*MIC (mg/L)*				*Reference*
		CAZ-AVI	*CAZ*	*PIP-TAZ*	*MER*	
OXA-1	*E. coli*	0.25	0.5	> 128	0.03	1
OXA-2	*E. coli*	0.12	0.5	2	0.03	2
OXA-3	*E. coli*	0.25	0.5	4	0.03	2
OXA-10	*P. aeruginosa*	2	2	64	2	3
OXA-11	*P. aeruginosa*	> 128	> 128	64	2	5
OXA-13	*P. aeruginosa*	1	8	16	4 [a]	4
OXA-14	*P. aeruginosa*	> 128	> 128	> 128	8	5
OXA-15	*P. aeruginosa*	64	> 128	16	1	5
OXA-16	*P. aeruginosa*	128	> 128	16	1	5
OXA-24 / 40	*E. coli*	0.25	0.5	64	0.25	1
OXA-28	*P. aeruginosa*	256	> 512	32	4 [a]	4
OXA-31	*P. aeruginosa*	2	4	128	4 [a]	4
OXA-32	*P. aeruginosa*	64	> 512	8	32 [a]	4
OXA-35	*P. aeruginosa*	2	4	64	4 [a]	4
OXA-40	*A. baumannii*	> 128	> 128	> 128	> 32	2
OXA-66	*A. baumannii*	16	8	> 128	8	2
OXA-69	*A. baumannii*	> 128	> 128	> 128	2	2
OXA-88	*A. baumannii*	> 128	> 128	> 128	> 32	2
OXA-93	*A. baumannii*	8	4	16	1	2
OXA-94	*A. baumannii*	16	8	32	1	2
OXA-95	*A. baumannii*	64	128	> 128	> 32	2
OXA-96	*A. baumannii*	128	> 128	> 128	> 32	2
OXA-206	*A. baumannii*	> 128	128	> 128	16	2

Abbreviations: CAZ = ceftazidime; AVI = avibactam; PIP-TAZ = piperacillin-tazobactam; MER = meropenem.
Source: [1] Study CAZ-AVI-M2-099; [2] Study CAZ-AVI-M2-125; [3] Study CAZ-AVI-M2-121; [4] Study CAZ104-M2-026-NXL104-AP0001; [5] Mushtaq et al 2010

Conclusions: Antimicrobial Spectrum of Activity:

The information submitted by the Applicant from the large prospective surveillance studies and other investigations of the in vitro activity of ceftazidime-avibactam do support the Applicant's claim of activity against some of the pathogens shown to be associated serious bacterial infections such as cUTi and cIAI. Ceftazidime-avibactam combination is capable of overcoming most AmpC-mediated resistance in *P. aeruginosa*, reducing MIC to levels ≤ 8 mcg/mL. Against the *Enterobacteriaceae*, ceftazidime-avibactam demonstrated activity against Class A, C and some Class D ESBL producing isolates. All *Enterobacteriaceae* demonstrated ceftazidime-avibactam MIC ≤ 4 mcg/mL.

MECHANISM OF ACTION

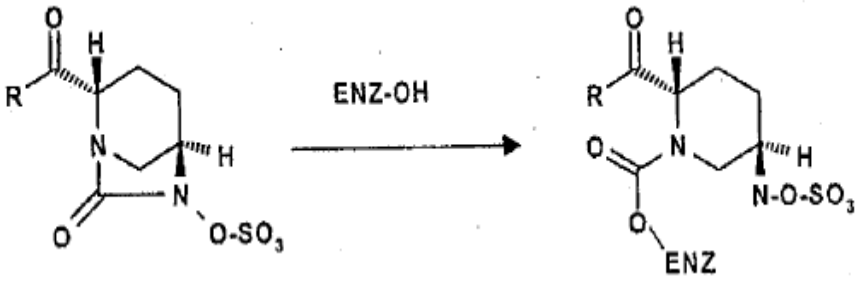
Mechanism of action of ceftazidime

Ceftazidime is a cephalosporin and is a β-lactam antibacterial drug. Mechanistically, its primary mode of action is the inhibition of bacterial cell wall synthesis. Ceftazidime shows high affinity for PBP3 of *P. aeruginosa* and *E. coli*, with IC50 values of 0.06-0.22 mg/L in competitive binding experiments. Ceftazidime also competes for binding to PBPs 1a and 1b, but with 2- to 84-fold lower affinity. Gram-negative bacteria form filaments when exposed to ceftazidime at concentrations similar to the IC50 for PBP3; however, upon exposure to higher concentrations, cell lysis occurs.

Mechanism of action of Avibactam

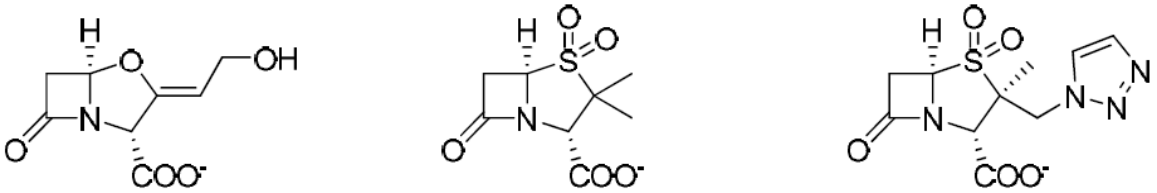
Avibactam is a diazabicyclooctanone non-β-lactam β-lactamase inhibitor. Avibactam inhibits class A ESBLs and carbapenemases, class C β-lactamases and some class D oxacillinases and carbapenemases. When used in combination with ceftazidime it primarily prevents hydrolysis. It is hypothesized that the inhibition of β-lactamases by avibactam occurs when the inhibitor binds to the catalytic serine residue in the active site of the enzyme, giving rise to a highly stable carbamoyl linkage (Figure 1).

Figure 1: Proposed Molecular mechanism of action of avibactam



Avibactam (Figure 1) differs from other β-lactamase inhibitors such as clavulanic acid, sulbactam, and tazobactam (Figure 2) in three key aspects.

Figure 2. Chemical structures of clavulanic acid, sulbactam, and tazobactam



Structurally, avibactam is a [3.2.1]-diazabicyclooctanone (DABCO) derivative that employs a reactive urea rather than a β-lactam to inhibit serine β-lactamases. Second, the mechanism of avibactam inhibition of β-lactamases is covalent, but reversible, in contrast to clavulanic acid, sulbactam and tazobactam which are also covalent but irreversible. Third, avibactam has an expanded spectrum of β-lactamase inhibition compared to the other three molecules, which are largely limited to coverage of class A enzymes. Avibactam inhibits class A ESBLs, class A carbapenemases such as KPC-2, some class C enzymes of the AmpC family, and some class D OXA enzymes.

Table 41 shows the biochemical inhibition (IC50) of class A, C and D β-lactamases. Avibactam was initially characterized biochemically against the class A β-lactamase TEM-1 and the class C *Enterobacter* P99 β-lactamase. Avibactam showed inhibition of both, relative to clavulanic acid and tazobactam, by IC50 measurement taken after a five minute using a reporter substrate. Further studies added class A ESBLs, CTX-M-15 and SHV-4, class A carbapenemases KPC-2 and KPC-3, class D carbapenemase OXA-40, and class C

Pseudomonas aeruginosa AmpC enzyme. Avibactam has demonstrated equivalent or higher inhibition to comparators and has an expanded spectrum of β-lactamase inhibition that covers members of classes A, C, and some D. Avibactam does not inhibit the activity of class B metallo-β-lactamases.

Table 41. Biochemical inhibition (IC50) of class A, C and D β-lactamases by avibactam after five minute preincubation using nitrocefin as reporter substrate.

Enzyme and class	*IC_{50} (nM)*			
	Avibactam	*Clavulanic acid*	*Tazobactam*	*Sulbactam*
Class A				
TEM-1	8	58, 130	32	1560
CTX-M-15	5	12	6	230
KPC-2	170	> 100000	50000	57000
KPC-3 [a]	28	4900	ND [b]	ND
SHV-4	3	4	55	260
Class C				
P99	100	> 100000	1300	21100
P. aeruginosa AmpC	128	> 100000	4600	27000
Class D				
OXA-40 [a]	5100	9200	ND	ND

a These enzymes were tested with a 40 min preincubation.
b ND = not determined
Source: Bonnefoy et al 2004, Stachyra et al 2010, Study CAZ104-M2-018-NXL104-BI0001

As mentioned above, avibactam is considered a reversible inhibitor and the effect of this inhibition controls product formation. In a series of experiments, the inhibition properties of avibactam against six β-lactamases are presented. The assumption is that the tighter avibactam binds to the larger molecular weight enzyme (β-lactamase) the lower the value of dissociation constant (K_d). Table 42 shows the comparison of the relative affinities of different enzymes-inhibitor complexes (K_d).

Table 42. Kinetic values for acylation and deacylation of avibactam against various β-lactamases.

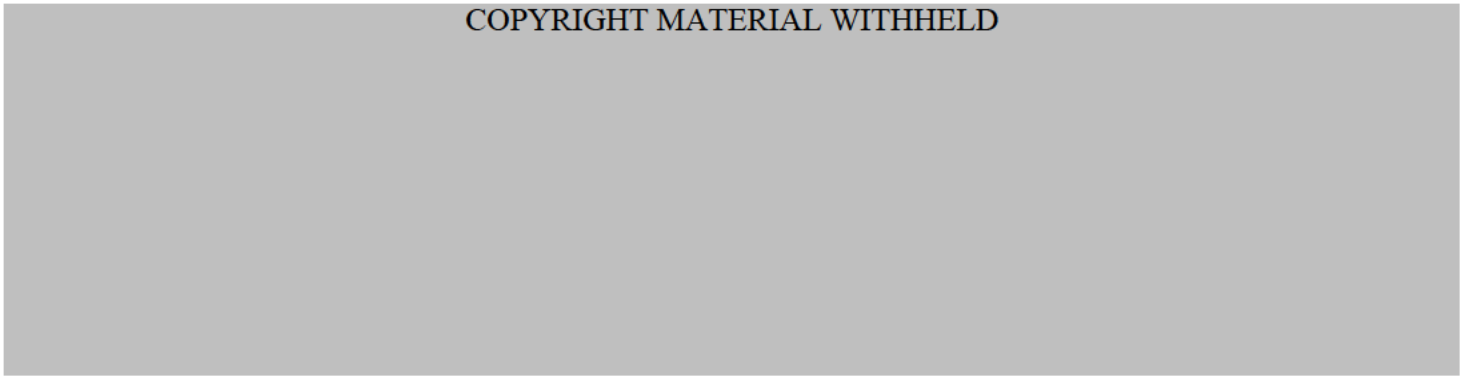
	Class A				*Class C*		*Class D*			
	TEM-1	*CTX-M-15*	*KPC-2*	*BlaC* [a]	*P99* [b]	*AmpC*	*OXA-10*	*OXA-48*	*OXA-23*	*OXA-24*
Acylation k_2/K_i ($M^{-1}\cdot s^{-1}$)	$1.6 \pm 0.1 \times 10^5$	$1.3 \pm 0.1 \times 10^5$	$1.3 \pm 0.1 \times 10^4$	$1.5 \pm 0.1 \times 10^1$	$5.1 \pm 0.1 \times 10^3$	$2.9 \pm 0.1 \times 10^3$	$1.1 \pm 0.1 \times 10^1$	$1.4 \pm 0.1 \times 10^3$	$3.0 \pm 0.2 \times 10^2$	$5.2 \pm 1.2 \times 10^1$
Deacylation k_{off} (s^{-1})	$8.0 \pm 4 \times 10^{-4}$	$3.0 \pm 1 \times 10^{-4}$	$1.1 \pm 0.1 \times 10^{-4}$	ND [c]	$3.8 \pm 0.2 \times 10^{-5}$	$1.9 \pm 0.6 \times 10^{-3}$	$< 1.6 \times 10^{-6}$	$1.2 \pm 0.4 \times 10^{-5}$	$8.0 \pm 0.4 \times 10^{-6}$	$6.3 \pm 0.4 \times 10^{-6}$
Deacylation $t_{1/2}$ min	16 ± 8	40 ± 10	82 ± 6	> 3000	300 ± 20	6 ± 2	> 7200	1000 ± 300	1436 ± 76	1823 ± 111
K_d (nM)	5	2	11	ND	7	660	< 150	9	27	120

a BlaC from Mycobacterium tuberculosis
b P99 from Enterobacter cloacae
c ND = not determined
Source: Ehmann 2012, Ehmann et al 2013, Xu 2012, Study CAZ-AVI-M2-084.

Avibactam demonstrated fast on-rates (acylation) and slower off rates (de-acylation) that result in low nM K_d values for the class A enzymes, TEM-1 CTX-M-15 and KPC-2. The class C enzymes acylation activity was similar

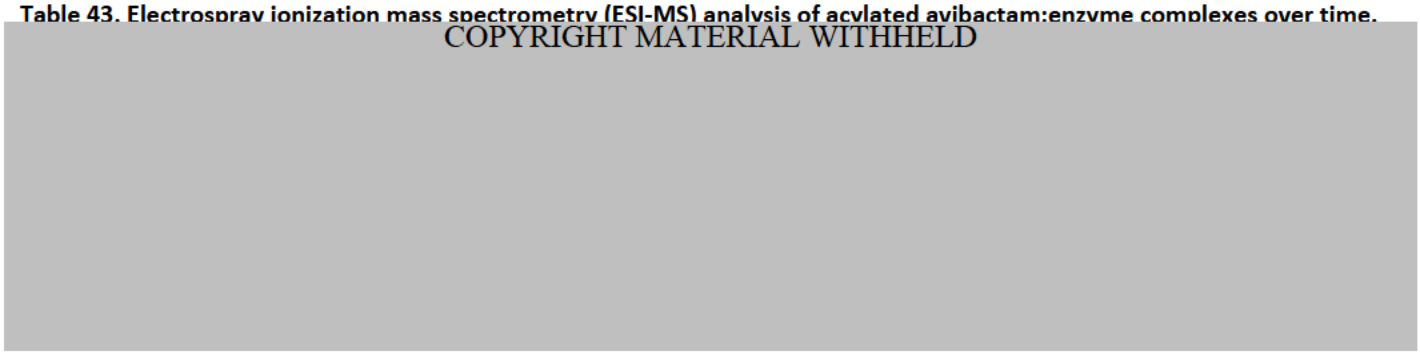
between *E. cloacae* P99 AmpC and *P. aeruginosa* PAO1 AmpC. Although the *P. aeruginosa* PAO1 AmpC K_d of 660 nM appear high, it is still capable of providing some β-lactamase protection. Figure 3 shows a graphic representation of the covalent, but reversible mechanism of inhibition. Data indicate that the covalent acylation of β-lactamases by avibactam was reversible to yield intact avibactam, which was then able to acylate a second β-lactamase. This mechanism is in contrast with the β-lactam-type β-lactamase inhibitors clavulanic acid, which irreversibly hydrolyzes upon deacylation and cannot acylate a second β-lactamase. For avibactam, it was noted that while the deacylated β-lactamase also regains activity, avibactam is able to rapidly re-acylate the enzyme and thus re-inhibit enzymatic activity.

Figure 3. Covalent, reversible mechanism of avibactam inhibition of serine β-lactamases



Additional studies were conducted to measure the stability of the acylated inactive enzyme complexes. Data indicate that the inactive enzyme form remained intact after 24 hours for all except OXA-10, AmpC and KPC-2 (Table 43). It was hypothesized that the relatively high K_d and rapid off-rate may have resulted in a partially acylated state at equilibrium at the concentrations tested. For KPC-2, the low acylated fraction represented a slow hydrolytic pathway. The slower KPC-2 deacylation rate appears to have minimal impact on the in vitro microbiological activity of ceftazidime-avibactam combination towards KPC-2 producing bacteria. It should be noted that the clinical significance on the impact of protection over time this will have on ceftazidime is unclear. The potential exist for the evolution of new KPC-2 or class A enzymes with increased hydrolytic activities.

Table 43. Electrospray ionization mass spectrometry (ESI-MS) analysis of acylated avibactam:enzyme complexes over time.



Acyl-enzymes were prepared by incubation of 1 μM enzyme with 5 μM avibactam at 37 °C and removal of free compound by ultrafiltration.

a CTX-M-15 exhibits loss of 17 Da due to pyroglutamate formation at the N-terminus.

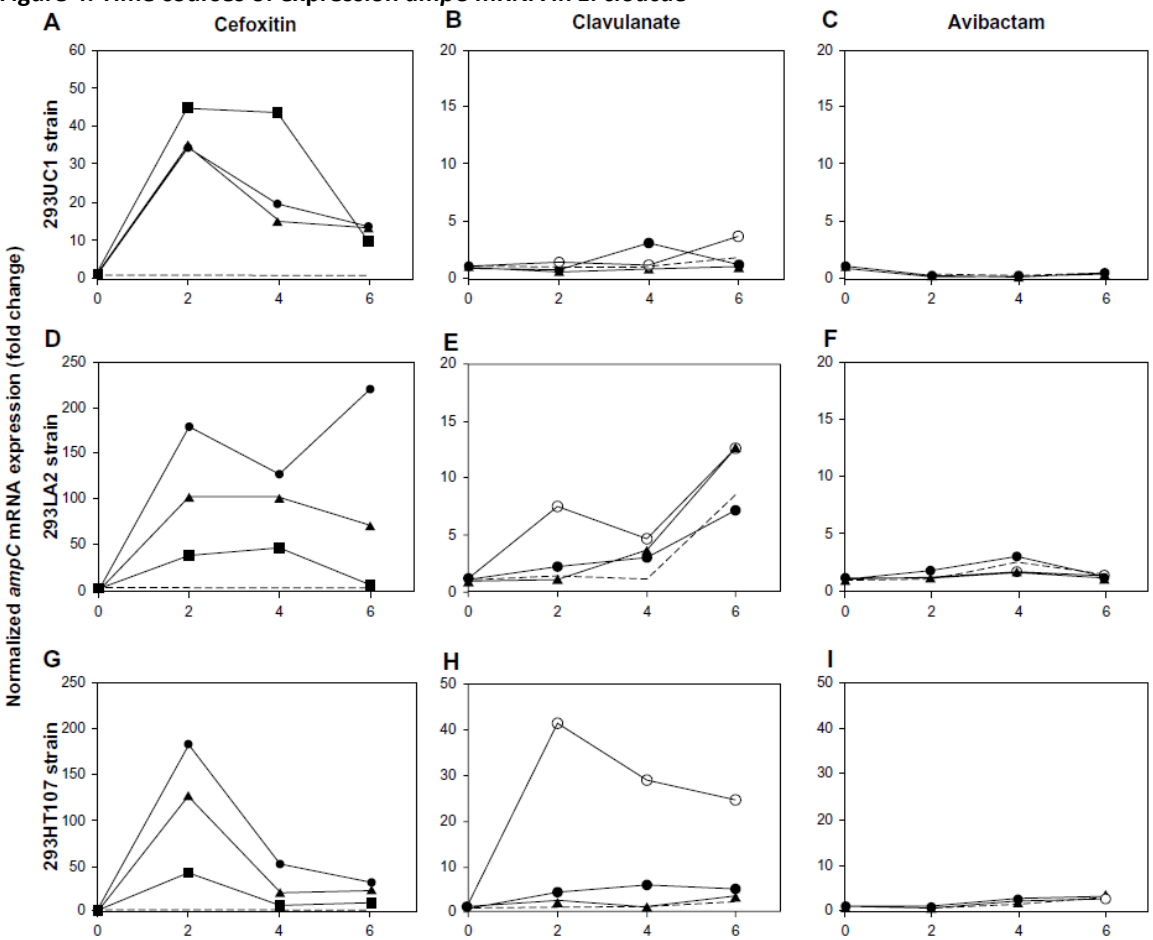
b OXA-10 reached 100% acylation after 3 h.

Source: Ehmann et al 2013

Action of avibactam on chromosomally-located ampC

Avibactam was tested for its ability to induce *E. cloacae ampC* in a series of quantitative RT-PCR experiments; clavulanic acid and cefoxitin were used as comparators. In each experiment, normalized *ampC* mRNA levels were measured in a time course over several concentrations of compound in three different *E. cloacae* strains possessing *ampC* and resistant to cefoxitin. Representative results are shown in Figure 4.

Figure 4. Time courses of expression *ampC* mRNA in *E. cloacae*



Potential for *ampC* induction of cefoxitin, clavulanate, and avibactam. *Enterobacter cloacae* strains 293UC1 (**A**–**C**), 293LA2 (**D**–**F**), and 293HT107 (**G**–**I**) were incubated with cefoxitin (**A**, **D** and **G**), clavulanate (**B**, **E** and **H**), or avibactam (**C**, **F** and **I**). Inducers were used at various concentrations: 8 mg/L(squares), 16 mg/L(triangles), 32 mg/L (filled circles), or 64 mg/L (open circles); control cultures are shown with dashed lines. *ampC* messenger ribonucleic acids were quantified by real-time polymerase chain reaction after 2, 4, and 6 hours of culture.

In each of the three isolates, no elevated expression of *ampC* over background was observed at any time point or concentration of avibactam tested. However, cefoxitin resulted in a 40-fold increase in *ampC* expression in strains 293UC1 and 293HT107 after 2 hours at 8 mg/L, and a 250-fold increase in strain 293LA2 after 2 hours. Clavulanate appeared to have had no effect on *ampC* induction in strain 293UC1; it did result in an 8-fold increase in *ampC* expression after 2 hours at 64 mg/L, and a 40-fold increase in strain 293HT107 after 2 hours at 64 mg/L. In summary, there was no evidence in this study that avibactam would compromise the

effectiveness of co-administered β-lactam antibiotics against *E. cloacae* as a consequence of the induction of *ampC*.

In a second study, five AmpC-inducible ceftazidime-susceptible strains of *Enterobacter* spp., *C. freundii*, and *P. aeruginosa* each were plated on agar with ceftazidime alone, and ceftazidime with avibactam at 1 mg/L or 4 mg/L, in each case at 8x MIC. Large numbers of colonies grew on ceftazidime-only plates. When avibactam was included, the numbers of colonies were reduced by > 75% in all cases, and for 13 of 15 strains, was below the detection limit (Study CAZ-AVI-M2-065). This supports the interpretation that in addition to not inducing *ampC*, avibactam largely prevents the selection of derepressed mutants in the presence of ceftazidime.

In a third study, the Applicant examined the induction of ampC in three species, *E. cloacae*, *C. freundii*, and *P. aeruginosa* (Study CAZ-AVI-M2-122). The study was also performed by measuring normalized *ampC* mRNA levels by RT-PCR in a time course over several concentrations of compound. Three of five strains in this study were induced by avibactam. The level of *ampC* induction was observed at 32 mg/L avibactam. The Applicant states that this level is above the free Cmax of 8.4-9.7 mg/L avibactam predicted at steady-state in patients with cIAI and cUTI following administration of 2000 mg ceftazidime + 500 mg avibactam q8h as a 2-hour infusion. In summary, avibactam is capable of inducing ampC at levels equivalent to 32 mg/L in certain gram-negative strains.

Activity of avibactam against laboratory created single β-lactamase producing bacteria

The activity of ceftazidime-avibactam was examined against characterized *E. coli* and *P. aeruginosa* strains producing only a single type of β-lactamase enzyme. These strains were laboratory-created by either plasmid transformation into an isogenic background. These laboratory strains produced single β-lactamases and permitted examination of both ceftazidime-hydrolyzing capability as well as the ability of avibactam to restore ceftazidime susceptibility. Comparators in the studies were piperacillin-tazobactam, and either meropenem or imipenem. Data are shown in Table 44, Table 45, and Table 46.

Table 44. MIC values (mg/L) for *E. coli* strain DH10B carrying a single β-lactamase gene on a plasmid

β-Lactamase	*CAZ*	*CAZ-AVI*	*PIP-TAZ*	*MER*
Empty vector	0.25	0.12	2	≤ 0.015
Class A				
CTX-M-15[a]	8	0.12	ND	0.03
SHV-2	4	0.25	4	0.03
SHV-7	32 - > 128	1	> 128	0.03
SHV-8	32	0.5	2	0.03
SHV-10	0.5	0.25	> 128	≤ 0.015
SHV-14	1	0.25	> 128	≤ 0.015
SHV-26	0.25	0.25	2	0.03
SHV-30	4	0.25	2	0.03
SHV-49	0.5	0.25	> 128	0.03
SHV-84	0.5	0.25	4	≤ 0.015
SHV-102	16	1	> 128	0.03
SHV-106	8	0.25	4 – 32	0.03
SHV-120	8	0.5	> 128	0.03
SHV-129[a]	32 - > 128	0.25	2	≤ 0.015
SHV-141	1	1	2	≤ 0.015
SHV-154	> 128	0.5	4	0.03
SHV-161	2	0.25	> 128	0.03
TEM-10	> 128	2	4	0.03
TEM-15	16	0.5	2	0.03
TEM-17	2	0.25	> 128	≤ 0.015
TEM-19	0.5	0.25	4	0.03
TEM-26	> 128	1	2	0.03
TEM-191	1	0.5	> 128	0.03
KPC-5	32	0.5	64	0.12
KPC-6	32	0.5	64	0.12
KPC-7	32	0.25	128	0.5
KPC-8	> 128	4	128	0.5
Class C				
ADC-7	32	0.5	32	≤ 0.015
CMY-32	32	0.25	2	≤ 0.015
CMY-33	128	0.5	4	≤ 0.015
PDC-3	1	0.25	4	0.03
P99	4	0.25	2	0.03
FOX-4[b]	128	0.5	4	0.03
β-Lactamase	*CAZ*	*CAZ-AVI*	*PIP-TAZ*	*MER*
Empty vector	0.25	0.12	2	≤ 0.015
Class D				
OXA-1	0.5	0.25	> 128	0.03
OXA-24/40	0.5	0.25	64	0.25

MIC values measured by CLSI broth microdilution method. ND = not determined. Avibactam and tazobactam concentrations were fixed at 4 mg/L. Testing was performed in triplicate (duplicate if a testing instance failed quality control and values were within one dilution) and modal values are reported.

Abbreviations: CAZ = ceftazidime; AVI = avibactam; PIP-TAZ = piperacillin-tazobactam; MER = meropenem.

a Strain for CTX-M-15 was W3110. SHV-129 was engineered via site-directed mutagenesis of SHV-1.

b Strain for FOX-4 was TG-1.

Source. Results from Study CAZ-AVI-M2-099, except Study CAZ-AVI-M2-082

Table 45. MIC values (mg/L) for reference strains carrying a transconjugated β-lactamase gene

β-Lactamase	*Organism*	*CAZ*	*CAZ-AVI*	*PIP-TAZ*	*IMP*
Class A					
CTX-M-9 [a]	*E. coli*	2	0.25	1	0.125
CTX-M-14 [a]	*E. coli*	2	0.06	1	0.125
CTX-M-15 [a]	*E. coli*	2	0.06	2	0.125
KPC-3 [a]	*E. coli*	128	0.25	> 128	8
GES-1	*E. coli*	> 512	1	16	1
GES-2	*E. coli*	32	1	4	1
GES-2	*P. aeruginosa*	32	4	64	32
GES-3	*E. coli*	128	0.25	16	4
GES-4	*E. coli*	128	1	2	1
CMT-4	*E. coli*	512	1	8	0.5
PER-1	*E. coli*	> 512	0.5	0.5	0.25
VEB-1	*E. coli*	> 512	1	4	0.5
BEL-1	*E. coli*	8	0.5	16	0.5
Class B					
VIM-1	*E. coli*	> 512	512	256	8
VIM-1 [b]	*P. aeruginosa*	> 512	512	512	512

Abbreviations: CAZ – ceftazidime; AVI – avibactam; PIP-TAZ – piperacillin-tazobactam; IMP – imipenem.
a MIC values measured by CLSI agar dilution method. Avibactam and tazobactam concentrations were fixed at 4 mg/L.
b VIM-1 on plasmid.
Source: Study CAZ104-M2-026-NXL104-AP0001, except † Study CAZ104-M2-029-NXL104-AP0009

Table 46. MIC values (mg/L) for *P. aeruginosa* strain PU21 carrying a transconjugated β-lactamase gene

β-Lactamase	*CAZ*	*CAZ-AVI*	*PIP-TAZ*	*MER*

Source : Mushtaq et al 2010

Against the class A ESBL family of enzymes (CTX-M, SHV, TEM, PER, VEB, and BEL) avibactam protected ceftazidime from hydrolysis at different levels based on MIC. The addition of avibactam restored ceftazidime susceptibility for strains carrying these single class A enzymes, and there appeared to be no antagonistic effect observed for the ceftazidime non-hydrolyzers. Ceftazidime-avibactam was effective against many β-lactamases that conferred resistance to piperacillin-tazobactam (e.g. SHV-7 in *E. coli*, GES-2 in *P. aeruginosa*).

Mechanisms of Resistance to Ceftazidime-Avibactam

Resistance to cephalosporins can be mediated through a variety of mechanisms including the alterations of PBPs, formation of cephalosporinases that inactivate the drug, a decrease in the ability of the drug to penetrate the cell wall and reach the drug target, or efflux of the drug thereby preventing the drug from

reaching its target. In gram-negative organisms, the predominant mode of resistance is the production of β-lactamase hydrolyzing enzyme such as extended spectrum β-lactamases (ESBLs). ESBLs are classified β-lactamases into classes (A, B, C, and D) based on primary amino acid sequence and catalytic mechanism. Table 47 shows the functional grouping of β-lactamases.

Table 47. Classifications of β-lactamases referred to in this application

Molecular class	*Functional grouping*	*Representative enzymes*
Class A	Extended spectrum β-lactamase (ESBL) [a]	CTX-M- type GES-1, -3, -7, -9 SHV- 2, 5, 12 and other (Jacoby and Bush 2013) TEM- 10, 12 and others (Jacoby and Bush 2013) VEB-type PER-type BEL-type
	Class A, non-ESBL, non-carbapenemase	SHV-1, 11, 20, 21, 22 and others (Jacoby and Bush 2013) TEM-1, 2, 13, 95 and others TEM-30 (IRT-2), TEM-31 (IRT-1) and others
	Class A carbapenemase	GES-2, -4, -5, -6, -8 IMI-1 KPC-sequence variants NMC-A SME-1 PSE
Class B	Metallo-β-lactamase	IMP- sequence variants NDM-1 SPM-1 VIM- sequence variants
Class C		ACC- sequence variants ACT- sequence variants AmpC CMY- sequence variants DHA- sequence variants FOX- sequence variants MOX- sequence variants MIR- sequence variants P99 PDC[b]
Class D	'OXA-type ESBL' [a], non-carbapenemase	OXA-1, 2, 10 (certain point mutations)[c], 11, 13, 16, 69 and others (Jacoby and Bush 2013)
	Class D carbapenemase	OXA-23, 40, 48, 54, 55, 58, 60, 62
	Carbapenemase activity unknown	OXA-2-group OXA-10-group OXA-13-group OXA-18 OXA-24-group OXA-45

a The following working definition of ESBLs has been used: ESBLs are class A β-lactamases that hydrolyze expanded-spectrum cephalosporins and aztreonam, but not carbapenems, and are inhibited by clavulanic acid. ESBLs confer resistance to ceftazidime, cefotaxime, cefpodoxime, ceftriaxone and aztreonam, but MIC values are reduced 8-fold in the presence of clavulanic acid. Additionally, the concept of 'OXA-type ESBL' has been introduced to describe class D OXA β-lactamases that confer the ESBL phenotype on Gram negative bacteria; although some of the enzymes so-classified are not susceptible to clavulanic acid (Naas et al 2008). These are not molecular class A β-lactamases, so do not fit the above working definition of 'ESBLs'. Hence the descriptor "OXA-type" is used when referring to these enzymes.

b The PDC nomenclature was created to classify sequence variants of the chromosomally-encoded AmpC β lactamase of *P. aeruginosa* (Rodríguez-Martínez et al 2009; see also Study CAZ-AVI-M2-064).

c The OXA-10 itself does not confer resistance to ceftazidime though it does confer resistance to other cephalosporins

Source: Poirel et al 2010.

It is noted that some organisms may exhibit a broad natural resistance to ceftazidime and avibactam offers little protection against ceftazidime hydrolysis. These organisms include most gram-positive pathogens, some non-fermenters such as *Acinetobacter baumannii*, and most anaerobic bacteria. Table 48 depicts data of the activity of ceftazidime-avibactam against a range of intermediate- and non-susceptible gram-negative bacteria. Ceftazidime did not have substantial activity against *A. baumannii* and avibactam did not increase the susceptibility of these isolates. Avibactam did not restore or improve susceptibility against isolates phenotypically characterized as imipenem- or ceftazidime resistant (*A. baumannii*, *A. calcoaceticus*, *Burkholderia cepacia*, and *Stenotrophomonas maltophilia*).

Table 48. In vitro activity of ceftazidime-avibactam and comparators against intermediate and non-susceptible Gram-negative bacteria

Organism	*Compound*	*MIC (mg/L) range for subgroup*	
Achromobacter xylosoxidans (N = 5)	CAZ	2-16	
	CAZ-AVI	4-8	
	Levofloxacin	0.06-8	
		NP (5)	
Acinetobacter baumannii (N = 10)	CAZ	2-64	IPM-R (5)
	CAZ-AVI	16-32	64-> 128
	Levofloxacin	0.06-32	8-> 128
		NP (16)	4-> 128
Acinetobacter calcoaceticus (N = 17)	CAZ	0.5-> 128	IPM-R (1)
	CAZ-AVI	0.5-> 128	128
	Levofloxacin	0.06-16	64
			2
Acinetobacter ursingii (N = 3)	CAZ	16	
	CAZ-AVI	16-32	
	Levofloxacin	0.25	
		NP (10)	
Burkholderia cepacia (N = 15)	CAZ	4-8	CAZ-R (5)
	CAZ-AVI	2-8	8-> 128
	Levofloxacin	0.5-16	64-> 128
			8-16
Ochrobactrum anthropi (N = 5)	CAZ	128-> 128	
	CAZ-AVI	16-> 128	
	Levofloxacin	0.12-0.25	
		NP (5)	
Stenotrophomonas maltophilia (N = 10)	CAZ	0.5-1	IPM-R (5)
	CAZ-AVI	0.12-2	2-> 128
	Levofloxacin	0.12-2	2-128
	Levofloxacin	0.12-2	0.25-1

The combination of ceftazidime-avibactam did not appear to significantly improve antibacterial activity against some anaerobic organisms. Against *Bacteroides fragilis*, avibactam lowered the MIC90 of ceftazidime to 16 mg/L from > 128 mg/L. *B. fragilis* possesses several β-lactamases, including class A and a class B metallo-β-lactamase CcrA3 (Table 49).

Table 49. In vitro activity of ceftazidime-avibactam and comparators against *Bacteroides fragilis*

Organism	*Compound*	*MIC range (mg/L)*	*MIC_{50} (mg/L)*	*MIC_{90} (mg/L)*
Bacteroides fragilis (N = 68)	CAZ	8 - 512	64	> 128
	CAZ-AVI	2 - > 128	8	16
	Metronidazole	< 0.12 - 2	0.5	1
	PIP-TAZ	< 0.12 - > 256	1	8
Bacteroides fragilis † (N = 98)	CAZ	0.5 - > 128	64	> 128
	CAZ-AVI	0.06 - > 64	4	32
	Metronidazole	< 0.06 - 4	1	2
	PIP-TAZ	0.06 - 32	0.25	4

MIC values were measured according to the CLSI agar dilution method. Avibactam and tazobactam were tested at a fixed concentration of 4 mg/L.

Abbreviations: CAZ = ceftazidime; AVI = avibactam; PIP-TAZ = piperacillin-tazobactam.

Source: Study CAZ104-M2-017-NXL104-AP0031 and Study CAZ104-M2-008-NXL104-AP0020.

Mechanisms of resistance to avibactam generated in resistance development studies using ceftaroline-avibactam

The Applicant investigated the risk of mutational resistance to avibactam. Both single- and multi-step mutants were sought and characterized from *Enterobacteriaceae* with ESBLs, AmpC β-lactamases and KPC β-lactamases. The tested organisms included 20 *Enterobacteriaceae* with ceftaroline MICs ≥32 mg/L and single ceftaroline-hydrolyzing enzymes [*Escherichia coli* with TEM-3, TEM-10, CTX-M-1, CTX-M-3, CTX-M-9, CTX-M-15 and CTX-M-40, *Klebsiella pneumoniae* with CTX-M-9, KPC (n=3) and SHV-4 (n=2), *Enterobacter cloacae* with derepressed AmpC (n=3) and KPC (n=2) and *Citrobacter braakii* and *Morganella morganii* with derepressed AmpC]. There also were five controls (*E. coli, K. pneumoniae, Klebsiella oxytoca* and two *E. cloacae*) lacking cephalosporin hydrolyzing β-lactamases and with ceftaroline MICs of 0.06–0.25 mg/L[19].

The result of the study indicated that overgrowth occurred on agar with low MIC multiples of ceftaroline+avibactam, but frequencies for single-step mutants were $<10^{-9}$. Most mutants were unstable, with only three remaining resistant on subculture. For one, from a CTX-M-15-positive *Escherichia coli*, the ceftaroline+avibactam MIC elevated from ≤ 0.06 mg/L to 8 mg/L, but the organism had reduced resistance to ceftaroline (> 64 to 32 mg/L) and lost resistance to ceftazidime (32 to 0.25 mg/L), with this profile retained when the mutant blaCTX-M-15 was cloned into *E. coli* DH5a. Sequencing identified a Lys237Gln substitution in the CTX-M-15 variant. The second and third stable single-step mutants were from AmpC-derepressed *E. cloacae*. Ceftaroline-avibactam MIC values increased from 0.25 mg/L to 4 and 16 mg/L for the two variants, while MIC values of cefpirome, piperacillin-tazobactam, and ertapenem were reduced by 8- to 16-fold. Additionally, sequence analysis revealed that both had amino acids 213–226 deleted from the V loop of AmpC. Further stable mutants were obtained from AmpC-inducible and -derepressed *E. cloacae* in multi-step selection, and these variously had reduced expression of OmpC and OmpF, and/or Asn366His/Ile substitutions in AmpC.

It was concluded that stable mutational resistance to ceftaroline+ avibactam was difficult to select in strains with ESBLs or KPC enzymes, though this was easier in AmpC-derepressed *Enterobacter*, where it was associated with (i) a 14 amino acid deletion in AmpC (in LN04004SS1 and LN04004SS2), (ii) loss of OmpC and/or OmpF and/or (iii) changes at position 366 of AmpC (in strains LN08032MS1 and SE06038MS1).

Mutations in porin proteins are sometimes selected by exposure to carbapenems, but can reduce overall bacterial fitness.

Mechanisms of resistance to ceftazidime-avibactam/resistance development studies–Enterobacteriaceae and P. aeruginosa

In another study, ceftazidime-avibactam-resistant mutants were selected using ceftazidime with avibactam at 1 or 4 mg/L from *Enterobacteriaceae* with SHV, CTX-M, TEM, derepressed AmpC or KPC β-lactamases and from *P. aeruginosa* with derepressed AmpC. Control strains lacking β-lactamases were included. The effect of avibactam on the propensity of ceftazidime to select AmpC-derepressed mutants of *E. cloacae*, *C. freundii*, and *P. aeruginosa* was also investigated. Mutants were obtained from strains with all enzyme families tested, largely at 2-4x MIC. Colonies were obtained from most strains at frequencies of 10^{-7} to 10^{-9} when the selection was conducted at 2x MIC for ceftazidime-avibactam (Table 50).

Table 50. Frequencies of mutants selected from 28 isolates in a single step on agar containing different MIC multiples of ceftazidime-avibactam, 4 mg/L

Organism	*Mechanism*	*MIC (mg/L)*			*Selection @ 2 × MIC CAZ+AVI 4*		*Selection @ 4 × MIC CAZ+AVI 4*		*Selection @ 8 × MIC CAZ+AVI 4*		*Selection @ 16 × MIC CAZ+AVI 4*	
		CAZ	*CAZ+ AVI*	*Initial count × 10^9*	*Count*	*freq × 10^{-9}*	*Count*	*freq × 10^{-9}*	*Count*	*freq × 10^{-9}*	*Count*	*freq × 10^{-9}*
K. pneumoniae	SHV-2	> 256	1	1.113	2	1.80	0	<	0	<	0	<
K. pneumoniae	SHV-2	64	0.5	1.23	4	3.25	0	<	0	<	0	<
K. pneumoniae	SHV-5	256	0.5	1.098	1120	1020.04	18	16.39	0	<	0	<
K. pneumoniae	SHV-5	> 256	1	1.629	0	<	0	<	0	<	0	<
K. pneumoniae	CTX-M-1	64	0.5	1.458	0	<	0	<	0	<	0	<
K. pneumoniae	CTX-M-1	256	0.5	1.401	0	<	0	<	0	<	0	<
E. coli	CTX-M-15	16	0.25	1.266	1	0.79	0	<	0	<	0	<
E. coli	CTX-M-15	32	0.25	0.921	0	<	0	<	0	<	0	<
E. coli	TEM-10	> 256	0.5	1.044	30	28.74	0	<	0	<	0	<
E. coli	TEM-10	> 256	1	1.215	23	18.93	8	6.58	0	<	0	<
K. pneumoniae	KPC	256	2	0.975	2026	2077.95	19	19.49	3	3.08	0	<
K. pneumoniae	KPC	128	2	1.25	60	48.00	22	17.60	10	8.00	2	1.60
E. cloacae	KPC	32	0.5	1.078	172	159.55	24	22.26	4	3.71	1	0.93
E. cloacae	KPC	32	0.5	1.005	3	2.99	0	<	2	1.99	0	<
E. cloacae	AmpC	64	0.5	1.506	0	<	0	<	0	<	0	<
E. cloacae	AmpC	64	0.5	1.04	22	21.15	5	4.81	2	1.92	0	<
C. freundii	AmpC	256	1	1.13	0	<	0	<	0	<	0	<
C. freundii	AmpC	128	0.5	0.909	8	8.80	2	2.20	2	2.20	0	<
E. coli	CAZS	0.125	0.125	1.098	0	<	0	<	0	<	0	<
E. coli	CAZS	0.125	0.125	1.005	14	13.93	0	<	0	<	0	<
E. cloacae	CAZS	0.5	0.25	1.598	2	1.25	0	<	0	<	0	<
E. cloacae	CAZS	0.25	0.25	1.625	0	<	0	<	0	<	0	<
K. pneumoniae	CAZS	0.125	0.125	1.14	0	<	0	<	0	<	0	<
K. pneumoniae	CAZS	0.125	0.25	1.398	1	0.72	0	<	0	<	0	<
P. aeruginosa	AmpC	64	4	1.155	1142	988.74	1	0.87	0	<	0	<
P. aeruginosa	AmpC	64	4	1.333	502	376.59	0	<	0	<	0	<
P. aeruginosa	CAZS	0.5	0.5	1.038	5	4.82	0	<	0	<	0	<
P. aeruginosa	CAZS	0.5	0.5	1.044	0	<	0	<	0	<	0	<

Abbreviations: CAZ = ceftazidime; AVI = avibactam; PIP-TAZ = piperacillin-tazobactam; MER = meropenem.
< : below detection limit of 0.5×10^{-9}
Source: Study CAZ-AVI-M2-065

In another experiment to determine frequencies of spontaneous single-step resistance, ten

Enterobacteriaceae and *P. aeruginosa* isolates were tested under 2x, 4x, and 8x MIC for ceftazidime with avibactam at 4 mg/L (Table 51, Study CAZ-AVI-M2-132). Ceftazidime-avibactam resistance frequencies ranged from 2.04×10^{-9} to 1.8×10^{-6} for 8 of 10 isolates tested when avibactam was tested at 4 mg/L. Two isolates expressing a *bla*ampC gene (CMY-2 in *E. coli* and ACT/MIR in *E. cloacae*) yielded no ceftazidime-avibactam resistant variants. The highest resistance frequencies were obtained with 2x ceftazidime-avibactam MIC concentration. Two isolates, a KPC producer and an AmpC producer, developed resistance with 8 x ceftazidime-avibactam MIC concentrations in one experiment.

Table 51. Ceftazidime-avibactam resistance frequencies with an average inoculum of 3.6×10^8 CFU

Organism	*β-lactamase*	*CAZ-AVI Resistance Frequency*					
		2X		*4X*		*8X*	
K. pneumoniae	KPC-2	6.33×10^{-8}	9.59×10^{-8}	2.04×10^{-9}	2.04×10^{-9}	ND	ND
K. pneumoniae	KPC-3	2.86×10^{-8}	2.86×10^{-8}	ND	ND	ND	ND
E. coli	AmpC (CMY-2)	ND	ND	ND	ND	ND	ND
E. cloacae	AmpC (ACT/MIR)	ND	ND	ND	ND	ND	ND
E. cloacae	KPC	1.84×10^{-8}	3.45×10^{-8}	4.6×10^{-9}	1.38×10^{-8}	2.30×10^{-9}	ND
K. pneumoniae	SHV-5	1.8×10^{-7}	2.84×10^{-7}	ND	ND	ND	ND
E. coli	CTX-M-14	5.47×10^{-7}	4.85×10^{-7}	2.67×10^{-8}	4.27×10^{-8}	ND	ND
E. coli	wild type	6.17×10^{-8}	7.1×10^{-8}	9.35×10^{-9}	3.74×10^{-9}	ND	ND
P. aeruginosa	AmpC	1.18×10^{-6}	1.84×10^{-6}	1.33×10^{-7}	7.62×10^{-8}	1.9×10^{-8}	1.9×10^{-8}
P. aeruginosa	ΔAmpC, ΔpoxB	2.77×10^{-7}	9.13×10^{-7}	ND	ND	ND	ND

ND, not detected, no isolates grew on plates tested at the indicated concentration. CAZ-AVI, ceftazidime-avibactam. Single-step resistance frequencies were determined at 2X, 4X, and 8X the ceftazidime-avibactam MIC with avibactam at 4 mg/L. Resistance frequencies were determined in duplicate for each condition so 2 calculations are shown per ceftazidime-avibactam concentration tested.

Source: Study CAZ-AVI-M2-132.

Ceftazidime-avibactam was active against fluoroquinolone-resistant *Enterobacteriaceae* and *P. aeruginosa* (Study CAZ-AVI-M2-120) Table 52.

Table 52. Activity of ceftazidime-avibactam and comparators against fluoroquinolone-resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa*-MIC50 and MIC90

Microorganism (no of strains tested)	*MIC (mg/L)*															
	IMI		*MER*		*PIP*		*CAZ*		*CPT*		*AZT*		*PIP-TAZ*[b]		*CAZ-AVT*[a]	
	50	**90**	**50**	**90**	**50**	**90**	**50**	**90**	**50**	**90**	**50**	**90**	**50**	**90**	**50**	**90**
***Enterobacteriaceae* (200):**																
E.coli ESBL (30)	< 0.06	0.125	< 0.06	< 0.06	> 128	> 128	4	64	> 128	> 128	32	128	4	128	< 0.125	0.25
K. pneumoniae-ESBL (20)	0.125	0.25	< 0.06	< 0.06	> 128	> 128	64	> 128	> 128	> 128	> 128	> 128	> 128	> 128	0.125	0.5
Ceftazidime-non-susceptible AmpC producing species (33)	1	4	< 0.06	1	> 128	> 128	128	> 128	>128	> 128	64	> 128	128	> 128	0.25	1
E. coli non-ESBL (30)	< 0.06	0.125	< 0.06	< 0.06	> 128	> 128	< 0.125	0.25	0.25	0.5	< 0.125	0.25	2	16	< 0.125	< 0.125
K. pneumoniae non-ESBL (20)	> 0.125	0.5	< 0.06	0.125	64	> 128	0.25	0.5	< 0.125	0.5	< 0.125	0.5	4	64	< 0.125	0.25
Ceftazidime-susceptible AmpC-producing species (67)	1	4	< 0.06	< 0.06	128	> 128	0.5	2	2	> 128	0.5	4	8	128	< 0.125	0.5
P. aeruginosa (25)	16	32	8	16	> 128	> 128	16	64	128	> 128	16	64	64	128	2	8

CAZ, ceftazidime; CAZ-AVI, ceftazidime-avibactam; PIP, piperacillin; PIP-TAZ piperacillin-tazobactam; CPT, ceftaroline; AZT, aztreonam; IMI, imipenem; MER, Meropenem

a Ceftazidime combined with avibactam at a fixed concentration of 4 mg/L

b Piperacillin combined with tazobactam at a fixed concentration of 4 mg/L

Source: Study CAZ-AVI-M2-120.

Ceftazidime-avibactam was active against a panel of *E. coli* with cell envelope changes that include the

following knockout efflux and LPS mutations *tolC, waaG, waaP, waaC, ompA, ompC, phoE, ompF, ompC+ompF, ompA+ompC, ompA+ompF,* and *tolC+wag* (Table 53).

Table 53. MIC values of Ceftazidime and Ceftazidime-Avibactam Against an Isogenic Panel of *E. coli* Cell Envelope Mutants

Strain	*Strain Characteristics*	*Ceftazidime MIC (mg/L)*	*Ceftazidime-Avibactam MIC (mg/L)*
ARC 4	ATCC 25922	0.12	0.06
ARC 16	ATCC 35218	0.12	0.03
ARC 4169	Parent + vector	0.25	0.12
ARC 4170	Parent + CTX-M-15	8	0.12
ARC 4171	Δ*tolC*	0.25	0.12
ARC 4172	Δ*tolC* + CTX-M-15	16	0.25
ARC 4173	Δ*waaG*	0.5	0.25
ARC 4174	Δ*waaG* + CTX-M-15	8	0.12
ARC 4175	Δ*waaP*	0.25	0.12
ARC 4176	Δ*waaP* + CTX-M-15	4	0.12
ARC 4177	Δ*waaC*	0.12	0.06
ARC 4178	Δ*waaC* + CTX-M-15	4	0.016
Strain	*Strain Characteristics*	*Ceftazidime MIC (mg/L)*	*Ceftazidime-Avibactam MIC (mg/L)*
ARC 4179	Δ*tolC* Δ*waaG*	0.12	0.06
ARC 4180	Δ*tolC* Δ*waaG* + CTX-M-15	8	0.06
ARC 4181	Δ*ompA*	0.25	0.12
ARC 4182	Δ*ompA* + CTX-M-15	4	0.06
ARC 4183	Δ*ompC*	0.25	0.03
ARC 4184	Δ*ompC* + CTX-M-15	4	0.06
ARC 4185	Δ*phoE*	0.25	0.06
ARC 4186	Δ*phoE* + CTX-M-15	8	0.06
ARC 4187	Δ*ompF*	0.5	0.12
ARC 4188	Δ*ompF* + CTX-M-15	16	0.12
ARC 4189	Δ*ompC* Δ*ompF*	0.5	0.06
ARC 4190	Δ*ompC* Δ*ompF* + CTX-M-15	8	0.12
ARC 4191	Δ*ompA* Δ*ompC*	0.12	0.12
ARC 4192	Δ*ompA* Δ*ompC* + CTX-M-15	1	0.06
ARC 4193	Δ*ompA* Δ*ompF*	0.25	0.25
ARC 4194	Δ*ompA* Δ*ompF* + CTX-M-15	8	0.25

MIC testing was conducted in LB media to facilitate growth of mutant strains. Each strain was tested in duplicate.
Source: Study CAZ-AVI-M2-082

Summary and conclusions

Avibactam is a non-β-lactam β-lactamase inhibitor that provides activity against Class C mediated resistance. It is a covalent inhibitor that acts via ring opening, but in contrast to other currently used β-lactamase inhibitors, this reaction is reversible. Avibactam inhibits Class A ESBLs and carbapenemases, Class C β-lactamases and some Class D oxacillinases and carbapenemases. The in vitro studies indicate a low propensity for the development of ceftazidime-avibactam resistance following serial passage experimental studies at 4 x MIC. The ceftazidime-avibactam mutation frequencies ranged from 10^{-7} to 10^{-9}. The highest mutation frequency (10^{-7}) was observed against a KPC producing *K. pneumoniae* strain.

Miscellaneous Microbiology Studies

Post-antibiotic and Post β-lactamase inhibitor effects

The PAE describes the suppression of bacterial growth that occurs after short exposure to an antibiotic. The PAE is a consequence of the initial exposure to high concentrations of antibiotics rather than to persistent sub-inhibitory levels. Additionally, PAE can be measured for combinations of a β-lactam/β-lactamase inhibitor. In these experiments, bacteria are exposed to the combination of drugs in the same way as the traditional PAE. However, at the washout stage, the β-lactam but not the β-lactamase inhibitor is replaced. The experiment continues as with the PAE and the time for the combination treated culture to grow 1-log10 CFU/mL is assessed. The difference in time for this regrowth to occur as compared to a control containing the β-lactam but not the β-lactamase inhibitor is called the post-β-lactamase inhibitor effect or PLIE and represents the time necessary for production of sufficient β-lactamase to overcome the presence of the β-lactam.

The PAE was determined for ceftazidime and ceftazidime-avibactam against 10 isolates of gram-negative pathogens including *E. coli*, *K. pneumoniae* and *P. aeruginosa* isolates with characterized β-lactamases (Study CAZ-AVI-M2-110). The characteristics of the isolates tested are listed in Table 54.

Table 54. MIC (mg/L) of ceftazidime (CAZ) with and without avibactam (AVI) against the evaluated isolates

Organism	*Strain*	*β-lactamase*	*CAZ MIC (mg/L)*	*CAZ-AVI MIC (mg/L)*
E. coli	ATCC 25922	-	0.25	0.25
E. coli	ARC3456	-	0.5	0.25
E. coli	ARC3457	CTX-M-15	2	0.03
K. pneumoniae	004-1893	-	0.12	0.12
K. pneumoniae	6860J	KPC-2	32	0.5
K. pneumoniae	24-1318A	CTX-M-15	128	0.5
E. cloacae	2-77C	derepressed *ampC*	> 128	0.5
P. aeruginosa	ATCC 27853	-	2	2
P. aeruginosa	ARC3610	ESBL	128	8
P. aeruginosa	061-5568	derepressed *ampC*	128	8

Source: Study CAZ-AVI-M2-110

In another study, the PAE was evaluated for ceftazidime with and without avibactam and the PLIE was evaluated for ceftazidime combined with avibactam. No PAE or PLIE was observed for ceftazidime alone or in combination with avibactam with the exception of a PLIE of 1.9 hours observed with ceftazidime-avibactam against a single isolate of *K. pneumoniae* (6860J; *bla*KPC-2). The PAE and PLIE results are summarized in Table 55 and Table 56 below, respectively. The negative values reported by the Applicant indicate conditions under which the treated control recovered slightly faster than the untreated control. These values were a result of small variations in the efficiency of plating and indicated situations where no PAE or PLIE was observed.

Table 55. Summary of PAE for ceftazidime (CAZ) alone and in combination with avibactam (AVI) at 4X MIC, 8X MIC or 128 mg/L

Organism	*Strain*	*β-lactamase*	*CAZ PAE (hours)*			*CAZ-AVI PAE (hours)*	
			4X MIC	*8X MIC*	*128 mg/L*	*4X MIC*	*8X MIC*
E. coli	ATCC 25922	-	-0.2	-0.3	-	0.1	0.2
E. coli	ARC3456	-	-0.5	-0.2	-	-0.1	-0.1
E. coli	ARC3457	CTX-M-15	-0.4	-0.4	-	-0.1	-0.5
K. pneumoniae	004-1893	-	-0.3	-0.1	-	0.5	0.5
K. pneumoniae	6860J	KPC-2	-	-	-0.5	0.2	0.2
K. pneumoniae	24-1318A	CTX-M-15	-	-	-0.2	0.3	0.2
E. cloacae	2-77C	derepressed AmpC	-	-	-0.4	-0.4	-0.5
P. aeruginosa	ATCC 27853	-	-0.5	-0.5	-	-0.4	-0.4
P. aeruginosa	ARC3610	ESBL	-	-	-0.1	0.1	-0.2
P. aeruginosa	061-5568	derepressed AmpC	-	-	-1.1	-0.7	-1.2

Source: Study CAZ-AVI-M2-110

Table 56. Summary of PLIE for ceftazidime (CAZ) in combination with avibactam (AVI) at 4X MIC

Organism	*Strain*	*β-lactamase*	*CAZ-AVI PLIE (hours)*
			4X MIC
E. coli	ARC3457	CTX-M-15	-0.6
K. pneumoniae	6860J	KPC-2	1.9
K. pneumoniae	24-1318A	CTX-M-15	0.4
E. cloacae	2-77C	derepressed AmpC	-0.8
P. aeruginosa	ARC3610	ESBL	-0.2
P. aeruginosa	061-5568	derepressed AmpC	-0.5

Source: Study CAZ-AVI-M2-110

BACTERICIDAL/BACTERIOSTATIC ACTIVITY

Minimum Bactericidal Concentration (MBC)

The bactericidal activities of ceftazidime-avibactam were determined against selected gram-negative bacteria. Studies were conducted in several independent laboratories and for the purpose of this review the Minimum Bactericidal Concentration (MBC) was defined as the lowest concentration of antimicrobial agent that killed ≥ 99.9 % of the starting inoculum. The term "bactericidal" was defined as an MBC/MIC ratio of ≤ 4. MBC activities were conducted using CLSI broth microdilution methods. Studies were conducted to investigate the bactericidal activity of ceftazidime-avibactam against Gram-negative pathogens by determination of minimum bactericidal concentrations (MBCs) and by time-kill studies.

Ceftazidime-avibactam demonstrated bactericidal activity based on MBC/MIC ratios of ≤ 4 in a single study against 20 *Pseudomonas aeruginosa* and 13 *Enterobacteriaceae*, including some isolates that produced a variety of β-lactamases. MBC determinations were performed according to CLSI guidelines (CLSI M26-A, 1999). The MBCs for most isolates were within one dilution of the MIC and an MBC/MIC ratio of ≤ 4 was observed for all isolates. The data are shown in Table 57.

Table 57. MIC and MBC values of isolates tested

			Ceftazidime-Avibactam MIC (mg/L)		
ID Number	***Organism***	***β-lactamase enzyme***	***MIC***	***MBC***	***MBC/MIC Ratio***
261GR3	*C. freundii*	AmpC	0.06	0.125	2
ATCC# 35218	*E. coli*	TEM	0.06	0.125	2
ATCC# 25922	*E. coli*	WT	0.03	0.06	2
250COL10	*E. coli*	KPC	0.5	0.5	1
250TN03	*E. coli*	CTX-M-15 TEM-1 OXA-1	0.25	1	4
TN05	*E. coli*	CTX-M-9	0.125	0.125	1
K. ox 1431	*K. oxytoca*	TEM-129	1	1	1
238	*K. pneumoniae*	CTX-M-2 SHV-2 TEM-12	0.25	0.5	2
Tun clone K4	*K. pneumoniae*	CTX-M-15 TEM-1 OXA-1	1	1	1
ATCC# 700603	*K. pneumoniae*	SHV	0.5	0.5	1
24-1318A	*K. pneumoniae*	CTX-M-15	0.5	0.5	1
283KB7	*K. pneumoniae*	KPC-2	1	2	2
27-908M	*K. pneumoniae*	KPC-2	1	1	1
4207J	*K. pneumoniae*	Cured of KPC gene	0.25	0.5	2
ATCC# 14756	*S. marcescens*	WT	0.25	1	4
391COL23	*P. aeruginosa*	OXA-23	16	32	2
391COL19	*P. aeruginosa*	KPC CTX-M	2	4	2
391COL20	*P. aeruginosa*	CTX-M VIM	32	64	2
391COL21	*P. aeruginosa*	KPC	4	8	2
391HG172	*P. aeruginosa*	AmpC OXA-9	4	8	1
391HG173	*P. aeruginosa*	AmpC	1	2	2
391HG176	*P. aeruginosa*	WT	2	2	1
ATCC# 27853	*P. aeruginosa*	WT	1	2	2
244-136-A	*P. aeruginosa*	AmpC	8	16	2

			Ceftazidime-Avibactam MIC (mg/L)		
ID Number	***Organism***	***β-lactamase enzyme***	***MIC***	***MBC***	***MBC/MIC Ratio***
5568-061-A	*P. aeruginosa*	AmpC TEM-24	2	4	2
1227-061-C	*P. aeruginosa*	Unknown	2	8	4
2154-422-D	*P. aeruginosa*	Unknown	4	16	4
465-107-A	*P. aeruginosa*	Unknown	8	16	2
5241-051-A	*P. aeruginosa*	Unknown	2	4	2
10783-091-A	*P. aeruginosa*	AmpC	8	16	2
12432-138-A	*P. aeruginosa*	Unknown	4	16	4
2740-127-A	*P. aeruginosa*	AmpC	4	8	2
2908-081-C	*P. aeruginosa*	Unknown	4	8	2

Source: Study CAZ-AVI-M2-077

In another experiment, the kinetics of ceftazidime-avibactam killing was assessed in time-kill studies against a variety of gram-negative isolates in two independent studies. The effects of antibiotic treatment at multiples of the MIC on the viability of bacteria in culture (measured as colony forming units per unit volume) were measured. The first study evaluated the activity of ceftazidime-avibactam against two strains of *C. freundii*, three strains of *E. cloacae* and four strains of *K. pneumoniae* (Study CAZ104-M2-027-NXL104-AP0003). This study used a fixed 4:1 ratio of ceftazidime to avibactam. The MIC values of ceftazidime and ceftazidime-avibactam are shown in Table 58.

Table 58. MIC values of ceftazidime and ceftazidime-avibactam (using a 4:1 ratio) against bacterial isolates used in time-kill studies

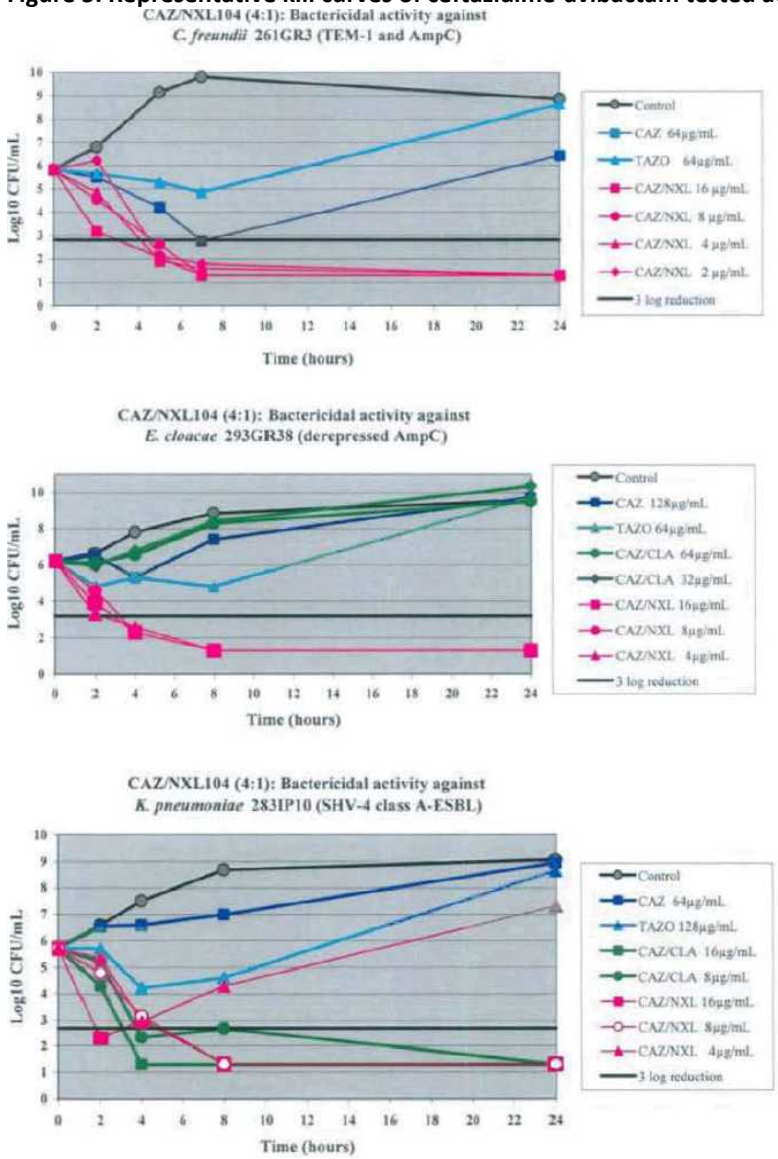
ID Number	***Species***	***β-lactamase enzyme***	***MIC (mg/L)***	
			CAZ[a]	***CAZ-AVI[a]***
261GR3	*C. freundii*	TEM-1 AmpC	64	2
261GR6	*C. freundii*	derepressed AmpC	> 32	2
293GR38	*E. cloacae*	derepressed AmpC	> 64	4
293GR8	*E. cloacae*	derepressed AmpC	> 128	4
293HT6	*E. cloacae*	derepressed AmpC	> 64	4
283IP35	*K. pneumoniae*	SHV-11	32	4
283IP10	*K. pneumoniae*	SHV-4	> 256	4
283KB4	*K. pneumoniae*	DHA-2	> 256	4
283KB5	*K. pneumoniae*	LAT-4 SHV-11	32	1

a CAZ = ceftazidime; CAZ-AVI = ceftazidime-avibactam (tested at a ceftazidime:avibactam ratio of 4:1)
Source: Study CAZ104-M2-027-NXL104-AP0003

The data show that ceftazidime-avibactam was bactericidal at low MIC within the first 6 hours and against all strains tested. Higher concentrations of ceftazidime-avibactam appear to have no effect on the speed of bacterial killing thereby suggesting that killing was not concentration dependent. Ceftazidime-avibactam

demonstrated time-dependent killing. Maximal rates of killing were generally seen at greater than or equal to two-times the MIC, with bactericidal effects (≥ 3-log10 killing) occurring within 5 to 24 hours. Selected kill-curves are shown in Figure 5. The concentrations shown in these figures represent the amount of listed drug or the amount of ceftazidime for testing of combinations.

Figure 5. Representative kill curves of ceftazidime-avibactam tested at a 4:1 ratio



CAZ = ceftazidime; TAZO = piperacillin-tazobactam; CAZ/CLA = ceftazidime-clavulanate; CAZ-NXL = ceftazidime-avibactam.

In another study, the killing kinetics of ceftazidime-avibactam was evaluated against three *E. coli*, one *K. oxytoca*, four *K. pneumoniae* and six *P. aeruginosa* (Study CAZ-AVI-M2-080). A fixed 4 mg/L avibactam was used in combination with various concentrations of ceftazidime. The characteristics and MIC values of the isolates studied are shown in Table 59. The addition of avibactam to ceftazidime extended the antimicrobial and bactericidal activity of ceftazidime against the ceftazidime- and meropenem-resistant isolates tested. The addition of avibactam to ceftazidime had no effect on the metallo-β-lactamase-producing and OXA-23-

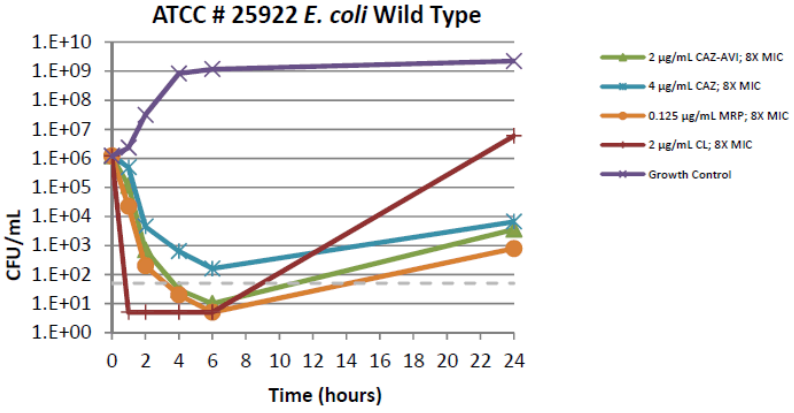
expressing *P. aeruginosa*. Ceftazidime-avibactam was bactericidal against all the *Enterobacteriaceae* tested in this study, at least a 3-log10 reduction in CFU/mL was observed at 6 hour. Bacterial killing was less pronounced against *P. aeruginosa* isolates, where a 1- to 2-log10 reduction in CFU/mL at 6 hours was observed. The results are summarized in Table 59 and selected kill curves are shown in Figure 6.

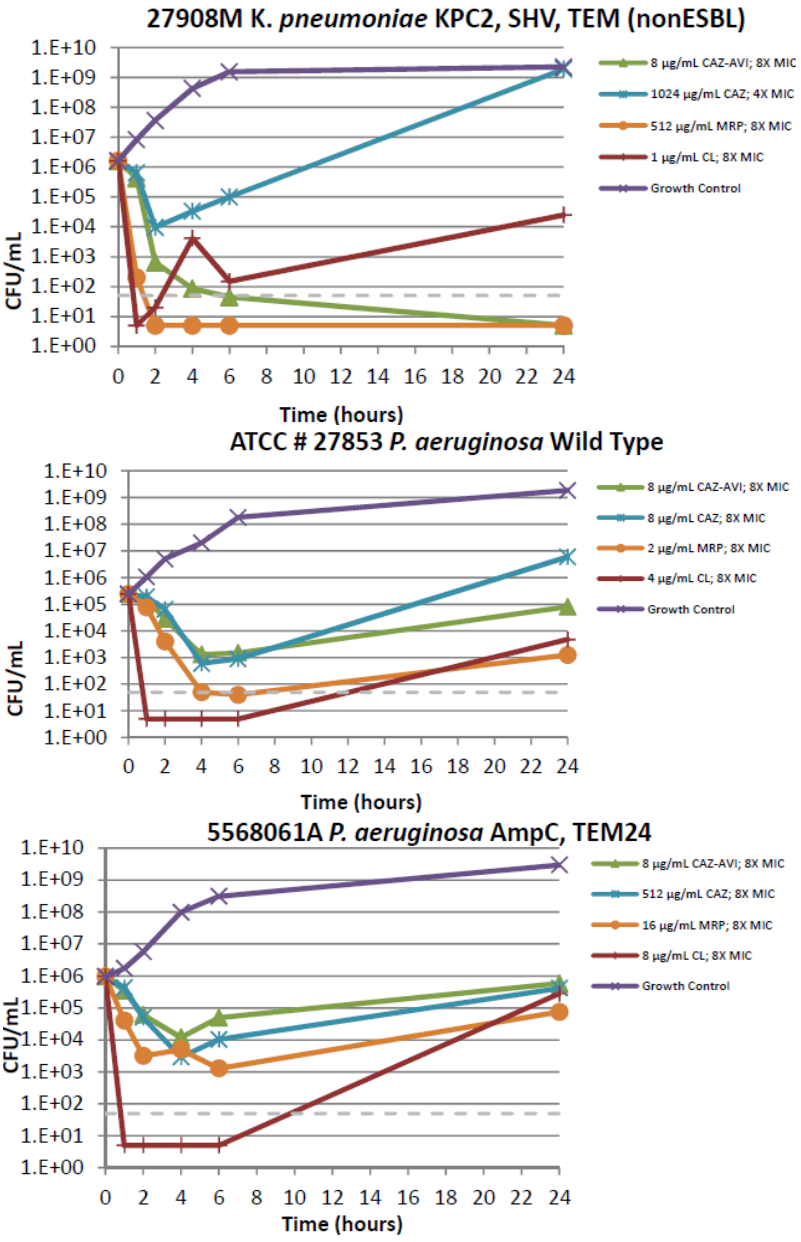
Table 59. Log10 change in CFU/mL from starting inoculum in time-kill studies

Strain ID	*Organism*	*β-Lactamase*	*Log_{10} change in CFU/mL at 6 h*				*Log_{10} change in CFU/mL at 24 h*			
			CAZ-AVI (fold MIC)			*CAZ 8X MIC*	*CAZ-AVI (fold MIC)*			*CAZ 8X MIC*
			2X	4X	8X		2x	4x	8x	
ATCC# 25922	*E. coli*	none	**-4.78**	**-5.08**	**-5.08**	**-3.88**	-0.88	**-5.38**	-2.52	-2.26
250COL10	*E. coli*	KPC	**-3.92**	**-4.40**	**-4.40**	**-4.45**	-0.53	-2.27	**-3.40**	-2.51
250TN03	*E. coli*	CTX-M-15 TEM-1 OXA-1	-2.46	**-4.29**	**-4.99**	**-4.99**	-0.74	0.01	**-4.99**	**-3.79**
K. ox 1431	*K. oxytoca*	TEM-129	-1.47	**-3.76**	**-3.76**	-0.74	2.58	-0.70	-0.45	2.72
4207J	*K. pneumoniae*	Cured of KPC gene	**-3.71**	**-4.88**	**-5.00**	**-5.48**	2.40	-1.11	-0.32	-2.92
Tun clone K4	*K. pneumoniae*	CTX-M-15 TEM-1 OXA-1	**-3.87**	**-4.29**	**-3.59**	**-3.52**	1.38	-0.66	-2.17	3.03
24-1318A	*K. pneumoniae*	CTX-M-15	**-3.41**	**-3.82**	**-3.67**	-0.94	-0.14	0.98	-0.37	0.54
27-908M	*K. pneumoniae*	KPC-2 SHV TEM (non-ESBL)	-2.33	**-4.47**	**-4.56**	-1.21	0.44	0.79	**-5.51**	3.07
ATCC# 27853	*P. aeruginosa*	none	**-3.53**	**-4.38**	-2.20	-2.43	-0.23	-0.72	-0.48	1.40
244-136-A	*P. aeruginosa*	AmpC	-0.91	-0.57	-2.25	-2.06	1.21	-0.24	-0.26	-1.46
5568-061-A	*P. aeruginosa*	AmpC TEM-24	-0.34	-1.71	-1.29	-1.97	1.99	1.69	-0.21	-0.36
2740-127-A	*P. aeruginosa*	AmpC	-0.31	-1.93	-1.93	-1.87	-0.05	-1.15	-0.95	-1.19
10783-091A	*P. aeruginosa*	AmpC	-0.12	-1.23	-1.09	-1.48	0.79	-0.93	-0.73	-0.76
465-107A	*P. aeruginosa*	unknown	-2.25	-2.71	-2.68	-2.02	2.29	1.31	-0.22	-0.23

A negative value indicates a decrease in counts over the starting inoculum. A positive value indicates an increase in counts over the starting inoculum. Bolded text indicates test results where a $\geq$ 3-log_{10} kill was achieved.
CAZ = ceftazidime; AVI = avibactam.
Source: Study CAZ-AVI-M2-080

Figure 6. Time-kill kinetics of ceftazidime-avibactam using a fixed 4 mg/L avibactam





Dashed line represents the limit of detection of the assay. CAZ-AVI = ceftazidime-avibactam; CAZ = ceftazidime; MRP = meropenem; CL = colistin.

Please note that even though ceftazidime-avibactam appears bactericidal for up to 6 hours, regrowth of some *P. aeruginosa* and *Enterobacteriaceae* strains were observed after 6 hours of incubation. Avibactam is always tested at a fixed concentration of 4 mg/L. Under such circumstances the concentration of avibactam tested may not be sufficient to protect the activity of ceftazidime over the 24 hour period of the study and this may explain some of the regrowth observed.

Intracellular Killing

This experiment examines if ceftazidime-avibactam can penetrate eukaryotic cells at concentrations sufficient to demonstrate activity against intracellular pathogens. Experiments were conducted with ceftazidime-avibactam against a panel of reference strains, clinical isolates and related pairs of ceftazidime-resistant and susceptible isolates of *P. aeruginosa.* The ceftazidime MIC values of the test organisms ranged from 2-128 mg/L. Briefly, the study to determine if ceftazidime-avibactam can penetrate eukaryotic cells was conducted in opsonized human THP-1 cells. Pseudomonas aeruginosa were allowed accumulate until intracellular counts reached approximately 10^5 CFU/mg. Non-phagocytized bacteria were removed and cells were exposed to ceftazidime-avibactam and comparators. After exposure, THP-1 cells were collected, washed and sonicated. The resulting bacterial lysate were plated for enumeration of viable intracellular bacteria. Data were expressed as change in inoculum after 24 hour exposure to drug. Values of 1 to 2 log10 CFU change from original inoculum were observed. Data also revealed that avibactam lowers the ceftazidime MIC against ceftazidime-resistant intracellular *P. aeruginosa* to below the susceptible breakpoint.

Summary/Conclusions:

Enterobacteriaceae used in the time-kill studies show at least a 3 log10 reduction in CFU/ml at 6 hours when exposed to ceftazidime-avibactam at 4x and 8X MIC. The data show that regrowth was observed at 24 hours for the isolates tested. Against *P. aeruginosa*, ceftazidime-avibactam demonstrated a decrease in the number of CFU/mL at 6 hours. However, this combination did not appear to be bactericidal against these isolates, as defined by a 3-$\log_{10}$ reduction in the number of CFU/ml for time-kill studies. The absence of bactericidal activity measured at 24 hours for the *Enterobacteriaceae* was a result of regrowth. For most *P. aeruginosa* isolates tested, a lower degree of initial killing combined with regrowth was observed. Only one *P. aeruginosa* isolate had a 3-$\log_{10}$ kill with 4× MIC ceftazidime-avibactam at 6 hours, whereas all 8 *Enterobacteriaceae* isolates had a 3-$\log_{10}$ kill with 4× MIC ceftazidime-avibactam at 6 hours.

Antimicrobial interactions (synergy between comparator agents)

Antimicrobial combination and synergy are important for treating pathogens in mixed infection, to enhance the killing of specific pathogens, and to prevent or delay the emergence of drug-resistant populations. The Applicant evaluated synergy of ceftazidime-avibactam in combination with different antibiotics using the checkerboard technique against a variety of bacterial isolates. The MIC and fractional inhibitory concentrations (FIC) and FIC indices (FICI) was used to assess drug interaction for ceftazidime-avibactam in combination with other antimicrobials. A “synergistic interaction” is evidenced by inhibition of organism growth by combinations that are at concentrations significantly below the MIC of either compound alone, resulting in a low FICI value (≤ 0.50). The interpretation of “no interaction” results in growth inhibition at concentrations below the MICs of the individual compounds, but the effect is not significantly different from the additive effects of the two compounds, resulting in an FICI value of > 0.50 but ≤ 4.0. (The interpretation “no interaction” has previously been referred to as “additivity” or “indifference.”) An “antagonistic interaction” results when the concentrations of the compounds in combination that are required to inhibit organism growth are greater than those for the compounds individually, resulting in an FIC value of > 4.0. Since there is no officially sanctioned set of FICI criteria, ≤ 0.50 was used to define synergism in this study.

Several experiments were conducted to show that there were minimal interactions between ceftazidime-avibactam and other agents that may be used in combination. A checkerboard assay was used to determine the interaction between ceftazidime or ceftazidime-avibactam and colistin, levofloxacin, linezolid, tigecycline, tobramycin and vancomycin. Twenty-seven isolates were tested, including three *E. cloacae*, five *E. coli*, seven *K. pneumoniae*, six *P. aeruginosa*, three *S. aureus* and three *E. faecalis*. Isolates with various resistance phenotypes were represented and are summarized in Table 60.

Table 60. Mean FICI values for all tested combinations.

Species	*Phenotype*	*Drug tested in combination with ceftazidime-avibactam (FICI/interpretation)*					
		Tobramycin	*Levofloxacin*	*Vancomycin*	*Linezolid*	*Tigecycline*	*Colistin*
E. cloacae	Basal MIC values	1.03 (NI)	1.17 (NI)	NT	NT	1.24 (NI)	1.48 (NI)
E. cloacae	Derepressed AmpC	1.28 (NI)	1.24 (NI)	NT	NT	1.67 (NI)	1.17 (NI)
E. cloacae	Derepressed AmpC	0.98 (NI)	1.23 (NI)	NT	NT	0.99 (NI)	1.21 (NI)
E. coli	Basal MIC values	1.14 (NI)	1.39 (NI)	NT	NT	1.25 (NI)	1.25 (NI)
E. coli	CTX-M-15	1.14 (NI)	1.12 (NI)	NT	NT	1.77 (NI)	1.58 (NI)
E. coli	TEM-4	1.34 (NI)	1.06 (NI)	NT	NT	1.82 (NI)	1.45 (NI)
E. coli	SHV-12	1.74 (NI)	1.16 (NI)	NT	NT	1.96 (NI)	1.24 (NI)
E. coli	SHV-2	0.76 (NI)	1.72 (NI)	NT	NT	1.89 (NI)	1.78 (NI)
K. pneumoniae	Basal MIC values	1.13 (NI)	1.65 (NI)	NT	NT	1.12 (NI)	1.17 (NI)
K. pneumoniae	TEM-4	1.35 (NI)	1.26 (NI)	NT	NT	1.60 (NI)	1.60 (NI)
K. pneumoniae	CTX-M-15	1.04 (NI)	1.21 (NI)	NT	NT	1.60 (NI)	1.48 (NI)
K. pneumoniae	SHV-12	1.31 (NI)	1.66 (NI)	NT	NT	1.14 (NI)	2.13 (NI)
K. pneumoniae	KPC-3	1.05 (NI)	1.21 (NI)	NT	NT	1.79 (NI)	1.23 (NI)
K. pneumoniae	KPC-3	1.23 (NI)	1.23 (NI)	NT	NT	1.87 (NI)	1.42 (NI)
K. pneumoniae	KPC-2	1.18 (NI)	1.14 (NI)	NT	NT	1.24 (NI)	1.24 (NI)
P. aeruginosa	Basal MIC values	1.23 (NI)	1.19 (NI)	NT	NT	1.24 (NI)	1.24 (NI)
P. aeruginosa	Derepressed AmpC	0.98 (NI)	1.12 (NI)	NT	NT	1.23 (NI)	1.05 (NI)
P. aeruginosa	Derepressed AmpC	0.81 (NI)	1.41 (NI)	NT	NT	0.96 (NI)	1.21 (NI)
P. aeruginosa	PER	0.73 (NI)	0.94 (NI)	NT	NT	1.10 (NI)	1.09 (NI)
P. aeruginosa	KPC-2	0.91 (NI)	1.13 (NI)	NT	NT	1.26 (NI)	1.21 (NI)
P. aeruginosa	KPC-2	0.72 (NI)	1.60 (NI)	NT	NT	1.57 (NI)	1.82 (NI)
S. aureus	Basal MIC	1.23 (NI)	1.21 (NI)	0.85 (NI)	1.21 (NI)	1.12 (NI)	NT
S. aureus	Basal MIC; penicillinase +	0.99 (NI)	1.32 (NI)	0.99 (NI)	1.10 (NI)	1.48 (NI)	NT
S. aureus	Basal MIC; penicillinase +	1.12 (NI)	1.21 (NI)	0.78 (NI)	1.21 (NI)	1.35 (NI)	NT
E. faecalis	Basal MIC	0.84 (NI)	0.99 (NI)	1.52 (NI)	1.81 (NI)	1.14 (NI)	NT
E. faecalis	Basal MIC	0.80 (NI)	1.19 (NI)	0.89 (NI)	1.24 (NI)	1.05 (NI)	NT
E. faecalis	Basal MIC	0.99 (NI)	1.11 (NI)	0.94 (NI)	0.87 (NI)	1.08 (NI)	NT

NI - No interaction; NT - Not Tested
Source: Study CAZ-AVI-M2-075

In another experiment, the potential for interaction between ceftazidime and ceftazidime-avibactam with metronidazole against target *Enterobacteriaceae* species grown under both aerobic and anaerobic conditions was evaluated (Study CAZ104-M2-057-CML-CAZ-002). Two isolates each of *E. coli* and *K. pneumoniae* expressing a variety of β-lactamases were included. The results are summarized in Table 61 and Table 62.

Table 61. Change in ceftazidime or ceftazidime-avibactam MIC with increasing metronidazole concentration under anaerobic conditions

Strain	*Organism*	*Change in CAZ or CAZ-AVI MIC with increasing [MTZ]* [a]					
		CAZ MIC (mg/L)	*MIC change*	*Interpretation*	*CAZ-AVI MIC (mg/L)*	*MIC change*	*Interpretation*
250COL10	*E. coli*	16	≤ 2-fold	No synergy	0.25	≤ 2-fold	No synergy
TN05	*E. coli*	2	≤ 2-fold [b]	No synergy	0.125	≤ 2-fold	No synergy
283KB7	*K. pneumoniae*	128	≤ 2-fold	No synergy	0.5	≤ 2-fold	No synergy
KP04	*K. pneumoniae*	32	≤ 2-fold	No synergy	0.5	≤ 2-fold	No synergy

a MTZ concentration was 16-1024 mg/L
b 4-fold at 256 mg/L
Source: Study CAZ104-M2-057-CML-CAZ-002

Table 62. Change in ceftazidime or ceftazidime-avibactam MIC with increasing metronidazole concentration under aerobic conditions

Strain	*Organism*	*Change in CAZ or CAZ-AVI MIC with increasing [MTZ]* [a]					
		CAZ MIC (mg/L)	*MIC change*	*Interpretation*	*CAZ-AVI MIC (mg/L)*	*MIC change*	*Interpretation*
250COL10	*E. coli*	16	≤ 2-fold	No synergy	0.25	≤ 2-fold	No synergy
TN05	*E. coli*	16	≤ 2-fold [b]	No synergy	0.125	≤ 2-fold	No synergy
283KB7	*K. pneumoniae*	≥ 128	≤ 2-fold	No synergy	0.5	≤ 2-fold	No synergy
KP04	*K. pneumoniae*	8	≤ 2-fold	No synergy	0.5	≤ 2-fold	No synergy

a MTZ concentration was 16-1024 mg/L
b 4-fold at 256 mg/L
Data Source: Study CAZ104-M2-057-CML-CAZ-002

Summary/conclusions:

Ceftazidime-avibactam tested in combination with other antibacterial agents against individual representative bacterial strains using the checkerboard method demonstrated a lack of synergy or antagonism between any other antibacterial agents. Except for one strain (*K. pneumoniae* SHV-12), the mean FICI values for each paring were below 2.0 demonstrating a lack of antagonism. One strain (*K. pneumoniae* SHV-12) had a value of 2.13 between ceftazidime-avibactam with colistin, however, this value was lower than the antagonism benchmark of >4. Additionally, no synergy/antagonism was observed when ceftazidime-avibactam was tested with metronidazole under anaerobic conditions.

Effect of Protein Binding in vitro susceptibility of ceftazidime-avibactam

The activity of β-lactams has been shown to be dependent upon the time the serum concentration exceeds the MIC of the drug. Clinical success usually occurs when the unbound serum concentration of the β-lactam exceeds the MIC of an infecting agent for more than 20-50% of the dosing interval. This dosing interval varies by the β-lactam class. For instance, 20-25% is generally required for carbapenems, 30-40% for penicillins, and 40-50% for cephalosporins. Therefore, the Applicant conducted protein binding studies to investigate the extent at which ceftazidime-avibactam binds to plasma protein.

Ceftazidime human protein binding was reported to be < 10% bound but values ranging from 5% to 22.8% bound have been reported. A value of 15% was used as the human plasma protein binding of ceftazidime when calculating free drug concentrations used in PK/PD analyses. The protein-binding properties of avibactam were evaluated in vitro in the plasma of mice, rats, rabbits, dogs and humans using an ultrafiltration method and [^{14}C]-avibactam. The protein binding was < 22% in mouse, rabbit, dog, rat plasma and ~8% in human plasma, and was not affected by concentration of anticoagulant.

Since protein-binding for ceftazidime is < 20% and of avibactam is < 10% in human serum at physiologically relevant concentrations, therefore, it is not expected that protein-binding would have a significant effect on the activity of the combination of ceftazidime and avibactam.

To determine the effect of human protein on MIC, the Applicant performed MIC testing using standard broth microdilution methods with 2-fold serial dilutions of ceftazidime-avibactam against a panel of Gram-negative clinical and reference isolates (Study CAZ-AVI-M2-078). Thirty-three isolates, including 20 *P. aeruginosa* and 13 *Enterobacteriaceae*, were used in this study. These tests revealed no significant differences (i.e. no greater than ± 1 log2 dilution) in MIC values from the CLSI reference conditions by the addition of 50% inactivated human serum or 4% human serum albumin. The results are summarized in Table 63.

Table 63. Effect of human serum and human serum albumin on ceftazidime-avibactam MIC values

ID Number[a]	*Organism*	*β-lactamase enzyme*	*ceftazidime-avibactam MIC (mg/L)*		
			CAMHB	*50% human serum*	*4% human serum albumin*
261GR3	*C. freundii*	AmpC	0.06 - 0.125	0.06	0.125
ATCC# 35218	*E. coli*	TEM	0.016 - 0.06	0.03 - 0.125	0.06 - 0.125
ATCC# 25922	*E. coli*	WT[b]	0.03 - 0.25	0.06 - 0.25	0.125 - 0.25
250COL10	*E. coli*	KPC	0.25 - 0.5	≤ 0.25	≤ 0.25
250TN03	*E. coli*	CTX-M-15 TEM-1 OXA-1	≤ 0.25	≤ 0.25 - 0.5	≤ 0.25
TN05	*E. coli*	CTX-M-9	0.125	0.06	0.125
K. ox 1431	*K. oxytoca*	TEM-129	0.5 - 1	0.5	0.5, 2
238	*K. pneumoniae*	CTX-M-2 SHV-2 TEM-12	0.125 - 0.25	0.25	0.25

ID Number[a]	*Organism*	*β-lactamase enzyme*	*ceftazidime-avibactam MIC (mg/L)*		
			CAMHB	*50% human serum*	*4% human serum albumin*
Tun clone K4	*K. pneumoniae*	CTX-M-15 TEM-1 OXA-1	0.5 - 1	0.25 - 0.5	0.5 - 1
ATCC# 700603	*K. pneumoniae*	SHV	0.5	0.25 - 0.5	0.25 - 0.5
24-1318A	*K. pneumoniae*	CTX-M-15	0.5	0.25	1
283KB7	*K. pneumoniae*	KPC-2	1	0.5 - 1	1
27-908M	*K. pneumoniae*	KPC-2	1	1	1 - 2
4207J	*K. pneumoniae*	Cured of KPC gene	0.25	0.25	0.25 - 0.5
ATCC# 14756	*S. marcescens*	WT	0.25	0.125 - 0.25	0.06, 0.25
391COL23	*P. aeruginosa*	OXA-23	16 - 32	8 - 16	8 - 16
391COL19	*P. aeruginosa*	KPC CTX-M	2 - 4	1 - 2	2 - 4
391COL20	*P. aeruginosa*	CTX-M VIM	16 - 32	16	16 - 32
391COL21	*P. aeruginosa*	KPC	1, 4	1 - 2	2 - 8
391HG172	*P. aeruginosa*	AmpC OXA-9	4	2	4 - 8
391HG173	*P. aeruginosa*	AmpC	1 - 2	0.5 - 1	1 - 2
391HG176	*P. aeruginosa*	WT	1 - 2	1	1
ATCC 27853	*P. aeruginosa*	WT	1 - 2	0.5	0.5 - 1
244-136-A	*P. aeruginosa*	AmpC	8 - 16	2	4
5568-061-A	*P. aeruginosa*	AmpC TEM-24	1 - 2	0.5 - 1	1 - 4
1227-061-C	*P. aeruginosa*	Unknown	1 - 2	0.5 - 1	1, 4
2154-422-D	*P. aeruginosa*	Unknown	4	2	4
465-107-A	*P. aeruginosa*	Unknown	8	4 - 8	8
5241-051-A	*P. aeruginosa*	Unknown	1 - 2	1 - 2	2
10783-091-A	*P. aeruginosa*	AmpC	8	2, 8	8
12432-138-A	*P. aeruginosa*	Unknown	4	2	4
2740-127-A	*P. aeruginosa*	AmpC	4	2 - 4	4
2908-081-C	*P. aeruginosa*	Unknown	2 - 4	1 - 4	2 - 8

a ID Number refers to the unique designation given by the source provider of the organism: Novexel, JMI, or ATCC.

b WT, wild type defined as ceftazidime susceptible and expresses no known β-lactamases genes other than the chromosomal inducible *ampC*.

Data Source: Study CAZ-AVI-M2-078

Effect of surfactant on in vitro susceptibility of ceftazidime-avibactam

No significant MIC increases were observed for ceftazidime, avibactam, or ceftazidime-avibactam against any of the gram-positive or gram-negative bacterial strains tested in up to 10 % pulmonary surfactant. For example, the MIC of ceftazidime-avibactam against one isolate of *E. coli* with both a CTX-M-15 and an SHV-12 β-lactamase was 0.12 mg/L when tested using standard conditions and in up to 10% surfactant. For this same isolate, ceftazidime had MIC values of 64 mg/L for all conditions tested. However, when the comparator daptomycin was tested, MIC values increased substantially (32 to > 128-fold) versus the *S. aureus* strains tested. As little as 1% pulmonary surfactant resulted in a 32-fold increase in daptomycin MIC values.

Effect of urine on in vitro susceptibility of ceftazidime-avibactam

Six β-lactamase-producing *Enterobacteriaceae* isolates from the trial were tested in broth microdilution assays to determine the effect of pooled human urine and acidic pH on ceftazidime-avibactam MIC values. Piperacillin-tazobactam and ceftazidime alone were used as comparators. Ceftazidime-avibactam MIC values

obtained in cation-adjusted Mueller-Hinton Broth (CAMHB) and urine at pH 7 were similar ranging from ≤ 0.016 to 0.5 mg/L in CAMHB and 0.03 to 0.25 mg/L in urine. However, ceftazidime-avibactam MIC values increased in both pH 5 CAMHB and pH 5 urine but it was reported that all MIC values were ≤ 4 mg/L.

In another experiment, a *K. pneumoniae* (TEM, SHV and CTX-M-1 group producer) isolate that had MIC value of 0.5 mg/L increased to 16 mg/L when tested at pH 5 in urine. A similar pattern of elevated MIC values at low pH was also seen with piperacillin-tazobactam and ceftazidime. MBC values for all antibiotics were typically within 4-fold the MIC regardless of medium and pH. Overall, the effect of urine on the bactericidal activity of ceftazidime-avibactam was minimal; however, pH 5 did seem to have some effect on the bactericidal activity of ceftazidime-avibactam against one isolate (*K. pneumoniae* 3039176), causing an increased MBC value. There was an effect of acidic pH on ceftazidime-avibactam antimicrobial activity; however, this was not unique to this combination as it was also observed with piperacillin-tazobactam and ceftazidime alone.

Bactericidal activity against biofilms

The combination of ceftazidime-avibactam was shown to be effective at eradicating biofilms produced by both ceftazidime-susceptible and resistant isolates of *E. coli*. Ceftazidime-avibactam had no effect on biofilms produced by either *S. aureus* or *P. aeruginosa*. The results are summarized in Table 64.

Table 64. The MIC and MBEC for ceftazidime and ceftazidime-avibactam against indicated isolates.

ID Number	*Organism*	*Resistance Type*	*CAZ*		*CAZ-AVI*	
			MIC (mg/L)	*MBEC (mg/L)*	*MIC (mg/L)*	*MBEC (mg/L)*
ATCC 25922	*E. coli*	-	≤ 0.25	16	≤ 0.25	≤ 1
ARC3520	*E. coli*	TEM-16	> 256	> 1024	≤ 0.25	64
ATCC27853	*P. aeruginosa*	-	2	> 1024	2	> 1024
ARC3470	*P. aeruginosa*	AmpC	16	> 1024	2	> 1024
ARC3483	*P. aeruginosa*	ΔAmpC	2	> 1024	2	> 1024
1674631	*S. aureus*	MRSA	32	> 1024	32	> 1024
ATCC6538	*S. aureus*	-	4	> 1024	4	> 1024
ATCC29213	*S. aureus*	-	8	> 1024	2	> 1024

Source: Study CAZ-AVI-M2-089

Summary/Conclusions;

These results suggest that there was no significant effect of human serum or human serum albumin on ceftazidime-avibactam MICs. This is to be expected for ceftazidime, since it binds very little to serum. In the presence of urine, ceftazidime-avibactam MIC values increased in both pH 5 CAMHB and pH 5 but it was reported that all MIC values were ≤ 4 mg/L.

Susceptibility Test Methods

The concentration of avibactam used in broth microdilution susceptibility testing

A fixed ratio of 4:1 was used for susceptibility testing early in the development of ceftazidime-avibactam. This method was changed to a fixed 4 mg/L concentration approach. MIC results with the fixed concentration approach were more consistently reproducible compared with those obtained using a fixed ratio.

Effect of medium and other variables on susceptibility tests

In Study CAZ104-M2-031-NXL104-AP0015, three reference strains (*E. coli* ATCC 35218, *K. pneumoniae* ATCC 700603 and *S. aureus* ATCC 29213) were tested to determine the effect of cations, pH, blood and CO_2 medium on MIC. MIC values for each condition were measured on five separate days and reported as a geometric mean. Table 65 shows the result of the above testing conditions in ceftazidime-avibactam MIC.

Table 65. Effect of testing conditions on ceftazidime-avibactam MIC

Testing Condition	*Geometric mean ceftazidime-avibactam MIC (mg/L)*		
	E. coli ATCC 35218	*K. pneumoniae ATCC 700603*	*S. aureus ATCC 29213*
Standard CLSI	0.079	0.758	16
Ca^{++} 5 mg/L Mg^{++} 5 mg/L	0.069	0.5	8.0
Ca^{++} 5 mg/L Mg^{++} 10 mg/L	0.06	0.574	9.19
Ca^{++} 10 mg/L Mg^{++} 10 mg/L	0.06	0.5	9.19
Ca^{++} 20 mg/L Mg^{++} 10 mg/L	0.06	0.5	9.19
Ca^{++} 25 mg/L Mg^{++} 5 mg/L	0.06	0.5	9.19
Ca^{++} 25 mg/L Mg^{++} 12.5 mg/L	0.06	0.574	8.0
Ca^{++} 25 mg/L Mg^{++} 15 mg/L	0.12	0.574	9.19
Ca^{++} 50 mg/L Mg^{++} 12.5 mg/L	0.06	0.5	9.19
pH 6.0	0.139	1.516	8.0
pH 6.5	0.139	1.516	8.0
pH 7.0	0.091	0.871	8.0
pH 7.2	0.06	0.574	8.0
pH 7.3	0.06	0.5	8.0
pH 7.4	0.06	0.574	9.19
pH 7.6	0.06	0.5	9.19

Testing Condition	*Geometric mean ceftazidime-avibactam MIC (mg/L)*		
	E. coli ATCC 35218	*K. pneumoniae ATCC 700603*	*S. aureus ATCC 29213*
pH 8.0	0.139	0.5	9.19
3-5% lysed horse blood	0.091	0.57	13.9
Incubation in %5 CO_2	0.12	1.149	8

Source: Study CAZ104-M2-031-NXL104-AP0015

There were no significant differences observed in the ceftazidime-avibactam MIC when Ca^{2+} and Mg^{2+} concentrations were evaluated over a range of 5–50 mg/L and 5–15 mg/L, respectively. Likewise, MIC values were stable in broth adjusted to pH 6.0, 6.5, 7.0, 7.2, 7.4, 7.6 and 8.0 with only small decreases of 2- to 2.5-fold noted for *E. coli* ATCC 35218 and *K. pneumoniae* ATCC 700603 when tested at pH 6.0. MIC values were determined in both ambient air and with panels incubated in 5-8% CO2. All ceftazidime-avibactam MIC values were within one doubling dilution of the reference method when tested in either 5% CO2 or in 3-5% lysed horse blood.

In a second study (Study CAZ-AVI-M2-133), nine *Enterobacteriaceae* and four *P. aeruginosa* strains were tested on two separate days to assess reproducibility of the results. It was noted that ceftazidime-avibactam MIC values were reproducible between test and not significant effects were observed under incubation conditions, medium composition and cation concentration. However, a variation was noted with changes in the MIC of 4- to 16-fold when testing at pH 5 and pH 6 suggesting a pH effect did occur.

Effect of inoculum size on the in vitro activity of ceftazidime-avibactam

In another experiment, the impact of variations in inoculum density was assessed between 10^3 and 10^7 CFU/mL (Study CAZ104-M2-031-NXL104-AP0015). The largest effect was noted with *S. aureus* ATCC 29213 where the geometric mean MIC increased from 8 mg/L to 42.2 mg/L across the range of inocula tested, the results of which are presented in Table 66. For the purpose of this review, increases in inoculum density do appear to have an adverse effect on the activity of ceftazidime-avibactam against *E. coli* (where a 4.67 fold increase was observed) and *K. pneumoniae* (where a 2-fold difference was observed).

Similar results were obtained in Study CAZ-AVI-M2-133 when inoculum densities between 5×10^4 CFU/mL and 5×10^6 CFU/ml were tested. Three isolates tested (*E. coli* CML00002255 and CML00001468; and *P. aeruginosa* CML00001047) tested with ceftazidime-avibactam. MIC values increased by 4- to 16-fold when a higher inoculum density of 5×10^6 CFU/mL was used suggesting that an inoculum effect occurs in MIC testing with higher densities of organisms.

Table 66. Effect of inoculum density on ceftazidime-avibactam broth microdilution MIC

Testing Condition	*Geometric mean ceftazidime-avibactam MIC (mg/L)*		
	E. coli ATCC 35218	*K. pneumoniae ATCC 700603*	*S. aureus ATCC 29213*
10^3 CFU/mL	0.06	0.57	8.0
10^4 CFU/mL	0.06	0.66	9.2
10^5 CFU/mL	0.79	0.76	16
10^6 CFU/mL	0.91	1.0	24
10^7 CFU/mL	0.28	1.15	42

Source: Study CAZ104-M2-031-NXL104-AP0015

Comparison of MIC values determined by agar dilution and MIC values determined by broth microdilution

Comparisons between MIC values generated by agar dilution with reference broth microdilution methods were conducted against 441 gram-negative bacterial isolates (Study CAZ104-M2-031-NXL104-AP0015). The Applicant indicated that 96.8% of the values observed were within ± 1 log2 dilution. Of the 441 isolates tested, there were only 7 *K. pneumoniae*, 2 *E. coli*, 3 *E. cloacae* and 1 isolate each of *A. baumannii* and *H. influenzae* which produced results greater than ± 1 log2 dilution.

Correlation between MIC values generated by reference broth microdilution and those generated by Sensititre dried susceptibility panels

Comparisons between MIC values generated by broth and Sensititre dried susceptibility panels were conducted using 200 *Enterobacteriaceae* clinical isolates (Study CAZ104-M2-021, Study CAZ104-M2-036-NXL104-AP0026) and according to CLSI method (M7-A7, 2006). The result of the study is shown in Figure 7. The data showed that 43/140 of the MIC values were in agreement and 97/140 was 1 dilution higher for the dried Sensititre dried susceptibility panels.

Figure 7. MIC distribution for clinical isolates vs. Ceftazidime-avibactam against *Enterobacteriaceae*

Ceftazidime avibactam results	MIC	Enterobacteriaceae											
		CLSI reference results											
		0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
Enterobacteriaceae Sensititre test results	0.03	4											
	0.06	28	11										
	0.12		24	7									
	0.25			13	9								
	0.5				13	4							
	1					11	1						
	2						6	2					
	4							2	1				
	8										1		
	16												
	32												
	>32												3
	TOTALS	32	35	20	22	15	7	4	1	0	1	0	3

For *Staphylococcus* species, 27/40 of the MIC values were in agreement and 13/40 was 1 dilution higher for the dried form (Figure 8).

Figure 8. MIC distribution for clinical isolates vs. Ceftazidime-avibactam against Staphylococci

Ceftazidime avibactam results	MIC	*Staphylococcus* spp.											
		CLSI reference results											
		0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
Staphylococcus spp. Sensititre test results	0.03												
	0.06												
	0.12												
	0.25												
	0.5												
	1												
	2						1						
	4								1				
	8								7	7			
	16									1	6		
	32										3	9	
	>32											1	4
	TOTALS	0	0	0	0	0	1	0	8	8	9	10	4

For *Haemophilus influenzae*, 17/20 of the MIC values were in absolute agreement, 3/20 was 1 dilution higher for the dried form (Data not shown). Additionally, stability testing of the dried panels was conducted; panels were tested at intervals of 3, 6, 9, 12, 18, and 24 months. No significant trend was noted over the 24 month

period for the development batch D8033 as the MIC values remained consistent over time. There was a slight loss in potency for ceftazidime by bioassay in the development batch but was said to have stabilized at 12 months. The data indicate that the performance of the ceftazidime-avibactam on dried panels is equivalent to ± 1 dilution standard to the CLSI broth microdilution reference method and stable for at least 24 months.

Development of a Kirby-Bauer test for diffusion tests

The Applicant performed a number of disk evaluation studies, and based on studies CAZ104-M2-009-09-NXL-01 and CAZ-AVI-M2-115, the 30 mcg ceftazidime/20 mcg avibactam disk content was chosen to be developed for both the *Enterobacteriaceae* and non-fermenters because this combination correctly categorized the largest number of susceptible and resistant isolates and avoided both major and very major discrepancies.

MIC and disk zone diameter test

The antimicrobial breakpoint may be defined as the drug concentration that differentiates between dissimilar populations of microorganisms, and isolates are subsequently classified as susceptible, intermediate or resistant. Methods using zone diameters to classify bacteria as susceptible or resistant to antibiotics depend on clinically meaningful MICs, a representative sample of bacteria, adequate and reproducible methods for determining MICs and zone diameters and a method for the relation of zone diameters to MICs. The classification scheme for showing a correlation between MIC and zone diameters is referred to as the error-rate bounded method and is presented by scattergrams.

The Applicant conducted two studies (Study CAZ104-M2-009-09-NXL-01, Study CAZ-AVI-M2-115) that established correlation between broth microdilution MIC and zone diameter for disk diffusion. A 30 mcg ceftazidime/20 mcg avibactam disk was used for testing against representative bacteria. Figures 8 and 9 show the correlation between the MIC verses disk diffusion MIC for β-lactamase producing *Enterobacteriaceae* and non-fermenters, respectively.

Figure 8. Ceftazidime-avibactam MIC values (avibactam at 4 mg/L) compared to ceftazidime-avibactam zones of inhibition (mm, 30/20 µg disk) against 60 β-lactamase producing *Enterobacteriaceae*

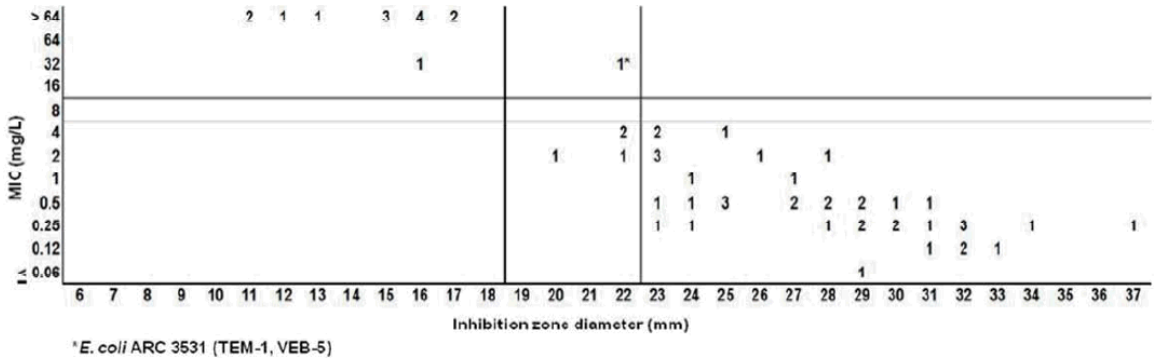
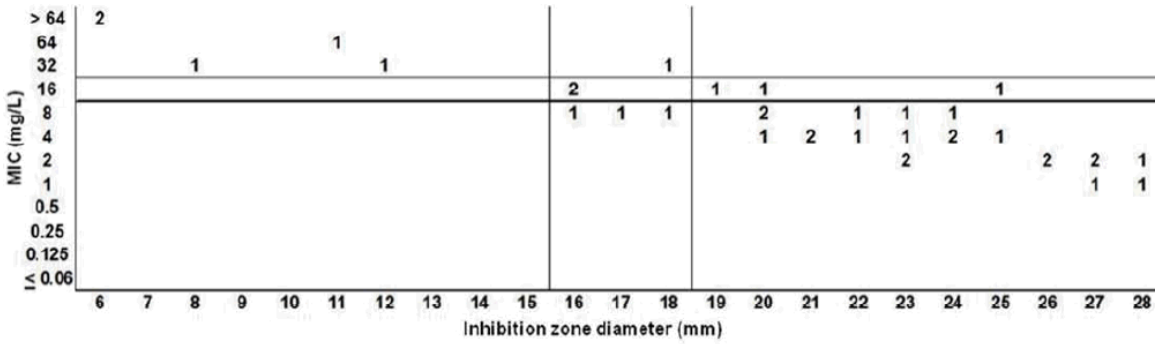


Figure 9. Ceftazidime-avibactam MIC values (avibactam at 4 mg/L) compared to ceftazidime-avibactam zones of inhibition (mm, 30/20 µg disk) against 36 β-lactamase producing non-fermenters[a]



Study CAZ-AVI-M2-115

Quality control (QC) limits for broth microdilution and disk diameter

Quality control limits for ceftazidime-avibactam have been established by the Clinical Microbiology Institute, Oregon, USA (Study CAZ104-M2-032-NXL104-AP0016, Study CAZ104-M2-048-CMI-11-16, and Study CAZ-AVI-M2-060-CMI-11-20). The study was done in accordance to CLSI guidance (CLSI M23-A2, 2001). The MIC QC ranges for the eight aerobic ATCC reference strains tested (*S. aureus* ATCC 29213, *E. coli* (ATCC 29522, and ATCC 35218), *K. pneumoniae* ATCC 700603, *P. aeruginosa* ATCC 27853, *H. influenzae* (ATCC 49247 and 49766) and *S. pneumoniae* ATCC 49619 were approved by the CLSI in 2012 (Table 67). The QC limits for ceftazidime-avibactam (30 mcg ceftazidime/20 mcg avibactam) against seven aerobic strains (*S. aureus* ATCC 29213, *E. coli* ATCC 29522 and ATCC 35218, *K. pneumoniae* ATCC 700603, *P. aeruginosa* ATCC 27853, *H. influenzae* ATCC 49247, and *S. pneumoniae* ATCC 49619) are shown in Table 68. The QC limits for ceftazidime-avibactam were approved by CLSI in 2012.

Table 67. Clinical and Laboratory Standards Institute approved MIC quality control ranges for ceftazidime-avibactam (avibactam tested at constant 4 mg/L)

Quality Control Organisms	*Expected ceftazidime-avibactam MIC range (mg/L)*
Staphylococcus aureus ATCC 29213	4/4–16/4
Escherichia coli ATCC 25922	0.06/4–0.5/4
Escherichia coli ATCC 35218	0.03/4–0.12/4
Klebsiella pneumoniae ATCC 700603	0.25/4–2/4
Pseudomonas aeruginosa ATCC 27853	0.5/4–4/4
Haemophilus influenzae ATCC 49247	0.12/4–0.5/4
Haemophilus influenzae ATCC 49766	0.015/4–0.06/4
Streptococcus pneumoniae ATCC 49619	0.25/4–2/4

Source: CLSI M100-S23, 2013

Table 68. Clinical and Laboratory Standards Institute approved disk quality control ranges for ceftazidime-avibactam 30 µg/20 µg disks

Quality Control Organisms	*Expected Ceftazidime-avibactam disk zone diameter range (mm)*
Staphylococcus aureus ATCC 25923	16 - 22
Escherichia coli ATCC 25922	27 - 35
Escherichia coli ATCC 35218	28 - 35
Klebsiella pneumoniae ATCC 700603	21 - 27
Pseudomonas aeruginosa ATCC 27853	25 - 31
Haemophilus influenzae ATCC 49247	25 - 31
Streptococcus pneumoniae ATCC 49619	23 - 31

Source: CLSI M100-S22, 2012

HUMAN AND ANIMAL STUDIES

Animal Disease Models

The Applicant has submitted data from a variety of animal models, including mouse peritoneal sepsis, mouse thigh infection, mouse pneumonia, mouse pyelonephritis and rabbit meningitis models. Activity was demonstrated in these infection models against gram-negative organisms. A summary of the infection models is shown in Table 70.

Table 70. Animal infection model studies of avibactam and ceftazidime-avibactam

Description	*Section*	*References*
Mouse peritoneal sepsis (PD_{50}) against *K. pneumoniae*, *E. cloacae*, *C. freundii* and *E. coli*	Section 4.3.1.2.1	Study CAZ104-M1-003-F-03-84726-502; Study CAZ-AVI-M1-063; Endimiani et al 2011
Mouse thigh infection (ED_{50}) against *K. pneumoniae*	Section 4.3.1.2.2	Endimiani et al 2011
Mouse pneumonia (ED_{50}) against *K. pneumoniae*	4.3.12.3	Study CAZ104-M1-004-NXL104-AP0004
Mouse pyelonephritis (efficacy) against *E. coli*, *C. freundii*, *E. cloacae*, *K. pneumoniae* and *M. morganii*	Section 4.3.1.2.4	Study CAZ104-M1-005-NXL104-AP0010
Rabbit meningitis (efficacy) against *K. pneumoniae*	Section 4.3.1.2.5	Study NXL104-PK0007
Mouse thigh infection (PK/PD studies) against *P. aeruginosa*	Section 4.4.1.3.3	Study CAZ-AVI-M1-066; Berkhout 2013b
Mouse lung infection (PK/PD studies) against *P. aeruginosa*	Section 4.4.1.3.4	Study CAZ-AVI-M1-066; Berkhout 2013c
Mouse thigh infection (simulated human PK) against *P. aeruginosa*	Section 4.4.2.2.1	Study CAZ104-M1-002; Crandon et al 2012
Mouse pneumonia (simulated human PK) against *P. aeruginosa*	Section 4.4.2.2.2	Study CAZ-AVI-M1-062; Housman et al 2014
Mouse thigh infection (simulated human PK) against *Serratia marcescens*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Enterobacter aerogenes*, *Klebsiella oxytoca* and *Providencia stuartii*	Section 4.4.2.2.3	Study CAZ-AVI-M1-067

a PD_{50}: 50% protective dose, based on study endpoints.
b ED_{50}: 50% protective dose, based on study endpoints.

Intraperitoneal infection in the mouse

The objective of this study (Study CAZ104-M1-003-F-03-84726-502) was to determine the efficacy of ceftazidime-avibactam (4:1 weight/weight and 8:1 w/w) in comparison to cefepime, piperacillin-tazobactam (8:1 w/w), amoxicillin-clavulanate (5:1 w/w), and ceftazidime alone, in experimental murine septicemia induced by infections with various species of *Enterobacteriaceae*, *H. influenzae*, *S. aureus*, and *S. pneumoniae*. Gram-positive and gram-negative systemic infections were established by intraperitoneal (IP) injection of bacteria. Mice were treated subcutaneously at 0 and 4 hours post-infection with ceftazidime-avibactam or comparators. At 6 to 8 days post infection, the PD50 values (defined as the dose permitting survival of 50 % mice) were calculated.

Intraperitoneal gram-positive infection in the mouse

In intraperitoneal infections caused by *S. aureus*, or *S. pneumoniae* (Study CAZ104-M1-003-F-03-84726-502), CAZ alone or in combination with avibactam exhibited similar efficacy (PD50 of 38-18 and 33-27 mg/kg at ratio 1/4, respectively). Amoxicillin-clavulanate (AMC) was the most active drug (PD50 less than 5 mg/kg) against staphylococci, while cefepime (CFP) was the most active drug (PD50 less than 5 mg/kg) against pneumococcus.

***K. pneumoniae* (SHV-4, SHV-11, and TEM) in a mouse intraperitoneal sepsis model**

In this infection model, 5 *K. pneumonia* isolates were used (Table 71). Two isolates were ceftazidime-susceptible, and 3 were ESBLs (SHV-4, SHV-11, or TEM-3). PD50 values of ceftazidime against the SHV-4- and SHV-11-producers were > 50 and > 90 mg/kg, respectively. The mean PD50 values of ceftazidime-avibactam (4:1 w/w) were 5 and 12 mg/kg, respectively for the SHV-4 and SHV-11 produces and remained unchanged for the two ceftazidime-susceptible isolates. In comparison, piperacillin-tazobactam and amoxicillin-clavulanate were not active (Data not shown). These results demonstrate that avibactam is capable of restoring the activity of ceftazidime in vivo when tested against *K. pneumoniae* SHV-4 and SHV-11 producing ESBLs.

Table 71. The activity of ceftazidime and ceftazidime-avibactam against *K. pneumoniae* in a mouse intraperitoneal sepsis model

Isolate	*β-lactamase*	*MIC[a] (mg/L)*		*Mean PD_{50} (mg/kg)*	
		CAZ[b]	*CAZ-AVT[b]*	*CAZ*	*CAZ-AVT[c]*
K. pneumoniae 283IP53	none	0.12	0.12	< 5	< 5
K. pneumoniae 283GR4	none	0.25	0.25	< 1.5	< 1.5
K. pneumoniae 283IP10	SHV-4	> 64	1	> 50	5
K. pneumoniae 283IP35	SHV-11	16	0.5	> 90	29
K. pneumoniae	TEM-3	8	2	6 (4–11)	< 5

a MIC values were measured by agar dilution. In the case of ceftazidime-avibactam, the compounds were diluted in a fixed 4:1 ratio, such that an MIC of 16 mg/L represents a ceftazidime concentration of 16 mg/L plus an avibactam concentration of 4 mg/L.

b CAZ = ceftazidime; CAZ-AVI = ceftazidime-avibactam

c Ceftazidime-avibactam PD50 values were for the compounds dosed in 4:1 ratio w/w (ceftazidime:avibactam)

Source: CAZ104-M1-003-F-03-84726-502

Intraperitoneal infection in the mouse against AmpC-producing Enterobacteriaceae

In another experiment, the in vivo activity of ceftazidime-avibactam was determined against Class C β-lactamase producers (derepressed chromosomal bla_{AmpC}). The study was conducted with three isolates of *E. cloacae* and two isolates of *C. freundii*. Ceftazidime MIC values ranged from 8-64 mg/L against all 5 isolates; the addition of avibactam reduced the MIC to 0.5-2 mg/l (Table 72).

Table 72. The activity of ceftazidime and ceftazidime-avibactam against ceftazidime resistant *E. cloacae* and *C. freundii* in a mouse intraperitoneal sepsis model (Study CAZ104-M1-003-F-03-84726-502)

Isolate	*Intrinsic*	*MIC[a] (mg/L)*		*PD_{50} (mg/kg)*	
	β-lactamase	*CAZ[b]*	*CAZ-AVT[b]*	*CAZ*	*CAZ-AVT[c]*
E. cloacae 293HT6	AmpC	16	0.5	11	< 10
E. cloacae 293GR38	AmpC	8	1	> 90	58
E. cloacae 293GR8	AmpC	64	1	> 90	< 10
C. freundii 261GR3	AmpC	32	1	> 50	13
C. freundii 261GR6	AmpC	64	2	> 50	< 5

a MIC values were measured by agar dilution. In the case of ceftazidime-avibactam, the compounds were diluted in a fixed 4:1 ratio, such that an MIC of 16 mg/L represents a ceftazidime concentration of 16 mg/L with an avibactam concentration of 4 mg/L.

b CAZ = ceftazidime; CAZ-AVI = ceftazidime-avibactam

c Ceftazidime-avibactam PD50 values were for the compounds dosed in 4:1 ratio w/w (ceftazidime:avibactam).

Source: CAZ104-M1-003-F-03-84726-502

Against the *E. cloacae* 293HT6 (contains the P99 AmpC sequence) ceftazidime alone demonstrated a survival PD50 of 11 mg/kg. Avibactam did not appear to significantly affect the activity since a PD50 of ceftazidime-avibactam was < 10 mg/kg (Table 72). The ceftazidime resistance of the other 4 strains translated to high PD50 values of > 50-90 mg/kg. Ceftazidime-avibactam lowered the PD50 to <5-58 mg/kg.

Intraperitoneal infection in the mouse against gram-negative and –positive

In another experiment, the efficacy of ceftazidime-avibactam against a number of gram-negative and gram-positive isolates in mouse intraperitoneal infection was investigated. The experiment focused on organisms known to be producing Class A or Class C β-lactamases and involved avibactam in combination with different cephalosporins. Briefly, mice were infected IP with organisms in 0.5 ml 5% hog gastric mucin containing 10^8-10^9 CFU and group of 10 mice were dosed subcutaneously (SC) with antibiotic or antibiotic-inhibitor combinations at 3 different doses (1 dose/group) in 0.2 ml saline. Dosing was done at 1 hour and 4 hours post-infection. The control group received only saline at the dosing intervals. Table 73 shows the varying ratios of ceftazidime (CAZ), ceftriaxone (CTR) and cefpodoxime (CFP) combined with avibactam (AVI) or clavulanate (CLA) against gram-negative isolates. Ceftazidime, ceftriaxone, cefpodoxime combined with avibactam (4/1 - w/w), appear to perform equally well against SHV producing strain of *K. pneumoniae*. However, against an AmpC producing *C. freundii* strain, lower ED50 values were reported for ceftazidime-avibactam and ceftriaxone-avibactam (4/1 –w/w). Combinations that had clavulanate resulted in higher ED50 values, suggesting that clavulanate is a poor inhibitor of AmpC.

Table 73. Mouse sepsis model data on three cephalosporins combined with the β-lactamases inhibitors avibactam and clavulanic acid (MIC1 in mcg/mL; unit dose ED50 in mg/kg).

Organism	Phenotype	Test Date	Andibiotic	Ratio (AB:IN)	Avibactam		Clavulanate	
					MIC	ED50	MIC	ED50
K. pneumoniae 283IP10	SHV4	10-Sep-02	Ceftazidime	8:1	4	8	4	6
				4:1	-	5	-	6
				2:1	-	3	-	3
				0:1*	>128	>15	32	>15
				1:0	>128	>30	>128	>30
			Ceftriaxone	8:1	1	<<3	1	<<3
				4:1	-	<<3	-	<<3
				2:1	-	<<3	-	<<3
				0:1*	>128	>15	32	>15
				1:0	>128	12	>128	12
			Cefpodoxime	8:1	1	6	1	1
				4:1	-	6	-	3
				2:1	-	4	-	3
				0:1*	>128	>15	32	>15
				1:0	>128	>30	>128	>30
			Augmentin PO	-	-	-	16	>>30
			Augmentin SC	-	-	-	>128	>30
E. cloacae 293GR38	AmpC	27-Nov-02	Ceftazidime	32:1		32		>30
				16:1	-	32	-	>30
				8:1	1	32	>8	>30
				0:1*	>128	>4	>128	>30
				1:0	>20	>50	>20	>50
			Ceftriaxone	32:1		>30		>30
				16:1	-	>30	-	>30
				8:1	2	>30	>8	>30
				0:1*	>128	>4	>128	>30
				1:0		>30		
			Cefpodoxime	32:1		>30		>30
				16:1		>30	-	>30
				8:1	8	>30	>8	>30
				0:1*	>128	>4	>128	>30
				1:0		>30		
			Augmentin PO	-	-	-	>64	>30
			Augmentin SC	-	-	-	>64	>30
C. freundii 261GR6	AmpC	24-Sep-02	Ceftazidime	8:1	2	17	>8	43
				4:1	-	11	-	91
				2:1	-	<<10	-	32
				0:1*	64	>45	32	>50
				1:0	128	88	128	88
			Ceftriaxone	8:1	2	9	>8	29
				4:1	-	8	-	25
				2:1	-	<10	-	33
				0:1*	64	>45	32	>50
				1:0	128	>90	128	>90
		28-Oct-02	Cefpodoxime	8:1	>8	>30	ND	ND
				4:1	-	>30	>8	>30
				2:1	-	26	-	>30
				0:1*	64	>45	32	>50
				1:0	>128	>30	>128	>30
			Augmentin PO	-	-	-	>64	>30
			Augmentin SC	-	-	-	>64	ND

Key: AB=antibiotic; IN=inhibitor; ED_{50} = 50% Effective (or curative) dose

1 = MIC of antibiotic in the presence of avibactam or clavulanate in the ratio listed in column

2 = Mice were dosed twice at 1 & 4 h post-infection. Unit dose ED_{50} is reported here

* The 0:1 data rows report the MIC of inhibitor alone, rather than the MIC of antibiotic

Table 74 shows the result of studies conducted in gram-positive infections caused by S. *pneumoniae,* ceftazidime alone or in combination with avibactam exhibited similar efficacy (unit dose ED50, respectively, 38-18 and 33-27 mg/kg at 4:1 ratio). Augmentin (AMC) was the most active drug (unit dose ED50 < 5 mg/kg) against the β-lactamase-producing S. *aureus,* while cefepime was the most active drug (unit dose ED50 <5 mg/kg) against S. *pneumoniae.* Against ceftazidime (CAZ)-susceptible strains of *Klebsiella pneumoniae* and *E. coli,* ceftazidime and ceftazidime-avibactam (AVI) were similar, displaying unit dose ED50 of <5 mg/kg. In comparison, tazocillin (TZC) and AMC were poorly active (Table 74). Against class A (β-lactamase-(TEM, SHV) producing strains of *K. pneumoniae* and *E. coli,* addition of AVI restored high efficacy to CAZ (unit dose ED50

<5- 29 mg/kg), especially against SHV -producing strains, where CAZ alone was poorly active. While TZC and AMC were inactive against the class C cephalosporinase producing species *Enterobacter, Citrobacter* and *Serratia,* the ED50s of CAZ+AVI were consistently lower than those of CAZ alone, with the 4: I and 8:1 ratios being equally active (Table 74). Against two strains of *H influenzae,* one strain of *Proteus mirabilis* and one of *Providencia stuartii,* no synergy was observed with AVI.

Table 74. Mouse sepsis model data on 4:1 and 8:1 CAZ:A VI against 21 β -lactamase producing strains (MIC1 in mcg/mL; unit dose ED50 in mg/kg).

Organism	Phenotype	Start Page	Date	Test*	Ceftazidime			Augmentin	Tazocillin	Cefepime
					Alone	+AVI 4:1	+AVI 8:1			
S. pneumoniae 030CR13	OXA-R	92	08/12/03	ED50	18	27	27	9	13	<5
				MIC	8	8	8	8	2	-
S. aureus 011HT18	CAZ-S	57	05/20/03	ED50	38	33	33	<5	11	6
				MIC	8	8	8	0.25	1	4
H. influenzae 350RD7	BLAR	87	07/22/03	ED50	<5	<5	<5	>50	>50	<5
				MIC	0.06	0.06	0.06	0.06	0.5	-
H. influenzae 351TO19	NBLAR	90	07/22/03	ED50	12	12	6	40	95	13
				MIC	1	1	1	1	1	-
E. coli 250GR12	Amp-S	61	05/27/03	ED50	<5	<5	<5	12	>50	<5
				MIC	0.06	0.06	0.06	2	2	0.015
E. coli 250GR43	Amp-R	78	07/02/03	ED50	9	5	6	22	>50	<5
				MIC	0.25	0.12	0.12	4	1	0.06
E. coli 250BE1	SHV-4	58	05/21/03	ED50	>50	16	16	49	39	18
				MIC	>64	2	4	8	16	16
K. pneumoniae 283GR4		50	05/05/03	ED50	<1.5	<1.5	<1.5	>50	>50	<1.5
				MIC	0.25	0.25	0.25	16	32	0.12
K. pneumoniae 283IP53		48	04/29/03	ED50	4	4.5	4.5	27	>50	<1.5
				MIC	0.12	0.12	0.12	4	4	0.06
K. pneumoniae 283IP84	TEM-3	64	06/04/03	ED50	6	<5	<5	43	>50	4
				MIC	8	2	8	32	32	4
K. pneumoniae 283IP10	SHV-4	75	06/26/03	ED50	50	5	9	20	>50	<5
				MIC	64	1	2	8	8	4
K. pneumoniae 283IP35	SHV11	79	07/03/03	ED50	>90	29	18	>90	>90	>90
				MIC	16	0.5	1	62	34	4
E.cloacae 93HTG	P99	42	04/06/03	ED50	>50	13.6	-	>50	>50	-
				MIC	>128	8	-	>64	32	-
E. cloacae 293GR38	AmpC	73	06/24/03	ED50	>90	58	65	>90	>90	19
				MIC	8	1	1	64	16	0.25
E.cloacae 93HT6	AmpC	66	06/11/03	ED50	11	<10	<10	>50	43	<10
				MIC	16	0.5	1	>64	16	0.25
E.cloacae 293GR8	AmpC	63	06/03/03	ED50	>90	<10	11	>90	>90	35
				MIC	64	1	2	>64	16	0.5
C. freundii 261GR3	AmpC	69	06/18/03	ED50	>50	13	14	>50	>50	9
				MIC	32	1	1	>64	32	0.25
C. freundii 261GR6	AmpC	74	06/26/03	ED50	>50	<5	<5	>50	>50	<5
				MIC	64	2	2	>64	32	1
S. marcescens 301UC6	AmpC	85	07/10/03	ED50	90	52	52	>90	>90	<10
				MIC	0.5	0.5	0.5	>64	2	0.5
P. mirabilis 312SJ1		71	06/20/03	ED50	22	22	>50	>50	>50	17
				MIC	0.12	0.12	0.12	1	0.5	0.06
P. stuartii 321UC1		91	07/30/03	ED50	6	5	4	>50	>50	4
				MIC	1	0.5	1	64	4	0.5

Key: AVI=Avibactam; BLAR=Resistance due to β-lactamase; NBLAR= Resistance not due to β-lactamase

1: MIC of ceftazidime in 4:1 or 8:1 ratio with avibactam

2: Mice were dosed twice at 1 & 4 h post-infection. Unit dose ED_{50} is reported here

In other experiments, the efficacy of ceftazidime-avibactam was compared with piperacillin (PIP) + tazobactam (TAZ), cefotazime alone and combined with AVI, and ceftriaxone in a mouse sepsis studies. The experiments were conducted with gram-negative bacterial isolates carrying multiple β-lactamase genes. The results are

presented in Table 75. Tazobactam is a poor inhibitor of AmpC and CTX-M enzymes and resulted in higher ED50 against isolates expressing these enzymes.

Table 75. Efficacy of ceftazidime-avibactam and comparators against AmpC- & ESBL-producing isolates of *Enterobacteriaceae* in a mouse sepsis model (Study CAZ-AVI-M1-063)

						Ceftazidime			Piperacillin			Ceftriaxone		Cefotaxime	
Organism	Phenotype	LNB#	Page	Date	Test	Alone	+AVI (4:1)	+CLA (4:1)	Alone	+AVI (4:1)	+TAZ[3] (4:1)	Alone	+AVI (4:1)	Alone	+AVI (4:1)
K. pneumoniae 283 IP10	AmpC; SHV-4	N-0011	102-103	03/30/06	ED50	>90	<10	-	>90	>90	>90	-	-	-	-
		N-0011	148-149	07/04/06	ED50	>90	7	-	-	-	-	30	<10	-	-
					MIC	>128	4 (1)	-	64	1	>128	64	1	-	-
E. cloacae 293HT6	AmpC	N-0011	102-103	03/30/06	ED50	72	<10	-	>90	31	>90	-	-	-	-
					MIC	128	4 (0.5)	-	128	8	128	-	-	-	-
E.coli TN06	CTX-M-2; TEM-1	N-0105		12/09/08	ED50	>45	21	-	-	-	-	-	-	>45	>30
		N-0112		04/02/09	ED50	-	27	-	>90	-	>90	-	-	>60	>90
					MIC	128	4 (0.5)	-	>128	-	16	-	-	>128	2 (0.5)
K. pneumoniae 465	CTX-M2; TEM-1	N-0112		03/19/09	ED50	>90	18	2*	>90	-	>90	-	-	>90	<10
		N-0112		04/02/09	ED50	-	-	-	-	-	-	-	-	>60	14
					MIC	64	8 (2)	4	>128	-	64	-	-	>128	ND (4)
E coli TN03	CTX-M-15; TEM-1; OXA1	N-0091		04/27/10	ED50	>60	2	-	>90	-	>90	-	-		
					MIC	>128	2 (0.25)	-	>128	-	2		-	>128	0.25
K. pneumoniae 253	CTX-M2; SHV2; TEM12	N-0112		03/18/09	ED50	127	27	148	>90	-	>90	-	-	165	70
					MIC	>128	8 (2)	2	>128	-	>128	-	-	>128	ND (4)
E.coli Tunisie E4	CTX-M-16; TEM-1	N-0091		03/24/09	ED50	-	-	-	-	-	-	-	-		
		N-0112		04/02/09	ED50	-	-	-	>90	-	>90	-	-	>90	>90
					MIC	>128	4 (1)	-	128	-	8	-	-	>128	1 (0.5)
K. pneumoniae Tunisie K4	CTX-M-15; TEM-1; OXA-1	N-0091		04/22/10	ED50	>90	21	-	>90	-	>90	-	-		
					MIC	>128	8 (2)	-	>128	-	>128	-	-	>128	≤0.125

Key: AVI=Avibactam, CLA=Clavulanic acid; TAZ=Tazobactam.

1: The MIC of ceftazidime is reported as a 4:1 ratio with AVI and with a fixed 4 µg/mL AVI (bracketed data)

2: Mice were dosed twice at 1 & 4 h post-infection. Unit dose ED_{50} is reported here

3: In these studies, a 4:1 combination of piperacillin:tazobactam was used; not the 8:1 commercial Tazocillin

Table 76 shows the result of sepsis studies that compared ceftazidime-avibactam with ceftaroline-avibactam. Ceftaroline-avibactam ratios of 4:1, 2:1 and 1:1 dosed 1 and 4 hour post-infection appear effective against AmpC, TEM-21 and SHV-1 producing *Enterobacteriaceae*; however, less effective against two CTX-M-producing stains of *E. coli*.

Table 76. Efficacy of ceftazidime-avibactam and comparators against AmpC- & ESBL-producing isolates of *Enterobacteriaceae* in a mouse sepsis model (Study CAZ-AVI-M1-063)

						Ceftazidime				Ceftaroline[3]				Cefotaxime		Imi
							+AVI				+AVI				+AVI	
Organism	Phenotype	LNB#	Page	Date	Test	Alone	4:1	2:1	1:1	Alone	4:1	2:1	1:1	Alone	(4:1)	Alone
K. pneumoniae 283 IP10	AmpC; SHV-4	N-0091		07/01/08	ED50	>60	2	3	4	>60	6	3	3	-	-	-
		N-0091			MIC	>128	4 (1)	-	-	64	1	-	-	-	-	-
K. pneumoniae 283 IP1	TEM-21	N-0091		07/01/08	ED50	>60	2	3	4	>60	6	3	3	-	-	-
					MIC	64	2 (0.5)	-	-	64	0.5 (4)	-	-	-	-	-
E. coli 250KB7	SHV-1	N-0091		07/01/08	ED50	6	8	4	2	1	1	<1	<1	-	-	-
					MIC	1	0.5 (0.25	-	-	<=0.125	<=0.125	-	-	-	-	-
E. cloacae 293HT6	AmpC	N-0091		07/22/08	ED50	82	10	5	4	68	6	5	4	-	-	-
					MIC	128	4 (0.5)	-	-	128	4 (0.25)	-	-	-	-	-
E.coli TN06	CTX-M-2; TEM-1	N-0091		07/22/08	ED50	50	2	1.8	0.7	79	>10	>10	>10	-	-	-
		N-0091		08/26/08	ED50	-	-	-	-	>60	24	24	33	-	-	-
		N-0091		09/08/08	ED50	>60	15	2	1.8	>60	>45	45	36	-	-	-
		N-0112		03/24/09	ED50	>60		-	-	>200	122	-	-	>200	>200	>10
		N-0091		08/27/09	ED50	>60	26	-	-	>100	59	-	-	>100	55	-
		N-0091		03/16/10	ED50	>90	10	-	-	>90	36	13	11	-	-	-
					MIC	128	4 (0.5)	-	-	128	2 (0.25)	-	-	128	2	-
E.coli Tunisie E4	CTX-M-16; TEM-1	N-0091		11/25/08	ED50	74	11	13	8	69	>45	>46	62	-	-	-
		N-0091		03/24/09	ED50	>60	13	-	-	>200	45	-	-	>200	60	>10
		N-0091		08/27/09	ED50	>60	20	-	-	>100	>100	-	-	>100	>100	-
		N-0091		12/16/09	ED50	-	-	-	-	>90	62	109	87	-	-	-
		N-0091		12/16/09	ED50	-	-	-	-	>90	38	40	22	-	-	-
					MIC	>128	4 (1)	-	-	>128	2 (4)	-	-	>128	1 (0.5)	<=0.125

1: The MIC of CAZ and CPT are reported as a 4:1 ratio with AVI and with a fixed 4 µg/mL AVI (bracketed data)

2: The free acid of ceftaroline was used for MIC determinations.

3: Mice dosed twice at 1 & 4 h post-infection or 1, 4 and 7 h post-infection (Underlined). Unit dose ED_{50} is reported here

4: Ceftaroline fosfamil was used for ED_{50} determinations, with the dosage corrected back to free acid

Intraperitoneal infection in the mouse against meropenem-non-susceptible K. pneumoniae carrying bla_{KPC-2}

The efficacy of ceftazidime-avibactam (NXL104) in a murine intraperitoneal (i.p.) sepsis model was also evaluated[20]. Briefly, intraperitoneal sepsis was caused by two KPC-2 carbapenemase-producing clinical isolates of *K. pneumoniae* (VA-361 and VA-406). The two isolates carried genes for KPC and other Class A β-lactamases. *K. pneumoniae* VA-361 carried $_{bla}$KPC-2, *bla*TEM-1, and *bla*SHV-11 and strain VA-406 carried $_{bla}$KPC-2, $bla_{TEM\ 1}$, bla_{SHV-11} and bla_{SHV-12}. The isolates were non-susceptible to meropenem (MIC = 4 mg/L and 256 mg/L for VA-361 and VA-406, respectively). The MIC values of the two KPC-producing isolates used in the in vivo experiment are shown in Table 77. The higher MIC value of VA-406 is thought to be a result of different OmpK and/or variable expression levels of KPC enzymes.

Table 77. MICs for the two KPC-producing *K. pneumoniae* isolates used for *in vivo* experiments

Antimicrobial	MIC (µg/ml)	
	VA-361	VA-406
Piperacillin	≥512	≥512
Piperacillin + NXL104 (1 µg/ml)	32	16
Piperacillin + NXL104 (2 µg/ml)	8	8
Piperacillin + NXL104 (4 µg/ml)	≤0.06	0.5
Piperacillin + tazobactam (4 µg/ml)	≥512	≥512
Cefotaxime	64	≥512
Cefotaxime + NXL104 (1 µg/ml)	0.5	0.5
Cefotaxime + NXL104 (2 µg/ml)	0.5	0.5
Cefotaxime + NXL104 (4 µg/ml)	0.125	0.125
Cefotaxime + clavulanate (4 µg/ml)	16	256
Cefotaxime + tazobactam (4 µg/ml)	16	256
Ceftazidime	256	≥512
Ceftazidime + NXL104 (1 µg/ml)	8	8
Ceftazidime + NXL104 (2 µg/ml)	4	2
Ceftazidime + NXL104 (4 µg/ml)	0.25	≤0.06
Ceftazidime + clavulanate (4 µg/ml)	128	256
Ceftazidime + tazobactam (4 µg/ml)	128	256
Cefepime	32	256
Cefepime + NXL104 (1 µg/ml)	0.5	0.5
Cefepime + NXL104 (2 µg/ml)	0.25	0.5
Cefepime + NXL104 (4 µg/ml)	≤0.06	0.125
Cefepime + clavulanate (4 µg/ml)	8	128
Cefepime + tazobactam (4 µg/ml)	16	128
Imipenem	4	256
Imipenem + clavulanate (4 µg/ml)	2	128
Imipenem + tazobactam (4 µg/ml)	4	256
Meropenem	4	256
Meropenem + clavulanate (4 µg/ml)	2	128
Meropenem + tazobactam (4 µg/ml)	4	128

The KPC-producing strains result in death of control animals within 24-48 hours. Mice were infected i.p. with 3.3×10^5 to 3.6×10^5 CFU in 5% hog gastric mucin. In this acute septicemia model, the survival ED50 values of ceftazidime were 1578 mg/kg when treating the infection caused by VA-361 and 709 mg/kg against the infection caused by VA-406 (Table 78).

Table 78. Efficacy of ceftazidime-avibactam against *K. pneumoniae* expressing *bla*KPC-2 and bla_{SHV}-variants in a murine peritoneal sepsis model (Endimiani et al 2011)

Organism [a]	*MIC (mg/L)*		*ED_{50} (mg/kg)*	
	CAZ [a]	*CAZ-AVI* [a]	*CAZ*	*CAZ-AVI* [a]

Source: Endimiani et al 2011.

Table 79 shows the results of the acute lethal septicemia analysis. For VA-361 and VA-406, ceftazidime alone exhibited ED50 values of 1,578 and 709 mg/kg, respectively. These elevated ED50s were reduced with the co-administration of NXL104 at the ratios tested. The administration of ceftazidime-avibactam at a ratio of 4:1 effectively reduced the ED50s for VA-361 and VA-406 to 15.1 and 3.8 mg/kg, respectively.

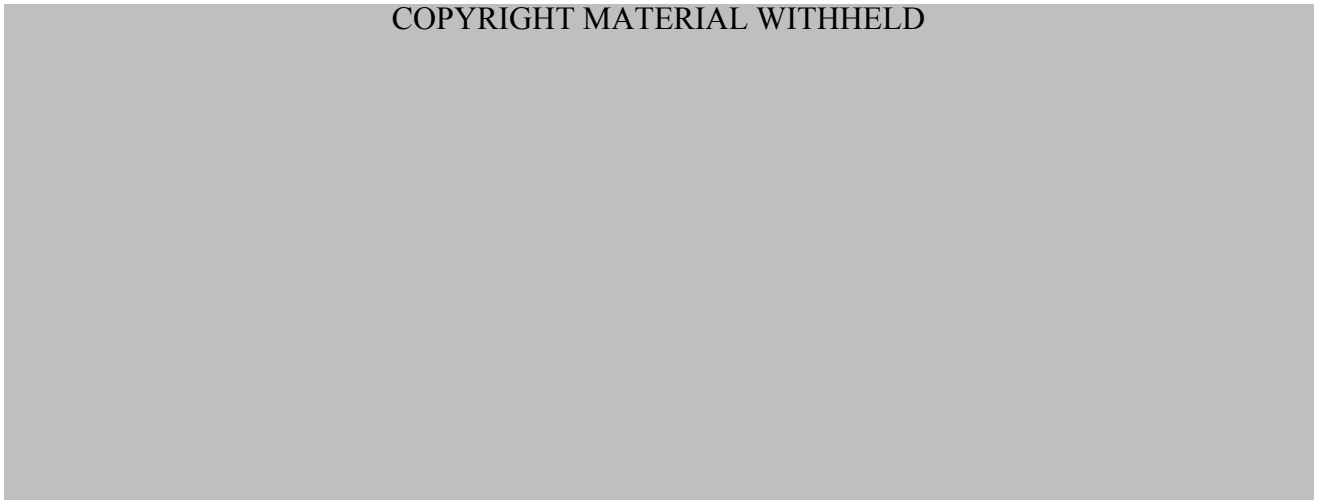
Table 79. ED50 for CAZ with and without NXL104 at selected ratios against a septicemia infection model due to *K. pneumoniae* isolates

Strain	ED_{50} (mg/kg) (95% confidence limit)[a]				
	CAZ	CAZ-NXL104 at ratio of:			
		2:1	4:1	8:1	16:1
ATCC 13883	1.9 (1.4–2.3)	1.0 (0.75–1.6)	1.1 (0.4–1.4)	0.62 (0.41–0.91)	NT
KPC-producing *K. pneumoniae* VA-361	1578 (1244–2011)	8.1 (6.2–10.3)	15.1 (12.1–18.7)	16.9 (13.6–20.8)	29.5 (21.9–39.8)
KPC-producing *K. pneumoniae* VA-406	709 (517–961)	3.5 (2.7–4.7)	3.8 (2.9–4.9)	7.2 (5.4–9.4)	12.1 (9.3–15.9)

[a] NT, not tested.

Figure 10 shows the percent survival as a function of the dose of ceftazidime with or without avibactam in varied ratios. As shown in Figure 10A and 10B, animal survival increased in relation to the ratio of ceftazidime to avibactam (NXL104) for both KPC-producing *K. pneumoniae* isolates tested. The addition of avibactam to ceftazidime reduced the amount of ceftazidime required to treat favorable the systemic infection in mice. Against the KPC-2 producer *K. pneumoniae* VA-361, the 4:1 and 8:1 (ceftazidime-avibactam) ratios yielded similar survival curves. Against the other KPC-2 producing isolate, *K. pneumoniae* VA-406, the survival curves generated by the 4:1 and the 2:1 (ceftazidime-avibactam w/w) ratios were also similar. Co-dosing of avibactam in all the ratios tested, including 16:1 (ceftazidime-avibactam w/w) resulted in greater survival than ceftazidime alone at any given ceftazidime dose.

Figure 10. Survival curves for mice treated with ceftazidime (CAZ) with and without NXL104 in the murine septicemia model due to KPC producing *K. pneumoniae*. (A) Data regarding KPC-producing *K. pneumoniae* strain VA-361. (B) Data regarding KPC-producing *K. pneumoniae* strain VA-406. (Endimiani et al 2011)



Mouse pneumoniae infection model

In another experiment, the efficacy of ceftazidime-avibactam (ratio 4/1) was evaluated against ceftazidime resistant *Enterobacteriaceae* in a mouse pneumoniae infection model. Briefly, mice were immunosuppressed with cyclophosphamide (induced neutropenia 1000/mm^3) and infected with 10^8 to 10^9 CFU of *K. pneumoniae* 283 KB4 (Class C ESBL) and *K. pneumoniae* (Class A and Class C ESBLs). Table 80 shows the MIC values for the infecting strains.

Table 80. MICs of *K. pneumoniae* strains in pneumoniae infection model

Strains	CAZ	CAZ + NXL104 (4:1 ratio)	CAZ + CLA (4:1 ratio)	Imipenem
K. pneumoniae 283 KB4 Amp C	>256	4	>32	1
K. pneumoniae 283 KB5 Amp C & Class A	32	1	>32	1

Treatment was initiated 16-18 hours post infection. Groups of 20-30 mice were subsequently treated with ceftazidime, ceftazidime-avibactam (150/75 mg/kg and 150/37.5 mg/kg), ceftazidime-clavulanic acid (150/75 mg/kg and 150/37.5 mg/kg), imipenem-cilastatin (150 mg/kg) and saline. Mice developed bacteremic pneumoniae and died within 2-4 days. Bacterial burden 16-18 hours pots-infection was 10^{11}-10^{12} cfu/gram. Figure 11 shows the lung bacterial counts in mice infected with *K. pneumoniae* 283KB4. At the start of therapy, mean log10 cfu in lungs of untreated mice was 11.25 ± 0.87. Compared to untreated mice, by 48 hours, a 3 log10 reduction in bacterial burden was observed with all treatment regimens excluding ceftazidime. Table 81 shows the summary data of *K. pneumoniae* strain 283KB4.

Figure 11: Lung counts of *K. pneumoniae* strain 283KB4 (DHA-2 AmpC)

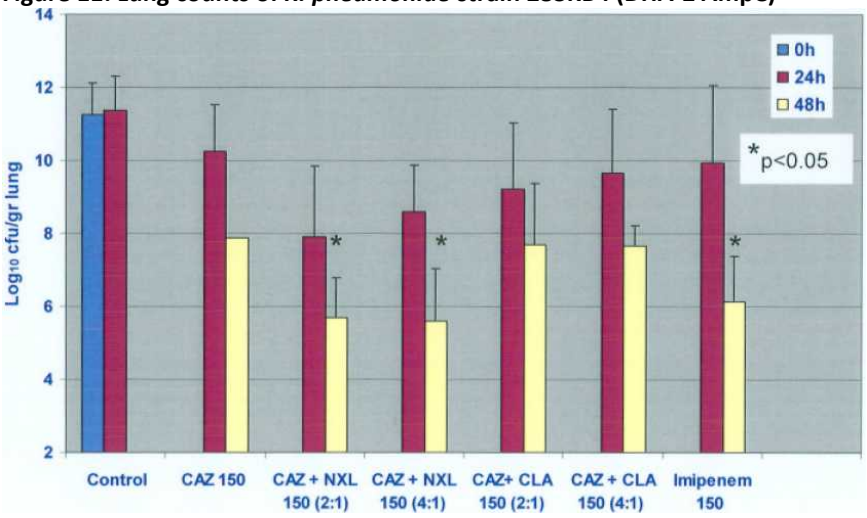


Table 81. Lung counts of *K. pneumoniae* strain 283KB4 (DHA-2 AmpC)

Treatment	At the start of therapy	24 hours after therapy	48 hours after therapy	δ - log 10 CFU vs Control**	
	Mean log10 Colony Forming Units +/- Standard Deviation			24 hours	48 hours
Control (saline)	11.25 +/- 0.87	11.36 +/- 0.95	NA	+ 0.11	NA
CAZ 150 mg/kg		10.24 +/- 1.29	7.87*	- 1.01*	
CAZ + NXL104 150 mg/kg (2:1) ratio		7.90 +/- 1.93	5.68 +/- 1.09	- 3.35	- 5.57
CAZ + NXL104 150 mg/kg (4:1) ratio		8.59 +/- 1.28	5.60 +/- 1.44	- 2.66	- 5.65
CAZ + CLA 150 mg/kg (2:1) ratio		9.22 +/- 1.80	7.69 +/- 1.68	- 2.03	- 3.56
CAZ + CLA 150 mg/kg (4:1) ratio		9.66 +/- 1.76	7.66 +/- 0.58	- 1.59	- 3.60
Imipenem 150 mg/kg		9.95 +/- 2.13	6.14 +/- 1.25	- 1.31	- 5.11

NA: by 48 hours all saline treated control animals succumbed to the infection
* represents one surviving animal
** : "+" denotes growth; "-" denotes reduction

Figure 12 shows the lung bacterial counts in mice infected with *K. pneumoniae* 283KB5 (LAT-4 AmpC and SHV-11 class A ESBL). At the start of therapy, mean log10 cfu in lungs of untreated mice was 11.19 ± 0.09. Compared to untreated mice, by 48 hours, a 3 log10 reduction in bacterial burden was observed for ceftazidime-avibactam treated animals. The data was similar to imipenem. Table 82 shows the summary data of *K. pneumoniae* strain 283KB5.

Figure 11: Lung counts of *K. pneumoniae* 283KB5 (LAT-4 AmpC class A and SHV-11 class C ESBL).

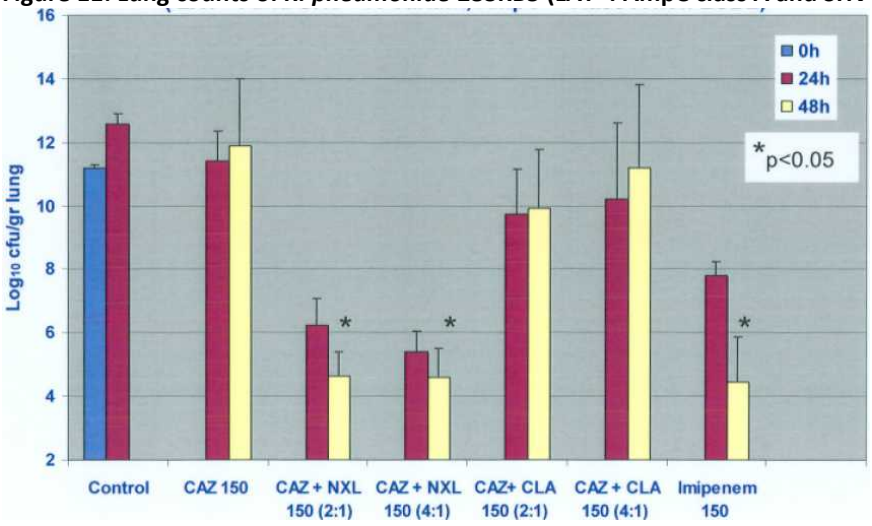


Table 82. Lung counts of *K. pneumoniae* 283KB5 (LAT-4 AmpC class A and SHV-11 class C ESBL).

Treatment	At the start of therapy	24 hours after therapy	48 hours after therapy	δ - log 10 CFU vs Control*	
	Mean log10 Colony Forming Units +/- Standard Deviation			24 hours	48 hours
Control (saline)	11.19 +/- 0.09	12.59 +/- 0.31	NA	+ 1.40	
CAZ 150 mg/kg		11.42 +/- 0.92	11.89 +/- 2.1	+ 0.23	- 0.70
CAZ + NXL104 150 mg/kg (2:1) ratio		6.23 +/- 0.82	4.61 +/- 0.78	- 4.96	- 6.58
CAZ + NXL104 150 mg/kg (4:1) ratio		5.40 +/- 0.66	4.59 +/- 0.92	- 5.79	- 6.60
CAZ + CLA 150 mg/kg (2:1) ratio		9.72 +/- 1.44	9.92 +/- 1.85	- 1.47	- 1.27
CAZ + CLA 150 mg/kg (4:1) ratio		10.20 +/- 2.40	11.17 +/- 2.66	- 0.99	- 0.02
Imipenem 150 mg/kg		7.78 +/- 0.47	4.45 +/- 1.41	- 3.41	- 6.74

NA: by 48 hours all saline treated control animals succumbed to the infection
* : "+" denotes growth; "-" denotes reduction

Pyelonephritis in the neutropenic mouse

The efficacy of ceftazidime-avibactam was evaluated against β-lactamase producing *Enterobacteriaceae* in a neutropenic mouse model of kidney infection. Briefly, kidney infections [with ceftazidime-resistant *K. pneumoniae* (SHV-11 and AmpC), *E. coli* (2 isolates: 1 Class A, SHV-4, and 1 AmpC), *E. cloacae* (AmpC), *M. morganii* (AmpC), or *C. freundii* (AmpC)] were induced in immunosuppressed anesthetized male CD1 mice by injection of 10^4 bacterial cells. Table 83 shows the in vitro susceptibilities and the result of the in vivo efficacy. Kidney burden increased to 10^5-10^7 within 48 hours. Therapy began subcutaneously 4 times at 4, 8, 24 and 32 hours after infection bid for 2 days. All strains were resistant to ceftazidime in vitro. CAZ/CLA (4:1) was active only *on E. coli* 250BE1 that produces a Class A enzyme. The presence of avibactam fully restored in vitro CAZ activity on all 6 strains expressing Class A and Class C β-lactamases. IPM was active against all strains.

Table 83. in vitro susceptibility of *Enterobacteriaceae* used in the mouse pyelonephritis model

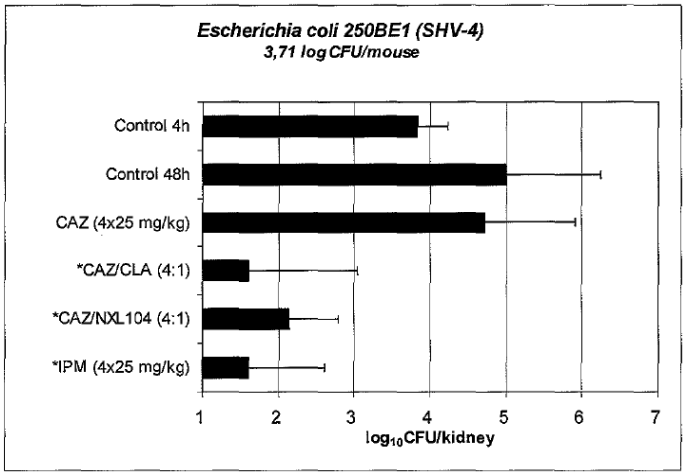
Species	ID	Enzyme	CAZ	CAZ/CLA (4:1)	CAZ/NXL104 (4:1)	IPM
Escherichia coli	250BE1	SHV·4	>128	1	2	0,5
Escherichia coli	250HT213	AmpC	16	16	1	1
Enterobacter cloacae	293HT96	AmpC	>128	>32	4	0,5
Klebsiella pneumoniae	283KB5	AmpC + SHV11	64	32	2	0,5
Morganella morganii	313HT26	AmpC	16	8	0,5	1
Citrobacter freundii	261GR10	AmpC	**>128**	32	4	0,5

Against E. coli 250BE1 (SHV-4)

Against *E. coli* 250BE1 (SHV-4), the inoculum was 3.7 log10 CFU/mouse and bacterial burden after 4 hours was 3.84 log10 and increased by 1.2log10 within 48 hours in non-treated control group. CAZ alone was ineffective against *E. coli* 250BE1 at 25 mg/kg compared to the non-treated control group. The association CAZ/CLA (4:1) had a significant effect against *E. coli* 250BE1, reduction of bacterial kidney burden being 3logl0 compared to

the CAZ treated group (p<0.05). This efficacy does correlate with the in vitro susceptibility data, as this strain bears a Class A enzyme. Figure 12 shows that imipenem and ceftazidime-avibactam was significantly effective against *E. coli* 250BE1. Bacterial loads in the infected kidney was reduced by > 3 log10 compared to the untreated control (p<0.05).

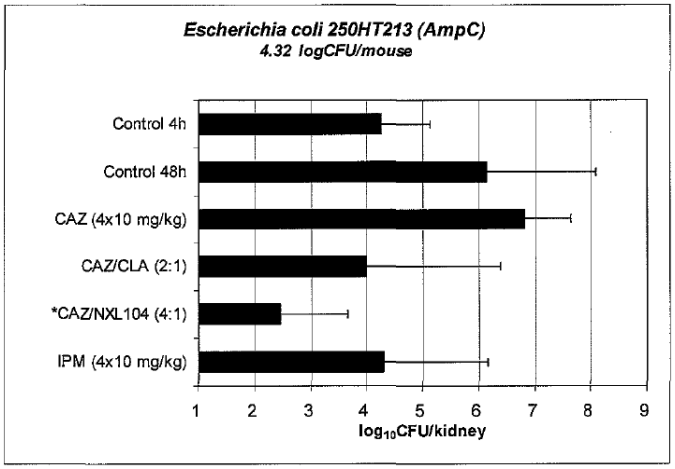
Figure 12. Efficacy of CAZ/NXL 104 (4:1) in a murine model of kidney infection with *E.* coli 250BE1. Statistical significance is expressed as* (p<0.05).



Against E. coli 250HT213 (AmpC)

Against *E. coli* 250HT213 (AmpC), the initial inoculum was 4.32 log10 CFU/mouse and was 4.25 log10 4 hours after infection. Figure 13 and Table 84 show the result of the infection. Ceftazidime alone was not effective against the strain of *E. coli* at 10 mg/kg. Ceftazidime-avibactam (4:1) was effective at 10 mg/kg and reduced bacterial burden more than 4 log10 compared to ceftazidime treatment group.

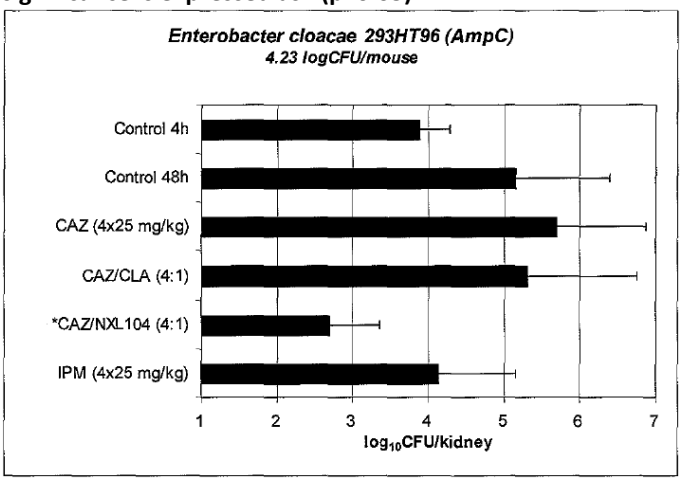
Figure 13. Efficacy of ceftazidime-avibactam (4:1) in a murine model of kidney infection with *E. coli* 250HT213. Statistical significance is expressed as* (p<0.05).



***Enterobacter cloacae* 293HT96 (AmpC)**

Against *E. cloacae* 293HT96 (AmpC), the initial inoculum was 4.23 log10 CFU/mouse. At 4 hours post infection, bacterial burden was 3.88 log10 CFU/kidney, and increased by 1.3 log10 within 48 hours in the untreated control group. Ceftazidime alone was ineffective against *E. cloacae* 293HT96 at 25 mg/kg compared to the non-treated control group (Figure 14). The association CAZ/CLA (4:1) was not active against this AmpC producing strain, and suggests that ceftazidime-avibactam is not active against all AmpC. Imipenem at 25 mg/kg reduced the inoculum by 1 log10 compared to the untreated control group, but was not statistically significance. The ceftazidime-avibactam (4:1) combination was significantly effective at 25 mg/kg in reducing the inoculum and preventing proliferation of this strain: ceftazidime-avibactam (4:1) reduced bacterial kidney burden by 3log10compared to the ceftazidime treated group ($p<0.05$).

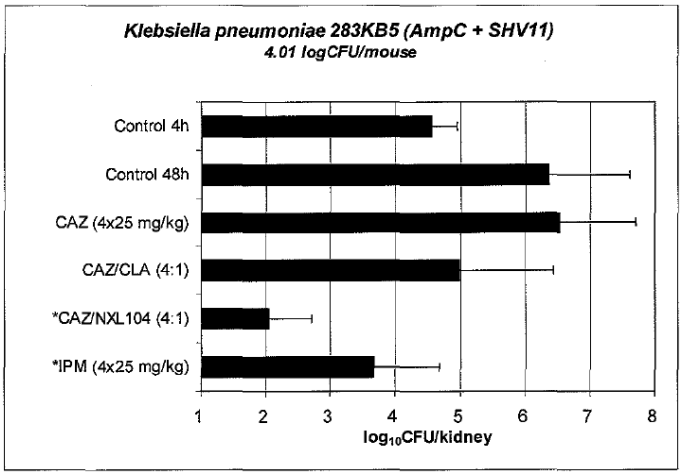
Figure 14. Efficacy of ceftazidime-avibactam (4:1) in a murine model of kidney infection with *E. cloacae* 293HT96. Statistical significance is expressed as* ($p<0.05$).



Klebsiella pneumoniae 283KB5(AmpC+SHV-11)

In this experiment, inoculum was 4.01 log10 CFU/mouse. Bacterial burden in the infected kidney 4 hours after infection with *K. pneumoniae* 283KB5 was 4.56 log10 CFU/kidney and increased by 1.8 log10 in non-treated control (Figure 15). Ceftazidime alone was not effective. However, both ceftazidime-avibactam and imipenem was significantly effective at reducing bacterial burden in the infected kidney. Ceftazidime-avibactam reduced kidney burden >4 log10 compared to the ceftazidime treated animals.

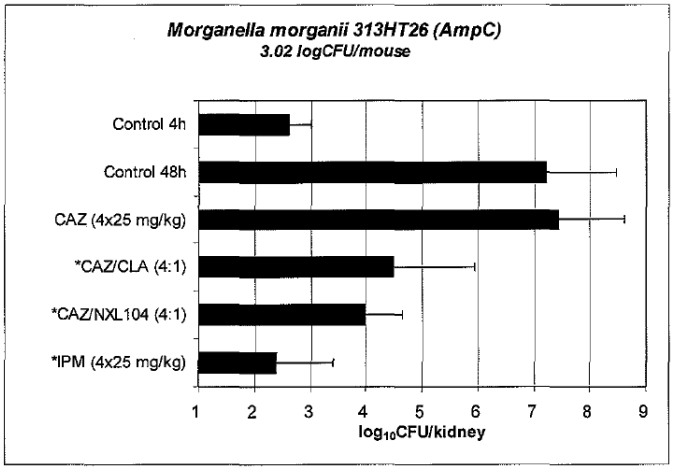
Figure 15. Efficacy of ceftazidime-avibactam (4:1) in a murine model of kidney infection with *K. pneumoniae* 283KB5. Statistical significance is expressed as * (p<0.05).



Morganella morganii 313HT26 (AmpC)

This strain was reported to be the most virulent since inoculum was reduced to 3.02 log10 CFU/mouse to avoid mortality in 48 hour period. The bacterial burden in infected kidney after infection was 2.6 log10 CFU/kidney, and increased by 4.6 log10 within 48 hours in the non-treated control group (Figure 16). Imipenem was significantly effective against *Morganella morganii* 313HT26, reducing bacterial burden in the infected kidney by 4.8log10 compared to the untreated control (p<0.05). The ceftazidime-avibactam (4:1) combination was significantly effective at 25 mg/kg, reducing bacterial kidney burden by 3.4log10 compared to the ceftazidime treated group (p<0.05).

Figure 16. Efficacy of ceftazidime-avibactam (4:1) in a murine model of kidney infection with *M. morganii* 313HT26. Statistical significance is expressed as* (p<0.05).

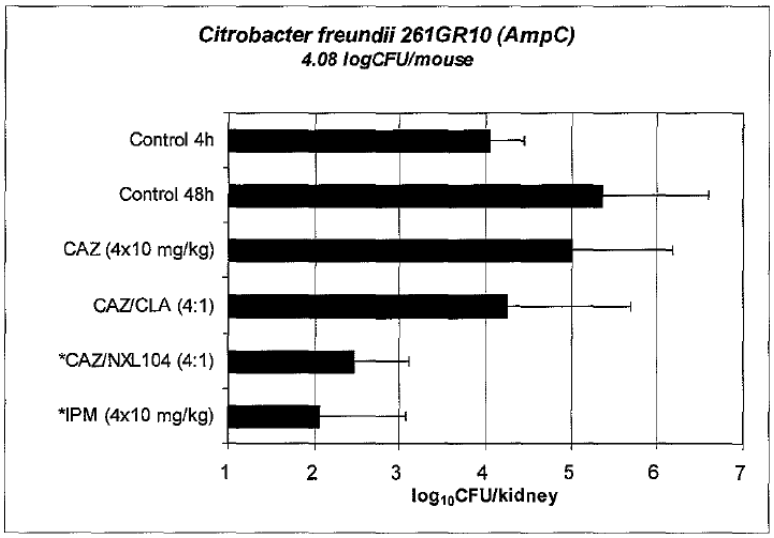


Citrobacter freundii 261GR10 (AmpC)

Inoculum was 4.08log10 CFU/mouse. The bacterial burden in the infected kidney 4hours after infection with

Citrobacter freundii 261GR10 was 4.05log10 CPU/kidney, and increased by 1.3log10 within 48 hours in the non-treated control group (Figure 17). Ceftazidime alone was ineffective. Ceftazidime- clavulanate (4:1) was not active against this strain. Imipenem was significantly effective against C. *freundi* 231 GR10, reducing bacterial burden in the infected kidney by 3.3log10 compared to the untreated control ($p<0.05$). The ceftazdime-avibactam (4:1) combination was significantly effective at 10 mg/kg, reducing the bacterial kidney burden by 2.51og10 compared to the CAZ treated group ($p<0.05$).

Figure 17. Efficacy of CAZ/NXL104 (4:1) in a murine model of kidney infection with *C. freundii* 261GR10. Statistical significance is expressed as* ($p<0.05$).



The data demonstrated the effectiveness of ceftazidime-avibactam against the six representative ceftazidime resistant *Enterobacteriaceae*. Ceftazidime-avibactam and imipenem restored efficacy against isolates producing class A and class C β-lactamases (Table 84).

Table 84. In vivo efficacy of ceftazidime-avibactam against *Enterobacteriaceae* in a mouse pyelonephritis model

Organism and β-lactamase		*CAZ[a] (10 mg/kg)*	*CAZ-AVT[b] (10 mg/kg, 4:1 ratio)*	*IPM[a] (10 mg/kg)*
E. coli 250HT213 (AmpC)	MIC[c] (mg/L)	16	1	1
	$\Delta\log_{10}$ CFU	+ 0.67	-4.37[d]	-1.84
C. freundii 261GR10 (AmpC)	MIC (mg/L)	> 128	4	0.5
	$\Delta\log_{10}$ CFU	-0.35	-2.55[d]	-3.29[e]
		CAZ (25 mg/kg)	*CAZ-AVI (25 mg/kg, 4:1 ratio)*	*IPM (25 mg/kg)*
E. coli 250BE1 (SHV-4)	MIC (mg/L)	> 128	2	0.5
	$\Delta\log_{10}$ CFU	-0.28	-2.60[d]	-3.41[e]
E. cloacae 293HT96 (AmpC)	MIC (mg/L)	> 128	4	0.5
	$\Delta\log_{10}$ CFU	+ 0.54	-3.00[d]	-1.02
K. pneumoniae 283KB5 (Lat-4 + SHV-11)	MIC (mg/L)	64	2	0.5
	$\Delta\log_{10}$ CFU	+ 0.16	-4.49[d]	-2.72[e]
M. morganii 313HT26 (AmpC)	MIC (mg/L)	16	0.5	1
	$\Delta\log_{10}$ CFU	+ 0.21	-3.45[e]	-4.83[e]

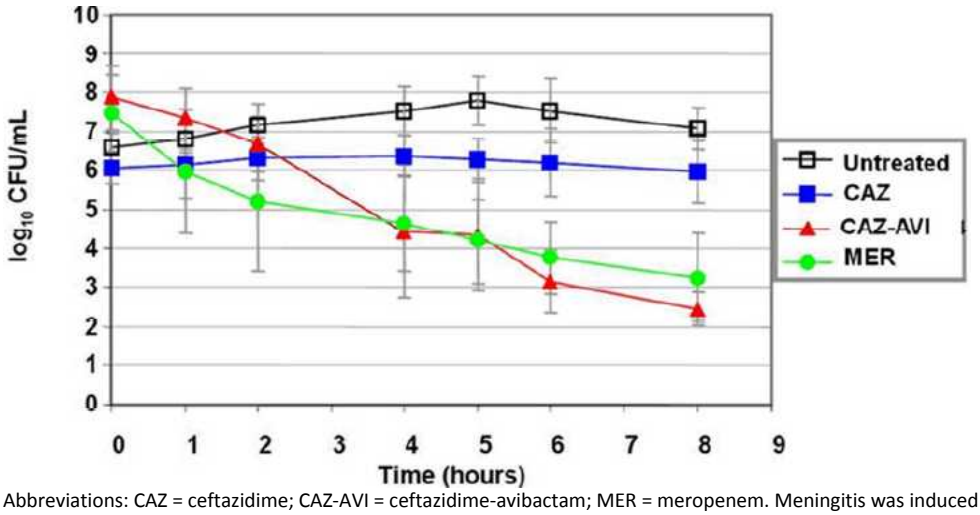
a CAZ = ceftazidime. IPM = imipenem. The variation in bacterial count (mean Δlog10 CFU/kidney) is expressed in relation to the control [i.e. (treated - control) log10 CFU/kidney].
b CAZ-AVI = ceftazidime-avibactam (4:1). The variation in bacterial count (mean Δlog10 CFU/kidney) is expressed in relation to the ceftazidime-dosed group [i.e. (CAZ-AVI-treated - CAZ-treated) log10 CFU/kidney].
c MIC values of ceftazidime avibactam were measured by diluting in 4:1 ratio: these experiments were performed before the current reference broth microdilution method was established of diluting ceftazidime while keeping the concentration of avibactam constant at 4 mg/L.
d $p < 0.05$ when bacterial load compared to that of group treated with CAZ alone.
e $p < 0.05$ when bacterial load compared to untreated group.
Source: Study CAZ104-M1-005-NXL104-AP0010.

Meningitis model in the rabbit

In another study, the Applicant examined the efficacy of ceftazidime-avibactam against an AmpC producing *K. pneumoniae* strain in a rabbit meningitis model (Study NXL104-PK0007). Briefly, Meningitis was induced in rabbits by intra-cisternal inoculation with 105 CFU *K. pneumoniae* 283KB4 (*bla*DHA-2; MIC of ceftazidime, ≥ 256 mg/L; MIC of ceftazidime-avibactam, tested in 4:1 fixed ratio, 4 mg/L). The antibacterial activity of ceftazidime-avibactam at 150 mg/kg (ratio 4:1) was compared to ceftazidime alone at 150 mg/kg/dose or meropenem (MIC = 2 mg/L) at 125 mg/kg/dose (NXL104-PK0007). Antibiotics were dosed IV approximately 8 and 12 hours post-infection with the ceftazidime and meropenem doses repeated at the second time point. In the case of ceftazidime-avibactam, the initial dose consisted of ceftazidime 150 mg/kg plus avibactam 37.5 mg/kg, but the second dose consisted of ceftazidime alone at 150 mg/kg.

The data showed no effect on treatment outcome with ceftazidime. Bacterial loads were reduced > 5 log10 within 8 hours with ceftazidime-avibactam therapy, and meropenem demonstrated a > 4 log10 reduction (Figure 18).

Figure 18. Time course of bacterial counts in a rabbit meningitis model induced by intra-cisternal inoculation of ceftazidime-resistant *Klebsiella pneumoniae*



Abbreviations: CAZ = ceftazidime; CAZ-AVI = ceftazidime-avibactam; MER = meropenem. Meningitis was induced in rabbits by intra cisternal inoculation of *K. pneumoniae* 283KB4 (blaDHA-2; MIC of ceftazidime, 256 mg/L; MIC of ceftazidime-avibactam, tested in 4:1 fixed ratio, 4 mg/L; MIC of meropenem, 2 mg/L). Antibiotics were dosed IV approximately 8 and 12 hours post infection (i.e. at time 0 and 4 hours on the x-axis); the doses of ceftazidime (150 mg/kg/dose) and meropenem (125 mg/kg/dose) being repeated at the second time point. In the case of ceftazidime-avibactam, the initial dose consisted of ceftazidime-avibactam (ceftazidime 150 mg/kg + avibactam 37.5 mg/kg), but the second dose consisted of ceftazidime alone at 150 mg/kg. Bacteria in cerebrospinal fluid samples were counted.
Source: Study NXL104-PK0007.

Murine Thigh infection

The efficacy of CAZ-AVI was evaluated in mouse neutropenic thigh infection model against *K. pneumoniae* (KPC; MIC ≥256 mg/L) and *P. aeruginosa* (CAZ-AVI MIC90 32 mg/L; MIC range 4-32 mg/L).

For *K. pneumoniae* thigh infection was induced by the intramuscular injection of KPC-producing strain into the right thigh in two separate studies. The KPC-producing strains VA-361 and VA-406 were examined in the intraperitoneal sepsis model described above. Mice were treated 1.5 hour post-infection with either CAZ alone or CAZ-AVI (4:1 w/w). After thighs were removed at 24 hours post-infection, a >2-$\log_{10}$ CFU reduction was observed for mice treated with CAZ-AVI (4:1 w/w) at doses of =128:32 mg/kg compared to CAZ doses of = 1,024 mg/kg which were unable to reduce the numbers of CFUs (Table 85).

Table 85. Efficacy of ceftazidime-avibactam in a neutropenic murine thigh infection model against *K. pneumoniae* carrying *bla*KPC-2 and *bla*SHV-variants

Organism	*MIC (mg/L)*		*Log_{10} (CFU/thigh)*			
			Pre-therapy (1.5 h)	*Post-therapy (24 h)*		
	CAZ[a]	*CAZ-AVI*[a]		Untreated	CAZ[a]	CAZ-AVI[a]

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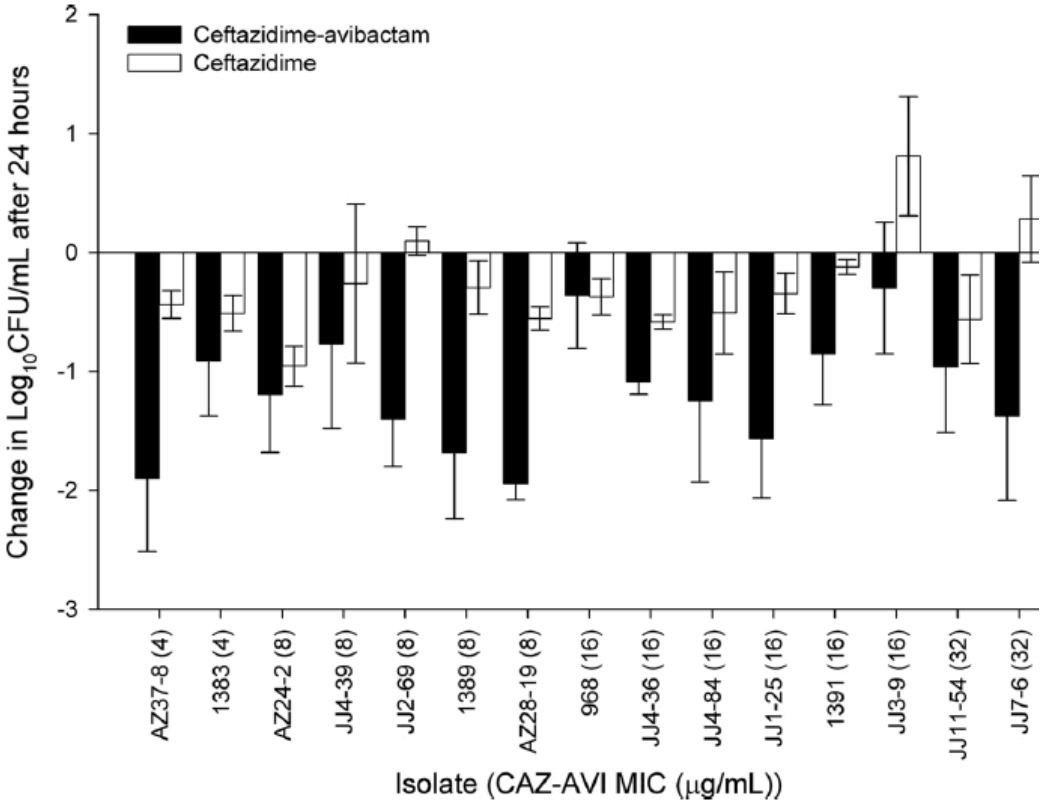
Source: Endimiani et al 2011

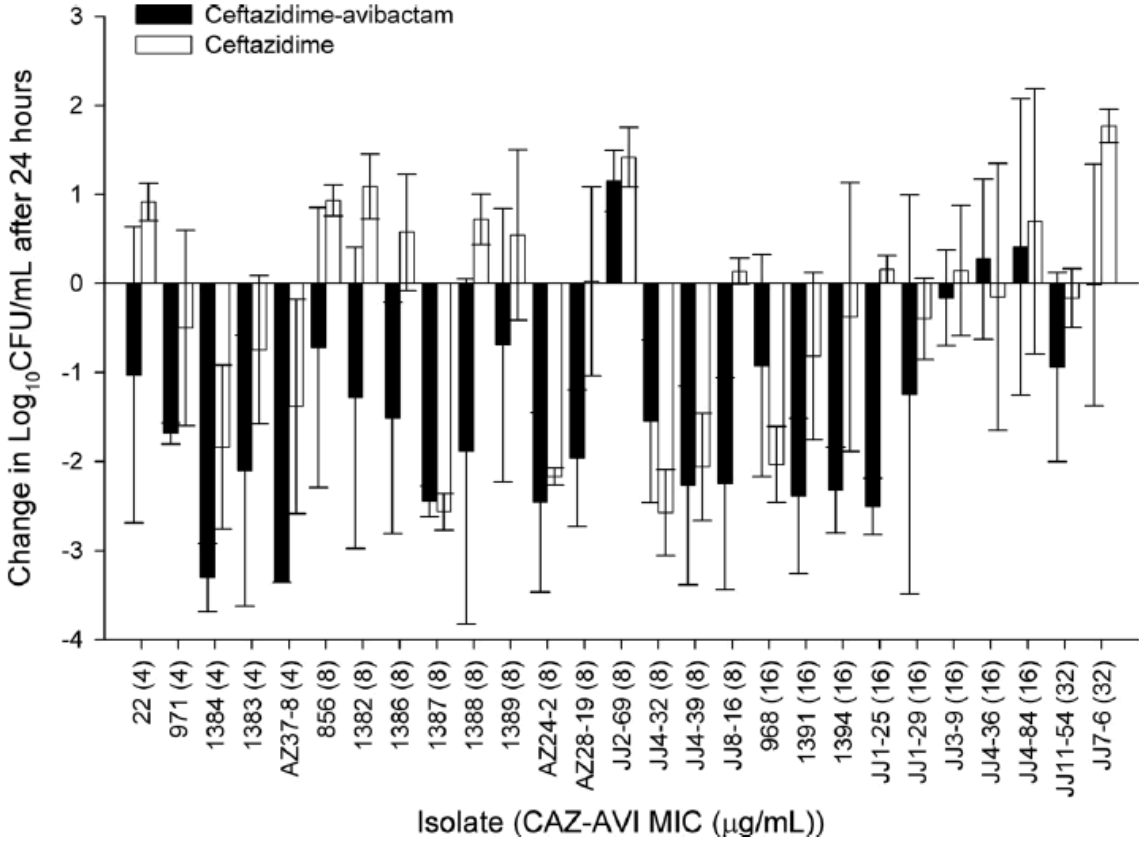
For *P. aeruginosa,* thigh infection was induced by an inoculum of 10^8 CFU in non-neutropenic mice and 10^7 CFU in neutropenic animals. Human simulated CAZ-AVI therapy commenced 2 hours after infection. In the neutropenic mouse, the control animals had a mean bacterial density of 5.03 ± 0.3 Log10 CFU per thigh and increased by an average of 3.25 ± 0.53 log10 units in untreated mice at 24 hours. For immunocompetent mice, a 6.59 ± 0.24 log10 CFU at 0 hours and increased by 1.52 ± 0.72 log units was observed after 24 hours. Human simulated dosage resulted in bacterial reductions of 0.3 to 1.95 log_{10} CFU, and 13 of 15 achieved a reduction of ≥ 0.75 log_{10} CFU in non-neutropenic mice which also included three animals in this group that had CAZ-AVI MICs of ≤16 mg/L. The result of the immunocompetent study is shown in Figure 19. The authors reported that within this group, 3 organisms with ceftazidime avibactam MICs of ≤ 16 mg/L and treatment of ceftazidime resulted in an increase in bacterial density in neutropenic animals, indicating that a functioning immune system contributed to bacterial log10 reduction at the ceftazidime avibactam MICs of ≤ 16 mg/L.

Figure 19 Comparative efficacies of ceftazidime-avibactam and ceftazidime alone against a distribution of *P. aeruginosa* in immunocompetent animals. Error bars represent standard deviations.



In the neutropenic study, CAZ-AVI treatment resulted in bacterial load reductions based on CAZ-AVI MIC; bacterial killing was observed for 16 of 17 isolates with CAZ-AVI MIC of ≤8mg/L and 5 of 8 isolates with CAZ-AVI MICs of ≤16 mg/L. The results of the neutropenic mouse study are shown in Figure 20.

Figure 20 Comparative efficacies of ceftazidime-avibactam (CAZ-AVI) and ceftazidime alone against a distribution of *P. aeruginosa* in neutropenic mice. Error bars represent standard deviations.



Summary

The Applicant evaluated the efficacy of ceftazidime-avibactam in several animal models of infection against ceftazidime resistant β-lactamase-producing *Enterobacteriaceae* and *P. aeruginosa*. Many of the isolates produced clinically important Class A and Class C β-lactamase including AmpC, KPC, SHV, CTX and TEM enzymes. Efficacy was established in these animal infection models using a simulated dosing regimen against ceftazidime resistant gram-negative pathogens.

PHARMACOKINETICS AND PHARMACODYNAMICS

Pharmacokinetic and measurements that quantify antimicrobial susceptibilities have been incorporated using PK/PD models to estimate clinical and microbiological outcomes in the treatment of bacterial infections. In vitro antimicrobial activity can be described as a function of drug concentration at the site of infection and the duration of time the pathogen is exposed to the drug. This phenomenon applies to in vitro and in vivo antimicrobial effects. For cephalosporins and other β-lactam antibiotics, the percentage of time during the dosing interval that the plasma free-drug concentration exceeds the MIC for the target organism (represented as %T > MIC) has been established as the PK/PD index that correlates with the therapeutic efficacy. To confirm that this relationship is applicable for ceftazidime-avibactam, the Applicant conducted a number of

studies using isolates of belonging to the *Enterobacteriaceae* family of organisms and *Pseudomonas aeruginosa.* The objectives for this study were to characterize the in vivo time course of antimicrobial activity of ceftaroline and to determine the PK/PD parameters and magnitudes predictive of efficacy to provide a guideline for dosing regimen design in human studies.

PK/PD targets of ceftazidime against Enterobacteriaceae

Figure 21 shows the relationship between microbial effect of ceftazidime and each of the pharmacodynamic indices against an isolate of *K. pneumoniae* in a lung model in neutropenic mice. Of the potential three PK/PD indices, the strongest relationship was observed when the microbiological effect was correlated with percent time above MIC (%T>MIC). The magnitude of the index related to bacteriostasis over 24 hours in the model against that strain was about 30% T > MIC. A bactericidal effect of 2–3 log10 killing of that strain over 24 hours was achieved by roughly 50% T > MIC.

Figure 21. The relationship among PK/PD indices for ceftazidime and log10 CFU per lung of *K. pneumoniae* after 24 hour of therapy

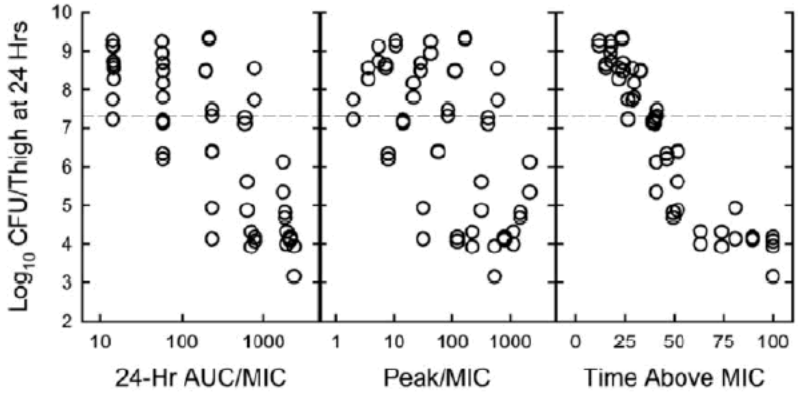


Table 86 shows the doses calculated to achieve a bacteriostatic effect after 24 hours of therapy for ceftazidime and comparator agents. The mean free-drug %T > MIC corresponding with these bacteriostatic doses varied from 27% to 42% T>MIC for ceftazidime.

Table 86. T > MIC required for a static effect against *Enterobacteriaceae* after 24 hours of therapy with each of four cephalosporins

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Source: Craig 2005

Table 87 shows a summary of all estimated *f*T > 1 mg/L associated with the bacterial response of stasis in the neutropenic mouse thigh. The arithmetic mean of these 8 magnitudes was 40.2% *f*T > 1 mg/L for stasis. The mean magnitude associated with 1-log10 kill was 50.3%. Three isolates responded with 2-log10 kill at avibactam *f*T > 1 mg/L of 45.0-48.4%.

Table 87. Magnitudes of avibactam exposures associated with stasis and 1- and 2-log10 kills of *P. aeruginosa* infecting the thighs of neutropenic CD-1 female mice in the background of 2-hourly dosing of ceftazidime

Strain	*Experiment*	*Avibactam fT > 1 mg/L yielding:*		
		Stasis	*1-log$_{10}$ kill*	*2-log$_{10}$ kill*
1	co-dosing	37.2%	65.7%	not reached
5	co-dosing	14.1%	32.9%	48.4%
7	AVI fractionation	30.2%		
7	co-dosing	50.4%	65.3%	not reached
11	co-dosing	29.1%	37.5%	46.8%
18	AVI fractionation	74.1%		
18	co-dosing	24.2%	33.2%	45.0%
19	co-dosing	62.5%	67.2%	not reached
Mean		40.2%	50.3%	

Source: CAZ-AVI-M1-066; Berkhout et al 2013b

Table 88 shows the PK/PD targets for the avibactam exposure in the neutropenic mouse lung infection model. The PK/PD target for stasis was 16-24% *f*T > 1 mg/L (mean 20.2%); although it was noted that it varied with the background exposure of ceftazidime. The PK/PD target for avibactam for a bactericidal response of 1-log10 kill was 18–35% (mean 24%) *f*T > 1 mg/L in combination with background dosing of ceftazidime. The PK/PD target for avibactam and a bactericidal response of 2-log10 was not observed with every *P. aeruginosa* strain tested; but of those where it did occur, the PK/PD target was 20-55% *f*T > 1 mg/L (mean 30.3%).

Table 88. Magnitudes of avibactam exposures associated with stasis and bacterial killing of *P. aeruginosa* in the lungs of neutropenic CD-1 female mice in the background of pharmacokinetic cycling of ceftazidime

Strain	*Experiment*	*Avibactam fT > 1 mg/L [a] associated with:*		
		stasis	*1-log$_{10}$ kill*	*2-log$_{10}$ kill*
5	co-dosing	19.4%	20.6%	21.5%
7	co-dosing	21.4%	22.4%	no data
11	co-dosing	19.7%	34.9%	55.3%
11	AVI fractionation	20.9%	21.6%	22.5%
18	co-dosing	23.5%	26.7%	31.8%
18	AVI fractionation	16.1%	17.8%	20.2%
Mean		20.2%	24.0%	30.3%

a Times are expressed as % of the dosing interval.
Source: CAZ-AVI-M10-066; Berkhout et al 2013c

PK/PD targets of ceftazidime against P. aeruginosa

Similar to studies conducted above with *K. pneumoniae*, the PK/PD index that best correlates with killing of *P. aeruginosa* is also represented by the mean free-drug %T > MIC. Stasis in a neutropenic thigh model with *P. aeruginosa* was achieved at about 40% T > MIC of ceftazidime (Figure 22). The exposure of 50% T > MIC achieved slightly less than a 1-log10 decrease in CFU/thigh. A 2-log10 decrease in bacterial counts over 24 hours was achieved by approximately 75% T > MIC. Although the stasis magnitude of 40% T > MIC is higher than the 36% quoted for *Enterobacteriaceae* above. However, with the amount of strain-to-strain and mouse-to-mouse variation that can occur, it is conceivable that these two values may be quite comparable.

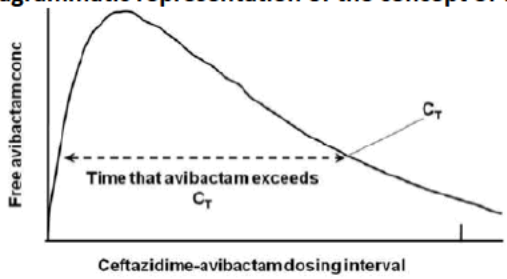
Figure 22. PK/PD of ceftazidime vs. *P. aeruginosa* in a neutropenic mouse thigh infection model

Source: Craig 2003

Determination of the PK/PD Index and Target for Avibactam (critical concentration, C_T)

Literature on β-lactam-β-lactamase inhibitor combinations were limited; therefore, the Applicant conducted a number of studies to model PK/PD of ceftazidime-avibactam combinations based on the concept that the sole function of the β-lactamase inhibitor was to protect the β-lactam drug (ceftazidime) from ESBL hydrolysis. The experimental approach was to define a 'critical' or 'threshold' concentration (C_T) of avibactam that would occur during the exponential decline of avibactam plasma concentrations during one dosing interval. This C_T is defined as the concentration of avibactam reached during the terminal phase below which the inhibition of β-lactamases was inadequate to prevent growth in the presence of ceftazidime. This is expressed diagrammatically in Figure 23.

Figure 23. Diagrammatic representation of the concept of the critical concentration, C_T, of avibactam.

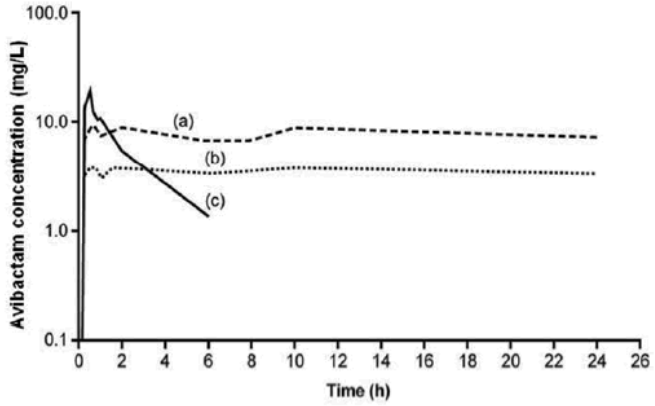


The diagram shows a generalized pharmacokinetic profile of the concentration of avibactam plotted against time as the independent variable. A single dosing interval between doses of ceftazidime plus avibactam is marked on the time axis. As avibactam declines to concentrations below CT, the β-lactamase inhibition is relieved, and any surviving bacteria can regrow, because the remaining ceftazidime is ineffective owing to hydrolysis by (periplasm-located) β-lactamase. For this model, the assumption is made that ceftazidime is still at a concentration above the MIC of the combination against the bacterium under treatment. Note that if the concentration of ceftazidime were below the MIC, then the concentration of avibactam would be irrelevant, because it is not a potent growth inhibitor in its own right.

A Hollow-fiber bioreactor was used to determine the critical concentration of avibactam against β-lactamase producing *Enterobacteriaceae*. The perfusion system developed allows for the growth of bacterial cells in the extracapillary chamber and nutrients are pumped through the system to support growth of the bacterial cells; and antibacterial drugs are added and removed at a rate which simulates human pharmacokinetic patterns for the antibacterial drugs. Samples are removed from the system's peripheral compartment at different time points and viable bacterial counts were determined by serial 2-fold dilutions.

Figure 24 shows an example of concentration-time profiles of ceftazidime and avibactam in hollow-fiber experiments used to estimate a critical concentration (CT) of avibactam. Briefly, a mixture of ceftazidime and avibactam was injected at time zero into the central compartment of the hollow-fiber cartridge to provide the necessary initial concentrations. For the cartridge where both components were infused continuously, a flow of fresh broth containing an appropriate concentration of both ceftazidime (8 or 16 mg/L) and avibactam (1, 2, or 4 mg/L) was infused for 24 hours. For the cartridge with the single-dose avibactam profile, fresh broth containing an appropriate concentration of ceftazidime was infused to generate the simulated avibactam human terminal half-life of 2 hour. Test strains were injected and confined to the hollow-fiber cartridge and test compounds and fresh medium were exchanged between the medium cycling through the central reservoir and the hollow-fiber cartridge by diffusion through the semi-permeable membrane. Ceftazidime concentrations were set constant at 16 mg/l or 8 mg/L to be in excess of the ceftazidime-avibactam MIC but below ceftazidime MIC for all bacterial strains tested, this is represented in Figure 24; Line a. Line b represents a 24 hours continuous constant rate infusion. Line c represents a single simulated human-like profile.

Figure 24. Example of concentration-time profiles of ceftazidime and avibactam in hollow-fiber experiments used to estimate a critical concentration (C_T) of avibactam



In this example: (a) ceftazidime (dashed line) was infused for 24 hours at a fixed concentration of 8 mg/L, while avibactam was either (b) infused at a fixed concentration of 1, 2 or 4 mg/L for 24 hours (4 mg/L in this example, dotted line) or (c) dosed to simulate a human-like profile (solid line) with α and β phase t½ values of 0.16 and 2.0 h, respectively, with roughly the same 24-h AUC as the avibactam continuous infusion.

The C_T was estimated as the minimum concentration of avibactam able to suppress growth of the β-lactamase-producing bacterium as judged by the concentration of avibactam in the hollow-fiber system at the time point when re-growth occurred. This is determined by extrapolation from the exponential-decline curves (marked c in Figure 24).

The activities of ceftazidime-avibactam against β-lactamase producing *Enterobacteriaceae* isolates were assessed in a hollow-fiber model. The magnitude of avibactam C_T for *Enterobacteriaceae* was estimated against β-lactamase producing *Enterobacteriaceae* isolates (*Enterobacter cloacae* 293HT96, *K. pneumoniae* 283CF5, and *K. pneumoniae* Tunisie K4). Table 89 shows the in vitro susceptibilities of strains used in the hollow-fiber cartridge and the estimations of C_T of avibactam. For C_T estimations, ceftazidime was maintained at a constant background concentration of about 8 mg/liter-9.8 for 3 strains and 20 for one strain while avibactam was instilled with simulated human-PK-like profiles with a C_{max} of 9, 31, 37 or 60 mg/liter and exponential-decline half-lives of 2 to 3 hours. Viable counts were monitored in the perfused compartment,

starting with inocula of $1x10^5$ to $3x10^5$ CFU/ml at time zero. With simulated bolus doses of avibactam, the variable growth suppression windows observed indicate that β-lactamase inhibition is inadequate when the avibactam concentration falls below a certain critical C_T. The C_T was ≤0.5 mcg/ml. In the regrowth suppression experiments, regrowth was occurring when avibactam dropped below the critical C_T. Table 89 shows that the avibactam CT was ≤0.28 mcg/ml (range ≤ 0.15 – ≤ 0.28 mg/L). There was no difference with isolates producing either ESBLs or a de-repressed Class C β-lactamase since these isolates yielded similar C_T values.

Table 89. *In vitro* susceptibilities of strains used in hollow-fiber studies; and estimations of the 'critical' or 'threshold' concentration, CT, of avibactam in hollow-fiber experiments

Species and strain	*β-Lactamase*	*MIC[a] (mg/L)*		*CAZ*		*AVI*		*Time at which C_T was estimated (h)*	*Estimated C_T (mg/L)*
		CAZ[a]	*CAZ-AVI[a]*	*Constant conc (mg/L)*	*AUC_{0-24} ($mg.h.L^{-1}$)*	*C_{max} (mg/L)*	*AUC_{0-24} ($mg.h.L^{-1}$)*		

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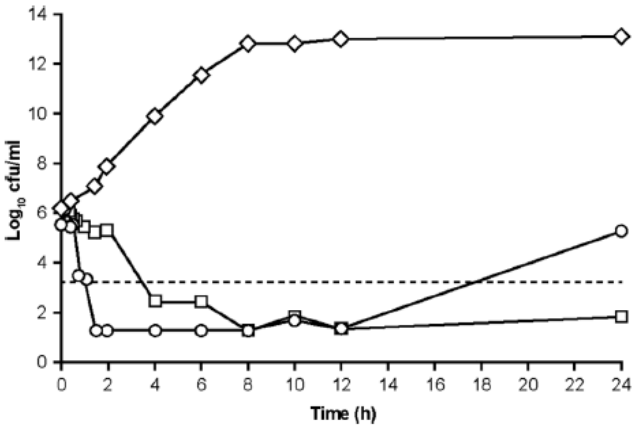
Source: Coleman et al 2014.

Figure 25 shows the responses of *E. cloacae* 293HT96 to continuous infusion of ceftazidime with different concentration-time profiles of avibactam in the hollow-fiber model. In all experiments, bacterial counts declined to below detectable in about 2 hours and stayed undetectable for a further 10 hours (i.e., *t*=12 h). Samples taken at 24 hours showed evidence of regrowth. The absence of repeated avibactam dosing (or continuous infusion of avibactam) allows for the return of β-lactamase activity and regrowth in the presence of ceftazidime (which is hydrolyzed by the β-lactamase).

Figure 25. Responses of *E. cloacae* 293HT96 to continuous infusion of ceftazidime combined with two different concentration-time profiles of avibactam in the hollow-fiber model: with monitoring of growth during the post-12-h critical regrowth period of 18 to 24 h



Responses of *E. cloacae* 293HT96 to continuous infusion of ceftazidime combined with two different concentration-time profiles of avibactam in the hollow-fiber model. Shown are results obtained with an untreated growth control (open diamonds), continuous infusion of ceftazidime (8.2 mcg/ml) and avibactam (1.6mcg/ml) (open squares), and continuous infusion of ceftazidime (8.2 mcg/ml) with a single-dose profile of avibactam (*C*max, 31 mcg/ml at 0.5 h) (open circles) and 99.9% bacterial killing (broken line).

In experiments where a continuous infusion of ceftazidime (8 or 16 mcg/ml) was administered and the concentration of avibactam rose to a peak then declined, rapid killing of all the strains was observed, with growth suppression windows of 10-24 hours for all the avibactam profiles with a 12-60µg/ml for C_{max}(Table 90).

Table 90. Growth suppression windows[a] obtained for 24-h ceftazidime infusion with avibactam infused for 24 h or administered once at time zero

	Constant ceftazidime-avibactam infusion[b]			Ceftazidime constant infusion, avibactam single dose at $t = 0$ h[c]		
Strain	Ceftazidime infused (µg/ml)	Avibactam infused (µg/ml)	Growth suppression window (h)	Ceftazidime infused (µg/ml)	Avibactam C_{max} (µg/ml)	Growth suppression window (h)
E. cloacae 293HT96	8	4	22	8	50	24
	16	4	24	16	60	14
	8	4	24	8	20	24
	8	2	24	8	30	16
	8	2	24	8	30	16
	8	2	24	8	30	24
K. pneumoniae 181	16	4	24	8	60	10
K. pneumoniae 236	16	4	24	8	60	24
K. pneumoniae 283CF5	16	2	24	16	60	24
	16	4	24	8	60	24
	8	2	24	8	30	24
	8	1	24	8	12	24
K. pneumoniae 283KB5	8	4	24	8	20	24
	8	2	24	8	30	24
	8	1	24	8	12	24
Citrobacter freundii 261GR3	8	4	24	8	20	24

[a] The growth suppression window is the period of time for which the viable count remained at least 10^3-fold lower than the starting inoculum.
[b] Both ceftazidime and avibactam were infused for 24 h at the concentrations listed.
[c] Ceftazidime was infused for 24 h at the concentrations listed, and avibactam was administered as a single dose with a $t_{1/2}$ of 2 h.

In another experiment, instead of critical concentration of avibactam being estimated after the attainment of it C_{max} (above), the critical concentration was investigated on the basis of short periods at a constant

concentration that used the equivalent of a 1-g dose of ceftazidime q8h in adults (C_{max}, 52 mcg/ml), a constant 0.25 mcg/ml avibactam for 24 hours gave a growth suppression window of 4 to 6 hours, while a constant 0.5 mcg/ml avibactam gave a growth suppression window of >24 h (Table 91).

Table 91. Ceftazidime peak[a] and exponential decline[b] cycled q8h for 24 hour with avibactam infused at fixed concentrations for various time periods

Strain	Ceftazidime C_{max} (μg/ml)	Avibactam infusion concn (μg/ml)	Avibactam infusion time (h)	Growth suppression window[c] (h)
E. cloacae 293HT96[d]	52	0.25	24	4–6
		0.5	3	8
			4.5	7–11
			6	6–8
			24	>24
	105	0.1	24	6
		0.25	24	8
K. pneumoniae 5761[e]	105	0.5	4.5	12
		1	4.5	>24

[a] t = 30 min.
[b] $t_{1/2}$ of 2 h.
[c] The growth suppression window is the period of time for which the viable count remained at least 10^3-fold lower than the starting inoculum. Ceftazidime 52-μg/ml growth suppression windows are averages of two or three results; ceftazidime 105-μg/ml growth suppression windows are single datum points.
[d] Produces AmpC; ceftazidime-avibactam MIC = 4 μg/ml.
[e] Produces KPC-3; ceftazidime-avibactam MIC = 4 μg/ml.

The equivalent of 2 g of ceftazidime q8h (C_{max}, 105 mcg/ml) gave a growth suppression window of 6 hour with 0.1 mcg/ml avibactam and 8 h with 0.25 mcg/ml avibactam infused for 24 hour. On the basis of these data, the C_T^{Q8} (where the superscript indicates this critical concentration of avibactam estimated in the background of rising-and-falling ceftazidime concentrations from the C_T obtained during the exponential decline in the avibactam concentration following a peak in the background of a constant ceftazidime concentration) must be >0.25 mcg/ml but ≤0.5 mcg/ml. When ceftazidime was administered at the equivalent of 1 g q8h and avibactam was infused for part of each dose interval at a fixed concentration of 0.5 mcg/ml against AmpC-producing *E. cloacae*, the growth suppression window was 8 hour with a 3-hour avibactam infusion, 7 to 11 hour with a 4.5-h avibactam infusion, and 6 to 8 hours with a 6-hours avibactam infusion. On the basis of these data, the *in vitro* continuous-infusion C_T^{Q8} was >0.5 mcg/ml when the background dose of ceftazidime was equivalent to 1 g q8h. When ceftazidime was administered at the equivalent of 2 g q8h and avibactam was infused for 4.5 hour at 0.5 or 1 mcg/ml at the start of each dose interval (Table 88), the growth suppression window was 12 to 24 hours. On the basis of these data, it appears that the *in vitro* intermittent continuous-infusion C_T^{Q8} in the background of a dose of ceftazidime of 2g q8h would be judged to be ≤0.5 mcg/ml.

The data show that the magnitude of the C_T is likely to be dependent on the MIC of the organism, the inoculum and the dose of the β-lactam used in therapy. Additionally, it was noted that the hollow-fiber system used in the study was impermeable to the β-lactamases produced by the bacteria, resulting in an unnatural accumulation of enzyme in the course of the experiment. This accumulation of β-lactamase may overestimate the C_T and C_T^{Q8} for the test inoculum.

HUMAN CLINICAL TRIALS

Clinical pharmacology studies in the ceftazidime-avibactam development program investigated the PK of avibactam after administration of avibactam alone or ceftazidime-avibactam by IV infusion in healthy subjects and subjects with different degrees of renal impairment. The studies in healthy subjects included young subjects, male and female subjects, ≥ 65 years of age, and Japanese subjects. Avibactam was administered as single IV infusions of 50 to 2000 mg or multiple IV infusions of 500 to 1000 mg q8h for up to 10 days. The PK of avibactam was also studied following the administration of [^{14}C]-avibactam to healthy male subjects.

Data obtained from Phase 1 CAZ-AVI and ceftaroline fosamil-avibactam (CXL) studies were used to explore PK/PD relationships and to evaluate the probability of pharmacokinetic/pharmacodynamic target attainment (PTA). The PTA analyses were used to support breakpoints and dose adjustments for CAZ-AVI in patients with renal impairment. Key findings from the Clinical Pharmacology studies, population PK analyses, and nonclinical drug metabolism and PK studies are summarized below:

- Avibactam maximum plasma drug concentration (Cmax) and area under the plasma concentration-time curve (AUC) increased approximately proportionally to dose over a range of 50 to 2000 mg
- The terminal elimination half-life ($T_{½}$) of avibactam was approximately 2 hours across studies. Little or no accumulation of avibactam was observed after repeated IV q8h doses.
- The $T_{½}$ of ceftazidime was approximately 1.9 hours following IV administration, and there was no accumulation observed (FORTAZ® package insert, 2010)
- No time-dependent PK changes were observed for avibactam or ceftazidime after repeated doses
- Avibactam and ceftazidime were approximately 100% eliminated through renal excretion. Dose adjustments for patients with moderate and severe renal impairment and patients with end-stage renal disease requiring hemodialysis are recommended.
- Both ceftazidime and avibactam are hemodialyzable; thus, CAZ-AVI should be administered after hemodialysis on days when patients receive CAZ-AVI and hemodialysis treatment
- No dose adjustment is needed for CAZ-AVI in patients with impaired hepatic function
- No dose adjustment is needed for CAZ-AVI based on age or gender
- Based on in vitro and clinical data, the potential for DDIs with CAZ-AVI is low. The only potential interaction identified in vitro was between avibactam and potent inhibitors of the renal transporters OAT1 and OAT3 (eg, probenicid).
- No PK interactions were observed between avibactam and ceftazidime or between CAZ-AVI and metronidazole
- CAZ-AVI showed no potential to prolong the QT/QTc interval in a thorough QTc study and in preclinical studies
- A 2-compartment model with first-order elimination from a central compartment was found to adequately describe the population PK of both avibactam and ceftazidime. The main predictor of CL for both avibactam and ceftazidime was creatinine clearance (CrCl). For apparent volume of distribution of the central or plasma compartment (V1), the main predictor was body weight for both compounds.
- The Phase 2 patient population (cIAI and cUTI) was identified as a significant covariate. Compared with Phase 1 subjects, increased CL was associated with the cIAI population, and increased V1 was associated with the cIAI and cUTI populations for both compounds.

- PK/PD relationships could not be established based on clinical data due to the limited data available from the Phase 2 studies in cIAI and cUTI. The PK/PD targets based on in vitro and in vivo nonclinical studies were, therefore, used to determine PTA for CAZ-AVI.
- Binding of avibactam and ceftazidime to human plasma proteins is low. Avibactam protein binding ranged from 5.7% to 8.2% in vitro, and reported values of ceftazidime binding to human plasma proteins ranged from 5% to 23%.
- Little or no biotransformation of avibactam occurred in human liver microsomes, indicating no cytochrome P450 enzyme (CYP) dependent metabolism. Ceftazidime also undergoes little or no metabolism and is eliminated almost entirely as unchanged drug in the urine.
- Avibactam showed no inhibition of CYP450 isoenzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1) or UGT1A1 in vitro at clinically relevant concentrations
- Avibactam showed no potential for in vitro induction of CYP1A2, CYP2B6, CY2C9 and CY3A4 isoenzymes in human hepatocytes. Against CYP2E1, avibactam showed a slight induction potential at very high concentrations that exceed any clinically relevant exposure. Ceftazidime was evaluated independently in human hepatocytes and showed no induction potential on the activity or messenger RNA expression of CYP1A1/2, CYP2B6, and CYP3A4/5.
- Avibactam and ceftazidime showed no inhibition of major renal and hepatic transporters (MDR1, BCRP, MRP4, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, or BSEP) in the clinically relevant exposure range
- Avibactam was not a substrate of MDR1, BCRP, MRP4, or OCT2 but was a substrate of OAT1 and OAT3 in vitro. In vitro uptake of avibactam by OAT1 and OAT3 was not inhibited by ceftazidime but was inhibited by probenecid.

Please refer to reviews filed by the Clinical Pharmacology reviewer of this Application, for details of additional studies.

Results from the population PK analysis were used to predict individual exposure metrics (C_{max}, total daily AUC, %*f*T > MIC, %*f*T > C_T) for CAZ-AVI in patients with cIAI and patients with cUTI from the Phase 2 studies, and to explore the respective datasets for a possible exposure-response relationship. In both studies, for both the subset of patients with a "favorable" overall microbiological response as well as the subset with an "unfavorable" overall microbiological response, a very high percentage (over 80%) of subjects met the pre-specified joint PK/PD target. Furthermore, nearly all subjects were clustered near the high range (well over 50%) of %*f*T > MIC for ceftazidime (using the CAZ-AVI MIC) and %*f*T > C_T for avibactam.

Since PK/PD targets could not be identified from the exposure-response analyses of the Phase 2 studies in cIAI and cUTI, PK/PD targets based on nonclinical microbiological data (eg, hollow fiber infection models and animal models of infection) were used in target attainment simulations. The target attainment results demonstrate that the proposed dose regimen for CAZ-AVI of 2.5 g (2 g ceftazidime + 0.5 g avibactam) given as a 2-hour IV infusion q8h for subjects with normal renal function and mild renal impairment (with adjustment for subjects with CrCl ≤ 50 mL/min) produces adequate target attainment for the joint PK/PD target of 50% *f*T > MIC at a CAZ-AVI MIC of 8 mg/L for ceftazidime and 50% *f*T > C_T for a C_T of 1 mg/L for avibactam. The target

attainment simulations therefore support a PK/PD "susceptible" breakpoint of ≤ 8 mg/L.

Phase 2 and Phase 3 cIAI and cUTI clinical studies

The safety and efficacy of ceftazidime-avibactam were evaluated in one Phase 2 clinical trial in individuals with complicated intra-abdominal infections (cIAI) (Report# NXL104/2002) and in one Phase 2 clinical trial in subjects with complicated urinary tract infections (cUTI) (Report# NXL104/2001). In addition to the Phase 2 studies, ceftazidime-avibactam is being evaluated in an ongoing open label, randomized, Phase 3 clinical trial verses best available therapy (BAT) for the treatment of cIAI or cUTI caused by ceftazidime-non-susceptible gram-negative organisms (Report# D4280C00006). The various dosing regimens for ceftazidime-avibactam and comparators that were evaluated in the clinical development program are summarized in Table 92.

Table 92. Ceftazidime-avibactam and Comparator Dosing Regimens Studies in the Clinical Development Program

Study	*Ceftazidime-avibactam*	*Comparator*
Phase 2 cIAI (NXL104/2002)	Ceftazidime 2000 mg plus avibactam 500 mg plus metronidazole 500 mg, each IV q8h. The infusion time for ceftazidime and avibactam was 30 minutes and the infusion time for metronidazole was 60 minutes	Meropenem 1000 mg plus placebo each IV q8h with an infusion time of 30 minutes
Phase 2 cUTI (NXL104/2001)	Ceftazidime 500 mg plus avibactam 125 mg, each IV q8h with an infusion time of 30 minutes	Imipenem-cilastatin 500 mg IV, q6h with an infusion time of 30 minutes
Resistant Pathogen Study (Clinical Study D4280C00006)	Ceftazidime 2000 mg plus avibactam 500 mg, each IV q8h with an infusion time of 120 minutes	Best Available Therapy (BAT) based on the investigators standard of care and local label recommendation. Preferred options of cUTI were meropenem, imipenem, doripenem and colistin. Preferred options for cIAI were meropenem, imipenem, doripenem, tigecycline and colistin.

Abbreviations: BAT = Best Available Therapy; cIAI = complicated Intra-abdominal Infections; cUTI = complicated urinary Tract Infections; IV = Intravenous

cIAI Phase 2 Study (NXL104/2002)

The dose regimen in the Resistant Pathogen Study the dosage regimen was ceftazidime 2000 mg plus avibactam 500 mg administered IV q8h over 120 minutes. Subjects randomized to receive ceftazidime-avibactam also received metronidazole 500 mg administered IV over 60 minutes. In the Resistant Pathogen Study the comparator was the best available therapy (BAT) where the subjects received doses based on the Investigator's standard of care and the local label recommendation. There were 85 subjects treated with ceftazidime-avibactam plus metronidazole and 89 subjects treated with comparator in the mMITT Population. In the Resistant Pathogen Study at the time of the interim data cut there was one subject with cIAI treated with ceftazidime-avibactam and three subjects treated with BAT in the mMITT Population. The Applicant-verified clinical responses for ceftazidime-avibactam and comparators in the mMITT Populations are summarized in Table 93 for all subjects with a cIAI caused by all pathogens and specifically for cIAI caused by ceftazidime-non-susceptible pathogens.

Table 93. Clinical Response in the mMITT Population for Ceftazidime-avibactam and Comparators in cIAI (Phase 2 and Resistant Pathogen Study)

cIAI Study	*Patients/Pathogen Phenotype*	*Sponsor-verified Clinical Response at TOC (mMITT Population)*	
		Ceftazidime-avibactam plus Metronidazole	*All Comparators*
Phase 2 (NXL104/2002)	All Subjects	70/85 (82.4%)	79/89 (88.8%)
	Subjects with ceftazidime-non-susceptible Pathogens	27/30 (90.0%)	19/23 (82.6%)
Resistant Pathogen Study	Subjects with ceftazidime-non-susceptible Pathogens	1/1 (100.0%)	1/3 (33.3%)
Pooled Phase 2 and Resistant Pathogen Study (D4280C00006)	Subjects with ceftazidime-non-susceptible Pathogens	28/31 (90.3%)	20/26 (76.9%)

Source: Module 2.7.3 - cIAI Appendix 2 Table 2.1.1.0.2 and Module 2.7.3 - cIAI Appendix 2 Table 6.2.1.2.1

The criteria for inclusion in the Microbiologically Evaluable population are as follows:
Microbiologically Evaluable (ME): A subset of the CE subjects who also had at least one etiologic pathogen isolated from a clinically relevant specimen (peritoneal fluid, abscess fluid, peritoneal surface of infected organ prior to the incision of a hollow viscus, or blood culture in appropriate clinical setting) in the initial/pre-study culture that was susceptible to both study agents. Patients with a polymicrobial infection where one or more pathogens were resistant in vitro to the study antibiotic were kept on study therapy at the discretion of the investigator, and were considered evaluable. For further details of the clinical design, inclusion/exclusion criteria, and a summary of the clinical efficacy and safety please refer to the Medical Officer's review.

Clinical and Microbiological Outcome Categories/Responses

Table 94 provides the definitions of the various clinical outcome categories.

Table 94. Clinical Outcome Categories Definitions

Clinical Response	*Definition*
Clinical Cure	Complete resolution or significant improvement of signs and symptoms of the index infection. No further antimicrobial therapy or surgical or radiological intervention is necessary
Clinical Failure	Death related to intra-abdominal infection at any time point Persisting or recurrent infection within the abdomen documented by the findings at re-intervention either percutaneously or operatively Postsurgical wound infections defined as an open wound with signs of local infection such as purulent exudates, erythema, or warmth that requires additional antibiotics and/or non-routine wound care, or Subjects who receive treatment with additional antibiotics for ongoing symptoms of intra-abdominal infection during the study antibiotic period
Indeterminate	Study data are not available for evaluation of efficacy for any reason, including: • Death occurred during the study period and the index infection was clearly noncontributory • Extenuating circumstances preclude classification as cure or failure

Microbiological assessments including Gram stain, WBC count, and culture were performed on specimens obtained from the intra-abdominal cavity or from the blood at baseline and as appropriate during the course of the study. Pathogens were identified as either gram-positive or gram-negative and as aerobes or anaerobes. Organisms were further categorized by genus and species. Microbiological response was determined for each baseline pathogen isolated from intra-abdominal sites and/or blood at DIVT, TOC, and LFU visits. If no post-baseline microbiological specimen was available for culture, the microbiological response was presumed based on the clinical response; eradication was presumed for favorable clinical responses and persistence was presumed for all unfavorable clinical responses.

Emergent pathogens were pathogens not present at baseline but were isolated post-baseline in subjects with clinical signs of infection. “Superinfection” was defined as isolation of a new pathogen(s) (other than the original baseline pathogen[s]) from intra-abdominal cultures which was accompanied by signs and symptoms of infection requiring alternative antimicrobial therapy during the period up to and including EOT. “New infection” was defined as isolation of a new pathogen(s) (other than the original baseline pathogen[s]) from intra-abdominal cultures which was accompanied by signs and symptoms of infection requiring alternative antimicrobial therapy in the time period after EOT. Table 95 depicts the microbiological outcome categories definitions.

Table 95. Microbiological Outcome Categories Definitions

Microbiological Response	***Definition***
Eradication	Absence of causative pathogens from appropriately obtained specimens at the site of infection
Presumptive Eradication	Absence of material to culture in a patient who had responded clinically to treatment.
Persistence	Any causative organism still present at or beyond the end of therapy from a culture of intra-abdominal abscess, peritonitis or surgical wound infection.
Persistence Acquiring Resistance[a]	Continued presence of the original pathogen in cultures from the original site of infection obtained during or upon completion of therapy, and the pathogens that were susceptible to study drug pretreatment have become resistant to study drug therapy post-treatment.
Presumed Persistence	Repeat cultures were not obtained because of the absence of material to culture in a patient who was assessed as clinical failure.
Indeterminate	• Entry culture either not obtained or no growth • Assessment not possible because of protocol violation • Any other circumstance which makes it impossible to define the microbiological response.

a Only persistence was assessed for CAZ-AVI, as breakpoints for CAZ-AVI have not been defined. This has been designated as “NA” in summary tables.

Microbiology and Laboratory Testing

For all cIAI subjects an adequate abdominal culture specimen such as tissue or aspirate suitable for the isolation of aerobic and anaerobic bacteria was collected from the site of the abdominal infection and from other relevant intra-abdominal sites as appropriate. Blood cultures were also collected for all cIAI subjects. All specimens were cultured, and Gram staining, organism identification and initial antimicrobial susceptibility testing were conducted at the local site as appropriate. All isolates were shipped to a central laboratory (b) (4) (b) (4) for identification confirmation (genus and species) and antimicrobial

susceptibility testing. Antimicrobial susceptibility testing was conducted using the Clinical and Laboratory Standards Institute (CLSI) reference broth microdilution method using frozen Sensititre MIC panels manufactured by Thermo Fisher (formerly Trek Diagnostics, Cleveland, OH). Ceftazidime-avibactam was tested with avibactam at a fixed concentration of 4 mg/L.

All ceftazidime-non-susceptible gram-negative organisms were characterized using molecular methods to identify specific β-lactamase resistance mechanisms (Study NXL104/2002 Addendum; Study CAZ104-M2-007-11-AZ-01). *Enterobacteriaceae* isolates displaying ceftriaxone and/or ceftazidime MIC values ≥ 2 mg/L were screened for plasmid AmpC and extended spectrum β-lactamases (ESBL)-encoding genes (PCR and sequencing). *Pseudomonas* spp. and *Acinetobacter* spp. with ceftazidime MIC values ≥ 16 mg/L were screened for ESBL genes. *Enterobacteriaceae* and non-fermentative isolates exhibiting imipenem MIC values ≥ 2 mg/L and ≥ 16 mg/L, respectively, were screened for carbapenemase-encoding genes. The most common sites of infection were appendix (48%), stomach/duodenum (22%) and the small bowel and colon (both 9.7%) (Table 96).

Table 96. Sites of Infection Among cIAI Subjects in Study NXL104/2002 (ME Population)

Site of Infection	*Ceftazidime-avibactam plus Metronidazole (N =68)*	*Meropenem (N = 76)*	*Total (N = 144)*
Stomach/duodenum	19 (27.9)	13 (17.1)	32 (22.2)
Gall bladder	3 (4.4)	9 (11.8)	12 (8.3)
Small bowel	4 (5.9)	10 (13.2)	14 (9.7)
Appendix	32 (47.1)	37 (48.7)	69 (47.9)
Colon	9 (13.2)	5 (6.6)	14 (9.7)
Parenchymal (Liver)	1 (1.5)	1 (1.3)	2 (1.4)
Parenchymal (Spleen)	0	0	0
Other	0	1 (1.3)	1 (0.7)

Source: Module 2.7.3 - cIAI Appendix 2 Table 1.4.1.2a

cIAI Efficacy Results

In the primary analysis population, at Test of Cure (TOC) visit, favorable microbiological and clinical responses of 62/68 for ceftazidime-avibactam plus metronidazole and 71/76 for Meropenem were reported (Table 96) for subjects in the ME population.

Table 96. Summary of Clinical and Microbiological Success of Ceftazidime-avibactam plus Metronidazole in Patients with Complicated Intra-abdominal Infections in cIAI Study NXL104/2002

Population	*Ceftazidime-avibactam plus Metronidazole n/N (%)*	*Meropenem n/N (%)*	*Difference*[a]	95% CI[b]
Overall Sponsor-verified Favorable[c] Microbiological Response at Test of Cure Visit (ME and mMITT Populations)				
ME	62/68 (91.2)	71/76 (93.4)	-2.2	-12.3, 7.0
mMITT	70/85 (82.4)	79/89 (88.8)	-6.4	-17.3, 4.2
Sponsor-verified Favorable Clinical Response at Test of Cure Visit (ME and mMITT Populations)				
ME	62/68 (91.2)	71/76 (93.4)	-2.2	-12.3, 7.0
mMITT	70/85 (82.4)	79/89 (88.8)	-6.4	-17.3, 4.2
Sponsor-verified Favorable Clinical Response at Test of Cure Visit for Ceftazidime-non-susceptible Pathogens (ME and mMITT Populations)				
ME	23/25 (92.0)	18/19 (94.7)	-2.7	-21.0, 18.1
mMITT	27/30 (90.0)	19/23 (82.6)	7.4	-11.8, 29.0

Source: Module 2.7.3 - cIAI Appendix 2 Tables 2.2.2.1.2a, 2.2.2.2.2a, 2.1.1.0.1, 2.1.1.0.2, 2.1.1.0.3, and 2.1.1.0.4.
Abbreviations: cIAI = complicated intra-abdominal infections; ME = Microbiologically Evaluable Population; mMITT = microbiological Modified Intent-to-Treat.
a Difference = % cures in the ceftazidime-avibactam plus metronidazole group minus % cures in the meropenem group.
b 95% Confidence interval for the difference between treatment groups using the Miettenen-Nurminen method.
c Favorable responses included eradication and presumed eradication.

According to the Applicant, monomicrobial infections accounted for 58 to 65% of the infections across the different treatment groups and populations and more than 50% of these infections were caused by gram-negative aerobes (Table 97). Among the polymicrobial infections, gram-negative aerobes were also the most prevalent pathogens either in combination with gram-positive aerobes or anaerobic bacteria.

Table 97. Monomicrobial and Polymicrobial Infections in the Sponsor-verified ME and mMITT Populations

Infection Type	*ME Population*		*mMITT Population*	
	Ceftazidime-avibactam plus Metronidazole (N = 68) N (%)	*Meropenem (N = 76) N (%)*	*Ceftazidime-avibactam plus Metronidazole (N = 85) N (%)*	*Meropenem (N = 89) N (%)*
Monomicrobial	**40 (58.8)**	**49 (64.5)**	**51 (60.0)**	**58 (65.2)**
Anaerobes only	3 (4.4)	0 (0.0)	3 (3.5)	3 (3.4)
Gram negative aerobes only	35 (51.5)	44 (57.9)	42 (49.4)	48 (53.9)
Gram positive aerobes only	2 (2.9)	5 (6.6)	6 (7.1)	7 (7.9)
Polymicrobial	**28 (41.2)**	**27 (35.5)**	**34 (40.0)**	**31 (34.8)**
Anaerobes only	1 (1.5)	1 (1.3)	1 (1.2)	1 (1.1)
Gram negative aerobes and anaerobe(s)	7 (10.3)	6 (7.9)	9 (10.6)	8 (9.0)
Gram negative aerobes only	5 (7.4)	10 (13.2)	7 (8.2)	11 (12.4)
Gram negative and gram positive aerobes	12 (17.6)	10 (13.2)	13 (15.3)	11 (12.4)
Gram negative and gram positive aerobes and anaerobe(s)	1 (1.5)	0 (0.0)	2 (2.4)	0 (0.0)
Gram positive aerobes and anaerobe(s)	1 (1.5)	0 (0.0)	1 (1.2)	0 (0.0)
Gram positive aerobes only	1 (1.5)	0 (0.0)	1 (1.2)	0 (0.0)

Source: Module 2.7.3 - cIAI Appendix 2 Table 1.3.3.9 and 1.3.3.10

Clinical and Microbiological Outcomes by Pathogen

Clinical and microbiological responses by pathogen for all subjects in the ME Population are shown in Table 98. In the ME population, at TOC a response rate of 54/59 (91%) was reported against all *Enterobacteriaceae* in the ceftazidime-avibactam plus metronidazole arm compared with 61/66 (92.4%) in the meropenem arm. Ceftazidime-avibactam plus metronidazole appear to do just as well as meropenem against non-fermenters (*Pseudomonas species* and *Acinetobacter baumannii*), 7/7 and 10/10, respectively. Against the anaerobes, ceftazidime-avibactam plus metronidazole had a response rate of 10/13 (76.9%), compared with 7/7 for meropenem. The low response rate reported for ceftazidime-avibactam plus metronidazole is a result of the 50% (3/6) response rate against *Bacteroides fragilis*.

Table 98. Favorable Sponsor-verified Clinical and Microbiological Response at TOC by Treatment Group and Baseline Pathogen in cIAI Study NXL104/2002 (ME Population)

Baseline Pathogen	*Favorable Sponsor-verified Microbiological Response at TOC by Treatment Group and Baseline Pathogen - Intra-abdominal and Blood Isolates Combined (Sponsor-verified ME Population)*		*Favorable Sponsor-verified Clinical Response at TOC by Treatment Group and Baseline Pathogen - Intra-abdominal and Blood Isolates Combined (Sponsor-verified ME Population)*	
	Ceftazidime-avibactam plus Metronidazole n/N (%)	*Meropenem n/N (%)*	*Ceftazidime-avibactam plus Metronidazole n/N (%)*	*Meropenem n/N (%)*
Enterobacteriaceae	**54/59 (91.5)**	**61/66 (92.4)**	**54/59 (91.5)**	**61/66 (92.4)**
Escherichia coli	47/52 (90.4)	52/56 (92.9)	47/52 (90.4)	52/56 (92.9)
Klebsiella pneumoniae	6/6 (100.0)	11/11 (100.0)	6/6 (100.0)	11/11 (100.0)
Klebsiella oxytoca	2/2 (100.0)	2/2 (100.0)	2/2 (100.0)	2/2 (100.0)
Enterobacter cloacae	1/1 (100.0)	4/4 (100.0)	1/1 (100.0)	4/4 (100.0)
Proteus mirabilis	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Citrobacter braakii	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)
Citrobacter freundii	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)
Enterobacter aerogenes	0/0 (0.0)	0/1 (0.0)	0/0 (0.0)	0/1 (0.0)
Non *Enterobacteriaceae*	**7/7 (100.0)**	**10/10 (100.0)**	**7/7 (100.0)**	**10/10 (100.0)**
Pseudomonas aeruginosa	5/5 (100.0)	5/5 (100.0)	5/5 (100.0)	5/5 (100.0)
Acinetobacter baumannii	1/1 (100.0)	2/2 (100.0)	1/1 (100.0)	2/2 (100.0)
Pseudomonas species	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)
Pseudomonas stutzeri	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)
Acinetobacter junii	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)
Comamonas testosteroni	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)
Pseudomonas fluorescens	0/0 (0.0)	2/2 (100.0)	0/0 (0.0)	2/2 (100.0)
Gram positive aerobes	**16/17 (94.1)**	**15/15 (100.0)**	**16/17 (94.1)**	**15/15 (100.0)**
Staphylococcus aureus	4/4 (100.0)	7/7 (100.0)	4/4 (100.0)	7/7 (100.0)
Enterococcus faecium	3/4 (75.0)	4/4 (100.0)	3/4 (75.0)	4/4 (100.0)
Enterococcus faecalis	2/2 (100.0)	2/2 (100.0)	2/2 (100.0)	2/2 (100.0)
Enterococcus avium	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)
Staphylococcus capitis	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)
Staphylococcus lugdunensis	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)
Streptococcus Group C	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)
Streptococcus constellatus	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)
Streptococcus intermedius	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Streptococcus pneumoniae	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)
Streptococcus salivarius	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)
Enterococcus durans	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)

Baseline Pathogen	*Favorable Sponsor-verified Microbiological Response at TOC by Treatment Group and Baseline Pathogen - Intra-abdominal and Blood Isolates Combined (Sponsor-verified ME Population)*		*Favorable Sponsor-verified Clinical Response at TOC by Treatment Group and Baseline Pathogen - Intra-abdominal and Blood Isolates Combined (Sponsor-verified ME Population)*	
	Ceftazidime-avibactam plus Metronidazole n/N (%)	*Meropenem n/N (%)*	*Ceftazidime-avibactam plus Metronidazole n/N (%)*	*Meropenem n/N (%)*
Staphylococcus hominis	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)
Streptococcus agalactiae	0/0 (0.0)	2/2 (100.0)	0/0 (0.0)	2/2 (100.0)
Streptococcus mitis	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)
Anaerobes	**10/13 (76.9)**	**7/7 (100.0)**	**10/13 (76.9)**	**7/7 (100.0)**
Bacteroides fragilis	3/6 (50.0)	3/3 (100.0)	3/6 (50.0)	3/3 (100.0)
Clostridium ramosum	3/3 (100.0)	1/1 (100.0)	3/3 (100.0)	1/1 (100.0)
Bacteroides caccae	2/2 (100.0)	0/0 (0.0)	2/2 (100.0)	0/0 (0.0)
Bacteroides uniformis	2/2 (100.0)	1/1 (100.0)	2/2 (100.0)	1/1 (100.0)
Clostridium perfringens	2/2 (100.0)	0/0 (0.0)	2/2 (100.0)	0/0 (0.0)
Bacteroides distasonis	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)
Bacteroides eggerthii	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)
Bacteroides thetaiotaomicron	1/1 (100.0)	2/2 (100.0)	1/1 (100.0)	2/2 (100.0)
Clostridium clostridioforme	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Finegoldia magna	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)
Fusobacterium varium	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)
Peptostreptococcus micros	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Prevotella intermedia	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)
Bacteroides vulgatus	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)
Eubacterium lentum	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)
Fusobacterium species	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)
Peptostreptococcus prevotii	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)
Prevotella oris	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)

Source: Module 2.7.3 - cIAI Appendix 2 Tables 2.2.3.1.3 and 2.2.1.1.3

Against Ceftazidime-non-susceptible isolates

The Applicant assessed the clinical response for subjects with cIAI infections caused by ceftazidime-non-susceptible pathogens (Table 99). Against all *Enterobacteriaceae*, the clinical response rates for subjects in the ME population was 22/24 (91.7%) for ceftazidime-avibactam plus metronidazole, and 17/18 (94.4%) for meropenem. The majority of the isolates were *E. coli* with efficacy rates of 18/20 (90%) and 14/15 (93.3%) for ceftazidime-avibactam plus metronidazole and meropenem, respectively.

Table 99. Favorable Sponsor-verified Clinical Response at TOC in Subjects with Ceftazidime-non-susceptible Pathogens (Sponsor-verified ME and mMITT Populations)

Baseline Pathogen	*Favorable Sponsor-verified Clinical Response at TOC by Treatment Group with Ceftazidime-non-susceptible Pathogens (mMITT Population)*		*Favorable Sponsor-verified Clinical Response at TOC by Treatment Group with Ceftazidime-non-susceptible Pathogens (Sponsor-verified ME Population)*	
	Ceftazidime-avibactam plus Metronidazole n/N (%)	*Meropenem n/N (%)*	*Ceftazidime-avibactam plus Metronidazole n/N (%)*	*Meropenem n/N (%)*
Enterobacteriaceae	**25/28 (89.3)**	**18/22 (81.8)**	**22/24 (91.7)**	**17/18 (94.4)**
Escherichia coli	20/22 (90.9)	15/17 (88.2)	18/20 (90.0)	14/15 (93.3)
Klebsiella pneumoniae	3/4 (75.0)	3/5 (60.0)	3/3 (100.0)	3/3 (100.0)
Proteus mirabilis	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)
Providencia stuartii	1/1 (100.0)	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)
Citrobacter braakii	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)
Enterobacter cloacae	0/0 (0.0)	0/1 (0.0)	0/0 (0.0)	0/0 (0.0)
Acinetobacter baumannii	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Pseudomonas aeruginosa	1/1 (100.0)	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)

Source: Module 2.7.3 - cIAI Appendix 2 Tables 2.2.1.1.6 and 2.2.1.1.5

The in vitro susceptibility test results for all baseline pathogens are shown in Table 100 and 101 (Study NXL104/2002). Table 102 depicts a listing of baseline pathogens that were considered ceftazidime non-susceptible. Table 103 depicts a list of pathogens associated with unfavorable outcomes from the ceftazidime-avibactam plus metronidazole treated subjects.

Table 100. In Vitro Susceptibility of Baseline Isolates from cIAI Study NXL104/2002 (All Isolates from Ceftazidime-avibactam plus Metronidazole-treated Patients)

Patient ID	COUNTRY	Baseline Pathogen	Req. #	Source	Ceftazidime MIC (mg/L)	Ceftazidime-avibactam MIC (mg/L)	Meropenem MIC (mg/L)	ME	mMITT	Microbiological Response at TOC	Clinical Response at TOC (mMITT)	β-Lactamase Enzymes
12002	United States	*Klebsiella pneumoniae*	A616583	Infection Site	0.25	0.06	0.03	Y	Y	Presumed Eradicated	CURE	
12002	United States	*Bacteroides caccae*	A616583	Infection Site	16	1	0.12	Y	Y	Presumed Eradicated	CURE	
12002	United States	*Bacteroides uniformis*	A616583	Infection Site	> 32	32	0.25	Y	Y	Presumed Eradicated	CURE	
12002	United States	*Fusobacterium varium*	A616583	Infection Site	> 32	> 32	2	Y	Y	Presumed Eradicated	CURE	
12004	United States	*Enterococcus faecalis*	A616574	Infection Site	16	8	1		Y	Presumed Eradicated	CURE	
12006	United States	*Citrobacter amalonaticus*	A616576	Infection Site	0.25	0.12	0.03		Y	Presumed Persistence	FAILURE	
12006	United States	*Escherichia hermannii*	A616576	Infection Site	0.12	≤ 0.03	0.015		Y	Presumed Persistence	FAILURE	
12006	United States	*Klebsiella pneumoniae*	A616576	Infection Site	1	0.25	0.03		Y	Presumed Persistence	FAILURE	
12007	United States	*Escherichia coli*	A616584	Infection Site	0.25	0.12	0.015	Y	Y	Presumed Persistence	FAILURE	
12007	United States	*Bacteroides fragilis*	A616584	Infection Site	8	2	0.12	Y	Y	Presumed Persistence	FAILURE	
12009	United States	*Clostridium ramosum*	A616555	Infection Site	4	4	0.5	Y	Y	Presumed Eradicated	CURE	
12009	United States	*Clostridium ramosum*	A616577	Infection Site	> 32	> 32	1	Y	Y	Presumed Eradicated	CURE	
13001	United States	*Bacteroides fragilis*	A616623	Infection Site	16	> 32	0.12	Y	Y	Presumed Persistence	FAILURE	
13002	United States	*Streptococcus Group C*	A616624	Infection Site	≤ 0.5	≤ 0.5	≤ 0.015	Y	Y	Presumed Eradicated	CURE	
13002	United States	*Escherichia coli*	A616624	Infection Site	0.06	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
13002	United States	*Pseudomonas aeruginosa*	A616624	Infection Site	2	1	0.25	Y	Y	Presumed Eradicated	CURE	
13002	United States	*Bacteroides eggerthii*	A616624	Infection Site	16	2	0.12	Y	Y	Presumed Eradicated	CURE	
13002	United States	*Peptostreptococcus micros*	A616624	Infection Site	0.5	0.25	≤ 0.015	Y	Y	Presumed Eradicated	CURE	
14004	United States	*Escherichia coli*	A616704	Infection Site	0.12	0.12	0.015		Y		FAILURE	
17001	United States	*Escherichia coli*	A616882	Infection Site	0.12	0.06	0.015		Y		FAILURE	
17001	United States	*Bacteroides splanchnicus*	A616882	Infection Site	16	1	0.06		Y		FAILURE	
17001	United States	*Bacteroides thetaiotaomicron*	A616882	Infection Site	> 32	> 32	0.25		Y		FAILURE	
17001	United States	*Clostridium clostridioforme*	A616882	Infection Site	4	2	0.5		Y		FAILURE	
22002	Bulgaria	*Enterococcus faecalis*	AA28424	Infection Site	> 32	> 32	4	Y	Y	Presumed Eradicated	CURE	
22002	Bulgaria	*Escherichia coli*	AA28424	Infection Site	0.25	0.12	0.015	Y	Y	Presumed Eradicated	CURE	
22006	Bulgaria	*Streptococcus bovis*	AA28426	Infection Site	≤ 0.5	≤ 0.5	≤ 0.015		Y	Presumed Eradicated	CURE	
23001	Bulgaria	*Escherichia coli*	AA26921	Infection Site	0.12	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
23003	Bulgaria	*Escherichia coli*	AA26892	Infection Site	0.12	0.06	0.03	Y	Y	Presumed Eradicated	CURE	

Patient ID	COUNTRY	Baseline Pathogen	Req. #	Source	Ceftazidime MIC (mg/L)	Ceftazidime-avibactam MIC (mg/L)	Meropenem MIC (mg/L)	ME	mMITT	Microbiological Response at TOC	Clinical Response at TOC (mMITT)	β-Lactamase Enzymes
23003	Bulgaria	*Clostridium perfringens*	AA26892	Infection Site	1	≤ 0.12	≤ 0.015	Y	Y	Presumed Eradicated	CURE	
27002	France	*Enterococcus avium*	A691133	Infection Site	8	32	2	Y	Y	Presumed Eradicated	CURE	
27002	France	*Bacteroides caccae*	A691131	Blood Site	> 32	8	0.5	Y	Y	Presumed Eradicated	CURE	
27003	France	*Escherichia coli*	A691132	Infection Site	0.12	0.12	0.015	Y	Y	Presumed Eradicated	CURE	
28002	France	*Escherichia coli*	AA03790	Infection Site	0.12	0.06	0.015		Y	INDETERMINATE	FAILURE	
32001	Poland	*Enterococcus avium*	AA47201	Infection Site	> 32	> 32	0.25		Y	INDETERMINATE	FAILURE	
32001	Poland	*Enterococcus avium*	AA47202	Infection Site	> 32	> 32	4		Y	INDETERMINATE	FAILURE	
32001	Poland	*Escherichia coli*	AA47201	Infection Site	0.12	0.06	0.015		Y	INDETERMINATE	FAILURE	
32001	Poland	*Escherichia coli*	AA47202	Infection Site	0.12	0.06	0.03		Y	INDETERMINATE	FAILURE	
32001	Poland	*Proteus mirabilis*	AA47202	Infection Site	≤ 0.03	0.12	0.06		Y	INDETERMINATE	FAILURE	
32001	Poland	*Fusobacterium necrophorum*	AA47202	Infection Site	≤ 0.12	≤ 0.12	≤ 0.015		Y	INDETERMINATE	FAILURE	
32001	Poland	*Prevotella melaninogenica*	AA47202	Infection Site	≤ 0.12	≤ 0.12	0.03		Y	INDETERMINATE	FAILURE	
40001	Romania	*Bacteroides fragilis*	AA03922	Infection Site	16	1	0.12	Y	Y	Presumed Eradicated	CURE	
40005	Romania	*Staphylococcus aureus*	AA03927	Infection Site	> 32	> 32	32	Y	Y	Presumed Eradicated	CURE	
40005	Romania	*Acinetobacter baumannii*	AA03927	Infection Site	> 32	32	> 16	Y	Y	Presumed Eradicated	CURE	OXA-51,PER-1,TEM-1
40005	Romania	*Pseudomonas aeruginosa*	AA03927	Infection Site	2	2	4	Y	Y	Presumed Eradicated	CURE	
40006	Romania	*Enterobacter cloacae*	AA03929	Infection Site	2	0.25	0.03	Y	Y	Presumed Eradicated	CURE	
40006	Romania	*Escherichia coli*	AA03929	Infection Site	0.12	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
40008	Romania	*Escherichia coli*	AA03928	Infection Site	0.06	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
40008	Romania	*Escherichia coli*	AA03928	Blood Site	0.06	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
40009	Romania	*Staphylococcus aureus*	AA03932	Infection Site	> 32	> 32	> 32	Y	Y	Presumed Eradicated	CURE	
40009	Romania	*Staphylococcus aureus*	AA03932	Blood Site	> 32	> 32	> 32	Y	Y	Presumed Eradicated	CURE	
40009	Romania	*Klebsiella oxytoca*	AA03932	Infection Site	0.12	0.12	0.015	Y	Y	Presumed Eradicated	CURE	
40010	Romania	*Escherichia coli*	AA03951	Infection Site	0.25	0.12	0.015	Y	Y	Presumed Eradicated	CURE	
40010	Romania	*Proteus mirabilis*	AA03951	Infection Site	> 32	1	0.25	Y	Y	Presumed Eradicated	CURE	ACC-4,TEM-1
40011	Romania	*Providencia stuartii*	AA03933	Infection Site	> 32	8	0.03		Y	Presumed Eradicated	CURE	ACC-4,TEM-1
40011	Romania	*Stenotrophomonas maltophilia*	AA03933	Infection Site	4	4	> 16		Y	Presumed Eradicated	CURE	

Patient ID	COUNTRY	Baseline Pathogen	Req. #	Source	Ceftazidime MIC (mg/L)	Ceftazidime-avibactam MIC (mg/L)	Meropenem MIC (mg/L)	ME	mMITT	Microbiological Response at TOC	Clinical Response at TOC (mMITT)	β-Lactamase Enzymes
40012	Romania	*Enterococcus faecium*	AA03934	Infection Site	> 32	> 32	> 32	Y	Y	Presumed Eradicated	CURE	
40012	Romania	*Klebsiella oxytoca*	AA03934	Infection Site	0.12	0.12	0.03	Y	Y	Presumed Eradicated	CURE	
42005	Romania	*Escherichia coli*	AA03860	Infection Site	0.12	0.06	0.008		Y		FAILURE	
42008	Romania	*Staphylococcus aureus*	AA03886	Infection Site	16	8	0.06		Y	Presumed Eradicated	CURE	
42008	Romania	*Escherichia coli*	AA03886	Infection Site	> 32	0.5	0.03		Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,TEM-1
42010	Romania	*Escherichia coli*	AA03885	Infection Site	0.06	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
42011	Romania	*Escherichia coli*	AA03883	Infection Site	0.25	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
43001	Romania	*Staphylococcus capitis*	AA03827	Infection Site	4	4	0.12	Y	Y	Presumed Eradicated	CURE	
43001	Romania	*Streptococcus constellatus*	AA03827	Infection Site	4	4	≤ 0.015	Y	Y	Presumed Eradicated	CURE	
43001	Romania	*Streptococcus constellatus*	AA03827	Blood Site	4	4	0.06	Y	Y	Presumed Eradicated	CURE	
43002	Romania	*Escherichia coli*	AA03828	Infection Site	0.12	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
43003	Romania	*Escherichia coli*	AA03832	Infection Site	0.5	0.25	0.015	Y	Y	Presumed Eradicated	CURE	
43004	Romania	*Staphylococcus aureus*	AA03833	Infection Site	16	16	0.25	Y	Y	Presumed Eradicated	CURE	
43004	Romania	*Escherichia coli*	AA03833	Infection Site	> 32	0.25	0.03	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30
43008	Romania	*Streptococcus intermedius*	AA03839	Infection Site	1	1	0.06	Y	Y	Presumed Eradicated	CURE	
43008	Romania	*Escherichia coli*	AA03839	Infection Site	> 32	0.25	0.03	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30
43008	Romania	*Pseudomonas aeruginosa*	AA03839	Infection Site	2	4	0.12	Y	Y	Presumed Eradicated	CURE	
43010	Romania	*Escherichia coli*	AA03843	Infection Site	0.25	0.25	0.015	Y	Y	Presumed Eradicated	CURE	
44002	Romania	*Streptococcus salivarius*	AA03796	Infection Site	2	2	0.25	Y	Y	Presumed Eradicated	CURE	
44007	Romania	*Staphylococcus aureus*	AA03824	Infection Site	16	8	0.06	Y	Y	Presumed Eradicated	CURE	
44007	Romania	*Escherichia coli*	AA03824	Infection Site	> 32	0.12	0.015	Y	Y	Presumed Eradicated	CURE	ACC-4,CTX-M-15,OXA-1/30,TEM-1
44007	Romania	*Klebsiella pneumoniae*	AA03824	Infection Site	0.25	0.25	0.015	Y	Y	Presumed Eradicated	CURE	
45003	Romania	*Escherichia coli*	AB19661	Infection Site	0.25	0.12	0.015	Y	Y	Presumed Eradicated	CURE	

Patient ID	COUNTRY	Baseline Pathogen	Req. #	Source	Ceftazidime MIC (mg/L)	Ceftazidime-avibactam MIC (mg/L)	Meropenem MIC (mg/L)	ME	mMITT	Microbiological Response at TOC	Clinical Response at TOC (mMITT)	β-Lactamase Enzymes
45006	Romania	*Escherichia coli*	AB19665	Infection Site	0.5	0.12	0.015	Y	Y	Presumed Eradicated	CURE	
45008	Romania	*Escherichia coli*	AB19667	Infection Site	0.25	0.12	0.015	Y	Y	Presumed Eradicated	CURE	
50001	Russian Federation	*Escherichia coli*	AA32531	Infection Site	0.12	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
50001	Russian Federation	*Escherichia coli*	AA32532	Blood Site	0.12	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
52001	Russian Federation	*Escherichia coli*	AA32467	Infection Site	0.12	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
52001	Russian Federation	*Pseudomonas aeruginosa*	AA32467	Infection Site	2	2	0.12	Y	Y	Presumed Eradicated	CURE	
52002	Russian Federation	*Escherichia coli*	AA32466	Infection Site	0.12	≤ 0.03	0.015	Y	Y	Presumed Eradicated	CURE	
52004	Russian Federation	*Escherichia coli*	AA32468	Infection Site	0.25	0.06	0.06	Y	Y	Presumed Eradicated	CURE	
52005	Russian Federation	*Escherichia coli*	AA32464	Infection Site	0.06	≤0.03	0.008	Y	Y	Presumed Persistence	FAILURE	
53009	Russian Federation	*Bacteroides thetaiotaomicron*	AA32419	Infection Site	> 32	32	0.12	Y	Y	Presumed Eradicated	CURE	
53009	Russian Federation	*Clostridium ramosum*	AA32419	Infection Site	> 32	32	0.5	Y	Y	Presumed Eradicated	CURE	
53010	Russian Federation	*Campylobacter gracilis*	AA32421	Infection Site	4	16	0.12		Y	INDETERMINATE	FAILURE	
53010	Russian Federation	*Bacteroides fragilis*	AA32421	Infection Site	> 32	32	0.12		Y	INDETERMINATE	FAILURE	
53010	Russian Federation	*Peptostreptococcus prevotii*	AA32421	Infection Site	0.5	0.25	≤ 0.015		Y	INDETERMINATE	FAILURE	
53011	Russian Federation	*Escherichia coli*	AA32422	Infection Site	0.5	0.25	0.03	Y	Y	Presumed Eradicated	CURE	
53011	Russian Federation	*Bacteroides distasonis*	AA32422	Infection Site	> 32	16	0.5	Y	Y	Presumed Eradicated	CURE	
53011	Russian Federation	*Bacteroides fragilis*	AA32422	Infection Site	16	2	0.12	Y	Y	Presumed Eradicated	CURE	
53011	Russian Federation	*Clostridium clostridioforme*	AA32422	Infection Site	32	> 32	1	Y	Y	Presumed Eradicated	CURE	
53011	Russian Federation	*Prevotella intermedia*	AA32422	Infection Site	0.5	≤0.12	0.03	Y	Y	Presumed Eradicated	CURE	
53012	Russian Federation	*Escherichia coli*	AA32423	Infection Site	0.25	0.12	0.015	Y	Y	Presumed Eradicated	CURE	
53012	Russian Federation	*Pseudomonas aeruginosa*	AA32423	Infection Site	8	2	0.12	Y	Y	Presumed Eradicated	CURE	
53012	Russian Federation	*Bacteroides fragilis*	AA32423	Infection Site	> 32	32	0.25	Y	Y	Presumed Eradicated	CURE	
53012	Russian Federation	*Bacteroides uniformis*	AA32423	Infection Site	32	16	0.12	Y	Y	Presumed Eradicated	CURE	
53012	Russian Federation	*Clostridium perfringens*	AA32423	Infection Site	≤ 0.12	≤ 0.12	≤ 0.015	Y	Y	Presumed Eradicated	CURE	
53012	Russian Federation	*Clostridium ramosum*	AA32423	Infection Site	4	2	0.5	Y	Y	Presumed Eradicated	CURE	
61001	India	*Pseudomonas aeruginosa*	A691333	Infection Site	> 32	> 32	16		Y	Presumed Eradicated	CURE	OXA-10,OXA-10,VEB-1,VEB-1
61008	India	*Klebsiella pneumoniae*	A691308	Infection Site	32	0.12	0.015	Y	Y	Presumed Eradicated	CURE	CTX-M-15,SHV-11,TEM-1
61010	India	*Escherichia coli*	A691310	Infection Site	> 32	2	0.03	Y	Y	Presumed Eradicated	CURE	CMY-42,OXA-1/30
62002	India	*Streptococcus pneumoniae*	A691371	Infection Site	≤ 0.5	≤ 0.5	0.03	Y	Y	Presumed Eradicated	CURE	
62012	India	*Pseudomonas stutzeri*	A691370	Blood Site	0.12	0.12	0.06	Y	Y	Presumed Eradicated	CURE	
62012	India	*Escherichia coli*	A691372	Infection Site	0.06	≤ 0.03	0.015	Y	Y	Presumed Eradicated	CURE	
63005	India	*Escherichia coli*	A691430	Infection Site	> 32	0.12	0.03	Y	Y	Presumed Eradicated	CURE	CTX-M-15,SHV-12
63007	India	*Klebsiella pneumoniae*	A691432	Infection Site	> 32	> 32	2		Y		FAILURE	CTX-M-15,NDM-1,TEM-1

Patient ID	COUNTRY	Baseline Pathogen	Req. #	Source	Ceftazidime MIC (mg/L)	Ceftazidime-avibactam MIC (mg/L)	Meropenem MIC (mg/L)	ME	mMITT	Microbiological Response at TOC	Clinical Response at TOC (mMITT)	β-Lactamase Enzymes
63008	India	*Escherichia coli*	A691433	Infection Site	> 32	0.25	0.015	Y	Y	Presumed Eradicated	CURE	CTX-M-15,TEM-1
64001	India	*Escherichia coli*	A691507	Infection Site	> 32	≤ 0.03	≤ 0.004	Y	Y	Presumed Eradicated	CURE	CMY-42,TEM-1
64004	India	*Escherichia coli*	A691521	Infection Site	32	0.06	≤ 0.004	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30
64006	India	*Escherichia coli*	A691515	Infection Site	0.12	≤0.03	≤ 0.004	Y	Y	Presumed Eradicated	CURE	
64010	India	*Escherichia coli*	A691493	Infection Site	16	≤0.03	0.015	Y	Y	Presumed Eradicated	CURE	SHV-12,TEM-1
64012	India	*Enterococcus faecium*	A691518	Infection Site	> 32	> 32	> 32	Y	Y	Presumed Persistence	FAILURE	
64012	India	*Escherichia coli*	A691518	Infection Site	16	≤ 0.03	≤ 0.004	Y	Y	Presumed Persistence	FAILURE	CTX-M-15,OXA-1/30,SHV-2
64013	India	*Escherichia coli*	A691495	Infection Site	32	≤ 0.03	0.015	Y	Y	Presumed Eradicated	CURE	SHV-12,TEM-1
64013	India	*Pseudomonas species*	A691495	Infection Site	2	2	0.06	Y	Y	Presumed Eradicated	CURE	
64014	India	*Klebsiella pneumoniae*	A691527	Infection Site	0.06	≤ 0.03	≤ 0.004	Y	Y	Presumed Eradicated	CURE	
64015	India	*Escherichia coli*	A691498	Infection Site	0.12	0.06	≤ 0.004	Y	Y	Presumed Eradicated	CURE	
64017	India	*Escherichia coli*	A691511	Infection Site	32	≤ 0.03	0.008	Y	Y	Presumed Eradicated	CURE	CTX-M-15
64019	India	*Escherichia coli*	A691501	Infection Site	0.25	0.12	0.008	Y	Y	Presumed Eradicated	CURE	
64020	India	*Escherichia coli*	A691497	Infection Site	0.12	0.06	0.03	Y	Y	Presumed Eradicated	CURE	
64027	India	*Enterococcus faecalis*	A691514	Infection Site	> 32	> 32	4		Y	Presumed Eradicated	CURE	
67001	India	*Escherichia coli*	A458660	Infection Site	> 32	2	0.015	Y	Y	Presumed Persistence	FAILURE	CMY-42,CTX-M-15,OXA-1/30
68001	India	*Enterococcus faecium*	AA43306	Infection Site	> 32	> 32	16	Y	Y	Presumed Eradicated	CURE	
68001	India	*Klebsiella pneumoniae*	AA43306	Infection Site	32	0.12	0.008	Y	Y	Presumed Eradicated	CURE	SHV-1
68002	India	*Enterococcus faecalis*	AA43308	Infection Site	> 32	> 32	2	Y	Y	Presumed Eradicated	CURE	
68002	India	*Escherichia coli*	AA43308	Infection Site	0.12	0.06	0.008	Y	Y	Presumed Eradicated	CURE	
68006	India	*Enterococcus faecalis*	AA43341	Infection Site	> 32	> 32	2		Y	Presumed Eradicated	CURE	
68007	India	*Escherichia coli*	AA43339	Infection Site	16	≤0.03	≤0.004	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,TEM-1

Patient ID	COUNTRY	Baseline Pathogen	Req. #	Source	Ceftazidime MIC (mg/L)	Ceftazidime-avibactam MIC (mg/L)	Meropenem MIC (mg/L)	ME	mMITT	Microbiological Response at TOC	Clinical Response at TOC (mMITT)	β-Lactamase Enzymes
68007	India	*Finegoldia magna*	AA43339	Infection Site	> 32	2	0.12	Y	Y	Presumed Eradicated	CURE	
68009	India	*Escherichia coli*	AA43336	Infection Site	32	0.06	0.008	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,TEM-1
68010	India	*Escherichia coli*	AA43334	Infection Site	32	0.12	0.008	Y	Y	Presumed Eradicated	CURE	CTX-M-15,SHV-1,TEM-1
68011	India	*Escherichia coli*	AA43331	Infection Site	> 32	2	0.015	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30
68015	India	*Klebsiella pneumoniae*	AA43325	Infection Site	> 32	0.5	0.03	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,SHV-11
68016	India	*Staphylococcus lugdunensis*	AA43317	Blood Site	4	4	0.06	Y	Y	Presumed Eradicated	CURE	
68016	India	*Escherichia coli*	AA43318	Infection Site	32	0.12	0.008	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,TEM-1
68020	India	*Enterococcus faecium*	AA43309	Infection Site	> 32	> 32	8	Y	Y	Presumed Eradicated	CURE	
68020	India	*Escherichia coli*	AA43309	Infection Site	> 32	0.12	0.008	Y	Y	Presumed Eradicated	CURE	CMY-42,TEM-1
68021	India	*Escherichia coli*	AA43310	Infection Site	16	0.06	0.008	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,TEM-1
69001	India	*Escherichia coli*	A691691	Infection Site	0.12	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
72003	Lebanon	*Escherichia coli*	A617035	Infection Site	1	0.12	0.03		Y		FAILURE	
73001	Lebanon	*Escherichia coli*	A617119	Infection Site	0.12	0.12	0.015	Y	Y	Presumed Persistence	FAILURE	
73001	Lebanon	*Bacteroides fragilis*	A617119	Infection Site	32	2	0.12	Y	Y	Presumed Persistence	FAILURE	
80004	India	*Escherichia coli*	RR00112	Infection Site	16	≤ 0.03	0.015		Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30

Table 101 In Vitro Susceptibility of Baseline Isolates from cIAI Study NXL104/2002 (All Isolates from Meropenem-treated Subjects)

Patient ID	COUNTRY	Baseline Pathogen	Req. #	Source	Ceftazidime MIC (mg/L)	Ceftazidime -avibactam MIC (mg/L)	Meropenem MIC (mg/L)	ME	mMITT	Microbiological Response at TOC	Clinical Response at TOC (mMITT)	β-Lactamase Enzymes
12001	United States	*Escherichia coli*	A616582	Infection Site	0.25	0.12	0.015	Y	Y	Presumed Eradicated	CURE	
12001	United States	*Bacteroides uniformis*	A616582	Infection Site	> 32	32	0.25	Y	Y	Presumed Eradicated	CURE	
12003	United States	*Escherichia coli*	A616572	Infection Site	0.06	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
12003	United States	*Klebsiella pneumoniae*	A616572	Infection Site	0.12	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
12005	United States	*Escherichia coli*	A616573	Infection Site	0.25	0.12	0.015	Y	Y	Presumed Eradicated	CURE	
12008	United States	*Escherichia coli*	A616575	Infection Site	0.12	0.12	0.015	Y	Y	Presumed Eradicated	CURE	
12008	United States	*Klebsiella oxytoca*	A616575	Infection Site	0.06	0.25	0.015	Y	Y	Presumed Eradicated	CURE	
12008	United States	*Bacteroides fragilis*	A616575	Infection Site	> 32	16	0.12	Y	Y	Presumed Eradicated	CURE	
14003	United States	*Escherichia coli*	A616703	Infection Site	0.12	0.12	0.015		Y	Presumed Eradicated	CURE	
21002	Bulgaria	*Escherichia coli*	AA28423	Blood Site	0.25	0.12	0.015	Y	Y	Presumed Eradicated	CURE	
21003	Bulgaria	*Escherichia coli*	AA28395	Infection Site	0.06	≤ 0.03	0.015	Y	Y	Presumed Eradicated	CURE	
21004	Bulgaria	*Escherichia coli*	AA28396	Blood Site	0.06	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
21005	Bulgaria	*Escherichia coli*	AA28397	Infection Site	0.12	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
21006	Bulgaria	*Escherichia coli*	AA28420	Infection Site	0.06	≤ 0.03	0.015	Y	Y	Presumed Eradicated	CURE	
21008	Bulgaria	*Streptococcus agalactiae*	AA28422	Infection Site	≤ 0.5	≤ 0.5	0.03	Y	Y	Presumed Eradicated	CURE	
22001	Bulgaria	*Enterobacter cloacae*	AA28453	Infection Site	0.25	0.25	0.03	Y	Y	Presumed Eradicated	CURE	
22003	Bulgaria	*Escherichia coli*	AA28425	Infection Site	0.06	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
23004	Bulgaria	*Enterobacter aerogenes*	AA26894	Infection Site	0.12	0.12	0.03	Y	Y	Presumed Persistence	FAILURE	
40002	Romania	*Escherichia coli*	AA03924	Blood Site	0.12	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
40003	Romania	*Acinetobacter baumannii*	AA03925	Infection Site	2	4	0.12	Y	Y	Presumed Eradicated	CURE	
40004	Romania	*Klebsiella pneumoniae*	AA03926	Infection Site	0.12	0.06	0.03	Y	Y	Presumed Eradicated	CURE	
40007	Romania	*Escherichia coli*	AA03930	Infection Site	32	0.12	0.015	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,TEM-1
40007	Romania	*Proteus mirabilis*	AA03930	Infection Site	≤ 0.03	≤ 0.03	0.06	Y	Y	Presumed Eradicated	CURE	
41001	Romania	*Escherichia coli*	AA03889	Infection Site	0.12	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
41002	Romania	*Escherichia coli*	AA03891	Infection Site	0.12	0.06	0.008	Y	Y	Presumed Eradicated	CURE	
41003	Romania	*Escherichia coli*	AA03892	Infection Site	0.12	0.06	0.015	Y	Y	Persisted	FAILURE	
41004	Romania	*Escherichia coli*	AA03890	Infection Site	0.12	0.12	0.015	Y	Y	Presumed Eradicated	CURE	
42001	Romania	*Enterococcus faecium*	AA03887	Infection Site	8	4	2	Y	Y	Presumed Eradicated	CURE	
42001	Romania	*Escherichia coli*	AA03887	Infection Site	0.25	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
42003	Romania	*Escherichia coli*	AA03858	Infection Site	0.12	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
42004	Romania	*Enterococcus faecalis*	AA03859	Infection Site	> 32	> 32	4	Y	Y	Presumed Eradicated	CURE	
42004	Romania	*Pseudomonas aeruginosa*	AA03859	Infection Site	2	2	0.25	Y	Y	Presumed Eradicated	CURE	
42006	Romania	*Enterobacter cloacae*	AA03861	Infection Site	0.5	0.25	0.03	Y	Y	Presumed Eradicated	CURE	
42006	Romania	*Klebsiella pneumoniae*	AA03861	Infection Site	4	0.25	0.03	Y	Y	Presumed Eradicated	CURE	SHV-1,TEM-1
42007	Romania	*Escherichia coli*	AA03862	Infection Site	0.12	0.06	0.015	Y	Y	Presumed Persistence	FAILURE	
42009	Romania	*Citrobacter braakii*	AA03884	Infection Site	> 32	0.12	0.015	Y	Y	Presumed Eradicated	CURE	CTX-M-15
42009	Romania	*Escherichia coli*	AA03884	Infection Site	0.12	≤ 0.03	0.015	Y	Y	Presumed Eradicated	CURE	
42012	Romania	*Escherichia coli*	AA03882	Infection Site	0.12	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
42012	Romania	*Pseudomonas aeruginosa*	AA03882	Infection Site	32	32	>16	Y	Y	Presumed Eradicated	CURE	OXA-10,OXA-4, VIM-2
43005	Romania	*Klebsiella pneumoniae*	AA03834	Infection Site	0.25	0.06	0.03	Y	Y	Presumed Eradicated	CURE	
43006	Romania	*Pseudomonas fluorescens*	AA03835	Infection Site	8	8	2	Y	Y	Presumed Eradicated	CURE	
43007	Romania	*Escherichia coli*	AA03836	Infection Site	0.12	≤ 0.03	0.008	Y	Y	Presumed Eradicated	CURE	
43009	Romania	*Escherichia coli*	AA03841	Infection Site	0.12	0.06	0.015		Y	INDETERMINATE	FAILURE	

Patient ID	COUNTRY	Baseline Pathogen	Req. #	Source	Ceftazidime MIC (mg/L)	Ceftazidime -avibactam MIC (mg/L)	Meropenem MIC (mg/L)	ME	mMITT	Microbiological Response at TOC	Clinical Response at TOC (mMITT)	β-Lactamase Enzymes
43009	Romania	*Bacteroides fragilis*	AA03841	Infection Site	16	2	0.12		Y	INDETERMINATE	FAILURE	
43009	Romania	*Bacteroides caccae*	AA03842	Infection Site	16	2	0.12		Y	INDETERMINATE	FAILURE	
44001	Romania	*Streptococcus intermedius*	AA03825	Infection Site	2	2	0.06	Y	Y	Presumed Eradicated	CURE	
44003	Romania	*Staphylococcus hominis*	AA03797	Infection Site	8	4	0.12	Y	Y	Presumed Eradicated	CURE	
44004	Romania	*Enterococcus faecalis*	AA03798	Infection Site	> 32	> 32	2		Y	Presumed Eradicated	CURE	
44005	Romania	*Staphylococcus aureus*	AA03799	Infection Site	16	8	0.03	Y	Y	Presumed Eradicated	CURE	
44005	Romania	*Staphylococcus aureus*	AA03800	Blood Site	8	8	0.06	Y	Y	Presumed Eradicated	CURE	
44005	Romania	*Escherichia coli*	AA03799	Infection Site	0.12	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
44005	Romania	*Klebsiella pneumoniae*	AA03799	Infection Site	0.25	0.06	0.03	Y	Y	Presumed Eradicated	CURE	
44006	Romania	*Staphylococcus aureus*	AA03802	Infection Site	> 32	> 32	> 32	Y	Y	Presumed Eradicated	CURE	
44006	Romania	*Escherichia coli*	AA03802	Infection Site	0.25	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
45004	Romania	*Enterobacter cloacae*	AB19663	Infection Site	0.25	0.12	0.03	Y	Y	Presumed Eradicated	CURE	
45004	Romania	*Klebsiella pneumoniae*	AB19663	Infection Site	> 32	0.5	0.03	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,SHV-5,TEM-1
45007	Romania	*Staphylococcus aureus*	AB19666	Infection Site	4	4	0.03	Y	Y	Presumed Eradicated	CURE	
45009	Romania	*Escherichia coli*	AB19668	Infection Site	0.12	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
45010	Romania	*Escherichia coli*	AB19656	Infection Site	0.12	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
47001	Romania	*Escherichia coli*	AB19580	Infection Site	0.06	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
51001	Russian Federation	*Enterococcus faecium*	AA32499	Infection Site	> 32	> 32	8	Y	Y	Presumed Eradicated	CURE	
51001	Russian Federation	*Staphylococcus aureus*	AA32499	Infection Site	8	8	0.03	Y	Y	Presumed Eradicated	CURE	
51001	Russian Federation	*Comamonas testosteroni*	AA32499	Infection Site	0.5	0.5	0.008	Y	Y	Presumed Eradicated	CURE	
51001	Russian Federation	*Klebsiella pneumoniae*	AA32499	Infection Site	0.06	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
51003	Russian Federation	*Staphylococcus aureus*	AA32471	Infection Site	> 32	> 32	1	Y	Y	Presumed Eradicated	CURE	
51003	Russian Federation	*Streptococcus agalactiae*	AA32471	Infection Site	≤ 0.5	≤ 0.5	0.25	Y	Y	Presumed Eradicated	CURE	
51003	Russian Federation	*Streptococcus mitis*	AA32471	Infection Site	1	≤ 0.5	≤ 0.015	Y	Y	Presumed Eradicated	CURE	
51003	Russian Federation	*Escherichia coli*	AA32471	Infection Site	0.12	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
51003	Russian Federation	*Klebsiella pneumoniae*	AA32471	Infection Site	0.12	0.12	0.03	Y	Y	Presumed Eradicated	CURE	
51003	Russian Federation	*Pseudomonas fluorescens*	AA32471	Infection Site	4	4	2	Y	Y	Presumed Eradicated	CURE	
51004	Russian Federation	*Enterococcus durans*	AA32472	Infection Site	> 32	> 32	16	Y	Y	Presumed Eradicated	CURE	
51004	Russian Federation	*Staphylococcus aureus*	AA32472	Infection Site	8	8	0.06	Y	Y	Presumed Eradicated	CURE	
51004	Russian Federation	*Escherichia coli*	AA32472	Infection Site	> 32	0.12	0.015	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,SHV-31,TEM-1
51004	Russian Federation	*Klebsiella pneumoniae*	AA32472	Infection Site	> 32	0.5	0.03	Y	Y	Presumed Eradicated	CURE	CTX-M-15,SHV-11,TEM-1
51004	Russian Federation	*Pseudomonas aeruginosa*	AA32472	Infection Site	4	0.5	0.5	Y	Y	Presumed Eradicated	CURE	
52003	Russian Federation	*Escherichia coli*	AA32465	Infection Site	0.06	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
52006	Russian Federation	*Escherichia coli*	AA32462	Infection Site	0.12	≤ 0.03	0.015	Y	Y	Presumed Eradicated	CURE	
53002	Russian Federation	*Lactobacillus acidophilus*	AA32408	Infection Site	> 32	> 32	16		Y	Presumed Eradicated	CURE	

Patient ID	COUNTRY	Baseline Pathogen	Req. #	Source	Ceftazidime MIC (mg/L)	Ceftazidime -avibactam MIC (mg/L)	Meropenem MIC (mg/L)	ME	mMITT	Microbiological Response at TOC	Clinical Response at TOC (mMITT)	β-Lactamase Enzymes
53003	Russian Federation	*Escherichia coli*	AA32411	Infection Site	0.06	0.06	0.015		Y	INDETERMINATE	FAILURE	
53003	Russian Federation	*Bacteroides thetaiotaomicron*	AA32411	Infection Site	> 32	32	0.25		Y	INDETERMINATE	FAILURE	
53003	Russian Federation	*Bacteroides vulgatus*	AA32411	Infection Site	32	8	0.12		Y	INDETERMINATE	FAILURE	
53003	Russian Federation	*Clostridium subterminale*	AA32411	Infection Site	32	32	1		Y	INDETERMINATE	FAILURE	
53004	Russian Federation	*Bacteroides vulgatus*	AA32410	Infection Site	> 32	32	0.25	Y	Y	Presumed Eradicated	CURE	
53004	Russian Federation	*Clostridium clostridioforme*	AA32410	Infection Site	16	32	1	Y	Y	Presumed Eradicated	CURE	
53004	Russian Federation	*Clostridium ramosum*	AA32410	Infection Site	2	2	0.5	Y	Y	Presumed Eradicated	CURE	
53004	Russian Federation	*Peptostreptococcus prevotii*	AA32410	Infection Site	0.5	0.5	0.06	Y	Y	Presumed Eradicated	CURE	
53005	Russian Federation	*Escherichia coli*	AA32413	Infection Site	0.06	≤0.03	0.015	Y	Y	Presumed Eradicated	CURE	
53005	Russian Federation	*Bacteroides fragilis*	AA32413	Infection Site	16	2	0.12	Y	Y	Presumed Eradicated	CURE	
53005	Russian Federation	*Bacteroides thetaiotaomicron*	AA32420	Infection Site	≤ 0.12	≤ 0.12	≤0.015	Y	Y	Presumed Eradicated	CURE	
53005	Russian Federation	*Fusobacterium species*	AA32426	Infection Site	≤ 0.12	≤ 0.12	≤0.015	Y	Y	Presumed Eradicated	CURE	
53006	Russian Federation	*Escherichia coli*	AA32414	Infection Site	0.12	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
53006	Russian Federation	*Klebsiella oxytoca*	AA32414	Infection Site	0.25	0.25	0.03	Y	Y	Presumed Eradicated	CURE	
53006	Russian Federation	*Prevotella oris*	AA32414	Infection Site	16	2	0.12	Y	Y	Presumed Eradicated	CURE	
53006	Russian Federation	*Bacteroides fragilis*	AA32416	Infection Site	32	2	0.25	Y	Y	Presumed Eradicated	CURE	

Patient ID	COUNTRY	Baseline Pathogen	Req. #	Source	Ceftazidime MIC (mg/L)	Ceftazidime -avibactam MIC (mg/L)	Meropenem MIC (mg/L)	ME	mMITT	Microbiological Response at TOC	Clinical Response at TOC (mMITT)	β-Lactamase Enzymes
53007	Russian Federation	*Enterobacter cloacae*	AA32415	Infection Site	1	0.5	0.015	Y	Y	Presumed Eradicated	CURE	
53007	Russian Federation	*Eubacterium lentum*	AA32415	Infection Site	> 32	> 32	0.25	Y	Y	Presumed Eradicated	CURE	
53007	Russian Federation	*Peptostreptococcus micros*	AA32415	Infection Site	1	0.25	0.06	Y	Y	Presumed Eradicated	CURE	
53008	Russian Federation	*Citrobacter freundii*	AA32418	Infection Site	0.12	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
53008	Russian Federation	*Bacteroides thetaiotaomicron*	AA32418	Infection Site	> 32	32	0.25	Y	Y	Presumed Eradicated	CURE	
55001	Russian Federation	*Escherichia coli*	AA60897	Infection Site	0.12	0.06	0.015	Y	Y	Persisted	FAILURE	
61002	India	*Staphylococcus aureus*	A691334	Infection Site	8	8	0.06	Y	Y	Presumed Eradicated	CURE	
61003	India	*Escherichia coli*	A691335	Infection Site	0.25	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
62003	India	*Escherichia coli*	A691375	Infection Site	0.12	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
62007	India	*Escherichia coli*	A691373	Infection Site	> 32	≤ 0.03	0.008	Y	Y	Presumed Eradicated	CURE	SHV-12
63002	India	*Escherichia coli*	A691428	Infection Site	> 32	2	0.03	Y	Y	Presumed Eradicated	CURE	CMY-42,CTX-M-15,OXA-1/30
63003	India	*Escherichia coli*	A691429	Infection Site	0.12	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
63006	India	*Klebsiella pneumoniae*	A691431	Infection Site	> 32	> 32	2		Y		FAILURE	CTX-M-15,NDM-1,SHV-11,TEM-1
64002	India	*Streptococcus pyogenes*	A691506	Infection Site	≤ 0.5	≤ 0.5	≤ 0.015		Y	Presumed Eradicated	CURE	
64002	India	*Escherichia coli*	A691490	Infection Site	> 32	0.12	0.015		Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,SHV-1
64003	India	*Pseudomonas aeruginosa*	A691489	Infection Site	2	2	0.03	Y	Y	Presumed Eradicated	CURE	
64003	India	*Escherichia coli*	A691520	Infection Site	0.12	0.12	0.008	Y	Y	Presumed Eradicated	CURE	
64005	India	*Escherichia coli*	A691488	Infection Site	> 32	0.12	0.015	Y	Y	Presumed Persistence	FAILURE	CTX-M-15,OXA-1/30,SHV-12,TEM-1

Patient ID	COUNTRY	Baseline Pathogen	Req. #	Source	Ceftazidime MIC (mg/L)	Ceftazidime -avibactam MIC (mg/L)	Meropenem MIC (mg/L)	ME	mMITT	Microbiological Response at TOC	Clinical Response at TOC (mMITT)	β-Lactamase Enzymes
64008	India	*Escherichia coli*	A691492	Infection Site	0.25	0.12	0.015	Y	Y	Presumed Eradicated	CURE	
64009	India	*Escherichia coli*	A691508	Infection Site	32	0.06	0.008	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,TEM-1
64016	India	*Klebsiella pneumoniae*	A691519	Infection Site	0.12	0.06	0.008	Y	Y	Presumed Eradicated	CURE	
64021	India	*Enterococcus faecalis*	A691512	Infection Site	> 32	> 32	> 32	Y	Y	Presumed Eradicated	CURE	
64021	India	*Escherichia coli*	A691525	Infection Site	0.12	≤ 0.03	≤ 0.004	Y	Y	Presumed Eradicated	CURE	
64024	India	*Pseudomonas aeruginosa*	A691500	Infection Site	2	2	0.06	Y	Y	Presumed Eradicated	CURE	
64024	India	*Acinetobacter junii*	A691510	Infection Site	1	0.5	0.015	Y	Y	Presumed Eradicated	CURE	
64026	India	*Escherichia coli*	A691509	Infection Site	> 32	0.12	0.008	Y	Y	Presumed Eradicated	CURE	OXA-1/30,SHV-11
68003	India	*Enterobacter cloacae*	AA43321	Infection Site	> 32	0.5	0.03		Y		FAILURE	CTX-M-15,OXA-1/30,SHV-1,TEM-1
68004	India	*Escherichia coli*	AA43345	Infection Site	0.25	≤ 0.03	≤ 0.004	Y	Y	Presumed Eradicated	CURE	
68005	India	*Escherichia coli*	AA43343	Infection Site	16	0.06	≤ 0.004	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30
68008	India	*Escherichia coli*	AA43319	Infection Site	> 32	0.12	0.015		Y		FAILURE	CTX-M-15,OXA-1/30
68008	India	*Klebsiella pneumoniae*	AA43319	Infection Site	16	0.12	0.015		Y		FAILURE	SHV-1,TEM-1
68012	India	*Enterococcus faecium*	AA43335	Infection Site	> 32	> 32	8	Y	Y	Presumed Eradicated	CURE	
68012	India	*Escherichia coli*	AA43335	Infection Site	32	0.06	0.015	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,TEM-1
68013	India	*Escherichia coli*	AA43329	Infection Site	32	0.12	0.008	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,SHV-1,TEM-1
68014	India	*Enterococcus faecium*	AA43327	Infection Site	> 32	> 32	16	Y	Y	Presumed Eradicated	CURE	
68014	India	*Escherichia coli*	AA43327	Infection Site	> 32	1	0.015	Y	Y	Presumed Eradicated	CURE	CMY-42,CTX-M-15,OXA-1/30
68017	India	*Escherichia coli*	AA43323	Infection Site	> 32	1	0.015	Y	Y	Presumed Eradicated	CURE	CMY-6

Patient ID	COUNTRY	Baseline Pathogen	Req. #	Source	Ceftazidime MIC (mg/L)	Ceftazidime -avibactam MIC (mg/L)	Meropenem MIC (mg/L)	ME	mMITT	Microbiological Response at TOC	Clinical Response at TOC (mMITT)	β-Lactamase Enzymes
68018	India	*Escherichia coli*	AA43315	Blood Site	16	0.06	≤ 0.004	Y	Y	Presumed Eradicated	CURE	
68018	India	*Escherichia coli*	AA43316	Infection Site	16	0.06	≤ 0.004	Y	Y	Presumed Eradicated	CURE	CTX-M-15
68019	India	*Acinetobacter baumannii*	AA43312	Blood Site	> 32	> 32	16	Y	Y	Presumed Eradicated	CURE	OXA-23,OXA-51
68019	India	*Escherichia coli*	AA43313	Infection Site	> 32	0.12	0.008	Y	Y	Presumed Eradicated	CURE	CTX-M-15,SHV-1
69002	India	*Escherichia coli*	A691692	Infection Site	0.12	0.06	0.015	Y	Y	Presumed Eradicated	CURE	
69002	India	*Klebsiella pneumoniae*	A691692	Infection Site	> 32	> 32	4	Y	Y	Presumed Eradicated	CURE	CTX-M-15,NDM-1,SHV-1,TEM-1
69003	India	*Escherichia coli*	A691697	Infection Site	0.25	0.12	0.03	Y	Y	Presumed Eradicated	CURE	
80003	India	*Staphylococcus aureus*	RR00111	Infection Site	> 32	> 32	1		Y	Presumed Eradicated	CURE	
80005	India	*Escherichia coli*	RR00110	Infection Site	32	0.12	0.015	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30

Abbreviations: mMITT = microbiological Modified Intent-to-Treat; ME = Microbiologically Evaluable; MIC = Minimum Inhibitory Concentration
Source: Module 5: Integrated Summary of Microbiology (Microbiology Database)

Table 102. Ceftazidime Non-susceptible, β-Lactamase-producing Gram-negative Pathogens from cIAI Study NXL104/2002 and Clinical and Microbiological Responses for Subjects Treated with Ceftazidime-avibactam plus Metronidazole

Patient ID	COUNTRY	Baseline Pathogen	Req. #	Source	Ceftazidime MIC (mg/L)	Ceftazidime -avibactam MIC (mg/L)	Meropenem MIC (mg/L)	ME	mMITT	Microbiological Response at TOC	Clinical Response at TOC (mMITT)	β-Lactamase Enzymes
40005	Romania	*Acinetobacter baumannii*	AA03927	Infection Site	> 32	32	> 16	Y	Y	Presumed Eradicated	CURE	OXA-51,PER-1,TEM-1
40010	Romania	*Proteus mirabilis*	AA03951	Infection Site	> 32	1	0.25	Y	Y	Presumed Eradicated	CURE	ACC-4,TEM-1
40011	Romania	*Providencia stuartii*	AA03933	Infection Site	> 32	8	0.03		Y	Presumed Eradicated	CURE	ACC-4,TEM-1
42008	Romania	*Escherichia coli*	AA03886	Infection Site	> 32	0.5	0.03		Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,TEM-1
43004	Romania	*Escherichia coli*	AA03833	Infection Site	> 32	0.25	0.03	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30
43008	Romania	*Escherichia coli*	AA03839	Infection Site	> 32	0.25	0.03	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30
44007	Romania	*Escherichia coli*	AA03824	Infection Site	> 32	0.12	0.015	Y	Y	Presumed Eradicated	CURE	ACC-4,CTX-M-15,OXA-1/30,TEM-1
61001	India	*Pseudomonas aeruginosa*	A691333	Infection Site	> 32	> 32	16		Y	Presumed Eradicated	CURE	OXA-10,OXA-10,VEB-1,VEB-1
61008	India	*Klebsiella pneumoniae*	A691308	Infection Site	32	0.12	0.015	Y	Y	Presumed Eradicated	CURE	CTX-M-15,SHV-11,TEM-1
61010	India	*Escherichia coli*	A691310	Infection Site	> 32	2	0.03	Y	Y	Presumed Eradicated	CURE	CMY-42,OXA-1/30
63005	India	*Escherichia coli*	A691430	Infection Site	> 32	0.12	0.03	Y	Y	Presumed Eradicated	CURE	CTX-M-15,SHV-12
63007	India	*Klebsiella pneumoniae*	A691432	Infection Site	> 32	> 32	2		Y		FAILURE	CTX-M-15,NDM-1,TEM-1
63008	India	*Escherichia coli*	A691433	Infection Site	> 32	0.25	0.015	Y	Y	Presumed Eradicated	CURE	CTX-M-15,TEM-1
64001	India	*Escherichia coli*	A691507	Infection Site	> 32	≤ 0.03	≤ 0.004	Y	Y	Presumed Eradicated	CURE	CMY-42,TEM-1
64004	India	*Escherichia coli*	A691521	Infection Site	32	0.06	≤ 0.004	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30
64010	India	*Escherichia coli*	A691493	Infection Site	16	≤ 0.03	0.015	Y	Y	Presumed Eradicated	CURE	SHV-12,TEM-1
64012	India	*Escherichia coli*	A691518	Infection Site	16	≤ 0.03	≤ 0.004	Y	Y	Presumed Persistence	FAILURE	CTX-M-15,OXA-1/30,SHV-2
64013	India	*Escherichia coli*	A691495	Infection Site	32	≤ 0.03	0.015	Y	Y	Presumed Eradicated	CURE	SHV-12,TEM-1
64017	India	*Escherichia coli*	A691511	Infection Site	32	≤ 0.03	0.008	Y	Y	Presumed Eradicated	CURE	CTX-M-15
67001	India	*Escherichia coli*	A458660	Infection Site	> 32	2	0.015	Y	Y	Presumed Persistence	FAILURE	CMY-42,CTX-M-15,OXA-1/30
68001	India	*Klebsiella pneumoniae*	AA43306	Infection Site	32	0.12	0.008	Y	Y	Presumed Eradicated	CURE	SHV-1
68007	India	*Escherichia coli*	AA43339	Infection Site	16	≤ 0.03	≤ 0.004	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,TEM-1
68009	India	*Escherichia coli*	AA43336	Infection Site	32	0.06	0.008	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,TEM-1
68010	India	*Escherichia coli*	AA43334	Infection Site	32	0.12	0.008	Y	Y	Presumed Eradicated	CURE	CTX-M-15,SHV-1,TEM-1
68011	India	*Escherichia coli*	AA43331	Infection Site	> 32	2	0.015	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30
68015	India	*Klebsiella pneumoniae*	AA43325	Infection Site	> 32	0.5	0.03	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,SHV-11
68016	India	*Escherichia coli*	AA43318	Infection Site	32	0.12	0.008	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,TEM-1
68020	India	*Escherichia coli*	AA43309	Infection Site	> 32	0.12	0.008	Y	Y	Presumed Eradicated	CURE	CMY-42,TEM-1
68021	India	*Escherichia coli*	AA43310	Infection Site	16	0.06	0.008	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,TEM-1
80004	India	*Escherichia coli*	RR00112	Infection Site	16	≤ 0.03	0.015		Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30

Table 103 Listing of Pathogens Associated with failures from Ceftazidime-avibactam plus Metronidazole-treated Subjects and Their Susceptibility to Ceftazidime-avibactam in cIAI Study NXL104/2002

Patient ID	COUNTRY	Baseline Pathogen	Req. #	Source	Ceftazidime MIC (mg/L)	Ceftazidime -avibactam MIC (mg/L)	Meropenem MIC (mg/L)	ME	mMITT	Microbiological Response at TOC	Clinical Response at TOC (mMITT)	β-Lactamase Enzymes
12006	United States	*Citrobacter amalonaticus*	A616576	Infection Site	0.25	0.12	0.03		Y	Presumed Persistence	FAILURE	
12006	United States	*Escherichia hermannii*	A616576	Infection Site	0.12	≤ 0.03	0.015		Y	Presumed Persistence	FAILURE	
12006	United States	*Klebsiella pneumoniae*	A616576	Infection Site	1	0.25	0.03		Y	Presumed Persistence	FAILURE	
12007	United States	*Escherichia coli*	A616584	Infection Site	0.25	0.12	0.015	Y	Y	Presumed Persistence	FAILURE	
12007	United States	*Bacteroides fragilis*	A616584	Infection Site	8	2	0.12	Y	Y	Presumed Persistence	FAILURE	
13001	United States	*Bacteroides fragilis*	A616623	Infection Site	16	> 32	0.12	Y	Y	Presumed Persistence	FAILURE	
14004	United States	*Escherichia coli*	A616704	Infection Site	0.12	0.12	0.015		Y		FAILURE	
17001	United States	*Escherichia coli*	A616882	Infection Site	0.12	0.06	0.015		Y		FAILURE	
17001	United States	*Bacteroides splanchnicus*	A616882	Infection Site	16	1	0.06		Y		FAILURE	
17001	United States	*Bacteroides thetaiotaomicron*	A616882	Infection Site	> 32	> 32	0.25		Y		FAILURE	
17001	United States	*Clostridium clostridioforme*	A616882	Infection Site	4	2	0.5		Y		FAILURE	
28002	France	*Escherichia coli*	AA03790	Infection Site	0.12	0.06	0.015		Y	INDETERMINATE	FAILURE	
32001	Poland	*Enterococcus avium*	AA47201	Infection Site	> 32	> 32	0.25		Y	INDETERMINATE	FAILURE	
32001	Poland	*Enterococcus avium*	AA47202	Infection Site	> 32	> 32	4		Y	INDETERMINATE	FAILURE	
32001	Poland	*Escherichia coli*	AA47201	Infection Site	0.12	0.06	0.015		Y	INDETERMINATE	FAILURE	
32001	Poland	*Escherichia coli*	AA47202	Infection Site	0.12	0.06	0.03		Y	INDETERMINATE	FAILURE	
32001	Poland	*Proteus mirabilis*	AA47202	Infection Site	≤ 0.03	0.12	0.06		Y	INDETERMIN	FAILURE	

Patient ID	COUNTRY	Baseline Pathogen	Req. #	Source	Ceftazidime MIC (mg/L)	Ceftazidime -avibactam MIC (mg/L)	Meropenem MIC (mg/L)	ME	mMITT	Microbiological Response at TOC	Clinical Response at TOC (mMITT)	β-Lactamase Enzymes
										ATE		
32001	Poland	*Fusobacterium necrophorum*	AA47202	Infection Site	≤ 0.12	≤ 0.12	≤ 0.015		Y	INDETERMINATE	FAILURE	
32001	Poland	*Prevotella melaninogenica*	AA47202	Infection Site	≤ 0.12	≤ 0.12	0.03		Y	INDETERMINATE	FAILURE	
42005	Romania	*Escherichia coli*	AA03860	Infection Site	0.12	0.06	0.008		Y		FAILURE	
52005	Russian Federation	*Escherichia coli*	AA32464	Infection Site	0.06	≤ 0.03	0.008	Y	Y	Presumed Persistence	FAILURE	
53010	Russian Federation	*Campylobacter gracilis*	AA32421	Infection Site	4	16	0.12		Y	INDETERMINATE	FAILURE	
53010	Russian Federation	*Bacteroides fragilis*	AA32421	Infection Site	> 32	32	0.12		Y	INDETERMINATE	FAILURE	
53010	Russian Federation	*Peptostreptococcus prevotii*	AA32421	Infection Site	0.5	0.25	≤ 0.015		Y	INDETERMINATE	FAILURE	
63007	India	*Klebsiella pneumoniae*	A691432	Infection Site	> 32	> 32	2		Y		FAILURE	CTX-M-15,NDM-1, TEM-1
64012	India	*Enterococcus faecium*	A691518	Infection Site	> 32	> 32	>32	Y	Y	Presumed Persistence	FAILURE	
64012	India	*Escherichia coli*	A691518	Infection Site	16	≤ 0.03	≤ 0.004	Y	Y	Presumed Persistence	FAILURE	CTX-M-15,OXA-1/30,SHV-2
67001	India	*Escherichia coli*	A458660	Infection Site	> 32	2	0.015	Y	Y	Presumed Persistence	FAILURE	CMY-42,CTX-M-15, OXA-1/30
72003	Lebanon	*Escherichia coli*	A617035	Infection Site	1	0.12	0.03		Y		FAILURE	
73001	Lebanon	*Escherichia coli*	A617119	Infection Site	0.12	0.12	0.015	Y	Y	Presumed Persistence	FAILURE	
73001	Lebanon	*Bacteroides fragilis*	A617119	Infection Site	32	2	0.12	Y	Y	Presumed Persistence	FAILURE	

It is difficult to determine which combination of β-lactamase enzymes responds favorably to ceftazidime-avibactam plus metronidazole or to meropenem since the presence of β-lactamases by PCR were not determined for all isolates. Failure rates associated with low MIC were observed among *Enterobacteriaceae*. The clinical and microbiological response rates for ceftazidime-avibactam and meropenem as a function of MIC against all *Enterobacteriaceae* collected from each treatment group is the mMITT and ME populations are shown in Table 104.

Table 104. Favorable Sponsor-verified Clinical and Microbiological Responses for Ceftazidime-avibactam and Meropenem Against All *Enterobacteriaceae* from cIAI Study NXL104/2002

	mMITT Population		*ME Population*	
	Favorable Sponsor-verified Clinical Responses n/N (%)	*Favorable Sponsor-verified Microbiological Response n/N (%)*	*Favorable Sponsor-verified Clinical Responses n/N (%)*	*Favorable Sponsor-verified Microbiological Response n/N (%)*
Ceftazidime-avibactam MIC (mg/L)				
≤ 0.03	10/12 (83.3)	10/12 (83.3)	9/11 (81.8)	9/11 (81.8)
0.06	18/21 (85.7)	18/21 (85.7)	18/18 (100.0)	18/18 (100.0)
0.12	15/20 (75.0)	15/20 (75.0)	15/17 (88.2)	15/17 (88.2)
0.25	8/9 (88.9)	8/9 (88.9)	8/8 (100.0)	8/8 (100.0)
0.5	2/2 (100.0)	2/2 (100.0)	1/1 (100.0)	1/1 (100.0)
1	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
2	2/3 (66.7)	2/3 (66.7)	2/3 (66.7)	2/3 (66.7)
8	1/1 (100.0)	1/1 (100.0)		
>3 2	0/1 (0.0)	0/1 (0.0)		
Meropenem MIC (mg/L)				
≤ 0.004	4/4 (100.0)	4/4 (100.0)	4/4 (100.0)	4/4 (100.0)
0.008	9/9 (100.0)	9/9 (100.0)	9/9 (100.0)	9/9 (100.0)
0.015	37/44 (84.1)	37/44 (84.1)	35/39 (89.7)	35/39 (89.7)
0.03	11/13 (84.6)	11/13 (84.6)	11/12 (91.7)	11/12 (91.7)
0.06	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
2	0/1 (0.0)	0/1 (0.0)		
4	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)

Abbreviations: mMITT = microbiological Modified-Intent-to-Treat; ME = Microbiologically Evaluable; MIC = Minimum Inhibitory Concentration

Source: Table 2.2.5.3.3, Table 2.2.5.2.2.3, Table 2.2.5.3.4 and Table 2.2.5.2.2.4

In the ME population, a response rate of 81.8-100% among the ceftazidime-avibactam MIC values ranged from ≤ 0.03 to 1 mg/L was observed among individuals infected with *Enterobacteriaceae*; however, at MIC of 2 mg/L a response rate of 66.7% was observed. For meropenem, a response rate of 89.7-100% was observed among MIC ranges of ≤ 0.004 to 4 mg/L (Table 101). Against the ceftazidime non-susceptible *Enterobacteriaceae*, a response rate of 83.3-100% was observed among ceftazidime-avibactam isolates with MIC ranging from ≤ 0.03 to 1 mg/L. At 2 mg/L a response rate of 66.7% was observed. Please note that in both analyses, the highest MIC value observed was 2 mg/L (Table 105). For meropenem, response rates of 85.7-100% were observed among MIC ranges of ≤ 0.004 to 0.03 mg/L.

Table 105. Favorable Sponsor-verified Clinical and Microbiological Responses for Ceftazidime-avibactam and Meropenem Against All Ceftazidime-nonsusceptible *Enterobacteriaceae* from cIAI Study NXL104/2002

	mMITT Population		*ME Population*	
	Favorable Sponsor-verified Clinical Responses n/N (%)	*Favorable Sponsor-verified Microbiological Response n/N (%)*	*Favorable Sponsor-verified Clinical Responses n/N (%)*	*Favorable Sponsor-verified Microbiological Response n/N (%)*
Ceftazidime-avibactam MIC (mg/L)				
≤ 0.03	6/7 (85.7)	6/7 (85.7)	5/6 (83.3)	5/6 (83.3)
0.06	3/3 (100.0)	3/3 (100.0)	3/3 (100.0)	3/3 (100.0)
0.12	7/7 (100.0)	7/7 (100.0)	7/7 (100.0)	7/7 (100.0)
0.25	3/3 (100.0)	3/3 (100.0)	3/3 (100.0)	3/3 (100.0)
0.5	2/2 (100.0)	2/2 (100.0)	1/1 (100.0)	1/1 (100.0)
1	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
2	2/3 (66.7)	2/3 (66.7)	2/3 (66.7)	2/3 (66.7)
8	1/1 (100.0)	1/1 (100.0)		
Meropenem MIC (mg/L)				
≤ 0.004	2/2 (100.0)	2/2 (100.0)	2/2 (100.0)	2/2 (100.0)
0.008	5/5 (100.0)	5/5 (100.0)	5/5 (100.0)	5/5 (100.0)
0.015	7/9 (77.8)	7/9 (77.8)	6/7 (85.7)	6/7 (85.7)
0.03	3/4 (75.0)	3/4 (75.0)	3/3 (100.0)	3/3 (100.0)
2	0/1 (0.0)	0/1 (0.0)		
4	1/1 (100.0)	1/1 (100.0)		

Abbreviations: mMITT = microbiological Modified-Intent-to-Treat; ME = Microbiologically Evaluable; MIC = Minimum Inhibitory Concentration

Source: Table 2.2.5.3.5, Table 2.2.5.2.2.5, Table 2.2.5.2.2.6, Table 2.2.5.3.6

Outcomes by MIC for Individual Enterobacteriaceae – Ceftazidime-avibactam plus Metronidazole Treated Subjects

Analyses of clinical and microbiological outcome, in relation to MIC, by individual members of the *Enterobacteriaceae* are shown in Table 106. Against *E. coli*, the ceftazidime-avibactam MIC ranged from ≤ 0.03 to 2 mg/L. The clinical and microbiological responses among three subjects with cIAI who were infected by *E. coli* isolates with a ceftazidime-avibactam MIC of 2 mg/L were both 2/3 (66.7%). Among *K. pneumoniae* the MIC values for ceftazidime-avibactam against isolates from ceftazidime-avibactam ranged from ≤ 0.03 to 0.5 mg/L in the ME population.

Table 106. Favorable Sponsor-verified Clinical and Microbiological Response by MIC for Ceftazidime-avibactam against Enteric Gram-negative Bacilli from cIAI Study NXL104/2002

Ceftazidime-avibactam MIC (mg/L)	*mMITT Population*		*ME Population*	
	Favorable Sponsor-verified Clinical Responses n/N (%)	*Favorable Sponsor-verified Microbiological Response n/N (%)*	*Favorable Sponsor-verified Clinical Responses n/N (%)*	*Favorable Sponsor-verified Microbiological Response n/N (%)*
Escherichia coli				
≤ 0.03	9/11 (81.8)	9/11 (81.8)	8/10 (80.0)	8/10 (80.0)
0.06	18/22 (81.8)	18/22 (81.8)	18/18 (100.0)	18/18 (100.0)
0.12	13/17 (76.5)	13/17 (76.5)	13/15 (86.7)	13/15 (86.7)
0.25	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)
0.5	1/1 (100.0)	1/1 (100.0)		
2	2/3 (66.7)	2/3 (66.7)	2/3 (66.7)	2/3 (66.7)
Klebsiella pneumoniae				
≤ 0.03	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
0.06	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
0.12	2/2 (100.0)	2/2 (100.0)	2/2 (100.0)	2/2 (100.0)
0.25	1/2 (50.0)	1/2 (50.0)	1/1 (100.0)	1/1 (100.0)
0.5	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
> 32	0/1 (0.0)	0/1 (0.0)		
Klebsiella oxytoca				
0.12	2/2 (100.0)	2/2 (100.0)	2/2 (100.0)	2/2 (100.0)
Enterobacter cloacae				
0.25	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)

Ceftazidime-avibactam MIC (mg/L)	*mMITT Population*		*ME Population*	
	Favorable Sponsor-verified Clinical Responses n/N (%)	*Favorable Sponsor-verified Microbiological Response n/N (%)*	*Favorable Sponsor-verified Clinical Responses n/N (%)*	*Favorable Sponsor-verified Microbiological Response n/N (%)*
Proteus mirabilis				
0.12	0/1 (0.0)	0/1 (0.0)		
1	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Citrobacter alamonatacus				
0.12	0/1 (0.0)	0/1 (0.0)		
Escherichia hermannii				
≤ 0.03	0/1 (0.0)	0/1 (0.0)		
Providencia stuartii				
8	1/1 (100.0)	1/1 (100.0)		

Abbreviations: mMITT = microbiological Modified-Intent-to-Treat; ME = Microbiologically Evaluable; MIC = Minimum Inhibitory Concentration; cIAI = complicated Intra-abdominal Infections

Source: Table 2.2.5.3.3, Table 2.2.5.2.2.3, Table 2.2.5.3.4, Table 2.2.5.2.2.4

Outcomes by MIC for Individual Ceftazidime-non-susceptible Enterobacteriaceae - Ceftazidime-avibactam Treated Subjects

In this analysis, clinical and microbiological responses by MIC for ceftazidime-avibactam against ceftazidime non-susceptible *E. coli* and *K. pneumoniae*, *P. mirabilis* and *P. stuartii* are depicted for subjects in the MITT and ME populations. The majority of the ceftazidime non-susceptible isolates were *E. coli*; a total of 20 isolates were identified with MIC ranging from ≤ 0.03-2 mg/L (Table 107). Additionally, there were 3 *K. pneumoniae* isolates and one *P. mirabilis* isolate.

Table 107. Favorable Sponsor-verified Clinical and Microbiological Responses by MIC for Ceftazidime-avibactam against Ceftazidime-non-susceptible Enteric Gram-negative Bacilli from cIAI Study NXL104/2002

Ceftazidime-avibactam MIC (mg/L)	*mMITT Population*		*ME Population*	
	Favorable Sponsor-verified Clinical Responses n/N (%)	*Favorable Sponsor-verified Microbiological Response n/N (%)*	*Favorable Sponsor-verified Clinical Responses n/N (%)*	*Favorable Sponsor-verified Microbiological Response n/N (%)*
***Escherichia coli* (Ceftazidime-non-susceptible)**				
≤ 0.03	6/7 (85.7)	6/7 (85.7)	5/6 (83.3)	5/6 (83.3)
0.06	3/3 (100.0)	3/3 (100.0)	3/3 (100.0)	3/3 (100.0)
0.12	5/5 (100.0)	5/5 (100.0)	5/5 (100.0)	5/5 (100.0)
0.25	3/3 (100.0)	3/3 (100.0)	3/3 (100.0)	3/3 (100.0)
0.5	1/1 (100.0)	1/1 (100.0)		
2	2/3 (66.7)	2/3 (66.7)	2/3 (66.7)	2/3 (66.7)
***Klebsiella pneumoniae* (Ceftazidime-non-susceptible)**				
0.12	2/2 (100.0)	2/2 (100.0)	2/2 (100.0)	2/2 (100.0)
0.5	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
> 32	0/1 (0.0)	0/1 (0.0)		
***Proteus mirabilis* (Ceftazidime-non-susceptible)**				
1	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
***Providencia stuartii* (Ceftazidime-non-susceptible)**				
8	1/1 (100.0)	1/1 (100.0)		

Abbreviations: mMITT = microbiological Modified-Intent-to-Treat; ME = Microbiologically Evaluable; MIC = Minimum Inhibitory Concentration

Table 108 shows the outcome by MIC for individual *Enterobacteriaceae* isolates in the meropenem treatment group from cIAI study NXL104/2002. Similar to the ceftazidime-avibactam treatment group, the majority of the *Enterobacteriaceae* isolates were *E. coli*. Efficacy rates of 90.5-100% were observed with most of the isolates registering an MIC 0.015 mg/L.

Table 108. Favorable Sponsor-verified Clinical and Microbiological Responses by MIC for Meropenem against Enteric Gram-negative Bacilli from cIAI Study NXL104/2002

Meropenem MIC (mg/L)	*mMITT Population*		*ME Population*	
	Favorable Sponsor-verified Clinical Responses n/N (%)	*Favorable Sponsor-verified Microbiological Response n/N (%)*	*Favorable Sponsor-verified Clinical Responses n/N (%)*	*Favorable Sponsor-verified Microbiological Response n/N (%)*
Escherichia coli				
≤ 0.004	4/4 (100.0)	4/4 (100.0)	4/4 (100.0)	4/4 (100.0)
0.008	8/8 (100.0)	8/8 (100.0)	8/8 (100.0)	8/8 (100.0)
0.015	40/47 (85.1)	40/47 (85.1)	38/42 (90.5)	38/42 (90.5)
0.03	2/2 (100.0)	2/2 (100.0)	2/2 (100.0)	2/2 (100.0)
Klebsiella pneumoniae				
0.008	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
0.015	2/3 (66.7)	2/3 (66.7)	2/2 (100.0)	2/2 (100.0)
0.03	7/7 (100.0)	7/7 (100.0)	7/7 (100.0)	7/7 (100.0)
2	0/1 (0.0)	0/1 (0.0)		
4	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Klebsiella oxytoca				
0.015	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
0.03	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Proteus mirabilis				
0.06	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Enterobacter cloacae				
0.015	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
0.03	3/4 (75.0)	3/4 (75.0)	3/3 (100.0)	3/3 (100.0)
Citrobacter braakii				
0.015	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Citrobacter freundii				
0.015	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Enterobacter aerogenes				
0.03	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)

Abbreviations: mMITT = microbiological Modified-Intent-to-Treat; ME = Microbiologically Evaluable; MIC = Minimum Inhibitory Concentration

Table 109 shows the clinical and microbiological response by MIC for meropenem against individual ceftazidime-non-susceptible enteric gram-negative bacilli for subjects in the mMITT and ME populations.

Table 109. Clinical and Microbiological Responses by MIC for Meropenem against Ceftazidime-non-susceptible Enteric Gram-negative Bacilli from cIAI Study NXL104/2002

Meropenem MIC (mg/L)	*mMITT Population*		*ME Population*	
	Favorable Sponsor-verified Clinical Responses n/N (%)	*Favorable Sponsor-verified Microbiological Response n/N (%)*	*Favorable Sponsor-verified Clinical Responses n/N (%)*	*Favorable Sponsor-verified Microbiological Response n/N (%)*
Escherichia coli				
≤ 0.004	2/2 (100.0)	2/2 (100.0)	2/2 (100.0)	2/2 (100.0)
0.008	5/5 (100.0)	5/5 (100.0)	5/5 (100.0)	5/5 (100.0)
0.015	7/9 (77.8)	7/9 (77.8)	6/7 (85.7)	6/7 (85.7)
0.03	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Klebsiella pneumoniae				
0.015	0/1 (0.0)	0/1 (0.0)		
0.03	2/2 (100.0)	2/2 (100.0)	2/2 (100.0)	2/2 (100.0)
2	0/1 (0.0)	0/1 (0.0)		
4	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Citrobacter brakii				
0.015	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Enterobacter cloacae				
0.03	0/1 (0.0)	0/1 (0.0)		

Abbreviations: mMITT = microbiological Modified-Intent-to-Treat; ME = Microbiologically Evaluable; MIC = Minimum Inhibitory Concentration

Resistance pathogen study ceftazidime-non-susceptible isolates

Table 110 and 111 shows a line listing of all individuals with ceftazidime-non-susceptible gram-negative pathogens, for individuals treated with ceftazidime-avibactam and meropenem, respectively. In this category, all isolates were characterized using molecular methods to identify specific β-lactamase enzymes. The data indicate that the majority of the isolates produced multiple β-lactamases with CTX-M being most prevalent.

Table 110 Ceftazidime Non-susceptible, β-Lactamase-producing Gram-negative Pathogens from cIAI Study NXL104/2002 and Clinical and Microbiological Responses for Subjects Treated with Ceftazidime-avibactam plus Metronidazole

Patient ID	COUNTRY	Baseline Pathogen	Req. #	Source	Ceftazidime MIC (mg/L)	Ceftazidime -avibactam MIC (mg/L)	Meropenem MIC (mg/L)	ME	mMITT	Microbiological Response at TOC	Clinical Response at TOC (mMITT)	β-Lactamase Enzymes
40005	Romania	*Acinetobacter baumannii*	AA03927	Infection Site	> 32	32	> 16	Y	Y	Presumed Eradicated	CURE	OXA-51,PER-1,TEM-1
40010	Romania	*Proteus mirabilis*	AA03951	Infection Site	> 32	1	0.25	Y	Y	Presumed Eradicated	CURE	ACC-4,TEM-1
40011	Romania	*Providencia stuartii*	AA03933	Infection Site	> 32	8	0.03		Y	Presumed Eradicated	CURE	ACC-4,TEM-1
42008	Romania	*Escherichia coli*	AA03886	Infection Site	> 32	0.5	0.03		Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,TEM-1
43004	Romania	*Escherichia coli*	AA03833	Infection Site	> 32	0.25	0.03	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30
43008	Romania	*Escherichia coli*	AA03839	Infection Site	> 32	0.25	0.03	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30
44007	Romania	*Escherichia coli*	AA03824	Infection Site	> 32	0.12	0.015	Y	Y	Presumed Eradicated	CURE	ACC-4,CTX-M-15,OXA-1/30,TEM-1
61001	India	*Pseudomonas aeruginosa*	A691333	Infection Site	> 32	> 32	16		Y	Presumed Eradicated	CURE	OXA-10,OXA-10,VEB-1,VEB-1
61008	India	*Klebsiella pneumoniae*	A691308	Infection Site	32	0.12	0.015	Y	Y	Presumed Eradicated	CURE	CTX-M-15,SHV-11,TEM-1
61010	India	*Escherichia coli*	A691310	Infection Site	> 32	2	0.03	Y	Y	Presumed Eradicated	CURE	CMY-42,OXA-1/30
63005	India	*Escherichia coli*	A691430	Infection Site	> 32	0.12	0.03	Y	Y	Presumed Eradicated	CURE	CTX-M-15,SHV-12
63007	India	*Klebsiella pneumoniae*	A691432	Infection Site	> 32	> 32	2		Y		FAILURE	CTX-M-15,NDM-1,TEM-1
63008	India	*Escherichia coli*	A691433	Infection Site	> 32	0.25	0.015	Y	Y	Presumed Eradicated	CURE	CTX-M-15,TEM-1
64001	India	*Escherichia coli*	A691507	Infection Site	> 32	≤ 0.03	≤ 0.004	Y	Y	Presumed Eradicated	CURE	CMY-42,TEM-1
64004	India	*Escherichia coli*	A691521	Infection Site	32	0.06	≤ 0.004	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30
64010	India	*Escherichia coli*	A691493	Infection Site	16	≤ 0.03	0.015	Y	Y	Presumed Eradicated	CURE	SHV-12,TEM-1
64012	India	*Escherichia coli*	A691518	Infection Site	16	≤ 0.03	≤ 0.004	Y	Y	Presumed Persistence	FAILURE	CTX-M-15,OXA-1/30,SHV-2
64013	India	*Escherichia coli*	A691495	Infection Site	32	≤ 0.03	0.015	Y	Y	Presumed Eradicated	CURE	SHV-12,TEM-1
64017	India	*Escherichia coli*	A691511	Infection Site	32	≤ 0.03	0.008	Y	Y	Presumed Eradicated	CURE	CTX-M-15
67001	India	*Escherichia coli*	A458660	Infection Site	> 32	2	0.015	Y	Y	Presumed Persistence	FAILURE	CMY-42,CTX-M-15,OXA-1/30
68001	India	*Klebsiella pneumoniae*	AA43306	Infection Site	32	0.12	0.008	Y	Y	Presumed Eradicated	CURE	SHV-1
68007	India	*Escherichia coli*	AA43339	Infection Site	16	≤ 0.03	≤ 0.004	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,TEM-1
68009	India	*Escherichia coli*	AA43336	Infection Site	32	0.06	0.008	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,TEM-1
68010	India	*Escherichia coli*	AA43334	Infection Site	32	0.12	0.008	Y	Y	Presumed Eradicated	CURE	CTX-M-15,SHV-1,TEM-1
68011	India	*Escherichia coli*	AA43331	Infection Site	> 32	2	0.015	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30
68015	India	*Klebsiella pneumoniae*	AA43325	Infection Site	> 32	0.5	0.03	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,SHV-11
68016	India	*Escherichia coli*	AA43318	Infection Site	32	0.12	0.008	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,TEM-1
68020	India	*Escherichia coli*	AA43309	Infection Site	> 32	0.12	0.008	Y	Y	Presumed Eradicated	CURE	CMY-42,TEM-1
68021	India	*Escherichia coli*	AA43310	Infection Site	16	0.06	0.008	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,TEM-1
80004	India	*Escherichia coli*	RR00112	Infection Site	16	≤ 0.03	0.015		Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30

Abbreviations: mMITT = microbiological Modified Intent-to-Treat; ME = Microbiologically Evaluable; MIC = Minimum Inhibitory Concentration
Source: Module 5: Integrated Summary of Microbiology (Microbiology Database)

Table 111. In Vitro Susceptibility of Ceftazidime Non-susceptible, β-Lactamase-producing Gram-negative Pathogens from cIAI Study NXL104/2002 and Clinical and Microbiological Response for Subjects Treated with Meropenem

Patient ID	COUNTRY	Baseline Pathogen	Req. #	Source	Ceftazidime MIC (mg/L)	Ceftazidime -avibactam MIC (mg/L)	Meropenem MIC (mg/L)	ME	mMITT	Microbiological Response at TOC	Clinical Response at TOC (mMITT)	β-Lactamase Enzymes
40007	Romania	*Escherichia coli*	AA03930	Infection Site	32	0.12	0.015	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,TEM-1
42009	Romania	*Citrobacter braakii*	AA03884	Infection Site	> 32	0.12	0.015	Y	Y	Presumed Eradicated	CURE	CTX-M-15
42012	Romania	*Pseudomonas aeruginosa*	AA03882	Infection Site	32	32	> 16	Y	Y	Presumed Eradicated	CURE	OXA-10,OXA-4,VIM-2
45004	Romania	*Klebsiella pneumoniae*	AB19663	Infection Site	> 32	0.5	0.03	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,SHV-5,TEM-1
51004	Russian Federation	*Escherichia coli*	AA32472	Infection Site	> 32	0.12	0.015	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,SHV-31,TEM-1
51004	Russian Federation	*Klebsiella pneumoniae*	AA32472	Infection Site	> 32	0.5	0.03	Y	Y	Presumed Eradicated	CURE	CTX-M-15,SHV-11,TEM-1
62007	India	*Escherichia coli*	A691373	Infection Site	> 32	≤ 0.03	0.008	Y	Y	Presumed Eradicated	CURE	SHV-12
63002	India	*Escherichia coli*	A691428	Infection Site	> 32	2	0.03	Y	Y	Presumed Eradicated	CURE	CMY-42,CTX-M-15,OXA-1/30
63006	India	*Klebsiella pneumoniae*	A691431	Infection Site	> 32	> 32	2		Y		FAILURE	CTX-M-15,NDM-1,SHV-11,TEM-1
64002	India	*Escherichia coli*	A691490	Infection Site	> 32	0.12	0.015		Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,SHV-1
64005	India	*Escherichia coli*	A691488	Infection Site	> 32	0.12	0.015	Y	Y	Presumed Persistence	FAILURE	CTX-M-15,OXA-1/30,SHV-12,TEM-1
64009	India	*Escherichia coli*	A691508	Infection Site	32	0.06	0.008	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,TEM-1
64026	India	*Escherichia coli*	A691509	Infection Site	> 32	0.12	0.008	Y	Y	Presumed Eradicated	CURE	OXA-1/30,SHV-11
68003	India	*Enterobacter cloacae*	AA43321	Infection Site	> 32	0.5	0.03		Y		FAILURE	CTX-M-15,OXA-1/30,SHV-1,TEM-1
68005	India	*Escherichia coli*	AA43343	Infection Site	16	0.06	≤ 0.004	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30
68008	India	*Escherichia coli*	AA43319	Infection Site	> 32	0.12	0.015		Y		FAILURE	CTX-M-15,OXA-1/30
68008	India	*Klebsiella pneumoniae*	AA43319	Infection Site	16	0.12	0.015		Y		FAILURE	SHV-1,TEM-1
68012	India	*Escherichia coli*	AA43335	Infection Site	32	0.06	0.015	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,TEM-1
68013	India	*Escherichia coli*	AA43329	Infection Site	32	0.12	0.008	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30,SHV-1,TEM-1
68014	India	*Escherichia coli*	AA43327	Infection Site	> 32	1	0.015	Y	Y	Presumed Eradicated	CURE	CMY-42,CTX-M-15,OXA-1/30
68017	India	*Escherichia coli*	AA43323	Infection Site	> 32	1	0.015	Y	Y	Presumed Eradicated	CURE	CMY-6
68018	India	*Escherichia coli*	AA43316	Infection Site	16	0.06	≤ 0.004	Y	Y	Presumed Eradicated	CURE	CTX-M-15
68019	India	*Acinetobacter baumannii*	AA43312	Blood Site	> 32	> 32	16	Y	Y	Presumed Eradicated	CURE	OXA-23,OXA-51
68019	India	*Escherichia coli*	AA43313	Infection Site	> 32	0.12	0.008	Y	Y	Presumed Eradicated	CURE	CTX-M-15,SHV-1
69002	India	*Klebsiella pneumoniae*	A691692	Infection Site	> 32	>32	4	Y	Y	Presumed Eradicated	CURE	CTX-M-15,NDM-1,SHV-1,TEM-1
80005	India	*Escherichia coli*	RR00110	Infection Site	32	0.12	0.015	Y	Y	Presumed Eradicated	CURE	CTX-M-15,OXA-1/30

Abbreviations: MITT = microbiological Modified Intent-to-Treat; ME = Microbiologically Evaluable; MIC = Minimum Inhibitory Concentration
Source: Module 5: Integrated Summary of Microbiology (Microbiology Database)

Other Gram-negative Pathogens

Table 112 shows the clinical and microbiological responses by MIC for ceftazidime-avibactam against *P. aeruginosa* from ceftazidime-avibactam treated subjects in the mMITT and ME Populations. There were 6 isolates of *P. aeruginosa* in the mMITT Population with ceftazidime-avibactam MIC values that ranged from 1 to > 32 mg/L. All subjects with cIAI who were infected with these pathogens were clinical and microbiological successes.

Table 112. Favorable Sponsor-verified Clinical and Microbiological Responses by MIC for Ceftazidime-avibactam against Other Gram-negative Pathogens from cIAI Study NXL104/2002

Ceftazidime-avibactam MIC (mg/L)	*mMITT Population*		*ME Population*	
	Favorable Sponsor-verified Clinical Responses n/N (%)	*Favorable Sponsor-verified Microbiological Response n/N (%)*	*Favorable Sponsor-verified Clinical Responses n/N (%)*	*Favorable Sponsor-verified Microbiological Response n/N (%)*
Pseudomonas aeruginosa				
1	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
2	3/3 (100.0)	3/3 (100.0)	3/3 (100.0)	3/3 (100.0)
4	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
> 32	1/1 (100.0)	1/1 (100.0)		
***Pseudomonas* spp.**				
2	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Acinetobacter baumanii				
32	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Campylobacter gracilis				
16	0/1 (0.0)	0/1 (0.0)		
Pseudomonas stutzeri				
0.12	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Stenotrophomonas maltophilia				
4	1/1 (100.0)	1/1 (100.0)		

Abbreviations: mMITT = microbiological Modified-Intent-to-Treat; ME = Microbiologically Evaluable; MIC = Minimum Inhibitory Concentration

Table 113 shows the clinical and microbiological responses by MIC for meropenem against *P. aeruginosa* and other non-fermenting Gram-negative pathogens. Among the five isolates of *P. aeruginosa* the meropenem MIC values ranged from 0.03 to > 16 mg/L and all pathogens were associated with subjects with favorable clinical and microbiological responses

Table 113. Favorable Sponsor-verified Clinical and Microbiological Responses by MIC for Meropenem Against Non-*Enterobacteriaceae* from cIAI Study NXL104/2002

Meropenem MIC (mg/L)	*mMITT Population*		*ME Population*	
	Favorable Sponsor-verified Clinical Responses n/N (%)	*Favorable Sponsor-verified Microbiological Response n/N (%)*	*Favorable Sponsor-verified Clinical Responses n/N (%)*	*Favorable Sponsor-verified Microbiological Response n/N (%)*
Pseudomonas aeruginosa				
0.03	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
0.06	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
0.25	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
0.5	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
> 16	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Acinetobacter jejuni				
0.015	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Acinetobacter baumanii				
0.12	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
16	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Comomonas testosteroni				
0.008	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Pseudomonas fluorescens				
2	2/2 (100.0)	2/2 (100.0)	2/2 (100.0)	2/2 (100.0)

Abbreviations: mMITT = microbiological Modified-Intent-to-Treat; ME = Microbiologically Evaluable; MIC = Minimum Inhibitory Concentration

One isolate of *P. aeruginosa* was reported to have a ceftazidime-avibactam MIC >32 mg/l and was associated with clinical and microbiological success. Additionally a single isolate of *A. baumanii* that was ceftazidime-non-susceptible that had an MIC of 32 mg/L for ceftazidime-avibactam that was associated with a subject that was a clinical and microbiological success (Table 114).

Table 114. Favorable Sponsor-verified Clinical and Microbiological Responses by MIC for Ceftazidime-avibactam Against Non-*Enterobacteriaceae* from cIAI Study NXL104/2002

Ceftazidime-avibactam MIC (mg/L)	*mMITT Population*		*ME Population*	
	Favorable Sponsor-verified Clinical Responses n/N (%)	*Favorable Sponsor-verified Microbiological Response n/N (%)*	*Favorable Sponsor-verified Clinical Responses n/N (%)*	*Favorable Sponsor-verified Microbiological Response n/N (%)*
***Pseudomonas aeruginosa* (Ceftazidime-non-susceptible)**				
> 32	1/1 (100.0)	1/1 (100.0)		
***Acinetobacter baumannii* (Ceftazidime-non-susceptible)**				
32	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)

Abbreviations: mMITT = microbiological Modified-Intent-to-Treat; ME = Microbiologically Evaluable; MIC = Minimum Inhibitory Concentration

Similar results were observed in the meropenem treatment group. Table 115 shows the clinical and microbiological responses by meropenem MIC and ceftazidime-non-susceptible *P. aeruginosa* and *A. baumanii* among subjects in the mMITT and ME Populations. Non-fermenting isolates having meropenem MIC ≥ 16 mg/L were associated with subjects that exhibited favorable clinical and microbiological responses.

Table 115. Favorable Sponsor-verified Clinical and Microbiological Responses by MIC for Meropenem against Non-*Enterobacteriaceae* from cIAI Study NXL104/2002

Meropenem MIC (mg/L)	*mMITT Population*		*ME Population*	
	Favorable Sponsor-verified Clinical Responses n/N (%)	*Favorable Sponsor-verified Microbiological Response n/N (%)*	*Favorable Sponsor-verified Clinical Responses n/N (%)*	*Favorable Sponsor-verified Microbiological Response n/N (%)*
Pseudomonas aeruginosa				
> 16	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Acinetobacter baumanii				
16	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)

Abbreviations: mMITT = microbiological Modified-Intent-to-Treat; ME = Microbiologically Evaluable; MIC = Minimum Inhibitory Concentration

Against Anaerobes cIAI study NXL104/2002

Bacteroides fragilis was identified as the most prevalent anaerobe identified among cIAI in the ceftazidime-avibactam treatment group in the mMITT and ME population (7 isolates). Ceftazidime-avibactam MIC values that ranged from 1 to > 32 mg/L. However, due to the limited number of isolates no correlation between clinical failure and the MIC of the baseline isolate was observed. The isolate with the highest MIC of > 32 mg/L was associated with a subject that was a clinical and microbiological failure. There were 3 isolates of *Clostridium ramosum* with ceftazidime-avibactam MIC values that ranged from 2 to > 32 mg/L and all isolates were associated with subjects that were clinical and microbiological successes (Table 116).

Table 116. Favorable Sponsor-verified Clinical and Microbiological Responses by MIC for Metronidazole and Anaerobic Pathogens from Ceftazidime-avibactam plus Metronidazole-treated Subjects in cIAI Study NXL104/2002

Ceftazidime-Avibactam MIC (mg/L)	*mMITT Population*		*ME Population*	
	Favorable Sponsor-verified Clinical Responses n/N (%)	*Favorable Sponsor-verified Microbiological Response n/N (%)*	*Favorable Sponsor-verified Clinical Responses n/N (%)*	*Favorable Sponsor-verified Microbiological Response n/N (%)*
Bacteroides fragilis				
1	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
2	1/3 (33.3)	1/3 (33.3)	1/3 (33.3)	1/3 (33.3)
32	1/2 (50.0)	1/2 (50.0)	1/1 (100.0)	1/1 (100.0)
> 32	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)
Clostridium ramosum				
2	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
32	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
> 32	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Bacteroides caccae				
1	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
8	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Bacteroides thetaiotaomicron				
32	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
> 32	0/1 (0.0)	0/1 (0.0)		
Bacteroides uniformis				
16	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
32	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Clostridium clostridioforme				
2	0/1 (0.0)	0/1 (0.0)		
> 32	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Clostridium perfringens				
≤ 0.12	2/2 (100.0)	2/2 (100.0)	2/2 (100.0)	2/2 (100.0)

Ceftazidime-Avibactam MIC (mg/L)	*mMITT Population*		*ME Population*	
	Favorable Sponsor-verified Clinical Responses n/N (%)	*Favorable Sponsor-verified Microbiological Response n/N (%)*	*Favorable Sponsor-verified Clinical Responses n/N (%)*	*Favorable Sponsor-verified Microbiological Response n/N (%)*
Bacteroides distasonis				
16	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Bacteroides eggerthii				
2	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Bacteroides splanchnicus				
1	0/1 (0.0)	0/1 (0.0)		
Finegoldia magna				
2	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Fusobacterium necrophorum				
≤ 0.12	0/1 (0.0)	0/1 (0.0)		
Fusobacterium varum				
> 32	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Peptostreptococcus micros				
0.25	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Peptostreptococcus prevotii				
0.25	0/1 (0.0)	0/1 (0.0)		
Prevotella intermedia				
≤ 0.12	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Peptostreptococcus melaninogenica				
≤ 0.12	0/1 (0.0)	0/1 (0.0)		

Abbreviations: mMITT = microbiological Modified-Intent-to-Treat; ME = Microbiologically Evaluable; MIC = Minimum Inhibitory Concentration

Table 117 shows the clinical and microbiological responses by MIC for meropenem against anaerobic pathogens from meropenem treated subjects in the mMITT and ME Populations.

Table 117. Favorable Sponsor-verified Clinical and Microbiological Responses by MIC for Meropenem and Anaerobic Pathogens from Meropenem-treated Subjects in cIAI Study NXL104/2002

Meropenem MIC (mg/L)	*mMITT Population*		*ME Population*	
	Favorable Sponsor-verified Clinical Responses n/N (%)	*Favorable Sponsor-verified Microbiological Response n/N (%)*	*Favorable Sponsor-verified Clinical Responses n/N (%)*	*Favorable Sponsor-verified Microbiological Response n/N (%)*
Bacteroides fragilis				
0.12	2/3 (66.7)	2/3 (66.7)	2/2 (100.0)	2/2 (100.0)
0.25	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Clostridium ramosum				
0.5	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Bacteroides caccae				
0.12	0/1 (0.0)	0/1 (0.0)		
Bacteroides thetaiotaomicron				
≤ 0.015	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
0.25	1/2 (50.0)	1/2 (50.0)	1/1 (100.0)	1/1 (100.0)
Clostridium clostridioforme				
1	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Peptostreptococcus micros				
0.06	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Peptostreptococcus prevotii				
0.06	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Bacteroides vulgatus				
0.12	0/1 (0.0)	0/1 (0.0)		
0.25	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Clostridium subterminale				
1	0/1 (0.0)	0/1 (0.0)		
***Fusobacterium* spp.**				
≤ 0.015	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Eubacterium lentum				
0.25	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Lactobacillus acidophilus				
16	1/1 (100.0)	1/1 (100.0)		
Prevotella oris				
0.12	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Bacteroides uniformis				
0.25	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)

Abbreviations: mMITT = microbiological Modified-Intent-to-Treat; ME = Microbiologically Evaluable; MIC = Minimum Inhibitory Concentration

cUTI Study NXL104/2001

The dosage regimen for ceftazidime-avibactam in the Phase 2 cUTI Study was 500 mg ceftazidime/125 mg avibactam as a 30 minute infusion IV administered q8h. The comparator agent was imipenem administered as 500 mg q6h. The dosage regimen for ceftazidime-avibactam in the Resistant Pathogen Study (Clinical Study D4280C00006) was 2000 mg ceftazidime/500 mg avibactam as 120 minute infusion administered q8h.The clinical response rates for ceftazidime-avibactam and comparators for subjects with cUTI in the Phase 2 Study, the Resistant Pathogen Study and for both studies pooled are shown in Table 118. The pooled clinical response data focused on cUTI pathogens that were non-susceptible (intermediate or resistant) to ceftazidime.

Table 118. Clinical Response in the mMITT Population for Ceftazidime-avibactam and comparators in cUTI (Phase 2 and Resistant Pathogen Study)

cUTI Study	*Patients/Pathogen Phenotype*	*Clinical Response at TOC (mMITT Population)*	
		Ceftazidime-avibactam	*All Comparators*
Phase 2 (NXL104/2001)	All Subjects	37/46 (80.4)	36/49 (73.5)
	Subjects with Ceftazidime-non-susceptible Pathogens	11/14 (78.6)	10/18 (55.6)
Resistant Pathogen Study (D4280C00006)	Subjects with Ceftazidime-non-susceptible Pathogens	19/21 (90.5)	18/23 (78.3)
Pooled Phase 2 and Resistant Pathogen Study	Subjects with Ceftazidime-non-susceptible Pathogens	30/35 (85.7)	28/41 (68.3)

Abbreviations: TOC = Test of Cure; mMITT = microbiological Modified-Intent-to-Treat; cUTI = complicated Urinary Tract Infections
Source: Module 2.7.3 - cUTI Appendix 2 Tables 2.1.5, 2.1.8 and 6.2.2.2.1

ME (Microbiological Evaluable): All subjects:

- Had confirmed diagnoses, including evidence of UTI and a positive admission urine culture defined as > 10^5 CFU/mL (10^4 CFU/mL if bacteremic) of an identified uropathogen.
- Had received a proper total duration of antimicrobial therapy of at least 7 days if therapy (IV alone or a combination of IV and oral therapy) or were classified as evaluable microbiological failures after completing at least 48 hours of IV study drug therapy
- Did not have major protocol violations that would affect assessment of efficacy.
- Each had a clinical and microbiological assessment at TOC, including a quantitative urine culture
- Each did not receive concomitant antibiotic therapy with a non-study drug antibiotic to which the uropathogen was susceptible between the time of admission culture and the TOC culture
- Each did not have the admission urine culture obtained > 48 hours prior to the start of study therapy
- Each had ≥ 1 baseline pathogen susceptible to the IV study antimicrobial

The microbiological outcome categories for the cUTI study are shown in Table 119.

Table 119. Microbiological Outcome Category Definitions - Study NXL104/2001

Outcome	*Definition*
At end of IV therapy and at TOC	
Eradication	A urine culture taken ≤ 48 hours prior to or after the last dose of study therapy (end of IV therapy) or within the 5 to 9 days post-therapy window (for TOC) showed that a uropathogen found at entry at ≥ 10^5 CFU/mL was reduced to < 10^4 CFU/mL, and pathogen is not present in the blood
Persistence	A urine culture taken any time after ≥ 48 hours of therapy grew ≥ 10^4 CFU/mL of an original uropathogen
Persistence with acquisition of resistance	A urine culture, taken after at least 2 full days of therapy, grew ≥ 10^4 CFU/mL of an original uropathogen species that was susceptible, moderately susceptible, or intermediately susceptible to study drug and that then had documented resistance to any study drug
Indeterminate	No urine culture was obtained at the end of IV therapy visit (or the TOC visit, as appropriate for endpoint), or culture results could not be interpreted for any reason
At LFU	
Sustained eradication	A urine culture obtained within the 4- to 6-week post-therapy window showed that the uropathogen found at entry at ≥ 10^5 CFU/mL remained < 10^4 CFU/m
Recurrence	A urine culture obtained any time after documented eradication at TOC up to and including LFU, grew ≥ 10^4 CFU/mL of an original uropathogen
Recurrence with acquisition of resistance	A urine culture obtained any time after documented eradication at TOC, up to and including LFU, grew ≥10^4 CFU/mL of an original uropathogen, which then had documented resistance to the study drug
Indeterminate	No LFU urine culture was obtained or culture results could not be interpreted for any reason

Abbreviations: IV = intravenous; LFU = Late Follow-up; TOC = Test-of-Cure.

Urine cultures were obtained at entry, at day 3 to 5 during therapy, at the end of therapy, at TOC, at LFU, and as clinically indicated. Culture results were tabulated according to organism, microbiologic outcome, and antibiotic susceptibility patterns. At each time point, a microbiological outcome was assessed separately for each pathogen identified in the urine culture. Organisms identified from blood at study entry were assigned microbiological outcomes like those given for urine cultures except that quantitation did not apply. For a favorable microbiological outcome, pathogens isolated at admission to the study at > 10^5 CFU/mL must, at follow-up, have met the CFU criteria for eradication from urine and must not be present in blood. If more than one causative pathogen was isolated from the pre-treatment culture(s) and the microbiological outcome was not the same for all pathogens, the subject was classified as an unfavorable outcome if the outcome of ≥ 1 pathogen was in this category. Pathogens first appearing after baseline were categorized as either superinfections or new infections.

Microbiology and Laboratory Testing

Quantitative urine cultures were performed at the local laboratory within 48 hours before enrollment. The urine samples collected were midstream, clean catch or catheterized urine samples, and subjects were required to have pyuria (≥ 10 WBC per HPF on standard examination of urine sediment or ≥ 10 WBC/mm3 in unspun urine) and positive urine culture (≥ 10^5 CFU/mL of a recognized uropathogen presumed or known to be susceptible to the parenteral study antibiotics). Patients could have been enrolled before urine culture

results were available if it was likely (based on urinalysis and clinical findings) for them to be positive and a urine Gram stain demonstrated Gram-negative bacilli before study entry. If the admission urine culture did not contain a recognized uropathogen in any amount, the subject was withdrawn from study. All specimens were cultured, and Gram staining, organism identification, and initial antimicrobial susceptibility testing were conducted at the local laboratory, as appropriate. Isolates from all local laboratories were shipped to the central laboratory ((b) (4)) for identification confirmation and susceptibility testing. Antimicrobial susceptibility testing was conducted using the Clinical and Laboratory Standards Institute (CLSI) reference broth microdilution method. Disk diffusion results are not available due to the fact that the disks that were being tested at the time of the study did not contain the 30/20 µg ceftazidime-avibactam concentrations now being developed for the commercial disks.

According to the Applicant, all ceftazidime-non-susceptible Gram-negative organisms were characterized using molecular methods to identify specific β-lactamase resistance mechanisms (Clinical Study Report NXL104/2001 Addendum; Study CAZ104-M2-007-11-AZ-01). *Enterobacteriaceae* isolates displaying ceftriaxone and/or ceftazidime MIC values ≥ 2 mg/L were screened for plasmid AmpC and extended spectrum β-lactamases (ESBL)-encoding genes (PCR and sequencing). Non-fermentative Gram-negative organisms (*Pseudomonas* spp. and *Acinetobacter* spp.) with ceftazidime MIC values ≥ 16 mg/L were screened for ESBL genes. *Enterobacteriaceae* and non-fermentative isolates exhibiting imipenem MIC values ≥ 2 mg/L and ≥ 16 mg/L, respectively, were screened for carbapenemase-encoding genes.

Isolates that were identified as persisters were further analyzed by pulsed-field gel electrophoresis (PFGE) to assess clonal relatedness within isolates recovered from the same subjects. Gel pattern analysis was performed using the GelCompar II software and percent similarities were identified on a dendrogram derived from the unweighted pair group method using arithmetic averages and based on Dice coefficients (CAZ104-M2-007-11-AZ-01**)**. Isolates with percent similarities ≥ 80% were assigned to the same PFGE type, which was defined by a capital letter and according to the bacterial species (e.g. EC-A for *E. coli*). Strains collected from the same patient with percent similarities ≥ 95% were assigned as belonging to the subtype, by applying an alphanumeric order (e.g. EC-A1). Subjects for whom no valid pathogen was isolated from samples were excluded from the mMITT, ME and CE Populations.

cUTI Efficacy Results

Table 120 depicts the microbiological and clinical response rates for ceftazidime-avibactam and imipenem-treated subjects in the mMITT and ME populations. In the ME Population the favorable microbiological response at TOC was 70.4% (19/27) for ceftazidime-avibactam treated subjects versus 71.4% (25/35) for subjects treated with imipenem (treatment difference, -1.1%; 95% CI -24.3 to 21.2%). Among the subjects in the ME Population with ceftazidime-non-susceptible pathogens the favorable microbiological response rate was 75% (6/8) for ceftazidime-avibactam treated subjects compared with 75% (9/12) for imipenem-treated subjects. It is unclear why a low microbiological response was observed. It may be that the low treatment dose selected may not have been adequate. Clinical response rates in the ME population were 85.2% for ceftazidime-avibactam versus 80.0% for imipenem-treated subjects.

Table 120. Summary of Clinical and Microbiological Response of Ceftazidime-avibactam and Imipenem-Cilastatin in Patients with Complicated Urinary Tract Infections in cUTI Study NXL104/2001

Population	*Ceftazidime-avibactam n/N (%)*	*Imipenem-Cilastatin n/N (%)*	*Difference*[a]	95% CI[b]
Favorable[c] Microbiological Response at Test of Cure Visit for All Subjects (ME and mMITT Populations)				
ME	19/27 (70.4)	25/35 (71.4)	-1.1	-24.3, 21.2
mMITT	31/46 (67.4)	31/49 (63.3)	4.1	-15.1, 22.9
Favorable[c] Microbiological Response at Test of Cure Visit for Subjects with Ceftazidime-non-susceptible Pathogens (ME and mMITT Populations)				
ME	6/8 (75.0)	9/12 (75.0)	0.0	-40.9, 36.7
mMITT	9/14 (64.3)	10/18 (55.6)	8.7	-25.4, 40.2
Favorable Clinical Response at Test of Cure Visit (ME and mMITT Populations)				
ME	23/27 (85.2)	28/35 (80.0)	5.2	-15.6, 24.2
mMITT	37/46 (80.4)	36/49 (73.5)	7.0	-10.4, 23.9

a Difference = % cures in the ceftazidime-avibactam group minus % cures in the meropenem group
b 95% Confidence interval for the difference between treatment groups using the Miettenen-Nurminen method
c Favorable responses included eradication and presumed eradication
Abbreviations: ME = Microbiologically Evaluable Population, mMITT = microbiological Modified Intent-to-Treat
cUTI = complicated urinary tract infections
Source: Module 2.7.3 - cUTI Appendix 2 Tables 2.0.3, 2.1.1b, 2.0.6, 2.0.4, 2.1.7 and 2.1.5

Table 121 shows the microbiological response rates at TOC visits by baseline pathogen from the ME and mMITT populations. *E. coli* was the most common uropathogen identified among subjects from both treatment groups. Among the *E. coli* isolates from subjects in the mMITT Population, the favorable microbiological outcomes at TOC were 72.1% for ceftazidime-avibactam and 61.9% for subjects treated with imipenem. Also in the imipenem arm, one patient had *Morganella morganii* (Imipenem MIC = 2 mg/L) that was eradicated. For subjects in the ME Population the microbiological response rates for ceftazidime-avibactam and imipenem against *E. coli* were 76.0% and 69.7%, respectively. Among the non-*Enterobacteriaceae* there were three isolates of *P. aeruginosa* from ceftazidime-avibactam treated subjects and two isolates from imipenem treated subjects in the mMITT all with unfavorable microbiological outcomes.

Table 121. By-Pathogen Favorable Microbiological Outcome at TOC (mMITT and ME Populations)

Baseline Pathogen	*By-Pathogen Favorable Microbiological Outcome at TOC (mMITT Population)*		*By-Pathogen Favorable Microbiological Outcome at TOC (ME Population)*	
	Ceftazidime-avibactam (N=46) n/N (%)	*Imipenem-Cilastatin (N=49) n/N (%)*	*Ceftazidime-avibactam (N=27) n/N (%)*	*Imipenem-Cilastatin (N=35) n/N (%)*
Gram negative aerobes	31/46 (67.4)	31/49 (63.3)	19/27 (70.4)	25/35 (71.4)
[a]Ceftazidime-susceptible	22/32 (68.8)	21/31 (67.7)	13/19 (68.4)	16/23 (69.6)
[a]Ceftazidime-intermediate	0/2 (0.0)	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)
[a]Ceftazidime-resistant	9/12 (75.0)	10/17 (58.8)	6/7 (85.7)	9/11 (81.8)
Enterobacteriaceae	31/43 (72.1)	31/47 (66.0)	19/25 (76.0)	25/35 (71.4)
Citrobacter koseri	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)
Enterobacter aerogenes	0/0 (0.0)	1/1 (100.0)		
Enterobacter cloacae	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)
Escherichia coli	31/43 (72.1)	26/42 (61.9)	19/25 (76.0)	23/33 (69.7)
Klebsiella oxytoca	0/0 (0.0)	1/1 (100.0)		
Morganella morganii	0/0 (0.0)	1/1 (100.0)		
Proteus mirabilis	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)
Non *Enterobacteriaceae*	0/3 (0.0)	0/2 (0.0)	0/2 (0.0)	0/0 (0.0)
Pseudomonas aeruginosa	0/3 (0.0)	0/2 (0.0)	0/2 (0.0)	0/0 (0.0)

a Interpretive criteria for ceftazidime were determined according to CLSI document M-100 S-20 (CLSI, 2010)
Source: Module 2.7.3 - cUTI Appendix 2 Tables 2.2.4, 2.2.5., 2.7.0.1 and 2.7.0.2

The microbiological response rates for ceftazidime-avibactam and imipenem against ceftazidime-non-susceptible baseline pathogens are shown in Table 122. Response rates were similar for both agents against ceftazidime-non-susceptible organisms in the ME population but were higher for ceftazidime-avibactam versus imipenem for subjects in the ME population.

Table 122. By Pathogen Favorable Microbiological Response at Test of Cure for Ceftazidime-non-susceptible Pathogens in cUTI Study NXL104/2001 (mMITT and ME Populations)

Baseline Pathogen	*By-Pathogen Favorable Microbiological Outcome at TOC (mMITT Population)*		*By-Pathogen Favorable Microbiological Outcome at TOC (ME Population)*	
	Ceftazidime-avibactam n/N (%)	*Imipenem-Cilastatin n/N (%)*	*Ceftazidime-avibactam n/N (%)*	*Imipenem-Cilastatin n/N (%)*
Gram negative aerobes	9/14 (64.3)	10/17 (58.8)	6/8 (75.0)	9/12 (75.0)
Enterobacteriaceae	9/14 (64.3)	10/17 (58.8)	6/8 (75.0)	9/12 (75.0)
Enterobacter cloacae	0/0 (0.0)	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)
Escherichia coli	9/14 (64.3)	9/16 (56.3)	6/8 (75.0)	8/11 (72.7)

Source: Module 2.7.3 - cUTI Appendix 2 Tables 2.2.6 and 2.2.7.

In Vitro Susceptibility of Baseline Isolates

Table 122 shows the MIC of all baseline pathogens in the cUTi study. All *Enterobacteriaceae* from the ceftazidime-avibactam treatment group demonstrated MIC values that ranged from ≤ 0.03 to 0.25 mg/L and an MIC90 of 0.25 mg/L. Among the three baseline isolates of *P. aeruginosa* the MIC values for ceftazidime-avibactam ranged from 2 to 4 mg/L. All the *Enterobacteriaceae* from the imipenem-treated subjects were susceptible to imipenem with MIC values that ranged from 0.06 to 2 mg/L and an MIC90 of 0.25 mg/L. There were two isolates of *P. aeruginosa* that were inhibited by imipenem at concentrations of 0.5 and 16 mg/L.

Table 122. Minimum Inhibitory Concentration (MIC) of the Study Drug Received by Baseline Pathogen - Uropathogens from Urine and Blood Combined (mMITT Population)

Organism[a]	*N*	*Ceftazidime-avibactam MIC (mg/L)*			*N*	*Imipenem MIC (mg/L)*		
		Range	*50%*	*90%*		*Range*	*50%*	*90%*
All *Enterobacteriaceae*	44	≤ 0.03 - 0.25	0.12	0.25	49	0.06 - 2	0.12	0.25
Escherichia coli	43	≤ 0.03 - 0.25	0.06	0.25	44	0.06 - 0.25	0.12	0.12
Klebsiella oxytoca					1	0.12		
Proteus mirabilis					1	0.25		
Citrobacter koseri	1	0.06						
Enterobacter aerogenes					1	0.25		
Enterobacter cloacae					1	0.25		
Morganella morganii					1	2		
Non-*Enterobacteriaceae*								
All Non-*Enterobacteriaceae*	3	2 - 4			2	0.5 - 16		
Pseudomonas aeruginosa	3	2 - 4			2	0.5 - 16		

a Subjects are counted if they have at least one pathogen of a given type. For subjects with more than one isolate of the same type, the isolate with the highest MIC is selected as the representative MIC for the subject. For subjects with a uropathogen that is also isolates from blood, the highest MIC is shown. Abbreviations: MIC = minimum inhibitory concentration.

In vitro susceptibility testing results of all baseline isolates and microbiological responses from ceftazidime-

avibactam treated subjects are shown Table 123. Table 124 shows the in vitro susceptibility results for ceftazidime-nonsusceptible baseline pathogens. Additionally, all ceftazidime-nonsusceptible baseline pathogens were characterized using molecular methods to identify specific β-lactamase resistance mechanisms. The ceftazidime-non-susceptible organisms were all *E. coli* and CTX-M-15 was the most prevalent β-lactamase followed closely by OXA-30 (OXA-1/30) and TEM-1; all were found to have multiple β-lactamase enzymes via PCR.

Table 123. In Vitro Susceptibility of Baseline Isolates from cUTI Study NXL104/2001 (All Isolates from Ceftazidime-avibactam-treated Subjects)

Patient ID	Country	Baseline Pathogen	Source	Ceftazidime MIC (mg/L) at Baseline	Ceftazidime-avibactam MIC (mg/L) at Baseline	Imipenem MIC (mg/L) at Baseline	ME	mMITT	Microbiological Response at TOC	Microbiological Outcome at TOC	β-Lactamase Enzyme(s)
11203	USA	*Escherichia coli*	Urine	32	0.12	0.12	N	Y	Indeterminate		CMY-2,TEM-1
11301	USA	*Escherichia coli*	Urine	0.12	0.06	0.12	N	Y	Eradication	Favorable MB outcome	
11302	USA	*Escherichia coli*	Urine	0.06	≤ 0.03	0.12	N	Y	Indeterminate		
11303	USA	*Escherichia coli*	Urine	0.12	0.06	0.12	N	Y	Indeterminate		
13802	USA	*Escherichia coli*	Urine	1	0.25	0.12	N	Y	Eradication	Favorable MB outcome	CTX-M-15,OXA-30,TEM-1
13803	USA	*Escherichia coli*	Urine	0.12	0.06	0.12	Y	Y	Eradication	Favorable MB outcome	
20203	LEBANON	*Escherichia coli*	Urine	2	0.12	0.12	Y	Y	Eradication	Favorable MB outcome	CTX-M-15,OXA-30
20209	LEBANON	*Escherichia coli*	Urine	16	0.12	0.12	Y	Y	Eradication	Favorable MB outcome	CTX-M-15,TEM-1
20210	LEBANON	*Escherichia coli*	Urine	0.12	0.12	0.12	Y	Y	Eradication	Favorable MB outcome	
20213	LEBANON	*Escherichia coli*	Urine	0.25	0.12	0.25	Y	Y	Persistence	MB Failure	
20306	LEBANON	*Escherichia coli*	Urine	0.06	0.06	0.12	Y	Y	Eradication	Favorable MB outcome	
20308	LEBANON	*Escherichia coli*	Urine	0.12	0.06	0.06	Y	Y	Eradication	Favorable MB outcome	
20312	LEBANON	*Escherichia coli*	Urine	0.12	0.06	0.25	Y	Y	Eradication	Favorable MB outcome	
20313	LEBANON	*Escherichia coli*	Urine	0.06	≤ 0.03	0.12	Y	Y	Persistence	MB Failure	
20407	LEBANON	*Escherichia coli*	Blood	0.12	0.06	0.12	Y	Y	Indeterminate		
20407	LEBANON	*Escherichia coli*	Urine	0.12	≤ 0.03	0.06	Y	Y	Persistence	MB Failure	
20408	LEBANON	*Pseudomonas aeruginosa*	Urine	2	2	1	N	Y	Indeterminate		
20412	LEBANON	*Escherichia coli*	Urine	16	0.12	0.12	Y	Y	Eradication	Favorable MB outcome	CTX-M-15,TEM-1
20413	LEBANON	*Citrobacter koseri*	Urine	0.12	0.06	0.06	Y	Y	Eradication	Favorable MB outcome	
20413	LEBANON	*Escherichia coli*	Urine	0.06	≤ 0.03	0.06	Y	Y	Eradication	Favorable MB outcome	
20415	LEBANON	*Escherichia coli*	Urine	> 32	0.25	0.06	Y	Y	Eradication	Favorable MB outcome	CTX-M-15,OXA-30
20602	LEBANON	*Escherichia coli*	Blood	0.12	0.06	0.12	Y	Y	Indeterminate		
20602	LEBANON	*Escherichia coli*	Urine	0.06	≤ 0.03	0.12	Y	Y	Eradication	Favorable MB outcome	
20603	LEBANON	*Escherichia coli*	Urine	8	0.12	0.06	N	Y	Indeterminate		TEM-1,upreg ampC
30106	JORDAN	*Pseudomonas aeruginosa*	Urine	4	4	0.5	Y	Y	Persistence	MB Failure	
30107	JORDAN	*Escherichia coli*	Urine	> 32	0.25	0.12	Y	Y	Eradication	Favorable MB outcome	CTX-M-15,OXA-30,TEM-1
30108	JORDAN	*Escherichia coli*	Urine	8	0.12	0.12	Y	Y	Persistence	MB Failure	CTX-M-15,OXA-30
30202	JORDAN	*Escherichia coli*	Urine	1	0.12	0.12	Y	Y	Persistence	MB Failure	CTX-M-14,TEM-1
30203	JORDAN	*Escherichia coli*	Urine	32	0.12	0.12	Y	Y	Persistence	MB Failure	CTX-M-15,TEM-1
30204	JORDAN	*Escherichia coli*	Urine	32	0.12	0.06	Y	Y	Eradication	Favorable MB outcome	CTX-M-15,OXA-30,TEM-1
30210	JORDAN	*Escherichia coli*	Urine	32	0.06	0.06	N	Y	Persistence	MB Failure	CMY-2,CTX-M-15,OXA-30
30212	JORDAN	*Escherichia coli*	Urine	0.12	0.06	0.06	N	Y	Eradication	Favorable MB outcome	
30215	JORDAN	*Escherichia coli*	Urine	32	0.12	0.12	N	Y	Eradication	Favorable MB outcome	CTX-M-15,OXA-30
30216	JORDAN	*Escherichia coli*	Urine	2	0.25	0.12	Y	Y	Eradication	Favorable MB outcome	CTX-M-14
40001	GUATEMALA	*Escherichia coli*	Urine	0.5	0.12	0.06	N	Y	Persistence	MB Failure	
40004	GUATEMALA	*Escherichia coli*	Urine	0.12	0.06	0.12	N	Y	Eradication	Favorable MB outcome	
40005	GUATEMALA	*Escherichia coli*	Urine	0.25	0.12	0.12	N	Y	Eradication	Favorable MB outcome	

Patient ID	Country	Baseline Pathogen	Source	Ceftazidime MIC (mg/L) at Baseline	Ceftazidime-avibactam MIC (mg/L) at Baseline	Imipenem MIC (mg/L) at Baseline	ME	mMITT	Microbiological Response at TOC	Microbiological Outcome at TOC	β-Lactamase Enzyme(s)
40006	GUATEMALA	*Escherichia coli*	Urine	0.25	≤ 0.03	≤ 0.03	N	Y	Eradication	Favorable MB outcome	
40011	GUATEMALA	*Escherichia coli*	Urine	0.12	0.06	0.12	N	Y	Eradication	Favorable MB outcome	
40012	GUATEMALA	*Escherichia coli*	Urine	16	0.06	0.06	N	Y	Eradication	Favorable MB outcome	SHV-12,TEM-1
40028	GUATEMALA	*Escherichia coli*	Urine	0.12	0.06	0.12	Y	Y	Eradication	Favorable MB outcome	
40103	GUATEMALA	*Escherichia coli*	Urine	0.12	≤ 0.03	0.06	Y	Y	Eradication	Favorable MB outcome	
40112	GUATEMALA	*Escherichia coli*	Urine	0.12	0.12	0.12	Y	Y	Eradication	Favorable MB outcome	
40115	GUATEMALA	*Escherichia coli*	Urine	0.12	0.06	0.12	Y	Y	Eradication	Favorable MB outcome	
50105	INDIA	*Escherichia coli*	Urine	0.12	0.12	0.12	Y	Y			
50105	INDIA	*Pseudomonas aeruginosa*	Urine	4	4	1	Y	Y	Persistence	MB Failure	
50207	INDIA	*Escherichia coli*	Urine	32	0.25	0.12	Y	Y	Eradication	Favorable MB outcome	CTX-M-15,OXA-30
50701	INDIA	*Escherichia coli*	Urine	> 32	0.25	0.12	N	Y	Eradication	Favorable MB outcome	CTX-M-15,OXA-30,TEM-1,upreg ampC

Abbreviations: mMITT = microbiological Modified Intent-to-Treat; ME = Microbiologically Evaluable; MIC = Minimum Inhibitory Concentration
Source: Module 5: Integrated Summary of Microbiology (Microbiology Database)

Table 124. *In Vitro* Susceptibility of Ceftazidime-non-susceptible β-Lactamase-producing Gram-negative Pathogens from cUTI Study NXL104/2001 and Microbiological Responses for Subjects Treated with Ceftazidime-avibactam

Patient ID	*Country*	*Baseline Pathogen*	*Source*	*Ceftazidime Phenotype*	*MIC (mg/L) at Baseline*			*Population*		*Microbiological Response at TOC*	*Microbiological Outcome at TOC*	*Baseline β-lactamase Enzymes*
					Ceftazidime	*Ceftazidime-avibactam*	*Imipenem*	*ME*	*mMITT*			
11203	USA	*Escherichia coli*	Urine	Resistant	32	0.12	0.12	N	Y	Indeterminate		CMY-2,TEM-1
20209	LEBANON	*Escherichia coli*	Urine	Resistant	16	0.12	0.12	Y	Y	Eradication	Favorable MB outcome	CTX-M-15,TEM-1
20412	LEBANON	*Escherichia coli*	Urine	Resistant	16	0.12	0.12	Y	Y	Eradication	Favorable MB outcome	CTX-M-15,TEM-1
20415	LEBANON	*Escherichia coli*	Urine	Resistant	> 32	0.25	0.06	Y	Y	Eradication	Favorable MB outcome	CTX-M-15,OXA-30
20603	LEBANON	*Escherichia coli*	Urine	Intermediate	8	0.12	0.06	N	Y	Indeterminate		TEM-1,upreg ampC
30107	JORDAN	*Escherichia coli*	Urine	Resistant	> 32	0.25	0.12	Y	Y	Eradication	Favorable MB outcome	CTX-M-15,OXA-30,TEM-1
30108	JORDAN	*Escherichia coli*	Urine	Intermediate	8	0.12	0.12	Y	Y	Persistence	MB Failure	CTX-M-15,OXA-30
30203	JORDAN	*Escherichia coli*	Urine	Resistant	32	0.12	0.12	Y	Y	Persistence	MB Failure	CTX-M-15,TEM-1
30204	JORDAN	*Escherichia coli*	Urine	Resistant	32	0.12	0.06	Y	Y	Eradication	Favorable MB outcome	CTX-M-15,OXA-30,TEM-1
30210	JORDAN	*Escherichia coli*	Urine	Resistant	32	0.06	0.06	N	Y	Persistence	MB Failure	CMY-2,CTX-M-15,OXA-30
30215	JORDAN	*Escherichia coli*	Urine	Resistant	32	0.12	0.12	N	Y	Eradication	Favorable MB outcome	CTX-M-15,OXA-30
40012	GUATEMALA	*Escherichia coli*	Urine	Resistant	16	0.06	0.06	N	Y	Eradication	Favorable MB outcome	SHV-12,TEM-1
50207	INDIA	*Escherichia coli*	Urine	Resistant	32	0.25	0.12	Y	Y	Eradication	Favorable MB outcome	CTX-M-15,OXA-30
50701	INDIA	*Escherichia coli*	Urine	Resistant	> 32	0.25	0.12	N	Y	Eradication	Favorable MB outcome	CTX-M-15,OXA-30,TEM-1,upreg ampC

Ceftazidime-avibactam susceptibility test results of isolates identified as persistent at either the TOC or LFU visits are shown in Table 125. The results show that two patients from Jordan (Patient ID 20313, 20407) and one patient from Lebanon (Patient ID 30106) exhibited a 4-fold difference in MIC between test conducted at baseline, TOC and LFU. Pulsed-field gel electrophoresis (PFGE) was performed on persisting isolates at the TOC and LFU visits to assess clonal relatedness of isolate recovered from the same patient. Data indicated that except for one patient (ID 20301-described above), all isolates at the TOC and LFU visits from the same patient were clonally related. One subject (ID # 20313) yielded an isolate of *E. coli* with a different PFGE type at TOC where the MIC values for ceftazidime-avibactam ranged from ≤ 0.03 mg/L for the baseline pathogen to 0.12 mg/L for the organism recovered at TOC. It is likely that the baseline pathogen (EC-Y) was eradicated;

however, a new pathogen (EC-Z) was identified at TOC.

Table 125. Listing of Persisting Pathogens Associated with Unfavorable Outcomes from Ceftazidime-avibactam-treated Subjects and their Susceptibility to Ceftazidime-avibactam in cUTI Study NXL104/2001

Patient ID	*Country*	*Pathogen*	*Source*	*Microbiological Response*		*Microbiological Outcome*		*CAZ-AVI MIC (mg/L)*			*PFGE*			*Population*	
				TOC	*LFU*	*TOC*	*LFU*	*Baseline*	*TOC*	*LFU*	*Baseline*	*TOC*	*LFU*	*ME*	*MMITT*
20213	LEBANON	*Escherichia coli*	Urine	Persistence	Persistence	MB Failure	MB Failure	0.12	0.12	0.12	EC-X	EC-X	EC-X	Y	Y
20313	LEBANON	*Escherichia coli*	Urine	Persistence	Persistence	MB Failure	MB Failure	≤ 0.03	0.12	0.06	EC-Y	EC-Z		Y	Y
20407	LEBANON	*Escherichia coli*	Urine	Persistence	Persistence	MB Failure	MB Failure	≤ 0.03	0.12	0.12				Y	Y
30106	JORDAN	*Pseudomonas aeruginosa*	Urine	Persistence	Persistence	MB Failure	MB Failure	4	2	8	PSA-D		PSA-D	Y	Y
30108	JORDAN	*Escherichia coli*	Urine	Persistence	Persistence	MB Failure	MB Failure	0.12	0.12		EC-R	EC-S		Y	Y
30202	JORDAN	*Escherichia coli*	Urine	Persistence	Persistence	MB Failure	MB Failure	0.12	0.12		EC-E	EC-E		Y	Y
30203	JORDAN	*Escherichia coli*	Urine	Persistence	Persistence	MB Failure	MB Failure	0.12	0.25	0.12	EC-G	EC-G	EC-G	Y	Y
30210	JORDAN	*Escherichia coli*	Urine	Persistence	Persistence	MB Failure	MB Failure	0.06	0.06	0.12	EC-W	EC-W	EC-W	N	Y
40001	GUATEMALA	*Escherichia coli*	Urine	Persistence	Persistence	MB Failure	MB Failure	0.12	0.12	0.12	EC-A	EC-A	EC-A	N	Y
50105	INDIA	*Pseudomonas aeruginosa*	Urine	Persistence	Persistence	MB Failure	MB Failure	4	4	4	PSA-B	PSA-B		Y	Y

Abbreviations: mMITT = microbiological Modified Intent-to-Treat; ME = Microbiologically Evaluable; MIC = Minimum Inhibitory Concentration; PFGE = Pulsed Field Gel Electrophoresis, MB = Microbiological

Source: Module 5: Integrated Summary of Microbiology (Microbiology Database)

Correlation of Microbiological Response with In Vitro Susceptibility Results

Table 126 shows the microbiological responses for ceftazidime-avibactam and imipenem in relation to MIC against all *Enterobacteriaceae* in the mMITT and ME populations in the cUTI study. The MIC values ranged from ≤ 0.03 to 0.25 mg/L with failures observed. Among the 35 isolates of *Enterobacteriaceae* from the imipenem group, the MIC values for imipenem ranged from 0.06 to 0.25 mg/L and failures were not observed.

Table 126. Favorable Microbiological Responses for Ceftazidime-avibactam and Imipenem-Cilastatin Against All *Enterobacteriaceae* from cUTI Study NXL104/2001

	mMITT Population	*ME Population*
	Favorable Microbiological Response to Study Drug Received at TOC n/N (%)	*Favorable Microbiological Response to Study Drug Received at TOC n/N (%)*
Ceftazidime-avibactam MIC (mg/L)		
≤ 0.03	4/6 (66.7)	2/2 (100.0)
0.06	12/14 (85.7)	7/9 (77.8)
0.12	8/15 (53.3)	6/10 (60.0)
0.25	6/6 (100.0)	4/4 (100.0)
Imipenem MIC (mg/L)		
0.06	7/11 (63.6)	6/8 (75.0)
0.12	20/29 (69.0)	16/24 (66.7)
0.25	3/5 (60.0)	2/3 (66.7)
2	1/1 (100.0)	

Abbreviations: cUTI = complicated Urinary Tract Infections; mMITT = microbiological Modified-Intent-to-Treat; ME = Microbiologically Evaluable; TOC = Test-of-Cure

Table 127 shows the microbiological response rate for ceftazidime-avibactam and imipenem against *Enterobacteriaceae* isolates that were ceftazidime-non-susceptible. There were 5 isolates with ceftazidime-avibactam MIC values of 0.12 mg/L that were associated with a 60% success rate (3/5). However, there were 3 ceftazidime-non-susceptible isolates with ceftazidime-avibactam MIC values of 0.25 mg/L in the ME

population and all isolates were associated with successful microbiological outcomes.

Table 127. Favorable Microbiological Responses for Ceftazidime-avibactam and Imipenem-Cilastatin Against All Ceftazidime-non-susceptible *Enterobacteriaceae* from cUTI Study NXL104/2001

	mMITT Population	*ME Population*
	Favorable Microbiological Response to Study Drug Received at TOC n/N (%)	*Favorable Microbiological Response to Study Drug Received at TOC n/N (%)*
Ceftazidime-avibactam MIC (mg/L)		
0.06	1/2 (50.0)	
0.12	4/8 (50.0)	3/5 (60.0)
0.25	4/4 (100.0)	3/3 (100.0)
Imipenem MIC (mg/L)		
0.06	2/2 (100.0)	2/2 (100.0)
0.12	7/13 (53.8)	6/9 (66.7)
0.25	1/2 (50.0)	1/1 (100.0)

Abbreviations: cUTI = complicated Urinary Tract Infections; mMITT = microbiological Modified-Intent-to-Treat; ME = Microbiologically Evaluable; TOC = Test-of-Cure

Microbiological responses for ceftazidime-avibactam and *E. coli* and *Citrobacter koseri* individual pathogens at TOC are shown in Table 128. Relatively low efficacy rates were observed at MIC ranges of ≤ 0.03-0.12 mg/L. However at 0.25 mg/L, a 100% (4/4) cure rate was reported.

Table 128. Favorable Microbiological Response by MIC for Ceftazidime-avibactam against Enteric Gram-negative Bacilli from Complicated Urinary Tract Infections in cUTI Study NXL104/2001

Ceftazidime-avibactam MIC (mg/L)	*mMITT Population*	*ME Population*
	Favorable Microbiological Response at TOC n/N (%)	*Favorable Microbiological Response at TOC n/N (%)*
Citrobacter koseri		
0.06	1/1 (100.0)	1/1 (100.0)
Escherichia coli		
≤ 0.03	4/7 (57.1)	2/3 (66.7)
0.06	11/13 (84.6)	6/8 (75.0)
0.12	8/15 (53.3)	6/10 (60.0)
0.25	6/6 (100.0)	4/4 (100.0)

Abbreviations: cUTI = complicated Urinary Tract Infections; mMITT = microbiological Modified-Intent-to-Treat; ME = Microbiologically Evaluable; TOC = Test-of-Cure

Source: Tables 2.5.1.1 and 2.5.1.2

Table 129 shows the microbiological response for Imipenem against individual enteric pathogens. Lower efficacy rates for *E. coli* were observed at MIC ranging from 0.06-0.12 mg/L and one failure was observed at 0.25 mg/L.

Table 129. Favorable Microbiological Response by MIC for Imipenem against Enteric Gram-negative Bacilli from Complicated Urinary Tract Infections in cUTI Study NXL104/2001

Imipenem MIC (mg/L)	*mMITT Population*	*ME Population*
	Favorable Microbiological Response at TOC n/N (%)	*Favorable Microbiological Response at TOC n/N (%)*
Enterobacter aerogenes		
0.25	1/1 (100.0)	
Enterobacter cloacae		
0.25	1/1 (100.0)	1/1 (100.0)
Escherichia coli		
0.06	7/11 (63.6)	6/8 (75.0)
0.12	19/28 (67.9)	16/24 (66.7)
0.25	0/2 (0.0)	0/1 (0.0)
Klebsiella oxytoca		
0.12	1/1 (100.0)	
Morganella morganii		
2	1/1 (100.0)	
Proteus mirabilis		
0.25	1/1 (100.0)	1/1 (100.0)

Abbreviations: cUTI = complicated Urinary Tract Infections; mMITT = microbiological Modified-Intent-to-Treat; ME = Microbiologically Evaluable; TOC = Test-of-Cure
Source: Tables 2.5.1.1 and 2.5.1.2

Microbiological responses as a function of MIC to the study drug received for ceftazidime-non-susceptible individual enteric Gram-negative pathogens are shown in Table 130 and Table 131.

Table 130. Favorable Microbiological Response by MIC for Ceftazidime-avibactam against Ceftazidime-non-susceptible *Escherichia coli* from Complicated Urinary Tract Infections in cUTI Study NXL104/2001(Isolates from Ceftazidime-avibactam treated subjects)

Ceftazidime-avibactam MIC (mg/L)	*mMITT Population*	*ME Population*
	Favorable Microbiological Response at TOC n/N (%)	*Favorable Microbiological Response at TOC n/N (%)*
***Escherichia coli* Ceftazidime-non-susceptible**		
0.06	1/2 (50.0)	
0.12	4/8 (50.0)	3/5 (60.0)
0.25	4/4 (100.0)	3/3 (100.0)

Abbreviations: cUTI = complicated Urinary Tract Infections; mMITT = microbiological Modified-Intent-to-Treat; ME = Microbiologically Evaluable; TOC = Test-of-Cure
Source :Tables 2.5.1.3 and 2.5.1.4

Table 131. Favorable Microbiological Response by MIC for Imipenem against Ceftazidime-non-susceptible *Enterobacteriaceae* from Complicated Urinary Tract Infections in cUTI Study NXL104/2001(Isolates from Imipenem-Cilastatin treated subjects)

Imipenem MIC (mg/L)	*mMITT Population*	*ME Population*
	Favorable Microbiological Response at TOC n/N (%)	*Favorable Microbiological Response at TOC n/N (%)*
***Enterobacter cloacae* Ceftazidime-non-susceptible**		
0.25	1/1 (100.0)	1/1 (100.0)
***Escherichia coli* Ceftazidime-non-susceptible**		
0.06	2/2 (100.0)	2/2 (100.0)
0.12	7/13 (53.8)	6/9 (66.7)
0.25	0/1 (0.0)	

Abbreviations: cUTI = complicated Urinary Tract Infections; mMITT = microbiological Modified-Intent-to-Treat; ME = Microbiologically Evaluable; TOC = Test-of-Cure
Source : Tables 2.5.1.3 and 2.5.1.4

The microbiological outcomes for ceftazidime-avibactam and imipenem against the limited number of *P. aeruginosa* are shown in Table 132. There were two patients with *P. aeruginosa* isolates (MIC 4 mg/L) and both isolates were reported to have persisted at test of cure. The Applicant stated that the likely cause for a lack of a favorable microbiological response may be a result of the ceftazidime-avibactam dose regimen used in the Phase 2 study (500 mg ceftazidime + 125 mg avibactam infused over 30 minutes.

Table 132. Favorable Microbiological Responses for Ceftazidime-avibactam and Imipenem-Cilastatin Against *Pseudomonas aeruginosa* from cUTI Study NXL104/2001

	mMITT Population	*ME Population*
	Favorable Microbiological Response at TOC n/N (%)	*Favorable Microbiological Response at TOC n/N (%)*
Ceftazidime-avibactam MIC (mg/L)		
2	0/1 (0.0)	
4	0/2 (0.0)	0/2 (0.0)
Imipenem MIC (mg/L)		
0.5	0/1 (0.0)	
16	0/1 (0.0)	

Abbreviations: cUTI = complicated Urinary Tract Infections; mMITT = microbiological Modified-Intent-to-Treat; ME = Microbiologically Evaluable; TOC = Test-of-Cure
Source:Tables 2.5.1.1 and 2.5.1.2

Resistant Pathogen Study (D4280C00006) - Focus on cUTI Subjects

The primary objective of the study is to estimate the per-patient clinical response to ceftazidime-avibactam and Best Available Therapy (BAT) at Test of Cure (TOC) in the treatment of selected serious infections caused by ceftazidime-resistant Gram-negative organisms. Ceftazidime resistance for *Enterobacteriaceae* and *Pseudomonas aeruginosa* is defined as those bacterial isolates whose susceptibility results were intermediate or resistant using Clinical and Laboratory Standards Institute (CLSI) methodology (CLSI M100-S23 2013). The study design for the Resistant Pathogen Study (Clinical Study D4280C00006) is shown in Table 133.

Table 133. CAZ-Resistant Study D4280C00006 Study Design

Screen	*Baseline*	*Study Drug Administration*	*TOC*	*Follow-Up 1*	*Follow-Up 2*
Day -1 to 0	Within 24 hours before first dose of study drug	Day 1 to EOT	7 days after last dose of study drug	cIAI: 28 days from randomization cUTI: 21 days from randomization	cIAI: no additional visit required cUTI: 21 days from randomization
Study eligibility	Confirmation of study eligibility Randomization to treatment and study entry BAT selection	IV study drug therapy for 5 to 21 days On-therapy clinical and laboratory assessments EOT assessments performed within 24 hours after completion of the last infusion of study therapy	Patients return to study center for assessment of efficacy and safety	Patients return to study center for efficacy and safety assessments	Patients return to study center for efficacy and safety assessments

Abbreviations: BAT = best available therapy; cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; EOT = end of therapy; IV = intravenous; LFU = Late Follow-up; TOC = Test-of-Cure.

Microbiology and Laboratory Testing

For an organism to be considered a pathogen on the pre-qualifying culture, it must be a gram-negative organism and be resistant to ceftazidime. Non-fermentative gram-negative organisms other than *P. aeruginosa* (*Acinetobacter* spp., *Stenotrophomonas maltophilia* etc.) were not expected to respond to ceftazidime-avibactam and were not considered for inclusion in this study. Blood cultures were collected for all subjects in both cIAI and cUTI. The following were shipped to the central microbiology laboratory for confirmation and identification:

- From the study-qualifying culture: the ceftazidime-resistant gram-negative uropathogen at ≥ 10^5 CFU/mL
- From the supplementary urine culture: all uropathogens identified regardless of the count
- From follow-up cultures at End of Therapy, Test of Cure and Follow Up visits all uropathogens quantified at ≥ 10^4 CFU/mL

Resistant pathogens Efficacy Results in cUTI

Table 134 shows the microbiological response rates for ceftazidime-avibactam and best available therapy-treated subjects in the mMITT population with cUTI infections caused by ceftazidime-non-susceptible pathogens. The favorable microbiological response rate was higher for ceftazidime-avibactam (68.6%) than all comparators (51.2%)

Table 134. Pooled Phase 2 (Studies 2001, 2002) and Resistant Pathogen Study (D-06) Microbiological Response at the Test of Cure Visit in Subjects with Ceftazidime Non-Susceptible Baseline Pathogens [a]cUTI Subjects mMITT Population

	Study 2001		Study D-06		Pooled 2001 and D-06	
	CAX-AVI (N=14) n (%)	Imipenem Cilastatin (N=18) n(%)	CAX-AVI (N=21) n(%)	Comparator (N=23) n(%)	CAX-AVI (N=35) n(%)	All Comparators (N=41) n(%)
Eradication	9 (64.3)	10 (55.6)	15 (71.4)	11 (47.8)	24 (68.6)	21 (51.2)
Difference (95% CI)	8.7 (-25.4-40.2		23.6 (-5.8-49.2)		17.4 (-5.1-38.0)	
Persistence	3 (21.4)	6 (33.3)	5 (23.8)	12 (52.2)	8 (22.9)	18 (43.9)
Indeterminate	2 (14.3)	2 (11.1)	1 (4.8)	0	3 (8.6)	2 (4.9)

Notes: Study 2001 = Study NXL104/2001 (Phase 2 cUTI); Study D-06 = Study D4280C00006 (Phase 3 Resistant Pathogen Study).
[a] Includes ceftazidime resistant (CAZ-R) (Study D-06) and ceftazidime nonsusceptible (CAZ-NS = CAZ-R or ceftazidime intermediate [CAZ-I], Study 2001) baseline pathogens. Susceptibility designations determined according to CLSI, 2013.
n=Number of subjects in specific category.
N=Number of subjects in mMITT (Microbiologically modified Intent to Treat) Population.
Percentages are calculated 100 x (n/N), percentage of subjects in the mMITT Population.
In Study 2001, the notation mITT was used to denote the microbiologically modified ITT Population or mMITT.

Table 135 shows the microbiological responses for ceftazidime-non-susceptible baseline pathogens in the mMITT population. *Enterobacteriaceae* response rates of 70.0% and 47.8% were reported for ceftazidime-avibactam and comparator, respectively. Ceftazidime-avibactam response rates of 75% and 80% were reported against *E. coli* and *K. pneumoniae*, respectively.

Table 135. Favorable Microbiological and Clinical Response by Pathogen at TOC for Ceftazidime-avibactam and Best Available Comparator against Ceftazidime non- susceptible Pathogens from cUTI in the Resistant Pathogen Study

Ceftazidime-non-susceptible	***By-Pathogen Favorable Microbiological Outcome at TOC (mMITT Population)***	
Baseline Pathogen	***Ceftazidime-avibactam (N = 21) n/N (%)***	***Comparator (N = 23) n/N (%)***
Enterobacteriaceae	14/20 (70.0)	11/23 (47.8)
Citrobacter freundii complex	1/1 (100.0)	0 (0.0)
Enterobacter aerogenes	1/1 (100.0)	0 (0.0)
Enterobacter cloacae	1/2 (50.0)	0/0 (0.0)
Escherichia coli	3/4 (75.0)	5/7 (71.4)
Klebsiella oxytoca	0/0 (0.0)	1/2 (50.0)
Klebsiella pneumoniae	8/10 (80.0)	5/14 (35.7)
Proteus mirabilis	0/2 (0.0)	0/0 (0.0)
Gram-negative aerobes other than *Enterobacteriaceae*	1/1 (100.0)	0/0 (0.0)
Pseudomonas aeruginosa	1/1 (100.0)	0/0 (0.0)

Abbreviations: cUTI = complicated Urinary Tract Infections; mMITT = microbiological Modified-Intent-to-Treat; TOC = Test-of-Cure
Source: Module 2.7.3 - cUTI Appendix 2 Tables 6.2.2.2.6 and 6.2.2.2.5

Table 136 shows the in vitro susceptibility data and microbiological outcome for the 21 ceftazidime-avibactam cUTI subjects in the resistant pathogen study. There was one subject (E6102012) where failure was associated with a ceftazidime-avibactam MIC of >256 mg/L. All other failures were associated with low MIC (range 0.06-1 mg/L) at test of cure. Table 137 shows a listing of the microbiological failures at TOC and LFU in the cUTI subjects in the mMITT population in the resistant pathogen study.

Table 136. In Vitro Susceptibility and Microbiological Outcomes for Ceftazidime-avibactam Treated cUTI Subjects with Ceftazidime Nonsusceptible Pathogens in the Resistant Pathogen Study (Clinical Study D4280C00006) - mMITT Population

Unique Subject Identifier	*Country*	*Pathogen Name*	*Sample ID*	*Microbiological Outcome*		*Baseline Ceftazidime MIC (mg/L)*	*Baseline Meropenem MIC (mg/L)*	*CAZ-AVI MIC (mg/L)*		
				TOC	*LFU*			*Baseline*	*TOC*	*LFU*
E0912001	Bulgaria	*Proteus mirabilis*	Urine	Indeterminate	Indeterminate	16 (R)	0.06	1		
E0912002	Bulgaria	*Enterobacter cloacae*	Urine	Eradication	Eradication	> 64 (R)	0.25	0.5		
E0913003	Bulgaria	*Klebsiella pneumoniae*	Urine	Eradication	Eradication	> 64 (R)	0.12	0.5		
E0913004	Bulgaria	*Klebsiella pneumoniae*	Urine	Persistence	Persistence	> 64 (R)	1	1	1	1
E0914003	Bulgaria	*Escherichia coli*	Urine	Eradication	Eradication	16 (R)	0.03	0.12		
E0914006	Bulgaria	*Pseudomonas aeruginosa*	Urine	Eradication	Eradication	> 64 (R)	0.5	8		
E0916001	Bulgaria	*Escherichia coli*	Urine	Eradication	Eradication	8 (I)	0.015	0.03		
E0916004	Bulgaria	*Klebsiella pneumoniae*	Urine	Persistence	Persistence	0.12 (S)	0.03	0.06	0.12	0.5
E0916004	Bulgaria	*Klebsiella pneumoniae*	Urine	Persistence	Persistence	32 (R)	0.03	0.12	0.12	0.5
E0920001	Bulgaria	*Citrobacter freundii complex*	Urine	Eradication	Eradication	8 (I)	0.03	0.12		
E0920002	Bulgaria	*Klebsiella pneumoniae*	Urine	Eradication	Eradication	64 (R)	0.06	0.5		
E0920003	Bulgaria	*Klebsiella pneumoniae*	Urine	Eradication	Eradication	32 (R)	0.03	0.12		
E4003001	Israel	*Klebsiella pneumoniae*	Urine	Eradication	Eradication	>64 (R)	0.03	0.5		
E6001001	Republic of Korea	*Enterobacter aerogenes*	Urine	Eradication	Eradication	64 (R)	0.03	0.25		
E6102003	Romania	*Proteus mirabilis*	Urine	Persistence	Indeterminate	32 (R)	0.12	0.5	0.5	
E6102006	Romania	*Klebsiella pneumoniae*	Urine	Eradication	Eradication	32 (R)	0.03	0.25		
E6102010	Romania	*Escherichia coli*	Urine	Persistence	Persistence	64 (R)	0.015	0.06	0.06	0.12
E6102012	Romania	*Enterobacter cloacae*	Urine	Persistence	Persistence	> 64 (R)	> 8	> 256	> 256	> 256
E6106001	Romania	*Klebsiella pneumoniae*	Urine	Eradication	Eradication	> 64 (R)	0.5	1		
E6107003	Romania	*Klebsiella pneumoniae*	Urine	Eradication	Eradication	> 64 (R)	> 8	1		
E6209002	Russia	*Escherichia coli*	Urine	Eradication	Persistence	4 (S)	0.015	0.06		
E6209002	Russia	*Escherichia coli*	Urine	Eradication	Eradication	8 (I)	0.015	0.06		
E6215002	Russia	*Klebsiella pneumoniae*	Urine	Eradication	Eradication	> 64 (R)	0.03	0.5		

Abbreviations: mMITT = microbiological Modified Intent-to-Treat; cUTI = complicated Urinary Tract Infections; MIC = Minimum Inhibitory Concentration; TOC = Test-of-Cure; LFU = Late Follow Up; (R) = Resistant; (I) = Intermediate

Source: Module 5: Integrated Summary of Microbiology (Microbiology Database)

Table 137. Listing of Microbiological Failures at TOC and LFU in cUTI Subjects in the Resistant Pathogen Study (mMITT Population)

Patient ID	*Study Drug*	*Source*	*Infection*	*Baseline Pathogen*	*MIC to Study Drug (mg/L)*			*Per Pathogen Response mMITT*	
					Baseline	*TOC*	*LFU*	*TOC*	*LFU*
E0916004	Ceftazidime-avibactam	Urine	cUTI w/o acute pyelonephritis	*Klebsiella pneumoniae*	0.12	0.12	0.5	Persistence	Persistence
E4901003	Doripenem	Urine	Acute pyelonephritis	*Escherichia coli*	0.03			Eradication	Eradication
E6102002	Imipenem	Urine	cUTI w/o acute pyelonephritis	*Klebsiella pneumoniae*	0.25	0.12	1	Persistence	Persistence
E6102003	Ceftazidime-avibactam	Urine	cUTI w/o acute pyelonephritis	*Proteus mirabilis*	0.5	0.5		Persistence	Indeterminate
E6102007	Imipenem	Urine	cUTI w/o acute pyelonephritis	*Escherichia coli*	0.12	0.12	0.12	Persistence	Persistence
E6102010	Ceftazidime-avibactam	Urine	cUTI w/o acute pyelonephritis	*Escherichia coli*	0.06	0.06	0.12	Persistence	Persistence
E6102012	Ceftazidime-avibactam	Urine	cUTI w/o acute pyelonephritis	*Enterobacter cloacae*	> 256	> 256	> 256	Persistence	Persistence
E6102013	Imipenem	Urine	cUTI w/o acute pyelonephritis	[a]*Klebsiella oxytoca/Klebsiella pneumoniae*	0.12			Eradication	Persistence
E6107001	Imipenem	Urine	cUTI w/o acute pyelonephritis	*Escherichia coli*	0.12			Eradication	Eradication
E6107002	Imipenem	Urine	cUTI w/o acute pyelonephritis	*Klebsiella pneumoniae*	0.25	0.25	0.12	Persistence	Persistence

Antimicrobial Susceptibility Data/microbiological response as a function of MIC

Table 138 shows the microbiological responses as a function of MIC for ceftazidime-non-susceptible and resistant pathogens. The ceftazidime-avibactam MIC ranged from 0.03 to > 256 mg/L against all *Enterobacteriaceae*. Failures were associated with MIC ranges from 0.06 to > 256 mg/L.

Table 138. Microbiological Response by MIC for Ceftazidime-avibactam and Comparator against Ceftazidime-non-susceptible Gram-negative Pathogens at TOC in the Resistant Pathogen Study, cUTI NXL104/2001 and Pooled (mMITT Population)

Baseline Pathogen and MIC (mg/L)	*Favorable Microbiological Response n/N (%) for Ceftazidime-non-susceptible Pathogens by MIC at TOC Visit from cUTI Subjects (mMITT Population)*					
	Resistant Pathogen cUTI D4280C00006		*Phase 2 cUTI (NXL104/2001)*		*Pooled Resistant Pathogen and Phase 2 cUTI*	
	Ceftazidime-avibactam MIC (mg/L)	*Best Available Comparator MIC (mg/L)*	*Ceftazidime-avibactam MIC (mg/L)*	*Imipenem MIC (mg/L)*	*Ceftazidime-avibactam MIC (mg/L)*	*Best Available Comparator MIC (mg/L)*
All Enterobacteriaceae						
0.015		1/1 (100.0)				1/1 (100.0)
0.03	1/1 (100.0)	1/1 (100.0)			1/1 (100.0)	1/1 (100.0)
0.06	1/1 (100.0)	2/4 (50.0)	1/2 (50.0)	2/2 (100.0)	2/3 (66.7)	4/6 (66.7)
0.12	3/5 (60.0)	5/10 (50.0)	4/8 (50.0)	7/13 (53.8)	7/13 (53.8)	12/23 (52.2)
0.25	2/2 (100.0)	1/5 (20.0)	4/4 (100.0)	1/2 (50.0)	6/6 (100.0)	2/7 (28.6)
0.5	5/6 (83.3)				5/6 (83.3)	
1	2/4 (50.0)	1/1 (100.0)			2/4 (50.0)	1/1 (100.0)
32		0/1 (0.0)				0/1 (0.0)

> 256	0/1 (0.0)				0/1 (0.0)	
Citrobacter freundii complex						
0.12	1/1 (100.0)				1/1 (100.0)	
Enterobacter aerogenes						
0.25	1/1 (100.0)				1/1 (100.0)	
Enterobacter cloacae						
0.25				1/1 (100.0)		1/1 (100.0)
0.5	1/1 (100.0)				1/1 (100)	
> 256	0/1 (0.0)				0/1 (100)	

Escherichia coli						
0.03	1/1 (100.0)	1/1 (100.0)			1/1 (100.0)	1/1 (100.0)
0.06	1/1 (100.0)	1/2 (50.0)	1/2 (50.0)	2/2 (100.0)	2/3 (66.7)	3/4 (75.0)
0.12	1/2 (50.0)	2/3 (66.7)	4/8 (50.0)	7/13 (53.8)	5/10 (50.0)	9/16 (56.3)
0.25		1/1 (100.0)	4/4 (100.0)	0/1 (0.0)	4/4 (100.0)	1/2 (50.0)
Klebsiella oxytoca						
0.12		1/1 (100.0)				1/1 (100.0)
0.25		0/1 (0.0)				0/1 (0.0)
Klebsiella pneumoniae						
0.015		1/1 (100.0)				1/1 (100.0)
0.06		1/2 (50.0)				1/2 (50.0)
0.12	1/2 (50.0)	2/6 (33.3)			1/2 (50.0)	2/6 (33.3)
0.25	1/1 (100.0)	0/3 (0.0)			1/1 (100.0)	0/3 (0.0)
0.5	4/4 (100.0)				4/4 (100.0)	
1	2/3 (66.7)	1/1 (100.0)			2/3 (66.7)	1/1 (100.0)
32		0/1 (0.0)				0/1 (0.0)
Proteus mirabilis						
0.5	0/1 (0.0)				0/1 (0.0)	
1	0/1 (0.0)				0/1 (0.0)	
Pseudomonas aeruginosa						
8	1/1 (100.0)				1/1 (100.0)	
16				0/1 (0.0)		0/1 (0.0)

Abbreviations: cUTI = complicated Urinary Tract Infections; mMITT = microbiological Modified-Intent-to-Treat; TOC = Test-of-Cure
Source: : Module 2.7.3 - cUTI Appendix 2 Tables 6.2.2.2.8

Pooled Response by pathogen cUTI and cIAI studies

Table 139 shows the overall clinical and microbiological response rates for ceftazidime-avibactam and comparator agents against ceftazidime-non-susceptible isolates collected from cUTI and cIAI across all studies (mMITT Population). Among all *Enterobacteriaceae*, a microbiological response rate of 77.8% for ceftazidime-avibactam treated subjects compared with 60.0% for subjects treated with the comparator agents. The most common isolates among both studies were *E. coli* and *K. pneumoniae*, and microbiological response rates for ceftazidime-avibactam of 80.5, and 78.6%, respectively were observed.

Table 139. Summary of Pooled Clinical and Microbiological Outcomes by Pathogen for Ceftazidime-non-susceptible Pathogens in cUTI and cIAI Studies

Ceftazidime Non-susceptible Baseline Pathogen	*Overall Favorable Microbiological Outcome at TOC (mMITT Population)*	
	Ceftazidime-avibactam (N = 66) n/N (%)	*Comparator (N = 67) n/N (%)*
Enterobacteriaceae	**49/63 (77.8)**	**39/65 (60.0)**
Citrobacter braakii		1/1 (100.0)
Citrobacter freundii complex	1/1 (100.0)	
Enterobacter aerogenes	1/1 (100.0)	
Enterobacter cloacae	1/2 (50.0)	1/2 (50.0)
Escherichia coli	33/41 (80.5)	28/42 (66.7)
Klebsiella oxytoca		1/2 (50.0)
Klebsiella pneumoniae	11/14 (78.6)	9/20 (45.0)
Proteus mirabilis	1/3 (33.3)	
Providencia stuartii	1/1 (100.0)	
Non-*Enterobacteriaceae*	3/3 (100.0)	2/3 (66.7)
Acinetobacter baumannii	1/1 (100.0)	1/1 (100.0)
Pseudomonas aeruginosa	2/2 (100.0)	1/2 (50.0)

Abbreviations: cIAI = complicated Intra-abdominal Infections; cUTI = complicated Urinary Tract Infections; mMITT = microbiological Modified-Intent-to-Treat; TOC = Test-of-Cure
Source: : Module 2.7.3 - cUTI Appendix 2 Tables 6.2.3.2.3 and 6.2.3.2.4

Table 140 shows the pooled microbiological outcomes by MIC for all ceftazidime-non-susceptible gram-negative pathogens collected from the cUTI and cIAI subjects in the mMITT populations in the Phase 2 studies (NXL104/2001 and NXL104/2002) and the Resistant Pathogen Study (Clinical Study D4280C00006).

Table 140. Summary of Overall Clinical and Microbiological Outcomes by MIC for Ceftazidime-avibactam and Comparators and Ceftazidime-non-susceptible Pathogens Collected from All cIAI and cUTI Subjects

Baseline Ceftazidime- non-susceptible Pathogen	***Favorable Microbiological Response at TOC mMITT Populations***	
	Ceftazidime- avibactam MIC (mg/L)	***Comparator MIC (mg/L)***
All *Enterobacteriaceae*		
≤ 0.004		2/2 (100.0)
0.008		5/5 (100.0)
0.015		8/11 (72.7)
≤ 0.03	6/7 (85.7)	
0.03	1/1 (100.0)	4/5 (80.0)
0.06	5/6 (83.3)	4/6 (66.7)
0.12	14/20 (70.0)	12/24 (50.0)
0.25	9/9 (100.0)	2/7 (28.6)
0.5	7/8 (87.5)	
1	3/5 (60.0)	1/1 (100.0)
2	2/3 (66.7)	0/1 (0.0)
4		1/1 (100.0)
8	1/1 (100.0)	
32		0/1 (0.0)
> 32	0/1 (0.0)	
> 256	0/1 (0.0)	
Citrobacter braakii		
0.015		1/1 (100.0)
***Citrobacter freundii* complex**		
0.12	1/1 (100.0)	
Enterobacter aerogenes		
0.25	1/1 (100.0)	
Enterobacter cloacae		
0.03		0/1 (0.0)
0.25		1/1 (100.0)
0.5		
> 256		
Escherichia coli		
≤ 0.004		2/2 (100.0)
0.008		5/5 (100.0)
0.015		7/10 (70.0)
≤ 0.03	6/7 (85.7)	
0.03	1/1 (100.0)	2/2 (100.0)
0.06	5/6 (83.3)	3/4 (75.0)
0.12	10/15 (66.7)	9/17 (52.9)
0.25	7/7 (100.0)	1/2(50.0)
0.5	1/1 (100.0)	
2	2/3 (66.7)	

Baseline Ceftazidime- non-susceptible Pathogen	*Favorable Microbiological Response at TOC mMITT Populations*	
	Ceftazidime- avibactam MIC (mg/L)	*Comparator MIC (mg/L)*
Klebsiella oxytoca		
0.12		1/1 (100.0)
0.25		0/1 (0.0)
Klebsiella pneumoniae		
0.015		1/2 (50.0)
0.03		2/2 (100.0)
0.06		1/2 (50.0)
0.12	3/4 (75.0%)	2/6 (33.3)
0.25	1/1 (100.0)	0/3 (0.0)
0.5	5/5 (100.0)	
1	2/3 (66.7)	1/1 (100.0)
2		0/1 (0.0)
4		1/1 (100.0)
32		0/1 (0.0)
> 32	0/1 (0.0)	
Proteus mirabilis		
0.5	0/1 (0.0)	
1	1/2 (50.0)	
Providencia stuartii		
8	1/1 (100.0)	
Non *Enterobacteriaceae*		
8	1/1 (100.0)	
16		1/2 (50.0)
> 16		1/1 (100.0)
32	1/1 (100.0)	
> 32	1/1 (100.0)	
Acinetobacter baumannii		
16		1/1 (100.0)
32	1/1 (100.0)	

Baseline Ceftazidime- non-susceptible Pathogen	***Favorable Microbiological Response at TOC mMITT Populations***	
	Ceftazidime-avibactam MIC (mg/L)	***Comparator MIC (mg/L)***
Pseudomonas aeruginosa		
8	1/1 (100.0)	
16		0/1 (0.0)
> 16		1/1 (100.0)
> 32	1/1 (100.0)	

Abbreviations: cIAI = complicated intra-abdominal infections; cUTI = complicated urinary tract infections; MIC = minimum inhibitory concentration; mMITT = microbiological modified intent to treat Source: Tables 6.2.3.2.5 and 6.2.3.2.6

ESTABLISHMENT OF FINAL QC PARAMETERS AND INTERPRETIVE CRITERIA

MIC susceptibility and resistance interpretive criteria are established by using three principles. The first is the MIC distribution patterns from large surveillance studies; second, is the observation of clinical response data with respect to the prescribed drug dose; third, is the PK/PD characteristics of the drug.

Table 141 shows the pooled clinical and microbiological responses for ceftazidime-avibactam against ceftazidime-non-susceptible pathogens. *Enterobacteriaceae* identified among subjects with cIAI and cUTI in the Phase 2 and Resistant Pathogen Studies. At TOC, the microbiological response for ceftazidime-avibactam was 77.8% versus 60.0% for the comparator agents combined against all *Enterobacteriaceae*. The most common pathogen was *E. coli* and an overall microbiological response rate of 80.5% versus 66.7% was observed for ceftazidime avibactam plus metronidazole and comparator, respectively.

Table 141. Summary of Pooled Clinical and Microbiological Outcomes by Pathogens Across All Clinical Studies

Ceftazidime Non-susceptible Baseline Pathogen	*Overall Favorable Clinical Outcome at TOC (mMITT Population)*		*Overall Favorable Microbiological Outcome at TOC (mMITT Population)*	
	Ceftazidime-avibactam plus Metronidazole n/N (%)	*Comparator n/N (%)*	*Ceftazidime-avibactam plus Metronidazole n/N (%)*	*Comparator n/N (%)*
Enterobacteriaceae	55/63 (87.3)	46/65 (70.8)	49/63 (77.8)	39/65 (60.0)
Citrobacter braakii		1/1 (100.0)		1/1 (100.0)
Citrobacter freundii complex	1/1 (100.0)		1/1 (100.0)	
Enterobacter aerogenes	1/1 (100.0)		1/1 (100.0)	
Enterobacter cloacae	2/2 (100.0)	0/2 (0.0)	1/2 (50.0)	1/2 (50.0)
Escherichia coli	35/41 (85.4)	30/42 (71.4)	33/41 (80.5)	28/42 (66.7)
Klebsiella oxytoca		2/2 (100.0)		1/2 (50.0)
Klebsiella pneumoniae	13/14 (92.9)	14/20 (70.0)	11/14 (78.6)	9/20 (45.0)
Proteus mirabilis	2/3 (66.7)		1/3 (33.3)	
Providencia stuartii	1/1 (100.0)		1/1 (100.0)	

Abbreviations: mMITT = microbiological Modified-Intent-to-Treat; TOC = Test-of-Cure
Source: : Module 2.7.3 - cUTI Appendix 2 Tables 6.2.3.2.3 and 6.2.3.2.4

Table 142 shows the clinical and microbiological outcomes as a function of MIC to study for all *Enterobacteriaceae* as well as for ceftazidime-non-susceptible organisms from both Phase 2 clinical studies as well as for cIAI and cUTI subjects enrolled in the Resistant Pathogen Study. A total 62 isolates of ceftazidime-non-susceptible *Enterobacteriaceae* were collected across all clinical studies from ceftazidime-avibactam treated subjects in the mMITT Population. There were two isolates with ceftazidime-avibactam MIC values that were ≥ 32 mg/L that were associated with subjects that were microbiological failures in the mMITT Population.

Table 142. Clinical and Microbiological Response Rates by MIC for Ceftazidime-avibactam Against all Clinical Isolates of Ceftazidime-non-susceptible *Enterobacteriaceae* from Ceftazidime-avibactam Treated Subjects

Baseline Ceftazidime-non-susceptible Pathogen	*Clinical Response at TOC mMITT Population*	*Favorable Microbiological Response at TOC mMITT Populations*
≤ 0.03	6/7 (85.7)	6/7 (85.7)
0.03	0/1 (0.0)	1/1 (100.0)
0.06	6/6 (100.0)	5/6 (83.3)
0.12	18/20 (90.0)	14/20 (70.0)
0.25	8/9 (88.9)	9/9 (100.0)
0.5	7/8 (87.5)	7/8 (87.5)
1	5/5 (100.0)	3/5 (60.0)
2	2/3 (66.7)	2/3 (66.7)
8	1/1 (100.0)	1/1 (100.0)
> 32	0/1 (0.0)	0/1 (0.0)
> 256	1/1 (100.0)	0/1 (0.0)
Total	**54/62 (87.1%)**	**48/62 (77.4%)**

Abbreviations: mMITT = microbiological Modified-Intent-to-Treat; TOC = Test-of-Cure; MIC = Minimum Inhibitory Concentration

Source: Tables 6.2.3.2.5 and 6.2.3.2.6

Since PK/PD targets could not be identified using the limited data from the Phase 2 cIAI and cUTI studies, data from the in vitro and in vivo nonclinical studies with ceftazidime-avibactam were used to set targets to be used in simulations to determine the probability of PK/PD target attainment. The population PK models for ceftazidime and avibactam were used to conduct simulations across six different levels of renal function, spanning normal renal function to end-stage-renal disease. The PTA was calculated as the percentage of the simulated subjects who met the PK/PD targets for both ceftazidime and avibactam simultaneously (referred to as joint PTA). The percent protein binding used to calculate free drug concentrations was 15% for ceftazidime and 8.2% for avibactam.

Table 143 shows the target attainment result by renal function group for MICs 4, 8, 16 and 32 mg/L with the proposed dosing regimen of ceftazidime-avibactam of 2.5 g (2000 mg ceftazidime + 500 mg avibactam) given as a 2-hour IV infusion q8h for patients with normal renal function and mild renal impairment. At 8 mg/L, all renal function categories met the pre specified threshold of over 90% target attainment. The target attainment simulations appear to support a PK/PD “susceptible” breakpoint of ≤ 8 mg/L. Additionally, the data show more than 50% target attainment at 16 mg/L for patient with normal renal function.

Table 143. Percentage of Simulated cIAI Patients Achieving PK/PD Targets for Different Renal Function Groups (5000 Simulated Patients per Group) with CAZ-AVI Given as a 120-Minute IV Infusion

Renal Function	*Dose Regimen*	*T1*	*T2*	*T3*	*T4*
MIC = 4 mg/L					
NORM	2000 mg CAZ+500 mg AVI, q8h	100	100	100	98.9
MILD	2000 mg CAZ + 500 mg AVI, q8h	100	100	100	99.9
MODE	1000 mg CAZ + 250 mg AVI, q12h	100	100	99.9	98.9
SEV1	1000 mg CAZ + 250 mg AVI, q24h	100	99.8	99.8	97.8
SEV2	500 mg CAZ + 125 mg AVI, q24h	100	100	100	100
ESRD	500 mg CAZ + 125 mg AVI, q48h	100	100	100	100
MIC = 8 mg/L					
NORM	2000 mg CAZ + 500 mg AVI, q8h	99.8	98.3	99.8	98.1
MILD	2000 mg CAZ + 500 mg AVI, q8h	100	100	100	99.9
MODE	1000 mg CAZ + 250 mg AVI, q12h	98.8	95.7	98.8	95.7
SEV1	1000 mg CAZ + 250 mg AVI, q24h	95.5	85.9	95.5	85.9
SEV2	500 mg CAZ + 125 mg AVI, q24h	97.3	94.4	97.3	94.4
ESRD	500 mg CAZ + 125 mg AVI, q48h	100	99.9	100	99.9
MIC = 16 mg/L					
NORM	2000 mg CAZ + 500 mg AVI, q8h	75.4	50.8	75.4	50.8
MILD	2000 mg CAZ + 500 mg AVI, q8h	98.1	93.8	98.1	93.8
MODE	1000 mg CAZ + 250 mg AVI, q12h	50.1	35.2	50.1	35.2
SEV1	1000 mg CAZ + 250 mg AVI, q24h	35.0	21.8	35.0	21.8
SEV2	500 mg CAZ + 125 mg AVI, q24h	47.5	40.8	47.5	40.8
Renal Function	*Dose Regimen*	*T1*	*T2*	*T3*	*T4*
ESRD	500 mg CAZ + 125 mg AVI, q48h	88.2	84.7	88.2	84.7
MIC = 32 mg/L					
NORM	2000 mg CAZ + 500 mg AVI, q8h	5.1	1.3	5.1	1.3
MILD	2000 mg CAZ + 500 mg AVI, q8h	41.3	27.5	41.3	27.5
MODE	1000 mg CAZ + 250 mg AVI, q12h	1.2	0.4	1.2	0.4
SEV1	1000 mg CAZ + 250 mg AVI, q24h	0.7	0.3	0.7	0.3
SEV2	500 mg CAZ + 125 mg AVI, q24h	3.3	2.3	3.3	2.3
ESRD	500 mg CAZ + 125 mg AVI, q48h	39.1	36.8	39.1	36.8

Abbreviations: AVI = avibactam; CAZ = ceftazidime; CrCL = creatinine clearance calculated by Cockcroft Gault formula; CT = threshold concentration of AVI associating with inhibition of β lactamase; ESRD = end stage renal disease (0 mL/min < CrCL ≤ 5 mL/min); IV = intravenous; MIC = minimum inhibitory concentration; MILD = mild renal impairment (31 mL/min ≤ CrCL ≤ 50 mL/min); MODE = moderate real impairment (31 mL/min ≤ CrCL ≤ 50 mL/min); NORM = normal renal function (CrCL > 80 mL/min); %$fT > C_T$=percent of time that free drug concentrations are above the critical concentration over a dose interval for AVI; %fT > MIC = percent of time that free drug concentrations are above the minimum inhibitory concentration over a dose interval for CAZ; q8h = every 8 hours; q12h = every 12 hours; q24h = every 24 hours; q48h = every 48 hours; SEV1 = severe renal impairment with 16 mL/min ≤ CrCL ≤ 30 mL/min; SEV2 = severe renal impairment with 6 mL/min ≤ CrCL≤ 15 mL/min; T1 = 40%fT > MIC for CAZ and 40%fT > CT of 0.5 mg/L for AVI; T2 = 50%fT > MIC for CAZ and 50%fT > CT of 0.5 mg/L for AVI; T3 = 40%fT > MIC for CAZ and 40%fT > CT of 1.0 mg/L for AVI; T4 = 50%fT > MIC for CAZ and 50%fT > CT of 0.5 mg/L for AVI.

The Applicant's PK/PD data in combination with the clinical efficacy by MIC information from the ceftazidime-avibactam Phase 2 studies lead to the proposed breakpoint of ≤ 8 mg/L for ceftazidime-avibactam for both *Enterobacteriaceae* and *Pseudomonas aeruginosa*. Supportive evidence for this proposed breakpoint is shown for both *Enterobacteriaceae* and *Pseudomonas aeruginosa* below. Ceftazidime-avibactam has demonstrated efficacy in a number of animal infection models against *P. aeruginosa* and a number of *Enterobacteriaceae* that were resistant to ceftazidime. Many of these isolates produced various Class A and C β-lactamases including the ESBLs, KPC and AmpC enzyme types and some OXA-type Class D enzymes. Table 144 shows a

summary of the animal studies presented and reviewed. The data suggest that ceftazidime-avibactam is efficacious in animal models of infection.

Table 144. Animal infection model studies of ceftazidime-avibactam

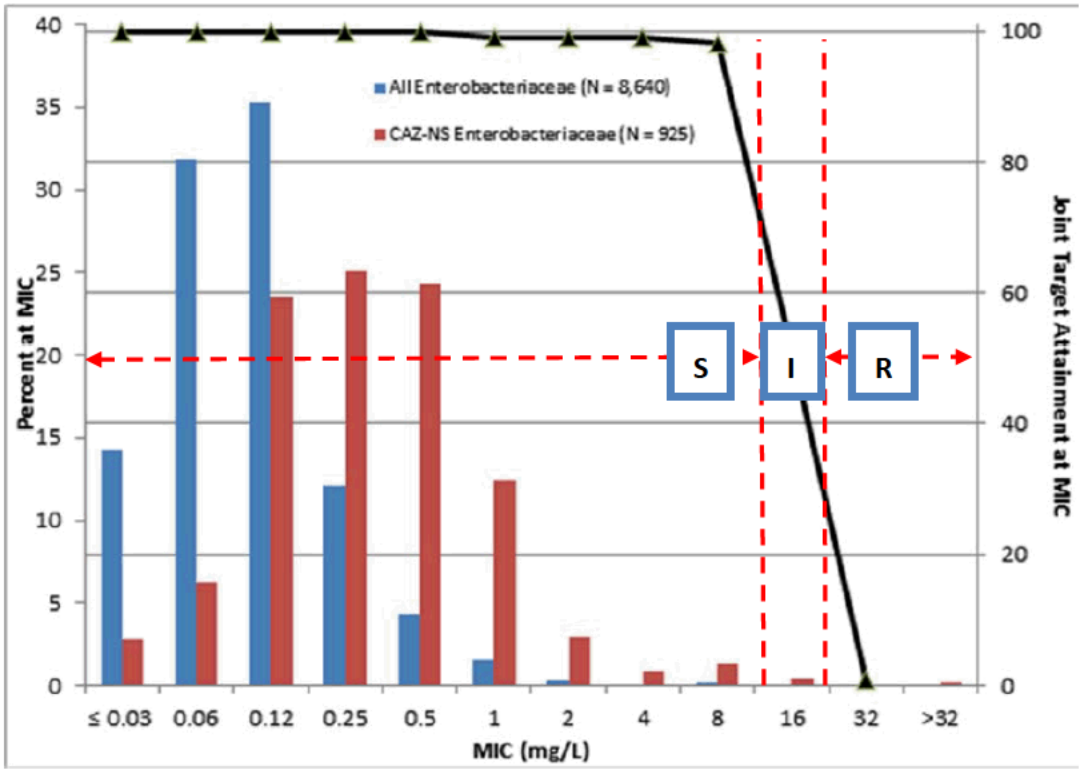
Infection Model and Species Tested	*CAZ-AVI MIC Range (mg/L)*	*CAZ MIC Range (mg/L)*	*Section*	*References*
Mouse peritoneal sepsis (PD_{50}) against *K. pneumoniae*, *E. cloacae*, *C. freundii* and *E. coli*	≤ 0.06- 2[a]	0.12 - ≥ 512	Section 4.3.1.2.1	Study CAZ104-M1-003-F-03-84726-502; Study CAZ-AVI-M1-063; Endimiani et al 2011
Mouse thigh infection (ED_{50}) against *K. pneumoniae*	≤ 0.06- 0.25[b]	256 - ≥ 512	Section 4.3.1.2.2	Endimiani et al 2011
Mouse pneumonia (ED_{50}) against *K. pneumoniae*	1-4 [a]	32-> 256	4.3.12.3	Study CAZ104-M1-004-NXL104-AP0004
Mouse pyelonephritis (efficacy) against *E. coli, C. freundii, E. cloacae, K. pneumoniae* and *M. morganii*	0.5-4 [a]	16-> 128	Section 4.3.1.2.4	Study CAZ104-M1-005-NXL104-AP0010
Rabbit meningitis (efficacy) against *K. pneumoniae*	4[b]	256	Section 4.3.1.2.5	Study NXL104-PK0007
Mouse thigh infection (PK/PD studies) against *P. aeruginosa*	2-16[b]	32-128	Section 4.4.1.3.3	Study CAZ-AVI-M1-066; Berkhout 2013b
Mouse lung infection (PK/PD studies) against *P. aeruginosa*	2-16[b]	32-128	Section 4.4.1.3.4	Study CAZ-AVI-M1-066; Berkhout 2013c
Mouse thigh infection (simulated human PK) against *P. aeruginosa*	4-32[b]	8-> 32	Section 4.4.2.2.1	Study CAZ104-M1-002; Crandon et al 2012
Mouse pneumonia (simulated human PK) against *P. aeruginosa*	4-64 [b]	8-> 128	Section 4.4.2.2.2	Study CAZ-AVI-M1-062; Housman et al 2014
Mouse thigh infection (simulated human dosing) against *Serratia marcescens*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Enterobacter aerogenes*, *Klebsiella oxytoca* and *Providencia stuartii*	8-32[b]	8-> 128	Section 4.4.2.2.3	Study CAZ-AVI-M1-067

a MIC values measured using a fixed 4:1 ratio of ceftazidime to avibactam
b MIC values measured using a fixed 4 mg/L avibactam

Ceftazidime-avibactam was evaluated in Phase 2 cIAI and cUTI studies against *Enterobacteriaceae* and *Pseudomonas aeruginosa*. Microbiological response rate of 49/63 (77.8%) were observed among *Enterobacteriaceae* at test of cure. *Enterobacteriaceae* response rates of 70.0% and 47.8% were reported for ceftazidime-avibactam and comparator, respectively. Ceftazidime-avibactam response rates of 75% and 80% were reported against *E. coli* and *K. pneumoniae*, respectively. Table 145 shows the pooled microbiological outcomes by MIC for all ceftazidime-non-susceptible gram-negative pathogens collected from the cUTi and cIAI subjects in the mMITT populations in the Phase 2 studies. Against *E. coli* the ceftazidime-avibactam MIC values ranged from ≤ 0.03 to 2 mg/L and among pooled isolates of *K. pneumoniae* the ceftazidime-avibactam MIC values ranged from 0.12 to > 32 mg/L. Favorable microbiological responses were observed for isolates with ceftazidime-avibactam MIC values that were ≤ 0.3 mg/L- 8 mcg/L. One microbiological failure was observed for the isolate with a ceftazidime MIC that was > 32 mg/L.

Figure 26 shows the PK/PD target attainment by MIC overlaid on a histogram showing MIC distributions of al *Enterobacteriaceae* (n=8,640) and ceftazidime-non-susceptible *Enterobacteriaceae* (n=925) collected during 2012 US surveillance program.

Figure 26. Percentage of Simulated Patients with Normal Renal Function Achieving 50% *f* T > MIC for Ceftazidime and 50% *f* T > CT of 1 mg/L Avibactam Following IV Administration of 2000 mg Ceftazidime/500 mg Avibactam q8h (2 hour infusion) Overlaid on a Histogram of MIC Distributions for *Enterobacteriaceae* collected during the 2012 United States surveillance program



Based on the data presented, PK/PD target attainment suggest that greater than 90% of subjects are predicted to achieve 50%*f*T > MIC for ceftazidime and 50%*f*T > CT of 1 mg/L avibactam for *Enterobacteriaceae* isolates with MIC values ≤ 8 mg/L for the following doses:

- Normal renal function; 2000 mg ceftazidime + 500 mg avibactam, q8h
- Mild renal impairment; 2000 mg ceftazidime + 500 mg avibactam, q8h

Surveillance data obtained from 8,640 US isolates of *Enterobacteriaceae* collected in 2012 show the MIC values for ceftazidime-avibactam ranged from ≤ 0.03 to > 32 mg/L. The MIC90 value for ceftazidime-avibactam was reported as 0.25 mg/L. Therefore, at the proposed PK/PD breakpoint of 8 mg/L 99.9 % of all US *Enterobacteriaceae* isolates would be considered susceptible to ceftazidime-avibactam. Among the 925 isolates that were non-susceptible (intermediate and resistant) to ceftazidime the ceftazidime-avibactam MIC values ranged from ≤ 0.03 to 16 mg/L MIC90 value of 1 mg/L. At the proposed breakpoint of either (b) (4) 8 mg/L 99.4% of US isolates of ceftazidime-non-susceptible *Enterobacteriaceae* would be reported as susceptible to ceftazidime-avibactam. Table 145 shows the MIC distributions for ceftazidime-avibactam and 2012 surveillance isolates.

Table 145. MIC Distributions for Ceftazidime-avibactam and 2012 US Surveillance Isolates of *Enterobacteriaceae* and Clinical Isolates Collected in the Phase 2 cIAI and cUTI Studies (mMITT Populations)

Organism group/phenotype		*Ceftazidime-avibactam MIC (mg/L)*											
		≤ 0.03	*0.06*	*0.12*	*0.25*	*0.5*	*1*	*2*	*4*	*8*	*16*	*32*	*>32*
All *Enterobacteriaceae* from 2012 US Surveillance (n = 8,640)	**N**	1228	2748	3052	1043	373	139	30	9	12	4	0	2
	%	14.2	31.8	35.3	12.1	4.3	1.6	0.4	0.1	0.1	0.1	0.0	0.0
	CUM%	14.2	46.0	81.3	93.4	97.7	99.3	99.7	99.8	99.9	100.0	100.0	100.0
Ceftazidime Non-susceptible *Enterobacteriaceae* from 2012 US Surveillance (n = 925)	**N**	26	57	217	232	225	115	27	8	12	4	0	2
	%	2.8	6.2	23.5	25.1	24.3	12.4	2.9	0.9	1.3	0.4	0	0.2
	CUM%	2.8	9.0	32.4	57.5	81.8	94.3	97.2	98.1	99.4	99.8	99.8	100.0
All Baseline Phase 2 *Enterobacteriaceae* from cUTI and cIAI (mMITT Population, n = 251)	**N**	33	92	82	26	6	3	5	0	1	0	0	3
	%	13.1	36.7	32.7	10.4	2.4	1.2	2.0	0.0	0.4	0.0	0.0	1.2
	CUM%	13.1	49.8	82.5	92.8	95.2	96.4	98.4	98.4	98.8	98.8	98.8	100.0
All Baseline Phase 2 Ceftazidime-non-susceptible *Enterobacteriaceae* from cUTI and cIAI, (mMITT Population, n = 81)	**N**	8	10	35	11	5	3	5	0	1	0	0	3
	%	9.9	12.3	43.2	13.6	6.2	3.7	6.2	0.0	1.2	0.0	0.0	3.7
	CUM%	9.9	22.2	65.4	79.0	85.2	88.9	95.1	95.1	96.3	96.3	96.3	100.0

Figure 27 shows the MIC distributions for ceftazidime-non-susceptible 2012 surveillance and Phase 2 clinical isolates. Figure 28 shows the MIC distribution for ceftazidime-avibactam and 2012 Phase 2 baseline clinical isolates of ceftazidime-non-susceptible *Enterobacteriaceae*

Figure 27. MIC Distributions for Ceftazidime-avibactam and 2012 US Surveillance and Phase 2 Baseline Clinical Isolates of *Enterobacteriaceae*

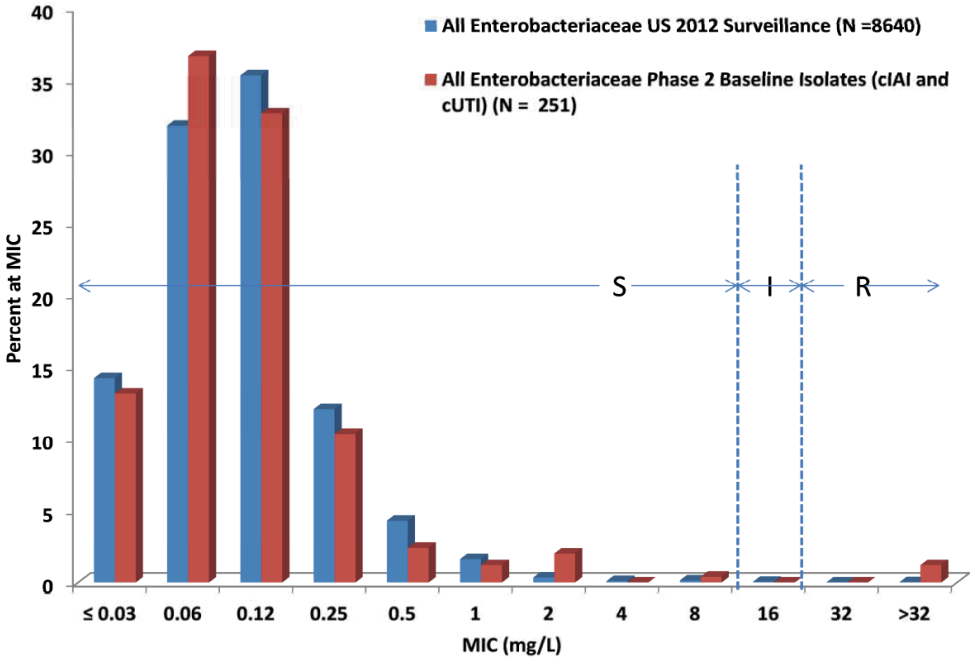
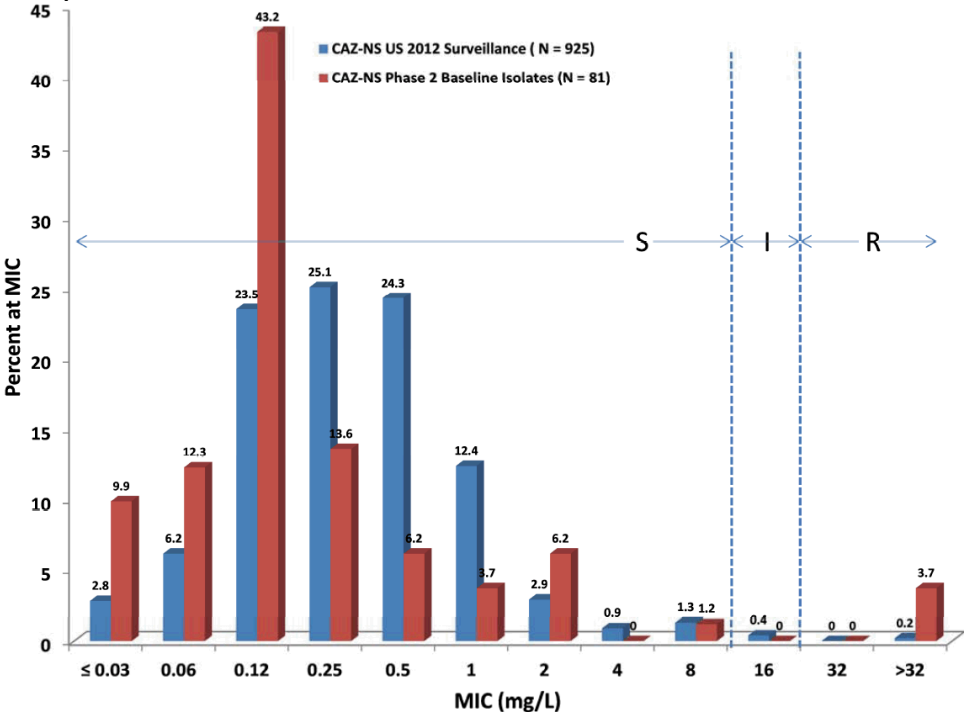


Figure 28. MIC Distributions for Ceftazidime-avibactam and 2012 and Phase 2 Baseline Clinical Isolates of Ceftazidime-non-susceptible *Enterobacteriaceae*



SCATTER PLOTS SHOWING MIC AND DISK DIFFUSION METHODS:

The in vitro antibacterial effect of ceftazidime-avibactam has been considered to be time-dependent. Based on information submitted by the Applicant, an MIC of up to 8 mg/L is supported by PK/PD data. However, the clinical data from the Phase 2 appear insufficient at this time.

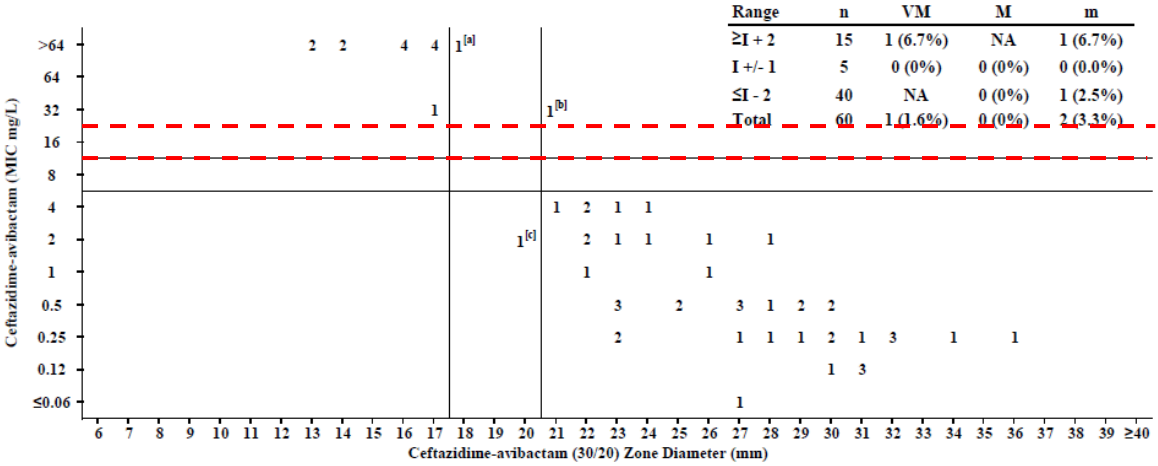
The error-rate bounded method classification is used to show a correlation between the MIC and zone diameter of bacteria encountered in the clinical trial. The zone diameters used to classify bacteria as susceptible or resistant to antibiotics depended on clinically relevant MIC breakpoints from the bacteria encountered in the clinical trials, as well as reproducible methods with adequate quality controls. Scatter plots with error rates comparing MIC and disk diffusion methods for the limited isolates encountered in the cIAI and cUTI Phase 2 studies are presented in Figures 29-31.

Scatter plot analysis for Enterobacteriaceae (proposed breakpoint of (b) (4) ≤8 mg/L)

Analyses using the proposed interpretive criteria for ceftazidime-avibactam of (b) (4) ≤8 mg/L to assess error rates between broth MIC and disk diffusion testing were conducted. Scatter plots showing MICs and ceftazidime-avibactam zone diameters for 60 Phase 2 isolates of *Enterobacteriaceae* from ceftazidime-avibactam treated subjects, and representing isolates collected in both the cUTI and cIAI studies are shown in Figure 29-31. Also shown are the error rates using the current CLSI interpretive criteria for ceftazidime (CLSI M100, S24).

Figure 29 shows the scatterplot for ceftazidime-avibactam and 60 isolates of β-lactamase-producing *Enterobacteriaceae* (including *C. freundii, E. cloacae, E. coli, K. oxytoca, P. stuartii* and *P. mirabilis*). The isolates that resulted in failure of antibiotic treatment included *K. pneumoniae* (ARC3603 and 3800) and *E. coli* (ARC3535). The isolates expressed bla_{NDM-1} (either integrated into the bacterial chromosome or on a plasmid), a Class B metallo-beta-lactamase, Class A (TEM, SHV, VEB and CTX-M types) and Class D (OXA-oxacillinases). Even though ceftazidime-avibactam demonstrates activity in vitro, clinical efficacy in patients may not be guaranteed. A phenomenon that may reduce clinical effect against ESBL-producing bacteria, despite good in vitro activity, is the inoculum effect. This may occur when the minimum inhibitory concentration of the antibiotic rises with increasing size of the number of bacteria. The effect has been described for β-lactams and β-lactamase-inhibitor combination (eg, piperacillin-tazobactam), where the enhanced susceptibility rate of piperacillin/tazobactam correlated with increased consumption of this antibiotic[21]. The error rates generated using the PK/PD breakpoint of 8 mg/L (b) (4)

Figure 29. Ceftazidime-avibactam MIC values vs. Ceftazidime-avibactam Zone Diameter (30/20 µg Disks) for Characterized β-Lactamase-producing *Enterobacteriaceae* (CLSI Breakpoints for Ceftazidime); showing error rates using susceptible breakpoints of (b) (4) ≤8 mg/L.



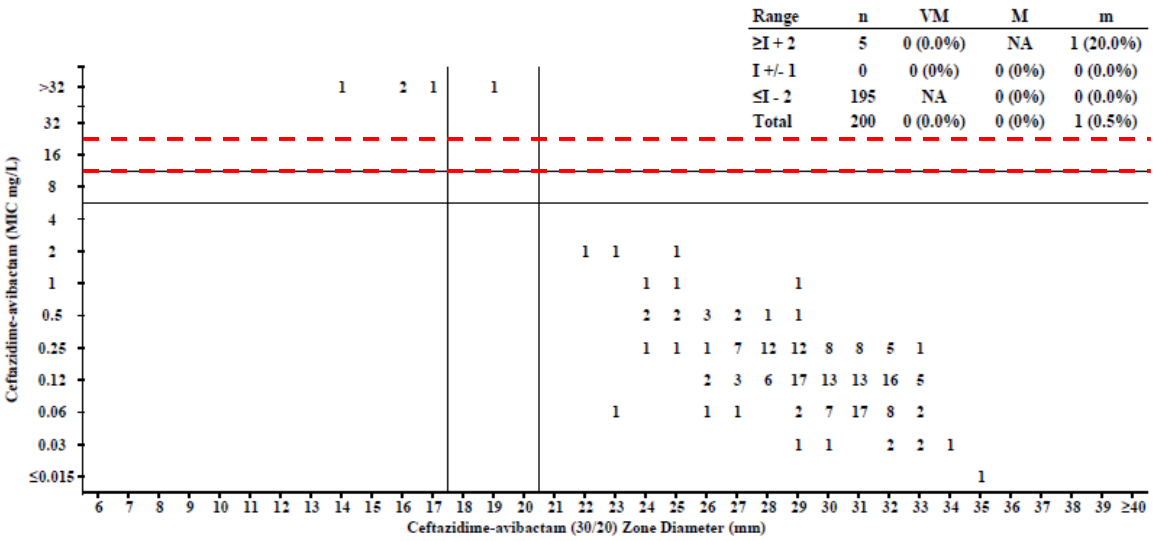
[a] *K. pneumoniae* ARC 3603 (NDM-1, TEM-1, CTX-M-15. SHV-11, CMY-6)
[b] *E. coli* ARC 3531 (VEB-5, TEM-1)
[c] *K. pneumoniae* ARC 3800 (TEM-1, CTX-M-15, SHV-1, OXA-1, OXA-9, OmpK 35)

Error rates using a susceptible breakpoint of ≤8 mg/L (red dotted line).

Range	n	VM	M	m
≥I + 2	13	0 (0.0%)	NA	1 (7.7%)
I +/- 1	2	1 (50.0%)	0 (0%)	0 (0.0%)
≤I - 2	45	NA	0 (0%)	1 (2.2%)
Total	60	1 (1.6%)	0 (0%)	2 (3.3%)

Figure 30 shows the scatter plot for 200 clinical isolates of *Enterobacteriaceae* that were collected from subjects with intra-abdominal and urinary tract infections as part of a surveillance program. No very major or major testing errors were observed using the current ceftazidime interpretive criteria.

Figure 30. Ceftazidime-avibactam MIC values vs. Ceftazidime-avibactam Zone Diameter (30/20 µg Disks) - Contemporary Clinical Isolates from 2013 (200 isolates) (FDA/CLSI Breakpoints for Ceftazidime against *Enterobacteriaceae*); showing error rates using susceptible breakpoints of (b) (4) ≤8 mg/L.

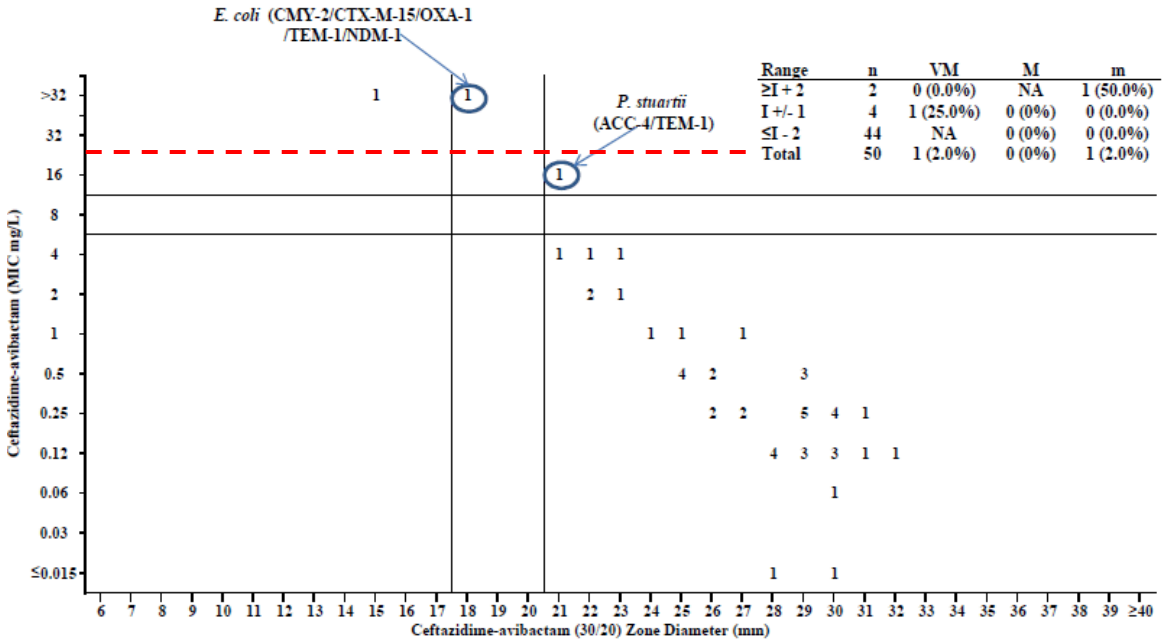


Error rates using a susceptible breakpoint of ≤8 mg/L (red dotted line).

Range	n	VM	M	m
≥I + 2	5	0 (0.0%)	NA	1 (20.0%)
I +/- 1	0	0 (0%)	0 (0%)	0 (0.0%)
≤I - 2	195	NA	0 (0%)	0 (0.0%)
Total	200	0 (0.0%)	0 (0%)	1 (0.5%)

Figure 31 shows the scatterplot for 50 ceftazidime-non-susceptible *Enterobacteriaceae* that were collected from subjects in the Phase 2 cIAI and cUTI clinical trials. The isolates were re-tested at (b) (4) to generate disk diffusion zone diameter results for the 30/20 µg ceftazidime-avibactam disks. One isolate of *Providencia staurtii*, was tested as susceptible via disk but resistant via MIC testing (Very Major Error). It contained a Class-A TEM enzyme, and the cephalosporinase ACC-4, an enzyme known to have high hydrolytic efficiency for ceftazidime and having characteristic of a Class C β-lactamase.

Figure 31. Ceftazidime-avibactam MIC values vs. Ceftazidime-avibactam Zone Diameter (30/20 µg Disks) - Phase 2 Clinical Isolates of Ceftazidime-non-susceptible Strains (50 isolates) (CLSI Breakpoints for Ceftazidime); showing error rates using susceptible breakpoints of (b) (4) ≤8 mg/L.



Range	n	VM	M	m
≥I + 2	2	0 (0.0%)	NA	1 (50.0%)
I +/- 1	4	1 (25.0%)	0 (0%)	0 (0.0%)
≤I - 2	44	NA	0 (0%)	0 (0.0%)
Total	50	1 (2.0%)	0 (0%)	1 (2.0%)

Error rates using a susceptible breakpoint of ≤8 mg/L (red dotted line).

Range	n	VM	M	m
≥I + 2	2	0 (0.0%)	NA	1 (50.0%)
I +/- 1	1	0 (0.0%)	0 (0%)	1(100.0%)
≤I - 2	47	NA	0 (0%)	0 (0.0%)
Total	50	0 (0.0%)	0 (0%)	2 (4.0%)

The CLSI approved ceftazidime-avibactam quality control ranges for aerobic ATCC strains are shown in Table 146.

Table146. CLSI Approved Ceftazidime-Avibactam Quality Control Ranges for Aerobic Reference Strains

Quality control strain	***MIC in mg/L***	***Disk diffusion zone diameter in mm (30/20***
Escherichia coli ATCC 25922	0.06/4-0.5/4	27-
Escherichia coli ATCC 35218	0.03/4-0.12/4	28-
Haemophilus influenzae ATCC 49247	0.06/4-0.5/4	28-
Haemophilus influenzae ATCC 49766	0.015/4-0.06/4	-
Klebsiella pneumoniae ATCC 700603	0.25/4-	21-
Pseudomonas aeruginosa ATCC 27853	0.5/4-	25-
Staphylococcus aureus ATCC 29213	4/4-	-
Staphylococcus aureus ATCC 25923	-	16-
Streptococcus pneumoniae ATCC 49619	0.25/4-	-

Abbreviations: ATCC = American type culture collection; CLSI = Clinical and Laboratory Standards Institute; MIC = minimum inhibitory concentration; NA = not applicable.
Source: CLSI M100-S23, 2013

The data submitted by the Applicant supports the findings that ceftazidime-avibactam is efficacious against indicated, susceptible bacterial isolates associated with complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI), including acute pyelonephritis (AP). Please note that susceptibility interpretive criteria for *Enterobacteriaceae* and *Pseudomonas aeruginosa* are based on an IV dose of 2 grams ceftazidime + 0.5 gram avibactam every 8 hours in patients with normal renal function.

FDA's version of the proposed label:

12.4 Microbiology

Mechanism of Action

The ceftazidime component of AVYCAZ is a cephalosporin with in vitro activity against gram-negative and gram-positive bacteria. The bactericidal action of ceftazidime is mediated through binding to essential penicillin-binding proteins (PBPs). The avibactam component of AVYCAZ is a non-beta-lactam beta-lactamase inhibitor that inactivates some beta-lactamases.

AVYCAZ demonstrated in vitro activity against Enterobacteriaceae in the presence of some extended-spectrum beta-lactamases (ESBLs) and other beta-lactamases of the following groups: TEM, SHV, CTX-M, certain cephalosporinases (AmpC), *Klebsiella pneumoniae* carbapenemase (KPCs), and OXA. AVYCAZ is not active against bacteria that produce metallo-beta lactamases.

Avibactam protects ceftazidime from degradation by beta-lactamases and restores the antibacterial spectrum of ceftazidime. Avibactam does not decrease the activity of ceftazidime against ceftazidime-susceptible organisms. AVYCAZ may not have activity against gram-negative bacteria that overexpress efflux pumps or have porin mutations.

Cross-Resistance

No cross-resistance with other classes of antimicrobials has been identified. Some isolates resistant to other cephalosporins (including ceftazidime) and to carbapenems may be susceptible to AVYCAZ.

Interaction with Other Antimicrobials

In vitro studies have not demonstrated antagonism between AVYCAZ and colistin, levofloxacin, linezolid, metronidazole, tigecycline, tobramycin, or vancomycin.

Activity against Ceftazidime-Nonsusceptible Bacteria in Animal Infection Models

Avibactam restored activity of ceftazidime in animal models of infection (e.g. thigh infection, pyelonephritis, systemic infection induced by intraperitoneal injection) caused by ceftazidime non-susceptible beta-lactamase-producing gram-negative bacteria.

AVYCAZ has been shown to be active against most isolates of the following bacteria, both in vitro and in clinical infections [*see Indications and Usage (1.1) and (1.2)*].

Complicated Intra-abdominal Infection (cIAI)

- Gram-negative bacteria

- *Escherichia coli*
- *Enterobacter cloacae*
- *Klebsiella pneumoniae*
- *Klebsiella oxytoca*
- *Proteus mirabilis*
- *Providencia stuartii*
- *Pseudomonas aeruginosa*

Complicated Urinary Tract Infection (cUTI), including Pyelonephritis

- Aerobic Gram-negative bacteria (including β-lactamase-producing strains)
  - *Citrobacter freundii*
  - *Citrobacter koseri*
  - *Escherichia coli*
  - *Pseudomonas aeruginosa*
  - *Enterobacter aerogenes*
  - *Enterobacter cloacae*
  - *Proteus* spp.
  - *Klebsiella pneumoniae*

The following in vitro data are available, but their clinical significance is unknown. AVYCAZ exhibits in vitro MIC values of ≤ 8 mcg/mL against most (≥ 90%) isolates of the following bacteria; however, the safety and effectiveness of AVYCAZ in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

- Gram-negative bacteria
  - *Morganella morganii*
  - *Providencia rettgeri*
  - *Serratia marcescens*

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

Dilution Techniques

Quantitative methods are used to determine antimicrobial MIC values. These MIC values provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC values should be determined using a standardized test method (broth or agar)[1-3]. MIC values should be determined using serial dilutions of ceftazidime combined with a fixed concentration of 4 mcg/mL of avibactam. Broth dilution MIC values need to be read within 18 hours because of degradation of ceftazidime activity by 24 hours. The MIC values should be interpreted according to the criteria in Table 9.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized method[2]. This procedure uses paper disks impregnated with 30 mcg of ceftazidime and 20 mcg avibactam to test the susceptibility of bacteria to AVYCAZ. The disk interpretive criteria are provided in Table 9.

Table 9. Susceptibility Interpretive Criteria for Ceftazidime/Avibactam

Pathogen	***Minimum Inhibitory Concentration (mg/L)***		***Disk Diffusion Zone Diameter (mm)***	
	S	*R*	*S*	*R*
Enterobacteriaceae	≤ 8/4	≥ 16/4	≥ 21	≤ 20
Pseudomonas aeruginosa	≤ 8/4	≥ 16/4	≥ 18	≤ 17

A report of "Susceptible" indicates that the antimicrobial drug is likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration at the site of infection. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the antimicrobial drug is not likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentrations usually achievable at the site of infection; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test[1-3]. Standard AVYCAZ powder should provide the following range of MIC values provided in Table 10. For the diffusion technique using the 30 mcg ceftazidime/20-mcg avibactam disk, the criteria provided in Table 10 should be achieved.

Table 10. Acceptable Quality Control Ranges for Susceptibility Testing

Quality Control Organism	***Minimum Inhibitory Concentration[a] (mg/L)***	***Disk Diffusion Zone Diameter (mm)***
Staphylococcus aureus ATCC 29213	4 - 16	-
Staphylococcus aureus ATCC 25923	-	16 - 22
Escherichia coli ATCC 25922	0.06 - 0.5	27 - 35
Escherichia coli ATCC 35218	0.03 - 0.12	28 - 35

Pseudomonas aeruginosa ATCC 27853	0.5 - 4	25 - 31
Klebsiella pneumoniae ATCC 700603[b]	0.25 - 2	-
Haemophilus influenzae ATCC 49247	0.06 - 0.5	28 - 34
Haemophilus influenzae ATCC 49766	0.015 - 0.06	-
Streptococcus pneumoniae ATCC 49619	0.25 - 2	-

a MIC for ceftazidime in the presence of a fixed concentration of 4 mg/L of avibactam.
b *K. pneumoniae* ATCC 700603 should be tested against ceftazidime-avibactam and ceftazidime alone to confirm the activity of avibactam in the combination and to ensure that the plasmid encoding the beta-lactamase has not been lost in this strain. The acceptable range for ceftazidime alone is > 16 mg/L.

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