CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206494Orig1s000

STATISTICAL REVIEW(S)

MEMORANDUM

Date	2/11/2015
From	Thamban Valappil, PhD, Statistical Team Leader
NDA#:	206494
Drug Name:	Ceftazidime-Avibactam
Applicant:	AztraZeneca-Forest-Cerexa
Indication(s):	Complicated intra-abdominal infections (cIAI) and Complicated urinary tract infections (cUTI)
Submission Date:	25 June, 2014
PDUFA due date:	25 February, 2015
Biometrics Division	DB4
Concurring Reviewer(s)	Dionne Price, PhD, Division Director
Primary Statistical Reviewer:	Margaret Gamalo-Siebers, PhD
Clinical Reviewer:	Benjamin Lorenz, MD
Project Manager:	Carmen DeBellas, PharmD

Subject : Secondary Statistical Review and Evaluation
Reference : Primary Statistical Review, and other Agency communications

1. Introduction and background

This secondary review is intended to summarize and highlight some of the findings in the primary statistical review of Dr. Gamalo-Siebers and includes some additional comments. In the statistical review, Dr. Gamalo-Siebers included a set of novel statistical approaches that warrant further exploration in the future. The findings from those exploratory analyses have not been included in this memorandum.

The new drug application (NDA) 206494 evaluates ceftazidime-avibactam (CAZ-AVI), which is a combination of ceftazidime, a third-generation cephalosporin antibacterial drug, and avibactam, a non-β-lactam, β-lactamase inhibitor (BLI). According to the Applicant, avibactam protects ceftazidime from degradation by β-lactamase enzymes and maintains the antibacterial activity of ceftazidime against isolates of *Enterobacteriaceae* and *Pseudomonas aeruginosa* that express several types of serine β-lactamases.

The Applicant is seeking approval of CAZ-AVI 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 for treating complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI). The submission is based on the 505(b)(2) pathway, relying on the Agency's previous findings of efficacy and safety of ceftazidime and findings based on published literature on ceftazidime.

2. Anti-Infective Drug Advisory Committee Meeting

An Anti-Infective Drug Advisory Committee (AIDAC) meeting was held on December 5, 2014 to discuss the overall evidence presented from the application. Based on deliberations, the majority of the committee members were in support of streamlined development programs in the areas of unmet medical need given limited treatment options available for particular organisms. The majority of members recommended approval for the indications of cUTI and cIAI with labeling restrictions.

3. Summary of Applicant's NDA Submission

Nonclinical and Phase 1 clinical data in the NDA included pharmacology/ toxicology studies, microbiological surveillance, data from animal models of infection, clinical pharmacology studies with avibactam, and pharmacokinetic/ pharmacodynamics (PK/PD) target attainment analyses.

The submission included descriptive clinical data from two Phase 2 trials, NXL104/2001 and NXL104/2002. Trial NXL104/2001 was designed to assess the efficacy and safety of CAZ-AVI compared to imipenem-cilastatin (IMP/CIL) in the treatment of subjects with cUTI. Trial NXL104/2002 was designed to assess the efficacy and safety of CAZ-AVI + metronidazole (MTZ) in the treatment of subjects with cIAI. These trials were not designed with any formal statistical hypotheses for inferential testing, and therefore, statistical analysis on efficacy was limited to descriptive data summaries with no objectively defined 'win' criteria.

The submission also included preliminary efficacy results from an ongoing, open-label Phase-3 study in hospitalized patients (Study D4280C00006), which included patients with cUTI or cIAI caused by CAZ-NS pathogens (ceftazidime-resistant and ceftazidime-intermediate pathogens).

Lastly, during the 120-day safety update, the Applicant submitted efficacy findings based on the Phase-3 trial in cIAI (D4280C00001/5), referred to as RECLAIM. The trial was

designed as a non-inferiority trial using a 10% NI margin and enrolled 1066 patients. A complete report of clinical trial data has not yet been submitted for Agency review.

4. Trials and Review of Findings:

4.1. Complicated Urinary Tract Infections (cUTI)

Study NXL104/2001

Study NXL104/2001 was a Phase 2, multicenter, randomized, investigator-blind, active-control study in adult subjects with cUTI. Patients were stratified by baseline type of infection (pyelonephritis and other types of cUTI without pyelonephritis) and randomized 1:1 to CAZ-AVI or imipenem-cilastatin (IMP/CIL) treatment groups.

Patients received at least 4 days of IV study antibiotic therapy while hospitalized. After at least 4 days of IV therapy, based on meeting the protocol-specified criteria for clinical improvement, they were permitted to switch to oral ciprofloxacin 500 mg every 12 hours to complete the treatment course. Patients received a minimum of 7 days and a maximum of 14 days of total antibiotic therapy (IV plus oral therapy).

All the analyses results discussed in this review are based on the mMITT population as recommended in the regulatory draft guidance document. The mMITT is defined based on baseline pathogen(s) and is a variant of the intent-to-treat (ITT) population which would preserve randomization. The mMITT population in this study includes patients who had a qualifying pre-treatment urine culture containing $>10^5$ CFU/mL of at least one pathogen and received at least one dose of study therapy.

In the mMITT population, 29/46 (63.0%) of the patients in the CAZ-AVI group and 25/49 (51.0%) of the patients in the IMP/CIL group had both clinical cure and microbiological response at test-of-cure (TOC), 5-9 days post-therapy (Table 1). For the late-follow-up visit, only clinical response was reported instead of the joint clinical and microbiological rate at TOC. The clinical response rates were lower than those observed at TOC.

Table 1: NXL-104-2001: Clinical and Microbiological response at TOC in the mMITT population

	CAZ-AVI N = 46 n (%)	IPM/CIL N = 49 n (%)
Microbiological Response		
Eradication	31 (67.4)	31 (63.3)
Persistence	10 (21.7)	14 (28.6)
Persistence with acquisition of resistance	0	0
Indeterminate	5 (10.9)	4 (8.2)

Clinical Response		
Cure	37 (80.4)	36 (73.5)
Failure	5 (10.9)	9 (18.4)
Indeterminate	4 (8.7)	4 (8.2)
Clinical & Microbiological Response(TOC)		
Cure + Eradication	29 (63.0)	25 (51.0)
Failure + Persistence or Indeterminate	17 (37.0)	24 (49.0)
Clinical Response(LFU)[1]		
Sustained Clinical Cure	33 (71.7)	32 (65.3)
Clinical relapse, failure or Indeterminate	13 (18.3)	17 (34.7)

Source: Primary statistical review Tables 3-13 and 3-15; [1]Combined clinical and microbiological outcome was not reported for late follow-up visit (LFU);

Ceftazidime non-susceptible (CAZ-NS) patient sub-group

In evaluating the contribution of avibactam as a non-β-lactam, β-lactamase inhibitor (BLI), the treatment effect in patients with cUTI caused by ceftazidime-non-susceptible (CAZ-NS) pathogens was assessed. This was the population in which avibactam was expected to restore the activity of ceftazidime administered as a combination therapy.

In patients with ceftazidime-non susceptible (CAZ-NS) pathogens, 8/14 (57.1%) of the patients in the CAZ-AVI group had both clinical cure and microbiologic response compared to 7/18 (38.9%) of patients in the IMP/CIL group (Table 2). The 95% confidence intervals for the difference in response rates presented in Dr. Gamalo-Siebers's review were intended to show the associated variability. Due to the lack of pre-specified hypothesis and inference testing, the small sample sizes, and the width of the intervals, caution should be exercised when interpreting the findings.

Table 2: NXL-104-2001: Clinical and Microbiological response at TOC and LFU in the CAZ-NS Subgroup (mMITT)

	CAZ-AVI N = 14 n (%)	**IPM/CIL N = 18 n (%)**
Microbiological Outcome		
Eradication	9 (64.3)	10 (55.6)
Persistence	3 (21.4)	6 (33.3)
Persistence with acquisition of resistance	0	0
Indeterminate	2 (14.3)	2 (11.1)
Clinical Response		
Cure	11 (78.6)	10 (55.6)
Failure	2 (14.3)	5 (27.8)
Indeterminate	1 (7.1)	3 (16.7)
Clinical & Microbiological Outcome (TOC)		
Cure + Eradication	8 (57.1)	7 (38.9)
Failure + Persistence or Indeterminate	6 (42.9)	11 (61.1)

Clinical & Microbiological Outcome (LFU)		
Sustained Clinical cure + Microbiologic eradication	6 (42.9)	7 (38.9)
Either clinical failure or microbiologic persistence or indeterminate	8 (57.1)	11 (61.1)

Source: Primary statistical review Table3-17 and 3-22; edited

4.2. Complicated Intra-Abdominal Infections (cIAI)

Study NXL104/2002

Study NXL104/1002 was a Phase-2 multi-center, randomized, double-blind trial designed to evaluate the efficacy and safety of CAZ-AVI + metronidazole compared to meropenem in adults with cIAI which include patients requiring surgical intervention. Patients received CAZ-AVI 2500 mg (2000 mg ceftazidime + 500 mg avibactam) IV q8h over 30 minutes + MTZ 500 mg IV q8h over 1 hour OR meropenem (1000 mg IV q8h over 30 minutes) + placebo MTZ (IV q8h over 1 hour).

In this study, the mMITT population included patients who had received at least one dose of study therapy and had at least one bacterial pathogen identified at study entry regardless of susceptibility. In the mMITT population, the Sponsor-verified clinical response at TOC (2 weeks post-therapy) was lower in the CAZ-AVI + MTZ group compared to meropenem treated group; 70/85 (82.4%) versus 79/89 (88.8%), as shown in Table 3.

Table 3: Study NXL104/1002; Clinical Response at TOC and LFU (mMITT Population)

	CAZ-AVI + MTZ N = 85 n (%)	**Meropenem N = 89 n (%)**
Sponsor-verified favorable clinical response **(TOC)**	70 (82.4)	79 (88.8)
Sponsor-verified clinical failure	15 (17.7)	10 (11.2)
Sponsor-verified favorable clinical response **(LFU)**	71 (83.5)	77 (86.5)
Sponsor-verified clinical failure	14 (16.5)	12 (13.5)

Source: Primary statistical review Tables 3-24 and 3-25; edited

Ceftazidime non-susceptible (CAZ-NS) patient sub-group

Ceftazidime non-susceptible isolates included those that could possibly be resistant (MIC≥32) or intermediate (MIC>8 and MIC<32). Table 4 includes a subgroup of patients with ceftazidime non-susceptible isolates. In these patients, the Sponsor verified favorable clinical response at TOC is 27/30 (90.0%) in the CAZ-AVI + MTZ group and 19/23 (82.6%) in the meropenem group (Table 4).

Table 4: Study NXL 104/2002; Clinical response at TOC in the CAZ-NS subgroup

	CAZ-AVI + MTZ N = 30 n (%)	Meropenem N = 23 n (%)
Sponsor verified Clinical Cure **(TOC)**	27 (90.0)	19 (82.6)
Sponsor verified Clinical Failure	3 (10.0)	4 (17.4)
Sponsor verified Clinical Cure **(LFU)**	27 (90.0)	19 (82.6)
Sponsor verified Clinical Failure	3 (10.0)	4 (17.4)

Source: Primary Statistical Review Table 3-32; edited

4.3. Study D4280C00006: Resistant Pathogens

Study D4280C00006 is a Phase 3, multinational, multicenter, randomized (1:1), open-label study in adult subjects with cIAI and cUTI caused by ceftazidime non-susceptible (CAZ-NS) gram-negative pathogens. At enrollment, subjects are stratified by baseline diagnosis (cIAI and cUTI) and region (North America and Western Europe, Eastern Europe, and the rest of the world) and randomized to CAZ-AVI or best available therapy (BAT) groups. The BAT therapy includes the carbapenem class of drugs, either meropenem or imipenem treatments. As of the Dec 9, 2013 interim data cutoff, the mMITT population included only 4 subjects diagnosed with cIAI and 44 subjects with cUTI, as shown in Table 5.

In contrast to the draft guidance which recommends both clinical and microbiological responses as the primary endpoint for cUTI, the Applicant has reported only clinical cure rates. The observed clinical cure rates in this study are higher than those reported for NXL104/2001 and are in favor of CAZ-AVI. For cIAI, the data is very limited (only 4 patients in total).

Table 5: Study D4280C00006 – Clinical Response at TOC (interim data)

	CAZ-AVI n/N1(%)	Comparators n/N1(%)
cUTI	**N1 = 21**	**N1 = 23**
Clinical Cure (n/N1%)	19 (90.5)	18 (78.3)
Clinical failure or Indeterminate (n/N1%)	2 (9.5)	5 (21.7)
cIAI	**N1 = 1**	**N1 = 3**
Clinical Cure (n/N1%)	1 (100.0)	1 (33.3)
Clinical failure or Indeterminate (n/N1%)	0	2 (66.7)

Source: Primary Statistical Review Table 3-35; edited; Applicant's study report

5. Phase-3 trial, D4280C00001/5 (cIAI)

Prior to the AIDAC meeting, the applicant provided some findings from a recently unblinded, Phase 3 trial (referred to as RECLAIM) in subjects with cIAI. RECLAIM was designed as a randomized, multi-center, double-blind, non-inferiority trial comparing

CAZ-AVI (2000 mg/500 mg, q8h) plus MTZ (0.5 g q8h) to meropenem (1 g q8h), using a 10% NI margin. The primary endpoint was the clinical cure at TOC, 28 to 35 days after randomization, in subjects who had at least one identified pathogen (mMITT population). The data from this trial has not been submitted to the Agency for review.

5.1. Efficacy in patients with renal impairment

Clinical cure rates were lower in a subgroup of patients with baseline creatinine clearance (CrCL) of 30 to 50 ml/min compared to those with CrCL >50 ml/min (Table 6). The reduction in clinical cure rate was pronounced in CAZ-AVI-treated patients (85% to 45%) compared to meropenem-treated patients (86% to 74%).

Table 6: Summary of clinical cure rate at Test of Cure, by baseline renal function: sub-group (RECLAIM-mMITT analysis population)

Baseline renal function subgroup	*Number of patients with clinical cure/Total number of patients (%)*	
	CAZ-AVI + Metronidazole	*Meropenem*
Normal function / mild impairment (CrCl > 50 mL/min	322/379 (85%)	321/373 (86%)
Moderate impairment at baseline (CrCl > 30 to ≤ 50 mL/min)	14/31 (45%)	26/35 (74%)

Source: Applicant's Table 2.1, General correspondence: Important new clinical information, October 9, 2014

5.2. Mortality Findings

In this trial, death occurred in 2.4% (13/532) CAZ-AVI-treated patients compared to 1.5% (8/534) meropenem-treated patients. In a subgroup of patients with baseline CrCL 30 to 50 mL/min, death occurred in 25.8% (8/31) CAZ-AVI-treated patients compared to 8.6% (3/35) meropenem-treated patients.

6. Conclusions and Recommendations

The applicant submitted a 505(b)(2) NDA for ceftazidime-avibactam for the treatment of complicated intra-abdominal and complicated urinary tract infections. The 505(b)(2) pathway allows prior findings of ceftazidime, a cephalosporin with in-vitro activity against gram negative and gram-positive bacteria, to factor into the determination of safety and efficacy for CAZ-AVI. A recognized limitation of the NDA was the lack of confirmatory data. The submitted trials were exploratory and lacked formal inferential testing. Dr. Gamalo-Siebers presented point estimates and the associated confidence intervals for differences in treatment arms for the endpoints of interest. She additionally conducted exploratory analyses to attempt to gain further insight into a possible treatment effect. All findings must be interpreted with caution due to the various limitations outlined in this review and that of Dr. Gamalo-Siebers.

The unmet medical need, prior findings of efficacy and safety of ceftazidime, published literature, in vitro data, animal models, and deliberations of the AIDAC must be considered, in total, by the review team for the final determination of the risks and

benefits of ceftazidime-avibactam. If CAZ-AVI is approved for limited use, we recommend inclusion of a warning in the label regarding imbalances in outcomes among patients with creatinine clearance ≤50 ml/min and the potential for increased mortality.

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/s/

THAMBAN I VALAPPIL
02/11/2015
Memorandum / Secondary Statistical Review

DIONNE L PRICE
02/12/2015
Concur with overall conclusions

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	206494
Drug Name:	Ceftazidime-Avibactam
Indication(s):	Complicated Intra-abdominal and complicated urinary tract infections (cIAI & cUTI)
Applicant:	AztraZeneca-Forest-Cerexa
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Statistical Reviewer:	Margaret Gamalo-Siebers, PhD
Concurring Reviewers:	Thamban Valappil, PhD and Dionne Price, PhD
Medical Division:	Anti-Infective
Clinical Team:	Benjamin Lorenz, MD
Project Manager:	Carmen DeBellas

Keywords:

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1 EXECUTIVE SUMMARY

Cerexa/Forest/AztraZeneca, hereafter referred to as Applicant, submits this new drug application (NDA) through the 505(b)(2) pathway, relying on the Agency's previous findings of efficacy and safety as well as published literature on post-approval experience with ceftazidime, to support the approval of intravenous (IV) CAZAVI 2.5 g (2 g ceftazidime + 0.5 g avibactam) every 8 hours (q8h) for the following indications:

- Complicated intra-abdominal infections (cIAI)
- Complicated urinary tract infections (cUTI), including acute pyelonephritis (AP)

The clinical data in the NDA package includes a description of the efficacy results of two Phase 2 trials that have been completed; one to assess the efficacy and safety of CAZAVI compared to imipenem-cilastatin (IMP/CIL) in the treatment of subjects with cUTI (NXL104/2001) conducted in 137 subjects (135 of whom received study drug), and the other to assess the efficacy and safety of ceftazidime avibactam + metronidazole (CAZAVI + MTZ) in the treatment of subjects with cIAI (NXL104/2002) conducted in 204 subjects (201 of whom received study drug). In these trials, there was no pre-specification of any formal hypotheses for inferential testing, and the statistical analysis was limited only to descriptive data summaries. The application also includes the interim efficacy results of a single ongoing open-label Phase 3 ceftazidime-resistant gram-negative trial (Resistant Pathogen Study D4280C00006) in hospitalized adults with cIAI and cUTI; the latter trial includes a subset of subjects with cUTI or cIAI caused by ceftazidime non-susceptible (CAZ-NS) pathogens, including ceftazidime-resistant (CAZ-R) and ceftazidime-intermediate (CAZ-I) pathogens. In combination with the individual results from these trials, the application also includes a pooled analysis of the three studies to borrow information across studies and increase precision of the results, a literature review to assess the historical efficacy of ceftazidime in cIAI and cUTI and serve as a benchmark for the treatment effect restored by the addition of avibactam to ceftazidime in infections caused by CAZ-NS pathogens, and topline results from the recently completed Phase 3 cUTI trials (D4280C00001/5), which was not submitted for the Agency review.

The Phase 2 study, NXL104/2001, was a multinational, multicenter, randomized, investigator-blind, active-control study in adult subjects with cUTI. One hundred thirty-five adult patients (>18 years of age and ≤90 years of age) with cUTI were enrolled. Patients who received >1 dose of another potentially effective systemic antibiotic after obtaining the admission urine culture were excluded from the study. In addition, patients who received more than 1 dose of a potentially effective systemic antibiotic therapy within 48 hours prior to the admission urine culture were also excluded from the study. Enrolled subjects were stratified by baseline type of infection (pyelonephritis and other types of cUTI without pyelonephritis) and randomized 1:1 to CAZAVI or IMP/CIL treatment groups. The pre-specified primary efficacy endpoint in the protocol was the by-subject microbiological outcome at test-of-cure (TOC) in the

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microbiologically evaluable (ME) Population which includes patients with qualifying pre-treatment pathogen, received at least 7 days of study drug, who had TOC assessment, and had no protocol violation. However, in accordance with current regulatory guidance, the primary endpoint is the joint microbiological and clinical outcome at TOC evaluated in the Microbiological Modified Intent-to-treat (mMITT) Population. This population includes patients who had at least one bacterial pathogen identified at study entry and who received at least one dose of study drug.

The results of the study show that CAZAVI has a numerically higher (not based on any inferential testing) treatment response than IMP/CIL in most pre-specified endpoints (clinical response, microbiological outcome, and joint clinical and microbiological outcome at the TOC visit in the mMITT population). In particular, evaluating the joint clinical and microbiological outcome, 63.0% (29/46) of the patients in the CAZAVI group achieved both clinical cure and microbiologic eradication while 51.0% (25/49) of the patients in the IMP/CIL group achieved the same clinical and microbiologic response. The difference in the response rates is 12.0 with a 95% confidence interval (CI) of (-9.1, 31.7). Since the study was not designed as a non-inferiority study, it cannot be claimed that CAZAVI is non-inferior to IMP/CIL at the 10% margin.

In the subgroup of patients where the addition of avibactam is presumed to have beneficial effect, i.e., patients with cUTI caused by a ceftazidime-nonsusceptible (CAZ-NS) pathogen, 57.1% (8/14) of the patients in the CAZAVI group achieved both clinical cure and microbiologic eradication while 38.9% (7/18) of the patients in the IMP/CIL group achieved clinical and microbiologic response. The difference in the response rates is 18.3 with a 95% CI of (-22.4, 58.9). Although the point estimate gives CAZAVI a numerical advantage against IMP/CIL, the confidence interval is wide and shows the associated uncertainty in treatment effect. Contrasting this result with patients whose infection was caused by ceftazidime sensitive pathogens, where the addition of avibactam is not expected to have any benefit, the clinical cure and microbiological eradication rate of CAZAVI was 65.6% (21/32) which reflects a similar response obtained in patients with cUTI caused by a ceftazidime-nonsusceptible (CAZ-NS) pathogen. Note, however, that the ceftazidime treatment response in a population similar to ME from published historical trials was estimated at 86.6% with a 95% confidence interval of (78.9, 91.8). This means that the observed overall treatment response in Study NXL104/2001 is lower than historical studies and that the historical treatment response may not serve as a proper reference to account for the treatment effect restored by the addition of avibactam in infections caused by CAZ-NS pathogens. Note that there are several limitations in the historical data as discussed in the later part of the review.

The second Phase 2 study, NXL104/2002, was a multicenter, double-blind, randomized study to estimate the safety, tolerability, and efficacy of CAZAVI + MTZ vs. meropenem (MER) in adults with cIAI. The major exclusion in this study is that patients who received systemic antibacterial agents within the 72-hour pre-study period were not permitted to be enrolled, unless the patient had a new infection (not considered a treatment failure) and had received no more

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than 24 hours of total antibiotic therapy (preoperatively prophylaxis) and/or postoperatively); or the patient was considered to have failed the previous treatment regimen. Two-hundred four hospitalized adult patients (18 to 90 years of age) with a presumed (preoperative) or definitive (intraoperative or postoperative) diagnoses of cIAI were enrolled. They were stratified by baseline severity of disease (Apache II score < 10, and > 10 but ≤ 25) and randomized 1:1 to CAZAVI + MTZ or meropenem. The protocol defined primary analysis variable for efficacy was the clinical outcome at Test of Cure (TOC) Visit, performed 2 weeks post-therapy in the microbiologically evaluable (ME) population. However, in this review, the primary analysis variable for efficacy is the clinical outcome at Test of Cure (TOC) Visit in the mMITT population.

The results of this study show that CAZAVI+ MTZ has numerically lower clinical response rates than meropenem, except in the CAZ-NS subgroup of the mMITT population. The Sponsor verified favorable clinical response in the CAZAVI + MTZ group is 82.4% (70/85) and 88.8% (79/89) in the meropenem group with a difference in clinical response of -6.4% and a 95% confidence interval of (-18.0, 5.2) as given in see Table 3-24). CAZAVI response rate in this trial is comparable to the CAZAVI favorable treatment response in published literature (see Table 3-39), although the latter is obtained from a population similar to a ME set, which is a subgroup that can be biased due to post-randomization exclusion of patients.

In a subgroup of patients with infections caused by CAZ-NS pathogens, the Sponsor verified favorable clinical response is 90.0% (27/30) in the CAZAVI + MTZ group and 82.6% (19/23) in the meropenem group with a difference of 7.4 (95% CI: -15.3, 30.0). On the other hand, in the subgroup of patients with infections caused by CAZ-S pathogens, the Sponsor verified favorable clinical response is 78.2% (43/55) in the CAZAVI + MTZ group and 90.9% (60/66) in the meropenem group with a difference of -11.7 (95% CI: -26.0, 2.9). This rate is at the lower end of what ceftazidime treatment response was associated with, approximately 86% (90% CI: 76.0, 96.1%), at post-therapy assessment time points in a population that is similar to an ME Population. Note that the former population is evaluated in the CAZ-S subgroup of the mMITT population instead of the ME population. Qualitatively, it seems that CAZAVI + MTZ may have a beneficial effect in the CAZ-NS subgroup if one assumes that the CAZ-S result and the historical are indeed comparable.

Lastly, the interim data from the ongoing Resistant Pathogen Study, D4280C00006, was included to provide supportive information on the clinical efficacy of CAZAVI against CAZ-NS pathogens. The study was a Phase 3 multinational, multicenter, randomized, open-label, study in adult subjects with cIAI and cUTI caused by CAZ-NS gram-negative pathogens. Subjects were stratified for entry diagnosis (cIAI and cUTI) and region (North America and Western Europe, Eastern Europe, and the rest of the world) and randomized 1:1 to CAZAVI or best available therapy (BAT) groups. The dosage of CAZAVI used was 2.5 g [2.0 g ceftazidime + avibactam 0.5 g] IV q8h infused over 2h). BAT was chosen, as a single antibiotic regime is unlikely to cover all possible resistance mechanisms. As of the data cutoff, all subjects randomized to the BAT group

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have received a carbapenem (e.g., imipenem, meropenem) alone or in combination with colistin or ciprofloxacin. The mMITT Population included 4 subjects with cIAI and 44 subjects with cUTI.

The results of the interim data show a numerically higher clinical response (cure) for CAZAVI, which is observed at 90.5% (19/21) compared to BAT which is 78.3% (18/23). The difference in clinical cure is 12.2 (-13.8, 36.0) as given in Table 3-35. Because of the small sample size, the point estimate of the treatment effect has substantial uncertainty as indicated by the wide confidence interval. The treatment response of CAZAVI is also higher than what was observed in Study NXL104/2001 but is comparable to ceftazidime treatment response from published studies (see Table 3-39). For cIAI, there is little data in this study to make useful supportive evidence for what was observed in NXL104/2002.

At the recent Anti-Infective Drug Advisory Committee (AIDAC) meeting, the Sponsor presented the top-line results from the completed cIAI trial, D4280C00001/5, although, it has not been formally submitted to the Agency for review. The study was a randomized, multi-center, double-blind trial to assess the noninferiority of CAZAVI (2000 mg/500 mg, q8h) plus MTZ (0.5 g q8h) versus meropenem (1 g q8h) in the treatment of cIAI. For the primary endpoint of clinical cure at TOC in the mMITT population, the lower and upper bounds of the 95% confidence interval were -8.64% and 1.58%, respectively. However, subgroup analyses indicated that cIAI patients with moderate renal impairment (CrCl > 30 to ≤ 50 mL/min) at baseline in the CAZAVI group had a lower clinical cure rate (14/31, 45%) compared to patients treated with meropenem (26/35, 74%). In subjects with normal renal function or mild renal impairment at baseline, the clinical cure rates were similar across treatment arms and higher than the cure rate for the corresponding moderately impaired subgroup. Furthermore, among subjects with moderate renal impairment, there was also a numerical imbalance of deaths between the treatment groups (8 deaths in the CAZ-AVI subgroup compared to 3 deaths in the meropenem subgroup).

In conclusion, absent reliance on the 505(b)(2) approval pathway, the evidence of efficacy of CAZAVI is scant and uncertain. There may be evidence of efficacy in cUTI through the consistent numerically higher (not statistically higher) treatment responses against IMP/CIL and BAT in Study NXL104/2001 and interim Resistant Pathogen Study, resp. However, the confidence intervals are wide reflecting potential uncertainty that it could also be lower than IMP/CIL or BAT more often. Furthermore, the result of Study NXL104/2001 is not compatible with historically associated clinical response rate of ceftazidime from published reports to warrant extrapolation on the beneficial effect of avibactam and this may be due to the dose that was used in the trial. The data, although very limited may suggest, that the to be marketed dose of 2.5 g [2.0 g ceftazidime + avibactam 0.5 g] will yield clinical cures that are comparable with the historical ceftazidime treatment response as evidenced by the result of the interim data from the Resistant Pathogen Study. Until that study is completed, evidence is short of something definitive. On the other hand, for cIAI, CAZAVI appears less effective than meropenem and

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more so in the subgroup of patients with CAZ-sensitive infecting pathogen, a subset where even the use of ceftazidime without avibactam is still adequate. The pooled study for cIAI did not give supportive evidence as it is composed mainly of cUTI. In the subgroup of patients with CAZ-NS infecting pathogen, CAZAVI treatment response is numerically better than meropenem. It would be hard pressed not to think if avibactam does not interfere with the effect of ceftazidime in infections caused by CAZ-sensitive pathogens (see Table 3-38). Otherwise, the two subgroups should have a more consistent treatment response in both subgroups, at least numerically. With that said, given that the cIAI trial, D4280C00001/5, is already complete and data is just waiting processing, it is interesting to find out if this hypothesis has any basis or that the result observed is purely sporadic due to the size of the trial. Together with dose adjustments for renally-impaired patients that only surmised due to the completion of D4280C00001/5 and its topline results, it is tempting but probably prudent, from a rigorous scientific standpoint, to withhold the decision on the limited use in CIAI until all new data have been completely analyzed.

However, the seriousness of the threat of resistant bacteria and the need for new antibiotics requires a smarter look at evidentiary data. For instance, a drug's efficacy is not measured by whether its treatment response exceeds a comparator. In fact, a drug does not need to show that it is better than an active drug for it to be approved. It only needs to show that it is better than placebo. By no means conclusive as previously stated, the CAZ-NS subgroup is probably the only result that gives clue that somehow the CAZAVI works alongside comparability of CAZAVI treatment response, from published literature, and supportive data from in vitro microbiology, PK/PD models, and animal studies. With this and with all the reservations mentioned, I support approval of this product for limited use in the indications sought.

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2 INTRODUCTION

2.1 Overview

CAZAVI is composed of ceftazidime, an established third-generation parenteral cephalosporin antimicrobial agent approved for use in the United States (US) since 1985 under the registered trade name FORTAZ®, and avibactam, a novel non-β-lactam β-lactamase inhibitor. The avibactam component is a new chemical entity that is not currently marketed in any country, either alone or in combination. Avibactam protects ceftazidime from degradation by β-lactamase enzymes and maintains the antibacterial activity of ceftazidime against strains of *Enterobacteriaceae* and *Pseudomonas aeruginosa* that express several types of serine β-lactamases associated with multidrug resistance. Avibactam alone has no direct antibacterial activity (at concentrations achieved in humans at the proposed dose) and does not affect the activity of ceftazidime against ceftazidime-susceptible (CAZ-S) organisms or most anaerobic gram-negative rods.

The goal of the CAZAVI NDA is to demonstrate the safety and efficacy of ceftazidime combined with avibactam in patients with serious gram-negative infections proven or suspected to be caused by ceftazidime-resistant but CAZAVI-susceptible, β-lactamase-producing, gram-negative organisms in the indications listed below:

- Complicated intra-abdominal infections (cIAI)
- Complicated urinary tract infections (cUTI), including acute pyelonephritis (AP)

The application includes a description of the efficacy results of two Phase 2 studies that have been completed; one to assess the efficacy and safety of CAZAVI compared to imipenem-cilastatin in the treatment of subjects with cUTI (NXL104/2001) conducted in 137 subjects (135 of whom received study drug), and the other to assess the efficacy and safety of CAZAVI + MTZ in the treatment of subjects with cIAI (NXL104/2002) conducted in 204 subjects (201 of whom received study drug). In these trials, there was no pre-specification of any formal hypotheses for inferential testing, and statistical analysis was limited to descriptive data summaries. The application also includes the interim efficacy results of a single ongoing Phase 3 ceftazidime-resistant gram-negative study (Resistant Pathogen Study D4280C00006) in hospitalized adult patients with cIAI and cUTI; the latter study includes a subset of subjects with cUTI or cIAI caused by CAZ-NS pathogens, including ceftazidime-resistant (CAZ-R) and ceftazidime-intermediate (CAZ-I) pathogens.

In combination with the individual results from these trials, the application also includes a pooled analysis of the three studies to borrow information across studies and increase precision of the results. In addition, the application also includes a literature review was to assess the efficacy of ceftazidime in cIAI and cUTI and estimate the treatment effect restored by the addition of avibactam in infections caused by CAZ-R pathogens. Lastly, during the review

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process, the Phase 3 cIAI trials (D4280C00001/5) were completed. Data from the Phase 3 cIAI trial are not yet available but its topline results were submitted together with the 120 day safety update. However, a final study report has not been officially submitted to the Agency and full review of these data is not expected for the completion of this NDA.

Table 2-1: List of all studies included in analysis

Study	Phase and Design	Treatment Period	Study Patients	# of Subjects per Arm	Endpoint
NXL104/2001	phase 2, randomized, double-blind	cUTI patients including pyelonephritis	CAZAVI 0.625 g IV q8h × 7-14 days Imipenem/Cilastatin (IMP/CIL) 0.5 g IV q6h × 7-14 days	CAZAVI : 68 IMP/CIL: 67	Microbiological outcome at TOC (5 to 9 days post-therapy) in the ME pop
NXL104/2002	phase 2, randomized, double-blind	cIAI patients	CAZAVI 2.5 g IV q8h + MTZ 0.5 g IV q8h × 5-14 days Meropenem 1 g IV q8h × 5-14 days	CAZAVI + MTZ: 102 Meropenem: 102	Clinical outcome at TOC (2 weeks post therapy) in the ME pop
D4280C00006	Phase 3, randomized, open-label	cUTI (44) and cIAI (4) patients	CAZAVI 2.5 g IV q8h + MTZ 0.5 g IV q8h × 5-14 days Best Available Therapy (BAT) × 5-21 days	CAZAVI : 22 BAT: 26	Clinical Outcome at TOC in the mMITT pop

Follow-up period is 4-6 weeks
Microbiologically Evaluable or ME includes patients with qualifying pre-treatment pathogen, received at least 7 days of study drug, who has TOC assessment, and had no protocol violation

2.2 Regulatory History

2.2.1 Milestones

The initial Investigational New Drug (IND) application was submitted by Novexel in January 2008. Novexel transferred ownership to AstraZeneca in April 2010, who then transferred ownership to Cerexa, Inc., a wholly owned subsidiary of Forest Laboratories, Inc. in October 2011. The Phase 3 development program was initially discussed with the Agency at a Type C meeting held in October 2010.

On 11 March 2013, the FDA granted CAZAVI QIDP designation for the indications of cIAI, cUTI, and hospital-acquired bacterial pneumonia , pursuant to the GAIN Act, Title VIII (Sections 801-806) of the United States Food and Drug Administration Safety and Innovation Act (FDASIA). The FDA granted Fast Track designation for CAZAVI on 11 Mar 2013, pursuant to 21 CFR 312 Subpart E, Drugs Intended to Treat Life-threatening and Severely-debilitating Illnesses, Section

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506 (21 U.S.C 356) of the Federal Food, Drug and Cosmetic Act, and the FDA Guidance entitled "Fast Track Development Programs-Designation, Development, and Application Review" (FDA, 2006).

A Type B Pre-NDA meeting was held on December 19, 2013, the Applicant and Agency agreed that an NDA package based upon nonclinical data, Phase 1 data, data from two Phase 2 studies, and published ceftazidime data could be submitted through the 505(b)(2) pathway. The Agency also stated that the NDA should include evidence of the safety of avibactam as well as the contribution of avibactam to the efficacy of CAZAVI.

A summary of completed and ongoing clinical studies are summarized in Table 2-2 and Table 2-3, respectively.

Table 2-2: Completed Clinical Studies

Study ID	Study Type/Population
Clinical Pharmacology Studies with CAZAVI or Avibactam Alone	
NXL104/1001	Single-dose escalation PK/Healthy adults
NXL104/1002	Multiple-dose escalation PK/Healthy adults
NXL104/1003	Single-dose PK avibactam, renal impairment/Healthy adults
NXL104/1004	Single-dose PK avibactam, age and gender/Healthy adults
D4280C00007	Thorough QT/Healthy adults
D4280C00008	DME/Healthy adults
D4280C00009	ELF/Healthy adults
D4280C00010	Single- and multiple-dose PK, Japanese subjects/Healthy adults
D4280C00011	DDI PK, ceftazidime and avibactam/Healthy adults
D4280C00012	DDI PK, metronidazole/Healthy adults
Clinical Pharmacology Study with Avibactam Alone (From CXL development program)	
CXL-PK-01	DDI PK, ceftaroline and avibactam/Healthy adults
Phase 2 Clinical Efficacy and Safety Studies	
NXL104/2001	cUTI/Infected hospitalized adults
NXL104/2002	cIAI/Infected hospitalized adults

Sponsor's table 1.6-1

Table 2-3: Ongoing Clinical Studies

Study ID	Study Type/Population	Blinded
Phase 3 Clinical Efficacy and Safety Studies		
D4281C00001	HABP/VABP/Infected hospitalized adults	yes
D4280C00001/5[a]	cIAI/Infected hospitalized adults	yes
D4280C00002/4[b]	cUTI/Infected hospitalized adults	yes
D4280C00006	Resistant Pathogen: cIAI and cUTI/Infected hospitalized adults	no
D4280C00018	cIAI (Asia)/Infected hospitalized Chinese adults	yes
Clinical Pharmacology Studies with CAZAVI		
D4280C00014	Single-dose PK/Infected pediatric patients	no

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D4280C00020	Single- and multiple-dose PK (China)/Healthy adults	yes
D4280C00023	Multiple-dose, effect on intestinal flora (CAZAVI and CXL)/Healthy adults	no

[a] Subjects enrolled under identical study protocols D4280C00001 and D4280C00005 are combined into one study database (D4280C00001/5).
[b] Subjects enrolled under identical study protocols D4280C00002 and D4280C00004 are combined into one study database (D4280C00002/4).
Sponsor's Table 1.6-2

2.2.2 505(B)(2) Pathway

Section 505 of the Federal Food, Drug, and Cosmetic Act describes three types of new drug applications. One of these types, described in section 505(b)(2), is an NDA that contains full reports of investigations of safety and effectiveness where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference. This provision expressly permits the FDA to rely on the Agency's previous finding of safety and effectiveness for an approved drug.

The currently approved indications as described in the current US package insert are summarized in Table 2-4.

Table 2-4: Currently Labeled Clinical Indications for Ceftazidime

Indication	Pathogens
Lower respiratory tract	*P. aeruginosa*, *H. influenzae*, *Klebsiella* spp, *Enterobacter* spp, *P. mirabilis*, *Pseudomonas* spp, *E. coli*, *Serratia* spp, *Citrobacter* spp, *S. pneumoniae*, *S. aureus* (methicillin-susceptible strains)
Skin and skin structure	*P. aeruginosa*, *Klebsiella* spp, *E. coli*, *Enterobacter* spp, *Proteus* spp including *P. mirabilis* and indole+ *Proteus*, *Serratia* spp, *S. aureus* (methicillin-susceptible strains), *S. pyogenes* (group A beta hemolytic streptococci)
Urinary tract	*P. aeruginosa*, *Enterobacter* spp, *Proteus* spp including *P. mirabilis* and indole+ *Proteus*, *Klebsiella* spp, and *E. coli*
Bacterial septicemia	*P. aeruginosa, Klebsiella* spp, *H. influenzae, E. coli*, *Serratia* spp, *S. pneumoniae*, *S. aureus* (methicillin-susceptible)
Gynecological	*E. coli*
Intra-abdominal	*E. coli*, *Klebsiella* spp, *S. aureus* (methicillin-susceptible) and polymicrobial infections caused by aerobic and anaerobic organisms and *Bacteroides* spp. (many strains of *B. fragilis* are resistant)
Central nervous system	*H. influenzae*, *N. meningitidis,* and limited: *P. aeruginosa, S. pneumoniae*

2.2.3 Fixed Drug Combinations

Since CAZAVI is a combination of ceftazidime and avibactam, the applicant must also demonstrate the contribution of each component in a combination under the requirements of 21 CFR § 300.50. When the combination rule is applied to a proposed BL-BLI combination product, however, confirmatory clinical trials comparing the β-lactam alone to the combination product may not be feasible. There are other ways to reach the conclusion that both

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components contribute, such as supportive data from in vitro microbiology, PK/PD models, and animal studies. Evidence from subgroups of patients with resistant pathogens can be described as well, when the BL-BLI combination is compared to the standard-of care.

2.3 Data Sources

The main submission, including the case study report and datasets, are located in \\Cdsesub1\evsprod\NDA204496\0000. Additional data are located in sequence \\Cdsesub1\...\0012.

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3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Overall, the submitted data have adequate quality. However, the naming of the variables was not consistent among datasets in the two studies. For example, in some datasets the subject ID was concatenated with the Study ID and the Site ID to form the unique subject ID while in some the subject ID was the unique subject ID. Field names are also not consistent across trials. These make it difficult to replicate analysis from one study to another. Future review of the data should consider these discrepancies.

The final statistical analysis plan (SAP) for Study NXL104/2001 was finalized on 07 May 2009 (Version 1.0) while for Study NXL104/2001, it was finalized on 12 February 2009 (Version 1.0).

All tables and figures were created by the reviewer except when they are indicated to be lifted from the Sponsor's Case Study Report.

3.2 Evaluation of Efficacy

3.2.1 Study Design

Study NXL104/2001 was a Phase 2 multinational, multicenter, randomized, investigator-blind, active-control study in adult subjects with cUTI. One-hundred thirty-seven adult patients (>18 years of age and ≤90 years of age) with cUTI due to Gram-negative pathogens and judged by the investigator to require parenteral therapy and to be treatable with 7 to 14 days of therapy were enrolled. Patients who had received >1 dose of another potentially effective systemic antibiotic after obtaining the admission urine culture were excluded from the study. In addition, patients who had received more than 1 dose of a potentially effective systemic antibiotic therapy within 48 hours prior to the admission urine culture were also excluded from the study. Enrolled subjects were stratified by baseline type of infection (pyelonephritis and other types of cUTI without pyelonephritis) and randomized 1:1 to CAZAVI or imipenem-cilastatin (IMP/CIL) treatment groups. The dosage regimen for CAZAVI was 0.625 g (0.5 g ceftazidime + 0.125 g avibactam) q8h administered as a 30-minute IV infusion which was based on the US labeling text for ceftazidime (FORTAZ® package insert, 2010).

Enrolled subjects received at least 4 days of IV study antibiotic therapy while hospitalized. After at least 4 days of IV therapy, if they met protocol-specified criteria for clinical improvement they were permitted to switch to oral ciprofloxacin 500 mg every 12 hours to complete the treatment course. Patients received a minimum of 7 days and a maximum of 14 days of total antibiotic therapy (IV plus oral therapy). An overall clinical assessment, detailed description and evaluation of the infectious process, urinalysis, safety laboratory assessments, and quantitative urine cultures were performed at baseline, during IV study antibiotic therapy (Day 3, 4, or 5), at

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the discontinuation of IV therapy, at the test of cure (TOC) visit 5 to 9 days post-antibiotic therapy, and at 4 to 6 weeks post-antibiotic therapy (late follow-up or LFU). Patients on IV therapy at Day 6 to 8, 9 to 11 and 12 to 14 were also assessed for safety laboratory assessments on Day 7, 10 and 13, respectively (±1 day in each case).

Study NXL104/2002 was a multicenter, double-blind, randomized study to estimate the safety, tolerability, and efficacy of CAZAVI plus metronidazole vs. meropenem (MER) in adults with cIAI, i.e., those intra-abdominal infections requiring surgical intervention and which extend beyond the hollow viscus into the peritoneal space. Patients who received systemic antibacterial agents within the 72-hour pre-study period were not permitted to be enrolled, unless the patient had a new infection (not considered a treatment failure) and had received no more than 24 hours of total antibiotic therapy (preoperatively (prophylaxis) and/or postoperatively); or the patient was considered to have failed the previous treatment regimen

Two-hundred four hospitalized adult patients (18 to 90 years of age) with a presumed (preoperative) or definitive (intraoperative or postoperative) diagnosis of cIAI were enrolled. Enrolled patients were stratified by baseline severity of disease (Apache II score < 10, and > 10 but ≤ 25) and randomized 1:1 to CAZAVI plus metronidazole or meropenem. Study medication included 500mg avibactam IV / 2000mg ceftazidime IV in 100 mL over 30 minutes every 8hr plus 500mg metronidazole IV in 100 mL over 1hr every 8hr or 1000mg meropenem IV in 100 mL over 30 min every 8hr plus metronidazole placebo (0.9% saline), 100 mL over 1hr every 8hr.

Each patient was planned to complete the study, including follow-up, within approximately 8 weeks. The minimum duration of therapy was 5 days, and the suggested maximum duration of therapy was 14 days. After at least 5 days of therapy, if clinical improvement was clearly demonstrated (the patient was afebrile for > 24 hours, WBC < 12500/µL, and oral intake and bowel function had resumed), study therapy was to be discontinued at the discretion of the Investigator.

An overall clinical assessment, vital signs, and detailed abdominal assessment were performed at baseline, daily during study therapy, at the discontinuation of study therapy, at the early follow-up or Test of Cure visit (2 weeks) post-antibiotic therapy, and at the late follow-up visit (4 to 6 weeks post-antibiotic therapy). The Investigator was responsible for assessing the patient's response to therapy, determining the appropriate duration of IV therapy, and assessing the relationship of adverse events to study therapy.

3.2.2 Analysis Population

The specific criteria for inclusion in each population are outlined below:

Safety
All patients who received study therapy were evaluable for safety.

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Modified Intent to Treat (mMITT)

In either of the studies, this population includes all patients who:

- Received at least 1 dose of study therapy,
- Had a study qualifying pre-treatment urine culture containing $>10^5$ CFU/mL of at least one pathogen; or
- Met the disease definition of IAI and had at least one bacterial pathogen identified at study entry regardless of susceptibility

Clinically Evaluable (CE)

In Study NXL104/2001, this population is defined as all patients who:

- Had clinical evidence of UTI
- Were compliant with study drug therapy (received at least 7 total days of antibiotic therapy) or classed as an evaluable clinical failure after completing at least 48 hours of IV study therapy.
- Had a clinical outcome assessment at TOC visit

On the other hand, in Study NXL104/2002, the CE population includes all randomized patients who

- Had an appropriate diagnosis of intraperitoneal infection confirmed by operative findings and received an adequate course of therapy and
- Had sufficient information to determine clinical outcome at TOC.

An 'adequate course of therapy' was defined as a minimum of 80% and no more than 120% of the scheduled drug administered over the number of days administered.

Microbiologically Evaluable (ME)

In Study NXL104/2001, this population consists of all patients who:

- Had confirmed diagnosis, including clinical evidence of UTI and a positive admission urine culture defined as $>10^5$ CFU/mL (10^4 CFU/ml if bacteraemic) of a pathogen.
- Had received a proper total duration of antimicrobial therapy, of at least 7 days of 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.
- Had a clinical and microbiological assessment at the TOC visit, including a quantitative urine culture.
- Did not receive concomitant antibiotic therapy with a non-study drug antibiotic to which the pathogen was susceptible between the time of admission culture and the TOC culture.
- Did not have the admission urine culture obtained more than 48 hours prior to the start of study therapy.

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- Had >1 baseline pathogen susceptible to the IV study antimicrobial.

For Study NXL104/2002, on the other hand, this set includes a subset of CE patients 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.

While on study therapy, patients may be considered evaluable as clinical or microbiological failure at any time provided that they have received at least 48 hours of IV study therapy.

In this review, the analyses will mainly involve the mMITT or the ME population, unless specified otherwise.

3.2.3 Endpoints

In Study NXL104/2001, the protocol-specified primary endpoint was by-subject microbiological outcome at TOC (5 to 9 days post-antibiotic therapy) in the ME Population. Microbiological outcome was determined by computerized rules and was based on urinalysis, quantitative urine culture, pathogen identification, susceptibility testing, and blood cultures. At the TOC visit, a positive microbiological response was defined as 'eradication', i.e., a urine culture taken within 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 pathogen found at study entry at $>10^5$ CFU/mL was reduced to $<10^4$ CFU/mL.

In accordance with current regulatory guidance and the FDA recommendation at the Pre-NDA meeting (19 Dec 2013, Type B Pre-NDA Meeting), the Sponsor considered microbiological outcome at TOC in the Microbiological Modified Intent-to-treat (mMITT) Population is considered the primary endpoint in the Integrated Summary of Efficacy. In this review, we will consider the joint microbiological and clinical outcome at TOC in the Microbiological Modified Intent-to-treat (mMITT) Population as the primary endpoint as defined in the current draft guidance.

On the other hand, the protocol defined secondary endpoint was the clinical outcome at end of IV (EIV), TOC, and LFU in the CE population performed by a blinded investigator. Clinical response is based on whether all or most pre-therapy signs and symptoms of the index infection had resolved and no additional antibiotic was required. At the LFU visit, a patient was considered to have a clinical response if all or most pre-therapy signs and symptoms of the index infection showed no evidence of resurgence and no additional antibiotic was required.

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Another secondary endpoint is the by-pathogen microbiological response at end of IV, TOC, and LFU in the ME population.

In Study NXL104/2002, the protocol defined primary analysis variable for efficacy was the clinical outcome at Test of Cure (TOC) Visit, performed 2 weeks post-therapy in the microbiologically evaluable (ME) population. However, in this review, the primary analysis variable for efficacy is the clinical outcome at Test of Cure (TOC) Visit, performed 2 weeks post-therapy in the mMITT population.

The protocol-specified secondary endpoints include the

- Clinical response in each population in the ME population at the end of IV therapy and at the late follow-up 4 to 6 weeks post-therapy,
- Clinical response in clinically evaluable patients at the end of IV therapy, at the Test of Cure visit, and at the late follow-up 4 to 6 weeks post therapy
- Microbiological response at the end of IV therapy, at the Test of Cure visit, and at the late follow-up 4 to 6 weeks post therapy

Clinical response was recorded as 'cure', 'failure' and 'indeterminate' using the results of all the other efficacy assessments. In this review, the favorable clinical response is 'cure' and the unfavorable clinical response is 'failure' or 'indeterminate'.

The microbiological response was determined using the culture results performed at site of infection at the end of IV therapy, TOC and LFU visits for each pathogen identified at baseline. Cultures from the intra-abdominal site of infection and blood were collected for all patients at the time of surgery, and collected subsequently as clinically indicated. Cultures may also be taken from other clinically relevant sites. The data were recorded as 'Eradication', 'Presumptive eradication', 'Persistence', 'Persistence acquiring resistance', 'Presumed resistance', 'Relapse' and 'Indeterminate'. These data were further categorized to provide an overall microbiological response of either 'favorable' (i.e., 'Eradication' or 'Presumptive eradication'), unfavorable (i.e., 'Persistence', 'Persistence acquiring resistance', 'Presumed resistance', 'Relapse' or 'Indeterminate').

3.2.4 Statistical Methodologies

Both NXL104/2001 and NXL104/2002 were Phase II studies. These studies were not designed based on any formal hypothesis and inferential testing. They were intended to provide an estimate of efficacy and safety and serve as basis for designing of pivotal Phase III studies.

In Study NXL104/2001, the microbiological and clinical outcome variables are summarized descriptively by treatment group at each visit. The number and percent of patients achieving favourable response levels are presented along with the difference in response rates between

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treatment groups and two-sided 95% confidence intervals (not specified as Clopper-Pearson). In Study NXL104/2002, the number and percent of patients achieving a clinical response level are presented along with the difference in response rates between treatment groups. The exact 95% Clopper-Pearson confidence intervals for the observed difference in response rates between treatment groups are used. For all other variables, the response percentages are reported.

This review takes a different analysis approach; confidence intervals were computed using Wilson's method with continuity correction. Logistic regressions for the relationship between treatment response and the minimum inhibitory concentration (MIC) at baseline of the primary pathogen are also computed to determine the predictive probability of treatment response at any given MIC for each treatment. This uses the whole mMITT data and should not be construed as a PK/PD analysis. The DerSimonian and Laird method was used to estimate the overall effect of ceftazidime in historical trials in cUTI and cIAI under the random effects model to control for trial-to-trial variability. Lastly, Bayesian shrinkage estimators of the overall mean for the pooled estimates are also computed to borrow information across subpopulations (subjects with the same infection type). In this approach, each subpopulation in the pooled data assumes that it has its own unknown mean and variance, but the goal is to estimate the overall mean and variance of these subpopulations. This is done by shrinking the estimates of each subpopulation, i.e., using Bayesian estimation with shrinkage priors (priors that are centered at zero) for each of the subpopulation the shrinkage estimates of the proportion in each of the subgroups are obtained.

3.2.5 Patient Disposition, Demographic and Baseline Characteristics

3.2.5.1 Populations

Table 3-1: Analysis populations by treatment in Study NXL104/2001 and Study NXL 104/2002

	Study NXL104/2001			Study NXL104/2002		
	CAZAVI (N=69) n(%)	IMP/CIL (N=68) n(%)	Total (N=137) n(%)	CAZAVI + MTZ (N=102) n(%)	MER (N=102) n(%)	Total (N=204) n(%)
Safety	68 (98.6)	67 (98.5)	135 (98.4)	101 (99.0)	102 (100.0)	203 (99.5)
mMITT	46 (66.7)	49 (72.1)	95 (69.3)	85 (83.3)	89 (87.3)	174 (85.3)
ME	27 (39.1)	35 (51.5)	62 (45.3)	66 (64.7)	75 (73.5)	141 (69.1)
CE	28 (40.6)	36 (52.9)	64 (46.7)	84 (82.4)	89 (87.3)	173 (84.8)

The number of patients in each analysis set is summarized in Table 3-1. This tables shows that there were more patients excluded due to lack of valid pathogens isolated at baseline in Study NXL104/2001 (~30%) than in Study NXL104/2002 (~15%). Table 3-2 on the other hand shows the Sponsor-verified analysis populations for Study NXL104/2002. The sponsor stated that although the protocol and SAP stated that the evaluability and outcomes would be based on

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investigator assessments, they wanted to ensure consistent application of the definition of favorable response outlined in the protocol.

Table 3-2: Sponsor-verified analysis populations by treatment in Study NXL 104/2002

	CAZAVI + MTZ (N=102) n(%)	MER (N=102) n(%)	Total (N=204) n(%)
Safety	101 (99.0)	102 (100.0)	203 (99.5)
mMITT	85 (83.3)	89 (87.3)	174 (85.3)
ME	68 (66.7)	76 (74.5)	144 (70.6)
CE	87 (85.3)	90 (88.2)	177 (86.8)

3.2.5.2 Patient Disposition

Overall, majority of patients in both treatment groups of Study NXL104/2001 completed study treatment (72.5% in the CAZAVI group and 82.4% in the IMP/CIL group) (see Table 3-3). Of those patients who discontinued study treatment, the majority (13 patients in the CAZAVI group and 10 patients in the IMP/CIL group) did so because they 'did not meet inclusion/exclusion criteria'. These patients were enrolled based on Gram stain results that showed Gram-negative bacteria, but subsequently had no growth on the baseline culture.

Likewise, the majority of patients in both treatment groups completed the study (71.0% in the CAZAVI group and 79.4% in the IMP/CIL group). Of those who discontinued the study, the majority were patients who were enrolled based on Gram stain results which showed Gram negative bacteria, but who subsequently had no growth on the baseline culture, as described above, (13 [18.8%] and 11 [16.2%] patients in the CAZAVI and imipenem groups, respectively).

Table 3-3: Patient Disposition in Study NXL104/2001

	CAZAVI (N=69) n(%)	IMP/CIL (N=68) n(%)	Total (N=137) n(%)
Randomized	69	68	137
Did not receive study medication	1	1	2
Completed the study treatment	50 (72.5%)	56 (82.4%)	106 (77.4%)
Did not complete the study treatment	18 (26.1%)	11 (16.2%)	29 (21.2%)
Did not meet inclusion/exclusion criteria	13 (18.8%)	10 (14.7%)	23 (16.8%)
Discontinued due to serious adverse event	1 (1.4%)	0	1 (0.7%)
Investigator decision	0	1 (1.5%)	1 (0.7%)
Protocol deviation	1 (1.4%)	1 (1.5%)	2 (1.5%)
Withdrew consent	2 (2.9%)	0	2 (1.5%)
Lost to follow-up	1 (1.4%)	0	1 (0.7%)
Other	1 (1.4%)	0	1 (0.7%)
Completed the study	49 (71.0%)	54 (79.4%)	103 (75.2%)
Did not complete the study	20 (29.0%)	14 (20.6%)	34 (24.8%)

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Did not meet inclusion/exclusion criteria	13 (18.8%)	11 (16.2%)	24 (17.5%)
Discontinued due to serious adverse event	1 (1.4%)	0	1 (0.7%)
Withdrew consent	2 (2.9%)	0	2 (1.5%)
Protocol deviation	1 (1.4%)	0	1 (0.7%)
Lost to follow-up	2 (2.9%)	3 (4.4%)	5 (3.6%)
Other	1 (1.4%)	0	1 (0.7%)

On the other hand, in Study NXL104/2002, 91.2% in the CAZAVI + MTZ group and 93.1% in the meropenem (MER) group completed the study treatment. The treatment groups were generally similar with respect to reasons that patients discontinued from the study. Furthermore, the majority of patients in both treatment groups completed the study (89.2% in the CAZAVI group and 94.1% in the MER group).

Table 3-4: Patient Disposition in Study NXL104/2002

	CAZAVI + MTZ (N=102) n(%)	**MER (N=102) n(%)**	**Total (N=204) n(%)**
Randomized	102	102	204
Did not receive study medication	1 (1.0)	0	1 (0.5)
Completed the study treatment	93 (91.2)	95 (93.1)	188 (92.2)
Did not complete the study treatment			
Discontinued due to adverse event	4 (3.9)	1 (1.0)	5 (2.5)
Discontinued due to serious adverse event	2 (2.0)	3 (2.9)	5 (2.5)
Investigator decision	1 (1.0)	0	1 (0.5)
Protocol deviation	1 (1.0)	0	1 (0.5)
Lost to follow-up	0	2 (2.0)	2 (1.0)
Other	1 (1.0)	1 (1.0)	2 (1.0)
Completed the study	91 (89.2)	96 (94.1)	187 (91.7)
Did not complete the study	11 (10.8)	6 (5.9)	17 (8.3)
Clinical failure	0	1 (1.0)	1 (0.5)
Discontinued due to adverse event	2 (2.0)	0	2 (1.0)
Discontinued due to serious adverse event	3 (2.9)	3 (2.9)	6 (2.9)
Protocol deviation	1 (1.0)	0	1 (0.5)
Lost to follow-up	1 (1.0)	2 (2.0)	3 (1.5)
Other	4 (3.9)	0	4 (2.0)

3.2.5.3 Demographics and Baseline Characteristics

The demographic and key baseline characteristics of patients included in the all randomized population are summarized in Table 3-5. Demographics and baseline characteristics were generally similar across the treatment groups. Forty-six patients (67.6%) in the IMP/CIL group and 45 patients (67.2%) patients in the CAZAVI had a baseline pathogen with a colony count of $\geq 10^5$ CFU/mL. A minority of patients had concurrent bacteremia, with 3 (4.4%) and 4 (6.0%) patients in the CAZAVI and IMP/CIL groups, respectively, having a pathogen identified on the

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baseline blood culture. Approximately two-thirds of patients enrolled in either treatment group had acute pyelonephritis, including 44 patients (64.7%) in the CAZAVI group and 41 patients (61.2%) in the IMP/CIL group.

Table 3-5: Demographic and selected baseline characteristics in Study NXL104/2001 safety population

	CAZAVI (N=68) n(%)	IMP/CIL (N=67) n(%)	Total (N=135) n(%)
Age; years			
18 to 44	31 (45.6)	26 (38.8)	57 (42.2)
45 to 64	26 (38.2)	29 (43.3)	55 (40.7)
65 to 74	5 (7.4)	2 (3.0)	7 (5.2)
75 to 90	6 (8.8)	10 (14.9)	16 (11.9)
Mean (SD)	46.4 (18.2)	49.9 (18.4)	48.2 (18.4)
Gender			
Male	17 (25.0)	18 (26.9)	35 (25.9)
Female	51 (75.0)	49 (73.1)	100 (74.1)
Ethnicity			
Hispanic or Latino	18 (26.5)	18 (26.9)	36 (26.7)
Not Hispanic or Latino	50 (73.5)	49 (73.1)	99 (73.3)
Race			
White	40 (58.8)	41 (61.2)	81 (60.0)
Black or African American	2 (2.9)	5 (7.5)	7 (5.2)
Asian	8 (11.8)	5 (7.5)	13 (9.6)
Other	18 (26.5)	16 (23.9)	34 (25.2)
BMI			
Mean (SD)	28.0 (7.4)	28.6 (7.2)	28.3 (7.3)
Baseline Pathogen(s) – Urine culture			
$\geq 10^5$ CFU/mL	46 (67.6)	45 (67.2)	91 (67.4)
$< 10^5$ CFU/mL	0	4 (6.0)	4 (3.0)
Baseline Etiologic Pathogen(s) – Blood Culture			
Present	3 (4.4)	4 (6.0)	7 (5.2)
Absent	65 (95.6)	63 (94.0)	128 (94.8)
Type of infection			
cUTI	24 (35.3)	26 (38.8)	50 (37.0)
Pylonephritis	44 (64.7)	41 (61.2)	85 (63.0)

The demographics of patients included in the safety population for Study NXL 104/2002 are summarized in Table 3-6. Race, gender, age, Apache II score, and BMI were generally similar across the treatment groups. There were more patients of ≥65 years of age in the meropenem group, with the mean/median ages similar across both treatment groups. The majority (83%) of patients enrolled had Apache II scores ≤10, with about half of the patients in either treatment

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group with scores of ≤5. There were more patients with Apache II scores of >15 in the CAZAVI + MTZ treatment group.

Table 3-6: Demographic characteristics in Study NXL104/2002 – Safety population

	CAZAVI + MTZ (N=101) n(%)	MER (N=102) n(%)	Total (N=203) n(%)
Age; years			
18 to 44	54 (53.5)	58 (56.9)	112 (55.2)
45 to 64	40 (39.6)	30 (29.4)	70 (34.5)
65 to 74	5 (5.0)	11 (10.8)	16 (7.9)
75 to 90	2 (2.0)	3 (2.9)	5 (2.5)
Mean (SD)	43.0 (15.9)	42.6 (18.1)	42.8 (17.0)
Gender			
Male	70 (69.3)	81 (79.4)	151 (74.4)
Female	31 (30.7)	21 (20.6)	52 (25.6)
Ethnicity			
Hispanic or Latino	3 (2.9)	2 (2.0)	5 (2.5)
Not Hispanic or Latino	98 (97.0)	100 (98.0)	198 (97.5)
Race			
White	56 (55.4)	65 (63.7)	121 (59.6)
Black or African American	0	1 (1.0)	1 (0.5)
Asian	32 (31.7)	23 (22.6)	55 (27.1)
Other	13 (12.9)	13 (12.8)	26 (12.8)
BMI			
Mean (SD)	24.2 (5.2)	25.3 (4.9)	24.8 (5.1)
APACHE II			
≤ 10	84 (83.2)	85 (83.3)	169 (83.3)
> 10 and ≤ 25	17 (16.8)	17 (16.7)	34 (16.7)
> 25	0	0	0
Mean (SD)	6.4 (4.4)	5.8 (4.0)	6.1 (4.2)

Primary diagnoses and surgical intervention are summarized in Table 3-7, below. About half the patients in either treatment arm were enrolled with appendicitis (~47%). Almost all patients had pre-operative infections and 90% underwent open laparotomy as the initial surgical intervention. Patients most commonly had peritonitis (localized or general). Overall, the types and sites of infection and operative procedures were similar across the treatment groups.

Table 3-7: Primary Diagnosis and Surgical Intervention by Treatment Group in Study NXL104/2002 – Safety Population

	CAZAVI + MTZ (N=101) n(%)	MER (N=102) n(%)	Total (N=203) n(%)

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Anatomical site of origin of current infection			
Stomach/Duodenum	29 (28.7)	23 (22.6)	52 (25.6)
Gall Bladder	5 (5.0)	9 (8.8)	14 (6.9)
Small Bowel	4 (4.0)	13 (12.8)	17 (8.4)
Appendix	49 (48.5)	47 (47.0)	96 (47.3)
Colon	12 (11.9)	6 (5.9)	18 (8.9)
Parenchymal (liver)	1 (1.0)	3 (2.9)	4 (2.0)
Parenchymal (spleen)	1 (1.0)	0	1 (0.5)
Other	0	2 (2.0)	2 (1.0)
Infection Process			
Single abscess	23 (22.8)	22 (21.6)	45 (22.2)
Multiple abscess	3 (3.0)	6 (5.9)	9 (4.4)
Localized peritonitis	39 (38.6)	42 (41.2)	81 (39.9)
Generalized Peritonitis	45 (44.6)	47 (46.1)	92 (45.3)
Visceral perforation	44 (43.6)	40 (39.2)	84 (41.4)
Other	0	0	0
Type of Procedure			
Open laparotomy	91 (90.1)	91 (89.2)	182 (89.7)
Laparoscopic procedure	9 (8.9)	9 (8.8)	18 (8.9)
Percutaneous drainage	1 (1.0)	2 (2.0)	3 (1.5)
Other	0	0	0
Is current process a post-op infection?			
Yes	3 (3.0)	2 (2.0)	5 (2.5)
No	98 (97.0)	100 (98.0)	198 (97.5)
If 'Yes' was previous procedure:			
Clean	2 (2.0)	2 (2.0)	4 (2.0)
Contaminated	1 (1.0)	0	1 (0.5)

3.2.5.4 Receipt of Prior Medications

As shown in Table 3-8, 13 patients (7 in CAZAVI and 6 in IMP/CIL) in Study NXL104/2001 received prior antibiotic therapy. The most common antibiotic used was ceftriaxone (4 patients) in the CAZAVI group and ciprofloxacin (5 patients) in the IMP/CIL arm. There is an imbalance in the receipt of concomitant antibiotics. Only 5 patients received them in the CAZAVI arm and 21 in the IMP/CIL arm. The most commonly used antibiotic concomitant medications were amoxicillin/clavulanate, ciprofloxacin, imipenem (3 patients in the IMP/CIL group), and metronidazole. Ciprofloxacin is approved as an oral switch.

Table 3-8: Use of prior and concomitant antibacterial medications in Study NXL104/2001 – mMITT Population

	CAZAVI (N= 46) n(%)	IMP/CIL (N= 49) n(%)	Total (N=95) n(%)

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Prior Antibacterial Medication (mMITT)			
Yes	7 (15.2)	6 (12.2)	13 (9.5)
No or Missing	39 (84.8)	43 (87.8)	82 (86.3)
Concomitant Antibacterial Medication (mMITT)			
Yes	5 (10.9)	21 (42.9))	26 (27.4)
No or Missing	41 (89.1)	28 (57.1)	69 (72.6)

In Study NXL104/2002, about half the patients in each treatment group in the mMITT population had received one or more doses of prior antibiotic therapy. Four patients (Subject ID 40005, 67001, 80002, and 80004 in the CAZAVI + MTZ group) received >24 hours of prior antibiotics. All 4 patients had failed prior antibiotics, meeting criteria for enrollment in the study.

Of the remaining patients, 41 (48.2%) and 44 (49.4%) patients in the CAZAVI + MTZ and meropenem groups, respectively, received only one dose of a prior antibiotic treatment regimen. Twenty-six (30.6%) and 16 (18.0%) in the CAZAVI + MTZ and meropenem groups, respectively, received multiple prior antibacterial medications.

Table 3-9: Use of prior antibacterial medications in Study NXL104/2002 – mMITT Population

	CAZAVI + MTZ (N= 85) n(%)	**MER (N= 89) n(%)**	**Total (N=174) n(%)**
Prior Antibacterial Medication (mMITT2)			
Yes	45 (52.9)	44 (49.4)	89 (51.1)
No or Missing	40 (47.1)	45 (50.6)	84 (48.3)
If 'Yes', how many doses			
1 in ≤ 24 hrs	41 (48.2)	44 (49.4)	85 (48.9)
2 in ≤ 24 hrs	4 (4.7)	0	4 (2.3)
Multiple Prior Antibacterial Medication			
Yes	26 (30.6)	16 (18.0)	42 (24.1)
No	19 (22.4)	28 (31.5)	47 (27.0)

Five patients received concomitant vancomycin (3 in CAZAVI + MTZ group and 2 in Meropenem group), and 5 patients received concomitant linezolid (3 in CAZAVI + MTZ group and 2 in Meropenem group). In the CAZAVI + MTZ group the patients who received vancomycin either discontinued from study therapy, had MRSA, or had enterococcous at baseline.

3.2.5.5 Susceptibility of Baseline Pathogens

In Study NXL 104/2001*, E. coli* was the most common pathogen isolated; it was identified in 40 patients in the CAZAVI group and 41 patients in the IMP/CIL group. Table 3-16 shows the list of

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pathogens and the frequency with which they were observed in the trial. Table 3-10 displays the in vitro non-susceptibility of baseline pathogens isolated from patients in the mMITT population. As shown, 14 baseline isolates in the CAZAVI arm are not susceptible to ceftazidime while 2 baseline isolates in the IMP/CIL arm are non-susceptible to IMP [Subject IDs 50477-48008, 50477-40010]. All of the 14 non-susceptible isolates were *E. coli* and the 2 isolates the IMP/CIL group were *P. aeruginosa* and *M. morganii*. The minimum inhibitory concentration (MIC) of *P. aeruginosa* is 16 and 2 for *M. morganii*.

Table 3-10: Study NXl 104/2001 baseline pathogens that are non-susceptibility in vitro to either ceftazidime (CAZ) or imipenem (IMP)

	CAZAVI (N= 46) n(%)	IMP/CIL (N= 49) n(%)	Total (N=95) n(%)
CAZ Not susceptible	14 (30.4)	18 (36.7)	32 (33.7)
Escherichia coli	14 (30.4)	17 (34.7)	31 (32.6)
Enterobacter cloacae	0	1 (2.0)	1 (1.1)
Pseudomonas aeruginosa	0	1 (2.0)	1 (1.1)
IMP Not susceptible	3 (6.5)	2 (4.1)	5 (5.3)
Escherichia coli	3 (6.5)	0	3 (3.2)
Pseudomonas aeruginosa	0	1 (2.0)	1 (1.1)
Morganella Morganii	0	1 (2.0)	1 (1.1)

As expected in patients with complicated intra-abdominal infections, *E. coli* was the most common pathogen isolated in Study NXL104-2002.

Table 3-11 shows the baseline pathogens that are non-susceptible in vitro to either CAZ or meropenem. In this table, 30 baseline isolates in the CAZAVI + MTZ group are not susceptible to ceftazidime while 4 baseline isolates in the MER group are non-susceptible to meropenem [Subject IDs 42012, 53002, 63006, 68019]. The pathogens isolated from these 4 patients are *P. Aeruginosa* (MIC >16), *L. acidophilus* (MIC >16), *K. pneumoniae* (MIC >2), and *A. baumanii* (MIC >16).

Table 3-11: Study NXL 104/2002 baseline pathogens that are non-susceptibility in vitro to either ceftazidime (CAZ) or meropenem

	CAZAVI + MTZ N = 85 n/N1(%)	Meropenem N = 89 n/N1(%)	Total N= 174 n/N1(%)
CAZ Not susceptible, N1	30	25	55
Acinetobacter baumannii	1 (3.3)	1 (4,0)	2 (3.6)
Citrobacter braakii	0	1 (4.0)	1 (1.8)
Enterobacter cloacae	0	1 (4.0)	1 (1.8)
Escherichia coli	22 (73.3)	17 (68.0)	39 (70.9)
Klebsiella pneumoniae	4 (13.3)	4 (16.0)	8 (14.5)
Proteus mirabilis	1 (3.3)	0	1 (1.8)
Providencia stuartii	1 (3.3)	0	1 (1.8)
Pseudomonas aeruginosa	1 (3.3)	1 (4.0)	2 (3.6)

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Meropenem Not susceptible, N1	4	4	9
Acinetobacter baumannii	1 (25.0)	1 (25.0)	2 (22.2)
Klebsiella pneumoniae	1 (25.0)	1 (25.0)	2 (22.2)
Lactobacillus acidophilus	0	1 (25.0)	1 (11.1)
Pseudomonas aeruginosa	2 (50.0)	1 (25.0)	3 (33.3)

3.2.6 Analysis Results

3.2.6.1 Study NXL104-2001

3.2.6.1.1 Clinical and Microbiological Response at TOC

Table 3-12 presents the Sponsor's primary efficacy analysis result for the cUTI study based on the microbiological response at the TOC visit (2 weeks post therapy) in the ME population. Nineteen patients out of 27 (70.4%) in the CAZAVI group and 25/35 (71.4%) in the imipenem group had a favourable microbiological response (eradication). The observed difference in response rates was –1.1%, with the corresponding 95% exact conference interval being (-27.2%, 25.0%).

Table 3-12: NXL-104-2001: Microbiological response at TOC in the ME population

	CAZAVI N = 27 n (%)	**IPM/CIL N = 35 n (%)**	**Observed Diff (95% CI)**
Microbiological Outcome			
Eradication	19 (70.4)	25 (71.4)	-1.1 (-27.2, 25.0)
Persistence	8 (29.6)	10 (28.6)	
Persistence with acquisition of resistance	0	0	
Indeterminate	0	0	

Due to changes in Guidance on recommended endpoints, Table 3-13 presents three endpoints, microbiological, clinical, and clinical + microbiological outcome based on the mMITT population. Thirty-one patients (67.4%) in the CAZAVI group and 31 (63.3%) in the IMP/CIL group had favorable microbiological response (eradication). The observed difference in response rates was 4.1%, with the corresponding 95% conference interval being (-16.1%, 23.8%). For the clinical response outcome, 37 (80.4%) patients in the CAZAVI group achieved clinical cure at TOC while 36 (73.5%) of the patients in the IMP/CIL group achieved cure. The difference in the rate of clinical cure is 7.0 with a 95% CI of (-11.6, 24.7). Lastly for the clinical and microbiological outcome, 29 (63.0%) of the patients in the CAZAVI group achieved both clinical cure and microbiologic eradication while 25 (51.0%) of the patients in the IMP/CIL group achieved the same clinical and microbiologic response. The difference in the response rates is 12.0 with a 95% CI of (-9.1%, 31.7%). In all of these endpoints, the point estimate of the difference shows that the response rate for CAZAVI is numerically higher than IMP/CIL. However, the wide

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confidence intervals about the difference in the response rates show the level of uncertainty in the results.

Table 3-13: NXL-104-2001: Clinical and Microbiological response at TOC in the mMITT population

	CAZAVI N = 46 n (%)	IPM/CIL N = 49 n (%)	Observed Diff (95% CI)
Microbiological Response			
Eradication	31 (67.4)	31 (63.3)	4.1 (-16.1, 23.8)
Persistence	10 (21.7)	14 (28.6)	
Persistence with acquisition of resistance	0	0	
Indeterminate	5 (10.9)	4 (8.2)	
Clinical Response			
Cure	37 (80.4)	36 (73.5)	7.0 (-11.6, 24.7)
Failure	5 (10.9)	9 (18.4)	
Indeterminate	4 (8.7)	4 (8.2)	
Clinical & Microbiological Response			
Cure + Eradication	29 (63.0)	25 (51.0)	12.0 (-9.1, 31.7)
Failure + Persistence or Indeterminate	17 (37.0)	24 (49.0)	

A logistic regression is used to fit the logarithm of the odds of clinical cure and microbiological eradication at TOC with treatment and the baseline MIC to the assigned treatment of the primary pathogen. Figure 1 shows the curve of predictive probability of achieving clinical cure and microbiological eradication as a function of the baseline treatment MIC for each of the treatment group and its associated confidence bands. The graph shows that as the MIC gets higher, the probability of achieving clinical cure and microbiological eradication gets lower. However, the confidence bands about the predictive probability curve are wide, for e.g. the true predictive probability at a MIC = 2 in CAZAVI can be anywhere within 5.8% to 75.6% with 95% confidence. Furthermore, the odds ratio between CAZAVI and IMP/CIL is 1.741 with a 95% Wald confidence limit of (0.7218, 4.1993), i.e., the odds that a patient achieves both clinical cure and microbiological eradication given that it is treated with CAZAVI is 1.741 times larger than the odds compared of the outcome occurring in the IMP/CIL group. The confidence interval, however, shows that it cannot be ruled out that the odds that a patient achieves both clinical cure and microbiological eradication given that it is treated with CAZAVI is larger at the 95% significance level. Note that this analysis uses the whole mMITT population instead of a select number of patients used to demonstrate PK/PD.

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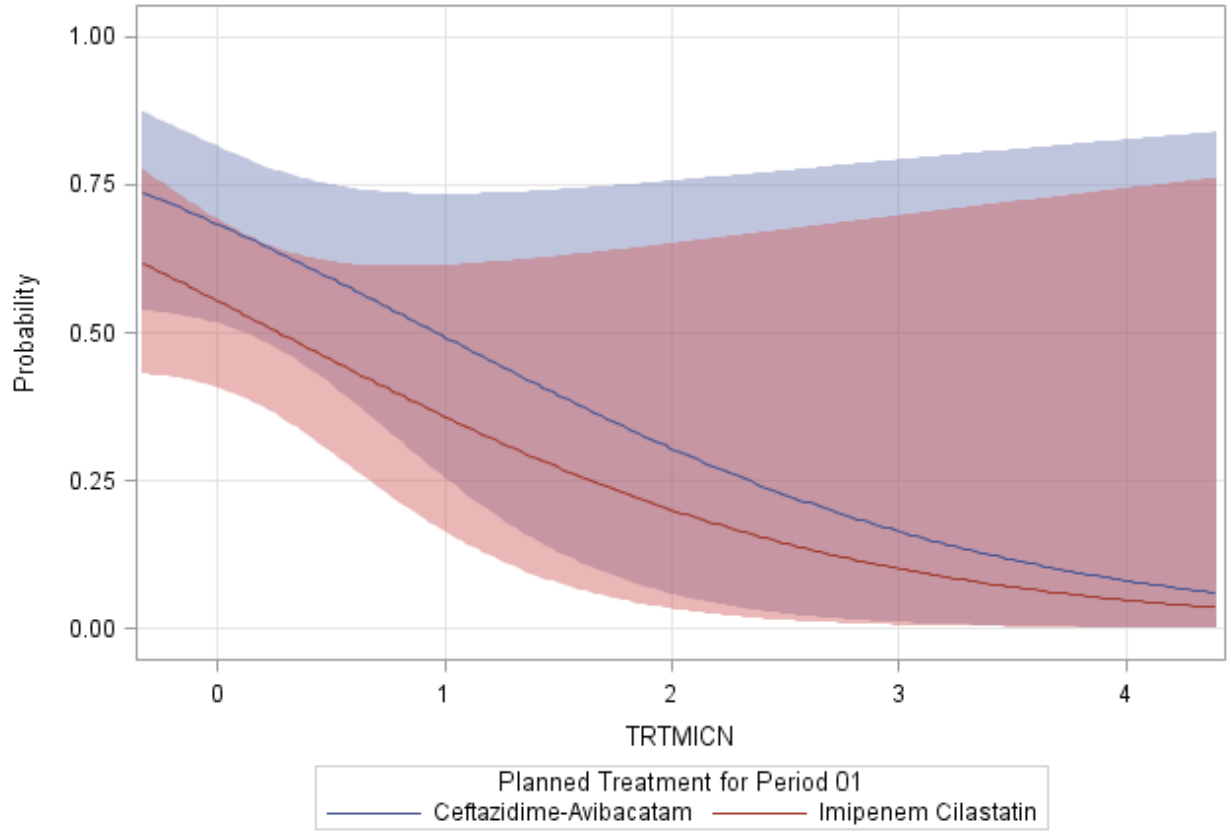
Figure 1: Predictive probability for achieving clinical cure and microbiological response as a function of treatment MIC – (mMITT Population)



3.2.6.1.2 Clinical and Microbiological Response at TOC by Primary Diagnosis

Patients were stratified by primary diagnosis at study entry (acute pyelonephritis vs other cUTI). In the CAZAVI group at TOC, 66.7% (20/30) patients with acute pyelonephritis and 56.3% (9/16) patients with other cUTI had a clinical cure and favorable microbiological response (see Table 3-14. In the IMP/CIL group at TOC, 51.7% (15/29) patients with acute pyelonephritis and 10/20 (50.0%) patients with other cUTI had clinical cure and favorable microbiological response.

Table 3-14: Summary of clinical cure + microbiological eradication by primary diagnosis –mMITT population

	CAZAVI N = 46 n (%)	IPM/CIL N = 49 n (%)	Observed Diff (95% CI)
Acute Pyelonephritis	30	29	
Clinical cure + Microbiologic eradication	20 (66.7)	15 (51.7)	14.9 (-13.3, 43.1)
Either clinical failure or microbiologic persistence or indeterminate	10 (33.3)	14 (48.3)	
cUTI without Acute Pyelonephritis	16	20	

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Clinical cure + Microbiologic eradication	9 (56.3)	10 (50.0)	6.3 (-32.1, 44.6)
Either clinical failure or microbiologic persistence or indeterminate	7 (43.8)	10 (50.0)	

3.2.6.1.3 Clinical and Microbiological Response at EOIV and LFU

The microbiological response could not be located at EOIV and LFU except for patients whose infections were cause by CAZ-NS pathogens, hence only the clinical outcome at EOIV and LFU will be presented (see Table 3-15).

Table 3-15: Clinical Response at EOIV and LFU - mMITT

	CAZAVI N = 46 n (%)	IPM/CIL N = 49 n (%)	Observed Diff (95% CI)
EOIV			
Clinical cure	43 (93.5)	46 (93.9)	-0.4 (-12.3, 11.1)
Clinical failure or indeterminate	3 (6.5)	3 (6.1)	
LFU			
Sustained Clinical cure	33 (71.7)	32 (65.3)	6.4 (-12.4, 24.7)
Clinical relapse, failure or indeterminate	13 (18.3)	17 (34.7)	

3.2.6.1.4 By Pathogen Clinical and Microbiological Response at TOC

Clinical cure and favorable microbiological response (eradication) at TOC was evaluated by pathogen, as shown in Table 3-16. *E. coli* was the most common pathogen, and was eradicated in 26/40 (65.0%) patients in the CAZAVI group and 22/41 (53.7%) patients in the IMP/CIL group. The number of patients with pathogens other than *E. coli* was extremely small prohibiting comparisons across treatment groups. In the CAZAVI group, *C. koseri* (1 pathogen) was eradicated and P. aeruginosa (3 pathogens) was not eradicated. In the IMP/CIL group, *E. cloacae* (1 pathogen), *M. morganii* (1 pathogen) and *P. mirabilis* (1 pathogen) were eradicated. There were two patients with 2 or more baseline pathogen: patient 20413 had *C. Koseri* and *E. coli* and patient 40408 had *A. baumanii*, *A. junii*, and *P. auruginosa.* There were 3 patients, including 2 in the CAZAVI group and 1 in the IMP/CIL group, that were flagged as members of the mMITT population but with no listed pathogen.

Table 3-16: Per pathogen response (clinical cure + eradication) in the mMITT population

Pathogen	CAZAVI (N= 46) n/N (%)	IMP/CIL (N= 49) n/N (%)	Observed Diff 95% CI
Acinetobacter baumanii	0/0	0/1 (0.0)	
Acinetobacter junii	0/0	0/1 (0.0)	

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Citrobacter koseri	1/1 (100)	0/0
Enterobacter aerogenes	0/0	0/1 (0.0)
Enterobacter cloacae	0/0	0/1 (0.0)
Escherichia coli	26/40 (65.0)	22/41 (53.7)
Klebsiella oxytoca	0/0	1/1 (100)
Morganella morganii	0/0	1/1 (100)
Proteus mirabilis	0/0	1/1 (100)
Pseudomonas aeruginosa	0/3 (0.0)	0/1 (0.0)

3.2.6.1.5 Subgroup Analysis: Ceftazidime Non-susceptible

3.2.6.1.5.1 Clinical and Microbiological Response at TOC

Table 3-17 presents the same endpoints based on a subgroup of mMITT patients with Ceftazidime-nonsusceptible (CAZ-NS) isolates on the mMITT population. Nine patients (64.3%) in the CAZAVI group and 10 (55.6%) in the IMP/CIL group had favorable microbiological response (eradication). The observed difference in response rates was 8.7%, with the corresponding 95% conference interval being (-27.4%, 41.3%). For the clinical response outcome, 11 (78.6%) patients in the CAZAVI group achieved clinical cure at TOC while 10 (55.6%) of the patients in the IMP/CIL group achieved clinical cure. The difference in the rate of clinical cure is 23.0 with a 95% CI of (-14.0%, 51.2%). Lastly for the clinical and microbiological outcome, 8 (57.1%) of the patients in the CAZAVI group achieved both clinical cure and microbiologic eradication while 7 (38.9%) of the patients in the IMP/CIL group achieved the same clinical and microbiologic response. The difference in the response rates is 18.3 with a 95% CI of (-22.4, 58.9).

Table 3-17: NXL-104-2001: Clinical and Microbiological response at TOC in the CAZ-NS Subgroup of the mMITT population

	CAZAVI N = 14 n (%)	IPM/CIL N = 18 n (%)	Observed Diff (95% CI)
Microbiological Outcome			
Eradication	9 (64.3)	10 (55.6)	8.7 (-27.4, 41.3)
Persistence	3 (21.4)	6 (33.3)	
Persistence with acquisition of resistance	0	0	
Indeterminate	2 (14.3)	2 (11.1)	
Clinical Response			
Cure	11 (78.6)	10 (55.6)	23.0 (-14.0, 51.2)
Failure	2 (14.3)	5 (27.8)	
Indeterminate	1 (7.1)	3 (16.7)	
Clinical & Microbiological Outcome			
Cure + Eradication	8 (57.1)	7 (38.9)	18.3 (-22.4, 58.9)
Failure + Persistence or Indeterminate	6 (42.9)	11 (61.1)	

Reference ID: 3687044

Table 3-18 shows the results for the clinical response by treatment and susceptibility to treatment. In this table, one can think of the patients in the IMP/CIL arm whose baseline pathogen are non-susceptible to imipenem as the "putative placebo" group since these patients received inadequate therapy. On the other hand, the addition of avibactam makes the treatment adequate even if the baseline pathogen is non-susceptible to ceftazidime. Note that since the clinical cure and microbiological eradiation rate in the CAZAVI group is 63.0% (see Table 3-13) and the patients with inadequate therapy is 1 (50.0%), the difference in clinical cure and microbiological eradiation rate between the CAZAVI group and the patients given inadequate therapy is 13.0 with a 95% CI of (-36.8, 62.2). The confidence intervals are wide because patient number in the inadequate therapy group is low (i.e., the group has 2 patients). This reflects the amount of uncertainty associated to this point estimate.

Table 3-18: Clinical Response by Treatment and Susceptibility of Pathogen to Treatment Assignment – mMITT population

	CAZAVI N = 46 n/N1(%)	IPM/CIL N = 49 n/N1(%)
Susceptible to	**Ceftazidime (N1 =32)**	**Imipenem (N1 = 47)**
Cure + Eradication (n/N1 %)	21 (65.6)	24 (51.1)
Failure + Persistence or Indeterminate (n/N1 %)	11 (34.4)	23 (48.9)
Nonsusceptible to	**Ceftazidime (N1 = 14)**	**Imipenem (N1= 2)**
Cure + Eradication (n/N1 %)	8 (57.1)	1 (50.0)
Failure + Persistence or Indeterminate (n/N1 %)	6 (42.9)	1 (50.0)

3.2.6.1.5.2 By Pathogen Clinical and Microbiological Response at TOC

Favourable microbiological response by pathogen at TOC is shown in Table 3-19. As was noted in Table 3-10, *E. coli* was the most common pathogen, and was eradicated in 8/14 (57.1%) cases in the CAZAVI group and 7/18 (43.8%) cases in the imipenem group at TOC.

Table 3-19: Per pathogen response (clinical cure + eradication) among CAZ-NS patients

	CAZAVI (N= 46) n/N1(%)	IMP/CIL (N= 49) n/N1(%)
Ceftazidime Non-susceptible, N1	14	18
Escherichia coli	8 (57.1)	7 (43.8)
Enterobacter cloacae	0	0/1
Pseudomonas aeruginosa	0	0/1

Reference ID: 3687044

3.2.6.1.5.3 Clinical and Microbiological Response at TOC by Primary Diagnosis

In the CAZAVI group at TOC, 66.7% (4/6) patients with acute pyelonephritis and 50.0% (4/8) patients with other cUTI had a clinical cure and favorable microbiological response (see Table 3-20) . In the IMP/CIL group at TOC, 25.0% (2/8) patients with acute pyelonephritis and 5/10 (50.0%) patients with other cUTI had clinical cure and favorable microbiological response.

Table 3-20: Summary of clinical cure + microbiological eradication by primary diagnosis –CAZ-NS subgroup of mMITT population

	CAZAVI N = 46 n/N1 (%)	IPM/CIL N = 49 n/N1 (%)	
Acute Pyelonephritis, N1	6	8	
Clin cure + Microbiologic eradication	4 (66.7)	2 (25.0)	41.7 (-16.4, 75.9)
Either clinical failure or microbiologic persistence or indeterminate	2 (33.3)	6 (75.0)	
cUTI without Acute Pyelonephritis, N1	8	10	
Clinical cure + Microbiologic eradication	4 (50.0)	5 (50.0)	0.0 (-44.2, 44.2)
Either clinical failure or microbiologic persistence or indeterminate	4 (50.0)	5 (50.0)	

3.2.6.1.5.4 Clinical and Microbiological Response at EOIV and LFU

Table 3-21 shows the clinical and microbiological outcome at EOIV in the CAZ-NS subgroup of the mMITT population. The three endpoints have similar rate, i.e., 13/14 (92.9) in the CAZAVI group and 18/18 in the IMP/CIL group.

Table 3-21: NXL-104-2001: Clinical and Microbiological response at EOIV in the CAZ-NS Subgroup of the mMITT population

	CAZAVI N = 14 n (%)	IPM/CIL N = 18 n (%)	Observed Diff 95% CI
Microbiological Outcome			
Eradication	13 (92.9)	18 (100.0)	-7.1 (-35.8, 15.8)
Persistence	0	0	
Recurrence	0	0	
Indeterminate	1 (7.1)	0	
Clinical Response			
Cure	13 (92.9)	18 (100.0)	-7.1 (-35.8, 15.8)
Failure	0	0	
Indeterminate	1 (7.1)	0	
Clinical & Microbiological Outcome			
Clinical cure + Microbiologic eradication	13 (92.9)	18 (100.0)	-7.1 (-35.8, 15.8)
Either clinical failure or microbiologic persistence or indeterminate	1 (7.1)		

Reference ID: 3687044

Table 3-22: NXL-104-2001: Clinical and Microbiological response at LFU in the CAZ-NS Subgroup of the mMITT population

	CAZAVI N = 14 n (%)	IPM/CIL N = 18 n (%)	Observed Diff 95% CI
Microbiological Outcome			
Eradication	7 (50.0)	7 (38.9)	11.1 (-24.9, 44.3)
Persistence	3 (14.3)	6 (33.3)	
Recurrence	2 (14.3)	0	
Indeterminate	2 (14.3)	5 (27.8)	
Clinical Response			
Sustained Cure	10 (71.4)	11 (61.1)	10.3 (-25.6, 41.7)
Clinical Relapse	1 (7.1)	1 (5.6)	
Clinical Failure	2 (14.3)	5 (27.8)	
Indeterminate	1 (7.1)	1 (5.6)	
Clinical & Microbiological Outcome			
Sustained Clin cure + Microbiologic eradication	6 (42.9)	7 (38.9)	4.0 (-30.7, 38.3)
Either clinical failure or microbiologic persistence or indeterminate	8 (57.1)	11 (61.1)	

Table 3-22 displays clinical and microbiological outcome at LFU in the CAZ-NS subgroup of the mMITT population. At this time point, 7/14 (50.0%) patients in the CAZAVI group and 7/18 (38.9%) patients in the IMP/CIL group had favourable microbiological responses (eradication). In terms of clinical outcome, 10/14 (71.4%) had sustained clinical cure in the CAZAVI group while 11/18 (61.1%) achieved the same clinical outcome in the IMP/CIL group. Lastly, the combined clinical cure and microbiological eradication rate in the CAZAVI group is 6/18 (42.9%) and 7/18 (38.9%) in the IMP/CIL group.

3.2.6.2 Study NXL104-2002

3.2.6.2.1 Clinical Response at TOC in the mMITT Population and CAZ-NS Subgroup of the mMMITT Population

The Sponsor's primary efficacy analysis was performed on the ME population at the test of cure/early follow-up (TOC/EFU) visit (2 weeks post therapy). In this analysis, 68/101 (67%) in the CAZAVI + MTZ group and 76/102 (75%) in the meropenem group were microbiologically evaluable (see Table 3-23). At the TOC, the proportion of patients with favorable clinical response is 91.2% (62/68) in CAZAVI + MTZ group and 93.4% (71/76) in the meropenem group had a favourable clinical response. The estimated difference in response rates was therefore -2.2% with the corresponding 95% exact confidence interval (calculated using Clopper-Pearson) being (-20.4%, 12.2%). The *p*-value using a Mantel-Haenszel test stratified for baseline Apache II score was 0.5659.

Reference ID: 3687044

Table 3-23: Clinical Response at TOC/EFU in the ME population

	CAZAVI + MTZ N = 68 n (%)	Meropenem N = 76 n (%)	Observed Diff (95% CI)
Sponsor verified Favorable Clinical resp	62 (91.2)	71 (93.4)	-2.2 (-20.4, 12.2)
Sponsor verified Clinical Failure	6 (8.8)	5 (6.6)	

The ME population excludes patients based on post-randomization criteria that could potentially bias the results of the trial. Hence, the primary analysis is computed based on the mMITT population which excludes patients without pathogen isolated. In the mMITT population, 85/101 (83.3%) patients were in the CAZAVI + MTZ group and 89/102 (87.3%) patients were in the meropenem group. Then the Sponsor verified favorable clinical response of 70/85 (82.4%) in the CAZAVI + MTZ group and 79/89 (88.8%) in the meropenem group with a difference in clinical response of -6.4% and a confidence interval of (-18.0, 5.2) (see Table 3-24). In a subgroup of patients with infections caused by CAZ-nonsusceptible (CAZ-NS) pathogens, the Sponsor verified favorable clinical response is 27/30 (90.0) in the CAZAVI + MTZ group and 19/23 (82.6%) in the meropenem group. Table 3-29 shows the results of the primary efficacy analysis performed on this population and in the subgroup of patients with infections cause by CAZ-NS at the TOC visit.

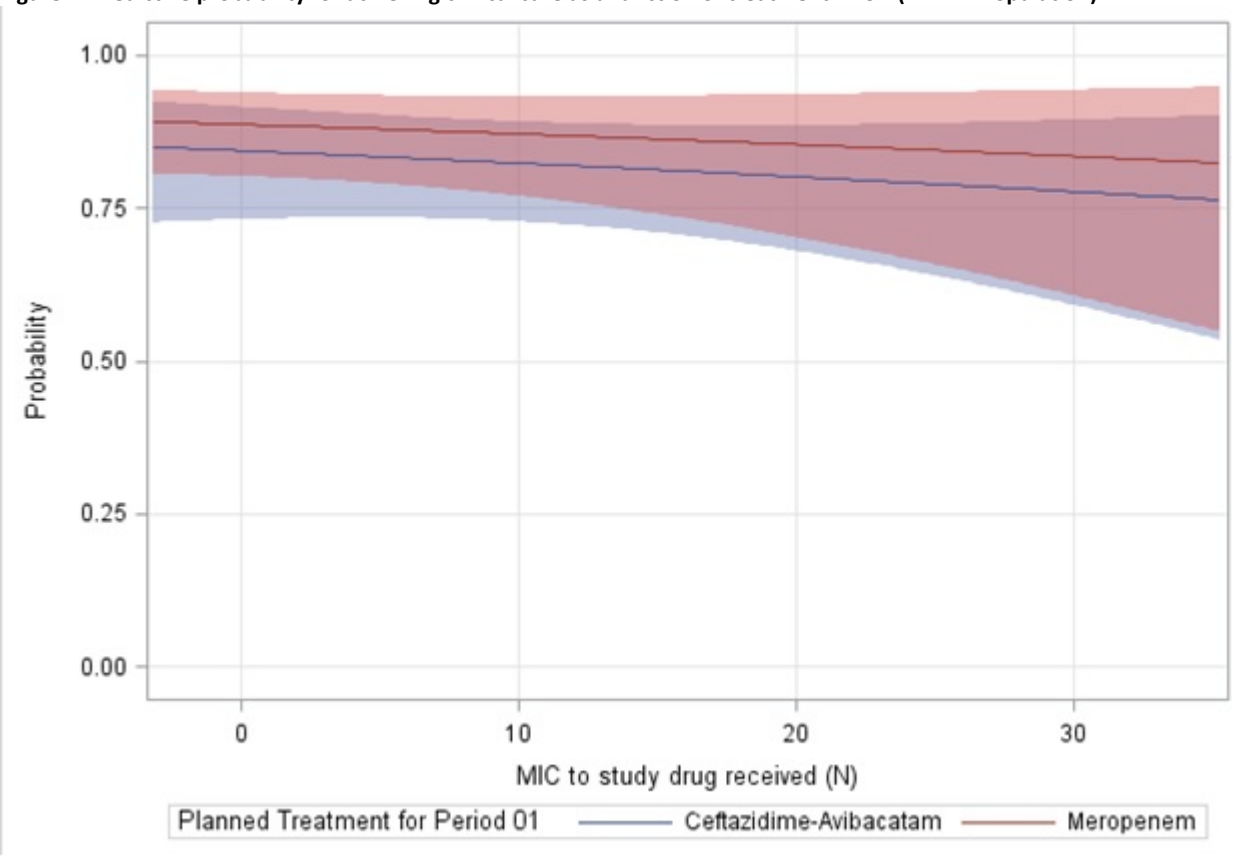
Table 3-24: Clinical Response at TOC/EFU—mMITT Population

	CAZAVI + MTZ N = 85 n (%)	Meropenem N = 89 n (%)	Observed Difference (95% CI)
Sponsor-verified favorable clinical response	70 (82.4)	79 (88.8)	-6.4 (-18.0, 5.2)
Sponsor-verified clinical failure	15 (17.7)	10 (11.2)	

A logistic regression is again used to fit the logarithm of the odds of achieving clinical cure at TOC with treatment and the baseline MIC to the assigned treatment of the primary. Figure 2 shows that, at TOC, the predictive probability of achieving clinical cure does not change as MIC gets higher. This may be because of the underlying patient characteristic that alters the pharmacodynamic relationship. Furthermore, and as expected from Table 3-24, the odds ratio between CAZAVI + MTZ and meropenem is less than 1 (OR=0.689) with 95% Wald confidence interval of (0.2751, 1.7256). The odds ratio increases at late follow-up (LFU) to 0.9877 (0.3995, 2.4418). Note again that this analysis uses the whole of the mMITT population and should not be construed as a PK/PD analysis.

Reference ID: 3687044

Figure 2: Predictive probability for achieving clinical cure as a function of treatment MIC – (mMITT Population)



3.2.6.2.2 Clinical Response at EOIV, TOC, and LFU in the mMITT Population and CAZ-NS Subgroup of the mMITT Population

Table 3-25 shows the clinical response at EOIV, TOC and LFU in the mMITT population. As expected, the clinical response decreases at each visit but the decrease is observed more in the CAZAVI group. Among patients with CAZ-NS baseline pathogens, the CAZAVI + MTZ group treatment response is relatively constant across visits.

Table 3-25: clinical response at EOIV, TOC and LFU in the mMITT population

	mMITT (Sponsor Verified)	End of IV	TOC	LFU
CAZAVI + MTZ	85	78 (91.8)	70 (82.4)	71 (83.5)
Meropenem	89	81 (91.0)	79 (88.8)	77 (86.5)

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3.2.6.2.3 By Pathogen Microbiological Response at TOC

More than a third of the patients in the mMITT population have polymicrobial infections (64/174). The most common pathogens identified from intra-abdominal sites were *E. coli, K. pneumoniae, S. aureus, P. aeruginosa, B. fragilis* and *E. faecium* (see Table 3-26).

For *E. coli*, the favorable microbiological response (presumed eradication) rate was for 48/55 (87.2%) of isolates in the CAZAVI + MTZ group and 52/58 (89.7%) of isolates in meropenem group. For all other Gram-negative aerobic isolates, favorable responses were seen in the CAZAVI + MTZ group (21/26) and also in the meropenem group (30/31).

Table 3-26: Per pathogen response (presumed eradication) in the mMITT population

	CAZAVI + MTZ N = 85 n/N1	**Meropenem N = 89 n/N1**
Gram Positive Aerobic Pathogens	22/24	22/22
Enterococcus avium	1/2	0/0
Enterococcus durans	0/0	1/1
Enterococcus faecalis	5/5	3/3
Enterococcus faecium	3/4	4/4
Staphylococcus aureus	5/5	8/8
Staphylococcus capitis	1/1	0/0
Staphylococcus epidermidis	0/0	0/0
Staphylococcus hominis	0/0	1/1
Staphylococcus lugdunensis	1/1	0/0
Streptococcus Group C	1/1	0/0
Streptococcus agalactiae	0/0	2/2
Streptococcus bovis	1/1	0/0
Streptococcus constellatus	1/1	0/0
Streptococcus intermedius	1/1	1/1
Streptococcus mitis	0/0	1/1
Streptococcus pneumoniae	1/1	0/0
Streptococcus pyogenes	0/0	1/1
Streptococcus salivarius	1/1	0/0
Gram Negative Aerobic Pathogens	69/81	82/89
Acinetobacter baumannii	1/1	2/2
Acinetobacter junii	0/0	1/1
Campylobacter gracilis	0/1	0/0
Citrobacter amalonaticus	0/1	0/0
Citrobacter braakii	0/0	1/1
Citrobacter freundii	0/0	1/1
Comamonas testosteroni	0/0	1/1
Enterobacter aerogenes	0/0	0/1
Enterobacter cloacae	1/1	4/4
Escherichia coli	48/55	52/58
Escherichia hermannii	0/1	0/0
Klebsiella oxytoca	2/2	2/2
Klebsiella pneumoniae	6/7	10/10
Proteus mirabilis	1/2	1/1
Providencia stuartii	1/1	0/0
Pseudomonas aeruginosa	6/6	5/5
Pseudomonas fluorescens	0/0	2/2

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Pseudomonas species	1/1	0/0
Pseudomonas stutzeri	1/1	0/0
Stenotrophomonas maltophilia	1/1	0/0
Anaerobic Pathogens	20/27	15/20
Bacteroides caccae	2/2	0/2
Bacteroides distasonis	1/1	0/1
Bacteroides eggerthii	1/1	0/1
Bacteroides fragilis	3/7	3/7
Bacteroides splanchnicus	0/0	0/0
Bacteroides thetaiotaomicron	1/1	2/1
Bacteroides uniformis	2/2	1/2
Bacteroides vulgatus	0/0	1/0
Clostridium clostridioforme	1/1	1/1
Clostridium perfringens	2/2	0/2
Clostridium ramosum	3/3	1/3
Clostridium subterminale	0/0	0/0
Eubacterium lentum	0/0	1/0
Finegoldia magna	1/1	0/1
Fusobacterium necrophorum	0/1	0/1
Fusobacterium species	0/0	1/0
Fusobacterium varium	1/1	0/1
Lactobacillus acidophilus	0/0	1/0
Peptostreptococcus micros	1/1	1/1
Peptostreptococcus prevotii	0/1	1/1
Prevotella intermedia	1/1	0/1
Prevotella melaninogenica	0/1	0/0
Prevotella oris	0/0	1/1

3.2.6.2.4 Clinical Response by Baseline Severity and Initial Diagnosis at TOC- mMITT population

In the mMITT population at TOC, 57/71 (80.3%) of patients in the CAZAVI + MTZ group and 66/73 (90.4%) of patients in the meropenem group in stratum 1 (Apache II score < 10) and 13/14 in CAZAVI + MTZ group and 13/16 in meropenem group had a favorable response (see Table 3-27). Numerically, patients in the CAZAVI + MTZ group by baseline APACHE of ≥ 10 have a higher clinical response rate. Table 3-28 shows the clinical response by anatomical site of infection, infection process and type of procedure used. For the appendix site of infection, CAZAVI + MTZ treatment response is 78.1% compared to 88.4 for meropenem. On the other hand the two treatment groups appear comparable with respect to peritonitis and visceral perforation infection processes. In open laparotomy, CAZAVI + MTZ treatment response is 83.9% while for meropenem it is 90.0%.

Reference ID: 3687044

Table 3-27: Clinical Response by APACHE II Score - mMITT Population

	CAZAVI + MTZ N = 85 n(%)	Meropenem N = 89 n(%)
APACHE Score Category		
0-5	37 (88.1)	43 (89.6)
6-10	20 (68.0)	23 (92.0)
11-15	10 (100.0)	13 (86.7)
16-19	3 (75.0)	0
APACHE Stratum		
1 (≤ 10)	57 (80.3)	66 (90.4)
2 (>10)	13 (92.9)	13 (81.3)

Table 3-28: Clinical Response by anatomical site of infection, infection process, and type of procedure – mMITT Population

	CAZAVI + MTZ N = 85 n (%)	Meropenem N = 89 n (%)
Anatomical site of origin of current infection		
Stomach/Duodenum	20 (87.0)	16 (88.9)
Gall Bladder	3 (75.0)	9 (100.0)
Small Bowel	4 (100.0)	10 (83.3)
Appendix	32 (78.1)	38 (88.4)
Colon	10 (83.3)	4 (80.0)
Parenchymal (liver)	1 (100.0)	1 (100.0)
Parenchymal (spleen)	0	0
Other	0	1 (100.0)
Infection Process		
Single abscess	17 (81.0)	15 (79.0)
Multiple abscess	1 (50.0)	1 (50.0)
Localized peritonitis	28 (87.5)	35 (92.1)
Generalized Peritonitis	33 (84.6)	34 (87.2)
Visceral perforation	31 (83.78)	32 (88.9)
Other	0	0
Type of Procedure		
Open laparotomy	63 (83.9)	72 (90.0)
Laparoscopic procedure	6 (75.0)	7 (77.8)
Percutaneous drainage	1 (100.0)	0
Other	0	0

Reference ID: 3687044

3.2.6.2.5 Subgroup Analysis: Ceftazidime Non-susceptible

3.2.6.2.5.1 Clinical and Microbiological Response at TOC

Table 3-29: Clinical response at TOC/EFU in the CAZ-NS subgroup (NXL 104/2002)

	CAZAVI + MTZ N = 30 n (%)	Meropenem N = 23 n (%)	Observed Diff (95% CI)
Sponsor verified Clinical Cure	27 (90.0)	19 (82.6)	7.4 (-15.3, 30.0)
Sponsor verified Clinical Failure	3 (10.0)	4 (17.4)	

Among patients assigned to CAZAVI + MTZ whose infection is caused by a CAZ-susceptible pathogen, the Sponsor-verified favorable clinical response is 43/55 (78.2%). For those who are not susceptible to CAZ, the Sponsor-verified clinical response rate is 27/30 (90.0%). On the other hand, in patients given inadequate therapy, i.e., patients randomized to meropenem but whose baseline pathogen is not susceptible to meropenem, the Sponsor verified clinical response rate is 3/4 (75.0%). The difference in response rate between those given CAZAVI and inadequate therapy is 7.4% with a confidence interval of (-18.4, 60.9).

Table 3-30: Clinical Response by Treatment group and Susceptibility of Pathogen to Treatment Assignment (NXL 104/2002)

	CAZAVI + MTZ N = 85 n (%)	Meropenem N = 89 n (%)
	Susceptible to Caz	Susceptible to MER
Clinical Cure	43 (50.6)	76 (85.4)
Clinical Failure	5 (5.9)	9 (10.1)
Indeterminate	7 (8.2)	0
	Nonsusceptible to Caz	Nonsusceptible to MER
Cure	27 (31.8)	3 (3.4)
Failure	2 (2.4)	1 (1.1)
Indeterminate	1 (1.2)	0

Among patients whose baseline pathogen is meropenem non-susceptible, 2 out of the 4 eventually turn out to be failures at LFU. See table Table 3-31.

Table 3-31: Clinical response of patients with meropenem non-susceptible pathogen

Patient	Pathogen	End of IV	TOC	LFU
42012	P. aeruginosa	Cure	Cure	Cure
53002	L. acidophilus	Cure	Cure	Failure
63006	K. pneumonia	Failure	Failure	Failure
68019	A. baumannii	Cure	Cure	Cure

Reference ID: 3687044

3.2.6.2.5.2 Clinical Response at EOIV, TOC, and LFU in the CAZ-NS Subgroup of the mMITT Population

Table 3-32 shows the clinical response at EOIV, TOC andn LFU in the subgroup of patients with CAZ-NS baseline pathogens. CAZAVI + MTZ group treatment response is relatively constant across visits.

Table 3-32: clinical response at EOIV, TOC and LFU in the mMITT population and subgroup of patients with CAZ-NS baseline pathogens

	mMITT (Sponsor Verified)	End of IV	TOC	LFU
Caz-NS Population				
CAZAVI + MTZ	30	27 (90.0)	27 (90.0)	27 (90.0)
Meropenem	23	20 (87.9)	19 (82.6)	19 (82.6)

3.2.6.2.5.3 By Pathogen Microbiological Response at TOC

Favourable microbiological response by baseline pathogen at TOC is shown in Table 3-33. *E. coli* was eradicated in 20/22 (90.1%) cases in the CAZAVI + MTZ group and 15/17 (93.8%) cases in the meropenem group at TOC. Eradication rate in either subgroup is relatively high.

Table 3-33: By Pathogen Response at TOC in the CAZ-NS Subgroup

	CAZAVI + MTZ N = 85 n/N1	Meropenem N = 89 n/N1
Presumed Eradicated		
Caz Not susceptible	29	21
Acinetobacter baumannii	1/1	1/1
Citrobacter braakii	0	1/1
Enterobacter cloacae	0	0/1
Escherichia coli	20/22	15/16
Klebsiella pneumoniae	3/3	2/2
Proteus mirabilis	1/1	0
Providencia stuartii	1/1	0
Pseudomonas aeruginosa	1/1	1/1

3.2.6.2.5.4 Clinical Response by Baseline Severity at TOC- CAZ-NS Subgroup

In the mMITT population at TOC, 57/71 (80.3%) of patients in the CAZAVI + MTZ group and 66/73 (90.4%) of patients in the meropenem group in stratum 1 (Apache II score < 10) and 13/14 in CAZAVI + MTZ group and 13/16 in meropenem group) had a favorable response.

Reference ID: 3687044

Numerically, patients in the CAZAVI + MTZ group by baseline APACHE of ≥ 10 have a higher clinical response rate.

Table 3-34: Clinical Response by APACHE II Score - CAZ-NS Subgroup

	CAZAVI + MTZ N = 30 n (%)	Meropenem N = 23 n (%)
APACHE Score Category		
0-5	10 (83.3)	6 (85.7)
6-10	7 (87.5)	5 (100.0)
11-15	8 (100.0)	8 (80.0)
16-19	2 (100.0)	0
APACHE Stratum		
1 (≤ 10)	17 (85.0)	10 (90.9)
2 (>10)	11 (91.7)	8 (72.3)

The clinical response rate for CAZ-NS not computed per anatomical site of infection, infection process, and type of procedure due to small patient numbers.

3.2.6.3 Pooled Analysis

In the pooled analysis, interim data from the ongoing Resistant Pathogen Study, D4280C00006, was included to provide additional supportive information on the clinical efficacy of CAZAVI against CAZ-NS pathogens. The study is a Phase 3 multinational, multicenter, randomized, open-label, study in adult subjects with cIAI and cUTI caused by CAZ-NS gram-negative pathogens. Subjects are stratified for entry diagnosis (cIAI and cUTI) and region (North America and Western Europe, Eastern Europe, and the rest of the world) and randomized 1:1 to CAZAVI or best available therapy (BAT) groups.

The dosage of CAZAVI used was 2.5 g [2.0 g ceftazidime + avibactam 0.5 g] IV q8h infused over 2h). BAT was chosen, as a single antibiotic regime is unlikely to cover all possible resistance mechanisms. As of the data cutoff, all subjects randomized to the BAT group have received a carbapenem (e.g., imipenem, meropenem) alone or in combination with colistin or ciprofloxacin. Subjects are to receive a minimum of 5 days and a maximum of 21 days of antibiotic therapy.

At the time of the data cut, the mMITT Population included 4 subjects with cIAI and 44 subjects with cUTI.

Table **3-35** shows the interim results of this study in terms of the infection type. The results show a similar trend in treatment effect for cUTI as observed in Table 3-13, i.e., the clinical response rate (cure) for CAZAVI is numerically higher than the comparators, but the point estimate of the treatment effect has substantial uncertainty expressed by the wide confidence interval.

Reference ID: 3687044

Table 3-35: Resistant Pathogen Study D4280C00006 - Clinical Response at TOC/EFU by Infection Type- Interim Data

	CAZAVI N = 22 n/N1%)	Comparators N = 26 n/N1(%)	Observed Difference (95% CI)
cUTI	**N1 = 21**	**N1 = 23**	
Clinical Cure (n/N1%)	19 (90.5)	18 (78.3)	12.2 (-13.8, 36.0)
Clincal failure or Indeterminate (n/N1%)	2 (9.5)	5 (21.7)	
cIAI	**N1 = 1**	**N1 = 3**	
Clinical Cure (n/N1%)	1 (100.0)	1 (33.3)	
Clincal failure or Indeterminate (n/N1%)	0	2 (66.7)	
Pooled cUTI and cIAI	**N1 = 22**	**N1 = 26**	
Clinical Cure (n/N1%)	20 (90.9)	19 (73.1)	17.8 (-8.2, 40.3)
Clincal failure or Indeterminate (n/N1%)	2 (9.9)	7 (26.9)	

Note that the Resistant Pathogen Study used CAZAVI at the 2.5 g [2.0 g ceftazidime + avibactam 0.5 g] dose while the NXL104/2001 dose was 0.625 g (0.5 g ceftazidime + 0.125 g avibactam) q8h administered as a 30-minute IV infusion. Since the Resistant Pathogen Study is predominantly composed of cUTI patients, the combined result presumably should be a conservative estimate of CAZAVI treatment response in cUTI at the 2.5 g [2.0 g ceftazidime + avibactam 0.5 g] dose. For cIAI on the other hand, the combined result should be the same as what was observed in NXL104/2002.

Table 3-36 shows the observed clinical response and the posterior predictive probability of clinical response (cure) in the pooled studies. In the pooled mMITT population, the observed clinical response rate of CAZAVI is 83.0% and the combined comparator response rate is 81.7%, based on simple pooling, with a treatment difference of 1.3 and 95% confidence interval about the point estimate of (-7.6, 10.1). The posterior predictive probability of clinical cure for the CAZAVI group is 86.2 and for the combined comparators that probability is 85.0. The difference in posterior predictive probabilities is 1.1 and a 95% credible interval of (-6.6, 8.8) which is narrower than the continuity corrected confidence interval of the difference in proportion. The posterior predictive probability is obtained using a shrinkage estimator to shrink the treatment response of each subgroup toward an overall mean. The amount of shrinkage is determined by the subgroup size and the estimated between group variability. Then using Bayesian estimation with shrinkage priors (i.e., normal priors that are centered at zero although other priors that assume non-exchnageability can also investigated) for each of the 4 subgroups (CAZAVI & cUTI, CAZAVI & cIAI, Comparators & cUTI and Comparators & cIAI), the shrinkage estimates of the proportion in each of the subgroups are obtained. Note that the credible intervals of these estimates are narrower, hence more precise, than the difference in proportions with continuity correction.

Reference ID: 3687044

Furthermore, since the Resistant Pathogen Study is composed mainly of patients with cUTI, the pooled result reflects similar results that were observed in Study NXL104/2001 and Study NXL104/2002, namely, that CAZAVI has a numerically higher treatment response than its comparators (IMP/CIL and BAT) in cUTI but it has a lower treatment response than its comparators (meropenem and BAT) in cIAI.

Table 3-36: Pooled Studies (NXL104/2001, NXL 104/2002, Resistant Study D4280C00006) - Clinical response at TOC/EFU by Infection Type

	CAZAVI n (%)	Comparators n (%)	Diff (95% CI or Cred I)
Pooled mMITT Population	**N = 153**	**N = 164**	
Observed Clinical Cure	127 (83.0)	134 (81.7)	1.3 (-7.6, 10.1)
Posterior Predictive Prob of Clinical Cure	**86.2**	85.0	1.1 (-6.6, 8.8)
Pooled cUTI Population	**N1 = 67**	**N1 = 72**	
Observed Clinical Cure	56 (83.6)	54 (75.0)	8.6 (-6.1, 22.6)
Posterior Predictive Prob of Clinical Cure	86.7	79.5	7.1 (-5.0, 19.5)
Pooled cIAI Population	**N1 = 86**	**N1 = 92**	
Observed Clinical Cure	71 (82.6)	80 (87.0)	-4.4 (-16.0, 7.0)
Posterior Predictive Prob of Clinical Cure	85.9	89.5	-3.5 (-13.2, 5.6)

As a cautionary note, pooling observations assume exchangeability of subjects, i.e., the sequence subjects in each subgroup (determined by Study, treatment group, or infection type) are assumed to have similar characteristics and were given comparable care, which is a strong assumption. The plausibility of the assumption of exchangeability of subgroups should always be investigated. For example, the dose used in NXL104/2001 is different from the other two studies NXL104/2002 and the Resistant Pathogen Study, and so a separate analysis is done with only the data from the latter two studies (see Table 3-37). The results show that the point estimates are consistent with what was observed in Table 3-36. The only difference is the confidence intervals due to reduced sample sizes.

Table 3-37: Pooled Studies (NXL 104/2002, Resistant Study D4280C00006) - Clinical response at TOC/EFU by Infection Type

	CAZAVI n (%)	Comparators n (%)	Diff (95% CI or Cred I)
Pooled mMITT Population			
Observed Clinical Cure	90 (84.1)	98 (85.2)	-1.1 (-11.4, 9.0)
Posterior Predictive Prob of Clinical Cure	87.4	88.3	-0.9 (-9.3, 7.3)
Pooled cUTI Population			
Observed Clinical Cure	19 (90.5)	18 (78.3)	12.2 (-13.8, 36.0)
Posterior Predictive Prob of Clinical Cure	91.4	84.4	7.0 (-8.6, 24.7)
Pooled cIAI Population			

Reference ID: 3687044

Observed Clinical Cure	71 (82.6)	80 (87.0)	-4.4 (-16.0, 7.0)
Posterior Predictive Prob of Clinical Cure	86.0	89.5	-3.4 (-12.9, 5.4)

Lastly, the following investigation is related to the differential treatment response of CAZAVI in patients with ceftazidime susceptible and non-susceptible pathogen seen in Table 3-30. The pooled data shows the same results (see Table 3-38) that the treatment response of CAZAVI in patients whose infection caused by ceftazidime susceptible pathogens is lower than the treatment response of CAZAVI in those patients with non-susceptible causative pathogens. Furthermore, the treatment response of CAZAVI is better than the comparators in the group of patients with non-susceptible pathogens. The treatment effect is 16.2 with a 95% CI of (1.4, 30.3). Its corresponding difference in median posterior probability using shrinkage estimates is 13.2 with a 95% credible interval of (1.5, 26.4). On the other hand, the treatment difference between CAZAVI and comparators (meropenem, imipenem/cilastitin, BAT) is -9.4 (-20.9, 2.0). The corresponding difference in median posterior probability is -7.4 and the 95% credible interval is (-17.4, 1.4).

Table 3-38: Pooled Studies (NXL104/2001, NXL 104/2002, Resistant Study D4280C00006) - Clinical response at TOC/EFU by Susceptibility to Ceftazidime

	CAZAVI n/N1 (%)	**Comparators n/N1 (%)**	**Observed Diff (95% CI)**
Pooled CAZ-NS Population	**N1 = 66**	**N1 = 67**	
Clinical Cure	58 (87.9)	48 (71.6)	16.2(1.4, 30.3)
Pooled cUTI Population – CAZ-NS	**N1 = 35**	**N1 = 41**	
Clinical Cure	30 (85.7)	28 (68.3)	17.4 (-2.4, 35.0)
Pooled cIAI Population – CAZ-NS	**N1 = 31**	**N1 = 26**	
Clinical Cure	28 (90.3)	20 (76.9)	13.4 (-8.6, 32.2)
Pooled CAZ-S Population	**N1 = 87**	**N1 = 97**	
Clinical Cure	69 (79.3)	86 (88.7)	-9.4 (-20.9, 2.0)
Pooled cUTI Population – CAZ-S	**N1 = 32**	**N1 = 31**	
Clinical Cure	26 (81.3)	26 (83.9)	-2.6 (-21.5, 16.6)
Pooled cIAI Population – CAZ-S	**N1 = 55**	**N1 = 66**	
Clinical Cure	43 (78.2)	60 (90.9)	-11.7 (-26.0, 2.9)

3.2.6.4 Meta-analysis of ceftazidime treatment response in cUTI and cIAI from published historical studies

The Sponsor provided a literature review in order to evaluate the efficacy of ceftazidime alone in adult patients with cUTI. The review identified 400 articles (112 from PubMed, 87 from Ovid, 153 from Cochrane, and 48 from ClinicalTrials.gov). From this initial pool of articles, 160 unique search results were assessed and 33 cUTI studies were submitted for manual Sponsor review.

Reference ID: 3687044

The criteria for article acceptance in a meta-analysis of the efficacy of ceftazidime in cUTI were as follows:

1. Study was a clinical trial in adult human subjects (ie, exclude in vitro, animal, or pediatric studies)
2. Study included a ceftazidime group and a control/comparator group. (NOTE: the comparator group may be a "BAT" or similar group representing a variety of comparative treatments)
    a. Combination therapy of ceftazidime administered with another antibiotic qualified as a "ceftazidime group"
    b. A combination product (eg, ceftazidime plus a β-lactamase inhibitor, such CAZAVI) did not qualify as a "ceftazidime group"
3. Study included subjects with UTI that is defined as complicated or potentially contains subjects with cUTI
4. Study was prospective and randomized
5. Total 24-hour dose of ceftazidime was ≥ 1000 mg for presumed cUTI (consistent with the minimum labeled dosing for cUTI) (FORTAZ® package insert, 2010)
    a. Lower doses were acceptable for patient populations with renal impairment
    b. Acceptable if study indicated the use of approved dosing without stating the specific dose
6. Microbiological and/or clinical outcomes were reported for ceftazidime efficacy in presumed cUTI
7. Ceftazidime/comparator results in presumed cUTI were presented such that sufficient information exists to extract or extrapolate the numerators and denominators for each relevant data point.

The above criteria yielded 15 studies (see Appendix). The meta-analysis is conducted using the DerSimonian & Laird random effects method. Overall, based on this meta-analysis of controlled trials, ceftazidime was associated with approximately 89.1% [95% CI: 85.0, 93.2%]) favorable microbiological response rates at TOC and 90.4% [95% CI: 85.5, 95.4%] favorable clinical outcome rates at TOC in the historical cUTI studies in a population that is similar to a ME Population. In general, the results of the meta-analysis gives a higher favorable rate for ceftazidime in both clinical and microbiological response than what was observed in Study NXL 104/2001 (see Table 3 13).

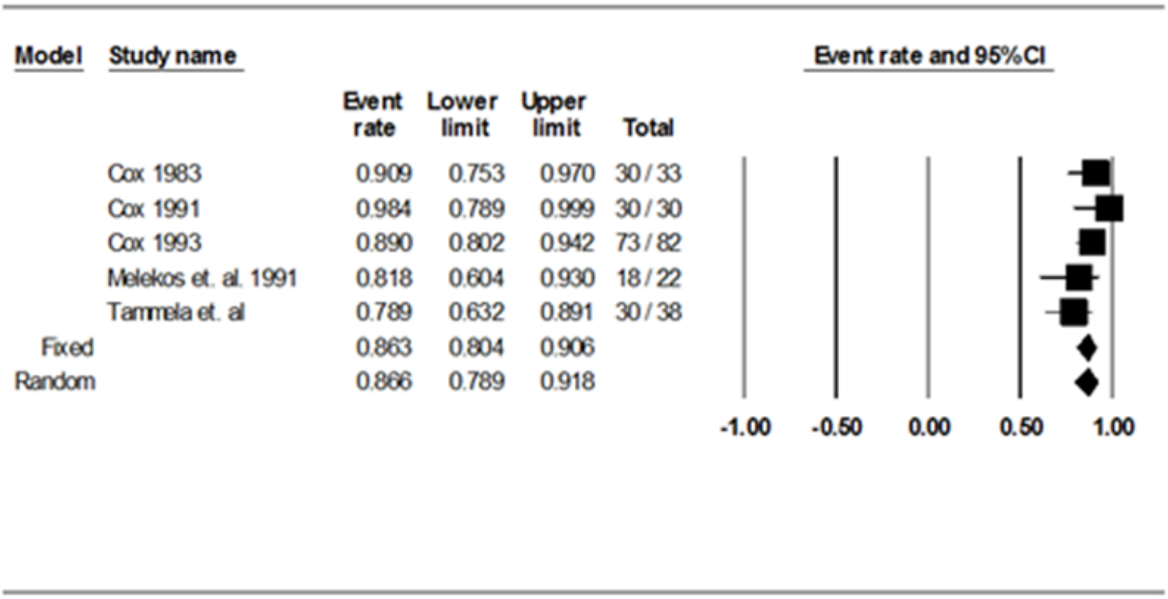
Table 3-39: Meta-analysis of historical trials of ceftazidime in the treatment of cUTI and cIAI

	cUTI Est. (95% Conf. Int)	cIAI Est. (95% Conf. Int)
Favorable Clinical Response	90.4 (85.5, 95.4)	86.1 (74.1, 98.0)
Favorable Microbiological Response	89.1 (85.0, 93.2)	
Favorable Clinical and Microbiological Response	86.6 (78.9, 91.8)	

Reference ID: 3687044

To better gauge the clinical cure and microbiological eradication rate of ceftazidime in historical trials, an approximation is used by taking the proportion that is the minimum of the observed clinical cure rate and the observed microbiological eradication rate. Furthermore, trials where cUTI subjects are a subgroup of the ME population are excluded. This narrows down the list of studies to five (Figure 3) and of the combined clinical cure and microbiological eradication rate using DerSimonian and Laird random effects estimate is 86.6% with a 95% confidence interval of (78.9, 91.8). Note that this response rate is still higher than what was observed in Study NXL104/2001 but comparable to the Open-label Resistant study.

Figure 3: Forest Plot of Historical Trials with Ceftazidime in the Treatment of cUTI



Note that the analysis population used in the analysis is the ME population, which removes patients who had major protocol deviations and who did not have post-therapy evaluations. These post randomization exclusions remove the unbiasedness protection inherited from randomization. Furthermore, most of the studies involved are open label which could potentially skew the results to reflect toward the goal of the study no matter how honest the intentions were of the investigator.

The criteria for article acceptance in the meta-analysis of the efficacy of ceftazidime in cIAI were as follows:

1. Study was a clinical trial in adult human subjects (ie, excluded in vitro, animal, pediatric studies)
2. Study included a ceftazidime group and a control/comparator group (NOTE: the comparator group may have been a “best available therapy” or similar group representing a variety of comparative treatments)

Reference ID: 3687044

a. Combination therapy of ceftazidime administered with another antibiotic (eg, MTZ) qualified as a "ceftazidime group"
b. A combination product (eg, ceftazidime plus a β-lactamase inhibitor, such CAZAVI) did not qualify as a "ceftazidime group"

3. Study included subjects with intra-abdominal infection (IAI) that is defined as complicated or potentially contains subjects with complicated IAI
4. Study was prospective and randomized
5. Total 24-hour dose of ceftazidime was ≥ 6 g for presumed cIAI
    a. Acceptable if study indicated the use of approved dosing without stating the specific dose
6. Clinical and/or microbiological outcomes were reported for ceftazidime efficacy in presumed cIAI
7. Ceftazidime/comparator results in presumed cIAI were presented such that sufficient information exists to extract or extrapolate the numerators and denominators for each relevant data point.

The above criteria yielded 2 cIAI articles (see Appendix), the ceftazidime dosage were 6 g IV daily, administered in 3 divided doses. The comparator regimen in both articles was tobramycin plus clindamycin. In 1 study, ceftazidime was administered with adjunctive clindamycin (Bubrick et al, 1990); in the other, ceftazidime was administered as monotherapy (Simmen et al, 1989). Neither the duration of therapy nor the time points at which favorable response was assessed was defined in either study.

Based on these studies, ceftazidime was associated with approximately 86% (95% CI: 74.1, 98.0%) favorable clinical response rates at post-therapy assessment time points in the cIAI studies in a population that is similar to an ME Population.

3.3 Evaluation of Safety

3.3.1 Summary of All Adverse Events

The Sponsor undertake a systematic review of the clinical safety of ceftazidime alone with ceftazidime safety data from multiple sources; the ceftazidime package inserts from the US and EU (FORTAZ package insert, 2010; ceftazidime SmPC, 2014; FORTUM® 1 g injection SmPC, 2013), signal detection analysis using the FDA AERS database, and a summary of available ceftazidime safety information from contemporary randomized comparative studies of cIAI and cUTI were reviewed and assessed in aggregate. Adverse reactions reported with ceftazidime alone include anaphylaxis, allergic reactions, urticaria, pain at injection site, hyperbilirubinemia, jaundice and renal impairment. In addition to the adverse reactions listed above, cephalosporin-class adverse reactions include colitis, toxic nephropathy, hepatic dysfunction (including cholestasis), aplastic anemia, hemorrhage. Altered laboratory tests include prolonged prothrombin time, false-positive test for urinary glucose, and pancytopenia. A review of FDA

Reference ID: 3687044

Adverse Event Reporting System (FAERS) Database yielded preferred terms myoclonus and status epilepticus which are similar to "myoclonia" and "siezures" in the current ceftazidime label. Published literature with post-marketing experience with ceftazidime revealed no additional safety signals.

The most common adverse reactions in subjects receiving CAZAVI in the pooled Phase 2 studies were headache, vomiting, and abdominal pain. The most common adverse reactions in the comparator group were headache and increased transaminases. See Medical officer's review for more details.

In the cumulative CAZAVI safety database, 38 deaths have been reported, including 7 in the Phase 2 studies (4 CAZAVI, 3 comparator) and 31 in the ongoing Phase 3 studies (2 comparator, 29 treatment blinded). No deaths occurred in any Phase 1 study.

In Study NXL104/2001, there was one death reported in the comparator group. In Study NXL104/20012002, there were 6 deaths (4 CAZAVI, 2 meropenem).

3.3.2 Treatment Emergent Adverse Events

The safety population in either Study NXL104/2001 or Study NXL104/2002 includes all patients who received any amount of study drug, and included 169 patients in the CAZAVI group, 67 patients in the imipenem group and 102 patients in the meropenem group. Table 3-40 displays treatment-emergent AEs and preferred term in which the risk difference between CAZAVI and IMP/CIL is ≥2% in Study NXL104/2001. Table 3-41 shows similar information for Study NXL104/2002. These tables show that vomiting, constipation, dizziness and abdominal pain are the most common TEAEs in subjects receiving CAZAVI.

Table 3-40: Study NXL104/2001: Adverse Events with Risk Difference Greater Than 2%

AE Term	CAZAVI 500mg/125mg IV q 8hr		IMP/CIL 500mg IV q6h		RD
	Number of subjects	%	Number of subjects	%	
Constipation	7	10.3	2	3.0	7.3
Dizziness	4	5.9	0	0.0	5.9
Abdominal pain upper	5	7.4	1	1.5	5.9
Diabetes mellitus	3	4.4	0	0.0	4.4
Fungus urine test positive	3	4.4	0	0.0	4.4
Abdominal pain	6	8.8	3	4.5	4.4
Anorexia	2	2.9	0	0.0	2.9
Chest discomfort	2	2.9	0	0.0	2.9
Rhinorrhea	2	2.9	0	0.0	2.9
Vaginal candidiasis	3	4.4	1	1.5	2.9
Hypertension	4	5.9	2	3.0	2.9
Anxiety	7	10.3	5	7.5	2.8

Lifted from MO's review

Reference ID: 3687044

Table 3-41: Study NXL104/2002: Adverse Events with Risk Difference Greater Than 2%

AE Term	CAZAVI 2000mg/500mg IV q8h + MTZ 500mg IV q8h		MER 1000mg IV q 8hr + placebo MTZ IV q8h		RD
	Number of subjects	%	Number of subjects	%	
Vomiting	14	13.9	5	4.9	9.0
Nausea	10	9.9	6	5.9	4.0
Anxiety	5	5.0	1	1.0	4.0
Hypokalemia	4	4.0	0	0.0	4.0
Blood alk phos increased	10	9.9	7	6.9	3.0
Abdominal pain	7	6.9	4	3.9	3.0
Constipation	4	4.0	1	1.0	3.0
Tachycardia	4	4.0	1	1.0	3.0
Pain	3	3.0	0	0.0	3.0
Urinary tract infection	3	3.0	0	0.0	3.0
Cough	6	5.9	4	3.9	2.0

Lifted from MO's review

Reference ID: 3687044

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Table 4-1and Table 4-2 shows the clinical and/or microbiological response rates by age, gender, race, and region. There is no noticeable difference between the two treatment arms in any of these subgroup categories.

Table 4-1: Study NXL104/2001 -Clinical cure and microbiological eradication rates by age, gender, race and region in the mMITT population

	CAZAVI (N=46) n(%)	IMP/CIL (N=49) n(%)	Total (N=85) n(%)
Age; years			
18 to 44	12 (54.6)	13 (65.0)	25 (59.5)
45 to 64	14 (73.7)	8 (40.0)	22 (56.4)
65 to 74	2 (66.7)	0 (0.00)	2 (40.0)
75 to 90	1 (50.0)	4 (57.1)	5 (55.5)
Gender			
Male	6 (66.7)	9 (64.3)	15 (65.2)
Female	23 (62.2)	16 (45.7)	39 (54.2)
Race			
White	15 (51.7)	14 (43.8)	29 (47.5)
Black or African American	1 (100.0)	2 (50.0)	3 (60.0)
Asian	3 (75.0)	3 (100.0)	6 (85.7)
Other	10 (83.3)	6 (60.0)	16 (72.7)
Region			
US	5 (62.5)	2 (33.3)	7 (50.0)
Europe	12 (60.0)	10 (45.5)	22 (52.4)
Rest of the World (ROW)	12 (66.7)	13 (61.9)	25 (64.1)

Table 4-2: Study NXL104/2002 -Clinical cure and microbiological eradication rates by age, gender, race and region in the mMITT population

	CAZAVI (N=85) n(%)	MER (N=89) n(%)	Total (N=174) n(%)
Age; years			
18 to 44	42 (87.5)	44 (88.0)	86 (87.8)
45 to 64	25 (75.7)	25 (92.6)	50 (83.3)
65 to 74	3 (100.0)	9 (90.0)	12 (92.3)
75 to 90	0 (0.0)	1 (50.0)	1 (33.3)
Gender			
Male	48 (80.0)	63 (88.7)	111 (84.7)
Female	22 (88.0)	16 (88.9)	38 (88.4)

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Race			
White	38 (76.0)	53 (89.8)	91 (83.5)
Black or African American			
Asian	21 (91.3)	18 (85.7)	39 (88.6)
Other	11 (91.7)	8 (88.9)	19 (90.5)
Region			
US	4 (44.4)	5 (100.0)	9 (64.3)
Europe	35 (87.5)	48 (88.9)	83 (88.3)
ROW	31 (86.1)	26 (86.7)	57 (86.4)

4.2 Special Subgroups- Subjects with Renal Impairment

Clinical cure and microbiological eradication rates from Study NXL104/2002 by baseline renal function category are shown in Table 4-3. While the Clinical cure and microbiological rates in the mMITT population with mild renal impairment were numerically lower than those for subjects with normal renal function (55.6% CAZAVI, 22.9%IMP/CIL), the number of subjects with mild renal impairment is small (9 CAZAVI and 11 IMP/CIL).

Table 4-3: Study NXL104/2001 -Clinical cure and microbiological eradication rates by baseline renal function in the mMITT population

Baseline renal function subgroup	Number of patients with clinical cure/ Total number of patients (%)	
	CAZAVI	IMP/CIL
Normal function (CrCl > 80 mL/min)	21/33 (63.6)	18/35 (72.9)
Mild impairment at baseline (CrCl > 50 to ≤ 80 mL/min)	5/9 (55.6)	5/11 (22.9)
Moderate impairment at baseline (CrCl > 30 to ≤ 50 mL/min)	1/2 (50.0)	1/2 (50.0)
Severe impairment at baseline (CrCl ≤ 30)	1/1 (100.0)	0

2 patients have missing creatinine clear clearance values

Clinical cure rates from Study NXL104/2002 by baseline renal function category are shown in Table 4-4. As seen in Study NXL104/2001, clinical cure rates in the mMITT population with mild renal impairment were numerically lower than those for subjects with normal renal function (77.3% CAZAVI, 85.7% meropenem) but the decrease is inconclusive due to small sample sizes. In the ongoing Phase 3 Resistant Pathogen Study (D4280C00006), only two cIAI subjects have been enrolled with impaired renal function (one with mild and one with moderate renal impairment). Both subjects received BAT and were clinical failures at TOC.

Reference ID: 3687044

Table 4-4: Clinical Cure Rate at TOC, by Baseline Renal Function Category—mMITT Population, Trial 2002

Baseline renal function subgroup	Number of patients with clinical cure/ Total number of patients (%)	
	CAZAVI + MTZ	Meropenem
Normal function (CrCl > 80 mL/min)	50/60 (83.3)	57/64 (89.1)
Mild impairment at baseline (CrCl > 50 to ≤ 80 mL/min)	17/22 (77.3)	18/21 (85.7)
Moderate impairment at baseline (CrCl > 30 to ≤ 50 mL/min)	0/0	4/4 (100.0)

From Sponsor's 120 day safety report

The Phase 3 trial in subjects with cIAI (from combined protocols D4280C00001/5, also referred to as RECLAIM) have been recently unblinded and the topline results were submitted along with the 120 safety update.

RECLAIM was a randomized, multi-center, double-blind trial to assess the noninferiority of CAZAVI (2000 mg/500 mg, q8h) plus MTZ (0.5 g q8h) versus meropenem (1 g q8h) in the treatment of cIAI. The primary endpoint was the clinical cure at TOC, 28 to 35 days after randomization, in subjects who have at least one identified pathogen (mMITT population) and the noninferiority margin was 10%. Patients with an estimated baseline creatinine clearance (CrCl) ≤ 30 mL/min were excluded (note, patients were excluded with CrCl < 50 mL/min in Trial 2001 and < 70mL/min in Trial 2002). Subgroup analyses indicated that cIAI patients with moderate renal impairment (CrCl > 30 to ≤ 50 mL/min) at baseline in the CAZAVI group had a lower clinical cure rate (14/31, 45%) compared to patients treated with meropenem (26/35, 74%). In subjects with normal renal function or mild renal impairment at baseline, the clinical cure rates were similar across treatment arms and higher than the cure rate for the corresponding moderately impaired subgroup (Table 4-5). In addition to the clinical cure rates described above, among subjects with moderate renal impairment, there was also a numerical imbalance of deaths between the treatment groups (8 deaths in the CAZAVI subgroup compared to 3 deaths in the meropenem subgroup).

Table 4-5: Clinical Cure at TOC by Baseline Renal Function Category—mMITT Population, RECLAIM Trial

Baseline renal function subgroup	Number of patients with clinical cure/ Total number of patients (%)	
	CAZAVI + MTZ	Meropenem
Normal function / mild impairment (CrCl > 50 mL/min)	322/379 (85%)	321/373 (86%)
Moderate impairment at baseline (CrCl > 30 to ≤ 50 mL/min)	14/31 (45%)	26/35 (74%)

Sponsor's 120 day safety report

Reference ID: 3687044

The Sponsor speculated that the results could be due to the lack of timely dose adjustment for some moderately impaired subjects whose CrCl improved rapidly after baseline. The baseline assessment of CrCl did not take account of how the patient's renal function might change post-baseline. The resulting lag between recovery of renal function and dose adjustment in some subjects may have contributed to underexposure and impacted their clinical outcome.

Reference ID: 3687044

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Limitations

There were several limitations in the summary of these results based on individual trials, pooled analysis and the supportive meta-analyses. In the Phase 2 trials for cUTI and cIAI, there were no pre-specified formal hypotheses for any inferential testing and statistical analyses are based only on descriptive data summaries. The sample sizes were small and the confidence intervals were wide showing the uncertainties in treatment effect. The primary endpoint that was evaluated in this review is different from the pre-specified primary endpoint.

In the pooled analysis, the assessments used interim data from the ongoing, open label Resistant Pathogen Study, D4280C00006, to provide additional supportive information for the clinical efficacy of CAZAVI against CAZ-NS pathogens. Because of pooling, there are concerns about exchangeability of subjects due to potential differences in doses and infusion time, baseline patient and disease characteristics, prognostic factors and the supportive care they had received. Although exchangeability can be potentially remedied, statistically, the analysis done did not account for this issue.

Exchangeability is also a problem in the meta-analysis of ceftazidime historical effect in published studies. The Applicant submitted several studies that have used microbiological evaluable (ME), subsets of ME and a few studies with MITT as the analyses populations. Furthermore, they are not similar with respect to design, dose, and duration of treatment, baseline disease characteristics, timing of assessment and other factors.

Furthermore, in the meta-analyses described earlier in Section 3.2.6.4, the Applicant submitted several studies that have used microbiological evaluable (ME), subsets of ME and a few studies with MITT as the analyses populations. There are considerable uncertainties in these studies and they are not similar with respect to design, dose, and duration of treatment, baseline disease characteristics, timing of assessment and other factors. Given the potential uncertainties in the pooled meta-analyses findings, such findings should only be considered as additional supportive evidence.

5.2 Collective Evidence

In cUTI, CAZAVI has a numerically higher treatment response than IMP/CIL in most pre-specified endpoints. In particular, in the clinical and microbiological outcome, 29 (63.0%) of the patients in the CAZAVI group achieved both clinical cure and microbiologic eradication while 25 (51.0%) of the patients in the IMP/CIL group achieved the same clinical and microbiologic response. The difference in the response rates is 12.0 with a 95% CI of (-9.1, 31.7). In patients with cUTI caused by a ceftazidime-nonsusceptible (CAZ-NS) pathogen, 8 (57.1%) of the patients in the CAZAVI group achieved both clinical cure and microbiologic eradication while 7 (38.9%)

Reference ID: 3687044

of the patients in the IMP/CIL group achieved the same clinical and microbiologic response. The difference in the response rates is 18.3 with a 95% CI of (-22.4, 58.9). The clinical cure and microbiological eradiation rate in the CAZAVI group is 63.0% (see Table 3-12) and the patients with inadequate therapy is 1 (50.0%), the difference in clinical cure and microbiological eradiation rate between the CAZAVI group and the patients given inadequate therapy is 13.0 with a 95% CI of (-36.8, 62.2). Although the point estimate of the difference, the confidence interval does not give enough support whether CAZAVI is an effective treatment.

In terms of clinical and microbiological outcome at other times of assessments, e.g., EOIV and LFU, microbiological assessment was not assessed at those times except in patients with infections caused by CAZ-NS. At EOIV, CAZAVI has a numerically lower clinical and microbiological response rate than IMP/CIL in the CAZ-NS subgroup [diff -7.1 with 95% CI (-35.8, 15.8)]. At LFU, the result is reversed; CAZAVI has a numerically higher response rate than IMP/CIL at this time point [diff 4.0 with 95% CI of (-30.7, 38.3)].

Clinical cure and favourable microbiological response (eradication) at TOC was evaluated by pathogen. *E. coli* was the most common pathogen, and was eradicated in 26/40 (65.0%) patients in the CAZAVI group and 22/41 (53.7%) patients in the IMP/CIL group. The number of patients with pathogens other than *E. coli* was extremely small prohibiting comparisons across treatment groups. In the CAZ-NS subgroup of the mMITT population, *E. coli* was eradicated in 8/14 (57.1%) cases in the CAZAVI group and 7/18 (43.8%) cases in the imipenem group at TOC.

In cIAI, CAZAVI has numerically lower clinical response rates than meropenem, except in the CAZ-NS subgroup of the mMITT population. The Sponsor verified favorable clinical response in the CAZAVI group is 70/85 (82.4%) and 79/89 (88.8%) in the meropenem group with a difference in clinical response of -6.4% and a confidence interval of (-18.0, 5.2) (see Table 3-29). In a subgroup of patients with infections caused by CAZ-nonsusceptible (CAZ-NS) pathogens, the Sponsor verified favorable clinical response is 27/30 (90.0) in the NXL104/CAZ/MTZ group and 19/23 (82.6%) in the meropenem group with a difference of 7.4 [95% CI: (-15.3, 30.0)]. Furthermore, the difference in clinical response rate between patients given CAZAVI and in patients given inadequate therapy, i.e., patients randomized to meropenem but whose baseline pathogen is not susceptible to meropenem, is 7.4% with a confidence interval of (-18.4, 60.9). Note that the Sponsor verified clinical response rate for inadequate therapy is 3/4 (75.0%) while the Sponsor verified favorable clinical response in the CAZAVI group is 70/85 (82.4%). This difference is increased at LFU since one of the patients in the inadequate therapy group did not have sustained clinical response.

In terms of the clinical response at EOIV, TOC and LFU in the mMITT population and subgroup of patients with CAZ-NS baseline pathogens, the clinical response decreases at each visit but the decrease is observed more in the CAZAVI group. Among patients with CAZ-NS baseline pathogens, the CAZAVI group clinical response is relatively constant across visits.

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The most common pathogens identified from intra-abdominal sites were *E. coli, K. pneumoniae, S. aureus, P. aeruginosa, B. fragilis* and *E. faecium*. For *E. coli*, the favorable microbiological response (presumed eradication) rate was for 48/55 (87.2%) of isolates in the CAZAVI group and 52/58 (89.7%) of isolates in meropenem group. For all other Gram-negative aerobic isolates, favorable responses were seen in the CAZAVI group (21/26) and also in the meropenem group (30/31). In the CAZ-NS subgroup, *E. coli* was eradicated in 20/22 (90.1%) cases in the CAZAVI group and 15/17 (93.8%) cases in the meropenem group at TOC. Eradication rate in either subgroup is relatively high.

Interim data from the ongoing Resistant Pathogen Study, D4280C00006, was included to provide additional supportive information on the clinical efficacy of CAZAVI against CAZ-NS pathogens. Note that the Resistant Pathogen Study used CAZAVI at the 2.5 g [2.0 g ceftazidime + avibactam 0.5 g] dose while the NXL104/2001 dose was 0.625 g (0.5 g ceftazidime + 0.125 g avibactam) q8h administered as a 30-minute IV infusion. Since the Resistant Pathogen Study is predominantly composed of cUTI patients, the combined result presumably should be a conservative estimate of CAZAVI treatment response in cUTI at the 2.5 g [2.0 g ceftazidime + avibactam 0.5 g] dose.

In the pooled mMITT population, the observed clinical response rate of CAZAVI is 83.6% and the combined comparator response rate is 81.7% with a treatment difference of 1.3 and 95% confidence interval about the point estimate of (-6.1, 10.1). The posterior predictive probability of clinical cure for the CAZAVI group is 86.2 and for the combined comparators that probability is 85.0. The difference in posterior predictive probabilities is 1.1 and a 95% credible interval of (-6.6, 8.8) which is narrower than the continuity corrected confidence interval of the difference in proportion. The posterior predictive probability is obtained using a shrinkage estimator to shrink the treatment response of each subgroup toward an overall mean. The amount of shrinkage is determined by the subgroup size and the estimated between group variability. Then using Bayesian estimation with shrinkage priors (i.e., priors that are centered at zero) for each of the 4 subgroups (CAZAVI & cUTI, CAZAVI & cIAI, Comparators & cUTI and Comparators & cIAI), the shrinkage estimates of the proportion in each of the subgroups are obtained. Note that the credible intervals of these estimates are narrower, hence more precise, than the difference in proportions with continuity correction.

Furthermore, since the Resistant Pathogen Study is composed mainly of patients with cUTI, the pooled result reflects similar results that were observed in Study NXL104/2001 and Study NXL104/2002, namely, that CAZAVI has a numerically higher treatment response than its comparators (IMP/CIL and BAT) in cUTI but it has a lower treatment response than its comparators (meropenem and BAT) in cIAI.

Since the NDA was submitted through the 505(b)(2) pathway whereby approval for the indications of cIAI and cUTI will rely in part upon the Agency's findings of safety and efficacy of ceftazidime, all the results in the studies discussed must be bridged to the historical treatment

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response of ceftazidime in cUTI and cIAI. Ceftazidime was initially approved in 1985 under the trade name FORTAZ. The meta-analysis was conducted using the DerSimonian & Laird random effects method where ceftazidime was associated with approximately 89.1% (95% CI: 85.0, 93.2%) favorable microbiological response rates at TOC and 90.4% (95% CI: 85.5, 95.4%) favorable clinical outcome rates at TOC and 86.6% (95% CI: 78.9, 91.8) joint favorable clinical and microbiological response. These results are comparable to the response rate seen in the Open-label Resistant Study but not Study NXL104/2001. For cIAI, ceftazidime was associated with favorable clinical response rate of 86.1% (95% CI: 74.1, 98.0) in published historical trials. This is comparable to the response rate seen in Study NXL104/2002. Note though that the analysis population used in the meta-analysis is the ME population.

5.3 Conclusions and Recommendations

In conclusion, absent reliance on the 505(b)(2) approval pathway, the evidence of efficacy of CAZAVI is scant and uncertain. There may be evidence of efficacy in cUTI through the consistent numerically higher treatment responses against IMP/CIL and BAT in Study NXL104/2001 and interim Resistant Pathogen Study, resp. However, the confidence intervals are wide and introduces uncertainty that it could also be lower than IMP/CIL or BAT. Furthermore, the result of Study NXL104/2001 is not compatible with historically associated clinical response rate of ceftazidime to warrant extrapolation on the beneficial effect of avibactam and this may be due to the dose that was used in the trial. There is a hope, however, that the to be marketed dose of 2.5 g [2.0 g ceftazidime + avibactam 0.5 g] will yield clinical cures that are comparable with the historical ceftazidime treatment response as evidenced by the result of the interim data from the Resistant Pathogen Study. Until that study is completed, evidence is short of something definitive. On the other hand, for cIAI, CAZAVI seems less effective than meropenem and more so in the subgroup of patients with CAZ-sensitive infecting pathogen, a subset where even the use of ceftazidime without avibactam is still adequate. The pooled study did not give supportive evidence as it is composed mainly of cUTI. In the subgroup of patients with CAZ-NS infecting pathogen, CAZAVI treatment response is numerically better than meropenem. It would be hard pressed not to think if avibactam does not interfere with the effect of ceftazidime in infections caused by CAZ-sensitive pathogens. Otherwise, the two subgroups should have a more consistent treatment response in both subgroups, at least numerically. With that said, given that the cIAI trial, D4280C00001/5, is already complete and data is just waiting processing, it is interesting to find out if this hypothesis has any basis or that the result is just sporadic due to thesize of the trial. Together with dose adjustments for renally-impaired patients that only surmised due to the completion of D4280C00001/5 and its topline results, it is tempting but probably prudent, from a rigorous scientific standpoint, to withhold the decision on the limited use in CIAI until all new data have been completely analyzed.

However, the seriousness of the threat of resistant bacteria and the need for new antibiotics requires a smarter look at evidentiary data. For instance, a drug's efficacy is not measured by whether its treatment response exceeds a comparator. In fact, a drug does not need to show

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that it is better than an active drug for it to be approved. It only needs to show that it is better than placebo. In the two investigations comparing CAZAVI with inadequate therapy (see discussion in previous paragraphs and in Table 3-18 and Table 3-30) both yielded results that point out that CAZAVI is numerically better than just inadequate therapy, albeit the confidence interval is wide. By no means conclusive as previously stated, this is probably the only clinical result that gives clue that somehow the CAZAVI works and it is not placebo, alongside comparability of CAZAVI treatment response, particularly in the CAZ-NS subgroup, from published literature, and supportive data from in vitro microbiology, PK/PD models, and animal studies. With this and with all the reservations mentioned, I support approval of this product for limited use in the indications sought.

As a recommendation, the predictive probability of clinical response as a function of the treatment MIC of the primary baseline pathogen provides and interesting insight at performing future clinical trials in cIAI. Note that in Study NXL 104/2002, there does not seem to be a relationship between clinical response and increasing resistance. I posit that this is due to the patient characteristic, e.g., comorbidity, disease severity, etc., that alters the presumed pharmacodynamic relationship of exposure and cure. Hence, it is probably advantageous to study drugs in patients that have targeted diseases to eliminate the effect of auxiliary patient characteristic. Though this might be seen as counterintuitive, as one usually thinks that studying in the sickest patients give the toughest test of a new drug, such a test does not illuminate whether a new drug works because of many potential factors that could have affected the results. However, such a test is beneficial when one looks at the general efficacy of a drug when it is already marketed.

5.4 Labeling Recommendations

To be determined during the labelling meeting.

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5.5 Appendix

Table 5-1: Published Studies with using Ceftazidime in cUTI

Citation	Study design	Ceftazidime Dosage	Clinical Assessment time point	Favorable Clinical Response		Microbiological Assessment Time-point	Favorable Microbiological Response		Analysis Population
				Ceftazidime	Comparator		Ceftazidime	Comparator	
Cox, 1983	Randomized	0.5 g IM q12h, 5-10 days	Follow-up	31/33	26/29	5-9 days post treatment	30/33	25/29	Possibly MITT
Cox, 1991	Randomized	1 g IV q12h for ≥3 days, then oral switch option	1 week following therapy	30/30	36/38	5-9 days after discontinuation of therapy	30/30	37/38	MITT
Cox, 1993	Randomized, open label	0.5-2 g IV TID or 1-2 g IV BID, 4-21 days	5-9 days post treatment	73/82	142/165	5-9 days post treatment	78/82	155/165	ME
Frimodt-Moller and Masen, 1983		0.5 g IM q12h, 7-10 days	N/A	N/A	N/A	5-9 days after treatment	16/22	13/21	Subset of ME
Gallis et al, 1989	Randomized, blinded	0.5 g q8-12h, 7-14 days	N/A	N/A	N/A	5-9 days after completion of therapy	0/1 (cUTI)	4/4	Subset of ME
Holloway and Palmer, 1996	Randomized, open label	2 g IV or IM q8h	1 week after end of therapy	38/48	42/48	After treatment	43/48	42/48	Subset of ME
Horowitz et al, 1985	Randomized, open label	0.5 g IV q12h	N/A	N/A	N/A	5-9 days post therapy	20/27	14/27	ME
Melekos et al, 1991	Randomized, open label	1 g IV or IM BID, 7 days	5-9 days post treatment	18/22	16/19 (aztreonam) 17/20 (amikacin)	5-9 days post treatment	22/23	20/22 (aztreonam) 19/21 (amikacin)	ME
Mouton and Beuscart, 1995	Randomized, open label	2 g q8h IV	N/A	N/A	N/A	5-9 days post treatment	12/12	5/9	Subset of ME
Romanelli and Cravarezza, 1995	Randomized, open label	0.5 g TID IM, 5-10 days	N/A	N/A	N/A	5-9 days post treatment	11/15	17/28	Subset of ME
Schalkhauser and Kohler, 1992	Randomized, open label	1 g IV BID, 7-10 days	3-5 days post treatment	76/78	83/85	3-5 days post treatment	69/78	74/85	ME
Sharifi et al, 1996	Randomized, open label	0.5 g q12h IM or IV, ≤ 14 days	5-9 days post treatment	43/50	83/93	5-9 days post treatment	39/50	83/98	Subset of ME
Sifuentes-Osornio et al, 1989	Randomized, blinded	1 g q8h IV 7-14 days	N/A	N/A	N/A	Day 3 or 4 and 5-9 days post treatment	8/9	14/16	Subset of ME
Study Group, 1992	Randomized, open label	1 g IV q12h, ≥5 days	N/A	N/A	N/A	2-15 days post treatment	174/200	337/377	ME
Tammela et al, 1990	Randomized	2 g BID IV for 3-4 days then mostly IM, 5-15 days	Days 5-9 of follow-up	31/38	29/39	Days 5-9 of follow-up	30/38	28/39	ME

Table 5-2: Articles Used to Evaluate the Efficacy of Ceftazidime Alone in Patients with cIAI

Citation	Dose	Clinical Assessment	Ceftazidime	Comparator
Bubrick et al, 1990	2 g IV q8h + clindamycin 900 mg IV q8h	Time point not defined	31/34	30/34
Simmen et al, 1989	2 g IV TID + 600 mg clindamycin	Time point not defined	26/33	16/33

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/s/

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01/15/2015

THAMBAN I VALAPPIL
01/15/2015
See my memorandum/secondary review