STUDY AI411-204

Medical Officer's Comment

Summaries of protocols in this review are generally excerpted from the sponsor's application, with the Medical Officer's comments set off in italic type.

General information

Title: A Double-Blind Randomized Trial of Cefepime Versus Ceftazidime for the Empiric Treatment of Febrile Episodes in Neutropenic Cancer Patients

Objective: To compare the clinical and microbiological efficacy and the safety of cefepime to ceftazidime in the treatment of febrile episodes in neutropenic cancer subjects.

Investigators/Study Centers: See Table 204.2.

Study design: This was a double-blind, randomized, comparative multicenter study conducted in the United States. Subjects were stratified and separately randomized (1:1) based on their underlying malignancy; solid tumor or hematologic malignancy. Enrollment of 250 subjects was planned.

Study Period: First subject enrolled January 16, 1993. Last subject completed therapy November 3, 1994.

Protocol summary

Study population

Diagnosis and main criteria for inclusion: Hospitalized oncology subjects, 18 years of age or older, who developed fever and neutropenia were eligible for enrollment. Subjects with an ANC of less than 500 cells/μL or those with an ANC between 500-1000 cells/μL whose counts were anticipated to fall below 500 cells/μL within the next 48 hours could be enrolled. Fever was defined as a temperature of greater than 38.5°C or two temperatures greater than 38.0°C during a 12 hour period.

Exclusion criteria: Subjects were excluded if they had a history of penicillin or cephalosporin allergy. They were not eligible if they were pregnant or lactating. HIV-positive subjects were excluded. Subjects with severe underlying disease (e.g. endocarditis), pre-existing sepsis syndrome or septic shock, subjects undergoing or who had had a bone marrow transplantation or stem cell harvesting and infusion were all excluded from the study. Individuals receiving an investigational agent, those requiring other systemic antibacterial drugs concomitantly (except vancomycin) or those who had received parenteral antibiotics within 24 hours prior to study enrollment were not eligible for enrollment. Subjects with severe renal disease, i.e. estimated or measured creatinine clearance <15 mL/min or those requiring dialysis, could not be enrolled. Subjects could be re-enrolled in the study; however, they could enroll only once per episode of neutropenia and they must have been off study for at least seven days.

Medical Officer's Comment

These criteria are consistent with the IDSA guidelines. However, the protocol does not indicate the mechanism for identifying and recruiting patients, or whether they were enrolled consecutively. The exclusion period of 24 hours for pre-existing antibiotic

administration is relatively short; however, an exclusion period of 72 hours was applied retrospectively by both the Medical Officer and the sponsor.

Study Procedures

***Pretreatment Procedures*:** Written informed consent was requested from subjects or their authorized representative. After obtaining informed consent, subjects were randomized to a blinded study treatment. Randomization was stratified by cancer diagnosis, i.e. hematologic versus solid organ malignancy. Medical history, complete examination, vital signs, height and weight were obtained (Table 204.1). Cultures of blood, urine, and any other suspected focal sites of infection were obtained within 48 hours prior to initiation of study therapy. A complete blood count (CBC), reticulocyte count, prothrombin time (PT), partial thromboplastin time (PTT), chemistries (albumin, alkaline phosphatase, ALT/AST, amylase, blood urea nitrogen, calcium, chloride, cholesterol, glucose, phosphorus, potassium, serum creatinine, sodium, total bilirubin, and uric acid) and urinalysis were collected on study day 1, defined as the start day of study drug therapy. A pregnancy test was performed on females of child-bearing potential within 24 hours prior to enrollment into the study, and a chest x-ray was performed within 48 hours prior to initiation of study therapy.

Treatment assignment: Consented subjects were randomized to receive cefepime or ceftazidime. Subjects were stratified into two groups: solid tumors and hematologic malignancies for the purpose of randomization. Investigators remained blinded to treatment assignment.

Study therapy: Cefepime was supplied in 2 gram vials to the study sites and administered at a dose of 2g q8h. Dosage was adjusted for decreased renal function based on guidelines in the protocol. Ceftazidime was supplied as a 2 gram vial and was administered at a dose of 2 g q8h. Dose adjustment for decreased renal function was specified in the protocol.

Medical Officer's Comment

Although there is no FDA-approved comparator for this indication, ceftazidime has been shown to be effective as monotherapy for febrile neutropenic patients (Pizzo et al. *1986), and is accepted in the medical community for this purpose. However, the evidence that it is effective as monotherapy in patients at high risk for infection (e.g., patients with severe neutropenia) is weak (Sanders* et al. *1991); results from clinical trials comparing different monotherapy regimens suggest that imipenem may be a more appropriate monotherapy comparator for high-risk patients (Liang* et al. *1990).*

Table 20-1
Time and Event Schedule

	Study Day 1	Daily during therapy	Study day 4	Every third study day thereafter	End of therapy evaluation	4-7 days post-therapy
Informed consent	X					
Blood culture	X		X[1]	X[1]	X	
Specimen obtained from site of infection for C&S	X		X[1]	X[1]	X[1]	
Medical history	X					
Physical examination	X		X[2]	X[2]	X[2]	X[2,3]
Vital signs[4]	X	X[5]	X	X	X	X[3]
Pregnancy test[6]	X					
Laboratory tests	X	X[7]	X	X	X	X[1,3]
Clinical evaluation	X		X	X	X[8]	X
Concomitant Medication	X		X	X	X	
Adverse Event Screening			X	X	X	X
Microbiologic Response						X
Clinical Response						X

[1] If clinically available or indicated.

[2] An abbreviated physical examination could be performed unless a complete examination was clinically indicated.

[3] A telephone follow-up was allowed for subjects who had been discharged from the hospital.

[4] Blood pressure, pulse, respiratory rate, and temperature (height and weight were to be measured only on enrollment.

[5] Maximal temperature only.

[6] Serum in females of child-bearing potential.

[7] Total leukocyte and absolute neutrophil counts only.

[8] Evaluation of clinical response was to occur no longer than 24 hours following the last dose of study drug.

Duration of therapy: Study therapy was to be continued until the subject had been afebrile for 48 hours and recovered an absolute neutrophil count of greater than 500 cells/μL, or received 14 days of study therapy.

Discontinuation of therapy: Study therapy could be discontinued early for any of the following reasons:

An infection caused by a bacterial organism resistant to study therapy.

A serious adverse event.

Poor clinical response.

Conditions requiring therapeutic intervention not permitted in the protocol.

Personal preference of the subject or guardian.

The investigator's opinion that continuation of the study was not in the subject's best interest.

Occurrence of pregnancy.

Subject lost to follow-up.

All adverse events resulting in discontinuation of study drug were followed until resolution or stabilization.

Medical Officer's Comment

Except for discontinuations due to adverse events, the protocol did not explicitly state how long patients who were discontinued from study therapy were followed. It was therefore not clear from the protocol if patients discontinued from the therapy were to be followed until resolution of fever or neutropenia had occurred, or until death occurred. However, the submission did generally contain follow-up data on such patients sufficient to allow determination of outcomes.

Concomitant medications: Concomitant medications other than systemic antimicrobial agents were allowed as clinically indicated. These were recorded in the case report form with the indication, the dates started and discontinued, and the total daily dose.

No other antibacterial agent was permitted during the study period except intravenous vancomycin. Vancomycin could be initiated for two reasons: 1) if fever persists for 72 hours after receipt of study drug and a gram-positive organism was suspected, or 2) if culture results demonstrated the presence of a methicillin-resistant staphylococci or enterococci at an infected site prior to 72 hours of study drug. Addition of vancomycin would be scored separately as a modification compared to other antibacterials. Antiviral and antifungal agents could be initiated and would be scored as a non-antibacterial modification.

Medical Officer's Comment

As with all protocols except AI411-137, the protocol did not specify what specific modifications were to be made with respect to additional anti-bacterial agents.

Prophylactic antimicrobial therapy was defined as any antimicrobial administered during the three days prior to the start of study therapy that was not intended to treat an established infection. Prophylactic antimicrobials were categorized according to the spectrum of antimicrobial activity (antibacterial, antifungal, or antiviral).

Medical Officer's Comment

The IDSA guidelines suggest that studies enrolling patients on prophylaxis should require that the same regimen be used for all subjects. Failing that, studies should either exclude or stratify patients on anti-microbial prophylaxis. In general, patients in this study were on a variety of regimens, but use of prophylaxis was not used as a stratum.

During Treatment Procedures: Procedures during treatment are summarized in Table 204.1. Maximal daily temperatures were recorded on the CRF. A temperature log was maintained by the subject if he/she was discharged home prior to end of treatment. The absolute neutrophil count was calculated daily. Seventy-two hours after study initiation, i.e., Study Day 4, the subject's clinical status was evaluated by the investigator. This included a physical examination with vital signs, assessment of the status of the infection, a blood culture as well as cultures of any site of focal infection. Serum chemistries were also repeated on this day. Adverse events, concomitant medications and administered blood products were recorded. Identical evaluations were performed every three days thereafter. After Day 4, cultures of blood and body sites were only obtained if clinically indicated.

The results of all cultures were recorded in the case report form. All organisms considered pathogenic were identified and speciated to the extent possible. Positive cultures had susceptibility tests for cefepime and ceftazidime performed using the Kirby-Bauer disk method and/or an MIC panel when available. Zones of inhibition were recorded in the case report form, and the investigator judged whether isolates were causative pathogens or contaminants.

Medical Officer's Comment

Except for coagulase-negative staphylococci, criteria for deciding whether organisms might be causative pathogens or contaminants were not explicitly stated in the protocol.

Post-Treatment Procedures: Post-treatment procedures are summarized in Table 204.1. Subjects were to be evaluated at two time points after the last dose of study drug was administered. The first post-treatment evaluation occurred within 24 hours of completion of study drug. A physical examination and vital signs were performed. All subjects had blood cultures repeated unless a previous culture had been negative. Specimens from focal sites of infection were obtained if clinically indicated. Laboratory studies, CBC, and chemistries were repeated.

Subjects were permitted to receive oral antimicrobials at the end of study therapy. This was recorded separately in the case report form.

The second post-treatment evaluation occurred between the fourth and seventh post-therapy days. Discharged subjects were interviewed by phone to assess any intervening events, the presence of fever, and the use of any antibiotic therapy. Those subjects re-

maining hospitalized had a physical examination and vital signs performed. At this time the investigator categorized the subject's clinical and bacteriologic outcome.

Medical Officer's Comment

The IDSA guidelines call for a fixed follow-up period with a suggested length of 7 days.

Sponsor's Criteria for Evaluation

Methods: Efficacy was determined by a consultant who had not participated in the study as an investigator, and who was blinded to patients' treatment assignments. The consultant classified subjects into four diagnostic categories based upon clinical and microbiologic data - microbiologically documented infection, clinically documented infection, fever of uncertain origin, and non-infectious fever.

Diagnoses: Infectious disease diagnoses were classified as:

> Microbiologically Documented Infection (MDI): Bacteremia or fungemia involving one or more organisms without a definable non-hematogenous site of infection (primary) OR an infection at a specific site (e.g., UTI, cellulitis) that is microbiologically confirmed with or without bacteremia or fungemia.
>
> Clinically Documented Infection (CDI): Signs and symptoms of infection at a specific site (e.g., UTI, cellulitis) but the microbial etiology could not be proven.
>
> Fever of Uncertain Origin (FUO): Fever in the absence of localizing clinical signs and the microbial etiology of fever could not be proven.
>
> Non-infectious fever: Fever in the absence of localizing clinical signs, no proven microbial etiology AND an alternative non-infectious cause is likely after thorough evaluation (e.g., tumor fever, drug fever).

Pathogens: All organisms obtained from cultures were classified by the investigators as causative, colonizer, contaminant, or normal flora and recorded in the case report form. Coagulase-negative staphylococci (CNS) required two or more separate blood cultures to be classified as a causative organism in bacteremia. CNS could be classified as a causative pathogen from a localized site only if it was the single organism isolated.

Efficacy: Efficacy was evaluated on the basis of changes in signs and symptoms, of which temperature was the critical parameter. The efficacy evaluation also included an assessment of a microbial endpoint, when applicable. Three categories of clinical outcome were defined by the consultant: success, failure, and unevaluable.

Success. The subject's fever and clinical signs of infection resolved, the infecting organism, whenever isolated, was eradicated without change in study therapy and the response was maintained for at least 4-7 days after discontinuation of study therapy.

Failure. One of the following events occurred during or following therapy:

- No response to study medication based on one of the following events:
  - Septic shock
  - Acute respiratory distress syndrome
  - Disseminated intravascular coagulation
  - Multiple organ failure
  - Progression of primary infection
  - Persistence of fever for 96 hours during study therapy
  - Pathogen resistant to study therapy
  - Persistent bacteremia (> 24 hours of study therapy)
  - Recurrent (breakthrough) bacteremia
  - Relapse of primary infection < 7 days post therapy
  - Death from primary infection

Unevaluable. A subject was considered unevaluable in the following situations:

- Initial infection caused by a virus, fungal, parasitic or mycobacterial organism.
- A major protocol violation occurred, e.g. clinically inappropriate addition of a concomitant antibiotic, inadequate follow-up, or subject did not meet temperature or ANC criterion.
- A non-infectious cause of fever was documented.
- Early discontinuation of study therapy for an adverse event if the subject was clinically stable at the time of discontinuation but criteria for success or failure were not met.

Medical Officer's Comment

As noted above, the protocol did not explicitly state whether patients who were discontinued from study therapy were to be followed until resolution of fever or neutropenia had occurred, or until death occurred, but such data were generally provided in the submission.

In the modified intent-to-treat analysis, subjects with non-bacterial infections, adverse events, inadequate follow-up or those receiving concomitant antibiotics were all considered treatment failures.

New infections were defined as infections, microbiologically or clinically documented, which had the onset of signs and symptoms during study therapy or during the

follow-up period. A new infection could represent a breakthrough bacteremia with a new organism or an infection at a new site. A relapse or recurrent infection was defined as an infection with the same organism or worsening at the original site. New infections were recorded in the case report form and tabulated by treatment group.

Medical Officer's Comment

Under the sponsor's set of definitions, the occurrence of a new infection does not per se *represent a treatment failure.*

The consultant then determined the evaluability of each case. Subjects were unevaluable if they did not meet a specified entry criteria (e.g., fever, neutropenia), have adequate post-treatment follow-up, or if the treatment regimen was modified within the first 72 hours or discontinued early without evidence for treatment failure. Evaluable subjects' responses were then assessed as success or failure. A success was the defervescence of the subject on the initial treatment regimen without the addition of a new antibiotic, the eradication of the pathogen (if determined), the resolution of clinical signs and symptoms (if present), and the maintenance of this response through a 4-7 day period post-therapy. Reasons for treatment failure were specified, i.e., no response to treatment and persistent fever, resistant pathogen, progression of infection, relapse, or new infection.

Medical Officer's Comment

In general, the Medical Officer's evaluability and efficacy criteria were similar to those of the sponsor (see Introduction to the Reviews of Clinical Studies section). The following criteria for exclusion were substantially different from those of the sponsor: 1) modification prior to 72 hours for any reason other than isolation of a resistant pathogen; 2) discontinuation at any point due to an adverse event; 3) absence of neutropenia within 48 hours of study entry. Episodes excluded for reasons 1) and 2) were included in the Medical Officer's MITT analysis.

Sponsor's Safety Assessment

All subjects receiving study therapy were evaluated for safety. All deaths, adverse events, and abnormal laboratory values were recorded. Their relationship to study therapy was assessed.

Sponsor's Statistical Methods

All subject characteristics as well as description of antibiotic therapy were tabulated by treatment group for first course only. Median and range were used to describe continuous variables. Comparisons between treatment groups were done by the Cochran-Mantel-Haenszel test for categorical data and the two way ANOVA procedure based on ranks for continuous variables, both controlling for infection diagnoses.

Success rates were analyzed for the first episode in the evaluable sample as well as in the modified Intent-to-Treat sample. The analyses of the difference in success rates were performed using the Cochran-Mantel-Haenszel test controlling for infection diagnoses. A stepwise logistic regression model was used to identify significant prognostic factors that may influence clinical outcome. The differences between the success rates for the treatment groups and its exact 95% confidence interval were reported.

Medical Officer's Comment

The IDSA guidelines suggest evaluation by both patient and by episode (i.e., analysis of first episodes and all episodes). One objection to analysis of all episodes is that episodes occurring in the same patient are not independent events, given that the patient remains the same. Analysis of all episodes would then give undue weight to patients enrolled more than once. Following the IDSA guidelines, in the Medical Officer's analysis, response rates were determined for both first episodes and all episodes. However, response rates for first episodes were used for the primary analysis.

Statistical Reviewer's Comment

The identification of prognostic risk factors by the sponsor appear to be post hoc *and may introduce a bias in the study results. Care needs to taken in interpretation of such results.*

Results - AI411-204

Study population characteristics

Demographics: Two hundred seventy-eight (278) subjects were enrolled at 11 sites for first course treatment in the trial. An additional seven (7) sites were registered for the study but did not enroll any participants. Two subjects never received a dose of study medication. No data were provided by the sponsor on these subjects, who were therefore not analyzed further. One hundred forty-three (143) subjects were randomized to receive first course cefepime and 133 subjects to receive first course ceftazidime. An additional thirty-nine (39) treatment courses were administered to 27 subjects who completed the first course. Table 204.2 shows the distribution of patient enrollment by center. Table 204.3 shows the demographics of patients enrolled in this study.

Table 20.4.2. Enrollment by Study Sites - First Episode				
		Number of Subjects		
Investigator Institution Location	**Center**	**Cefepime**	**Ceftazidime**	**Total**
James W. Hathorn Duke University Durham, NC	005	37	37	74
P.H. Chandrasekar Harper Hospital Detroit, MI	016	31	29	60
Ian Baird Riverside Methodist Hospital Columbus, OH	010	28	23	51
Paul Arnow University of Chicago Chicago, IL	014	12	15	27
William Velasquez St. Louis University St. Louis, MO	012	12	8	20
John Heimenz Moffitt Hospital Tampa, FL	018	6	5	11
Thomas Hardin Audie Murphy VAMC San Antonio, TX	008	5	5	10
George Udeani University of Illinois Chicago, IL	017	4	5	9
Elizabeth E. Campbell Rex Hospital Raleigh, NC	013	3	3	6
Robert Swenson Fox Chase Cancer Center Philadelphia, PA	007	3	2	5
Arnold Markowitz St. Joseph's Hospital Pontiac, MI	003	2	1	3
Totals		**143**	**133**	**276**

Table 204.3. Demographics of all enrolled patients				
	Overall	**Cefepime**	**Ceftazidime**	**CMH p-value**
Total	276	143	133	
Age				0.065
Median (y)	57.0	55.0	58.0	—
Mean (y)	54.1 ± 14.7	53.2 ± 14.3	55.6 ± 14.9	
Range (y)				
≥ 65 y	79 (28.6%)	34 (23.8%)	45 (33.8%)	
< 65 y	197 (71.4%)	109 (76.2%)	88 (66.2%)	
Sex				0.390
Male	142 (51.4%)	70 (49.0%)	72 (54.1%)	
Female	134 (48.6%)	73 (51.0%)	61 (45.9%)	
Race				0.611
White	216 (78.3%)	114 (79.7%)	102 (76.7%)	
Black	44 (15.9%)	21 (14.7%)	23 (17.3%)	
Other	16 (5.8%)	8 (5.6%)	8 (6.0%)	
Underlying disease				0.379
Leukemia	75 (27.2%)	42 (29.4%)	33 (24.8%)	
OHM	62 (22.5%)	33 (23.1%)	29 (21.8%)	
OHD	3 (1.1%)	0 (0.0%)	3 (2.3%)	
Solid tumor	136 (49.3%)	68 (47.5%)	68 (51.1%)	
ANC nadir				0.811
Median	40.0	30.0	50.0	
Mean	122.8 ± 189.3	109.7 ± 162.8	136.8 ± 213.2	
≤100	189 (68.5%)	97 (67.8%)	92 (69.2%)	
>100	87 (31.5%)	46 (32.2%)	41 (30.8%)	
Duration ANC≤500				0.352
Median (d)	5.0	5.0	5.0	
Mean (d)	6.3 ± 4.8	6.4 ± 5.2	6.1 ± 4.1	
<7 d	186 (67.4%)	100 (69.9%)	86 (64.7%)	
≥7 d	90 (32.6%)	43 (30.1%)	47 (35.3%)	
Bone marrow graft	0 (0.0%)	0 (0.0%)	0 (0.0%)	—
Indwelling catheter	198 (71.7%)	103 (72.0%)	95 (71.4%)	0.912
Prophylactic Abx	55 (19.9%)	29 (20.3%)	26 (19.5%)	0.879
SBP <90 at entry	14 (5.1%)	9 (6.3%)	5 (3.8%)	0.339
Multiple enrollments	27 (9.8%)	15 (10.5%)	12 (9.0%)	0.682

OHM, hematologic malignancy other than leukemia; OHD, other hematologic disease; ANC, absolute neutrophil count; SBP, systolic blood pressure

Medical Officer's Comment

The treatment arms appear balanced for demographic factors, except as described by the Statistical Reviewer, and for prognostic factors predicting the risk of bacterial infection.

Statistical Reviewer's Comment

There is a marginal imbalance (p-value < 0.15) in the age distribution of the patient population due to enrollment of more elderly patients in the ceftazidime arm. This was not considered to have sufficient clinical significance to warrant any further statistical analysis.

Antimicrobial Prophylaxis: Prophylactic antimicrobial usage was infrequent and similar between the two groups (Table 204.4A). Seventeen percent of the population had received a systemic or non-systemic antibiotic within three days of study entry. Quinolone agents accounted for half of antibiotic prophylaxis. Eight percent of the study group received systemic antifungal prophylaxis, predominantly fluconazole. An additional ten percent were receiving non-systemic agents such as nystatin. Antiviral treatment with acyclovir had been received by seven percent of study subjects.

Table 204.4A. Pretreatment Prophylaxis (First Episode)[1]

	Number (%) of subjects			
Prophylactic agent	**Cefepime (N = 143)**	**Ceftazidime (N = 133)**	**Total (N = 276)**	**p-value**
Any prophylaxis	29 (20)	26 (20)	55 (20)	0.879
Antibacterial	26 (18)	20 (15)	46 (17)	
Norfloxacin	8 (6)	6 (5)	14 (5)	
Ciprofloxacin	8 (6)	4 (3)	12 (4)	
TMP-SMX	2 (1)	2 (2)	4 (1)	
Other	8 (6)	8 (6)	16 (6)	
Antifungal	13(9)	8 (6)	21 (8)	
Fluconazole	12 (8)	8 (6)	20 (7)	
Ketoconazole	1 (1)	--	1 (1)	
Antiviral	8 (6)	10 (8)	18 (7)	
Acyclovir	8 (6)	10 (8)	18 (7)	

[1] Subjects may have received two or more classes of antimicrobial.

After the initiation of the empiric treatment, five subjects in the cefepime arm continued to receive oral antibiotics (ciprofloxacin (2 subjects), metronidazole, sulfacetamide, and oral vancomycin) as did two subjects in the ceftazidime arm (cephalexin and metronidazole). Antifungals and acyclovir were continued during at least part of the treatment phase in all subjects who received these agents pretreatment (Table 204.4B).

Medical Officer's Comment

These antibiotics are all oral agents typically used for GI tract decontamination; although the efficacy of anti-microbial prophylaxis in this setting has not been proven, their use has been relatively routine in the United States.

Statistical Reviewer's Comment

There is no obvious imbalance between the treatment arms with respect to pre-treatment prophylactic agents.

Table 204.4B
Antimicrobial Prophylaxis
Continued Concomitantly with Study Medication[1]
First Course

	Number (%) of Subjects		
Prophylactic agent	**Cefepime (N = 143)**	**Ceftazidime (N = 133)**	**Total (N = 276)**
Antibacterial	5 (3)	2 (2)	7 (3)
Antifungal	13 (9)	8 (6)	21 (8)
Fluconazole	12 (8)	8 (6)	20 (7)
Ketoconazole	1 (<1)	--	1 (<1)
Antiviral			
Acyclovir	8 (6)	10 (8)	18 (7)

* p-value = 0.203

The use of colony-stimulating factors, parenteral nutrition, and blood components was similar between treatment arms.

Statistical Reviewer's Comment

The two treatment arms appear to be balanced with respect to use of antimicrobial prophylaxis continued concomitantly with the study medication.

Episode evaluability

Evaluability assessment gave the results shown in Table 204.5.

1 Subjects may have received two or more classes of antimicrobial.

Table 204.5. Episode evaluability				
	1° evaluability criteria		MITT evaluability criteria	
	Medical Officer	Sponsor	Medical Officer	Sponsor
All episodes	193/315 (61.3%)	219/315 (69.5%)	289/315 (91.7%)	295/315 (93.7%)
Cefepime	103/163 (63.2%)	116/163 (71.2%)	151/163 (92.6%)	155/163 (95.1%)
Ceftazidime	90/152 (59.2%)	103/152 (67.8%)	138/152 (90.8%)	140/152 (92.1%)

One hundred and twenty-two episodes (122) were excluded from the primary FDA analysis; 60/163 (36.8%) from the cefepime arm and 62/152 (40.8%) from the ceftazidime arm. Reasons for exclusion of episodes from the primary FDA analysis are shown in Table 204.6.

Table 204.6. Medical Officer's reasons for exclusion from analysis			
Reason	**Overall**	**Cefepime**	**Ceftazidime**
Early modification	43/315 (13.6%)	20/163 (12.3%)	23/152 (15.1%)
Non-bacterial infection	18/315 (5.7%)	11/163 (6.7%)	7/152 (4.6%)
Not neutropenic	17/315 (5.4%)	7/163 (4.3%)	10/152 (6.6%)
Lost to follow-up	13/315 (4.1%)	4/163 (2.5%)	9/152 (5.9%)
Regimen D/C'd for ADR	12/315 (3.8%)	8/163 (4.9%)	4/152 (2.6%)
Non-study Abx	10/315 (3.1%)	5/163 (3.1%)	5/152 (3.3%)
Not febrile	6/315 (1.9%)	4/163 (2.5%)	2/152 (1.3%)
Pre-existing infection	5/315 (1.6%)	4/163 (2.5%)	1/152 (0.7%)
Non-infectious fever	3/315 (1.0%)	1/163 (0.6%)	2/152 (1.3%)

Medical Officer's Comment

Modification prior to 72 hours was the most common reason for unevaluability. This was done most often because the patient's clinical status had deteriorated. Such patients were scored as failures by the sponsor. Although considered unevaluable under the primary analysis by the Medical Officer, these patients were treated as failures in the Medical Officer's MITT analysis.

Statistical Reviewer's Comment

The two treatment arms are balanced with respect to Medical Officer's reasons for exclusion from analysis.

Episode evaluability by treatment center is shown in Table 204.7.

Table 204.7 Episode evaluability by treatment center			
Center	**Overall**	**Cefepime**	**Ceftazidime**
All centers	193/315 (61.3%)	103/163 (63.2%)	90/152 (59.2%)
003	0/3 (0.0%)	0/2 (0.0%)	0/1 (0.0%)
005	69/94 (73.4%)	37/48 (77.1%)	32/46 (0.0%)
007	1/5 (20.0%)	1/3 (33.3%)	0/2 (0.0%)
008	6/10 (60.0%)	3/5 (60.0%)	3/5 (60.0%)
010	30/55 (54.5%)	15/29 (51.7%)	15/26 (0.0%)
012	9/21 (42.9%)	5/12 (41.7%)	4/9 (44.4%)
013	5/6 (83.3%)	3/3 (100.0%)	2/3 (66.7%)
014	24/33 (72.7%)	11/16 (68.7%)	13/17 (0.0%)
016	39/67 (58.2%)	22/34 (64.7%)	17/33 (0.0%)
017	4/9 (44.4%)	2/4 (50.0%)	2/5 (40.0%)
018	6/12 (50.0%)	4/7 (57.1%)	2/5 (40.0%)

Patients in the evaluable and MITT populations had demographics similar to those in the total sample of enrolled patients.

Statistical Reviewer's Comment

Of the 11 centers participating in the trial, only 4 centers enrolled 10 patients per treatment group as suggested by the DAIDP Points to Consider document.

Infectious Disease Diagnoses

The infectious disease diagnoses assigned by the Medical Officer and the sponsor for patients in the FDA evaluable, FDA MITT, and sponsor evaluable populations are shown in Tables 204.8A, 8B, and 8C, respectively.

Table 204.8A FDA infectious disease diagnoses for evaluable population			
Infection type	Overall	Cefepime	Ceftzazidime
Any	193 (100%)	103 (100%)	90 (100%)
MDI with bacteremia	36 (18.6%)	20 (12.3%)	16 (10.5%)
MDI	18 (9.3%)	9 (5.5%)	9 (5.9%)
CDI	10 (5.2%)	6 (3.7%)	4 (2.6%)
FUO	129 (66.8%)	68 (41.7%)	61 (40.1%)

Table 204.8B. FDA infectious disease diagnoses for MITT population			
Infection type	Overall	Cefepime	Ceftzazidime
Any	289 (100%)	151 (100%)	138 (100%)
MDI with bacteremia	59 (20.4%)	32 (21.2%)	27 (19.6%)
MDI	27 (9.3%)	11 (7.3%)	16 (11.6%)
CDI	20 (6.9%)	12 (7.9%)	8 (5.8%)
FUO	183 (63.3%)	96 (63.6%)	87 (63.0%)

Table 204.8C. Sponsor's infectious disease diagnoses for evaluable population			
Infection type	Overall	Cefepime	Ceftzazidime
Any	219 (100%)	116 (100%)	103 (100%)
MDI with bacteremia	36 (16.4%)	20 (17.2%)	16 (15.5%)
MDI	13 (5.9%)	7 (6.0%)	6 (5.8%)
CDI	11 (5.0%)	5 (4.3%)	6 (5.8%)
FUO	159 (72.6%)	84 (72.4%)	75 (72.8%)

Medical Officer's Comment

These results demonstrate that majority of infections in both arms were due to fever without microbiologic or clinical evidence of infection.

Statistical Reviewer's Comment

The treatment arms are balanced with respect to infectious disease diagnoses for each of the patient populations considered – FDA evaluable and MITT population – as well as the sponsor's evaluable population.

Efficacy analysis

Primary efficacy analysis: The primary efficacy variable was defined as the combined clinical and microbiologic response and was determined by the Medical Officer for each patient. The definitions of response are shown in Table 9.3A. The primary endpoint was outcome definition 1B applied to the evaluable population; for the MITT analysis, definition 1A was applied to the MITT population. Tables 204.9A, B, and C show response rates for all evaluable episodes as determined by the Medical Officer and by the sponsor; response rates for first episodes, and rates by treatment center, respectively. Because different definitions of outcome were applied to the FDA evaluable and MITT populations, the numerators differ between these two analyses.

Table 204.9A. All episode response rates			
Population	**Cefepime**	**Ceftazidime**	**95% Confidence Interval**
FDA evaluable[1]	57/103 (55.3%)	56/90 (62.2%)	$_{103,90}$ (-0.2180, 0.0803) $_{55.3\%,\ 62.2\%}$
FDA MITT[2]	37/151 (24.5%)	38/138 (27.5%)	$_{151,138}$ (-0.1386, 0.0779) $_{24.5\%,\ 27.5\%}$
Sponsor evaluable	65/116 (56.0%)	61/103 (59.2%)	$_{116,103}$ (-0.1721, 0.1083) $_{56.0\%,59.2\%}$
Sponsor MITT	65/155 (41.9%)	61/140 (43.6%)	$_{155,140}$ (-0.1362, 0.1035) $_{41.9\%,\ 43.6\%}$

Table 204.9B. First episode response rates			
Population	**Cefepime**	**Ceftazidime**	**95% Confidence Interval**
FDA evaluable	49/88 (55.7%)	47/76 (61.8%)	$_{88,76}$ (-0.2245, 0.1013) $_{55.7\%,\ 61.8\%}$
FDA MITT	30/131 (22.9%)	33/119 (27.7%)	$_{131,119}$ (-0.1642, 0.0676) $_{22.9\%,\ 27.7\%}$
Sponsor evaluable	58/101 (57.4%)	52/87 (59.8%)	$_{101,87}$ (-0.1753, 0.1284) $_{57.4\%,\ 59.8\%}$
Sponsor MITT	58/136 (42.6%)	52/121 (43.0%)	$_{136,121}$ (-0.1323, 0.1257) $_{42.6\%,\ 43.0\%}$

The 95% confidence intervals are reported as n_t,n_c (95% C.I.) p_t,p_c where n_t = number in the test group, n_c = number in the control group, p_t = response rate in the test group, p_c = response rate in the control group.

Statistical Reviewer's Comment

If all febrile neutropenic episodes in study AI411-204 are considered, cefepime fails to establish therapeutic equivalence to ceftazidime with respect to response rates for the patients who are FDA evaluable. Cefepime is therapeutically equivalent to ceftazidime with respect to response rates in patients included in the FDA MITT, sponsor evaluable and sponsor MITT populations.

If the first febrile neutropenic episode is considered, cefepime fails to establish therapeutic equivalence to ceftazidime with respect to response rates for the patients who are FDA evaluable. Cefepime is therapeutically equivalent to ceftazidime with respect to first episode response rates in patients included in the FDA MITT, sponsor evaluable and sponsor MITT populations.

Medical Officer's Comment

According to the DAIDP Points to Consider document, if the response rates for both test drug and comparator are below 80%, the 95% confidence interval around the difference in response rates should be have a lower bound of no more than 20% for the drugs to be declared therapeutically equivalent. Under this criterion, the response rate obtained in the FDA analysis of the evaluable population does not demonstrate therapeutic equivalence. The differences between the Medical Officer's analysis and the spon-

1 Definition 1B was applied to the FDA evaluable population for the primary FDA analysis (clinical improvement and sustained defervescence achieved without modification of treatment (successful treatment of primary episode without new episode); completion of therapy with an oral antibiotic agent allowed.

2 Definition 1A was applied to the FDA MITT population for the main FDA MITT analysis (clinical improvement and sustained defervescence achieved without modification of treatment (successful treatment of primary episode without new episode); no post-therapy with oral antibiotic agents allowed.

sor's analysis result from the smaller size of the FDA evaluable population, as well as differences in assessment of outcomes. The sponsor supplied the Medical Officer with additional material derived from the case report forms; the response rates shown reflect review of this material in addition to the case report tabulations.

Table 204.9: Response rates by treatment center

	Cefepime	Ceftazidime
All centers	57/103 (63.2%)	56/90 (59.2%)
003	0/0	0/0
005	18/37 (48.6%)	18/32 (56.2%)
007	0/1 (0.0%)	0/0
008	3/3 (100.0%)	1/3 (33.3%)
010	12/15 (80.0%)	11/15 (73.3%)
012	2/5 (40.0%)	3/4 (75.0%
013	3/3 (100.0%)	2/2 (100.0%)
014	8/11 (72.7%)	9/13 (69.2%)
016	10/22 (45.5%)	10/17 (58.8%)
017	1/2 (50.0%)	0/2 (0.0%)
018	0/4 (0.0%)	2/2 (100.0%)

Reasons for failure: A summary of the Medical Officer's assessments of reasons for failure in evaluable patients is shown in Table 204.10.

Table 204.10: Reasons for treatment failure

Reason for failure	Cefepime	Ceftazidime	p value
Persistent fever	18/103 (17.5%)	11/90 (12.2%)	0.483
Poor microbiologic response, initial isolate resistant	7/103 (7.0%)	5/90 (5.6%)	
Poor microbiologic response, initial isolate susceptible	1/103 (1.0%)	0/90 (0.0%)	
Death from primary infection	1/103 (1.0%)	2/90	
Death from secondary infection	5/103 (4.9%)	0/90 (0.0%)	
Poor clinical response	7/103 (7.0%)	9/90 (10.0%)	
Bacteriologic relapse	0/103 (0.0%)	0/90 (0.0%)	
New MDI, susceptible isolate	0/103 (0.0%)	0/90 (0.0%)	
New MDI, resistant isolate	1/103 (1.0%)	4/90 (4.4%)	
New CDI	1/103 (1.0%)	0/90 (0.0%)	
New FUO	5/103 (4.9%)	3/90 (3.3%)	
Total failures	**46/103 (44.7%)**	**34/90 (37.8%)**	

Medical Officer's Comment

Except for deaths due to secondary infection, there was not a significant difference between the treatment arms with respect to reasons for treatment failure. The deaths due to secondary infection in the cefepime arm were due to enterococcal bacteremia in two cases, an aspiration pneumonia in one case, and Aspergillus *pneumonia in one case; the fifth death was attributed to infection but occurred in the setting of fever without a documented source of infection.*

There was only one case in the cefepime arm in which failure occurred due to a poor microbiologic response with infection by a susceptible isolate, and none in the ceftazidime arm. There were no cases of bacteriologic relapse in either arm.

Statistical Reviewer's Comment

The two treatment arms are balanced with respect to reasons for treatment failure.

Microbiologic efficacy: Patients with microbiologically documented infections (MDIs) have the best documented evidence for having true bacterial infections. Response rates for MDIs in evaluable episodes as determined by the Medical Officer and the sponsor are shown in Table 204.11. Microbiologic efficacy by pathogen is analyzed in the integrated summary of efficacy (section 10).

Table 204.11 MDI response rates

Population	Cefepime	Ceftazidime	95% Confidence Interval
FDA evaluable	9/29 (31.0%)	6/25 (24.0%)	$_{29,25}(-0.2043, 0.3450)_{31\%,24\%}$ Exact 95% Confidence Interval $_{29,25}(-0.2012, 0.3574)_{31\%,24\%}$
Sponsor evaluable	9/27 (33.3%)	4/22 (18.2%)	$_{27,22}(-0.1297, 0.4328)_{33.3\%,18.2\%}$ Exact 95% Confidence Interval $_{27,22}(-0.1328, 0.4449)_{33.3\%,18.2\%}$

Statistical Reviewer's Comment

The sample size of patients who had microbiologically documented infection is too small to ensure an acceptable power level for statistical inferences. However, based on the exact confidence intervals, cefepime fails to establish therapeutic equivalence with ceftazidime in patients with microbiologically documented infections included in the FDA evaluable population. The two treatment arms are therapeutically equivalent in the evaluable patient population defined by the sponsor.

Efficacy with respect to various definitions of success in primary outcome: The analysis of treatment failures indicated a broad distribution of reasons for discontinuation or modification of the empiric regimen. Some of these outcomes may have masked successful aspects of treatment (e.g., resolution of the initial episode with failure to prevent further infections while on therapy). Response rates were therefore analyzed using different measures of outcome, as described in Methods. The definitions of success outlined in Table 9.3B were used. In comparing response rates with these different definitions, the size of the patient population (either evaluable or MITT) was held constant. Tables

204.12A and 12B show response rates for the FDA evaluable and MITT populations based on different outcome measures. The primary outcome measures for each population are shown in boldface.

Table 204.12A: Evaluable population response rates with different outcome measures

Outcome	Cefepime	Ceftazidime	95% Confidence Interval
Definition 1A	37/103 (35.9%)	36/90 (40.0%)	$_{103,90}(-0.1884, 0.1069)_{35.9\%, 40.0\%}$
Definition 1B[1]	**57/103 (55.3%)**	**56/90 (62.2%)**	$_{103,90}(-0.2180, 0.0803)_{55.3\%, 62.2\%}$
Definition 2A	44/103 (42.7%)	43/90 (47.8%)	$_{103,90}(-0.2016, 0.1004)_{42.7\%, 47.8\%}$
Definition 2B	64/103 (62.1%)	63/90 (70.0%)	$_{103,90}(-0.2222, 0.0650)_{62.1\%, 70.0\%}$
Definition 3	97/103 (94.2%)	88/90 (97.8%)	$_{103,90}(-0.1010, 0.0289)_{94.2\%, 97.8\%}$

Table 204.12B: MITT population response rates with different outcome measures

Outcome	Cefepime	Ceftazidime	95% Confidence Interval
Definition 1A[2]	**37/151 (24.5%)**	**38/138 (27.5%)**	$_{151,138}(-0.1386, 0.0779)_{24.5\%, 27.5\%}$
Definition 1B	57/151 (37.7%)	58/138 (42%)	$_{151,138}(-0.1627, 0.0779)_{37.7\%, 42\%}$
Definition 2A	48/151 (31.8%)	49/138 (35.5%)	$_{151,138}(-0.1532, 0.0788)_{31.8\%, 35.5\%}$
Definition 2B	58/151 (38.4%)	59/138 (42.7%)	$_{151,138}(-0.1636, 0.0768)_{38.4\%, 42.7\%}$
Definition 3	139/151 (92.1%)	133/138 (96.4%)	$_{151,138}(-0.1034, 0.0169)_{92.1\%, 96.4\%}$

The 95% confidence intervals are reported as n_t,n_c (95% C.I.) p_t,p_c where n_t = number in the test group, n_c = number in the control group, p_t = response rate in the test group, p_c = response rate in the control group. Subdefinitions A and B are shown in Table 9.3B.

As expected, the response rate monotonically increased with gradual relaxation of the criteria and definition for success.

Statistical Reviewer's Comment

Cefepime fails to establish therapeutic equivalence with respect to every definition in the evaluable patient population except Definition 1A. In the patient population included in the MITT analyses, cefepime is deemed therapeutically equivalent to ceftazidime based on every definition except Definition 3.

Care needs to be taken in the interpretation of these results since multiple *post hoc* comparisons of data increase the Type I error (probability of a false positive result).

Modifications

A summary of the frequency of modification as determined by the Medical Officer, both overall and for specific classes of anti-microbial agents is presented in Table 204.13 for the evaluable AI411-204 population.

[1] Primary definition of success for the evaluable patient population.
[2] Primary definition of success for the MITT patient population.

Table 204.13. Frequency of modification			
	Cefepime (N=103)	**Ceftazidime (N=90)**	**Overall (N=193)**
Any	65 (63.1%)	55 (61.1%)	120 (62.2%)
Any anti-bacterial	59 (57.3%)	49 (54.4%)	108 (55.4%)
vancomycin	27 (26.2%)	24 (26.7%)	51 (26.4%)
aminoglycoside	12 (11.6%)	3 (3.3%)	15 (7.8%)
cephalosporin	27 (26.2%)	12 (13.3%)	39 (20.2%)
ß-lactam/penem/mono-bactam	16 (15.5%)	20 (22.2%)	36 (18.7%)
quinolone	12 (11.6%)	8 (8.9%)	20 (10.4%)
metronidazole	3 (3.3%)	1 (1.1%)	4 (2.1%)
anaerobic coverage	15 (14.6%)	7 (7.8%)	22 (11.4%)
Anti-fungal	22 (21.4%)	18 (20.0%)	40 (20.7%)
Anti-viral	12 (11.6%)	9 (10.0%)	21 (10.9%)
Mean time to modification (d)	4.78 ± 3.36	4.27 ± 2.98	4.55 ± 3.17

Medical Officer's Comment

It is difficult to interpret differences in the frequency of modification by anti-bacterial class, since they may have been affected by local practice patterns and generally occur in the absence of microbiologic data.

Superinfections or new febrile episodes

A summary of the frequency of new febrile episodes or documented infections in evaluable patients is presented in Table 204.14. There did not appear to be a significant difference between the treatment arms. Interestingly, the majority of new episodes in both arms were due to fever without a clinical or microbiologic source.

Table 204.14. Frequency of new febrile episodes or infection			
Nature of 2nd event	**Cefepime (N=103)**	**Ceftazidime (N=90)**	**Overall (N=193)**
All	14 (13.6%)	8 (8.9%)	22 (11.4%)
MDI (same isolate)	0 (0.0%)	0 (0.0%)	0 (0.0%)
MDI (new pathogen)	5 (4.9%)	3 (3.3%)	8 (4.1%)
susceptible	0 (0.0%)	0 (0.0%)	0 (0.0%)
resistant	5 (4.9%)	4 (4.4%)	9 (4.7%)
CDI	1 (1.0%)	0 (0.0%)	1 (0.5%)
FUO	8 (7.8%)	4 (4.4%)	12 (5.2%)

Safety analysis

Mortality: Thirty-two subjects died in association with the first episode of febrile neutropenia during the course of the trial, for an overall mortality rate of 11.6%. There were 22 deaths in the cefepime treatment group and 10 in the ceftazidime group. An analysis of deaths by specific cause is shown in Table 204.15.

Table 204.15
Cause of Subjects' Deaths by Investigator - First Episode

	Cefepime (N = 143)	Ceftazidime (N = 133)	Total (N = 276)	p-value[1]
Total deaths	22 (15.4%)	10 (7.5%)	32 (11.6%)	0.038
Initial infection	3 (2.1%)	3 (2.3%)	6 (2.2%)	1.00
Secondary infection	9 (6.3%)	2 (1.5%)	11 (4.0%)	0.062
Underlying disease	10 (13.3%)	5 (3.8%)	15 (5.4%)	0.293

Two-thirds of deaths occurred eight days or more after initiation of empiric therapy in both arms; time to death and degree of neutropenia did not differ significantly between groups. Examination of cases of death due to secondary infection in the cefepime arm revealed two cases of bacteremic superinfection *with Enterococcus faecium*, one each of superinfection with *Staphylococcus epidermidis*, *Clostridium septicum*, and a *Bacillus* species, one case of candidemia, one case of *Aspergillus* pneumonia, one case of aspiration pneumonia, and two cases of fever of uncertain origin. In the ceftazidime arm, one superinfection death was due to candidemia and one to fever of uncertain origin.

Medical Officer's Comment

Some of these deaths occurred well after the study drug had been stopped; in particular, the death due to C. septicum *infection occurred sufficiently long after study drug discontinuation that the patient involved was scored as a treatment success. There does not appear to be a discernible pattern to the deaths by secondary infection in either arm.*

Statistical Reviewer's Comment

There was a statistically significant difference in total deaths due to a higher mortality rate with cefepime. This appears to be due to deaths from secondary infections or underlying disease.

Discontinuations due to adverse events: Reasons for discontinuation of study therapy due to adverse events are shown in Table 204.16. There was no significant difference between treatment arms.

[1] Fisher's exact test

Table 204.16 Discontinuation of Study Therapy Due to an Adverse Event, First Episode			
	Number (%) of Subjects		
	Cefepime (N = 143)	Ceftazidime (N = 133)	Total (N = 276)
Any Adverse Event	10 (7)	6 (5)	16 (6)
Rash	7 (5)	2 (2)	9 (3)
Sepsis	1 (1)	2 (2)	3 (1)
Hypotension	1 (1)	1 (1)	2 (1)
Fever and Rash	--	1 (1)	1 (1)
Epiglottitis	1 (1)	--	1 (1)
Cochran-Mantel-Haenszel p-value = 0.293			

Statistical Reviewer's Comment

The two treatment arms are balanced with respect to reasons for discontinuation due to adverse events.

Clinical adverse events: Adverse events were generally evenly distributed between the treatment groups. Nausea was the most frequent event with 28 reported events occurring with cefepime and 27 with ceftazidime. Diarrhea was more frequent in the ceftazidime group compared to cefepime (16% versus 23%). Other important differences between the treatment groups were noted for the incidence of abdominal pain (17% versus 10%) and hypotension (15% versus 3%).

Laboratory adverse events: Laboratory abnormalities in subjects with normal baseline values were infrequent with the exception of electrolyte imbalance. Abnormalities of renal function occurred similarly between the two treatment groups and no subject with a normal baseline creatinine developed a clinically relevant degree of renal insufficiency as determined by serum creatinine. Transaminase elevations were more frequent in the ceftazidime arm than the cefepime arm. No clinically relevant transaminase abnormalities developed in those receiving cefepime. Elevations of total bilirubin occurred in 12% of individuals receiving cefepime compared to 4% receiving ceftazidime but both groups had two subjects develop clinically relevant elevations. Electrolyte disturbances were common but similar between the two treatment arms. Hypophosphatemia reached clinically relevant ranges in 11% of subjects in both treatment arms.

Final comments/conclusions - study 411-204

This was a large, multi-center, double-blind, randomized controlled trial comparing the efficacy of cefepime with that of ceftazidime for empiric therapy of febrile neutropenia. Noteworthy aspects of this trial include its reliance on the IDSA guidelines for key aspects of design.

The trial enrolled a total of 276 patients, accounting for 315 episodes. Baseline demographic and prognostic factors were balanced between the treatment arms. Patients had a broad range of underlying diseases; although patients had been stratified by malignancy, comparability between treatment arms for patients with a given type of malignancy was not demonstrated. One hundred ninety-three (193) (61.3%) of enrolled patient episodes were found to be evaluable for efficacy by the FDA Medical Officer. The most common reasons for unevaluability were modification of the initial regimen before assessment at 72 hours, fever due to a non-bacterial infection, absence of neutropenia, and loss to follow-up. The FDA analysis led to a larger number of patients being deemed unevaluable than in the sponsor's analysis; this accounted for most of the differences in the efficacy analysis between the FDA and the sponsor.

Efficacy rates in the evaluable population, as determined by the Medical Officer and assessed either in terms of resolution of the initial episode or survival of infection, were similar for cefepime and ceftazidime. This was true for all febrile episodes, first episodes, and microbiologically documented infections. The point estimate for the difference in response rates was -0.069 for all episodes and -0.061 for first episodes. In order to be deemed therapeutically equivalent as per the DAIDP Points to Consider document, the 95% confidence interval of the difference in cure rates between the test product and the control should lie above -0.20 and include zero. Based on these criteria, cefepime fails to establish therapeutic equivalence in the patient population deemed evaluable by the FDA reviewing Medical Officer when either the first or all febrile episodes are considered, as well as in patients with microbiologically documented infections. Thus, this study alone cannot demonstrate therapeutic equivalence between cefepime and ceftazidime. However, its design allows pooling of results with similar trials

Equivalence was shown under the MITT analysis.

Safety analysis showed a higher all-cause mortality rate in the cefepime arm, primarily due to a higher incidence of secondary infection deaths in the cefepime arm. These deaths occurred after prolonged neutropenia, which is an independent risk factor for infection, and were due to a variety of pathogens. Of note, the incidence of treatment failures due to secondary infection in the FDA evaluable patient population was similar between treatment groups. Thus, there does not appear to be a clear association between cefepime administration and mortality due to new infections.

Adverse event rates with cefepime were somewhat higher than in premarketing experience with this drug, presumably because of the use of a higher daily dose (2 g IV q8h). There was no significant difference in the incidence of clinical adverse events or the incidence of discontinuation due to clinical adverse events between treatment arms. There was no significant difference in the incidence of laboratory adverse events.

In conclusion, study AI411-204 does not by itself demonstrate therapeutic equivalence between cefepime and ceftazidime for empiric therapy of febrile neutropenia; its design features allow pooling of its results with those of similarly designed and conducted studies. This study does demonstrate an acceptable safety profile for cefepime in this indication.