Protocol summary

Study Population

Diagnosis and inclusion criteria: Subjects for the study were cancer patients with neutropenia who developed fever. Hospitalized men and women, 18 years or older, with an underlying cancer and an anticipated survival of 3 months were eligible to be enrolled if they were neutropenic and developed a fever. In the study protocol, neutropenia was defined as an absolute neutrophil count (ANC) of 1000 neutrophils/μL, and fever was defined as a temperature >38°C occurring at least twice in a 24-hour period or a single temperature of >38.5°C.

Medical Officer's Comment

The definition of neutropenia for this study was less stringent than in the other monotherapy studies (AI411-204 and -189), using a threshold of 1000 neutrophils/μL. In order to maintain consistency with analysis of the other studies, patients with an absolute neutrophil count >500 cells/μL were excluded from analysis by the Medical Officer.

Exclusion criteria:. Patients were to be excluded if they had a history of a serious allergy to penicillins, cephalosporins or aminoglycosides, had received any parenteral antibiotics within the preceding 72 hours, or had received a prior course of treatment under this protocol during the current hospital admission or within 2 weeks prior to the current enrollment. Patients were not eligible if they were pregnant or lactating. Other exclusion criteria included serum creatinine >2 mg/dL, or symptomatic cardiovascular abnormalities (hypotension, systolic blood pressure <90 mm Hg). Patients who had requested no resuscitation measures including ventilatory support ("No code status") were also to be excluded.

Patients were also to be excluded if they had or were suspected to have infections which would require long-term therapy (>28 days) or would be likely to require therapy with antimicrobial drugs other than cefepime or ceftazidime (*e.g.* diarrhea associated with *C. difficile*, infection of the central nervous system, infection of a intravenous line requiring vancomycin, anaerobic infection, fungal infection, infection with cytomegalovirus, *Mycobacterium avium-intracellulare*, or *Pneumocystis carinii*). Patients with osteomyelitis, infected burns, or infections requiring amputation were also not eligible for the study.

Study procedures

Study procedures are summarized in Table 131.1.

Pretreatment Procedures: All subjects had a medical history with specific information on the underlying cancer, including cancer treatment and hematologic support (bone marrow transplantation and use of hematopoietic growth factors) (Table 131.1). At onset of fever, a complete clinical evaluation and physical exam including documentation of temperature, other signs and symptoms of infection, and a chest X-ray were to be obtained.

Hematologic tests (WBC, differential, platelets, hemoglobin, Coombs' test) and serum chemistries, including tests of liver function (alkaline phosphatase, alanine aminotransferase [ALT], aspartate aminotransferase [AST], and total bilirubin), renal function (BUN and creatinine) and electrolytes (Na^+, K^+, Ca^{++}, PO_4) were to be obtained within

two days prior to study therapy. A urinalysis (albumin, glucose, and microscopic analysis) was also to be performed.

Prior to initiating therapy, at least two blood cultures were to be drawn. In addition, a urine culture and cultures from any local site suspected to be infected were to be collected. All organisms causing infection were identified, speciated to the extent possible, and tested for susceptibility to cefepime and ceftazidime. Cefepime and ceftazidime were tested by the NCCLS disc-diffusion method using 30 µg discs. When Minimal Inhibitory Concentration (MICs) were obtained, they were performed according to NCCLS standards. Quality assurance for disc-diffusion and MIC testing was performed using standard American Type Culture Collection control organisms.

Table 6.1.1 Study Parameters

Event	Pre-Treatment (Within 48 hours)	During Treatment (Days 3-5 then weekly)	End of Treatment (Last Day of Rx to Day 4 post-therapy)	Post-Treatment (10-14 Days post-therapy)
Informed Consent	X	-	-	-
Medical History	X	-	-	-
Physical Exam	X	X	X	-
Clinical Evaluation	X	X	X	X
Chest X-ray	X	X[1]	X[1]	-
Cultures	X	X[2]	X[2]	X[2,3]
Laboratory Tests	X	X	X	-

During Treatment Procedures: All subjects were examined at least once a day either by residents assigned to the patient's care, the subject's attending physician, or the investigator. Additional evaluations were performed as often as necessary to assess clinical status, the presence of new infections, or to evaluate any evidence of systemic or local adverse reactions. Signs and symptoms and laboratory tests (hematology and chemistry) were to be recorded on the case report form for day 3-5 during therapy, and at least weekly thereafter. Signs and symptoms of new infections were to be recorded when they occurred.

[1] Only for subjects with pneumonia.

[2] If a source to culture was available.

[3] Subjects with UTIs were to have a urine culture 5-9 days post-therapy and 4-6 weeks post-therapy (complicated UTI).

A repeat chest X-ray was to be obtained for all subjects with pneumonia. A blood culture and cultures of any infected local site were to be repeated, including sites at which new infections developed. The results for both positive and negative cultures were recorded on the case report form along with susceptibility testing for pathogens causing infection. If an appropriate specimen could not be obtained, "No source to culture" was recorded.

Post-Treatment Procedures: The subject was to be evaluated at the end-of-therapy (between the last day of study therapy and 4 days after its completion) and again during the post-treatment period (days 10-14 post study therapy). The end-of-treatment evaluation included a physical exam and an assessment of clinical signs and symptoms of infection. A chest X-ray was to be obtained for subjects with pneumonia. Blood cultures were repeated for subjects with bacteremia, and cultures of infected local sites were performed when an appropriate specimen could be obtained. Laboratory tests were also to be performed. The post-treatment evaluation included a clinical evaluation which could be performed in the hospital, doctor's office, clinic, or by telephone contact. For urinary tract infections, cultures were to be obtained 5 to 9 days following therapy and also, for complicated UTI, 4-6 weeks following therapy.

Treatment Group Assignment: Randomization was performed using sealed envelopes. For each study site, the Biostatistics and Data Management group at Bristol-Myers Squibb provided to the investigator computer-generated randomization schedules and sequentially-numbered, sealed envelopes containing a card with the treatment assignment. The sealed envelopes were maintained in the pharmacy at the study site. At the time the subject provided informed consent, the next available sealed envelope was opened by the pharmacist and the treatment assignment was provided to the physician responsible for that subject.

Medical Officer's Comment

As with study AI411-189, patients were not stratified by underlying disease.

Study Therapy: Each subject was assigned to study therapy with either cefepime or ceftazidime, using a 1:1 randomization scheme. Vials containing 1 or 2 grams of cefepime powder were supplied by Bristol-Myers Squibb. Cefepime was reconstituted in the vial using sterile water to make a solution with a cefepime concentration of 250 mg/ml. Cefepime was further diluted in 50 to 100 mL of sterile normal saline. Cefepime was administered intravenously over approximately 30 minutes at a dose of 2 grams every 8 hours. The guidelines for dose adjustment for renal impairment were not specified in the protocol, but were provided in the Investigator's Brochure. Subjects with a serum creatinine >2.0 mg/dL were excluded.

Ceftazidime was supplied by Bristol-Myers Squibb in 1 or 2 gram vials obtained from the manufacturer and prepared for infusion according to instructions in the approved package insert. Ceftazidime was administered intravenously over approximately 30 minutes at a dose of 2 grams every 8 hours.

Duration of Study Therapy: Study therapy was to be continued based on the response of the subject's fever and other signs and symptoms of infection. If the subject responded

satisfactorily to treatment, study therapy was to be terminated when both of the following conditions were satisfied:

1) the subject's absolute neutrophil count recovered to 1000 cells/μL

2) a minimum of 7 days of study therapy had been administered, if the subject had a microbiologically or clinically documented infection.

Discontinuation of Therapy: Study therapy (cefepime or ceftazidime) could be discontinued early for any of the following conditions:

- An infection caused by a bacterial organism resistant to study therapy
- Poor clinical response, including persistence of fever (>72 hours)
- Intercurrent illness (e.g. new infection, new fever, or *C. difficile* toxin-positive diarrhea)
- An adverse event that was serious or possibly related to study therapy
- A situation for which discontinuation was in the subject's best interest
- By request of the subject

When an adverse event resulted in discontinuation, the subject was examined as often as necessary to determine if the reaction had subsided and whether any adverse sequelae had resolved. Subjects who were removed from the study for other reasons had a final clinical and physical assessment at the time study therapy was terminated.

Concomitant Therapy: Subjects were to receive study therapy without other systemic antibacterial antibiotics with the exception of vancomycin which could be added if the pathogen(s) isolated was resistant to cefepime or ceftazidime but susceptible to vancomycin or if the subject had persistent fever for more than 96 hours. There was no specific provision for the addition of antifungal or antiviral drugs.

Concomitant medications, other than systemic antimicrobial agents, and concomitant non-drug therapies were allowed as clinically indicated. Concomitant medications and non-drug therapies were recorded on the case report form.

Sponsor's Criteria for Evaluation

Criteria for evaluability, infectious disease diagnosis, and efficacy were the same as those for study AI411-189.

Medical Officer's Comment

These were actually applied retrospectively in a blinded fashion; the original criteria were similar but required a longer follow-up period of 10-14 days.

Sponsor's safety analysis

Safety analyses were performed in the entire subject population who received at least one dose of study treatment. Safety analyses included an assessment of deaths, adverse clinical events and an assessment of laboratory results. The definitions and methods used were the same as those for study AI411-189.

Sponsor's statistical methods

The analyses were performed for the first febrile episode treated with study drugs

in 90 subjects. Safety results were based on data from subjects who received at least one dose of study medication. The primary efficacy analyses were based on the population of subjects who were evaluable for response. A modified intent-to-treat analysis was performed excluding only those subjects without fever at entry, without neutropenia at entry or during study treatment, or who were receiving ongoing treatment for an established or suspected infection at entry. A supplemental analysis was produced for all 104 treatment courses. Due to the limited sample size, no formal statistical testing was performed.

Results

Study population characteristics

Demographics: Ninety adult subjects were enrolled between August 30, 1989 and November 26, 1991 at two institutions. Due to slow accrual, the study was closed prematurely at the St. John's Hospital when only four subjects were enrolled. Twelve of these 90 subjects were randomized more than once for separate febrile episodes. These 90 subjects received a total of 104 separate courses of therapy. Enrollment by center is shown in Table 131.2.

Table 131.2
Enrollment by Study Site for all Febrile Episodes

	Number of Subjects		
	Shands Hospital (Site 001)	St. John's Hospital (Site 002)	Total
Subject Accrual	**86**	**4**	**90**
Single Episode	74	4	78
Multiple Episodes	12	0	12
Second episode	12	0	12
Third episode	2	0	2
Total febrile episodes	**100**	**4**	**104**

Medical Officer's Comment

Given the small number of patients enrolled at site 002, this should be considered a single center trial.

Patient demographics are shown in Table 131.3.

Table 16.1.3. Demographics of all enroled patients				
	Overall	**Cefepime**	**Ceftazidime**	**p value**
Total	90	45	45	
Age				1.0
Median (y)	41.5	39.0	43.0	
Mean (y)	43.5 ± 14.6	41.9 ± 14.9	45.1 ± 14.0	
Range (y)				
≥ 65 y	8 (8.9%)	4 (8.9%)	4 (8.9%)	
< 65 y	82 (91.1%)	41 (91.1%)	41 (91.1%)	
Sex				0.671
Male	52 (57.8%)	25 (55.6%)	27 (60.0%)	
Female	38 (42.2%)	20 (44.4%)	18 (40.0%)	
Race				0.391
White	83 (92.2%)	41 (91.1%)	42 (93.3%)	
Black	5 (5.6%)	2 (4.4%)	3 (6.7%)	
Other	2 (2.2%)	2 (4.4%)	0 (0.0%)	
Underlying disease				0.356
Leukemia	52 (57.8%)	25 (55.6%)	27 (60.0%)	
OHM	15 (16.7%)	6 (13.3%)	9 (20.0%)	
OHD	1 (1.1%)	1 (2.2%)	0 (0.0%)	
Solid tumor	22 (24.4%)	13 (28.9%)	9 (20.0%)	
ANC nadir				0.505
Median	20.0	10.0	40.0	
Mean	54.8 ± 74.3	52.4 ± 81.6	57.1 ± 66.1	
≤100	80 (88.9%)	41 (91.1%)	39 (86.7%)	
>100	10 (11.1%)	4 (8.9%)	6 (13.3%)	
Duration ANC≤500				0.779
Median (d)	15.5	16.0	15.0	
Mean (d)	16.6 ± 10.7	17.0 ± 11.2	16.2 ± 9.9	
<7 d	15 (16.6%)	7 (15.5%)	8 (17.8%)	
≥7 d	75 (83.4%)	38 (84.5%)	37 (82.2%)	
Bone marrow graft	26 (28.9%)	12 (26.7%)	14 (31.1%)	
Indwelling catheter	72 (80.0%)	34 (75.6%)	38 (84.4%)	
Prophylactic Abx	47 (52.2%)	23 (51.1%)	24 (53.3%)	
SBP <90 at entry	1 (1.1%)	1 (0.6%)	0 (0.0%)	
Multiple	12 (13.3%)	7 (15.6%)	5 (11.1%)	

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

Medical Officer's Comment

The proportion of patients with severe (<100 PMN/μL) or prolonged (duration of at least 1 week) neutropenia was greater in this study than in studies AI411-204 or 189. This may reflect the limited use of colony stimulating factors in patients in this study; it is worth noting that this study was conducted between 1989 and 1991, when use of such factors was not as common.

Statistical Reviewer's Comment

The two treatment arms appear to be balanced with respect to demographic as well as selected prognostic risk factors.

Anti-microbial prophylaxis:. Half of the subjects received antimicrobial prophylaxis, mostly with non-absorbable antifungal agents. Clotrimazole was the most common anti-fungal agent. Oral nystatin was administered alone or in combination to fourteen subjects. The use of fluconazole for prophylaxis was uncommon. Seventeen subjects received antibacterial prophylaxis. Thirteen of these subjects were given trimethoprim-sulfamethoxazole. The four remaining subjects received short-term prophylaxis with broad-spectrum antibiotics in the period just prior to starting study therapy. Two cefepime subjects received cephalosporins (cefotetan, cefazolin) as prophylaxis for insertion of a Hickman catheter. Another cefepime-treated subject received amoxacillin as prophylaxis for gum surgery prior to entry. Finally, a ceftazidime-treated subject received amoxicillin, ampicillin and gentamicin as prophylaxis for the removal of 13 teeth during the six days prior to entry. Acyclovir was the only antiviral agent used for prophylaxis and was administered to 23 subjects. Four subjects (3 cefepime, 1 ceftazidime) received one monthly dose of pentamidine prophylaxis during the treatment period.

The majority of prophylactic agents were continued during therapy, including eight subjects (5 cefepime, 3 ceftazidime) with trimethoprim-sulfamethoxazole, 28 subjects (17 cefepime, 11 ceftazidime) with clotrimazole, and all subjects with nystatin, fluconazole, ketoconazole, miconazole and acyclovir.

Medical Officer's Comment

Six patients received anti-microbial therapy prior to study entry for a documented or suspected infection. These patients were included in the sponsor's analysis; they were included in the Medical Officer's MITT analysis but excluded from the primary FDA analysis.

The use of blood components was similar between the treatment groups. Slightly more patients received colony stimulating factors and nutritional support in the ceftazidime arm (4 patients, vs. 2 in the cefepime arm).

Episode evaluability

Evaluability assessment gave the results shown in Table 131.4 for study 131.

Table 131.4, Episode evaluability				
	1° evaluability criteria		MITT evaluability criteria	
	FDA	Sponsor	FDA	Sponsor
All episodes	79/104 (76.0%)	86/104 (82.7%)	102/104 (98.1%)	104/104 (100.0%)
Cefepime	40/52 (76.9%)	45/52 (86.5%)	51/52 (98.1%)	52/52 (100.0%)
Ceftazidime	39/52 (75.0%)	41/52 (78.8%)	51/52 (98.1%)	52/52 (100.0%)

Twenty-five episodes were excluded from the primary FDA analysis; 12 from the cefepime arm and 13 from the ceftazidime arm. Modification of the empiric regimen prior to 72 hours was the most common reason for exclusion by the Medical Officer.

Infectious Disease Diagnoses

Infectious disease diagnoses assigned by the Medical Officer and the sponsor are shown in Tables 131.5A and 5B, respectively. FUO was the most common diagnosis in both arms.

Table 131.5A, FDA infectious disease diagnoses for evaluable population				
Infection type	Overall	Cefepime	Ceftzazidime	CMH p value
Any	79 (100%)	40 (100%)	39 (100%)	0.933
MDI with bacteremia	19 (24.0%)	9 (22.5%)	10 (25.6%)	
MDI	2 (2.5%)	2 (5.0%)	0 (0.0%)	
CDI	13 (16.5%)	6 (15.0%)	7 (17.9%)	
FUO	45 (57.0%)	23 (57.5%)	22 (56.4%)	
Table 131.5B, Sponsor's infectious disease diagnoses for evaluable population				
Infection type	Overall	Cefepime	Ceftzazidime	CMH p value
Any	86 (100%)	45 (100%)	41 (100%)	0.994
MDI with bacteremia	22 (25.6%)	11 (24.4%)	11 (26.8%)	
MDI	3 (3.5%)	2 (4.4%)	1 (2.4%)	
CDI	12 (14.0%)	7 (15.6%)	5 (12.2%)	
FUO	49 (57.0%)	25 (55.6%)	24 (58.5%)	

Statistical Reviewer's Comment

The two treatment arms appear to be balanced with respect to infectious disease diagnoses.

Efficacy analysis

Primary efficacy analysis: Overall efficacy rates are shown in Tables 131.6A and 6B, and rates for microbiologically documented infections in Table 131.7. 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.

Table 13.1.6A. All episode response rates - study AI411-131			
Population	**Cefepime**	**Ceftazidime**	**95% Confidence Interval**
FDA evaluable[1]	12/40 (30.0%)	10/39 (25.6%)	$_{40,39}$ (-0.1791, 0.2663) $_{30.0\%,\ 25.6\%}$
FDA MITT[2]	7/51 (13.7%)	9/51 (17.6%)	$_{51,51}$ (-0.1998, 0.1213) $_{13.7\%,\ 17.6\%}$
Sponsor evaluable	21/45 (46.7%)	16/41 (39.0%)	$_{45,41}$ (-0.1556, 0.3084) $_{46.7\%,\ 39.0\%}$
Sponsor MITT	21/52 (40.4%)	16/52 (30.8%)	$_{52,52}$ (-0.1062, 0.2985) $_{40.4\%,\ 30.8\%}$

Table 13.1.6B. First episode response rates - study AI411-131			
Population	**Cefepime**	**Ceftazidime**	**95% Confidence Interval**
FDA evaluable[1]	10/34 (29.4%)	9/34 (26.5%)	$_{34,34}$ (-0.2132, 0.2720) $_{29.4\%,\ 26.5\%}$
FDA MITT[2]	6/44 (13.6%)	8/44 (18.2%)	$_{44,44}$ (-0.2207, 0.1298) $_{13.6\%,\ 18.2\%}$
Sponsor evaluable	19/39 (48.7%)	13/35 (37.1%)	$_{39,35}$ (-0.1355, 0.3670) $_{48.7\%,\ 37.1\%}$
Sponsor MITT	19/45 (42.2%)	13/45 (28.9%)	$_{45,45}$ (-0.0848, 0.3514) $_{42.2\%,\ 28.9\%}$

Table 13.1.7. MDI response rates			
Population	**Cefepime**	**Ceftazidime**	**95% Confidence Interval**
FDA evaluable	3/11 (27.3%)	1/10 (10.0%)	$_{11,10}$ (-0.2450, 0.5904) $_{27.3\%,\ 10\%}$ Exact 95% Confidence Interval $_{11,10}$ (-0.2373, 0.6392) $_{27.3\%,\ 10\%}$
Sponsor evaluable	5/13 (38.5%)	3/9 (33.3%)	$_{13,9}$ (-0.4487, 0.5513) $_{38.5\%,\ 33.3\%}$ Exact 95% Confidence Interval $_{13,9}$ (-0.3772, 0.5080) $_{38.5\%,\ 33.3\%}$

Medical Officer's Comment

The overall response rate results for all episodes demonstrate equivalence between cefepime and ceftazidime, although the number of evaluable episodes is significantly less than in studies AI411-204 and -189, and the response rates in both arms of this study are lower than in studies AI411-204 and -189. These lower response rates may be have be due to the greater proportion of patients in this study with severe or prolonged neutropenia.

Statistical Reviewer's Comment

The number of episodes is too small to ensure adequate power for statistical inferences. However, the two treatment arms are therapeutically equivalent with respect to

---

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.

overall response rates. In patients with microbiologically documented infection, based on the exact confidence intervals, cefepime fails to establish therapeutic equivalence in patients deemed evaluable by either the FDA or the sponsor.

In the FDA analysis, the most common overall reason for failure in both arms was persistent fever. For MDIs, in the cefepime arm, failures were due to primary infection with a resistant organism (2 cases), secondary infections with resistant or susceptible organisms (1 case of each), death due to the primary infection (1 case), breakthrough bacteremia (1 case) and persistent fever (2 cases). In the ceftazidime arm, there were 2 deaths due to the primary infection, 2 cases of persistence of a susceptible organism, and 5 cases of persistent fever despite microbial eradication.

Safety analysis

Ten deaths occurred within 30 days of discontinuing study therapy, six in the cefepime and four in the ceftazidime group (Table 131.8). None was related to study therapy. Five deaths were related to possible or proven infection, four pneumonia (1 cefepime, 3 ceftazidime) and one intra-abdominal infection (cefepime). The other five deaths were related to the underlying malignancy or its treatment. In these five subjects, the infectious process was controlled at the time of death. Three of these deaths were associated with hemorrhage, two with episodes of intracranial bleeding (cefepime, ceftazidime), and one with pulmonary hemorrhage (cefepime). The remaining two deaths occurred in subjects with end-stage malignancies.

Table 131.8 Principal Cause of Death

	Number of Subjects		
	Cefepime (N=45)	**Ceftazidime (N=45)**	**Total (N=90)**
All deaths	**6 (13.3%)**	**4 (8.9%)**	**10 (11.1%)**
Infection	2 (4.4%)	3 (6.6%)	5 (5.6%)
Hemorrhage	2 (4.4%)	1 (2.2%)	3 (3.3%)
Progression of Cancer	2 (4.4%)	0 (0.0%)	2 (2.2%)
CMH p-value = 0.158			

Statistical Reviewer's Comment

The two treatment arms appear balanced with respect to principal cause of death.

Discontinuation of Study Therapy Due to Adverse Events

Reasons for study therapy discontinuation for first episodes are shown in Table 131.9. There was no significant difference between groups.

Table 18.19. Reasons for discontinuation -first episodes (%)			
	Cefepime	**Ceftazidime**	**Total**
Treatment Completed	**29 (64)**	**33 (73)**	**62 (69)**
Early Discontinuation	**16 (36)**	**12 (27)**	**28 (31)**
Adverse Events	8 (18)	4 (9)	12 (13)
Treatment Ineffective	3 (7)	4 (9)	7 (8)
Subject Died	1 (2)	2 (4)	3 (3)
Other Antibiotic Prescribed	2 (4)	0	2 (2)
Intercurrent Illness	1 (2)	0	1 (1)
Problem with Drug Supply	1 (2)	0	1 (1)
Pathogen Resistant	0	1 (2)	1 (1)
Subject Decision	0	1 (2)	1 (1)

Medical Officer's Comment

The rate of early discontinuation was higher in the cefepime arm. The reasons include prescription of another antibiotic for a cause other than an adverse event or ineffective treatment, intercurrent illness, or a problem with drug supply. None of these are specific enough to explain the higher rate in the cefepime arm.

Serious Adverse Events

Fifteen serious adverse events (5 cefepime, 10 ceftazidime) were reported for nine subjects (4 cefepime, 5 ceftazidime) during the study period. None were thought to be related to study therapy.

Adverse Events

Approximately 90% of subjects in both treatment groups experienced at least one adverse event. Most events were not related or of unknown relationship to study therapy. The most common adverse events were rash and diarrhea which occurred in more than one-third of the subjects. Among subjects with diarrhea, testing for *C. difficile* toxin was performed infrequently (three subjects in each treatment group). The test was positive in three cefepime and two ceftazidime subjects.

Chills, nausea, vomiting and headache affected more than 20% of the subjects and probably represented complications of the subject's infection or side-effects of treatment for the subject's underlying malignancy. None of these events were judged related to study therapy.

Fifteen subjects (7 cefepime and 8 ceftazidime) experienced seventeen drug-related adverse events. None were life-threatening and only one judged severe. The most frequent drug-related event was rash which occurred in eight subjects (5 cefepime and 3 ceftazidime). Although rashes were usually mild to moderate in severity, seven of these eight subjects had treatment discontinued.. One subject had a rash on the chest and upper extremities which was described as severe because it was associated with the recurrence

of high fever; the fever and rash gradually resolved with the addition of vancomycin and amphotericin, followed by the discontinuation of cefepime. Three other subjects treated with cefepime experienced drug-related adverse events; one had moderate diarrhea associated with a positive *C. difficile* toxin assay and a mild drug-related rash, one had recurrent fever late in the course of cefepime without evidence of infection, and one had mild tingling in the toes after a cefepime infusion. In the ceftazidime group, other drug-related adverse events included diarrhea, fever, oral thrush, pruritus, erythema, and vaginitis.

Medical Officer's Comment

Review of Table 131.9 shows that there was no significant difference in the rate of discontinuation due to adverse events between treatment arms.

Laboratory abnormalities, especially clinically relevant values, were infrequent in subjects with normal baseline values. Abnormalities for BUN and creatinine were documented with similar frequency in both treatment groups. Changes in liver function tests occurred in about half of the subjects; however, only the minority experienced abnormalities which were clinically relevant. Clinically relevant electrolyte abnormalities were also uncommon and asymptomatic. A small number of subjects had Coombs tests performed prior to, and during or following treatment. Six of the 24 subjects tested developed a positive Coombs test during or following study treatment; no hemolysis was associated with this abnormality.

Three subjects (1 cefepime-treated, 2 ceftazidime-treated) with normal renal function tests developed clinically relevant abnormalities during therapy. Two, one in each treatment group, suffered acute deterioration of renal function. Dialysis was required in the cefepime-treated subjects; both subjects recovered. One ceftazidime-treated subject developed pre-renal azotemia due to fluid overload and congestive heart failure.

For liver function tests which were normal at baseline, clinically relevant values developed somewhat more commonly in cefepime-treated compared to control subjects. These findings should be interpreted with caution since normal and abnormal baseline values for liver function tests may occur in the same subject, and multiple clinically relevant values may be associated with the same subject. Three cefepime-treated subjects who developed clinically relevant values had normal values at baseline for all four liver function tests. In one subject the abnormalities were possibly due to parenteral hyperalimentation, and the abnormalities improved while still on cefepime treatment. The other two subjects had asymptomatic elevations of ALT and AST or ALT alone.

Clinically relevant electrolyte abnormalities in cefepime-treated subjects included asymptomatic hypokalemia and hypophosphatemia. In addition three subjects experienced hypocalcemia or hyperphosphatemia. Two ceftazidime-treated subjects experienced asymptomatic hypophosphatemia. Replacement potassium and phosphate was administered as needed.

Abnormal laboratory values on entry to the study were relatively infrequent except for hypocalcemia. Five subjects (2 cefepime-treated, 3 ceftazidime-treated) with abnormal BUN's at baseline developed clinically relevant rises in BUN without clinically relevant rises in creatinine. The abnormalities were generally attributed to fluid overload

causing congestive heart failure. All three ceftazidime-treated subjects were transferred to the ICU for intubation because of respiratory distress. The cefepime-treated subjects did not require aggressive measures.

For liver function tests which were abnormal at baseline, clinically relevant values developed with similar frequency in both treatment groups. In cefepime-treated subjects possible etiologies for these abnormalities included hepatosplenic candidiasis, Hepatitis C, and septic shock. One ceftazidime-treated subjects had liver function abnormalities related to veno-occulsive disease.

Clinically relevant electrolyte abnormalities were asymptomatic, including hypocalcemia in two subjects and hypophosphatemia in two subjects. Replacement phosphorus was given as indicated.

Final comments/conclusions - study 411-131

This was essentially a single center, randomized controlled trial comparing the efficacy of cefepime with that of ceftazidime for empiric therapy of febrile neutropenia. Although designed in the late 1980's, this trial was largely compliant with the IDSA guidelines.

The trial enrolled a total of 90 patients, accounting for 104 episodes. Baseline demographic and prognostic factors were balanced between the treatment arms. 79 (75.9%) 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.

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. However, absolute response rates were substantially lower than in studies AI411-189 and -204. This most likely reflects the original protocol design, which allowed for addition of vancomycin; under both the Medical Officer's criteria and the sponsor's retrospective criteria, use of vancomycin represented a treatment failure. This is borne out by analysis of the number of treatment failures due to addition of vancomycin as the sole additional anti-bacterial agent. 15/28 (53.6%) of cefepime treatment failures and 17/29 (58.6%) of ceftazidime treatment failures were due to addition of vancomycin alone; in study AI411-204, the corresponding figures were 8/46 (17.4%) and 8/34 (23.5%). The relatively limited use of colony stimulating factors in this study, resulting in more severe and prolonged neutropenia than in the other monotherapy studies, may also have contributed to the lower response rates.

The number of episodes is too small to ensure adequate power for statistical inferences. However, the two treatment arms were therapeutically equivalent with respect to overall response rates. In patients with microbiologically documented infection, cefepime failed to establish therapeutic equivalence in patients deemed evaluable by either the FDA or the sponsor.

Pooling of this study with AI411-189 and -204 is problematic because of the difference in response rates, which, as described above, most likely reflects differences in study design and conduct. At the March 5, 1997 meeting of the Anti-Infective Drug Products Advisory Committee, the statistical consultant to the committee, Dr. Donald Parker stated that this trial should not be pooled with the other two monotherapy trials.

Safety analysis showed similar all-cause and specific cause mortality rates for the two treatment arms in the cefepime arm. 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 AI411-131 supports therapeutic equivalence between cefepime and ceftazidime for empiric therapy of febrile neutropenia, although the number of evaluable episodes studied was small. This study demonstrates an acceptable safety profile for cefepime in this indication.

STUDY AI411-118

Medical Officer's Comment

Data on 96 patients from this study were included in the original NDA submission. Review of the study at that time by FDA Medical Officer William Erhardt, M.D. found that the data did not demonstrate therapeutic equivalence between cefepime and the comparator regimen, and that the study was underpowered to detect a difference between treatment groups. The current submission contains data on an additional 20 patients.

General Information

Title: A Multi-Investigator Comparative Study of Cefepime and Piperacillin/Gentamicin in the Treatment of Cancer Patients with Fever and Neutropenia.

Objective: To evaluate the clinical efficacy and safety of cefepime, administered at a dose of 2 grams every eight hours, in comparison to the combination of piperacillin administered at a dose of 3 grams every 4 hours and gentamicin administered at a dose of 1.5 mg/kg every 8 hours, for the empiric treatment of febrile episodes in neutropenic cancer subjects.

Investigators: Rasim Gucalp, M.D. (Bronx, NY) and Coleman Rotstein, M.D. and Brian Lipman, M.D. (Buffalo, NY).

Study Centers: Montefiore Medical Center (Site -001

Roswell Park Cancer Institute (Site -002)

Study design: A two arm, comparative, open-label, randomized (1:1) multi-center study conducted in the United States. Initially, subjects were planned to be enrolled over a period of approximately two years. Two study sites enrolled subjects; site -001 enrolled 68 subjects, one did not receive study therapy; site -002 enrolled 50 subjects, one did not receive study therapy. Enrollment was terminated at each site after an enrollment period of approximately two years. A total of one hundred and sixteen subjects were treated at the two study sites.

Study period: First subject enrolled June 23, 1989. Last subject completed therapy December 12, 1991.

Protocol summary

Study population

Diagnosis and main criteria for inclusion: Adult men and women (negative pregnancy test prior to enrollment), 18 years or older, undergoing treatment for cancer were eligible for enrollment for empiric treatment of a febrile episode (sustained temperature >38.0°C; single temperature >38.3°C) while neutropenic (<500 neutrophils/μL).

Exclusion criteria: Patients were to be excluded if they had a history of a serious allergy to penicillins, cephalosporins or aminoglycosides, had received any parenteral antibiotics within the preceding 72 hours, or had received a prior course of treatment under this protocol. Patients were not eligible if they were pregnant or lactating or if they had previously been enrolled in the study. Other exclusion criteria included serum creatinine >2

mg/dL, or symptomatic cardiovascular abnormalities (hypotension, systolic blood pressure <90 mm Hg). Patients with underlying illness with a poor immediate prognosis (*e.g.* blast crisis with chronic myelogenous leukemia) and those who had requested no resuscitation measures including ventilatory support ("No code status") were also to be excluded.

Patients with established or suspected infections which would require long-term therapy (>28 days) were to be excluded as were those likely to require therapy with antimicrobial drugs other than cefepime or piperacillin and gentamicin (*e.g.* diarrhea associated with *C. difficile*, infection of the central nervous system, infection of an intravenous line requiring vancomycin, anaerobic infection, fungal infection, infection with cytomegalovirus, *Mycobacterium avium-intracellurare*, or *Pneumocystis carinii*). Also excluded were patients with osteomyelitis, infected burns, or infections requiring amputation.

Study procedures

Except for the dosing and susceptibility testing for the comparator regimen used in this study, study procedures were essentially the same as those in Study AI411-131.

Study therapy: Cefepime was supplied as a 2 gram vial and administered intravenously at a dose of 2g q8h. The dose could be adjusted for renal insufficiency based on the cefepime Investigators Brochure. Piperacillin was supplied as a 3 gram vial and administered intravenously at a dose of 3g q4h. (Note: Three subjects received at least one dose of piperacillin not supplied by Bristol-Myers Squibb for which lot numbers were not recorded.) The dose of piperacillin could be adjusted for renal insufficiency according to the approved package insert. Gentamicin was supplied as an 80 mg and administered intravenously at a dose of 1.5mg/kg q8h. (Note: One subject received at least one dose of gentamicin not supplied by Bristol-Myers Squibb.) The dosing and frequency for gentamicin could be adjusted, based on serum gentamicin levels during therapy. Gentamicin and piperacillin were administered sequentially. The sequence of administration was not specified in the protocol.

Medical Officer's Comment

The comparator regimens used in this study and AI411-137, although not FDA-approved for this indication, are widely accepted in the medical community for empiric therapy of febrile neutropenia (Hathorne and Lyke 1997).

Susceptibility testing: All organisms causing infection were identified, speciated to the extent possible, and tested for susceptibility to cefepime, piperacillin, and gentamicin. Cefepime was tested by the NCCLS disc-diffusion method using a 30 µg disc. Piperacillin and gentamicin were tested by the NCCLS disc-diffusion method using approved discs. Testing for minimal inhibitory concentrations could also be performed using NCCLS methods.

Sponsor's criteria for evaluation

Criteria for evaluability, infectious disease diagnosis, and efficacy were the same as those for study AI411-189.

Sponsor's Safety Analysis

Safety evaluations were performed for all subjects who received study therapy and included an assessment of deaths, adverse events, including those which resulted in discontinuation of therapy, and abnormal laboratory values which developed during or post study therapy.

Sponsor's Statistical Methods:

The primary efficacy analysis was performed for the 116 subjects who received study therapy. Safety results were based on data from subjects who received at least one dose of study medication. The primary efficacy analyses were based on the population of subjects who were evaluable for response. In addition, a modified intent-to-treat efficacy analysis was performed.

Results

Patient enrollment by center is shown in Table 118.1

Table 118.1 - Enrollment by center

	Number (%) Subjects		
	Cefepime (N=59)	Piperacillin/ gentamicin (N=57)	Total (N=116)
Montefiore Medical Center (Site -001)	**34 (58)**	**33 (56)**	**67 (58)**
Montefiore Oncology Unit	24 (41)	17 (30)	41 (35)
Albert Einstein Oncology Unit	10 (17)	16 (28)	26 (23)
Roswell Park Cancer Institute (Site -002)	**25 (42)**	**24 (42)**	**49 (42)**

Demographics for all enrolled patients are shown in Table 118.2.

Table 11.8.2. Demographics - all patients enrolled in A101-118				
	Overall	**Cefepime**	**Piperacillin/gentamicin**	**p value**
Total	116	59	57	
Age				0.175
Median (y)	50.5	50.0	52.0	
Mean (y)	50.4 ± 17.4	48.8 ± 17.3	52.1 ± 17.4	
Range (y)				
≥ 65 y	32 (27.6%)	13 (22.0%)	19 (33.3%)	
< 65 y	84 (73.4%)	46 (78.0%)	38 (66.7%)	
Sex				0.997
Male	59 (50.9%)	30 (50.8%)	29 (50.9%)	
Female	57 (49.1%)	29 (49.2%)	28 (49.1%)	
Race				0.962
White	89 (76.7%)	45 (76.3%)	44 (78.9%)	
Black	8 (6.9%)	5 (8.5%)	3 (5.3%)	
Other	19 (16.3%)	9 (15.3%)	10 (17.5%)	
Underlying disease				0.212
Leukemia	36 (31.0%)	20 (33.9%)	16 (28.1%)	
OHM	38 (32.8%)	21 (35.6%)	17 (29.8%)	
OHD	2 (1.7%)	1 (1.7%)	1 (1.8%)	
Solid tumor	40 (34.5%)	17 (28.8%)	23 (40.3%)	
ANC nadir				0.066
Median	40.0	50.0	30.0	
Mean	116.6 ± 175.8	141.94 ± 208.6	90.5 ± 128.5	
≤100	53 (45.7%)	22 (37.3%)	31 (54.4%)	
>100	63 (54.3%)	37 (62.7%)	26 (45.6%)	
Duration ANC≤500				0.714
Median (d)	7.0	7.0	6.0	
Mean (d)	12.1 ± 15.1	12.7 ± 16.1	11.5 ± 13.9	
<7 d	57 (49.1%)	28 (47.5%)	29 (50.9%)	
≥7 d	59 (50.9%)	31 (52.5%)	28 (49.1%)	
Bone marrow graft	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Indwelling catheter	68 (58.6%)	37 (64.9%)	31 (54.4%)	
Prophylactic Abx	21 (18.1%)	9 (15.3%)	12 (21.1%)	
SBP <90 at entry	2 (1.7%)	2 (3.4%)	0 (0.0%)	
Multiple enrollments	0 (0.0%)	0 (0.0%)	0 (0.0%)	

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

Medical Officer's Comment

A higher proportion of patients in the control arm than in the cefepime arm had severe neutropenia (ANC nadir ≤100 cells/μL). The difference was on the verge of statistical significance. The reasons for this imbalance are not clear from the study protocol or study report. Since patients with severe neutropenia are more likely to have infection, and less likely to respond to empiric therapy, this difference would tend to favor the cefepime arm.

Statistical Reviewer's Comment

The two treatment arms appear to be balanced with respect to key demographic variables at baseline. Except for the ANC nadir, prognostic risk factors are also statistically balanced between two treatment arms.

Antibiotic Prophylaxis: Antibiotic prophylaxis was uncommon. Twenty-one subjects received prophylaxis which was administered somewhat more frequently in the control group compared with cefepime-treated subjects.

Antibacterial prophylaxis was prescribed for only eight subjects. Three cefepime-treated subjects and one control subject received ciprofloxacin; two additional control subjects received trimethoprim-sulfamethoxazole. One subject (control group) received a single dose of cefazolin prior to entry as prophylaxis for the insertion of a central intravenous line. Another subject (control group) received cephalexin as prophylaxis following a cholecystectomy.

Antifungal prophylaxis was administered to 17 of the 21 subjects who received prophylaxis. The non-absorbable agents nystatin or clotrimazole were administered to 10 subjects (4 cefepime, 6 control) and the combination to one (control). Fluconazole or ketoconazole was prescribed for five subjects. Intravenous amphotericin was prescribed in combination with fluconazole in one subject for "the prevention of fungal infection." Acyclovir ointment was administered to one (cefepime) subject for prevention of "recurrence of zoster lesions" on the chest. Intravenous acyclovir was substituted for topical acyclovir when this subject entered the study.

Fourteen subjects, equally divided between treatment groups, continued prophylaxis during study therapy. Only two subjects, both in the control group, continued antibacterial prophylaxis during treatment. Both continued receiving trimethoprim-sulfamethoxazole in combination with the antifungal agents fluconazole or ketoconazole. Thirteen subjects continued antifungal prophylaxis. Antiviral prophylaxis was continued in one subject; intravenous acyclovir replaced topical acyclovir on entry to the study.

Use of blood components was similar in both groups. Use of colony stimulating factors was somewhat more frequent in the control group (11% vs. 3%).

Episode evaluability

Evaluability assessment gave the results shown in Table 118.3.

Table 118.3. Episode evaluability				
	1° evaluability criteria		MITT evaluability criteria	
	FDA	Sponsor	FDA	Sponsor
All episodes	78/116 (67.2%)	92/116 (79.3%)	103/116 (88.8%)	106/116 (91.4%)
Cefepime	36/59 (61.0%)	42/59 (71.2%)	51/59 (86.4%)	51/59 (86.4%)
Piperacillin /gentamicin	42/57 (73.7%)	50/57 (87.7%)	52/57 (91.2%)	55/57 (96.5%)

Thirty-eight (38) episodes were excluded from the primary FDA analysis; 23 (39.0%) from the cefepime arm and 15 (26.3%) from the piperacillin/gentamicin arm. Early modification of the initial regimen was the most common reason for unevaluability, accounting for almost half of exclusions in both arms.

The MITT and evaluable populations had demographics similar to those of the enrolled population.

Infectious disease diagnoses

Infectious disease diagnoses as assigned by the FDA Medical Officer and the sponsor are shown in Tables 118.4A and 4B.

Table 118.4A. FDA infectious disease diagnoses for evaluable population				
Infection type	Overall	Cefepime	Piperacillin/gentamicin	CMH p-value
Any	78 (100%)	36 (100%)	42 (100%)	0.874
MDI with bacteremia	16 (20.5%)	9 (25.0%)	7 (16.7%)	
MDI	14 (17.9%)	5 (13.9%)	9 (21.4%)	
CDI	8 (10.3%)	3 (8.3%)	5 (11.9%)	
FUO	40 (51.3%)	19 (52.3%)	21 (50.0%)	
Table 118.4B. Sponsor's infectious disease diagnoses for evaluable population				
Infection type	Overall	Cefepime	Piperacillin/gentamicin	CMH p-value
Any	92 (100%)	42 (100%)	50 (100%)	0.909
MDI with bacteremia	23 (25.0%)	12 (28.6%)	11 (22.0%)	
MDI	14 (15.2%)	5 (11.9%)	9 (18.0%)	
CDI	11 (12.0%)	4 (9.5%)	7 (14.0%)	
FUO	44 (47.8%)	21 (50.0%)	23 (46.0%)	

Statistical Reviewer's Comment

The two treatment arms appear to be balanced with respect to infectious disease diagnoses.

Efficacy analysis

Primary efficacy analysis: Overall response rates are shown in Table 118.5A, and response rates in MDIs in Table 118.5B.

Table 118.5A. Response rates			
Population	**Cefepime**	**Piperacillin/ gentamicin**	**95% Confidence Interval**
FDA evaluable[1]	19/36 (52.8%)	27/42 (64.3%)	$_{36,42}(-0.3590, 0.1289)_{52.8\%, 64.3\%}$
FDA MITT[2]	17/51 (33.3%)	23/52 (42.2%)	$_{51,52}(-0.3154, 0.0974)_{33.3\%, 42.2\%}$
Sponsor evaluable	26/42 (61.9%)	33/50 (66.0%)	$_{42,50}(-0.2599, 0.1780)_{61.9\%, 66.0\%}$
Sponsor MITT	26/51 (51.0%)	33/55 (60.0%)	$_{51,55}(-0.2977, 0.1173)_{51.0\%, 60.0\%}$
Table 118.5B. MDI response rates			
Population	**Cefepime**	**Piperacillin/ gentamicin**	**95% Confidence Interval**
FDA evaluable	5/14 (35.7%)	11/16 (68.8%)	$_{14,16}(-0.7358, 0.0751)_{35.7\%, 68.8\%}$ Exact 95% confidence interval $_{14,16}(-0.6802, 0.0467)_{35.7\%, 68.8\%}$
Sponsor evaluable	9/17 (52.9%)	12/20 (60.0%)	$_{17,20}(-0.4450, 0.3038)_{52.9\%, 60.0\%}$ Exact 95% confidence interval $_{17,20}(-0.4199, 0.2596)_{52.9\%, 60.0\%}$

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

Cefepime fails to establish therapeutic equivalence to the control combination therapy when overall response rates are considered, in the evaluable population as well as in patients included in the MITT analyses as per FDA as well as the sponsor. In patients with microbiologically documented infection, cefepime fails to establish therapeutic equivalence to the control combination therapy in patients deemed evaluable by either the FDA or the sponsor.

Medical Officer's Comment

The failure to establish equivalence with the combination regimen is striking in view of the higher proportion of patients in the control arm with severe neutropenia.

Safety analysis

Nine deaths (5 cefepime; 4 control) occurred within 30 days of termination of study therapy; none were related to study therapy. Four subjects, two in each treatment group died of infection with either bacteremia or fungemia. The other five subjects died of complications associated with their underlying cancer or its treatment. Only nine subjects had adverse events judged related to study therapy. These events were of mild to

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.

moderate severity except for drug-related renal failure in two control subjects which was considered life-threatening. Otherwise, laboratory abnormalities when they occurred were generally mild and asymptomatic. However, clinically relevant laboratory abnormalities were more common in the control group than in cefepime-treated subjects for creatinine (4 vs. 0) and hepatic function tests (9 vs. 4). In one control subject intravascular hemolysis attributed to a low phosphorus level (0.9 mg/dL) unrelated to study therapy was felt to be the precipitating event for the development of renal and respiratory failure.

Final comments/conclusions - study 411-118

This was a two center, randomized controlled trial comparing the efficacy of cefepime with that of piperacillin and gentamicin for empiric therapy of febrile neutropenia. Although designed in the late 1980's, this trial was largely compliant with the IDSA guidelines.

The trial enrolled a total of 116 patients, accounting for 116 episodes. Baseline demographic and prognostic factors were balanced between the treatment arms. 78 (67.2%) 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.

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 the control arm. Cefepime fails to establish therapeutic equivalence to the control combination therapy when overall response rates are considered, in the evaluable population as well as in patients included in the MITT analyses as per FDA as well as the sponsor. In patients with microbiologically documented infection, cefepime fails to establish therapeutic equivalence to the control combination therapy in patients deemed evaluable by either the FDA or the sponsor. Thus, this study alone cannot demonstrate therapeutic equivalence between cefepime and the comparator regimen.

The control arm had a higher proportion of patients with severe neutropenia, a factor which should have favored cefepime, yet cefepime failed to demonstrate equivalence with the comparator regimen. Furthermore, the point estimate of the difference in response rates is relatively large (-11.5%), suggesting that in settings where combination therapy is required, cefepime monotherapy may not be adequate.

Safety analysis showed similar all-cause and specific cause mortality rates for the two treatment arms. 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 a somewhat higher incidence of laboratory adverse events in the control arms.

In conclusion, study AI411-118 does not by itself demonstrate therapeutic equivalence between cefepime and piperacillin/gentamicin for empiric therapy of febrile neutropenia. This study demonstrates an acceptable safety profile for cefepime in this indication, which may represent a safety advantage for cefepime compared to the combination of piperacillin/gentamicin.

STUDY AI411-137

Title: A Comparative Study of Cefepime vs. Mezlocillin/Gentamicin in the Treatment of Fever in Cancer Subjects with Fever and Neutropenia.

Investigator: Michael Lew, M.D.

Study center: Dana Farber Cancer Institute

Study period: First subject enrolled July 28, 1990. Last subject completed therapy August 14, 1992.

Objective: To evaluate the clinical efficacy and safety of cefepime administered at a dose of 2 grams every eight hours in comparison to the combination of mezlocillin administered at a dose of 3 grams every 4 hours and gentamicin administered at a dose of 1.5 mg/kg every eight hours, for the empiric treatment of febrile episodes in neutropenic cancer subjects.

Study design: A two arm, comparative, open-label, randomized (1:1) single-center study conducted in the United States. A total of 200 subjects were planned with a projected accrual of 2 to 3 subjects per week over a period of two years. However, enrollment was terminated at the end of two years with 71 subjects enrolled.

Protocol Summary

Study population

Diagnosis and main criteria for inclusion: Adult men and women (negative pregnancy test prior to enrollment), 18 years or older, undergoing treatment for cancer were eligible for enrollment for empiric treatment of a febrile episode (sustained temperature >38°C; single temperature >38.3°C) while neutropenic (<500 neutrophils/μL).

Exclusion criteria: These were similar to the criteria in studies AI411-118 and -131; patients on prophylaxis with ciprofloxacin or trimethoprim-sulfamethoxazole could be enrolled.

Study procedures

Study procedures were similar to those in study AI411-131, with the exception of treatment assignment, study therapy, and use of concomitant antibiotics.

Treatment assignment: All potentially eligible subjects who provided informed consent were randomly assigned at time of admission to the cancer center to receive one of the two treatments (cefepime or the combination of gentamicin and mezlocillin). Five stratification groups were defined by the underlying cancer, the need for bone marrow transplantation and the cancer therapy:

- Solid tumor; autologous bone marrow transplant; any type of cancer therapy
- Hematologic cancer; autologous bone marrow transplant; any type of cancer therapy
- Any cancer; allogenic bone marrow transplant; any type of cancer therapy
- Any cancer; no bone marrow transplant; chemotherapy only
- Any cancer; no bone marrow transplant; combination of chemo- and radiotherapy

Medical Officer's Comment

The number of strata (5) is high for a study with so few patients, and may decrease the power of the study to detect differences within individual strata.

For each stratum, computer-generated randomization schedules for treatment assignment (1:1 ratio) and sequentially numbered sealed envelopes containing a card with the treatment assignment were provided by the statistical group at Dana Farber Cancer Center for each stratum. At the time a subject provided informed consent, the next available envelope in the stratum to which the subject belonged was placed unopened in the subject's medical chart. When the subject became neutropenic and fever developed, the subject's eligibility for enrollment was determined and if eligible, the sealed envelope was opened and the assigned treatment begun. Consenting subjects, who had fever and neutropenia on admission to the center and were eligible for the study, were immediately randomized within the proper stratum and the assigned treatment was begun.

If an eligible subject withdrew consent, did not develop fever with neutropenia, or became ineligible for other reasons and the sealed envelope had not been opened, the envelope was returned to the top of the sequence within the proper stratum and assigned to the next consenting subject in that stratum.

Study therapy: Cefepime was supplied as a 2 gram vial and administered intravenously at a dose of 2g q8h. Mezlocillin was supplied as a 3 gram vial and administered intravenously at a dose of 3g q4h (Note: Three subjects received at least one dose of mezlocillin not supplied by Bristol-Myers Squibb for which lot numbers were not available. Gentamicin was supplied as an 80 mg vial and administered intravenously at a dose of 1.5 mg/kg q8h. The dose and frequency of dosing for gentamicin could be adjusted, based on serum gentamicin levels during therapy.

Cefepime susceptibility was tested by the NCCLS disc-diffusion method using a 30 μg cefepime disc. Mezlocillin and gentamicin susceptibilities were also tested using standard discs. Quality assurance for disc-diffusion testing was performed using standard American Type Culture Collection control organisms.

Concomitant antibiotics: Subjects were to receive study therapy without other systemic antibacterial antibiotics for 48 hours at which time the temperature response was evaluated. The protocol specified that three antibiotics, vancomycin, tobramycin or amphotericin, could be added to either primary antibiotic regimen following evaluations of a subject's response during the first 72 hours of study therapy

If the subject was not afebrile after 48 hours of study therapy, therapy was to be modified based on whether the subject had a documented infection or a fever of uncertain origin (FUO). For gram-positive cocci in the blood, the protocol indicated that vancomycin was to be added. For gram-negative bacilli in the blood, the protocol indicated that tobramycin was to be added to the regimen for subjects treated with cefepime, and tobramycin was to be substituted for gentamicin for subjects receiving control. For other clinically or microbiologically documented infections, the protocol allowed selection of vancomycin, an aminoglycoside, amphotericin, or an anaerobic agent based on the best clinical judgment of the attending clinicians. For subjects with FUO, tobramycin was to

be added to the regimen for subjects treated with cefepime, and tobramycin was to be substituted for gentamicin for subjects treated with control. All subjects were to be evaluated again for temperature response following 72 hours of study therapy. If fever persisted whatever the initial type of infection, amphotericin was to be added.

Use of concomitant clotrimazole for prophylaxis of fungal infections and acyclovir for prophylaxis of viral infections was permitted by the protocol. Prophylactic use of the non-systemic antifungal agents, miconazole and nystatin was not specifically addressed by the protocol.

Concomitant medications other than systemic antimicrobial agents and concomitant non-drug therapies were allowed as clinically indicated.

Sponsor's criteria for evaluation

Evaluability and Efficacy: Criteria for evaluability, infectious disease diagnosis, and efficacy were the same as those for study AI411-189.

Safety: Safety evaluations were performed for all subjects who received study therapy and included an assessment of deaths, adverse events, including those which resulted in discontinuation of therapy, and abnormal laboratory values which developed during or following study therapy.

Sponsor's statistical methods: Safety results were based on data from all subjects who were randomized. The primary efficacy analyses were based on the population of subjects who were evaluable for response. In addition, a modified intent-to-treat efficacy analysis was performed.

Results

Study population characteristics

Demographics: 71 patients were enrolled in study AI411-137. Demographic characteristics are shown in Table 137.1.

Table 13.1.1 Demographics for all enrolled patients in AI 11-137				
	Overall	**Cefepime**	**Mezlocillin/gentamicin**	**CMH p value**
Total	71	35	36	
Age				1.0
Median (y)	42.0	44.0	42.0	
Mean (y)	41.5 ± 9.4	42.5 ± 7.6	40.6 ± 10.9	
Range (y)				
≥ 65 y	0 (0.0%)	0 (0.0%)	0 (0.0%)	
< 65 y	71 (100.0%)	35 (100.0%)	36 (100.0%)	
Sex				0.957
Male	42 (59.1%)	20 (57.1%)	22 (61.1%)	
Female	29 (40.9%)	15 (42.9%)	14 (38.9%)	
Race				0.984
White	69 (97.2%)	34 (97.1%)	35 (97.2%)	
Black	2 (2.8%)	1 (2.9%)	1 (2.8%)	
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Underlying disease				0.748
Leukemia	10 (14.1%)	4 (11.4%)	6 (16.7%)	
OHM	53 (74.6%)	27 (77.1%)	26 (7.2%)	
OHD	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Solid tumor	8 (11.3%)	4 (11.5%)	4 (11.1%)	
ANC nadir				0.310
Median	0.0	0.0	0.0	
Mean	4.8 ± 21.7	7.1 ± 28.2	2.5 ± 11.9	
≤100	70 (98.6%)	34 (97.1%)	36 (100.0%)	
>100	1 (1.4%)	1 (2.9%)	0 (0.0%)	
Duration ANC≤500				0.160
Median (d)	17.0	17.0	17.5	
Mean (d)	17.8 ± 7.2	16.6 ± 5.1	19.0 ± 8.6	
<7 d	2 (2.8%)	0 (0.0%)	2 (5.6%)	
≥7 d	69 (97.2%)	35 (100.0%)	34 (94.4%)	
Bone marrow graft	68 (95.8%)	34 (97.1%)	34 (94.4%)	
Indwelling catheter	68 (95.8%)	34 (97.1%)	34 (94.4%)	
Prophylactic Abx	70 (98.6%)	35 (100.0%)	35 (97.2%)	
SBP <90 at entry	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Multiple enrollments	0 (0.0%)	0 (0.0%)	0 (0.0%)	

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