Results

Study population characteristics

Demographics: Enrollment by center is shown in Table 198.1, and the demographics of patients enrolled in AI411-198 in Table 198.2.

Table 198.1
Enrollment By Investigator/Site For All Febrile Episodes

	-001 Boogaerts (Leuven)	-002 Schots (Brussels)	-003 Bosly (Yvoir)	-004 Aoun (Brussels)	Total
Total enrollment	27	25	28	31	111
Single episode	27	25	28	31	111
Multiple episodes					
Second episode	5	6	4	1	16
Third episode	-	1	-	-	1
Total febrile episodes	32	32	32	32	128

Table 19.2. Demographics - all patients enrolled in A1411-198				
	Overall	**Cefepime**	**Ceftazidime**	**CMH p value**
Total	111	54	57	
Age				0.475
Mean (y)	48.8 ± 14.9	48.1 ± 14.7	49.5 ± 15.3	
Range (y)				
≥ 65 y	15 (13.5%)	9 (16.7%)	6 (10.5%)	
< 65 y	96 (86.5%)	45 (83.3%)	51 (89.5%)	
Sex				0.141
Male	69 (62.1%)	30 (55.6%)	39 (68.4%)	
Female	42 (37.9%)	24 (44.4%)	18 (31.6%)	
Underlying disease				0.998
Leukemia	62 (55.9%)	32 (59.3%)	30 (52.6%)	
OHM	44 (39.6%)	20 (37.0%)	24 (42.1%)	
OHD	2 (1.8%)	0 (0.0%)	2 (3.5%)	
Solid tumor	3 (2.7%)	2 (3.7%)	1 (1.8%)	
ANC nadir				0.904
Mean	30.7 ± 64.9	27.4 ± 54.5	33.9 ± 73.7	
≤100	103 (92.8%)	50 (92.6%)	53 (93.0%)	
>100	8 (7.2%)	4 (7.4%)	4 (7.0%)	
Duration ANC≤500				0.613
Mean (d)	9.8 ± 7.0	9.4 ± 5.2	10.1 ± 8.4	
<7 d	26 (23.4%)	11 (20.3%)	15 (26.3%)	
≥7 d	85 (76.6%)	43 (79.7%)	42 (73.7%)	
Bone marrow graft	25 (22.5%)	13 (24.1%)	12 (21.1%)	
Indwelling catheter	32 (28.8%)	16 (29.6%)	16 (28.1%)	
Prophylactic Abx	99 (89.2%)	47 (87.0%)	52 (91.2%)	
Multiple enrollments	17 (15.3%)	9 (16.7%)	8 (14.0%)	

Statistical Reviewer's Comment

There is a marginal imbalance in the gender distribution between the two treatment arms for the enrolled patient population. This was not felt to be significant enough to warrant further analysis. The two treatment arms are balanced with respect to other key demographic and prognostic risk factors.

Antimicrobial Prophylaxis: Eighty-six percent of study subjects received antimicrobial prophylaxis, with the majority receiving some combination of antibacterial, antifungal, or antiviral agents (47/54, 87 percent in the cefepime/vancomycin group; 52/57, 91 percent in the ceftazidime/vancomycin group). The oral quinolones were widely used for gut decontamination. Ciprofloxacin, norfloxacin, ofloxacin, and pefloxacin were administered prophylactically a total of 91 times in 89 subjects. Of these 89 subjects receiving pretreatment quinolone prophylaxis, forty-one continued it beyond the start of study therapy. Five subjects were on isoniazid, presumably for tuberculosis prophylaxis.

Ninety subjects received systemic antifungal prophylaxis with oral azoles: 48 with fluconazole, 42 with itraconazole. These agents were continued past the start of study therapy in all cases. In addition to systemic agents, eighteen of these subjects received concomitant topical nystatin, also continued past the start of study therapy in all cases.

Twenty-one subjects were on acyclovir prophylaxis; this was continued during study therapy in all but two subjects.

The use of colony stimulating factors, nutritional support, and blood components was comparable between treatment arms.

Episode evaluability

Evaluability assessment gave the results shown in Table 198.3 for study 198.

Table 198.3: Episode evaluability

	1° evaluability criteria		MITT evaluability criteria	
	FDA	Sponsor	FDA	Sponsor
All episodes	50/128 (39.1%)	96/128 (75.0%)	120/128 (93.7%)	—
Cefepime	24/63 (38.1%)	48/63 (76.2%)	60/63 (95.2%)	—
Ceftazidime	26/65 (40.0%)	48/65 (73.8%)	60/65 (92.3%)	—

The most common reasons for exclusion was lack of follow-up data (27.6% of episodes in the ceftazidime arm, 23.8% of episodes in the cefepime arm). The next most common reason was modification prior to 72 hours (10.8% in the ceftazidime arm, 22.2% in the cefepime arm).

Medical Officer's Comment

For a substantial number of patients, the last data available for fever and clinical status was the end of therapy evaluation, with no further follow-up available. Given the possibility that such patients relapsed once therapy was stopped, such patients were scored as unevaluable by the Medical Officer under the primary analysis, and as failures under the MITT analysis. As in study AI411-186, there was a substantial difference between the evaluability rates in the FDA analysis and the sponsor's analysis.

Infectious Disease diagnoses

Infectious disease diagnoses for the evaluable episodes are shown in Tables 198.4A and B.

Table 198.4A. FDA infectious disease diagnoses for evaluable population				
Infection type	**Overall**	**Cefepime**	**Ceftazidime**	**CMH p value**
Any	50 (100%)	24 (100%)	26 (100%)	0.829
MDI with bacteremia	21 (42.0%)	10 (41.6%)	11 (42.3%)	
MDI	1 (2.0%)	0 (0.0%)	1 (3.8%)	
CDI	6 (12.0%)	3 (12.5%)	3 (11.5%)	
FUO	22 (44.0%)	11 (45.8%)	11 (42.3%)	

Table 198.4B. Sponsor's infectious disease diagnoses for evaluable population				
Infection type	**Overall**	**Cefepime**	**Ceftazidime**	**CMH p value**
Any	96 (100%)	48 (100%)	48 (100%)	0.230
MDI with bacteremia	34 (35.4%)	14 (29.2%)	20 (41.7%)	
MDI	1 (1.0%)	0 (0.0%)	1 (2.1%)	
CDI	16 (16.7%)	10 (20.8%)	6 (12.5%)	
FUO	45 (46.9%)	24 (50.0%)	21 (43.7%)	

Statistical Reviewer's Comment

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

Efficacy analysis

Primary analysis: Response rates and MDI response rates are shown in Tables 198.5A and 5B.

Table 198.5A. Response rates - study A1411-198			
Population	**Cefepime**	**Ceftazidime**	**95% Confidence Interval**
FDA evaluable[1]	6/24 (25%)	10/26 (38.5%)	$_{24,26}(-0.4296, 0.1604)_{25\%, 38.5\%}$ Exact 95% Confidence Interval $_{24,26}(-0.4386, 0.1404)_{25\%, 38.5\%}$
FDA MITT[2]	6/60 (10.0%)	8/60 (13.3%)	$_{60,60}(-0.1647, 0.0981)_{10.0\%, 13.3\%}$ Exact 95% Confidence Interval $_{60,60}(-0.1903, 0.1234)_{10.0\%, 13.3\%}$
Sponsor evaluable	29/48 (60.4%)	28/48 (58.3%)	$_{48,48}(-0.1964, 0.2381)_{60.4\%, 58.3\%}$ Exact 95% Confidence Interval $_{48,48}(-0.1892, 0.2295)_{60.4\%, 58.3\%}$

[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.

Table 198.5B MDI Response rates - study AI411-198			
Population	**Cefepime**	**Ceftazidime**	**95% Confidence Interval**
FDA evaluable	3/10 (30.0%)	4/11 (36.4%)	$_{10,11}(-0.5609, 0.4337)_{30.0\%, 36.4\%}$ Exact 95% Confidence Interval $_{10,11}(-0.5559, 0.3575)_{30.0\%, 36.4\%}$
Sponsor	9/14 (64.3%)	12/21 (57.1%)	$_{14,21}(-0.3164, 0.4593)_{64.3\%, 57.1\%}$ Exact 95% Confidence Interval $_{14,21}(-0.2756, 0.4487)_{64.3\%, 57.1\%}$

Medical Officer's Comment

Under the FDA primary analysis, the data do not demonstrate therapeutic equivalence by the 20% lower bound criterion. It is noteworthy that even in the sponsor's evaluable population, which would be expected to reflect the most favorable assumptions with respect to evaluability, the confidence interval lower bound almost reaches 20%.

Statistical Reviewer's Comment

The sample sizes in this trial are too small for inferences to have adequate statistical power. Based on the exact confidence intervals, cefepime in combination with vancomycin fails to establish therapeutic equivalence to ceftazidime in combination with vancomycin in the FDA evaluable database. Cefepime is deemed therapeutically equivalent to ceftazidime in combination with vancomycin as per the FDA MITT or the sponsor's evaluable database.

Safety analysis

Mortality: Eight subjects died either while on study or within 30 days of completion of study therapy: five in the cefepime/vancomycin group, three in the ceftazidime/vancomycin group. One of the deaths in the ceftazidime/vancomycin group was felt to be related, in part, to study therapy. This subject developed renal insufficiency that was attributed to vancomycin. Four deaths were related to possible or proven infection; four were attributed to pneumonia and one to a new *S. oralis* bacteremia. One subject died of a cerebral hemorrhage in the setting of thrombocytopenia. The death of one subject was attributed to ARDS. Refractory leukemia was the cause of death in one subject. One of the deaths (subject occurred during enrollment for a second febrile episode.

Discontinuation due to adverse events: Eleven subjects, six in the cefepime/vancomycin group, five in the ceftazidime/vancomycin group, had study therapy discontinued because of adverse events. Rash and/or erythema occurred in three of the five subjects in each treatment group. One subject in each treatment group had therapy discontinued because of the development of renal insufficiency (combined with rash in the ceftazidime/vancomycin subject). Other reasons for discontinuation included pharyngitis/cervical edema and pulmonary aspergillosis. One discontinuation occurred in a subject enrolled for a second febrile episode

The average length of therapy for those subjects in the cefepime/vancomycin group who withdrew because of an adverse event was 11 days of cefepime, 10 days of vancomycin. For those in the ceftazidime/vancomycin group, it was 9 days of ceftazidime, 7 days of vancomycin. One subject in the ceftazidime/vancomycin group who developed a rash had only two

days of study therapy.

Clinical adverse events: Adverse events were recorded for over half of the subjects in each of the two treatment groups. Overall, events occurred somewhat less frequently in the cefepime/vancomycin group (60 percent vs. 69 percent for ceftazidime/vancomycin). In both treatment groups, the majority of events were felt to be unrelated to drug therapy. The gastrointestinal tract and skin were the organ systems most frequently affected by adverse events. The incidence of both diarrhea and skin rash was somewhat higher in the ceftazidime/vancomycin group.

Sixteen subjects (6 cefepime/vancomycin, 10 ceftazidime/vancomycin) experienced a total of 17 drug-related adverse events. The most frequent drug-related event was rash, occurring in a total of six subjects, two treated with cefepime/vancomycin and four treated with ceftazidime/vancomycin. All six subjects had study drug discontinued or interrupted because of rash. Renal insufficiency developed in two subjects receiving cefepime/vancomycin. One case was mild and led to a reduction in the dose of study therapy, while one case was severe and led to discontinuation of drug. In the ceftazidime/vancomycin group, there were three instances of renal dysfunction. In two mild cases, study drug was discontinued. In the life-threatening case, the dose of study drug was reduced; that subject ultimately expired from an undefined respiratory infection. The remaining probably drug-related events in the cefepime/vancomycin group were a "red man's syndrome" attributed to vancomycin, and colonization with a non-*Candida albicans* fungus, and in the ceftazidime/vancomycin group diarrhea, a granuloma, pruritis, and stomatitis.

Laboratory adverse events: Among subjects with normal pretreatment laboratory values, abnormalities in renal function tests developed with similar frequency in both treatment groups. One cefepime/vancomycin-treated subject developed a clinically relevant elevation of serum creatinine (3.0 mg/dL) on the fifth day of study therapy. Hypophosphatemia occurred in 18 of the 39 subjects with normal pretreatment values; seven of these subjects developed clinically relevant decreases in serum phosphorus, ranging from mg/dL (normal range mg/dL). Although aberrations in liver function tests developed more frequently overall in the cefepime/vancomycin group, clinically relevant abnormalities were noted with almost equal frequency in the two groups (seven cefepime/vancomycin subjects, six ceftazidime/vancomycin subjects). Of the four liver function tests, the serum ALT/SGPT (normal range U/L) was the one for which clinically relevant abnormalities most often occurred (range U/L among cefepime/vancomycin subjects and U/L among ceftazidime/vancomycin subjects.

Of the subjects entering the study with abnormal renal function tests, one cefepime/vancomycin-treated subject developed a clinically relevant increase in creatinine. This particular subject's initial creatinine was 1.2 mg/dL; while on study therapy, the level increased to 1.7 mg/dL. The deterioration in renal function was attributed to study therapy, which was discontinued. Serum creatinine subsequently peaked at 3.1 mg/dL on post-study Day 2. The subject required hemodialysis. Two ceftazidime/vancomycin-treated subjects developed clinically relevant increases in blood urea. There were no clinically relevant changes in serum sodium or potassium levels. The prevalence of liver function abnormalities at study onset was essentially equal among the two treatment groups. While any deterioration in alkaline phos-

phatase was noted more often among cefepime/vancomycin-treated subjects, clinically relevant abnormalities occurred with equal frequency in both groups. In no instance was alkaline phosphatase elevation attributed to study therapy. One subject in the cefepime/vancomycin treatment group developed clinically relevant elevations of SGOT and SGPT, 297 and 412 U/L, respectively. These elevations were felt to be possibly related to the vancomycin component of the study regimen.

Final comments/conclusions

This was a randomized multi-center trial comparing cefepime in combination with vancomycin with the corresponding ceftazidime combination for empiric therapy of febrile neutropenia. The study accrued 111 patients, representing 128 episodes of febrile neutropenia. However, many of these episodes were unevaluable because of lack of follow-up data. As a result, only 50 episodes were considered evaluable.

Response rates in the evaluable population were comparable between the cefepime and control arms. However, the 95% confidence interval around the difference in response rates was very broad, with a lower bound of 43%, due to the low number of evaluable episodes. Again, as in the other combination therapy study (AI411-186), even after applying less stringent definitions of success (such as simply survival from infection), the lower confidence interval bound remained sufficiently great that it was not possible to conclude that the combination of cefepime with vancomycin was therapeutically equivalent to ceftazidime in combination with vancomycin. Although the FDA MITT analysis showed therapeutic equivalence, it does so by including patients without follow-up data. Such patients were scored as treatment failures, and may have diluted true treatment failures, leading to an artificially narrow confidence interval. The sponsor's analysis included such patients and scored them as successes or failures depending on their status at the end of therapy evaluation. The sponsor's rationale for not following the protocol's requirements for follow-up data was not given, making conclusions from such an analysis unreliable. Thus, the primary FDA analysis, using the FDA evaluable population, would seem to reflect a more accurate scientific perspective on the therapeutic efficacy of each treatment arm. Under this analysis, cefepime in combination with vancomycin is not equivalent to the corresponding ceftazidime combination.

The safety profile of cefepime in combination with vancomycin in this trial was similar to that in other trials. However, the use of a lower dose of cefepime (2 q IV q12h) makes it difficult to predict the safety profile of this drug when used at the proposed dosage of 2 g IV q8h in combination with an aminoglycoside.

In conclusion, the data in this study are insufficient to support the claim of effectiveness of cefepime in combination with vancomycin for the indication of empiric therapy of febrile neutropenia. Given the data supporting the use of cefepime as monotherapy for empiric treatment of febrile neutropenia, it would be reasonable to compare, in a future study, the efficacy of cefepime alone with that of cefepime in combination with vancomycin.

STUDY AI411-143

Medical Officer's Comment

Data 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 were supportive of the comparative studies submitted with the original NDA (AI411-118 and 131) with regard to demonstration of the efficacy of cefepime for this indication.

Title: Non-Comparative Study of Cefepime as Empiric Therapy of Fever in Cancer Patients with Granulocytopenia

Investigators: Michel P. Glauser, M.D.; Françoise Meunier, M.D.

Study centers: Centre Hospitalier, Universitaire Vaudois, Lausanne, Switzerland (Glauser)
Institut Bordet, Brussels, Belgium (Meunier)

Study period: First patient enrolled January 28, 1990; last patient assessed June 25, 1991

Objective: This study was intended to provided "additional safety data and preliminary efficacy data for cefepime administered intravenously in the empiric treatment of cancer patients with fever and neutropenia".

Design: Open-label, non-comparative phase II trial. 84 patients representing 108 episodes were enrolled.

Protocol summary

Study population

Inclusion criteria: Male and female subjects with a presumed infection were eligible if they were at least 16 years of age, had a fever greater than or equal to 38°C, and a neutrophil count of less than or equal to 1000 per mm^3 and had provided oral witnessed informed consent. Female subjects were eligible only if they had had a pregnancy test with negative results immediately before enrollment, were taking oral contraceptives in the prescribed manner, were surgically sterilized, or were post-menopausal.

Medical Officer's Comment

This criterion for fever is quite loose; protocols for studies AI411-189 and 204 required a higher temperature cut-off or multiple measurements at a lower temperature.

Exclusion criteria: Subjects were excluded if they were pregnant or nursing, if they had an infection requiring long-term therapy or if they were hypotensive due to shock, if they had impaired renal function, if they were likely to receive drug therapy constituting empiric treatment of a contaminated body site or other antimicrobial concomitantly or during the two-week follow-up period or if they had received intravenous antibiotic therapy within four days prior to study treatment, if they had cystic fibrosis, a CNS infection, a disorder likely to influence the results of the study, history of a serious reaction to a cephalosporin or penicillin or if they had been placed on "do not resuscitate" or "no code" status. Patients were also excluded if they had entered the study more than once during the same granulocytopenic episode.

Study therapy: Cefepime was supplied in vials containing a dry-fill powder blend containing cefepime dihydrochloride and L-arginine, representing an activity of 1 gram of cefepime per vial. Cefepime was administered intravenously over a period of 30 minutes in doses of 2 gram every 8

hours. The actual duration of therapy was up to a maximum of 28 days.

Pre-treatment procedures (medical history, physical examination, evaluation of clinical signs and symptoms, culture(s) from infected site(s) or blood, chest X-rays and laboratory tests) were conducted within 48 hours prior to treatment or 24 hours after start of treatment. ***During-treatment procedures*** (abbreviated physical examination, evaluation of clinical signs and symptoms, culture(s) and laboratory tests) were performed on Day 3 to 5. Blood cultures, temperature recording and neutrophil count were performed daily during study treatment. ***End-of-treatment procedures*** (abbreviated physical examination, evaluation of clinical signs and symptoms, culture(s) and laboratory tests) were performed between the last day of treatment and 4 days post-treatment. ***Follow-up procedures*** (evaluation of clinical signs and symptoms and culture(s) were conducted between 10 and 14 days after completing treatment.

Efficacy criteria: Infections were classified according to clinical findings, course of the febrile episode and microbiological data. After completion of treatment or at the time of a treatment failure, the Clinical Response category was assessed by the investigator for each disease type of each patient. All the following criteria had to be met for a satisfactory Clinical Response: 1) the patient recovered from fever and neutropenia without the need for additional antimicrobial agents or the modification of the initially assigned regimen; and 2) all clinical signs and symptoms relevant to the infection were resolved or improved and no new clinical signs or symptoms relevant to the infection were present at the time of end-of-treatment evaluation. For patients with pneumonia, if the chest X-ray showed worsening of the infiltrate but signs and symptoms of the infection had improved, the investigator could determine the response based on the clinical setting.

Medical Officer's Comment

The original study report did not include follow-up data, but only end of treatment evaluations. Under the criteria previously used, all such cases would be considered unevaluable for efficacy. Although this study report describes follow-up procedures, it appears that efficacy rates were still reported on the basis of end of treatment evaluation, rather than end of follow-up evaluation.

If a case met any of the following criteria, the Clinical Response was unsatisfactory: 1) the presence or worsening of clinical signs and symptoms relevant to the infection for 72 hours or more after the initiation of therapy and an accompanying clinical decision to change the initially assigned regimen; 2) the increase, persistence or worsening of any clinical signs and symptoms that were related to the original site of infection following initial improvement. This classification was used unless specific criteria for a new infection were met; or 3) death resulting from a documented or presumed infection during the neutropenic episode.

The clinical response was defined as unable to determine for the following reasons: 1) the cause of fever was not of infectious nature; 2) the cause of fever was a resistant organism; 3) the patient entered the study twice during the same neutropenic episode; 4) cefepime treatment was interrupted before response could be established; or 5) the patient received interfering concomitant treatment.

For bacteriologically documented infections, cultures obtained pre-, during and after treatment were used to assess pathogens for bacteriologic response.

Medical Officer's Comment

For empiric therapy, cases with resistant isolates should be regarded as treatment failures rather than as unevaluable.

Statistical analysis: All subjects who received at least 1 dose of cefepime and to whom a clinical and/or a bacteriologic assessment was assigned by the investigator were included in the fever and neutropenia Intent-To-Treat sample. Evaluations of efficacy were based on assessments of the Clinical Response and on both the Clinical and Bacteriologic Response for bacteriologically documented infections.

Medical Officer's Comment

This study was also intended to provide safety and efficacy information for the indication of septicemia/bacteremia; a data set from patients meeting criteria for this indication was analyzed separately. That analysis does not affect this review; for further details, see the review of the original NDA by FDA Medical Officer Linda Sherman, M.D.

Safety analysis: The safety analyses included all subjects during all episodes who received at least one dose of cefepime. Evaluations of safety were based on assessments of the reported ACE and the results of the laboratory data.

Results

Study population characteristics

Two principal investigators, Dr. Michel P. Glauser, located in Lausanne, Switzerland and Dr. Françoise Meunier, located in Brussels, Belgium, participated in this trial. Eighty-four (84) patients were enrolled between January 28, 1990 and May 30, 1991. A total of 108 episodes were recorded for these 84 patients. Sixty-eight episodes of 51 patients were reported in Lausanne, 40 episodes of 33 patients were reported in Brussels. All 84 patients gave informed consent and received at least one dose of study drug.

Characteristics of the study population are shown in Table 143.1.

Table 148.1 Patient characteristics	
Sex	
Female	39 (46)
Male	45 (54)
Race	
Black	1 (1)
White	71 (85)
Hispanic	5 (6)
Oriental	5 (6)
Other	2 (2)
Age (years)	
Mean	46.9 ± 17.4
Median	50.0
Range	
Underlying disease	
Leukemia	39%
OHM	22%
OHD	4%
Solid tumor	34%

Medical Officer's Comment

No data were provided on the duration or severity of neutropenia in this population.

Infectious disease diagnoses

Of the 84 patients with fever and neutropenia, 21 (25%) had a bacteriologically documented infection, 38 (45%) had an infection without bacteriologic documentation and 25 (30%) patients had fever of uncertain origin.

Efficacy analysis

Eighty-four patients with fever and neutropenia received at least one dose of cefepime during each of the 108 episodes. All patients and all episodes were included in the intent-to-treat analysis. The clinical response rates by infection etiology in the patient sample were similar to the clinical response rates of the episode sample.

The clinical response was satisfactory for 50 (68%), unsatisfactory for 24 (32%) and unevaluable for 10 patients.

Of the 21 patients with a bacteriologically documented infection, 10 (56%) had a satisfactory clinical response. For 3 patients, the clinical response could not be determined. The bacteriological response could be determined for 22 of the 38 pathogens isolated during 108 episodes; 20 (91 %) pathogens were eradicated.

Of the 38 patients with infections without bacteriologically documentation, 27 (73%) had a satisfactory clinical response. The clinical response could not be determined for one patient.

Of the 25 patients with fever of uncertain origin, 13 (68%) had a satisfactory clinical response; the response could not be determined in 6 patients.

Forty-one new infections occurred in 27 of the 108 episodes with fever and neutropenia. Thirteen new infections were caused by bacterial pathogens, 8 new infections were caused by viruses, 7 new infections were caused by fungi. For 1 new infection, no pathogen was identified, no culture was done for 5 new infections and the culture was negative for 7 new infections.

Safety analysis

There were 10 deaths: 5 during treatment, 4 within one month post-treatment and 1 39 days post-treatment. None of these deaths was attributed to the use of cefepime. For 4 subjects, the infection treated with cefepime contributed to death. For three subjects, a new infection contributed to death. The underlying disease was a contributing factor to all deaths.

Thirty-two adverse clinical events were reported during 23 episodes for 19 subjects. At least one cefepime related adverse clinical event was reported for 12 (11%) of the 108 episodes for 10 (12%) of the 84 subjects. Cefepime related events included diarrhea, abdominal pain, nausea, rash and urticaria. Cefepime treatment was discontinued due to ACE's (rashes, urticaria and nausea) during 6 (6%) episodes for 5 (6%) subjects. Cefepime treatment was discontinued because of local intolerance at the infusion site for one subject. The subject refused the placement of another catheter for cefepime infusion after phlebitis was reported at the initial site.

Nineteen (23%) out of all study subjects had 25 normal pre-treatment laboratory values that developed to clinically relevant abnormal during- or post-treatment values during 20 episodes. Five tests were considered to be possibly related to cefepime administration, they were all liver function tests and occurred in 3 (4%) of the 84 subjects. Thirty-five study subjects showed 43 abnormal laboratory tests, following an abnormal pre-treatment value and worsened to a clinically relevant level during- or post-treatment during 38 episodes. Thirty-two cases concerned hematological tests, 9 were liver function tests, 1 concerned an electrolyte test and one was a coagulation test. Four cases were considered to be possibly related to cefepime administration, these 4 were all liver function tests, they occurred in 4 (5%) of the 84 subjects. None of the abnormal laboratory tests led to discontinuation of cefepime.

Final comments/conclusions

This noncomparative open-label study was intended to provide initial data regarding the efficacy of cefepime for empiric therapy of febrile neutropenia. 84 patients were enrolled. The patients were not adequately characterized as to the severity and duration of neutropenia, although information is reported on the underlying malignancies of these patients, which may serve as markers for the risk of bacterial infection.

Response rates ranged from 56% for patients with microbiologically documented infections to 73% to non-documented infections, with a response rate of 68% overall. These would seem comparable to results in the controlled studies described previously. However, two important caveats need to be kept in mind. First, the inclusion criterion only required a single temperature of 38.0°C; this is an low threshold for fever and many patients may have been en-

rolled who were not truly infected, especially those with fever of uncertain origin. Secondly, evaluations were only reported for end of treatment; although the incidence of new infections was reported, it is not possible to determine from the data provided which patients who were scored as successes developed new infections. Such patients might in fact have represented treatment failures, lowering the response rates. Thus, only limited conclusions should be drawn regarding the comparability of the response rates in this trial with those in the controlled trials. This is consistent with study AI411-143 being a phase II trial intended to explore the use of cefepime for this indication, rather than to provide pivotal trial data.

The safety profile in this study was consistent with previous data on adverse events with cefepime.

In conclusion, this study may be regarded as having shown preliminary efficacy data for cefepime in the treatment of febrile neutropenic patients, and supporting the design and conduct of phase III comparative trials.

STUDY AI411-158

General Information

Title: A Noncomparative Prospective Multicenter Study Evaluating Efficacy and Safety of Cefepime as Empirical Therapy of Febrile Episodes in Granulocytopenic Patients

Investigator: B. De Pauw, M.D.

Study Center: Sint-Radboudziekenhuis, University Hospital, Nijmegen, The Netherlands

Study Period: First subject enrolled 3 February 1991. Last subject completed therapy 20 November 1991.

Study Design and Methodology: This was a single center, open-label, non-comparative pilot trial. A total of 30 patients were enrolled.

Objectives: To evaluate the safety and efficacy of cefepime as monotherapy in the empiric treatment of fever in neutropenic patients; and to evaluate the outcome of cefepime treatment with or without treatment modification in neutropenia patients presenting with fever.

Duration of Treatment: Cefepime was administered at a dose of 2 g/q8h for a maximum duration of therapy of 28 days. Subjects were to receive a minimum of 21 doses (7 days therapy). Study drug was given empirically for the first 72 hours. If the subject's condition improved or remained stable after 72 hours, cefepime therapy was continued for up to 5 additional days without fever and a neutrophil count of $\geq$ 500/µl. If after 72 hours there was worsening of the clinical condition, the empiric regimen was to have been modified by adding a second antibiotic depending on the specificity of the documented infection. This regimen was continued for up to 5 additional days without fever, signs or symptoms or infection and a neutrophil count $\geq$ 500/µL.

Protocol summary

Study population

Diagnosis and main criteria for inclusion: Subjects were eligible for this study if they were $\geq$ 16 years of age, neutropenic (< 1000 neutrophils/:l) in association with hematologic malignancy and presenting with fever ($\geq$ 38°C) presumably of infectious origin.

Exclusion criteria: Subjects were excluded from the study if they had a history of hypersensitivity to penicillins or cephalosporins, were of childbearing potential and not using adequate contraception, were pregnant or lactating, had severe renal or hepatic insufficiencies, were HIV positive, had a history of drug or alcohol abuse or had a life expectancy of less than 72 hours. Also excluded were subjects who had received any antibiotic therapy within 4 days prior to the start of the study, with the exception of antibiotics known to have been clinical or bacteriologic failures or those used for prophylaxis of fungal infections or selective bowel decontamination. Subjects who had been enrolled in the study during a previous febrile episode were also ineligible.

Study therapy: Cefepime was supplied as 1 g vials. After reconstitution with sterile water and dilution with sterile isotonic saline, each 1 g dose of cefepime was infused over 30 minutes three times daily for a period of up to 28 days (2g q8h). Cefepime was administered at a dose of 2 g every 8 hours, for a maximum duration of therapy of 28 days. Subjects were to receive a minimum of 21 doses (7 days therapy) of cefepime. Study drug was given empirically for the first 72 hours. If the subject's condition improved or remained stable after 72 hours, cefepime therapy

was continued for up to 5 additional days without fever and a neutrophil count of $\geq$ 500/µl. If after 72 hours there was worsening of the clinical condition, the empiric regimen was to have been modified as follows: For bacteriologically documented infections: i) Gram positive organism: Cefepime + Vancomycin 500 mg q8h; ii) Gram negative organism: Cefepime + Amikacin 15 mg/kg q8h. For non-bacteriologically documented infections: Cefepime + Vancomycin 500 mg q8h. In practice, subjects with gram positive infections or non-bacteriologically documented infection were given teicoplanin and not vancomycin. This regimen was continued for up to 5 additional days without fever, signs or symptoms of infection and a neutrophil count of $\geq$ 500/µl.

Pre-treatment procedures: At enrollment, all subjects had a medical history and underwent a physical examination, including documentation of fever. A clinical evaluation of specific signs and symptoms of infection as well as a chest X-ray were performed. Serum chemistry tests included liver function tests (SGPT, SGOT and total bilirubin), renal function tests (BUN, creatinine), electrolytes (sodium, potassium, phosphorus and calcium) and alkaline phosphatase. Hematologic evaluations were RBC count, hemoglobin and hematocrit, total WBC count and differential and platelet count. Urinalysis (specific gravity, pH, WBC, sediment, albumin and glucose) was also requested.

The pre-treatment bacteriologic assessment included 2 blood cultures, a urine culture as well as cultures of any other site(s) of infection. Strains were tested for *in vitro* sensitivity to cefepime using 30 µg susceptibility discs.

During-Treatment Procedures: A during-treatment evaluation was performed between Day 3 to at least 5 days without fever and/or signs and symptoms. Clinical assessments, including physical examination and signs and symptoms of presumed infection were performed daily; as was the evaluation for safety and tolerability of cefepime. Positive cultures were repeated until negative. Laboratory assessments were performed between 2 and 3 times weekly. Chest X-rays were repeated if a lower respiratory tract infection was identified.

End-of-Treatment Procedures: At the end of treatment with study drug, the physical examination, clinical evaluation, laboratory tests and safety evaluations were repeated. Follow-up cultures were taken if not previously negative. In the case of confirmed respiratory tract infection, another chest X-ray was performed.

***Post-Treatment Procedures*:** Within 4 to 7 days following completion of study drug treatment, a physical examination and clinical evaluation were performed daily. Any safety issues were noted. Laboratory tests were conducted and bacteriologic tests, if applicable, were repeated. A follow-up chest X-ray was performed in the case of previously diagnosed respiratory tract infection.

Criteria for Evaluation: According to the protocol, all subjects who satisfied the inclusion and exclusion criteria and received at least 72h of cefepime monotherapy were evaluable for efficacy. In practice, all subjects who received cefepime therapy were evaluable for efficacy and safety.

Subjects' infections were classified as: Microbiologically Documented Infection (MDI), Clinically Documented Infection (CDI), or Fever of Unknown Origin (FUO). There were two clinical endpoints indicated in the protocol: Primary Endpoint (after 72 h of cefepime monotherapy); and Secondary Endpoint (at the end of the full treatment period). At the primary endpoint the clinical response categories were Response (improvement or lack of worsening of fever or

signs and symptoms of infection) or Non-Response (worsening fever or clinical condition). At the secondary endpoint the clinical response categories were Improvement (afebrile for > 5 days of treatment; resolution of clinical signs or symptoms of infection) or Failure (Worsening fever or lack of clinical improvement; or the antibiotic regimen was modified differently from the regimen described above; or the pathogen was resistant to cefepime; or the subject died from the primary infection).

In the case of microbiologically documented infections, there were two bacteriologic endpoints indicated in the protocol: Primary Endpoint (after 72 h of cefepime monotherapy); and Secondary Endpoint (within 4 to 7 days after completion of treatment). In practice, the final bacteriologic evaluation was not performed at 4 to 7 days post-treatment if previous repeat cultures were shown to be negative.

The bacteriologic response categories were: Eradicated (eradication of the initial causative pathogen); Persistence (failure to eradicate the initial causative pathogen); Relapse (following initial eradication, the original causative pathogen was isolated from the initial site of infection within the 7 days following completion of study drug therapy); Reinfection (following eradication of the primary causative pathogen, isolation of a new pathogen at the original site of infection, or at a new site of infection within the 7 days following completion of study drug therapy; and Superinfection (isolation of a new pathogen during treatment, irrespective of eradication or persistence of the original causative pathogen).

Safety analysis: Safety evaluations included assessments of deaths, adverse clinical events and laboratory results.

Statistical Methods: According to the protocol, all subjects satisfying the inclusion and exclusion criteria were evaluable for efficacy if they received at least 72h of cefepime monotherapy. In practice, all patients who received at least one dose of cefepime monotherapy were considered as evaluable for efficacy. Efficacy evaluations including clinical outcome at 72 hours and at the end of study therapy, modification of the empiric regimen for clinical successes and new infections were tabulated by classification of infection in the evaluable sample. In addition, clinical response by pathogen, bacteriologic response at 72 hours and at the end of study therapy were tabulated in the evaluable subjects with microbiologically documented infections. Safety evaluations were based on data from subjects who received at least one dose of study medication.

Results

Pre-treatment characteristics: Thirty (30) subjects were enrolled in the study. Median age at entry was 39 years (range , 53% of the patients were male and 97% were white. All subjects had hematological malignancy; the majority (77%) had a diagnosis of leukemia (AML, CML or ALL). All but one subject were hospitalized for bone marrow transplantation. The majority of subjects received systemic antimicrobial prophylaxis within the 3 days prior to receiving study drug; 87% received a combination of antibacterial, antifungal and antiviral prophylaxis. 80% of subjects had severe neutropenia (ANC < 100 cells/μL. The median duration of neutropenia was 10 days; for severe neutropenia the median duration was 9 days. Twelve (40%) subjects had microbiologically documented infections (MDI), 17 (57%) had a diagnosis of fever of unknown origin (FUO) and 1 had a clinically documented infection (CDI). A total of 13 patho-

gens were isolated from the 12 patients with MDI. The majority of the pathogens were Gram-positive. The 2 Gram-negative pathogens were both isolates of *E. coli*.

Treatment: The median duration of treatment was 10 days. Treatment was discontinued early in 7 (23%) subjects. Of these 7 subjects, 3 discontinued due to adverse events, 2 due to intercurrent illness, 1 because of a resistant pathogen and 1 because treatment was considered to have been ineffective. Half of the subjects had their empiric therapy modified with other antimicrobials; of these, 53% received antimicrobials within the first 3 days of therapy. The most common treatment modification was teicoplanin, with antifungals or antivirals being added less frequently.

Efficacy: The clinical response at 72h was 73%; at end of therapy 70% of subjects reported an improved clinical response. For the 12 subjects with MDI (with or without bacteremia), the clinical response was 83% at 72h and at the end of therapy. In the group of subjects with FUO, 12 of 17 (71%) reported clinical response at 72h and 11 (65%) reported improvement at the end of therapy. One subject reported a reinfection.

Safety: There were 4 deaths within the 30 days of completing study medication and 1 death reported at 54 days following cefepime treatment. None was considered to have been related to study drug therapy. Seven patients reported adverse events during treatment with cefepime. The most frequently reported adverse events were skin conditions. Two cases of skin rash were judged to have been probably related to cefepime therapy, the remainder were considered as non-related. Two adverse events (mucositis and lung infiltrate) were judged by the investigator as severe. The most frequently reported clinically relevant laboratory tests were for liver function tests (AST, ALT or total bilirubin) and renal function tests (blood urea and creatinine). The highest incidence of clinically relevant laboratory tests amongst patients with normal pre-treatment values was for ALT (4/17, 24% of subjects).

Final comments/conclusions

This study suffers from the same weaknesses as study AI411-143. The trial is non-comparative; a relatively loose definition was used for fever and neutropenia; and end of treatment, rather than end of follow-up, was used as the timepoint for assessment of clinical response. These weaknesses reflect the fact that this was a pilot trial not intended to demonstrate efficacy but rather to provide a basis for phase III studies. Thus, the overall response rates and those for patients with MDIs and FUOs in this study should not be regarded as representative of those obtained in controlled trials, which were clearly lower. In conclusion, this study may be regarded as having shown preliminary efficacy data for cefepime in the treatment of febrile neutropenic patients, and supporting the design and conduct of phase III comparative trials.

10 INTEGRATED ANALYSIS OF EFFICACY

Pooling of trials

Two of the three monotherapy trials with ceftazidime as the active control (AI411-204 and 189) had similar designs, were suitable for consistent application of a uniform set of evaluability criteria, had individual response rates which did not show unusual variability, and had comparable individual attrition rates. Thus, pooling of these studies was justifiable. The third monotherapy study, AI411-131, although sharing design features with AI411-204 and 189, differed sufficiently that pooling of this study was not felt to be justified. Study AI411-131 differed in its design (essentially a single center trial), inclusion criteria (using a definition of neutropenia of <1000 cells/μL), exclusion criteria (excluding significant classes of infected patients included in studies 189 and 204), patient demographics (a higher proportion of patients had severe or prolonged neutropenia) and conduct (a considerably lower proportion of patients in study 131 received colony stimulating factor support). Finally, study 131 was conducted considerably earlier than the other monotherapy studies and showed significantly lower response rates, which may have been related to the proportion of patients with severe or prolonged neutropenia. During the March 5, 1997 meeting of the Anti-Infective Drug Products Advisory Committee, the statistical consultant to the committee, Dr. Donald Parker stated that he would recommend against pooling study 131 with the other monotherapy trials.

When meta-analytic methods for pooling (DerSimonian and Laird 1986) were applied to studies AI411-204 and 411-189, the p-value obtained from the Breslow-Day test for heterogeneity of trials was 0.9427 (a p-value <0.05 was considered statistically significant). Therefore, these two monotherapy studies showed homogenous treatment effects and were pooled; unless otherwise indicated, pooled results from studies AI411-189 and AI411-204 will be presented below in subsequent analyses.

The combined response rates for the pooled studies in the evaluable population were 95/192 (49.5%) for cefepime and 98/176 (55.7%) for ceftazidime, with a point estimate for the difference in response rates of -6.2%. The 95% confidence interval obtained by the DerSimonian-Laird pooling procedure was $_{192,176}(-0.1663, 0.0356)_{49.5\%,55.7\%}$ for the two pooled monotherapy studies, using definition 1B. This indicates that cefepime is therapeutically equivalent to ceftazidime in the pooled population database.

Some patients were enrolled multiple times in these trials. Because episodes in the same patient may not represent independent events, analysis of first episodes in the pooled patient database was performed, as recommended in the IDSA guidelines. This analysis gave response rates of 83/164 (50.6%) for cefepime and 84/153 (54.9%) for ceftazidime in the pooled evaluable patient population, with a point estimate for the difference in response rates of -4.3%. The 95% confidence interval around the difference in response rates was $_{164,153}(-0.1591, 0.0733)_{50.6\%,54.9\%}$. This indicates that cefepime is therapeutically equivalent to ceftazidime in the pooled population database when analyzed by patient.

The two studies that had combination therapies as their active control (Study Group 2; studies AI411-118 and 137) were deemed not to be poolable on the basis of use of different comparators, different patient populations, and significantly different response rates. The p-value obtained from the Breslow-Day test was 0.0152 for these two studies. This statistically signifi-

cant result indicates that there may be trial by treatment interaction in studies AI411-118 and AI411-137, precluding pooling.

Confidence intervals for differences in response rates (for all episodes and first episodes) for individual studies, as well as the pooled monotherapy studies are shown in Figures 1A and B.

Reasons for failure

A summary of reasons for failure in the pooled evaluable database is shown in Table 10.1.

Table 10.1 Reasons for treatment failure - pooled evaluable database

Reason for failure	Cefepime (N=192)	Ceftazidime (N=176)
Persistent fever	37 (19.3%)	27 (15.3%)
Poor microbiologic response - initial isolate resistant	11 (5.7%)	11 (6.2%)
Poor microbiologic response - initial isolate susceptible	3 (1.6%)	1 (0.6%)
Death from primary infection	4 (2.1%)	7 (4.0%)
Death from secondary infection	5 (2.6%)	0
Poor clinical response	12 (6.2%)	10 (5.7%)
Bacteriologic relapse	0	0
New MDI - susceptible isolate	0	0
New MDI - resistant isolate	6 (3.1%)	9 (5.1%)
New CDI	1 (0.5%)	4 (2.3%)
New FUO	18 (9.4%)	9 (5.1%)
Total failures	**97 (50.5%)**	**78 (44.3%)**

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 the fourth; the other death was attributed to infection but occurred in the setting of fever without a documented source of infection.

Efficacy with respect to different definitions of outcome

As discussed in the reviews for the individual studies, 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. Use of this method was endorsed by the Advisory Committee at the March 5, 1997 AIDPAC meeting.

Figure 1A. 95% confidence intervals around differences in response rates analyzed by episode (i.e., all episodes). Heavy vertical bars indicate point estimates of differences in response rates between cefepime and comparator. The dashed lines indicate the therapeutic equivalence zone. The negative side of axis favors comparator; positive side favors cefepime.

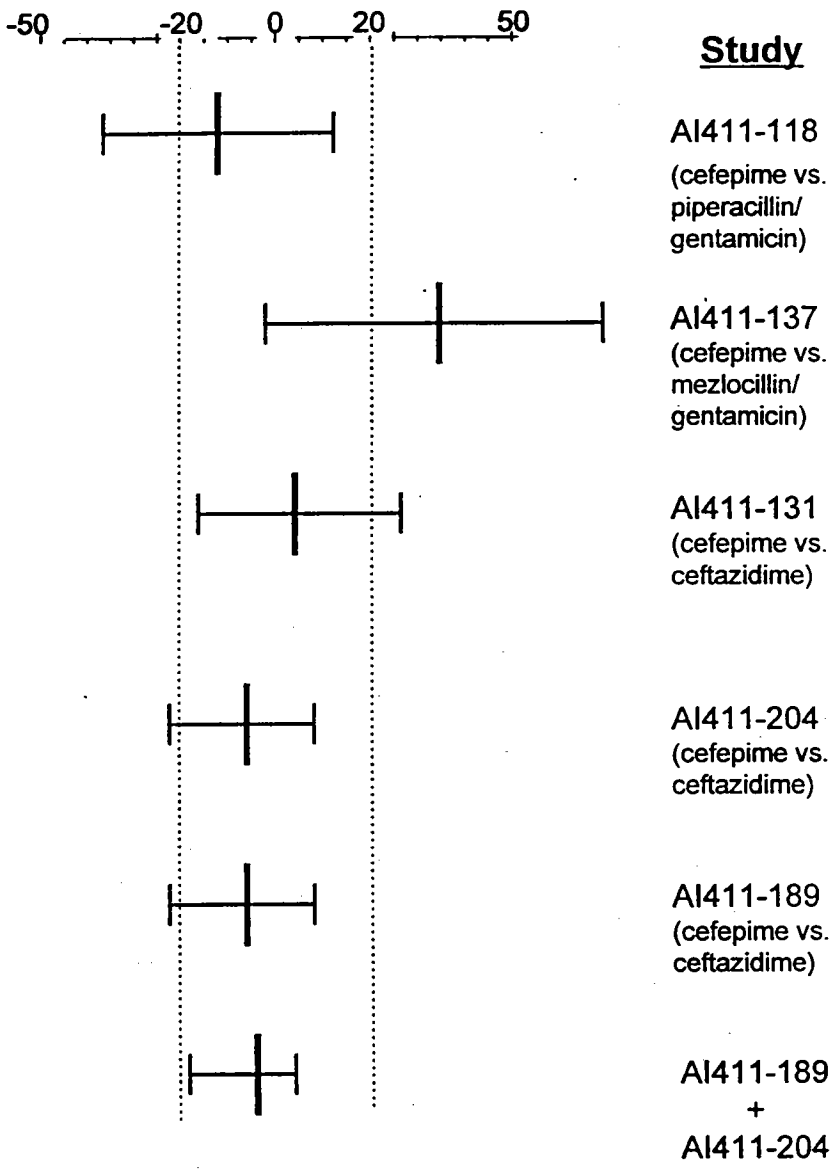
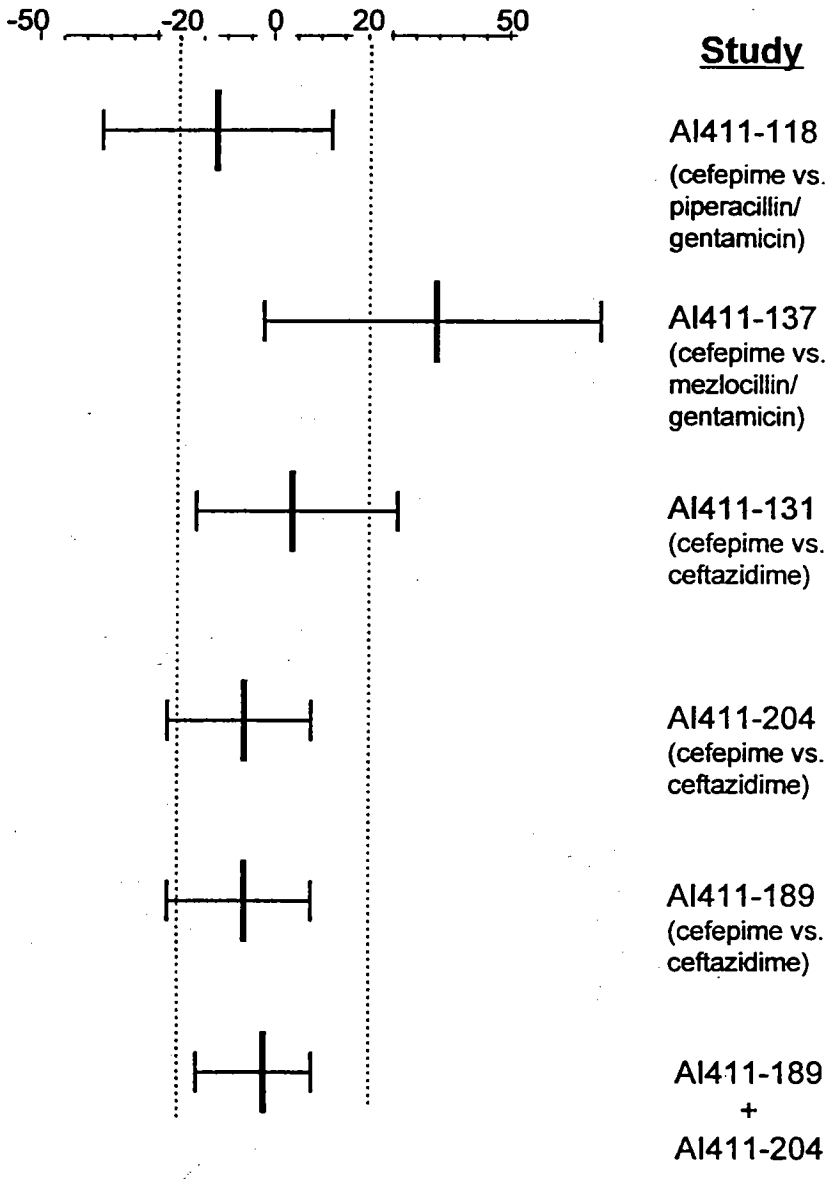


Figure 1B. 95% confidence intervals around differences in response rates analyzed by patient (i.e., first episodes only). Heavy vertical bars indicate point estimates of differences in response rates between cefepime and comparator. The dashed lines indicate the therapeutic equivalence zone. The negative side of axis favors comparator; the positive side favors cefepime.



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 10.2A and B shows response rates for these populations based on different outcome measures. Table 10.2C shows the response rates for these populations when analyzing first episodes; this analysis avoids possible confusion caused by counting events in the same patient more than once.

Table 10.2A Response rates by outcome measures - Pooled Evaluable population

Outcome	Cefepime	Ceftazidime	95% Confidence Interval
Definition 1A	67/192 (34.9%)	68/176 (38.6%)	$_{192,\ 176}(-0.1414, 0.0666)_{34.9\%,\ 38.6\%}$
Definition 1B[1]	**95/192 (49.5%)**	**98/176 (55.7%)**	$_{192,\ 176}$ **(-0.1694, 0.0453)** $_{49.5\%,\ 55.7\%}$
Definition 2A	91/192 (47.4%)	89/176 (50.6%)	$_{192,\ 176}(-0.1394, 0.0759)_{47.4\%,\ 50.6\%}$
Definition 2B	119/192 (62.0%)	119/176 (67.6%)	$_{192,\ 176}(-0.1592, 0.0465)_{62.0\%,\ 67.6\%}$
Definition 3	181/192 (94.3%)	170/176 (96.6%)	$_{192,\ 176}(-0.0711, 0.0247)_{94.3\%,\ 96.6\%}$

Table 10.2B Response rates based on different outcome measures - MITT population

Outcome	Cefepime	Ceftazidime	95% Confidence Interval
Definition 1A[2]	**67/311 (21.5%)**	**70/289 (24.2%)**	$_{311,\ 289}$**(-0.0974, 0.0438)**$_{21.5,\ 24.2\%}$
Definition 1B	96/311 (30.9%)	101/289 (34.9%)	$_{311,\ 289}(-0.1194, 0.0378)_{30.9\%,\ 34.9\%}$
Definition 2A	96/311 (30.9%)	96/289 (33.2%)	$_{311,\ 289}(-0.1016, 0.0546)_{30.9\%,\ 33.2\%}$
Definition 2B	115/311 (37.0%)	117/289 (40.5%)	$_{311,\ 289}(-0.1164, -0.0463)_{37.0\%,\ 40.5\%}$
Definition 3	294/311 (94.5%)	278/289 (96.2%)	$_{311,\ 289}(-0.0535, 0.0203)_{94.5\%,\ 96.2\%}$

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.

Table 10.2C Response rates by outcome measures - Pooled Evaluable population (first episodes)

Outcome	Cefepime	Ceftazidime	95% Confidence Interval
Definition 1A	56/164 (34.1%)	59/153 (38.6%)	$_{164,\ 153}(-0.1564, 0.0681)_{34.1\%,\ 38.6\%}$
Definition 1B[1]	**83/164 (50.6%)**	**84/153 (54.9%)**	$_{164,\ 153}$ **(-0.1591, 0.0733)** $_{50.6\%,\ 54.9\%}$
Definition 2A	75/164 (45.7%)	78/153 (51.0%)	$_{164,\ 153}(-0.1687, 0.0638)_{45.7\%,\ 51.0\%}$
Definition 2B	102/164 (62.2%)	103/153 (67.3%)	$_{164,\ 153}(-0.1626, 0.0601)_{62.2\%,\ 67.3\%}$
Definition 3	153/164 (93.3%)	148/153 (96.7%)	$_{164,\ 153}(-0.0882, 0.0195)_{93.3\%,\ 96.7\%}$

A graphical presentation of these results is shown in Figures 2A, B, and C. As expected, the response rate monotonically increased with gradual relaxation of the criteria and definition for success. For the evaluable population, cefepime was therapeutically equivalent to ceftazidime

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

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

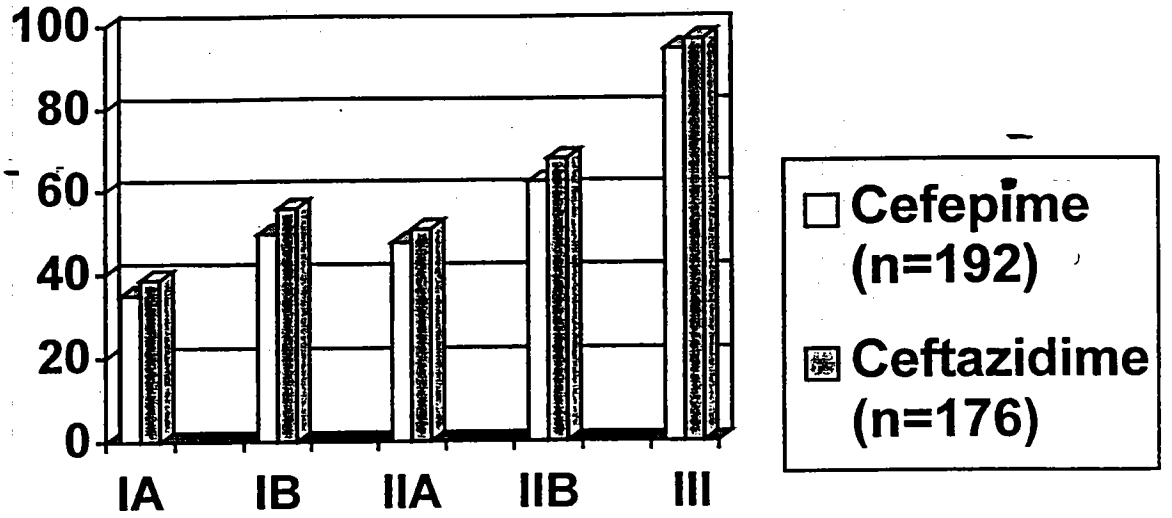


Figure 2A. Response rates for different outcome measures for all episodes in the pooled evaluable population from studies AI411-204 and AI411-189. See Table 9.3B for outcome definitions.

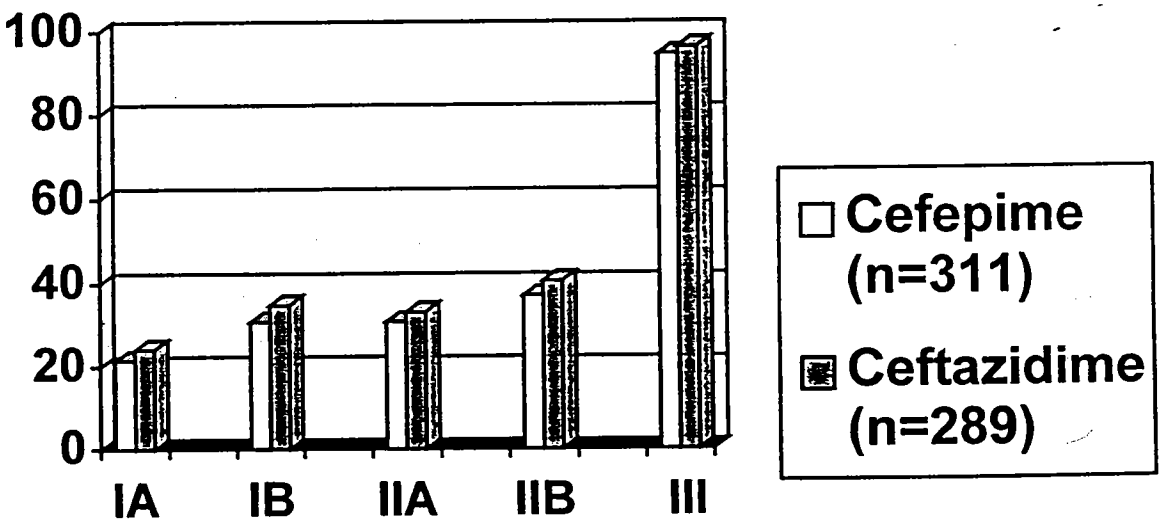


Figure 2A. Response rates for different outcome measures for all episodes in the pooled MITT population from studies AI411-204 and AI411-189. See Table 9.3B for outcome definitions.

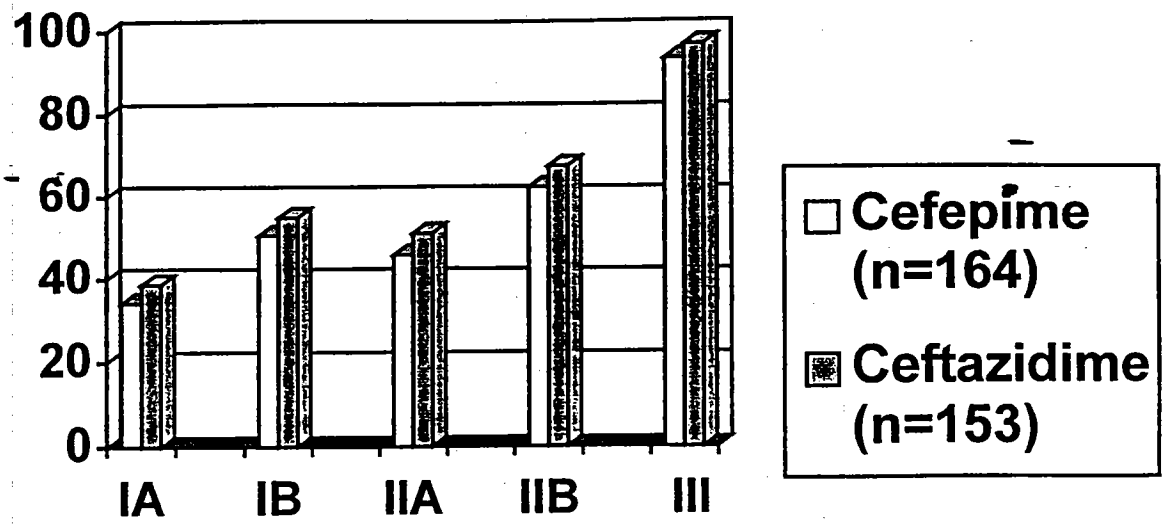


Figure 2C. Response rates for different outcome measures for first episodes in the pooled evaluable population from studies AI411-204 and AI411-189. See Table 9.3B for outcome definitions.

for all outcome definitions, whether analyzed by patient or by episode. For the MITT population, cefepime was therapeutically equivalent to ceftazidime for all definitions.

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). However, these analyses support the conclusion that cefepime is therapeutically equivalent to ceftazidime for empiric therapy of febrile neutropenic patients.

Efficacy in clinically relevant subpopulations

The Medical Officer identified a number of patient subpopulations of special clinical interest. It must be noted that the studies were neither designed nor powered to test hypotheses associated with these subpopulations defined *post hoc*. Furthermore, these subsets are not mutually exclusive nor has any adjustment in the test level been taken to account for this or the multiple comparisons bias. As noted in the previous section, these statistical results need to be interpreted with care because of the possibility that multiple *post hoc* comparisons of the data may lead to Type I errors. These comparisons are offered only as a means of ascertaining homogeneity of conclusions regardless of underlying condition(s) of patients treated. Any highly significant differences uncovered will only generate a hypothesis to be further explored for clinical importance.

Table 10.3 summarizes the efficacy of cefepime in subpopulations identified as clinically important by the Medical Officer. These analyses are based on patients deemed evaluable by the Medical Officer in the pooled monotherapy database with ceftazidime as the active control. Definition 1B was taken to be the criterion for success.

No significant difference in response rates was established between cefepime and comparator for patients with major risk factors for infection (severe or prolonged neutropenia, leukemia as the underlying disease, history of bone marrow transplantation, and presence of an indwelling catheter. With regard to severity of infection at presentation, the only physiologic variable available for subset analysis was systolic blood pressure; the subset of patients who were hypotensive (SBP < 90 mm Hg) at presentation was too small to allow statistically valid comparisons. Therapeutic equivalence between the two treatment groups was not established in patients with hematologic malignancies other than leukemia (e.g., lymphoma), patients who did not have severe neutropenia (ANC>100), and when response rates were analyzed by individual infection type. In interpreting these results, it should be emphasized that these studies were not intended or designed to demonstrate therapeutic equivalence between the treatment arms for these subpopulations.

Although the response rates are comparable between the treatment arms for these subgroups, no conclusions can be drawn with regard to therapeutic equivalence for specific subgroups, since these represent post hoc analyses, and comparability of the treatment groups when retrospectively stratified by these subgroups cannot be assured. It is, however, interesting, that patients with factors thought to represent an increased risk for infection (severe or prolonged neutropenia, presence of an indwelling catheter, a hematologic malignancy, bone marrow transplant) had lower response rates in both arms than patients without such factors.

Table 10.3: Response Rates in clinically relevant subpopulations

Subpopulation	Cefepime	Ceftazidime	95% Confidence Interval
First febrile episode only	83/164 (50.6%)	84/153 (54.9%)	$_{164,153}$ (-0.1591, 0.0733) $_{50.6\%,\ 54.9\%}$
•Patients with leukemia	30/82 (36.6%)	27/64 (42.2%)	$_{82,64}$ (-0.2296, 0.1176) $_{36.6\%,\ 42.2\%}$
•Patients with other hematologic malignancies	19/50 (38.0%)	21/41 (51.2%)	$_{50,41}$ (-0.3581, 0.0937) $_{38.0\%,\ 51.2\%}$
Patients with other hematologic diseases	1/2 (50.0%)	3/9 (33.3%)	Insufficient sample size
Patients with solid tumors	45/58 (77.6%)	47/62 (75.8%)	$_{58,62}$ (-0.1502, 0.1858) $_{77.6\%,\ 75.8\%}$
•Patients on prophylactic antibiotics	28/75 (37.3%)	28/66 (42.4%)	$_{75,66}$ (-0.2270 , 0.1252) $_{37.3\%,\ 42.4\%}$
Patients not on prophylactic antibiotics	67/117 (57.3%)	70/110 (63.6%)	$_{117,110}$ (-0.1995, 0.0721) $_{57.3\%,\ 63.6\%}$
Patients with severe neutropenia (ANC ≤ 100)	65/134 (48.5%)	67/132 (50.8%)	$_{134,132}$ (-0.1502, 0.1052) $_{48.5\%,\ 50.8\%}$
•Patients with ANC > 100	30/58 (51.7%)	31/44 (70.5%)	$_{58,44}$ (-0.3936, 0.0190) $_{51.7\%,\ 70.5\%}$
•Patients with MDIs	24/62 (38.7%)	23/54 (42.6%)	$_{62,54}$ (-0.2353, 0.1576) $_{38.7\%,\ 42.6\%}$
•Patients with CDIs	12/26 (46.2%)	11/19 (57.9%)	$_{26,19}$ (-0.4562, 0.2214) $_{46.2\%,\ 57.9\%}$
•Patients with FUOs	59/104 (56.7%)	64/103 (62.1%)	$_{104,103}$ (-0.1973, 0.0892) $_{56.7\%,\ 62.1\%}$
Patients without prolonged neutropenia (< 7 d)	64/100 (64%)	70/105 (66.7%)	$_{100,105}$ (-0.1667, 0.1134) $_{64\%,\ 66.6\%}$
•Patients with prolonged neutropenia (≥ 7 d)	31/92 (33.7%)	28/71 (39.4%)	$_{92,71}$ (-0.2191, 0.1042) $_{33.7\%,\ 39.4\%}$
•Patients with an indwelling catheter	42/112 (37.5%)	48/103 (46.6%)	$_{112,103}$ (-0.2319, 0.0499) $_{37.5\%,\ 46.6\%}$
Patients with no indwelling catheter	53/80 (66.3%)	50/73 (68.5%)	$_{80,83}$ (-0.1842, 0.1393) $_{66.3\%,\ 68.5\%}$
•Bone marrow transplant recipients	1/10 (10%)	1/7 (14.3%)	$_{10,7}$ (-0.4833, 0.3976) $_{10\%,\ 14.3\%}$
No bone marrow transplant	94/182 (51.6%)	97/169 (57.4%)	$_{182,169}$ (-0.1673, 0.0523) $_{51.6\%,\ 57.4\%}$
Patients with systolic BP <90 at entry	2/8 (25.0%)	1/2 (50.0%)	Insufficient sample size
Patients with systolic BP ≥90 at entry	93/184 (50.5%)	97/174 (55.7%)	$_{184,174}$ (-0.1343, 0.0652) $_{50.5\%,\ 55.7\%}$

[1] The 95% confidence intervals are reported as nt,nc (95% C.I.) pt,pc where nt = number in the test group, nc = number in the control group, pt = response rate in the test group, pc = response rate in the control group. • denotes lack of therapeutic equivalency between cefepime and ceftazidime in the subpopulation.