***Medical Officer's Comment***

*The duration and severity of neutropenia were greater in this study than the other studies examining cefepime monotherapy. This presumably reflects the patient population, which was made up almost entirely of bone marrow transplant recipients; such patients typically receive more intensive and myelosuppressive chemotherapy than other patients with malignancies, increasing the depth and prolonging the length of their neutropenia.*

***Statistical Reviewer's Comment***

*The two treatment arms appear to be balanced with respect to key demographic and prognostic risk factors.*

***Bone Marrow Transplantation:*** Sixty-eight subjects, equally distributed in the two treatment arms, received bone marrow transplantation, usually autologous transplants. Three subjects did not receive bone marrow transplantation: two had breast cancer and one had ANLL.

***Prophylaxis:*** Use of prophylactic antibiotics was almost universal. Only one control subject received no antibiotic prophylaxis. This subject had been transferred from an emergency room where he presented with fever and bacteremia and was immediately started on therapeutic antibiotics. Approximately 90% of subjects enrolled received at least three agents to provide prophylaxis against bacteria, fungi, and viruses.

Antibacterial: Nearly all subjects received systemic antibacterial agents, specifically, trimethoprim-sulfamethoxazole, ciprofloxacin, or both. The median duration of prophylaxis with these two antibiotics prior to the start of study therapy was 13 days (range 4-21) in the cefepime group and 13 days (range 1-18) in the control group. All antibacterial prophylaxis was stopped prior to starting study therapy with the exception of one subject whose trimethoprim-sulfamethoxazole was continued one day into therapy.

Antifungal: Nearly all subjects received non-systemic antifungal prophylaxis. These subjects received either nystatin (administered orally) or clotrimazole (frequently administered in the form of a troche) or both. One subject (cefepime group) received the combination of miconazole and nystatin. Sixty-four subjects (90%) continued antifungal prophylaxis during study therapy.

Antiviral: Nearly all subjects received acyclovir prophylaxis. Sixty-seven subjects (94%) had acyclovir continued during study therapy.

Episode evaluability

Evaluability assessment gave the results shown in Table 137.2.

Table 137.2. Episode evaluability

| | 1° evaluability criteria | | MITT evaluability criteria | |
|---|---|---|---|---|
| | FDA | Sponsor | FDA | Sponsor |
| All episodes | 32/71 (45.1%) | 40/71 (56.3%) | 71/71 (100.0%) | 69/71 (97.2%) |
| Cefepime | 17/35 (48.6%) | 19/35 (54.2%) | 35/35 (100.0%) | 34/35 (97.1%) |
| Mezlocillin/ gentamicin | 15/36 (41.7%) | 21/36 (58.3%) | 36/36 (100.0%) | 35/36 (97.2%) |

Under the FDA primary analysis, less than half of the enrolled patient population was evaluable. This resulted from use of a minimum period of 72 hours before modification for patients to be considered evaluable. Using the original protocol, with a minimum period of 48 hours, evaluability was 51/71 (71.8%) episodes overall; 25/35 (71.4%) for cefepime and 26/36 (72.2%) for mezlocillin/gentamicin.

Infectious disease diagnoses

Infectious disease diagnoses for the evaluable population, as assigned by the Medical Officer and the sponsor, are shown in Tables 137.3A and 3B.

Table 137.3A. FDA infectious disease diagnoses for evaluable population

| Infection type | Overall | Cefepime | Mezlocillin/ gentamicin | CMH p value |
|---|---|---|---|---|
| Any | 32 (100%) | 17 (100%) | 15 (100%) | 0.385 |
| MDI with bacteremia | 3 (9.4%) | 1 (5.9%) | 2 (13.3%) | |
| MDI | 4 (12.5%) | 2 (11.8%) | 2 (13.3%) | |
| CDI | 1 (3.1%) | 0 (0.0%) | 1 (6.7%) | |
| FUO | 24 (75.0%) | 14 (82.4%) | 10 (66.7%) | |

Table 137.3B. Sponsor's infectious disease diagnoses for evaluable population

| Infection type | Overall | Cefepime | Mezlocillin/ gentamicin | CMH p value |
|---|---|---|---|---|
| Any | 40 (100%) | 19 (100%) | 21 (100%) | 0.726 |
| MDI with bacteremia | 3 (7.5%) | 1 (5.3%) | 2 (9.5%) | |
| MDI | 4 (10.0%) | 2 (10.5%) | 2 (9.5%) | |
| CDI | 6 (15.0%) | 2 (10.5%) | 4 (21.1%) | |
| FUO | 27 (67.5%) | 14 (73.7%) | 13 (61.9%) | |

***Statistical Reviewer's Comment***

*The two treatment arms are balanced with respect to the infectious disease diagnoses in the evaluable population as per the FDA as well as the sponsor.*

**Efficacy analysis**

***Primary efficacy analysis:*** Overall efficacy response rates are shown in Table 137.4. With respect to efficacy in microbiologically documented infections, in the FDA analysis, none of the evaluable patients in either arm with MDIs were successfully treated; in the sponsor's analysis, one MDI patient in the mezlocillin/gentamicin arm was successfully treated but all other MDI patients failed therapy.

| Table 1B7.4 Response rates - study A011-137 | | | |
|---|---|---|---|
| **Population** | **Cefepime** | **Mezlocillin/ gentamicin** | **95% Confidence Interval** |
| FDA evaluable[1] | 8/17 (47.1%) | 2/15 (13.3%) | $_{17,15}$ (-0.0186, 0.6931) $_{47.1\%, 13.3\%}$<br>Exact 95% Confidence Interval<br>$_{17,15}$ (-0.0087, 0.6786) $_{47.1\%, 13.3\%}$ |
| FDA MITT[2] | 9/35 (25.7%) | 2/36 (5.6%) | $_{35,36}$ (0.0104, 0.3928) $_{25.7\%, 5.6\%}$<br>Exact 95% Confidence Interval<br>$_{35,36}$ (-0.0194, 0.4216) $_{25.7\%, 5.6\%}$ |
| Sponsor evaluable | 10/19 (52.6%) | 7/21 (33.3%) | $_{19,21}$ (-0.1589, 0.5449) $_{52.6\%, 33.3\%}$<br>Exact 95% Confidence Interval<br>$_{19,21}$ (-0.1321, 0.5251) $_{52.6\%, 33.3\%}$ |
| Sponsor MITT | 10/34 (29.4%) | 7/35 (20.0%) | $_{34,35}$ (-0.1374, 0.3256) $_{29.4\%, 20.0\%}$<br>Exact 95% Confidence Interval<br>$_{34,35}$ (-0.1483, 0.3378) $_{29.4\%, 20.0\%}$ |
| Original protocol[3] | 8/25 (32.0%) | 2/26 (7.7%) | $_{25,26}$ (-0.0057, 0.4919) $_{32\%, 7.7\%}$<br>Exact 95% Confidence Interval<br>$_{25,26}$ (-0.0357, 0.5101) $_{32\%, 7.7\%}$ |

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.

***Medical Officer's Comment***

*The low response rate with mezlocillin and gentamicin is surprising, given that at the time of the study this was a standard regimen for treatment of febrile neutropenic patients. It would be helpful to see the antibiotic resistance pattern for isolates at Dana-Farber Cancer Center at the time this study was conducted in order to interpret these results; if there was a high incidence of resistance to mezlocillin or aminoglycosides, then the comparator regimen may not have been an appropriate one for this institution.*

***Statistical Reviewer's Comment***

*Based on the exact confidence (the preferred test due to limited event numbers and imbalance in the data), cefepime is deemed therapeutically equivalent to mezlocillin/gentamicin as defined in the original protocol, evaluable and MITT patient popula-*

[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.

[3] Definition 1B was applied to the evaluable population defined by the original protocol, in which evaluability required 48 hours of treatment with the initial empiric regimen before assessment and modification, unless cultures revealed a resistant isolate.

*tion as per the FDA as well as the sponsor. The sample size is not adequate to ensure an acceptable level of statistical power to the inferences.*

**Safety analysis**

Two deaths occurred: one due to "alveolar hemorrhage syndrome" (cefepime group) and one due to veno-occlusive disease (control group). Neither death was related to study therapy. Serious adverse events were reported in five subjects, none were related to study therapy. Rash was the most common adverse event to cause discontinuation of study therapy. The most common adverse events probably related to study therapy were diarrhea, rash, nausea and vomiting. Diarrhea was the most common and occurred more frequently in the control group (cefepime 11/35, 31% vs. gentamicin /mezlocillin 17/36, 47%); rash occurred in one-third of subjects in both treatment groups. Of drug-related events only four were considered severe (cefepime, 2 rashes; control, 1 rash, 1 diarrhea). Among 11 cases of diarrhea tested, *C.difficile* toxin was present in only two. Laboratory abnormalities when they occurred were generally mild.

***Final comments/conclusions***

*This was a single center, randomized controlled trial comparing the efficacy of cefepime with that of the combination of mezlocillin and gentamicin in febrile neutropenic patients. The study contained 71 patients, almost all of whom had undergone bone marrow transplantation; randomization was stratified by type of bone marrow transplant.*

*Of the 71 episodes, only 32 were evaluable under the FDA analysis; this was due to the original study protocol, which mandated a change in antibiotic therapy at 48 hours for persistent fever or* Pseudomonas *infection. Patients modified at 48 hours, except for those with resistant isolates, were thus considered unevaluable under the FDA analysis. Use of the original protocol criteria by the Medical Officer led to a total of 51 episodes being considered evaluable.*

*Based on the exact confidence interval (the preferred test due to limited event numbers and imbalance in the data), cefepime is deemed therapeutically equivalent to mezlocillin/gentamicin as defined in the original protocol, and in the evaluable and MITT patient populations as per the FDA as well as the sponsor. However, the sample size is not adequate to ensure an acceptable level of statistical power to the inferences. The safety profile of cefepime in this study was at least equivalent to that of the comparator regimen, and possibly superior, given the lower incidence of diarrhea in the cefepime group.*

*Thus, this study does not prove the claim of effectiveness for this indication, particularly in the population studied (bone marrow transplant patients). It may be regarded as supportive.*

## STUDY AI411-186

### General information

**Title:** A Multi-Investigator Comparative Study of Cefepime and Ceftazidime, in Combination with Amikacin in the Treatment of Patients with Fever and Neutropenia.

***Investigators and Centers:*** See Table 186.1

***Study period:*** First subject enrolled October 10, 1992. Last subject completed therapy November 4, 1993.

***Objective:*** To evaluate the safety and efficacy of cefepime (administered at 2 g q12h) and amikacin (administered at 7.5 mg/kg q12h) versus ceftazidime (administered at 2 g q8h) and amikacin in the treatment of subjects with fever and neutropenia.

***Study design:*** A two arm, comparative, open-label, randomized (2:1) multi-center study conducted in France. Enrollment of approximately 300 subjects was planned. The actual accrual was 353 subjects at 31 sites. Each subject was treated for a single febrile episode during a period of neutropenia.

### Protocol summary

***Medical Officer's Comment***

*The trial was conducted according to a protocol designed by the Bristol-Myers Squibb Company. Amendment 1 to the protocol slightly modified one of the inclusion criteria and two of the exclusion criteria, with the intent to define better the disease treated by this protocol. Amendment 2 to the protocol modified the randomization schedule from a 1:1 cefepime:ceftazidime ratio to a 2:1 ratio, and increased the sample size from 200 to 300 subjects. Both amendments were in effect before the first subject was enrolled.*

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 >38.5°C) while neutropenic (<500 neutrophils/μL).

***Exclusion criteria:*** Subjects were to be excluded if they had a history of a serious allergy to cephalosporins or aminoglycosides; had received any systemic antimicrobial agents within the preceding 72 hours; or had previously been enrolled in this trial. Subjects were also not eligible if they were pregnant or lactating; in a state of septic shock; had chronic myelogenous leukemia in blast crisis; or were in a course of treatment for a solid malignancy, unless they had received an autologous bone marrow transplant.

Other exclusion criteria included the presence of a medically significant disease or disorder which might have a bearing on the outcome of the study; a serum creatinine ≥1.8 mg/dL; a history of gastrointestinal decontamination with a systemic antibacterial; signs and symptoms of central nervous system (CNS) infection; known seropositivity for human immunodeficiency virus; and known infection caused by pathogens which were resistant to cefepime.

Study procedures

***Treatment Group Assignment***: Subjects were randomly assigned to one of the two treatment groups (cefepime/amikacin or ceftazidime/amikacin) in a 2:1 cefepime:ceftazidime ratio.

***Medical Officer's Comment***

*The patient population was not stratified by underlying disease.*

***Study therapy:*** Cefepime was supplied in 1 gram vials and was administered intravenously at a dose of 2 g q12h. The dose could be adjusted for decreased renal function based on guidelines in the protocol. Ceftazidime was supplied in 1 or 2 gram vials, and was administered intravenously at a dose of 2 g q8h. The dose could be adjusted for decreased renal function based on guidelines in the French approved package insert.

***Medical Officer's Comment***

*The dosage for cefepime in this study was 50% lower than in the other trials. The rationale for choosing this dose was not explicitly stated in the protocol. This discrepancy between this dosage and the dosage proposed for this indication raises questions about extrapolation of safety data from this application to situations in which cefepime is used at 2 g IV q8h in combination with an aminoglycoside. In addition, comparison of efficacy rates in this study with those of other studies is problematic; one might expect lower efficacy rates, particularly for Gram-positive organisms, given that the clinical course of infected neutropenic patients depends strongly on the use of appropriate doses of antibiotics.*

Amikacin was supplied in 500 milligram vials and was administered intravenously at a dose of 7.5 mg/kg q12h. Peak and trough serum concentrations of amikacin were obtained, and the dose could be adjusted according to these peak and trough concentrations and the subject's renal function based on guidelines in the French-approved package insert.

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

- an infection caused by a bacterial pathogen which was resistant to both cefepime and ceftazidime;
- a poor clinical response, including persistence or recurrence of fever, and subjects were not likely to benefit from the use of vancomycin or antifungal medications;
- an adverse event which was serious or possibly related to study therapy;
- the subject reached an ANC >1000 neutrophils/μL, and the clinical and bacteriologic responses were satisfactory;
- intercurrent illness (e.g., new infection, new fever);
- the subject's decision not to continue participation;
- the investigator felt that he could no longer adequately carry out the requirements of the protocol;

- early results from all subjects enrolled under the protocol indicated that it would not be in the best interests of future subjects to continue enrollment; or
- administrative reasons by mutual agreement between the investigator and BMS.

***Concomitant Therapy***: Subjects were to receive study therapy without the use of other concomitant systemic antimicrobials except under defined circumstances. Antifungals and antivirals were allowed according to the routine indications in the participating centers, with the exception of prophylactic IV amphotericin B, which was not allowed because of possible febrile side effects. Vancomycin (or teicoplanin in the case of a known vancomycin hypersensitivity) could be added to the treatment regimen under the following four circumstances:

- between 48 and 72 hours of study drug dosing if the subject's fever persisted and/or the subject exhibited symptoms of clinical deterioration;
- after 72 hours of study drug dosing if the subject's fever persisted and no pathogen had been identified;
- if a methicillin-resistant (MR) *Staphylococcus* species (or another gram-positive pathogen) had been identified in at least two out of three blood cultures (from a peripheral intravenous line or central catheter) obtained at the start of the study or at Day 3 or Day 7; or
- if a methicillin-resistant pathogen (e.g., *S. aureus* or *S. epidermidis*) was judged to be the only causative organism recovered, the antibiotic regimen could be established by the investigator according to the *in vitro* susceptibility results and the clinical status of the subject.

If used, vancomycin was to be administered intravenously at a dose of 15 mg/kg every 12 hours for at least seven days, including four consecutive days without fever. Vancomycin was prepared for administration according to the approved package insert. Vancomycin could not be used alone; the administration of the other study drugs had to be prolonged until the day vancomycin was discontinued.

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

***Duration of treatment:*** Study therapy was to be continued for a minimum of seven days. Treatment could be continued either as a combination (cefepime/amikacin or ceftazidime/amikacin) or as monotherapy (cefepime or ceftazidime) for up to 21 days. Study therapy could be discontinued early for the following reasons: an infection caused by a bacterial pathogen which was resistant to study cefepime or ceftazidime; a poor clinical response (including persistence or recurrence of fever); an adverse event which was serious or possibly related to study therapy; the subject reached an ANC >1000 neutrophils/μL, and the clinical and bacteriologic responses were satisfactory; intercurrent illness; or when discontinuation of study therapy was requested by the subject.

***Pre-treatment procedures:*** All subjects had a medical history obtained which sought specific information on the underlying cancer, including cancer treatment and any history of bone marrow transplantation. Information regarding other prior medical history and underlying medical conditions was not recorded on the case report form. At the onset of fever, a complete clinical evaluation and physical examination, including documentation of temperature and other signs and symptoms of infection, and a chest X-ray were obtained.

Baseline laboratory tests were obtained within four days prior to the initiation of study therapy. Hematology tests consisted of hemoglobin, white blood cell (WBC) count with differential, absolute neutrophil count (ANC), and platelet count. Liver function tests consisted of alkaline phosphatase, aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/serum glutamate pyruvate transaminase (ALT/SGPT), and total bilirubin. Renal function tests consisted of blood urea nitrogen (BUN) and creatinine. Electrolytes consisted of sodium, potassium, calcium, and phosphorus. A urinalysis was also obtained to test for the presence of albumin and glucose, and a microscopic examination of the urine was performed if a urinary tract infection was suspected.

Prior to the initiation of therapy, at least three sets of blood cultures were drawn from different sites, and cultures were obtained from any local site suspected to be infected, including urine, skin, and throat. In the event a pulmonary infection was suspected, only adequate samples such as those obtained by a shielded bronchial brush or bronchoalveolar lavage were cultured. All causative pathogens were identified, speciated to the extent possible, and tested for susceptibility to cefepime, ceftazidime, and amikacin by either the disk diffusion or the minimal inhibitory concentration method, using the usual procedures employed at each investigator's laboratory. If using the disk diffusion method, investigators were asked to record the actual size for the zones of inhibition in millimeters in the laboratory records and on the case report form.

***During Treatment Procedures:*** All subjects were examined at least once each day by the investigator or his/her designee, or more frequently if indicated. Additional evaluations were performed as often as necessary to assess clinical status, the presence of new infections, or to evaluate any evidence of local or systemic adverse reactions. Temperature was measured several times daily (as many times as clinically indicated) from the start of therapy to posttreatment Day 4. The highest and the lowest value of each day was recorded in the case report form.

All the subjects were evaluated for efficacy on Day 3 and on Day 7 of treatment, and the results of these evaluations were entered into the case report forms. On both of these days, a clinical evaluation and an abbreviated physical examination were performed. Signs and symptoms of new infections, regardless of when they occurred, were also entered into the case report forms.

A repeat chest X-ray was obtained for subjects with pneumonia, and for subjects newly suspected of having pneumonia. On Day 3, at least two blood cultures were drawn, and repeat cultures of previously infected sites (including blood) and sites where

new infections had developed were also obtained. Additional cultures from previously or newly infected sites were obtained as necessary, until eradication was documented, or until treatment was changed. Any pathogens that were isolated were identified and tested for susceptibility to the three study antibiotics. If an appropriate specimen could not be obtained, a notation that "no source to culture" was entered into the case report form. Laboratory tests were repeated according to each investigator's judgment; the requirement was to repeat only those tests which had been abnormal at baseline.

***Post-Treatment Procedures:*** All subjects were evaluated again between the last day of therapy and Day +4 after the completion of study therapy, and also at any time that a clinical event led to a modification in antimicrobial therapy. This evaluation included a physical examination and an assessment of clinical signs and symptoms of infection. Three blood cultures were obtained, and a repeat chest X-ray was performed on all subjects with a previously abnormal chest X-ray. Cultures were performed of infected local sites in instances where an appropriate specimen could be obtained. All baseline laboratory tests were repeated. Laboratory tests which were abnormal after completion of study therapy were repeated until the abnormal values returned to the normal range, or were documented as clinically insignificant by the investigator.

**Sponsor's criteria for evaluation**

***Efficacy:*** The criteria used for evaluability and efficacy were essentially those of study AI411-189, with the exception that only three days of follow-up were required for a patient to be declared successfully treated.

***Sponsor's Safety analysis:*** Safety evaluations were performed for all subjects who received at least one dose of study therapy, and included an assessment of deaths, adverse events, including those which resulted in discontinuation of therapy, abnormal laboratory test values which developed during or following study therapy, and local tolerance to intravenous infusion of the study drugs.

***Sponsor's statistical methods:*** Safety results and pretreatment characteristics 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.

**Results**

Study population characteristics

***Demographics:*** The 31 active sites in this trial enrolled a total of 353 subjects between October 10, 1992 and November 4, 1993. For eight subjects, the actual drug combination taken was different from the randomized treatment. Seven of these subjects were randomized to ceftazidime plus amikacin, but actually received cefepime plus amikacin; one subject was randomized to cefepime plus amikacin, but actually received ceftazidime plus amikacin. Those eight subjects were analyzed according to the actual treatment, not to the assigned regimen. Of the 353 subjects, 242 were treated with the combination of cefepime and amikacin, and 111 were treated with the combination of ceftazidime and amikacin.

Table 186.1 shows enrollment by center for all patients enrolled in AI411-186;

Table 186.2 shows demographics for all patients enrolled in AI411-186.

Table 186.1 Enrollment by center (all sites in France)

| Site | Investigator | Cefepime +Amikacin | Ceftazidime +Amikacin | Total |
|---|---|---|---|---|
| 001 | Dr. Catherine Cordonnier, Hôpital Henri Mondor, Service Hématologie Clinique, Créteil | 10 | 5 | 15 |
| 002 | Dr. Alain Delmer, Hôtel Dieu, Service Hématologie,Paris | 13 | 6 | 19 |
| 003 | Dr. Véronique LeBlond Hôpital de la Pitié Salpétrière Service Hématologie Paris | 11 | 4 | 15 |
| 004 | Dr. Raoul Herbrecht , Hôpital de Hautepierre, Service Hématologie-Oncologie, Strasbourg | 24 | 12 | 36 |
| 005 | Dr. Claude Martin, C.H.G., Annecy | 1 | 0 | 1 |
| 006 | Pr. Daniel Hollard, C.H.R.U. Grenoble, Hôpital A. Michallon, Grenoble | 6 | 3 | 9 |
| 008 | Dr. Marc Simon, C.H. Valenciennes, Valenciennes | 7 | 3 | 10 |
| 009 | Dr. Gilles Auzanneau, Hôpital du Val de Grâce, Paris | 8 | 3 | 11 |
| 010 | Dr. Francis Witz, C.H.U. de Brabois, Vandoeuvre les Nancy, Nancy | 8 | 4 | 12 |
| 011 | Dr. Bruno Audhuy, Hôpital Louis Pasteur, Service Hématologie, Colmar | 6 | 2 | 8 |
| 012 | Dr. Brigitte Dupriez, C.H. Lens, Lens | 1 | 1 | 2 |
| 013 | Dr. Henri Guy, CHR de Dijon, Service Hématologie, Dijon | 1 | 1 | 2 |

Table 186.1. Enrollment by center (cont.)

| Site | Investigator | Cefepime +Amikacin | Ceftazidime +Amikacin | Total |
|---|---|---|---|---|
| 014 | Pr. Jean-Luc Harousseau, Hôtel Dieu Nantes, Service Hématologie, Nantes | 11 | 6 | 17 |
| 015 | Pr. Jean-Yves Cahn, Hôpital Jean Minjoz - C.H.U., Service Hématologie, Besançon | 2 | 2 | 4 |
| 017 | Pr. Jean-Louis Misset, Hôpital Paul Brousse, Maladies Sanguines et Tumorales, Villejuif | 3 | 0 | 3 |
| 018 | Pr. Michel LePorrier, CHRU Caen; Service Hématologie, Caen | 1 | 2 | 3 |
| 019 | Pr. Jean Briere, Hôpital Beaujon, Service Hématologie, Clichy | 5 | 3 | 8 |
| 020 | Dr. François Dreyfus, Hôpital Cochin, Service Hématologie, Paris | 9 | 4 | 13 |
| 021 | Pr. Christian Gisselbrecht, Hôpital St-Louis, Service Hématologie, Paris | 5 | 2 | 7 |
| 023 | Pr. Bernard Desablens, CHU - Hôpital SUD, Service des Maladies du Sang, Amiens | 8 | 2 | 10 |
| 026 | Dr. José-Luis Pico, Institut Gustave Roussy, Hématologie - Médecine D, Villejuif | 20 | 11 | 31 |
| 027 | Dr. Hervé Tilly, Centre Becquerel, Service d'Hématologie, Rouen | 10 | 5 | 15 |
| 028 | Pr. Denis Fiere, Centre Edouard Herriot, Service d'Hématologie, Lyon | 9 | 6 | 15 |
| 029 | Pr. Marc Boasson, C.H.U. Angers, Maladies du Sang-Médecine, Interne-Médecine D, Angers | 13 | 7 | 20 |

Table 18.1 Enrollment by center (cont.)

| Site | Investigator | Cefepime +Amikacin | Ceftazidime + Amikacin | Total |
|---|---|---|---|---|
| 030 | Pr. Jean-Albert Gasteau, Institut J. Paoli - I. Calmettes, Service d'Hématologie Générale, Marseille | 7 | 3 | 10 |
| 031 | Dr. Bernard Pignon, CHRU de Reims, Hôpital Robert Debré, Clinique Médicale - Maladies du Sang, Reims | 8 | 2 | 10 |
| 032 | Pr. Philippe Colombat, CHU Bretonneau, Service d'Hématologie, Tours | 13 | 4 | 17 |
| 033 | Pr. Denis Guyotat, Hôpital Nord, CHRU de St-Etienne, St-Etienne | 4 | 2 | 6 |
| 034 | Pr. Jacques Pris, CHU Hôpital de Purpan, Service d'Hématologie, Toulouse | 7 | 3 | 10 |
| 035 | Pr. Josy Reiffers, CHRU Bordeaux, Service des Maladies du Sang, Groupe Hospitalier Sud, Pessac | 4 | 2 | 6 |
| 036 | Dr. Pierre Biron, Centre Léon Bérard, Département de Chimiothérapie et de Greffe de Moëlle, Lyon | 7 | 1 | 8 |
| **Total** | | **242** | **111** | **353** |

***Statistical Reviewer's Comment***

*Of the 31 centers participating in this study, only 2 centers enrolled more than 10 patients per treatment arm as recommended by the DAIDP Points to Consider document.*

| Table 1862. Demographics - all patients enrolled in AI911-486 | | | | |
|---|---|---|---|---|
| | **Overall** | **Cefepime** | **Ceftazidime** | **p value** |
| Total | 353 | 242 | 111 | |
| Age | | | | 0.718 |
| Mean (y) | 44.7 ± 13.7 | 44.6 ± 13.5 | 44.9 ± 14.1 | |
| Range (y) | | | | |
| ≥ 65 y | 26 (7.4%) | 17 (7.0%) | 9 (8.1%) | |
| < 65 y | 327 (92.6%) | 225(93.0%) | 102 (91.9%) | |
| Sex | | | | 0.646 |
| Male | 194 (55.0%) | 131 (54.1%) | 63 (56.8%) | |
| Female | 159 (45.0%) | 111 (45.9%) | 48 (43.2%) | |
| Race | Data were not collected on the racial composition of the population. | | | |
| Underlying disease | | | | |
| Leukemia | 207 (58.6%) | 142 (58.7%) | 65 (58.6%) | 0.936 |
| OHM | 129 (36.5%) | 88 (36.4%) | 41 (36.9%) | |
| OHD | 2 (0.6%) | 2 (0.8%) | 0 (0.0%) | |
| Solid tumor | 15 (4.2%) | 10 (4.1%) | 5 (4.5%) | |
| ANC nadir | | | | |
| Mean | 68.6 ± 95.5 | 72.9 ± 103.1 | 59.4 ± 75.7 | 0.469 |
| ≤100 | 298 (84.4%) | 202 (83.5%) | 96 (86.5%) | |
| >100 | 55 (15.6%) | 40 (16.5%) | 15 (13.5%) | |
| Duration ANC≤500 | | | | |
| Mean (d) | 16.9 ± 12.1 | 17.9 ± 13.0 | 14.7 ± 9.6 | 0.903 |
| <7 d | 56 (15.9%) | 38 (15.7%) | 18 (16.2%) | |
| ≥7 d | 297 (84.1%) | 204 (84.3%) | 93 (83.8%) | |
| Bone marrow graft | 144 (40.8%) | 97 (40.1%) | 47 (42.3%) | |
| Indwelling catheter | 331 (93.8%) | 226 (72.0%) | 105 (71.4%) | |
| Prophylactic Abx | 288 (81.6%) | 202 (83.5%) | 86 (77.5%) | |
| Multiple enrollments | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | |
| SBP <90 at entry | No data provided by sponsor | | | |

***Statistical Reviewer's Comment***

*The two treatment arms are balanced with respect to key demographic and prognostic risk factors at baseline.*

***Antimicrobial prophylaxis:*** Two hundred (83 percent) of the subjects in the cefepime treatment group and 78 (70 percent) of the subjects in the ceftazidime treatment group

were administered systemic antimicrobial prophylaxis in the three-day period prior to the onset of study therapy (Table 186.3). It consisted of single antimicrobials in 44 (18 percent) cefepime and 14 (13 percent) ceftazidime subjects, and multiple antimicrobials in 156 (64 percent) cefepime and 64 (58 percent) ceftazidime subjects. The particular parenteral agents employed were the choice of the individual investigators.

Almost two thirds of the subjects received antibacterials, which were used in 161 (67 percent) of cefepime subjects and 67 (60 percent) of ceftazidime subjects. Antibacterials were administered as single agents in approximately one in seven subjects (cefepime 13 percent; ceftazidime 15 percent). The most commonly used single antibacterial agent was colistin, which was administered to 25 (10 percent) of cefepime and 10 (9 percent) of ceftazidime subjects. Various aminoglycosides (tobramycin, netilmicin, amikacin, and gentamicin) were used in five (2 percent) of cefepime subjects and four (4 percent) of ceftazidime subjects. Other single agents included phenoxymethylpenicillin, rifampin, amoxicillin/clavulanate, lincomycin, and vancomycin; these comprised the remainder of the antibacterials used. Neither trimethoprim/sulfamethoxazole nor any quinolones were used as single-agent prophylaxis.

Combinations of antibacterials were administered to approximately half of all subjects (cefepime 53 percent; ceftazidime 45 percent). The combinations employed were numerous; the most common one was a combination of colistin, tobramycin, and vancomycin, administered to 12 percent of the subjects in both treatment groups. Colistin was part of the antimicrobial prophylaxis in 55 (23 percent) cefepime and 23 (21 percent) ceftazidime subjects. An aminoglycoside was part of the combination in over 85% of the subjects in both treatment groups (cefepime: 39/45, 87 percent; ceftazidime: 12/14, 86 percent). Trimethoprim/sulfamethoxazole was used only a single time in combination, in a cefepime subject. The only quinolone employed in prophylaxis was ciprofloxacin, also used only a single time, in a cefepime subject.

Antifungals were used in nearly one-third of the subjects, with 77 (32 percent) cefepime and 36 (32 percent) ceftazidime subjects receiving these agents (Table 8). Antifungals were administered as single agents in most instances; only six (2 percent) cefepime and five (5 percent) ceftazidime subjects received combinations of antifungals. The most common single antifungal used in cefepime subjects was fluconazole (17 percent), followed by amphotericin B (9 percent); these two agents were used at similar frequencies (12 percent and 14 percent, respectively) in ceftazidime subjects. Miconazole, itraconazole, and flucytosine were the remaining antifungals used as single agents.

Antivirals were administered to 67 (28 percent) cefepime and 27 (24 percent) ceftazidime subjects. Acyclovir was the sole antiviral used for this purpose.

| Table 136.3. Pretreatment Systemic Antimicrobial Prophylaxis | | | |
|---|---|---|---|
| | Number (%) of Subjects | | |
| | Cefepime/ Amikacin (N=242) | Ceftazidime/ Amikacin (N=111) | Total (N=353) |
| **Any Prophylaxis**[a] | 200 (83) | 78 (70) | 278 (79) |
| | | | |
| *Any Antibacterial* | 161 (67) | 67 (60) | 228 (65) |
| Single Agents | 32 (13) | 17 (15) | 49 (14) |
| Colistin | 25 (10) | 10 (9) | 35 (10) |
| Aminoglycosides | 5 (2) | 4 (4) | 9 (3) |
| Others | 2 (<1) | 3 (3) | 5 (1) |
| Combinations of Antibacterials | 129 (53) | 50 (45) | 179 (51) |
| COL, TOB, VAN | 29 (12) | 13 (12) | 42 (12) |
| COL + Others | 55 (23) | 23 (21) | 78 (22) |
| Other combinations | 45 (19) | 14 (13) | 59 (17) |
| | | | |
| *Any Antifungal* | 77 (32) | 36 (32) | 113 (32) |
| Single Agents | 71 (29) | 31 (28) | 102 (29) |
| Fluconazole | 41 (17) | 13 (12) | 54 (15) |
| Amphotericin B | 22 (9) | 16 (14) | 38 (11) |
| Others | 8 (3) | 2 (2) | 10 (3) |
| | | | |
| Combinations of Antifungals | 6 (2) | 5 (5) | 11 (3) |
| | | | |
| Any Antiviral | 67 (28) | 27 (24) | 94 (27) |
| Acyclovir (ACV) | 67 (28) | 27 (24) | 94 (27) |

COL = Colistin; TOB = Tobramycin; VAN = Vancomycin.

[a] A subject could have received more than one prophylactic pretreatment systemic antimicrobial agent.

Pretreatment non-systemic antimicrobials were also administered orally to 126 (52 percent) cefepime and 57 (51 percent) ceftazidime subjects in an attempt to de-

contaminate the gastrointestinal tract. Forty percent of all subjects in both treatment groups received single oral antimicrobials as prophylaxis, while 12 percent in both groups received more than one oral agent.

Antibacterials were administered to only a small number of subjects, and always as single agents. Neomycin was the most common antibacterial selected, employed in 26 (11 percent) cefepime and 10 (9 percent) ceftazidime subjects. In contrast, antifungals were used in approximately half of all subjects, in most cases as a single agent. Oral amphotericin B was the antifungal most frequently selected, employed in 42 percent of the subjects in both treatment groups. Nystatin alone was used in a small number of subjects, and the combination of amphotericin B and nystatin was likewise administered to a few subjects.

***Medical Officer's Comment***

*The prophylaxis practices in this study make interpretation of any response rates problematic. The efficacy of prophylaxis against infection in this setting has not been demonstrated, and the use of parenteral antibiotics as prophylaxis, especially when continued during therapy, confuses interpretation of efficacy. Use of this sort of prophylaxis prevents attribution of a therapeutic effect to the study regimen alone, thereby preventing strong conclusions as to the efficacy of the study regimen. Furthermore, from a regulatory perspective, it is not clear how drugs studied under these conditions should be labeled, except perhaps with multiple qualifiers as to their use (e.g., 'efficacy shown only in the setting of prophylaxis with the following regimens'). The IDSA guidelines recommend that if patients on prophylaxis are enrolled into a study of empiric therapy of febrile neutropenia, then all patients should be on the same, identifiable regimen. Failing that, such patients should be stratified or excluded. Since a wide variety of prophylactic regimens were used, without stratification, the analysis performed by the Medical Officer excluded these patients.*

Use of colony stimulating factors was similar between treatment groups.

**Episode evaluability**

Evaluability assessment gave the results shown in Table 186.4. The investigator's assessment of evaluability, as used on the case report tabulation, was used

Table 186.4. Episode evaluability

| | 1° evaluability criteria | | MITT evaluability criteria | |
|---|---|---|---|---|
| | FDA | Sponsor | FDA | Sponsor |
| All episodes | 85/353 (24.1%) | 344/353 (97.5%) | 332/353 (94.0%) | — |
| Cefepime | 63/242 (26.0%) | 233/242 (96.2%) | 225/242 (93.0%) | — |
| Ceftazidime | 22/111 (19.8%) | 111/111 (100.0%) | 107/111 (96.4%) | — |

The most common reason for exclusion in both arms was administration of parenteral antibiotics within 72 hours of study entry, with 45% of the patients in the cefepime arm and 50% in the ceftazidime arm being excluded for this reason. The parenteral antibiotics generally consisted of an aminoglycoside and/or vancomycin as part of

a prophylactic regimen, and were in most cases continued through the duration of treatment with study drug. Such patients were excluded from analysis on the grounds that the treatment effect provided by the empiric regimen could not be distinguished from that of the superimposed parenteral prophylactic regimen. The second most common reason was early modification (18.2% in the cefepime arm and 10.8% in the ceftazidime arm).

Infectious Disease diagnoses

Tables 186.5A and 5B shows infectious disease diagnoses assigned by the Medical Officer and the sponsor, respectively.

Table 186.5A, FDA infectious disease diagnoses for evaluable population

| Infection type | Overall | Cefepime | Ceftazidime | CMH p value |
|---|---|---|---|---|
| Any | 85 (100%) | 63 (100%) | 22 (100%) | 0.488 |
| MDI with bacteremia | 25 (29.4%) | 21 (33.3%) | 4 (18.2%) | |
| MDI | 3 (3.5%) | 1 (1.6%) | 2 (9.1%) | |
| CDI | 7 (8.2%) | 4 (6.3%) | 3 (13.6%) | |
| FUO | 50 (58.8%) | 37 (58.7%) | 13 (59.1%) | |

Table 186.5B, Sponsor's infectious disease diagnoses for evaluable population

| Infection type | Overall | Cefepime | Ceftazidime | CMH p value |
|---|---|---|---|---|
| Any | 344 (100%) | 233 (100%) | 111 (100%) | 0.315 |
| MDI with bacteremia | 94 (27.3%) | 69 (29.6%) | 25 (22.5%) | |
| MDI | 9 (2.6%) | 5 (2.1%) | 4 (3.6%) | |
| CDI | 27 (7.8%) | 16 (6.9%) | 11 (9.9%) | |
| FUO | 214 (62.2%) | 143 (61.3%) | 71 (64.0%) | |

***Statistical Reviewer's Comment***

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

***Medical Officer's Comment***

*As with the other studies, fevers of uncertain origin made up the majority of febrile episodes. The differences between the proportion of febrile episodes in the ceftazidime arm classified as bacteremias by the Medical Officer and the proportion classified as such by the sponsor is due largely to the approach used for positive blood cultures for coagulase-negative staphylococci. For a febrile episode to be classified as being due to bacteremia with coagulase-negative staphylococci, at least two positive cultures (with all isolates showing the same antibiotic susceptibilities) within a 2 day period were required for this diagnosis, or a positive blood culture and a positive catheter tip culture. These criteria were applied consistently by the Medical Officer; for reasons that are unclear, some febrile episodes for which there was only one positive blood culture were classified*

*as coagulase-negative staphylococcal bacteremias by the sponsor. The Medical Officer treated such isolated positive cultures as reflecting growth of skin contaminants, and these episodes were scored according to the clinical data at hand. Most such episodes were rescored by the Medical Officer as FUOs.*

**Efficacy analysis**

***Primary efficacy analysis:*** Tables 186.6A and 6B show overall response rates and response rates for MDIs, respectively.

**Table 186.6A Response rates - study A4111-186**

| Population | Cefepime | Ceftazidime | 95% Confidence Interval |
|---|---|---|---|
| FDA evaluable[1] | 16/63 (25.4%) | 7/22 (31.8%) | $_{63,22}$ (-0.3172, 0.1888) $_{25.4\%, 31.8\%}$ |
| FDA MITT[2] | 28/225 (12.4%) | 14/107 (13.1%) | $_{225,107}$ (-0.0904, 0.0776) $_{12.4\%, 13.1\%}$ |
| Sponsor evaluable | 61/233 (26.2%) | 25/111 (22.5%) | $_{233,111}$ (-0.0661, 0.1393) $_{26.2\%, 22.5\%}$ |

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.

**Table 186.6B MDI Response rates - study A4111-186**

| Population | Cefepime | Ceftazidime | 95% Confidence Interval |
|---|---|---|---|
| FDA evaluable | 5/22 (22.7%) | 1/6 (16.7%) | $_{22,6}$ (-0.3913, 0.5125) $_{22.7\%, 16.7\%}$<br>Exact 95% Confidence Interval<br>$_{22,6}$ (-0.3984, 0.4747) $_{22.7\%, 16.7\%}$ |
| Sponsor | 17/74 (23.0%) | 5/29 (17.2%) | $_{74,29}$ (-0.1343, 0.2489) $_{23.0\%, 17.2\%}$<br>Exact 95% Confidence Interval<br>$_{74,29}$ (-0.1552, 0.2550) $_{23.0\%, 17.2\%}$ |

*Medical Officer's Comment*

*Because of the large number of excluded patients, these results do not show therapeutic equivalence between cefepime combination therapy and ceftazidime combination therapy. The confidence interval obtained in the primary FDA analysis and the sponsor's analysis were considerably different, with the FDA confidence interval being relatively wide and the sponsor's quite narrow. This result reflects the difference in the number of evaluable episodes between the two analyses; in the sponsor's analysis, the higher number of evaluable episodes led to a narrower confidence interval. It is worth*

[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.

*noting that in the sponsor's analysis, the proportion of enrolled patients deemed evaluable for efficacy was extremely high, at 97.5% (see Table 186.4).*

*In addition, in the primary FDA analysis, there was a substantial difference in the response rates for all infections and for microbiologically documented infections in the ceftazidime arm. This probably reflects the small number of evaluable MDIs in the ceftazidime arm; had one additional evaluable MDI been successfully treated in the ceftazidime arm, the overall and MDI response rates would have been similar.*

***Statistical Reviewer's Comment***

*For overall response rates, cefepime combination therapy fails to establish therapeutic equivalence with ceftazidime combination therapy in the FDA evaluable database. The two treatments are therapeutically equivalent in the FDA MITT and the evaluable patient population as per the sponsor.*

*The sample sizes of patients who had microbiologically documented infections were inadequate to ensure that statistical inferences had adequate power. Due to paucity and imbalance of the data, exact confidence intervals were used. Cefepime combination therapy fails to establish therapeutic equivalence to ceftazidime combination therapy on the evaluable patients defined by the FDA. The two treatments are deemed therapeutically equivalent in the evaluable database defined by the sponsor.*

**Safety analysis**

Seventeen deaths occurred within the 30-day period after study treatment ended; none occurred during treatment. None of the deaths were considered related to study therapy. Although over two-thirds of all subjects experienced one or more adverse events, the vast majority of these were considered to be unrelated or of unknown relationship to study therapy.

Serious adverse events occurred in 21 (9 percent) cefepime and four (4 percent) ceftazidime subjects; this difference was not statistically significant. All were considered unrelated to study therapy except for a single case of abnormal kidney function in a cefepime subject, and a single case of fever in a ceftazidime subject. Laboratory abnormalities were generally mild, and occurred with equal frequency in both treatment groups. No subject was reported to have developed local intolerance to intravenous infusion of the study medications.

***Final comments/conclusions***

*This was a large, randomized multi-center trial comparing cefepime in combination with amikacin with ceftazidime with amikacin for empiric therapy of febrile neutropenia. Notable features of this trial include the use of a cefepime dose lower than that proposed by the sponsor in their labeling, as well as the extensive use of parenteral antibiotics for antimicrobial prophylaxis.*

*The study accrued 353 patients, representing 353 episodes of febrile neutropenia. However, many of these episodes were unevaluable because of use of parenteral antibiotics for prophylaxis, modification prior to 72 hours, and lack of follow-up data. As a result, only 85 episodes were considered evaluable by the Medical Officer.*

*Response rates in the evaluable population were comparable between the cefepime and control arms. On overall response rates, cefepime combination therapy fails to establish therapeutic equivalence with ceftazidime combination therapy in the FDA evaluable database. The two treatments are therapeutically equivalent in the FDA MITT and the evaluable patient population as per the sponsor. The sample sizes of patients who had microbiologically documented infection were inadequate to ensure that statistical inferences had adequate power. Due to paucity and imbalance of the data, exact confidence intervals were used. Cefepime combination therapy fails to establish therapeutic equivalence to ceftazidime combination therapy on the evaluable patients defined by the FDA. The two treatments are deemed therapeutically equivalent in the evaluable database defined by the sponsor.*

*The differences in conclusions reached by the sponsor and the Medical Officer with respect to therapeutic equivalence result from dramatic differences in the number of evaluable episodes. Almost three-quarters of the patients enrolled were deemed unevaluable by the Medical Officer, frequently because of concomitant administration of parenteral antibiotics. In contrast, the sponsor found virtually all of the enrolled patients to be evaluable for efficacy, even those for whom no follow-up data was provided; thus, from a practical point of view the sponsor's evaluable patient population actually represented an intent-to-treat analysis. The greater number of evaluable episodes in the sponsor's analysis thus led to a narrower confidence interval, allowing the conclusion of therapeutic equivalence to be drawn. In agreement with this, the FDA MITT analysis also showed therapeutic equivalence.*

*Thus, these discordant results reflect very different approaches to the determination of evaluability. Although the MITT approach allows one to conclude that the arms are therapeutically equivalent, it does so by inflating the number of evaluable episodes and narrowing the confidence interval; in this approach true treatment failures may be diluted by the presence of patients scored as failures due to lack of follow-up data. Given the non-standard nature (relative to clinical practice in the U. S.) of the prophylactic regimens used, and the impossibility of determining whether relapses occurred following therapy when no follow-up data were provided, 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 amikacin is not equivalent to ceftazidime in combination with amikacin.*

*The safety profile of cefepime in combination with amikacin 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 an aminoglycoside 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 an aminoglycoside.*

## STUDY AI411-198

### General Information

***Title:*** A Multicenter, Randomized, Prospective, Comparative Study of Cefepime Plus Vancomycin Versus Ceftazidime Plus Vancomycin as Empiric Therapy in the Treatment of Febrile Episodes in Granulocytopenic Patients With Hematological Malignancies

***Investigators:*** Dr. Michel Aoun
Dr. M. A. Boogaerts
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***Study centers:***

| | |
|---|---|
| Site 001 | Gasthuisberg Leuven (Boogaerts)<br>Leuven, Belgium |
| Site 002 | Akademisch Ziekenhuis V.U.B. (Schots)<br>Brussels, Belgium |
| Site 003 | Cliniques Universitaires UCL de Mont-Godinnes (Bosly)<br>Yvoir, Belgium |
| Site 004 | Institut Jules Bordet (Aoun)<br>Brussels, Belgium |

***Study period:*** First subject enrolled 3 February 1993; last subject completed therapy 21 February 1994.

***Objectives:*** To evaluate the safety and clinical efficacy of cefepime, 2 g q8h, plus vancomycin, 30 mg/kg/day compared with ceftazidime, 2 g q8h, plus vancomycin, 30 mg/kg/day, as empiric therapy in the treatment of febrile neutropenic episodes.

***Study design:*** A multicenter, open, randomized (1:1), prospective clinical trial conducted in Belgium. One hundred and eleven subjects were treated for a total of 128 febrile episodes at the four study sites. There were 53 subjects in the cefepime/vancomycin group and 58 in the ceftazidime/vancomycin group

### Protocol summary

Study population

***Diagnosis and main criteria for inclusion:*** Adult men and women (negative pregnancy test required for women of childbearing potential), 18 years or older, were eligible for enrollment if they presented with an absolute neutrophil count (ANC) <500/μL in association with a hematologic malignancy and a fever (temperature >38.5°C **or** two temperatures of >38.0°C occurring at least 30 minutes apart **or** a temperature >38.0°C with chills).

***Exclusion criteria:*** Subjects were to be excluded if they had a history of a serious allergy to cephalosporins or vancomycin or had received other parenteral antimicrobials within 72 hours of enrollment. Entry into the study more than once during a single neutropenic episode or less than seven days since recovery from the most recent episode of neutro-

penia was not allowed. Subjects were not eligible if they were pregnant or lactating. Other exclusion criteria included a serum creatinine >2 mg/dL, confirmed or suspected HIV infection, and a history of fever related to the use of blood products. Subjects with a high probability of mortality within 48 hours were also to be excluded, as were subjects who were likely to require long-term (>28 days) antimicrobial therapy for treatment of clinical symptoms or eradication of the causative pathogen(s).

***Treatment assignment:*** Subjects were assigned to receive either cefepime or ceftazidime, to be given together with vancomycin, according to a computer-generated randomization schedule (1 cefepime: 1 ceftazidime). Subject numbers were assigned sequentially starting with the lowest number in the block of sealed envelopes assigned to the study center. Identification of the treatment was contained in the sealed envelope. The envelope was to be opened only after a subject had met all the inclusion/exclusion criteria and had been enrolled in the study.

***Study therapy:*** Vials containing cefepime powder were supplied by Bristol-Myers Squibb. Cefepime was reconstituted in the vial using sterile water, and then further diluted with sterile isotonic saline. The drug was administered intravenously over a 30 minute period at a dose of 2 grams every 8 hours. The guidelines for dose adjustment for renal impairment were specified in the protocol. Subjects with a baseline creatinine >2.0 mg/dL were excluded from the study.

Ceftazidime was purchased commercially. Ceftazidime infusions were prepared according to instructions in the approved package insert. The drug was administered intravenously at a dose of 2 grams every 8 hours.

Vancomycin was purchased commercially. Vancomycin infusions were prepared according to instructions in the approved package insert. The drug was administered intravenously at a dose of 30 mg/kg/day in three divided doses, via a separate IV route from cefepime and ceftazidime.

***Medical Officer's Comment***

*The protocol does not indicate whether the dosage of ceftazidime or vancomycin was adjusted for renal insufficiency.*

***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. The investigator assessed subjects at 48-72h of therapy. If a subject was stable or improved at this time, the treatment regimen was to be continued for at least 4 consecutive days beyond resolution of fever; the total duration of treatment was not to exceed 28 days. If a subject's condition at 48-72h was worsening, the investigator was to decide how the treatment regimen should be modified. Any change in, or addition to, the treatment regimen depended on the results of pre-therapy cultures and the subject's clinical status. The modified regimen was to be continued for at least four consecutive days beyond resolution of fever.

***Discontinuation of Therapy:*** Study therapy could be prematurely discontinued for any of the following reasons:

- Resistance of the pathogen to the study drug(s) received;

- Adverse events;
- Intercurrent illness;
- Administrative reasons;
- Subject's decision not to participate any further; or
- If, in the investigator's opinion, it was in the best interest of the subject.

Subjects experiencing adverse events that resulted in treatment discontinuation were to be followed until the identified event had resolved or stabilized.

***Concomitant Therapy:*** Subjects were to receive study therapy without other systemic antimicrobials for 48-72 hours, at which time the clinical outcome was evaluated. If the subject was stable or improved at the time of the 48-72h evaluation, the empiric regimen was continued for at least four consecutive days beyond resolution of fever, with total duration of treatment not to exceed 28 days. If the subject's condition was worsening at 48-72h, the investigator decided how the empiric regimen should be modified, basing any changes on the results of pre-therapy cultures and the subject's clinical status. Any changes in therapy were to be recorded on the case report form. The modified regimen was to be continued for at least four consecutive days beyond resolution of fever. Medications other than anti-infective agents were administered as indicated and were also recorded on the subject's case report form.

Although not specifically addressed in the protocol, prophylaxis started pre-study, such as a fluoroquinolone, itraconazole, or acyclovir, was frequently continued during the study period.

***Study therapy:*** Cefepime was supplied as a dry fill in vials containing 1000 mg of cefepime per vial and administered intravenously at a dose of 2 g q8h. Both ceftazidime and vancomycin were purchased commercially and the lot numbers were not recorded. Ceftazidime was administered intravenously at a dose of 2 g q8h; vancomycin was given intravenously at a dose of 30 mg/kg/day in three divided doses.

***Duration of treatment:*** Study therapy was to be continued based on the response of the subject's fever and other signs and symptoms of infection. The investigator assessed subjects at 48-72h of therapy; if a subject was stable or improved at this time, the treatment regimen was to be continued for at least 4 consecutive days beyond resolution of fever. The total duration of treatment was not to exceed 28 days.

***Pretreatment Procedures***: A complete medical history assessing both past and present health status was obtained on all subjects entering the study (Table 1). A physical examination, including documentation of temperature, vital signs, and evaluation of any signs and symptoms of infection was performed. Several laboratory tests were to be performed within 48 hours of therapy initiation. These included a CBC with differential, liver function tests (total bilirubin, alkaline phosphatase, AST and ALT), serum electrolytes, blood urea and creatinine, and a urinalysis. A chest radiograph was also performed.

Bacteriologic confirmation of infection was attempted by culturing blood or any other suspected infected site. Cultures taken up to 72 hours before the start of study therapy were accepted as long as no other antimicrobial therapy was given between the time

of pre-therapy cultures and initiation of study drug. Any isolated pathogen felt to be causative was tested for *in vitro* susceptibility to the study drugs using either disk diffusion or minimum inhibitory concentration methods.

***During treatment procedures:*** A physical examination and clinical evaluation of signs and symptoms was performed on every subject once a day. In the event of persistent fever, blood cultures were taken every day. When bacteremia was present, blood cultures were repeated until they were negative. Laboratory tests were done three times a week. Bacterial culture and susceptibility testing was to be recorded at least once a week, as was an assessment of endogenous bowel flora. Chest radiographs were repeated as clinically indicated.

***Posttreatment Procedures:*** Each subject was to be evaluated both on the last day of therapy and during the posttreatment period (Day 1 to Day 14 after treatment). The end-of-treatment evaluation consisted of a physical examination, including vital signs, a clinical assessment of signs and symptoms of infection, culture and susceptibility testing when appropriate specimens could be obtained, a chest radiograph if clinically indicated, and laboratory tests. The posttreatment evaluation included an assessment of signs, symptoms, and temperature, a culture and susceptibility testing of infected sites, if appropriate material was available.

There was one amendment made to the protocol during the course of the study. This amendment changed the duration of empiric therapy prior to evaluation from 72-96 hours to 48-72 hours.

*Medical Officer's Comment*

*The rationale for this change was not stated explicitly in the protocol. In general, a fixed assessment time would be preferable to avoid bias, given that this was an unblinded study.*

**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 after study therapy.

***Sponsor's Statistical methods:*** The primary analysis was performed for the first febrile episode. Safety results and pretreatment characteristics 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 analysis was performed. A supplemental analysis was produced for all treatment courses. No formal statistical testing was conducted.