## STUDY AI411-189

### General information

***Title:*** A Multicenter Comparative Study of Cefepime vs. Ceftazidime as Empiric Therapy in the Treatment of Febrile Episodes in Neutropenic Patients.

***Objective:*** To evaluate the clinical efficacy and safety of cefepime administered at a dose of 2 grams every eight hours in comparison to ceftazidime administered at a dose of 2 grams every eight hours as empiric treatment of febrile episodes in neutropenic subjects ≥ 16 years of age.

***Investigators/Study Centers:*** See Table 189.2.

***Study design:*** This was a multi-center, open-label, comparative, randomized (1:1) clinical trial conducted in Europe. A sample size of 120 subjects (60 per treatment arm) was originally planned as sufficient to rule out a difference in clinical response rate of >21% between treatment groups with 80% power. During the course of the study, it was decided to exceed this target of 120 in order to provide for more meaningful statistical comparisons and to extend the experience with cefepime in this indication.

***Study period:*** First subject enrolled February 20, 1993. Last subject completed therapy June 28, 1995.

### Protocol summary

*Medical Officer's Comment*

*According to the study report, the original protocol was amended five times as follows. Amendment #1, which applied to all study sites, clarified that no new antibacterial, antifungal or antiviral agent should be initiated during the first 72-96 hours of the study; prophylactic antifungal or antiviral agents which were in place at the start of study therapy could be continued. Amendment #2, which applied only to sites in the United Kingdom, made minor revisions to storage and mixing requirements consistent with that country's regulations. Amendment #3, which applied to sites in the Netherlands, allowed for the concomitant use of prophylactic doses of certain quinolone antibiotics for suppression of gram negative bowel flora in subjects with hematologic malignancies. Amendment #4, which applied to Site #9 in Switzerland, specified circumstances for the modification of empiric therapy within first 72 hours. These included: the addition of vancomycin in the face of organisms resistant to the study drug, (e.g., methicillin-resistant* Staphylococcus aureus *(MRSA), or* Corynebacterium jeikeium*); or in the face of frank clinical deterioration in a subject with infection due to a gram positive organism. In addition, amikacin was to be added in this time interval in the face of microbiologically documented gram negative sepsis in profoundly neutropenic subjects (<100 PMN/μL). Amendment #5, which applied to sites in Sweden, provided for the exclusion of subjects with solid tumor only, revised slightly the procedures for the collection of bacterial cultures, and allowed for addition of an aminoglycoside or vancomycin in the first 72 hours of study therapy for specific clinical indications. An aminoglycoside was to be added to the empiric regimen for frank clinical deterioration or the persistence of bacteremia; vancomycin was to be added in the face of MRSA or* C. jeikeium. *Such ad-*

*ditions were to constitute failures of the empiric regimen.*

*Given that this was a multi-center trial, it is to be expected that different institutions should have varying practice patterns; it is, after all, one of the goals of multi-center trials to test therapies in different practice settings that approximate the real world. However, it is concerning that the protocol was amended so as to create a situation in which there would be non-uniform practice patterns. This raises the issue as to whether the need for these amendments was driven by a non-random distribution of patients at the involved centers, or whether these amendments, by not being applied to all centers, could lead to a bias in the outcome.*

Study population

***Diagnosis and main criteria for inclusion:*** Subjects for the study were sought among cancer subjects at the participating centers in Europe. The protocol defined that hospitalized men and non-pregnant women, 16 years or older, with an underlying cancer were eligible to be enrolled if they had neutropenia in association with their cancer or cancer therapy, and developed fever. Neutropenia was defined as an absolute neutrophil count (ANC) of 500/μL. Eligible cancer types and/or therapies included leukemia, bone marrow transplantation, marrow aplasia, lymphoma or Hodgkin's disease, or a solid tumor. (Subjects with solid tumors were excluded from eligibility in Sweden in Protocol Amendment #5). Fever was defined as a sustained temperature ≥38.0 C (measured at least 3 times in 24 hours taken at a minimum interval of 4 hours), or a single temperature of ≥38.5 C.

***Exclusion criteria:*** Subjects were to be excluded if they had a history of a serious allergy to penicillins or cephalosporins or had received parenteral antibiotic therapy within 96 hours of enrollment. Pregnant or lactating women, or subjects with suspected or confirmed HIV infection were excluded, as were subjects with severe renal insufficiency (defined as serum creatinine >2 mg/dL, or requiring hemo- or peritoneal dialysis). Also ineligible were subjects who investigators judged would require >28 days of antibiotic therapy for treatment of their infection, or who had a limited life expectancy at enrollment (defined as expected to live <72 hours or requesting no cardio-pulmonary resuscitation, i.e., "No Code" or "DNR"). Finally, subjects could be enrolled more than once in the study, however, they could be enrolled only once per episode of neutropenia, provided it had been 7 or more days since recovery from the previous episode.

***Medical Officer's Comment***

*These criteria are consistent with those of the IDSA guidelines; they differ somewhat from those of AI411-204, particularly with respect to the definition of fever.*

Study Procedures

***Pre-Treatment Procedures:*** Pre-treatment procedures are summarized in Table 189.1. All subjects had a medical history with specific information on underlying cancer, including cancer treatment and hematologic support (bone marrow transplantation and use of hematopoietic growth factors) and previous antibiotic use. At onset of fever, a complete clinical evaluation and physical examination were obtained with emphasis on identification of an infectious etiology. Assessment included documentation of temperature,

other symptoms and signs of infection and chest X-ray for subjects with suspected lower respiratory tract infection.

Screening laboratories were to be obtained within 48 hours of study therapy. These included serum chemistries, complete hematologic profile with differential, coagulation parameters and erythrocyte sedimentation rate. A urinalysis was also to be performed.

Prior to initiating therapy, appropriate cultures of potential sites of infection were to be obtained. This included two blood cultures on all subjects. Site specific cultures of respiratory tract secretions, lesions of skin/skin structures and urine ($10^5$ CFU/mL required) were to be collected if suspected as etiologic sites. All organisms causing infection were identified, speciated to the extent possible, and tested for susceptibility to cefepime and ceftazidime using either the disc diffusion or Minimum Inhibitory Concentration (MIC) method.

**Table 1891: Study Parameters**

| Event | Pre-Treatment (Within 48 hours) | During Treatment (Days #3-5) | End of Treatment (Last Day of Rx) | Post-Treatment ( 14 Days post) |
|---|---|---|---|---|
| Informed Consent | X | - | - | - |
| Medical History | X | - | - | - |
| Physical Exam | X | X | X | - |
| Clinical Evaluation[1] | X | X | X | X |
| Clinical response | - | - | - | X |
| Chest X-ray[2] | X | X | X | - |
| Cultures | X | X | X | X |
| Laboratory Tests | X | X | X | - |

***Treatment Group Assignment:*** Subjects were randomly assigned (1:1) to one of two treatment groups: cefepime or ceftazidime.

***Medical Officer's Comment***

*Unlike study AI411-204, randomization was not stratified by underlying disease, i.e., by hematologic malignancy or solid tumor.*

***Study therapy:*** Cefepime was supplied as a 1 or 2 gram vial. After reconstitution with sterile water and dilution with sterile isotonic saline, each 2 gram dose of cefepime was administered intravenously over thirty minutes three times daily for a period of up to 28 days (2g IV q8h). Ceftazidime was supplied by Bristol-Myers Squibb, or hospital supply

[1] Included temperature.

[2] For subjects with suspected lower respiratory tract infections.

stock was utilized. After reconstitution and preparation as outlined in the approved package insert of the country where the study was conducted, each 2 gram dose of ceftazidime was administered intravenously three times daily for a period of up to 28 days (2g IV q8h).

***Duration of therapy:*** Empiric monotherapy with either cefepime or ceftazidime was to be given for a maximum of up to 28 days. Based on the clinical assessment and/or pre-treatment cultures, at 72-96 hours after initiating the empiric therapy, the subject's therapy could be modified. If the subject had improved or was in stable condition, the empiric monotherapy was to be continued for a minimum of 4 additional consecutive days without fever (defined as 38.0° C at least 3 times in 24 hours with a minimum interval between measurements of 4 hours, or a single measurement of 38.5° C). In the case of worsening of the subject's condition as judged at the 72-96 hour interval, the investigator was given the option of modifying the antibiotic regimen by adding one or more antibiotics to the empiric cephalosporin (i.e., combination antibiotic therapy), or of discontinuing the subject from the study. The choice of antibiotic to be added was to be at the discretion of the investigator based on the clinical status of the subject at the 72-96 hour evaluation, and on the results of the pre-therapy cultures. In cases where it was elected to continue the subject on the study with combination therapy, this therapy was to be continued for a minimum of 4 additional consecutive days without fever. In all cases, the duration of monotherapy, or combination therapy which included the study drugs, was not to exceed 28 days.

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

- an infection caused by a bacterial organism resistant to study therapy;
- poor clinical response;
- an adverse event;
- a situation for which discontinuation was in the subject's best interest;
- by request of the subject.

When an adverse event resulted in discontinuation, the subject was examined as frequently as necessary to determine whether the reaction had subsided and adverse sequelae did not persist. Subjects who were removed from the study for other reasons had a final clinical and physical assessment at the time study therapy was terminated.

***Concomitant medications:*** Subjects were to receive study therapy (cefepime or ceftazidime alone) without initiation of any other anti-infective agent (antibacterial, antifungal or antiviral) between the time of the pre-treatment culture and the 72-96 hour evaluation. If, at that time, the investigator judged that additional antibiotic coverage was warranted, additional anti-infective agents could be added to the empiric regimen. This would be considered as modification of the empiric regimen.

Other site-specific amendments were implemented which allowed for addition of specific anti-infectives prior to the 72-96 hour evaluation in the case of specific clinical or microbiological findings. In addition, certain specific anti-infective prophylaxis regimens

were allowed to be maintained. In all cases, medications other than anti-infective agents were allowed as needed.

***Medical Officer's Comment***

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

***During Treatment Procedures:*** During treatment procedures are summarized in Table 189.1. All subjects were assessed clinically at least once daily by a medical professional with measurement of temperature and assessment for adverse events or signs/symptoms of a new infection. In all cases, the highest daily temperature was recorded. Between Days #3 and #5 of treatment a full medical assessment was performed including physical examination, evaluation of the signs and symptoms of the infection; cultures and appropriate susceptibility testing, chest X-ray (for suspected lower respiratory tract infection) and the entire laboratory panel were to be repeated.

***End of Treatment/Follow-up:*** End of treatment procedures are summarized in Table 189.1. The subject was to be evaluated at the end of therapy (last day) with a recording of temperature, complete physical examination, evaluation of the signs and symptoms of the infection, repeat cultures and chest X-ray (as appropriate) and repeat of the entire laboratory panel. An assessment of the clinical response to therapy was to be made at the end of treatment, and before any modification to the empiric antibiotic regimen. In the case of treatment successes, this assessment was to be made within fourteen days following completion of the study therapy.

***Medical Officer's Comment***

*In practice, for many subjects data were only supplied for the end of therapy evaluation, without any further follow-up. This prevented assessment of the possibility of relapse. This was true both for patients discontinued from study therapy and those who remained on study therapy for the time specified by the protocol. Such patients were scored by the Medical Officer as unevaluable under the primary FDA analysis, and as failures under the FDA MITT analysis.*

Sponsor's Criteria for Evaluation

***Methods:*** A blinded review of the efficacy data was performed by a consultant for the sponsor. Data reviewed in the blinded evaluation included the infectious disease diagnosis, the evaluability for response with an assessment of the reasons for unevaluable responses, the assessment of outcome as well as the reasons for treatment failures, and comments on new infections where applicable. The criteria used in this analysis were similar to those described in current recommendations by the IDSA and IHS for the analysis of febrile neutropenic subjects. Some definitions of eligibility/evaluability, as well as response criteria, may therefore have differed from those originally included in the protocol. The criteria used for these assessments are outlined below.

The infection diagnoses were classified as:

- Microbiologically Documented Infection (MDI) (with or without bacteremia): Bacteremia or fungemia involving one or more organisms, without a definable non-hematogenous site of infection OR an infection at a specific site (e.g., cellulitis, pneumonia) with or without a concomitant fungemia or bacteremia.
- Clinically documented infection (CDI): Signs and symptoms of infection at a specific site (e.g., cellulitis or pneumonia) but the site was inaccessible or the microbial etiology could not be proven.
- Fever of uncertain origin (FUO): A new fever accompanied by neither clinical nor microbiological evidence of infection.
- Non-infectious Fever: Fever was due to a non-infectious condition (e.g., tumor, chemotherapy).

***Pathogens:*** All organisms obtained from cultures were categorized as causative, colonizer, contaminant or normal flora and recorded in the case report form. For coagulase-negative staphylococci, two or more separate blood cultures with organisms of the same genus and similar susceptibility patterns, were required. They were also considered causative pathogens, if they were isolated as the only organism for inflamed wounds or catheter insertion sites.

***Vital Signs:*** Maximum temperature, heart rate, and blood pressure prior to the initiation of study antibiotics (last value obtained within the two-day period (for temperature) and four-day period (for heart rate and blood pressure) before study start (included) were evaluated. In this analysis temperature was reported according to the FDA/IDSA and European guidelines for febrile episodes during neutropenia. Fever was defined as a temperature >38.0 C; tachycardia as a heart rate >90 beats per minute; and hypotension as a systolic blood pressure <90 mm Hg. Other signs and symptoms were tabulated.

***Hematology:*** Baseline hematology test results were defined as the worst value obtained within the four-day period before the start of study treatment (included) and summarized by classification of toxicity and treatment arm.

A missing pre-treatment neutrophil value was replaced by the WBC value if less than 500 cells/μL. The definition of neutropenia was based on IDSA/FDA and European guidelines and was defined as an absolute neutrophil count (ANC) <500 neutrophils/μL. Severe neutropenia corresponded to an ANC <100 neutrophils/μL.

Duration of neutropenia was calculated as the number of calendar days from the start of neutropenia (ANC <500 neutrophils/μL) to recovery from neutropenia (ANC >500 neutrophils/μL). Duration of severe neutropenia was calculated as the number of calendar days from the start of neutropenia (ANC ≤100 neutrophils/μL) to recovery from neutropenia (ANC >100 neutrophils/μL).

***Medical Officer's Comment***

*This definition was assumed to refer to the duration of neutropenia during the entire study period, not just the duration prior to study entry.*

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

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

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

- No response to empirical therapy
  - Septic shock
  - Adult respiratory distress syndrome
  - Disseminated intravenous coagulation
  - Multiple organ failure
  - Progression of primary infection
  - Persistence of fever for 96 hrs. during study therapy
- Pathogen resistant to study therapy
- Persistent bacteremia ( >24 hrs. of study therapy)
- Recurrent ("break-through") bacteremia
- Relapse of primary infection <7 days post therapy
- Death from primary infection

*Unevaluable.* A subject was considered unevaluable in the following conditions:

- initial infection caused by a viral, fungal, parasitic or mycobacterial organism
- a major protocol violation occurred (e.g., clinically inappropriate addition of a concomitant antibiotic)
- a non-infectious cause of fever was documented

Early discontinuation of study therapy for an adverse event also qualified as a condition for unevaluable response if the subject was clinically stable at the time study therapy was discontinued, but criteria for success or failure were not met.

New infections were defined as infections, either clinically or microbiologically documented, for which the onset of signs and symptoms occurred during study therapy or during the follow-up period. New infections were recorded by the consultant and tabulated by treatment group.

Sponsor's safety analysis

Safety analyses were performed in the entire subject population who received at least one dose of study treatment. Safety analyses included an assessment of deaths, adverse clinical events, and an assessment of laboratory results.

***Deaths:*** All deaths which occurred from the first dose of study therapy through the period ending 30 days after the last dose of study therapy were reported. The causes of death and the investigator assessment of causality were summarized.

***Adverse Clinical Events:*** Adverse clinical events were summarized by treatment group, and classified according to severity and relationship to study drug. A serious adverse event was defined as, but was not restricted to, an event that: 1) resulted in a life threatening situation or death; 2) resulted in, or prolonged, hospitalization; 3) resulted in a congenital anomaly or malignancy; 4) was the result of an overdose; or 5) resulted in a permanent disability.

***Abnormal Laboratory Results:*** Laboratory data were evaluated by comparing the pre-treatment values with the most abnormal during or post-treatment values and with laboratory normal ranges. Two sets of analyses were performed. The first analysis was on laboratory test values that were in the normal range at pre-treatment, and the second analysis was on laboratory test values that were abnormal at pre-treatment. If a subject's pre-treatment value for a given test was normal, that subject's most abnormal during- or post-treatment result was examined to determine if a change to a level outside the normal range in the direction of toxicity had occurred, and if so, whether the change reached the clinically relevant level for that test. If a subject's pre-treatment value for a given test was abnormal, that subject's most abnormal during- or post-treatment result was examined to detect any worsening.

Sponsor's statistical methods

The primary analysis was performed for the first febrile episode treated. Safety results and pre-treatment characteristics were based on data from subjects who received at least one dose of study medication. Baseline and on-study characteristics were compared between treatment arms. Clinical outcome was the primary efficacy variable and was analyzed in the evaluable subjects and in a modified intent-to-treat sample. Success rate was compared between treatment arms using the CMH test (adjusted for classification of infection), and a logistic regression model was applied to investigate the influence of other prognostic factors. A 95% exact confidence interval for difference in success rates was calculated. A supplemental analysis was produced for all episodes.

## Results

Study population characteristics

***Demographics:*** Two hundred eighty-one (281) subjects were enrolled and treated between February, 1993 and June, 1995 across 15 sites in northern Europe. An additional ten centers were registered for the study but did not enroll any patients. Table 189.2 shows the distribution of patient enrollment by center. Enrollment exceeded the originally planned 120 in an effort to achieve a sample size sufficient for meaningful statistical analysis, and to gain additional experience with cefepime in this indication.

For two subjects, the actual drug received was different from the randomized treatment: subjects were randomized to ceftazidime and treated with cefepime. These two subjects are analyzed in the cefepime group. Subject was treated in the protocol with ceftazidime, however, she was not randomized; this subject was analyzed in the ceftazidime group. One subject was randomized to ceftazidime but withdrew consent and was never treated; this subject was not included in the analyses.

Thirty-eight (38) of the 281 subjects were randomized more than once for separate febrile episodes. These 281 subjects received a total of 324 separate courses of therapy. Table 189.3 shows the demographics of patients enrolled in study AI411-189.

**Table 189.2. Enrollment of Subjects by Investigator and Treatment Group**

| First Course Principal Investigator | Location/Site No. | Cefepime | Ceftazidime | Total |
|---|---|---|---|---|
| Glauser, M. | Lausanne, Switzerland/009 | 24 | 29 | 53 |
| Dekker, A.W. | Utrecht, Netherlands/010 | 26 | 27 | 53 |
| Van Marwijk-Kooy, M. | Zwolle, Netherlands/016 | 11 | 13 | 24 |
| Palmblad, J. | Stockholm, Sweden/019 | 13 | 10 | 23 |
| Wood, M. | Birmingham, UK/005 | 10 | 11 | 21 |
| Harper, P. | London, UK/007 | 10 | 10 | 20 |
| Hedenus, M. | Sundsvall, Sweden/022 | 11 | 9 | 20 |
| Newland, A. | London, UK/006 | 9 | 9 | 18 |
| Braide, I. | Gothenburg, Sweden/020 | 7 | 9 | 16 |
| Maicke, A. | Helsinki, Finland/018 | 7 | 4 | 11 |
| Shah, P. | Frankfurt, Germany/025 | 5 | 6 | 11 |
| Coleman, R. | Sheffield, UK/003 | 2 | 3 | 5 |
| Strand, T. | Sandviken, Sweden/023 | 1 | 2 | 3 |
| Muller, H. | Blaricum, Netherlands/011 | 2 | 0 | 2 |
| Lehtinen, T. | Kagasala, Finland/017 | 1 | 0 | 1 |
| **Total** | | **139** | **142** | **281** |

| Table 189.3. Demographics - all patients enrolled in A1411-189 | | | | |
|---|---|---|---|---|
| | **Overall** | **Cefepime** | **Ceftazidime** | **CMH p value** |
| Total | 281 | 139 | 142 | |
| Age | | | | 0.600 |
| Median (y) | 52.0 | 55.0 | 51.0 | |
| Mean (y) | 50.1 ± 16.6 | 51.2 ± 16.1 | 49.1 ± 17.0 | |
| Range (y) | | | | |
| ≥ 65 y | 63 (22.4%) | 33 (23.7%) | 30 (21.1%) | |
| < 65 y | 218 (77.6%) | 106 (76.3%) | 112 (78.9%) | |
| Sex | | | | 0.835 |
| Male | 162 (57.7%) | 81 (58.3%) | 81 (57.0%) | |
| Female | 119 (42.3%) | 58 (41.7%) | 61 (43.0%) | |
| Race | | | | 0.011 |
| White | 270 (96.1%) | 130 (93.5%) | 140 (98.6%) | |
| Black | 4 (1.4%) | 2 (1.5%) | 2 (1.4%) | |
| Other | 7 (2.5%) | 7 (5.0%) | 0 (0.0%) | |
| Underlying disease | | | | 0.753 |
| Leukemia | 138 (49.1%) | 69 (49.6%) | 69 (48.6%) | |
| OHM | 88 (31.3%) | 43 (30.9%) | 45 (31.7%) | |
| OHD | 14 (5.0%) | 3 (2.2%) | 11 (7.7%) | |
| Solid tumor | 41 (14.6%) | 24 (17.3%) | 17 (12.0%) | |
| ANC nadir | | | | 0.253 |
| Median | 30.0 | 20.0 | 40.0 | |
| Mean | 123.5 ± 266.4 | 118.3 ± 253.8 | 128.6 ± 278.2 | |
| ≤100 | 196 (69.8%) | 101 (72.7%) | 95 (66.9%) | |
| >100 | 85 (30.2%) | 38 (27.3%) | 48 (33.1%) | |
| Duration ANC≤500 | | | | 0.730 |
| Median (d) | 8.0 | 8.0 | 9.0 | |
| Mean (d) | 9.6 ± 6.4 | 9.1 ± 5.7 | 10.0 ± 7.1 | |
| <7 d | 110 (39.1%) | 53 (38.1%) | 57 (40.1%) | |
| ≥7 d | 171 (60.9%) | 86 (61.9%) | 85 (59.9%) | |
| Bone marrow graft | 35 (12.5%) | 16 (11.5%) | 19 (13.4%) | 0.636 |
| Indwelling catheter | 128 (45.6%) | 63 (45.3%) | 65 (45.8%) | 0.940 |
| Prophylactic Abx | 182 (64.8%) | 84 (60.4%) | 98 (69.0%) | 0.133 |
| SBP <90 at entry | 5 (1.8%) | 3 (2.2%) | 2 (1.4%) | 0.635 |
| Multiple enrollments | 38 (13.5%) | 24 (17.3%) | 14 (9.9%) | 0.070 |

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

***Medical Officer's Comment***

*The treatment arms appear balanced with respect to demographic factors and risk factors for infection.*

***Statistical Reviewer's Comment***

*There appears to be a statistical imbalance in the racial composition of the enrolled population due to a higher enrollment of patients other than white or black. Patients receiving prophylactic antibiotics at baseline appear to be marginally higher in the ceftazidime arm (*vide infra*). These findings were not deemed to be of sufficient clinical significance to warrant any further statistical analyses.*

***Antimicrobial Prophylaxis:*** Use of antimicrobial prophylaxis prior to study was common in this population (Table 189.4A). More than half of the subjects were receiving an antibacterial agent as prophylaxis; nearly one-third were on a systemic antifungal, and/or were receiving acyclovir for antiviral prophylaxis. The choice of agents varied markedly by study site, likely reflecting local preferences of the particular oncology team. Overall, the most frequently used antibacterial was ciprofloxacin for suppression of bowel flora in subjects with hematologic malignancies. Fluconazole, usually dosed at 50-100 mg/day, was the most frequently used prestudy systemic antifungal agent. Non-systemic antifungals were also used frequently including oral amphotericin B and oral nystatin. Acyclovir doses ranged from 200-2000 mg/day. Overall, the two treatment groups were similar in regards to frequency and type of their prestudy antimicrobial prophylaxis regimens.

Protocol amendments 1 and 3 allowed for the continuation of antimicrobial prophylaxis in subjects who had been receiving prophylaxis at study entry. Continuation of antiviral, antifungal, and certain antibacterial regimens was permitted by protocol, as long as the regimen was not initiated subsequent to the start of study therapy. In particular, Amendment #3 (Netherlands) required concomitant use of one of the oral fluoroquinolones in subjects with hematologic malignancies for suppression of gram negative bowel flora.

As a result, most subjects on a prestudy antimicrobial regimen continued this regimen into study therapy (Table 189.4B). One-third of the subjects continued on an antibacterial regimen. Concomitant use of antibacterial prophylaxis was more common among the ceftazidime subjects than among cefepime subjects (35% versus 32%). For both treatment arms, ciprofloxacin 500 mg b.i.d. was the most frequently utilized antibacterial regimen. Trimethoprim-sulfamethoxazole was used occasionally (20 subjects, 7%) at prophylactic doses. Two ceftazidime subjects , entered study on oral vancomycin for suspected *C. difficile*-associated diarrhea. One cefepime subject continued metronidazole as empiric therapy for diarrhea of unknown etiology.

About one-third of the subjects received systemic antifungal prophylaxis while on study. Oral fluconazole was used most frequently, followed by itraconazole. Non-systemic antifungals were also used commonly. The study arms were comparable in regards to use of prophylactic antifungal agents.

Prophylactic acyclovir was continued into study for 27% of the subjects. As with antibacterial and antifungal prophylaxis, antiviral use was slightly more frequent in the ceftazidime arm (30% versus 24%).

Table 13.9.4A
Prevalent Systemic Antimicrobial Prophylaxis

| | Number (%) of Subjects | | |
|---|---|---|---|
| | Cefepime (N=139) | Ceftazidime (N=142) | Total (N=281) |
| **Any Prophylaxis** | 84(60) | 98(69) | 182(65) |
| **Any Antibacterial**[1] | 73(53) | 82(58) | 155(55) |
| Ciprofloxacin | 45(32) | 49(35) | 94(33) |
| TMP-SMX | 17(12) | 17(12) | 34(12) |
| Penicillins | 11(8) | 17(12) | 28(10) |
| Roxithromycin | 9(6) | 7(5) | 16(6) |
| Colistin | 10(7) | 7(5) | 17(6) |
| Norfloxacin | 5(4) | 6(4) | 11(4) |
| Metronidazole | 2(1) | 2(1) | 4(1) |
| Tetracyclines | 0 | 3(2) | 3(1) |
| Cephalosporins | 2(1) | 0 | 2(<1) |
| Ofloxacin | 2(1) | 0 | 2(<1) |
| Vancomycin | 0 | 2(1) | 2(<1) |
| Isoniazid | 1(<1) | 1(<1) | 2(<1) |
| Clindamycin | 1(<1) | 1(<1) | 2(<1) |
| Methenamine hippurate | 0 | 1(<1) | 1(<1) |
| **Any antifungal** | 41(29) | 48(34) | 89(32) |
| Fluconazole | 33(24) | 36(25) | 69(25) |
| Itraconazole | 8(6) | 12(8) | 20(7) |
| Any Antiviral | 34(24) | 44(31) | 78(28) |
| Acyclovir | 34(24) | 44(31) | 78(28) |

[1] Subjects may have received more than one drug.

**Table 189.4B.**
**Systemic Antimicrobial Prophylaxis**
**Continued into Study Therapy**

| | Number (%) of Subjects | | |
|---|---|---|---|
| | Cefepime (N=139) | Ceftazidime (N=142) | Total (N=281) |
| Any Antimicrobial | 70(50) | 83(58) | 153(54) |
| | | | |
| **Any Antibacterial** | **45(32)** | **50(35)** | **95(34)** |
| Ciprofloxacin | 28(20) | 27(19) | 55(20) |
| Trimethoprim-sulfamethoxazole | 10(7) | 10(7) | 20(7) |
| Norfloxacin | 4(3) | 6(4) | 10(4) |
| Colistin | 6(4) | 4(3) | 10(4) |
| Roxithromycin | 1(<1) | 4(3) | 5(2) |
| Penicillins | 2(1) | 1(<1) | 3(1) |
| Vancomycin | 0 | 2(1) | 2(<1) |
| Isoniazid | 1(<1) | 1(<1) | 2(<1) |
| Metronidazole | 1(<1) | 0 | 1(<1) |
| Oxytetracycline | 0 | 1(<1) | 1(<1) |
| Minocycline | 0 | 1(<1) | 1(<1) |
| Methenamine hippurate | 0 | 1(<1) | 1(<1) |
| | | | |
| **Any Antifungal** | 40(29) | 47(33) | 87(31) |
| Fluconazole | 32(23) | 35(25) | 67(24) |
| Itraconazole | 8(6) | 12(8) | 20(7) |
| | | | |
| Any Antiviral | 34(24) | 42(30) | 76(27) |
| Acyclovir | 34(24) | 42(30) | 76(27) |

***Medical Officer's Comment***

*Use of prophylactic antibiotics was far more common in this study than in AI411-204. This presumably reflects different practice patterns in Europe. However, the regimens employed were similar to those used in the U.S., e.g., fluoroquinolones and trimethoprim-sulfamethoxazole. Thus, these patients were not excluded from analyses simply because of use of prophylaxis. It is worth noting, however, that the clinical efficacy of prophylaxis has never been demonstrated in this setting; thus, the use of prophylaxis in this trial and AI411-204 represents superimposition of an unproved therapeutic*

*maneuver onto the study design, potentially complicating interpretation of results; in addition, not all patients were on prophylaxis. To address this issue, analysis of response rates according to use of prophylaxis is presented in the Integrated Summary of Efficacy (section 10).*

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

Episode evaluability

Evaluability assessment gave the results shown in Table 189.5.

**Table 189.5 Episode evaluability**

| | 1° evaluability criteria | | MITT evaluability criteria | |
|---|---|---|---|---|
| | FDA | Sponsor | FDA | Sponsor |
| All episodes | 175/324 (54.0%) | 250/324 (77.2%) | 311/324 (96.0%) | 316/324 (97.5%) |
| Cefepime | 89/166 (53.6%) | 132/166 (79.5%) | 160/166 (96.4%) | 160/166 (96.4%) |
| Ceftazidime | 86/158 (54.4%) | 118/158 (74.7%) | 151/158 (95.6%) | 156/158 (98.7%) |

One hundred and forty-nine episodes were excluded from the FDA analysis; 77/166 (46.4%) from the cefepime arm and 72/158 (45.6%) from the ceftazidime arm. Reasons for exclusion of episodes from the primary FDA analysis are shown in Table 189.6.

**Table 189.6 Medical Officer's reasons for exclusion from analysis**

| | **Overall** | **Cefepime** | **Ceftazidime** | **CMH p-value** |
|---|---|---|---|---|
| Any reason | 149/324 (46.0%) | 77/166 (46.4%) | 72/158 (45.6%) | 0.420 |
| Early modification | 67/324 (20.7%) | 30/166 (18.1%) | 37/158 (23.4%) | |
| Lost to follow-up | 64/324 (19.8%) | 36/166 (21.7%) | 28/158 (17.7%) | |
| Pre-existing infection | 9/324 (2.8%) | 5/166 (3.0%) | 4/158 (2.5%) | |
| Not neutropenic | 7/324 (2.2%) | 3/166 (1.8%) | 4/158 (2.5%) | |
| Non-study Abx | 7/324 (2.2%) | 3/166 (1.8%) | 4/158 (2.5%) | |
| Non-bacterial infection | 6/324 (1.9%) | 3/166 (1.8%) | 3/158 (1.9%) | |
| Not febrile | 4/324 (1.2%) | 1/166 (0.6%) | 3/158 (1.9%) | |
| Regimen D/C'd for ADR | 2/324 (0.6%) | 2/166 (1.2%) | 0/158 (0.0%) | |
| Non-infectious fever | 2/324 (0.6%) | 2/166 (1.2%) | 0/158 (0.0%) | |

***Medical Officer's Comment***

*Reasons for unevaluability were similar to those in study AI411-204. However, there was a significantly greater proportion of patients who were considered unevaluable by the Medical Officer because of lack of follow-up data beyond the end of therapy. It was not clear if this was due to actual loss of follow-up, or to problems with data capture during the study.*

***Statistical Reviewer's Comment***

*The two treatment arms are balanced with respect to the Medical Officer's reasons for exclusion. There is no statistically significant single reason or group of reasons for exclusion from analysis or evaluation.*

Episode evaluability by treatment center is shown in Table 189.7.

Table 189.7 Medical Officer episode evaluability by treatment center

| | Overall | Cefepime | Ceftazidime |
|---|---|---|---|
| All centers | 175/324 (54.0%) | 89/166 (53.6%) | 86/158 (54.4%) |
| 003 | 1/5 (20.0%) | 0/2(0.0%) | 1/3 (33.3%) |
| 005 | 9/28 (32.1%) | 3/14 (21.4%) | 6/14 (42.8%) |
| 006 | 11/22 (50.0%) | 7/12 (58.3%) | 4/10 (4.0%) |
| 007 | 14/23 (60.9%) | 9/12 (75.0%) | 5/11 (45.5%) |
| 009 | 19/60 (31.7%) | 10/30 (33.3%) | 9/30 (30.0%) |
| 010 | 41/58 (70.7%) | 22/29 (75.9%) | 19/29 (65.5%) |
| 011 | 1/2 (50.0%) | 1/2 (50.0%) | 0/0 |
| 016 | 19/25 (76.0%) | 9/12 (75.0%) | 10/13 (76.9%) |
| 017 | 1/1 (100.0%) | 1/1 (100.0%) | 0/0 |
| 018 | 6/11 (54.5%) | 3/7 (42.9%) | 3/4 (75.0%) |
| 019 | 9/25 (36.0%) | 6/13 (46.1%) | 9/12 (75.0%) |
| 020 | 11/22 (50.0%) | 6/11 (54.5%) | 5/11 (45.5%) |
| 022 | 19/26 (73.1%) | 9/13 (69.2%) | 10/13 (76.9%) |
| 023 | 3/3 (100.0%) | 1/1 (100.0%) | 2/2 (100.0%) |
| 025 | 5/13 (38.5%) | 2/7 (28.6%) | 3/6 (50.0%) |

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

The infectious disease diagnoses assigned by the FDA Medical Officer and the sponsor for patients in the FDA evaluable, FDA MITT, and sponsor evaluable populations are shown in Tables 189.8A, 8B, and 8C, respectively.

Table 189.8A FDA infectious disease diagnoses for evaluable population

| Infection type | Overall | Cefepime | Ceftzazidime | CMH p value |
|---|---|---|---|---|
| Any | 175 (100%) | 89 (100%) | 86 (100%) | 0.518 |
| MDI with bacteremia | 43 (24.6%) | 22 (24.7%) | 21 (24.4%) | |
| MDI | 19 (10.9%) | 11 (12.4%) | 8 (9.3%) | |
| CDI | 35 (20.0%) | 20 (22.5%) | 15 (17.4%) | |
| FUO | 78 (44.6%) | 36 (40.4%) | 42 (48.8%) | |

| Table 189.8B. FDA infectious disease diagnoses for MITT population | | | | |
|---|---|---|---|---|
| Infection type | Overall | Cefepime | Ceftzazidime | p value |
| Any | 311 (100%) | 160 (100%) | 151 (100%) | .649 |
| MDI with bacteremia | 75 (24.1%) | 40 (25.0%) | 35 (23.2%) | |
| MDI | 31 (10.0%) | 17 (10.6%) | 14 (9.3%) | |
| CDI | 63 (20.3%) | 31 (19.4%) | 32 (21.2%) | |
| FUO | 142 (45.7%) | 72 (45.0%) | 70 (46.4%) | |

| Table 189.8C. Sponsor's infectious disease diagnoses for evaluable population | | | | |
|---|---|---|---|---|
| Infection type | Overall | Cefepime | Ceftzazidime | p value |
| Any | 250 (100%) | 132 (100%) | 118 (100%) | .329 |
| MDI with bacteremia | 66 (26.4%) | 38 (28.8%) | 28 (23.7%) | |
| MDI | 22 (8.8%) | 14 (10.6%) | 8 (6.8%) | |
| CDI | 51 (20.4%) | 27 (20.5%) | 24 (20.3%) | |
| FUO | 111 (44.4%) | 57 (43.2%) | 54 (45.8%) | |

***Medical Officer's Comment***

*As with study AI411-204, the treatment arms in AI411-189 were balanced with respect to infection diagnoses, and the majority of infections in both arms were due to fever without microbiologic or clinical evidence of infection.*

***Statistical Reviewer's Comment***

*For the FDA evaluable and MITT population, as well as the sponsor's evaluable population, the treatment arms are balanced with respect to infectious disease diagnoses.*

Efficacy analysis

***Primary efficacy analysis.*** The same approach was used to determine efficacy as for study AI411-204. The definitions of response are shown in Table 9.3A. The primary endpoint was outcome definition 1B applied to the evaluable population; for the MITT analysis, definition 1A was applied to the MITT population. Table 189.9A shows response rates for all evaluable episodes as determined by the Medical Officer and by the sponsor; table 189.9B shows response rates for first episodes, and Table 189.9C shows rates by treatment center. Because different definitions of outcome were applied to the FDA evaluable and MITT populations, the numerators differ between these two analyses.

| Table 189.9A. All episode response rates | | | |
|---|---|---|---|
| **Population** | **Cefepime** | **Ceftazidime** | **95% Confidence Interval** |
| FDA evaluable[1] | 38/89 (42.7%) | 42/86 (48.8%) | $_{89,86}$ (-0.2202, 0.0974) $_{42.7\%,48.8\%}$ |
| FDA MITT[2] | 30/160 (18.8%) | 32/151 (21.2%) | $_{160,151}$ (-0.1198, 0.0709) $_{18.8\%,21.2\%}$ |
| Sponsor evaluable | 71/132 (53.8%) | 68/118 (57.6%) | $_{132,118}$ (-0.1696, 0.0929) $_{53.8\%,57.6\%}$ |
| Sponsor MITT | 71/160 (44.4%) | 68/156 (43.6%) | $_{160,156}$ (-0.1079, 0.1236) $_{44.4\%,43.6\%}$ |

| Table 189.9B. First episode response rates | | | |
|---|---|---|---|
| **Population** | **Cefepime** | **Ceftazidime** | **95% Confidence Interval** |
| FDA evaluable[1] | 34/76 (44.7%) | 37/77 (48.1%) | $_{76,77}$ (-0.2042, 0.1379) $_{44.7\%,48.1\%}$ |
| FDA MITT[2] | 27/133 (20.3%) | 29/136 (21.3%) | $_{133,136}$ (-0.1147, 0.0942) $_{20.3\%,21.3\%}$ |
| Sponsor evaluable | 56/109 (51.4%) | 61/106 (57.5%) | $_{109,106}$ (-0.2039, 0.0805) $_{51.4\%,57.5\%}$ |
| Sponsor MITT | 56/133 (42.1%) | 61/140 (43.6%) | $_{133,140}$ (-0.1394, 0.1101) $_{42.1\%,43.6\%}$ |

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 189.9C. Response rate by treatment center | | |
|---|---|---|
| | **Cefepime** | **Ceftazidime** |
| All centers | 38/89 (42.7%) | 42/86 (48.8%) |
| 003 | 0/0 | 0/1 (0.0%) |
| 005 | 0/3 (0.0%) | 3/6 (50.0%) |
| 006 | 0/7 (0.0%) | 0/4 (0.0%) |
| 007 | 0/9 (0.0%) | 1/5 (20.0%) |
| 009 | 5/10 (50.0%) | 4/9 (44.4%) |
| 010 | 14/22 (63.6%) | 14/19 (73.7%) |
| 011 | 1/1 (100.0%) | 0/0 |
| 016 | 5/9 (55.6%) | 3/10 (30.0%) |
| 017 | 1/1 (100.0%) | 0/0 |
| 018 | 1/3 (33.3%) | 3/3 (100.0%) |
| 019 | 3/6 (50.0%) | 5/9 (55.6%) |
| 020 | 4/6 (66.7%) | 2/5 (40.0%) |
| 022 | 3/9 (33.3%) | 4/10 (40.0%) |
| 023 | 1/1 (100.0%) | 0/2 (0.0%) |
| 025 | 0/2 (0.0%) | 3/3 (100.0%) |

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.

***Statistical Reviewer's Comment***

*If all febrile neutropenic episodes are considered, cefepime fails to establish therapeutic equivalence with ceftazidime in the patients who are deemed FDA evaluable. The two treatment arms are therapeutically equivalent in patients included in the FDA MITT analyses and patients who are either evaluable or in the MITT population according to the sponsor.*

*If only the first febrile episode is considered, cefepime fails to establish therapeutic equivalence with ceftazidime in the patients who are deemed evaluable as per FDA or the sponsor. The two treatment arms are therapeutically equivalent in patients included in the MITT analyses as per FDA and the sponsor.*

***Reasons for failure:*** A summary of the Medical Officer's assessments of reasons for failure in evaluable patients is shown in Table 189.10.

**Table 189.10: Reasons for treatment failure**

| Reason for failure | Cefepime | Ceftazidime | p value |
|---|---|---|---|
| Persistent fever | 19/89 (21.3%) | 16/86 (18.6%) | 0.791 |
| Poor microbiologic response - initial isolate resistant | 4/89 (4.5%) | 6/86 (7.0%) | 0.531 |
| Poor microbiologic response - initial isolate susceptible | 2/89 (2.2%) | 1/86 (1.2%) | 1.00 |
| Death from primary infection | 3/89 (3.4%) | 5/86 (5.8%) | 0.720 |
| Death from secondary infection | 0/89 (0.0%) | 0/86 (0.0%) | — |
| Poor clinical response | 5/89 (5.6%) | 1/86 (1.2%) | 0.211 |
| Bacteriologic relapse | 0/89 (0.0%) | 0/86 (0.0%) | — |
| New MDI: susceptible isolate | 0/89 (0.0%) | 0/86 (0.0%) | — |
| New MDI: resistant isolate | 5/89 (5.6%) | 5/86 (5.8%) | 1.00 |
| New CDI | 0/89 (0.0%) | 4/86 (4.7%) | 0.056 |
| New FUO | 13/89 (14.6%) | 6/86 (7.0%) | 0.145 |
| **Total failures** | **51/89 (57.3%)** | **44/86 (51.2%)** | **0.507** |

***Statistical Reviewer's Comment***

*Except for patients who were deemed failures due to new clinically documented infections, the two treatment arms appear to be balanced with respect to reasons for treatment failure.*

***Microbiologic efficacy:*** Response rates for MDIs in evaluable patients as determined by the Medical Officer and the sponsor are shown in Table 189.11.

| Table 189.11, MDI response rates | | | |
|---|---|---|---|
| **Population** | **Cefepime** | **Ceftazidime** | **95% Confidence Interval** |
| FDA evaluable | 15/33 (45.5%) | 14/29 (48.3%) | $_{33,29}$ (-0.3095, 0.2531) $_{45.5\%, 48.3\%}$<br>Exact 95% Confidence Interval<br>$_{33,29}$ (-0.3060, 0.2251) $_{45.5\%, 48.3\%}$ |
| Sponsor evaluable | 28/52 (53.8%) | 22/36 (61.1%) | $_{52,36}$ (-0.3052, 0.1599) $_{53.8\%, 61.1\%}$<br>Exact 95% Confidence Interval<br>$_{52,36}$ (-0.3080, 0.1433) $_{53.8\%, 61.1\%}$ |

***Statistical Reviewer's Comment***

*The sample sizes are inadequate to ensure adequate statistical power for valid inferences. Based on the exact 95% confidence interval (the preferred test due to limited event numbers and imbalance in the data), cefepime fails to establish therapeutic equivalence with ceftazidime in patients deemed evaluable by the FDA or the sponsor who had microbiologically documented infection.*

***Efficacy with respect to various definitions of success in primary outcome:*** As with study AI411-204, response rates were analyzed using different measures of outcome, as described in Methods. The definitions of success outlined in Table 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 189.12A and 12B show response rates for Study AI411-189 based on different outcome measures. The primary outcome measures for each population are shown in boldface.

| Table 189.12A, Evaluable population response rates with different outcome measures | | | |
|---|---|---|---|
| **Outcome** | **Cefepime** | **Ceftazidime** | **95% Confidence Interval** |
| Definition 1A | 30/89 (33.7%) | 32/86 (37.2%) | $_{89,86}$(-0.1882, 0.1181)$_{33.7\%, 37.2\%}$ |
| **Definition 1B[1]** | **38/89 (42.7%)** | **42/86 (48.8%)** | $_{89,86}$ **(-0.2202, 0.0974)** $_{42.7\%, 48.8\%}$ |
| Definition 2A | 47/89 (52.8%) | 46/86 (53.5%) | $_{89,86}$(-0.1661, 0.1525)$_{52.8\%, 53.5\%}$ |
| Definition 2B | 55/89 (61.8%) | 56/86 (65.1%) | $_{89,86}$(-0.1872, 0.1209)$_{61.8\%, 65.1\%}$ |
| Definition 3 | 84/89 (94.4%) | 82/86 (95.3%) | $_{89,86}$(-0.0864, 0.0671)$_{94.4\%, 95.3\%}$ |
| **Table 12B, MITT population response rates with different outcome measures** | | | |
| **Outcome** | **Cefepime** | **Ceftazidime** | **95% Confidence Interval** |
| **Definition 1A[2]** | **30/160 (18.8%)** | **32/151 (21.2%)** | $_{160,151}$**( -0.1198, 0.0709)**$_{18.8\%, 21.2\%}$ |
| Definition 1B | 39/160 (24.3%) | 43/151 (28.5%) | $_{160,151}$(-0.1455, 0.0634)$_{24.3\%, 28.5\%}$ |
| Definition 2A | 48/160 (30.0%) | 47/151 (31.1%) | $_{160,151}$(-0.1201, 0.0976)$_{30.0\%, 31.1\%}$ |
| Definition 2B | 57/160 (35.6%) | 58/151 (38.4%) | $_{160,151}$(-0.1416, 0.0859)$_{35.6\%, 38.4\%}$ |
| Definition 3 | 155/160 (96.9%) | 145/151 (96.0%) | $_{160,151}$(-0.0392, 0.0561)$_{96.9\%, 96.0\%}$ |

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

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

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 for all three definitions of success. For the MITT population, cefepime was therapeutically equivalent to ceftazidime for all definitions. As mentioned before, these results should be interpreted with care since multiple *post hoc* analyses may give rise to type I errors.

***Statistical Reviewer's Comment***

*Except for Definition 1B (the primary analysis), cefepime is therapeutically equivalent to ceftazidime in the evaluable patient population for each definition considered. In the patients included in the MITT analyses, cefepime is therapeutically equivalent to ceftazidime with respect to each definition considered.*

Modifications

A summary of the frequency of modification is presented in Table 189.13 for the evaluable AI411-189 population.

**Table 189.13: Frequency of modification - evaluable population**

| | Cefepime (N=89) | Ceftazidime (N=86) | Overall (N=175) |
|---|---|---|---|
| **Any** | 57 (64%) | 51 (61%) | 108 (62%) |
| **Any anti-bacterial** | 49 (55%) | 42 (49%) | 91 (53%) |
| vancomycin/glycopeptide | 30 (34%) | 30 (35%) | 51 (29%) |
| aminoglycoside | 6 (7%) | 9 (10%) | 15 (9%) |
| cephalosporin | 9 (10%) | 5 (6%) | 39 (22%) |
| ß-lactam/penem/monobactam | 20 (22%) | 21 (24%) | 36 (21%) |
| quinolone | 9 (10%) | 7 (8%) | 20 (11%) |
| metronidazole | 5 (6%) | 5 (6%) | 4 (2%) |
| anaerobic coverage | 1 (1%) | 0 (0%) | 22 (13%) |
| **Anti-fungal** | 18 (20%) | 17 (20.0%) | 35 (21%) |
| **Anti-viral** | 12 (13%) | 14 (16%) | 26 (15%) |
| Mean time to modification (days) | 4.81 ± 3.36 | 5.20 ± 3.36 | 4.99 ± 3.33 |

Superinfections or new febrile episodes

A summary of the frequency of new febrile episodes or documented infections in evaluable patients in AI411-189 is presented in Table 189.14. There did not appear to be a significant difference between the treatment arms. As in AI411-204, the majority of new episodes were due to fever without a clinical or microbiologic source.

| Table 189.14. Frequency of new febrile episodes or infection | | | |
|---|---|---|---|
| **Nature of 2nd event** | **Cefepime (N=89)** | **Ceftazidime (N=86)** | **Overall (N=175)** |
| All | 18 (20.2%) | 15 (17.4%) | 33 (18.9%) |
| MDI (same isolate) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| MDI (new pathogen) | 5 (5.6%) | 5 (5.8%) | 10 (5.2%) |
| susceptible | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| resistant | 5 (5.6%) | 5 (5.8%) | 10 (5.2%) |
| CDI | 0 (0.0%) | 4 (4.7%) | 4 (2.3%) |
| FUO | 13 (14.6%) | 6 (7.0%) | 19 (9.8%) |

**Safety analysis**

***Mortality:*** Seventeen subjects died in association with the first episode of febrile neutropenia during the course of the trial, for an overall mortality rate of 6.0%. There were 8 deaths in the cefepime treatment group and 9 in the ceftazidime group. An analysis of deaths by specific cause is shown in Table 189.15.

| Table 189.15<br>Cause of Subjects' Deaths by Investigator - First Episode | | | | |
|---|---|---|---|---|
| | Cefepime (N = 139) | Ceftazidime (N = 142) | Total (N = 281) | p-value |
| Total deaths | 8 (6%) | 9 (6%) | 17 (6%) | 1.00 |
| Initial infection | 1 | 2 | 3 | — |
| Secondary infection | 1 | 3 | 4 | — |
| Underlying disease or other etiology | 2 | 3 | 5 | — |

***Medical Officer's Comment***

*In contrast to study AI411-204, there was no significant difference in specific cause mortality between treatment arms.*

***Discontinuations due to adverse events:*** Reasons for discontinuation of study therapy due to adverse events are shown in Table 189.16. There was no significant difference between treatment arms.

| Table 139.16<br>Discontinuation of Study Therapy Due to an Adverse Event, First Episode | | | |
|---|---|---|---|
| | Number (%) of Subjects | | |
| | Cefepime (N=139) | Ceftazidime (N=142) | Total (N=281) |
| **Any Adverse Event** | 8 (6) | 5 (4) | 13 (5) |
| Rash | 4 | 4 | 8 |
| Nausea | 0 | 1 | 1 |
| Vomiting | 0 | 1 | 1 |
| Diarrhea | 0 | 1 | 1 |
| Erythema | 1 | 0 | 1 |
| Septic shock | 1 | 0 | 1 |
| Infection, increase | 1 | 0 | 1 |
| Urinary tract infection (UTI) | 1 | 0 | 1 |
| Laboratory Abnormality | 0 | 1 (<1) | 1 (<1) |

***Clinical adverse events:*** Seventy-one percent of the subjects in both treatment groups experienced at least one adverse event. Most events were not related or were of unknown relationship to study therapy. The most frequent adverse events, all of which occurred in about 10% of the subjects, were rash, diarrhea and pain (at various locations) for cefepime-treated subjects and headache, rash , pain (at various locations) and diarrhea for ceftazidime. Among subjects with diarrhea, testing for *C. difficile* toxin was performed infrequently and was correlated with diarrhea in only one ceftazidime subject. Most other adverse events were infrequent.

The incidence of drug-related adverse events was slightly higher in cefepime than ceftazidime subjects (17% versus 11%) (Table 42). Most of this difference was due to the occurrence of single isolated events in individual subjects. The drugs were comparable in the incidence of the most frequently reported drug-related events: rash, phlebitis/injection site reaction and nausea/vomiting. Nearly all drug-related events were of mild to moderate severity. No subjects experienced a drug-related adverse event which was judged life-threatening. Four events were judged "severe." One cefepime subject became confused on day #3 of therapy; this resolved within 2 days without discontinuation of therapy. One cefepime subject discontinued medication due to a severe rash and one was diagnosed with a peri-anal abscess one day after discontinuation of cefepime. One ceftazidime subject stopped therapy due to persistent nausea and vomiting.

***Laboratory adverse events:*** The treatment groups were similar in regards to the proportions of subjects who developed abnormal laboratory tests on study, including those which became clinically relevant. Disturbances in electrolytes, namely decreases in potassium, sodium, calcium and phosphorous were most common. However, few subjects developed clinically relevant decreases. Most of these changes likely reflect the nutritional disruptions of these hospitalized subjects who were receiving intravenous fluids. Liver function test elevations were also fairly common, although they were rarely clinically relevant. Disruption in renal function was uncommon in both treatment arms. Elevations in serum BUN or BUR were evenly distributed across the treatment groups; creatinine elevation, a more specific marker of renal insufficiency, was more common among ceftazidime subjects. Few abnormalities were clinically relevant.

***Final comments/conclusions - study 411-189***

*This was a large, multi-center, randomized controlled trial comparing the efficacy of cefepime with that of ceftazidime for empiric therapy of febrile neutropenia. As with study AI411-204, the design of this trial was based on the IDSA guidelines.*

*The trial enrolled a total of 281 patients, accounting for 324 episodes. Baseline demographic and prognostic factors were balanced between the treatment arms. 175 (54.0%) of enrolled patient episodes were found to be evaluable for efficacy by the FDA Medical Officer. The most common reasons for unevaluability were modification of the initial regimen before assessment at 72 hours and loss to follow-up. The FDA analysis led to a larger number of patients being deemed unevaluable than in the sponsor's analysis; this accounted for most of the differences in the efficacy analysis between the FDA and the sponsor.*

*There were a number of differences between the patient populations in studies AI411-189 and AI411-204; study 189 had a significantly greater proportion of patients on prophylactic antimicrobial agents at study entry, and such patients were much more likely to have prophylaxis continued during study therapy. However, the prophylactic regimens used were similar to those in study AI411-204, consisting of a fluoroquinolone or trimethoprim-sulfamethoxazole. Thus, this patient population is not* per se *different from that in study 204 because of the use of prophylaxis. In addition, there was a significantly higher rate of loss to follow-up in this study. In all likelihood, the latter reflects problems with data capture during the study rather than actual loss to follow-up, since patients recovering from an episode of febrile neutropenia tend to be followed closely by their oncologist or other physicians. Thus, this does not necessarily reflect a difference in the patient populations between studies 204 and 189.*

*The FDA analysis was similar to that for study AI411-204. Efficacy rates in the evaluable population, as determined by the Medical Officer and assessed either in terms of resolution of the initial episode or survival of infection, were similar for cefepime and ceftazidime, although the rates for cefepime were lower than for ceftazidime. This was true for all febrile episodes, first episodes, and microbiologically documented infections. In order to be deemed therapeutically equivalent as per the DAIDP Points to Consider document, the 95% confidence interval of the difference in cure rates between the test product and the control should lie above -0.20 when the control drug cure rate is <80%,*

*and include zero. Based on this criterion, cefepime fails to establish therapeutic equivalence in the patient population deemed evaluable by the FDA reviewing Medical Officer when either the first or all febrile episodes are considered, as well as in patients with microbiologically documented infections. Thus, this study alone cannot demonstrate therapeutic equivalence between cefepime and ceftazidime. However, its design allows pooling of results with similar trials (see the Integrated Summary of Efficacy, section 10).*

*Safety analysis showed similar all-cause and specific cause mortality rates for the two treatment arms in the cefepime arm. There was no significant difference in the incidence of clinical adverse events or the incidence of discontinuation due to clinical adverse events between treatment arms. There was no significant difference in the incidence of laboratory adverse events.*

*In conclusion, study AI411-189 does not by itself demonstrate therapeutic equivalence between cefepime and ceftazidime for empiric therapy of febrile neutropenia; however, its design features allow pooling of its results with those of similarly designed and conducted studies. This study demonstrates an acceptable safety profile for cefepime in this indication.*

## STUDY AI411-131

***Medical Officer's Comment***

*Data on 54 episodes (representing 47 patients) from this study were included in the original NDA submission. Review of the study at that time by FDA Medical Officer William Erhardt, M.D. found that the data demonstrated therapeutic equivalence between cefepime and the comparator regimen, but that the study contained data on a small number of patients. The current submission contains data on an additional 50 episodes (representing an additional 42 patients).*

**General Information**

***Title.*** A Comparative Study of Cefepime vs. Ceftazidime in the Treatment of Adult Cancer Patients with Fever and Neutropenia.

***Objective.*** To evaluate the clinical efficacy and safety of cefepime, administered at a dose of 2 grams every eight hours, in comparison to ceftazidime administered at a dose of 2 grams every eight hours for the empiric treatment of febrile episodes in neutropenic cancer subjects.

***Investigators:*** Reuben Ramphal, M.D. (Shands Hospital, Gainesville, FL); Alastair Haddow, M.D. (St. John's Regional Medical Center, Springfield, MO); George H. McCracken, M.D. (Children's Medical Center of Dallas, Dallas, TX)

***Study Centers:*** Shands Hospital, University of Florida, Gainesville, FL (site -001)
St. John's Hospital, Springfield, MO (site -002)
Children's Medical Center of Dallas, Dallas, TX (site -003)

***Study design.*** A two arm, comparative, open-label, randomized (1:1) study conducted in the United States. The original protocol was amended to add a second site for adult subjects and a third site for enrollment of pediatric subjects. Ninety subjects were treated for a total of 104 febrile episodes at the two study sites. Initially, a single study site (Florida) planned to enroll 100 adult subjects over a period of approximately two years. A second adult study site (Missouri) was added and planned to accrue 100 adult subjects. Study site 001 (Florida) enrolled 87 subjects. One subject did not receive study drug, ten subjects were enrolled for two febrile episodes, and two subjects were enrolled for three. Study site 002 (Missouri) had difficulty enrolling subjects and the study was terminated early after four subjects were accrued. Study site 003 (Dallas) accrued 104 pediatric patients.

***Medical Officer's Comment***

*Data from study site 003 (Dallas) was submitted separately as part of an efficacy supplement seeking approval for use of cefepime for treatment of infections pediatric patients (NDA 50,679/SE1-006); for the purposes of the present review ,only the data from adult patients (sites 001 and 002) was analyzed by the Medical Officer.*

***Study period.*** First subject enrolled August 30, 1989. Last subject completed therapy November 26, 1991.