6.4 Complicated Skin and Skin Structure Infections

6.4.1 Reviewer: Janice Pohlman, MD
6.4.2 Date First Draft: 10/5/01, Date Revised Draft: 10/11/01, Final Draft: 11/16/01
6.4.3 Proposed Label for Indication: Reproduced from the Sponsor's submitted label.

INDICATIONS AND USAGE
INVANZ is indicated for the treatment of adult patients with the following moderate to severe infections caused by susceptible strains of the designated microorganisms (see DOSAGE AND ADMINISTRATION):

Complicated Skin and Skin Structure Infections due to *Staphylococcus aureus*, *Streptococcus pyogenes*, *Escherichia coli*, *Peptostreptococcus* species,

MO Comment: Based on my review that follows, I agree with the Sponsor's assessment that INVANZ is indicated in the treatment of complicated skin and skin structure infections.

Specific clinical information used to support this indication is cited in the Clinical Studies section of the label and is reproduced from the Sponsor's proposed label.

Complicated Skin and Skin Structure Infections

Ertapenem was evaluated in adults for the treatment of complicated skin and skin structure infections in a randomized, multicenter, double-blind, controlled clinical trial. This study compared ertapenem (1 g IV once a day) with piperacillin/tazobactam (3.375 g IV every 6 hours) for 7 to 14 days and enrolled 540 patients including patients with diabetic lower extremity infection, deep soft tissue abscess, posttraumatic wound infection and cellulitis with purulent drainage. The clinical success rates at 10 to 21 days posttherapy (test of cure) were 82.2% (152/185) for ertapenem and 84.5% (147/174) for piperacillin/tazobactam. The clinical success rates for ertapenem and piperacillin/tazobactam, respectively, at the test of cure for the infections under study were:
deep soft tissue abscess, 96.7% (29/30) and 94.4% (34/36); posttraumatic wound infection, 83.3% (25/30) and 84.6% (22/26); and cellulitis with purulent drainage, 93.1% (27/29) and 87.5% (21/24). The clinical success rates at the test of cure by pathogen in the microbiologically evaluable patients are presented in Table 9.

TABLE 1 (Reproduced from the Sponsor's study report)

Clinical Success Rates at the Test of Cure by Pathogen for Clinically Evaluable Patients With Complicated Skin and Skin Structure Infections		
Pathogen	Ertapenem % (n/N)*	Piperacillin/Tazobactam % (n/N)*
Staphylococcus aureus	76.1 (54/71)	78.9 (56/71)
Streptococcus pyogenes	81.3 (13/16)	93.8 (15/16)
Escherichia coli	94.1 (16/17)	80.0 (12/15)
Peptostreptococcus species	87.1 (27/31)	90.9 (20/22)

* Number of isolates with favorable response assessment/Total number of isolates

MO comment: The Clinical Studies section of the label should convey the evidence supporting effectiveness for the given indication, along with the critical design aspects of the study. Microbiologic efficacy is reflected in the Microbiology section of the label.

The Clinical Studies section of the label was revised to the following:

Complicated Skin and Skin Structure Infections
Ertapenem was evaluated in adults for the treatment of complicated skin and skin structure infections in a clinical trial. This study compared ertapenem (1 g intravenously once a day) with piperacillin/tazobactam (3.375 g intravenously every 6 hours) for 7 to 14 days and enrolled 540 patients including patients with deep soft tissue abscess, posttraumatic wound infection and cellulitis with purulent drainage. The clinical success rates at 10 to 21 days posttherapy (test of cure) were 83.9% (141/168) for ertapenem and 85.3% (145/170) for piperacillin/tazobactam.

6.4.4 Materials Reviewed:

Protocol 016 Clinical Study Report (Pivotal Study)
Protocol 003 Phase (Phase IIa Study)
Protocol 019 Skin Blister
Literature

Regulatory Background:
Protocol 016 submitted as Amendment
March 19, 1998) – Comments and answers to questions conveyed to sponsor on May 28, 1998 by teleconference.

December 21, 1999 teleconference discussing the Division's comments on the Sponsor's Data Analysis Plan (DAP) provided to the Sponsor via fax on December 20, 1999.

6.4.5 Protocol 016: A Prospective, Multicenter, Double-Blind, Randomized Comparative Study to Evaluate the Safety, Tolerability, and Efficacy of MK-0826 (Ertapenem) Versus Piperacillin/Tazobactam in the Treatment of Complicated Skin and Skin Structure Infections in Adults.

6.4.5.1 Objective/Rationale:

Primary:

- To compare the clinical efficacy of ertapenem versus piperacillin/tazobactam in the treatment of patients with serious complicated skin and skin structure infections (CSSSI) at the test-of-cure (TOC) visit 10 to 21 days posttherapy.
- To compare the safety profile of ertapenem versus piperacillin/tazobactam in the treatment of patients with serious CSSI, with regard to drug-related serious adverse events (SAE) and drug-related adverse events leading to drug discontinuation.

MO Comment: The specific safety objectives were outlined in protocol amendment 016-02.

Secondary:

- To compare the microbiologic efficacy of ertapenem versus piperacillin/tazobactam at the TOC visit in patients with serious CSSSI.
- To compare the efficacy of ertapenem versus piperacillin/tazobactam with respect to clinical and microbiologic assessment at the time of discontinuation of antibiotic therapy in individuals with CSSSI.
- To compare the tolerability of IV ertapenem versus piperacillin/tazobactam in patients with serious CSSSI.

6.4.5.2 Study Design:

The study was a prospective, multicenter, double-blind, randomized (1:1 ratio), active-treatment controlled trial. It was designed to demonstrate equivalence (noninferiority) of treatment with ertapenem versus piperacillin/tazobactam in the treatment of CSSSI. Forty-four centers participated in this study including 33 sites from the U.S. and 11 international sites (Central and South America).

MO Comment: Four of the 44 centers did not enroll any patients in the study (two in the U.S. and two international sites).

6.4.4.3 Protocol Overview

6.4.4.3.1 Study Population:

The targeted study population was adults with moderate to severe CSSSI likely to be treated with seven to fourteen days of parenteral antibiotics. Additionally, the inclusion criteria were designed to stratify the subjects into specific subgroups of CSSSI, including a population with diabetic lower extremity infections.

There were three major protocol amendments that refined these diagnostic criteria and the final version is summarized below from the sponsor's clinical study report (CSR).

Inclusion Criteria:

1. Adults, with a clinically and/or bacteriologically documented CSSSI, judged by the investigator to be serious (requiring parenteral therapy) and treatable within a 14-day period.

2. Clinical diagnosis of CSSSI required well-documented signs and symptoms of acute infection (present for approximately 7 days or less):

   MO Comment: The original protocol limited acute infection to present < seven days; this definition was revised in Protocol Amendment 016-01 to approximately seven days or less. This change allowed subjects with a longer duration of symptoms to enroll. Subjects with longer duration of symptoms were also likely to have been treated with prior antibiotics increasing the potential for resistant bacteria or confounding of results due to prior antibiotic therapy.

   Signs and Symptoms:
   Purulent drainage or collection related to the wound
   OR
   The presence of at least three of the following:
   1) Fever, T>37.8°C (100°F) oral, T>38.2°C (100.8°F) tympanic, T>38.4°C (101.0°F) rectal, within the 24 hours prior to enrollment.

   MO Comment: The sponsor's case report form (CRF) only recorded the temperature at the initial prestudy visit and there was not a means to capture the information about the subject's temperature in the preceding 24 hours. This limited the ability to use fever as a diagnostic criterion, since it confined measurement of temperature to one timepoint in a 24 hour period.

   2) White blood cell (WBC) count >10,000 with >5% bands.

   MO Comment: Many of the study sites utilized an automated CBC and did not have values for the percent of immature forms present, limiting the utility of

this parameter. In my review, I allowed use of a WBC > 10,000, without regard to differential, as a parameter.

3) Local erythema, >1 cm away from the wound edge or abscess cavity.
4) Localized swelling.
5) Localized tenderness or pain.
6) Localized fluctuance.
7) Lymphangitis associated with a skin lesion.
8) Localized warmth.
9) Localized induration.

Subjects with chronic skin diseases or indwelling foreign materials were excluded.

MO Comment: Subjects enrolled under the subcategory of traumatic wounds included patients with signs of infection at prior peripheral or central catheter sites. The difficulty in using subjects enrolled with these infections was in discerning whether the primary problem was intravascular versus involving skin and skin structure. In my analysis, I allowed subjects to be included if a peripheral site was involved, but excluded subjects with central catheter site infections because of increased risk for secondary intravascular complications, such as thrombus in the central veins.

3. Patients with either of the following 2 broad classifications of complicated skin and skin structure infections were included in this study:

A. Complicating underlying disease states such as:

[redacted]

2) Acutely infected pressure ulcers.

MO Comment: Per protocol, ulcers in these patients should have been of no greater than 14 days in duration and without underlying [redacted]. Subjects with ulcers of more chronic duration were enrolled if there was an acute sign of infection in the surrounding soft tissue. This presented problems in analysis, since these subjects had increased potential to be colonized with more resistant organisms such as Pseudomonas aeruginosa and methicillin-resistant Staphylococcus aureus.

B. All others, with subgroups:

1) Perineal abscesses, cellulitis, deep tissue infection where anaerobes or Enterobacteriaceae are likely.
2) Traumatic or surgical wounds.
3) Deep SSSI that develop in absence of known injury.
4) Extensive abscesses and infection of deep soft tissues requiring surgical incision and drainage.
5) Areas of extensive cellulitis (>10 cm.) accompanied by purulent drainage (PMN's and/or bacteria on gram stain) or purulent fluid collection.

MO Comment: The definition of purulence was modified by Protocol Amendment 016-01. The initial criterion of polymorphonuclear leukocytes (PMN's) and bacteria was modified to PMN's and/or bacteria.

4. Patients entered into the study had to have a wound culture obtained in the 48-hour period prior to study treatment. Persons with negative cultures were allowed to remain in the trial for assessment of clinical efficacy.

Exclusion Criteria: The complete list of criteria can be found in the Sponsor's clinical study report (Pages 41-45). The following list contains the criteria most pertinent to my review.

1. Patients with the following infections:

a) Uncomplicated skin infections: such as simple abscesses requiring only needle aspiration or surgical drainage, impetigo, furunculosis, carbunculosis, cellulitis (other than perineal), or folliculitis in normal hosts.
b) Infected burn wounds.
c) Necrotizing fasciitis.

[redacted]

e) Infections of prosthetic materials.
f) Wounds with concomitant gangrene likely to require amputation.

2. Infections known at admission to be caused by pathogens resistant to either study drug.

3. Patients treated with >24 hours of systemic antibiotic therapy known to be effective against the presumed or documented etiologic pathogen(s) within the 72-hour period immediately prior to consideration for entry into the study.

- Patients who had received up to 3 days of prior antibiotic therapy were entered if they had clinical evidence of treatment failure and a positive deep tissue bacterial culture. If culture results were not yet available at the time of admission, patients with a positive gram stain (demonstrating bacteria) could have been granted a waiver for admission to the study pending the culture results.
- Patients with clinical evidence of treatment failure who had received >3 days of prior antibiotic therapy were enrolled only if a deep wound culture demonstrated the presence of a susceptible pathogen and excluded the presence of a resistant pathogen such as methicillin-resistant *S. aureus* (MRSA) prior to enrollment.

MO Comment: The interpretation of prior antibiotic treatment is important in evaluating the results of this study. This was a heavily pretreated study population, with the sponsor's clinical study report indicating that 171 subjects (62.4%) of MK-0826 group and 155 (58.3%) of piperacillin/tazobactam subjects received antibiotics prior to study drug. The sponsor also outlined in their data analysis plan that subjects could receive up to one dose of a nonstudy antibiotic in the period between the admission culture and first dose of study drug. It was difficult to determine the precise timing and number of doses that a patient had received both from the datasets submitted and the actual CRFs that were submitted by the investigators.

- ***In my analysis of the data, if a patient had received more than one dose of nonstudy antibiotic in the 24 hours prior to study entry, I analyzed those individuals according to the "<3 days of antibiotic therapy rule". This required that a pathogen be isolated on entry culture for that subject to be clinically evaluable. This will be addressed further in my analysis of efficacy to follow.***
- ***Although the sponsor allowed individuals receiving < 3 days of prior treatment to be enrolled on the basis of a positive gram stain, there was still a requirement that there be a pathogen isolated for evaluability.***

5. The need for concomitant systemic antibacterials in addition to study drugs.

6. Concurrent infections interfering with the evaluation of response to the study antibiotic.

7. Immunodeficient patients such as patients with AIDS, or patients whose absolute neutrophil count (ANC) was <1000 cells/mm ^{3}. Also included were patients on immunosuppressive therapy or high-dose (e.g., $\geq$ 40 mg of prednisone or equivalent per day) corticosteroids.

8. Patients requiring peritoneal dialysis or hemodialysis or hemofiltration.

6.4.4.3.2 Procedures:

All patients had clinical and laboratory assessments as outlined in table 2 below .

TABLE 2 (reproduced from the Sponsor's study report, page 13, Table1)

Schedule of Clinical Observations and Laboratory Measurements					
Assessment/ Procedures	Eligibility Screening	On-Therapy Assessment	Every 4 to 5 Days After On-Therapy Assessment	Discontinuation of Therapy	Follow-up (10 to 21 Days Posttherapy)†
Medical history obtained (including wound history)	X				
Pregnancy test	X‡				
Physical exam and VS	X	X		X	X
Monitored for AE		Daily During Therapy§	Daily During Therapy	X	X
Monitored local tolerability		Daily During Therapy	Daily During Therapy	X	
Hematology	X	X	X		X
Chemistry	X	X	X		X
Urinalysis	X	X	X		X
Clinical Efficacy Evaluation					
Signs and symptoms, wound description	X	X		X	X
Clinical response rating				X	X
Microbiological Efficacy Evaluation					
Blood culture and susceptibility	X%	X¶		X¶	X¶
Wound culture and susceptibility	X	X#		X#	X#
Gram stain	X	X#		X#	X#

† Or after early withdrawal.
‡ Performed on all women of childbearing potential.
§ Monitored for adverse experiences daily during therapy and for 14 days after completion of therapy.
% Two sets were to be obtained.
¶ Blood cultures (2 sets) were to be performed only if prior blood culture was positive or if clinically indicated.
# Obtained culture only if there were signs of ongoing or relapsing infection and if a valid sample was available.

Stratification
In order to achieve balance (comparability), patients were stratified based on the presence of a significant underlying disease state that may have complicated their response to therapy.
1. Stratum I included patients with complicating underlying disease states such as:

b. Acutely infected pressure ulcers: ulcers should have been no greater than 2 weeks in duration, although more chronic ulcers could be included if a significant acute change was present

2. Stratum II included patients with all other diagnoses of CSSSI.

MO Comment: The CRF provided the following categories for Stratum II:

- ***Perineal cellulitis or abscess***
- ***Cutaneous abscess***
- ***Deep soft tissue abscess (specify)***
- ***Cellulitis with purulent drainage (including positive gram stain)***
- ***Surgical site infection***
- ***S/P trauma wound infection***
- ***Other (specify)***

These categories are reflective of those CSSSI outlined in the protocol and are generally acceptable to this reviewer, although the diagnosis of cutaneous abscess is potentially one where uncomplicated SSSI might be included in this study. The Division's 1992 Points to Consider Document and 1998 Guidance for Developing Antimicrobial Drugs for Treatment of Uncomplicated and Complicated SSSI consider the following categories: infected ulcers, burns, and major abscesses or skin structure infections requiring significant surgical intervention along with antimicrobial treatment and infections of the deeper soft tissues. The 1998 guidance document also allows for the inclusion of infections where a significant underlying disease state complicates the response to treatment.

Wound Care

Complete surgical drainage or debridement of infected wounds or abscesses was required before patient enrollment. Wound management procedures during the study and considered by the investigator to be "standard of care," including periodic local debridement of devitalized tissue, were permitted. Patients requiring nonroutine surgical treatment more than 48 hours after the first dose of study antibiotic therapy because of failure to improve, clinical worsening, or the discovery of a new purulent collection necessitating incision and drainage, were considered clinical failures.

Bacterial Cultures / Susceptibilities

An appropriate deep wound culture (anaerobic and aerobic) and gram stain from the site of the SSSI were required at the time of enrollment. Cultures of superficial surface swabs were not acceptable. Acceptable methods of sample collection included needle or surgical aspiration of abscess material, swabbing of the wound base after surgical debridement of devitalized tissue, leading edge aspiration of cellulitis, punch biopsy, and curettage of the wound base after debridement. Subsequent wound cultures may have been obtained if there were signs of ongoing or relapsing infection and if an appropriate sample was available.

MO Comment: Despite these outlined methodologies for culture collection, the specimens were often labeled "exudate", implying a more superficial, swabbing of the wound site. This makes interpretation of cultures containing normal skin flora difficult and potentially confounds results.

Blood cultures to test for bacteremia were also performed at admission and were repeated at subsequent time points only if the patient was bacteremic at admission or if clinically indicated.

In Vitro Antibiotic Susceptibilities of Etiologic Pathogens

Susceptibilities of etiologic pathogens to MK-0826 and piperacillin/ tazobactam were determined by disk diffusion or by MIC according to the standard testing methodology used by the investigator's microbiology laboratory. The National Committee for Clinical Laboratory Standards (NCCLS) interpretive criteria were used for determining the susceptibilities to antimicrobial agents other than MK-0826.
A definitive interpretive standard for the determination of susceptibility to MK-0826 has not yet been established. NCCLS-approved provisional breakpoints were used as tentative interpretive standards for MK-0826 to determine susceptibility.

Randomization, Allocation, Dosing, and Administration

Patients with complicating underlying disease states (Stratum I) and those with other CSSSI (Stratum II) were randomized separately. At each site, patients were randomized in a 1:1 fashion, according to the randomization schedule provided by the Sponsor.

MK-0826 was given as a single daily dose of 1.0 g intravenously infused over a 30-minute interval. Piperacillin/tazobactam was given every 6 hours, 3.375 g per IV dose, infused over a 30-minute interval. In order to maintain blinding, a piperacillin/tazobactam placebo was administered intravenously at hours 6, 12,and 18 of the daily dosing interval to patients randomized to receive MK-0826. Doses were adjusted for renal insufficiency (creatinine clearance < 30 for ertapenem and ≤ 40 for piperacillin/tazobactam as outlined in the sponsor's study report.

The investigator, study nurse, patient, and person administering the study drug were blinded to the specific antibiotic regimen. A piperacillin/tazobactam look-alike placebo, consisting of 0.9% sodium chloride for injection, was used for the MK-0826 group. While the study was ongoing, it was noted that when MK-0826 was visualized beside a placebo infusion, there may have been a slight color variation. Consequently an enhanced blinding procedure including infusion bag covers was implemented.

Efficacy Variables

Clinical Signs and Symptoms
An evaluation of clinical signs and symptoms of infection and a detailed description and assessment of the infected area was performed at admission, at the on-therapy assessment (Day 3, 4, or 5), at the discontinuation of IV therapy (DCIV), and at the TOC visit.

Wound assessment included:

- The detailed description and measurement of the infected area.
- Presence of lymphangitis.

- The following signs and symptoms were graded by the investigator as none, mild, moderate, or severe (0-3 scale) based upon the extent of each at the site of the wound: pain or tenderness, erythema, warmth, swelling, induration, and fluctuance.

Safety Variables

Monitoring for Adverse Experiences
All patients who received at least 1 dose of parenteral study drug were evaluated for safety. The safety of IV MK-0826 and of IV piperacillin/ tazobactam was evaluated by determining the presence or absence of adverse clinical or laboratory experiences. Patients were monitored during the IV study period and for 14 days after the discontinuation of IV study antibiotic therapy.

Serious Adverse Experiences
Serious adverse experiences (SAE) were to be reported within 24 hours to Merck. SAE definitions corresponded to those outlined in 21 CFR 312.32. Additionally, events that might jeopardize the patient and require medical or surgical intervention to prevent one of the defined serious outcomes could be considered serious. Merck & Co., Inc. also required the reporting of cancer and overdose (whether accidental or intentional).

Selected adverse experiences of special interest, whether serious or not, and whether or not considered related to study drug, were to be reported within 24 hours to Merck. These included:

- Seizures (regardless of prior seizure history)
- Elevated transaminases (AST and/or ALT) defined as: Values >3 × ULN or >3 × the baseline value for patients with elevated transaminases at entry.
- Neutropenia defined as ANC <1.8 ths/mm^3 or ANC decrease to <50% of entry value (or <0.5 ths/mm^3) for those who enter the study with ANC 0.5 to 1.8 ths/mm^3.
- Rash of sufficient severity to require discontinuing study antibiotic.

Laboratory Studies for Safety

Table 3 lists the laboratory safety tests that were completed for all patients.
The investigator was required to identify and comment on any laboratory test abnormality and repeat the laboratory test until the abnormal parameter had normalized, stabilized, or returned to baseline.

TABLE 3 (Reproduced from sponsor's study report, page 39, Table 11)

Laboratory Safety Tests

Hematology	Blood Chemistry	Urinalysis
Hemoglobin	Albumin	Protein
Platelet count	Alkaline phosphatase	Glucose
Prothrombin time	Blood urea nitrogen (BUN)	Microscopic:
Partial thromboplastin time	Calcium	WBCs, red blood cells (RBCs), bacteria
White blood cell (WBC) count, total and differential	Serum β-hCG†	Casts other than hyaline
	Serum bicarbonate	
	Serum creatinine	
	Serum glucose	
	Serum electrolytes: Chloride, potassium, sodium	
	Total protein	
	Total bilirubin‡	
	Aspartate transaminase (AST)	
	Alanine transaminase (ALT)	

† β-hCG = beta-human chorionic gonadotrophin. Test required for woman of childbearing potential only.
‡ Bilirubin was fractionated (direct/indirect) if total bilirubin was greater than the upper limit of normal.

Data Source: [3.3.4]

Local Tolerability
The tolerability of IV MK-0826 and piperacillin/tazobactam at the local infusion site was evaluated by the investigator or person infusing the study drug. At the discretion of the investigator, local reactions may also have been reported as adverse experiences. The intensity ratings and rating criteria used to assess the tolerability symptoms are in Table 12.

6.4.5.3.5 Evaluation (Data Analysis Plan)

Efficacy Evaluation

Efficacy variables were assessed using an "evaluable patients only" approach and a "modified intent-to-treat" approach.
The sponsor's definition of the modified intent-to-treat (MITT) population included all patients who received at least one dose of study medication and met the minimum criteria for disease outlined in their evaluability document. This diagnosis required a subject to have a CSSSI requiring parenteral antibiotics as evidenced by the presence of one of two broad classifications of CSSSI defined in the protocol and a purulent drainage or collection or at least three well-documented signs and symptoms. In addition to being clinically evaluable, these patients were also microbiologically evaluable if there was a pathogen identified in the baseline culture.

MO Comment: In defining my MITT population I used <u>both</u> the inclusion and exclusion criteria outlined in the study protocol for enrollment. By incorporating exclusion criteria evident at study entry (example: gangrenous toe present in a patient with a CSSSI of the foot) I eliminated five subjects (4 MK-0826, 1

piperacillin/tazobactam) from the MITT population after a review of 60% (325/540) of the CRFs.

The "Evaluable Patients" or "per protocol" (PP) population included all patients that met the evaluability criteria outlined in the Sponsor's data analysis plan. In addition to being clinically evaluable, these subjects were also microbiologically evaluable if a pathogen was isolated on baseline culture. The Merck Clinical Monitor, blinded to treatment assignment, identified those patients who were considered evaluable for inclusion in the "evaluable-patients-only" analysis.

Efficacy Evaluability Criteria for Protocol 016: (Appendix 3.4, page 1293-1295 of CSR)

A) Diagnosis: CSSSI requiring parenteral antibiotics as evidenced by:
   Purulent (Gram stain with bacteria and/or WBC) drainage or at least three well documented signs and symptoms.
   One of two broad classifications of CSSSI defined in protocol.
   Complicated cellulitis should meet size and drainage requirements, although cellulitis without purulence is complicated if admission blood culture is positive.

B) TOC visit 7-30 days after the end of study therapy.

C) Missed or erroneous doses: Patients should receive ≥ 80% of the intended doses (blinded assessment 4 doses/day, unblinded confirmation MK-00826 1 dose/day and piperacillin/tazobactam 4 doses/day).

D) Duration of therapy:
   - ≥5 and ≤17 days of study treatment to be considered evaluable cure
   - >48 hours to be considered evaluable failure

E) Evaluability Exclusions:
   1) Prior antimicrobials:
      a) ≥ 24 hours prior to enrollment, unless there is clinical failure with a persistent pathogen identified on culture.

MO Comment: The exclusion criteria outlined in the protocol did specify patients receiving >24 hours of antibiotic therapy prior to study entry would be excluded if they failed to have a pathogen isolated on the entry culture. Subjects receiving >24 hours of antibiotics were further subdivided into a group receiving up to three days and a group receiving greater than three days of prior antibiotic therapy, but both of these groups ultimately had to have a pathogen isolated in culture to be included.

      b) > one dose of effective non-study antibiotic between the time of culture and the first dose of study drug.

MO Comment: Based on information presented in the CRFs, it was not always possible to determine if antibiotics given in the 24 hours prior to the first dose occurred before or after the time of pre-study culture. Therefore, in my review, subjects who received more than one dose of non-study drug in the day corresponding to study entry were excluded from analysis.

2) Concomitant antimicrobials
    a) from study entry through TOC, more than one dose of a systemic antimicrobial with activity against the pathogen under study for reasons other than clinical failure.
    b) > 24 hours of topical antibiotics.
3) Exclusion due to baseline or intercurrent events:
    a) Patients must not have any of the following at entry or within 48 hours of entry to study
        - Infections excluded at baseline as specified previously under exclusion criteria.
        - ANC < 500 cells/mm^3 prior to treatment
    b) Patients must not have any of the following at entry through TOC:
        - DVT
        - Concurrent infection which interferes with evaluation of response to study antibiotic
        - Concurrent medical or surgical condition which interferes with assessment of response to therapy.
        - Chronic immunosuppressive therapy or AIDS.
4) Exclusion due to baseline microbiology: isolation of a pathogen which is not susceptible to either study drug.

MO Comment: Evaluability status of subjects with non-susceptible pathogens may not have been consistently applied due to somewhat conflicting statements in the sponsor's study report. The evaluability exclusion in #4 above was inconsistent with the statement made in the protocol about discontinuation of patients from therapy. "If the admission pathogen (unknown at admission) was found during the study to be resistant to either of the study drugs, and there was no clinical improvement, the patient was discontinued as a failure; if the patient was improved, he/she could have remained in the study at the discretion of the investigator." (study report, page 21). This could have led to confounding of results, although it tends to influence in a negative fashion because failures are counted and cures made non evaluable.

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6.4.5.3.4 Endpoints

Clinical Response
The primary efficacy parameter was the proportion of patients who had a favorable clinical response assessment at the 10- to 21-day post-treatment follow-up (TOC) visit. The clinical responses and definitions used at TOC are in Table 4.

TABLE 4 (Reproduced from sponsor's study report, Table 9, page 33)

Clinical Responses and Definitions at Test of Cure	
Clinical Response	Rating Criteria
Cure	All or most pretherapy signs and symptoms of the index infection had resolved and showed no evidence of resurgence, and no further antibiotic therapy was required. (Fever, lymphangitis, and purulent drainage must have been resolved.)
Failure	Patients carried forward from the DCIV assessment. Patients who were missing a DCIV clinical assessment were also considered failures if there was no response to therapy; persistence or progression of most/all pretherapy signs and symptoms.
Relapse	Patients with a favorable response (cure) at the DCIV assessment who had worsening signs and symptoms by the 10- to 21-day follow-up visit and required antibiotic therapy.
Indeterminate	Study data were not available for evaluation of efficacy for any reasons, including: (a) complication related to underlying medical condition (b) patient was withdrawn for any reason before sufficient data had been obtained to permit evaluation of clinical outcome (c) extenuating circumstances precluded classification as a cure or failure

The clinical responses assigned at DCIV were similar, but did not include the relapse category. For an overall favorable clinical response rating at either time point, each infected wound clinically assessed at admission to the study must have received a favorable clinical response rating at that time point.

Microbiologic Response

The microbiology of each subject's infectious process was determined by aerobic and anaerobic cultures of blood, wound, and other appropriate samples. A microbiological response was assessed separately for each pathogen identified in the admission wound and blood cultures at the on-therapy assessment (Day 3, 4, or 5), at DCIV, at TOC, and for any unscheduled visit at which an additional culture was obtained. The microbiological responses and their definitions are in Table 5.

TABLE 5 (Reproduced from sponsor's study report, Table 10, page 35)

Microbiological Responses and Definitions	
Microbiological Response	Definition
FOR PATHOGENS ISOLATED IN THE ADMISSION CULTURE	
Eradication	Original pathogen was absent from the culture of an adequate specimen obtained from the original site of infection.
Presumptive eradication	The patient showed a favorable clinical response and no appropriate material was available to culture from the original site of infection, or the collection of such a specimen would have caused the patient undue discomfort.
Persistence	Continued presence of the original pathogen in cultures from the original site of infection obtained during or upon completion of therapy, with or without clinical evidence of inflammation or infection.
Persistence acquiring resistance	Continued presence of the original pathogen in cultures from the original site of infection obtained during or upon completion of therapy, with or without clinical evidence of inflammation or infection and the pathogen that was susceptible, moderately susceptible, or intermediate to study drug pretreatment had become resistant to study drug therapy posttreatment.
Presumed persistence	In patients who are judged to be clinical failures, and a culture was not possible or was not done, it was presumed that there was persistence of the original pathogen.
Relapse	A pathogen originally identified in the admission culture and subsequently eradicated from the original site of infection reappeared in subsequent cultures obtained (at any time) from the original site of infection.
Relapse with resistance	A pathogen originally identified in the admission culture and subsequently eradicated from the original site of infection reappears in subsequent cultures obtained (at any time) from the original site of infection and the pathogen that was susceptible, moderately susceptible, or intermediate to study drug pretreatment had become resistant to study drug.
Indeterminate	(a) Follow-Up cultures were not available due to patient death or withdrawal from study; (b) microbiological data were incomplete; (c) pretreatment culture was negative; (d) any other circumstance which makes it impossible to define the microbiological response.
FOR PATHOGENS FIRST ISOLATED AFTER THE ADMISSION CULTURE	
Superinfection	Emergence of a new pathogen during therapy, either at the site of infection or at a distant site with emergence or worsening of associated clinical or laboratory evidence of infection (e.g., local inflammation, purulence, fever, leukocytosis, new infiltrate).
New infection	After the completion of therapy, the appearance of a new bacterial species or, a new serotype or biotype of an admission pathogen at the original site of infection, or at a site distant from the primary infection, with signs or symptoms of infection.

Microbiological responses other than "indeterminate" were classified as favorable or unfavorable. Favorable microbiological response assessments include "eradication" and "presumptive eradication." Unfavorable microbiological response assessments include "persistence," "presumed persistence," or "relapse." For patients from whom more than 1 pathogen was isolated, the overall microbiological response assessment was "favorable" only if the microbiological response assessment for each of the pathogens isolated was "favorable."

6.4.5.3.5 Statistical Considerations

This study was designed to show equivalence (non-inferiority of MK-0826) of efficacy for the 2 treatment groups. The definition of equivalence is that the 95% (two-sided) CI for the difference in response rates between the 2 treatment groups

(test drug group minus control group) contains zero and the lower limit of the CI is not less than -10 percentage points if a 90% or better response rate is observed for the control group; -15 percentage points if a response rate <90% and =80% is observed for the control group; and -20 percentage points if a response rate <80% and =70% is observed for the control group.

MO Comment: The sponsor used a graduated scale for determining the acceptable difference in response rates necessary to demonstrate equivalence of the two products. While this had been the practice of the Division prior to 1998, the Sponsor was aware that the Division was revisiting statistical guidance on definitions of noninferiority. During discussions of the protocol, the Division and sponsor agreed that a 10% delta would be applied to this indication.

For clinically evaluable patients, the following endpoints were analyzed:

- The proportion of patients with a favorable clinical response assessment at the 10- to 21-day post-therapy follow-up visit (TOC visit).
- The proportion of patients with a favorable clinical response assessment at the discontinuation of antibiotic therapy visit (DCIV).

For clinically and microbiologically evaluable patients, the following endpoints were analyzed:

- The proportion of patients with a favorable clinical and microbiological response assessment at the TOC visit.
- The proportion of patients with a favorable clinical and microbiological response assessment at the DCIV.

An analysis was also performed on the population of microbiologically evaluable patients to determine the proportion with a favorable microbiological assessments at DCIV and at TOC .

Once a patient had an "unfavorable" clinical assessment, the patient was counted as having that "unfavorable" response at all subsequent time points. For the MITT analysis, in patients missing a TOC assessment, the last evaluation before TOC was used.

MO Comment: The sponsor was informed by the Division that there was agreement in failures being carried forward to TOC; however without an assessment at TOC, it was not acceptable for cures to be carried forward.

The 2 treatment groups were compared for the efficacy parameters at each relevant time point. The differences in proportions (MK-0826 minus piperacillin/tazobactam) were calculated, along with the corresponding 95% CI. CIs were calculated using the normal approximation to the binomial distribution. The estimated CIs for the difference between treatment groups account for stratification based on the Cochran-Mantel-Haenszel (CMH) approach.

Examination of Subgroups

Subgroup analyses for stratum (diagnoses complicated by underlying disease versus all other diagnoses of complicated skin and skin structure infections), age, race, and gender were performed for the primary efficacy endpoint in the per protocol "evaluable-patients-only" population. The minimum sample size needed in order for the analysis to be performed was at least 10 patients in either subgroup.

6.4.5.4. **STUDY RESULTS**

6.4.5.4.1. Evaluability

The sponsor's assessment of evaluability was based on entry criteria and modifications or clarifications as outlined in the data analysis plan. The sponsor's study report indicates that 540 patients in this study (274 in the Invanz group and 266 in the piperacillin/tazobactam group) were randomized to study treatment. Of these 540 subjects, 359 (185 in the Invanz group and 174 in the piperacillin/tazobactam group) were clinically evaluable ("per protocol" group).

> ***MO Comment: A random sample, blinded with respect to treatment group, of 57 subjects (approximately 10% of subjects enrolled) was selected by the Division's statistician and individual CRFs were examined by the medical officer. The results of this review and comparison to the sponsor's evaluation is presented in Appendix A.***
>
> ***The statistician applied a bootstrap methodology to determine whether the MO determinations matched those of the sponsor. Based on the MO's determination, there was a difference in clinical evaluability status and outcome in four subjects, all in the Invanz treatment group. These results indicated that there were statistically significant differences in the sponsor's and medical officer's assessment of evaluability and outcome determinations.***
>
> ***Factors that accounted for the differences were identified and a review of additional CRFs with these factors was undertaken. The five areas of discrepancy identified and discussed below include:***
>
> 1. ***Prior antibiotic administration***
> 2. ***Concomitant and post study antibiotic administration***
> 3. ***Diagnostic category of purulent cellulitis***
> 4. ***TOC visits***
> 5. ***Stratum of "diabetic lower extremity" infection***

MO Subgroup Analysis
Prestudy Antibiotic Administration
The sponsor had specific exclusion criteria and statements in the data analysis plan that outlined the conditions necessary for evaluability of subjects receiving antibiotics prior to study entry (for example, $\geq$ 24 hours of treatment within the 72-hour period immediately prior to study entry required the presence of a pathogen on culture).

MO Comment: A review of the sponsor's datasets, indicated that 81 subjects had a history of prestudy antibiotic administration and admission cultures that were either negative or contained organisms consistent with normal flora (MK-0826: 171/271, 62.4% / P/T: 155/266, 58.3%). The CRFs of these subjects were reviewed by the MO blinded to treatment status. The sponsor had considered 40 patients evaluable. The MO changed evaluability or outcome in 17 subjects as noted in the table below:

TABLE 6

Subject	Clinical Evaluability Change		Micro Evaluability Change		Reason
	Sponsor	MO	Sponsor	MO	
6-4050	PP NE	PP E	MITT E	MITT NE	Antibiotics 6 days prior Coag neg *Staph* not groin pathogen
6-4053*	PP E	PP NE	MITT E PP E	MITT NE PP NE	Prior antibiotics unknown duration Culture respiratory flora, no pathogen
6-4571	PP E	PP NE	MITT E PP E	MITT NE PP NE	Antibiotics in 72 hours prior to entry Coag neg *Staph* not pathogen
6-4574	PP E	PP NE	MITT E PP E	MITT NE PP NE	Prior antibiotics for 2 weeks Culture diphtheroids and viridans *Strep*
13-4174	PP E	PP NE	MITT NE PP NE	no change	1 dose pre-op antibiotics, no pathogen Abdominal wall inflammation secondary to incarcerated hernia, not CSSSI
13-4724	PP E	PP NE	MITT E PP E	MITT NE PP NE	Antibiotics in 48 hours prior to entry Culture mixed flora, no pathogen
17-4352	PP E	PP NE	MITT E PP E	MITT NE PP NE	1 dose 48 hours prior to entry Purulent cellulitis, gram stain neg Coag neg *Staph* not pathogen
24-4633	PP E	PP NE	PP E	PP NE	Prestudy antibiotics Osteomyelitis within 48 hours entry
24-4635	PP E	PP NE	MITT NE	no change	>1 dose 24 hr prior to entry Neg gram stain, neg culture
24-4642	PP E	PP NE	MITT NE	no change	Antibiotics 2 days prior to entry Coag neg *Staph* not pathogen
24-4644	PP E	PP NE	MITT NE	no change	2 doses in 24 hours prior to entry neg culture
26-4807*	PP E	PP NE	MITT NE	no change	3 days prestudy antibiotics *Bacillus* sp. isolated, contaminant
28-4548	PP E	PP NE	MITT E PP E	MITT NE PP NE	1 dose prior antibiotics, Coag neg *Staph* not pathogen in foot pus Entry X-ray suspicious for osteomyelitis
39-4486	PP E	PP NE	MITT NE	no change	Multiple doses in 24 hr prior neg culture

- * Subjects included in random sample.
- MITT-modified intent to treat, PP-per protocol, E-evaluable, NE-non evaluable
- Three subjects (7-4359, 7-4373, 13-4182) not included in the table were considered failures (indeterminate result in MITT population) because they did not have a TOC visit.

Concomitant or Post-Study Antibiotic Treatment:

The next group of subjects identified with possible discrepancies between sponsor and MO interpretation, were those subjects, who by review of the sponsor's datasets, had received antibiotics during or following study treatment. Evaluability criteria for these individuals was outlined in the sponsor's data analysis plan.

MO Comment: One hundred ninety one patients were identified and the CRFs of these individuals were reviewed by the MO blinded to treatment assignment. The sponsor considered 95 of these subjects evaluable (and 96 of these subjects unevaluable).

Sponsor Excluded:

The MO changed evaluability and/or outcome of 11 of the sponsor's excluded population.

- ***Three subjects considered to be clinically nonevaluable by the sponsor were changed to clinically evaluable by the MO.***
    - ***6-4699: concomitant superficial antiseptic, required operative debridement of hematoma and infection four days after study entry (failure).***
    - ***29-4820: post study antibiotics for continued treatment of pressure ulcers (failure).***
    - ***36-4975: post study antibiotics for late myositis secondary to Strep. pyogenes facial cellulitis (failure).***
- ***One subject, considered to be MITT evaluable cure (clinically and microbiologically) by the sponsor, was considered MITT nonevaluable by the MO.***
    - ***28-4567: MO concern with possible intravascular infection, central venous catheter.***
- ***One subject (3-4219) considered to be clinically MITT evaluable by both sponsor and MO, was also felt to be microbiologically MITT evaluable by the MO (sponsor nonevaluable) because pathogens were isolated on entry culture.***
- ***Six additional subjects (ANs: 13-4169, 18-4138, 20-4019, 23-4428, 24-4523, 25-4446) had outcome changes based on MO review. These changes are not outlined here, since the changes only affected the MITT analyses.***

Sponsor Included:

The MO changed the evaluability and/or outcome status of 13 of the sponsor's included subjects.

- ***Four subjects, MITT and PP evaluable both clinically and microbiologically by the sponsor, were considered to be nonevaluable in these aspects by the MO because of exclusion criteria outlined in the protocol.***
    - ***6-4049: furuncle considered to be uncomplicated SSSI by MO***
    - ***7-4368: chronic skin condition (hidradenitis)***
    - ***7-4374: chronic skin condition (hidradenitis)***
- ***Seven subjects, PP evaluable both clinically and microbiologically by the sponsor, were considered to be nonevaluable by the MO.***

- ***6-4701: concomitant viral infection (varicella zoster) which precluded evaluation of bacterial infection***
- ***7-3703: no clinical exam at TOC (phone follow-up not sufficient)***

- ***39-4479: no TOC visit (patient transferred to another institution)***
- ***39-4491: concomitant infection (sacroilitis) confounding response to treatment***

- ***One subject, 2-4038, who the sponsor had considered a PP clinical evaluable cure, was changed to clinical evaluable failure because of surgical I & D procedure four days after study entry.***
- ***One subject, 34-3561, had a minor change in microbiologic data, with MO determining that one of the identified pathogens (Streptococcus intermedius) was a colonizing organism.***

Purulent Cellulitis Category:
The diagnostic category of cellulitis with purulent drainage was then examined in detail. In Protocol Amendment 016-001, the sponsor had altered the definition of purulence to include WBC's and/or bacteria on gram stain.

MO Comment: There were 53 evaluable subjects out of 75 randomized subjects with this diagnosis. MO review of gram stain results of subjects with this diagnosis: 41 subjects with both WBC and bacteria, 4 subjects with WBC, but no bacteria (accepted by MO), 3 subjects with bacteria, but no WBC (sponsor accepted, 1 P/T, 1 E), and 5 subjects with no WBC or bacteria on gram stain. Analysis of the CRFs from the five individuals with no purulence (as defined by the sponsor) on gram stain were reviewed and were found acceptable to the MO based on composite of systemic symptoms or isolation of true pathogens (one of the five subjects had an alternate diagnosis). Therefore, no adjustment was felt to be necessary.

Test of Cure Visits:

MO Comment: In reviewing the random sample, I noted that one subject (7-3073) did not have a TOC visit at study end as was specified in the protocol. The sponsor had considered this patient to be clinically evaluable and a "cure". Telephone discussions were held with the sponsor on May 23 and 24, 2001 and the sponsor provided a written response stating this was the only subject without an actual follow-up visit that was designated as a cure. Because the protocol had required a visit and wound assessment at TOC, I considered this subject to be nonevaluable. Five other subjects (2-4035, 19-4302, 6-4696, 7-4358, and 25-4448) were considered evaluable "failure", the first four secondary to amputation of affected limb (no exam possible) and the fifth for initiation of concomitant antibiotic for clinical failure without specific wound assessment the same day.

2 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Approximately two thirds of the subjects randomized to treatment were "Per Protocol" clinically evaluable. Medical Officer review yielded fewer subjects in the clinically evaluable "per protocol" population in both groups, although the Invanz treatment group was affected the most, with the loss of 17 evaluable subjects.

TABLE 8

NUMBER OF RANDOMIZED SUBJECTS INCLUDED IN EACH EVALUATION GROUP				
EVALUATION GROUP	APPLICANT		MO	
	INVANZ N=274	PIPERACILLIN/ TAZOBACTAM N=266	INVANZ N=274	PIPERACILLIN/ TAZOBACTAM N=266
Clinical MITT Subjects	269 (98.2%)	258 (97.0%)	265 (96.7%)	257 (96.6%)
Micro. MITT Subjects	192 (70.1%)	190 (71.4%)	187 (68.2%)	186 (69.9%)
Clinically Evaluable Subjects	185 (67.5%)	174 (65.4%)	168 (61.3%)	170 (63.9%)
Micro. Evaluable Subjects	155 (56.6%)	151 (56.8%)	144 (52.6%)	146 (54.9%)

6.4.5.4.2 Demographics

TABLE 9 (Reproduced from the sponsor's study report, page 62, Table 18)

Baseline Patient Characteristics by Treatment Group
(Randomized Population)

	MK-0826 (N=274)	Piperacillin/ Tazobactam (N=266)	Total (N=540)
	n (%)	n (%)	n (%)
Gender			
Female	93 (33.9)	96 (36.1)	189 (35.0)
Male	181 (66.1)	170 (63.9)	351 (65.0)
Race			
Asian	0 (0.0)	2 (0.8)	2 (0.4)
Black	47 (17.2)	50 (18.8)	97 (18.0)
Caucasian	160 (58.4)	145 (54.5)	305 (56.5)
Hispanic	48 (17.5)	50 (18.8)	98 (18.1)
Mestizo	15 (5.5)	16 (6.0)	31 (5.7)
Mexican	0 (0.0)	1 (0.4)	1 (0.2)
Mulatto	2 (0.7)	1 (0.4)	3 (0.6)
Spanish American	2 (0.7)	1 (0.4)	3 (0.6)
Age (Years)			
18 to 40	87	98	185
41 to 64	138	109	247
65 to 74	27	36	63
≥75	22	23	45
Mean	48.7	48.0	48.4
SD	16.5	17.4	16.9
Median	47.0	45.0	46.0
Range	18 to 99	18 to 89	18 to 99

MO Comment: Table 9 illustrates the demographic distribution of subjects enrolled in this trial. The subsequent determination of the clinically evaluable population for each treatment group yielded a population that was similar in distribution in terms of race, gender, and age. (This will be illustrated in a table indicating results stratified by subgroup later in this review).

Table 10 illustrates the number of patients enrolled by each investigator and those subsequently considered "Per Protocol" clinically evaluable by the sponsor.

TABLE 10

NUMBER OF PATIENTS ENROLLED AND SUBSEQUENTLY CONSIDERED EVALUABLE BY SITE AND INVESTIGATOR							
Site	Investigator	MK—0826		P/T		TOTAL	
		Entered N=274	Evaluable N=185	Entered N=266	Evaluable N=174	Entered N=540	Evaluable N=359
002	Bauwens, J. Eric	8	6	10	7	18	13
003	Eng, Robert	5	3	3	2	8	5
004	Gainer, Robert Brooks	1	1	1	0	2	1
005	Gezon, John	2	0	1	0	3	0
006	Graham, Donald	29	19	28	11	57	30
007	Klein, Stanley	12	6	13	8	25	14
008	Kurtz, Terrance	1	1	0	0	1	1
010	Livingston, David	2	0	1	0	3	0
011	Mader, Jon T.	4	2	4	2	8	4
012	Nahass, Ronald	4	3	2	2	6	5
013	Nichols, Ronald Lee	14	7	15	6	29	13
015	Parish, Lawrence C.	10	7	10	8	20	15
016	Salomone, Jeffrey	3	0	3	1	6	1
017	Schwartz, Robert	10	8	10	7	20	15
018	Standiford, Harold C.	4	2	4	3	8	5
019	Tan, James	3	1	2	2	5	3
020	Ekengren, Francie H.	5	2	6	4	11	6
022	Gelfand, Michael	1	0	0	0	1	0
023	Wilson, Samuel Eric	3	1	2	0	5	1
024	Lucasti, Christopher	20	14	19	10	39	24
025	Tice, Alan	6	5	6	4	12	9
026	Lema Osores, Juan	14	12	14	10	28	22
027	Wittmann, Dietmer	4	3	3	0	7	3
028	Mangiante, Eugene	0	0	2	1	2	1
029	Lopardo, Gustavo	3	2	1	1	4	3
030	Jasovich, Abel	6	6	5	5	11	11
031	Poole, John	1	1	3	3	4	4
033	Lima, Ana Lucia	10	9	10	8	20	17
034	Quintero Perez, Nora	15	13	15	14	30	27
036	Garreaud, Claudia	5	2	5	5	10	7
037	Marcano, Hector	10	10	9	9	19	19
039	Patzakis, Michael	23	13	23	17	46	30
040	Miskin, Barry	2	2	2	1	4	3
042	Postier, Russell	5	3	6	2	11	5
043	Okhuysen, Pablo	5	2	4	2	9	4
045	Hanna, Charles	2	2	2	1	4	3
046	Geckler, Ronald	2	0	2	0	4	0
049	Malafaia, Osvaldo	20	17	20	18	40	35

6.4.5.4.3 Efficacy

6.4.5.4.3.1 Clinical Efficacy

The primary endpoint for the study was the clinical response rate at the TOC visit. The results are presented in Table 11.

TABLE 11

CLINICAL RESPONSES OF CLINICALLY EVALUABLE SUBJECTS AT TOC VISIT				
CLINICAL RESPONSE	APPLICANT		MO	
	INVANZ (N=185)	PIPERACILLIN/ TAZOBACTAM (N=174)	INVANZ (N=168)	PIPERACILLIN/ TAZOBACTAM (N=170)
Favorable	152 (82.2%)	147 (84.5%)	141 (83.9%)	145 (85.3%)
Unfavorable	33 (17.8%)	27 (15.5%)	27 (16.1%)	25 (14.7%)
Invanz Versus P/T: Difference in Favorable Rate	-2.3% 95% C.I.:-10.6%, 5.9%		-1.4% 95% C.I.:-9.7%, 6.9%	

MO Comment: The sponsor's analysis demonstrated a 2.3% higher success rate in the comparator arm, while the result from the Medical Officer review yielded a 1.4% higher success rate in the piperacilllin/tazobactam arm. Based on my review, the clinical efficacy rate for Invanz in the treatment of CSSSI fulfills the criteria for demonstration of equivalence between treatment arms.

An enhanced blinding process was implemented after approximately one third of subjects were enrolled due to a slight color variation noted between the ertapenem and placebo infusions. Ertapenem response improved relative to piperacillin/tazobactam after the blinding process was enhanced (overall response rates for ertapenem and piperacillin/tazobactam were 71.6% and 82.3%, respectively, before enhanced blinding versus 88.1% and 85.7% after enhanced blinding). Lack of a blinding procedure until approximately one-third of subjects were enrolled may have had a negative impact on overall response rates to ertapenem.

Table 12 displays the clinical response rates of the MITT population at the TOC visit.

TABLE 12

CLINICAL RESPONSES OF CLINICAL MITT SUBJECTS AT TOC VISIT				
CLINICAL RESPONSE	APPLICANT		MO	
	INVANZ (N=269)	PIPERACILLIN/ TAZOBACTAM (N=258)	INVANZ (N=265)	PIPERACILLIN/ TAZOBACTAM (N=257)
Favorable	176 (65.4%)	173 (67.1%)	173 (65.3%)	172 (66.9%)
Unfavorable	93 (34.6%)	85 (32.9%)	92 (34.7%)	85 (33.1%)
Invanz Versus P/T: Difference in Favorable Rate	-1.6% 95% C.I.:-10.1%, 6.8%		-1.6% 95% C.I.:-10.1, 6.9%	

MO Comment: The results seen in the clinical MITT population yields similar response rates for both treatment groups. Response rates in the MITT analysis tend to be more conservative estimates of overall efficacy and may be more reflective of clinical practice than a clinical trial setting.

Clinical Efficacy by Stratum

The sponsor chose to examine the primary endpoint, favorable clinical response at the TOC visit by stratum. The MO analysis was done on the patients who were clinically evaluable after review of individual CRFs as noted earlier. This included revision of the "diabetic lower extremity infection" category to those with diabetic foot infections and reclassification of non-foot infections to the appropriate "other" category of infection.

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TABLE 13

PROPORTION OF SUBJECTS WITH FAVORABLE CLINICAL RESPONSES OF CLINICALLY EVALUABLE SUBJECTS AT TOC VISIT DISPLAYED BY STRATUM				
STRATUM	APPLICANT		MO	
	INVANZ (N=185)	PIPERACILLIN/ TAZOBACTAM (N=174)	INVANZ (N=168)	PIPERACILLIN/ TAZOBACTAM (N=170)
COMPLICATED UNDERLYING DISEASE	28/42 (66.7%)	27/36 (75%)	16/26 (61.5%)	23/31 (74.2%)
ALL OTHERS	124/143 (86.7%)	120/138 (87.0%)	125/142 (88%)	122/139 (87.8%)
OVERALL	152/185 (82.2%)	147/174 (84.5%)	141/168 (83.9%)	145/170 (85.3%)

MO Comment: The results of this analysis indicate that for individuals with Stratum II infections (deep abscesses, complicated cellulitis, post-traumatic or surgical site infections), overall clinical response rates were similar in the two treatment groups. In Stratum I, there is a higher frequency of favorable clinical response in the piperacillin/tazobactam group. This difference is noted in the sponsor's evaluable population which is comprised of patients with diabetic foot infections, neuropathic foot ulcers, acute changes in pressure sores, in addition to diabetic patients with CSSSI more proximally located in the lower extremity. The magnitude of difference is greater in the MO clinically evaluable population which does not contain CSSSI in diabetics located in the proximal lower extremity.

Table 14 displays the favorable clinical response rates at TOC in the MITT population.

TABLE 14

PROPORTION OF CLINICAL MITT SUBJECTS WITH FAVORABLE CLINICAL RESPONSES AT TOC VISIT DISPLAYED BY STRATUM				
STRATUM	APPLICANT		MO	
	INVANZ (N=269)	PIPERACILLIN/ TAZOBACTAM (N=258)	INVANZ (N=265)	PIPERACILLIN/ TAZOBACTAM (N=257)
COMPLICATED UNDERLYING DISEASE	35/66 (53%)	34/56 (60.7%)	22/54 (40.7%)	30/52 (57.7%)
ALL OTHERS	141/203 (69.5%)	139/202 (68.8%)	151/211 (71.6%)	142/205 (69.3%)
OVERALL	176/269 (65.4%)	173/258 (67.1%)	173/265 (65.3%)	172/257 (66.9%)

MO Comment: When the results are examined for the clinical MITT population under less stringently controlled mechanisms, the magnitude of treatment difference is even greater, with MO review indicating a difference in response rate of 17% in favor of treatment with piperacillin/tazobactam.

The two strata were further subdivided into specific diagnostic categories to illustrate clinical response rates in these categories. Table 15 displays favorable clinical response rates observed in those subjects with a particular diagnosis, in terms of absolute numbers and percent. Categories of infection in Stratum II with less than 10 subjects are not included in this table.

TABLE 15

STUDY P016: PROPORTION OF SUBJECTS WITH FAVORABLE CLINICAL RESPONSES OF CLINICALLY EVALUABLE SUBJECTS AT TOC VISIT DISPLAYED BY PRIMARY INFECTION DIAGNOSIS				
	APPLICANT		MEDICAL OFFICER	
Primary Diagnosis	Invanz (N=185)	Pip/Tazo (N=174)	Invanz (N=168)	Pip/Tazo (N=170)
Complicating Underlying Disease Stratum				
All Other Strata				
Cellulitis with purulent drainage	27/29 (93.1%)	21/24 (87.5%)	29/32 (90.6%)	23/26 (88.5%)
Cutaneous abscess	16/20 (80.0%)	23/24 (95.8%)	19/23 (82.6%)	23/24 (95.8%)
Deep soft tissue abscess	29/30 (96.7%)	34/36 (94.4%)	29/30 (96.7%)	35/37 (94.6%)
Perineal cellulitis/ abscess	18/20 (90.0)	9/11 (81.8%)	16/18 (88.9%)	9/11 (81.8%)
Post-traumatic wound infection	25/30 (83.3%)	22/26 (84.6%)	21/25 (84.0%)	19/21 (90.5%)
Surgical site infection	7/9 (77.8%)	8/10 (80.0%)	8/10 (80.0%)	10/13 (76.9%)

The following table presents the information about clinical efficacy in the clinically evaluable population by demographic subgroup. Response rates are given for both the sponsor's and MO clinically evaluable population.

TABLE 16

PROPORTION OF SUBJECTS WITH FAVORABLE CLINICAL RESPONSES OF CLINICALLY EVALUABLE SUBJECTS AT TOC VISIT DISPLAYED BY DEMOGRAPHICS				
	Applicant		Medical Officer	
	Invanz (N=185)	Pip/Tazo (N=174)	Invanz (N=168)	Pip/Tazo (N=170)
GENDER				
Female	48/62 (77.4%)	47/58 (81.0%)	42/57 (73.7%)	47/57 (82.5%)
Male	104/123 (84.6%)	100/116 (86.2%)	99/111 (89.2%)	98/113 (86.7%)
AGE				
< 65	136/158 (86.1%)	124/141 (87.9%)	128/144 (88.9%)	121/136 (89.0%)
≥ 65	16/27 (59.3%)	23/33 (69.7%)	13/24 (54.2%)	24/34 (70.6%)
< 75	148/174 (85.1%)	140/164 (85.4%)	138/157 (87.9%)	137/159 (86.2%)
≥ 75	4/11 (36.4%)	7/10 (70.0%)	3/11 (27.3%)	8/11 (72.7%)
RACE				
Black	21/26 (80.8%)	22/28 (78.6%)	21/23 (91.3%)	22/27 (81.5%)
Caucasian	81/108 (75.0%)	75/89 (84.3%)	75/98 (76.5%)	73/88 (83.0%)
Hispanic	34/35 (97.1%)	37/41 (90.2%)	30/32 (93.8%)	37/39 (94.9%)
Mestizo	13/13 (100%)	13/15 (86.7%)	13/13 (100%)	13/15 (86.7%)
Mexican	0/0 (NA)	0/1 (0)	0/0 (NA)	0/1 (0)
Mulatto	2/2 (100%)	0/0 (NA)	2/2 (100%)	0/0 (NA)
Spanish American	1/1 (100%)	0/0 (NA)	0/0 (NA)	0/0 (NA)

MO Comment: Analysis by gender indicates a slightly higher response rate in males than females for both treatment groups. There also appears to be a trend toward more favorable clinical response in females treated with piperacillin/tazobactam versus ertapenem.

Analysis by age indicates a higher favorable response rate in the adult population <65 years of age. The favorable clinical response rate appears to be significantly less in the ≥75 years of age category treated with ertapenem, however the number of subjects in this subgroup are small. This difference may be due to the fact that the ertapenem treated individuals in the ≥75 years subgroup were slightly older, with more compromised immune systems, than those in the piperacillin/tazobactam group (mean age 83.5 years in ertapenem group versus 79.8 in piperacillin/tazobactam group). The difference did not correspond to differences in disease severity or diagnostic category (stratum I versus stratum II) between the two groups.

The variation in response rates across racial groups appears to be random.

6.4.5.4.3.2 Microbiologic Efficacy

Approximately 85% of the clinically evaluable population were also microbiologically evaluable. The microbiologic response rates at TOC are illustrated in Table 17.

TABLE 17

MICROBIOLOGIC RESPONSES OF MICROBIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT				
	SPONSOR		MO	
Microbiologic Response	INVANZ	PIPERACILLIN/TAZOBACTAM	INVANZ	PIPERACILLIN/TAZOBACTAM
	N=155	N=151	N=144	N=146
Favorable	128 (82.6%)	126 (83.4%)	122 (84.7%)	123 (84.2%)
Unfavorable	27 (17.4%)	25 (16.6%)	22 (15.3%)	23 (15.8%)
Invanz Versus P/T: Difference in Favorable Rate	-0.9% 95% C.I.:-9.9%, 8.2%		0.5% 95% C.I.:-8.5%, 9.5%	

MO Comment: The difference in success rate in the medical officer's evaluable population was 0.5% in favor of Invanz and 0.9% in favor of piperacillin/tazobactam in the sponsor's evaluable population. The 95% confidence intervals are within the specified range for this equivalence trial.

6.4.5.4.3.3 Microbiology by Pathogen

The sponsor has provided a comprehensive list of bacterial isolates and favorable microbiologic response rates in Table 41 (pages 135-142) of the study report. The MO has changed the clinical and microbiology evaluable populations based on prior review of CRFs. The following table illustrates the organisms isolated from > 7 subjects (approximately 5%) in each treatment group and provides microbiologic response rates observed in the MO review.

TABLE 18

Total Isolates	Treatment Group				Observed Difference (A-B)
	MK-0826 (A)		Piperacillin/Tazobactam (B)		
	n/m	% response	n/m	% response	
Staph. aureus	54/67	80.6	58/69	84.1	-3.5
Strep. pyogenes	14/17	82.4	15/16	93.8	-11.4
Strep. agalactiae	7/9	77.8	7/10	70.0	7.8
Strep. β-hemolytic	7/7	100	5/8	62.5	37.5
E. coli	16/17	94.1	12/15	80.0	14.1
Ent. cloacae	5/5	100	9/11	81.8	18.2
Kleb. pneumoniae	5/6	83.3	4/5	80.0	3.3
Prot. mirabilis	4/6	66.7	8/8	100	-33.3
Pseud. aeruginosa	7/10	70.0	4/5	80.0	-10.0
Peptostrep. sp	27/30	90.0	21/22	95.5	-5.5

The sponsor also chose to evaluate the combined clinical and microbiological efficacy for the evaluable population.

TABLE 19

CLINICAL AND MICROBIOLOGIC RESPONSES OF MICROBIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT				
Clinical and Microbiologic Response	SPONSOR		MO	
	INVANZ (N=155)	PIPERACILLIN/T AZOBACTAM (N=151)	INVANZ (N=144)	PIPERACILLIN/T AZOBACTAM (N=146)
Both Favorable	127 (81.9%)	124 (82.1%)	122 (84.7%)	122 (83.6%)
Not Both Favorable	28 (18.1%)	27 (17.9%)	22 (15.3%)	24 (16.4%)
Invanz Versus P/T: Differences in Favorable Rate	-0.2% 95% C.I.:-9.4%, 9.1%		1.2% 95% C.I.:-7.9%, 10.3%	

MO Comment: Response rates were similar to those seen for clinical efficacy, although often times the microbiologic endpoint was derived from clinical assessment (microbiologic outcome presumed).

6.4.5.5 Reviewer's Comments / Conclusions on Efficacy

- ***Based on the data presented in this review, the sponsor has demonstrated the necessary evidence for approval of Invanz in the treatment of complicated skin and skin structure infections. This has been accomplished by demonstrating equivalence with piperacillin/tazobactam, a drug currently approved for use in treatment of CSSSI.***
- ***Based on the evidence provided by this clinical trial, the sponsor has shown efficacy of Invanz in the treatment of CSSSI including deep soft tissue abscesses, posttraumatic wound infections, surgical site infections, and cellulitis with purulent drainage.***

[redacted]

- ***Microbiologic evidence from this clinical trial also demonstrates equivalence of Invanz to piperacillin/tazobactam in the treatment of complicated skin and skin***

structure infections. Based on the percentage of isolates included, the following organisms may be cited for approval: Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli, and Peptostreptococcus species.

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7.4 **Safety**
7.4.1 Complicated Skin and Skin Structure Infection
7.4.1.1 Reviewer: Janice Pohlman, MD
7.4.1.2 Protocol 016

7.4.1.2.1 Extent of Exposure:

The sponsor's safety database included 529 subjects (of 540 enrolled) who received at least one dose of study drug. These 529 subjects included 271 in the MK-026 group and 258 in the piperacillin/tazobactam group. The MK-026 group received treatment for a mean duration of 8.1 days (range of treatment 1-21 days). The piperacillin/tazobactam group received treatment for a mean of 8.9 days (range of treatment 1- 24 days).

The sponsor's primary objective from a safety standpoint was to compare the safety profiles of MK-0826 versus piperacillin/tazobactam in terms of drug-related SAEs and drug-related adverse events leading to discontinuation of study treatment.

MO Comment: Table 20 provides an overview of the adverse event profile during the period of study treatment and fourteen-day follow-up period. The rates of adverse experiences were slightly less in the MK-0826 group, although the rates of drug-related adverse events and discontinuations due to adverse events were similar between the two treatment groups. The majority of adverse events occurred during the actual study treatment period and are reflected in the sponsor's study report (Page 164, Table 51).

TABLE 20 (Reproduced from sponsor's study report, page 170, Table 54)

Clinical Adverse Experience Summary
During Study Therapy and 14-Day Follow-Up Period†
(Treated Population)

	MK-0826 (N=271)		Piperacillin/ Tazobactam (N=258)	
	n	(%)	n	(%)
Number (%) of patients:				
with one or more adverse experiences	160	(59.0)	166	(64.3)
with no adverse experience	111	(41.0)	92	(35.7)
with drug-related adverse experiences‡	69	(25.5)	66	(25.6)
with serious adverse experiences	25	(9.2)	22	(8.5)
with serious drug-related adverse experiences	3	(1.1)	1	(0.4)
who died	3	(1.1)	3	(1.2)
discontinued due to an adverse experience	16	(5.9)	14	(5.4)
discontinued due to a drug-related adverse experience	3	(1.1)	7	(2.7)
discontinued due to a serious adverse experience	7	(2.6)	4	(1.6)
discontinued due to a serious drug-related adverse experience	1	(0.4)	0	(0.0)

† Only adverse experiences that occurred during study drug therapy and 14 days after the discontinuation of study drug therapy are counted. Adverse experiences or deaths reported more than 14 days after the discontinuation of study drug therapy are not counted.
‡ Determined by the investigator to be possibly, probably, or definitely drug related.

Data Source: [4.1.12; 4.1.20; 4.1.21]

7.4.1.2.2 Deaths:

There were four deaths in the MK-0826 group (one death occurred after the designated 14 day follow-up period and is not depicted in the table above) and three deaths in the piperacillin/tazobactam group during study treatment and follow-up. No deaths were attributed to study drug administration by the investigator.

MO Comment: I have examined the narrative summaries of the deaths provided by the sponsor and concur with the investigator's findings. I have provided annotated versions of the sponsor's narratives and my clinical impressions below:

- ***Ertapenam:***
  - ***AN 4035: A 99 year old female with a severe cellulitis (wound culture with Streptococcus pyogenes and Stapylococcus. aureus) of the left upper extremity and Streptococcus pyogenes bacteremia was treated with MK-0826. The patient underwent debridement of the wound approximately 24 hours into study therapy with pathology revealing necrotizing fasciitis. The patient developed respiratory failure and required mechanical ventilation on Day 4. On Day 10, the patient became febrile and was reported to be suffering from systemic inflammatory response syndrome, with a catheter related bacteremia (coagulase negative Staphylococcus) later discovered. Study drug was discontinued and therapy with vancomycin and ceftazidime was initiated. On Day 13, the patient experienced no significant improvement and medical support was withdrawn. The patient died on Day 14 with cause of death reported as respiratory failure in the setting of Group A Streptococcus sepsis and systemic inflammatory response.***
  - ***AN 4695: A 93 year old male with chronic thrombocytopenia, histiocytosis, diabetes, atrial fibrillation, and history of transient ischemic attacks (TIA) was treated with MK-0826 for a deep soft tissue abscess in the left groin. The platelet count at study entry was 52 ths/mm^3. On Day 3, the platelet count had decreased to 33 ths/mm^3. Study drug was discontinued on Day 6. On Day 11, the platelet count was noted to be 61 ths/mm^3, but decreased to 23 ths/mm^3 on Day 12 and remained between 23 and 46 ths/mm^3. On Day 18, the patient was noted to have a TIA and CT scan of the brain revealed bilateral subdural hematomas considered chronic in nature. On Day 11, EEG revealed evidence of complex partial seizures. The patient developed aspiration pneumonia on Day 12. A craniotomy was performed on Day 13 to drain the subdural hematomas but the patient did not improve. The patient died on Day 17 with worsening pneumonia.***
  - ***AN 4801: A 66 year old female with [redacted] cirrhosis was treated for a [redacted] with MK-0826. On Day5, a resistant Pseudomonas aeruginosa was isolated and the patient was discontinued from study drug therapy. Ciprofloxacin and amikacin were chosen as alternative antibiotics. On Day 13, the patient experienced septic shock and was started on imipenem. The patient developed multiple organ failure on Day 14 and died.***

- ***AN 4032: An 85 year old male was treated with MK-0826 for a severe necrotizing soft tissue infection of the arm. On Day 6, the infection had progressed and involved fascial tissue. The patient was changed to an alternate antibiotic regimen of cefazolin and clindamycin. The patient underwent a fasciotomy and was discontinued from antibiotics on Day 10. The patient also developed abdominal pain, diarrhea, and confusion on Day 10 due to <u>Clostridium difficile</u> related pseudomembranous colitis and was treated with metronidazole. The patient developed respiratory failure on Day 17 and required mechanical ventilation on Day 18. On Day 23, the patient developed Pseudomonas urosepsis and was treated with ciprofloxacin. The patient died on Day 27 with cause of death noted as urosepsis***

- ***Piperacillin/Tazobactam:***

  - ***AN 4699: A 72 year old male with coagulopathy (elevated PT and PTT) and complex vascular disease (including left lower extremity vascular surgery and abdominal aortic aneurysm repair) was treated for an infected right groin hematoma with piperacillin/tazobactam. A blood culture was positive for <u>Staphylococcus aureus</u> and a wound culture contained polymicrobial flora. The patient was noted to have a markedly elevated PT (PT 36.9 seconds; INR 8.1) and his anticoagulation therapy was stopped. On Day 5, the patient underwent evacuation of a hematoma in the right groin, as well as debridement. He required re-exploration for continued bleeding. The patient's PT remained elevated and was noted to be 21.1 seconds on Day 8. On Day 8, the patient had an episode of ventricular tachycardia with hypotension and epigastric pain. A CT revealed massive rupture of a retroperitoneal hematoma. The patient then had a cardio-respiratory arrest that did not respond to resuscitation and died.***
  - ***AN 4453: A 74 year old male was treated with piperacillin/tazobactam for a severe necrotizing infection of the right thigh, along with surgical debridement. The OR cultures revealed polymicrobic flora, including <u>Pseudomonas aeruginosa</u>. He received 4 doses of study drug and was then noted to be septic. A concurrent intra-abdominal infection was discovered and study drug was discontinued with initiation of imipenem. Surgery was performed revealing necrotic bowel with vascular insufficiency and an enterocutaneous fistula. The patient underwent a hemicolectomy and further debridement of the right thigh. Acute renal failure requiring hemodialysis developed on Day 2 and the patient remained on the ventilator post-op until his death on Day 10. The cause of death was intestinal ischemia with sepsis and acute renal failure, which the investigator did not believe were related to study drug.***
  - ***AN 4023: A 72 year old female with diabetes, COPD, and CHF was treated with piperacillin/tazobactam for a left thigh soft tissue infection. The patient was also thought to have pneumonia. Study treatment was discontinued on Day 5. On Day 6, the patient developed hypotension and bradycardia and became unresponsive. The patient died on Day 6, with probable cause of death cited by the investigator to be pulmonary embolus or vasovagal reaction leading to cardiac ischemia.***

7.4.1.2.3 Serious Adverse Events (excluding deaths):

The sponsor's clinical study report indicates that there were 23 subjects with serious clinical adverse events (SAE) during study treatment. Thirteen patients (4.8% of the 271 subjects) receiving MK-0826 and ten patients (3.9% of the 258 subjects) receiving piperacillin/tazobactam had SAEs. Additional SAEs were noted in the follow-up period. Fourteen additional events occurred in the MK-0826 group (total study and follow-up 27 or 10.0%) and 13 additional events occurred in the piperacillin/tazobactam group (total study and follow-up 23 or 8.9%). The events that occurred during study treatment are illustrated in Table 21 below by body system.

TABLE 21 (reproduced from sponsor's study report, pages 177-178, Table 59)

Number (%) of Patients With Serious Clinical Adverse Experiences (Incidence >0% in One or More Treatment Groups) by Body System During Parenteral Therapy (Treated Population)

	MK-0826 (N=271)		Piperacillin/ Tazobactam (N=258)	
	n	(%)	n	(%)
Patients with one or more serious adverse experiences	13	(4.8)	10	(3.9)
Patients with no serious adverse experience	258	(95.2)	248	(96.1)
Body as a Whole/Site Unspecified	**4**	**(1.5)**	**6**	**(2.3)**
Death	0	(0.0)	1	(0.4)
Fever	0	(0.0)	1	(0.4)
Infection	0	(0.0)	1	(0.4)
Inflammation	1	(0.4)	0	(0.0)
Necrosis	2	(0.7)	1	(0.4)
Neoplasm, malignant	1	(0.4)	1	(0.4)
Septicemia	1	(0.4)	1	(0.4)
Cardiovascular System	**2**	**(0.7)**	**2**	**(0.8)**
Gangrene	1	(0.4)	0	(0.0)
Hemorrhage	0	(0.0)	1	(0.4)
Hemorrhage, retroperitoneal	0	(0.0)	1	(0.4)
Occlusion, arterial, lower extremity	0	(0.0)	1	(0.4)
Thrombosis	1	(0.4)	0	(0.0)
Digestive System	**0**	**(0.0)**	**1**	**(0.4)**
Vascular insufficiency, intestinal	0	(0.0)	1	(0.4)
Endocrine System	**1**	**(0.4)**	**0**	**(0.0)**
Diabetes w/ketoacidosis	1	(0.4)	0	(0.0)
Metabolic,Nutritional,Immune	**0**	**(0.0)**	**1**	**(0.4)**
Hypoglycemia	0	(0.0)	1	(0.4)
Musculoskeletal System	**1**	**(0.4)**	**0**	**(0.0)**
Fasciitis, necrotizing	1	(0.4)	0	(0.0)
Nervous System and Psychiatric Disorder	**1**	**(0.4)**	**0**	**(0.0)**
Confusion	1	(0.4)	0	(0.0)
Respiratory System	**1**	**(0.4)**	**0**	**(0.0)**
Respiratory failure	1	(0.4)	0	(0.0)
Skin and Skin Appendage	**2**	**(0.7)**	**2**	**(0.8)**
Cellulitis	1	(0.4)	1	(0.4)
Delay, wound healing	1	(0.4)	0	(0.0)
Infection, skin	0	(0.0)	1	(0.4)
Urogenital System	**2**	**(0.7)**	**1**	**(0.4)**
Abortion	1	(0.4)	0	(0.0)
Bleeding, genital	1	(0.4)	0	(0.0)
Neoplasm, vaginal, malignant	1	(0.4)	0	(0.0)
Renal insufficiency, acute	0	(0.0)	1	(0.4)

Although a patient may have had 2 or more serious adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories. All body systems are listed in which at least 1 patient had a serious adverse experience.

SAEs that were considered drug related by the investigators numbered four. Three occurred in the MK-0826 group and one occurred in the piperacillin/tazobactam group.

Ertapenem:

AN 4804: A 62 year old female with hypertension, diabetes, and history of stroke was treated [redacted]. On Day 8, the patient experienced confusion without focal neurologic signs. The patient experienced a fall on Day 10 and again, a neurologic exam showed no focal signs. Study drug was discontinued on Day 10. On Day 11, the patient had a hypertensive crisis and was treated with IV nitroglycerin. The hypertension and confusion were resolved by Days 13 and 14 respectively. The investigator felt the confusion was possibly related to the study drug, with other possible contributors of anemia, dehydration, and malnutrition.
AN 4986: A 22 year old female was treated with MK-026 for a perineal abscess. The β-HCG result from study entry was not available until Day 6 and was then noted to be positive. The patient began to experience genital bleeding on Day 6 related to an incomplete spontaneous abortion which was confirmed by ultrasound on Day 7 and a uterine curettage was performed. The investigator felt the spontaneous abortion was likely related to study drug.
AN 4032: Discussed previously under Deaths. The serious adverse event that developed on Day 10, pseudomembranous colitis and confusion, were felt to be probably related to study drug treatment (although study drug was discontinued on Day 6 and alternate antibiotics, cefazolin and clindamycin were started at that time).

Piperacillin/Tazobactam:

AN 4694: A 41 year old male with diabetes was treated with piperacillin/tazobactam for a left thigh infection. The patient was discharged on Day 9 to continue study treatment at home with a WBC of 8,700/mm^3. The patient was readmitted to the hospital on Day 17 with fever and discontinued from study treatment on Day 18 as previously planned. On Day 18, the WBC was 1,700/mm^3. By Study Day 20, the WBC had risen to 11,100/mm^3. A follow-up WBC on Day 36 was 4,900/mm^3.

MO Comment: I have reviewed the narratives submitted by the sponsor on the SAEs not considered by the investigators to be related to study drug and concur with their opinions.

7.4.1.2.4 Drug Discontinuation Secondary to Adverse Events/Dropouts:

Sixteen subjects (5.9%) in the MK-0826 group and 12 subjects (4.7%) in the piperacillin/tazobactam group were discontinued from study therapy due to clinical adverse events. Table 62 (page 186-188) provided in the Sponsor's study report provides a listing of patients due to these events.

- Four patients in the MK-0826 group (ANs 4032, 4044, 4412, and 4724) were discontinued from study drug due to worsening of their primary infection associated

with treatment failure versus three patients in the piperacillin/tazobactam group (ANs 4603, 4650, and 4796). An additional patient in the MK-0826 group (AN 4696) developed another site of gangrene separate from the initial site of infection and was discontinued as a treatment failure.

- Three patients in the MK-0826 group were discontinued due to infections of the bone or joint. Two patients (ANs 4724 and 4633) developed [redacted] that was contiguous with the site of the original infection. The third patient (AN 4572) developed a joint infection that was separate from the site of the primary infection.
- Three patients in the MK-0826 group and seven patients in the piperacillin/tazobactam group were discontinued due to clinical adverse events that were considered by the investigator to be possibly, probably, or definitely related to study drug.
  - Rash in four patients (MK-0826: AN 4974 and P/T: ANs 4180, 4450, and 4577).
  - One patient in the MK-0826 group (AN 4279) experienced dizziness, pruritis, and arrhythmia of moderate intensity approximately 20 minutes after the second infusion of study drug. The subject was discontinued from study treatment and treated with diphenylhydramine for an acute allergic reaction. The subject's symptoms resolved in 45 minutes.
  - One patient in the MK-0826 group (AN 4986) was pregnant at study entry, which was discovered on Day 6 of study treatment. The subject experienced a spontaneous abortion on study day 6 and was discontinued from study therapy.
  - Two patients in the P/T group (ANs 4173 and 4135) were discontinued secondary to severe nausea (both) and vomiting (AN 4173); events probably related to study drug in the opinion of the investigator.
  - One patient in the P/T group (AN 4185) was discontinued from study treatment due to severe symptoms of intolerance at the site of infusion.

7.4.1.2.5 Other Treatment Emergent Adverse Events:

The overall number of clinical adverse events that occurred during the study treatment and follow-up period are illustrated in the table below.

TABLE 22

	MK-0826	Piperacillin/Tazoactam
AE During Treatment	150 (55.4%)	147 (57.0%)
AE During Rx & F/U	160 (59.0%)	166 (64.3%)

Frequently occurring clinical adverse events that the sponsor defined as ≥ 5% of the treatment group are displayed in Table 23 below.

TABLE 23 (Reproduced from sponsor's study report, page 174, Table 57)

Frequently Occurring Clinical Adverse Experiences (Occurring in ≥5% of Patients in Any Treatment Group) During Study Therapy and 14-Day Follow-up Period (Treated Population)				
Adverse Experience	MK-0826 (N=271)		Piperacillin/ Tazobactam (N=258)	
	n	(%)	n	(%)
Constipation	15	(5.5)	10	(3.9)
Diarrhea	29	(10.7)	36	(14.0)
Dizziness	4	(1.5)	13	(5.0)
Fever	16	(5.9)	15	(5.8)
Infused vein complication	26	(9.6)	23	(8.9)
Insomnia	18	(6.6)	18	(7.0)
Nausea	28	(10.3)	21	(8.1)

N = Number of patients with at least 1 dose of study therapy.
n = Number of patients with adverse experience.

The sponsor chose to display all clinical adverse events in terms of those occurring in ≥3% of the study population and drug-related clinical adverse events occurring in ≥1% of the study population. The individual investigators determined whether or not the event had a possible, probable, or likely connection with study drug administration.

MO Comment: I have chosen to display the events that the investigator determined could have been related to study drug administration in Table 24.

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TABLE 24 (Reproduced from sponsor's study report, page 173, Table 56)

Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence ≥1% in One or More Treatment Groups) by Body System During Study Therapy and 14-Day Follow-up Period – (Treated Population) Drug Related†

	MK-0826 (N=271)		Piperacillin/Tazobactam (N=258)	
	n	(%)	n	(%)
Patients with one or more drug-related adverse experiences	69	(25.5)	66	(25.6)
Patients with no drug-related adverse experience	202	(74.5)	192	(74.4)
Body as a Whole/Site Unspecified	**8**	**(3.0)**	**8**	**(3.1)**
Pain, abdominal	3	(1.1)	2	(0.8)
Cardiovascular System	**20**	**(7.4)**	**16**	**(6.2)**
Infused vein complication	17	(6.3)	14	(5.4)
Digestive System	**30**	**(11.1)**	**34**	**(13.2)**
Diarrhea	16	(5.9)	24	(9.3)
Nausea	10	(3.7)	7	(2.7)
Vomiting	1	(0.4)	4	(1.6)
Metabolic, Nutritional, Immune	**1**	**(0.4)**	**0**	**(0.0)**
Musculoskeletal System	**2**	**(0.7)**	**0**	**(0.0)**
Nervous System and Psychiatric Disorder	**12**	**(4.4)**	**9**	**(3.5)**
Dizziness	2	(0.7)	3	(1.2)
Headache	4	(1.5)	2	(0.8)
Respiratory System	**0**	**(0.0)**	**2**	**(0.8)**
Skin and Skin Appendage	**9**	**(3.3)**	**13**	**(5.0)**
Pruritus	5	(1.8)	4	(1.6)
Rash	5	(1.8)	4	(1.6)
Special Senses	**1**	**(0.4)**	**0**	**(0.0)**
Urogenital System	**2**	**(0.7)**	**2**	**(0.8)**

† Determined by the investigator to be possibly, probably, or definitely drug related. Although a patient may have had 2 or more drug-related adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories. All body systems are listed in which at least 1 patient had a drug-related adverse experience.

MO Comment: Adverse events that occurred in ≥3 % of subjects in a treatment group provided evidence independent of investigator determination that infused vein complications, diarrhea, nausea, and dizziness appear to be related to administration of study drug.

7.4.1.2.6 Laboratory Findings:

The majority of laboratory adverse events were noted during study treatment: 69 (27.3%) in MK-0826 versus 63 (25.5%) in piperacillin/tazobactam groups. Table 25 illustrates the number of individuals with laboratory adverse events that occurred during study treatment and follow-up, including the severity and relationship of laboratory adverse events to study drug.

TABLE 25 (Reproduced from sponsor's study report, page 222, Table 75)

Laboratory Adverse Experience Summary
During Study Therapy and 14-Day Follow-Up Period
(Treated Population)

Number of patients with at least 1 laboratory test postbaseline	MK-0826 (N=258)		Piperacillin/Tazobactam (N=250)	
Number (%) of patients:	n	(%)	n	(%)
with one or more adverse experiences	81	(31.4)	70	(28.0)
with no adverse experience	177	(68.6)	180	(72.0)
with drug-related adverse experiences[†]	40	(15.5)	40	(16.0)
with serious adverse experiences	1	(0.4)	2	(0.8)
with serious drug-related adverse experiences	1	(0.4)	1	(0.4)
who died	0	(0.0)	0	(0.0)
discontinued due to an adverse experience	0	(0.0)	2	(0.8)
discontinued due to a drug-related adverse experience	0	(0.0)	2	(0.8)
discontinued due to a serious adverse experience	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related adverse experience	0	(0.0)	0	(0.0)

N = Number of treated patients with at least 1 laboratory test postbaseline.
[†] Determined by the investigator to be possibly, probably, or definitely drug related.
Data Source: [4.1.4; 4.1.12; 4.1.20; 4.1.21]

MO Comment: There were two serious drug-related laboratory adverse events noted during study therapy and follow-up, with one occurring in each of the treatment groups:

- ***MK-0826: AN 4695 had worsening thrombocytopenia and the clinical narrative was previously presented in the Deaths section.***
- ***P/T: AN 4694 developed leukopenia on therapy and the clinical narrative was previously presented in the section on clinical SAE.***

Two patients in the piperacillin/tazobactam group were discontinued from therapy due to drug-related laboratory adverse events.

- ***AN 4690 developed thrombocytopenia***
- ***AN 4702 had an increased prothrombin time***

The most common laboratory abnormalities noted were abnormalities in liver function studies and appeared to occur with similar frequencies in both study populations. Table 26 indicates laboratory adverse events that were felt to be potentially related to study drug administration by the investigator and occurred in ≥1% of the treated population.

TABLE 26 (Adapted from sponsor's study report, page 215, Table 70)

Number (%) of Patients With Specific Laboratory Adverse Experiences (Incidence ≥1 % in One or More Treatment Groups) by Laboratory Test Category During Study Treatment and 14-Day Follow-Up Period (Treated Population) Drug Related †

	MK-0826 (N=271)		Piperacillin/ Tazobactam (N=258)	
	n/m	(%)	n/m	(%)
Patients with one or more drug-related adverse experiences	40/258	(15.5)	40/250	(16.0)
Patients with no drug-related adverse experience	218/258	(84.5)	210/250	(84.0)
Blood Chemistry	**23/256**	**(9.0)**	**21/250**	**(8.4%)**
ALT increased	12/220	(5.5)	9/220	(4.1)
AST increased	13/244	(5.3)	11/244	(4.5)
BUN increased	1/223	(0.4)	3/217	(1.4)
Serum alkaline phosphatase increased	4/243	(1.6)	5/244	(2.0)
Serum creatinine increased	0/255	(0.0)	3/249	(1.2)
Hematology	**19/258**	**(7.4)**	**18/249**	**(7.2)**
Eosinophils increased	2/248	(0.8)	3/241	(1.2)
Platelet count decreased	4/257	(1.6)	1/246	(0.4)
Platelet count increased	8/257	(3.1)	4/246	(1.6)
Prothrombin time increased	0/234	(0.0)	7/239	(2.9)
PTT increased	2/233	(0.9)	5/238	(2.1)
Segmented neutrophils decreased	3/248	(1.2)	0/241	(0.0)
Urinalysis	**5/236**	**(2.1)**	**9/231**	**(3.9)**
Urine RBCs increased	2/196	(1.0)	3/193	(1.6)
Urine yeast present	1/196	(0.5)	3/193	(1.6)
Miscellaneous	**2/3**	**(66.7)**	**1/1**	**(100)**
Clostridium difficile toxin, positive	2/3	(66.7)	1/1	(100)

† Determined by the investigator to be possibly, probably, or definitely drug related.
N = Total number of treated patients per treatment group.
n/m = Number of patients with laboratory adverse experience/number of patients with laboratory test postbaseline.
Although a patient may have had 2 or more drug-related adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories. All categories are listed in which at least 1 patient had a drug-related adverse experience.

The sponsor provided additional information about the adverse laboratory events identifying patients that had worsening of a value from baseline that met the definition of a clinically significant laboratory abnormality (CSLA) which was predefined. In order to be considered in the population for CSLAs, patients had to have a baseline laboratory value, at least 1 post-baseline laboratory test, and normal ranges in the database.

MO Comment: Table 27 below provides treatment group specific information in regard to CSLAs which occurred during study therapy and 14-day follow-up. Although this table includes all significant laboratory adverse events (not just those considered drug-related by the investigator), a similar trend is noted for the MK-0826 group in regard to

decreased neutrophil counts, decreased platelet counts, and elevated liver transaminases.

TABLE 27 (Adapted from sponsor's study report, page 241, Table 87)

Number (%) of Patients With a Clinically Significant Laboratory Abnormality By Treatment Group During Study Therapy and 14-Day Follow-up Period (Treated Population)					
Laboratory Test	CSLA Criteria	Number (%) with CSLA			
		MK-0826 (N=271)		Piperacillin/Tazobactam (N=258)	
		n/m	%	n/m	%
Absolute neutrophil count (ths/mm^3)	<1.8	19/227	8.4	5/233	2.1
	<1.0	2/227	0.9	1/233	0.4
Hemoglobin (gm/dL)	<8	6/253	2.4	4/245	1.6
Hematocrit (%)	<24	7/253	2.8	6/245	2.4
Platelet count (ths/mm^3)	<75	5/250	2.0	1/242	0.4
	<50	3/250	1.2	1/242	0.4
ALT (U/L)	>2.5 × ULN	11/198	5.6	2/191	1.0
	>5.0 × ULN	1/198	0.5	0/191	0.0
AST (U/L)	>2.5 × ULN	14/231	6.1	10/225	4.4
	>5.0 × ULN	4/231	1.7	0/225	0.0
Serum alkaline phosphatase (U/L)	>2.5 × ULN	3/223	1.3	3/224	1.3
	>5.0 × ULN	1/223	0.4	1/224	0.4
Total serum bilirubin (mg/dL)	>1.5 × ULN	2/230	0.9	4/226	1.8
	>2.5 × ULN	1/230	0.4	2/226	0.9
Direct serum bilirubin (mg/dL)	>1.5 × ULN	4/141	2.8	7/139	5.0
	>2.5 × ULN	2/141	1.4	3/139	2.2
Serum creatinine (mg/dL)	>1.5 × ULN	5/252	2.0	8/245	3.3
	>3 × ULN	1/252	0.4	2/245	0.8

CSLA = Clinically significant laboratory abnormality.
N = The total number of treated patients in treatment group.
n/m =Number of patients with CSLA/Number of patients with the laboratory test at baseline and postbaseline.
ULN = Upper limit of normal range of values.

7.4.1.2.7 Assessment of Tolerability:

Tolerability at the site of study drug infusion was assessed daily while on study therapy. The number (percentages) of patients who experienced one or more local reactions at the site of infusion were similar with respect to the incidence and intensity of local reactions (71/270 or 26.3% in the MK-0826 group versus 74/258 or 28.7% in the piperacillin/tazobactam group).

If local tolerance was felt by the investigator to reach the level of a clinical adverse experience, it could be characterized as a syndrome and is contained in the "infused vein complication" category of adverse events. This AE was reported in 26/271 (9.6%) of MK-0826 treated patients versus 23/258 (8.9%) in the piperacillin/tazobactam group.

7.4.1.2.8 Adverse Events of Special Interest:

Adverse events of special interest considered by the sponsor included those associated with β-lactam antibiotics as a class (liver function elevations, neutropenia, and rash) and other carbapenem antibiotics (seizures).

Seizures
The past medical history of treated subjects included seizure in 7/271 (2.6%) of the MK-0826 group and 11/258 (4.1%) of the piperacillin/tazobactam group. No seizures were reported in either group during study therapy. Two patients in the MK-0826 had reported seizures in the follow-up period. Neither of these patients had a prior history of seizure. The following narratives from the sponsor's study report describe the clinical course of these two subjects:

- AN 4376

A 47-year-old male with a history of peripheral vascular disease, and hypertension received 9 days of MK-0826 therapy for the treatment of an On Day 11, the patient was admitted to the hospital for the onset of sudden uncontrollable jerking movements in the lower extremities. These lasted 1 to 4 minutes. At the time of admission, the
The patient was treated with IV phenytoin ε
The investigator reported that the focal motor seizure was likely secondary to hyperglycemia and was not considered to be related to the study drug therapy.

- AN 4695

Reported previously in the Deaths section. A 93-year-old male with chronic thrombocytopenia, diabetes mellitus, histocytosis, atrial fibrillation, peripheral vascular disease, and a history of transient ischemic attacks received 6 days of IV MK-0826 therapy for the treatment of a deep soft tissue abscess in the left groin. On Study Day 10 (4 days after study drug was discontinued), the patient experienced a transient ischemic attack. A brain scan was performed, revealing bilateral subdural hematomas. This finding was considered by the investigator to be a chronic condition. On Study Day 11, an electroencephalogram was performed revealing evidence of complex partial seizures. The patient was treated for seizures with fosphenytoin and did not experience another seizure.

Rash
25 patients experienced an adverse event of rash during study treatment and the follow-up period. (12 MK-0826 versus 13 piperacillin/tazobactam). Eleven patients had drug-related rash (5 MK-0826 versus 6 piperacillin/tazobactam) and four patients were discontinued from therapy because of rash (1 MK-0826 versus piperacillin/tazobactam).

Elevated Liver Function Tests
The sponsor considered liver function abnormalities, including AST and ALT elevations to more than 3 x the ULN (or more than 3 x the baseline value in patients with elevated transaminases at study entry).

MO Comment: The sponsor had prespecified CSLA thresholds of 2.5 and 5.0 x ULN to examine. Using the 2.5 x ULN threshold, ALT abnormalities were note in 11/198 (5.6%) of the MK-0826 group and 2/191 (1.0%) of the piperacillin/tazobactam. AST

abnormalities, utilizing the 2.5 x ULN threshold were noted in 14/231 (6.1%) of the MK-0826 group and 10/225 (4.4%) of the piperacillin/tazobactam group. Elevations of transaminases to >5.0 x ULN were uncommon, but were seen only in the MK-0826 group.

Neutropenia

The sponsor chose to look at ANC decreases to <1.8ths/mm^3 (or to <50% of the baseline value in patients with ANC <1.8ths/mm^3 at study entry). The number of events meeting this criteria during study treatment and follow-up are: 18/227 (7.9%) of the MK-0826 group and 5/233 (2.1%) of the piperacillin/tazobactam group.

Laboratory Abnormalities of Special Interest Neutropenia-During Study Therapy and 14-Day Follow-Up Period (Treated Population)

	MK-0826 (A)			Piperacillin/ Tazobactam (B)			Relative Risk	
Laboratory Abnormality	n	N	(%)	n	N	(%)	A/B	(95% CI)
Decreased ANC†	18	227	(7.9)	5	233	(2.1)	3.70	(1.36, 8.79)

N = Number of treated patients who had the laboratory test at baseline and postbaseline.
n = Number of patients with adverse experience.
CI = Confidence interval.
ANC = Absolute neutrophil count.
† This table counts patients with ANC values decreased to <1.8 ths/mm^3 in patients with baseline values ≥1.8 ths/mm^3 and patients with ANC values decreased to <50% of the baseline value in patients with baseline ANCs below 1.8 ths/mm^3.

MO Comment: These data indicate that MK-0826 has a higher incidence of neutropenia than does piperacillin/tazobactam.

7.4.1.2.9 Safety Conclusions for Protocol 016 – Complicated Skin and Skin Structure Infections

- ***The results of Protocol 016 indicate that the safety profile of ertapenem in the treatment of CSSSI is similar to the comparator, piperacillin/tazobactam, with regard to the occurrence of drug-related adverse events and drug-related adverse events leading to drug discontinuation.***
- ***None of the four deaths noted during the course of treatment and follow-up in the ertapenem group was attributable to study drug.***
- ***Serious adverse events were rare and occurred in 13/271 (4.8%) of the ertapenem group. Three of these events were felt to be possibly related to study drug by the investigator and included an episode of confusion, a spontaneous abortion, and an episode of pseudomembranous colitis secondary to Clostridium difficile.***
- ***The most common clinical adverse events associated with ertapenem were: infused vein complications (17/271 or 6.3%), gastrointestinal disturbances including diarrhea (16/271 or 5.9%), nausea (10/271 or 3.7%), and abdominal pain (3/271 or 1.1%), headache (4/271 or 1.5%), and rash and pruritis (5/271 or 1.8%). These***

adverse events were comparable to those seen with the comparator, piperacillin/tazobactam, and occurred with similar frequencies except for diarrhea which was more common in the comparator group (24/258 or 9.3%).

- ***Drug-related laboratory adverse events with ertapenem included increased liver transaminases (2.5 x ULN: AST in 6.1%, ALT in 5.6%), neutropenia (<1.8 ths/mm^3 in 8.4%), thrombocytopenia (1.6%), and thrombocytosis (3.1%).***
- ***No seizures occurred in the ertapenem group during study therapy.***

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Appendix A: Random Sample Table

	Treatment Group	Control Group
# Subjects Enrolled	274	266
Cure Rate (Evaluable Subjects)	152/185 (82.2%)	147/174 (84.5%)
# Subjects Sampled (N=57)	28	29
# Originally Nonevaluable	11	15
MO Kept Nonevaluable	10	15
MO Changed to Evaluable Fail	1 (4820)	0
MO Changed to Evaluable Cure	0	0
# Originally Evaluable Fail	0	2
MO Changed to Nonevaluable	0	0
MO Kept Evaluable Fail	0	2 (4727, 4839)
MO Changed to Evaluable Cure	0	0
# Originally Evaluable Cure	17	12
MO Changed to Nonevaluable	3 (4053, 3073, 4807)	0
MO Changed to Evaluable Fail	0	0
MO Kept Evaluable Cure	14	12

Discrepancies from sponsor data and targeted CRF review:
Patient #
06-4053: subject with complicated cellulitis, prior antibiotic treatment of unknown duration (including day prior to study entry), no purulence on gram stain or pathogen on culture (culture with respiratory flora)
07-3073: subject with traumatic right calf injury, prior antibiotics for 1-1/2 days, gram stain with WBC's and culture with mixed aerobic and anaerobic flora, no TOC visit (phone follow-up)
26-4807: subject with cellulitis with purulent drainage, antibiotic treatment for 3 days prior, culture with *Bacillus* sp. (contaminant, not pathogen)
29-4820: subject with pressure ulcer with acute change, surgically debrided, culture with *Pseudomonas aeruginosa*, *Proteus mirabilis*, and Group G streprococcus, treated IV for 7 days and then investigator used oral ciprofloxacin and rifampin for 2 additional weeks.

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