6.5. Complicated Urinary Tract Infections

6.5.1. Reviewer: Thomas Smith, M.D.

6.5.2. Review Dates
6.5.2.1. Date Received by Reviewer: 12/06/00
6.5.2.2. Date Review Begun: 2/15/01
6.5.2.3. Date Review Completed: 9/20/01

6.5.3. Proposed Labeling for Indication

> "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 Urinary Tract Infections including pyelonephritis** due to *Escherichia coli*, *Klebsiella pneumoniae* or *Proteus mirabilis*."

6.5.4. Material Reviewed

The applicant conducted three clinical efficacy studies in patients with urinary tract infections (UTIs):

1. Protocol 007 was a pilot study of 33 adult patients with serious uncomplicated UTIs and was intended to provide information about the safety, tolerability, and efficacy of ertapenem as compared with ceftriaxone. The sample size was insufficient to permit conclusions about relative efficacy.

2. Protocol 014 was designed to be a statistically adequate pivotal trial demonstrating the noninferiority of ertapenem as compared with ceftriaxone in the treatment of adult patients with complicated UTIs.

3. Protocol 021 was a supportive trial intended to provide additional evidence of the efficacy of ertapenem as compared with ceftriaxone in the treatment of adult patients with complicated UTIs.

Protocols 014 and 021 are reviewed in detail.

6.5.5. Protocol 014: "A Prospective, Multicenter, Double-Blind, Randomized Comparative Study to Evaluate the Safety, Tolerability, and Efficacy of MK-0826 Versus Ceftriaxone Sodium in the Treatment of Complicated Urinary Tract Infections in Adults"

6.5.5.1. Objectives

The applicant's stated objectives were to compare ertapenem with ceftriaxone in the initial treatment of complicated UTIs in adults, using the following outcome measures:

Primary:
1. Microbiological response at 5 to 9 days posttherapy
2. Safety profile at end of parenteral therapy

Secondary:
1. Overall clinical response
2. Tolerability profile

6.5.5.2. Design: Randomized (1:1 ratio), double-blind, comparative, multicenter trial

6.5.5.3. Protocol Overview

6.5.5.3.1. Population

6.5.5.3.1.1. Inclusion Criteria

Adult patients ≥18 years of age with a clinical or bacteriologic diagnosis of complicated UTI or acute pyelonephritis necessitating parenteral therapy were eligible for enrollment. Major diagnostic criteria included:

1. Acute pyelonephritis

   a. Fever: body temperature >37.8°C orally, >38.2°C tympanically, or >38.4°C rectally, and chills documented within 12 hours of study entry, and

   b. Flank pain or costovertebral angle tenderness, and

   c. Pyuria: from a clean-catch midstream or catheterized specimen, ≥10 white blood cells (WBCs) per high powered field on microscopy of urine sediment or ≥10 WBCs/mm^3 of unspun urine, and

   d. Positive urine culture: from a clean-catch midstream or catheterized specimen collected in a sterile fashion, any amount of a recognized uropathogen known or believed to be susceptible to ertapenem and ceftriaxone. Patients could be enrolled before culture results were available but were required to be withdrawn from the study if the culture did not contain a recognized uropathogen.

2. Other complicated UTI

   a. Signs or symptoms of upper or lower UTI, and

   b. Pyuria (as defined above), and

   c. Positive urine culture (as defined above), and

d. Male gender, or

e. For female patients, historical or clinical evidence of urologic abnormality, including:

(1) catheterization or instrumentation of urinary tract

(2) functional or anatomical urinary tract abnormality

6.5.5.3.1.2. Exclusion Criteria

Noteworthy exclusion criteria included:

1. Admission urine culture known to contain a pathogen resistant to one or both study drugs

2. Receipt of any amount of effective antimicrobial therapy after collection of the admission urine culture and before administration of the first dose of study therapy

3. Treatment of UTI with >24 hours of effective antimicrobial therapy within the 72 hour period before collection of the admission urine culture; patients receiving UTI prophylaxis were eligible only if the admission urine culture contained $\geq 10^5$ cfu/mL of a uropathogen.

4. Complete urinary tract obstruction (any portion), perinephric or renal abscess, prostatis, or other conditions that could confound interpretation of the study or place patients at additional risk

5. Azotemia: requirement for peritoneal dialysis, hemodialysis, or hemofiltration; serum creatinine >1.5 times the upper limit of normal for patients ≤65 years of age (or >1.25 times the upper limit of normal for patients >65 years of age); or creatinine clearance <30 mL/min

6. Renal transplantation

6.5.5.3.2. Study Procedures

6.5.5.3.2.1. Study Drug Administration

Ertapenem was administered as a dose of 1 g IV q24h. The comparator, ceftriaxone, was also administered as a dose of 1 g IV q24h. Patients received intravenous study therapy for a minimum of three doses, after which a switch to oral therapy (ciprofloxacin in most cases) was permitted for patients who met criteria indicating clinical improvement. Total duration of antimicrobial therapy was from 10 to 14 days.

Upon study enrollment, patients were stratified by diagnosis: acute pyelonephritis or other complicated UTI. They were then randomized to one of the study therapies (1:1 ratio) according to a schedule provided by the applicant. This was a double-blind, double-dummy study. Because there was a slight difference in the appearance of the study drug preparations, all patients received a daily placebo infusion in addition to the study drug infusion.

6.5.5.3.2.2. Study Evaluations

Prestudy
- History
- Description of signs and symptoms
- Physical examination
- Laboratory studies for safety: hematology, blood chemistry, urinalysis
- Pregnancy test for women of childbearing potential
- Culture and susceptibility testing
  - Urine (quantitative culture)
  - Blood: if patient febrile or if otherwise clinically indicated
- Additional evaluations as indicated

During IV therapy
- Measurement of body temperature (every 8 hours for first 5 days of IV therapy)
- Adverse experience monitoring (daily)
- Local tolerability assessment (daily)
- Additional evaluations on day 3, 4, or 5 of IV therapy and at discontinuation of IV therapy (if not on day 3, 4, or 5)
  - Description of signs and symptoms
  - Physical examination
  - Laboratory studies for safety
  - Culture and susceptibility testing
    - Urine
    - Blood: if initial culture positive or if otherwise clinically indicated

Early follow-up 5 to 9 days posttherapy (test of cure)
- Description of signs and symptoms
- Adverse experience monitoring
- Physical examination
- Laboratory studies for safety
- Culture and susceptibility testing
  - Urine
  - Blood (if indicated)
- Clinical and microbiological response rating

Late follow-up 4 to 6 weeks posttherapy
- Description of signs and symptoms

- Adverse experience monitoring
- Urine culture
- Urinalysis
- Clinical and microbiological response rating

6.5.5.3.3. Evaluability Criteria

The following is taken directly from Protocol 014, Amendment 02 (vol 9, p. 801):

"In order to be considered evaluable for efficacy patients must meet the following criteria:

> 1. Confirmed diagnosis, including a positive urine culture at admission, containing $\geq 10^5$ CFU/mL of a uropathogen. Recognized uropathogens include: Enterobacteriaceae (e.g., *E. coli*, *Klebsiella*, *Proteus*, *Citrobacter*, *Enterobacter*, *Serratia*, and *Morganella* spp.); *Staphylococcus saprophyticus* (not other coagulase-negative staph.); nonfermentative Gram-negative rods (e.g., *Pseudomonas*, *Acinetobacter* spp.) and *Enterococcus* spp.
>
> 2. Have received a proper total duration of antimicrobial therapy, of at least 7 days of I.V. alone or a combination of I.V. and oral therapy.
>
> 3. Have no major protocol violations that would affect assessment of efficacy.
>
> 4. Have a clinical and microbiological assessment at the test-of-cure visit.
>
> 5. Have not had effective concomitant antibiotic therapy between the time of admission culture and the test-of-cure culture.
>
> 6. Have not had the admission urine culture obtained >48 hours prior to the start of study therapy.

"While on study therapy, patients may be considered evaluable as clinical or microbiological failure at any time provided that they have received at least 48 hours of parenteral study therapy.

"All patients who receive at least 1 dose of study therapy are evaluable for safety."

6.5.5.3.4. Endpoints

The following is taken directly from Protocol 014, Amendment 02 (vol 9, pp. 835-836):

"Variables/Time Points of Interest

> Primary

The primary efficacy parameter will be the proportion of patients who have a favorable microbiological response assessment at the early follow-up 5 to 9 days posttherapy visit.

The primary safety variables will be the proportion of patients within each treatment group that experience any drug-related AEs leading to discontinuation of parenteral study drug and the proportion of patients within each treatment group with any drug-related SAE during parenteral treatment.

Secondary

The proportion of patients who have a favorable clinical response assessment at the early follow-up 5 to 9 days posttherapy visit.

The proportion of patients who experience a microbiological relapse or clinical relapse at the late follow-up visit 4 to 6 weeks posttherapy.

The proportion of patients who experience a favorable microbiological response and a favorable response in clinical signs and symptoms at the time points of (1) Study Day 3, 4, or 5 assessment and (2) the time of discontinuation of I.V. therapy.

Proportion of patients within each treatment group with no symptoms present at each time point.

The proportion of patients within each treatment group that experience local reactions at the injection site (i.e., erythema, induration, pain, tenderness, warmth, swelling, ulceration, local phlebitis, etc.)."

6.5.5.3.5. Statistical Considerations

This study was designed to demonstrate the noninferiority of ertapenem when compared with ceftriaxone. Using a two-sided 95% confidence interval (CI) for the difference in response rates between treatments, power of 80%, noninferiority criterion of -10%, and estimated response rate of 90% for each study drug, the applicant calculated that 150 evaluable patients per group were needed.

The primary efficacy analysis was performed on the per protocol population as defined by the evaluability criteria in Section 6.5.5.3.3. Additional analysis was performed on the modified intent-to-treat population, which was the subset of patients meeting the minimal case definition (Section 6.5.5.3.1.1, Inclusion Criteria) and receiving at least one dose of study therapy.

MO comment: The inclusion and exclusion criteria, study procedures, evaluability criteria, and endpoints are acceptable. The primary outcome

measure is consistent with the recommendation in the FDA draft guidance on complicated UTIs and pyelonephritis.

6.5.5.4. Study Results

6.5.5.4.1. Demographics

Five hundred ninety-two patients were randomized to receive one of the study therapies: 298 to receive ertapenem and 294 to receive ceftriaxone. Table 014-1, adapted from applicant's Table 17, shows the baseline characteristics of randomized patients. Baseline characteristics appeared similar between treatment groups. Twenty-five domestic and foreign sites enrolled patients in this study. Applicant's Tables 14 and 15 list the study sites and numbers of patients enrolled and evaluable. No study site enrolled more than 15% of the patients.

Table 014-1
Baseline Patient Characteristics by Treatment Group
(All Randomized Patients)

	Ertapenem (N=298)		Ceftriaxone (N=294)		Total (N=592)	
	n	(%)	n	(%)	n	(%)
Gender						
Male	92	(30.9)	97	(33.0)	189	(31.9)
Female	206	(69.1)	197	(67.0)	403	(68.1)
Race						
Caucasian	194	(65.1)	206	(70.1)	400	(67.6)
Black	32	(10.7)	21	(7.1)	53	(9.0)
Hispanic	35	(11.7)	34	(11.6)	69	(11.6)
Mestizo	25	(8.4)	25	(8.5)	50	(8.4)
Other	12	(4.0)	8	(2.7)	20	(3.4)
Age (Years)						
≤40	109		98		207	
41 to 64	96		93		189	
65 to 74	46		44		90	
≥75	47		59		106	
Mean	51.3		53.0		52.1	
Median	51.5		53.0		52.1	
Range	18 to 97		17 to 98		17 to 98	
Stratum						
Acute pyelonephritis	143	(48.0)	118	(40.1)	261	(44.1)
Other complicated UTI	155	(52.0)	176	(59.9)	331	(55.9)

Adapted from Volume 9, Table 17

6.5.5.4.2. Evaluability

Table 014-2, adapted from applicant's Table 16, shows the disposition of the randomized patient population. The microbiological protocol evaluable population was used for the primary efficacy analysis. The most common reason for exclusion from the microbiological and clinical protocol evaluable populations was lack of isolation of a uropathogen, which therefore meant that the disease definition was not met.

Table 014-2
Patient Accounting of Evaluability
(Randomized Population)

Population	Ertapenem (N=298)		Ceftriaxone (N=294)	
	n	(%)	n	(%)
Microbiologic Protocol Evaluable Population				
Microbiologic protocol evaluable	159	(53.4)	171	(58.2)
Microbiologic protocol nonevaluable	139	(46.6)	123	(41.8)
Not clinically evaluable	136	(45.6)	118	(40.1)
Disease definition not met	76	(25.5)	57	(19.4)
Test-of-cure window violation	32	(10.7)	27	(9.2)
Inadequate/inappropriate study therapy	50	(16.8)	36	(12.2)
Prior antibiotics violation	4	(1.3)	5	(1.7)
Concomitant antibiotics violation	11	(3.7)	8	(2.7)
Baseline microbiology—resistant pathogen	10	(3.4)	17	(5.8)
Baseline uropathogen but $<10^5$ CFU/mL	26	(8.7)	25	(8.5)
Baseline/intercurrent medical events	0	(0.0)	4	(1.4)
Baseline microbiology inadequate	28	(9.4)	26	(8.8)
Baseline microbiology—no pathogen isolated	64	(21.5)	40	(13.6)
Test-of-cure microbiology inadequate	36	(12.1)	35	(11.9)

Adapted from Volume 9, Table 16

MO comment: A blinded review of a random sample of case report forms revealed that several patients received prestudy antibiotic therapy after the baseline urine culture was obtained and before administration of study therapy. Review of the case report tabulations revealed 9 such cases: 5 patients randomized to receive ertapenem and 4 patients randomized to receive ceftriaxone. All 9 cases had been identified by the applicant as protocol deviations but were left in the protocol evaluable populations. These patients should have been excluded from these populations. Exclusion of these patients and recalculation of efficacy rates did not result in a significant change in the submitted analysis. The applicant's data were otherwise reported satisfactorily and have been accepted for the remainder of this review.

6.5.5.4.3. Efficacy

6.5.5.4.3.1. Microbiological Efficacy

The primary outcome measure was the microbiological response at the test of cure visit 5 to 9 days following completion of all therapy. Table 014-3, adapted from applicant's Tables 32 and 33, shows the proportion of patients with a favorable microbiological response at the test of cure visit. The results are presented for the combined patient population as well as for the acute pyelonephritis and other complicated UTI strata. Overall, 146 of 159 patients (91.8%) in the ertapenem group and 159 of 171 patients (93.0%) in the ceftriaxone group had favorable microbiological responses. The

difference in response rate for ertapenem compared with ceftriaxone was -1.2% (95% CI, -7.6% to 5.1%). The lower bound of the 95% CI is greater than -10% and satisfies the prespecified noninferiority criterion. For the acute pyelonephritis stratum, 71 of 75 ertapenem recipients (94.7%) and 74 of 78 ceftriaxone recipients (94.9%) had favorable microbiological responses. For other complicated UTIs, 75 of 84 ertapenem recipients (89.3%) and 85 of 93 ceftriaxone recipients (91.4%) had favorable microbiological responses.

Table 014-3
Proportion of Patients with Favorable Microbiological Response Assessments at Test of Cure Visit–
Microbiologically Evaluable Population

	Treatment Group							
	Ertapenem (N=159)			Ceftriaxone (N=171)			Difference	
		Response			Response			
Stratum	n/m	%	(95% CI)	n/m	%	(95% CI)	%	(95% CI)
Overall	146/159	91.8	(87.6, 96.1)	159/171	93.0	(89.1, 96.8)	-1.2	(-7.6, 5.1)
Acute pyelonephritis	71/75	94.7	(89.5, 99.8)	74/78	94.9	(89.9, 99.8)	-0.2	
Other complicated UTI	75/84	89.3	(82.6, 95.9)	85/93	91.4	(85.7, 97.1)	-2.1	

n/m = Number of patients with favorable assessment/number of patients with assessment
CI = Confidence interval

Adapted from Volume 9, Tables 32 and 33

MO comment: These primary efficacy results support the applicant's noninferiority claim for ertapenem compared with ceftriaxone in the treatment of complicated UTIs including pyelonephritis.

Table 014-4 categorizes the microbiological outcome at the test of cure visit according to baseline pathogen. The most frequently isolated pathogens were *E. coli*, *K. pneumoniae*, and *P. mirabilis*.

Table 014-4
Proportion of Favorable Microbiological Response Assessments at Test of Cure Displayed by Baseline Pathogen—
Microbiologically Evaluable Population

	Treatment Group			
	Ertapenem (N=159)		Ceftriaxone (N=171)	
	Response		Response	
Total Isolates	n/m	%	n/m	%
Gram-Positive Aerobic Cocci	**6/9**	**66.7**	**4/7**	**57.1**
Gram-Negative Aerobic Rods	**146/158**	**92.4**	**161/170**	**94.7**
Escherichia coli	104/111	93.7	112/117	95.7
Klebsiella pneumoniae	21/22	95.5	20/21	95.2
Proteus mirabilis	8/9	88.9	5/6	83.3
Other Enterobacteriaceae (12 species)	9/10	90.0	22/24	91.7
Pseudomonas spp.	4/6	66.7	2/2	100

n/m = number of pathogens with favorable assessment/number of pathogens with assessment

Adapted from Volume 9, Table 37

MO comment: The number of complicated UTIs due to *P. mirabilis* in the ertapenem group is inadequate to support inclusion of this organism in the labeling for this indication.

6.5.5.4.3.1.1. Bacteremia

Thirty-five patients in the microbiologically evaluable population were bacteremic: 20 patients in the ertapenem group and 15 patients in the ceftriaxone group. Seventeen of the 20 ertapenem patients (85%) and 13 of the 15 ceftriaxone patients (86.7%) had favorable microbiological responses at the test of cure visit. *E. coli* was the most common blood isolate (17/20 and 10/15, respectively). In those with *E. coli* bacteremia, 15 of the 17 ertapenem patients (88.2%) and 9 of the 10 ceftriaxone patients (90%) had favorable microbiological responses at the test of cure visit. No patients demonstrated persistence of a baseline blood pathogen in follow-up blood cultures.

6.5.5.4.3.1.2. Microbiological Recurrence

For patients who were microbiologically evaluable at late follow-up, the microbiological recurrence rate was 7.6% (8/105) in the ertapenem group and 8.3% (10/121) in the ceftriaxone group.

6.5.5.4.3.2. Clinical Efficacy

Table 014-5, adapted from applicant's Tables 40 and 41, shows the proportion of microbiologically evaluable patients with a favorable clinical response. The results are presented for the combined patient population as well as for the acute pyelonephritis and other complicated UTI strata. Overall, 143 of 159 patients (89.9%) in the ertapenem group and 160 of 171 patients (93.6%) in the ceftriaxone group had favorable clinical responses. The difference in response rate for ertapenem compared with ceftriaxone was -3.7% (95% CI, -10.3% to 2.8%). For the acute pyelonephritis stratum, 71 of 75 ertapenem recipients (94.7%) and 74 of 78 ceftriaxone recipients (94.9%) had favorable clinical responses. For other complicated UTIs, 72 of 84 ertapenem recipients (85.7%) and 86 of 93 ceftriaxone recipients (93.6%) had favorable microbiological responses.

Table 014-5
Proportion of Patients with Favorable Clinical Response Assessments at Test of Cure Visit–
Microbiologically Evaluable Population

Stratum	Treatment Group: Ertapenem (N=159) n/m	Response %	Response (95% CI)	Treatment Group: Ceftriaxone (N=171) n/m	Response %	Response (95% CI)	Difference %	Difference (95% CI)
Overall	143/159	89.9	(85.2, 94.6)	160/171	93.6	(89.9, 97.3)	-3.7	(-10.3, 2.8)
Acute pyelonephritis	71/75	94.7	(89.5, 99.8)	74/78	94.9	(89.9, 99.8)	-0.2	
Other complicated UTI	72/84	85.7	(78.2, 93.2)	86/93	92.5	(87.1, 97.9)	-6.8	

n/m = Number of patients with favorable assessment/number of patients with assessment
CI = Confidence interval

Adapted from Volume 9, Tables 40 and 41

6.5.5.4.3.2.1. Clinical Relapse

For patients who were clinically evaluable at late follow-up, the reported clinical relapse rate was 5.4% in the ertapenem group and 8.3% in the ceftriaxone group.

6.5.5.4.3.3. Modified Intent-to-Treat (MITT) Population Analyses

The MITT population was the subset of randomized patients meeting the minimal inclusion criteria and receiving at least one dose of study therapy. MITT outcomes were determined at the test of cure visit (or at the time of clinical failure). According to the Data Analysis Plan for this study, patients missing the test of cure visit could have an outcome imputed. A late follow-up visit outcome that was a success could be carried back to the test of cure visit. Otherwise, the test of cure outcome was assigned according to the last evaluation available, which for this study was either the day 3, 4, or 5 of IV therapy visit or the discontinuation of IV therapy visit (if not on day 3, 4, or 5).

> **MO comment: For patients with MITT outcomes imputed on the basis of last evaluation carried forward, the outcomes would almost invariably be successful, since these patients were on IV antimicrobial therapy at the time this urine culture specimen was obtained. Imputation of these outcomes had the effect of overstating the response rates for both study drugs at the test of cure visit. We therefore requested that the applicant reanalyze these cases using the more conservative approach of imputing the missing outcomes as failures. The following discussion uses the reanalyzed outcomes submitted by the applicant on 4/4/01 and 4/9/01.**

Table 014-6 shows the proportion of patients in the microbiological MITT population who had a favorable microbiological response. The observed response rate was 89.0% (195/219) for the ertapenem group and 84.7% (205/242) for the ceftriaxone group (observed difference 4.3%).

Table 014-6
Proportion of Patients with Favorable Microbiological Response Assessments–
Microbiological MITT Population

	Treatment Group							
	Ertapenem (N=219)			Ceftriaxone (N=242)			Difference	
Time Point	n/m	Response %	(95% CI)	n/m	Response %	(95% CI)	%	(95% CI)
Test of Cure	195/219	89.0	(84.9, 93.2)	205/242	84.7	(80.2, 89.3)	4.3	(-2.2, 10.9)

n/m = Number of patients with favorable assessment/number of patients with assessment
CI = Confidence interval

Adapted from 4/4/01 amendment, Table 3

Table 014-7 shows the proportion of patients in the microbiological MITT population who had a favorable clinical response assessment. The observed response rate was 84.5% (185/219) for the ertapenem group and 84.7% (205/242) for the ceftriaxone group (observed difference -0.2%).

Table 014-7
Proportion of Patients with Favorable Clinical Response Assessments–
Microbiological MITT Population

	Treatment Group							
	Ertapenem (N=219)			Ceftriaxone (N=242)			Difference	
		Response			Response			
Time Point	n/m	%	(95% CI)	n/m	%	(95% CI)	%	(95% CI)
Test of Cure	185/219	84.5	(79.7, 89.3)	205/242	84.7	(80.2, 89.3)	-0.2	(-7.3, 6.8)

n/m = Number of patients with favorable assessment/number of patients with assessment
CI = Confidence interval

Adapted from 4/4/01 amendment, Table 4

MO comment: Analyses of the microbiological and clinical responses in the microbiological MITT population support the per protocol analyses.

6.5.5.5. Conclusions

The primary outcome measure for Protocol 014 was the microbiological response at the test of cure visit 5 to 9 days following completion of all therapy. Overall, 146 of 159 patients (91.8%) in the ertapenem group and 159 of 171 patients (93.0%) in the ceftriaxone group had favorable microbiological responses. The difference in response rate for ertapenem compared with ceftriaxone was -1.2% (95% CI, -7.6% to 5.1%). The lower bound of the 95% CI is greater than -10% and satisfies the prespecified noninferiority criterion. Microbiological response rates were similar for both drugs across the acute pyelonephritis and other complicated UTI strata. Eradication rates were similar for the most commonly isolated pathogens in this study, *E. coli*, *K. pneumoniae*, and *P. mirabilis*. The secondary outcome measures of clinical response at the test of cure visit and clinical and microbiological recurrence at late follow-up were similar between treatment groups. Analyses of microbiological and clinical responses in the microbiological MITT population support the per protocol analyses.

6.5.6. Protocol 021: "A Supportive, Prospective, Multicenter, Double-Blind, Randomized, Comparative Study to Evaluate the Safety, Tolerability, and Efficacy of MK-0826 Versus Ceftriaxone Sodium in the Treatment of Complicated Urinary Tract Infections in Adults"

6.5.6.1. Objectives

The applicant's objectives were similar to those of Protocol 014 (Section 6.5.5.1). An additional objective was to combine the efficacy data from this study with those of Protocol 014 to support the noninferiority of ertapenem when compared with ceftriaxone.

6.5.6.2. Design: Randomized (2:1 ratio), double-blind, comparative, multicenter trial

6.5.6.3. Protocol Overview

6.5.6.3.1. Population

6.5.6.3.1.1. Inclusion Criteria

Inclusion criteria were identical to those of Protocol 014 (Section 6.5.5.3.1.1).

6.5.6.3.1.2. Exclusion Criteria

Exclusion criteria were identical to those of Protocol 014 (Section 6.5.5.3.1.2) except that patients with severe renal insufficiency not requiring dialysis were allowed into the study with an adjustment of study drug dose.

6.5.6.3.2. Study Procedures

Study procedures were identical to those of Protocol 014 (Section 6.5.5.3.2) except that study drug randomization was 2:1 in favor of ertapenem and a provision was included for intramuscular dosing of study drugs at the discretion of the investigator.

MO comment: An insufficient number of patients received intramuscular dosing to permit evaluation of the efficacy of this method of administration.

6.5.6.3.3. Evaluability Criteria

Evaluability criteria were identical to those of Protocol 014 (Section 6.5.5.3.3).

6.5.6.3.4. Endpoints

Endpoints were similar to those of Protocol 014 (Section 6.5.5.3.4).

6.5.6.3.5. Statistical Considerations

This study was intended to be supportive of Protocol 014, and the applicant therefore chose a more liberal noninferiority criterion of -20%. With 100 evaluable patients in the ertapenem group, 50 evaluable patients in the ceftriaxone group, and an estimated response rate of 90% for each study drug, the applicant calculated that this study would have 97% power to determine that the lower bound of the 95% CI around the difference in response rates between treatments was not less than -20%.

The primary efficacy analysis was performed on the per protocol population as defined by the evaluability criteria in Section 6.5.5.3.3. Additional analysis was performed on the modified intent-to-treat population, which was the subset of patients meeting the minimal case definition (Section 6.5.5.3.1.1, Inclusion Criteria) and receiving at least one dose of study therapy.

MO comment: The inclusion and exclusion criteria, study procedures, evaluability criteria, and endpoints are acceptable. The primary outcome

measure is consistent with the recommendation in the FDA draft guidance on complicated UTIs and pyelonephritis.

6.5.6.4. Study Results

6.5.6.4.1. Demographics

Two hundred fifty-eight patients were randomized to receive one of the study therapies: 175 to receive ertapenem and 83 to receive ceftriaxone. Table 021-1, adapted from applicant's Table 18, shows the baseline characteristics of randomized patients. Baseline characteristics appeared similar between treatment groups. Twenty-six domestic and foreign sites enrolled patients in this study. Applicant's Tables 15 and 16 list the study sites and numbers of patients enrolled and evaluable. No study site enrolled more than 21% of the patients.

Table 021-1
Baseline Patient Characteristics by Treatment Group
(All Randomized Patients)

	Ertapenem (N=175)		Ceftriaxone (N=83)		Total (N=258)	
	n	(%)	n	(%)	n	(%)
Gender						
Male	69	(39.4)	40	(48.2)	109	(42.2)
Female	106	(60.6)	43	(51.8)	149	(57.8)
Race						
Caucasian	130	(74.3)	58	(69.9)	188	(72.9)
Black	8	(4.6)	8	(9.6)	16	(6.2)
Hispanic	33	(18.9)	16	(19.3)	49	(19.0)
Other	4	(2.3)	1	(1.2)	5	(1.9)
Age (Years)						
≤40	58		27		85	
41 to 64	57		30		87	
65 to 74	29		19		48	
≥75	31		7		38	
Mean	52.7		51.1		52.2	
Median	55		50		55	
Range	18 to 90		18 to 90		18 to 90	
Stratum						
Acute pyelonephritis	94	(53.7)	41	(49.4)	135	(52.3)
Other complicated UTI	81	(46.3)	42	(50.6)	123	(47.7)

Adapted from Volume 19, Table 18

6.5.6.4.2. Evaluability

Table 021-2, adapted from applicant's Table 17, shows the disposition of the randomized patient population. The microbiological protocol evaluable population was used for the primary efficacy analysis. The most common reason for exclusion from the microbiological and clinical protocol evaluable populations was lack of isolation of a uropathogen, which therefore meant that the disease definition was not met.

Table 021-2
Patient Accounting of Evaluability
(Randomized Population)

Population	Ertapenem (N=175) n	(%)	Ceftriaxone (N=83) n	(%)
Microbiologic Protocol Evaluable Population				
Microbiologic protocol evaluable	97	(55.4)	53	(63.9)
Microbiologic protocol nonevaluable	78	(44.6)	30	(36.1)
Not clinically evaluable	72	(41.1)	28	(33.7)
Disease definition not met	32	(18.3)	9	(10.8)
Test-of-cure window violation	18	(10.3)	8	(9.6)
Inadequate/inappropriate study therapy	12	(6.9)	4	(4.8)
Prior antibiotics violation	1	(0.6)	1	(1.2)
Concomitant antibiotics violation	4	(2.3)	2	(2.4)
Baseline microbiology—resistant pathogen	11	(6.3)	5	(6.0)
Baseline uropathogen but $<10^5$ CFU/mL	8	(4.6)	3	(3.6)
Other	1	(0.6)	1	(1.2)
Baseline microbiology inadequate	5	(2.9)	0	(0.0)
Baseline microbiology—no pathogen isolated	29	(16.6)	9	(10.8)
Test-of-cure microbiology inadequate	27	(15.4)	9	(10.8)

Adapted from Volume 19, Table 17

MO comment: A blinded review of a 20% random sample of the case report forms revealed three errors in determination of evaluability. Two patients received prestudy antibiotic therapy after the baseline urine culture was obtained and before administration of study therapy. In one of these cases the start and stop dates of the disqualifying therapy were miscoded in the dataset. A third patient had urine cultures growing *Flavobacterium* spp., which are not considered recognized uropathogens. These patients should have been excluded from the protocol evaluable population. Review of the case report tabulations revealed no other evidence of systematic occurrence of these errors. Exclusion of these patients and recalculation of efficacy rates did not result in a significant change in the submitted analysis. The applicant's data were otherwise reported satisfactorily and have been accepted for the remainder of this review.

6.5.6.4.3. Efficacy

6.5.6.4.3.1. Microbiological Efficacy

The primary outcome measure was the microbiological response at the test of cure visit 5 to 9 days following completion of all therapy. Table 021-3, adapted from applicant's Tables 33 and 34, shows the proportion of patients with a favorable microbiological response at the test of cure visit. The results are presented for the combined patient population as well as for the acute pyelonephritis and other complicated UTI strata. Overall, 83 of 97 patients (85.6%) in the ertapenem group and 45 of 53 patients (84.9%) in the ceftriaxone group had favorable microbiological responses. The difference in

response rate for ertapenem compared with ceftriaxone was 0.7% (95% CI, -12.7% to 14.0%). For the acute pyelonephritis stratum, 45 of 52 ertapenem recipients (86.5%) and 25 of 28 ceftriaxone recipients (89.3%) had favorable microbiological responses. For other complicated UTIs, 38 of 45 ertapenem recipients (84.4%) and 20 of 25 ceftriaxone recipients (80.0%) had favorable microbiological responses.

Table 021-3
Proportion of Patients with Favorable Microbiological Response Assessments at Test of Cure Visit–
Microbiologically Evaluable Population

Stratum	Treatment Group: Ertapenem (N=97) n/m	Response %	Response (95% CI)	Treatment Group: Ceftriaxone (N=53) n/m	Response %	Response (95% CI)	Difference %	Difference (95% CI)
Overall	83/97	85.6	(78.5, 92.6)	45/53	84.9	(75.2, 94.6)	-0.7	(-12.7, 14.0)
Acute pyelonephritis	45/52	86.5	(77.2, 95.9)	25/28	89.3	(77.6, 100)	-2.7	
Other complicated UTI	38/45	84.4	(73.7, 95.2)	20/25	80.0	(64.0, 96.0)	4.4	

n/m = Number of patients with favorable assessment/number of patients with assessment
CI = Confidence interval

Adapted from Volume 19, Tables 33 and 34

MO comment: These primary efficacy results support the applicant's noninferiority claim for ertapenem compared with ceftriaxone in the treatment of complicated UTIs including pyelonephritis. The overall response rates are nearly identical for the two drugs. The smaller sample size for this study compared with Protocol 014 results in a wider 95% CI.

Table 021-4 categorizes the microbiological outcome at the test of cure visit according to baseline pathogen. The most frequently isolated pathogens were *E. coli*, *K. pneumoniae*, and *P. mirabilis*.

Table 021-4
Proportion of Favorable Microbiological Response Assessments at Test of Cure Displayed by Baseline Pathogen—
Microbiologically Evaluable Population

Total Isolates	Treatment Group: Ertapenem (N=97) Response n/m	Response %	Treatment Group: Ceftriaxone (N=53) Response n/m	Response %
Gram-Positive Aerobic Cocci	**1/1**	**100**	**2/3**	**66.7**
Gram-Negative Aerobic Rods	**83/97**	**85.6**	**43/50**	**86.0**
Escherichia coli	72/80	90.0	31/38	81.6
Klebsiella pneumoniae	3/6	50.0	4/4	100
Proteus mirabilis	1/3	33.3	2/2	100
Other Enterobacteriaceae (9 species)	6/6	100	5/5	100
Pseudomonas aeruginosa	1/2	50.0	1/1	100

n/m = number of pathogens with favorable assessment/number of pathogens with assessment

Adapted from Volume 19, Table 41

MO comment: There are few *K. pneumoniae* and *P. mirabilis* isolates in this study, and the eradication rates for ertapenem are low. These results do not support the applicant's claim of efficacy against these pathogens.

6.5.6.4.3.1.1. Bacteremia

Nineteen patients in the microbiologically evaluable population were bacteremic: 9 patients in the ertapenem group and 10 patients in the ceftriaxone group. Eight of the 9 ertapenem patients (88.9%) and 8 of the 10 ceftriaxone patients (80.0%) had favorable microbiological responses at the test of cure visit. *E. coli* was the most common blood isolate (7/9 and 7/10, respectively). In those with *E. coli* bacteremia, all 7 ertapenem patients (100%) and 5 of the 7 ceftriaxone patients (71.4%) had favorable microbiological responses at the test of cure visit. No patients demonstrated persistence of a baseline blood pathogen in follow-up blood cultures.

6.5.6.4.3.1.2. Microbiological Recurrence

For patients who were microbiologically evaluable at late follow-up, the microbiological recurrence rate was 11.1% (7/63) in the ertapenem group and 5.4% (2/37) in the ceftriaxone group.

6.5.6.4.3.2. Clinical Efficacy

Table 021-5, adapted from applicant's Tables 44 and 45, shows the proportion of microbiologically evaluable patients with a favorable clinical response. The results are presented for the combined patient population as well as for the acute pyelonephritis and other complicated UTI strata. Overall, 90 of 97 patients (92.8%) in the ertapenem group and 47 of 53 patients (88.7%) in the ceftriaxone group had favorable clinical responses. The difference in response rate for ertapenem compared with ceftriaxone was 4.1% (95% CI, -7.4% to 15.6%). For the acute pyelonephritis stratum, 49 of 52 ertapenem recipients (94.2%) and 26 of 28 ceftriaxone recipients (92.9%) had favorable clinical responses. For other complicated UTIs, 41 of 45 ertapenem recipients (91.1%) and 21 of 25 ceftriaxone recipients (84.0%) had favorable microbiological responses.

Table 021-5
Proportion of Patients with Favorable Clinical Response Assessments at Test of Cure Visit–
Microbiologically Evaluable Population

Stratum	Treatment Group: Ertapenem (N=97) n/m	Ertapenem Response %	Ertapenem Response (95% CI)	Treatment Group: Ceftriaxone (N=53) n/m	Ceftriaxone Response %	Ceftriaxone Response (95% CI)	Difference %	Difference (95% CI)
Overall	90/97	92.8	(87.6, 98.0)	47/53	88.7	(80.1, 97.3)	4.1	(-7.4, 15.6)
Acute pyelonephritis	49/52	94.2	(87.8, 100)	26/28	92.9	(83.1, 100)	1.4	
Other complicated UTI	41/45	91.1	(82.7, 99.5)	21/25	84.0	(69.3, 98.7)	7.1	

n/m = Number of patients with favorable assessment/number of patients with assessment
CI = Confidence interval

Adapted from Volume 19, Tables 44 and 45

6.5.6.4.3.2.1. Clinical Relapse

For patients who were clinically evaluable at late follow-up, the reported clinical relapse rate was 4.7% in the ertapenem group and 5.4% in the ceftriaxone group.

6.5.6.4.3.3. Modified Intent-to-Treat (MITT) Population Analyses

The MITT population was the subset of randomized patients meeting the minimal inclusion criteria and receiving at least one dose of study therapy. MITT outcomes were determined at the test of cure visit (or at the time of clinical failure). According to the Data Analysis Plan for this study, patients missing the test of cure visit could have an outcome imputed. A late follow-up visit outcome that was a success could be carried back to the test of cure visit. Otherwise, the test of cure outcome was assigned according to the last evaluation available, which for this study was either the day 3, 4, or 5 of IV therapy visit or the discontinuation of IV therapy visit (if not on day 3, 4, or 5).

> **MO comment: For patients with MITT outcomes imputed on the basis of last evaluation carried forward, the outcomes would almost invariably be successful, since these patients were on IV antimicrobial therapy at the time this urine culture specimen was obtained. Imputation of these outcomes had the effect of overstating the response rates for both study drugs at the test of cure visit. We therefore requested that the applicant reanalyze these cases using the more conservative approach of imputing the missing outcomes as failures. The following discussion uses the reanalyzed outcomes submitted by the applicant on 4/4/01 and 4/9/01.**

Table 021-6 shows the proportion of patients in the microbiological MITT population who had a favorable microbiological response. The observed response rate was 75.6% (99/131) for the ertapenem group and 71.8% (51/71) for the ceftriaxone group (observed difference 3.7%).

Table 021-6
Proportion of Patients with Favorable Microbiological Response Assessments–
Microbiological MITT Population

	Treatment Group							
	Ertapenem (N=131)			Ceftriaxone (N=71)			Difference	
Time Point	n/m	Response %	(95% CI)	n/m	Response %	(95% CI)	%	(95% CI)
Test of Cure	99/131	75.6	(68.2, 83.0)	51/71	71.8	(61.3, 82.4)	3.7	(-10.1, 17.6)

n/m = Number of patients with favorable assessment/number of patients with assessment
CI = Confidence interval

Adapted from 4/4/01 amendment, Table 25

Table 021-7 shows the proportion of patients in the microbiological MITT population who had a favorable clinical response assessment. The observed response rate was 85.5% (112/131) for the ertapenem group and 77.5% (55/71) for the ceftriaxone group (observed difference 8.0%).

Table 021-7
Proportion of Patients with Favorable Clinical Response Assessments–
Microbiological MITT Population

	Treatment Group							
	Ertapenem (N=131)			Ceftriaxone (N=71)			Difference	
Time Point	n/m	Response %	(95% CI)	n/m	Response %	(95% CI)	%	(95% CI)
Test of Cure	112/131	85.5	(79.4, 91.5)	55/71	77.5	(67.7, 87.3)	8.0	(-4.5, 20.6)

n/m = Number of patients with favorable assessment/number of patients with assessment
CI = Confidence interval

Adapted from 4/4/01 amendment, Table 26

MO comment: Analyses of the microbiological and clinical responses in the microbiological MITT population support the per protocol analyses.

6.5.6.5. Conclusions

The primary outcome measure for Protocol 021 was the microbiological response at the test of cure visit 5 to 9 days following completion of all therapy. Overall, 83 of 97 patients (85.6%) in the ertapenem group and 45 of 53 patients (84.9%) in the ceftriaxone group had favorable microbiological responses. The difference in response rate for ertapenem compared with ceftriaxone was 0.7% (95% CI, -12.7% to 14.0%). This study was designed to support the conclusions of Protocol 014; the wider CI for the treatment difference in Protocol 021 reflects the smaller sample size. Microbiological response rates were similar for both drugs across the acute pyelonephritis and other complicated UTI strata. Eradication rates were similar for the most commonly isolated pathogen in this study, *E. coli*. There were few *K. pneumoniae* and *P. mirabilis* isolates in this study, and the eradication rates for ertapenem were low. The secondary outcome measures of clinical response at the test of cure visit and clinical and microbiological recurrence at late follow-up were similar between treatment groups. Analyses of microbiological and clinical responses in the microbiological MITT population support the per protocol analyses.

6.5.7. Complicated Urinary Tract Infections Conclusion

Table 014/021 shows the per-pathogen efficacy results for the combined studies.

Table 014/021
Proportion of Favorable Microbiological Response Assessments at Test of Cure
Displayed by Baseline Pathogen—
Microbiologically Evaluable Population
Protocols 014 and 021

Total Isolates	Treatment Group: Ertapenem (N=256) n/m	Ertapenem Observed Response %	Ertapenem Observed Response (95% CI)	Ceftriaxone (N=224) n/m	Ceftriaxone Observed Response %	Ceftriaxone Observed Response (95% CI)	Observed Difference %
Gram-Positive Aerobic Cocci	**7/10**	**70.0**	**(40.1, 99.9)**	**6/10**	**60.0**	**(28.0, 92.0)**	**10.0**
Gram-Negative Aerobic Rods	**229/255**	**89.8**	**(86.1, 93.5)**	**205/221**	**92.8**	**(89.3, 96.2)**	**-3.0**
Escherichia coli	176/191	92.1	(88.3, 96.0)	143/155	92.3	(88.0, 96.5)	-0.1
Klebsiella pneumoniae	24/28	85.7	(72.5, 98.9)	24/25	96.0	(88.2, 100)	-10.3
Proteus mirabilis	9/12	75.0	(49.4, 100)	7/8	87.5	-	-12.5

N = Number of microbiologically evaluable patients in each treatment group
CI = Confidence interval
n/m = Number of pathogens with favorable assessment/number of pathogens with assessment

Adapted from Integrated Summary of Efficacy, Table D-42

The results of Protocols 014 and 021 demonstrate similar effectiveness of ertapenem to the approved comparator ceftriaxone for the treatment of adult patients with complicated UTIs including pyelonephritis due to susceptible strains of *E. coli*. The response rate for *K. pneumoniae* complicated UTIs to ertapenem, while lower than that for ceftriaxone, is satisfactory. Only 4.7% of the complicated UTIs in the ertapenem group were due to *P. mirabilis*, however, and the response rate was 75% with a wide confidence interval. Neither the number of *P. mirabilis* isolates nor the observed response rate are adequate to support inclusion of this organism in the labeling for this indication.

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Smith
11/29/01 05:44:41 PM
MEDICAL OFFICER
Efficacy review of complicated UTI indication
Please sign off for Dr. Makhene; she and Dr.
Soreth have reviewed.

David Ross
11/30/01 04:47:15 PM
MEDICAL OFFICER
David Ross signing for Dr. Mamodikoe Makhene

Janice Soreth
12/11/01 01:28:32 PM
MEDICAL OFFICER