Proportion of Favorable Microbiological Response Assessments at Test of Cure in the Microbiologically Evaluable Population Displayed by Baseline Pathogen Blood Isolates (Observed† Data)

Blood Isolates	Treatment Group: MK-0826 (A) (N=10) n/m	Observed† Response %	(95% CI)	Ceftriaxone (B) (N=16) n/m	Observed† Response %	(95% CI)	Observed Difference (A-B) %
Gram-Positive Aerobic Cocci	**9/9**	**100**	-	**16/16**	**100**	**(79.4, 100)**	**0.0**
Staphylococcus aureus	1/1	100	-	-	-	-	-
Streptococcus pneumoniae	6/6	100	-	16/16	100	(79.4, 100)	0.0
Streptococcus milleri group	2/2	100	-	-	-	-	-
Gram-Negative Aerobic Rods	**1/1**	**100**	-	-	-	-	-
Haemophilus influenzae	1/1	100	-	-	-	-	-

† Computed from a statistical model pooling across strata.
N = Number of microbiologically evaluable patients with a baseline blood pathogen in each treatment group.
n/m = Number of pathogens with associated favorable assessment/number of pathogens with an assessment at Test of Cure.
CI = Confidence interval.

(Applicant's Table 45, Volume 15 of 22, page 134)

Medical Officer's Comment: ***The MO did not feel that patients who were otherwise evaluable failures should be excluded from this analysis based on the absence of repeat blood cultures, but that they should be considered to have presumed persistence and be considered to have an unfavorable outcome. Two patients with S. pneumoniae (Patient 6365 in the MK-0826 group and Patient 7082 in the ceftriaxone group) on entry blood cultures are therefore considered failures based on presumed persistence by the MO. The MO has also changed the outcome for Patient 6083 in the MK-0826 group who had H. influenzae (β lactamase positive) on entry blood cultures to failure because the patient was considered a clinical failure and had H. influenzae (β lactamase positive) isolated from a blood culture 3 days after the discontinuation from IV visit. The MO's revised table for outcome of patients with baseline pathogen blood isolates is provided below.***

Proportion of Favorable Microbiological Response Assessments at Test of Cure in the Microbiologically Evaluable Population Displayed by Baseline Pathogen Blood Isolates According to the MO (Observed Data)

Blood Isolates	Treatment Group: MK-0826 (A) (N=11) Observed Response n/m	%	Ceftriaxone (B) (N=17) Observed Response n/m	%	Observed Difference (A-B) %
Gram-Positive Aerobic Cocci	9/10	90	16/17	94	-4.0
Staphylococcus aureus	1/1	100	-	-	-
Streptococcus pneumoniae	6/7	86	16/17	94	-8.0
Streptococcus milleri group	2/2	100	-	-	-
Gram-Negative Aerobic Rods	0/1	0	-	-	-
Haemophilus influenzae	0/1	0	-	-	-

N = Number of microbiologically evaluable patients with a baseline blood pathogen in each treatment group.
n/m = Number of pathogens with associated favorable assessment/number of pathogens with an assessment at Test of Cure.
CI = Confidence interval.

Penicillin-Resistant *Streptococcus pneumoniae* (PRSP)

Patients infected with PRSP (penicillin MIC ≥2 µg/mL) were excluded from the primary clinical and microbiological analyses and analyzed both separately and overall with non-PRSP *S. pneumoniae* isolates. A total of four (4) patients with PRSP were clinically and microbiologically evaluable and all 4 patients had a favorable clinical and microbiological outcome. PRSP was not isolated from blood in any patients in this study.

The Applicant's comparison of the clinical responses and microbiologic responses in patients infected with *S. pneumoniae* according to the susceptibility to penicillin are shown in the following tables.

Proportions of Favorable Clinical Response Assessments at Test of Cure in the Microbiologically Evaluable Patients Infected With *Streptococcus pneumoniae* Displayed According to Penicillin Susceptibility (Unique Sputum or Blood Isolates)

Penicillin Susceptibility	Treatment Group	
	MK-0826 (N=48)	Ceftriaxone (N=60)
	n/m (%)	n/m (%)
Penicillin susceptible†	28/32 (87.5)	32/35 (91.4)
Penicillin nonsusceptible‡	11/11 (100)	12/13 (92.3)
Penicillin resistant‡	1/1 (100)	3/3 (100)
Unknown‖	5/5 (100)	12/12 (100)
All	44/48 (91.7)	56/60 (93.3)

† Based on Kirby Bauer disk zone size ≥20 mm or MIC <0.1 (E-test <0.09) µg/mL.
‡ Based on Kirby Bauer disk zone size ≤19 mm or MIC ≥0.1 (E-test >0.09) µg/mL.
‖ Unknown = Inadequate in vitro penicillin susceptibility result reported.
N = Number of microbiologically evaluable patients in treatment group with *S. pneumoniae* isolated.
n/m = Number of favorable assessments at Test of Cure/number with specified isolate.

(Applicant's Table 46, Volume 15 of 22, page 136)

APPEARS THIS WAY
ON ORIGINAL

Proportions of Favorable Microbiologic Response Assessments at Test of Cure in the Microbiologically Evaluable Population Infected With *Streptococcus pneumoniae* Displayed According to Penicillin Susceptibility (Unique Sputum and Blood Isolates)

	Treatment Group	
	MK-0826 (N=48)	Ceftriaxone (N=60)
Penicillin Susceptibility	n/m (%)	n/m (%)
Penicillin susceptible†	31/32 (96.9)	34/35 (97.1)
Penicillin nonsusceptible‡	11/11 (100)	13/13 (100)
Penicillin resistant§	1/1 (100)	3/3 (100)
Unknown‖	5/5 (100)	12/12 (100)
All	47/48 (97.9)	59/60 (98.3)

† Based on Kirby Bauer disk zone size ≥20 mm or MIC <0.1 (E-test <0.09) µg/mL.
‡ Based on Kirby Bauer disk zone size ≤19 mm or MIC ≥0.1 (E-test >0.09) µg/mL.
§ Based on MIC ≥2 (E-test ≥1.5) µg/mL.
‖ Unknown = inadequate in vitro penicillin susceptibility result reported.
N = Number of microbiologically evaluable patients in treatment group with *S. pneumoniae* isolated.
n/m = Number with favorable assessments at Test of Cure/number with specified isolate.

(Applicant's Table 47, Volume 15 of 22, page 136)

Medical Officer's Comment: ***It should be noted that in the preceding two tables the penicillin resistant isolates are a subset of the penicillin nonsusceptible isolates and are not counted again in the overall totals. The clinical and microbiologic response rates are similar regardless of the penicillin susceptibility of the pneumococcal isolates.***

6.3.5.5 Reviewer's Comments/Conclusions of Study

In adult patients with community-acquired pneumonia (CAP) treated for 10 to 14 days, including a minimum of 3 days of parenteral MK-0826 followed by an oral antibiotic switch option (Augmentin) after clinical improvement, the following conclusions can be drawn:

1. MK-0826 1 gm IV once daily was as clinically effective as ceftriaxone 1 gm IV once daily in treating community acquired pneumonia in adults.
2. For conclusions regarding the safety tolerability of MK-0826, in this study, see section 7.1.3.1 of this review.

6.3.6 PROTOCOL 020: 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 SERIOUS COMMUNITY-ACQUIRED PNEUMONIA IN ADULTS

6.3.6.1 Objective/Rationale

The objectives of the study, as stated by the Applicant, were:

Primary Objectives

1. To compare the efficacy of MK-0826 versus ceftriaxone sodium with respect to the clinical response assessment profile in the treatment of patients with serious CAP and without documented PRSP at the EFU visit.

2. To compare the safety profile of MK-0826 versus ceftriaxone sodium with respect to parenteral drug-related clinical and/or laboratory adverse experiences leading to discontinuation of study drug and with respect to drug-related serious adverse experiences.

Secondary Objectives

1. To combine the efficacy data from this supportive study with those of Protocol 018 to support a conclusion that MK-0826 was as efficacious as ceftriaxone sodium, with respect to all clinically evaluable patients without PRSP at the EFU visit.

2. To combine the efficacy data from this supportive study with those of Protocol 018 to support a conclusion that MK-0826 was as efficacious as ceftriaxone sodium with respect to all clinically and microbiologically evaluable patients irrespective of PRSP.

Tertiary Objectives

1. To estimate the efficacy of MK-0826 and ceftriaxone sodium at EFU visit with respect to the clinical response assessment profile in the treatment of patients with serious CAP and without documented PRSP.

2. To estimate the tolerability profile of MK-0826 and ceftriaxone sodium in patients with serious CAP.

3. To estimate the clinical cure rates of MK-0826 in all clinically evaluable patients, without documented PRSP and irrespective of PRSP.

4. To estimate the microbiological and clinical cure rates of MK-0826 within all clinically and microbiologically evaluable patients with and without documented PRSP and irrespective of PRSP.

5. To combine the efficacy data from this supportive study with those of Protocol 018, in order to support a conclusion that MK-0826 was as efficacious as ceftriaxone sodium, with respect to all clinically and microbiologically evaluable patients with documented PRSP.

6.3.6.2 Design

This was a prospective, multicenter, double-blind, randomized (2:1 ratio), comparative study. Twenty-five (25) centers in the United States and 20 centers internationally (9 from Latin America and 11 from Europe/Russia) enrolled patients between October 8, 1998 and May 2, 2000.

Eligible patients were stratified at study entry for balance between the treatment groups according to disease severity (Pneumonia Severity Index ≤3 or >3) and age (≤65 years or >65 years). Stratified patients were then randomly assigned to receive ertapenem 1 gm once daily or ceftriaxone 1 gm once daily (2:1 ratio). For patients with penicillin resistant *Streptococcus pneumoniae* (PRSP), the investigator had the option to increase the dose of either drug to 2 gm once daily if it was felt that the patient had a suboptimal response to the 1 gm dose. Each treatment regimen was to be administered for a minimum of 3 full days and a maximum of 14 days. The protocol was amended to allow a switch to intramuscular (IM) parenteral therapy after at least one dose of intravenous (IV) parenteral therapy, after the study began. After at least 3 days of parenteral therapy the Investigators had the option to switch patients to oral antibiotic therapy, based on protocol specified switch criteria, to complete a total duration of antimicrobial therapy that was not to exceed 14 days (parenteral plus oral). Augmentin 875 mg twice daily was the oral antimicrobial recommended in the protocol, but, alternate oral regimens were allowed at the discretion of the Investigator.

Patients were evaluated for clinical progress at Day 3, 4, or 5; at the time of discontinuation of parenteral therapy (if different from Day 3, 4, or 5); at 7- to 14-days posttherapy (early follow-up visit [EFU]); and at 21 to 28 days posttherapy (the final study visit [LFU]). The TOC assessment was at the EFU visit.

The safety of parenteral MK-0826 and of parenteral ceftriaxone was evaluated by determining the presence or absence of clinical or laboratory adverse experiences. Patients were monitored for adverse experiences on a daily basis during the parenteral study antibiotic period, and for 14 days after the discontinuation of all study therapy (parenteral plus oral). Adverse experiences of special interest, included: seizures (regardless of prior seizure history); elevated transaminases; neutropenia; and rash of sufficient severity to require discontinuing study antibiotic. The schedule of clinical observations and laboratory measurements is in Appendix 18.

The clinical response was determined by the investigator based on an assessment of signs and symptoms associated with pneumonia as well as vital signs, oxygen saturation, and chest radiography. The microbiologic response was based on isolation of a respiratory pathogen from specimens obtained at the time of study entry, and the documented eradication or persistence of this pathogen at the time of follow-up, when an adequate specimen could be obtained. In cases of clinical resolution when sputum was no longer produced or an adequate sample could not be obtained for culture, the microbiologic response was considered presumptive eradication.

Medical Officer's Comment:: With the exception of the 2:1 randomization schedule, the design of Protocol 020 is essentially identical to Protocol 018.

Like Protocol 018, it is notable that this protocol was amended during the course of the study to provide additional blinding procedures when it was recognized that a slight color difference could sometimes be detected between MK-0826 and placebo. Measures implemented by the Applicant to assure that the study drug blind was maintained included: limits on the time of reconstitution; limits on the choice of the final infusion container; prompt disposal of study infusion bags after use; and the use of amber-colored translucent bag covers.

6.3.6.3 Protocol Overview
6.3.6.3.1 Population/Procedures
6.3.6.3.2 Evaluability Criteria
6.3.6.3.3 Endpoints

Medical Officer's Comment: The parameters used by the Applicant for "Population", "Procedures", "Evaluability Criteria", and "Endpoints" were identical in this protocol to those used in Protocol 018 and will not be further reviewed in this section. For a description of these parameters the reader is referred to section 6.3.5.3 of this review.

6.3.6.3.4 Statistical Considerations

The Applicant's sample size calculation assumed a 90% favorable clinical response rate at the EFU visit in the microbiologically evaluable population (the primary efficacy analysis) for both groups, and a significance level of 0.025. Based on this assumption, 150 evaluable patients (100 in the MK-0826 group and 50 in the ceftriaxone group) were needed to have an 97% probability that the lower limit of the 95% (two-sided) CI for the difference in the response rates between the 2 groups did not exceed –20 percentage points. According to the Applicant:

> "The definition of equivalence was that the 95% (2-sided) CI for the difference in response rates between the 2 treatment groups (response rate for MK-0826 minus response rate for control group) contains zero and the lower limit of the CI does not exceed -20 percentage points. This study was meant to be supportive of the first, statistically adequate study (Protocol 018) and was powered only with a large equivalence margin. Thus, a less strict definition of equivalence between MK-0826 and ceftriaxone was used.
>
> When data from the 2 studies were combined, the definition of equivalence was that the 95% (two-sided) CI for the difference in response rates between the 2 treatment groups contains zero and the lower limit of the CI does not exceed -10

percentage points if a 90% or better response rate is observed for the control group; -15 percentage points if a response rate that is <90% and ≥80% is observed for the control group; -20 percentage points if a response rate that is <80% and ≥70% is observed for the control group."

Medical Officer's Comment: ***Regarding the Applicant's proposal to combine data from the 2 studies, the Applicant was told by the Division at the January 28, 2000 teleconference that if Protocol 018 fails to show equivalence and only with the addition of data from Protocol 020 is equivalence shown, the submission will be considered inadequate to obtain an indication for community acquired pneumonia.***

The efficacy variables were analyzed using an evaluable population only approach and a modified intent-to-treat (MITT) approach. The evaluable population approach was specified as the primary efficacy analysis. The primary endpoints were analyzed by stratum (4 strata formed by the combinations of PSI and age strata). A test of treatment-by-stratum interaction (Breslow-Day Test of Homogeneity of Odds-Ratios) was performed. When the nominal p-value of the test was >0.05, it was concluded that the odds ratios were similar across the strata and that strata could be combined. Results were then displayed combined over strata for each treatment group.

The 2 treatment groups were compared for each of the efficacy parameters and the differences in proportions (MK-0826 minus ceftriaxone) were calculated, along with the corresponding 95% confidence intervals (CIs). 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. The observed proportions and the corresponding CIs are displayed. The CIs around the individual proportions were calculated using the CMH approach applied to one sample. The observed differences between the treatment groups were computed by pooling data across the strata.

For MITT analyses, the proportion of clinical MITT evaluable patients with a favorable clinical response assessment, and the proportion of clinical and microbiological MITT evaluable patients with a favorable clinical and microbiological response assessment, are displayed, along with their corresponding 95% CIs. For the Applicant's MITT analysis, in patients missing a TOC assessment, the last evaluation before TOC was used.

Medical Officer's Comment: ***During the January 28, 2000 teleconference between the Applicant and the Division, the Applicant was informed that patients with missing or indeterminate outcomes were generally considered failures in the MITT analyses by the Division and that additional sensitivity analyses using this approach should be performed. These sensitivity analyses were not provided in the original NDA and were requested again at the March 12, 2001 teleconference between the Applicant and the Division. The Applicant provided the requested analyses in an April 4, 2001 amendment to the NDA.***

The Applicant also performed subgroup analyses for stratum (PSI ≤3 or >3), age (≤65 years versus >65 years, <75 years versus ≥75), race, and gender 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.) In addition, the primary efficacy endpoint is displayed for the groups

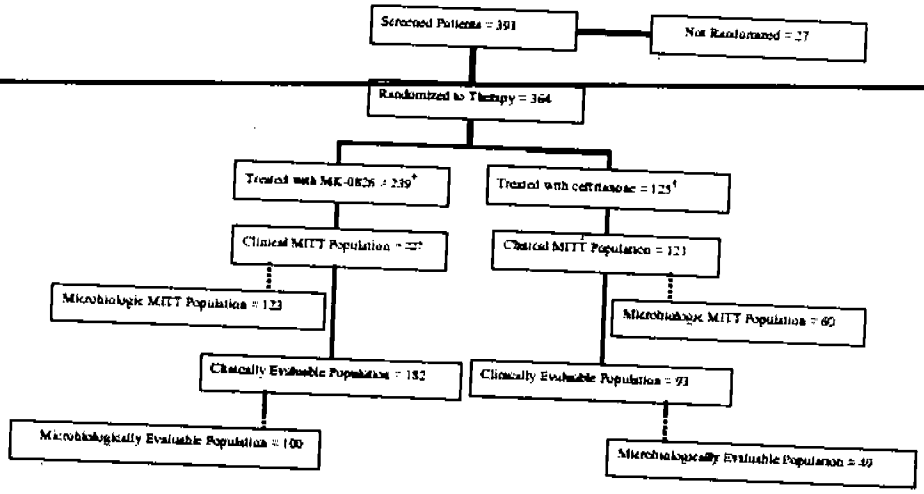
of evaluable patients randomized before and after new blinding procedures for infusion bags was implemented.

6.3.6.4 Study Results

6.3.6.4.1 Evaluability

Three hundred sixty-four (364) patients from 45 study sites (of the 71 sites receiving study drug supplies, 45 study sites enrolled 1 or more patients) were randomized, 239 patients were analyzed in the MK-0826 treatment group and 125 patients were analyzed in the ceftriaxone treatment group. The primary efficacy analysis (clinical response in the microbiologically evaluable population) included 149 patients, 100 received MK-0826 and 49 received ceftriaxone. The accounting of patients randomized into the study and the reasons patients discontinued from study therapy and study are in Appendix 19. The figure below (Applicant's Figure 1, Volume 17 of 22, page 88) provides a profile of study enrollment and summarizes the number of patients in each of the evaluable populations.

Profile of Patient Enrollment



† Three (3) patients in the MK-0826 group (ANs 2701, 2885, and 3297) and 2 patients in the ceftriaxone group (ANs 4033 and 4106) were randomized to a treatment group but did not receive study drug.

In the overall study population, the most common reason for patients not being randomized to study medication was that patients did not meet the minimal disease definition for enrollment as defined by clinical (6 patients), radiographic (8 patients), or microbiological study inclusion criteria (6 patients).

The number and percent of patients in each study population and the reasons that patients were considered to be non-evaluable for the per-protocol, MITT and other efficacy analyses are displayed in the Applicant's table below.

Patient Accounting of Evaluability
(Randomized Population)

Reasons Not Evaluable	MK-0826 (N=239) n	%	Ceftriaxone (N=125) n	%
Clinical Protocol Evaluable Population				
Clinical protocol evaluable	182	(76.2)	93	(74.4)
Clinical protocol non-evaluable	57	(23.8)	32	(25.6)
Disease definition not met	8	(3.3)	2	(1.6)
Test-of-cure window violation	13	(5.4)	7	(5.6)
Inadequate/inappropriate study therapy	18	(7.5)	9	(7.2)
Prior antibiotics violation	5	(2.1)	6	(4.8)
Concomitant antibiotics violation	16	(6.7)	7	(5.6)
Baseline/intercurrent medical events	3	(1.3)	0	(0.0)
Baseline microbiology-resistant pathogen	7	(2.9)	6	(4.8)
Microbiologic Protocol Evaluable Population				
Microbiologic protocol evaluable	100	(41.8)	49	(39.2)
Microbiologic protocol non-evaluable	139	(58.2)	76	(60.8)
Not clinically evaluable	57	(23.8)	31	(24.8)
Baseline microbiology not performed/inadequate	1	(0.4)	2	(1.6)
Baseline microbiology-no pathogen isolated	109	(45.6)	63	(50.4)
Test-of-cure microbiology inadequate	8	(3.3)	1	(0.8)
Clinical Late Follow-up Evaluable Population				
Clinical late follow-up evaluable	134	(56.1)	70	(56.0)
Clinical late follow-up non-evaluable	105	(43.9)	55	(44.0)
Not a protocol evaluable success	67	(28.0)	34	(27.2)
Concomitant antibiotic violations	21	(8.8)	13	(10.4)
Intercurrent medical events	5	(2.1)	0	(0.0)
Late follow-up window violation	56	(23.4)	24	(19.2)
Other	1	(0.4)	0	(0.0)
Microbiologic Late Follow-up Evaluable Population				
Microbiologic late follow-up evaluable	71	(29.7)	35	(28.0)
Microbiologic late follow-up non-evaluable	168	(70.3)	90	(72.0)
Not clinically evaluable	105	(43.9)	55	(44.0)
Baseline microbiology not performed/inadequate	1	(0.4)	2	(1.6)
Baseline microbiology-no pathogen isolated	109	(45.6)	63	(50.4)
Late follow-up microbiology inadequate	18	(7.5)	8	(6.4)

Reasons Not Evaluable	MK-0826 (N=239) n	%	Ceftriaxone (N=125) n	%
Clinical MITT Population				
Clinical MITT evaluable	227	(95.0)	121	(96.8)
Clinical MITT non-evaluable	12	(5.0)	4	(3.2)
Patient did not receive at least 1 dose of study therapy	4	(1.7)	2	(1.6)
Minimal disease definition not met	8	(3.3)	2	(1.6)
Microbiologic MITT Population				
Microbiologic MITT evaluable	123	(51.5)	60	(48.0)
Microbiologic MITT non-evaluable	116	(48.5)	65	(52.0)
Not clinically evaluable	12	(5.0)	4	(3.2)
Baseline microbiology not performed/inadequate	1	(0.4)	2	(1.6)
Baseline microbiology—no pathogen isolated	109	(45.6)	63	(50.4)
Follow-up microbiology inadequate	5	(2.1)	2	(1.6)
PRSP Population				
PRSP evaluable	2	(0.8)	0	(0.0)
PRSP non-evaluable	237	(99.2)	125	(100.0)
PRSP not baseline pathogen	237	(99.2)	125	(100.0)
PRSP Late Follow-up Population				
PRSP late follow-up evaluable	2	(0.8)	0	(0.0)
PRSP late follow-up non-evaluable	237	(99.2)	125	(100.0)
Not PRSP evaluable	237	(99.2)	125	(100.0)

This table contains counts of patient evaluability. Therefore, although a patient may have one or more reasons for being non-evaluable, the patient was counted only once in the nonevaluable category.
MITT = Modified intent-to-treat.
PRSP = Penicillin-resistant *Streptococcus pneumoniae*.

(Applicant's Table 22, Volume 17 of 22, pages 89-90)

Medical Officer's Comment: ***The primary reasons patients were discontinued from therapy in the randomized population, were clinical adverse experience (15 in MK-0826 group and 9 in ceftriaxone group), clinical or microbiologic failure (7 in MK-0826 group and 4 in ceftriaxone group), and patient withdrew consent (6 in MK-0826 group and 0 in ceftriaxone group). Given the 2:1 randomization scheme, with the possible exception of patient withdrew consent, the reasons were generally similar.***

Considering the 2:1 randomization schedule, within each population, the treatment groups were similar with respect to reasons that patients were not evaluable.

Site 020038 (Norbert Vetter, Austria), was the site that enrolled the most evaluable patients (17 patients). US sites enrolled 36% of the microbiologically evaluable patients in the MK-0826 group and 49% of the microbiologically evaluable patients in the ceftriaxone group. The number of clinically evaluable patients in each treatment group that was entered by each investigator is in Appendix 20.

6.3.6.4.2 Demographics

The table below displays the baseline characteristics for the microbiologically evaluable group.

Baseline Patient Characteristics by Treatment Group
(Microbiologically Evaluable Population)

	MK-0826 (N=100)	Ceftriaxone (N=49)	Total (N=149)
	n (%)	n (%)	n (%)
Gender			
Male	66 (66.0)	29 (59.2)	95 (63.8)
Female	34 (34.0)	20 (40.8)	54 (36.0)
Race			
Asian	1 (1.0)	0 (0.0)	1 (0.7)
Black	12 (12.0)	7 (14.3)	19 (12.7)
Caucasian	55 (55.0)	29 (59.2)	84 (56.0)
Hispanic	27 (27.0)	10 (20.4)	37 (24.7)
Mestizo	4 (4.0)	3 (6.1)	7 (4.7)
Spanish	1 (1.0)	0 (0.0)	1 (0.7)
Age (Years)			
18 to 40	18	11	29
41 to 64	41	14	55
65 to 74	21	10	31
≥75	20	14	34
Mean	57.9	60.0	58.6
SD	17.7	20.4	18.6
Median	60.0	64.0	61.0
Range	18 to 90	20 to 93	18 to 93
Stratum			
PSI Score ≤3/Age ≤65 (IA)	50 (50.0)	21 (42.9)	71 (47.7)
PSI Score ≤3/Age >65 (IIA)	19 (19.0)	12 (24.5)	31 (20.7)
PSI Score >3/Age ≤65 (IB)	11 (11.0)	4 (8.2)	15 (10.0)
PSI Score >3/Age >65 (IIB)	20 (20.0)	12 (24.5)	32 (21.3)
Risk Group			
1	12 (12.0)	5 (10.2)	17 (11.3)
2	37 (37.0)	14 (28.6)	51 (34.2)
3	20 (20.0)	14 (28.6)	34 (22.7)
4	23 (23.0)	11 (22.4)	34 (22.7)
5	8 (8.0)	5 (10.2)	13 (8.7)

PSI = Pneumonia Severity Index. Values range from 1 (low risk) to 5 (high risk).
SD = Standard deviation.

(Applicant's Table 24, Volume 17 of 22, pages 92-93)

Medical Officer's Comment: *The 2 treatment groups appeared to be similar with respect to age stratum and PSI risk group. A higher percentage of patients were male or hispanic in the MK-0826 treatment group. The 2 treatment groups were similar with respect to concomitant diagnoses and prior and concomitant therapies (including anti-infective therapies).*

The baseline characteristics of patients enrolled in this protocol are similar to those of patients enrolled in Protocol 018.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

The table below displays the extent of exposure to all study drugs (duration) by treatment group for the microbiologically evaluable population.

Extent of Exposure (Duration of Therapy) by Treatment Group
(Microbiologically Evaluable Population)

	MK-0826 (N=100)	Ceftriaxone (N=49)	Total (N=149)
Days on Study Therapy			
n	100	49	149
Mean	11.5	11.9	11.6
SD	2.9	3.3	3.0
Median	11.0	11.0	11.0
Range			
Days on Parenteral Therapy			
n	100	49	149
Mean	5.8	6.4	6.0
SD	2.6	3.2	2.8
Median	5.0	5.0	5.0
Range			
Days on IV Therapy			
n	100	49	149
Mean	5.6	6.2	5.8
SD	2.8	3.3	3.0
Median	5.0	5.0	5.0
Range			
Days on IM Therapy			
n	5	1	6
Mean	3.6	7.0	4.2
SD	1.3		1.8
Median	3.0	7.0	4.0
Range			
Days on Oral Therapy			
n	83	38	121
Mean	6.9	7.2	7.0
SD	2.5	2.6	2.5
Median	6.0	7.0	6.0
Range			
Days Missed Therapy			
n	2	3	5
Mean	1.0	1.0	1.0
SD	0.0	0.0	0.0
Median	1.0	1.0	1.0
Range			

IM = Intramuscular.
IV = Intravenous.
N = Total number of patients in each treatment group.
n = Total number of patients in category.
SD = Standard deviation.

(Applicant's Table 32, Volume 17 of 22, pages 108-109)

Medical Officer's Comment: ***The 2 treatment groups appeared similar with respect to extent of exposure to IV therapy and combined parenteral plus oral therapy. The numbers of microbiologically evaluable patients that received IM therapy (5 patients in the MK-0826 group and 1 patient in the ceftriaxone group) are too small to make a meaningful comparison of extent of exposure.***

The 2 treatment groups were similar with respect to the oral switch agents utilized. The majority of patients received the protocol-specified agent amoxicillin/clavulanate (in the microbiologically evaluable population:

77% of patients in the MK-0826 group and 67% of patients in the ceftriaxone group). A table showing the oral switch agents used in the study by treatment group for the microbiologically evaluable population is in Appendix 21.

6.3.6.4.3 Efficacy

6.3.6.4.3.1 Clinical

The primary efficacy analysis was clinical response in the microbiologically evaluable patient population at the EFU visit (TOC). Additional secondary analyses were done on the clinically evaluable and MITT population groups. For the TOC analysis, 100/236 treated patients (42.4%) in the MK-0826 group and 49/123 treated patients (39.8%) in the ceftriaxone group were microbiologically evaluable. To address the primary hypothesis, the proportion, adjusted for stratum, of microbiologically evaluable patients with a favorable clinical response assessment was evaluated in both treatment groups. The following table displays the proportion of microbiologically evaluable patients with a favorable clinical response.

Proportion of Patients With Favorable Clinical Response Assessments in the Microbiologically Evaluable Population
(Estimated Data)

	Treatment Group							
	MK-0826 (N=100)			Ceftriaxone (N=49)			Estimated† Difference (A-B)	
Time Point	n	Estimated† Response (%) (95% CI)		n	Estimated† Response (%) (95% CI)		%	(95% CI)
DCIV	100	94.3	(89.6, 99.0)	49	92.0	(85.3, 98.7)	2.3	(-8.2, 12.8)
Test of cure	100	91.5	(85.8, 97.1)	49	92.0	(85.3, 98.7)	-0.5	(-11.5, 10.4)

† Computed from a statistical model adjusting for strata.
N = Number of microbiologically evaluable patients in each treatment group.
n = Number of microbiologically evaluable patients included in the analysis.
DCIV = Discontinuation of parenteral therapy.
CI = Confidence interval.

(Applicant's Table 38, Volume 17 of 22, page 118)

Medical Officer's Comment: *A blinded 10% sample of CRFs from this study was reviewed to validate the Applicant's analysis of the primary efficacy parameter. Based on this review, no systematic errors in the Applicant's analysis were detected. Therefore the Applicant's analyses of efficacy parameters were accepted.*

In the microbiologically evaluable population, at the TOC analysis, the difference in the clinical response rates between the 2 treatment groups, adjusted for stratum, was –0.5% (91.5% of patients in the MK-0826 group and 92.0% of patients in the ceftriaxone group had a favorable clinical response) with a 95% CI of -11.5%, 10.4%. In the Applicant's revised clinical MITT population, the difference in the clinical response rates between the 2 treatment groups, adjusted for stratum, was -2.6% (80.8% of patients in the MK-0826 group and 83.3% of patients in the ceftriaxone group had a favorable clinical response) with a 95% CI of -15.9%, 10.8% (see Appendix 22 for the Applicant's original and revised MITT analyses).

Although a delta of 10 has been exceeded, given that this is a supportive study, the MO feels that the data are adequate to indicate that the clinical response rates in the microbiologically evaluable populations for the 2 treatment groups were equivalent for the treatment of CAP.

The assessment of clinical relapse rates was done at the late follow-up visit. No patient in either of the 2 microbiologically evaluable populations had a clinical relapse at LFU.

Patients were stratified at study entry for balance between the treatment groups according to 2 factors (PSI and age), thus creating 4 strata for random allocation (in a 2:1 ratio) to the 2 treatment groups. The Applicant performed separate analyses for each dichotomous factor individually and for the combined factors (4 strata). The Applicant's results for these analyses are displayed in the following tables.

Proportion of Patients With a Favorable Clinical Response Assessment Displayed by Pneumonia Severity Index (PSI) Categories in the Microbiologically Evaluable Population at Test of Cure (Observed Data)

	Treatment Group						
	MK-0826 (A) (N=100)			Ceftriaxone (B) (N=49)			Observed Difference (A-B)
PSI‡	n/m	Observed† Response %	(95% CI)	n/m	Observed† Response %	(95% CI)	%
≤3	64/69	92.8	(86.6, 98.9)	32/33	97.0	(91.0, 100)	-4.2
>3	27/31	87.1	(75.1, 99.1)	13/16	81.3	(61.5, 100)	5.8
Overall	91/100	91.0	(85.4, 96.6)	45/49	91.8	(84.1, 99.6)	-0.8

† Computed from a statistical model pooling across age strata.
‡ PSI = Pneumonia Severity Index. Possible values range from 1 (mild) to 5 (severe).
N = Number of microbiologically evaluable patients in each treatment group.
n/m = Number of microbiologically evaluable patients with favorable assessment/number of microbiologically evaluable patients with assessment.
CI = Confidence interval.

(Applicant's Table 39, Volume 17 of 22, page 119)

Proportion of Patients With a Favorable Clinical Response Assessment Displayed by Age Categories in the Microbiologically Evaluable Population at Test of Cure (Observed Data)

	Treatment Group						
	MK-0826 (A) (N=100)			Ceftriaxone (B) (N=49)			Observed Difference (A-B)
Age Category	n/m	Observed† Response %	(95% CI)	n/m	Observed† Response %	(95% CI)	%
≤65	56/62	90.3	(82.9, 97.7)	25/26	96.2	(88.6, 100)	-5.8
>65	35/38	92.1	(83.4, 100)	20/23	87.0	(72.9, 100)	5.1
Overall	91/100	91.0	(85.4, 96.6)	45/49	91.8	(84.1, 99.6)	-0.8

† Computed from a statistical model pooling across Pneumonia Severity Index strata.
N = Number of microbiologically evaluable patients in each treatment group.
n/m = Number of microbiologically evaluable patients with favorable assessment/number of microbiologically evaluable patients with assessment.
CI = Confidence interval.

(Applicant's Table 40, Volume 17 of 22, page 120)

Proportion of Patients with a Favorable Clinical Response Assessment Displayed by Age and Pneumonia Severity Index (PSI) Categories in the Microbiologically Evaluable Population at Test of Cure (Observed Data)

Stratum	Treatment Group: MK-0826 (A) (N=100) n/m	Observed[1] Response %	(95% CI)	Ceftriaxone (B) (N=49) n/m	Observed[1] Response %	(95% CI)	Observed Difference (A-B) %
Age ≤65, PSI ≤3	47/50	94.0	(87.4, 100)	22/22	100	(84.6, 100)	-6.0
Age >65, PSI ≤3	17/19	89.5	(75.3, 100)	10/11	90.9	(73.1, 100)	-1.4
Age ≤65, PSI >3	9/12	75.0	(49.4, 100)	3/4	75.0		0.0
Age >65, PSI >3	18/19	94.7	(84.4, 100)	10/12	83.3	(61.3, 100)	11.4
Overall	91/100	91.0	(85.4, 96.6)	45/49	91.8	(84.1, 99.6)	-0.8

[1] Computed from a statistical model pooling across strata.
PSI = Pneumonia Severity Index. Possible values range from 1 (mild) to 5 (severe).
N = Number of microbiologically evaluable patients in each treatment group.
n/m = Number of microbiologically evaluable patients with favorable assessment/number of microbiologically evaluable patients with assessment at this time point.

(Applicant's Table 41, Volume 17 of 22, page 120)

Medical Officer's Comment: ***The difference in response rates between the 2 treatment groups based on PSI, age, and combined PSI and age strata were similar.***

The Applicant also assessed clinical response in the microbiologically evaluable population by gender, age, race, and before and after institution of the enhanced blinding procedure. The results are displayed in the following table:

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Proportion of Patients With Favorable Clinical Response Assessments at Test of Cure Displayed by Gender, Age Category, Race, and Enhanced Blinding Procedure (Microbiologically Evaluable Population)
Observed Data

	Treatment Group						Observed Difference (A-B) %
	MK-0826 (A) (N=100)			Ceftriaxone (B) (N=49)			
	n/m	Observed† Response %	(95% CI)	n/m	Observed† Response %	(95% CI)	
Gender							
Female	31/34	91.2	(81.5, 100)	19/20	95.0	(85.2, 100)	-3.8
Male	60/66	90.9	(83.9, 97.9)	26/29	89.7	(78.4, 100)	1.3
Age Category‡							
<65	53/59	89.8	(82.1, 97.6)	24/25	96.0	(88.2, 100)	-6.2
≥65	38/41	92.7	(84.6, 100)	21/24	87.5	(74.0, 100)	5.2
<75	73/80	91.3	(85.0, 97.5)	34/35	97.1	(91.5, 100)	-5.9
≥75	18/20	90.0	(76.5, 100)	11/14	78.6	(56.3, 100)	11.4
Race							
Asian	1/1	100	-				
Black	11/12	91.7	(61.5, 99.8)	6/7	85.7	-	6.0
Caucasian	51/55	92.7	(82.4, 98.0)	26/29	89.7	(72.6, 97.8)	3.1
Hispanic	25/27	92.6	(75.7, 99.1)	10/10	100		-7.4
Mestizo	2/4	50.0	-	3/3	100	-	-50.0
Spanish	1/1	100	-				
Enhanced Blinding Procedure							
No	11/11	100	(71.5, 100)	5/6	83.3	-	16.7
Yes	80/89	89.9	(81.7, 95.3)	40/43	93.0	(80.9, 98.5)	-3.1

† Computed from a statistical model pooling across strata.
‡ The age categories separated at ≤65 and > 65 years appears in Table 40.
N = Number of microbiologically evaluable patients in each treatment group.
n/m = Number of microbiologically evaluable patients with favorable assessment/number of microbiologically evaluable patients with assessment at the visit.
CI = Confidence interval.

(Applicant's Table 42, Volume 17 of 22, page 123)

Medical Officer's Comment: ***Given the small number of Mestizos enrolled, the significance of the -50.0% observed difference in clinical response between treatment groups (favorable response: 50% for MK-0826 and 100% for ceftriaxone) is difficult to interpret. Of note, Mestizo patients enrolled in Protocol 018 had a 90% (9/10) favorable response rate in the MK-0826 group and a 71.4% (10/14) favorable response rate in the ceftriaxone group.***

Based on point estimates, the difference before and after the institution of new blinding procedures between the two treatment groups is substantial; however, the small number of patients enrolled prior to institution of the enhanced blinding procedure makes it unlikely that this difference is clinically significant.

6.3.6.4.3.2 Microbiologic

The proportion of microbiologically evaluable patients with a favorable overall microbiologic assessment (eradication or presumed eradication) was evaluated in both

treatment groups at TOC. Favorable microbiologic assessment was required for all baseline pathogens in order for the overall microbiologic response to be considered favorable. The proportion of patients with a favorable overall microbiologic response at the TOC, according to the Applicant, is displayed in the following table.

Proportion of Patients With a Favorable Microbiological Response Assessments at Test of Cure in the Microbiologically Evaluable Population
(Observed Data)

	Treatment Group						Observed Difference (A-B) %
	MK-0826 (A) (N=100)			Ceftriaxone (B) (N=49)			
Time Point	n/m	Observed† Response %	(95% CI)	n/m	Observed† Response %	(95% CI)	
Test of Cure	91/100	91.0	(85.4, 96.6)	45/49	91.8	(84.1, 99.6)	-0.8

† Computed from a statistical model pooling across strata.
N = Number of microbiologically evaluable patients in each treatment group.
n/m = Number of microbiologically evaluable patients with favorable assessment/number of microbiologically evaluable patients with assessment at the visit.
CI = Confidence interval.

(Applicant's Table 45, Volume 17 of 22, page 129)

Medical Officer's Comment: The MO's results (using the MO's criteria for microbiologic evaluability) for the MO's microbiologically evaluable population with favorable overall microbiologic response are presented in the following table.

Proportion of Patients (Protocol 020) With a Favorable Microbiologic Response Assessment at Test of Cure in the Microbiologically Evaluable Population <u>According to the MO</u>
(Observed† Data)

	Treatment Group						Observed Difference (A-B) %
	MK-0826 (A) (N=98)			Ceftriaxone (B) (N=49)			
Time Point	n/m	Observed† Response %	(95% CI)	n/m	Observed† Response %	(95% CI)	
Test of Cure	89/98	90.8	(83.3, 95.7)	45/49	91.8	(84.1, 99.6)	-1.0

† Computed from a statistical model pooling across strata.
N = Number of microbiologically evaluable patients in each treatment group.
n/m = Number of microbiologically evaluable patients with favorable assessment/number of microbiologically evaluable patients with assessment at the visit.
CI = Confidence interval.

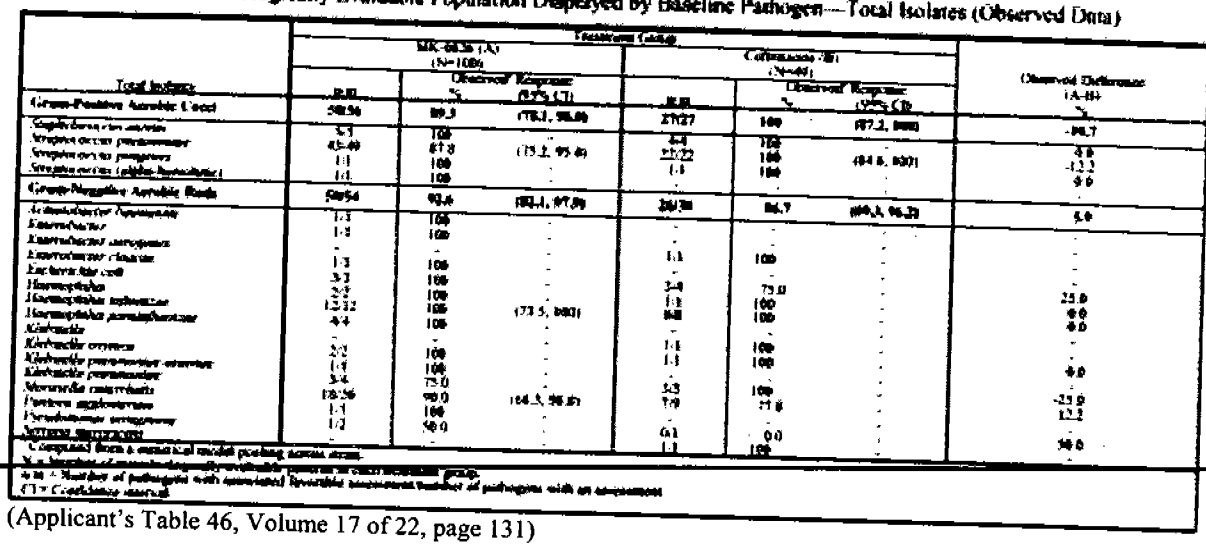
In the Applicant's revised microbiologic MITT population, the difference in the microbiologic response rates between the 2 treatment groups was 0.5% (85.7% of patients in the MK-0826 group and 85.2% of patients in the ceftriaxone group had a favorable clinical response). See Appendix 6.3-L for the Applicant's original and revised MITT analyses.

6.3.6.4.3.3 By Pathogen

The Applicant compared the microbiologic response rates in microbiologically evaluable patients between the 2 treatment groups for all unique baseline pathogens obtained from respiratory secretions or blood (if the same pathogen was isolated from both blood and respiratory secretions it was only counted once in the overall list). The following table

displays the proportion of favorable microbiologic response assessments per pathogen in the microbiologically evaluable population at the TOC visit, according to the Applicant (the 95% CI was calculated for those bacterial species isolated in at least 10 patients in either treatment group).

Proportion of Favorable Microbiological Response Assessments at Test of Cure in the Microbiologically Evaluable Population Displayed by Baseline Pathogen—Total Isolates (Observed Data)



(Applicant's Table 46, Volume 17 of 22, page 131)

Medical Officer's Comment: ***In the MO's analysis 2 patients, who had been considered microbiologically evaluable by the Applicant, were considered microbiologically unevaluable because sputum gram stains suggested upper airway contamination (≥10 epithelial cells per 100x) and the resulting sputum culture grew multiple organisms consistent with upper airway contamination. Culture data for these 2 patients with inadequate gram stains is given in the following table.***

Patients Changed to Microbiologically Unevaluable by MO

AN	Organisms in Applicant's Database as Pre-Study Sputum Pathogens	All Organisms listed by Investigator on Pre-Study Sputum Culture Reports (CRF form CR1)
MK-0826		
4171	*M. catarrhalis* *E. agglomerans*	*M. catarrhalis* *E. agglomerans* *Alpha hemolytic streptococcus* *Candida spp.*
4212	*M. catarrhalis*	*M. catarrhalis* *S. viridans*

The MO also did not feel that patients who were otherwise evaluable failures should be excluded from this analysis based on the absence of repeat blood cultures, but that they should be considered to have presumed persistence and be considered to have an unfavorable outcome. One patient with S. pneumoniae (AN 4298 in the MK-0826 group) on entry blood cultures was therefore considered a failure based on presumed persistence by the MO. The changes made by the MO resulted in changes in the overall proportion of by-pathogen favorable microbiologic response assessments at test-of-cure (see table below). (The MO also determined outcome by beta-lactamase status for H. influenzae and M. catarrhalis, in doing this the MO accepted the outcome reported by the Investigator or if no outcome was reported by the Investigator, then the one reported by the central laboratory.)

Proportion of Favorable Microbiologic Response Assessments at Test of Cure in the Microbiologically Evaluable Population According to the MO (Observed Data)

Isolates	Treatment Group						Observed Difference (A-B) %
	MK-0826 (A) (N=98)			Ceftriaxone (B) (N=49)			
	n/m	Observed Response %	(95% CI)	n/m	Observed Response %	(95% CI)	
Gram-Positive Aerobic Cocci	**50/57**	**87.7**	**(76.3, 94.9)**	**27/27**	**100**	**(87.2, 100)**	**-12.3**
Staphylococcus aureus	5/5	100	-	4/4	100	-	0.0
Streptococcus pneumoniae	43/50	86.0	(73.3, 94.2)	22/22	100	(84.6, 100)	-12.2
Streptococcus pyogenes	1/1	100	-	1/1	100	-	-
Streptococcus (alpha-hemolytic)	1/1	100	-	-	-	-	-
Gram-Negative Aerobic Rods	**47/51**	**92.2**	**(81.1, 97.8)**	**26/30**	**86.7**	**(69.3, 96.2)**	**5.5**
Acinetobacter baumanii	1/1	100	-	-	-	-	-
Enterobacter	1/1	100	-	-	-	-	-
Enterobacter aerogenes	-	-	-	1/1	100	-	-
Enterobacter cloacae	1/1	100	-	-	-	-	-
Escherichia coli	3/3	100	-	3/4	75.0	-	25.0
Haemophilus species	2/2	100	-	1/1	100	-	0.0
Haemophilus influenzae	12/12	100	(73.5, 100)	8/8	100	(63.1, 100)	0.0
Beta lactamase negative	6/6	100	-	7/7	100	-	0.0
Beta lactamase positive	5/5	100	-	-	-	-	-
Beta lactamaxe not available	1/1	100	-	1/1	100	-	0.0
Haemophilus parainfluenzae	4/4	100	-	-	-	-	-
Klebsiella species	-	-	-	1/1	100	-	-
Klebsiella oxytoca	2/2	100	-	1/1	100	-	0.0
Klebsiella pneumoniae ozaenae	1/1	100	-	-	-	-	-
Klebsiella pneumoniae	3/4	100	-	3/3	100	-	0.0
Moraxella catarrhalis	16/18	88.9	(71.3, 99.9)	7/9	77.8	(40.0, 97.2)	11.1
Beta lactamase negative	-	-	-	-	-	-	-
Beta lactamase positive	3/3	100	-	1/1	100	-	-
Beta lactamase not available	13/15	86.7	(59.4, 98.3)	6/8	75.0	(34.9, 96.8)	11.7
Pseudomonas aeruginosa	1/2	50	-	0/1	0.0	-	50.0
Serratia marscens	-	-	-	1/1	100	-	-

The table shows only unique baseline isolates for each patient.
N = Number of microbiologically evaluable patients in each treatment group.
n/m = Number of pathogens with associated favorable assessment/number of pathogens with an assessment at Test of Cure.
CI = Confidence interval.

Medical Officer's Comment: ***The 1992 FDA Points-to-Consider document discussed when an organism should be included in a granted indication. This document recommended the following criteria when making this determination:***

1. ***Only those microorganisms considered to be an etiologic agent (pathogen) in at least 10% of the evaluable cases of the specific infection successfully treated with the investigative agent should be included.***
2. ***The "at least 10%" should be understood to mean "at least 10% of the evaluable cases meeting both clinical and microbiological evaluability criteria or 10 total cases (as just defined), whichever is higher."***
3. ***The eradication rate of the pathogen should be clinically acceptable in order for that pathogen to be included in this section of the labeling.***

The Points-to-Consider document goes on to discuss how pathogens might be included in the label when <10% of cases were associated with the pathogen and states that "in such situations, explicit labeling to inform the physician of the actual extent of data available should be included in the product labeling."

The situations in which the Points-to-Consider document suggests it is appropriate to consider this approach are when pathogens:

1. ***Are generally accepted as pathogens at the site of infection under investigations (however in numbers less than 10%) and the number of such infections studied in the clinical trials is consistent with the percentage of such infection due to these pathogens in the general population.***

2. *Have in vitro activity that is at least similar to that of other pathogens more substantially evaluated in the clinical trials.*
3. *Have a mechanism(s) of resistance that is similar to other pathogens more substantially evaluated in the clinical trials.*
4. *Have no scientific data to suggest any differences in the management of the infection due to these pathogens or in the prognosis of patients with the infection due to these pathogens.*

Based on the above comments and the combined results of Protocols 018 and 020, the pathogens that the MO feels should be granted for this indication are: S. pneumoniae (penicillin susceptible only), H. influenzae (beta lactamase negative strains only), and M. catarrhalis. Since >90% of M. catarrhalis strains that are clinically isolated are beta lactamase positive, the Division agreed with the Applicant that M. catarrhalis would be listed without additional qualification as to beta lactamase susceptability. The Applicant has not provided adequate data to support granting the indication for S. aureus (total of 12 microbiologically evaluable patients in both MK-0826 groups with 100% favorable microbiologic response of which only 7 were isolated in pure culture), beta-lactamase producing H. influenzae (total of 9 microbiologically evaluable patients in both MK-0826 groups with 78% favorable microbiologic response), or beta-lactamase producing M. catarrhalis (total of 5 microbiologically evaluable patients in both MK-0826 groups with 100% favorable microbiologic response).

Blood Isolates

The Applicant also compared the microbiologic response rates in the 2 treatment groups by baseline blood isolates. In this analysis a microbiologically evaluable patient had to have a baseline blood pathogen (presumed responsible for pneumonia) to be included. In the Applicant's analysis of microbiologic responses for blood isolates, the only presumed outcome that was considered valid was presumed eradication; presumed persistence was not considered a valid outcome by the Applicant. (Failure to obtain a blood culture in the setting of a clinical failure was not used to presume persistent bacteremia. Rather, in this setting, the outcome of these pathogens was excluded from the Applicant's per-pathogen analysis of blood isolates.) The following table displays the proportion of favorable microbiologic response assessments in patients with baseline blood isolates, according to the Applicant.

Proportion of Favorable Microbiological Response Assessments at Test of Cure
in the Microbiologically Evaluable Population
Displayed by Baseline Blood Pathogen—Blood Isolates
(Observed Data)

Blood Isolates	Treatment Group: MK-0826 (A) (N=12) n/m	Observed Response %	(95% CI)	Ceftriaxone (B) (N=8) n/m	Observed Response %	(95% CI)	Observed Difference (A-B) %
Gram-Positive Aerobic Cocci	11/11	100	(71.5, 100)	7/7	100	-	0.0
Streptococcus pneumoniae	11/11	100	(71.5, 100)	6/6	100	-	0.0
Streptococcus pyogenes	-	-	-	1/1	100	-	-
Gram-Negative Aerobic Rods	1/1	100	-	1/1	100	-	0.0
Escherichia coli	1/1	100	-	1/1	100	-	0.0

[1] Computed from a statistical model pooling across strata.
N = Number of microbiologically evaluable patients with a baseline blood pathogen in each treatment group.
n/m = Number of pathogens with associated favorable assessment/number of pathogens with an assessment.
CI = Confidence interval.

(Applicant's Table 47, Volume 17 of 22, page 133)

***Medical Officer's Comment:** The MO did not feel that patients who were otherwise evaluable failures should be excluded from this analysis based on the absence of repeat blood cultures, but that they should be considered to have presumed persistence and be considered to have an unfavorable outcome. One patient with S. pneumoniae (AN 4298 in the MK-0826 group) on entry blood cultures was therefore considered a failure based on presumed*

persistence by the MO. The MO's revised table for outcome of patients with baseline pathogen blood isolates is provided below.

Proportion of Favorable Microbiological Response Assessments at Test of Cure in the Microbiologically Evaluable Population Displayed by Baseline Pathogen Blood Isolates According to the MO

Blood Isolates	(Observed Data) Treatment Group				Observed Difference (A-B) %
	MK-0826 (A) (N=13) Observed Response		Ceftriaxone (B) (N=8) Observed Response		
	n/m	%	n/m	%	
Gram-Positive Aerobic Cocci	**11/12**	**92**	**7/7**	**100**	**-8.0**
Streptococcus pneumoniae	11/12	92	6/6	100	-8.0
Streptococcus pyogenes	-	-	1/1	100	-
Gram-Negative Aerobic Rods	1/1	100	1/1	100	0.0
E. coli	1/1	100	1/1	100	0.0

N = Number of microbiologically evaluable patients with a baseline blood pathogen in each treatment group.
n/m = Number of pathogens with associated favorable assessment/number of pathogens with an assessment at Test of Cure.
CI = Confidence interval.

Penicillin-Resistant *Streptococcus pneumoniae* (PRSP)

Patients infected with PRSP (penicillin MIC ≥2 µg/mL) were excluded from the primary clinical and microbiological analyses and analyzed both separately and overall with non-PRSP isolates by the Applicant. A total of two (2) patients (AN 4009 and 4292 in the MK-0826 group) with PRSP were clinically and microbiologically evaluable and both patients had a favorable clinical and microbiological outcome in the Applicant's analyses. PRSP was not isolated from blood in any patients in this study.

The Applicant's comparison of the clinical responses and microbiologic responses in patients infected with *S. pneumoniae* according to the susceptibility to penicillin are shown in the following tables.

Proportion of Favorable Clinical Response Assessments at Test of Cure in the Microbiologically Evaluable Patients Infected With *Streptococcus pneumoniae* Displayed According to Penicillin Susceptibility (Unique Sputum or Blood Isolates)

	Treatment Group	
	MK-0826 (N=51)	Ceftriaxone (N=22)
Penicillin Susceptibility	n/m (%)	n/m (%)
Penicillin susceptible†	28/33 (84.8)	14/14 (100)
Penicillin nonsusceptible‡	9/9 (100)	5/5 (100)
Penicillin resistant§	2/2 (100)	-
Unknown‖	8/9 (88.9)	2/3 (66.7)
All	45/51 (88.2)	21/22 (95.5)

† Based on Kirby Bauer disk zone size ≥20 mm or MIC <0.1 (E-test <0.09) µg/mL.
‡ Based on Kirby Bauer disk zone size ≤19 mm or MIC ≥0.1 (E-test >0.09) µg/mL.
§ Based on MIC ≥2 (E-test ≥1.5) µg/mL.
‖ Unknown = Inadequate in vitro penicillin susceptibility result reported.
N = Number of microbiologically evaluable patients in treatment group with *Streptococcus pneumoniae* isolated.
n/m = Number with favorable assessments at Test of Cure/number with specified isolate.

(Applicant's Table 49, Volume 17 of 22, page 135)

Proportion of Favorable Microbiological Response Assessments at Test of Cure in the Microbiologically Evaluable Population Infected With *Streptococcus pneumoniae* Displayed According to Penicillin Susceptibility (Unique Sputum and Blood Isolates)

	Treatment Group	
	MK-0826 (N=51)	Ceftriaxone (N=22)
Penicillin Susceptibility	n/m (%)	n/m (%)
Penicillin susceptible†	28/33 (84.8)	14/14 (100)
Penicillin nonsusceptible‡	9/9 (100)	5/5 (100)
Penicillin resistant§	2/2 (100)	-
Unknown‖	8/9 (88.9)	3/3 (100)
All	45/51 (88.2)	22/22 (100)

† Based on Kirby Bauer disk zone size ≥20 mm or MIC <0.1 (E-test <0.09) µg/mL.
‡ Based on Kirby Bauer disk zone size ≤19 mm or MIC ≥0.1 (E-test >0.09) µg/mL.
§ Based on MIC ≥2 (E-test ≥1.5) µg/mL.
‖ Unknown = Inadequate in vitro penicillin susceptibility result reported.
N = Number of microbiologically evaluable patients in treatment group with *Streptococcus pneumoniae* isolated.
n/m = Number with favorable assessments at Test of Cure/number with specified isolate.

(Applicant's Table 50, Volume 17 of 22, page 136)

Medical Officer's Comment: ***It should be noted that in the preceding two tables the penicillin resistant isolates are a subset of the penicillin nonsusceptible isolates and are not counted again in the overall totals. Based on point estimates the favorable clinical and microbiologic response rates in the microbiologically evaluable population are lower for penicillin susceptible strains in the MK-0826 group.***

This trend was not as pronounced in the patients enrolled in Protocol 018. When data for Protocols 018 and 020 are combined, the trend for less favorable clinical and microbiologic response rates in the MK-0826 group persists, but is less pronounced. Overall response rates do not appear to differ substantially between treatment groups. The tables below display the comparison of the clinical responses and microbiologic responses in patients infected with S. pneumoniae according to the susceptibility to penicillin for both studies combined. (Note that in the following two tables the penicillin resistant isolates are a subset of the penicillin nonsusceptible isolates and are not counted again in the overall totals.)

Proportion of Favorable Clinical Response Assessments at Test of Cure in the Microbiologically Evaluable Patients Infected With *Streptococcus pneumoniae* Displayed According to Penicillin Susceptibility Combined Protocol 018 and 020 (Unique Sputum or Blood Isolates)

	Treatment Group	
	MK-0826 (N=99)	Ceftriaxone (N=82)
Penicillin Susceptibility	n/m (%)	n/m (%)
Penicillin susceptible†	56/65 (86%)	46/49 (94%)
Penicillin nonsusceptible‡	20/20 (100%)	17/18 (94%)
Penicillin resistant§	3/3 (100%)	3/3 (100%)
Unknown*	13/ 14 (90%)	14/15 (93%)
All	89/99 (90%)	77/82 (94%)

† Based on Kirby Bauer disk zone size ≥20 mm or MIC <0.1 (E-test <0.09) ug/mL.
‡ Based on Kirby Bauer disk zone size ≤19 mm or MIC ≥0.1 (E-test >0.09) ug/mL.
§ Based on MIC ≥2 (E-test ≥1.5) ug/mL.
*Unknown = Inadequate in vitro penicillin susceptibility result reported.
N = Number of microbiologically evaluable patients in treatment group with *Streptococcus pneumoniae* isolated.
n/m = Number with favorable assessments at Test of Cure/number with specified isolate.

Proportion of Favorable Microbiologic Response Assessments at Test of Cure in the Microbiologically Evaluable Patients Infected With *Streptococcus pneumoniae* Displayed According to Penicillin Susceptibility Combined Protocol 018 and 020 (Unique Sputum or Blood Isolates)

	Treatment Group	
	MK-0826 (N=51)	Ceftriaxone (N=22)
Penicillin Susceptibility	n/m (%)	n/m (%)
Penicillin susceptible†	59/65 (91%)	48/49 (98%)
Penicillin nonsusceptible‡	20/20 (100%)	18/18 (100%)
Penicillin resistant§	3/3 (100%)	3/3 (100%)
Unknown*	13/14 (93%)	15/15 (100%)
All	92/99 (93%)	81/82 (99%)

† Based on Kirby Bauer disk zone size ≥20 mm or MIC <0.1 (E-test <0.09) ug/mL.
‡ Based on Kirby Bauer disk zone size ≤19 mm or MIC ≥0.1 (E-test >0.09) ug/mL.
§ Based on MIC ≥2 (E-test ≥1.5) ug/mL.
*Unknown = Inadequate in vitro penicillin susceptibility result reported.
N = Number of microbiologically evaluable patients in treatment group with *Streptococcus pneumoniae* isolated.
n/m = Number with favorable assessments at Test of Cure/number with specified isolate.

6.3.6.5 Reviewer's Comments/Conclusions of Study

In adult patients with community-acquired pneumonia treated for 10 to 14 days, including a minimum of 3 days of parenteral MK-0826 and followed by an oral antibiotic switch option (Augmentin) after clinical improvement, the following conclusions can be drawn:

1. MK-0826 1 gm IV once daily was as clinically and microbiologically effective as ceftriaxone 1 gm IV once daily in treating community acquired pneumonia in adults.
2. For conclusions regarding the safety tolerability of MK-0826, in this study, see section 7.1.3.1 of this review.

6.3.7 Indication Conclusion

The Applicant has provided adequate data to support the granting of the Community Acquired Pneumonia indication for parenteral MK-0826 1 gm once daily, with a switch to oral therapy after a minimum of 3 days parenteral therapy, for a total of10 to 14 days therapy (parenteral and oral) in adults.

In adult patients with community-acquired pneumonia treated for 10 to 14 days, including a minimum of 3 days of parenteral MK-0826 and followed by an oral antibiotic switch option (Augmentin) after clinical improvement, the following conclusions can be drawn:

1. The results of the pivotal Protocol 018 and the supportive Protocol 020 support the conclusion that MK-0826 1 gm IV once daily is as clinically and microbiologically effective as ceftriaxone 1 gm IV once daily in treating adult patients with community acquired pneumonia caused by susceptible pathogens.
2. Based on the combined (Protocols 018 and 020) "By-Pathogen" efficacy results, MK-0826 is clinically effective in the treatment of community acquired pneumonia due to *S. pneumoniae* (penicillin susceptible strains only), *H. influenzae* (beta-lactamase negative strains only), and *M. catarrhalis* and these organisms should be included in the INDICATIONS AND ADMINISTRATION section of the label for this indication.
3. Based on the microbiologically evaluable populations in studies 018 and 020, the Applicant has not provided adequate evidence to grant claims within the community acquired pneumonia indication for: *S. aureus* (12/12 cures in the MK-0826 1 gm group of which only 6 were isolated in pure culture), beta-lactamase producing *H. influenzae* (7/9 cures in the MK-0826 1 gm group), or penicillin resistant *S. pneumoniae* (3/3 cures in the MK-0826 1 gm group).
4. The CLINICAL STUDIES section of the label should be revised to include overall efficacy results and results by disease stratum (Pneumonia Severity Index and age) to reflect key study design features and outcome findings. Each study should be displayed separately. The table of efficacy by-pathogen should not be included in the CLINICAL STUDIES section of the label for this indication.
5. Based on the combined results of Protocols 018 and 020, MK-0826 is effective in the treatment of patients with community acquired pneumonia and concurrent bacteremia due to penicillin susceptible *S. pneumonia* (favorable clinical response in 16 of 18 patients [88.9%]).
6. MK-0826 by IV administration was generally safe and well tolerated by patients with community acquired pneumonia. (See section 7.1.3 of this review.)
7. The safety profile of MK-0826 is generally similar to ceftriaxone 1 g daily based on the overall safety profile including the frequency of drug-related serious adverse experiences, discontinuations due to drug-related adverse experiences, and the assessment of infusion-related local tolerability in patients with community acquired pneumonia; although, findings from Protocols 018 and 020 suggest that drug-related seizures and decreased absolute neutrophil counts (<1800 cells/*u*L) may be more common in patients treated with MK-0826. (See section 7.1.3 of this review.)

6.4 Complicated Skin and Skin Structure Infections

Please see review by Dr. Janice Pohlman for this indication. (Dr. Pohlman's review was entered into DFS as a separate file.)

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

6.5 Complicated UTI

Please see review by Dr. Thomas Smith for this indication. (Dr. Smith's review was entered into DFS as a separate file.)

7.0 Integrated Review of Safety

7.1 By Indication
7.1.1 Complicated Intra-Abdominal Infections Indication

7.1.1.1 Reviewer: Jean M. Mulinde
Medical Officer, HFD-520

7.1.1.2 PROTOCOL 017: A PROSPECTIVE, MULTICENTER, DOUBLE-BLIND, RANDOMIZED, COMPARATIVE STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF MK-0826 VERSUS PIPERACILLIN-TAZOBACTAM IN THE TREATMENT OF COMPLICATED INTRA-ABDOMINAL INFECTIONS IN HOSPITALIZED ADULTS

Adverse experiences were recorded during IV study therapy and for 14 days after the end of study therapy (safety follow-up period). The study therapy plus 14-day follow-up period is the primary focus of the Applicant's safety discussion; however, the Applicant also provided analyses of the adverse experiences that occurred during the parenteral period only.

Of the 665 patients enrolled, 655 patients received at least 1 dose of IV study therapy and were included in the analysis of adverse experiences. Patients randomized to 1 treatment group who, due to dispensing errors, mistakenly received study therapy with the other study treatment for the entire parenteral study period were analyzed based on the study therapy actually received. Patients who, due to dispensing errors, received both parenteral study drugs at any time during the course of the study were analyzed based on the treatment group to which they were originally randomized. The table below provides an overall summary of safety during the parenteral period and 14-day follow-up period.

Clinical adverse experiences (AEs) Number (%) of patients:	MK-0826 1 g (N=316)		MK-0826 1.5 g (N=14)		Piperacillin/Tazobactam (N=325)	
	n	(%)	n	(%)	N	(%)
with one or more AEs	204	(64.6)	12	(85.7)	215	(66.2)
with no AE	112	(35.4)	2	(14.3)	110	(33.9)
with drug-related AEs†	68	(21.5)	4	(28.6)	71	(21.8)
with serious AEs	52	(16.5)	2	(14.3)	55	(16.9)
with serious drug-related AEs	4	(1.3)	0	(0.0)	1	(0.3)
who died	17	(5.4)	2	(14.3)	9	(2.8)
discontinued due to an AE	15	(4.7)	0	(0.0)	20	(6.2)
discontinued due to a drug-related AE	4	(1.3)	0	(0.0)	6	(1.8)
discontinued due to a serious AE	13	(4.1)	0	(0.0)	9	(2.8)
discontinued due to a serious drug-related AE	3	(0.9)	0	(0.0)	1	(0.3)
Laboratory AEs						
Number of patients with at least 1 laboratory test postbaseline	MK-0826 1 g (N=310)		MK-0826 1.5 g (N=13)		Piperacillin/Tazobactam (N=321)	
Number (%) of patients:	n	(%)	n	(%)	n	(%)
with one or more AEs	115	(37.1)	7	(53.8)	127	(39.6)
with no AE	195	(62.9)	6	(46.2)	194	(60.4)
with drug-related AEs†	40	(12.9)	2	(15.3)	44	(13.7)
with serious AEs	1	(0.3)	1	(7.7)	7	(2.2)
with serious drug-related AEs	0	(0.0)	0	(0.0)	1	(0.3)
who died	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to an AE	1	(0.3)	0	(0.0)	2	(0.6)
discontinued due to a drug-related AE	1	(0.3)	0	(0.0)	1	(0.3)
discontinued due to a serious AE	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related AE	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by investigator to be possibly, probably, or definitely drug related.

(Applicant's Synopsis Table, Volume 13 of 22, page 32)

Medical Officer's Comment: ***The Applicant combined piperacillin/tazobactam patients that were enrolled with both the ertapenem1 gm and ertapenem 1.5 gm cohorts into one group in all of their safety analyses and displays.***

7.1.1.2.1 Extent of Exposure

Of the 665 randomized patients, 655 patients (316 in the MK-0826 1 gm group, 14 in the MK-0826 1.5 gm group, and 325 in the piperacillin/tazobactam group) received at least 1 dose of study therapy. The table below shows the extent of exposure to IV therapy by dose and duration for all patients who received at least 1 dose of study therapy. The number of patients receiving each total daily dose of parenteral therapy is displayed. A patient was counted multiple times if, during the course of the study, the patient's daily dose changed, but was counted once in the any dose display.

The table indicates there were 30 patients who received MK-0826 2 gms therapy for 1 to 2 days. The majority of these patients fall into one of two groups: a) patients may have received 5 doses in a calendar day (equivalent to two ertapenem and three placebo doses in the ertapenem group) due to the 6-hour dosing schedule, if the fifth dose was begun within the 24 hour period, or b) a patient's dosing schedule was shifted based on the

protocol specified rule that a dosing shift (the 12-hour dosing shift resulted in patients receiving two 1 gm doses in the first 24 hours) was allowed to aid drug administration scheduling once during the course of the study for each patient at the discretion of the Investigator. In addition, one patient (AN 5054) who received 2 doses of MK-0826 1.5 gms given 12 hours apart due to dosing shift adjustment appears in the table as having received 3 g in 1 day.

The dosing shift, although implemented in the piperacillin/tazobactam treatment group, did not alter the dosing schedule since every dose dispensed was piperacillin/tazobactam. Due to the every 6-hour dosing regimen over a 24-hour period, some patients actually received a fifth dose within a calendar day. Therefore, 34 patients in the piperacillin/tazobactam group received 16.875 g of study drug for 2 or less days.

Extent of Exposure by Dose and Duration
(Treated Population)

Treatment Group	Number of Days on Parenteral Therapy[1]											
	≤2	3 to 4	5 to 6	7 to 8	9 to 10	11 to 12	13 to 14	≥15	Total Patients	Range	Total Days	Mean
MK-0826												
Any Dose	18	21	142	60	33	13	33	11	331[2]	1 to 28	2421	7.3
1 g	18	27	134	58	30	15	25	10	317[3]	1 to 28	2261	7.1
1.5 g	2	2	2	2	1	0	6	0	15[4]	1 to 14	129	8.6
2 g	30	0	0	0	0	0	0	0	30	1 to 1	30	1.0
3 g	1[5]	0	0	0	0	0	0	0	1	1 to 1	1	1.0
Piperacillin/Tazobactam												
Any Dose	10	13	134	77	39	22	25	7	327[1]	1 to 18	2467	7.5
3.375 g	152	0	0	0	0	0	0	0	152	1 to 2	172	1.1
6.75 g	215	1	0	0	0	0	0	0	216	1 to 3	297	1.4
10.125 g	138	9	1	0	0	0	0	0	148	1 to 5	203	1.4
13.5 g	26	115	84	45	26	11	9	1	317	1 to 15	1756	5.5
16.875 g	34	0	0	0	0	0	0	0	34	1 to 2	39	1.1

[1] The table displays the number of patients receiving each daily dose. A patient may be counted multiple times if during the course of the study, the patient's daily dosage changed.
[2] Includes AN 5775 in the piperacillin/tazobactam treatment group who inadvertently received MK-0826 1 g for 2 days.
[3] Includes AN 5112 randomized to MK-0826 1-g group; patient received therapy for 8 days including MK-0826 1.5 g on the last 2 days.
[4] AN 5054 in the MK-0826 1.5-g group was given 2 doses of MK-0826, 12 hours apart due to adjusted dosing schedule, which was allowed per protocol.
[5] Includes AN 5343 in the MK-0826 1-g treatment group who inadvertently received 2 doses of 3.375 g of piperacillin/tazobactam for 1 day.
[6] Includes AN 5513 in the MK-0826 1-g treatment group who inadvertently received 1 dose of 3.375 g of piperacillin/tazobactam for 1 day.

(Applicant's Table 59, Volume 13 of 22, page 215)

The extent of exposure to IV study drugs by treatment group for the treated population is displayed in the table below.

Extent of Exposure (Duration of Therapy) by Dose and Treatment Group (Treated Population)

	MK-0826 1 g (N=316)	MK-0826 1.5 g (N=14)	Piperacillin/ Tazobactam (N=325)	Total (N=655)
Days on Parenteral Therapy				
n	316	14	325	655
Mean	7.3	9.1	7.6	7.5
SD	3.7	4.6	3.0	3.4
Median	6.0	9.0	7.0	6.0
Range				
Days Missed Therapy				
n	86†	1	0	87†
Mean	1.0	1.0	0.0	1.0
SD	0.2			0.2
Median	1.0	1.0	0.0	1.0
Range				

† Includes 77 patients who did not actually miss any days of study therapy, but were counted in the total because the last day of study infusions were placebos.
n = Number of patients in category.
SD = Standard deviation.

(Applicant's Table 26, Volume 13 of 22, page 121)

Medical Officer's Comment: ***The MK-0826 1 gm treatment group and the piperacillin/tazobactam treatment group (combined 1 gm and 1.5 gm cohorts) were similar with respect to extent of exposure to study therapy.***

7.1.1.2.2 Deaths

Thirty-four deaths were reported during the entire study period (not limited to the 14-day follow-up period). Of the 34 deaths reported, 20 were in the MK-0826 1 gm treatment group (ANs 0217, 0283, 0302, 0372, 0388, 0405, 0491, 0513, 0528, 0542, 0694, 0919, 0923, 5331, 5335, 5340, 5609, 5644, 5784, and 5947), 2 were in the MK-0826 1.5 gm treatment group (ANs 5103 and 5135), and 12 were in the piperacillin/tazobactam treatment group (ANs 0270, 0454, 0520, 0532, 0695, 0732, 0922, 5052, 5334, 5394, 5399, and 5975). Three (3) patients (ANs 0513, 5335, and 5340) in the MK-0826 1 gm group and 3 patients (ANs 0454, 0532, and 5399) in the piperacillin/tazobactam group died or had onset of their fatal adverse experience after the 14-day follow-up period.

Thirteen patients (ANs 0283, 0302, 0372, 0388, 0405, 0528, 0542, 0923, 5331, 5609, 5664, 5784, and 5947) in the MK-0826 1 gm group, 1 patient (AN 5103) in the MK-0826 1.5 gm group, and 4 patients (ANs 0520, 0695, 0922, and 5052) in the piperacillin

tazobactam group died or had the onset of the fatal adverse experience during the parenteral therapy.

None of the deaths was considered related to study drug by the Investigators or Applicant. Narratives of these deaths are provided in Appendix 28. The table below lists all deaths reported during the entire study period.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Listing of Patients With Clinical Adverse Experiences Resulting in Death During Entire Study Period* (Treated Population)

AN	Study Number	Gender	Race	Age	Daily Dose†^	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Intensity	Drug Relationship	Action Taken	Outcome
MK-0826 1 gm												
5331	017001	M	Caucasian	52	P/100 mL	2	Death		Severe	Definitely not		
5335‡	017001	F	Caucasian	67	P/100 mL	2	Acidosis	82 minutes	Severe	Definitely not	None	Still present
5340‡	017002	M	Asian	76	Off drug	32	Death		Severe	Definitely not		
					Off drug	37	Myocardial infarction	15 days	Severe	Definitely not	None	Still present
5609	017013	F	Caucasian	36	Off drug	51	Death		Severe	Definitely not		
					A/1 g	2	Septicemia	28 days	Severe	Definitely not	None	Still present
					P/50 mL							
5644	017014	F	Caucasian	66	Off drug	29	Death		Severe	Definitely not		
5947	017019	F	Asian	68	Off drug	20	Death		Severe	Definitely not		
					A/1 g	7	Death		Severe	Definitely not		
					A/1 g	7	Obstruction, airway	1 day	Severe	Definitely not	Discontinued	Still present
5784	017023	M	Caucasian	68	A/1 g	9	Septicemia	7 days	Severe	Definitely not	None	Still present
					Off drug	15	Death		Severe	Definitely not		
0217	017027	M	Caucasian	74	Off drug	18	Multiple organ failure	6 days	Severe	Definitely not	None	Still present
					Off drug	23	Death		Severe	Definitely not		
0283	017033	M	Hispanic	19	A/1 g	2	Death		Severe	Definitely not		
					A/1 g	2	Shock, septic	4 hours	Severe	Definitely not	Discontinued	Still present
0302	017045	F	Caucasian	88	P/100 mL	14	Fistula, abdominal	6 days	Severe	Probably not	Discontinued	Still present
					Off drug	19	Death		Severe	Probably not		
0372	017049	M	Caucasian	72	P/50 mL	2	Death		Severe	Definitely not		
					P/50 mL	2	Shock	5 minutes	Severe	Definitely not	Discontinued	Still present
0388	017050	F	Caucasian	92	P/50 mL	2	Heart failure	7 days	Severe	Probably not	Discontinued	Still present
					Off drug	8	Death		Severe	Probably not		
0405	017051	F	Caucasian	70	A/1 g	3	Death		Severe	Probably not		
					A/1 g	3	Embolism/infarction, pulmonary	30 minutes	Severe	Probably not		Still present
0491	017052	M	Black	71	Off drug	9	Death		Severe	Definitely not		
					Off drug	9	Edema, pulmonary	1 hours	Severe	Definitely not	None	Still present
0513‡	017053	M	Mixed	37	Off drug	24	Multiple organ failure	16 days	Severe	Definitely not	None	Still present
					Off drug	39	Death		Severe	Definitely not		
0694	017054	M	Black	19	Off drug	2	Death		Severe	Probably not		
					Off drug	2	Cardiac arrest	45 minutes	Severe	Probably not	Discontinued	Still present
0542	017058	F	Caucasian	84	A/1 g	5	Death		Severe	Probably not		
					A/1 g	5	Cardiopulmonary failure	1 minutes	Severe	Probably not	None	Still present
0528	017059	F	Caucasian	59	A/1 g	8	Multiple organ failure	4 days	Severe	Definitely not	None	Still present
					P/50 mL							
0919	017059	M	Caucasian	73	P/50 mL	11	Death		Severe	Definitely not		
					Off drug	12	Respiratory failure	8 days	Severe	Definitely not	Discontinued	Still present
0923	017059	F	Caucasian	54	Off drug	19	Death		Severe	Definitely not		
					A/1 g	1	Cardiac arrest	15 hours	Severe	Definitely not	Discontinued	Still present
					P/50 mL	2	Death		Severe	Definitely not		
MK-0826 1.5 gm												
5103	017010	M	Caucasian	65	A/1.5 g	9	Shock, septic	3 days	Severe	Probably not	None	Still present
					P/150 mL							
5135	017013	M	Caucasian	59	P/150 mL	11	Death		Severe	Probably not		
					Off drug	6	Death		Severe	Definitely not		

AN	Study Number	Gender	Race	Age	Daily Dose†^	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Intensity	Drug Relation-ship	Action Taken	Outcome
Piperacillin/Tazobactam 3.375 gm												
5334	017001	F	Caucasian	85	Off drug	17	Death		Severe	Probably not		
5975	017001	M	Caucasian	66	Off drug	17	Respiratory failure	1 day	Moderate	Probably not	None	Still present
					Off drug	14	Death		Severe	Definitely not		
					Off drug	14	Embolism/ infarction, pulmonary	1 hour	Severe	Definitely not	None	Still present
5394	017004	F	Caucasian	83	Off drug	13	Death		Severe	Definitely not		
					Off drug	13	Multiple organ failure	1 day	Severe	Definitely not	None	Still present
5399‡	017004	F	Caucasian	54	Off drug	29	Death		Severe	Definitely not		
					Off drug	29	Unknown cause of death	1 day	Severe	Definitely not		Still present
5052	017005	M	Caucasian	87	B/13.5 g	5	Shock, septic	3 days	Severe	Definitely not	Discontinued	Still present
0270	017039	F	Hispanic	35	Off drug	7	Death		Severe	Definitely not		
					Off drug	23	Death		Severe	Definitely not		
					Off drug	23	Myocardial infarction	1 hour	Severe	Definitely not	None	Still present
0454‡	017043	F	Caucasian	56	Off drug	34	Death		Severe	Definitely not		
					Off drug	34	Heart failure	45 minutes	Severe	Definitely not	None	Still present
0732	017053	M	Black	74	Off drug	7	Death		Severe	Probably not		
					Off drug	7	Myocardial infarction	60 secs	Severe	Probably not	None	Still present
0695	017054	M	Black	56	B/6.75 g	2	Septicemia	11 days	Moderate	Definitely not	Discontinued	Still present
0520	017059	M	Caucasian	71	Off drug	12	Death		Severe	Definitely not		
					B/6.75 g	2	Myocardial infarction	1 day	Severe	Definitely not	Discontinued	Still present
0532‡	017059	F	Caucasian	92	Off drug	50	Pneumonia	10 days	Severe	Definitely not	Discontinued	Still present
0922	017059	M	Caucasian	81	Off drug	59	Death		Severe	Definitely not		
					B/6.75 g	1	Myocardial infarction	3 days	Severe	Definitely not	Discontinued	Still present
					B/13.5 g B/10.125 g B/10.125 g	3	Death		Severe	Definitely not		

† Displays any change of daily dose that occurred within the duration of the adverse experience.
‡ ANs 5335, 5340, 0513, 5399, 0454, and 0532 had serious clinical adverse experiences that occurred more than 14 days after the discontinuation of study drug therapy.
* Entire study period includes study therapy and entire follow-up period, not limited to 14 days.
^ Drug A is MK-0826. Drug B is piperacillin/tazobactam 3.375 g. Drug P is placebo.

(Applicant's Table 65, Volume 13 of 22, pages 231-234)

Medical Officer's Comment: ***The mortality rate in the MK-0826 groups was higher than the mortality rate in the piperacillin/tazobactam group during both the parenteral therapy period and during the entire study period. Although, deaths in this study are not unexpected due to the severity of infection, based on baseline demographics the groups appeared similar with respect to severity of illness and underlying diseases. In addition, the MO calculated the mean baseline APACHE II scores for the treated populations and found no significant difference between the treatment groups for this variable that would explain this discrepancy in mortality rates. The table below summarizes deaths by treatment phase in the 1 gm cohort and the statistical comparison performed by Dr Joel Jiang, Biometrics reviewer.***

Mortality Outcomes	Invanz 1g (N=316)	P/T (1 g cohort) (N=307)	Fisher's P-value
Died			
Died Or Had Onset of Fatal AEs During Parenteral Therapy	13 (4.1%)	3 (1.0%)	0.020
Deaths During Study Therapy and 14-Day Follow-Up Period	17 (5.4%)	8 (2.6%)	0.102
Deaths During Entire Study Period	20 (6.3%)	11 (3.6%)	0.141

At the MO's request the Applicant further examined the deaths that occurred in this study and in the NDA data base overall. The Applicant submitted an amendment to the NDA on August 24, 2001 that contained further analyses of deaths that occurred in the Phase II and III studies with particular emphasis on deaths in study 017. Based on the Applicant's additional analyses, they believe that the greater incidnce of death in the MK-0826 1 gm group in this study resulted from a greater proportion of patients in the MK-0826 1 gm group that had an APACHE II score ≥20 and thus a greater predicted mortality. When the Applicant further displayed the observed deaths by subsets of APACHE score a trend for higher mortality in the ertapenem 1 gm group remained in all but the APACHE >25 group. While the death rate was lower than predicted for both groups overall, the persistent trend for higher death rates in the ertapenem 1 gm group compared to the pipercillin/tazobactam group in this study is concerning. It is also notable that 1 death in the piperacillin/tazobactam group (AN 5052, APACHE score =14) is actually derived from the ertapenem 1.5 g cohort of enrollees from study 017. The following table displays the mortality during the entire study period by baseline APACHE score.

Mortality by Baseline APACHE II Score During Entire Study
Protocol 017

APACHE Score	Expected Mortality[1]		Observed Mortality					
	Assumption 1[2] (%)	Assumption 2[3] (%)	Ertapenem 1 g		Piperacillin/ Tazobactam		Total	
			n/m	(%)	n/m	(%)	n/m	(%)
0 - 4	0 - 5	0 - 8	0/93	(0)	0/92	(0)	0/185	(0)
5 - 9	6 - 10	9 - 15	7/130	(5.4)	5/139	(3.6)	12/269	(4.5)
10 - 14	12 - 20	17 - 27	4/60	(6.7)	2/64	(3.1)	6/124	(4.8)
15 - 19	22 - 33	30 - 44	5/20	(25.0)	4/23	(17.4)	9/43	(21.0)
20 - 24	37 - 51	48- 62	3/9	(33.3)	0/5	(0)	3/14	(21.4)
25 - 30	55 - 72	65 - 89	1/4	(25.0)	1/1	(100)	2/5	(40.0)
Overall			20/316	(6.3)	12/324	(3.7)	32/640	(5.0)

n/m = Number of deaths/ number of patients in the APACHE score category in the treatment group.
[1]Calculated as described in (NDA 21-337, Item 8, Ref. 147).
[2]Assuming standard (not post-emergency) postoperative ICU admission for GI perforation/obstruction without sepsis.
[3]Assuming sepsis (non-operative weighting) from GI source and non-post-emergency surgery.

(Applicant's Table 9, August 24, 2001 submission)

Based on the MO's review of CRFs and narratives for all patients that died during the study, the MO agrees with the Applicant that deaths appear to be attributable to underlying disease(s) and/or efficacy failure (12 patients in the MK-0826 group and 5 patients in the piperacillin/tazobactam group were considered efficacy failures by the Investigators). Despite additional CRF review and review of the Applicant's datasets, the MO was unable to identify any clinically significant differences in the treatment groups as regards duration of therapy, concurrent therapies, medical histories, microbiology, or other adverse events that would explain the higher rate of deaths observed in the MK-0826 1 gm group.

The rate of deaths in this study will be further discussed in conjunction with the overall death rate in the NDA database in the Integrated Summary of Safety in section 7.2.

7.1.1.2.3 Other Serious Adverse Events

The following table displays, by body system, the number (percent) of patients with serious clinical adverse experiences with an incidence of >0% in one or more treatment groups that occurred during the entire study period. Fifty-seven patients (18.0%) in the MK-0826 1 gm group, 2 patients (14.3%) in the MK-0826 1.5 gm group, and 60 patients (18.5%) in the piperacillin/tazobactam group (1 and 1.5 gm cohorts combined) had serious clinical adverse experiences (this included 5 patients in the MK-0826 1 gm group

and 5 patients in the piperacillin/tazobactam groups that had serious adverse experiences reported more than 14 days after discontinuation of study drug therapy).

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

	MK-0826 1 g (N=316)		MK-0826 1.5 g (N=14)		Piperacillin/ Tazobactam (N=325)	
	n	(%)	n	(%)	n	(%)
Patients with one or more serious adverse experiences	57	(18.0)	2	(14.3)	60	(18.5)
Patients with no serious adverse experience	259	(82.0)	12	(85.7)	265	(81.5)
Body as a Whole/Site Unspecified	**23**	**(7.3)**	**2**	**(14.3)**	**17**	**(5.2)**
Adenocarcinoma	1	(0.3)	0	(0.0)	0	(0.0)
Cardiopulmonary failure	1	(0.3)	0	(0.0)	0	(0.0)
Death	20	(6.3)	2	(14.3)	12	(3.7)
Drug overdose	0	(0.0)	0	(0.0)	1	(0.3)
Edema/swelling	0	(0.0)	1	(7.1)	1	(0.3)
Fever	0	(0.0)	1	(7.1)	1	(0.3)
Fungemia	0	(0.0)	0	(0.0)	1	(0.3)
Hernia	1	(0.3)	0	(0.0)	0	(0.0)
Hernia, abdominal	1	(0.3)	0	(0.0)	0	(0.0)
Multiple organ failure	5	(1.6)	0	(0.0)	1	(0.3)
Pain, abdominal	1	(0.3)	0	(0.0)	1	(0.3)
Septicemia	3	(0.9)	0	(0.0)	1	(0.3)
Shock, septic	4	(1.3)	1	(7.1)	2	(0.6)
Unknown cause of death	0	(0.0)	0	(0.0)	1	(0.3)
Cardiovascular System	**12**	**(3.8)**	**1**	**(7.1)**	**17**	**(5.2)**
Angina pectoris	0	(0.0)	0	(0.0)	1	(0.3)
Arrhythmia	1	(0.3)	1	(7.1)	2	(0.6)
Asystole	1	(0.3)	0	(0.0)	0	(0.0)
Atrial fibrillation	0	(0.0)	1	(7.1)	2	(0.6)
Bleeding, postoperative	1	(0.3)	0	(0.0)	0	(0.0)
Bradycardia	0	(0.0)	0	(0.0)	1	(0.3)
Cardiac arrest	5	(1.6)	0	(0.0)	0	(0.0)
CVA	0	(0.0)	0	(0.0)	1	(0.3)
Embolism/infarction, pulmonary	1	(0.3)	0	(0.0)	2	(0.6)
Heart failure	2	(0.6)	1	(7.1)	2	(0.6)
Hemorrhage	0	(0.0)	0	(0.0)	1	(0.3)
Hypertension	0	(0.0)	0	(0.0)	1	(0.3)
Hypotension	2	(0.6)	1	(7.1)	1	(0.3)
Idioventricular rhythm	0	(0.0)	1	(7.1)	0	(0.0)
Intraventricular conduction delay	0	(0.0)	0	(0.0)	1	(0.3)
Left bundle branch block	0	(0.0)	1	(7.1)	0	(0.0)
Myocardial infarction	1	(0.3)	0	(0.0)	5	(1.5)
Shock	1	(0.3)	0	(0.0)	2	(0.6)

APPEARS THIS WAY
ON ORIGINAL

	MK-0826 1 g (N=316)		MK-0826 1.5 g (N=14)		Piperacillin/ Tazobactam (N=325)	
	n	(%)	n	(%)	n	(%)
Sinus arrest	0	(0.0)	0	(0.0)	1	(0.3)
Supraventricular tachycardia	0	(0.0)	0	(0.0)	1	(0.3)
Tachycardia	0	(0.0)	0	(0.0)	1	(0.3)
Thrombosis, deep vein	0	(0.0)	1	(7.1)	1	(0.3)
Ventricular tachycardia	0	(0.0)	1	(7.1)	1	(0.3)
Digestive System	**23**	**(7.3)**	**0**	**(0.0)**	**26**	**(8.0)**
Abscess, appendiceal	1	(0.3)	0	(0.0)	0	(0.0)
Abscess, liver	1	(0.3)	0	(0.0)	0	(0.0)
Adhesion, peritoneum	0	(0.0)	0	(0.0)	1	(0.3)
Biliary disorder	1	(0.3)	0	(0.0)	1	(0.3)
Cholangitis	0	(0.0)	0	(0.0)	1	(0.3)
Cholecystitis	1	(0.3)	0	(0.0)	0	(0.0)
Diarrhea	2	(0.6)	0	(0.0)	0	(0.0)
Fistula, abdominal	1	(0.3)	0	(0.0)	2	(0.6)
Fistula, intestinal	2	(0.6)	0	(0.0)	1	(0.3)
Gastroenteritis	0	(0.0)	0	(0.0)	1	(0.3)
Hematemesis	1	(0.3)	0	(0.0)	0	(0.0)
Hemoperitoneum	0	(0.0)	0	(0.0)	1	(0.3)
Hemorrhage, gastrointestinal	3	(0.9)	0	(0.0)	3	(0.9)
Ileus	3	(0.9)	0	(0.0)	2	(0.6)
Infection, abdominal wall	0	(0.0)	0	(0.0)	1	(0.3)
Infection, intra-abdominal	3	(0.9)	0	(0.0)	5	(1.5)
Nausea	1	(0.3)	0	(0.0)	1	(0.3)
Neoplasm, intestinal	0	(0.0)	0	(0.0)	1	(0.3)
Obstruction, intestinal	1	(0.3)	0	(0.0)	4	(1.2)
Perforation, intestinal	0	(0.0)	0	(0.0)	3	(0.9)
Peritonitis	3	(0.9)	0	(0.0)	1	(0.3)
Stenosis, pyloric	1	(0.3)	0	(0.0)	0	(0.0)
Surgery, intestinal, complication	0	(0.0)	0	(0.0)	4	(1.2)
Vomiting	1	(0.3)	0	(0.0)	0	(0.0)
Hemic and Lymphatic System	**1**	**(0.3)**	**0**	**(0.0)**	**0**	**(0.0)**
Thrombocytopenia	1	(0.3)	0	(0.0)	0	(0.0)
Metabolic, Nutritional, Immune	**4**	**(1.3)**	**1**	**(7.1)**	**1**	**(0.3)**
Acidosis	2	(0.6)	1	(7.1)	0	(0.0)
BUN increased	0	(0.0)	1	(7.1)	0	(0.0)
Dehydration	1	(0.3)	0	(0.0)	1	(0.3)
Nutritional abnormality	1	(0.3)	0	(0.0)	1	(0.3)

APPEARS THIS WAY
ON ORIGINAL

	MK-0826 1 g (N=316)		MK-0826 1.5 g (N=14)		Piperacillin/ Tazobactam (N=325)	
	n	(%)	n	(%)	n	(%)
Musculoskeletal System	**1**	**(0.3)**	**0**	**(0.0)**	**1**	**(0.3)**
Infection, joint	0	(0.0)	0	(0.0)	1	(0.3)
Pain, back	1	(0.3)	0	(0.0)	0	(0.0)
Nervous System and Psychiatric Disorder	**4**	**(1.3)**	**0**	**(0.0)**	**3**	**(0.9)**
Confusion	2	(0.6)	0	(0.0)	0	(0.0)
Motor neuron disease	0	(0.0)	0	(0.0)	1	(0.3)
Seizure disorder	0	(0.0)	0	(0.0)	2	(0.6)
Seizure, grand mal	1	(0.3)	0	(0.0)	0	(0.0)
Somnolence	1	(0.3)	0	(0.0)	0	(0.0)
Stupor	0	(0.0)	0	(0.0)	1	(0.3)
Respiratory System	**18**	**(5.7)**	**0**	**(0.0)**	**10**	**(3.1)**
Edema, pulmonary	1	(0.3)	0	(0.0)	0	(0.0)
Effusion, pleural	1	(0.3)	0	(0.0)	2	(0.6)
Empyema	2	(0.6)	0	(0.0)	1	(0.3)
Hemothorax	0	(0.0)	0	(0.0)	1	(0.3)
Hypoxemia	1	(0.3)	0	(0.0)	1	(0.3)
Obstruction, airway	1	(0.3)	0	(0.0)	0	(0.0)
Pain, pleuritic	1	(0.3)	0	(0.0)	0	(0.0)
Pneumonia	5	(1.6)	0	(0.0)	4	(1.2)
Pneumothorax	1	(0.3)	0	(0.0)	0	(0.0)
Respiratory distress	3	(0.9)	0	(0.0)	1	(0.3)
Respiratory distress syndrome	2	(0.6)	0	(0.0)	0	(0.0)
Respiratory failure	2	(0.6)	0	(0.0)	2	(0.6)
Respiratory insufficiency	1	(0.3)	0	(0.0)	1	(0.3)
Skin and Skin Appendage	**10**	**(3.2)**	**0**	**(0.0)**	**12**	**(3.7)**
Abscess	1	(0.3)	0	(0.0)	2	(0.6)
Abscess, incision	1	(0.3)	0	(0.0)	0	(0.0)
Dehiscence, wound	3	(0.9)	0	(0.0)	2	(0.6)
Infection, soft tissue	3	(0.9)	0	(0.0)	3	(0.9)
Infection, wound	1	(0.3)	0	(0.0)	5	(1.5)
Infection, wound, postoperative	1	(0.3)	0	(0.0)	1	(0.3)
Sloughing skin	0	(0.0)	0	(0.0)	1	(0.3)
Special Senses	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.3)**
Inner ear disorder	0	(0.0)	0	(0.0)	1	(0.3)
Urogenital System	**6**	**(1.9)**	**1**	**(7.1)**	**7**	**(2.2)**
Hemorrhage, vaginal	0	(0.0)	0	(0.0)	1	(0.3)
Infection, urinary tract	1	(0.3)	0	(0.0)	0	(0.0)
Neoplasm, ovary, malignant	1	(0.3)	0	(0.0)	0	(0.0)
Oliguria/anuria	0	(0.0)	1	(7.1)	0	(0.0)
Renal insufficiency	0	(0.0)	1	(7.1)	4	(1.2)
Renal insufficiency, acute	3	(0.9)	0	(0.0)	1	(0.3)
Surgery, urogenital	1	(0.3)	0	(0.0)	0	(0.0)
Urinary incontinence	0	(0.0)	0	(0.0)	1	(0.3)

Entire study period includes study therapy and follow-up period, not limited to 14 days.
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.

(Applicant's Table 66, Volume 13 of 22, pages 236-239)

Medical Officer's Comment: ***With the exception of the death rate, which was commented on in the previous section, the incidence of serious clinical adverse events was similar between the MK-0826 1 gm group and the piperacillin/tazobactam group.***

The following table displays, by body system, the number (percent) of patients with serious drug-related clinical adverse experiences with an incidence of >0% in one or more treatment groups that occurred during the entire study period. Four patients (1.3%) in the MK-0826 1 gm group and 1 patient (0.3%) in the piperacillin/tazobactam group had serious drug-related clinical adverse experiences.

Number (%) of Patients With Serious Clinical Adverse Experiences
(Incidence >0% in One or More Treatment Groups) by Body System
During Entire Study Period
(Treated Population)
Drug Related

	MK-0826 1 g (N=316)		MK-0826 1.5 g (N=14)		Piperacillin/ Tazobactam (N=325)	
	n	(%)	n	(%)	n	(%)
Patients with one or more serious drug-related[1] adverse experiences	4	(1.3)	0	(0.0)	1	(0.3)
Patients with no serious drug-related adverse experience	312	(98.7)	14	(100.0)	324	(99.7)
Cardiovascular System	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.3)**
Hypertension	0	(0.0)	0	(0.0)	1	(0.3)
Hemic and Lymphatic System	**1**	**(0.3)**	**0**	**(0.0)**	**0**	**(0.0)**
Thrombocytopenia	1	(0.3)	0	(0.0)	0	(0.0)
Nervous System and Psychiatric Disorder	**2**	**(0.6)**	**0**	**(0.0)**	**1**	**(0.3)**
Confusion	1	(0.3)	0	(0.0)	0	(0.0)
Seizure disorder	0	(0.0)	0	(0.0)	1	(0.3)
Seizure, grand mal	1	(0.3)	0	(0.0)	0	(0.0)
Urogenital System	**1**	**(0.3)**	**0**	**(0.0)**	**0**	**(0.0)**
Renal insufficiency, acute	1	(0.3)	0	(0.0)	0	(0.0)

[1] Determined by the investigator to be possibly, probably, or definitely drug related.
Entire study period includes study therapy and follow-up period, not limited to 14 days.
Although a patient may have had 2 or more serious 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 serious drug-related adverse experience.

(Applicant's Table 67, Volume 13 of 22, page 240)

Medical Officer's Comment: *After reviewing the narratives and CRFs for patients with serious adverse events, the MO agrees with the Applicant's assessment that the majority of events are most likely due to efficacy failures and/or underlying disease. However, the MO feels that study drug cannot be excluded as a contributing factor for the acute renal failure experienced by AN 0140 (piperacillin/tazobactam group) and the nausea, vomiting, and somnolence experience by AN 5456 (MK-0826 1 gm group) and that these events should be considered possibly study drug related. The narratives, provided by the Applicant, for these two patients are as follows:*

AN 0140

A 53-year-old male with seborrheic dermatitis, varices, angioma, and a rectal fistula began IV therapy with piperacillin/tazobactam for treatment of an abdominal abscess subsequent to a resection of rectal carcinoma. On Study Day 6, the patient experienced an increased serum creatinine of 3.5 mg/100 mL (normal range 0.6 to 1.1 mg/mL), increased potassium of 5.4 mEq/L (normal range 3 to 5 mEq/L) and increased BUN of 121 mg/100 mL (normal range 20 to 40 mg/mL). On Study Day 7, an increased leukocyte count (16.44 ths/mm3) was observed and the serum potassium increased to 5.9 mEq/L. The serum creatinine increased to 3.7 mg/100 mL and the BUN increased to 145 mg/100 mL. The increase of these laboratory parameters led to a diagnosis of renal insufficiency. On Study Day 7, IV study drug was discontinued. On Study Day 16, the leukocyte count and serum potassium returned to normal. On Study Day 16, the patient still experienced a serum creatinine increase of 2.9 mg/100 mL and an increased BUN of 137 mg/100 mL. On Study Day 21, a spontaneous diuresis occurred (9 liters of urine in a day) and there was a normalization of the renal function. The investigator felt that the renal insufficiency, hyperkalemia, increased serum creatinine and increased BUN were probably not related to study drug therapy.

AN 5456

A 83-year-old female with diabetes mellitus, hypertension, chronic obstructive pulmonary disease, coronary artery disease, and a history of a cholecystectomy, congestive heart failure, and gout began IV therapy with MK-0826 for treatment of an intra-abdominal infection. On Study Day 1, the patient showed improvement and was discharged to a skilled nursing home to continue IV study drug therapy. Study drug was completed on Study Day 5. On Study Day 6, the patient developed nausea and vomiting. According to the CRF, the patient was given perphenazine to control the nausea, but this resulted in somnolence. The patient was readmitted to the hospital, a nasogastric tube was inserted and after a few hours the patient's symptoms resolved. On Study Day 6, the patient was also given IV empiric ceftriaxone. It was reported that the vomiting was due to a mild ileus. The investigator felt that the nausea, somnolence, and vomiting were definitely not study drug related.

7.1.1.2.4 Dropouts

Fifteen patients (4.7%) in the MK-0826 1 gm group, no patients in the MK-0826 1.5 gm group, and 20 patients (6.1%) in the piperacillin/tazobactam group were discontinued due to clinical adverse experiences reported during study therapy and 14-day follow-up period. All of the adverse experiences leading to discontinuation of study therapy occurred during parenteral therapy or within 1 day of the last dose of study therapy. Four (4) patients (ANs 0201, 0217, 0955, and 0180) in the MK-0826 1 gm group and six (6) patients (ANs 0272, 5329, 5394, 5427, 5674, and 5791) in the piperacillin/tazobactam group were discontinued due to drug-related clinical adverse experiences. These included 1 rash, 1 confusion, 1 seizure, and 1 thrombocytopenia in the MK-0826 1 gm group; and 2 rashes, 1 deep venous thrombosis, 1 seizure and hypertension, 1 infused vein complication and 1 jaundice and confusion in the piperacillin/tazobactam group.

The following table lists all patients discontinued from study therapy due to a clinical adverse experience, patients highlighted are those that were discontinued due to a drug-related adverse experience.

Listing of Patients Discontinued Due to Clinical Adverse Experiences During Entire Study Period (Treated Population)

AN	Study Number	Gender	Race	Age	Daily Dose†	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Relative Day of Discont‡	Intensity	Drug Relation-ship	Serious	Outcome
MK-0826 1 g													
5496	017007	M	Black	39	P/100 mL	3	Infection, wound, postoperative	11 days	54	Moderate	Probably not	No	Recovered
5947	017019	F	Asian	68	A/1 g	7	Obstruction, airway	1 day	7	Severe	Definitely not	Yes	Still present
5799	017023	M	Caucasian	71	A/1 g	10	Empyema	5 days	13	Severe	Definitely not	Yes	Recovered
[redacted]	017027	M	Caucasian	74	A/1 g	10	Thrombocytopenia	14 days	18	Severe	Possibly	Yes	Recovered
[redacted]	017027	M	Caucasian	78	A/1 g	5	Seizure, grand mal	1 minutes	20	Severe	Possibly	Yes	Recovered
[redacted]	017029	M	Caucasian	65	A/1 g	5	Confusion	4 days	75	Moderate	Possibly	Yes	Recovered
0283	017033	M	Hispanic	19	A/1 g	2	Peritonitis	1 day	2	Severe	Definitely not	Yes	Still present
					A/1 g	2	Multiple organ failure	4 hours		Severe	Definitely not	Yes	Still present
0302	017045	F	Caucasian	88	A/1 g	2	Shock, septic	4 hours		Severe	Definitely not	Yes	Still present
					P/100 mL	14	Shock, septic	5 days	14	Severe	Probably not	Yes	Recovered
[redacted]	017046	M	Caucasian	49	P/100 mL	14	Fistula, abdominal	6 days		Severe	Probably not	Yes	Still present
0372	017049	M	Caucasian	72	P/100 mL	8	Rash	4 days	65	Moderate	Definite	No	Recovered
					A/1 g	1	Shock, septic	2 days	2	Severe	Definitely not	Yes	Still present
					P/50 mL								
					P/50 mL	2	Shock	5 minutes		Severe	Definitely not	Yes	Still present
0388	017050	F	Caucasian	92	P/50 mL	2	Heart failure	7 days	2	Severe	Probably not	Yes	Still present
0405	017051	F	Caucasian	70	A/1 g	3	Cardiac arrest	0.5 minutes	3	Severe	Probably not	Yes	Still present

					A/1 g	3	Acidosis	1.5 hours		Moderate	Probably not	Yes	Still present
					A/1 g	3	Embolism/infarction, pulmonary	30 minutes		Severe	Probably not	Yes	Still present
0513	017053	M	Mixed	37	A/1 g	4	Pneumonia	36 days	22	Severe	Definitely not	Yes	Still present
					A/1 g	5	Septicemia	35 days		Severe	Probably not	Yes	Still present
0694§	017054	M	Black	19	Off drug	2	Cardiac arrest	45 minutes	1	Severe	Probably not	Yes	Still present
0923	017059	F	Caucasian	54	A/1 g	1	Cardiac arrest	15 hours	2	Severe	Definitely not	Yes	Still present
Piperacillin/Tazobactam 3.375 g													
[redacted]	017001	M	Caucasian	23	B/3.375 g	1	Rash	2 days	38	Moderate	Probably	No	Recovered
5333	017001	F	Caucasian	69	B/3.375 g	8	Pneumonia	7 days	39	Moderate	Definitely not	No	Recovered
[redacted]	017004	F	Caucasian	83	B/13.500 g	2	Rash	6 days	3	Moderate	Probably	No	Recovered
5399	017004	F	Caucasian	54	B/13.500 g B/10.125 g B/16.875 g B/3.375 g	2	Fever	28 days	24	Moderate	Probably not	No	Still present
5052	017005	M	Caucasian	87	B/13.500 g	5	Shock, septic	3 days	6	Severe	Definitely not	Yes	Still present
[redacted]	017005	F	Caucasian	53	B/3.375 g	6	Thrombosis, deep vein	6 days	6	Severe	Possibly	No	Still present
5432	017005	M	Caucasian	47	B/6.750 g	7	Infection, intra-abdominal	9 days	15	Severe	Definitely not	No	Recovered
5442	017005	F	Caucasian	67	B/6.750 g	8	Surgery, intestinal, complication	8 days	8	Severe	Definitely not	Yes	Recovered
5470	017007	F	Hispanic	20	B/13.500 g B/10.125 g	7	Infection, intra-abdominal	8 days	48	Moderate	Probably not	No	Recovered
5516	017008	F	Caucasian	43	B/10.125 g	4	Pericarditis	15 days	41	Moderate	Definitely not	No	Recovered
[redacted]	017016	F	Caucasian	32	B/6.750 g	3	Infused vein complication	2 hours	16	Moderate	Definite	No	Recovered
					B/6.750 g	3	Infused vein complication	2 hours		Moderate	Definite	No	Recovered
[redacted]	017023	M	Hispanic	19	B/13.500 g B/3.375 g	3	Confusion	7 days	15	Moderate	Possibly	No	Recovered
					B/13.500 g B/3.375 g	5	Jaundice	7 days		Moderate	Possibly	No	Recovered
0964	017027	M	Caucasian	56	B/13.500 g	5	Atelectasis	4 hours	24	Moderate	Definitely not	No	Recovered
[redacted]	017039	F	Hispanic	35	B/6.750 g	7	Hypertension	1 day	7	Severe	Possibly	Yes	Still present
					B/6.750 g	7	Seizure disorder	2 minutes		Severe	Possibly	Yes	Recovered
0140	017048	M	Caucasian	53	B/13.500 g B/6.750 g	6	Renal insufficiency	15 days	35	Severe	Probably not	Yes	Recovered
0485	017052	M	Black	47	B/10.125 g B/13.500 g B/6.750 g	7	Surgery, intestinal, complication	5 days	21	Severe	Definitely not	No	Recovered
					B/10.125 g B/13.500 g B/6.750 g	7	Distention, abdominal	5 days		Severe	Definitely not	No	Recovered
					B/10.125 g B/13.500 g B/6.750 g	7	Atelectasis	5 days		Severe	Definitely not	No	Recovered
0695	017054	M	Black	56	B/6.750 g	2	Septicemia	11 days	11	Moderate	Definitely not	Yes	Still present
0564	017056	F	Caucasian	67	B/13.500 g B/16.875 g	3	Drug overdose	2 days	5	Mild	Definitely not	Yes	Recovered
0520	017059	M	Caucasian	71	B/6.750 g	2	Myocardial infarction	1 day	2	Severe	Definitely not	Yes	Still present
0922	017059	M	Caucasian	81	B/6.750 g B/13.500 g B/10.125 g	1	Myocardial infarction	3 days	3	Severe	Definitely not	Yes	Still present

† Displays any change of daily dose that occurred within the duration of the adverse experience.
‡ Day of the last scheduled clinical or laboratory assessment performed, relative to the first day of study drug therapy.
§ Includes AN 0694 who discontinued from study drug therapy due to a clinical adverse experience with the onset on the day after the last dose of study drug therapy.
Drug A is MK-0826.
Drug B is piperacillin/tazobactam 3.375 gm.
Drug P is placebo.
Entire study period includes study therapy and entire follow-up period, not limited to 14 days.

(Applicant's Table 69, Volume 13 of 22, pages 263-266)

Medical Officer's Comment: ***The reasons for discontinuation from study therapy were primarily related to efficacy failure and underlying disease. The number of patients discontinued from study therapy due to adverse event and the number of patients discontinued from study therapy due to drug-related adverse event were similar in the MK-0826 1 gm group and the piperacillin/tazobactam group (1 gm and 1.5 gm cohorts combined).***

7.1.1.2.5 Other Treatment Emergent Adverse Events

Overall, 431 of 655 treated patients (65.8%) had clinical adverse experiences reported during study therapy and the 14-day follow-up period (204 [64.6%] in the MK-0826 1 gm group, 12 [85.7%] in the MK-0826 1.5 gm group, and 215 [66.2%] in the piperacillin/tazobactam group).

Medical Officer's Comment: *The Applicant displayed adverse events in tables broken down by ≥3% or ≥0%. In the MO's tables that follow, the number of patients with specific clinical adverse experiences and the number of patients with drug-related specific clinical adverse experiences ≥2% during the parenteral therapy period and 14-day follow-up period are displayed. Tables displaying the number of patients with specific clinical adverse experiences and the number of patients with drug-related specific clinical adverse experiences ≥2% during the IV study only period are displayed in Appendix 24.*

Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence ≥2% in One or More Treatment Groups) by Body System During Study Therapy and Follow-Up Period (Treated Population)

	MK-0826 1.0 g (N=316)		MK-0826 1.5 g (N=14)		Piperacillin/Tazobactam (N=325)	
Patients with one or more adverse experiences	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
	204	(64.6)	12	(85.7)	215	(66.2)
Patients with no adverse experience	112	(35.4)	2	(14.3)	110	(33.8)
Body as a Whole/Site Unspecified	**78**	**(24.7)**	**7**	**(50.0)**	**91**	**(28.0)**
Death	15	(4.7)	2	(14.3)	9	(2.8)
Discharge, abdominal	1	(0.3)	1	(7.1)	2	(0.6)
Distention, abdominal	7	(2.2)	0	(0.0)	12	(3.7)
Edema/swelling	14	(4.4)	2	(14.3)	11	(3.4)
Fever	21	(6.6)	6	(42.9)	34	(10.5)
Pain, abdominal	14	(4.4)	1	(7.1)	23	(7.1)
Pain, postoperative	5	(1.6)	0	(0.0)	12	(3.7)
Shock, septic	4	(1.3)	1	(7.1)	2	(0.6)
Cardiovascular System	**63**	**(19.9)**	**3**	**(21.4)**	**72**	**(22.2)**
Arrhythmia	2	(0.6)	1	(7.1)	4	(1.2)
Atrial fibrillation	3	(0.9)	1	(7.1)	5	(1.5)
Blood pressure increased	0	(0.0)	1	(7.1)	1	(0.3)
Bradycardia	2	(0.6)	1	(7.1)	1	(0.3)
Heart failure	5	(1.6)	1	(7.1)	2	(0.6)
Hypertension	7	(2.2)	0	(0.0)	7	(2.2)
Hypotension	13	(4.1)	1	(7.1)	5	(1.5)
Idioventricular rhythm	0	(0.0)	1	(7.1)	0	(0.0)
Infused vein complication	6	(1.9)	0	(0.0)	9	(2.8)
Left bundle branch block	0	(0.0)	1	(7.1)	0	(0.0)
Peripheral pulse decreased	0	(0.0)	1	(7.1)	1	(0.3)
Peripheral vascular disorder	0	(0.0)	1	(7.1)	0	(0.0)
Phlebitis/thrombophlebitis	14	(4.4)	0	(0.0)	14	(4.3)
T-wave abnormality	0	(0.0)	1	(7.1)	0	(0.0)
Tachycardia	7	(2.2)	0	(0.0)	5	(1.5)
Thrombosis, deep vein	0	(0.0)	1	(7.1)	5	(1.5)
Ventricular tachycardia	1	(0.3)	1	(7.1)	3	(0.9)
Digestive System	**100**	**(31.6)**	**8**	**(57.1)**	**134**	**(41.2)**
Anorexia	0	(0.0)	1	(7.1)	4	(1.2)
Ascites	2	(0.6)	1	(7.1)	3	(0.9)
Candidiasis, oral	0	(0.0)	0	(0.0)	9	(2.8)
Constipation	12	(3.8)	2	(14.3)	21	(6.5)
Diarrhea	40	(12.7)	1	(7.1)	51	(15.7)
Discoloration, tongue	0	(0.0)	1	(7.1)	0	(0.0)
Ileus	3	(0.9)	1	(7.1)	11	(3.4)
Incontinence, fecal	0	(0.0)	1	(7.1)	3	(0.9)
Infection, intra-abdominal	4	(1.3)	0	(0.0)	14	(4.3)

Nausea	28	(8.9)	2	(14.3)	40	(12.3)
Pancreas disorder	0	(0.0)	1	(7.1)	0	(0.0)
Vomiting	16	(5.1)	0	(0.0)	24	(7.4)
Endocrine System	**1**	**(0.3)**	**1**	**(7.1)**	**1**	**(0.3)**
Hypothyroidism	0	(0.0)	1	(7.1)	0	(0.0)
Hemic and Lymphatic System	**15**	**(4.7)**	**1**	**(7.1)**	**8**	**(2.5)**
Anemia	12	(3.8)	0	(0.0)	3	(0.9)
Petechiae	0	(0.0)	1	(7.1)	0	(0.0)
Metabolic, Nutritional, Immune	**19**	**(6.0)**	**3**	**(21.4)**	**12**	**(3.7)**
Acidosis	7	(2.2)	1	(7.1)	1	(0.3)
BUN increased	0	(0.0)	1	(7.1)	0	(0.0)
Fluid overload	0	(0.0)	1	(7.1)	0	(0.0)
Hypoglycemia	0	(0.0)	1	(7.1)	2	(0.6)
Musculoskeletal System	**12**	**(3.8)**	**0**	**(0.0)**	**20**	**(6.2)**
Nervous System and Psychiatric Disorder	**60**	**(19.1)**	**4**	**(28.6)**	**62**	**(19.1)**
Confusion	16	(5.1)	1	(7.1)	11	(3.4)
Depression	2	(0.6)	1	(7.1)	3	(0.9)
Hallucinations	3	(0.9)	1	(7.1)	3	(0.9)
Headache	13	(4.1)	0	(0.0)	15	(4.6)
Insomnia	8	(2.5)	0	(0.0)	21	(6.5)
Mental status change	1	(0.3)	1	(7.1)	1	(0.3)
Nervousness	3	(0.9)	1	(7.1)	2	(0.6)
Respiratory System	**60**	**(19.1)**	**6**	**(42.9)**	**56**	**(17.2)**
Atelectasis	3	(0.9)	1	(7.1)	6	(1.8)
Chest sound abnormality	4	(1.3)	1	(7.1)	7	(2.2)
Cough decreased	0	(0.0)	1	(7.1)	0	(0.0)
Dyspnea	16	(5.1)	2	(14.3)	9	(2.8)
Edema, pulmonary	2	(0.6)	1	(7.1)	1	(0.3)
Effusion, pleural	4	(1.3)	2	(14.3)	9	(2.8)
Hiccups	2	(0.6)	1	(7.1)	2	(0.6)
Hypoxemia	4	(1.3)	1	(7.1)	7	(2.2)
Infiltrate, pulmonary	0	(0.0)	1	(7.1)	0	(0.0)
Mediastinum disorder	0	(0.0)	1	(7.1)	0	(0.0)
Pneumonia	8	(2.5)	1	(7.1)	8	(2.5)
Rales/rhonchi	6	(1.9)	2	(14.3)	5	(1.5)
Respiratory distress	5	(1.6)	2	(14.3)	3	(0.9)
Tachypnea	4	(1.3)	1	(7.1)	1	(0.3)
Wheezing	5	(1.6)	1	(7.1)	4	(1.2)
Skin and Skin Appendage	**58**	**(18.4)**	**4**	**(28.6)**	**63**	**(19.4)**
Dehiscence, wound	6	(1.9)	1	(7.1)	3	(0.9)
Erythema	8	(2.5)	1	(7.1)	8	(2.5)
Infection, soft tissue	4	(1.3)	0	(0.0)	7	(2.2)
Infection, wound	9	(2.8)	0	(0.0)	12	(3.7)
Infection, wound, postoperative	6	(1.9)	1	(7.1)	5	(1.5)
Pruritus	3	(0.9)	0	(0.0)	10	(3.1)
Rash	8	(2.5)	0	(0.0)	9	(2.8)
Sweating	3	(0.9)	1	(7.1)	2	(0.6)
Special Senses	**2**	**(0.6)**	**0**	**(0.0)**	**8**	**(2.5)**
Urogenital System	**26**	**(8.2)**	**3**	**(21.4)**	**34**	**(10.5)**
Infection, urinary tract	5	(1.6)	1	(7.1)	6	(1.8)
Oliguria/anuria	5	(1.6)	1	(7.1)	8	(2.5)
Renal insufficiency	5	(1.6)	1	(7.1)	3	(0.9)
Urinary incontinence	1	(0.3)	1	(7.1)	3	(0.9)

Although a patient may have had 2 or more 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 an adverse experience.

(Modified from Applicant's Table 120, Volume 13 of 22, pages 480-488)

Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence ≥2% in One or More Treatment Groups) by Body System During Study Therapy and 14-Day Follow-up Period (Treated Population) Drug Related

	MK-0826 1.0 g (N=316)		MK-0826 1.5 g (N=14)		Piperacillin/ Tazobactam (N=325)	
	n	(%)	n	(%)	n	(%)
Patients with one or more drug-related adverse experiences[†]	68	(21.5)	4	(28.6)	71	(21.8)
Patients with no drug-related adverse experience	248	(78.5)	10	(71.4)	254	(78.2)
Body as a Whole/Site Unspecified	**6**	**(1.9)**	**0**	**(0.0)**	**11**	**(3.4)**
Cardiovascular System	**16**	**(5.1)**	**0**	**(0.0)**	**16**	**(4.9)**
Phlebitis/thrombophlebitis	13	(4.1)	0	(0.0)	10	(3.1)
Digestive System	**29**	**(9.2)**	**2**	**(14.3)**	**46**	**(14.2)**
Candidiasis, oral	0	(0.0)	0	(0.0)	8	(2.5)
Diarrhea	18	(5.7)	1	(7.1)	26	(8.0)
Discoloration, tongue	0	(0.0)	1	(7.1)	0	(0.0)
Nausea	6	(1.9)	0	(0.0)	16	(4.9)
Nervous System and Psychiatric Disorder	**11**	**(3.5)**	**2**	**(14.3)**	**7**	**(2.2)**
Confusion	2	(0.6)	1	(7.1)	1	(0.3)
Hallucinations	0	(0.0)	1	(7.1)	1	(0.3)
Headache	7	(2.2)	0	(0.0)	2	(0.6)
Mental status change	0	(0.0)	1	(7.1)	0	(0.0)
Respiratory System	**3**	**(0.9)**	**1**	**(7.1)**	**0**	**(0.0)**
Dyspnea	2	(0.6)	1	(7.1)	0	(0.0)
Skin and Skin Appendage	**9**	**(2.8)**	**0**	**(0.0)**	**13**	**(4.0)**

[†] Determined by the investigator to be possibly, probably, or definitely drug related.
Although a patient may have 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.

(Modified Applicant's Table 121, Volume 13 of 22, pages 489-491)

Medical Officer's Comment: ***Phlebitis/thrombophlebitis (4.1% in the MK-0826 1 gm group and 3.1% in the piperacillin/tazobactam combined cohort group) and headache (2.2% in the MK-0826 1 gm group and 0.6% in the piperacillin/tazobactam combined cohort group) were the only drug-related clinical adverse experiences that occurred in a higher percentage of patients in the MK-0826 1 gm group.***

7.1.1.2.6 Laboratory Findings

Of the treated patients who had at least 1 laboratory test postbaseline, 115 (37.1%) in the MK-0826 1 gm group, 7 (53.8%) in the MK-0826 1.5 gm group, and 127 (39.6%) in the piperacillin/tazobactam group had a laboratory adverse experience during study therapy and the 14-day follow-up period. The most common laboratory adverse experiences were increased liver transaminases (ALT and AST) and increased serum alkaline phosphatase. The incidence of ALT increase was 12.0% in the MK-0826 1 gm group, 23.1% in the MK-0826 1.5 gm group, and 10.8% in the piperacillin/tazobactam group. The incidence of AST increase was 9.8% in the MK-0826 1 gm group, 15.4% in the MK-0826 1.5 gm group, and 13.0% in the piperacillin/tazobactam group. The incidence of alkaline phosphatase increase was 10.4% in the MK-0826 1 gm group, 7.7% in the MK-0826 1.5 gm group, and 12.9% in the piperacillin/tazobactam group. Decreased hematocrit and hemoglobin were also reported at similar frequencies in the treatment groups, as would be anticipated in a population of postoperative patients.

Three patients were discontinued from study therapy due to a laboratory adverse experience. AN 5568 in the MK-0826 1 gm group discontinued due to increased BUN and serum creatinine (the investigator judged this laboratory adverse experience as nonserious and possibly study drug related). AN 5579 in the piperacillin/tazobactam group discontinued due to leukocyte count increase to 12.9 ths/mm^3 (the investigator judged this laboratory adverse experience as nonserious and not study drug related). AN 5791 in the piperacillin/tazobactam group was discontinued due to elevated AST (the investigator judged this laboratory adverse experience as nonserious and possibly study drug related).

The number (percent) of patients with specific laboratory adverse experiences with an incidence ≥0% in one or more treatment groups by laboratory test category and the number (percent) of patients with specific drug-related laboratory adverse experiences with an incidence ≥0% in one or more treatment groups by laboratory test category occurring during study therapy and 14-day follow-up are displayed in the following tables.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL