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

Total Isolates	Treatment Group: MK-0826 (A) (N=128) n/m	Observed Response %	(95% CI)	Piperacillin/Tazobactam (B) (N=129) n/m	Observed Response %	(95% CI)	Observed Difference (A-B) %
Gram-Positive Aerobic Rods	**5/6**	**83.3**	-	2/2	100	-	-16.7
Arcanobacterium hemarthae	-	-	-	1/1	100	-	-
Bacillus	1/1	100	-	-	-	-	-
Corynebacterium	3/4	75.0	-	1/1	100	-	-25.0
Listeria monocytogenes	1/1	100	-	-	-	-	-
Gram-Positive Aerobic Cocci	**88/90**	**97.8**	**(92.2, 99.7)**	**95/100**	**95.0**	**(88.7, 98.4)**	**2.8**
Enterococcus	15/15	100	(78.2, 100)	21/21	100	(83.9, 100)	0.0
Enterococcus faecalis	7/7	100	-	8/9	88.9	-	11.1
Enterococcus faecium	1/1	100	-	1/1	100	-	0.0
Gemella morbillorum	2/2	100	-	-	-	-	-
Micrococcus	1/1	100	-	-	-	-	-
Staphylococcus	2/2	100	-	2/2	100	-	0.0
Staphylococcus aureus anaerobius	1/1	100	-	-	-	-	-
Staphylococcus aureus	9/9	100	-	16/16	100	(79.4, 100)	0.0
Staphylococcus auricularis	1/1	100	-	-	-	-	-
Staphylococcus epidermidis	9/9	100	-	7/8	87.5	-	12.5
Staphylococcus haemolyticus	1/1	100	-	-	-	-	-
Staphylococcus hominis	-	-	-	1/1	100	-	-
Staphylococcus saprophyticus	1/1	100	-	-	-	-	-
Staphylococcus, coagulase negative	2/2	100	-	5/5	100	-	-
Streptococcus	6/6	100	-	4/5	80.0	-	20.0
Streptococcus (alpha-hemolytic)	2/2	100	-	2/2	100	-	0.0
Streptococcus (beta-hemolytic)	3/3	100	-	2/3	66.7	-	33.3
Streptococcus (group D)	2/3	66.7	-	3/3	100	-	-33.3
Streptococcus (group F)	-	-	-	1/1	100	-	-
Streptococcus (non-hemolytic)	4/4	100	-	-	-	-	-
Streptococcus agalactiae	11/11	100	(71.5, 100)	16/16	100	(79.4, 100)	0.0
Streptococcus bovis	-	-	-	1/1	100	-	-
Streptococcus intermedius	1/1	100	-	1/1	100	-	0.0
Streptococcus milleri group	1/1	100	-	1/2	50.0	-	50.0
Streptococcus pyogenes	1/2	50.0	-	3/4	75.0	-	-25.0
Viridans Streptococcus group	5/5	100	-	-	-	-	-
Gram-Negative Aerobic Rods	**60/67**	**89.6**	**(79.7, 95.7)**	**62/65**	**95.4**	**(87.1, 99.0)**	**-5.8**
Actinobacter	-	-	-	1/1	100	-	-
Acinetobacter baumannii	0/1	0.0	-	1/1	100	-	-100
Acinetobacter lwoffi	1/1	100	-	1/1	100	-	0.0
Campylobacter gracilis	-	-	-	1/1	100	-	-
Gatecea davisae	-	-	-	1/1	100	-	-
Citrobacter	-	-	-	1/1	100	-	-
Citrobacter freundii	1/1	100	-	2/2	100	-	0.0
Citrobacter koseri	1/1	100	-	-	-	-	-
Enterobacter aerogenes	1/2	50.0	-	1/1	100	-	-50.0
Enterobacter cloacae	2/2	100	-	3/3	100	-	0.0
Escherichia	1/1	100	-	-	-	-	-
Escherichia coli	37/41	90.2	(76.9, 97.3)	36/39	92.3	(79.1, 98.4)	-2.1
Haemophilus	-	-	-	1/1	100	-	-
Klebsiella pneumoniae	4/4	100	-	7/7	100	-	0.0
Morganella morganii	1/2	50.0	-	1/1	100	-	-50.0
Proteus mirabilis	9/9	100	-	5/5	100	-	0.0
Pseudomonas	1/1	100	-	-	-	-	-
Pseudomonas luteola	1/1	100	-	-	-	-	-
Gram-Negative Aerobic Cocci	**1/1**	**100**	-	**1/1**	**100**	-	**0.0**
Neisseria gonorrhoeae	-	-	-	1/1	100	-	-
Neisseria lactamica	1/1	100	-	-	-	-	-
Gram-Positive Anaerobic Rods	**18/18**	**100**	**(81.5, 100)**	**21/23**	**91.3**	**(72.0, 98.9)**	**8.7**
Actinomyces naeslundii	-	-	-	1/1	100	-	-
Clostridium clostridiiformae	1/1	100	-	2/2	100	-	0.0
Clostridium innocuum	-	-	-	1/1	100	-	-
Clostridium paraputrificum	-	-	-	3/3	100	-	0.0
Clostridium ramosum	0/0	100	-	-	-	-	-
Eubacterium	1/1	100	-	4/4	100	-	0.0
Peptococcus	3/3	100	-	-	-	-	-
Peptostreptococcus	1/1	100	-	-	-	-	-
Propionibacterium	2/2	100	-	-	-	-	-
Propionibacterium acnes	-	-	-	-	-	-	-
Gram-positive anaerobic rods	-	-	-	1/1	50.0	-	-
Gram-positive anaerobic rods, non-sporing	-	-	-	1/1	100	-	-
Lactobacillus	-	-	-	2/2	100	-	-
Lactobacillus plantarum	1/1	100	-	-	-	-	-
Peptostreptococcus anaerobius	-	-	-	2/2	100	-	0.0
				4/4	100	-	-
				0/1	0.0	-	-

Total Isolates	Treatment Group						Observed Difference (A-B) %
	MK-0826 (A) (N=128)			Piperacillin/Tazobactam (B) (N=129)			
	n/m	Observed[†] Response %	(95% CI)	n/m	Observed[†] Response %	(95% CI)	
Gram-Positive Anaerobic Cocci	**81/83**	**97.6**	**(91.6, 99.7)**	**77/83**	**92.8**	**(84.9, 97.3)**	**4.8**
Gram-positive anaerobic cocci	-	-	-	1/1	100	-	-
Peptostreptococcus	8/8	100	-	7/8	87.5	-	12.5
Peptostreptococcus anaerobius	23/24	95.8	(78.9, 99.9)	18/20	90.0	(68.3, 98.8)	5.8
Peptostreptococcus asaccharolyticus	20/21	95.2	(76.2, 99.9)	22/22	100	(84.6, 100)	-4.8
Peptostreptococcus indolicus	-	-	-	1/1	100	-	-
Peptostreptococcus ivorii	1/1	100	-	1/1	100	-	0.0
Peptostreptococcus lacrimalis	2/2	100	-	2/2	100	-	0.0
Peptostreptococcus magnus	9/9	100	-	12/14	85.7	(57.2, 98.2)	14.3
Peptostreptococcus micros	4/4	100	-	2/2	100	-	0.0
Peptostreptococcus prevotii	1/1	100	-	3/3	100	-	0.0
Peptostreptococcus tetradius	13/13	100	(75.3, 100)	8/9	88.9	-	11.1
Gram-Negative Anaerobic Rods	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	2/2	100	-	-	-	-	7.7
[illegible]	-	-	-	1/1	100	-	-
[illegible]	10/10	100	[illegible]	5/5	100	-	-
[illegible]	3/5	100	-	4/4	100	-	[illegible]
[illegible]	13/15	100	[illegible]	19/20	95.0	[illegible]	[illegible]
[illegible]	1/1	100	-	-	-	-	[illegible]
[illegible]	2/2	100	-	-	-	-	-
[illegible]	-	-	-	1/1	100	-	-
[illegible]	4/4	100	-	5/6	[illegible]	-	-
[illegible]	2/2	100	-	-	-	-	16.7
[illegible]	2/2	100	-	1/1	100	-	-
[illegible]	4/4	100	-	1/2	[illegible]	-	[illegible]
[illegible]	4/4	100	-	1/1	100	-	[illegible]
[illegible]	5/5	100	-	5/5	100	-	[illegible]
[illegible]	11/11	100	[illegible]	[illegible]	71.4	-	[illegible]
[illegible]	-	-	-	3/3	100	-	[illegible]
[illegible]	1/1	100	-	1/1	100	-	-
[illegible]	1/1	100	-	-	-	-	[illegible]
[illegible]	4/4	100	-	2/2	100	-	-
[illegible]	2/2	100	-	-	-	-	[illegible]
[illegible]	7/7	100	-	5/5	100	-	-
[illegible]	14/14	100	[illegible]	12/13	[illegible]	[illegible]	[illegible]
[illegible]	2/2	100	-	-	-	-	[illegible]
[illegible]	1/1	100	-	6/6	100	-	-
[illegible]	8/8	100	-	11/11	100	[illegible]	[illegible]
[illegible]	24/29	100	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	2/2	100	-	1/1	100	-	[illegible]
[illegible]	6/6	100	-	1/1	100	-	-
[illegible]	3/3	100	-	2/2	100	-	[illegible]
[illegible]	4/4	100	-	-	-	-	[illegible]
[illegible]	2/2	100	-	1/2	[illegible]	-	-
[illegible]	1/1	100	-	-	-	-	[illegible]
[illegible]	-	-	-	3/3	100	-	-
[illegible]	-	-	-	1/1	100	-	[illegible]
Gram-Negative Anaerobic Cocci	[illegible]	[illegible]	-	[illegible]	100	-	[illegible]
[illegible]	-	-	-	1/1	100	-	[illegible]
[illegible]	-	-	-	1/1	100	-	-
[illegible]	[illegible]	100	-	-	-	-	-
Other Bacteria	[illegible]	100	-	[illegible]	75.0	-	[illegible]
[illegible]	[illegible]	100	-	1/2	[illegible]	-	[illegible]
[illegible]	1/1	100	-	-	-	-	[illegible]
[illegible]	1/1	100	-	1/1	100	-	[illegible]
[illegible]	-	-	-	1/1	100	-	-

[illegible]
N=Number of [illegible]
n/m=Number of [illegible]
CI=Confidence interval.

(Applicant's Table 41, Volume 20 of 22, pages 153-161)

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.***

Although not stated in the Points-to-Consider document, it seems reasonable to extrapolate pathogen data from other treatment indications to support efficacy in the treatment indication under review as long as that extrapolation is clinically and pharmacodynamically reasonable. In addition, if data are to be extrapolated between studies for different indications, the MO believes that the severity of illness, dose, and duration of therapy should be similar between the indications.

Based on the above comments, the pathogens that the MO feels should be granted for this indication are: E. coli, S. agalactiae B. fragilis, P. asaccharolytica, P. bevia, and Peptostreptococcus spp. (Because of variability in MIC data for Bacteriodes spp., Prevotella spp., Clostridia spp., and Eubacterium spp., only those pathogens identified to the species level that have been demonstrated in adequate numbers with adequate efficacy in this study should be granted in the label.)

Because the severity of illness and duration of therapy for patients treated in Protocol 023 (acute pelvic infections) were not comparable to Protocol 017, the MO does not believe pathogen data from Protocol 017 should be considered in determining which pathogens will be granted for the acute pelvic infections indication.

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 at least partially responsible for API) 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
Displayed by Baseline Pathogen
in the Microbiologically Evaluable Population – Blood Isolates
(Observed Data)

Blood Isolates	Treatment Group				Observed Difference (A-B) %
	MK-0826 (A) (N=10)		Piperacillin/Tazobactam (B) (N=6)		
	n/m	Observed Response % (95% CI)	n/m	Observed Response % (95% CI)	
Gram-Positive Aerobic Rods	1/1	100 -	2/2	100 -	-
Arcanobacterium bernardiae	-	- -	1/1	100 -	-
Corynebacterium	-	- -	1/1	100 -	-
Listeria monocytogenes	1/1	100 -	-	- -	-
Gram-Positive Aerobic Cocci	-	- -	2/2	100 -	-
Streptococcus (alpha-hemolytic)	-	- -	1/1	100 -	-
Streptococcus pyogenes	-	- -	1/1	100 -	-
Gram-Negative Aerobic Rods	8/8	100 -	3/3[1]	100 -	-
Enterobacter cloacae	1/1	100 -	1/1	100 -	-
Escherichia coli	6/6	100 -	2/2[1]	100 -	-
Klebsiella pneumoniae	1/1	100 -	-	- -	-
Gram-Positive Anaerobic Cocci	-	- -	1/1	100 -	-
Peptostreptococcus asaccharolyticus	-	- -	1/1	100 -	-
Gram-Negative Anaerobic Rods	1/1	100 -	-	- -	-
Prevotella loescheii	1/1	100 -	-	- -	-

[1] Computed from an exact statistical model pooling across strata.
[2] AN 7522's blood isolate of *E. coli* was not included in the analysis. The patient was microbiologically evaluable and had a favorable outcome.
N=Number of microbiologically evaluable patients with baseline blood-borne pathogen isolates 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 42, Volume 20 of 22, pages 163-164)

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 (AN 7154 in the MK-0826 group), with positive entry blood culture for S. aureus, was therefore considered a failure based on presumed persistence by the MO. The MO's revised table for outcome of patients with baseline pathogen isolates is provided below.***

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

Blood Isolates	Treatment Group			
	MK-0826 1 g (A) (N=11)		Piperacillin/Tazobactam (B) (N=8)	
	Observed Response		Observed Response	
	n/m	%	n/m	%
Gram-Positive Aerobic Rods	1/1	100	2/2	100
Arcanobacterium bernardiae	-	-	1/1	100
Corynebacterium	-	-	1/1	100
Listeria monocytogenes	1/1	100	-	-
Gram-Positive Aerobic Cocci	0/1	0	2/2	100
Streptococcus (alpha-hemolytic)	-	-	1/1	100
Streptococcus pyogenes	-	-	1/1	100
Staphylococcus aureus	0/1	0	-	-
Gram-Negative Aerobic Rods	8/8	100	4/4	100
Enterobacter cloacae	1/1	100	1/1	100
Escherichia coli	6/6	100	3/3	100
Klebsiella pneumoniae	1/1	100	-	-
Gram-Positive Anaerobic Rods	-	-	1/1	100
Peptostreptococcus asaccharolyticus	-	-	1/1	100
Gram-Negative Anaerobic Rods	1/1	100	-	-
Prevotella loescheii	1/1	100	-	-

N = Number of microbiologically evaluable patients with baseline pathogens isolated from blood in each treatment group.
n/m = Number of pathogens with associated favorable microbiologic response assessment/number of pathogens with an assessment.
CI = Confidence interval.

6.2.5.5 Reviewer's Comments/Conclusions of Study

In adult female patients with acute pelvic infection treated for 3 to 10 days with intravenous administration of MK-0826 1 gm per day, the following conclusions can be drawn:

1. MK-0826 1 gm IV once daily was clinically and microbiologically as effective as piperacillin/tazobactam 3.375 gms every 6 hours in treating postpartum endomyometritis, septic abortion, and gynecologic postoperative infections in adults.
2. Based on the results of Protocol 023, the Applicant has provided adequate data, for the disease strata studied, to grant an indication for the treatment of postpartum endomyometritis, septic abortion, and post surgical gynecologic infections.
3. Based on the results of Protocol 023, the Applicant has provided adequate data to substantiate the inclusions of the following organism list in the INDICATIONS AND ADMINISTRATION section of the label for acute pelvic infections: "*Escherichia coli, Streptococcus agalactiae, Bacteroides fragilis, Porphyramonas saccharolytica, Prevotella bivia, and Peptostreptococcus species,*."
4. Based on the results of Protocol 023, the Applicant has not provided adequate data to substantiate the inclusion of a statement regarding patients with bacteremia due to *E. coli* in the INDICATIONS AND ADMINISTRATION or CLINICAL STUDIES sections of the label for this indication.
5. For specific conclusions regarding the safety and tolerability of MK-0826 in this study, see section 7.1.2 of this review.

6.2.6 Indication Conclusion

The Applicant has provided adequate data to support the granting of the Acute Pelvic Infections indication for MK-0826 1 gm IV once daily for 3 to 10 days in adults.

In adult female patients with acute pelvic infection treated for 3 to 10 days with intravenous administration of MK-0826 1 gm per day, the following conclusions can be drawn:

1. The results of Protocol 023 support the conclusion that MK-0826 1 gm IV once daily was clinically and microbiologically as effective as piperacillin/tazobactam 3.375 gms every 6 hours in treating postpartum endomyometritis, septic abortion, and gynecologic postoperative infections in adults.
2. The results of the pivotal Phase IIB, Protocol 017 (complicated intra-abdominal infections protocol) provide supportive evidence for the efficacy of MK-0826 in the treatment of acute pelvic infections in adults.

3. Based on the results of Protocol 023, the Applicant has provided adequate data to substantiate the inclusions of the following organism list in the INDICATIONS AND ADMINISTRATION section of the label for acute pelvic infections: "*Escherichia coli, Streptococcus agalactiae, Bacteroides fragilis, Porphyramonas saccharolytica, Prevotella bivia, and Peptostreptococcus* species,."
4. Based on the results of Protocol 023, the Applicant has not provided adequate data to substantiate the inclusion of a statement regarding patients with bacteremia due to *E. coli* in the INDICATIONS AND ADMINISTRATION or CLINICAL STUDIES sections of the label for this indication.
5. The CLINICAL STUDIES section of the label should be revised to include overall efficacy results and results by disease stratum (postpartum including septic abortion and gynecologic postoperative) to reflect key study design features and outcome findings. A table of efficacy by-pathogen should not be included in the CLINICAL STUDIES section of the label for this indication.
6. MK-0826 1 gm IV once daily for 3 to 10 days was generally safe and well tolerated in adult patients with acute pelvic infection.

APPEARS THIS WAY
ON ORIGINAL

6.3 Community Acquired Pneumonia (CAP)

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

6.3.2 Review Dates

6.3.2.1 Received by reviewer:	December 5, 2000
6.3.2.2 Review begun:	May 8, 2001
6.3.2.3 Review completed:	June 15, 2001
6.3.2.4 Review revised:	September 18, 2001

6.3.3 Indication Specific Proposed Label Claims and Critical Differences From Applicant's Proposed Label Claims

The Applicant has proposed the following label claims in reference to the CAP indication:

- In the **INDICATIONS AND USAGE** section of the label:

[redacted]

And at the end of the entire section, as a separate paragraph:

[redacted]

Medical Officer's Comment: ***Based on the MO review that follows the MO recommends that this section be amended to the following:***

"**Community Acquired Pneumonia** caused by *Streptococcus pneumoniae* (penicillin susceptible strains only) including cases associated with concurrent bacteremia, *Haemophilus influenzae* (beta-lactamase negative strains only), *and Moraxella catarrhalis."*

The separate paragraph above should be completely removed from the label. The Applicant has not provided adequate data to support bacteremia claims for complicated intra-abdominal infections or acute pelvic infections. Statements regarding E. coli bacteremia in patients with complicated urinary tract infections and S. pneumoniae in patients with community acquired pneumonia should be incorporated into the specific indication statements.

- In the **DOSAGE AND ADMINISTRATION** section of the label:

[redacted]

Table 7
Dosage Guidelines for Adults With Normal Renal Function* and Body Weight

Infection†	Daily Dose (IV or IM)	Recommended Duration of Total Antimicrobial Treatment
Complicated intra-abdominal infections	1 g	5 to 14 days
Complicated skin and skin structure infections,	1 g	7 to 14 days
Community acquired pneumonia	1 g	10 to 14 days‡
Complicated urinary tract infections, including Pyelonephritis	1 g	10 to 14 days‡
Acute pelvic infections including postpartum Endomyometritis, septic abortion and post surgical Gynecologic infections	1 g	3 to 10 days

* defined as creatinine clearance >90 mL/min/1.73 m^2

† due to the designated pathogens (see INDICATIONS AND USAGE)

‡ duration includes a possible switch to an appropriate oral therapy once clinical improvement has been demonstrated.

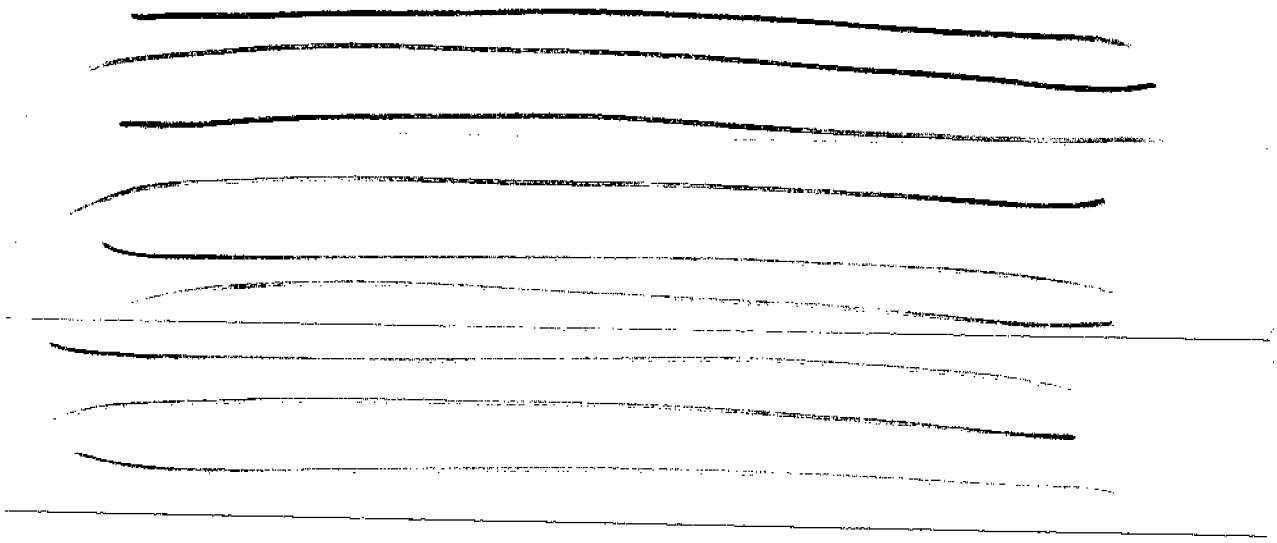
Medical Officer's Comment: ***Many of the statements in the text and table are repetitive. In the first sentence of the "Dosage and Administration" section, the statement "usual dose" is too vague to provide meaningful dosing instructions. The paragraph that follows Table 7 provides limited information beyond that in the table and is therefore not needed. In Table 7, the footnote "‡" should be revised to state "duration includes a possible switch to an appropriate oral therapy, after at least 3 days of parenteral therapy, once clinical improvement has been demonstrated." This change will reflect the design of the studies used to support the indications for which an oral switch was allowed.***

Based on the MO review that follows and the prior MO comment, the MO recommends that the "Dosage and Administration" section be amended to the following:

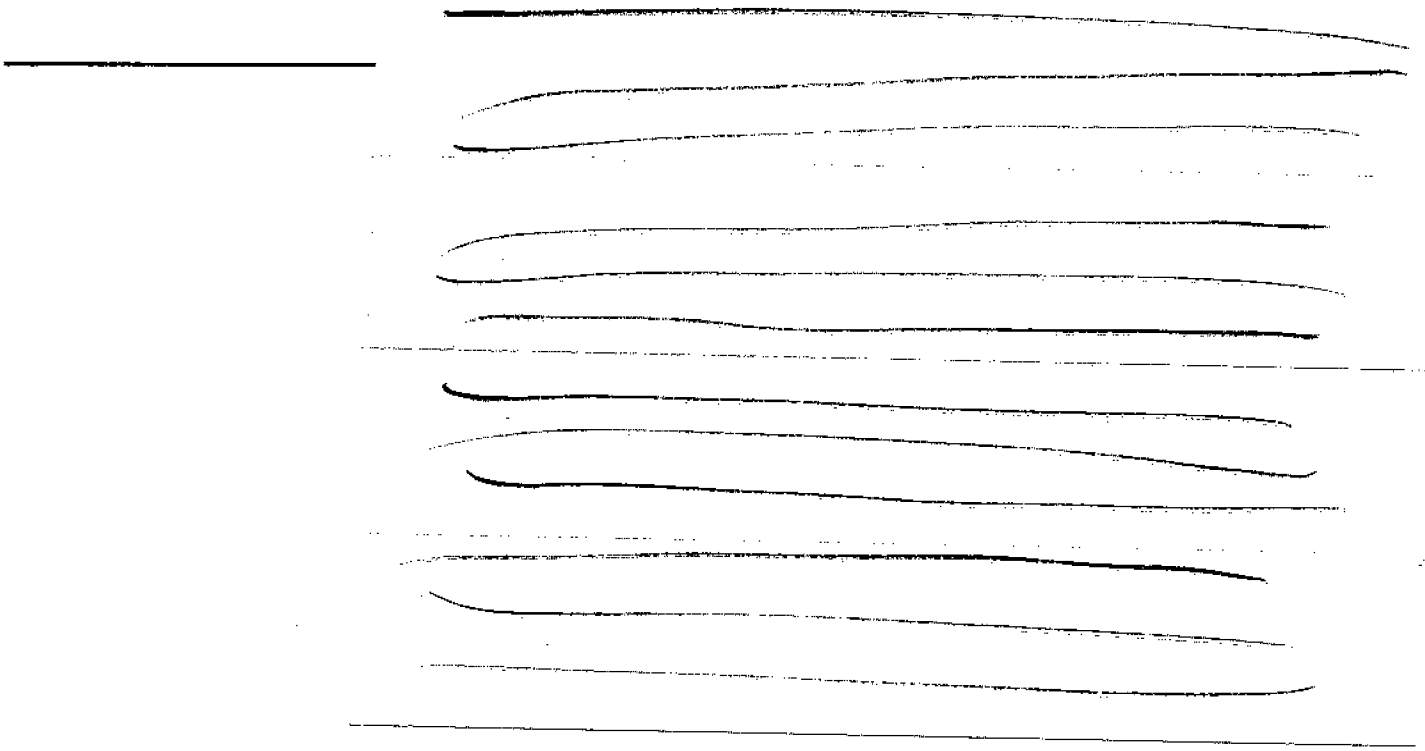
"The dose of INVANZ in adults with normal renal function is 1 gram (g) given once a day.

INVANZ may be administered by intravenous infusion for up to 14 days or by intramuscular injection for up to 7 days. When administered intravenously, INVANZ should be infused over a period of 30 minutes.

DO NOT MIX OR CO-INFUSE INVANZ WITH OTHER MEDICATIONS. DO NOT USE DILUENTS CONTAINING DEXTROSE (α-D-GLUCOSE).



- In the **CLINICAL STUDIES** section of the label:



Medical Officer's Comment: ***Based the recently published draft Guidance for Industry on the clinical studies section of labels[10] and on the MO review that follows the MO recommends that this section be amended to the following:***

[10] Guidance for Industry. Clinical Studies Section of Labeling for Prescription Drugs and Biologics—Content and Format. Published 6/29/01.

"*Community Acquired Pneumonia*

Ertapenem was evaluated in adults for the treatment of community acquired pneumonia in two clinical trials. Both studies compared ertapenem (1 g parenterally once a day) with ceftriaxone (1 g parenterally once a day) and enrolled a total of 866 patients. Both regimens allowed the option to switch to oral amoxicillin/clavulante for a total of 10 to 14 days of treatment (parenteral and oral). In the first study the primary efficacy parameter was the clinical success rate in the clinically evaluable population and success rates were 92.3% (168/182) for ertapenem and 91.0% for ceftriaxone at 7 to 14 days posttherapy (test of cure). In the second study the primary efficacy parameter was the clinical success rate in the microbiologically evaluable population and success rates were 91% (91/100) for ertapenem and 91.8% (45/49) for ceftriaxone at 7 to 14 days posttherapy (test of cure).

APPEARS THIS WAY
ON ORIGINAL

6.3.4 General Review Approach to Review of the Efficacy of the Drug for the CAP Indication

Three clinical efficacy studies were conducted in patients with CAP. The Applicant conducted a small exploratory phase IIa study (made up to 2 Protocols, 002 conducted in sites outside of the United States and 008 conducted in the United States) in patients with uncomplicated lower respiratory tract infection, including CAP and acute exacerbation of chronic bronchitis (AECB). This Phase IIa study was intended to provide a preliminary estimate of the clinical efficacy of 1 gm or 2 gms of ertapenem given as a single daily dose as compared with a standard treatment regimen (ceftriaxone). Given that this study enrolled only a limited number of patients (28 patients receiving 1 gm MK-0826 daily and 30 patients receiving 2 gms MK-0826 daily) and that patients had either CAP or AECB, this study will not be reviewed further in this document.

The Phase IIb/III program conducted by the Applicant in support of a CAP indication included a pivotal, statistically adequate, noninferiority study (018) and a supportive study (020) that both compared ertapenem to ceftriaxone. The efficacy results of studies 018 and 020 are reviewed in detail in the sections 6.3.5 and 6.3.6, respectively, of this review.

The following table displays summary data for the three clinical studies in patients with CAP that were conducted by the Applicant.

APPEARS THIS WAY
ON ORIGINAL

Summary of CAP Clinical Studies

Protocol	Location†	Pivotal/ Supportive	Study Regimens						Oral Switch?	IM Therapy?	Primary Analysis	
			Ertapenem	N (n)‡		Comparator	N (n)‡				Evaluable Population	Primary Analysis Response
Community Acquired Pneumonia												
002/008#	US/Int	IIa	ETP 1 g q.d.	28	(16)	CRO 2 g q.d.	27	(19)	Yes	No	Clinical	Clinical response
			ETP 2 g q.d.	30	(24)							
018	US/Int	Pivotal	ETP 1 g q.d.††	244	(182)	CRO 1 g q.d.††	258	(201)	Yes	Yes	Clinical	Clinical response
020	US/Int	Supportive	ETP 1 g q.d.††	239	(100)	CRO 1 g q.d.††	125	(49)	Yes	Yes	Microbiologic	Clinical response

† Abbreviations used in this table: CRO, ceftriaxone; ETP, ertapenem; IIa, Phase IIa study; Int, international; P/T, piperacillin/tazobactam; US, United States.
‡ N, number of patients randomized to each regimen; n, number of patients in primary analysis evaluable population.
# Protocols 002 and 008 were studies of uncomplicated lower respiratory tract infection, including acute exacerbation of chronic bronchitis, and are reported in a single study report.
†† For patients with documented penicillin-resistant *Streptococcus pneumoniae* pneumonia and inadequate clinical response, the dose of ETP or CRO could have been increased to 2 g q.d. in a blinded fashion.

[Modified from Applicant's Table 1, page 15, Volume 1 of 1]

APPEARS THIS WAY
ON ORIGINAL

6.3.5 PROTOCOL 018: A PROSPECTIVE, MULTICENTER, DOUBLE-BLIND, RANDOMIZED, COMPARATIVE STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF MK-0826 VERSUS CEFTRIAXONE SODIUM IN THE TREATMENT OF SERIOUS COMMUNITY-ACQUIRED PNEUMONIA IN ADULTS

6.3.5.1 Objective/Rationale

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

Primary Objectives

1. To compare the clinical response assessment profile of MK-0826 with that of ceftriaxone sodium in the treatment of patients with serious CAP and without documented PRSP at the early follow-up TOC visit.

2. At the end of parenteral therapy, to compare the proportions of MK-0826-treated patients with ceftriaxone-treated patients with drug-related adverse experiences leading to discontinuation of study drug and also with drug-related serious adverse experiences.

Secondary Objectives

1. To compare the clinical response and microbiologic response assessment profiles of MK-0826 with those of ceftriaxone sodium in the treatment of patients with serious CAP and without documented PRSP at the early follow-up visit.

2. To compare the clinical response assessment profile of MK-0826 with that of ceftriaxone sodium in the treatment of patients with serious CAP irrespective of documented PRSP at the early follow-up visit.

Tertiary Objectives

1. To compare the clinical response and microbiologic response assessment profiles of MK-0826 with those of ceftriaxone sodium in the treatment of patients with serious CAP and with documented PRSP at the early follow-up visit.
2. To compare the clinical response profile, the microbiologic response profile, and the composite clinical and microbiologic response profile in patients with CAP and without documented PRSP, in patients with CAP irrespective of documented PRSP, and in patients with CAP and documented PRSP at the time points of discontinuation of parenteral therapy and at the late follow-up.
3. To determine the tolerability of parenteral MK-0826 in patients with serious CAP compared with ceftriaxone sodium.

4. At selected study sites, to evaluate the drug levels in patients at 6 and 12 hours postdose on Days 1 and 3 of parenteral therapy for pharmacodynamic analysis.

6.3.5.2 Design

This was a prospective, multicenter, double-blind, randomized, comparative study conducted at 34 centers in the United States and 28 centers internationally (14 from Latin America; 4 from Europe; 9 from Asia, Australia, and New Zealand; and 1 from South Africa) between July 15, 1998 and December 8, 1999.

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 (1:1 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 parenteral 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, identified by the Applicant, 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 13.

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: ***Although a switch to oral therapy after only 3 days of parenteral therapy is not specifically recommended in the Agency's Draft Guidance on developing antimicrobial drug products for the treatment of CAP, the Applicant discussed the design of the protocol with the DAIDP and obtained concordance with this design feature.***

Even though allowed, no patients with PRSP had their dose of either study drug increased to 2 gm once daily in this study. In addition, although the protocol was amended to allow a switch to IM therapy, no patients received IM dosing in this study.

It is notable that the 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 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.

6.3.5.3 Protocol Overview

6.3.5.3.1 Population/Procedures

Inclusion and exclusion criteria were applied in order to enroll patients with CAP that were likely to be treatable with parenteral therapy or parenteral plus oral therapy. The following are noteworthy inclusion and exclusion criteria:

Noteworthy Inclusion Criteria:

1. The patient had a clinically suspected and/or bacteriologically documented CAP, according to the following diagnostic criteria:

a. Clinical Criteria

New onset of a clinical picture compatible with bacterial pneumonia with at least 2 of the following signs and symptoms:

1) Cough
2) Production of purulent sputum or an increase or a change in the character of sputum (see microbiologic criteria for definitions of adequate sputum Gram stain findings)
3) Auscultatory findings on pulmonary examination of rales and/or evidence of pulmonary consolidation (dullness on percussion, diminished breath sounds, bronchial breath sounds, rales, rhonchi, wheezing, or egophony)
4) Dyspnea, tachypnea, hypoxemia, pleuritic chest pain, particularly if any or all of these were progressive in nature
5) Organism consistent with a respiratory pathogen isolated from blood culture

AND at least one of the following:

6) Fever, defined as body temperature >38°C (100.4°F) orally, >38.5°C (101.2°F) tympanically, or >39°C (102.2°F) rectally
7) Chills

8) An elevated total peripheral white blood cell (WBC) count >10,000/mm^3; or >15% immature neutrophils (bands), regardless of total peripheral WBC; or leukopenia with total WBC <4500/mm^3

9) Hypothermia, defined as a rectal or core temperature of ≤36°C (96.8°F)

b. Radiographic Criteria

Within 48 hours prior to or after the initiation of therapy, the chest radiograph had to show the presence of a new or progressive infiltrate, consolidation, cavitation, or pleural effusion in order to establish the diagnosis. The state of hydration of the patient at the time of the initial radiograph was taken into consideration. Repeat films taken after hydration or diuresis were acceptable, provided they were taken within the above time frame.

c. Microbiological Criteria

1) Within 24 hours prior to the time of enrollment, all patients had to have a sample of respiratory secretions obtained by any of the following means: deep expectoration, nasotracheal aspiration, intubation with endotracheal suctioning, bronchoscopy with bronchoalveolar lavage (BAL) or protected-brush sampling, transtracheal aspiration, or percutaneous lung or pleural fluid aspiration. The sample was sent to the study site's microbiology laboratory for the following tests: Gram stain, culture, and susceptibility testing.
2) Microscopic examination of the Gram-stained respiratory secretions had to show presence of microorganisms, >25 polymorphonuclear (PMN) cells and <10 squamous epithelial cells/field at 100 times magnification (low-power, 10 times objective). Only appropriate specimens were cultured. (For BAL specimens and respiratory secretions other than expectorated sputum, Gram stain had to show the presence of any PMNs.)
3) Blood culture and susceptibility testing were done for all patients. If blood culture results were known and a common respiratory pathogen was present, the patient was eligible for enrollment in the absence of a positive sputum, regardless of age.

2. Patient's infection had been treated with <24 hours of systemic antibiotic therapy known to be effective against the presumed or documented etiologic pathogen(s) within the 72-hour period immediately prior to entry into the study. If a patient had received >24 hours of systemic antimicrobial therapy, there had to be clear evidence that the patient had failed this regimen. Such evidence included continued fever and persistence of other symptoms consistent with pneumonia.

3. Patients with medical histories, signs, symptoms, or radiographic changes suggestive of a pulmonary infection with *Mycobacterium tuberculosis* had to have a negative acid-fast bacillus (AFB) sputum smear (i.e., examination for *M. tuberculosis*). Such patients could have been enrolled prior to the result of the sputum AFB examination provided the investigator felt that there was compelling clinical evidence of acute CAP. If either the final AFB smear result or the subsequent culture result

demonstrated a mycobacterial infection, then the patient was discontinued from blinded therapy and managed as deemed appropriate by the investigator.

4. Patients with presumed Legionellosis could not be enrolled in this study. Either urine was assayed for Legionella antigen and/or sputum was cultured for Legionella species on appropriate medium and using appropriate culture conditions. Patients with a positive urinary Legionella antigen were permitted to remain in the study only if a typical bacterial pathogen was also suspected. (In countries where the incidence of Legionella infection was low and this test was not a standard practice, this requirement was waived after discussion with the Merck Clinical Monitor.)

Noteworthy Exclusion Criteria

1. Patients with rapidly progressive or terminal illness, patients in whom a response to antibiotic therapy was considered unlikely, or patients who were considered unlikely to survive the study period.
2. Patients with sepsis syndrome with acute hemodynamic instability (such as requirement of pressors to maintain systolic blood pressure >90 mm Hg) or adult respiratory distress syndrome were excluded. Volume repletion (but not pressors) for support of blood pressure and mechanical ventilation for patients with severe pneumonia was allowed.
3. Signs of meningitis, such as nuchal rigidity, papilledema, or other findings of meningitis. Cerebral spinal fluid (CSF) penetration of MK-0826 has not yet been determined.
4. Patients who received appropriate antimicrobial therapy for 24 hours or more prior to enrollment, unless there was a clear indication that the patient failed this regimen as specified in the inclusion criteria.
5. Hematocrit <25%; or Hemoglobin <8 g/dL.
6. Neutropenia with absolute neutrophil count (ANC) $\leq 1000/mm^3$. Patients with ANC as low as $500/mm^3$ could have been enrolled if this was directly related to the acute infection.
7. Platelet count $<75,000/mm^3$; patients with platelet counts as low as $50,000/mm^3$ could have been enrolled if this value was historically stable.
8. Coagulation (Prothrombin time [PT] and partial thromboplastin time [PTT] and/or International Normalized Ratio [INR]) tests >1.5 times the upper limit of the range of normal values used by the laboratory performing the test. Patients who were on anticoagulant therapy with values >1.5 times ULN were enrolled, provided these values were stable and within the therapeutic range.
9. Patients requiring peritoneal dialysis or hemodialysis, or hemofiltration were excluded. For patients with renal insufficiency, not requiring dialysis, the dose of study drug (MK-0826 and amoxicillin/clavulanate only) should have been adjusted based upon the degree of renal function impairment as determined by the estimated or actual creatinine clearance.
10. Abnormal liver function tests:
    a. Alanine transaminase (ALT), and/or aspartate transaminase (AST) >6 times ULN values used by the laboratory performing the test. Patients with documented

elevations of AST and/or ALT up to 10 times ULN were allowed if these elevations were acute and directly related to the infectious process being treated.

b. Bilirubin >3.0 times ULN, unless isolated hyperbilirubinemia was directly related to the acute infection.
c. Alkaline Phosphatase >3.0 times ULN. Patients with values >3.0 times ULN and <5.0 times ULN were eligible if this value was historically stable.
d. Patients with acute hepatic failure or acute decompensation of chronic hepatic failure were excluded.

11. Patients with cystic fibrosis.
12. Patients with neurologic disease preventing normal clearance of secretions (i.e., a fully or partially paralyzed patient due to a stroke), or patients who were at risk for recurrent episodes of aspiration. Patients with well-controlled seizure disorders were eligible.
13. Patients with known bronchial obstruction, a history of postobstructive pneumonia, or other structural lung disease associated with large airway obstruction (e.g., bronchiectasis). Patients who had chronic obstructive pulmonary disease [COPD] were eligible.
14. Patients with primary lung cancer or another malignancy metastatic to the lungs.
15. Chronic immunosuppressive therapy, including use of high dose corticosteroids (≥40 mg prednisone daily or equivalent), or diagnosis of acquired immune deficiency syndrome (AIDS) by current Center for Disease Control (CDC) criteria.
16. Empyema defined as pleural fluid that was frank pus with or without microorganisms in an exudative pleural fluid or pleural fluid with all the following characteristics:
    a. pH <7.2
    b. Lactic dehydrogenase (LDH) >3 x ULN for serum
    c. glucose <40 mg/dL

Medical Officer's Comment: ***The Applicant's inclusion and exclusion criteria are acceptable and in general accordance with the criteria described in the Agency's Draft Guidance on developing antimicrobial drug products for the treatment of CAP.***

6.3.5.3.2 Evaluability Criteria

According to the Applicant, determinations of evaluability for the per protocol and MITT populations were made prior to unblinding using the prespecified criteria stated in the Data Analysis Plan (DAP). The following criteria were used by the Applicant to define study populations for analysis:

Screened population: all patients who signed a consent form for the study. This population includes those patients who were not randomized to therapy and those patients who were randomized to therapy.

Randomized population: a subset of the screened population comprising patients who were randomized to a study regimen, irrespective of whether the patient actually received therapy. 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 and displayed throughout 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.

Treated population: a subset of the randomized population comprising patients who received at least 1 dose of study therapy. Only treated patients are included in the analysis of safety.

Clinical MITT population: a subset of the treated population comprising patients who met the minimum requirements for the diagnosis of pneumonia.

Microbiologic MITT population: a subset of the clinical MITT population, comprised those clinical MITT patients who had a baseline pathogen identified, regardless of susceptibility to study agents, and had a microbiologic response assessed.

Clinically evaluable population: a subset of the clinical MITT population comprising patients for whom sufficient information was available to determine the patients' outcome and no confounding factors were present that interfered with the assessment of that outcome; furthermore, it was required that if baseline pathogens were identified, one or more of these pathogens were susceptible to both parenteral study therapies. Patients with pneumonia caused by PRSP were excluded from the clinically evaluable population.

Study specific criteria for the CAP indication that were provided in the Applicants DAP required that the patient meet the clinical, radiographic, and microbiologic criteria as specified in the inclusion criteria. The following additional criteria were also provided in the DAP:

1) The test-of-cure visit is 7-20 days after the end of study therapy.
2) Both MK-0826 and ceftriaxone are administered once per day in a double-dummy format. In the blinded preliminary assessment, patients must receive ≥80% of the intended doses of study drug. In the unblinded confirmatory assessment, patients must receive ≥80% of the intended doses of specific randomized therapy.
3) Patients must receive at least 3 days of parenteral-study therapy and must receive ≥7 and ≤17 d of total study therapy to be considered an evaluable success. Patients must receive >48 hours of parenteral therapy to be considered an evaluable failure.

Medical Officer's Comment: ***The MO considers the TOC window of 7-20 days acceptable.***

The DAP also included the following "Evaluability exclusions" for the CAP studies:

1) Exclusions resulting from prior antimicrobials
   a) ≥24 h appropriate systemic antimicrobial therapy in the 72 hours prior to enrollment unless there is evidence of clinical failure with a persistent pathogen.
2) Exclusions resulting from concomitant antimicrobials
   b) from study entry through the test-of-cure visit, use of more than one dose of a non-study systemic antimicrobial with activity against the pathogen under study for reasons other than clinical failure. If a non-study systemic antimicrobial with

activity against the pathogen under study is used after study therapy is completed and the patient is subsequently a clinical failure prior to or at the test-of-cure visit, then the patient can still be a "protocol-evaluable" failure.

3) Exclusions due to baseline or intercurrent medical events
   c) Patients must not have any of the following at the time of study entry or within 48 hours of admission:
      v) ventilator-acquired pneumonia, hospital- or nursing home-acquired pneumonia
      vi) empyema
      vii) absolute neutrophil counts <500 cells/mm^3 prior to therapy
   d) Patients must not have had any of the following at study entry through the test-of-cure visit:
      iv) concurrent infection which interferes with evaluation of the response to study therapy
      v) active tuberculosis
      vi) chronic immunosuppressive therapy (chemotherapy/immunosuppressants or prednisone >40 mg/d or its equivalent) or AIDS; HIV-infection without AIDS is acceptable
      vii) cystic fibrosis
      viii) bronchial obstruction and/or bronchiectasis (not including COPD)
      ix) lung malignancy, primary or secondary

4) Exclusion due to base-line microbiology
   b) isolation of an aerobic pathogen not susceptible (I orR) to either parenteral study drug.

Microbiologically evaluable population: a subset of the clinically evaluable population comprising those clinically evaluable patients who had a baseline pathogen identified and a microbiologic response assessed. As all microbiologically evaluable patients were required to be clinically evaluable, the clinically and microbiologically evaluable population was identical to the microbiologically evaluable population; for all data presented hereafter, this group will be referred to as the microbiologically evaluable population.

The Applicant's DAP also required that for microbiologic evaluability that "patients must have a respiratory pathogen that is susceptible to MK-0826 or comparator isolated from an adequate sputum or blood obtained prior to therapy, have at test-of-cure either a microbiology specimen collected or be presumed eradicated/persistent, and not have PRSP."

Medical Officer's Comment: ***The protocol stated that only sputum specimens that were considered adequate based on gram stain findings of presence of microorganisms, >25 polymorphonuclear (PMN) cells and <10 squamous epithelial cells/field at 100 times magnification (low-power, 10 times objective) were to be cultured. However, in cases where the specimen was cultured despite an inadequate gram stain the Applicant did not define microbiologic evaluability criteria for how these patients were to be handled. In many cases patients who had inadequate sputum gram stains and growth on sputum cultures were considered microbiologically evaluable, by the Applicant. The MO used the following criteria for determining microbiologic evaluability in the subset of patients that had entry sputum gram stains with ≥10 epithelial cells at 100 times magnification (suggesting upper airway contamination):***

1) ***The patient met all other criteria for clinical and microbiologic evaluability, defined by the Applicant.***
2) ***The sputum culture showed growth of a single organism consistent with a respiratory pathogen.***
3) ***The patient has a entry blood culture positive for an organism consistent with a respiratory pathogen.***

Late follow-up clinically evaluable population: a subset of the clinically evaluable population comprising patients who were clinical cures at TOC and for whom sufficient information was available to determine the patients' outcome and no confounding factors were present that interfered with the assessment of that outcome at late follow-up.

Late follow-up microbiologically evaluable population: a subset of the clinically late follow-up evaluable population comprising those patients who had a baseline pathogen identified and a microbiologic response assessed. Determinations of late follow-up evaluability were made prior to unblinding using prespecified criteria as indicated in the DAP.

PRSP evaluable population: a subset of the clinical MITT population comprising patients with PRSP isolated at baseline who would have otherwise been clinically evaluable if not for the presence of PRSP. Determinations of PRSP evaluability were made prior to unblinding using prespecified criteria as indicated in the DAP.

PRSP late follow-up evaluable population: a subset of the PRSP evaluable population comprising patients who were clinical cures at TOC and for whom sufficient information was available to determine the patients' outcome and no confounding factors were present that interfered with the assessment of that outcome at late follow-up. Determinations of PRSP late follow-up evaluability were made prior to unblinding using prespecified criteria as indicated in the DAP.

6.3.5.3.3 Endpoints

The primary efficacy endpoint in this study was the clinical success rate in the clinically evaluable population. The Applicant provided the following endpoint definitions:

Clinical Response

Favorable clinical response assessments were "cure" and "improvement" at the discontinuation from parenteral therapy visit and "cure" at the EFU and LFU visits. Once a patient had an "unfavorable" clinical assessment, the patient was counted as having that "unfavorable" response at all subsequent time points.

The definitions of clinical responses assigned at discontinuation of parenteral therapy were:

Clinical Response	Definition
Cure	Resolution of signs and symptoms associated with active infection. Oral therapy could have been used.
Improvement	Resolution or improvement in signs and symptoms associated with active infection. Oral therapy could have been used. Any additional therapy should have been documented.
Failure	After at least 48 hours of therapy: (a) Death due to index infection; or (b) Persistence, incomplete resolution, or worsening of entry signs and symptoms; and/or (c) Emergence of new signs or symptoms of pneumonia; and/or (d) Treatment with additional antimicrobial therapy for pneumonia—this additional therapy must have been recorded. (if switch to planned oral did not meet switch criteria)
Indeterminate	Study data are not available for evaluation of efficacy for any reason, including: (a) Complication relating to underlying medical condition; (b) Patient was withdrawn for any reason before sufficient data had been obtained to permit evaluation of clinical outcome; (c) Death occurred during the study period and the index infection was clearly noncontributory; (d) Extenuating circumstances precluded classification as cure or failure; (e) Death or antibiotic treatment change in the first 48 hours.

The definitions of clinical responses assigned at the EFU (TOC) visit were:

Clinical Response	Definition
Cure	Complete or substantial resolution of signs and symptoms of active infection with worsening of none; an improvement in, or lack of progression of chest x-ray findings; and no additional antibiotic therapy was required.
Failure	After at least 48 hours of therapy: (a) Death due to index infection; or (b) Persistence, incomplete resolution, or worsening of entry signs and symptoms; and/or (c) Emergence of new signs or symptoms of pneumonia; and/or (d) Treatment with additional antimicrobial therapy for pneumonia. (if switch to planned oral did not meet switch criteria)
Indeterminate	Study data were not available for evaluation of efficacy for any reason, including: (a) Complication relating to underlying medical condition; (b) Patient was withdrawn for any reason before sufficient data had been obtained to permit evaluation of clinical outcome; (c) Death occurred during the study period and the index infection was clearly noncontributory; (d) Extenuating circumstances precluded classification as cure or failure; (e) Death or antibiotic treatment change in the first 48 hours.

The definitions of clinical responses assigned at the LFU visit were:

Clinical Response	Definition
Cure	Complete or substantial resolution of signs and symptoms of active infection with worsening of none; an improvement in, or lack of progression of, chest x-ray findings; and no additional antibiotic therapy was required.
Relapse	Resolution or improvement of signs and symptoms (response of Cure) at the Test Of Cure (Early Follow-Up) evaluation followed by reappearance or worsening of signs and symptoms of pneumonia.
Indeterminate	Study data are not available for evaluation of efficacy for any reason, including: (a) Complication relating to underlying medical condition; (b) Patient was withdrawn for any reason before sufficient data had been obtained to permit evaluation of clinical outcome; (c) Death occurred during the study period and the index infection was clearly noncontributory; (d) Extenuating circumstances precluded classification as cure or failure; (e) Death or antibiotic treatment change in the first 48 hours.

APPEARS THIS WAY
ON ORIGINAL

Microbiological Rsponse

Favorable microbiological response assessments were "eradication" and "presumptive eradication."

The definitions of microbiological responses assigned at all study visits were:

Microbiological Response	Definitions
Eradication	Original pathogen was absent from the culture of an adequate specimen obtained from the original site of infection.
Presumptive eradication	No appropriate material (e.g., sputum) was available for culture from the original site of infection, or collection of such a specimen would have caused the patient undue discomfort, in the setting of resolution of clinical signs and symptoms.
Persistence	The continued presence of the original pathogen in cultures from the original site of infection obtained during or after completion of therapy, up to the Test-Of-Cure (TOC) visit.
Persistence acquiring resistance	The continued presence of the original pathogen in cultures from the original site of infection during or after completion of therapy up to the TOC visit, and the pathogens that were susceptible, moderately susceptible, or intermediate to study drug pretreatment became resistant to study drug posttreatment.
Presumed persistence	In patients who were judged to be clinical failures, and for whom a culture was not possible or was not done, it was presumed that there was persistence of the original pathogen.
Recurrence	The isolation of the original pathogen from a culture taken after the TOC visit, if it was considered eradicated at the TOC visit in the setting of clinical signs and symptoms of infection (Note: the isolation of the original pathogen at or before the TOC visit was considered persistence).
Indeterminate	(a) Follow-up cultures were not available due to patient death (only if the primary infection was clearly noncontributory), or withdrawal from study (for reasons other than clinical failure); (b) microbiological data were incomplete; (c) effective concomitant nonstudy antimicrobial therapy; or (d) any other circumstance that made it impossible to define the microbiological response.
For Pathogens First Isolated After the Entry Culture (Emergent Pathogens)	
Superinfection	Emergence of a new pathogen during therapy either at the site of infection or at a distant site with emergence or worsening of signs and symptoms of infection.
New infection	Isolation of a new pathogen from a posttreatment culture from the same site in a patient with signs and symptoms of infection.

Medical Officer's Comment: ***The Applicant's endpoint definitions are acceptable and in general accordance with the criteria described in the Agency's Draft Guidance on developing antimicrobial drug products for the treatment of CAP.***

6.3.5.3.4 Statistical Considerations

The Applicant's sample size calculation assumed a 90% favorable response rate at the EFU visit in the clinically evaluable population (the primary efficacy analysis) for both groups, and a significance level of 0.025. Based on this assumption, 150 evaluable patients per group were needed to have an 80% 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 –10 percentage points.

According to the Applicant, "the study was designed to show equivalence (noninferiority for MK-0826) of the 2 treatment groups. The definition of equivalence is that the 95% (two-sided) CI for the difference in response rates between the 2 treatment groups (MK-0826 response rate minus the ceftriaxone response rate) contains zero (FDA Points to Consider) and the lower limit of the CI is not less than: -10 percentage points if we observe a 90% or better response rate for the control group; -15 percentage points if we observe a response rate which is <90% and ≥80% for the control group: and –20 percentage points if we observe a response rate which is <80% and ≥70% for the control group."

Medical Officer's Comment: ***At the time the protocol was reviewed by the Division this definition of equivalence was considered acceptable, however, the Applicant has been told at multiple teleconferences since that time that the Division has moved away from this definition in the 1992 FDA Points to Consider. The Applicant has been informed that the Division is revisiting the approach to definitions of non-inferiority. One such definition is that of a "fixed" delta of 10%, regardless of response rate to demonstrate equivalence. The Division recognizes that the Applicant based their development plan on earlier guidances and that the determination of approvability for this indication would be based on the overall package provided for review.***

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 Pneumonia Severity Index [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, were 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.***

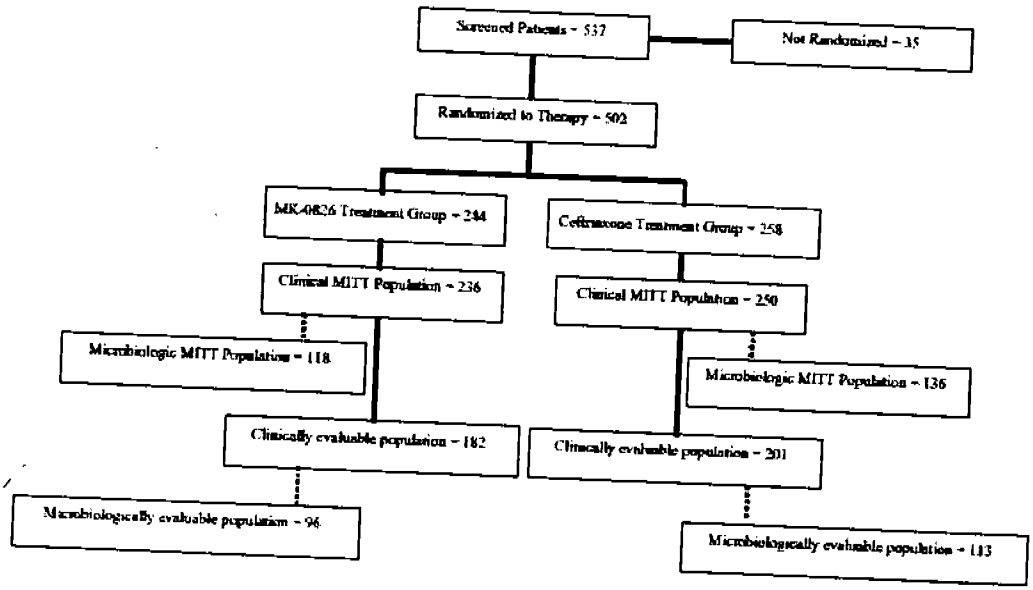
The Applicant also performed subgroup analyses for stratum (PSI ≤3 or >3), age (≤65 years versus >65 years, <75 years versus ≥75), race, and gender for the primary efficacy endpoint in the per-protocol "evaluable-patients-only" population. (The minimum sample size needed in order for the analysis to be performed was at least 10 patients in either subgroup.) In addition, the primary efficacy endpoint was displayed for the groups of evaluable patients randomized before and after new blinding procedures for infusion bags was implemented.

6.3.5.4 Study Results

6.3.5.4.1 Evaluability

Five hundred two (502) patients from 49 US and international sites were randomized, 244 were analyzed in the MK-0826 treatment group and 258 were analyzed in the ceftriaxone treatment group. The primary efficacy analysis (clinical response in the clinically evaluable population) included 383 patients, 182 were analyzed in the MK-0826 treatment group and 201 were analyzed in the ceftriaxone treatment group. The accounting of patients randomized into the study and the reasons patients discontinued from study therapy and study are in Appendix 14. The figure below (Applicant's Figure 1, Volume 15 of 22, page 86) provides a profile of study enrollment and summarizes the number of patients in each of the evaluable populations.

Profile of Patient Enrollment



In the overall patient population, the most common reasons for patients not being randomized to study medication were that patients: did not meet the study entry criteria

(sufficient clinical and radiographic evidence of pneumonia and ability to produce a respiratory secretion specimen) (48.6%); had a history of allergy to a β-lactam agent (11.4%); had an elevated serum creatinine severe enough to exclude them from the study (11.4%).

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=244)		Ceftriaxone (N=258)	
	n	(%)	n	(%)
Clinically Evaluable Population				
Clinically evaluable	182	(74.6)	201	(77.9)
Clinically non-evaluable	62	(25.4)	57	(22.1)
Disease definition not met	4	(1.6)	4	(1.6)
Test-of-cure window violation	11	(4.5)	6	(2.3)
Inadequate/inappropriate study therapy	27	(11.1)	28	(10.9)
Prior antibiotics violation	9	(3.7)	8	(3.1)
Concomitant antibiotics violation	9	(3.7)	7	(2.7)
Baseline/intercurrent medical events	8	(3.3)	7	(2.7)
Baseline pathogen resistant to either study drug	6	(2.5)	3	(1.2)
Other	2	(0.8)	2	(0.8)
Microbiologically Evaluable Population				
Microbiologically evaluable	96	(39.3)	113	(43.8)
Microbiologically non-evaluable	148	(60.7)	145	(56.2)
Not clinically evaluable	61	(25.0)	56	(21.7)
Baseline microbiology—no pathogen isolated	109	(44.7)	105	(40.7)
Test-of-cure microbiology inadequate	0	(0.0)	2	(0.8)
Clinically Late Follow-Up Evaluable Population				
Clinically late follow-up evaluable	148	(60.7)	157†	(60.9)
Clinically late follow-up non-evaluable	96	(39.3)	101	(39.1)
Not a protocol evaluable success	74	(30.3)	75	(29.1)
Concomitant antibiotic violations	3	(1.2)	7	(2.7)
Intercurrent medical events	1	(0.4)	1	(0.4)
Late follow-up window violation	25	(10.2)	32	(12.4)

Reasons Not Evaluable	MK-0826 (N=244) n	(%)	Ceftriaxone (N=258) n	(%)
Microbiologically Late Follow-Up Evaluable Population				
Microbiologically late follow-up evaluable	75	(30.7)	89[‡]	(34.5)
Microbiologically late follow-up non-evaluable	169	(69.3)	169	(65.5)
Not clinically evaluable	96	(39.3)	101	(39.1)
Baseline microbiology—no pathogen isolated	105	(43.0)	97	(37.6)
Late follow-up microbiology inadequate	1	(0.4)	3	(1.2)
Clinical MITT Population				
Clinical MITT evaluable	236	(96.7)	250	(96.9)
Clinical MITT non-evaluable	8	(3.3)	8	(3.1)
Patient did not receive at least 1 dose of study therapy	2	(0.8)	2	(0.8)
Minimal disease definition not met	6	(2.5)	6	(2.3)
Pharmacy dispensing errors preclude evaluability	1	(0.4)	0	(0.0)
Microbiologic MITT Population				
Microbiologic MITT evaluable	118	(48.4)	136	(52.7)
Microbiologic MITT non-evaluable	126	(51.6)	122	(47.3)
Not clinically evaluable	8	(3.3)	8	(3.1)
Baseline microbiology not performed/inadequate	1	(0.4)	0	(0.0)
Baseline microbiology—no pathogen isolated	113	(46.3)	108	(41.9)
Follow-up microbiology inadequate	6	(2.5)	8	(3.1)
PRSP Population				
PRSP evaluable	1	(0.4)	3	(1.2)
PRSP non-evaluable	243	(99.6)	255	(98.8)
Not clinically evaluable except for PRSP	44	(18.0)	32	(12.4)
PRSP not baseline pathogen	222	(93.0)	241	(93.4)
PRSP Late Follow-up Population				
PRSP late follow-up evaluable	1	(0.4)	3	(1.2)
PRSP late follow-up non-evaluable	243	(99.6)	255	(98.8)
Not PRSP evaluable	243	(99.6)	255	(98.8)

Although a patient may have had more than one reason for being non-evaluable, the patient was counted only once in the non-evaluable category total.
[†] Two patients (ANs 6017 and 6063) included in this total were recorded as clinically late follow-up evaluable; however, their late follow-up visits were done earlier than allowed (at 16 days and 15 days posttherapy, respectively).
[‡] One patient (AN 6017) was recorded as microbiologically late follow-up evaluable; however, the late follow-up visit was done earlier than allowed (at 16 days posttherapy).
MITT = Modified intent-to-treat approach.
PRSP = penicillin-resistant *Streptococcus pneumoniae*.

(Applicant's Table 18, Volume 15 of 22, pages 87-88)

Medical Officer's Comment: ***The primary reasons patients were discontinued from therapy in the randomized population, were clinical adverse experience (18 in MK-0826 group and 17 in ceftriaxone group), clinical or microbiologic failure (3 in MK-0826 group and 8 in ceftriaxone group), and patient withdrew consent (5 in MK-0826 group and 6 in ceftriaxone group). With the possible exception of clinical or microbiologic failure, the reasons were generally similar.***

Within each population, the treatment groups were similar with respect to reasons that patients were not evaluable.

The number of clinically evaluable patients in each treatment group that was entered by each investigator is in Appendix 15. Site 018015 (Ortiz-Ruiz, Colombia), was the site that enrolled the most evaluable patients (31/502, 6%). Thirty-six percent and 64% of clinically evaluable patients were enrolled from US and non-US sites, respectively.

6.3.5.4.2 Demographics

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

Baseline Patient Characteristics by Treatment Group
(Clinically Evaluable Population)

	MK-0826 (N=182)	Ceftriaxone (N=201)	Total (N=383)
	n (%)	n (%)	n (%)
Gender			
Male	107 (58.8)	115 (57.2)	222 (58.0)
Female	75 (41.2)	86 (42.8)	161 (42.0)
Race			
Black	24 (13.2)	24 (11.9)	48 (12.5)
Caucasian	94 (51.6)	109 (54.2)	203 (53.0)
Hispanic	51 (28.0)	52 (25.9)	103 (26.9)
Latin American	1 (0.5)	0 (0.0)	1 (0.3)
Maori	0 (0.0)	1 (0.5)	1 (0.3)
Mestizo	10 (5.5)	14 (7.0)	24 (6.3)
Mulatto	1 (0.5)	1 (0.5)	2 (0.5)
Polynesian	1 (0.5)	0 (0.0)	1 (0.3)
Age (Years)			
<18	1	1	2
18 to 40	49	46	95
41 to 64	58	74	132
65 to 74	37	38	75
>74	37	42	79
Mean	56.4	56.2	56.3
SD	19.9	19.9	19.9
Median	60.0	59.0	60.0
Range	17 to 92	17 to 96	17 to 96
Stratum*			
PSI ≤3/Age ≤65 (IA)	100 (54.9)	109(54.2)	209 (54.6)
PSI ≤3/Age >65 (IIA)	37 (20.3)	37(18.4)	74 (19.3)
PSI >3/Age ≤65 (IB)	10 (5.5)	17 (8.5)	27 (7.0)
PSI >3/Age >65 (IIB)	35 (19.2)	38(18.9)	73 (19.1)
PSI Risk Group			
1	27 (14.8)	34 (16.9)	61 (15.9)
2	59 (32.4)	72 (35.8)	131 (34.2)
3	51 (28.0)	38 (18.9)	89 (23.2)
4	39 (21.4)	49 (24.4)	88 (23.0)
5	5 (2.7)	8 (4.0)	13 (3.4)

* Patients are shown according to the stratum assigned by the investigator. Incorrect stratum determinations were not corrected in this table.
PSI = Pneumonia Severity Index. Values range from 1 (low risk) to 5 (high risk).

(Applicant's Table 20, Volume 15 of 22, page 91)

Medical Officer's Comment: ***The 2 treatment groups appeared to be similar with respect to gender, race, age, stratum, and PSI risk group. The 2 treatment groups were also similar (not shown here) with respect to concomitant diagnoses and prior and concomitant therapies (including anti-infective therapies).***

APPEARS THIS WAY
ORIGINAL

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

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

	MK-0826 (N=182)	Ceftriaxone (N=201)	Total (N=383)
Days on Study Therapy (IV and oral)			
n	182	201	383
Mean	11.7	11.8	11.7
SD	2.7	2.5	2.6
Median	12.0	12.0	12.0
Range			
Days on IV Therapy[1]			
n	182	201	383
Mean	4.9	5.1	5.0
SD	2.7	2.6	2.7
Median	4.0	4.0	4.0
Range			
Days on Oral Therapy			
n	165	180	345
Mean	7.4	7.6	7.5
SD	2.4	2.3	2.4
Median	7.0	7.0	7.0
Range			
Days Missed Therapy[2]			
n	5	5	8
Mean	3.7	1.0	2.0
SD	4.6	0.0	2.8
Median	1.0	1.0	1.0
Range			

[1] The option to administer parenteral study therapy by the intramuscular route was not used in any patient in this study, thus all parenteral therapy was given intravenously.
[2] Total number of days a patient missed 24 hours of study therapy.
[3] Due to an artifact in the database, one patient (AN 6482) appears to have missed 9 days of therapy. This patient actually received 4 days of parenteral therapy followed by 11 days of oral therapy without missing any days.
IV = Intravenous.
N = Number of patients in each treatment group.
n = Number of patients in category.

(Applicant's Table 28, Volume 15 of 22, page 108.)

Medical Officer's Comment: ***The 2 treatment groups appeared similar with respect to extent of exposure to IV therapy, oral therapy, and combined IV plus oral therapy. 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 clinically evaluable population: 83.5% of patients in the MK-0826 group and 82.1% of patients in the ceftriaxone group). A table showing the oral switch agents used in the study by treatment group for the clinically evaluable population is in Appendix 16.***

6.3.5.4.3 Efficacy

6.3.5.4.3.1 Clinical

The primary efficacy analysis was clinical response in the clinically evaluable patient population at the EFU visit (TOC). Additional secondary analyses were done on the microbiologically evaluable and MITT population groups. For the TOC analysis, 182/244 patients (74.6%) randomized to the MK-0826 group and 201/258 patients (77.9%) randomized to the ceftriaxone group were clinically evaluable. To address the primary hypothesis, the proportion, adjusted for stratum, of clinically evaluable patients

with a favorable clinical response assessment was evaluated in both treatment groups. The following table displays the proportion of clinically evaluable patients with a favorable clinical response assessment.

Proportion of Patients With Favorable Clinical Response Assessments
in the Clinically Evaluable Population
(Estimated†)

	Treatment Group							
	MK-0826 (A) (N=182)			Ceftriaxone (B) (N=201)				
Time Point	n	Estimated† Response %	(95% CI)	n	Estimated† Response %	(95% CI)	Estimated† Difference (A-B) %	(95% CI)
Discontinuation of intravenous therapy	182	96.1	(93.4, 98.9)	200	93.9	(90.5, 97.3)	2.3	(-2.5, 7.1)
Test of Cure	182	92.4	(88.5, 96.2)	201	91.3	(87.3, 95.3)	1.0	(-4.9, 7.0)

† Computed from a statistical model adjusting for strata.
N = Number of clinically evaluable patients in each treatment group.
n = Number of clinically evaluable patients at the specified visit.
CI = Confidence interval.

(Applicant's Table 34, Volume 15 of 22, page117)

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 clinical efficacy parameters were accepted.***

In the clinically evaluable population, at the TOC analysis, the difference in the clinical response rates between the 2 treatment groups, adjusted for stratum, was 1.0% (92.4% of patients in the MK-0826 group and 91.3% of patients in the ceftriaxone group had a favorable clinical response) with a 95% CI of -4.9%, 7.0%. In the Applicant's revised clinical MITT population, the difference in the clinical response rates between the 2 treatment groups, adjusted for stratum, was -2.1% (80.1% of patients in the MK-0826 group and 82.1% of patients in the ceftriaxone group had a favorable clinical response) with a 95% CI of -9.4%, 5.3% (see Appendix 17 for the Applicant's original and revised MITT analyses). Therefore, the data indicate that the clinical response rates in the clinically evaluable populations for the 2 treatment groups were equivalent for the treatment of CAP.

The assessment of relapse rates (those patients who had a favorable clinical response at Test of Cure but who relapsed subsequently) was done at the LFU. The relapse rate was 3/148 (2.0%) in the MK-0826 group and 1/155 (0.6%) in the ceftriaxone group. None of the four patients had the same pathogen isolated on sputum cultures at relapse.

The Applicant also asssessed clinical response before and after institution of the enhanced blinding procedure. The results are displayed in the following table:

Proportion of Patients With Favorable Clinical Response Assessments at Test of Cure
Displayed by Blinding Procedure
(Clinically Evaluable Population)
Observed† Data

	Treatment Group						Observed† Difference (A-B) %
	MK-0826 (A) (N=182)			Ceftriaxone (B) (N=201)			
	n/m	Observed† Response %	(95% CI)	n/m	Observed† Response %	(95% CI)	
Enhanced Blinding Procedure							
No	33/36	91.7	(82.5, 100)	40/45	88.9	(79.6, 98.2)	2.8
Yes	135/146	92.5	(88.2, 96.8)	143/156	91.7	(87.3, 96.0)	0.8

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

(Applicant's Table 39, Volume 15 of 22, page 123)

Medical Officer's Comment: ***The MO agrees with the Applicant that the results suggest that the enhanced blinding procedure had no significant effect on the determination of clinical outcome.***

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 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 by Pneumonia Severity Index Category in the Clinically Evaluable Population at Test of Cure (Observed† Data)

PSI‡	Treatment Group: MK-0826 (A) (N=182) n/m	Observed† Response %	(95% CI)	Ceftriaxone (B) (N=201) n/m	Observed† Response %	(95% CI)	Observed Difference (A-B) %
≤3	128/138	92.8	(88.4, 97.1)	134/144	93.1	(88.9, 97.2)	-0.3
>3	40/44	90.9	(82.3, 99.5)	49/57	86.0	(76.9, 95.1)	4.9
Overall	168/182	92.3	(88.4, 96.2)	183/201	91.0	(87.1, 95.0)	1.3

† 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 clinically evaluable patients in each treatment group.
n/m = Number of patients with favorable assessment/number of patients with assessment.
CI = Confidence interval.

(Applicant's Table 35, Volume 15 of 22, page 118)

Proportion of Patients With a Favorable Clinical Response Assessment by Age Stratum in the Clinically Evaluable Population at Test of Cure (Observed† Data)

Age (years)	Treatment Group: MK-0826 (A) (N=182) n/m	Observed† Response %	(95% CI)	Ceftriaxone (B) (N=201) n/m	Observed† Response %	(95% CI)	Observed† Difference (A-B) %
≤65	101/110	91.8	(86.7, 97.0)	115/126	91.3	(86.3, 96.2)	0.5
>65	67/72	93.1	(87.1, 99.0)	68/75	90.7	(84.0, 97.3)	2.4
Overall	168/182	92.3	(88.4, 96.2)	183/201	91.0	(87.1, 95.0)	1.3

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

(Applicant's Table 36, Volume 15 of 22, page 119)

APPEARS THIS WAY
ON ORIGINAL

Proportion of Patients With Favorable Clinical Response Assessment by Age and Disease Severity Strata in the Clinically Evaluable Population at Test of Cure (Observed Data)

Stratum‡	Treatment Group: MK-0826 (A) (N=182) n/m	MK-0826 (A) (N=182) Observed† Response % (95% CI)	Ceftriaxone (B) (N=201) n/m	Ceftriaxone (B) (N=201) Observed† Response % (95% CI)	Observed† Difference (A-B) %
Age ≤65, PSI ≤3	92/101	91.1 (85.5, 96.7)	100/108	92.6 (87.6, 97.6)	-1.5
Age >65, PSI ≤3	36/37	97.3 (92.0, 100.0)	34/36	94.4 (86.9, 100)	2.9
Age ≤65, PSI >3	9/9	100	15/18	83.3 (65.6, 100)	16.7
Age >65, PSI >3	31/35	88.6 (77.9, 99.3)	34/39	87.2 (76.5, 97.8)	1.4
Overall	168/182	92.3 (88.4, 96.2)	183/201	91.0 (87.1, 95.0)	1.3

† For overall, computed from a statistical model pooling across strata.
‡ The strata for 13 patients misclassified by the investigator were corrected.
N = Number of clinically evaluable patients in each treatment group.
n/m = Number of patients with favorable assessment / number of patients with assessment at test of cure.
CI = Confidence interval.
PSI = Pneumonia Severity Index. Possible values range from 1 (mild) to 5 (severe).

(Applicant's Table 37, Volume 15 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, except for the trend toward higher cure rates, in the MK-0826 group, for patients with a PSI >3 and Age≤65/PSI >3 based on point estimates.***

The Applicant also analyzed the proportions of clinically evaluable patients with favorable clinical response assessments classified by gender, age, and race. The results of these analyses are displayed in the following table.

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

	Treatment Group: MK-0826 (A) (N=182) n/m	MK-0826 (A) (N=182) Observed† Response %	MK-0826 (A) (N=182) Observed† Response (95% CI)	Ceftriaxone (B) (N=201) n/m	Ceftriaxone (B) (N=201) Observed† Response %	Ceftriaxone (B) (N=201) Observed† Response (95% CI)	Observed† Difference (A-B) %
Gender							
Female	71/75	94.7	(89.5, 99.8)	77/86	89.5	(83.6, 96.0)	5.1
Male	97/107	90.7	(85.1, 96.2)	106/115	92.2	(87.2, 97.3)	-1.5
Age Category							
<65	99/108	91.7	(86.4, 96.9)	115/121	95.0	(89.9, 97.5)	-3.3
≥65	69/74	93.2	(87.5, 99.0)	71/80	88.8	(81.8, 95.7)	4.5
<75	135/145	93.1	(88.2, 98.2)	146/159	91.8	(87.6, 96.1)	1.3
≥75	33/37	94.6	(87.2, 100)	35/42	83.3	(70.2, 96.5)	11.3
Race							
Black	23/24	95.8	(87.2, 100)	23/24	91.7	(80.4, 100.0)	4.2
Caucasian	84/96	87.5	(81.1, 95.9)	105/109	96.3	(90.2, 98.5)	-8.8
Hispanic	40/41	97.6	(90.7, 100)	46/52	88.5	(79.1, 97.2)	7.9
Latin American	1/1	100	-	-	-	-	-
Oriental	9/10	90.0	(70.4, 100)	14/14	71.4	(46.9, 96.0)	18.6
Mulatto	1/1	100	-	1/1	100	-	0.0
Other	1/1	100	-	1/1	100	-	0.0

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

(Applicant's Table 38, Volume 15 of 22, page 122)

Medical Officer's Comment: ***The clinical responses appeared similar in the 2 treatment groups with respect to gender, age category, and race. Given the small number of Mestizo's enrolled the significance of the 18.6% observed difference in clinical response between treatment groups (favorable response: 90% for MK-0826 and 71.4% for ceftriaxone) is difficult to interpret.***

6.3.5.4.3.2 Microbiologic

Microbiological efficacy parameters were analyzed as secondary endpoints in this study. The proportions of randomized patients who were microbiologically evaluable for the TOC analysis were 96/244 (39.3%) in the MK-0826 group and 113/258 (43.8%) in the ceftriaxone group. These patients represented 52.7% and 56.2% of the clinically evaluable patients in the MK-0826 group and ceftriaxone group, respectively.

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
Microbiologic Response Assessment at Test of Cure
in the Microbiologically Evaluable Population
(Observed† Data)

	Treatment Group						Observed Difference (A-B) %
	MK-0826 (A) (N=96)			Ceftriaxone (B) (N=113)			
Time Point	n/m	Observed† Response %	(95% CI)	n/m	Observed† Response %	(95% CI)	
Test of Cure	89/96	92.7	(87.5, 97.9)	107/113	94.7	(90.5, 98.8)	-2.0

† 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.

(Applicant's Table 43, Volume 15 of 22, page 130)

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 018) With a Favorable Microbiologic Response Assessment at Test of Cure in the Microbiologically Evaluable Population According to the MO (Observed Data)

	Treatment Group						Observed Difference (A-B)	
	MK-0826 (A) (N=96)			Ceftriaxone (B) (N=113)				
Time Point	n/m	Observed† Response %	(95% CI)	n/m	Observed† Response %	(95% CI)	%	(95% CI)
Test of Cure	86/92	93.5	(86.3, 97.6)	102/108	94.4	(88.3, 97.9)	-0.9	(-0.14, 0.08)

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 2.3% (89.8% of patients in the MK-0826 group and 87.5% of patients in the ceftriaxone group had a favorable clinical response). See Appendix 17 for the Applicant's original and revised MITT analyses.

6.3.5.4.3.3 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 Microbiologic Response Assessments at Test of Cure in the Microbiologically Evaluable Population Displayed by Baseline Pathogen—Total Isolates (Respiratory Secretions and Blood) (Observed[1] Data)

	Treatment Group						
	MK-0826 (A) (N=86)			Ceftriaxone (B) (N=113)			Observed Difference (A-B)
Isolates	n/m	Observed[1] Response %	(95% CI)	n/m	Observed[1] Response %	(95% CI)	%
Gram-Positive Aerobic Cocci	**38/40**	**95.7**	**(85.5, 99.5)**	**64/67**	**95.5**	**(87.5, 99.1)**	**1.1**
Staphylococcus aureus	8/8	100	-	4/5	80.0	-	20.0
Streptococcus species	-	-	-	1/1	100	-	-
Streptococcus pneumoniae	45/47	95.7	(85.5, 99.5)	56/57	98.2	(90.6, 100)	-2.5
Streptococcus pyogenes	-	-	-	1/1	100	-	-
Streptococcus agalactiae	1/1	100	-	1/1	100	-	0.0
Streptococcus milleri group	2/2	100	-	0/1	0.0	-	100
Streptococcus (β-hemolytic)	2/2	100	-	-	-	-	-
Viridans Streptococcus group	-	-	-	1/1	100	-	-
Gram-Negative Aerobic Rods	**42/47**	**89.4**	**(76.9, 96.5)**	**62/66**	**93.9**	**(85.2, 98.3)**	**-4.6**
Acinetobacter lwoffi	-	-	-	1/1	100	-	-
Enterobacter cloacae	2/2	100	-	-	-	-	-
Enterobacter intermedius	-	-	-	1/1	100	-	-
Escherichia coli	2/2	100	-	1/1	100	-	0.0
Haemophilus species	2/2	100	-	4/4	100	-	0.0
Haemophilus haemolyticus	1/1	100	-	-	-	-	-
Haemophilus influenzae	18/21	85.7	(63.7, 97.0)	22/23	95.7	(78.1, 99.9)	-9.9
Haemophilus parahaemolyticus	1/1	100	-	-	-	-	-
Haemophilus parainfluenzae	3/3	100	-	10/10	100	(69.2, 100)	0.0
Klebsiella species	1/1	100	-	-	-	-	-
Klebsiella oxytoca	-	-	-	3/3	100	-	-
Klebsiella pneumoniae	2/2	100	-	1/1	100	-	0.0
Moraxella catarrhalis	8/10	80.0	(44.4, 97.5)	15/18	83.3	(58.6, 96.4)	-3.3
Proteus mirabilis	1/1	100	-	2/2	100	-	0.0
Pseudomonas aeruginosa	1/1	100	-	-	-	-	-

[1] Compared from a statistical model pooling across strata.
The table shows only unique baseline isolates for each pathogen.
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.

(Applicant's Table 44, Volume 15 of 22, pages 132-133)

Medical Officer's Comment: ***In the MO's analysis 9 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 9 patients with inadequate gram stains is given in the following table.***

Patients Changed to Microbiologically Unevaluable by MO

AN	Organisms listed 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		
6302	*M. catarrhalis*	*M. catarrhalis* *P. aeruginosa* *S. viridans*
6307	*M. catarrhalis*	*M. catarrhalis* *S. viridans*
6424	*M. catarrhalis*	*M. catarrhalis* *S. viridans*
7191	*S. aureus*	*S. aureus* *C. parapsilosis*
Ceftriaxone		
6425	*M. catarrhalis*	*M. catarrhalis* *P. aeruginosa* *S. viridans*
6446	*S. aureus*	*S. aureus* *M. catarrhalis* *S. viridans* *C. albicans*
7011	*M. catarrhalis*	*M. catarrhalis* *S. aureus* *Alpha hemolytic streptococcus*
7031	*K. oxytoca* *Heamophilus spp.* *S. aureus*	*K. oxytoca* *Heamophilus spp.* *S. viridans*
7060	*H. influenzae* *E. cloacae*	*H. influenzae* *E. cloacae* *C. albicans* *S. viridans* *Neiserria spp.*

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. 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 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-lactamse 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=92)			Ceftriaxone (B) (N=108)			
	n/m	Observed† Response %	(95% CI)	n/m	Observed† Response %	(95% CI)	
Gram-Positive Aerobic Cocci	**57/60**	**95.0**	**(86.1, 99.0)**	**63/67**	**94.0**	**(83.4, 98.4)**	**1.0**
Staphylococcus aureus	7/7	100	-	3/4	75.0	-	25.0
Streptococcus species	-	-	-	1/1	100	-	-
Streptococcus pneumoniae	45/48	93.8	(82.8, 98.7)	56/58	96.6	(88.1, 99.6)	-2.8
Streptococcus pyogenes	-	-	-	1/1	100	-	-
Streptococcus agalactiae	1/1	100	-	1/1	100	-	0.0
Streptococcus milleri group	2/2	100	-	0/1	0.0	-	100
Streptococcus (β-hemolytic)	2/2	100	-	-	-	-	-
Viridans *Streptococcus* group	-	-	-	1/1	100	-	-
Gram-Negative Aerobic Rods	**40/43**	**93.0**	**(80.9, 98.5)**	**57/61**	**93.4**	**(84.1, 98.2)**	**0.4**
Acinetobacter lwoffi	-	-	-	1/1	100	-	-
Enterobacter cloacae	2/2	100	-	-	-	-	-
Enterobacter intermedius	-	-	-	1/1	100	-	-
Escherichia coli	2/2	100	-	1/1	100	-	0.0
Haemophilus species	2/2	100	-	3/3	100	-	0.0
Haemophilus haemolyticus	1/1	100	-	-	-	-	-
Haemophilus influenzae	17/20	85.0	(62.1, 96.8)	21/22	95.5	(77.2, 99.9)	-15.5
Beta lactamase negative	13/13	100	(75.3, 100)	17/18	94.4	(72.7, 99.9)	6.6
Beta lactamase positive	2/4	50.0	-	1/1	100	-	-50.0
Beta lactamase not available	2/3	66.7	-	3/3	100	-	-33.3
Haemophilus parahaemolyticus	1/1	100	-	-	-	-	-
Haemophilus parainfluenzae	3/3	100	-	10/10	100	(69.2, 100)	0.0
Klebsiella species	1/1	100	-	-	-	-	-
Klebsiella oxytoca	-	-	-	2/2	100	-	-
Klebsiella pneumoniae	2/2	100	-	3/3	100	-	0.0
Moraxella catarrhalis	6/7	85.7	(42.1, 99.6)	13/16	81.3	(54.4, 96.0)	4.4
Beta lactamase negative	0/1	0	-	1/1	100	-	-100
Beta lactamase positive	2/2	100	-	3/3	100	-	0.0
Beta lactamase not available	4/4	100	(39.8, 100)	9/12	75.0	(42.8, 94.5)	25.0
Proteus mirabilis	1/1	100	-	2/2	100	-	0.0
Pseudomonas aeruginosa	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 (Exact Clopper-Pearson Formula)

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.