

Total Isolates	Treatment Group				Observed Difference (A-B) %
	MK-0826 1 g (A) (N=203)		Piperacillin/Tazobactam (B) (N=193)		
	n/n	% Observed ¹ Response (95% CI)	n/n	% Observed ¹ Response (95% CI)	
Gram-Negative Aerobic Cocci					
<i>Neisseria</i>	-	-	1/1	100	-
Gram-Positive Anaerobic Rods	132/140	94.3 (89.1, 97.5)	102/112	91.1 (84.3, 95.6)	3.2
<i>Actinomyces</i>					
<i>Actinomyces naeslundii</i>	1/1	100	-	-	-
<i>Actinomyces visnui</i>	1/1	100	-	-	-
<i>Bifidobacterium breve</i>	1/1	100	1/1	100	-
<i>Clostridium</i>					
<i>Clostridium baratii</i>	4/4	100	-	-	-
<i>Clostridium bifermentans</i>	1/1	100	5/6	83.3	16.7
<i>Clostridium butyricum</i>	2/2	100	-	-	-
<i>Clostridium caespitosum</i>	3/3	100	1/1	100	0.0
<i>Clostridium clostridioforme</i>	3/3	100	1/1	100	0.0
<i>Clostridium cochlearium</i>	18/19	94.7 (74.0, 99.9)	21/21	100 (83.9, 100)	-5.3
<i>Clostridium innocuum</i>	17/17	100	1/1	100	-
<i>Clostridium leptum</i>	1/1	100	9/9	100	0.0
<i>Clostridium perfringens</i>	13/14	92.9 (66.1, 99.8)	10/13	76.9 (46.2, 95.0)	15.9
<i>Clostridium ramosum</i>	8/8	100	4/6	66.7	33.3
<i>Clostridium sordidum</i>	2/2	100	0/2	0.0	100
<i>Clostridium sporogenes</i>	1/1	100	1/1	100	-
<i>Clostridium symbiosum</i>	2/4	50.0	1/1	100	-50.0
<i>Clostridium tertium</i>	1/1	100	1/1	100	0.0
<i>Collinsella aerofaciens</i>	1/3	33.3	-	-	-
<i>Eubacterium</i>					
<i>Eubacterium aerofaciens</i>	10/20	95.0 (75.1, 99.9)	-	-	-
<i>Eubacterium concoloratum</i>	1/1	100	16/16	100 (79.4, 100)	-5.0
<i>Eubacterium lentum</i>	20/21	95.2 (76.2, 99.9)	-	-	-
<i>Eubacterium limosum</i>	-	-	12/12	100 (73.5, 100)	-4.8
Gram-positive anaerobic rods²					
<i>Lactobacillus</i>					
<i>Lactobacillus casei</i>	4/4	100	1/1	100	-
<i>Lactobacillus casei</i>	3/3	100	6/7	85.7	14.3
<i>Lactobacillus casei</i>	1/1	100	2/3	66.7	33.3
<i>Lactobacillus casei</i>	-	-	-	-	-
<i>Lactobacillus fermentum</i>	1/1	100	2/2	100	-
<i>Lactobacillus plantarum</i>	1/1	100	-	-	-
<i>Propionibacterium</i>					
<i>Propionibacterium aceti</i>	1/1	100	1/1	100	0.0
<i>Propionibacterium aceti</i>	1/1	100	2/2	100	0.0
<i>Streptococcus</i>					
<i>Streptococcus</i>	1/1	100	2/2	100	0.0
Gram-Positive Anaerobic Cocci	34/39	87.2 (71.6, 95.7)	27/29	93.1 (77.2, 99.2)	-5.9
Gram-positive anaerobic cocci²					
<i>Peptostreptococcus</i>	3/3	100	1/3	33.3	-66.7
<i>Peptostreptococcus anaerobius</i>	11/12	91.7 (69.9, 98.1)	-	-	-
<i>Peptostreptococcus asaccharolyticus</i>	4/5	80.0	10/10	100 (69.2, 100)	-15.4
<i>Peptostreptococcus magnus</i>	1/1	100	2/2	100	-20.0
<i>Peptostreptococcus magnus</i>	2/2	100	-	-	-
<i>Peptostreptococcus micros</i>	10/12	83.3 (51.6, 97.9)	3/3	100	0.0
<i>Peptostreptococcus prevotii</i>	1/1	100	10/10	100 (69.2, 100)	-16.7
<i>Peptostreptococcus tetralolus</i>	1/1	100	1/1	100	0.0
<i>Ruminococcus prodigiosus</i>	1/1	100	-	-	-
Gram-Negative Anaerobic Rods	284/312	91.0 (87.3, 94.0)	272/295	92.2 (88.5, 95.8)	-1.2
Bacteroides					
<i>Bacteroides caccae</i>	4/5	80.0	10/12	83.3 (31.6, 97.9)	-3.3
<i>Bacteroides capillosus</i>	8/9	88.9	10/12	83.3 (51.6, 97.9)	5.6
<i>Bacteroides distans</i>	2/2	100	1/1	100	0.0
<i>Bacteroides eggerthii</i>	16/19	84.2 (60.4, 96.6)	25/25	100 (86.3, 100)	-15.8
<i>Bacteroides fragilis</i>	1/1	100	-	-	-
<i>Bacteroides merdus</i>	62/75	86.7 (76.8, 93.4)	60/68	88.2 (78.1, 94.8)	-1.6
<i>Bacteroides moryella</i>	1/1	100	2/2	100	0.0
<i>Bacteroides ovatus</i>	20/21	95.2 (76.2, 99.9)	22/22	100 (84.6, 100)	-4.8
<i>Bacteroides pumilus</i>	1/4	25.0	32/32	100	-75.0
<i>Bacteroides spiculisporus</i>	2/2	100	1/1	100	0.0
<i>Bacteroides stercoris</i>	5/5	100	5/5	100	0.0
<i>Bacteroides thetaiotaomicron</i>	44/47	93.6 (82.5, 98.7)	3/3	100	0.0
<i>Bacteroides uniformis</i>	21/22	95.5 (77.2, 99.9)	32/34	94.1 (80.3, 99.3)	-0.5
<i>Bacteroides univoltus</i>	-	-	20/21	95.2 (76.2, 99.9)	0.2
<i>Bacteroides vulgatus</i>	8/10	80.0 (44.4, 97.5)	1/1	100	-
<i>Bifidobium</i>	3/2	100	19/19	100 (82.4, 100)	-20.0
Bifidobium					
<i>Bifidobium wadsworthii</i>	28/29	96.6 (82.2, 99.9)	24/27	88.9 (70.8, 97.6)	7.7
Dialister					
<i>Dialister pneumosinus</i>	1/1	100	-	-	-
Fusobacterium					
<i>Fusobacterium</i>	2/2	100	-	-	-
<i>Fusobacterium goniloliformans</i>	2/2	100	1/1	100	0.0
<i>Fusobacterium morphoferum</i>	1/1	100	-	-	-
<i>Fusobacterium necrophorum</i>	2/2	100	2/2	100	0.0
<i>Fusobacterium nucleatum</i>	6/6	100	3/3	100	0.0
<i>Fusobacterium varium</i>	3/3	100	2/2	100	0.0
<i>Gardnerella vaginalis</i>	2/2	100	2/3	66.7	33.3
Gram-negative anaerobic rods²					
<i>Porphyromonas</i>					
<i>Porphyromonas</i>	5/5	100	1/1	100	0.0
<i>Porphyromonas asaccharolytica</i>	1/1	100	3/6	50.0	50.0
<i>Porphyromonas asaccharolytica</i>	5/5	100	1/1	100	0.0
<i>Porphyromonas gingivitis</i>	2/2	100	5/6	83.3	16.7
<i>Prevotella</i>					
<i>Prevotella blava</i>	4/4	100	-	-	-
<i>Prevotella buxae</i>	-	-	5/5	100	0.0
<i>Prevotella buxae</i>	5/5	100	2/2	100	0.0
<i>Prevotella corporis</i>	1/1	100	3/3	100	0.0
<i>Prevotella denticola</i>	0/1	0.0	-	-	0.0
<i>Prevotella divisa</i>	-	-	-	-	-
<i>Prevotella heparinolytica</i>	-	-	1/1	100	-
<i>Prevotella intermedia</i>	8/9	88.9	1/1	100	-
<i>Prevotella intermedia</i>	-	-	3/3	100	-11.1

Total Isolates	Treatment Group				Observed Difference (A-B) %
	MK-0826 1 g (A) (N=203)		Piperacillin/Tazobactam (B) (N=193)		
	n/m	Observed Response % (95% CI)	n/m	Observed Response % (95% CI)	
<i>Prevotella melaninogenica</i>	4/4	100	2/2	100	0.0
<i>Prevotella oralis</i>	1/1	100	-	-	-
<i>Prevotella proteococcus</i>	1/1	100	-	-	-
<i>Actinomyces fermentans</i>	1/1	100	-	-	-
Gram-Negative Anaerobic Cocci	2/2	100	1/1	100	0.0
<i>Fusillanella</i>	1/1	100	3/3	100	0.0
Bacteria	-	-	2/2	100	0.0
Bacteria	-	-	1/1	100	0.0
Other Bacteria	-	-	1/1	100	-
Other Bacteria	5/5	100	3/4	75.0	25.0
Aerobic gram-variable rods ¹	-	-	1/1	100	-
Anaerobes, gram-negative ²	1/1	100	-	-	-
Gram-negative bacteria ²	1/1	100	-	-	-
Gram-negative rods ²	1/1	100	-	-	-
Gram-positive bacteria ¹	1/1	100	1/2	50.0	-
Gram-positive rods ¹	1/1	100	-	-	50.0
	1/1	100	1/1	100	0.0

¹ Computed from an exact statistical model pooling across strata.
² These organisms were not further categorized by the investigative site.
N = Number of microbiologic evaluable patients 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 48, Volume 13 of 22, pages 167-175)

**Proportion of Favorable Microbiologic 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 1 g (A) (N=9)		Piperacillin/Tazobactam (B) (N=17)		
	n/m	Observed Response % (95% CI)	n/m	Observed Response % (95% CI)	
Gram-Positive Aerobic Cocci	1/1	100	7/7	100	0.0
<i>Enterococcus faecalis</i>	-	-	1/1	100	-
<i>Micrococcus</i>	-	-	1/1	100	-
<i>Staphylococcus</i> , coagulase negative	-	-	3/3	100	-
<i>Streptococcus</i> (Group D)	-	-	1/1	100	-
<i>Streptococcus pneumoniae</i>	-	-	1/1	100	-
<i>Viridans Streptococcus</i> group	1/1	100	-	-	-
Gram-Negative Aerobic Rods	7/7	100	7/7	100	0.0
<i>Acinetobacter</i>	-	-	1/1	100	-
<i>Acinetobacter calcoaceticus</i>	2/2	100	1/1	100	-
<i>Escherichia coli</i>	3/3	100	3/3	100	0.0
<i>Klebsiella oxytoca</i>	1/1	100	-	-	0.0
<i>Klebsiella pneumoniae</i>	-	-	-	-	-
<i>Pantoea agglomerans</i>	-	-	1/1	100	-
<i>Proteus vulgaris</i>	1/1	100	1/1	100	-
Gram-Positive Anaerobic Rods	-	-	1/1	100	-
<i>Proptombacterium</i>	-	-	1/1	100	-
Gram-Negative Anaerobic Rods	1/1	100	1/1	100	0.0
<i>Bacteroides</i>	1/1	100	1/1	100	0.0
Other Bacteria	-	-	1/1	100	0.0
Gram-negative rods¹	-	-	1/1	100	-

¹ Computed from a statistical model pooling across strata.
² These organisms were not further categorized by the investigative site.
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.

(Applicant's Table 49, Volume 13 of 22, page 177)

Protocol 017
Applicant's MITT Efficacy Analyses

Appendix 8

Original table from November 30, 2000 NDA 21,337 submission:

Proportion of Patients With Favorable Clinical Response Assessments
in the Microbiological MITT Population
(Estimated)
1-g and 1.5-g Cohort Combined

Time Point	Treatment Group				Estimated [†] Difference (A-B) (%) (95% CI)
	MK-0826 1g or 1.5g (A) (N=264)		Piperacillin/Tazobactam(B) (N=259)		
	n	Estimated [†] Response (%) (95% CI)	n	Estimated [†] Response (%) (95% CI)	
Test of Cure	264	81.8 (77.3, 86.3)	259	77.0 (72.1, 81.9)	4.8 (-2.3, 11.9)

[†] Computed from a statistical model adjusting for strata.
N = Number of microbiological MITT patients in each treatment group at the test-of-cure visit.
n = Number of microbiological MITT patients included in the analysis.
CI = Confidence Interval.

(Applicant's Table 54, Volume 13 of 22, page 201)

Revised table from April 4, 2001, Amendment to NDA 21,337:

Proportion of Patients With Favorable Clinical Response Assessment-
Microbiological MITT Population (Revised MITT Analysis)
(Estimated[†])
1-g and 1.5-g Cohort Combined
Protocol 017

Time Point	Treatment Group				Estimated [†] Difference (A-B) (95% CI)
	Ertapenem 1g or 1.5g (A) (N=264)		Piperacillin/Tazobactam 3.375g (B) (N=259)		
	n	Estimated [†] Response % (95% CI)	n	Estimated [†] Response % (95% CI)	
Test of Cure	264	76.9 (72.0, 81.8)	259	70.7 (65.4, 76.0)	6.2 (-1.4, 13.8)

[†] Computed from a statistical model adjusting for strata.
N = Number of microbiological MITT patients in each treatment group at the Test of Cure visit.
n = Number of microbiological MITT patients included in the analysis.
CI = Confidence Interval.

Protocol 023

Appendix 9

Schedule of Clinical Observations and Laboratory Measurements

Procedures/Assessments	Eligibility Screening		Study Antibiotic During IV Antibiotic Therapy	Discontinuation of IV Therapy (Final Day)	Follow-Up Period (Posttherapy) Follow-Up (2 to 4 Weeks)
	≤24 Hours Prior to Study Therapy	IV Antibiotic Therapy			
Medical history	X				
Complete physical examination	X				
Targeted physical examination	X				
Pelvic examination	X		Day 3, 4, or 5	X	X
Vital signs	X			X ¹	X
Assessment of pelvic signs and symptoms	X		daily	X	X
Summary of case	X		daily	X	X
Assessment of Clinical Outcome	X		X	X	X
Blood and urine for safety tests	X		Day 3, 4, or 5 then every 4 to 5 days	X	X
Monitor for adverse experiences	X		daily	X	X ¹
Monitor for local tolerability	X		daily	X	X ¹
Site of infection culture	X		daily	X	X ¹
Blood culture (if clinically indicated)	X			As clinically indicated	
Other site culture	X			As clinically indicated, or if prestudy culture was positive, draw at 48 to 72 hours and follow-up	
Assessment of Microbiologic Outcome	X			As clinically indicated	
Serum B-hCG ²	X			X	X

¹ Pelvic examination (with cultures) must have been performed at the time of discontinuation of IV therapy only in the setting of clinical failure.
² With study entry and any subsequent procedure.
³ Clinical failures must have had safety laboratory tests performed at 2 weeks posttherapy visit; all others had safety laboratory tests at 2- to 4-week follow-up visit.
⁴ Monitored for adverse experiences for 14 days after the completion of study therapy.
⁵ These assessments were used to determine microbiologic outcome.
⁶ Serum B-Human Chorionic Gonadotropin was required only for women who were neither postpartum, nor posthysterectomy, and who were of childbearing potential. Required for all women of childbearing potential, except postpartum women enrolled within 2 weeks of delivery.

(Applicant's Table 1, Volume 20 of 22, page 38)

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Protocol 023

Appendix 10

**Patient Accounting
(Randomized Population)**

	MK-0826	Piperacillin/ Tazobactam	Total
ENTERED:	216	196	412
Female (age range)	216 (15 to 53)	196 (16 to 68)	412 (15 to 68)
COMPLETED THERAPY:	182	168	350
DISCONTINUED THERAPY:	34	28	62
Clinical adverse experience	12	8	20
Laboratory adverse experience	0	0	0
Lost to follow-up	0	0	0
Deviation from protocol	7	2	9
Withdrew from study	1	1	2
Inclusion/exclusion criteria not met	2	2	4
Clinical/microbiologic failure	6	8	14
Patient withdrew consent	4	7	11
Patient had no medical insurance	1	0	1
Personal reasons	1	0	1
COMPLETED STUDY:	190	177	367
DISCONTINUED STUDY:	26	19	45
Clinical adverse experience	4	1	5
Laboratory adverse experience	0	0	0
Lost to follow-up	7	8	15
Deviation from protocol	4	0	4
Withdrew from study	0	1	1
Inclusion/exclusion criteria not met	2	1	3
Clinical/microbiologic failure	4	2	6
Patient withdrew consent	4	6	10
Patient had no medical insurance	1	0	1
All patients were female.			

(Applicant's Table 13, volume 20 of 22, page 72)

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Appendix 11

Protocol 023

Number of Patients Entered by Investigator and Treatment Group
(Clinically Evaluable)

Study Number	Investigator	Location	MK-0826 (N=216)			Piperacillin/ Tazobactam (N=196)		
			Enrolled	Eval	% Eval	Enrolled	Eval	% Eval
023002	McGregor, James A.	Denver, CO	1	1	100%	0	-	-
023003	Sweet, Richard	Pittsburgh, PA	4	3	75%	0	-	-
023005	Martens, Mark	Minneapolis, MN	6	6	100%	5	5	100%
023006	Roy, Subir	Los Angeles, CA	18	15	83%	19	18	95%
023007	Hemsell, David L.	Dallas, TX	6	2	33%	6	3	50%
023008	Gilstrap, Larry	Houston, TX	4	4	100%	4	4	100%
023009	O'Brien, William	Tampa, FL	4	2	50%	1	1	100%
023010	Stovall, Thomas G.	New York, NY	7	6	86%	7	5	71%
023011	Ledger, William J.	New York, NY	1	1	100%	2	1	50%
023013	McNeeley, S. Gene	Detroit, Michigan	4	2	50%	6	4	67%
023014	Maurizio, Maccato	Houston, TX	1	1	100%	0	-	-
023016	Duff, Patrick W.	Gainesville, FL	1	0	-	0	-	-
023017	Ismail, Mahmoud	Chicago, IL	8	6	75%	7	6	86%
023018	Chatwani, Ashwin	Philadelphia, PA	8	0	-	7	5	71%
023020	Coonrod, Dean Victor	Phoenix, AZ	7	6	86%	7	4	57%
023024	Lindeque, Baren Ger	Canada	3	0	-	2	2	100%
023025	De Jonge, Eric Tony	Canada	5	1	20%	1	1	100%
023026	Msibi, Thembeni Luci	Canada	3	2	67%	2	2	100%
023027	Angel Muller, Edith	Colombia	13	11	85%	13	11	85%
023028	Garcia-Lara, Enrique	Mexico	4	2	50%	3	3	100%
023029	Aldini, Amadeo	Argentina	10	8	80%	10	10	100%
023030	Lipszyc, Pedro Saul	Argentina	7	6	86%	8	6	75%
023031	Sander, Kay	Costa Rica	12	9	75%	13	11	85%
023033	Judlin, Philippe	Belgium	3	3	100%	1	0	-
023034	Ciudad, Manuel Anton	Peru	13	12	92%	13	10	77%
023035	Trelles, Juan Gualbe	Peru	10	10	100%	10	9	90%
023038	Gall, Stanley	Louisville, KY	5	4	80%	8	2	25%
023039	Baker, David A.	Stony Brook, NY	3	3	100%	1	1	100%
023040	Carmona Pertuz, Vice	Columbia	3	2	67%	2	2	100%
023041	Millar, Lynnae K.	Honolulu, HI	0	-	-	1	0	-
023043	Higareda, Iliana	Mexico	13	12	92%	14	10	71%
023044	Newton, Ed	Greenville, NC	2	0	-	0	-	-
023051	Magann, Everett	Jackson, MS	4	4	100%	3	3	100%
023052	Benrubi, Guy	Jacksonville, FL	1	0	-	2	1	50%
023053	Goepfert, Alice	Birmingham, AL	6	6	100%	7	6	86%
023054	Devoe, Lawrence	Augusta, GA	1	1	100%	0	-	-
023055	Parker, R. Lamar	Winston-Salem, NC	1	1	100%	2	2	100%
023056	Heyl, Peter	Norfolk, VA	0	0	-	1	0	-
023058	Korn, Abner	San Francisco, CA	1	0	-	0	-	-
023059	Van Nostrand, Kristi	Oklahoma City, OK	2	1	50%	1	1	100%
023061	Harrison, Mark	Berrien Center, MI	2	2	100%	0	-	-
023062	Apuzzio, Joseph	Newark, NJ	0	-	-	1	0	-
023064	Jacob, Denis	France	1	1	100%	1	1	100%
023066	Davidov, Alexander	Russia	5	5	100%	4	3	75%
023067	Savelieva, Galina	Russia	1	1	100%	0	-	-
023068	Malafaia, Osvaldo	Brazil	1	0	-	1	0	-
023071	Greig, Phillip	Greenville, SC	1	1	100%	0	-	-

(Modified Applicant's Tables 15 and 16, Volume 20 of 22, pages 76-77)

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**Protocol 023
Clinical MITT**

Appendix 12

Original table from November 30, 2000 NDA 21,337 submission:

**Proportion of Patients With a Favorable Clinical Response Assessment
in the Clinical MITT Population
(Estimated)**

Treatment Group		Piperacillin/Tazobactam (B) (N=191)		Estimated [†] Difference (A-B) % (95% CI)
MK-0826 (A) (N=211)		Piperacillin/Tazobactam (B) (N=191)		
n	Estimated [†] Response % (95% CI)	n	Estimated [†] Response (%) (95% CI)	
211	85.9 (81.2, 90.6)	191	88.0 (83.3, 92.6)	-2.1 (-9.2, 5.0)

[†] Computed from a statistical model adjusting for strata.
N=Number of clinical MITT patients in each treatment group.
n=Number of clinical MITT patients included in the analysis.
CI=Confidence interval.

(Applicant's Table 46, Volume 20 of 22, page 170)

Revised table from April 4, 2001, Amendment to NDA 21,337:

**Proportion of Patients With Favorable Clinical Response Assessment-
Clinical MITT Population (Revised MITT Analysis)
(Estimated[†])
Protocol 023**

Time Point	Treatment Group				Estimated [†] Difference (A-B)	
	Ertapenem 1g (A) (N=211)		Piperacillin/Tazobactam 3.375g (B) (N=191)			
	n	Estimated [†] Response % (95% CI)	n	Estimated [†] Response % (95% CI)		
Test of Cure	211	82.0 (76.8, 87.3)	191	83.8 (78.6, 89.1)	-1.8	(-9.7, 6.1)

[†] Computed from a statistical model adjusting for strata.
N = Number of clinical MITT patients in each treatment group at the Test of Cure visit.
n = Number of clinical MITT patients included in the analysis.
CI = Confidence Interval.

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Protocol 023
Microbiologic MITT

Original table from November 30, 2000 NDA 21,337 submission:

Proportion of Patients With a Favorable Microbiological Response Assessment
in the Microbiological MITT Population
(Estimated)

Treatment Group						Estimated [†] Difference (A-B) % (95% CI)
MK-0826 (A) (N=161)			Piperacillin/Tazobactam (B) (N=158)			
n	Estimated [†] Response % (95% CI)		n	Estimated [†] Response % (95% CI)		
161	87.6	(82.5, 92.7)	158	88.6	(83.6, 93.6)	-1.0 (-8.8, 6.8)

[†] Computed from a statistical model adjusting for strata.
N=Number of microbiological MITT patients in each treatment group.
n=Number of microbiological MITT patients included in the analysis.
CI=Confidence interval.

(Applicant's Table 47, Volume 20 of 22, page 171)

Revised table from April 4, 2001, Amendment to NDA 21,337:

Proportion of Patients With Favorable Microbiological Response Assessment-
Microbiological MITT Population (Revised MITT Analysis)
(Estimated[†])
Protocol 023

Time Point	Treatment Group					Estimated [†] Difference (A-B) % (95% CI)	
	Ertapenem 1g (A) (N=161)			Piperacillin/Tazobactam 3.375g (B) (N=158)			
	n	Estimated [†] Response % (95% CI)		n	Estimated [†] Response % (95% CI)		
Test of Cure	161	83.9	(78.2, 89.6)	158	84.8	(79.2, 90.4)	-0.9 (-9.6, 7.7)

[†] Computed from a statistical model adjusting for strata.
N = Number of microbiological MITT patients in each treatment group at the Test of Cure visit.
n = Number of microbiological MITT patients included in the analysis.
CI = Confidence Interval.

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Appendix 13

Protocol 018

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Schedule of Clinical Observations and Laboratory Measurements (Protocol 018)

Procedures/Assessments	Eligibility Screening <24 Hours Prior to Study Therapy	Day 1	Parenteral Study On Therapy Days 3, 4, or 5	Antibiotic Treatment Period During Parenteral Therapy Days 5 to 14	Discontinuation of Parenteral Therapy [†]	Posttherapy Period	
						Early Follow-Up 7 to 14 Days (Test of Cure)	Late Follow-Up 21 to 28 Days
Medical history	X		X		X	X	X
Physical examination (complete)	X		X		X	X	X
Physical examination (targeted)	X		X		X	X	X
Vital signs	X		X [§]		X	X	X [§]
Signs and symptoms	X		X		X	X	X
Chest x-ray	X		X		X	X	X
O2 saturation	X		X		X	X	X
Assessment of clinical outcome	X		X		X	X	X
Sera for antibody testing	X		X		X	X	X
Blood and urine for safety tests	X	X	X	Every 5 to 5 days	X	X	X
Monitor for adverse experiences [†]	X	X	Daily	Daily	X	X	X
Monitor for local tolerability	X		Daily	Daily	X	X	X
Sputum culture and Gram stain [‡]	X		X [¶]		X [¶]	X [¶]	X [¶]
Sputum AFB smear and culture	X		X [¶]		X [¶]	X [¶]	X [¶]
Blood culture	X		X [¶]	As clinically indicated	X [¶]	X [¶]	X [¶]

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Schedule of Clinical Observations and Laboratory Measurements (Protocol 018)

Procedures/Assessments	Eligibility		Parenteral Study Antibiotic Treatment Period [†]		Discontinuation of Parenteral Therapy [†]	Posttherapy Period	
	Screening <24 Hours Prior to Study Therapy	Day 1	On Therapy Days 3, 4, or 5	During Parenteral Antibiotic Therapy Days 6 to 14		Early Follow-Up (7 to 14 Days) (Test of Cure)	Late Follow-Up (21 to 28 Days)
Legionella Ag (urine or sputum)	X						
Assessment of microbiologic outcome							
Drug levels	X [¶]	X	X		X		
Serum β-hCG [¶]	X						X
Compliance with oral antibiotics							
If patient was switched to oral antibiotic therapy during study, he/she was monitored according to the investigator's usual clinical practice while on oral therapy.							
Minimum of 3 days parenteral therapy required prior to switch to oral therapy.							
If clinical response was suboptimal.							
If laboratory studies (laboratory safety tests) were performed 2 days before the discontinuation of parenteral therapy and were normal, then repeat blood draws were not required at discontinuation of parenteral therapy visit.							
Daily while on parenteral therapy and for at least 14 days after discontinuation of study agents (parenteral or oral).							
For this evaluation, material for culture from other respiratory tract sources, if available, could have been used.							
Only valid specimens were to be submitted for culture.							
If eligibility screening blood culture was positive then a repeat blood culture had to be done at 48 to 72 hours poststudy entry, and at the EFU visit.							
Baseline samples could have been used to generate protein binding curves at selected study sites only.							
Drug levels measured 6 and 12 hours postdose on Day 1 and Day 3 of parenteral therapy at selected study sites only.							
Serum levels of α-human chorionic gonadotropin only for women of childbearing potential.							

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Protocol 018

Appendix 14

Patient Accounting
(Randomized Population)

ENTERED: Total	MK-0826		Ceftriaxone	Total		
	244		258	502		
Male (age range)	142 (17 to 90)		145 (18 to 96)	287 (17 to 96)		
Female (age range)	102 (18 to 92)		113 (17 to 92)	215 (17 to 92)		
COMPLETED:	COMPLETED THERAPY			COMPLETED STUDY		
	MK-0826	Ceftriaxone	Total	MK-0826	Ceftriaxone	Total
DISCONTINUED: Total	199	213	412	203 [†]	228	431 [†]
Clinical adverse experience	45	45	90	40	30	70
Laboratory adverse experience	18	17	35	13	11	24
Lost to follow-up	1	0	1	1	0	1
Deviation from protocol	4	3	7	5	6	11
Withdrew from study	-4	3	7	3	2	5
Inclusion/exclusion criteria not met	2	1	3	2	0	2
Clinical/microbiologic failure	6	0	6	4	0	4
Patient withdrew consent	3	8	11	4	2	6
Pathogen resistant	5	6	11	5	5	10
Mycobacterial species identified	0	2	2	0	1	1
Personal reasons	0	1	1	1	0	1
Tuberculosis identified	1	1	2	1	1	2
Confounder illness	0	2	2	0	1	1
	1	1	2	1	1	2

[†] One additional patient (AN 7061) completed the study according to the protocol but did not have study status recorded in the clinical database and is not counted here.

Applicant's Table 14, Volume 15 of 22, page 79.

Patient Accounting
(Clinically Evaluable Population)

ENTERED: Total	MK-0826		Ceftriaxone	Total		
	182		201	383		
Male (age range)	107 (17 to 90)		115 (18 to 96)	222 (17 to 96)		
Female (age range)	75 (18 to 92)		86 (17 to 92)	161 (17 to 92)		
COMPLETED:	COMPLETED THERAPY			COMPLETED STUDY		
	MK-0826	Ceftriaxone	Total	MK-0826	Ceftriaxone	Total
DISCONTINUED: Total	173	187	360	176 [†]	196	372 [†]
Clinical adverse experience	9	14	23	5	5	10
Laboratory adverse experience	7	7	14	3	3	6
Lost to follow-up	0	0	0	0	0	0
Deviation from protocol	0	0	0	0	0	0
Clinical/microbiologic failure	0	1	1	0	0	0
	2	6	8	2	2	4

[†] One additional patient (AN 7061) completed the study according to the protocol but did not have study status recorded in the clinical database.

Applicant's Table 15, Volume 15 of 22, page 80.

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Appendix 15

Number of Patients (Protocol 018) Entered and Clinically Evaluable by Investigator and Treatment Group
(Randomized Population)

Study Number	Investigator	Location	MK-0826 N=244			Ceftriaxone N=258		
			Enrolled	Eval	% Eval	Enrolled	Eval.	% Eval
018001	Boylen, C. Thomas	Los Angeles, CA	4	0	-	3	2	67%
018002	Dunbar, Lala	New Orleans, LA	6	4	67%	6	4	67%
018003	Farkas, Stephen	Akron, OH	9	4	44%	11	8	73%
018004	Fogarty, Charles	Spartanburg, SC	10	8	80%	9	7	78%
018005	Geckler, Ronald	Baltimore, MD	7	6	86%	7	6	86%
018006	Hawes, Jr. Stephen	Charlotte, NC	1	1	100%	2	1	50%
018007	Fuller, Michael	Savannah, GA	2	2	100%	2	1	50%
018009	Nelson, Michael	Shawnee Mission, KA	7	5	71%	6	5	83%
018011	Player, Rick	Birmingham, AL	4	2	50%	4	2	50%
018012	Beneitone, Roger J.	Springfield, MA	4	3	75%	6	4	67%
018014	Caballero Lopez, Jose	Peru	14	11	77%	12	11	92%
018015	Ortiz-Ruiz, Guillermo	Colombia	19	16	84%	17	15	88%
018016	Herrera, Maria	Chile	1	1	100%	0	0	-
018017	Lopardo, Gustavo	Argentina	2	1	50%	2	2	100%
018018	Jasovich, Abel	Argentina	10	7	70%	10	9	90%
018020	Correa da Silva, Luiz	Brazil	7	7	100%	10	9	90%
018021	Montes de Oca, Maria	Venezuela	12	11	92%	12	10	83%
018022	Parkes, Scott Nicholas	Canada	1	1	100%	2	0	-
018023	Bremner, Peter	Australia	13	9	69%	12	10	83%
018024	Rubinfield, Abraham	Canada	4	3	75%	3	2	67%
018025	Phillips, Martin	Australia	6	6	100%	6	5	83%
018026	Morales-Reyes, Juan	Mexico	9	8	89%	11	11	100%
018027	Gremillion, David	Raleigh, NC	5	1	20%	5	3	60%
018028	Koffler, Howard	Sellersville, PA	13	10	77%	13	9	69%
018029	Santiago, Silverio	Los Angeles, CA	0	0	-	1	1	100%
018030	Levison, Matthew E.	Philadelphia, PA	0	0	-	1	0	-
018031	Reinhardt, John F.	Newark, DE	3	3	100%	5	3	60%
018033	Standiford, Harold C.	Baltimore, MD	3	2	67%	3	1	33%
018034	Filler, Scott G.	Torrance, CA	2	?	60%	2	0	-
018036	Many, Wickliffe J.	Montgomery, AL	5	3	60%	4	4	100%
018037	Maslow, Melanie	New York, NY	3	3	100%	3	3	100%
018038	Siami, Ghodrat	Nashville, TN	6	3	50%	7	3	43%
018041	Ramirez, Julio	Louiseville, KY	0	0	-	1	1	100%
018043	Frank, Elliot	Neptune, NJ	6	2	33%	8	2	25%
018045	Reed, Kevin	Baton Rouge, LA	2	2	100%	2	2	100%
018048	Uribe, Alfonso	Peru	2	2	100%	4	3	75%
018052	Moser, Roy	Crestview Hills, KY	1	0	-	0	0	-
018053	Lampasso, James G.	Williamsville, NY	1	1	100%	0	0	-
018055	Tan, Keng	Singapore	1	0	-	1	0	-
018056	Sinopalnikov, Alexander	Moscow	6	4	67%	8	7	88%
018058	Hincapie, Gustavo	Colombia	8	7	88%	7	7	100%
018059	Cipullo, Jose Paulo	Brazil	10	8	80%	9	8	89%
018061	Noriega-Ricalde, Luis	Chile	5	5	100%	7	6	86%
018063	Dalhoff, Klaus	Germany	0	0	-	1	1	100%
018065	Richards, Guy Anthony	South Africa	3	3	100%	5	5	100%
018067	Singh, Gagrath	New Zealand	2	2	100%	3	3	100%
018068	Godfrey, Catherine	New Zealand	4	2	50%	4	4	100%
018069	Langton, David	Australia	0	0	-	1	1	100%
018070	Gonzalez-Fuenzalida, Saul	Chile	1	1	100%	0	0	-

(Modified Applicant's Tables 16 and 17, volume 15 of 22, pages 83-85)

Appendix 16

Protocol 018

Oral Switch Agents by Treatment Group
(Clinically Evaluable Population)

	MK-0826 (N=182)		Ceftriaxone (N=201)		Total (N=383)	
	n	(%)	n	(%)	n	(%)
No oral therapy	17	(9.3)	21	(10.4)	38	(9.9)
Received oral therapy	165	(90.7)	180	(89.6)	345	(90.1)
Amoxicillin	2	(1.1)	2	(1.0)	4	(1.0)
Amoxicillin/clavulanate	132	(72.5)	146	(72.6)	278	(72.6)
Amoxicillin/clavulanate 500 mg/125 mg	0	(0.0)	2	(1.0)	2	(0.5)
Amoxicillin/clavulanate 875 mg/125 mg	20	(11.0)	19	(9.5)	39	(10.2)
Azithromycin						
Cefaclor	1	(0.5)	0	(0.0)	1	(0.3)
Ceftin	1	(0.5)	4	(2.0)	5	(1.3)
Cefuroxime	3	(1.6)	0	(0.0)	3	(0.8)
Ciprofloxacin	0	(0.0)	1	(0.5)	1	(0.3)
Clarithromycin	2	(1.1)	2	(1.0)	4	(1.0)
Erythromycin	1	(0.5)	0	(0.0)	1	(0.3)
Levaquin	1	(0.5)	0	(0.0)	1	(0.3)
Levofloxacin	0	(0.0)	4	(2.0)	4	(1.0)
Roxithromycin	1	(0.5)	0	(0.0)	1	(0.3)
Trovaflaxacin	3	(1.6)	1	(0.5)	4	(1.0)
	1	(0.5)	0	(0.0)	1	(0.3)

N = The number of patients per treatment group.
n = The total number of patients with the therapy.

(Applicant's Table 29, Volume 15 of 22, page 109)

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Appendix 17

Protocol 018

Original table from November 30, 2000 NDA 21,337 submission:

Table 50

Proportion of Patients With a Favorable Clinical Response Assessment
in the Clinical MITT Population
(Estimated[†])

		Treatment Group					
		MK-0826 (A) (N=236)		Ceftriaxone (B) (N=250)			
n	Estimated [†] Response (95% CI)		n	Estimated [†] Response (95% CI)		Estimated [†] Difference (A-B) (95% CI)	
	%			%		%	
236	85.1	(80.6, 89.6)	250	85.0	(80.5, 89.4)	0.1	(-6.6, 6.9)

[†] Computed from a statistical model adjusting for strata.
N = Number of clinical MITT patients in each treatment group.
n = Number of clinical MITT patients included in the analysis.
CI = Confidence interval.

Data Source: [4.1.11; 4.1.15]

Revised table from April 4, 2001, Amendment to NDA 21,337 submission:

Table 15

Proportion of Patients With Favorable Clinical Response Assessment-
Clinical MITT Population (Revised MITT Analysis)
(Estimated[†])
Protocol 018

		Treatment Group					
		Ertapenem Ig (A) (N=236)		Ceftriaxone Ig (B) (N=250)			
Time Point	n	Estimated [†] Response (95% CI)		n	Estimated [†] Response (95% CI)		Estimated [†] Difference (A-B) (95% CI)
		%			%		
Test of Cure	236	80.1	(75.0, 85.1)	250	82.1	(77.4, 86.9)	-2.1 (-9.4, 5.3)

[†] Computed from a statistical model adjusting for strata.
N = Number of clinical MITT patients in each treatment group at the Test of Cure visit.
n = Number of clinical MITT patients included in the analysis.
CI = Confidence Interval.

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Protocol 018

Original table from November 30, 2000 NDA 21,337 submission:

**Proportion of Patients With Favorable Microbiological Response Assessments
in the Microbiological MITT Population
(Observed[†] Data)**

Time Point	Treatment Group					Observed Difference (A-B) %	
	MK-0826 (A) (N=118)			Ceftriaxone (B) (N=136)			
	n/m	Observed [†] Response %	(95% CI)	n/m	Observed [†] Response %		(95% CI)
Test of Cure	111/118	94.1	(89.8, 98.3)	124/136	91.2	(86.4, 96.0)	2.9

[†] Computed from a statistical model pooling across strata.
 N = Number of microbiological modified intent-to-treat (MITT) patients in each treatment group at the test of cure visit.
 n/m = Number of microbiological MITT patients with favorable assessment/number of microbiological MITT patients with assessment at the visit.
 CI = Confidence interval.

(Applicant's Table 51, Volume 15 of 22, page 140)

Revised table from April 4, 2001, Amendment to NDA 21,337 submission:

**Proportion of Patients With Favorable Microbiological Response Assessment-
Microbiological MITT Population (Revised MITT Analysis)
(Observed[†])
Protocol 018**

Time Point	Treatment Group					Observed [†] Difference (A-B) %	
	Ertapenem 1g (A) (N=118)			Ceftriaxone 1g (B) (N=136)			
	n/m	Observed [†] Response %	(95% CI)	n/m	Observed [†] Response %		(95% CI)
Test of Cure	106/118	89.8	(84.4, 95.3)	119/136	87.5	(81.9, 93.1)	2.3

[†] Computed from a statistical model pooling across strata.
 N = Number of microbiological MITT patients in each treatment group at the Test of Cure visit.
 n/m = Number of microbiological MITT patients with favorable assessment/number of microbiological MITT patients with assessment at the visit.
 CI = Confidence Interval.

Appendix 18

Protocol 020

Schedule of Clinical Observations and Laboratory Measurements

Procedures/Assessments	Eligibility Screening	Parenteral Study Antibiotic Treatment Period				Posttherapy Period After Discontinuation of All Study Agents (Parenteral and Oral)	
	24 Hours Prior to Study Therapy	Day 1	On Therapy Day 3, 4, or 5	During Parenteral Antibiotic Therapy Days 6 to 14	Discontinuation of Parenteral Therapy	Early Follow-Up 7 to 14 Days (Test of Cure)	Late Follow-Up 21 to 28 Days
Medical history	X						
Physical examination (complete)	X						
Physical examination (focused)			X				
Vital signs	X		X		X	X	X
Signs and symptoms	X		X		X	X	X
Chest X-ray	X		X		X	X	X
Cultures	X		X		X	X	X
Assessment of clinical outcome	X		X		X	X	X
Specs for antibiotic testing	X				X	X	
Blood and urine for safety	X		X		X	X	X
Monitor for adverse experiences*		X	Daily	Every 4 to 5 Days	X	X	X
Monitor for local tolerability		X	Daily	Daily	X	X	
Specimen culture and Gram stain†	X		X	Daily	X		
Specimen acid-fast bacillus (AFB) stain and culture	X		X		X	X	X
Blood culture	X		X		X		
Legionella Ag (urine and/or sputum)	X		X		X		
Assessment of microbiologic outcome					X	X	X
Drug levels	X	X	X				
Seven B-HCG‡	X						
Compliance with oral antibiotics						X	

* If patient was switched to oral antibiotic therapy during study, he/she was monitored according to the investigator's usual clinical practice while on oral therapy.
 † Minimum of 3 days parenteral therapy required prior to switch to oral therapy.
 ‡ If laboratory studies (laboratory reference) were performed 1 day before the discontinuation of parenteral therapy and were normal, these repeat blood draws were not required at parenteral discontinuation visit.
 • Daily while on parenteral therapy and for at least 14 days after discontinuation of study agents (parenteral or oral).
 • For this evaluation, material for culture from other respiratory tract sources, if available, could have been used.
 • Only valid specimens were to be submitted for culture.
 • If clinically indicated.
 • If eligibility screening blood culture was positive then a repeat blood culture had to be done at 48 to 72 hour poststudy entry, and at the early follow-up visit.
 • Baseline samples could have been used to generate protein binding curves at selected study sites only.
 • Drug levels measured 6 and 12 hours postdose on Day 1 and Day 3 of parenteral therapy at selected study sites only.
 • Only for sources of chills/rigors potential.

(Applicant's Table 1, Volume 17 of 22, pages 39-40)

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Protocol 020

Appendix 19

Patient Accounting
(Randomized Population)

	MK-0826	Ceftriaxone	Total
ENTERED: Total	239	125	364
Male (age range)	149 (18 to 97)	74 (19 to 89)	223 (18 to 97)
Female (age range)	90 (23 to 92)	51 (20 to 96)	141 (20 to 96)
COMPLETED THERAPY:	197	103	300
DISCONTINUED THERAPY:	42	22	64
Clinical adverse experience	15	9	24
Laboratory adverse experience	0	1	1
Lost to follow-up	4	2	6
Deviation from protocol	5	2	7
Inclusion/exclusion criteria not met	3	3	6
Clinical/microbiologic failure	7	4	11
Patient withdrew consent	6	0	6
Pathogen resistant	1	0	1
Positive AFB test	0	1	1
Confounding illness	1	0	1
COMPLETED STUDY:	209	110	319
DISCONTINUED STUDY:	30	15	45
Clinical adverse experience	9	6	15
Laboratory adverse experience	0	0	0
Lost to follow-up	7	2	9
Deviation from protocol	1	1	2
Inclusion/exclusion criteria not met	2	2	4
Clinical/microbiologic failure	4	3	7
Patient withdrew consent	6	0	6
Positive AFB test	0	1	1
Confounding illness	1	0	1

(Applicant's Table 18, Volume 17 of 22, page 81)

Patient Accounting (Microbiologically Evaluable Population)

	MK-0826	Ceftriaxone	Total
ENTERED: Total	100	49	149
Male (age range)	66 (18 to 90)	29 (24 to 89)	95 (18 to 90)
Female (age range)	34 (23 to 89)	20 (20 to 93)	54 (20 to 93)
COMPLETED THERAPY:	94	45	139
DISCONTINUED THERAPY:	6	4	10
Clinical adverse experience	2	0	2
Laboratory adverse experience	0	0	0
Lost to follow-up	0	0	0
Deviation from protocol	0	0	0
Clinical/microbiologic failure	4	4	8
COMPLETED STUDY:	97	47	144
DISCONTINUED STUDY:	3	2	5
Clinical adverse experience	1	0	1
Laboratory adverse experience	0	0	0
Lost to follow-up	0	0	0
Deviation from protocol	0	0	0
Clinical/microbiologic failure	2	2	4

(Applicant's Table 19, Volume 17 of 22, page 82)

Protocol 020

Appendix 20

Number of Patients (Protocol 020) Entered and Microbiologically Evaluable by Investigator and Treatment Group
(Randomized Population)

Study Number	Investigator	Location	MK-0826 N=244			Ceftriaxone N=258		
			Enrolled	Eval	% Eval	Enrolled	Eval.	% Eval
020002	Greiger, Paola	Mount Vernon, NY	7	2	29%	3	1	33%
020005	Chmel, Herman	Trenton, NJ	13	5	38%	7	5	71%
020011	James, Adrian	New Orleans, LA	5	2	40%	3	1	33%
020013	Dedhia, Harakh	Morgantown, WV	1	1	100%	1	0	-
020016	Fidelholtz, James I.	Cincinnati, OH	1	0	-	1	0	-
020018	Giessel, Glenn	Richmond, VA	3	1	33%	2	1	50%
020021	Honsinger, Richard	Los Alamos, NM	2	1	50%	4	1	25%
020024	Krumpe, Peter	Ren, NV	2	2	100%	3	2	67%
020026	Pesin, Jeffrey	Edison, NJ	4	1	25%	2	1	50%
020028	Rainey, Deborah	Jackson, TN	7	2	29%	3	1	33%
020029	Blumer, Jeffrey L.	Cleveland, OH	1	0	-	0	0	-
020032	Simon, Stuart	Austell, GA	30	3	10%	16	1	6%
020036	Cambroner-Hernandez, E.	Costa Rica	17	12	71%	8	3	38%
020037	Graninger, Wolfgang	Austria	3	2	67%	0	0	-
020038	Vetter, Norbert	Austria	14	13	93%	6	4	67%
020043	Segura, Ferran	Spain	2	0	-	2	2	100%
020047	Marquez-Solero, Manuel	Spain	8	1	13%	4	0	-
020052	Kunst, M.	Netherlands	3	2	67%	0	0	-
020054	Martinot, Jean Benoit	Belgium	8	2	25%	4	2	50%
020055	Pezzarossi, Hugo	Guatemala	5	2	40%	4	1	25%
020059	Mensa-Pueyo, Jose	Spain	6	2	33%	2	1	50%
020060	Aspa, Javier	Spain	4	1	25%	4	0	-
020061	Van Noord, J.A.	Netherlands	5	1	20%	3	0	-
020064	Wainz, Ronald	Toledo, OH	1	0	-	0	0	-
020072	Daugherty, Stephen	Springfield, Missouri	2	1	50%	2	1	50%
020073	Hsiao, Chiu-Bin	Buffalo, NY	3	3	100%	1	0	-
020075	Mikolich, Dennis J.	Cranston, RI	0	0	-	1	1	100%
020076	Ellison, W. Travis	Greer, SC	2	0	-	1	0	-
020079	Sinopalnikov, Alexander	Russia	16	9	56%	8	3	38%
020081	Seas Ramos, Carlos	Peru	8	8	100%	3	2	67%
020084	Snyder, Richard	Allentown, PA	2	0	-	2	0	-
020085	Dalhoff, Klaus	Germany	1	0	-	2	0	-
020086	Saavedra Leveau, Carlos	Peru	6	3	50%	2	2	100%
020093	Morales Reyes, Juan	Mexico	6	2	33%	4	3	75%

rows represent those Investigator's that also enrolled patients in Protocol 018
(Modified Applicant's Tables 20 and 21, volume 17 of 22, pages 85-87)

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Appendix 21

Protocol 020

Oral Switch Agents by Treatment Group
(Microbiologically Evaluable Population)

	MK-0826		Ceftriaxone		Total	
	(N=100)		(N=49)		(N=149)	
	n	(%)	n	(%)	n	(%)
No oral therapy	17	(17.0)	11	(22.4)	28	(18.8)
Received oral therapy	83	(83.0)	38	(77.6)	121	(81.2)
Amoxicillin/clavulanate	76	(76.0)	33	(67.3)	109	(73.2)
Amoxicillin/clavulanate 875 mg/125 mg	1	(1.0)	0	(0.0)	1	(0.7)
Azithromycin	1	(1.0)	0	(0.0)	1	(0.7)
Bactrim DS	0	(0.0)	1	(2.0)	1	(0.7)
Cefprozil	0	(0.0)	1	(2.0)	1	(0.7)
Ceftin	1	(1.0)	0	(0.0)	1	(0.7)
Cephalexin	1	(1.0)	0	(0.0)	1	(0.7)
Ciprofloxacin	1	(1.0)	0	(0.0)	1	(0.7)
Levofloxacin	3	(3.0)	2	(4.1)	5	(3.4)
Moxifloxacin	0	(0.0)	1	(2.0)	1	(0.7)

This table counts patients. Although a patient may have more than 1 oral therapy, the patient was counted only once in the total for patient with oral therapy.
 N = Total number of patients in each treatment group.
 n = Total number of patient with the therapy.

(Applicant's Table 33, Volume 17 of 22, page 109)

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Protocol 020

Appendix 22

Original table from November 30, 2000 NDA 21,337 submission:

**Proportion of Patients With a Favorable Clinical Response Assessment
in the Microbiological MITT Population
(Estimated Data)**

Treatment Group						Estimated [†] Difference (A-B)	
MK-0826 (A) (N=123)			Ceftriaxone (B) (N=60)				
n	Estimated [†] Response (95% CI)		n	Estimated [†] Response (95% CI)			
123	88.9	(83.3, 94.6)	60	90.0	(83.1, 97.0)	-1.1	(-11.9, 9.7)

[†] Computed from a statistical model adjusting for strata.
 N = Number of microbiological MITT patients in each treatment group.
 n = Number of microbiological MITT patients included in the analysis.
 CI = Confidence interval.

(Applicant's Table 56, Volume 17 of 22, page 144)

Revised table from April 4, 2001, Amendment to NDA 21,337 submission:

**Proportion of Patients With Favorable Clinical Response Assessment-
Microbiological MITT Population (Revised MITT Analysis)
(Estimated[†])
Protocol 020**

Time Point	Treatment Group						Estimated [†] Difference (A-B)	
	Ertapenem 1g (A) (N=123)			Ceftriaxone 1g (B) (N=60)				
	n	Estimated [†] Response (95% CI)		n	Estimated [†] Response (95% CI)			
Test of Cure	123	80.8	(73.7, 87.9)	60	83.3	(74.1, 92.5)	-2.6	(-15.9, 10.8)

[†] Computed from a statistical model adjusting for strata.
 N = Number of microbiological MITT patients in each treatment group at the Test of Cure visit.
 n = Number of microbiological MITT patients included in the analysis.
 CI = Confidence Interval.

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Original table from November 30, 2000 NDA 21,337 submission:

**Proportion of Patients With a Favorable Microbiological Response Assessment
in the Microbiological MITT Population
(Estimated Data)**

Treatment Group						Estimated [†] Difference (A-B)	
MK-0826 (A) (N=123)			Ceftriaxone (B) (N=60)				
n	Estimated [†] Response		N	Estimated [†] Response		%	(95% CI)
	%	(95% CI)		%	(95% CI)		
123	92.1	(87.2, 96.9)	60	91.9	(84.8, 98.9)	0.2	(-9.5, 9.8)

[†] Computed from a statistical model adjusting for strata.
N = Number of microbiological MITT patients in each treatment group.
n = Number of microbiological MITT patients included in the analysis.
CI = Confidence interval.

(Applicant's Table 57, Volume 17 of 22, page 145)

Revised table from April 4, 2001, Amendment to NDA 21,337 submission:

**Proportion of Patients With Favorable Microbiological Response Assessment-
Microbiological MITT Population (Revised MITT Analysis)
(Estimated[†])
Protocol 020**

Time Point	Treatment Group						Estimated [†] Difference (A-B)	
	Ertapenem Ig (A) (N=123)			Ceftriaxone Ig (B) (N=60)				
	n	Estimated [†] Response		n	Estimated [†] Response		%	(95% CI)
	%	(95% CI)		%	(95% CI)			
Test of Cure	123	85.7	(79.3, 92.0)	60	85.2	(76.0, 94.3)	0.5	(-11.8, 12.8)

[†] Computed from a statistical model adjusting for strata.
N = Number of microbiological MITT patients in each treatment group at the Test of Cure visit.
n = Number of microbiological MITT patients included in the analysis.
CI = Confidence Interval.

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Protocol 017

Appendix 23

Number (%) of Patients With Specific Clinical Adverse Experiences
(Incidence $\geq 2\%$ in One or More Treatment Groups) by Body System
During Parenteral Therapy
(Treated Population)

	MK-0826 1 g (N=316)		MK-0826 1.5 g (N=14)		Piperacillin/ Tazobactam (N=325)	
	n	(%)	n	(%)	n	(%)
Patients with one or more adverse experiences	187	(59.2)	12	(85.7)	196	(60.3)
Patients with no adverse experience	129	(40.8)	2	(14.3)	129	(39.7)
Body as a Whole/Site Unspecified	68	(21.5)	7	(50.0)	80	(24.6)
Death	8	(2.5)	1	(7.1)	2	(0.6)
Discharge, abdominal	1	(0.3)	1	(7.1)	1	(0.3)
Distention, abdominal	6	(1.9)	0	(0.0)	11	(3.4)
Edema/swelling	13	(4.1)	2	(14.3)	10	(3.1)
Fever	20	(6.3)	6	(42.9)	27	(8.3)
Pain, abdominal	10	(3.2)	1	(7.1)	20	(6.2)
Pain, postoperative	5	(1.6)	0	(0.0)	11	(3.4)
Shock, septic	4	(1.3)	1	(7.1)	2	(0.6)
Cardiovascular System	57	(18.0)	3	(21.4)	63	(19.4)
Arrhythmia	1	(0.3)	1	(7.1)	2	(0.6)
Atrial fibrillation	3	(0.9)	1	(7.1)	4	(1.2)
Bradycardia	1	(0.3)	1	(7.1)	0	(0.0)
Heart failure	3	(0.9)	1	(7.1)	2	(0.6)
Hypertension	6	(1.9)	0	(0.0)	7	(2.2)
Hypotension	10	(3.2)	1	(7.1)	4	(1.2)
Idioventricular rhythm	0	(0.0)	1	(7.1)	0	(0.0)
Infused vein complication	6	(1.9)	0	(0.0)	9	(2.8)
Left bundle branch block	0	(0.0)	1	(7.1)	0	(0.0)
Peripheral pulse decreased	0	(0.0)	1	(7.1)	1	(0.3)
Peripheral vascular disorder	0	(0.0)	1	(7.1)	0	(0.0)
Phlebitis/thrombophlebitis	14	(4.4)	0	(0.0)	12	(3.7)
T-wave abnormality	0	(0.0)	1	(7.1)	0	(0.0)
Thrombosis, deep vein	0	(0.0)	1	(7.1)	4	(1.2)
Ventricular tachycardia	1	(0.3)	1	(7.1)	2	(0.6)
Digestive System	87	(27.5)	8	(57.1)	115	(35.4)
Ascites	1	(0.3)	1	(7.1)	2	(0.6)
Candidiasis, oral	0	(0.0)	0	(0.0)	9	(2.8)
Constipation	9	(2.8)	2	(14.3)	17	(5.2)
Diarrhea	36	(11.4)	1	(7.1)	43	(13.2)
Discoloration, tongue	0	(0.0)	1	(7.1)	0	(0.0)
Ileus	1	(0.3)	1	(7.1)	7	(2.2)
Incontinence, fecal	0	(0.0)	1	(7.1)	2	(0.6)
Infection, intra-abdominal	3	(0.9)	0	(0.0)	9	(2.8)
Nausea	24	(7.6)	2	(14.3)	34	(10.5)
Pancreas disorder	0	(0.0)	1	(7.1)	0	(0.0)
Vomiting	10	(3.2)	0	(0.0)	19	(5.8)
Hemic and Lymphatic System	12	(3.8)	1	(7.1)	6	(1.8)
Anemia	9	(2.8)	0	(0.0)	3	(0.9)
Petechiae	0	(0.0)	1	(7.1)	0	(0.0)
Metabolic, Nutritional, Immune	16	(5.1)	2	(14.3)	9	(2.8)
Acidosis	7	(2.2)	1	(7.1)	1	(0.3)
BUN increased	0	(0.0)	1	(7.1)	0	(0.0)
Hypoglycemia	0	(0.0)	1	(7.1)	1	(0.3)
Musculoskeletal System	9	(2.8)	0	(0.0)	17	(5.2)
Nervous System and Psychiatric Disorder	48	(15.2)	4	(28.6)	53	(16.3)
Confusion	16	(5.1)	1	(7.1)	9	(2.8)
Depression	1	(0.3)	1	(7.1)	2	(0.6)
Hallucinations	3	(0.9)	1	(7.1)	3	(0.9)
Headache	12	(3.8)	0	(0.0)	11	(3.4)
Insomnia	7	(2.2)	0	(0.0)	14	(4.3)

Mental status change	1	(0.3)	1	(7.1)	1	(0.3)
Nervousness	1	(0.3)	1	(7.1)	2	(0.6)
Respiratory System	51	(16.1)	6	(42.9)	44	(13.5)
Atelectasis	3	(0.9)	1	(7.1)	6	(1.8)
Chest sound abnormality	4	(1.3)	1	(7.1)	4	(1.2)
Dyspnea	13	(4.1)	2	(14.3)	7	(2.2)
Edema, pulmonary	0	(0.0)	1	(7.1)	0	(0.0)
Effusion, pleural	3	(0.9)	2	(14.3)	8	(2.5)
Hiccups	2	(0.6)	1	(7.1)	2	(0.6)
Hypoxemia	3	(0.9)	1	(7.1)	6	(1.8)
Infiltrate, pulmonary	0	(0.0)	1	(7.1)	0	(0.0)
Pneumonia	4	(1.3)	1	(7.1)	4	(1.2)
Rales/rhonchi	6	(1.9)	2	(14.3)	4	(1.2)
Tachypnea	2	(0.6)	1	(7.1)	1	(0.3)
Wheezing	5	(1.6)	1	(7.1)	4	(1.2)
Skin and Skin Appendage	47	(14.9)	4	(28.6)	40	(12.3)
Dehiscence, wound	4	(1.3)	1	(7.1)	2	(0.6)
Erythema	8	(2.5)	1	(7.1)	7	(2.2)
Infection, wound, postoperative	3	(0.9)	1	(7.1)	4	(1.2)
Pruritus	3	(0.9)	0	(0.0)	8	(2.5)
Rash	6	(1.9)	0	(0.0)	8	(2.5)
Sweating	3	(0.9)	1	(7.1)	2	(0.6)
Urogenital System	19	(6.0)	2	(14.3)	26	(8.0)
Infection, urinary tract	1	(0.3)	1	(7.1)	2	(0.6)
Oliguria/anuria	4	(1.3)	1	(7.1)	8	(2.5)
Renal insufficiency	3	(0.9)	1	(7.1)	3	(0.9)

Although a patient may have had 2 or more adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

All body systems are listed in which at least 1 patient had an adverse experience.

(Modified Applicant's Table 116, Volume 13 of 22, pages 465-472)

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Protocol 023

Appendix 24

**Number (%) of Patients With Specific Clinical Adverse Experiences
(Incidence $\geq 2\%$ in One or More Treatment Groups) by Body System
During Parenteral Therapy
(Treated Population)**

	MK-0826 (N=214)		Piperacillin/Tazobactam (N=192)	
	n	(%)	n	(%)
Patients with one or more adverse experiences	97	(45.3)	92	(47.9)
Patients with no adverse experience	117	(54.7)	100	(52.1)
Body as a Whole/Site Unspecified	29	(13.6)	16	(8.3)
Pain, abdominal	9	(4.2)	4	(2.1)
Cardiovascular System	39	(18.2)	40	(20.8)
Extravasation	9	(4.2)	6	(3.1)
Hematoma	4	(1.9)	4	(2.1)
Infused vein complication	25	(11.7)	28	(14.6)
Digestive System	29	(13.6)	25	(13.0)
Constipation	5	(2.3)	7	(3.6)
Diarrhea	12	(5.6)	7	(3.6)
Nausea	7	(3.3)	5	(2.6)
Vomiting	6	(2.8)	5	(2.6)
Musculoskeletal System	6	(2.8)	7	(3.6)
Nervous System and Psychiatric Disorder	26	(12.1)	21	(10.9)
Dizziness	7	(3.3)	5	(2.6)
Headache	21	(9.8)	15	(7.8)
Respiratory System	10	(4.7)	15	(7.8)
Cough	5	(2.3)	6	(3.1)
Skin and Skin Appendage	10	(4.7)	17	(8.9)
Rash	1	(0.5)	6	(3.1)
Urogenital System	14	(6.5)	8	(4.2)

Although a patient may have had 2 or more adverse experiences, the patient is counted only once within a category.
The same patient may appear in different categories.

All body systems are listed in which at least 1 patient had an adverse experience.

(Modified Applicant's Table 102, Volume 20 of 22, pages 339-343)

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**Number (%) of Patients With Specific Clinical Adverse Experiences
(Incidence \geq 2% in One or More Treatment Groups) by Body System
During Parenteral Therapy
(Treated Population)
Drug Related**

	MK-0826 (N=214)		Piperacillin/Tazobactam (N=192)	
	n	(%)	n	(%)
Patients with one or more drug-related adverse experiences [†]	48	(22.4)	42	(21.9)
Patients with no drug-related adverse experience	166	(77.6)	150	(78.1)
Body as a Whole/Site Unspecified				
Cardiovascular System	9	(4.2)	3	(1.6)
Extravasation	24	(11.2)	28	(14.6)
Infused vein complication	7	(3.3)	4	(2.1)
Digestive System	17	(7.9)	24	(12.5)
Diarrhea	15	(7.0)	8	(4.2)
Nausea	7	(3.3)	4	(2.1)
Vomiting	5	(2.3)	2	(1.0)
Nervous System and Psychiatric Disorder	5	(2.3)	3	(1.6)
Headache	6	(2.8)	7	(3.6)
Skin and Skin Appendage	4	(1.9)	5	(2.6)
Rash	4	(1.9)	5	(2.6)
	1	(0.5)	4	(2.1)

[†] Determined by the investigator to be possibly, probably, or definitely drug related.
 -Although a patient may have had 2 or more drug-related adverse experiences, the patient was counted only once within a category. The same patient may appear in different categories.
 -All body systems are listed in which at least 1 patient had a drug-related adverse experience.
 (Modified Applicant's Table 103, Volume 20 of 22, page 344)

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Protocol 017

**Number (%) of Patients With Specific Clinical Adverse Experiences
(Incidence $\geq 2\%$ in One or More Treatment Groups) by Body System
During Parenteral Therapy
(Treated Population)
Drug Related**

	MK-0826 1 g (N=316)		MK-0826 1.5 g (N=14)		Piperacillin/Tazobactam (N=325)	
	n	(%)	n	(%)	n	(%)
Patients with one or more drug-related adverse experiences†	64	(20.3)	4	(28.6)	69	(21.2)
Patients with no drug-related adverse experience	252	(79.7)	10	(71.4)	256	(78.8)
Body as a Whole/Site Unspecified						
Cardiovascular System	4	(1.3)	0	(0.0)	9	(2.8)
Phlebitis/thrombophlebitis	16	(5.1)	0	(0.0)	16	(4.9)
Digestive System						
Diarrhea	13	(4.1)	0	(0.0)	10	(3.1)
Nausea	27	(8.5)	2	(14.3)	44	(13.5)
Nervous System and Psychiatric Disorder						
Confusion	18	(5.7)	1	(7.1)	24	(7.4)
Hallucinations	5	(1.6)	0	(0.0)	16	(4.9)
Headache	11	(3.5)	2	(14.3)	6	(1.8)
Mental status change	2	(0.6)	1	(7.1)	1	(0.3)
	0	(0.0)	1	(7.1)	1	(0.3)
	7	(2.2)	0	(0.0)	1	(0.3)
	0	(0.0)	1	(7.1)	0	(0.0)
Respiratory System						
Dyspnea	3	(0.9)	1	(7.1)	0	(0.0)
	2	(0.6)	1	(7.1)	0	(0.0)
Skin and Skin Appendage						
	9	(2.8)	0	(0.0)	10	(3.1)

† Determined by the investigator to be possibly, probably, or definitely drug related.
Although a patient may have had 2 or more drug-related adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.
All body systems are listed in which at least 1 patient had a drug-related adverse experience.
(Modified Applicant's Table 118, Volume 13 of 22, pages 476-478)

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Protocol 018

Appendix 25

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

	MK-0826 (N=242)		Ceftriaxone (N=256)	
	n	(%)	n	(%)
Patients with one or more adverse experiences	149	(61.6)	159	(62.1)
Patients with no adverse experience	93	(38.4)	97	(37.9)
Body as a Whole/Site Unspecified	47	(19.4)	45	(17.6)
Asthenia/fatigue	6	(2.5)	4	(1.6)
Death	7	(2.9)	5	(2.0)
Edema/swelling	8	(3.3)	8	(3.1)
Fever	5	(2.1)	2	(0.8)
Infection, fungal	1	(0.4)	5	(2.0)
Pain, abdominal	9	(3.7)	7	(2.7)
Pain, chest	5	(2.1)	13	(5.1)
Cardiovascular System	44	(18.2)	68	(26.6)
Extravasation	5	(2.1)	6	(2.3)
Hypotension	6	(2.5)	1	(0.4)
Infused vein complication	19	(7.9)	27	(10.5)
Phlebitis/thrombophlebitis	4	(1.7)	5	(2.0)
Digestive System	59	(24.4)	68	(26.6)
Candidiasis, oral	6	(2.5)	10	(3.9)
Constipation	13	(5.4)	7	(2.7)
Diarrhea	24	(9.9)	27	(10.5)
Nausea	13	(5.4)	12	(4.7)
Vomiting	7	(2.9)	4	(1.6)
Hemic and Lymphatic System	9	(3.7)	4	(1.6)
Metabolic, Nutritional, Immune	6	(2.5)	13	(5.1)
Musculoskeletal System	17	(7.0)	13	(5.1)
Pain, back	2	(0.8)	6	(2.3)
Nervous System and Psychiatric Disorder	38	(15.7)	36	(14.1)
Anxiety	2	(0.8)	6	(2.3)
Headache	13	(5.4)	13	(5.1)
Insomnia	8	(3.3)	10	(3.9)
Respiratory System	60	(24.8)	55	(21.5)
Chronic obstructive pulmonary disease	2	(0.8)	5	(2.0)
Dyspnea	1	(0.4)	6	(2.3)
Effusion, pleural	7	(2.9)	11	(4.3)
Hypoxemia	9	(3.7)	3	(1.2)
Pneumonia	6	(2.5)	6	(2.3)
Skin and Skin Appendage	24	(9.9)	29	(11.3)
Rash	6	(2.5)	5	(2.0)
Special Senses	2	(0.8)	5	(2.0)
Urogenital System	14	(5.8)	10	(3.9)

N = Number of patients with at least 1 dose of study therapy.
n = Number of patients with the adverse experience.
Although a patient may have had 2 or more adverse experiences, the patient is counted only once within a body system category. The same patient may appear in different categories.
All body systems are listed in which at least 1 patient had an adverse experience.

(Modified Applicant's Table 119, Volume 15 of 22, pages 458-456)

Protocol 018

**Number (%) of Patients With Specific Clinical Adverse Experiences
(Incidence $\geq 2\%$ in One or More Treatment Groups) by Body System
During Study Therapy and 14-Day Follow-Up Period
(Treated Population)
Drug Related[†]**

	MK-0826 (N=242)		Ceftriaxone (N=256)	
	n	(%)	n	(%)
Patients with one or more drug-related adverse experiences	42	(17.4)	61	(23.8)
Patients with no drug-related adverse experience	200	(82.6)	195	(76.2)
Body as a Whole/Site Unspecified				
Cardiovascular System	6	(2.5)	5	(2.0)
Infused vein complication	12	(5.0)	26	(10.2)
Digestive System	8	(3.3)	15	(5.9)
Candidiasis, oral	21	(8.7)	32	(12.5)
Diarrhea	3	(1.2)	6	(2.3)
Nervous System and Psychiatric Disorder	16	(6.6)	15	(5.9)
Skin and Skin Appendage	4	(1.7)	5	(2.0)
	4	(1.7)	6	(2.3)

[†] Determined by the investigator to be possibly, probably, or definitely drug related.
N = Number of patients with at least 1 dose of study drug.
n = Number of patients with the adverse experience.

Although a patient may have had 2 or more drug-related adverse experiences, the patient is counted only once within a body system category. The same patient may appear in different categories.
All body systems are listed in which at least 1 patient had a drug-related adverse experience.
(Modified Applicant's Table 120, Volume 15 of 22, page 342)

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Appendix 26

Protocol 020

**Number (%) of Patients With Specific Clinical Adverse Experiences
(Incidence $\geq 2\%$ in One or More Treatment Groups) by Body System
During Study Therapy and 14-Day Follow-Up Period
(Treated Population)**

	MK-0826 (N=236)		Ceftriaxone (N=123)	
	n	(%)	n	(%)
Patients with one or more adverse experiences	141	(59.7)	73	(59.3)
Patients with no adverse experience	95	(40.3)	50	(40.7)
Body as a Whole/Site Unspecified	37	(15.7)	19	(15.4)
Death	2	(0.8)	3	(2.4)
Edema/swelling	11	(4.7)	9	(7.3)
Fever	6	(2.5)	3	(2.4)
Pain, abdominal	9	(3.8)	1	(0.8)
Cardiovascular System	25	(10.6)	19	(15.4)
Blood pressure increased	4	(1.7)	3	(2.4)
Infused vein complication	12	(5.1)	10	(8.1)
Digestive System	61	(25.8)	33	(26.8)
Candidiasis, oral	7	(3.0)	2	(1.6)
Constipation	17	(7.2)	4	(3.3)
Nausea	10	(4.2)	6	(4.9)
Vomiting	3	(1.3)	3	(2.4)
Heme and Lymphatic System	3	(1.3)	3	(2.4)
Metabolic, Nutritional, Immune	7	(3.0)	5	(4.1)
Musculoskeletal System	8	(3.4)	5	(4.1)
Nervous System and Psychiatric Disorder	46	(19.5)	23	(18.7)
Anxiety	5	(2.1)	4	(3.3)
Confusion	5	(2.1)	0	(0.0)
Dizziness	5	(2.1)	2	(1.6)
Headache	15	(6.4)	7	(5.7)
Insomnia	11	(4.7)	10	(8.1)
Respiratory System	54	(22.9)	22	(17.9)
Chronic obstructive pulmonary disease	6	(2.5)	3	(2.4)
Dyspnea	2	(0.8)	4	(3.3)
Effusion, pleural	10	(4.2)	1	(0.8)
Hypoxemia	5	(2.1)	0	(0.0)
Pneumonia	6	(2.5)	5	(4.1)
Wheezing	1	(0.4)	3	(2.4)
Skin and Skin Appendage	16	(6.8)	9	(7.3)
Pruritus	3	(1.3)	4	(3.3)
Rash	5	(2.1)	1	(0.8)
Special Senses	6	(2.5)	0	(0.0)
Urogenital System	13	(5.5)	11	(8.9)
Vaginitis	3	(1.3)	3	(2.4)

Although a patient may have had 2 or more adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.
All body systems are listed in which at least 1 patient had an adverse experience.
(Modified Applicant's Table 144, Volume 17 of 22, pages 392-398)

Protocol 020

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

	MK-0826 (N=236)		Ceftriaxone (N=123)	
	n	(%)	n	(%)
Patients with one or more drug-related† adverse experiences	48	(20.3)	25	(20.3)
Patients with no drug-related adverse experience	188	(79.7)	98	(79.7)
Cardiovascular System	10	(4.2)	10	(8.1)
Infused vein complication	8	(3.4)	9	(7.3)
Digestive System	24	(10.2)	8	(6.5)
Diarrhea	8	(3.4)	2	(1.6)
Nausea	5	(2.1)	1	(0.8)
Nervous System and Psychiatric Disorder	7	(3.0)	2	(1.6)
Urogenital System	4	(1.7)	5	(4.1)
Vaginitis	3	(1.3)	3	(2.4)

† Determined by the investigator to be possibly, probably, or definitely drug related.
Although a patient may have had 2 or more drug-related adverse experiences, the patient is
counted only once within a category. The same patient may appear in different categories.
All body systems are listed in which at least 1 patient had a drug-related adverse experience.
(Modified Applicant's Table 145, Volume 17 of 22, pages 399-400)

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Appendix 27
Protocol 020: Patients With Non-Fatal Drug-Related Serious Adverse Events

MK-0826 Treatment Group

AN 3833

A 72-year-old female with asthma, gonarthrosis, Parkinson's disease, insomnia, esophagitis, venous insufficiency, and a history of angioneurotic edema began IV therapy with MK-0826 for the treatment of CAP. On Study Day 8, the fever persisted, the clinical status of the patient worsened, and an x-ray showed a metapneumonic effusion. The IV study drug therapy was discontinued and therapy with piperacillin/tazobactam and ciprofloxacin was started. In the opinion of the investigator, the worsening pneumonia was possibly related to study drug therapy.

AN 3843

A 76-year-old male with hypertension, controlled epilepsy, COPD and a history of aneurysm, hernia inguinal, tonsillectomy, gastroduodenal ulcer, benign prostatic hypertrophy, and frontal meningioma (resected) began IV therapy with MK-0826 for the treatment of CAP. Concomitant therapy included valproic acid and phenytoin. Because of a persistent tremor, the dosage of valproate sodium was progressively decreased and the phenytoin was progressively increased. On Study Day 5, the valproic acid was stopped and the therapy with phenytoin was continued. On Study Day 9, the dosage of MK-0826 was increased by the investigator to 2 g daily because the pathogen *S. pneumonia* had an intermediate susceptibility to penicillin and the patient's clinical response remained suboptimal. On Study Day 10, following the administration of the study drug, the patient experienced 2 separate seizures from which the patient recovered. At the time of the adverse experience, the clinical status of patient improved and the *S. pneumoniae* was eradicated. On Study Day 10, therapy with study drug was discontinued and replaced by cefotaxime. In the opinion of the investigator, the seizure disorder was possibly related to the study drug therapy.

AN 4092

A 73-year-old male with chronic bronchitis, hypertension, cerebrovascular insufficiency, duodenal ulcer, pancreatitis, colitis, benign prostatic hypertrophy, and congestive heart failure began IV therapy with MK-0826 for the treatment of CAP. On Study Day 12, during gastroscopy for control of the duodenum ulcer, a gastric ulcer was diagnosed and a biopsy was performed indicating a nonmalignant gastric ulcer. The patient was treated with aluminum phosphate and famotidine. On Study Day 13, the IV therapy was completed and the patient was switched to oral therapy with amoxicillin/clavulanate as per protocol until completion on Study Day 19. The patient recovered from gastric ulcer. In the opinion of the investigator, the gastric ulcer was probably related to study drug therapy.

AN 4140

A 68-year-old male with COPD and congestive heart failure began IV therapy with MK-0826 for the treatment of CAP. On Study Day 8, the patient experienced acute gastroenterocolitis. On Study Day 9, the IV therapy was completed and the patient was switched to oral therapy with amoxicillin/clavulanate as per protocol until completion on Study Day 14. The patient recovered from colitis. In the opinion of the investigator, the colitis was possibly related to the study drug therapy.

AN 4200

An 82-year-old male with hypertension, congestive heart failure, benign prostate hyperplasia, anemia, cerebrovascular accident, and history of renal insufficiency and hepatic disorder began IV therapy with MK-0826 for the treatment of CAP. On Study Day 2, the patient had abdominal distension and tenderness, bowel sounds were decreased, and an abdominal ultrasound showed gallbladder increase and dilated biliary tract. The patient was diagnosed with acute cholecystitis and surgery was performed. The IV study therapy was discontinued and the patient was placed on therapy with ceftriaxone and metronidazole. The patient was in respiratory failure and was placed on mechanical ventilation. Subsequently, the endotracheal tube was withdrawn. After eating some food, the patient had severe dyspnea caused by aspiration pneumonia that rapidly developed to respiratory failure. On Study Day 22, the patient died due to respiratory failure and aspiration pneumonia. In the opinion of the investigator, the

cholecystitis was possibly related to the study drug therapy and the respiratory failure and aspiration pneumonia were definitely not related to the study drug therapy.

Ceftriaxone Treatment Group

AN 3869

A 75-year-old female with a history of insomnia, hiatal hernia, tuberculosis, recurrent pneumonia, mastitis surgery, appendectomy, and allergies to vaccines and paracetamol began IV therapy with ceftriaxone for the treatment of CAP. On Study Day 2, the patient experienced an allergic reaction with dyspnea, pruritus and exanthema, causing discontinuation of the study drug therapy. The patient recovered from the allergic reaction. In the opinion of the investigator, the allergic reaction was probably related to the study drug therapy.

AN 4038

A 73-year-old male with hypercholesterolemia, hydrocephalus, and a history of myocardial infarction and anal fistula began IV therapy with ceftriaxone for the treatment of CAP. On Study Day 2, the patient experienced hepatitis; however, the serology tests for hepatitis A, B, and C were negative. On Study Day 4, the IV study drug therapy was discontinued and the patient was placed on therapy with levofloxacin. The patient recovered from the hepatitis. In the opinion of the investigator, the hepatitis was probably related to the study drug therapy.

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Appendix 28

**NARRATIVES OF DEATHS FOR PATIENTS ENROLLED IN PHASE II/III
STUDIES**

PROTOCOL 002C-Phase IIA Lower Respiratory Tract Infections

MK-0826 1 gm Treatment Group

No deaths occurred in this group.

Ceftriaxone

Medical Officer's Comment: *The Applicant provided only WAES narratives for the following two patients in the ceftriaxone group in P002c.*

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0254

Information has been received concerning a 68 year old male with hemoglobin decreased; limping; consolidation, lower lobe; a history of earache; injury, leg; wound, stab, chest and drainage, effusion, intercostal who entered a multiclinic, double-blind, randomized comparative study to evaluate the safety, tolerability, and efficacy of L-749,345 versus ceftriaxone sodium in the treatment of serious uncomplicated lower respiratory tract infections of mild to moderate severity in adults. On 15-APR-97 the patient was placed on therapy with L-749,345 or control, inj. Concomitant therapy included augmentin and cough syrup. The cause of death was unknown. The reporting physician felt that sudden death was not related to therapy with L-749,345 or control. Investigators Comments: Patient was well during the day (22/04/97). Patient was found by nursing staff to be gasping at 19h00. Patient was examined by doctor at 19h15 and was found to be dead.

1302

Information has been received concerning a 76 year old male with copd and respiratory insufficiency and cancer, liver (biopsy never performed because patient always refused) and cardiomyopathy, ischemic and cardiomyopathy, hypertensive who entered a prospective multiclinic, double-blind, randomized comparative estimation study to evaluate the safety, tolerability, and afficacy of L-749,345 versus ceftriaxone sodium in the treatment of serious uncomplicated lower respiratory tract infections of mild to moderate severity in adults. On 20-MAR-97 the patient was placed on therapy with l-749,345, inj or control . Concomitant therapy included ceftriaxone sodium or control, inj for the treatment of infection, respiratory, lower . Other concomitant therapy included cefotaxime and aminophylline and hydrocortisone and methylprednisolone and ranitidine and digoxin iv and ipatropium and budesonide inhaler and methylprednisolone and methylprednisolone and nadroparine and nifedipine and furosemide iv and deflazacort and salbutamol and budesonide inhaler. On 25-MAR-97 therapy with l-749,345 or control and therapy with ceftriaxone sodium or control were discontinued. On 03-APR-97 the patient died due to respiratory insufficiency due to desviation of protocol. The cause of death was respiratory insufficiency. The reporting physician felt that death and respiratory insufficiency were not related to therapy with l-749,345 or control. Adverse event of special interest have also occured. Additional information is not expected.

PROTOCOL 004-Phase IIA Complicated Intra-Abdominal Infections

MK-0826 1 gm Treatment Group

3597

A physician reported that a 76 year old man died from asystole after completing blinded ertapenem therapy. The patient, with history of cholecystitis and gangrenous peritonitis, was randomized to therapy with ertapenem 1 g every 24 hours IV for the treatment of intraabdominal infection. On Study Day 14, study therapy stopped. On Study Day 25 the patient died in his sleep. He was found asystole and without breath sounds by a nurse. Prior to his death it was noted that he appeared to be doing well: he was afebrile and no signs of sepsis were present. No autopsy was performed and his death is apparently of natural causes. The reporting physician felt that asystole was definitely not related to therapy with study drugs.

MK-0826 1.5 gm Treatment Group

0837

A physician reported that a 75-year-old male developed fungemia, perforating duodenal ulcer, abscess, pleural effusion, respiratory distress and multiple organ failure and subsequently died after completion of blinded ertapenem therapy. The patient had surgery that repaired a bowel perforation probably due to tumor lysis. The surgeon believed that after the patient received a dose of chemotherapy that his small bowel carcinoma shrank and the adhesions pulled away from the intestinal wall. The shrinkage resulted in a tear in his bowel and subsequent peritonitis for which he was enrolled in the study. The patient was placed on therapy with ertapenem 1500 mg daily intravenously for the treatment of intraabdominal infection. Concomitant therapy included cimetidine, digoxin, furosemide, hydrocortisone, diltiazem, calcium gluconate and morphine. On Study Day 6, the patient developed candidemia. While the patient was hospitalized, he developed a perforated duodenal ulcer on Study Day 15. That day, the ulcer was repaired during surgery. The patient recovered from the candidemia while he recovered from the surgery on the perforated ulcer. On Study Day 19, the patient was diagnosed with an intraabdominal abscess and pleural effusion. CT guided drainages were performed for the abscess and effusion. He developed respiratory distress which was treated with an oxygen mask since the patient's family had not wanted him re-intubated due to his underlying disease. His respiratory distress worsened and he became bradycardic and developed signs of renal failure. The patient was resuscitated, however he was unable to breath without assistant. He died on Study Day 21 due to multiple organ system failure due to continued deterioration of the patient's health. The reporting physician felt that the patient's experience was definitely not related to study drug therapy.

3049

A physician reported that a 70-year-old male study patient developed asystole and sepsis while on blinded ertapenem therapy. The patient entered the study and was placed on ertapenem injection 1.5 g daily for the treatment of an intraabdominal infection. The patient underwent surgery on Study Day 1 for the repair of a perforated cecum. On Study Day 5, cultures revealed the presence of *Escherichia coli*, *Klebsiella pneumoniae*, methicillin-resistant *Staphylococcus aureus*, *Enterococcus faecium* and *Bacteroides distonis*. He was sent back to the operating room on Study Day 5 for wound debridement and further repair. The patient was placed on a ventilator and weaning was difficult. He began to develop signs of sepsis including a reduced platelet count. On Study Day 5, the patient was made a "do not resuscitate" with continuation of unspecified antibiotics. No action was taken regarding study drug therapy. On Study Day 6 he was removed from the ventilator. Subsequently, the patient died on Study Day 7 of asystole presumably from the progression of sepsis. The patient remained on study therapy through Study Day 7. The reporting physician felt that sepsis and asystole were definitely not related to the blinded study therapy.

Ceftriaxone

Medical Officer's Comment: The Applicant provided only WAES narratives for the following two patients in the ceftriaxone group in P002c.

0658

Information has been received concerning a 60-year-old female patient who developed a worsening of thrombocytopenia while on blinded study therapy and died of multiple organ failure after discontinuing blinded study therapy.

The patient with thrombocytopenia and history of stage III cervical cancer, tobacco use, peripheral vascular disease, and bilateral pedal edema, entered a study, as title stated above. Prior to being entered into the study, the patient was hospitalized with peritonitis due to an irradiation-induced perforation of the distal ileum. The patient underwent surgery where an ileostomy and mucus fistula in a combined fashion was established. The patient had evidence of mild disseminated intravascular coagulation (DIC) as manifested by falling platelet count and mild acidosis. The patient was randomized into the study due to a post operative intra-abdominal infection. On 02-AUG-1997, the patient was allocated to receive either L-749,345 injection, 550 mg daily or placebo or ceftriaxone sodium injection, 2 g or placebo, metronidazole injection, 500 mg q8h or placebo. Concomitant therapy included vancomycin. On 02AUG97 the patient developed thrombocytopenia with a platelet count (PLT) of 38 (low). On 03-AUG-1997 the patient's PLT was 20 (low). On 04-AUG-1997, her PLT was 41. On 05-AUG-1997 the patient's PLT was 17. The investigator felt the magnitude of the ~~platelet depression was out of proportion to the infection. The~~ experience prolonged the patient's hospitalization. The primary investigator felt that the thrombocytopenia was probably not related to blinded study therapy since the platelet count was low prior to the initiation of blinded study therapy. However, on 05-AUG-1997, the patient was taken off all blinded study therapy and vancomycin and was replaced with imipenem therapy. On 13-AUG-1997 the patient's platelet count was 162 (normal) and she recovered from the thrombocytopenia. On 26-AUG-1997 the patient died due to multiple organ failure and the primary investigator felt that this was definitely not related to blinded study therapy. No additional information is available.

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0682

A physician reported that a 42-year-old male developed adult respiratory distress syndrome while on blinded MK-826 therapy. Following discontinuation of blinded therapy, the patient developed multiple organ failure and died of cardiac arrest.

The patient, who had a cecum perforation with abscess and with a history of gunshot wound, entered a study, title as stated above. On 11-OCT-97 the patient was placed on therapy with MK-826 or placebo, 1500 mg IV, ceftriaxone sodium or placebo 2 grams IV, and metronidazole or placebo, 500 mg TID, for the treatment of intra-abdominal infection. Other concomitant therapy included famotidine (MSD), heparin sodium, ampicillin, gentamicin and metronidazole. On 11-OCT-97 the patient underwent a cecectomy and exploratory laparotomy which revealed the presence of an abscess. He had a temporary abdominal closure with Marlex mesh and a bowel bag. He returned to the operating room on 12-OCT-97 for an ileostomy and mucous fistula. On 15-OCT-97 the patient's hospitalization was prolonged and considered life threatening because it was noted that his oxygen saturation level was decreasing and respiratory rate was increasing. He was intubated and placed on mechanical ventilation with positive end expiratory pressure. Bilateral chest tubes were inserted and the patient was diagnosed with adult respiratory distress syndrome secondary to intra-abdominal sepsis or aspiration pneumonia. On 15-OCT-97, blinded therapy MK-826 or placebo and ceftriaxone sodium or placebo were discontinued. On 16-OCT-97 blinded therapy metronidazole or placebo was discontinued. The patient was switched to other unspecified antibiotic therapy. The patient's adult respiratory distress syndrome persisted. On 19-OCT-1999, the patient's serum magnesium was abnormal (no value provided). As of 21-OCT-97, the patient remained on a ventilator and bronchoscopy revealed tracheobronchitis. On 22-OCT-1997, the patient's BUN was elevated (no value provided) and he progressed to multiple organ system failure. On 27-OCT-1999, the patient's serum creatinine was elevated (no value provided). As of 30-OCT-97, the patient required multiple bronchoscopies to manage his pseudomembranous tracheitis. He had ongoing sepsis with Pseudomonas and Candida being returned from his peritoneal cavity. Three abdominal lavage procedures were performed to treat these infections. On 28-OCT-1997, the patient developed acute renal failure/acute tubular necrosis secondary to therapy with gentamycin, vancomycin, and amphotericin B. He died on 29-NOV-97 apparently from cardiac arrest following erosion around his tracheostomy and bleeding. The primary investigator felt that adult respiratory distress syndrome and multiple organ failure were lifethreatening and disabling but not related to study drug therapy. Additional information was not available.

0721

A physician reported that a 64 year old male developed leukocytosis, acute renal failure, dehydration, electrolyte imbalance, hypotension, and died of metastatic neoplasm of known primary after completing therapy with blinded therapy L 749,345.

The patient had metastatic fibrohistocytoma of the kidney, post-surgical incisional pain, nausea, vomiting, insomnia and a history of abdominal surgery, abdominal aortic aneurysm and colon polyp who entered a prospective multiclinic, double-blind, randomized comparative estimation study to evaluate the safety, tolerability and efficacy of L-749,345 versus ceftriaxone sodium plus metronidazole in the treatment of serious complicated intra-abdominal infections of mild-to-moderate severity. On 25MAR97, the patient was placed on therapy with L-749,345, 550 mg single daily dose or control IV, ceftriaxone sodium, 2 gm daily or control, IV and metronidazole 500 mg every eight hours or control, IV : all for the treatment of intra-abdominal infection. Other concomitant therapy included heparin sodium, morphine sulfate, prochlorperazine (Compazine), metoclopramide

(Reglan) and temazepam (Restoril). Therapy with L-749,345 or control and ceftriaxone sodium or control was discontinued on 30MAR97. Therapy with metronidazole or control was discontinued and the patient was discharged from the hospital on 31MAR97. On

05APR97, the patient's visiting nurse noted that the patient was lethargic and there was a decrease in the patient's blood pressure. Laboratory evaluation revealed abnormal findings which included a BUN of 67 mg/dl, uric acid of 12.8 mg/dl, serum creatinine of 1.6 mg/dl, sodium of 128 mmol/L, potassium of 5.6 mmol/L, CO2 of 18 mmol/L, white blood cell (WBC) count of 60.8 k/ml and platelets of 685 k/ml. A urinalysis revealed 3+ uric acid crystals. He was admitted to the hospital with dehydration, acute renal insufficiency, electrolyte abnormalities, hypotension and leukemoid reaction with an increase in WBC and platelet counts. The patient was treated with ofloxacin and metronidazole. His urine and blood cultures were negative. The patient was afebrile with a slightly distended non-tender abdomen. The patient had a CT scan of his abdomen which revealed a necrotic tumor with two ill-defined areas on the right kidney extending into the abdomen.

In follow-up information the patient had a CT guided aspiration of the peritoneal fluid which revealed a negative gram stain and culture, hence showing no relapse or evidence of infection. The presumptive diagnosis was abdominal carcinomatosis while cytology results were still pending. The patient was afebrile and was not on antibiotics. On 10APR97, the patient died which was attributed to metastatic cancer with paraneoplastic syndrome. The reporting physician felt the patient's experiences and death was definitely not related to study drug therapy.

0834

A physician reported a 79 year old male developed multiple organ failure, arterial thrombosis, pneumothorax, gastrointestinal bleeding, pneumonia, and hypovolemic shock while on blinded study therapy.

On 11OCT97, surgery was performed to repair a perforated gastric ulcer (unknown duration). On 11-OCT-1997, the patient was placed on therapy with L349-345 or control, 550 mg injection (form) 1500 mg once a day, ceftriaxone sodium or control, 2000 mg injection daily and metronidazole or control 500 mg injection every eight hours for the treatment of intra-abdominal infection (duration unknown). Concomitant therapy included sucralfate (Carafate), fluconazole (Diflucan), haloperidol (Haldol), amphotericin B, cimetidine (Tagamet), Morphine Sulfate, furosemide (Lasix), naloxone HCL (Narcan), electrolyte replacement, adenosine, vecuronium bromide (Norcuron), dopamine and nitroglycerin paste. At 1750 hours on 13OCT97, the patient developed hypovolemic shock and was found to have a severe upper gastrointestinal bleed at 1800 hours. The patient was transfused with approximately six units of blood. The duration of the

gastrointestinal bleed was reported to be four hours and the hypovolemic shock continued for fourteen hours. Subsequently, the patient improved. On 14-OCT-1999, the patient developed pneumonia. On 15OCT97, the patient resumed bleeding. The bleeding was considered by the physician to be life threatening and an exploratory laparoscopy was performed. A gastric oversew was performed after a second bleeding [gastric] ulcer had been found. On 15-OCT-1999, the patient developed supraventricular tachycardia. Subsequently, the patient recovered. On 17OCT97, the patient was diagnosed with a thrombosed radial artery which resulted in necrosis of his fingers. Surgery was performed and considered successful and the patient recovered. On 17-OCT-1999 blinded study therapy was discontinued. On 18OCT97, the patient was switched from blinded study therapy to vancomycin for staphylococcus coverage. Amikacin and imipenem(MSD) therapy was added for broad spectrum antibiotic coverage. On 22OCT97, a possible tension pneumothorax was suspected. Subsequently the patient recovered from the possible tension pneumothorax. On 25OCT97, the patient died as a result of worsening multiple organ system failure (MOSF). The reporting physician felt the patient's experience was definitiely not related to study therapy.

APPEARS THIS WAY
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3022

A physician reported a 70 year old female who developed sepsis and peritonitis then died following blinded therapy with L749,345.

The patient had pneumothorax, intestinal diverticulitis, abdominal aortic aneurysm, hyperglycemia, acid reflux, hyperlipidemia and white blood cell count of 16.6 on 10SEP97. On 11SEP97, the patient was placed on blinded therapy with L749,345 550 mg intravenous daily or control, ceftriaxone sodium intravenous 2,000 mg daily or control, and metronidazole intravenous 500 mg daily every eight hours or control for the treatment of peritonitis.

On 11SEP97, the patient developed polymicrobial peritonitis that prolonged the hospitalization and was considered life threatening. On 13SEP97, study drug therapy was completed the patient was withdrawn from the study after cultures (unspecified) revealed *Pseudomonas aeruginosa*. Subsequently therapy with gentamycin was started for the treatment of the intra-abdominal sepsis until 24SEP97. Other treatment medications included therapy with vancomycin, tobramycin, ceftazidime, and metronidazole. Therapy with fluconazole was also administered for the presence of yeast. Little improvement in the patient's condition was seen with this change in therapy. On 27SEP97, an exploratory laparotomy was performed to drain the recurrent intra-abdominal abscesses. On 03OCT97, the patient developed MRSE (methicillin-resistant *Staphylococcus epidermis*) line sepsis that was considered life threatening and prolonged the patient's hospitalization. On 05OCT97, the patient was diagnosed with polymicrobial peritonitis and a chest tube was inserted that prolonged the patient's hospitalization and was considered life threatening. Subsequently, the patient denied any further surgery and requested withdrawal of any heroic measures. Her family consented but some antibiotic therapy was continued through 11OCT97. Then her family opted for the patient to receive comfort measures only. On 13OCT97 the patient died. The cause of death was reported as polymicrobial peritonitis and MRSE (methicillin-resistant *Staphylococcus epidermis*) line sepsis. The reporting physician felt the patient's sepsis and peritonitis were definitely not related to the study drug therapy.

APPEARS THIS WAY

ORIGINAL

3600

A physician reported that a 74 year old female experienced a cerebrovascular accident and subsequently died while on blinded therapy with L-749,345.

The patient was enrolled for treatment following a partial colectomy for a diverticular abscess and gangrenous peritonitis. It was noted by study personnel that there was no growth in cultures taken at surgery. On 05-MAR-1998 the patient was randomized to therapy with L-749,345 IV 1000 mg every 24 hours or control, ceftriaxone sodium 2 g IV every 24 hours or control and metronidazole 1500 mg IV every 8 hours or control for the treatment of intra-abdominal infection. On 06-MAR-1998, the patient developed acute respiratory failure. The patient was withdrawn from the study at her family's request on 06-MAR-1998. Her private physician placed her on therapy with clindamycin and ceftriaxone disodium salt hemiheptahydrate (Rocephin) on 06-MAR-1998.

On 06-MAR-1998 her pO₂ was low and she was intubated. She also experienced a series of ischemic attacks. On 07-MAR-1998, the patient developed acute renal failure. The patient began to develop clots post-surgery which resulted in at least two cerebrovascular accidents on 07-MAR-1998. On 09-MAR-1998 the patient died. Shock resulting from the cerebrovascular accident and respiratory failure were reported as the cause of death. The primary investigator felt that the cerebrovascular accident, acute respiratory failure, and acute renal failure were definitely not related to therapy with study drug. Additional information has been requested.

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PROTOCOL 014-Complicated Urinary Tract Infections

MK-0826 1 gm Treatment Group

2202

An 81-year-old female with hypertension and anxiety was admitted to the hospital with a right thalamic hemorrhage and began IV ertapenem therapy for the treatment of complicated urinary tract infection. On Study Day 9, the patient completed IV ertapenem therapy. On Study Day 15, the patient experienced hypoventilation. The patient's family requested that the patient be placed on "do not resuscitate" orders. The patient continued to worsen and on Study Day 23, was found unresponsive and pronounced dead. The reporting physician felt that the patient's death was probably not related to study drug therapy.

2859

A 76-year-old male with a history of urinary tract infection was hospitalized and began IV ertapenem therapy for the treatment of urinary tract infection. On Study Day 14, the patient completed IV study drug therapy. On Study Day 16, the patient developed a cough, purulent sputum, dyspnea and was diagnosed with nosocomial pneumonia. On Study Day 17, the patient was started on IV ceftazidime plus amikacin and heparin. On Study Day 22, the patient developed respiratory insufficiency and septic shock. These events were considered life-threatening. The patient was placed on a mechanical ventilator and central line catheter was inserted. On Study Day 23, IV dopamine, clindamycin and ranitidine were started and amikacin was discontinued. On Study Day 24, haemaccel was added to the patient's therapy. On Study Day 27, the patient died of septic shock. The reporting physician felt that the patient's nosocomial pneumonia, insufficiency respiratory, septic shock, and death were definitely not related to study drug therapy.

2877

A 64-year-old female with type 2 diabetes mellitus entered the study and received IV ertapenem therapy for the treatment of complicated urinary tract infection. The patient did not have any urologic abnormalities and the baseline urine culture result was no growth. A susceptible *Escherichia coli* was isolated from the baseline blood culture. On Study Day 2, the patient developed septicemia and septic shock, considered to be life threatening, and was admitted to the intensive care unit (ICU). On Study Day 4, laboratory evaluations revealed increased prothrombin time, increased blood urea nitrogen and increased serum creatinine. Study therapy was discontinued on Day 4 and the patient was treated with a different antibiotic. Laboratory evaluations on Study Day 5 revealed decreased serum bicarbonate. On Study Day 5, the patient had ventricular fibrillation and ventricular asystolia due to septic shock and died. The reporting physician felt that these events were definitely not related to study drug therapy.

Ceftriaxone

AN 2202

An 81-year-old female with hypertension and anxiety was admitted to the hospital with a right thalamic hemorrhage and began IV MK-0826 therapy for the treatment of complicated urinary tract infection. On Study Day 8, the patient completed IV MK-0826 therapy. On Study Day 15, the patient experienced hypoventilation. The patient's family requested that the patient be placed on "do not resuscitate" orders. The patient continued to worsen and on Study Day 23, was found unresponsive and pronounced dead. The reporting physician felt that the patient's death was probably not related to study drug therapy.

AN 2553

An 87-year-old female with stroke, cerebrovascular and coronary heart disease, mitral regurgitation, and atrial fibrillation began IV ceftriaxone study therapy for the treatment of complicated urinary tract infection. On Study Day 6, the patient was switched to oral ciprofloxacin 1 gram daily as per protocol and completed on Study Day 14. Subsequently, the investigator was informed by the patient's family members that the patient developed acute pneumonia on Study Day 27 and was hospitalized. On Study Day 30, the patient died of acute pneumonia. The reporting physician felt that the patient's pneumonia and death was definitely not related to the study drug therapy.

AN 2203

Medical Officer's Comment: *A narrative was not provided by the Applicant for this patient. The following is the a narrative based on the MO review of the CRF for this patient.*

The patient was a 75 year old male with a history of micronodular cirrhosis, hepatitis B, hepatic encephalopathy, coronary artery disease and CABG, splenectomy, and degenerative arthritis that was place on study with ertapenem 1 gm every 24 hours for complicated urinary tract infection due to E. coli and K. pneumoniae with associated K. pneumoniae bacteremia. On study day 4 the patient developed abdominal pain and was discontinued from study drug due to this AE which was considered probably not related to study drug by the Investigator. The patient developed progressive organ failure (renal and hepatic) and on discontinuation from study drug was placed empirically on vancomycin, ciprofloxacin, and metronidazole. Study day 4 blood cultures subsequently returned positive for P. aeruginosa and cefipime was added to the patients antimicrobial regimen on study day 9. The patient's condition continued to deteriorate and the patient died on study day 18.

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PROTOCOL 016-Complicated Skin and Skin Structure Infections

MK-0826 1 gm Treatment Group

4032

An 85-year-old male received 6 days of IV ertapenem therapy for treatment of a severe soft tissue infection in the arm. On Study Day 6, the patient's infection had worsened and involved the fascial tissue. The patient was switched to an alternative antibiotic therapy regimen of cefazolin and clindamycin. The patient underwent a surgical fasciotomy on Study Day 9 and was discontinued from antibiotic therapy on Study Day 10. On Study Day 10, the patient developed abdominal pain, diarrhea, and confusion related to pseudomembranous colitis. An assay for *Clostridium difficile* toxin was positive. The patient was treated with metronidazole. In the opinion of the investigator, the patient's pseudomembranous colitis was probably related to the study drug therapy. On Study Day 17, the patient developed respiratory failure and was placed on a ventilator until Study Day 18. On Study Day 23, the patient developed pseudomonal urosepsis. The patient was treated for 3 days with ciprofloxacin. The respiratory failure, worsening infection, and pseudomembranous colitis did not resolve. The patient died on Study Day 27. The cause of death was reported as urosepsis. In the opinion of the investigator, the urosepsis, fascial infection, and respiratory failure were not related to the study drug therapy.

4035

A 99-year-old female began IV ertapenem therapy for treatment of severe cellulitis of the left upper extremity. A culture of the wound drainage revealed *Streptococcus pyogenes* and *Staphylococcus aureus*. Blood cultures revealed *S. pyogenes*. The patient underwent debridement of the wound area. Pathological assessment of the wound showed evidence of necrotizing fasciitis, and further debridement was performed. The patient's baseline AST level was 47 IU/L. On Study Day 4, the patient developed respiratory failure and required mechanical ventilation for the duration of her hospital course. On Study Day 10, the patient spiked a fever, presumed to be secondary to intravenous catheter sepsis. Subsequent blood cultures were positive for coagulase negative *Staphylococcus*. The patient was discontinued from study drug therapy on Study Day 10. An antibiotic regimen of vancomycin and ceftazidime pentahydrate was started. On Study Day 10, laboratory results revealed that the patient's AST level was elevated to 196 IU/L, more than 4 times the baseline value. The patient was reported to have developed a systemic inflammatory response syndrome. On Study Day 12, therapy with ceftazidime was discontinued and the intravenous line sepsis was resolved. On Study Day 13, the patient demonstrated no significant improvement and medical support was discontinued. The patient expired on Study Day 13. The cause of death was reported as respiratory failure in the setting of sepsis from Group A *Streptococcus*. Systemic inflammation response syndrome was also reported to be related to the patient's death. The reporting physician felt that the elevated AST may have been related to the patient's IV line sepsis, but may also have been possibly related to study drug therapy. The respiratory failure, systemic inflammation response syndrome and intravenous line sepsis were felt to be definitely not related to study drug therapy.

4695

A 93-year-old male with chronic thrombocytopenia, diabetes mellitus, histiocytosis, atrial fibrillation, peripheral vascular disease, and a history of transient ischemic attacks received 6 days of IV ertapenem therapy for the treatment of a deep soft tissue abscess in the left groin. At study entry, the patient's platelet count was 52 ths/mm³. On Study Day 3, the platelet count was decreased to 33 ths/mm³. The count increased to 61 ths/mm³ on Study Day 11, but then decreased again on Study Day 12 and remained low, between 23 ths/mm³ and 46 ths/mm³ for the remainder of the study. On Study Day 10, the patient experienced a transient ischemic attack. A brain scan was performed, revealing bilateral subdural hematomas. This finding was considered by the investigator to be a chronic condition. On Study Day 11, an electroencephalogram was performed revealing evidence of complex partial seizures. The patient was treated for seizures with fosphenytoin and did not experience another seizure. The patient experienced an episode of vomiting on Study Day 11. In the opinion of the investigator, this episode was related to the increased intracranial pressure resulting from the subdural hematomas. As a result of the vomiting episode, the patient developed aspiration pneumonia and resulting respiratory failure. The patient was placed on a ventilator. An x-ray on Study Day 12 showed that the right lung was completely infiltrated. On Study Day 13, the patient underwent a craniotomy to drain the subdural hematomas, however, the patient did not improve clinically. A chest x-ray on Study Day 16 revealed worsening pneumonia involving both lungs. The patient died on Study Day 17. The cause of death was worsening pneumonia and respiratory failure. In the opinion of the investigator, the hematomas,

transient ischemic attack, seizure, pneumonia, and respiratory failure were not related to the study drug therapy. The investigator reported that the patient's death was related to the patient's advanced age and serious medical condition.

4801

A 66-year-old female with diabetes mellitus and cirrhosis began IV ertapenem therapy for the treatment of a diabetic lower extremity infection. On Study Day 5, resistant *Pseudomonas aeruginosa* was isolated in the skin secretion culture and the patient was discontinued from study drug therapy. An alternative antibiotic regimen of ciprofloxacin and amikacin was started. On Study Day 13, the patient experienced septic toxic shock, and was started on imipenem therapy. The patient was placed on mechanical ventilation. On Study Day 14, the patient presented multiple organ failure and subsequently died. The reporting physician felt that the multiple organ failure due to septic toxic shock was definitely not related to study drug therapy.

Ceftriaxone

AN 4023

A 72-year-old female with diabetes mellitus, chronic obstructive pulmonary disease, and congestive heart failure began IV piperacillin/tazobactam therapy for the treatment of diabetic infection in the left thigh. At the time of study entry, the patient was considered to have possible pneumonia and to be probably becoming hypovolemic. On Study Day 5, the patient was discontinued from study drug therapy. On Study Day 6, the patient developed hypotension and bradycardia leading to unresponsiveness after being assisted to the commode. The patient at that time, was believed to have had a vasovagal reaction, perhaps leading to cardiac ischemia. The investigator also believed that it was possible that the patient may have had a pulmonary embolism. The patient died on Study Day 6. The reporting physician felt that possible pulmonary embolism and/or vasovagal reaction were definitely not related to study drug therapy.

AN 4453

A 74-year-old male with intestinal necrosis and a history of colon cancer and prostate cancer began IV piperacillin/tazobactam therapy for treatment of a severe necrotizing soft tissue infection of the right thigh. The patient had been febrile with fevers up to 103°F (39.4°C) for several days. The patient underwent incision, drainage, and debridement of the wound. A culture of a tissue sample from the wound revealed *Escherichia coli*, *Morganella morganii*, *Pseudomonas aeruginosa*, *Peptostreptococcus*, *Bacteroides thetaiotaomicron*, and *Bacteroides fragilis*. The patient received 4 doses of study antibiotic therapy. On Study Day 1, the patient was reported to be septic and in worsening condition. A concurrent intra-abdominal infection was discovered and study drug therapy was discontinued. The patient was started on imipenem therapy. The patient was returned to the operating room and was found to have necrotic bowel with intestinal vascular insufficiency and an enterocutaneous fistula. The patient underwent a hemicolectomy and further incision and drainage of the right lower extremity infection. On Study Day 2, subsequent to surgery the patient developed acute onset of renal failure and was placed on hemodialysis. The patient also remained on ventilator support after the surgery due to his inability to breath independently. The patient died on Study Day 10. The probable cause of death was reported as sepsis, necrotic bowel, and acute renal failure. The investigator felt that sepsis, acute renal failure and intestinal vascular insufficiency were definitely not related to study drug therapy.

AN 4699

A 72-year-old male with elevated PT and PTT, atrial fibrillation, transient ischemic attacks, pain and a history of a left femoral popliteal artery bypass, left tibial bypass grafting and a right groin angiography and abdominal aortic aneurysm repair began IV piperacillin/tazobactam therapy for the treatment of an infected hematoma in the right groin area. Concomitant therapy included enoxaparin, warfarin, heparin, hydroxyzine, recombinant human T-PA (alteplase), amiodarone, acetaminophen/propoxyphene, propoxyphene napsylate, meperidine, aspirin, and acetaminophen. A blood culture grew *Staphylococcus aureus*. A wound culture grew *Proteus mirabilis*, *Escherichia coli*, *Staphylococcus aureus*, *Enterococcus* sp., and *Streptococcus agalactiae*. At the time of enrollment the patient had elevated coagulation tests (PT, 36.9 seconds; PTT, 53 seconds; INR, 8.1). This was

considered to be possibly related to the patient's infectious process. Anticoagulation was stopped at the time of enrollment into the study. On Study Day 5, the patient underwent surgical evacuation of the hematoma and debridement of the right groin area. The patient experienced increased postsurgical bleeding. He was returned to the operating room for re-exploration of the groin area. On Study Day 7, the patient's hemoglobin level decreased to 6.5 mg/dL. The patient was transfused with 3 units of packed red blood cells. The patient's coagulation tests continued to be elevated throughout the study treatment period. On Study Day 8, the patient's PT was 21.1 seconds. The patient's PTT ranged from 53 to 63 seconds, INR ranged from 8.1 to 2.6 and platelet count ranged from 105 to 397 ths/mm³. On Study Day 8, the patient experienced ventricular tachycardia with hypotension and epigastric abdominal pain. The patient underwent a computed axial tomography (CAT) scan of the abdomen. The CAT scan revealed a massive rupture of a retroperitoneal hematoma. Upon return from the CAT procedure, the patient developed cardio-respiratory arrest. Efforts at resuscitating the patient failed. The patient expired due to the retroperitoneal hematoma on Study Day 8. In the opinion of the investigator, these events were probably not related to study therapy.

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PROTOCOL 017-Complicate Intra-Abdominal Infections

MK-0826 1 gm Treatment Group

AN 0217

A 74-year-old male with a history of emphysema, cerebrovascular accident, an abdominal aortic aneurysm, gastric hyperacidity, and chronic obstructive lung disease began IV therapy with MK-0826 for treatment of diffuse peritonitis. The postoperative diagnosis described an ischemic colon with fecal peritonitis. On Study Day 9, the patient experienced respiratory distress and cardiac arrest and the patient was intubated. No action was taken with regard to study therapy. Subsequently, the patient recovered from the cardiac arrest and respiratory distress. On Study Day 10, the patient's platelet count was low despite intervening measures, which prompted the physician to diagnose the patient with thrombocytopenia. Consequently, all study medication was stopped. The patient was classified as a failure of study therapy on that day. Additional antibiotics were not started at that time. On Study Day 15, the patient experienced wound dehiscence, which was considered as life threatening. The patient underwent an unplanned surgical intervention to repair the dehiscence with gortex mesh. The patient was placed on vancomycin, piperacillin, cloxacillin, piperacillin/tazobactam and erythromycin. The patient's condition continued to deteriorate and on Study Day 18 was diagnosed with multiple organ failure (MOF). On Study Day 23, the patient died. The cause of death was determined to be MOF. The reporting physician felt that the respiratory distress, cardiac arrest, wound dehiscence, multiple organ failure and death were definitely not related to study therapy and the thrombocytopenia was possibly related to study therapy.

AN 0283

A 19-year-old male with a prior history of asthma began IV therapy with MK-0826 for the treatment of peritonitis. On Study Day 1, the patient experienced hypotension. On Study Day 2, the patient experienced septic shock and multiple organ failure, which were unresponsive to ventilatory support, therapy with dopamine, fentanyl, and adrenalin as well as volume replacement therapy with albumin. The patient had positive blood cultures for E. coli. The patient died on Study Day 2. The reporting physician felt that hypotension, multiple organ failure, peritonitis, septic shock and death were definitely not related to study therapy.

AN 0302

An 88-year-old female with decreased visual acuity, insomnia, cholestasis, arrhythmia, peripheral edema, hematoma, left pleural effusion, arterial occlusion, abdominal fistula, hemorrhages and an ovarian cyst began IV therapy with MK-0826 for the treatment of an intra-abdominal infection. On Study Day 2, the patient returned to surgery for an anastomosis, cholecystectomy and rectum resection, possibly due to the intra-abdominal infection. During surgery, a fistula with local peritonitis was found. The patient experienced septic shock during surgery. On Study Day 3, the patient's septic shock persisted and worsened with multiple organ failure. Subsequently, the patient recovered from septic shock and multiple organ failure. On Study Day 14, the patient experienced septic shock again with a new abdominal fistula. Study therapy was then discontinued. Subsequently, the patient recovered from septic shock. On Study Day 19, the patient died from the second abdominal fistula. The reporting physician felt that the recurrent septic shock, multiple organ failure, abdominal fistula, and death were probably not related to study therapy.

AN 0372

A 72-year-old male entered an emergency room with tachypnea, dyspnea, and uncoordinated breathing. The patient began IV therapy with MK-0826 following abdominal surgery for septic peritonitis. On Study Day 1, the patient was in septic shock. On Study Day 2, the patient died due to the septic shock. The investigator felt that the septic shock and death were definitely not related to study therapy.

AN 0388

A 92-year-old female with a history of heart failure, cor pulmonale, chronic bronchitis, hypothyroidism, and diabetes mellitus began IV therapy with MK-0826 for treatment of an intra-abdominal infection. The patient was on maintenance furosemide and losartan for the heart failure. On Study Day 2, the patient experienced worsening of heart failure and was transferred to ICU and IV study drug therapy was discontinued. The patient was put on a dopamine drip and given volume replacement with albumin. The patient's heart failure persisted. The patient eventually died on Study Day 8 due to the heart failure. The reporting physician felt that heart failure and death were probably not related to study drug therapy.

AN 0405

A 70-year-old female with a history of diabetes mellitus, and anemia began IV therapy with MK-0826 for treatment of an intra-abdominal infection. On Study Day 3, the physician noticed indurative edema in the right latero-cervical region, and modified the position of the venous catheter, which was first positioned in the internal jugular vein. After some attempts, the catheter was positioned correctly in the right atrium by means of a new percutaneous puncture in the right subclavian vein. Later, the patient experienced hypotension, sweating, and became cyanotic. A blood gas analysis was performed, which showed anemia and metabolic acidosis. Notwithstanding all the efforts to perform a cardiorespiratory reanimation, the patient died. The cause of death was cardiac arrest and pulmonary embolism. The reporting physician felt that the acidosis, pulmonary embolism, cardiac arrest, and death were probably not related to study therapy.

AN 0491

A 71-year-old male with a history of thumb amputation and hypoalbuminemia began IV therapy with MK-0826 for treatment of an intra-abdominal infection. On Study Day 9, the patient developed pulmonary edema and cardiac arrhythmias. The patient subsequently died due to the arrhythmia and pulmonary edema. The reporting physician felt that the cardiac arrhythmia, pulmonary edema, and death were definitely not related to study therapy.

Medical Officer's Comment: Additional information regarding this patient's death was requested from the Applicant and the Applicant submitted the requested information in their July 30, 2001 submission to the NDA. Additional information provided included the WAES report for this patient and ECGs from time of enrollment on study. No additional ECGs around the time of death (2 days post discontinuation of study drug) were provided.

AN 0513

A 37-year-old male who sustained a small bowel perforation began IV therapy with MK-0826 for treatment of an intra-abdominal infection. On Study Day 4, the patient developed postoperative pneumonia. This resulted in respiratory distress and the patient was intubated and ventilated. On Study Day 5, the patient had a repeat laparotomy to exclude an abdominal focus of sepsis, and was diagnosed with an uncontrolled septicemia. The patient had baseline blood cultures performed that were negative. On Study Day 6, study drug therapy was discontinued. The patient was then placed on piperacillin/tazobactam, amikacin, cefepime, metronidazole, and vancomycin for the septicemia. On Study Day 11, the patient was diagnosed with an intestinal fistula. The patient's postoperative pneumonia persisted. On Study Day 24, the patient experienced multiple organ failure and died on Study Day 39. The reporting physician felt that uncontrolled septicemia was probably not related and operative pneumonia, small bowel fistula, multiple organ failure, and death were definitely not related to study drug therapy.

AN 0528

A 59-year-old female with thrombocytopenia and anemia began IV therapy with MK-0826 for treatment of an intra-abdominal infection. On Study Day 5, the patient was placed on teicoplanin. On Study Day 8, the patient experienced peritonitis and multiple organ failure. On Study Day 11, IV study therapy was discontinued due to fasciitis and a deep soft tissue infection and the patient subsequently died that day. The reporting physician felt that the multiple organ failure, peritonitis, and death were definitely not related to study therapy.

AN 0542

An 84-year-old female with a history of arterial hypertension, arthritis, and hysterectomy began IV therapy with MK-0826 for treatment of peritonitis. On Study Day 1, the patient was diagnosed with adenocarcinoma. On Study Day 5, the patient developed a sudden and progressive arterial hypotension with severe acidosis and hypoxemia.

Subsequently, the patient experienced cardiopulmonary failure and died. The reporting physician felt that the cardiopulmonary failure, death, and adenocarcinoma were probably not related to study therapy.

AN 0694

A 19-year-old male with no significant prior history, began IV therapy with MK-0826 for treatment of an intra-abdominal infection. On Study Day 2, the patient rapidly developed a bradycardia and had a cardiac arrest. A full cardiopulmonary resuscitation was started. The patient was intubated, ventilated, and received cardiac massage. The patient also received adrenaline and atropine. Despite resuscitation attempts, no response was seen and the patient was declared dead. The reporting physician felt that the cardiac arrest and death were probably not related to study therapy.

***Medical Officer's Comment:** Additional information regarding this patient's death was requested from the Applicant and the Applicant submitted the requested information in their July 30, 2001 submission to the NDA. Additional useful information obtained from the patient's hospital record of the time preceding death included that on the first post-operative evening the patient developed progressive hypotension unresponsive to fluid bolus or pressor support, progressive dyspnea, and eventually bradycardia and cardiac arrest from which medical staff was unable to resuscitate the patient. The autopsy report provided includes the statement that patient was HIV positive (CD4 count unreported) and the findings of hemoperitoneum and an additional 30 cm of necrotic small bowel at postmortem. Based on the additional information provided by the Applicant, the MO believes that this patient's death most likely resulted from inadequate surgical intervention, persistent intraperitoneal bleeding, and inadequate source control of the initial infection.*

AN 0919

A 73-year-old male with a history of hip replacement, rheumatoid arthritis, chronic heart failure, chronic respiratory failure, chronic bronchitis, and prostate cancer began IV therapy with MK-0826 for treatment of an intra-abdominal infection. On Study Day 3, the patient experienced a wound infection. On Study Day 7, the patient was considered a failure of therapy due to fasciitis and placed on cefotaxime, and ceftazidime. On Study Day 9, it was discovered that the patient had an abdominal hernia that was repaired with surgery. On Study Day 11, the patient experienced pneumonia. On Study Day 12, the patient experienced respiratory insufficiency and IV study therapy was discontinued. On Study Day 16, the patient experienced heart failure and subsequently died on Study Day 19. The reporting physician felt that abdominal hernia, heart failure, wound infection, pneumonia, respiratory insufficiency, and death were definitely not related to study therapy.

AN 0923

A 54-year-old female with a history of diabetes mellitus and systolic murmur began therapy with MK-0826 for treatment of generalized peritonitis. On Study Day 1, the patient experienced hypotension and cardiac arrest. The patient was placed on dobutamine, noradrenalin, and atropine. The patient died on Study Day 2. The reporting physician felt that the hypotension, cardiac arrest and death were definitely not related to study therapy.

***Medical Officer's Comment:** Additional information regarding this patient's death was requested from the Applicant and the Applicant submitted the requested information in their July 30, 2001 submission to the NDA. Additional useful information obtained from this patient's hospital records included that the patient required reintubation in the proximate post-operative time period due to the development of bradycardia that was also initially treated with atropine. The patient was re-extubated 4 hours later and transferred to a general floor bed the next day. That day the patient experience a cardiopulmonary arrest and was reintubated and resuscitated and transferred to the ICU, however, the patient experienced persistent bradycardia and hypotension despite attempts at resuscitation and died on hospital day 2.*

AN 5331

A 52-year-old male with a history of St. Jude's valve replacement began IV MK-0826 1.0 gram therapy for treatment of a postoperative intra-abdominal abscess with anastomotic leak, following abscess drainage. On Study Day 2, his abdomen was again distended with increasing right quadrant pain and he developed an increased respiratory rate. Subsequently, he was returned to the operating room for exploration where a left colon resection, transverse colostomy, Hartman's pouch, and drainage of an intra-abdominal abscess were performed. He was extubated in the recovery room. Shortly thereafter, he became very tachypneic, tachycardic, hypotensive and diaphoretic. He received meperidine over a two and one-half hour period for pain and was re-intubated. An arterial