Number (%) of Patients With Specific Laboratory Adverse Experiences (Incidence >0% in One or More Treatment Groups) by Laboratory Test Category During Study Therapy and 14-Day Follow-Up Period (Treated Population)

	MK-0826 1.0 g (N=316)		MK-0826 1.5 g (N=14)		Piperacillin/Tazobactam (N=325)	
	n/m	(%)	n/m	(%)	n/m	(%)
Patients with one or more adverse experiences	115/310	(37.1)	7/13	(53.8)	127/321	(39.6)
Patients with no adverse experience	195/310	(62.9)	6/13	(46.2)	194/321	(60.4)
Blood Chemistry	**79/309**	**(25.6)**	**6/13**	**(46.2)**	**102/321**	**(31.8)**
ALT increased	34/283	(12.0)	3/13	(23.1)	32/295	(10.8)
Amylase increased	0/0	(0.0)	0/0	(0.0)	2/2	(100)
Arterial pH decreased	1/1	(100)	0/0	(0.0)	0/0	(0.0)
Arterial PO_2 decreased	1/1	(100)	0/0	(0.0)	1/1	(100)
AST increased	29/297	(9.8)	2/13	(15.4)	40/308	(13.0)
Blood urea increased	0/41	(0.0)	0/0	(0.0)	4/38	(10.5)
BUN decreased	1/255	(0.4)	0/13	(0.0)	1/273	(0.4)
BUN increased	2/255	(0.8)	1/13	(7.7)	4/273	(1.5)
Direct serum bilirubin increased	9/181	(5.0)	2/4	(50.0)	6/177	(3.4)
Indirect serum bilirubin increased	4/123	(3.3)	0/0	(0.0)	0/117	(0.0)
Lipase decreased	1/1	(100)	0/0	(0.0)	0/1	(0.0)
Lipase increased	0/1	(0.0)	0/0	(0.0)	1/1	(100)
PCO_2 increased	1/1	(100)	0/0	(0.0)	0/0	(0.0)
Serum albumin decreased	11/290	(3.8)	1/13	(7.7)	8/303	(2.6)
Serum alkaline phosphatase increased	31/298	(10.4)	1/13	(7.7)	40/310	(12.9)
Serum bicarbonate decreased	4/276	(1.4)	1/10	(10.0)	3/279	(1.1)
Serum calcium decreased	2/300	(0.7)	0/13	(0.0)	1/309	(0.3)
Serum chloride increased	0/307	(0.0)	0/13	(0.0)	1/319	(0.3)
Serum CO_2 decreased	1/1	(100)	0/0	(0.0)	1/1	(100)
Serum creatinine phosphokinase increased	1/1	(100)	0/0	(0.0)	0/0	(0.0)
Serum creatinine decreased	1/309	(0.3)	0/13	(0.0)	0/321	(0.0)
Serum creatinine increased	6/309	(1.9)	1/13	(7.7)	12/321	(3.7)
Serum gamma-glutamyl transferase increased	0/0	(0.0)	0/0	(0.0)	2/2	(100)
Serum glucose decreased	1/309	(0.3)	0/13	(0.0)	2/319	(0.6)
Serum glucose increased	5/309	(1.6)	0/13	(0.0)	8/319	(2.5)
Serum iron decreased	0/0	(0.0)	0/0	(0.0)	1/1	(100)
Serum magnesium decreased	1/1	(100)	1/1	(100)	3/3	(100)
Serum magnesium increased	1/1	(100)	0/1	(0.0)	0/3	(0.0)
Serum phosphate decreased	0/1	(0.0)	1/1	(100)	2/2	(100)
Serum phosphorus increased	1/1	(100)	0/1	(0.0)	0/2	(0.0)
Serum potassium decreased	10/309	(3.2)	0/13	(0.0)	18/321	(5.6)
Serum potassium increased	4/309	(1.3)	1/13	(7.7)	2/321	(0.6)
Serum sodium decreased	1/309	(0.3)	0/13	(0.0)	1/321	(0.3)
Serum sodium increased	3/309	(1.0)	1/13	(7.7)	0/321	(0.0)
Serum uric acid decreased	0/0	(0.0)	0/0	(0.0)	1/1	(100)
Thyroid function abnormal	1/1	(100)	0/0	(0.0)	0/0	(0.0)
Total serum bilirubin decreased	0/298	(0.0)	0/13	(0.0)	1/311	(0.3)
Total serum bilirubin increased	10/298	(3.4)	3/13	(23.1)	8/311	(2.6)
Total serum protein decreased	7/289	(2.4)	0/13	(0.0)	8/303	(2.6)
Total serum protein increased	0/289	(0.0)	0/13	(0.0)	1/303	(0.3)
TSH increased	0/0	(0.0)	0/0	(0.0)	1/1	(100)

	MK-0826 1.0 g (N=316)		MK-0826 1.5 g (N=14)		Piperacillin/Tazobactam (N=325)	
	n/m	(%)	n/m	(%)	n/m	(%)
Hematology	**58/310**	**(18.7)**	**4/13**	**(30.8)**	**60/321**	**(18.7)**
Band neutrophils increased	2/301	(0.7)	0/13	(0.0)	1/310	(0.3)
Basophils increased	1/301	(0.3)	0/13	(0.0)	0/310	(0.0)
Eosinophils increased	1/301	(0.3)	0/13	(0.0)	1/310	(0.3)
Hematocrit decreased	14/310	(4.5)	2/13	(15.4)	18/321	(5.6)
Hematocrit increased	1/310	(0.3)	0/13	(0.0)	0/321	(0.0)
Hemoglobin decreased	24/310	(7.7)	1/13	(7.7)	25/321	(7.8)
INR increased	1/270	(0.4)	0/13	(0.0)	4/281	(1.4)
Lymphocytes decreased	1/301	(0.3)	0/13	(0.0)	2/310	(0.6)
Lymphocytes, atypical	1/301	(0.3)	0/13	(0.0)	0/310	(0.0)
Metamyelocytes increased	1/301	(0.3)	0/13	(0.0)	0/310	(0.0)
Monocytes decreased	1/301	(0.3)	0/13	(0.0)	0/310	(0.0)
Monocytes increased	1/301	(0.3)	0/13	(0.0)	1/310	(0.3)
Myelocytes increased	1/301	(0.3)	0/13	(0.0)	0/310	(0.0)
Platelet count decreased	2/310	(0.6)	1/13	(7.7)	7/321	(2.2)
Platelet count increased	20/310	(6.5)	1/13	(7.7)	22/321	(6.9)
Prothrombin time decreased	1/271	(0.4)	0/13	(0.0)	1/276	(0.4)
Prothrombin time increased	7/271	(2.6)	0/13	(0.0)	6/276	(2.2)
PTT increased	2/282	(0.7)	0/13	(0.0)	7/289	(2.4)
RBC count decreased	1/1	(100)	0/0	(0.0)	0/0	(0.0)
RDW, increased	0/0	(0.0)	0/0	(0.0)	1/1	(100)
Segmented neutrophils decreased	1/301	(0.3)	0/13	(0.0)	1/310	(0.3)
Segmented neutrophils increased	6/301	(2.0)	0/13	(0.0)	4/310	(1.3)
WBC decreased	2/310	(0.6)	0/13	(0.0)	1/321	(0.3)
WBC increased	12/310	(3.9)	2/13	(15.4)	19/321	(5.9)
Urinalysis	**19/296**	**(6.4)**	**3/13**	**(23.1)**	**24/305**	**(7.9)**
Creatinine clearance decreased	0/0	(0.0)	0/0	(0.0)	2/2	(100)
Unspun urine WBCs increased	4/256	(1.6)	0/11	(0.0)	5/275	(1.8)
Urine bacteria increased	5/256	(2.0)	1/11	(9.1)	7/275	(2.5)
Urine bilirubin increased	1/256	(0.4)	0/11	(0.0)	0/275	(0.0)
Urine blood increased	3/256	(1.1)	1/10	(10.0.1)	5/281	(1.8)
Urine crystals increased	0/256	(0.0)	0/11	(0.0)	1/275	(0.4)
Urine epithelial cells increased	3/256	(1.2)	0/11	(0.0)	4/275	(1.5)
Urine glucose increased	1/293	(0.3)	0/13	(0.0)	0/301	(0.0)
Urine granular casts increased	0/256	(0.0)	0/11	(0.0)	1/275	(0.4)
Urine protein increased	2/295	(0.7)	1/13	(7.7)	3/301	(1.0)
Urine RBCs increased	5/256	(2.0)	1/11	(9.1)	6/275	(2.2)
Urine transitional cells increased	0/0	(0.0)	0/0	(0.0)	1/1	(100)
Urine WBC casts present	0/256	(0.0)	0/11	(0.0)	1/275	(0.4)
Urine WBCs increased	8/256	(3.1)	2/11	(18.2)	13/275	(4.7)
Urine yeast present	2/256	(0.8)	1/11	(9.1)	1/275	(0.4)
Urine 24 hr urea increased	1/1	(100)	0/0	(0.0)	0/0	(0.0)
Miscellaneous	**2/3**	**(66.7)**	**0/1**	**(0.0)**	**1/2**	**(50.0)**
C. difficile toxin, positive.	1/3	(33.3)	0/1	(0.0)	0/1	(0.0)
Fecal occult blood	0/0	(0.0)	0/0	(0.0)	1/1	(100)
Guaiac positive	1/1	(100)	0/0	(0.0)	0/0	(0.0)

N = Total number of patients per treatment group.
n/m = Number of patients with laboratory adverse experience/number of patients with laboratory test.
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 categories are listed in which at least 1 patient had an adverse experience.

(Applicant's Table 136, Volume 13 of 22, pages 529-531)

Number (%) of Patients With Specific Laboratory Adverse Experiences (Incidence >0% in One or More Treatment Groups) by Laboratory Test Category During Study Therapy and 14-Day Follow-Up Period (Treated Population) Drug Related

	MK-0826 1.0 g (N=316)		MK-0826 1.5 g (N=14)		Piperacillin/Tazobactam (N=325)	
	n/m	(%)	n/m	(%)	n/m	(%)
Patients with one or more drug-related[1] adverse experiences	40/310	(12.9)	2/13	(15.4)	44/321	(13.7)
Patients with no drug-related adverse experience	270/310	(87.1)	11/13	(84.6)	277/321	(86.3)
Blood Chemistry	**32/309**	**(10.4)**	**2/13**	**(15.4)**	**35/321**	**(10.9)**
ALT increased	19/283	(6.7)	1/13	(7.7)	18/295	(6.1)
AST increased	18/297	(6.1)	1/13	(7.7)	20/308	(6.5)
BUN decreased	0/255	(0.0)	0/13	(0.0)	1/273	(0.4)
BUN increased	1/255	(0.4)	0/13	(0.0)	0/273	(0.0)
Direct serum bilirubin increased	5/181	(2.8)	1/4	(25.0)	1/177	(0.6)
Indirect serum bilirubin increased	2/123	(1.6)	0/0	(0.0)	0/117	(0.0)
Serum alkaline phosphatase increased	21/298	(7.0)	1/13	(7.7)	20/310	(6.5)
Serum bicarbonate decreased	1/276	(0.4)	0/10	(0.0)	0/279	(0.0)
Serum creatinine decreased	1/309	(0.3)	0/13	(0.0)	0/321	(0.0)
Serum creatinine increased	2/309	(0.6)	0/13	(0.0)	0/321	(0.0)
Serum gamma-glutamyl transferase increased	0/0	(0.0)	0/0	(0.0)	1/2	(50.0)
Serum glucose decreased	0/309	(0.0)	0/13	(0.0)	1/319	(0.3)
Serum iron decreased	0/0	(0.0)	0/0	(0.0)	1/1	(100)
Serum phosphorus increased	1/1	(100)	0/1	(0.0)	0/2	(0.0)
Serum potassium decreased	1/309	(0.3)	0/13	(0.0)	0/321	(0.0)
Total serum bilirubin increased	6/298	(2.0)	1/13	(7.7)	2/311	(0.6)
Hematology	**12/310**	**(3.9)**	**1/13**	**(7.7)**	**17/321**	**(5.3)**
Band neutrophils increased	1/301	(0.3)	0/13	(0.0)	0/310	(0.0)
Hematocrit decreased	0/310	(0.0)	0/13	(0.0)	2/321	(0.6)
Hemoglobin decreased	0/310	(0.0)	0/13	(0.0)	2/321	(0.6)
INR increased	0/270	(0.0)	0/13	(0.0)	2/281	(0.7)
Lymphocytes decreased	1/301	(0.3)	0/13	(0.0)	0/310	(0.0)
Lymphocytes, atypical	1/301	(0.3)	0/13	(0.0)	0/310	(0.0)
Metamyelocytes increased	1/301	(0.3)	0/13	(0.0)	0/310	(0.0)
Myelocytes increased	1/301	(0.3)	0/13	(0.0)	0/310	(0.0)
Platelet count decreased	0/310	(0.0)	1/13	(7.7)	2/321	(0.6)
Platelet count increased	7/310	(2.3)	0/13	(0.0)	12/321	(3.7)
Prothrombin time increased	0/271	(0.0)	0/13	(0.0)	2/276	(0.7)
Segmented neutrophils increased	2/301	(0.7)	0/13	(0.0)	0/310	(0.0)
WBC decreased	2/310	(0.6)	0/13	(0.0)	0/321	(0.0)
WBC increased	2/310	(0.6)	0/13	(0.0)	1/321	(0.3)
Urinalysis	**3/296**	**(1.0)**	**0/13**	**(0.0)**	**2/303**	**(0.7)**
Urine bacteria increased	1/256	(0.4)	0/11	(0.0)	0/275	(0.0)
Urine epithelial cells increased	2/256	(0.8)	0/11	(0.0)	1/275	(0.4)
Urine protein increased	0/295	(0.0)	0/13	(0.0)	1/301	(0.3)
Miscellaneous	**1/3**	**(33.3)**	**0/1**	**(0.0)**	**0/2**	**(0.0)**
C. difficile toxin, positive	1/3	(33.3)	0/1	(0.0)	0/1	(0.0)

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

(Applicant's Table 137, Volume 13 of 22, page 532)

Medical Officer's Comment: ***The incidence of laboratory adverse experiences was similar among the treatment groups.***

One patient (0.3%) in the MK-0826 1 gm group (AN 0219), 1 patient (7.7%) in the MK-0826 1.5 gm group (AN 5103), and 7 patients (2.2%) in the piperacillin/tazobactam

group (ANs 0140, 0286, 0303, 0473, 0640, 0695, and 5399) had serious laboratory adverse experiences. These all occurred during parenteral therapy. There were no additional serious laboratory adverse experiences that occurred during or after the 14-day follow-up period. One patient (AN 0286) in the piperacillin/tazobactam group experienced serious laboratory adverse events (increased serum AST, ALT, and alkaline phosphatase) that were judged by the investigator to be possibly study drug related. The table below displays a summary for patients with serious laboratory adverse experiences that occurred during the entire study period.

Listing of Patients With Serious Laboratory Adverse Experiences During Parenteral Therapy and 14-Day Follow-Up Period (Treated Population)

AN	Study Number	Gender	Race	Age	Daily Dose†	Relative Day of Test	Adverse Experience	Lab Value (Unit)	Normal Range	Drug Relationship	Action Taken
MK-0826 1 g											
0219	017027	F	Caucasian	78	A/1 g	4	Hemoglobin decreased	86 g/L	120 to 160 g/L	Definitely not	None
MK-0826 1.5 g											
5103	017010	M	Caucasian	65	A/1.5 g	8	BUN increased	121 mg/dL	7 to 23 mg/dL	Definitely not	None
					A/1.5 g	8	Hematuria	26 /hpf	0 to 3/hpf	Definitely not	None
					A/1.5 g	8	Serum creatinine increased	1.9 mg/dL	0.5 to 1.2 mg/dL	Probably not	None
					A/1.5 g	8	Hematuria	26/hpf	0 to 3/hpf	Definitely not	None
					A/1.5 g	8	Hematuria	2 qual no	0 to 0 qual no	Definitely not	None
					A/1.5 g	11	Bicarbonate decreased	17 mEq/L	24 to 32 mEq/L	Definitely not	None
					A/1.5 g	11	BUN increased	170 mg/dL	7 to 23 mg/dL	Definitely not	None
					A/1.5 g	11	Serum creatinine increased	4 mg/dL	0.5 to 1.2 mg/dL	Probably not	None
					A/1.5 g	11	Leukocyte count increased	29.4 ths/mm^3	4.3 to 10.3 ths/mm^3	Definitely not	None
					A/1.5 g	11	Bicarbonate decreased	16 mEq/L	24 to 32 mEq/L	Definitely not	None
Piperacillin/Tazobactam 3.375 g											
5399	017004	F	Caucasian	54	B/10.125 g	2	Hypomagnesemia	1.2 mg/dL	1.6 to 2.7 mg/dL	Probably not	None
0286	017033	M	Hispanic	57	B/13.5 g	5	AST increased	177 IU	0 to 38 IU	Possibly	None
					B/13.5 g	5	ALT increased	213 IU	0 to 41 IU	Possibly	None
					OFF drug	13	Alkaline phosphatase increased	1041 IU	0 to 270 IU	Possibly	None
0640	017035	F	Caucasian	69	B/3.375 g	2	Creatinine clearance decreased	29 mL/min/1.73 m^2	75 to 127 mL/min/1.73 m^2	Probably not	Reduce
					B/13.5 g						
					B/3.375 g	3	Creatinine clearance decreased	28 mL/min/1.73 m^2	75 to 127 mL/min/1.73 m^2	Probably not	Reduce
					B/13.5 g						
					B/13.5 g	3	Serum creatinine increased	139 micromol/L	45 to 102 micromol/L	Probably not	Reduce
					B/13.5 g	3	BUN increased	11.9 mmol/L	1.8 to 6.4 mmol/L	Probably not	Reduce
					B/3.375 g	4	Creatinine clearance decreased	26.6 mL/min/1.73 m^2	75 to 127 mL/min/1.73 m^2	Probably not	Reduce
					B/13.5 g						
					B/3.375 g	5	Creatinine clearance decreased	33 mL/min/1.73 m^2	75 to 127 mL/min/1.73 m^2	Probably not	Reduce
					B/13.5 g						
					B/13.5 g	6	Serum creatinine increased	141 micromol/L	45 to 102 micromol/L	Probably not	Reduce
					B/3.375 g	7	Creatinine clearance decreased	30 mL/min/1.73 m^2	75 to 127 mL/min/1.73 m^2	Probably not	Reduce
					B/13.5 g						
					B/13.5 g	7	Serum creatinine increased	137 micromol/L	45 to 102 micromol/L	Probably not	Reduce
					B/13.5 g	7	BUN increased	21.4 mmol/L	1.8 to 6.4 mmol/L	Probably not	Reduce
0303	017045	M	Caucasian	82	B/13.5 g	3	Creatinine clearance decreased	15.5 mL/min/1.73 m^2	91 to 130 mL/min/1.73 m^2	Definitely not	Reduce

					B/10.125 g B/13.5 g	4	Creatinine clearance decreased	24.2 mL/min/1.73 m^2	91 to 130 mL/min/1.73 m^2	Definitely not	Reduce
					B/10.125 g B/13.5 g	5	Creatinine clearance decreased	37 mL/min/1.73 m^2	91 to 130 mL/min/1.73 m^2	Definitely not	Reduce
0140	017048	M	Caucasian	53	B/10.125 g B/13.5 g	6	Serum creatinine increased	3.5 mg/100 mL	0.6 to 1.1 mg/100 mL	Probably not	None
					B/13.5 g	6	Hyperkalemia	5.4 mEq/L	3 to 5 mEq/L	Probably not	None
					B/13.5 g	6	BUN increased	121 mg/100 mL	20 to 40 mg/100 mL	Probably not	None
					B/13.5 g	7	Serum creatinine increased	3.7 mg/100 mL	0.6 to 1.1 mg/100 mL	Probably not	None
					B/13.5 g	7	Hyperkalemia	5.9 mEq/L	3 to 5 mEq/L	Probably not	None
					B/13.5 g	7	BUN increased	145 mg/100 mL	20 to 40 mg/100 mL	Probably not	None
					B/13.5 g	7	Leukocyte count increased	16.44 ths/mm^3	3.8 to 10.6 ths/mm^3	Probably not	None
					B/13.5 g	16	Serum creatinine increased	2.9 mg/100 mL	0.6 to 1.1 mg/100 mL	Probably not	None
					B/13.5 g	16	BUN increased	137 mg/100 mL	20 to 40 mg/100 mL	Probably not	None
0473	017054	M	Black	25	B/13.5 g	4	Hemoglobin decreased	8.1 g/dL	14.3 to 18.3 gm/dL	Definitely not	None
0695	017054	M	Black	56	B/6.75 g	2	Serum creatinine increased	340 U/mol/L	60 to 120 U/mol/L	Definitely not	None

[f] Displays daily dose 1 day prior to laboratory adverse experience.
Drug A is MK-0826.
Drug B is piperacillin/tazobactam 3.375 g.

(Applicant's Table 76, Volume 13 of 22, pages 284-287)

Medical Officer's Comment: ***As previously noted in MO's comments, the MO does not feel that study drug relatedness can be excluded as a cause of laboratory adverse events for AN 0140, who is not included in the preceding table.***

7.1.1.2.7 Assessment of Tolerability

An assessment of tolerability at the IV study drug infusion site was performed daily while the patient was on study therapy. The intensity of specified local infusion-related symptoms was rated as mild, moderate, or severe. Of patients who experienced one or more local reactions at the infusion site, 60/317 (18.9%) were in the MK-0826 1 gm group and 57/325 (17.5%) were in the piperacillin/tazobactam group. If local intolerance was felt by the Investigator to reach the level of a clinical adverse experience, the adverse experience was reported as a clinical syndrome (e.g. local phlebitis/thrombophlebitis) and was displayed as "infused vein complication" in the counts of clinical adverse experiences. A clinical adverse experience of "infused vein complication" was reported for 6/316 (1.9%) of patients in the MK-0826 1 gm group and 9/325 (2.8%) of patients in the piperacillin/tazobactam group. The following table presents the proportions of patients reporting any local reactions and the proportions of patients reporting one or more symptoms of moderate to severe intensity.

Number (%) of Patients With Symptoms of Intravenous (IV) Therapy Intolerance During Intravenous (IV) Therapy
(Treated Population)

	Treatment Group						Difference (A-B) % (95% CI)
	MK-0826 1 g (A) (N=316)			Piperacillin/Tazobactam (B) (N=325)			
	n/m	(%)	(95% CI)	n/m	(%)	(95% CI)	
Patients with one or more symptoms	60/317[1]	(18.9)	(14.6, 23.6)	57/325	(17.5)	(13.4, 21.7)	1.4 (-4.6, 7.4)
Patients with one or more symptoms of moderate-to-severe intensity	26/317[1]	(8.2)	(5.2, 11.2)	20/325	(6.2)	(3.5, 8.8)	2.0 (-1.9, 6.0)

[1] AN 5380 in the MK-0826 1-g group is counted in error; this patient was randomized but never received study drug.
N = Number of treated patients in each treatment group.
n/m = Number of patients reporting intolerability symptom/ number of patients with an assessment. Patients with an assessment "Not Done" were not counted.
CI = Confidence interval.

(Applicant's Table 82, Volume 13 of 22, page 295)

Medical Officer's Comment: ***Overall the rates of local reactions were similar in the 2 treatment groups.***

7.1.1.2.8 Adverse Experiences of Special Interest

Four adverse experiences were prespecified for more detailed review because of preclinical findings (neutropenia), adverse experiences associated with β-lactam antibiotics as a class (liver function elevations and rash), and adverse experiences associated with other carbapenem antimicrobials (seizures).

Seizures

One patient in the MK-0826 1 gm group (AN 0955) reported a seizure (grand mal) during parenteral therapy; judged by investigator to be serious and possibly drug related. Two patients (ANs 0272 and 5399) in the piperacillin/tazobactam reported a seizure disorder during parenteral therapy. AN 0272's adverse experience was considered by the investigator to be serious and probably related to the study drug therapy. AN 5399's adverse experience was considered serious by the investigator but definitely not study drug related. AN 0955 and AN 0272 did not have a prior history of seizure disorder (these patients were previously described in Section 7.1.1.2.4 of this review).

AN 5399 had a prior history of epilepsy and was being treated with phenobarbital and valproic acid and was reported to have had a single seizure on study day 4 that consisted of "left side of her mouth was twitching, her eyes rolled back". This patient's hospital course was also complicated by hypomagnesemia, efficacy failure, elevated blood pressure, sinus arrest, a deep vein thrombosis of the left internal jugular (no intravenous line had been present), and SVT. The patient was discontinued from study drug on Day 10. The patient subsequently experienced 1 minute of ventricular tachycardia on Day 22, atrial fibrillation on Day 23, and death on Day 29 due to unknown causes.

Neutropenia/Liver Enzyme Elevations

In addition to reviewing investigator-reported laboratory adverse experiences, the Applicant performed an assessment of the relative laboratory safety of each treatment group by using predefined Clinically Significant Laboratory Abnormalities (CSLAs) for specified tests and identifying patients whose worst laboratory value represented a

worsening from baseline and met the criteria for a CSLA. In order to be considered in the analysis for CSLAs, patients had to have a baseline laboratory value, at least 1 post-baseline laboratory test and have normal ranges in the database. For platelet count, absolute neutrophil count, hematocrit, and hemoglobin, the CSLA criteria were defined in terms of a fixed bound. For creatinine, total bilirubin, direct bilirubin, ALT, AST, and alkaline phosphatase, the CSLA criteria were defined in terms of a fixed bound greater than the upper limit of normal (ULN). The following table displays CSLAs for neutropenia and liver function assays during the parenteral therapy period and the total study therapy plus the follow-up period.

Number (%) of Patients With a Clinically Significant Laboratory Abnormality (CSLA)
by Treatment Group
During Study Therapy and 14-Day Follow-Up Period
(Treated Population)

Laboratory Test	CSLA Criteria	MK0826 1 g (N=316)		MK0826 1.5 g (N=14)		Piperacillin/ Tazobactam (N=325)	
		n/m	%	n/m	%	n/m	%
Absolute neutrophil count (ths/mm^3)	<1.8	5/279	1.8	0/12	0.0	5/293	1.7
	<1.0	2/279	0.7	0/12	0.0	1/293	0.3
ALT (U/L)	>2.5 × ULN	20/265	7.5	1/11	9.1	23/264	8.7
	>5.0 × ULN	4/265	1.5	0/11	0.0	1/264	0.4
AST (U/L)	>2.5 × ULN	30/288	10.4	2/12	16.7	22/289	7.6
	>5.0 × ULN	6/288	2.1	1/12	8.3	3/289	1.0
Direct serum bilirubin (mg/dL)	>1.5 × ULN	19/146	13.0	0/1	0.0	25/150	16.7
	>2.5 × ULN	13/146	8.9	0/1	0.0	16/150	10.7
Hematocrit (%)	<24	11/308	3.6	0/13	0.0	11/319	3.4
Hemoglobin (gm/dL)	<8	16/308	5.2	1/13	7.7	14/319	4.4
Platelet count (ths/mm^3)	<75	7/304	2.3	1/13	7.7	8/316	2.5
	<50	6/304	2.0	1/13	7.7	2/316	0.6
Serum alkaline phosphatase (U/L)	>2.5 × ULN	17/281	6.0	2/12	16.7	20/286	7.0
	>5.0 × ULN	3/281	1.1	0/12	0.0	2/286	0.7
Serum creatinine (mg/dL)	>1.5 × ULN	8/304	2.6	2/13	15.4	10/318	3.1
	>3 × ULN	2/304	0.7	1/13	7.7	2/318	0.6
Total serum bilirubin (mg/dL)	>1.5 × ULN	19/283	6.7	3/12	25.0	16/288	5.6
	>2.5 × ULN	10/283	3.5	1/12	8.3	7/288	2.4

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

(Applicant's Table 85, Volume 13 of 22, page 302)

Rash

During parenteral therapy and the 14-day follow-up period 9 patients in the MK-0826 group and 10 patients in the piperacillin/tazobactam group had an adverse experience of rash, which included the terms rash and drug eruption. Drug-related rash was reported for 1 patient (AN 0201) in the MK-0826 1-g group and 2 patients (ANs 5329 and 5394) in the piperacillin/tazobactam group. Each of these 3 patients had a rash that was classified as moderate in severity, nonserious, drug related, and led to discontinuation of therapy.

Medical Officer's Comment: *Although AN 5399 had multiple other potential reasons that may have contributed to her having a "seizure", the MO does not believe that the role of the study drug (piperacillin/tazobactam) can be completely excluded.*

Overall the rates of neutropenia, liver function abnormalities, and rash were comparable between the two treatment groups.

The two patients (ANs 5398 and 5713) in the MK-0826 1 gm group that had ANC < 1.0 cells/uL are notable; however, both patients had probable alternate explanations for neutropenia. AN 5398 received chemotherapy one day prior to entering the study for Non-Hodgkins lymphoma and on study day 7 had an ANC of 234 cells/uL, which returned to normal prior the to the DCIV visit. AN 5713 was HIV positive and the Investigator attributed this patients persitantly low ANC (640-1409 cells/uL) during study therapy to his HIV status; however, no follow-up WBC beyond the DCIV visit was available. Therefore it is difficult to exclude a contribution of MK-0826 to this patient's low ANC.

7.1.1.2.9 Indication Safety and Tolerability Conclusion

In adult patients with complicated intra-abdominal infections (IAI) treated for 5 to 14 days with intravenous administration of MK-0826 1 gm per day the following conclusions regarding the safety and tolerability can be drawn:

1. The safety profile of MK-0826 1 gm per day was similar to piperacillin/tazobactam 3.375 gm every 6 hours with the exception of deaths occurring during the study period. Deaths appear attributable to underlying disease.
2. A statistically significant larger percentage of deaths occurred in the MK-0826 1 gm group (13/316) compared to the piperacillin/tazobactam 1 gm cohort group (3/307), when the groups that died or had the onset of fatal adverse events during the parenteral therapy period are considered (Fisher's p-value=0.020). The trend for a higher percentage of deaths in the MK-0826 1 gm group compared to the piperacillin/tazobactam 1 gm cohort group persisted in the parenteral therapy plus 14-day follow-up and entire study period phases; however, the differences in these phases were not statistically significant.
3. The tolerability at the IV infusion site for MK-0826 was similar to that of piperacillin/tazobactam.
4. The frequency of adverse events of special interest (seizure, rash, liver function test abnormality, and neutropenia) for MK-0826 was similar to that of piperacillin/tazobactam.

7.1.2 Acute Pelvic Infections Indication
7.1.2.1 Reviewer: Jean M. Mulinde
Medical Officer, HFD-520

7.1.2.2 PROTOCOL 023: A PROSPECTIVE, MULTICENTER, DOUBLE-BLIND, RANDOMIZED, COMPARATIVE STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF MK-0826 VERSUS PIPERACILLIN/TAZOBACTAM IN THE TREATMENT OF ACUTE PELVIC INFECTION IN HOSPITALIZED WOMEN

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

Of the 412 patients enrolled, 406 patients received at least 1 dose of IV study therapy and were included in the analysis of adverse experiences. Patients randomized to 1 treatment group who, due to dispensing errors, mistakenly received study therapy with the other study treatment for the entire parenteral study period were analyzed based on the study therapy actually received. Patients who, due to dispensing errors, received both parenteral study drugs at any time during the course of the study were analyzed based on the treatment group to which they were originally randomized. The table below provides an overall summary of safety during the parenteral period and 14-day follow-up period.

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Clinical adverse experiences (AEs) Number (%) of patients	MK-0826 (N=214)		Piperacillin/ Tazobactam (N=192)	
	n	(%)	n	(%)
with one or more AEs	105	(49.1)	98	(51.0)
with no AE	109	(50.9)	94	(50.0)
with drug-related AEs†	48	(22.4)	43	(22.4)
with serious AEs	14	(6.5)	12	(6.3)
with serious drug-related AEs	3	(1.4)	0	(0.0)
who died	2	(0.9)	0	(0.0)
discontinued due to an AE	12	(5.6)	8	(4.2)
discontinued due to a drug-related AE	3	(1.4)	0	(0.0)
discontinued due to a serious AE	10	(4.7)	6	(3.1)
discontinued due to a serious drug-related AE	3	(1.4)	0	(0.0)

Laboratory Adverse Experiences Number of patients with at least one laboratory test postbaseline Number (%) of patients	MK-0826 (N=197)		Piperacillin/ Tazobactam (N=185)	
	n	(%)	n	(%)
with one or more AEs	38	(19.3)	37	(20.0)
with no AE	159	(80.7)	148	(80.0)
with drug-related AEs†	26	(13.2)	29	(15.7)
with serious AEs	3	(1.5)	2	(1.1)
with serious drug-related AEs	3	(1.5)	2	(1.1)
who died	0	(0.0)	0	(0.0)
discontinued due to an AE	1	(0.5)	0	(0.0)
discontinued due to a drug-related AE	1	(0.5)	0	(0.0)
discontinued due to a serious AE	1	(0.5)	0	(0.0)
discontinued due to a serious drug-related AE	1	(0.5)	0	(0.0)

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

(Applicant's Synopsis Table, Volume 20 of 22, page 30)

7.1.2.2.1 Extent of Exposure

Of the 412 randomized patients, 406 patients (214 in the MK-0826 1 gm group and 192 in the piperacillin/tazobactam group) received at least 1 dose of study therapy. The table below shows the extent of exposure to IV therapy by dose and duration for all patients who received at least 1 dose of study therapy. The number of patients receiving each total daily dose of parenteral therapy is displayed. A patient was counted multiple times if, during the course of the study, the patient's daily dose changed, but was counted once in the any dose display.

The table indicates there were 20 patients who received MK-0826 2 gms therapy for 1 to 2 days. The majority of these patients fall into one of two groups: a) patients may have received 5 doses in a calendar day (equivalent to two ertapenem and three placebo doses in the ertapenem group) due to the 6-hour dosing schedule, if the sixth dose was begun within the 24 hour period, or b) a patient's dosing schedule was shifted based on the protocol specified rule that a dosing shift (the 12-hour dosing shift resulted in patients receiving two 1 gm doses in the first 24 hours) was allowed to aid drug administration

scheduling once during the course of the study for each patient at the discretion of the Investigator.

In the piperacillin/tazobactam group, the dosing shift did not alter the dosing schedule since every dose dispensed was piperacillin/tazobactam. Due to the every 6-hour dosing regimen over a 24-hour period, some patients actually received a fifth dose within a calendar day. Therefore, 11 patients in the piperacillin/tazobactam group received 16.875 g of study drug for 2 or less days.

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Extent of Exposure by Dose and Duration
(Treated Population)

Treatment Group	Number of Days on Parenteral Therapy											
	≤2	3 to 4	5 to 6	7 to 8	9 to 10	11 to 12	13 to 14	≥15	Total Patients	Range	Total Days	Mean
MK-0826												
Any Dose	25	116	51	14	7	1	1	0	215[†]		908	4.2
0.5 g	1	0	0	0	0	0	0	0	1		1	1.0
1 g	33	109	48	14	7	1	1	0	213		879	4.1
2 g	20[‡]	0	0	0	0	0	0	0	20		22	1.1
3 g	2[§]	0	0	0	0	0	0	0	2		2	1.0
4 g	0	1[¶]	0	0	0	0	0	0	1		4	4.0
Piperacillin/Tazobactam												
Any Dose[#]	9	107	48	19	7	4	0	0	194[††]		929	4.8
2.25 g	1	0	0	0	0	0	0	0	1		1	1.0
3.375 g[‡]	100	0	0	0	0	0	0	0	100[§]		113	1.1
4.5 g	3	0	0	0	0	0	0	0	3		4	1.3
6.75 g	106	0	0	0	0	0	0	0	106		153	1.4
9 g	2	0	0	0	0	0	0	0	2		4	2.0
10.125 g	77	0	0	0	0	0	0	0	77		92	1.2
13.5 g	87	62	20	6	2	2	0	0	179		549	3.1
16.875 g	11	0	0	0	0	0	0	0	11		13	1.2

† AN 8036 was incorrectly reported in the piperacillin/tazobactam treatment group. The patient received doses of MK-0826 and piperacillin/tazobactam.

‡ Includes ANs 7680 and 7709 who each received 2 g MK-0826 for 2 days.

§ Includes AN 8238 who received 3 g MK-0826 for 1 day.

¶ AN 7177 was incorrectly recorded as receiving 4 g MK-0826 for 4 days and 3 g MK-0826 for 1 day.

Includes ANs 7134 and 7354 in the MK-0826 treatment group who inadvertently received one 3.375-g dose of piperacillin/tazobactam.

Note: The table displays the number of patients receiving each daily dose. A patient may be counted multiple times if during the course of the study, the patient's daily dosage changed.

(Applicant's Table 50, Volume 20 of 22, page 182)

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

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

	MK-0826 (N=214)	Piperacillin/ Tazobactam (N=192)	Total (N=406)
Days on Study Therapy			
n	214	192	406
Mean	4.2	4.8	4.5
SD	2.0	1.8	1.9
Median	4.0	4.0	4.0
Range			
Days Missed Therapy			
n	56†		56†
Mean	1.0		1.0
SD	0.0		0.0
Median	1.0		1.0
Range			

N=Number of patients in each treatment group.
n=Number of patients in category.
† Fifty-six (56) patients were counted as missing a dose of study therapy because they received only placebo doses on the last day of study therapy.

(Applicant's Table 24, Volume 20 of 22, page 97)

Medical Officer's Comment: ***Although the median days of therapy were equivalent between the two groups, the mean extent of exposure was 0.6 days greater in the piperacillin/tazobactam group.***

7.1.2.2.2 Deaths

Two deaths were reported during the entire study period (not limited to the 14-day follow-up period), both in the MK-0826 group (AN 7500 and AN 8618). Neither death was considered to be related to study drug by the Investigators. Narratives of these deaths are provided in Appendix 28. The table below lists all deaths reported during the entire study period.

Listing of Patients With Death
During Study Therapy and 14-Day Follow-Up
(Treated Population)

AN	Study Number	Gender	Race	Age	Daily Dose†	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Intensity	Drug Relation-ship	Action Taken‡	Outcome
MK-0826												
7500	023029	F	Caucasian	42	A /1 g P /50 mL	4	Shock, septic	4 days	Severe	Definitely not	Discontinued	Still present
8618	023068	F	Caucasian	17	P /50 mL A /1 g Off drug	7 1 2	Death Septicemia Death	7 hours	Severe Severe Severe	Definitely not Definitely not Definitely not	Discontinued	Still present

Drug A is MK-0826.
Drug P is placebo.
† Displays any change of daily dose that occurred within the duration of the adverse experience.
‡ Action taken with regard to the study drug therapy due to the adverse experience.

(Applicant's Table 57, Volume 20 of 22, page 198)

Medical Officer's Comment: ***Based on the MO's review of the CRFs and narratives for these patients, it appears that these deaths can be attributed to uncontrolled infection and severe sepsis.***

7.1.2.2.3 Other Serious Adverse Events

The following table displays, by body system, the number (percent) of patients with serious clinical adverse experiences with an incidence of >0% in one or more treatment groups that occurred during the entire study period. Fifteen patients (7.0%) in the MK-0826 group and 12 patients (6.3%) in the piperacillin/tazobactam group had serious clinical adverse experiences, this included 1 patient in the MK-0826 group (AN 7096 who developed recurrent endometritis) who had a serious adverse experience reported more than 14 days after discontinuation of study drug therapy).

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

	MK-0826 (N=214)		Piperacillin/ Tazobactam (N=192)	
	n	(%)	n	(%)
Patients with one or more serious adverse experiences	15	(7.0)	12	(6.3)
Patients with no serious adverse experience	199	(93.0)	180	(93.8)
Body as a Whole/Site Unspecified	**6**	**(2.8)**	**3**	**(1.6)**
Bacteremia	1	(0.5)	0	(0.0)
Death	2	(0.9)	0	(0.0)
Drug overdose	3	(1.4)	1	(0.5)
Fever	1	(0.5)	0	(0.0)
Septicemia	1	(0.5)	1	(0.5)
Shock, septic	1	(0.5)	1	(0.5)
Cardiovascular System	**3**	**(1.4)**	**3**	**(1.6)**
Cardiac arrest	1	(0.5)	0	(0.0)
Embolism/infarction, pulmonary	0	(0.0)	1	(0.5)
Hematoma	1	(0.5)	1	(0.5)
Hemorrhage, subdural	1	(0.5)	0	(0.0)
Phlebitis/thrombophlebitis	0	(0.0)	1	(0.5)
Digestive System	**0**	**(0.0)**	**1**	**(0.5)**
Abscess, subfascial	0	(0.0)	1	(0.5)
Hemic and Lymphatic System	**1**	**(0.5)**	**0**	**(0.0)**
Anemia, hemolytic	1	(0.5)	0	(0.0)
Nervous System and Psychiatric Disorder	**2**	**(0.9)**	**1**	**(0.5)**
Delirium	1	(0.5)	0	(0.0)
Depressive disorder	0	(0.0)	1	(0.5)
Seizure disorder	1	(0.5)	0	(0.0)
Respiratory System	**2**	**(0.9)**	**4**	**(2.1)**
Edema, pulmonary	1	(0.5)	0	(0.0)
Effusion, pleural	0	(0.0)	1	(0.5)
Pneumonia	0	(0.0)	1	(0.5)
Respiratory distress	1	(0.5)	0	(0.0)
Respiratory distress syndrome	0	(0.0)	1	(0.5)
Superinfection, pulmonary	0	(0.0)	1	(0.5)
Skin and Skin Appendage	**0**	**(0.0)**	**1**	**(0.5)**
Infection, wound, postoperative	0	(0.0)	1	(0.5)
Urogenital System	**6**	**(2.8)**	**2**	**(1.0)**
Breast-feeding, use during	0	(0.0)	1	(0.5)
Endometritis	1	(0.5)	0	(0.0)
Hemorrhage, uterine	1	(0.5)	0	(0.0)
Infection, pelvic	2	(0.9)	1	(0.5)
Labor abnormality	1	(0.5)	0	(0.0)
Pyelonephritis	1	(0.5)	0	(0.0)
Renal insufficiency	1	(0.5)	0	(0.0)

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

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

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

(Applicant's Table 58, Volume 20 of 22, pages 199-200)

The following table displays, by body system, the number (percent) of patients with serious drug-related clinical adverse experiences with an incidence of >0% in one or more treatment groups that occurred during the entire study period. Three patients (1.4%) in the MK-0826 group and no patients in the piperacillin/tazobactam group had serious drug-related clinical adverse experiences.

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

	MK-0826 (N=214)		Piperacillin/ Tazobactam (N=192)	
	n	(%)	n	(%)
Patients with one or more serious drug-related adverse experiences†	3	(1.4)	0	(0.0)
Patients with no serious drug-related adverse experience	211	(98.6)	192	(100)
Body as a Whole/Site Unspecified	**2**	**(0.9)**	**0**	**(0.0)**
Drug overdose	2	(0.9)	0	(0.0)
Urogenital System	**1**	**(0.5)**	**0**	**(0.0)**
Renal insufficiency	1	(0.5)	0	(0.0)

† Determined by the investigator to be possibly, probably, or definitely drug related.
Entire study period includes study therapy and follow-up period, not limited to 14 days.
Although a patient may have had 2 or more serious drug-related adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.
All body systems are listed in which at least 1 patient had a serious drug-related adverse experience.

(Applicant's Table 59, Volume 20 of 22, page 202)

Medical Officer's Comment: *After reviewing the narratives and CRFs for patients with serious adverse events, the MO agrees with the Applicant's assessment that the majority of events were most likely due to efficacy failures and/or underlying disease. However, the MO feels that study drug cannot be excluded as a contributing factor for the delerium experienced by AN 7116 (MK-0826 group) and the dizziness experienced by AN 8238 (MK-0826 group). The Applicant's narratives for these two patients are as follows:*

AN 7116

A 24-year-old female with no significant prior history, 4 days status post an emergent cesarean section was placed on therapy with IV MK-0826 for the treatment of endometritis. The patient received 2 doses of the study medication. On Study Day 1, the patient began screaming and moving her tongue around in an abnormal fashion. The patient was diagnosed with acute onset delirium and was given 5 mg of haloperidol intramuscularly. The patient was seen by psychiatry who verified a diagnosis of transient delirium. Study drug therapy was then discontinued. The patient's symptoms subsequently resolved. The reporting physician felt that the delirium was probably not related to study drug therapy.

AN 8238

A 21-year-old female was placed on IV MK-0826 for endometritis. On Study Day 2, the patient experienced an overdose: 1 dose of MK-0826 was infused every 6 hours. The patient was then

discontinued from the study. The patient experienced mild dizziness that resolved the same day. No other adverse experiences were reported in relation to the overdose. The investigator felt the drug overdose was not related to study therapy.

Of the 3 patients in the MK-0826 group that had drug related serious adverse events, 2 patients (ANs 7680 and 7709) had drug overdose due to pharmacy dispensing errors and received 4 doses of MK-0826 within a 24 hour period. Neither of these patients was reported to have had any other clinical or laboratory adverse event. They were both discontinued from study drug on study day 2 after dosage administration errors were detected. The third patient (AN 7319) developed an elevated creatinine (2.2 mg/dL) on study day 3 and was discontinued from study therapy and placed on clindamycin and ampicillin. On study day 5, creatinine continued to increase (3.3 mg/dL) and the clindamycin and ampicillin were discontinued. A nephrology consult was obtained and it was felt that the most likely etiology for the elevated creatinine was acute interstitial nephritis or an acute renal insult with the most likely etiology being nonsteriodal anti-inflammatory drug use (the patient had received concomitant ibuprofen). The patient's creatinine slowly improved and was reduced to 1.5 mg/dL by study day 9. While nonsteriodal use may have been the source of this patient's acute renal failure, the MO agrees with the Investigator that the beta lactams administered may have also been the cause of this patient's episode of acute renal failure.

7.1.2.2.4 Dropouts

Eleven patients (5.1%) in the MK-0826 group and 8 patients (4.2%) in the piperacillin/tazobactam group discontinued study therapy due to clinical adverse experiences. No additional patients discontinued from the study due to clinical adverse event beyond the intravenous phase of the study. The most common reason for study drug discontinuation in the MK-0826 group was drug overdose (1.9%), which occurred in 4 patients (ANs 7772, 7680, 7709, and 8238). One patient (AN 8439) in the piperacillin/tazobactam group was also reported as having a study drug overdose, which led to discontinuation of study drug. Apart from a single patient (AN 8238) who noted mild dizziness and mild diarrhea, there did not appear to be any clinical complications associated with the study drug overdoses. The most common reason for study drug discontinuation in the piperacillin/tazobactam group was fever (1.0%), which occurred in 2 patients (ANs 7111 and 7359). Two patients (ANs 7340 and 7600) in the MK-0826 group were also reported as having fever, which led to discontinuation of study drug.

Three patients in the MK-0826 group (ANs 7319, 7680 and 7709) were reported to have had a drug-related clinical adverse experience that led to discontinuation of study therapy. These are the same patients that were previously described as having had serious drug-related adverse experiences. No patients in the piperacillin/tazobactam group had a drug-related clinical adverse event that led to discontinuation of study drug.

<u>Medical Officer's Comment:</u> As was previously noted in the section on serious adverse events, the MO does not feel that study drug can be excluded as possibly related to the delirium experienced by patient AN 7116. The following table lists all patients that were discontinued from study therapy due to a clinical adverse experience; patients highlighted are those patients that were discontinued due to drug-related adverse experience in the opinion of the Applicant and/or the MO. The reasons for discontinuation from study therapy were primarily related to efficacy failure and pharmacy dispensing errors resulting in study drug overdose.

Listing of Patients Discontinued Due to Clinical Adverse Experiences During Parenteral Therapy (Treated Population)

AN	Study Number	Gender	Race	Age	Daily Dose[†]	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Relative Day of Discontinuance	Intensity	Drug Relation-ship	Serious	Outcome
MK-0826													
[redacted]	023006	F	Hispanic	24	A /1 g	1	Delirium	13.5 hours	24	Moderate	Probably not	Yes	Recovered
[redacted]	023016	F	Caucasian	23	P /100 mL	3	Renal insufficiency	7 days	3	Severe	Probably	Yes	Recovered
7340	023018	F	Black	20	A /2 g A /1 g P /50 mL	1	Pyelonephritis	19 days	19	Moderate	Definitely not	No	Recovered
					A /2 g A /1 g P /50 mL	1	Ileus	4 days		Mild	Definitely not	No	Recovered
					A /1 g P /50 mL	2	Diarrhea	6 days		Moderate	Definitely not	No	Recovered
					A /1 g P /50 mL	2	Fever	5 days		Moderate	Definitely not	No	Recovered
7772	023024	F	Black	24	A /1 g	1	Drug overdose	2 hours	77	Mild	Definitely not	No	Recovered
[redacted]	023028	F	Hispanic	22	A /2 g	1	Drug overdose	2 days	24	Mild	Definite	Yes	Recovered
[redacted]	023028	F	Hispanic	17	A /2 g	1	Drug overdose	10 hours	32	Mild	Definite	Yes	Recovered
7500	023029	F	Caucasian	42	A /1 g	4	Shock, septic	4 days	7	Severe	Definitely not	Yes	Still present
7600	023034	F	Hispanic	21	P /50 mL	8	Fever	8 days	22	Moderate	Probably not	Yes	Recovered
7945	023040	F	Hispanic	30	A /1 g A /1 g	1	Hemorrhage, uterine	1 hour	15	Severe	Definitely not	Yes	Recovered
8238	023052	F	Black	21	A /3 g	1	Labor abnormality	1 hour		Severe	Definitely not	Yes	Recovered
8618	023068	F	Caucasian	17	A /1 g	2	Drug overdose	12 hours	2	Moderate	Definitely not	Yes	Recovered
					A /1 g	1	Cardiac arrest	1 day	2	Severe	Definitely not	Yes	Recovered
					A /1 g	1	Septicemia	7 hours		Severe	Definitely not	Yes	Still present
					Off drug	2	Cardiac arrest	1 day		Severe	Definitely not	Yes	Still present
						2	Edema, pulmonary	1 day		Severe	Definitely not	Yes	Still present
Piperacillin/Tazobactam													
7111	023006	F	Hispanic	25	B /6.750 g	6	Fever	7 hours	31	Moderate	Probably not	No	Recovered
7359	023018	F	Hispanic	17	B /10.125 g	4	Fever	5 days	41	Mild	Definitely not	No	Recovered
7798	023024	F	Black	37	B /6.750 g	10	Infection, pelvic	1 day	10	Severe	Definitely not	Yes	Recovered
7514	023029	F	Caucasian	41	B /6.750 g	5	Respiratory distress syndrome	4 days	20	Severe	Probably not	Yes	Recovered
7908	023035	F	Hispanic	19	B /10.125 g	8	Infection, wound, postoperative	40 days	26	Moderate	Definitely not	Yes	Recovered
8035	023038	F	Caucasian	17	B /3.375 g	2	Pneumonia	6 days	18	Severe	Definitely not	Yes	Recovered
8561	023043	F	Mestizo	21	B /6.750 g	1	Shock, septic	11 days	25	Severe	Definitely not	Yes	Recovered
8439	023062	F	Black	19	B /13.500 g	2	Drug overdose	1 day	35		Definitely not	Yes	Recovered

Drug A is MK-0826. Drug B is piperacillin/tazobactam. Drug P is placebo.
† Displays any change of daily dose that occurred within the duration of the adverse experience.

(Modified Applicant's Table 56, Volume 20 of 22, pages 195-196)

7.1.2.2.5 Other Treatment Emergent Adverse Events

Overall, 203 of 406 treated patients (65.8%) had clinical adverse experiences reported during study therapy and the 14-day follow-up period (105 [49.1%] in the MK-0826 group and 98 [51.0%] in the piperacillin/tazobactam group).

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

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

	MK-0826 (N=214)		Piperacillin/Tazobactam (N=192)	
	n	(%)	n	(%)
Patients with one or more adverse experiences	105	(49.1)	98	(51.0)
Patients with no adverse experience	109	(50.9)	94	(49.0)
Body as a Whole/Site Unspecified	**32**	**(15.0)**	**18**	**(9.4)**
Edema/swelling	5	(2.3)	1	(0.5)
Pain, abdominal	9	(4.2)	5	(2.6)
Cardiovascular System	**41**	**(19.2)**	**44**	**(22.9)**
Extravasation	9	(4.2)	6	(3.1)
Hematoma	6	(2.8)	5	(2.6)
Infused vein complication	25	(11.7)	29	(15.1)
Digestive System	**35**	**(16.4)**	**31**	**(16.1)**
Constipation	5	(2.3)	11	(5.7)
Diarrhea	14	(6.5)	7	(3.6)
Nausea	12	(5.6)	6	(3.1)
Vomiting	8	(3.7)	7	(3.6)
Musculoskeletal System	**6**	**(2.8)**	**7**	**(3.6)**
Nervous System and Psychiatric Disorder	**29**	**(13.6)**	**23**	**(12.0)**
Dizziness	7	(3.3)	5	(2.6)
Headache	23	(10.7)	17	(8.9)
Respiratory System	**18**	**(8.4)**	**17**	**(8.9)**
Cough	5	(2.3)	6	(3.1)
Skin and Skin Appendage	**12**	**(5.6)**	**20**	**(10.4)**
Rash	1	(0.5)	6	(3.1)
Urogenital System	**21**	**(9.8)**	**15**	**(7.8)**

-Only adverse experiences that occurred during study drug therapy and 14 days after discontinuation of study drug therapy were counted. Adverse experiences or deaths reported more than 14 days after discontinuation of study drug therapy were not counted.
-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 105, Volume 20 of 22, page 347-350)

Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence >0% in One or More Treatment Groups) by Body System During Study Therapy and 14-Day Follow-Up Period (Treated Population) Drug Related

	MK-826 (N=214)		Piperacillin/Tazobactam (N=192)	
	n	(%)	n	(%)
Patients with one or more drug-related adverse experiences†	48	(22.4)	43	(22.4)
Patients with no drug-related adverse experience	166	(77.6)	149	(77.6)
Body as a Whole/Site Unspecified	**9**	**(4.2)**	**3**	**(1.6)**
Cardiovascular System	**24**	**(11.2)**	**28**	**(14.6)**
Extravasation	7	(3.3)	4	(2.1)
Infused vein complication	17	(7.9)	24	(12.5)
Digestive System	**16**	**(7.5)**	**9**	**(4.7)**
Diarrhea	8	(3.7)	4	(2.1)
Nausea	6	(2.8)	3	(1.6)
Vomiting	5	(2.3)	4	(2.1)
Nervous System and Psychiatric Disorder	**7**	**(3.3)**	**7**	**(3.6)**
Headache	5	(2.3)	5	(2.6)
Skin and Skin Appendage	**4**	**(1.9)**	**5**	**(2.6)**
Rash	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 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.
-Only adverse experiences that occurred during study drug therapy and 14 days after discontinuation of study drug therapy were counted. Adverse experiences or deaths reported more than 14 days after discontinuation of study drug therapy were not counted.

(Modified Applicant's Table 106, Volume 20 of 22, pages 351-352)

Medical Officer's Comment: ***With the exception of asthenia/fatigue, candidiasis, drug overdose, edema, fever, injection site induration, dysphagia, cough, and pharyngeal discomfort that occurred in one or two patients in the MK-0826 group, extravasation (3.3%% MK-0826 1 gm group and 2.1% piperacillin/tazobactam group), diarrhea (3.7% MK-0826 1 gm group and 2.1% piperacillin/tazobactam group), nausea (2.8% MK-0826 1 gm group and 1.6% piperacillin/tazobactam group), and dizziness (1.4% MK-0826 1 gm group and 0.5% piperacillin/tazobactam group) were the only drug-related clinical adverse experiences that occurred in a higher percentage of patients in the MK-0826 1 gm group.***

7.1.2.2.6 Laboratory Findings

Of the treated patients that had at least 1 laboratory test postbaseline, 38/197 (19.3%) in the MK-0826 group and 37/185 (20.0%) in the piperacillin/tazobactam group had a laboratory adverse experience during study therapy and the 14-day follow-up period. The most common laboratory adverse experiences overall were increased platelet count (10.6%), increased transaminases (AST [2.2%] and ALT [2.6%]) and increased alkaline phosphatase (3.5%). Increased platelet count occurred in 10.0% (19/190) of patients receiving MK-0826 and 11.2% (20/178) of patients receiving piperacillin/tazobactam. Increased AST occurred in 3.2% (6/185) of patients receiving MK-0826 and 1.1% (2/175) of patients receiving piperacillin/tazobactam. Increased ALT occurred in 3.3% (6/180) of patients receiving MK-0826 and 1.8% (3/171) of patients receiving piperacillin/tazobactam. Increased alkaline phosphatase occurred in 4.6% (8/175) of

patients receiving MK-0826 and 2.4% (4/169) of patients receiving piperacillin/tazobactam.

One patient (AN 7319) was discontinued from study therapy due to a laboratory adverse experience of increased creatinine. This patient has been previously described in the serious drug-related adverse events section of this review.

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

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Number (%) of Patients With Specific Laboratory Adverse Experiences (Incidence >0% in One or More Treatment Groups) by Laboratory Test Category During Study Therapy and 14-Day Follow-Up Period (Treated Population)

	MK-0826 (N=214)		Piperacillin/ Tazobactam (N=192)	
	n/m	(%)	n/m	(%)
Patients with one or more adverse experiences	38/197	(19.3)	37/185	(20.0)
Patients with no adverse experience	159/197	(80.7)	148/185	(80.0)
Blood Chemistry	**16/188**	**(8.5)**	**12/178**	**(6.7)**
ALT decreased	1/180	(0.6)	0/171	(0.0)
ALT increased	6/180	(3.3)	3/171	(1.8)
AST decreased	1/185	(0.5)	0/175	(0.0)
AST increased	6/185	(3.2)	2/175	(1.1)
Direct serum bilirubin increased	1/145	(0.7)	0/140	(0.0)
Serum albumin decreased	0/177	(0.0)	1/170	(0.6)
Serum alkaline phosphatase increased	8/175	(4.6)	4/169	(2.4)
Serum calcium decreased	0/168	(0.0)	1/162	(0.6)
Serum creatinine increased	2/180	(1.1)	2/172	(1.2)
Serum glucose decreased	1/184	(0.5)	0/176	(0.0)
Serum glucose increased	1/184	(0.5)	1/176	(0.6)
Serum potassium decreased	1/183	(0.5)	2/176	(1.1)
Total serum bilirubin increased	1/175	(0.6)	1/169	(0.6)
Total serum protein decreased	0/167	(0.0)	1/157	(0.6)
Hematology	**26/195**	**(13.3)**	**26/183**	**(14.2)**
Eosinophils increased	1/177	(0.6)	2/167	(1.2)
Hematocrit decreased	3/192	(1.6)	1/182	(0.5)
Hemoglobin decreased	3/192	(1.6)	2/182	(1.1)
Platelet count decreased	2/190	(1.1)	0/178	(0.0)
Platelet count increased	19/190	(10.0)	20/178	(11.2)
PTT increased	1/169	(0.6)	1/169	(0.6)
Segmented neutrophils decreased	2/177	(1.1)	1/167	(0.6)
WBC decreased	2/192	(1.0)	3/182	(1.6)
WBC increased	1/192	(0.5)	1/182	(0.5)
Urinalysis	**5/177**	**(2.8)**	**5/160**	**(3.1)**
Urine bacteria increased	2/175	(1.1)	1/160	(0.6)
Urine glucose increased	0/176	(0.0)	1/155	(0.6)
Urine RBCs increased	2/175	(1.1)	1/160	(0.6)
Urine WBCs increased	4/175	(2.3)	3/160	(1.9)
Miscellaneous	**1/1**	**(100)**	**0/0**	**(0.0)**
Clostridium difficile toxin, positive	1/1	(100)	0/0	(0.0)

N=Total number of patients per treatment group.
* n/m = Number of patients with laboratory adverse experience/number of patients with laboratory test.
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 categories are listed in which at least 1 patient had an adverse experience.
Only adverse experiences that occurred during study drug therapy and 14 days after discontinuation of study drug therapy were counted. Adverse experiences or deaths reported more than 14 days after discontinuation of study drug therapy were not counted.

(Applicant's Table 124, Volume 20 of 22, page 374)

Number (%) of Patients With Specific Laboratory Adverse Experiences
(Incidence >0% in One or More Treatment Groups) by Laboratory Test Category
During Study Therapy and 14-Day Follow-Up Period
(Treated Population)
Drug Related

	MK-0826 (N=214)		Piperacillin/ Tazobactam (N=192)	
	n/m	(%)	n/m	(%)
Patients with one or more drug-related adverse experiences†	26/197	(13.2)	29/185	(15.7)
Patients with no drug-related adverse experience	171/197	(86.8)	156/185	(84.3)
Blood Chemistry	**13/188**	**(6.9)**	**8/178**	**(4.5)**
ALT increased	6/180	(3.3)	3/171	(1.8)
AST increased	6/185	(3.2)	2/175	(1.1)
Serum alkaline phosphatase increased	8/175	(4.6)	4/169	(2.4)
Serum creatinine increased	1/180	(0.6)	1/172	(0.6)
Serum glucose increased	1/184	(0.5)	0/176	(0.0)
Total serum bilirubin increased	0/175	(0.0)	1/169	(0.6)
Hematology	**17/195**	**(8.7)**	**22/183**	**(12.0)**
Eosinophils increased	0/177	(0.0)	2/167	(1.2)
Hemoglobin decreased	1/192	(0.5)	0/182	(0.0)
Platelet count decreased	1/190	(0.5)	0/178	(0.0)
Platelet count increased	14/190	(7.4)	18/178	(10.1)
PTT increased	1/169	(0.6)	1/169	(0.6)
Segmented neutrophils decreased	1/177	(0.6)	1/167	(0.6)
WBC decreased	2/192	(1.0)	2/182	(1.1)
Urinalysis	**1/177**	**(0.6)**	**4/160**	**(2.5)**
Urine bacteria increased	0/175	(0.0)	1/160	(0.6)
Urine RBCs increased	0/175	(0.0)	1/160	(0.6)
Urine WBCs increased	1/175	(0.6)	3/160	(1.9)
Miscellaneous	**1/1**	**(100)**	**0/0**	**(0.0)**
Clostridium difficile toxin, positive	1/1	(100)	0/0	(0.0)

† Determined by the investigator to be possibly, probably, or definitely drug related.
N=Total number of patients per treatment group.
‡ n/m = Number of patients with laboratory adverse experience/number of patients with laboratory test.
Although a patient may have had 2 or more drug-related adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.
All categories are listed in which at least 1 patient had a drug-related adverse experience.
Only adverse experiences that occurred during study drug therapy and 14 days after discontinuation of study drug therapy were counted. Adverse experiences or deaths reported more than 14 days after discontinuation of study drug therapy were not counted.

(Applicant's Table 125, Volume 20 of 22, page 375)

Medical Officer's Comment: ***With the exception of increased ALT, AST, and alkaline phosphatase, which occurred approximately twice as frequently in the MK-0826 group, the incidence of laboratory adverse experiences and drug-related laboratory adverse experiences was similar in the two treatment groups.***

Five patients (2.5%) in the MK-0826 group and 3 patients (1.6%) in the piperacillin/tazobactam group had serious laboratory adverse experiences that occurred during the entire study period, all of which were considered drug related by the investigators. For two patients in the MK-0826 group (ANs 7530 and 7912) and 1 patient (AN 7554) in the piperacilllin/tazobactam group the reported serious laboratory

adverse experience occurred after the 14-day follow-up period. The table below displays a summary for patients with serious laboratory adverse experiences that occurred during the entire study period.

Listing of Patients With Serious Laboratory Adverse Experiences During Entire Study Period (Treated Population)

AN	Study Number	Gender	Race	Age	Daily Dose*	Relative Day of Test	Adverse Experience	Laboratory Value (Unit)	Normal Range	Drug Relationship	Action Taken
MK-0826											
7319	023016	F	Caucasian	23	A /1 g	3	Serum creatinine increased	2.2 mg/dL		Definitely	Discontinued
					P /100 mL						
					A /1 g	4	Serum creatinine increased	2.9 mg/dL		Definitely	None
					Off drug	5	Serum creatinine increased	3.3 mg/dL		Definitely	None
					Off drug	6	Serum creatinine increased	2.7 mg/dL		Definitely	None
					Off drug	7	Serum creatinine increased	2.2 mg/dL		Definitely	None
					Off drug	8	Serum creatinine increased	1.6 mg/dL		Definitely	None
					Off drug	9	Serum creatinine increased	1.5 mg/dL		Definitely	None
7391	023020	F	Hispanic	23	A /1 g	5	Alkaline phosphatase increased	335 U/L		Possibly	None
7530‡	023027	F	Hispanic	41	Off drug	34	ALT increased	118 U/L		Possibly	None
7911	023035	F	Mestizo	19	Off drug	22	ALT increased	128 U/L		Probably	None
					A /1 g	5	Neutrophils decreased	33 %		Probably	None
					A /1 g	5	Leukocytes decreased	2.8 ths/μL		Probably	None
7912‡	023035	F	Mestizo	24	Off drug	25	Neutrophils decreased	44 %		Definitely	None
Piperacillin/Tazobactam											
7554‡	023027	F	Hispanic	20	Off drug	23	Neutrophils decreased	56 %		Probably	None
					Off drug	23	Leukocytes decreased	2.8 ths/mm^3		Probably	None
7519	023029	F	Caucasian	40	B /13.500 g	4	Activated PTT increased	75 seconds		Possibly	None
8252	023053	F	Black	16	B /13.500 g	11	Serum creatinine increased	3.5 mg/dL		Probably	None

* Displays the dosage received 1 day before the laboratory test.
‡ Three patients had serious laboratory adverse experiences after 14-day follow-up period.
Entire study period includes laboratory adverse experiences that occurred more than 14 days after discontinuation of study therapy.
Drug A is MK-0826. Drug B is piperacillin/tazobactam. Drug P is placebo.

(Applicant's Table 66, Volume 20 of 22, pages 223-224)

Medical Officer's Comment: ***Notably, the association of study drug with decreased leukocyte and neutrophil counts (absolute neutrophil count = 924 ths/mm^3) on study day 5 for AN 7911, in the MK-0826 group, is particularly strong since this patient was not receiving other concomitant medications and did not have any other underlying medical events that would explain this adverse laboratory experience. By study day 8 (3 days after completing study therapy) the patient had normal neutrophil and lymphocyte counts.***

At the DCIV visit and at the TOC visit (20 days post-therapy) AN 7912, in the MK-0826 group, was noted to have leukocyte counts of 5.7 ths/mm^3 with 47% neutrophils and 1% bands (absolute neutrophil count = 2736 ths/mm^3) and 3.3 ths/mm^3 with 44% neutrophils (absolute neutrophil count = 1452 ths/mm^3), respectively. Three days after the follow-up visit an unscheduled laboratory was obtained and the leukocyte count had risen to 4.1 ths/mm^3 with 43% neutrophils (absolute neutrophil count = 1763 ths/mm^3). Based on the available information the nadir for the absolute neutrophil count may have occurred at some time point between the DCIV and TOC

visits. While this patient also received misoprostol 3 days prior to study entry and clonixin lysinate from day -1 to 2 of study and these drugs can not be excluded as possible contributing factors to the serious laboratory adverse event experienced by this patient, given the timing of events, MK-0826 seems the more likely source of the event.

AN 7554, in the piperacillin/tazobactam was also noted to have a decreased leukocyte counts of 2.8 ths/mm^3 with 56% neutrophils (absolute neutrophil count = 1568 ths/mm^3) at the TOC visit (occurring 18 days post-therapy). At the DCIV visit this patient had a leukocyte count of 5.4 ths/mm^3 with 57% neutrophils (absolute neutrophil count = 3078 ths/mm^3). Additional unscheduled follow-up WBCs were performed at 25, 29, and 59 days post-therapy and revealed absolute neutrophil counts of 2255 ths/mm^3, 1936 ths/mm^3, and 5916 ths/mm^3, respectively. Based on the available information the nadir for the absolute neutrophil count may have occurred at some time point between the DCIV and TOC visits. The interpretation of the role of study drug in this event is confounded by the fact that the patient received concomitant therapy with captropril from study day -4 to 5.

7.1.2.2.7 Assessment of Tolerability

An assessment of tolerability at the IV study drug infusion site was performed daily while the patient was on study therapy. The intensity of specified local infusion-related symptoms was rated as mild, moderate, or severe. Of patients who experienced one or more local reactions at the infusion site, 67/213 (31.5%) were in the MK-0826 group and 69/192 (35.9%) were in the piperacillin/tazobactam group. If local intolerance was felt by the Investigator to reach the level of a clinical adverse experience, the adverse experience was reported as a clinical syndrome (e.g. local phlebitis/thrombophlebitis) and was displayed as "infused vein complication" in the counts of clinical adverse experiences. A clinical adverse experience of "infused vein complication" was reported for 25/214 (11.7%) of patients in the MK-0826 group and 29/192 (15.1%) of patients in the piperacillin/tazobactam group. The following table presents the proportions of patients reporting any local reactions and the proportions of patients reporting one or more symptoms of moderate to severe intensity.

Number (%) of Patients With Local Reaction Symptoms
During Intravenous (IV) Therapy
(Treated Population)

	Treatment Group						Difference (A - B)
	MK-0826 1g (A) (N=214)			Piperacillin/Tazobactam (B) (N=192)			
	n/m	(%)	(95% CI)	n/m	(%)	(95% CI)	% (95% CI)
Patients with one or more symptoms	67/213	(31.5)	(25.2, 37.7)	69/192	(35.9)	(29.1, 42.7)	-4.48 (-13.7, 4.7)
Patients with one or more symptoms of moderate-to-severe intensity	26/213	(12.2)	(7.8, 16.6)	24/192	(12.5)	(7.8, 17.2)	-0.29 (-6.7, 6.1)

N=Number of treated patients in each treatment group.

n/m=Number of patients reporting an intolerability symptom/number of patients with an assessment. Patients with an assessment "Not Done" were not counted.

CI=Confidence interval.

(Applicant's Table 72, Volume 20 of 22, page 234)

Medical Officer's Comment: *Overall the rates of local reactions were similar in the 2 treatment groups.*

7.1.2.2.8 Adverse Experiences of Special Interest

Four adverse experiences were prespecified for more detailed review because of preclinical findings (neutropenia), adverse experiences associated with β-lactam antibiotics as a class (liver function elevations and rash), and adverse experiences associated with other carbapenem antimicrobials (seizures).

Seizures

One patient in the MK-0826 1-g group (AN 7478) reported a seizure during the entire study period. The patient was off study drug at the time of the seizure. The seizure ocurred on the evening following surgical evacuation of a subdural hematoma and empyema and was judged by the investigator to be unrelated to study drug.

Neutropenia/Liver Enzyme Elevations

In addition to reviewing investigator-reported laboratory adverse experiences, the Applicant performed an assessment of the relative laboratory safety of each treatment group by using predefined Clinically Significant Laboratory Abnormalities (CSLAs) for specified tests and identifying patients whose worst laboratory value represented a worsening from baseline and met the criteria for a CSLA. In order to be considered in the analysis for CSLAs, patients had to have a baseline laboratory value, at least 1 post-baseline laboratory test and have normal ranges in the database. For platelet count, absolute neutrophil count, hematocrit, and hemoglobin the CSLA criteria were defined in terms of a fixed bound. For creatinine, total bilirubin, direct bilirubin, ALT, AST, and alkaline phosphatase, the CSLA criteria were defined in terms of a fixed bound greater than the upper limit of normal (ULN). The following table displays CSLAs for neutropenia and liver function assays during the study therapy and 14-day follow-up period.

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Number (%) of Patients With a Clinically Significant Laboratory Abnormality (CSLA) by Treatment Group
During Study Therapy and 14-Day Follow-Up Period
(Treated Population)

Laboratory Test	CSLA Criteria	Number (%) With CSLA			
		MK-0826 (N=214)		Piperacillin/Tazobactam (N=192)	
		n/m	%	n/m	%
Absolute neutrophil count (ths/mm³)	<1.8	4/166	2.4	2/154	1.3
	<1.0	0/166	0.0	0/154	0.0
ALT (U/L)	>2.5 × ULN	3/166	1.8	1/164	0.6
	>5.0 × ULN	1/166	0.6	0/164	0.0
AST (U/L)	>2.5 × ULN	6/175	3.4	1/166	0.6
	>5.0 × ULN	2/175	1.1	0/166	0.0
Direct Serum Bilirubin (mg/dL)	>1.5 × ULN	6/131	4.6	2/125	1.6
	>2.5 × ULN	5/131	3.8	1/125	0.8
Hematocrit (%)	<24	17/191	8.9	12/182	6.6
Hemoglobin (gm/dL)	<8	19/190	10.0	13/182	7.1
Platelet Count (ths/mm³)	<75	2/189	1.1	0/177	0.0
	<50	1/189	0.5	0/177	0.0
Serum alkaline phosphatase (U/L)	>2.5 × ULN	3/164	1.8	2/159	1.3
	>5.0 × ULN	0/164	0.0	0/159	0.0
Serum Creatinine (mg/dL)	>1.5 × ULN	1/178	0.6	3/168	1.8
	>3 × ULN	0/178	0.0	0/168	0.0
Total Serum Bilirubin (mg/dL)	>1.5 × ULN	3/167	1.8	1/162	0.6
	>2.5 × ULN	1/167	0.6	0/162	0.0

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

(Applicant's Table 74, Volume 20 of 22, page 240)

Rash

During parenteral therapy and the 14-day follow-up period 1 patient in the MK-0826 group and 6 patients in the piperacillin/tazobactam group had an adverse experience of rash, which included the terms rash and drug eruption. Drug-related rash was reported for 1 patient in the MK-0826 group and 4 patients in the piperacillin/tazobactam group. Each of these 5 patients had a rash that was classified as mild in intensity and none was considered serious or led to discontinuation of therapy.

Medical Officer's Comment: ***The seizure that was experienced by AN 7478 was unlikely to be related to study therapy, given that the timing of the event followed intracranial surgery. Although the numbers of patients that experienced rash (drug related or overall) were small, the trend in this study suggested it occurred less frequently for patients treated with MK-0826. Overall, liver function abnormalities and neutropenia were approximately twice as common in the MK-0826 group.***

Of the four patients in the MK-0826 group reported by the Applicant with ANC < 1800 ths/mm^3, two patients (ANs 7517 and 7528) experienced transient decreases in ANC during therapy that had normalized prior to the DCIV visit, and two patients (ANs 7858 and 7911) experienced decreases in ANC identified at the TOC visit. AN 7911 had normalization of ANC by 59 days post-therapy (see discussion of this patient in the MO's comment in the serious laboratory adverse experiences section of this review). No further follow-up laboratories were available for AN 7858. Of the 2 patients (ANs 7704 and 7918) in the piperacillin/tazobactam group reported by the Applicant with ANC < 1800 ths/mm^3, both patients had decreased counts at the DCIV visit. The ANC had normalized by the TOC visit for AN 7704, but AN 7918 was lost to follow-up and no further laboratory information is available. In addition to the patients with decreased ANC reported in the Applicant's table, the MO believes 2 additional patients (AN 7912 in the MK-0826 group and AN 7554 in the piperacillin/tazobactam group) that had ANC < 1800 at TOC visits beyond 14 days post-therapy should be included (these 2 patients were previously discussed in the MO's comment in the serious laboratory adverse experiences section). A revised table, including these 2 patients, is displayed below. The incorporation of the 2 additional patients by the MO actually decreases the relative risk of ANC <1800 ths/mm^3 from 1.86, reported by the Applicant, to 1.58.

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

Laboratory Abnormality	MK-0826 (A) n	m	(%)	Piperacillin/Tazobactam (B) n	m	(%)	Relative Risk A/B
ANC decreased[†]	5	166	(3.0)	3	154	(1.9)	1.58

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

(Modified Applicant's Table 75, Volume 20 of 22, page 242)

7.1.2.2.9 Indication Safety and Tolerability Conclusion

In adult patients with acute pelvic infections treated for 3 to 10 days with intravenous administration of MK-0826 1 gm per day the following conclusions regarding safety and tolerability can be made:

1. The safety profile of MK-0826 1 gm per day was similar to pipercillin/tazobactam 3.375 gm every 6 hours with the exceptions of mild to moderate liver function test abnormalities and the development of decreased absolute neutrophil counts in patients receiving MK-0826.
2. The liver function abnormalities and decreases in absolute neutrophil counts that were seen in patients in the MK-0826 group were not associated with clinically significant adverse clinical events.
3. The tolerability at the IV infusion site for MK-0826 was similar to that of piperacillin/tazobactam.

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7.1.3 Community-Acquired Pneumonia Indication

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

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

Adverse experiences were recorded during parenteral study therapy and oral study therapy and for 14 days after the end of study therapy (safety follow-up period). According to the Applicant, adverse experiences that occurred during the study parenteral therapy period were more likely to be related to the parenteral study therapy than those that occurred after completion of the parenteral therapy (i.e., during oral therapy or the follow-up period). For this reason, the Applicant performed separate analyses for adverse experiences that occurred specifically within the parenteral treatment period and for those that occurred during study therapy and the 14-day follow-up period (i.e., parenteral and oral antibiotic therapy and 14-day follow-up period).

Medical Officer's Comment: ***During the January 28, 2000 telecon between the Applicant and the Division, the Applicant was told that the Division would consider both time periods equally in the Division's assessment of the safety database. In the following sections of the Safety review, the Applicant's analyses for the parenteral period (PP) will be presented and any significant differences that are noted between this period and the parenteral plus oral through TOC period (TP) will be mentioned.***

Of the 502 patients randomized, 498 received at least 1 dose of parenteral study therapy and are included in the Applicant's analysis of adverse experiences. Patients randomized to 1 treatment group who, due to dispensing errors, mistakenly received study therapy with the other study treatment for the entire parenteral study period were analyzed based on the study therapy actually received. Patients who, due to dispensing errors, received both parenteral study drugs at any time during the course of the study were analyzed based on the treatment group to which they were originally randomized. The table below provides an overall summary of safety during the PP and during the TP.

Clinical adverse experiences (AEs)	Parenteral Therapy				Study Therapy and 14-Day Follow-Up			
	MK-0826 (N=242)		Ceftriaxone (N=256)		MK-0826 (N=242)		Ceftriaxone (N=256)	
Number (%) of patients	n	(%)	n	(%)	n	(%)	n	(%)
with one or more AEs	113	(46.7)	126	(49.2)	149	(61.6)	159	(62.1)
with no AE	129	(53.3)	130	(50.8)	93	(38.4)	97	(37.9)
with drug-related AEs[1]	27	(11.2)	43	(16.8)	42	(17.4)	61	(23.8)
with serious AEs	18	(7.4)	14	(5.5)	31	(12.8)	31	(12.1)
with serious drug-related AEs	1	(0.4)	0	(0.0)	1	(0.4)	0	(0.0)
who died	2	(0.8)	0	(0.0)	7	(2.9)	5	(2.0)
discontinued due to an AE	13	(5.4)	8	(3.1)	18	(7.4)	18	(7.0)
discontinued due to a drug-related AE	0	(0.0)	0	(0.0)	1	(0.4)	3	(1.2)
discontinued due to a serious AE	9	(3.7)	8	(3.1)	12	(5.0)	15	(5.9)
discontinued due to a serious drug-related AE	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Laboratory AEs								
Number of patients with at least 1 laboratory test	(N=232)		(N=243)		(N=234)		(N=247)	
Number (%) of patients	n	(%)	n	(%)	n	(%)	n	(%)
with one or more AEs	58	(25.0)	55	(22.6)	77	(32.9)	73	(29.6)
with no AE	174	(75.0)	188	(77.4)	157	(67.1)	174	(70.4)
with drug-related AEs[1]	31	(13.4)	26	(10.7)	36	(15.4)	31	(12.6)
with serious AEs	7	(3.0)	4	(1.6)	9	(3.8)	4	(1.6)
with serious drug-related AEs	5	(2.2)	4	(1.6)	6	(2.6)	4	(1.6)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to an AE	1	(0.4)	2	(0.8)	1	(0.4)	2	(0.8)
discontinued due to a drug-related AE	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious AE	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related AE	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[1] Determined by the investigator to be possibly, probably, or definitely drug related.

(Applicant's Table Volume 15 of 22, page 30)

7.1.3.2.1 Extent of Exposure

The table below shows the extent of exposure to parenteral therapy by dose and duration for all patients who received at least 1 dose of study therapy ("Any dose" in the following table). The number of patients who received each total daily dose of parenteral therapy is displayed. A patient was counted twice if during the course of the study, the patient's daily dose changed (i.e counted in both the 1 gm and 2 gm dose groups in the following table). No patients received IM therapy and no adjustments to dose were made for any patients due to their renal function. The protocol allowed a one-time adjustment in dosing interval between the first and second parenteral study drug doses, to accommodate local medication administration schedules; 15 patients in the MK-0826 group and 13 patients in the ceftriaxone group had this dosing interval adjustment and received two 1 gm doses within the first 24 hour period (i.e., Day 1 of therapy).

Extent of Exposure by Dose and Duration
(Treated Population)

Treatment Group	Number of Days on Parenteral Therapy*								Total Patients	Range	Total Days	Mean
	≤2	3 to 4	5 to 6	7 to 8	9 to 10	11 to 12	13 to 14	≥15				
MK-0826												
Any dose	21	133	51	18	8	7	8	1	242[†]	1 to 17	1112	4.6
1 g	36	129	49	19	7	2	6	1	241[†]	1 to 17	1096	4.5
2 g[‡]	14[§]	0	0	0	0	0	0	0	14	1 to 1	14	1.0
Ceftriaxone												
Any dose	22	133	58	23	8	5	8	0	257[¶,#]	1 to 14	1209	4.7
1 g	30	125	60	23	6	4	7	0	255[¶,†]	1 to 14	1165	4.6
2 g[‡]	14	1	0	1	2	0	0	0	18	1 to 10	44	2.4

* The table displays the number of patients receiving each daily dose. A patient was counted more than once if, during the course of the study, the patient's daily dosage changed. "Any dose" reflects the total duration of parenteral therapy, regardless of dosage.
† Includes AN 6487, who was randomized to the ceftriaxone treatment group but received MK-0826 in error for the duration of parenteral therapy.
‡ Includes patients who received 1 daily dose of 2 g and patients who received two 1-g doses on the same day.
§ Includes AN 6918, who received two 1-g doses on Study Day 3.
¶ Includes AN 6294 from the MK-0826 treatment group, who received a 1-g dose of ceftriaxone on Study Day 4.
# Includes AN 6494, who was randomized to the MK-0826 treatment group but received ceftriaxone in error for the duration of parenteral therapy.

(Applicant's Table 56, Volume 15 of 22, Page 157)

The extent of exposure to all study drugs (parenteral and oral) by treatment group for the treated population is displayed in the table below.

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

	MK-0826 (N=242)	Ceftriaxone (N=256)	Total (N=498)
Days on Study Therapy (IV and oral)			
n	242	256	498
Mean	10.5	10.9	10.7
SD	4.0	3.8	3.9
Median	11.0	12.0	11.0
Range			
Days on IV Therapy[†]			
n	242	256	498
Mean	4.6	4.7	4.7
SD	2.7	2.6	2.7
Median	4.0	4.0	4.0
Range			
Days on Oral Therapy			
n	192	208	400
Mean	7.4	7.6	7.5
SD	2.5	2.3	2.4
Median	7.0	7.0	7.0
Range			
Days Missed Therapy[‡]			
n	6	8	14
Mean	3.5	1.3	2.2
SD	3.9	0.7	2.7
Median	1.0	1.0	1.0
Range			

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

(Applicant's Table 27, Volume 15 of 22, page 107)

Medical Officer's Comment: ***The 2 treatment groups were similar with respect to extent of exposure of both parenteral and oral study therapy by dose, duration, and days of missed therapy.***

7.1.3.2.2 Deaths

There were 8 deaths in the MK-0826 group and 6 deaths in the ceftriaxone group among patients enrolled in Protocol 018 (7 deaths in the MK-0826 group and 5 deaths in the ceftriaxone group occurred during study therapy or the 14-day follow-up period). The mortality rate was similar between the 2 treatment groups. None of the deaths, nor the adverse experiences associated with the death, was considered study-drug related, by the Investigators or Applicant. Narratives of these deaths are found in Appendix 28. The table below lists all deaths reported during the entire study period, including 2 that occurred after the 14-day follow-up period (AN 6272 in the MK-0826 group and AN 6197 in the ceftriaxone group).

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Listing of Patients Who Died During the Entire Study Period[†]
(Treated Population)

AN	Study Number	Gender	Race	Age	Daily Dose[‡]	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Intensity	Drug Relationship	Action Taken
MK-0826											
6281	018003	M	Caucasian	55	MK-0826 1 g	2	Cardiac arrhythmias	2 days	Severe	Probably not	Discontinued
					Off drug	3	Death		Severe	Probably not	
6431	018014	F	Hispanic	81	MK-0826 1 g	5	Respiratory failure	2 days	Severe	Probably not	Discontinued
					Off drug	6	Death		Severe	Probably not	
7227	018017	F	Caucasian	86	MK-0826 1 g	2	Heart failure, Worsening	3 days	Severe	Definitely not	Discontinued
					MK-0826 1 g	4	Death		Severe	Definitely not	
6376	018023	F	Caucasian	88	MK-0826 1 g	1	Cardiac arrest	1 day	Severe	Probably not	Discontinued
					MK-0826 1 g	1	Death		Severe	Probably not	
7079	018026	F	Mestizo	75	Off drug	22	Cardiac arrest	15 minutes	Severe	Definitely not	None
					Off drug	22	Death		Severe	Definitely not	
6272[§]	018052	F	Caucasian	57	Off drug	44	Sepsis, abdominal 2° *C. dificile* infection	15 days	Severe	Probably not	None
					Off drug	58	Death		Severe	Probably not	
6624	018055	M	Asian	58	Off drug	4	Pneumonia, worsening	7 days	Severe	Probably not	Discontinued
					Off drug	10	Death		Severe	Probably not	
7055	018059	M	Caucasian	76	Off drug	12	Death		Severe	Definitely not	
					Off drug	12	Myocardial infarction	6 hours	Severe	Definitely not	None
Ceftriaxone											
6795	018004	F	Caucasian	86	Off drug	3	Death		Severe	Definitely not	
					Off drug	3	Respiratory failure	15 minutes	Severe	Definitely not	Discontinued
6312	018015	M	Hispanic	78	Ceftriaxone 1 g	7	Pneumonia, bilateral	3 days	Severe	Probably not	Discontinued
					Off drug	9	Death		Severe	Probably not	
6441	018015	M	Hispanic	74	Off drug	13	Sepsis, pulmonary	5 days	Severe	Probably not	Discontinued
					Off drug	17	Death		Severe	Probably not	
7082	018021	F	Hispanic	35	Ceftriaxone 1 g	7	Pericarditis, bacterial	3 days	Severe	Definitely not	Discontinued
					Off drug	9	Death		Severe	Probably not	
7077	018026	F	Mestizo	73	Off drug	8	Cardiac arrest	1 day	Severe	Probably not	Discontinued
					Off drug	8	Death		Severe	Probably not	
6197[§]	018038	M	Black	77	Off drug	29	Death		Severe	Definitely not	
					Off drug	29	Respiratory failure 2° to pulmonary edema and adenocarcinoma of the lung.	1 day	Severe	Definitely not	None

[†] Includes adverse experiences reported after the 14-day follow-up period.
[‡] Displays any change of daily dose that occurred during the adverse experience.
[§] The serious adverse experiences and deaths in these patients occurred more than 14 days after discontinuation of study drug.

(Modified Applicant's Table 69, Volume 15 of 22, page 184)

Medical Officer's Comment: ***The majority of deaths in the ceftriaxone group appear clearly related to failure of study therapy (ANs 6312, 6441, 7082, and 7077) or underlying disease (AN 6197). The cause of death of patient AN 6795, although considered "Definitely Not" related to study therapy by the Investigator, is unexplained since the patient was found in cardiac arrest, but was thought to have improvement in CAP symptoms at the last visit prior to death.***

The majority of deaths in the MK-0826 group appear related to failure of study therapy (ANs 6431, 7227, 6376, and 6624) and/or underlying disease (AN 6431, 7227, 6376, 7079, and 7055). Patient AN 6281 experienced cardiac arrhythmias prior to death that are not further defined in the CRF, but that were treated with adenosine and digoxin suggesting a supraventricular tachycardia (additional information regarding this patient was provided in an amendment to the NDA and confirmed that the arrythmia was supraventricular-atrial flutter/atrial fibrillation). The Investigator felt that the AEs were "Probably Not" related to study medication, however, in the absence of additional information regarding this patient, the MO does not feel an effect of MK-0826 can be absolutely excluded. Patient AN 6272 died 45 days post completion of study therapy due to abdominal sepsis related to C. dificile infection (after receiving additional antimicrobial therapy for AECB) according to the Investigator; the MO feels that MK-0826 therapy can not be completely excluded as a contributory factor in this patient's death.

7.1.3.2.3 Other Serious Adverse Events

The following table displays, by body system, the number (percent) of patients with serious clinical adverse experiences with an incidence >0% in one or more treatment groups that occurred during PP. Eighteen (18) patients (7.4%) in the MK-0826 group and 14 patients (5.5%) in the ceftriaxone group had serious clinical adverse experiences. One patient (0.4%), AN 7057 (seizure disorder), in the MK-0826 group and no patients in the ceftriaxone group had serious drug-related clinical adverse experiences, according to Investigator's assessments. The Applicant's narrative for patient AN 7057 is as follows:

~~This 89-year-old female, treated with MK-0826 for CAP, experienced a~~ generalized tonic-clonic seizure on Study Day 10, the last scheduled day of IV study therapy. The seizure lasted 1 minute and she recovered without the administration of any anti-seizure medication. Her pneumonia was considered cured and no action was taken relative to study therapy. On the day of the seizure no procedures were done. On Study Day 53, an electroencephalogram (EEG) was done with a normal result. Her neurologic examination at follow-up was without sequelae. The investigator reported that the patient's experience was probably related to study drug.

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

	MK-0826 (N=242)		Ceftriaxone (N=256)	
	n	(%)	n	(%)
Patients with one or more serious clinical adverse experiences	18	(7.4)	14	(5.5)
Patients with no serious clinical adverse experience	224	(92.6)	242	(94.5)
Body as a Whole/Site Unspecified	**3**	**(1.2)**	**1**	**(0.4)**
Bacteremia	1	(0.4)	0	(0.0)
Death	2	(0.8)	0	(0.0)
Infection	0	(0.0)	1	(0.4)
Cardiovascular System	**7**	**(2.9)**	**4**	**(1.6)**
Arrhythmia	1	(0.4)	0	(0.0)
AV block, third degree	1	(0.4)	0	(0.0)
Cardiac arrest	1	(0.4)	0	(0.0)
Cardiac tamponade	0	(0.0)	1	(0.4)
Cor pulmonale	0	(0.0)	1	(0.4)
CVA	1	(0.4)	0	(0.0)
Heart failure	2	(0.8)	1	(0.4)
Myocardial infarction	0	(0.0)	2	(0.8)
Pericarditis	0	(0.0)	1	(0.4)
Transient ischemic attack	1	(0.4)	0	(0.0)
Digestive System	**1**	**(0.4)**	**2**	**(0.8)**
Hemorrhage, gastrointestinal	1	(0.4)	1	(0.4)
Liver disorder	0	(0.0)	1	(0.4)
Liver function abnormality	1	(0.4)	0	(0.0)
Hemic and Lymphatic System	**1**	**(0.4)**	**0**	**(0.0)**
Arterial pO_2 decreased	1	(0.4)	0	(0.0)
Leukemia, lymphoid, chronic	1	(0.4)	0	(0.0)
pCO_2 increased	1	(0.4)	0	(0.0)

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Metabolic, Nutritional, Immune	**2**	**(0.8)**	**0**	**(0.0)**
Acidosis	1	(0.4)	0	(0.0)
Hypoglycemia	1	(0.4)	0	(0.0)
Nervous System and Psychiatric Disorder	**1**	**(0.4)**	**0**	**(0.0)**
Seizure disorder	1	(0.4)	0	(0.0)
Respiratory System	**9**	**(3.7)**	**9**	**(3.5)**
Aspiration	0	(0.0)	1	(0.4)
Asthma	1	(0.4)	0	(0.0)
Atelectasis	0	(0.0)	1	(0.4)
Chronic obstructive pulmonary disease	0	(0.0)	1	(0.4)
Effusion, pleural	0	(0.0)	1	(0.4)
Empyema	1	(0.4)	0	(0.0)
Epistaxis	1	(0.4)	0	(0.0)
Hypoxemia	2	(0.8)	0	(0.0)
Neoplasm, lung, malignant	0	(0.0)	1	(0.4)
Neoplasm, pleural, malignant	0	(0.0)	1	(0.4)
Pneumonia	1	(0.4)	2	(0.8)
Pneumonia, *Pneumocystis*	0	(0.0)	1	(0.4)
Radiodensity, pulmonary	0	(0.0)	2	(0.8)
Respiratory failure	2	(0.8)	1	(0.4)
Respiratory insufficiency	2	(0.8)	0	(0.0)
Urogenital System	**2**	**(0.8)**	**1**	**(0.4)**
Renal insufficiency	1	(0.4)	0	(0.0)
Urinary retention	1	(0.4)	1	(0.4)

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

(Applicant's Table 65, Volume 15 of 22, pages 170-171)

Medical Officer's Comment: ***After reviewing the narratives and CRFs for these patients, the MO agrees with the Applicant's assessment that with the exception of patient AN 7057 (who had a seizure while receiving MK-0826), these reported serious adverse events are most likely due to efficacy failures or underlying diseases.***

There were a further 31 patients (12.8%) in the MK-0826 group and 31 patients (12.1%) in the ceftriaxone group with serious clinical adverse experiences that occurred after the parenteral therapy period. An additional 6 patients (3 in each group) had serious clinical adverse experiences after the 14-day follow-up. Significant serious clinical adverse experiences occurring in the parenteral period plus oral therapy through TOC visit included: death (8 in the MK-0826 group and 6 in the ceftriaxone group), cardiac arrest (3 in the MK-0826 group and 1 in the ceftriaxone group), pneumonia (4 in the MK-0826 group and 6 in the ceftriaxone group), and respiratory failure (3 in the MK-0826 group and 5 in the ceftriaxone group). Three patients in the MK-0826 group (ANs 6794, 6413, and 6417) experienced seizures after the parenteral therapy period, however, all three patients had an underlying seizure disorder and the seizures did not appear temporally related to MK-0826 therapy. The majority of the additional serious adverse experiences appear related to efficacy failure or complications of baseline conditions.

7.1.3.2.4 Dropouts

Thirteen (13) patients (5.4%) in the MK-0826 group and 8 patients (3.1%) in the ceftriaxone group discontinued parenteral therapy due to clinical adverse experiences. No patients were discontinued from study therapy, in the parenteral period, in either treatment group due to clinical adverse experiences felt to be drug-related by the Investigators. There were 2 patients (ANs 6083 and 6624) in the MK-0826 group and 5 patients (ANs 6009, 6087, 6441, 6795, and 7077) in the

ceftriaxone group who were reported as discontinued from study drug during the off drug portion of the study. These patients had adverse experiences 1 day after the last recorded dose of parenteral therapy and resulted in discontinuation because the next intended dose of study drug was not administered (counted in the Applicant's summary table for study therapy and 14-day follow-up period, but exclude from the Applicant's parenteral therapy summary table).

An additional 3 patients (ANs 6365, 7026, and 7230) in the MK-0826 group and 5 patients (ANs 6015, 6414, 6623, 7126, and 7229) in the ceftriaxone group discontinued during oral study therapy. One patient (AN 6365) in the MK-0826 treatment group and 3 patients (ANs 6015, 6623, and 7126) in the ceftriaxone group were discontinued due to drug-related clinical adverse experiences during oral study therapy. AN 6365 experienced a lower respiratory tract infection while on oral amoxicillin/clavulanate, which resulted in discontinuation. AN 6015 was discontinued due to an allergic reaction to oral amoxicillin/clavulanate and was placed on oral levofloxacin for the duration of oral therapy. AN 6623 reported vomiting while on oral amoxicillin/clavulanate, which resulted in discontinuation from therapy. AN 7126 was discontinued due to diarrhea while on oral amoxicillin/clavulanate and was given oral cefaclor for the duration of oral therapy.

Medical Officer's Comment: ***The following table lists all patients discontinued from parenteral study therapy due to a clinical adverse experience. The table also includes 2 patients (ANs 6083 and 6624) in the MK-0826 group and 5 patients (ANs 6009, 6087, 6441, 6795, and 7077) in the ceftriaxone group who were reported by the Applicant as discontinuing therapy after the parenteral period, but, whom the MO feels are more appropriately included in the parenteral period table due to the proximity of the discontinuation to the last dose of parenteral therapy.***

The reasons for discontinuation in both treatment groups, in both the parenteral period and the study therapy plus 14 day follow-up period, were primarily related to efficacy failure. The number of patients discontinued from study therapy was similar in both treatment groups.

Listing of Patients Discontinued Due to Clinical Adverse Experiences During Parenteral Therapy According to the Medical Officer (Treated Population)

AN	Study Number	Gender	Race	Age	Daily Dose†	Relative Day Of Onset	Adverse Experience	Duration of Adverse Experience	Relative Date Of Discont.‡	Intensity	Drug Relationship	Serious	Outcome
MK-0826													
6915	018002	F	Black	46	MK-0826 1 g	2	Stomatitis	2 days	35	Severe	Probably not	No	Recovered
6281	018003	M	Caucasian	55	MK-0826 1 g	2	Arrhythmia	2 days	3	Severe	Probably not	Yes	Still presen
6301	018014	M	Hispanic	25	MK-0826 1 g	5	Tuberculosis, Pulmonary	24 days	28	Moderate	Definitely not	No	Still presen
6431	018014	F	Hispanic	81	MK-0826 1 g	5	Respiratory failure	2 days	6	Severe	Probably not	Yes	Still presen
6451	018014	F	Hispanic	68	MK-0826 1 g	5	Tuberculosis, Pulmonary	30 days	34	Moderate	Definitely not	No	Recovered
6413	018015	M	Hispanic	43	MK-0826 1 g	3	Pneumonia	21 days	27	Severe	Probably not	Yes	Recovered
					MK-0826 1 g	5	Deterioration, General	11 days		Severe	Probably not	No	Recovered
6485	018015	M	Hispanic	46	MK-0826 1 g	3	Empyema	14 days	25	Moderate	Probably not	Yes	Recovered
7227	018017	F	Caucasian	86	MK-0826 1 g	2	Heart failure	3 days	4	Severe	Definitely not	Yes	Still present
6376	018023	F	Caucasian	88	MK-0826 1 g	1	Cardiac arrest	1 day	1	Severe	Probably not	Yes	Still present
7079	018026	F	Mestizo	75	MK-0826 1 g	9	CVA	14 days	19	Severe	Definitely not	Yes	Still present
6072	018027	M	Caucasian	29	MK-0826 1 g	2	Fever	2 days	6	Moderate	Definitely not	No	Recovered
					MK-0826 1 g	3	Hyperthermia	2 days		Moderate	Definitely not	No	Recovered
6782	018028	M	Caucasian	77	MK-0826 1 g	1	AV block, third Degree	2 days	2	Severe	Definitely not	Yes	Still present
7042	018059	M	Caucasian	18	MK-0826 2 g	1	Respiratory Insufficiency	15 days	1	Severe	Probably not	Yes	Recovered
6083	018031	M	Caucasian	56	Off drug§	4	Respiratory failure	22 days	25	Severe	Definitely not	Yes	Still present
6624	018055	M	Asian	58	Off drug§	4	Pneumonia	7 days	4	Severe	Probably not	Yes	Still present
Ceftriaxone													
6135	018005	F	Caucasian	74	Ceftriaxone 1 g	2	Myocardial Infarction	13 days	9	Severe	Probably not	Yes	Recovered
6312	018015	M	Hispanic	78	Ceftriaxone 1 g	7	Somnolence	3 days	8	Severe	Probably not	No	Still present
					Ceftriaxone 1 g	7	Aspiration	3 days		Moderate	Probably not	Yes	Still present
					Ceftriaxone 1 g	7	Pneumonia	3 days		Severe	Probably not	Yes	Still present
7082	018021	F	Hispanic	35	Ceftriaxone 1 g	7	Cardiac tamponade	3 days	8	Severe	Definitely not	Yes	Still present
					Ceftriaxone 1 g	7	Pericarditis	3 days		Severe	Definitely not	Yes	Still present
6073	018027	M	Caucasian	46	Ceftriaxone 1 g	3	Pneumonia, *Pneumocystis*	8 days	24	Moderate	Definitely not	Yes	Recovered
6107	018030	F	Black	67	Ceftriaxone 1 g	1	Lymphadenopathy, Mediastinum	15 days	1	Moderate	Definitely not	No	Still present
					Ceftriaxone 1 g	1	Neoplasm, lung, Malignant	15 days		Moderate	Definitely not	Yes	Still present
6208	018034	M	Hispanic	52	Ceftriaxone 1 g	2	Radiodensity, Pulmonary	22 days	3	Severe	Probably not	Yes	Still present
7012	018048	M	Mestizo	62	Ceftriaxone 2 g	9	Pneumonia	21 days	29	Moderate	Definitely not	Yes	Recovered
7038	018058	F	Hispanic	77	Ceftriaxone 1 g	9	Infection	13 days	20	Severe	Probably not	Yes	Still present
6009	018011	F	Black	64	Off drug§	3	Respiratory failure	1 day	3	Severe	Definitely not	Yes	Still present
6087	018031	F	Caucasian	72	Off drug§	3	Impaction, fecal	2 days	12	Severe	Definitely not	Yes	Recovered
					Off drug§	3	Obstruction, Intestinal	2 days		Severe	Definitely not	Yes	Recovered
6441	018015	M	Hispanic	74	Off drug§	12	Deterioration, General	6 days	12	Severe	Probably not	Yes	Still Present
					Off drug§	12	Hypoxemia	6 days		Moderate	Probably not	No	Still Present
					Off drug§	13	Sepsis, pulmonary	5 days		Severe	Probably not	Yes	Still Present
6795	018004	F	Caucasian	86	Off drug§	3	Respiratory failure	15 minutes	2	Severe	Definitely not	Yes	Still Present
7077	018026	F	Mestizo	73	Off drug§	8	Cardiac Arrest	1 day	8	Severe	Probably not	Yes	Still Present

† Displays any change of daily dose that occurred during the adverse experience.
‡ Day of the last clinical or laboratory assessment performed, relative to the first day of study therapy.
§ Patients added to table by Medical Officer

(Modified Applicant's Tables 68 and 73, Volume 15 of 22, pages179-180, 204-207)

7.1.3.2.5 Other Treatment Emergent Adverse Events

Overall 162 patients had clinical adverse experiences during the parenteral therapy period (109 [46.2%] in the MK-0826 group and 53 [43.1%] in the ceftriaxone group) and 214 patients had clinical adverse experiences during the study therapy and follow-up period (141 [59.7%] in the MK-0826 group and 73 [59.3%] in the ceftriaxone group).

Medical Officer's Comment: ***The Applicant displayed adverse events in tables broken down by ≥3% or ≥0%. In the MO's tables that follow, the number of patients with specific clinical adverse experiences and the number of patients with drug-related specific clinical adverse experiences ≥2% during the parenteral therapy period are displayed. Diarrhea (2.9% vs 2.7%, MK-0826 vs Ceftriaxone respectively) was the only drug-related clinical adverse experience that occurred in a higher percentage of patients in the MK-0826 group.***

Tables displaying the number of patients with specific clinical adverse experiences and the number of patients with drug-related specific clinical adverse experiences ≥2% during the study therapy and follow-up period are displayed in Appendix 25.

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

	MK-0826 (N=242)		Ceftriaxone (N=256)	
	n	(%)	n	(%)
Patients with one or more adverse experiences	113	(46.7)	126	(49.2)
Patients with no adverse experience	129	(53.3)	130	(50.8)
Body as a Whole/Site Unspecified	**19**	**(7.9)**	**22**	**(8.6)**
Pain, abdominal	5	(2.1)	5	(2.0)
Pain, chest	2	(0.8)	5	(2.0)
Cardiovascular System	**36**	**(14.9)**	**47**	**(18.4)**
Extravasation	5	(2.1)	6	(2.3)
Hypotension	5	(2.1)	0	(0.0)
Infused vein complication	18	(7.4)	23	(9.0)
Digestive System	**36**	**(14.9)**	**41**	**(16.0)**
Constipation	11	(4.5)	5	(2.0)
Diarrhea	9	(3.7)	15	(5.9)
Nausea	7	(2.9)	8	(3.1)
Metabolic, Nutritional, Immune	**3**	**(1.2)**	**6**	**(2.3)**
Musculoskeletal System	**8**	**(3.3)**	**8**	**(3.1)**
Nervous System and Psychiatric Disorder	**30**	**(12.4)**	**29**	**(11.3)**
Anxiety	1	(0.4)	6	(2.3)
Headache	10	(4.1)	12	(4.7)
Insomnia	7	(2.9)	9	(3.5)
Respiratory System	**30**	**(12.4)**	**28**	**(10.9)**
Hypoxemia	6	(2.5)	1	(0.4)
Skin and Skin Appendage	**13**	**(5.4)**	**17**	**(6.6)**
Special Senses	**1**	**(0.4)**	**5**	**(2.0)**
Urogenital System	**6**	**(2.5)**	**4**	**(1.6)**

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 117, Volume 15 of 22, pages 367-372)

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

	MK-0826 (N=242)		Ceftriaxone (N=256)	
	n	(%)	n	(%)
Patients with one or more drug-related adverse experiences	27	(11.2)	43	(16.8)
Patients with no drug-related adverse experience	215	(88.8)	213	(83.2)
Cardiovascular System	**11**	**(4.5)**	**21**	**(8.2)**
Infused vein complication	8	(3.3)	12	(4.7)
Digestive System	**10**	**(4.1)**	**16**	**(6.3)**
Diarrhea	7	(2.9)	7	(2.7)
Nausea	2	(0.8)	5	(2.0)
Nervous System and Psychiatric Disorder	**2**	**(0.8)**	**5**	**(2.0)**

† Determined by the investigator to be possibly, probably, or definitely drug related.
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 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 118, Volume 15 of 22, page 373)

7.1.3.2.6. Laboratory Findings

Of the patients in the treated population, 58 (25.0%) in the MK-0826 group and 55 (22.6%) in the ceftriaxone group had a laboratory adverse experience during parenteral therapy. The most common laboratory adverse experiences were increased ALT and AST concentrations, increased serum alkaline phosphatase, and increased platelet count. The tables below display the number (percent) of patients with specific laboratory adverse experiences with an incidence ≥3% in one or more treatment groups, by laboratory test category, occurring during parenteral therapy and the number (percent) of patients with specific drug-related laboratory adverse experiences with an incidence ≥1% in one or more treatment groups by laboratory test category occurring during parenteral therapy.

Number (%) of Patients With Specific Laboratory Adverse Experiences (Incidence ≥3% in One or More Treatment Groups) by Laboratory Test Category During Parenteral Therapy (Treated Population)

	MK-0826 (N=242)		Ceftriaxone (N=256)	
	n/m	(%)	n/m	(%)
Patients with one or more laboratory adverse experiences	58/232	(25.0)	55/243	(22.6)
Patients with no laboratory adverse experience	174/232	(75.0)	188/243	(77.4)
Blood Chemistry	**41/230**	**(17.8)**	**33/238**	**(13.9)**
ALT increased	23/199	(11.6)	18/207	(8.7)
ANA positive	1/1	(100)	0/0	(0.0)
AST increased	17/203	(8.4)	16/208	(7.7)
HIV positive	1/1	(100)	0/0	(0.0)
Serum alkaline phosphatase increased	9/209	(4.3)	9/215	(4.2)
Serum cholesterol increased	0/0	(0.0)	1/1	(100)
Serum GGT increased	0/0	(0.0)	1/1	(100)
Serum glucose increased	8/225	(3.6)	9/231	(3.9)
Serum uric acid decreased	1/1	(100)	0/0	(0.0)
Hematology	**25/229**	**(10.9)**	**25/241**	**(10.4)**
CD4 count decreased	1/1	(100)	0/0	(0.0)
ESR increased	1/1	(100)	0/0	(0.0)
Hematocrit decreased	7/226	(3.1)	7/238	(2.9)
Hemoglobin decreased	7/226	(3.1)	7/238	(2.9)
Platelet count increased	9/225	(4.0)	11/236	(4.7)
Urinalysis	**10/188**	**(5.3)**	**12/199**	**(6.0)**
Urine *Trichomonas*	0/0	(0.0)	1/1	(100)
Urine yeast, nondiagnostic	0/0	(0.0)	1/1	(100)
Miscellaneous	**0/0**	**(0.0)**	**1/1**	**(100)**
C. difficile toxin, positive	0/0	(0.0)	1/1	(100)

N = Total number of patients per treatment group.
n/m = Number of patients with laboratory adverse experience/number of patients with laboratory test postbaseline.
Although a patient may have had 2 or more adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.
All categories are listed in which at least one patient had an adverse experience.

(Applicant's Table 75, Volume 15 of 22, page 211)

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Number (%) of Patients With Specific Laboratory Adverse Experiences (Incidence ≥1% in One or More Treatment Groups) by Laboratory Test Category During Parenteral Therapy (Treated Population) Drug Related†

	MK-0826 (N=242)		Ceftriaxone (N=256)	
	n/m	(%)	n/m	(%)
Patients with one or more drug-related laboratory adverse experiences	31/232	(13.4)	26/243	(10.7)
Patients with no drug-related laboratory adverse experience	201/232	(86.6)	217/243	(89.3)
Blood Chemistry	**20/230**	**(8.7)**	**20/238**	**(8.4)**
ALT increased	18/199	(9.0)	15/207	(7.2)
AST increased	15/203	(7.4)	13/208	(6.3)
Serum alkaline phosphatase increased	3/209	(1.4)	6/215	(2.8)
Hematology	**11/229**	**(4.8)**	**5/241**	**(2.1)**
Hematocrit decreased	4/226	(1.8)	0/238	(0.0)
Hemoglobin decreased	4/226	(1.8)	0/238	(0.0)
Platelet count increased	4/225	(1.8)	3/236	(1.3)
WBC decreased	3/226	(1.3)	2/238	(0.8)
Urinalysis	**2/188**	**(1.1)**	**2/199**	**(1.0)**
Urine *Trichomonas*	0/0	(0.0)	1/1	(100)
Urine yeast, nondiagnostic	0/0	(0.0)	1/1	(100)
Miscellaneous	**0/0**	**(0.0)**	**1/1**	**(100)**
C. difficile toxin, positive	0/0	(0.0)	1/1	(100)

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

(Applicant's Table 76, Volume 15 of 22, page 212)

Medical Officer's Comment: ***In both the all and drug-related adverse events displays, ALT and AST elevations were slightly more common in the MK-0826 group during parenteral therapy.***

Of treated patients with at least 1 laboratory test, 77 (32.9%) in the MK-0826 group and 73 (29.6%) in the ceftriaxone group had a laboratory adverse experience during the study therapy and the follow-up period. Of these, adverse experiences occurred in 58 patients in the MK-0826 group and in 55 patients in the ceftriaxone group during parenteral therapy. There were 36 (15.4%) patients in the MK-0826 group and 31 (12.6%) patients in the ceftriaxone group who had drug-related laboratory adverse experiences. Of these, 31 patients in the MK-0826 group and 26 patients in the ceftriaxone group had a drug-related adverse experience during parenteral therapy. As was seen during parenteral therapy, the most common laboratory adverse experiences were increased ALT and AST and these findings were again slightly more common in the MK-0826 group.

Seven patients (3.0%) in the MK-0826 group (5 drug-related) and 4 patients (1.6%) in the ceftriaxone group (4 drug-related) had serious laboratory adverse experiences. The only serious laboratory adverse experiences that occurred in more than one patient during parenteral therapy were increased ALT and AST

concentrations. The following table lists all patients with serious laboratory- and serious drug-related laboratory adverse experiences occurring during parenteral therapy.

Listing of Patients With Serious Laboratory Adverse Experiences During Parenteral Therapy (Treated Population)

AN	Study Number	Gender	Race	Age	Daily Dose†	Relative Day of Test	Adverse Experience	Laboratory Value (Unit)	Normal Range	Drug Relationship	Action Taken
MK-0826											
6064	018001	M	Hispanic	39	MK-0826 1 g	2	CD4 count decreased	163 cells/mm^3	436 to 1394 cells/mm^3	Definitely not	None
					MK-0826 1 g	4	HIV positive	1 qual no	0 to 0 qual no	Definitely not	None
6199	018038	M	Black	76	MK-0826 1 g	4	Hypernatremia	150 mmol/L	135 to 145 mmol/L	Definitely not	None
Ceftriaxone											

† Displays the daily dose received one day before the laboratory test.
[redacted] = patients with serious drug-related laboratory adverse events.

(Modified from Applicant's Table 77, Volume 15 of 22, pages 214-215)

Medical Officer's Comment: ***No patients with drug-related laboratory adverse events were discontinued from study drug during the parenteral period. The MO has reviewed the narratives and CRFs for the above patients and agrees with the Applicant's presentation of drug-relatedness.***

There were 10 patients in the MK-0826 group and 4 patients in the ceftriaxone group in whom serious laboratory adverse experiences were reported during the study therapy and follow-up period. Of these, 7 patients from the MK-0826 group and 4 patients from the ceftriaxone group had serious laboratory adverse experiences that occurred during parenteral therapy. In the three additional patients with serious adverse laboratory events in the parenteral period plus oral therapy through TOC visit period, the events were: increased ALT and AST in AN 6488 (mild elevations occurring on study day 17), fecal C. difficile test positive in AN 6272 (this patient has previously been presented in the Deaths section of the review), and leukocytes decreased in AN 7032 (occurring on study day 12 after 4 days parenteral and 7 days oral therapy in a patient with multiple myeloma). Only the event in patient AN 6488 was considered drug-related.

Overall the proportions of serious laboratory- and serious drug-related laboratory adverse events were similar for the two treatment groups.

7.1.3.2.7 Assessment of Tolerability

An assessment of tolerability at the IV study drug infusion site was performed daily while the patient was on study therapy. No patient received IM study drug therapy during this study. The intensity of specified local infusion-related symptoms was rated as mild, moderate, or severe. Of patients who experienced one or more local reactions at the infusion site, 37/242 (15.3%) were in the MK-0826 group and 44/255 (17.3%) were in the ceftriaxone group. If local intolerance was felt by the Investigator to reach the level of a clinical adverse experience, the adverse experience was reported as a clinical syndrome (e.g. local phlebitis/thrombophlebitis) and was displayed as "infused vein complication" in the counts of clinical adverse experiences. A clinical adverse experience of "infused vein complication" was reported for 19/242 (7.9%) of patients in the Mk-0826 group and 27/256 (10.5%) of patients in the ceftriaxone group. The following table presents the proportions of patients reporting any local reactions and the 95% CI of (-8.5, 4.5) about the difference.

Number (%) of Patients With Symptoms of Intravenous Therapy Intolerance During Intravenous Therapy (Treated Population)

	Treatment Group						Difference (A - B) % (95% CI)
	MK-0826 (A) (N=242)			Ceftriaxone (B) (N=255)			
Patients with one or more symptoms	n/m 37/242	(%) (15.3)	(95% CI) (10.8, 19.8)	n/m 44/255	(%) (17.3)	(95% CI) (12.6, 21.9)	- 2.0 (-8.5, 4.5)
Patients with one or more symptoms of moderate to severe intensity	13/242	(5.4)	(2.5, 8.2)	19/255	(7.5)	(4.2, 10.7)	-2.1 (-6.4, 2.2)

N = Number of treated patients in each treatment group with an assessment.
n/m = Number of patients reporting an intolerability symptom/number of patients with an assessment.
CI = Confidence interval.

(Applicant's Table 87, Volume 15 of 22, page 234)

Medical Officer's Comment: Overall the rates of local reactions of any intensity were not different in the 2 treatment groups.

7.1.3.2.8 Adverse Experiences of Special Interest

Four adverse experiences were prespecified for more detailed review because of preclinical findings (neutropenia), adverse experiences associated with β-lactam antibiotics as a class (liver function elevations and rash), and adverse experiences associated with other carbapenem antimicrobials (seizures).

Seizures

One patient (AN 7057) in the MK-0826 had a seizure, while on parenteral therapy, that was judged by the Investigator to be study drug-related. This patient was previously described in Section 7.1.3.2.3 of this review.

Neutropenia/Liver Enzyme Elevations

In addition to reviewing investigator-reported laboratory adverse experiences, the Applicant performed an assessment of the relative laboratory safety of each treatment group by using predefined Clinically Significant Laboratory Abnormalities (CSLAs) for specified tests and identifying patients whose worst laboratory value represented a worsening from baseline and met the criteria for a CSLA. In order to be considered in the analysis for CSLAs, patients had to have a baseline laboratory value, at least 1 post-baseline laboratory test and have normal ranges in the database. For platelet count, absolute neutrophil count, hematocrit, and hemoglobin, the CSLA criteria were defined in terms of a fixed bound. For creatinine, total bilirubin, direct bilirubin, ALT, AST, and alkaline phosphatase, the CSLA criteria were defined in terms of a fixed bound greater than the upper limit of normal (ULN). The following table displays CSLAs for neutropenia and liver function assays during the parenteral therapy period and the total study therapy plus the follow-up period.

Number (%) of Patients With a Clinically Significant Laboratory Abnormality (CSLA) by Treatment Group

		During Parenteral Therapy				During Study Therapy and Follow-up			
		Number (%) with CSLA				Number (%) with CSLA			
Laboratory Test	CSLA Criteria	MK-0826 (N=242)		Ceftriaxone (N=256)		MK-0826 (N=242)		Ceftriaxone (N=256)	
		n/m	(%)	n/m	(%)	n/m	(%)	n/m	(%)
Absolute neutrophils (cells/μL)	<1800	7/208	(3.4)	7/220	(3.2)	14/219	(6.4)	11/229	(4.8)
	<1000	1/208	(0.5)	2/220	(0.9)	4/219	(1.8)	2/229	(0.9)
ALT (U/L)	>2.5 x ULN	13/187	(7.0)	16/198	(8.1)	16/202	(7.9)	20/213	(9.4)
	>5 x ULN	4/187	(2.1)	5/198	(2.5)	6/202	(3.0)	7/213	(3.3)
AST (U/L)	>2.5 x ULN	12/195	(6.2)	13/197	(6.6)	15/205	(7.3)	16/212	(7.5)
	>5 x ULN	4/195	(2.1)	1/197	(0.5)	5/205	(2.4)	1/212	(0.5)
Direct serum bilirubin (mg/dL)	>1.5 x ULN	2/122	(1.6)	6/126	(4.8)	2/126	(1.6)	7/133	(5.3)
	>2.5 x ULN	1/122	(0.8)	2/126	(1.6)	1/126	(0.8)	3/133	(2.3)
Hematocrit (%)	<24	1/225	(0.4)	2/238	(0.8)	2/231	(0.9)	3/244	(1.2)
Hemoglobin (g/dL)	<8	1/225	(0.4)	1/238	(0.4)	2/231	(0.9)	1/244	(0.4)
Platelet count (cells/μL)	<75,000	3/222	(1.4)	1/234	(0.4)	3/229	(1.3)	1/241	(0.4)
	<50,000	0/222	(0.0)	0/234	(0.0)	0/229	(0.0)	0/241	(0.0)
Serum alkaline phosphatase (U/L)	>2.5 x ULN	5/203	(2.5)	4/210	(1.9)	6/219	(2.7)	5/225	(2.2)
	>5 x ULN	0/203	(0.0)	0/210	(0.0)	0/219	(0.0)	1/225	(0.4)
Serum creatinine (mg/dL)	>1.5 x ULN	3/226	(1.3)	2/235	(0.9)	3/231	(1.3)	3/239	(1.3)
	>3 x ULN	1/226	(0.4)	0/235	(0.0)	1/231	(0.4)	0/239	(0.0)
Total serum bilirubin (mg/dL)	>1.5 x ULN	1/206	(0.5)	3/208	(1.4)	1/221	(0.5)	4/224	(1.8)
	>2.5 x ULN	0/206	(0.0)	2/208	(1.0)	0/221	(0.0)	2/224	(0.9)

N = The total number of patients in treatment group.
n/m = Number of patients with CSLA/number of patients with laboratory test at baseline and postbaseline.
(Modified Applicant's Tables 88 and 91, Volume 15 of 22, pages 237 and 244)

Rash

Rash occurred in 6 patients in the MK-0826 group and in 6 patients in the ceftriaxone group during study therapy or the 14-day follow-up period. These numbers included patients with urticaria. Of the rashes reported, 2 (ANs 6309 and 7061) in the MK-0826 group and 3 (ANs 6096, 6308, and 7060) in the ceftriaxone group were considered drug-related. No cases of rash causing discontinuation of the study drug were reported in either treatment group.

Medical Officer's Comment: ***The seizure that occurred in the patient on MK-0826 during parenteral therapy may represent a real signal in the database, given the known association of seizures with carbapenem antimicrobials. This issue will be addressed in more detail in the Integrated Summary of Safety.***

Overall the rates of neutropenia, liver function abnormalities (with the exception of AST >5x ULN), and rash were comparable between the two treatment groups.

7.1.3.2.9 Conclusion

In adult patients with serious community-acquired pneumonia (CAP) treated for up to 14 days with intravenous administration of MK-0826 1 g per day, with an oral antibiotic switch option (Augmentin) after clinical improvement, the following conclusions regarding safety and tolerability can be drawn:

1. The safety profile of MK-0826 was similar to ceftriaxone 1 g daily based on the overall safety profile including the frequency of drug-related serious adverse experiences, discontinuations due to drug-related adverse experiences, and the assessment of infusion-related local tolerability in patients with CAP.
2. The seizure reported for AN 7057, in the MK-0826 group, is notable and consistent with a drug-related adverse event.
3. The tolerability at the IV infusion site for MK-0826 was similar to that of ceftriaxone.
4. Since no patients in the MK-0826 group were treated with IM therapy, no conclusions can be made about the tolerability of IM administration of MK-0826 based on this study.

7.1.3.3 PROTOCOL 020: A SUPPORTIVE, PROSPECTIVE, MULTICENTER, DOUBLE-BLIND, RANDOMIZED, COMPARATIVE STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF MK–0826 VERSUS CEFTRIAXONE SODIUM IN THE TREATMENT OF SERIOUS COMMUNITY-ACQUIRED PNEUMONIA IN ADULTS

Adverse experiences were recorded during parenteral study therapy and oral study therapy and for 14 days after the end of study therapy (safety follow-up period). According to the Applicant adverse experiences that occurred during the study parenteral therapy period were more likely to be related to the parenteral study therapy than those that occurred after completion of the parenteral therapy (i.e., during oral therapy or the follow-up period). For this reason, the Applicant performed separate analyses for adverse experiences that occurred specifically within the parenteral treatment period and for those that occurred during study therapy and the 14-day follow-up period (i.e., parenteral and oral antibiotic therapy and 14-day follow-up period).

Medical Officer's Comment: ***During the January 28, 2000 telecon between the Applicant and the Division, the Applicant was told that the Division would consider both time periods equally in the Division's assessment of the safety database. In the following sections of the Safety review the Applicant's analyses for the parenteral period (PP) will be presented and any significant differences that are noted between this period and the parenteral plus oral through TOC period (TP) will be mentioned.***

Of the 364 patients enrolled, 359 received at least 1 dose of parenteral study therapy and are included in the Applicant's analysis of adverse experiences. Patients randomized to 1 treatment group who, due to dispensing errors, mistakenly received study therapy with the other study treatment for the entire parenteral study period were analyzed based on the study therapy actually received. Patients who, due to dispensing errors, received both parenteral study drugs at any time during the course of the study were analyzed based on the treatment group to which they were originally randomized. The table below provides an overall summary of safety during the PP and during the TP.

Clinical Adverse Experiences (AEs)	During Parenteral Therapy		During Study Therapy and 14-Day Follow-Up	
	MK-0826 (N=236)	Ceftriaxone (N=123)	MK-0826 (N=236)	Ceftriaxone (N=123)
Number (%) of patients:	n (%)	n (%)	n (%)	n (%)
with one or more AEs	109 (46.2)	53 (43.1)	141 (59.7)	73 (59.3)
with no AE	127 (53.8)	70 (56.9)	95 (40.3)	50 (40.7)
with drug-related AEs†	36 (15.3)	19 (15.4)	48 (20.3)	25 (20.3)
with serious AEs	23 (9.7)	9 (7.3)	36 (15.3)	21 (17.1)
with serious drug-related AEs	5 (2.1)	2 (1.6)	7 (3.0)	3 (2.4)
who died	0	0	2 (0.8)	3 (2.4)
discontinued due to an AE	13 (5.5)	7 (5.7)	15 (6.4)	9 (7.3)
discontinued due to a drug-related AE	4 (1.7)	3 (2.4)	5 (2.1)	3 (2.4)
discontinued due to a serious AE	10 (4.2)	5 (4.1)	12 (5.1)	7 (5.7)
discontinued due to a serious drug-related AE	3 (1.3)	2 (1.6)	4 (1.7)	2 (1.6)
Laboratory AEs				
Number of patients with at least 1 laboratory test postbaseline	(N=224)	(N=118)	(N=230)	(N=121)
Number (%) of patients:	n (%)	n (%)	n (%)	n (%)
with one or more AEs	48 (21.4)	29 (24.6)	59 (25.7)	37 (30.6)
with no AE	176 (78.6)	89 (75.4)	171 (74.3)	84 (69.4)
with drug-related AEs†	26 (11.6)	15 (12.7)	28 (11.9)	18 (14.6)
with serious AEs	2 (0.8)	0	3 (1.3)	2 (1.6)
with serious drug-related AEs	1 (0.4)	0	1 (0.4)	2 (1.6)
who died	0	0	0	0
discontinued due to an AE	0	1 (0.9)	0	1 (0.8)
discontinued due to a drug-related AE	0	1 (0.9)	0	1 (0.8)
discontinued due to a serious AE	0	0	0	0
discontinued due to a serious drug-related AE	0	0	0	0

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

(Applicant's Summary Table, Volume 17 of 22, page 31)

7.1.3.3.1 Extent of Exposure

The table below shows the extent of exposure to parenteral therapy by dose and duration for all patients who received at least 1 dose of study therapy. The number of patients who received each total daily dose of parenteral therapy is displayed. A patient was counted twice during the course of the study, if the patient's daily dose changed. Seven patients in the MK-0826 group had their dose adjusted due to renal function (to 500 mg once daily). The protocol allowed a one-time adjustment in dosing interval between the first and second parenteral study drug doses, to accommodate local medication administration schedules: 5 patients in the MK-0826 group and 7 patients in the ceftriaxone group had this dosing interval adjustment and received two 1 gm doses within the first 24 hour period (i.e. Day 1 of therapy). Four (4) patients in the MK-0826 treatment group (ANs 2862, 3718, 3722, and 3843) received a total daily dose of 2 g in erroneously for up to 6 days. None of these patients had documented PRSP.

Extent of Exposure by Dose and Duration
(Intravenous and Intramuscular Therapy) in the Treated Population

Treatment Group	Number of Days on Parenteral Therapy[1]											
	≤2	3 to 4	5 to 6	7 to 8	9 to 10	11 to 12	13 to 14	≥15	Total Patients	Range	Total Days	Mean
MK-0826												
Any dose	11	104	63	24	24	3	7	0	236	[redacted]	1256	5.3
0.5 g	5	1	0	0	0	0	1	0	7	[redacted]	25	3.6
1 g	12	101	61	27	20	3	6	0	230	[redacted]	1207	5.2
2 g[2]	6	0	3	0	0	0	0	0	9	[redacted]	24	2.7
Ceftriaxone												
Any dose	5	54	29	21	10	1	2	1	123	[redacted]	666	5.4
1 g	7	52	29	22	9	1	2	1	123	[redacted]	659	5.4
2 g[2]	7	0	0	0	0	0	0	0	7	[redacted]	7	1.0

[1] The table displays the number of patients receiving each daily dose. A patient was counted multiple times if during the course of the study the patient's daily dosage was changed.
[2] Patients who had the time of their daily dose adjusted may have received two 1-g doses in a 24-hour period and were subsequently counted as having 2 g of study therapy as a daily dose. ANs 2862, 3718, 3722, and 3843 in the MK-0826 group received a 2-g daily dose.

(Applicant's Table 62, Volume 17 of 22, page 165)

Fourteen patients, 9 in the MK-0826 group and 5 in the ceftriaxone group received IM parenteral therapy in this study. The table below shows the extent of exposure to IM therapy by dose and duration for all patients who received at least 1 dose of IM therapy.

Extent of Exposure by Dose and Duration
(Intramuscular Therapy) in the Treated Population

Treatment Group	Number of Days on Parenteral Therapy[1]											
	≤2	3 to 4	5 to 6	7 to 8	9 to 10	11 to 12	13 to 14	≥15	Total Patients	Range	Total Days	Mean
MK-0826												
Any dose	1	3	3	1	1	0	0	0	9	[redacted]	44	4.9
1 g	1	3	3	1	1	0	0	0	9	[redacted]	44	4.9
Ceftriaxone												
Any dose	0	1	3	1	0	0	0	0	5	[redacted]	29	5.8
1 g	0	1	3	1	0	0	0	0	5	[redacted]	29	5.8

[1] The table displays the number of patients receiving each daily dose. A patient was counted multiple times if during the course of the study the patient's daily dosage was changed.

(Applicant's Table 63, Volume 17 of 22, page 166)