U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-337 / SE1-018
Drug Name:	Invanz® (Ertapenem for injection)
Indication(s):	Community Acquired Pneumonia (CAP), Complicated Urinary Tract Infections including Pyelonephritis (UTI), Complicated Skin and Skin Structure Infections (cSSSI), Complicated Intra-abdominal Infections (IAI) and Acute Pelvic Infections (API) in pediatric patients
Applicant:	Merck
Date(s):	Submitted: 11/19/04
Review Priority:	Standard
Biometrics Division:	DBIII
Statistical Reviewer:	Scott Komo, Dr.P.H.
Concurring Reviewers:	Daphne Lin, Ph.D.
Medical Division:	Division of Anti-Infective and Ophthalmologic Drug Products (HFD-520)
Clinical Team:	Linda Forsyth, M.D, Medical Reviewer; Tom Smith, M.D. Secondary Medical Reviewer
Project Manager:	Susmita Samanta, M.D

Keywords: NDA review, pediatric exclusivity

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

This review focuses on efficacy only. The only issue was the Sponsor's definition of their modified intent-to-treat (MITT) population which excludes patients without any posttreatment observations and uses any valid posttreatment assessment as the Test-of-Cure (TOC) assessment if the TOC assessment is missing; valid is defined as at least 4 days posttreatment for urinary tract infection (UTI) or at least 1 day posttreatment for the community-acquired pneumonia (CAP), complicated skin and soft tissue infection (cSSSI), complicated intra-abdominal infections (IAI) and acute pelvic infections (API) indications Patients without a post-treatment assessment were excluded from these MITT analyses unless they had previously failed, in which case their outcome was unfavorable. Rather than using the Sponsor's MITT analyses, the results of the MITT sensitivity analyses, where patients with a missing TOC assessment are classified as failures, should be used as primary if one would like to draw any inference from the MITT results.

1.2 Brief Overview of Clinical Studies

This submission contains two safety/efficacy studies. The first study (Protocol 036) is a prospective, multicenter, double-blind, randomized, comparative study to evaluate the Safety, Local Tolerability, and Clinical Outcome of ertapenem vs. ceftriaxone sodium in pediatric patients with UTI, cSSSI, or CAP. The second study (Protocol 038) is a prospective, multicenter, randomized, open-label, comparative study to evaluate the safety, tolerability, and efficacy of ertapenem vs. ticarcillin/clavulanate in the treatment of complicated IAI and API in pediatric patients.

The primary objective of the studies was to assess the safety profile of ertapenem in treating pediatric patients with CAP, cSSSI, UTI, complicated IAI, or API. The demonstration of efficacy was a secondary objective to be supported additionally in each indication by evidence of efficacy in adults.

1.3 Statistical Issues and Findings

The primary objective of this submission was the demonstration of safety of ertapenem in the pediatric population. Efficacy was a secondary objective and the studies were not designed to demonstrate efficacy. I reviewed the efficacy results and had an issue with the Sponsor's definition of the MITT population. The Sponsor included all patients in the MITT population who had a valid posttreatment assessment; defined as at least 4 days posttreatment for UTI or at least 1 day posttreatment for the CAP, cSSSI, IAI and API indications. Patients without a post-treatment assessment were excluded from these MITT analyses unless they had previously failed, in which case their outcome was unfavorable.

Excluding patients without any posttreatment observations violates the ITT principle and could introduce bias. In addition, using any posttreatment assessment as the TOC assessment if the TOC assessment is missing is not recommended because the timing of the TOC visit has clinical relevance and using any posttreatment assessment ignores this fact. However, the Sponsor included sensitivity analyses that used a preferable definition for the MITT population where patients with missing TOC assessment were classified as failures. The results of the MITT

sensitivity analyses should be used as primary one would like to draw any inference from the MITT results.

2 INTRODUCTION

2.1 Overview

Ertapenem is a sterile, synthetic, parenteral, 1-β methyl-carbapenem that is structurally related to beta-lactam antibiotics. It is currently approved in adults for the treatment of the following diseases: CAP, complicated UTI including Pyelonephritis, cSSSI, complicated IA1, and API. The Sponsor proposes to extend the use of ertapenem to children 3 months to 17 years of age for the infectious disease indications currently approved in adults.

This submission contains two safety/efficacy studies. The first study (Protocol 036) is a prospective, multicenter, double-blind, randomized, comparative study to evaluate the Safety, Local Tolerability, and Clinical Outcome of ertapenem vs. ceftriaxone sodium in pediatric patients with complicated UTI, cSSSI, or CAP. The second study (Protocol 038) is a prospective, multicenter, randomized, open-label, comparative study to evaluate the safety, tolerability, and efficacy of ertapenem vs. ticarcillin/clavulanate in the treatment of complicated IAI and API in pediatric patients.

2.2 Data Sources

The Sponsor's study reports for studies 036 and 038 are available on the EDR at \\Cdsesub1\n21337\S_018\2004-11-19\clinstat\studies\p036.pdf and \\Cdsesub1\n21337\S_018\2004-11-19\clinstat\studies\p038.pdf respectively.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The primary objective of the studies was to assess the safety profile of ertapenem in treating pediatric patients with CAP, cSSSI, UTI, complicated IAI, or API. The demonstration of efficacy was a secondary objective to be supported additionally in each indication by evidence of efficacy in adults. Thus Protocols 036 and 038 were not designed to demonstrate statistical equivalency with the comparators for these indications.

Objectives

For Protocol 036
Primary: To evaluate the incidence of any clinical and/or laboratory drug-related serious adverse experience during the parenteral therapy period in pediatric patients treated with ertapenem.
Secondary: (1) To compare the safety of ertapenem versus ceftriaxone during the parenteral therapy period with respect to the proportion of patients with any drug-related adverse experiences in pediatric patients with UTI, cSSSI, or CAP. (2) To compare the local tolerability of ertapenem versus ceftriaxone during the parenteral therapy period in pediatric patients with complicated UTI, cSSSI, or CAP. (3) In the MITT population, to compare the efficacy of ertapenem versus ceftriaxone in pediatric patients with UTI, cSSSI, or CAP.

For Protocol 038

Primary: To evaluate the incidence of any clinical and/or laboratory drug-related serious adverse experience during the study drug therapy period plus 14 days posttherapy in pediatric patients treated with ertapenem. Secondary: (1) To evaluate the incidence of pediatric patients with any clinical and/or laboratory drug-related AEs during the study drug therapy period plus 14 days posttherapy in pediatric patients treated with ertapenem versus ticarcillin/clavulanate. (2) To evaluate the incidence of moderate-to-severe reactions at the site of administration of the medication during the study drug therapy period in pediatric patients treated with ertapenem versus ticarcillin/clavulanate. (3) In the MITT population, to evaluate the proportion of pediatric patients treated with ertapenem for IAI or API who have a favorable efficacy response at the posttreatment follow-up assessment versus ticarcillin/clavulanate.

3.1.1 Study Design and Endpoints

Protocol 036 was a randomized, double-blind comparative study involving 404 pediatric patients with CAP, cSSSI or UTI. The other study, Protocol 038, was an open-label comparative study enrolling a total of 112 pediatric patients with either IAI or API. In both studies, patients were randomized in a 3:1 ratio of ertapenem to comparator in order to obtain as much safety and efficacy information as possible on ertapenem.

Patients in both studies were randomized at study entry, stratifying for balance by age group (3 to 23 months,, 2-12 years, and 13 to 17 years of age) and infectious disease indication. Efficacy was to be assessed at protocol-specified time points that included discontinuation of parenteral therapy (DCPT) and post-treatment follow-up, with the timing of the post-treatment TOC assessment specified for each indication.

The Sponsor considered the MITT analyses as the principal analyses in order to include as many patients as possible within the limited sample enrolled in each infectious disease indication. Efficacy analyses were done on the clinical MITT population for cSSSI, CAP, IAI and API indications, and the microbiologic MITT population for UTI indication. The principal MITT analyses included all patients in the MITT population who had a valid posttreatment assessment; defined as at least 4 days posttreatment for UTI or at least 1 day posttreatment for the CAP, cSSSI, IAI and API indications. Patients without a post-treatment assessment were excluded from these MITT analyses unless they had previously failed, in which case their outcome was unfavorable.

Patients in the Evaluable per-protocol (EPP) analyses were assessed at the test-of-cure (TOC), visit defined for each indication. Patients with one or more baseline pathogens were included in the EPP analyses if at least one baseline pathogen was susceptible to both parenteral study therapies in Protocol 036, or to the study therapy they received in Protocol 038.

Pediatric patients with CAP or UTI were permitted to switch to an appropriate oral therapy after at least 3 days of parenteral therapy provided Protocol defined improvement criteria were met. Pediatric patients with cSSSI in Protocol 036 were also permitted to switch to oral therapy. Protocol 038 did not allow for an oral switch.

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

Table 1: Patient Disposition (Sponsor Table 2.5:1

	Location	Design	Study Regimens	
Prot 036	U.S/Int.	Double-Blind	N Ertapenem (15 mg/kg b.i.d.†; 1 g q.d‡)	N Ceftriaxone§ (25 mg/kg b.i.d.†; 50 mg/kg q.d‡)
CAP			Treated = 108 cMITT = 105 cEPP = 77 mMITT = 21 mEPP = 16	Treated = 35 cMITT =35 cEPP = 28 mMITT = 4 mEPP = 3
SSSI			Treated = 95 cMITT = 94 cEPP = 67 mMITT = 51 mEPP = 31	Treated = 30 cMITT = 28 cEPP = 26 mMITT = 16 mEPP = 14
UTI			Treated = 100 cMITT = 85 cEPP = 52 mMITT = 85 mEPP = 46	Treated = 34 cMITT = 32 cEPP = 23 mMITT = 32 mEPP = 20
Prot 038	U.S./Int.	Open-label	N Ertapenem (15 mg/kg b.i.d.†; 1 g q.d‡)	N T/C (<60 kg [50 mg/kg]; >60 kg [3.0 g])
IAI	.		Treated = 56 cMITT = 56 cEPP = 43 mMITT = 44 mEPP = 33	Treated = 16 cMITT = 16 cEPP = 11 mMITT = 12 mEPP = 8
API			Treated = 25 cMITT = 25 cEPP = 23 mMITT = 20 mEPP = 18	Treated = 8 cMITT = 8 cEPP = 4 mMITT = 8 mEPP = 4
Overall			Treated = 384 cMITT = 365 cEPP = 262 mMITT = 242 mEPP = 144	Treated = 124§ cMITT = 119 cEPP = 92 mMITT = 72 mEPP = 49

Table 2: Demographics (Sponsor Table 2.7.3:2)

	Ertapenem	Ceftriaxone	Ticarcillin/Clavulanate	Total
	(N =365)	(N=95)	(N=24)	(N=484)
	n (%)	n (%)	n (%)	n (%)
Gender				
Female	222 (60.8)	54 (56.8)	14 (58.3)	290 (59.9)
Male	143 (39.2)	41 (43.2)	10 (41.7)	194 (40.1)
Race				
Asian	36 (9.9)	5 (5.3)	1 (4.2)	42 (8.7)
Black	36 (9.9)	7 (7.4)	3 (12.5)	46 (9.5)
European	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)
Hispanic American Multi-	164 (44.9)	38 (40.0)	15 (62.5)	217 (44.8)
Racial	15 (4.1)	9 (9.5)	1 (4.2)	25 (5 2)
Polynesian	2 (0.5)	1 (1.1)	0 (0.0)	3 (0.6)
White	111 (30.4)	35 (36.8)	4 (16.7)	150 (31.0)
Age (Months)				
3 to 23 months	106 (29.0)	35 (36.8)	0 (0.0)	141 (29.1)
N	106	35	0 (0.0)	141
Mean	12.4	12.9	-	12.5
SD	5.6	6.6	-	5.8
Median	12.0	13.0	-	12.0
Range	3 to 23	4 to 23	-	3 to 23
Age (Years)				
2 to 12 years	198 (54.2)	53 (55.8)	10 (41.7)	261 (53.9)
N	198	53	10	261
Mean	5.4	5.5	8.4	5.5
SD	3.1	3.2	3.3	3.2
Median	5.0	4.0	9.5	5.0
Range	2 to 12	2 to 12	2 to 12	2 to 12
13 to 17 years	61 (16.7)	7 (7.4)	14 (58.3)	82 (16.9)
N	61	7	14	82
Mean	15.0	14.6	15.1	15.0
SD	1.4	1.5	1.6	1.4
Median	15.0	14.0	15.5	15.0
Range	13 to 17	13 to 17	13 to 17	13 to 17
Stratum by Diagnosis and Age				
Acute pelvic infection	25 (6.8)	-	8 (33.3)	33 (6.8)
13 to 17 years	25 (6.8)	-	8 (33.3)	33 (6.8)
Community acquired pneumonia	105 (28.8)	35 (36.8)	-	140 (28.9)
3 to 23 months	40 (11.0)	15 (15.8)	--	55 (11.4)
2 to 12 years	62 (17.0)	17 (17.9)		79 (16.3)
13 to 17 years	3 (0.8)	3 (3.2)	-	6 (1.2)
Complicated urinary tract infection	85 (23.3)	32 (33.7)	-	117 (24.2)
3 to 23 months	34 (9.3)	13 (13.7)	-	47 (9.7)
2 to 12 years	47 (12.9)	17 (17.9)	--	64 (13.2)
13 to 17 years	4 (1.1)	2 (2.1)		6 (1.2)
Complicated intra-abdominal infection	56 (15.3)	-	16 (66.7)	72 (14.9)
2 to 12 years	37 (10.1)	-	10 (41.7)	47 (9.7)
13 to 17 years	19 (5.2)		6 (25.0) -	25 (5.2)
Skin and soft tissue infection	94 (25.8)	28 -(29.5)		122 (25.2)
3 to 23 months	32 (8.8)	7 (7.4)	-	39 (8.1)
2 to 12 years	52 (14.2)	19 (20.0)	--	71 (14.7)
13 to 17 years	10 (2.7)	2 (2.1)		12 (2.5)

3.1.3 Statistical Methodologies

The primary evaluation of efficacy was based upon the MITT population; additional efficacy evaluations were also performed based on the evaluable per-protocol (EPP) population. The MITT population included patients who had received at least one parenterally administered dose of study drug and had a correct clinical diagnosis. The EPP population (a subset of the MITT population) included patients who had received a proper course of therapy, correct clinical diagnosis, no major protocol violations, one or more baseline pathogens susceptible to study therapy and had a clinical response at the test-of cure (TOC) visit. All patients who received at least 1 dose of study therapy were included in the safety evaluations. For cSSSI, CAP, IAI, and API, the efficacy population for the MITT and EPP analysis was the clinical MITT population and clinical EPP populations respectively. In contrast, for UTI, the efficacy populations for the MITT and EPP analyses were the microbiological MITT and microbiological EPP populations respectively. To assess the sensitivity of efficacy evaluations in the MITT population, an additional efficacy evaluation done on MITT population was performed in which all patients who had missing or indeterminate outcomes at the TOC visit (5 to 21 days after completion of study therapy) were considered "failures".

The adjusted proportions of patients with a favorable efficacy response (adjusted for age within each disease stratum, and adjusted for age for overall, using the Cochran-Mantel-Haenszel weights) were presented unless the sample sizes were small, where the observed proportions are presented.

3.1.4 Results and Conclusions

The comparison of response between the treatment groups is presented in Table 3. For cSSSI, CAP, IAI, and API, the efficacy population for the MITT and EPP analysis was the clinical MITT population and clinical EPP populations respectively. In contrast, for UTI, the efficacy populations for the MITT and EPP analyses were the microbiological MITT and microbiological EPP populations respectively.

Table 4 contains the comparison of the response is compared between the pediatric studies presented in this submission and the adult studies conducted earlier.

Table 3: Rate of Favorable Response

Disease Stratum Population / Time Point	*Treatment Group*				*Treatment Difference*	
Protocol 036						
	Ertapenem		Ceftriaxone		Ertapenem – Ceftriaxone	
	n/m	%	n/m	%	Adjusted diff. (%)	Adjusted 95% CI
UTI						
MITT / Posttreatment	58/69	84.1	23/25	92.0	-7.9	(-30.3, 14.8)
MITT / TOC	56/85	66.1	23/32	71.7	-5.6	(-26.4, 15.3)
EPP	40/46	87.0	18/20	90.0	-3.0	(-29.1, 22.9)
cSSSI						
MITT / Posttreatment	78/88	88.6	27/27	100.0	-11.4	(-32.4, 9.5)
MITT / TOC	73/94	77.7	27/28	96.4	-18.8	(-39.2, 2.3)
EPP	64/67	95.5	26/26	100.0	-4.5	(-26.8, 17.1)
CAP						
MITT / Posttreatment	89/95	93.7	32/33	97.0	-3.2	(-13.3, 6.9)
MITT / TOC	84/105	80.0	30/35	85.7	-5.9	(-21.6, 9.8)
EPP	74/77	96.1	27/28	96.4	-0.3	(-21.9, 20.9)
Protocol 038						
	Ertapenem		Ticarcillin / clavulanate		Ertapenem - Ticarcillin / clavulanate	
	n/m	%	n/m	%	Unadjusted diff. (%)	Unadjusted 95% CI
IAI						
MITT / Posttreatment	43/50	86.0	11/15	73.3	12.7	(-7.5, 39.4)
MITT / TOC	37/56	66.1	8/16	50.0	16.1	(-9.9, 41.5)
EPP	36/43	83.7	7/11	63.6	20.1	(-5.4, 50.3)
API						
MITT/Posttreatment	25/25	100.0	8/8	100.0	0	(-13.3, 32.4)
MITT/TOC	25/25	100.0	8/8	100.0	0	(-13.3, 32.4)
EPP	23/23	100.0	4/4	(100.0)	0	(-14.3, 49.0)

For cSSSI, CAP, IAI, and API, the efficacy population for the MITT and EPP analysis was the clinical MITT population and clinical EPP populations respectively. In contrast, for UTI, the efficacy populations for the MITT and EPP analyses were the microbiological MITT and microbiological EPP populations respectively.

Table 4: Rate of Favorable Response in Ertapenem patients for the EPP population (Sponsor Table 2.7.3: 15)

Disease Stratum	*Pediatric Study*			*Adult Studies*			
		Observed				Observed	
	n/m	%	95% CI	Study	n/m	%	95% CI
CAP	74/77	96.1	(89.0, 99.2)	018	168/182	92.3	(87.4, 95.7)
				020	167/182	91.8	(86.8, 95.3)
				Total	335/364	92.0	(88.8, 94.6)
UTI	40/46	87.0	(73.7, 95.1)	014	146/159	91.8	(86.4, 95.6)
				021	83/97	85.6	(77.0, 91.9)
				Total	229/256	89.5	(85.0, 92.9)
cSSSI	64/67	95.5	(87.5, 99.1)	016	152/185	82.2	(75.9, 87.4)
IAI	36/43	83.7	(69.3, 93.2)	017	200/230	87.0	(81.9, 91.0)
API	23/23	100.0	(85.2, 100)	023	153/163	93.9	(89.0, 97.0)

For cSSSI, CAP, IAI, and API, the efficacy population was the clinical EPP population. In contrast, for UTI, the efficacy population was the microbiological EPP populations.

3.2 Evaluation of Safety

Please see the review of the medical officer Dr. Linda Forsyth for details.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The proportion of patients with a favorable response in the clinical MITT and EPP populations by age group, gender, and race in Table 5, Table 6, and Table 7 respectively. For the age group comparison, the response rates appear similar across the various ages and between treatment groups. For the gender comparison, the response rates by gender were higher in Protocol 038 and the combined analysis for females in both treatment groups primarily resulting from the 100% response rate in the API indication in which all patients were female. With this noted exception, overall the response rates by gender were similar both within and across treatment groups. Finally, for the race comparison, the response rates between the treatment groups appear generally similar with respect to race.

Table 5: Proportion of Patients with a Favorable Response by Age Group (Sponsor Table 2.7.3:10)

Subgroup	Population†/ Time Point	Treatment Group	
Protocol 036			
		Ertapenem n/m (%)‡	Ceftriaxone n/m (%)‡
3 to 23 months	MITT/Posttreatment	82/96 (85.4)	30/30 (100.0)
	EPP/TOC	57/61 (93.4)	22/22 (100.0)
2 to 12 years	MITT/Posttreatment	140/152 (92.1)	50/52 (96.2)
	EPP/TOC	114/122 (93.4)§	46/48 (95.8)
13 to 17 years	MITT/Posttreatment	14/15 (93.3)	7/7 (100.0)
	EPP/TOC	13/13 (100.0)	7/7 (100.0)
Protocol 038			
		Ertapenem	Ticarcillin/clavulanate
		n/m (%)‡	n/m (%)‡
2 to 12 years	MITT/Posttreatment	28/34 (82.4)	7/9 (77.8)
	EPP/TOC	22/28 (78.6)	5/7 (71.4)
13 to 17 years	MITT/Posttreatment	40/41 (97.6)	12/14 (85.7)
	EPP/TOC	37/38 (97.4)	6/8 (75.0)
Ertapenem Versus Comparator			
		Ertapenem	Comparator
		n/m (%)‡	n/m (%)‡
3 to 23 months	MITT/Posttreatment	82/96 (85.4)	30/30 (100.0)
	EPP/TOC	57/61 (93.4)	22/22 (100.0)
2 to 12 years	MITT/Posttreatment	168/186 (90.3)	57/61 (93.4)
	EPP/TOC	136/150 (90.7)	51/55 (92.7)
13 to 17 years	MITT/Posttreatment	54/56 (96.4)	19/21 (90.5)
	EPP/TOC	50/51 (98.0)	13/15 (86.7)

† The efficacy populations used were the Clinical MITT and Clinical EPP populations. ‡Observed proportions. § One patient (AN 2360) in the ertapenem treatment group with MRSA as a sole pathogen is mistakenly included in this analysis; the clinical TOC outcome was unfavorable for this patient. n/m = Number of patients with favorable clinical response in category/number of patients in category. EPP = Evaluable per protocol. TOC = Test-of-cure visit. MITT = Modified intent to treat.

Table 6: Proportion of Patients with a Favorable Response by Gender (Sponsor Table 2.7.3:11)

Subgroup	Population†/ Time Point	Treatment Group	
Protocol 036			
		Ertapenem n/m (%)‡	Ceftriaxone n/m (%)‡
Female	MITT/Posttreatment	146/159 (91.8)	49/49 (100.0)
	EPP/TOC	108/115 (93.9)	44/44 (100.0)
Male	MITT/Posttreatment	90/104 (86.5)	38/40 (95.0)
	EPP/TOC	76/81 (93.8)	31/33 (93.9)
Protocol 038			
		Ertapenem	Ticarcillin/clavulanate
		n/m (%)‡	n/m (%)‡
Female	MITT/Posttreatment	47/49 (95.9)	12/14 (85.7)
	EPP/TOC	43/45 (95.6)	7/9 (77.8)
Male	MITT/Posttreatment	21/26 (80.8)	7/9 (77.8)
	EPP/TOC	16/21 (76.2)	4/6 (66.7)
Ertapenem Versus Comparator			
		Ertapenem	Comparator
		n/m (%)‡	n/m (%)‡
Female	MITT/Posttreatment	193/208 (92.8)	61/63 (96.8)
	EPP/TOC	151/160 (94.4)	51/53 (96.2)
Male	MITT/Posttreatment	111/130 (85.4)	45/49 (91.8)
	EPP/TOC	92/102 (90.2)	35/39 (89.7)

† The efficacy populations used were the Clinical MITT and Clinical EPP populations. ‡Observed proportions. n/m = Number of patients with favorable clinical response in category/number of patients in category. EPP = Evaluable per protocol. TOC = Test-of-cure visit. MITT = Modified intent to treat.

Table 7: Proportion of Patients with a Favorable Response by Race (Sponsor Table 2.7.3:12)

Subgroup	Population †/ Time Point	Treatment Group	
Protocol 036			
		Ertapenem n/m (%‡)	Ceftriaxone n/m (%‡)
Asian	MITT/Posttreatment	29/32 (90.6)	4/5 (80.0)
	EPP/TOC	26/28 (92.9)	3/4 (75.0)
Black	MITT/Posttreatment	24/30 (80.0)	4/4 (100.0)
	EPP/TOC	21/24 (87.5)	4/4 (100.0)
Hispanic	MITT/Posttreatment	96/107 (89.7)	36/36 (100.0)
	EPP/TOC	79/84 (94.0)	32/32 (100.0)
White	MITT/Posttreatment	78/84 (92.9)	33/34 (97.1)
	EPP/TOC	51/53 (96.2)	28/29 (96.6)
Other	MITT/Posttreatment	9/10 (90.0)	10/10 (100.0)
	EPP/TOC	7/7 (100.0)	8/8 (100.0)
Protocol 038			
		Ertapenem	Ticarcillin/clavulanate
		n/m (%‡)	n/m (%‡)
Asian	MITT/Posttreatment	0/1 (0.0)	1/1 (100.0)
	EPP/TOC	0/1 (0.0)	1/1 (100.0)
Black	MITT/Posttreatment	4/4 (100.0)	0/2 (0.0)
	EPP/TOC	2/2 (100.0)	0/2 (0.0)
Hispanic	MITT/Posttreatment	46/49 (93.9)	13/15 (86.7)
	EPP/TOC	40/43 (93.0)	7/9 (77.8)
White	MITT/Posttreatment	17/20 (85.0)	4/4 (100.0)
	EPP/TOC	16/19 (84.2)	2/2 (100.0)
Other	MITT/Posttreatment	1/1 (100.0)	1/1 (100.0)
	EPP/TOC	1/1 (100.0)	1/1 (100.0)
Ertapenem Versus Comparator			
		Ertapenem	Comparator
		n/m (%‡)	n/m (%‡)
Asian	MITT/Posttreatment	29/33 (87.9)	5/6 (83.3)
	EPP/TOC	26/29 (89.7)	4/5 (80.0)
Black	MITT/Posttreatment	28/34 (82.4)	4/6 (66.7)
	EPP/TOC	23/26 (88.5)	4/6 (66.7)
Hispanic	MITT/Posttreatment	142/156 (91.0)	49/51 (96.1)
	EPP/TOC	119/127 (93.7)	39/41 (95.1)
White	MITT/Posttreatment	95/104 (91.3)	37/38 (97.4)
	EPP/TOC	67/72 (93.1)	30/31 (96.8)
Other	MITT/Posttreatment	10/11 (90.9)	11/11 (100.0)
	EPP/TOC	8/8 (100.0)	9/9 (100.0)

† The efficacy populations used were the Clinical MITT and Clinical EPP populations. ‡Observed proportions. n/m = Number of patients with favorable clinical response in category/number of patients in category. EPP = Evaluable per protocol. TOC = Test-of-cure visit. MITT = Modified intent to treat.

4.2 Other Special/Subgroup Populations

Not performed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The primary objective of this submission was the demonstration of safety of ertapenem in the pediatric population. Efficacy was a secondary objective and the studies were not designed to demonstrate efficacy. I reviewed the efficacy results and had an issue with the Sponsor's definition of the MITT population. The Sponsor included all patients in the MITT population who had a valid posttreatment assessment; defined as at least 4 days posttreatment for UTI or at least 1 day posttreatment for the CAP, cSSSI, IAI and API indications. Patients without a post-treatment assessment were excluded from these MITT analyses unless they had previously failed, in which case their outcome was unfavorable.

Excluding patients without any posttreatment observations violates the ITT principle and could introduce bias. In addition, using any posttreatment assessment as the TOC assessment if the TOC assessment is missing is not recommended because the timing of the TOC visit has clinical relevance and using any posttreatment assessment ignores this fact. However, the Sponsor included sensitivity analyses that used a preferable definition for the MITT population where patients with missing TOC assessment were classified as failures. The results of the MITT sensitivity analyses should be used as primary if one would like to draw any inference from the MITT results.

5.2 Conclusions and Recommendations

This review focuses on efficacy only. The only issue was the Sponsor's definition of their MITT population which excludes patients without any posttreatment observations and uses any valid posttreatment assessment as the TOC assessment if the TOC assessment is missing; valid is defined as at least 4 days posttreatment for UTI or at least 1 day posttreatment for the CAP, cSSSI, complicated IAI and API indications Patients without a post-treatment assessment were excluded from these MITT analyses unless they had previously failed, in which case their outcome was unfavorable. Rather than using the Sponsor's MITT analyses, the results of the MITT sensitivity analyses, where patients with a missing TOC assessment are classified as failures, should be used as primary if one would like to draw any inference from the MITT results.

6 SIGNATURES/DISTRIBUTION LIST (Optional)

Primary Statistical Reviewer: Scott Komo, Dr.P.H.
Date: 18 May 2005

Concurring Reviewer(s): Daphne Lin, Ph.D.

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Scott Komo
5/18/05 10:20:57 AM
BIOMETRICS

Please sign off. Thank you.

Daphne Lin
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