CLINICAL REVIEW

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Reviewer Name	Linda M. Forsyth, M.D.
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Established Name	Ertapenem sodium
Trade Name	Invanz™
Therapeutic Class	Carbapenem antimicrobial
Applicant	Merck
Priority Designation	P
Formulation	Injection
Dosing Regimen	Intravenous/Intramuscular 3 months to 12 years-15 mg/kg twice daily 13 to 17 years-1 g once daily
Indication	Complicated Urinary Tract Infections, Complicated Skin and Skin Structure Infections, Community-Acquired Pneumonia, Complicated Intra-abdominal Infections and Acute Pelvic Infections
Intended Population	Pediatric patients $\geq$ 3 months of age

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1 Executive Summary

1.1 Recommendation on Regulatory Action

The applicant has submitted a response to a final amended Pediatric Written Request (PWR) from May 4, 2004 to provide information on the use of ertapenem in pediatric patients. Ertapenem is currently approved for adults at a dose of 1 g once a day for treatment of complicated urinary tract infection (UTI) including pyelonephritis, complicated skin and soft tissue infection (SSSI), community-acquired pneumonia (CAP), complicated intra-abdominal infection (IAI) and acute pelvic infection (API).

The overall safety profile for ertapenem in the pediatric studies submitted is similar to that of the comparators, ceftriaxone and ticarcillin/clavulanate, and is similar to the profile described in the current ertapenem labeling for adults. The most frequently reported drug-related adverse events in patients receiving ertapenem were diarrhea and infusion site pain.

The efficacy findings from this submission, together with safety and pharmacokinetic data presented and the previous demonstration of efficacy of ertapenem in adult patients support the use of ertapenem for the approved indications in pediatric patients 3 months to 17 years of age. The appropriate dosing regimen of ertapenem is 15 mg/kg BID for pediatric patients 3 months to 12 years of age and 1 g once daily for patients 13 to 17 years of age.

Pediatric Exclusivity was granted by the Agency on February 11, 2005.

From a clinical perspective, the recommended regulatory action for this efficacy supplement is approval.

1.2 Recommendation on Postmarketing Actions

Ertapenem was approved in the United States (U.S.) in 2001 for the same indications in adults, and no changes in current postmarketing requirements are recommended.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Ertapenem is a broad-spectrum carbapenem antimicrobial for intravenous/intramuscular administration approved in the United States for use as single-agent therapy in adults for the treatment of community-acquired pneumonia, complicated urinary tract infections, complicated skin and skin structure infections, complicated intra-abdominal infections and acute pelvic infections. This application contains information on the pharmacokinetics, safety and efficacy of ertapenem in the treatment of serious infections in pediatric patients 3 months to 17 years of age.

The clinical development program for ertapenem in pediatric patients consisted of the following studies:

Pharmacokinetic (PK) Studies

1. Protocol 028: An Open, Intravenous Study to Evaluate the Plasma Concentration Profiles of MK-0826 in Patients Aged 3 Months Through 17 Years.

   This was an open-label, single intravenous (IV) dose, multicenter, parallel group study in pediatric patients 3 months to 17 years. This study enrolled 84 patients who had with infections requiring antibiotic therapy and hospitalization. Single IV doses of 15, 20 and 40 mg/kg were infused over 30 minutes.

2. Protocol 031/32: An Open, Intravenous Study to Evaluate the Cerebrospinal Fluid Concentration Profiles in Patients 3 Months to 17 Years of Bacterial Meningitis.

   This was an open-label, multicenter, single IV dose study of 15 or 20 mg/kg of ertapenem to evaluate the cerebrospinal fluid concentration profile in pediatric patients 3 months to 17 years of age with bacterial meningitis. There were 13 patients entered into this study.

Safety/Efficacy Studies

3. Protocol 036: A Prospective, Multicenter, Double-Blind, Randomized, Comparative Study to Evaluate the Safety, Local Tolerability, and Clinical Outcome of Ertapenem Sodium (MK-0826) Versus Ceftriaxone Sodium in Pediatric Patients With Complicated Urinary Tract Infection, Skin and Soft Tissue Infection, or Community-Acquired Pneumonia.

   This was a double-blind, randomized, multicenter, comparative study of ertapenem versus ceftriaxone in pediatric patients with complicated urinary tract infection, skin and soft tissue infection, or community-acquired pneumonia. There were 404 patients randomized into this study.

4. Protocol 038: A Prospective, Multicenter, Randomized, Open-Label, Comparative Study to Evaluate the Safety, Tolerability, and Efficacy of Ertapenem Sodium (MK-0826) Versus Ticarcillin/Clavulanate in the Treatment of Complicated Intra-abdominal Infections and Acute Pelvic Infections in Pediatric Patients.

   This was an open-label, multicenter, randomized (3:1 ratio), prospective, comparative study to evaluate safety and tolerability and to assess the efficacy of ertapenem versus ticarcillin/clavulanate in pediatric patients with complicated intra-abdominal infections and acute pelvic infections. There were 112 patients randomized into this study.

1.3.2 Efficacy

In this pediatric development program, the primary objective was to evaluate the plasma pharmacokinetics and to assess the overall safety and tolerability of ertapenem in indications previously shown to be effectively treated in adults. Pediatric efficacy can be demonstrated by results from the comparator-controlled pediatric studies, supported additionally by data from adequate, well-controlled clinical trials in adults which were the basis of the original approval. The indications studied for ertapenem in children had previously been studied in adequate, well-controlled clinical trials in adults and ertapenem was shown to be generally safe, well-tolerated and efficacious. Therefore, pediatric efficacy in each of these indications was not considered the primary objective for these studies.

For study 036, in the evaluable per protocol (EPP) population, clinical response rates in patients with SSSI were 95.5% (64/67) for ertapenem and 100% for ceftriaxone (26/26). In patients with CAP, clinical response rates were 96.1% (74/77) for ertapenem and 96.4% (27/28) for ceftriaxone. In patients with UTI, microbiologic response rates were 87.0% (40/46) for ertapenem and 90.0% (18/20) for ceftriaxone.

For study 038, in the EPP population, clinical response rates in patients with IAI were 83.7% (36/43) for ertapenem and 63.6% (7/11) for ticarcillin/clavulanate. In patients with API, clinical response rates were 100% (23/23) for ertapenem and 100% (4/4) for ticarcillin/clavulanate.

Overall, the combined (Protocol 036 and Protocol 038) clinical response rate in the EPP analysis for the ertapenem treatment group was 92.7% and 93.5% for the comparators combined. Overall, the combined (Protocol 036 and Protocol 038) microbiologic response rate for the EPP population in the ertapenem treatment group was 88.9% and 89.8% in the comparator groups combined.

The ertapenem response rates in pediatric patients were comparable to the rates observed in clinical studies in adults.

1.3.3 Safety

The primary objective of the pediatric program was to characterize the overall safety and tolerability of ertapenem in pediatric patients treated for infectious disease indications previously studied and currently licensed in adults.

A total of 480 patients ages 3 months to 17 years were treated with ertapenem: 96 patients in the pharmacokinetic studies and 384 patients in the clinical studies. In the clinical studies, the mean duration for patients receiving ertapenem was 4.9 days with a range of 1 to 36 days. Approximately 70% of the patients treated with ertapenem were switched (as allowed per

protocol) from parenteral to an appropriate oral follow-up antimicrobial agent which they received for a mean duration of 8.3 days.

There were a total of 508 patients enrolled in the clinical safety/efficacy trials, 384 in the ertapenem group, 100 in the ceftriaxone group and 24 patients in the ticarcillin/clavulanate group. Safety was assessed by the investigator throughout the study and up to the 14-day posttreatment follow-up visit.

The most common drug-related clinical adverse events are diarrhea, vomiting, infusion-site erythema and infusion-site pain. The most common drug-related laboratory adverse experiences are increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST) and decreased neutrophil count.

The safety profile observed in children is similar to that observed in adults. The specific clinical adverse experiences reported most frequently in the ertapenem group during study therapy and 14-day follow-up were diarrhea (11.7%), vomiting (10.2%), infusion-site pain (7%), pyrexia (4.9%), abdominal pain (4.7%), diaper dermatitis (4.7%), headache (4.4%), and cough (4.4%). Similar frequencies were also reported in the ceftriaxone and ticarcillin/clavulanate groups. In the ertapenem group, diarrhea (6.5%), vomiting (2.1%), infusion-site erythema (2.6%) and infusion-site pain (5.5%) were the most common drug-related adverse events reported.

The serious adverse events and discontinuations due to adverse events were generally comparable between ertapenem and the comparators in these studies, ceftriaxone and ticarcillin/clavulanate.

1.3.4 Dosing Regimen and Administration

The appropriate dosing regimen of ertapenem is 15 mg/kg BID for pediatric patients 3 months to 12 years of age and 1 g once daily for patients 13 to 17 years of age.

Cerebrospinal fluid level concentrations were not adequate to cover all relevant pathogens and pursue bacterial meningitis as an indication. This information is to be included in the label.

1.3.5 Drug-Drug Interactions

No new information regarding drug-drug interactions was identified.

1.3.6 Special Populations

This submission was a response to a Pediatric Written Request.

2 Introduction and Background

2.1 Product Information

Ertapenem (ertapenem sodium), a 1-β-methyl carbapenem, is a recent addition to the β-lactam class of antimicrobials. Due to the relative stability of ertapenem against renal dehydropeptidase-1, coadministration with cilastatin is not required. Ertapenem blocks bacterial cell-wall synthesis by binding to specific penicillin binding proteins. Ertapenem has limited activity against hospital acquired pathogens such as methicillin-resistant staphylococci and enterococci, and the in vitro activity of ertapenem against *Pseudomonas* and *Acinetobacter* species is considerably less than that of the two other currently licensed carbapenems, imipenem-cilstatin and meropenem.

2.5 Presubmission Regulatory Activity

Ertapenem was approved by the U.S. Food and Drug Administration (FDA) on November 21, 2001, for the treatment of adult patients with the following infections caused by susceptible pathogens: IAI due to *Escherichia coli*, *Clostridium clostridioforme*, *Eubacterium lentum*, *Peptostreptococcus* species, *Bacteroides fragilis*, *Bacteroides distasonis*, *Bacteroides ovatus*, *Bacteroides thetaiotaomicron*, or *Bacteroides uniformis*; SSTI due to *Staphylococcus aureus* (methicillin susceptible strains only), *Streptococcus pyogenes*, *Escherichia coli*, or *Peptostreptococcus* species; CAP due to *Streptococcus pneumoniae* (penicillin susceptible strains only) including cases with concurrent bacteremia, *Haemophilus influenzae* (beta-lactamase negative strains only), or *Moraxella catarrhalis*; UTI due to *Escherichia coli*, including cases with concurrent bacteremia, or *Klebsiella pneumoniae*; API due to *Streptococcus agalactiae, Escherichia coli*, *Bacteroides fragilis, Porphyromonas asaccharolytica, Peptostreptococcus* species, or *Prevotella bivia*. The dose in adult patients is 1 g a day.

Regulatory guidance from the FDA for the ertapenem pediatric program was given in the form of a PWR, issued on May 15, 2000, which was subsequently amended on April 12, 2002, with the Final Amended PWR dated May 4, 2004.

In summary, the FDA requested that the applicant assess in children 3 months to 17 years of age, the pharmacokinetics of ertapenem and the safety and efficacy of ertapenem in each of the infectious disease indications previously studied and approved in adults. The initial PWR also requested a pilot PK study to determine the degree of ertapenem cerebrospinal fluid (CSF) penetration in children with meningitis and, if data from the pilot study supported it, a subsequent pediatric meningitis efficacy trial. However, preliminary results of the CSF penetration study demonstrated that CSF concentrations were insufficient to cover all relevant pathogens. This finding was discussed with the FDA and the Agency agreed to remove the meningitis study from the in the Final Amended PWR.

Comment: The requested studies were performed in response to and in accordance with the PWR and its amendments. Pediatric Exclusivity was granted on February 11, 2005.

4 Data Sources, Review Strategy, and Data Integrity

4.1 Sources of Clinical Data

This submission contains data from the following studies:

Protocol 028: "An Open, Intravenous Study to Evaluate the Plasma Concentration Profiles of MK-0826 in Patients Aged 3 Months Through 17 Years".

Protocol 031/32: "An Open, Intravenous Study to Evaluate the Cerebrospinal Fluid Concentration Profiles in Patients 3 Months to 17 Years of Age with Bacterial Meningitis".

Protocol 036: "A Prospective, Multicenter, Double-Blind, Randomized, Comparative Study to Evaluate the Safety, Local Tolerability, and Clinical Outcome of Ertapenem Sodium (MK-0826) Versus Ceftriaxone Sodium in Pediatric Patients With Complicated Urinary Tract Infection, Skin and Soft Tissue Infection, or Community-Acquired Pneumonia".

Protocol 038: "A Prospective, Multicenter, Randomized, Open-Label, Comparative Study to Evaluate the Safety, Tolerability, and Efficacy of Ertapenem Sodium (MK-0826) Versus Ticarcillin/Clavulanate in the Treatment of Complicated Intra-abdominal Infections and Acute Pelvic Infections in Pediatric Patients".

4.2 Tables of Clinical Studies

The table below summarizes the submitted trials.

Table 1 Listing of Clinical Trials

Study Number	Patient Population	Test Drugs	Enrollment
Pharmacokinetics			
Protocol 028	Infection requiring antibiotic therapy and hospitalization	Ertapenem 15, 20 or 40 mg/kg single dose IV infusion	84 (84 ertapenem)
Protocol 031/32	Bacterial meningitis	Ertapenem 15 and 20 mg/kg	13 (12 ertapenem)
Safety/Efficacy			
Protocol 036	Complicated urinary tract infection, skin and soft tissue infection, or community-acquired pneumonia	Ertapenem 1 g IV or IM single daily dose 13-17 years; 15 mg/kg BID <13 years Ceftriaxone 50 mg/kg/day IV once or twice-daily dosing based on the age group parameters of the corresponding ertapenem patients in order to maintain the double-blind without the need for matching placebo infusions	404 (304 ertapenem, 100 ceftriaxone)
Protocol 038	Complicated intra-abdominal infections and acute pelvic infections	Ertapenem 1 g IV or IM single daily dose 13-17 years; 15 mg/kg BID <13 years Ticarcillin/Clavulanate 50 mg/kg <60 kg, 3 g >60 kg IV q 4 or 6 hours	112 (84 ertapenem, 28 ticarcillin/clavulanate)

4.3 Review Strategy

Detailed reviews of the data from trials 036 and 038 are presented in the Appendix and in the integrated reviews of efficacy and safety. The trials 028 and 031/32 were reviewed in detail by Chandra S. Chaurasia, PhD, the clinical pharmacology reviewer. Findings are summarized under Section 5.

4.4 Data Quality and Integrity

The FDA requested a random sample of the case report forms (CRF). From study 036, we requested random sampling from 60 ertapenem and 30 ceftriaxone patients and from study 038, 30 ertapenem and 15 ticarcillin/clavulanate patients. These were submitted in electronic format rather than scanned from the original CRFs. The FDA also requested submission of the

applicant's Critical Change Memos to evaluate changes that may have been made to the database after database lock and unblinding.

Comment: The CRFs and Critical Change Memos were reviewed by the medical officer and the data and changes appear acceptable.

4.5 Compliance with Good Clinical Practices

The applicant stated in the study protocols that institutional review board approval was to be obtained for each center by the investigator and a signed statement that the studies were conducted consistent with International Conference on Harmonization good clinical practice guidance. Informed consent was obtained from all patients before the start of any study procedures.

4.6 Financial Disclosures

The applicant submitted Form FDA 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) stating that it had not entered into any financial arrangement with the listed clinical investigators in which compensation to the investigator could be affected by the outcome of the study.

Comment: The reviewer considers the stated disclosure to be acceptable.

5 Clinical Pharmacology

Chandra S. Chaurasia, PhD, reviewed the two PK studies, 028 and 031/32.

The pivotal PK study (protocol 028) was conducted to investigate the PK, safety, and tolerability of ertapenem in patients 3 months to 17 years of age and to determine a therapeutic dose for this population. The study enrolled 84 male and female patients distributed among the following age strata: 3 months to 23 months (N=43), 2 to 12 years (N=28), and 13 to 17 years (N=13). A single 20 or 40 mg/kg IV dose of ertapenem was administered IV to these patients. Various PK parameters were studied.

Analysis of the PK profiles of the 20 and 40 mg/kg doses demonstrated that plasma clearance of ertapenem in pediatric patients 3 months to 12 years of age is more rapid than in adults and that once daily dosing might be inadequate. A 15 mg/kg BID dosing regimen had a better PK profile in patients 3 months to 12 years of age and was therefore chosen for use in the clinical safety and efficacy studies. The PK profile of ertapenem in patients 13 to 17 years of age is similar to that in adults. The standard 1 g daily regimen was therefore chosen for use in adolescent patients in the clinical studies.

Study protocol 031/32 was conducted to evaluate the cerebrospinal fluid concentrations of ertapenem after intravenous administration in pediatric patients with meningitis. There were a total of 13 patients randomized to the studies with only 12 (5 in the 15 mg/kg group and 7 in the

20 mg/kg group) receiving a dose of ertapenem. Of the 12 patients there were 7 males (3 months to 10 year olds) and 5 females (1 to 13 year olds).The results of the study showed insufficient CSF concentrations to cover all relevant pathogens. This finding was discussed with the FDA and the Agency agreed to remove the meningitis study from the in the Final Amended PWR.

Please refer to Dr. Chaurasia's review for further details.

6 Integrated Review of Efficacy

6.1 Indications

Protocols 036 and 038 provided information about the efficacy of ertapenem in the treatment of the following infections in pediatric patients:

Complicated Intra-abdominal Infections
Complicated Skin and Skin Structure Infections
Community-Acquired Pneumonia
Complicated Urinary Tract Infections including pyelonephritis
Acute Pelvic Infections including postpartum endomyometritis, septic abortion and post surgical gynecologic infections

6.1.1 Methods

The applicant performed four clinical trials to support pediatric dosing for ertapenem for the approved indications. There were two pharmacokinetic trials and two safety/efficacy multicenter, controlled trials. Summaries of the two clinical safety/efficacy trials follow. More complete information in about each study is included in the Appendix.

6.1.2 General Discussion of Endpoints

The primary goal of the studies was to collect safety information, and the studies were not designed to demonstrate noninferiority of ertapenem to the comparators for the approved indications. The efficacy endpoint was the proportion of patients within each treatment group who had a favorable efficacy response at the posttreatment visit in the modified intent to treat (MITT) analyses and at the test of cure (TOC) visit in the evaluable per-protocol (EPP) analyses. For CAP, SSTI, IAI and API, the primary efficacy assessment was based on clinical efficacy response; for UTI, the primary efficacy assessment was based on microbiological efficacy response. The applicant considered the MITT analyses as their primary analyses. The MITT posttreatment analyses counted all assessments made at least 1 day after completion of study therapy for CAP, SSTI, IAI, and API and at least 4 days after the completion of study therapy for UTI; patients missing a posttreatment assessment were excluded from these analyses unless they had previously failed, in which case their outcome was unfavorable. The FDA requested that MITT sensitivity analysis also be performed in which patients with missing outcome values were

considered failures. To account for potential confounders affecting the TOC outcome and to use the standard approach to analysis in anti-bacterial clinical studies, efficacy analyses were done in the EPP population at the TOC for each indication. The TOC visit was defined in the protocol for each indication (7 to 14 days [CAP, SSTI, and UTI], 2 to 4 weeks [IAI], and 3 to 5 weeks [API] after the last day of antimicrobial therapy).

The following terms describe the EPP and MITT populations used in the efficacy analyses:

EPP Population

- Clinically evaluable population: a subset of the clinical MITT population comprising patients who received an appropriate course of study therapy and in whom sufficient information was available to determine the patient's clinical outcome at the TOC, with no confounding factors present that interfered with the assessment of that outcome; additionally, it was required that if baseline pathogens were identified, one or more of these pathogens needed to be susceptible to both parenteral study therapies.
- Microbiologically evaluable population: a subset of the clinically evaluable population comprising those clinically evaluable patients who had a baseline pathogen identified and a microbiologic response assessed at TOC.

MITT Population

- Clinical MITT population: all randomized patients that met the minimal definition of the disease and who received at least 1 dose of study therapy.
- Microbiologic MITT population: a subset of the clinical MITT population comprising those clinical MITT patients with a baseline pathogen identified, regardless of susceptibility to study agents, and a subsequent microbiologic response assessment.

6.1.3 Study Design

Clinical Study: Protocol 036

This phase 2 study was a double-blind, randomized (3:1 ratio), multicenter study to investigate the safety and tolerability of ertapenem in pediatric patients aged 3 months-17 years with UTI, SSTI and CAP. The comparator arm in this study was ceftriaxone. The objective of the study was to assess the safety of administration of ertapenem in the pediatric population. There were 49 study sites which participated in this study, 23 in the U.S. and 26 internationally. Patients enrolled in this study required parenteral therapy. Ertapenem was administered IV or IM as a single daily dose of 1 g for patients 13-17 years of age or 15 mg/ kg BID for patients <13 years of age and ceftriaxone was administered 50 mg/kg/day IV once or twice daily dosing based on the age group parameters of the corresponding ertapenem patients in order to maintain the double-blind without the need for matching placebo infusions over 30 minutes or IM after patient screening within 24 hours of study entry. The oral switch drug was amoxicillin/clavulanate after a minimum of 3 days. The clinical response was evaluated at the discontinuation of parenteral therapy (DCPT) and the TOC visit at 7-14 days following the completion of therapy. Microbiological response was assessed separately for each pathogen identified at prestudy. At selected study sites, patients 13-17 years of age could elect to participate in an optional pharmacokinetic analysis, and these data were utilized in analysis of pharmacokinetic parameters

in this age group. The protocol was amended twice (see Protocol Amendments for Protocol 036). The study was conducted with randomization to ertapenem or ceftriaxone based upon disease and age category (3-23 months, 2-12 years, 13-17 years).

Clinical Study: Protocol 038

This phase 2 study was a multicenter, randomized (3:1 ratio), open-label, comparative study to investigate the safety and tolerability of ertapenem in pediatric patients in the treatment of IAI or API. The primary objective was to evaluate safety. Evaluation of efficacy was a secondary objective. There were 15 study sites participating in this study, 12 in the U.S. and 3 internationally. Patients with API were given antibiotic therapy for 3-14 days and 5-14 days for IAI. Ertapenem was given IV or IM as a single daily dose of 1 g for patients 13-17 years of age or 15 mg/ kg BID for patients <13 years of age. Ticarcillin/clavulanate was the comparator and was given 50 mg/kg <60 kg, 3 g >60 kg IV q 4 or 6 hours. Patients were screened within 24 hours prior to study entry. Clinical response was assessed at DCPT and TOC. Microbiological response was assessed separately for each pathogen identified at prestudy. The protocol was amended three times (see Protocol Amendments for Protocol 038). TOC was at 2-4 weeks posttherapy in API and at 3-5 weeks posttherapy in complicated IAI.

6.1.4 Efficacy Findings

6.1.4.1 Demographics and Baseline Characteristics

Clinical Studies: Protocols 036 and 038

There were a total of 508 patients enrolled in the clinical safety/efficacy trials, 384 in the ertapenem group, 100 in the ceftriaxone group and 24 patients in the ticarcillin/clavulanate group.

The table below shows the demographic and baseline patient characteristics of the combined studies (Protocol 036 and 038) for the clinical MITT population. The distribution of patients by these characteristics was generally comparable across the treatment groups.

Table 2 Baseline Patient Characteristics by Treatment Group (Clinical MITT Population)

	Ertapenem (N=365)		**Ceftriaxone** (N=95)		**Ticarcillin/Clavulanate** (N=24)		Total (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	1	0.2
Hispanic	164	44.9	38	40	15	62.5	217	44.8
Multiracial	15	4.1	9	9.5	1	4.2	25	5.2
Polynesian	2	0.5	1	1.1	0	0	3	0.6
White	111	30.4	35	36.8	4	16.7	150	31
Age								
3-23 months	106	29	35	36.8	0	0	141	29.1
2-12 years	198	54.2	53	55.8	10	41.7	261	53.9
13-17 years	61	16.7	7	7.4	14	58.3	82	16.9
Stratum by Diagnosis and Age								
API	25	6.8	-	-	8	33.3	33	6.8
13-17 years	25	6.8	-	-	8	33.3	33	6.8
CAP	105	28.8	35	36.8	-	-	140	28.9
3-23 months	40	11	15	15.8	-	-	55	11.4
2-12 years	62	17	17	17.9	-	-	79	16.3
13-17 years	3	0.8	3	3.2	-	-	6	1.2
UTI	85	23.3	32	33.7	-	-	117	24.2
3-23 months	34	9.3	13	13.7	-	-	47	9.7
2 to 12 years	47	12.9	17	17.9	-	-	64	13.2
13-17 years	4	1.1	2	2.1	-	-	6	1.2
IAI	56	15.3	-	-	16	66.7	72	14.9
2-12 years	37	10.1	-	-	10	41.7	47	9.7
13-17 years	19	5.2	-	-	6	25	25	5.2
SSTI	94	25.8	28	29.5	-	-	122	25.2
3-23 months	32	8.8	7	7.4	-	-	39	8.1
2-12 years	52	14.2	19	20	-	-	71	14.7
13-17 years	10	2.7	2	2.1	-	-	12	2.5

Adapted from integrated summary of efficacy Table 2.7.3:2.

In the ertapenem treatment group, across both studies, 106 children between 3 and 23 months of age and 198 children 2 and 12 years of age are included in the clinical MITT population. There was a lower rate in adolescent patients requiring hospitalization and parenteral therapy for CAP, UTI or skin infections. The absence of patients in the youngest cohort of 3 to 23 months of age for indications included in Protocol 038 (IAI and API in which ticarcillin/clavulanate was the

comparator) may be a reflection of the age distribution of pediatric patients with complicated appendicitis and the fact that the API indication by definition is limited to adolescent females of child-bearing potential.

Comment: Demographic characteristics were otherwise well-balanced with respect to gender, age and ethnic origin.

6.1.4.2 Evaluability

The table below shows the number of patients in each analysis group.

Table 3 Number of Patients in Each Analysis Population

		Ertapenem	Ceftriaxone	Ticarcillin/Clavulanate
UTI	EPP	52	23	-
	MITT	80	29	-
	MITT sensitivity	85	32	-
SSTI	EPP	67	26	-
	MITT	88	27	-
	MITT sensitivity	94	28	-
CAP	EPP	77	28	-
	MITT	95	28	-
	MITT sensitivity	105	35	-
IAI	EPP	43	-	11
	MITT	50	-	15
	MITT sensitivity	56	-	16
API	EPP	23	-	4
	MITT	25	-	8
	MITT sensitivity	25	-	8

Adapted from Tables 7-5, 036 and 038 study reports.

Please refer to the tables in the Appendix for a complete breakdown of the study populations and patient evaluability.

6.1.4.3 Results

Clinical Outcome

Presented below are proportions of patients with favorable clinical response assessments by disease for the various efficacy analysis populations.

Table 4 Proportion of Patients With a Favorable Clinical Response Assessment Displayed by Disease Stratum (Efficacy Population)

Disease	Analysis	Treatment			
Protocol 036					
		Ertapenem		**Ceftriaxone**	
		n/m	%	n/m	%
UTI	EPP	46/52	88.4	22/23	95.7
	MITT	69/80	86.3	28/29	96.6
	MITT sensitivity	67/85	79	28/32	87.4
SSTI	EPP	64/67	95.5§	26/26	100
	MITT	78/88	88.6	27/27	100
	MITT sensitivity	73/94	79.2	27/28	96.4
CAP	EPP	74/77	96.1	27/28	96.4
	MITT	89/95	93.7	32/33	97
	MITT sensitivity	84/105	79.8	30/35	85.7
Protocol 038					
		Ertapenem		**Ticarcillin/Clavulanate**	
IAI	EPP	36/43	83.7	7/11	63.6
	MITT	43/50	86	11/15	73.3
	MITT sensitivity	37/56	66.4	8/16	50
API	EPP	23/23	100	8/8	100
	MITT	25/25	100	8/8	100
	MITT sensitivity	25/25	100	16/24	66.7

Adapted from the integrated summary of efficacy Table 2.7.3:7. §One patient 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.

The response rates were lower in the MITT populations than the EPP populations in the UTI, SSTI and CAP indications. In protocol 036, there were a number of resistant organisms from patients on the ertapenem arm and this may have had some contribution to the lower efficacy in the MITT populations.

Efficacy was generally similar and comparable to the results reported in the adult clinical studies. In the adult studies, for IAI the combined clinical and microbiological success rates in the microbiologically evaluable population at 4 to 6 weeks posttherapy (test of cure) were 83.6% (163/195) for ertapenem. For SSTI, the clinical success rates at 10 to 21 days posttherapy were 83.9% (141/168) for ertapenem. For CAP, the clinical success rate in the clinically evaluable population and success rates were 92.3% (168/182) for ertapenem. For UTI, the microbiological success rates (combined studies) at 5 to 9 days posttherapy were 89.5% (229/256) for ertapenem. For API, the clinical success rates in the clinically evaluable population at 2 to 4 weeks posttherapy were 93.9% (153/163) for ertapenem.

Microbiological Outcome

The table below displays the proportions of patients with favorable microbiological response assessments, by disease.

Table 5 Proportion of Patients With a Favorable Microbiological Response Assessment Displayed by Disease Stratum (Efficacy Population)

Protocol 036					
		Ertapenem		**Ceftriaxone**	
		n/m	(%)[‡]	n/m	(%)[‡]
UTI	EPP	40/46	87	18/20	90
	MITT	58/69	84.1	23/25	92
	MITT sensitivity	67/85	79	28/32	87.4
SSTI	EPP	29/31	93.5[¶]	14/14	100
	MITT	38/46	82.6	15/15	100
	MITT sensitivity	73/94	79.2	27/28	96.4
CAP	EPP	14/16	87.5	2/3	66.7
	MITT	16/19	84.2	2/3	66.7
	MITT sensitivity	84/105	79.8	30/35	85.7
Protocol 038					
		Ertapenem		**Ticarcillin/Clavulanate**	
IAI	EPP	27/33	81.8	6/8	75
	MITT	33/39	84.9	9/11	81.8
	MITT sensitivity	27/44	61.7	7/12	58.3
API	EPP	18/18	100	4/4	100
	MITT	20/20	85.5	8/8	100
	MITT sensitivity	20/20	75.4	8/8	100

Adapted from the integrated summary of efficacy Table 2.7.3:8 and study reports 036 and 038 Tables 7-7, 7-8, 7-9. Efficacy populations used with the Microbiological MITT and EPP populations. EPP=Evaluable per protocol. TOC=Test-of-cure visit. n/m=Number of patients with favorable microbiologic response in category/number of patients in category. [‡]Observed proportions. [¶]One patient 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.

The results from the microbiological efficacy evaluation for the EPP population at the TOC visit appear comparable to those from the applicant's microbiological efficacy evaluation for the MITT population at the posttreatment visit. The response rates for the MITT population are generally lower than in the EPP populations, for IAI, however, for both treatment groups, the EPP response rates were slightly lower than the rates in the MITT analysis.

Efficacy Evaluation by Pathogen

Response rates were also assessed according to the baseline pathogen.

The table below presents the proportions of favorable response assessments by pathogen in the applicant's MITT population at the posttreatment visit, by disease.

Table 6 Proportion of Favorable Response Assessment by Pathogen (≥5 Pathogens) at Posttreatment Visit Displayed by Disease Stratum—Total Isolates (Microbiologic MITT Population)

Protocol 036							
		Ertapenem (N=284)			**Ceftriaxone** (N=95)		
		n/m	%	(95% CI)	n/m	%	(95% CI)
SSTI	**Gram-positive aerobic cocci**	**40/48**	**83.3**	**(69.8, 92.5)**	**16/16**	**100**	**(79.4, 100)**
	Staphylococcus aureus	24/30	80	(61.4, 92.3)	10/10	100	(69.2, 100)
	-Methicillin Resistant	2/7	28.6	-	-	-	-
	-Methicillin Susceptible	21/22	95.5	(77.2, 99.9)	9/9	100	-
	-Methicillin Unknown	1/1	100	-	1/1	100	-
	Streptococcus pyogenes	10/10	100	(69.2, 100)	5/5	100	-
CAP	**Gram-positive aerobic cocci**	**10/13**	**76.9**	**(46.2, 95)**	**2/2**	**100**	-
	Streptococcus pneumoniae	7/9	77.8	-	1/1	100	-
	-Penicillin Intermediate	3/4	75	-	-	-	-
	-Penicillin Susceptible	4/4	100	-	1/1	100	-
	-Penicillin Unknown	0/1	0	-	1/1	100	-
	Gram-negative aerobic coccobacilli	**5/5**	**100**	-	**1/1**	**100**	-
	Haemophilus influenzae	5/5	100	-	1/1	100	-
	-Beta Lactamase Negative	1/1	100	-	1/1	100	-
	-Beta Lactamase Positive	4/4	100	-	-	-	-
UTI	**Gram-negative aerobic bacilli**	**60/69**	**87**	**(76.7, 93.9)**	**26/28**	**92.9**	**(76.5, 99.1)**
	Escherichia coli	51/59	86.4	(75, 94)	21/23	91.3	(72, 98.9)
Protocol 038							
		Ertapenem (N=64)			**Ticarcillin/Clavulanate** (N=20)		
IAI	**Gram-positive aerobic cocci**	**15/21**	**71.4**	**(47.8, 88.7)**	3/4	75	-
	Streptococcus viridans	6/8	75	-	1/1	100	-
	Gram-negative aerobic bacilli	**42/51**	**82.4**	**(69.1, 91.6)**	**9/12**	**75**	**(42.8, 94.5)**
	Escherichia coli	29/35	82.9	(66.4, 93.4)	6/8	75	-
	Pseudomonas aeruginosa	9/10	90	(55.5, 99.7)	1/2	50	-
	Gram-negative anaerobic coccobacilli	**32/39**	**82.1**	**(66.5, 92.5)**	**9/12**	**75**	**(42.8, 94.5)**
	Bacteroides fragilis	12/13	92.3	(64, 99.8)	3/4	75	-
	Bacteroides thetaiotaomicr	10/11	90.9	(58.7, 99.8)	2/3	66.7	-

	on						
API	**Gram-positive aerobic cocci**	**10/10**	**100**	**(69.2, 100)**	**6/6**	**100**	**-**
	Enterococcus faecalis	6/6	100		1/1	100	-
	Gram-negative aerobic bacilli	**14/14**	**100**	**(76.8, 100.0)**	**2/2**	**100**	**-**
	Escherichia coli	8/8	100	-	2/2	100	-

Adapted from the integrated summary of efficacy report Table 2 7 3:9 UTI=Urinary tract infections SSTI=Skin and soft tissue infection CAP=Community-acquired pneumonia IAI=Intra-abdominal infection API=Acute pelvic infection CI=Confidence interval N=Number of evaluable patients in each treatment group n/m=Number of pathogens associated with a favorable assessment /number of pathogens with an assessment IAI, API, SSTI and CAP display the clinical response per pathogen UTI stratum display the microbiological response per pathogen †Computed from an exact statistical model pooling across strata

The most common species identified were *E. coli* for UTI; *Staphylococcus aureus* and *Streptococcus pyogenes* for SSTI; *Streptococcus pneumoniae* and *Haemophilus influenzae* for CAP; *E. coli* and *Bacteroides* species for IAI; and *E. coli* for API.

The tables for the EPP response rates per pathogen are listed in the Appendix.

The applicant analyzed clinical outcomes by gender, age and race. Ertapenem appears to be generally effective irrespective of gender, age category or race.

6.1.5 Clinical Microbiology

The microbiology reviewer, Connie Mahon, M.S. recommended that portions of the clinical microbiology section of the label be updated. Please see Ms. Mahon's review for full details.

6.1.6 Efficacy Conclusions

The results from these studies suggest that ertapenem, in parenteral doses of 15 mg/kg twice daily for children ages 3 months to 12 years not to exceed 1 g, and 1 g once daily for children ages 13 years to 17 years is effective in the treatment of UTI, SSTI, CAP, IAI, and API.

For the indications, ertapenem was comparable to the comparators ceftriaxone and ticarcillin/clavulanate. Efficacy was generally similar and comparable to the results reported in the adult clinical studies. The point estimates of efficacy in the pediatric studies are within the observed in the adult studies.

7 Integrated Review of Safety

7.1 Methods and Findings

The primary objective of the pediatric program was to evaluate the overall safety and tolerability of ertapenem in pediatric patients treated for indications previously studied and currently licensed in adults.

A total of 480 patients ages 3 months to 17 years were treated with ertapenem: 96 patients in the pharmacokinetic studies and 384 patients in the clinical studies. In the clinical studies, the mean duration for patients receiving ertapenem was 4.9 days with a range of 1 to 36 days. Approximately 70% of the patients treated with ertapenem were switched (as allowed per protocol) from parenteral to an appropriate oral follow-up antimicrobial agent which they received for a mean duration of 8.3 days.

There were a total of 508 patients enrolled in the clinical safety/efficacy trials, 384 in the ertapenem group, 100 in the ceftriaxone group and 24 patients in the ticarcillin/clavulanate group.

Safety was assessed by the investigator throughout the study and up to the 14-day posttreatment follow-up visit.

The most common drug-related clinical adverse events are diarrhea, vomiting, infusion-site erythema and infusion-site pain. The most common drug-related laboratory adverse experiences are increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST) and decreased neutrophil count.

The safety profile observed in children is similar to that observed in adults. The specific clinical adverse experiences reported most frequently in the ertapenem group during study therapy and 14-day follow-up were diarrhea (11.7%), vomiting (10.2%), infusion-site pain (7%), pyrexia (4.9%), abdominal pain (4.7%), diaper dermatitis (4.7%), headache (4.4%), and cough (4.4%). Similar frequencies were also reported in the ceftriaxone and ticarcillin/clavulanate groups. In the ertapenem group, diarrhea (6.5%), vomiting (2.1%), infusion-site erythema (2.6%) and infusion-site pain (5.5%) were the most common drug-related adverse events reported.

The incidence of clinical or laboratory adverse events was generally comparable between ertapenem and the comparators in these studies, ceftriaxone and ticarcillin/clavulanate. There were no deaths reported in any patient in the pediatric studies.

Ertapenem therapy both IV and IM was generally well tolerated. There were only 8 patients total who received IM therapy.

Ertapenem appears to be generally well tolerated irrespective of gender, age category, or race.

The applicant included, in the pediatric ADVERSE REACTIONS sections of the proposed labeling, text and tables summarizing common clinical and laboratory AEs occurring during study therapy and the 14-day follow-up period.

7.1.1 Deaths

There were no patient deaths reported in this application.

7.1.2 Other Serious Adverse Events

Pharmacokinetic Studies: Protocols 028 and 031/032

There were a total of 11 patients who experienced a serious adverse event: 1 patient in the 15 mg/kg group, 4 patients in the 20 mg/kg group, and 6 patients in the 40 mg/kg group. The SAEs included: pneumonia respiratory syncytial virus, hypoxia, pulmonary empyema, arrhythmia, supraventricular tachycardia, stoma site pain, abscess drainage, pulmonary embolism, respiratory distress, and vascular occlusion. There was one serious drug related adverse event reported in a patient who received an overdose of study medication; however, there was no adverse event associated with this overdose.

Clinical Studies: Protocols 036 and 038

Overall, 30 (5.9%) of the 508 patients had at least 1 serious clinical adverse event: 21 (5.5%) in the ertapenem group, 6 (6%) in the ceftriaxone group, and 3 (12.5%) in the ticarcillin/clavulanate group. The SAEs in the ertapenem group included: 2 cases of vomiting, 2 cases of pyrexia, 2 cases of small intestine obstructions, 2 cases of pelvic abscesses, 4 cases of abdominal abscesses, and 1 case of diarrhea, constipation, abdominal pain, gastroenteritis, influenza, lung abscess, pneumonia, sepsis, UTI, pregnancy, epistaxis, obstructive airways disorder, pleural effusion, and respiratory distress. The SAEs in the ceftriaxone group included: vomiting, pyrexia, gastroenteritis, influenza, pneumonia, and rash. The SAEs in the ticarcillin/clavulanate group include: abdominal pain, postoperative infection, and hydrocele. There were 4 patients with serious clinical adverse experiences determined by the investigator to be possibly, probably, or definitely related to study therapy: 2 (0.5%) in the ertapenem group, 2 (2%) in the ceftriaxone group, and none in the ticarcillin/clavulanate group. The ertapenem drug-related SAEs were diarrhea and vomiting.

7.1.3 Dropouts and Other Significant Adverse Events

Pharmacokinetic Studies: Protocols 028 and 031/032

No patients in either of the pharmacokinetic studies discontinued therapy due to a clinical adverse event.

Clinical Studies: Protocols 036 and 038

There were 11 discontinuations from study therapy as a result of a clinical adverse event, including 8 (2.1%) in the ertapenem group, 1 (1%) in the ceftriaxone group and 2 (8.3%) in the ticarcillin/clavulanate group. The most common cause for a discontinuation in the ertapenem group was diarrhea, which occurred in 4 patients, 2 of these cases were considered to be drug-related by the investigator.

7.1.5 Common Adverse Events

Protocol 028

Of the 84 patients enrolled, 31 (36.9%) patients reported at least 1 clinical adverse event, with a total of 58 nonserious clinical adverse events. Two episodes of nausea and 1 episode of injection-site infiltration were considered by the investigator to be possibly drug-related. The remaining 55 nonserious adverse events were considered to be probably not (14 adverse events) or definitely not (41 adverse events) drug-related by the investigator. The most common nonserious adverse events were fever (5 episodes) and nausea (3 episodes).

Protocols 031/032

Overall, clinical adverse events were reported in 6 of the 12 treated patients (50%). The most common clinical adverse events occurred in the 20 mg/kg treatment group: 2 patients (28.6%) with conjunctivitis, 3 patients (42.9%) with pyrexia, and 2 patients (28.6%) with maculopapular rash. Seizures have been associated with other carbapenem agents, generally with doses exceeding guidelines for renal insufficiency, underlying central nervous system (CNS) disorder and prior history of seizures. There was only 1 report of seizure in any of the pediatric patients who received ertapenem during the pediatric program. This occurred in a patient in the CSF PK study (Protocol 031/032) with severe CNS complications of bacterial meningitis. Seizure in this patient was considered not to be related to study therapy by the investigator and more likely attributable to the severe brain injury suffered as a result of meningitis.

Protocols 036 and 038

During study therapy and the 14-day follow-up period, of the 508 patients, 312 (61.4%) reported at least 1 clinical adverse event: 233 (60.7%) in the ertapenem group, 63 (63%) in the ceftriaxone group and 16 (66.7%) in the ticarcillin/clavulanate group. Two (0.5%) patients in the ertapenem treatment group, 2 (2%) patients in the ceftriaxone treatment group, and none in the ticarcillin/clavulanate treatment group had a serious drug-related adverse event. The most frequently reported adverse events in the ertapenem group were diarrhea (11.7%), vomiting (10.2%), infusion-site pain (7%), pyrexia (4.9%), abdominal pain (4.7%), diaper dermatitis (4.7%), headache (4.4%), and cough (4.4%) with similar frequencies also in the ceftriaxone and ticarcillin/clavulanate groups. In the ertapenem group, diarrhea (6.5%), vomiting (2.1%), infusion-site erythema (2.6%), and infusion-site pain (5.5%) were the most common drug-related adverse events reported. In the pediatric clinical studies, the majority of the patients had parenteral therapy followed by a switch to an appropriate oral antimicrobial. The following drug-related adverse events occurred during the oral therapy or 14-day follow-up period only: upper abdominal pain, faeces discolored, melaena, candida nappy rash, candidiasis, skin infection, allergic dermatitis, and exanthema.

The table below displays the adverse events reported in ≥1% of pediatric patients during the study and follow-up periods.

Table 7 Incidence (%) of Adverse Events Reported During Study and 14-Day Follow-Up in ≥1% of Pediatric Patients

	Eratpenem (N=384)	**Ceftriaxone** (N=100)	**Ticarcillin/Clavulanate** (N=24)
Local:			
Infusion Site Erythema	3.9	3	8.3
Infusion Site Induration	1	1	0
Infusion Site Pain	7	4	20.8
Infusion Site Phlebitis	1.8	3	0
Infusion Site Swelling	1.8	1	4.2
Infusion Site Warmth	1.3	1	4.2
Systemic:			
Abdominal Pain	4.7	3	4.2
Upper Abdominal Pain	1	2	0
Constipation	2.3	0	0
Diarrhea	11.7	17	4.2
Loose Stools	2.1	0	0
Nausea	1.6	0	0
Vomiting	10.2	11	8.3
Pyrexia	4.9	6	8.3
Abdominal Abscess	1	0	4.2
Herpes Simplex	1	1	4.2
Nasopharyngitis	1.6	6	0
Upper Respiratory Tract Infection	2.3	3	0
Viral Pharyngitis	1	0	0
Hypothermia	1.6	1	0
Dizziness	1.6	0	0
Headache	4.4	4	0
Cough	4.4	3	0
Wheezing	1	0	0
Dermatitis	1	1	0
Pruritus	1.6	0	0
Diaper Dermatitis	4.7	4	0
Rash	2.9	2	8.3

Adapted from the proposed label.

Drug-Related Adverse Events

The table below displays the drug-related adverse events occurring in ≥1% of ertapenem patients during parenteral therapy and 14-day follow-up.

Table 8 Number (%) of Patients With Specific Clinical Adverse Events (Incidence ≥1% in Ertapenem Treatment Group) During Parenteral Therapy and 14-Day Follow-Up Period—Drug Related (Treated Population Protocols 036 and 038)

	Ertapenem (N=384)		**Ceftriaxone** (N=100)		**Ticarcillin/Clavulanate** (N=24)	
	n	%	n	%	n	%
Abdominal pain	3	0.8	1	1	-	-
Diarrhea	22	5.7	11	11	1	4.2
Loose stools	5	1.3	0	0	-	-
Vomiting	8	2.1	2	2	-	-
Infusion-site erythema	9	2.3	2	2	0	0
Infusion-site pain	21	5.5	1	1	3	12.5
Infusion-site phlebitis	7	1.8	3	3	-	-
Infusion-site swelling	4	1	0	0	-	-
Dermatitis diaper	5	1.3	0	0	-	-
Rash	5	1.3	1	1	1	4.2

Adapted from clinical review Tables 29 and 50.

7.1.7 Laboratory Findings

Pharmacokinetic Studies: Protocols 028 and 031/032

Protocol 028. Of the 84 patients with at least 1 laboratory test postbaseline, 2 (10%) patients in the 15 mg/kg group and 2 (6.1%) patients in the 40 mg/kg group had a laboratory adverse event. One patient in the 15 mg/kg group experienced an increased eosinophil count the investigator determined to be possibly related to study therapy. One patient in the 40 mg/kg group experienced ALT and AST increases the investigator considered drug related. No serious laboratory adverse events were reported.

Protocols 031/032. Of the treated patients who had at least 1 laboratory test postbaseline, no patients in the ertapenem 15 mg/kg group and 3 (42.9%) patients in the ertapenem 20 mg/kg group had laboratory adverse event. The laboratory adverse events of increased platelet and lymphocyte counts in one patient were reported 4 days after ertapenem administration as nonserious and possibly drug-related. No other laboratory adverse events were considered drug-related. No serious laboratory adverse events were reported.

Clinical Studies: Protocols 036 and 038

Of the 500 patients treated who had a laboratory test postbaseline, 63 patients (16.6%) in the ertapenem group, 9 patients (9.3%) in the ceftriaxone group, and 4 patients (16.7%) in the ticarcillin/clavulanate group had a laboratory adverse event during study therapy and the 14-day follow-up period. The incidence of laboratory adverse events or drug-related laboratory adverse events was generally similar for all treatment groups. There were no serious drug-related laboratory adverse events reported in any of the treatment groups, and there were no patients who discontinued study therapy because of a drug-related laboratory adverse event. The most common drug-related laboratory adverse events in the ertapenem group were increased ALT (2.2%), increased AST (2.1%) and neutrophil count decreased (3%).

Table 9 Incidence of Specific Laboratory Adverse Events Reported During Study Therapy Plus 14-Day Follow-Up in ≥0% of Pediatric Patients

	Ertapenem (N=379)	**Ceftriaxone** (N=97)	**Ticarcillin/Clavulanate**(N=24)
ALT increased	3.8	1.1	4.3
Alakine Phosphatase increased	1.1	0	0
AST increased	3.8	1.1	4.3
Eosinophil count increased	1.1	2.1	0
Neutrophil count increased	5.8	3.1	0
Platelet count increased	1.3	0	8.7

Adapted from the proposed label.

Serious Laboratory Adverse Events

Two patients (0.5%) in the ertapenem group, 1 patient (1%) in the ceftriaxone group and no patients in the ticarcillin/clavulanate group experienced a serious laboratory adverse event. In the ertapenem treatment group, 1 patient had a white blood cell count decreased and 1 patient had a platelet count decreased reported as a serious laboratory adverse event. None of the serious laboratory adverse events were reported as drug-related or resulted in discontinuation of study therapy.

9 Overall Assessment

9.1 Conclusions

In pediatric patients, ertapenem given 15 mg/kg BID for ages 3 months to 12 years and 1 g once daily for ages 13 to 17 years is safe and effective therapy for the treatment of complicated UTI, SSTI, CAP, IAI and API.

This conclusion is supported by PK data from studies 028 and 031/32, safety data from studies 036 and 038, and previous findings of efficacy for the approved indications in adults. The studies in this supplement were not designed to provide efficacy data to demonstrate the noninferiority of ertapenem to the comparators for these indications. The estimates of efficacy reported in these studies are acceptable and in the same range as those reported in the clinical studies in adults.

9.2 Recommendation on Regulatory Action

This efficacy supplement may be approved and safety, dosing and clinical studies information added to the label for pediatric patients 3 months to 17 years of age.

9.3 Recommendation on Postmarketing Actions

Ertapenem was approved in the U.S. in 2001 for the same indications in adult patients, and no changes in current postmarketing requirements are recommended.

9.4 Labeling Review

The applicant's proposed labeling is generally acceptable. The following modifications have been accepted by the applicant:

1. Add the following sentence to the Pediatric Use section: "Invanz is not recommended in the treatment of meningitis in the pediatric population due to lack of sufficient CSF penetration."
2. Modify the adverse event tables in the proposed label to be comparable to the tables for adults, using the cutoff point of ≥1% (b) (4)

10 Appendices

10.1 Review of Individual Study Reports

Protocol 036-Complicated Urinary Tract Infection, Complicated Skin and Soft Tissue Infection, or Community-Acquired Pneumonia

A Prospective, Multicenter, Double-Blind, Randomized, Comparative Study to Evaluate the Safety, Local Tolerability, and Clinical Outcome of Etrapenem Sodium (MK-0826) Versus Ceftriaxone Sodium in Pediatric Patients With Complicated Urinary Tract Infection, Skin and Soft Tissue Infection, or Community-Acquired Pneumonia.

STUDY DESIGN

The 036 phase 2 study was a double-blind, randomized (3:1 ratio), multicenter study to investigate the safety and tolerability of ertapenem in pediatric patients aged 3 months-17 years with UTI, SSTI and CAP. The comparator arm in this study was ceftriaxone. The objective of the study was to assess the safety of administration of ertapenem in the pediatric population. There were 49 study sites which participated in this study, 23 in the U.S. and 26 internationally. Patients enrolled in this study required parenteral therapy and the study drug was administered intravenously (IV) over 30 minutes or intramuscularly (IM) after patient screening within 24 hours of study entry. The oral switch drug was amoxicillin/clavulanate after a minimum of 3 days. The clinical response was evaluated at the discontinuation of parenteral therapy (DCPT) and the test of cure (TOC) visit at 7-14 days following the completion of therapy. Microbiological response was assessed separately for each pathogen identified at prestudy. At selected study sites, patients 13-17 years of age could elect to participate in an optional pharmacokinetic analysis, and these data were utilized in analysis of pharmacokinetic parameters in this age group. The protocol was amended twice (see Protocol Amendments for Protocol 036). The study was conducted with randomization to ertapmenem of ceftriaxone based upon disease and age category (3-23 months, 2-12 years, 13-17 years).

Inclusion Criteria

Selection of Study Population

The inclusion and exclusion criteria were designed to enroll patients likely to be treatable with 5-14 days of total therapy and not complicated by any preexisting conditions which may interfere in the evaluation of the safety profiles or efficacy of the study drugs. The following inclusion/exclusion criteria were taken from the protocol.

General Inclusion Criteria

1. Patient was a male or female, aged 3 months to 17 years with one of the following infections: community-acquired pneumonia (CAP), skin or soft tissue infection (SSTI), or urinary tract infection (UTI) that required a minimum of 3 days of parenteral therapy but no more than 14 days of total therapy (parenteral alone or parenteral and oral combined).

2. Females, in whom menarche had been confirmed had a negative serum pregnancy test. NOTE: Females of childbearing potential with a negative urine pregnancy test were eligible for enrollment; however, they must have had a confirmed negative serum pregnancy test (β-hCG). Use of adequate birth control measures were to be discussed with the patient.

3. The patient's infection was known or thought by the investigator to be caused by microorganisms susceptible to both parenteral study antibiotics.

4. The patient's infection was treated with ≤24 hours of systemic antibiotic therapy known to be effective against the presumed or documented etiologic pathogen(s) within the 72-hour period immediately prior to entry into the study. NOTE: If the patient received >24 hours of systemic antimicrobial therapy, there had to be clear evidence that the patient failed this regimen. Such evidence included continued fever, and persistence or worsening of symptoms related to the index infection, and/or persistent laboratory or radiographic changes, and positive cultures.

5. The parent/legal guardian was available to give informed consent and was deemed sufficiently reliable to return for the child's follow-up visit.

Inclusion Criteria for Patients with Community-Acquired Pneumonia

The patient had clinically suspected bacterial CAP, according to the following diagnostic criteria:

1. Patient had a fever, defined as body temperature >37.8°C (100°F) orally, >38.2°C (100.8°F) tympanically, or >38.4°C (101°F) rectally.

2. New infiltrate(s) compatible with bacterial pneumonia on the chest x-ray, which included the presence of a new alveolar/lobar infiltrate or consolidation.

3. Patient had a new onset of a clinical presentation compatible with bacterial pneumonia with at least ONE of the following signs and symptoms: cough, tachypnea, dyspnea, retraction or grunting, production of purulent sputum, auscultatory findings on pulmonary examination of rales and/or evidence of pulmonary consolidation (included dullness on percussion, diminished breath

sounds, nasal flaring, bronchial breath sounds, rales, rhonchi, wheezing, or egophony)

4. AND at least ONE of the following:
a) organism consistent with a respiratory pathogen identified or isolated from a sputum or blood culture; OR
b) an elevated total peripheral WBC >15,000/mm^3 or >15% immature neutrophils (bands), regardless of total peripheral WBC, or leucopenia with total WBC <4500/mm^3 provided the leukopenia was felt to be caused by the bacterial infection.

Inclusion Criteria for Patients with Skin and Soft Tissue Infections

1. The patient had a clinical diagnosis of bacterial skin or soft tissue infection that warranted at least initial parenteral antibacterial therapy, with signs and symptoms of acute infection (present for ~10 days or less) in the absence of associated indwelling foreign material (such as a central venous catheter, peripheral intravenous line, or pacemaker).

2. At least one sign or symptom that had a moderate or severe rating.

3. The patient had an infection meeting at least one of the following:
a) Infected wounds or skin lesions as evidenced by purulent drainage or collection adjacent to the wound or lesion.
b) Acute extensive bacterial cellulitis (e.g., erythema, swelling, tenderness, warmth, induration).
c) Patients with other complicated SSTI such as abscesses or infected traumatic wounds.
d) Patients with uncomplicated skin infections such as impetigo, furunculosis, or carbunculosis may be enrolled provided the infection was of sufficient severity to warrant at least 3 days of parenteral therapy.

Inclusion Criteria for Patients with Complicated Urinary Tract Infections

The patients with suspected complicated UTI met the following criteria:

1. Pyuria present, defined as urine white blood cell count of at least 10 cells per HPF on standard examination of sediment or ≥10 WBCs/mm^3 in unspun urine.

2. A urine culture obtained within 48 hours prior to enrollment containing $\geq 10^5$ CFU/mL (or $\geq 5x10^4$ CFU/mL if obtained by straight catheterization) of a recognized uropathogen presumed or known to be susceptible to the parenteral study antibiotics (ertapenem and ceftriaxone). *Some patients were enrolled before the urine culture results were available if it was likely (based upon the presence of bacteria in the microscopic analysis of urine and clinical findings) to be*

positive. Note: Bag-collected urine cultures were avoided whenever possible for the baseline culture as it is generally difficult to accurately document the presence of UTI with this method.

3. In addition the patient had to have either, or both, pyelonephritis or complicated UTI:

a) Pyelonephritis defined as: Fever (body temperature >37.8°C [100°F] orally, >38.2°C [100.8°F] tympanically, or >38.4°C [101°F] rectally) or documented history of fever within 12 hours of enrollment) **and** children between the age of 4 to 17 years also had CVA or flank pain/tenderness, or evidence of pyelonephritis by renal scan or ultrasound.

b) **OR** Other Complicated UTI defined as: At least one or more signs or symptoms of upper or lower urinary tract infection in a patient with either an indwelling catheter, or who required intermittent bladder catheterization, or who had a documented congenital structural or functional urologic abnormality, or, if this was the initial UTI episode in an infant, was suspected of having an acquired or congenital structural or functional urologic abnormality.

Exclusion Criteria

General Exclusion Criteria

1. The patient was <3 months or ≥18 years of age.

2. The patient was in a situation (e.g., unreliable foster care) or had a condition which, in the opinion of the investigator, interfered with optimal participation in the study.

3. The patient had an infection known at admission to be caused by pathogen(s) resistant to either of the study drugs.

4. The patient had a history of serious allergy, hypersensitivity (e.g., anaphylaxis), or any adverse reaction to carbapenem antibiotics (such as imipenem), meropenem, any cephalosporins or penicillins or to lidocaine or other similar local anesthetic agents if IM injection is to be use. NOTE: Patients with a history of mild (non-urticarial) rash to penicillins or other β-lactams were allowed to be enrolled at the investigator's discretion.

5. The patient had clinically significant laboratory abnormalities:
   - Absolute neutrophil count (ANC) <1000/mm^3
   - Platelet count <50,000/mm^3
   - Bilirubin >3 times the age-specific upper limit of normal (ULN)
   - ALT or AST >3 times the age-specific ULN

- Creatinine >1.25 times the age-specific ULN
- Alkaline phosphatase >3 times the age-specific ULN

6. If the patient was female and was pregnant or fertile and was not practicing adequate methods of contraception, was planning to become pregnant within 1 month of the study, or was nursing. NOTE: Females who were nursing were not discouraged from breast-feeding for the sole purpose of enrolling in the study. Females who chose to defer breast-feeding until 5 days after the last dose of study drug to allow elimination of drug from breast milk were eligible.

7. Patients who had septic shock or acute hemodynamic instability including those requiring pressor support. NOTE: The requirement of volume repletion (but not pressors) for support of blood pressure was allowed.

8. Patients with acute or chronic renal insufficiency.

9. Patients in whom one of the following conditions were present: rapidly progressive or terminal illness, response to antibiotic regimens described in this study were considered unlikely, or the patient was considered unlikely to survive the study period.

10. The patient had signs of meningitis, such as nuchal rigidity, papilledema, or findings of meningitis. NOTE: CSF penetration of ertapenem had not been determined when protocol was initially written.

11. The patient had received >24 hours of systemic antimicrobial therapy known to be effective against the presumed or documented etiologic pathogen(s) within the 72-hour period immediately prior to enrollment, unless there was a clear indication that the patient had failed the prior regimen. NOTE: Evidence that the patient had failed the prior antibiotic regimen included continued fever, persistence or worsening of symptoms related to the index infection, and/or persistent laboratory or radiographic changes, and positive cultures consistent with the index infection.

12. The patient required effective concomitant systemic antimicrobials in addition to the study antibiotics.

13. The patient had a concurrent infection or other illness that, in the opinion of the investigator, would interfere with the evaluation of the response to the study antibiotic or pose additional risk in administering the study drug to the patient.

14. The patient was receiving chronic immunosuppressive therapy such as the use of high dose corticosteroids (≥1 mg/kg of prednisone daily or equivalent).

15. The patient had a clinical diagnosis of AIDS by current CDC criteria or another congenital or acquired immune deficiency resulting in a compromised response to bacterial infection.

16. Organ transplant patients that received chronic immunosuppressive therapy.

17. The patient had acute hepatic failure or acute decompensation of chronic hepatic dysfunction.

18. Participation in any other clinical study involving the administration of investigational medication, biological products, or use of a device at the time of presentation, during the course of the study, or during the previous 30 days. NOTE: Participation in clinical studies involving currently marketed medications was permitted.

19. Previous participation in this study at any time.

20. The patient had a history of seizures other than an uncomplicated febrile seizure.

21. Inability to obtain signed informed consent from a patient capable of giving consent, or, when a parent/legal representative had provided consent, the inability to obtain assent from a patient considered capable of giving assent.

Exclusion Criteria for Patients with Community-Acquired Pneumonia

1. Patient was on mechanical ventilation prior to onset of pneumonia (ventilator-associated pneumonia) or patient was likely to require ventilatory support for their pneumonia.

2. Patient had cystic fibrosis or chronic lung disease.

3. Patient had a neurologic disease preventing normal clearance of secretions or who were at risk for recurrent episodes of aspiration.

4. Patient had an empyema. NOTE: Patients with an effusion could be enrolled provided all clinically significant effusions are tapped and empyema had been ruled out.

Exclusion Criteria for Patients with Skin and Soft Tissue Infections

1. Patient had an infected burn wound.

2. Patient had necrotizing fasciitis.

3. Patient had evidence of associated osteomyelitis or septic arthritis. NOTE: If clinically suspected, osteomyelitis was determined by clinical assessment **and** by at least one of the following: x-ray, magnetic resonance imaging, bone culture/pathology, technetium bone scanning, indium-labeled white blood cell scanning.

4. Patient had a skin infection associated with prosthetic materials.

5. Patient had an infection known or presumed to be caused by ceftriaxone resistant anaerobes such as *Bacteroides* species.

Exclusion Criteria for Patients with Complicated Urinary Tract Infections

1. Patient had a complete obstruction of any portion of the urinary tract.

2. Patient had a perinephric or intrarenal abscess.

Protocol Amendments for Protocol 036

There were 2 amendments to the original protocol implemented before the breaking of the study blinding. The following is a listing of the noteworthy changes included in those amendments taken from the applicant:

Protocol Amendment 036-01

The first protocol amendment included noteworthy changes such as:

- The age enrollment criteria was changed to allow enrollment of patients 3 months to 17 years of age.
- For both ertapenem and ceftriaxone, redefined the once daily dosing to be for the 13 to 17 year old children and added the twice daily dosing for the 3 month to 12-year-old children.
- Added the requirement of 2 sets of blood cultures for all indications.
- Added the pharmacokinetic analysis section for patients 13 to 17 years of age.
- Added "phlebitis and pruritus" to the list of local reactions assessed by the investigator.
- Added "vomiting (1%)" to the list of most common drug-related clinical adverse experiences to be consistent with the patient informed consent.
- Added the Protocol 028 (single-dose pediatric pharmacokinetic and safety study) data for the children 3 to 23 months of age. Entire section was updated with the most current data and analysis from Protocol 028.
- Updated the SSTI inclusion criteria for at least one sign or symptom to have a moderate or severe rating.
- Changed the randomization to randomize patients based on disease and age category.
- Defined the amount of total study therapy required for UTI patients with pyelonephritis.
- Defined the process for keeping a blind at the site for IM injections.
- Redefined the evidence of prior therapy failure for patients with UTI.
- Defined the method for measuring cellulitis in the SSTI patients.
- Explained the requirement of a follow-up chest x-ray for CAP patients with persistent clinical abnormalities.
- Redefined the MITT analysis of UTI patients.

Protocol Amendment 036-02

The second amendment included mostly administrative items which did not affect the performance of the protocol. The Sponsor defined the use of systemic antimicrobials during the study and added requirements for *S. pneumoniae* and *H. influenzae* isolates for susceptibility testing.

RESULTS

Demographics and Baseline Characteristics

There were 304 patients enrolled in the ertapenem arm and 100 patients enrolled in the ceftriaxone arm. There were 135 patients enrolled in UTI indication, 125 in the SSTI indication and 143 in the CAP indication.

The data presented in the following tables summarize the baseline characteristics and demographics found in both the ertapenem and ceftriaxone groups.

Gender

Below is a summary of gender in both treatment groups and in the total number of patients.

Table 10 Baseline Distribution of Gender

	Ertapenem (N=304)		**Ceftriaxone** (N=99)		Total (N=403)	
Gender	n	%	n	%	n	%
Female	184	60.5	57	57.6	241	59.8
Male	120	39.5	42	42.4	162	40.2

Adapted from 036 study report Table 6-5

The data presented above show treatment groups well-balanced with respect to gender. Within the total number of patients, 40% of the patients were males and 60% were females.

Ethnic Origin

Below is a summary of the ethnic origin in both treatment groups and in the total number of patients.

Table 11 Baseline Distribution of Ethnic Origin

	Ertapenem (N=304)		**Ceftriaxone** (N=99)		Total (N=403)	
Race	n	%	n	%	n	%
Asian	37	12.2	5	5.1	42	10.4
Black	32	10.5	8	8.1	40	9.9
Hispanic	121	39.8	39	39.4	160	39.7
Multiracial	15	4.9	9	9.1	24	6
Polynesian	2	0.7	1	1	3	0.7
White	97	31.9	37	37.4	134	33.3

Adapted from 036 study report Table 6-5

The data presented above show treatment groups with respect to age. There are slight imbalances between treatment groups exist within several ethnic origin groups, however, patient numbers are small.

Age

Below is a summary of age classes in both treatment groups and in the total number of patients.

Table 12 Baseline Distribution of Age

	Ertapenem (N=304)		**Ceftriaxone** (N=99)		Total (N=403)	
Age	n	%	n	%	n	%
3-23 months	117	38.5	36	36.4	153	38
Mean	12 1		12.7		12.3	
Median	12		12 5		12	
Range	3-23		4-23		3-23	
2-12 years	169	55.6	56	56.6	225	55.8
Mean	4.9		5.6		5.1	
Median	4		5		4	
Range	2 -12		2 -12		2-12	
13-17 years	18	5.9	7	7.1	25	6.2
Mean	14.4		14.6		14.5	
Median	14		14		14	
Range	13-17		13-17		13-17	

Adapted from 036 study report Table 6-5

Comment*: *The data presented above show treatment groups well-balanced with respect to age.

Presented below is a summary of the diagnosis and age found in the treatment groups.

Table 13 Baseline Distribution of Age by Diagnosis

	Ertapenem (N=304)		**Ceftriaxone** (N=99)		**Total** (N=403)	
	n	%	n	%	n	%
CAP	108	35.5	35	35.4	143	35.5
3-23 months	43	14.1	15	15.2	58	14.4
2-12 years	62	20.4	17	17.2	79	19.6
13-17 years	3	1	3	3	6	1.5
UTI	101	33.2	34	34.3	135	33.5
3-23 months	42	13.8	14	14.1	56	13.9
2-12 years	54	17.8	18	18.2	72	17.9
13-17 years	5	1.6	2	2	7	1.7
SSTI	95	31.3	30	30.3	125	31
3-23 months	32	10.5	7	7.1	39	9.7
2-12 years	53	17.4	21	21.2	74	18.4
13-17 years	10	3.3	2	2	12	3

Adapted from 036 study report Table 6-5

Comment: Treatment groups with respect to age, gender, and race appear to be well-balanced.

Patient Evaluability

There were 404 patients randomized into treatment groups; 304 patients were randomized to receive ertapenem and 100 patients were randomized to receive ceftriaxone. The primary analysis for this study was safety. There were 403 patients were included in the safety analysis; 303 patients received ertapenem and 100 patients received ceftriaxone. For the SSTI indication, 122 SSTI patients were included in MITT population; 94 patients received ertapenem and 28 patients received ceftriaxone. For the CAP indication, 140 CAP patients were included in MITT population; 105 patients received ertapenem and 35 patients received ceftriaxone. For the UTI indication, 117 UTI patients were included in MITT population; 85 patients received ertapenem and 32 patients received ceftriaxone. Overall for the study, there were 379 patients included in these MITT populations; 284 patients received ertapenem and 95 patients received ceftriaxone.

There were 7 patients in the ertapenem treatment group who discontinued parenteral therapy due to lack of efficacy. Three of these patients had a baseline pathogen of *Staphylococcus aureus* (MRSA) that was resistant to blinded study therapy. One additional patient in the ertapenem treatment group had a baseline pathogen of *Stenotrophomonas maltophilia* that was resistant to blinded study therapy. There were no patients in the ceftriaxone group who discontinued study therapy because of a resistant baseline pathogen. Overall, 3 patients (1%) in the ertapenem treatment group and 1 patient (1%) in the ceftriaxone treatment group had to discontinue study therapy due to a clinical adverse experience. A patient who returned to the posttherapy follow-up visit and was assigned a clinical outcome at that visit was considered to have completed the study, regardless of any action taken regarding discontinuation of study drug therapy.

The table below displays the number and proportion of patients in each study population who were considered to be non-evaluable for the per protocol and the MITT efficacy analyses. The most common reasons why patients were excluded from the clinically evaluable population were test-of-cure window violations and inadequate or inappropriate courses of study therapy and most of these patients were lost to follow-up.

Table 14 Patient Accounting of Evaluability (Randomized Population)†

Population	**Ertapenem** (N=304) n (%)	**Ceftriaxone** (N=100) n (%)	**Total** (N=404) n (%)
Clinically MITT Evaluable Population			
Clinically MITT evaluable	284 (93.4)	95 (95)	379 (93.8)
Clinically MITT non-evaluable	20 (6.6)	4 (4)	24 (5.9)
Minimal disease definition not met	15 (4.9)	3 (3)	18 (4.5)
Patient did not receive at least one dose of study therapy	2 (0.7)	0 (0)	2 (0.5)
Pharmacy dispensing error precludes evaluability	3 (1)	1 (1)	4 (1)
Clinically Evaluable Population			
Clinically evaluable‡ #	197 (64.8)	77 (77)	274 (67.8)
Clinically non-evaluable	107 (35.2)	22 (22)	129 (31.9)
Baseline microbiology - resistant pathogen¶	11 (3.6)¶	0 (0)¶	11 (2.7)¶
Baseline uropathogen but cfu/mL criteria not met	12 (3.9)	1 (1)	13 (3.2)
Baseline/intercurrent medical events	1 (0.3)	0 (0)	1 (0.2)
Concomitant antibiotics violation	14 (4.6)	6 (6)	20 (5)
Disease definition not met	22 (7.2)	5 (5)	27 (6.7)
Inadequate/inappropriate study therapy	37 (12.2)	11 (11)	48 (11.9)
Prior antibiotics violation	7 (2.3)	0 (0)	7 (1.7)
Test-of-cure window violation	34 (11.2)	9 (9)	43 (10.6)
Microbiologically MITT Evaluable Population			
Microbiologically MITT evaluable	157 (51.6) ††	52 (52)	209 (51.7)
Microbiologically MITT non-evaluable	147 (48.4)	47 (47)	194 (48)
Baseline microbiology – nopathogen isolated	139 (45.7)	44 (44)	183 (45.3)
Baseline microbiology notperformed/inadequate	4 (1.3)	1 (1)	5 (1.2)
Not clinically evaluable _	18 (5.9)_	3 (3)	21 (5.2)
Microbiologically Evaluable Population			
Microbiologically evaluable#	93 (30.6)	37 (37)	130 (32.2)
Microbiologically non-evaluable	211 (69.4)	62 (62)	273 (67.6)
Baseline microbiology – no pathogen isolated	135 (44.4)	44 (44)	179 (44.3)
Baseline microbiology not performed/inadequate	2 (0.7)	0 (0)	2 (0.5)
Not clinically evaluable§	100 (32.9)§	20 (20) §	120 (29.7)
Test-of-cure microbiology inadequate	19 (6.3)	5 (5)	24 (5.9)

Adapted from 036 study report Table 6-4 This table contains counts of patient evaluability Therefore, although a patient may have one or more reasons for being non-evaluable, the patient will be counted only once in the non-evaluable category

† One patient (AN 9906) from the ceftriaxone treatment group is included in the overall counts but is not included in any of the evaluable populations since minimal demographic and no efficacy data were available due to withdrawal of consent
‡ One patient (AN 2370) in the ertapenem treatment group was lost to follow-up and was mistakenly included in the clinically evaluable population This patient was not included in the EPP population of the efficacy analyses
§ Seven patients (AN 1601, AN 1691, AN 3691, AN 7690, AN 8479, AN 8822, and AN 9810) in the ertapenem group and 2 (AN 7599 and AN 9823) in the ceftriaxone group were inadvertently missing the not clinically evaluable reason for not being microbiologically evaluable per protocol All 9 patients were correctly marked as not microbiologically evaluable for other reasons
_ Two patients (AN 1691 and AN 7407) in the ertapenem group and 1 patient (AN 7599) in the ceftriaxone group were inadvertently missing the not clinically evaluable reason for not being microbiological MITT evaluable per protocol All 3 patients were correctly marked as not microbiological MITT evaluable for other reasons
¶ One patient (AN 2980) in the ceftriaxone treatment group was inadvertently missing the baseline microbiology – resistant pathogen reason for not being clinically evaluable per protocol This patient was correctly marked as not clinically or microbiologically evaluable per protocol for other reasons
# One patient (AN 2360) in the ertapenem treatment group had a sole pathogen of MRSA at baseline and was inadvertently marked as clinically and microbiologically evaluable
†† One patient (AN 2264) in the ertapenem treatment group did not have a pathogen at baseline and was inadvertently included in the Microbiologic MITT population for all analyses, including the efficacy analyses

Comment: Within the evaluable per protocol population, there were 11 patients (3.6%) in the ertapenem treatment group as compared with 1 patient (1%) in the ceftriaxone treatment group were identified as non-evaluable because of resistant baseline pathogens. The treatment groups appear to be similar with respect to reasons not evaluable.

Prior and Concomitant Therapy

There were 43/284 patients (15.1%) in the ertapenem treatment group and 7/95 patients (7.4%) in the ceftriaxone treatment group who received systemic nonstudy systemic antibacterial therapy during the study. The most common nonstudy concomitant antibacterials in both treatment groups were sulfamethoxazole (+) trimethoprim, cefuroxime, amoxicillin, and ceftriaxone sodium. In settings other than clinical failure, more than one dose of an effective systemic concomitant antibacterial agent or regimen with activity against the documented or presumed pathogens rendered a patient nonevaluable for the evaluable per protocol analyses. Antiviral agents and antifungal agents were allowed as concomitant therapy since they were not considered potentially confounding. Amoxicillin/clavulanate was the protocol specified oral switch agent, so is not listed as a concomitant antibacterial agent unless additional courses not specified in the protocol were prescribed. If a different oral switch agent was utilized due to baseline resistance or intolerance to amoxicillin/clavulanate, then this was considered study therapy and is not listed as a concomitant antibacterial agent.

Duration of Therapy

The median duration of study therapy was 11 days in each treatment group and median duration of parenteral study therapy was 4 days in each treatment group. Both treatment groups appear similar with respect to extent of exposure.

Baseline Characteristics of Patients with Community-Acquired Pneumonia

The table below displays the clinical MITT evaluable community-acquired pneumonia patients x-ray findings and oxygen supplementation entered by treatment group. There were 140 community-acquired pneumonia patients from 28 sites who were clinical MITT evaluable; 105 patients received ertapenem and 35 patients received ceftriaxone.

Table 15 Number (%) of Patients With X-Ray Findings and Oxygen by Treatment Group Clinical MITT Population

	Ertapenem (N=105)		**Ceftriaxone** (N=35)		Total (N=140)	
	n	%	n	%	n	%
Pulmonary Infiltration/Consolidation	**105**	**100**	**35**	**100**	**140**	**100**
Lobar infiltration/consolidation	100	95.2	33	94.3	133	95
Interstitial infiltration/consolidation	22	21	7	20	29	20.7
Supplemental Oxygen	**23**	**21.9**	**4**	**11.4**	**27**	**19.3**
Increased oxygen requirement for present pneumonia	23	21.9	4	11.4	27	19.3

Adapted from 036 study report Table 6-16 n=The number of patients with a given assessment N=The number of patients with community-acquired pneumonia

There are more patients with lobar infiltration (95%) as opposed to interstitial infiltration (21%).

Comment: Patients requiring supplemental oxygen may be sicker patients. 22% ertapenem vs. 11% ceftriaxone received oxygen supplementation.

Baseline Characteristics of Skin and Soft Tissue Infection

The table below displays the numbers of patients with their wound infections for the skin and soft tissue infection clinical MITT population.

Table 16 Number (%) of Patients With Wound Description by Treatment Group Clinical MITT Population

	Ertapenem (N=94)		**Ceftriaxone** (N=28)		Total (N=122)	
	n	%	n	%	n	%
With more than one wound	13	13.8	4	14.3	17	13.9
Abscess	21	22.3	6	21.4	27	22.1
Cellulitis	58	61.7	14	50	72	59
Impetigo	6	6.4	2	7.1	8	6.6
Lymphadenitis	1	1.1	1	3.6	2	1.6
Phlegmon	2	2.1	1	3.6	3	2.5
Post-traumatic wound infection	7	7.4	4	14.3	11	9
Postoperative wound infection	1	1.1	1	3.6	2	1.6

Adapted from 036 study report Table 6-23 n=The number of patients with a given wound description detail N=The number of patients with skin and soft tissue infection

Comment: There were 17 patients (13.9%) with more than one infected wound. The most common wounds in the ertapenem treatment group were cellulitis (61.7%), abscess (22.3%),

and posttraumatic wound infections (7.4%). The 2 treatment groups appeared similar with respect to these frequencies.

Baseline Characteristics of Complicated Urinary Tract Infection

There were 117 complicated urinary tract infection patients from 26 sites who were microbiological MITT evaluable. Of these, 85 patients received ertapenem and 32 patients received ceftriaxone.

The table presented below displays patients with urinary tract abnormalities and pre-existing urinary catheters.

Table 17 Number of Patients with Urinary Tract Assessment by Treatment Group Microbiologic MITT Population

	Ertapenem (N=85)		**Ceftriaxone** (N=32)		Total (N=117)	
	n	%	n	%	n	%
Pyelonephritis at Prestudy	69	81.2	30	93.8	99	84.6
Recurrent Pyelonephritis	16	18.8	4	12.5	20	17.1
Urinary Tract Abnormalities	24	28.2	5	15.6	29	24.8
Partial Obstruction	4	4.7	1	3.1	5	4.3
Structural and/or Functional Abnormality	21	24.7	5	15.6	26	22.2
Intermittent Urinary Catheterization	5	5.9	1	3.1	6	5.1
Indwelling Urinary Catheterization	10	11.8	2	6.3	12	10.3

Adapted from 036 study report Table 6-30 N=The number of patients with complicated urinary tract infections n=The number of patients with the assessment This report contains counts of patients Therefore, although a patient may be counted multiple times in the subsets for the abnormalities and catherization categories, the patient will be only counted once in the total for each category

From the table above, it can be noted 99/117 patients (84.6%) had pyelonephritis, 29/177 patients (24.8%) had a urinary tract abnormality, 6/177 patients (5.1%) required chronic intermittent urinary catheterization and 12/177 patients (10.3%) required indwelling urinary catheterization.

Comment: There are a larger proportion of patients in the ertapenem treatment group who had underlying urologic abnormalities, including structural/functional abnormalities and indwelling catheters or stents.

EFFICACY

Evaluation of clinical response was made for all patients at the time of discontinuation from parenteral study antibiotic and at the 7-14 day posttherapy endpoint visit.

Clinical Outcome

EPP Clinical Efficacy Evaluation

The table below presents the proportion of patients, in the clinical EPP population with a favorable clinical response assessment at the TOC visit.

Table 18 Proportion of Patients With a Favorable Clinical Response Assessment at Test-of-Cure Visit Displayed by Disease Stratum (Clinical EPP Population)

	Ertapenem (A) (N=196)			**Ceftriaxone** (B) (N=77)		Adjusted Difference (A-B)	
	n/m	%	(95% CI)	n/m	%	(95% CI)‡	%	(95% CI)
UTI	46/52	88.4	(79.7, 97.1)	22/23	95.7	(78.1, 99.9)	-7.2	(-31.1, 17.1)
SSTI	64/67¶	95.5	(90.5, 100)	26/26	100	(86.8, 100)	-4.5	(-26.8, 17.1)
CAP	74/77	96.1	(91.8, 100)	27/28	96.4	(81.7, 99.9)	-0.3	(-21.9, 20.9)
Overall	184/196¶	94	(90.7, 97.3)	75/77	97.4	(93.8, 100)	-3.4	(-9.2, 2.4)

Adapted from 036 study report Table 7-6 CI=Confidence interval n/m=Number of patients with favorable assessment/number of patients with an assessment at the test-of-cure visit EPP=Evaluable per protocol N=Number of clinical EPP patients in the treatment group ¶ One patient 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

In this clinical EPP analysis, there were 7 bacteremic patients included, consisting of 5 CAP and 2 SSTI in the ertapenem treatment group and 3 bacteremic patients consisting of 2 CAP and 1 SSTI in the ceftriaxone treatment group. One SSTI patient in the ertapenem treatment group had both *Staphylococcus aureus* and pyogenic *Streptococci* isolated simultaneously. No patient in either treatment group demonstrated persistent bacteremia. The clinical response rate for these patients were 6/7 (86%) (4/5 CAP; 2/2 SSTI) in the ertapenem treatment group and 3/3 (100%) in the ceftriaxone treatment group. The one CAP clinical failure had documented eradication of the baseline bacteremic *S. aureus* isolate at TOC but had acquired a new infection. All patients with a resistant bacterial isolate identified as the sole baseline pathogen were to be excluded from the EPP analyses. One SSTI patient in the ertapenem treatment group had MRSA as a sole baseline pathogen but was mistakenly included in the EPP analyses which follow.

The table below presents patients in the clinical EPP population with a favorable clinical response assessment at the TOC visit, by age strata and disease diagnosis.

Table 19 Proportion of Patients With a Favorable Clinical Response Assessment at Test-of-Cure Visit Displayed by Disease and Age Strata (Clinical EPP Population)

		Ertapenem (N=196)		**Ceftriaxone** (N=77)		Observed Difference
	Age	n/m	% (95% CI)	n/m	% (95% CI)	% (95% CI)
UTI	3-23 months	14/15	93.3 (68.1, 99.8)	6/6	100 -	-6.7 -
	2-12 years	28/33	84.8 (72.6, 97.1)	14/15	93.3 (68.1, 99.8)	-8.5 (-38, 22.5)
	13-17 years	4/4	100 -	2/2	100 -	0 -
SSTI	3-23 months	17/18	94.4 (72.7, 99.9)	6/6	100 -	-5.6 -
	2-12 years	40/42†	95.2 (88.8, 100)	18/18	100 (81.5, 100)	-4.8 (-32, 22.9)
	13-17 years	7/7	100 -	2/2	100 -	0 -
CAP	3-23 months	26/28	92.9 (76.5, 99.1)	10/10	100 (69.2, 100)	-7.1 (-41.8, 28.3)
	2-12 years	46/47	97.9 (93.7, 100)	14/15	93.3 (68.1, 99.8)	4.5 (-18.7, 33.3)
	13-17 years	2/2	100 -	3/3	100 -	0 -
Overall	3-23 months	57/61	93.4 (87.2, 99.7)	22/22	100 (84.6, 100)	-6.6 (-30.6, 17.4)
	2-12 years	114/122†	93.4 (89.1, 97.8)	46/48	95.8 (90.2, 100)	-2.4 (-9.5, 4.8)
	13-17 years	13/13	100 (75.3, 100)	7/7	100 -	0 -

Adapted from 036 study report Table 7-7 EPP=Evaluable per protocol CI=Confidence interval N=Number of EPP patients in the treatment group n/m=Number of patients with favorable assessment/number of patients with an assessment at the test-of-cure visit † One patient 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

Comment: The results from the clinical efficacy evaluation for the EPP population, displayed by disease and age strata at the TOC visit appear to comparable to those from the clinical efficacy evaluation for the MITT population, displayed by disease and age strata, at the posttreatment visit.

MITT Clinical Efficacy Evaluation

Note that this is the applicant's clinical MITT analysis. Clinical efficacy evaluations for the MITT population were done at the discontinuation of parenteral therapy (DCPT) and at the post-treatment visit. The post-treatment principal MITT analyses counted all assessments made at least 1 day after completion of study therapy for CAP and SSTI and at least 4 days after completion of study therapy for UTI. Patients missing a post-treatment assessment were excluded from these analyses unless they had previously failed, in which case their outcome was unfavorable. In order to assess the sensitivity of clinical efficacy evaluation in the MITT population, an additional evaluation was done on the MITT population in which all patients who have missing or indeterminate outcomes at the TOC visit (5 to 21 days after completion of study therapy) were considered "failures."

The table below presents the proportion of patients in the clinical MITT population, with a favorable clinical response assessment at the posttreatment visit.

Table 20 Proportion of Patients With a Favorable Clinical Response Assessment at Posttreatment Visit Displayed by Disease Stratum (Clinical MITT Population)

	Ertapenem (N=284)			**Ceftriaxone** (N=95)			Adjusted Difference	
	n/m	%	(95% CI)	n/m	%	(95% CI)	%	(95% CI)
UTI	69/80	86.4	(78.9, 93.9)	28/29	96.6	(82.2, 99.9)	-10.3	(-31, 10.6)
SSTI	78/88	90.1	(83.8, 96.3)	27/27	100	(87.2, 100)	-11.4	(-32.4, 9.5)
CAP	89/95	93.6	(88.7, 98.5)	32/33	96.8	(90.8, 100)	-3.2	(-13.3, 6.9)
Overall	236/263	89.9	(86.2, 93.5)	87/89	97.8	(94.7, 100)	-7.9	(-13.4, -2.4)

Adapted from 036 study report Table 7-1. CI=Confidence interval. n/m=Number of patients with favorable assessment/number of patients with an assessment at the relevant time point. N=Number of clinical MITT patients in the treatment group. MITT=Modified intention to treat. Adjusted Difference (A-B) =Ertapenem (A) – Ceftriaxone (B).

Response rates ranged from 86.4% (UTI) to 93.6% (CAP), for the ertapenem group, and ranged from 96.6% (UTI) to 100% (SSTI), for the ceftriaxone group. The percentage point differences between the 2 treatment groups (ertapenem—ceftriaxone) ranged from -11.4% (SSTI) to -3.2% (CAP). While treatment successes were high in both treatment groups, there were a small number of failures in the ertapenem group within each disease indication.

MITT Clinical Efficacy Evaluation-Sensitivity Analysis

We requested a sensitivity analysis be performed to additionally evaluate patients, in the MITT population, in which all patients who have missing values or indeterminate outcome at the TOC visit were considered "failures."

The table below presents the sensitivity analysis in patients in the clinical MITT population by disease stratum.

Table 21 Proportion of Patients With a Favorable Clinical Response Assessment at Test-of-Cure Visit Displayed by Disease Stratum—Sensitivity Analysis (Clinical MITT Population)

	Ertapenem (N=284)			**Ceftriaxone** (N=95)			Adjusted Difference	
	n/m	%	(95% CI)	n/m	%	(95% CI)	%	(95% CI)
UTI	67/85	79	(70.3, 87.6)	28/32	87.4	(76, 98.9)	-8.5	(-25.3, 8.4)
SSTI	73/94	79.2	(71, 87.4)	27/28	96.4	(81.7, 99.9)	-18.8	(-39.2, 2.3)
CAP	84/105	79.8	(72.1, 87.5)	30/35	85.7	(74, 97.3)	-5.9	(-21.6, 9.8)
Overall	224/284	78.9	(74.2, 83.6)	85/95	89.4	(83.2, 95.6)	-10.5	(-18.9, -2.1)

Adapted from study report 036 Table 7-5.

Comment: The results from the clinical efficacy evaluation for the EPP population at the TOC visit compared to those from the applicant's clinical efficacy evaluation for the MITT population at the posttreatment visit show an overall adjusted difference variation with -3.4 in the EPP analysis and -7.9 with MITT in the applicant's MITT analysis. The sensitivity analysis had an overall adjusted difference of -10.5. The pediatric point estimates are within range of what was seen in adults.

Microbiological Outcome

EPP Microbiologic Efficacy Evaluation

The table below presents patients with a favorable microbiological response at the TOC visit by disease stratum.

Table 22 Proportion of Patients With a Favorable Microbiological Response Assessment at Test-of-Cure Visit Displayed by Disease Stratum (Microbiological EPP Population)

	Ertapenem (N=93)			**Ceftriaxone** (N=37)			Adjusted Difference	
	n/m	%	(95% CI)	n/m	%	(95% CI)	%	(95% CI)
UTI	40/46	87.4	(77.8, 97)	18/20	90	(68.3, 98.8)	-3	(-29.1, 22.9)
SSTI	29/31	92.4	(83, 100)	14/14	100	(76.8, 100)	-6.5	(-36.5, 24.4)
CAP	14/16	87.5	(61.7, 98.4)	2/3	66.7	-	20.8	-
Overall	83/93	88.9	(82.5, 95.3)	34/37	91.9	(83.1, 100)	-3	(-15.8, 9.8)

Adapted from study report 036 Table 7-13. n/m=number of patients with favorable assessment/number of patients with an assessment at TOC.

Comment: The results from the microbiological efficacy evaluation for the EPP population at the TOC visit appear comparable to those from the applicant's microbiological efficacy evaluation for the MITT population at the posttreatment visit. The response rates for the MITT population are lower than the EPP populations.

MITT Microbiologic Efficacy Evaluation

The table below presents patients, in the microbiologic MITT population with a favorable microbiological response assessment at the posttreatment visit. Note, that this is the applicant's clinical MITT analysis.

Table 23 Proportion of Patients With a Favorable Microbiological Response Assessment During the Posttreatment Visits Displayed by Disease Stratum Microbiologic MITT Population)

	Ertapenem (N=157) ¶			**Ceftriaxone** (N=52)			Adjusted Difference	
	n/m	%	(95% CI)	n/m	%	(95% CI)	%	(95% CI)
UTI	58/69	84.6	(76.1, 93.1)	23/25	92	(74, 99)	-7.9	(-30.3,14.8)
SSTI	38/46	85.6	(75.5, 95.8)	15/15	100	(78.2,100)	-17.4	(-44.8,11.4)
CAP	16/19	84.2	(60.4, 96.6)	2/3	66.7	-	17.5	-
Overall	112/134	83.3	(77.0, 89.7)	40/43	93.1	(85.5,100)	-9.7	(-21.1, 1.7)

Adapted from 036 study report Table 7-9 CI=Confidence interval n/m=Number of patients with favorable assessment/number of patients with an assessment at the relevant time point N=Number of microbiologic MITT patients in the treatment group MITT=Modified Intention to treat ¶ One patient in the ertapenem treatment group did not have a pathogen at baseline and was inadvertently included in the overall Microbiologic MITT population

As displayed in the table above, response rates ranged from 84.2% (CAP) to 85.6% (SSTI), for the ertapenem treatment group; and ranged from 66.7% (CAP) to 100% (SSTI), for the ceftriaxone treatment group. The percentage point differences between the 2 treatment groups (ertapenem-ceftriaxone) ranged from -17.4% (SSTI) to 17.5% (CAP). While treatment successes

were high in both treatment groups, there were a small number of failures in the ertapenem treatment group within each disease indication.

MITT Microbiologic Efficacy Evaluation-Sensitivity Analysis

The table below presents the microbiological MITT population, patients with a favorable microbiological response assessment at TOC, by disease diagnosis.

Table 24 Proportion of Patients With a Favorable Microbiological Response Assessment at Test-of-Cure Visit Displayed by Disease Stratum—Sensitivity Analysis (Microbiological MITT Population)

	Ertapenem (N=157)			**Ceftriaxone** (N=52)			Adjusted Difference	
	n/m	%	(95% CI)	n/m	%	(95% CI)	%	(95% CI)
UTI	56/85	66.1	(56.1, 76.2)	23/32	71.7	(56.1, 87.3)	-5.6	(-26.4, 15.3)
SSTI	35/50	72	(59.5, 84.4)	15/16	93.8	(69.8, 99.8)	-23.8	(-50.5, 4.6)
CAP	15/21	71.4	(47.8, 88.7)	2/4	50	-	21.4	-
Overall	106/156	67.5	(60.2, 74.9)	40/52	77.1	(65.6, 88.5)	-9.5	(-24.5, 5.4)

Adapted from study report 036 Table 7-12. n/m = Number of patients with favorable assessment/number of patients with an assessment at TOC

Comment: The results from the microbiological efficacy sensitivity evaluation for the MITT population at the TOC visit appear comparable to those from the microbiological efficacy evaluation for the applicant's MITT population at the posttreatment visit. Response rates for the MITT sensitivity analysis are lower than the MITT and EPP populations.

Pathogen Outcome

EPP Clinical Efficacy Evaluation by Pathogen

The table below presented the proportion of patients by pathogen, with favorable clinical response assessments at TOC, for SSTI and CAP.

The most common pathogens isolated were *Staphylococcus aureus* for SSTI and *Streptococcus pneumoniae* for CAP.

Table 25 Proportion of Favorable Clinical Response Assessment by Pathogen at Test-of-Cure Visit Displayed by Disease Stratum (SSTI and CAP)—Total Isolates (Microbiologic EPP Population)

		Ertapenem (N=47)		**Ceftriaxone** (N=17)	
		n/m	%	n/m	%
SSTI	**Gram-Positive Aerobic Cocci**	**28/31**	**90 3**	**15/15**	**100**
	Staphylococcus aureus	17/18‡	94 4	9/9	100
	-Methicillin Susceptible	16/16	100	8/8	100
	Streptococcus pneumoniae	1/1	100	-	-
	-Penicillin Susceptible	1/1	100	-	-
	Streptococcus pyogenes	7/7	100	5/5	10
	Streptococcus sanguinis	1/2	50	-	-
	Group A *Streptococcus*	2/2	100	-	-
	Gram-Positive Anaerobic Cocci	**1/1**	**100**	-	-
	Peptostreptococcus anaerobius	1/1	100	-	-
	Gram-Negative Aerobic Bacilli	**1/3**	**33 3**	**1/1**	**100**
	Escherichia coli	-	-	1/1	100
CAP	**Gram-Positive Aerobic Cocci**	**9/10**	**90**	**2/2**	**100**
	Streptococcus pneumoniae	6/6	100	1/1	100
	-Penicillin Intermediate	2/2	100	-	-
	-Penicillin Susceptible	4/4	100	-	-
	-Penicillin Unknown	-	-	1/1	100
	Gram-Negative Aerobic Bacilli	**2/2**	**100**	-	-
	Moraxella catarrhalis	1/1	100	-	-
	Gram-Negative Aerobic Coccobacilli	**5/5**	**100**	**1/1**	**100**
	Haemophilus influenzae	5/5	100	1/1	100
	-Beta Lactamase Negative	1/1	100	1/1	100
	-Beta Lactamase Positive	4/4	100	-	-
Overall	**Gram-Positive Aerobic Cocci**	**37/41**	**90.2**	**17/17**	**100**
	Staphylococcus aureus	19/21‡	90 5	9/9	100
	-Methicillin Susceptible	18/19	94 7	8/8	100
	Streptococcus pneumoniae	7/7	100	1/1	100
	-Penicillin Susceptible	5/5	100	1/1	100
	Streptococcus pyogenes	7/7	100	5/5	100
	Group A *Streptococcus*	2/2	100	-	-
	Gram-Positive Anaerobic Cocci	**1/1**	**100**	-	-
	Peptostreptococcus anaerobius	1/1	100	-	-
	Gram-Negative Aerobic	**3/5**	**60**	**1/1**	**100**

	Bacilli				
	Escherichia coli	-	-	1/1	100
	Klebsiella pneumoniae	1/2	50	-	-
	Moraxella catarrhalis	1/1	100	-	-
	Gram-Negative Aerobic Coccobacilli	**5/5**	100	**1/1**	**100**
	Haemophilus influenzae	5/5	100	1/1	100
	-Beta Lactamase Negative	1/1	100	1/1	100

Adapted from 036 study report Table 7-8 †Computed from an exact statistical model pooling across strata ‡ One patient in the ertapenem treatment group with MRSA as a sole pathogen is mistakenly included in this analysis N=Number of evaluable patients in each treatment group n/m=Number of pathogens associated with a favorable clinical assessment/number of pathogens with an assessment CI=Confidence interval EPP=Evaluable per protocol

EPP Microbiological Efficacy Evaluation by Pathogen

The table below presents patients (by baseline pathogen-total isolates), in the microbiologic EPP population, with a favorable microbiological response assessment at the TOC visit, for UTI.

Table 26 Proportion of Favorable Microbiological Response Assessment by Pathogen at Test-Of-Cure Visit Displayed for UTI—Total Isolates (Microbiologic EPP Population)

		Ertapenem (N=46)			**Ceftriaxone** (N=20)			Observed† Difference	
		n/m	%	(95% CI)	n/m	%	(95% CI)	%	(95% CI)
UTI	**Gram-Negative Aerobic Bacilli**	**41/47**	**87.2**	**(74.3, 95.2)**	**18/20**	**90**	**(68 3, 98.8)**	**-2.8**	**(-28.5, 23)**
	Enterobacter cloacae	4/4	100						
	Escherichia coli	34/40	85	(70 2, 94 3)	16/18	88 9	(65 3, 98 6)	-3 9	(-31 4, 23 5)
	Klebsiella	1/1	100	-	-	-	-	-	-
	Klebsiella oxytoca	-	-	-	1/1	100	-	-	-
	Proteus mirabilis	1/1	100	-	1/1	100	-	0	(-97 5, 97 5)
	Pseudomonas aeruginosa	1/1	100	-	-	-	-	-	-

Adapted from study report 036 Table 7-15.

The most common species identified, for UTI, was *Escherichia coli.* There were no UTI microbiologic EPP patients who were bacteremic at baseline.

SAFETY

Clinical Adverse Events

The primary objective was to assess the safety profile of ertapenem in treating pediatric patients with CAP, SSTI or UTI. No unanticipated safety issues were identified.

The table below displays the number of treated patients with clinical adverse events, by category, occurring during parenteral therapy and during study therapy (including oral therapy, if administered) and the 14-day follow-up period (14 days after the discontinuation of study therapy).

Table 27 Clinical Adverse Events Summary During Parenteral Therapy and the Study Therapy and 14-Day Follow-Up—Treated Population

	During Parenteral Therapy				**During Study Therapy and 14-Day Follow-Up**			
	Ertapenem (N=303)		**Ceftriaxone** (N=100)		**Ertapenem** (N=303)		**Ceftriaxone** (N=100)	
Number of patients:	n	%	n	%	n	%	n	%
With 1 or more AE	147	48.5	41	41	201	66.3	63	63
With no AE	156	51.5	59	59	102	33.7	37	37
With drug-related AE	70	23.1	23	23	78	25.7	25	25
With SAE	5	1.7	1	1	10	3.3	6	6
With drug-related SAE	1	0.3	1	1	1	0.3	2	2
Who died	0	0	0	0	0	0	0	0
Discontinued due to AE	4	1.3	1	1	6	0	1	1
Discontinued due to drug-related AE	1	0.3	1	1	2	0.7	1	1
Discontinued due to SAE	1	0.3	1	1	2	0.7	1	1
Discontinued due to drug-related SAE	0	0	1	1	0	0	1	1

Adapted from 036 study report Tables 8-2 and 8-6 AE=adverse event. SAE=serious adverse event.

Overall, 188 out of 403 treated patients had one or more clinical adverse experiences during parenteral therapy and 264 patients had clinical adverse experiences during study therapy and 14-day follow-up.

Comment: The incidence of clinical adverse events, including serious adverse events, drug-related adverse events and discontinuations due to adverse events, appears relatively comparable in the 2 treatment groups.

The table below displays patients, by body system irrespective of drug relationship, with specific clinical adverse events that had an incidence of ≥3% in one or more treatment group during study therapy and 14-day follow-up period.

Table 28 Number (%) of Patients With Specific Clinical Adverse Events (Incidence ≥3 % in One or More Treatment Groups) by System Organ Class

	Ertapenem (N=303)		**Ceftriaxone** (N=100)	
	n	%	n	%
Patients with 1 or more AE	201	66.3	63	63
Patients with no AE	102	33.7	37	37
Gastrointestinal Disorders	94	31	29	29
Abdominal pain	14	4.6	3	3
Diarrhea	40	13.2	17	17
Vomiting	36	11.9	11	11
General Disorders and Administration Site Conditions	66	21.8	19	19
Infusion site erythema	14	4.6	3	3
Infusion site pain	20	6.6	4	4
Infusion site phlebitis	7	2.3	3	3
Pyrexia	16	5.3	6	6
Infections and Infestations	59	19.5	25	25
Nasopharyngitis	6	2	6	6
Pharyngitis	1	0.3	3	3
Upper respiratory tract infection	8	2.6	3	3
Injury, Poisoning and Procedural Complications	**24**	**7.9**	**4**	**4**
Overdose†	11	3.6	2	2
Nervous System Disorders	**20**	**6.6**	**6**	**6**
Headache	16	5.3	4	4
Respiratory, Thoracic and Mediastinal Disorders	**31**	**10.2**	7	7
Cough	14	4.6	3	3
Skin and Subcutaneous Tissue Disorders	**52**	**17.2**	**13**	**13**
Dermatitis diaper	18	5.9	4	4
Rash	9	3	2	2

Adapted from study report 036 Table 8-7 Although a patient may have had 2 or more clinical adverse events, the patient is counted only once within a category The same patient may appear in different categories † Accidental overdoses refer to reports of unintentional overdose where no associated adverse effects were noted Duration of reported overdoses is reflected in the dose by duration table

Comment: The most common clinical adverse experiences reported during study therapy and 14-day follow-up were diarrhea, vomiting and infusion site pain.

Drug-Related Clinical Adverse Events Reported During Study Therapy and Follow-Up Period

The table below displays patients with drug-related clinical adverse events with an incidence ≥1 % by system organ class occurring during study therapy and 14-day follow-up period. The most common types of drug-related clinical adverse events reported during oral therapy and 14-day follow-up were gastrointestinal disorders.

Table 29 Number of Patients With Specific Clinical Adverse Events (Incidence ≥1 % in One or More Treatment Groups) by System Organ Class—Drug-Related During Study Therapy and 14-Day Follow-Up Period (Treated Population)

	Ertapenem (N=303)		**Ceftriaxone** (N=100)	
	n	%	n	%
Patients with 1 or more drug-related AE	78	25.7	25	25
Patients with no drug-related AE	225	74.3	75	75
Gastrointestinal Disorders	**40**	**13.2**	**15**	**15**
Abdominal pain	3	1	1	1
Diarrhea	22	7.3	11	11
Loose stools	5	1.7	0	0
Perianal erythema	0	0	1	1
Vomiting	8	2.6	2	2
General Disorders and Administration Site Conditions	**34**	**11.2**	**11**	**11**
Chest pain	1	0.3	1	1
Infusion site erythema	9	3	2	2
Infusion site induration	3	1	0	0
Infusion site pain	15	5	1	1
Infusion site phlebitis	7	2.3	3	3
Infusion site pruritus	2	0.7	1	1
Infusion site reaction	2	0.7	1	1
Infusion site swelling	4	1.3	0	0
Infusion site warmth	2	0.7	1	1
Pyrexia	0	0	1	1
Infections and Infestations	**4**	**1.3**	**0**	**0**
Injury, Poisoning and Procedural Complications	**1**	**0.3**	**1**	**1**
Hypothermia	1	0.3	1	1
Nervous System Disorders	**2**	**0.7**	**1**	**1**
Headache	2	0.7	1	1
Psychiatric Disorders	**0**	**0**	**1**	**1**
Agitation	0	0	1	1
Respiratory, Thoracic and Mediastinal Disorders	**1**	**0.3**	**1**	**1**
Cough	0	0	1	1
Skin and Subcutaneous Tissue Disorders	**16**	**5.3**	**2**	**2**
Dermatitis	0	0	1	1
Dermatitis diaper	5	1.7	0	0
Rash	5	1.7	1	1

Vascular Disorders	**5**	**1.7**	**0**	**0**
Phlebitis	3	1	0	0

Adapted from study report 036 Table 8-8 AE=adverse event Although a patient may have had 2 or more clinical adverse events, the patient is counted only once within a category The same patient may appear in different categories

A drug-related AE is one that is determined by the investigator to be possibly, probably or definitely drug related.

Comment: Overall, the incidence of clinical adverse events was comparable between the two treatment groups.

Drug-Related Clinical Adverse Events Reported During Parenteral Therapy

There were 70 patients (23.1%) in the ertapenem treatment group and 23 patients (23%) in the ceftriaxone treatment group had one or more drug-related clinical adverse events during parenteral therapy. The most common drug-related clinical adverse events reported during parenteral therapy were diarrhea, infusion site pain and infusion site erythema.

The table below presents patients with specific adverse drug related events occurring ≥ 1% during parenteral therapy.

Table 30 Number (%) of Patients With Specific Clinical Adverse Events (Incidence ≥1% in One or More Treatment Groups) by System Organ Class Drug-Related During Parenteral Therapy (Treated Population)

	Ertapenem (N=303)		**Ceftriaxone** (N=100)	
	n	%	n	%
Patients with 1 or more drug-related AE	70	23.1	23	23
Patients with no drug-related AE	233	76.9	77	77
Gastrointestinal Disorders	**29**	**9.6**	**13**	**13**
Abdominal pain	1	0.3	1	1
Diarrhea	18	5.9	10	10
Vomiting	6	2	2	2
General Disorders and Administration Site Conditions	**34**	**11.2**	**11**	**11**
Chest pain	1	0.3	1	1
Infusion site erythema	9	3	2	2
Infusion site induration	3	1	0	0
Infusion site pain	15	5	1	1
Infusion site phlebitis	7	2.3	3	3
Infusion site pruritus	2	0.7	1	1
Infusion site reaction	2	0.7	1	1
Infusion site swelling	4	1.3	0	0
Infusion site warmth	2	0.7	1	1
Pyrexia	0	0	1	1
Injury, Poisoning and Procedural Complications	1	0.3	1	1
Hypothermia	1	0.3	1	1
Nervous System Disorders	**2**	**0.7**	**1**	**1**
Headache	2	0.7	1	1
Psychiatric Disorders	**0**	**0**	**1**	**1**
Agitation	0	0	1	1
Respiratory, Thoracic and Mediastinal Disorders	**1**	**0.3**	**1**	**1**
Cough	0	0	1	1
Skin and Subcutaneous Tissue Disorders	**10**	**3.3**	**2**	**2**
Dermatitis	0	0	1	1
Rash	5	1.7	1	1
Vascular Disorders	5	1.7	0	0
Phlebitis	3	1	0	0

Adapted from 036 study report Table 8-5 AE=adverse event Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category The same patient may appear in different categories

There were 18 patients (5.9%) who received ertapenem and 10 patients (10%) who received ceftriaxone who experienced diarrhea. There were 15 patients (5%) who received ertapenem and

1 patient (1%) who received ceftriaxone which experienced infusion site pain. There were 9 patients (3%) who received ertapenem and 2 patients (2%) ceftriaxone who experienced infusion site erythema. There was a low frequency of drug-related rashes in both treatment groups.

Comment: The incidence of drug-related clinical adverse events was comparable between the 2 treatment groups.

A drug-related adverse event was one determined by the investigator to be possibly, probably, or definitely related to study drug. As compared to the drug-related events reported during parenteral therapy, 8 additional patients from the ertapenem treatment group and 1 patient (1%) in the ceftriaxone treatment group had serious clinical adverse events.

Serious Adverse Events

The table below displays patients with serious clinical adverse events with incidence >0% by system organ class, occurring during study therapy and the 14-day follow-up period.

Table 31 Number (%) of Patients With Specific Serious Clinical Adverse Events (Incidence >0% in One or More Treatment Groups) by System Organ Class During Study Therapy and 14-Day Follow-Up Period Treated Population

	Ertapenem (N=303)		**Ceftriaxone** (N=100)	
	n	%	n	%
Patients with 1 or more AE	10	3.3	6	6
Patients with no AE	293	96.7	94	94
Gastrointestinal Disorders	**2**	**0.7**	**1**	**1**
Vomiting	2	0.7	1	1
General Disorders and Administration Site Conditions	**1**	**0.3**	**1**	**1**
Pyrexia	1	0.3	1	1
Infections and Infestations	**6**	**2**	**3**	**3**
Gastroenteritis	0	0	1	1
Gastroenteritis rotavirus	1	0.3	0	0
Influenza	1	0.3	1	1
Lung abscess	1	0.3	0	0
Pneumonia	1	0.3	1	1
Sepsis	1	0.3	0	0
Urinary tract infection	1	0.3	0	0
Pregnancy, Puerperium and Perinatal Conditions	**1**	**0.3**	**0**	**0**
Pregnancy	1	0.3	0	0
Respiratory, Thoracic and Mediastinal Disorders	**3**	**1**	**0**	**0**
Epistaxis	1	0.3	0	0
Obstructive airways disorder	1	0.3	0	0
Pleural effusion	1	0.3	0	0
Respiratory distress	1	0.3	0	0
Skin and Subcutaneous Tissue Disorders	**0**	**0**	**1**	**1**
Rash	0	0	1	1

Adapted from study report 036 Table 8-12. Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories. AE=adverse event.

Comment: There were 10 patients (3%) on the ertapenem arm compared to 6 patients (6%) on the ceftriaxone arm who experienced SAEs during the study drug and 14-day follow-up period.

One patient, in the ertapenem treatment group, reported a serious drug-related clinical and/or laboratory adverse event (0.3%, 95% CI [0,1.8]) and this patient experienced vomiting due to an overdose of ceftriaxone.

During the parenteral period, there were 5 patients (1.7 %) on the ertapenem arm compared to 1 patient on the ceftriaxone arm (1%) who experienced SAEs. On the ertapenem arm, this included: 5-year-old male developed moderate obstructive airway disorder; 16-month-old female experienced severe respiratory distress and pleural effusion; 7-month-old male experienced epitaxis associated with sepsis and thrombocytopenia; 2-year-old female had moderate rotavirus gastroenteritis and vomiting; 4-year-old male experienced mild vomiting who received mistakenly both ceftriaxone and ertapenem and received 1 dose of ceftriaxone in an amount 20% greater than the calculated dosage. The patient subsequently vomited twice which the investigator reported as being possibly related to the overdose of ceftriaxone. After the overdose of ceftriaxone, the patient received a total of 10 doses of ertapenem with no reported adverse events. On the ceftriaxone arm, a 6-year-old male developed a rash of mild intensity. One patient from the ertapenem treatment group and 1 patient from the ceftriaxone treatment group experienced serious drug-related clinical adverse events during parenteral therapy.

Discontinuations Due to Clinical Adverse Event During Parenteral Therapy

Four patients (1.3%) on the ertapenem treatment arm and 1 patient (1%) in the ceftriaxone treatment group discontinued parenteral therapy due to clinical adverse events. Patients who discontinued ertapenem due to clinical adverse event during parenteral included patients experiencing: severe cellulitis; epistaxis; and diarrhea; and one patient experiencing three different AEs including decreased appetite, diarrhea and lethargy. On the ceftriaxone arm, one patient was discontinued due to rash.

In the investigator's opinion, drug-related adverse events causing discontinuation of therapy on the ertapenem arm included: a 19-month old male who was discontinued from ertapenem therapy on Study Day 4 due to the development of severe diarrhea on Study Day 3. On the ceftriaxone arm, a 6-year old female was discontinued on Study Day 4 due to the development of a serious drug-related rash. In the investigator's opinion, the non drug-related adverse events causing discontinuation of patient's therapy included: cellulitis; moderate decreased appetite, diarrhea and lethargy; and epistaxis associated with sepsis and thrombocytopenia.

Overdose

Overdose is defined in the protocol as the administration of a dose of study drug exceeding the protocol specified dose by greater than 20%. Twelve patients had nonserious clinical adverse events of overdose during the parenteral therapy period. Ten patients (3.3%) receiving ertapenem and 2 patients (2%) receiving ceftriaxone experienced protocol defined overdoses during parenteral therapy administration. None of the overdoses were associated with an adverse event, and therefore all were considered nonserious adverse events. One patient from the ertapenem treatment group experienced a serious adverse event (vomiting) that, in the opinion of the investigator, was possibly related to study therapy. This patient however, mistakenly received an overdose of ceftriaxone prior to the adverse event and then continued to receive 10 doses of ertapenem with no additional events reported.

Deaths Reported During Study

There were no deaths reported during this study.

Laboratory Adverse Events

Laboratory Adverse Events Reported During Study Therapy and Follow-Up Period

The table below displays the number of patients with laboratory adverse events that occurred during study therapy and 14-day follow-up. There were 397 patients had at least one laboratory test and 66 of these patients had laboratory adverse events. There were 3 serious laboratory adverse events reported during parenteral study therapy. There were no additional serious laboratory adverse events reported in either group during oral therapy or the 14-day follow-up period.

Table 32 Laboratory Adverse Events Summary During Study Therapy and 14-Day Follow-Up Period (Treated Population)

	Ertapenem (N=303)		**Ceftriaxone** (N=100)	
Number of patients:	n	(%)‡	n	(%)‡
With at least 1 lab test postbaseline	300	-	97	-
With 1 or more AE	57	19	9	9.3
With no AE	243	81	88	90.7
With drug-related AE	25	8.3	4	4.1
With SAE	2	0.7	1	1
With drug-related SAE	0	0	0	0
Who died	0	0	0	0
Discontinued due to AE	0	0	0	0
Discontinued due to drug-related AE	0	0	0	0
Discontinued due to SAE	0	0	0	0
Discontinued due to drug-related SAE	0	0	0	0

Adapted from 036 study report Table 8-21. ‡The percent=number of patients within the laboratory adverse event category/number of patients with one or more laboratory tests postbaseline. AE=adverse event. SAE=serious adverse event.

The table below displays a comparison of laboratory adverse events during parenteral therapy and during study therapy and 14 day follow up.

Table 33 Laboratory Adverse Event Summary During Parenteral Therapy and During Study Therapy and 14-Day Follow-Up (Treated Population)

	During Parenteral Therapy				During Study Therapy and 14-Day Follow-Up			
	Ertapenem		Ceftriaxone		Ertapenem		Ceftriaxone	
Number of patients with at least 1 lab test postbaseline	(N=297)	-	(N=97)	-	(N=300)	-	(N=97)	-
Number (%) of patients:	n	%	n	%	n	%	n	%
With 1 or more AE	36	12.1	6	6.2	57	19	9	9.3
With no AE	261	87.9	91	93.8	243	81	88	90.7
With drug-related AE	18	6.1	2	2.1	25	8.3	4	4.1
With SAE	2	0.7	1	1	2	0.7	1	1
Who died	0	0	0	0	0	0	0	0
Discontinued due to AE	0	0	0	0	0	0	0	0
Discontinued due to SAE	0	0	0	0	0	0	0	0
Discontinued due to drug-related SAE	0	0	0	0	0	0	0	0

Adapted from 036 study report Table 8-15. AE=adverse event. SAE=serious adverse event.

The table below displays the number of patients with specific laboratory adverse events with an incidence ≥3% by laboratory test category occurring during the study therapy and 14-day follow-up period.

Table 34 Number (%) of Patients With Specific Laboratory Adverse Events (Incidence ≥3% in One or More Treatment Groups) by Laboratory Test Category During Study Therapy and 14-Day Follow-Up Period (Treated Population)

	Ertapenem (N=303)		**Ceftriaxone** (N=100)	
	n/m	%	n/m	%
Patients with 1 or more AE	57/300	19	9/97	9.3
Patients with no AE	243/300	81	88/97	90.7
Blood Chemistry Test	22/297	7.4	1/95	1.1
Alanine aminotransferase increased	**12/295**	**4.1**	**1/95**	**1.1**
Aspartate aminotransferase increased	**12/295**	**4.1**	**1/95**	**1.1**
C-reactive protein increased	1/8	12.5	0/3	0
Gamma-glutamyltransferase increased	1/8	12.5	0/2	0
Oxygen saturation decreased	1/1	100	0/†	-
Clinical Microbiology Test	2/11	18.2	0/†	-
Culture positive	1/1	100	0/†	-
Culture urine positive	1/2	50	0/†	-
Hematology Laboratory Test	36/295	12.2	7/97	7.2
Neutrophil count decreased	**21/292**	**7.2**	**3/96**	**3.1**
Reticulocyte count increased	1/1	100	0/†	-

Adapted from 036 study report Table 8-22. AE=adverse event. †Indicates there was no associated laboratory test or there were no patients for laboratory test was recorded postbaseline. n/m=Number of patients with laboratory adverse events/number of patients for whom the laboratory test was recorded postbaseline. Although a patient may have had 2 or more laboratory adverse events, the patient is counted only once in a category. The same patient may appear in different categories.

The most common laboratory adverse events during study therapy and 14-day follow-up were increased liver transaminases (AST and ALT) and decreased neutrophil count. In patients for whom follow-up information was available, the elevations were transient with follow-up values normalizing or within normal limits. None of these liver transaminases elevations were considered serious by the investigator and none resulted in the discontinuation of study therapy. None of the decreased neutrophil counts reported during oral therapy or 14-day follow-up were considered serious by the investigator or resulted in the discontinuation of study therapy.

Comment: Patients on the ertapenem arm demonstrated more frequently an increase in liver enzymes (ALT and AST) and decreases in neutrophil count compared with ceftriaxone.

Drug-Related Laboratory Adverse Events Reported During Study Therapy and Follow-Up Period

The table below displays patients with specific drug-related laboratory adverse events with an incidence ≥1% by laboratory test category occurring during the study therapy and follow-up period. As compared to the drug-related laboratory adverse events reported during parenteral therapy seven additional patients from the ertapenem treatment group and 2 from the ceftriaxone treatment group had drug-related laboratory adverse events during the oral therapy or 14-day follow-up period. Two additional patients in the ertapenem group and 1 additional patient in the ceftriaxone treatment group reported neutrophil count decreases during the oral therapy or 14-day follow-up period. One additional patient in the ertapenem treatment group and 1 additional patient in the ceftriaxone treatment group reported an increased AST and an increased ALT during the 14-day follow-up period.

Table 35 Number (%) of Patients With Specific Laboratory Adverse Events (Incidence ≥1 % in One or More Treatment Groups) by Laboratory Test Category During Study Therapy and 14-Day Follow-Up Period Treated Population Drug Related

	Ertapenem (N=303)		**Ceftriaxone** (N=100)	
	n/m	%	n/m	%
Patients with 1 or more drug-related AE	25/300	8.3	4/97	4.1
Patients with no drug-related AE	275/300	91.7	93/97	95.9
Blood Chemistry Test	10/297	3.4	1/95	1.1
Alanine aminotransferase increased	**6/295**	**2**	**1/95**	**1.1**
Aspartate aminotransferase increased	**6/295**	**2**	**1/95**	**1.1**
Blood urea decreased	2/107	1.9	0/36	0
Hematology Laboratory Test	18/295	6.1	3/97	3.1
Atypical lymphocytes increased	2/202	1	0/70	0
Eosinophil count increased	3/290	1	1/96	1
Neutrophil count decreased	**11/292**	**3.8**	**2/96**	**2.1**
White blood cell count decreased	3/295	1	0/97	0

Adapted from 036 study report Table 8-23. n/m=Number of patients with drug-related laboratory adverse events/number of patients for whom the laboratory test was recorded postbaseline. Although a patient may have had 2 or more laboratory adverse events, the patient is counted only once in a category. The same patient may appear in different categories.

Comment: The most commonly reported AE deemed by the investigator to have a relationship with the drug were neutrophil count decrease and increases in liver enzymes ALT and AST.

Drug-Related Laboratory Adverse Events Reported During Parenteral Therapy

The most common drug-related laboratory adverse events were increased liver transaminases (AST and ALT) and decreased neutrophil count during parenteral therapy. During parenteral therapy, 6 patients in the ertapenem treatment group reported adverse events of increased liver transaminases (AST, ALT). Two of these patients had elevated transaminase levels at baseline. In patients for whom follow-up information was available, elevations were transient with follow-up values normalizing or within normal limits. The highest liver transaminase values reported during ertapenem therapy were reported in one patient but the patient baseline ALT and AST values were reported within normal limits. The patient received 9 days (16 doses) of ertapenem and 4 days of oral amoxicillin/clavulanate. The highest ALT was reported as 8.2 times the upper limit of normal (ULN) and the highest AST was 8.9 times ULN (both elevated values were reported on Study Day 9). ALT and AST values obtained at the 14-day follow-up visit for this patient were normal. None of the increased liver transaminases reported during parenteral therapy were considered serious by the investigator or resulted in the discontinuation of study therapy.

Decreased neutrophil count was reported as an adverse clinical event during parenteral therapy with ertapenem in 9 patients (3.1%) and in 1 patient (1.1%) treated with ceftriaxone. None of the decreased neutrophil counts reported during parenteral therapy were considered serious by the investigator or resulted in the discontinuation of study therapy.

There were 3 patients (1.1 %) in the ertapenem group and 1 patient (1.1%) in the ceftriaxone treatment group reported drug-related eosinophilia. None of these patients experienced serious symptoms of systemic allergic reaction. Drug-related laboratory abnormalities were generally uncommon in both treatment groups and the incidence of drug-related laboratory adverse events was comparable between the two treatment groups.

Comment: The trend with laboratory AE during parenteral therapy is similar to study drug therapy and 14-day follow-up.

Serious Laboratory Adverse Events Reported During Parenteral Therapy

According to the number of patients with serious laboratory adverse events occurring during parenteral therapy, 2 patients (0.7%) in the ertapenem treatment group had serious laboratory adverse events during parenteral therapy: decreased white blood cell count and decreased platelet count and 1 patient (1%) in the ceftriaxone treatment group reported experiences of blood in urine and protein in urine.

There were no serious laboratory adverse events considered by the investigator to be drug-related during parenteral therapy. Of the patients experiencing laboratory SAEs occurring during parenteral therapy on ertapenem, a 7-month male experienced decreased platelet count and 10-year female experienced a decrease in white blood cell count. On the ceftriaxone arm, a 12-year female presented with blood and protein in the urine. There were no discontinuations from study therapy due to a laboratory adverse event during the administration of parenteral therapy.

Safety Conclusions

Ertapenem is generally well tolerated. The safety profile of ertapenem in children appears similar to that of ertapenem in adults. The safety profile of ertapenem is comparable to ceftriaxone in children based on the overall safety profile including the frequency of drug-related serious adverse events, drug-related adverse events, discontinuations due to drug-related adverse events, and the assessment of infusion-related local tolerability.

CONCLUSIONS:

Discussion

Ertapenem was previously demonstrated to be safe, effective and well-tolerated in adults. Ceftriaxone was administered at dosing frequencies similar to ertapenem thus allowing for a double-blind design without the need for placebo infusions. The dosing for ceftriaxone once or twice daily, based on the age group parameters, to maintain the double-blind. Ertapenem dosing regimens used in this study were based on the results from the single-dose PK study (protocol 028). Similar to the adult studies, this trial was limited to immune competent patients and because specific guidelines for pediatric patients with renal insufficiency were not available, patients with significant renal impairment (serum creatinine > 1.25 ULN) were excluded. Patients enrolled in this appear to generally be representative of the general pediatric population requiring parenteral antibiotics for UTI, SSTI and CAP.

The primary objective of this study was to evaluate safety and tolerability of ertapenem in pediatric patients in indications approved in adults. Safety data were collected in children receiving one or more doses of parenteral study therapy, thus collectively combining safety experience in children over 3 infectious diseases and allowing a comparison to safety results for ceftriaxone as well as to previously observed safety data with adults. A secondary objective was to evaluate efficacy, although the study was not designed as a noninferiority study. There were 404 patients enrolled, and 403 included in the evaluation of safety, 303 on ertapenem and 100 on ceftriaxone, who were distributed across the three disease indications. There were 153 patients 3-23 months of age, 225 patients 2-12 years and 25 patients 13-17 years. Although this age distribution is not equally distributed within age categories, safety data has been collected in younger age groups.

There were 93.8% of patients included in the MITT analysis, and 67.8% of all randomized patients were considered EPP. The clinical response was evaluated at the time of DCPT and at the follow-up visit 7-14 days after completing the study therapy (parenteral plus oral if given) which was defined as the TOC. The Sponsor considered the MITT approach primary for efficacy. Patients in the MITT who had a valid post-treatment assessment, defined as at least 4 days post treatment for UTI or at least 1 day for CAP and SSTI, were included in the analyses and patients lost to follow up were excluded from the analyses unless they had previously failed. The FDA requested an MITT sensitivity analysis be performed per indication, in which all patients missing an assessment within the TOC window were assumed to be failures. EPP analyses were performed accounting for potential confounders affecting TOC. The primary efficacy response was evaluated on the clinical EPP and MITT populations for CAP and SSTI and microbiologically for UTI. The TOC response rates for ertapenem were 96% for CAP, 87% for UTI, and 95% for SSTI in the EPP analyses and 94% for CAP, 85% for UTI and 90% for SSTI in the applicant's MITT analysis. The response rates overall were lower for ertapenem than for ceftriaxone; however, there was no statistically meaningful differences between the groups. Overall, ertapenem is comparable to ceftriaxone for the indications studied. A large number of the failures observed in the ertapenem group may be attributable to a baseline imbalance of drug-

resistant pathogens. The response rates for ertapenem in the pediatric population overall appear to be consistent with those observed in the adult population.

The most commonly reported adverse events during the parenteral therapy were diarrhea, infusion site pain, and vomiting. The AE profile is similar to that observed in adults. There were no seizures reported and no patient who discontinued therapy due to drug-related rash. The most common laboratory adverse events reported were decreases in neutrophil count and increase in ALT and AST. The incidence of drug-related AST and ALT elevations were similar and tended to be lower in pediatric patients as compared to adults. As noted with adults, transaminase elevations in pediatric patients tended to peak during drug treatment and resolve or improve with the completion of therapy. The laboratory safety profile can be compared with ceftriaxone. Adverse events included in the 14-day follow-up period are similar. Diarrhea is a known side effect of amoxicillin/clavulanate and was increased in both treatment groups during the oral therapy period. Seven patients received ertapenem therapy IM and reportedly tolerated it well.

Conclusion

Ertapemen appears to be safe and effective for the treatment of pediatric patients 3 months to 17 years of age with serious community-acquired pneumonia, urinary tract infection or skin and soft tissue infection treated.

Protocol 038-Complicated Intra-Abdominal Infection and Acute Pelvic Infection

A Prospective, Multicenter, Randomized, Open-Label, Comparative Study to Evaluate the Safety, Tolerability, and Efficacy of Ertapenem Sodium (MK-0826) Versus Ticarcillin/Clavulanate in the Treatment of Complicated Intra-abdominal Infections and Acute Pelvic Infections in Pediatric Patients

STUDY DESIGN

The 038 phase 2 study was a multicenter, randomized (3:1 ratio), open-label, comparative study to investigate the safety and tolerability of ertapenem in pediatric patients in the treatment of IAI or API. The primary objective was to evaluate safety. Evaluation of efficacy was a secondary objective. There were 15 study sites participating in this study, 12 in the U.S. and 3 internationally. Patients with API were given antibiotic therapy for 3-14 days and 5-14 days for IAI. Ertapenem was given IV or IM 1 g single daily dose for patients 13-17 years or 15 mg/ kg BID for patients <13 years. Ticarcillin/clavulanate was the comparator and given IV every 4-6 hours. Patients were screened within 24 hours prior to study entry. Clinical response was assessed at DCPT and TOC. Microbiological response was assessed separately for each pathogen identified at prestudy. The protocol was amended three times (see Protocol Amendments for Protocol 038). TOC was at 2-4 weeks posttherapy in API. TOC was at 3-5 weeks posttherapy with complicated IAI.

Inclusion Criteria

The following inclusion and exclusion criteria are taken from the protocol.

General Inclusion Criteria

1. Patient was male or female, aged 3 months to 17 years.

2. Patient had one of the following infections: complicated intra-abdominal infection or acute pelvic infection, which required parenteral therapy.

3. Female patients who had reached menarche had a negative serum pregnancy test (β-hCG) prior to enrollment into the study (except in patients with acute pelvic infections who had just delivered within 2 weeks of study entry). NOTE: Females of childbearing potential with a negative urine pregnancy test were eligible for enrollment; however, this had to be followed-up with a confirmed negative serum pregnancy test (β-hCG) as soon as possible. Use of adequate birth control measures were discussed with the investigator.

4. Patient had an infection known or thought by the investigator to be caused by microorganisms susceptible to both parenteral study antibiotics.

5. Patient had a parent or legal guardian available to give informed consent and deemed sufficiently reliable to return for the child's follow-up visit. If capable, patients 12 years and older provided assent.

Inclusion Criteria for Patients With Intra-abdominal Infections

1. Patient had one of the following diagnoses with evidence of intraperitoneal infection: appendicitis complicated by either appendiceal perforation or periappendicular abscess; acute gastric, duodenal, or gall bladder perforations, only if operated on >24 hours after perforation occurred; traumatic perforation of the intestines, only if operated on >12 hours after perforation occurred; secondary peritonitis due to perforated viscus, postoperative or other focus of infection (but not spontaneous bacterial peritonitis, or peritonitis associated with cirrhosis or chronic ascites); other intra-abdominal bacterial abscess (including of liver and spleen).

2. Patient had an intra-abdominal infection judged by the investigator to require 5 to 14 days of parenteral therapy.

3. Patient was enrolled postoperatively (or intraoperatively), based upon visual confirmation (presence of pus within the abdominal cavity) of an intraabdominal infection **OR** was enrolled preoperatively on the basis of compelling preoperative clinical findings (evidence of systemic inflammatory response). NOTE: Postoperative (or intraoperative) enrollment was encouraged. If, however, preoperative data were available that strongly suggested an appropriate diagnosis for entry, then preoperative enrollment was allowed.

4. Patient had received adequate surgical intervention.

OR

Patient was anticipated to undergo such surgical intervention within 24 hours of study entry **AND** met EACH of the following criteria:

- Evidence of systemic inflammatory response as demonstrated by AT LEAST ONE of the following:
- fever defined as oral temperature >38°C (100.4°F), tympanic temperature >38.5°C (101.2°F), or rectal/core temperature >38.6°C (101.5°F)
- elevated WBC (>15,000/mm^3)
- drop in blood pressure (except for patients with septic shock, who were excluded)
- increased pulse and respiratory rates
- hypoxemia
- altered mental status

- **AND** Physical findings consistent with intra-abdominal infection, such as abdominal pain and/or tenderness, localized or diffuse abdominal wall rigidity, a mass, ileus.
- **AND** Supportive radiologic findings in abdomen such as intraperitoneal abscess detected on CT scan films or an ultrasound. NOTE: Appropriate procedures were ones in which all communications between the gastrointestinal tract and the

peritoneal cavity were closed, no necrotic intestine was left, and all infected collections were drained and may have included open laparotomy, percutaneous drainage of an abscess, or laparoscopic surgery, at the initial procedure.

Inclusion Criteria for Patients With Acute Pelvic Infections

1. Patient had a diagnosis of acute pelvic infection, judged by the investigator to require 3 to 14 days of parenteral therapy.

2. Patient had AT LEAST ONE of the following: oral temperature >38°C (100.4°F), tympanic temperature >38.5°C (101.2°F), or a rectal/core temperature >38.6°C (101.5°F); WBC >10,500/mm^3; WBC differential indicating >10% immature granulocytes (band forms).

3. Patient had AT LEAST ONE of the following: pelvic, abdominal, or uterine pain, or cramping; pelvic, abdominal, or uterine tenderness; sonographic or other imaging study that suggested a pelvic abscess or infection.

4. Patient had experienced ONE OF the following: vaginal delivery, cesarean section, or gynecologic surgery ≥24 hours and within 1 month prior to enrollment; symptoms of acute pelvic infection within the first 24 hours following any of the above procedures and their oral temperature had been at least 101.5°F (38.6°C) in this time period; diagnosis of septic abortion and an illness of enough severity to require a minimum of 3 full days of parenteral IV therapy.

5. Patient had microbiological specimens from the endometrium or other infected site collected within 24 hours of enrollment into the study and prior to administration of study antibiotic using a method that avoided vaginal contamination (e.g., Unimar Pipelle™) and was sent for culture and susceptibility testing.

Exclusion Criteria

General Exclusion Criteria

1. Patient was <3 months or ≥18 years of age.

2. Patient was in a situation (e.g., unreliable foster care) or had a condition which, in the opinion of the investigator, might interfere with optimal participation in the study.

3. The patient had an infection known at admission to be caused by pathogens resistant to either of the study drugs.

4. Patient had a history of serious allergy, hypersensitivity (e.g., anaphylaxis), or any adverse reaction to carbapenem antibiotics (such as imipenem), meropenem, or any cephalosporins or penicillins or to lidocaine or other similar local anesthetic agents if IM

injection was to be used. NOTE: Patients with a history of mild (nonurticarial) rash to penicillins or other β-lactams could be enrolled at the investigator's discretion.

5. Patient had clinically significant laboratory abnormalities:
    - Absolute neutrophil count (ANC) <1000/mm^3
    - Platelet count <50,000/mm^3
    - Bilirubin >3 times the age-specific upper limit of normal (ULN)
    - ALT or AST >3 times the age-specific ULN
    - Creatinine >1.25 times the age-specific ULN
    - Alkaline phosphatase >3 times the age-specific ULN

6. Patient was female AND: was pregnant or fertile and was not practicing adequate methods of contraception; was planning to become pregnant within 1 month of the study; or was nursing. NOTE: Females who were nursing were not to be discouraged from breastfeeding for the sole purpose of enrolling in the study. Females who chose to defer breast-feeding until 5 days after the last dose of study drug to allow elimination of drug from breast milk were eligible.

7. Patient had acute or chronic renal insufficiency.

8. Patient had septic shock or acute hemodynamic instability including those requiring pressor support. NOTE: The requirement of volume repletion (but not pressors) for support of blood pressure was allowed.

9. Patient had cystic fibrosis.

10. Patient had one of the following conditions: rapidly progressive or terminal illness; response to antibiotic regimens described in this study was considered unlikely; patient was considered unlikely to survive the study period.

11. Patient required concomitant systemic antibacterials in addition to those designated in the 2 study groups.

12. Patient had signs of meningitis, such as nuchal rigidity, papilledema, or findings of meningitis. NOTE: CSF penetration of ertapenem has not yet been determined.

13. Patient had received >24 hours of systemic antimicrobial therapy known to be effective against the presumed or documented etiologic pathogen(s) within the 72-hour period immediately prior to enrollment, unless there was a clear indication that the patient had failed the prior regimen. NOTE: Evidence that the patient had failed the prior antibiotic regimen would include continued fever, persistence or worsening of symptoms related to the index infection, and/or persistent laboratory or radiographic changes, and positive cultures consistent with the index infection.

14. Patient had a concurrent infection or other illness that, in the opinion of the investigator, that would interfere with the evaluation of the response to the study antibiotic or pose additional risk in administering the study drug to the patient.

15. Patient was receiving chronic immunosuppressive therapy such as use of high dose corticosteroids (≥1 mg/kg of prednisone daily or equivalent), including organ transplant patients.

16. Patient had a clinical diagnosis of AIDS by current CDC criteria or another congenital or acquired immune deficiency resulting in a compromised response to bacterial infection.

17. Patient had acute hepatic failure or acute decompensation of chronic hepatic dysfunction.

18. Patient was participating in or had participated in any other clinical study involving the administration of investigational medication, biological products, or use of a device at the time of presentation, during the course of the study, or during the previous 30 days. NOTE: Participation in clinical studies involving currently marketed medications was permitted.

19. Patient had previously participated in this study at any time.

20. The patient had a history of seizures other than an uncomplicated febrile seizure.

21. Inability to obtain signed informed consent from a patient capable of giving consent, or when a parent/legal representative had provided consent, the inability to obtain assent from a patient considered capable of giving assent for any reason.

Exclusion Criteria for Patients With Intra-abdominal Infections

1. Patient had any of the following primary diagnoses: infections limited to the hollow viscus, such as simple cholecystitis and simple appendicitis; ischemic bowel disease without perforation; acute suppurative cholangitis or acute necrotizing pancreatitis. NOTE: These diagnoses were not eligible because the primary intervention for the former is ERCP, and for the latter, a single operative intervention is not definitive; traumatic bowel perforation with surgery within 12 hours or perforation of gastro duodenal ulcers with surgery within 24 hours. NOTE: These were considered situations of peritoneal soiling before infection had become established; other intra-abdominal processes in which the primary etiology was not likely to be infectious.

2. Patient was to be managed by Staged Abdominal Repair (STAR) or open abdomen technique.

Exclusion Criteria for Patients With Acute Pelvic Infections

1. Patient had a diagnosis of a) pelvic inflammatory disease; b) tubo-ovarian abscess; or c) postoperative abdominal wall infection.

2. Patient had a positive test for chlamydia. NOTE: Patients were to be tested for chlamydia infection if appropriate, as judged by the investigator.

3. Patient had an active gynecologic malignancy unless the tumor had been adequately resected by surgery.

4. Patient was receiving chemotherapy or radiation therapy.

Protocol Amendments for Protocol 038

There were 3 protocol amendments to the original protocol were implemented during the study. The following are some of the noteworthy changes included in those amendments taken from the applicant:

Protocol Amendment 038-01

- Modified protocol to allow enrollment of children 3 months to 23 months of age. Redefined the dosage for ertapenem from a single daily dose to 15 mg/kg twice daily dosing for children 3 months to 12 years, while ertapenem dosing for 13 to 17 year olds remained a single 1-g dose.
- Updated randomization by indication (HAP, complicated IAI, or API) to include age category (3 to 23 months, 2 to 12 years and 13 to 17 years).
- The test-of-cure follow-up visit was changed for patients enrolled with complicated IAI and will be performed between 3 and 5 weeks rather than at 2 to 4 weeks for the other indications (HAP & API).
- Redefined the safety analysis period to be study therapy plus 14 days posttherapy.
- Added vomiting (1%) to the list of most common drug-related clinical adverse experiences to be consistent with the patient's informed consent.
- Added the Protocol 028 (single-dose pediatric pharmacokinetic and safety study) data for the children 3 to 23 months of age. Entire section was updated with the most current data and analysis from Protocol 028.
- Redefined the Inclusion criteria to allow enrollment of patients 3 months to 17 years, added the necessity for assent of patients 12 years of age and older. Inclusion criteria for fever based upon indication was replaced with a fever definition for all patients in the study.
- Redefined the General Exclusion Criteria for prior treatment failure, breast feeding females, grossly overweight or grossly underweight patients, and removed exclusion of patients younger than 2 years.
- Redefined the Data Analysis Variables and Time Points of Interest.
- Modified preparation instructions for ertapenem IM and IV preparation to include patients age 3 months to 23 months and modified the dosage calculations to reflect twice daily administration of 15 mg/kg to patients age 3 months to 12 years. Storage requirement for vials was changed from ≤25°C to <25°C. Reconstitution volumes for ertapenem were modified.

Protocol Amendment 038-02

- Redefined prestudy pregnancy test requirements for patients who delivered within 2 weeks of study entry.

- Redefined Unit for total WBC <4500 was changed to/mm^3 for consistency with other units in the inclusion criteria.
- Added additional information about study drug overdose.
- Added susceptibility testing requirements for *Streptococcus pneumoniae* and *Haemophilus influenzae* isolates, microbiological testing requirements for penicillin resistant pathogens and that testing for beta-lactamase production or susceptibility to ampicillin testing for all *H. influenzae* pathogens identified.
- Redefined the zone diameter range for *Haemophilus influenzae*.

Protocol Amendment 038-03

- Deleted the Hospital-Acquired Pneumonia (HAP) indication from the study.
- Redefined patient enrollment to "Approximately 75 patients will be randomized to treatment with ertapenem, about 50 patients in the IAI indication and 25 patients in the API indication"
- Added daily dose should not exceed 500 mg (total daily dose not to exceed 1 g/day) for children 3 to 12 years old.

RESULTS

Demographics and Baseline Characteristics

The table below displays the baseline characteristics of all randomized patients in the study.

Table 36 Baseline Patient Characteristics by Treatment Group (Randomized Population)

	Ertapenem (N=84)		**Ticarcillin/Clavulanate** (N=28)		Total (N=112)	
	n	%	n	%	n	%
Gender						
Female	52	61.9	16	57.1	68	60.7
Male	32	38.1	12	42.9	44	39.3
Race						
Asian	1	1.2	1	3.6	2	1.8
Black	5	6	4	14.3	9	8
European	1	1.2	0	0	1	0.9
Hispanic	54	64.3	17	60.7	71	63.4
Multiracial	1	1.2	1	3.6	2	1.8
White	22	26.2	5	17.9	27	24.1
Age (Years)						
2-12 years	39	46.4	13	46.4	52	46.4
Mean	7.8		8.2		7.9	
Median	8		9		8.5	
Range	2-12		2-12		2-12	
13-17 years	45	53.6	15	53.6	60	53.6
Mean	15.2		15.1		15.1	
Median	15		15		15	
Range	13-17		13-17		13-17	
Stratum by Diagnosis and Age						
API	25	29.8	8	28.6	33	29.5
13-17 years	25	29.8	8	28.6	33	29.5
IAI	59	70.2	20	71.4	79	70.5
2-12 years	39	46.4	13	46.4	52	46.4
13-17 years	20	23.8	7	25	27	24.1

Adapted from 038 study report Table 6-6

The 2 treatment groups were generally similar with respect to these baseline characteristics. The female population is somewhat larger than the male population because all the patients enrolled in the API stratum were female. Both male and female patients were enrolled in the IAI stratum. Acute pelvic infection (not to be confused with pelvic inflammatory disease), consists of infectious complications of vaginal delivery, cesarean section or gynecologic surgery such as hysterectomy, and is therefore uncommon in children, being limited to females of child-bearing age.

Comment: Treatment groups with respect to age, gender, and race appear to be well-balanced, considering only female patients were enrolled in the API stratum.

Patient Evaluability

There were 112 patients from 13 of the 15 participating sites randomized into treatment groups; 84 were randomized to receive ertapenem and 28 were randomized to receive ticarcillin/clavulanate. There were 79 patients randomized in the IAI stratum, 59 to receive ertapenem and 20 to receive ticarcillin/clavulanate. Of the 79 patients with IAI, 7 patients never received study therapy, 3 in the ertapenem group and 4 in the ticarcillin/clavulanate group. These patients are included in the demographic displays but are excluded from the safety analysis, the evaluable per-protocol and MITT populations. There were 33 patients were randomized to API, 25 to receive ertapenem and 8 to receive ticarcillin/clavulanate. One API patient, was randomized to the ticarcillin/clavulanate treatment group but is not included in any of the patient population, including the randomized population, or demographic displays. Although randomized to the study, a signed consent was not obtained, the patient was not treated with study therapy and no data are available for this patient.

The primary analysis for this study was evaluation of safety. Of the 112 patients enrolled, 105 patients received at least one dose of study therapy and are included in the safety analysis. There were 81 patients who received ertapenem and 24 patients who received ticarcillin/clavulanate. All 105 of the treated patients are included in the clinical MITT population used for the efficacy analysis. For the IAI indication, 72 intra-abdominal infection patients were included in MITT population; 56 patients received ertapenem and 16 patients received ticarcillin/clavulanate. For the API indication, 33 acute pelvic infection patients were included in MITT population; 25 patients received ertapenem and 8 patients received ticarcillin/clavulanate.

The 2 treatment groups were generally similar with respect to reasons that patients discontinued from study. Any patient who returned to the posttherapy follow-up visit and was assigned a clinical outcome at that visit was considered to have completed the study, regardless of the clinical outcome assigned or any action taken regarding discontinuation of study drug therapy. Each patient was assigned only one reason for discontinuation from study drug therapy and one reason for discontinuation from study.

The table below displays the number and the proportion of patients in each of the study populations and the reasons that patients were considered to be non-evaluable for the per protocol and the MITT efficacy analyses.

Table 37 Patient Accounting of Evaluability (Randomized Population)

Population	**Ertapenem** (N=84) n (%)	**Ticarcillin/Clavulanate** (N=28) n (%)	**Total** (N=112) n (%)
Clinically MITT Evaluable Population			
Clinically MITT evaluable	81 (96.4)	24 (85.7)	105 (93.8)
Clinically MITT non-evaluable	3 (3.6)	4 (14.3)	7 (6.3)
Minimal disease definition not met	0 (0)	1 (3.6)	1 (0.9)
Patient did not receive at least one dose of study therapy	3 (3.6)	4 (14.3)	7 (6.3)
Clinically Evaluable Population			
Clinically evaluable	66 (78.6)	15 (53.6)	81 (72.3)
Clinically non-evaluable	18 (21.4)	13 (46.4)	31 (27.7)
Baseline microbiology—resistant pathogen	2 (2.4)	4 (14.3)	6 (5.4)
Concomitant antibiotics violation	1 (1.2)	3 (10.7)	4 (3.6)
Disease definition not met	1(1.2)	1 (3.6)	2 (1.8)
Inadequate/inappropriate study therapy	6 (7.1)	5 (17.9)	11 (9.8)
Prior antibiotics violation	1 (1.2)	0 (0)	1 (0.9)
Test-of-cure window violation	10 (11.9)	4 (14.3)	14 (12.5)
Microbiologically MITT Evaluable Population			
Microbiologically MITT evaluable	64 (76.2)	20 (71.4)	84 (75)
Microbiologically MITT non-evaluable	20 (23.8)	8 (28.6)	28 (25)
Baseline microbiology—no pathogen isolated	15 (17.9)	2 (7.1)	17 (15.2)
Baseline microbiology notperformed/inadequate	4 (4.8)	4 (14.3)	8 (7.1)
Not clinically MITT evaluable	3 (3.6)	4 (14.3)	7 (6.3)
Microbiologically Evaluable Population			
Microbiologically evaluable	51 (60.7)	12 (42.9)	63 (56.3)
Microbiologically non-evaluable	33 (39.3)	16 (57.1)	49 (43.8)
Baseline microbiology—no pathogen isolated	15 (17.9)	2 (7.1)	17 (15.2)
Baseline microbiology not performed/inadequate	4(4.8)	4 (14.3)	8 (7.1)
Not clinically evaluable	18 (21.4)	13 (46.4)	31 (27.7)

Adapted from 038 study report Table 6-5 This table contains counts of patient evaluability Therefore, although a patient may have one or more reasons for being non- evaluable, the patient will be counted only once in the non-evaluable category

The most common reasons why patients were excluded from the clinically evaluable population were test-of-cure window violations and inadequate or inappropriate courses of study therapy. Most of these patients were lost to follow-up. Within each population, the treatment groups were considered similar with respect to reasons not evaluable.

Baseline Characteristics of Patients With Intra-Abdominal Infections

The table below displays a summary of primary diagnoses, including the primary site of infection and infectious process, specific to the intra-abdominal infection for the clinical MITT population.

Table 38 Summary of Primary Diagnoses and Related Baseline Characteristics (Clinical MITT Population) Intra-abdominal Infection Stratum

	Ertapenem (N=56)		**Ticarcillin/Clavulanate** (N=16)		Total (N=72)	
	n	%	n	%	n	%
Infection Start Details						
Post operative infection	0	0	1	6.3	1	1.4
Spontaneous infection	56	100	15	93.8	71	98.6
Anatomic Site of Origin of Current Infection						
Small intestine	1	1.8	0	0	1	1.4
Vermiform appendix	55	98.2	16	100	71	98.6
Infectious Process †						
Abscess	17	30.4	6	37.5	23	31.9
-Multiple	5	8.9	2	12.5	7	9.7
-Single	12	21.4	4	25	16	22.2
Gangrene	5	8.9	3	18.8	8	11.1
Pelvic abscess	1	1.8	0	0	1	1.4
Peritonitis‡	35	62.5	10	62.5	45	62.5
-Generalized	22	39.3	7	43.8	29	40.3
-Localized	12	21.4	3	18.8	15	20.8
Other:						
Appendicitis perforated	7	12.5	2	12.5	9	12.5
Gastrointestinal perforation	4	7.1	0	0	4	5.6
Glasgow Coma Score §						
N	54		15		69	
Mean	14 9		14.7		14.9	
Range	13-15		12-15		12-15	

Adapted from 038 study report Table 6-15 †Patients could have more than one infectious process recorded ‡Peritonitis was not specified as localized or generalized for one patient §Glasgow Coma Score or Modified Coma Score for Infants Glasgow coma score was not done for 3 patients because the patients were too sedated from surgery to be examined N=Total number of patients in the treatment group n=Total number of patients with the diagnosis

In the clinical MITT population there were 72 intra-abdominal infection patients, 56 in the ertapenem treatment group and 16 in the ticarcillin/clavulanate treatment group, enrolled from 10 study sites. All treated patients are included in the clinical MITT population.

The treatment groups appeared similar with respect to the distribution of patients among the primary sites of infection and infectious processes. There were 55 patients (98.2%) in the

ertapenem group and 16 patients (100%) in the ticarcillin/clavulanate group who had a primary diagnosis of complicated appendicitis defined as appendiceal perforation or periappendicular abscess. Only 1 patient in the ertapenem treatment group had a primary diagnosis of a gastrointestinal perforation of the small intestine. All infectious processes that were active in a patient were counted, that is, a patient may have had more than 1 infectious process counted. The most common infectious processes were peritonitis and abscess. The Glasgow Coma Score mean, median and distribution were similar between the 2 treatment groups.

The table below displays the number of types of initial interventions including types of irrigation, drains, and wound closures for the intra-abdominal infection clinical MITT population. All surgical procedures were done prior to the first dose of study therapy. The most common type of intervention in both treatment groups was open, occurring in 43 patients (76.8%) in the ertapenem group and 12 patients (75%) in the ticarcillin/clavulanate group.

Table 39 Summary of Abdominal Procedures—Initial Procedures Clinical MITT Population) Intra-abdominal Infection Stratum

	Ertapenem (N=56)		**Ticarcillin/Clavulanate** (N=16)		Total (N=72)	
	n	%	n	%	n	%
Timing of Procedure						
Initial procedure; before first dose of study drug	56	100	16	100	72	100
Procedure						
Laparoscopic	11	19.6	3	18.8	14	19.4
Open	43	76.8	12	75	55	76.4
Percutaneous	2	3.6	1	6.3	3	4.2
Irrigation						
Entire abdomen	34	60.7	14	87.5	48	66.7
Local	16	28.6	2	12.5	18	25
None	6	10.7	0	0	6	8.3
Drains						
No	29	51.8	6	37.5	35	48.6
Yes	27	48.2	10	62.5	37	51.4
Wound						
Delayed primary closure	8	14.3	1	6.3	9	12.5
Primary closure	48	85.7	15	93.8	63	87.5

Adapted from 038 study report Table 6-16 n=The total number of patients with procedure type Patients could have more than one procedure recorded N=Number of patients per treatment group stratified as complicated intra-abdominal infection

Baseline Characteristics of Patients With Acute Pelvic Infections

The table below presents the baseline characteristics of patients with acute pelvic infections in the clinical MITT population. There were 33 API patients, 25 in the ertapenem treatment group and 8 in the ticarcillin/clavulanate treatment group, enrolled from 3 study sites. All patients

enrolled in the API stratum were female. Obstetrical infection included infections after vaginal delivery, cesarean section or miscarriage.

Table 40 Summary of Primary Diagnoses and Related Baseline Characteristics (Clinical MITT Population) Acute Pelvic Infection Stratum

	Ertapenem (N=25)		**Ticarcillin/Clavulanate** (N=8)		Total (N=33)	
	n	%	n	%	n	%
Infection Start Details						
Post operative obstetrical infection	8	32	4	50	12	36.4
Spontaneous obstetrical infection	17	68	4	50	21	63.6
Infectious Process						
Endomyometritis	12	48	4	50	16	17
Septic abortion	13	52	4	50	17	51.5

Adapted from study report 038 Table 6-20 N=Total number of patients in the treatment group n=Total number of patients with the diagnosis

Eight patients (32%) in the ertapenem group and 4 patients (50%) in the ticarcillin/clavualante group had post-operative obstetrical infection. Seventeen patients (68%) in the ertapenem group and 4 patients (50%) in the ticarcillin/clavualante group had spontaneous obstetrical infection.

Comment: The treatment groups appear to be evenly distributed between endomyometritis and septic abortion. There are slight more discrepancies between the numbers of treatment groups with post operative and spontaneous obstetrical infections, however the numbers of patients are small with treatment groups, so one cannot make meaningful conclusions.

EFFICACY

Clinical Outcome

EPP Clinical Efficacy Evaluation

The table below presents patients, in the clinical EPP population, with a favorable clinical response assessment at the TOC visit.

Table 41 Proportion of Patients With a Favorable Clinical Response Assessment At Test-of-Cure Visit Displayed by Disease Stratum (Clinical EPP Population)

	Ertapenem (N=66)			**Ticarcillin/Clavulanate** (N=15)		
	n/m	%	(95% CI)	n/m	%	(95% CI)
IAI	36/43	83.7	(69.3, 93.2)	7/11	63.6	(30.8, 89.1)
API	23/23	100	(85.2, 100)	4/4	100	-
Overall	59/66	89.4	(79.4, 95.6)	11/15	73.3	(44.9, 92.2)

Adapted from study report 038 Table 7-6 EPP=Evaluable per protocol N=Number of Clinical EPP patients in each treatment group n/m=Number of patients with favorable assessment /number of patients in the Clinical EPP population

Comment: The observed response rates in the IAI indication were higher in the ertapenem group than in ticarcillin/clavulanate with 84% vs. 64%.

MITT Clinical Efficacy Evaluation

The table below presents patients, in the Clinical MITT population, with a favorable clinical response assessment at the posttreatment visit.

Table 42 Proportion of Patients With a Favorable Clinical Response Assessment At Posttreatment Visit Displayed by Disease Stratum (Clinical MITT Population)

	Ertapenem (N=81)			**Ticarcillin/Clavulanate** (N=24)		
	n/m	%	(95% CI)	n/m	%	(95% CI)
IAI	43/50	86.7	(77.3, 96.1)	11/15	73.3	(44.9, 92.2)
API	25/25	100	(86.3, 100)	8/8	100	-
Overall	68/75	91.4	(85, 97.7)	19/23	82.6	(61.2, 95)

Adapted from study report 038 Table 7-1.

At the posttreatment visit, the response rates were 86.7% (IAI) and 100% (API), in the ertapenem group; and were 73.3% (IAI) and 100% (API), in the ticarcillin/clavulanate group. In the ertapenem treatment group the clinical response rates were generally high.

In both treatment groups, lower IAI response rates were observed in this clinical EPP analysis than in the clinical MITT analysis. This resulted primarily from the exclusion of patients whose final assessment of “cure” in the MITT analysis occurred prior to the TOC window. The EPP results are consistent with the findings in the clinical MITT analysis.

MITT Clinical Efficacy Evaluation–Sensitivity Analysis

The table presented below displays the sensitivity analysis performed in the MITT population.

Table 43 Proportion of Patients With a Favorable Clinical Response Assessment At Test-of-Cure Visit Displayed by Disease Stratum—Sensitivity Analysis (Clinical MITT Population)

	Ertapenem (N=81)			**Ticarcillin/Clavulanate** (N=24)		
	n/m	%	(95% CI)	n/m	%	(95% CI)
IAI	37/56	66.4	(54, 78.8)	8/16	50	(24.7, 75.3)
API	25/25	100	(86.3, 100)	8/8	100	-
Overall	62/81	77.4	(68.3, 86.5)	16/24	66.7	(44.7, 84.4)

Adapted from protocol 038 Table 7-5.

Notably, response rates for IAI patients in the clinical efficacy sensitivity evaluation for the MITT population at the TOC visit were approximately 20 percentage points lower for both treatment groups compared to those from the clinical efficacy evaluation for the MITT population posttreatment visit. This may have been due to the fact that 6 patients in the ertapenem group and 1 patient in the ticarcillin group were considered failures and did not have any posttreatment assessments. An additional 6 patients in the ertapenem group and 3 in the ticarcillin/clavulanate group were assessed as clinical cures by the investigator prior to the TOC window but were consequently classified as failures in the sensitivity analysis because they did not have an assessment within the TOC window. The response rates for API patients from the clinical efficacy sensitivity evaluation for the MITT population TOC visit, were the same as those from the clinical efficacy evaluation for the MITT population posttreatment visit.

Microbiological Outcome

EPP Microbiological Efficacy Evaluation

The table below presents the proportion of patients, in the Microbiologic EPP population, with a favorable microbiological response assessment at the TOC visit.

Table 44 Proportion of Patients With a Favorable Microbiological Response Assessment at Test-of-Cure Visit Displayed by Disease Stratum (Microbiologic EPP Population)

	Ertapenem (N=51)			**Ticarcillin/Clavulanate** (N=12)		
	n/m	%	(95% CI)	n/m	%	(95% CI)
IAI	27/33	81.8	(64.5, 93)	6/8	75	-
API	18/18	100	(81.5, 100)	4/4	100	-
Overall	45/51	88.2	(76.1, 95.6)	10/12	83.3	(51.6, 97.9)

Adapted from 038 study report Table 7-9. n/m=Number of patients with favorable assessment /number of patients in the Microbiologic EPP population. CI=Confidence interval. IAI=Complicated intra-abdominal infection. API Acute pelvic infection. EPP=Evaluable per protocol.

These results are consistent with the findings in the microbiologic MITT analysis. In both treatment groups, lower IAI response rates in this analysis relative to the microbiologic MITT

analysis resulted primarily from the exclusion of patients who had a final overall "favorable" microbiologic response assessment in the MITT analysis prior to the TOC window. Observed response rates in the IAI indication were higher in the ertapenem group than in the ticarcillin/clavulanate group.

MITT Microbiologic Efficacy Evaluation

The table below presents the proportion of patients, in the microbiologic MITT population, with a favorable microbiological response assessment at the posttreatment visit.

Table 45 Proportion of Patients With a Favorable Microbiological Response Assessment At Posttreatment Visit Displayed by Disease Stratum (Microbiologic MITT Population)

	Ertapenem (N=64)			**Ticarcillin/Clavulanate** (N=20)		
	n/m	%	(95% CI)	n/m	%	(95% CI)
IAI	33/39	85.6	(74.5, 96.6)	9/11	81.8	(48.2, 97.7)
API	20/20	100	(83.2, 100)	8/8	100	-
Overall	53/59	91.4	(84.2, 98.5)	17/19	89.5	(66.9, 98.7)

Adapted from study report 038 Table 7-7.

At the posttreatment visit, the response rates were 85.6% (IAI) and 100% (API), in the ertapenem group; and were 81.8% (IAI) and 100% (API), in the ticarcillin/clavulanate group. In both treatment groups the microbiologic response rates were generally high.

MITT Microbiological Efficacy Evaluation-Sensitivity Analysis

A sensitivity analysis was performed in an additional evaluation of the proportion of patients, in the MITT population, with a favorable microbiological response assessment. All patients who had missing or indeterminate outcome at the TOC visit were considered "failures."

The table below presents patients in the microbiologic MITT population who had a favorable microbiological response assessment at the TOC visit.

Table 46 Proportion of Patients With a Favorable Microbiological Response Assessment at Test-of-Cure Visit Displayed by Disease Stratum–Sensitivity Analysis (Microbiologic MITT population)

	Ertapenem (N=64)			**Ticarcillin/Clavulanate** (N=20)		
	n/m	%	(95% CI)	n/m	%	(95% CI)
IAI	27/44	61.7	(47.3, 76)	7/12	58.3	(27.7, 84.8)
API	20/20	100	(83.2, 100)	8/8	100	-
Overall	47/64	75.4	(64.29, 86)	15/20	75	(50.9, 91.3)

Adapted from study report 038 Table 7-8.

The response rates for IAI patients from the microbiologic efficacy sensitivity evaluation for the MITT population, at the TOC visit, were approximately 24 percentage points lower for both treatment groups compared to those from the clinical efficacy evaluation for the MITT population, at the posttreatment visit. This was primarily due to the fact that 5 patients in the ertapenem group and 1 patient in the ticarcillin/clavulanate group were considered failures in this more conservative analysis because they did not have any posttreatment assessments. An additional 6 patients in the ertapenem group and 2 patients in the ticarcillin/clavulanate group were assessed as having an overall favorable microbiologic response prior to the TOC window but were consequently classified as failures in the sensitivity analysis because they did not have an assessment within the TOC window.

Comment: Response rates for API patients from the microbiologic efficacy sensitivity evaluation for the MITT population, at the TOC visit, appear to be similar to those from the clinical efficacy evaluation for the MITT population, at the posttreatment visit.

Pathogen Outcome

MITT Clinical Efficacy Evaluation by Pathogen

The table below presents the proportion of favorable clinical response assessment at TOC, by disease and pathogens as indicated in the approved label.

To be included in this evaluation, a clinical MITT patient had to have a baseline pathogen isolated. The most common species was *Escherichia coli* for both IAI and API patients. *Bacteroides* species, including *B. fragilis* and *B. thetaiotaomicron* were also commonly treated in IAI patients. The observed response rates for these pathogens were higher in the ertapenem treatment group.

Table 47 Proportion of Favorable Clinical Response Assessment at Test-of-Cure Visit Displayed by Disease Stratum and Baseline Pathogen (Total Isolates) (Microbiological EPP Population)

		Ertapenem (N=51)			**Ticarcillin/Clavulanate** (N=12)		
		Observed† Response (%)			Observed† Response (%)		
		n/m	%	(95% CI)	n/m	%	(95% CI)
IAI	**Gram-positive anaerobic bacilli**	**2/2**	**100**	-	-	-	-
	Eubacterium lentum	1/1	100	-	-	-	-
	Gram-positive anaerobic cocci	**8/10**	**80**	**(44.4, 97.5)**	**4/4**	**100**	-
	Peptostreptococcus anaerobius	1/1	100	-	-	-	-
	Peptostreptococcus micros	2/2	100	-	1/1	100	-
	Peptostreptococcus sp.	-	-	-	-	100	-
	Gram-negative aerobic bacilli	**33/42**	**78.6**	**(63.2, 89.7)**	**7/10**	**70**	**34.8, 93.3)**
	Escherichia coli	24/30	80	(61 4, 92 3)	4/6	66 7	-
	Gram-negative anaerobic coccobacilli	**23/30**	**76.7**	**(57.7, 90.1)**	**7/10**	**70**	**(34 8, 93.3)**
	Bacteroides	1/1	100	-	-	-	-
	Bacteroides caccae	2/3	66 7	-	1/1	100	-
	Bacteroides distasonis	0/1	0	-	0/1	0	-
	Bacteroides fragilis	9/10	90	(55 5, 99 7)	2/3	66 7	-
	Bacteroides sp	0/1	0	-	-	-	-
	Bacteroides splanchnicus	1/1	100	-	-	-	-
	Bacteroides thetaiotaomicron	7/8	87 5	-	2/3	66 7	-
	Bacteroides uniformis	1/2	50	-	-	-	-
	Bacteroides vulgatus	1/2	50	-	-	-	-
API	**Gram-positive anaerobic cocci**	**3/3**	**100**	-	-	-	-
	Peptostreptococcus anaerobius	1/1	100	-	-	-	-
	Gram-negative aerobic bacilli	**14/14**	**100**	**(76.8, 100)**	**1/1**	**100**	-
	Escherichia coli	8/8	100	-	1/1	100	-
	Gram-negative anaerobic bacilli	**1/1**	**100**	-	**1/1**	**100**	-
	Prevotella melaninogenica	-	-	-	1/1	100	-
	Gram-negative anaerobic coccobacilli	**3/3**	**100**	-	**2/2**	**100**	-
	Bacteroides thetaiotaomicron	1/1	100	-	-	-	-

Adapted from study report 038 Table 11-34 N=Number of Microbiologic EPP patients in each treatment group n/m=Number of pathogens associated with a favorable clinical assessment/number of baseline pathogens for patients who had a clinical assessment CI=Confidence interval

SAFETY

Clinical Adverse Events

Clinical Adverse Events Reported During Study Therapy and Follow-Up Period

The table below displays the number of all treated patients with clinical adverse events, by category, which occurred during study therapy and the 14-day follow-up period.

Table 48 Clinical Adverse Event Summary During Study Therapy and 14-Day Follow-Up Period (Treated Population)

	Ertapenem (N=81)		**Ticarcillin/Clavulanate** (N=24)	
	n	%	n	%
Number of patients:				
With 1 or more AE	32	39.5	16	66.7
With no AE	49	60.5	8	33.3
With drug-related AE	10	12.3	6	25
With SAE	11	13.6	3	12.5
With drug-related SAE	1	1.2	0	0
Who died	0	0	0	0
Discontinued due to AE	2	2.5	2	8.3
Discontinued due to drug-related AE	1	1.2	1	4.2
Discontinued due to SAE	2	2.5	0	0
Discontinued due to drug-related SAE	1	1.2	0	0

Adapted from 038 study report Table 8-5. AE=adverse event. SAE=serious adverse event.

The table below displays the number of patients with specific clinical adverse events, irrespective of drug relationship, with an incidence ≥3% in one or more treatment groups, by system organ class, occurring during study therapy and the 14-day follow-up period.

Table 49 Number (%) of Patients With Specific Clinical Adverse Events (Incidence ≥3% in One or More Treatment Groups) by System Organ Class During Study Therapy and 14-Day Follow-Up Period (Treated Population)

	Ertapenem (N=81)		**Ticarcillin/Clavulanate** (N=24)	
	n	%	n	%
Patients with one or more AE	32	39.5	16	66.7
Patients with no AE	49	60.5	8	33.3
Gastrointestinal Disorders	**15**	**18.5**	**3**	**12.5**
Abdominal pain	4	4.9	1	4.2
Diarrhea	5	6.2	1	4.2
Diarrhea hemorrhagic	0	0	1	4.2
Nausea	3	3.7	0	0
Vomiting	3	3.7	2	8.3
General Disorders and Administration Site Conditions	**10**	**12.3**	**9**	**37.5**
Infusion-site burning	1	1.2	1	4.2
Infusion-site erythema	1	1.2	2	8.3
Infusion-site pain	7	8.6	5	20.8
Infusion-site reaction	0	0	1	4.2
Infusion-site swelling	1	1.2	1	4.2
Infusion-site warmth	2	2.5	1	4.2
Edema peripheral	0	0	1	4.2
Edema peripheral	0	0	1	4.2
Pyrexia	3	3.7	2	8.3
Infections and Infestations	**8**	**9.9**	**7**	**29.2**
Abdominal abscess	4	4.9	1	4.2
Bronchitis	0	0	1	4.2
Herpes simplex	0	0	1	4.2
Postoperative infection	0	0	1	4.2
Vaginal candidiasis	0	0	1	4.2
Wound infection	0	0	2	8.3
Injury, Poisoning and Procedural Complications	**4**	**4.9**	**1**	**4.2**
Lumbar puncture headache	0	0	1	4.2
Overdose[†]	3	3.7	0	0
Musculoskeletal and Connective Tissue Disorders	**1**	**1.2**	**1**	**4.2**
Arthralgia	1	1.2	1	4.2
Psychiatric Disorders	**1**	**1.2**	**1**	**4.2**
Insomnia	1	1.2	1	4.2

Renal and Urinary Disorders	**0**	**0**	**1**	**4.2**
Renal insufficiency	0	0	1	4.2
Reproductive System and Breast Disorders	**0**	**0**	**1**	**4.2**
Hydrocele	0	0	1	4.2
Respiratory, Thoracic and Mediastinal Disorders	**5**	**6.2**	**2**	**8.3**
Cough	3	3.7	0	0
Pleural effusion	1	1.2	1	4.2
Respiratory distress	0	0	1	4.2
Respiratory failure	0	0	1	4.2
Skin and Subcutaneous Tissue Disorders	**4**	**4.9**	**4**	**16.7**
Erythema	0	0	1	4.2
Rash	2	2.5	2	8.3
Scab	0	0	1	4.2

Adapted from 038 study report Table 8-6 AE=adverse event †Accidental overdoses refer to reports of unintentional overdose where no associated adverse effects were noted Duration of reported overdoses is reflected in the dose by duration table Although a patient may have had two or more clinical adverse experiences, the patient is counted only once within a category The same patient may appear in different categories

Of the 105 patients treated, 32 patients (39.5%) in the ertapenem group, and 16 patients (66.7%) in the ticarcillin/clavulanate group had a clinical adverse experience during the study therapy and the follow-up period. The incidence of clinical adverse events was similar between the two treatment groups.

The table below displays patients with drug-related clinical adverse events with an incidence >0% in one or more treatment groups, by system organ class, that occurred during the study therapy and the 14-day follow-up period. A drug-related adverse event was one determined by the investigator to be possibly, probably, or definitely related to study drug.

Table 50 Number (%) of Patients With Specific Clinical Adverse Events (Incidence >0% in One or More Treatment Groups) by System Organ Class During Study Therapy and 14-Day Follow-Up Period Treated Population) Drug Related

	Ertapenem (N=81)		**Ticarcillin/Clavulanate** (N=24)	
	n	%	n	%
Patients with 1 or more drug-related AE	10	12.3	6	25
Patients with no drug-related AE	71	87.7	18	75
Gastrointestinal Disorders	3	3.7	1	4.2
Diarrhea	3	3.7	1	4.2
General Disorders and Administration Site Conditions	6	7.4	3	12.5
Infusion-site burning	1	1.2	1	4.2
Infusion-site erythema	1	1.2	0	0
Infusion-site pain	6	7.4	3	12.5
Infusion-site pruritus	1	1.2	0	0
Infusion-site reaction	0	0	1	4.2
Infusion-site warmth	1	1.2	1	4.2
Infections and Infestations	0	0	1	4.2
Vaginal candidiasis	0	0	1	4.2
Psychiatric Disorders	0	0	1	4.2
Insomnia	0	0	1	4.2
Skin and Subcutaneous Tissue Disorders	0	0	1	4.2
Rash	0	0	1	4.2
Vascular Disorders	1	1.2	0	0
Hot flush	1	1.2	0	0

Adapted from 038 study report Table 8-7 AE=adverse event Although a patient may have had two or more clinical adverse events, the patient is counted only once within a category The same patient may appear in different categories

The incidence of clinical drug-related adverse events was similar between the two treatment groups and is identical to the drug-related adverse events reported during parenteral therapy. No additional drug-related adverse events were reported during the 14-day follow-up period.

Overall, 48 patients (45.7%) had clinical adverse events reported during study therapy and the 14-day follow-up period. The incidence of clinical adverse events, including serious adverse events, deaths, drug-related adverse events, and discontinuations due to adverse events, were similar in the two treatment groups.

Clinical Adverse Events Reported During Parenteral Therapy

Overall, 39 patients (37.1%) had clinical adverse events. The incidence of clinical adverse events including SAEs, deaths, drug-related adverse events, and discontinuations due to adverse events, appear to be similar in the two treatment groups. There was 1 patient with a serious drug-related clinical adverse event, which caused discontinuation of study therapy, reported in the ertapenem group and none reported in the ticarcillin/clavulanate group.

Of the 105 treated patients, there were 25 patients (30.9%) in the ertapenem group, and 14 patients (58.3%) in the ticarcillin/clavulanate group who had clinical AEs during parenteral therapy. The most common clinical AE for the ertapenem group were infusion-site pain (8.6%), diarrhea (6.2%) and nausea (3.7%). There were 3 patients (3.7%) in the ertapenem group reporting a nonserious clinical AE of overdose during the parenteral therapy period. The most common clinical adverse events for the ticarcillin/clavulanate group were infusion-site pain (20.8%), infusion-site erythema (8.3%), pyrexia (8.3%) and rash (8.3%).

Of the 105 treated patients, there were 10 patients (12.3%) in the ertapenem group and 6 patients (25%) in the ticarcillin/clavulanate group who had a drug-related clinical AE during parenteral therapy. The most common drug-related clinical adverse events were infusion-site pain and diarrhea. The incidence of infusion site pain was 7.4% in the ertapenem group and 12.5% in the ticarcillin/clavulanate group. There were 3 patients (3.7%) in the ertapenem group and 1 patient (4.2%) in the ticarcillin/clavulanate group had an AE of diarrhea considered drug-related by the investigator. The cases of diarrhea were mild or moderate in intensity with duration of 2-6 days. One patient on ertapenem had diarrhea of moderate intensity which the investigator considered serious and drug-related and caused discontinuation of study therapy.

Comment: Overall, the incidence of clinical drug-related adverse events was similar between the two treatment groups.

Serious Adverse Events

Serious Clinical Adverse Events Reported During Study Therapy and Follow-Up Period

The table below displays patients with serious clinical adverse events with incidence >0% in one or more treatment groups, by system organ class occurring during study therapy and the 14-day follow-up period.

Table 51 Number (%) of Patients With Specific Serious Clinical Adverse Events (Incidence >0% in One or More Treatment Groups) by System Organ Class During Study Therapy and Follow-Up Period (Treated Population)

	Ertapenem (N=81)		**Ticarcillin/Clavulanate** (N=24)	
	n	%	n	%
Patients with 1 or more AE	11	13.6	3	12.5
Patients with no AE	70	86.4	21	87.5
Gastrointestinal Disorders	5	6.2	1	4.2
Abdominal pain	1	1.2	1	4.2
Constipation	1	1.2	0	0
Diarrhea	1	1.2	0	0
Small intestinal obstruction	2	2.5	0	0
Vomiting	0	0	1	4.2
General Disorders and Administration Site Conditions	1	1.2	0	0
Pyrexia	1	1.2	0	0
Infections and Infestations	6	7.4	1	4.2
Abdominal abscess	4	4.9	0	0
Pelvic abscess	2	2.5	0	0
Postoperative infection	0	0	1	4.2
Reproductive System and Breast Disorders	0	0	1	4.2
Hydrocele	0	0	1	4.2

Adapted from 038 study report Table 8-11 AE=adverse event Although a patient may have had two or more clinical adverse events, the patient is counted only once within a category The same patient may appear in different categories

Of the total 105 treated patients, 11 patients (13.6%) in the ertapenem group and 3 patients (12.5%) in the ticarcillin/clavulanate group had clinical SAEs. In addition to the serious clinical adverse events reported during parenteral therapy, there are 7 patients (8.6%) in the ertapenem group and 2 patients (8.3%) in the ticarcillin/clavulanate group who reported serious clinical adverse events during the 14-day follow-up period. There were no serious drug-related adverse events with an onset occurring during the 14-day follow-up period.

There were a total of 11 patients on the ertapenem arm that experienced serious clinical adverse events during study therapy and 4-day follow-up period and 3 on the ticarcillin/clavulanate arm.

A 9-year-old female experienced pelvic abscess and pyrexia; a 11-year-old male abdominal abscess; a 3-year-old male with small intestinal obstruction; a 3-year-old with diarrhea; a 12-year-old female with pelvic abscess; a 13-year-old male with abdominal abscess; a 6-year-old male with constipation; 11-year-old male with abdominal abscess; a 7-year-old male with abdominal abscess; and a 15-year-old male with small intestinal obstruction. On the ticarcillin arm, a 12-year-old male with postoperative infection; a 16-year-old male with abdominal pain and vomiting; and a 7-year-old with hydrocele.

There were no serious laboratory adverse events reported during the study in either treatment group.

Serious Clinical Adverse Events Reported During Parenteral Therapy

There were 4/81 patients (4.9%) in the ertapenem group, and 1/24 patient (4.2%) in the ticarcillin/clavulanate group had serious clinical adverse events occur during parenteral therapy. The majority of serious adverse events occurring during parenteral therapy were related to complications resulting from the primary infection under study. There were 2 patients who experienced gastrointestinal disorders: a 3-year-old male who developed small intestinal obstruction and a 3-year-old male with diarrhea. There were two patients who experienced abscesses: a 12-year-old female with pelvic abscess and a 7-year-old male with abdominal abscess. On the ticarcillin arm, only one patient experienced a serious adverse event during the parenteral therapy period: a 7-year-old male who experienced hydrocele.

Comment: Overall, the incidence of serious adverse events reported during parenteral therapy was similar between the 2 treatment groups.

Discontinuations from Parenteral Therapy Due to AE

Patients discontinued from parenteral study therapy due to a clinical adverse event irrespective of drug relationship occurring during parenteral therapy, included 2 patients (2.5%) in the ertapenem treatment group and 2 patients (8.3%) in the ticarcillin/clavulanate treatment group. Of these, 1 patient in the ertapenem treatment group and 1 patient in the ticarcillin/clavulanate treatment group were discontinued from study therapy due to non drug-related AE, and 1 patient on ertapenem and 1 patient on ticarcillin/clavulanate were discontinued due to drug-related AEs. Patients discontinued due to clinical adverse event during parenteral therapy on the ertapenem arm included: 3-year male with moderate diarrhea which was considered drug-related; and a 7-year-old male with abdominal abscess which was considered non drug-related. On the ticarcillin/clavulanate patients included: 16-year old male with a mild rash which was considered drug-related; and 17-year-old female with a wound infection which was considered non drug-related.

Overdose

Overdose defined in the protocol is the administration of a dose of study drug exceeding the protocol specified dose by greater than 20%. None of these were associated with an adverse

event therefore all were considered nonserious adverse events. None of the patients in the ticarcillin/clavulanate group reported overdose as an adverse event.

Deaths Reported During Study Therapy

There were no deaths reported during the study in either treatment group.

Laboratory Adverse Events

The table below presents a summary of laboratory adverse events occurring during study therapy and 14-day follow-up.

Table 52 Laboratory Adverse Event Summary During Study Therapy and 14-Day Follow-Up Period (Treated Population)

	Ertapenem (N=81)		**Ticarcillin/Clavulanate** (N=24)	
	n	%	n	%
Number of patients:				
With at least 1 lab test postbaseline	79	-	24	-
With 1 or more AE	6	7.6	4	16.7
With no AE	73	92.4	20	83.3
With drug-related AE	3	3.8	2	8.3
With SAE	0	0	0	0
With drug-related SAE	0	0	0	0
Who died	0	0	0	0
D/c due to AE	0	0	0	0
D/c due to drug-related AE	0	0	0	0
D/c due to SAE	0	0	0	0
D/c due to drug-related SAE	0	0	0	0

Adapted from study report 036 Table 8-18. AE=adverse event. SAE=serious adverse event. D/c=discontinued.

The table below presents patients with specific laboratory adverse events >0% during study therapy and 14-day follow-up by test category.

Table 53 Number of Patients With Specific Laboratory Adverse Events (Incidence >0% in One or More Treatment Groups) by Laboratory Test Category During Study Therapy and 14-Day Follow-Up Period (Treated Population)

	Eratpenem (N=81)		**Ticarcillin/Clavulante** (N=24)	
	n/m	%	n/m	%
Patients with 1 or more AE	6/79	7.6	4/24	
Patients with no AE	73/79	92.4	20/24	83.3
Blood Chemistry Test	5/79	6.3	2/24	8.3
Alanine aminotransferase increased	2/75	2.7	1/23	4.3
Asparate aminotransferase increased	2/78	2.6	1/23	4.3
Blood albumin decreased	1/78	1.3	0/23	0
Blood glucose decreased	1/78	1.3	0/23	0
Gamma-glutamyltransferase increased	1/1	100	0	-
Protein total increased	0/77	0	1/23	34.3
Hematology Laboratory Test	3/78	3.8	3/24	12.5
Hematocrit decreased	0/78	0	1/24	4.2
Hemoglobulin decreased	1/78	1.3	1/24	4.2
Red blood cell count decreased	1/77	1.3	2/23	8.7
White blood cell count decreased	1/78	1.3	0/24	0
Hemostatic Function Test	1/61	1.6	0/19	0
Activated partial thromboplastin time prolonged	1/59	1.7	0/19	0
Prothrombin time prolonged	1/59	1.7	0/19	0
Urinalysis Test	1/73	1.4	1/22	4.5
Glucose urine present	1/73	1.4	0/22	0
Nitrate urine present	0	-	1/1	100

Adapted from study report 038 Table 8-19. n/m=number of patients with laboratory adverse events/number of patients for whom the laboratory test was recorded postbaseline.

Drug-Related Laboratory Adverse Events

The table below presents the laboratory adverse events with > 0% incidence considered drug-related, occurring during study therapy and follow-up period.

Table 54 Number (%) of Patients With Specific Laboratory Adverse Events (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

	Ertapenem (N=81)		**Ticarcillin/Clavulanate** (N=24)	
	n/m	%	n/m	%
Patients with 1 or more drug-related AE	3/79	3.8	2/24	8.3
Patients with no drug-related AE	76/79	96.2	22/24	91.7
Blood Chemistry Test	**2/79**	**2.5**	**1/24**	**4.2**
Alanine aminotransferase increased	2/75	2.7	1/23	4.3
Aspartate aminotransferase increased	2/78	2.6	1/23	4.3
Hematology Laboratory Test	**2/78**	**2.6**	**1/24**	**4.2**
Haemoglobin decreased	1/78	1.3	0/24	0
Platelet count increased	1/77	1.3	1/23	4.3
Hemostatic Function Test	**1/61**	**1.6**	**0/19**	**0**
Activated partial thromboplastin time prolonged	1/59	1.7	0/19	0
Prothrombin time prolonged	1/59	1.7	0/19	0

Adapted from 038 study report Table 8-17 AE=adverse event n/m = number of patients with laboratory adverse events/number of patients for whom the laboratory test was recorded postbaseline Although a patient may have had two or more laboratory adverse events, the patient is counted only once in a category The same patient may appear in different categories

Safety Conclusions

Ertapenem is generally well tolerated. The safety profile of ertapenem in children appears similar to that of ertapenem in adults. The safety profile of ertapenem is comparable to ticarcillin/clavulanate in children based on the overall safety profile including the frequency of drug-related serious adverse events, drug-related adverse events, discontinuations due to drug-related adverse events, and the assessment of infusion-related local tolerability.

CONCLUSIONS

Discussion

Ertapenem in complicated IAI or API is approved for adults and appears to be well-tolerated. The same dosing regimen was utilized in this study as protocol 036 using 15 mg/kg BID for 3 months-12 years and 1 g once a day for 13-17 years, based on protocol 028, the PK single dose study. An open-label study design was implemented as the comparator, ticarcillin/clavulanate, is administered every 4-6 hours which would have necessitated matching placebo administration. The inclusion/exclusion criteria were designed to enroll patients who would require parenteral therapy up to 14 days, with 3:1 randomization to ertapenem or ticarcillin. As with study 036, patients with significant renal impairment were excluded as there were no specific guidelines available for pediatric use.

This study randomized 112 patients from the U.S., Mexico and Brazil, of whom 105 received one or more doses of study drug and were included in the safety evaluation. There were 47 patients 2-12 years of age and 58 patients 13-17 years of age, with two thirds with IAI and one third with API. Patients enrolled with API were all female, as expected.

The primary objective of this study was to evaluate safety in indications previously studied in adults. Efficacy evaluation was a secondary objective.

There were 93.8% of patients included in the MITT and 73.2% in the EPP. EPP overall response rates were 89% for ertapenem and 73% for ticarcillin/clavulanate and the MITT response rates in the applicant's analysis were 91% for ertapenem and 83% for ticarcillin/clavulanate. The TOC was defined as 2-4 weeks posttherapy for API and 3-5 weeks posttherapy for IAI. All patients with a valid posttreatment assessment, defined as at least 1 day, were included in the MITT analyses and patients lost to follow-up prior to that point were excluded unless they had previously failed. To address this, an MITT sensitivity analysis was performed by indication where all patients missing an assessment within the TOC window were assumed to be failures. EPP analyses accounted for potential confounders affecting the TOC outcome.

There was one patient in the IAI stratum that had a perforated Meckel's diverticulum with localized peritonitis. All other IAI patients had a ruptured appendix; more than 30% of these had intra-abdominal abscess and 62% in each treatment group had evidence of peritonitis. There were 75% or more patients who were managed initially by an open surgical procedure; 20% had laparoscopy and 4% had a percutaneous procedure only. In API, half of the patients had endomyometritis associated with an obstetrical procedure and the remainder had septic abortion. This study enrolled patients into two age strata, from 3 months of age; however, the study failed to enroll any patients from 3 months to 2 years of age. This fact may be attributed to fewer patients in that age group experiencing API or IAI. The mean duration of therapy was 5.9 days in the ertapenem arm and 7 days in the ticarcillin/clavulanate group. Adverse events were common in this group of patients with complicated and surgically managed infections. There was one

serious adverse event reported of diarrhea in a patient with IAI. This was the only patient to discontinue ertapenem due to a drug-related AE. No patients reported serious laboratory AE nor were discontinued. The proportion of patients with drug-related laboratory events were 13% in the ertapenem group and 33% in the ticarcillin/clavulanate group. The most commonly reported drug-related AEs during therapy and follow-up were diarrhea and infusion site pain. Neither seizures nor drug-related rashes were reported. The most common drug-related laboratory adverse events were ALT and AST elevations. There were no reports of neutrophil count decreases, as reported in the previous study. The liver enzyme increases tended to occur during therapy and improve or resolve upon completion of therapy, as observed in the adult population and in protocol 036. Therapy administered by IM was only given to 1 patient in the ertapenem group and appeared well tolerated.

Overall, ertapenem appears comparable to ticarcillin/clavunate for the indications studied. The response rates for ertapenem in the pediatric population overall appear to be consistent with the rates observed in the adult population.

Conclusion

In pediatric patients 2 to 17 years of age with complicated IAI and API treated for up to 14 days with parenteral administration of ertapenem (15 mg/kg BID for 2 to 12 year olds or 1 g per day for 13 to 17 year olds) ertapenem appears generally well tolerated. The safety profile of ertapenem in children is similar to that of ertapenem in adults and is comparable to ticarcillin/clavulanate in children based on the overall safety profile including the frequency of drug-related adverse events, discontinuations due to drug-related adverse events, and the assessment of infusion-related local tolerability.

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