European Medicines Agency

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Product name: **Invanz**
Procedure No. **Invanz-H-389-II-11**

SCIENTIFIC DISCUSSION

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1 Introduction

Ertapenem sodium is a sterile, synthetic, long-acting, parental, 1β-methylcarbapenem, that is structurally related to β-lactam antibiotics with activity against a wide range of gram-positive and gram-negative aerobic and anaerobic bacteria.

The bactericidal activity of ertapenem results from the inhibition of cell wall synthesis and is mediated through ertapenem binding to penicillin binding proteins.
Ertapenem sodium is a white to off-white hygroscopic, crystalline solid. It is soluble in water and 0.9% sodium chloride solution, practically insoluble in ethanol, and insoluble in isopropyl acetate and tetrahydrofuran.

Invanz is supplied as sterile lyophilized powder for intravenous infusion after reconstitution with appropriate diluent and transfer to 50 ml 0.9% Sodium Chloride Injection; or for intramuscular injection following reconstitution with 3.2 ml of 1% lidocaine hydrochloride. Each vial contains 1.046 grams (g) ertapenem sodium, equivalent to 1 g ertapenem.

The initial Marketing Authorisation was granted on 18 April 2002 by the European Commission.

In November 2004 the MAH submitted the present type II variation to include children 3 months to 17 years for the current approved indications:
"Treatment of the following infections in adults when caused by bacteria known or very likely to be susceptible to ertapenem and when parenteral therapy is required:

- Intra-abdominal infections
- Community acquired pneumonia
- Acute gynaecological infections"

This variation application is based on a MAH´s commitment, when the product was first authorised in the EU, to provide paediatric data by the end of 2004. The MAH is also in the process of complying with an FDA written request for paediatric data and that Agency has given guidance on the design of the studies, including the choice of comparators for the safety/efficacy clinical trials. These safety/efficacy trials go beyond the scope of the EU Marketing Authorisation (MA) in that only three of the five infectious diseases that are licensed in the USA are also authorised in the EU for adults. The EU MA indications are for community acquired pneumonia (CAP), acute gynaecological infections and intra-abdominal infections (IAI). The two following indications: skin and soft tissue infections (SSTI) and urinary tract infections (UTI) were applied for but are not authorised in the EU.

Dosages used in the safety/efficacy clinical trials were based on data from PK trials covering the age ranges 3 to 23 months, 2 to 12 years and 13 to 17 years. The goal of the PK investigations was to identify dosages in the children that resulted in plasma levels similar to those seen in adults receiving the standard, authorised dose of 1 g daily.

Two separate safety/efficacy clinical trials were conducted:

Protocol 036 (P036) was a double-blind RCT comparing Invanz with ceftriaxone in the treatment of children with CAP, UTI or SSTI. There were 303 treated in the Invanz group (108 CAP) and 94 in the ceftriaxone group (35 CAP). Ceftriaxone was chosen as comparator, because it is licensed for paediatric use in the USA for the three indications. It is likely that the product is also nationally licensed widely in the EU for paediatric use in CAP.

Protocol 038 (P038) was an open RCT comparing Invanz with ticarcillin/clavulanate (T/C) in the treatment of children with IAI or acute pelvic infections (API). There were 56 IAI and 25 API treated in the Invanz group and 25 IAI and 8 API in the T/C group. T/C is licensed for paediatric use in the USA for both indications. This combination is licensed nationally for these indications in the EU and there is a paediatric posology. Actual usage may differ, however, across the EU, where in some countries the drug is regarded largely as an antipseudomonal penicillin. The open nature of the trial was justified on ethical grounds: the different dosage schedules for the two treatments would have required unacceptable interventions in order to preserve blind administration.

The choice of comparators can sometimes raise issues. However, in this instance, further information on comparative efficacy has come from comparing the responses to treatment in this group of paediatric patients with those in adults in the RCTs previously submitted for the EU MA application for Invanz for the same types of infectious diseases.

The MAH stated that the primary objective of the paediatric programme 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. In accordance with regulatory guidance, paediatric efficacy in these indications is demonstrated by results from the comparator controlled paediatric studies supported additionally by data from adequate, well controlled clinical trials in adults which were the basis of the original Marketing Application.

2 Non-clinical aspects

Non-clinical studies of Invanz submitted with the original application for the MA included an intravenous five-week infant rhesus monkey study and intravenous studies of 5, 14 and 27 weeks in juvenile rhesus monkeys.
The overall repeat dose toxicity findings are presented in the Module 6 of this EPAR (p. 7-8).
In addition, in the dossier supporting this variation application, the MAH has reviewed the toxicological findings in the infant and juvenile monkeys.
Further to the assessment of the above-mentioned data, there is no concern over the use of Invanz at the doses used in the clinical trials in children.

3 Clinical aspects

3.1. Clinical pharmacology

Pharmacokinetic studies
The main PK study was Protocol 028 (P028). The goal of P 028 was to establish dosages in children aged 3 to 23 months, 2 to 12 years and 13 to 17 years that would replicate the plasma concentrations achieved in adults with the standard 1 g dose given daily by means of a 30 minute infusion. The summary of the study design is given in a tabulated form overleaf.

Protocol (Title) [Reference]	Study Objectives	Study Design	Treatment Groups	Total Number of Patients N (M/F)
028 (An open, intravenous study to evaluate the plasma concentration profiles of MK-0826 in patients aged 3 months to 17 years)	(1) To evaluate and compare ertapenem plasma concentration profiles and pharmacokinetic parameters [AUC(0-∞), clearance, Ceoi, and t½] obtained from 3- to 23-month-, 2- to 12-year-, and 13- to 17-year-old children or adolescents administered ertapenem 20-mg/kg or 40-mg/kg IV and 3- to 23-month and 2- to 12-year olds administered 15-mg/kg IV to historical data from adults administered ertapenem 1 g or 2 g IV; (2) To evaluate and compare ertapenem plasma concentration profiles and pharmacokinetic parameters [AUC(0-∞), clearance, and t½] among 3- to 23-month-, 2- to 12-year-, and 13- to 17-year-old children or adolescents administered ertapenem 20-mg/kg or 40-mg/kg IV and among 3- to 23-month and 2-to 12-year olds administered 15 mg/kg IV; (3) To evaluate and compare ertapenem plasma concentration profiles and pharmacokinetic parameters [AUC(0-∞), clearance, and t½] obtained from 3- to 6-month-, 7- to 12-month-, 13- to 23-month-, 2- to 6-year-, 7- to 12-year-, and 13- to 17-year-old children or adolescents administered ertapenem 15, 20, or 40 mg/kg to each other and to historical data from adults administered ertapenem 1 g or 2 g IV; (4) To evaluate whether the total ertapenem plasma concentrations 12 hours postinfusion (C12 hr) are ≥4 µg/ml (the MIC breakpoint for anticipated pathogens) after administration of 20 mg/kg or 40 mg/kg IV to 3- to 6-month-, 7- to 12-month-, 13- to 23-month-, 2- to 6-year-, 7- to 12-year-, and 13- to 17-year-old children or adolescents; (5) To determine the total ertapenem plasma concentrations 6 hours postinfusion (C6 hr) after administration of 15 mg/kg IV to children ages 3 to 23 months and 2 to 12 years; (6) To evaluate the fraction of unbound ertapenem at selected time points for 3- to 23-month-, 2- to 6-year-, 7- to 12-year-, and 13- to 17-year-old age groups; (7) To calculate the estimated AUC(0-24 hr) at steady state of ertapenem that would occur after administration of 15 mg/kg IV b.i.d. in children aged 3 to 23 months and 2 to 12 years [calculated by multiplying the AUC(0-∞) of ertapenem obtained after single doses of 15 mg/kg by a factor of 2]; (8) To evaluate the safety and tolerability of ertapenem 15, 20, or 40 mg/kg in children ages 3 to 23 months and 2 to 12 years and 20 mg/kg or 40 mg/kg in children or adolescents ages 13 to 17 years.	An open-label, single IV dose study design in hospitalized, clinically stable patients. Blood samples collected at specified time points up to 24 hours postdose were assayed for total and unbound ertapenem for determination of plasma ertapenem pharmacokinetic parameters. Urine samples collected up to 24 hours postdose were assayed for ertapenem for the determination of urinary excretion of unchanged drug.	Single I.V. doses of 20- or 40-mg/kg infused over 30 minutes to patients 3 to 23 months, 2 to 12 years, and 13 to 17 years of age. Single I.V. doses of 15 mg/kg infused over 30 minutes to patients 3 to 23 months and 2 to 12 years of age.	Total N=84 3 to 23 months (24/19) 2 to 12 years (10/18) 13 to 17 years (8/5)

Ceoi = concentration at **e**nd **o**f **i**nfusion (i.e. after 30 min)

Pharmacokinetic data for an additional 3 patients in the 13 to 17 years group were obtained during the course of the safety/efficacy trial P036.

The following Tables illustrate PK data relevant to the trial objectives set out in the summary tabulation in the previous page.

Table 1

Mean Plasma Concentrations of Total Ertapenem Following Single 15-, 20-, and 40-mg/kg IV Doses Administered to 3- to 23-Month and 2- to 12-Year-Old Paediatric Patients

Age Group (Dose)	Arithmetic Mean Plasma Concentrations (µg/ml)							
	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	24 hr
3 to 23 months								
(15 mg/kg)	103.8	57.3	43.6	23.7	13.5	8.2	2.5	--
(20 mg/kg)	126.8	87.6	58.7	28.4	--	12.0	3.4	0.4
(40 mg/kg)	199.1	144.1	95.7	58.0	--	20.2	7.7	0.6
2 to 12 years								
(15 mg/kg)	113.2	63.9	42.1	21.9	12.8	7.6	3.0	--
(20 mg/kg)	147.6	97.6	63.2	34.5	--	12.3	4.9	0.5
(40 mg/kg)	241.7	152.7	96.3	55.6	--	18.8	7.2	0.6

Ceoi = concentration at **e**nd **o**f **i**nfusion (i.e. after 30 min)

Table 2

$C_{6\,hr}$ (µg/ml) of Total Ertapenem in Paediatric Patients 3 to 23 Months and 2 to 12 Years of Age Following Administration of a Single 15-mg/kg Dose Versus $C_{12\,hr}$ (µg/ml) in Young Healthy Adult Subjects Following Administration of a Single 1-g Dose of Ertapenem (Control From Protocol 009)

Age Group	N	GM	GMR (Children/Adults)	90% CI
Adults	16	8.890	--	--
2 to 12 Years	8	10.700	1.204	(0.88, 1.64)
3 to 23 Months	12	12.723	1.431	(1.09, 1.88)

See objective "(5)" in the tabulated summary at the start of this set of Tables.
This is an extrapolation of data from the single dose of 15 mg/kg used in the trial to twice daily dosing (15 mg/kg twelve hourly) that will be necessary to replicate the kinetics following the standard adult dose of 1 g daily.

Observations
The plasma $AUC_{(0-\infty)}$, C_{12hr}, C_{eoi}, and $t_{½}$ for total ertapenem following a single 20-mg/kg IV dose (up to a maximum of 1 g) in children 3 to 23 months and 2 to 12 years of age were generally lower and CL_p higher, compared to healthy adult subjects (historical controls) administered a 1-g dose of ertapenem.

This dose would result in unsatisfactorily low concentrations, approaching the target MIC break point of 4ug/ml at the mid-point of the dosing interval.

The $C_{6\ hr}$ for total ertapenem following the administration of single 15-mg/kg IV doses to patients 3 to 23 months and 2 to 12 years of age are similar to slightly higher than the concentration of total ertapenem at the midpoint of the dosing interval ($C_{12\ hr}$) following the administration of a single 1-g IV dose of ertapenem in healthy young adults (historical controls). The $C_{6\ hr}$ values are well above the established highest aerobic susceptibility breakpoint (2 µg/ml).

The plasma $AUC_{(0-\infty)}$ for total ertapenem following a single 20-mg/kg IV dose (up to a maximum of 1 g) in adolescents 13 to 17 years of age is similar compared to the plasma $AUC_{(0-\infty)}$ following a single 1-g IV dose of ertapenem in healthy adult subjects (historical controls). $C_{12\ hr}$, C_{eoi}, CL_p, and $t_{½}$ following the administration of a single 20-mg/kg IV dose (up to a maximum of 1 g) of ertapenem in adolescents 13 to 17 years of age are generally comparable to healthy adult subjects (historical controls) administered a 1-g dose of ertapenem.

Single IV doses of ertapenem up to 40 mg/kg are generally safe and well tolerated in children 3 to 23 months, 2 to 12 years, and 13 to 17 years of age.
However, a 20mg/kg twice daily regime for the age range 3 months to 12 years would result in an unnecessarily high extrapolated child/adult GMR for AUC of about 1.2 to 1.4, as well as in a child/adult GMR for the end of infusion concentration of about 1.1 to 1.6 (i.e. unnecessarily high).

Conclusions
Administration of either a single daily or twice daily 20-mg/kg dose of ertapenem in children 3 to 23 months and 2 to 12 years is not recommended.

No dose adjustment is recommended from the standard 1-g dose of ertapenem in children 13 to 17 years of age.

A 15-mg/kg b.i.d. dosing regimen for ertapenem is recommended in children 3 to 23 months and 2 to 12 years of age. This regimen most closely replicates the 1g once daily regime approved for adults and strikes the best balance between efficacious concentrations and avoidance of concentration-dependent side effects.
Given the constraints associated with obtaining comprehensive PK data in paediatric patients, there are sufficient data from these studies to support the recommended dosage. The extrapolation from the single dose intravenous data to estimates of plasma levels following twice daily dosage in the younger age groups is justified.

3.2. Clinical efficacy

Main studies

Protocol 036 (P036) was a prospective, multicentre (US and international), double-blind RCT comparing Invanz with ceftriaxone in the treatment of children with CAP, UTI or SSTI. There were 303 treated in the Invanz group (108 CAP) and 94 in the ceftriaxone group (35 CAP).

Protocol 038 (P038) was a prospective, multicentre (US and international), open RCT comparing Invanz with ticarcillin/clavulanate (T/C) in the treatment of children with IAI or acute pelvic infections (API). There were 56 IAI and 25 API treated in the Invanz group and 25 IAI and 8 API in the T/C group.

[The data of primary interest are those for the three EU-authorised indications: CAP, IAI and acute gynaecological infections (“acute pelvic infections”, API)]

Methods

Enrollment

Patients were between 3 months and 17 years of age.

For CAP, patients were required to have suggestive symptoms; and new infiltrate(s) compatible with bacterial pneumonia on the chest x-ray, which included the presence of a new alveolar/lobar infiltrate or consolidation.

For IAI, patients enrolled had a primary diagnosis of complicated appendicitis (localised or with peritonitis) defined as appendiceal perforation or periappendicular abscess. One patient had a perforated Meckel's; this was consistent with the protocol, which included several other causes of intra-abdominal infection, perforated DU, GU and others.

For API, patients were required to have signs, symptoms or sonographic evidence of API following vaginal delivery, caesarean section, gynaecological operation or septic abortion.

Randomisation

In both studies (P036 and P038), patients were randomised 3 to 1: Invanz to comparator

Dosage

For both studies (P036 and P038), dosage of Invanz was based on the results of formal PK studies. Children between the ages of 3 months and 12 years received 15mg/kg parenterally twice daily and patients between the ages of 13 and 17 years received 1g once daily.

For CAP patients, Invanz treatment was always initiated by the IV route, but when they were determined to be haemodynamically stable a switch to the IM route could be made. After at least 3 days parenteral treatment a switch to an oral antibiotic (amoxicillin/clavulanic acid) could be made if predefined criteria had been met. Overall, patients were treated from 3 to 14 days by a parenteral route.

For IAI and API patients, treatment was always initiated by the IV route, but when they were determined to be haemodynamically stable a switch to the IM route could be made. Patients continued to receive parenteral treatment throughout the duration of therapy; 5 -14 days for IAI and 3 – 14 days for API.

Efficacy evaluation

Clinical response: predefined criteria for assessing the clinical response to treatment were used to assay cure, improvement (CAP only), failure or indeterminate response at the time of discontinuation of parenteral treatment (DCPT) and at the post-treatment follow-up visit, the "test of cure" (TOC) visit. "Improvement" was not used as a classification of response at the TOC visit.

Microbiological response: this was based on the microbiological findings at baseline and at the TOC visit.

The TOC visit occurred 7 – 14 days post treatment for CAP, 2 – 4 weeks post treatment for API and 3 – 5 weeks post treatment for IAI.

Definitions of populations

Randomised population**:** patients who were randomised to a study regimen, irrespective of whether the patient actually received therapy.

Treated Population**:** (a subset of the randomised population) patients who received at least 1 dose of study therapy.

Clinical Modified Intent-to-Treat (cMITT) Population: (a subset of the treated population) patients who met the minimal disease definition.

Microbiologic MITT (mMITT) Population: (a subset of the clinical MITT population) clinical MITT patients who had a baseline pathogen identified, regardless of the susceptibility to study agents, and a microbiologic response assessed.
[Determination of the clinical (cMITT) and microbiologic MITT (mMITT) populations were made using prespecified criteria]

Clinically Evaluable Population or Evaluable Per Protocol (cEPP) Population**:** (a subset of the clinical MITT population) patients in whom sufficient information was available to determine the patient's outcome and no confounding factors were present that interfered with the assessment of outcome; furthermore, it was required that if baseline pathogens were identified, one or more of these pathogens were susceptible to the study therapy the patient was receiving.

Microbiologically Evaluable Population or mEPP Population: (a subset of the clinically evaluable population) clinically evaluable patients who had a baseline pathogen identified and a microbiologic response assessed.
[Determinations of Evaluability were made using pre specified criteria]

Analysis populations

The primary analysis population was the cMITT and the assessment was made at the TOC visit. Additional analyses were performed on the mMITT and on the clinical and microbiological EPPs.

As a sensitivity analysis, an additional evaluation of the proportion of patients, in the MITT population, with a favourable clinical response assessment was performed, in which all patients who have missing or indeterminate outcome at the TOC visit were considered "failures."

Results

The following Tables show the results of the efficacy analyses for the various analysis populations. The key Tables included in this report are those for the cMITT population, the cEPP population and the data from cEPP populations comparing the responses in children in P036 and P038 with the responses from the historic adult studies submitted with the MA application.

Table 7-1

Proportion of Patients With a Favorable Clinical Response Assessment
at DCPT and Posttreatment Visits
Displayed by Disease Stratum
(Clinical MITT Population)

Time Point	Disease Stratum	Treatment Group: Ertapenem (A) (N=284) Adjusted Response n/m	Ertapenem (A) (N=284) Adjusted Response %[†] (95% CI)[‡]	Ceftriaxone (B) (N=95) Adjusted Response n/m	Ceftriaxone (B) (N=95) Adjusted Response %[†] (95% CI)[‡]	Adjusted Difference (A-B) %[§] (95% CI)[‖]
DCPT	UTI	80/84	95.3 (90.8, 99.9)	31/31	100.0 (100.0, 100.0)	-4.7 (-11.3, 2.0)
	SSTI	86/92	94.0 (89.1, 98.8)	28/28	100.0 (87.7, 100.0)	-6.5 (-27.4, 13.9)
	CAP	101/103	98.1 (95.4, 100.0)	34/34	100.0 (100.0, 100.0)	-1.9 (-6.6, 2.7)
	Overall	267/279	95.8 (93.5, 98.2)	93/93	100.0 (100.0, 100.0)	-4.2 (-7.2, -1.2)
Posttreatment	UTI	69/80	86.4 (78.9, 93.9)	28/29	96.6 (82.2, 99.9)	-10.3 (-31.0, 10.6)
	SSTI	78/88	90.1 (83.8, 96.3)	27/27	100.0 (87.2, 100.0)	-11.4 (-32.4, 9.5)
	CAP	89/95	93.6 (88.7, 98.5)	32/33	96.8 (90.8, 100.0)	-3.2 (-13.3, 6.9)
	Overall	236/263	89.9 (86.2, 93.5)	87/89	97.8 (94.7, 100.0)	-7.9 (-13.4, -2.4)

[†] If m≥30 ,the response was computed using Cochran-Mantel-Haenszel weights, adjusting for age within each disease stratum and adjusting for age for "Overall". If m<30, then the observed response was computed.

[‡] If m≥30, then the CI was calculated using the normal approximation to the binomial distribution and Cochran-Mantel-Haenszel weights were used to adjust for stratification (age within each disease stratum, and age for "Overall"). If 10≤m<30, then the exact CI was computed based on Clopper and Pearson's method. If m<10, then no CI was calculated.

[§] If m≥30, then the percentage point difference was calculated using the Cochran-Mantel-Haenszel weights to adjust for stratification (age within each disease stratum,and age for "Overall"). If m<30, then the observed difference was computed.

[‖] If m≥30, then the CI was calculated using the Blackwelder method with Cochran-Mantel-Haenszel weights to adjust for stratification (age within each disease stratum, and age for "Overall"). If 10≤m<30, then the exact CI was computed. If m<10, then no CI was computed.

MITT = Modified intention to treat.

N = Number of clinical MITT patients in the treatment group.

n/m = Number of patients with favorable assessment/number of patients with an assessment at the relevant time point.

CI = Confidence interval.

UTI = Urinary tract infection.

SSTI = Skin and soft tissue infection.

CAP = Community-acquired pneumonia.

Data Source: [4.3.9; 4.3.15; 4.3.17]

Table 7-2

Proportion of Patients With a Favorable Clinical Response Assessment
at Posttreatment Visit
Displayed by Disease and Age Strata
(Clinical MITT Population)

Disease Stratum	Age Stratum	Treatment Group: Ertapenem (A) (N=284) Observed Response (%)			Treatment Group: Ceftriaxone (B) (N=95) Observed‡ Response (%)			Observed Difference (A-B)	
		n/m	%	(95% CI)†	n/m	%	(95% CI)†	%	(95% CI)†
UTI	3 to 23 months	27/31	87.1	(70.2, 96.4)	11/11	100.0	(71.5, 100.0)	-12.9	(-44.9, 20.9)
	2 to 12 years	38/45	84.4	(70.5, 93.5)	15/16	93.8	(69.8, 99.8)	-9.3	(-37.1, 19.0)
	13 to 17 years	4/4	100.0	-	2/2	100.0	-	0.0	-
SSTI	3 to 23 months	24/30	80.0	(61.4, 92.3)	6/6	100.0	-	-20.0	-
	2 to 12 years	47/50	94.0	(83.5, 98.7)	19/19	100.0	(82.4, 100.0)	-6.0	(-31.5, 20.1)
	13 to 17 years	7/8	87.5	-	2/2	100.0	-	-12.5	-
CAP	3 to 23 months	31/35	88.6	(73.3, 96.8)	13/13	100.0	(75.3, 100.0)	-11.4	(-41.7, 20.2)
	2 to 12 years	55/57	96.5	(87.9, 99.6)	16/17	94.1	(71.3, 99.9)	2.4	(-18.7, 28.9)
	13 to 17 years	3/3	100.0	-	3/3	100.0	-	0.0	-
Overall	3 to 23 months	82/96	85.4	(76.7, 91.8)	30/30	100.0	(88.4, 100.0)	-14.6	(-34.6, 5.1)
	2 to 12 years	140/152	92.1	(86.6, 95.9)	50/52	96.2	(86.8, 99.5)	-4.0	(-19.4, 10.1)
	13 to 17 years	14/15	93.3	(68.1, 99.8)	7/7	100.0	-	-6.7	-

† If m ≥10 then the exact confidence interval was computed based on Clopper and Pearson's method. If m<10 then no confidence interval was computed.

‡ If m ≥10 then the exact confidence interval was computed. If m<10 then no confidence interval was computed.

N = Number of clinical MITT patients in the treatment group.

n/m = Number of patients with favorable assessment/number of patients with assessment at the post treatment visit.

CI = Confidence interval.

MITT = Modified Intention to treat.

UTI = Urinary tract infection.

SSTI = Skin and soft tissue infection.

CAP = Community-acquired pneumonia.

Data Source: [4.1.3; 4.3.9; 4.3.15; 4.3.17]

Table 7-5

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

Disease Stratum	Treatment Group						Adjusted Difference (A-B)	
	Ertapenem (A) (N=284) Adjusted Response			Ceftriaxone (B) (N=95) Adjusted Response				
	n/m	%[†]	(95% CI)[‡]	n/m	%[†]	(95% CI)[‡]	%[§]	(95% CI)[‖]
UTI	67/85	79.0	(70.3, 87.6)	28/32	87.4	(76.0, 98.9)	-8.5	(-25.3, 8.4)
SSTI	73/94	79.2	(71.0, 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	(74.0, 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)

[†] If m ≥30, the response was computed using Cochran-Mantel-Haenszel weights, adjusting for age within each disease stratum and adjusting for age for "Overall". If m <30, then the observed response was computed.

[‡] If m ≥30, then the CI was calculated using normal approximation to the binomial distribution and Cochran-Mantel-Haenszel weights were used to adjust for stratification (age within each disease stratum, and age for "Overall"). If 10 ≤m <30, then the exact CI was computed based on Clopper and Pearson's method. If m <10, then no CI was calculated.

[§] If m ≥30, then the percentage point difference was calculated using the Cochran-Mantel-Haenszel weights to adjust for stratification (age within each disease stratum, and age for "Overall"). If m<30, then the observed difference was computed.

[‖] If m ≥30, then the CI was calculated using Blackwelder method with Cochran-Mantel-Haenszel weights to adjust for stratification (age within each disease stratum, and age for "Overall"). If 10 ≤m <30, then the exact CI computed.. If m <10, then no CI was calculated.

MITT = Modified intention to treat.

N = Number of MITT 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.

CI = Confidence interval.

UTI = Urinary tract infection.

SSTI = Skin and soft tissue infection.

CAP = Community-acquired pneumonia.

Data Source: [1.2.8; 4.3.9; 4.3.15; 4.3.17]

Table 7-6

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

Disease Stratum	Treatment Group: Ertapenem (A) (N=196) Adjusted Response n/m	Ertapenem (A) Adjusted Response %† (95% CI)‡		Treatment Group: Ceftriaxone (B) (N=77) Adjusted Response n/m	Ceftriaxone (B) Adjusted Response %† (95% CI)‡		Adjusted Difference (A-B) %§ (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¶	95.4	(90.5, 100.0)	26/26	100.0	(86.8, 100.0)	-4.5	(-26.8, 17.1)
CAP	74/77	96.1	(91.8, 100.0)	27/28	96.4	(81.7, 99.9)	-0.3	(-21.9, 20.9)
Overall	184/196¶	94.0	(90.7, 97.3)	75/77	97.4	(93.8, 100.0)	-3.4	(-9.2, 2.4)

† If m≥30 ,the response was computed using Cochran-Mantel-Haenszel weights, adjusting for age within each disease stratum and adjusting for age for "Overall." If m<30, then the observed response was computed.

‡ If m≥30, then the CI was calculated using the normal approximation to the binomial distribution and Cochran-Mantel-Haenszel weights were used to adjust for stratification (age within each disease stratum, and age for "Overall"). If 10≤m<30, then the exact CI was computed based on Clopper and Pearson's method. If m<10, then no CI was calculated.

§ If m≥30, then the percentage point difference was calculated using the Cochran-Mantel-Haenszel weights to adjust for stratification (age within each disease stratum, and age for "Overall"). If m<30, then the observed difference was computed.

‖ If m≥30, then the CI was calculated using the Blackwelder method with Cochran-Mantel-Haenszel weights to adjust for stratification (age within each disease stratum, and age for "Overall"). If 10≤m<30, then the exact CI was computed. If m<10, then no CI was computed.

¶ One patient (AN 2360) in the ertapenem treatment group with MRSA as a sole pathogen is mistakenly included in this analysis; the clinical TOC outcome was unfavorable for this patient.

EPP = Evaluable per protocol.

N = Number of clinical 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.

CI = Confidence interval.

UTI = Urinary tract infection.

SSTI = Skin and soft tissue infection.

CAP = Community-acquired pneumonia.

Data Source: [4.3.9; 4.3.15; 4.3.17]

Table 7-7
Proportion of Patients With a Favorable Clinical Response Assessment
at Test-of-Cure Visit
Displayed by Disease and Age Strata
(Clinical EPP Population)

Disease Stratum	Age Stratum	Treatment Group: Ertapenem (A) (N=196) Observed Response n/m	%	(95% CI)‡	Ceftriaxone (B) (N=77) Observed Response n/m	%	(95% CI)‡	Observed Difference (A-B) %	(95% CI)§
UTI	3 to 23 months	14/15	93.3	(68.1, 99.8)	6/6	100.0		-6.7	
	2 to 12 years	28/33	84.8	(72.6, 97.1)	14/15	93.3	(68.1, 99.8)	-8.5	(-38.0, 22.5)
	13 to 17 years	4/4	100.0	-	2/2	100.0	-	0.0	-
SSTI	3 to 23 months	17/18	94.4	(72.7, 99.9)	6/6	100.0	-	-5.6	-
	2 to 12 years	40/42†	95.2	(88.8, 10.0)	18/18	100.0	(81.5, 100.0)	-4.8	(-32.0, 22.9)
	13 to 17 years	7/7	100.0	-	2/2	100.0	-	0.0	-
CAP	3 to 23 months	26/28	92.9	(76.5, 99.1)	10/10	100.0	(69.2, 100.0)	-7.1	(-41.8, 28.3)
	2 to 12 years	46/47	97.9	(93.7, 100.0)	14/15	93.3	(68.1, 99.8)	4.5	(-18.7, 33.3)
	13 to 17 years	2/2	100.0	-	3/3	100.0	-	0.0	-
Overall	3 to 23 months	57/61	93.4	(87.2, 99.7)	22/22	100.0	(84.6, 100.0)	-6.6	(-30.6, 17.4)
	2 to 12 years	114/122†	93.4	(89.1, 97.8)	46/48	95.8	(90.2, 100.0)	-2.4	(-9.5, 4.8)
	13 to 17 years	13/13	100.0	(75.3, 100.0)	7/7	100.0	-	0.0	-

† One patient (AN 2360) in the ertapenem treatment group with MRSA as a sole pathogen is mistakenly included in this analysis; the clinical TOC outcome was unfavorable for this patient.

‡ If m ≥30, then the CI was calculated using normal approximation to the binomial distribution. If 10 ≤m <30, then the exact CI was calculated based on the binomial distribution. For "Overall" the data were pooled over disease categories within age strata, no adjustment was made for disease strata. If m <10, then no CI was calculated.

§ If m ≥30, then the CI was calculated using normal approximation to the binomial distribution. If 10 ≤m <30, then the exact CI was calculated based on the method described in Proc-StatXact user manual. If m <10, then no CI was calculated.

EPP = Evaluable per protocol.

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.

CI = Confidence interval.

UTI = Urinary tract infection.

SSTI = Skin and soft tissue infection.

CAP = Community-acquired pneumonia.

Data Source: [1.2.8; 4.1.3; 4.3.9; 4.3.15; 4.3.17]

Table 7-9

Proportion of Patients With a Favorable Microbiological Response Assessment at DCPT and Posttreatment Visits Displayed by Disease Stratum (Microbiologic MITT Population)

Time Point	Disease Stratum	Treatment Group: Ertapenem (A) (N=157)¶ Adjusted Response n/m	Ertapenem (A) Adjusted Response %† (95% CI)‡		Ceftriaxone (B) (N=52) Adjusted Response n/m	Ceftriaxone (B) Adjusted Response %† (95% CI)‡		Adjusted Difference (A-B) %§ (95% CI)‖	
DCPT	UTI	71/75	94.8	(89.8, 99.8)	28/28	100.0	(87.7, 100.0)	-5.3	(-26.6, 15.2)
	SSTI	42/49	87.7	(78.4, 96.9)	16/16	100.0	(79.4, 100.0)	-14.3	(-41.1, 13.6)
	CAP	19/21	90.5	(69.6, 98.8)	4/4	100.0	-	-9.5	-
	Overall	132/145	91.3	(86.7, 95.9)	48/48	100.0	(100.0, 100.0)	-8.7	(-14.7, -2.8)
Posttreatment	UTI	58/69	84.6	(76.1, 93.1)	23/25	92.0	(74.0, 99.0)	-7.9	(-30.3, 14.8)
	SSTI	38/46	85.6	(75.5, 95.8)	15/15	100.0	(78.2, 100.0)	-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, 100.0)	-9.7	(-21.1, 1.7)

† If m≥30 ,the response was computed using Cochran-Mantel-Haenszel weights, adjusting for age within each disease stratum and adjusting for age for "Overall." If m<30, then the observed response was computed.

‡ If m≥30, then the CI was calculated using the normal approximation to the binomial distribution and Cochran-Mantel-Haenszel weights were used to adjust for stratification (age within each disease stratum, and age for "Overall"). If 10≤m <30, then the exact CI was computed based on Clopper and Pearson's method. If m<10, then no CI was calculated.

§ If m≥30, then the percentage point difference was calculated using the Cochran-Mantel-Haenszel weights to adjust for stratification (age within each disease stratum, and age for "Overall"). If m <30, then the observed difference was computed.

‖ If m≥30, then the CI was calculated using the Blackwelder method with Cochran-Mantel-Haenszel weights to adjust for stratification (age within each disease stratum, and age for "Overall"). If 10≤m<30, then the exact CI was computed. If m<10, then no CI was computed.

¶ One patient (AN 2264) in the ertapenem treatment group did not have a pathogen at baseline and was inadvertently included in the overall Microbiologic MITT population.

MITT = Modified Intention to treat.

N = Number of microbiologic MITT patients in the treatment group.

n/m = Number of patients with favorable assessment/number of patients with an assessment at the relevant time point.

CI = Confidence interval.

UTI = Urinary tract infection.

SSTI = Skin and soft tissue infection.

CAP = Community-acquired pneumonia.

Data Source: [4.3.9; 4.3.10; 4.3.17]

Table 7-10

Proportion of Patients With a Favorable Microbiological Response Assessment at Posttreatment Visit
Displayed by Disease and Age Strata
(Microbiologic MITT Population)

Disease Stratum	Age Stratum	Treatment Group: Ertapenem (A) (N=157)[†] Observed Response n/m	%	(95% CI)[‡]	Ceftriaxone (B) (N=52) Observed Response n/m	%	(95% CI)[‡]	Observed Difference (A-B) %	(95% CI)[§]
UTI	3 to 23 months	20/23	87.0	(66.4, 97.2)	10/10	100.0	(69.2, 100.0)	-13.0	(-47.8, 24.3)
	2 to 12 years	34/42	81.0	(69.1, 92.8)	11/13	84.6	(54.6, 98.1)	-3.7	(-34.2, 27.4)
	13 to 17 years	4/4	100.0	-	2/2	100.0	-	0.0	-
SSTI	3 to 23 months	14/20	70.0	(45.7, 88.1)	5/5	100.0	-	-30.0	-
	2 to 12 years	19/20	95.0	(75.1, 99.9)	10/10	100.0	(69.2, 100.0)	-5.0	(-43.3, 34.3)
	13 to 17 years	5/6	83.3	-	-	-	-	-	-
CAP	3 to 23 months	7/8	87.5	-	2/2	100.0	-	-12.5	-
	2 to 12 years	8/10	80.0	(44.4, 97.5)	0/1	0.0	-	80.0	-
	13 to 17 years	1/1	100.0	-	-	-	-	-	-
Overall	3 to 23 months	41/51	80.4	(69.5, 91.3)	17/17	100.0	(80.5, 100.0)	-19.6	(-46.3, 8.8)
	2 to 12 years	61/72	84.7	(76.4, 93.0)	21/24	87.5	(67.6, 97.3)	-2.8	(-26.2, 20.8)
	13 to 17 years	10/11	90.9	(58.7, 99.8)	2/2	100.0	-	-9.1	-

[†] One patient (AN 2264) in the ertapenem treatment group did not have a pathogen at baseline and was inadvertently included in the overall Microbiologic MITT population.

[‡] If m ≥30, then the CI was calculated using normal approximation to the binomial distribution. If 10 ≤m <30, then the exact CI was calculated based on the binomial distribution. For Overall the data were pooled over disease categories within age strata, no adjustment was made for disease strata. If m <10, then no CI was calculated.

[§] If m ≥30, then the CI was calculated using normal approximation to the binomial distribution. If 10 ≤m <30, then the exact CI was calculated based on the method described in Proc-StatXact user manual. If m <10, then no CI was calculated.

MITT = Modified intention to treat.
N = Number of MITT patients in the treatment group
n/m = Number of patients with favorable assessment/number of patients with an assessment at the post treatment visit.
CI = Confidence interval.
UTI = Urinary tract infection.
SSTI = Skin and soft tissue infection.
CAP = Community-acquired pneumonia.

Data Source: [1.2.8; 4.1.3; 4.3.9; 4.3.15; 4.3.17]

Table 7-12

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

Disease Stratum	Treatment Group: Ertapenem (A) (N=157)¶ Adjusted Response n/m	% †	(95% CI)‡	Ceftriaxone (B) (N=52) Adjusted Response n/m	% †	(95% CI)‡	Adjusted Difference (A-B) % §	(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	72.0	(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	50.0	-	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)

† If m≥30 ,the response was computed using Cochran-Mantel-Haenszel weights, adjusting for age within each disease stratum and adjusting for age for "Overall". If m<30, then the observed response was computed.

‡ If m≥30, then the CI was calculated using the normal approximation to the binomial distribution and Cochran-Mantel-Haenszel weights were used to adjust for stratification (age within each disease stratum, and age for "Overall"). If 10 ≤m <30, then the exact CI was computed based on Clopper and Pearson's method. If m<10, then no CI was calculated.

§ If m≥30, then the percentage point difference was calculated using the Cochran-Mantel-Haenszel weights to adjust for stratification (age within each disease stratum, and age for "Overall"). If m <30, then the observed difference was computed.

‖ If m≥30, then the CI was calculated using the Blackwelder method with Cochran-Mantel-Haenszel weights to adjust for stratification (age within each disease stratum, and age for "Overall"). If 10 ≤m <30, then the exact CI was computed. If m<10, then no CI was computed.

¶ One patient (AN 2264) in the ertapenem treatment group did not have a pathogen at baseline and was inadvertently included in the overall Microbiologic MITT population.

MITT = Modified intention to treat.

N = Number of microbiologic MITT 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.

CI = Confidence interval.

UTI = Urinary tract infection.

SSTI = Skin and soft tissue infection.

CAP = Community-acquired pneumonia.

Data Source: [4.3.9; 4.3.10; 4.3.17]

Table 7-13

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

Disease Stratum	Treatment Group: Ertapenem (A) (N=93) Adjusted Response n/m	%†	(95% CI)‡	Ceftriaxone (B) (N=37) Adjusted Response n/m	%†	(95% CI)‡	Adjusted Difference (A-B) %§	(95% CI)‖
UTI	40/46	87.4	(77.8, 97.0)	18/20	90.0	(68.3, 98.8)	-3.0	(-29.1, 22.9)
SSTI	29/31¶	92.4	(83.0, 100.0)	14/14	100.0	(76.8, 100.0)	-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, 100.0)	-3.0	(-15.8, 9.8)

† If m≥30 ,the response was computed using Cochran-Mantel-Haenszel weights, adjusting for age within each disease stratum and adjusting for age for "Overall". If m<30, then the observed response was computed.

‡ If m≥30, then the CI was calculated using the normal approximation to the binomial distribution and Cochran-Mantel-Haenszel weights were used to adjust for stratification (age within each disease stratum, and age for "Overall"). If 10≤m<30, then the exact CI was computed based on Clopper and Pearson's method. If m<10, then no CI was calculated.

§ If m≥30, then the percentage point difference was calculated using the Cochran-Mantel-Haenszel weights to adjust for stratification (age within each disease stratum, and age for "Overall"). If m<30, then the observed difference was computed.

‖ If m≥30, then the CI was calculated using the Blackwelder method with Cochran-Mantel-Haenszel weights to adjust for stratification (age within each disease stratum, and age for "Overall"). If 10≤m<30, then the exact CI was computed. If m<10, then no CI was computed.

¶ One patient (AN 2360) in the ertapenem treatment group with MRSA as a sole pathogen is mistakenly included in this analysis; the clinical TOC outcome was unfavorable for this patient.

EPP = Evaluable per protocol.

N = Number of microbiologic 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.

CI = Confidence interval.

UTI = Urinary tract infection.

SSTI = Skin and soft Tissue infection.

CAP = Community-acquired pneumonia.

Data Source: [4.3.9; 4.3.10; 4.3.17]

Table 7-14

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

Disease Stratum	Age Stratum	Treatment Group: Ertapenem (A) (N=93) Observed Response n/m	%	(95% CI)[‡]	Ceftriaxone (B) (N=37) Observed Response n/m	%	(95% CI)[‡]	Observed Difference (A-B) %	(95% CI)[§]
UTI	3 to 23 months	13/13	100.0	(75.3, 100.0)	6/6	100.0		0.0	
	2 to 12 years	23/29	79.3	(60.3, 92.0)	10/12	83.3	(51.6, 97.9)	-4.0	(-37.0, 29.2)
	13 to 17 years	4/4	100.0	-	2/2	100.0	-	0.0	-
SSTI	3 to 23 months	9/10	90.0	(55.5, 99.7)	5/5	100.0	-	-10.0	-
	2 to 12 years	15/16[†]	93.8	(69.8, 99.8)	9/9	100.0	-	-6.3	-
	13 to 17 years	-	-	-	-	-	-	-	-
CAP	3 to 23 months	6/7	85.7	-	2/2	100.0	-	-14.3	-
	2 to 12 years	8/9	88.9	-	0/1	0.0	-	88.9	-
	13 to 17 years	-	-	-	-	-	-	-	-
Overall	3 to 23 months	28/30	93.3	(84.4, 100.0)	13/13	100.0	(75.3, 100.0)	-6.7	(-38.2, 25.6)
	2 to 12 years	46/54	85.2	(75.7, 94.7)	19/22	86.4	(65.1, 97.1)	-1.2	(-25.9, 23.3)
	13 to 17 years	9/9	100.0	-	2/2	100.0	-	0.0	-

[†] One patient (AN 2360) in the ertapenem treatment group with MRSA as a sole pathogen is mistakenly included in this analysis; the clinical TOC outcome was unfavorable for this patient.

[‡] If m ≥30, then the CI was calculated using normal approximation to the binomial distribution. If 10 ≤m <30, then the exact CI was calculated based on the binomial distribution. For Overall the data were pooled over disease categories within age strata, no adjustment was made for disease strata. If m <10, then no CI was calculated.

[§] If m ≥30, then the CI was calculated using normal approximation to the binomial distribution. If 10 ≤m <30, then the exact CI was calculated based on the method described in Proc-StatXact user manual. If m < 10, then no CI was calculated.

EPP = Evaluable per protocol.

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 relevant time point.

CI = Confidence interval.

UTI = Urinary tract infection.

SSTI = Skin and soft tissue infection.

CAP = Community-acquired pneumonia.

Data Source: [1.2.8; 4.1.3; 4.3.9; 4.3.15; 4.3.17]

Table 7-19

Proportion of Patients Who Received Ertapenem and Had a Favorable Response Assessment[†] at Test-of-Cure Visit Displayed by Disease Stratum Pediatric Study versus Adult Studies[§] (EPP Population)

	Ertapenem Treatment Group				
	Pediatric Study		Adult Studies		
Disease Stratum	n/m	Observed Response % (95% CI)[‡]	Study	n/m	Observed Response % (95% CI)[‡]
CAP	74/77	96.1 (89.0, 99.2)	p018	168/182	92.3 (87.4, 95.7)
			p020	167/182	91.8 (86.8, 95.3)
			Total	335/364	92.0 (88.8, 94.6)
UTI	40/46	87.0 (73.7, 95.1)	p014	146/159	91.8 (86.4, 95.6)
			p021	83/97	85.6 (77.0, 91.9)
			Total	229/256	89.5 (85.0, 92.9)
SSTI	64/67	95.5 (87.5, 99.1)	p016	152/185	82.2 (75.9, 87.4)

[†] Favorable clinical response for CAP and SSTI. Favorable microbiological response for UTI. Clinically evaluable population for CAP and SSTI. Microbiologically evaluable population for UTI.

[‡] If m ≥10 then the exact confidence interval was computed based on Clopper and Pearson's method. If m<10 then no confidence interval was computed.

[§] Results of the adult studies are cited from the clinical study report for protocol 016 for SSTI, protocols 014 and 021 for UTI, and protocols 018 and 020 for CAP.

n/m = Number of patients with favorable assessment/number of patients with an assessment at the relevant time point.

p = Protocol.

EPP = Evaluable per protocol.

CI =Confidence interval.

CAP =Community-acquired pneumonia.

UTI = Urinary tract infection.

SSTI = Skin and soft tissue infection

Data Source: [2.2.2; 2.2.3; 2.2.7; 2.2.8; 2.2.9; 4.3.9; 4.3.10; 4.3.15; 4.3.17]

Table 7-20

Proportion of Patients Who Received Ertapenem and Had a Favorable Assessment[†] at Test-of-Cure Visit Displayed by Disease Stratum—Sensitivity Analysis Pediatric Study Versus Adult Studies (MITT Population)

	Ertapenem Treatment Group			
	Pediatric Study		Adult Studies	
Disease Stratum	n/m	Observed Response % (95% CI)[‡]	n/m	Observed Response % (95% CI)[‡]
CAP	84/105	80.0 (71.1, 87.2)	189/236	80.1 (74.4, 85.0) (p018)
			181/227	79.7 (73.9, 84.8) (p020)
			370/463	79.9 (76.0, 83.5) (Total)
UTI	56/85	65.9 (54.8, 75.8)	195/219	89.0 (84.1, 92.9) (p014)
			99/131	75.6 (67.3, 82.7) (p021)
			294/350	84.0 (79.7, 87.7) (Total)
SSTI	73/93	78.5 (68.8, 86.3)	174/269	64.7 (58.6, 70.4) (p016)

[†] Favorable clinical response for CAP and SSTI. Favorable microbiological response for UTI. Clinically evaluable population for CAP and SSTI. Microbiologically evaluable population for UTI.

[‡] If m ≥10 then the exact confidence interval was computed based on Clopper and Pearson's method. If m<10 then no confidence interval was computed.

n = n/m=Number of patients with favorable assessment/number of patients with an assessment at the relevant time point.

p = Protocol.

EPP = Evaluable per protocol.

CI = Confidence interval.

CAP =Community-acquired pneumonia.

UTI = Urinary tract infection.

SSTI = Skin and soft tissue infection

Data Source: [2.2.1; 4.3.9; 4.3.10; 4.3.17]

Table 7-1

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

Disease Stratum	Treatment Group: Ertapenem (N=81) Adjusted Response n/m	% [†]	(95% CI) [‡]	Ticarcillin/Clavulanate (N=24) Adjusted Response n/m	% [†]	(95% CI) [‡]
IAI	43/50	86.7	(77.3, 96.1)	11/15	73.3	(44.9, 92.2)
API	25/25	100.0	(86.3, 100.0)	8/8	100.0	
Overall	68/75	91.4	(85.0, 97.7)	19/23	82.6	(61.2, 95.0)

[†] If m≥30 ,the response was computed using Cochran-Mantel-Haenszel weights, adjusting for age within each disease stratum and adjusting for age for "Overall." If m<30, then the observed response was computed.
[‡] If m≥30, then the CI was calculated using the normal approximation to the binomial distribution and Cochran-Mantel-Haenszel weights were used to adjust for stratification (age within each disease stratum, and age for "Overall"). If 10≤m<30, then the exact CI was computed based on Clopper and Pearson's method. If m<10, then no CI was calculated.
N = Number of Clinical MITT patients in each treatment group.
n/m = Number of patients with favorable assessment/number of patients with a posttreatment assessment.
CI = Confidence interval.
IAI = Complicated intra-abdominal infection.
API = Acute pelvic infection.
MITT = Modified intention to treat.

Data Source: [4.3.3; 4.3.14; 4.3.15]

Table 7-2

Proportion of Patients With a Favorable Clinical Response Assessment
At Posttreatment Visit
Displayed by Disease and Age Strata
(Clinical MITT Population)

Disease Stratum	Age Stratum	Treatment Group: Ertapenem (N=81) Observed Response (%) n/m	%	(95% CI) [†]	Ticarcillin/Clavulanate (N=24) Observed Response (%) n/m	%	(95% CI) [†]
IAI	2 to 12 years	28/34	82.4	(65.5, 93.2)	7/9	77.8	.
	13 to 17 years	15/16	93.8	(69.8, 99.8)	4/6	66.7	.
API	13 to 17 years	25/25	100.0	(86.3, 100.0)	8/8	100.0	.
Overall	2 to 12 years	28/34	82.4	(65.5, 93.2)	7/9	77.8	.
	13 to 17 years	40/41	97.6	(87.1, 99.9)	12/14	85.7	(57.2, 98.2)

[†] If m≥10, then the exact CI was computed based on Clopper and Pearson's method. If m<10, then no CI was calculated.
N = Number of Clinical MITT patients in each treatment group.
n/m = Number of patients with favorable assessment/number of patients with a posttreatment assessment.
CI = Confidence interval.
IAI = Complicated intra-abdominal infection.
API = Acute pelvic infection.
MITT = Modified intention to treat.

Data Source: [4.3.3; 4.3.14; 4.3.15]

Table 7-5

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

Disease Stratum	Treatment Group					
	Ertapenem (N=81) Adjusted Response			Ticarcillin/Clavulanate (N=24) Adjusted Response		
	n/m	%†	(95% CI)‡	n/m	%†	(95% CI)‡
IAI	37/56	66.4	(54.0, 78.8)	8/16	50.0	(24.7, 75.3)
API	25/25	100.0	(86.3, 100.0)	8/8	100.0	
Overall	62/81	77.4	(68.3, 86.5)	16/24	66.7	(44.7, 84.4)

† If m≥30 ,the response was computed using Cochran-Mantel-Haenszel weights, adjusting for age within each disease stratum and adjusting for age for "Overall." If m<30, then the observed response was computed.
‡ If m≥30, then the CI was calculated using the normal approximation to the binomial distribution and Cochran-Mantel-Haenszel weights were used to adjust for stratification (age within each disease stratum, and age for "Overall"). If 10≤m<30, then the exact CI was computed based on Clopper and Pearson's method. If m<10, then no CI was calculated.
N = Number of Clinical MITT patients in each treatment group.
n/m = Number of patients with favorable assessment at the relevant time point/number of patients in the Clinical MITT population.
CI = Confidence interval.
IAI = Complicated intra-abdominal infection.
API = Acute pelvic infection.
MITT = Modified intention to treat.

Data Source: [4.3.3; 4.3.14; 4.3.15]

Table 7-6

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

Disease Stratum	Treatment Group					
	Ertapenem (N=66) Observed Response (%)			Ticarcillin/Clavulanate (N=15) Observed Response (%)		
	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	100.0	(85.2, 100.0)	4/4	100.0	.
Overall	59/66	89.4	(79.4, 95.6)	11/15	73.3	(44.9, 92.2)

† If m≥10, then the exact CI was computed based on Clopper and Pearson's method. If m<10, then no CI was calculated.
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.
CI = Confidence interval.
IAI = Complicated intra-abdominal infection.
API = Acute pelvic infection.
EPP = Evaluable per protocol.

Data Source: [4.3.3; 4.3.14; 4.3.15]

Table 7-7

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

Disease Stratum	Treatment Group: Ertapenem (N=64) Adjusted Response n/m	% †	(95% CI) ‡	Ticarcillin/Clavulanate (N=20) Adjusted Response n/m	% †	(95% CI) ‡
IAI	33/39	85.6	(74.5, 96.6)	9/11	81.8	(48.2, 97.7)
API	20/20	100.0	(83.2, 100.0)	8/8	100.0	
Overall	53/59	91.4	(84.2, 98.5)	17/19	89.5	(66.9, 98.7)

† If m≥30 ,the response was computed using Cochran-Mantel-Haenszel weights, adjusting for age within each disease stratum and adjusting for age for "Overall." If m<30, then the observed response was computed.
‡ If m≥30, then the CI was calculated using the normal approximation to the binomial distribution and Cochran-Mantel-Haenszel weights were used to adjust for stratification (age within each disease stratum, and age for "Overall"). If 10≤m<30, then the exact CI was computed based on Clopper and Pearson's method. If m<10, then no CI was calculated.
N = Number of Microbiologic MITT patients in each treatment group.
n/m = Number of patients with favorable assessment/number of patients with a posttreatment assessment.
CI = Confidence interval.
IAI = Complicated intra-abdominal infection.
API = Acute pelvic infection.
MITT = Modified intention to treat.

Data Source: [4.3.13; 4.3.14; 4.3.15]

Table 7-8

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

Disease Stratum	Treatment Group: Ertapenem (N=64) Adjusted Response n/m	% †	(95% CI) ‡	Ticarcillin/Clavulanate (N=20) Adjusted Response n/m	% †	(95% CI) ‡
IAI	27/44	61.7	(47.3, 76.0)	7/12	58.3	(27.7, 84.8)
API	20/20	100.0	(83.2, 100.0)	8/8	100.0	
Overall	47/64	75.4	(64.9, 86.0)	15/20	75.0	(50.9, 91.3)

† If m≥30 ,the response was computed using Cochran-Mantel-Haenszel weights, adjusting for age within each disease stratum and adjusting for age for "Overall." If m<30, then the observed response was computed.
‡ If m≥30, then the CI was calculated using the normal approximation to the binomial distribution and Cochran-Mantel-Haenszel weights were used to adjust for stratification (age within each disease stratum, and age for "Overall"). If 10≤m<30, then the exact CI was computed based on Clopper and Pearson's method. If m<10, then no CI was calculated.
N = Number of Microbiologic MITT patients in each treatment group.
n/m = Number of patients with favorable assessment at the relevant time point/number of patients in the Microbiologic MITT population.
CI = Confidence interval.
IAI = Complicated intra-abdominal infection.
API = Acute pelvic infection.
MITT = Modified intention to treat.

Data Source: [4.3.13; 4.3.14; 4.3.15]

Table 7-9

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

	Treatment Group					
	Ertapenem (N=51) Observed Response (%)			Ticarcillin/Clavulanate (N=12) Observed Response (%)		
Disease Stratum	n/m	%	(95% CI) †	n/m	%	(95% CI) †
IAI	27/33	81.8	(64.5, 93.0)	6/8	75.0	.
API	18/18	100.0	(81.5, 100.0)	4/4	100.0	.
Overall	45/51	88.2	(76.1, 95.6)	10/12	83.3	(51.6, 97.9)

† If m≥10, then the exact CI was computed based on Clopper and Pearson's method. If m<10, then no CI was calculated.
N = Number of Microbiologic EPP patients in each treatment group.
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.

Data Source: [4.3.13; 4.3.14; 4.3.15]

Table 7-11

Proportion of Patients With Improvement or Resolution of Overall Baseline Clinical Signs and Symptoms (Clinical MITT Population)

		Treatment Group			
		Ertapenem (N=81)		Ticarcillin/Clavulanate (N=24)	
Disease Stratum	Time Point	Improved n/m (%) (95% CI)†	Resolved n/m (%) (95% CI)†	Improved n/m (%) (95% CI)†	Resolved n/m (%) (95% CI)†
IAI	DCPT	54/56 (96.4) (87.7, 99.6)	25/56 (44.6) (31.3, 58.5)	16/16 (100.0) (79.4, 100.0)	6/16 (37.5) (15.2, 64.6)
	Posttreatment	49/50 (98.0) (89.4, 99.9)	40/50 (80.0) (66.3, 90.0)	15/16 (93.8) (69.8, 99.8)	11/16 (68.8) (41.3, 89.0)
API	DCPT	25/25 (100.0) (86.3, 100.0)	25/25 (100.0) (86.3, 100.0)	8/8 (100.0) (63.1, 100.0)	8/8 (100.0) (63.1, 100.0)
	Posttreatment	25/25 (100.0) (86.3, 100.0)	25/25 (100.0) (86.3, 100.0)	8/8 (100.0) (63.1, 100.0)	8/8 (100.0) (63.1, 100.0)

† If m≥10, then the exact CI was computed based on Clopper and Pearson's method. If m<10, then no CI was calculated.
N = Number of Clinical MITT patients in each treatment group.
n/m = Number of patients with improvement or resolution of symptom/number of patients who experienced the symptom at baseline and assessed at a subsequent time point including patients with a worsening of the symptom.
All signs and symptoms include patients who experienced at least one sign and symptom at baseline and were assessed at a subsequent visit. 'Improved' was defined as improvement in at least one sign or symptom without worsening in any other category as compared to baseline. 'Resolved' was defined as the resolution of all signs and symptoms.
The assessment of signs and symptoms for a patient with an unfavorable clinical response at the DCPT time point, will have the same assessment at the posttreatment time point.
DCPT = Discontinuation of parenteral therapy.
CI = Confidence interval.
IAI = Complicated intra-abdominal infection.
API = Acute pelvic infection.
MITT = Modified intention to treat.

Data Source: [4.2.10; 4.3.14; 4.3.15; 4.3.18]

Table 7-14

Proportion of Patients Who Received Ertapenem and had a
Favorable Clinical Response Assessment at Test-of-Cure Visit
Displayed by Disease Stratum
Pediatric Study versus Adult Studies
(Clinical EPP Population)

	Ertapenem Treatment Group				
	Pediatric Study (N= 66)		Adult Studies[†]		
Disease Stratum	n/m	Observed Response % (95% CI)[‡]	N	n/m	Observed Response % (95% CI)[‡]
IAI	36/43	83.7 (69.3, 93.2)	231	200/230 [§ ¶]	87.0 (81.9, 91.0) (p017)[†]
API	23/23	100.0 (85.2, 100)	163	153/163	93.9 (89.0, 97.0) (p023)[†]

[†] Results of the adult studies are cited from the clinical study report for protocol 17 (p017) for IAI and from the clinical study report for protocol 23 (p023) for API.
[‡] If m≥10, then the exact CI was computed based on Clopper and Pearson's method. If m<10, then no CI was calculated.
[§] AN 5586, who was evaluable as a clinical cure, was incorrectly excluded from the analysis because the test-of-cure was entered incorrectly.
[¶] An observed response was not available from the clinical study report for protocol 17. The observed response was derived from the original database used in the calculation of the estimated response.
N = Number of Clinical EPP patients who received Ertapenem.
n/m = Number of patients with favorable assessment /number of patients in the Clinical EPP population.
CI = Confidence interval.
IAI = Complicated intra-abdominal infection.
API = Acute pelvic infection.
EPP = Evaluable per protocol.

Data Source: [2.1.7; 2.1.8; 4.3.3; 4.3.14; 4.3.15]

Table 7-15

Proportion of Patients Who Received Ertapenem and had a
Favorable Clinical Response Assessment at Test-of-Cure Visit
Displayed by Disease Stratum – Sensitivity Analysis
Pediatric Study versus Adult Studies
(Clinical MITT Population)

	Ertapenem Treatment Group				
	Pediatric Study (N= 81)		Adult Studies[†]		
Disease Stratum	n/m	Observed Response % (95% CI)[‡]	N	n/m	Observed Response % (95% CI)[‡]
IAI	37/56	66.1 (52.2, 78.2)	325	234/325	72.0 (66.8, 76.8) (p017)[†]
API	25/25	100.0 (86.3, 100)	211	173/211	82.0 (76.1, 86.9) (p023)[†]

[†] Results of the adult studies are cited from the clinical study report for protocol 17 (p017) for IAI and from the clinical study report for protocol 23 (p023) for API.
[‡] If m≥10, then the exact CI was computed based on Clopper and Pearson's method. If m<10, then no CI was calculated.
N = Number of Clinical MITT patients who received Ertapenem.
n/m = Number of patients with favorable assessment at the relevant time point/number of patients in the Clinical MITT population.
CI = Confidence interval.
IAI = Complicated intra-abdominal infection.
API = Acute pelvic infection.
MITT = Modified intention to treat.

Data Source: [2.1.1; 4.3.3; 4.3.14; 4.3.15]

Table 7-16

Proportion of IAI Patients Who Received Ertapenem and had a
Favorable Clinical and Microbiological Response Assessment at Test-of-Cure Visit
Displayed by Disease Stratum
Pediatric Study versus Adult Study
(Microbiologic EPP Population)

	Ertapenem Treatment Group			
	Pediatric Study (N= 51)		Adult Study[†] (N=203)	
Disease Stratum	n/m	Observed Response % (95% CI[‡])	n/m	Observed Response % (95% CI[‡])
IAI	27/33	81.8 (64.5, 93.0)	176/203	86.7 (81.2, 91.0) (p017)[†]

[†] Results of the adult study are cited from the clinical study report for protocol 17 (p017) for IAI.
[‡] If m≥10, then the exact CI was computed based on Clopper and Pearson's method. If m<10, then no CI was calculated.
N = Number of Microbiologic EPP patients who received Ertapenem.
n/m = Number of patients with favorable assessment /number of patients in the Microbiologic EPP population.
CI = Confidence interval.
IAI = Complicated intra-abdominal infection.
EPP = Evaluable per protocol.

Data Source: [2.1.7; 4.3.3; 4.3.13; 4.3.14; 4.3.15]

Protocols 036 and 038

Baseline Pathogens. All Isolates in ≥5 Patients in a Treatment Group
Microbiological MITT Population

Stratum	Pathogen	Treatment Group	
Protocol 036			
		Ertapenem	Ceftiaxone
		n/m	n/m
UTI (N=117)	*Escherichia coli*	74/85	30/32
SSTI (N=67)	*Staphylococcus aureus*	34/51	12/16
	Streptococcus pyogenes	10/51	5/16
CAP (N=25)	*Haemophilus influenzae*	5/21	2/4
	Streptococcus pneumoniae	11/21	1/4
Protocol 038			
		Ertapenem	T/C
		n/m	n/m
IAI (N=56)	*Bacteroides caccae*	5/44	1/12
	Bacteroides fragilis	16/44	4/12
	Bacteroides thetaiotaomicron	12/44	3/12
	Escherichia coli	38/44	8/12
	Pseudomonas aeruginosa	12/44	2/12
	Streptococcus viridans	9/44	1/12
API (N=28)	*Enterococcus faecalis*	6/20	1/8
	Escherichia coli	8/20	2/8

N = Number of patients in the microbiological MITT population for that indication.
n/m = Number of patients with a baseline pathogen/number of patients in the microbiological MITT population per treatment group.
UTI = Urinary tract infection. IAI = Intra abdominal infection.
SSTI = Skin and soft tissue infection. API = Acute pelvic infection.
CAP = Community acquired pneumonia. T/C= Ticacillin/clavulanate.

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

Disease Stratum	Pathogen	Treatment Group					
Protocol 036							
		Ertapenem (N=284) Observed† Response (%)			Ceftriaxone (N=95) Observed† Response (%)		
		n/m	%	(95% CI)	n/m	%	(95% CI)
SSTI	**gram-positive aerobic cocci**	**40/48**	**83.3**	**(69.8, 92.5)**	**16/16**	**100.0**	**(79.4, 100.0)**
	Staphylococcus aureus	24/30	80.0	(61.4, 92.3)	10/10	100.0	(69.2, 100.0)
	-Methicillin Resistant	2/7	28.6	.	.	.	.
	-Methicillin Susceptible	21/22	95.5	(77.2, 99.9)	9/9	100.0	.
	-Methicillin Unknown	1/1	100.0	.	1/1	100.0	.
	Streptococcus pyogenes	10/10	100.0	(69.2, 100.0)	5/5	100.0	.
CAP	**gram-positive aerobic cocci**	**10/13**	**76.9**	**(46.2, 95.0)**	**2/2**	**100.0**	**.**
	Streptococcus pneumoniae	7/9	77.8	.	1/1	100.0	.
	-Penicillin Intermediate	3/4	75.0	.	.	.	.
	-Penicillin Susceptible	4/4	100.0	.	.	.	.
	-Penicillin Unknown	0/1	0.0	.	1/1	100.0	.
	gram-negative aerobic coccobacilli	**5/5**	**100.0**	**.**	**1/1**	**100.0**	**.**
	Haemophilus influenzae	5/5	100.0	.	1/1	100.0	.
	-Beta Lactamase Negative	1/1	100.0	.	1/1	100.0	.
	-Beta Lactamase Positive	4/4	100.0	.	.	.	.
UTI	**gram-negative aerobic bacilli**	**60/69**	**87.0**	**(76.7, 93.9)**	**26/28**	**92.9**	**(76.5, 99.1)**
	Escherichia coli	51/59	86.4	(75.0, 94.0)	21/23	91.3	(72.0, 98.9)

Protocol 038							
		Ertapenem (N=64) Observed† Response (%)			Ticarcillin/Clavulanate (N=20) Observed† Response (%)		
		n/m	%	(95% CI)	n/m	%	(95% CI)
IAI	**Gram-positive aerobic cocci**	**15/21**	**71.4**	**(47.8, 88.7)**	**3/4**	**75.0**	**.**
	Streptococcus viridans	6/8	75.0	.	1/1	100.0	.
	Gram-negative aerobic bacilli	**42/51**	**82.4**	**(69.1, 91.6)**	**9/12**	**75.0**	**(42.8, 94.5)**
	Escherichia coli	29/35	82.9	(66.4, 93.4)	6/8	75.0	.
	Pseudomonas aeruginosa	9/10	90.0	(55.5, 99.7)	1/2	50.0	.
	Gram-negative anaerobic coccobacilli	**32/39**	**82.1**	**(66.5, 92.5)**	**9/12**	**75.0**	**(42.8, 94.5)**
	Bacteroides fragilis	12/13	92.3	(64.0, 99.8)	3/4	75.0	.
	Bacteroides thetaiotaomicron	10/11	90.9	(58.7, 99.8)	2/3	66.7	.
API	**Gram-positive aerobic cocci**	**10/10**	**100.0**	**(69.2, 100.0)**	**6/6**	**100.0**	**.**
	Enterococcus faecalis	6/6	100.0	.	1/1	100.0	.
	Gram-negative aerobic bacilli	**14/14**	**100.0**	**(76.8, 100.0)**	**2/2**	**100.0**	**.**
	Escherichia coli	8/8	100.0	.	2/2	100.0	.

† Computed from an exact statistical model pooling across strata.
N = Number of evaluable patients in each treatment group.
n/m = Number of pathogens associated with a favourable 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.
CI = Confidence interval.
SSTI = Skin and soft tissue infection. CAP = Community-acquired pneumonia. UTI = Urinary tract infections.
IAI = Intra-abdominal infection. API = Acute pelvic infection.

MAH´s Responses to the Request for Supplementary Information adopted in March 2005. Efficacy conclusions.

It is perhaps because efficacy was regarded as a secondary issue that the type of trial in respect of efficacy evaluation (equivalence or non-inferiority) and appropriate equivalence margins were not pre-specified. Such omissions might be considered arguable.

The MAH claimed that efficacy in these indications is demonstrated by results from the comparator controlled paediatric studies supported additionally by data from RCT in adults at the time of the original MA. However, the CHMP requested the MAH (Request for Supplementary adopted on 17 March 2005) to justify the extrapolation of the results of adult treatment to the paediatric populations by a comparison of the patterns of microbiological pathogens isolated.
In his responses, the MAH detailed the most common isolated pathogens in paediatric patients for each infectious disease indication and concluded that these are comparable to those most commonly isolated in the adult studies submitted with the original Marketing Application.
In addition, the MAH provided a table of the proportion of favourable response assessment by pathogen at TOC visit in patients in the EPP population treated with ertapenem displayed by disease stratum comparing paediatric vs. adults.
As shown in the table, the "per pathogen" response rates observed in each indication for paediatric studies were comparable to that observed in the previously submitted adult studies.

Table 2.7-1: 1

Proportion of Favorable Response Assessment by Pathogen
at Test-of-Cure in Patients Treated With Ertapenem
Displayed by Disease Stratum
Pediatric Versus Adult Studies - Evaluable Population

Disease Stratum	Pathogen	Pediatric Studies Observed[†] Response (%)			Adult Studies Observed[†] Response (%)		
		n/m	%	(95% CI)	n/m	%	(95% CI)
SSTI	*Staphylococcus aureus*	17/18[‡]	94.4	(72.7, 99.9)	54/71	76.1	(66.1, 86.1)
	Streptococcus pyogenes	7/7	100.0		13/16	81.3	(61.5, 100)
CAP	*Streptococcus pneumoniae*	6/6	100.0		86/96	89.6	(83.4, 95.7)
	Haemophilus influenzae	5/5	100.0		29/33	87.9	(76.6, 99.2)
UTI	*Escherichia coli*	34/40	85.0	(70.2, 94.3)	176/191	92.1	(88.3, 96.0)
IAI	*Escherichia coli*	24/30	80.0	(61.4, 92.3)	137/158	86.7	(80.4, 91.6)
	Bacteroides fragilis	9/10	90.0	(55.5, 99.7)	63/76	82.9	(72.5, 90.6)
	Bacteroides thetaiotaomicron	7/8	87.5		41/47	87.2	(74.3, 95.2)
API	*Escherichia coli*	8/8	100.0		36/41	87.8	(73.8, 95.9)

[†] Computed from an exact statistical model pooling across strata.
[‡] One patient (AN 2360) with MRSA as a sole pathogen is mistakenly included in this analysis; the clinical outcome was unfavorable for this patient.
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.
CI = Confidence interval.
SSTI = Skin and soft tissue infection. CAP = Community-acquired pneumonia. UTI = Urinary tract infections.
IAI = Intra-abdominal infection. API = Acute pelvic infection.

The CHMP considered that this response is persuasive and provides a satisfactory justification for the extrapolation of the ertapenem adult efficacy results to the treatment of paediatric patients 3 months to 17 years of ages for the indications studied.

The summary statistics initially submitted indicated that Invanz might not be sufficiently efficacious in children aged 3 to 23 months, particularly in the case of the treatment of Community Acquired Pneumonia (Study 036). As a consequence, the CHMP requested the MAH (Request for Supplementary adopted on 17 March 2005) to provide additional information with respect to the concentrations of the drug achieved (or estimated) with the proposed posology for this age group, to the clearance of the drug in this age group, and to an analysis of relevant PK/PD data. The MAH was also requested to discuss for Study 036, the treatment failures in the youngest age group (3 – 23 months) in respect of age, comorbidity and isolated pathogens.
In their responses, the MAH explained the following:
The posology proposed for ertapenem in paediatric patients (15 mg/kg) twice daily in children 3 months to 12 years of age and 1 g once daily in children ≥13 years of age) is based on pharmacokinetic (PK) data obtained in Protocol 028 a study involving 84 paediatric patients 3 months to 17 years of age. Although the greater variability observed in this paediatric PK study as compared with previously conducted PK studies in adults may have in part resulted from the fact that the paediatric study was by necessity conducted in treated, hospitalised patients rather than in healthy volunteers, greater clearance of ertapenem was clearly observed in patients less than 12 years of age as compared with older children and adults.

The purpose of Protocol 028 was to determine a rational dosing strategy for treating infections in paediatric patients. Given that the key PK/PD determinant for ertapenem as well as other beta-lactam antimicrobials is the time the plasma concentration exceeds the minimum inhibitory concentration (MIC) of the infecting organism, a twice-divided daily dosing regimen was decided upon as a conservative measure to account for the somewhat greater clearance of ertapenem in the younger age groups (3 months to 12 years of age). A regimen was chosen (15 mg/kg twice daily) so that: 1) the paediatric exposure as measured by plasma AUC would approximate that of adults receiving the standard 1 g once daily ertapenem dose, 2) peak plasma concentrations would not be unnecessarily high and 3) the plasma concentration midway through the dosing interval in children would be similar to that of adults and exceed the highest established susceptibility breakpoint for targeted aerobic pathogens (2 µg/ml). Based on broad-based and extensive *in vitro* susceptibility surveillance studies

summarized with the original Marketing Application these established breakpoints for ertapenem are above (considerably above in most cases) the MIC of more than 90% (MIC90) of the targeted pathogens in each of the approved indications.

In children aged 3 to 23 months, in Study 028, a single intravenous dose of 15 mg/kg was associated with an ertapenem plasma AUC0-∞ (doubled to simulate 15 mg/kg twice daily dosing) of approximately 530 µg•hr/ml. The expected ertapenem plasma exposure following a 15 mg/kg twice daily regimen in 3 to 23 month old children is therefore generally comparable to that observed in healthy young adults receiving the approved 1-g IV dose [(geometric mean AUC approximately 568 µg•hr/ml), i.e. the AUC geometric mean ratio (3 to 23 month/adult) and corresponding 90% CI were 0.93 (0.80, 1.09)]. Similarly, this regimen resulted in comparable AUC values for children 2 to 12 years of age: AUC geometric mean ratio (2 to 12 years/adult) and corresponding 90% CI were 0.89 (0.74, 1.07). The geometric mean plasma clearance (Clp) in 3 to 23 month old children was approximately 2-fold higher than that observed in adults [approximately 0.94 ml/min/kg and approximately 0.43 ml/min/kg respectively, i.e., the Clp geometric mean ratio (3 to 23 month/adult) and corresponding 90% CI were 2.2 (1.9, 2.6)]. Again, these Clp values are comparable for children 2 to 12 years old: Clp geometric mean ratio (2 to 12-year/adult) and corresponding 90% CI were 2.3 (1.9, 2.8).

Renal clearance of ertapenem in 3 to 23 month old children has not been determined: complete and accurate urine collection in this age group was very difficult and the recovery of urine samples in Study 028 was not reliable. The renal clearance of ertapenem in children 2 to 12 years of age was somewhat greater than that in adults. Thus the underlying reasons behind the observed differences in plasma clearance in children 3 months to 12 years of age as compared to adults are not completely known. Nevertheless, despite the apparent differences in plasma clearance in children 3 to 23 months and 2 to 12 years of age, as compared to adults, a 15 mg/kg twice daily dose in these age groups is predicted to deliver bactericidal concentrations of ertapenem at C6 hr, the midpoint of the dosing interval, that are substantially higher than the established highest aerobic susceptibility breakpoint (2 µg/ml) as described in the product circular. In Study 028, the geometric mean of C6 hr values, the midpoint of the dosing interval in 3 to 23 month old children, was approximately 12.7 µg/ml in children 3 to 23 months old, as compared to C12 hr values,the midpoint of the dosing interval in adults, of approximately 8.9 µg/ml in adults receiving a once daily 1-g IV dose [the GMR (3 to 23 month old/adult) and corresponding 90% CI for ertapenem concentrations at the midpoint of the dosing interval were 1.43 (1.09, 1.88)]. The C6 hr values in the 3 to 23 month old children are also comparable to that observed in 2 to 12 year old children following a 15 mg/kg intravenous dose (the geometric mean of C6 hr ertapenem values in 2 to 12 year olds was 10.7 µg/ml).
Thus, based on PK/PD considerations and also upon the clinical experience with ertapenem in adults a 15 mg/kg twice daily regimen provides a conservative therapeutic margin for children 3 months to 12 years of age.

The 15 mg/kg twice daily ertapenem regimen was studied for safety and efficacy in children 3 months to 12 years of age in the paediatric Protocols 036 and 038. This regimen was found to be generally safe, well tolerated and effective. Protocol 038, because of the infectious disease indications studied (acute pelvic infection and appendicitis), enrolled only patients 2 years of age or older. Protocol 036 (UTI, CAP and SSTI) enrolled children as young as 3 months of age. Given the limitations of the sample size in Protocol 036, the efficacy responses were not substantially different between the 3 to 23 month old and the 2 to 12 year old age cohorts who received ertapenem. In each of the three infectious disease indications clinical response rates (95% CI) in the evaluable per protocol (EPP) population were excellent and not substantially different between the two age cohorts who received the twice daily regimen. In UTI the response rate for children 3 to 23 months was 93.3% (68.1, 99.8) and was 84.8% (72.6, 97.1) in the 2 to 12 year old cohort. In SSTI the rate for the youngest cohort, 94.4% (71.7, 99.9) was again not substantially different from that in 2 to 12 year olds, 95.2% (88.8, 100). In CAP the rate was 92.9% (76.5, 95.1) in children 3 to 23 months and 97.9% (93.7, 100) in children 2 to 12 years old; these rates in paediatric CAP were comparable to that observed overall for adults treated for CAP (92.0% [88.8, 94.6]) in the original Marketing Application. In paediatric patients identified as having more severe CAP by virtue of either requiring oxygen supplementation, having multi-lobar pneumonia or concomitant bacteraemia, the clinical response rates again were

excellent and comparable between the two age groups (Table 2.7-2:1). The one bacteremic clinical failure in the 3 to 23 month cohort (AN 9681) had documented clearance of the bacteraemia after ertapenem therapy and is further described below.

Table 2.7-2: 1

Proportion of CAP Patients with Severe Pneumonia Characteristics and a Favorable Clinical Response Assessment
Ertapenem Patients in the 3-23 Month and 2-12 Year Age Cohorts
Clinical Evaluable Population

Characteristic	Ertapenem 3 -23 months		Ertapenem 2-12 years	
	n/m	%	n/m	%
Oxygen Supplementation	4/4	100	11/12	91.7
Multi Lobar Pneumonia	11/11	100	16/17	94.1
Bacteremia	1/2	50	3/3	100
Any of the Above	12/13	92.3	24/25	96.0
n/m = patients with characteristic who had a favorable response/patients with characteristic				

In the clinical EPP analysis, overall across all 3 infectious disease indications in Protocol 036, the proportion of patients cured with study therapy in these 2 age cohorts were identical; 57/61 (93.4% [87.2, 99.7]) in patients 3 to 23 months of age and 114/122 (93.4% [89.1, 97.8]) in patients 2 to 12 years of age. In total there were 4 patients between 3 and 23 months of age who clinically failed study therapy. Two of these patients (AN7884 and AN9897) appeared to have been cured of their baseline infection with therapy but had developed new infections when assessed at the post-treatment test-of-cure visit. A third patient (AN2989) initially responded to ertapenem therapy but experienced a recrudescent wound infection after having received oral follow-up therapy to which an important baseline pathogen (Enterobacter cloacae) was resistant. The fourth patient (AN9681), a 17 month old with CAP and Staphylococcus aureus bacteraemia at baseline, was improving with documented clearance of the bacteraemia after having received 4 days of ertapenem therapy and went on to receive 8 additional days of oral follow-on therapy. Symptoms worsened in this patient while receiving oral therapy and he was found subsequently at follow-up to have a pleural effusion and lung abscess as well as a blood culture positive for an Haemophilus spp (the baseline S. aureus bacteraemia had been cleared). Since the Haemophilus spp. is an unlikely abscess forming organism, it is possible that the pulmonary infection at follow-up was attributable to the baseline Staphylococcus aureus (a known abscess forming organism often requiring extended therapy), in which case the patient most certainly would have benefited from an extended course of parenteral antimicrobial therapy.
Unfortunately further cultures to confirm the organism at follow-up were not done.

Final conclusión on efficacy.
The CHMP considered that this issue had been satisfactorily answered by the MAH. The posology is appropriate for all age groups taking into account PK/PD relationships.

Power calculations for the safety/efficacy trials, P036 and P038, were based on considerations of the analysis of safety outcomes; efficacy outcomes were designated as secondary.
Further to the assessment of the MAH's responses provided, the CHMP considered that based on PK/PD consideration and the clinical experience with standard 1 g once daily ertapenem dosing in adults, the 15 mg/kg twice daily posology is conservative and appropriate for children 3 to 23 months as well as 2 to 12 years of age. In the paediatric safety/efficacy trials this regimen was generally safe and well tolerated with efficacy comparable to that observed previously for ertapenem in adults for the approved indications.
However, following discussions at the May 2005 CHMP meeting, it was agreed that for children aged 3 to 23 months, particularly in the case of CAP, where the success response rates could be lower, a warning should be incorporated in the Product Information.

3.3. Clinical safety

Patient exposure

Single dose studies

1. Single dose study *P028*

	3 to 23 Months	2 to 12 Years	13 to 17 Years
	N = 43	N = 28	N = 13
	n	n	n
Gender			
Female	19	18	5
Male	24	10	8
Race			
Black	17	5	3
Hispanic American	14	6	2
Multi-Racial	1	0	0
White	11	17	8
Age			
Mean	11.7	6.5	14.2
Range	3 to 23 months	2 to 12 years	13 to 16 years
Treatment Group— Ertapenem			
15 mg/kg maximum 1g	12	8	0
20 mg/kg maximum 1g	12	9	6
40 mg/kg maximum 2g	15	11	7

2. Single dose studies *P031/032*
Total N = 12; M/F : 7/5; Age 3 months – 13 years Treatment groups: 15mg/kg (n = 5); 20mg/kg (n= 7)

Multiple dose studies (P036 and P038)

- Dose groups:

15mg/kg twice daily (age 3 months to 12 years) n = 322

1g daily (age 13 to 17 years) n = 62

- Baseline characteristics:

Baseline Characteristics by Treatment Group
(Protocols 036 and 038 Treated Population)

	Ertapenem (N =384) n (%)	Ceftriaxone (N=99) † n (%)	Ticarcillin/ Clavulanate (N=24) n (%)	Total (N=507) n (%)
Gender				
Female	235 (61.2)	57 (57.6)	14 (58.3)	306 (60.4)
Male	149 (38.8)	42 (42.4)	10 (41.7)	201 (39.6)
Race				
Asian	38 (9.9)	5 (5.1)	1 (4.2)	44 (8.7)
Black	37 (9.6)	8 (8.1)	3 (12.5)	48 (9.5)
European	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)
Hispanic American	173 (45.1)	39 (39.4)	15 (62.5)	227 (44.8)
Multi-Racial	16 (4.2)	9 (9.1)	1 (4.2)	26 (5.1)
Polynesian	2 (0.5)	1 (1.0)	0 (0.0)	3 (0.6)
White	117 (30.5)	37 (37.4)	4 (16.7)	158 (31.2)
Age (Months)				
3 to 23 months	116 (30.2)	36 (36.4)	0 (0.0)	152 (30.0)
N	116	36	0 (0.0)	152
Mean	12.2	12.7	-	12.3
SD	5.7	6.6	-	5.9
Median	12.0	12.5	-	12.0
Range	3 to 23	4 to 23	-	3 to 23
Age (Years)				
2 to 12 years	206 (53.6)	56 (56.6)	10 (41.7)	272 (53.6)
N	206	56	10	272
Mean	5.4	5.6	8.4	5.6
SD	3.1	3.2	3.3	3.2
Median	5.0	5.0	9.5	5.0
Range	2 to 12	2 to 12	2 to 12	2 to 12
13 to 17 years	62 (16.1)	7 (7.1)	14 (58.3)	83 (16.4)
N	62	7	14	83
Mean	15.0	14.6	15.1	15.0
SD	1.4	1.5	1.6	1.4
Median	15.0	14.0	15.5	15.0
Range	13 to 17	13 to 17	13 to 17	13 to 17

- Extent of exposure by treatment group:

Extent of Exposure by Route of Administration
and Treatment Group
(Protocols 036 and 038 Treated Population)

	Ertapenem (N =384)	Ceftriaxone (N=100)	Ticarcillin/Clavulanate (N=24)
Days on Study Therapy			
n	384	100	24
Mean	10.2	11.2	7.0
SD	5.1	3.7	4.9
Median	10.0	11.0	6.0
Range	1.0 to 45.0	1.0 to 23.0	3.0 to 28.0
Days on Parenteral Therapy			
n	384	100	24
Mean	4.9	4.3	7.0
SD	2.7	1.3	4.9
Median	4.0	4.0	6.0
Range	1.0 to 36.0	1.0 to 8.0	3.0 to 28.0
Days on Oral Therapy			
n	269	94	0
Mean	8.3	8.0	-
SD	3.5	3.0	-

Days on parenteral therapy = days on IV or IM treatment for ertapenem/ceftriaxone before switch to oral antibiotic, amoxicillin/clavulanic acid.

Adverse events

A display of Adverse Experiences/ Adverse Reactions in the Treated Populations from the multiple dose trials P036 and P038 is shown below:

During Parenteral Therapy—Total and Drug Related
(Protocols 036 and 038 Treated Population)

	Ertapenem (N=384)				Ceftriaxone (N=100)				Ticarcillin/Clavulanate (N=24)			
	Overall		Drug Related		Overall		Drug Related		Overall		Drug Related	
	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)
Patients with one or more adverse experiences	172	(44.8)	80	(20.8)	41	(41.0)	23	(23.0)	14	(58.3)	6	(25.0)
Patients with no adverse experience	212	(55.2)	304	(79.2)	59	(59.0)	77	(77.0)	10	(41.7)	18	(75.0)
Eye Disorders	**3**	**(0.8)**	**0**	**(0.0)**	**1**	**(1.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Eye pain	0	(0.0)	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
Eye swelling	0	(0.0)	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
Gastrointestinal Disorders	**68**	**(17.7)**	**32**	**(8.3)**	**24**	**(24.0)**	**13**	**(13.0)**	**2**	**(8.3)**	**1**	**(4.2)**
Abdominal pain	9	(2.3)	1	(0.3)	2	(2.0)	1	(1.0)	0	(0.0)	0	(0.0)
Abdominal pain upper	0	(0.0)	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
Aphthous stomatitis	1	(0.3)	0	(0.0)	2	(2.0)	0	(0.0)	0	(0.0)	0	(0.0)
Constipation	4	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Diarrhoea	26	(6.8)	21	(5.5)	12	(12.0)	10	(10.0)	1	(4.2)	1	(4.2)
Diarrhoea haemorrhagic	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.2)	0	(0.0)
Loose stools	4	(1.0)	2	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nausea	5	(1.3)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Oral soft tissue disorder	1	(0.3)	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
Stomatitis	0	(0.0)	0	(0.0)	2	(2.0)	0	(0.0)	0	(0.0)	0	(0.0)
Vomiting	25	(6.5)	6	(1.6)	8	(8.0)	2	(2.0)	1	(4.2)	0	(0.0)
General Disorders and Administration Site Conditions	**64**	**(16.7)**	**40**	**(10.4)**	**15**	**(15.0)**	**11**	**(11.0)**	**9**	**(37.5)**	**3**	**(12.5)**
Chest pain	2	(0.5)	1	(0.3)	1	(1.0)	1	(1.0)	0	(0.0)	0	(0.0)

Number (%) of Patients With Specific Clinical Adverse Experiences
(Incidence ≥1% in One or More Treatment Groups) by System Organ Class
During Parenteral Therapy—Total and Drug Related
(Protocols 036 and 038 Treated Population)

	Ertapenem (N=384)				Ceftriaxone (N=100)				Ticarcillin/Clavulanate (N=24)			
	Overall		Drug Related		Overall		Drug Related		Overall		Drug Related	
	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)
General Disorders and Administration Site Conditions (Cont.)												
Infusion-site burning	2	(0.5)	2	(0.5)	0	(0.0)	0	(0.0)	1	(4.2)	1	(4.2)
Infusion-site erythema	15	(3.9)	10	(2.6)	3	(3.0)	2	(2.0)	2	(8.3)	0	(0.0)
Infusion-site induration	4	(1.0)	3	(0.8)	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
Infusion-site pain	27	(7.0)	21	(5.5)	4	(4.0)	1	(1.0)	5	(20.8)	3	(12.5)
Infusion-site phlebitis	7	(1.8)	7	(1.8)	3	(3.0)	3	(3.0)	0	(0.0)	0	(0.0)
Infusion-site pruritus	3	(0.8)	3	(0.8)	1	(1.0)	1	(1.0)	0	(0.0)	0	(0.0)
Infusion-site reaction	2	(0.5)	2	(0.5)	1	(1.0)	1	(1.0)	1	(4.2)	1	(4.2)
Infusion-site swelling	7	(1.8)	4	(1.0)	1	(1.0)	0	(0.0)	1	(4.2)	0	(0.0)
Infusion-site warmth	5	(1.3)	3	(0.8)	1	(1.0)	1	(1.0)	1	(4.2)	1	(4.2)
Oedema peripheral	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.2)	0	(0.0)
Pyrexia	8	(2.1)	0	(0.0)	2	(2.0)	1	(1.0)	2	(8.3)	0	(0.0)
Infections and Infestations	**23**	**(6.0)**	**1**	**(0.3)**	**4**	**(4.0)**	**0**	**(0.0)**	**5**	**(20.8)**	**1**	**(4.2)**
Abdominal abscess	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.2)	0	(0.0)
Bronchitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.2)	0	(0.0)
Ear infection	0	(0.0)	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
Herpes simplex	4	(1.0)	0	(0.0)	1	(1.0)	0	(0.0)	1	(4.2)	0	(0.0)
Nasopharyngitis	0	(0.0)	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
Tinea pedis	0	(0.0)	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
Vaginal candidiasis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.2)	1	(4.2)

Number (%) of Patients With Specific Clinical Adverse Experiences
(Incidence ≥1% in One or More Treatment Groups) by System Organ Class
During Parenteral Therapy—Total and Drug Related[†]
(Protocols 036 and 038 Treated Population)

	Ertapenem (N=384)				Ceftriaxone (N=100)				Ticarcillin/Clavulanate (N=24)			
	Overall		Drug Related		Overall		Drug Related		Overall		Drug Related	
	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)
Infections and Infestations (Cont.)												
Wound infection	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.2)	0	(0.0)
Injury, Poisoning,and Procedural Complications	**23**	**(6.0)**	**1**	**(0.3)**	**4**	**(4.0)**	**1**	**(1.0)**	**1**	**(4.2)**	**0**	**(0.0)**
Blister	0	(0.0)	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hypothermia	5	(1.3)	1	(0.3)	1	(1.0)	1	(1.0)	0	(0.0)	0	(0.0)
Lumbar puncture headache	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.2)	0	(0.0)
Overdose[‡]	13	(3.4)	0	(0.0)	2	(2.0)	0	(0.0)	0	(0.0)	0	(0.0)
Metabolism and Nutrition Disorders	**3**	**(0.8)**	**1**	**(0.3)**	**2**	**(2.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Decreased appetite	2	(0.5)	1	(0.3)	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dehydration	1	(0.3)	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
Musculoskeletal and Connective Tissue Disorders	**4**	**(1.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(4.2)**	**0**	**(0.0)**
Arthralgia	2	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.2)	0	(0.0)
Nervous System Disorders	**15**	**(3.9)**	**2**	**(0.5)**	**3**	**(3.0)**	**1**	**(1.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Headache	12	(3.1)	2	(0.5)	2	(2.0)	1	(1.0)	0	(0.0)	0	(0.0)
Somnolence	1	(0.3)	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)

Number (%) of Patients With Specific Clinical Adverse Experiences
(Incidence ≥1% in One or More Treatment Groups) by System Organ Class
During Parenteral Therapy—Total and Drug Related[†]
(Protocols 036 and 038 Treated Population)

	Ertapenem (N=384)				Ceftriaxone (N=100)				Ticarcillin/Clavulanate (N=24)			
	Overall		Drug Related		Overall		Drug Related		Overall		Drug Related	
	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)
Psychiatric Disorders	**2**	**(0.5)**	**0**	**(0.0)**	**1**	**(1.0)**	**1**	**(1.0)**	**1**	**(4.2)**	**1**	**(4.2)**
Agitation	0	(0.0)	0	(0.0)	1	(1.0)	1	(1.0)	0	(0.0)	0	(0.0)
Insomnia	2	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.2)	1	(4.2)
Renal and Urinary Disorders	**2**	**(0.5)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(4.2)**	**0**	**(0.0)**
Renal insufficiency	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.2)	0	(0.0)
Reproductive System and Breast Disorders	**2**	**(0.5)**	**1**	**(0.3)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(4.2)**	**0**	**(0.0)**
Hydrocele	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.2)	0	(0.0)
Respiratory, Thoracic, and Mediastinal Disorders	**24**	**(6.3)**	**1**	**(0.3)**	**4**	**(4.0)**	**1**	**(1.0)**	**2**	**(8.3)**	**0**	**(0.0)**
Cough	9	(2.3)	0	(0.0)	2	(2.0)	1	(1.0)	0	(0.0)	0	(0.0)
Pharyngeal erythema	0	(0.0)	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pleural effusion	3	(0.8)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.2)	0	(0.0)
Respiratory distress	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.2)	0	(0.0)
Respiratory failure	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.2)	0	(0.0)
Rhinorrhoea	2	(0.5)	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)

Number (%) of Patients With Specific Clinical Adverse Experiences
(Incidence ≥1% in One or More Treatment Groups) by System Organ Class
During Parenteral Therapy—Total and Drug Related[†]
(Protocols 036 and 038 Treated Population)

	Ertapenem (N=384)				Ceftriaxone (N=100)				Ticarcillin/Clavulanate (N=24)			
	Overall		Drug Related		Overall		Drug Related		Overall		Drug Related	
	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)	m	(%)
Skin and Subcutaneous Tissue Disorders	**28**	**(7.3)**	**10**	**(2.6)**	**7**	**(7.0)**	**2**	**(2.0)**	**4**	**(16.7)**	**1**	**(4.2)**
Dermatitis	1	(0.3)	0	(0.0)	1	(1.0)	1	(1.0)	0	(0.0)	0	(0.0)
Dermatitis diaper	10	(2.6)	2	(0.5)	3	(3.0)	0	(0.0)	0	(0.0)	0	(0.0)
Erythema	1	(0.3)	1	(0.3)	1	(1.0)	0	(0.0)	1	(4.2)	0	(0.0)
Heat rash	0	(0.0)	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pruritus	4	(1.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Rash	9	(2.3)	5	(1.3)	1	(1.0)	1	(1.0)	2	(8.3)	1	(4.2)
Rash papular	1	(0.3)	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
Scab	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.2)	0	(0.0)
Vascular Disorders	**7**	**(1.8)**	**6**	**(1.6)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**

[†] Determined by the investigator to be possibly, probably, or definitely drug related.
[‡] 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.
N=Number of patients in treatment group.
n=Number of patients in category.
m=Number of patients with adverse experience.
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.

[Ref. 5.3.5.1: P036, P038]

Serious adverse events and deaths

There were no deaths reported in any of the studies.

Summaries are set out in italics below together with the relevant Tables:

Pharmacokinetic Studies: Protocols 028 and 031/032

The table lists the serious adverse experiences for those patients enrolled in Protocol 028. There were a total of 11 patients that 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 1 serious drug related adverse experience was reported in a patient who received an overdose of study medication; however, there was no adverse experience associated with this overdose.

Listing of Patients With Serious Clinical Adverse Experiences
Protocol 028

AN	Age	Gender	Race	Ertapenem Dose (mg/kg)	Relative Day of Onset	Adverse Experience	Duration	Action	Intensity	Drug Relationship	Outcome
0103	6 months	Male	Hispanic	40	Day 9	Pneumonia respiratory syncytial viral	11 days	None	Mild	Definitely not	Recovered
0122	18 months	Female	Black	40	Day 18	Hypoxia	3 days	None	Moderate	Definitely not	Recovered
0124	22 months	Female	Hispanic	20	Day 14	Pyothorax (pulmonary empyema)	Ongoing	None	Moderate	Definitely not	Not recovered
0128	6 years	Female	White	20	Day 1	Overdose nos[†]	1 day	None	Mild	Definitely	Recovered
0134	10 years	Male	White	40	Day 3	Arrhythmia nos	3 days	None	Moderate	Definitely not	Recovered
0134	10 years	Male	White	40	Day 27	Supraventricular tachycardia	5 days	None	Moderate	Definitely not	Recovered
0143	16 years	Male	White	40	Day -2	Pain nos (stoma site pain)[‡]	0.88 hour	None	Severe	Definitely not	Recovered
0145	13 years	Male	White	20	Day 5	Abscess drainage (appendiceal)	5 days	None	Moderate	Definitely not	Recovered
0148	15 years	Female	Hispanic	40	Day 15	Pulmonary embolism	1.05 months	None	Moderate	Definitely not	Recovered

0170	21 months	Female	Hispanic	20	Day 24	Respiratory distress	5 days	None	Severe	Definitely not	Recovered
0181	10 years	Female	Black	40	Day 8	Vascular occlusion	4 days	None	Moderate	Definitely not	Recovered
0253	4 years	Male	White	15	Day 1	Overdose nos[†]	0.5 hour	None	--	--	Recovered

[†] Overdose with ertapenem without any associated adverse experiences was reported. For AN *0253 (bottom row)*, the investigator did not report intensity and drug relationship.

[‡] Occurred at prestudy.

The following table displays a listing of the 2 patients with serious clinical adverse experiences for Protocol 031/032. The serious clinical adverse experiences reported were not study drug related, and no action regarding study drug was taken.

Listing of Patients With Serious Clinical Adverse Experiences
During Drug Administration and 14-Day Follow-Up Period
Protocols 031/032

Gender	Race	Age	Therapy	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Intensity	Relative Day of Discontinuation	Drug Relation-ship	Action Taken	Outcome
M	Hispanic	10 yrs	Off drug 8 days	9	Rash maculo-papular	4 days	Mild	1	Probably not	None	Recovered
M	Hispanic	4 months	Off drug 1 day	2	Brain damage	Continuous	Severe	1	Definitely not	None	Not recovered
			Off drug 2 days	3	Convulsions NOS†	4 days	Severe	1	Probably not	None	Recovered
			Off drug 6 days	7	Coma	Continuous	Severe	1	Probably not	None	Not recovered
			Off drug 6 days	7	Inappropriate antidiuretic hormone secretion	2 days	Moderate	1	Probably not	None	Recovered
			Off drug 27 days	28	Pneumonia NOS	12 days	Severe	1	Definitely not	None	Recovered

The narrative in the adverse experience report states that the investigator considered convulsions as definitely not study drug related. The dose was 20mg/kg IV (single dose).

Clinical Studies: Protocols 036 and 038

Serious Clinical Adverse Experiences During Study Therapy and 14-Day Follow-Up

Overall, 30 (5.9%) of the 508 patients had at least one serious clinical adverse experience: 21 (5.5%) in the ertapenem group, 6 (6.0%) in the ceftriaxone group, and 3 (12.5%) in the ticarcillin/clavulanate group. 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 (2.0%) in the ceftriaxone group, and none in the ticarcillin/clavulanate group.

The following tables display a listing of the serious clinical adverse experiences found in the clinical study reports: protocols 036 and 038:

Listing of Patients With Serious Clinical Adverse Experiences
During Study Therapy and 14-Day Follow-Up Period
(Protocols 036 and 038 Treated Population)

Study Number	AN	Gender	Race	Age	Therapy	Total Daily Dose	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Relative Day of Discontinuance	Intensity	Drug Relationship	Action Taken	Outcome
Treatment group: ertapenem														
036004	2036	F	Black	15 yr	Off drug 8 days		22	Pregnancy	NA	14		Definitely not	No action with test drug	Not recovered
	2370	M	White	5 yr	Ertapenem	15.02 mg/kg	1	Obstructive airways disorder	2 days	11	Moderate	Definitely not	No action with test drug	Recovered
	3703	F	Multi-Racial	16 mo	Ertapenem	30.71 mg/kg	3	Respiratory distress	2 days	13	Severe	Definitely not	No action with test drug	Recovered
					Ertapenem	30.71 mg/kg	6	Pleural effusion	2 days	13	Severe	Definitely not	No action with test drug	Recovered
036032	7396	F	Hispanic American	2 yr	Ertapenem	30.00 mg/kg	2	Gastroenteritis rotavirus	3 days	10	Moderate	Definitely not	No action with test drug	Recovered
					Ertapenem	30.00 mg/kg	2	Vomiting	3 days	10	Moderate	Definitely not	No action with test drug	Recovered
036041	7884	M	Asian	4 mo	Off drug 5 days		14	Urinary tract infection	5 days	9	Moderate	Probably not	No action with test drug	Recovered

Study Number	AN	Gender	Race	Age	Therapy	Total Daily Dose	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Relative Day of Discontinuance	Intensity	Drug Relationship	Action Taken	Outcome
036045	8591	M	White	4 yr	Ceftriaxone	31.13 mg/kg	2	Vomiting	6 hours	16	Mild	Possibly	No action with test drug	Recovered
					Ertapenem†	9.62 mg/kg	2	Vomiting	6 hours	16	Mild	Possibly	No action with test drug	Recovered
036048	9680	M	White	7 mo	Off drug 9 days		20	Pneumonia	Continuing	11	Moderate	Probably not	No action with test drug	Not recovered
	9681	M	Black	17 mo	Off drug 7 days		19	Pyrexia	5 days	12	Moderate	Probably not	No action with test drug	Recovered
					Off drug 10 days		22	Lung abscess	16 days	12	Severe	Probably not	No action with test drug	Recovered

Listing of Patients With Serious Clinical Adverse Experiences
During Study Therapy and 14-Day Follow-Up Period
(Protocols 036 and 038 Treated Population), (Cont.)

Study Number	AN	Gender	Race	Age	Therapy	Total Daily Dose	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Relative Day of Discontinuance	Intensity	Drug Relationship	Action Taken	Outcome
Treatment group: ertapenem (Cont.)														
	9682	M	White	7 mo	Ertapenem	30.00 mg/kg	2	Epistaxis		2		Probably not	Discontinued test drug	Not recovered
					Ertapenem	30.00 mg/kg	2	Sepsis	3 days	2	Moderate	Probably not	No action with test drug	Recovered
036058	9661	F	White	10 yr	Amoxicillin (+) clavulanate potassium	49.71 mg/kg	7	Influenza	4 days	15	Moderate	Probably not	No action with test drug	Recovered
038007	5040	F	Hispanic American	9 yr	Off drug 7 days		15	Pelvic abscess	6 days	8	Moderate	Definitely not	No action with test drug	Recovered
					Off drug 7 days		15	Pyrexia	6 days	8	Moderate	Definitely not	No action with test drug	Recovered
	5047	M	White	11 yr	Off drug 4 days		10	Abdominal abscess	15 days	6	Moderate	Definitely not	No action with test drug	Recovered
	5060	M	Hispanic American	3 yr	Ertapenem	15.00 mg/kg	11	Small intestinal obstruction	7 days	11	Severe	Definitely not	No action with test drug	Recovered
	5241	M	Asian	3 yr	Ertapenem	30.00 mg/kg	3	Diarrhoea	5 days	4	Moderate	Probably	Discontinued test drug	Recovered
038008	5046	F	Hispanic American	12 yr	Ertapenem	30.00 mg/kg	7	Pelvic abscess	10 days	10	Severe	Definitely not	No action with test drug	Recovered
038009	5096	M	White	13 yr	Off drug 4 days		12	Abdominal abscess	4 days	8	Severe	Definitely not	No action with test drug	Recovered

Listing of Patients With Serious Clinical Adverse Experiences
During Study Therapy and 14-Day Follow-Up Period
(Protocols 036 and 038 Treated Population), (Cont.)

Study Number	AN	Gen-der	Race	Age	Therapy	Total Daily Dose	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Relative Day of Dis-continuance	Intensity	Drug Relationship	Action Taken	Outcome
Treatment group: ertapenem (Cont.)														
038011	5053	M	Hispanic American	6 yr	Off drug 4 days		9	Constipation	2 days	5	Moderate	Definitely not	No action with test drug	Recovered
	5251	M	Hispanic American	11 yr	Off drug 7 days		13	Abdominal abscess	10 days	6	Moderate	Probably not	No action with test drug	Recovered
038014	5061	M	White	7 yr	Ertapenem	30.00 mg/kg	9	Abdominal abscess	5 days	10	Moderate	Definitely not	Discontinued test drug	Recovered
	5092	F	White	13 yr	Off drug 9 days		14	Abdominal pain	6 days	5	Mild	Definitely not	No action with test drug	Recovered
038015	5105	M	Europe	15 yr	Off drug 6 days		8	Small intestinal obstruction	8 days	2	Moderate	Definitely not	No action with test drug	Recovered
Treatment group: ceftriaxone														
036014	1827	F	Hispanic American	4 mo	Off drug 9 days		24	Gastroenteritis	6 days	15	Moderate	Definitely not	No action with test drug	Recovered
036028	9419	F	Hispanic American	6 yr	Ceftriaxone	24.71 mg/kg	4	Rash	3 days	10	Mild	Definitely	Discontinued test drug	Recovered
					Clarithromycin	7.35 mg/kg	4	Rash	3 days	10	Mild	Definitely	Discontinued test drug	Recovered
036047	7667	M	Black	4 mo	Off drug 9 days		11	Vomiting	3 days	2	Moderate	Definitely not	No action with test drug	Recovered
036048	9348	M	White	5 yr	Off drug 4 days		16	Pneumonia	18 days	12	Moderate	Probably not	No action with test drug	Recovered

Listing of Patients With Serious Clinical Adverse Experiences
During Study Therapy and 14-Day Follow-Up Period
(Protocols 036 and 038 Treated Population), (Cont.)

Study Number	AN	Gender	Race	Age	Therapy	Total Daily Dose	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Relative Day of Discontinuance	Intensity	Drug Relationship	Action Taken	Outcome
Treatment group: ceftriaxone (Cont.)														
036058	7991	F	White	22 mo	Amoxicillin (+) clavulanate potassium	40.44 mg/kg	7	Influenza	4 days	23	Moderate	Definitely not	No action with test drug	Recovered
	9664	F	White	11 yr	Amoxicillin (+) clavulanate potassium	51.95 mg/kg	10	Pyrexia	2 days	22	Mild	Probably	No action with test drug	Recovered
reatment group: ticarcillin/clavulanate														
038007	5043	M	Hispanic American	12 yr	Off drug 3 days		12	Postoperative infection	29 days	9	Moderate	Definitely not	No action with test drug	Recovered
038008	5085	M	White	16 yr	Off drug 7 days		35	Abdominal pain	4 days	28	Severe	Definitely not	No action with test drug	Recovered
					Off drug 7 days		35	Vomiting	4 days	28	Severe	Definitely not	No action with test drug	Recovered
038014	5067	M	Black	7 yr	Ticarcillin/clavulanate	150.00 mg/kg	3	Hydrocele	11 days	8	Moderate	Definitely not	No action with test drug	Recovered

† AN 8591 was randomised to the ertapenem treatment group. On Day 2 the patient mistakenly received 1 dose of ceftriaxone in an amount 20% greater than the calculated dosage. The patient subsequently vomited 2 times 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 experiences.

AN = allocation number.

Discontinuations Due to Clinical Adverse Experiences

Pharmacokinetic Studies: Protocols 028 and 031/032

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

Clinical Studies: Protocols 036 and 038

There were 11 discontinuations from study therapy as a result of a clinical adverse experience, including 8 (2.1%) in the ertapenem group, 1 (1.0%) in the ceftriaxone group and 2 (8.3%) in the ticarcillin/clavulanate group. The tables below display a listing of patients who discontinued therapy due to clinical adverse experiences. In the ertapenem group, 2 patients discontinued ertapenem therapy because of diarrhea, which was considered drug related by the investigator. The remaining 6 study drug discontinuations in the ertapenem group, 2 of which (diarrhoea, vomiting) were discontinuations of oral follow-up therapy, were for adverse experiences not considered by the investigators to have been related to ertapenem. Overall, discontinuations due to clinical adverse experiences were infrequent and were similar between treatment groups.

Listing of Patients Discontinued Due to Clinical Adverse Experiences
During Study Therapy and 14-Day Follow-Up Period
(Protocols 036 and 038 Treated Population)

Study Number	AN	Gen-der	Race	Age	Therapy	Total Daily Dose	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Relative Day of Dis-Continuance	Intensity	Drug Relationship	Ser-ious	Outcome
Treatment group: Ertapenem														
036002	3678	M	White	19 mo	Amoxicillin (+) clavulanate potassium	98.36 mg/kg	7	Diarrhoea	1 days	18	Moderate	Definitely not	N	Recovered
					Amoxicillin	160.66 mg/kg	7	Diarrhoea	1 days	18	Moderate	Definitely not	N	Recovered
036004	2702	F	White	14 mo	Ertapenem	14.95 mg/kg	3	Cellulitis	Continuing	3	Severe	Definitely not	N	Not recovered
036021	2906	M	Multi-Racial	22 mo	Ertapenem	14.97 mg/kg	2	Decreased appetite	3 days	4	Moderate	Probably not	N	Recovered
					Clindamycin	30.61 mg/kg	2	Decreased appetite	3 days	4	Moderate	Probably not	N	Recovered
					Ertapenem	14.97 mg/kg	2	Diarrhoea	3 days	4	Moderate	Probably not	N	Recovered
					Clindamycin	30.61 mg/kg	2	Diarrhoea	3 days	4	Moderate	Probably not	N	Recovered

Study Number	AN	Gen-der	Race	Age	Therapy	Total Daily Dose	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Relative Day of Dis-Continuance	Intensity	Drug Relationship	Ser-ious	Outcome
					Ertapenem	14.97 mg/kg	2	Lethargy	3 days	4	Moderate	Probably not	N	Recovered
					Clindamycin	30.61 mg/kg	2	Lethargy	3 days	4	Moderate	Probably not	N	Recovered
036030	7382	F	Hispanic America n	4 yr	Amoxicillin (+) clavulanate potassium	44.14 mg/kg	11	Vomiting	24 hours	12	Mild	Probably	N	Recovered
036048	9682	M	White	7 mo	Ertapenem	30.00 mg/kg	2	Epistaxis		2		Probably not	Y	Not recovered
036058	9990 †	M	White	19 mo	Ertapenem	30.56 mg/kg	3	Diarrhoea	6 days	10	Severe	Definitely	N	Recovered

Listing of Patients Discontinued Due to Clinical Adverse Experiences
During Study Therapy and 14-Day Follow-Up Period
(Protocols 036 and 038 Treated Population) (Cont.)

Study Number	AN	Gen-der	Race	Age	Therapy	Total Daily Dose	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Relative Day of Dis-Continuance	Intensity	Drug Relationship	Ser-ious	Outcome
Treatment group: Ertapenem (Cont.)														
038007	5241	M	Asian	3 yr	Ertapenem	30.00 mg/kg	3	Diarrhoea	5 days	4	Moderate	Probably	Y	Recovered
038014	5061	M	White	7 yr	Ertapenem	30.00 mg/kg	9	Abdominal abscess	5 days	10	Moderate	Definitely not	Y	Recovered
Treatment group: Ceftriaxone														
036028	9419	F	Hispanic American	6 yr	Ceftriaxone	24.71 mg/kg	4	Rash	3 days	10	Mild	Definitely	Y	Recovered
					Clarithromycin	7.35 mg/kg	4	Rash	3 days	10	Mild	Definitely	Y	Recovered
Treatment group: Ticarcillin/Clavulanate														
038008	5085	M	White	16 yr	Ticarcillin/clavulanate	149.01 mg/kg	28	Rash	3 days	28	Mild	Probably	N	Recovered
038013	5095	F	Black	17 yr	Ticarcillin/clavulanate	0.20 gm/kg	7	Wound infection	Continuing	9	Severe	Probably not	N	Not recovered

† AN 9990 completed parenteral therapy (ertapenem) and continued on oral therapy (amoxicillin/clavulanate potassium). According to the investigator comments, the intensity of the diarrhoea increased during the administration of amoxicillin/clavulanate potassium and was considered by the investigator to be definitely related to the oral administration resulting in the switch to an other oral agent (ceflacor).

AN = allocation number.

Adverse Reactions of Special Interest

Four (4) adverse reactions (seizures, liver enzyme elevations, neutropaenia, and rash leading to discontinuation of study therapy) were prespecified for more detailed review because of preclinical findings (neutropaenia, liver enzyme elevations), adverse reactions associated with β-lactam antibiotics as a class (neutropaenia, liver function elevations, rash), and adverse reactions associated with other carbapenem antimicrobials (seizures).

Rash

The incidence of general rash was low and similar between the comparator groups: 11 (2.9%) patients in the ertapenem group, 2 (2.0%) patients in the ceftriaxone group, and 2 (8.3%) patients in the ticarcillin/clavulanate group. In addition to the 1.3% (5 patients) of drug-related adverse reactions of rash, there were drug-related adverse events of erythema in 1 patient (0.3%), exanthema in 1 patient (0.3%), and macular rash in 1 patient (0.3%) in the ertapenem group. There were no reports in any paediatric patient of rash that was considered serious or that resulted in the discontinuation of ertapenem study therapy.

Seizures

Of the 480 patients that received at least one dose of ertapenem in the 5 paediatric studies, there was one reported incident of seizure in Protocol 031/032, a CSF PK study in patients with bacterial meningitis. This was reported in a 4-month-old male patient with pneumococcal meningitis who received 1 dose of 20 mg/kg of ertapenem on Day 2 of admission to the hospital. The day after the administration of ertapenem (Study Day 2), it was reported that the patient had a left frontal infarction and subdural collection both believed to be consequences of the meningitis. On Study Day 3, surgical drainage was performed and the patient experienced a right focal seizure with secondary generalization. Despite treatment with phenytoin, phenobarbital and midazolam, the patient experienced intermittent focal seizures Study Day 3 through Study Day 6. The investigator reported that the convulsions were probably related to the subdural effusion and underlying brain injury (a result of meningitis) and were not considered drug-related. The patient subsequently recovered from the convulsions.

Laboratory findings

The following table displays the clinically significant laboratory abnormalities that occurred in the two multiple dose clinical trials P036 and 038:

Proportion of Patients With a
Clinically Significant Laboratory Abnormalities (CSLA)
During Study Therapy and 14-Day Follow-up Period
(Protocols 036 and 038 Treated Population)

		Treatment Group									
		Ertapenem						Ceftriaxone		Ticarcillin/ Clavulanate	
Laboratory Test (Unit)	CSLA Criteria	Study 36 (N=303) n/m	(%)	Study 38 (N=81) n/m	(%)	Total (N=384) n/m	(%)	Study 36 (N=100) n/m	(%)	Study 38 (N=24) n/m	(%)
Total serum bilirubin mg/dL	>1.5 x ULN	3/281	(1.1)	0/77	(0.0)	3/358	(0.8)	2/94	(2.1)	0/23	(0.0)
	>2.5 x ULN	2/281	(0.7)	0/77	(0.0)	2/358	(0.6)	1/94	(1.1)	0/23	(0.0)
Serum direct bilirubin mg/dL	>1.5 x ULN	1/170	(0.6)	0/37	(0.0)	1/207	(0.5)	1/50	(2.0)	0/10	(0.0)
	>2.5 x ULN	1/170	(0.6)	0/37	(0.0)	1/207	(0.5)	0/50	(0.0)	0/10	(0.0)

Serum alanine aminotransferase IU/L	>2.5 x ULN	9/289	(3.1)	1/73	(1.4)	10/362	(2.8)	2/94	(2.1)	2/23	(8.7)
	>5 x ULN	3/289	(1.0)	1/73	(1.4)	4/362	(1.1)	1/94	(1.1)	0/23	(0.0)
Serum aspartate aminotransferase IU/L	>2.5 x ULN	10/287	(3.5)	1/76	(1.3)	11/363	(3.0)	2/94	(2.1)	0/22	(0.0)
	>5 x ULN	4/287	(1.4)	0/76	(0.0)	4/363	(1.1)	0/94	(0.0)	0/22	(0.0)
Serum alkaline phosphatase IU/L	>2.5 x ULN	2/260	(0.8)	0/76	(0.0)	2/336	(0.6)	0/87	(0.0)	0/23	(0.0)
	> 5 x ULN	1/260	(0.4)	0/76	(0.0)	1/336	(0.3)	0/87	(0.0)	0/23	(0.0)
Serum creatinine mg/dL	>1.5 x ULN	2/291	(0.7)	0/77	(0.0)	2/368	(0.5)	0/93	(0.0)	0/23	(0.0)
	>3 x ULN	0/291	(0.0)	0/77	(0.0)	0/368	(0.0)	0/93	(0.0)	0/23	(0.0)
ANC /microl	<1800	85/286	(29.7)	4/73	(5.5)	89/359	(24.8)	26/94	(27.7)	0/21	(0.0)
	<1000	21/286	(7.3)	0/73	(0.0)	21/359	(5.8)	3/94	(3.2)	0/21	(0.0)
	≤500	3/286	(1.0)	0/73	(0.0)	3/359	(0.8)	0/94	(0.0)	0/21	(0.0)
Platelet count 10[3]/microl	<75	1/293	(0.3)	0/73	(0.0)	1/366	(0.3)	0/96	(0.0)	0/23	(0.0)
	<50	1/293	(0.3)	0/73	(0.0)	1/366	(0.3)	0/96	(0.0)	0/23	(0.0)
Hematocrit %	<24	3/294	(1.0)	1/77	(1.3)	4/371	(1.1)	0/97	(0.0)	0/24	(0.0)
Hemoglobin gm/dL	<8	3/294	(1.0)	1/77	(1.3)	4/371	(1.1)	0/97	(0.0)	0/24	(0.0)

ULN = upper limit of normal range.
ANC = absolute neutrophil count.
N = number of patients who received at least one dose of study medication.
n/m = number of patients with CSLA/number of patients with laboratory test at baseline and postbaseline.

In P038 RCT there were no reports of ANC decreases <1000/µl in any of the patients receiving ertapenem during study therapy or the 14-day post-therapy follow-up period.

There seemed to be one noteworthy difference in ADE rates: decreased absolute neutrophil counts (ANC), particularly relatively severe reductions (less than 500/µl), were more common in the ertapenem group than in the ceftriaxone group in the P036 RCT. The rate for ANC <1000/ µl was 21/286 (7.3%) in the ertapenem group and 3/94 (3.2%) in the ceftriaxone group; and the rate for ANC <500/µl was 3/286 (1.0 %) and 0/94 in the ceftriaxone group.

The MAH was requested further information on the occurrence of the neutropaenia events in relation to the timing of their onset, the baseline values, the nadir values, the time to and extent of recovery and the sequelae.

Concerning the above-mentioned rates for ANC decreases of <1000/µl and <500/µl observed in protocol 036 during study therapy (IV and oral) or during the 14 day post-therapy follow-up period, the MAH provided a new table detailing the statistical difference and 95% CI for both treatment groups and explained that these rates were not statistically different than those observed for the

comparator (ceftriazone): (difference and 95% CI; ANC/µl <1000/µl: 4.1 (-2.0, 8.5) and ANC/µl <500/µl: 1.0 (-2.9, 3.0).

The MAH also provided a listing of the 21 patients from P036 who received ertapenem and had an ANC decreased to <1000/ µl during study therapy or the 14 day post-therapy follow-up period, including age of patient, baseline ANC, ANC at discontinuation of parental therapy with the corresponding study day, ANC during Follow-up with the corresponding study day, possible drug causal relationship, seriousness and need for discontinuation of therapy.
None of these laboratory abnormalities was considered a serious adverse reaction by the investigator and no patient was discontinued from ertapenem therapy because of these haematological findings. There were no adverse sequelae reported by the investigator to have resulted from the observed neutrophil decreases in any patient.
Three patients experienced ANC decreases after the DCPT visit (discontinuation of parental therapy), while 18 patients were first noted to have ANC decreases at the DCPT visit. Of these 18 patients, 3 had an ANC decrease to <500/µl, the lowest value reported to be 236/µl in a patient receiving 4 days of ertapenem for UTI. Repeat testing in each of the three patients showed the ANC to have returned to normal by the time of the next follow-up assessment and no sequelae were observed in any of the patients.
In conclusion, similar to the experience in adults treated with ertapenem, and to both adults and children treated with other beta-lactam agents for acute bacterial infections, neutropaenia observed in paediatric patients treated with ertapenem is, in general, transient and reversible without sequelae.
Based on the frequency of neutropaenia observed in the ertapenem paediatric studies, the SPC will now be amended to list these ANC decreases in the section for children and adolescents (3 months to 17 years of age) as a common (frequency ≥ 1/100) undesirable effect.

The CHMP considered that the MAH had provided reassuring evidence as to the recoverability of the neutropenia with some indication that this is a disease-related phenomenon associated with community acquired pneumonia.

3.4. Overall conclusion and benefit-risk assessment

The studies submitted represent a coherent development programme for the extension of the Marketing Authorisation to include patients in the paediatric age group. The choice of dosage in the various age groups is supported by the results of appropriate pharmacokinetic studies. Although comparison of efficacy outcomes was regarded as a secondary objective (the determination of sample size and power analysis specifically addressed the primary safety hypothesis), the efficacy evaluations consistently demonstrated comparable efficacy between Invanz (ertapenem) and the comparator antibiotics. In addition, the efficacy results for Invanz in the paediatric age groups were comparable to those achieved in adult studies with the same product.
However, following discussions at the May 2005 CHMP meeting, it was agreed that for children aged 3 to 23 months, particularly in the case of CAP, where the success response rates could be lower, a warning should be incorporated into the Product Information.
The safety data were reassuring with the exception of an apparently higher incidence of neutropenia than that seen in patients with pneumonia, skin and soft tissue infections and urinary tract infections who were treated with ceftriaxone. The MAH provided reassuring evidence as to the recoverability of the neutropenia with some indication that this is a disease-related phenomenon associated with community acquired pneumonia.

4. Changes to the Product Information

The MAH proposed to amend the relevant sections of the SPC and Package Leaflet as follows:

- **Section 4.1. “Therapeutic indications” of the SPC:**
  This section has been modified to include the intended new indication by deleting the words “in adults”.

- **Section 4.2. "Posology and method of administration" of the SPC:**

This section has been amended to include dosage recommendations for adolescents aged 13 to 17 years and for children 3 months to 12 years of age.
Following CHMP discussions at the May 2005 meeting, a cross-reference to Section 4.4 has been added.

- **Section 4.4. "Special warnings and precautions for use" of the SPC:**

This section has been corrected to clearly specify that the already existing information on the clinical studies mentioned therein only applies to adults.
Following CHMP discussions at the May 2005 meeting, a warning has been introduced in this section regarding the use of the product in children *less than 2 years of age*.

- **Section 4.8. "Undesirable events" of the SPC:**

This section has been updated to include information on the adverse reactions in children and adolescents 3 months to 17 years of age reported during the paediatric clinical studies, as well as on the laboratory abnormalities for children aged 3 months to 17 years reported either during Post-marketing Experience or during the paediatric clinical studies.

- **Section 4.9. "Overdose" of the SPC:**

This section has been updated to include information from the paediatric clinical studies regarding the non-toxicity of a single IV dose of ertapenem 40 mg/kg up to a maximum of 2 g.

- **Section 5.1. "Pharmacodynamic properties" of the SPC:**

This section has been updated to present the results of the paediatric studies for the primary endpoints broken down by indication and age group.
Additionally, the ATC code has been updated in accordance with the approved WHO code.

- **Section 5.2. "Pharmacokinetic properties" of the SPC:**

This section has been updated to include information from the paediatric pharmacological studies on plasma concentrations, distribution and elimination for children aged 3 months to 12 years and for adolescents 13 to 17 years of age.

- **Section 6.6. "Instructions for use and handling" of the SPC:**

This section has been updated to include specific instructions for children 3 months to 12 years of age for the reconstitution, dilution and infusion of the product.

- **The Package Leaflet** has been updated in Section 3. "Before you are given INVANZ", Section 4. "How is INVANZ given?", Section 5. "What undesirable effects may INVANZ have?" and the Section intended for medical or healthcare professionals, in accordance with the above-mentioned SPC proposed changes.