STATISTICAL REVIEW

NDA Number:	21-337
Drug Trade Name:	INVANZ
Drug Generic Name:	Ertapenem
Formulation:	Intravenous/Intramuscular
Applicant:	Merck Research Labs.
Indication:	Community-Acquired Pneumonia
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1 Executive Summary: Statistical

The evidence to support claims of clinical and microbiological efficacy, and tolerability of ertapenem when administered intravenously at a dose of 1 g in adult patients with community-acquired pneumonia (CAP) was provided by 2 controlled, comparative, double-blind, randomized, equivalence (non-inferiority) clinical trials (Protocols 018, 020). The data demonstrated that ertapenem was non-inferior to ceftriaxone in clinical response, favorable microbiological response, and signs and symptoms of intolerability at the intravenous site. The primary endpoint was clinical cure at the test-of-cure (TOC) time point in the clinically evaluable population for protocol 018 and clinical response in the microbiologically evaluable population for protocol 020. A -10% lower bound of the 2-sided, 95% confidence interval (CI) was used to determine statistical non-inferiority of ertapenem compared to ceftriaxone.

Clinical Cure Rates: In Protocol 018 the difference in clinical response (ertapenem minus ceftriaxone) in the clinically evaluable (per-protocol) patient population at TOC was 1% (92.3% [168/182] for ertapenem; 91.3% [184/201] for ceftriaxone) with a 95% CI of -4.9% to 7%. The difference in clinical cure rates in the modified intent-to-treat (MITT) population at TOC was -2% (80.1% [189/236] for ertapenem; 82.1% [205/250] for ceftriaxone) with a 95% CI of -9.4% to 5.3%. In Protocol 020 the difference in clinical response in the clinically evaluable patient population at TOC was -0.8% (91.7% [167/182] for ertapenem; 92.5% [86/93] for ceftriaxone) with a 95% CI of -6.8% to 8.2%. The difference in clinical cure rates in the MITT population at TOC was -2.9% (79.7% [181/227] for ertapenem; 82.6% [100/121] for ceftriaxone) with a 95% CI of -9.3% to 5.4%.

Bacteriologic Cure Rates: The bacteriologically evaluable populations showed that ertapenem was effective in the treating patients CAP who had one of the three important pathogens in CAP: *S. pneumoniae*, *H. influenzae* or *M. catarrhalis*. The clinical cure rates were 96.6% (86/96) (95% CI [90.5%, 99.3%]) for patients with *S. pneumoniae* (penicillin susceptible strains only); 84.9% (29/33) (95% CI [69.2%, 93.8%]) for patients with *H. influenzae*; and 93.3% (28/30) (95% CI [79.5%, 98.4%]) for patients with *M. catarrhalis* at baseline. Of all microbiologically evaluable patients in both studies, 49 had bacteremia at baseline: 23 in the ertapenem group and 26 in the ceftriaxone group. Favorable microbiological response was observed in 20/23 (87.0%) (95% CI [68.3%, 96.4%]) in the ertapenem group and 23/26(88.5%) (95% CI [70.1%, 96.8%]) in the ceftriaxone group. *S. pneumoniae* accounted for 41 of these bacteremias: 18 in the ertapenem group, and 23 in the ceftriaxone group. Favorable microbiological response was observed in 16/18 (88.9%) (95% CI [67.5%, 98.0%]) in the ertapenem group, and 21/23 (91.3%) (95% CI [73.2%, 98.4%]) in the ceftriaxone group.

The rates of moderate to severe symptoms of local intolerability among those with at least one sign or symptom of intolerability of moderate or severe intensity were about 5% to 8% for ertapenem and 7% to 11% for ceftriaxone. The differences in signs and symptoms of intolerability were not statistically significant.

2 Introduction

Ertapenem is a long-acting parenteral $1-\beta-$methyl carbapenem anti-infective drug product which appears to demonstrate antibacterial activity against both gram-positive and gram-negative aerobic and anaerobic bacteria. The antibacterial activity of ertapenem is obtained by the inhibition of bacterial cell-wall synthesis by binding to specific penicillin-binding proteins.

This report summarizes the findings of the statistical review of the clinical and bacteriological efficacy data from 2 studies of similar design and conduct to support claims of efficacy for the treatment of adults with CAP with the parenteral (intravenous or intramuscular) formulation of ertapenem. Ertapenem was to be administered a minimum of 3 days and a maximum of 10 to 14 days in adults with CAP with severity of infection at presentation that warranted parenteral treatment. When the minimum course of treatment was completed patients were could be switched to an oral antimicrobial therapy if they were hemodynamically stable and showed appropriated clinical improvement. The recommended oral switch therapy was Augmentin.

3 Study Hypotheses

3.1 Primary Hypothesis

3.1.1 Study 018

It is expected that, in patients who are clinically evaluable and without documented penicillin-resistant *Streptococcus pneumoniae* 90% of the patients receiving ceftriaxone sodium 1 g will have a favorable clinical response at TOC, and that the result for the ertapenem 1-g group will be similar.

3.1.2 Study 020

It is expected that, in patients who are both clinically and microbiologically evaluable and without documented PRSP, 90% of the patients receiving ceftriaxone sodium 1 g will have both a clinical *cure* and a favorable microbiological response TOC. It was expected that the microbiological response for the patients who receive ertapenem 1 g will be similar.

3.2 Secondary Hypothesis

3.2.1 Study 018

It is expected that, in patients who are both clinically and microbiologically evaluable and without documented PRSP, 90% of the patients receiving ceftriaxone sodium 1 g will have both a clinical *cure* and a favorable microbiological response TOC. It was expected that the microbiological response will be similar for subjects who receive ertapenem 1 g.

3.2.2 Study 020

It is expected that, in patients who are clinically evaluable and without documented penicillin-resistant *Streptococcus pneumoniae* 90% of the patients receiving ceftriaxone sodium 1 g will have a favorable clinical response at TOC, and that the clinical response for the ertapenem 1-g group will be similar.

4 Study Design and Conduct

Two clinical trials were conducted to support claims of efficacy and tolerability of ertapenem versus ceftriaxone in the treatment of CAP in adults. Protocols 018 and 020 were designed as statistically-adequate, double-blind, randomized, well-controlled equivalence clinical trials. Study 018 enrolled subjects from 64 study centers: 30 non-US and 34 US sites. Protocol 020 enrolled patients from 71 centers: 26 non-US and 45 US sites. The total enrollment consisted of 866 patients in two trials of which 483 were randomized to treatment with ertapenem.

4.1 Overall Study Design

Men and women, at least 18 years of age, with a diagnosis of CAP were randomized to 1 of the 2 study regimens (ertapenem 1 g or ceftriaxone). Patients were randomized in a 1-to-1 ratio (ertapenem to comparator) in Protocol 018 and in a 2-to-1 ratio in Protocol 020. At randomization subjects were stratified into 4 groups based upon defined age and severity risk groups, as defined by the Pneumonia Severity Index (PSI) (PSI $\leq$ 3 or >3) (Fine et al., 1997) and age ($\leq$65 or >65 years). The stratification was identical for both studies. PSI scores of 1 to 3 indicate mild to moderate disease and PSI scores of 4 or 5 indicate severe illness.

4.2 Analytical Assessment of Efficacy Endpoints

In each protocol, clinical and microbiological response assessments were made by the investigator at TOC. Each study tested a primary efficacy hypothesis that the clinical response to ertapenem therapy was equivalent to the response to ceftriaxone in adult patients with CAP. The primary efficacy endpoint was the proportion of evaluable patients (without documented PRSP) who had a favorable clinical response assessment at the TOC visit in the clinically evaluable and MITT populations. Secondary endpoints included:

- The proportions of patients (excluding those with documented PRSP infection) with favorable clinical response assessments at TOC in the microbiologically evaluable population.
- The proportions of patients with favorable clinical response assessments in the clinical MITT population and in the microbiological MITT popu-

lation. The MITT microbiological population included all patients with pneumococcal infection, regardless of penicillin susceptibility.

- The proportion of patients with a favorable clinical response assessment at TOC in clinically and microbiologically evaluable patients with *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* pathogens at baseline.

The primary endpoints are displayed by age and severity strata. A test of treatment-by-stratum interaction using the Breslow-Day Test of Homogeneity of Odds-Ratios (Breslow & Day, 1980) and the Zelen's Test for Homogeneity of Odds Ratios (Zelen, 1971) are performed. If the nominal p-values of the tests were >0.05, it is concluded that the odds ratios were similar across the strata, and the strata could be combined for further analyses.

The 2 treatment groups were compared for the efficacy parameters at TOC visit. The differences in proportions (ertapenem minus ceftriaxone) were calculated, along with the corresponding 95% CIs. CIs were generally calculated using the normal approximation to the binomial distribution. Exact confidence intervals (Blythe-Still-Casella) are used for sample sizes of less than 30 and are computed using the StatXact Version 4.1 (1999). The estimated CIs for the difference between treatment groups account for stratification based on the Cochran-Mantel-Haenszel (CMH) approach (Mantel, Haenszel, 1959). The CIs around the individual proportions were calculated using the CMH approach applied to one sample. The observed differences between the treatment groups were computed by pooling data across the strata. A fixed delta, margin of the lower bound of the 2-sided, 95% CI for difference in cure rates between the two treatments of no less than -10% is used as a statistical criteria for declaring therapeutic equivalence. CIs other than for the primary endpoint are shown for descriptive purposes.

4.3 Determination of Sample Size and Power Analysis

The sample size for this study was calculated using Blackwelder's formula (Blackwelder, 1982). The Type I error rate was set at 0.025 (one-sided). The Type II error rate was set at 0.20. The response rate for each of the treatment groups was set at 90% ($\pi_1 = \pi_2 = 0.90$). Given these assumptions, 150 evaluable patients per group were needed in order to have 80% probability that the lower limit of the 95% (two-sided) confidence interval (CI) for the difference in the response rates between the 2 groups did not exceed -10 percentage points. There were no interim analyses planned. Multiplicity issues were not considered since there was only one primary hypothesis tested. Center by treatment effects were not considered. Both studies were powered to assess the primary endpoint.

4.4 Evaluation of Clinical Response

The primary efficacy parameter was the proportion of patients (without PRSP) who had a favorable clinical response assessment at TOC. Microbiological responses other than *indeterminate* were classified as favorable or unfavorable.

Bacterial pathogens that were not identified in the admission cultures, but which were isolated later, were classified as *superinfection* if first isolated during study therapy, or as *new infection* if first isolated after the discontinuation of study therapy. For patients from whom only one pathogen was isolated, the overall microbiological response assessment was based on the assessment for that pathogen. Although most cases of CAP are caused by single pathogens, in situations where more than one pathogen was isolated the overall microbiological response assessment was *favorable* only if the microbiological response assessment for each of the pathogens isolated was *favorable*.

4.5 Study Populations

The following terms are used to describe the study populations as analyzed in this report:

- **Screened population:** all patients who signed a consent form for the study (randomized and non-randomized to study drug).
- **Randomized population:** a subset of the screened population comprising patients who were randomized to a study regimen.
- **Clinical MITT population:** a subset of the treated population comprising patients who met the minimum requirements for the diagnosis of pneumonia.
- **Microbiologic MITT population:** a subset of the clinical MITT population, comprised those clinical MITT patients who had a baseline pathogen identified, regardless of susceptibility to study agents, and had a microbiologic response assessed.
- **Clinically evaluable population:** a subset of the clinical MITT population comprising patients for whom sufficient information was available to determine the patients' outcome and no confounding factors were present that interfered with the assessment of that outcome.
- **Microbiologically evaluable population:** a subset of the clinically evaluable population comprising those clinically evaluable patients who had a baseline pathogen identified and a microbiologic response assessed.

4.6 Subject Accounting and Baseline Characteristics

A total of 886 patients were randomized in the two clinical trials. These studies were conducted between July 1998 and May 2000. There were 502 patients randomized under Protocol 018 and 364 under Protocol 020. An accounting of the populations used in various analyses is shown in Table 1.

For Protocol 018, 383 patients (76.3% of the randomized population) were considered clinically evaluable: 182 received ertapenem and 201 received ceftriaxone. In Protocol 020, 275 were clinically evaluable (75.5 % of the randomized

population): 182 received ertapenem and 93 received ceftriaxone. In Protocol 018, 209 patients were microbiologically evaluable (41.6% of the randomized population): 96 received ertapenem and 113 received ceftriaxone. For Protocol 020, 149 patients (40.9% of the randomized population) were considered microbiologically evaluable: 100 received ertapenem and 49 received ceftriaxone.

Table 1: Patient accounting of the randomized population and percentage of subjects retained in various populations

	Protocol 018		Protocol 020	
Screened Patients	$N = 537$		$N = 391$	
Not randomized	*N=35*		*N=27*	
Randomized	*N=502*		*N=364*	
Population	**Ertapenem**	**Ceftriaxone**	**Ertapenem**	**Ceftriaxone**
	N (%)	*N* (%)	*N* (%)	*N* (%)
Randomized	244 (100)	258 (100)	239 (100)	125 (100)
Clinical MITT	236 (97)	250 (97)	227 (95)	121 (97)
Bacteriological MITT	118 (48)	136 (53)	123 (52)	60 (48)
Clinically evaluable	182 (75)	201 (78)	182 (76)	93 (74)
Micro. evaluable	96 (39)	113 (44)	100 (42)	49 (39)

MITT=*Modified intent-to-treat*

Table 2 displays reasons why patients were discontinued from the study and/or study drug. The treatment groups were similar with respects to reasons for discontinuation from study. The most common reasons patients were considered clinically non-evaluable were failure to receive sufficient study therapy or failure to have a TOC assessment in the appropriate time window. The most common reasons patients were considered microbiologically non-evaluable were that they were not clinically evaluable or that they did not have a baseline pathogen isolated at study entry.

4.7 Demographic and Baseline Characteristics

Table 3 displays the baseline characteristics of all randomized patients by study protocol. In each study, patients in both treatment groups were comparable with respect to age, gender, race, and clinical signs and symptoms. Approximately 25% to 30% of patients had PSI scores of 4 or 5.

The most commonly isolated pathogens in the 2 CAP studies were *S. pneumoniae* (220 isolates), *H. influenzae* (82 isolates), and *M. catarrhalis* (64 isolates). Within each protocol and in the 2 studies combined (studies were combined only for bacteriologic by pathogen information), the 2 treatment groups were similar with respect to the distribution and susceptibility patterns of baseline pathogens. Patients with resistant baseline pathogens were excluded from the evaluable populations unless at least one susceptible pathogen was isolated at the same time. Of all microbiologically evaluable patients in both studies, 49 had bacteremia at baseline: 23 in the ertapenem group and 26 in the ceftri-

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Table 2: Reasons why patients were discontinued from the study and/or study drug

	Protocol 018		Protocol 020	
	Ertapenem	Ceftriaxone	Ertapenem	Ceftriaxone
Enrolled	$N = 244$	$N = 258$	$N = 239$	$N = 125$
Male	142	145	149	74
(Age range)	(17 – 90)	(18 – 96)	(18 – 97)	(19 – 89)
Female	102	113	90	51
(Age range)	(18 – 92)	(17 – 92)	(23 – 92)	(20 – 96)
Completed Study	199	213	197	103
Discontinued Study	45	45	42	22
Clinical adverse event	18	17	15	9
Laboratory adverse event	1	0	0	1
Lost to follow-up	4	3	4	2
Protocol deviation	4	3	5	2
Patient withdrew	2	1	3	2
Criteria not met	6	0	3	3
Therapeutic failure	3	8	7	4
Withdrew consent	5	6	6	0
Resistant pathogen	0	2	1	0
Mycobacteria present	0	1	0	1
Tuberculosis	1	1	0	0
Confounding illness	1	1	1	0
Personal reasons	1	1	0	0

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Table 3: Demographic and baseline characteristics by treatment group in the randomized population

Characteristic	Protocol 018		Protocol 020	
	Ertapenem ($N = 244$)	Ceftriaxone ($N = 258$)	Ertapenem ($N = 239$)	Ceftriaxone ($N = 125$)
	n (%)	n (%)	n (%)	n (%)
Gender				
Male	142 (58)	145 (56)	149 (62)	74 (59)
Female	102 (42)	113 (44)	90 (38)	51 (41)
Race				
Asian	2 ($\leq$ 1)	1 ($\leq$ 1)	1 ($\leq$ 1)	0 (0)
Black	38 (16)	35 (14)	35 (15)	14 (11)
Caucasian	125 (51)	144 (56)	142 (59)	85 (68)
Hispanic	63 (26)	61 (24)	50 (21)	22 (18)
Other	15 (6)	17 (7)	11 (5)	4 (3)
Age (Years)				
< 18	1 ($\leq$ 1)	1 ($\leq$ 1)	0 (0)	0 (0)
$18 - 40$	66 (27)	54 (21)	43 (18)	26 (21)
$41 - 64$	81 (33)	94 (36)	100 (42)	45 (36)
$65 - 74$	45 (18.4)	51 (20)	54 (23)	30 (24)
> 74	51 (20.9)	58 (23)	42 (18)	24 (19)
Mean	55.7	57.3	57.5	58.1
SD	20.0	19.7	17.6	18.8
Median	59.0	60.5	59.0	62.0
(Range)	(17 – 92)	(17 – 96)	(18 – 97)	(19 – 96)
Strata				
PSI ≤ 3/*Age* ≤ 65	137 (56)	135 (52)	124 (52)	66 (53)
PSI ≤ 3/*Age* > 65	46 (19)	52 (20)	53 (22)	22 (18)
PSI > 3/*Age* ≤ 65	14 (6)	20 (8)	20 (8)	9 (7)
PSI > 3/*Age* > 65	47 (19)	51 (20)	42 (18)	28 (22)
PSI Risk Group				
$1 - 3$	182 (75)	184 (71)	176 (74)	88 (70)
$4 - 5$	61 (25)	74 (29)	63 (26)	37 (30)

axone group. *S. pneumoniae* accounted for 41 of these bacteremias: 18 in the ertapenem group, and 23 in the ceftriaxone group.

4.8 Duration of Therapy

Patients in the 2 treatment groups received similar durations of therapy as displayed in Table 4. Approximately 88% of the patients in both treatment groups completed therapy with an oral agent. About 93% of those who completed therapy in both treatment groups received amoxicillin/clavulanate, the recommended therapy for oral switch. Both the mean and the median of oral follow-up therapy were nearly identical in the 2 treatment groups within and across both studies. The treatments groups within and between studies were similar with respect to drug exposure and compliance.

Table 4: Duration of therapy by treatment group in the clinically evaluable population

	Protocol 018		Protocol 020	
	Ertapenem N = 182	Ceftriaxone N = 201	Ertapenem N = 182	Ceftriaxone N = 93
Clinically evaluable				
Days on study therapy				
n	182	201	182	93
Mean (SD)	11.7 (2.7)	11.8 (2.5)	11.5 (2.7)	11.7 (3.0)
Median (Range)	12.0	12.0	11.0	11.1
Days on parenteral therapy				
n	182	201	182	93
Mean (SD)	4.9 (2.7)	5.1 (2.6)	5.5 (2.6)	5.6 (2.8)
Median (Range)	4.0	4.0	5.0	5.0
Days on IV therapy				
n	182	201	182	93
Mean (SD)	4.9 (2.7)	5.1 (2.6)	5.4 (2.7)	5.4 (2.9)
Median (Range)	4.0	4.0	5.0	4.0
Days on oral therapy				
n	165	180	156	78
Mean (SD)	7.4 (2.4)	7.6 (2.3)	6.9 (2.3)	7.3 (2.3)
Median (Range)	7.0	7.0	7.0	7.0

4.9 Efficacy Ascertainment

The primary efficacy analysis was performed on the clinically evaluable and MITT populations. Efficacy outcome as demonstrated in the MITT population is considered equally important to results obtained from the clinically evaluable population. Additional secondary analyses were done on the microbiologically evaluable group and microbiological MITT populations. The difference in response rates between the 2 treatment groups in each protocol was calculated as (ertapenem response rate [%] minus ceftriaxone response rate [%]). TOC was assessed at the TOC visit, 7 to 14 days after the completion of study therapy (parenteral and oral). Additional efficacy assessments were done at the LFU visit, 21 to 28 days after completion of all study therapy. Evaluable patients who were clinical failures prior to the TOC visit were carried forward as treatment failures for all subsequent time points. Subjects who were in the MITT populations and who did not have an assessment at the TOC visit were similarly considered treatment failures for the TOC visit and any other later assessment time points regardless of their status prior to the TOC visit.

5 Efficacy Results

5.1 Clinical Efficacy by Subject

A test of treatment-by-strata interaction was performed using the Breslow-Day Test of Homogeneity of Odds-Ratios at the TOC assessment time point. Since some strata have sparse data the Breslow and Day Test might not yield accurate asymptotic p-values and the Zelen Exact Test of Homogeneity is preferred. Both tests were performed. For protocol 018, the p-values were: ≥ 0.535 by the Breslow-Day test, and ≥ 0.682 when the Zelen Exact Test was used. Similarly for protocol 020, the p-value were: ≥ 0.470 Breslow and Day Test, and ≥ 0.813 when the Zelen Exact Test was used. The p-values of the tests were greater than 0.05 indicating that the odds ratios were similar across the 4 strata and that no significant interaction between treatment groups and strata existed at these 2 time points for both studies. Both tests led to the same conclusion, that there is not sufficient statistical basis to believe that the efficacy outcome was different for different age by severity strata. For all further efficacy analyses, the strata were combined in each treatment group. Table 5 displays the proportion of clinically evaluable patients with favorable clinical response assessments stratified by age and severity in the clinically evaluable population.

Table 6 displays the clinical response by age and severity strata in the microbiologically evaluable population in study 020 since this was the primary population for this study in which a 2:1 randomization was implemented.

Table 7 displays the results of clinical response at the TOC visit in both populations. The results for the MITT populations are consistent with sponsor's re-analysis submitted to the electronic database on April 4, 2001. In protocol 018, the difference in the clinical response rates between the 2 treatment groups, was 1.0% with a 95% CI of -4.9% to 7.3%. In the MITT population, 80.1%

Table 5: Proportion of patients with favorable clinical response assessment by age and disease severity in the clinically evaluable population at test-of-cure

Test of Cure	Treatment Group				Observed Difference
	Ertapenem (E)		Ceftriaxone (C)		
	n/m	% (95% CI)[a]	n/m	% (95% CI)[a]	(E - C)
Strata (Clinically Evaluable)					
Protocol 018	($N = 182$)		($N = 201$)		
PSI≤3/Age≤65	92/101	91.1 (85.5, 96.7)	100/108	92.6 (87.6, 97.6)	-1.5
PSI≤3/Age>65	36/37	97.3 (92.0, 100)	34/36	94.4 (86.9, 100)	2.9
PSI>3/Age≤65	9/9	100 (66.4, 100)	15/18	83.3 (65.6, 100)	16.7
PSI>3/Age>65	31/35	88.6 (77.9, 99.3)	34/39	87.2 (76.5, 97.8)	1.4
Overall	168/182	92.3 (88.4, 96.2)	183/201	91.3 (87.1, 95.0)	1.3

[a] *Confidence Interval on the observed clinical response rate.*
N=# of subjects in each treatment group at the test of cure visit.
n= # of subjects with favorable assessment at TOC.
m=# of subjects with assessments at TOC
PSI=Pneumonia severity index

of patients in the ertapenem group and 82.3% of patients in the ceftriaxone group had a favorable clinical response. The estimated difference in cure rates was -2.0% with a 2-sided, 95% CI of -9.4% to 5.3%. The MITT population demonstrated about a 10% lower clinical efficacy than the clinically evaluable population.

For Protocol 020 TOC analysis in the clinically evaluable population, 91.7% of patients in the ertapenem group and 92.5% of patients in the ceftriaxone group had a favorable clinical response. The difference in the clinical response rates between the 2 treatment groups, adjusted for stratum, was -0.8% with a 95% CI of -6.8% to 8.2%. In the MITT population at the TOC analysis, 79.7% of patients in the ertapenem group and 82.6% of patients in the ceftriaxone group had a favorable clinical response. The difference in clinical response rates was -2.9% with a 95% CI of -9.3% to 5.4%. The 2-sided, 95% CIs achieved a lower bound of not less than -10% for both the clinically evalauble and the MITT populations. The clinical per patient response was consistent between populations, within and between study protocols.

Ertapenem demonstrated a clinical success rate of about 92% in the clinically evaluable population and about 80% in the clinical MITT population. These results were consistent across both protocols. Therefore, the per patient clinical response from both studies demonstrated that ertapenem was not statistically inferior to ceftriaxone in the treatment of moderate to severe CAP in adults when used as a 1 g dose intravenously for at least 3 days, with a recommended treatment duration of 10 to 14 days.

As a secondary efficacy variable in each protocol, the proportion of clinically evaluable patients with a favorable clinical response assessment at the discontinuation of parenteral therapy visit was evaluated to provide some evidence of the

Table 6: Proportion of patients with favorable clinical response assessment by age and disease severity in the microbiologically evaluable population at test-of-cure

Test of Cure	Treatment Group: Ertapenem (E)		Ceftriaxone (C)		Observed Difference
Strata	n/m	% (95%CI)[a]	n/m	% (95%CI)	(E-C)
Protocol 020		$N = 100$		$N = 49$	
PSI≤3/Age≤65	47/50	94.0 (83.8, 98.3)	22/22	100 (86.1, 100)	-6.0
PSI≤3/Age>65	17/19	89.5 (68.5, 98.1)	10/11	90.9 (61.0, 99.5)	-1.4
PSI>3/Age≤65	9/12	75.0 (45.0, 92.8)	3/4	75.0 (24.5, 96.7)	0.0
PSI >3/Age>65	18/19	94.7 (75.6, 99.7)	10/12	83.3 (55.0, 97.0)	11.4
Overall	91/100	91.0 (83.9, 95.4)	45/49	91.8 (81.5, 97.2)	-0.8

[a] *Exact confidence interval using the Blythe-Still-Casella method (StatXact 4).*
N=# of subjects in each treatment group at the test of cure visit.
n= # of subjects with favorable assessment at TOC.
m=# of subjects with assessments at TOC
PSI=Pneumonia severity index

clinical efficacy prior to oral switch. Table 8 displays the results by treatment group for each protocol and show high response rates to both parenteral agents, at the time of discontinuation of parenteral therapy. The response rates were similar for treatment groups within and between the trials.

5.2 Microbiological Response by Subject

As a secondary analysis, the proportion of microbiologically evaluable patients with a favorable microbiological response assessment was evaluated for each treatment group in each CAP protocol at the TOC visit as displayed in Table 9. The lower bound of the 95% CIs were within -10% for study 018 and within -15% for study 020. These CIs are shown for descriptive purposes.

Table 7: Proportion of patients with favorable clinical per patient response assessments in the clinically evaluable and the clinical modified intent-to-treat populations

	Treatment Group: Ertapenem (E)		Ceftriaxone (C)		Difference (E-C)
Test of Cure	N	%	N	%	(95% CI)
Protocol 018					
Clinical Evaluable	182	92.3	201	91.3	1.0 (−4.9, 7.0)
Clinical MITT	236	80.1	250	82.1	−2.0 (−9.4, 5.3)
Protocol 020					
Clinical Evaluable	182	91.7	93	92.5	−0.8 (−6.8, 8.2)
Clinical MITT	227	79.7	121	82.6	−2.9 (−9.3, 5.4)

Table 8: Proportion of patients with favorable clinical response assessments at the discontinuation of parenteral therapy in the clinically evaluable population

Discontinuation of Intravenous Drug	Treatment Group Ertapenem			Ceftriaxone		
Response Rate	*N*	%	95% *CI*	*N*	%	95% *CI*
Protocol 018	182	96.2	(92.3, 98.2)	200[a]	93.9	(90.1, 96.6)
Protocol 020	181[a]	94.7	(90.4, 97.2)	93	95.8	(89.8, 98.5)

[a]One subject did not have a discontinuation of intravenous drug assessment.

Table 9: Proportion of patients with favorable per patient microbiologic response in the microbiologically evaluable and microbiological MITT populations

Test of Cure	Treatment Group Ertapenem (E)		Ceftriaxone (C)		Difference (E - C)
	N	%	*N*	%	% (95% CI)
Protocol 018					
Microbiological MITT	118	89.8	136	87.5	2.3 (−6.2, 10.6)
Microbiologically Evaluable	96	92.7	113	94.7	−2.0 (−9.6, 5.6)
Protocol 020					
Microbiological MITT	123	80.8	60	83.3	−2.6 (−15.9, 10.8)
Microbiologically Evaluable	100	91.0	49	92.0	−1.0 (−11.5, 10.4)

5.3 Clinical Efficacy by Baseline Pathogen

The microbiological outcomes in the microbiologically evaluable population were assessed at TOC. The microbiologic outcome for all baseline pathogens was determined at follow-up study visits. Table 10 displays the proportion of favorable clinical response assessments for the principal respiratory pathogens in the microbiologically evaluable population at TOC. Exact CIs are provided for the observed response rate shown for each pathogen.

For *S. pneumoniae*, favorable clinical responses were documented in 86/96 patients (89.6% , 95% CI [82.3,94.8]) in the ertapenem group and in 74/79 patients (93.7%, 95% CI [85.9,97.5])) in the ceftriaxone group. For *H. influenzae* favorable clinical responses were recorded in 29/33 patients (87.9%, 95% CI [71.9,95.8])) in the ertapenem group and in 29/31 patients (93.5%, 95% CI [80.0, 98.8])) in the ceftriaxone group. For *M. catarrhalis*, favorable clinical responses were recorded in 28/30 patients (93.3%, 95% CI [79.5,98.8])) in the ertapenem group and in 22/27 patients (81.5%, 95% CI [63.6, 92.4])) in the ceftriaxone group. The microbiologic response was similar for both treatment groups.

Of all microbiologically evaluable patients in both studies, 49 had bacteremia at baseline: 23 in the ertapenem group and 26 in the ceftriaxone group. Favorable microbiological response was observed in 20/23 (87.0%) in the ertapenem

Table 10: Proportion of patients with favorable clinical response assessments at the test-of-cure visit for the microbiologically evaluable population displayed by baseline pathogen - Total isolates (Respiratory secretions and blood)

Test of Cure	Treatment Group			
	Ertapenem		Ceftriaxone	
	($N = 96$)		($N = 113$)	
Total Isolates	n/m	% (95%CI)[b]	n/m	% (95%CI)
Protocol 018				
S. pneumoniae[a]	43/47	91.5 (80.8, 97.1)	53/57	93.0 (83.0, 97.6)
H. influenzae	17/21	81.0 (60.2, 93.2)	22/23	95.7 (80.2, 99.8)
M. catarrhalis	10/10	80.0 (69.2, 100)	15/18	83.3(59.0, 95.3)
Protocol 020				
S. pneumoniae[a]	43/49	87.8 (76.4, 94.5)	22/22	100(86.2, 100)
H. influenzae	12/12	100 (76.4, 100)	8/8	100(85.1, 100)
M. catarrhalis	18/20	90.0 (68.5, 98.2)	7/9	77.8(44.2, 95.9)
Protocols 018 and 020 Combined				
S. pneumoniae[a]	86/96	89.6 (82.3, 94.8)	74/79	93.7(85.9, 97.5)
H. influenzae	29/33	87.9 (71.9, 95.8)	29/31	93.5(80.0, 98.8)
M. catarrhalis	28/30	93.3 (79.5, 98.8)	22/27	81.5(63.6, 92.4)

[a]= *penicillin sensitive S. pneumoniae*
[b]*Exact CIs for point estimate-Blythe-Still-Casella method*
N=*# in microbiologically evaluable patients in each treatment group.*
n=*# of pathogens with associated favorable assessment at TOC.*
m=*Number of pathogens with an assessment at TOC*

group and 23/26 (88.5%) in the ceftriaxone group. *S. pneumoniae* accounted for 41 of these bacteremias: 18 in the ertapenem group, and 23 in the ceftriaxone group. Favorable microbiological response was observed in 16/18 (88.9%) in the ertapenem group, and 21/23 (91.3%) in the ceftriaxone group. Although there were not many bacteremic patients ertapenem appears to demonstrate a therapeutic efficacy among bacteremias that is similar to its efficacy among non-bacteremic patients.

6 Local Tolerability

The tolerability of parenteral ertapenem and ceftriaxone at the local administration site was evaluated by the investigator and recorded daily. Evaluation was based on investigator inspection and patient comments regarding the intensity of signs and symptoms of intolerance (i.e., erythema, induration, pain, tenderness, warmth, swelling, ulceration, phlebitis) at the local site of infusion. The intensity ratings and rating criteria used to assess the tolerability symptoms are described in Table 11. All subjects who received at least 1 dose of study therapy were included.

Table 11: Intensity rating criteria for documenting signs and symptoms of tolerability at local administration site

Intensity	Rating Criteria
None	*No sign or symptom of intolerance to parenteral drug.*
Mild	*Patient was aware of sign or symptom, but it was easily tolerated.*
Moderate	*The sign or symptom caused enough discomfort to interfere with the patient's usual activities.*
Severe	*The patient was incapacitated by the sign or symptom and was unable to perform usual activity.*

6.1 Tolerability Results

Table 12 displays the incidence of local signs and symptoms of intolerability of moderate or severe intensity. For protocol 018, in the ertapenem group, 13/242 patients (5.4%) experienced one or more local reactions of moderate to severe intensity at the injection site compared with 19/255 (7.5%) in the ceftriaxone group. The difference between the groups was -2.1% with a 2-sided, 95% CI for this difference of (-6.4, 2.2). For protocol 020, in the ertapenem group, 16/233 patients (6.9%) experienced one or more local reaction of moderate to severe intensity at the injection site compared with 13/123 patients (10.6%) in the ceftriaxone group. The difference in tolerability rates between the groups was -3.7% with a 2-sided, 95% CI for this difference of (-13.6, 3.5). Overall, the rates of moderate to severe symptoms of local intolerability among those with at least one sign or symptom of intolerability of moderate or severe intensity were about 5% to 8% for ertapenem and 7% to 11% for ceftriaxone. These rates were not different between the 2 treatment groups.

7 Efficacy Discussion

The evidence to support claims of clinical and microbiological efficacy and tolerability of ertapenem when administered intravenously at a dose of 1 g in adult patients with community-acquired pneumonia was provided by 2 controlled, comparative, double-blind, randomized, non-inferiority studies. The primary endpoint was clinical cure at TOC. A -10% lower bound of the 2-sided, 95% CI was used to determine statistical non-inferiority of ertapenem compared to ceftriaxone. The data demonstrated that ertapenem was non-inferior to ceftriaxone in favorable clinical response, favorable microbiological response, and signs and symptoms of intolerability at the intravenous site.

Clinical Cure Rates: In Protocol 018 the difference in clinical response (ertapenem minus ceftriaxone) in the clinically evaluable (per-protocol) patient population at TOC was 1% (92.3% [168/182] for ertapenem; 91.3% [184/201] for ceftriaxone) with a 95% CI of -4.9% to 7%. The difference in clinical cure rates in the modified intent-to-treat (MITT) population at TOC was -2% (80.1% [189/236] for ertapenem; 82.1% [205/250] for ceftriaxone) with a 95% CI of -

Table 12: Number of subjects with local reaction symptoms of moderate to severe intensity during intravenous therapy in the treated population

	Protocol 018		Protocol 020	
	Ertapenem	Ceftriaxone	Ertapenem	Ceftriaxone
% Patients with ≥1 symptom/sign*	N=242 ($n = 13$) %	N=256 ($n = 19$) %	N=233 ($n = 16$) %	N=123 ($n = 13$) %
	5.4	7.5	6.9	10.6
Erythema	1.7	2.4	2.1	4.1
Induration	1.2	1.2	2.6	4.1
Local phlebitis	1.7	2.4	2.1	4.9
Pain	3.3	3.1	3.4	2.4
Pruritus	0.0	0.0	0.0	0.0
Swelling	1.7	2.7	1.3	3.3
Tenderness	1.7	2.0	2.6	4.9
Ulceration	0.0	0.0	0.0	0.0
Warmth	0.4	2.0	1.3	3.3
Burning sensation	0.0	0.4	0.0	0.0
Stinging at site	0.4	0.0	0.0	0.0
Bruising at site	0.0	0.0	0.0	0.8

** Each subject is counted once even though a subject could have had ≥ 2 signs.*
N = # of subject in the treatment group.
% = percent of subjects reporting the tolerability symptom.
Note: subjects who did not have tolerability assessments are not counted.

9.4% to 5.3%. In Protocol 020 the difference in clinical response in the clinically evaluable patient population at TOC was -0.8% (91.7% [167/182] for ertapenem; 92.5% [86/93] for ceftriaxone) with a 95% CI of -6.8% to 8.2%. The difference in clinical cure rates in the MITT population at TOC was -2.9% (79.7% [181/227] for ertapenem; 82.6% [100/121] for ceftriaxone) with a 95% CI of -9.3% to 5.4%.

Bacteriologic Cure Rates: The bacteriologically evaluable populations showed that ertapenem was effective in the treating patients CAP who had one of the three important pathogens in CAP: *S. pneumoniae*, *H. influenzae* or *M. catarrhalis*. The clinical cure rates were 96.6% (86/96) (95% CI [90.5%, 99.3%]) for patients with *S. pneumoniae* (penicillin susceptible strains only); 84.9% (29/33) (95% CI [69.2%, 93.8%]) for patients with *H. influenzae*; and 93.3% (28/30) (95% CI [79.5%, 98.4%]) for patients with *M. catarrhalis* at baseline. Of all microbiologically evaluable patients in both studies, 49 had bacteremia at baseline: 23 in the ertapenem group and 26 in the ceftriaxone group. Favorable microbiological response was observed in 20/23 (87.0%) (95% CI [68.3%, 96.4%]) in the ertapenem group and 23/26(88.5%) (95% CI [70.1%, 96.8%]) in the ceftriaxone group. *S. pneumoniae* accounted for 41 of these bacteremias: 18 in the ertapenem group, and 23 in the ceftriaxone group. Favorable microbiological response was observed in 16/18 (88.9%) (95% CI [67.5%, 98.0%]) in the

ertapenem group, and 21/23 (91.3%) (95% CI [73.2%, 98.4%]) in the ceftriaxone group.

The rates of moderate to severe symptoms of local intolerability among those with at least one sign or symptom of intolerability of moderate or severe intensity were about 5% to 8% for ertapenem and 7% to 11% for ceftriaxone. The differences in signs and symptoms of intolerability were not statistically significant.

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