CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-337

STATISTICAL REVIEW(S)

NDA 21-337
Invanz™ (Ertapenem Sodium) Injection

Date of Submission: November 30, 2000
Electronic NDA Submission

October 10, 2001

STATISTICAL REVIEW AND EVALUATION

NDA: 21-337
DRUG: Invanz™ (Ertapenem Sodium) For Injection
SPONSOR: Merck & Co., Inc
INDICATIONS: 1. Complicated Intra-abdominal Infections in Hospitalized Adults
2. Complicated Urinary Tract Infections in Adults
3. Acute Pelvic Infections in Hospitalized Women
4. Complicated Skin and Skin Structure Infections in Adults
For the indication of community acquired pneumonia of this NDA, see statistical review reports by George Rochester, Ph.D.

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Review's Note: Throughout the review, the following terms are abbreviated and referred to as: CAP = community acquired pneumonia; DCIV = discontinuation of intravenous therapy, EFU = early follow-up post-treatment, FU = follow-up post-treatment, IAI = intra-abdominal infection, IV = intravenous, LFU = late follow-up post-treatment, MITT = modified-intent-to-treat, MO = Medical Officer; SSSI = skin and skin structure infection, TOC = Test of Cure, UTI = urinary tract infection.

The study populations (evaluation groups) across the studies of this NDA were defined as below. Although in efficacy analyses, the Medical Officers also used the evaluation groups such as clincial MITT, microbiologic MITT, clinically evaluable, and microbiologically evaluable populations, their assessments of these populations were not always coincident with the Sponsor's.

Screened population: all subjects who signed a consent for the study. This population included those subjects who were not randomized to therapy and those subjects who were randomized to therapy.

Randomized population: a subset of the screened population comprised of subjects who were randomized to a study regimen, irrespective of whether the subject actually received therapy. Subjects randomized to one treatment group who, due to dispensing errors, mistakenly received study therapy with the other study treatment for the entire parenteral study period were analyzed and displayed throughout based on the study therapy actually received. Subjects who, due to dispensing errors, received both parenteral study drugs at any time during the course of the study were analyzed based on the treatment group to which they were originally randomized.

Treated population: a subset of the randomized population comprised of subjects who received at least 1 dose of study therapy. Only treated subjects were included in the analysis of safety.

Clinical MITT population: a subset of the treated population comprised of subjects that met the minimal disease definition.

Microbiologic MITT population, a subset of the clinical MITT population, was comprised of those clinical MITT subjects who had a baseline pathogen identified, regardless of susceptibility to study agents, and a microbiologic response assessed.

**Determination of the clinical and microbiologic MITT populations was made prior to unblinding].*

Clinically evaluable population: a subset of the clinical MITT population comprised of subjects in whom sufficient information was available to determine the subject's outcome and no confounding factors were present that interfered with the assessment of that outcome. Furthermore, it was required that if baseline pathogens were identified, one or more of these pathogens were susceptible to both parenteral study therapies.

Microbiologically evaluable population, a subset of the clinically evaluable population, comprised of those clinically evaluable subjects who had a baseline pathogen identified and a microbiologic response assessed. As all microbiologically evaluable subjects were required to be clinically evaluable, the population of clinically and microbiologically evaluable subjects was identical to the microbiologically evaluable population; for all data presented hereafter, this group was referred to as the microbiologically evaluable population.

**Determinations of evaluability were made prior to unblinding using prespecified criteria.*

Reviewer comments are given in italics throughout the review.

I. EXECUTIVE SUMMARY

Invanz™ (Ertapenem Sodium), developed internationally by Merck & Co., Inc, is a long-acting parenteral 1-β-methyl carbapenem antibiotic characterized by a broad spectrum of antibacterial activity against both gram-positive and gram-negative aerobic and anaerobic bacteria, and is also very active against many bacterial strains resistant to other agents. Invanz represents a new molecular entity.

Preliminary safety, tolerability, and efficacy of Invanz were investigated in couples of phase IIa studies. In light of the positive study results, several phase IIb or III programs were developed, which were comprised in this NDA submission. The NDA seeks approval for the use of Invanz for the following indications: complicated IAI, complicated UTI, acute pelvic infection, complicated SSSI, and CAP. This review covers the first four indications.

I.A. COMPLICATED INTRA-ABDOMINAL INFECTIONS

To support this indication, one pivotal phase IIb study was submitted for review. Study P017 was a prospective, multicenter (57 centers, including 26 USA sites), multinational, double-blind, randomized comparative study to evaluate the safety, tolerability, and efficacy of an IV antibiotic therapy with Invanz (1g QD) versus piperacillin/tazobactam (3.375g Q6H) in the treatment of complicated IAIs in hospitalized adults. According to the inclusion/exclusion criteria, a total of 633 subjects were enrolled in the study (the 1g cohort) and were randomized in a 1:1 ratio to receive either Invanz (323 subjects) or piperacillin/tazobactam (310 subjects). The duration of treatment was minimum 5, maximum 14 full days. It was initiated on April 22, 1998 and completed on October 15, 1999.

The primary objective of Study P017 was to compare the efficacy of Invanz with respect to both the clinical response assessment profile and the microbiologic assessment profile in the treatment of subjects with complicated IAIs with that of piperacillin/tazobactam at the LFU (TOC) visit.

In this review, statistical evaluation of efficacy was primarily based upon the two-sided 95% confidence interval of the difference in clinical and microbiologic favorable rates at TOC between the Invanz group and the piperacillin/tazobactam group for MO microbiologically evaluable subjects and MO microbiologic MITT subjects. A delta value of 0.1 is defined as an equivalence margin.

For MO microbiologically evaluable population, a total of 163/195 (83.6%) Invanz subjects were considered favorable clinical and microbiologic outcome, while 152/189 (80.4%) piperacillin/tazobactam subjects were considered favorable clinical and microbiologic outcome. The efficacy results demonstrated therapeutic equivalence between the two treatments with a clinical and microbiologic favorable rate difference in favor of Invanz of 3.2% (95% CI: -5.0%, 11.4%).

For MO microbiologic MITT population, a total of 183/256 (71.5%) Invanz subjects were considered favorable clinical and microbiologic outcome, while 167/244 (68.4%) piperacillin/tazobactam subjects were considered favorable clinical and microbiologic outcome. The efficacy results demonstrated therapeutic equivalence between the two treatments with a clinical and microbiologic favorable rate difference in favor of Invanz of 3.0% (95% CI: -5.4%, 11.5%).

I.B. COMPLICATED URINARY TRACT INFECTIONS IN ADULTS

To support this indication, one pivotal phase IIb controlled study P014, and one supportive phase III controlled study P021 were submitted for review. Study P014 was a prospective, multicenter (31 centers, including 25 USA sites), multinational, double-blind, randomized comparative study to evaluate the safety, tolerability, and efficacy of an IV antibiotic therapy with Invanz (1g QD) followed by oral ciprofloxacin (500mg BID) versus ceftriaxone (1g QD) followed by oral ciprofloxacin (500mg BID) in the treatment of complicated UTIs in adults. According to the inclusion/exclusion criteria, a total of 592 subjects were enrolled in the study and were randomized in a 1:1 ratio to receive either Invanz (298 subjects) or ceftriaxone (294 subjects). The duration of treatment was minimum 3 full days, with the option to switch to an oral antibiotic (ciprofloxacin) therapy, minimum 10, maximum 14 full days of total antibiotic therapy. It was initiated on April 13, 1998 and completed on February 4, 2000. Study P021 was a prospective, multicenter (34 centers), double-blind, randomized comparative study to evaluate the safety, tolerability, and efficacy of an IV antibiotic therapy with Invanz (1g QD) followed by oral ciprofloxacin (500mg BID) versus ceftriaxone (1g QD) followed by oral ciprofloxacin (500mg BID) in the treatment of complicated UTIs in adults. According to the inclusion/exclusion criteria, a total of 258 subjects were enrolled in the study and were randomized in a 2:1 ratio to receive either Invanz (175 subjects) or ceftriaxone (83 subjects). The duration of treatment was minimum 3 full days, with the option to switch to an oral antibiotic (ciprofloxacin) therapy, minimum 10, maximum 14 full days of total antibiotic therapy. It was initiated on September 24, 1998 and completed on March 9, 2000.

The primary objective of Studies P014 and P021 was to compare the efficacy of Invanz with respect to the microbiological response assessment profile in the treatment of subjects with serious complicated UTIs including acute pyelonephritis as compared to ceftriaxone sodium at the 5 to 9 days EFU (TOC) visit.

In this review, statistical evaluation of efficacy was primarily based upon the two-sided 95% confidence interval of the difference in microbiologic favorable rates at TOC between the Invanz group and the ceftriaxone group for microbiologically evaluable subjects and microbiologic MITT subjects. A delta value of 0.1 is defined as an equivalence margin.

In the pivotal Study P014, for microbiologically evaluable population, a total of 141/154 (91.6%) Invanz subjects were considered favorable microbiologic outcome, while 155/167 (92.8%) ceftriaxone subjects were considered favorable microbiologic outcome. The efficacy results demonstrated therapeutic equivalence between the two treatments with a microbiologic favorable rate difference in favor of ceftriaxone of 1.3% (95% CI: -7.8%, 5.3%).

In the pivotal Study P014, for microbiologic MITT population, a total of 195/219 (89.0%) Invanz subjects were considered favorable microbiologic outcome, while 205/242 (84.7%) ceftriaxone subjects were considered favorable microbiologic outcome. The efficacy results demonstrated therapeutic equivalence between the two treatments with a microbiologic favorable rate difference in favor of Invanz of 4.3% (95% CI: -2.2%, 10.9%).

In the supportive Study P021, for microbiologically evaluable population, a total of 83/97 (85.6%) Invanz subjects were considered favorable microbiologic outcome, while 45/53 (84.9%) ceftriaxone subjects were considered favorable microbiologic outcome. The efficacy results failed to show therapeutic equivalence between the two treatments with a microbiologic favorable rate difference in favor of Invanz of 0.4% (95% CI: -12.7%, 14.0%).

In the supportive Study P021, for microbiologic MITT population, a total of 99/131 (75.6%) Invanz subjects were considered favorable microbiologic outcome, while 51/71 (71.8%) ceftriaxone subjects were considered favorable microbiologic outcome. The efficacy results demonstrated therapeutic equivalence between the two treatments with a microbiologic favorable rate difference in favor of Invanz of 3.7% (95% CI: -10.1%, 17.6%).

I.C. ACUTE PELVIC INFECTIONS

To support this indication, one pivotal phase III study was submitted for review. Study P023 was a prospective, multicenter (66 centers, including 47 USA sites), multinational, double-blind, randomized comparative study to evaluate the safety, tolerability, and efficacy of an IV antibiotic therapy with Invanz (1g QD) versus piperacillin/tazobactam (3.375g Q6H) in the treatment of acute pelvic infections in hospitalized women. According to the inclusion/exclusion criteria, a total of 412 subjects were enrolled in the study and were randomized in a 1:1 ratio to receive either Invanz (216 subjects) or piperacillin/tazobactam (196 subjects). The duration of treatment was minimum 3, maximum 10 full days. It was initiated on November 3, 1998 and completed on May 9, 2000.

The primary objective of Study P017 was that in subjects with acute pelvic infection who are clinically evaluable, the proportion of subjects who have a favorable clinical response is equivalent for Invanz and piperacillin/tazobactam at the FU (TOC) visit at 2 to 4 weeks post-treatment. It was expected that approximately 90% of the clinically evaluable subjects in each group would have a favorable clinical response.

In this review, statistical evaluation of efficacy was primarily based upon the two-sided 95% confidence interval of the difference in clinical favorable rates at TOC between the Invanz group and the piperacillin/tazobactam group for clinically evaluable subjects and clinical MITT subjects. A delta value of 0.1 is defined as an equivalence margin.

For clinically evaluable population, a total of 153/163 (93.9%) Invanz subjects were considered favorable clinical outcome, while 140/153 (91.5%) piperacillin/tazobactam subjects were considered favorable clinical outcome. The efficacy results demonstrated therapeutic equivalence between the two treatments with a clinical favorable rate difference in favor of Invanz of 2.4% (95% CI: -4.0%, 8.7%).

For clinical MITT population, a total of 173/211 (82.0%) Invanz subjects were considered favorable clinical and microbiologic outcome, while 160/191 (83.8%) piperacillin/tazobactam subjects were considered favorable clinical and microbiologic outcome. The efficacy results demonstrated therapeutic equivalence between the two treatments with a clinical and microbiologic favorable rate difference in favor of piperacillin/tazobactam of 1.8% (95% CI: -9.6%, 6.1%).

I.D. COMPLICATED SKIN AND SKIN STRUCTURE INFECTIOUS

To support this indication, one pivotal phase IIb study was submitted for review. Study P016 was a prospective, multicenter (44 centers, including 33 USA sites), multinational, double-blind, randomized comparative study to evaluate the safety, tolerability, and efficacy of an IV antibiotic therapy with Invanz (1g QD) versus piperacillin/tazobactam (3.375g Q6H) in the treatment of complicated SSSIs in adults. According to the inclusion/exclusion criteria, a total of 540 subjects were enrolled in the study and were randomized in a 1:1 ratio to receive either Invanz (274 subjects) or piperacillin/tazobactam (266 subjects). The duration of treatment was minimum 7, maximum 14 full days. It was initiated in April, 1998 and completed on November 2, 1999.

The primary objective of Study P017 was to compare the efficacy of Invanz at 10 to 21 days post-therapy, with respect to the overall clinical response assessment profile in the treatment of subjects with serious complicated SSSIs as compared to a piperacillin/tazobactam control group.

In this review, statistical evaluation of efficacy was primarily based upon the two-sided 95% confidence interval of the difference in clinical favorable rates at TOC between the Invanz group and the piperacillin/tazobactam group for MO clinically evaluable subjects and MO clinical MITT subjects. A delta value of 0.1 is defined as an equivalence margin.

For MO clinically evaluable population, a total of 141/168 (83.9%) Invanz subjects were considered favorable clinical outcome, while 145/170 (85.3%) piperacillin/tazobactam subjects were considered favorable clinical outcome. The efficacy results demonstrated therapeutic equivalence between the two treatments with a clinical favorable rate difference in favor of piperacillin/tazobactam of 1.4% (95% CI: -9.7%, 6.9%).

For MO clinical MITT population, a total of 173/265 (65.3%) Invanz subjects were considered favorable clinical outcome, while 172/257 (66.9%) piperacillin/tazobactam subjects were considered favorable clinical outcome. The efficacy results demonstrated marginal equivalence between the two treatments with a clinical favorable rate difference in favor of piperacillin/tazobactam of 1.6% (95% CI: -10.1%, 6.9%).

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ON ORIGINAL

II. COMPLICATED INTRA-ABDOMINAL INFECTIONS

II.A. INTRODUCTION

The Sponsor submitted one pivotal phase IIb controlled study, P017, as evidence to support that Invanz was safe and efficacious for the treatment of complicated IAIs in hospitalized adults when compared with current established therapies. Statistical review focuses on this comparative clinical trial which formed the basis of this application.

II.B. STUDY P017

II.B.1. METHODS

Primary Objectives

1. To compare the efficacy of Invanz with respect to both the clinical response assessment profile and the microbiologic assessment profile in the treatment of subjects with complicated IAIs with that of piperacillin/tazobactam at the LFU (TOC) visit.
2. To evaluate the safety profile of Invanz versus piperacillin/tazobactam with respect to the proportion of subjects with any drug-related adverse experiences leading to discontinuation of study drug and also with respect to the proportion of subjects with any drug-related serious adverse experience.

Study Design

Study P017 was a prospective, multicenter (57 centers, including 26 USA sites), multinational, double-blind, randomized comparative study to evaluate the safety, tolerability, and efficacy of an IV antibiotic therapy with Invanz (1g QD) versus piperacillin/tazobactam (3.375g Q6H) in the treatment of complicated IAIs in hospitalized adults. The duration of treatment was minimum 5, maximum 14 full days. It was initiated on April 22, 1998 and completed on October 15, 1999.

This study was anticipated to achieve completion of 150 microbiologically evaluable subjects in each treatment group. Each subject was expected to complete the study, including FU, within approximately 8 weeks. Hospitalized male or female subjects, at least 18 years of age with a diagnosis of complicated IAIs requiring at least 5 to 14 days of parenteral therapy, who met the inclusion/exclusion criteria, were randomized in a 1:1 ratio at each study site to receive one of the treatments.

Initially, Invanz was given as a single daily dose of 1.5g IV. After implementation of dose reduction, the dose of Invanz was reduced to 1g IV daily. Invanz was then given as a single daily dose of 1g IV infused over a 30-minute interval.

Overall study was scheduled for following clinical observation and laboratory measurements: 1. eligibility screening (≤ 24 hours prior to study therapy); 2. study antibiotic IV treatment period: during IV antibiotic therapy and DCIV (final day); 3. FU period (post-therapy): EFU (1 to 2 weeks) and LFU (TOC) (4 to 6 weeks).

Assessment of Efficacy

The primary assessment for efficacy outcome was the LFU visit (TOC visit). Clinical response definitions were "cure", "failure", and "indeterminate". The favorable final clinical response assessment was "cure". The unfavorable final clinical response assessment was "failure". Subjects with a final clinical response assessment of "indeterminate" were considered to be not clinically evaluable. Favorable microbiological response assessments included "eradication" and "presumptive eradication". Unfavorable microbiological response assessments included "persistence", "persistence acquiring resistance", "presumed persistence", "superinfection", and "new infection". Subjects with a microbiological response assessment of "indeterminate" were considered to be not microbiologically evaluable.

The primary analytic population was the microbiologically evaluable subjects, which was defined as a subset of the clinically evaluable population, and was comprised of those clinically evaluable subjects who had a baseline pathogen identified and a microbiologic response assessed at LFU (TOC). The primary efficacy endpoint was the proportion of microbiologically evaluable subjects within each treatment group who had both a favorable clinical response assessment and a favorable microbiological response assessment at LFU (TOC).

Reviewer's Note: *The MO defined her evaluation populations, and assessed the efficacy outcomes according to her clinical and microbiologic criteria.*

Please refer to MO's review for detailed descriptions of Sponsor's and MO's efficacy outcome definitions.

Our efficacy evaluations solely focused on the 1g cohort study, and we considered that it was inappropriate and inconsistent to combine the 1g cohort and the 1.5g cohort, which was used in Sponsor's efficacy analyses. There were 28 subjects enrolled in the 1.5g cohort in contrast with 633 subjects enrolled in the 1g cohort.

The clinical and microbiologic favorable rate of microbiologic MITT subjects should be the co-primary efficacy variable.

Statistical Methods

The comparisons of interest in this study were conducted between Invanz and piperacillin/tazobactam, which was designed to show equivalence of the two treatment groups.

Reviewer's Note: *The following statistical analyses were performed by the reviewer to evaluate the efficacy and safety of Invanz versus piperacillin/tazobactam.*

Equivalence between the test treatment Invanz and the control (piperacillin/tazobactam) with respect to the primary efficacy parameters was assessed by computing the two-tailed 95% confidence interval of the difference in clinical and microbiologic favorable rates. The confidence intervals were computed using a normal approximation to the binomial, and included a continuity correction. The evaluation of whether the treatment groups were considered equally effective was judged based on the delta value 0.1, which is considered a clinically acceptable equivalence margin with respect to this indication. The confidence interval results for subset analyses should be interpreted cautiously since it was not adjusted by multiple comparison analysis.

Prior to performing efficacy analyses, this reviewer assessed the comparability of the treatment groups.

II.B.2. EFFICACY RESULTS

Of the 633 subjects who enrolled in the study (the 1g cohort), 323 were randomized to the Invanz treatment group, and 310 were randomized to the piperacillin/tazobactam treatment group. Two hundred forty nine subjects (128 Invanz and 121 piperacillin/tazobactam) were excluded from the MO microbiologically evaluable analyses. The most common reasons subjects were excluded from the microbiologically evaluable population were "clinically not evaluable" and "no baseline pathogen isolated."

***Reviewer's Note**: The number and the proportion of subjects included in each evaluation group are presented in Table 1. There were no notable treatment differences with respect to the percentage of subjects included in each evaluation group.*

TABLE 1: STUDY P017: NUMBER OF SUBJECTS INCLUDED IN EACH EVALUATION GROUP

Evaluation Group	Number of Subjects	
	Invanz 1g	Piperacillin/ Tazobactam
All Randomized Subjects	323	310
Sponsor Clinical MITT Subjects	311 (96.3%)	304 (98.1%)
MO Clinical MITT Subjects	310 (96.0%)	303 (97.7%)
Sponsor Micro. MITT Subjects	256 (79.3%)	244 (78.7%)
MO Micro. MITT Subjects	256 (79.3%)	244 (78.7%)
Sponsor Clinically Evaluable Subjects	231 (71.5%)	225 (72.6%)
MO Clinically Evaluable Subjects	219 (67.8%)	219 (70.6%)
Sponsor Micro. Evaluable Subjects	203 (62.8%)	193 (62.3%)
MO Micro. Evaluable Subjects	195 (60.4%)	189 (61.0%)

***Reviewer's Note**: The clinical and microbiologic responses are shown for MO microbiologically evaluable subjects and Sponsor microbiologically evaluable subjects in Tables 2 and 3, respectively. Both confidence interval results showed Invanz and piperacillin/tazobactam were therapeutically equivalent with respect to the clinical and microbiologic favorable rates at TOC.*

TABLE 2: STUDY P017: CLINICAL AND MICROBIOLOGIC RESPONSES OF MICROBIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT (MO)

Clinical and Microbiologic Response	Invanz 1g (N=195)	Piperacillin/ Tazobactam (N=189)
Both Favorable	163 (83.6%)	152 (80.4%)
Not Both Favorable	32 (16.4%)	37 (19.6%)
Invanz Versus P/T: Difference in Favorable Rate	3.2%, 95% C.I.: -5.0%, 11.4%	

TABLE 3: STUDY P017: CLINICAL AND MICROBIOLOGIC RESPONSES OF MICROBIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT (Sponsor)		
Clinical and Microbiological Response	Invanz 1g (N=203)	Piperacillin/ Tazobactam (N=193)
Both Favorable	176 (86.7%)	157 (81.3%)
Not Both Favorable	27 (13.3%)	36 (18.7%)
Invanz Versus P/T: Difference in Favorable Rate	5.4%, 95% C.I.: -2.4%, 13.1%	

***Reviewer's Note**: The 95% confidence interval of the difference in clinical and microbiologic favorable rate of microbiologic MITT population between Invanz minus piperacillin/tazobactam illustrated the therapeutic equivalence of the two treatment groups, which are presented in Tables 4 and 5 for MO microbiologic MITT subjects and Sponsor microbiologic MITT subjects, respectively.*

TABLE 4: STUDY P017: CLINICAL AND MICROBIOLOGIC RESPONSES OF MICROBIOLOGIC MITT SUBJECTS AT TOC VISIT (MO)		
Clinical and Microbiologic Response	Invanz 1g (N=256)	Piperacillin/ Tazobactam (N=244)
Both Favorable	183 (71.5%)	167 (68.4%)
Not Both Favorable	73 (28.5%)	77 (31.6%)
Invanz Versus P/T: Difference in Favorable Rate	3.0%, 95% C.I.: -5.4%, 11.5%	

TABLE 5: STUDY P017: CLINICAL AND MICROBIOLOGIC RESPONSES OF MICROBIOLOGIC MITT SUBJECTS AT TOC VISIT (Sponsor)		
Clinical and Microbiologic Response	Invanz 1g (N=256)	Piperacillin/ Tazobactam (N=244)
Both Favorable	191 (74.6%)	171 (70.1%)
Not Both Favorable	65 (25.4%)	73 (29.9%)
Invanz Versus P/T: Difference in Favorable Rate	4.5%, 95% C.I.: -3.7%, 12.8%	

***Reviewer's Note**: The following six tables demonstrate the observed proportions of subjects with favorable clinical and microbiologic response as per MO microbiologically evaluable subjects and Sponsor microbiologically evaluable subjects, respectively. Tables 6 and 7 displays by the site of infection. Tables 8 and 9 displays by the APACHE II score stratum. Tables 10 and 11 displays by site of infection and apache II score strata. It is noteworthy that in Tables 8 and 9, the Invanz subjects with APACHE II score of >15 had notably lower clinical and microbiologic favorable rate than the piperacillin/tazobactam subjects, however, the meaningful conclusions could not be drawn because of the small number of subjects.*

TABLE 6: STUDY P017: PROPORTION OF MICROBIOLOGICALLY EVALUABLE SUBJECTS WITH FAVORABLE CLINICAL AND MICROBIOLOGIC RESPONSES AT TOC VISIT BY SITE OF INFECTION STRATUM (MO)

Site of Infection	Invanz 1g (N=195)	Piperacillin/ Tazobactam (N=189)	Difference in Favorable Rate
Complicated Appendicitis	80/89 (89.9%)	81/91 (89.0%)	0.9%, (-9.2%, 11.0%)
All Other Diagnoses	83/106 (78.3%)	71/98 (72.5%)	5.9%, (-7.0%, 18.7%)
Overall	163/195 (83.6%)	152/189 (80.4%)	3.2%, (-5.0%, 11.4%)

TABLE 7: STUDY P017: PROPORTION OF MICROBIOLOGICALLY EVALUABLE SUBJECTS WITH FAVORABLE CLINICAL AND MICROBIOLOGIC RESPONSES AT TOC VISIT BY SITE OF INFECTION STRATUM (Sponsor)

Site of Infection	Invanz 1g (N=203)	Piperacillin/ Tazobactam (N=193)	Difference in Favorable Rate
Complicated Appendicitis	85/94 (90.4%)	82/91 (90.1%)	0.3%, (-9.3%, 9.9%)
All Other Diagnoses	91/109 (83.5%)	75/102 (73.5%)	10.0%, (-2.0%, 21.9%)
Overall	176/203 (86.7%)	157/193 (81.4%)	5.4%, (-2.4%, 13.1%)

TABLE 8: STUDY P017: PROPORTION OF MICROBIOLOGICALLY EVALUABLE SUBJECTS WITH FAVORABLE CLINICAL AND MICROBIOLOGIC RESPONSE AT TOC VISIT BY APACHE II SCORE STRATUM (MO)

Apache II Score	Invanz 1g	Piperacillin/ Tazobactam	Difference in Favorable Rate
MICROBIOLOGICALLY EVALUABLE SUBJECTS			
≤ 15	158/187 (84.5%)	144/179 (80.4%)	4.0%, (-4.3%, 12.4%)
> 15	5/8 (62.5%)	8/10 (80.0%)	-17.5%,(-70.5%,35.5%)
Overall	163/195 (83.6%)	152/189 (80.4%)	3.2%, (-5.0%, 11.4%)
MICROBIOLOGICAL MITT SUBJECTS			
≤ 15	176/238 (73.9%)	157/227 (69.2%)	4.8%, (-3.8%, 13.3%)
> 15	7/18 (38.9%)	10/17 (58.8%)	-19.9%,(-58.1%,18.3%)
Overall	183/256 (71.5%)	167/244 (68.4%)	3.0%, (-5.4%, 11.5%)

TABLE 9: STUDY P017: PROPORTION OF MICROBIOLOGICALLY EVALUABLE SUBJECTS WITH FAVORABLE CLINICAL AND MICROBIOLOGIC RESPONSE AT TOC VISIT BY APACHE II SCORE STRATUM (Sponsor)

Apache II Score	Invanz 1g	Piperacillin/ Tazobactam	Difference in Favorable Rate
MICROBIOLOGICALLY EVALUABLE SUBJECTS			
≤ 15	169/192 (88.0%)	147/181 (81.2%)	6.8%, (-1.0%, 14.7%)
> 15	7/11 (63.6%)	10/12 (83.3%)	-19.7%,(-63.8%,24.4%)
Overall	176/203 (86.7%)	157/193 (81.4%)	5.4%, (-2.4%, 13.1%)
MICROBIOLOGIC MITT SUBJECTS			
≤ 15	183/238 (76.9%)	161/227 (70.9%)	6.0%, (-2.4%, 14.4%)
> 15	8/18 (44.4%)	10/17 (58.8%)	-14.4%,(-52.9%,24.1%)
Overall	191/256 (74.6%)	171/244 (70.1%)	4.5%, (-3.7%, 12.8%)

TABLE 10: STUDY P017: PROPORTION OF MICROBIOLOGICALLY EVALUABLE SUBJECTS WITH FAVORABLE CLINICAL AND MICROBIOLOGIC RESPONSES AT TOC VISIT BY SITE OF INFECTION AND APACHE II SCORE STRATA (MO)

Stratum	Invanz 1g (N=195)	Piperacillin/ Tazobactam (N=189)	Difference in Favorable Rate
Complicated Appendicitis Apache II Score ≤ 15	78/87 (89.7%)	78/88 (88.6%)	1.0%, (-9.3%, 11.4%)
Complicated Appendicitis Apache II Score > 15	2/2 (100%)	3/3 (100%)	0%, (-41.7%, 41.7%)
All Other Diagnoses Apache II Score ≤ 15	80/100 (80.0%)	66/91 (72.5%)	7.5%, (-5.6%, 20.6%)
All Other Diagnoses Apache II Score > 15	3/6 (50.0%)	5/7 (71.4%)	-21.4%,(-89.1%,46.2%)
Overall	163/195 (83.6%)	152/189 (80.4%)	3.2%, (-5.0%, 11.4%)

TABLE 11: STUDY P017: PROPORTION OF MICROBIOLOGICALLY EVALUABLE SUBJECTS WITH FAVORABLE CLINICAL AND MICROBIOLOGIC RESPONSES AT TOC VISIT BY SITE OF INFECTION AND APACHE II SCORE STRATA (Sponsor)

Stratum	Invanz 1g (N=203)	Piperacillin/ Tazobactam (N=193)	Difference in Favorable Rate
Complicated Appendicitis Apache II Score ≤ 15	83/92 (90.2%)	79/88 (89.8%)	0.4%, (-9.4%, 10.3%)
Complicated Appendicitis Apache II Score > 15	2/2 (100%)	3/3 (100%)	0%, (-41.7%, 41.7%)
All Other Diagnoses Apache II Score ≤ 15	86/100 (86.0%)	68/93 (73.1%)	12.9%, (0.6%, 25.2%)
All Other Diagnoses Apache II Score > 15	5/9 (55.6%)	7/9 (77.8%)	-22.2%,(-75.7%,31.2%)
Overall	176/203 (86.7%)	157/193 (81.4%)	5.4%, (-2.4%, 13.1%)

***Reviewer's Note**: The proportions of subjects with a favorable clinical and microbiologic response assessment in each primary anatomic site of infection at test of cure are displayed as per MO microbiologically evaluable subjects and Sponsor microbiologically evaluable subjects in Tables 12 and 13.*

TABLE 12: STUDY P017: PROPORTION OF MICROBIOLOGICALLY EVALUABLE SUBJECTS WITH FAVORABLE CLINICAL AND MICROBIOLOGICAL RESPONSES AT TOC VISIT BY PRIMARY SITE OF INFECTION (MO)

Primary Site of Infection	Invanz 1g (N=195)	Piperacillin/ Tazobactam (N=189)
Appendix	104/118 (88.1%)	101/113 (89.4%)
Biliary-cholangitis	0/0 (NA)	0/2 (0)
Biliary-cholecystitis	10/12 (83.3%)	10/10 (100%)
Colon	26/35 (74.3%)	22/32 (68.8%)
Parenchymal liver	0/1 (0)	1/2 (50.0%)
Parenchymal spleen	0/0 (NA)	0/1 (0)
Pelvic inflammatory disease	1/1 (100%)	0/0 (NA)
Small bowel	9/13 (69.2%)	8/11 (72.7%)
Stomach/duodenum	8/8 (100%)	6/7 (85.7%)
Other	5/7 (71.4%)	4/11 (36.4%)

TABLE 13: STUDY P017: PROPORTION OF MICROBIOLOGICALLY EVALUABLE SUBJECTS WITH FAVORABLE CLINICAL AND MICROBIOLOGICAL RESPONSES AT TOC VISIT BY PRIMARY SITE OF INFECTION (Sponsor)

Primary Site of Infection	Invanz 1g (N=203)	Piperacillin/ Tazobactam (N=193)
Appendix	109/123 (88.6%)	102/113 (90.3%)
Biliary-cholangitis	0/0 (NA)	0/2 (0)
Biliary-cholecystitis	12/13 (92.3%)	10/10 (100%)
Colon	28/36 (77.8%)	25/36 (69.4%)
Parenchymal liver	0/1 (0)	1/2 (50.0%)
Parenchymal spleen	0/0 (NA)	0/1 (0)
Pelvic inflammatory disease	1/1 (100%)	0/0 (NA)
Small bowel	11/13 (84.6%)	8/11 (72.7%)
Stomach/duodenum	9/9 (100%)	7/8 (87.5%)
Other	6/7 (85.7%)	4/10 (40.0%)

***Reviewer's Note**: Tables 14 and 15 display the proportion of subjects with a favorable clinical and microbiologic response assessment for the demographic subgroups for the Invanz and piperacillin/tazobactam groups as per MO microbiologically evaluable subjects and Sponsor microbiologically evaluable subjects. A notable heterogeneity of treatment effect was observed between the age subgroups, and the treatment effects more favored piperacillin/tazobactam group in elder subjects, however, the results should be interpreted cautiously due to the small sample size.*

TABLE 14: STUDY P017: PROPORTION OF MICROBIOLOGICALLY EVALUABLE SUBJECTS WITH FAVORABLE CLINICAL AND MICROBIOLOGIC RESPONSES AT TOC VISIT BY DEMOGRAPHICS (MO)

Stratum	Invanz 1g (N=195)	Piperacillin/ Tazobactam (N=189)
GENDER		
Female	57/70 (81.4%)	45/60 (75.0%)
Male	106/125 (84.8%)	107/129 (83.0%)
AGE CATEGORY		
< 65	146/167 (87.4%)	127/162 (78.4%)
≥ 65	17/28 (60.7%)	25/27 (92.6%)
< 75	156/182 (85.7%)	141/178 (79.2%)
≥ 75	7/13 (53.9%)	11/11 (100%)
RACE		
African	0/0 (NA)	0/0 (NA)
Armenian	1/1 (100%)	0/0 (NA)
Asian	2/3 (66.7%)	2/4 (50.0%)
Black	5/5 (100%)	4/6 (66.7%)
Caucasian	80/99 (80.8%)	76/96 (79.2%)
Colored	1/1 (100%)	1/1 (100%)
Hispanic	65/73 (89.0%)	57/67 (85.1%)
Mestizo	1/3 (33.3%)	2/2 (100%)
Mixed	8/10 (80.0%)	9/12 (75.0%)
Not specified	0/0 (NA)	1/1 (100%)

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TABLE 15: STUDY P017: PROPORTION OF MICROBIOLOGICALLY EVALUABLE SUBJECTS WITH FAVORABLE CLINICAL AND MICROBIOLOGIC RESPONSES AT TOC VISIT BY DEMOGRAPHICS (Sponsor)

Stratum	Invanz 1g (N=203)	Piperacillin/ Tazobactam (N=193)
GENDER		
Female	60/70 (85.7%)	48/62 (77.4%)
Male	116/133 (87.2%)	109/131 (83.2%)
AGE CATEGORY		
< 65	154/170 (90.6%)	129/162 (79.6%)
≥ 65	22/33 (66.7%)	28/31 (90.3%)
< 75	167/188 (88.8%)	146/182 (80.2%)
≥ 75	9/15 (60.0%)	11/11 (100%)
RACE		
African	1/1 (100%)	0/0 (NA)
Armenian	1/1 (100%)	0/0 (NA)
Asian	2/3 (66.7%)	2/4 (50.0%)
Black	5/5 (100%)	4/6 (66.7%)
Caucasian	90/107 (84.1%)	81/100 (81.0%)
Colored	1/1 (100%)	1/1 (100%)
Hispanic	66/72 (91.7%)	57/67 (85.1%)
Mestizo	2/3 (66.7%)	2/2 (100%)
Mixed	8/10 (80.0%)	9/12 (75.0%)
Not specified	0/0 (NA)	1/1 (100%)

***Reviewer's Note**: Tables 16 and 17 display the proportion of subjects with a favorable clinical response assessment at TOC for the groups of microbiologically evaluable subjects enrolled before and after the implementation of the enhanced blinding procedures.*

TABLE 16: STUDY P017: PROPORTION OF MICROBIOLOGICALLY EVALUABLE SUBJECTS WITH FAVORABLE CLINICAL AND MICROBIOLOGIC RESPONSES AT TOC VISIT BY BLINDING PROCEDURE (MO)

Enhanced Blinding Procedure	Invanz 1g (N=195)	Piperacillin/ Tazobactam (N=189)	Difference in Favorable Rate
No	102/124 (82.3%)	98/123 (79.7%)	2.6%, (-8.0%, 13.2%)
Yes	61/71 (85.9%)	54/66 (81.8%)	4.1%, (-9.7%, 17.9%)
Overall	163/195 (83.6%)	152/189 (80.4%)	3.2%, (-5.0%, 11.4%)

TABLE 17: STUDY P017: PROPORTION OF MICROBIOLOGICALLY EVALUABLE SUBJECTS WITH FAVORABLE CLINICAL AND MICROBIOLOGIC RESPONSES AT TOC VISIT BY BLINDING PROCEDURE (Sponsor)			
Enhanced Blinding Procedure	Invanz 1g (N=203)	Piperacillin/ Tazobactam (N=193)	Difference in Favorable Rate
No	112/131 (85.5%)	101/126 (80.2%)	5.3%, (-4.7%, 15.3%)
Yes	64/72 (88.9%)	56/67 (83.6%)	5.3%, (-7.6%, 18.2%)
Overall	176/203 (86.7%)	157/193 (81.4%)	5.4%, (-2.4%, 13.1%)

***Reviewer's Note**: The following tables display analyses for secondary efficacy endpoints, where each analyses covered MO evaluation populations and Sponsor evaluation populations as well. The clinical responses are shown for microbiologically evaluable subjects in Tables 18 and 19. The clinical responses are shown for clinically evaluable subjects in Tables 20 and 21. The clinical responses are shown for clinical MITT subjects in Tables 22 and 23. The results from these analyses demonstrated that favorable rates of Invanz were comparable to those of piperacillin/tazobactam in all of the evaluation groups.*

TABLE 18: STUDY P017: CLINICAL RESPONSES OF MICROBIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT (MO)		
Clinical Response	Invanz 1g (N=195)	Piperacillin/ Tazobactam (N=189)
Favorable	163 (83.6%)	152 (80.4%)
Unfavorable	32 (16.4%)	37 (19.6%)
Invanz Versus P/T: Difference in Favorable Rate	3.2%, 95% C.I.: -5.0%, 11.4%	

TABLE 19: STUDY P017: CLINICAL RESPONSES OF MICROBIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT (Sponsor)		
Clinical Response	Invanz 1g (N=203)	Piperacillin/ Tazobactam (N=193)
Favorable	176 (86.7%)	157 (81.3%)
Unfavorable	27 (13.3%)	36 (18.7%)
Invanz Versus P/T: Difference in Favorable Rate	5.4%, 95% C.I.: -2.4%, 13.1%	

TABLE 20: STUDY P017: CLINICAL RESPONSES OF CLINICALLY EVALUABLE SUBJECTS AT TOC VISIT (MO)		
Clinical Response	Invanz 1g (N=219)	Piperacillin/ Tazobactam (N=219)
Favorable	183 (83.6%)	180 (82.2%)
Unfavorable	36 (16.4%)	39 (17.8%)
Invanz Versus P/T: Difference in Favorable Rate	1.4%, 95% C.I.: -6.1%, 8.9%	

TABLE 21: STUDY P017: CLINICAL RESPONSES OF CLINICALLY EVALUABLE SUBJECTS AT TOC VISIT (Sponsor)		
Clinical Response	Invanz 1g (N=231)	Piperacillin/ Tazobactam (N=225)
Favorable Unfavorable	200 (86.6%) 31 (13.4%)	187 (83.1%) 38 (16.9%)
Invanz Versus P/T: Difference in Favorable Rate	3.5%, 95% C.I.: -3.5%, 10.5%	

TABLE 22: STUDY P017: CLINICAL RESPONSES OF CLINICAL MITT SUBJECTS AT TOC VISIT (MO)		
Clinical Response	Invanz 1g (N=310)	Piperacillin/ Tazobactam (N=303)
Favorable Unfavorable	212 (68.4%) 98 (31.6%)	201 (66.3%) 102 (33.7%)
Invanz Versus P/T: Difference in Favorable Rate	2.1%, 95% C.I.: -5.7%, 9.8%	

TABLE 23: STUDY P017: CLINICAL RESPONSES OF CLINICAL MITT SUBJECTS AT TOC VISIT (Sponsor)		
Clinical Response	Invanz 1g. (N=311)	Piperacillin/ Tazobactam (N=304)
Favorable Unfavorable	221 (71.1%) 90 (28.9%)	206 (67.8%) 90 (32.2%)
Invanz Versus P/T: Difference in Favorable Rate	3.3%, 95% C.I.: -4.3%, 10.9%	

***Reviewer's Note**: Tables 24, 25, 26, 27, 28, 29, 30, 31, and 32 display the proportion of favorable microbiologic response assessments per baseline pathogen in MO microbiologically evaluable population at the TOC visit. The most common species identified were E. coli, B. fragilis, B. thetaiotaomicron, B. wadsworthia, and P. aeruginosa, each with at least 50 isolates in the microbiologically evaluable population. Also common in both treatment groups were 11 other species: E. faecalis, K. pneumoniae, C. clostridiiforme, C. innocuum, C. perfringens, E. lentum, P. micros, B. distasonis, B. ovatus, B. uniformis, and B. vulgatus, each with at least 10 isolates having response assessments at TOC in one of the treatment groups.*

TABLE 24: STUDY P017: PROPORTION OF FAVORABLE MICROBIOLOGIC RESPONSE ASSESSMENTS AT TOC BY BASELINE PATHOGEN IN THE MICROBIOLOGICALLY EVALUABLE SUBJECTS: TOTAL ISOLATES 1 (MO)

Isolates	Invanz 1g (N=195)	Piperacillin/ Tazobactam (N=189)
Gram-Positive Aerobic Cocci	**111/129 (86.1%)**	**94/115 (81.7%)**
	Difference: 4.3%, 95% C.I.: -5.8%, 14.4%	
Enterococcus	14/16 (87.5%)	9/10 (90.0%)
Enterococcus avium	8/10 (80.0%)	3/4 (75.0%)
Enterococcus casseliflavus	0/0 (NA)	1/1 (100%)
Enterococcus faecalis	22/25 (88.0%)	11/12 (91.7%)
Enterococcus faecium	6/7 (85.7%)	1/5 (20.0%)
Enterococcus gallinarum	1/1 (100%)	0/1 (0)
Gemella morbillorum	1/1 (100%)	0/0 (NA)
Micrococcus	0/0 (NA)	1/1 (100%)
Staphylococcus	1/1 (100%)	1/1 (100%)
Staphylococcus aureus	4/6 (66.7%)	3/3 (100%)
Staphylococcus epidermidis	3/3 (100%)	3/4 (75.0%)
Staphylococcus haemolyticus	3/3 (100%)	0/0 (NA)
Staphylococcus , coagulase negative	3/4 (75.0%)	5/7 (71.4%)
Streptococcus	5/6 (83.3%)	7/8 (87.5%)
Streptococcus (alpha- hemolytic)	4/5 (80.0%)	5/6 (83.3%)
Streptococcus (beta- hemolytic)	5/5 (100%)	2/4 (50.0%)
Streptococcus (Group C)	0/0 (NA)	1/1 (100%)
Streptococcus (Group D)	5/5 (100%)	4/5 (80.0%)
Streptococcus (Group F)	2/2 (100%)	0/0 (NA)
Streptococcus (microaerophilic)	0/0 (NA)	0/0 (NA)
Streptococcus (nonhemolytic)	0/1 (0)	0/0 (NA)
Streptococcus agalactiae	1/1 (100%)	1/2 (50.0%)
Streptococcus anginosus	1/1 (100%)	1/1 (100%)
Streptococcus bovis	1/1 (100%)	3/3 (100%)
Streptococcus constellatus	1/1 (100%)	3/3 (100%)
Streptococcus intermedius	2/2 (100%)	4/4 (100%)
Streptococcus milleri group	5/6 (83.3%)	4/6 (66.7%)
Streptococcus mitis	1/1 (100%)	0/0 (NA)
Streptococcus pneumoniae	0/0 (NA)	4/4 (100%)
Streptococcus pyogenes	0/0 (NA)	2/2 (100%)
Streptococcus salivarius	2/2 (100%)	0/0 (NA)
Streptococcus sanguinis	1/1 (100%)	0/0 (NA)
Streptococcus viridans group	9/12 (75.0%)	15/17 (88.2%)

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TABLE 25: STUDY P017: PROPORTION OF FAVORABLE MICROBIOLOGIC RESPONSE ASSESSMENTS AT TOC BY BASELINE PATHOGEN IN THE MICROBIOLOGICALLY EVALUABLE SUBJECTS: TOTAL ISOLATES 2 (MO)

Isolates	Invanz 1g (N=195)	Piperacillin/ Tazobactam (N=189)
Gram-Negative Aerobic Rods	**220/241 (91.3%)**	**199/222 (89.6%)**
	Difference: 1.6%, 95% C.I.: -4.1%, 7.4%	
Acinetobacter	0/0 (NA)	2/2 (100%)
Acinetobacter baumannii	2/2 (100%)	0/0 (NA)
Acinetobacter calcoaceticus	5/5 (100%)	2/3 (66.7%)
Acinetobacter lwoffi	1/1 (100%)	1/1 (100%)
Aeromonas hydrophila	1/1 (100%)	0/0 (NA)
Alcaligenes faecalis	1/1 (100%)	0/0 (NA)
Campylobacter gracilis	0/1 (0)	3/3 (100%)
Citrobacter	0/0 (NA)	0/0 (NA)
Citrobacter amalonaticus	0/0 (NA)	1/1 (100%)
Citrobacter freundii	0/0 (NA)	1/2 (50.0%)
Citrobacter koseri	0/0 (NA)	0/1 (0)
Comamonas testosteroni	0/0 (NA)	0/1 (0)
Eikenella corrodens	1/1 (100%)	1/1 (100%)
Enterobacter	1/2 (50.0%)	2/2 (100%)
Enterobacter aerogenes	1/1 (100%)	3/3 (100)
Enterobacter cloacae	3/3 (100%)	6/6 (100%)
Enterobacter gergoviae	1/1 (100%)	0/0 (NA)
Enterobacter intermedius	0/0 (NA)	1/1 (100%)
Enterobacter sakazakii	1/1 (100%)	0/0 (NA)
Escherichia coli	138/149 (92.6%)	116/128 (90.6%)
Gram- negative aerobic rods	1/1 (100%)	0/0 (NA)
Haemophilus parainfluenzae	0/0 (NA)	1/2 (50.0%)
Hafnia alvei	0/0 (NA)	1/1 (100%)
Klebsiella	4/5 (50.0%)	2/2 (100%)
Klebsiella oxytoca	6/6 (100%)	4/4 (100%)
Klebsiella ozaenae	1/1 (100%)	3/3 (100%)
Klebsiella pneumoniae	13/14 (92.9%)	12/16 (75.0%)
Morganella morganii	2/2 (100%)	1/1 (100%)
Pantoea agglomerans	2/2 (100%)	4/4 (100%)
Proteus mirabilis	6/7 (85.7%)	3/3 (100%)
Proteus vulgaris	6/6 (100%)	1/1 (100%)
Pseudomonas	0/0 (NA)	1/1 (100%)
Pseudomonas aeruginosa	21/26 (80.7%)	23/25 (92.0%)
Pseudomonas alcaligenes	0/0 (NA)	1/1 (100%)
Pseudomonas fluorescens	0/0 (NA)	1/1 (100%)
Pseudomonas mendocina	0/0 (NA)	1/1 (100%)
Pseudomonas stutzeri	0/0 (NA)	1/1 (100%)
Serratia marcescens	0/0 (NA)	1/1 (100%)
Shewanella putrefaciens	1/1 (100%)	0/0 (NA)
Sphingomonas paucimobilis	1/1 (100%)	0/0 (NA)

TABLE 26: STUDY P017: PROPORTION OF FAVORABLE MICROBIOLOGIC RESPONSE ASSESSMENTS AT TOC BY BASELINE PATHOGEN IN THE MICROBIOLOGICALLY EVALUABLE SUBJECTS: TOTAL ISOLATES 3 (MO)

Isolates	Invanz 1g (N=195)	Piperacillin/ Tazobactam (N=189)
Gram-Negative Aerobic Cocci	**0/0 (NA)**	**1/1 (100%)**
Neisseria	0/0 (NA)	1/1 (100%)

TABLE 27: STUDY P017: PROPORTION OF FAVORABLE MICROBIOLOGIC RESPONSE ASSESSMENTS AT TOC BY BASELINE PATHOGEN IN THE MICROBIOLOGICALLY EVALUABLE SUBJECTS: TOTAL ISOLATES 4 (MO)

Isolates	Invanz 1g (N=195)	Piperacillin/ Tazobactam (N=189)
Gram-Positive Anaerobic Rods	**131/141 (92.9%)**	**102/111 (91.9%)**
	Difference: 1.0%, 95% C.I.: -6.4%, 8.4%	
Actinomyces	1/1 (100%)	0/0 (NA)
Actinomyces naeslundii	1/1 (100%)	0/0 (NA)
Actinomyces odontolyticus	0/0 (NA)	1/1 (100%)
Bifidobacterium breve	1/1 (100%)	0/0 (NA)
Clostridium	3/4 (75.0%)	5/7 (71.4%)
Clostridium barati	1/1 (100%)	0/0 (NA)
Clostridium bifermentans	2/2 (100%)	1/1 (100%)
Clostridium butyricum	3/3 (100%)	1/1 (100%)
Clostridium cadaveris	3/3 (100%)	1/1 (100%)
Clostridium clostridiiforme	18/19 (94.7%)	21/21 (100%)
Clostridium cochlearium	0/0 (NA)	1/1 (100%)
Clostridium innocuum	17/17 (100%)	9/9 (100%)
Clostridium leptum	1/1 (100%)	0/0 (NA)
Clostridium perfringens	13/15 (86.7%)	10/13 (76.9%)
Clostridium ramosum	8/8 (100%)	4/4 (100%)
Clostridium sordellii	2/2 (100%)	0/2 (0)
Clostridium sphenoides	0/0 (NA)	1/1 (100%)
Clostridium sporogenes	1/1 (100%)	0/0 (NA)
Clostridium symbiosum	2/4 (50.0%)	1/1 (100%)
Clostridium tertium	1/1 (100%)	1/1 (100%)
Collinsella aerofaciens	1/3 (33.3%)	0/0 (NA)
Eubacterium	19/20 (95.0%)	16/16 (100%)
Eubacterium contortum	1/1 (100%)	0/0 (NA)
Eubacterium lentum	20/21 (95.2%)	12/12 (100%)
Eubacterium limosum	0/0 (NA)	1/1 (100%)
Gram- positive anaerobic rods	4/4 (100%)	6/7 (85.7%)
Lactobacillus	3/3 (100%)	2/3 (66.7%)
Lactobacillus casei	1/1 (100%)	0/0 (NA)
Lactobacillus catenaformis	0/0 (NA)	2/2 (100%)
Lactobacillus fermentum	1/1 (100%)	0/0 (NA)
Lactobacillus plantarum	1/1 (100%)	1/1 (100%)
Propionibacterium	1/1 (100%)	2/2 (100%)
Propionibacterium acnes	1/1 (100%)	2/2 (100%)
Weissella confusa	0/0 (NA)	1/1 (100%)

TABLE 28: STUDY P017: PROPORTION OF FAVORABLE MICROBIOLOGIC RESPONSE ASSESSMENTS AT TOC BY BASELINE PATHOGEN IN THE MICROBIOLOGICALLY EVALUABLE SUBJECTS: TOTAL ISOLATES 5 (MO)

Isolates	Invanz 1g (N=195)	Piperacillin/ Tazobactam (N=189)
Gram-Positive Anaerobic Cocci	**34/39 (87.2%)**	**27/29 (93.1%)**
	Difference: -5.9%, 95% C.I.: -22.9%, 11.1%	
Gram- positive anaerobic cocci	3/3 (100%)	1/3 (33.3%)
Peptostreptococcus	11/13 (84.6%)	10/10 (100%)
Peptostreptococcus anaerobius	4/5 (80.0%)	2/2 (100%)
Peptostreptococcus asaccharolyticus	1/1 (100%)	0/0 (NA)
Peptostreptococcus magnus	2/2 (100%)	3/3 (100%)
Peptostreptococcus micros	10/12 (83.3%)	10/10 (100%)
Peptostreptococcus prevotii	1/1 (100%)	1/1 (100%)
Peptostreptococcus tetradius	1/1 (100%)	0/0 (NA)
Ruminococcus productus	1/1 (100%)	0/0 (NA)

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TABLE 29: STUDY P017: PROPORTION OF FAVORABLE MICROBIOLOGIC RESPONSE ASSESSMENTS AT TOC BY BASELINE PATHOGEN IN THE MICROBIOLOGICALLY EVALUABLE SUBJECTS: TOTAL ISOLATES 6 (MO)

Isolates	Invanz 1g (N=195)	Piperacillin/ Tazobactam (N=189)
Gram-Negative Anaerobic Rods	**284/309 (91.9%)**	**272/289 (94.1%)**
	Difference: -2.2%, 95% C.I.: -6.6%, 2.2%	
Bacteroides	4/5 (80.0%)	10/12 (83.3%)
Bacteroides caccae	8/9 (88.9%)	10/12 (83.3%)
Bacteroides capillosus	2/2 (100%)	1/1 (100%)
Bacteroides distasonis	16/19 (84.2%)	25/25 (100%)
Bacteroides eggerthii	1/1 (100%)	0/0 (NA)
Bacteroides fragilis	65/74 (87.8%)	60/65 (92.3%)
Bacteroides merdae	1/1 (100%)	2/2 (100%)
Bacteroides ovatus	20/21 (95.2%)	22/22 (100%)
Bacteroides putredinis	1/4 (25.0%)	1/1 (100%)
Bacteroides splanchnicus	2/2 (100%)	5/5 (100%)
Bacteroides stercoris	5/5 (100%)	3/3 (100%)
Bacteroides thetaiotaomicron	44/46 (95.7%)	32/33 (97.0%)
Bacteroides uniformis	21/22 (95.5%)	20/21 (95.2%)
Bacteroides ureolyticus	0/0 (NA)	1/1 (100%)
Bacteroides vulgatus	8/9 (88.9%)	19/19 (100%)
Bilophila	2/2 (100%)	0/0 (NA)
Bilophila wadsworthia	28/29 (96.6%)	24/26 (92.3%)
Desulfovibrio	1/1 (100%)	0/0 (NA)
Dialister pneumosintes	2/2 (100%)	0/0 (NA)
Fusobacterium	2/2 (100%)	1/1 (100%)
Fusobacterium gonidiaformans	1/1 (100%)	0/0 (NA)
Fusobacterium mortiferum	2/2 (100%)	2/2 (100%)
Fusobacterium necrophorum	6/6 (100%)	3/3 (100%)
Fusobacterium nucleatum	3/3 (100%)	2/2 (100%)
Fusobacterium varium	2/2 (100%)	2/2 (100%)
Gardnerella vaginalis	0/0 (NA)	1/1 (100%)
Gram- negative anaerobic rods	5/5 (100%)	3/6 (50.0%)
Porphyromonas	1/1 (100%)	1/1 (100%)
Porphyromonas asaccharolytica	5/5 (100%)	5/6 (83.3%)
Porphyromonas gingivalis	2/2 (100%)	0/0 (NA)
Prevotella	4/4 (100%)	5/5 (100%)
Prevotella bivia	0/0 (NA)	2/2 (100%)
Prevotella buccae	5/5 (100%)	3/3 (100%)
Prevotella corporis	1/1 (100%)	0/0 (NA)
Prevotella denticola	0/1 (0)	0/0 (NA)
Prevotella disiens	0/0 (NA)	1/1 (100%)
Prevotella heparinolytica	0/0 (NA)	1/1 (100%)
Prevotella intermedia	8/9 (88.9%)	3/3 (100%)
Prevotella melaninogenica	4/4 (100%)	2/2 (100%)
Prevotella oris	1/1 (100%)	0/0 (NA)
Tissierella praeacuta	1/1 (100%)	0/0 (NA)

TABLE 30: STUDY P017: PROPORTION OF FAVORABLE MICROBIOLOGIC RESPONSE ASSESSMENTS AT TOC BY BASELINE PATHOGEN IN THE MICROBIOLOGICALLY EVALUABLE SUBJECTS: TOTAL ISOLATES 7 (MO)

Isolates	Invanz 1g (N=195)	Piperacillin/ Tazobactam (N=189)
Gram-Negative Anaerobic Cocci	**2/2 (100%)**	**3/3 (100%)**
Acidaminococcus fermentans	1/1 (100%)	1/1 (100%)
Veillonella	1/1 (100%)	2/2 (100%)

TABLE 31: STUDY P017: PROPORTION OF FAVORABLE MICROBIOLOGIC RESPONSE ASSESSMENTS AT TOC BY BASELINE PATHOGEN IN THE MICROBIOLOGICALLY EVALUABLE SUBJECTS: TOTAL ISOLATES 8 (MO)

Isolates	Invanz 1g (N=195)	Piperacillin/ Tazobactam (N=189)
Bacteria	**0/0 (NA)**	**1/1 (100%)**
Bacteria	0/0 (NA)	1/1 (100%)

TABLE 32: STUDY P017: PROPORTION OF FAVORABLE MICROBIOLOGIC RESPONSE ASSESSMENTS AT TOC BY BASELINE PATHOGEN IN THE MICROBIOLOGICALLY EVALUABLE SUBJECTS: TOTAL ISOLATES 9 (MO)

Isolates	Invanz 1g (N=195)	Piperacillin/ Tazobactam (N=189)
Other Bacteria	**5/5 (100%)**	**3/4 (75.0%)**
Aerobic gram- variable rods	0/0 (NA)	1/1 (100%)
Anaerobes, gram- negative	1/1 (100%)	0/0 (NA)
Gram- negative bacteria	1/1 (100%)	0/0 (NA)
Gram- negative rods	1/1 (100%)	1/2 (50.0%)
Gram- positive bacteria	1/1 (100%)	0/0 (NA)
Gram- positive rods	1/1 (100%)	1/1 (100%)

III. COMPLICATED URINARY TRACT INFECTIONS

III.A. INTRODUCTION

The Sponsor submitted one pivotal phase IIb controlled study, P014, and one supportive phase III controlled study, P021, as evidence to support that Invanz was safe and efficacious for the treatment of complicated UTIs in adults when compared with current established therapies. Statistical review focuses on these comparative clinical trials which formed the basis of this application.

III.B. STUDY P014

III.B.1. METHODS

Primary Objectives

1. To compare the efficacy of Invanz with respect to the microbiological response assessment profile in the treatment of subjects with serious complicated UTIs including acute pyelonephritis as compared to ceftriaxone sodium at the 5 to 9 days EFU (TOC) visit.
2. To evaluate and compare the safety profile of Invanz versus ceftriaxone at the end of parenteral therapy with respect to the proportion of subjects with any drug-related adverse experiences leading to discontinuation of study drug and also with respect to the proportion of subjects with any drug-related serious adverse experience.

Study Design

Study P014 was a prospective, multicenter (31 centers, including 25 USA sites), multinational, double-blind, randomized comparative study to evaluate the safety, tolerability, and efficacy of an IV antibiotic therapy with Invanz (1g QD) followed by oral ciprofloxacin (500mg BID) versus ceftriaxone (1g QD) followed by oral ciprofloxacin (500mg BID) in the treatment of complicated UTIs in adults. The duration of treatment was minimum 3 full days, with the option to switch to an oral antibiotic (ciprofloxacin) therapy, minimum 10, maximum 14 full days of total antibiotic therapy. It was initiated on April 13, 1998 and completed on February 4, 2000.

This study was anticipated to achieve enrollment of 30 subjects diagnosed with acute pyelonephritis and 150 total evaluable subjects enrolled in each treatment arm. Male or female subjects, at least 18 years of age with a diagnosis of complicated UTIs or acute pyelonephritis, who met the inclusion/exclusion criteria, were randomized in a 1:1 ratio at each study site to receive one of the treatments.

Overall study was scheduled for following clinical observation and laboratory measurements: 1. eligibility screening (≤ 24 hours prior to study therapy); 2. study antibiotic treatment period: during IV therapy (Day 3, 4, or 5), DCIV (final day); 3. FU period (post-therapy): EFU (TOC)(5 to 9 days) and LFU (4 to 6 weeks).

Assessment of Efficacy

Primary assessment for efficacy outcome was the EFU (TOC) visit scheduled 5 to 9 days after the subject had completed all therapy. The clinical response was assessed as "cured", "improved", "failed" or "indeterminate" based on comparison to admission signs and symptoms. Favorable clinical response ratings included "cure" or "improved." A clinical response rating of "failure" was considered to be unfavorable. The overall microbiologic response was determined as "favorable" (eradication) or "unfavorable" (persistence) for each subject by comparing the urine culture results at FU to those at admission. Subjects with a clinical or microbiologic response rating of "indeterminate" were considered to be not clinically or microbiologic evaluable.

The primary analytic population was the microbiologically evaluable subjects, which was defined as a subset of the clinically evaluable population, was comprised of those clinically evaluable subjects who had a baseline pathogen identified and a microbiologic response assessed at the EFU visit. The primary efficacy endpoint was the proportion of microbiologically evaluable subjects in each treatment group having a favorable microbiologic response assessment at EFU (TOC).

Reviewer's Note: *The MO agreed with Sponsor's evaluability criteria for constructing analytic populations and defining time points, and consented with Sponsor's assessment for clinical and microbiological outcomes. However, the MO pointed out there were nine subjects, who were classified as "Protocol Deviations" in CRF (because of receiving the last dose of prestudy therapy after the baseline urine culture had been obtained), and were inadequately included in Sponsor's evaluable population. All analysis related to this correction are re-done by this reviewer.*

Please refer to MO's review for detailed descriptions for this correction.

The microbiologic favorable rate of microbiologic MITT subjects should be the co-primary efficacy variable.

Statistical Methods

The comparisons of interest in this study were conducted between Invanz and ceftriaxone, which was designed to show equivalence of the two treatment groups.

Reviewer's Note: *The following statistical analyses were performed by the reviewer to evaluate the efficacy and safety of Invanz versus ceftriaxone.*

Equivalence between the test treatment Invanz and the control (ceftriaxone) with respect to the primary efficacy parameters was assessed by computing the two-tailed 95% confidence interval of the difference in microbiologic favorable rates. The confidence intervals were computed using a normal approximation to the binomial, and included a continuity correction. The evaluation of whether the treatment groups were considered equally effective was judged based on the delta value 0.1, which is considered a clinically acceptable equivalence margin with respect to this indication. The confidence interval results for subset analyses should be interpreted cautiously since it was not adjusted by multiple comparison analysis.

Prior to performing efficacy analyses, this reviewer assessed the comparability of the treatment groups.

III.B.2. EFFICACY RESULTS

Of the 592 subjects who enrolled in the study, 298 were randomized to the Invanz treatment group, and 294 were randomized to the ceftriaxone treatment group. Two hundred seventy one subjects (144 Invanz and 127 ceftriaxone) were excluded from the microbiologically evaluable analyses. The most common

reason subjects were excluded from the microbiologically evaluable populations was that a uropathogen was not isolated and therefore the disease definition was not met.

Reviewer's Note: *The number and percentage of subjects included in each evaluation group are presented in Table 33. There were no notable treatment differences with respect to the percentage of subjects included in each evaluation group.*

TABLE 33: STUDY P014: NUMBER OF SUBJECTS INCLUDED IN EACH EVALUATION GROUP

Evaluation Group	Number of Subjects	
	Invanz	Ceftriaxone
All Randomized Subjects	298	294
Clinical MITT Subjects	227 (96.3%)	248 (97.9%)
Micro. MITT Subjects	219 (79.3%)	242 (79.0%)
Clinically Evaluable Subjects	157 (71.5%)	172 (73.2%)
Micro. Evaluable Subjects	154 (62.8%)	167 (63.1%)

Reviewer's Note: *The microbiologic responses are shown for microbiologically evaluable population in Table 34. The confidence interval result showed that Invanz and ceftriaxone were therapeutically equivalent with respect to microbiologic favorable rates at TOC.*

TABLE 34: STUDY P014: MICROBIOLOGIC RESPONSES OF MICROBIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT

Microbiologic Response	Invanz (N=154)	Ceftriaxone (N=167)
Favorable	141 (91.6%)	155 (92.8%)
Unfavorable	13 (8.4%)	12 (7.2%)
Invanz Versus Ceft.: Difference in Favorable Rate	-1.3%, 95% C.I.: -7.8%, 5.3%	

Reviewer's Note: *The 95% confidence interval of the difference in microbiologic favorable rate of microbiologic MITT population between Invanz minus ceftriaxone illustrated the therapeutic equivalence of the two treatment groups, which is presented in Table 35.*

TABLE 35: STUDY P014: MICROBIOLOGIC RESPONSES OF MICROBIOLOGICAL MITT SUBJECTS AT TOC VISIT

Microbiologic Response	Invanz (N=219)	Ceftriaxone (N=242)
Favorable	195 (89.0%)	205 (84.7%)
Unfavorable	24 (11.0%)	37 (15.3%)
Invanz Versus Ceft.: Difference in Favorable Rate	4.3%, 95% C.I.: -2.2%, 10.9%	

Reviewer's Note: *Table 36 displays the proportion of microbiologically evaluable subjects with favorable microbiologic response by stratum. Table 37 displays the proportion of microbiologically evaluable subjects with a favorable microbiologic response assessment by severity of the baseline infection for the*

Invanz and ceftriaxone groups. The observed differences in the favorable microbiologic response rates between the two treatment groups for each subgroup are displayed in Table 38, where most of the individual sample sizes were small. Table 39 displays the proportion of subjects with a favorable microbiologic response assessment at TOC for the groups of microbiologically evaluable subjects enrolled before and after the implementation of the enhanced blinding procedures.

TABLE 36: STUDY P014: PROPORTION OF MICROBIOLOGICALLY EVALUABLE SUBJECTS WITH FAVORABLE MICROBIOLOGIC RESPONSES AT TOC VISIT BY STRATUM

Stratum	Invanz (N=154)	Ceftriaxone (N=167)	Difference in Favorable Rate
Acute pyelonephritis	69/73 (94.5%)	71/75 (94.7%)	-0.1%, (-8.8%, 8.5%)
Other complicated UTI	72/81 (88.9%)	84/92 (91.3%)	-2.4%, (-12.5%, 7.7%)
Overall	141/154 (91.6%)	155/167 (92.8%)	-1.3%, (-7.8%, 5.3%)

TABLE 37: STUDY P014: PROPORTION OF SUBJECTS WITH FAVORABLE MICROBIOLOGIC RESPONSES OF MICROBIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT DISPLAYED BY SEVERITY OF INFECTION

Severity of Infection	Invanz (N=154)	Ceftriaxone (N=167)	Difference in Favorable Rate
Mid to Moderate	77/84 (91.7%)	85/92 (92.4%)	-0.7%, (-9.9%, 8.4%)
Severe	64/70 (91.4%)	70/75 (93.3%)	-1.9%, (-11.9%, 8.1%)
Overall	141/154 (91.6%)	155/167 (92.8%)	-1.3%, (-7.8%, 5.3%)

TABLE 38: STUDY P014: PROPORTION OF SUBJECTS WITH FAVORABLE MICROBIOLOGIC RESPONSES OF MICROBIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT DISPLAYED BY DEMOGRAPHICS

	Invanz (N=154)	Ceftriaxone (N=167)
GENDER		
Female	108/115 (93.9%)	110/117 (94.0%)
Male	33/39 (84.6%)	45/50 (90.0%)
AGE CATEGORY		
< 65	136/158 (86.1%)	124/141 (87.9%)
≥ 65	16/27 (59.3%)	23/33 (69.7%)
< 75	148/174 (85.1%)	140/164 (85.4%)
≥ 75	4/11 (36.4%)	7/10 (70.0%)
RACE		
Asian	1/1 (100%)	1/1 (100%)
Black	14/15 (93.3%)	13/14 (92.9%)
Caucasian	101/109 (92.7%)	103/112 (92.0%)
Hispanic	11/13 (84.6%)	17/17 (100%)
Hispanic/White	0/0 (NA)	2/2 (100%)
Latin American	1/1 (100%)	2/2 (100%)
Mestizo	10/12 (83.3%)	14/16 (87.5%)
Mulatto	3/3 (100%)	2/2 (100%)
Philippino	0/0 (NA)	1/1 (100%)

TABLE 39: STUDY P014: PROPORTION OF SUBJECTS WITH FAVORABLE MICROBIOLOGIC RESPONSES OF MICROBIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT DISPLAYED BY BLINDING PROCEDURE

Enhanced Blinding Procedure	Invanz (N=154)	Ceftriaxone (N=167)	Difference in Favorable Rate
No	59/65 (90.8%)	68/76 (89.5%)	1.3%, (-10.0%, 12.6%)
Yes	82/89 (92.1%)	87/91 (95.6%)	-3.5%, (-11.6%, 4.6%)
Overall	141/154 (91.6%)	155/167 (92.8%)	-1.3%, (-7.8%, 5.3%)

***Reviewer's Note**: The following tables display analyses for secondary efficacy endpoints. The clinical responses of overall assessments, and assessments by stratum are shown for microbiologically evaluable subjects in Tables 40 and 41, respectively. The clinical and microbiologic responses are shown for microbiologically evaluable population in Table 42. The clinical responses are shown for microbiologic MITT subjects in Table 43. The results from all these analyses demonstrated that favorable rates of Invanz were comparable to those of ceftriaxone in these evaluation groups, except for the clinical and microbiologic responses of microbiologically evaluable population.*

TABLE 40: STUDY P014: CLINICAL RESPONSES OF MICROBIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT

Clinical Response	Invanz (N=154)	Ceftriaxone (N=167)
Favorable	138 (89.6%)	153 (91.6%)
Unfavorable	16 (10.4%)	14 (8.4%)
Invanz Versus Ceft.: Difference in Favorable Rate	-2.0%, 95% C.I.: -9.0%, 5.0%	

TABLE 41: STUDY P014: PROPORTION OF SUBJECTS WITH FAVORABLE CLINICAL RESPONSES OF MICROBIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT DISPLAYED BY SEVERITY OF INFECTION

Stratum	Invanz (N=154)	Ceftriaxone (N=167)	Difference in Favorable Rate
Acute pyelonephritis	69/73 (94.5%)	71/75 (94.7%)	-0.1%, (-8.8%, 8.5%)
Other complicated UTI	69/81 (85.2%)	85/92 (92.4%)	-7.2%, (-17.8%, 3.4%)
Overall	138/154 (89.6%)	156/167 (93.4%)	-3.8%, (-10.5%, 2.9%)

TABLE 42: STUDY P014: CLINICAL AND MICROBIOLOGIC RESPONSES OF MICROBIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT

Clinical and Microbiologic Response	Invanz (N=154)	Ceftriaxone (N=167)
Both Favorable	134 (87.0%)	152 (91.0%)
Not Both Favorable	20 (13.0%)	15 (9.0%)
Invanz Versus Ceft.: Difference in Favorable Rate	-4.0%, 95% C.I.: -11.5%, 3.5%	

TABLE 43: STUDY P014: CLINICAL RESPONSES OF MICROBIOLOGICAL MITT SUBJECTS AT TOC VISIT		
Clinical Response	Invanz (N=219)	Ceftriaxone (N=242)
Favorable	185 (84.5%)	205 (84.7%)
Unfavorable	34 (15.5%)	37 (15.3%)
Invanz Versus Ceft.: Difference in Favorable Rate	-0.2%, 95% C.I.: -7.3%, 6.8%	

III.C. STUDY P021

III.C.1. METHODS

Study P021 was a prospective, multicenter (34 centers), double-blind, randomized comparative study to evaluate the safety, tolerability, and efficacy of an IV antibiotic therapy with Invanz (1g QD) followed by oral ciprofloxacin (500mg BID) versus ceftriaxone (1g QD) followed by oral ciprofloxacin (500mg BID) in the treatment of complicated UTIs in adults. The duration of treatment was minimum 3 full days, with the option to switch to an oral antibiotic (ciprofloxacin) therapy, minimum 10, maximum 14 full days of total antibiotic therapy. It was initiated on September 24, 1998 and completed on March 9, 2000.

Reviewer's Note: *For Study P021, primary objectives, study design, assessment of efficacy, analytic populations, and statistical methods were similar to those described for Study P014 in Section II.B.1, except that Study P021 was anticipated to achieve enrollment of 150 total evaluable subjects with randomization ratio at 2:1 (100 subjects to Invanz and 50 to ceftriaxone).*

The MO agreed with Sponsor's evaluability criteria for constructing analytic populations and defining time points, and consented with Sponsor's assessment for clinical and microbiological outcomes.

III.C.2. EFFICACY RESULTS

Of the 258 subjects who enrolled in the study, 175 were randomized to the Invanz treatment group, and 83 were randomized to the ceftriaxone treatment group. One hundred eight subjects (78 Invanz and 30 ceftriaxone) were excluded from the microbiologically evaluable analyses. The most common reason subjects were excluded from the microbiological evaluable population was that a uropathogen was not isolated and therefore the disease definition was not met.

Reviewer's Note: *The number and percentage of subjects included in each evaluation group are presented in Table 44. There were no notable treatment differences with respect to the percentage of subjects included in each evaluation group.*

TABLE 44: STUDY P021: NUMBER OF SUBJECTS INCLUDED IN EACH EVALUATION GROUP		
Evaluation Group	Number of Subjects	
	Invanz	Ceftriaxone
All Randomized Subjects	175	83
Clinical MITT Subjects	139 (79.4%)	73 (88.0%)
Micro. MITT Subjects	131 (74.9%)	71 (85.5%)
Clinically Evaluable Subjects	103 (58.9%)	55 (66.3%)
Micro. Evaluable Subjects	97 (55.4%)	53 (63.9%)

Reviewer's Note: *The microbiologic responses are shown for microbiologically evaluable population in Table 45. The confidence interval result failed to show that Invanz and ceftriaxone were therapeutically equivalent with respect to the favorable rates at TOC.*

TABLE 45: STUDY P021: MICROBIOLOGIC RESPONSES OF MICROBIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT		
Microbiologic Response	Invanz (N=97)	Ceftriaxone (N=53)
Favorable	83 (85.6%)	45 (84.9%)
Unfavorable	14 (14.4%)	8 (15.1%)
Invanz Versus Ceft.: Difference in Favorable Rate	0.4%, 95% C.I.: -12.7%, 14.0%	

Reviewer's Note: *The 95% confidence interval of the difference in microbiologic favorable rate of microbiologic MITT population between Invanz minus ceftriaxone illustrated the marginal equivalence of the two treatment groups, which is presented in Table 46.*

TABLE 46: STUDY P021: MICROBIOLOGIC RESPONSES OF MICROBIOLOGICAL MITT SUBJECTS AT TOC VISIT		
Microbiologic Response	Invanz (N=131)	Ceftriaxone (N=71)
Favorable	99 (75.6%)	51 (71.8%)
Unfavorable	32 (24.4%)	20 (28.2%)
Invanz Versus Ceft.: Difference in Favorable Rate	3.7%, 95% C.I.: -10.1%, 17.6%	

Reviewer's Note: *Table 47 displays the proportion of microbiologically evaluable subjects with favorable microbiologic response by stratum. Table 48 displays the proportion of microbiologically evaluable subjects with a favorable microbiologic response assessment by severity of the baseline infection for the Invanz and ceftriaxone groups. The observed differences in the favorable microbiologic response rates between the two treatment groups for each subgroup are also displayed in Table 49, where most of the individual sample sizes were small. Table 50 displays the proportion of subjects with a favorable microbiologic response assessment at TOC for the groups of microbiologically evaluable subjects enrolled before and after the implementation of the enhanced blinding procedures.*

TABLE 47: STUDY P021: PROPORTION OF MICROBIOLOGICALLY EVALUABLE SUBJECTS WITH FAVORABLE MICROBIOLOGIC RESPONSES AT TOC VISIT BY STRATUM

Stratum	Invanz (N=97)	Ceftriaxone (N=53)	Difference In Favorable Rate
Acute pyelonephritis	45/52 (86.5%)	25/28 (89.3%)	-2.7%, (-20.2%, 14.7%)
Other complicated UTI	38/45 (84.4%)	20/25 (80.0%)	4.4%, (-17.6%, 26.5%)
Overall	83/97 (85.6%)	45/53 (84.9%)	0.7%, (-12.7%, 14.0%)

TABLE 48: STUDY P021: PROPORTION OF MICROBIOLOGICALLY EVALUABLE SUBJECTS WITH FAVORABLE MICROBIOLOGIC RESPONSES AT TOC VISIT BY SEVERITY OF INFECTION

Severity of Infection	Invanz (N=97)	Ceftriaxone (N=53)	Difference In Favorable Rate
Mild to Moderate	40/51 (78.4%)	22/28 (78.6%)	-0.1%, (-21.8%, 21.6%)
Severe	43/46 (93.5%)	23/25 (92.0%)	1.5%, (-14.4%, 17.4%)
Overall	83/97 (85.6%)	45/53 (84.9%)	0.7%, (-12.7%, 14.0%)

TABLE 49: STUDY P021: PROPORTION OF MICROBIOLOGICALLY EVALUABLE SUBJECTS WITH FAVORABLE MICROBIOLOGIC RESPONSES AT TOC VISIT BY DEMOGRAPHICS

	Invanz (N=97)	Ceftriaxone (N=53)
GENDER		
Female	56/65 (86.2%)	27/32 (84.4%)
Male	27/32 (84.4%)	18/21 (86.7%)
AGE CATEGORY		
< 65	57/63 (90.5%)	32/38 (84.2%)
≥ 65	26/34 (76.5%)	13/15 (86.7%)
< 75	70/81 (86.4%)	41/48 (85.4%)
≥ 75	13/16 (81.3%)	4/5 (80.0%)
RACE		
Asian	1/1 (100%)	0/0 (NA)
Black	3/3 (100%)	5/6 (83.3%)
Caucasian	64/73 (87.7%)	32/37 (86.5%)
Hispanic	15/20 (75.0%)	7/9 (77.8%)
Latin American	0/0 (NA)	1/1 (100%)

TABLE 50: STUDY P021: PROPORTION OF MICROBIOLOGICALLY EVALUABLE SUBJECTS WITH FAVORABLE MICROBIOLOGIC RESPONSES AT TOC VISIT BY BLINDING PROCEDURE

Enhanced Blinding Procedure	Invanz (N=97)	Ceftriaxone (N=53)	Difference In Favorable Rate
No	6/7 (85.7%)	0/2 (0%)	85.7%,(27.6%,143.8%)
Yes	77/90 (85.6%)	45/51 (88.2%)	-2.7%, (-15.7%, 10.3%)
Overall	83/97 (85.6%)	45/53 (84.9%)	0.7%, (-12.7%, 14.0%)

***Reviewer's Note**: The following tables display analyses for secondary efficacy endpoints. The clinical responses of overall assessments and assessments by stratum are shown for microbiologically evaluable subjects in Tables 51 and 52, respectively. The clinical and microbiologic responses are shown for microbiologically evaluable population in Table 53. The clinical responses are shown for microbiologic MITT subjects in Table 54. The results from all these analyses demonstrated that favorable rates of Invanz were comparable to those of ceftriaxone in these evaluation groups, except for the clinical and microbiologic responses of microbiologically evaluable population.*

TABLE 51: STUDY P021: CLINICAL RESPONSES OF MICROBIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT

Clinical Response	Invanz (N=97)	Ceftriaxone (N=53)
Favorable Unfavorable	90 (92.8%) 7 (7.2%)	47 (88.7%) 6 (11.3%)
Invanz Versus Ceft.: Difference in Favorable Rate	4.1%, 95% C.I.: -7.3%, 15.5%	

TABLE 52: STUDY P021: CLINICAL FAVORABLE RATES OF MICROBIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT BY STRATUM

Stratum	Invanz (N=154)	Ceftriaxone (N=167)	Difference in Favorable Rate
Acute pyelonephritis	49/52 (94.2%)	26/28 (92.9%)	1.4%, (-12.8%, 15.6%)
Other complicated UTI	41/45 (91.1%)	21/25 (84.0%)	7.1%, (-12.6%, 26.8%)
Overall	90/97 (92.8%)	47/53 (88.7%)	4.1%, (-7.3%, 15.5%)

TABLE 53: STUDY P021: CLINICAL AND MICROBIOLOGIC RESPONSES OF MICROBIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT

Clinical and Microbiologic Response	Invanz (N=97)	Ceftriaxone (N=53)
Both Favorable Not Both Favorable	83 (85.6%) 14 (14.4%)	45 (84.9%) 8 (15.1%)
Invanz Versus Ceft.: Difference in Favorable Rate	0.7%, 95% C.I.: -12.7%, 14.0%	

TABLE 54: STUDY P021: CLINICAL RESPONSES OF MICROBIOLOGICAL MITT SUBJECTS AT TOC VISIT

Clinical Response	Invanz (N=131)	Ceftriaxone (N=71)
Favorable Unfavorable	112 (85.5%) 19 (14.5%)	55 (77.5%) 16 (22.5%)
Invanz Versus Ceft.: Difference in Favorable Rate	8.0%, 95% C.I.: -4.5%, 20.6%	

IV. ACUTE PELVIC INFECTIONS

IV.A. INTRODUCTION

The Sponsor submitted one pivotal phase III controlled study, P023, as evidence to support that Invanz was safe and efficacious for the treatment of acute pelvic infections in hospitalized women when compared with current established therapies. Statistical review focuses on this comparative clinical trial which formed the basis of this application.

IV.B. STUDY P023

IV.B.1. METHODS

Primary Objectives

1. In subjects with acute pelvic infection who are clinically evaluable, the proportion of subjects who have a favorable clinical response is equivalent for Invanz and piperacillin/tazobactam at the FU (TOC) visit at 2 to 4 weeks post-treatment. It was expected that approximately 90% of the clinically evaluable subjects in each group would have a favorable clinical response.
2. It was expected that Invanz would be similar to the comparator with respect to the proportion of subjects with any drug-related adverse experience leading to discontinuation of study drug and also with respect to the proportion of subjects with any drug-related serious adverse experience.

Study Design

Study P023 was a prospective, multicenter (66 centers, including 47 USA sites), multinational, double-blind, randomized comparative study to evaluate the safety, tolerability, and efficacy of an IV antibiotic therapy with Invanz (1g QD) versus piperacillin/tazobactam (3.375g Q6H) in the treatment of acute pelvic infections in hospitalized women. The duration of treatment was minimum 3, maximum 10 full days. It was initiated on November 3, 1998 and completed on May 9, 2000.

This study was anticipated to achieve 150 clinically evaluable subjects in each treatment group. Each subject was expected to complete the study in 4 to 6 weeks. Hospitalized female subjects, at least 18 years of age, who met all of the entry criteria and had a clearly defined pelvic infection characterized by the investigator as requiring parenteral therapy, were randomized to one of the two study regimens in a 1:1 ratio. Allocations were stratified for balance based upon the diagnosis of obstetric/postpartum infection or gynecologic/postoperative infection.

Overall study was scheduled for following clinical observation and laboratory measurements: 1. eligibility screening (≤ 24 hours prior to study therapy); 2. study antibiotic IV treatment period: during IV therapy (Day 3, 4, or 5) and DCIV (final day); 3. FU (TOC) period (post-therapy, 2 to 4 weeks).

Assessment of Efficacy

The primary assessment of clinical response for each subject was the assessment made at the 2 to 4 week post-therapy FU visit (TOC visit). The favorable final clinical response assessment was "cure" or

"presumptive cure". The unfavorable final clinical response assessment was "failure". Subjects with a final clinical response assessment of "indeterminate" were considered to not be clinically evaluable. Microbiological responses other than "indeterminate" were classified as "favorable" and "unfavorable."

The primary efficacy analysis approach was the clinically evaluable population analysis. The primary efficacy endpoint was the proportion of clinically evaluable subjects in each treatment group having a favorable clinical response assessment at the TOC visit.

Reviewer's Note: *The MO agreed with Sponsor's evaluability criteria for constructing analytic populations and defining time points, and consented with Sponsor's assessment for clinical and microbiological outcomes.*

The clinical favorable rate of clinical MITT subjects should be the co-primary efficacy variable.

Statistical Methods

The comparisons of interest in this study were conducted between Invanz and piperacillin/tazobactam, which was designed to show equivalence of the two treatment groups.

Reviewer's Note: *The following statistical analyses were performed by the reviewer to evaluate the efficacy and safety of Invanz versus piperacillin/tazobactam.*

Equivalence between the test treatment Invanz and the control (piperacillin/tazobactam) with respect to the primary efficacy parameters was assessed by computing the two-tailed 95% confidence interval of the difference in clinical favorable rates. The confidence intervals were computed using a normal approximation to the binomial, and included a continuity correction. The evaluation of whether the treatment groups were considered equally effective was judged based on the delta value 0.1, which is considered a clinically acceptable equivalence margin with respect to this indication. The confidence interval results for subset analyses should be interpreted cautiously since it was not adjusted by multiple comparison analysis.

Prior to performing efficacy analyses, this reviewer assessed the comparability of the treatment groups.

III.B.2. EFFICACY RESULTS

Of the 412 subjects who enrolled in the study, 216 were randomized to the Invanz treatment group, and 196 were randomized to the piperacillin/tazobactam treatment group. Ninety six subjects (53 Invanz and 43 piperacillin/tazobactam) were excluded from the clinically evaluable analyses. The most common reasons subjects were excluded from the clinically evaluable population were inadequate or inappropriate course of study therapy and TOC window violations. Most TOC window violations were subjects who were lost to FU.

Reviewer's Note: *The number and the proportion of subjects included in each evaluation group are presented in Table 55. There were no notable treatment differences with respect to the percentage of subjects included in each evaluation group.*

TABLE 55: STUDY P023: NUMBER OF SUBJECTS INCLUDED IN EACH EVALUATION GROUP		
Evaluation Group	Number of Subjects	
	Invanz	Piperacillin/ Tazobactam
All Randomized Subjects	216	196
Clinical MITT Subjects	211 (97.7%)	191 (97.4%)
Microbiologic MITT Subjects	161 (74.5%)	158 (80.6%)
Clinically Evaluable Subjects	163 (75.5%)	153 (78.1%)
Microbiologically Evaluable Subjects	128 (59.3%)	129 (65.8%)

***Reviewer's Note**: The clinical responses are shown for clinically evaluable population in Table 56. The confidence interval result showed that Invanz and piperacillin/tazobactam were therapeutically equivalent with respect to clinical favorable rates at TOC.*

TABLE 56: STUDY P023: CLINICAL RESPONSES OF CLINICALLY EVALUABLE SUBJECTS AT TOC VISIT		
Clinical Response	Invanz (N=163)	Piperacillin/ Tazobactam (N=153)
Favorable	153 (93.9%)	140 (91.5%)
Unfavorable	10 (6.1%)	13 (8.5%)
Invanz Versus P/T: Difference in Favorable Rate	2.4%, 95% C.I.: -4.0%, 8.7%	

***Reviewer's Note**: The 95% confidence interval of the difference in clinical favorable rate of clinical MITT population between Invanz minus piperacillin/tazobactam illustrated the therapeutic equivalence of the two treatment groups, which is presented in Table 57.*

TABLE 57: STUDY P023: CLINICAL RESPONSES OF CLINICAL MITT SUBJECTS AT TOC VISIT		
Clinical Response	Invanz (N=211)	Piperacillin/ Tazobactam (N=191)
Favorable	173 (82.0%)	160 (83.8%)
Unfavorable	38 (18.0%)	31 (16.2%)
Invanz Versus P/T: Difference in Favorable Rate	-1.8%, 95% C.I.: -9.6%, 6.1%	

***Reviewer's Note**: Table 58 displays the proportion of the clinically evaluable subjects with a favorable clinical response by stratum.*

TABLE 58: STUDY P023: PROPORTION OF CLINICALLY EVALUABLE SUBJECTS WITH FAVORABLE CLINICAL RESPONSES AT TOC VISIT BY STRATUM			
Stratum	Invanz (N=163)	Piperacillin/ Tazobactam (N=153)	Difference in Favorable Rate
Obstetric/Postpartum Infection	129/137 (94.2%)	121/132 (91.7%)	2.5%, (-4.4%, 9.4%)
Gynecologic/Post-operative Infection	24/26 (92.3%)	19/21 (90.5%)	1.8%, (-18.7%, 22.3%)
Overall	153/163 (93.9%)	140/153 (91.5%)	2.4%, (-4.0%, 8.7%)

***Reviewer's Note**: Table 59 displays the proportion of clinically evaluable subjects with a favorable clinical by severity for the Invanz and piperacillin/tazobactam groups .*

TABLE 59: STUDY P023: PROPORTION OF CLINICALLY EVALUABLE SUBJECTS WITH FAVORABLE CLINICAL RESPONSES AT TOC VISIT BY SEVERITY OF INFECTION			
Severity of Infection	Invanz (N=163)	Piperacillin/ Tazobactam (N=153)	Difference in Favorable Rate
Moderate	113/121 (93.4%)	110/118 (93.2%)	0.2%, (-7.0%, 7.3%)
Severe	40/42 (95.2%)	30/35 (85.7%)	9.5%, (-6.4%, 25.4%)
Overall	153/163 (93.9%)	140/153 (91.5%)	2.4%, (-4.0%, 8.7%)

***Reviewer's Note**: Table 60 displays the proportion of subjects with a favorable clinical response at TOC for the groups of clinically evaluable subjects who had polymicrobial infection or nonpolymicrobial infection for the Invanz and piperacillin/tazobactam treatment groups.*

TABLE 60: STUDY P023: PROPORTION OF CLINICALLY EVALUABLE SUBJECTS WITH FAVORABLE CLINICAL RESPONSES AT TOC VISIT BY POLYMICROBIAL OR NONPOLYMICROBIAL INFECTION			
	Invanz (N=163)	Piperacillin/ Tazobactam (N=153)	Difference in Favorable Rate
Nonpolymicrobial	64/70 (91.4%)	52/58 (89.7%)	1.8%, (-10.0%, 13.6%)
Polymicrobial	89/93 (95.7%)	88/95 (92.6%)	3.1%, (-4.7%, 10.8%)
Overall	153/163 (93.9%)	140/153 (91.5%)	2.4%, (-4.0%, 8.7%)

***Reviewer's Note**: Table 61 displays the proportion of clinically evaluable subjects with a favorable clinical response in the demographic subgroups between the two treatment groups.*

TABLE 61: STUDY P023: PROPORTION OF CLINICALLY EVALUABLE SUBJECTS WITH FAVORABLE CLINICAL RESPONSES AT TOC VISIT BY DEMOGRAPHICS		
	Invanz (N=163)	Piperacillin/ Tazobactam (N=153)
GENDER		
Female	48/62 (77.4%)	47/58 (81.0%)
Male	104/123 (84.6%)	100/116 (86.2%)
AGE CATEGORY		
< 65	136/158 (86.1%)	124/141 (87.9%)
≥ 65	16/27 (59.3%)	23/33 (69.7%)
< 75	148/174 (85.1%)	140/164 (85.4%)
≥ 75	4/11 (36.4%)	7/10 (70.0%)
RACE		
Asian	21/26 (80.8%)	22/28 (78.6%)
Black	81/108 (75.0%)	75/89 (84.3%)
Caucasian	34/35 (97.1%)	37/41 (90.2%)
Hispanic	13/13 (100%)	13/15 (86.7%)
Indian	0/0 (NA)	0/1 (0)
Mestizo	0/0 (NA)	0/1 (0)

***Reviewer's Note**: Table 62 displays the proportion of subjects with a favorable clinical response at TOC for the groups of clinically evaluable subjects enrolled before and after the implementation of the enhanced blinding procedures.*

TABLE 62: STUDY P023: PROPORTION OF CLINICALLY EVALUABLE SUBJECTS WITH FAVORABLE CLINICAL AND MICROBIOLOGIC RESPONSES AT TOC VISIT BY BLINDING PROCEDURE			
Enhanced Blinding Procedure	Invanz (N=163)	Piperacillin/ Tazobactam (N=153)	Difference in Favorable Rate
No	17/18 (94.4%)	15/16 (93.8%)	0.7%, (-21.1%, 22.5%)
Yes	136/145 (93.8%)	125/137 (91.2%)	2.6%, (-4.3%, 9.4%)
Overall	153/163 (93.9%)	140/153 (91.5%)	2.4%, (-4.0%, 8.7%)

***Reviewer's Note**: The following tables display analyses for secondary efficacy endpoints. The microbiologic responses are shown for microbiologically evaluable subjects in Table 63. The clinical and microbiologic responses are shown for microbiologically evaluable population in Table 64. The clinical and microbiologic responses are shown for microbiologic MITT subjects in Table 65. The results from all these analyses demonstrated that favorable rates of Invanz were comparable to those of piperacillin/tazobactam in these evaluation groups.*

TABLE 63: STUDY P023: MICROBIOLOGIC RESPONSES OF MICROBIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT		
Microbiological Response	Invanz (N=128)	Piperacillin/ Tazobactam (N=129)
Favorable Unfavorable	120 (93.7%) 8 (6.3%)	121 (93.8%) 8 (6.2%)
Invanz Versus P/T: Difference in Favorable Rate	-0.1%, 95% C.I.: -6.7%, 6.6%	

TABLE 64: STUDY P023: CLINICAL AND MICROBIOLOGIC RESPONSES OF MICROBIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT		
Clinical and Microbiological Response	Invanz (N=128)	Piperacillin/ Tazobactam (N=129)
Both Favorable Not Both Favorable	120 (93.7%) 8 (6.3%)	118 (91.5%) 11 (8.5%)
Invanz Versus P/T: Difference in Favorable Rate	2.3%, 95% C.I.: -4.9%, 9.4%	

TABLE 65: STUDY P023: MICROBIOLOGIC RESPONSES OF MICROBIOLOGIC MITT SUBJECTS AT TOC VISIT		
Microbiological Response	Invanz (N=161)	Piperacillin/ Tazobactam (N=158)
Favorable Unfavorable	135 (83.9%) 26 (16.1%)	134 (84.8%) 24 (15.2%)
Invanz Versus P/T: Difference in Favorable Rate	-1.0%, 95% C.I.: -9.6%, 7.6%	

V. COMPLICATED SKIN AND SKIN STRUCTURE INFECTIOUS

V.A. INTRODUCTION

The Sponsor submitted one pivotal phase IIb controlled study, P016, as evidence to support that Invanz was safe and efficacious for the treatment of complicated SSSIs in adults when compared with current established therapies. Statistical review focuses on this comparative clinical trial which formed the basis of this application.

V.B. STUDY P016

V.B.1. METHODS

Primary Objectives

1. To compare the efficacy of Invanz at 10 to 21 days post-therapy, with respect to the overall clinical response assessment profile in the treatment of subjects with serious complicated SSSIs as compared to a piperacillin/tazobactam control group.
2. To evaluate and compare the safety profile of Invanz versus piperacillin/tazobactam with respect to the proportion of subjects with any drug-related adverse experiences leading to the discontinuation of study drug and also with respect to the proportion of subjects with any drug-related serious adverse experience.

Study Design

Study P016 was a prospective, multicenter (44 centers, including 33 USA sites), multinational, double-blind, randomized comparative study to evaluate the safety, tolerability, and efficacy of an IV antibiotic therapy with Invanz (1g QD) versus piperacillin/tazobactam (3.375g Q6H) in the treatment of complicated SSSIs in adults. The duration of treatment was minimum 7, maximum 14 full days. It was initiated in April, 1998 and completed on November 2, 1999.

This study was anticipated to achieve completion of 150 clinically evaluable subjects in each treatment group. Each subject was expected to complete the study (including FU) within 3 to 5 weeks. The adult subjects, who met the inclusion/exclusion criteria, were randomized in a 1:1 ratio at each study site to receive one of the treatments.

Overall study was scheduled for following clinical observation and laboratory measurements: 1. eligibility screening (≤ 24 hours prior to study therapy); 2. study antibiotic treatment period: on-therapy assessment (Day 3, 4, or 5), every 4 to 5 days after on-therapy assessment, DCIV (within 72 hours of final day); 3. FU (TOC)(10 to 21 days post-therapy).

Efficacy Assessment

The primary assessment for efficacy outcome was the post-treatment FU visit (TOC visit). The clinical response was assessed as "cure", "improved and not requiring antibiotics", "failure", or "indeterminate"

based on comparison to admission signs and symptoms. Favorable clinical response ratings included "cure" or "improved and not requiring antibiotics". A clinical response rating of "failure" was considered to be unfavorable. Subjects with a clinical response rating of "indeterminate" were considered to be not clinically evaluable. Microbiological responses other than "indeterminate" were classified as "favorable" or "unfavorable". "Favorable" microbiological response assessments included "eradication" and "presumptive eradication". Subjects with a microbiological response assessment of "indeterminate" were considered to be not microbiologically evaluable.

The primary analytic population was the clinically evaluable subjects, which was defined as a subset of the clinical MITT population. The clinically evaluable population was comprised of subjects in whom sufficient information was available to determine the subject's outcome and no confounding factors were present that interfered with the assessment of that outcome. The primary efficacy endpoint was the proportion of clinically evaluable subjects in each treatment group having a favorable clinical response assessment at the TOC visit.

Reviewer's Note: Reviewer's Note: *The MO defined her evaluation populations, and assessed the efficacy outcomes according to her clinical and microbiologic criteria.*

Please refer to MO's review for detailed descriptions of Sponsor's and MO's efficacy outcome definition.

The clinical favorable rate of clinical MITT subjects should be the co-primary efficacy variable.

Statistical Methods

The comparisons of interest in this study were conducted between Invanz and piperacillin/tazobactam, which was designed to show equivalence of the two treatment groups.

Reviewer's Note: *The following statistical analyses were performed by the reviewer to evaluate the efficacy of Invanz versus piperacillin/tazobactam.*

Equivalence between the test treatment Invanz and the control (piperacillin/tazobactam) with respect to the primary efficacy parameters was assessed by computing the two-tailed 95% confidence interval of the difference in clinical favorable rates. The confidence intervals were computed using a normal approximation to the binomial, and included a continuity correction. The evaluation of whether the treatment groups were considered equally effective was judged based on the delta value 0.1, which is considered a clinically acceptable equivalence margin with respect to this indication. The confidence interval results for subset analyses should be interpreted cautiously since it was not adjusted by multiple comparison analysis.

Prior to performing efficacy analyses, this reviewer assessed the comparability of the treatment groups.

V.B.2. EFFICACY RESULTS

Of the 540 subjects who enrolled in the study, 274 were randomized to the Invanz treatment group, and 266 were randomized to the piperacillin/tazobactam treatment group. Two hundred two subjects (106 Invanz and 96 piperacillin/tazobactam) were excluded from the MO clinically evaluable analyses. The most common reasons why subjects were excluded from the clinically evaluable population were TOC window violations and inadequate or inappropriate courses of study therapy. Most of these subjects were lost to FU.

***Reviewer's Note**: The number and the proportion of subjects included in each evaluation group are presented in Table 66. There were no notable treatment differences with respect to the percentage of subjects included in each evaluation group.*

TABLE 66: STUDY P016: NUMBER OF SUBJECTS INCLUDED IN EACH EVALUATION GROUP

Evaluation Group	Number of Subjects	
	Invanz	Piperacillin/ Tazobactam
All Randomized Subjects	274	266
Sponsor Clinical MITT Subjects	269 (98.2%)	258 (97.0%)
MO Clinical MITT Subjects	265 (96.7%)	257 (96.6%)
Sponsor Micro. MITT Subjects	192 (70.1%)	190 (71.4%)
MO Micro. MITT Subjects	187 (68.2%)	186 (69.9%)
Sponsor Clinically Evaluable Subjects	185 (67.5%)	174 (65.4%)
MO Clinically Evaluable Subjects	168 (61.3%)	170 (63.9%)
Sponsor Micro. Evaluable Subjects	155 (56.6%)	151 (56.8%)
MO Micro. Evaluable Subjects	144 (52.6%)	146 (54.9%)

***Reviewer's Note**: The clinical responses are shown for MO clinically evaluable and Sponsor clinically evaluable populations in Tables 67 and 68, respectively. The confidence interval result of MO clinically evaluable subjects showed Invanz and piperacillin/tazobactam were therapeutically equivalent with respect to the clinical favorable rates at TOC. The two treatment groups were shown marginally equivalent in Sponsor clinically evaluable subjects.*

TABLE 67: STUDY P016: CLINICAL RESPONSES OF CLINICALLY EVALUABLE SUBJECTS AT TOC VISIT (MO)

Clinical Response	Invanz (N=168)	Piperacillin/ Tazobactam (N=170)
Favorable	141 (83.9%)	145 (85.3%)
Unfavorable	27 (16.1%)	25 (14.7%)
Invanz Versus P/T: Difference in Favorable Rate	-1.4%, 95% C.I.: -9.7%, 6.9%	

TABLE 68: STUDY P016: CLINICAL RESPONSES OF CLINICALLY EVALUABLE SUBJECTS AT TOC VISIT (Sponsor)

Clinical Response	Invanz (N=185)	Piperacillin/ Tazobactam (N=174)
Favorable	152 (82.2%)	147 (84.5%)
Unfavorable	33 (17.8%)	27 (15.5%)
Invanz Versus P/T: Difference in Favorable Rate	-2.3%, 95% C.I.: -10.6%, 5.9%	

***Reviewer's Note**: The 95% confidence interval of the difference in clinical favorable rate of clinical MITT population between Invanz minus piperacillin/tazobactam illustrated marginal equivalence of the two*

treatment groups, which are presented in Tables 69 and 70 as per MO clinical MITT subjects and Sponsor clinical MITT subjects.

TABLE 69: STUDY P016: CLINICAL RESPONSES OF CLINICAL MITT SUBJECTS AT TOC VISIT (MO)

Clinical Response	Invanz (N=265)	Piperacillin/ Tazobactam (N=257)
Favorable Unfavorable	173 (65.3%) 92 (34.7%)	172 (66.9%) 85 (33.1%)
Invanz Versus P/T: Difference in Favorable Rate	-1.6%, 95% C.I.: -10.1%, 6.9%	

TABLE 70: STUDY P016: CLINICAL RESPONSES OF CLINICAL MITT SUBJECTS AT TOC VISIT (Sponsor)

Clinical Response	Invanz (N=269)	Piperacillin/ Tazobactam (N=258)
Favorable Unfavorable	176 (65.4%) 93 (34.6%)	173 (67.1%) 85 (32.9%)
Invanz Versus P/T: Difference in Favorable Rate	-1.6%, 95% C.I.: -10.1%, 6.8%	

***Reviewer's Note**: Tables 71 and 72 display the observed proportion of as per MO clinically evaluable subjects and Sponsor clinically evaluable subjects with a favorable clinical response assessment at TOC between the two treatment groups by stratum. Tables 73 and 74 display the observed difference in response rates between the two treatment groups for each primary infection diagnosis in MO clinically evaluable subjects and Sponsor clinically evaluable subjects, respectively.*

TABLE 71: STUDY P016: PROPORTION OF CLINICALLY EVALUABLE SUBJECTS WITH FAVORABLE CLINICAL RESPONSES AT TOC VISIT BY STRATUM (MO)

Stratum	Invanz (N=168)	Piperacillin/ Tazobactam (N=170)	Difference in Favorable Rate
Complicated Underlying Disease	16/26 (61.5%)	23/31 (74.2%)	-12.7%,(-40.4%,15.1%)
All Other	125/142 (88.0%)	122/139 (87.8%)	0.3%, (-8.1%,8.6%)
Overall	141/168 (83.9%)	145/170 (85.3%)	-1.4%, (-9.7%, 6.9%)

TABLE 72: STUDY P016: PROPORTION OF CLINICALLY EVALUABLE SUBJECTS WITH FAVORABLE CLINICAL RESPONSES AT TOC VISIT BY STRATUM (Sponsor)

Stratum	Invanz (N=185)	Piperacillin/ Tazobactam (N=174)	Difference in Favorable Rate
Complicated Underlying Disease	28/42 (66.7%)	27/36 (75.0%)	-8.3%, (-31.0%, 14.3%)
All Other	124/143 (86.7%)	120/138 (87.0%)	-0.2%, (-8.9%, 8.4%)
Overall	152/185 (82.2%)	147/174 (84.5%)	-2.3%, (-10.6%, 5.9%)

TABLE 73: STUDY P016: PROPORTION OF CLINICALLY EVALUABLE SUBJECTS WITH FAVORABLE CLINICAL RESPONSES AT TOC VISIT BY PRIMARY INFECTION DIAGNOSIS (MO)

Primary Diagnosis	Invanz (N=168)	Piperacillin/ Tazobactam (N=170)
Complicating Underlying Disease Stratum		
Acutely infected pressure ulcer	2/5 (40.0%)	5/5 (100%)
Lower extremity infection complicated by neuropathy	3/3 (100%)	0/1 (0)
All Other Stratum		
Cellulitis with purulent drainage	29/32 (90.6%)	23/26 (88.5%)
Complicated cellulitis with systemic signs	2/3 (66.7%)	2/3 (66.7%)
Cutaneous abscess	19/23 (82.6%)	23/24 (95.8%)
Deep soft tissue abscess	29/30 (96.7%)	35/37 (94.6%)
Deep soft tissue infection or ulcer	0/0 (NA)	1/2 (50.0%)
Infected pyoderma	0/0 (NA)	0/1 (0)
Perineal cellulitis/ abscess	16/18 (88.9%)	9/11 (81.8%)
Posttraumatic wound infection	21/25 (84.0%)	19/21 (90.5%)
Suppurative hydradenitis	1/1 (100%)	0/0 (NA)
Surgical site infection	8/10 (80.0%)	10/13 (76.9%)
Tenosynovitis	0/0 (NA)	0/1 (0)

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TABLE 74: STUDY P016: PROPORTION OF CLINICALLY EVALUABLE SUBJECTS WITH FAVORABLE CLINICAL RESPONSES AT TOC VISIT BY PRIMARY INFECTION DIAGNOSIS (Sponsor)

Primary Diagnosis	Invanz (N=185)	Piperacillin/ Tazobactam (N=174)
Complicating Underlying Disease Stratum		
Acutely infected pressure ulcer	2/4 (50.0%)	5/5 (100%)
Lower extremity infection complicated by neuropathy	3/3 (100%)	0/1 (0)
All Other Stratum		
Cellulitis with purulent drainage	27/29 (93.1%)	21/24 (87.5%)
Complicated cellulitis with systemic signs	1/2 (50.0%)	2/3 (66.7%)
Cutaneous abscess	16/20 (80.0%)	23/24 (95.8%)
Deep soft tissue abscess	29/30 (96.7%)	34/36 (94.4%)
Deep soft tissue infection or ulcer	0/1 (0)	1/2 (50.0%)
Infected pyoderma	0/0 (NA)	0/1 (0)
Perineal cellulitis/ abscess	18/20 (90.0)	9/11 (81.8%)
Posttraumatic wound infection	25/30 (83.3%)	22/26 (84.6%)
Suppurative hydradenitis	1/2 (50.0%)	0/0 (NA)
Surgical site infection	7/9 (77.8%)	8/10 (80.0%)
Tenosynovitis	0/0 (NA)	0/1 (0)

***Reviewer's Note**: Tables 75 and 76 display the observed proportion of as per MO clinically evaluable subjects and Sponsor clinically evaluable subjects with a favorable clinical response assessment at TOC by severity of infection for the Invanz and piperacillin/tazobactam groups.*

TABLE 75: STUDY P016: PROPORTION OF CLINICALLY EVALUABLE SUBJECTS WITH FAVORABLE CLINICAL RESPONSES AT TOC VISIT BY SEVERITY OF INFECTION (MO)

Severity of Infection	Invanz (N=168)	Piperacillin/ Tazobactam (N=170)	Difference in Favorable Rate
Moderate	111/133 (83.5%)	123/140 (87.9%)	5.3%, (-4.7%, 15.3%)
Severe	30/35 (85.7%)	22/30 (73.3%)	5.3%, (-7.6%, 18.2%)
Overall	141/168 (83.9%)	145/170 (85.3%)	-1.4%, (-9.7%, 6.9%)

TABLE 76: STUDY P016: PROPORTION OF CLINICALLY EVALUABLE SUBJECTS WITH FAVORABLE CLINICAL RESPONSES AT TOC VISIT BY SEVERITY OF INFECTION (Sponsor)

Severity of Infection	Invanz (N=185)	Piperacillin/ Tazobactam (N=174)	Difference in Favorable Rate
Moderate	120/145 (82.8%)	125/143 (87.4%)	-4.7%, (-13.6%, 4.2%)
Severe	32/40 (80.0%)	22/31 (71.0%)	9.0%, (-14.1%, 32.1%)
Overall	152/185 (82.2%)	147/174 (84.5%)	-2.3%, (-10.6%, 5.9%)

***Reviewer's Note**: The observed differences in the favorable clinical response rates between the two treatment groups for each demographic subgroup are displayed in Tables 77 and 78 as per MO clinically evaluable subjects and Sponsor clinically evaluable subjects.*

TABLE 77: STUDY P016: PROPORTION OF CLINICALLY EVALUABLE SUBJECTS WITH FAVORABLE CLINICAL RESPONSES AT TOC VISIT BY DEMOGRAPHICS (MO)

	Invanz (N=168)	Piperacillin/ Tazobactam (N=170)
GENDER		
Female	42/57 (73.7%)	47/57 (82.5%)
Male	99/111 (89.2%)	98/113 (86.7%)
AGE CATEGORY		
< 65	128/144 (88.9%)	121/136 (89.0%)
≥ 65	13/24 (54.2%)	24/34 (70.6%)
< 75	138/157 (87.9%)	137/159 (86.2%)
≥ 75	3/11 (27.3%)	8/11 (72.7%)
RACE		
Black	21/23 (91.3%)	22/27 (81.5%)
Caucasian	75/98 (76.5%)	73/88 (83.0%)
Hispanic	30/32 (93.8%)	37/39 (94.9%)
Mestizo	13/13 (100%)	13/15 (86.7%)
Mexican	0/0 (NA)	0/1 (0)
Mulatto	2/2 (100%)	0/0 (NA)
Spanish American	0/0 (NA)	0/0 (NA)

TABLE 78: STUDY P016: PROPORTION OF CLINICALLY EVALUABLE SUBJECTS WITH FAVORABLE CLINICAL RESPONSES AT TOC VISIT BY DEMOGRAPHICS (Sponsor)

	Invanz (N=185)	Piperacillin/ Tazobactam (N=174)
GENDER		
Female	48/62 (77.4%)	47/58 (81.0%)
Male	104/123 (84.6%)	100/116 (86.2%)
AGE CATEGORY		
< 65	136/158 (86.1%)	124/141 (87.9%)
≥ 65	16/27 (59.3%)	23/33 (69.7%)
< 75	148/174 (85.1%)	140/164 (85.4%)
≥ 75	4/11 (36.4%)	7/10 (70.0%)
RACE		
Black	21/26 (80.8%)	22/28 (78.6%)
Caucasian	81/108 (75.0%)	75/89 (84.3%)
Hispanic	34/35 (97.1%)	37/41 (90.2%)
Mestizo	13/13 (100%)	13/15 (86.7%)
Mexican	0/0 (NA)	0/1 (0)
Mulatto	2/2 (100%)	0/0 (NA)
Spanish American	1/1 (100%)	0/0 (NA)

***Reviewer's Note**: Tables 79 and 80 display the proportion of subjects with a favorable clinical response at TOC for the groups of clinically evaluable subjects enrolled before and after the implementation of the enhanced blinding procedures.*

TABLE 79: STUDY P016: PROPORTION OF CLINICALLY EVALUABLE SUBJECTS WITH FAVORABLE CLINICAL AND MICROBIOLOGIC RESPONSES AT TOC VISIT BY BLINDING PROCEDURE (MO)

Enhanced Blinding Procedure	Invanz (N=168)	Piperacillin/ Tazobactam (N=170)	Difference in Favorable Rate
No	42/59 (71.2%)	50/60 (83.3%)	-12.1%, (-28.7%, 4.4%)
Yes	99/109 (90.8%)	95/110 (86.4%)	4.5%, (-4.8%, 13.8%)
Overall	141/168 (83.9%)	145/170 (85.3%)	-1.4%, (-9.7%, 6.9%)

TABLE 80: STUDY P016: PROPORTION OF CLINICALLY EVALUABLE SUBJECTS WITH FAVORABLE CLINICAL AND MICROBIOLOGIC AT TOC VISIT BY BLINDING PROCEDURE (Sponsor)

Enhanced Blinding Procedure	Invanz (N=185)	Piperacillin/ Tazobactam (N=174)	Difference in Favorable Rate
No	48/67 (71.6%)	51/62 (82.3%)	-10.6%, (-26.6%, 5.3%)
Yes	104/118 (88.1%)	96/112 (85.7%)	2.4%, (-7.2%, 12.0%)
Overall	152/185 (82.2%)	147/174 (84.5%)	-2.3%, (-10.6%, 5.9%)

***Reviewer's Note**: The following tables display analyses for secondary efficacy endpoints, where each analyses covered MO evaluation population and Sponsor population as well. The microbiologic responses are shown for microbiologically evaluable subjects in Tables 81 and 82. The clinical and microbiologic responses are shown for microbiologically evaluable population in Tables 83 and 84. The clinical and microbiologic responses are shown for microbiologic MITT subjects in Tables 85 and 86. The results from these analyses demonstrated that favorable rates of Invanz were comparable to those of piperacillin/tazobactam in all of the evaluation groups.*

TABLE 81: STUDY P016: MICROBIOLOGIC RESPONSES OF MICROBIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT (MO)

Microbiological Response	Invanz (N=144)	Piperacillin/ Tazobactam (N=146)
Favorable	122 (84.7%)	123 (84.2%)
Unfavorable	22 (15.3%)	23 (15.8%)
Invanz Versus P/T: Difference in Favorable Rate	0.5%, 95% C.I.: -8.5%, 9.5%	

TABLE 82: STUDY P016: MICROBIOLOGIC RESPONSES OF MICROBIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT (Sponsor)		
Microbiological Response	Invanz (N=155)	Piperacillin/ Tazobactam (N=151)
Favorable Unfavorable	128 (82.6%) 27 (17.4%)	126 (83.4%) 25 (16.6%)
Invanz Versus P/T: Difference in Favorable Rate	-0.9%, 95% C.I.: -9.9%, 8.2%	

TABLE 83: STUDY P016: CLINICAL AND MICROBIOLOGIC RESPONSES OF MICROBIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT (MO)		
Clinical and Microbiological Response	Invanz (N=144)	Piperacillin/ Tazobactam (N=146)
Both Favorable Not Both Favorable	122 (84.7%) 22 (15.3%)	122 (83.6%) 24 (16.4%)
Invanz Versus P/T: Difference in Favorable Rate	1.2%, 95% C.I.: -7.9%, 10.3%	

TABLE 84: STUDY P016: CLINICAL AND MICROBIOLOGIC RESPONSES OF MICROBIOLOGICALLY EVALUABLE SUBJECTS AT TOC VISIT (Sponsor)		
Clinical and Microbiological Response	Invanz (N=155)	Piperacillin/ Tazobactam (N=151)
Both Favorable Not Both Favorable	127 (81.9%) 28 (18.1%)	124 (82.1%) 27 (17.9%)
Invanz Versus P/T: Difference in Favorable Rate	-0.2%, 95% C.I.: -9.4%, 9.1%	

TABLE 85: STUDY P016: CLINICAL AND MICROBIOLOGIC RESPONSES OF MICROBIOLOGIC MITT SUBJECTS AT TOC VISIT (MO)		
Clinical and Microbiological Response	Invanz (N=187)	Piperacillin/ Tazobactam (N=186)
Both Favorable Not Both Favorable	136 (72.7%) 51 (27.3%)	134 (72.0%) 52 (28.0%)
Invanz Versus P/T: Difference in Favorable Rate	0.7%, 95% C.I.: -8.9%, 10.3%	

TABLE 86: STUDY P016: CLINICAL AND MICROBIOLOGIC RESPONSES OF MICROBIOLOGIC MITT SUBJECTS AT TOC VISIT (Sponsor)		
Clinical and Microbiological Response	Invanz (N=192)	Piperacillin/ Tazobactam (N=190)
Both Favorable	140 (72.9%)	138 (72.6%)
Not Both Favorable	52 (27.1%)	52 (27.4%)
Invanz Versus P/T: Difference in Favorable Rate	0.3%, 95% C.I.: -9.2%, 9.7%	

APPEARS THIS WAY
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VI. SUMMARY AND CONCLUSIONS
(Which May be Conveyed to the Sponsor)

***Reviewer's Note**: In this section, confidence intervals for differences in outcome favorable rates (Invanz minus control) are reported as $_{n1,n2}(l, u)_{p1,p2}$, where n1 is the number of Invanz subjects, n2 is the number of control subjects, l and u are the lower and upper bounds of the 95% confidence interval, respectively, p1 is the response rate in Invanz subjects, and p2 is the response rate in control subjects.*

COMPLICATED INTRA-ABDOMINAL INFECTIONS

This indication was primarily supported by one controlled study to demonstrate the efficacy and safety of Invanz.

Statistical evaluation of efficacy was primarily based upon the two-sided 95% confidence interval of the difference in clinical and microbiologic favorable rates at TOC between the Invanz group and the piperacillin/tazobactam group for MO microbiologically evaluable subjects and MO microbiologic MITT subjects.

Reviewer's Summary for the Primary Efficacy Results of One Study P017:

- *The 95% confidence interval of the difference in clinical and microbiologic favorable rate of Invanz minus piperacillin/tazobactam for MO microbiologically evaluable subjects was $_{195,\ 189}(-5.0\%,\ 11.4\%)_{83.6\%,\ 80.4\%}$, which demonstrated equivalence in efficacy of two treatments in the treatment of complicated IAIs.*

- *The 95% confidence interval from MO microbiologic MITT subjects also demonstrated that Invanz was therapeutically equivalent to piperacillin/tazobactam $_{256,\ 244}(-5.4\%,\ 11.5\%)_{71.5\%,\ 68.4\%}$.*

COMPLICATED URINARY TRACT INFECTIONS INCLUDING PYELONEPHRITIS

This indication was supported by one pivotal controlled study and one supportive study to demonstrate the efficacy and safety of Invanz.

Statistical evaluation of efficacy was primarily based upon the two-sided 95% confidence interval of the difference in microbiologic favorable rates at TOC between the Invanz group and the ceftriaxone group for microbiologically evaluable subjects and microbiologic MITT subjects.

Reviewer's Summary for the Primary Efficacy Results of Two Studies P014 and P021:

- *In the pivotal Study P014, the 95% confidence interval of the difference in microbiologic favorable rates of Invanz minus ceftriaxone for microbiologically evaluable subjects was $_{154,\ 167}(-7.8\%,\ 5.3\%)_{91.6\%,\ 92.8\%}$, which demonstrated equivalence in efficacy of two treatments in the treatment of complicated UTIs.*

- *In Study P014, the 95% confidence interval from microbiologic MITT subjects also demonstrated that Invanz was therapeutically equivalent to ceftriaxone $_{219,\ 242}(-2.2\%,\ 10.9\%)_{89.0\%,\ 84.7\%}$.*

- *In the supportive Study P021, the 95% confidence interval of the difference in microbiologic favorable rates of Invanz minus ceftriaxone for microbiologically evaluable subjects was $_{97,\ 53}$(-12.7%, 14.0%)$_{85.6\%,\ 84.9\%}$, which failed to show therapeutically equivalence in efficacy of two treatments in the treatment of complicated UTIs.*

- *In Study P021, the 95% confidence interval from microbiologic MITT subjects demonstrated that Invanz was marginally equivalent to ceftriaxone $_{131,\ 71}$(-10.1%, 17.6%)$_{75.6\%,\ 71.8\%}$.*

ACUTE PELVIC INFECTIONS

This indication was primarily supported by one controlled study to demonstrate the efficacy and safety of Invanz.

Statistical evaluation of efficacy was primarily based upon the two-sided 95% confidence interval of the difference in clinical favorable rates at TOC between the Invanz group and the piperacillin/tazobactam group for clinically evaluable subjects and clinical MITT subjects.

Reviewer's Summary for the Primary Efficacy Results of One Study P023:

- *The 95% confidence interval of the difference in clinical favorable rate of Invanz minus piperacillin/tazobactam for clinically evaluable subjects was $_{163,\ 153}$(-4.0%, 8.7%)$_{93.9\%,\ 91.5\%}$, which demonstrated equivalence in efficacy of two treatments in the treatment of acute pelvic infections.*

- *The 95% confidence interval from clinical MITT subjects also demonstrated that Invanz was therapeutically equivalent to piperacillin/tazobactam $_{211,\ 191}$(-9.6%, 6.1%)$_{82.0\%,\ 83.8\%}$.*

COMPLICATED SKIN AND SKIN STRUCTURE INFECTIOUS

This indication was primarily supported by one controlled study to demonstrate the efficacy and safety of Invanz.

Statistical evaluation of efficacy was primarily based upon the two-sided 95% confidence interval of the difference in clinical favorable rates at TOC between the Invanz group and the piperacillin/tazobactam group for MO clinically evaluable subjects and MO clinical MITT subjects.

Reviewer's Summary for the Primary Efficacy Results of One Study P016:

- *The 95% confidence interval of the difference in clinical favorable rate of Invanz minus piperacillin/tazobactam for MO clinically evaluable subjects was $_{168,\ 170}$(-9.7%, 6.9%)$_{83.9\%,\ 85.3\%}$, which demonstrated equivalence in efficacy of two treatments in the treatment of complicated SSSIs.*

- *The 95% confidence interval from MO clinical MITT subjects demonstrated that Invanz was marginally equivalent to piperacillin/tazobactam $_{265,\ 257}$(-10.1%, 6.9%)$_{65.3\%,\ 66.9\%}$.*

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Statistician, DBIII

Concur: Daphne Lin, Ph.D.
Team Leader, DBIII

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Division Director, DBIII

cc:
Archival: NDA: 21-337
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HFD-725/Dr.Huque
HFD-725/Dr.Lin
HFD-725/Dr.Jiang
HFD-344/Dr.Thomas
HFD-725/Chron.
This review contains 51 pages, 86 tables.
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/s/

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