

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

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**STATISTICAL REVIEW(S)**



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

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

<b>NDA/Serial Number:</b>	<b>21, 821</b>
<b>Drug Name:</b>	Tigecycline
<b>Indication(s):</b>	Complicated Skin and Skin Structure Infections (cSSSI), Complicated Intra Abdomen Infections (cIAI)
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# **1. EXECUTIVE SUMMARY**

## **1.1 Conclusions and Recommendations**

### **1.1.1 Complicated Skin and Skin Structure Infections (cSSSI)**

In the primary efficacy analyses of clinical response at test-of-cure, tigecycline demonstrated noninferiority to vancomycin/aztreonam in the Clinically Evaluable (CE) and Clinical Modified Intent-to-Treat (c-mITT) populations in studies 3074A1-300-US/CA and 3074A1-305-US/WW.

In the FDA analyses of study 3074A1-300-US/CA, clinical response was evaluated for duration of up to 35 days after the last dose of the study drug, as per the protocol. The 95% Confidence Intervals for the difference in clinical cure rates at the TOC (Table 4) in the CE, c-mITT and ITT populations were; CE (95%CI: -7.8, 8.3), c-mITT (95%CI: -8.8, 6.6) and ITT (95% CI: -9.2, 5.6). Based on the 95% Confidence Interval (CI), Tigecycline demonstrated noninferiority to vancomycin/aztreonam using a non-inferiority margin of 15%.

In the FDA analyses of study 3074A1-305-US/WW, clinical response was evaluated for duration of up to 35 days after the last dose of the study drug as in the previous study. The 95% Confidence Intervals for the difference in clinical cure rates at the TOC (Table 9) in the CE, c-mITT and ITT populations were; CE (95%CI: -10.4, 1.0), c-mITT (95%CI: -9.2, 4.0) and ITT (95% CI: -9.0, 3.6). Based on the 95% Confidence Interval (CI), Tigecycline demonstrated noninferiority to vancomycin/aztreonam using a margin of 15%.

### **1.1.2 Complicated Intra Abdomen Infections (cIAI)**

In the primary efficacy analyses of clinical response at test-of-cure, tigecycline demonstrated noninferiority to imipenem/cilastatin in the ME and micro-mITT populations in studies 3074A1-301-WW and 3074A1-306-WW.

In the FDA analyses of study 3074A1-301-WW, clinical response (unadjusted for APACHE scores) was evaluated for duration of up to 35 days after the last dose of the study drug. The 95% Confidence Intervals for the difference in clinical cure rates at the TOC (Tables 16-17) in the ME, micro-mITT and ITT populations were; ME (95%CI: -9.3, 5.3), micro-mITT (95%CI: -11.9, 2.4) and ITT (95%CI: -11.8, 0.3). Tigecycline demonstrated noninferiority to imipenem/ cilastatin in both the ME and micro-mITT using a margin of 15%.

In the FDA analyses of study 3074A1-306-WW, clinical response (unadjusted) was evaluated for duration of up to 35 days based after the last dose of the study drug. The 95% Confidence Intervals for the difference in clinical cure rates at the TOC (Tables 23-24) in the ME, micro-mITT and ITT populations were; ME (95%CI: -4.8, 6.9), micro-mITT (95%CI: -4.6, 7.8) and ITT(95%CI: -5.0, 5.5). Tigecycline demonstrated noninferiority to imipenem/ cilastatin in both the ME and micro-mITT using a margin of 15%.

### **1.1.3 Safety Issues**

Based on the safety review, a total of 57 deaths were reported from studies 3074A1-300-US/CA, 3074A1-301-WW, 3074A1-305-US/WW and 3074A1-306-WW. In studies submitted for Complicated Skin and Skin Structure Infections, there were 6 deaths reported in the Tigecycline arm. Of which, 5 deaths were reported from study 3074A1-300-US/CA and one death in study 3074A1-305-US/WW. In studies submitted for Complicated Intra Abdomen Infections, there were 26 deaths reported in the Tigecycline arm. Of which, 19 deaths were reported from study 3074A1-301-WW and 7 deaths were reported from study 3074A1-306-WW. Based on the review, no specific safety issues could be attributed to the cause of these deaths. The medical officer, Dr. Cooper's clinical review would provide more detailed safety information. Approval of this product would be based on the overall evidence of safety and efficacy and the labeling should indicate all the major safety issues for this product.

## **1.2 Brief Overview of Clinical Studies**

### **Pivotal Clinical Studies:**

There were a total of four (4) phase-3 studies submitted, 2 each for cSSSI and cIAI indications, evaluated the safety and efficacy of tigecycline in the treatment of subjects with complicated and serious infections. The phase 3 studies were conducted worldwide in over 45 countries in North and South America, Europe, Asia, Africa, and Australia. The studies are listed under each of the indications as follows:

### **I. Complicated Skin and Skin Structure Infections (cSSSI)**

#### **1. Study 3074A1-300-US/CA (study 300)**

This was a phase-3 multicenter, randomized, double-blind (third-party unblinded) comparison of the safety and efficacy of tigecycline with placebo versus vancomycin/aztreonam in subjects with cSSSI that involved deep soft tissue, required significant surgical intervention, or was associated with a significant underlying disease that complicated response to treatment. Subjects were randomly assigned (1:1 ratio) to receive either tigecycline with placebo or vancomycin with aztreonam intravenously for up to 14 days.

A total of 596 subjects were enrolled in this study; 13 were screen failures and the remaining 583 subjects were randomly assigned to treatment and constituted the intent-to-treat (ITT) population. Ten (10) subjects did not receive study drug. A total of 573 subjects received at least 1 dose of the assigned study drug and constituted the mITT population: 292 subjects received tigecycline and 281 subjects received vancomycin/aztreonam.

## **2. Study 3074A1-305-US/WW (study 305)**

This was a phase-3, multicenter, randomized, double-blind (third-party unblinded), comparison study of the safety and efficacy of tigecycline versus vancomycin/aztreonam in Subjects with cSSSI. cSSSI includes infections that involve deep soft tissue or require significant surgical intervention or are associated with a significant underlying disease state that complicates response to treatment. Subjects were randomly assigned in a 1:1 ratio to receive either tigecycline or vancomycin with aztreonam via intravenous (IV) administration for up to 14 days.

A total of 557 subjects were enrolled into the study; 11 were screen failures. The other 546 subjects were randomly assigned to 1 of the treatment arms and constituted the intent-to-treat (ITT) population. Three (3) subjects did not receive study drug. Altogether, 543 subjects received the study drug and constituted the mITT population: 274 subjects received tigecycline and 269 subjects received vancomycin/aztreonam.

## **II. Complicated Intra Abdomen Infections (cIAI)**

### **1. Study 3074A1-301-WW (study 301)**

This was a phase-3, multicenter, double-blind (third-party unblinded) study comparing the safety and efficacy of tigecycline to imipenem/cilastatin in hospitalized subjects with cIAI. Subjects were stratified at randomization into 2 groups based on their scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II: 15 or less, or over 15 but less than 31. Subjects with scores over 30 were excluded. Subjects were randomly assigned in a 1:1 ratio to receive either intravenous (IV) tigecycline or IV imipenem/cilastatin.

A total of 898 subjects were screened into the study; 64 subjects were screen failures and the remaining 834 subjects (ITT) were randomly assigned to 1 of the treatment arms. A total of 825 subjects received the study drug and constituted the mITT population: 413 subjects received tigecycline and 412 subjects received imipenem/cilastatin.

### **2. Study 3074A1-306-WW (study 306)**

This was a phase-3, multi-center, double-blind (third-party unblinded) study comparing the safety and efficacy of tigecycline to imipenem/cilastatin in hospitalized subjects with complicated intra-abdominal infections. Subjects were stratified at randomization into 2 groups based on their scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II: 15 or less, or over 15 but less than 31. Subjects with scores over 30 were excluded. Subjects were randomly assigned in a 1:1 ratio to receive either intravenous (IV) tigecycline or IV imipenem/cilastatin.

A total of 861 subjects were screened for the study; 37 were screen failures (10 additional subjects were screen failures that were not captured in the database). The remaining 824 subjects were randomly assigned to 1 of the treatment arms and constituted the intent-to-treat (ITT) population. Seven (7) subjects did not receive study drug. Altogether, 817 subjects received the study drug and constituted the mITT population: 404 subjects received tigecycline and 413 subjects received imipenem/cilastatin.

### **1.3 Statistical Issues and Findings**

From studies 300, 301, 305 and 306, a total of 54 deaths were reported. In studies submitted for Complicated Skin and Skin Structure Infections, there were 6 deaths reported in the Tigecycline arm. Of which, 5 deaths were reported from study 3074A1-300-US/CA and one death in study 3074A1-305-US/WW. In studies submitted for Complicated Intra Abdomen Infections, there were 26 deaths reported in the Tigecycline arm. Of which, 19 deaths were reported from study 3074A1-301 and 7 deaths reported from study 3074A1-306-WW. Based on the review, no specific safety issues could be attributed to the cause of these deaths. However, medical officer, Dr. Cooper's clinical review would provide detailed safety information.

## **2. INTRODUCTION**

### **2.1 Overview**

Tigecycline is an intravenously administered glycylicycline antibiotic and acts by binding to the 30S bacterial ribosomal subunit and by blocking entry of amino-acyl transfer RNA (tRNA) molecules into the A site of the ribosome. There were four (4) phase 3 studies submitted, 2 each for cSSSI and cIAI indications, evaluated the safety and efficacy of tigecycline in the treatment of subjects with complicated and serious infections. The phase 3 studies were conducted worldwide in over 45 countries in North and South America, Europe, Asia, Africa, and Australia.

Studies 300-US/CA and 305-US/WW were submitted to evaluate the efficacy and safety of tigecycline compared with vancomycin/ aztreonam in complicated subjects with cSSSI. Patients with deep soft tissue infections including wound infections and cellulitis ( $\geq 10$  cm, requiring surgery/drainage or with complicated underlying disease), major abscesses, infected ulcers, and burns were enrolled in these studies.

Studies 301-WW and 306-WW were submitted to evaluate the efficacy and safety of tigecycline compared with imipenem/cilastatin in the treatment of complicated subjects with cIAI. Patients with diagnoses including appendicitis, cholecystitis, diverticulitis, gastric/duodenal perforation, intra-abdominal abscess, perforation of intestine, and peritonitis were enrolled in these studies.

### **2.2 Data Sources**

The review documents and the SAS datasets were available on the EDR at \\CDSESUB1\EVSPROD\N021821\0003.

## **3. STATISTICAL EVALUATION**

### **3.1 Evaluation of Efficacy**

#### **3.1.1 Complicated Skin and Skin Structure Infections (cSSSI)**

##### **3.1.1.1 Study 3074A1-300-US/CA**

###### **Study Design:**

This was a phase 3 multicenter, randomized, double-blind (third-party unblinded) comparison of the safety and efficacy of tigecycline with placebo versus vancomycin/aztreonam in subjects with cSSSI that involved deep soft tissue, required significant surgical intervention, or was associated with a significant underlying disease that complicated

response to treatment. Subjects were randomly assigned (1:1 ratio) to receive either tigecycline with placebo or vancomycin with aztreonam intravenously for up to 14 days.

### **Primary Efficacy Endpoint:**

The primary efficacy endpoint is the clinical response at the test-of-cure assessment which took place at least 12 days after the last dose of study drug. The efficacy assessments were based on CE and c-mITT (co-primary populations), where c-mITT population consisted of all mITT subjects who received study drug and met the minimum disease criteria for cSSSI. According to the sponsor, detailed assessments of the clinical status of each subject were recorded at baseline, on the last day of therapy and at the test-of-cure assessment. These assessments included the presence or absence of drainage and/or discharge, fever, erythema, swelling and/or pain and/or tenderness to palpation, extent of infection (width and length), and localized warmth. For subjects withdrawn from therapy early, the clinical indicators of infection were assessed on the last day of therapy.

### **Statistical Reviewers Comments:**

*In an amendment to the protocol, the timing for the TOC assessment was redefined to occur at least 14 days and up to 35 days after the last dose of study drug. However, the sponsor included patients up to 92 days after the last dose of study drug in the primary efficacy analysis. This was discussed with the Sponsor at the teleconference dated February 15, 2005.*

*Accordingly, in the FDA analysis, the primary efficacy endpoint of clinical response was evaluated for a duration of up to 35 days at the test-of-cure assessment. The primary efficacy assessments were based on CE and c-mITT as co-primary populations and analysis based on the ITT population was also evaluated in this review to assess the robustness of evidence while retaining all randomized patients.*

*Noninferiority of tigecycline compared with vancomycin/aztreonam for clinical and microbiologic responses was evaluated based on a 2-sided 95% confidence interval (CI) for the true difference in efficacy (tigecycline - vancomycin/aztreonam). Noninferiority was concluded in this review if the lower limit of the 2-sided 95% CI for the true difference in efficacy was higher than -15%.*

The sponsor's clinical response based on the submission was as follows:

#### **Cure:**

- Resolution of all clinical indicators of the infection (healing of chronic underlying skin ulcer was not required).
- Improvement of the clinical indicators of the infection to such an extent that no further antibacterial therapy was necessary.

#### **Failure:**

- Lack of response and need for additional antibacterial therapy.
- Initial recovery from the infection was followed by deterioration before the test-of-cure assessment, requiring further antibacterial therapy.
- Required clinically unanticipated extirpative surgical intervention for management of the infection.
- Required non-routine surgical treatment at the original site of the infection more than 48 hours after the first dose of study drug because of failure to improve, clinical worsening, or the discovery of a new purulent collection.
- Death caused by the infection more than 2 days after randomization.
- Discontinued treatment with study drug or died because of a treatment-related adverse event (as the primary reason).
- Received more than 120% of the expected number of doses of study drug.

## Patient Disposition, Demographic and Baseline Characteristics

### Disposition of Subjects

A total of 596 subjects were enrolled in this study; 13 were screen failures and the remaining 583 subjects were randomly assigned to treatment and constituted the intent-to-treat (ITT) population. Ten (10) subjects did not receive study drug. A total of 573 subjects received at least 1 dose of the assigned study drug and constituted the mITT population: 292 subjects received tigecycline and 281 subjects received vancomycin/aztreonam.

**Table 1: Number of Subjects in Each Population Category**

	<b>Tigecycline n (% ITT)</b>	<b>Vancomycin/ Aztreonam n (% ITT)</b>	<b>Total n (% ITT)</b>
Screened			596
Screened failures			13
<b>Intent-to-Treat (ITT)</b>	295	288	583
No treatment received	3	7	10
<b>Modified intent-to-treat (mITT)</b>	292 (99.0)	281 (97.6)	573 (98.3)
Did not meet minimum disease criteria for cSSSI	15	21	36
<b>Clinical mITT (c-mITT)</b>	277 (93.9)	260 (90.3)	537 (92.1)
Did not meet clinical evaluability criteria	78	62	140
<b>Clinically evaluable (CE)</b>	199 (67.5)	198 (68.8)	397 (68.1)
No baseline and/or susceptible pathogens	84	85	169
<b>Microbiologically evaluable (ME)</b>	115 (39.0)	113 (39.2)	228 (39.1)
Microbiologic mITT (m-mITT)	186 (63.1)	171 (59.4)	357 (61.2)
No baseline pathogen identified from c-mITT	91	89	180

Sponsor's Table

Demographic and other baseline characteristics of the mITT population, including age, sex,

ethnicity, weight, and creatinine clearance, are given in Table 2 below.

**Table 2: Demographic and Baseline Characteristics: mITT Population**

Characteristic	Tigecycline (n = 292)	Vancomycin/ Aztreonam (n = 281)	Total (n = 573)
Age, years			
Mean	49.41	48.36	48.90
Standard deviation	15.44	16.57	16.00
Minimum, maximum	18.00, 90.00	18.00, 92.00	18.00, 92.00
Median	49.00	48.00	48.00
Sex, n (%)			
Male	180 ( 61.6)	188 ( 66.9)	368 ( 64.2)
Female	112 ( 38.4)	93 ( 33.1)	205 ( 35.8)
Ethnic origin, n (%)			
White	154 ( 52.7)	149 ( 53.0)	303 ( 52.9)
Black	28 ( 9.6)	23 ( 8.2)	51 ( 8.9)
Asian	1 ( 0.3)	2 ( 0.7)	3 ( 0.5)
Hispanic	54 ( 18.5)	53 ( 18.9)	107 ( 18.7)
Other	55 ( 18.8)	54 ( 19.2)	109 ( 19.0)
Weight, kg			
Mean	81.53	81.95	81.73
Standard deviation	22.94	27.00	24.99
Minimum, maximum	40.00, 167.00	36.00, 255.00	36.00, 255.00
Median	79.30	75.00	77.27
Creatinine clearance, mL/minute			
Mean	109.47	110.07	109.76
Standard deviation	47.09	64.15	56.07
Minimum, maximum	28.60, 363.00	6.70, 720.60	6.70, 720.60
Median	103.00	100.00	102.00

**Statistical Reviewer’s Comments:**

*As given in the table above, the demographic and other baseline characteristics of the mITT population (including age, sex, ethnicity, weight, and creatinine clearance) were almost similar in the two treatment groups.*

**EFFICAY RESULTS:**

**Table 3: Clinical Response at TOC (CE, c-mITT and ITT Populations)**

Visit	Response	Tigecycline		Vancomycin/Aztreonam		95% CI
		n/N	%	n/N	%	
<b>CE Population</b>						
Test-of-Cure	Cure	165/199	82.9%	163/198	82.3%	(-7.4, 8.6)
	Failure	34/199	17.1%	35/198	17.7%	
<b>c-mITT Population</b>						
Test-of-Cure	Cure	209/277	75.5%	200/260	76.9%	(-9.0, 6.1)
	Failure	48/277	17.3%	46/260	17.7%	
	Indeterminate	20/ 277	7.2%	14/ 260	5.4%	
<b>ITT Population</b>						
Test-of-Cure	Cure	217/ 295	73.6%	217/ 288	75.3%	(-9.2, 5.6)
	Failure	53/ 295	18.0%	49/ 288	17.0%	
	indeterminate	25/ 295	8.5%	22/ 288	7.6%	

**Sponsor’s analysis**

**Statistical Reviewer’s Comments:**

*In the Sponsor’s analysis (Table 3), the clinical response was evaluated at the TOC, 92 days after the last dose of study drug. Based on the 95% Confidence Interval (CI) for the difference in clinical cure rates at the TOC, Tigecycline demonstrated noninferiority to vancomycin/aztreonam using a non-inferiority margin of 15%. The Confidence Intervals in the CE, cmITT and ITT populations were; CE (95%CI: -7.4, 8.6); cmITT (95%CI: -9.0, 6.1) and ITT (95%CI: -9.2, 5.6), respectively.*

**Table 4: FDA Analysis: Clinical Response (TOC Visit <=35 days post-therapy)**

Visit	Response	Tigecycline		Vancomycin/Aztreonam		95% CI
		n/N	%	n/N	%	
<b>CE Population</b>						
Test-of-Cure	Cure	162/196	82.7%	159/193	82.4%	(-7.8, 8.3)
	Failure	34/196	17.3%	34/193	17.6%	

<b>c-mITT Population</b>						
<b>Test-of-Cure</b>	<b>Cure</b>	203/268	75.7%	196/255	76.9%	(-8.8, 6.6)
	<b>Failure</b>	48/268	17.9%	45/255	17.6%	
	<b>Indeterminate</b>	17/ 268	6.3%	14/ 255	5.5%	

**Statistical Reviewer’s Comments:**

*In the FDA analyses (Table 4), clinical response was evaluated for duration of up to 35 days at the test-of-cure assessment. The Confidence Intervals in the CE and cmITT populations were; CE (95%CI: (-7.8, 8.3) and cmITT (95%CI: -8.8, 6.6). Based on the 95% Confidence Interval (CI) for the difference in clinical cure rates at the TOC, Tigecycline demonstrated noninferiority to vancomycin/aztreonam using a non-inferiority margin of 15%. The efficacy conclusions were not affected upon evaluating the clinical responses at the TOC<=35 days or TOC<=92 days (sponsor’s analysis) after the last dose of study drug.*

**Table 5: Clinical Response by Monomicrobial/Polymicrobial Infection:  
ME population**

<b>Infection</b>	<b>Response</b>	<b>Tigecycline</b>		<b>Vancomycin/Aztreonam</b>		<b>95% CI</b>
		<b>n/N</b>	<b>%</b>			
<b>Monomicrobial</b>	<b>Cure</b>	56/ 71	78.9%	55/ 69	79.7 %	( -15.2, 13.6)
	<b>Failure</b>	15/ 71	21.1%	14/ 69	20.3%	
<b>Polymicrobial</b>	<b>Cure</b>	37/ 44	84.1%	33/ 44	75.0 %	( -9.5, 27.0)
	<b>Failure</b>	7/ 44	15.9%	11/ 44	25.0%	

**Statistical Reviewer’s Comments:**

*At the test-of-cure assessment, the cure rate for monomicrobial infections in the ME population was 78.9% in the tigecycline group and 79.7% in the vancomycin/ aztreonam group. For polymicrobial infections, the cure rate was 84.1% in the tigecycline group and 75.0% in the vancomycin/aztreonam group.*

**3.1.1.2 Study 3074A1-305-US/WW**

**Study Design:**

This was a phase 3, multicenter, randomized, double-blind (third-party unblinded), comparison study of the safety and efficacy of tigecycline versus vancomycin/aztreonam in Subjects with cSSSI. cSSSI includes infections that involve deep soft tissue or require significant surgical intervention or are associated with a significant underlying disease state that complicates response to treatment. Subjects were randomly assigned in a 1:1 ratio to receive either tigecycline or vancomycin with aztreonam via intravenous (IV) administration for up to 14 days.

**Objectives:**

The primary objective was to determine the safety and the efficacy of tigecycline as compared with vancomycin/aztreonam in treating hospitalized subjects with complicated skin and/or skin structure infections (cSSSI).

**Primary Efficacy Endpoint:**

The primary efficacy endpoint was clinical response in the CE and c-mITT populations (co-primary populations) at the test-of-cure assessment.

**Patient Disposition, Demographic and Baseline Characteristics****Disposition of Subjects:**

A total of 557 subjects were enrolled into the study; 11 were screen failures. The other 546 subjects were randomly assigned to 1 of the treatment arms and constituted the intent-to-treat (ITT) population. Three (3) subjects did not receive study drug. Altogether, 543 subjects received the study drug and constituted the mITT population: 274 subjects received tigecycline and 269 subjects received vancomycin/aztreonam.

**Statistical Reviewers Comments:**

*Similar to the previous study, the sponsor's analysis at the TOC included patients up to 92 days after the last dose of study drug in the primary efficacy analysis. In the FDA analysis, the primary efficacy endpoint of clinical response was evaluated for duration of up to 35 days at the test-of-cure assessment. The primary efficacy assessments were based on CE and c-mITT as co-primary populations and analysis based on the ITT population was also evaluated to assess the robustness of evidence.*

*Noninferiority of tigecycline compared with vancomycin/aztreonam for clinical and microbiologic responses was evaluated based on a 2-sided 95% confidence interval (CI) for the true difference in efficacy (tigecycline - vancomycin/aztreonam). Noninferiority was concluded in this review if the lower limit of the 2-sided 95% CI for the true difference in efficacy was higher than -15%.*

**Table 6: Number of Subjects in Each Population Category**

<b>Population</b>	<b>Tigecycline n (% ITT)</b>	<b>Vancomycin/ Aztreonam n (% ITT)</b>	<b>Total n (% ITT)</b>
Screened			557
Screened Failures			11
Intent-to-Treat (ITT)	275	271	546
No treatment received	1	2	3
Modified Intent-to-Treat (mITT)	274 (99.6)	269 (99.3)	543 (99.5)

cSSSI did not meet severity criteria	13	10	23
Clinical mITT (c-mITT)	261 (94.9)	259 (95.6)	520 (95.2)
Did not meet clinical evaluability criteria	38	46	84
Clinically evaluable (CE)	223 (81.1)	213 (78.6)	436 (79.9)
No baseline and/or susceptible pathogens	59	65	124
Microbiologically evaluable (ME)	164 (59.6)	148 (54.6)	312 (57.1)
Microbiologic mITT (m-mITT)	209 (76.0)	203 (74.9)	412 (75.5)
No baseline pathogens (from c-mITT population)	52	56	108

**Sponsor's Table:** ITT = all randomized subjects; mITT = ITT subjects who received at least 1 dose of study drug; c-mITT = mITT subjects with evidence of cSSSI; m-mITT = mITT subjects with identified baseline pathogen.

The demographic and other baseline characteristics (age, sex, ethnicity, weight, and creatinine clearance) of the mITT population, are given below in Table 7.

**Table 7: Demographic and Baseline Characteristics of the mITT Population**

Characteristic	Tigecycline (n = 274)	Vancomycin/ Aztreonam (n = 269)	Total (n = 543)
Age, years			
Mean	48.75	50.06	49.40
Standard deviation	16.97	17.77	17.37
Minimum, maximum	18.00, 87.00	18.00, 88.00	18.00, 88.00
Median	49.00	49.00	49.00
Sex, n (%)			
Male	167 (60.9)	163 (60.6)	330 (60.8)
Female	107 (39.1)	106 (39.4)	213 (39.2)
Ethnic origin, n (%)			
White	227 (82.8)	223 (82.9)	450 (82.9)
Black	20 ( 7.3)	20 ( 7.4)	40 ( 7.4)
Asian	19 ( 6.9)	22 ( 8.2)	41 ( 7.6)
Other	8 ( 2.9)	4 ( 1.5)	12 ( 2.2)
Weight, kg			
Mean	82.46	81.47	81.97
Standard deviation	20.96	20.50	20.72
Minimum, maximum	40.00, 200.00	44.00, 160.00	40.00, 200.00
Median	80.00	78.00	79.00
Creatinine clearance, mL/min			
Mean	109.35	104.27	106.83
Standard deviation	42.41	41.21	41.85
Minimum, maximum	27.00, 336.00	26.00, 273.00	26.00, 336.00

Median	105.00	100.00	103.00
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**Statistical Reviewer’s Comments:**

*As given in the table 7, the demographic and other baseline characteristics of the mITT population, including age, sex, ethnicity, weight, and creatinine clearance were almost similar in the two treatment groups.*

**EFFICACY RESULTS:**

**Table 8: Clinical Response at TOC: (CE, c-mITT and ITT populations)**

Visit	Response	Tigecycline		Vancomycin/ Aztreonam		95% CI
		n/N	%	n/N	%	
<b>CE Population</b>						
Test-of-Cure	Cure	200/223	89.7%	201/213	94.4%	(-10.2, 0.8)
	Failure	23/223	10.3%	12/213	5.6%	
<b>c-mITT Population</b>						
Test-of-Cure	Cure	220/261	84.3%	225/259	86.9%	(-9.0, 3.8)
	Failure	31/261	11.9%	26/259	10.0%	
	Indeterminate	10/261	3.8%	8/259	3.1%	
<b>ITT Population</b>						
Test-of-Cure	Cure	231/ 275	84.0%	235/ 271	86.7%	(-9.0, 3.6)
	Failure	33/ 275	12.0%	26/ 271	9.6%	
	Indeterminate	11/ 275	4.0%	10/ 271	3.7%	

**Statistical Reviewer’s Comments:**

*In the Sponsor’s analysis (Table 8), the clinical response was evaluated at the TOC assessment, 92 days after the last dose of study drug. Based on the 95% Confidence Interval (CI) for the difference in clinical cure rates at the TOC, Tigecycline demonstrated noninferiority to vancomycin/aztreonam using a non-inferiority margin of 15%. Tigecycline demonstrated noninferiority to vancomycin/aztreonam in the CE (95%CI: -10.2, 0.8), cmITT (95%CI: -9.0, 3.8) and ITT (95%CI: -9.0, 3.6) populations.*

**Table 9: FDA Analysis: Clinical Response (TOC Visit <=35 days post-therapy)**

Visit	Response	Tigecycline		Vancomycin/ Aztreonam		95% CI
		n/N	%	n/N	%	
<b>CE Population</b>						
Test-of-Cure	Cure	195/218	89.4%	193/205	94.1%	(-10.4, 1.0)
	Failure	23/218	10.6%	12/205	5.9%	
<b>c-mITT Population</b>						
Test-of-Cure	Cure	212/253	83.8%	216/250	86.4%	(-9.2, 4.0)
	Failure	31/253	12.3%	26/250	10.4%	
	Indeterminate	10/253	4.0%	8/250	3.2%	

**Statistical Reviewer’s Comments:**

*In the FDA analyses (Table 9), clinical response was evaluated for duration of up to 35 days at the test-of-cure assessment. The Confidence Intervals in the CE and cmITT populations were; CE (95%CI: (-10.4, 1.0) and cmITT (95%CI: -9.2, 4.0). Based on the 95% Confidence Interval (CI) for the difference in clinical cure rates at the TOC, Tigecycline demonstrated noninferiority to vancomycin/aztreonam using a non-inferiority margin of 15%. The efficacy conclusions were not affected upon evaluating the clinical responses at TOC<=35 days or TOC<=92 days after the last dose of study drug.*

**Table 10: Clinical Response by Monomicrobial/Polymicrobial Infection:  
ME population**

TOC	Infection	Response	Tigecycline	Vancomycin/ Aztreonam	95% CI
	Monomicrobial	Cure	83/90 (92.2%)	78/81 (96.3%)	(-12.6, 4.6)
		Failure	7/90	3/81	
	Polymicrobial	Cure	65/74 (87.8%)	65/67 (97.0%)	(-19.6, 1.2)
		Failure	9/74	2/67	

**Statistical Reviewer’s Comments:**

*At the test-of-cure assessment, the cure rates for monomicrobial infections in the ME population was 92.2% in the tigecycline group and 96.3% in the vancomycin/ aztreonam group. For polymicrobial infections, the cure rate was 87.8% in the tigecycline group and 97.0% in the vancomycin/aztreonam group.*

### 3.1.2 Complicated Intra Abdomen Infections (cIAI)

#### 3.1.2.1 Study 3074A1-301-WW

##### **Study Design:**

This was a phase 3, multicenter, double-blind (third-party unblinded) study comparing the safety and efficacy of tigecycline to imipenem/cilastatin in hospitalized subjects with cIAI. Subjects were stratified at randomization into 2 groups based on their scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II: 15 or less, or over 15 but less than 31. Subjects with scores over 30 were excluded. Subjects were randomly assigned in a 1:1 ratio to receive either intravenous (IV) tigecycline or IV imipenem/cilastatin.

##### **Duration of Subject Participation (Based on the protocol)**

Approximately 4 to 7 weeks: up to 1 day for screening, up to 2 weeks of test article administration, 9 days (+5 days) post therapy for an early follow-up visit, and  $\geq 14$  days and not more than 35 days after the last dose of test article for the test-of-cure assessment. Subjects who are clinical failures will have the test-of-cure assessment performed prior to the initiation of non-study antibiotic.

##### **Primary Objective:**

The primary objective of the study was to determine the efficacy and safety of tigecycline compared with imipenem/cilastatin in treating hospitalized subjects with cIAI. The primary efficacy endpoint was the clinical response within the ME and m-mITT populations (co-primary populations) at the test-of-cure assessment.

**Cure:** The study medication and the initial intervention (operative or radiologically controlled drainage procedure) resolved the intra-abdominal infection.

**Failure:** The subject met at least one of the following criteria:

- Required additional surgical or radiologic intervention or received additional antibacterial therapy to cure the infection (including surgical wound infections).
- Died after study day 2 because of the infection or a treatment-related adverse event (as primary reason).
- Discontinued from study drug after receiving at least 8 doses in less than 5 days because of a treatment-related adverse event as primary reason

##### **Microbiologic Response:**

The microbiologic endpoints were secondary efficacy endpoints. Microbiologic efficacy was evaluated at both the subject and pathogen level. Specimens obtained at baseline included 2 sets of blood cultures and aerobic and anaerobic cultures from the primary intra-abdominal site of infection.

## Statistical Reviewers Comments:

*In the FDA analysis, the primary efficacy endpoint of clinical response was evaluated for duration of up to 35 days at the test-of-cure assessment. The primary efficacy assessments were based on ME and micro-mITT as co-primary populations and analysis based on the ITT population was also evaluated in this review to assess the robustness of evidence.*

*Noninferiority of tigecycline compared with vancomycin/aztreonam for clinical and microbiologic responses was evaluated based on a 2-sided 95% confidence interval (CI) for the true difference in efficacy (tigecycline - imipenem/cilastatin). Noninferiority was concluded in this review if the lower limit of the 2-sided 95% CI for the true difference in efficacy was higher than -15%.*

## Disposition of Subjects:

A total of 898 subjects were screened into the study; 64 subjects were screen failures and the remaining 834 subjects were randomly assigned to 1 of the treatment arms and constituted the ITT population. A total of 825 subjects received the study drug and constituted the mITT population: 413 subjects received tigecycline and 412 subjects received imipenem/cilastatin.

**Table 11: Number of Subjects**

<b>Population</b>	<b>Tigecycline n (% ITT)</b>	<b>Imipenem/ Cilastatin n (% ITT)</b>	<b>Total n (% ITT)</b>
Screened			898
Screen Failures			64
<b>Intent-to-Treat (ITT)</b>	<b>417</b>	<b>417</b>	<b>834</b>
No treatment received	4	5	9
Modified Intent-to-treat (mITT)	413 (99.0)	412 (98.8)	825 (98.9)
cIAI did not meet minimal disease criteria	5	13	18
Clinical mITT (c-mITT)	408 (97.8)	399 (95.7)	807 (96.8)
Did not meet clinical evaluability criteria	67	48	115
Clinically evaluable (CE)	341 (81.8)	351 (84.2)	692 (83.0)
No baseline and/or susceptible isolates	94	96	190
<b>Microbiologically evaluable (ME)</b>	<b>247 (59.2)</b>	<b>255 (61.2)</b>	<b>502 (60.2)</b>
<b>Microbiological mITT (m-mITT)</b>	<b>309 (74.1)</b>	<b>312 (74.8)</b>	<b>621 (74.5)</b>
No baseline isolate identified from c-mITT	99	87	186

### Sponsor's Table.

mITT = modified intent-to-treat, ie, all intent-to-treat subjects who received at least 1 dose of study drug; c-mITT = clinical mITT, ie, mITT subjects who met minimal disease requirements with clinical evidence of cIAI; CE = clinically evaluable, ie, c-mITT subjects who met inclusion/exclusion criteria, received appropriate and sufficient treatment to determine cure or failure, had a test-of-cure assessment of cure or failure, and Received no more than 1 dose of a prohibited antibacterial treatment after the baseline intra-abdominal culture Was obtained, but before the first dose of study medication;

## Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics of the mITT population, including age, sex, ethnicity, weight, Creatinine Clearance (CLCR) and APACHE scores are given below.

**Table 12: Demographic and Baseline Characteristics of the mITT Population**

Characteristic	Tigecycline (n = 413)	Imipenem/ Cilastatin (n = 412)	Total (n = 825)
Age, years			
Mean	43.87	43.42	43.64
Standard Deviation	18.21	17.53	17.86
Minimum, maximum	18.00, 91.00	18.00, 90.00	18.00, 91.00
Median	42.00	42.00	42.00
Sex, n (%)			
Male	274 (66.3)	263 (63.8)	537 (65.1)
Female	139 (33.7)	149(36.2)	288 (34.9)
Ethnic origin, n (%)			
White	165 (40.0)	160 (38.8)	325 (39.4)
Black	35 ( 8.5)	39 ( 9.5)	74 ( 9.0)
Asian	49 (11.9)	44 (10.7)	93 (11.3)
Other	88 (21.3)	90 (21.8)	178 (21.6)
Hispanic	76 (18.4)	79 (19.2)	155 (18.8)
Weight, kg			
Mean	69.38	69.04	69.21
Standard Deviation	15.70	16.31	16.00
Minimum, maximum	39.00, 147.43	37.65, 179.00	37.65, 179.00
Median	66.50	65.32	66.00
Creatinine clearance, mL/min/1.73m <sup>2</sup>			
Mean	92.85	94.00	93.42
Standard Deviation	33.63	34.26	33.93
Minimum, maximum	1.30, 281.00	28.00, 257.00	1.30, 281.00
Median	90.00	90.50	90.30
APACHE II score			
n	412	412	824
Mean	5.70	5.58	5.64
Standard Deviation	4.42	4.10	4.26
Minimum, maximum	0.00, 25.00	0.00, 25.00	0.00, 25.00
Median	5.00	5.00	5.00
APACHE II Score by category, n (%)			
≤15	396 (96.1)	398 ( 96.6)	794 ( 96.4)
> 15	16 (3.9)	14 ( 3.4)	30 ( 3.6)

Sponsor's Table

**Statistical Reviewer’s Comments:**

*Based on the demographic and other baseline characteristics of the mITT population, there were no major differences observed between the two treatment groups. They were almost similar with respect to age, sex, ethnicity, weight, creatinine clearance and APACHE scores were almost similar in the two treatment groups.*

**Efficacy Analyses:**

**Statistical Reviewer’s Comments:**

*The efficacy endpoint of clinical response was evaluated based on the co-primary ME and m-mITT populations at the test-of-cure assessment. Non-inferiority of tigecycline to imipenem/cilastatin was concluded, if the lower bound of the 2-sided 95% confidence interval (CI) for the difference in cure proportion was higher than the margin of –15%.*

**Table 13: Clinical Response: Microbiological Evaluable (ME) Population**

TOC	APACHE Score	Tigecycline		Imipenem/ Cilastatin		Test for Difference (95%CI)
		n/N	%	n/N	%	
Cure	≤ 15	195/238	81.9	208/247	84.2	(-9.4, 4.8)
	> 15	4/ 9	44.4	2/ 8	25.0	(-36.6, 75.5)
Overall	Unadjusted	199/247	80.6	210/255	82.4	<b>(-9.0, 5.4)</b>
	Adjusted					(-8.4, 5.1)
Failure		48/247	19.4	45/255	17.6	

**Table 14: Clinical Response at TOC: Microbiological mITT Population**

	APACHE Score	Tigecycline		Imipenem/ Cilastatin		Test for Difference (95%CI)
		n/N	%	n/N	%	
Cure	≤ 15	219/295	74.2	242/302	80.1	(-13.0, 1.2)
	> 15	8/14	57.1	2/10	20.0	(-7.3, 81.6)
Overall	Unadjusted	227/309	73.5	244/312	78.2	<b>(-11.8, 2.3)</b>
	Adjusted					(-11.0, 2.5)
Failure		63/309	20.4	55/312	17.6	
Indeterminate		19/309	6.1	13/312	4.2	

**Table 15: Clinical Response: ITT Population**

Test-of-Cure	APACHE Score	Tigecycline		Imipenem/Cilastatin		Test for Difference
		n/N	%	n/N	%	(95%CI)
Cure	≤ 15	295/401	73.6	324/404	80.2	(-12.7, -0.6)
	> 15	9/17	52.9	5/15		(-20.3, 59.5)
Overall	Unadjusted	304/418	72.7	329/419	33.3	<b>(-11.8, 0.3)</b>
	Adjusted					(-11.5, 0.1)
Failure		81/418	19.4	64/419	78.5	
Indeterminate		33/418	7.9	26/419	15.3	

**Statistical Reviewer's Comments:**

*In the Sponsor's analysis (Tables 13-15), the clinical response was evaluated at the TOC assessment, 92 days after the last dose of study drug. Based on the 95% CI for the difference in clinical response (unadjusted) at the TOC, Tigecycline demonstrated noninferiority to imipenem/cilastatin in the ME (95% CI: -9.0, 5.4), micro-mITT (95% CI: -11.8, 2.3) and ITT (95% CI: -11.8, 0.3).*

**Table 16: FDA Analysis: Clinical Response in the Microbiological Evaluable (ME) Population (TOC Visit ≤35 days post-therapy)**

Visit Response	APACHE Score	Tigecycline		Imipenem/Cilastatin		Test for Difference
		n/N	%	n/N	%	(95%CI)
Overall	Unadjusted	193/241	80.1%	206/251	82.1%	(-9.3, 5.3)
Failure		48/241	19.9%	45/251	17.9%	

**Table 17: FDA Analysis: Clinical Response in the Microbiological mITT Population (TOC Visit ≤35 days post-therapy)**

Visit Response	APACHE Score	Tigecycline		Imipenem/Cilastatin		Test for Difference
		n/N	%	n/N	%	(95%CI)
Overall	Unadjusted	221/302	73.2%	240/308	77.9%	(-11.9, 2.4)
Failure		63/302	20.9%	55/308	17.9%	
Indeterminate		18/302	5.9%	13/308	4.2%	

**Statistical Reviewer's Comments:**

*In the FDA analyses (Tables 16-17), clinical response (unadjusted) was evaluated for a duration of up to 35 days at the test-of-cure assessment. The 95% Confidence Intervals in the ME and micro-mITT populations were; ME (95%CI: (-9.3, 5.3) and micro-mITT (95%CI: (-11.9, 2.4). Tigecycline demonstrated noninferiority to imipenem/cilastatin in the ME and micro-mITT using a margin of 15%. The efficacy conclusions were not changed upon evaluating the clinical responses at TOC<=35 days or TOC<=92 days after the last dose of study drug.*

**3.1.2.2 Study 3074A1-306-WW****Study Design:**

This was a phase 3, multi-center, double-blind (third-party unblinded) study comparing the safety and efficacy of tigecycline to imipenem/cilastatin in hospitalized subjects with complicated intra-abdominal infections.

Subjects were stratified at randomization into 2 groups based on their scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II: 15 or less, or over 15 but less than 31. Subjects with scores over 30 were excluded. Subjects were randomly assigned in a 1:1 ratio to receive either intravenous (IV) tigecycline or IV imipenem/cilastatin.

**Duration of Subject Participation (Based on the protocol)**

Approximately 4 to 7 weeks: up to 1 day for screening, up to 2 weeks of test article administration, 9 days (+5 days) post therapy for an early follow-up visit, and >=14 days and not more than 35 days after the last dose of test article for the test-of-cure assessment. Subjects who are clinical failures will have the test-of-cure assessment performed prior to the initiation of non-study antibiotic. No Day 9 post therapy follow-up visit will be performed for subjects who are declared failures.

**Primary Efficacy Variables**

The primary efficacy endpoint was the clinical response in the ME and m-mITT populations (co-primary populations) at the test-of-cure assessment.

**Cure:** The study medication and the initial intervention (operative or radiologically controlled drainage procedure) resolved the intra-abdominal infection.

**Disposition of Subjects:**

A total of 861 subjects were screened for the study; 37 were screen failures (10 additional subjects were screen failures that were not captured in the database). The remaining 824 subjects were randomly assigned to 1 of the treatment arms and constituted the intent-to-treat (ITT) population. Seven (7) subjects did not receive study drug. Altogether, 817

subjects received the study drug and constituted the mITT population: 404 subjects received tigecycline and 413 subjects received imipenem/cilastatin.

**Table 18: Number of Subjects in Each Population Category**

Population	Tigecycline n (% ITT)	Imipenem/ Cilastatin n (% ITT)	Total n (% ITT)
Screened			861
Screen failures			37
Intent-to-treat (ITT)	409	415	824
No treatment received	5	2	7
Modified intent-to-treat (mITT)	404 ( 98.8)	413 ( 99.5)	817 ( 99.2)
cIAI did not meet severity criteria Clinical mITT (c-mITT)	11	12	23
Did not meet clinical evaluability criteria	49	55	104
Clinically evaluable (CE)	344 ( 84.1)	346 ( 83.4)	690 ( 83.7)
No baseline or susceptible pathogen	79	88	167
Microbiologically evaluable	265 ( 64.8)	258 ( 62.2)	523 ( 63.5)
Microbiologic mITT (m-mITT)	322 ( 78.7)	319 ( 76.9)	641 ( 77.8)
No baseline isolate identified (from c-mITT population)	71	82	153

**Sponsor's Table.** ITT = all randomized subjects.; mITT = ITT subjects who received at least 1 dose of study drug.  
c-mITT = mITT subjects with evidence of cIAI. ; m-mITT = c-mITT subjects with identified baseline isolate.

### Statistical Reviewers Comments:

*In the FDA analysis, the primary efficacy endpoint of clinical response was evaluated for duration of up to 35 days at the test-of-cure assessment as in the previous study. The primary efficacy assessments were based on ME and micro-mITT as co-primary populations and analysis based on the ITT population was also evaluated in this review to assess the robustness of evidence.*

*Noninferiority of tigecycline compared with vancomycin/aztreonam for clinical and microbiologic responses was evaluated based on a 2-sided 95% confidence interval (CI) for the true difference in efficacy (tigecycline - imipenem/cilastatin). Noninferiority was concluded in this review if the lower limit of the 2-sided 95% CI for the true difference in efficacy was higher than -15%.*

### Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics of the mITT population, including age, sex, Ethnicity, weight, and Creatinine Clearance (CLCR) and APACHE-II score are shown below.

**Table 19: Demographic and Baseline Characteristics: mITT Population**

Characteristic	Tigecycline (n = 404)	Imipenem/ Cilastatin (n = 413)	Total (n = 817)
Age, years			
Mean	48.28	49.52	48.91
Standard deviation	18.37	17.96	18.17
Minimum, maximum	18.00, 86.00	18.00, 88.00	18.00, 88.00
Median	47.00	51.00	49.00
Sex, n (%)			
Male	239 ( 59.2)	240 ( 58.1)	479 ( 58.6)
Female	165 ( 40.8)	173 ( 41.9)	338 ( 41.4)
Ethnic origin, n (%)			
White	349 ( 86.4)	370 ( 89.6)	719 ( 88.0)
Black	12 ( 3.0)	13 ( 3.1)	25 ( 3.1)
Asian	29 ( 7.2)	23 ( 5.6)	52 ( 6.4)
Other	14 ( 3.5)	7 ( 1.7)	21 ( 2.6)
Weight, kg			
Mean	74.08	74.50	74.29
Standard deviation	14.93	15.72	15.32
Minimum, maximum	44.00, 157.00	42.00, 130.00	42.00, 157.00
Median	73.00	73.00	73.00
Creatinine clearance (CLCR) mL/min/1.73m <sup>2</sup>			
n	404	410	814
Mean	65.41	64.81	65.11
Standard deviation	28.89	27.40	28.13
Minimum, maximum	10.81, 194.00	15.57, 174.00	10.81, 194.00
Median	58.07	57.93	58.03
APACHE II Score			
Mean	6.44	6.41	6.43
Standard deviation	3.95	3.61	3.78
Minimum, maximum	0.00, 20.00	0.00, 24.00	0.00, 24.00
Median	6.00	6.00	6.00
APACHE II Score by Category, n (%)			
≤15	395 ( 97.8)	410 ( 99.3)	805 ( 98.5)
>15	9 ( 2.2)	3 ( 0.7)	12 ( 1.5)

Sponsor's Table

**Statistical Reviewer's Comments:**

*There were no major differences observed between treatment groups with respect to the demographic and other baseline characteristics (age, sex, ethnicity, weight, CLCR and APACHE-II scores) in the mITT population.*

**Table 20: Clinical Response: Microbiological Evaluable (ME) Population**

Test-of-cure		Tigecycline		Imipenem/ Cilastatin		Test for Difference
		n/N	%	n/N	%	(95%CI)
	APACHE Score					
Cure	≤15	237/260	91.2%	232/258	89.9	(-4.2, 6.7)
	> 15	5/ 5	100.0%	0/ 0		
Overall	<b>Unadjusted</b>	242/265	91.3%	232/258	89.9	<b>(-4.0, 6.8)</b>
	<b>Adjusted</b>					N/A
Failure		23/265	8.7%	26/258	10.1	

**Table 21: Clinical Response: Microbiological mITT Population**

Test-of-Cure		Tigecycline		Imipenem/ Cilastatin		Test for Difference
		n/N	%	n/N	%	(95%CI)
	APACHE Score					
Cure	≤ 15	271/314	86.3%	268/316	84.8%	(-4.3, 7.3)
	> 15	8/8	100.0%	2/3	66.7%	(-42.9, 100.0)
	<b>Unadjusted</b>	279/322	86.6%	270/319	84.6%	(-3.7, 7.7)
	<b>Adjusted</b>					(-3.7, 7.5)
Failure		34/322	10.6%	36/319	11.3%	
Indeterminate		9/322	2.8%	13/319	4.1%	

**Table 22: Clinical Response: ITT Population**

Test-of-Cure		Tigecycline		Imipenem/ Cilastatin		Test for Difference
		n/N	%	n/N	%	(95%CI)
	APACHE Score					
Cure	≤ 15	336/400	84.0%	347/412	84.2%	(-5.5, 5.1)
	> 15	9/9	100.0%	2/3	66.7%	(-42.2, 100.0)
Overall	<b>Unadjusted</b>	345/409	84.4%	349/415	84.1%	(-5.0, 5.5)
	<b>Adjusted</b>					(-4.9, 5.3)
Failure		44/409	10.8%	46/415	11.1%	
Indeterminate		20/409	4.9%	20/415	4.8%	

**Statistical Reviewer’s Comments:**

*In the Sponsor’s analysis (Tables 20-22), the clinical response (unadjusted) was evaluated at the TOC assessment, 92 days after the last dose of study drug. Based on the 95% CI for the difference in clinical response at the TOC, Tigecycline demonstrated noninferiority to imipenem/cilastatin in the ME (95% CI: -4.0, 6.8), micro-mITT (95% CI: -3.7, 7.7) and ITT (95% CI: -5.0, 5.5).*

**Table 23: FDA Analysis: Clinical Response in the Microbiological Evaluable (ME) Population TOC Visit <=35 days post-therapy**

	APACHE Score	Tigecycline		Imipenem/ Cilastatin		Test for Difference (95%CI)
		n/N	%	n/N	%	
Overall	<b>Unadjusted</b>	215/238	90.3%	216/242	89.3%	(-4.8, 6.9)
<b>Failure</b>		23/238	9.7%	26/242	10.7%	

**Table 24: FDA Analysis: Clinical Response in the Microbiological mITT Population**

Test-of-Cure	APACHE Score	Tigecycline		Imipenem/ Cilastatin		Test for Difference (95%CI)
		n/N	%	n/N	%	
Overall	<b>Unadjusted</b>	246/288	85.4%	248/296	83.4%	(-4.6, 7.8)
<b>Failure</b>		34/288	11.8%	35/296	11.8%	
<b>Indeterminate</b>		8/288	2.8%	13/296	4.4%	

**Statistical Reviewer’s Comments:**

*In the FDA analyses (Tables 23-24), clinical response (unadjusted) was evaluated for a duration of up to 35 days at the test-of-cure assessment. The 95% Confidence Intervals in the ME and micro-mITT populations were; ME (95%CI: -4.8, 6.9) and micro-mITT (95%CI: -4.6, 7.8). Tigecycline demonstrated noninferiority to imipenem/cilastatin in the ME and micro-mITT using a margin of 15%. The efficacy conclusions were not changed upon evaluating the clinical responses at TOC<=35 days or TOC<=92 days after the last dose of study drug.*

## 3.2 Evaluation of Safety

### Mortality Analyses (Overall)

Based on the submission, a total of 57 subject deaths were reported from studies 300, 301, 305, and 306, and 307 (Table 25). This review was only focused on the controlled studies 300, 305, 301 and 306. There were 54 deaths reported in total from these studies.

**Table 25: Subjects in the Phase 3 Studies with Adverse Events Resulting in Death: Number (%) of Subjects Who Died**

Indication	Tigecycline n/N (%)		Comparator Treatment n/N (%)
			Vancomycin/Aztreonam
cSSSI	6/566	(1.1)	1/550 ( 0.2)
cIAI	26 <sup>a</sup> /817	(3.2)	Imipenem/Cilastatin 21 <sup>b</sup> /825 ( 2.5)
cSSSI and cIAI	32 <sup>a</sup> /1383	(2.3)	Combined Comparators 22 <sup>b</sup> /1375 ( 1.6)
RPc	3/32	(9.4)	0/7 (0.0)

**Sponsor's Table:** Source: /Clinical R&D/Clinical Programming SAS reports/3074A1 GAR-936/ISS/DEATH DOCUMENT/ae5\_dth, 18FEB05, 08:33

a: Includes 2 deaths that occurred after the active reporting period and were not included in the database.

b: Includes 4 deaths that occurred after the active reporting period and were not included in the database.

c: Subjects in this study (RP = resistant pathogen ) were randomized 3:1 to tigecycline or an active control.

### Statistical Reviewer's Comments:

*A total of 54 deaths were reported from studies 300, 301, 305, and 306. In studies submitted for Complicated Skin and Skin Structure Infections, there were 6 deaths reported in the Tigecycline arm. Of which, 5 deaths were reported from study 3074A1-300-US/CA and one death in study 3074A1-305-US/WW. In studies submitted for Complicated Intra Abdomen Infections, there were 26 deaths reported in the Tigecycline arm. Of which, 19 deaths were reported from study 3074A1-301 and 7 deaths reported from study 3074A1-306-WW. Based on the review, no specific safety issues could be attributed to the cause of these deaths. Dr. Cooper's clinical review would provide more detailed safety information.*

*For Complicated Intra Abdomen Infection studies, increased age, increased APACHE II score, and baseline clinical diagnosis were not the same between subjects who died and subjects who have survived (based on sponsor's submission). The mean age of subjects who died were; 59.4 years in the tigecycline group; 64.4 years in the comparator group and subjects who survived were approximately 47.2 years in both treatment groups. Mean APACHE scores, which are available for subjects in the cIAI studies only, were relatively higher in subjects who died (9.83 in the tigecycline group; 9.18 in the comparator group).*

**Table 26: Median Days From Start of Treatment to Date of Death: Subjects Who Died in cSSSI Studies**

Study Number	Tigecycline		Vancomycin/Aztreonam	
	No. Deaths	Days	No. Deaths	Days
300	5	11	1	11
305	1	8	0	n/a
Total	6	10.5	1	11

Sponsor's Table Source: 3074A1 GAR-936/300/mdeath\_onset\_3, 17FEB05; 3074A1 GAR-936/305/mdeath\_onset\_3, 17FEB05; 3074A1 GAR-936/300\_305/mdeath\_onset\_3, 17FEB05.

**Statistical Reviewer's Comments:**

*In study 300, there were 5 deaths reported in the Tigecycline arm and 1 death in the Vancomycin/Aztreonam arm. The median "days to death" was 11 days in the tigecycline arm and for the one death in the Vancomycin/Aztreonam group, the time to death was 11 days. In study 305, 1 death was reported with a time to death of 8 days.*

**Table 27: Demographic and Clinical Characteristics of Subjects Who Died in Study 300**

Characteristic	Tigecycline (n = 5)	Vancomycin/Aztreonam (n = 1)	Total (n = 6)
<b>Distribution of Days to Death</b>			
5	1		1
10	1		1
11	1	1	2
22	1		1
44	1		1
<b>Event Related to Infection</b>			
Yes	1		1
No	4	1	5

**Statistical Reviewer's Comments:**

*Among the 5 deaths reported in study 300, there was no visible trend observed based on the distribution of "days to death" (Table 27). 4/5 deaths were related to non-infection.*

**Table 28: Median Days From Start of Treatment to Date of Death: Subjects Who Died in cIAI Studies**

Median Days From Start of Treatment to Date of Death: Subjects Who Died in cIAI Studies				
Study Number	Tigecycline		Imipenem/Cilastatin	
	No. Deaths	Days	No. Deaths	Days
301	19	10	12	11
306	7	22	5	13
Total	26	12.5	17	11

**Statistical Reviewer’s Comments:**

*In study 301, the median “days to death” was 10 days in the tigecycline arm and 11 days in the Imipenem/Cilastatin arm. In study 306, the median “days to death” was 22 days in the tigecycline arm and 13 days in the Imipenem/Cilastatin arm. There were more deaths reported in study 301 compared to study 306.*

**Table 29: Demographic and Clinical Characteristics of Subjects in the cIAI Studies Who Died**

Characteristic	Tigecycline (n = 26)	Imipenem/ Cilastatin (n = 21)
<b>Distribution of Days to Death, n (%)</b>		
1	1	0
2	0	2
3	1	0
4	4	0
6	0	2
8	1	0
9	0	2
10	3	2
11	0	3
12	2	0
13	2	1
15	3	0
16	0	1
17	2	2
20	1	0
22	1	0
27	1	0
30	1	0
31	0	1
32	0	1
41	0	1
45	1	0
49	1	0
53	1	0
93	0	1
unknown	-	2

**Statistical Reviewer’s Comments:**

*Based on the distribution of “days to death”, there was no clustering of events observed in either of the treatment arms. There was no trend observed in the distribution of days.*

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race and Age

#### Statistical Reviewers Comments:

*Clinical responses in the special or subgroup populations (based on Gender, Race and Age) were reviewed to evaluate the evidence comparing tigecycline to imipenem/cilastatin. It should be noted that these subgroup analyses were not powered for non-inferiority testing.*

#### Study 3074A1-300-US/CA:

**Table 30: Clinical Response at TOC by Age (<65 or ≥65): c-mITT Population**

Age group	Response	Tigecycline		Vancomycin/Aztreonam		95% CI
		n/N (%)		n/N	%	
<65	Cure	175/ 232 (75.4)		165/ 217 (76.0)		(-8.8, 7.7)
	Failure	37/ 232 (15.9)		39/ 217 (18.0)		
	Indeterminate	20/ 232 (8.6)		13/ 217 (6.0)		
≥65	Cure	34/ 45 (75.6)		35/ 43 (81.4)		(-24.0, 13.0)
	Failure	11/ 45 (24.4)		7/ 43 (16.3)		
	Indeterminate	0/ 45 (0.0)		1/ 43 (2.3)		

**Table 31: Clinical Response at TOC by Gender: c-mITT Population**

Gender	Response	Tigecycline		Vancomycin/Aztreonam		95% CI
		n/N	%	n/N	%	
Male	Cure	127/170	74.7	137/176	77.8	(-12.5, 6.2)
	Failure	29/170	17.1	25/176	14.2	
	Indeterminate	14/170	8.2	14/176	8.0	
Female	Cure	82/107	76.6	63/84	75.0	(-11.0, 14.8)
	Failure	19/107	17.8	21/84	25.0	
	Indeterminate	6/107	5.6	0/84	0.0	

**Table 32: Clinical Response by Ethnic Origin: c-mITT Population**

Race	Response	Tigecycline n/N(%)	Vancomycin/ Aztreonam n/N (%)	95% CI
White	Cure	107/ 144 (74.3)	109/ 135 (80.7)	(-16.5, 3.9)
	Failure	27/ 144 (18.8)	20/ 135 (14.8)	
	Indeterminate	10/ 144 (6.9)	6/ 135 (4.4)	
Black	Cure	15/ 27 (55.6)	12/ 22 (54.5)	(-27.5, 29.6)
	Failure	7/ 27 (25.9)	7/ 22 (31.8)	
	Indeterminate	5/ 27 (18.5)	3/ 22 (13.6)	
Oriental (Asian)	Cure	1/ 1 (100.0)	1/ 1 (100.0)	
	Failure	0/ 1 (0.0)	0/ 1 (0.0)	
	Indeterminate	0/ 1 (0.0)	0/ 1 (0.0)	
Hispanic	Cure	45/ 52 (86.5)	45/ 50 (90.0)	(-17.8, 11.2)
	Failure	3/ 52 (5.8)	3/ 50 (6.0)	
	Indeterminate	4/ 52 (7.7)	2/ 50 (4.0)	
Other	Cure	41/ 53 (77.4)	33/ 52 (63.5)	(-4.8, 31.5)
	Failure	11/ 53 (20.8)	16/ 52 (30.8)	
	Indeterminate	1/ 53 (1.9)	3/ 52 (5.8)	

**Study 3074A1-305-US/WW:****Table 33: Clinical Response at TOC by Age (<65 or ≥65): c-mITT Population**

Age group	Response	Tigecycline n/N (%)	Vancomycin/ Aztreonam n/N ( % )	95% CI
<65	Cure	181/ 210 (86.2)	167/ 191 (87.4)	(-8.2, 5.9)
	Failure	22/ 210 (10.5)	17/ 191 (8.9)	
	Indeterminate	7/ 210 (3.3)	7/ 191 (3.7)	
≥65	Cure	39/ 51 (76.5)	58/ 68 (85.3)	(-24.8, 6.3)
	Failure	9/ 51 (17.6)	9/ 68 (13.2)	
	Indeterminate	3/ 51 (5.9)	1/ 68 (1.5)	

**Table 34: Clinical Response at TOC by Gender (c-mITT Populations)**

Gender	Response	Tigecycline		Vancomycin/Aztreonam		95% CI
		n/N	%	n/N	%	
Male	Cure	139/ 162	85.8	134/ 157	85.4	(-7.8, 8.7)
	Failure	14/ 162	8.6	18/ 157	11.5	
	Indeterminate	9/ 162	5.6	5/ 157	3.2	
Female	Cure	81/ 99	81.8	91/ 102	89.2	(-18.0, 3.1)
	Failure	17/ 99	17.2	8/ 102	7.8	
	Indeterminate	1/ 99	1.0	3/ 102	2.9	

**Table 35: Clinical Response by Ethnic Origin: c-mITT Population**

Race	Response	Tigecycline n/N(%)	Vancomycin/ Aztreonam n/N (%)	95% CI
White	Cure	185/ 218 (84.9)	191/ 219 (87.2)	(-9.2, 4.5)
	Failure	25/ 218 (11.5)	22/ 219 (10.0)	
	Indeterminate	8/ 218 (3.7)	6/ 219 (2.7)	
Black	Cure	17/ 20 (85.0)	19/ 20 (95.0)	(-34.3, 14.6)
	Failure	1/ 20 (5.0)	0/ 20 (0.0)	
	Indeterminate	2/ 20 (10.0)	1/ 20 (5.0)	
Oriental (Asian)	Cure	11/ 15 (73.3)	12/ 16 (75.0)	(-34.7, 31.1)
	Failure	4/ 15 (26.7)	3/ 16 (18.8)	
	Indeterminate	0/ 15 (0.0)	1/ 16 (6.3)	
Other	Cure	7/ 8 (87.5)	3/ 4 (75.0)	(-34.7, 66.9)
	Failure	1/ 8 (12.5)	1/ 4 (25.0)	
	Indeterminate	0/ 8 (0.0)	0/ 4 (0.0)	

**Statistical Reviewers Comments:**

*Based on Tables 30-35, there were numerical differences observed in these subgroups with respect to gender, race and age. However, numbers of subjects were small in the sub groups and were reflected in the wide confidence intervals. Efficacy conclusions based on these subgroups must be drawn with caution.*

**Study 3074A1-301-WW:**

**Table 36: Clinical Response by Age (<65 or ≥65): Microbiologically Evaluable Population**

Age	Response	Tigecycline		Imipenem/Cilastatin		95%CI
		n/N	%	n/N	%	
<65	Cure	171/210	81.4	188/223	84.3	(-10.4, 4.6)
	Failure	39/210	18.6	35/223	15.7	
≥65	Cure	28/ 37	75.7	22/ 32	68.8	(-15.6, 29.3)
	Failure	9/ 37	24.3	10/ 32	31.3	

**Table 37: Clinical Response by Gender: Microbiologically Evaluable Population**

Gender	Tigecycline		Imipenem/Cilastatin		95%CI	
	n/N	%	n/N	%		
Male	Cure	144/173	83.2	139/166	83.7	(-8.8, 7.9)
	Failure	29/173	16.8	27/166	16.3	
Female	Cure	55/ 74	74.3	71/ 89	79.8	(-19.3, 8.2)
	Failure	19/ 74	25.7	18/ 89	20.2	

**Table 38: Clinical Response by Ethnic Origin: Microbiologically Evaluable Population**

Ethnic origin	Response	Tigecyclinen/N		Imipenem/Cilastatin-		95%CI
		%	n/N	%	n/N	
White	Cure	81/104	77.9	82/106	77.4	(-11.4, 12.4)
	Failure	23/104	22.1	24/106	22.6	
Black	Cure	12/ 16	75.0	19/ 25	76.0	(-31.9, 26.2)
	Failure	4/ 16	25.0	6/ 25	24.0	
Asian	Cure	24/ 30	80.0	26/ 30	86.7	(-27.8, 15.0)
	Failure	6/ 30	20.0	4/ 30	13.3	
Hispanic	Cure	44/ 54	81.5	39/ 44	88.6	(-22.3, 9.4)
	Failure	10/ 54	18.5	5/ 44	11.4	
Other	Cure	38/ 43	88.4	44/ 50	88.0	(-15.5, 15.3)
	Failure	5/43	11.6	6/50	12.0	

**Study 3074A1-306-WW:**

**Table 39: Clinical Response by Age (<65 or ≥65): ME Population**

Age	Response	Tigecycline		Imipenem/Cilastatin		95%CI
		n/N	%	n/N	%	
<65	Cure	187/202	92.6	192/207	92.8	(-5.8, 5.4)
	Failure	15/202	7.4	15/207	7.2	
≥65	Cure	55/ 63	87.3	40/ 51	78.4	(-6.1, 24.5)
	Failure	8/ 63	12.7	11/ 51	21.6	

**Table 40: Clinical Response by Gender: ME Population**

Sex	Response	Tigecycline		Imipenem/Cilastatin-		95%CI
		n/N	%	n/N	%	
Male	Cure	142/157	90.4	144/161	89.4	(-6.3, 8.2)
	Failure	15/157	9.6	17/161	10.6	
Female	Cure	100/108	92.6	88/ 97	90.7	(-6.6, 10.8)
	Failure	8/108	7.4	9/ 97	9.3	

**Table 41: Clinical Response by Ethnic Origin: ME Population**

Ethnic origin	Response	Tigecycline		Imipenem/Cilastatin		95% CI
		n/N	%	n/N	%	
White	Cure	222/238	93.3	207/229	90.4	(-2.5, 8.4)
	Failure	16/238	6.7	22/229	9.6	
Black	Cure	4/ 6	66.7	6/ 7	85.7	(-63.7, 32.5)
	Failure	2/ 6	33.3	1/ 7	14.3	
Asian	Cure	12/ 16	75.0	16/ 17	94.1	(-47.3, 10.8)
	Failure	4/ 16	25.0	1/ 17	5.9	
Other	Cure	4/ 5	80.0	3/ 5	60.0	(-39.9, 67.0)
	Failure	1/ 5	20.0	2/ 5	40.0	

**Statistical Reviewers Comments:**

*Based on Tables 36-41, there were numerical differences observed in subgroups with respect to gender, race and age. However, the numbers of subjects in the subgroups were small. Conclusions based on these subgroups must be drawn with caution.*

## 4.2 Other Special /Subgroup Populations

No other special/subgroups were reviewed.

# 5. SUMMARY AND CONCLUSIONS

## 5.1 Statistical Issues and Collective Evidence

### **Complicated Skin and Skin Structure Infections:**

In study 3074A1-300-US/CA, the primary efficacy endpoint was the clinical response at the test-of-cure assessment in the CE and cmITT populations. In the FDA analyses (Table 4), clinical response was evaluated for duration of up to 35 days at the test-of-cure assessment as specified in the protocol. The Confidence Intervals in the CE, cmITT and ITT populations were; CE (95%CI: -7.8, 8.3), cmITT (95%CI: -8.8, 6.6) and ITT (95% CI: -9.2, 5.6). Based on the 95% Confidence Interval (CI) for the difference in clinical cure rates at the TOC in all these three populations, Tigecycline demonstrated noninferiority to vancomycin/aztreonam using a non-inferiority margin of 15%. The efficacy conclusions remained the same based on evaluating the clinical responses at the TOC $\leq$ 35 days or TOC $\leq$ 92 days after the last dose of study drug.

In study 3074A1-305-US/WW, the primary efficacy endpoint was the clinical response at the test-of-cure assessment in the CE and cmITT populations. In the FDA analyses (Table 9), as per the protocol, the clinical response was evaluated for duration of up to 35 days at the test-of-cure assessment. The Confidence Intervals in the CE, cmITT and ITT populations were; CE (95%CI: -10.4, 1.0), cmITT (95%CI: -9.2, 4.0) and ITT (95% CI: -9.0, 3.6). Based on the 95% Confidence Interval (CI) for the difference in clinical cure rates at the TOC in these populations, Tigecycline demonstrated noninferiority to vancomycin/aztreonam using a non-inferiority margin of 15%. The efficacy conclusions were not affected upon evaluating the clinical responses at TOC $\leq$ 35 days or TOC $\leq$ 92 days after the last dose of study drug.

### **Complicated Intra Abdomen Infections (cIAI)**

In study 3074A1-301-WW, the primary efficacy endpoint was the clinical response at the test-of-cure assessment in the ME and m-mITT populations. In the FDA analyses (Tables 16-17), clinical response (unadjusted) was evaluated for a duration of up to 35 days at the test-of-cure assessment. The 95% Confidence Intervals in the ME, micro-mITT and ITT populations were; ME (95%CI: -9.3, 5.3), micro-mITT (95%CI: -11.9, 2.4) and ITT (95% CI: -11.8, 0.3). Tigecycline demonstrated noninferiority to imipenem/cilastatin in the ME and micro-mITT using a margin of 15%. The efficacy conclusions were not changed upon evaluating the clinical responses at TOC $\leq$ 35 days or TOC $\leq$ 92 days after the last dose of study drug.

In study 3074A1-306-WW, the primary efficacy endpoint was the clinical response at the test-of-cure assessment in the ME and m-mITT populations. In the FDA analyses (Tables 23-24), clinical response (unadjusted) was evaluated for a duration of up to 35 days at the

test-of-cure assessment. The 95% Confidence Intervals in the ME, micro-mITT and ITT populations were; ME (95%CI: -4.8, 6.9), micro-mITT (95%CI: -4.6, 7.8) and ITT(95% CI: -5.0, 5.5). Tigecycline demonstrated noninferiority to imipenem/cilastatin in the ME and micro-mITT using a margin of 15%. Assessing efficacy at TOC<=35 days or TOC<=92 days after the last dose of study drug, provided consistent results.

Based on the safety review, a total of 57 deaths (in total), was reported from studies 300, 301, 305, 306, and 307. However, 54 deaths were from the controlled studies 300, 305, 301 and 306. In studies submitted for Complicated Skin and Skin Structure Infections, there were 6 deaths reported in the Tigecycline arm. Of which, 5 deaths were reported from study 3074A1-300-US/CA and one death in study 3074A1-305-US/WW. In studies submitted for Complicated Intra Abdomen Infections, there were 26 deaths reported in the Tigecycline arm. Of which, 19 deaths were reported from study 3074A1-301 and 7 deaths reported from study 3074A1-306-WW. Based on the review, no specific safety issue could be attributed to the cause of these deaths. However, Dr. Cooper's clinical review would provide detailed safety information.

## **5.2 Conclusions and Recommendations**

### **Complicated Skin and Skin Structure Infections (cSSSI):**

In the primary efficacy analyses of clinical response at test-of-cure, tigecycline demonstrated noninferiority to vancomycin/aztreonam in the CE and c-mITT populations in studies 3074A1-300-US/CA and 3074A1-305-US/WW.

### **Complicated Intra Abdomen Infections (cIAI):**

In the primary efficacy analyses of clinical response at test-of-cure, tigecycline demonstrated noninferiority to imipenem/cilastatin in the ME and micro-mITT populations in studies 3074A1-301-WW and 3074A1-306-WW.

### **Safety Issues**

A total of 57 deaths were reported from studies 300, 301, 305, 306, and 307. However, 54 deaths were from the controlled studies 300, 305, 301 and 306. In studies submitted for Complicated Skin and Skin Structure Infections, there were 6 deaths reported in the Tigecycline arm. Of which, 5 deaths were reported from study 3074A1-300-US/CA and one death in study 3074A1-305-US/WW. In studies submitted for Complicated Intra Abdomen Infections, there were 26 deaths reported in the Tigecycline arm. Of which, 19 deaths were reported from study 3074A1-301 and 7 deaths reported from study 3074A1-306-WW. Based on the review, no specific safety issues could be attributed to the cause of these deaths. However, medical officer, Dr. Cooper's clinical review would provide more detailed safety information. Approval of this product would be based on the overall evidence of safety and efficacy and the labeling should indicate all the major safety issues for this product.

## SIGNATURES/DISTRIBUTION LIST

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Statistical Review of Tigecycline

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