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PROPRIETARY DRUG NAME® / GENERIC NAME: Tygacil® / Tigecycline

PROTOCOL NO.: 3074A1-900 (B1811008)

PROTOCOL TITLE: A Multicenter, Randomized, Open-label Comparison of the Safety and Efficacy of Tigecycline With That of Ampicillin-Sulbactam or Amoxicillin-Clavulanate to Treat Complicated Skin and Skin Structure Infections

Study Centers: A total of 78 centers took part in the study and enrolled subjects; 36 in the United States (US), 9 in Canada, 4 each in the Republic of Korea and South Africa, 3 each in Philippines and Taiwan, 2 each in Germany, Hong Kong, India, Israel, Malaysia, and Spain, 1 each in Brazil, Italy, Lebanon, Mexico, Saudi Arabia, Singapore, and Thailand.

Study Initiation Date and Final Completion Date: 27 September 2006 to 22 September 2008

Phase of Development: Phase 3b/4

Study Objectives:

Primary Objective: To compare the safety and efficacy of tigecycline with that of the comparator (ampicillin-sulbactam or amoxicillin-clavulanate) in treating subjects with complicated skin and skin structure infection (cSSSI). The primary endpoint was the clinical response in the clinically evaluable (CE) population at the test-of-cure (TOC) visit.

Secondary Objectives:

- To compare the microbiologic efficacy of tigecycline with that of the comparator in the microbiologically evaluable (ME) population.
- To evaluate in vitro susceptibility data on tigecycline for a range of pathogenic bacteria that cause cSSSI.
- To compare the healthcare utilization between the treatment groups.

METHODS:

Study Design: This was a Phase 3b/4, multicenter, randomized, open-label, comparative study of the safety and efficacy of tigecycline versus that of the comparator in hospitalized subjects with cSSSI.

Eligible subjects were randomly assigned in a 1:1 ratio to receive intravenous (IV) tigecycline or IV comparator for up to 2 weeks. Subjects were not allowed to switch to oral treatment.

The total duration of the study was 24 months. The maximum duration of the study was 6 weeks per subject. A subject's participation included 1 day for screening, a minimum of 4 days and up to 2 weeks of study drug administration, and 1 TOC visit, 10 to 28 days after the last study drug administration.

Subjects declared failures at the end-of-treatment (EOT) visit were to receive appropriate treatment as decided by the Investigator. These subjects, as well as subjects who prematurely discontinued from the study, were to return for a TOC visit, 10 to 28 days after their last study drug administration. All abnormal laboratory values were followed up until resolution or until the subject was clinically stable.

The schedule of activities during the study is provided in Table 1.

Table 1. Schedule of Activities

Procedure	Baseline	On-Treatment[a]		End-of-Treatment (EOT)	Test-of-Cure (TOC)[b] 10-28 Days After Last Dose of Test Article
		Day 1-14	Day 3		
Inclusion and exclusion criteria	X				
Informed consent	X				
Demographics	X				
Medical and medication history	X				
Complete physical examination[c]	X				
Imaging for osteomyelitis[d]	X				
Pregnancy test[e]	X				
Physical exam/signs and symptoms[f]		X	X	X	X
Daily temperature[g]		X	X		
Hematology[h]	X		X	X	X[i]
Coagulation[j]	X		X	X	X[i]
Serum chemistry[k]	X		X	X	X[i]
Urinalysis[l]	X				
Blood and infection site cultures	X	X[m]	X[m]	X[m]	X[m]
Assessment of clinical response				X	X
Skin infection site assessment		X	X	X	X
Test article administration[n]		X----------X			
Drug accountability[o]		X----------X			
Record concomitant medications[p]		X----------X			
Record concomitant treatments[p]		X----------X			
Resource utilization data[q]		X----------X			
Collection of adverse events[r]	X----------X				

ALT = alanine aminotransferase; AP = alkaline phosphatase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CO_2 = carbon dioxide; cSSSI = complicated skin and skin structure infection; EOT = end-of-treatment; HCO_3 = bicarbonate; HCT = hematocrit; HGB = hemoglobin; INR = international normalized ratio; PT = prothrombin time; RBC = red blood cell count; TA = test article; TOC = test-of-cure; WBC = white blood cell count.

a. In a hospital setting, TA was administered for a minimum of 4 days and not more than 14 days at the Investigator's discretion.
b. All subjects, including failures at EOT and those who discontinued prematurely, had a TOC visit performed 10 to 28 days after the last dose of TA.
c. Complete physical examination included the following vital signs: blood pressure, heart rate, respiratory rate, temperature, height, and weight. An assessment of intercurrent illness was performed.
d. Could be waived based on the clinical judgment of the Investigator if medical history and physical examination were negative with respect to any infectious bone involvement.
e. Urine or serum pregnancy test was performed before the first dose of TA on all women of childbearing potential.
f. Physical examination was performed to assess any new abnormal body systems, adverse events, vital signs, and clinical signs and symptoms of cSSSI.
g. Maximum temperature was collected daily.
h. Hematology testing included CBC consisting of RBC and WBC with differential counts, platelet count, HGB, and HCT.
i. All laboratory values that became clinically significantly abnormal after TA administration were repeated until the values return to normal or baseline values.
j. Coagulation studies included aPTT, PT, and INR (if available). If PT was not available, then prothrombin activity was obtained.
k. Serum chemistry included creatinine, BUN or urea, sodium, potassium, chloride, carbon dioxide (total CO_2 or HCO_3), total and direct bilirubin, total protein, AST, ALT, AP, and amylase.
l. Urinalysis included dipstick analysis, microscopic evaluation, specific gravity, and pH.
m. If baseline blood cultures were positive, repeat blood cultures were obtained until results were negative. Timing of the cultures was at the discretion of the Investigator.
n. TA was administered for a minimum of 4 days and up to 14 days at the discretion of the Investigator.

Table 1. Schedule of Activities

After 72 hours of receiving TA, subjects could be discharged from the hospital, when medically indicated, and continued to receive the test article.

o. All TAs that were dispensed and then returned to the pharmacy were recorded on the study drug accountability records. All unused prepared TAs were returned to the hospital pharmacy and stored until after the Sponsor had performed accountability.

p. Concomitant medications and treatments were recorded through the TOC visit or the final laboratory visit for an abnormal laboratory value, whichever was later.

q. Resource utilization data such as start and stop dates, days of stay in the intensive care unit (ICU), and discharge date were recorded.

r. Information on all adverse events was recorded from the time the subject signed the informed consent form until (1) the TOC visit or (2) all laboratory tests with values that became clinically significantly abnormal after TA administration returned to normal or baseline values, or (3) 15 days after the last day of TA administration, whichever was later.

Number of Subjects (Planned and Analyzed): A total of 500 subjects were planned to be enrolled and a total of 550 subjects were randomly assigned to either of the treatment groups. Nineteen subjects did not receive the study drug. A total of 531 subjects received at least 1 dose of study drug: 268 subjects received tigecycline and 263 subjects received comparator.

Of the 550 subjects; 268 were randomized in the US, 63 in Canada, 41 in South Africa, 40 in the Republic of Korea, 24 in Israel, 21 in Philippines, 20 in Taiwan, 12 each in Germany and India, 8 in Singapore, 6 each in Malaysia, Spain, and Thailand, 5 each in Italy, Lebanon, and Saudi Arabia, 4 in Mexico, 3 in Hong Kong, and 1 in Brazil.

Diagnosis and Main Criteria for Inclusion: Males and females aged 18 years and older with a clinical diagnosis of cSSI who were in need of IV treatment for 4 to 14 days were included in the study. Subjects with skin infection that could be treated by surgery and wound care alone; diabetic foot ulcers or bedsores where the infection had been present longer than 1 week; or poor circulation such that amputation of the infected site was likely within a month, were excluded from the study.

Study Treatment: Tigecycline was supplied by the Sponsor as sterile lyophilized powder in 5 mL vials containing 53 mg of tigecycline.

Ampicillin-sulbactam and amoxicillin-clavulanate were supplied as sterile powder in glass vials containing 1500 mg (1000 mg ampicillin plus 500 mg sulbactam) and 1200 mg (1000 mg amoxicillin plus 200 mg clavulante), respectively. Vancomycin and teicoplanin were supplied as sterile powder in glass vials containing 1000 mg vancomycin and 200 mg teicoplanin, respectively.

Each subject was randomly assigned in a 1:1 ratio to 1 of the following 2 treatment groups:

Group A: Tigecycline administered IV every 12 hours (an initial dose of 100 mg followed by 50 mg every 12 hours), or

Group B: Ampicillin-sulbactam 1500 mg (1000 mg ampicillin plus 500 mg sulbactam) to 3000 mg (2000 mg ampicillin plus 1000 mg sulbactam) IV every 6 hours or amoxicillin-clavulanate 1200 mg (1000 mg amoxicillin plus 200 mg clavulanate) IV every 6 to 8 hours.

If infection with methicillin-resistant *Staphylococcus aureus* (MRSA) was suspected or confirmed within the first 72 hours of enrollment, a glycopeptide antibiotic (either vancomycin 1000 mg IV every 12 hours or teicoplanin IV loading dose of 400 mg the first day followed by a maintenance dose of 200 mg daily) could have been added to the aminopenicillin/beta-lactamase inhibitor regimen. If culture results failed to show a resistant organism, use of the glycopeptide could be discontinued.

Efficacy, Outcome Research, and Safety Endpoints:

Primary Efficacy Endpoint: Clinical response in the CE population at the TOC assessment.

Secondary Efficacy Endpoints:

- Clinical response in the ME population.
- Microbiologic response (eradication, presumed eradication, persistence, presumed persistence, or indeterminate) at the subject level.
- Microbiologic response (eradication, presumed eradication, persistence, presumed persistence, or indeterminate) at the isolate level.
- Clinical response rates by baseline isolate.
- Response rates for subjects with polymicrobial infections and monomicrobial infections.
- Response rates by baseline isolate and minimum inhibitory concentration (MIC) values.
- Susceptibility data by isolate (the MIC_{50} and MIC_{90} values represent the minimum concentrations of antibiotic that inhibited the growth of 50% and 90% of the isolates, respectively).

A clinical response of cure, failure, or indeterminate was assessed by the Investigator with respect to the infection at the EOT and TOC visits for each subject.

Cure: A subject was considered to be a clinical cure if they had resolution of all clinical signs and symptoms of infection (healing of chronic underlying skin ulcer not required); or had improvement of signs or symptoms of the infection to such an extent that no further antibacterial therapy was necessary.

Failure: A subject was considered a clinical failure if they had a lack of response during treatment and required antibacterial therapy other than or in addition to test article (TA); had initial recovery from the infection followed by deterioration before the TOC assessment that required additional antibacterial therapy; required clinically unanticipated additional extirpative surgical intervention for the management of the infection; received nonroutine surgical treatment at the original infection site more than 48 hours after the first dose of TA because of failure to improve, clinical worsening, or discovery of a new purulent collection(s); died due to the infection >2 days after randomization; discontinued treatment or died due to a treatment-related adverse event (AE) (primary reason); or received >120% of the planned number of doses of TA. Subjects could be declared failures after receiving at least 4 doses (2 days) of tigecycline or 8 doses (2 days) of ampicillin-sulbactam or 6 doses (2 days) of amoxicillin-clavulanate. If a subject had a clinical response of failure while receiving TA, the clinical response of failure was carried forward through the TOC assessment (regardless of whether the subject was cured with other antibiotics).

Indeterminate: A subject was considered to have an indeterminate response if they were lost to follow-up; had no clinical response determined for the TOC assessment; died within

2 days after being randomly assigned to TA; or died due to non-infection-related reasons before the TOC assessment (as judged by the Investigator).

Microbiologic response (secondary efficacy endpoint) was defined at both the subject and isolate levels. The outcome of the microbiologic response at the subject level at the EOT and TOC visits was determined by combining the microbiologic responses at the isolate level for all baseline isolates identified from skin and blood cultures according to the following definitions:

- Eradication (documented or presumed): None of the baseline isolates were present in a repeat culture taken from the original site of infection (documented) or a clinical response of cure precluded the availability of a specimen for culture (presumed).

- Persistence (documented or presumed): Any baseline isolate was present in a repeat culture obtained from the original site of infection (documented) or culture data were not available for a subject with a clinical response of failure (presumed).

- Indeterminate: Subjects who died during therapy for non-infection-related reasons (as judged by the Investigator), died within 48 hours after being randomly assigned toTA, were lost to follow-up (ie, did not have an assigned clinical response), or had no baseline isolates.

A microbiologic response at the isolate level was programmatically determined at the EOT and TOC visits for those subjects who had an isolate(s) identified at baseline from either a skin or blood culture according to the following definitions:

- Eradication (documented or presumed): The baseline isolate was not present in the repeat culture taken from the original site of infection (documented) or a clinical response of cure precluded the availability of a specimen for culture (presumed).

- Persistence (documented or presumed): The baseline isolate was present in a repeat culture obtained from the original site of infection (documented) or culture data were not available for a subject with a clinical response of failure (presumed).

- Indeterminate: Subjects without a baseline isolate or who were lost to follow-up.

Gram-positive or gram-negative bacteria newly isolated at the TOC visit, or EOT visit if the subject did not progress to the TOC visit, were assessed according to the following definition: Superinfection required both that (1) a culture from the primary site of infection was positive with a new isolate that was not identified as a baseline isolate, and (2) the subject's clinical response was failure.

Health Outcome Assessments: Assessment of health resource utilization encompassed the period of hospitalization as well as post-hospital discharge outcomes up to the TOC visit. Health resource utilization assessment during the initial hospitalization phase included:

- Length of hospital stay; duration of IV antibiotic study drug; days in the intensive care unit (ICU; with date of admission to the ICU and transfer/discharge out of the

ICU, in relation to the start of study drug); incidence of drainage, debridement, or incision by day(s) of procedure (in relation to the start of study drug); any other major procedures in the operating room by day(s) of procedure in relation to the start of study drug administration.

- Use of concomitant antibiotics including the following information: proportion of subjects, specific concomitant antibiotic (IV or oral), duration (day of start and end of administration in relation to study drug during initial hospitalization).

- Discharge status: home to unassisted care, home health care, nursing home/extended care facility, outpatient IV treatment center, another acute care hospital, discharged dead.

Assessment of prestudy characteristics included admission status (from home [unassisted status], home health care, nursing home, outpatient IV treatment center, or another acute care facility).

Assessment of health resource utilization in the post-hospital discharge phase included postdischarge readmission to the hospital; postdischarge emergency room visit; postdischarge use of other medical services relating to the cSSSI; concomitant antibiotics.

Safety Evaluations: Safety assessments included a daily physical examination to assess signs and symptoms of infection; daily recording of temperature; recordings of vital sign measurements (heart rate and blood pressure) at baseline, Day 3, EOT visit, and TOC visit; and laboratory determinations, including hematology, coagulation, and blood chemistry evaluations, at baseline, Day 3, EOT visit, and TOC visit. Adverse events (AEs) were recorded throughout the study.

Statistical Methods:

Analysis Populations:

Intent-to-treat (ITT): The ITT population consisted of all subjects who were randomly assigned to TA.

Modified-ITT (mITT): The mITT population consisted of ITT subjects who received at least 1 dose of TA.

Clinical-mITT (c-mITT): All mITT subjects who had a cSSSI diagnosis were included in the c-mITT population.

Microbiologic-mITT (m-mITT): All c-mITT subjects who also had an organism isolated in their baseline culture from the infection site or blood were included in the m-mITT population.

CE Population: Subjects in the c-mITT population were considered CE if the following criteria were met: met all major inclusion/exclusion criteria, did not have *Pseudomonas aeruginosa* isolated at baseline as a sole isolate, received no more than 24 hours of prior

antibiotic therapy, received no more than 2 doses of potentially effective concomitant antibiotic treatment after the first dose of TA through the TOC assessment, met the criteria for either a clinical cure or a clinical failure, completed TOC assessment of cure or failure (but not indeterminate) in the 8-50 day window after last dose of TA or; in the case of a subject who discontinued prematurely due to lack of efficacy; had completed the EOT assessment such that an assessment of clinical response could be made, and met the criteria for a clinical failure.

ME Population: A subject was considered ME if the following criteria were met: subject was CE and had a baseline culture with at least 1 identified isolate, and at least 1 isolate was susceptible to both TA (ie, the isolate was susceptible to tigecycline and comparator).

The primary efficacy endpoint was the clinical response at the TOC assessment. Clinical response was analyzed as (1) cure or (2) failure. The primary analysis was applied to the CE population, which excluded subjects with a clinical response of indeterminate. The noninferiority of tigecycline compared with the comparator was evaluated for clinical and microbiologic response using a 2-sided 95% confidence interval (CI) for the true difference in efficacy (tigecycline minus comparator). The CI was corrected for continuity. Noninferiority was concluded if the lower limit of the 2-sided CI was greater than or equal to -15%.

Based on the strategy described for the primary endpoint, supplementary analyses were performed on the mITT, c-mITT, m-mITT, ME, and CE populations. Additional analysis of responses that were binary, other than efficacy endpoints, were analyzed by the Fisher exact test and used to compare proportions (eg, AEs). Responses that were quantitative were analyzed by analysis of covariance (ANCOVA) with the baseline measurement used as the covariate. Treatment group differences in the length of hospitalization and duration of IV antibiotic treatment were presented using analysis of variance (ANOVA); time to defervescence was presented using the log-ranked test.

RESULTS:

Subject Disposition and Demography: Subject disposition by treatment group is presented in Table 2.

A total of 550 subjects were randomly assigned to either of the treatment groups and comprised the ITT population. Nineteen subjects did not receive the study drug. A total of 531 subjects received at least 1 dose of study drug and constituted the mITT population: 268 subjects received tigecycline and 263 subjects received comparator. The CE population (n=405) which was the primary efficacy population consisted of 209 tigecycline-treated subjects and 196 comparator–treated subjects. The ME population (n=219) consisted of 120 subjects in the tigecycline treatment group and 99 subjects in the comparator treatment group.

Table 2. Number of Subjects Included in Each Population by Treatment Group

Population	Tigecycline 50 mg N (% ITT)	Comparator N (% ITT)	Total N (% ITT)
Intent-to-treat (ITT)	281	269	550
Modified intent-to-treat (mITT), n (%)	268 (95.4)	263 (97.8)	531 (96.5)
Clinical modified intent-to-treat (c-mITT), n (%)	268 (95.4)	263 (97.8)	531 (96.5)
Clinically evaluable (CE), n (%)	209 (74.4)	196 (72.9)	405 (73.6)
ITT subjects excluded from the CE population, n (% ITT)[a]	72 (25.6)	73 (27.1)	145 (26.4)
Inclusion/exclusion criteria not met	10 (3.6)	23 (8.6)	33 (6.0)
Insufficient treatment duration	12 (4.3)	14 (5.2)	26 (4.7)
No clinical evaluation at TOC	21 (7.5)	19 (7.1)	40 (7.3)
Overall non-compliance to study drug administration	1 (0.4)	1 (0.4)	2 (0.4)
P. aeruginosa sole isolate	2 (0.7)	2 (0.7)	4 (0.7)
TOC after last dose[b]	1 (0.4)	1 (0.4)	2 (0.4)
Use of prohibited / concomitant medication	23 (8.2)	16 (5.9)	39 (7.1)
ITT subjects excluded from the ME population, n (% ITT)[c]	161 (57.3)	170 (63.2)	331 (60.2)
No organism isolated at baseline	109 (38.8)	121 (45.0)	230 (41.8)
Resistant isolate(s)[d]	4 (1.4)	1 (0.4)	5 (0.9)
Microbiologic modified intent-to-treat (m-mITT), n (%)	159 (56.6)	142 (52.8)	301 (54.7)
Microbiologically evaluable (ME), n (%)	120 (42.7)	99 (36.8)	219 (39.8)

Subjects could have had more than 1 reason for exclusion.
Comparator: amoxicillin-clavulanate or ampicillin-sulbactam, with or without vancomycin.
CE = clinically evaluable; c-mITT = clinical modified intent-to-treat; mITT = modified intent-to-treat; ITT = intent-to-treat; n = number of intent-to-treat subjects in each population; N = total number of intent-to-treat subjects; TOC = test-of-cure.
a. Subjects could beexcluded from the CE population for more than 1 reason; did not include subjects previously excluded from the mITT and c-mITT populations.
b. Subject did not have TOC assessment within the 8 to 50 day window.
c. Did not include subjects previously excluded from the mITT, c-mITT, and CE populations.
d. Baseline isolate(s) resistant to either the study drug or both the study drug and the comparator.

Table 3 summarizes the reasons why subjects in the mITT population withdrew from the study. Forty-eight (9.0%) subjects withdrew from the study before the TOC assessment: 24 (9.0%) subjects in the tigecycline group and 24 (9.1%) subjects in the comparator group.

Table 3. Summary of Reasons for Subject Discontinuation, mITT Population

Discontinuation Status Reason	p-Value[a]	Tigecycline 50 mg N=268	Comparator N=263	Total N=531
Discontinued, n (%)	1.000	24 (9.0)	24 (9.1)	48 (9.0)
Lost to follow-up	0.859	16 (6.0)	17 (6.5)	33 (6.2)
Death	0.621	1 (0.4)	2 (0.8)	3 (0.6)
Consent withdrawn	0.752	6 (2.2)	4 (1.5)	10 (1.9)
Other event	1	1 (0.4)	1 (0.4)	2 (0.4)

"Discontinued" refers to the sum of the individual reasons because reasons for discontinuation were mutually exclusive.
Comparator: amoxicillin-clavulanate or ampicillin-sulbactam, with or without vancomycin.
mITT = modified intent-to-treat; n = number of mITT subjects; N = total number of mITT subjects.
a. p-value: calculated using the Fisher exact test (2-tail). Statistical significance at the 0.05 level.

A summary of reasons for subjects discontinuing the use of study drug in the study is presented in Table 4.

Table 4. Summary of Reasons for Discontinuation of Study Drug Administration, mITT Population

Discontinuation Status Reason	p-Value[a]	Tigecycline 50 mg N=268	Comparator N=263	Total N=531
Discontinued, n (%)	0.802	38 (14.2)	35 (13.3)	73 (13.7)
Adverse event	0.143	16 (6.0)	8 (3.0)	24 (4.5)
Study drug ineffective	0.722	3 (1.1)	4 (1.5)	7 (1.3)
Causative organism(s) was not susceptible to study drug	0.414	5 (1.9)	8 (3.0)	13 (2.4)
Consent withdrawn	1.000	5 (1.9)	4 (1.5)	9 (1.7)
Subject required non-permitted therapy/procedure	1.000	2 (0.7)	2 (0.8)	4 (0.8)
Other major protocol violation	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Other event	0.799	7 (2.6)	8 (3.0)	15 (2.8)

"Discontinued" refers to the sum of the individual reasons because reasons for discontinuation were mutually exclusive.
Comparator: amoxicillin-clavulanate or ampicillin-sulbactam, with or without vancomycin.
mITT = modified intent-to-treat; n = number of mITT subjects; N = total number of mITT subjects.
a. p-value: calculated using the Fisher exact test (2-tail). Statistical significance at the 0.05 level.

Demographic and other baseline characteristics of the mITT population are presented in Table 5.

Table 5. Demographic and Baseline Characteristics, mITT Population

Characteristic	p-Value[a]	Tigecycline 50 mg N=268	Comparator N=263	Total N=531
Age (years)	0.755[b]			
N		268	263	531
Mean		51.10	51.54	51.32
Standard Deviation		16.11	16.90	16.49
Minimum		18	18	18
Maximum		92	92	92
Median		50	52	51
Gender, n (%)	0.413[c]			
Male		163 (60.8)	169 (64.3)	332 (62.5)
Female		105 (39.2)	94 (35.7)	199 (37.5)
Ethnic origin, n (%)	0.952[c]			
White		141 (52.6)	146 (55.5)	287 (54.0)
Black		44 (16.4)	40 (15.2)	84 (15.8)
Asian		60 (22.4)	58 (22.1)	118 (22.2)
Hispanic		15 (5.6)	13 (4.9)	28 (5.3)
Other		8 (3.0)	6 (2.3)	14 (2.6)
Prior antibiotic failure, n (%)	0.592[c]			
Yes		55 (20.5)	59 (22.4)	114 (21.5)
No		213 (79.5)	204 (77.6)	417 (78.5)
Clinical diagnosis of infection, n (%)	0.374[c]			
Burns		3 (1.1)	1 (0.4)	4 (0.8)
Deep soft tissue infection		186 (69.4)	176 (66.9)	362 (68.2)
Cellulitis		168 (62.7)	166 (63.1)	334 (62.9)
Wound infection		8 (3.0)	6 (2.3)	14 (2.6)
IV catheter infection		2 (0.7)	0 (0.0)	2 (0.4)
Human/animal bites		8 (3.0)	4 (1.5)	12 (2.3)
Infected ulcers		31 (11.6)	26 (9.9)	57 (10.7)
Major abscess		47 (17.5)	60 (22.8)	107 (20.2)
Other		1 (0.4)	0 (0.0)	1 (0.2)

Comparator: amoxicillin-clavulanate or ampicillin-sulbactam, with or without vancomycin.
Prior antibiotic failure: Subjects who received prior antibiotics for ≥3 days prior to first dose of study drug with no improvement in signs/symptoms of infection.
IV = intravenous; mITT = modified intent-to-treat; n = number of mITT subjects with data; N = total number of mITT subjects.
a. Statistical significance at the 0.05 level.
b. p-value: calculated using 1-way analysis of variance with treatment as factor.
c. p-value: calculated using chi-square statistic.

Efficacy Results:

Primary Endpoint Result: The summary of clinical response in the CE population at the TOC assessment is presented in Table 6. The limit difference, or delta, for the true cure rates of the 2 treatments was set at 15% (that is, the lower bound of the 2-sided 95% CI for the difference in cure proportion had to be no lower than -15% to support the conclusion that antibiotic monotherapy with tigecycline was non-inferior to therapy with comparator).

In the analysis of clinical response, tigecycline met the statistical criteria of noninferiority to comparator at the TOC assessment (the primary endpoint) and at the EOT assessment in the CE population. For the CE population, the lower bound of the CI was -8.7% at the TOC assessment and -6.1% at the EOT assessment (the adjusted upper bounds were 8.6% and 9.1%, respectively).

Table 6. Clinical Response (Rate of Success), CE Population

Visit	Tigecycline 50 mg		Comparator		Difference (Tigecycline-Comparator)		
	n/N	% (95% CI)[a]	n/N	% (95% CI)[a]	% (95% CI)	p-Value[b]	p-Value[c]
EOT	178/209	85.2 (79.6, 89.7)	164/196	83.7 (77.7, 88.6)	1.5 (-6.1, 9.1)[d]	0.000[d]	0.782[d]
TOC	162/209	77.5 (71.2, 83.0)	152/196	77.6 (71.1, 83.2)	0.0 (-8.7, 8.6)[d]	0.000[d]	1.000[d]

Comparator: consisted of amoxicillin-clavulanate or ampicillin-sulbactam with or without adjuvant therapy vancomycin.
% = percentage of CE subjects; CE = clinically evaluable; CI = confidence interval; EOT = end-of-treatment; n = number of CE subjects with a 'success' (cure); N = total number of CE subjects; TOC = test-of-cure.
a. Within treatment CI: exact 95% CI calculated for a single binomial proportion.
b. One-sided p-value: test for non-inferiority.
c. Two-sided p-value: test for superiority.
d. Between treatment CI: calculated using asymptotic method corrected for continuity.

Secondary Endpoints Results:

Clinical Response in the ME Population: Table 7 compares cure and failure rates at the EOT and TOC assessments for the ME population.

In the analysis of clinical response, tigecycline met the statistical criteria of noninferiority to comparator at the TOC assessment and EOT assessment in the ME population. For the ME population, the adjusted lower bound of the CI was -9.6% at the TOC assessment and -4.9% at the EOT assessment (the adjusted upper bounds were 14.0% and 16.2%, respectively).

Table 7. Clinical Response (Rate of Success), ME Population

Visit	Tigecycline 50 mg		Comparator		Difference (Tigecycline-Comparator)		
	n/N	% (95% CI)[a]	n/N	% (95% CI)[a]	% (95% CI)	p-Value[b]	p-Value[c]
EOT	105/120	87.5 (80.2, 92.8)	81/ 99	81.8 (72.8, 88.9)	5.7 (-4.9, 16.2)[d]	0.000[d]	0.333[d]
TOC	96/120	80.0 (71.7, 86.7)	77/ 99	77.8 (68.3, 85.5)	2.2 (-9.6, 14.0)[d]	0.002[d]	0.815[d]

Comparator: consisted of amoxicillin-clavulanate or ampicillin-sulbactam with or without adjuvant therapy vancomycin.
% = percentage of ME subjects; CI = confidence interval; EOT = end-of-treatment; ME = microbiologically evaluable; n = number of ME subjects with a 'success' (cure); N = total number of ME subjects; TOC = test-of-cure.
a. Within treatment CI: exact 95% CI calculated for a single binomial proportion.
b. One-sided p-value: test for non-inferiority.
c. Two-sided p-value: test for superiority.
d. Between treatment CI: calculated using asymptotic method corrected for continuity.

Microbiologic Response at the Subject Level: Table 8 presents the responses in the ME and m-mITT population at the EOT and TOC assessments. Within both the ME and m-mITT populations, tigecycline met the statistical criteria for noninferiority compared with comparator for microbiologic responses at the subject level. Within the ME population, infections were eradicated in 79.2% of tigecycline-treated subjects and 76.8% of comparator-treated subjects at the TOC assessment. The difference in eradication rates was 2.4% (95% CI, -9.6, 14.4). Within the m-mITT population, infections were eradicated in 72.3% of tigecycline-treated subjects and 66.2 % of comparator-treated subjects at the TOC assessment. The adjusted difference in eradication rates was 6.1% (95% CI, -5.0, 17.2).

No significant differences in the development of superinfection were observed between treatment groups within the ME and m-mITT populations. Two subjects in the tigecycline treatment group and 1 subject in the comparator treatment group in the ME population had

superinfections. Two subjects in each treatment group developed a superinfection in the m-mITT population.

Table 8. Microbiologic Response (Eradication Rate at the Subject Level)

		Tigecycline 50 mg		Comparator		Difference (Tigecycline-Comparator)		
	Visit Response	n/N	% (95% CI)[a]	n/N	% (95% CI)[a]	% (95% CI)	p-Value[b]	p-Value[c]
ME Population								
EOT	Eradication	99/120	82.5 (74.5, 88.8)	77/ 99	77.8 (68.3, 85.5)	4.7 (-6.8, 16.3)[d]	0.000[d]	0.484[d]
	Documented	0/120	0	4/99	4.0 (1.1, 10.0)	-4.0 (-8.8, 0.8)[d]		
	Presumed	99/120	82.5 (74.5, 88.8)	73/99	73.7 (63.9, 82.1)	8.8 (-3.2, 20.7)[d]		
	Persistence	21/120	17.5 (11.2, 25.5)	22/99	22.2 (14.5, 31.7)	-4.7 (-16.3, 6.8)[d]		
	Documented	9/120	7.5 (3.5, 13.8)	6/99	6.1 (2.3, 12.7)	1.4 (-6.1, 9.0)[d]		
	Presumed	12/120	10.0 (5.3, 16.8)	16/99	16.2 (9.5, 24.9)	-6.2 (-16.1, 3.8)[d]		
	Superinfection	1/120	0.8 (0.0, 4.6)	1/99	1.0 (0.0, 5.5)	-0.2 (-3.7, 3.3)[d]		
	Indeterminate	0/ 0	0	0/0	0			
TOC	Eradication	95/120	79.2 (70.8, 86.0)	76/99	76.8 (67.2, 84.7)	2.4 (-9.6, 14.4)[d]	0.002[d]	0.793[d]
	Documented	3/120	2.5 (0.5, 7.1)	2/99	2.0 (0.2, 7.1)	0.5 (-4.4, 5.3)[d]		
	Presumed	92/120	76.7 (68.1, 83.9)	74/99	74.7 (65.0, 82.9)	1.9 (-10.4, 14.3)[d]		
	Persistence	25/120	20.8 (14.0, 29.2)	23/99	23.2 (15.3, 32.8)	-2.4 (-14.4, 9.6)[d]		
	Documented	7/120	5.8 (2.4, 11.6)	3/99	3.0 (0.6, 8.6)	2.8 (-3.5, 9.1)[d]		
	Presumed	18/120	15.0 (9.1, 22.7)	20/99	20.2 (12.8, 29.5)	-5.2 (-16.3, 5.9)[d]		
	Superinfection	2/120	1.7 (0.2, 5.9)	1/99	1.0 (0.0, 5.5)	0.7 (-3.3, 4.6)[d]		
	Indeterminate	0/0	0	0/0	0			
m-mITT Population								
EOT	Eradication	123/159	77.4 (70.1, 83.6)	100/142	70.4 (62.2, 77.8)	6.9 (-3.7, 17.5)[d]	0.000[d]	0.216[d]
	Documented	0/159	0	5/142	3.5 (1.2, 8.0)	-3.5 (-7.2, 0.2)[d]		
	Presumed	123/159	77.4 (70.1, 83.6)	95/142	66.9 (58.5, 74.6)	10.5 (-0.3, 21.2)[d]		
	Persistence	31/159	19.5 (13.6, 26.5)	35/142	24.6 (17.8, 32.6)	-5.2 (-15.2, 4.9)[d]		
	Documented	13/159	8.2 (4.4, 13.6)	6/142	4.2 (1.6, 9.0)	4.0 (-2.1, 10.0)[d]		
	Presumed	18/159	11.3 (6.8, 17.3)	29/142	20.4 (14.1, 28.0)	-9.1 (-18.0, -0.2)[d]		
	Superinfection	1/159	0.6 (0.0, 3.5)	1/142	0.7 (0.0, 3.9)	-0.1 (-2.6, 2.4)[d]		
	Indeterminate	5/159	3.1 (1.0, 7.2)	7/142	4.9 (2.0, 9.9)	-1.8 (-6.9, 3.4)[d]		
TOC	Eradication	115/159	72.3 (64.7, 79.1)	94/142	66.2 (57.8, 73.9)	6.1 (-5.0, 17.2)[d]	0.000[d]	0.305[d]
	Documented	3/159	1.9 (0.4, 5.4)	4/142	2.8 (0.8, 7.1)	-0.9 (-5.0, 3.2)[d]		
	Presumed	112/159	70.4 (62.7, 77.4)	90/142	63.4 (54.9, 71.3)	7.1 (-4.2, 18.4)[d]		
	Persistence	32/159	20.1 (14.2, 27.2)	36/142	25.4 (18.4, 33.3)	-5.2 (-15.4, 4.9)[d]		
	Documented	8/159	5.0 (2.2, 9.7)	3/142	2.1 (0.4, 6.0)	2.9 (-1.9, 7.7)[d]		
	Presumed	24/159	15.1 (9.9, 21.6)	33/142	23.2 (16.6, 31.1)	-8.1 (-17.7, 1.4)[d]		
	Superinfection	2/159	1.3 (0.2, 4.5)	2/142	1.4 (0.2, 5.0)	-0.2 (-3.4, 3.1)[d]		
	Indeterminate	12/159	7.5 (4.0, 12.8)	12/142	8.5 (4.4, 14.3)	-0.9 (-7.7, 5.9)[d]		

Table 8. Microbiologic Response (Eradication Rate at the Subject Level)

Comparator: consisted of amoxicillin-clavulanate or ampicillin-sulbactam with or without adjuvant therapy vancomycin.
% = percentage of ME subjects; CI = confidence interval; EOT = end-of-treatment; ME = microbiologically evaluable; m-mITT = microbiologically modified intent-to-treat; n = number of subjects in each response category; N = total number of subjects; TOC = test-of-cure.

a. Within treatment CI: exact 95% CI calculated for a single binomial proportion.
b. One-sided p-value: test for non-inferiority.
c. Two-sided p-value: test for superiority.
d. Between treatment CI: calculated using asymptotic method corrected for continuity.

Microbiologic Response at the Isolate Level: The eradication rates of the baseline isolates at the TOC assessment in tigecycline-treated subjects were similar to those observed in subjects treated with comparator. In the ME population, *S. aureus* was eradicated in 74.6% (53/71) of tigecycline-treated subjects and 77.0% (47/61) of comparator-treated subjects. Similar results were seen in the m-mITT population with eradication rates of 70.8% and 65.5% for tigecycline- and comparator-treated subjects, respectively. All other baseline isolates were reported for a small minority (<10%) of subjects overall.

Clinical Response Rates by Baseline Isolate: The clinical response rates of subjects with baseline isolates in the tigecycline treatment group were similar to those observed in the comparator treatment group. In the ME population, subjects with baseline *S. aureus* were cured at the TOC assessment in 76.1% (54/71) of tigecycline-treated subjects and 80.3% (49/61) of comparator-treated subjects. In the m-mITT population, 71.9% and 66.7% of tigecycline- and comparator-treated subjects, respectively, were cured at the TOC assessment.

In the ME population clinical cure rates were higher in subjects with baseline methicillin-susceptible *S. aureus* (MSSA) compared to subjects with MRSA. For subjects with baseline MSSA, 82.9% of tigecycline-treated subjects were cured compared with 87.5% of comparator-treated subjects. For subjects with baseline MRSA, 69.4% of tigecycline-treated subjects were cured compared with 72.4% of comparator-treated subjects. In the m-mITT population, 76.1% and 73.8% of tigecycline- and comparator-treated subjects with MSSA, respectively, were cured at the TOC assessment while 67.4% and 60.0% of tigecycline-and comparator-treated subjects with MRSA were cured at the TOC assessment.

In the ME population, 69.4% (25/36) of tigecycline-treated subjects with MRSA at baseline were cured at the TOC assessment compared to 75% (18/24) of comparator-treated subjects who also received vancomycin. Three of 5 subjects (60%) in the comparator arm who did not receive adjuvant therapy for MRSA infection were cured at the TOC assessment. In the m-mITT population, 67.4% (29/43) of tigecycline-treated subjects with MRSA at baseline were cured at the TOC assessment compared to 61.5% (24/39) comparator-treated subjects who also received vancomycin. Three of 6 subjects (50%) in the comparator arm who did not receive adjuvant therapy for MRSA infection were cured at the TOC assessment.

Response Rates for Subjects With Polymicrobial and Monomicrobial Infections: Table 9 presents clinical cure and failure rates at the EOT and TOC assessments for subjects having either monomicrobial or polymicrobial infections in the ME and m-mITT populations.

Table 9. Clinical Response (Rate of Success) by Monomicrobial/Polymicrobial Infection

			Tigecycline 50 mg		Comparator		Difference (Tigecycline-Comparator)
Visit	**Infection Type**	**Response**	**n/N**	**% (95% CI)[a]**	**n/N**	**% (95% CI)[a]**	**% (95% CI)**
ME Population							
EOT	Monomicrobial	Success	60/66	90.9 (81.3, 96.6)	45/58	77.6 (64.7, 87.5)	13.3 (-1.1, 27.7)[b]
		Failure	6/66	9.1 (3.4, 18.7)	13/58	22.4 (12.5, 35.3)	
	Polymicrobial	Success	45/54	83.3 (70.7, 92.1)	36/41	87.8 (73.8, 95.9)	-4.5 (-20.7, 11.8)[b]
		Failure	9/54	16.7 (7.9, 29.3)	5/41	12.2 (4.1, 26.2)	
	Overall						adjusted difference[c] =5.9 (-4.0, 15.9)
TOC	Monomicrobial	Success	57/66	86.4 (75.7, 93.6)	42/58	72.4 (59.1, 83.3)	13.9 (-1.8, 29.7)[b]
		Failure	9/66	13.6 (6.4, 24.3)	16/58	27.6 (16.7, 40.9)	
	Polymicrobial	Success	39/54	72.2 (58.4, 83.5)	35/41	85.4 (70.8, 94.4)	-13.1 (-31.4, 5.1)[b]
		Failure	15/54	27.8 (16.5, 41.6)	6/41	14.6 (5.6, 29.2)	
	Overall						adjusted difference[c] =2.9 (-8.3, 14.1)
m-mITT Population							
EOT	Monomicrobial	Success	73/85	85.9 (76.6, 92.5)	62/86	72.1 (61.4, 81.2)	13.8 (0.6, 27.0)[b]
		Failure	12/85	14.1 (7.5, 23.4)	24/86	27.9 (18.8, 38.6)	
	Polymicrobial	Success	59/74	79.7 (68.8, 88.2)	42/56	75.0 (61.6, 85.6)	4.7 (-11.4, 20.9)[b]
		Failure	15/74	20.3 (11.8, 31.2)	14/56	25.0 (14.4, 38.4)	
	Overall						adjusted difference[c] =10.2 (0.8, 19.5)
TOC	Monomicrobial	Success	67/85	78.8 (68.6, 86.9)	54/86	62.8 (51.7, 73.0)	16.0 (1.5, 30.6)[b]
		Failure	18/85	21.2 (13.1, 31.4)	32/86	37.2 (27.0, 48.3)	
	Polymicrobial	Success	49/74	66.2 (54.3, 76.8)	40/56	71.4 (57.8, 82.7)	-5.2 (-22.8, 12.4)[b]
		Failure	25/74	33.8 (23.2, 45.7)	16/56	28.6 (17.3, 42.2)	
	Overall						adjusted difference[c] =7.3 (-3.2, 17.8)

Comparator: consisted of amoxicillin-clavulanate or ampicillin-sulbactam with or without adjuvant therapy vancomycin.
% = percentage of ME/m-mITT subjects; CI = confidence interval; EOT = end-of-treatment; ME = microbiologically evaluable; m-mITT = microbiologically modified intent-to-treat; n = number of subjects in each response category; N = total number of subjects; TOC = test-of-cure.

a. Within treatment CI: exact 95% CI calculated for a single binomial proportion.
b. Between treatment CI: calculated using asymptotic method corrected for continuity.
c. Difference between treatments: adjusted difference and 95% CI calculated using a generalized linear model with binomial probability function and identity link.

Table 10 presents the microbiologic responses at the subject level for ME and m-mITT subjects who had monomicrobial or polymicrobial infections.

Table 10. Microbiologic Response at Subject Level by Monomicrobial/Polymicrobial Infection

			Tigecycline 50 mg		Comparator		Difference (Tigecycline-Comparator)
Visit	**Infection Type**	**Response**	**n/N**	**% (95% CI)[a]**	**n/N**	**% (95% CI)**	**% (95% CI)**
ME Population							
EOT	Monomicrobial	Eradication	57/66	86.4 (75.7, 93.6)	45/58	77.6 (64.7, 87.5)	8.8 (-6.4, 24.0)[b]
		Persistence	9/66	13.6 (6.4, 24.3)	13/58	22.4 (12.5, 35.3)	
		Superinfection	0/66	0	1/58	1.7 (0.0, 9.2)	
		Indeterminate	0/66	0	0/58	0	
	Polymicrobial	Eradication	42/54	77.8 (64.4, 88.0)	32/41	78.0 (62.4, 89.4)	-0.3 (-19.3, 18.7)[b]
		Persistence	12/54	22.2 (12.0, 35.6)	9/41	22.0 (10.6, 37.6)	
		Superinfection	1/54	1.9 (0.0, 9.9)	0/41	0	
		Indeterminate	0/54	0	0/41	0	
	Overall						adjusted difference[c] =5.3 (-5.3, 15.9)
TOC	Monomicrobial	Eradication	57/66	86.4 (75.7, 93.6)	43/58	74.1 (61.0, 84.7)	12.2 (-3.4, 27.8)[b]
		Persistence	9/66	13.6 (6.4, 24.3)	15/58	25.9 (15.3, 39.0)	
		Superinfection	1/66	1.5 (0.0, 8.2)	1/58	1.7 (0.0, 9.2)	
		Indeterminate	0/66	0	0/58	0	
	Polymicrobial	Eradication	38/54	70.4 (56.4, 82.0)	33/41	80.5 (65.1, 91.2)	-10.1 (-29.5, 9.2)[b]
		Persistence	16/54	29.6 (18.0, 43.6)	8/41	19.5 (8.8, 34.9)	
		Superinfection	1/54	1.9 (0.0, 9.9)	0/41	0	
		Indeterminate	0/54	0	0/41	0	
	Overall						adjusted difference[c] =3.8 (-7.4, 14.9)
m-mITT Population							
EOT	Monomicrobial	Eradication	70/85	82.4 (72.6, 89.8)	62/86	72.1 (61.4, 81.2)	10.3 (-3.4, 23.9)[b]
		Persistence	13/85	15.3 (8.4, 24.7)	20/86	23.3 (14.8, 33.6)	
		Superinfection	0/85	0	1/86	1.2 (0.0, 6.3)	
		Indeterminate	2/85	2.4 (0.3, 8.2)	4/86	4.7 (1.3, 11.5)	
	Polymicrobial	Eradication	53/74	71.6 (59.9, 81.5)	38/56	67.9 (54.0, 79.7)	3.8 (-13.8, 21.3)[b]
		Persistence	18/74	24.3 (15.1, 35.7)	15/56	26.8 (15.8, 40.3)	
		Superinfection	1/74	1.4 (0.0, 7.3)	0/56	0	
		Indeterminate	3/74	4.1 (0.8, 11.4)	3/56	5.4 (1.1, 14.9)	
	Overall						adjusted difference[c] =7.8 (-2.1, 17.7)
TOC	Monomicrobial	Eradication	67/85	78.8 (68.6, 86.9)	56/86	65.1 (54.1, 75.1)	13.7 (-0.8, 28.2)[b]
		Persistence	13/85	15.3 (8.4, 24.7)	22/86	25.6 (16.8, 36.1)	
		Superinfection	1/85	1.2 (0.0, 6.4)	2/86	2.3 (0.3, 8.1)	
		Indeterminate	5/85	5.9 (1.9, 13.2)	8/86	9.3 (4.1, 17.5)	
	Polymicrobial	Eradication	48/74	64.9 (52.9, 75.6)	38/56	67.9 (54.0, 79.7)	-3.0 (-20.9, 14.9)[b]
		Persistence	19/74	25.7 (16.2, 37.2)	14/56	25.0 (14.4, 38.4)	
		Superinfection	1/74	1.4 (0.0, 7.3)	0/56	0	
		Indeterminate	7/74	9.5 (3.9, 18.5)	4/56	7.1 (2.0, 17.3)	
	Overall						adjusted difference[c] =7.1 (-3.4, 17.5)

Table 10. Microbiologic Response at Subject Level by Monomicrobial/Polymicrobial Infection

Comparator: consisted of amoxicillin-clavulanate or ampicillin-sulbactam with or without adjuvant therapy vancomycin.
% = percentage of ME/m-mITT subjects; CI = confidence interval; EOT = end-of-treatment; ME = microbiologically evaluable; m-mITT = microbiologically modified intent-to-treat; n = number of subjects in each response category; N = total number of subjects; TOC = test-of-cure.

a. Within treatment CI: exact 95% CI calculated for a single binomial proportion.
b. Between treatment CI: calculated using asymptotic method corrected for continuity.
c. Difference between treatments: adjusted difference and 95% CI calculated using a generalized linear model with binomial probability function and identity link.

Response Rates by Baseline Isolate and MIC Values: In the ME population, 32 subjects received adjuvant therapy for treatment of a *S. aureus* infection and 26 of 32 subjects (81.3%) were cured at the TOC assessment. The single subject with a *S. aureus* infection and a vancomycin MIC of 2 µg/mL was cured, as were 25 of 31 (80.6%) subjects with a vancomycin MIC of 1 µg/mL.

In the m-mITT population, 50 subjects received adjuvant therapy for treatment of a *S. aureus* infection and 32 of 50 subjects (64.0%) were cured at the TOC assessment. The single subject with a *S. aureus* infection and a vancomycin MIC of 2 µg/mL was cured, as were 31 of 49 (63.3%) subjects with a vancomycin MIC of 1 µg/mL.

Susceptibility Data by Isolate: Table 11 summarizes the MIC_{50} and MIC_{90} values of tigecycline and comparator against selected baseline isolates in the ME and m-mITT population.

Table 11. Summary of MIC_{50} and MIC_{90} Data By Baseline Isolate

	Tigecycline			Amoxicillin/Clavulanate_			Vancomycin		
Baseline Isolate	**n**	**MIC_{50}**	**MIC_{90}**	**n**	**MIC_{50}**	**MIC_{90}**	**n**	**MIC_{50}**	**MIC_{90}**
ME Population									
Enterococcus faecalis	12	0.12	0.25	12	1.00	1.00	12	1.00	4.00
Escherichia coli	21	0.25	0.50	21	8.00	16.00	-	-	-
Klebsiella pneumoniae	11	0.50	2.00	11	2.00	8.00	-	-	-
Staphylococcus aureus	132	0.12	0.25	132	2.00	8.00	132	1.00	1.00
Staphylococcus epidermidis	15	0.12	0.25	15	0.50	4.00	15	2.00	2.00
Streptococcus agalactiae	15	0.06	0.06	15	0.12	0.12	15	0.50	1.00
Streptococcus pyogenes	16	0.03	0.06	16	0.06	0.06	16	0.50	0.50
m-mITT Population									
Enterobacter cloacae	14	0.50	1.00	14	64.00	64.00	-	-	-
Enterococcus faecalis	20	0.12	0.25	20	1.00	1.00	20	1.00	4.00
Escherichia coli	29	0.25	0.50	29	8.00	32.00	-	-	-
Klebsiella pneumoniae	13	0.50	2.00	13	2.00	8.00	-	-	-
Proteus mirabilis	11	2.00	2.00	11	1.00	8.00	-	-	-
Pseudomonas aeruginosa	18	8.00	16.00	18	64.00	64.00	-	-	-
Staphylococcus aureus	176	0.12	0.25	176	2.00	8.00	176	1.00	1.00
Staphylococcus epidermidis	23	0.25	0.25	23	1.00	4.00	23	2.00	2.00
Staphylococcus hominis	10	0.06	0.12	10	0.50	4.00	10	1.00	1.00
Streptococcus agalactiae	18	0.03	0.06	18	0.12	0.12	18	0.50	1.00
Streptococcus anginosus	10	0.03	0.06	10	0.06	0.25	10	1.00	1.00
Streptococcus pyogenes	18	0.03	0.06	18	0.06	0.06	18	0.50	0.50

Values above or below the limit of quantification were imputed prior to calculating summary statistics.
ME = microbiologically evaluable; MIC = minimum inhibitory concentration (mcg/ml); MIC_{50} = concentration of antibiotic that inhibits the growth of 50% of the isolates; MIC_{90} = concentration of antibiotic that inhibits the growth of 90% of the isolates; m-mITT = microbiologically modified intent-to-treat; n = number of baseline isolates.

Results of Health Outcome Assessments: Table 12 presents the findings on inpatient components of health care resource utilization.

Table 12. Inpatient Health Care Resource Utilization, mITT Population

Health Outcomes Variables	p-Value[a]	Tigecycline 50 mg N=268	Comparator N=263	Total N=531
Days of overall inpatient hospitalization, mean	0.771[b]	9.41	9.24	9.32
Days of primary inpatient hospitalization, mean	0.650[b]	8.54	8.78	8.66
Proportion of subjects with ICU visit, n (%)	0.444[b]	6 (2.2)	9 (3.4)	-
Days of ICU treatment, mean	0.265[b]	9.17	5.22	6.80
Proportion of subjects with inpatient hospitalization, non-ICU, n (%)	-	268 (100)	263 (100)	-
Days of inpatient hospitalization, non-ICU, mean	0.663[b]	9.35	9.09	9.22
Time to defervescence, median days	0.134[c]	2.0	2.5	-
Proportion of subjects provided concomitant antibiotics, n (%)	0.275[d]	63 (23.5)	73 (27.8)	136 (25.6)
Proportion of subjects provided medication for treatment or prevention of nausea/vomiting, n (%)	<0.001[d]	98 (36.6)	42 (16.0)	140 (26.4)

Only median available for "time to defervescense" variable (log rank test used).
Comparator: amoxicillin-clavulanate or ampicillin-sulbactam, with or without vancomycin.
ANOVA = analysis of variance; ICU = intensive care unit; mITT = modified intent-to-treat; n = number of mITT subjects with data; N = total number of mITT subjects.
a. Statistical significance at the 0.05 level.
b. p-value: calculated using 1-way ANOVA with treatment as factor.
c. p-value: calculated using log-rank test.
d. p-value: calculated using Fisher exact test (2-tail).

Table 13 summarizes outpatient health care resource utilization and hospital readmission requirements by treatment group.

Table 13. Outpatient Health Care Resource Utilization, mITT Population

Health Outcomes Variables	p-Value[a]	Tigecycline 50 mg N=268	Comparator N=263	Total N=531
Proportion of subjects requiring home health care services, n (%)	0.268[b]	55 (20.5)	44 (16.7)	-
Days of home healthcare services, mean	0.157[b]	10.18	7.32	8.91
Proportion of subjects admitted to a nursing home/extended care facility, n (%)	0.599[b]	6 (2.2)	8 (3.0)	-
Days of nursing home/extended care facility, mean	0.809[b]	12.83	12.00	12.36
Proportion of subjects requiring re-admission to hospital, n (%)	0.645[b]	25 (9.3)	21 (8.0)	-
Proportion of subjects requiring re-admission to ICU, n (%)	1.000[b]	2 (0.7)	1 (0.4)	-
Proportion of subjects requiring re-admission to hospital, non-ICU, n (%)	0.307[b]	22 (8.2)	15 (5.7)	-
Proportion of subjects requiring other services, n (%)	0.856[b]	17 (6.3)	15 (5.7)	-
Days of other, mean	0.866[b]	3.09	2.79	2.92
Proportion of subjects in outpatient IV treatment center, n (%)	0.376[b]	20 (7.5)	14 (5.3)	-
Days of outpatient IV treatment center, mean	0.562[b]	4.25	3.71	4.03
Proportion of subjects with post-discharge emergency room visit	0.335[b]	3 (1.1)	6 (2.3)	-
Days of post-discharge emergency room visit, mean	0.170[b]	2.00	1.00	1.33

Comparator: amoxicillin-clavulanate or ampicillin-sulbactam, with or without vancomycin.
ANOVA = analysis of variance; ICU = intensive care unit; IV = intravenous; mITT = modified intent-to-treat; n = number of mITT subjects with data; N = total number of mITT subjects.
a. Statistical significance at the 0.05 level.
b. p-value: calculated using Fisher exact test (2-tail).

Safety Results:

Treatment-Emergent AEs (TEAEs, All Causality): The most common TEAEs (incidence ≥3% of the subjects in any treatment group) are summarized in Table 14.

The percentage of subjects reporting TEAEs in the tigecycline treatment arm (201/268, 75.0%) was significantly higher than that reported in the comparator treatment arm (169/263, 64.3%; p-value = 0.008). The digestive system was the most common system organ class for subjects reporting TEAEs. Tigecycline was significantly associated with TEAEs of the digestive system. The TEAE of hypokalemia was reported more frequently in subjects receiving comparator than subjects who received tigecycline. The TEAE of infection was not statistically greater in the tigecycline treatment group than in the comparator group (2.6% [7/268] versus 0.4% [1/263]; p-value = 0.068).

Table 14. Number (%) of Subjects Reporting ≥3% Treatment-Emergent Adverse Events in Either Treatment Group, mITT Population

Body System[a] Adverse Event	p-Value[b]	Tigecycline 50 mg N=268	Comparator N=263	Total N=531
Digestive system, n (%)	<0.001[b]	157 (58.6)	82 (31.2)	239 (45.0)
Nausea	<0.001[b]	117 (43.7)	44 (16.7)	161 (30.3)
Vomiting	<0.001[b]	64 (23.9)	14 (5.3)	78 (14.7)
Diarrhea	<0.001[b]	39 (14.6)	14 (5.3)	53 (10.0)
Constipation	0.408	17 (6.3)	22 (8.4)	39 (7.3)
Dyspepsia	0.058	17 (6.3)	7 (2.7)	24 (4.5)
Body as a whole, n (%)	0.924	78 (29.1)	78 (29.7)	156 (29.4)
Headache	0.749	20 (7.5)	22 (8.4)	42 (7.9)
Pain	0.593	15 (5.6)	18 (6.8)	33 (6.2)
Abdominal pain	0.058	17 (6.3)	7 (2.7)	24 (4.5)
Fever	0.602	9 (3.4)	6 (2.3)	15 (2.8)
Chest pain	0.599	6 (2.2)	8 (3.0)	14 (2.6)
Nervous system, n (%)	0.108	53 (19.8)	38 (14.4)	91 (17.1)
Insomnia	0.507	22 (8.2)	17 (6.5)	39 (7.3)
Anxiety	0.801	9 (3.4)	7 (2.7)	16 (3.0)
Dizziness	0.602	9 (3.4)	6 (2.3)	15 (2.8)
Metabolic and nutritional, n (%)	0.907	44 (16.4)	42 (16.0)	86 (16.2)
Hypokalemia	0.019[b]	6 (2.2)	17 (6.5)	23 (4.3)
Skin and appendages, n (%)	0.627	42 (15.7)	37 (14.1)	79 (14.9)
Pruritus	0.855	15 (5.6)	16 (6.1)	31 (5.8)
Cardiovascular system, n (%)	1.000	28 (10.4)	27 (10.3)	55 (10.4)
Hypertension	0.810	8 (3.0)	9 (3.4)	17 (3.2)
Hemic and lymphatic system, n (%)	0.727	19 (7.1)	16 (6.1)	35 (6.6)
Anemia	1.000	8 (3.0)	7 (2.7)	15 (2.8)

Adverse events and serious adverse events are not separated out.
p-value: calculated using the Fisher exact test (2-tail).
Comparator: amoxicillin-clavulanate or ampicillin-sulbactam, with or without vancomycin.
Treatment-emergent adverse event (TEAE): Defined as all adverse events starting at or after the first administration of test article until last administration of test article +15 days, or if started prior to first administration of test article worsened after first intake.
mITT = modified intent-to-treat; n = number of mITT subjects; N = total number of mITT subjects.
a. Subjects might have reported more than 1 adverse event in the same body system.
b. Statistical significance at the 0.05 level.

Treatment-Related TEAEs: Table 15 summarizes TEAEs that were considered to be drug related.

Table 15. Number (%) of Subjects Reporting Treatment-Related Treatment-Emergent Adverse Events, mITT Population

Body System[a] Adverse Event	p-Value[b]	Tigecycline 50 mg N=268 N (M)=163 N (F)=105	Comparator N=263 N (M)=169 N (F)=94	Total N=531 N (M)=332 N (F)=199
Any adverse event	0.000[b]	116 (43.3)	56 (21.3)	172 (32.4)
Digestive system	0.000[b]	104 (38.8)	33 (12.5)	137 (25.8)
Nausea	0.000[b]	87 (32.5)	23 (8.7)	110 (20.7)
Vomiting	0.000[b]	43 (16.0)	6 (2.3)	49 (9.2)
Diarrhea	0.001[b]	30 (11.2)	9 (3.4)	39 (7.3)
Liver function tests abnormal	0.286	6 (2.2)	2 (0.8)	8 (1.5)
Dyspepsia	0.061	5 (1.9)	0 (0.0)	5 (0.9)
Anorexia	0.624	3 (1.1)	1 (0.4)	4 (0.8)
Constipation	0.621	1 (0.4)	2 (0.8)	3 (0.6)
Gastroesophageal reflux disease	0.249	3 (1.1)	0 (0.0)	3 (0.6)
Oral moniliasis	1.000	1 (0.4)	1 (0.4)	2 (0.4)
Dry mouth	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Fecal incontinence	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Gastritis	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Increased appetite	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Mouth ulceration	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Rectal disorder	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Tongue edema	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Body as a whole	1.000	15 (5.6)	15 (5.7)	30 (5.6)
Headache	0.335	3 (1.1)	6 (2.3)	9 (1.7)
Abdominal pain	0.007[b]	8 (3.0)	0 (0.0)	8 (1.5)
Moniliasis	0.683	2 (0.7)	3 (1.1)	5 (0.9)
Injection site pain	0.121	0 (0.0)	3 (1.1)	3 (0.6)
Chest pain	0.499	2 (0.7)	0 (0.0)	2 (0.4)
Injection site reaction	1.000	1 (0.4)	1 (0.4)	2 (0.4)
Allergic reaction	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Chills	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Fever	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Malaise	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Overdose	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Metabolic and nutritional	0.100	17 (6.3)	8 (3.0)	25 (4.7)
SGPT increased	0.282	2 (0.7)	5 (1.9)	7 (1.3)
SGOT increased	1.000	2 (0.7)	2 (0.8)	4 (0.8)
Alkaline phosphatase increased	0.249	3 (1.1)	0 (0.0)	3 (0.6)
Bilirubinemia	1.000	1 (0.4)	1 (0.4)	2 (0.4)
Hypokalemia	0.499	2 (0.7)	0 (0.0)	2 (0.4)
Hypomagnesemia	0.499	2 (0.7)	0 (0.0)	2 (0.4)
Hyponatremia	0.499	2 (0.7)	0 (0.0)	2 (0.4)
Acidosis	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Cachexia	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Creatinine increased	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Dehydration	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Hyperglycemia	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Hyperkalemia	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Hypocalcemia	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Hypoglycemia	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Skin and appendages	0.810	8 (3.0)	9 (3.4)	17 (3.2)
Pruritus	0.379	4 (1.5)	7 (2.7)	11 (2.1)
Urticaria	0.499	2 (0.7)	0 (0.0)	2 (0.4)
Cutaneous moniliasis	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Dry skin	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Erythema	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Fungal dermatitis	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Rash	1.000	1 (0.4)	0 (0.0)	1 (0.2)

Table 15. Number (%) of Subjects Reporting Treatment-Related Treatment-Emergent Adverse Events, mITT Population

Body System[a] Adverse Event	p-Value[b]	Tigecycline 50 mg N=268 N (M)=163 N (F)=105	Comparator N=263 N (M)=169 N (F)=94	Total N=531 N (M)=332 N (F)=199
Hemic and lymphatic system	0.106	8 (3.0)	2 (0.8)	10 (1.9)
Activated partial thromboplastin time prolonged	0.249	3 (1.1)	0 (0.0)	3 (0.6)
Eosinophilia	1.000	1 (0.4)	1 (0.4)	2 (0.4)
Thrombocythemia	0.499	2 (0.7)	0 (0.0)	2 (0.4)
Anemia	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Iron deficiency anemia	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Lymphocytosis	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Neutropenia	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Prothrombin time prolonged	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Nervous system	0.450	5 (1.9)	2 (0.8)	7 (1.3)
Insomnia	0.499	2 (0.7)	0 (0.0)	2 (0.4)
Abnormal dreams	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Anxiety	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Dizziness	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Encephalopathy	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Euphoria	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Urogenital system	1.000	3 (1.1)	3 (1.1)	6 (1.1)
Vaginal moniliasis	F, 0.683	2 (1.9)	3 (3.2)	5 (2.5)
Acute kidney failure	1.000	1 (0.4)	1 (0.4)	2 (0.4)
Special senses	0.213	1 (0.4)	4 (1.5)	5 (0.9)
Taste perversion	0.369	1 (0.4)	3 (1.1)	4 (0.8)
Abnormal vision	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Cardiovascular system	0.059	0 (0.0)	4 (1.5)	4 (0.8)
Thrombophlebitis	0.245	0 (0.0)	2 (0.8)	2 (0.4)
Bradycardia	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Hypertension	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Vasodilatation	0.495	0 (0.0)	1 (0.4)	1 (0.2)

Adverse events and serious adverse events are not separated out.
p-value: calculated using Fisher's exact test (2-tail).
One subject received only vancomycin as test article.
Treatment-emergent adverse event (TEAE): Defined as all adverse events starting at or after the first administration of test article until last administration of test article +15 days, or if started prior to first administration of test article worsened after first intake.
Comparator: consisted of amoxicillin-clavulanate or ampicillin- sulbactam with or without adjuvant therapy vancomycin.
F = female; M = male; mITT = modified intent-to-treat; n = number of mITT subjects; N = total number of mITT subjects; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase.
a. Body system totals were not necessarily the sum of the individual adverse events since a subject might report more than 1 adverse event in the same body system.
b. Statistical significance at the 0.05 level.

Treatment-Emergent Serious AEs (SAEs): Table 16 presents treatment-emergent SAEs (all-causality) reported during the study. A total of 67 of 531 (12.6%) subjects had 1 or more SAEs during the study: 38 of 268 (14.2%) subjects in the tigecycline group and 29 of 263 (11.0%) subjects in the comparator group.

There were no statistically significant differences between treatment groups in the overall incidence of subjects reporting 1 or more SAEs (p-value = 0.297). There were no statistically significant differences between treatment groups in the incidences of any reported SAE term or body system.

The most frequently reported SAEs overall were cellulitis and infection. The most frequently reported SAEs in tigecycline-treated subjects were cellulitis, infection, heart arrest, pneumonia, and acute kidney failure. The most frequently reported SAEs in comparator-treated subjects were cellulitis, abscess, heart arrest, and necrotizing fasciitis.

Table 16. Number (%) of Subjects Reporting Serious Adverse Events, mITT Population

Body System[a] Adverse Event	p-Value[b]	Tigecycline 50 mg N=268	Comparator N=263	Total N=531
Any adverse event, n (%)	0.297	38 (14.2)	29 (11.0)	67 (12.6)
Body as a whole	0.215	21 (7.8)	13 (4.9)	34 (6.4)
Cellulitis	1.000	7 (2.6)	6 (2.3)	13 (2.4)
Infection	0.123	6 (2.2)	1 (0.4)	7 (1.3)
Abscess	0.621	1 (0.4)	2 (0.8)	3 (0.6)
Chest pain	0.499	2 (0.7)	0 (0.0)	2 (0.4)
General physical health deterioration	1.000	1 (0.4)	1 (0.4)	2 (0.4)
Asthenia	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Carcinoma	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Fever	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Generalized edema	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Overdose	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Retroperineal hemorrhage	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Sepsis	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Septic shock	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Traumatic hematoma	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Cardiovascular system	0.222	8 (3.0)	3 (1.1)	11 (2.1)
Heart arrest	1.000	3 (1.1)	2 (0.8)	5 (0.9)
Pulmonary embolus	1.000	1 (0.4)	1 (0.4)	2 (0.4)
Deep vein thrombosis	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Myocardial infarct	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Occlusion	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Ventricular tachycardia	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Digestive system	1.000	5 (1.9)	4 (1.5)	9 (1.7)
Cholecystitis	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Diarrhea	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Esophageal hemorrhage	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Gastrointestinal hemorrhage	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Hepatic failure	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Liver function tests abnormal	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Nausea	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Peptic ulcer	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Stomach ulcer	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Vomiting	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Respiratory system	0.504	6 (2.2)	3 (1.1)	9 (1.7)
Pneumonia	0.249	3 (1.1)	0 (0.0)	3 (0.6)
Lung edema	1.000	1 (0.4)	1 (0.4)	2 (0.4)
Respiratory failure	1.000	1 (0.4)	1 (0.4)	2 (0.4)
Carcinoma of lung	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Chronic obstructive airways disease	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Urogenital system	1.000	4 (1.5)	3 (1.1)	7 (1.3)
Acute kidney failure	0.624	3 (1.1)	1 (0.4)	4 (0.8)
Kidney failure	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Kidney function abnormal	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Urinary tract infection	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Metabolic and nutritional	0.683	2 (0.7)	3 (1.1)	5 (0.9)
Dehydration	1.000	1 (0.4)	1 (0.4)	2 (0.4)
Hypoglycemia	1.000	1 (0.4)	1 (0.4)	2 (0.4)
Healing abnormal	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Skin and appendages	0.624	3 (1.1)	1 (0.4)	4 (0.8)
Skin necrosis	1.000	2 (0.7)	1 (0.4)	3 (0.6)
Herpes simplex	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Musculoskeletal system	0.121	0 (0.0)	3 (1.1)	3 (0.6)
Necrotising fasciitis	0.245	0 (0.0)	2 (0.8)	2 (0.4)
Osteomyelitis	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Nervous system	1.000	1 (0.4)	1 (0.4)	2 (0.4)

Table 16. Number (%) of Subjects Reporting Serious Adverse Events, mITT Population

Body System[a] Adverse Event	p-Value[b]	Tigecycline 50 mg N=268	Comparator N=263	Total N=531
Convulsion	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Encephalopathy	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Hemic and lymphatic system	0.495	0 (0.0)	1 (0.4)	1 (0.2)
International normalized ratio increased	0.495	0 (0.0)	1 (0.4)	1 (0.2)

p-value: calculated using the Fisher exact test (2-tail).
Comparator: amoxicillin-clavulanate or ampicillin-sulbactam, with or without vancomycin.
mITT = modified intent-to-treat; n = number of mITT subjects; N = total number of mITT subjects.
a. Subjects might have reported more than 1 adverse event in the same body system.
b. Statistical significance at the 0.05 level.

SAEs that were considered to be treatment-related were reported by a minority of subjects; 4 subjects (1.5%) in the tigecycline group and 2 subjects (0.8%) in the comparator group. Treatment-related SAEs were nausea, vomiting, diarrhea, dehydration, chest pain and acute renal failure in the tigecycline group and acute kidney failure, encephalopathy and liver function tests abnormal in the comparator group.

Permanent Discontinuations Due to AEs: Subjects who discontinued study drug because of an AE are summarized in Table 17.

Overall, 24 of 531 subjects (4.5%) discontinued therapy because of an AE. Sixteen of 268 tigecycline-treated subjects (6.0%) and 8 of 263 comparator-treated subjects (3.0%) discontinued study drug because of an AE, a nonsignificant difference (p-value = 0.143). Overall, the most frequently reported AEs leading to discontinuation of study drug were nausea in 10 of 531 subjects (1.9%) and vomiting in 6 of 531 subjects (1.1%). There were no significant differences between treatment groups in the frequency of any single AE leading to the discontinuation of study drug.

Table 17. Study Drug Discontinuations Due to Adverse Events: Number (%) of Subjects, mITT Population

Body System[a] Adverse Event	p-Value[b]	Tigecycline 50 mg N=268	Comparator N=263	Total N=531
Any adverse event, n (%)	0.143	16 (6.0)	8 (3.0)	24 (4.5)
Digestive system	0.142	9 (3.4)	3 (1.1)	12 (2.3)
Nausea	0.106	8 (3.0)	2 (0.8)	10 (1.9)
Vomiting	0.216	5 (1.9)	1 (0.4)	6 (1.1)
Liver function test abnormal	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Body as a whole	1.000	3 (1.1)	3 (1.1)	6 (1.1)
Abscess	1.000	1 (0.4)	1 (0.4)	2 (0.4)
Abdominal pain	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Headache	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Injection site pain	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Sepsis	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Skin and appendages	0.373	4 (1.5)	1 (0.4)	5 (0.9)
Rash	0.499	2 (0.7)	0 (0.0)	2 (0.4)
Skin necrosis	1.000	1 (0.4)	1 (0.4)	2 (0.4)
Urticaria	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Metabolic and nutritional	1.000	2 (0.7)	1 (0.4)	3 (0.6)
Acidosis	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Cachexia	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Dehydration	1.000	1 (0.4)	0 (0.0)	1 (0.2)
Hyperkalemia	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Musculoskeletal system	0.121	0 (0.0)	3 (1.1)	3 (0.6)
Necrotising fasciitis	0.245	0 (0.0)	2 (0.8)	2 (0.4)
Osteomyelitis	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Cardiovascular system	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Vasodilatation	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Nervous system	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Encephalopathy	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Mental status changes	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Special senses	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Taste perversion	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Urogenital system	0.495	0 (0.0)	1 (0.4)	1 (0.2)
Acute kidney failure	0.495	0 (0.0)	1 (0.4)	1 (0.2)

p-value: calculated using Fisher exact test (2-tail).
Comparator: amoxicillin-clavulanate or ampicillin-sulbactam, with or without vancomycin.
mITT = modified intent-to-treat; n = number of mITT subjects; N = total number of mITT subjects.
a. Subjects might have reported more than 1 adverse event in the same body system.
b. Statistical significance at the 0.05 level.

Deaths: Table 18 summarizes subjects who died during the study. Eleven subjects died during or after the study: 6 subjects in the tigecycline treatment group and 5 subjects in the comparator treatment group. All of the SAEs with an outcome of death occurring during the study were assessed by the Investigators as either probably not or definitely not related to study drug. None of the SAEs with an outcome of death occurred at statistically different proportion between the 2 treatment groups.

Table 18. Adverse Events With Outcome of Death, mITT Population

Serial Number/Age/ Gender	Relative Day	Adverse Event(s) Preferred Term	Duration of Event (Days)	Study Drug Relationship
Tigecycline 50 mg				
1/88/Male	33	Heart arrest	1	Not
2/75/Male	31	Respiratory failure	1	Not
3/78/Female	12	General physical health deterioration	2	Not
4/86/Female	43	Heart arrest	1	Not
5/74/Female	66	Heart arrest	1	Not
6/72/Female	10	Myocardial infarct	2	Not
Comparator				
7/69/Female	18	Chronic obstructive airways disease	1	Not
8/53/Male	14	Heart arrest	1	Not
9/86/Male	22	Dehydration	2	Not
10/35/Male	61	Heart arrest	1	Not
11/84/Male	11	Respiratory failure	1	Not

Relative day was calculated relative to the first day of study drug administration.
Comparator: amoxicillin-clavulanate or ampicillin-sulbactam, with or without vancomycin.
mITT = modified intent-to-treat.

Other Safety Related Findings: There was no difference in the number of laboratory values of potential clinical importance (PCI) recorded during the on-therapy period between the treatment groups. Tigecycline-treated subjects experienced minor changes in measures of clotting function, including prothrombin activity, prothrombin time (PT), partial thromboplastin time (PTT), and International Normalized Ratio (INR), consistent with previous observations in large-scale studies of the compound. These changes were not accompanied by differences in clinical AEs of related body systems or events. Tigecycline-treated subjects experienced minor differences in changes in total protein and blood urea during treatment compared to subjects receiving comparator. These changes are consistent with the known effects of tigecycline on these laboratory parameters. There were no significant differences in PCI vital signs or in changes over the course of the study between the treatment groups.

CONCLUSIONS:

- Based on the lower bound of the 2-sided CI for the difference in cure proportion (-8.7%), tigecycline met the statistical criterion for noninferiority to ampicillin-sulbactam or amoxicillin-clavulanate with or without vancomycin in the CE population. At the TOC assessment, 162 of 209 (77.5%) tigecycline-treated subjects and 152 of 196 (77.6%) comparator-treated subjects were clinically cured (difference 0.0; 95% CI, -8.7, 8.6).

- Subpopulation analyses of clinical responses within the CE population were generally consistent with the findings from the primary endpoint in the CE population.

- In the ME population, the cure rates at the TOC assessment also met the noninferiority criteria for efficacy of tigecycline compared with comparator, with the adjusted lower bound of the CI being -9.6% for the difference in cure proportion. At the TOC assessment, 96 of 120 (80.0%) tigecycline-treated subjects and 77 of 99 (77.8%) comparator-treated subjects were cured (adjusted 95% CI, 9.6, 14.0).

- Efficacy comparisons at the microbiologic level confirmed the results of the primary analysis. At the subject level, the eradication rates for the ME population were 79.2% in the tigecycline treatment group and 76.8% in the comparator treatment group (difference 2.4%; 95% CI, -9.6, 14.4) at the TOC assessment.

- At the isolate level in the ME population, eradication rates for the most common pathogens encountered in cSSSI were as follows: *S. aureus*, 53 of 71 (74.6%) for tigecyclin- treated subjects, and 47 of 61 (77.0%) for comparator-treated subjects; *S. pyogenes*, 8 of 11 (72.7%) for tigecycline-treated subjects and 5 of 5 (100%) for comparator-treated subjects.

- Cure rates at the TOC assessment in subjects with baseline MRSA were similar for tigecycline and comparator treatment groups. In the ME population, 69.4% of tigecycline-treated subjects, and 72.4% of comparator-treated subjects were cured (difference -3.0; 95% CI, -28.2, 22.3).

- Efficacy comparisons in the primary CE population of subjects known to be bacteremic at baseline, excluding skin contaminants, were 5 of 8 (62.5%) tigecycline-treated subjects and 4 of 5 (80.0%) comparator-treated subjects. No subject remained bacteremic following the first dose of either study drug.

- Multiple population analyses of clinical responses were internally consistent with the findings from the primary population: tigecycline met the statistical criteria for noninferiority to comparator in treating hospitalized subjects with cSSSI.

The data from this study demonstrate that tigecycline appears safe for the treatment of subjects with cSSSI.

- The percentage of subjects reporting TEAEs in the tigecycline treatment arm was significantly higher than that reported in the comparator treatment arm (p-value = 0.008).

- The 3 most frequently reported TEAEs in the tigecycline treatment groups were nausea, vomiting, and diarrhea. The severity of nausea and vomiting experienced in this study was similar to that seen in previous controlled trials involving tigecycline, namely, the events were almost exclusively mild to moderate in severity.

- The TEAE of hypokalemia occurred at significantly lower rates in subjects receiving tigecycline than in those who received comparator (p-value = 0.019).

- When nausea and vomiting were excluded, the percentage of subjects reporting TEAEs in the tigecycline treatment arm was not significantly higher than that reported in the comparator treatment arm (p-value = 0.326).

- There were no statistically significant differences between treatment groups in the overall incidence of subjects reporting 1 or more SAEs (p-value = 0.297).

- There were no significant differences between treatment groups in the frequency of any single AE leading to the discontinuation of study drug (p-value = 0.143). The most frequently reported AEs leading to discontinuation of study drug were nausea in 10 of 531 subjects (1.9%) and vomiting in 6 of 531 subjects (1.1%).

- Eleven subjects died during or after the study: 6 subjects in the tigecycline treatment group and 5 subjects in the comparator treatment group. All of the SAEs with an outcome of death occurring during the study were assessed by the investigators as either probably not or definitely not related to study drug.

- Tigecycline-treated subjects experienced minor changes in measures of clotting function, including prothrombin activity, PT, PTT, and INR, consistent with previous observations in large-scale studies of the compound. These changes were not accompanied by differences in clinical AEs of related body systems or events.

- Tigecycline-treated subjects experienced minor differences in changes in total protein and blood urea during treatment compared to subjects receiving comparator. These changes are consistent with the known effects of tigecycline on these laboratory parameters.