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

PROTOCOL NO.: 3074K6-2000 (B1811004)

PROTOCOL TITLE: A Phase 2, Multicenter, Randomized, Double-Blind, Comparative Study of the Safety and Efficacy of 2 Doses of Tigecycline Versus Imipenem/Cilastatin for the Treatment of Subjects With Hospital-Acquired Pneumonia

Study Centers: A total of 75 centers took part in the study and randomized subjects to test article. The 75 centers were located as follows: 11 in Argentina; 10 in the United States (US); 9 in the Russian Federation; 5 each in Canada, and Romania; 4 each in France, Hungary, Israel, and the Republic of Korea; 3 each in Australia, Brazil, Croatia, Latvia, and Taiwan; 2 in Colombia; and 1 each in Chile, and Estonia.

Study Initiation Date and Final Completion Date: 05 December 2008 to 14 June 2011. The study was terminated prematurely.

Phase of Development: Phase 2

Study Objectives:

Primary Objective: To compare the safety and efficacy of 2 higher tigecycline dosing regimens with that of an imipenem/cilastatin regimen in order to determine the dose(s) of tigecycline that was/were to have been tolerable and noninferior to imipenem/cilastatin in treating subjects with hospital-acquired pneumonia (HAP).

Secondary Objectives:

- To evaluate tigecycline efficacy in treating the ventilator-associated pneumonia (VAP)/non-VAP subject subpopulations
- To evaluate the microbiologic efficacy of tigecycline
- To obtain in vitro susceptibility data on tigecycline for a range of bacteria that cause HAP
- To obtain pharmacokinetic (PK)/pharmacodynamic (PD) information for these higher dose regimens of tigecycline in subjects with HAP
- To compare procalcitonin levels between treatment groups and explore the relationship between procalcitonin concentrations and response to treatment in subjects with HAP
- To compare health care resource utilization between treatment groups

METHODS

Study Design: This study was a Phase 2, multicenter, randomized, double-blind (third-party unblinded) study comparing the safety and efficacy of tigecycline versus imipenem/cilastatin for the treatment of HAP. In this study, the safety, tolerability, and efficacy of 2 new dose levels of tigecycline (ie, 75 mg once every 12 hours [q12h] and 100 mg q12h) were assessed in parallel. Qualifying subjects were randomly assigned (in a 1:1:1 ratio) to receive 1 of the tigecycline dose levels or imipenem/cilastatin for up to 14 consecutive days, the exact duration to be at the discretion of the Investigator based on the subject's condition. Additional adjunctive therapy was also to have been administered from the start of therapy and subsequently discontinued, if appropriate, based on the baseline culture results and clinical course of the subject.

An independent data monitoring committee (DMC) was to have evaluated the safety, tolerability, and efficacy of tigecycline on an ongoing basis (eg, every 30 subjects; unless they deemed otherwise). The study was allowed to continue if the DMC deemed the safety, tolerability, and efficacy profile acceptable in at least 1 of the tigecycline dose levels. This decision was based on a review of the safety, tolerability, and efficacy data.

Subjects were stratified at randomization by VAP versus non-VAP. The total number enrolled in the study and in each treatment group was to have included at least 70% VAP and no more than 30% non-VAP subjects. Subjects were to have been followed for safety and efficacy until the test-of-cure (TOC) assessment 10 to 21 days after the last day of therapy (LDOT). In addition, serious adverse events (SAEs) occurring within 15 days (pre-amendment to Protocol) or 30 days (post-amendment to Protocol) of LDOT were reported.

The schedule of activities for the study is presented in Table 1.

Table 1. Timetable of Study Procedures/Evaluations

Procedure	-24 Hours (Screening/Day 1)[a,b]	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9-13[c]	Day 14 or Last Day of Therapy (LDOT)[d]	TOC[d,e]
Informed consent	X										
Inclusion/exclusion criteria	X										
Demographics; medical/medication history/current pneumonia history	X										
APACHE II	X										
Physical examination[f]	X									X[f]	X
Height and weight	X										
CPIS	X										
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X
Assessment of clinical signs and symptoms of pneumonia[h]	X	X	X	X	X	X	X	X	X	X	X
Chest radiograph[i]	X										X
12-lead ECGs[j]	X		X[j]							X	X
Pulse oximetry or ABG	X										
FiO_2[k]	X	X	----------X----------								X
Pregnancy test[l]	X										
Blood cultures[m]	X----------X										
Gram stain and culture of respiratory secretions[n]	X----------X										
Hematology[o]	X		X		X			X		X	X
White blood cell count with differentials		X		X		X	X		X[o]		
Serum chemistries[p]	X		X[p]	X[p]-------X[p]				X		X	X
Calculated creatinine clearance[q]	X----------X										
Coagulation studies[r]	X		X		X			X		X	X
PK samples[s]	X		X[s]								
Biomarker samples (procalcitonin)[t]	X	X	X	X	X	X					
Evaluation of clinical response										X	X
Test article administration	X----------X										
Collection of adverse events	X----------X										
Nonstudy medications/nonpharmacologic treatments/procedures	X----------X										

ABG = arterial blood gas; AE = adverse event; APACHE II = Acute Physiologic and Chronic Health Evaluation Scale; CRF = case report form; CPIS = Clinical Pulmonary Infection Score; ECGs = electrocardiograms; FiO_2 = fraction of inspired oxygen; LDOT = last day of therapy; PK = pharmacokinetic; TOC = test of cure; VAP = ventilator-associated pneumonia.

a. Obtained within 24 hours before the first dose of test article (Day 1), unless otherwise noted.

b. For screen failure subjects, the demography, inclusion/exclusion (eligibility) and conclusion of subject participation CRFs were completed. For subjects who were randomly assigned but did not receive test article, the demography, inclusion/exclusion (eligibility), randomization, test article administration, conclusion of subject

Table 1. Timetable of Study Procedures/Evaluations

participation, AE and AE nausea and vomiting CRFs were completed.

c. Assessments for Days 8 to 13 were required only while the subject was still receiving test article and hospitalized.

d. For subjects who had discontinued taking test article early and had their LDOT and TOC assessments performed on the same day, the CRFs for TOC were completed in addition to any pages which were unique to LDOT.

e. Occurred 10 to 21 days after LDOT. However, subjects who were deemed clinical failures were to have the TOC assessment performed before the initiation of nonstudy antibiotic therapy. Serious AEs occurring within 30 days of LDOT were reported.

f. At LDOT, a limited physical examination (including any abnormalities within a body system or worsening of a baseline condition) was performed.

g. Vitals signs included blood pressure, heart rate, respiratory rate, and temperature (oral, axillary, tympanic, or rectal/core). The most abnormal values for each of the vital signs were recorded on the CRF.

h. Evaluation of signs and symptoms including: sputum character, sputum production, auscultatory findings, dyspnea, severity of cough, pleuritic chest pain, rigors, or shaking chills.were read locally.

i. Baseline chest radiograph was obtained within 48 hours before first dose of test article. Chest radiographs were read locally.

j. All ECGs were taken in triplicate; 1 to 2 minutes apart. Baseline ECGs were obtained within 24 hours before start of test article. ECGs were obtained on Day 3 and LDOT within 5 to 10 minutes following the end of the first primary therapy infusion (tigecycline or imipenem, Hour 0). If for any reason ECGs could not be obtained on Day 3, ECGs could have been performed at Day 4 or Day 5. ECG interpretation was performed locally and centrally.

k. FiO_2 was recorded at Baseline if the subject was receiving oxygen. Subsequently, FiO_2 was recorded daily while the subject was receiving oxygen. The highest value of the day was recorded on the CRF.

l. A urine or serum pregnancy test was performed during screening on women of childbearing potential before the first dose of test article. A negative result was required for study enrollment. Results were to have been recorded on the source documents but were not collected on the CRF.

m. Blood samples for blood cultures were collected on Day 3 if screening blood cultures were to have been positive and repeated at the discretion of the Investigator until negative and/or if the subject was a treatment failure. If the screening blood cultures were negative, cultures did not have to be repeated unless clinically indicated.

n. Gram stain and culture were performed for each respiratory specimen at local microbiology laboratories at the following time points: Baseline, and, if obtainable (ie, subject was still producing sputum or was intubated), at Day 3, Day 14, or LDOT, and at the TOC assessment. Isolates considered as pathogens were sent to the laboratory. If a subject was unable to produce a sample, the attempt was documented on the CRF. For subjects in whom new antibiotic therapy was initiated, a specimen was collected. Pulmonary specimens in all VAP subjects (and non-VAP subjects who were intubated) were collected by an invasive method of collection such as bronchoscopy with bronchoalveolar lavage, bronchoscopy with protected-brush sampling, or bronchoscopy with distal protected specimen. If the use of bronchoscopy was not possible, then another method of collection such as blind bronchoalveolar lavage or blind telescopic catheter method could have been used.

o. Full hematology was required at Baseline, Day 3, Day 5, Day 8, LDOT, and TOC. Hematology examinations were to have included complete blood cell count with total white blood cell with differential counts, platelet count, hemoglobin, and hematocrit. On other days, while still receiving test article, only the white blood cell with differential counts was required.

p. Serum chemistry was to have included: creatinine, blood urea nitrogen/urea, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, serum amylase, lipase if available, total and direct bilirubin, albumin, total protein, carbon dioxide (total carbon dioxide or bicarbonate), glucose, sodium, potassium, chloride, calcium, magnesium and phosphorus. These were obtained at Baseline, Day 3, Day (4 or 5), Day 8, LDOT, and TOC. At Baseline, Day 3 (or Day 4 or Day 5, pending ECG recordings), LDOT and TOC, samples for serum chemistry were collected just after the ECG recordings.

q. Creatinine levels were obtained for calculation of creatinine clearance when necessary and appropriate (eg, subjects receiving vancomycin, ceftazidime or an aminoglycoside). Results were recorded on the source documents, but were not collected on the CRF.

r. Coagulation tests included activated partial thromboplastin time, prothrombin time, and international normalized ratio (if available). If prothrombin time was not available then prothrombin activity was obtained. These were obtained at Baseline, Day 3, Day 5, Day 8, LDOT, and TOC.

s. For subjects in whom PK samples were collected, these were obtained within 6 hours before the first active dose of test article (Day 1) and at Day 3 (recommended in order to have PK sampling along with the ECG recording) while the subject was receiving active test article. If possible, the samples on Day 3 were collected

Table 1. Timetable of Study Procedures/Evaluations

immediately before the first primary therapy infusion (tigecycline or imipenem, Hour 0), at the end of infusion (following ECG recordings), and approximately 2, 4, and 8 hours from the start of infusion. If for any reason PK samples could not have been collected at Day 3, the samples were collected at Day 4 or Day 5 (same day as the ECG recordings).

t. After the screening visit, blood samples were collected daily until Day 6 (while on therapy). The actual date/time of the blood sample collection were recorded on the CRF.

Number of Subjects (Planned and Analyzed): Approximately 210 subjects were planned to be enrolled in the study (70 per group [in each of the 2 tigecycline dose levels and the comparator]). A total of 108 subjects were randomized to the test article and 105 subjects were treated in this study, (19 in the Republic of Korea; 18 in the Russian Federation; 14 in Hungary; 10 in France; 9 in Taiwan; 8 in Brazil; 7 in Colombia; 5 in Chile; 4 each in Argentina, Canada, and Croatia; 3 in Latvia; 2 in the US; and 1 in Australia). Of the 105 subjects who received at least 1 dose of test article, 36 received tigecycline 75 mg, 35 received tigecycline 100 mg, and 34 received imipenem/cilastatin 1 g.

Diagnosis and Main Criteria for Inclusion: Male or female subjects aged 18 years and older who were known or suspected to have acute HAP with the presence of a new or evolving infiltrate on a chest X-ray film, presence of fever or leukocytosis, respiratory failure requiring mechanical ventilation or presence of 2 of the clinical signs and symptoms: cough, dyspnea or tachypnea, pleuritic chest pain, rales and/or evidence of pulmonary consolidation, hypoxemia, or purulent sputum production were enrolled in the study. Acute HAP was defined as pneumonia with onset of symptoms: ≥48 hours after admission to an acute care hospital or chronic care facility such as a skilled nursing home facility or rehabilitation unit or ≤7 days after the subject was discharged from the hospital. The initial hospitalization had to be ≥3 days duration. VAP was defined as: onset of symptoms of pneumonia ≥48 hours after endotracheal intubation.

Exclusion Criteria: Subjects with other significant underlying conditions that would make it difficult to evaluate the subjects or make it unlikely to complete the therapy or that would increase their risk by participating in the study. Subjects with infection caused by organisms known to be resistant, subjects with contraindication, or hypersensitivity to any of the test articles were excluded from the study.

Study Treatment: The primary test articles included tigecycline and imipenem/cilastatin. The adjunctive test articles included ceftazidime (for *Pseudomonas aeruginosa* coverage in the tigecycline group), vancomycin (for methicillin-resistant *Staphylococcus aureus* [MRSA] coverage in the imipenem/cilastatin group), and an aminoglycoside (tobramycin or amikacin; for *P. aeruginosa* coverage in both groups).

The duration of the primary test article administration was planned to be a minimum of 7 days and not longer than 14 days. These test articles were infused over a period of approximately 30 to 60 minutes.

Subjects were randomly assigned to 1 of the following treatment groups:

- An initial intravenous (IV) loading dose of tigecycline 150 mg was administered followed by 75 mg of IV tigecycline approximately q12h. Ceftazidime 2 g IV approximately every 8 hours, an aminoglycoside (tobramycin 7 mg/kg daily or amikacin 20 mg/kg daily) and vancomycin placebo were administered at the start of therapy (unless it was known at Baseline that the subject did not have *P. aeruginosa* or MRSA)

- An initial IV loading dose of tigecycline 200 mg was administered followed by 100 mg of IV tigecycline approximately q12h. Ceftazidime 2 g IV approximately every 8 hours,

an aminoglycoside (tobramycin 7 mg/kg daily or amikacin 20 mg/kg daily) and vancomycin placebo were administered at the start of therapy (unless it was known at Baseline that the subject did not have *P. aeruginosa* or MRSA)

- Imipenem/cilastatin 1 g IV was administered approximately every 8 hours. In addition, vancomycin 15 mg/kg IV approximately q12h, an aminoglycoside (tobramycin 7 mg/kg daily or amikacin 20 mg/kg daily) and ceftazidime placebo were to have been given at the start of therapy (unless it was known at Baseline that the subject did not have *P. aeruginosa* or MRSA)

Tigecycline was supplied as a sterile lyophilized powder in a 5-mL flint glass containing 53 mg of tigecycline lyophilized powder for IV infusion to be reconstituted with 5.3 mL of sterile fluid for infusion (normal saline [0.9% NS in water] or 5% dextrose in water). Each vial was for single use only. The resultant solution in each vial had a concentration of 10 mg/mL.

Imipenem/cilastatin for injection was supplied as a sterile lyophilized powder. Each vial contained 500 mg of imipenem and 500 mg of cilastatin. Sterile vancomycin for injection was supplied as a lyophilized powder. Each vial contained vancomycin hydrochloride equivalent to either 500 mg or 1 g vancomycin. Sterile ceftazidime for injection was supplied as a lyophilized powder. Each vial contained ceftazidime pentahydrate equivalent to either 1 g or 2 g ceftazidime. Commercially available aminoglycoside (tobramycin or amikacin) could be used at the site as directed by the Investigator. Imipenem/cilastatin, ceftazidime, and vancomycin were prepared according to the instructions in the package insert.

Efficacy, Pharmacokinetic, Pharmacodynamic, and Outcome Research Endpoints:

Efficacy Endpoints:

Primary Endpoint: Clinical response in the clinically evaluable (CE) population at the TOC assessment, 10 to 21 days post-therapy (primary time point).

The clinical response was determined by the Investigator and was defined by 1 of the following: cure, failure, or indeterminate.

Cure: All signs and symptoms of pneumonia present at the time of enrollment were improved or resolved, the chest radiographs were improved or not worsening, no further antibiotic therapy was necessary for treatment of pneumonia, and there was no worsening or appearance of new signs and symptoms of pneumonia.

Failure: The subject had a lack of response during treatment and required additional intervention and/or received additional antibacterial therapy in addition to the test articles and allowed adjunctive therapies to cure the infection; or there was initial recovery from the infection followed by deterioration or death after study Day 2 due to the pneumonia.

If a subject was a clinical failure while receiving the test article, the subject's clinical response of failure was carried forward through the TOC assessment (regardless of whether

the subject was cured with other antibiotics). Subjects who were clinical failures should have the TOC assessment performed prior to the initiation of nonstudy antibiotic therapy.

Indeterminate: Subjects who did not have an outcome determination for reasons unrelated to test article or infection (eg, lost to follow-up, withdrawal of consent, withdrawn from the study following *Pseudomonas* identification from baseline cultures); or died within 2 days after the first dose of test article for any reason; or died after 2 days but prior to the assessment due to an infection other than pneumonia or for non-infection related reasons (as judged by the Investigator).

Secondary Endpoints: Clinical response in the clinical modified intent-to-treat (c-mITT) population at the TOC assessment, clinical response in the VAP/non-VAP subject subpopulations, and microbiological responses at the subject level and at the pathogen level. Subjects were evaluated for microbiological efficacy if the screening respiratory culture contained an identifiable pathogen.

The microbiological response at the pathogen level for baseline pathogens was described according to the following definitions of microbiological efficacy:

Eradication (documented or presumed): The baseline pathogen was absent in repeat cultures obtained from the original site of infection; or a clinical response of cure precluded the necessity of, or ability to obtain, a repeat culture specimen.

Persistence (documented or presumed): Any baseline pathogen was present in repeat cultures obtained from the original site of infection; or the subject's clinical response was failure and no repeat microbiological data were available.

Indeterminate: Subjects who did not have an outcome determination for reasons unrelated to test article or infection (eg, lost to follow-up, withdrawal of consent, withdrawn from the study following *Pseudomonas* identification from the baseline cultures); or no baseline pathogens identified; or died within 2 days after the first dose of test article for any reason; or died after 2 days but prior to the assessment due to an infection other than pneumonia; or for non-infection related reasons (as judged by the Investigator).

The outcome of the microbiological response at the subject level was described according to the following definitions of microbiological efficacy:

Eradication: (documented or presumed): No baseline pathogens were present in repeat cultures taken from the original site of infection or a clinical response of cure precluded the necessity of, or ability to obtain a repeat culture specimen.

Persistence: (documented or presumed): Any baseline pathogen was present in cultures obtained from the original site of the infection or the subject's clinical response was failure and no repeat microbiological data were available.

Superinfection: A new pathogen emerged, at the initial site of infection, with emergence or worsening of signs and symptoms of infection (ie, deemed a clinical failure).

Indeterminate: Subjects who did not have an outcome determination for reasons unrelated to test article or infection (eg, lost to follow-up, withdrawal of consent, withdrawn from the study following *Pseudomonas* identification from the baseline cultures); or no baseline pathogens identified; or died within 2 days after the first dose of test article for any reason; or died after 2 days but prior to the assessment due to an infection other than pneumonia or for non-infection related reasons (as judged by the Investigator).

Pharmacokinetic Endpoint: PK analyses were performed to characterize tigecycline PK.

All concentration-time data were to have been combined and analyzed using population PK methods to investigate potential causes of intersubject variability, including weight, height, ideal body weight, body mass index, body surface area, age, gender, creatinine clearance, race, and VAP diagnosis. Model-predicted area under the curve from 0 to 24 hours ($AUC_{0\text{-}24h}$) values for each individual were to have been determined and used in subsequent PD evaluations.

Pharmacodynamic Endpoint: PD assessments included measurement of procalcitonin concentrations to test for response to antibiotic therapy (procalcitonin concentrations below 0.5 ng/mL were interpreted as clinically insignificant), as well as the investigation of the relationship between tigecycline $AUC_{0\text{-}24h}$, the occurrence of nausea and vomiting, investigation of the relationship between the ratio of unbound tigecycline $AUC_{0\text{-}24h}$ ($fuAUC_{0\text{-}24h}$)/minimum inhibitory concentration [MIC], and clinical and microbiological outcome.

Health Outcome Endpoints: Health care resource utilization was assessed in terms of 3 components: (1) duration of IV antibiotic treatment, (2) hospital length of stay (LOS), and (3) intensive care unit (ICU)-LOS.

Safety Evaluations: Safety evaluations included physical examination, clinical monitoring, vital signs (heart rate, blood pressure, respiratory rate, and temperature), 12-lead electrocardiograms (ECGs), AEs, and safety laboratory tests.

Statistical Methods:

Analysis Sets:

Clinically Evaluable Population: The primary population for the efficacy analysis was the CE population that included subjects who met the following criteria:

- Met the eligibility criteria
- Not received any potentially effective concomitant systemic or aerosolized antibacterial treatment, other than study medications, after the first dose of test article through the TOC assessment unless declared a clinical failure. If the subject had received 1 or 2 doses of a concomitant bacterially effective systemic or aerosolized antibiotic with a dosing frequency less than once daily (eg, q12h or every 8 hours), other than study medications, the subject was considered evaluable. If a subject required another

antibiotic without documented (ie, in the package insert) activity against the baseline pathogen, for an infection other than HAP, the subject was declared evaluable

- No *P. aeruginosa* identified from baseline cultures
- Received no more than 24 hours of an antibacterial agent before the first dose of test article administration (except as noted in the inclusion criteria)
- Completed the TOC assessment with a response of cure or failure (ie, not indeterminate)
- Remained blinded (subject and blinded study and Sponsor personnel) in regards to treatment regimen throughout the entire study duration
- Met the following requirements for timing of the TOC assessment and for test article administration:
    - To be evaluable as a success: completed the TOC assessment at least 10 days and not more than 21 days after the last dose of test article was administered, and received at least 5 days of primary therapy, and received 80% to 120% of the planned number of doses of primary therapy based on the number of days of actual dosing, respectively
    - To be evaluable as a failure: completed the TOC assessment on or after Day 3, and received at least 8 doses of the primary therapy medication (active and placebo), respectively
- Completed the TOC assessment with a response of cure or failure (ie, not indeterminate)
- Remain blinded (subject and blinded study and Sponsor personnel) in regards to treatment regimen throughout the entire study duration

Microbiologically Evaluable (ME) Population: Subjects who met the following criteria were included in the ME population:

- Satisfied all the above criteria for the CE population
- The culture taken from the infected site before the first dose of test article had at least 1 isolate
- At least 1 baseline isolate had been susceptible to the tigecycline regimen and the imipenem/cilastatin regimen

Only microorganisms accepted as pathogens were considered valid in the microbiologic evaluability of a subject.

Other analysis populations were ITT population (all subjects who had been randomly assigned to test article); modified ITT [mITT] population (ITT subjects who had received at least 1 dose of primary test article); c-mITT population (mITT subjects who had satisfied

minimal disease requirements); and microbiologic mITT (m-mITT) population (those c-mITT subjects who had an identifiable causative pathogen).

Safety Analysis Set: Safety analysis set was the mITT population.

Statistical Methods: Noninferiority of each tigecycline dose group as compared to imipenem/cilastatin was evaluated for clinical and microbiological response by using a 2-sided 70% confidence interval (CI) for the true difference in efficacy (tigecycline regimen minus imipenem/cilastatin regimen).

The microbiological response at the subject level and at the pathogen level were analyzed in a manner similar to the primary analysis. All other secondary endpoints were summarized.

Summary statistics, including mean, standard deviation, median, minimum and maximum, for the PK parameters peak drug concentration (C_{max}), time to peak concentration (T_{max}), area under the concentration-time curve over 12 hours (AUC_{0-12h}), and clearance (CL) were to have been calculated for the noncompartmental analysis.

Individual model-predicted AUC_{0-24h} values were to have been used to calculate individual AUC/MIC ratios, which were summarized by clinical and microbiological outcome for subjects with and without VAP. Individual procalcitonin PD values were to have been summarized by clinical and microbiological outcomes for subjects with and without VAP.

AEs were summarized for each treatment group. Laboratory results were summarized both as continuous and categorical endpoints for each treatment group.

RESULTS

Subject Disposition and Demography: A summary of subject disposition is presented in Table 2.

Table 2. Subject Disposition

Conclusion Status Reason[a]	Overall p-Value	Treatment			Total
		Tigecycline 75 mg (n=36)	Tigecycline 100 mg (n=35)	Imipenem/Cilastatin 1 g (n=34)	(N=105)
Total	-	36 (100)	35 (100)	34 (100)	105 (100)
Completed	0.183	18 (50.0)	25 (71.4)	21 (61.8)	64 (61.0)
Study completed	0.183	18 (50.0)	25 (71.4)	21 (61.8)	64 (61.0)
Discontinued	0.183	18 (50.0)	10 (28.6)	13 (38.2)	41 (39.0)
Adverse event	0.598	5 (13.9)	3 (8.6)	2 (5.9)	10 (9.5)
Death	0.625	3 (8.3)	1 (2.9)	3 (8.8)	7 (6.7)
Investigator request	0.691	1 (2.8)	1 (2.9)	2 (5.9)	4 (3.8)
Other	0.269	8 (22.2)	3 (8.6)	5 (14.7)	16 (15.2)
Protocol violation	0.324	0	0	1 (2.9)	1 (1.0)
Unsatisfactory response - efficacy	0.654	1 (2.8)	2 (5.7)	0	3 (2.9)

Overall p-value refers to number of subjects' data. Fisher's exact test p-value (2-tail).
N = total number of subjects; n = number of subjects in each group; mITT = modified intent-to-treat.
a. Total discontinued is the sum of individual reasons since they were mutually exclusive by subject.

A summary of data sets analyzed is presented in Table 3.

Table 3. Data Sets Analyzed

Number (%) of Subjects	Tigecycline 75 mg	Tigecycline 100 mg	Imipenem/Cilastatin 1 g	Total
Screened	-	-	-	114
ITT	37	36	35	108 (94.7)
mITT	36 (97.3)	35 (97.2)	34 (97.1)	105 (97.2)
Clinical mITT	36 (100)	35 (100)	34 (100)	105 (100)
Clinically evaluable	23 (63.9)	20 (57.1)	24 (70.6)	67 (63.8)
Microbiologic mITT	25 (69.4)	19 (54.3)	21 (61.8)	65 (61.9)
Microbiologically evaluable	13 (36.1)	10 (28.6)	15 (44.1)	38 (36.2)

ITT = intent-to-treat; mITT = modified intent-to-treat.

A summary of demographic and baseline characteristics is presented in Table 4.

Table 4. Demographic and Baseline Characteristics, mITT Population

Characteristic	Overall p-Value	Treatment			Total
		Tigecycline 75 mg (n=36)	Tigecycline 100 mg (n=35)	Imipenem/Cilastatin 1 g (n=34)	(N=105)
Age (year)					
n		36	35	34	105
Mean	0.445[a]	60.31	61.46	64.85	62.16
Standard deviation		14.82	16.05	15.33	15.37
Minimum		29.00	20.00	22.00	20.00
Maximum		84.00	90.00	94.00	94.00
Median		59.50	65.00	65.50	64.00
Sex, n (%)	0.019[b]				
Female		13 (36.11)	16 (45.71)	5 (14.71)	34 (32.38)
Male		23 (63.89)	19 (54.29)	29 (85.29)	71 (67.62)
Race, n (%)	0.037[b]				
Asian		7 (19.44)	7 (20.00)	15 (44.12)	29 (27.62)
Black or African American		2 (5.56)	0	0	2 (1.90)
Other		7 (19.44)	3 (8.57)	2 (5.88)	12 (11.43)
White		20 (55.56)	25 (71.43)	17 (50.00)	62 (59.05)
Inclusion criteria, n (%)	0.364[b]				
No		0	1 (2.86)	0	1 (0.95)
Yes		36 (100)	34 (97.14)	34 (100)	104 (99.05)
Exclusion criteria, n (%)	0.348[b]				
No		0	0	1 (2.94)	1 (0.95)
Yes		36 (100)	35 (100)	33 (97.06)	104 (99.05)
Baseline height (cm)					
n		36	34	32	102
Mean	0.045[a]	167.77	165.80	171.71	168.35
Standard deviation		9.88	9.31	9.71	9.85
Minimum		145.00	150.00	148.00	145.00
Maximum		185.00	182.00	190.00	190.00
Median		168.00	165.50	170.00	168.00
Missing (n)		0	1	2	3
Baseline weight (kg)					
n		36	35	34	105
Mean	0.770[a]	71.81	70.62	73.71	72.03
Standard deviation		16.24	20.31	16.97	17.79
Minimum		42.00	41.00	45.00	41.00
Maximum		105.00	140.00	112.00	140.00
Median		71.50	68.00	71.50	70.00
Body Mass Index (kg/m^2)					
n		36	34	32	102
Mean	0.907[a]	25.53	25.84	25.21	25.53
Standard deviation		5.81	6.69	4.40	5.68
Minimum		17.33	16.97	18.92	16.97
Maximum		41.85	55.38	34.57	55.38
Median		23.81	24.84	25.55	24.83
Missing		0	1	2	3
Calculated creatinine clearance BSA ($mL/min/1.73\ m^2$)					
n		36	34	32	102
Mean	0.512[a]	96.67	90.22	85.04	90.87
Standard deviation		49.42	41.49	29.66	41.25
Minimum		26.11	33.13	33.92	26.11
Maximum		280.13	215.74	146.74	280.13
Median		90.47	84.65	82.85	83.88
Missing (n)		0	1	2	3

Table 4. Demographic and Baseline Characteristics, mITT Population

BSA = body surface area; mITT = modified intent-to-treat; N = total number of subjects; n = number of subjects.
a. One-way analysis of variance with treatment as factor.
b. p-Value for chi-square.

Overall, 64 (60.95%) subjects had a diagnosis of non-VAP and 41 (39.05%) had a diagnosis of VAP. There was a significant (p=0.033) difference in prior antibiotic failure, with 12 (34.29%) subjects in the tigecycline 100-mg group with prior antibiotic failure compared to 4 (11.11%) in the tigecycline 75-mg group and 5 (14.71%) in the imipenem/cilastatin group. There were no statistically significant differences among the treatment groups in CPIS scores or Acute Physiologic and Chronic Health Evaluation Scale II (APACHE II) scores. At least two-thirds of the subjects in each of the 3 treatment groups had APACHE II scores ≤15.

Efficacy, Pharmacokinetic, Pharmacodynamic, and Outcome Research Results: Due to difficulty in enrolling subjects, specifically the VAP subjects, the Sponsor decided to terminate the study early.

Efficacy Results: Due to the small sample size, no formal statistical analysis was conducted. Evaluation of the data consisted primarily of summary displays.

The clinical responses (rates of cure) were 69.6% (16/23) for the tigecycline 75-mg group, 85.0% (17/20) for the tigecycline 100-mg group, and 75.0% (18/24) for the imipenem/cilastatin group. The treatment difference between the tigecycline 75-mg and imipenem/cilastatin groups was -5.4 (70% CI: -21.6, 10.9) and between the tigecycline 100-mg and imipenem/cilastatin groups was 10.0 (70% CI: -6.1, 24.8). Table 5 presents a summary of the clinical response at the TOC assessment for the CE population.

Table 5. Summary of Clinical Response at the Test of Cure Visit, CE Population

Clinical Response	Treatment					
	Tigecycline 75 mg		Tigecycline 100 mg		Imipenem/Cilastatin 1 g	
	n/N (%)	70% CI[a,b]	n/N (%)	70% CI[a,b]	n/N (%)	70% CI[a,b]
Cure	16/23 (69.6)	(56.7, 80.3)	17/20 (85.0)	(72.2, 93.2)	18/24 (75.0)	(62.7, 84.7)
Failure	7/23 (30.4)	(19.7, 43.3)	3/20 (15.0)	(6.8, 27.8)	6/24 (25.0)	(15.3, 37.3)
Treatment difference	-5.4	(-21.6, 10.9)	10.0	(-6.1, 24.8)		

CE = clinically evaluable; CI = confidence interval; N = number of subjects evaluated in each group; n = number of subjects with specified criteria.
a. The 70% CI for individual treatment groups was calculated by using the methods of Clopper and Pearson.
b. The 70% CI for differences between treatment groups was calculated by using the Wilson score method corrected for continuity.

The clinical responses (rates of cure) were 52.8% (19/36) for the tigecycline 75-mg group, 71.4% (25/35) for the tigecycline 100-mg group, and 52.9% (18/34) for theimipenem/cilastatin group. The treatment difference between the tigecycline 75-mg and imipenem/cilastatin groups was -0.2 (70% CI: -14.3, 14.0) and between the tigecycline 100-mg and imipenem/cilastatin groups was 18.5 (70% CI: 4.3, 31.8). Table 6 presents a summary of the clinical response at the TOC assessment for the c-mITT population.

Table 6. Summary of Clinical Response at the Test of Cure Visit, c-mITT Population

Clinical Response	Treatment					
	Tigecycline 75 mg		Tigecycline 100 mg		Imipenem/Cilastatin 1 g	
	n/N (%)	70% CI[a,b]	n/N (%)	70% CI[a,b]	n/N (%)	70% CI[a,b]
Cure	19/36 (52.8)	(42.8, 62.5)	25/35 (71.4)	(61.5, 79.9)	18/34 (52.9)	(42.7, 63.0)
Failure	10/36 (27.8)	(19.5, 37.5)	5/35 (14.3)	(8.1, 23.1)	6/34 (17.6)	(10.7, 27.0)
Indeterminate	7/36 (19.4)	(12.4, 28.6)	5/35 (14.3)	(8.1, 23.1)	10/34 (29.4)	(20.7, 39.6)
Treatment Difference	-0.2	(-14.3, 14.0)	18.5	(4.3, 31.8)		

CI = confidence interval; c-mITT = clinical modified intent-to-treat; N = number of subjects evaluated in each group; n = number of subjects with specified criteria.
a. The 70% CI for individual treatment groups was calculated by using the methods of Clopper and Pearson.
b. The 70% CI for differences between treatment groups was calculated by using the Wilson score method corrected for continuity.

Table 7 presents a summary of the clinical response at the TOC assessment for the VAP and non-VAP subgroups in the CE population.

Table 7. Summary of Clinical Response at the Test of Cure Visit for the VAP and Non-VAP Subgroups, CE Population

Clinical Response	Treatment					
	Tigecycline 75 mg		Tigecycline 100 mg		Imipenem/Cilastatin 1 g	
	n/N (%)	70% CI[a]	n/N (%)	70% CI[a]	n/N (%)	70% CI[a]
VAP subjects						
Cure	5/7 (71.4)	(44.8, 90.0)	6/7 (85.7)	(59.3, 97.7)	7/9 (77.8)	(55.0, 92.3)
Failure	2/7 (28.6)	(10.0, 55.2)	1/7 (14.3)	(2.3, 40.7)	2/9 (22.2)	(7.7, 45.0)
Non-VAP subjects						
Cure	11/16 (68.8)	(52.7, 81.8)	11/13 (84.6)	(67.3, 94.7)	11/15 (73.3)	(56.8, 85.9)
Failure	5/16 (31.3)	(18.2, 47.3)	2/13 (15.4)	(5.3, 32.7)	4/15 (26.7)	(14.1, 43.2)

CE = clinically evaluable; CI = confidence interval; N = number of subjects evaluated in each group; n = number of subjects with specified criteria; VAP = ventilator-associated pneumonia.
a. The 70% CI for individual treatment groups was calculated by using the methods of Clopper and Pearson.

Table 8 presents a summary of the subject-level microbiological response at the TOC assessment for the ME population.

Table 8. Summary of Subject-Level Microbiological Response at the Test of Cure Visit, ME Population

Clinical Response	Treatment					
	Tigecycline 75 mg		Tigecycline 100 mg		Imipenem/Cilastatin 1 g	
	n/N (%)	70% CI[a,b]	n/N (%)	70% CI[a,b]	n/N (%)	70% CI[a,b]
Eradication	8/13 (61.5)	(43.4, 77.4)	8/10 (80.0)	(58.9, 93.0)	12/15 (80.0)	(63.8, 90.9)
Persistence	5/13 (38.5)	(22.6, 56.6)	2/10 (20.0)	(7.0, 41.1)	2/15 (13.3)	(4.6, 28.7)
Superinfection	0/13 (0.0)	(0.0, 13.6)	0/10 (0.0)	(0.0, 17.3)	1/15 (6.7)	(1.1, 20.8)
Treatment difference	-18.5	(-39.6, 4.2)	0.0	(-23.8, 20.9)		

CI = confidence interval; c-mITT = clinical modified intent-to-treat; ME = microbiologically evaluable; N = number of subjects evaluated in each group; n = number of subjects with specified criteria.
a. The 70% CI for individual treatment groups was calculated by using the methods of Clopper and Pearson.
b. The 70% CI for differences between treatment groups was calculated by using the Wilson score method corrected for continuity.

Table 9 presents a summary of the pathogen-level microbiological response at the TOC assessment for the ME population.

Table 9. Pathogen-Level Microbiological Response at Test of Cure Visit, ME Population

Baseline Pathogen	Response	Indication	Treatment						Total	
			Tigecycline 75 mg		Tigecycline 100 mg		Imipenem/Cilastatin 1 g			
			n/N	%	n/N	%	n/N	%	n/N	%
Acinetobacter calcoaceticus	Eradication	VAP	1/1	100.0	-	-	2/3	66.7	3/5	60.0
		Non-VAP	1/2	50.0	1/1	100.0	-	-	2/3	66.7
		Overall	2/3	66.7	1/2	50.0	2/3	66.7	5/8	62.5
	Persistence	VAP	-	-	1/1	100.0	1/3	33.3	2/5	40.0
		Non-VAP	1/2	50.0	-	-	-	-	1/3	33.3
		Overall	1/3	33.3	1/2	50.0	1/3	33.3	3/8	37.5
Enterobacter cloacae	Eradication	Non-VAP	-	-	-	-	1/1	100.0	1/1	100.0
		Overall	-	-	-	-	1/2	50.0	1/2	50.0
	Persistence	VAP	-	-	-	-	1/1	100.0	1/1	100.0
		Overall	-	-	-	-	1/2	50.0	1/2	50.0
Escherichia coli	Eradication	Non-VAP	-	-	-	-	1/1	100.0	1/3	33.3
		Overall	-	-	-	-	1/2	50.0	1/4	25.0
	Persistence	VAP	-	-	-	-	1/1	100.0	1/1	100.0
		Non-VAP	1/1	100.0	1/1	100.0	-	-	2/3	66.7
		Overall	1/1	100.0	1/1	100.0	1/2	50.0	3/4	75.0
Haemophilus haemolyticus	Eradication	VAP	1/1	100.0	-	-	-	-	1/1	100.0
		Overall	1/1	100.0	-	-	-	-	1/1	100.0
Haemophilus influenzae	Eradication	VAP	-	-	1/1	100.0	-	-	1/2	50.0
		Overall	-	-	1/1	100.0	-	-	1/2	50.0
	Persistence	VAP	-	-	-	-	1/1	100.0	1/2	50.0
		Overall	-	-	-	-	1/1	100.0	1/2	50.0
Klebsiella oxytoca	Eradication	Non-VAP	1/1	100.0	-	-	-	-	1/1	100.0
		Overall	1/1	100.0	-	-	-	-	1/1	100.0
Klebsiella pneumoniae	Eradication	VAP	1/2	50.0	-	-	1/2	50.0	2/4	50.0
		Non-VAP	-	-	1/2	50.0	3/3	100.0	4/5	80.0
		Overall	1/2	50.0	1/2	50.0	4/5	80.0	6/9	66.7
	Persistence	VAP	1/2	50.0	-	-	1/2	50.0	2/4	50.0
		Non-VAP	-	-	1/2	50.0	-	-	1/5	20.0
		Overall	1/2	50.0	1/2	50.0	1/5	20.0	3/9	33.3
Serratia marcescens	Eradication	VAP	-	-	1/1	100.0	-	-	1/1	100.0
		Non-VAP	-	-	1/1	100.0	-	-	1/1	100.0
		Overall	-	-	2/2	100.0	-	-	2/2	100.0
Staphylococcus aureus	Eradication	VAP	2/4	50.0	1/1	100.0	5/6	83.3	8/11	72.7
		Non-VAP	3/4	75.0	4/5	80.0	3/3	100.0	10/12	83.3
		Overall	5/8	62.5	5/6	83.3	8/9	88.9	18/23	78.3
	Persistence	VAP	2/4	50.0	-	-	1/6	16.7	3/11	27.3
		Non-VAP	1/4	25.0	1/5	20.0	-	-	2/12	16.7
		Overall	3/8	37.5	1/6	16.7	1/9	11.1	5/23	21.7
Staphylococcus aureus (MRSA)	Eradication	VAP	-	-	-	-	2/2	100.0	2/3	66.7
		Non-VAP	2/3	66.7	2/2	100.0	2/2	100.0	6/7	85.7
		Overall	2/4	50.0	2/2	100.0	4/4	100.0	8/10	80.0
	Persistence	VAP	1/1	100.0	-	-	-	-	1/3	33.3
		Non-VAP	1/3	33.3	-	-	-	-	1/7	14.3
		Overall	2/4	50.0	-	-	-	-	2/10	20.0
Staphylococcus aureus (MSSA)	Eradication	VAP	2/3	66.7	1/1	100.0	3/4	75.0	6/8	75.0
		Non-VAP	1/1	100.0	2/3	66.7	1/1	100.0	4/5	80.0
		Overall	3/4	75.0	3/4	75.0	4/5	80.0	10/13	76.9
	Persistence	VAP	1/3	33.3	-	-	1/4	25.0	2/8	25.0
		Non-VAP	-	-	1/3	33.3			1/5	20.0
		Overall	1/4	25.0	1/4	25.0	1/5	20.0	3/13	23.1
Streptococcus anginosus	Eradication	Non-VAP	1/1	100.0	-	-	-	-	1/1	100.0
		Overall	1/1	100.0	-	-	-	-	1/1	100.0
Streptococcus mitis	Eradication	Non-VAP	1/1	100.0	-	-	-	-	1/1	100.0
		Overall	1/1	100.0	-	-	-	-	1/1	100.0

Table 9. Pathogen-Level Microbiological Response at Test of Cure Visit, ME Population

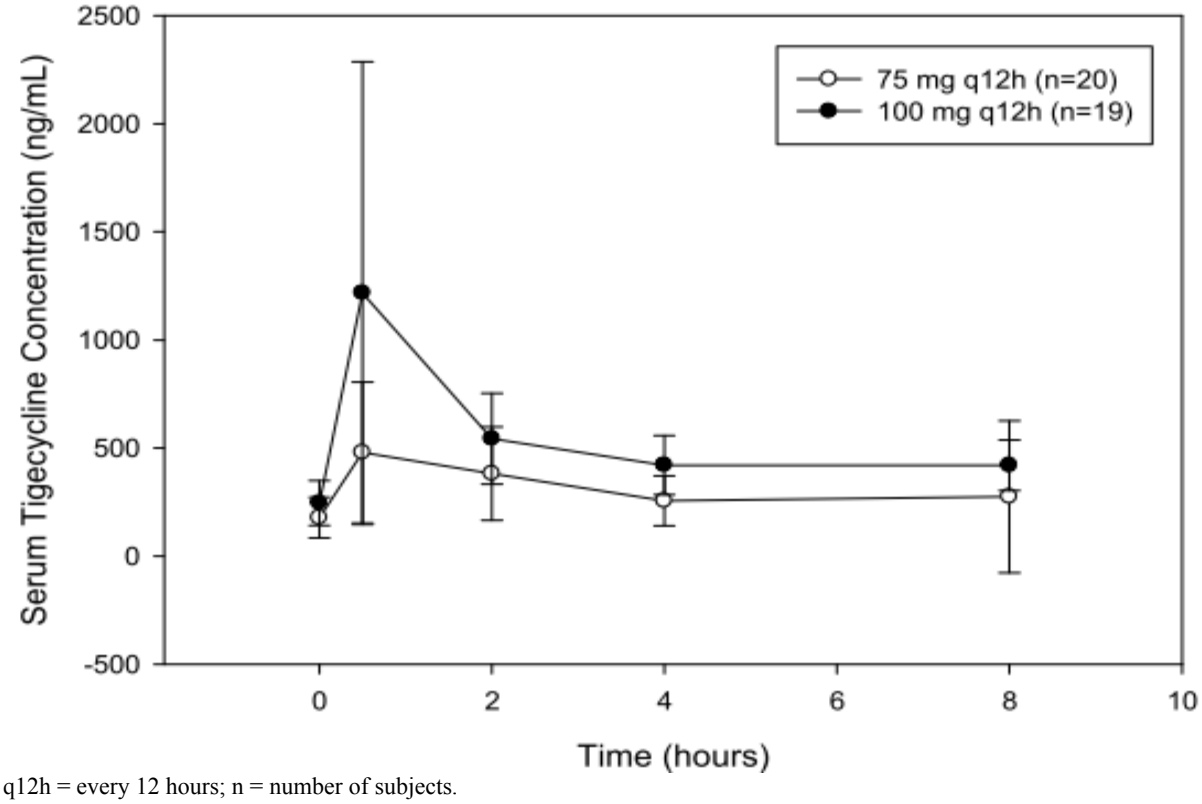
Baseline Pathogen	Response	Indication	Treatment						Total	
			Tigecycline 75 mg		Tigecycline 100 mg		Imipenem/Cilastatin 1 g			
			n/N	%	n/N	%	n/N	%	n/N	%
Streptococcus oralis	Eradication	VAP	-	-	-	-	1/1	100.0	1/1	100.0
		Overall	-	-	-	-	1/1	100.0	1/1	100.0
Streptococcus pneumoniae	Eradication	VAP	1/1	100.0	1/1	100.0	-	-	2/2	100.0
		Overall	1/1	100.0	1/1	100.0	-	-	2/2	100.0

ME = microbiologically evaluable; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*; N = number of subjects evaluated in each group; n = number of subjects with specified criteria; VAP = ventilator-associated pneumonia.

Pharmacokinetic and Pharmacodynamic Results:

A total of 197 tigecycline serum concentrations were reported for 39 subjects, of whom 20 were in the tigecycline 75-mg group and 19 were in the tigecycline 100-mg group. A plot of mean concentration versus time observed after 3 days of treatment is shown in Figure 1.

Figure 1. Plot of Mean Concentration Versus Time Observed After 3 Days of Treatment



q12h = every 12 hours; n = number of subjects.

The tigecycline PK parameters observed in this study were consistent with what has been reported by others. The mean $AUC_{0\text{-}24h}$ observed after multiple doses was 4.7 mg•h/L. Tigecycline is dose proportional and so the predicted $AUC_{0\text{-}24h}$ for the 75 and 100 mg doses

would be 7.05 and 9.40 mg•h/L respectively, which are in close agreement with the mode-predicted values observed in this study.

Previous population PK analyses have shown body size, gender, and creatinine clearance to be significant, although not clinically important covariates. Of particular interest was the observation that the presence of VAP did not appear to affect the estimate of CL, and by extension, $AUC_{0\text{-}24h}$ and $AUC_{0\text{-}24h}$/MIC.

Procalcitonin was not found to be changed with treatment and did not seem to be related to clinical outcome in the subjects with HAP in this study.

No relationship was observed between tigecycline $AUC_{0\text{-}24h}$ and either nausea or vomiting. The very small number of MIC observations made the exploration of the relationship between $AUC_{0\text{-}24h}$/MIC and clinical or microbiological outcome impossible.

Health Outcome Assessments: A summary of results of health outcome assessments is presented in Table 10. Subjects in the imipenem/cilastatin group stayed in the hospital the longest amount of time as well as in the ICU, but the differences were not statistically significant.

Table 10. Summary of Duration of Therapy, Time to Discharge, Duration of ICU, and Time to Defervescence, mITT Population

Variables	Treatment												
	Tigecycline 75 mg				Tigecycline 100 mg				Imipenem/Cilastatin 1 g				
	n	Mean	Median	95% CI	n	Mean	Median	95% CI	n	Mean	Median	95% CI	p-Value[a]
Duration of therapy (days)	36	7.47	8.00	(7.00, 8.00)	35	8.94	9.00	(8.00, 11.00)	34	8.56	8.50	(7.00, 11.00)	0.0983
Time to discharge from initial hospital stay[b] (days)	36	12.36	18.00	(14.00, 29.00)	35	13.94	23.00	(17.00, U)	33	14.24	24.00	(17.00, 31.00)	0.6917
Time to discharge from initial/re-admission hospital stay[b]	36	12.36	18.00	(14.00, 29.00)	35	13.94	23.00	(17.00, U)	34	14.65	24.00	(19.00, U)	0.5659
Duration of intensive care stay (days)	25	7.64	9.00	(8.00, 13.00)	25	9.52	13.00	(8.00, 19.00)	29	10.59	14.00	(10.00, U)	0.2221
Time to defervescence (days)	14	3.00	3.00	(2.00, 4.00)	17	3.06	3.00	(2.00, 4.00)	17	2.41	2.00	(2.00, 3.00)	0.2400

Except for the duration of hospitalization, duration is based on subject with an event.
CI = confidence interval; ICU = intensive care unit; mITT = modified intent-to-treat; n = number of subjects; U = confidence interval cannot be estimated.
a. For hospitalization that began before the start of test article, the duration is calculated from the first day of test article.
b. Log-rank test.

Most of the subjects in the tigecycline 75-mg group were discharged on Day 21 (36.1%), while most of those who were in the tigecycline 100-mg group were discharged on Day 14 (28.6%) and Day 28 (28.6%). Most of the subjects in the imipenem/cilastin group were discharged on Day 7 (30.3%).

There was a higher number of subjects on imipenem/cilastatin to be re-admitted to the hospital (5.88%) relative to the tigecycline 75-mg and 100-mg groups.

In terms of use of concomitant nonstudy antibiotics and medications for nausea and vomiting, subjects in the tigecycline 75-mg group had the most frequent use (27.78%) versus 11.76% of subjects in the imipenem/cilastatin group, and 8.57% in the tigecycline 100-mg group.

Safety Results:

The most frequently occuring AEs in this study were diarhea, hypokalemia, anemia, and vomiting. Table 11 presents a summary of the incidence of all-causality nonserious treatment-emergent AEs (TEAEs) in ≥3% of subjects in any group in the mITT population.

Table 11. Number (%) of Subjects Reporting (Percentages ≥3%) Treatment-Emergent Nonserious Adverse Events, mITT Population

Preferred Term	Overall p-Value	Treatment			Total
		Tigecycline 75 mg n=36 (%)	Tigecycline 100 mg n=35 (%)	Imipenem/ Cilastatin 1 g n=34 (%)	N=105 (%)
Any adverse event	0.847	28 (77.8)	25 (71.4)	26 (76.5)	79 (75.2)
Activated partial thromboplastin time prolonged	0.212	0	2 (5.7)	0	2 (1.9)
Agitation	0.103	0	0	2 (5.9)	2 (1.9)
Anaemia	0.92	3 (8.3)	4 (11.4)	3 (8.8)	10 (9.5)
Atrial fibrillation	<0.001*	0	0	6 (17.6)	6 (5.7)
Bronchospasm	0.077	0	1 (2.9)	3 (8.8)	4 (3.8)
Constipation	0.083	1 (2.8)	2 (5.7)	6 (17.6)	9 (8.6)
Decubitus ulcer	0.605	1 (2.8)	3 (8.6)	2 (5.9)	6 (5.7)
Diarrhoea	1	6 (16.7)	6 (17.1)	5 (14.7)	17 (16.2)
Hypertension	0.186	0	3 (8.6)	3 (8.8)	6 (5.7)
Hypocalcaemia	0.105	3 (8.3)	0	0	3 (2.9)
Hypokalaemia	0.926	4 (11.1)	3 (8.6)	4 (11.8)	11 (10.5)
Hyponatraemia	0.362	4 (11.1)	1 (2.9)	1 (2.9)	6 (5.7)
Hypophosphataemia	0.032†	0	0	3 (8.8)	3 (2.9)
Insomnia	0.691	1 (2.8)	1 (2.9)	2 (5.9)	4 (3.8)
Leukocytosis	0.691	1 (2.8)	1 (2.9)	2 (5.9)	4 (3.8)
Lipase increased	0.695	3 (8.3)	3 (8.6)	1 (2.9)	7 (6.7)
Liver disorder	0.425	0	2 (5.7)	1 (2.9)	3 (2.9)
Nausea	0.394	2 (5.6)	4 (11.4)	1 (2.9)	7 (6.7)
Oedema peripheral	0.654	2 (5.6)	0	1 (2.9)	3 (2.9)
Oxygen saturation decreased	0.327	2 (5.6)	0	0	2 (1.9)
Pain	0.103	0	0	2 (5.9)	2 (1.9)
Phlebitis	0.327	2 (5.6)	0	0	2 (1.9)
Postoperative wound infection	0.327	2 (5.6)	0	0	2 (1.9)
Pyrexia	0.835	3 (8.3)	4 (11.4)	2 (5.9)	9 (8.6)
Rash	0.103	0	0	2 (5.9)	2 (1.9)
Thrombocytopenia	0.691	1 (2.8)	1 (2.9)	2 (5.9)	4 (3.8)
Thrombocytosis	0.425	0	2 (5.7)	1 (2.9)	3 (2.9)
Vomiting	0.707	4 (11.1)	2 (5.7)	4 (11.8)	10 (9.5)

Statistical significance at the 0.05, 0.001 levels is denoted by †, *, respectively.
Classifications of adverse events were based on the Medical Dictionary for Regulatory Activities.
Overall p-value: Refers to the number of subjects' data. Fisher's exact test p-value (2-tail).
mITT = modified intent-to-treat; N = total number of subjects; n = number of subjects.

Table 12 presents a summary of the incidence of drug-related TEAEs in the mITT population.

Table 12. Number (%) of Subjects Reporting Drug-Related Treatment Emergent Adverse Events, mITT Population

System Organ Class[a] Preferred Term	Overall p-Value	Treatment			Total
		Tigecycline 75 mg n=36 (%)	Tigecycline 100 mg n=35 (%)	Imipenem/ Cilastatin 1 g n=34 (%)	N=105 (%)
Any adverse event	0.441	10 (27.8)	13 (37.1)	8 (23.5)	31 (29.5)
Blood and lymphatic system disorders	0.843	1 (2.8)	2 (5.7)	1 (2.9)	4 (3.8)
Leukocytosis	0.769	1 (2.8)	0	1 (2.9)	2 (1.9)
Thrombocytopenia	0.657	0	1 (2.9)	0	1 (1.0)
Thrombocytosis	0.657	0	1 (2.9)	0	1 (1.0)
Gastrointestinal disorders	0.002*	2 (5.6)	10 (28.6)	1 (2.9)	13 (12.4)
Diarrhoea	0.190	1 (2.8)	5 (14.3)	1 (2.9)	7 (6.7)
Nausea	0.218	1 (2.8)	3 (8.6)	0	4 (3.8)
Pancreatitis	0.657	0	1 (2.9)	0	1 (1.0)
Vomiting	0.654	1 (2.8)	2 (5.7)	0	3 (2.9)
General disorders and administration site conditions	0.769	1 (2.8)	0	1 (2.9)	2 (1.9)
Generalised oedema	0.769	1 (2.8)	0	1 (2.9)	2 (1.9)
Hepatobiliary disorders	0.545	0	1 (2.9)	1 (2.9)	2 (1.9)
Liver disorder	0.545	0	1 (2.9)	1 (2.9)	2 (1.9)
Investigations	0.573	4 (11.1)	5 (14.3)	2 (5.9)	11 (10.5)
Activated partial thromboplastin time prolonged	0.212	0	2 (5.7)	0	2 (1.9)
Alanine aminotransferase increased	0.212	0	2 (5.7)	0	2 (1.9)
Aspartate aminotransferase increased	0.212	0	2 (5.7)	0	2 (1.9)
Bilirubin conjugated increased	0.657	0	1 (2.9)	0	1 (1.0)
Blood alkaline phosphatase increased	0.324	0	0	1 (2.9)	1 (1.0)
Blood amylase increased	0.545	0	1 (2.9)	1 (2.9)	2 (1.9)
Blood bilirubin increased	0.657	0	1 (2.9)	0	1 (1.0)
Blood urea increased	1.000	1 (2.8)	0	0	1 (1.0)
Haemoglobin decreased	0.324	0	0	1 (2.9)	1 (1.0)
International normalised ratio increased	0.657	0	1 (2.9)	0	1 (1.0)
Lipase increased	0.695	3 (8.3)	3 (8.6)	1 (2.9)	7 (6.7)
Prothrombin time prolonged	1.000	1 (2.8)	1 (2.9)	0	2 (1.9)
Prothrombin time shortened	0.657	0	1 (2.9)	0	1 (1.0)
Metabolism and nutrition disorders	0.324	0	0	1 (2.9)	1 (1.0)
Hypokalaemia	0.324	0	0	1 (2.9)	1 (1.0)
Musculoskeletal and connective tissue disorders	1.000	1 (2.8)	0	0	1 (1.0)
Pain in extremity	1.000	1 (2.8)	0	0	1 (1.0)
Nervous system disorders	0.545	0	1 (2.9)	1 (2.9)	2 (1.9)
Partial seizures	0.657	0	1 (2.9)	0	1 (1.0)
Vocal cord paresis	0.324	0	0	1 (2.9)	1 (1.0)
Renal and urinary disorders	1.000	1 (2.8)	0	0	1 (1.0)
Polyuria	1.000	1 (2.8)	0	0	1 (1.0)
Skin and subcutaneous tissue disorders	1.000	1 (2.8)	1 (2.9)	0	2 (1.9)
Seborrhoeic dermatitis	1.000	1 (2.8)	0	0	1 (1.0)
Urticaria	0.657	0	1 (2.9)	0	1 (1.0)
Vascular disorders	0.105	3 (8.3)	0	0	3 (2.9)
Phlebitis	0.327	2 (5.6)	0	0	2 (1.9)
Thrombophlebitis superficial	1.000	1 (2.8)	0	0	1 (1.0)

Statistical significance at the 0.01 levels is denoted by *, respectively.
Adverse events and serious adverse events results are not separated out.
Classifications of adverse events were based on the Medical Dictionary for Regulatory Activities.
Overall p-value refers to the number of subjects' data. Fisher's exact test p-value (2-tail).
mITT = modified intent-to-treat; n = number of subjects.
a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels since a subject may have reported 2 or more different adverse events within the higher level category.

Thirty-one subjects experienced SAEs: 12 (33.3%) in the tigecycline 75-mg group, 9 (25.7%) in the tigecycline 100-mg group, and 10 (29.4%) in the imipenem/cilastatin group. One SAE (pancreatitis) in the tigecycline 100-mg group was considered to be related to study medication. Table 13 presents a summary of the incidence of SAEs in the mITT population.

Table 13. Number (%) of Subjects Reporting Serious Adverse Events, mITT Population

System Organ Class[a] Preferred Term	Overall p-Value	Treatment			Total
		Tigecycline 75 mg n=36 (%)	Tigecycline 100 mg n=35 (%)	Imipenem/ Cilastatin 1 g n=34 (%)	N=105 (%)
Any adverse event	0.801	12 (33.3)	9 (25.7)	10 (29.4)	31 (29.5)
Cardiac disorders	0.441	1 (2.8)	2 (5.7)	3 (8.8)	6 (5.7)
Atrial flutter	1.000	1 (2.8)	0	0	1 (1.0)
Cardiac arrest	0.103	0	0	2 (5.9)	2 (1.9)
Sinoatrial block	0.657	0	1 (2.9)	0	1 (1.0)
Tachyarrhythmia	0.657	0	1 (2.9)	0	1 (1.0)
Ventricular fibrillation	0.324	0	0	1 (2.9)	1 (1.0)
Gastrointestinal disorders	0.322	2 (5.6)	3 (8.6)	0	5 (4.8)
Gastrointestinal haemorrhage	1.000	1 (2.8)	0	0	1 (1.0)
Gastrointestinal necrosis	1.000	1 (2.8)	0	0	1 (1.0)
Haematemesis	0.657	0	1 (2.9)	0	1 (1.0)
Oesophageal fistula	0.657	0	1 (2.9)	0	1 (1.0)
Pancreatitis	0.657	0	1 (2.9)	0	1 (1.0)
General disorders and administration site conditions	0.324	0	0	1 (2.9)	1 (1.0)
Multi-organ failure	0.324	0	0	1 (2.9)	1 (1.0)
Systemic inflammatory response syndrome	0.324	0	0	1 (2.9)	1 (1.0)
Infections and infestations	0.149	8 (22.2)	5 (14.3)	2 (5.9)	15 (14.3)
Candida sepsis	0.657	0	1 (2.9)	0	1 (1.0)
Meningitis	1.000	1 (2.8)	0	0	1 (1.0)
Pneumonia	0.654	1 (2.8)	2 (5.7)	0	3 (2.9)
Postoperative wound infection	1.000	1 (2.8)	0	0	1 (1.0)
Sepsis	1.000	1 (2.8)	1 (2.9)	0	2 (1.9)
Septic shock	0.445	4 (11.1)	1 (2.9)	2 (5.9)	7 (6.7)
Musculoskeletal and connective tissue disorders	0.324	0	0	1 (2.9)	1 (1.0)
Systemic lupus erythematosus	0.324	0	0	1 (2.9)	1 (1.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0.654	2 (5.6)	0	1 (2.9)	3 (2.9)
Malignant melanoma	0.324	0	0	1 (2.9)	1 (1.0)
Mediastinum neoplasm	1.000	1 (2.8)	0	0	1 (1.0)
Oesophageal carcinoma	1.000	1 (2.8)	0	0	1 (1.0)
Nervous system disorders	1.000	1 (2.8)	0	0	1 (1.0)
Brain oedema	1.000	1 (2.8)	0	0	1 (1.0)
Renal and urinary disorders	0.324	0	0	1 (2.9)	1 (1.0)
Renal failure acute	0.324	0	0	1 (2.9)	1 (1.0)
Respiratory, thoracic, and mediastinal disorders	0.707	4 (11.1)	2 (5.7)	4 (11.8)	10 (9.5)
Acute respiratory distress syndrome	0.324	0	0	1 (2.9)	1 (1.0)
Atelectasis	1.000	1 (2.8)	0	0	1 (1.0)
Haemothorax	1.000	1 (2.8)	0	0	1 (1.0)
Pneumonia aspiration	1.000	1 (2.8)	0	0	1 (1.0)
Pneumothorax	0.317	1 (2.8)	0	2 (5.9)	3 (2.9)
Pulmonary embolism	0.657	0	1 (2.9)	0	1 (1.0)
Respiratory disorder	0.657	0	1 (2.9)	0	1 (1.0)
Respiratory distress	0.324	0	0	1 (2.9)	1 (1.0)
Tracheal disorder	1.000	1 (2.8)	0	0	1 (1.0)
Vascular disorders	0.771	2 (5.6)	1 (2.9)	0	3 (2.9)
Deep vein thrombosis	1.000	1 (2.8)	0	0	1 (1.0)
Shock	1.000	1 (2.8)	1 (2.9)	0	2 (1.9)

Classifications of adverse events are based on Medical Dictionary for Regulatory Activities.
Overall p-value refers to the number of subjects' data. Fisher's exact test p-value (2-tail).
mITT = modified intent-to-treat; N = total number of subjects; n = number of subjects.
a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels since a subject may report 2 or more different adverse events within the higher level category.

Four (11.1%) subjects in the tigecycline 75-mg group, 3 (8.6%) subjects in the tigecycline 100-mg group, and 3 (8.8%) subjects in the imipenem/cilastatin group discontinued due to AEs. Table 14 presents a summary of TEAEs that caused discontinuation of study drug and withdrawal from the study.

Table 14. Number (%) of Subjects Reporting Adverse Events Causing Discontinuation of Test Article and Withdrawal From Study, mITT Population

System Organ Class[a] Preferred Term	Overall p-Value	Treatment			Total
		Tigecycline 75 mg n=36 (%)	Tigecycline 100 mg n=35 (%)	Imipenem/ Cilastatin 1 g n=34 (%)	N=105 (%)
Adverse Events Causing Discontinuation of Test Article					
Any adverse event	1.000	4 (11.1)	3 (8.6)	3 (8.8)	10 (9.5)
Cardiac disorders	0.324	0	0	1 (2.9)	1 (1.0)
Cardiac arrest	0.324	0	0	1 (2.9)	1 (1.0)
Infections and infestations	1.000	2 (5.6)	1 (2.9)	1 (2.9)	4 (3.8)
Abdominal infection	0.324	0	0	1 (2.9)	1 (1.0)
Meningitis	1.000	1 (2.8)	0	0	1 (1.0)
Sepsis	1.000	1 (2.8)	0	0	1 (1.0)
Septic shock	0.657	0	1 (2.9)	0	1 (1.0)
Investigations	1.000	1 (2.8)	1 (2.9)	0	2 (1.9)
Lipase increased	1.000	1 (2.8)	0	0	1 (1.0)
Prothrombin time prolonged	0.657	0	1 (2.9)	0	1 (1.0)
Nervous system disorders	0.324	0	0	1 (2.9)	1 (1.0)
Vocal cord paresis	0.324	0	0	1 (2.9)	1 (1.0)
Respiratory, thoracic and mediastinal disorders	0.657	0	1 (2.9)	0	1 (1.0)
Respiratory disorder	0.657	0	1 (2.9)	0	1 (1.0)
Vascular disorders	1.000	1 (2.8)	0	0	1 (1.0)
Shock	1.000	1 (2.8)	0	0	1 (1.0)
Adverse Events Causing Withdrawal From Study					
Any adverse event	0.785	5 (13.9)	3 (8.6)	3 (8.8)	11 (10.5)
Cardiac disorders	0.324	0	0	1 (2.9)	1 (1.0)
Cardiac arrest	0.324	0	0	1 (2.9)	1 (1.0)
General disorders and administration site conditions	1.000	1 (2.8)	0	0	1 (1.0)
Injury associated with device	1.000	1 (2.8)	0	0	1 (1.0)
Infections and infestations	1.000	2 (5.6)	1 (2.9)	1 (2.9)	4 (3.8)
Abdominal infection	0.324	0	0	1 (2.9)	1 (1.0)
Meningitis	1.000	1 (2.8)	0	0	1 (1.0)
Sepsis	1.000	1 (2.8)	0	0	1 (1.0)
Septic shock	0.657	0	1 (2.9)	0	1 (1.0)
Investigations	1.000	1 (2.8)	1 (2.9)	0	2 (1.9)
Lipase increased	1.000	1 (2.8)	0	0	1 (1.0)
Prothrombin time prolonged	0.657	0	1 (2.9)	0	1 (1.0)
Nervous system disorders	0.324	0	0	1 (2.9)	1 (1.0)
Vocal cord paresis	0.324	0	0	1 (2.9)	1 (1.0)
Respiratory, thoracic and mediastinal disorders	0.657	0	1 (2.9)	0	1 (1.0)
Respiratory disorder	0.657	0	1 (2.9)	0	1 (1.0)
Vascular disorders	1.000	1 (2.8)	0	0	1 (1.0)
Shock	1.000	1 (2.8)	0	0	1 (1.0)

Classifications of adverse events were based on the Medical Dictionary for Regulatory Activities.
Overall p-value refers to the number of subjects' data. Fisher's exact test p-value (2-tail).
mITT = modified intent-to-treat; N = total number of subjects; n = number of subjects.
a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels since a subject may have reported 2 or more different adverse events within the higher level category.

A total of 17 subjects died during the study: 7 (19.4%) in the tigecycline 75-mg group, 3 (8.6%) in the tigecycline 100-mg group, and 7 (20.6%) in the imipenem/cilastatin group.

None of the deaths was considered to be related to study medication. Table 15 presents a summary of the incidence of AEs with an outcome of death in the mITT population. None of the deaths was considered to be related to study medication.

Table 15. Number (%) of Subjects Reporting Adverse Events With Outcome of Death, mITT Population

System Organ Class[a] Preferred Term	Overall p-Value	Treatment			Total
		Tigecycline 75 mg n=36 (%)	Tigecycline 100 mg n=35 (%)	Imipenem/ Cilastatin 1 g n=34 (%)	N=105 (%)
Any adverse event	0.340	7 (19.4)	3 (8.6)	7 (20.6)	17 (16.2)
Cardiac disorders	0.103	0	0	2 (5.9)	2 (1.9)
Cardiac arrest	0.103	0	0	2 (5.9)	2 (1.9)
General disorders and administration site conditions	0.324	0	0	1 (2.9)	1 (1.0)
Multi-organ failure	0.324	0	0	1 (2.9)	1 (1.0)
Systemic inflammatory response syndrome	0.324	0	0	1 (2.9)	1 (1.0)
Infections and infestations	0.290	5 (13.9)	3 (8.6)	1 (2.9)	9 (8.6)
Pneumonia	0.657	0	1 (2.9)	0	1 (1.0)
Sepsis	1.000	1 (2.8)	1 (2.9)	0	2 (1.9)
Septic shock	0.362	4 (11.1)	1 (2.9)	1 (2.9)	6 (5.7)
Nervous system disorders	1.000	1 (2.8)	0	0	1 (1.0)
Brain oedema	1.000	1 (2.8)	0	0	1 (1.0)
Renal and urinary disorders	0.324	0	0	1 (2.9)	1 (1.0)
Renal failure acute	0.324	0	0	1 (2.9)	1 (1.0)
Respiratory, thoracic and mediastinal disorders	0.278	1 (2.8)	1 (2.9)	4 (11.8)	6 (5.7)
Acute respiratory distress syndrome	0.324	0	0	1 (2.9)	1 (1.0)
Pneumonia aspiration	1.000	1 (2.8)	0	0	1 (1.0)
Pneumothorax	0.103	0	0	2 (5.9)	2 (1.9)
Pulmonary embolism	0.657	0	1 (2.9)	0	1 (1.0)
Respiratory distress	0.324	0	0	1 (2.9)	1 (1.0)
Vascular disorders	1.000	1 (2.8)	0	0	1 (1.0)
Shock	1.000	1 (2.8)	0	0	1 (1.0)

Classifications of adverse events were based on the Medical Dictionary for Regulatory Activities.
Overall p-value refers to the number of subjects' data. Fisher's exact test p-value (2-tail).
mITT = modified intent-to-treat; N = total number of subjects; n = number of subjects.
a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels since a subject may have reported 2 or more different adverse events within the higher level category.

Most subjects (>93%) had a laboratory test result that was considered to be of potential clinical importance (PCI) during the treatment period. A little more than half of the subjects had magnesium (50.0%) or lymphocytes (56.9%) values that met the criteria for PCI.

There was a significant (p=0.038) difference in the incidence of glucose values of PCI, with 35.3% and 31.3% subjects in the tigecycline 75-mg or 100-mg groups, respectively, compared to 60.6% in the imipenem/cilastatin group.

There was a significant (p=0.037) difference in the incidence of direct bilirubin values of PCI, with 12.1% and 31.0% subjects in the tigecycline 75-mg or 100-mg groups, respectively, compared to 6.5% in the imipenem/cilastatin group. One subject in the tigecycline 100-mg group had a total bilirubin ≥2 × upper limit of normal (ULN) and an aspartate transaminase (AST) ≥3 × ULN. Two subjects in the tigecycline 100-mg group and 1 subject in the tigecycline 75-mg group had a total bilirubin ≥2 × ULN and an alanine transaminase (ALT) ≥3 × ULN. The changes were not of clinical importance.

There was a significant (p=0.012) difference in the incidence of coagulation profile values (such as prothrombin activity and partial thrombin time) of PCI, with 20.0% and 18.8% subjects in the tigecycline 75-mg or 100-mg groups, respectively, compared to none in the imipenem/cilastatin group.

Half of the subjects had vital signs of PCI during the treatment period. The incidence among the groups was similar; there were no statistically significant differences.

A little more than one-third of the subjects had an ECG value of PCI during the treatment period. The incidence among the groups was similar; there were no statistically significant differences. The incidences of increases from baseline in QTc values among the groups was similar; there were no statistically significant differences.

One subject in the tigecycline 75-mg group had a QTc interval >500 msec (with a baseline value ≤450 msec). One subject had a QTcF interval of 539 msec on Day 3 of the study. Repeat values on Day 3 were 520 msec and 525 msec. The baseline value was 378 msec. The subject discontinued the study on Day 5 due to growth of *P. aeruginosa*. On Day 5, the QTcF interval was 511 msec.

CONCLUSION: Overall, results with higher doses of tigecycline trended toward improved outcomes in comparison to control and previous Phase 3 data. A signal for improved efficacy at the tigecycline 100 mg twice-daily dose was observed; however, conclusions regarding this dose are speculative given study size and early study termination with small numbers of VAP subjects enrolled, and limited microbiology to correlate to clinical outcomes. Tigecycline dosed at 100 mg twice daily for the treatment of HAP requires further exploration and validation. The treatment-related and all-causality AEs reported in this study were consistent with the subject population and their underlying conditions. The safety profile observed in this study was similar to the known safety profile for tigecycline.