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

PROTOCOL NO.: 3074K5-319 (B1811168)

PROTOCOL TITLE: A Multicenter, Randomized, Double-Blind, Comparison Study of the Safety And Efficacy of a Once-Daily Dose of Tigecycline Versus Ertapenem for the Treatment of Foot Infections in Subjects With Diabetes

Study Centers: One-nineteen (119) centers took part in the study and randomized subjects; 17 in Argentina, 1 in Australia, 1 in Austria, 1 in Belgium, 5 in Canada, 3 in Chile, 4 in China, 3 in Columbia, 3 in Croatia, 3 in Estonia, 1 in Finland, 4 in Germany, 5 in Hungary, 4 in India, 4 in the Republic of Korea, 1 in Latvia, 3 in Lithuania, 4 in Mexico, 1 in Panama, 2 in Poland, 5 in Romania, 9 in the Russian Federation, 4 in Slovakia, 3 in South Africa, 3 in Spain, 1 in Switzerland, 2 in Taiwan, 7 in Ukraine, 2 in the United Kingdom (UK), 13 in the United States (US).

Study Initiation and Final Completion Dates: 14 January 2007 to March 2009

Phase of Development: Phase 3

Study Objectives: The primary objective was to compare the relative safety and clinical efficacy of a once-daily dose of tigecycline versus ertapenem in the treatment of subjects with diabetic foot infections. The goal was to demonstrate noninferiority.

Secondary objectives:

- To evaluate the microbiologic efficacy of tigecycline
- To obtain in vitro susceptibility data on tigecycline for a range of bacterial pathogens isolated from diabetic foot infections
- To compare health care resource utilization between treatment arms
- To examine the pharmacokinetic profile of tigecycline in subjects with diabetic foot infections after once-daily administration and after prolonged administration
- To evaluate the safety and efficacy of a once-daily dose of tigecycline in the treatment of subjects who are identified as having a diabetic foot infection with confirmed osteomyelitis

METHODS

Study Design: This was a phase 3, multicenter, randomized, double-blind (third-party unblinded) study comparing the safety and relative efficacy of a once-daily dose of tigecycline versus ertapenem for the treatment of moderate to severe foot infections in subjects with diabetes. A separate substudy was performed in subjects with severe foot infections complicated by osteomyelitis.

For the primary study, subjects were randomly assigned (in a 1:1 ratio) to receive either tigecycline or ertapenem for up to 28 consecutive days.

Subjects who had osteomyelitis diagnosed at baseline were not evaluable for the primary study but were eligible for enrollment into an osteomyelitis substudy, where they were evaluable for some secondary endpoints. Subjects were randomly assigned (in a 2:1 ratio) to receive either tigecycline or ertapenem for up to 42 consecutive days in the osteomyelitis substudy.

Subjects receiving ertapenem could also receive vancomycin for methicillin-resistant *Staphylococcus aureus* (MRSA), coagulase-negative staphylococci (CNS), or enterococci coverage at the investigator's discretion. If the baseline cultures did not reveal MRSA, CNS, or enterococci, adjunctive therapy was to be discontinued at the discretion of the investigator.

After a minimum of 4 doses (at least 72 hours) of primary therapy (ie, tigecycline or ertapenem), subjects could be discharged from the hospital on IV therapy and receive outpatient therapy, at the Investigator's discretion. No oral follow-on therapy was permitted as part of the study treatment. Subjects receiving oral switch therapy were considered clinical failures.

The schedule of activities for the subjects without osteomyelitis is provided in Table 1 and for subjects with osteomyelitis in Table 2.

Table 1. Schedule of Activities - Subjects With Foot Infections Without Osteomyelitis

Study Procedure	Hour -24 (Screening to Day 1)[a]	Day 3	Day 6 to Penultimate Day of IV Test Article Administration[b]	Last Day of IV Test Article Administration	Test-of-Cure Visit[c]
Visit ID (for sponsor use only)	1	2	3-24	40	42
Informed consent	X				
Medical /medication history	X				
Physical examination[d]	X	X			X
Assessment of clinical signs and symptoms[e]	X[f]	X		X	X[f]
Clinical evaluation[g]				X	X
Vital signs[h]	X	X	X	X	X
Height and weight	X				
Peripheral perfusion assessment[i]	X				X
Pregnancy test	X[j]				
Creatinine clearance	X[k]				
Hemoglobin A1c	X				
Hematology[l]	X	X	X[m,n]	X	X
Coagulation tests[l]	X	X		X	X
Serum chemistry[l]	X	X	X[n]	X	X
Urinalysis[o]	X	X		X	X[p]
12-lead electrocardiogram	X	X[q]		X[q]	X
Imaging[r]	X				
Pharmacokinetics[s,t]	X	X	X[u]	X[v]	
Wound cultures[w]	X[x]			X[y]	X[y]
Blood cultures[z]	X				
Healthcare resource utilization data and concomitant treatments	X	X	X	X	X
Intravenous test article administration	X	X	X	X	
Collection of adverse events	X[aa]	X	X	X	X

ID = Identification; IV = intravenous; PEDIS = diabetic foot ulcer classification system measuring perfusion, extent, depth/tissue loss, infection, and sensation; TOC = test-of-cure.

a. All procedures must be completed within 1 day before the first dose of intravenous test article administration (Day 1) unless otherwise noted.
b. Beginning on day 6 through the day before the last day of intravenous test article administration, the assessments were to be done daily unless otherwise indicated and were to be done only while the subject was still receiving intravenous test article.
c. The test-of-cure visit was 14 to 21 days after the last day of intravenous test article administration.
d. Physical examination for subjects with open ulcers may have included a probe-to-bone assessment for presumptive osteomyelitis. If a probe-to-bone assessment was used, a sterile blunt stainless-steel probe should have been used. If baseline probe-to-bone assessment indicated osteomyelitis, subject may have been considered for the osteomyelitis substudy arm.
e. Signs and symptoms included drainage, erythema, induration, tenderness, pain, and local warmth. If applicable, this may have also included an evaluation of the ulcer including size, depth, and undermining.
f. Where feasible, assessment included a photograph or diagram of the infection to be stored at the investigational site.
g. The clinical evaluation was the Investigator's assessment of the subject's response to therapy (ie, cure, failure or indeterminate). This evaluation should have been done for all visits indicated, even if the subject discontinued test article and/or withdrew from the study. Subjects who are declared to be clinical failures and required nonstudy antibiotics or extirpative surgery should have had all outstanding clinical evaluations performed before the initiation of a nonstudy antibiotic or surgery.
h. Vital signs included temperature, respiratory rate, heart rate, and blood pressure. Vital signs were monitored daily while subject was receiving test article, but were only recorded as indicated in the flowchart.
i. Peripheral perfusion assessment for PEDIS grade classification.
j. For women of childbearing potential, a negative urine or serum pregnancy test result must have been observed before the first dose of intravenous test article was administered.
k. Creatinine clearance was repeated as clinically indicated throughout the treatment period.

Table 1. Schedule of Activities - Subjects With Foot Infections Without Osteomyelitis

l. Hematology included complete blood count (with total white blood cell count with differential, platelet count, hemoglobin, and hematocrit). Coagulation tests included activated partial thromboplastin time, prothrombin time, and international normalized ratio (if available). If prothrombin time was not available, prothrombin activity was obtained. Serum chemistry included C-reactive protein, creatinine, blood urea nitrogen or urea, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, direct bilirubin, albumin, total protein, glucose, sodium, potassium, chloride, carbon dioxide or bicarbonate, calcium, amylase, lipase (optional), and phosphorus.
m. Complete blood count only.
n. To be done weekly while subject was taking test article.
o. Urinalysis included specific gravity, pH, albumin (protein), urine glucose (sugar), ketones, hemoglobin, nitrites, urine leukocyte esterase.
p. To be repeated at TOC visit if there were any clinically significant abnormal values on the last day of intravenous test article administration.
q. Performed as soon as possible after the end of primary test article infusion (within 2 hours).
r. Baseline radiograph obtained within 48 hours before the first dose of intravenous test article administration. If radiograph indicated osteomyelitis, subject may have been considered for the osteomyelitis substudy arm.
s. For hospitalized subjects at selected investigational sites. Samples were analyzed for tigecycline.
t. Subjects who are scheduled for surgical procedures or amputation while receiving test article may have had a bone sample collected at that time. A blood sample should also have been collected at approximately the same time as the bone sample collection.
u. Only on day 14, if subject was still receiving test article.
v. Only if the last day of test article administration was day 28.
w. Samples for baseline bacterial culture (aerobic and anaerobic) and Gram stain must have been obtained before the administration of the first dose of test article (note: culture results were not required at screening unless subject was a prior antibiotic failure as noted below). Wound cultures were obtained from curettage of wound base, biopsy tissue samples, or aspiration of secretions. Swabs specimens were not acceptable.
x. Wound cultures taken prior to the 24 screening window may have been used to satisfy the prior antibiotic failure inclusion criteria. However, if this was the case, for the purposes of the baseline culture sample required for the study, a second sample for culture was taken within the 24 hour screening period and results recorded appropriately.
y. Wound cultures performed if healing did not preclude the availability of material for culture. Cultures obtained if the subject was a treatment failure.
z. If baseline blood cultures were positive, repeat cultures were obtained at the discretion of the investigator until negative, or if the subject was a treatment failure. If the baseline blood cultures were negative, cultures were repeated if clinically indicated.
aa. All adverse events were recorded on source documents. For subjects who were randomly assigned to treatment, all adverse events were recorded on the case report form. Adverse events were recorded from the time the subject signed the informed consent through the TOC visit or 15 days after the last day of IV test article administration, whichever was later.

Table 2. Schedule of Activities - Subjects With Foot Infections With Osteomyelitis

Study Procedure	Hour -24 (Screening to Day 1)[a]	Day 3	Day 6 to Penultimate Day of IV Test Article Administration [b]	Last Day of IV Test Article Administration	Early Follow-Up Visit [c]	Test-of-Cure Visit [d]
Visit ID (for sponsor use only)	1	2	3-38	40	41	42
Informed consent	X					
Medical /medication history	X					
Physical examination[e]	X	X			X	X
Assessment of clinical signs and symptoms[f]	X[g]	X		X	X	X[g]
Clinical evaluation[h]				X	X	X
Vital signs[i]	X	X	X	X	X	X
Height and weight	X					
Peripheral perfusion assessment[j]	X					X
Pregnancy test[k]	X					
Creatinine clearance	X[l]					
Hemoglobin A1c	X					X
Hematology[m]	X	X	X[n,o]	X	X	X
Coagulation tests[m]	X	X		X	X	X
Serum chemistry[m]	X	X	X[o]	X	X	X
Urinalysis[p]	X	X		X	X[q]	X[q]
12-lead electrocardiogram	X	X[r]		X[r]	X	X[s]
Imaging[t, u]	X[v]				X[v]	X[v]
Pharmacokinetics[w, x,]	X	X	X[y]	X[z]		
Wound cultures[aa]	X[bb, cc]			X[dd]	X[dd]	X[dd]
Blood cultures[ee]	X					
Healthcare resource utilization data and concomitant treatments	X	X	X	X	X	X
Intravenous test article administration	X	X	X	X		
Collection of adverse events	X[ff]	X	X	X	X	X

ID = Identification; IV = intravenous; PEDIS = diabetic foot ulcer classification system measuring perfusion, extent, depth/tissue loss, infection, and sensation; TOC = test-of-cure.

a. All procedures completed within 1 day before the first dose of intravenous test article administration (day 1) unless otherwise noted.
b. Beginning on day 6 through the day before the last day of intravenous test article administration, the assessments were to be done daily unless otherwise indicated and were to be done only while the subject was still receiving intravenous test article.
c. The early follow-up visit was 11 to 13 weeks (i.e. 77 to 91 days) after the last day of IV test article administration.
d. The TOC visit was 25 to 27 weeks (i.e. 175 to 189 days) after the last day of IV test article administration.
e. Physical examination for subjects with open ulcers may have included a probe-to-bone assessment for presumptive osteomyelitis. If a probe-to-bone assessment was used, a sterile blunt stainless-steel probe should have been used. Subject may have been randomly assigned to the osteomyelitis substudy arm if baseline probe-to-bone assessment suggested osteomyelitis. For subjects to be evaluable for the osteomyelitis substudy arm, however, osteomyelitis must have been confirmed by magnetic resonance imaging (MRI), or bone biopsy if MRI was contraindicated, as soon as possible after randomization (within 14 days).
f. Signs and symptoms included drainage, erythema, induration, tenderness, pain, and local warmth. If applicable, this may have also included an evaluation of the ulcer including size, depth, and undermining.
g. Where feasible, assessment may have included a photograph or diagram of the infection to be stored at the investigational site.
h. The clinical evaluation was the Investigator's assessment of the subject's response to therapy (ie, cure, failure or indeterminate). This evaluation was done for all visits indicated, even if the subject discontinued test article and/or withdrrew from the study. Subjects who were declared to be clinical failures and required nonstudy antibiotics or extirpative surgery had all outstanding clinical evaluations performed before the initiation of a nonstudy antibiotic or surgery.
i. Vital signs included temperature, respiratory rate, heart rate, and blood pressure. Vital signs were monitored daily

Table 1. Schedule of Activities - Subjects With Foot Infections Without Osteomyelitis

while subject was receiving test article, but were only recorded as indicated in the flow chart.

j. Peripheral perfusion assessment for PEDIS grade classification.

k. For women of childbearing potential, a negative urine or serum pregnancy test result must have been observed before the first dose of intravenous test article was administered.

l. Creatinine clearance was repeated as clinically indicated throughout the treatment period.

m. Hematology included complete blood count (with total white blood cell count with differential, platelet count, hemoglobin, and hematocrit). 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. Serum chemistry included C-reactive protein, creatinine, blood urea nitrogen or urea, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, direct bilirubin, albumin, total protein, glucose, sodium, potassium, chloride, carbon dioxide or bicarbonate, calcium, amylase, lipase (optional), and phosphorus.

n. Complete blood count only.

o. Performed weekly while subject was taking test article.

p. Urinalysis included specific gravity, pH, albumin (protein), urine glucose (sugar), ketones, hemoglobin, nitrites, urine leukocyte esterase.

q. Was repeated if there are any clinically significant abnormal values at the prior assessment.

r. Baseline electrocardiogram obtained within 24 hours before the first day of intravenous test article administration. Electrocardiogram on day 3 performed as soon as possible after the end of primary test article infusion (within 2 hours).

s. Electrocardiogram was repeated if it was abnormal at the prior assessment.

t. Subject may have been randomly assigned to the osteomyelitis substudy arm if baseline radiograph (obtained within 48 hours before the first dose of IV test article administration) suggested osteomyelitis. For subjects to have been evaluable for the osteomyelitis substudy arm, however, osteomyelitis must have been confirmed by MRI, or bone biopsy if MRI was contraindicated, as soon as possible after randomization (within 14 days).

u. Positive MRI findings may have included decreased marrow signal T1-weighted images, increased marrow signal on T2-weighted images, and contrast enhancement on T1-weighted post-contrast images. This may have been associated with findings of soft tissue mass, cortical destruction, sequestrum formation, and sinus tracts with ulceration.

v. MRI performed at baseline as soon as possible after randomization (within 14 days) and at the early follow-up and TOC visits (within the visit window). If MRI was contraindicated, a bone biopsy was done at baseline and a radiograph was done at the early follow-up and TOC visits.

w. For hospitalized subjects at selected investigational sites. Samples were analyzed for tigecycline.

x. Subjects who are scheduled for surgical procedures or amputation while receiving test article may have had a bone sample collected at that time. A blood sample was also collected at approximately the same time as the bone sample collection.

y. Only on days 14 and 28, while subject was still receiving test article.

z. Only if last day of test article administration was day 42.

aa. Samples for baseline bacterial culture (aerobic and anaerobic) and Gram stain must have been obtained before the administration of the first dose of test article (note: culture results not required at screening unless subject was a prior antibiotic failure as noted below). Wound cultures obtained from curettage of wound base, biopsy tissue samples, or aspiration of secretions. Swabs specimens were not acceptable.

bb. Percutaneous bone biopsy was strongly encouraged at baseline, and, if MRI was contraindicated, must have been done for subject to be considered evaluable.

cc. Wound cultures taken prior to the 24 Screening window may have been used to satisfy the prior antibiotic failure inclusion criteria. However, if this was the case, for the purposes of the baseline culture sample required for the study, a second sample for culture was taken within the 24 hour screening period and results recorded appropriately.

dd. Wound cultures performed if healing did not preclude the availability of material for culture. Cultures were obtained if the subject was a treatment failure.

ee. If baseline blood cultures were positive, repeat cultures were obtained at the discretion of the investigator until negative, or if the subject was a treatment failure. If the baseline blood cultures were negative, cultures may be repeated if clinically indicated.

ff. All adverse events must have been recorded on source documents. For subjects who were randomly assigned to treatment, adverse events were recorded in the case report form. Adverse events were recorded from the time the subject signed the informed consent through the TOC visit or 15 days after the last day of IV test article administration, whichever was later.

Number of Subjects (Planned and Analyzed): A combined total of approximately 1065 subjects were planned to be enrolled in the study (954 in primary study and 111 in the osteomyelitis substudy arm). A combined total of 1061 subjects (944 subjects in primary study and 117 subjects in substudy) received treatment, comprising the modified intent-to-treat (mITT) population; 76 in Argentina, 9 in Australia, 2 in Austria, 3 in Belgium, 22 in Canada, 17 in Chile, 61 in China, 17 in Colombia, 10 in Croatia, 27 in Estonia, 6 in Finland, 14 in Germany, 101 in Hungary, 60 in India, 53 in Korea, 2 in Latvia, 15 in Lithuania, 40 in Mexico, 3 in Panama, 29 in Poland, 41 in Romania, 99 in the Russian Federation, 28 in Slovakia, 43 in South Africa, 24 in Spain, 5 in Switzerland, 22 in Taiwan, 117 in the US, 98 in Ukraine, 17 in the UK.

Diagnosis and Main Criteria for Inclusion: The study included male and female subjects aged 18 years and older with diabetes and a qualifying diabetic foot infection. Subjects with evidence of a diabetic foot infection with osteomyelitis may have qualified for the osteomyelitis substudy arm.

Exclusion Criteria: Subjects with additional significant disease, infection with resistant pathogens, contraindication, or hypersensitivity to any test article or related antibiotic were excluded from the study.

Study Treatment: Subjects were randomly assigned (in a 1:1 ratio) to receive either tigecycline or ertapenem for up to 28 consecutive days in the primary study and (in a 2:1 ratio) to receive either tigecycline or ertapenem for up to 42 consecutive days in the osteomyelitis substudy. Subjects received either IV tigecycline 150 mg or IV ertapenem 1 g, infused over a period of approximately 30 minutes, every 24 hours. After a minimum of 4 doses (at least 72 hours) of primary therapy (ie, tigecycline or ertapenem), subjects could have been discharged from the hospital and continued IV therapy on an outpatient basis.

Efficacy Endpoints:

Primary Endpoint: The primary efficacy endpoint was the clinical response rate at the test-of-cure (TOC) visit for 2 co-primary populations: the clinically evaluable (CE) population and the clinical mITT (c-mITT) population.

Secondary Endpoints: Secondary endpoints included microbiologic responses at the subject level and at the pathogen level, cure rate by baseline pathogen, response rate by baseline pathogen and minimum inhibitory concentration (MIC) value, response rates for polymicrobial/monomicrobial infections, and susceptibility evaluations.

Safety Evaluations: Physical examinations, vital signs, clinical signs and symptoms of infection, adverse events (AEs), laboratory tests, and electrocardiograms were evaluated.

Statistical Methods: The randomized or intent-to-treat (ITT) population consisted of screened subjects who were randomly assigned to test article. The mITT population consisted of ITT subjects who received at least one dose of test article.

The c-mITT population included all subjects who were randomly assigned to receive test article, received at least 1 dose of test article, and who had clinical evidence of a diabetic foot infection (DFI) without osteomyelitis as defined in the inclusion criteria.

The microbiologic mITT (m-mITT) population consisted of c-mITT subjects who had one or more baseline isolates.

The clinically evaluable (CE) population included all subjects who met all protocol inclusion/exclusion criteria, received at least 5 days and between 80% and 120% of the prescribed number of doses (or were declared clinical failures), received ≤24 hours of a potentially effective concomitant antibacterial treatment after receiving the first dose of test article through the TOC visit, had a TOC assessment of cure or failure and did not develop osteomyelitis ≤14 days after the first dose of test article.

The primary DFI study and the osteomyelitis substudy were analyzed separately. The primary efficacy endpoint was the clinical response rate at the TOC visit for 2 co-primary populations: the CE population and the c-mITT population. Noninferiority of tigecycline compared with ertapenem was evaluated for clinical response by using the lower limit of a 2-sided 95% confidence interval for the true difference in efficacy (tigecycline minus ertapenem) adjusted for the stratification variable used at the time of randomization (ie, PEDIS infection severity score). Noninferiority was concluded if the lower limit of the 2-sided 95% confidence interval was not less than –10%. Because of the descriptive nature of the osteomyelitis substudy, no formal statistical analysis was planned. Two (2)-sided 95% confidence intervals for the true proportion of favorable responses in each treatment group were reported.

Secondary analyses included 1) microbiologic response (eradication, persistence, superinfection, indeterminate) at the subject level; 2) microbiologic response (eradication, persistence, or indeterminate) at the pathogen level; 3) clinical cure rates by baseline pathogen; 4) response rates for subjects with monomicrobial and polymicrobial infections; 5) decreased susceptibility (≥4-fold increase in MIC; 6) response rates by baseline pathogen and MIC values; and 7) susceptibility data (MIC 50 [50% inhibition], MIC 90 [90% inhibition]) by pathogen.

The analysis of microbiologic response at the subject level was similar to the primary analysis. All other secondary endpoints were summarized, including 95% confidence limits, where appropriate.

RESULTS

Subject Disposition and Demography: Subject disposition is summarized by treatment group in the primary study, in the osteomyelitis substudy, and overall in Table 3.

Table 3. Subject Disposition

	Primary			Substudy			Total		
Population	**Tigecycline (n=483)**	**Ertapenem (n=472)**	**Total (n=985)**	**Tigecycline (n=77)**	**Ertapenem (n=41)**	**Total (n=135)**	**Tigecycline (n=560)**	**Ertapenem (n=513)**	**Total (n=1123)**
Screened			985 (100)			135 (100)			1123 (100)
Screen Failure			30 (3.0)			17 (12.6)			50 (4.5)
Intent-to-treat (ITT)	483 (100)	472 (100)	955 (97.0)	77 (100)	41 (100)	118 (87.4)	560 (100)	513 (100)	1073 (95.5)
No treatment received	6 (1.2)	5 (1.1)	11 (1.1)	1 (1.3)	0	1 (0.7)	7 (1.3)	5 (1.0)	12 (1.1)
Modified Intent-to-Treat (mITT)	477 (98.8)	467 (98.9)	944 (95.8)	76 (98.7)	41 (100)	117 (86.7)	553 (98.8)	508 (99.0)	1061 (94.5)
Did not meet minimum disease criteria	1 (0.2)	1 (0.2)	2 (0.2)	23 (29.9)	8 (19.5)	31 (23.0)	24 (4.3)	9 (1.8)	33 (2.9)
Clinical mITT (c-mITT)	476 (98.6)	466 (98.7)	942 (95.6)	53 (68.8)	33 (80.5)	86 (63.7)	529 (94.5)	499 (97.3)	1028 (91.5)
Did not meet clinical evaluability criteria	68 (14.1)	61 (12.9)	129 (13.1)	15 (19.5)	9 (22.0)	24 (17.8)	83 (14.8)	70 (13.6)	153 (13.6)
Clinical evaluable (CE)	408 (84.5)	405 (85.8)	813 (82.5)	38 (49.4)	24 (58.5)	62 (45.9)	446 (79.6)	429 (83.6)	875 (77.9)
No baseline and/or susceptible isolates	92 (19.0)	88 (18.6)	180 (18.3)	10 (13.0)	6 (14.6)	16 (11.9)	102 (18.2)	94 (18.3)	196 (17.5)
Microbiologically evaluable	316 (65.4)	317 (67.2)	633 (64.3)	28 (36.4)	18 (43.9)	46 (34.1)	344 (61.4)	335 (65.3)	679 (60.5)
Microbiologic mITT (m-mITT)	378 (78.3)	372 (78.8)	750 (76.1)	37 (48.1)	27 (65.9)	64 (47.4)	415 (74.1)	399 (77.8)	814 (72.5)
No baseline isolate identified from c-mITT	97 (20.1)	94 (19.9)	191 (19.4)	16 (20.8)	6 (14.6)	22 (16.3)	113 (20.2)	100 (19.5)	213 (19.0)

c-mITT = mITT subjects with evidence of disease; ITT = all randomized subjects; mITT = ITT subjects who received at least 1 dose of investigational product; m-mITT = c-mITT subjects with identified baseline isolates; n = number of subjects.

The number of subjects who discontinued investigational product in the primary study is summarized in Table 4.

Table 4. Discontinuations in the Primary Study - mITT Population

Conclusion Status Reason[a]	Overall p-Value[b]	Tigecycline (n=477)	Ertapenem (n=467)	Total (n=944)
Discontinued	0.029*	100 (21.0)	72 (15.4)	172 (18.2)
Adverse event	0.081	42 (8.8)	27 (5.8)	69 (7.3)
Investigator request	1.000	3 (0.6)	2 (0.4)	5 (0.5)
Other	0.371	27 (5.7)	20 (4.3)	47 (5.0)
Protocol violation	0.621	1 (0.2)	2 (0.4)	3 (0.3)
Subject request	0.029*	14 (2.9)	4 (0.9)	18 (1.9)
Unsatisfactory response - efficacy	0.462	13 (2.7)	17 (3.6)	30 (3.2)

mITT = modified intent-to-treat; n = number of subjects.
a. Total discontinued is the sum of individual reasons since they are mutually exclusive by subject.
b. Overall p-value refers to the number of subjects data and was determined using Fisher exact test p-value (2-tail); statistical significance at the 0.05 level is denoted by *.

The number of subjects who discontinued investigational product in the osteomyelitis substudy is summarized in Table 5.

Table 5. Discontinuations in the Osteomyelitis Substudy - mITT Population

Conclusion Status Reason[a]	Overall p-Value[b]	Tigecycline (n=76)	Ertapenem (n=41)	Total (n=117)
Discontinued	0.004**	31 (40.8)	6 (14.6)	37 (31.6)
Adverse event	0.054	11 (14.5)	1 (2.4)	12 (10.3)
Death	0.350	0	1 (2.4)	1 (0.9)
Investigator request	0.541	2 (2.6)	0	2 (1.7)
Lost to follow-up	0.541	2 (2.6)	0	2 (1.7)
Other	0.296	4 (5.3)	0	4 (3.4)
Subject request	0.296	4 (5.3)	0	4 (3.4)
Unsatisfactory response - efficacy	1.000	8 (10.5)	4 (9.8)	12 (10.3)

mITT = modified intent-to-treat; n = number of subjects.
a. Total discontinued is the sum of individual reasons since they are mutually exclusive by subject.
b. Overall p-value refers to the number of subjects data and was determined using Fisher exact test p-value (2-tail); statistical significance at the 0.01 level is denoted by **.

The demographic and baseline characteristics of the mITT population are shown in Table 6.

Table 6. Demographic and Baseline Characteristics - mITT Population

Characteristic	Primary Study				Osteomyelitis Substudy			
	p-Value[a]	Tigecycline (n=477)	Ertapenem (n=467)	Total (n=944)	p-Value[a]	Tigecycline (n=76)	Ertapenem (n=41)	Total (n=117)
Age (Year)								
n		477	467	944		76	41	117
Mean	0.526[a]	59.64	59.16	59.41	0.175[a]	57.61	54.05	56.36
Standard deviation		11.84	11.41	11.63		13.20	13.93	13.51
Minimum		22.00	22.00	22.00		27.00	22.00	22.00
Maximum		88.00	88.00	88.00		85.00	83.00	85.00
Median		60.00	59.00	60.00		57.50	55.00	56.00
Sex, n (%)	0.142[b]				0.756[b]			
Male		300 (62.89)	315 (67.45)	615 (65.15)		54 (71.05)	28 (68.29)	82 (70.09)
Female		177 (37.11)	152 (32.55)	329 (34.85)		22 (28.95)	13 (31.71)	35 (29.91)
Ethnic origin, n (%)	0.564 b				0.819 b			
American Indian or Alaska native		0	0	0		1 (1.32)	0	1 (0.85)
Asian		70 (14.68)	70 (14.99)	140 (14.83)		1 (1.32)	0	1 (0.85)
Black or African American		17 (3.56)	23 (4.93)	40 (4.24)		4 (5.26)	3 (7.32)	7 (5.98)
White		325 (68.13)	321 (68.74)	646 (68.43)		35 (46.05)	17 (41.46)	52 (44.44)
Other		65 (13.63)	53 (11.35)	118 (12.50)		35 (46.05)	21 (51.22)	56 (47.86)
Body mass index (kg/m 2)								
n		473	465	938		75	41	116
Mean	0.977[a]	28.78	28.76	28.77	0.135[a]	26.32	28.28	27.01
Standard deviation		6.72	6.39	6.56		6.47	7.10	6.73
Minimum		16.11	15.57	15.57		15.43	15.73	15.43
Maximum		89.56	62.31	89.56		47.88	43.94	47.88
Median		27.61	27.68	27.63		24.63	26.78	25.23
Missing		4	2	6		1	0	1
Creatinine clearance (mL/min)								
n		477	467	944		74	41	115
Mean	0.807[a]	115.56	109.82	112.72	0.268[a]	82.83	91.64	85.97
Standard deviation		423.96	283.18	361.06		29.95	54.99	40.66
Minimum		26.99	23.04	23.04		33.83	31.48	31.48
Maximum		9315.66	6132.05	9315.66		161.74	328.76	328.76
Median		91.97	86.42	88.64		81.26	78.05	78.61
Missing		0	0	0		2	0	2
Study duration (days)								

Table 6. Demographic and Baseline Characteristics - mITT Population

Characteristic	Primary Study				Osteomyelitis Substudy			
	p-Value[a]	Tigecycline (n=477)	Ertapenem (n=467)	Total (n=944)	p-Value[a]	Tigecycline (n=76)	Ertapenem (n=41)	Total (n=117)
n		477	467	944		76	41	117
Mean	0.051[a]	27.50	29.04	28.26	0.035[a]	115.11	151.32	127.79
Standard deviation		13.64	10.27	12.11		92.81	76.49	88.81
Minimum		2.00	2.00	2.00		2.00	10.00	2.00
Maximum		176.00	59.00	176.00		241.00	238.00	241.00
Median		28.00	29.00	28.00		97.00	187.00	123.00
Therapy duration (days)								
n		477	467	944		76	41	117
Mean	0.116[a]	13.07	13.82	13.44	0.026[a]	25.13	31.22	27.26
Standard deviation		7.49	7.22	7.36		14.24	13.19	14.13
Minimum		1.00	1.00	1.00		2.00	5.00	2.00
Maximum		29.00	30.00	30.00		43.00	45.00	45.00
Median		11.00	12.00	12.00		25.00	39.00	28.00

mITT = modified intent-to-treat; n = number of subjects.

a. One-way analysis of variance with treatment as factor.

b. p-Value for chi-square test.

Efficacy Results: The results of the analysis for clinical response in the primary study, CE population are shown in Table 7. Cure rates at the TOC assessment in the CE population were lower in the tigecycline group than in the ertapenem group (77.5% and 82.5% respectively). The adjusted difference in efficacy (tigecycline minus ertapenem) was -5.5%, with a lower bound of the 95% CI of -11.0%. Therefore, tigecycline did not meet the statistical criteria for noninferiority to ertapenem at the TOC assessment in the CE population.

The results of the analysis for clinical response in the primary study, c-mITT population are shown in Table 8. Cure rates at the TOC assessment in the c-mITT population were lower in the tigecycline group than in the ertapenem group (71.4% and 77.9%respectively). The adjusted difference in efficacy (tigecycline minus ertapenem) was -6.7%, with the lower limit of the 95% CI of -12.3%. Consistent with the findings from the CE population, tigecycline did not meet the statistical criteria for noninferiority to ertapenem at the TOC assessment in the c-mITT population.

Table 7. Summary of Clinical Response Results in the Primary Study, CE Population

				Tigecycline[a]		Ertapenem[a]		Difference (Tigecycline-Ertapenem)[b]		
Visit	Response	PEDIS Infection Score	Category	n /N	% (95% CI)	n /N	% (95% CI)	% (95% CI)	Test for Noninferiority p-Value	Test for Difference p-Value
LDOT	Cure	Grade 2, 3		320/373	85.8 (81.8, 89.2)	324/361	89.8 (86.1, 92.7)	-4.0 (-9.0, 1.0)	0.0084	0.1263
		Grade 4		27/35	77.1 (59.9, 89.6)	33/44	75.0 (59.7, 86.8)	2.1(-19.3, 23.6)	0.1603	1
		Overall	Unadjusted	347/408	85.0 (81.2, 88.4)	357/405	88.1 (84.6, 91.1)	-3.1 (-8.0, 1.8)	0.0026	0.2319
			Adjusted					-3.5 (-8.2, 1.1)	0.0030	0.1430
	Failure	Overall		61/408	15.0 (11.6, 18.8)	48/405	11.9 (8.9, 15.4)			
TOC	Cure	Grade 2, 3		291/373	78.0 (73.5, 82.1)	305/361	84.5 (80.3, 88.1)	-6.5(-12.4, -0.6)	0.1282	0.0307
		Grade 4		25/35	71.4 (53.7, 85.4)	29/44	65.9 (50.1, 79.5)	5.5(-17.5, 28.6)	0.1077	0.7776
		Overall	Unadjusted	316/408	77.5 (73.1, 81.4)	334/405	82.5 (78.4, 86.0)	-5.0(-10.8, 0.7)	0.0455	0.0885
			Adjusted					-5.5(-11.0, 0.1)	0.0550	0.0540
	Failure	Overall		92/408	22.5 (18.6, 26.9)	71/405	17.5 (14.0, 21.6)			

CE = clinically evaluable; CI = confidence interval; LDOT = last day of therapy; N = number of subjects; n = number of subjects with clinical response; PEDIS = perfusion, extent, depth/tissue loss, infection, and sensation (diabetic foot ulcer classification system); TOC = test-of-cure.

a. 95% CI for individual treatment groups is calculated by using the methods of Clopper and Pearson.

b. 95% CI for differences within strata is calculated based on asymptotical method corrected for continuity. Estimates of differences between treatment groups, corresponding CIs and hypothesis tests are weighted by using minimum risk weights (methods of Mehrotra and Railkar).

Table 8. Summary of Clinical Response Results in the Primary Study, c-mITT Population

				Tigecycline[a]		Ertapenem[a]		Difference (Tigecycline-Ertapenem)[b]		
Visit	Response	PEDIS Infection Score	Category	n /N	% (95% CI)	n /N	% (95% CI)	% (95% CI)	Test for Noninferiority p-Value	Test for Difference p-Value
LDOT	Cure	Grade 2, 3		346/431	80.3 (76.2, 83.9)	364/415	87.7 (84.2, 90.7)	-7.4(-12.6, -2.3)	0.1760	0.0041
		Grade 4		32/45	71.1 (55.7, 83.6)	37/51	72.5 (58.3, 84.1)	-1.4(-21.6, 18.7)	0.2410	1
		Overall	Unadjusted	378/476	79.4 (75.5, 83.0)	401/466	86.1 (82.6, 89.1)	-6.6(-11.7, -1.6)	0.0996	0.0087
			Adjusted					-7.0(-11.8, -2.1)	0.1120	0.0050
	Failure	Overall		85/476	17.9 (14.5, 21.6)	60/466	12.9 (10.0, 16.3)			
	Indeterminate	Overall		13/476	2.7 (1.5, 4.6)	5/466	1.1 (0.3, 2.5)			
TOC	Cure	Grade 2, 3		311/431	72.2 (67.7, 76.3)	330/415	79.5 (75.3, 83.3)	-7.4(-13.3, -1.4)	0.2061	0.0050
		Grade 4		29/45	64.4 (48.8, 78.1)	33/51	64.7 (50.1, 77.6)	-0.3(-21.5, 21.0)	0.2172	1
		Overall	Unadjusted	340/476	71.4 (67.1, 75.4)	363/466	77.9 (73.9, 81.6)	-6.5(-12.2, -0.7)	0.1200	0.0268
			Adjusted					-6.7(-12.3, -1.1)	0.1290	0.0180
	Failure	Overall		117/476	24.6 (20.8, 28.7)	86/466	18.5 (15.0, 22.3)			
	Indeterminate	Overall		19/476	4.0 (2.4, 6.2)	17/466	3.6 (2.1, 5.8)			

CI = confidence interval; c-mITT = clinical modified intent-to-treat; LDOT = last day of therapy; N = number of subjects; n = number of subjects with clinical response; PEDIS = perfusion, extent, depth/tissue loss, infection, and sensation (diabetic foot ulcer classification system); TOC = test-of-cure.

a. 95% CI for individual treatment groups is calculated by using the methods of Clopper and Pearson.

b. 95% CI for differences within strata is calculated based on asymptotical method corrected for continuity. Estimates of differences between treatment groups, corresponding CIs and hypothesis tests are weighted by using minimum risk weights (methods of Mehrotra and Railkar).

The results of the analysis for clinical response in the osteomyelitis substudy, CE population are shown in Table 9.

Table 9. Analysis of Clinical Response in the Osteomyelitis Substudy, CE Population

Visit	Response	PEDIS Infection Score	Tigecycline[a]		Ertapenem[a]	
			n /N	% (95% CI)	n /N	% (95% CI)
LDOT	Cure	Grade 2, 3	19/35	54.3 (36.6, 71.2)	17/21	81.0 (58.1, 94.6)
		Grade 4	2/3	66.7 (9.4, 99.2)	2/3	66.7 (9.4, 99.2)
		Overall	21/38	55.3 (38.3, 71.4)	19/24	79.2 (57.8, 92.9)
Early follow up	Cure	Grade 2, 3	13/28	46.4 (27.5, 66.1)	13/19	68.4 (43.4, 87.4)
		Grade 4	2/3	66.7 (9.4, 99.2)	2/2	100.0 (15.8,100.0)
		Overall	15/31	48.4 (30.2, 66.9)	15/21	71.4 (47.8, 88.7)
TOC	Cure	Grade 2, 3	11/35	31.4 (16.9, 49.3)	11/21	52.4 (29.8, 74.3)
		Grade 4	1/3	33.3 (0.8, 90.6)	2/3	66.7 (9.4, 99.2)
		Overall	12/38	31.6 (17.5, 48.7)	13/24	54.2 (32.8, 74.4)

CE = clinically evaluable; CI = confidence interval; LDOT = last day of therapy; N = number of subjects; n = number of subjects with clinical response; PEDIS = perfusion, extent, depth/tissue loss, infection, and sensation (diabetic foot ulcer classification system); TOC = test-of-cure.
a. 95% CI for individual treatment groups is calculated by using the methods of Clopper and Pearson.

The results of the analysis for clinical response in the osteomyelitis substudy, c-mITT population are shown in Table 10.

Table 10. Analysis of Clinical Response in the Osteomyelitis Substudy, c-mITT Population

Visit	Response	PEDIS Infection Score	Tigecycline[a]		Ertapenem[a]	
			n /N	% (95% CI)	n /N	% (95% CI)
LDOT	Cure	Grade 2, 3	28/49	57.1 (42.2, 71.2)	25/29	86.2 (68.3, 96.1)
		Grade 4	3/4	75.0 (19.4, 99.4)	3/4	75.0 (19.4, 99.4)
		Overall	31/53	58.5 (44.1, 71.9)	28/33	84.8 (68.1, 94.9)
	Failure	Overall	18/53	34.0(21.5, 48.3)	5/33	15.2(5.1, 31.9)
	Indeterminate	Overall	4/53	7.5(2.1, 18.2)	0/33	0.0(0.0, 10.6)
Early follow up	Cure	Grade 2, 3	19/38	50.0 (33.4, 66.6)	21/27	77.8 (57.7, 91.4)
		Grade 4	3/4	75.0 (19.4, 99.4)	3/3	100.0 (29.2,100.0)
		Overall	22/42	52.4 (36.4, 68.0)	24/30	80.0 (61.4, 92.3)
	Failure	Overall	17/42	40.5(25.6, 56.7)	6/30	20.0(7.7, 38.6)
	Indeterminate	Overall	3/42	7.1(1.5, 19.5)	0/30	0.0(0.0, 11.6)
TOC	Cure	Grade 2, 3	18/49	36.7 (23.4, 51.7)	18/29	62.1 (42.3, 79.3)
		Grade 4	1/4	25.0 (0.6, 80.6)	3/4	75.0 (19.4, 99.4)
		Overall	19/53	35.8 (23.1, 50.2)	21/33	63.6 (45.1, 79.6)
	Failure	Overall	27/53	50.9(36.8, 64.9)	12/33	36.4(20.4, 54.9)
	Indeterminate	Overall	7/53	13.2(5.5, 25.3)	0/33	0.0(0.0, 10.6)

CI = confidence interval; c-mITT = clinical modified-intent-to-treat; LDOT = last day of therapy; N = number of subjects; n = number of subjects with clinical response; PEDIS = perfusion, extent, depth/tissue loss, infection, and sensation (diabetic foot ulcer classification system); TOC = test-of-cure.
a. 95% CI for individual treatment groups is calculated by using the methods of Clopper and Pearson.

Microbiologic Response at the Subject Level: The microbiologic responses at the TOC assessment, in the primary study, are presented in Table 11 for the ME population and in Table 12 for the m-mITT population. In the primary study, the eradication rate was lower in the tigecycline group than in the ertapenem group both the ME population (66.1% vs 72.2% respectively) and the m-mITT population (61.1% vs 68.5% respectively) at the TOC assessment.

The results in the osteomyelitis substudy were similar, showing that the eradication rate was lower, the persistence rate was higher, and the occurrence of superinfection was more frequent in the tigecycline group than in the ertapenem group in both the ME and m-mITT populations.

Table 11. Analysis of Microbiologic Response at the Subject Level at TOC Assessment in the Primary Study and Osteomyelitis Substudy, ME Population

			Tigecycline[a]		Ertapenem[a]		Difference (Tigecycline-Ertapenem)[b]		
Response	PEDIS Infection Score	Category	n /N	% (95% CI)	n /N	% (95% CI)	% (95% CI)	Test for Noninferiority p-Value	Test for Difference p-Value
Primary study									
Eradication	Grade 2 3		189/287	65.9 (60.1, 71.3)	208/281	74.0 (68.5, 79.0)	-8.2(-16.0, -0.3)	0.3496	0.0414
	Grade 4		20/29	69.0 (49.2, 84.7)	21/36	58.3 (40.8, 74.5)	10.6(-15.8, 37.0)	0.0703	0.5271
	Overall	Unadjusted	209/316	66.1 (60.6, 71.3)	229/317	72.2 (67.0, 77.1)	-6.1(-13.6, 1.4)	0.1639	0.1142
		Adjusted					-6.3(-13.6, 1.0)	0.1640	0.0930
Documented			24/209	11.5 (7.5, 16.6)	30/229	13.1 (9.0, 18.2)			
Presumed			185/209	88.5 (83.4, 92.5)	199/229	86.9 (81.8, 91.0)			
Persistence			86/316	27.2 (22.4, 32.5)	76/317	24.0 (19.4, 29.1)			
Documented			53/86	61.6 (50.5, 71.9)	45/76	59.2 (47.3, 70.4)			
Presumed			33/86	38.4 (28.1, 49.5)	31/76	40.8 (29.6, 52.7)			
Superinfection			21/316	6.6	12/317	3.8			
Substudy									
Eradication	Grade 2 3		8/25	32.0(14.9, 53.5)	8/ 15	53.3(26.6, 78.7)			
	Grade 4		2/ 3	66.7(9.4, 99.2)	2/ 3	66.7(9.4, 99.2)			
	Overall		10/ 28	35.7(18.6, 55.9)	10/ 18	55.6(30.8, 78.5)			
Documented			1/ 10	10.0(0.3, 44.5)	0/ 10	0.0(0.0, 30.8)			
Presumed			9/ 10	90.0(55.5, 99.7)	10/ 10	100.0(69.2,100.0)			
Persistence			16/ 28	57.1(37.2, 75.5)	7/ 18	38.9(17.3, 64.3)			
Documented			2/ 16	12.5(1.6, 38.3)	1/ 7	14.3(0.4, 57.9)			
Presumed			14/ 16	87.5(61.7, 98.4)	6/ 7	85.7(42.1, 99.6)			
Superinfection			2/ 28	7.1	1/ 18	5.6			

CI = confidence interval; ME = microbiologically evaluable; N = number of subjects; n = number of subjects with microbiologic response; PEDIS = perfusion, extent, depth/tissue loss, infection, and sensation (diabetic foot ulcer classification system); TOC = test-of-cure.
The clinical cure rate at the TOC assessment was the primary endpoint.

a. 95% CI for individual treatment groups is calculated by using the methods of Clopper and Pearson.

b. 95% CI for differences within strata is calculated based on asymptotical method corrected for continuity. Estimates of differences between treatment groups, corresponding CIs and hypothesis tests are weighted by using minimum risk weights.

Table 12. Analysis of Microbiologic Response at the Subject Level at TOC Assessment in the Primary Study and Osteomyelitis Substudy, m-mITT Population

			Tigecycline[a]		Ertapenem[a]		Difference (Tigecycline-Ertapenem)[b]		
Response	PEDIS Infection Score	Category	n /N	% (95% CI)	n /N	% (95% CI)	% (95% CI)	Test for Noninferiority p-Value	Test for Difference p-Value
Primary Study									
Eradication	Grade 2 3		207/340	60.9 (55.5, 66.1)	230/329	69.9 (64.6, 74.8)	-9.0(-16.5, -1.6)	0.4269	0.0171
	Grade 4		24/38	63.2 (46.0, 78.2)	25/43	58.1 (42.1, 73.0)	5.0(-18.7, 28.8)	0.1240	0.8150
	Overall	Unadjusted	231/378	61.1 (56.0, 66.1)	255/372	68.5 (63.6, 73.2)	-7.4(-14.5, -0.4)	0.2545	0.0391
		Adjusted					-7.5(-14.4, -0.6)	0.2500	0.0330
Documented			27/231	11.7 (7.8, 16.5)	32/255	12.5 (8.7, 17.3)			
Presumed			204/231	88.3 (83.5, 92.2)	223/255	87.5 (82.7, 91.3)			
Persistence			107/378	28.3 (23.8, 33.1)	92/372	24.7 (20.4, 29.4)			
Documented			59/107	55.1 (45.2, 64.8)	49/92	53.3 (42.6, 63.7)			
Presumed			48/107	44.9 (35.2, 54.8)	43/92	46.7 (36.3, 57.4)			
Superinfection			27/378	7.1	15/372	4.0			
Indeterminate			13/378	3.4	10/372	2.7			
Substudy									
Eradication	Grade 2 3		11/ 33	33.3(18.0, 51.8)	15/ 24	62.5(40.6, 81.2)			
	Grade 4		2/ 4	50.0(6.8, 93.2)	2/ 3	66.7(9.4, 99.2)			
	Overall		13/ 37	35.1(20.2, 52.5)	17/ 27	63.0(42.4, 80.6)			
Documented			1/ 13	7.7(0.2, 36.0)	0/ 17	0.0(0.0, 19.5)			
Presumed			12/ 13	92.3(64.0, 99.8)	17/ 17	100.0(80.5,100.0)			
Persistence			18/ 37	48.6(31.9, 65.6)	9/ 27	33.3(16.5, 54.0)			
Documented			2/ 18	11.1(1.4, 34.7)	1/ 9	11.1(0.3, 48.2)			
Presumed			16/ 18	88.9(65.3, 98.6)	8/ 9	88.9(51.8, 99.7)			
Superinfection			2/ 37	5.4	1/ 27	3.7			
Indeterminate			4/ 37	10.8	0/ 27	0.0			

CI = confidence interval; m-mITT = microbiologic modified intent-to-treat; N = number of subjects; n = number of subjects with microbiologic response; PEDIS = perfusion, extent, depth/tissue loss, infection, and sensation (diabetic foot ulcer classification system); TOC = test-of-cure.

a. 95% CI for individual treatment groups is calculated by using the methods of Clopper and Pearson.

b. 95% CI for differences within strata is calculated based on asymptotical method corrected for continuity. Estimates of differences between treatment groups, corresponding CIs and hypothesis tests are weighted by using minimum risk weights.

Microbiologic Response by Monomicrobial/Polymicrobial Infection: The results of microbiologic response by monomicrobial / polymicrobial infection in the primary study, ME population are presented in Table 13. The eradication rates for monomicrobial and polymicrobial infections were lower in the tigecycline group than in the ertapenem group in the primary study in the ME population at the TOC assessment.

Similar results were seen for the m-mITT population in the primary study and in the ME and m-mITT populations in the osteomyelitis substudy.

Table 13. Microbiologic Response by Monomicrobial/Polymicrobial Infection in the Primary Study and Osteomyelitis Substudy, ME Population

			Tigecycline 150 mg		Ertapenem		Difference (Tigecycline - Ertapenem)
Visit	**Infection**	**Response**	**n /N**	**% (95% CI)**	**n /N**	**% (95% CI)**	**% (95% CI)**
Primary Study							
TOC	Monomicrobial	Eradication	107/147	72.8 (64.8, 79.8)	94/115	81.7 (73.5, 88.3)	-9.0 (-19.2, 2.0)
		Persistence	32/147	21.8	18/115	15.7	
		Superinfection	8/147	5.4	3/115	2.6	
	Polymicrobial	Eradication	102/169	60.4 (52.6, 67.8)	135/202	66.8 (59.9, 73.3)	-6.5 (-16.6, 3.7)
		Persistence	54/169	32.0	58/202	28.7	
		Superinfection	13/169	7.7	9/202	4.5	Adjusted Diff Interact -8.0 (-15.1, -1.0) 0.7391
Substudy							
TOC	Monomicrobial	Eradication	6/ 16	37.5(15.2, 64.6)	4/ 6	66.7(22.3, 95.7)	
		Persistence	10/ 16	62.5	1/ 6	16.7	
		Superinfection	0/ 16	0.0	1/ 6	16.7	
	Polymicrobial	Eradication	4/ 12	33.3(9.9, 65.1)	6/ 12	50.0(21.1, 78.9)	
		Persistence	6/ 12	50.0	6/ 12	50.0	
		Superinfection	2/ 12	16.7	0/ 12	0.0	

Adjusted difference and its 95% CI are calculated from a generalized linear main-effects model with a binomial probability function and an identity link.
Calculations are based on asymptotic properties, which may not be verified in case of small sample sizes.
The 95% CI for differences within strata are calculated based on the Wilson score method corrected for continuity. 95% CI for individual treatment groups is calculated by using the methods of Clopper and Pearson.
CI = confidence interval; LDOT = last day of therapy; ME = microbiologically evaluable; N = number of subjects; n = number of subjects with microbiologic response; TOC = test-of-cure.

The summary of microbiologic response by monomicrobial / polymicrobial infection, m-mITT population are presented in Table 14.

Table 14. Microbiologic Response by Monomicrobial/Polymicrobial Infection, m-mITT Population

Visit	Infection	Response	Tigecycline 150 mg n /N	Tigecycline 150 mg % (95% CI)	Ertapenem n /N	Ertapenem % (95% CI)	Difference (Tigecycline - Ertapenem) % (95% CI)
Primary Study							
TOC	Monomicrobial	Eradication	117/181	64.6 (57.2, 71.6)	108/147	73.5 (65.6, 80.4)	-8.8 (-18.9, 1.7)
		Persistence	46/181	25.4	30/147	20.4	
		Superinfection	11/181	6.1	6/147	4.1	
		Indeterminate	7/181	3.9	3/147	2	
	Polymicrobial	Eradication	114/197	57.9 (50.6, 64.9)	147/225	65.3 (58.7, 71.5)	-7.5 (-16.9, 2.1)
		Persistence	61/197	31	62/225	27.6	
		Superinfection	16/197	8.1	9/225	4	
		Indeterminate	6/197	3	7/225	3.1	
							Adjusted Diff -8.2 (-15.0, -1.4) Interact 0.8616
Substudy							
TOC	Monomicrobial	Eradication	8/ 22	36.4 (17.2, 59.3)	7/ 10	70.0 (34.8, 93.3)	
		Persistence	12/ 22	54.5	2/ 10	20.0	
		Superinfection	0/ 22	0.0	1/ 10	10.0	
		Indeterminate	2/ 22	9.1	0/ 10	0.0	
	Polymicrobial	Eradication	5/ 15	33.3 (11.8, 61.6)	10/ 17	58.8 (32.9, 81.6)	
		Persistence	6/ 15	40.0	7/ 17	41.2	
		Superinfection	2/ 15	13.3	0/ 17	0.0	
		Indeterminate	2/ 15	13.3	0/ 17	0.0	

Adjusted difference and its 95% CI were calculated from a generalized linear main-effects model with a binomial probability function and an identity link.
Calculations were based on asymptotic properties, which might not be verified in case of small sample sizes. The 95% CI for differences within strata were calculated based on the Wilson score method corrected for continuity. 95% CI for individual treatment groups was calculated by using the methods of Clopper and Pearson.
CI = confidence interval; m-mITT = microbiologic modified intent-to-treat; N = number of subjects; n = number of subjects with microbiologic response; TOC = test-of-cure.

Microbiologic Response at the Pathogen Level: For the selected pathogens, in the primary study, the eradication rates (documented or presumed, primarily the latter) for the following pathogens were higher in the tigecycline group than in the ertapenem group in the ME population at the TOC assessment: *Klebsiella (K) oxytoca, K. pneumoniae,* and *Streptococcus agalactiae*. The eradication rates (documented or presumed, primarily the latter) for the following pathogens were lower in the tigecycline group than in the ertapenem group in the primary study in the ME population at the TOC assessment: *Enterobacter cloacae, Proteus mirabilis*, and MRSA. Results were similar in the m-mITT population for these selected pathogens.

In the osteomyelitis substudy, the number of subjects with each baseline isolate was very small, so no conclusions could be reached regarding these data.

The microbiologic response at the pathogen level for selected baseline isolates at the TOC assessment for the ME population is shown in Table 15 and for the m-mITT population is shown in Table 16.

Table 15. Microbiologic Response at the Pathogen Level in the Primary Study, ME Population

Pathogen	Response	Tigecycline 150 mg[a]		Ertapenem[a]	
		n /N	% (95% CI)	n /N	% (95% CI)
Acinetobacter calcoaceticus / baumannii complex	Eradication	8/10	80.0 (44.4, 97.5)	14/17	82.4 (56.6, 96.2)
Enterobacter cloacae	Eradication	18/23	78.3 (56.3, 92.5)	27/31	87.1 (70.2, 96.4)
Enterococcus faecalis (Non-VRE)	Eradication	55/67	82.1 (70.8, 90.4)	54/67	80.6 (69.1, 89.2)
Escherichia coli	Eradication	22/28	78.6 (59.0, 91.7)	30/38	78.9 (62.7, 90.4)
Klebsiella oxytoca	Eradication	14/15	93.3 (68.1, 99.8)	15/ 19	78.9 (54.4, 93.9)
Klebsiella pneumoniae	Eradication	12/15	80.0 (51.9, 95.7)	15/21	71.4 (47.8, 88.7)
Proteus mirabilis	Eradication	16/24	66.7 (44.7, 84.4)	26/30	86.7 (69.3, 96.2)
Pseudomonas aeruginosa	Eradication	12/19	63.2 (38.4, 83.7)	10/17	58.8 (32.9, 81.6)
Staphylococcus aureus (MRSA)	Eradication	21/44	47.7 (32.5, 63.3)	16/26	61.5 (40.6, 79.8)
Staphylococcus aureus (Non-MRSA)	Eradication	83/116	71.6 (62.4, 79.5)	103/137	75.2 (67.1, 82.2)
Streptococcus agalactiae	Eradication	34/40	85.0 (70.2, 94.3)	38/48	79.2 (65.0, 89.5)

CI = confidence interval; ME = microbiologically evaluable; MRSA = methicillin-resistant Staphylococcus aureus; N = number of subjects; n = number of subjects with microbiologic response; VRE = vancomycin-resistant Enterococcus.
a. Treatment group confidence intervals are calculated by using the method of Clopper and Pearson.

Table 16. Microbiologic Response at the Pathogen Level in the Primary Study, m-mITT Population

Pathogen	Response	Tigecycline 150 mg[a]		Ertapenem[a]	
		n /N	% (95% CI)	n /N	% (95% CI)
Acinetobacter calcoaceticus / baumannii complex	Eradication	12/ 15	80.0 (51.9, 95.7)	17/ 22	77.3 (54.6, 92.2)
Enterobacter cloacae	Eradication	18/ 24	75.0 (53.3, 90.2)	31/ 36	86.1 (70.5, 95.3)
Enterococcus faecalis (Non-VRE)	Eradication	57/ 72	79.2 (68.0, 87.8)	58/ 77	75.3 (64.2, 84.4)
Escherichia coli	Eradication	24/ 30	80.0 (61.4, 92.3)	32/ 40	80.0 (64.4, 90.9)
Klebsiella oxytoca	Eradication	15/ 18	83.3 (58.6, 96.4)	17/ 22	77.3 (54.6, 92.2)
Klebsiella pneumoniae	Eradication	15/ 18	83.3 (58.6, 96.4)	17/ 24	70.8 (48.9, 87.4)
Proteus mirabilis	Eradication	20/ 30	66.7 (47.2, 82.7)	29/ 33	87.9 (71.8, 96.6)
Pseudomonas aeruginosa	Eradication	13/ 24	54.2 (32.8, 74.4)	12/ 25	48.0 (27.8, 68.7)
Staphylococcus aureus (MRSA)	Eradication	22/ 49	44.9 (30.7, 59.8)	18/ 31	58.1 (39.1, 75.5)
Staphylococcus aureus (Non-MRSA)	Eradication	91/138	65.9 (57.4, 73.8)	110/153	71.9 (64.1, 78.9)
Streptococcus agalactiae	Eradication	40/ 51	78.4 (64.7, 88.7)	41/ 53	77.4 (63.8, 87.7)

CI = confidence interval; m-mITT = microbiologic modified intent-to-treat; MRSA = methicillin-resistant Staphylococcus aureus; N = number of subjects; n = number of subjects with microbiologic response; VRE = vancomycin-resistant Enterococcus.
a. Treatment group confidence intervals were calculated by using the method of Clopper and Pearson.

Response Rate by Baseline Pathogen and MIC Value: The response rates by selected baseline pathogen and MIC value in the ME population are summarized in Table 17. In both the ME and m-mITT population of the primary study, the cure rates for tigecycline were lower than would be expected given the overall MIC values.

In the osteomyelitis substudy, the number of subjects with each baseline isolate was very small, so no conclusions could be reached regarding these data.

Table 17. Clinical and Microbiologic Response by MIC Value and Baseline Isolate for Selected Pathogens in the Primary Study, ME Population

Pathogen	MIC (µ/mL)	Tigecycline		Ertapenem		Vancomycin	
		CR[a]	MR[b]	CR[a]	MR[b]	CR[a]	MR[b]
Acinetobacter calcoaceticus/baumannii complex	0.06	1/2	2/2	0/0	0/0	0/0	0/0
	0.12	1/1	1/1	0/0	0/0	0/0	0/0
	0.5	3/3	2/3	0/0	0/0	0/0	0/0
	1	3/4	3/4	0/0	0/0	0/0	0/0
	2	0/0	0/0	3/3	3/3	0/0	0/0
	4	0/0	0/0	5/5	5/5	0/0	0/0
	8	0/0	0/0	4/5	2/5	0/0	0/0
	16	0/0	0/0	1/2	2/2	0/0	0/0
	35	0/0	0/0	1/1	1/1	0/0	0/0
	64	0/0	0/0	1/1	1/1	0/0	0/0
	128	0/0	0/0	0/0	0/0	15/17	14/17
	Total	8/10	8/10	15/17	14/17	15/17	14/17
Enterobacter cloacae	0.03	0/0	0/0	19/22	21/22	0/0	0/0
	0.06	0/0	0/0	4/4	2/4	0/0	0/0
	0.12	0/0	0/0	2/2	2/2	0/0	0/0
	0.25	5/5	5/5	1/1	1/1	0/0	0/0
	0.5	13/16	11/16	1/2	1/2	0/0	0/0
	1	2/2	2/2	0/0	0/0	0/0	0/0
	128	0/0	0/0	0/0	0/0	27/31	27/31
	Total	20/23	18/23	27/31	27/31	27/31	27/31
Enterococcus faecalis (Non-VRE)	0.06	6/7	6/7	0/0	0/0	0/0	0/0
	0.12	33/38	33/38	0/0	0/0	0/0	0/0
	0.25	17/22	16/22	0/0	0/0	0/0	0/0
	0.5	0/0	0/0	0/0	0/0	1/1	1/1
	1	0/0	0/0	0/0	0/0	24/29	23/29
	2	0/0	0/0	0/0	0/0	24/30	24/30
	4	0/0	0/0	1/1	1/1	7/7	6/7
	8	0/0	0/0	31/34	28/34	0/0	0/0
	16	0/0	0/0	22/29	23/29	0/0	0/0
	32	0/0	0/0	2/3	2/3	0/0	0/0
	Total	56/67	56/67	56/67	54/67	56/67	54/67
Escherichia coli	0.03	0/0	0/0	23/31	26/31	0/0	0/0
	0.06	1/1	1/1	0/0	0/0	0/0	0/0
	0.12	8/11	8/11	3/3	2/3	0/0	0/0
	0.25	9/11	10/11	0/2	0/2	0/0	0/0
	0.5	3/5	3/5	1/1	1/1	0/0	0/0
	1	0/0	0/0	1/1	1/1	0/0	0/0
	128	0/0	0/0	0/0	0/0	28/38	30/38
	Total	21/28	22/28	28/38	30/38	28/38	30/38
Klebsiella oxytoca	0.03	0/ 0	0/ 0	16/ 19	15/ 19	0/ 0	0/ 0
	0.25	11/ 14	13/ 14	0/ 0	0/ 0	0/ 0	0/ 0
	0.5	1/ 1	1/ 1	0/ 0	0/ 0	0/ 0	0/ 0
	128	0/0	0/0	0/ 0	0/ 0	16/ 19	15/ 19
	Total	12/ 15	14/ 15	16/ 19	15/ 19	16/ 19	15/ 19
Klebsiella pneumoniae	0.03	0/0	0/0	16/ 19	14/19	0/0	0/0
	0.25	5/6	5/6	0/0	0/0	0/0	0/0
	0.5	5/8	7/8	1/1	1/1	0/0	0/0
	2	0/1	0/1	0/1	0/1	0/0	0/0
	128	0/0	0/0	0/0	0/0	17/21	15/21
	Total	10/15	12/15	17/21	15/21	17/21	15/21

Table 17. Clinical and Microbiologic Response by MIC Value and Baseline Isolate for Selected Pathogens in the Primary Study, ME Population

Pathogen	MIC (µ/mL)	Tigecycline		Ertapenem		Vancomycin	
		CR[a]	MR[b]	CR[a]	MR[b]	CR[a]	MR[b]
Proteus mirabilis	0.03	0/0	0/0	23/28	25/28	0/0	0/0
	0.25	0/0	0/0	2/2	1/2	0/0	0/0
	0.5	0/1	0/1	0/0	0/0	0/0	0/0
	1	1/2	1/2	0/0	0/0	0/0	0/0
	2	9/11	7/11	0/0	0/0	0/0	0/0
	4	5/7	6/7	0/0	0/0	0/0	0/0
	8	3/3	3/3	0/0	0/0	0/0	0/0
	128	0/0	0/0	0/0	0/0	25/30	26/30
	Total	18/24	16/24	25/30	26/30	25/30	26/30
Pseudomonas aeruginosa	1	0/0	0/0	0/1	1/1	0/0	0/0
	2	0/0	0/0	2/2	2/2	0/0	0/0
	4	0/1	0/1	4/4	3/4	0/0	0/0
	8	8/11	8/11	1/3	0/3	0/0	0/0
	16	3/5	3/5	2/2	2/2	0/0	0/0
	32	0/1	0/1	0/2	0/2	0/0	0/0
	64	0/1	0/1	3/3	2/3	0/0	0/0
	128	0/0	0/0	0/0	0/0	12/17	10/17
	Total	11/19	12/19	12/17	10/17	12/17	10/17
Staphylococcus aureus (MRSA)	0.06	2/3	2/3	0/0	0/0	0/0	0/0
	0.12	14/21	12/21	0/0	0/0	0/0	0/0
	0.25	12/18	6/18	0/1	0/1	0/0	0/0
	0.5	1/2	1/2	3/4	3/4	1/1	1/1
	1	0/0	0/0	3/5	3/5	14/20	13/20
	2	0/0	0/0	6/8	6/8	2/5	2/5
	4	0/0	0/0	2/3	2/3	0/0	0/0
	64	0/0	0/0	3/5	2/5	0/0	0/0
	Total	29/44	21/44	17/26	16/26	17/26	16/26
Staphylococcus aureus (Non-MRSA)	0.06	5/6	3/6	0/1	0/1	0/0	0/0
	0.12	61/72	58/72	44/51	36/51	0/0	0/0
	0.25	26/37	21/37	72/78	62/78	0/0	0/0
	0.5	0/1	1/1	6/6	4/6	0/0	0/0
	1	0/0	0/0	0/0	0/0	97/108	78/108
	2	0/0	0/0	0/0	0/0	26/29	25/29
	4	0/0	0/0	1/1	1/1	0/0	0/0
	Total	92/116	83/116	123/137	103/ķ	123/137	103/137
Streptococcus agalactiae	0.03	15/17	15/17	3/3	2/3	0/0	0/0
	0.06	17/20	16/20	35/42	34/42	0/0	0/0
	0.12	3/3	3/3	2/3	2/3	0/0	0/0
	0.5	0/0	0/0	0/0	0/0	17/18	16/18
	1	0/0	0/0	0/0	0/0	23/30	22/30
	Total	35/40	34/40	40/48	38/48	40/48	38/48

CR = clinical response; ME = microbiologically evaluable; MIC = minimum inhibitory concentration; MR = microbiologic response; MRSA = methicillin-resistant Staphylococcus aureus; N = number of subjects; n = number of subjects with response; VRE = vancomycin-resistant Enterococcus.

a. Clinical cure rate (n/N).

b. Eradication rate (n/N).

The response rate by baseline pathogen and MIC value in m-mITT population is summarized in Table 18.

Table 18. Clinical and Microbiologic Response by MIC Value and Baseline Isolate for Selected Pathogens in the Primary Study, m-mITT Population

Pathogen	MIC (µ/mL)	Tigecycline		Ertapenem		Vancomycin	
		CR[a]	MR[b]	CR[a]	MR[b]	CR[a]	MR[b]
Acinetobacter calcoaceticus/baumannii complex	0.06	2/3	2/3	0/0	0/0	0/0	0/0
	0.12	2/2	2/2	0/0	0/0	0/0	0/0
	0.25	1/1	1/1	0/0	0/0	0/0	0/0
	0.5	4/4	3/4	0/0	0/0	0/0	0/0
	1	3/5	3/5	0/0	0/0	0/0	0/0
	2	0/0	0/0	3/4	3/4	0/0	0/0
	4	0/0	0/0	5/6	6/6	0/0	0/0
	8	0/0	0/0	4/5	2/5	0/0	0/0
	16	0/0	0/0	2/3	3/3	0/0	0/0
	32	0/0	0/0	2/2	2/2	0/0	0/0
	64	0/0	0/0	2/2	1/2	0/0	0/0
	128	0/0	0/0	0/0	0/0	18/22	17/22
	Total	12/15	12/15	18/22	17/22	18/22	17/22
Enterobacter cloacae	0.03	0/0	0/0	22/27	25/27	0/0	0/0
	0.06	0/0	0/0	4/4	2/4	0/0	0/0
	0.12	0/0	0/0	2/2	2/2	0/0	0/0
	0.25	5/5	5/5	1/1	1/1	0/0	0/0
	0.5	13/17	11/17	1/2	1/2	0/0	0/0
	1	2/2	2/2	0/0	0/0	0/0	0/0
	128	0/0	0/0	0/0	0/0	30/36	31/36
	Total	20/24	18/24	30/36	31/36	30/36	31/36
Enterococcus faecalis (Non-VRE)	0.06	6/8	6/8	0/0	0/0	0/0	0/0
	0.12	35/41	35/41	0/0	0/0	0/0	0/0
	0.25	17/23	16/23	0/0	0/0	0/0	0/0
	0.5	0/0	0/0	0/0	0/0	1/1	1/1
	1	0/0	0/0	0/0	0/0	26/32	25/32
	2	0/0	0/0	0/0	0/0	26/35	26/35
	4	0/0	0/0	1/3	1/3	7/9	6/9
	8	0/0	0/0	33/39	30/39	0/0	0/0
	16	0/0	0/0	24/32	25/32	0/0	0/0
	32	0/0	0/0	2/3	2/3	0/0	0/0
	Total	58/72	57/72	60/77	58/77	60/77	58/77
Escherichia coli	0.03	0/0	0/0	25/33	28/33	0/0	0/0
	0.06	1/1	1/1	0/0	0/0	0/0	0/0
	0.12	9/12	9/12	3/3	2/3	0/0	0/0
	0.25	10/12	11/12	0/2	0/2	0/0	0/0
	0.5	3/5	3/5	1/1	1/1	0/0	0/0
	1	0/0	0/0	1/1	1/1	0/0	0/0
	128	0/0	0/0	0/0	0/0	30/40	32/40
	Total	23/30	24/30	30/40	32/40	30/40	32/40
Klebsiella oxytoca	0.03	0/ 0	0/ 0	17/ 22	17/ 22	0/ 0	0/ 0
	0.12	0/ 1	0/ 1	0/ 0	0/ 0	0/ 0	0/ 0
	0.25	12/ 16	14/ 16	0/ 0	0/ 0	0/ 0	0/ 0
	0.5	1/ 1	1/ 1	0/ 0	0/ 0	0/ 0	0/ 0
	128	0/0	0/0	0/ 0	0/ 0	17/ 22	17/ 22
	Total	13/ 18	15/ 18	17/ 22	17/ 22	17/ 22	17/ 22
Klebsiella pneumoniae	0.03	0/0	0/0	18/22	16/22	0/0	0/0
	0.25	5/6	5/6	0/0	0/0	0/0	0/0
	0.5	6/9	8/9	1/1	1/1	0/0	0/0
	2	1/2	1/2	0/1	0/1	0/0	0/0

Table 18. Clinical and Microbiologic Response by MIC Value and Baseline Isolate for Selected Pathogens in the Primary Study, m-mITT Population

Pathogen	MIC (µ/mL)	Tigecycline		Ertapenem		Vancomycin	
		CR[a]	MR[b]	CR[a]	MR[b]	CR[a]	MR[b]
	4	1/1	1/1	0/0	0/0	0/0	0/0
	128	0/0	0/0	0/0	0/0	19/24	17/24
	Total	13/18	15/18	19/24	17/24	19/24	17/24
Proteus mirabilis	0.03	0/0	0/0	24/31	28/31	0/0	0/0
	0.25	0/0	0/0	2/2	1/2	0/0	0/0
	0.5	0/1	0/1	0/0	0/0	0/0	0/0
	1	1/3	1/3	0/0	0/0	0/0	0/0
	2	11/14	9/14	0/0	0/0	0/0	0/0
	4	7/9	8/9	0/0	0/0	0/0	0/0
	8	3/3	3/3	0/0	0/0	0/0	0/0
	128	0/0	0/0	0/0	0/0	26/33	29/33
	Total	22/30	20/30	26/33	29/33	26/33	29/33
Pseudomonas aeruginosa	1	0/0	0/0	0/1	1/1	0/0	0/0
	2	0/0	0/0	2/3	2/3	0/0	0/0
	4	0/1	1/1	4/5	3/5	0/0	0/0
	8	8/14	8/14	1/3	0/3	0/0	0/0
	16	4/6	4/6	3/5	3/5	0/0	0/0
	32	1/2	0/2	1/3	0/3	0/0	0/0
	64	0/1	0/1	4/5	3/5	0/0	0/0
	128	0/0	0/0	0/0	0/0	15/25	12/25
	Total	13/24	13/24	15/25	12/25	15/25	12/25
Staphylococcus aureus (MRSA)	0.06	2/3	2/3	0/0	0/0	0/0	0/0
	0.12	14/22	12/22	0/0	0/0	0/0	0/0
	0.25	13/21	7/21	0/1	0/1	0/0	0/0
	0.5	1/3	1/3	3/4	3/4	1/1	1/1
	1	0/0	0/0	4/6	4/6	16/23	15/23
	2	0/0	0/0	6/9	6/9	2/7	2/7
	4	0/0	0/0	3/4	3/4	0/0	0/0
	16	0/0	0/0	0/1	0/1	0/0	0/0
	64	0/0	0/0	3/6	2/6	0/0	0/0
	Total	30/49	22/49	19/31	18/31	19/31	18/31
Staphylococcus aureus (Non-MRSA)	0.03	0/1	0/1	0/0	0/0	0/0	0/0
	0.06	6/8	5/8	0/1	0/1	0/0	0/0
	0.12	66/83	62/83	48/61	40/61	0/0	0/0
	0.25	28/44	23/44	75/84	65/84	0/0	0/0
	0.5	0/2	1/2	6/6	4/6	0/0	0/0
	1	0/0	0/0	0/0	0/0	103/122	84/122
	2	0/0	0/0	0/0	0/0	27/31	26/31
	4	0/0	0/0	1/1	1/1	0/0	0/0
	Total	100/138	91/138	130/153	110/153	130/153	110/153
Streptococcus agalactiae	0.03	16/21	18/21	3/3	2/3	0/0	0/0
	0.06	20/27	19/27	38/47	37/47	0/0	0/0
	0.12	3/3	3/3	2/3	2/3	0/0	0/0
	0.5	0/0	0/0	0/0	0/0	20/22	19/22
	1	0/0	0/0	0/0	0/0	23/31	23/31
	Total	39/51	40/51	43/53	41/53	43/53	41/53

Table 18. Clinical and Microbiologic Response by MIC Value and Baseline Isolate for Selected Pathogens in the Primary Study, m-mITT Population

Pathogen	MIC (µ/mL)	Tigecycline		Ertapenem		Vancomycin	
		CR[a]	MR[b]	CR[a]	MR[b]	CR[a]	MR[b]

CR = clinical response; MIC = minimum inhibitory concentration; m-mITT = microbiologic modified intent-to-treat; MR = microbiologic response; MRSA = methicillin-resistant Staphylococcus aureus; N = number of subjects; n = number of subjects with response; VRE = vancomycin-resistant Enterococcus.
a. Clinical cure rate (n/N).
b. Eradication rate (n/N).

Cure Rate by Baseline Pathogen: A summary of clinical response at the TOC for selected pathogens in the primary study, ME population is presented in Table 19. Cure rates were higher in the ertapenem group than in the tigecycline group for infections related to *K. pneumoniae, P. aeruginosa*, and methicillin-susceptible *Staphylococcus aureus* (MSSA). Cure rates were generally similar in the 2 treatment groups for infections due to the other isolates.

A summary of clinical response at the TOC for selected pathogens in the primary study, m-mITT population is presented in Table 20. Cure rates were higher in the ertapenem group than in the tigecycline group for infections related to MSSA. Cure rates were generally similar in the 2 treatment groups for infections due to the other isolates.

In the substudy in the ME and m-mITT populations, the numbers of subjects with each type of infection were too small to draw any meaningful conclusions comparing the tigecycline and ertapenem groups.

Table 19. Summary of Clinical Response at the TOC Assessment by Baseline Isolate for Selected Pathogens in the Primary Study, ME Population

Pathogen	Tigecycline[a]		Ertapenem[a]	
	n /N	% (95% CI)	n /N	% (95% CI)
Acinetobacter calcoaceticus/baumannii complex	8/10	80.0 (44.4, 97.5)	15/17	88.2 (63.6, 98.5)
Enterobacter cloacae	20/23	87.0 (66.4, 97.2)	27/31	87.1 (70.2, 96.4)
Enterococcus faecalis (Non-VRE)	56/67	83.6 (72.5, 91.5)	56/67	83.6 (72.5, 91.5)
Escherichia coli	21/28	75.0 (55.1, 89.3)	28/38	73.7 (56.9, 86.6)
Klebsiella oxytoca	12/15	80.0 (51.9, 95.7)	16/19	84.2 (60.4, 96.6)
Klebsiella pneumoniae	10/15	66.7 (38.4, 88.2)	17/21	81.0 (58.1, 94.6)
Proteus mirabilis	18/24	75.0 (53.3, 90.2)	25/30	83.3 (65.3, 94.4)
Pseudomonas aeruginosa	11/19	57.9 (33.5, 79.7)	12/17	70.6 (44.0, 89.7)
Staphylococcus aureus (MRSA)	29/44	65.9 (50.1, 79.5)	17/26	65.4 (44.3, 82.8)
Staphylococcus aureus (Non-MRSA)	92/116	79.3 (70.8, 86.3)	123/137	89.8 (83.4, 94.3)
Streptococcus agalactiae	35/40	87.5 (73.2, 95.8)	40/48	83.3 (69.8, 92.5)

CI = confidence interval; ME = microbiologically evaluable; MRSA = methicillin-resistant Staphylococcus aureus; TOC = Test-of-Cure; VRE = vancomycin-resistant Enterococcus.
a. Treatment group confidence intervals were calculated by using the method of Clopper and Pearson.

Table 20. Summary of Clinical Response at the TOC Assessment by Baseline Isolate for Selected Pathogens in the Primary Study, m-mITT Population

Pathogen	Tigecycline[a]		Ertapenem[a]	
	n /N	% (95% CI)	n /N	% (95% CI)
Acinetobacter calcoaceticus/baumannii complex	12/15	80.0 (51.9, 95.7)	18/22	81.8 (59.7, 94.8)
Enterobacter cloacae	20/24	83.3 (62.6, 95.3)	30/36	83.3 (67.2, 93.6)
Enterococcus faecalis (Non-VRE)	58/72	80.6 (69.5, 88.9)	60/77	77.9 (67.0, 86.6)
Escherichia coli	23/30	76.7 (57.7, 90.1)	30/40	75.0 (58.8, 87.3)
Klebsiella oxytoca	13/ 18	72.2 (46.5, 90.3)	17/ 22	77.3 (54.6, 92.2)
Klebsiella pneumoniae	13/ 18	72.2 (46.5, 90.3)	19/24	79.2 (57.8, 92.9)
Proteus mirabilis	22/30	73.3 (54.1, 87.7)	26/33	78.8 (61.1, 91.0)
Pseudomonas aeruginosa	13/24	54.2 (32.8, 74.4)	15/25	60.0 (38.7, 78.9)
Staphylococcus aureus (MRSA)	30/49	61.2 (46.2, 74.8)	19/31	61.3 (42.2, 78.2)
Staphylococcus aureus (Non-MRSA)	100/138	72.5 (64.2, 79.7)	130/153	85.0 (78.3, 90.2)
Streptococcus agalactiae	39/51	76.5 (62.5, 87.2)	43/53	81.1 (68.0, 90.6)

CI = confidence interval; m-mITT = microbiologic modified intent-to-treat; MRSA = methicillin-resistant Staphylococcus aureus; TOC = Test-of-Cure; VRE = vancomycin-resistant Enterococcus.
a. Treatment group confidence intervals were calculated by using the method of Clopper and Pearson.

Decreased Susceptibility to Tigecycline: Decreased susceptibly to tigecycline was determined based on a ≥4-fold increase in the MIC value from baseline or an increase from baseline to an MIC value above the provisional breakpoint specified in the protocol or the subsequently established breakpoint (Table 21). Three Subjects in the tigecycline group of the primary study and 1 subject in the tigecycline group of the osteomyelitis substudy had organisms showing decreased susceptibility to tigecycline on-therapy.

Table 21. Decreased Susceptibility in the Primary Study and Osteomyelitis Substudy, ME and m-mITT Populations

Primary/Substudy	Organism	Baseline MIC	On Therapy MIC	Clinical /Microbiologic Response
Primary	Staphylococcus epidermidis	0.06	1.00	Failure /Persistence
Primary	Enterobacter cloacae	0.50	2.00	Cure /Persistence
Primary	Proteus mirabilis	1.00	4.00	Failure /Persistence
Substudy	Morganella morganii	1.00	4.00	Failure /Eradication

ME = microbiologically evaluable; MIC = minimum inhibitory concentration; m-mITT = microbiologic modified intent-to-treat.

Safety Results: In the primary study, 605 (64.1%) subjects reported 1 or more treatment emergent AEs, with significantly more subjects treated with tigecycline (339, 71.1%) reporting AEs than subjects treated with ertapenem (266, 57.0%). AEs were most commonly associated with the digestive system in the tigecycline group and with the digestive system and body as a whole in the ertapenem group.

A summary of treatment emergent AEs in the primary study reported by ≥3% of subjects are summarized in Table 22.

Table 22. Treatment Emergent Adverse Events at ≥3% Threshold in Primary Study -mITT Population

Body System[a] Adverse Event	Overall p-Value[b]	Tigecycline 150 mg N=477 n (%)	Ertapenem 1 g N=467 n (%)	Total N=944 n (%)
Any adverse event	<0.001***	339 (71.1)	266 (57.0)	605 (64.1)
Body as a whole	0.935	95 (19.9)	92 (19.7)	187 (19.8)
Fever	0.602	19 (4.0)	15 (3.2)	34 (3.6)
Headache	0.637	23 (4.8)	19 (4.1)	42 (4.4)
Infection	0.017*	7 (1.5)	19 (4.1)	26 (2.8)
Pain	0.355	18 (3.8)	12 (2.6)	30 (3.2)
Cardiovascular system	0.788	76 (15.9)	71 (15.2)	147 (15.6)
Hypertension	0.901	34 (7.1)	35 (7.5)	69 (7.3)
Digestive system	<0.001***	244 (51.2)	92 (19.7)	336 (35.6)
Diarrhea	0.526	54 (11.3)	46 (9.9)	100 (10.6)
Nausea	<0.001***	190 (39.8)	39 (8.4)	229 (24.3)
Vomiting	<0.001***	118 (24.7)	22 (4.7)	140 (14.8)
Hemic and lymphatic system	1	40 (8.4)	40 (8.6)	80 (8.5)
Metabolic and nutritional	0.36	95 (19.9)	82 (17.6)	177 (18.8)
Hypoglycemia	0.224	34 (7.1)	24 (5.1)	58 (6.1)
SGOT increased	0.488	15 (3.1)	19 (4.1)	34 (3.6)
SGPT increased	0.598	15 (3.1)	18 (3.9)	33 (3.5)
Musculoskeletal system	0.082	27 (5.7)	15 (3.2)	42 (4.4)
Osteomyelitis	0.075	22 (4.6)	11 (2.4)	33 (3.5)
Nervous system	0.566	39 (8.2)	44 (9.4)	83 (8.8)
Insomnia	0.018*	15 (3.1)	4 (0.9)	19 (2.0)
Respiratory system	0.661	23 (4.8)	26 (5.6)	49 (5.2)
Skin and appendages	0.276	33 (6.9)	24 (5.1)	57 (6.0)
Urogenital system	0.115	16 (3.4)	26 (5.6)	42 (4.4)

AEs and SAEs are not separated out.
AEs = adverse events; m-mITT = microbiologic modified intent-to-treat; N = number of subjects; n = number of subjects with adverse events; SAEs = serious adverse events; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.
a. Body system totals for the number of subjects are not necessarily the sum of the individual adverse events since a subject had reported two or more different adverse events in the same body system.
b. Overall p-value refers to the number of subjects data and was determined using Fisher exact test p-value (2-tail); statistical significance at the 0.05, 0.01, 0.001 levels is denoted by *, **, *** respectively.

In the osteomyelitis substudy, significantly more subjects treated with tigecycline than ertapenem reported AEs (p=0.003). AEs were most commonly associated with the digestive system in the tigecycline group and with the digestive system and body as a whole in the ertapenem group.

A summary of treatment emergent AEs in the osteomyelitis substudy reported by ≥3% of subjects are summarized Table 23.

Table 23. Treatment Emergent Adverse Events at ≥3% Threshold in Osteomyelitis Substudy-mITT Population

Body System[a] Adverse Event	Overall p-Value[b]	Tigecycline 150 mg N=76 n (%)	Ertapenem 1 g N=41 n (%)	Total N=117 n (%)
Any adverse event	0.003**	67 (88.2)	26 (63.4)	93 (79.5)
Body as a whole	0.693	29 (38.2)	14 (34.1)	43 (36.8)
Abdominal pain	0.711	6 (7.9)	2 (4.9)	8 (6.8)
Asthenia	0.158	8 (10.5)	1 (2.4)	9 (7.7)
Chest pain	0.611	2 (2.6)	2 (4.9)	4 (3.4)
Fever	1	8 (10.5)	4 (9.8)	12 (10.3)
Headache	1	3 (3.9)	1 (2.4)	4 (3.4)
Infection	0.161	5 (6.6)	0	5 (4.3)
Malaise	0.551	3 (3.9)	0	3 (2.6)
Pain	0.751	7 (9.2)	5 (12.2)	12 (10.3)
Cardiovascular system	0.652	17 (22.4)	11 (26.8)	28 (23.9)
Electrocardiogram abnormal	0.281	1 (1.3)	2 (4.9)	3 (2.6)
Hemorrhage	0.121	0	2 (4.9)	2 (1.7)
Hypertension	0.05	2 (2.6)	5 (12.2)	7 (6.0)
Hypotension	1	3 (3.9)	1 (2.4)	4 (3.4)
Phlebitis	0.421	3 (3.9)	3 (7.3)	6 (5.1)
Thrombosis	1	3 (3.9)	1 (2.4)	4 (3.4)
Digestive system	0.010**	53 (69.7)	18 (43.9)	71 (60.7)
Anorexia	0.161	5 (6.6)	0	5 (4.3)
Constipation	0.021*	2 (2.6)	6 (14.6)	8 (6.8)
Diarrhea	0.065	21 (27.6)	5 (12.2)	26 (22.2)
Dyspepsia	0.711	6 (7.9)	2 (4.9)	8 (6.8)
Nausea	<0.001***	37 (48.7)	7 (17.1)	44 (37.6)
Vomiting	<0.001***	33 (43.4)	3 (7.3)	36 (30.8)
Hemic and lymphatic system	0.362	19 (25.0)	7 (17.1)	26 (22.2)
Activated partial thromboplastin time prolonged	0.419	6 (7.9)	1 (2.4)	7 (6.0)
Anemia	0.448	4 (5.3)	4 (9.8)	8 (6.8)
Leukocytosis	0.656	4 (5.3)	1 (2.4)	5 (4.3)
Prothrombin time prolonged	0.551	3 (3.9)	0	3 (2.6)
Thrombocythemia	0.656	4 (5.3)	1 (2.4)	5 (4.3)
Metabolic and nutritional	0.12	38 (50.0)	14 (34.1)	52 (44.4)
Acidosis	0.281	1 (1.3)	2 (4.9)	3 (2.6)
Alkaline phosphatase increased	0.419	6 (7.9)	1 (2.4)	7 (6.0)
Amylase increased	0.551	3 (3.9)	0	3 (2.6)
Bilirubinemia	1	3 (3.9)	1 (2.4)	4 (3.4)
Bun increased	0.161	5 (6.6)	0	5 (4.3)
Creatinine increased	0.421	3 (3.9)	3 (7.3)	6 (5.1)
Dehydration	0.296	4 (5.3)	0	4 (3.4)
Healing abnormal	0.281	1 (1.3)	2 (4.9)	3 (2.6)
Hyperglycemia	1	5 (6.6)	2 (4.9)	7 (6.0)
Hyperkalemia	1	5 (6.6)	2 (4.9)	7 (6.0)
Hypocalcemia	1	3 (3.9)	1 (2.4)	4 (3.4)
Hypoglycemia	0.001**	16 (21.1)	0	16 (13.7)
Hypokalemia	1	3 (3.9)	1 (2.4)	4 (3.4)
Hypoproteinemia	1	4 (5.3)	2 (4.9)	6 (5.1)
Lipase increased	1	3 (3.9)	1 (2.4)	4 (3.4)
Peripheral edema	1	4 (5.3)	2 (4.9)	6 (5.1)
SGOT increased	1	5 (6.6)	2 (4.9)	7 (6.0)

Table 23. Treatment Emergent Adverse Events at ≥3% Threshold in Osteomyelitis Substudy-mITT Population

Body System[a] Adverse Event	Overall p-Value[b]	Tigecycline 150 mg N=76 n (%)	Ertapenem 1 g N=41 n (%)	Total N=117 n (%)
SGPT increased	1	4 (5.3)	2 (4.9)	6 (5.1)
Musculoskeletal system	1	6 (7.9)	3 (7.3)	9 (7.7)
Osteomyelitis	1	3 (3.9)	1 (2.4)	4 (3.4)
Nervous system	0.221	17 (22.4)	5 (12.2)	22 (18.8)
Agitation	0.281	1 (1.3)	2 (4.9)	3 (2.6)
Anxiety	0.611	2 (2.6)	2 (4.9)	4 (3.4)
Dizziness	1	6 (7.9)	3 (7.3)	9 (7.7)
Insomnia	1	3 (3.9)	1 (2.4)	4 (3.4)
Mental status changes	0.611	2 (2.6)	2 (4.9)	4 (3.4)
Somnolence	0.551	3 (3.9)	0	3 (2.6)
Respiratory system	0.537	9 (11.8)	3 (7.3)	12 (10.3)
Cough increased	0.258	7 (9.2)	1 (2.4)	8 (6.8)
Dyspnea	1	3 (3.9)	2 (4.9)	5 (4.3)
Hypoxia	0.121	0	2 (4.9)	2 (1.7)
Skin and appendages	0.768	10 (13.2)	4 (9.8)	14 (12.0)
Fungal dermatitis	0.551	3 (3.9)	0	3 (2.6)
Rash	0.281	1 (1.3)	2 (4.9)	3 (2.6)
Urogenital system	0.158	8 (10.5)	1 (2.4)	9 (7.7)
Albuminuria	0.551	3 (3.9)	0	3 (2.6)
Vaginal moniliasis	0.519	2 (9.1)	0	2 (5.7)
Vaginitis	1	1 (4.5)	0	1 (2.9)
Adverse event associated with misc. factors	1	10 (13.2)	5 (12.2)	15 (12.8)
Device malfunction	0.711	6 (7.9)	2 (4.9)	8 (6.8)
Local reaction to procedure	0.739	6 (7.9)	4 (9.8)	10 (8.5)

AEs and SAEs are not separated out.
AEs = adverse events; m-mITT = microbiologic modified intent-to-treat; N = number of subjects; n = number of subjects with adverse events; SAEs = serious adverse events; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.
a. Body system totals for the number of subjects are not necessarily the sum of the individual adverse events since a subject had reported 2 or more different adverse events in the same body system.
b. Overall p-value refers to the number of subjects data and was determined using Fisher exact test p-value (2-tail); statistical significance at the 0.05, 0.01, 0.001 levels is denoted by *, **, *** respectively.

A summary of treatment related AEs in the primary study and osteomyelitis substudy are presented in Table 24.

Table 24. Treatment Related AEs - mITT Population

Body System[a] Adverse Event	Overall p-Value[b]	Primary TGC N=477 n (%)	Primary ERT N=467 n (%)	Substudy TGC N=76 n (%)	Substudy ERT N=41 n (%)	Total TGC N=553 n (%)	Total ERT N=508 n (%)
Any adverse event	<0.001***	224 (47.0)	107 (22.9)	48 (63.2)	14 (34.1)	272 (49.2)	121 (23.8)
Body as a whole	0.89	19 (4.0)	26 (5.6)	9 (11.8)	1 (2.4)	28 (5.1)	27 (5.3)
Abdominal pain	0.755	3 (0.6)	3 (0.6)	3 (3.9)	1 (2.4)	6 (1.1)	4 (0.8)
Allergic reaction	1	1 (0.2)	1 (0.2)	0	0	1 (0.2)	1 (0.2)
Asthenia	0.071	4 (0.8)	1 (0.2)	3 (3.9)	0	7 (1.3)	1 (0.2)
Chest pain	0.5	2 (0.4)	0	0	0	2 (0.4)	0
Chills	0.251	2 (0.4)	0	1 (1.3)	0	3 (0.5)	0
Face edema	1	0	0	1 (1.3)	0	1 (0.2)	0
Fever	0.626	3 (0.6)	1 (0.2)	0	0	3 (0.5)	1 (0.2)
Headache	0.465	7 (1.5)	10 (2.1)	0	0	7 (1.3)	10 (2.0)
Infection	0.162	0	6 (1.3)	2 (2.6)	0	2 (0.4)	6 (1.2)
Injection site pain	1	1 (0.2)	0	0	0	1 (0.2)	0
Injection site reaction	1	1 (0.2)	1 (0.2)	0	0	1 (0.2)	1 (0.2)
Lab test abnormal	0.229	0	2 (0.4)	0	0	0	2 (0.4)
Malaise	1	0	0	1 (1.3)	0	1 (0.2)	0
Moniliasis	0.229	0	2 (0.4)	0	0	0	2 (0.4)
Pain	1	1 (0.2)	0	0	0	1 (0.2)	0
Sepsis	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Cardiovascular system	1	8 (1.7)	9 (1.9)	3 (3.9)	1 (2.4)	11 (2.0)	10 (2.0)
Angina pectoris	1	1 (0.2)	0	0	0	1 (0.2)	0
Bundle branch block	0.5	2 (0.4)	0	0	0	2 (0.4)	0
Hypertension	0.229	0	2 (0.4)	0	0	0	2 (0.4)
Hypotension	1	1 (0.2)	0	0	0	1 (0.2)	0
Palpitation	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Phlebitis	0.369	2 (0.4)	6 (1.3)	2 (2.6)	1 (2.4)	4 (0.7)	7 (1.4)
QT interval prolonged	1	1 (0.2)	0	0	0	1 (0.2)	0
Tachycardia	1	1 (0.2)	0	0	0	1 (0.2)	0
Thrombosis	1	0	0	1 (1.3)	0	1 (0.2)	0
Vasculitis	1	1 (0.2)	0	0	0	1 (0.2)	0
Vasodilatation	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Ventricular extrasystoles	1	1 (0.2)	0	0	0	1 (0.2)	0
Digestive system	<0.001***	194 (40.7)	54 (11.6)	41 (53.9)	9 (22.0)	235 (42.5)	63 (12.4)
Abdominal distension	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Anorexia	0.063	3 (0.6)	0	2 (2.6)	0	5 (0.9)	0
Cholestatic jaundice	1	1 (0.2)	0	0	0	1 (0.2)	0
Constipation	1	2 (0.4)	2 (0.4)	0	0	2 (0.4)	2 (0.4)
Diarrhea	0.109	30 (6.3)	24 (5.1)	14 (18.4)	3 (7.3)	44 (8.0)	27 (5.3)
Dyspepsia	0.111	7 (1.5)	1 (0.2)	1 (1.3)	1 (2.4)	8 (1.4)	2 (0.4)
Enterocolitis	0.5	2 (0.4)	0	0	0	2 (0.4)	0
Gastritis	0.251	3 (0.6)	0	0	0	3 (0.5)	0
Hematemesis	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Hepatitis	1	0	0	1 (1.3)	1 (2.4)	1 (0.2)	1 (0.2)
Liver function tests abnormal	0.032*	1 (0.2)	7 (1.5)	0	0	1 (0.2)	7 (1.4)
Nausea	<0.001***	164 (34.4)	27 (5.8)	34 (44.7)	6 (14.6)	198 (35.8)	33 (6.5)
Stools abnormal	1	1 (0.2)	0	0	0	1 (0.2)	0
Vomiting	<0.001***	97 (20.3)	15 (3.2)	23 (30.3)	2 (4.9)	120 (21.7)	17 (3.3)
Hemic and lymphatic system	0.216	13 (2.7)	12 (2.6)	8 (10.5)	0	21 (3.8)	12 (2.4)
Activated partial thromboplastin time prolonged	0.126	3 (0.6)	0	1 (1.3)	0	4 (0.7)	0
Eosinophilia	1	3 (0.6)	3 (0.6)	0	0	3 (0.5)	3 (0.6)
International normalised ratio increased	1	1 (0.2)	0	0	0	1 (0.2)	0
Leukocytosis	1	0	1 (0.2)	1 (1.3)	0	1 (0.2)	1 (0.2)

Table 24. Treatment Related AEs - mITT Population

Body System[a] Adverse Event	Overall p-Value[b]	Primary TGC N=477 n (%)	Primary ERT N=467 n (%)	Substudy TGC N=76 n (%)	Substudy ERT N=41 n (%)	Total TGC N=553 n (%)	Total ERT N=508 n (%)
Leukopenia	0.716	2 (0.4)	4 (0.9)	1 (1.3)	0	3 (0.5)	4 (0.8)
Lymphocytosis	1	1 (0.2)	0	0	0	1 (0.2)	0
Neutropenia	1	1 (0.2)	1 (0.2)	0	0	1 (0.2)	1 (0.2)
Normocytic anemia	0.229	0	2 (0.4)	0	0	0	2 (0.4)
Prothrombin time prolonged	0.032*	3 (0.6)	0	3 (3.9)	0	6 (1.1)	0
Prothrombin time shortened	1	1 (0.2)	0	0	0	1 (0.2)	0
Purpura	1	1 (0.2)	0	0	0	1 (0.2)	0
Thrombocythemia	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Thrombocytopenia	0.291	4 (0.8)	2 (0.4)	2 (2.6)	0	6 (1.1)	2 (0.4)
Metabolic and nutritional	0.729	30 (6.3)	29 (6.2)	14 (18.4)	8 (19.5)	44 (8.0)	37 (7.3)
Acidosis	1	1 (0.2)	0	0	0	1 (0.2)	0
Alkaline phosphatase increased	0.229	4 (0.8)	3 (0.6)	4 (5.3)	0	8 (1.4)	3 (0.6)
Amylase increased	0.533	3 (0.6)	6 (1.3)	1 (1.3)	0	4 (0.7)	6 (1.2)
Bilirubinemia	0.5	1 (0.2)	0	1 (1.3)	0	2 (0.4)	0
BUN increased	0.22	4 (0.8)	1 (0.2)	1 (1.3)	0	5 (0.9)	1 (0.2)
Creatine phosphokinase increased	0.479	0	0	0	1 (2.4)	0	1 (0.2)
Creatinine increased	0.354	1 (0.2)	0	0	3 (7.3)	1 (0.2)	3 (0.6)
Dehydration	1	1 (0.2)	0	0	0	1 (0.2)	0
Edema	0.479	0	0	0	1 (2.4)	0	1 (0.2)
Hypercalcemia	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Hyperkalemia	0.626	1 (0.2)	0	2 (2.6)	1 (2.4)	3 (0.5)	1 (0.2)
Hypernatremia	1	0	0	1 (1.3)	0	1 (0.2)	0
Hypocalcemia	1	0	0	1 (1.3)	0	1 (0.2)	0
Hypoglycemia	0.728	2 (0.4)	3 (0.6)	3 (3.9)	0	5 (0.9)	3 (0.6)
Hypoproteinemia	1	0	0	1 (1.3)	0	1 (0.2)	0
Lipase increased	0.369	3 (0.6)	6 (1.3)	1 (1.3)	1 (2.4)	4 (0.7)	7 (1.4)
Peripheral edema	1	0	0	1 (1.3)	0	1 (0.2)	0
SGOT increased	1	14 (2.9)	13 (2.8)	3 (3.9)	2 (4.9)	17 (3.1)	15 (3.0)
SGPT increased	0.729	16 (3.4)	13 (2.8)	3 (3.9)	2 (4.9)	19 (3.4)	15 (3.0)
Weight loss	1	0	0	1 (1.3)	0	1 (0.2)	0
Musculoskeletal system	0.5	2 (0.4)	0	0	0	2 (0.4)	0
Muscle cramp	1	1 (0.2)	0	0	0	1 (0.2)	0
Myalgia	1	1 (0.2)	0	0	0	1 (0.2)	0
Nervous system	0.559	12 (2.5)	11 (2.4)	4 (5.3)	0	16 (2.9)	11 (2.2)
Agitation	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Anxiety	1	1 (0.2)	0	0	0	1 (0.2)	0
Confusion	0.052	0	4 (0.9)	0	0	0	4 (0.8)
Convulsion	0.609	0	2 (0.4)	1 (1.3)	0	1 (0.2)	2 (0.4)
Dizziness	0.51	4 (0.8)	3 (0.6)	2 (2.6)	0	6 (1.1)	3 (0.6)
Hallucinations	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Hyperkinesia	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Insomnia	0.126	4 (0.8)	0	0	0	4 (0.7)	0
Mental status changes	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Motion sickness	1	1 (0.2)	0	0	0	1 (0.2)	0
Paresthesia	1	1 (0.2)	1 (0.2)	0	0	1 (0.2)	1 (0.2)
Somnolence	1	0	0	1 (1.3)	0	1 (0.2)	0
Stupor	1	0	0	1 (1.3)	0	1 (0.2)	0
Vertigo	0.5	1 (0.2)	0	1 (1.3)	0	2 (0.4)	0
Respiratory system	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Rhinitis	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Skin and appendages	0.291	10 (2.1)	7 (1.5)	4 (5.3)	1 (2.4)	14 (2.5)	8 (1.6)

Table 24. Treatment Related AEs - mITT Population

Body System[a] Adverse Event	Overall p-Value[b]	Primary TGC N=477 n (%)	Primary ERT N=467 n (%)	Substudy TGC N=76 n (%)	Substudy ERT N=41 n (%)	Total TGC N=553 n (%)	Total ERT N=508 n (%)
Eczema	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Exfoliative dermatitis	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Fungal dermatitis	1	0	0	1 (1.3)	0	1 (0.2)	0
Maculopapular rash	1	1 (0.2)	0	0	0	1 (0.2)	0
Pruritus	0.728	3 (0.6)	3 (0.6)	2 (2.6)	0	5 (0.9)	3 (0.6)
Rash	0.354	1 (0.2)	2 (0.4)	0	1 (2.4)	1 (0.2)	3 (0.6)
Skin hypertrophy	1	1 (0.2)	0	0	0	1 (0.2)	0
Sweating	0.251	2 (0.4)	0	1 (1.3)	0	3 (0.5)	0
Urticaria	0.5	2 (0.4)	0	0	0	2 (0.4)	0
Special senses	0.251	2 (0.4)	0	1 (1.3)	0	3 (0.5)	0
Abnormal vision	1	0	0	1 (1.3)	0	1 (0.2)	0
Taste loss	1	1 (0.2)	0	0	0	1 (0.2)	0
Taste perversion	1	1 (0.2)	0	0	0	1 (0.2)	0
Urogenital system	0.51	3 (0.6)	3 (0.6)	3 (3.9)	0	6 (1.1)	3 (0.6)
Acute kidney failure	1	1 (0.2)	0	0	0	1 (0.2)	0
Albuminuria	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Hematuria	1	1 (0.2)	0	0	0	1 (0.2)	0
Leukorrheaf	0.453	0	1 (0.7)	0	0	0	1 (0.6)
Pyuria	1	1 (0.2)	0	0	0	1 (0.2)	0
Urinary tract infection	1	0	0	1 (1.3)	0	1 (0.2)	0
Urine abnormality	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Vaginal moniliasis	0.254	2 (1.1)	0	1 (4.5)	0	3 (1.5)	0
Vaginitis	1	0	1 (0.7)	1 (4.5)	0	1 (0.5)	1 (0.6)
Adverse event associated with miscellaneous factors	1	0	0	1 (1.3)	0	1 (0.2)	0
Local reaction to procedure	1	0	0	1 (1.3)	0	1 (0.2)	0

∗ 0.05 statistical significance. ∗∗ 0.01 statistical significance.∗∗∗ 0.001 statistical significance.
AE/SAE results are not sepatated out.
AE = adverse events; ERT = ertapenem; MITT = modified intent-to-treat; N = number of subjects; n = number of subjects with adverse events; SAE = serious adverse event; TGC = tigecycline.

a. Body system totals for the number of subjects are not necessarily the sum of the individual adverse events since a subject may have reported 2 or more different adverse events in the same body system.
b. Overall p-value refers to the number of subjects data and was determined using Fisher exact test p-value (2-tail).

A summary of treatment emergent serious adverse events (SAEs) in the primary study and osteomyelitis substudy are presented in Table 25. In both the primary study and the osteomyelitis substudy, the frequencies of SAEs were similar in the 2 treatment groups.

Table 25. Treatment Emergent Serious Adverse Events - mITT Population (All Causality)

Body System[a] Adverse Event	Overall p-Value[b]	Primary		Substudy		Total	
		TGC n=477	ERT n=467	TGC n=76	ERT n=41	TGC n=553	ERT n=508
Any adverse event	0.365	57 (11.9)	50 (10.7)	22 (28.9)	12 (29.3)	79 (14.3)	62 (12.2)
Body as a whole	1.000	17 (3.6)	19 (4.1)	9 (11.8)	5 (12.2)	26 (4.7)	24 (4.7)
Abdominal pain	1.000	0	0	1 (1.3)	0	1 (0.2)	0
Abscess	0.063	5 (1.0)	0	0	0	5 (0.9)	0
Accidental injury	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Allergic reaction	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Asthenia	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Carcinoma	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Cellulitis	1.000	0	0	1 (1.3)	0	1 (0.2)	0
Chest pain	1.000	0	1 (0.2)	2 (2.6)	0	2 (0.4)	1 (0.2)
Fever	0.126	2 (0.4)	0	2 (2.6)	0	4 (0.7)	0
Gangrene	1.000	3 (0.6)	2 (0.4)	0	0	3 (0.5)	2 (0.4)
Infection	0.110	7 (1.5)	11 (2.4)	2 (2.6)	5 (12.2)	9 (1.6)	16 (3.1)
Pain	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Sepsis	1.000	1 (0.2)	1 (0.2)	0	0	1 (0.2)	1 (0.2)
Septic shock	1.000	0	0	1 (1.3)	0	1 (0.2)	0
Sudden death	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Cardiovascular system	0.500	17 (3.6)	12 (2.6)	4 (5.3)	3 (7.3)	21 (3.8)	15 (3.0)
Arterial thrombosis	1.000	1 (0.2)	1 (0.2)	0	0	1 (0.2)	1 (0.2)
Atrial fibrillation	0.500	2 (0.4)	0	0	0	2 (0.4)	0
Bundle branch block	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Cardiomegaly	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Cerebral ischemia	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Cerebrovascular accident	0.229	0	2 (0.4)	0	0	0	2 (0.4)
Congestive heart failure	0.609	0	2 (0.4)	1 (1.3)	0	1 (0.2)	2 (0.4)
Coronary artery disorder	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Deep vein thrombosis	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Heart arrest	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Heart failure	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Hemorrhage	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Left heart failure	0.500	2 (0.4)	0	0	0	2 (0.4)	0
Myocardial infarct	0.126	3 (0.6)	0	1 (1.3)	0	4 (0.7)	0
Occlusion	0.609	1 (0.2)	2 (0.4)	0	0	1 (0.2)	2 (0.4)
Peripheral gangrene	0.500	1 (0.2)	0	1 (1.3)	0	2 (0.4)	0
Peripheral vascular disorder	0.609	1 (0.2)	0	0	2 (4.9)	1 (0.2)	2 (0.4)
Pulmonary embolus	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Shock	0.500	2 (0.4)	0	0	0	2 (0.4)	0
Syncope	0.609	1 (0.2)	1 (0.2)	0	1 (2.4)	1 (0.2)	2 (0.4)
Tachycardia	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Thrombophlebitis	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Thrombosis	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Vascular disorder	1.000	0	1 (0.2)	1 (1.3)	0	1 (0.2)	1 (0.2)
Vasculitis	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Digestive system	0.002**	7 (1.5)	1 (0.2)	6 (7.9)	0	13 (2.4)	1 (0.2)
Cholelithiasis	1.000	0	0	1 (1.3)	0	1 (0.2)	0
Cirrhosis of liver	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Diarrhea	1.000	0	1 (0.2)	1 (1.3)	0	1 (0.2)	1 (0.2)
Gastritis	1.000	0	0	1 (1.3)	0	1 (0.2)	0
Gastroenteritis	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Gastrointestinal hemorrhage	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Ileus	1.000	0	0	1 (1.3)	0	1 (0.2)	0
Liver damage	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Nausea	0.032*	3 (0.6)	0	3 (3.9)	0	6 (1.1)	0
Stomach atony	1.000	0	0	1 (1.3)	0	1 (0.2)	0
Vomiting	0.032*	2 (0.4)	0	4 (5.3)	0	6 (1.1)	0

Table 25. Treatment Emergent Serious Adverse Events - mITT Population (All Causality)

Body System[a] Adverse Event	Overall p-Value[b]	Primary		Substudy		Total	
		TGC n=477	ERT n=467	TGC n=76	ERT n=41	TGC n=553	ERT n=508
Hemic and lymphatic system	1.000	0	1 (0.2)	1 (1.3)	0	1 (0.2)	1 (0.2)
Leukocytosis	1.000	0	0	1 (1.3)	0	1 (0.2)	0
Neutropenia	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Metabolic and nutritional	0.755	3 (0.6)	2 (0.4)	3 (3.9)	2 (4.9)	6 (1.1)	4 (0.8)
Acidosis	1.000	0	0	1 (1.3)	0	1 (0.2)	0
Alkaline phosphatase increased	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Dehydration	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Diabetic ketoacidosis	0.479	0	0	0	1 (2.4)	0	1 (0.2)
Healing abnormal	1.000	1 (0.2)	1 (0.2)	0	0	1 (0.2)	1 (0.2)
Hypoglycemia	0.251	1 (0.2)	0	2 (2.6)	0	3 (0.5)	0
Hypoglycemic reaction	0.479	0	0	0	1 (2.4)	0	1 (0.2)
Lipase increased	1.000	0	0	1 (1.3)	0	1 (0.2)	0
Musculoskeletal system	0.024*	13 (2.7)	4 (0.9)	6 (7.9)	2 (4.9)	19 (3.4)	6 (1.2)
Arthrosis	1.000	0	1 (0.2)	1 (1.3)	0	1 (0.2)	1 (0.2)
Osteomyelitis	0.018*	12 (2.5)	3 (0.6)	5 (6.6)	2 (4.9)	17 (3.1)	5 (1.0)
Pyogenic arthritis	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Nervous system	0.131	0	7 (1.5)	3 (3.9)	1 (2.4)	3 (0.5)	8 (1.6)
Convulsion	0.434	0	4 (0.9)	2 (2.6)	0	2 (0.4)	4 (0.8)
Hallucinations	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Hypesthesia	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Mental status changes	1.000	0	1 (0.2)	1 (1.3)	0	1 (0.2)	1 (0.2)
Neuropathy	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Somnolence	1.000	0	0	1 (1.3)	0	1 (0.2)	0
Stupor	0.479	0	0	0	1 (2.4)	0	1 (0.2)
Respiratory system	1.000	3 (0.6)	4 (0.9)	1 (1.3)	0	4 (0.7)	4 (0.8)
Aspiration	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Aspiration pneumonia	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Cough increased	1.000	0	0	1 (1.3)	0	1 (0.2)	0
Dyspnea	0.500	1 (0.2)	0	1 (1.3)	0	2 (0.4)	0
Lung edema	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Pleuritic pain	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Pneumonia	1.000	1 (0.2)	1 (0.2)	1 (1.3)	0	2 (0.4)	1 (0.2)
Respiratory failure	1.000	1 (0.2)	1 (0.2)	0	0	1 (0.2)	1 (0.2)
Skin and appendages	1.000	6 (1.3)	6 (1.3)	0	0	6 (1.1)	6 (1.2)
Skin necrosis	1.000	4 (0.8)	3 (0.6)	0	0	4 (0.7)	3 (0.6)
Skin ulcer	1.000	2 (0.4)	2 (0.4)	0	0	2 (0.4)	2 (0.4)
Vesiculobullous rash	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Urogenital system	1.000	2 (0.4)	2 (0.4)	0	0	2 (0.4)	2 (0.4)
Acute kidney failure	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Kidney function abnormal	0.229	0	2 (0.4)	0	0	0	2 (0.4)
Urinary tract infection	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Adverse event associated with miscellaneous factors	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Local reaction to procedure	0.479	0	1 (0.2)	0	0	0	1 (0.2)

∗ 0.05 statistical significance.

∗∗ 0.01 statistical significance.

ERT = ertapenem; MITT = modified intent-to-treat; TGC = tigecycline.

a. Body system totals for the number of subjects are not necessarily the sum of the individual adverse events since a subject may have reported 2 or more different adverse events in the same body system.

b. Overall p-value refers to the number of subjects data and was determined using Fisher exact test p-value (2-tail) based on selected treatments.

A total of 15 subjects experienced 23 SAEs considered treatment related in the primary study and osteomyelitis substudy. A total of 11 subjects experienced 18 treatment related SAEs in the tigecycline group and 4 subjects experienced 5 treatment related SAEs in the ertapenem group. The most common treatment related SAEs were vomiting, nausea, convulsion and diarrhea. The other treatment related SAEs were acute kidney failure, vasculitis, dehydration, allergic reaction, mental status changes, alkaline phosphatase increased and lipase increased.

Safety-Related Discontinuations: AEs leading to subject discontinuation are summarized in Table 26.

Table 26. AEs Causing Discontinuation- mITT Population

Body System[a] Adverse Event	Overall p-Value[b]	Primary		Substudy		Total	
		TGC n=477	ERT n=467	TGC n=76	ERT n=41	TGC n=553	ERT n=508
Any adverse event	0.015*	42 (8.8)	27 (5.8)	11 (14.5)	1 (2.4)	53 (9.6)	28 (5.5)
Body as a whole	1.000	4 (0.8)	5 (1.1)	1 (1.3)	0	5 (0.9)	5 (1.0)
Abdominal pain	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Allergic reaction	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Asthenia	1.000	0	0	1 (1.3)	0	1 (0.2)	0
Gangrene	0.5	2 (0.4)	0	0	0	2 (0.4)	0
Infection	0.109	0	3 (0.6)	0	0	0	3 (0.6)
Lab test abnormal	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Sepsis	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Cardiovascular system	0.126	4 (0.8)	0	0	0	4 (0.7)	0
Arterial thrombosis	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Myocardial infarct	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Pulmonary embolus	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Vasculitis	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Digestive system	<0.001***	25 (5.2)	5 (1.1)	6 (7.9)	0	31 (5.6)	5 (1.0)
Diarrhea	1.000	1 (0.2)	1 (0.2)	0	0	1 (0.2)	1 (0.2)
Liver damage	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Liver function tests abnormal	0.229	0	2 (0.4)	0	0	0	2 (0.4)
Nausea	0.003**	13 (2.7)	2 (0.4)	2 (2.6)	0	15 (2.7)	2 (0.4)
Vomiting	<0.001***	11 (2.3)	0	4 (5.3)	0	15 (2.7)	0
Hemic and lymphatic system	0.025*	0	5 (1.1)	0	0	0	5 (1.0)
Leukopenia	0.229	0	2 (0.4)	0	0	0	2 (0.4)
Neutropenia	0.229	0	2 (0.4)	0	0	0	2 (0.4)
Thrombocytopenia	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Metabolic and nutritional	1.000	2 (0.4)	2 (0.4)	1 (1.3)	1 (2.4)	3 (0.5)	3 (0.6)
Alkaline phosphatase increased	0.479	0	1 (0.2)	0	0	0	1 (0.2)
BUN increased	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Creatinine increased	0.479	0	0	0	1 (2.4)	0	1 (0.2)
Dehydration	1.000	0	0	1 (1.3)	0	1 (0.2)	0
Hypoglycemia	1.000	1 (0.2)	0	0	0	1 (0.2)	0
SGPT increased	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Musculoskeletal system	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Arthrosis	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Nervous system	0.200	0	4 (0.9)	1 (1.3)	0	1 (0.2)	4 (0.8)
Agitation	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Confusion	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Convulsion	1.000	0	1 (0.2)	1 (1.3)	0	1 (0.2)	1 (0.2)
Mental status changes	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Respiratory system	0.609	0	2 (0.4)	1 (1.3)	0	1 (0.2)	2 (0.4)
Pneumonia	1.000	0	1 (0.2)	1 (1.3)	0	1 (0.2)	1 (0.2)
Upper respiratory infection	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Skin and appendages	0.510	5 (1.0)	3 (0.6)	1 (1.3)	0	6 (1.1)	3 (0.6)
Pruritus	0.251	2 (0.4)	0	1 (1.3)	0	3 (0.5)	0
Rash	1.000	1 (0.2)	1 (0.2)	0	0	1 (0.2)	1 (0.2)
Skin necrosis	0.609	1 (0.2)	2 (0.4)	0	0	1 (0.2)	2 (0.4)
Urticaria	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Urogenital system	0.500	2 (0.4)	0	0	0	2 (0.4)	0
Acute kidney failure	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Creatinine clearance decreased	1.000	1 (0.2)	0	0	0	1 (0.2)	0

Table 26. AEs Causing Discontinuation- mITT Population

Body System[a] Adverse Event	Overall p-Value[b]	Primary		Substudy		Total	
		TGC n=477	ERT n=467	TGC n=76	ERT n=41	TGC n=553	ERT n=508

∗ 0.05 statistical significance.
∗∗ 0.01 statistical significance.
∗∗∗ 0.001 statistical significance.
AE = adverse event; ERT = ertapenem; MITT = modified intent-to-treat; TGC = tigecycline.
a. Body system totals for the number of subjects are not necessarily the sum of the individual adverse events since a subject had reported 2 or more different adverse events in the same body system.
b. Overall p-value refers to the number of subjects data and was determined using Fisher exact test p-value (2-tail) based on selected treatments.

Deaths: Overall, the percentage of subjects who died was higher in the tigecycline group compared with the ertapenem group. A total of 10 subjects died. In the primary study, 6 subjects died in the tigecycline group and 2 subjects died in the ertapenem group. In the osteomyelitis substudy, 1 subject in the tigecycline group and 1 subject in the ertapenem group died. All of the deaths were reported by the Investigators as not related to investigational product. A summary of adverse events leading to death are presented in Table 27.

Table 27. Adverse Events with Outcome of Death - mITT Population

Body System[a] Adverse Event	Overall p-Value	Primary		Substudy		Total	
		TGC n=477	ERT n=467	TGC n=76	ERT n=41	TGC n=553	ERT n=508
Any adverse event	0.346	6 (1.3)	2 (0.4)	1 (1.3)	1 (2.4)	7 (1.3)	3 (0.6)
Body as a whole	0.500	1 (0.2)	0	1 (1.3)	0	2 (0.4)	0
Chest pain	1.000	0	0	1 (1.3)	0	1 (0.2)	0
Sudden death	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Cardiovascular system	0.220	5 (1.0)	1 (0.2)	0	0	5 (0.9)	1 (0.2)
Cerebrovascular accident	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Coronary artery disorder	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Deep vein thrombosis	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Left heart failure	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Myocardial infarct	0.500	2 (0.4)	0	0	0	2 (0.4)	0
Pulmonary embolus	1.000	1 (0.2)	0	0	0	1 (0.2)	0
Shock	0.500	2 (0.4)	0	0	0	2 (0.4)	0
Nervous system	0.479	0	0	0	1 (2.4)	0	1 (0.2)
Stupor	0.479	0	0	0	1 (2.4)	0	1 (0.2)
Respiratory system	1.000	1 (0.2)	1 (0.2)	0	0	1 (0.2)	1 (0.2)
Aspiration	0.479	0	1 (0.2)	0	0	0	1 (0.2)
Pneumonia	1.000	1 (0.2)	0	0	0	1 (0.2)	0

ERT = ertapenem; MITT = modified intent-to-treat; TGC = tigecycline.
Overall P-value: refers to number of subjects data. Fisher's exact test P-value (2-Tail) based on selected treatments.
a. Body system totals for the number of subjects are not necessarily the sum of the individual adverse events since a subject may have reported 2 or more different adverse events in the same body system.

Clinical Laboratory Evaluations: In the primary study, potentially clinically important (PCI) laboratory test results occurred significantly more frequently in the ertapenem group (87.4% of subjects) than in the tigecycline group (82.6% of subjects, p=0.045). Among the blood chemistry test results, elevated sodium, decreased and increased calcium, and low phosphorus occurred more frequently in the ertapenem group. Low sodium and glucose and

elevated BUN, direct bilirubin, and alkaline phosphatase were observed more frequently in the tigecycline group.

In the substudy, the following PCI changes in laboratory test results occurred more frequently in the tigecycline group than in the ertapenem group: increased carbon dioxide levels and elevated platelet counts. In the ertapenem group, the following PCI changes occurred more frequently than in the tigecycline group: high glucose levels, increased lymphocytes, and increased hematocrit.

Of note, in both the primary study and the osteomyelitis substudy, changes in transaminase values were present in the tigecycline group but were not clinically meaningful.

The percentages of subjects with PCI vital signs results were similar in the 2 treatment groups in both the primary study and the osteomyelitis substudy. The incidences of PCI heart rate results were low in both treatment groups.

CONCLUSION: In the primary study, tigecycline did not meet the criteria for noninferiority compared with ertapenem. No new or unexpected safety concerns were observed with tigecycline in this subject population. For the osteomyelitis substudy, the cure rates for tigecycline were low. The substudy was not powered and the numbers of subjects in the substudy were small, making it difficult to draw conclusions.