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Phase 3 study comparing tigecycline and ertapenem in patients with diabetic foot infections with and without osteomyelitis

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ABSTRACT

A phase 3, randomized, double-blind trial was conducted in subjects with diabetic foot infections without osteomyelitis (primary study) or with osteomyelitis (substudy) to determine the efficacy and safety of parenteral (intravenous [iv]) tigecycline (150 mg once-daily) versus 1 g once-daily iv ertapenem ± vancomycin. Among 944 subjects in the primary study who received ≥1 dose of study drug, >85% had type 2 diabetes; ~90% had Perfusion, Extent, Depth/tissue loss, Infection, and Sensation infection grade 2 or 3; and ~20% reported prior antibiotic failure. For the clinically evaluable population at test-of-cure, 77.5% of tigecycline- and 82.5% of ertapenem ± vancomycin–treated subjects were cured. Corresponding rates for the clinical modified intent-to-treat population were 71.4% and 77.9%, respectively. Clinical cure rates in the substudy were low (<36%) for a subset of tigecycline-treated subjects with osteomyelitis. Nausea and vomiting occurred significantly more often after tigecycline treatment ($P = 0.003$ and $P < 0.001$, respectively), resulting in significantly higher discontinuation rates in the primary study (nausea $P = 0.007$, vomiting $P < 0.001$). In the primary study, tigecycline did not meet criteria for noninferiority compared with ertapenem ± vancomycin in the treatment of subjects with diabetic foot infections.

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1. Introduction

Over 200 million individuals worldwide have diabetes mellitus, and with a rapidly increasing prevalence; that number is expected to exceed 300 million in the next 20 years (Andersen and Roukis, 2007; Boulton et al., 2005; Wieman, 2005). As longevity and body mass index of populations around the globe continue to increase, the incidence of complications related to diabetes is also rising (Andersen and Roukis, 2007). Complications of the lower extremities are the most common cause of morbidity and mortality in persons with diabetes, with approximately 20% requiring hospitalization for infection (Lipsky et al., 2004; Schweitzer and Morrison, 2004; Tomas et al., 2000). Globally, every 30 seconds, an amputation of a lower limb occurs as a result of diabetes (Boulton et al., 2005). In the United States, diabetes is responsible for 50% of all non-traumatic amputations (Edmonds and Foster, 2004; Levin, 2002). Amputations occur approximately 40 times more frequently in persons with diabetes than in those without (Schweitzer and Morrison, 2004). Globally, foot infections in persons with diabetes contribute to significant economic and social burdens (Rao, 2005).

The diagnosis of infection is primarily clinical (Lipsky et al., 2004; Rao, 2005), and at times, detection of diabetic foot infections may be challenging (Tomas et al., 2000). A number of classification systems have been devised to characterize diabetic foot infections in an effort to aid diagnosis, but none have been shown to be reliable (Abbas et al., 2008; Rao, 2005; Schaper, 2004). In general, diabetic foot infection is diagnosed when there is presence of purulent secretions or at least 2 signs or symptoms of inflammation such as erythema, warmth, tenderness, pain, or induration (Cavanagh et al., 2005; Edmonds and Foster, 2004; Lipsky et al., 2004; Rao, 2005). The majority of foot infections in persons with diabetes are caused by Gram-positive species, in particular, *Staphylococcus aureus* and β-hemolytic streptococci (especially group B) (Cavanagh et al., 2005; Lipsky et al., 2004). Infections may also be

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polymicrobial, caused by aerobic Gram-negative bacilli and obligate anaerobic organisms (Lipsky et al., 2004; Rao, 2005). Polymicrobial infection usually occurs in persons with chronic ulcers or a history of prior antibiotic treatment (Cavanagh et al., 2005; Lipsky et al., 2004; Lipsky et al., 2005). In addition to infection, all open wounds become colonized with microorganisms, which may ultimately result in superinfections with virulent pathogens such as *S. aureus* (Cavanagh et al., 2005; Lipsky et al., 2004). Of note, methicillin-resistant *S. aureus* (MRSA) has been recognized as a significant concern in treating diabetic foot infections (Andersen and Roukis, 2007; Lipsky et al., 2004; Rao, 2005).

While most mild diabetic foot infections can be treated with oral antimicrobial agents targeting a relatively narrow spectrum of bacteria, many moderate and almost all severe infections require therapy with intravenous (iv), broad-spectrum antibiotics administered either alone or in combination (Lipsky et al., 2004; Lipsky et al., 2005). The optimal antimicrobial regimen depends on the culture results and which organisms are believed to be pathogens, colonizers, or contaminants (Lipsky et al., 2004; Lipsky et al., 2005). The consequence of inadequately treated diabetic foot infections is substantial morbidity and, possibly, lower extremity amputations (Edmonds and Foster, 2004; Levin, 2002).

Tigecycline is a glycylcycline-class antimicrobial agent with broad-spectrum *in vitro* activity including Gram-positive, Gram-negative, and anaerobic organisms. It is currently approved for use for the treatment of complicated skin and skin structure infections (cSSSI). Another attribute of tigecycline that made it appropriate to consider as an option for patients with diabetes is that it does not require dose adjustment because of renal impairment (Wyeth Pharmaceuticals Inc, 2012). Based on its *in vitro* activity and its effectiveness in subjects with cSSSI, including results of a subpopulation of subjects with diabetes evaluated in 2 large-scale phase 3 cSSSI trials (Ellis-Grosse et al., 2005), and demonstrated penetration of tigecycline into bone (Ji et al., 2008), a dedicated study to evaluate the role of tigecycline for the treatment of diabetic foot infections was conducted. The present efficacy and safety study compared the noninferiority of tigecycline 150 mg once daily to ertapenem 1 g once daily, with or without adjunctive vancomycin, in persons with diabetic foot infections requiring iv therapy for infections of PEDIS (Perfusion, Extent, Depth/tissue loss, Infection, and Sensation diabetic foot ulcer classification system from the International Working Group on the Diabetic Foot measuring severity) grades 2 through 4 (American Diabetes Association, 2006) (i.e., moderate to severe severity).

As noted above, tigecycline has been shown to be effective in the treatment of cSSSI using a dose of 100 mg followed by 50 mg every 12 hours. Diabetic foot infections are slow to resolve, and as prolonged treatment may be required, once-daily dosing regimens are desirable. A steady-state half-life of 42.4 hours (Wyeth Pharmaceuticals Inc, 2012) and the observation that the pharmacodynamic parameter most predictive of clinical outcome was the ratio of area under the concentration time curve (AUC) to MIC supported the investigation of once-daily administration of tigecycline. Single-dose and multiple-dose administration ranging between 12.5 mg and 300 mg and 25 mg and 100 mg every 12 hours, respectively, in healthy volunteers showed that tigecycline had dose proportional exposure over the range (Muralidharan et al., 2005). The predicted $AUC_{0\text{-}24}$ of 7.1 mg·h/L (1.5 times the observed steady-state AUC of 4.7 mg·h/L) (Wyeth Pharmaceuticals Inc, 2012) for the 150 mg every 24-hour dose would be expected to result in an $AUC_{0\text{-}24}$/MIC of 7.1 to 28.4, assuming infections by bacteria with MICs of 0.25–1 μg/mL. These $AUC_{0\text{-}24h}$/MIC ratios were within the range shown to be associated with efficacy in previous clinical studies (MacGowan, 2008).

Using a tigecycline dose of 150 mg once daily is certain to cause nausea and vomiting. Previous clinical studies have shown that it causes nausea and vomiting at rates of 26% and 18%, respectively (Wyeth Pharmaceuticals Inc, 2012), when administered twice daily. It was anticipated that potentially higher rates might be observed with the increased dose used, but the influence of once-daily dosing was unknown. Given the morbidity associated with diabetic foot infections, it was hoped that subjects and clinicians would be motivated to continue treatment.

2. Materials and methods

2.1. Subjects

A phase 3, randomized, double-blind study was conducted between November 2006 and March 2009, to assess individuals with diabetic foot infection without osteomyelitis (primary study) and with osteomyelitis (substudy). The international protocol involved 119 investigational sites in 30 countries. Sites were located in Europe, the United States, Canada, Latin America, Asia, India, Australia, and South Africa.

The study protocol was reviewed and approved by the institutional review board or ethical review committee of each participating center before any study-specific screening procedure, or informed consent was obtained. This study was conducted in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice and the ethical principles that have their origins in the Declaration of Helsinki.

Eligible subjects included hospitalized men and women aged 18 years or older with diabetes mellitus (per the American Diabetes Association criteria) (American Diabetes Association, 2006) who had a foot infection that did not extend above the knee. Signs and symptoms of the infection had to show a PEDIS infection grade from 2 to 4 and a perfusion grade from 1 to 2 (Schaper, 2004). In addition, the infection had to be of acute onset or a worsening within 14 days prior to the screening visit. Subjects who had osteomyelitis diagnosed at baseline [as evidenced magnetic resonance imaging (MRI) or bone biopsy] were not evaluable for the primary study but were eligible for enrollment into the osteomyelitis substudy. Subjects could not have received more than 48 hours of a prior antibiotic treatment unless considered a prior treatment failure, defined as worsening or no improvement in the clinical signs and symptoms of their diabetic foot infection despite exposure to antibiotic therapy and institution of nonpharmacological standards of care, and either: 1) a Gram stain from the infection site showing white blood cells and a potential pathogen or 2) culture results showing a pathogen resistant to prior antibiotics.

Potential study participants were excluded if they had infections that were categorized as necrotizing fasciitis, crepitant cellulitis, wet gangrene, gas gangrene, ecthyma gangrenosum, or which involved implanted prosthetic material or devices that were not to be removed, or infection known or suspected to be caused by a pathogen known to be resistant to either study drug. Once enrolled, subjects who were found to have a pathogen that was resistant to tigecycline or comparator as part of a polymicrobial infection could continue to receive the investigational product if they were responding favorably (based on the investigator's medical judgment). Subjects found to have a monomicrobial infection with a pathogen that was resistant to tigecycline or comparator had the investigational product discontinued and were withdrawn from the study. Subjects with severely impaired arterial supply to any portion of the affected foot or requiring anticipated complete resection or amputation of the infected anatomical site within 1 month were also excluded. Participants were also excluded if they were undergoing hemodialysis, hemofiltration, peritoneal dialysis, or plasmapheresis; had a concomitant condition that would impair the eradication of the causative bacteria; had a contraindication or hypersensitivity to any of the study medications or related antibiotics; were neutropenic or were receiving concomitant immunosuppressive therapy (including the use of more than 40 mg of prednisone or equivalent); had a creatinine clearance lower than 30 mL/min, any significant hepatic disease with aspartate aminotransferase levels or alanine aminotransferase levels more than 10

times the upper limit of normal (ULN), a bilirubin level more than 3 times the ULN, or the presence of acute hepatic failure or acute decompensation of chronic hepatic failure; or had a known or suspected infection (other than the diabetic foot infection), which would require treatment with a systemic antibacterial agent. Pregnant or lactating women or fertile women without contraception were excluded.

Subjects meeting the inclusion and exclusion criteria who were randomized were included in the intent-to-treat (ITT) population; participants who received at least 1 dose of study drug were included in the modified ITT (mITT) population; and subjects in the mITT population who had clinical evidence of a diabetic foot infection, with or without osteomyelitis, by meeting the minimal disease criteria were included in the clinically mITT (c-mITT) population (Fig. 1). Subjects in the c-mITT population were considered to be clinically evaluable (CE) if they remained blinded to study drug treatment throughout the trial, met minimal treatment duration requirements, had a test-of-cure (TOC) assessment of cure or failure in the appropriate time frame (12–92 days after the last dose for the primary study without osteomyelitis and 25–27 weeks for subjects in the substudy arm with osteomyelitis), and did not develop osteomyelitis within 14 days after the start of the study medication (subjects who developed osteomyelitis >14 days after the first dose of investigational product were evaluable). Subjects included in the microbiologically evaluable (ME) population were CE subjects for whom one or more causative isolates were identified from the baseline culture to be susceptible to both treatment regimens and for whom classification of the microbiologic response at the TOC visit could be determined.

2.2. Procedures

The primary objective of the present study was to determine the safety and efficacy of a once-daily dose of tigecycline compared with ertapenem ± vancomycin for the treatment of moderate to severe diabetic foot infections without osteomyelitis. The secondary objectives were 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, and to evaluate the safety and efficacy of a once-daily dose of tigecycline in the treatment of persons who are identified as having a diabetic foot infection with confirmed osteomyelitis.

A computerized randomization/enrollment system for automatic transtelephonic randomization was used to generate a randomization schedule for each site. At the time of the randomization, study subjects were stratified by the presence or absence of osteomyelitis and by the infection severity component of the PEDIS classification system for diabetic foot infection (grade 2 or 3 versus grade 4). The subjects who were randomized (1:1) to the arm without osteomyelitis were randomly assigned to receive either iv tigecycline or ertapenem, with or without adjunctive iv vancomycin placebo (tigecycline arm) or vancomycin (ertapenem arm) for up to 28 days, while the subjects randomized (2:1) to the arm with osteomyelitis were treated for up to 42 days. For subjects assigned to the tigecycline group, 150 mg of iv tigecycline was administered once daily in 100 mL of normal saline and infused over 30 minutes every 24 hours. For subjects assigned to the ertapenem group, 1 g of ertapenem in 100 mL normal saline was administered over 30 minutes every 24 hours. The adjunctive therapy was initiated at the investigator's discretion for coverage against MRSA, coagulase-negative staphylococci, or enterococci and was also discontinued at the investigator's discretion. The study medications were prepared by an unblinded dispenser, and adjunctive therapy dosage was adjusted by the unblinded dispenser at the request of the investigator according to the package insert and investigational site's standard of care. After a minimum of 4 doses (at least 72 hours), study participants could be discharged from the hospital and receive outpatient therapy at the investigator's discretion.

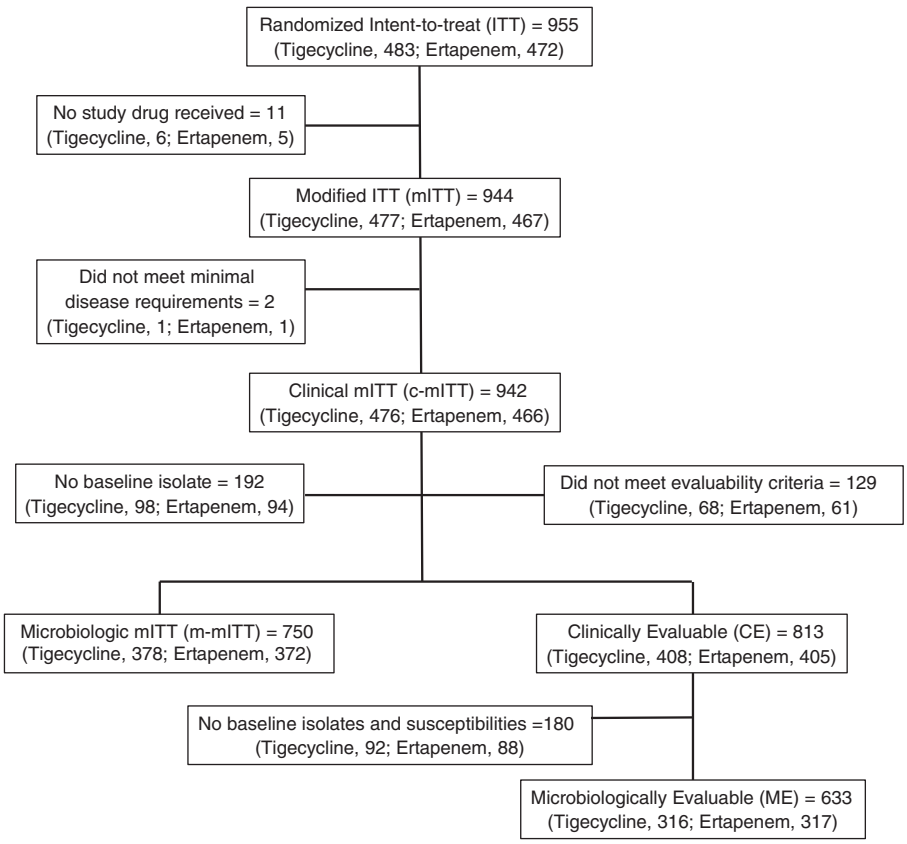

Fig. 1. Patient distribution – primary study.

At screening, the investigator obtained a medical history and performed a clinical assessment that included a complete physical examination, an assessment of clinical signs and symptoms of the infection, a peripheral perfusion assessment and specified blood chemistry, hematology, and urinalysis and also imaging with a plain radiograph of the infected limb. In situations where osteomyelitis was suspected, a MRI was performed in order to confirm the presence of osteomyelitis within 14 days after the randomization; a bone biopsy was accepted when MRI was contraindicated. All sites were allowed to enroll subjects in the osteomyelitis arm; however, this was dependent on regional regulatory requirements. The 10 sites that enrolled patients included Argentina, Canada, Colombia, India, Mexico, Panama, Russian Federation, South Africa, Switzerland, and the United States. The MRI was evaluated in a central laboratory, and if the presence of osteomyelitis could not be confirmed for subjects in the substudy, the participant was not included in the c-mITT population. At baseline and during the study, topical antiseptics were permitted for surgical procedure or debridement, and standard wound care (e.g., off-loading and wet-to-dry saline dressings) was allowed. In addition, investigators were encouraged to sharply debride ulcerated wounds at baseline and as often as clinically indicated. Wounds could be irrigated with sterile water or sterile normal saline. Concomitant antibiotics and concomitant topical antimicrobial agents were prohibited during the study.

2.3. Clinical and microbiologic assessment

A baseline blood culture isolate was collected, and a sample of the infection site for culture was obtained from curettage of the wound base, biopsy tissue samples, or aspiration of secretions (a swab was not permitted). Percutaneous bone biopsy was encouraged for subjects in the osteomyelitis arm.

The clinical response within the CE and the c-mITT populations at the TOC visit was the primary endpoint. An investigator blinded to treatment assessed the nature of the drainage (purulent versus non-purulent), erythema, induration, tenderness, pain, local warmth, and extent of the infection. Based on these assessments, the investigator evaluated the subject's clinical response to therapy (cure, failure, or indeterminate). At the TOC assessment, a subject was considered by the investigator to be clinically cured if there had been resolution of signs and symptoms of infection such that no further antibiotic therapy was required. A study subject was considered a clinical failure in the following situations: if there had been inadequate response to therapy requiring additional antibacterial therapy; if initial recovery was followed by deterioration requiring further antibacterial therapy or surgery; if the subject required extirpative surgical intervention for management of the target infection or required non-routine surgical treatment more than 48 hours after the first dose of study medication because of failure to improve; or if there was a development of a new purulent infection. If no evaluation was possible for any reason (e.g., lost to follow-up), the response to therapy was deemed indeterminate.

Microbiologic efficacy was evaluated at both the participant level (eradication [documented or presumed], persistence [documented or presumed], superinfection, or indeterminate) and the isolate level (eradication [documented or presumed], persistence [documented or presumed], or indeterminate). Skin cultures were the principal source of the baseline isolate; however, a blood isolate could have been used if no baseline isolate was identified from the infection site. All specimens were sent to local laboratories for initial identification of the isolates and were tested for susceptibility to tigecycline by Kirby-Bauer disk diffusion tests by procedures published by the Clinical and Laboratory Standards Institute. Primary identification and susceptibility were performed centrally by Covance Central

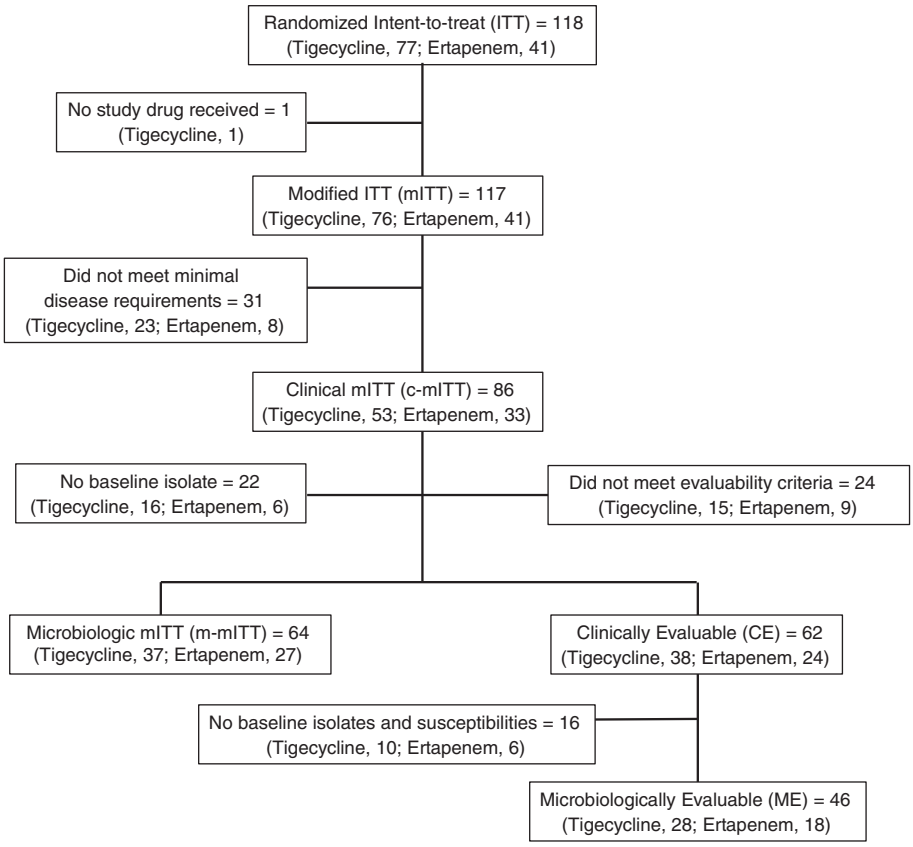

Fig. 2. Patient distribution – substudy.

Table 1
Demographic and baseline characteristics – primary study and substudy (mITT population).

Characteristic	Primary study		Substudy	
	Tigecycline	Ertapenem	Tigecycline	Ertapenem
	($n = 477$)	($n = 467$)	($n = 76$)	($n = 41$)
Age (mean ± SD) (y)	59.6 ± 11.8	59.2 ± 11.4	57.6 ± 13.2	54.1 ± 12.0
Weight (mean ± SD) (kg)	83.1 ± 20.9	83.3 ± 20.8	76.0 ± 21.5	81.1 ± 25.3
Sex				
Men, *n* (%)	300 (62.9)	315 (67.5)	54 (71.1)	28 (68.3)
Women, *n* (%)	177 (37.1)	152 (32.6)	22 (28.9)	13 (31.7)
PEDIS infection grade				
2, *n* (%)	244 (51.2)	228 (48.8)	10 (13.2)	7 (17.1)
3, *n* (%)	187 (39.2)	187 (40.0)	62 (81.6)	30 (73.2)
4, *n* (%)	46 (9.6)	52 (11.1)	4 (5.3)	4 (9.0)
CrCl (mL/min/1.73 m^2) (mean ± SD)	105.2 ± 434.7	98.8 ± 297.9	77.5 ± 27.2	83.0 ± 43.2
Type of diabetes				
Type I, *n* (%)	65 (13.6)	68 (14.6)	10 (13.2)	10 (24.4)
Type II, *n* (%)	412 (86.4)	399 (85.4)	66 (86.8)	31 (75.6)

CrCl = creatinine clearance.
There were no statistically significant differences in any characteristics between the treatment groups.

Laboratory Services Inc. (Indianapolis, IN, USA). MICs for tigecycline were determined using a reference broth microdilution method with fresh Mueller-Hinton medium. Food and Drug Administration (FDA) breakpoint criteria were used for susceptibility. All strains of *S. aureus*, *Streptococcus* spp., *S. pneumoniae*, and vancomycin-susceptible *Enterococcus faecalis* with tigecycline MIC values of ≤0.5 μg/mL, ≤0.25 μg/mL, ≤0.06 μg/mL, and ≤0.25 μg/mL, respectively, were considered susceptible (Wyeth Pharmaceuticals Inc, 2012). Tigecycline MIC breakpoints for Enterobacteriaceae were ≤2 μg/mL for susceptible, 4 μg/mL for intermediate susceptible, and ≥8 μg/mL for resistant and for anaerobes were ≤4 μg/mL for susceptible, 8 μg/mL for intermediate susceptible, and ≥16 μg/mL for resistant (Wyeth Pharmaceuticals Inc, 2012).

2.4. Safety evaluation

The safety (mITT) population comprised all subjects who received at least 1 dose of study medication. Safety assessments included a physical examination and a 12-lead electrocardiogram (ECG) at baseline, day 3, last day of study medication, and at the TOC visit; all ECG readings were interpreted at a validated central laboratory, eResearch Technology, Inc., (Philadelphia, PA, USA, and Cambridge, UK). Vital signs (temperature, heart rate, blood pressure, respiratory rate) and clinical laboratory parameters (hematology, blood chemistry and coagulation parameters, and urinalysis) were assessed at baseline, day 3, and once a week from day 6 to the last day of study medication, on the last day of study medication, and at the TOC visit. Adverse events (AEs) were coded and summarized according to MedDRA, version 11.1 (IFPMA, Geneva, Switzerland). A treatment-emergent AE (TEAE) was defined as an event that emerged during the on-therapy period (or 5 days after administration of the last dose) that was absent before treatment or worsened during the treatment period relative to the pretreatment state. All AEs and serious AEs (SAEs) were followed up until the events subsided, returned to baseline or, in case of permanent impairment, until the condition stabilized.

2.5. Statistical analysis

The noninferiority of tigecycline to ertapenem ± vancomycin was evaluated for clinical response by using the lower limit of a 2-sided 95% confidence interval (CI) for the true difference in efficacy (tigecycline minus ertapenem ± vancomycin) adjusted for the stratification variable used at the time of the randomization (i.e., infection severity). Noninferiority was concluded if the lower limit of the 2-sided 95% CI was not less than −10%. The method of Mehrotra was used to calculate a CI that adjusts for stratification (Mehrotra and Railkar, 2000). The analysis of the microbiologic response was similar to the primary analysis. Because of the descriptive nature of the osteomyelitis substudy arm, no formal statistical analysis was planned.

3. Results

Of the 1073 subjects randomized (955 in the primary study and 118 in the substudy), 1061 received treatment and were thus included in the mITT (safety) population (Figs. 1 and 2). Importantly, 26 subjects (16 tigecycline, 10 ertapenem ± vancomycin) in the

Table 2
Infection characteristics – primary study and substudy.

Characteristics	Primary study		Substudy	
mITT population	Tigecycline ($n = 477$)	Ertapenem ($n = 467$)	Tigecycline ($n = 76$)	Ertapenem ($n = 41$)
Prior antibiotic failure, *n* (%)	100 (21.0)	93 (19.9)	34 (44.7)	19 (46.3)
Etiology				
New/acute onset, *n* (%)	288 (60.4)	305 (65.3)	33 (43.4)	16 (40.0)
Worsening of prior infection, *n* (%)	189 (39.6)	162 (34.7)	43 (56.6)	24 (60.0)
Prior amputation at site of infection				
Yes, *n* (%)	82 (17.2)	80 (17.1)	17 (22.4)	4 (9.8)
No, *n* (%)	395 (82.8)	387 (82.9)	59 (77.6)	37 (90.2)
ME population	Tigecycline ($n = 316$)	Ertapenem ($n = 317$)	Tigecycline ($n = 28$)	Ertapenem ($n = 18$)
Bacteremia, *n* (%)	19 (6.0)	24 (7.6)	2 (7.1)	1 (5.6)

There were no statistically significant differences in any characteristics between the treatment groups.

Table 3
Clinical response at TOC in the primary study and substudy.

Population category	Tigecycline	Ertapenem	Absolute difference (95% CI)	Test for noninferiority, *P*-value
Primary study				
CE population	$n = 408$	$n = 405$		
Cure	316 (77.5)	334 (82.5)	−5.5 (−11.0, 0.1)[a]	0.055[a]
			−5.0 (−10.8, 0.7)[b]	0.0455[b]
Failure	92 (22.5)	71 (17.5)		
c-mITT population	$n = 476$	$n = 466$		
Cure	340 (71.4)	363 (77.9)	−6.7 (−12.3, –1.1)[a]	0.129[a]
			−6.5 (−12.2, –0.7)[b]	0.120[b]
Failure	117 (24.6)	86 (18.5)		
Indeterminate	19 (4.0)	17 (3.6)		
Substudy				
CE population	$n = 38$	$n = 24$		
Cure	12 (31.6)	13 (54.2)		
Failure	26 (68.4)	11 (45.8)		
c-mITT population	$n = 53$	$n = 33$		
Cure	19 (35.8)	21 (63.6)		
Failure	27 (50.9)	12 (36.4)		
Indeterminate	7 (13.2)	0 (0.0)		

[a] Adjusted analysis.
[b] Unadjusted analysis.

c-mITT population in the primary study were subsequently diagnosed with osteomyelitis, although originally thought to have an uncomplicated tissue infection. The co-primary efficacy populations included 1028 subjects (942 in the primary study and 86 in the substudy) in the c-mITT population and 875 subjects (813 in the primary study and 62 in the substudy) in the CE population.

Differences were not observed between the treatment groups for demographic or baseline medical characteristics for either the primary study or the substudy (Table 1). Ninety percent of all subjects in the primary study had a baseline PEDIS infection grade of 2 or 3. In general, baseline PEDIS infection grades were similar between the tigecycline and ertapenem ± vancomycin groups. Twenty percent of the subjects in the primary study and 45% of the subjects in the substudy had experienced prior antibiotic failure, despite concomitant nonpharmacological standards of care (e.g., routine debridement) (Table 2). Subjects who failed prior antibiotics prior to study enrollment were commonly receiving beta-lactam antibiotics (72.5% primary study, 69.8% substudy), quinolones (28.0% primary study, 37.7% substudy), clindamycin (15.0% primary study, 13.2% substudy), and metronidazole (13.5% primary study, 13.2% substudy). Seventeen percent of subjects in the primary study and 18% of subjects in the substudy had an infection at an amputation site. In the primary study, bacteremia was detected in 6.0% and 7.6% of the ME subjects in the tigecycline and ertapenem ± vancomycin groups, respectively, on the last day of therapy. In the ME population of the substudy, 2 of 28 tigecycline subjects and 1 of 18 ertapenem ± vancomycin subjects had bacteremia on the last day of therapy.

Importantly, in the primary study, there were no statistically significant differences between treatment groups regarding the proportions of subjects receiving nonpharmacologic treatments or procedures for their infection (35% of subjects in the tigecycline group and 38% of subjects in the ertapenem group had debridement at baseline or while on therapy). Likewise, in the substudy, debridement at baseline or while on therapy was similar (53% in the tigecycline group and 44% in the ertapenem group).

The median duration of treatment in the primary study was 11 days (range, 1–29 days) for subjects treated with tigecycline and 12 days (range, 1–30 days) for those treated with ertapenem ± vancomycin. In the substudy, the median duration of tigecycline treatment was 25 days (range, 2–43 days) and ertapenem ± vancomycin treatment was 39 days (range, 5–45 days). Vancomycin placebo was administered to 17.6% (84/477) of the tigecycline-treated subjects, and adjunctive vancomycin, to 15.6% (73/467) of ertapenem ± vancomycin subjects in the primary study (c-mITT population). In the substudy, vancomycin placebo was administered to 17.1% (13/76) of tigecycline-treated subjects, and vancomycin was administered to 34.1% (14/41) of ertapenem ± vancomycin–treated subjects. It is noteworthy that, in both the primary study and substudy, more participants discontinued study medication in the tigecycline group (21.0% and 40.8%, respectively) than in the ertapenem ± vancomycin group (15.4% and 14.6%, respectively). In the primary study, a significantly higher proportion of the subjects treated with tigecycline had medication stopped due to an AE (see safety section) and per participant request than the ertapenem ± vancomycin group (2.9% versus 0.9%, $P =$

Table 4
Clinical cure rates with respect to baseline pathogen ($n > 10$ isolates/group) – primary study and substudy (ME population).

Baseline isolate	Primary study		Substudy	
	Tigecycline, *n*/*N* (%)	Ertapenem, *n*/*N* (%)	Tigecycline, *n*/*N* (%)	Ertapenem, *n*/*N* (%)
Acinetobacter baumannii	8/10 (80.0)	15/17 (88.2)	1/2 (50.0)	0/0 (0.0)
E. cloacae	20/23 (87.0)	27/31 (87.1)	0/1 (0.0)	0/0 (0.0)
E. faecalis	56/67 (83.6)	56/67 (83.6)	3/7 (42.9)	3/5 (60.0)
E. coli	21/28 (75.0)	28/38 (73.7)	3/6 (50.0)	0/1 (0.0)
Klebsiella oxytoca	12/15 (80.0)	16/19 (84.2)	-	-
K. pneumoniae	10/15 (66.7)	17/21 (81.0)	1/2 (50.0)	2/2 (100.0)
P. mirabilis	18/24 (75.0)	25/30 (83.3)	-	-
Pseudomonas aeruginosa	11/19 (57.9)	12/17 (70.6)	0/1 (0.0)	1/1 (100.0)
MSSA	92/116 (79.3)	123/137 (89.8)	4/11 (36.4)	1/5 (20.0)
MRSA	29/44 (65.9)	17/26 (65.4)	0/3 (0.0)	2/3 (66.7)
S. agalactiae	35/40 (87.5)	40/48 (83.3)	1/6 (16.7)	3/4 (75.0)

Table 5
Summary of MIC data and response for the most clinically relevant baseline isolates – primary study (ME population).

Baseline isolate	*N*	Tigecycline MIC range (μg/mL)	Tigecycline, MIC_{50}	Tigecycline, MIC_{90}	Clinical cure at TOC, *n*/*N* (%)	Eradication at TOC, *n*/*N* (%)
A. baumannii	27	0.06–4.00	0.50	2.00	8/10 (80.0)	8/10 (80.0)
E. cloacae	54	0.25–1.00	0.50	0.50	20/23 (87.0)	18/23 (78.3)
E. faecalis	134	0.06–0.25	0.12	0.25	56/67 (83.6)	55/67 (82.1)
E. coli	66	0.06–1.00	0.25	0.50	21/28 (75.0)	22/28 (78.6)
K. oxytoca	34	0.25–1.00	0.25	0.50	12/15 (80.0)	14/15 (93.3)
K. pneumoniae	36	0.25–2.00	0.50	2.00	10/15 (66.7)	12/15 (80.0)
P. mirabilis	54	0.50–8.00	2.00	4.00	18/24 (75.0)	16/24 (66.7)
P. aeruginosa	36	4.00–64.00	8.00	32.00	11/19 (57.9)	12/19 (63.2)
MSSA	253	0.03–0.50	0.12	0.25	92/116 (79.3)	83/116 (71.6)
MRSA	70	0.06–0.50	0.12	0.25	29/44 (65.9)	21/44 (47.7)
S. agalactiae	88	0.03–0.25	0.06	0.06	35/40 (87.5)	34/40 (85.0)

0.029). Similar findings for discontinuation due to an AE were observed in the substudy.

3.1. Efficacy

At the TOC assessment in the primary study, 77.5% of tigecycline-treated subjects and 82.5% of ertapenem ± vancomycin-treated subjects in the CE population were considered cured, and 71.4% of those treated with tigecycline subjects and 77.9% of those who received ertapenem ± vancomycin in the c-mITT population were considered cured (Table 3). The tigecycline regimen did not meet the primary study endpoint of noninferiority to the ertapenem ± vancomycin regimen for the CE population (true difference in efficacy of tigecycline minus ertapenem ± vancomycin regimen, −5.5%; 95% CI, −11.0 to 0.1) or c-mITT population (true difference in efficacy of tigecycline minus ertapenem ± vancomycin regimen, −6.7; 95% CI, −12.3 to −1.1), as the lower limit of the 95% CI was less than −10% in both the adjusted and unadjusted analyses. In addition, the ertapenem ± vancomycin regimen had a significantly higher cure rate compared with tigecycline in the c-mITT population, based on the upper 95% CI interval.

The clinical cure rates by baseline isolates for the ME population in both the primary study and substudy are shown in Table 4. In the primary study, the cure rates for most baseline isolates were either slightly higher or similar for ertapenem ± vancomycin as compared with tigecycline-treated subjects. However, participants in the tigecycline regimen with *Escherichia coli* (21/28; 75.0%), MRSA (29/44; 65.9%), and *S. agalactiae* infections (35/40; 87.5%) had higher cure rates compared to subjects receiving ertapenem ± vancomycin (28/38, 73.7%; 17/26, 65.4%; and 40/48, 83.3%; respectively). The cure rates for tigecycline-treated participants with methicillin-susceptible *S. aureus* (MSSA) or *Klebsiella pneumoniae* infections were lower than expected compared with those treated with ertapenem ± vancomycin. For subjects with baseline bacteremia, excluding contaminants, in the primary study, the clinical cure rate at the TOC visit was 6/7 (86%) for tigecycline-treated subjects and 14/14 (100%) for ertapenem-treated subjects.

MIC_{50} and MIC_{90} data for the tigecycline-treated subjects in the primary study and substudy ME populations are shown in Tables 5 and 6, respectively, and were generally low for most isolates. In the primary study, superinfection occurred more frequently in the tigecycline group than in the ertapenem group (6.6% [21/316] of tigecycline versus 3.8% [12/317] of ertapenem ± vancomycin). No single pathogen accounted for the superinfections that occurred in the primary study, and the organisms associated with the superinfections in the tigecycline group were generally susceptible to tigecycline. Three subjects in the tigecycline group of the primary study and 1 subject in the tigecycline group of the osteomyelitis substudy had microorganisms with decreased susceptibility to tigecycline during therapy. Specifically, *S. epidermidis* (0.06–1.0 mg/L), *Proteus mirabilis* (1.0–4.0 mg/L), and *Morganella morganii* (1.0–4.0 mg/L) isolates developed resistance as defined by the MIC crossing the susceptible breakpoint. One *Enterobacter cloacae* isolate had a 4-fold increase in MIC (0.5–2.0 mg/L).

3.2. Safety

There were no significant differences in underlying medical conditions between treatment groups. One or more TEAEs were reported by 71.1% of the tigecycline-treated subjects and 57.0% of ertapenem ± vancomycin–treated participants in the primary study ($P < 0.001$) and 88.2% of tigecycline-treated subjects and 63.4% of ertapenem ± vancomycin–treated subjects in the substudy ($P < 0.01$). Table 7 lists the TEAEs that occurred in the primary study and substudy in ≥3% of subjects in either treatment group of the primary study. The most commonly reported TEAEs for tigecycline-treated subjects in the primary study were nausea (39.8%), vomiting (24.7%), diarrhea (11.3%), hypertension (7.1%), and hypoglycemia (7.1%). The most commonly reported TEAEs for tigecycline-treated subjects in the substudy were nausea (48.7%), vomiting (43.4%), diarrhea (27.6%), and hypoglycemia (21.1%). In the primary study, nausea and vomiting ($P < 0.001$), as well as insomnia ($P < 0.05$), occurred significantly more often in the tigecycline group. In the substudy, nausea and vomiting ($P < 0.001$), as well as hypoglycemia ($P < 0.05$), occurred significantly more often in the tigecycline group.

Table 6
Summary of MIC data and response for the most clinically relevant baseline isolates – substudy (ME population).

Baseline isolate	*N*	Tigecycline MIC range (μg/mL)	Tigecycline, MIC_{50}	Tigecycline, MIC_{90}	Clinical cure at TOC, *n*/*N* (%)	Eradication at TOC, *n*/*N* (%)
A. baumannii	2	0.12–1.00	NA	NA	1/2 (50.0)	1/2 (50.0)
E. cloacae	1	0.50–0.50	NA	NA	0/1 (0.0)	0/1 (0.0)
E. faecalis	12	0.03–0.25	0.12	0.25	3/7 (42.9)	3/7 (42.9)
E. coli	7	0.12–0.50	NA	NA	3/6 (50.0)	5/6 (83.3)
K. pneumoniae	4	0.25–0.50	NA	NA	1/2 (50.0)	1/2 (50.0)
P. aeruginosa	2	8.00–16.00	NA	NA	0/1 (0.0)	0/1 (0.0)
MSSA	16	0.06–0.25	0.12	0.25	4/11 (36.4)	4/11 (36.4)
MRSA	6	0.12–0.25	NA	NA	0/3 (0.0)	0/3 (0.0)
S. agalactiae	10	0.03–0.06	0.06	0.06	1/6 (16.7)	2/6 (33.3)

Table 7
TEAEs that occurred in ≥3% of subjects in either treatment group of the primary study.

AE	Primary study		Substudy	
	Tigecycline $N = 477$, n (%)	Ertapenem $N = 467$, n (%)	Tigecycline $N = 76$, n (%)	Ertapenem $N = 41$, n (%)
Any AE	339 (71.1)[a]	266 (57.0)	67 (88.2)[b]	26 (63.4)
Fever	19 (4.0)	15 (3.2)	8 (10.5)	4 (9.8)
Headache	23 (4.8)	19 (4.1)	3 (3.9)	1 (2.4)
Pain	18 (3.8)	12 (2.6)	7 (9.2)	5 (12.2)
Hypertension	34 (7.1)	35 (7.5)	2 (2.6)	5 (12.2)
Diarrhea	54 (11.3)	46 (9.9)	21 (27.6)	5 (12.2)
Nausea	190 (39.8)[a]	39 (8.4)	37 (48.7)[a]	7 (17.1)
Vomiting	118 (24.7)[a]	22 (4.7)	33 (43.4)[a]	3 (43.4)
Anemia	10 (2.1)	14 (3.0)	4 (5.3)	4 (9.8)
Hypoglycemia	34 (7.1)	24 (5.1)	16 (21.1)[b]	–
SGOT increased	15 (3.1)	19 (4.1)	5 (6.6)	2 (4.9)
SGPT increased	15 (3.1)	18 (3.9)	4 (5.3)	2 (4.9)
Osteomyelitis	22 (4.6)	11 (2.4)	3 (3.9)	1 (2.4)
Insomnia	15 (3.1)[c]	4 (0.9)	3 (3.9)	1 (2.4)

SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.
TEAE definition = events from first dose through last day of treatment + 5 days.
[a] $P < 0.001$.
[b] $P < 0.01$.
[c] $P < 0.05$.

More participants in the tigecycline treatment arm of the primary study discontinued study drug as a result of an AE ($n = 42$) compared with the ertapenem ± vancomycin–treated subjects ($n = 27$) ($P = 0.081$). The AEs leading to tigecycline discontinuation were primarily nausea (2.7%) and vomiting (2.3%); these occurred significantly more frequently than in ertapenem ± vancomycin–treated subjects ($P < 0.01$ and $P < 0.001$, respectively). Tigecycline-treated subjects in the primary study also had significantly more AEs leading to study withdrawal (2.1%) than ertapenem ± vancomycin–treated subjects (0.4%) ($P = 0.038$); however, the reasons were varied. Overall reasons for study drug discontinuation and study withdrawal, respectively, in the primary study and substudy are shown in Tables 8 and 9.

A total of 141 (13.3%) of the subjects reported 1 or more SAEs during the study: in the primary study, 11.9% in the tigecycline group and 10.7% in the ertapenem ± vancomycin group, and in the substudy, 28.9% in the tigecycline group and 29.3% in the ertapenem ± vancomycin group. These differences were not statistically significant. The most frequently reported SAEs for tigecycline-treated subjects in the primary study (occurring in >1% of subjects) were infection and osteomyelitis. Significantly ($P < 0.05$) more participants in the primary study in the tigecycline group (2.5%) had osteomyelitis reported as an SAE compared to subjects in the ertapenem ± vancomycin group (0.6%).

There were a total of 10 deaths in the mITT population (primary study, 6/477 [1.3%] subjects in the tigecycline group and 2/467 [0.4%] subjects in the ertapenem ± vancomycin group; substudy, 1/76 [1.3%] subjects in the tigecycline group and 1/41 [2.4%] subjects in the ertapenem ± vancomycin group). Most of the AEs with an outcome of death were related to a vascular or thrombotic event, and none of the deaths were considered related to study drug by the investigator. Five of 7 deaths in the tigecycline group and 2 of 3 deaths in the ertapenem ± vancomycin group occurred more than 1 week after the end of study treatment. All 7 subjects who died in the tigecycline group were considered cured at the last day of therapy, although 4 assessments of cure were deemed "indeterminate" at TOC because of non–infection-related death. Note that 7 deaths were recorded as study withdrawals because they occurred before the TOC visit.

In the primary study, of the 944 participants in the mITT population with laboratory data, 394 (82.6%) of tigecycline- and 408 (87.4%) of ertapenem ± vancomycin–treated subjects had an abnormal laboratory test result during therapy considered of potential clinical importance based on predefined criteria. For individual laboratory tests, elevated sodium, potassium, and glucose levels were observed more frequently in the ertapenem ± vancomycin arm, and low potassium, decreased carbon dioxide, low glucose, and elevated blood, urea, nitrogen (BUN) values were observed more frequently in the tigecycline arm. In the primary study, the mean change from baseline for the final on-therapy vital sign measurements was similar in both treatment arms.

There were no significant differences in change from baseline for ECG intervals between treatment groups in the primary study. Using the log-linear correction for QTc interval, the median on-study change from baseline within 3 hours after dosing in the primary study was

Table 8
Study drug discontinuations – primary study and substudy (mITT population).

Reason, n (%)	Primary study			Substudy		
	Tigecycline ($n = 477$)	Ertapenem ($n = 467$)	P-value[a]	Tigecycline ($n = 76$)	Ertapenem ($n = 41$)	P-value[a]
Total	100 (21.0)	72 (15.4)	0.029[b]	31 (40.8)	6 (14.6)	0.004[b]
AE	42 (8.8)	27 (5.8)	0.081	11 (14.5)	1 (2.4)	0.054
Death	–	–	–	–	1 (2.4)	0.350
Investigator request	3 (0.6)	2 (0.4)	1.000	2 (2.6)	–	0.541
Lost to follow-up	–	–	–	2 (2.6)	–	0.541
Other[c]	27 (5.7)	20 (4.3)	0.371	4 (5.3)	–	0.296
Protocol violation	1 (0.2)	2 (0.4)	0.621	–	–	–
Patient request	14 (2.9)	4 (0.9)	0.029[b]	4 (5.3)	–	0.296
Unsatisfactory response – efficacy	13 (2.7)	17 (3.6)	0.462	8 (10.5)	4 (9.8)	1.000

[a] Fisher exact test.
[b] $P < 0.05$.
[c] The most common other reason was osteomyelitis status.

Table 9
Study withdrawals – primary study and substudy (mITT population).

Reason, *n* (%)	Primary study			Substudy		
	Tigecycline ($n = 477$)	Ertapenem ($n = 467$)	*P*-value[a]	Tigecycline ($n = 76$)	Ertapenem ($n = 41$)	*P*-value[a]
Total	55 (11.5)	38 (8.1)	0.082	25 (32.9)	9 (22.0)	0.286
AE	10 (2.1)	2 (0.4)	0.038[b]	5 (6.6)	6 (14.6)	0.190
Death	4 (0.8)	1 (0.2)	0.374	1 (1.3)	1 (2.4)	1.000
Investigator request	1 (0.2)	1 (0.2)	1.000	1 (1.3)	–	1.000
Lost to follow-up	4 (0.8)	11 (2.4)	0.072	2 (2.6)	–	0.541
Other[c]	27 (5.7)	14 (3.0)	0.055	5 (6.6)	–	0.161
Protocol violation	–	1 (0.2)	0.495	1 (1.3)	–	1.000
Patient request	5 (1.0)	2 (0.4)	0.452	5 (6.6)	–	0.161
Unsatisfactory response – efficacy	4 (0.8)	6 (1.3)	0.543	5 (6.6)	2 (4.9)	1.000

[a] Fisher exact test.
[b] $P < 0.05$.
[c] The most common other reason was osteomyelitis status.

58 ms for tigecycline and 1.1 ms for ertapenem ± vancomycin, with upper bounds of the 2-sided 90% CI 7.6 and 3.9 ms, respectively. There were 2 individuals in both treatment arms of the primary study with QTc intervals that increased by >60 ms within 3 hours after dosing and 1 individual in the tigecycline arm with a QTc interval that was >500 ms within 3 hours after dosing, but none of these subjects developed proarrhythmic AEs.

4. Discussion

The finding of lack of tigecycline noninferiority was unexpected by the investigators with higher-than-expected cure rates. When the study was planned, a cure rate of approximately 70% in the CE population was expected. In a study comparing ertapenem against piperacillin/tazobactam, the cure rate was 75% (153/204) for ertapenem and 70.8% (143/202) for piperacillin/tazobactam (Lipsky et al., 2005). Although it is difficult to compare results from different clinical trials, the cure rate observed for tigecycline in the current study (77.5%) was similar to that reported previously for ertapenem, while the cure rate for ertapenem ± vancomycin in the current trial (82.5%) was higher than that reported in the previous trial. Of note, the Lipsky et al (2005) trial used the University of Texas Diabetic Wound Classification scheme to measure the severity of diabetic foot infection rather than PEDIS.

The tigecycline dosing regimen performed as predicted. Tigecycline serum concentrations were collected in 106 patients receiving tigecycline. After 3 days of treatment, the $AUC_{0\text{-}24h}$ was 7.42 ± 3.21 mg·h/L, which was the exposure anticipated for the dose of 150 mg every 24 hours.

Post hoc analyses were performed to try to understand the study results. Multiple populations and treatment factors were assessed individually and in combination, including demographic and baseline factors, co-morbidities, adjunctive therapy, geographic region, frequency of baseline pathogens, infection characteristics, and prior antibiotic failure. Other analyses explored whether appropriate therapy (e.g., if the subject received an antibiotic to which the organism was susceptible) had been administered. While the findings of these exploratory analyses do not change the outcome or explain the differences in cure rates observed in this study, some possible explanations are suggested.

Compared with ertapenem ± vancomycin, more subjects in the tigecycline group considered to have been cured on the last day of therapy were subsequently categorized as failures at the TOC assessment, and duration of therapy for these subjects was shorter in the tigecycline group. While duration of therapy overall was similar between the 2 treatment groups, it may be that subjects who ultimately failed would have had better outcomes with longer treatment. Also, in the primary study, more subjects in the tigecycline group ($n = 16$) than ertapenem ± vancomycin ($n = 10$) group were diagnosed with osteomyelitis during the first 14 days of therapy. For the primary study, magnetic resonance imaging as radiographic assessment at baseline was not a requirement. It is reasonable to assume that these subjects had osteomyelitis at baseline and were considered treatment failures.

Differences in bacteria causing the infection and related susceptibility could also cause a difference between treatment outcomes. Where microbiologic data were available (approximately 78% of randomized participants), most of the infections were caused by pathogens with tigecycline MICs that were low, which theoretically should have led to clinical cure. Decreasing susceptibility or increasing MIC values has also been reported in small numbers in prior studies, and the small numbers of individuals with MIC increases on therapy in this trial do not appear to have contributed to the overall results. Despite known lower serum concentrations with tigecycline, baseline bacteremia did not appear to affect the outcomes of the trial given similar clinical responses.

There were more discontinuations of study medication overall and for AEs, particularly nausea and vomiting, in the tigecycline arm. Most of these subjects received additional antibiotic therapy after discontinuing study treatment and were, therefore, considered failures. This may have further contributed to the differences in efficacy observed. Finally, it may be that ertapenem ± vancomycin is more effective in subjects with diabetic foot infection than once-daily tigecycline.

For the osteomyelitis substudy, the cure rates for tigecycline were low. The substudy was not powered, and the numbers of participants in the substudy were small, making it difficult to draw conclusions. Nevertheless, the median treatment duration of 25 days in the tigecycline group (versus 39 days in the ertapenem ± vancomycin group) is considered short for the treatment of osteomyelitis and was due to the relatively high discontinuation and study withdrawal rate in the tigecycline arm.

From a safety perspective, the frequencies of nausea and vomiting, as well as discontinuations for these AEs, were higher than in other tigecycline studies (Babinchak et al., 2005; Ellis-Grosse et al., 2005; Tanaseanu et al., 2008). When combined, the rates reported in previous studies, where tigecycline was administered every 12 hours, are 26% and 18%, respectively, compared with 13% and 9% for comparators (Wyeth Pharmaceuticals Inc, 2012). Pharmacodynamic assessment of nausea and vomiting by Rubino et al (2012) in 289 patients with community-acquired pneumonia or hospital-acquired pneumonia who were treated with 100 mg then 50 mg every 12 hours using classification and regression tree analysis showed a threshold $AUC_{0\text{-}24}$ of 6.87 mg·h/L to be predictive of the occurrence of nausea and/or vomiting. Patients with $AUC_{0\text{-}24}$ values above and below the threshold value had an incidence of nausea and/or vomiting of 40.4% and 17.2%, respectively ($P = 0.00015$, Chi-square test). The mean $AUC_{0\text{-}24}$ of 7.42 mg·h/L observed in the current study and its incidence of nausea and vomiting of 39.8% and 24.7% are consistent with Rubino's results, suggesting that once-daily treatment did not improve tolerability.

Importantly, the increases in BUN values observed in this study after tigecycline were similar to those reported previously and do not appear to be indicative of decreased renal function (Babinchak et al., 2005; Ellis-Grosse et al., 2005; Tanaseanu et al., 2008). Finally, there was no signal that once-daily tigecycline was associated with QTc prolongation and no proarrhythmic events were reported, similar to prior phase 3 tigecycline studies (Babinchak et al., 2005; Ellis-Grosse et al., 2005; Tanaseanu et al., 2008). The frequency of SAEs was similar between treatment arms. As expected, the mortality rate in this study was low, with 6 (1.3%) and 2 (0.4%) deaths for tigecycline- and ertapenem ± vancomycin–treated subjects, respectively, in the primary study. Most of the deaths were cardiovascular in nature, which would not be unexpected for this population. Median time to death was similar between treatment arms, with most of the deaths occurring after subjects had stopped study treatment and most of the subjects had been deemed cured at the last day of therapy. This numerical imbalance is similar to what has been reported in other tigecycline studies. For the substudy, 1 subject in each treatment group died.

There are a number of limitations in the present study. Enrollment was by central randomization, rather than by region, country, or site. Although the treatment arms were generally balanced by region, there could have been some differences between treatment arms in the types of subjects enrolled or differences with respect to standard practice. One regional difference is that the European Union did not participate in the osteomyelitis substudy because they required additional preclinical data due to the longer duration of tigecycline therapy than what had been evaluated in prior tigecycline studies. The substudy was not a powered trial, with only descriptive statistics planned. Although large for an osteomyelitis study, the numbers were relatively small, particularly for the evaluable population.

The evaluation of new antimicrobial agents for the treatment of cSSSIs, such as diabetic foot infections, is complex and can be confounded by many factors (e.g., clinical manifestations influenced by immune status, ambiguity of true etiology, and consensus on evaluable markers of resolution of infection; need and influence of surgical intervention on outcomes) (Stevens, 2009). Furthermore, a recent review, which sought to define the magnitude of efficacy of antimicrobial agents and resulting noninferiority margins for studies of cSSSIs in the absence of placebo-controlled trials, argues that the current FDA-mandated noninferiority margins for these infections require updating (Spellberg et al., 2009). It has been suggested that reasonable noninferiority margins are needed for each type of cSSSI, which should be weighted for the proportion of enrolled subjects with cellulitis/erysipelas, wound, or ulcer infections and major abscesses. Specifically, they propose that noninferiority margins of 21% for wound/ulcer infections would preserve at least 50% of antibiotic efficacy versus placebo in certain patient subpopulations, such as those with diabetic foot infections.

In summary, although tigecycline has been shown to be efficacious in subjects with cSSSI, the 150 mg once-daily regimen of tigecycline evaluated in this trial did not meet the criteria for noninferiority compared with ertapenem ± vancomycin in the primary study in subjects with diabetic foot infections. For the substudy in subjects with osteomyelitis, the cure rates for tigecycline were low. Higher rates of nausea and vomiting were observed for tigecycline in this trial than in other phase 3 studies, with higher discontinuation rates for these AEs. The safety profile of tigecycline was otherwise generally similar to what has already been established.

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Appendix A. Supplementary Table

Percentage (*n*/*N*) of subjects with a clinical cure at TOC (%), stratified by geographic region and PEDIS grade in the primary study (clinically evaluable population).

PEDIS grade	Tigecycline						Ertapenem ± vancomycin					
	Asia	Eastern Europe	Western Europe	USA/ Canada	Latin America	Other/ India	Asia	Eastern Europe	Western Europe	USA/ Canada	Latin America	Other/ India
2	75.0 (12/16)	84.0 (105/125)	33.3 (3/9)	56.3 (9/16)	86.2 (25/29)	80.0 (16/20)	86.4 (19/22)	90.6 (87/96)	75.0 (12/16)	52.4 (11/21)	76.2 (16/21)	87.0 (20/23)
3	65.5 (19/29)	84.2 (64/76)	53.8 (7/13)	88.9 (8/9)	76.5 (13/17)	71.4 (10/14)	87.1 (27/31)	91.8 (78/85)	66.7 (8/12)	57.1 (4/7)	89.5 (17/19)	75.0 (6/8)
4	71.4 (5/7)	81.3 (13/16)	0.0 (0/1)	50.0 (1/2)	62.5 (5/8)	100.0 (1/1)	55.6 (5/9)	78.9 (15/19)	50.0 (1/2)	25.0 (1/4)	0.0 (0/2)	87.5 (7/8)

Within each PEDIS grade, cure rates varied by geographic region. For patients with a PEDIS grade of 2, clinical cure rates after tigecycline and ertapenem ± vancomycin therapy were lower in Western Europe and the USA/Canada compared with other regions, despite the fact that a higher proportion of patients in the USA/Canada had a PEDIS grade suggestive of less severe illness. For patients with a PEDIS grade of 3, clinical cure rates were lower for tigecycline-treated patients in Western Europe and for ertapenem ± vancomycin–treated patients in Western Europe and the USA/Canada. For patients with a PEDIS grade of 4, clinical cure rates between treatment groups were highly variable (>15% different) across regions with the exception of Eastern Europe and Other/India.

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