International Journal of Surgery (2005) 3, 35–47

ELSEVIER

INTERNATIONAL JOURNAL OF SURGERY

www.int-journal-surgery.com

Tigecycline is efficacious in the treatment of complicated intra-abdominal infections☆

Peter Fomin [a,*], Mircea Beuran [b,h], Audrius Gradauskas [c,i], Giedrius Barauskas [d,j], Alexey Datsenko [e,k], Nathalie Dartois [f,l], Evelyn Ellis-Grosse [g,m], Evan Loh [g,n], on behalf of the 306 Study Group

[a] *National Medical University, Surgical Department, City Hospital No 12, Podvysotskogo Street 4-a, 01 103 Kyiv, Ukraine*
[b] *General Surgery Department, Bucharest Clinical Emergency Hospital, 2nd Floor, 8 Floreasca Avenue, 71406 Bucharest, Romania*
[c] *General Surgery Department, Vilnius City University Hospital, Antakalnio 57, Physicians Room, LT-2040 Vilnius, Lithuania*
[d] *General Surgery Department, Kaunas Medical University Hospital, Eiveniu 2, P.O. Box 1018, LT-50010 Kaunas, Lithuania*
[e] *Kharkov Medical Academy, City Clinical Multiple-Discipline Hospital, N°2, 97, Moskovskii Pr, 1001 Kharkov, Ukraine*
[f] *Office 06TA024, Coeur Défense — Tour A — La Defense 4, 92 931 Paris La Defense Cédex, France*
[g] *Clinical Research Group, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, USA*

☆ These results were presented in part at the 44th Annual Meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy, October 30 to November 2, 2004, Washington, DC, abstract #3841, Control Number L-992c.

This study was supported by Wyeth Research.

* Corresponding author. Tel.: +380 50 558 4725; fax: +380 44 451 8603.
E-mail addresses: peter_fomin@yahoo.com (P. Fomin), beuranm@hotmail.com (M. Beuran), gradauskasa@one.lt (A. Gradauskas), giedrius.barauskas@kmu.lt (G. Barauskas), adatsenko@mail.ru (A. Datsenko), dartoin@wyeth.com (N. Dartois), ellise@wyeth.com (E. Ellis-Grosse), lohe@wyeth.com (E. Loh).
[h] Tel.: +40 722 247 044; fax: +40 21 230 6175.
[i] Tel.: +370 685 44800; fax: +370 234 6966.
[j] Tel.: +370 686 525 96; fax: +370 37 326 179.
[k] Tel.: +380 67 280 6489 or +380 572 90 5471; fax: +380 572 265 026.
[l] Tel.: +33 1 41 02 7414; fax: +33 1 41 02 7435.
[m] Tel.: +484 865 2729; fax: +484 865 9262.
[n] Tel.: +484 865 4206; fax: +484 865 9262.

1743-9191/$ - see front matter
doi:10.1016/j.ijsu.2005.03.011

KEYWORDS
Complicated intra-abdominal infections;
Tigecycline;
Glycylcycline;
Imipenem/cilastatin;
Efficacy;
Safety;
In vitro activity

Abstract *Background:* Empiric treatment of complicated intra-abdominal infections (cIAI) represents a clinical challenge because of the diverse bacteriology and the emergence of bacterial resistance. The efficacy and safety of tigecycline (TGC), a first-in-class, expanded broad-spectrum glycylcycline antibiotic, were compared with imipenem/cilastatin (IMI/CIS) in patients with cIAI.
Methods: In this prospective, double-blind, phase 3, multinational trial, patients were randomly assigned to intravenous (IV) TGC (100 mg initial dose, then 50 mg every 12 h) or IV IMI/CIS (500/500 mg every 6 h) for 5—14 days. Clinical response was assessed at the test-of-cure (TOC) visit (14—35 days after therapy) for microbiologically evaluable (ME) and microbiologically modified intent-to-treat (m-mITT) populations (co-primary efficacy endpoint populations in which cure/failure response rates were determined).
Results: Of 817 mITT patients (i.e., received $\geq$ 1 dose of study drug), 641 (78%) comprised the m-mITT cohort (322 TGC, 319 IMI/CIS) and 523 (64%) were ME (266 TGC, 256 IMI/CIS). Patients were predominantly white (88%) and male (59%) with a mean age of 49 years. The primary diagnoses for the mITT group were complicated appendicitis (41%), cholecystitis (22%), and intra-abdominal abscess (11%). For the ME population, clinical cure rates at TOC were 91.3% (242/265) for TGC versus 89.9% (232/258) for IMI/CIS (95% CI -4.0, 6.8; $P < 0.001$). Corresponding clinical cure rates within the m-mITT population were 86.6% (279/322) for TGC versus 84.6% (270/319) for IMI/CIS (95% CI -3.7, 7.5; $P < 0.001$ for noninferiority TGC versus IMI/CIS). The most commonly reported adverse events for TGC and IMI/CIS were nausea (17.6% TGC versus 13.3% IMI/CIS; $P = 0.100$) and vomiting (12.6% TGC versus 9.2% IMI/CIS; $P = 0.144$).
Conclusions: TGC is efficacious in the treatment of patients with cIAIs and TGC met per the protocol-specified statistical criteria for noninferiority to the comparator, IMI/CIS.

Introduction

Intra-abdominal infections encompass a broad variety of pathological conditions ranging from a localized infection to multi-system organ failure. These infections are most often categorized as a primary infection of the peritoneal space (i.e., spontaneous bacterial peritonitis), infection contained within the site of origin (i.e., simple appendicitis, cholecystitis), infection due to breach of the bowel wall (i.e., perforated appendicitis), or a secondary infection of the peritoneal cavity due to penetrating injuries or surgical procedures, and abscesses of the solid intra-abdominal organs (i.e., liver abscess). Complicated intra-abdominal infections are specifically defined as secondary infections that extend through a physical hole in the gastrointestinal tract or through a necrotic gut wall into the peritoneal space leading to abscess formation or peritonitis.[1]

The majority of complicated intra-abdominal infections are polymicrobial, involving multiple bacterial isolates that are normally present within the gastrointestinal tract.[2] Overall, Enterobacteriaceae are the most commonly isolated organisms (typically *Escherichia coli*); however, enterococci, as well as anaerobes such as *Bacteroides* spp and anaerobic streptococci, are usually present in varying combinations and proportions.[1,3] Although isolation of enterococci from an intra-abdominal source was once dismissed as indigenous flora, these bacteria are now recognized as true pathogens, with approximately 14%—33% of cultures yielding enterococci.[2] Anaerobes are a common etiology, especially when infection occurs beyond the proximal ileum.[1] Empiric antimicrobial treatment of complicated intra-abdominal infections must consider a broad array of potential bacteria. Furthermore, the likelihood that the implicated isolates may possess resistance factors (e.g., extended spectrum beta-lactamases [ESBLs]) that convey antimicrobial resistance in some patients (e.g., immunocompromised and ICU patients) makes the selection of agents with activity against a variety of potentially resistant isolates crucial when choosing the optimal therapy.[4] Adequate source control must complement appropriate antimicrobial therapy in order to achieve the desired outcome.[1] There is also growing evidence that the use of an inappropriate empiric antimicrobial

regimen to treat intra-abdominal infections is associated with a worse outcome and an increased risk of mortality.[5,6]

Tigecycline is a novel, expanded broad-spectrum, glycylcycline antibiotic with in vitro activity against aerobic and facultative gram-positive and gram-negative bacteria and anaerobic bacteria typically implicated as causes of complicated intra-abdominal infections.[7–10] Of relevance to intra-abdominal infections, tigecycline also provides activity against antibiotic-resistant bacteria such as vancomycin-resistant *Enterococcus faecalis*, extended-spectrum beta-lactamase-producing enteric gram-negative bacteria, and methicillin-resistant *Staphylococcus aureus*.[7–15] The primary purpose of the current trial was to assess the efficacy and safety of tigecycline monotherapy compared with imipenem/cilastatin in the treatment of hospitalized adult patients with complicated intra-abdominal infections. This study also evaluated the in vitro susceptibility data of tigecycline against the range of bacteria present in these infections.

Patients and methods

Study design and antimicrobial regimens

This was a phase 3, multicenter, double-blind (third-party unblinded) trial of adult patients who were candidates for or had undergone a laparotomy, laparoscopy, or percutaneous drainage of an intra-abdominal abscess and had a known or suspected diagnosis of complicated intra-abdominal infections. The protocol was reviewed and approved by the institutional review board or ethical review committee at each participating center. Written informed consent was obtained from each patient or his or her legal representative before the administration of any study procedures. The trial was conducted in accordance with the Declaration of Helsinki.

Patients were stratified at randomization into 2 groups based on their scores on the Acute Physiologic and Chronic Health Evaluation (APACHE) II: $\leq$15, or $>$15 but $<$31. Using a 1:1 ratio, patients were then assigned to receive tigecycline (initial 100-mg dose given by intravenous [IV] infusion over a 30-min period, followed by 50 mg IV every 12 h) or IV imipenem/cilastatin (500 mg/500 mg every 6 h or dose-adjusted based on weight and creatinine clearance) according to a randomization schedule generated by the Wyeth Research Global Biostatistics Technology department. A computerized randomization and enrollment system of automatic telephonic randomization (CORE) was used and provided access 24 h a day. After a patient was screened and deemed eligible for the study, the unblinded dispenser (pharmacist or accredited nurse) called the telephone number provided to determine the treatment assignment. If a randomization number was obtained from CORE but not used (e.g., a patient was assigned to treatment but did not receive the study drug), the reuse of the randomization number was prohibited. Unless the patient was a clinical failure (see Section Clinical and bacteriologic assessments and evaluation below), the duration of study drug therapy ranged from 5 to 14 days.

Study drug was administered only when there was a strong suspicion (i.e., elevated white blood cell count, elevated band cell counts [''shift to the left''], fever, or highly suggestive radiographic findings) or a confirmed diagnosis of an intra-abdominal infection (presence of pus within the abdominal cavity). A baseline intra-abdominal culture was obtained from the site of infection in all patients. Patients could be enrolled before drainage of the intra-abdominal infection and may have received up to 2 doses of study drug before the baseline cultures were obtained. Patients did not receive more than 1 dose (or combination) of parenteral nonstudy antibacterial drugs after the baseline intra-abdominal cultures were obtained. However, wound irrigation solutions of sterile water or normal saline and topical antiseptics were permitted throughout the course of the study.

Baseline aerobic and anaerobic cultures from the primary intra-abdominal site of infection and 2 sets of blood cultures were obtained within 24 h of the first dose of study drug. All aerobic and anaerobic bacterial isolates, regardless of the source of cultured material, were identified and tested at a central laboratory (Covance Central Laboratory Services, Inc., Indianapolis, IN, or Geneva, Switzerland) by using a standard procedure approved by the National Committee of Clinical Laboratory Standards (NCCLS) Subcommittee on Antimicrobial Susceptibility Testing. For tigecycline, provisional minimum inhibitory concentration (MIC) breakpoints were used (susceptible $\leq$ 2 mg/L; intermediate 4 mg/L; resistant $\geq$ 8 mg/L).

Entry criteria

Hospitalized patients were eligible for inclusion if they were at least 18 years of age and required a surgical procedure for a complicated intra-abdominal infection. Complicated intra-abdominal infections included conditions such as an intra-abdominal abscess (including liver and spleen) that

developed in a postsurgical patient after receiving standard antibacterial therapy; appendicitis complicated by perforation and/or a periappendiceal abscess; perforated diverticulitis complicated by abscess formation or fecal contamination; complicated cholecystitis with evidence of perforation, empyema, or gangrene; perforation of the stomach or duodenum for a period not to exceed 24 h; or perforation of the large or small intestine for a period longer than 12 h. In addition, patients could not have received more than 1 dose of an antibiotic (single broad-spectrum agent or 1 dose of each antibiotic in a combination regimen such as metronidazole, ampicillin, and gentamicin) after the baseline intra-abdominal culture was obtained from the infected site.

Patients were excluded for the following primary reasons: pregnant or breastfeeding women; preoperative suspicion of a diagnosis of spontaneous bacterial peritonitis, simple cholecystitis, gangrenous cholecystitis without rupture, simple appendicitis, acute suppurative cholangitis, pancreatic abscess, or infected necrotizing pancreatitis; APACHE II score greater than 30; active or treated leukemia or systemic malignancy or metastatic malignancy to the abdomen; presence of any uncontrolled central nervous system disease, including seizures; known or suspected hypersensitivity to either study antibiotic or other compounds related to the glycylcycline or carbapenem classes; presence of hepatic disease (i.e., aspartate aminotransferase [AST] or alanine aminotransferase [ALT] $>$ 10 times the upper limit of normal [ULN] or total bilirubin value $>$ 3 times the ULN) or acute hepatic failure or acute decompensation of chronic hepatic failure; presence of renal disease, defined as a calculated creatinine clearance $<$ 41 mL/min/1.73 m^2 after adequate hydration; neutropenia with absolute neutrophil count $<$ 1000/mm^3, with counts as low as 500/mm^3 permitted if due to the acute infectious process; current intra-abdominal infection known to be caused by one or more bacterial isolates not likely to be susceptible to both of the study drugs; surgical procedure requiring that fascia or deep muscular layers be left open or planned abdominal re-exploration; and administration of intra-operative antibacterial irrigants or peritoneal antibacterial agents (e.g., irrigants, antibiotic-impregnated sponges).

Analysis populations

Several subpopulations of patients were assessed for safety, clinical, and bacteriologic outcomes. Patients who satisfied the inclusion/exclusion criteria were included in the intent-to-treat (ITT) population, whereas the subset of patients who received at least 1 dose of study drug made up the modified intent-to-treat (mITT or safety) population. Patients in the mITT population who had clinical evidence of a complicated intra-abdominal infection (clinically modified intent-to-treat [c-mITT] population), by meeting the minimal disease criteria, and had a confirmed baseline isolate constituted the microbiologically modified (m-mITT) population. From this latter group, the microbiologically evaluable (ME) population was defined as those who met all inclusion/exclusion criteria or received an exemption before enrollment in study; had at least 5 days of therapy; did not receive concomitant antibiotics after the baseline intra-abdominal culture was obtained through the test-of-cure visit; had a test-of-cure visit 14—35 days after the first dose of study drug; and had a baseline intra-abdominal culture containing at least 1 causative isolate that was susceptible to both study drugs. If these criteria were not met at any time during the study, the patient was declared a clinical failure. Patients were considered nonevaluable for inclusion in the ME population if death occurred or if they withdrew from the study $<$ 48 h after the first dose of study drug.

Clinical and bacteriologic assessments and evaluation

Patients were evaluated at serial visits throughout the study. The clinical response was determined by the investigator and was defined at the test-of-cure visit (14—35 days after therapy) as one of the following: *Cure* — the course of study drug and the initial intervention (operative and/or radiologically guided drainage procedure) resolved the intra-abdominal infectious process; *Failure* — the patient had a lack of response during treatment and required additional antibacterial therapy other than the study drug, or the initial recovery from the infection was followed by deterioration before the test-of-cure visit that required further antimicrobial therapy, the patient required additional surgical or radiologic intervention to cure the infection, death due to infection occurred after 48 h of therapy, or the patient received an extended course of study drug (i.e., $>$120% of the planned number of doses); and *Indeterminate* — the patient was lost to follow-up (failure to have an outcome determination), or died within 48 h after the first dose of tigecycline for any reason, or died after 48 h because of noninfectious-related reasons (as judged by the investigator).

Based on the results of the baseline intra-abdominal culture, the susceptibilities of identified organisms, and the clinical outcome of the patient, the investigator also evaluated the microbiologic response at the isolate and patient level at the test-of-cure visit. The microbiologic response by isolate for each baseline isolate included: eradication, persistence, or indeterminate. Microbiologic response by patient was categorized as eradication, persistence, superinfection (i.e., the emergence of a new isolate was documented at the site of infection or at a distant site with worsening signs and symptoms of infection), and indeterminate. Microbiologic responses, by isolate or patient, were often presumed and based on clinical response (e.g., eradication in the case of clinical cure) because no follow-up culture was available.

Safety/tolerability assessments

Any patient who received at least 1 dose of study drug was included in the evaluation for safety (mITT population). Safety was assessed via medical history and physical examination findings, reports of clinical adverse events, and findings from routine electrocardiograms (ECGs), and serum chemistry, hematology, coagulation, and urinalysis tests. Adverse events were recorded throughout the study period, up to and including the test-of-cure visit. Before unblinding, the investigator categorized the severity of each adverse event and the relationship to study drug. Serious adverse events (i.e., those that were life-threatening, led to prolongation of the existing hospitalization, or caused persistent or significant disability or incapacity, or death) were also recorded.

Statistical analysis

Statistical analysis was performed by the Clinical Biostatistics department of Wyeth Research, Collegeville, PA. The primary endpoints of the study were clinical response at the test-of-cure visit (14—35 days after therapy) for the ME and m-mITT populations. Secondary analyses included bacteriologic response at the test-of cure visit by patient and isolate, as well as clinical response rates stratified as monomicrobial versus polymicrobial, and by isolate.

Categorical baseline demographic and medical variables were analyzed using the Fisher exact test. For continuous variables, a 1-way analysis of variance (ANOVA) model was used to compare the 2 treatment groups. The difference between treatment groups in the percentage of premature discontinuations from study drug was evaluated by using a 2-sided Fisher exact test. Between-group comparisons of adverse events were analyzed by using the Fisher exact test.

The noninferiority of tigecycline compared with imipenem/cilastatin was evaluated for clinical and microbiologic responses by using a 2-sided 95% confidence interval (CI) for the true difference in efficacy (tigecycline minus imipenem/cilastatin) adjusted for the stratification variable APACHE II score and corrected for continuity. Noninferiority was concluded if the lower limit of the 2-sided 95% CI was greater than or equal to −15%. For all subpopulation analyses (e.g., monomicrobial versus polymicrobial), an adjusted difference between treatment groups with its 95% CI was calculated from a generalized linear model with a binomial probability function and an identity link.

By assuming an evaluability rate of at least 50%, approximately 788 patients were to be randomly assigned to obtain 394 ME patients. Based on the assumption that the 2 treatments were equally effective, with favorable clinical cure rates of 70% at the test-of-cure assessment, 197 patients per treatment group were required to ensure with 90% probability (i.e., 90% power) that the lower limit of a 1-sided 97.5% confidence interval for the true difference (tigecycline minus imipenem/cilastatin) does not exceed 0.15.

Results

Patient disposition and analysis populations

A total of 861 patients were screened for study participation at 94 sites in 27 countries in Europe, South Africa, Australia, and Asia from November 2002 to May 2004, of these, 37 failed to satisfy protocol requirements (Fig. 1). The remaining 824 patients were randomly assigned to 1 of the 2 treatment regimens and constituted the ITT population, although 7 patients never received study drug. As such, 817 patients constituted the mITT or safety population (404 tigecycline, 413 imipenem/cilastatin), with 794 patients exhibiting clinical evidence of a complicated intra-abdominal infection (clinical mITT). Within this latter cohort, 690 patients were clinically evaluable (CE population) and 641 patients had a pretherapy isolate recovered and comprised the m-mITT population. A total of 523 patients (265 tigecycline, 258 imipenem/cilastatin) met clinical evaluability criteria and had a pretherapy isolate isolated from an intra-abdominal source (ME population). The

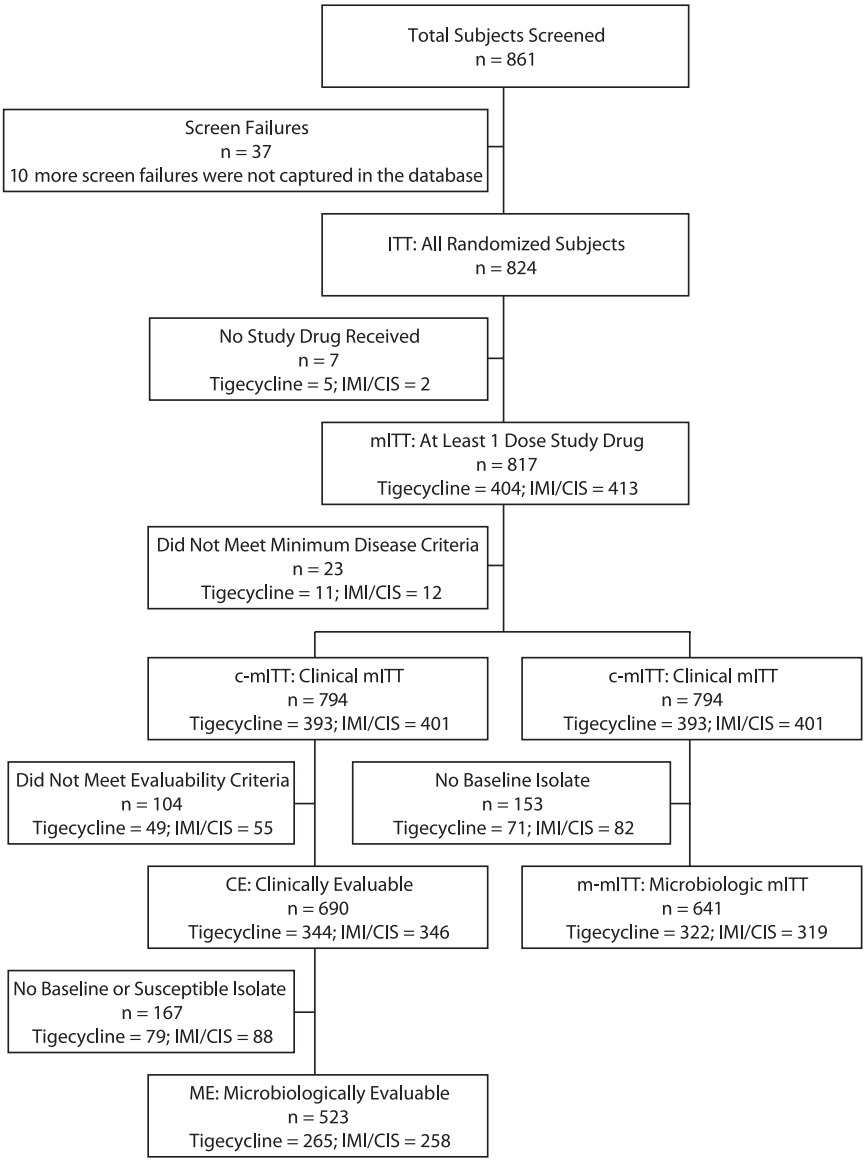

Figure 1 Patient disposition and analysis population.

primary reasons for exclusion from the CE population were no clinical evaluation at the test-of-cure visit ($n = 33$); entry criteria not met ($n = 31$); received concomitant antimicrobials ($n = 28$); blind broken ($n = 18$); and did not receive required number of study drug doses (i.e., at least 8 doses for those who failed; $n = 16$).

Demographic/baseline medical characteristics

Overall, the mITT population was primarily white (88%) men (59%) with a mean age of 49 years (Table 1). Demographic characteristics were well balanced between the 2 treatments. The most common intra-abdominal infection diagnoses were complicated appendicitis (41%), followed by complicated cholecystitis (22%) and intra-abdominal abscess (11%). There were no significant differences between the treatment groups in the number or types of infections diagnosed at baseline. The mITT patients received an average of 7—8 days of antimicrobial treatment.

Clinical efficacy

Overall, clinical cure was reported for 86.6% of tigecycline and 84.6% of imipenem/cilastatin

Table 1 Demographic and baseline medical characteristics (mITT population)[a,b]

	Tigecycline ($N = 404$)	Imipenem/cilastatin ($N = 413$)
Mean ± SD age, years	48.3 ± 18.4	49.5 ± 18.0
Sex, *n* (%) male	239 (59.2)	240 (58.1)
Ethnic origin, *n* (%)		
White	349 (86.4)	370 (89.6)
Black	12 (3.0)	13 (3.1)
Asian	29 (7.2)	23 (5.6)
Other	14 (3.5)	7 (1.7)
Mean ± SD weight, kg	74.1 ± 14.9	74.5 ± 15.7
Mean ± SD creatinine clearance, mL/min	99.7 ± 36.3	97.3 ± 30.6
Mean ± SD therapy duration, days	7.7 ± 2.7	7.8 ± 2.7
Mean APACHE II score	6.44	6.41
Primary intra-abdominal diagnosis, *n* (%)		
Complicated appendicitis	158 (41.6)	167 (40.4)
Complicated cholecystitis	80 (19.8)	98 (23.7)
Complicated diverticulitis	21 (5.2)	25 (6.1)
Intra-abdominal abscess	46 (11.4)	46 (11.1)
Peritonitis	9 (2.2)	7 (1.7)
Gastric/duodenal perforation	32 (7.9)	36 (8.7)
Perforation of intestine	42 (10.4)	31 (7.5)
Other[a]	6 (1.5)	3 (0.7)

[a] Other diagnoses included complicated salpingitis, pyosalpinx, tubo-ovarial abscess, peritonitis due to left pyo-ovarium (local abscess), right and left purulent salpingitis, perforated suppurative left ovary cyst, intra-abdominal abscess after ovarian cystectomy, acute salpingitis with purulent peritonitis, and septic incomplete abortion with traumatized uterus and perforation.
[b] All differences were not statistically significant ($P > 0.05$).

recipients in the m-mITT population (95% CI −3.7, 7.5; Table 2). Corresponding clinical cure rates for the ME population were 91.3% and 89.9% (95% CI −4.0, 6.8). The results indicated that tigecycline is efficacious for these 2 populations by meeting statistical criteria for the noninferiority compared with imipenem/cilastatin.

In addition, no significant treatment differences in clinical response were observed between the 2 antimicrobial groups when patients were stratified by number of pretherapy isolates—monomicrobial versus polymicrobial (Table 2). For the ME population, tigecycline was associated with 94.5% and 89.7% clinical cure rates at the test-of-cure visit for monomicrobial versus polymicrobial infections, respectively. Patients given imipenem/cilastatin had similar clinical cure rates 92.2% and 88.7%, respectively. In general, patients with polymicrobial intra-abdominal infection tended to have lower clinical cure rates compared with those who had infections due to a single isolate.

For complicated appendicitis, the most frequent diagnosis, clinical cure at the test-of-cure visit was nearly identical between the 2 treatment groups: 93.7% for tigecycline versus 93.2% for imipenem/cilastatin (Table 3). Similar clinical cure rates were found for those with complicated cholecystitis (98.2% tigecycline versus 96.6% imipenem/cilastatin). Patients in both treatment groups with intra-abdominal abscess, complicated diverticulitis, and intestinal perforation had lower cure rates regardless of treatment assignment (70%—85%; Table 3). Based on primary intra-abdominal diagnosis, there were no significant differences in clinical cure rates between tigecycline and imipenem/cilastatin. A total of 26 tigecycline- and 23 imipenem/cilastatin-treated patients had concomitant bacteremia. Clinical cure in patients with bacteremia was reported for 88.5% of tigecycline-treated and 87% of imipenen/cilastatin-treated patients.

Microbiologic efficacy

For the ME population, eradication at the patient level was reported for 91.3% of tigecycline and 89.9% of imipenem/cilastatin recipients (95% CI −4.0, 6.8), indicating that tigecycline was noninferior to imipenem/cilastatin in eradicating complicated intra-abdominal infections (Table 4). No significant differences between the treatment groups were discernable when eradication rates were stratified by monomicrobial versus polymicrobial infection.

Table 2 Clinical cure rates at test-of-cure visit

	Tigecycline		Imipenem/cilastatin		Difference (tigecycline−imipenem/cilastatin), % (95% CI)	Test for noninferiority, *P* value	Test for differences
	n/*N*	% (95% CI)	*n*/*N*	% (95% CI)			
CE	312/344	90.7 (87.1, 93.6)	312/346	90.2 (86.5, 93.1)	0.5 (−4.2, 5.2)	<0.0001	0.9166
Overall							0.4 (−4.1, 4.9)[a]
c-mITT	336/393	85.5 (81.6, 88.8)	339/401	84.5 (80.6, 87.9)	1.0 (−4.3, 6.2)	<0.0001	0.7806
Overall							0.9 (−4.2, 6.0)[a]
ME	242/265	91.3 (87.3, 94.4)	232/258	89.9 (85.6, 93.3)	1.4 (−4.0, 6.8)	<0.0001	0.6904
Monomicrobial	86/91	94.5 (87.6, 98.2)	83/90	92.2 (84.6, 96.8)	2.3 (−6.3, 11.1)		
Polymicrobial	156/174	89.7 (84.1, 93.8)	149/168	88.7 (82.9, 93.1)	1.0 (−6.1, 8.2)		
Overall							0.2 (−4.0, 4.4)[a]
m-mITT	279/322	86.6 (82.4, 90.2)	270/319	84.6 (80.2, 88.4)	2.0 (−3.7, 7.5)	<0.0001	0.5406
Monomicrobial	108/120	90.0 (83.2, 94.7)	102/119	85.7 (78.1, 91.5)	4.3 (−4.7, 13.4)		
Polymicrobial	171/202	84.7 (78.9, 89.3)	168/200	84.0 (78.2, 88.8)	0.7 (−6.8, 8.2)		
Overall							2.2 (−3.2, 7.6)[a]

[a] Adjusted difference and its 95% CI are calculated from a generalized linear model with a binomial probability function and an identity link. CI, confidence interval; CE, clinically evaluable; c-mITT, clinically modified intent-to-treat (patients exhibiting clinical evidence of complicated intra-abdominal infections); ME, microbiological evaluable; m-mITT, microbiological modified intent-to-treat (patients with a confirmed baseline isolate).

Table 3 Clinical cure rate by baseline diagnosis (Microbiologically Evaluable Population) at test-of-cure visit

Clinical diagnosis	Tigecycline		Imipenem/cilastatin		Difference (tigecycline−imipenem/cilastatin), % (95% CI)
	n/*N*	% (95% CI)	*n*/*N*	% (95% CI)	
Complicated appendicitis	104/111	93.7 (87.4, 97.4)	109/117	93.2 (87.0, 97.0)	0.5 (−7.1, 8.0)
Complicated diverticulitis	11/15	73.3 (44.9, 92.2)	12/17	70.6 (44.0, 89.7)	2.7 (−31.0, 34.7)
Complicated cholecystitis	56/57	98.2 (90.6, 100.0)	56/58	96.6 (88.1, 99.6)	1.7 (−7.6, 11.3)
Intra-abdominal abscess	29/34	85.3 (68.9, 95.0)	23/28	82.1 (63.1, 93.9)	3.2 (−17.3, 24.9)
Peritonitis	4/4	100.0 (39.8, 100.0)	3/4	75.0 (19.4, 99.4)	25.0 (−39.9, 78.1)
Gastric and duodenal perforations	12/12	100.0 (73.5, 100.0)	13/15	86.7 (59.5, 98.3)	13.3 (−18.7, 41.6)
Perforations of the intestines	25/30	83.3 (65.3, 94.4)	14/17	82.4 (56.6, 96.2)	1.0 (−21.8, 29.5)
Other	1/2	50.0 (1.3, 98.7)	2/2	100.0 (15.8, 100.0)	−50.0 (−97.3, 43.1)
Concomitant bacteremia	23/26	88.5 (69.8, 97.6)	20/23	87.0 (66.4, 97.2)	1.5 (−20.5, 24.7)

CI, confidence interval.

Table 4 Microbiologic response at the patient level (Microbiologically Evaluable Population) at test-of-cure visit

Response	Tigecycline		Imipenem/cilastatin		Difference (tigecycline—imipenem/cilastatin), % (95% CI)	Test for noninferiority, *P* value	Test for differences
	n/N	% (95% CI)	*n/N*	% (95% CI)			
Eradication	242/265	91.3 (87.3, 94.4)	232/258	89.9 (85.6, 93.3)	1.4 (−4.0, 6.8)	<0.0001	0.6904
Monomicrobial	86/91	94.5 (87.6, 98.2)	83/90	92.2 (84.6, 96.8)	2.3 (−6.3, 11.1)		
Polymicrobial	156/174	89.7 (84.1, 93.8)	149/168	88.7 (82.9, 93.1)	1.0 (−6.1, 8.2)		
Persistence	21/265	7.9 (5.0, 11.9)	26/258	10.1 (6.7, 14.4)			
Monomicrobial	5/91	5.5 (1.8, 12.4)	7/90	7.8 (3.2, 15.4)			
Polymicrobial	16/174	9.2 (5.3, 14.5)	19/168	11.3 (6.9, 17.1)			
Superinfection	2/265	0.8 (0.1, 2.7)	0/258	0.0 (0.0, 1.4)			
Monomicrobial	0/91	0.0 (0.0, 4.0)	0/90	0.0 (0.0, 4.0)			
Polymicrobial	2/174	1.1 (0.1, 4.1)	0/168	0.0 (0.0, 2.2)			
Overall					1.6 (−3.3, 6.4)[a]		

[a] Adjusted difference and its 95% confidence interval are calculated from a generalized linear model with a binomial probability function and an identity link.

The microbial eradication rates at the test-of-cure visit for several selected isolates of clinical interest were comparable between the 2 treatment groups (Table 5). For *E. coli*, the most commonly isolated aerobe, eradication rates were 91.7% for tigecycline versus 91.1% for imipenem/cilastatin. Eradication rates for *Klebsiella pneumoniae*, the second most frequently isolated aerobe, were also high (92.7% tigecycline versus 94.4% imipenem/cilastatin). Tigecycline also appeared effective based on eradication/presumed eradication rates against *E. faecalis* (non-vancomycin-resistant enterococci [VRE]), as well as methicillin-sensitive and -resistant *S. aureus* were eradicated at rates $\geq$ 94% following tigecycline therapy. Eradication rates for *Bacteroides fragilis* were also similar between the 2 treatment groups (86.4% tigecycline versus 91.2% imipenem/cilastatin). Pretherapy in vitro activity against these isolates for tigecycline and imipenem/cilastatin are shown in Table 6.

Adverse events

Data from all patients in the mITT population were analyzed for safety. The safety and tolerability of tigecycline, including the frequency and distribution of adverse events, were similar to those of imipenem/cilastatin. Regardless of study drug causality, treatment-emergent adverse events occurred in 60.4% (244 of 404) of tigecycline-treated patients and 59.3% (245 of 413) of imipenem/cilastatin-treated patients. The majority of these adverse events was not related to study medication and was mild to moderate in intensity. The frequency and distribution of the most common treatment-emergent adverse events (i.e., occurring in $\geq$3% of patients) for the tigecycline group were similar to those observed after imipenem/cilastatin therapy (Table 7). Nausea (17.5% tigecycline, 13.3% imipenem/cilastatin; $P = 0.100$) and vomiting (12.6% tigecycline, 9.2% imipenem/cilastatin; $P = 0.144$) were the most frequently reported adverse events in both groups. There was no significant difference between the treatment groups in the number of patients who required antiemetic therapy for nausea and/or vomiting.

One hundred and eight (108) serious adverse events were noted during the study (59 tigecycline and 49 imipenem/cilastatin patients). The most frequently reported serious adverse events were abscess ($n = 13$) and infection and abnormal healing (each, $n = 9$) in tigecycline-treated patients, compared with abscess ($n = 10$) and local reaction to a procedure ($n = 7$) among imipenem/cilastatin-treated patients.

Table 5 Microbiologic response at the isolate level: selected baseline isolates at test-of-cure visit (Microbiologically Evaluable Population)

Isolate	Tigecycline		Imipenem/cilastatin	
	n/*N*	% (95% CI)	*n*/*N*	% (95% CI)
Bacteroides fragilis	38/44	86.4 (72.6, 94.8)	31/34	91.2 (76.3, 98.1)
Citrobacter spp.	11/13	84.6 (54.6, 98.1)	6/9	66.7 (29.9, 92.5)
Clostridium spp.	26/27	96.3 (81.0, 99.9)	23/26	88.5 (69.8, 97.6)
Enterobacter spp.	16/16	100.0 (79.4, 100.0)	12/12	100.0 (73.5, 100.0)
Enterococcus faecalis (non-VRE)	16/17	94.1 (71.3, 99.9)	26/29	89.7 (72.6, 97.8)
Escherichia coli	144/157	91.7 (86.3, 95.5)	144/158	91.1 (85.6, 95.1)
Fusobacterium spp.	6/6	100.0 (54.1, 100.0)	6/6	100.0 (54.1, 100.0)
Klebsiella spp.	38/41	92.7 (80.1, 98.5)	34/36	94.4 (81.3, 99.3)
Peptostreptococcus spp.	11/13	84.6 (54.6, 98.1)	11/13	84.6 (54.6, 98.1)
Staphylococcus aureus (MRSA)	3/3	100.0 (29.2, 100.0)	1/2	50.0 (1.3, 98.7)
S. aureus (non-MRSA)	18/19	94.7 (74.0, 99.9)	19/20	95.0 (75.1, 99.9)
Veillonella spp.	7/7	100.0 (59.0, 100.0)	3/3	100.0 (29.2, 100.0)
Proteus spp.	7/9	77.8 (40.0, 97.2)	11/15	73.3 (44.9, 92.2)
Pseudomonas aeruginosa	19/21	90.5 (69.6, 98.8)	12/15	80.0 (51.9, 95.7)

CI = confidence interval; MRSA = methicillin-resistant *Staphylococcus aureus*; VRE = vancomycin-resistant enterococci.

Adverse events were the primary reason for early withdrawal of study drug (19 [4.7%] tigecycline-treated and 21 [5.1%] imipenem/cilastatin-treated patients). Seven tigecycline patients discontinued treatment because of vomiting, whereas 6 impenem/cilastatin-treated patients discontinued treatment secondary to nausea. There were no significant differences between treatment groups in any single adverse event leading to the discontinuation of study drug.

Twelve patients died during the study: 7 patients in the tigecycline treatment group and 5 in the imipenem/cilastatin treatment group. None of the deaths was considered by the investigators to be related to study drug.

No clinically important or unexpected changes in any routine hematologic or serum chemistry tests, vital signs, or ECG data were associated with the use of tigecycline or impenem/cilastatin. However, significantly more patients treated with tigecycline had increased amylase ($P < 0.01$) and increased BUN values ($P < 0.001$). The reported amylase elevations in the tigecycline group were mild and not associated with pancreatitis, nausea, or vomiting. Furthermore, the increased BUN values were not associated with increases in serum creatinine. No significant changes in QTc interval were observed in either treatment group.

Discussion

Rising rates of antibiotic resistance, especially in the hospital setting, have heightened the need

Table 6 Minimal Inhibitory Concentration (MIC) Range, and MIC_{50} and MIC_{90} values, of selected primary baseline isolates (Microbiologically Evaluable Population)

Isolate	*n*	Tigecycline			Imipenem/cilastatin		
		MIC range	MIC_{50}	MIC_{90}	MIC range	MIC_{50}	MIC_{90}
Bacteroides fragilis	78	0.12—16.0	0.5	2.0	0.12—1.0	0.12	0.50
Clostridium spp.	1	0.06—0.06	NA	NA	0.25—0.25	NA	NA
Enterococcus faecalis (non-VRE)	46	0.06—1.0	0.25	0.25	0.50—8.0	2.0	4.0
Escherichia coli	315	0.06—1.0	0.25	0.50	0.12—1.0	0.12	0.25
Fusobacterium spp.	2	0.12—0.25	NA	NA	0.12—0.50	NA	NA
Staphylococcus aureus (MRSA)	5	0.12—0.25	NA	NA	0.12—32.0	NA	NA
S. aureus (non-MRSA)	39	0.06—0.50	0.12	0.25	0.12—4.0	0.12	0.12
Veillonella spp.	10	0.12—1.0	0.25	1.0	0.12—0.12	0.12	0.12
Pseudomonas aeruginosa	36	4.0—32.0	16.0	16.0	0.50—16.0	1.0	8.0

NA = MIC_{50} and MIC_{90} values are not valid if the number of isolates is less than 10; MRSA = methicillin-resistant *Staphylococcus aureus*; VRE = vancomycin-resistant enterococci.

Table 7 Common treatment-emergent adverse events[a]

Body system adverse event	Tigecycline ($N = 404$)	Imipenem/ cilastatin ($N = 413$)
Any adverse event	244 (60.4)	245 (59.3)
Body as a whole	109 (27.0)	101 (24.5)
Abdominal pain	15 (3.7)	14 (3.4)
Asthenia	15 (3.7)	10 (2.4)
Fever	18 (4.5)	30 (7.3)
Headache	9 (2.2	18 (4.4)
Infection[b]	27 (6.7)	14 (3.4)
Cardiovascular system	41 (10.1)	49 (11.9)
Hypertension	16 (4.0)	13 (3.1)
Digestive system	128 (31.7)	120 (29.1)
Diarrhea	25 (6.2)	31 (7.5)
Nausea	71 (17.6)	55 (13.3)
Vomiting	51 (12.6)	38 (9.2)
Hemic and lymphatic system	50 (12.4)	50 (12.1)
Anemia	17 (4.2)	19 (4.6)
Thrombocythemia	23 (5.7)	25 (6.1)
Metabolic and nutritional	77 (19.1)	68 (16.5)
Amylase increased	15 (3.7)	4 (1.0)
Hypoproteinemia	15 (3.7)	13 (3.1)
Lactic dehydrogenase increased	16 (4.0)	14 (3.4)
AST/SGOT	10 (2.5)	13 (3.1)
Local reaction to procedure	28 (6.9)	27 (6.5)

AST/SGOT = aspartate aminotransferase/serum glutamic oxaloacetic transaminase.
[a] Defined as those occurring in $\geq$3% of patients.
[b] Significant between-group difference at 0.05 level.

to develop new antimicrobial therapies for the treatment of complicated intra-abdominal infections.[16,17] Tigecycline is a first-in-class glycylcycline antibiotic that has expanded broad-spectrum in vitro activity against common aerobic and anaerobic isolates found in intra-abdominal infections, including coverage against resistant isolates.[7–15] In this phase 3 trial, the efficacy and safety of tigecycline monotherapy for the treatment of complicated intra-abdominal infections were compared with imipenem/cilastatin, which is a commonly recommended antibiotic therapy.[1,18,19] The main finding of this large phase 3 trial is that tigecycline (50 mg infusion every 12 h after an initial dose of 100 mg) was efficacious and statistically noninferior to imipenem/cilastatin (500 mg/500 mg every 6 h), as observed in predefined patient populations (m-mITT and ME) at the test-of-cure visit. Notably, these findings were consistent across different types of infection and against the broad array of bacterial species encountered.

Tigecycline was effective at eradicating the most common aerobic and anaerobic bacteria implicated in complicated intra-abdominal infections, with overall eradication rates exceeding 90%. In addition to *E. coli* and *K. pneumoniae* (the most frequently recovered isolates overall), tigecycline also was effective at eradicating organisms that typically convey resistance, including *E. faecalis* (non-VRE) and methicillin-sensitive and -resistant *S. aureus* (all $\geq$ 90%). The effectiveness of tigecycline against difficult-to-treat gram-positive organisms is also encouraging (e.g., $MIC_{90} \leq 0.25$ mg/L against methicillin-resistant *S. aureus*), despite the fact that few resistant isolates were identified. Emergence of tigecycline resistance during therapy was not observed.

Clinical trial data from phase 1 and phase 2 studies suggest that IV tigecycline is well tolerated.[20–25] The results of the current trial are consistent with earlier findings and demonstrated that both tigecycline and imipenem/cilastatin were generally well tolerated with similar rates of treatment-emergent adverse events. Nausea and vomiting were the most frequently reported adverse events in both treatment groups, with slightly higher rates reported after tigecycline therapy. There also was no evidence of clinically significant changes following routine serum chemistry and hematology testing.

The effectiveness of tigecycline demonstrated in this large phase 3 trial extends the findings of a phase 2 tigecycline trial in 66 hospitalized patients with predominantly perforated appendicitis.[23] The validity of the current trial is also evident in that the response rates after imipenem/cilastatin therapy were similar to the findings of several published studies in which imipenem/cilastatin had similar cure rates compared with either meropenem, ciprofloxacin, piperacillin/tazobactam, or gentamicin/clindamycin.[26–29]

Conclusion

The findings reported herein, coupled with the increasing need for antibiotics with improved activity against resistant isolates, suggest that tigecycline is a promising new monotherapy for the treatment of complicated intra-abdominal infections where empiric coverage is needed against both gram-positive and gram-negative bacteria.

Acknowledgments

We thank the tigecycline 306 study group investigators for their valuable involvement in this study: Giedrius Barauskas, Mircea Beuran, Krzystof Bielecki, Robert Bleichrodt, Govert Diederik Brombacher, Oleg Budantsev, Markus Buechler, Daniel Candinas, Luis Capitán, Fransisco Castro-Sousa, Pierre-Alain Clavien, Mircea Ciurea, Konstantin Danilov, Alexey Datsenko, Georgi Deenitchin, Slobodan Deskovic, Gerard Desvignes, Marko Doko, Matthew Dryden, Daniel Johannes du Toit, Eric Hans Eddes, Peter Fomin, Jorge Garbino, Juan Carlos Garcia-Valdecasas, Janis Gardovskis, Audrius Gradauskas, Tatana Grosmannova, Ioan Gugila, Robert Gurlich, Ors Horvath, Martin Hutan, Tsann-Long Hwang, Veselin Ivanov, Arkadiusz Jawien, Reinhold Kafka-Ritsch, Vladimir Klimushev, Wen-je Ko, Peter Kujath, Uldis Kupcs, Nicolay Kuznetsov, Zdzislaw Andrew Machowski, Jean Mantz, David McGechie, Slobodan Milutinovic, Adrian Miron, Attila Nagy, Maris Nalivaiko, Borislav Ninov, Natalia Obidina, Attila Oláh, Igor Osipov, Marek Ostrowski, Dariusz Patrzalek, Andrejs Pavars, Nuno Pinherio, Irinel Popescu, Jan Philip Pretorius, Guntars Pupelis, Arturas Razbadauskas, Brent Richards, Konrad Richter, Grigoriy Rodoman, Jan Rohac, Valery Saenko, Jose Luis Sanchez, Cyril Sauka, Yan-Shen Shan, Olga Shapovalova, Sorin Simion, Ladislav Sinkovic, Fang Gao Smith, David Sowden, Herbert Spapen, Edward Stanowski, Jacek Szmidt, Alexander Tcherveniakov, Jose Maria Tellado, Jüri Teras, Marian Todoran, Antonio José Torres, Milan Travnik, Richard Turner, Franco Uggeri, Tiit Vaasna, Viliam Vadrna, Yves Van Laethem, Johannes Hendrik van Rensburg, Krasimir Vasilev, Vladimir Visokai, Jindrich Vomela, Dionysious Voros, Brian Leigh Warren, Janusz Wasiak, Dah-Shyong Yu.

We thank Wyeth Research employees Patricia Bradford for microbiological analysis and Upside Endeavors for professional medical writing services. Wyeth Research, Collegeville, PA, supported and funded this study. Conflict of interest: Drs. Fomin, Beuran, Ninov, Gradauskas, and Barauskas are investigators for this tigecycline study sponsored by Wyeth. Drs. Dartois, Ellis-Grosse, and Loh are employees of Wyeth.

References

1. Solomkin JS, Mazuski JE, Baron EJ, et al. Guidelines for the selection of anti-infective agents for complicated intra-abdominal infections. *Clin Infect Dis* 2003;**37**:997—1005.
2. Gorbach SL. Intra-abdominal infections [comment]. *Clin Infect Dis* 1993;**17**:961—5.
3. Lorber B, Swenson RM. The bacteriology of intra-abdominal infections. *Surg Clin North Am* 1975;**55**:1349—54.
4. de Vera ME, Simmons RL. Antibiotic-resistant enterococci and the changing face of surgical infections. *Arch Surg* 1996;**131**:338—42.
5. Krobot K, Yin D, Zhang Q, Sen S, Altendorf-Hofmann A, Scheele J, et al. Effect of inappropriate initial empiric antibiotic therapy on outcome of patients with community-acquired intra-abdominal infections requiring surgery. *Eur J Clin Microbiol Infect Dis* 2004;**23**:682—7.
6. Valles J, Rello J, Ochagavia A, Garnacho J, Alcala MA. Community-acquired bloodstream infection in critically ill adult patients: impact of shock and inappropriate antibiotic therapy on survival. *Chest* 2003;**123**:1615—24.
7. Petersen PJ, Jacobus NV, Weiss WJ, Sum PE, Testa RT. In vitro and in vivo antibacterial activities of a novel glycylcycline, the 9-*t*-butylglycylamido derivative of minocycline (GAR-936). *Antimicrob Agents Chemother* 1999;**43**:738—44.
8. Gales AC, Jones RN. Antimicrobial activity and spectrum of the new glycylcycline, GAR-936 tested against 1,203 recent clinical bacterial isolates. *Diagn Microbiol Infect Dis* 2000; **36**:19—36.
9. Petersen PJ, Bradford PA, Weiss WJ, Murphy TM, Sum PE, Projan SJ. In vitro and in vivo activities of tigecycline (GAR-936), daptomycin, and comparative antimicrobial agents against glycopeptide-intermediate *Staphylococcus aureus* and other resistant gram-positive pathogens. *Antimicrob Agents Chemother* 2002;**46**:2595—601.
10. Milatovic D, Schmitz FJ, Verhoef J, Fluit AC. Activities of the glycylcycline tigecycline (GAR-936) against 1,924 recent European clinical bacterial isolates. *Antimicrob Agents Chemother* 2003;**47**:400—4.
11. Patel R, Rouse MS, Piper KE, Steckelberg JM. In vitro activity of GAR-936 against vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae*. *Diagn Microbiol Infect Dis* 2000;**38**:177—9.
12. Boucher HW, Wennersten CB, Eliopoulos GM. In vitro activities of the glycylcycline GAR-936 against gram-positive bacteria. *Antimicrob Agents Chemother* 2000;**44**: 2225—9.
13. Cercenado E, Cercenado S, Gomez JA, Bouza E. In vitro activity of tigecycline (GAR-936), a novel glycylcycline, against vancomycin-resistant enterococci and staphylococci with diminished susceptibility to glycopeptides. *J Antimicrob Chemother* 2003;**52**:138—9.
14. Low DE, Kreiswirth BN, Weiss K, Willey BM. Activity of GAR-936 and other antimicrobial agents against North American isolates of *Staphylococcus aureus*. *Int J Antimicrob Agents* 2002;**20**:220—2.
15. Biedenbach DJ, Beach ML, Jones RN. In vitro antimicrobial activity of GAR-936 tested against antibiotic-resistant gram-positive blood stream infection isolates and strains producing extended-spectrum beta-lactamases. *Diagn Microbiol Infect Dis* 2001;**40**:173—7.
16. Emori TG, Gaynes RP. An overview of nosocomial infections including the role of the microbiology laboratory. *Clin Microbiol Rev* 1993;**6**:428—42.
17. Falagas ME, Barefoot L, Griffith J, Ruthazar R, Snydman DR. Risk factors leading to clinical failure in the treatment of intra-abdominal or skin/soft tissue infection. *Eur J Clin Microbiol Infect Dis* 1996;**15**:913—21.
18. Mazuski JE, Sawyer RG, Nathens AB, DiPiro JT, Schein M, Kudsk KA, et al. The Surgical Infection Society guidelines on antimicrobial therapy for intra-abdominal infections: an executive summary. *Surg Infect (Larchmt)* 2002;**3**:161—73.

19. Rocha LA, Azanza JR, Balibrea JL, Cainzos M, Garcia-Rodriguez JA, Gomis M, et al. Guidelines for empirical antibiotic treatment of intra-abdominal infections. Spanish Society of Chemotherapy. *Rev Esp Quimioter* 2000;**13**: 65—72.
20. Muralidharan G, Micalizzi M, Speth J, Raible D, Troy S. Pharmacokinetics of tigecycline after single and multiple doses in healthy subjects. *Antimicrob Agents Chemother* 2005;**49**:220—9.
21. Muralidharan G, Fruncillo RJ, Micalizzi M, Raible DG, Troy SM. Effects of age and sex on single-dose pharmacokinetics of tigecycline in healthy subjects. *Antimicrob Agents Chemother* 2005;**49**:1656—9.
22. Sesoko S, Umemura K, Nakashima M. *Pharmacokinetics (PK), safety and tolerability of tigcycline (GAR-936) in healthy Japanese males*. Presented at the 42nd Interscience Conference of Antimicrobial Agents and Chemotherapy. 2002;**42**:22.
23. Murray JA, Wilson S, Klein S, Yellin A, Loh E. *The clinical response to tigecycline in the treatment of complicated intra-abdominal infections in hospitalized patients. A phase 2, clinical trial*. Presented at the 43rd Interscience Conference of Antimicrobial Agents and Chemotherapy. 2003;**43**:416.
24. Postier RG, Green SL, Klein SR, Ellis-Grosse EJ, Loh E, Tigecycline 200 Study Group. Results of a multicenter, randomized, open-label efficacy and safety study of two doses of tigecycline for complicated skin and skin-structure infections in hospitalized patients. *Clin Ther* 2004;**26:** 704—14.
25. Troy SM, Mauralidharan G, Micalizzi M, Mojavarian P, Salacinski L, Raible D. *The effects of renal disease on the pharmacokinetics of tigecycline (GAR-936)*. Presented at the 43rd Interscience Conference of Antimicrobial Agents and Chemotherapy. Poster A-22; 2003.
26. Basoli A, Meli EZ, Mazzocchi P, Speranza V. Imipenem/cilastatin (1.5 g daily) versus meropenem (3.0 g daily) in patients with intra-abdominal infections: results of a prospective, randomized, multicentre trial. *Scand J Infect Dis* 1997;**29**:503—8.
27. Solomkin J, Reinhart H, Dellinger E, Bohnen JM, Rotstein OD, Vogel SB. Results of a randomized trial comparing sequential intravenous/oral treatment with ciprofloxacin plus metronidazole to imipenem/cilastatin for intra-abdominal infections. *Ann Surg* 1996;**223:** 303—15.
28. Brismar B, Malmborg A, Tunevall G, Wretlind B, Bergman L, Mentzing LO, et al. Piperacillin—tazobactam versus imipenem—cilastatin for treatment of intra-abdominal infections. *Antimicrob Agents Chemother* 1992;**36**:2766—73.
29. Solomkin JS, Dellinger EP, Christou NV, Busuttil RW. Results of a multicenter trial comparing imipenem/cilastatin to tobramycin/clindamycin for intra-abdominal infections. *Ann Surg* 1990;**212**:581—91.