CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-821

MEDICAL REVIEW(S)

Team Leader Memorandum

Application: NDA 21-821
Product: Tygacil (Tigecycline) for Injection
Sponsor: Wyeth Pharmaceuticals, Inc.

Date of Submission: December 15, 2004
Date of Memorandum: June 15, 2005

Tygacil (tigecycline) for injection, developed by Wyeth Pharmaceuticals, Inc., is the first glycylcycline class antibacterial drug. NDA 21-821 for tigecycline was submitted on December 15, 2004 seeking approval for complicated intra-abdominal infections (cIAI) and complicated skin and skin structure infections (cSSSI). The indications list a variety of Gram-positive and Gram-negative bacteria, including MRSA, based on the results of the clinical trials. The application was granted a priority review as a new intravenous (IV) antibacterial drug, intended for the treatment of life-threatening disease, including MRSA infections, for which there are few treatment options.

Glycylcyclines are structurally related to tetracycline antibiotics. Tigecycline is a derivative of minocycline, with a glycylamido- moiety attached to the 9 position of the tetracycline ring. The modification results in a compound that retains *in vitro* activity against bacteria that are tetracycline resistant. The *in vitro* data submitted by the sponsor show that tigecycline has broad spectrum activity. Tigecycline is active against several Gram-positive bacteria: *Staphylococcus* spp. including *aureus, Streptococcus* spp. including *pyogenes,* and *Enterococcus* spp. including *faecalis*. Tigecycline is also active against many Enterobacteriaceae: *Escherichia coli, Klebsiella* spp., *Enterobacter aerogenes, Citrobacter freundii,* and *Acinetobacter* spp. It is also active against other Gram-negative bacteria (*Neisseria gonorrhoeae, Pasteurella multocida, Aeromonas hydrophila,* and *Stenotrophomonas maltophilia*), with the notable exception of poor activity against *Pseudomonas*. Activity against anaerobes (*Bacteroides* spp., *Clostridium* spp.) was also reported.

The clinical pharmacology of tigecycline shows that it is not orally absorbed, hence it is only available in a formulation for intravenous injection. Tigecycline has a long half-life ($t_{½}$ = 44 hours after multiple doses). It also has a high steady-state volume of distribution, indicating extensive distribution to some tissues. Tigecycline is primarily excreted unchanged in the gall bladder, with a portion of the administered dose recovered unchanged in the urine. Tigecycline is not extensively metabolized, though there is some glucuronidation, N-acetylation, and conversion to an epimer (each no more than 10% of an administered dose). In initial studies, nausea was found to be a dose-limiting adverse effect. Based on the pharmacokinetic studies, a 100 mg IV loading dose followed by 50 mg IV twice daily was used in clinical trials.

There were four pivotal phase 3 trials in the NDA submission for tigecycline, two for each indication. The results of these clinical trials are discussed by indication.

Complicated Intra-abdominal Infections: Two phase 3, randomized, double-blind, multi-center trials compared tigecycline to imipenem/cilastatin in cIAI infections (Studies 301 and 306). The studies were independent trials, but a combined analysis of primary study results was pre-specified. Male or female patients (≥ 18 years of age) meeting the selection criteria were stratified by APACHE II score and randomized to study drug or comparator. Diagnoses included appendicitis, cholecystitis, diverticulitis, gastric/duodenal perforation, intra-abdominal abscess, perforation of intestine, and peritonitis. Patients could receive tigecycline or comparator for 5-14 days, though >50% of patients received 6-8 days of study drug. The studies were designed to compare clinical outcome at the test-of-cure visit in the microbiological Intent-to-Treat (m-mITT) and microbiologically evaluable (ME) populations. Clinical outcome for the two trials are shown in the following table:

Studies	**Population**	**Tigecycline [a] n/N (%)**	**Imipenem/Cilastatin [b] n/N (%)**	**95% CI [c]**
Study 307A1-301	ME	199/247 (80.6)	210/255 (82.4)	(-9.0, 5.4)
	m-mITT	227/309 (73.5)	244/312 (78.2)	(-11.8, 2.3)
Study 307A1-306	ME	242/265 (91.3)	232/258 (89.9)	(-4.0, 6.8)
	m-mITT	279/322 (86.6)	270/319 (84.6)	(-3.7, 7.7)

[a] 100 mg initially, followed by 50 mg every 12 hours
[b] Imipenem/Cilastatin (500 mg every 6 hours)
[c] 95% Confidence Intervals for the difference in clinical cure rates

The clinical outcomes by pathogen in the ME population are shown in the table below:

Pathogen	Tigecycline n/N (%)	Imipenem/Cilastatin n/N (%)
Citrobacter freundii	12/16 (75.0)	3/4 (75.0)
Enterobacter cloacae	14/16 (87.5)	16/17 (94.1)
Escherichia coli	281/329 (85.4)	298/343 (86.9)
Klebsiella oxytoca	19/20 (95.0)	18/20 (90.0)
Klebsiella pneumoniae	46/52 (88.5)	53/60 (88.3)
Enterococcus faecalis (vancomycin-susceptible only)	25/33 (75.8)	35/47 (74.5)
Methicillin-susceptible *Staphylococcus aureus* (MSSA)	26/29 (89.7)	22/24 (91.7)
Streptococcus anginosus grp.[b]	102/120 (85.0)	61/81 (75.3)
Bacteroides fragilis	67/87 (77.0)	60/74 (81.1)
Bacteroides thetaiotaomicron	36/41 (87.8)	31/36 (86.1)
Bacteroides uniformis	12/17 (70.6)	14/17 (82.4)
Bacteroides vulgatus	14/16 (87.5)	5/7 (71.4)
Clostridium perfringens	19/20 (95.0)	20/22 (90.9)
Peptostreptococcus micros	14/18 (77.8)	9/12 (75.0)

The two studies demonstrated non-inferiority of tigecycline to the approved comparator with successful clinical outcomes in patients with a variety of intra-abdominal pathogens.

Complicated Skin and Skin Structure Infections: Two phase 3, randomized, double-blind, multi-center trials compared tigecycline to the combination of vancomycin and aztreonam in cSSSI infections (Studies 300 and 305). The studies were independent trials, but a combined analysis of primary study results was pre-specified. Male or female patients (≥ 18 years of age) meeting the selection criteria were randomized to study drug or comparator. The main diagnoses were deep soft tissue infections or major abscesses. Diabetes and peripheral vascular disease were underlying conditions in approximately 20% and 7% of patients, respectively. Patients could receive tigecycline or comparator for up to 14 days. The studies were designed to compare clinical outcome at the test-of-cure visit in the clinical modified Intent-to-Treat (c-mITT) and clinically evaluable (CE) populations. Clinical outcome for the two trials are shown in the following table:

Studies	Population	Tigecycline [a] n/N (%)	Vancomycin/Aztreonam [b] n/N (%)	95% CI [c]
Study 3074A1-300	CE	165/199 (82.9)	163/198 (82.3)	(-7.4, 8.6)
	c-mITT	209/277 (75.5)	200/260 (76.9)	(-9.0, 6.1)
Study 3074A1-305	CE	200/223 (89.7)	201/213 (94.4)	(-10.2, 0.8)
	c-mITT	220/261 (84.3)	225/259 (86.9)	(-9.0, 3.8)

[a] 100 mg initially, followed by 50 mg every 12 hours
[b] Vancomycin (1 g IV every 12 hours)/Aztreonam (2 g IV every 12 hours)
[c] 95% Confidence Intervals for the difference in clinical cure rates

The clinical outcomes by pathogen in the ME population are shown in the table below:

Pathogen	TYGACIL n/N (%)	Vancomycin/ Aztreonam n/N (%)
Escherichia coli	27/32 (84.4)	26/30 (86.7)
Enterococcus faecalis (vancomycin-susceptible only)	13/17 (76.5)	24/29 (82.8)
Methicillin-susceptible *Staphylococcus aureus* (MSSA)	125/139 (89.9)	118/126 (93.7)
Methicillin-resistant *Staphylococcus aureus* (MRSA)	29/37 (78.4)	26/34 (76.5)
Streptococcus agalactiae	8/8 (100)	11/13 (84.6)
Streptococcus anginosus grp. [a]	16/20 (80.0)	9/10 (90.0)
Streptococcus pyogenes	31/33 (93.9)	24/27 (88.9)
Bacteroides fragilis	6/8 (75.0)	4/5 (80.0)

[a] Includes *Streptococcus anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*

The trials demonstrated non-inferiority of tigecycline to the combination of vancomycin and aztreonam in the treatment of cSSSI patients. Similar clinical outcomes were seen for patients with documented baseline pathogens treated with tigecycline and comparator. Of note, similar outcomes were reported for patients with cSSSI due to MRSA treated with tigecycline or vancomycin.

Safety data were collected from 1,415 tigecycline-treated patients and 1382 comparator-treated patients in phase 3 clinical trials. The most common adverse reactions were nausea, vomiting, and diarrhea. The following table shows the incidence of nausea and vomiting as treatment-emergent adverse events in all four comparative trials, and also separated by indication. Of note, nausea and vomiting are reported at a much higher rate in tigecycline-treated patients than vancomycin/aztreonam-treated patients in the cSSSI trials. This difference between treatments is much smaller in the cIAI trials, mostly due to an increase in the rate of nausea and vomiting among comparator-treated patients. Nausea and vomiting are treatment-related adverse events occurring in tigecycline-treated patients.

	Tigecycline		**Comparator**	
	n/N*	**%**	**n/N***	**%**
Nausea				
All Pivotal Trials	460/1396	33.0	274/1391	19.7
cSSSI Trials	207/570	36.3	54/559	9.7
cIAI Trials	253/826	30.6	220/832	26.4
Vomiting				
All Pivotal Trials	307/1396	22.0	185/1391	13.3
cSSSI Trials	117/570	20.5	25/559	4.5
cIAI Trials	190/826	23.0	160/832	19.2

* This analysis only includes patients participating in the four studies (300, 301, 305, and 306)

In the serious adverse events associated with tigecycline use, it was noted that there were more deaths in the tigecycline-treated patients, 32/1383 (2.3%), than in comparator-treated patients 22/1375 (1.6%). This was not a statistically significant difference, and deaths in an even higher percentage of patients hospitalized due to these types of infections would be understandable. However, an intensive review of the deaths occurring in these trials was conducted, to try to understand whether specific drug-related factors (whether safety issues or lack of efficacy) may have contributed to this difference. No specific safety or efficacy findings could be found to account for this difference.

Infection-related serious adverse events were also reported more frequently in tigecycline-treated patients (6.7%) than in the comparator group (4.6%). The main difference appeared to be related to reports of sepsis/septic shock in patients with intestinal perforation occurring in 6 tigecycline-treated patients vs. 2 imipenem-treated patients in cIAI trials. While differences in the APACHE II scores between treatment arms may contribute to this differential rate of sepsis/septic shock, the numbers of reports were too few to draw any conclusions about the relationship of these events to tigecycline treatment. A precaution was included in the label regarding use of tigecycline as monotherapy for patients with clinically apparent intestinal perforation.

Because tigecycline is structurally similar to tetracyclines, the tigecycline label also includes warnings and precautions regarding the risk for adverse effects associated with the tetracycline class. The warnings include the risk of fetal harm in pregnant women

and the risk of tooth discoloration in children to the age of 8 years. Animal studies performed with tigecycline have demonstrated decreased fetal weights in rats and rabbits and bone discoloration in rats. It is clear that these tetracycline class effects are also likely to occur with tigecycline. Precautions regarding the potential for other tetracycline-related adverse effects (photosensitivity, pseudotumor cerebri, pancreatitis and anti-anabolic action) are also in the tigecycline label. Of note in clinical trials, there was one case of a tigecycline-treated patient who developed pancreatitis. However, the case was confounded by treatment with another agent associated with pancreatitis. The risk management program for tigecycline includes monitoring for reports of adverse events related to pancreatitis.

In summary, substantial evidence of efficacy and safety has been provided to support the use of tigecycline in the treatment of cSSSI and cIAI infections. The team leader concurs with the medical officer's recommendations for approval of tigecycline.

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/s/

John Alexander
6/15/05 06:24:20 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
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Reviewer Name	Charles Cooper, M.D.
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Established Name	tigecycline
(Proposed) Trade Name	Tygacil
Therapeutic Class	Antibiotic
Applicant	Wyeth Pharmaceuticals
Priority Designation	{P}
Formulation	Intravenous
Dosing Regimen	100 mg loading dose followed by 50 mg BID
Indication	complicated intra-abdominal infections, complicated skin and skin structure infections
Intended Population	adults

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

- The evidence from the submitted adequate and well-controlled studies support that tigecycline has shown substantial evidence of efficacy for the indications of complicated intraabdominal infections and complicated skin and skin structure infection (including resulting from MRSA infection).
- Tigecycline has been shown to be safe for its intended use. There are particular safety issues that were identified including: rising LFT's in patients who did not have sufficient follow-up; increased rates of infection-related serious adverse events such as sepsis, pneumonia, and surgical wound infection; non-statistically significant increase in death rates in tigeycline arm. In addition, there was a single case of diffuse pancreatitis requiring discontinuation of tigecycline with the only identifiable confounder being concomitant pantoprazole administration. Many of these issues may need to be sorted out in the post-marketing setting; however, the degree of uncertainty that may exist with regard to these potential toxicities is acceptable for approval because this drug will be used for the treatment of more serious infections which could be potentially life-threatening.
- There are sufficient data to provide adequate directions for use. The route of elimination is thought to be primarily hepatic excretion into the intestinal tract, and dose adjustment is only necessary in cases of severe hepatic impairment.

1.2 Recommendation on Postmarketing Actions

1.2.1 1.2.1 Risk Management Activity

Specific risk management activities should include periodic assessments and reports to the FDA regarding the status of post-marketing reports of liver dysfunction, pancreatitis, and serious infectious processes such as sepsis, pneumonia, etc.

1.2.2 1.2.2 Required Phase 4 Commitments

No specific study commitments have been identified for the phase 4 period.

1.2.3 1.2.3 Other Phase 4 Requests

No other requests have been identified.

1.3 Summary of Clinical Findings

1.3.1 1.3.1 Brief Overview of Clinical Program

- Product name: tigecycline; drug class: glycylcyclines; route of administration: I.V. only

- Indications and populations studied: complicated intraabdominal infections and complicated skin and skin structure infections
- Number of pivotal efficacy and safety trials: 2 studies for cSSSI (Studies 300 and 305) and 2 studies for cIAI (Studies 301 and 306). There were also studies for resistant pathogens (Studies 307, 309, (b) (4) however, these studies did not enroll many patients and the majority of the data supporting treatment of MRSA in cSSSI came from Studies 300 and 305.
- There were a total of 1,415 tigecycline-treated patients and 1,382 comparator-treated patients enrolled in the phase 3 studies.
- The overall number of patients in the tigecycline safety database, including the phase 1, 2, and 3 studies was 2,219.
- There was no post-marketing data. This drug has not been approved in any markets to date.

1.3.2 1.3.2 Efficacy

There were 2 studies per indication that were conducted to assess the effectiveness of tigecycline in the treatment of complicated skin and skin structure infections (cSSSI) and complicated intraabdominal infections (cIAI). Studies within each indication were "harmonized" to be nearly identical for the purposes of combining data for efficacy analysis. With regard to the study conduct, study design, and the study results, there were no significant differences between the studies for each indication that would suggest it be inappropriate to combine the efficacy data.

The results of the 2 phase 3 blinded, controlled studies for cIAI (Studies 301 and 306) and the 2 phase 3 blinded controlled studies for cSSSI (Studies 300 and 305) successfully demonstrated non-inferiority. In addition, sufficient data were collected to demonstrate the effectiveness of tigecycline in the treatment of cSSSI in patients with complicated skin and skin structure infections due to MRSA.

For cIAI, the per protocol efficacy analysis (called the ME population analysis) demonstrated similar efficacy rates between tigecycline and comparator, 86.1% vs. 86.2% for the point estimates with a 95% CI of (-4.5, 4.4) around the treatment difference. The other important analysis was the ITT analysis (called the m-mITT population analysis). For this analysis, the efficacy rates were also similar between tigecycline and comparator with point estimates of 80.2% vs. 81.5% with a 95% CI around the treatment difference of (-5.8, 3.2). Integrated and individual study analyses are presented in the following table

Clinical Cure Rates from Two Pivotal Studies in Complicated Intra-abdominal Infections after 5 to 14 Days of Therapy

	TYGACIL[a] n/N (%)	Imipenem/Cilastatin[b] n/N (%)
Integrated		
ME	441/512 (86.1)	442/513 (86.2)
m-mITT	506/631 (80.2)	514/631 (81.5)
Study 301		
ME	199/247 (80.6)	210/255 (82.4)
m-mITT	227/309 (73.5)	244/312 (78.2)
Study 306		
ME	242/265 (91.3)	232/258 (89.9)
m-mITT	279/322 (86.6)	270/319 (84.6)

[a] 100 mg initially, followed by 50 mg every 12 hours
[b] Imipenem/Cilastatin (500 mg every 6 hours)

For cSSSI, the per protocol efficacy analysis (called the CE population analysis) demonstrated similar efficacy rates between tigecycline and comparator, 86.5% vs. 88.6% for the point estimates with a 95% CI of (-6.8, 2.7) around the treatment difference. The other important analysis was the ITT analysis (called the c-mITT population analysis). For this analysis, the efficacy rates were also similar between tigecycline and comparator with point estimates of 79.7% vs. 81.9% with a 95% CI around the treatment difference of (-7.1, 2.8). Integrated and individual study analyses are presented in the following table.

Clinical Cure Rates from Two Pivotal Studies in Complicated Skin and Skin Structure Infections after 5 to 14 Days of Therapy

	TYGACIL[a] n/N (%)	Vancomycin/Aztreonam[b] n/N (%)
Integrated		
CE	365/422 (86.5)	364/411 (88.6)
c-mITT	429/538 (79.7)	425/519 (81.9)
Study 300		
CE	165/199 (82.9)	163/198 (82.3)
c-mITT	209/277 (75.5)	200/260 (76.9)
Study 305		
CE	200/223 (89.7)	201/213 (94.4)
c-mITT	220/261 (84.3)	225/259 (86.9)

[a] 100 mg initially, followed by 50 mg every 12 hours
[b] Vancomycin (1 g IV every 12 hours)/Aztreonam (2 g IV every 12 hours)

For patients who had cSSSI due to MRSA from combined phase 3 studies (Studies 300, 305, and 307), the point estimates were 78.4% (29/37 with 95% CI: 61.8, 90.2) for tigecycline and 76.5% (26/34 with 95% CI: 58.8, 89.3) for vancomycin.

Other resistant pathogens: Additional data were collected assessing the efficacy of tigecycline in the treatment of infections due to VRE and resistant gram-negative

pathogens; however, this amounted to a relatively small total number of subjects and, therefore, was not sufficient to assess efficacy.

1.3.3 1.3.3 Safety

The size of the safety database includes 1415 patients in phase 3 studies, 328 patients in phase 2 studies and 424 patients in phase 1 studies. For patients in the cSSSI studies, the mean duration of therapy was 8.19 days while in cIAI studies it was 7.70 days and for the resistant pathogens studies, the mean duration of therapy was 11.9 days. For all phase 3 studies combined, the mean duration of therapy was 7.99 with a median of 7.00 and minimum and maximum exposures being 1.00 and 29.0 days.

Important identified and potential safety signals include the following:

Nausea and vomiting – Tigecycline-treated patients had a higher rate of nausea than comparator-treated patients in all phase 3 combined studies, 31.6% vs. 18.5%, and also for vomiting, 21.2% vs. 12.1%. The majority of this difference, however, is derived from the cSSSI studies where the rates of nausea for tigecycline vs. comparator (vanco/aztreonam) were 35.3% vs. 9.3% and the rates of vomiting were 20.4% vs. 4.3%. In the cIAI studies, the rates of nausea and vomiting were more similar between tigecycline and the comparator (imipenem/cilastin). For nausea in the cIAI studies, tigecycline vs. comparator, the rates were 29.1% vs. 24.6% and for vomiting, the rates were 21.8% vs. 17.3%. It is difficult from this information to know whether the differences in rates of nausea and vomiting by indiction are related to differences between the comparators or the result of a disease interaction. The number of patients in whom nausea and vomiting resulted in withdrawal from the studies was 8 for tigecycline vs. 5 for comparator while the number of nausea and vomiting SAE reports was 10 for tigecycline vs. 4 for comparator. For the most part, the nausea and vomiting associated with tigecycline were manageable.

Amongst SAE's in tigecycline treated patients, there were more instances of infection related events such as sepsis, abscess, pneumonia, peritonitis, "infection", and septic shock. Detailed review of these cases did not provide an explanation, except for the preferred term of "infection." Review of all cases of infection revealed that 15 of 19 were surgical wound infections and in 9 of these cases, infection resulted from resistant and intermediate-susceptible *Pseudomonas*, *Klebsiella*, and *Proteus*.

There were also differences in the death rates for tigecycline vs. comparator. Overall, the death rate for tigecycline in the 4 combined cIAI and cSSSI studies was 2.2% for tigecycline vs. 1.3% for comparator (30/1383 deaths in tigecycline-treated patients vs. 18/1377 deaths for comparator-treated patients). When looking only at death rates by indication, the results are, for tigecycline vs. comparator, 2.9% (24/817) vs 2.1% (17/825) for cIAI, and 1.1% (6/566) vs. 0.2% (1/550). From these statistics, it can be seen that although there is a difference between treatment arms in the death rate in the cIAI indication, it is not as great as the difference in the cSSSI death rates between treatment arms. The 5 additional deaths in the cSSSI studies are responsible for a significant proportion of the overall difference in the death rates. Detailed review of the deaths in the

cSSSI studies revealed that they were unlikely to be related to study drug as they included such events as pulmonary embolism, cardiac failure, and myocardiac infection. Review of the deaths in the cIAI studies did not result in a clear explanation for the difference in the death rate.

1.3.4 1.3.4 Dosing Regimen and Administration

Only one dosing regimen has been used in all phase 3 clinical trials. That regimen is a 100 mg intravenous loading dose followed by 50 mg intravenously every 12 hours. No oral formulation exists. In phase 1 studies, patients who received more than 50 mg I.V. every 12 hours experienced high rates of intolerable nausea and vomiting.

1.3.5 1.3.5 Drug-Drug Interactions

This product is not metabolized by the P450 enzyme system. Concomitant administration of TYGACIL (100 mg followed by 50 mg every 12 hours) and warfarin (25 mg single-dose) to healthy subjects resulted in a decrease in clearance of R-warfarin and S-warfarin by 40% and 23%, an increase in C_{max} by 38% and 43% and an increase in AUC by 68% and 29%, respectively. Tigecycline did not significantly alter the effects of warfarin on INR. In addition, warfarin did not affect the pharmacokinetic profile of tigecycline. However, prothrombin time or other suitable anticoagulation test should be monitored if tigecycline is administered with warfarin.

1.3.6 1.3.6 Special Populations

This product has not been used in children. Given the issues of pediatric use of other related compounds (tetracycline class antibiotics), use of tigecycline in the pediatric population should only be considered when there is a clear benefit to risk advantage, such as when dealing with an infection due to a resistant organism without other treatment options.

The area under the curve for this product is approximately doubled when it is administered to patients with Childs Pugh Class C hepatic insufficiency. When this product is used in such patients, it is recommended that the dose be halved.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Description
This drug is the first of a new drug class called "glycylcyclines" and is the 9-*t*-butylglycylamido derivative of minocycline.

Generic Name: Tigecycline

Proposed Trade Name: Tygacil

Chemical class: new molecular entity

Pharmacological class: glycylcycline (related to tetracyclines)

Proposed indications, dosing regimens, age groups:
Complicated skin and skin structure infections, complicated intra-abdominal infections
100 mg IV loading dose followed by 50 mg IV BID
Adults

2.2 Currently Available Treatment for Indications

Complicated skin and skin structure infections:
Invanz (ertapenem), Levaquin (levofloxacin), Zosyn (piperacillin/tazobactam), Zyvox (linezolid), Merem (meropenem), Cubicin (daptomycin).

The following medications have an indication for "Skin and skin structure infeciton" which was granted prior to when a distinction was made for complicated vs. uncomplicated:
Cipro (ciprofloxacin), Azactam (aztreonam), Claforan (cefotaxime), Fortaz (ceftazidime), Primaxin (imipenem/cilastin), Rocephin (ceftriaxone), Timentin (ticarcillin/clavulanate), Unasyn (ampicillin/sulbactam)

Complicated Intra-abdominal Infections

Maxipime (cefepime), Invanz (ertapenem), Cipro (ciprofloxacin)

The following medications have an indication for "Intra-abdominal infections" which was granted prior to when a distinction was made for complicated vs. uncomplicated:
Fortaz (ceftazidime), Claforan (cefotaxime), Primaxin (imipenem/cilastin), Rocephin (ceftriaxone), Timentin (ticarcillin/clavulanate), Unasyn (ampicillin/sulbactam), Zosyn (piperacillin/tazobactam for peritonitis), Merrem (meropenem)

2.3 Availability of Proposed Active Ingredient in the United States

The active moiety in this product has not been marketed in the United States.

2.4 Important Issues with Products of the Same Pharmacologic Class

This product is the first gylcylcycline. It is pharmacologically related to the tetracycline class of antibiotics. The structure is essentially minocycline with a glycyl side-chain added. Because of this, tigecycline may have similar adverse effects to tetracyclines. Such effects may include: photosensitivity, pseudotumor cerebri, pancreatitis, and anti-anabolic action (which has lead to increased BUN, azotemia, acidosis, and hypophosphatemia).

2.5 Presubmission Regulatory Activity

A significant amount of discussion between the sponsor and the Division took place regarding the issue of the choice of an appropriate non-inferiority margin. In the initial discussion, the division expressed its opinion that the non-inferiority margin should be set at -10; however, this issue required further discussion and clarification with the sponsor. The division communicated to the sponsor that a non-inferiority margin of -10 would be consistent with a clear positive result that would warrant approval in the absence of serious safety concerns. Furthermore, if study results indicated a lower bound of the 95% confidence interval that was between -10 and -15, then product could still potentially be approved, after carefully weighing the strength of the efficacy results against possible safety signals that arose. The sponsor communicated to the division that their intention was to "harmonize" the two complicated intra-abdominal infection studies with each other and to do the same for the complicated skin and skin structure infection studies. The sponsor indicated that the studies in each indication would be of similar design and be conducted as similarly to each other as possible. The reasoning behind this was to allow for a more meaningful integrated analysis of the two studies in each indication.

2.6 Other Relevant Background Information

This product has not been approved in other countries at this time.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Please refer to chemistry review by Suresh Pagay.

3.2 Animal Pharmacology/Toxicology

Please refer to pharmacology/toxicology review conducted by Dr. Wendy Schmidt.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary source of clinical data came from four controlled, blinded clinical trials conducted by the sponsor. Two of the studies were conducted for the study of complicated intra-abdominal infections and the other two were for the study of complicated skin and skin structure infections. There were some additional uncontrolled studies; however, these were actually phase 2 studies and were mainly examined by the medical officer for the assessment of safety.

There was no additional information used by the division during the review process. There were no data from the NIH, literature, foreign post-marketing safety data, external consultants, or other literature reports.

4.2 Tables of Clinical Studies

Protocol No. *Clinical Study Report No.* Country(ies)	Study Design	No. Subjects Randomized	Demography:[a] Sex, Age Range (Mean Age) *Ethnic Origin*	Study Population(s)	Study Drug(s)	IV Dose and Frequency (Duration of Treatment)	Type o Report
Reports of Human Pharmacokinetic Studies							
Healthy Subject PK and Initial Tolerability Study Reports							
3074A1-100-EU *CSR-35495* France	Double-blind, placebo-controlled single ascending dose study to assess safety, tolerability, and PK of tigecycline	90	90 M 18-44 years (26.6 years) *1 O* *89 Wh*	Healthy men	Tigecycline Placebo	12.5, 25, 50, 75, 100, 200, 300 mg (single dose) Normal saline (single dose)	Final, Full
3074A1-101-US *CSR-39534* United States	Double-blind, placebo-controlled multiple ascending dose study to assess safety, tolerability, and PK of tigecycline	32	32 M 26-45 years (35.9 years) *11 B* *4 H* *17 Wh*	Healthy men	Tigecycline Placebo	25, 50, 75, 100 mg q12h for 10 days/19 doses (planned); terminated 75 mg (day 5) and 100 mg (day 9) doses levels early Normal saline q12h (10 days; total 19 doses)	Final, Full
3074A1-104-US *CSR-52364* United States	Radiolabeled IV tigecycline to determine metabolic disposition and mass balance	12	12 M 19–42 years (25.6 years) *2 B* *10 Wh*	Healthy men	Tigecycline [^{14}C]-tigecycline	100 mg loading, 50 mg q12h maintenance (3 days, total 6 doses) 50 mg (single dose)	Final, Full

Protocol No. *Clinical Study Report No.* Country(ies)	Study Design	No. Subjects Randomized	Demography:[a] Sex, Age Range (Mean Age) *Ethnic Origin*	Study Population(s)	Study Drug(s)	IV Dose and Frequency (Duration of Treatment)	Type Repor
Healthy Subject PK and Initial Tolerability Study Reports (continued)							
3074A1-106-CN *CSR-54367* China	Double-blind, placebo-controlled single ascending dose study to assess safety, tolerability, and PK of tigecycline	48	48 M 19–38 years (28.7 years) *48 A*	Healthy Chinese men	Tigecycline Placebo	25, 50, 100, 150 mg (single dose) Normal saline (single dose)	Final, Full
3074A1-107-JA *CSR-54680* Japan	Single ascending dose study to assess safety, tolerability, and PK of tigecycline	40	40 M Age range NA (25.8 years) *40 A*	Healthy Japanese men	Tigecycline Placebo	25, 50, 100, 150 mg (single dose) Normal saline (single dose)	Final, Synop
3074A1-109-US *CSR-46380* United States	Double-blind, placebo-controlled, multiple dose concentration and infusion rate study to evaluate safety and tolerability of tigecycline	28	28 M 27-50 years (36.8 years) *18 B* *2 H* *8 Wh*	Healthy men and women	Tigecycline Placebo	100 mg loading, 50 mg q12h in various infusion rates/concentrations (5 days, total 10 doses) Normal saline q12h (5 days)	Final, Full

Protocol No. *Clinical Study Report No.* Country(ies)	Study Design	No. Subjects Randomized	Demography:[1] Sex, Age Range (Mean Age) *Ethnic Origin*	Study Population(s)	Study Drug(s)	IV Dose and Frequency (Duration of Treatment)	Type of Report
Healthy Subject PK and Initial Tolerability Study Reports (continued)							
3074A1-112-US *CSR-53846* United States	Open-label, multiple dose study to determine the PK profile of tigecycline in serum, lung epithelial lining fluid, and alveolar cells after reaching steady state	34	25 M, 9 W 18–53 years (33.4 years) *3 A* *4 B* *27 Wh*	Healthy men and women	Tigecycline	100 mg loading, 50 mg q12h maintenance (4 days; total 7 doses)	Final, Full
3074A1-113-US *CSR-53610* United States	Open-label, multiple dose study to determine the PK profile of tigecycline in serum and blister fluid after multiple administrations	10	10 M 20–37 years (26.7 years) *1 B* *2 O* *7 Wh*	Healthy men and women	Tigecycline	100 mg loading, 50 mg q12h maintenance (4 days; total 7 doses)	Final, Full
3074A1-114-JA *CSR-54709* Japan	Multiple ascending dose study to assess safety, tolerability, and PK of tigecycline	10	10 M Age NA *10 A*	Healthy Japanese men	Tigecycline	Step 1: 25 mg q12h (ascending doses planned for Steps 2 and 3 were not administered) 4 days (10 days planned)	Final, Synopsis
					Placebo	Normal saline q12h 4 days (10 days planned)	

Protocol No. *Clinical Study Report No.* Country(ies)	Study Design	No. Subjects Randomized	Demography:[a] Sex, Age Range (Mean Age) *Ethnic Origin*	Study Population(s)	Study Drug(s)	IV Dose and Frequency (Duration of Treatment)	Type o Report
Healthy Subject PK and Initial Tolerability Study Reports (continued)							
3074A1-117-US *CSR-53852* United States	Open-label, single dose study to determine tissue and corresponding serum concentration of tigecycline at selected time points	54	18 M, 36 W 24–83 years (58.8 years) *1 B* *3 O* *50 Wh*	Men and women scheduled for planned surgery or procedure	Tigecycline	100 mg (single dose)	Interim Full
3074A1-118-JA *CSR-55508* Japan	Multiple ascending dose study to assess safety, tolerability, and PK of tigecycline	30	30 M Age NA *30 A*	Healthy Japanese men	Tigecycline	25 mg q12h, 50 mg q12h, 100 mg loading + 50 mg q12h maintenance (10 days)	Interim Synops
					Placebo	Normal saline q12h (10 days)	
Intrinsic Factor PK Study Reports							
3074A1-102-US *CSR-41557* United States	Open-label, parallel-group, nonrandomized single dose study to compare PK of tigecycline in healthy men and women in 3 age groups (young, young-elderly, and elderly)	46	25 M, 21 W 25-84 years (58.3 years) *14 B* *2 H* *30 Wh*	Healthy men and women	Tigecycline	100 mg (single dose)	Final, Full

Protocol No. *Clinical Study Report No.* Country(ies)	Study Design	No. Subjects Randomized	Demography:[3] Sex, Age Range (Mean Age) *Ethnic Origin*	Study Population(s)	Study Drug(s)	IV Dose and Frequency (Duration of Treatment)	Type of Report
3074A1-103-US *CSR-43752* United States	Open-label, parallel-group, nonrandomized single dose study to compare PK of tigecycline in healthy subjects and subjects with severe renal impairment	20	15 M, 5 W 25–75 years (49.0 years) *11 B* *9 Wh*	Healthy men and women and men and women with severe renal impairment or end-stage renal disease	Tigecycline	100 mg (single dose)	Final, Full
3074A1-105-EU *CSR-53265* France, Germany	Open-label, parallel-group, nonrandomized single dose study to compare PK of tigecycline in healthy subjects and subjects with hepatic impairment	48	40 M, 8 W 31–64 years (49.4 years) *4 A* *1 B* *43 Wh*	Healthy men and women and men and women with compensated / decompensated cirrhosis	Tigecycline	100 mg (single dose)	Final, Full
Extrinsic Factor PK Study Reports							
3074A1-111-US *CSR-53262* United States	Open-label, 3-period, nonrandomized study to assess potential PK interaction between tigecycline and digoxin and safety of concomitant administration	30	30 M 24–45 years (36.0 years) *19 B* *1 O* *10 Wh*	Healthy men and women	Tigecycline Digoxin	100 mg on day 1 and day 15, 50 mg q12h maintenance (days 15-19) Oral: 500 µg on day 7, then 250 µg qd (days 8-14 and days 15-19)	Final, Full

Protocol No. *Clinical Study Report No.* Country(ies)	Study Design	No. Subjects Randomized	Demography:[a] Sex, Age Range (Mean Age) *Ethnic Origin*	Study Population(s)	Study Drug(s)	IV Dose and Frequency (Duration of Treatment)	Type of Report
3074A1-115-US *CSR-52363* United States	Open-label, 2-period (2A, 2B), nonrandomized study to assess potential PK interaction between tigecycline and warfarin and safety of concomitant administration	19	19 M 19–41 years (26.9 years) *3 A* *5 B* *1 O* *10 Wh*	Healthy men	Warfarin Tigecycline	Oral 25 mg, single dose (period 1 and period 2B) 100 mg loading, 50 mg q12h maintenance (period 2A-2B, 8 days)	Final, Full
Healthy Subject PD and PK/PD Study Reports							
3074A1-116-EU *CSR-55069* Sweden	Open-label, multiple dose study to investigate the impact of tigecycline on the oropharyngeal and intestinal microflora after 10 days of administration	13	7 M, 6 W 20–31 years (25.5 years) *13 Wh*	Healthy men and women	Tigecycline	100 mg loading, 50 mg q12h maintenance (10 days; total 19 doses)	Interim, Full

Abbreviations: IV = intravenous; CSR = clinical study report; PK = pharmacokinetics; M = Men; W = Women; A = Asian; B = Black; H = Hispanic; O = Other ethnicity; Wh = White; NA = not applicable/not available.
a: Demography is for all subjects who received at least 1 dose of study drug (safety population).

Protocol No. *Clinical Study Report No.* Country(ies)	Study Design	No. Subjects Randomized	Demography:[a] Sex, Age Range (Mean Age), *Ethnic Origin*	Study Population	Study Drug(s)	IV Dose and Frequency (Duration of Treatment)	Type o Report
3074A1-300-US/CA *CSR-52108* Argentina, Canada, Chile, Guatemala, India, Mexico, Peru, United States	Double-blind (third-party unblinded), randomized control comparison study of tigecycline + placebo and vancomycin + aztreonam to treat cSSSI	583	368 M, 205 W 18–92 years (48.9 years) *3 A* *51 B* *107 H* *109 O* *303 Wh*	Subjects with cSSSI	Tigecycline + placebo	100 mg loading + 100 mL normal saline placebo, 50 mg + 100 mL placebo maintenance q12h (5–14 days)	Final, Full
					Vancomycin + aztreonam	1 g vancomycin + 2 g aztreonam q12h (5–14 days)	
3074A1-305-WW *CSR-52110* Australia, Austria, Belgium, Bulgaria, Croatia, Czech Republic, Estonia, Germany, Greece, Hungary, Latvia, Lithuania, Poland, South Africa, Romania, Russia, Slovak Republic, Spain, Taiwan, Ukraine, United Kingdom	Double-blind (third-party unblinded), randomized control comparison study of tigecycline + placebo and vancomycin + aztreonam to treat cSSSI	546	330 M, 213 W 18–88 years (49.4 years) *41 A* *40 B* *12 O* *450 Wh*	Hospitalized subjects with cSSSI	Tigecycline + placebo	100 mg loading + 100 mL normal saline placebo, 50 mg + 100 mL placebo maintenance q12h (5–14 days)	Final, Full
					Vancomycin + aztreonam	1 g vancomycin + 2 g aztreonam q12h (5–14 days)	

Table of Clinical Studies: Phase 2/3

Protocol No. *Clinical Study Report No.* Country(ies)	Study Design	No. Subjects Randomized	Demography:[a] Sex, Age Range (Mean Age), *Ethnic Origin*	Study Population	Study Drug(s)	IV Dose and Frequency (Duration of Treatment)	Type of Report
Study Reports of Uncontrolled Clinical Studies Pertinent to Claimed Indication: cSSSI							
3074A1-200-US *CSR-44339* United States	Open-label study of 2 dose levels of tigecycline to treat cSSSI	164	118 M, 42 W 18-82 years (49.0 years) *31 B* *40 H* *6 O* *83 Wh*	Hospitalized subjects with cSSSI	Tigecycline Tigecycline	50 mg loading, 25 mg q12h maintenance (7-14 days) 100 mg loading, 50 mg q12h maintenance (7-14 days)	Final, Full
Study Reports of Controlled Clinical Studies Pertinent to Claimed Indication: cIAI							
3074A1-301-WW *CSR-52109* Argentina, Brazil, Canada, Chile, China, Estonia, Guatemala, India, Korea, Latvia, Lithuania, Mexico, Panama, Peru, Taiwan, Ukraine, United States	Double-blind (third-party unblinded), randomized control comparison study of tigecycline and imipenem/cilastatin to treat cIAI	834	537 M, 288 W 18–91 years (43.6 years) *93 A* *74 B* *155 H* *178 O* *325 Wh*	Hospitalized subjects with cIAI	Tigecycline + placebo Imipenem/ Cilastatin	100 mg loading, 50 mg q12h maintenance; 6 h later, 100 mL normal saline placebo q12h (5-14 days) Dose = local data sheets q6h, adjusted for weight and creatinine clearance (5-14 days)	Final, Full

Table of Clinical Studies: Phase 2/3

Protocol No. *Clinical Study Report No.* Country(ies)	Study Design	No. Subjects Randomized	Demography:[a] Sex, Age Range (Mean Age), *Ethnic Origin*	Study Population	Study Drug(s)	IV Dose and Frequency (Duration of Treatment)	Type of Report
Study Reports of Controlled Clinical Studies Pertinent to Claimed Indication: cIAI (continued)							
3074A1-306-WW *CSR-52111* Australia, Austria, Belgium, Bulgaria, Croatia, Czech Republic, Estonia, France, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Netherlands, Poland, Portugal, Romania, Russia, Slovak Republic, Spain, South Africa, Switzerland, Taiwan, Ukraine, United Kingdom	Double-blind (third-party unblinded), randomized control comparison study of tigecycline and imipenem/cilastatin to treat cIAI	824	479 M, 338 W 18–88 years (48.9 years) *52 A* *25 B* *21 O* *719 Wh*	Hospitalized subjects with cIAI	Tigecycline + placebo Imipenem/ Cilastatin	100 mg loading, 50 mg q12h maintenance; 6 h later, 100 mL normal saline placebo q12h (5-14 days) Dose = local data sheets q6h, adjusted for weight and creatinine clearance (5-14 days)	Final, Full
Study Reports of Uncontrolled Clinical Studies Pertinent to Claimed Indication: cIAI							
3074A1-202-US *CSR-44333* United States	Open-label study of tigecycline to treat cIAI	118	77 M, 34 W 18-80 years (42.6 years) *1 A* *12 B* *56 H* *2 O* *40 Wh*	Hospitalized subjects with cIAI	Tigecycline	100 mg loading, 50 mg q12h maintenance (5-14 days)	Final, Full

Table of Clinical Studies: Phase 2/3

Protocol No. *Clinical Study Report No.* Country(ies)	Study Design	No. Subjects Randomized	Demography:[a] Sex, Age Range (Mean Age), *Ethnic Origin*	Study Population	Study Drug(s)	IV Dose and Frequency (Duration of Treatment)	Type of Report
Study Reports of Controlled Clinical Studies Pertinent to Claimed Indication: RP							
3074A1-307-WW *CSR-52112* Romania, South Africa, United States	Double-blind, randomized control (3:1) study to compare tigecycline and linezolid to treat selected serious infections in subjects with VRE and to compare tigecycline and vancomycin to treat selected serious infections in subjects with MRSA	29 5 VRE 24 MRSA	15 M, 14 W 22–80 years *6 B* *3 H* *20 Wh* VRE: 2 M, 3 W 65-77 years (71.0 years) *1 B* *4 Wh* MRSA: 13 M, 11 W 22-80 years (51.7 years) *5 B* *3 H* *16 Wh*	Subjects infected with VRE or MRSA (cIAI, cSSSI, CAP, HAP, or bacteremia)	Tigecycline Linezolid (for VRE) Vancomycin (for MRSA)	100 mg loading, 50 mg q12h maintenance (7–28 days) 600 mg q12h (7–28 days) 1 g q12h (7–28 days)	Interim, Full

Table of Clinical Studies: Phase 2/3

Protocol No. *Clinical Study Report No.* Country(ies)	Study Design	No. Subjects Randomized	Demography:[a] Sex, Age Range (Mean Age), *Ethnic Origin*	Study Population	Study Drug(s)	IV Dose and Frequency (Duration of Treatment)	Type o Report
Study Reports of Uncontrolled Clinical Studies Pertinent to Claimed Indication: RP (continued)							
3074A1-309-WW *CSR-52113* Romania, South Africa, United States	Open-label, noncomparative safety and efficacy study of tigecycline to treat serious infections caused by resistant gram-negative bacteria in subjects who have failed or cannot tolerate other antibiotic therapy	10	5 M, 5 W 44–83 years (59.6 years) *1 B* *2 H* *7 Wh*	Subjects with serious resistant gram-negative infections (cIAI, cSSSI, CAP, HAP, or bacteremia)	Tigecycline	100 mg loading, 50 mg q12h maintenance (7–28 days)	Interim Full
(b) (4) United States	(b) (4)	1	1 M 51 years (51 years) *1 Wh*	(b) (4)	Tigecycline	100 mg loading, 50 mg q12h maintenance; or 50 mg qd for subjects with rapidly growing mycobacterial infection (duration dependent on type of infection and investigator discretion)	Interim Synops
Other Study Reports							
(b) (4) Austria, Germany, Netherlands, Sweden	(b) (4)	74	40 M, 34 W 26–80 years (65.8 years) *74 Wh*	(b) (4)	Tigecycline (b) (4)	100 mg loading, 50 mg q12h maintenance (5-14 days)	Final, Abbrev

4.3 Review Strategy

The primary sources of data that were emphasized in this review were the 4 blinded, controlled, phase 3studies. Two were conducted to study cSSSI (300, 305), and the other two were conducted to study cIAI (301, 306). There uncontrolled studies submitted for this NDA were phase 2 studies that were intended for guiding the future clinical development plan. These uncontrolled studies were examined for safety; in particular, they were examined most closely to assess for SAE's and possible sentinel adverse events.

The integrated review of safety includes comparisons of adverse events in the study drug vs. the control drugs for the controlled phase3 blinded clinical trials. Uncontrolled data were not combined in this analysis, because of the differences in study data collection and study design. The safety analysis, was however, conducted in a way that rates of adverse events were examined with both indications separated and also combined. As mentioned, the phase 1 and 2 data were examined for the presence of unusual or serious adverse events.

The integrated review of efficacy includes analyses of efficacy with both studies for each indication combined as well as separated. Where there are differences in the analyses when separated vs. combined, these are pointed out.

4.4 Data Quality and Integrity

The Division of Scientific Investigation conducted audits of 2 study sites. The results of these audits are pending.

A randomly generated patient list was used to assess the quality of data transcription from the CRF's to the data sets. It was also used to ensure that the MO was in agreement with the investigator's conduct of the trial and assessment of the patients.

4.5 Compliance with Good Clinical Practices

Please refer to review by Dr. Matthew Thomas for details. Dr. Thomas' review summarizes the extent of identified study conduct violations. Taken together, these violations did not rise to a level where the integrity of the application was in question. There were two sites identified where DSI recommended that the data not be used as primary evidence to support efficacy and safety. Efficacy analyses excluding these sites were performed and the results of these analyses did not change the overall efficacy conclusions. For safety, it was noted that some adverse events were reported by these investigators, however, it was not felt that exclusion of the safety data from these sites was warranted.

4.6 Financial Disclosure

The sponsor submitted FDA form 3454 certification of financial interest for each of the phase 2 and 3 clinical studies. The sponsor identified a handful of investigators who reported significant payments of other sorts in excess of $25,000.00 from Wyeth Research. The number of patients enrolled by these investigators as a group could not significantly effect the overall assessment of efficacy and safety, even if all were excluded from the analyses. The sponsor also listed the investigators from which they were unable to obtain financial disclosure reports. For most of the phase 3 studies, there were fewer than 10 such sponsors per study.

5 CLINICAL PHARMACOLOGY

Please refer to pharmacology reviewer reports by Jeff Tworzanski, Pharm. D. and Yaning Wang, Ph.D.for details. A few brief broad points will be presented in this section.

5.1 Pharmacokinetics/ Pharmacodynamics

Tigecycline has relatively low serum levels and a very high volume of distribution. Tissue levels are thought to exceed serum levels and tissue bioaccumulation is likely to occur. The serum half-life of this drug is 40 hours, however, the tissue half-life is not known. The most likely route of excretion is unchanged via the gastrointestinal tract. There is relatively little drug excreted renally, and although it is suspected that bone deposition occurs (in accordance with the animal models and similar structured tetracyclines, the degree of bone deposition is not known.

5.2 Exposure-Response Relationships

There were no exposure-response data generated. All efficacy data were generated using the same dosing regimen.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication – Complicated Skin and Skin Structure Infection (cSSSI)

Complicated skin and skin structure infections include infections either involving deeper soft tissue or requiring significant surgical intervention, such as infected ulcers, burns, and major abscesses or a significant underlying disease state that complicates the response to treatment. Superficial infections or abscesses in an anatomical site, such as the rectal area, where the risk of anaerobic or Gram-negative pathogen involvement is higher, should be considered complicated infections. This is different than uncomplicated skin and skin structure infections, which usually include such clinical entities as simple abscesses, impetiginous lesions, furuncles, and cellulitis.

6.1.1 Methods

The primary clinical data that were reviewed in support of this indication were those submitted from Studies 300 and 305. These studies were designed and conducted to be as similar as possible. The sponsor purposely made efforts to "harmonize" the protocols. Case report forms, datasets, and the sponsor's study report were reviewed.

6.1.2 General Discussion of Endpoints

For the most part, the endpoints employed for studies 300 and 305 incorporated standard response definitions and outcome assessment methods that are consistent with the FDA's guidance to industry for the development of antibiotics for this indication. The studies called for "co-primary" endpoints which were the clinical outcome at Test of Cure visit for the Clinically Evaluable (CE) and clinical modified Intent-to-Treat populations (c-mITT). Although these are referred to as co-primary endpoints, there was no adjustment for multiplicity, as agreed upon with the division prior to submission of the NDA. The detailed definitions for these populations can be found in the detailed study reviews in Appendix 10. The CE population was essentially a per-protocol population, and the c-mITT population was essentially an intent-to-treat population. Detailed assessments of the clinical status of each subject were recorded at baseline, on the last day of therapy and at the test-of-cure assessment. These assessments included the presence or absence of drainage and/or discharge, fever, erythema, swelling and/or induration, pain and/or tenderness to palpation, extent of infection (width and length), and localized warmth. Clinical cure was defined as: resolution of all clinical indicators of the infection (healing of chronic underlying skin ulcer was not required) AND improvement of the clinical indicators of the infection to such an extent that no further antibacterial therapy was necessary. The definition of failure is consistent with general guidelines. It is more detailed and extensive; it can be found in Appendix 10.

The window of assessment for the TOC visit was from 12 days after end of therapy up to 92 days after end of therapy. Given the long half-life of tigecycline, it was determined that 12 days after the end of therapy would be preferable to 7 days for the beginning of the TOC window. This approach is referred to in the FDA's Guidance to Industry when dealing with a drug that has a long half-life. Allowing the TOC assessment to occur up to 92 days after the end of therapy is unusual and not consistent with the FDA guidance. However, FDA reviewers performed a reanalysis in which the TOC visit was limited to only 31 days after end of therapy. The results of this analysis did not differ overall, and therefore, it is not felt that the use of such a long period of evaluability affects the analysis of efficacy.

Secondary analyses were conducted and include microbiologic response at the pathogen and patient levels and efficacy assessments were made for monomicrobial vs. polymicrobial infections. Additional analyses have been done looking at efficacy by the presence or absence of surgical intervention.

6.1.3 Study Design

Studies 300 and 305 were multicenter, randomized, double-blind, active-controlled studies. Subjects with cSSSI were randomly assigned (1:1 ratio) to receive either tigecycline with placebo or vancomycin with aztreonam intravenously for up to 14 days. Bias was minimized by the use of blinding, randomization, and a prospective statistical analysis plan with identification of endpoints. The control group therapy included aztreonam, which has been approved for the therapy of skin and skin structure infections plus vancomycin which was an important addition because of aztreonam's lack of Gram-positive coverage. Vancomycin has excellent coverage of Gram-positive organisms and has been widely used in this setting.

This study design is appropriate for the study of cSSSI and is consistent with the definition of an adequate and well-controlled study as described in 21CFR314.126. Per that section, an adequate and well-controlled study may include the following:

"Active treatment concurrent control. The test drug is compared with known effective therapy; for example, where the condition treated is such that administration of placebo or no treatment would be contrary to the interest of the patient."

The entry criteria for these studies (see Appendix 9.1) allowed for the selection of study populations which provide adequate generalization of the study results to a typical post-approval clinical setting for this indication.

6.1.4 Efficacy Findings

Because Studies 300 and 305 were conducted using identical study designs and because the results of the two studies are consistent with each other, the efficacy findings for Studies 300 and 305 will be presented in a combined, integrated fashion. Differences between the two studies will be pointed out. For a detailed review of the results of each individual study, please refer to Appendix 9.1.

Subject Disposition

The disposition of subjects is contained in the following table. The two primary analysis populations were the CE and c-mITT populations.

Number of Subjects in Each Population Category–Pooled Data for Studies 300 and 305

	Tigecycline	Vancomycin/ Aztreonam	Total
	n (% ITT)	n (% ITT)	n (% ITT)
Screened			1153
Screened Failures			24
Intent-to-Treat (ITT)	570	559	1129
No treatment received	4	9	13
Modified Intent-to-treat (mITT)	566 (99.3)	550 (98.4)	1116 (98.8)

cSSSI did not meet minimal disease criteria	28	31	59
Clinical mITT (c-mITT)	**538 (94.4)**	**519 (92.8)**	**1057 (93.6)**
Did not meet clinical evaluability criteria	116	108	224
Clinically evaluable (CE)	**422 (74.0)**	**411 (73.5)**	**833 (73.8)**
No baseline and/or susceptible pathogens	143	150	293
Microbiologically evaluable (ME)	279 (48.9)	261 (46.7)	540 (47.8)
Microbiologic mITT (m-mITT)	395 (69.3)	374 (66.9)	769 (68.1)
No baseline pathogen identified from c-mITT	143	145	288

ITT = all randomized subjects; mITT = ITT subjects who received at least 1 dose of study drug; cSSSI = complicated skin and/or skin structure infection; c-mITT = mITT subjects with evidence of cSSSI; m-mITT = mITT subjects with identified baseline pathogen.

The following table shows the reasons for subject exclusion from the CE population for Studies 300 and 305. The most common reason for exclusion from the CE population was "blind broken." In total, 7.2% of subjects had their blind broken, which was allowable, according to the study protocols, in the event of a medical emergency. Since the patients enrolled in these studies had severe infections, this rate of unblinding, mainly due to worsening of medical condition, seems reasonable. Review of the subjects whose blind were broken revealed no significant differences between the two treatment arms in terms of outcome or cause for breaking of the blind.

Categories and Number (%) of mITT Subjects Excluded From the CE Population–Pooled Data for Studies 300 and 305

Categories[a]	Tigecycline (n = 566)	Vanco/Aztreo (n = 550)	Total (n = 1116)
Excluded from CE population, n (% of mITT)	144 (25.4)	139 (25.3)	283 (25.4)
Reason for exclusion as a CE cure/failure Blind broken[b]	42 (7.4)	38 (6.9)	80 (7.2)
Inclusion/exclusion criteria not met [c]	28 (4.9)	32 (5.8)	60 (5.4)
Pseudomonas at baseline [d]	3 (0.5)	4 (0.7)	7 (0.6)
> 2 doses of prior antibiotic after baseline culture	8 (1.4)	4 (0.7)	12 (1.1)
No clinical evaluation at test-of-cure	32 (5.7)	23 (4.2)	55 (4.9)
Reason for exclusion from CE cure group			
Test article compliance [e]	9 (1.6)	3 (0.5)	12 (1.1)
Received concomitant antibiotics	23 (4.1)	38 (6.9)	61 (5.5)
Test-of-cure after last dose [f]	8 (1.4)	5 (0.9)	13 (1.2)
Reason for exclusion from CE failure group [g]			
Did not receive at least 4 doses of study drug	7 (1.2)	17 (3.1)	24 (2.2)
Test-of-cure after 2 days [h]	3 (0.5)	11 (2.0)	14 (1.3)

CE = clinically evaluable; mITT = modified intent-to-treat population.

a: Subjects could have been excluded from the CE population for more than 1 reason.

b: A subject's study drug assignment was to be unblinded only in the case of a medical emergency

c: In 59 cases, cSSSI did not meet minimal disease criteria.

d: Sole causative pathogen.
e: Subject received less than 5 days of study drug or did not receive 80%-120% of expected dose.
f: Subject did not have test-of-cure evaluation within 12-92 day window.
g: Two (2) subjects in study 305 were excluded as CE failures because they received potentially effective antibiotics during study treatment. (Both subjects were counted in the total row of this table.)
h: Subjects did not have test-of-cure evaluation at least 2 days after start of study drug.

Patients excluded from the CE cure group in the category of "received concomitant antibiotics" were reviewed and determined to be appropriately excluded. Most of these patients received antibiotics for other indications, such as respiratory infections, and the use of such antibiotics has the potential to confound an outcome assessment of cure. Amongst patients excluded from the CE analysis because of concomitant antibiotics, there were more patients (38 or 6.9%) in the comparator arm than in the study drug arm (23 or 4.1%).

Discontinuations
The following table provides a list of the primary reasons for discontinuation from study drug for the mITT population (Studies 300 and 305 combined). Most subjects who discontinued did so because of adverse events. Unsatisfactory response occurred at a similar rate between treatment arms and was an infrequent reason for discontinuation.

Drug Discontinuations by Primary Reason Within the mITT Population: Number (%) of Subjects–Pooled Data for Studies 300 and 305

Reason[a]	Tigecycline (n = 566)	Vanco/Aztreo (n = 550)	Total (n =1116)	Fisher Exact p-Value
Total patient discontinuations	64 (11.3)	70 (12.7)	134 (12.0)	0.519
Adverse event	23 (4.1)	26 (4.7)	49 (4.4)	0.662
Patient request unrelated to study	5 (0.9)	4 (0.7)	9 (0.8)	1.000
Patient culture contained *Pseudomonas aeruginosa*[a]	2 (0.4)	0 (0.0)	2 (0.2)	0.500
Culture contained nonsusceptible pathogen	4 (0.7)	6 (1.1)	10 (0.9)	0.542
Unsatisfactory response (lack of efficacy)	9 (1.6)	16 (2.9)	25 (2.2)	0.159
Other event[b]	21 (3.7)	18 (3.3)	39 (3.5)	0.746

a: "Culture contains nonsusceptible pathogen" was specified instead of "Pseudomonas aeruginosa" for 2 subjects in study 300 (300-087-2573; 300-107-3039).

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Demography

Demographic and Baseline Characteristics of the CE Population– Pooled Data for Studies 300 and 305

Characteristic	Tigecycline (n = 422)	Vancomycin/ Aztreonam (n = 411)	Total (n = 833)	p-Value
Age, years				0.914[a]
Mean	48.36	48.49	48.43	
Standard deviation	16.44	17.20	16.81	
Minimum, maximum	18.00, 90.00	18.00, 88.00	18.00, 90.00	
Median	48.00	48.00	48.00	
≥55	150 (35.5)	151 (36.7)	301 (36.1)	0.773[b]
≥65	69 (16.4)	86 (20.9)	155 (18.6)	0.092[b]
≥75	28 (6.6)	32 (7.8)	60 (7.2)	0.592[b]
Sex, n (%)				0.830[b]
Male	260 (61.6)	257 (62.5)	517 (62.1)	
Female	162 (38.4)	154 (37.5)	316 (37.9)	
Ethnic origin, n (%)				0.872[b]
White	286 (67.8)	282 (68.6)	568 (68.2)	
Black	33 (7.8)	29 (7.1)	62 (7.4)	
Hispanic	45 (10.7)	44 (10.7)	89 (10.7)	
Asian	15 (3.6)	10 (2.4)	25 (3.0)	
Other	43 (10.2)	46 (11.2)	89 (10.7)	
Weight, kg				0.546[a]
Mean	82.09	81.16	81.63	
Standard deviation	21.41	22.77	22.09	
Minimum, maximum	40.00, 200.00	36.00, 181.00	36.00, 200.00	
Median	79.55	77.00	78.00	
Creatinine clearance, mL/min				0.168[a]
n	421	411	832	
Mean	109.08	104.90	107.02	
Standard deviation	44.35	43.13	43.78	
Minimum, maximum	28.00, 363.00	6.70, 314.00	6.70, 363.00	
Median	103.90	100.00	102.00	

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

b: Fisher exact test (2-tailed).

The demographic characteristics for the CE population were similar between the two treatment arms in terms of the various characteristics including gender, weight, creatinine clearance, gender, and ethnic background.

Diagnosis at Baseline

There were a variety of different baseline clinical diagnoses for subjects entered into Studies 300 and 305. A comparison between the two treatment arms of the different baseline diagnoses shown in the following table reveals no meaningful differences. The most common baseline diagnosis of subjects was deep soft tissue infection.

Clinical Diagnosis of Infections Within the CE Population: Number (%) of Subjects–Pooled Data for Studies 300 and 305

Clinical Diagnosis	Tigecycline (n = 422)	Vancomycin/ Aztreonam (n = 411)	Total (n = 833)	Chi-Square p-Value
Any diagnosis				0.937
Deep soft tissue infection	263 (62.3)	259 (63.0)	522 (62.7)	
Cellulitis [a]	249 (59.0)	242 (58.9)	491 (58.9)	
≥10 cm (where anatomically applicable)	226 (53.6)	215 (52.3)	441 (52.9)	
Requiring surgery/drainage	109 (25.8)	119 (29.0)	228 (27.4)	
Complicated underlying disease	51 (12.1)	67 (16.3)	118 (14.2)	
Wound infection	14 (3.3)	17 (4.1)	31 (3.7)	
Major abscesses	116 (27.5)	116 (28.2)	232 (27.9)	
Infected ulcers	30 (7.1)	23 (5.6)	53 (6.4)	
Burns	9 (2.1)	9 (2.2)	18 (2.2)	
Other	4 (0.9)	4 (1.0)	8 (1.0)	

a: Some subjects with cellulitis met more the 1 diagnostic criterion.

Underlying Medical Conditions

Because the indication sought is complicated and not uncomplicated skin and skin structure infection, the studies were designed to allow for the enrollment of subjects who had underlying illnesses that could potentially affect success rates and outcome. Such diseases include diabetes mellitus, peripheral vascular disease, IV drug use, and HIV infection. The following table shows that the distribution of these underlying conditions was similar between treatment arms.

Comorbid Medical Conditions at Baseline Within the CE Population: Number (%) of Subjects–Pooled Data for Studies 300 and 305

Comorbidity	Tigecycline (n = 422)	Vancomycin/ Aztreonam (n = 411)	Total (n = 833)	Chi-Square p-Value
Diabetes mellitus	83 (19.7)	85 (20.7)	168 (20.2)	0.716
Peripheral vascular disease	29 (6.9)	28 (6.8)	57 (6.9)	0.981
IV drug abuse (injection drug abuse)	8 (1.9)	7 (1.7)	15 (1.8)	0.834
Known HIV positive	4 (1.0)	2 (0.5)	6 (0.7)	0.440

Efficacy Results for Studies 300 and 305 Separate and Combined

The co-primary endpoints were the clinical responses for the CE and c-mITT populations at the test of cure assessment. The following tables show these efficacy analyses. The cure rates between the two treatment arms were not significantly different.

Presented below are the efficacy results for each individual study and the integrated combined analysis. Please refer to Appendix 9.1 for a detailed review of the individual studies.

Study 300: Analysis of Clinical Response: cmITT and CE Population at TOC

Visit	Response	Tigecycline		Vancomycin/ Aztreonam		Tigecycline – Vancomycin/Aztreonam	
		n/N	%	n/N	%	Difference	95% CI
c-mITT Test-of-Cure	Cure	209/277	75.5	200/260	76.9	-1.5	(-9.0, 6.1)
	Failure	48/277	17.3	46/198	17.7		
	Indeterminate	20/277	7.2	14/260	5.4		
CE Test-of-Cure	Cure	165/199	82.9	163/198	82.3	0.6	(-7.4, 8.6)
	Failure	34/199	17.1	35/198	17.7		

Study 305 Analysis of Clinical Response: cmITT and CE Population at TOC

Visit	Response	Tigecycline		Vancomycin/ Aztreonam		Tigecycline – Vancomycin/Aztreonam	
		n/N	%	n/N	%	Difference	95% CI
c-mITT Test-of-Cure	**Cure**	220/261	84.3	225/259	86.9	-2.6	(-9.0, 3.8)
	Failure	31/261	11.9	26/259	10.0		
	Indeterminate	10/261	3.8	8/259	3.1		
CE Test-of-Cure	**Cure**	200/203	89.7	201/213	94.4	-4.7	(-10.2, 0.8)
	Failure	23/223	10.3	12/213	5.6		

Analysis of Clinical Response: cmITT and CE Population at TOC for Studies 300 and 305

TOC Visit	Response	Tigecycline		Vancomycin/ Aztreonam		Tigecycline – Vancomycin/Aztreonam	
		n/N	%	n/N	%	Difference	95% CI
c-mITT	Cure	429/538	79.7	425/519	81.9	-2.1	(-7.1, 2.8)
	Failure	79/538	14.7	72/519	13.9		
	Indeterminate	30/538	5.6	22/519	4.2		
CE	Cure	365/422	86.5	364/411	88.6	-2.1	(-6.8, 2.7)
	Failure	57/422	13.5	47/411	11.4		

a: Treatment group confidence intervals calculated by using the method of Clopper and Pearson.
b: Estimates of differences between treatment groups and corresponding confidence intervals and hypothesis tests are done by using the asymptotic method (corrected for continuity).

Because the TOC assessment window included a timeframe that extended out to 92 days, it was decided that additional analyses needed to be done to determine whether the efficacy results would be significantly different if the TOC window were limited to a shorter period. Statistical reviewer, Thamban Valappil Ph. D., conducted an efficacy analysis in which he used 35 days instead of 92 days. The results of that analysis, which can be found in his review, did not result in any meaningful change in the lower bound of the 95% CI. and, therefore, did not change the overall findings of the efficacy analysis.

The sponsor conducted a logistic regression analysis for all clinical failures to determine if there were underlying factors, such as assigned treatment arm, resulting in an increased risk of clinical failure. The following factors were included in the regression analysis: treatment group, protocol, age, gender, ethnic group, geographic region, comorbid conditions such as diabetes mellitus, peripheral vascular disease, IV drug use, and HIV infection), creatinine clearance, clinical diagnosis (such as cellulitis, abscess, wound, etc.), baseline pathogen isolated, combinations of baseline pathogens isolated (including *Staphylococcus aureus* and *Streptococcus pyogenes, Staphylococcus aureus* and *Escherichia coli, Escherichia coli* and *Bacteroides*, *Staphylococcus aureu*s and *Bacteroides).*

Analysis of Failures Within the CE and c-mITT Populations – Pooled Data From Studies 300 and 305

Population	n	Significant Factors	Characterization of Response[a]	Wald p-Value	Odds Ratio	95% Wald CI
CE	831	Diabetes	**Yes** vs No	<0.0001	2.97	1.90, 4.63
		Geographical Region	**Other Countries** vs Eastern Europe	0.0009	2.50	1.46, 4.28
c-mITT	1052	Diabetes	**Yes** vs No	0.0001	2.03	1.42, 2.90
		Geographical Region	**Other Countries** vs Eastern Europe	0.0024	1.81	1.24, 2.66
		Creatinine Clearance		0.0167		
			30 to 70 vs ≥ 70		1.10	0.73, 1.65
			<30 vs ≥ 70		10.50	2.03, 54.30
		PVD	**Yes** vs No	0.0190	1.87	1.11, 3.15
		Pseudomonas as a Polymicrobial Infection	**Yes** vs No	0.0255	2.72	1.13, 6.58

a: Response modeled is bolded. Only odds ratios (and CIs) for statistically significant comparisons (p<0.05) are shown. These odds ratios should be considered as descriptive statistics.
Source: Failure Analysis/fail06d, fail07d

The factors found to be associated with a higher rate of clinical failure are ones that have been previously recognized, such as diabetes, renal insufficiency, and peripheral vascular disease. It is unclear why Eastern European subjects had a lower risk of clinical failure than subjects from other regions. The patient population enrolled from Eastern Europe did have some fundamental differences from the subject population enrolled from other regions. These differences include lower rates of diabetes mellitus (10.7% vs. 25.4%), IV drug use (0.0% vs. 2.8%), MRSA infection (3.0% vs. 10.5%), initial diagnosis of cellulitis (38.3% vs. 70.5%), and higher rates of abscesses (43.3% vs. 19.3%), and MSSA infections (49.0% vs. 32.9%). Since the Eastern European subjects had a lower rate of diabetes mellitus, it is tempting to ascribe the higher success rate to this. However, the difference in diabetes rates, as well as other differences, should have been controlled for in the regression analysis, so they cannot necessarily explain why there is a lower failure rate in the subjects from Eastern Europe. The noted differences do indicate that there are

some fundamental differences between the Eastern European subject population and those from other regions that has resulted in higher cure rates. Because study 305 was the study that enrolled patients from Eastern Europe, the overall cure rates in this study were somewhat higher than those for study 300, and this difference is largely driven by the efficacy results of the subjects enrolled from the Eastern European region.

Efficacy Analyses for Subpopulations
The sponsor conducted several efficacy analyses for various subpopulations. The factors defining the subpopulations included: age; gender; ethnicity; creatinine clearance; initial clinical diagnosis; presence of diabetes mellitus; presence of peripheral vascular disease; and presence of bacteremia. Medical officer review of these analyses did not reveal any differences great enough to suggest that there might be a difference in efficacy amongst these subpopulations. The number of patients with bacteremia was small. The following table summarizes the clinical response in bacteremia patients for studies 300 and 305.

Tigecycline-Treated Subjects With Bacteremia at Baseline in the CE Population and Clinical Response at the Test-of-Cure Assessment

Bacteremia at baseline Blood isolate	Clinical Response [a]
Total Contaminants [b]	9/10
Staphylococcus epidermidis	4/5
Staphylococcus hominis	3/3
Micrococcus lylae	1/1
Staphylococcus cohnii	1/1
Staphylococcus sanguis	1/1
Staphylococcus warneri	1/1
Non-contaminants[b]	10/13
Staphylococcus aureus	6/8
Staphylococcus epidermidis	1/2
Enterobacter aerogenes	0/1
Enterococcus faecalis	1/1
Enterococcus faecium	1/1
Klebsiella oxytoca	1/1
Propionibacterium acnes	1/1
Staphylococcus hominis	0/1
Streptococcus oralis	1/1
Streptococcus pyogenes	1/1
Streptococcus salivarius	1/1

a: At the test-of-cure assessment
b: More than one blood isolate may have been present in a subject with bacteremia.

6.1.5 Clinical Microbiology

The following table shows an analysis of the microbiolgic response at the Subject level for the microbiological modified Intent-to-Treat population separated by study.

Analysis of Microbiologic Response at the Subject Level Within the m-mITT Population at the TOC visit

Response		Tigecycline n/N	Tigecycline %	Vancomycin/Aztreonam n/N	Vancomycin/Aztreonam %	Difference (Tigecycline-Vancomycin/Aztreonam) Test for % (95% CI) Noninferiority
Study 300-US/CA						
Eradication		135/ 186	72.6	125/ 171	73.1	-0.5 (-10.3, 9.3)
	Documented	7/ 135	5.2	10/ 125	8.0	
	Presumed	128/ 135	94.8	115/ 125	92.0	
Persistence		34/ 186	18.3	33/ 171	19.3	
	Documented	11/ 34	32.4	9/ 33	27.3	
	Presumed	23/ 34	67.6	24/ 33	72.7	
Superinfection		5/ 186	2.7	7/ 171	4.1	
Study 305-WW						
Eradication		166/209	79.4	171/203	84.2	-4.8 (-12.7, 3.1)
	Documented	12/166	7.2	18/171	10.5	
	Presumed	154/166	92.8	153/171	89.5	
Persistence		34/209	16.3	22/203	10.8	
	Documented	18/34	52.9	7/22	31.8	
	Presumed	16/34	47.1	15/22	68.2	
Superinfection		5/209	2.4	4/203	2.0	

The following tables show the microbiologic response for selected baseline isolates at the Test of Cure for the microbiologically evaluable population

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Microbiologic Response for Selected Baseline Isolates at Test-of-Cure in the ME Population - Study 3074A1-300-US/CA

		--Tigecycline 50 mg---		--Vancomycin/Aztreonam---	
Pathogen	Response	n/Total	% (95% CI)	n/Total	% (95% CI)
Staphylococcus aureus (MRSA)	Eradication	16/22	72.7(49.8, 89.3)	21/26	80.8(60.6, 93.4)
	Documented	1/16	6.3	4/21	19.0
	Presumed	15/16	93.8	17/21	81.0
	Persistence	6/22	27.3	5/26	19.2
	Documented	1/6	16.7	1/5	20.0
	Presumed	5/6	83.3	4/5	80.0
Staphylococcus aureus (MSSA)	Eradication	41/45	91.1(78.8, 97.5)	35/43	81.4(66.6, 91.6)
	Documented	3/41	7.3	3/35	8.6
	Presumed	38/41	92.7	32/35	91.4
	Persistence	4/45	8.9	8/43	18.6
	Documented	1/4	25.0	4/8	50.0
	Presumed	3/4	75.0	4/8	50.0
Streptococcus pyogenes	Eradication	6/7	85.7 (42.1, 99.6)	6/8	75.0 (34.9, 96.8)
	Documented	0/6	0.0	0/6	0.0
	Presumed	6/6	100.0	6/6	100.0
	Persistence	1/7	14.3	2/8	25.0
	Documented	0/1	0.0	1/2	50.0
	Presumed	1/1	100.0	1/2	50.0
Streptococcus agalactiae	Eradication	3/3	100.0 (29.2,100.0)	7/9	77.8 (40.0, 97.2)
	Documented	0/3	0.0	1/7	14.3
	Presumed	3/3	100.0	6/7	85.7
	Persistence	0/3	0.0	2/9	22.2
	Documented	0/0	NA	1/2	50.0
	Presumed	0/0	NA	1/2	50.0
Enterococcus faecalis[a]	Eradication	8/8	100.0 (63.1,100.0)	8/10	80.0 (44.4, 97.5)
	Documented	3/8	37.5	3/8	37.5
	Presumed	5/8	62.5	5/8	62.5
	Persistence	0/8	0.0	2/10	20.0
	Documented	0/0	NA	1/2	50.0
	Presumed	0/0	NA	1/2	50.0
Escherichia coli	Eradication	4/7	57.1 (18.4, 90.1)	5/7	71.4 (29.0, 96.3)
	Documented	1/4	25.0	1/5	20.0
	Presumed	3/4	75.0	4/5	80.0
	Persistence	3/7	42.9	2/7	28.6
	Documented	3/3	100.0	1/2	50.0
	Presumed	0/3	0.0	1/2	50.0
Bacteroides fragilis	Eradication	2/2	100.0 (15.8,100.0)	1/2	50.0 (1.3, 98.7)
	Documented	1/2	50.0	1/1	100.0
	Presumed	1/2	50.0	0/1	0.0
	Persistence	0/2	0.0	1/2	50.0
	Documented	0/0	NA	0/1	0.0
	Presumed	0/0	NA	1/1	100.0

Microbiologic Response for Selected Baseline Isolates at Test-of-Cure in the ME Population - Study 3074A1-305-WW

Pathogen	Response	--Tigecycline 50 mg--- n/Total	% (95% CI)	--Vancomycin/Aztreonam--- n/Total	% (95% CI)
Staphylococcus aureus (MRSA)	Eradication	8/9	88.9 (51.8, 99.7)	4/7	57.1 (18.4, 90.1)
	Documented	0/8	0.0	0/4	0.0
	Presumed	8/8	100.0	4/4	100.0
	Persistence	1/9	11.1	3/7	42.9
	Documented	0/1	0.0	1/3	33.3
	Presumed	1/1	100.0	2/3	66.7
Staphylococcus aureus (MSSA)	Eradication	79/90	87.8 (79.2, 93.7)	74/77	96.1 (89.0, 99.2)
	Documented	8/79	10.1	2/74	2.7
	Presumed	71/79	89.9	72/74	97.3
	Persistence	11/90	12.2	3/77	3.9
	Documented	8/11	72.7	3/3	100.0
	Presumed	3/11	27.3	0/3	0.0
Streptococcus pyogenes	Eradication	24/25	96.0 (79.6, 99.9)	19/19	100.0 (82.4,100.0)
	Documented	3/24	12.5	3/19	15.8
	Presumed	21/24	87.5	16/19	84.2
	Persistence	1/25	4.0	0/19	0.0
	Documented	1/1	100.0	0/0	NA
	Presumed	0/1	0.0	0/0	NA
Streptococcus agalactiae	Eradication	4/5	80.0 (28.4, 99.5)	4/4	100.0 (39.8,100.0)
	Documented	1/4	25.0	0/4	0.0
	Presumed	3/4	75.0	4/4	100.0
	Persistence	1/5	20.0	0/4	0.0
	Documented	1/1	100.0	0/0	NA
	Presumed	0/1	0.0	0/0	NA
Enterococcus faecalis[a]	Eradication	6/8	75.0 (34.9, 96.8)	14/14	100.0 (76.8,100.0)
	Documented	2/6	33.3	3/14	21.4
	Presumed	4/6	66.7	11/14	78.6
	Persistence	2/8	25.0	0/14	0.0
	Documented	1/2	50.0	0/0	NA
	Presumed	1/2	50.0	0/0	NA
Escherichia coli	Eradication	20/22	90.9 (70.8, 98.9)	22/23	95.7 (78.1, 99.9)
	Documented	1/20	5.0	1/22	4.5
	Presumed	19/20	95.0	21/22	95.5
	Persistence	2/22	9.1	1/23	4.3
	Documented	1/2	50.0	0/1	0.0
	Presumed	1/2	50.0	1/1	100.0
Bacteroides fragilis	Eradication	6/6	100.0 (54.1,100.0)	3/3	100.0 (29.2,100.0)
	Documented	1/6	16.7	0/3	0.0
	Presumed	5/6	83.3	3/3	100.0

The following summarizes the test-of-cure clinical cure rates of selected baseline isolates in the ME population in studies 300 and 305. The clinical cure rates of the selected pathogens correlate with their microbiologic eradication rates at the test-of-cure assessment.

Clinical Cure Rates of Selected Baseline Isolates at Test-of-Cure for ME Population

	Cured/Total (%)			
	-------- Tigecycline -----		-- Vancomycin/Aztreonam--	
Pathogen	n/N	% (95% CI)	n/N	% (95% CI)
Study 3074A1-300-US/CA				
Staphylococcus aureus (MRSA)	16/22	72.7(49.8, 89.3)	20/26	76.9(56.4, 91.0)
Staphylococcus aureus (MSSA)	39/46	84.8(71.1, 93.7)	36/43	83.7(69.3, 93.2)
Streptococcus pyogenes	6/7	85.7 (42.1, 99.6)	6/8	75.0 (34.9, 96.8)
Streptococcus agalactiae	3/3	100.0 (29.2,100.0)	7/9	77.8 (40.0, 97.2)
Enterococcus faecalis a	7/8	87.5 (47.3, 99.7)	8/12	66.7 (34.9, 90.1)
Escherichia coli	4/8	50.0 (15.7, 84.3)	4/7	57.1 (18.4, 90.1)
Bacteroides fragilis	1/2	50.0 (1.3, 98.7)	1/2	50.0 (1.3, 98.7)
Study 3074A1-305-WW				
Staphylococcus aureus(MRSA)	8/9	88.9 (51.8, 99.7)	5/7	71.4 (29.0, 96.3)
Staphylococcus aureus(MSSA)	84/90	93.3 (86.1, 97.5)	77/77	100.0 (95.3,100.0)
Streptococcus pyogenes	25/25	100.0 (86.3,100.0)	18/19	94.7 (74.0, 99.9)
Streptococcus agalactiae	5/5	100.0 (47.8,100.0)	4/4	100.0 (39.8,100.0)
Enterococcus faecalis a	5/8	62.5 (24.5, 91.5)	13/14	92.9 (66.1, 99.8)
Escherichia coli	21/22	95.5 (77.2, 99.9)	22/23	95.7 (78.1, 99.9)
Bacteroides fragilis	5/6	83.3 (35.9, 99.6)	3/3	100.0 (29.2,100.0)

6.1.6 Efficacy Conclusions for complicated Skin and Skin Structure Infection

Tigecycline was found to be non-inferior to comparator for the co-primary efficacy endpoints. This finding was supported by multiple secondary and subgroup analyses including presence or absence of diabetes mellitus. Microbiologic analyses of outcome at the subject and pathogen levels did not show significant differences between the study drug and the comparator.

6.2 Indication – Complicated Intra-abdominal Infection (cIAI)

In general, this indication encompasses intra-abdominal infections that require surgical intervention, including those caused by penetrating or blunt trauma. These infections are ones that extend beyond the hollow viscus of organ into the peritoneal space and are associated with abscess formation and/or peritonitis. Such infections may be community-acquired or health care-associated infections (such as complications of previous elective or emergent intra-abdominal operations).

6.2.1 Methods

The primary clinical data which were used in this efficacy review to support the proposed indication were collected from two nearly identically designed pivotal studies, Study 301 and Study 306. These two studies were purposely "harmonized" by the sponsor so that a meaningful combined analysis could be conducted. Case report forms, datasets, and the sponsor's study report were reviewed. Individual review of these studies can be found in Appendix 9.1. In this section, a combined analysis will be presented.

6.2.2 General Discussion of Endpoints

The primary efficacy endpoint was the clinical response for the Microbiologically Evaluable (ME) and Microbiologic Modified Intent-to-Treat (m-mITT) populations at the test-of-cure assessments. These two efficacy assessments were regarded as "co-primary" endpoints; however, there was no adjustment for multiplicity. The m-mITT population included patients who met the clinical criteria for cIAI as defined in the inclusion criteria, had at least 1 or more baseline pathogens isolated, and received at least one dose of study drug. The ME population is a per protocol population who also had 1 or more pathogens isolated at baseline from an intra-abdominal culture. These populations were selected for the analysis of the primary endpoints in order to ensure a high degree of certainty that the patients who were included in the analysis actually had the disease under study.

The timing of the TOC visit was between 12 and 44 days after the last dose of study drug (except for subjects with a clinical response of failure). Because of tigecycline's long half-life, it was preferable to have the TOC visit occur far enough out that it could be ensured that there was no lingering drug effect.

Detailed assessments of the subjects' clinical status were performed by the investigators at each study visit, including at baseline. Based on these assessments, the investigators evaluated the subjects' response to therapy using pre-specified definitions of cure and failure.

As part of the complicated intra-abdominal infection studies, a surgical review board (SRB) composed of investigators and non-investigators assessed the adequacy of the initial surgical or interventional radiology procedure for subjects with intra-abdominal infections classified as clinical failures and for subjects whose deaths met criteria to be classified as clinically indeterminate. The purpose of this review was to attempt to distinguish between true antibiotic failure vs. an inadequate initial procedure which could

preclude any chance of antibiotic success. The SRB also determined whether there was evidence of clinical failure at the time of a second surgical procedure in subjects determined to be clinical cures who had a second surgical procedure performed prior to the test-of-cure assessment. All subjects considered for review were identified before the database was unblinded. These adjudicated assessments were documented according to the charter of the SRB and were used in secondary efficacy analyses.

6.2.3 Study Design

The study design for Studies 301 and 306 were harmonized to be nearly identical to each other. These studies were phase 3, multicenter, double-blind, studies which compared the safety and efficacy of tigecycline to imipenem/cilastin in hospitalized subjects with cIAI. Patients were stratified at randomization according to severity of disease (APACHE II score of ≤ 15, or APACHE II score of >15), although the most severely ill patients (those with APACHE II score>30) were excluded. Subjects were randomly assigned in a 1:1 ratio to receive either intravenous (IV) tigecycline or IV imipenem/cilastatin. Treatment duration was 5-14 days, with those whose anticipated duration of therapy was possibly <5 days excluded from the study. Assessment of cure at TOC was conducted no earlier than 12 day after the end of therapy and no later than 44 days.

Choice of comparator
Imipenem/cilastin is an acceptable choice for use as a comparator. It has broad coverage against most of the typical causative organisms for this disease and is approved for the treatment of intra-abdominal infections.

Entry Criteria
The full entry criteria can be found in Appendix 9.1. The criteria employed by Studies 301 and 306 were designed to allow for the exclusion of patients who had uncomplicated intra-abdominal infections. The entry criteria required that subjects have either had or were candidates for a surgical procedure such as a laparotomy, laparoscopy, or percutaneous drainage of an intra-abdominal abscess. Multiple examples of acceptable cIAI infections were provided in the inclusion criteria and include a broad range of infections such as traumatic bowel perforations, peritonitis with fecal contamination, perforated appendicitis, and other perforations (small and large intestines, gastric or duodenal ulcer), and perforated diverticulitis with abscess formation or fecal contamination. The primary exclusion criteria mainly addressed patients with concomitant conditions that could confound the assessment of efficacy. Examples include patients immunosuppressed as the result of malignancy or HIV infection, patients with significant hepatic or renal insufficiency, neutropenia, and extremely ill subjects (APACHE II >30).

These entry criteria are specific enough to ensure the right patient population was studied, yet broad enough to allow for good generalizability to the patients likely to be treated in the post-marketing setting.

6.2.4 Efficacy Findings

The co-primary efficacy populations were the ME and m-mITT populations and the endpoints were the clinical outcome of these populations at TOC. A more detailed discussion of endpoints can be found in section 6.2.2. For the purposes of the integrated review of efficacy, data from Studies 301 and 306 have been merged. For individual study results, please refer to Appendix 9.1.

Study Populations

The following table shows the disposition of patients to the various population categories for studies 301 and 306.

Number of Subjects in Each Population Category – Pooled Data From Studies 301 and 306

Population	Tigecycline n (% ITT)	Imipenem/ Cilastatin n (% ITT)	Total n (% ITT)
Screened			1759
Screen failures	NA	NA	101
Intent-to-Treat (ITT)	826	832	1658
No treatment received	9	7	16
Modified Intent-to-treat (mITT)	817 (98.9)	825 (99.2)	1642 (99.0)
cIAI did not meet minimal disease criteria	16	25	41
Clinical mITT (c-mITT)	801 (97.0)	800 (96.2)	1601 (96.6)
Did not meet clinical evaluability criteria	116	103	219
Clinically evaluable (CE)	685 (82.9)	697 (83.8)	1382 (83.4)
No baseline and/or susceptible isolate	173	184	357
Microbiologically evaluable (ME)	512 (62.0)	513 (61.7)	1025 (61.8)
Microbiologic mITT (m-mITT)	631 (76.4)	631 (75.8)	1262 (76.1)
No baseline isolate identified from c-mITT	170	169	339

ITT = all randomized subjects; mITT = ITT subjects who received at least 1 dose of study drug; NA = not applicable; c-mITT = mITT subjects with evidence of cIAI; m-mITT = mITT subjects with identified baseline isolate.

The following table provides the primary reasons for discontinuation from the study drug for the mITT population. The most frequent reason reported for discontinuation of therapy was an adverse event. A relatively small number of patients withdrew due to lack of efficacy.

Drug Discontinuations by Primary Reason With Intra-abdominal Infection Within the mITT Population – Pooled Data From Studies 301 and 306

Reason	Tigecycline (n = 817)	Imipenem/ Cilastatin (n = 825)	Total (n = 1642)	Fisher Exact p-Value
Total subject discontinuations	99 (12.1)	72 (8.7)[a]	171 (10.4)	0.029
Adverse event	41 (5.0)	32 (3.9)	73 (4.4)	0.283
Subject request unrelated to study	16 (2.0)	4 (0.5)	20 (1.2)	0.007
Subject culture contained *Pseudomonas aeruginosa*	1 (0.1)	2 (0.2)	3 (0.2)	1.000
Culture contains nonsusceptible pathogen	11 (1.3)	5 (0.6)	16 (1.0)	0.140
Unsatisfactory response (lack of efficacy)	10 (1.2)	13 (1.6)	23 (1.4)	0.676
Other event[b]	20 (2.4)	17 2.1)	37 (2.3)	0.622

a: One subject (081-1579) is represented in more than one category (discontinued for 2 reasons: culture contains pathogen and unsatisfactory response).
b: Other events included death, protocol violation, withdrawal of consent, subject request, subject recovery, and clinical failure.

Demography
The following table shows demographic information for patients in the ME population. No significant differences were seen. This was also true for the mITT population as well.

Demographic and Baseline Characteristics Within the ME Population – Pooled Data From Studies 301 and 306

Characteristic	Tigecycline (n = 512)	Imipenem/ Cilastatin (n = 513)	Total (n = 1025)	p-Value [a,b]
Age, years				0.911 [a]
Mean	45.90	46.03	45.96	
Standard deviation	18.22	18.02	18.11	
Minimum, maximum	18.00, 91.00	18.00, 90.00	18.00, 91.00	
Median	45.00	47.00	46.00	
Sex, n (%)				0.813 [b]
Male	330 (64.5)	327 (63.7)	657 (64.1)	
Female	182 (35.5)	186 (36.3)	368 (35.9)	
Ethnic origin, n (%)				0.489 [b]
White	342 (66.8)	335 (65.3)	677 (66.0)	
Black	22 (4.3)	32 (6.2)	54 (5.3)	
Asian	46 (9.0)	47 (9.2)	93 (9.1)	
Hispanic	54 (10.5)	44 (8.6)	98 (9.6)	
Other	48 (9.4)	55 (10.7)	103 (10.0)	
Weight, kg				0.802 [a]
N	512	512	1024	
Mean	72.38	72.14	72.26	
Standard deviation	15.34	15.82	15.58	
Minimum, maximum	39.00, 136.09	40.00, 179.00	39.00, 179.00	
Median	70.00	70.00	70.00	
Creatinine clearance, mL/min				0.490 [a]
N	511	513	1024	
Mean	94.69	93.33	94.01	
Standard deviation	32.55	30.57	31.57	
Minimum, maximum	30.04, 281.00	33.78, 207.08	30.04, 281.00	
Median	92.19	91.00	91.76	
APACHE II Score				0.948 [a]
N	511	513	1024	
Mean	5.92	5.90	5.91	
Standard deviation	4.18	3.76	3.97	
Minimum, maximum	0.00, 25.00	0.00, 25.00	0.00, 25.00	
Median	5.00	6.00	5.00	
APACHE II Score, n (%)				0.193 [b]
N	511	513	1024	
≤15	497 (97.3)	505 (98.4)	1002 (97.9)	
> 15	14 (2.7)	8 (1.6)	22 (2.1)	

The following table provides information on the baseline clinical diagnosis for patients in the ME population. The rates of each type of infection were similar between the

treatment arms. The same analysis was performed for the mITT population which also showed no significant differences.

Clinical Diagnosis of Infections Within the m-mITT Population – Pooled Data From Studies 301 and 306

Characteristic	Tigecycline (n = 631)	Imipenem/ Cilastatin (n = 631)	Total (n = 1262)	p-Value[a]
Clinical Diagnosis, n (%)				0.728 [a]
Complicated appendicitis	319 (50.6)	307 (48.7)	626 (49.6)	
Complicated cholecystitis	81 (12.8)	95 (15.1)	176 (13.9)	
Intra-abdominal abscess	68 (10.8)	58 (9.2)	126 (10.0)	
Perforation of intestine	67 (10.6)	59 (9.4)	126 (10.0)	
Complicated diverticulitis	39 (6.2)	49 (7.8)	88 (7.0)	
Gastric/duodenal perforation	33 (5.2)	36 (5.7)	69 (5.5)	
Peritonitis	21 (3.3)	22 (3.5)	43 (3.4)	
Other[b]	3 (0.5)	5 (0.8)	8 (0.6)	

a: Chi-Square test.

b: Other diagnoses included (not limited to one per patient) infected hematoma, pelvic inflammatory disease, acute abdomen subocclusion, acute inflammatory abdomen, disease pelvic infectious, tubo-ovarian abscess, right tubal abscess, infected left subphrenic hematoma, complicated salpingitis, pyosalpinx, peritonitis due to left pyoovarium (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.

The following table shows a summary of the surgical assessment within the mITT population for patients in studies 301 and 306. The purpose of this table is to compare detailed characteristics of the subjects' infections to ensure that there were no fundamental differences in the types of infections between the two treatment arms.

Summary of Initial Surgical Assessment within the mITT Population from Studies 301 and 306

Characteristic	Tigecycline (n = 817)	Imipenem/ Cilastatin (n = 825)	Total (n = 1642)	p-Value [a]
Presence of abscess, n (%)				0.588
n	816	824	1640	
No abscess	249 (30.5)	267 (32.4)	516 (31.5)	
Single abscess	482 (59.1)	466 (56.6)	948 (57.8)	
Multiple abscess	85 (10.4)	91 (11.0)	176 (10.7)	
Size of abscess, n (%)				0.471
n	560	557	1117	
<10 mL	89 (15.9)	86 (15.4)	175 (15.7)	
10 to 100 mL	284 (50.7)	302 (54.2)	586 (52.5)	
>100 mL	187 (33.4)	169 (30.3)	356 (31.9)	
Extent of residual contamination, n (%)				0.144
n	810	818	1628	
None	241 (29.8)	276 (33.7)	517 (31.8)	
Minimal	425 (52.5)	396 (48.4)	821 (50.4)	
Moderate	138 (17.0)	134 (16.4)	272 (16.7)	
Extensive	6 (0.7)	12 (1.5)	18 (1.1)	
Fecal contamination, n (%)				0.765
n	809	809	1618	
Yes	182 (22.5)	177 (21.9)	359 (22.2)	
No	627 (77.5)	632 (78.1)	1259 (77.8)	
Peritonitis, n (%)				0.153
n	816	821	1637	
Yes	621 (76.1)	649 (79.1)	1270 (77.6)	
No	195 (23.9)	172 (21.0)	367 (22.4)	

Exposure

The following table shows the duration of treatment in days and the number doses of study drug that were administered for the treatment arms. There were no significant differences in the duration of exposure or number of doses received between the study and control drugs.

Duration of Treatment and Number of Doses Received for the mITT population for Studies 301 and 306

Characteristic	Tigecycline (n = 817)	Imipenem (n = 825)	Total (n = 1642)	p-Value
Distribution of days of therapy duration, n(%)				0.598
< 5	53 (6.5)	36 (4.4)	89 (5.4)	
5	75 (9.2)	84 (10.2)	159 (9.7)	
6	191 (23.4)	201 (24.4)	392 (23.9)	
7	156 (19.1)	147 (17.8)	303 (18.5)	
8	93 (11.4)	118 (14.3)	211 (12.9)	
9	73 (8.9)	69 (8.4)	142 (8.6)	
10	44 (5.4)	47 (5.7)	91 (5.5)	
11	41 (5.0)	38 (4.6)	79 (4.8)	
12	22 (2.7)	21 (2.5)	43 (2.6)	
13	21 (2.6)	15 (1.8)	36 (2.2)	
14	32 (3.9)	28 (3.4)	60 (3.7)	
15	14 (1.7)	20 (2.4)	34 (2.1)	
> 15	2 (0.2)	1 (0.1)	3 (0.2)	
Therapy duration in days				0.898
Mean	7.70	7.71	7.71	
Standard deviation	2.81	2.71	2.76	
Minimum, maximum	1.00, 17.00	1.00, 17.00	1.00, 17.00	
Median	7.00	7.00	7.00	

Clinical Outcome

The following table show the clinical outcome for the two phase 3, controlled, blinded clinical trials that studied cIAI. The co-primary endpoints were clinical outcome at the test of cure visit for the ME and the m-mITT populations. There were no significant differences between tigecycline and study drug for the two analysis populations.

Studies 301 and 306 Combined - Clinical Response: Microbiologically Evaluable and m-m-ITT Populations							
		Tigecycline		Imipenem/Cilastatin		(Tigecycline - Imipenem/Cilastatin)	
Analysis Response	APACHE II Score	n/N	%	n/N	%	Difference	(95%CI)
ME							
Cure	≤15	432/498	86.7	440/505	87.1	-0.4	(-4.8, 4.0)
	> 15	9/14	64.3	2/ 8	25.0	39.3	(-9.7, 88.2)
	Overall	441/512	86.1	442/513	86.2	0.0	(-4.5, 4.4)
Failure		71/512	13.9	71/513	13.8		
m-mITT							
Cure	≤15	490/609	80.5	510/618	82.5	-2.1	(-6.6, 2.4)
	> 15	16/ 22	72.7	4/ 13	30.8	42.0	(4.6, 79.3)
	Overall	506/631	80.2	514/631	81.5	-1.3	(-5.8, 3.2)
Failure		97/631	15.4	91/631	14.4		
Indeterminate		28/631	4.4	26/631	4.1		

The sponsor conducted a subgroup analysis of clinical responses n the ME population on the pooled data from Studies 301 and 306 using a generalized linear model. The interaction effects of treatment were examined for the following factors: age, gender, ethnicity, clinical diagnosis, creatinine clearance, and bacteremia status. No significant interactions were identified.

Secondary Analyses

Multiple secondary efficacy analyses for the ME and MITT populations were conducted by the sponsor including the following: adequate vs. inadequate source control as determined by a blinded independent surgical review board; monomicrobial vs. polymicrobial infection; microbiological response at the subject level; microbiological response at the pathogen level; and clinical cure at the pathogen level. A detailed review of these analyses was performed by the Medical Officer, and no significant differences between treatment arms were noted.

6.2.5 Clinical Microbiology

The following table shows the microbiologic response at the pathogen level for the most common organisms at the test of cure assessment for the ME population, pooled by studies 301 and 306. Analyses were conducted for all organisms isolated. For those organisms where there were no differences in outcome amongst the different sub-species, the organisms are presented grouped. Analyses of microbiologic response at the pathogen level were also done for the m-mITT population, and a detailed review revealed no significant differences between them and the ME analyses. These analyses were also conducted for selected "primary pathogen" isolates which were felt to be the etiologic infecting organism; these analyses also did not differ in a meaningful way from the ones presented in the following table.

It is interesting to note that although tigecycline does not have activity against *Pseudomonas aeruginosa*, in contrast to the comparator which has excellent activity against *Pseudomonas aeruginosa*, when comparing eradication rates for pseudomonas between the arms, there was no appreciable difference (84.6% eradication for tigecycline-treated patients vs. 86.1% eradication for imipenem-treated patients). This finding is reassuring, and may have to do with factors such as the relatively low virulence in immunocompetent patients, the dynamics of polymicrobial infections, and the beneficial effects of surgical drainage and irrigation.

Microbiologic Response at the Pathogen Level by Selected Baseline Isolate at the Test-Of-Cure Assessment Within the ME Population – Pooled Data From Studies 301 and 306

			Tigecycline			Imipenem/Cilastatin		
Isolate	Response		n/N	%	(95% CI)	n/N	%	(95%CI)
Bacteroides sp.	Eradication		153/184	83.2	(76.9, 88.3)	139/171	81.3	(74.6, 86.8)
		Documented	7/153	4.6	(1.9, 9.2)	1/139	0.7	(0.0, 3.9)
		Presumed	146/153	95.4	(90.8, 98.1)	138/139	99.3	(96.1,100.0)
	Persistence		31/184	16.8	(11.7, 23.1)	32/171	18.7	(13.2, 25.4)
		Documented	1/ 31	3.2	(0.1, 16.7)	0/ 32	0.0	(0.0, 10.9)
		Presumed	30/ 31	96.8	(83.3, 99.9)	32/ 32	100.0	(89.1,100.0)
Citrobacter sp.	Eradication		24/ 28	85.7	(67.3, 96.0)	11/ 16	68.8	(41.3, 89.0)
		Documented	0/ 24	0.0	(0.0, 14.2)	0/ 11	0.0	(0.0, 28.5)
		Presumed	24/ 24	100.0	(85.8,100.0)	11/ 11	100.0	(71.5,100.0)
	Persistence		4/ 28	14.3	(4.0, 32.7)	5/ 16	31.3	(11.0, 58.7)
		Documented	0/ 4	0.0	(0.0, 60.2)	0/ 5	0.0	(0.0, 52.2)
		Presumed	4/ 4	100.0	(39.8,100.0)	5/ 5	100.0	(47.8,100.0)
Clostridium sp.	Eradication		43/ 47	91.5	(79.6, 97.6)	39/ 46	84.8	(71.1, 93.7)
		Documented	2/ 43	4.7	(0.6, 15.8)	0/ 39	0.0	(0.0, 9.0)
		Presumed	41/ 43	95.3	(84.2, 99.4)	39/ 39	100.0	(91.0,100.0)
	Persistence		4/ 47	8.5	(2.4, 20.4)	7/ 46	15.2	(6.3, 28.9)
		Documented	0/ 4	0.0	(0.0, 60.2)	0/ 7	0.0	(0.0, 41.0)
		Presumed	4/ 4	100.0	(39.8,100.0)	7/ 7	100.0	(59.0,100.0)
Enterobacter sp.	Eradication		22/ 24	91.7	(73.0, 99.0)	17/ 22	77.3	(54.6, 92.2)
		Documented	1/ 22	4.5	(0.1, 22.8)	0/ 17	0.0	(0.0, 19.5)
		Presumed	21/ 22	95.5	(77.2, 99.9)	17/ 17	100.0	(80.5,100.0)
	Persistence		2/ 24	8.3	(1.0, 27.0)	5/ 22	22.7	(7.8, 45.4)
		Documented	0/ 2	0.0	(0.0, 84.2)	0/ 5	0.0	(0.0, 52.2)
		Presumed	2/ 2	100.0	(15.8,100.0)	5/ 5	100.0	(47.8,100.0)

Microbiologic Response at the Pathogen Level by Selected Baseline Isolate at the Test-Of-Cure Assessment Within the ME Population – Pooled Data From Studies 301 and 306

			Tigecycline			Imipenem/Cilastatin		
Isolate	Response		n/N	%	(95% CI)	n/N	%	(95%CI)
Enterococcus sp. (non-VRE)	Eradication		63/ 82	76.8	(66.2, 85.4)	77/ 98	78.6	(69.1, 86.2)
		Documented	2/ 63	3.2	(0.4, 11.0)	3/ 77	3.9	(0.8, 11.0)
		Presumed	61/ 63	96.8	(89.0, 99.6)	74/ 77	96.1	(89.0, 99.2)
	Persistence		19/ 82	23.2	(14.6, 33.8)	21/ 98	21.4	(13.8, 30.9)
		Documented	2/ 19	10.5	(1.3, 33.1)	0/ 21	0.0	(0.0, 16.1)
		Presumed	17/ 19	89.5	(66.9, 98.7)	21/ 21	100.0	(83.9,100.0)
Escherichia coli	Eradication		280/325	86.2	(81.9, 89.7)	296/340	87.1	(83.0, 90.4)
		Documented	5/280	1.8	(0.6, 4.1)	0/296	0.0	(0.0, 1.2)
		Presumed	275/280	98.2	(95.9, 99.4)	296/296	100.0	(98.8,100.0)
	Persistence		45/325	13.8	(10.3, 18.1)	44/340	12.9	(9.6, 17.0)
		Documented	6/ 45	13.3	(5.1, 26.8)	2/ 44	4.5	(0.6, 15.5)
		Presumed	39/ 45	86.7	(73.2, 94.9)	42/ 44	95.5	(84.5, 99.4)
Klebsiella oxytoca	Eradication		19/ 20	95.0	(75.1, 99.9)	17/ 19	89.5	(66.9, 98.7)
		Documented	0/ 19	0.0	(0.0, 17.6)	0/ 17	0.0	(0.0, 19.5)
		Presumed	19/ 19	100.0	(82.4,100.0)	17/ 17	100.0	(80.5,100.0)
	Persistence		1/ 20	5.0	(0.1, 24.9)	2/ 19	10.5	(1.3, 33.1)
		Documented	0/ 1	0.0	(0.0, 97.5)	0/ 2	0.0	(0.0, 84.2)
		Presumed	1/ 1	100.0	(2.5,100.0)	2/ 2	100.0	(15.8,100.0)
Klebsiella pneumoniae	Eradication		46/ 52	88.5	(76.6, 95.6)	54/ 60	90.0	(79.5, 96.2)
		Documented	0/ 46	0.0	(0.0, 7.7)	1/ 54	1.9	(0.0, 9.9)
		Presumed	46/ 46	100.0	(92.3,100.0)	53/ 54	98.1	(90.1,100.0)
	Persistence		6/ 52	11.5	(4.4, 23.4)	6/ 60	10.0	(3.8, 20.5)
		Documented	1/ 6	16.7	(0.4, 64.1)	0/ 6	0.0	(0.0, 45.9)
		Presumed	5/ 6	83.3	(35.9, 99.6)	6/ 6	100.0	(54.1,100.0)

Microbiologic Response at the Pathogen Level by Selected Baseline Isolate at the Test-Of-Cure Assessment Within the ME Population – Pooled Data From Studies 301 and 306

			Tigecycline			Imipenem/Cilastatin		
Isolate	Response		n/N	%	(95% CI)	n/N	%	(95%CI)
Peptostreptococcus	Eradication		17/ 23	73.9	(51.6, 89.8)	19/ 24	79.2	(57.8, 92.9)
		Documented	0/ 17	0.0	(0.0, 19.5)	0/ 19	0.0	(0.0, 17.6)
		Presumed	17/ 17	100.0	(80.5,100.0)	19/ 19	100.0	(82.4,100.0)
	Persistence		6/ 23	26.1	(10.2, 48.4)	5/ 24	20.8	(7.1, 42.2)
		Documented	0/ 6	0.0	(0.0, 45.9)	0/ 5	0.0	(0.0, 52.2)
		Presumed	6/ 6	100.0	(54.1,100.0)	5/ 5	100.0	(47.8,100.0)
Staph aureus (non-MRSA)	Eradication		26/ 28	92.9	(76.5, 99.1)	22/ 24	91.7	(73.0, 99.0)
		Documented	0/ 26	0.0	(0.0, 13.2)	1/ 22	4.5	(0.1, 22.8)
		Presumed	26/ 26	100.0	(86.8,100.0)	21/ 22	95.5	(77.2, 99.9)
	Persistence		2/ 28	7.1	(0.9, 23.5)	2/ 24	8.3	(1.0, 27.0)
		Documented	0/ 2	0.0	(0.0, 84.2)	0/ 2	0.0	(0.0, 84.2)
		Presumed	2/ 2	100.0	(15.8,100.0)	2/ 2	100.0	(15.8,100.0)
Streptococcus sp.	Eradication		141/167	84.4	(78.0, 89.6)	105/137	76.6	(68.7, 83.4)
		Documented	7/141	5.0	(2.0, 10.0)	1/105	1.0	(0.0, 5.2)
		Presumed	134/141	95.0	(90.0, 98.0)	104/105	99.0	(94.8,100.0)
	Persistence		26/167	15.6	(10.4, 22.0)	32/137	23.4	(16.6, 31.3)
		Documented	3/ 26	11.5	(2.4, 30.2)	0/ 32	0.0	(0.0, 10.9)
		Presumed	23/ 26	88.5	(69.8, 97.6)	32/ 32	100.0	(89.1,100.0)
Prevotella sp.	Eradication		10/ 11	90.9	(58.7, 99.8)	13/ 17	76.5	(50.1, 93.2)
		Documented	0/ 10	0.0	(0.0, 30.8)	0/ 13	0.0	(0.0, 24.7)
		Presumed	10/ 10	100.0	(69.2,100.0)	13/ 13	100.0	(75.3,100.0)
	Persistence		1/ 11	9.1	(0.2, 41.3)	4/ 17	23.5	(6.8, 49.9)
		Documented	0/ 1	0.0	(0.0, 97.5)	0/ 4	0.0	(0.0, 60.2)
		Presumed	1/ 1	100.0	(2.5,100.0)	4/ 4	100.0	(39.8,100.0)

Microbiologic Response at the Pathogen Level by Selected Baseline Isolate at the Test-Of-Cure Assessment Within the ME Population – Pooled Data From Studies 301 and 306

			Tigecycline			Imipenem/Cilastatin		
Isolate	Response		n/N	%	(95% CI)	n/N	%	(95%CI)
Proteus sp.	Eradication		12/ 19	63.2	(38.4, 83.7)	14/ 18	77.8	(52.4, 93.6)
		Documented	0/ 12	0.0	(0.0, 26.5)	0/ 14	0.0	(0.0, 23.2)
		Presumed	12/ 12	100.0	(73.5,100.0)	14/ 14	100.0	(76.8,100.0)
	Persistence		7/ 19	36.8	(16.3, 61.6)	4/ 18	22.2	(6.4, 47.6)
		Documented	2/ 7	28.6	(3.7, 71.0)	0/ 4	0.0	(0.0, 60.2)
		Presumed	5/ 7	71.4	(29.0, 96.3)	4/ 4	100.0	(39.8,100.0)
Pseudomonas aeruginosa	Eradication		33/ 39	84.6	(69.5, 94.1)	31/ 36	86.1	(70.5, 95.3)
		Documented	1/ 33	3.0	(0.1, 15.8)	0/ 31	0.0	(0.0, 11.2)
		Presumed	32/ 33	97.0	(84.2, 99.9)	31/ 31	100.0	(88.8,100.0)
	Persistence		6/ 39	15.4	(5.9, 30.5)	5/ 36	13.9	(4.7, 29.5)
		Documented	0/ 6	0.0	(0.0, 45.9)	0/ 5	0.0	(0.0, 52.2)
		Presumed	6/ 6	100.0	(54.1,100.0)	5/ 5	100.0	(47.8,100.0)

6.2.6 Efficacy Conclusions

For the treatment of complicated intraabdominal infection, tigecycline was found to be non-inferior to imipenem/cilastin in studies 301 and 306. Secondary analyses including microbiological assessments by organism and subject; interaction analyses by age, gender, initial diagnosis, creatinine clearance; and analyses according to monomocribial vs. polymicrobial infection were consistent with the primary efficacy analysis. Surprisingly, outcome by organisms known to be resistant to tigecycline, specifically *Pseudomonas*, also was not different between the treatment arms. However, effectiveness cannot be assumed for *Pseudomonas*, and there are patients reviewed in the Integrated Review of Safety who either failed therapy due to *Pseudomonas* infection or developed secondary wound infections due to *Pseudomonas*.

6.3 INDICATION – Resistant pathogens (RP)

6.3.1 Methods

Tigecycline is a first-in-class glycylcycline that is unaffected by the most common mechanisms of resistance among gram-negative bacteria. In addition, tigecycline is able to overcome the most common tetracycline-resistance mechanisms and thereby restore tigecycline's activity against tetracycline-resistant pathogens. It is active against multiple resistant Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) species, as well as Gram-negative isolates that produce extended-spectrum beta lactamases (ESBL). As part of the clinical development plan for tigecycline, (b) (4) phase 3 studies are currently being conducted in subjects with any of these serious infections or with bacteremia caused by known resistant pathogens (RP). The (b) (4) studies that are under way are protocols 307, 309, (b) (4), however at the time of NDA submission, there were relatively few patients enrolled, especially in studies 309 (b) (4). Efficacy data against resistant organisms was also collected and examined from the controlled phase 3 studies (studies 300, 301, 305, 306). During the review process, case report forms, narratives (where available), and datasets were examined).

Ongoing Phase 3 Studies of Tigecycline to Treat Known Resistant Pathogens

Study (CSR Number)	Targeted Pathogens	Study Populations	Primary Diagnoses	Tigecycline Dose (IV)	Active Control Dose (IV)	Duration of Treatment[a]
307	• Methicillin-resistant *Staphylococcus aureus* (MRSA) • Vancomycin-resistant *Enterococcus*(VRE)	Adults 18 years or older with selected serious infections	Serious infections involving MRSA or VRE, eg, cSSSI, cIAI, bacteremia, HAP, CAP	100 mg, followed every 12 hours by 50 mg	• MRSA: Vancomycin 1 g every 12 h • VRE: Linezolid 600 mg q 12 h	7 to 28 days depending on infection site and severity
309	Gram-negative bacteria, including ESBLproducing strains, eg, • *Enterobacter*species • *Klebsiella pneumoniae* • *Acinetobacter baumannii*	Adults 18 years or older who have failed previous antibiotic therapies or cannot tolerate alternative therapy	Serious gram-negative infections, eg, cSSSI, cIAI, bacteremia, HAP, and CAP	100 mg, followed every 12 hours by 50 mg	NA (noncomparative open-label study)	7 to 28 days depending on infection site and severity

(b) (4)

6.3.2 General Discussion of Endpoints

The majority of resistant pathogens submitted for review in this NDA come from the phase 3 controlled clinical trials; a discussion of the endpoints for these studies can be found in the Integrated Review of Efficacy as well as in Appendix 9.1. With regard to the specific Resistant Pathogen protocols, the primary and secondary efficacy analyses were:

The primary efficacy analyses for clinical response at the test-of-cure assessment include the following:

- Clinical response (cure or failure) in the ME population by baseline isolate for MRSA, VRE, and resistant Gram-negative pathogens.
- Clinical response (cure, failure, or indeterminate) in the m-mITT population by baseline isolate for MRSA, VRE, and resistant Gram-negative pathogens.

Secondary analyses for clinical response include the following:

- Clinical response by MRSA, VRE, and each baseline RP for ME subjects with a mono-microbial infection at the test-of-cure assessment.
- Clinical response by MRSA, VRE, and each baseline RP for m-mITT subjects with a mono-microbial infection at the test-of-cure assessment.
- Clinical response by MRSA, VRE, and each baseline RP for ME subjects with a poly-microbial infection at the test-of-cure assessment.
- Clinical response by MRSA, VRE, and each baseline RP for m-mITT subjects with a polymicrobial infection at the test-of-cure assessment.

Definition of Clinical Response

The clinical response is assigned by the investigator according to the protocol-specified guidelines. The clinical response is defined by one of the following:

Cure: The subject meets one of the following criteria:

- Resolution of signs and symptoms of the infection (healing of chronic underlying skin ulcer is not required).
- Improvement of signs and symptoms of the infection to such an extent that no further antibacterial therapy is necessary.
- If the subject undergoes a percutaneous drainage at baseline, does not respond to treatment within 72 hours of the initial drainage, and needs to undergo an operation and then improves, he or she is considered a clinical cure.

Failure: The subject meets one of the following criteria:

- Does not respond and requires additional antibacterial therapy having activity against MRSA, VRE, or the resistant gram-negative organism.
- Requires additional surgical or radiological intervention to cure the infection.

• The subject dies after study day 2 as a result of the infection.
• The subject discontinues treatment or dies due to a treatment-related adverse event (as the primary reason).
• The subject receives more than 120% of the expected number of doses of study drug.
A subject can be declared a failure after having received at least 4 doses of study drug. If the subject has a clinical response of failure while receiving study drug, the response of failure is carried forward through to the test-of-cure assessment (regardless of whether the subject is cured with other antibiotics). Subjects who are clinical failures have the test-of cure assessment performed before the initiation of nonstudy antibiotic therapy.

Indeterminate: The subject meets one of the following criteria:

• Is lost to follow-up (no clinical response is assigned).
• Dies for any reason within 2 days after first dose of study drug.
• Dies after study day 2 but before the test-of-cure assessment because of noninfectious-related reasons (as judged by the investigator).

6.3.3 Study Design

Study 307
Started in November 2003, study 307 is a phase 3, multicenter, double-blind, active controlled study being conducted to evaluate tigecycline and vancomycin for the treatment of selected serious infections in subjects whose primary pathogen is MRSA and to evaluate tigecycline and linezolid for the treatment of selected serious infections in subjects whose primary pathogen is VRE. Included infections are cSSSI, cIAI, pneumonia, and bacteremia. Adult subjects are randomly assigned in a 3:1 fashion (tigecycline:vancomycin or tigecycline: linezolid) for the purpose of an active control. At the time of randomization, subjects are stratified by type of pathogen (MRSA or VRE). Subjects with MRSA are then stratified by cSSSI or other infection; subjects with VRE are stratified to cIAI or other infection. Finally, subjects are also stratified by their baseline Acute Physiologic and Chronic Health Evaluation (APACHE) II score (≤ 15 or >15).

Study 309
Study 309 began in November 2003 and continues as an open-label, noncomparative, multicenter study to evaluate the safety and efficacy of tigecycline in adult subjects with a confirmed diagnosis of a serious infection (cSSSI, cIAI, pneumonia, or bacteremia) caused by resistant Gram-negative bacteria and requiring administration of intravenous (IV) antibiotic therapy for at least 7 days. Subjects may participate if they have failed to respond to previous antibiotic therapy or are unable to tolerate other appropriate antimicrobial therapies, and they have a resistant Gram-negative organism. An organism is considered resistant if it is an ESBL-producing strain or is resistant in vitro to at least 1 antibiotic from 3 or more classes of antimicrobial agents commonly prescribed for gram-negative pathogens, ie, penicillins; cephalosporins; carbapenems; aminoglycosides; quinolones; and aztreonam. (Note: if a subject has clinically failed or is allergic to or

intolerant of an antibiotic from among these classes, that class is counted as 1 of the 3 commonly prescribed classes for purposes of enrollment.) Subject participation in the study involves 1 day for screening, up to 28 days of therapy, and, unless the subject is a clinical failure, a test-of-cure assessment at least 14 days but no more than 35 days (± 2 days at either extreme) after the last dose of tigecycline, for a maximum of 66 days.

(b) (4)

[redacted]

6.3.4 Efficacy Findings

CONTROLLED CLINICAL STUDIES FOR RP
Study 307
29 subjects, 24 MRSA and 5 VRE
Although there were 24 subjects with MRSA enrolled, 14 were not included in the ME analysis population for the following reasons: 4 did not meet minimal disease criteria, 8 did not meet evaluability criteria, and 2 did not have a baseline susceptible MRSA. As can be seen in the following tables, there were small numbers of patients by indication with MRSA who were treated with tigecycline. Overall cure rates were 5/8 and 8/12 for the ME and m-mITT populations. Because of the small number of patients, it is difficult to draw conclusions about the efficacy against MRSA based on these data alone.

Clinical Diagnoses: ME Subjects With MRSA (Study 307)

Clinical Diagnosis	Tigecycline (n = 8)	Vancomycin (n = 2)	Total (n = 10)	Fisher Exact p-Value
Primary diagnosis, n (%)				0.222
cSSSI	6 (75.0)	1 (50.0)	7 (70.0)	
Hospital-acquired pneumonia	2 (25.0)	0	2 (20.0)	
Bacteremia	0	1 (50.0)	1 (10.0)	

MRSA = methicillin-resistant *S. aureus,* cSSSI = complicated skin and skin structure infections.

Clinical Cure Rates at Test-of-Cure by APACHE II Score: ME and m-mITT Subjects With MRSA (Study 307)

Study Population	APACHE II Score	Site of Infection	Tigecycline n/N	Tigecycline (%)	Tigecycline 95% CI	Vancomycin n/N	Vancomycin (%)	Vancomycin 95% CI[a]
ME	≤15	cSSSI	5/6	(83.3)	35.9, 99.6	1/1	(100.0)	2.5,100.0
		Other	(b) (4)					
	> 15	cSSSI	0/0	(NA)		0/0	(NA)	
		Other	(b) (4)					
	Overall		(b) (4)					
m-mITT	≤15	cSSSI	6/8	(75.0)	34.9, 96.8	1/3	(33.3)	0.8, 90.6
		Other	(b) (4)					
	> 15	cSSSI	0/0	(NA)		0/0	(NA)	
		Other	(b) (4)					
	Overall		(b) (4)					

Data with VRE infected patients, as shown in the following table, for study 307 was even more sparse with only 3 patients total in the ME population (and 6 in the m-mITT population)

Clinical Diagnoses: ME Subjects With VRE (Study 307)

Clinical Diagnosis	Tigecycline (n = 2)	Linezolid (n = 1)	Total (n = 3)	Fisher Exact p-Value
Primary diagnosis, n (%)				1.0
cIAI	1 (50.0)	0 (0.0)	1 (33.3)	
cSSSI	0 (0.0)	1 (100.0)	1 (33.3)	
Bacteremia	1 (50.0)	0 (0.0)	1 (33.3)	

UNCONTROLLED CLINICAL STUDIES FOR RP

Study 309

This open-label,noncomparative safety and efficacy study of tigecycline designed to treat serious infections caused by resistant Gram-negative bacteria in subjects who have failed or cannot tolerate other antibiotic therapy, only succeeded in enrolling 10 patients total by the time of NDA submission. There were only 5 in the ME population as is shown in the following table. It is difficult to draw any conclusions about efficacy against resistant Gram-negative organisms based on these data alone.

Clinical Diagnoses of Infection: ME Subjects with Gram-Negative RPs (Study 309)

Clinical Diagnosis	ME Population (n = 5)
Primary diagnosis, n (%)	
Complicated intra-abdominal infection	1 (20.0)
Complicated skin/skin structure infection	2 (40.0)
Community-acquired pneumonia	1 (20.0)
Bacteremia	1 (20.0)
Infecting organism, n (%)	
*Enterobacter*species	1 (20.0)
Acinetobacter baumannii	1 (20.0)
Klebsiella pneumoniae	1 (20.0)
Escherichia coli	1 (20.0)
Serratia marcescens	1 (20.0)

Clinical Cure Rates at Test-of-Cure: ME and m-mITT Subjects With Gram-Negative RPs (Study 309)

(b) (4)

ALL PHASE III COMBINED: VRE

Even when all Phase 3 data are combined, the information available for evaluation of tigecycline's effectiveness against VRE is scant. It is not possible to make any determination of efficacy against VRE based on these data.

Clinical Cure Rates at Test-of-Cure: ME and m-mITT

(b) (4)

ALL PHASE III COMBINED: MRSA

MRSA obtained from phase 3 studies constitutes the most significant data submitted in the NDA to support efficacy against a resistant pathogen, as is seen in the following table. The second table shows that the majority of these pathogens were isolated from patients with cSSSI's. Vancomycin was used as the comparator, and the clinical response rates for tigecycline vs. vancomycin are similar for the treatment of cSSSI.

Clinical Cure Rates at Test-of-Cure: ME and m-mITT Subjects With MRSA (Studies 300, 301, 305, 306, and 307)

Study Population	Response	Tigecycline n/N (%)	Tigecycline 95% CI[b]	Comparator n/N (%)	Comparator 95% CI[b]
ME	Cure	32/43 (74.4)	58.8, 86.5	28/38 (73.7)	56.9, 86.6
	Failure	11/43 (25.6)		10/38 (26.3)	
m-mITT	Cure	53/75 (70.7)	59.0, 80.6	45/63 (71.4)	58.7, 82.1
	Failure	14/75 (18.7)		15/63 (23.8)	
	Indeterminate	8/75 (10.7)		3/63 (4.8)	

Analysis of Clinical Response Within the ME Population– Pooled Data for Subjects with MRSA in Studies 300, 305 and 307 (CSSSI)

		Tigecycline[a]			Vancomycin/Aztreonam[a]		
Visit	Response	n/N	%	(95% CI)	n/N	%	(95% CI)
Last Day of Therapy	Cure	30/ 37	81.1	(64.8, 92.0)	29/ 34	85.3	(68.9, 95.0)
	Failure	7/ 37	18.9		5/ 34	14.7	
Test-of-Cure	**Cure**	**29/ 37**	**78.4**	**(61.8, 90.2)**	**26/ 34**	**76.5**	**(58.8, 89.3)**
	Failure	**8/ 37**	**21.6**		**8/ 34**	**23.5**	

The following tableshows that very few of the phase 3 MRSA isolates were obtained from cIAI studies. Based on this information, it is difficult to assess the efficacy of tigecycline in the treatment of cIAI as caused by MRSA.

Analysis of Clinical Response Within the ME Population in Subjects with MRSA – Pooled Data From Studies 301 and 306 (cIAI)

(b) (4)

ESBL-Producing Gram-Negative Organisms

The following table summarizes the phase 3 experience for ESBL-producing Gram-negative bacteria. There were 16 total tigecycline-treated patients with infection due to an ESBL-producing organism; however, these were spread out over 3 different organisms. *E. coli* was the most common. (b) (4)

Clinical Cure Rates at Test of Cure by Clinical Diagnosis: Tigecycline-Treated ME Subjects With ESBL-Producing Strains of *E. coli*, *K. pneumoniae*, or *P. mirabilis* (Studies 300, 301, 305, 306, and 309)

(b) (4)

6.3.5 Efficacy Conclusions

The data submitted support the efficacy of tigecycline in the treatment of patients with cSSSI due to MRSA. There are not enough data to determine efficacy of tigecycline in the treatment of cIAI caused by MRSA, or the treatment of resistant Gram-negative pathogens at this time.

6.4 BACTEREMIC PATIENTS

Bacteremia is not an indication that the sponsor is applying for or developing the drug for at this time. However, it is often reviewed and assessed as a means of adding further understanding of a drug's efficacy. The effectiveness of tigecycline in patients who have underlying concomitant bacteremia is of special interest because of the pharmacokinetic profile of tigecycline. Tigecycline has a large volume of distribution and is distributed rapidly to the tissues. As a result, it does not achieve very high blood levels (peak post-dose levels around 1 mcg/L).

When cumulated across the cSSSI and cIAI indications, 46 tigecycline subjects in the ME population had bacteremia documented at entry. Causative organisms were those expected per indication. The clinical cure rate for the tigecycline cSSSI subjects was 765.9% (10 of 12); for cIAI subjects, it was 77.4% (24 of 31). The following tableshows the clinical cure rate by pathogen. Of note, response was 78.6% (11 of 14) in subjects who received tigecycline and were found to have *S. aureus* bacteremia (cIAI and cSSSI combined); however, there were no MRSA blood isolates. A trend towards efficacy was shown for small numbers of cases of streptococcal, enterococcal, *Bacteroides* spp., and Gram-negative bacillary bacteremia.

These findings are not conclusive but they are suggestive that that tigecycline's relatively low blood levels are not predictive of a lack of efficacy in patients with bacteremia.

Clinical Cure Rates of Baseline Isolates at the Test-of-Cure Assessment in Subjects with Bacteremia, Phase 3 Studies: Cure/Total (%) . Pooled Data for Studies by Indication				
	Tigecycline		Comparator	
Isolate	n/N	%	n/N	%
cSSSI				
Staphylococcus aureus [a]	6/8	75.0	8/9	88.9
Streptococcus pyogenes	1/1	100.0	1/1	100.0
Enterococcus faecalis (Non-VRE)	1/1	100.0	1/1	100.0
Klebsiella oxytoca	1/1	100.0	--	--
Enterobacter aerogenes	0/1	0.0	--	--
Bacteroides fragilis	--	--	1/1	100.0
Enterobacter cloacae	--	--	2/2	100.0
Salmonella spp.	--	--	1/1	100.0
cIAI				
Bacteroides spp	6/8	75.0	3/3	100.0
Escherichia coli	4/7	57.1	11/12	91.2
Staphylococcus aureus[a]	5/6	83.3	2/2	100.0
Klebsiella spp	5/5	100.0	3/3	100.0
Enterococcus faecalis (Non-VRE)	2/2	100.0	1/3	33.3
Streptococcus oralis	0/1	0.0	--	--
Streptococcus anginosus group [b]	1/1	100.0	4/5	80.0
Enterobacter limosum	1/1	100.0	--	--
Streptococcus salivarius	--	--	1/1	100.0
Streptococcus pneumoniae	--	--	1/1	100.0
Acinetobacter calcoaceticus	--	--	1/1	100.0
Citrobacter freundii	--	--	1/1	100.0
Serratia marcescens	--	--	0/1	0.0
Enterobacter cloacae	--	--	0/1	0.0

A: All strains were methicillin-susceptible.

B: The *Streptococcus anginosus*category includes: *S. anginosus, S. intermedius, and S. constellatus*.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The data sources for the safety review included phase 1, 2, and 3 clinical trials as listed in the Table of Clinical Trials in section 4.1. Phase 1and 2 data were used to explore dose-related safety issues as well as to examine for serious adverse events (SAE's) and idiosyncratic reactions. The phase 3 data were the primary data source used for the purposes of comparing rates of adverse events between treatment arms and also to explore differences in rates of adverse events by treatment indication.

7.1.1 Deaths

All deaths that occurred during Phase 3 clinical trials were reviewed in detail. Narratives, case report forms, and data from datasets were reviewed in detail. In total, there were 51 deaths that occurred during Phase 3 testing, 41 in cIAI trials, 7 in cSSSI, and 3 in study 307, the resistant pathogen study. There were more deaths in the tigecycline-treated patients than there were in the comparator-treated patients. This finding is true across studies and across indications. Because of the significant differences in the patient populations studied for the two proposed indications, it is reasonable to present a review of the deaths separated by indication. NOTE: Brief narrative summaries/MO comments for all deaths can be found in Appendix 9.2.

Deaths in cIAI Trials (301, 306)
In the two cIAI active controlled trials, there were more deaths in the tigecycline-treated patients than in the comparator-treated patients. The following table shows the number of deaths in each study as well as the totals for this indication.

	Tigecycline-treated Deaths		Imipenem- treated Deaths	
Study	Deaths (total # in study)	%	Deaths (# in study)	%
301	17 (413)	4.1	12 (412)	2.9
306	7 (404)	1.7	5 (413)	1.2
301 + 306	24 (817)	2.9	17 (825)	2.1

The following table shows that there are an increased number of deaths in tigecycline-treated patients compared to imipenem-treated patients for both studies 301 and 306. This difference is not statistically significant. However, because these studies were not powered to detect a difference in death rates between the two treatment arms, it cannot be concluded from this information alone that a true difference does not exist. To determine if such a difference is likely, further analysis is necessary.

APACHE II scoring has been shown to be a reliable and useful means of classifying ICU patients, and increased APACHE II score is associated with increased risk of subsequent death. The sponsor has pointed out that there are more patients with higher APACHE II scores in the tigecycline group. Furthermore, the median APACHE II score of tigecycline-treated patients who died is higher than that of imipenem-treated patients who died (9.5 vs. 7.0). One possible explanation is that, by chance, despite proper randomization, the number of more severely ill patients was greater in the tigecycline-treated patients than in the imipenem-treated patients. The following table shows that the percentage of patients in the higher APACHE II categories is slightly greater in the tigecycline-treated patients than in the imipenem-treated patients.

APACHE II Scores for Patients in Studies 301 and 306		
APACHE II Score	Tigecycline-treated patients, n (%)	Imipenem-treated patients, n (%)
21-25	4 (0.5)	4 (0.5)
16-20	22 (2.7)	13 (1.6)
11-15	95 (11.6)	74 (9.0)
6-10	272 (33.3)	321 (39)
0-5	383 (46.9)	373 (45.3)
0	41 (5)	38 (4.6)
Total	817	823

However, this fact alone doesn't answer the question of whether differences in APACHE II scores play a role in the increased death rate in tigecycline-treated patients. To answer this question, death rates have to be examined by stratification of APACHE II score as is demonstrated in the following table. Note that a risk factor analysis examining potential differences between treatment arms for risk factors such as age, co-morbid medical conditions, severity of disease at presentation, as well as other such risk factors, in this situation is not necessary. This is because such risk factors are already incorporated into the APACHE II score determination.

Death Rate by APACHE II Score of All Patients: Studies 301 and 306, Safety Population				
APACHE II Score	Tigecycline (n=817)		Imipenem (n=823)	
	Deaths / patients	%	Deaths / patients	%
21-25	1 / 4	25	0 / 4	0.0
16-20	2 / 22	9.1	4 / 13	30.8
11-15	6 / 95	6.3	2 / 74	2.7
6-10	12 / 272	4.4	7 / 321	2.2
1-5	3 / 383	0.8	4 / 373	1.1
0	0 / 41	0.0	0 / 38	0.0

Among patients with the lowest APACHE II scores, the rate of deaths is similar across the two treatment groups. Patients who fall into the APACHE II score range of 0-5 are less severely ill and therefore have a lower death rate. Given this lower death rate, any potential differences between the two treatment arms is likely to be smaller if it exists at all, and would be more difficult to demonstrate in a relatively small patient population.

Note that in the table above, the death rate for tigecycline-treated patients is 2 times higher for patients with APACHE II scores of 6-10 and 2.3 times higher for patients with APACHE II scores of 11-16. When looking at the most severely ill patients with an APACHE II score of between 16 and 25, we see that although the death rate is much higher, the total number of such patients is very small, which also makes it difficult to determine if a difference between treatment arms exists. However, when looking at the subset of patients with APACHE II scores between 6 and 15, there are both an adequate death rate and total number of patients in this category for the purposes of exploring a potential difference in death rate between the two treatment arms. Based on this analysis, it does not appear as though higher APACHE II scores among tigecycline-treated patients provide a full explanation for the difference in rates of death. Because such a difference in the death rate has been found in patients with an APACHE II score between 6 and 15, a more detailed examination of the individual patients is required to attempt to determine if specific reasons for this observation exist.

A detailed review of all deaths was performed. Case report forms, narratives, and data from datasets were examined concurrently. Deaths were categorized broadly according to overall potential that the death was related to severity of underlying disease, lack of treatment effect, or possible drug-related toxicity. This analysis was not intended to be definitive, but instead, was intended to allow for a way of sorting through deaths which occurred in a group of highly complex and severely ill patients. Appendix 9.2 contains a listing of all summary narratives of deaths, the category in which each one was included, and an explanation for why the patients were placed into the particular categories. Typical patients who were considered to have not died as a result of harmful effects of the study drug include patients who:

- were severely ill at the time of enrollment and died very soon after starting study drug
- died some time after the discontinuation of study drug for reasons not related to efficacy
- died of causes consistent with ongoing underlying co-morbid illness (such as MI's in patients who had significant documented underlying cardiac disease).

This analysis does not take into account that, for example, patients with underlying coronary artery disease may have MI's at a higher rate in one arm vs. another or that patients who are severely ill at enrollment may survive at a higher rate in one arm vs. another. It is not possible to perform such analyses in a meaningful way with this safety database given the small number of patients who experienced such events.

Typical patients who were considered to have died as a result of a possible drug-related toxicity or non-efficacy related characteristics of the drug include patients who:

- developed an unexpected adverse event while on study drug and which caused or contributed significantly to the patients death
- died of infections (other than cIAI) that are typically treated by drugs approved for the treatment of cIAI

Inclusion of patients in this category does not at all allow for a determination of causality. However, it may allow for the formation of hypotheses which could potentially be tested in future trials, if warranted.

Typical patients who were considered to have died possibly as a result of lack of treatment effect include patients who:

- died as a result of cIAI as caused by organisms not covered by the antibiotic which the patient received
- were relatively stable at enrollment, but who died as a result of worsening of their protocol defined illness while on therapy with the antibiotic

Patients in this category cannot be definitively determined to have died because of lack of treatment effect. This is because of complexity of such patients and the fact that the investigators (who are most familiar with these patients) often are unsure of the exact cause of death. Most of these patients did not have autopsies.

Patients who died in the cIAI studies who did not fit into any of these categories were categorized as "indeterminate."

Although this analysis has methodologic limitations and cannot be considered as definitive, it is useful in that it allows for a broad understanding of why differences in the death rates were seen in the cIAI studies. The following table shows the results of this analysis.

Categorization of Possible Causes of Death: Studies 301, 306		
Category	Tigecycline	Imipenem
Lack of Treatment Effect	8	6
Possible Drug Effect/toxicity	3	1
Unlikely Related to Study Drug	12	9
Indeterminate	1	1
Total	24	17

Based on this analysis, it is difficult to explain the difference in deaths based on a lack of treatment effect. There does not appear to be a single category that accounts for the differences in the number of deaths. Two of the patients who were in the "Possible Drug Effect/toxicity" category died of pneumonia which may have been the result of organisms (such as Pseudomonas) not covered by tigecycline, but that are typically covered by antibiotics with a cIAI indication. However, since no pulmonary-source organisms were reported as being isolated, it is not known if this is the case. The fact that there were also more non-death SAE's caused by pneumonia in the tigecycline arm than in the imipenem arm, supports this possibility.

Deaths in the cSSSI Trials

Six deaths occurred in the tigecycline arm and 1 death in the vancomycin/aztreonam arm during the cSSSI trials. All 7 deaths were reviewed in detail, including the CRF's, narratives, and data from the datasets. Based on this review, the imbalance in deaths does not appear to be related to the study drug.

Time to Death Analysis

A time to death analysis was conducted by FDA statistician, Thamban Valappil, Ph.D., and is presented in Tables X and X for cIAI and cSSSI. These analyses reveal a similar pattern in the time to death for deaths occurring in each treatment arm.

cSSSI

This table shows the median days to death for the deaths from Study 300 and 305.

Median Days From Start of Treatment to Date of Death: Subjects Who Died in cSSSI Studies					
Study Number	———— Tigecycline ————		—— Vancomycin/Aztreonam		Log Rank p-Value
	No. Deaths	Days	No. Deaths	Days	
300	5	11.0	1	11.0	0.8572
305	1	8.0	0	n/a	n/a
Total	6	10.5	1	11.0	0.9907

The following table shows the distribution of deaths by number of days to death for those subjects who died in Study 300.

Demographic and Clinical Characteristics of Subjects Who Died in Study 300			
Characteristic	**Tigecycline (n = 5)**	**Vancomycin/ Aztreonam (n = 1)**	**Total (n = 6)**
Distribution of Days to Death			
5	1		1
10	1		1
11	1	1	2
22	1		1
44	1		1
Event Related to Infection,			
Yes	1		1
No	4	1	5

With the small number of deaths in Study 300, it is not possible to draw meaningful comparisons in the time to death between treatment arms, but the distribution shows that some patients died well beyond the time of treatment. There does not appear to be a specific pattern in the time of death in relation to tigecycline treatment.

The following tables show the median days from start of treatment to date of death and the distribution of days to death for subjects who died in the phase 3 cIAI studies.

Median Days From Start of Treatment to Date of Death: Subjects Who Died In cIAI Studies (Studies 301 and 305)

Study Number	**Tigecycline**		**Imipenem/Cilastatin**		**Log Rank p-Value**
	No. Deaths	**Days**	**No. Deaths**	**Days**	
301	17	10.0	12	11.0	0.458
306	7	22.0	5	13.0	0.371
Total	24	12.5	17	11.0	0.750

Demographic and Clinical Characteristics of Subjects in the cIAI Studies Who Died (Studies 301 and 305)

Characteristic	Tigecycline (n = 24)	Imipenem/ Cilastatin (n = 17)	Total (n = 41)
Distribution of Days to Death, n (%)			
1	1 (4.2)	0 (0.0)	1 (2.4)
2	0 (0.0)	1 (5.9)	1 (2.4)
3	1 (4.2)	0 (0.0)	1 (2.4)
4	4 (16.7)	0 (0.0)	4 (9.8)
6	0 (0.0)	2 (11.8)	2 (4.9)
8	1 (4.2)	0 (0.0)	1 (2.4)
9	0 (0.0)	1 (5.9)	1 (2.4)
10	3 (12.5)	2 (11.8)	5 (12.2)
11	0 (0.0)	3 (17.6)	3 (7.3)
12	2 (8.3)	0 (0.0)	2 (4.9)
13	1 (4.2)	1 (5.9)	2 (4.9)
15	3 (12.5)	0 (0.0)	3 (7.3)
16	0 (0.0)	1 (5.9)	1 (2.4)
17	1 (4.2)	2 (11.8)	3 (7.3)
20	1 (4.2)	0 (0.0)	1 (2.4)
22	1 (4.2)	0 (0.0)	1 (2.4)
27	1 (4.2)	0 (0.0)	1 (2.4)
30	1 (4.2)	0 (0.0)	1 (2.4)
31	0 (0.0)	1 (5.9)	1 (2.4)
32	0 (0.0)	1 (5.9)	1 (2.4)
41	0 (0.0)	1 (5.9)	1 (2.4)
45	1 (4.2)	0 (0.0)	1 (2.4)
49	1 (4.2)	0 (0.0)	1 (2.4)
53	1 (4.2)	0 (0.0)	1 (2.4)
93	0 (0.0)	1 (5.9)	1 (2.4)
Event Related to Infection, n (%)			
Yes	13 (54.2)	7 (41.2)	20 (48.8)
No	11 (45.8)	10 (58.8)	21 (51.2)

The results of these analyses show no meaningful differences between the two treatment arms.

The sponsor submitted additional information on 6 additional deaths that occurred after those patients had completed the study. Two of the deaths were in tigecycline-treated patients in cIAI studies, while 4 of them occurred in comparator-treated patients in cIAI studies. Review of these patients reveals that it may be reasonable to include them in the deaths analyses (refer to the deaths analyses of Dr. Thamban Valappil, Ph. D.). One of the comparator deaths, however, should be excluded since it occurred around 90 days after completion of the study.

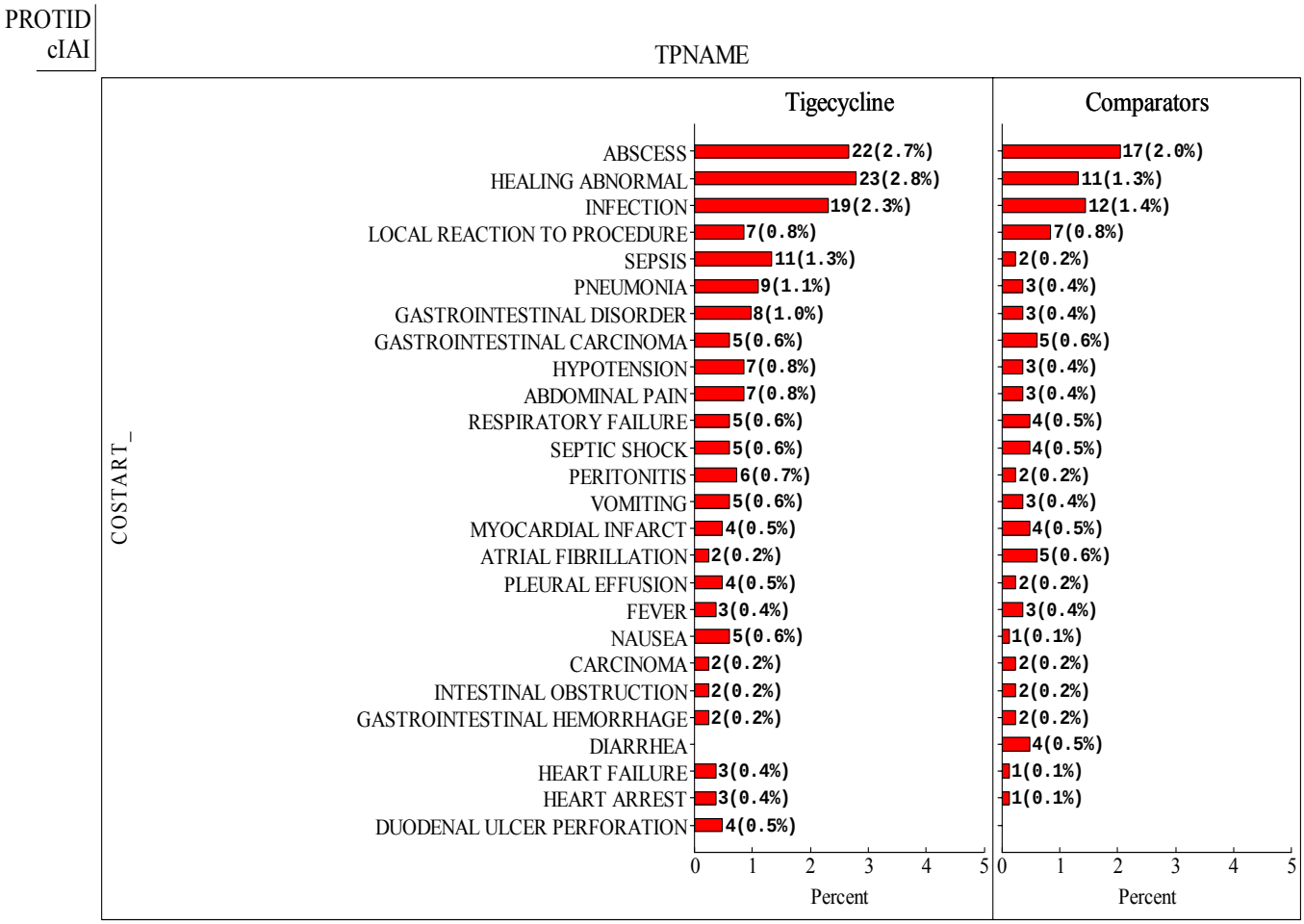
Overall Conclusion - Deaths

Although there was an increased number of deaths observed among tigecycline-treated patients in both the cSSSI and cIAI studies, it is not possible, based on the data in this NDA, to explain this difference on the basis of lack of treatment effect or other properties of tigecycline. The possible increased risk of pneumonia that may exist in cIAI patients treated with tigecycline needs to be explored further.

7.1.2 Other Serious Adverse Events (SAE's)

Rates of serious adverse events were examined in the controlled blinded clinical trials and separated by indication.

Treatment-emergent SAE's for studies 301 and 306 combined are presented in the following graph (note: subjects may have had more than one SAE, but SAE's within each preferred term include only unique subject identifiers). Overall, the rates are relatively similar; however, there are increased rates in the tigecycline arm for several infection-related adverse events including the following preferred terms: infection, pneumonia, sepsis, peritonitis, and abscess.



All cases of sepsis and septic shock were reviewed in detail. Of the 11 cases of sepsis, 5 were deaths that are reviewed in detail in the deaths section (301-011-000102, 301-082-003571, 306-125-002446, 301-401-006038, 306-127-002487)

Subject 301-080-003435 was an 80 year-old male who developed worsening sepsis (in addition to acute MI and coagulopathy) on the first day of study drug administration. The patient remained on treatment with tigecycline for a total of 7 days after which time it was discontinued because the infectious process was considered to be resolved. The patient eventually recovered and was discharged. This is an example of a patient who was very ill at the time of study drug initiation and whose infection was successfully treated with the study drug. (APACHE II score 14)

306-014-000271 – This was a 24 year-old female who was enrolled with complicated cholecystitis who, one day after start of tigecycline, developed sepsis. The sepsis was determined to be caused by E. coli pyelonephritis which was treated with ceftazidime.

The tigecycline was continued. Tigecycline does not get good penetration into the urine, so it is possible that this factor contributed to the episode of sepsis. The E. coli isolate was susceptible to tigecycline. (APACHE II score 13)

301-405-006276. Patient was a 54 year-old male who developed an anastomotic leak with abdominal abscess after undergoing sigmoid colectomy secondary to diverticulitis. The patient underwent a percutaneous aspiration of pus and fecal contamination on the day of study enrollment. The investigator believed the leak would heal with antibiotics and the aspiration. The subject experienced clinical improvement for the first 6 days of therapy, but sepsis began on the 7th day and a CT showed an increase in pneumoperitoneum (the leak did not heal). The patient had a laparotomy during which 2 liters of purulent fluid were drained. The isolated organisms included *E. coli* and *Enterococcus*, both of which were susceptible to tigecycline. This case appears to be an example of poor source control more than antibiotic ineffectiveness. (APACHE II score 8)

301-402-006164- This patient was a 55 year-old woman who presented with peritonitis, thought to be secondary to mesenteric ischemia. She underwent laparotomy and was enrolled in the study. For the ensuing 8 days, the patient improved; she became afebrile, bowel function normalized, and she was ambulating. On study day 9, the patient was assessed and found to be doing well; however, 45 minutes later, she collapsed and was found to be hypoglycemic and hypotensive. She was thought to be septic, cultures grew budding yeast, and no other foci of infection were identified. She continued to do poorly and 5 days later, she suffered cardiac arrest and died. This patient had a very sudden and unexpected deterioration, which may have been the result of sepsis, however, the etiology of the possible sepsis is not clear; it is possible that she developed disseminated candidemia, but this could not be tied to lack of tigecycline efficacy. (APACHE II score 13)

301-405-006289 – This patient was a 54 year-old woman who was admitted with symptoms of a strangulated incisional hernia with intestinal perforation. She had a laparotomy and was enrolled in the study. Post-op, she did well and improved until study day 10 when she developed sepsis. She was discontinued from the study and was taken to the OR where an anastomotic dehiscence was found. She was treated with other antibiotics and eventually recovered. It is difficult to implicate the study drug as a cause for the dehiscence although it cannot be ruled out. (APACHE II score 25)

306-057-001041 – This patient was a 52 year-old female who was enrolled in the study after undergoing laparotomy for acute cholecystitis. Culture from the operation grew *E. coli, B. fragilis,* and *E. avium*. One day after the operation, the patient developed respiratory failure which worsened and, the next day, was accompanied by sepsis. A new abdominal abscess was identified which required repeat operation and which grew the same organisms as the first procedure. The patient developed pneumonia later in the ICU, but eventually recovered. (APACHE II score 5)

Summary: Although it is possible that a lack of treatment effect could explain the increased rate of sepsis in patients treated with tigecycline, review of the individual cases offers no clear pattern or explanation for the difference.

7.1.3 Septic Shock

Of the five patients who developed septic shock, four died and were discussed in the deaths section (301-172-008093, 301-136-006466, 306-109-002165, 301-407-007990).

The other one is described below:

301-157-007213 – This patient was a 53 year-old woman with a history of rheumatoid arthritis who presented to the hospital with peritonitis due to a small intestinal perforation. She was taken to surgery where an ileostomy was performed after which she was started on study drug. Postoperatively, her condition deteriorated and she developed hypotension and septic shock (on the same day as the surgery). Later the same day, she was transferred to the ICU, discontinued from the study, and started on different antibiotics. She underwent a second laparotomy ten days later which revealed diffuse peritonitis. Eventually, she recovered and was discharged from the hospital. This patient had not received 24 hours of study drug before she began to deteriorate. Although it's possible there was a lack of treatment effect, it is also possible that the study drug wasn't given enough time to be effectve. (APACHE II score 13)

Conclusion for Cases of Sepsis/Septic Shock
It is difficult from review of the individual cases to determine if a lack of treatment effect is the cause for the increased number of cases of sepsis and septic shock. Although an increased number of patients with higher APACHE II scores is not an adequate explanation for the increased number of deaths in the tigecycline arm (see deaths section for explanation), this may not be the case for the non-death sepsis and septic shock cases. When examining the APACHE II scores at entry for the subjects who developed sepsis or septic shock, but did not die, there is a difference between the two treatment arms, although the numbers are so small that definite conclusions cannot be reached. There were a greater overall number of patients in the tigecycline arm than the imipenem arm who had APACHE II scores that were 11 or higher. This more severely ill patient subgroup is where the majority of the non-death sepsis patients originated. Patients with complicated intraabdominal infections who are more severely ill could be expected to have a higher risk of more severe events such as sepsis. However, there are multiple possible interpretations of these analyses, and low rates of events in either treatment arm do not allow for a clear explanation.

	Tigecycline	Imipenem/Cilastin
APACHE II Values	14, 13, 8,13, 25, 5	3, 6, 7
Mean	15.6	5.3
Median	13	6

7.1.4 "Infection" SAE's

There were a total of 19 cases of infection in tigecycline treated patients vs. 11 in the imipenem treated patients. 15 of these were surgical wound infections. The other four were "persistence of infection", "lower respiratory tract infection", "catheter infection", and "intraabdominal infection."

Review of the organisms which caused these infections reveals that in 9 patients, the organisms were either intermediate or resistant to tigecycline. Among these patients, there were the following:

7.1.5 Resistant Isolates

One patient had an intraabdominal infection with *Pseudomonas* (301-087-003787).
Three patients had wound infections caused by *Pseudomonas* (306-053-000969, 301-076-003242, 306-040-000737).
One patient had a wound infection caused by a resistant *Klebsiella* (306-106-002074).

Intermediate Susceptibility Isolates

One patient had a catheter infection with *Klebsiella pnemoniae* (301-157-007213).
One patient had a wound and peritoneal infection with *Proteus mirabilis* (306-079-001541).
One patient had a surgical site infection with *Proteus mirabilis* (306-106-002065).
One patient had a wound infection caused by *Klebsiella* (306-106-002074). This patient has both resistant and intermediate susceptibility isolates of *Klebsiella*.

In total, there were 4 patients with *Pseudomonas* infection, two with *Klebsiella* infection, and two with *Proteus* infection.

<u>Pneumonia</u>
Of the 9 cases of tigecycline-associated pneumonia, 4 were deaths (306-126-002462, 301-172-008093, 301-103-004550, 306-127-002487) which are described in the deaths section.

301-002-000012 – A 64 year-old male with COPD was enrolled in the study for post-colectomy abscesses. He was successfully treated with tigecycline for 7 days and developed pneumonia 13 days after the end of his treatment with the study drug. The infecting organism was *Stenotrophomonas maltophilia*. Information about this organism is not contained in the microbiology datasets.

301-119-005181 – A 77 year-old woman was successfully treated with 11 days tigecycline for a perforation of the large intestine. On the day she completed her last dose

of study drug, she developed pneumonia which required the use of mechanical ventilation.

301-140-006666 – This patient was a 72 year-old woman who was successfully treated with 8 days of tigecycline for acute cholecystitis. Five days after the end of therapy, she developed pneumonia which resulted in a prolonged hospital stay. She eventually recovered and was discharged.

301-136-006456 – This patient was a 74 year-old male who was successfully treated with 6 days of tigecycline. Four days after the end of therapy, the patient developed pneumonia which required therapy with cefotaxime.

306-017-000324 – The patient was a 73 year-old male who was treated with tigecycline for a large intestine perforation. On day 5 of treatment, the patient developed pneumonia requiring additional therapy.

306-127-002487– This patient, as described in the death section, had MRSA in lungs, but was on vancomycin at the time of pneumonia diagnosis and death.

It is somewhat reassuring that most of these pneumonia cases occurred several days after the patient had completed treatment with tigecycline. There does not seem to be a pattern of the occurrence of pneumonia caused by resistant organisms while on tigecycline therapy. There was not much information submitted with regard to the organisms isolated in these patients who developed pneumonia, because most of them developed pneumonia many days after they completed study drug.

Other notable differences for tigecycline vs. imipenem for SAE's occurring in the cIAI indication are: Nausea, 5 vs. 1; hypotension, 7 vs. 3; and duodenal perforation, 4 vs. 0, respectively.

Abnormal Healing

The rate of the serious adverse event "Healing abnormal" was different between tigecycline and comparator for the cIAI indication studies. Further review of these events revealed that the majority of these were cases of wound dehiscence, while a few were related to anastsomotic leak. The following is a listing of the cases:

301-034-001138 – septic wound dehiscence
301-055-002182 – wound dehiscence associated with abscess
301-084-003636 – incision infection with resulting wound dehiscence and evisceration
301-084-003661 – wound dehiscence associated with subcutaneous abscess
301-091-003981 – evisceration
301-103-004560 – evisceration
301-139-006608 – incision fissure associated with malnutrition and incision infection
301-182-008442 – wound infection with eventration
301-400-005948 – anastomotic leak
301-404-006226 – wound dehiscence

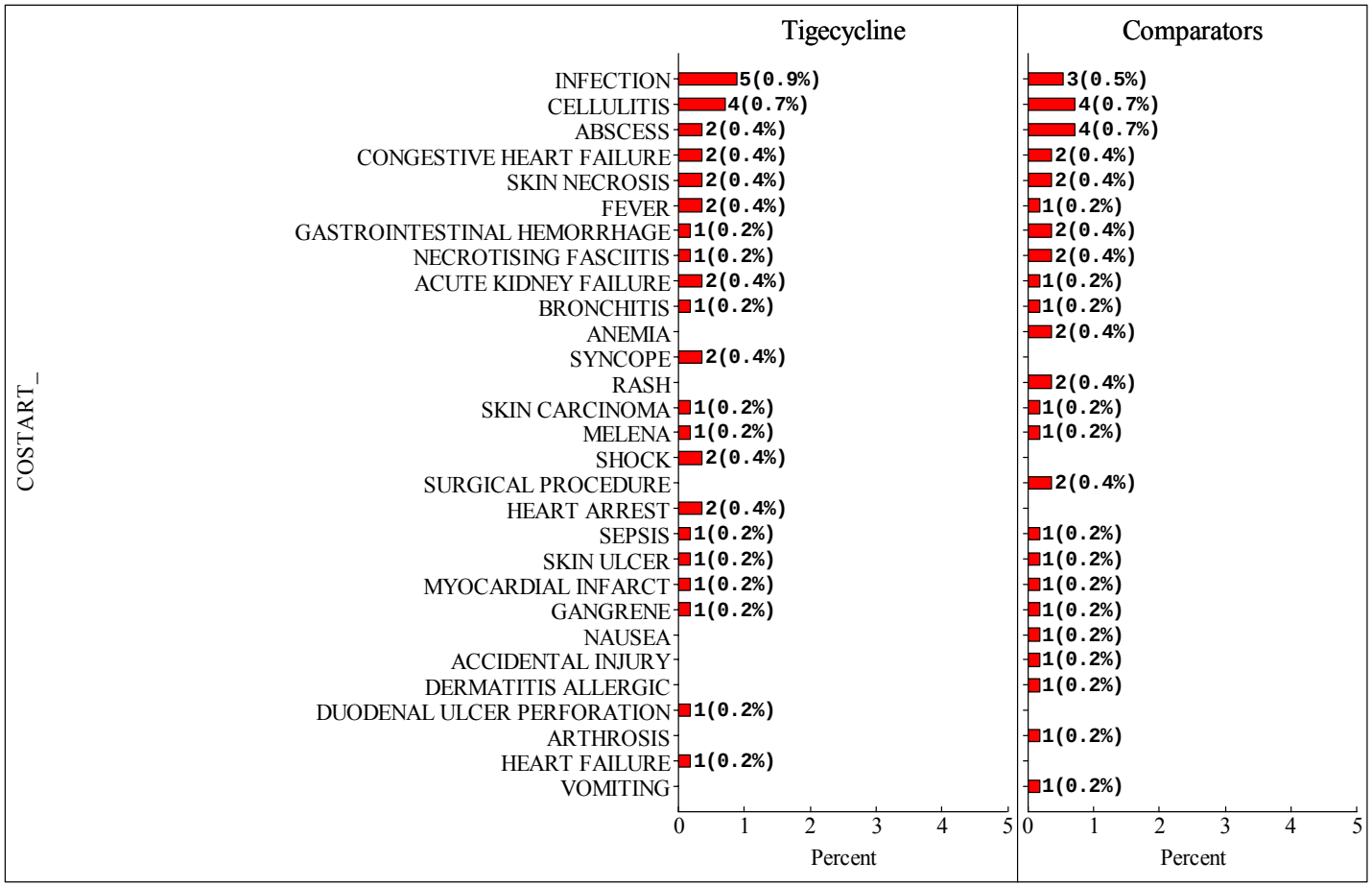
301-405-006276 – uncontrolled anastomotic leak
301-405-006277 – abdominal wound dehiscence
301-405-006289 – anastomotic dehiscence associated with peritonitis and sepsis
301-407-007947 – "burst abdomen" (wound dehiscence)
306-009-000163 – surgical wound dehiscence associated with sub-hepatic abscess
306-019-000355 – dehiscence of duodenal stump
306-021-000392 – complete wound dehiscence
306-069-001304 – "incompetence of intestinal sutures"
306-079-001541 – evisceration due to wound infection and peritonitis
306-112-002218 – abdominal incision dehiscence
306-124-002427 – wound dehiscence
306-125-002446 – wound dehiscence
306-129-002515 – wound infection with dehiscence

Review of the comparator cases of the preferred term "healing abnormal" reveals very similar types of events, however, at a lower overall rate.

In the skin and skin structure infections, there were too few SAE's to make comparisons between the two treatment arms. There was only one cases of sepsis (as well as one in the comparator arm). The following graph shows SAE's for the cSSSI indication (studies 300 and 305 combined).

PROTID
cSSSI

TPNAME



Counting the records in dataset ALL_TE_S, uniquing them by variable UNIQUE_S.
Normalize by dataset DEMOW, uniquing the record count by variable UNIQ_SUB.
Get normalization denominator from current cell in current layer, with a scope of the whole cell.

It is interesting to note that although there were higher rates of nausea and vomiting in the cSSSI tigecycline-treated patients, there were no related SAE's.

All SAE's were reviewed in an attempt to identify those adverse events which may occur very rarely but which are of critical importance. A few examples of such adverse events may include: TEN, Torsades, idiosyncratic hepatic reactions, anaphylaxis, aplastic anemia, acute renal failure.

Renal SAE's
There were 4 cases of tigecycline-associated acute renal failure and 1 case of "toxic nephropathy."

(b) (4)6 – This patient died and his case is summarized in the death section. Tigecycline is an unlikely explanation for this patient's renal failure because the patient developed multi-organ failure on the first day of study drug.

301-092-004051 – This patient was a 55 year-old woman who required right colectomy/ileal resection because of abdominal infection. Twelve days after discharge for successful antibiotic therapy, the patient was re-admitted with cholestatic hepatitis and renal failure. There is no clear explanation provided as to the etiology of these events; however, with hospitalization, hydration, and an adequate diet, the patient made a full recovery.

306-048-0892 – This patient was a 66 year-old female admitted for complicated appendicitis and periappendiceal abscess. The abscess was drained and the patient successfully completed therapy with tigecycline. Twenty-one days after the end of therapy with the study drug, the patient developed an acute allergic reaction, which, 7 days after that, was followed by acute renal failure. She required dialysis for a few days, but she recovered.

300-090-2642 – This patient was a 66 year-old male with a complicated right foot infection, which was successfully treated with 13 days of tigecycline. On the day after completion of the study drug, the patient developed acute renal failure and pancytopenia. A renal biopsy was performed which revealed diabetic nephropathy and the renal failure was considered to be a complication of the pre-existing diabetic nephropathy. The renal function did not improve, and the pancytopenia, which was thought to be secondary to the renal event, partially resolved.

300-063-001862 – This patient was a 74 year-old female with a history of diabetes mellitus (on insulin) who was admitted for treatment of a right foot abscess. On day 10 of the study, the patient developed increased creatinine to 1.9 mg/dL. Study drug was discontinued that day and the patient's renal event resolved. Creatinine returned to a normal baseline value.

For the most part, these cases do not provide a clear enough signal to be able to draw a cause and effect relationship between tigecycline and renal failure. They also do not allow such an association to be ruled out. Case 300-063-001862 is probably the least confounded case and provides a potential association for renal insufficiency with tigecycline administration. Further information as may be collected in the post-marketing setting may provide a better understanding of the association between tigecycline and renal adverse events.

Pancreatitis – There were two cases of pancreatitis associated with tigecycline exposure. One of these cases (306-127-002488), upon review doesn't appear to be significant and was deemed by the investigator to be "probably not" related to study drug. The other (301-008-000073) was reported as an SAE and was deemed by the investigator to be "possibly" related to tigecycline administration. The patient was a 76 year-old woman who was enrolled after hospital admission for intestinal perforation with abscess and suspicion of colon cancer. After percutaneous drainage of the abscess, the patient was treated with study drug for 9 days during which time she was improving. However, on treatment day 7, the patient developed pancreatitis; a CT scan revealed diffuse pancreatitis with no necrosis and the abscess had resolved. The patient was also on pantoprazole which has been reported to be associated with pancreatitis. However, given that on examination of the laboratory data, tigecycline exposure was associated with increases in amylase levels beyond what was seen in the control-treated patients, the possibility exists that this drug may cause pancreatitis. Therefore, it will be important to monitor for this possibility during post-marketing.

Skin Necrosis – There were 2 cases each in the tigycycline and vancomycin treatment arms. None of these cases was consistent with a systemic reaction such as TEN.

Adrenal Cortical Insufficiency – This patient had a past history of renal insufficiency for which she was being treated with hydrocortisone.

Cardiovascular disorder – This was a 50 year-old woman with a history of rheumatoid arthritis who suffered an MI and died as a result of subsequent cardiopulmonary arrest.

ECG Abnormal – A 22 year-old male was found on day 3 of study drug therapy to have "aberrancies and S-T elevation in V1-V4". The patient had a workup including echocardiography, cardiac enzymes, and a stress test with nuclear imaging, which were all normal.

Hydrocephalus – A 30 year-old woman was admitted for perforation of the small intestine after trauma to the head and abdomen. She was diagnosed during her hospital course as having hepatitis C and hydrocephalus.

Ophthalmoplegia – A 76 year-old male had visual impairment which began during hospitalization. An ophthalmology consultant diagnosed Tolosa-Hunt Syndrome, a superior orbital fissure syndrome secondary to herpes-zoster infection.

Panycytopenia – This patient was discussed in the renal failure section. Pancytopenia was thought to be secondary to acute renal failure.

7.1.5.1 Overall profile of dropouts

This information was presented earlier in the review.

7.1.5.2 Adverse events associated with dropouts

There were a total of 51 adverse events in studies 300, 301, 305, and 306 that resulted in withdrawal from the studies. This is compared to a total of 67 for the comparators combined for those same studies. A listing of adverse events resulting in withdrawal from the study is presented in the following table. The numbers and types of these adverse events are relatively similar. It is interesting that although there were more adverse events of "healing abnormal" in the tigecycline treated patients, there were less such patients who were withdrawn from the studies than in the comparator-treated patients. There were more patients in the tigecycline treatment group who withdrew due to nausea and vomiting than in the comparator treatment group (8 vs. 4).

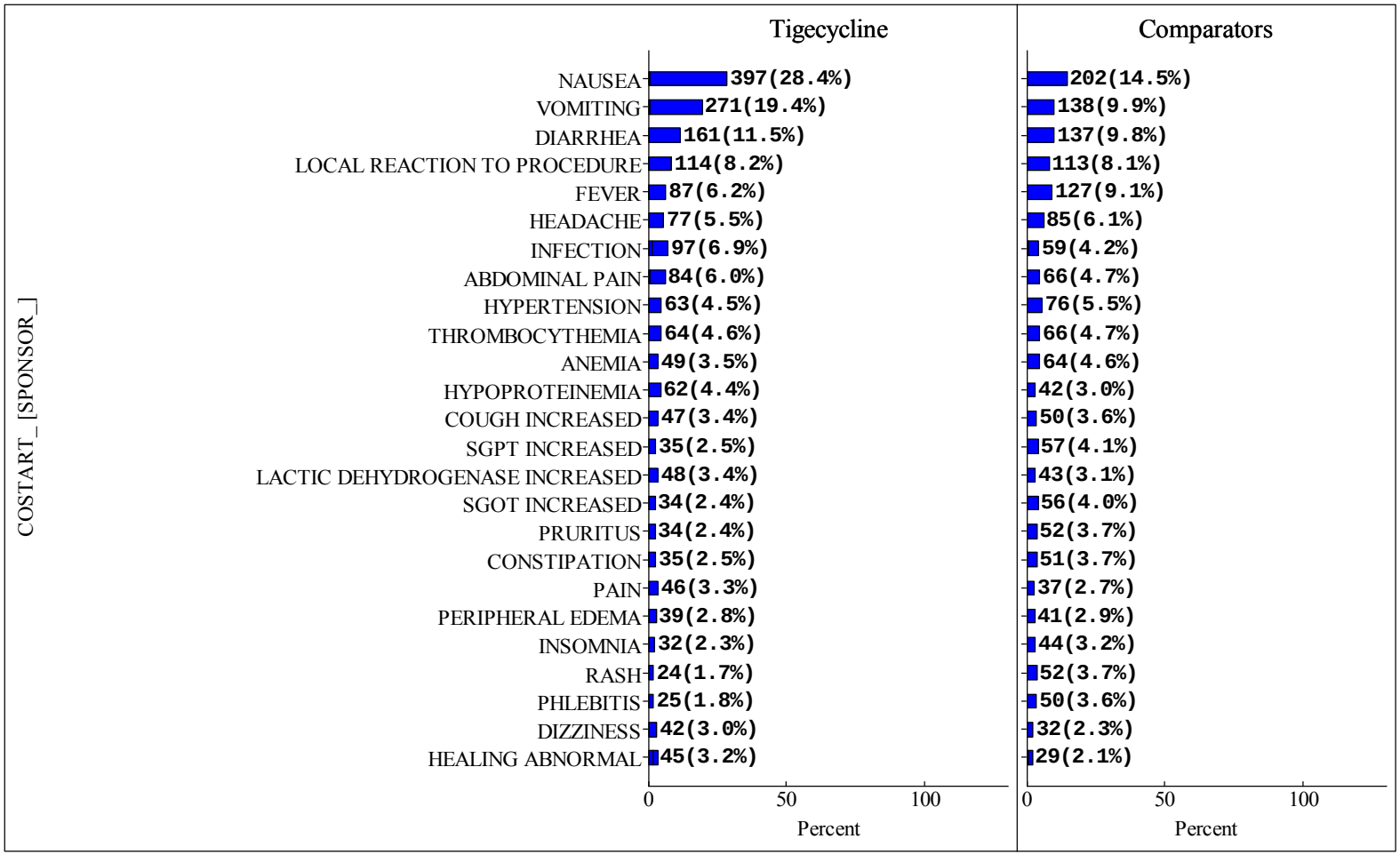
Adverse Events Resulting in Withdrawal from Study, cIAI and cSSSI (studies 300, 301, 305, 306)			
Tigecyclient		**Comparator**	
Adverse Event Preferred Term	N	Adverse Event Preferred Term	N
NAUSEA	5	RASH	8
LEUKOCYTOSIS	4	PRURITUS	5
HEALING ABNORMAL	3	HEALING ABNORMAL	4
INFECTION	3	ACCIDENTAL INJURY	3
SEPSIS	3	DYSPNEA	3
VOMITING	3	INFECTION	3
KIDNEY FUNCTION ABNORMAL	2	CHEST PAIN	2
PERITONITIS	2	DERMATITIS ALLERGIC	2
SEPTIC SHOCK	2	NAUSEA	2
ABDOMINAL PAIN	1	NECROTISING FASCIITIS	2
ANGINA PECTORIS	1	OSTEOMYELITIS	2
ASPIRATION PNEUMONIA	1	PARESTHESIA	2
BILIRUBINEMIA	1	VOMITING	2
CARCINOMA	1	ABNORMAL VISION	1
CHILLS	1	ABSCESS	1
DIARRHEA	1	ALLERGIC REACTION	1
DUODENAL ULCER PERFORATION	1	ANAPHYLACTOID REACTION	1
FEVER	1	ANEMIA	1
GANGRENE	1	ASCITES	1
GRANULOCYTOSIS	1	CELLULITIS	1
HEART FAILURE	1	COLITIS	1
HYPOTENSION	1	COUGH INCREASED	1
LIVER DAMAGE	1	ERYTHEMA	1
LOCAL REACTION TO PROCEDURE	1	FACE EDEMA	1
NAUSEA AND VOMITING	1	FEVER	1
NECROTISING FASCIITIS	1	HEADACHE	1
PAIN	1	HEART ARREST	1
PNEUMONIA	1	KIDNEY FAILURE	1
RASH	1	LEFT HEART FAILURE	1
RESPIRATORY FAILURE	1	LEUKOCYTOSIS	1
SHOCK	1	LOCAL REACTION TO PROCEDURE	1
SWEATING	1	MACULOPAPULAR RASH	1
TOXIC NEPHROPATHY	1	RESPIRATORY DISTRESS SYNDROME	1
		RHINITIS	1
		SEPSIS	1
		SKIN DISORDER	1
		SOMNOLENCE	1
		TREMOR	1
		URTICARIA	1
		VASODILATATION	1

7.1.6 Common Adverse Events

Adverse Events

The following graph displays the most common treatment emergent adverse events (TEAE) for all controlled trials combining cIAI and cSSSI (studies 300, 301, 305, 306). The most common adverse events for both tigecycline and comparators were nausea and vomiting. Rates of nausea, vomiting, and infection were higher for tigeycline-treated patients than those for comparator-treated patients. There were also slightly higher rates of fever, rash, phlebitis, and SGPT increases in the comparator-treated group than in the tigecycline-treated group.

THERAPYT [DEMO_ALL]



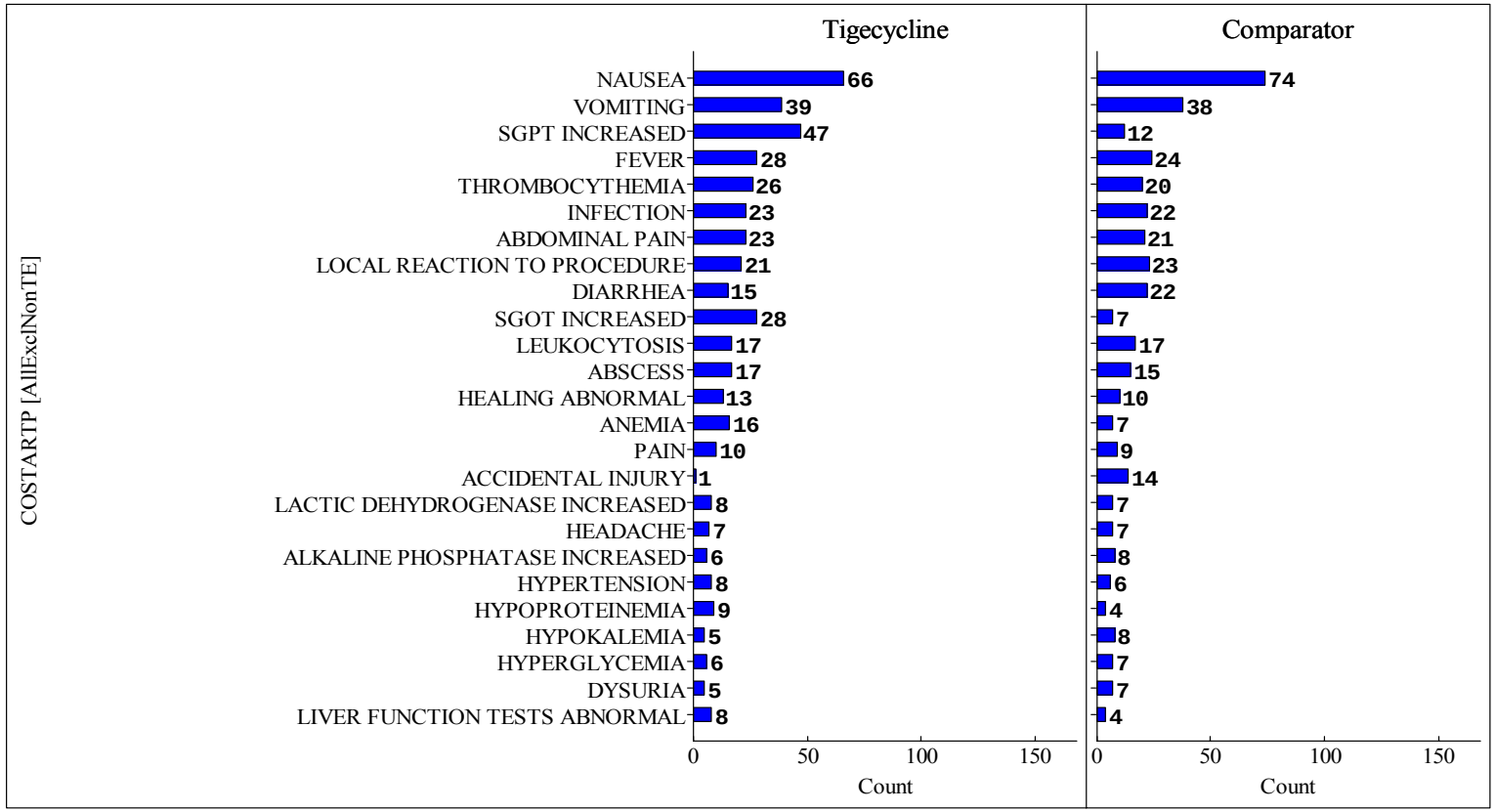
Counting the records in dataset SPONSOR , uniquing them by variable UNIQUE_S [SPONSOR].
Normalize by dataset DEMO_ALL, uniquing the record count by variable UNIQUE_S [DEMO_ALL].
Get normalization denominator from current cell in current layer, with a scope of the whole cell.

Important differences between the Medical Officer's analysis and the sponsor's submitted analysis includes that all reported adverse events occurring between first dose and test-of-cure which were identified by the sponsor as having been non-treatment emergent, yet were not categorized that way during the conduct of the trial, were included in the Medical Officer's analysis as being treatment emergent. This provides a more conservative analysis.

It is also important to note that this analysis as submitted by the sponsor defined treatment emergent adverse events as adverse events occurring after the first dose of therapy and up to 5 days after the last dose of therapy. This definition does not take into account the fact that tigecycline has a very long half-life (40 hours) and a tissue half-life which is likely to be even longer. For this reason, it is likely that at the time point of 5 days after the final dose of tigecycline, there is a high likelihood that most patients would still be experiencing tigecycline exposure. Therefore, a more reasonable analysis would include a treatment-emergent definition that included adverse events which occurred in a time frame that extends further out than 5 days after last dose. This is also important because certain adverse events, such as liver toxicity, have been well described to potentially occur after the period of drug exposure.

To explore this issue of inappropriate adverse event exclusion, an analysis was done comparing all adverse events from controlled clinical studies which were excluded from the above analysis because they were classified as non-treatment emergent. If the excluded adverse events (sponsor designated non-treatment emergent) in this analysis were truly not related to study drug, then there should no significant differences between the two treatment groups with regard to particular adverse events. The following graph shows the most common adverse events which were considered to be non-treatment emergent and thus excluded from the sponsor's analysis. The vast majority of these events were excluded on the basis of having occurred beyond the 5 day post-treatment window.

THERAPYT [AllExclNonTE]



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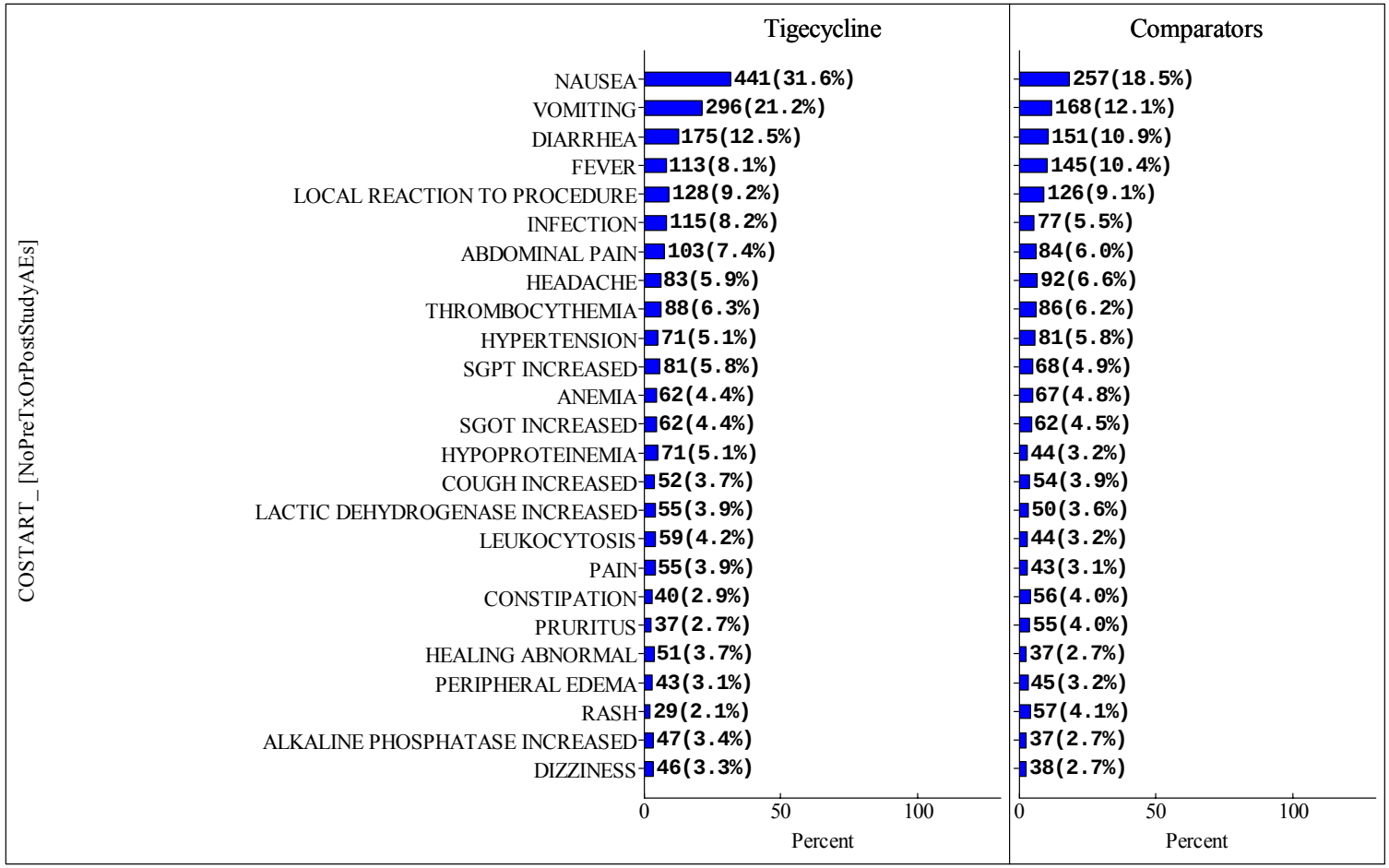
Display 'count' at level of exterior breakdown.

Sorting by order in layer's total cell in total layer.

Showing first 25 glyphs.

Review of excluded adverse events reveals that most of them are similar in number between the treatment groups. The only marked differences include accidental injury and liver enzyme abnormalities. Review of the causes of the accidental injuries revealed that there was no likely treatment-related explanation for the difference. The number of liver function abnormalities was markedly higher in the tigecycline-treated group as compared with the comparator group, raising the issue of a possible difference between tigecycline-treated patients and comparator-treated patients in the onset of liver function abnormalities. An additional analysis is contained in the following graph, which shows all adverse events occurring after the first dose of study drug, but excludes those adverse events which were determined by the sponsor to have occurred after the study was completed (after TOC and after the late follow-up period).

THERAPYT [DEMO_ALL]



Counting the records in dataset NoPreTxOrPostStudyAEs, uniquing them by variable UNIQUE_S [NoPreTxOrPostStudyAEs].
Normalize by dataset DEMO_ALL, uniquing the record count by variable UNIQUE_S [DEMO_ALL].
Get normalization denominator from current cell in current layer, with a scope of the whole cell.

The most obvious difference between this analysis and the sponsor's originally submitted analysis is that tigecycline, which in the sponsor's analysis, had a lower rate of liver function abnormalities, now, in this new analysis, has a higher rate of liver function abnormalities. This is consistent with what was seen in in the Medical Officer's analysis in which excluded adverse events were depicted. This change suggests that although the overall rate of liver function abnormalities was, in this new analysis, more similar to the comparator treated group, there could be a difference between tigecycline and comparator drugs in the time of onset of these liver events. For this reason, the sponsor was asked to submit to the FDA additional analyses which explored not only the timing of onset of liver function abnormalities but also the severity of these abnormalities as well. Ladder analyses were conducted by ALT, AST, and total bilirubin, also separated by indication and integrated for patients with baseline normal liver function tests and baseline abdnormal liver function tests. The table below shows the ladder analysis for all integrated phase 3 studies for ALT in those patients whose baseline liver functions were normal. This analysis comfirms what was previously suspected that liver function abnormalities associated with tigecycline occurred at a later timepoint than those in comparator.

Tigecycline 3074A1 Protocols 300, 301, 305 and 306 Combined

Summary of Liver Function Test Abnormalities

Lab Parameter = ALT
Population = Baseline Normal

Changes	On-Therapy Tigecycline	On-Therapy Comparator	TOC Tigecycline	TOC Comparator
	N= 790 n(%)	N= 755 n(%)	N= 790 n(%)	N= 755 n(%)
<UNL	673(85.2)	548(72.6)	507(64.2)	572(75.8)
>UNL to <=2x UNL	79(10)	139(18.4)	131(16.6)	91(12.1)
>2 to <=3x UNL	13(1.6)	30(4)	37(4.7)	6(0.8)
>3 to <=5x UNL	8(1)	12(1.6)	11(1.4)	4(0.5)
>5 to <=8x UNL	1(0.1)	4(0.5)	6(0.8)	0(0)
>8x UNL	0(0)	1(0.1)	3(0.4)	1(0.1)
Missing	16(2)	21(2.8)	95(12)	81(10.7)

Statistical Report <FDA_LFT_300_301_305_306 02MAR2005>

Further analysis was conducted to explore the completeness of the follow-up of liver function abnormalities. The table below shows that there were more tigecycline-treated patients with ALT abnormalities which were abnormal at the time of the last measurement than in the comparator arm.

Abnormal ALT at time of Final Measurement						
ALT incr above ULN	Tigecycline			Comparators		
	cIAI	cSSSI	Total	cIAI	cSSSI	Total
2.0-2.5	24	18	42	18	9	27
2.6-3.0	8	7	15	9	1	10
3.1-4.0	11	1	12	3	3	6
4.1-5.0	2	4	6	3	2	5
>5.0	5	2	7	3	3	6

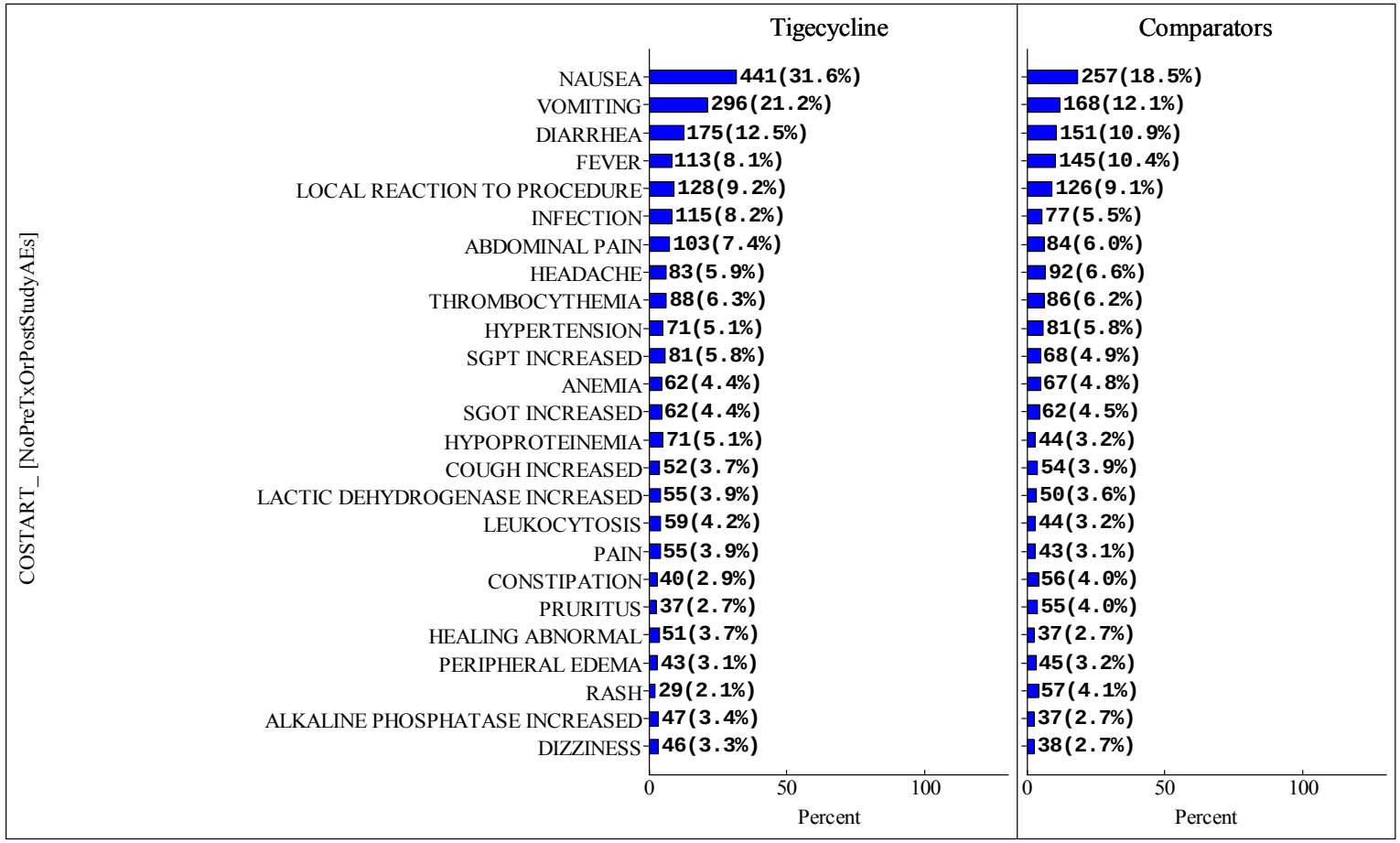
In conclusion, the data support the concept that tigecycline-treated patients with associated liver function test abnormalities tend to experience these abnormalities later, and often after the end of therapy, than the comparator-treated patients who experienced liver function abnormalities on-therapy. This pattern leads to a larger number of patients whose last measured liver enzymes were abnormal, and presents difficulties in fully understanding the liver toxicity profile of this drug. While there were not cases in the database which support the possibility of idiosyncratic hepatic reactions, this possibility cannot be excluded at this time, and further assessment will be needed during the post-marketing period.

Also of note in the Medical Officer's analysis, the rates of adverse events of "amylase increased" were seen more often in tigecycline-treated patients, than in comparator-treated patients (3.5% vs. 2.0%). These cases were reviewed and the majority did not appear to be significant, however, given the case of acute pancreatitis which occurred in a tigecycline-treated patient (see SAE section), this increase in amylase adverse events may be important.

7.1.7 Adverse Events by Indication

To further understand the adverse event profile of tigecycline, analyses of the most common treatment-emergent adverse events by indication were examined. The following graphs show the most common TEAE by indication. In this analysis, TEAE excluded only pretreatment and post-study AEs.

THERAPYT [DEMO_ALL]



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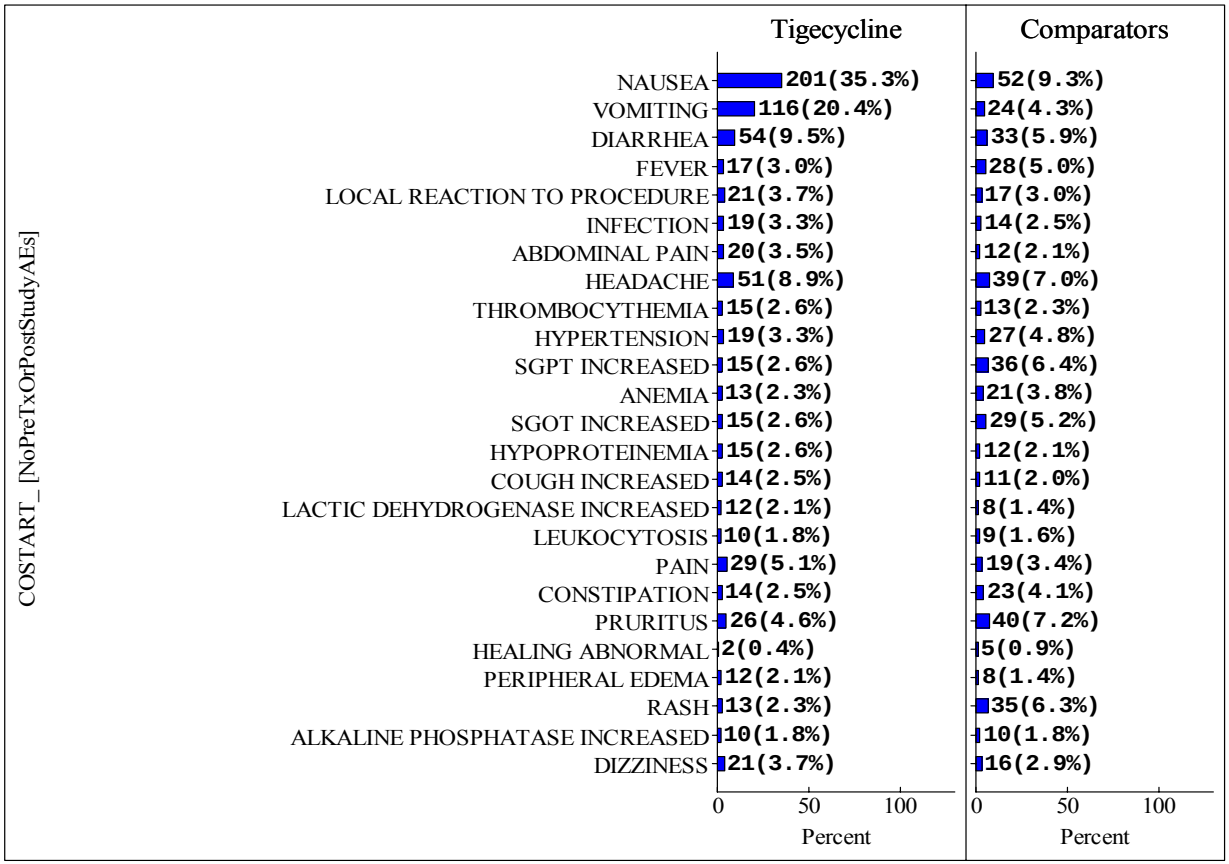
Normalize by dataset DEMO_ALL, uniquing the record count by variable UNIQUE_S [DEMO_ALL].
Get normalization denominator from current cell in current layer, with a scope of the whole cell.

PROTOCOL [DEMO_ALL]
cSSSI

THERAPYT [DEMO_ALL]



Counting the records in dataset NoPreTxOrPostStudyAEs, uniquing them by variable UNIQUE_S [NoPreTxOrPostStudyAEs].
Normalize by dataset DEMO_ALL, uniquing the record count by variable UNIQUE_S [DEMO_ALL].
Get normalization denominator from current cell in current layer, with a scope of the whole cell.

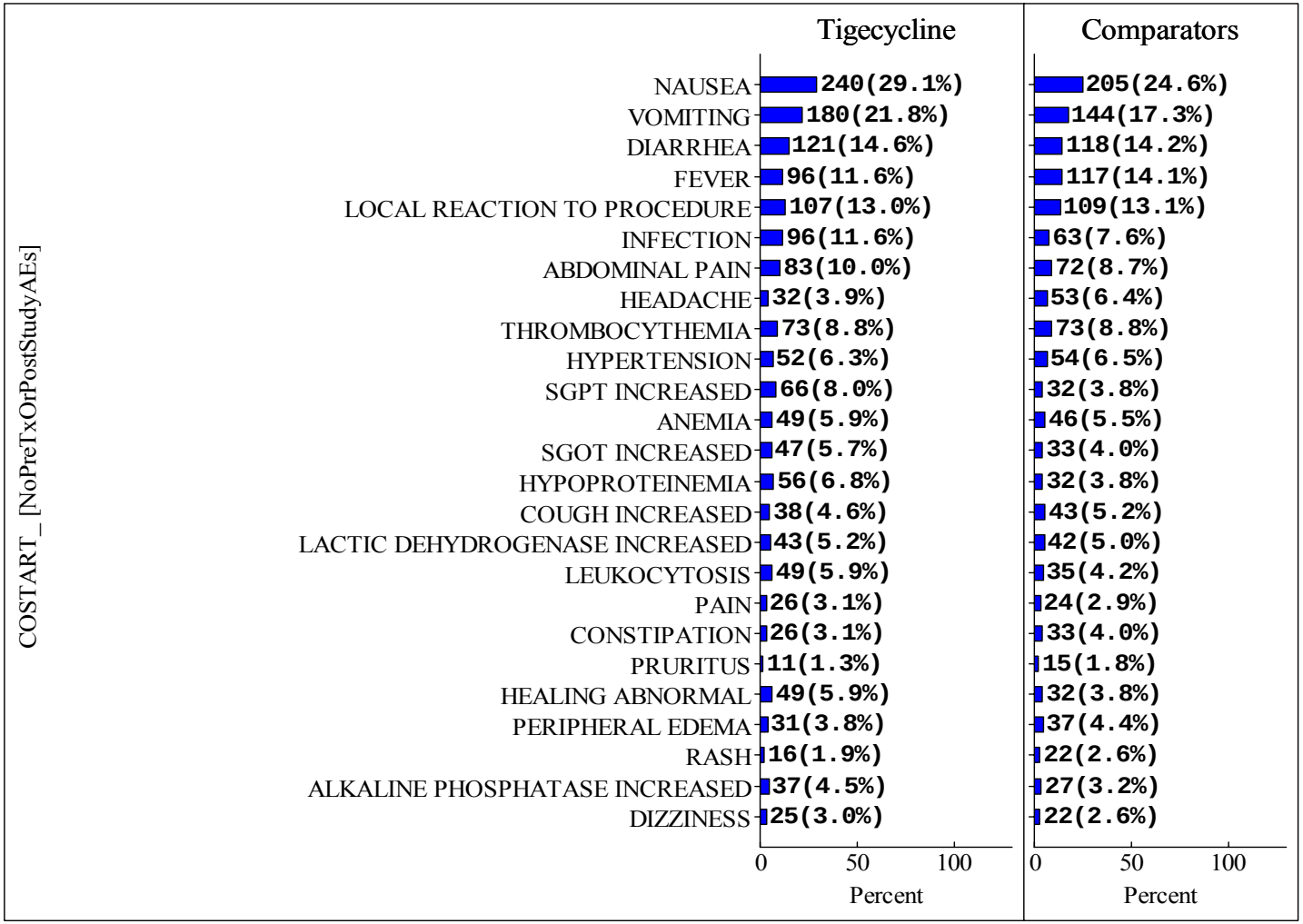
After assessment of the results of the analyses shown in these graphs, the differences in the AE profile of tigecycline according to indication become clear with regard to nausea and vomiting. In the controlled cSSSI studies, nausea and vomiting are markedly more common in the tigecycline treated patients as compared to the vancomycin/aztreonam patients

Adverse Events by Indication

To further understand the adverse event profile of tigecycline, analyses of the most common treatment-emergent adverse events by indication were examined. The following graphs show the most common TEAEs by indication using the definition of treatment emergent (excluding only pretreatment and post-study AEs).

PROTOCOL [DEMO_ALL]
cIAI

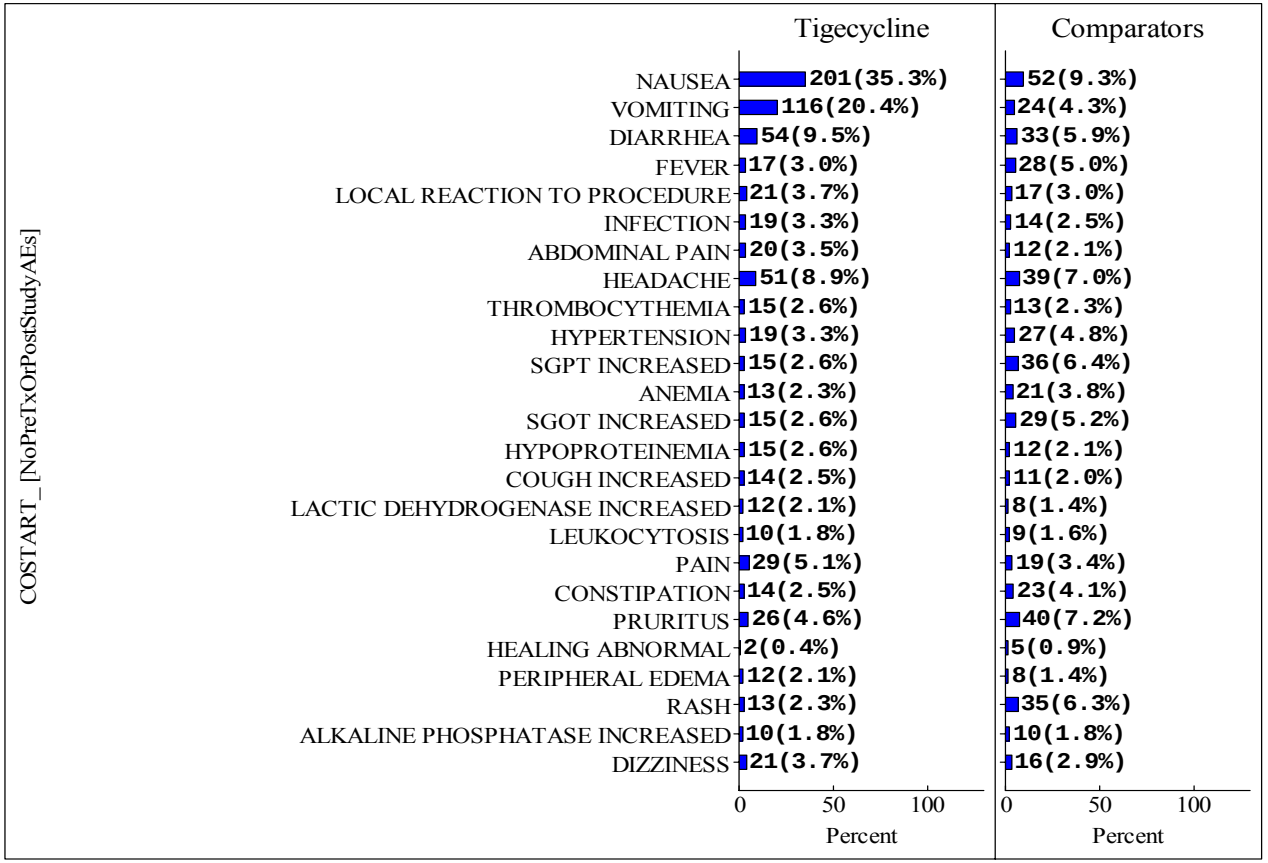
THERAPYT [DEMO_ALL]



Counting the records in dataset NoPreTxOrPostStudyAEs, uniquing them by variable UNIQUE_S [NoPreTxOrPostStudyAEs].
Normalize by dataset DEMO_ALL, uniquing the record count by variable UNIQUE_S [DEMO_ALL].
Get normalization denominator from current cell in current layer, with a scope of the whole cell.

PROTOCOL [DEMO_ALL]
cSSSI

THERAPYT [DEMO_ALL]



Counting the records in dataset NoPreTxOrPostStudyAEs, uniquing them by variable UNIQUE_S [NoPreTxOrPostStudyAEs].
Normalize by dataset DEMO_ALL, uniquing the record count by variable UNIQUE_S [DEMO_ALL].
Get normalization denominator from current cell in current layer, with a scope of the whole cell.

Assessment of the results of the analyses shown in graphs above, the differences in the AE profile of tigecycline according to indication become clear. In the controlled cSSSI studies, nausea and vomiting are markedly more common in the tigecycline treated patients as compared to the vancomycin/aztreonam-treated patients; however, liver function abnormalities are less frequent in tigecycline-treated patients in this indication. When assessing the adverse event rates for the cIAI studies, the rates of nausea and vomiting are much more similar between the two treatment groups, but the rates of liver function tests are higher in the tigecycline-treated patients compared to the imipenem-treated patients.

Hy's Law

The sponsor was asked to identify all possible cases which could fulfill the criteria of Hy's Law. Typically, the criteria identify those patients who, while on therapy, developed liver function abnormalities which include an ALT of at least 3X the upper limit of normal (ULN), a total bilirubin of at least 1.5 in the setting of a normal alkaline phosphatase. The Hy's Law criteria were intended to identify a pattern of liver injury that could result in high risk of development of a potentially dangerous, idiosyncratic liver reaction. The requirement of a normal alkaline phosphatase is included as a way of filtering out those patients whose liver function abnormalities are related to cholestatic processes, rather than hepatocellular mechanisms of injury, because, it is generally thought that patients with a cholestatic pattern of liver injury have a lower risk for progression to hepatic failure.

In attempting to identify patients with possible liver injury, the sponsor chose a potentially more sensitive method of identifying cases. Instead of requiring patients to have a total bilirubin of 1.5X ULN, the sponsor included all patients whose total bilirubin increased by at least 50% above baseline. The following table shows the ten patients that were identified.

PID	Study Drug	Age/Sex/ Diagn	LFT Pattern	Outcome	Confounders
300-315-4266	Tige-cycline	37 m leg abscess	Initial incr. Alk phos,then decr; incr ALT at last visit; Tbili incr but stayed nl		Ketorolac 1 day b/f last visit
301-142-6760	Tige-cycline	69 m abdom abscess	Tbili incr to 1.4Xuln,nl on d.19 ; ALT incr 4.8xuln on d. 19 ;APnl throughout; Tig tx stopped d.8	ALT nl at d. 40	
306-023-0443	Tige-cycline	45 f complic cholecystitis	Tx d1-6 ;Tbili incr 2.5xbut Nl throughout;alt abn at bl, incr to 4.1 on d.3, then decr to below bl but remained elevated; AP incr peak d.14, then decr but still abn	Alt incr at bl, declined to near nl	Complic cholecystitis; tramadol, omeprazole
306-107-2103	Tige-cycline	26 m complic appi	Alt incr from 1.2 at bl to 3.5 at d. 27. Tbili incr by 50% but was always below ULN. AP nl throughout	?	Acetominophen
306-126-2462	Tige-cycline	37 m complic appi	Tx to d11. Tbili incr to 2.4xuln by tx d3 and decr to nl by last day of tx. ALT incr to 1.9 by d.3 and 2.1 by d17; AP incr to 1.3 on day 17 and 1.5 on day 46 (toc)	Pt adm c pn and died of sepsis.	Sl elev tbili and ast at b/s (both 1.2 x uln)
306-127-2487	Tige-cycline	76f compl divertic colon ca	Alt incr to 6.1x uln on d.6; tbili incr to 3.1x uln on d.6; AP incr to 1.8x uln by day 6.	Died on d.8	Mrsa pn, dvt, blood tx, paracoxib
305-006-0099	Vanco/ atreo	69m rt gluteal abscess	Tbili incr 1.6x but remained nl; alt sl incr at bl (1.1x) incr to 3.3x uln; AP nl throughout.	Alt, tbili nl at last visit	Sl incr at bl
305-092-2184	Vanco/ atreo	64f cellulitis	Bili incr 2.4x but nl; alt 3.3x uln at d3 decr to 1.4 by last day of tx then nl; AP nl;	Lfts norm-alized	Tylenol started on d1
301-084-3663	Imi-cilast	42f "pelvic infection"	Alt incr 3.2x uln on d6. AP nl; tbili incr 50% but was nl	Lft's normalized	Ranitidine, tenoxicam, dipyrone
301-125-5492	Imi-cilast	67m large bowel perf	Tbili incr to 1.2xuln d3(only other measurement); alt incr 46.3xUln d3. AP nl.	Liver failure	Initial severe sepsis with multi-org failure
301-404-6217	Imi-cilast	40m S.I. perf/ peritonitis	Tbili 1.5x uln at bl, incr to 3.2x uln by d5; ALT incr to 2.3x uln by last day of tx (d5); AP nl	Cardiac arrest/died	Sepsis/resp distress at bl

The sponsor's method of including patients whose total bilirubin levels increased by 50% may have been more sensitive in detecting possible cases of hepatoxicity, however, after review of the identified cases, it appears that it is also less specific. Several cases were identified in which the patient's measured bilirubin rose by at least 50%, but remained below the ULN during the study. It is uncertain how these cases should be interpreted. Because Hy's Law has never been tested prospectively, it is not possible to assign a level of risk to this particular subset of patients. However, since the magnitude of LFT changes are directly related to the magnitude of the severity of liver damage (in acute hepatic processes), it is unlikely that these cases represent hepatotoxicity of significant concern.

Tigecycline-treated patients who developed increases in LFT's consistent with the traditional Hy's Law were significantly confounded by concomitant medications and acute illnesses such that assigning causality is not possible. None of the cases reviewed represents a clear, non-confounded instance of drug-related liver toxicity, and there are no cases in which there was severe hepatic failure without a reasonable non-drug related explanation.

Nausea and Vomiting

There is a marked difference in the rates of nausea and vomiting between tigecycline-treated patients and comparator-treated patients as is seen in the following table. This difference is driven, primarily by the difference in nausea and vomiting rates in the cSSSI trials (300, 305). The difference in rates of nausea and vomiting is also present in the cIAI trials (301, 306), but these differences are much smaller.

	Tigecycline		**Comparator**	
	n/N	**%**	**n/N**	**%**
Nausea				
All Controlled Trials	460/1396	33.0	274/1391	19.7
cSSSI Trials	207/570	36.3	54/559	9.7
cIAI Trials	253/826	30.6	220/832	26.4
Vomiting				
All Controlled Trials	307/1396	22.0	185/1391	13.3
cSSSI Trials	117/570	20.5	25/559	4.5
cIAI Trials	190/826	23.0	160/832	19.2

Possible explanations for the pronounced difference in the rate of nausea and vomiting that is seen between the cSSSI and cIAI involve differences that may exist between the patient populations of the two indications. To explore this, the following analyses were conducted:

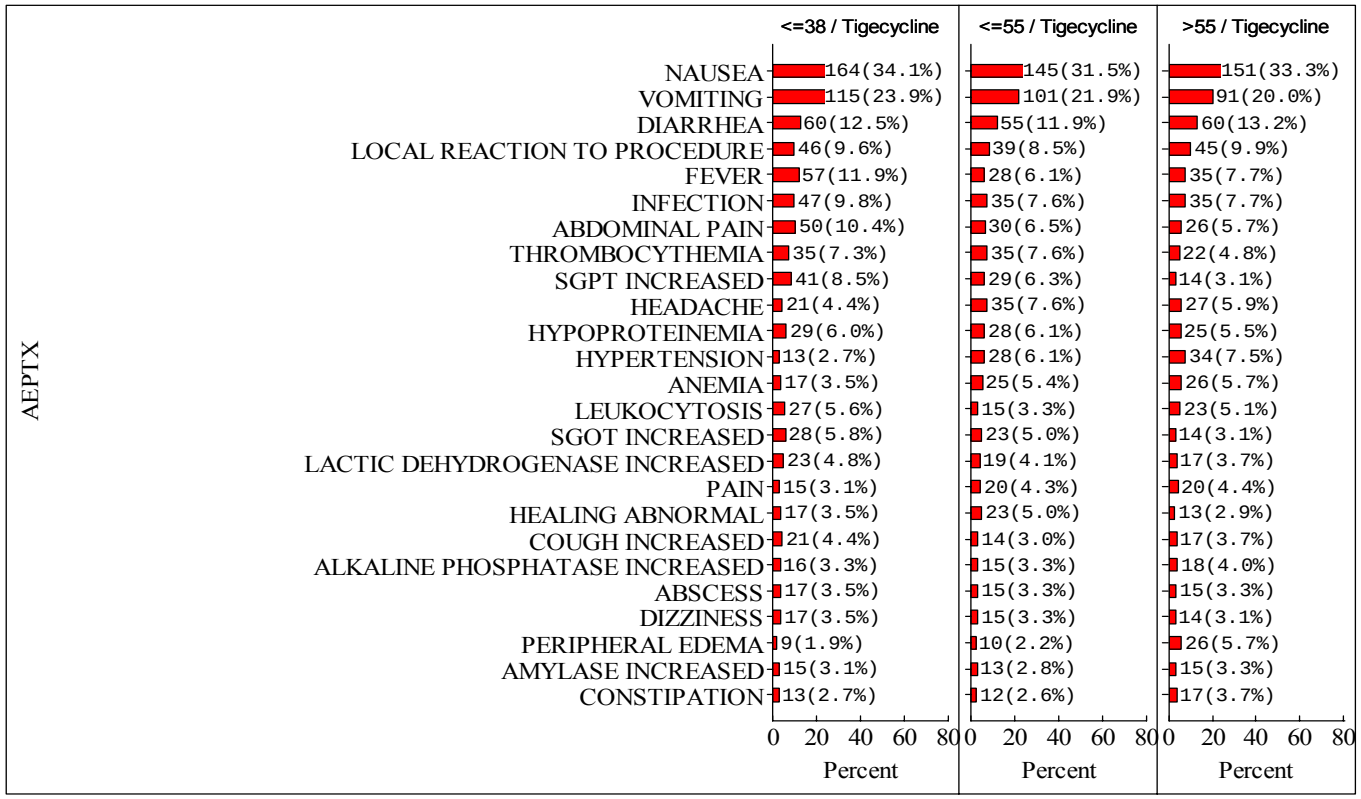
The results of these analyses did not reveal any factors which were associated with increased rates of nausea and vomiting. The increase in rates of nausea and vomiting in the cSSSI studies was not related to specific factors, and instead, was seen to be spread across the different analysis factors.

Age and Gender

The rates of adverse events were examined by Age and Gender. These analyses are shown in the following graphs. There were no clear trends or associations of adverse events with particular age groups.

PROTID [DEMOWWIT]
Total

AGE [DEMOWWIT]/TPNAME [DEMOWWIT]



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Normalize by dataset DEMOWWIT, uniquing the record count by variable UNIQ_SUB [DEMOWWIT].
Get normalization denominator from current cell in current layer, with a scope of the whole cell.

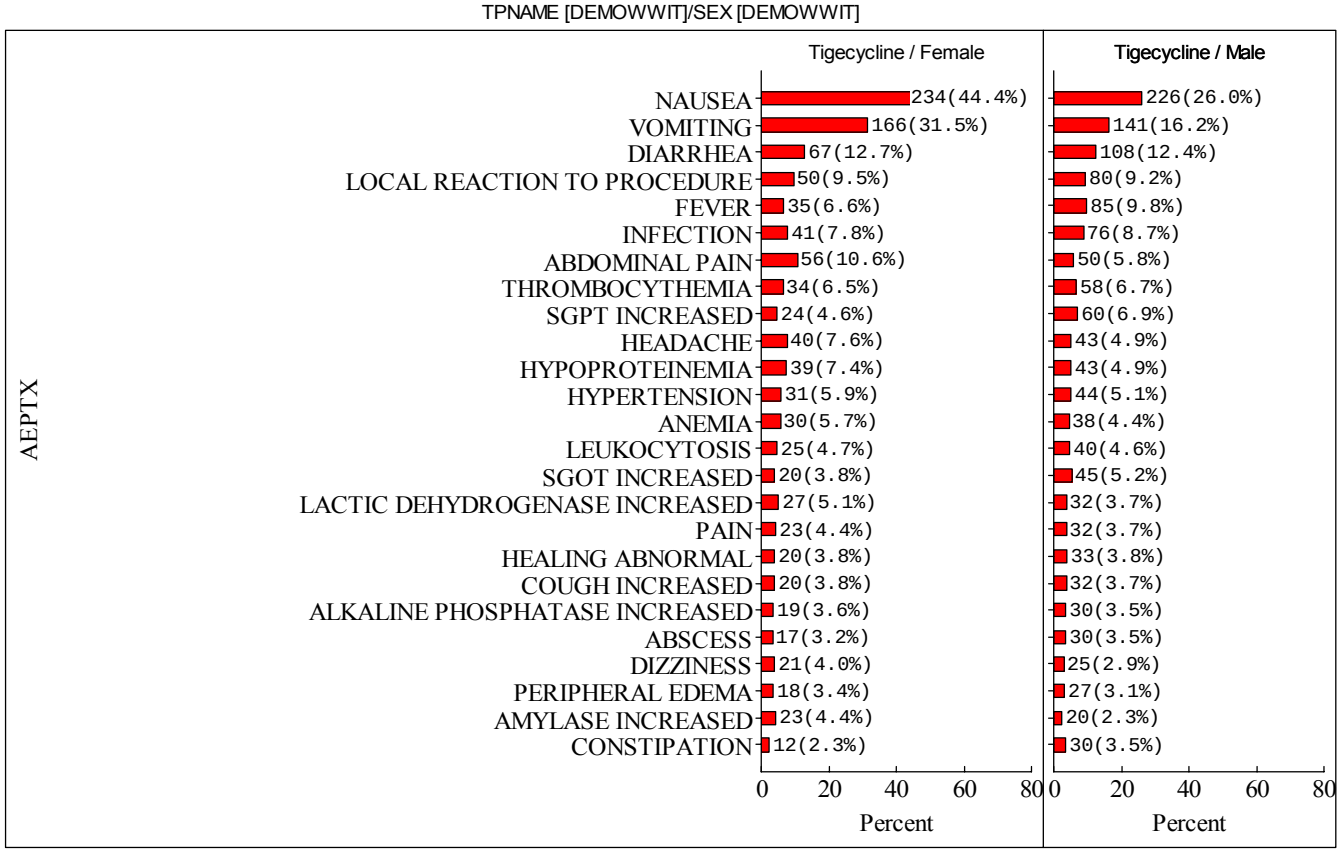
Display 'count(normalized percent)' at level of exterior breakdown.

Sorting by order in layer's total cell in total layer.

Showing first 25 glyphs.

The following graphs shows adverse events by gender. Of note, the rates of nausea and vomiting rates were higher in females than in males, as was noted previously. The rate of abdominal pain was also higher in females than in males.

PROTID [DEMOWWIT]
Total



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Get normalization denominator from current cell in current layer, with a scope of the whole cell.

Display 'count(normalized percent)' at level of exterior breakdown.

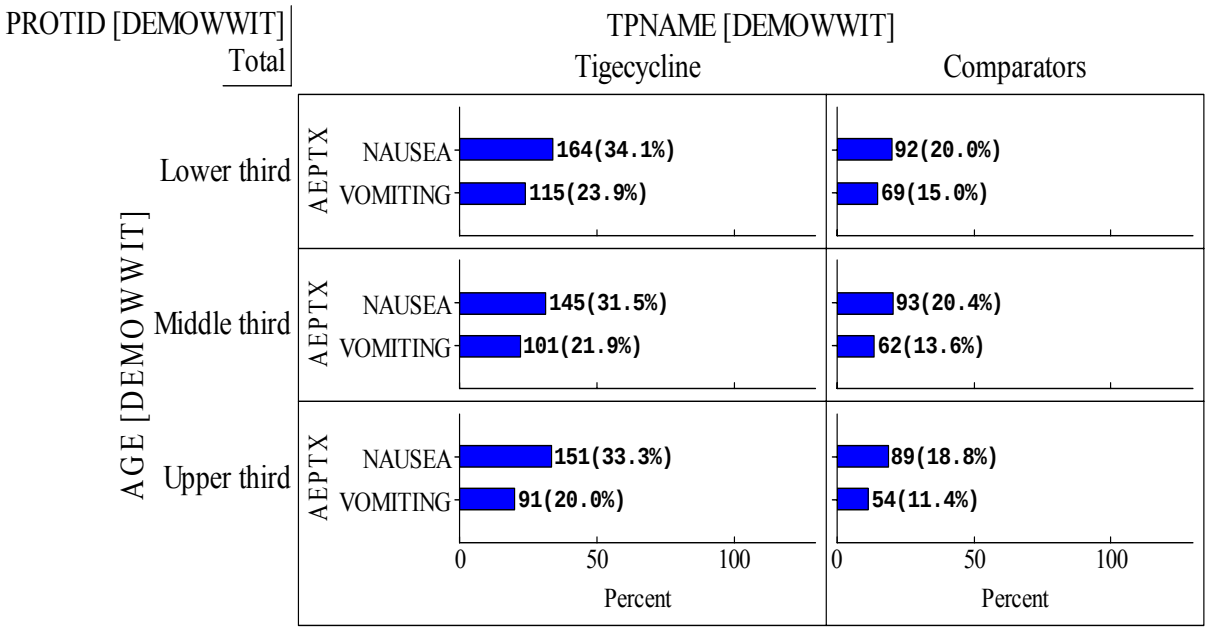
Sorting by order in layer's total cell in total layer.

Showing first 25 glyphs.

Additional analyses were conducted in an attempt to better characterize the rates of nausea and vomiting that occurred with tigecycline-treated patients. These included analyses of nausea and vomiting by indication, gender, age, body mass index, duration of therapy, and be severity of underlying illness.

Nausea and Vomiting Analyses

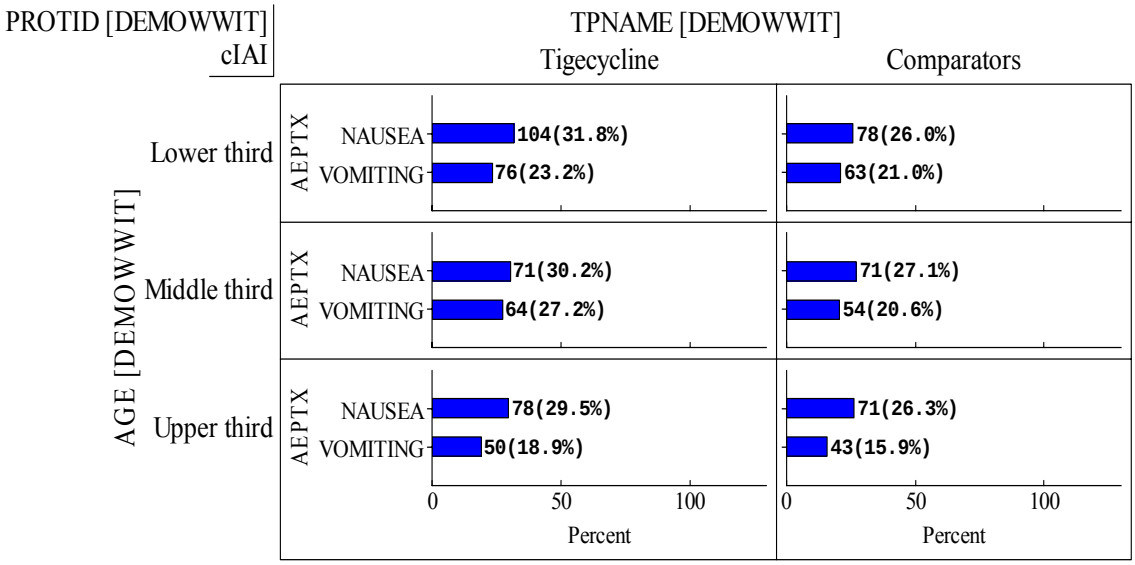
1. Nausea Rates by Age, Studies 300, 301, 305, 306 (cIAI and cSSSI combined)



Counting the records in dataset ADVERSEW, uniquing them by variable UNIQ_SUB [ADVERSEW].
Normalize by dataset DEMOWWIT, uniquing the record count by variable UNIQ_SUB [DEMOWWIT].
Get normalization denominator from current cell in current layer, with a scope of the whole cell.

Display 'count(normalized percent)' at level of exterior breakdown.

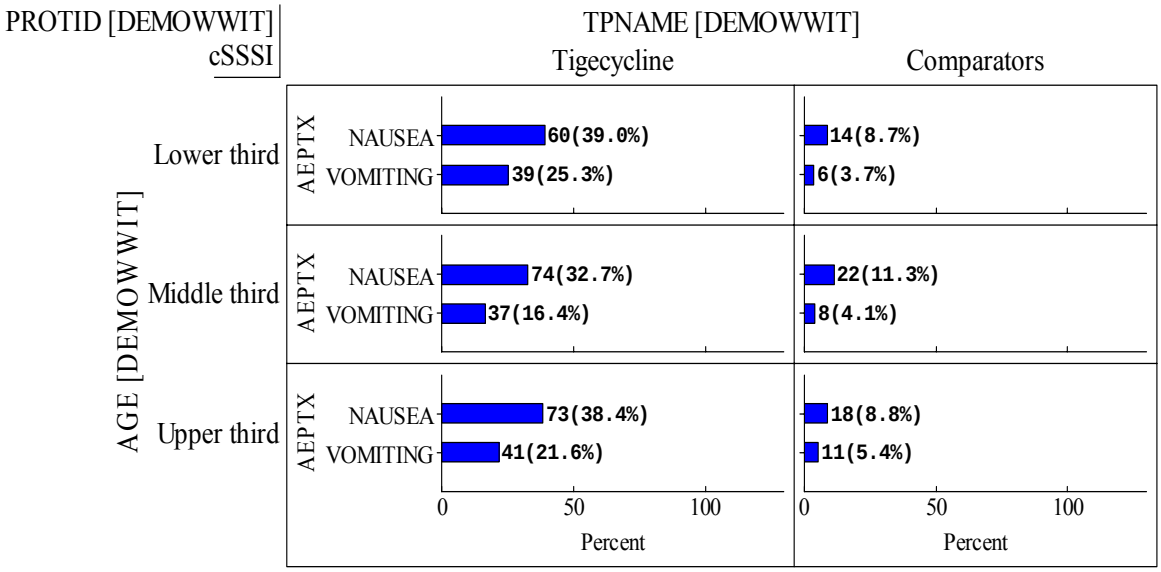
2. Nausea Rates by Age, Studies 301, 306 Combined (cIAI)



Counting the records in dataset ADVERSEW, uniquing them by variable UNIQ_SUB [ADVERSEW]
Normalize by dataset DEMOWWIT, uniquing the record count by variable UNIQ_SUB [DEMOWWIT]
Get normalization denominator from current cell in current layer, with a scope of the whole cell

Display 'count(normalized percent)' at level of exterior breakdown

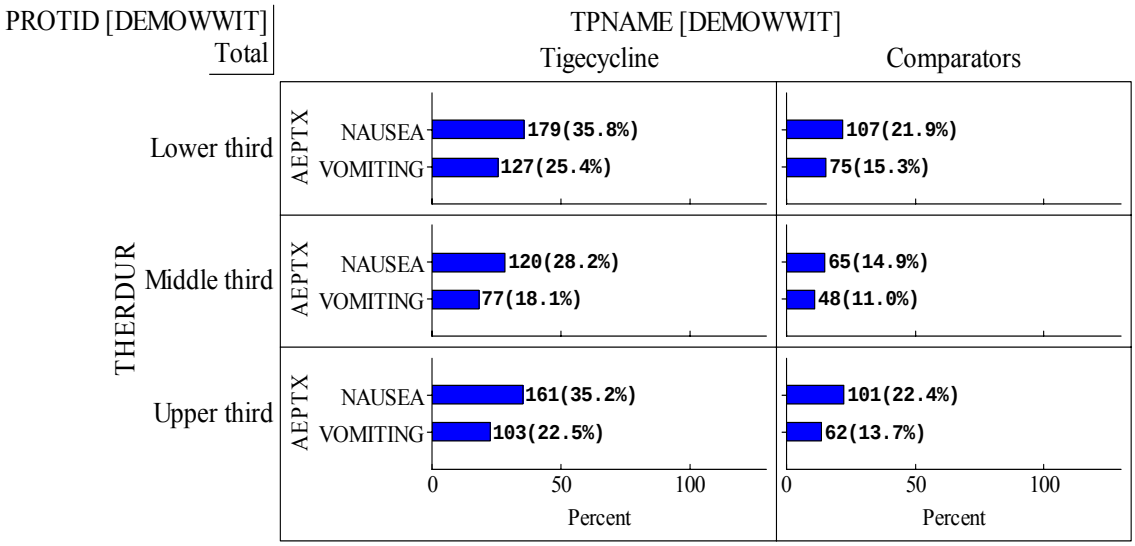
3. Nausea Rates by Age and Indication, cSSI (studies 300 and 305)



Counting the records in dataset ADVERSEW, uniquing them by variable UNIQ_SUB [ADVERSEW]
Normalize by dataset DEMOWWIT, uniquing the record count by variable UNIQ_SUB [DEMOWWIT]
Get normalization denominator from current cell in current layer, with a scope of the whole cell

Display 'count(normalized percent)' at level of exterior breakdown

4. Nausea and Vomiting by Duration of Therapy



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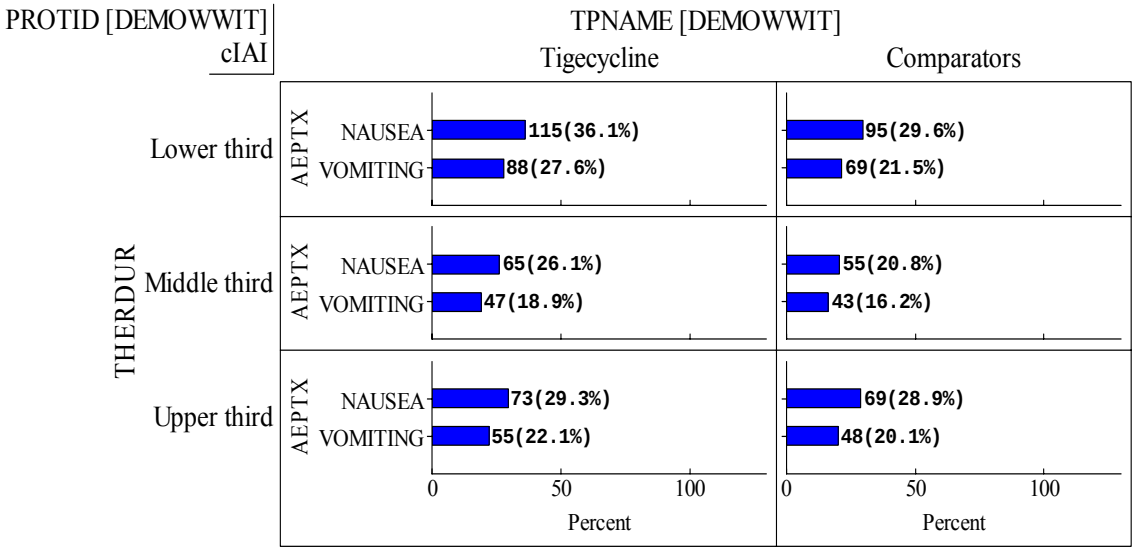
Normalize by dataset DEMOWWIT, uniquing the record count by variable UNIQ_SUB [DEMOWWIT]
Get normalization denominator from current cell in current layer, with a scope of the whole cell

Display 'count(normalized percent)' at level of exterior breakdown

5. Nausea and Vomiting by Duration of Therapy and Indication (cIAI – studies 301, 306)



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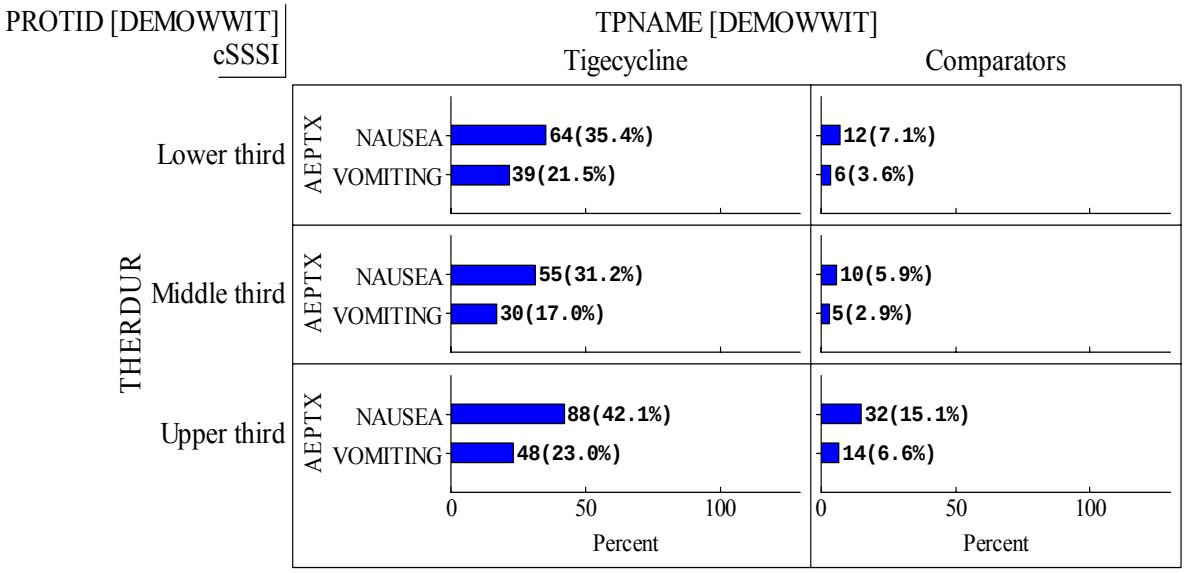
Normalize by dataset DEMOWWIT, uniquing the record count by variable UNIQ_SUB [DEMOWWIT]
Get normalization denominator from current cell in current layer, with a scope of the whole cell

Display 'count(normalized percent)' at level of exterior breakdown

6. Nausea and Vomiting by Therapy Duration and Indication (cSSSI – studies 300, 305)



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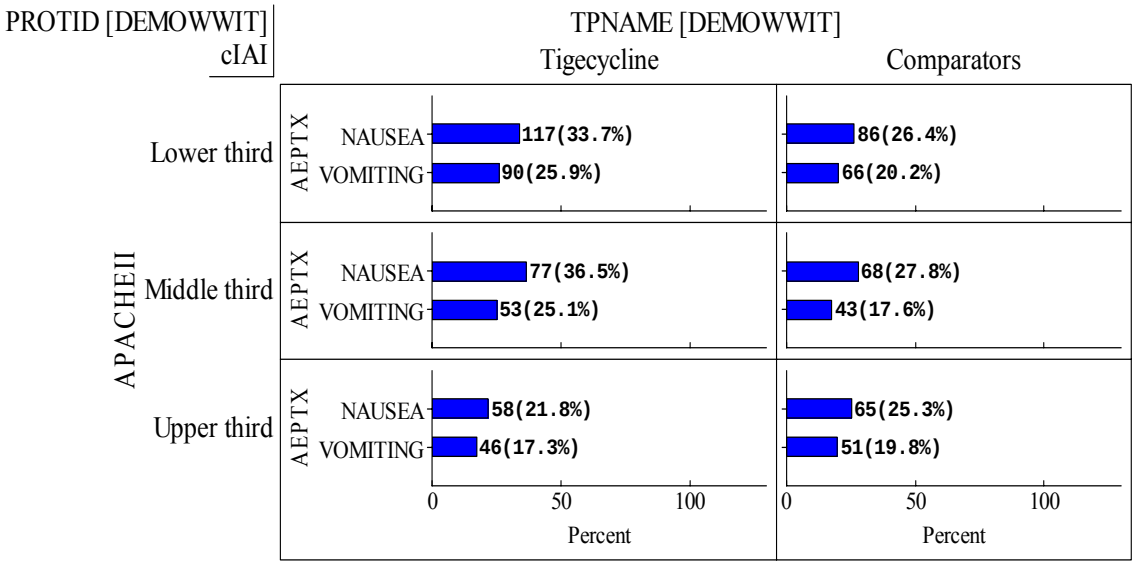
Get normalization denominator from current cell in current layer, with a scope of the whole cell.

Display 'count(normalized percent)' at level of exterior breakdown.

7. Nausea and Vomiting by Severity of Ilness (APACHE II score) for cIAI patients.



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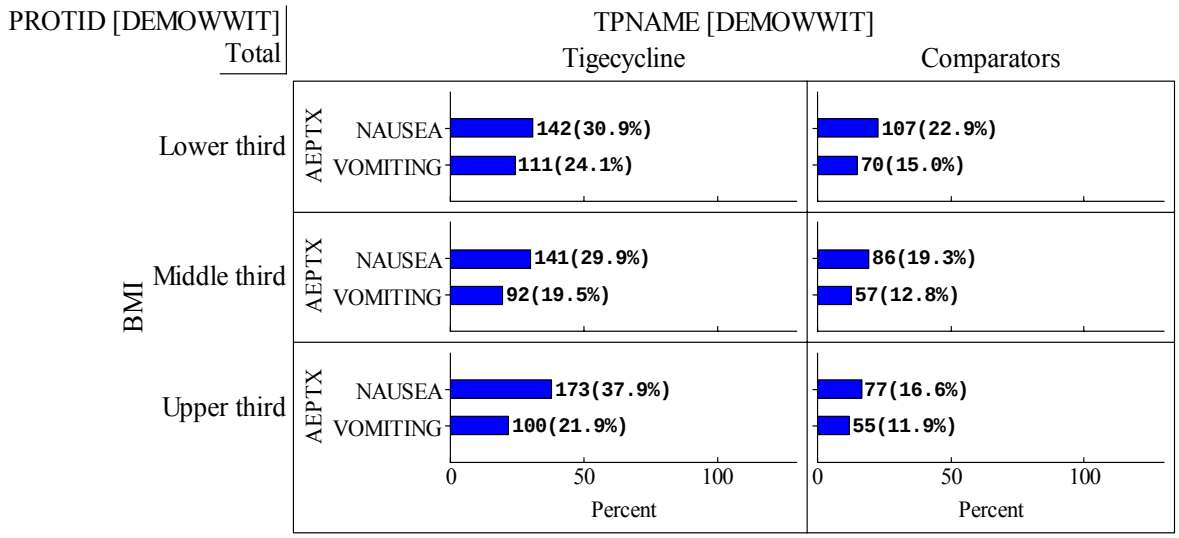
Normalize by dataset DEMOWWIT, uniquing the record count by variable UNIQ_SUB [DEMOWWIT]
Get normalization denominator from current cell in current layer, with a scope of the whole cell

Display 'count(normalized percent)' at level of exterior breakdown

8. a, b, c. Nausea and Vomiting by Indication (cIAI, cSSSI) and Body Mass Index

a. total



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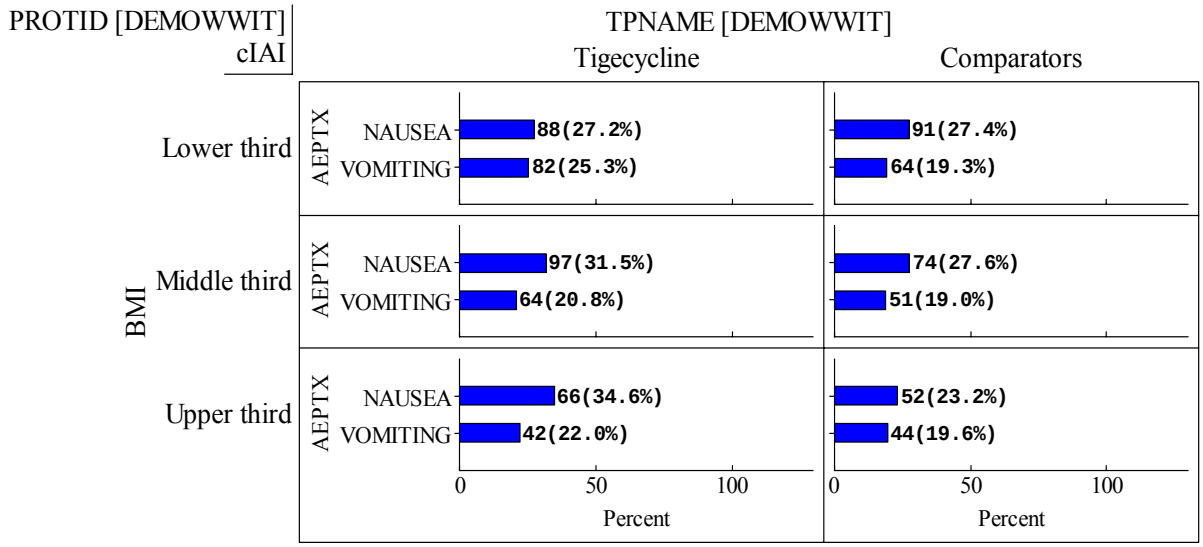
Normalize by dataset DEMOWWIT, uniquing the record count by variable UNIQ_SUB [DEMOWWIT].
Get normalization denominator from current cell in current layer, with a scope of the whole cell.

Display 'count(normalized percent)' at level of exterior breakdown.

b. cIAI



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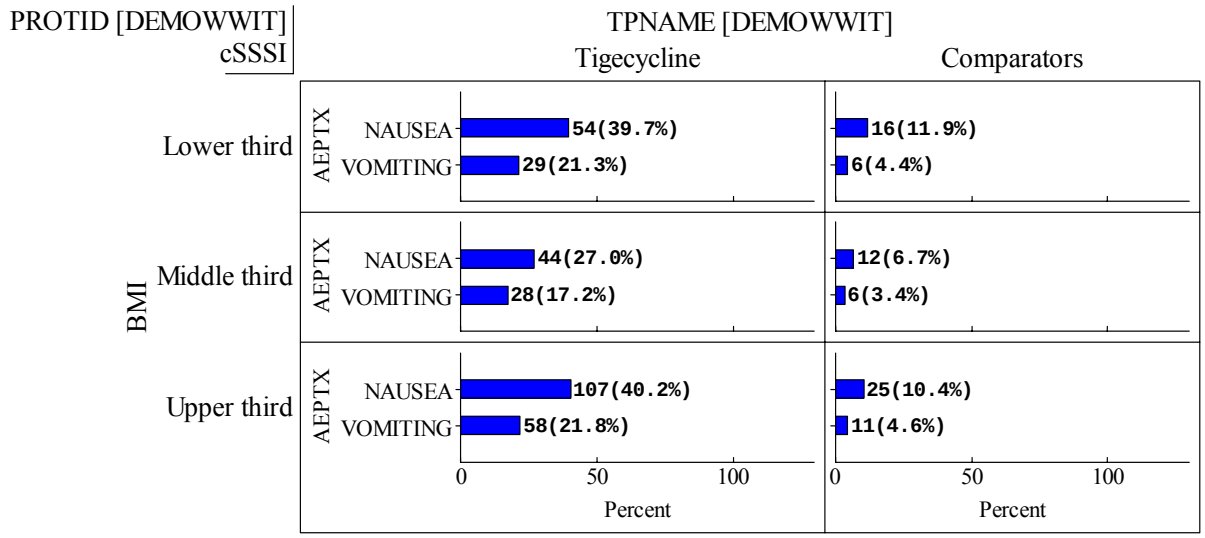
Normalize by dataset DEMOWWIT, uniquing the record count by variable UNIQ_SUB [DEMOWWIT].
Get normalization denominator from current cell in current layer, with a scope of the whole cell.

Display 'count(normalized percent)' at level of exterior breakdown.

c. cSSSI



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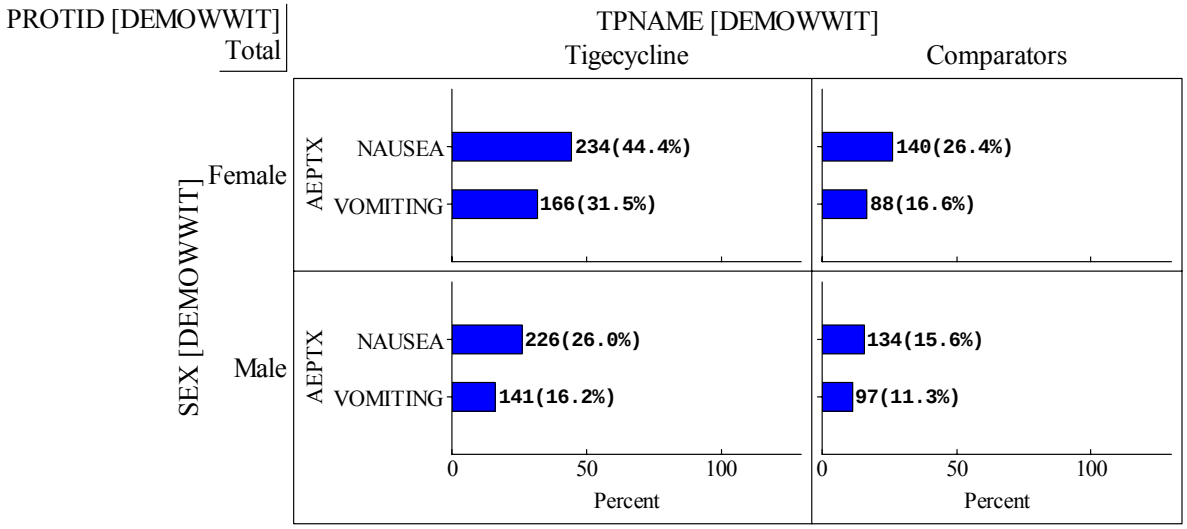
Normalize by dataset DEMOWWIT, uniquing the record count by variable UNIQ_SUB [DEMOWWIT].
Get normalization denominator from current cell in current layer, with a scope of the whole cell.

Display 'count(normalized percent)' at level of exterior breakdown.

9. a. b. c. Nausea and Vomiting by Gender and Indication

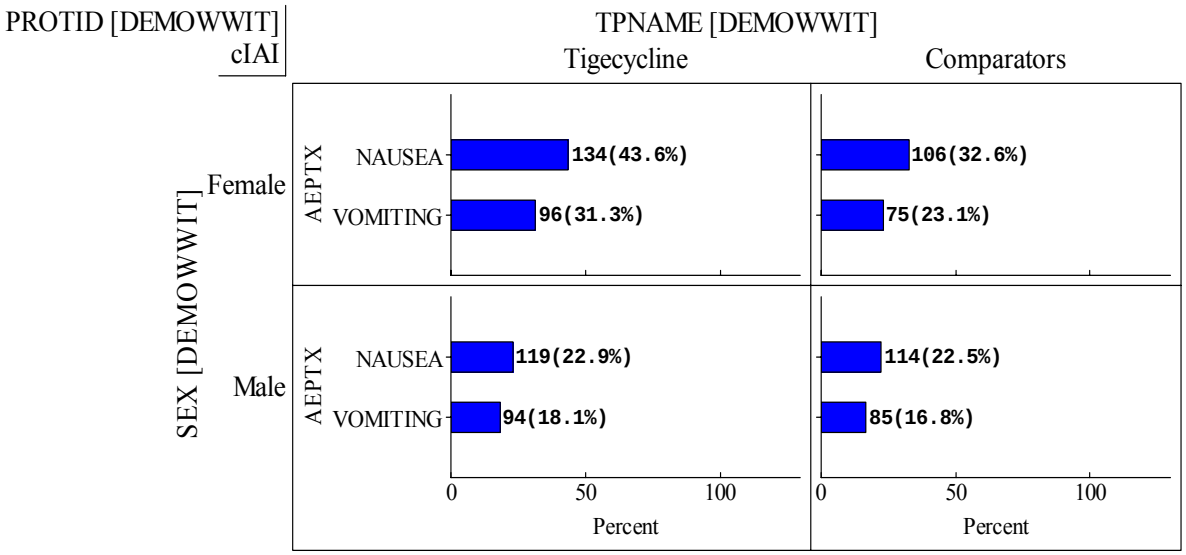
a. total



Counting the records in dataset ADVERSEW, uniquing them by variable UNIQ_SUB [ADVERSEW].
Normalize by dataset DEMOWWIT, uniquing the record count by variable UNIQ_SUB [DEMOWWIT].
Get normalization denominator from current cell in current layer, with a scope of the whole cell.

Display 'count(normalized percent)' at level of exterior breakdown.

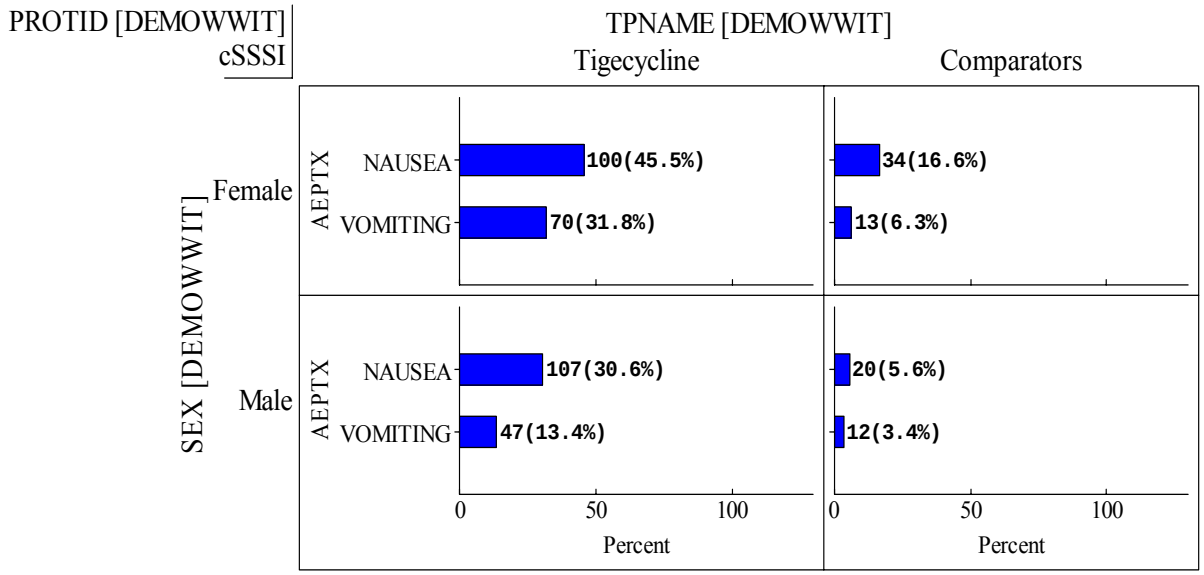
b. cIAI



Counting the records in dataset ADVERSEW, uniquing them by variable UNIQ_SUB [ADVERSEW].
Normalize by dataset DEMOWWIT, uniquing the record count by variable UNIQ_SUB [DEMOWWIT].
Get normalization denominator from current cell in current layer, with a scope of the whole cell.

Display 'count(normalized percent)' at level of exterior breakdown.

c. cSSSI



Counting the records in dataset ADVERSEW, uniquing them by variable UNIQ_SUB [ADVERSEW].
Normalize by dataset DEMOWWIT, uniquing the record count by variable UNIQ_SUB [DEMOWWIT].
Get normalization denominator from current cell in current layer, with a scope of the whole cell.

Display 'count(normalized percent)' at level of exterior breakdown.

7.1.8 Laboratory Findings

7.1.8.1 Overview of laboratory testing in the development program

For the laboratory values in phase 2 and 3 studies, baseline values were obtained within 24 hours before the first dose of test article, and changes from baseline were computed for the on-therapy, follow-up, test-of-cure, poststudy, and final-on-therapy periods. During the active phase of all trials, laboratory results for each subject were reviewed on an ongoing basis for any potentially important changes in clinical laboratory parameters in a blinded fashion by the sponsor's medical monitors. In addition, laboratory results were evaluated with regard to each subject's medical history, concomitant medications, AEs, and other safety data sets.

7.1.8.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Analyses for laboratory values are presented for the combined phase 3 studies. These best studies represent the patient population in whom this drug is intended for use. The analyses submitted by the sponsor include a comparison between study drug and comparators for laboratory findings of potential clinical significance. For each laboratory parameter, a range of abnormality was specified for the purposes of identifying potentially significant clinical findings. In addition, analyses of measures of central tendency were submitted. Although these types of analyses are standard, they are frought with inherent deficiencies which make them of value only for the purposes of hypothesis generation. The deficiencies include:

1. Because of the large number of labs that were collected, relatively small differences have the potential to generate statistically significant p-values, even though there may be no clinical significance to such small changes.
2. These types of statistical analyses are not done with the proper adjustment for multiplicity. This is a critical issue since the analyses involve hundreds of comparisons of thousands of lab values that were not pre-specified.
3. These comparisons don't take into account factors such as hemolysis of blood in the test tube, pre-existing conditions which may explain the laboratory derangements, and the possible contribution of the specific medical condition under study.
4. The definitions of what constitutes a lab result that is of "potential clinical significance" are not standardized. Therefore, the results of such an analysis can change markedly (as the result of chance) depending on the exact definition.

For these reasons, there is often discordance with the reported adverse event data and the laboratory data. For example, in this NDA, tigecycline had a slightly higher rate of elevated transaminase-related adverse events reported by the investigators, and yet, it also had a lower rate of elevated transaminases as calculated in the laboratory data analyses. It may be difficult to understand the significance of the findings of these laboratory analyses, when they don't agree with the adverse event analyses.

Thus, presented in this section are only those findings from the sponsor's submitted analyses which the reviewing Medical Officer has determined may be of importance, based on existing pre-clinical data and phase 1, 2, and 3 adverse event reporting.

7.1.8.3 Standard analyses and explorations of laboratory data

7.1.8.3.1 Analyses focused on measures of central tendency

There were several instances where there were differences between the study drug and the comparator with regard to measures of central tendency for lab values. Changes did not result in mean values that were outside the normal range and most either resolved by test-of-cure or were so small as to lack meaning. The following table shows changes in mean values for selected laboratory measures for all controlled phase 3 studies combined.

Mean and Mean Changes From Baseline in Laboratory Test Results: Safety Population in Studies 300 US/CA/305-WW, 301-WW/306-WW, and 307-WW/309-WW

	-------Tigecycline--------			-------Comparator---------			
Parameter (units) Time period	Mean n	Mean	Change	Mean n	Mean	Change	p-Value[a]
Total Protein (g/L)							
Screening/day 1	1357	65.43		1323	65.44		
Final on-therapy	1323	63.03	-2.38	1285	66.60	1.18	<0.001*
Test-of-cure	1078	72.45	6.38	1037	73.60	7.78	<0.001*
Amylase (U/L)							
Screening/day 1	1249	59.61		1224	54.61		
Final on-therapy	1219	71.36	12.72	1183	73.16	18.24	0.226
Test-of-cure	975	73.93	15.65	959	69.25	15.09	0.141
Prothrombin Time (s)							
Screening/day 1	646	14.59		626	15.46		
Final on-therapy	224	16.0	1.41	221	13.39	-1.68	<0.001*
Test-of-cure	207	13.20	-0.72	190	13.45	-1.76	0.664
Parital thrombo. time (s)							
Screening/day 1	1289	35.56		1251	36.55		
Final on-therapy	472	39.86	6.13	448	34.54	-1.05	<0.001*
Test-of-cure	441	33.31	-0.57	399	33.30	-2.30	0.435

There are multiple possible mechanisms for a decrease in serum total protein, and it is not clear if this finding is meaningful. However, given that hypoproteinemia occurred at a higher rate as a reported adverse event (5.1% vs. 3.2%) in controlled phase 3 studies, it is worthy of mention. Only one of the 71 total reported hypoproteinemia AE's was categorized as serious. This patient (301-139-006608) was a 52 year-old male who was successfully treated with tigecycline for peritonitis secondary to intestinal obstruction. One week after discharge to home, the patient developed cachexia, malnutrition, surgical wound infection, and hypoproteinemia. After antibiotics and "nutritional treatment" the patient recovered. In this case, the most likely cause of the low protein is the cachexia/malnutrition, which presumably resulted from the infection.

With regard to the increases in amylase, there were increases in both treatment groups in the amylases, and the mean of neither group returned to baseline by the time of the TOC visit. The increase in mean for the comparator group was greater than that for the study drug; however, given the reported SAE of pancreatitis in a patient who received tigecycline, the increase in mean is noteworthy. Further information will have to be collected in the post-marketing setting for a better understanding of this possible association.

Certain drugs in the tetracycline class have been noted to have an effect on the coagulation cascade. This may be the result of the effect of antibiotics on the vitamin k producing flora of the gut as well as a direct effect that these drugs have on the clotting

cascade. In addition, pre-clinical animal data indicate a significant effect of tigecycline on coagulation. The mean value changes for patients in the tigecycline arm are consistent with such an effect. However, it is important to point out that review of all AE's and SAE's did not show an increase in the rates of bleeding events or hemorrhage in the tigecycline-treated patients.

From the screening visit to the final on-therapy evaluation, serum BUN values increased among tigecycline-treated subjects by 1.54 mmol/L to a final on-therapy value of 7.087 mmol/L (n = 540), compared with a decrease of -0.65 mmol/L from screening to a value of 4.564 mmol/L at the final on-therapy evaluation for comparator-treated subjects(n = 496; $p < 0.001$). Similarly, serum urea values increased by 0.95 mmol/L from the screening visit to a final on-therapy value of 6.47 mmol/L among tigecycline-treated subjects (n = 840), compared with a decrease of –0.97 mmol/L from screening to a final ontherapy value of 4.353 mmol/L among the comparator-treated subjects (n = 840; $p < 0.001$). Mean serum creatinine values were statistically significantly decreased in both treatment arms; a greater decrease was observed in comparator-treated subjects at the final on-therapy measurement. The changes in BUN and urea values may be related to previously reported minocycline anti-anabolic effects. Tetracycline class antibiotics have been found to have anti-anabolic action (which has lead to increased BUN, azotemia, acidosis, and hypophosphatemia). Review of serious adverse events in the controlled phase 3 trials did not reveal events such as acidosis. There were a few cases of azotemia; however, review of these cases could not be clearly linked to tigecycline (although such an effect could also not be ruled out). Hypophosphatemia was not a commonly reported adverse event in the phase 3 studies.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

The following table shows the laboratory results of potential clinical importance. This analysis shows the frequency of lab values which have reached a potentially meaningful degree of abnormality. The results in this table are consistent with those examining the central tendencies of lab values.

Laboratory Findings of Potential Clinical Importance During Therapy: Number/Number Subjects Tested (%) in Safety Population of Studies 300 US/CA/305-WW, 301-WW/306-WW, and 307-WW/309-WW

Parameter	Skin/Skin Structure Infections		Intra-abdominal Infections				
	3074A1-300-US; -305-WW		3074A1-301-US; -306-WW				
	Tigecycline	Vanco/Aztreonam	Tigecycline	Imipenem/ Cilastatin	Total Tigecycline Incl.Studies307/309[b]	Total Comparator	p-Value
Albumin (g/L) Low/decrease (≤20 g/L or a decrease of >30%)	8/ 528 (1.5)	4/ 506 (0.8)	27/ 757 (3.6)	18/ 774 (2.3)	37/1317 (2.8)	22/1286 (1.7)	0.065
Total protein (g/L) Low (≤35 g/L)	6/ 537 (1.1) 6/ 537 (1.1)	6/ 514 (1.2) 6/ 514 (1.2)	20/ 790 (2.5) 20/ 790 (2.5)	3/ 805 (0.4) 3/ 805 (0.4)	28/1359 (2.1) 28/1359 (2.1)	9/1325 (0.7)	0.002
Prothrombin time High (≥2 x ULN)	8/ 225 (3.6)	1/ 221 (0.5)	0/ 1	0/ 2	8/ 226 (3.5)	1/ 223 (0.4)	0.037
Partial thrombo. time High (≥2 x ULN)	12/ 479 (2.5)	6/ 463 (1.3)	0/ 1	0/ 2	12/ 480 (2.5)	6/ 465 (1.3)	0.234

7.1.8.4 Overview of vital signs testing

Vital Signs – cSSSI

Vital signs were compared between tigecycline-treated patients and control drug-treated patients by both mean changes from baseline and according to potential importance.

The following tables show these comparisons. No significant differences were seen.

Vital Signs of Potential Clinical Importance: Number/Number of Subjects Tested (%) in the Safety Population of Studies 300-US/CA and 305-WW

Parameter	Tigecycline	Vancomycin/ Aztreonam	Total	Fisher Exact p-Value
Total[a]	57/ 563 (10.1)	66/ 544 (12.1)	123/1107 (11.1)	0.294
Systolic BP (mmHg)	40/ 563 (7.1)	39/ 544 (7.2)	79/1107 (7.1)	1.000
High/increase (≥180 mmHg and increase of ≥20 mmHg)	30/ 563 (5.3)	25/ 544 (4.6)	55/1107 (5.0)	0.584
Low/Decrease (≤90 mmHg and decrease of ≥20 mmHg)	11/ 563 (2.0)	14/ 544 (2.6)	25/1107 (2.3)	0.547
Diastolic BP (mmHg)	24/ 563 (4.3)	33/ 544 (6.1)	57/1107 (5.1)	0.221
High/increase (≥105 mmHg and increase of ≥15 mmHg)	10/ 563 (1.8)	11/ 544 (2.0)	21/1107 (1.9)	0.828
Low/Decrease (≤50 mmHg and decrease of ≥15 mmHg)	14/ 563 (2.5)	22/ 544 (4.0)	36/1107 (3.3)	0.175
Heart rate (beats/min)	6/ 563 (1.1)	7/ 544 (1.3)	13/1107 (1.2)	0.786
High/increase (≥120 beats/minute and increase ≥30 beats/minute)	4/ 563 (0.7)	4/ 544 (0.7)	8/1107 (0.7)	1.000
Low/Decrease (≤50 beats/minute and decrease ≥30 beats/minute)	2/ 563 (0.4)	3/ 544 (0.6)	5/1107 (0.5)	0.682

Mean Changes From Baseline in Vital Signs: Safety Population of Studies 300-US/CA and 305-WW

	Tigecycline			Vancomycin/Aztreonam			
Parameter (unit) Time period	n	Mean	Mean Change	n	Mean	Mean Change	p-Value[a]
Systolic BP (mmHg)							
Screening/day 1	565	130.8		550	129.6		
Final on-therapy	562	127.2	-3.58	544	127.3	-2.31	0.523
Test of cure	502	128.8	-2.43	482	128.3	-1.23	0.857
Diastolic BP (mmHg)							
Screening/day 1	564	77.2		550	76.4		
Final on-therapy	561	75.5	-1.80	544	75.6	-0.84	0.504
Test of cure	502	77.7	0.04	482	77.4	0.84	0.962
Heart rate (beats/min)							
Screening/day 1	565	85.7		550	84.5		
Final on-therapy	562	75.8	-9.81	544	76.6	-7.97	0.063
Test of cure	501	77.1	-7.91	480	76.9	-6.97	0.945
Temperature axillary (°C)							
Screening/day 1	566	37.1		549	37.1		
Final on-therapy	562	36.3	-0.84	543	36.3	-0.76	0.053
Test of cure	504	36.3	-0.85	482	36.3	-0.84	0.802

Abbreviations: BP = blood pressure; °C = degree Celsius.
a. One-way analysis of covariance, unadjusted for multiplicity.

For cIAI, vital signs were also compared according to individual subject changes and mean changes from baseline. These analyses are shown in tables the following tables. Examination of the vital signs according to individual subject changes reveals that there were small differences overall. These changes were determined to not be of clinical importance.

Vital Signs of Potential Clinical Importance: Number/Number Subjects Tested (%) in the Safety Population of Studies 301-WW and 306-WW

Parameter	---Tigecycline ---	Imipenem/ Cilastatin	Total	Fisher Exact p-Value
Total[a]	131/ 814 (16.1)	95/ 822 (11.6)	226/1636 (13.8)	0.008*
Systolic BP (mm Hg)	71/ 811 (8.8)	53/ 820 (6.5)	124/1631 (7.6)	0.092
High/increase (≥180 mm Hg and increase ≥20 mm Hg)	38/ 811 (4.7)	27/ 820 (3.3)	65/1631 (4.0)	0.165
Low/decrease (≤90 mm Hg and decrease ≥20 mm Hg)	34/ 811 (4.2)	27/ 820 (3.3)	61/1631 (3.7)	0.363
Diastolic BP (mm Hg)	69/ 811 (8.5)	47/ 820 (5.7)	116/1631 (7.1)	0.034*
High/increase (≥105 mm Hg and increase ≥15 mm Hg)	27/ 811 (3.3)	16/ 820 (2.0)	43/1631 (2.6)	0.090
Low/decrease (≤50 mm Hg and decrease ≥15 mm Hg)	44/ 811 (5.4)	32/ 820 (3.9)	76/1631 (4.7)	0.159
Heart rate (beats/min)	22/ 812 (2.7)	19/ 820 (2.3)	41/1632 (2.5)	0.638
High/increase (≥120 beats/min and increase ≥30 beats/min)	18/ 812 (2.2)	14/ 820 (1.7)	32/1632 (2.0)	0.481
Low/decrease (≤50 beats/min and decrease ≥30 beats/min)	4/ 812 (0.5)	5/ 820 (0.6)	9/1632 (0.6)	1.000

Abbreviation: BP = blood pressure.

* Significant between-group difference at the 0.05 level.

a. Subjects from safety population with vital signs data available.

Mean Changes From Baseline in Vital Signs: Safety Population in Studies 301-WW and 306-WW

Parameter (units) Time period	Tigecycline n	Tigecycline Mean	Tigecycline Mean Change	Imipenem / Cilastatin n	Imipenem / Cilastatin Mean	Imipenem / Cilastatin Mean Change	p-Value[a]
Systolic BP (mm Hg)							
Screening/day 1	816	124.9		825	124.9		
Final on-therapy	810	123.7	-1.15	820	124.8	-0.08	0.163
Test of cure	718	123.7	-0.97	748	124.2	-0.57	0.554
Diastolic BP (mm Hg)							
Screening/day 1	816	74.2		825	73.7		
Final on-therapy	810	74.8	0.53	820	74.4	0.82	0.746
Test of cure	718	75.7	1.35	748	76.1	2.27	0.311
Heart rate (beats/min)							
Screening/day 1	816	90.8		824	91.3		
Final on-therapy	811	78.1	-12.78	820	78.7	-12.65	0.382
Test of cure	719	76.9	-13.66	750	77.4	-13.64	0.472
Temp, axillary (°C)							
Screening/day 1	815	37.2		825	37.2		
Final on-therapy	812	36.5	-0.70	821	36.5	-0.66	0.314
Test of cure	719	36.4	-0.85	743	36.4	-0.85	0.414

Abbreviations: BP = blood pressure; C=Celsius.

a. One-way analysis of covariance, unadjusted for multiplicity.

7.1.8.5 Overview of ECG testing in the development program, including brief review of preclinical results

There were no adverse events reported that could be reasonably attributed to a drug-related prolongation of the QT interval. Examination of the available QT data did not reveal that there was a potential problem with QT prolongation associated with tigecycline exposure.

Electrocardiograms (ECGs) collected during the controlled phase 3 trials were read at a centralized ECG laboratory. The data were then analyzed by the sponsor in an attempt to identify subjects with potentially clinically important results at the various timepoints of the studies.

Of the phase 2 studies, only study 202 collected ECG data in a systematic fashion. In all phase 2 studies, there were no subjects who discontinued treatment or were withdrawn from a study because of changes in the QT interval. Assessment of the available data for phase 2 studies did not reveal a potential QT safety signal.

In the majority of phase1 studies, ECG interval data were collected from investigator read ECG's, however, for studies 100, 101, 102, 103, 105, and 108, the ECG's were read by a central ECG lab. Review of this data did not reveal a potential QT safety signal.

7.1.8.6 Selection of studies and analyses for overall drug-control comparisons

Drug-control comparisons were made by indication (cIAI and cSSSI) for the blinded, controlled phase 3studies. Since both studies within each indication were conducted almost identical fashion, it is reasonable to combine these data. In addition, the data for all 4 phase 3 blinded controlled studies were combined for the purposes of conducting a drug-control comparison. Since the comparisons which were made within each individual indication did not reveal differences, the combined comparison is presented in this review.

7.1.8.7 Standard analyses and explorations of ECG data

7.1.8.7.1 Analyses focused on measures of central tendency

The following table shows changes in median QTc intervals within 3 hours after dosing on days 3, 4, or 5 for all phase 3 controlled studies combined.

Changes in Median Baseline QTc Intervals (msec) Within 3 Hours After Dosing on Days 3, 4, or 5 Using Nonparametric Analysis: Safety Population in Studies 300-US/CA, 305-WW, 301-WW, and 306-WW

	Tigecycline				Comparator[a]				
Parameter (units) Time period	n[b]	Median	Median Change	Within Group 95% CI	n[b]	Median	Median Change	Within Group 95% CI	Between Group 95% CI[c]
QTc (L), msec									
Screening/day 1	773	396.2			788	394.5			
Day 3/4 or 5	773	398.9	3.3	2, 5	788	397.4	0.6	-1, 3	0.4, 4.9
Test-of-cure	665	394.2	-2.5	-5, -1	697	395.1	-0.8	-3, 1	-4.2, 0.9
QT (B), msec									
Screening/day 1	773	413.0			788	413.0			
Day 3/4 or 5	773	410.0	-2.0	-4, 0	788	408.0	-4.0	-7, -2	-1.0, 4.0
Test-of-cure	665	403.0	-9.0	-11, -7	697	406.0	-7.0	-9, -5	-5.0, 1.0
QT (F), msec									
Screening/day 1	773	389.0			788	388.0			
Day 3/4 or 5	773	396.0	6.0	4, 7	788	392.5	3.0	2, 5	1.0, 5.0
Test-of-cure	665	391.0	1.0	-2, 3	697	391.0	2.0	0, 4	-4.0, 1.0

Note: CI = confidence interval; QTc (B) = Bazett's correction; QTc (F) = Fridericia's correction; QTc(L) = log linear regression correction; CI = confidence interval.

a. Comparator refers to vancomycin/aztreonam for studies 300-US/CA and 305-WW, imipenem/cilastatin for studies 301-WW and 306-WW.

b. Subjects who had ECG evaluation at the 3 visits (screening; day 3, 4, or 5; and the test-of-cure).

c. Analysis of variance is based on the change from baseline to day 3, 4, or 5; 3 hours after the dosing.

Source: Biostat ecg

7.1.8.7.2 Analyses focused on outliers or shifts from normal to abnormal

The following table shows the number of patients for tigecycline and comparator by degree of QT prolongation within all controlled phase 3 trials. Review of this data did not reveal any potential tigecycline-related QT safety signals.

Categorical Analysis of QTc Interval Data by Cutoff Values of 30 and 60 msec Within 3 Hours After Dosing on Days 3, 4, or 5: Safety Population in Studies 300-CA/US, 305-WW, 301-WW, and 306-WW

Parameter (units)	Tigecycline				Comparator[a]				
		≤ 30 ms	> 30 ms and < 60 ms	≥ 60 ms		≤ 30 ms	> 30 ms and < 60 ms	≥ 60 ms	Between Group
Time period	n[b]	n (%)	n (%)	n (%)	n[b]	n (%)	n (%)	n (%)	p-Value[c]
QTc (L)									
Day 3/4 or 5	773	673 (87.1)	90 (11.6)	10 (1.3)	788	714 (90.6)	69 (8.8)	5 (0.6)	0.065
Test-of-cure	665	616 (92.6)	45 (6.8)	4 (0.6)	697	630 (90.4)	63 (9.0)	4 (0.6)	0.275
QTc (B)									
Day 3/4 or 5	773	700 (90.6)	65 (8.4)	8 (1.0)	788	735 (93.3)	49 (6.2)	4 (0.5)	0.117
Test-of-cure	665	621 (93.4)	41 (6.2)	3 (0.5)	697	639 (91.7)	49 (7.0)	9 (1.3)	0.215
QTc (F)									
Day 3/4 or 5	773	642 (83.1)	117 (15.1)	14 (1.8)	788	696 (88.3)	86 (10.9)	6 (0.8)	0.007
Test-of-cure	665	599 (90.1)	62 (9.3)	4 (0.6)	697	612 (87.8)	77 (11.0)	8 (1.1)	0.317

Note: QTc (B) = Bazett's correction; QTc (F) = Fridericia's correction; QTc(L) = log linear regression correction; CI = confidence interval.

a. Comparator refers to vancomycin/aztreonam for studies 300-US/CA and 305-WW, imipenem/cilastatin for studies 301-WW and 306-WW.

b. Subjects who had ECG evaluations at baseline and during the treatment (days 3, 4, or 5).

c. p-Values are based on 2-sided Fisher exact test.

Source: Biostat SAS report

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.2 Study type and design/patient enumeration

Sufficient numbers of patients were studied in a blinded comparative manner so as to be able to make assessments as to the rates of common adverse events in tigecycline-treated patients compared to control-treated patients.

7.2.3 Demographics

This drug was studied in adults aged 18 and over. No data was generated regarding the safety or efficacy of this drug in the treatment of children. It should be anticipated that many or all of the same problems encountered in the treatment of children with tetracycline class antibiotics may also be seen with tigecycline.

7.2.4 Extent of exposure (dose/duration)

Drug exposure in this NDA was limited to relatively short courses of therapy (around 14 days). Therefore, the safety profile of this product when used to treat patients for longer durations is not known. This is an important point since this drug has a pharmacodynamic profile in which tissue accumulation is pronounced. Longer term treatment with this product may result in the emergence of previously unrecognized toxicities, or may increase the frequency or intensity/severity of already known toxicities.

7.2.5 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.5.1 Other studies

Phase 1 and 2 studies were examined for safety data. The adverse events contained in these data primarily support what was seen in the phase 3 studies.

7.2.5.2 Postmarketing experience

This drug has no post-marketing experience anywhere in the world at this time.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Nausea and vomiting are the primary adverse events most commonly seen in patients who were treated with tigecycline. Although the rate of vomiting was similar across both indications, vomiting was seen with a higher frequency in the cSSSI tigecycline-treated patients vs. comparator than in the cIAI tigeycline-treated patients vs. comparator. These events were mostly mild to moderate and did not result in substantial numbers of SAE's or drug discontinuation.

The liver function abnormality pattern in tigecycline-treated patients was different than that of the comparator-treated patients. The LFT abnormalities occurring in comparator-treated patients were found more often while on-therapy, whereas the LFT abnormalities associated with tigecycline exposure occurred more often post-therapy. Because of a significant portion of tigecycline-treated patients whose final ALT measurement was elevated (and rising), a complete understanding of this LFT pattern is not yet available. Additional information as obtained by other ongoing phase 3 trials as well as in post-marketing data should help improve our understanding of the hepatic profile of this drug.

There was one case of diffuse pancreatitis which was confounded only by the presence of pantoprazole. If this is caused by tigecycline, then the frequency of such events in tigecycline-treated patients may be relatively very high. This is a potential safety signal of importance, and should be monitored in the post-marketing setting.

There were increased rates of infection-related SAE's and deaths in the tigecycline-treated patients than in comparator-treated patients in controlled, blinded phase 3 trials. Close examination of these differences did not result in a clear understanding of the cause of these differences. These differences should be conveyed in the label, and hopefully, future data as collected in ongoing phase 3 clinical trials and post-marketing data will help to provide a better understanding.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The dose/aministration that was studied in all Phase 3 clinical trials was an initial 100 mg I.V. loading dose followed by 50 mg I.V. q 12 hours.

8.2 Drug-Drug Interactions

This drug has no effect on the cyctochrome P450 system. However, an effect on warfarin was identified. Concomitant administration of TYGACIL (100 mg followed by 50 mg every 12 hours) and warfarin (25 mg single-dose) to healthy subjects resulted in a decrease in clearance of R-warfarin and S-warfarin by 40% and 23%, an increase in C_{max} by 38% and 43% and an increase in AUC by 68% and 29%, respectively. Tigecycline did not significantly alter the effects of warfarin on INR. In addition, warfarin did not affect the pharmacokinetic profile of tigecycline. However, prothrombin time or other suitable anticoagulation test should be monitored if tigecycline is administered with warfarin.

8.3 Special Populations

Pharmacokinetic parameters for tigecycline were increased significantly (approximately doubled for AUC) in those patients with advanced liver dysfunction (Childs-Pugh C). In

these patients, it is recommended that the dosing of tigecycline be half the usual amount. No clinical data has been collected for these patients, and this recommendation is based on collected PK data.

8.4 Pediatrics

This drug has not been studied in pediatric patients. Because it is closely related to tetracyclines, many of the same toxicity concerns exist. Issues of bone deposition, effects on growth rates, and tooth development toxicity are some of the concerns. For these reasons, this drug has not been evalued in the pediatric population.

8.5 Postmarketing Risk Management Plan

The postmarketing risk management plan has been submitted by the sponsor and includes efforts to monitor for infection-related SAE's, deaths, liver toxicity, and pancreatic toxicity. This plan has been reviewed and accepted by the Agency.

9 OVERALL ASSESSMENT

9.1 Conclusions

The results from phase 3 studies support that this product is not worse than chosen comparators for the treatment of cSSSI and cIAI.

9.2 Recommendation on Regulatory Action

It is recommended that this product be approved for the treatment of cIAI and cSSSI based on the assessment of risk/benefit. Phase 3 studies demonstrated that tigecycline is not worse than comparator. Potential safety questions that remain at this point are determined to be acceptable because of the fact that this product has shown efficacy in the treatment of potentially life-threatening diseases as well as resistant organisms, most notably, MRSA in cSSSI.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The postmarketing risk management plan has been submitted by the sponsor and includes efforts to monitor for infection-related SAE's, deaths, liver toxicity, and pancreatic toxicity. This plan has been reviewed and accepted by the Agency.

9.3.2 Required Phase 4 Commitments

No phase 4 commitments have been requested by the division.

9.4 Labeling Review

A labeling review was conducted, and a label was agreed upon. The main changes (to the clinical section) that the division requested involved inclusion of the differences in deaths and infection related SAE's, adverse event table with analysis out to TOC, mention of the pattern of late onset LFT abnormalities in tigecycline-treated patients, breakdown of efficacy rates by study, and the inclusion of some WARNINGS and PRECAUTIONS statements that indicate the potential occurrence of tetracycline-associated toxicities with the use of this drug. These changes were accepted by the sponsor.

10 APPENDICES

10.1 Review of Individual Study Reports

Individual Efficacy Reviews for cIAI

This section contains individual reviews of Studies 301 and 306. These studies were planned with the exact same design.

Protocol 301

Protocol Description
This was a phase 3, multicenter, double-blind (third-party unblinded) study comparing the safety and efficacy of tigecycline to imipenem/cilastatin in hospitalized subjects with cIAI. Subjects were stratified at randomization into 2 groups based on their scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II: 15 or less, or over 15 but less than 31. Subjects with scores over 30 were excluded. Subjects were randomly assigned in a 1:1 ratio to receive either intravenous (IV) tigecycline or IV imipenem/cilastatin. Unless a subject was deemed a clinical failure, the duration of study treatment was 5 to 14 days. Subject participation in the study involved up to 1 day for screening, up to 14 days of study drug administration, and, unless the subject was a clinical failure, 1 posttherapy visit 9 plus or minus 5 days after the last dose of study drug, and a test-of-cure assessment at least 12 but not more than 44 days after the last dose of study drug; thus, the maximum duration of participation was 59 days. The test-of-cure window at 12 to 44 days to harmonize the time across protocol amendments and to allow -2/+2 days to the extremes in consideration of weekend follow-up schedules.

Amendments
The original protocol dated 04 June 2002 was amended 4 times: on 04 February 2003, 29 January 2004, 04 March 2004, and 19 March 2004. The purpose of Amendment 1 was to incorporate suggestions made by investigators from Europe, the United States, Canada, and Latin America during investigators' meetings held in August and September of 2002; to clarify the statistical analysis section; to harmonize certain procedures and definitions with those specified in the protocols for the complicated skin/skin structure infection studies and the similar cIAI study to promote consistency in data collection and evaluation; and to make minor administrative changes and corrections. Amendment 1 addressed requirements that were applicable to all sites participating in the study while amendments 2, 3, and 4 addressed country-specific and/or region-specific requirements. The purpose of Amendment 2 was to add investigative sites in Europe and Taiwan and to instruct these sites to refer to country-specific product labeling for the preparation and administration of the comparator agent. Shortly after Amendment 2 was finalized, region-specific requirements for administering imipenem/cilastatin were changed; Amendment 3 addressed these changes. While Amendment 3 was in development, the supplier of the comparator agent in Brazil changed. The new supplier was able to supply

imipenem/cilastatin only in the form of monovials. Because of the timing of these changes, Amendment 2 was not distributed to any sites; however, Amendment 3, which incorporated the provisions of Amendment 2, was distributed to all applicable sites in Europe, Taiwan, and Brazil. The purpose of Amendment 4 was to satisfy the country-specific requirements in Bulgaria for a scratch skin test to detect potential allergies to study drugs. Amendments 2, 3, and 4 did not require any changes to the CRFs, and only minor changes to the informed consent form within the specific regions. Amendment 3 allowed selected investigators who participated in cIAI study 301, to participate in the current study. Study 306 had a nearly identical study plan, and inclusion and exclusion criteria to the current study. It was not possible for investigators participating in both studies to enroll subjects in both studies simultaneously. Study 306 remained blinded so that bias could not be introduced by investigators who had previously participated in that study. Investigative sites selected for participation in the current study were monitored by regional personnel during study 306 to ensure good compliance with GCP guidelines, the protocol, and data quality. The distribution of subject diagnoses enrolled in study 306 must also have been similar to the overall global distribution of diagnoses in the cIAI studies. All amendments that were distributed were filed with the appropriate regulatory agencies.

Post-Hoc Changes

Before the study data were unblinded, refinements were made to the Statistical Analysis Plan to supplement protocol descriptions of the criteria for efficacy populations and statistical analysis methods for efficacy data, to further define the analysis plan, and to harmonize it with that in 306. The main refinements to the study and planned analyses included the following items:

1. The noninferiority of tigecycline was compared with imipenem/cilastatin as evaluated by using a 2-sided 95% CI adjusted for the stratification variable APACHE II score (≤15 or >15).
2. Supplementary diagnostic criteria.
3. Supplementary evaluability criteria and algorithm for subjects who received potentially effective antibiotics after randomization.
4. Supplementary evaluability criteria and algorithm to determine clinical response of subjects who discontinued study treatment because of a TEAE.
5. Clarification of the SRB's role.
6. Harmonization of the timing of test-of-cure assessments across the protocol amendments by setting the window for the test-of-cure assessment at 12 to 44 days. This window was based on amendment 2, which allowed a test-of-cure assessment within 14 to 35 days after the last dose of study drug plus or minus 2 days on either side of the window in consideration of subjects whose test-of-cure assessments were scheduled over a weekend.
7. Inclusion of noninferiority tests to compare the efficacy of tigecycline with that of imipenem/cilastatin.

These changes were reviewed by the Medical Officer and determined to be acceptable.

Inclusion/Exclusion Criteria

6.3.1 Inclusion Criteria

Subjects were enrolled in the study if they satisfied the following inclusion criteria:

1. Hospitalized male or female subjects, at least 18 years of age.
2. Candidate for, or had, a laparotomy, laparoscopy, or percutaneous drainage of an intra-abdominal abscess.
3. Complicated intra-abdominal infection, such as:
    a. An intra-abdominal abscess.
    b. An intra-abdominal abscess (including liver and spleen) that developed in a postoperative subject who received more than 48 hours but not more than 5 days of a nonstudy antibiotic and an intra-abdominal culture was obtained from the infected site.
    c. Appendicitis complicated by perforation (grossly visible) and abscess or periappendicular abscess.
    d. Perforated diverticulitis complicated by abscess formation or fecal contamination.
    e. Complicated cholecystitis with evidence of perforation or empyema.
    f. Perforation of the large or small intestine with abscess or fecal contamination.
    g. Purulent peritonitis or peritonitis associated with fecal contamination.
    h. Gastric or duodenal ulcer perforation with symptoms lasting at least 24 hours before operation.
    i. Traumatic bowel perforation with symptoms lasting at least 12 hours before operation.
4. No 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, gentamicin) after the baseline intra-abdominal culture was obtained from the infected site.
5. Informed consent was signed preoperatively; however, study drug was not to be given unless there was a strong suspicion (i.e., elevated white blood cell count, elevated band cell counts, fever, or highly suggestive radiographic findings) or a confirmed diagnosis of an intra-abdominal infection (presence of pus within the abdominal cavity), and a baseline intra-abdominal culture was obtained or was planned to be obtained from the site of infection.
6. Signed and dated written informed consent form approved by the IRB or IEC. If any subject was unable to give consent, it was to be obtained from the subject's next of kin or legal representative if in accordance with local laws and regulations; subjects would then sign an informed consent form as soon as possible.

6.3.2 Exclusion Criteria

Subjects were excluded from participation in the study if they fulfilled any one of the following criteria:

1. Any concomitant condition that, in the opinion of the investigator, precluded an evaluation of a response or made it unlikely that the contemplated course of therapy or follow-up visits could have been completed.

2. Active or treated leukemia or systemic malignancy that required treatment with chemotherapy, immunotherapy, radiation therapy, or other antineoplastic therapy within the 3 months before entry into the study, or any metastatic malignancy to the abdomen with life expectancy less than 6 months.
3. Anticipated length of antibiotic therapy less than 5 days.
4. Presence of any uncontrolled central nervous system disease, including epilepsy or unexplained seizures.
5. Concomitant treatment with ganciclovir.
6. Known or suspected hypersensitivity to tigecycline, tetracycline agents, imipenem, cilastatin, or other compounds related to these classes of antibacterial agents.
7. Presence of hepatic disease:

a. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels more than 10 times the upper limit of normal (ULN) values.
b. Bilirubin more than 3 times ULN, unless isolated hyperbilirubinemia was directly related to the acute process.
c. Acute hepatic failure or acute decompensation of chronic hepatic failure.

8. Calculated CLCR less than 41 mL/min/1.73m^2 after adequate hydration. The CLCR may be calculated from the serum creatinine (SCR) concentration by the following equation:

Male: CLCR mL/min = (140 – age) x weight (kg) / 72 x SCR (mg/dL)
Female: CLCR mL/min = 0.85 x CLCR derived by the above formula

To adjust the CLCR for body size, compute the body surface area (BSA):
BSA (m^2) = (weight [kg]) 0.425 x 0.007184(height [cm]) 0.725
and use the value obtained in the equation
CLCR / (BSA x 1.73) = CLCR mL/min/1.73 m^2
9. Neutropenia with absolute neutrophil count less than 1000/mm^3. Subjects with neutrophil counts as low as 500/mm^3 were permitted if the investigator thought the reduction was due to the acute infectious process.
10. Intra-abdominal infection known to be caused by 1 or more bacterial pathogens not susceptible to both of the study drugs (e.g., *P. aeruginosa, Proteus mirabilis*) and in the investigator's opinion required treatment with an additional antibacterial agent.
11. Administration of any investigational drugs (defined as not approved for any indication by the local regulatory agency) within 4 weeks before administration of the first dose of the study drug (day 1).
12. Previous participation in this study.
13. Anticipation of leaving the fascia or deep muscular layers open or expectation of planned abdominal reexploration either in or out of the operating room.
14. Pregnant women or nursing mothers.
15. Female subjects of childbearing potential who did not agree to practice sexual abstinence or use a medically accepted method of contraception throughout the duration of the study and for at least 1 month after the last dose of study drug.
16. Subjects suspected preoperatively to have had a diagnosis of spontaneous bacterial peritonitis, simple cholecystitis, gangrenous cholecystitis without rupture, simple appendicitis, acute suppurative cholangitis, pancreatic abscess, or infected necrotizing pancreatitis.

17. APACHE II score greater than 30.
18. Weight less than 40 kg.
19. Immunosuppressive therapy that, in the opinion of the investigator, would have decreased the subject's ability to eradicate the infection, including use of high-dose corticosteroids (e.g., 40 mg or more prednisone or equivalent per day) or known diagnosis of acquired immunodeficiency syndrome (AIDS).
20. Administration of intra-operative antibacterial irrigants or peritoneal antibacterial agents (e.g., irrigants, antibiotic-impregnated sponges).
21. Presence of infection requiring systemic antimicrobial therapy at a site other than the abdomen (e.g., urinary tract).

Analysis Populations
Definitions of subject populations are as follows:
1. Screened population: all subjects who signed an informed consent form and were screened.
2. Intent-to-treat (ITT) population: screened subjects who were randomly assigned to a treatment arm.
3. Modified intent-to-treat (mITT) population: ITT subjects who received at least 1 dose of study drug.
4. Clinical modified intent-to-treat (c-mITT) population: mITT subjects who had clinical evidence of a complicated intra-abdominal infection, as defined in the inclusion criteria.
5. Microbiologic modified intent-to-treat (m-mITT) population: c-mITT subjects for whom 1 or more baseline isolates were identified.

Clinically evaluable (CE) population: c-mITT subjects who met the following criteria:

All subjects

a. Met inclusion and exclusion criteria as stated in the protocol under which the subject was enrolled. Any exemptions from these criteria were decided while the data were blinded and included:
- Prospective exemptions, considered by the medical monitor on a case-by-case basis.
- Prospective or retrospective exemptions, for CLCR for subjects enrolled under any version of the protocol, if the CLCR was not lower than 41 mL/min (-15%).

b. Had a test-of-cure assessment of cure or failure (but not indeterminate).
c. Met the criteria for either a clinical cure or a clinical failure.
d. Received no more than 1 dose of a prohibited antibacterial treatment after the baseline intra-abdominal culture was obtained, but before the first dose of study medication (1 dose of a single broad-spectrum agent or 1 dose of each antibiotic in a combination regimen such as metronidazole, ampicillin, gentamicin).
e. Treatment regimen remained blinded throughout the study duration.

Clinically Evaluable Cure

a. Met the criteria for clinically evaluable for all subjects.
b. Met the criteria for clinical cure.

c. Received no potentially effective concomitant antibacterial treatment after the first dose of study drug through the test-of-cure assessment (exception: 1 or 2 doses of perioperative antibiotic prophylaxis for reoperations performed for reasons not related to the infection, e.g., planned bowel reanastomosis).
d. Had the test-of-cure assessment at least 12 days but not more than 44 days after the last dose of study medication was administered.
e. Received at least 5 days of treatment and received between 80% and 120% of the prescribed number of doses.

Clinically Evaluable Failure

a. Met the criteria for clinically evaluable for all subjects.
b. Met the criteria for clinical failure.
c. Completed the test-of-cure assessment on or after day 3.
d. Received at least 8 doses of study medication
e. Received at least 8 doses of study medication in less than 5 days and discontinued treatment due to a treatment-related adverse event (TRAE).

Microbiologically evaluable (ME) population: CE subjects who met the following criteria:

a. Had an intra-abdominal culture taken from the infection site at baseline that identified 1 or more isolate(s). At least 1 baseline isolate had to be susceptible to tigecycline and imipenem/cilastatin).
b. Had microbiologic or clinical information available to allow classification of a microbiologic response of eradication, persistence, or superinfection at the test-of-cure assessment.

Note that the assignment of a primary baseline pathogen to assist in pharmacokinetic analysis was performed by a single medical monitor in a blinded fashion, based only on the knowledge of the baseline culture isolated and the primary site of infection. Organisms isolated from baseline cultures were considered to be the primary pathogen based on the frequency with which those organisms are identified in the particular disease state. In polymicrobial infections, co-pathogens (secondary isolates) were identified based on Gram stain (i.e., Gram-positive or Gram-negative staining) and ability to grow aerobically or anaerobically. Intra-abdominal cultures were considered the principal source of the primary pathogen. If no primary pathogen was identified from the intra-abdominal source, a blood isolate could be considered the source of the primary pathogen, if clinically applicable.

Primary Efficacy Analysis

The primary efficacy endpoint was the clinical response within the ME and m-mITT populations (co-primary populations) at the test-of-cure assessment, which took place at least 12 days but not more than 44 days after the last dose of study drug was administered, except for subjects with a clinical response of failure. The ME population was chosen because it included those subjects who met all protocol criteria for evaluating clinical efficacy. During pre-NDA discussions, it was agreed upon that even though there

were two primary endpoints, no adjustment for multiplicity was needed. Detailed assessments of the subjects' clinical status were recorded at baseline through the last day of therapy, at the early follow-up assessment, and at the test-of-cure assessment. For subjects withdrawn from therapy early, clinical signs and symptoms of infection were assessed on the last day of therapy. Based on these assessments, the investigator evaluated the subject's clinical response to therapy. The clinical response was defined by one of the following:

Cure: The study medication and the initial intervention (operative or radiologically-controlled drainage procedure) resolved the intra-abdominal infection. If the subject underwent a percutaneous drainage at baseline, did not respond to treatment within 72 hours of the initial drainage, and needed to undergo an operation and then improved while remaining on the randomized antibiotic, he or she could have been considered a clinical cure. The reason for the failed percutaneous drainage (e.g., bowel perforation) was recorded. The subject must not have received additional antibacterial agents during treatment.

Failure: The subject met at least one of the following criteria:
• Required additional surgical or radiologic intervention or received additional antibacterial therapy to cure the infection (including surgical wound infections).
• Died after study day 2 because of the infection or a treatment-related adverse event (as primary reason).
• Discontinued from study drug after receiving at least 8 doses in less than 5 days because of a treatment-related adverse event as primary reason.
• Received greater than 120% of the planned number of doses of study drug.

Subjects who had TRAEs, who received at least 8 doses of study medication in at least 5 days, and did not receive other antibiotic therapy or surgical or radiologic intervention could have been declared a clinical cure if all other criteria for a clinical cure were met. If a subject had a clinical response of failure while receiving study drug, that response was to be carried forward through the test-of-cure assessment, whether or not he or she was cured with other antibiotics.

Indeterminate: The subject met at least one of the following criteria:
• Was lost to follow-up (failed to have an outcome determination).
• Died within 2 days after the first dose of study drug for any reason.
• Died before the test-of-cure assessment because of reasons not related to the infection.

Secondary Efficacy Variables
Secondary variables for clinical response included the following:
• Clinical response for the ME and m-mITT populations at the test-of-cure assessment, excluding subjects whose surgical procedure at the time of study entry provided inadequate source control (as determined by the surgical review board).
• Clinical response for the ME and m-mITT populations at the test-of-cure assessment, including subjects (deemed cures) whose surgical procedure at the time of study entry provided inadequate source control (as determined by the surgical review board).

• Clinical response by baseline isolate for the ME and m-mITT populations at the test-of-cure assessment, summarized overall and by susceptible and resistant pathogens.
• Clinical response for the ME and m-mITT populations with monomicrobial infections at the test-of-cure assessment.
• Clinical response for the ME and m-mITT populations with polymicrobial infections at the test-of-cure assessment.

Microbiologic Response
The microbiologic endpoints were secondary efficacy endpoints. Microbiologic efficacy was evaluated at both the subject and pathogen level. Specimens obtained at baseline included 2 sets of blood cultures and aerobic and anaerobic cultures from the primary intra-abdominal site of infection. Additional cultures were obtained throughout the study if clinically indicated. Based on the results of these cultures, susceptibilities of identified organisms, and the clinical outcome of the subject, responses were assigned programmatically at the subject and pathogen levels based on 1 of the definitions of microbiologic efficacy stated below. Ribotyping of isolates from subjects who had more than 1 isolate of the same genus and species of bacteria was performed. For the current study report, when a subject had more than 1 isolate of the same organism, only the first isolate (as determined by date and time) was used in the pathogen-level analysis.

Results
Disposition

Number of Subjects in Each Population Category			
Population	Tigecycline n (% ITT)	Imipenem/Cilastatin n (% ITT)	Total n (% ITT)
Screened			898[a]
Screen Failures			64[a]
Intent-to-Treat (ITT)	417	417	834[a]
No treatment received	4	5	9[a]
Modified Intent-to-treat (mITT)	413 (99.0)	412 (98.8)	825 (98.9)
cIAI did not meet minimal disease criteria	5	13	18
Clinical mITT (c-mITT)	408 (97.8)	399 (95.7)	807 (96.8)
Did not meet clinical evaluability criteria	67	48	115
Clinically evaluable (CE)	341 (81.8)	351 (84.2)	692 (83.0)
No baseline and/or susceptible isolates	94	96	190
Microbiologically evaluable (ME)	247 (59.2)	255 (61.2)	502 (60.2)
Microbiological mITT (m-mITT)	309 (74.1)	312 (74.8)	621 (74.5)
No baseline isolate identified from c-mITT	99	87	186

Abbreviations: ITT = all randomized subjects; mITT = ITT subjects who received at least 1 dose of study drug; cIAI = complicated intra-abdominal infection; c mITT = mITT subjects with evidence of cIAI;
m-mITT = c-mITT subjects with identified baseline isolate.
a: Three (3) subjects (301-080-3432, 301-080-3447, and 301-157-7201) identified as screen failures were actually drop-no med subjects

Discontinuations
The following table summarizes the primary reasons for discontinuation of study drug for 102 subjects: 64 (15.5%) subjects in the tigecycline group and 38 (9.2%) subjects in the imipenem/cilastatin group. Significantly more subjects treated with tigecycline than those treated with imipenem/cilastatin discontinued study drug for any reason (p = 0.008).

Subjects treated with tigecycline were significantly more likely to discontinue study drug for an adverse event (p = 0.048) or for a subject request unrelated to the study (p = 0.001) than subjects treated with imipenem/cilastatin. Investigators identified adverse events as the primary reason for discontinuation of study drug for 26 (6.3%) subjects in the tigecycline group and 13 (3.2%) subjects in the imipenem/cilastatin group.

Study Drug Discontinuations by Primary Reason in the mITT Population: Number (%) of Subjects

Reason	Tigecycline (n = 413)		Imipenem/ Cilastatin(n = 412)		Total (n = 825)		Fisher Exact p-Value
Total	64	(15.5)	38	(9.2)	102	(12.4)	0.008*
Adverse event[a]	26	(6.3)	13	(3.2)	39	(4.7)	0.048*
Subject request unrelated to study	11	(2.7)	0	(0.0)	11	(1.3)	0.001*
Culture contains non-susceptible pathogen	7	(1.7)	2	(0.5)	9	(1.1)	0.177
Unsatisfactory response (lack of efficacy)	9 11	(2.2)	11	(2.7)	20 23	(2.4)	0.659
Other event[a,b]	11	(2.7)	12	(2.9)	23	(2.8)	0.836

a: One (1) tigecycline-treated subject discontinued study drug for an adverse event that was not captured on the database (301-050-1933). One (1) additional tigecycline-treated subject discontinued study drug for an adverse event that was classified as "other event" (301-402-6138).
b: Other events included death, protocol violation, withdrawal of consent, subject request, subject recovery, and clinical failure

* Significant between-group difference at the 0.05 level.

Medical Officer review of those subjects who discontinued due to the category of "other" showed that the explanations were reasonable and similar between the two treatment arms.

Protocol Deviations

A total of 18 subjects (5 in the tigecycline group and 13 in the imipenem/cilastatin group) did not have cIAI that met the minimal disease criteria. These mITT subjects were excluded from the c-mITT population. In addition, some subjects did not meet 1 or more eligibility criteria but received exemptions to enroll in the study (prospective waivers). Nineteen (19) subjects received prospective waivers. Review of those patients who received exemptions revealed that the eligibility criteria which the patients did not meet were relatively minor and unlikely to have had an effect on assessment of outcome. Also, there were only a small number of such patients.

Demographics

Demographic and other baseline characteristics of the mITT population, including age, sex, ethnicity, weight, and CLCR are shown in the following table. There were no significant differences between treatment groups in demographic or baseline characteristics in the mITT population.

Demographic and Baseline Characteristics of the mITT Population				
Characteristic	Tigecycline (n = 413)	Imipenem/Cilastatin (n = 412)	Total (n = 825)	p-Value[a,b]
Age, years				0.715[a]
Mean	43.87	43.42	43.64	
Standard Deviation	18.21	17.53	17.86	
Minimum, maximum	18.00, 91.00	18.00, 90.00	18.00, 91.00	
Median	42.00	42.00	42.00	
Sex, n (%)				0.450[b]
Male	274 (66.3)	263 (63.8)	537 (65.1)	
Female	139 (33.7)	149 (36.2)	288 (34.9)	
Ethnic origin, n (%)				0.958[b]
White	165 (40.0)	160 (38.8)	325 (39.4)	
Black	35 (8.5)	39 (9.5)	74 (9.0)	
Asian	49 (11.9)	44 (10.7)	93 (11.3)	
Other	88 (21.3)	90 (21.8)	178 (21.6)	
Hispanic	76 (18.4)	79 (19.2)	155 (18.8)	
Weight, kg				0.756[a]
Mean	69.38	69.04	69.21	
Standard Deviation	15.70	16.31	16.00	
Minimum, maximum	39.00, 147.43	37.65, 179.00	37.65, 179.00	
Median	66.50	65.32	66.00	
Creatinine clearance, mL/min/1.73m2				0.627[a]
Mean	92.85	94.00	93.42	
Standard Deviation	33.63	34.26	33.93	
Minimum, maximum	1.30, 281.00	28.00, 257.00	1.30, 281.00	
Median	90.00	90.50	90.30	
APACHE II score				0.683[a]
n	412	412	824	
Mean	5.70	5.58	5.64	
Standard Deviation	4.42	4.10	4.26	
Minimum, maximum	0.00, 25.00	0.00, 25.00	0.00, 25.00	
Median	5.00	5.00	5.00	
APACHE II Score by category, n (%) ≤15	396 (96.1)	398 (96.6)	794 (96.4)	0.710[b]
> 15	16 (3.9)	14 (3.4)	30 (3.6)	

Abbreviations: APACHE= Acute Physiology and Chronic Health Evaluation.

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

b: Fisher exact test (2-tailed).

The following table summarizes the specific diagnoses for baseline infections in the mITT population. The most common diagnosis in both treatment groups was complicated appendicitis (51.6% overall). There were no significant differences between treatment groups in the number or types of infections diagnosed at baseline.

Clinical Diagnosis of Infections Within the mITT Population: Number (%) of Subjects				
Clinical Diagnosis	Tigecycline (n = 413)	Imipenem/Cilastatin (n = 412)	Total (n = 825)	p-Value[a]
Any diagnosis				0.402[a]
Complicated appendicitis	223 (54.0)	203 (49.3)	426 (51.6)	
Perforation of intestine	45 (10.9)	41 (10.0)	86 (10.4)	
Gastric/duodenal perforation	41 (9.9)	40 (9.7)	81 (9.8)	
Complicated cholecystitis	31 (7.5)	38 (9.2)	69 (8.4)	
Intra-abdominal abscess	33 (8.0)	29 (7.0)	62 (7.5)	
Complicated diverticulitis	23 (5.6)	32 (7.8)	55 (6.7)	
Peritonitis	15 (3.6)	23 (5.6)	38 (4.6)	
Other[b]	2 (0.5)	6 (1.5)	8 (1.0)	

a: Fisher exact test (2-tailed).

b: Other diagnoses included infected hematoma, pelvic inflammatory disease, acute abdomen subocclusion, acute inflammatory abdomen, disease pelvic infectious, tubo-ovarian abscess, right tubal abscess, infected left subphrenic hematoma.

Efficacy

Populations Analyzed

The co-primary efficacy populations were the ME and m-mITT populations. There were 133 mITT subjects excluded from the CE population for the reasons summarized in the

following table.

Table 9.1-1: Categories and the Number (%) of mITT Subjects Excluded From the Clinically Evaluable and Microbiologically Evaluable Populations

Categories[a]	Tigecycline (n = 413)	Imipenem/Cilastatin (n = 412)	Total (n = 825)
mITT subjects excluded from the CE population, n (% mITT)[a]	72 (17.4)	61 (14.8)	133 (16.1)
All subjects			
Blind Broken	14 (3.4)	8 (1.9)	22 (2.7)
Inclusion/exclusion criteria not met[b]	10 (2.4)	18 (4.4)	28 (3.4)
> 1 doses of prior antibiotic after baseline culture	7 (1.7)	5 (1.2)	12 (1.5)
No clinical evaluation at test-of-cure	28 (6.8)	19 (4.6)	47 (5.7)
Cure subjects			
Test article compliance[c]	3 (0.7)	3 (0.7)	6 (0.7)
Received concomitant antibiotics	12 (2.9)	7 (1.7)	19 (2.3)
Test-of-cure after last dose[d]	6 (1.5)	5 (1.2)	11 (1.3)
Failure subjects			
Did not receive at least 8 doses of study drug	5 (1.2)	2 (0.5)	7 (0.8)
Test-of-cure after 2 days[e]	5 (1.2)	0 (0.0)	5 (0.6)
mITT subjects excluded from the ME population, n (% mITT)[a]	166 (40.2)	157 (38.1)	323 (39.2)
Isolate without susceptibility	94 (22.8)	96 (23.3)	190 (20.3)

Abbreviations: CE = clinically evaluable; mITT = modified intent-to-treat population; ME = microbiologically evaluable.
a: Subjects could have been excluded from the CE population for more than 1 reason.
b: Includes 18 subjects excluded from the c-mITT population for not meeting minimal disease criteria.
c: Subject received less than 5 days of study drug or did not receive 80% - 120% of expected dose.
d: Subject did not have test-of-cure assessment within 12-44 day window.
e: Subject did not have test-of-cure assessment at least 2 days after start of study drug.
Source: eff4; 24SEP04:10:56

Demographics for Analysis Populations

The ME and m-mITT treatment groups were similar in terms of age, sex, ethnicity, weight, creatinine clearance, and APACHE II score. There were no significant differences between the treatment groups in the demographic characteristics in the CE or ME populations.

Clinical Diagnosis

The following table summarizes the clinical diagnoses for infections in the ME population at baseline. There were no significant differences between treatment groups in clinical diagnoses at baseline in the ME population. More than half (59.2%) of all infections in the ME population were diagnosed as complicated appendicitis at baseline.

Number (%) Clinical Diagnosis of Infections: Microbiologically Evaluable Population				
	Tigecycline	Imipenem/ Cilastin	Total	
Clinical Diagnosis	(n = 247)	(n = 255)	(n = 502)	p-Value
Any diagnosis of the infection				0.808[a]
Complicated appendicitis	152 (61.5)	145 (56.9)	297 (59.2)	
Perforation of intestine	21 (8.5)	23 (9.0)	44 (8.8)	
Complicated diverticulitis	17 (6.9)	25 (9.8)	42 (8.4)	
Intra-abdominal abscess	17 (6.9)	17 (6.7)	34 (6.8)	
Peritonitis	14 (5.7)	16 (6.3)	30 (6.0)	
Complicated cholecystitis	12 (4.9)	16 (6.3)	28 (5.6)	
Gastric/duodenal perforation	13 (5.3)	10 (3.9)	23 (4.6)	
Other	1 (0.4)	3 (1.2)	4 (0.8)	
a: p-Value for chi-square.				

Primary

The co-primary efficacy endpoints were the clinical responses within the ME and m-mITT populations at the test-of-cure assessment. 15% was set as the limit difference, or delta, for the true cure rates of the 2 treatments, i.e., the lower bound of the 2-sided 95% confidence interval (CI) for the difference in cure proportion had to be no lower than –15% to support the conclusion that antibiotic monotherapy with tigecycline was noninferior to therapy with imipenem/cilastatin. The following table compares cure and failure rates on the last day of therapy and at the test-of-cure assessment for the ME and m-mITT populations, respectively.

In the analysis of clinical responses, tigecycline met the statistical criteria of non-inferiority to imipenem/cilastatin at the test-of-cure assessment (the primary endpoint) and on the last day of therapy for both co-primary populations. For the ME population, the adjusted lower bound of the CI was -8.4% overall at the test-of-cure assessment and -8.5% overall on the last day of therapy (the adjusted upper bounds were 5.1% and 2.9%, respectively). For the m-mITT population, the adjusted lower bound of the CI was -11% overall at the test-of-cure assessment and -10.7% overall on the last day of therapy (the adjusted upper bounds were 2.5% and 0.8%, respectively).

Comparisons of clinical responses in the CE, c-mITT, mITT, and ITT sensitivity populations were examined. The results for these 4 populations also met statistical criteria for the non-inferiority comparisons of tigecycline to imipenem/cilastatin at the test-of-cure and last day of therapy assessments. There was a significant difference between treatment groups in the proportion of subjects deemed cures in the mITT population at the test-of-cure assessment. A higher proportion of subjects treated with imipenem/cilastatin than those treated with tigecycline were deemed cures at the test-of-cure assessment in the mITT population (79.9% versus 73.6%; p = 0.0366).
The lower bound of the 95% CI was -11.8.

Clinical Response: Microbiologically Evaluable and m-mITT Populations											
		----------Tigecycline----------			------Imipenem/Cilastatin-----			--------(Tigecycline -Imipenem/Cilastatin)---------			
Visit Response	APACHE Score	n/N	%	(95%CI)[a]	n/N	%	(95%CI)[a]	%	(95%CI)	Test for NonInf. p-Value	Test for Difference p-Value
m-m-ITT at TOC											
Cure	≤15	219/295	74.2	(68.8, 79 1)	242/302	80.1	(75.2, 84 5)	-5.9	(-13.0, 1 2)	0.0053	0.1049
	> 15	8/ 14	57.1	(28 9, 82 3)	2/10	20.0	(2.5, 55.6)	37.1	(-7 3, 81.6)	0.0086	0.1185
	Overall	227/309	73.5	(68 2, 78 3)	244/312	78.2	(73.2, 82.7)	**-4.7**	**(-11.8, 2 3)**	0.0019	0.1976
Failure		63/309	20.4	(16.0, 25 3)	55/312	17.6	(13.6, 22 3)				
Indeterminate		19/309	6.1	(3.7, 9.4)	13/312	4.2	(2.2, 7.0)				
ME at TOC											
Cure	≤15	195/238	81.9	(76.4, 86.6)	208/247	84.2	(79.1, 88 5)	-2.3	(-9.4, 4.8)	0.0002	0.5840
	> 15	4/ 9	44.4	(13.7, 78.8)	2/ 8	25.0	(3.2, 65.1)	19.4	(-36.6, 75.5)	0.1578	0.7349
	Overall	199/247	80.6	(75 1, 85 3)	210/255	82.4	(77.1, 86.8)	**-1.8**	**(-9.0, 5.4)**	0.0001	0.6892
Failure		48/247	19.4	(14.7, 24 9)	45/255	17.6	(13.2, 22.9)				

Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence intervals; Noninf = noninferiority.

a: Treatment group CIs are unweighted and calculated by using the method of Clopper and Pearson.

b: CIs and hypothesis tests are calculated by the asymptotical method, corrected for continuity.

c: Estimates of differences between treatment groups, corresponding CIs, and hypothesis tests are weighted by using minimum risk weights (method of Mehrotra and Railkar).

Secondary
The sponsor conducted numerous secondary analyses including: clinical response for ME and m-mITT populations by adequate vs. inadequate source control (as determined by blinded surgery review board), clinical response for ME and m-mITT populations by mono-microbial vs. polymicrobial infections, microbiologic response at the subject level for ME and m-mITT populations, microbiologic response by baseline isolate for the ME and m-mITT populations, clinical cure rate by baseline isolate for the ME and m-mITT populations, clinical cure rate by pathogen and MIC for both ME and m-mITT populations. Subgroup analyses were also done for multiple comparisons examining clinical responses for characteristics such as age, sex, ethnicity, region, clinical diagnosis, creatinine clearance, and bacteremia status. All of these secondary and exploratory analyses were reviewed in detail by the Medical Officer. Although the study was not powered or designed to determine statistical significance for these analyses, the results of these analyses were found to be consistent with the overall findings of the primary efficacy analysis results.

For the majority of the analyses by organism, there were too few organisms isolated to be able to make any determinations. The most common organisms isolated in this study included: *Bacteroides* species, *Citrobacter* species, *Clostridium* species, *Enterobacter* species, *Enterococcus* species, *Escherichia* species, *Klebsiella* species, *Pseudomonas* species, *Staphylococcus aureus*, *Streptococcus* species, and *Peptostreptococcus* species. The table below summarizes the outcomes for tigecycline vs. imipenam by these most common isolated organisms for the m-mITT population. This analysis was also done for the ME population and the results were consistent with those for the m-mITT population analysis.

Clinical Cure Rate by Baseline Pathogen at the TOC Visit for the Microbiologic-Modified Intent-to-Treat Population

	Tigecycline			Imipenem/Cilastin		
	n/N	%	95% CI	n/N	%	95% CI
Escherichia species	141/192	73.4	66.6, 79.5	168/211	79.6	73.5, 84.8
Bacteroides species	66/95	69.5	59.2, 78.5	72/95	75.8	65.9, 84.0
Streptococcus species	62/86	72.1	61.4, 81.2	53/81	65.4	54.0, 75.7
Enterococcus species	22/40	55.0	38.5, 70.7	31/52	59.6	45.1, 73.0
Klebsiella species	26/35	74.3	56.7, 87.5	36/46	78.3	63.6, 89.1
Pseudomonas species	19/32	59.4	40.6, 76.3	25/29	86.2	68.3, 96.1
Clostridium species	16/21	76.2	52.8, 91.8	14/20	70.0	45.7, 88.1
Citrobacter species	12/14	85.7	57.2, 98.2	6/9	66.7	29.9, 92.5
Staphylococcus sp.	11/14	78.6		4/7	57.1	18.4, 90.1
Enterobacter species	8/11	72.7	39.0, 94.0	5/11	45.5	16.7, 76.6
Peptostreptococcus sp.	6/10	60.0	26.2, 87.8	6/9	66.7	29.9, 92.5

The most significant difference in outcome by organism was found with *Pseudomonas* infections. This is not unexpected, because tigecycline does not have anti-bacterial activity against *Pseudomonas* species.

Resistant Pathogens
Infectious due to resistant organisms in this study are reviewed in the Resistant Pathogens section of the ISE.

Conclusions/Summary
The lower bounds of the 95% CI's for the primary endpoint in the Microbiologically Evaluable and m-m-ITT Populations, were -9.0 and -11.8, respectively. The secondary endpoints support the non-inferiority conclusions of the primary endpoint analyses. The secondary microbiologic endpoint of clinical cure according to baseline pathogen showed a difference in the point estimates for *Pseudomonas aeruguinosa* (59.4% for tigecycline vs 86.2% for imipenem). This difference is expected since tigecycline has no activity against *Pseudomonas*, while imipenem has excellent activity.

Protocol 306

Protocol Description
The protocol for study 306 was harmonized to be identical to that of Study 301. For details, please refer to the review of Study 301.

Amendments
The original protocol, dated 22 May 2001 was amended 3 times. The study began in all regions with amendment 1; most of the sites were initiated with amendment 1 and some with amendment 2. Amendment 3 was a country-specific amendment to comply with the regulatory agencies in Bulgaria.

Amendment 1 was added prior to the start of the study. The primary changes that were included in this amendment were:

1. Stratification was added according to the Acute Physiology and Chronic Health Evaluation (APACHE) II score.
2. Electrocardiograms were added at screening, day 3, and the test-of-cure assessment.
3. The surgical review board (SRB) was added.
4. The inclusion/exclusion criteria were modified as follows:
    a. The definition of what constituted a complicated intra-abdominal infection was clarified.
    b. What antibiotics were permitted before the study was modified.
    c. The requirements for the presence of baseline signs and symptoms of infection were modified.
    d. Exclusions were added for limitations on prior immunosuppressive therapy, known diagnosis with acquired immunodeficiency syndrome (AIDS), and active or treated leukemia or other systemic malignancy.
    e. The creatinine clearance exclusion was modified from <50 mL/min to <70 mL/min. Modifications were also made to other laboratory finding exclusion criteria.

Added to the protocol: If *Pseudomonas aeruginosa* was isolated in the baseline culture, test article was to be discontinued and appropriate antibiotic therapy instituted per the investigator's judgment.

Amendment 2 included the important following changes:
1. Subjects with known or suspected infections with *Pseudomonas aeruginosa* at baseline were to be withdrawn from the study; however, any subject with a baseline polymicrobial infection that included *P. aeruginosa* was allowed to continue in the study if the investigator considered it appropriate to do so, on the basis of the subject's clinical status. Oral follow-on therapy was prohibited unless it was considered by an investigator to be clinically indicated.
2. Dose administration for imipenem/cilastatin was revised to allow adjustments for subjects with body weights <70 kg and with a creatinine clearance between 41 mL/min/1.73m^2 and 70 mL/min/1.73m^2. To maintain the blind for the study, all doses

were to be administered every 6 hours instead of every 8 hours as specified in the product labeling for the comparator agent. The shortened dose interval allowed subjects with a creatinine clearance as low as 41 mL/minute/1.73m^2 and a body weight as low as 40 kg to be randomized into the study. The 2 g/day dose of imipenem/cilastatin was considered to be appropriate for moderately severe to severe infections. The increase in the doses was to minimize both overdosing and underdosing of imipenem/cilastatin and to maintain the blind for the study.

-Revisions were made to the inclusion and exclusion criteria as follows:

a. The nature of complicated intra-abdominal infection (cIAI) was clarified in the inclusion criteria and defined in accordance with the guidelines of the Infectious Diseases Society of America.

b. The time of active or treated leukemia or systemic malignancy was decreased in the exclusion criteria to within 1 year to 3 months.

c. Because of the provision for home health care as an added option, the exclusion criterion for an anticipated hospital stay of a minimum of 5 days was changed to an anticipated duration in antibiotic therapy of a minimum of 5 days.

d. Contraceptive requirements for male subjects were removed from the exclusion criteria.

e. Preoperative diagnoses were added to the exclusion criteria to narrow the population to subjects with cIAI that required a minimum of 5 days.

f. The use of antibacterial irrigants during surgical procedures and any concurrent infection requiring systemic antibacterial therapy were added to the exclusion criteria.

g. The creatinine clearance exclusion was changed from <70 mL/min/1.73m^2 to <41 mL/min/1.73m^2.

Amendment 3 pertained only to Bulgaria and involved the inclusion of a skin scratch test for detection of potential allergies to test articles.

Post-Hoc Changes

Before the study data were unblinded, refinements were made to the Statistical Analysis Plan to supplement protocol descriptions of the criteria for efficacy populations and statistical analysis methods for efficacy data, to further define the analysis plan, and to harmonize it with that in protocol 301. The main refinements to the study and planned analyses included the following items:

1. The noninferiority of tigecycline compared with imipenem/cilastatin was evaluated by using a 2-sided 95% CI adjusted for the stratification variable APACHE II score (15 or lower, or more than 15 but less than 31).
2. Supplementary evaluability criteria and algorithm for subjects who received potentially effective antibiotics after randomization.
3. Supplementary evaluability criteria and algorithm to determine the clinical response of subjects who discontinued study treatment because of a treatment-related adverse event.
4. Clarification of the SRB's role.
5. Harmonization of the timing of test-of-cure assessments across the protocol amendments by setting the window for the test-of-cure assessment at 12 to 44 days,

including plus or minus 2 days on either side of the window in consideration of subjects whose test-of-cure assessments were scheduled over a weekend. This window was based on amendment 2, which allowed a test-of-cure assessment within 14 to 35 days after the last dose of study drug.
6. Inclusion of non-inferiority tests to compare the efficacy of tigecycline with that of imipenem/cilastatin.

Inclusion/Exclusion Criteria
Please refer to the review of Study 301

Analysis Populations
Please refer to the review of Study 301

Results
Disposition
A total of 861 subjects were screened for the study; 47 were screen failures. The remaining 824 subjects were randomly assigned to 1 of the treatment arms and constituted the intent-to-treat (ITT) population. Seven (7) subjects did not receive study drug. Altogether, 817 subjects received the study drug and constituted the mITT population: 404 subjects received tigecycline and 413 subjects received imipenem/cilastatin.

Table 8.1-1: Number of Subjects in Each Population Category

Population	Tigecycline n (% ITT)	Imipenem/ Cilastatin n (% ITT)	Total n (% ITT)
Screened			861
Screen failures[a]			37
Intent-to-treat (ITT)[b]	409	415	824
No treatment received	5	2	7
Modified intent-to-treat (mITT)[c]	404 (98.8)	413 (99.5)	817 (99.2)
cIAI did not meet severity criteria	11	12	23
Clinical mITT (c-mITT)[d]	393 (96.1)	401 (96.6)	794 (96.4)
Did not meet clinical evaluability criteria	49	55	104
Clinically evaluable (CE)	344 (84.1)	346 (83.4)	690 (83.7)
No baseline or susceptible pathogen	79	88	167
Microbiologically evaluable	265 (64.8)	258 (62.2)	523 (63.5)
Microbiologic mITT (m-mITT)[e]	322 (78.7)	319 (76.9)	641 (77.8)
No baseline isolate identified (from c-mITT population)	71	82	153

Abbreviation: cIAI = complicated intra-abdominal infection.
a: Ten (10) additional subjects were screen failures that were not captured on the database (see section 14, Clinical Data Errata).
b: ITT = all randomized subjects.
c: mITT = ITT subjects who received at least 1 dose of study drug.
d: c-mITT = mITT subjects with evidence of cIAI.
e: m-mITT = c-mITT subjects with identified baseline isolate.
Source: FINAL(21AUG04)/tpop4, 16SEP04:11:36

Discontinuations

The following table summarizes the primary reasons for discontinuation of study drug for 69 subjects: 35 (8.7%) in the tigecycline group and 34 (8.2%) in the imipenem/cilastatin group. Investigators identified adverse events as the primary reason for discontinuation of study drug for 15 (3.7%) subjects in the tigecycline group and 19 (4.6%) subjects in the imipenem/cilastatin group. Medical Officer review of the primary reasons for discontinuation revealed that there were no significant differences between treatment groups in the primary reasons for discontinuation of study drug.

Table 8.1.1-1: Study Drug Discontinuations by Primary Reason: Number (%) of Subjects, mITT Population

Reason	Tigecycline (n = 404)	Imipenem/ Cilastatin (n = 413)	Total (n = 817)	Fisher Exact p-Value
Total	35 (8.7)	34 (8.2)	69 (8.4)	0.900
Adverse event	15 (3.7)	19 (4.6)	34 (4.2)	0.601
Culture contained nonsusceptible pathogen	4 (1.0)	3 (0.7)	7 (0.9)	0.723
Subject request unrelated to study	5 (1.2)	4 (1.0)	9 (1.1)	0.750
Subject culture contained *P. aeruginosa*	1 (0.2)	2 (0.5)	3 (0.4)	1.000
Unsatisfactory response (lack of efficacy)	1 (0.2)	2 (0.5)	3 (0.4)	1.000
Other event[a]	9 (2.2)	5 (1.2)	14 (1.7)	0.293

a: Other events included adverse event, protocol violation, withdrawal of consent, and early hospitalization discharge. See Table 8.1.1-2 for verbatim descriptions of all "other events" cited as the primary reason for discontinuation of study drug.

Source: FINAL(21AUG04)/cpp5_ta, 23AUG04:10:31

Nine (9) tigecycline-treated subjects and 5 imipenem/cilastatin-treated subjects discontinued study drug for "other event." Review of these subjects revealed the reason for discontinuation to include protocol violation, consent withdrawal, and early hospitalization discharge.

The following table summarizes the primary reasons for withdrawal from the study for 55 subjects who withdrew from the study before the test-of-cure assessment: 25 (6.2%) subjects in the tigecycline group and 30 (7.3%) subjects in the imipenem/cilastatin group. The most common reason for withdrawal from the study in either treatment group was "other event." Medical Officer review of the reasons for withdrawal revealed that there were no significant differences between treatment groups in the primary reasons for withdrawal from the study.

Table 8.1.1-3: Summary of Study Withdrawals by Primary Reason: Number (%) of Subjects, mITT Population

Reason	Tigecycline (n = 404)	Imipenem/Cilastatin (n = 413)	Total (n = 817)	Fisher Exact p-Value
Total	25 (6.2)	30 (7.3)	55 (6.7)	0.578
Death	3 (0.7)	5 (1.2)	8 (1.0)	0.725
Failed to Return	9 (2.2)	9 (2.2)	18 (2.2)	1.000
Other event[a,b]	13 (3.2)	16 (3.9)	29 (3.5)	0.707

a: One (1) additional subject in the tigecycline-treated group (306-109-2165) had an adverse event resulting in withdrawal from the study that was not captured on the database as "other event" (see section 14, Clinical Data Errata). Three (3) subjects in the imipenem/cilastatin-treated group (306-052-0952, 306-106-2073, 306-107-2105) and 1 in the tigecycline-treated group (306-106-2074) are listed as having withdrawn from the study but had test-of-cure assessments performed (see section 14, Clinical Data Errata).

b: Other events included serious adverse event, adverse event, protocol violation, withdrawal of consent, sponsor request, and early hospitalization discharge. See Table 8.1.1-4 for verbatim descriptions of all "other events" cited as the primary reason for early withdrawal from the study.

Source: FINAL(21AUG04)/cpp5_d, 23AUG04:10:31

Thirteen (13) tigecycline-treated subjects and 16 imipenem/cilastatin-treated subjects withdrew early from the study for an "other event." These subjects were reviewed and found to have withdrawn due to protocol violations, withdrawal of consent, early hospital discharge, and sponsor request.

Demographics

Demographic and other baseline characteristics of the mITT population, including age, sex, ethnicity, weight, and CLCR, are shown in the following table. There were no significant differences between treatment groups in demographic or baseline characteristics in the mITT population.

Demographic and Baseline Characteristics: mITT Population				
Characteristic	Tigecycline (n = 404)	Imipenem (n = 413)	Total (n = 817)	p-Value[a,b]
Age, years				0.330[a]
Mean	48.28	49.52	48.91	
Standard deviation	18.37	17.96	18.17	
Minimum, maximum	18.00, 86.00	18.00, 88.00	18.00, 88.00	
Median	47.00	51.00	49.00	
Sex, n (%)				0.761[b]
Male	239 (59.2)	240 (58.1)	479 (58.6)	
Female	165 (40.8)	173 (41.9)	338 (41.4)	
Ethnic origin, n (%)				0.310[b]
White	349 (86.4)	370 (89.6)	719 (88.0)	
Black	12 (3.0)	13 (3.1)	25 (3.1)	
Asian	29 (7.2)	23 (5.6)	52 (6.4)	
Other	14 (3.5)	7 (1.7)	21 (2.6)	
Weight, kg				0.697[a]
Mean	74.08	74.50	74.29	
Standard deviation	14.93	15.72	15.32	
Minimum, maximum	44.00, 157.00	42.00, 130.00	42.00, 157.00	
Median	73.00	73.00	73.00	
Creatinine Cl, mL/min/1.73m2				0.762[a]
n	404	410	814	
Mean	65.41	64.81	65.11	
Standard deviation	28.89	27.40	28.13	
Minimum, maximum	10.81, 194.00	15.57, 174.00	10.81, 194.00	
Median	58.07	57.93	58.03	
APACHE II Score				0.913[a]
Mean	6.44	6.41	6.43	
Standard deviation	3.95	3.61	3.78	
Minimum, maximum	0.00, 20.00	0.00, 24.00	0.00, 24.00	
Median	6.00	6.00	6.00	
APACHE II Score, n (%)				0.075[b]
≤15	395 (97.8)	410 (99.3)	805 (98.5)	
>15	9 (2.2)	3 (0.7)	12 (1.5)	

Abbreviation: APACHE = Acute Physiology and Chronic Health Evaluation

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

b: Chi-square test.

The following table summarizes the specific diagnoses for baseline infections in the mITT population. The most common diagnosis in both treatment groups was complicated appendicitis (41.0% overall). There were no significant differences between treatment groups in the number or types of infections diagnosed at baseline.

Table 8.2-2: Clinical Diagnosis of Infections: Number (%) of Subjects, mITT Population

Characteristic	----Tigecycline--- (n = 404)	Imipenem/ Cilastatin (n = 413)	--------Total------ (n = 817)	p-Value[a]
Clinical Diagnosis,[b] n (%)				0.634[a]
Complicated appendicitis	168 (41.6)	167 (40.4)	335 (41.0)	
Complicated cholecystitis	80 (19.8)	98 (23.7)	178 (21.8)	
Intra-abdominal abscess	46 (11.4)	46 (11.1)	92 (11.3)	
Perforation of intestine	42 (10.4)	31 (7.5)	73 (8.9)	
Gastric/duodenal perforation	32 (7.9)	36 (8.7)	68 (8.3)	
Complicated diverticulitis	21 (5.2)	25 (6.1)	46 (5.6)	
Peritonitis	9 (2.2)	7 (1.7)	16 (2.0)	
Other	6 (1.5)	3 (0.7)	9 (1.1)	

a: Chi-square test.

b: Other diagnoses included complicated salpingitis, pyosalpinx, tubo-ovarial abscess, peritonitis due to left pyoovarium (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.

Source: INTEXT/demo5_diag_mitt, 06OCT04:22:10

Efficacy

The co-primary efficacy endpoints were the clinical responses within the ME and m mITT populations at the test-of-cure assessment. 15% was set as the limit difference, or delta, for the true cure rates of the 2 treatments. The following table compares cure and failure rates at the test-of-cure assessment for the ME and m-mITT populations, respectively.

Clinical Response: ME and m-mITT Populations									
		Tigecycline			Imipenem/Cilastatin			Tigecycline - Imipenem/Cilastatin	
TOC Visit Response	**APACHE Score**	**n/N**	**%**	**(95%CI)a**	**n/N**	**%**	**(95%CI)a**	**% Differ-ence**	**(95% CI)**
ME Population									
Cure	≤15 b	237/260	91.2	(86.3, 93.2)	232/258	89.9	(87.8, 94.3)		
	>15 b	5/5	100.0	(63.1,100.0)	0/0	0.0	(29.2,100.0)		
	Overall	242/265	91.3	(86.6, 93.4)	232/258	89.9	(87.9, 94.3)	**1.4**	**(-4.0, 6.8)**
Failure		23/265	8.7	(5.9, 12.3)	26/258	10.1	(5.1, 11.4)		
m-mITT									
Cure	≤15 b	271/314	86.3	(82.0, 89.9)	268/316	84.8	(80.4, 88.6)		
	>15 b	8/ 8	100.0	(63.1,100.0)	2/ 3	66.7	(9.4, 99.2)		
	Overall	279/322	86.6	(82.4, 90.2)	270/319	84.6	(80.2, 88.4)	**2.0**	**(-3.7, 7.7)**
Failure		34/322	10.6	(7.4, 14.4)	36/319	11.3	(8.0, 15.3)		
Indeterminate		9/322	2.8	(1.3, 5.2)	13/319	4.1	(2.2, 6.9)		

Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence intervals; Noninf = noninferiority.
A: Treatment group CIs are unweighted and calculated by using the method of Clopper and Pearson.
B: Between-group CIs and hypothesis tests are calculated by the asymptotic method, corrected for continuity.
C: Estimates of differences between treatment groups, corresponding CIs, and hypothesis tests are weighted by using minimum risk weights (method of Mehrotra and Railkar).

Secondary

The secondary analyses for study 306 were the same as the ones done for study 301 and include the following: clinical response for ME and m-mITT populations by adequate vs. inadequate source control (as determined by blinded surgery review board), clinical response for ME and m-mITT populations by mono-microbial vs. polymicrobial infections, microbiologic response at the subject level for ME and m-mITT populations, microbiologic response by baseline isolate for the ME and m-mITT populations, clinical cure rate by baseline isolate for the ME and m-mITT populations, clinical cure rate by pathogen and MIC for both ME and m-mITT populations. Subgroup analyses were also done for multiple comparisons examining clinical responses for characteristics such as age, sex, ethnicity, region, clinical diagnosis, creatinine clearance, and bacteremia status.

All of these secondary and exploratory analyses were reviewed in detail by the Medical Officer. Although the study was not powered or designed to determine statistical significance for these analyses, the results of these analyses were found to be consistent with the overall findings of the primary efficacy analysis results.

For the majority of the analyses by organism, there were too few organisms isolated to be able to make any determinations. The most common organisms isolated in this study included: *Bacteroides* species, *Citrobacter* species, *Clostridium* species, *Enterobacter* species, *Enterococcus* species, *Escherichia* species, *Klebsiella* species, *Pseudomonas* species, *Staphylococcus aureus* and coagulase-negative *Staphylococcus* species, *Streptococcus* species, *Prevotella* species, and *Peptostreptococcus* species. The table below summarizes the outcomes for tigecycline vs. imipenam by these most common isolated organisms for the m-mITT population. This analysis was also done for the ME population and the results were consistent with those for the m-mITT population analysis.

It is interesting to note that the outcome for patients with *Pseudomonas* infection in this study was different than that in study 301. In this study, patients with *Pseudomonas* infection did not appear to have a decreased response rate.

Clinical Cure Rate by Baseline Pathogen at the TOC Visit for the Microbiologic-Modified Intent-to-Treat Population.

	Tigecycline			Imipenem/Cilastin		
Organism	n/N	%	95% CI	n/N	%	95% CI
Escherichia species	156/181	86.2	80.3, 90.9	162/188	86.2	80.4, 90.8
Streptococcus species	82/95	86.3	77.7, 92.5	64/81	79.0	68.5, 87.3
Bacteroides species	69/85	81.2	71.2, 88.8	60/75	80.0	69.2, 88.4
Staphylococcus sp.	48/57	84.2	72.1, 92.5	44/49	89.8	77.8, 96.6
Enterococcus species	49/58	84.5	72.6, 92.7	52/61	85.2	73.8, 93.0
Klebsiella species	42/49	85.7	72.8, 94.1	37/41	90.2	76.9, 97.3
Pseudomonas species	24/30	80.0	61.4, 93.7	22/27	81.5	61.9, 93.7
Clostridium species	28/30	93.3	77.9, 99.2	27/32	84.4	67.2, 94.7
Citrobacter species	13/16	81.3	54.4, 96.0	8/12	66.7	34.9, 90.1
Peptostreptococcus sp.	12/17	70.6	44.0, 89.7	11/14	78.6	49.2, 95.3
Prevotella sp.	10/12	83.3	51.6, 97.9	8/10	80.0	44.4, 97.5
Enterobacter species	8/11	72.7	39.0, 94.0	5/11	45.5	16.7, 76.6

Resistant Pathogens

Patients in this study who had resistant pathogens are reviewed in the Resistant Pathogens section of the ISE.

Conclusions/Summary

The results of Study 306 are consistent with those of Study 301. The lower bounds of the 95% CI's for the primary endpoint in the Microbiologically Evaluable and m-m-ITT Populations were -5.9 and -3.7, respectively. The secondary endpoints support the non-inferiority conclusions of the primary endpoint analyses. In contrast to the results of Study 301, the secondary microbiologic endpoint of clinical cure according to baseline pathogen for Study 306 did not show a large difference in the point estimates for *Pseudomonas aeruguinosa* (80.0% for tigecycline vs 81.5% for imipenem). This lack of a difference is un-expected since tigecycline has no activity against *Pseudomonas*. This finding points to the complexity of this infectious process in which other factors, such as individual patient response to infection, the presence of other more virulent and sometimes inter-dependent micro-organisms, and the effects of thorough surgical drainage play a vital role.

Individual Efficacy Reviews cSSSI Studies

cSSSI Studies
This section contains individual reviews of Studies 300 and 305. These studies were planned with the exact same design.

Protocol 300

Protocol Description
This was a phase 3, multi-center, randomized, double-blind study to determine the safety and efficacy of tigecycline compared with vancomycin/aztreonam to treat complicated skin and/or skin structure infections. Enrolled subjects had cSSSI that involved deep soft tissue, required significant surgical intervention, or was associated with a significant underlying disease that complicated response to treatment. Subjects were randomly assigned (in a 1:1 ratio) to receive either tigecycline with placebo or vancomycin with aztreonam intravenously for up to 14 days. Approximately 500 subjects were to be enrolled. A total of 89 sites were initiated in 8 countries (United States, Canada, Argentina, Chile, Guatemala, Mexico, Peru, and India). Over half of all enrolled patients were enrolled in the U.S. and Canada.

Amendments
A number of protocol amendments were made to this protocol. The majority of these were relatively minor; however, the more significant ones are listed below:

1. Allowing inclusion of non-hospitalized patients (to allow for home healthcare therapy)
2. Including collection of pharmacokinetic profiles of certain subjects
3. Clarification – patients receiving oral switch therapy will be considered failures
4. In the control arm, investigators may decide to continue aztreonam (along with the vancomycin) even in the absence of a gram-negative pathogen on baseline cultures
5. The definition of complicated skin/skin structure infection was clarified further.
6. Crepitant cellulitis, chronic diabetic foot infections, and suspicion of ecthyma gangrenosum were added diseases for exclusion from the study as were patients with HIV and a CD4 count <350, and those on immunosuppressive therapy

All amendment changes were reviewed in detail and determined to be acceptable. None of them had the potential to decrease the quality of the study conduct or analysis.

Post-Hoc Changes

The following were the primary Post-Hoc changes that were made:

- Patients must have received no more than 2 doses of a prohibited antibacterial treatment after the baseline culture and prior to test article administration to be clinically evaluable.
- All aerobic pathogen isolates must be susceptible to both test articles. Anaerobic isolates must be susceptible to both test articles if they are isolated as the sole

causative pathogen for a patient to be included in the Microbiological Evaluable Population.

- The primary analysis had been the clinical response rates for all clinically evaluable patients at the test of cure visit (≥14 days and <36 days post therapy), however, this was changed to be no more than 90 days post-therapy.

All post-hoc changes were reviewed in detail and determined to be acceptable.

Inclusion/Exclusion Criteria

Subjects were enrolled in the study if they satisfied the following inclusion criteria:

1. Male and female subjects, 18 years of age or older.

2. Anticipated need for intravenous (IV) antibiotic therapy of 5 days' duration or longer.

3. Subjects known or suspected to have a cSSSI, including cSSSI that involved deep soft tissue, or required significant surgical intervention or that was associated with a significant underlying disease state that complicated response to treatment (such as diabetes mellitus, PVD, peripheral neuropathy, or lower venous insufficiency). This included clinical entities such as 1 of the following:

a. Infected ulcers that had developed signs of erythema, swelling, tenderness, pus, or warmth.

b. Burns (less than 5% body surface area, nonfull-skin thickness). Subjects with burns up to 25% of body surface area (nonfull-skin thickness) could be enrolled at selected study centers.

c. Major abscess (not treatable through surgery alone).

d. Deep or extensive cellulitis, either associated with an underlying disease state or greater than 10 cm in width or length.

e. Peripheral IV catheter sites with documented purulent drainage, provided that the catheter line was removed.

f. Infected human or animal bites.

4. Subjects with 2 of the following indicators of infection:

a. Drainage and/or discharge.

b. Fever: body temperature higher than 37.8°C (100°F) oral, 37.9°C (100.2°F) axillary, 38.2°C (100.8°F) tympanic, or 38.4°C (101.0°F) rectal (core), within 24 hours before enrollment.

c. Erythema.

d. Swelling and/or induration.

e. Localized warmth.

f. Pain and/or tenderness to palpation.

g. White blood cell count greater than 10,000/mm^3.

5. Subjects who had not received more than 2 doses of any non-study antibacterial drug after the original culture of the infected site had been obtained, except for subjects who were considered prior antibiotic failures.

6. For subjects who were considered therapeutic failures for prior antibiotic therapy with another agent at entry, a Gram stain or baseline culture of the infected site showing a potential pathogen was obtained before the first dose of study drug was administered. Once a subject began treatment with study drug, no other concomitant antibiotics could be given.

7. A written ICF, which had been approved by the IRB or IEC, was signed and dated by each subject before any screening procedures specific to the study were performed. If a subject was able to give consent, it must have been obtained. If any subject enrolled under Amendment 1 of the protocol was unable to give consent, it could have been obtained from the subject's next of kin or legal representative in accordance with local laws and regulations.

Subjects were **excluded** from participation in the study if they fulfilled any 1 of the following criteria:

1. Subjects with any concomitant condition that, in the opinion of the investigator, would preclude an evaluation of a response or make it unlikely that the contemplated course of therapy could be completed.

2. Subjects with severely impaired arterial blood supply and insufficiency such that amputation of the infected anatomical site was likely within 1 month.

3. Infected diabetic foot ulcers or decubitus ulcers where the infection was present for longer than 1 week or chronically infected ulcers in subjects who could not be compliant with measures necessary for chronic wound healing.

4. Necrotizing fasciitis or gangrene.

5. An uncomplicated skin and/or skin structure infection (eg, simple abscesses, folliculitis, impetiginous lesions, furunculosis, superficial cellulitis).

6. Subjects with suspected or known infection with *Pseudomonas aeruginosa*. However, subjects in whom the initial wound culture showed evidence of infection with *Pseudomonas aeruginosa* could continue to receive study drug at the investigator's discretion if the subject was showing signs of substantial and continuous clinical improvement on a daily basis.

7. Clinical suspicion of ecthyma gangrenosum.

8. Osteomyelitis contiguous to the infected site.

9. Crepitant cellulitis (gas gangrene).

10. Concurrent plasmapheresis or hemoperfusion.

11. Known or suspected hypersensitivity to tigecycline, tetracyclines, minocycline, vancomycin, aztreonam, or related antibiotics.

12. Presence of any of the following laboratory findings:
    a. Neutropenia (absolute neutrophil count less than 1000/mm^3).
    b. Presence of hepatic disease:
        i. Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transferase (SGOT) or alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase greater than 10 times the upper limit of normal (ULN) values.
        ii. Bilirubin values greater than 3 times the ULN.
        iii. Subjects with acute hepatic failure or acute decompensation of chronic hepatic failure.
    c. Calculated creatinine clearance (CL_{CR}) less than 30 mL/minute. Creatinine clearance (in mL/min) was calculated from the serum creatinine (S_{CR}, in mg/dL) by the following equations:
        i. CL_{CR} for men = [(140-age) x weight (kg)]/[72 x S_{CR}]
        ii. CL_{CR} for women = 0.85 x (CL_{CR} for men).

13. Known or suspected concomitant infection (e.g., *Pseudomonas aeruginosa*, anaerobes) that required treatment with an additional antibacterial agent(s).

14. Any investigational drugs taken within 4 weeks before administration of the first dose of study drug (day 1).

15. Previous participation in this study.

16. Pregnant or breastfeeding women.

17. Female subjects of childbearing potential who did not agree either to practice sexual abstinence or to use a medically acceptable method of contraception for the duration of the study and for at least 1 month after receiving the last dose of study drug.

18. Subjects with a skin and/or skin structure infection that could be treated by surgery alone.

19. Subjects who were HIV positive with a CD4 count of less than 350/mm^3 and an unstable viral load.

20. Immunosuppressive therapy, including use of high-dose corticosteroids (e.g., 40 mg or more of prednisone or equivalent per day) or any condition or medication that would impair the ability of the subject to eradicate infections.

Analysis Populations

Definitions of subject populations are as follows:

1. Screened population: all subjects who signed an ICF and were screened.

2. Intent-to-treat (ITT) population: screened subjects who were randomly assigned to a treatment arm.
3. Modified intent-to-treat (mITT) population: ITT subjects who received at least 1 dose of study drug.
4. Clinical modified intent-to-treat (c-mITT) population: mITT subjects who had clinical evidence of cSSSI, as defined in the inclusion criteria.

a. Subjects with cellulitis must have met at least 1 of the following diagnostic criteria:

1) Cellulitis ≥ 10 cm (where anatomically applicable).
2) Underlying medical condition (including diabetes mellitus, PVD, injection drug use, or known infection with HIV).
3) Cellulitis with drainage or requiring surgery.

b. Subjects who received more than 48 hours of antibiotic therapy before study entry (failure of antibiotic therapy) must have met all entry criteria and have had a Gram stain or culture of the infected site to document the presence of a potential baseline pathogen. If a Gram stain or culture could not be obtained from a subject with cellulitis, objective clinical evidence of active disease was ascertained by means of each of the following:

1) Fever and/or white blood cell count greater than 10,000/mm^3.
2) At least 2 of the following clinical indicators of infection: erythema, pain/tenderness to palpation, swelling/ induration, localized warmth, edema.

5. Microbiologic modified intent-to-treat (m-mITT) population: c-mITT subjects for whom at least 1 baseline pathogen had been identified.

6. Clinically evaluable (CE) population: c-mITT subjects who met the following criteria:

a. All subjects

1) Met inclusion and exclusion criteria as stated in the protocol under which the subject was enrolled. Any exemptions from these criteria were decided while the data were blinded and included:
   - Prospective exemptions were considered by the medical monitor on a case-by-case basis.
   - Prospective or retrospective exemptions for creatinine clearance for subjects enrolled under any version of the protocol, if the creatinine clearance was not lower than 30 mL/minute (–15%).
2) Did not have *Pseudomonas aeruginosa* isolated at baseline as the primary pathogen.

3) Received no more than 2 doses of a prohibited antibacterial treatment after the baseline culture was obtained and before the first dose of study drug.
4) Treatment regimen remained blinded throughout the duration of the study.
5) Had a test-of-cure assessment of cure or failure, but not indeterminate.

b. Clinically evaluable cure
1) Met the first 5 criteria for clinical evaluability of all subjects.
2) Met the pre-specified criteria for clinical cure.
3) Received at least 5 days of study drug and received between 80% and 120% of the expected number of doses of study drug.
4) Received no *potentially effective* concomitant antibiotic treatment (other than 1 dose of a topical antibacterial) after the first dose of study drug through the test-of-cure assessment.
5) Completed the test-of-cure assessment at least 12 days but not more than 92 days after the last dose of study drug.

c. Clinically evaluable failure
1) Met the first 5 criteria for clinical evaluability of all subjects.
2) Met the pre-specified criteria for clinical failure.
3) Received at least 4 doses of study drug.
4) Received at least 4 doses of study drug in fewer than 5 days and discontinued treatment because of a treatment-related adverse event
5) Had a test-of-cure assessment on or after day 3.

7. Microbiologic evaluable (ME) population: CE subjects who met the following criteria:

a) Had a culture taken from the infection site at baseline, which identified 1 or more potentially causative pathogens(s), and the primary pathogen was susceptible to both study drugs (i.e., tigecycline and either vancomycin or aztreonam).
b) Had microbiologic or clinical information available to allow classification of a microbiologic response of eradication, persistence, or superinfection at the test of cure assessment.
Note that the assignment of a primary baseline pathogen to assist in pharmacokinetic analysis was performed by a single medical monitor in a blinded fashion, based only on the knowledge of the baseline culture isolated and the primary site of infection. Organisms isolated from baseline cultures were considered to be the primary pathogen based on the frequency with which those organisms are identified in the particular disease state as determined by an extensive review of the medical literature. In polymicrobial infections, co-pathogens (secondary isolates) were identified on the basis of a Gram stain (i.e., Gram-positive or Gram-negative staining) and ability to grow aerobically or anaerobically). Skin cultures were considered the principal source of the primary causative pathogen. If no primary causative pathogen was identified from the skin source, a blood isolate could be considered the source of the primary causative pathogen, if clinically applicable.

Assessments of Subjects Who Received Concomitant Antibiotics
If a subject had a clinical response of cure at the test-of-cure assessment and received no potentially effective concomitant antibiotic for a distant site infection, then the subject was considered to be a CE cure. If a subject had received potentially effective concomitant antibiotic coverage for a distant site infection between the last day of therapy and the test-of-cure assessment, he or she could be considered a clinical cure in the c-mITT population but was not included in the CE population. If a subject met criteria for clinical evaluability and a concomitant antibiotic was prescribed because of clinical failure at or after the last day of therapy, the subject was considered to be a CE failure. If a subject received potentially effective concomitant antibiotics between the first and fourth doses of study drug, the subject was considered to be a nonevaluable failure (i.e., he or she was included in the c-mITT population but not in the CE population).

Efficacy Measurements
Both the clinical and microbiologic efficacy of tigecycline and vancomycin with aztreonam were evaluated. Because pathogens could not be cultured from every specimen, clinical and microbiologic efficacy measurements were made separately.

Primary Efficacy Variables
Clinical response at the test-of-cure assessment (which took place at least 12 days but not more than 92 days after the last dose of study drug) was the primary efficacy endpoint. The CE population, which comprised those subjects who met all evaluability criteria for efficacy specified in the protocol, was selected as 1 of 2 co-primary populations for determining clinical response. The c-mITT population, which consisted of all mITT subjects who received study drug and met the minimum disease criteria for cSSSI, was included as the other co-primary population for determining clinical response at the request of the FDA. Detailed assessments of the clinical status of each subject were recorded at baseline, on the last day of therapy and at the test-of-cure assessment. These assessments included the presence or absence of drainage and/or discharge, fever, erythema, swelling and/or induration, pain and/or tenderness to palpation, extent of infection (width and length), and localized warmth. For subjects withdrawn from therapy early, the clinical indicators of infection were assessed on the last day of therapy. Based on these assessments, the investigator evaluated each subject's clinical response to therapy.

Clinical response was defined by 1 of the following:

Cure: The subject met 1 of the following criteria:
- Resolution of all clinical indicators of the infection (healing of chronic underlying skin ulcer was not required).
- Improvement of the clinical indicators of the infection to such an extent that no further antibacterial therapy was necessary.

Failure: The subject met 1 of the following criteria:
- Lack of response and need for additional antibacterial therapy.

- Initial recovery from the infection was followed by deterioration before the test-of-cure assessment, requiring further antibacterial therapy.
- Required clinically unanticipated extirpative surgical intervention for management of the infection.
- Required non-routine surgical treatment at the original site of the infection more than 48 hours after the first dose of study drug because of failure to improve, clinical worsening, or the discovery of a new purulent collection.
- Death caused by the infection more than 2 days after randomization.
- Discontinued treatment with study drug or died because of a treatment-related adverse event (as the primary reason).
- Received more than 120% of the expected number of doses of study drug.

Note: Routine procedures defined as procedures consistent with the local standard of care did not constitute a clinical failure. A subject could be declared a therapeutic failure (unresponsive to study drug) after having received at least 4 doses (2 days) of study drug. If the subject had a clinical response of failure while receiving study drug, the response of failure was carried forward to the test of cure assessment.

Indeterminate: A subject from the c-mITT population could have an indeterminate response if 1 of the following criteria were met:

- Was lost to follow-up (no outcome determined).
- No clinical response was determined for the test-of-cure assessment.
- Died less than 2 days (received ≤ 4 doses of study drug) after random assignment to study drug.
- Died because of reasons not related to infection (as judged by the investigator) before the test-of-cure assessment.

Secondary Efficacy Variables

Secondary Variables for Clinical Response

Secondary variables for clinical response included the following:

- Clinical response (cure or failure) by baseline pathogen for the ME and m-mITT populations at the test-of-cure assessment, summarized overall and by susceptible and resistant pathogens.
- Clinical response (cure or failure) for subjects in the ME and m-mITT populations with a monomicrobial infection at the test-of-cure assessment.
- Clinical response (cure or failure) for subjects in the ME and m-mITT populations with a polymicrobial infection at the test-of-cure assessment.
- Clinical response (cure or failure) by baseline pathogen and minimum inhibitory concentration (MIC) values for subjects in the ME and m-mITT populations at the test-of-cure assessment. Sensitivity analyses were designed to evaluate the robustness of the results and to characterize the results more fully.

Microbiologic Response

The secondary efficacy endpoints were microbiologic responses at both the subject and the pathogen level. Specimens obtained at baseline included 2 sets of blood cultures and aerobic and anaerobic cultures from the primary site of infection. Additional cultures (blood, skin and/or skin structure site, etc) were obtained throughout the study if clinically indicated. Responses (i.e., susceptibilities of identified organisms and the clinical outcome of the subject) based on the results of these cultures were assigned programmatically using 1 of the definitions of microbiologic response at both the subject and the pathogen level. If multiple isolates of the same species and genus were obtained, microbiologic responses were evaluated only for the first isolate identified. Ribotyping was then performed to determine if there were unique isolates.

Results

Disposition

Number of Subjects in Each Population Category

Population	Tigecycline n (% ITT)	Vancomycin/ Aztreonam n (% ITT)	Total n (% ITT)
Screened			596
Screened failures			13
Intent-to-Treat (ITT)	295	288	583
No treatment received	3	7	10
Modified intent-to-treat (mITT)	292 (99.0)	281 (97.6)	573 (98.3)
Did not meet minimum disease criteria for cSSSI	15	21	36
Clinical mITT (c-mITT)	277 (93.9)	260 (90.3)	537 (92.1)
Did not meet clinical evaluability criteria	78	62	140
Clinically evaluable (CE)	199 (67.5)	198 (68.8)	397 (68.1)
No baseline and/or susceptible pathogens	84	85	169
Microbiologically evaluable (ME)	115 (39.0)	113 (39.2)	228 (39.1)
Microbiologic mITT (m-mITT)	186 (63.1)	171 (59.4)	357 (61.2)
No baseline pathogen identified from c-mITT[a]	91	89	180

Discontinuation of Study Drug by Primary Reason: Number (%) of Subjects in the mITT Population

Primary Reason	Tigecycline (n = 292)	Vancomycin/ Aztreonam (n = 281)	Total (n = 573)	Fisher Exact p-Value
Total	48 (16.4)	42 (14.9)	90 (15.7)	0.647
Adverse event	18 (6.2)	13 (4.6)	31 (5.4)	0.463
Subject request unrelated to study	3 (1.0)	2 (0.7)	5 (0.9)	1.000
Culture contains nonsusceptible pathogen[a]	2 (0.7)	1 (0.4)	3 (0.5)	1.000
Unsatisfactory response (lack of efficacy)	7 (2.4)	12 (4.3)	19 (3.3)	0.248
Other event [b]	18 (6.2)	14 (5.0)	32 (5.6)	0.588

a: "Culture contains nonsusceptible pathogen" was specified instead of "*Pseudomonas aeruginosa*" for 2 subjects (300-087-2573; 300-107-3039).(Source: resp1)

b: The reasons cited as *other events* were verbatim descriptions of events given by the investigators for study drug discontinuations.

(page 75, sponsor's study report)

Details of patients whose discontinuation was categorized as "other event" were reviewed. Review of these details revealed no specific concerns. Among patients in this category, typical explanations included: significant improvement such that participation in study was discontinued, death, patient left against medical advice, withdrawal of consent, and received other antibiotic/other protocol violations. One patient in the

tigecycline arm (300-408-5367) should have been categorized as having discontinued due to vomiting, instead of "other event," as this was the primary reason why the patient withdrew consent.

Demographics

Demographic and Baseline Characteristics: mITT Population

Characteristic	Tigecycline (n = 292)	Vancomycin/ Aztreonam (n = 281)	Total (n = 573)	p-Value
Age, years				0.435[a]
Mean	49.41	48.36	48.90	
Standard deviation	15.44	16.57	16.00	
Minimum, maximum	18.00, 90.00	18.00, 92.00	18.00, 92.00	
Median	49.00	48.00	48.00	
Sex, n (%)				0.192[b]
Male	180 (61.6)	188 (66.9)	368 (64.2)	
Female	112 (38.4)	93 (33.1)	205 (35.8)	
Ethnic origin, n (%)				0.960[b]
White	154 (52.7)	149 (53.0)	303 (52.9)	
Black	28 (9.6)	23 (8.2)	51 (8.9)	
Asian	1 (0.3)	2 (0.7)	3 (0.5)	
Hispanic	54 (18.5)	53 (18.9)	107 (18.7)	
Other	55 (18.8)	54 (19.2)	109 (19.0)	
Weight, kg				0.840[a]
Mean	81.53	81.95	81.73	
Standard deviation	22.94	27.00	24.99	
Minimum, maximum	40.00, 167.00	36.00, 255.00	36.00, 255.00	
Median	79.30	75.00	77.27	
Creatinine clearance, mL/minute				0.897[a]
Mean	109.47	110.07	109.76	
Standard deviation	47.09	64.15	56.07	
Minimum, maximum	28.60, 363.00	6.70, 720.60	6.70, 720.60	
Median	103.00	100.00	102.00	

a: One-way analysis of variance with treatment as factor.
b: Fisher exact test (2-tailed).

Baseline Characteristics/ Etiology of Infections

Clinical Diagnosis of Infections in the mITT Population: Number (%) of Subjects

Clinical Diagnosis	Tigecycline (n = 292)	Vancomycin/ Aztreonam (n = 281)	Total (n = 573)	Chi-Square p-Value
Any diagnosis				0.232
Infected ulcers	17 (5.8)	13 (4.6)	30 (5.2)	
Major abscesses	88 (30.1)	76 (27.0)	164 (28.6)	
Burns	2 (0.7)	6 (2.1)	8 (1.4)	
Deep soft tissue infection	174 (59.6)	181 (64.4)	355 (62.0)	
Cellulitis[a]	161 (55.1)	169 (60.1)	330 (57.6)	
Complicated underlying disease	56 (19.2)	60 (21.4)	116 (20.2)	
≥10 cm (where anatomically applicable)	141 (48.3)	145 (51.6)	286 (49.9)	
Requiring surgery/drainage	73 (25.0)	77 (27.4)	150 (26.2)	
Wound infection	13 (4.5)	12 (4.3)	25 (4.4)	
Other	11 (3.8)	5 (1.8)	16 (2.8)	

A: Subjects may have met more than 1 of the diagnostic criteria for cellulitis.

The majority of subjects in both treatment groups (62.0%) had *deep soft tissue infection* as the primary diagnosis at baseline. At least 1 diagnostic criterion for cellulitis was met by 57.6% of subjects. For 49.9% of subjects, the infections were characterized as deep or extensive cellulitis involving at least 10 cm of tissue.

Etiology of Infections in the mITT Population: Number (%) of Subjects

Cause of Infection	Tigecycline (n = 292)	Vancomycin/ Aztreonam (n = 281)	Total (n = 573)	Chi-Square p-Value
Any cause				0.713
Trauma	71 (24.3)	83 (29.5)	154 (26.9)	
Spontaneous	159 (54.5)	137 (48.8)	296 (51.7)	
Bite (human, insect, animal)	21 (7.2)	17 (6.0)	38 (6.6)	
Surgery	30 (10.3)	32 (11.4)	62 (10.8)	
Injection	7 (2.4)	8 (2.8)	15 (2.6)	
Other	4 (1.4)	4 (1.4)	8 (1.4)	

Overall, 51.7% of infections in the mITT population were spontaneous in nature, 26.9% were caused by trauma, and 10.8% resulted from surgery.

Efficacy

Primary

The CE population was selected as 1 of 2 co-primary populations for determining clinical response. The c-mITT population was selected as the other co-primary population for determining clinical response.

Clinical Evaluability: Exclusion Categories and Number (%) of mITT Subjects Excluded From the CE Population

Clinically Evaluable Exclusion Categories[a]	Tigecycline (n = 292)		Vancomycin/ Aztreonam (n = 281)		Total (n = 573)	
Exclusion from CE population, n (% of mITT)	93	(31.8)	83	(29.5)	176	(30.7)
Reason for exclusion as CE cure/failure						
Blind broken	30	(10.3)	21	(7.5)	51	(8.9)
Inclusion/exclusion criteria not met[b]	15	(5.1)	21	(7.5)	36	(6.3)
Pseudomonas at baseline[c]	2	(0.7)	1	(0.4)	3	(0.5)
> 2 doses of prior antibiotic after baseline culture	7	(2.4)	2	(0.7)	9	(1.6)
No clinical evaluation at test-of-cure	22	(7.5)	15	(5.3)	37	(6.5)
Reason for exclusion as CE cure						
Study drug (test article) compliance[d]	7	(2.4)	2	(0.7)	9	(1.6)
Received concomitant antibiotics	12	(4.1)	26	(9.3)	38	(6.6)
Test-of-cure after last dose[e]	7	(2.4)	4	(1.4)	11	(1.9)
Reason for exclusion as CE failure						
Did not receive at least 4 doses of study drug	4	(1.4)	8	(2.8)	12	(2.1)
Test-of-cure after 2 days[f]	3	(1.0)	7	(2.5)	10	(1.7)

CE = clinically evaluable; mITT = modified intent-to-treat population; cSSSI = complicated skin and skin structure infection.
A: Subjects could have been excluded from the CE population for more than 1 reason.
B: For 36 subjects, the minimum disease criteria for cSSSI were not met.
C: Sole causative pathogen.
D: Subject received less than 5 days of study drug or did not receive 80% to 120% of expected dose.
e: Subject did not have the test-of-cure assessment within the 12- to 92-day window after the last dose of study drug.

Overall, the most frequently reported reason for exclusion from the CE population was breaking of the blind. A total of 44 of the 51 unblindings occurred at 3 sites (046; 119; and 402). Routine monitoring of these sites uncovered blinding practices that raised concerns about the possible unblinding of site study staff on some or all subjects. To take the most conservative position, WR excluded these 44 subjects from the CE population. All of these subjects were included in the mITT population. If they met minimum disease criteria for cSSSI, they were included in the c-mITT population. If a baseline pathogen was isolated, they were included m-mITT population.

Review of the demographic information for the CE Population was reviewed and revealed no meaningful differences between the two treatment arms.

Clinical Diagnosis of Infections in the CE Population: Number (%) of Subjects

Clinical Diagnosis	Tigecycline (n = 199)	Vancomycin/ Aztreonam (n = 198)	Total (n = 397)	Chi-Square p-Value
Any diagnosis				0.706
Infected ulcers	12 (6.0)	11 (5.6)	23 (5.8)	
Major abscesses	50 (25.1)	41 (20.7)	91 (22.9)	
Burns	0 (0)	1 (0.5)	1 (0.3)	
Deep soft tissue infection	133 (66.8)	141 (71.2)	274 (69.0)	
Cellulitis[a]	124 (62.3)	131 (66.2)	255 (64.2)	
Complicated underlying disease	40 (20.1)	47 (23.7)	87 (21.9)	
≥10 cm (where anatomically applicable)	112 (56.3)	112 (56.6)	224 (56.4)	
Requiring surgery/drainage	53 (26.6)	59 (29.8)	112 (28.2)	
Wound infection	9 (4.5)	10 (5.1)	19 (4.8)	
Other	4 (2.0)	4 (2.0)	8 (2.0)	

A: Subjects with cellulitis could have met more than 1 diagnostic criterion.

(sponsor's report, page 96)

Subjects in both treatment groups were similar in terms of their clinical diagnoses. The majority of subjects in both treatment groups (69.0%) had *deep soft tissue infection* as the primary diagnosis at baseline; 64.2% of subjects met at least 1 diagnostic criterion for cellulitis. For 56.4% of subjects, infections were characterized as deep or extensive cellulitis involving at least 10 cm of tissue. The table above provides the clinical diagnosis of each subject in the CE population. Spontaneous infection was the most frequently cited etiology in both treatment arms, accounting for 54.7% of all infections. Trauma was cited as the cause of infection in 23.9% of subjects. Bite, surgery, and injection were other, less common causes.

The table below summarizes the baseline distribution of diabetes mellitus, PVD, injection drug abuse, and infection with HIV among subjects in the CE population. No significant differences in the presence or absence of these comorbidities were observed between treatment groups.

Comorbid Medical Conditions at Baseline in the CE Population: Number (%) of Subjects

Comorbidity	Tigecycline (n = 199)	Vancomycin/ Aztreonam (n = 198)	Total (n = 397)	Chi-Square p-Value
Diabetes mellitus				0.974
Present	58 (29.1)	58 (29.3)	116 (29.2)	
Absent	141 (70.9)	140 (70.7)	281 (70.8)	
PVD				0.617
Present	19 (9.5)	16 (8.1)	35 (8.8)	
Absent	180 (90.5)	181 (91.9)	361 (91.2)	
IV drug abuse (injection drug abuse)				0.800
Present	8 (4.0)	7 (3.5)	15 (3.8)	
Absent	191 (96.0)	191 (96.5)	382 (96.2)	
Known HIV positive				0.433
Present	4 (2.1)	2 (1.1)	6 (1.6)	
Absent	191 (97.9)	187 (98.9)	378 (98.4)	

Abbreviations: PVD = peripheral vascular disease; IV = intravenous; HIV = human immunodeficiency virus.
Note: The sum of individual numbers for a comorbidity may not reflect the total because of missing values.
(page 97, Sponsor's report)

The table below shows the clinical response for the two primary endpoint analyses, cmITT and CE populations at TOC. The lower bounds of the 95% CI's for the cmITT and CE clinical response at TOC analyses were -9.0 and -7.4. These lower bounds were within the pre-defined delta for this study and support a conclusion of non-inferiority.

Analysis of Clinical Response: cmITT and CE Population at TOC

		Tigecycline		Vancomycin/ Aztreonam		Tigecycline – Vancomycin/Aztreonam			
Visit	**Response**	**n/N**	**%**	**n/N**	**%**	**Differ-ence**	**95% CI**	**Test for NI P-Value**	**Test for Differences p-Value**
c-mITT Test-of-Cure	**Cure**	209/277	75.5	200/260	76.9	-1.5	(-9.0, 6.1)	<0.001*	0.7650
	Failure	48/277	17.3	46/198	17.7				
	Indeterminate	20/277	7.2	14/260	5.4				
CE Test-of-Cure	**Cure**	165/199	82.9	163/198	82.3	0.6	(-7.4, 8.6)	<0.001*	0.9816
	Failure	34/199	17.1	35/198	17.7				

a: Treatment group confidence intervals calculated by using the method of Clopper and Pearson.

b: Estimates of differences between treatment groups and corresponding confidence intervals and hypothesis tests are done by using the asymptotic method (corrected for continuity).

Secondary

Secondary efficacy analyses were performed by monomicrobial and polymicrobial infections. The results of these analyses are contained in the table below.

Clinical Response by Mono- and Poly- microbial Infections: ME and m-mITT Populations

Visit	Response	Tigecycline		Vanco/ Aztreonam		Tigecycline – Vanco/Aztreonam	
		n/N	% (95% CI)	n/N	% (95% CI)	Difference	95% CI
ME Test-of-Cure	**Mono/Cure**	56/71	78.9 (67.6, 87.7)	55/69	79.7 (68.3. 88.4)	-0.8	(-15.2, 13.6)
	Mono/Failure	15/71	21.2	14/69	20.3		
	Poly/Cure	37/44	84.1 (69.9, 93.4)	33/44	75.0 (59.7, 86.8)	9.1	(-9.5, 27.0)
	Poly/Failure	7/44	7/44	11/44			
m-mITT Test-of-Cure	**Mono/Cure**	81/103	78.6 (69.5, 86.1)	84/103	81.6 (72.7, 88.5)	-2.9	(-14.5, 8.7)
	Mono/Failure	22/103	21.4	19/103	18.4		
	Poly/Cure	57/70	81.4 (70.3, 89.7)	43/61	70.5 (57.4, 81.5)	10.9	(-4.7, 26.4)
	Poly/Failure	13/70	18.6	18/61	29.5		

a: Treatment group confidence intervals calculated by using the method of Clopper and Pearson.
b: Estimates of differences between treatment groups and corresponding confidence intervals and hypothesis tests are done by using the asymptotic method (corrected for continuity).

Efficacy at Baseline Subject Level

The following tabble shows the microbiologic response at the subject level for the microbiologically evaluable population. The majority of subjects had a presumed eradication. There were no significant differences between the two study arms. This analysis was also conducted for the microbiologic- modified intent to treat population which was consistent with the analysis shown.

Microbiologic Response at the Subject Level: Microbiologically Evaluable Population

		-------Tigecycline -------		---Vancomycin/Aztreonam---		----------Difference---------- (Tigecycline-Vancomycin/Aztreonam)--			
Visit	Response	n/N % (95% CI)[a]		n/N % (95% CI)[a]		% Diff	(95% CI)[b]	Non-Inferiority p-Value	Differences p-Value
Test of Cure	**Eradication**	**90/ 115**	**78.3(69.6, 85.4)**	**87/ 113**	**77.0(68.1, 84.4)**	**1.3**	**(-10.4, 13.0)**	**0.0026**	**0.9433**
	Documented	**4/ 90**	**4.4**	**7/ 87**	**8.0**				
	Presumed	**86/ 90**	**95.6**	**80/ 87**	**92.0**				
	Persistence	**20/ 115**	**17.4**	**22/ 113**	**19.5**				
	Documented	**6/ 20**	**30.0**	**7/ 22**	**31.8**				
	Presumed	**14/ 20**	**70.0**	**15/ 22**	**68.2**				
	Superinfection	**5/ 115**	**4.3**	**4/ 113**	**3.5**				

A: Treatment group confidence intervals calculated by using the method of Clopper and Pearson.

B: Estimates of differences between treatment groups and corresponding confidence intervals and hypothesis tests are done by using the asymptotic method (corrected for continuity).

Efficacy at the Primary Pathogen Level
The following shows the clinical cure rates for selected primary pathogens at TOC for the Microbiologic Population. Cure rates are similar between treatment arms. The same analysis was conducted for the microbiologically modified intent to treat analysis and all pathogen outcomes were reviewed for both analyses. There were no meaningful differences between the two treatment arms.

Clinical Cure Rates for Selected Primary Baseline Pathogens at Test-of-Cure in the ME Population: Cure/Total (%)

	---------Tigecycline-------		----Vancomycin/Aztreonam---	
Pathogen	n/N	% (95% CI)	n/N	% (95% CI)
Enterococcus faecalis(all)	5/ 6	83.3(35.9, 99.6)	4/ 7	57.1(18.4, 90.1)
Enterococcus faecalis(non-VRE)	5/ 6	83.3(35.9, 99.6)	4/ 7	57.1(18.4, 90.1)
Escherichia coli	4/ 6	66.7(22.3, 95.7)	2/ 4	50.0(6.8, 93.2)
Staphylococcus aureus(all)	46/ 56	82.1(69.6, 91.1)	49/ 59	83.1(71.0, 91.6)
Staphylococcus aureus(MRSA)	16/ 21	76.2(52.8, 91.8)	17/ 21	81.0(58.1, 94.6)
Staphylococcus aureus(MSSA)	30/ 35	85.7(69.7, 95.2)	32/ 38	84.2(68.7, 94.0)
Streptococcus agalactiae	3/ 3	100.0(29.2,100.0)	7/ 9	77.8(40.0, 97.2)
Streptococcus pyogenes	6/ 7	85.7(42.1, 99.6)	6/ 8	75.0(34.9, 96.8)
Bacteroides fragilis	0/0	NA	0/0	NA

Resistant Pathogens
Review of the efficacy by resistant pathogens is located in the Resistant Pathogens Section.

Conclusions/ Summary
The results of Study 300 are consistent with a determination of non-inferiority for tigecycline when compared to the control therapy. The lower bounds of the 95% CI's for the two primary endpoints, CE and c-m-ITT Populations, were -7.4 and -9.0, respectively. The secondary endpoints support the non-inferiority conclusions of the primary endpoint analyses.

Study 305

Study 305 was specifically "harmonized" to have the same study design as Study 300.

Protocol
Refer to the protocol description for Study 300.

Ammendments
1. Sample size changed to 500 based on modified estimates of evaluability and clinical response rates
2. Hospitalization requested during treatment phase
3. Exclusion of subjects with *P. aeruginosa*
4. Timing of test of cure assessments was revised to no more than 90 days after the last dose
5. PK analyses added as a secondary objective
6. Patients found to have *P. aeruginosa* did not have to withdraw if they demonstrated objective clinical signs of substantial clinical improvement.
7. SAE's to be reported up to 14 days after last dose of study drug for subjects who were clinical failures.

Post-Hoc Changes
None.

Results

Disposition
The following table shows the disposition of patients in Study 305.

Number of Subjects in Each Population Category

Population	Tigecycline N (% ITT)	Vancomycin/ Aztreonam n (% ITT)	Total n (% ITT)
Screened			557
Screened failures			11
Intent-to-Treat (ITT)	275	271	546
No treatment received	1	2	3
Modified intent-to-treat (mITT)	274	269	543
Did not meet minimum disease criteria for cSSSI	13	10	23
Clinical mITT (c-mITT)	261	259	520
Did not meet clinical evaluability criteria	38	46	84
Clinically evaluable (CE)	223	213	436
No baseline and/or susceptible pathogens	59	65	124
Microbiologically evaluable (ME)	164	148	312
Microbiologic mITT (m-mITT)	209	203	412
No baseline pathogen identified from c-mITT	52	56	108

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Baseline Characteristics
The most common diagnosis in both the tigecycline and the vancomycin/aztreonam groups (50.5% overall) was deep soft tissue infection involving cellulitis that covered at least 10 cm; the second most common diagnosis (28.9%) was major abscess.

Table 8.2-2: Clinical Diagnosis of Infections Within the mITT Population: Number (%) of Subjects

Clinical Diagnosis	Tigecycline (n = 274)	Vancomycin/ Aztreonam (n = 269)	Total (n = 543)	Chi-Square p-Value
Any diagnosis				0.573
Infected ulcers	25 (9.1)	19 (7.1)	44 (8.1)	
Major abscesses	73 (26.6)	84 (31.2)	157 (28.9)	
Burns	9 (3.3)	8 (3.0)	17 (3.1)	
Deep soft tissue infection	167 (60.9)	157 (58.4)	324 (59.7)	
Cellulitis[a]	160 (58.4)	148 (55.0)	308 (56.7)	
Complicated underlying disease	26 (9.5)	26 (9.7)	52 (9.6)	
≥10 cm (where anatomically applicable)	144 (52.6)	130 (48.3)	274 (50.5)	
Requiring surgery/drainage	71 (25.9)	73 (27.1)	144 (26.5)	
Wound infection	7 (2.6)	9 (3.3)	16 (2.9)	
Other[b]		1 (0.4)	1 (0.2)	

a: Some subjects with cellulitis met more than 1 diagnostic criterion.
b: This subject had purulent drainage at peripheral IV catheter sites.
Source: demo5_diag_mitt1, 21 Jul 2004

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Demographic and other baseline characteristics of the mITT population, including age, sex, ethnicity, weight, and creatinine clearance, are shown in the following table. The two treatment arms were well matched.

Demographic and Baseline Characteristics of the mITT Population

Characteristic	Tigecycline (n = 274)	Vancomycin/ Aztreonam (n = 269)	Total (n = 543)	p-Value[a,b]
Age, years				0.381[a]
Mean	48.75	50.06	49.40	
Standard deviation	16.97	17.77	17.37	
Minimum, maximum	18.00, 87.00	18.00, 88.00	18.00, 88.00	
Median	49.00	49.00	49.00	
Sex, n (%)				1.000[b]
Male	167 (60.9)	163 (60.6)	330 (60.8)	
Female	107 (39.1)	106 (39.4)	213 (39.2)	
Ethnic origin, n (%)				0.690[b]
White	227 (82.8)	223 (82.9)	450 (82.9)	
Black	20 (7.3)	20 (7.4)	40 (7.4)	
Asian	19 (6.9)	22 (8.2)	41 (7.6)	
Other	8 (2.9)	4 (1.5)	12 (2.2)	
Weight, kg				0.581[a]
Mean	82.46	81.47	81.97	
Standard deviation	20.96	20.50	20.72	
Minimum, maximum	40.00, 200.00	44.00, 160.00	40.00, 200.00	
Median	80.00	78.00	79.00	
Creatinine clearance, mL/min				0.158[a]
Mean	109.35	104.27	106.83	
Standard deviation	42.41	41.21	41.85	
Minimum, maximum	27.00, 336.00	26.00, 273.00	26.00, 336.00	
Median	105.00	100.00	103.00	

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

b: Fisher exact test (2-tailed).

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Efficacy

The co-primary efficacy populations were the CE and c-mITT populations. The CE population excluded 107 mITT subjects for the reasons summarized in the table below.

Clinical Evaluability Exclusion Categories and the Number (%) of mITT Subjects Excluded From the CE Population

Clinical Evaluability Exclusion Categories[a]	Tigecycline (n = 274)	Vancomycin/ Aztreonam (n = 269)	Total (n = 543)
Exclusion from the CE population	51 (18.6)	56 (20.8)	107 (19.7)
Reason for exclusion as CE cure or failure			
Blind broken	12 (4.4)	17 (6.3)	29 (5.3)
Inclusion/exclusion criteria not met[b]	13 (4.7)	11 (4.1)	24 (4.4)
Pseudomonas at baseline[c]	1 (0.4)	3 (1.1)	4 (0.7)
> 2 doses of prior antibiotic after baseline culture	1 (0.4)	2 (0.7)	3 (0.6)
No clinical evaluation at test-of-cure	10 (3.6)	8 (3.0)	18 (3.3)
Reason for exclusion as CE cure			
Test article compliance[d]	2 (0.7)	1 (0.4)	3 (0.6)
Received concomitant antibiotics	11 (4.0)	12 (4.5)	23 (4.2)
Test-of-cure after last dose[e]	1 (0.4)	1 (0.4)	2 (0.4)
Reason for exclusion as CE failure			
Did not receive at least 4 doses of study drug	3 (1.1)	9 (3.3)	12 (2.2)
Test-of-cure after 2 days[g]		4 (1.5)	4 (0.7)

CE = clinically evaluable; mITT = modified intent-to-treat population.

a: Subjects could have been excluded from the CE population for more than 1 reason.

b: In 23 cases, subjects did not meet severity criteria

c: Sole causative pathogen.

d: Subject received less than 5 days of study drug or did not receive 80% to 120% of expected dose.

e: Subject did not have test-of-cure evaluation within the 12 to 92 day window.

f. Two (2) subjects were excluded as CE failures because they received potentially effective antibiotics during study treatment. (Both subjects were counted in the total row of this table.)

g: Subject did not have test-of-cure evaluation at least 2 days after starting study drug.

The CE population consisted of 223 tigecycline subjects and 213 vancomycin/aztreonam subjects.

Primary

The co-primary efficacy endpoints were the clinical responses within the CE and c-mITT populations at the test-of-cure assessment. 15% was set as the limit difference, or delta, for the true cure rates of the 2 treatments, i.e., the lower bound of the 2-sided 95% CI for the difference in cure proportion had to be no lower than -15% to support the conclusion that therapy with tigecycline was non-inferior to therapy with vancomycin/aztreonam.

Analysis of Clinical Response: cmITT and CE Population at TOC

Visit	Response	Tigecycline		Vancomycin/ Aztreonam		Tigecycline – Vancomycin/Aztreonam			
		n/N	%	n/N	%	Difference	95% CI	NI P-Value	Differences p-Value
c-mITT Test-of-Cure	Cure	220/261	84.3	225/259	86.9	-2.6	(-9.0, 3.8)	<0.001*	0.4755
	Failure	31/261	11.9	26/259	10.0				
	Indeterm	10/261	3.8	8/259	3.1				
CE Test-of-Cure	Cure	200/223	89.7	201/213	94.4	-4.7	(-10.2, 0.8)	<0.001*	0.1015
	Failure	23/223	10.3	12/213	5.6				

a: Treatment group confidence intervals calculated by using the method of Clopper and Pearson.

b: Estimates of differences between treatment groups and corresponding confidence intervals and hypothesis tests are done by using the asymptotic method (corrected for continuity).

*Tigecycline was statistically noninferior to vancomycin/aztreonam.

In the analysis of clinical responses, the lower limit of the 95% CI for the difference in efficacy (i.e., tigecycline minus vancomycin/aztreonam) was not less than -15%. More specifically, the lower bound of the CI was -10.2% at the test-of-cure assessment for the CE population and -9.0 for the c-mITT population.

Secondary Endpoints
This table shows the clinical response by mono- and poly-microbial infections.

Clinical Response by Mono- and Poly- microbial Infections: ME and m-mITT Populations

Visit	Response	Tigecycline		Vanco/ Aztreonam		Tigecycline – Vanco/Aztreonam	
		n/N	% (95% CI)	n/N	% (95% CI)	Difference	95% CI
ME Test-of-Cure	**Mono/Cure**	83/90	92.2 (84.6, 96.8)	78/81	96.3 (89.6, 99.2)	-4.1	(-12.6, 4.6)
	Mono/Failure	7/90	7.8	3/81	3.7		
	Poly/Cure	65/74	87.8 (78.2, 94.3)	65/67	97.0 (89.6, 99.6)	-9.2	(-19.6, 1.2)
	Poly/Failure	9/74	12.2	2/67	3.0		
m-mITT Test-of-Cure	**Mono/Cure**	104/114	91.2 (84.5, 95.7)	99/111	89.2 (81.9, 94.3)	2.0	(-6.6, 10.8)
	Mono/Failure	10/114	8.8	12/111	10.8		
	Poly/Cure	76/90	84.4 (75.3, 91.2)	78/85	91.8 (83.8, 96.6)	-7.3	(-17.9, 3.4)
	Poly/Failure	14/90	15.6	7/85	8.2		

a: Treatment group confidence intervals calculated by using the method of Clopper and Pearson.
b: Estimates of differences between treatment groups and corresponding confidence intervals and hypothesis tests are done by using the asymptotic method (corrected for continuity).
*Tigecycline was statistically noninferior to vancomycin/aztreonam.

Examination of outcome by mono- and polymicrobial infections for study 305 was generally consistent with the primary outcome analyses. The point estimates for clinical response in polymicrobial infections was worse for tigecycline than comparator. However, this is likely secondary to variability, and the study was not designed to detect such differences, if they exist. This interpretation is supported by the fact that the opposite pattern was seen for Study 300. Examination of the effect of underlying diabetes did not reveal this to be a contributing factor in these findings.

Sub-Group Analyses
Sensitivity analyses explored other factors that could possibly affect clinical response to tigecycline and differences between treatment groups. Several analyses of CE subgroups (based on demographic and other baseline characteristics) were presented by the sponsor. These included examination of outcome according to the following sub-groups: age, gender, ethnic group, geographical region, by clinical diagnosis, diabetes, peripheral vascular disease, creatinine clearance, and bacteremia. Medical Officer's review of these analyses did not reveal significant differences between the study drug and comparator for these sub-group analyses.

Efficacy at the Pathogen Level
Medical officer's review of efficacy response at the pathogen level revealed that the response rates by baseline pathogen were similar between the two treatment arms. The three pathogens which were isolated most commonly were *S. aureus, S. pyogenes, E. coli*. Review of the response rates for these baseline pathogens revealed a similar response rate between the study drug and comparator.

Baseline Pathogen	**Response Rate by Treatment Arm (ME Population)**			
	Tigecycline		Vanco/Aztreo	
	N/Total (%)	95% CI	N/Total (%)	95% CI
E. coli	15/16 (93.8)	69.8, 99.8	13/14 (92.9)	66.1, 99.8
MSSA	54/62 (87.1)	76.1, 94.3	55/58 (94.8)	85.6, 98.9
MRSA	5/6 (83.3)	35.9, 99.6	3/6 (50.0)	11.8, 88.2
S. pyogenes	21/22 (95.5)	77.2, 99.9	16/16 (100.0)	79.4, 100.0

Efficacy at the Subject Level
The following table shows the microbiologic response at the subject level within the m-mITT population. Although the response rate between the two treatment arms was different at TOC, this was not found to be significant statistically.

Analysis of Microbiologic Response at the Subject Level Within the m-mITT Population

		——— Tigecycline ———		—— Vancomycin/Aztreonam——		Difference (Tigecycline – Vancomycin/Aztreonam)		
Visit	Response	n/N	% 95% CI)	n/N	% (95% CI)	% (95% CI)	Test for Noninferiority (p-Value)	Test for Differences (p-Value)
Test-of-Cure	**Eradication**	**166/209**	**79.4 (73.3, 84.7)**	**171/203**	**84.2 (78.5, 89.0)**	**-4.8 (-12.7, 3.1)**	**0.0052**	**0.2537**
	Documented	**12/166**	**7.2**	**18/171**	**10.5**			
	Presumed	**154/166**	**92.8**	**153/171**	**89.5**			
	Persistence	**34/209**	**16.3**	**22/203**	**10.8**			
	Documented	**18/34**	**52.9**	**7/22**	**31.8**			
	Presumed	**16/34**	**47.1**	**15/22**	**68.2**			
	Superinfection	**5/209**	**2.4**	**4/203**	**2.0**			
	Indeterminate	**4/209**	**1.9**	**6/203**	**3.0**			

Resistant Pathogens
Review of the efficacy by resistant pathogens is located in the Resistant Pathogens Section in the Integrated Review of Efficacy.

Safety Data
The safety data from this study is discussed in the Integrated Review of Safety.

Conclusions/Summary
The results of Study 305 are consistent with a determination of non-inferiority for tigecycline when compared to the control therapy. The lower bounds of the 95% CI's for the primary endpoint in the CE and and c-m-ITT Populations, were -10.2 and -9.0, respectively. The secondary endpoints support the non-inferiority conclusions of the primary endpoint analyses. The results of this study support the findings of Study 300.

10.2 Summary Narratives of All Deaths

ALL DEATHS in cIAI TRIALS

Sorted byTreatment and Medical Officer Assessment (Lack of Treatment Effect, Possible Drug Effect/Toxicity, or Unrelated)

TIGECYCLINE

Lack of Treatment Effect

301-011-0102
Possible Lack of Treatment Effect: The patient was called a failure by the investigator and developed (fatal) pneumonia 2 days after completing 15 days of tigecycline therapy. The patient was placed on ceftriaxone/flagyl/ampicillin. There is no microbiology information available for the pneumonia and there is no information in the CRF that allows for a determination of why the patient's intra-abdominal process was deemed a failure. A surgical review board assessed the patient as having had inadequate source control as the problem; however, this is not at all clear from review of the narrative and CRF. The patient's hospital course is not clearly documented in the CRF. For example, a laparotomy was performed on (b) (6) yet the patient stays on the study drug for 3 more days. There is no further information on this. The basis for calling the patient a treatment failure is not clearly stated.

301-017-0286
Possible Lack of Treatment Effect: On day 4 of therapy, the patient experienced overwhelming sepsis secondary to peritonitis. The investigator states that because of the patient's age and malnutrition (alb <2.5), he did not believe the patient had a good chance for survival at the beginning of the study.

301-103-4545
Lack of Treatment Effect: This was a 67 year-old with complicated appendicitis. On day 4 of treatment (post-op day 4), the patient developed an enteric fistula, went to surgery, and on the following day, required vasopressors for severe hypotension. At that time, the patient was called a treatment failure and discontinued from the study drug.

301-136-6466
Possible Lack of Treatment Effect: This was a 78 year-old female with DM and "diffuse liver nodes" who was on treatment for 7 days (peritonitis due to perforation of the large intestine). She developed increasing bilirubin which necessitated stopping the study drug

(Total Bilirubin – 9.72 mg/dl). Soon after stopping tigecycline treatment, the patient deteriorated sharply having developed infectious shock which was thought to possibly related to study drug.

301-172-8093
Lack of Treatment Effect: A 23 year-old woman (APACHE II of 8) with bowel perforation required laparotomy. The laparotomy revealed fecal contamination/diffuse peritonitis and cultures subsequently grew *Klebsiella* and *Pseudomonas* spp. Post-operatively, the patient's fever resolved, but she remained hypotensive and tachycardic. There was no mention in CRF of additional antibiotics given for treatment. On day 3 of treatment, the patient developed pneumonia (no organism), sepsis, hypotension, and multi-organ failure. The patient died on day 4 of tigecycline treatment.

301-186-8521
Lack of Treatment Effect: A 42 year-old presented with multiple abscesses s/p esophageal-jejunal anastomosis for stomach cancer. The patient had a poor response to study drug and after 6 days of treatment, he had persisting fever and went back to OR for revision of the anastomosis. Cultures grew *Klebsiella* spp., *Enterococcus* spp., and *Proteus mirabilis*. He was kept on the tigecycline treatment, but continued to deteriorate after the surgery, and died 5 days later.

306-109-2165
Lack of Treatment Effect: On study day 6, blood cultures grew *Pseudomonas* spp., and the patient died as a result of *Pseudomonas* sepsis/peritonitis.

306-125-2446
Lack of Treatment Effect: The patient developed a recurrent abdominal abscess and resulting sepsis with death. Cultures grew *Enterobacter, Klebsiella, Pseudomonas*, and *Clostridium* spp. A possible lack of source control cannot be excluded.

Possible Drug Effect/Toxicity

301-103-4550
Pneumonia case: A 39 year-old male with a history of alcoholism and peptic ulcer disease (PUD) presented with a possible appendicitis, He was found to have several abscesses, and peritonitis. On day 3 of study (and day 3 after surgery), the patient died suddenly. Autopsy stated that primary cause of death was bronchopneumonia. No organism was reported.

301-407-7956
Possible drug-related toxicity: A 62 year-old patient with a history of tobacco and alcohol use was admitted with a perforated duodenal ulcer. During tigecycline treatment, the

patient developed continuously increasing bilirubin, clinical jaundice, and increases in other liver enzymes, which the investigator thought was related to study drug. Therefore, tigecycline was stopped on day 5 and no alternative drug was started. The CRF lists liver failure as a primary drug-related factor in the patient's death. The patient appears to have been doing well with regard to the peritonitis, until the discontinuation of the drug. Three days later, the patient developed a perforation, peritonitis, and septicemia due to either a new duodenal ulcer perforation or perforation closure leakage – this caused his death. A Surgical Review Board believes the liver failure was a case of hepatic decompensation as a result of surgical trauma and intra-abdominal infection, but does not discount possible contribution by the study drug.

306-127-2487
Pneumonia Case: Death appears to be the result of bilateral pneumonia which was discovered at the time of deterioration. Initial pulmonary cultures grew MRSA 7 days earlier; however, the patient was on vancomycin at the time of deterioration. Repeat cultures of sputum were not reported, so it is possible that other organisms were involved.

Unlikely Related to Study Drug

301-003-0021
This case does not appear to be related to treatment failure or a drug-related AE. On day 3 of tigecycline, the patient underwent surgery and post-operatively had the complications of atrial fibrillation and pace-maker failure leading to respiratory failure and multi-organ failure, eventually leading to death.

301-004-0032
This case does not appear to be related to treatment failure or a drug related AE. However, it is unclear from CRF how the diagnosis of a mucous plug was made. A patient with a perforated bowel had total colectomy and appeared to be doing better, but on day 12 of tigecycline, experienced sudden respiratory deterioration, reportedly due to a large right-sided mucous plug with lung collapse. The patient's family refused to allow intubation and the patient died.

301-082-3571
The case does not appear to be related to lack of efficacy or toxicity. It is difficult to implicate lack of treatment effect since patient had AIDS. The presence of AIDS means that the patient had a significant degree of immunosuppression and, therefore, the effect of antibiotic cannot be measured.

301-401-6038
This was an extremely ill patient, whose outcome could be predicted to be poor regardless of which antibiotic was used. She was a 25 year-old female with antecedent viral hepatitis, who presented with sepsis/hypotension secondary to small intestine diverticulitis/perforation. She was too ill for open procedure and so had percutaneous

drains placed. At time of admission, PT/PTT was 38.4/106.3. On day 3 of tigecycline, the patient developed respiratory distress, worsening coagulopathy and died on day 5.

301-136-6469
In this patient, it would be difficult to implicate study drug given an unorthodox surgical procedure and potential complicating factors of pregnancy. She was a 27 year-old pregnant woman with complicated appendicitis, who received 9 days of study drug, and was discharged as a cure. Two days later, the patient developed septic shock and a suspected amniotic fluid embolus. The surgeon apparently left in a tube in the appendiceal stump which may have contributed to the recurrence of infection – details of this procedure are not clear.

301-407-7971
This was not an efficacy-related death. It is possible that tigecycline treatment contributed to gastro-intestinal bleeding (GIB), possibly by disturbing coagulation, but it is more likely that the patient's underlying disease caused the recurrent GIB. This was a 45 year-old man with a history of PUD who underwent surgery for a perforated duodenal ulcer and was started on study drug. The patient had a satisfactory response and completed therapy. However, 2 days after completing study drug treatment, he had massive GIB and died from uncontrollable hypovolemic shock.

301-407-7990
Given that the patient was severely ill and received only one dose of tigecycline, it is difficult to attribute death to lack of treatment effect. This was a 25 year-old male who had a laparotomy performed for perforated peritonitis. He developed sepsis post-operatively. He received only 1 dose of study drug before death.

301-180-8404
Given the short duration of drug exposure and given that there is a reason for the pancreatitis (s/p cholecystectomy), and that acute pancreatitis is a very likely cause for this patient's death, lack of treatment effect and/or toxicity of the tigecycline are unlikely. This was a 69 year-old man s/p laparoscopic cholecystectomy with peritonitis/abscess who developed acute pancreatitis (amylase 791) on study day 2. Subsequent to that, the patient developed multi-organ failure and ultimately died on day 3.

306-034-0629
There is a possible infectious cause of death, but based on the investigator's opinion, this is less likely. The patient had initial cultures of an abdominal abscess that grew several organisms, including *Pseudomonas*. The investigator did not add additional coverage for this organism. The patient received tigecycline for 11 days but died several days after the end of therapy. The investigator states the cause of death as cardiac failure. A possible pulmonary embolus was also reported. The details of the case are too sketchy to rule out an infectious cause of death.

306-047-2643
This death is unlikely to be related to tigecycline. The patient had known coronary artery disease, was cured at TOC visit, but one day later, she had a fatal cardiac event.

306-109-2158
Death appears to be unlikely related to lack of treatment effect, as the patient was found on autopsy to have disseminated bronchogenic carcinoma. Potential safety issues include possible contribution of tigecycline to deterioration of existing liver disease, and the patient also developed right lower lobe (RLL) pneumonia while on therapy.

Indeterminate

306-126-2462
This was a pneumonia case, but occurred several days after treatment with tigecycline ended. Five days after the end of treatment, the patient presented (at TOC visit) with fever and a RLL pneumonia. This progressed to disseminated pneumonia or adult respiratory distress syndrome, which resulted in death.

301-080-3434
The cause of death in this patient is unclear. The patient is an 83 year-old woman with multiple co-morbidities who was enrolled in study for a perforation of the large intestine due to diverticulitis and a left-sided groin abscess (possibly an incarcerated hernia). Supposedly, she was improving and then was discharged to a nursing home where she died secondary to the following listed reasons:
- "overall condition of the subject deteriorated; however the intra-abdominal infection was declared cured."
- acute perforated diverticulitis, renal failure, Alzheimer's disease
- secondary to incarcerated hernia

It is not clear from the narrative and CRF exactly what happened to result in death. There is a question of whether residual renal failure, continuing after successful treatment of infection, contributed to her death, but lab data do not support this (last BUN/creatinine – 34/0.5).

IMIPENEM

Lack of Treatment Effect

301-003-0022
Lack of Treatment Effect: This was an 81 year-old female who died after 7 days of imipenem treatment for diverticulitis with an abdominal abscess. The investigator reported an inadequate response to treatment, and the patient was noted to have an anastomotic leak on repeat surgery at the end of study treatment. "Septic/cardiogenic shock was diagnosed on the day after surgery. She was placed on ventilatory support and

received multiple vasopressors. According to the narrative, she died on the next day secondary to a pulmonary embolism.

301-080-3445
Lack of Treatment Effect: This was an 81 year-old man with a perforated duodenal ulcer. He received 4 days of imipenem treatment, but the study drug was discontinued because of an unsatisfactory response. The patient was switched to vancomycin, but did not improve. He died from respiratory failure 11 days after stopping imipenem treatment.

301-082-3553
Possible Lack of Treatment Effect: This 34 year-old man underwent surgery for a perforated jejunal ulcer and diffuse peritonitis. As a complication of surgery, his spleen was lacerated, requiring splenectomy. He was started on imipenem as his study drug, but developed tension pneumothorax (considered to be a complication from perforation of his pleura by a catheter during surgery) and septic shock on the same day. The patient's condition further deteriorated with renal insufficiency reported on day 3 and cerebral hemorrhage on day 5. The course of events surrounding death is not sufficiently detailed in the CRF, but the investigator assessed the patient as a treatment failure.

301-404-6217
Possible Lack of Treatment Effect: This 40 year-old male patient presented with symptoms of hollow viscous perforation, septicemia, and acute renal failure. He underwent a laparotomy that showed diffuse fecal peritonitis with 2 perforations and was started on imipenem. Five days later, the patient developed respiratory distress, worsening septicemia and wound dehiscence – this led to death.

301-407-7976
Possible Lack of Treatment Effect: This patient had a possible treatment failure, although more likely it was a volvulus recurrence (according to surgical review board). This 50 year-old female patient underwent a laparotomy with closure of a perforation of the small intestine and received 10 days of imipenem. She did well post-operatively, but 7 days after discontinuation of study drug, deteriorated due to an anastomotic leak. She developed sepsis and died.

306-069-1305
Lack of Treatment Effect: The patient had recurrence of his abdominal process (*E.coli*) after 7 days of therapy with imipenem, day 7 after laparotomy.

Possible Drug Effect/toxicity

306-017-0321
Pneumonia Case: This was not a lack of treatment effect, but the patient's course was complicated by pneumonia followed by cardiac complications, and then stroke. No organism was identified as the cause of the pneumonia.

Unlikely Related to Study Drug

301-011-0107
This case was unlikely related to imipenem. The patient's j-tube was spilling into his abdomen. He developed peritonitis/sepsis and went to laparotomy. He started on imipenem one day after surgery and died on second day after surgery. He received a total of only 3 doses of study drug.

301-017-0285
The death appears unlikely to be related to lack of treatment effect or drug toxicity. The patient was a 68 year-old female with a history of lung cancer and perforation of a sigmoid mass. She started on imipenem on the day after her exploratory laparotomy and three days later, a colonoscopy showed severe necrosis. She went back to the OR for colon resection and washout of her pelvic abscess on study day 7. Imipenem was stopped at that time for unsatisfactory response but surgical board review states that the surgeon was satisfied with source control at time of the second operation and that the real problem was a necrotic colostomy stoma resulting from poor blood supply or technical compromise.

301-080-3436
The death appears unlikely to be related to lack of treatment effect or drug toxicity. This 66 year-old male patient had an invasive neoplastic process of the spine. He was admitted for laminectomy with decompression. His post-operative course was complicated by pneumoperitoneum. The patient returned to the OR for resection of the colon, ileum, and partial omentectomy for perforated cecum with multiple abdominal abscesses. Study drug treatment was completed and the patient was discharged in satisfactory condition. He died at a nursing home 10 days after hospital discharge. The death certificate identified malignant vertebral neoplasm as the immediate cause of death.

301-094-4133
The death was unlikely related to study drug. The patient died of cardiac arrest, and already had a diagnosis of respiratory distress prior to starting study drug. Respiratory distress continued, worsened, and ultimately led to cardiac arrest.

301-405-6285
This patient may have been a clinical failure (not completely clear from CRF), but death was related to MRSA pneumonia which began 2 days after stopping imipenem. This MRSA infection was inadequately treated with clindamycin and amoxicillin and the patient subsequently died.

301-407-7951

The death appears unlikely related to treatment failure. This patient with COPD presented with peritonitis, underwent closure of a perforation of the terminal jejunum, and was enrolled in the study. Five days later while still on imipenem, he developed respiratory failure not thought to be related to infection and died the same day.

306-023-0435
The death was unlikely related to study drug. The patient was cured and was discharged in good condition but had an MI and died on the way home from the hospital.

306-029-0535
The death was not related to insufficient treatment effect. This patient died suddenly 2 days after discharge from the hospital. Pulmonary embolism and a sudden cardiac event were considered possible causes.

306-055-1008
The death was unlikely related to study drug. This patient had sudden death without explanation but this occurred >2 weeks after the end of study drug treatment. Post-operatively, patient experienced an external biliary fistula.

Indeterminate

301-091-3982
This patient had a sudden death and the investigator was unable to offer a cause. Death does not appear to be related to treatment failure since symptoms improved. The patient was on amiodarone for an adverse event of atrial fibrillation and also had a complication of a subphrenic abscess.

7.1.1.2 – ALL DEATHS OCCURRING DURING cSSSI TRIALS

cSSSI

TIGECYCLINE
300-309-3973
This patient likely died from a PE. The patient was a 48 year-old female with DM and other comorbidities. Ten days after the end of treatment, the patient presented with dyspnea. She soon developed cardiac arrest thought to be secondary to PE. An ECG revealed no MI. The chest X-ray showed pulmonary congestion. No autopsy was performed.

(b) (4)

The death appears unlikely to be related to study drug. The patient was already very sick at time of enrollment. She was a 58 year-old patient with chronic heart failure and DM. She developed cardiac failure and renal failure on first day of tigecycline. Sepsis could

not be ruled out, the patient's status progressively worsened and she died 9 days later. She had been treated with 2 doses of unasyn prior to enrollment in the study.

300-401-4987
The death appears unlikely to be related to study drug. This 50 year-old female patient with RA presented with an extensive abscess over the right back/breast and required surgical drainage. Death was the result of MI and septicemic shock. The patient began experiencing sepsis prior to initiation of study drug. On admission, her systolic blood pressure was 80 mm Hg and from there, she rapidly deteriorated. One day after start of tigecycline, the patient developed cardiogenic shock secondary to acute MI and died a few days later.

300-405-5255
The death appears unlikely related to study drug except that there was a lack of treatment effect which could have contributed to complications. This 52 year-old male patient had a history of "acid peptic disease". He died of perforated duodenum and peritonitis with septic shock. The patient received 14 days of study drug which was stopped because of unsatisfactory response/clinical failure. Ulcer perforation was reported one day prior to discontinuation of tigecycline. The patient died 3 days after discontinuation of study drug.

300-406-5268
The death appears unlikely related to study drug. This was a 64 year-old male patient with DM on valdecoxib. He was successfully treated with tigecycline for a peri-anal abscess. Seventeen days after the TOC visit, the patient was brought to hospital and pronounced DOA. No autopsy was performed, so the cause of death is unknown. The investigator thinks the patient had a MI after hypoglycemia.

305-077-1490
The death appears unlikely secondary to study drug. The patient was a 74 year-old male with GI obstruction, angina, cellulitis, heart failure, asthma, hypertension, and COPD. The patient enrolled in the study to treat a central catheter infection. He went to surgery for gastric outflow obstruction which revealed carcinomatosis of suspected pancreatic origin on the third day of tigecycline treatment. Three days after the surgery, the patient experienced sudden fever, tachycardia, desaturation and then cardiac/respiratory arrest.

VANCOMYCIN
300-405-5231
The death appears unlikely to be the result of study drug. The patient was a 60 year-old male with CHF, COPD, and severe anemia. The patient completed 6 days of vancomycin for cellulitis of the left leg and was considered cured. He developed severe CHF caused by anemia that worsened over the time of hospitalization and COPD. The patient died on the last day of study drug with the cause of death reported as CHF.

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