

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-821

PHARMACOLOGY REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 21-821
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: 10/22/04—rolling submission
PRODUCT: Tygacil (tigecycline)
INTENDED CLINICAL POPULATION: patients with complicated skin/skin structure
infections or complicated intra-abdominal infections
SPONSOR: Wyeth Pharmaceuticals
DOCUMENTS REVIEWED: Electronic submission.
REVIEW DIVISION: Division of Anti-Infective Drug Products (HFD-520)
PHARM/TOX REVIEWER: Wendelyn J. Schmidt, Ph.D.
PHARM/TOX SUPERVISOR: Robert Osterberg, Ph.D.
DIVISION DIRECTOR: Janice Soreth, M.D.
PROJECT MANAGER: Judit Milstein

Date of review submission to Division File System (DFS): 6/14/05

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EXECUTIVE SUMMARY

1. Recommendations

1.1 Recommendation on approvability: Tigecycline can be approved on the basis of pharmacology/toxicology.

1.2 Recommendation for nonclinical studies: There are no recommendations at this time.

1.3 Recommendations on labeling:

The sponsor stated that the human AUC used for comparisons was 6.1 ug.h/mL and noted that a conservative estimate would be obtained with this system. Similar values were obtained when using the human AUC of 4.7 ug.h/mL from the pool efficacy studies in the annotated label, pharmacokinetics section.

- 1) "in vivo micronucleus assay" should read in vivo mouse micronucleus assay".
- 2) Comparison factor for fertility, is 5.
- 3) Teratology should use a comparison factor of 5 for rat, 1 for rabbit.
- 4) "An increased incidence of fetal loss was observed at maternotoxic doses in the rabbits with _____"
- 5) In the animal toxicology section, the AUC comparison for rats and dogs should be _____ . It should be noted that this is from a 2 week study.
- 6) The _____ data is not as relevant given the difference in infusion times bolus vs. 30-60 minutes and should be deleted.
- 7) Tigecycline should be a Pregnancy Category D, _____ based on tetracycline class effects.

2. Summary of nonclinical findings

2.1 Brief overview of nonclinical findings

2.2 Pharmacologic activity

2.3 Nonclinical safety issues relevant to clinical use

Tigecycline is a minocycline analog and member of the tetracycline antibiotic class. Like other tetracyclines, tigecycline has activity against both Gram positive and negative bacteria. Drug is widely distributed, particularly into bone and teeth (where permanent stains can be seen from prenatal and childhood use). Gastrointestinal irritation (nausea/vomiting, diarrhea with oral administration) are common with the class. Other major toxicities with the class are photosensitivity, hepatic toxicity, and renal toxicity.

The main toxicities from the human clinical trials with tigecycline were nausea, vomiting and diarrhea. Some liver enzyme elevations were observed. However, renal changes and decreases in RBC, WBC and platelet number were rare in the trials.

Tigecycline is administered intravenously. Minimal gender differences were noted in the rat or dog; however, the toxicokinetic studies investigated females only. In humans, gender differences were observed. Distribution was widespread, except for within the blood-brain barrier. The drug did cross the placental barrier. Tigecycline tended to localize in bone and persist there. Excretion was via both urine and feces in

both rats and dogs. A similar pattern was seen in humans. Tigecycline was also excreted in milk in rats but excretion in milk was not investigated in humans. Protein binding was in the range of 80-90% in mouse, rat, rabbit, dog and human. Cytochrome P450 enzyme functions were unaffected by tigecycline.

Toxic effects were extremely similar in the rat and dog with tigecycline. The AUCs at the NOAEL in dogs and rats were within 2 fold of each other. Although no cardiac *in vitro* tests were conducted (e.g. hERG assay), no effects on telemeterized dogs on QT intervals were noted at doses up to 12 mg/kg in the dog in safety pharmacology studies. Further, no significant changes in ECG profiles have been seen in clinical trials. Although tetracyclines are not known for prolonging the QT interval, the class has not been studied extensively. Histamine was released in the rat and dog upon tigecycline administration with confirmation shown by measuring histamine levels in the toxicology studies. Vomiting has been observed in the shorter dog studies, but in the 13 week study, doses were low enough that this was not an issue. Gastrointestinal distress is the major toxicity in the clinical trials. Elevations in liver enzymes were seen in the clinical trials as well, but no liver toxicity (either enzyme elevation or histopathology change) other than occasional decrements in total protein and "fatty changes in the liver" were noted in the 2 week dog at 20 mg/kg. These changes could be attributed to vomiting and diarrhea. Another common human toxicity with tetracyclines, uremia, was not observed with tigecycline.

A major toxicity seen in the animal studies, that did not appear to carry over to humans at the doses in the clinical trials, was myelosuppression. Both rats and dogs had decreased numbers of red and white cells as well as platelets. Marrow hypocellularity, lymphoid depletion and atrophy in the thymus and lymph nodes, indicative of immunosuppression, were also observed.

Tigecycline was not phototoxic and was negative in an antigenicity assay. Local tolerance (eye, skin) was not tested.

Tigecycline affected male fertility at doses of 4 mg/kg in the rat (decreased sperm count). Decreased testes' weights were also noted in dogs treated daily with 20 mg/kg tigecycline for 2 weeks. Tigecycline was not teratogenic in either the rat or the rabbit at maternotoxic doses; decreased fetal viability was seen at 12 mg/kg in the rat (AUC 28.5 ug.h/mL) and > 4 mg/kg in the rabbit (AUC >7 ug.h/mL). There were no effects on post-natal development when dams were administered tigecycline at up to 12 mg/kg through weaning.

Tigecycline was negative for mutagenicity and clastogenicity in the ICH battery of genotoxicity tests including mouse lymphoma L5178Y, CHO HGPRT, CHO chromosomal aberrations, and mouse micronucleus assays. Carcinogenicity testing was not required for the short-term, intermittent use of this drug.

PHARMACOLOGY/TOXICOLOGY REVIEW**3.1 INTRODUCTION AND DRUG HISTORY****NDA number:** 21821**Review number:** 1**Sequence number/date/type of submission:** 000/October 22, 2004/rolling submission**Information to sponsor:** Yes () No ()**Sponsor and/or agent:**Wyeth Pharmaceuticals
P.O. Box 8299
Philadelphia, PA 19101-8299**Manufacturer for drug substance:****Reviewer name:** Wendelyn J. Schmidt, Ph.D.**Division name:** Division of Anti-Infective Drug Products**HFD #:** 520**Review completion date:** 5/27/05**Drug:**

Trade name: Tygacil

Generic name: Tigecycline

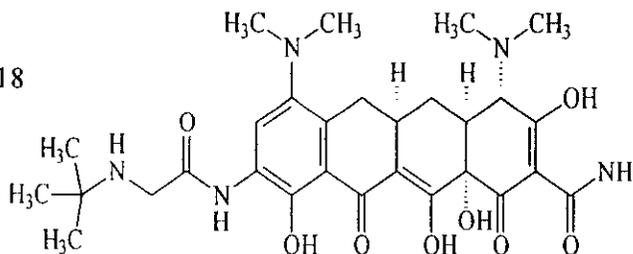
Code name: GAR-936

Chemical name: (4*S*,4*aS*,5*aR*,12*aS*)-9-[2-(*tert*-butylamino)acetamido]-4,7-bis(dimethylamino)-1,4,4*a*,5,5*a*,6,11,12*a*-octahydro-3,10,12,12*a*-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide

CAS registry number: information not found.

Molecular formula/molecular weight: C₂₉H₃₉N₅O₈, mw = 585.65.

Structure:

Relevant INDs/NDAs/DMFs: IND 56518**Drug class:** Tetracycline antibiotic**Indication:** Treatment of complicated skin and skin structure infections and complicated intra-abdominal infections.**Clinical formulation:** Lyophilized powder reconstituted in 0.9% NaCl or 5% dextrose**Route of administration:** Intravenous**Clinical Dose:** 100 mg infused over 30-60 minutes followed by 50 mg every 12 hours for 5-14 days

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission: Almost all studies have been previously reviewed by Dr. Terry Peters. The study reviewed by W. Schmidt is starred. The submission numbers for the reviews are noted.

Pharmacology:

Primary Pharmacodynamics: Reviewed by the Microbiologists.

Secondary Pharmacodynamics:

1. RPT-55502: Tigecycline (GAR-936): — , side effect profile of CL346635 (monohydrochloride salt of tigecycline and WAY 152288 (PAM-minocycline). Serial #000

Safety Pharmacology:

1. RPT-51794: Tigecycline (GAR 936): single dose intravenous central nervous system safety pharmacology study in male rats. Study # 02 1397.
2. RPT-50293: Tigecycline (GAR-936): single dose i.v. respiratory safety pharmacology study in male rats. Study # 02 1398.
3. GTR-30524: CLX 346635 and WAY 152288: A single dose intravenous infusion cardiovascular study in conscious male rats. Study # 95390. Serial # 000
4. GTR-32072: GAR-936: An escalating dose intravenous infusion cardiovascular study in dogs. Study # 96262. Serial # 000
5. RPT-42292: GAR-936: Safety pharmacology study. Serial # 072

Pharmacokinetics:

1. GTR-36282: GAR 936: single dose pharmacokinetics of GAT-936 given intravenously to cannulated rats. Study # 95571. Serial # 000
2. GTR-37282: GAR-936: pharmacokinetics of total radioactivity and unchanged drug following a single (5.0 mg/kg) i.v. dose of ¹⁴C-GAR-936 in male rats. Study # 95718. Serial #072
3. GTR-31749: GAR-936: single ¹⁴C intravenous dose (5.0 mg/kg) pharmacokinetics and metabolism study in male dogs (study # 95685). Serial # 032
4. GTR-37280: GAR-936: a single intravenous (5 mg/kg) and oral (15 mg/kg) dose pharmacokinetic study in monkeys (study # 95714PR). Serial # 032
5. GTR-36470: GAR-936: tissue distribution in male Sprague-Dawley rats following a single intravenous infusion dose (3 mg/kg) of ¹⁴C-GAR-936. Study # 95631.
6. RPT-40186: GAR-936: tissue distribution of ¹⁴C-GAR-936-derived radioactivity by whole-body autoradiography following a single 3 mg/kg/intravenous infusion (30minute) dose of ¹⁴C-GAR-936 in male Sprague Dawley and Long-Evans rats. Study # 95631.
7. RPT-49970: GAR-936: Tissue distribution of ¹⁴C-tigecycline following a single bolus intravenous (3 mg/kg) administration and once daily bolus intravenous (3 mg/kg) for 6 and 10 days in male (Sprague-Dawley) rats. Study 96652.
8. GTR-37511: ¹⁴C-GAR-936: in vitro protein binding in mouse, rat, rabbit, dog and human plasma. Study # 96450. Serial # 032

9. RPT-53963: Tigecycline: in vitro protein binding of ^{14}C -tigecycline in mouse, rat, rabbit, dog, and human plasma using ultracentrifugation. Study # 04-0129/04-0465/04-1156. Serial # 065
10. RPT-47491: GAR-936: placental transfer of ^{14}C -GAR-936 following a single bolus intravenous (3 mg/kg) administration to gravid Sprague-Dawley rats. Study # 96666. Serial #
11. RPT-43753: GAR-936: transfer of ^{14}C -GAR-936 in breast milk of rats following a single 5 mg/kg iv dose. Study # 96664. Serial # 000
12. GTR-37286: GAR-936 (WAY156936): metabolism in male rats following intravenous administration of ^{14}C -GAR936 (30 mg/kg). Study # 98806. Serial # 072
13. GTR-37285: GAR-936 (WAY156936): metabolism in male dogs following intravenous administration of ^{14}C -GAR-936 (5 mg/kg). Study # 95685. Serial # 072
14. RPT-55407: Tigecycline: analysis of serum and urine from humans, dogs, and rats for the N-acetyl-9-amino-minocycline metabolite. Study # 3074A1-104-US/04-1368/041373.
15. RPT-42931: GAR-936 (WAY156936): in vitro metabolism of GAR-936 in cryopreserved human hepatocytes, human liver slices and liver microsomes of Sprague-Dawley rats, beagle dogs, and humans. Study # 01-0026. Serial # 104
16. RPT-42413: GAR-936 (WAY156936): evaluation of the inhibition of human cytochromes P450 3A4, 2D6, 2C9, 2C19, 2C8, and 1A2 by GAR-936. Serial #072
17. GTR-35418: GAR-936: single ^{14}C intravenous dose (5 mg/kg mass balance study in male rats. Study # 95605.
18. GTR-37697: GAR-936: urinary and biliary excretion of the parent compound after a single intravenous administration of GAR-936 to male rats
19. GTR-33020: GAR-936: single ^{14}C intravenous dose (5 mg/kg) mass balance study in male dogs. Study # 95590.
20. RPT-42293: Preliminary pharmacokinetic interaction studies between GAR-936 and thiopental in mice.
21. RPT-54958: Tigecycline (GAR-936): multiple intravenous (bolus) dose pharmacokinetics study in male rats. Study # 04 0931.
22. Miracl-24491: A 2-week pharmacokinetic (gavage) study of CL318,614 (antibacterial) in rats. Study # 91022.
23. Miracl-25293: Absorption, bioavailability and pharmacokinetics following a single intravenous and oral dose of ^{14}C -CL318614 in the dog. Study # A9163.
24. Miracl-23899: Mass balance, excretion, and metabolic profiles following a single oral dose of ^{14}C -CL318,614 in the rat. Study # A9146.

Toxicology:

Acute

1. GTR-31860: GAR- 936: acute intravenous toxicity study in mice. Study # 96214. Serial # 000
2. GTR-31861: GAR-936: acute intravenous toxicity study in rats. Study # 96215. Serial # 000

Repeat dose

3. GTR-31411: GAR-936: Three day intravenous tolerability study in male rats. Study # 96196. Serial # 000

4. GTR-31741: A seven day intravenous infusion toxicity study of antibacterial analogs in the albino rat. Study # 95287. Serial # 000
5. Miracl-26228: An exploratory infusion two-week tolerability study of CL 346,790 (TBG MIMO) in surgically catheterized rats. Study E 93-3504. Serial # 000
6. GTR-32074: CL 346,635 and WAY 152,288 A 14 day intravenous infusion pilot toxicology study in male rats. Study # 95354. Serial # 000
7. GTR-31608: GAR-936: Fourteen day intravenous toxicity and toxicokinetic study in rats. Study # 96195. Serial # 000
8. RPT-42195: A 14 day intravenous toxicity study of GAR-936 in the albino rat with a 3-week recovery. Study # 98209.
9. RPT-41074: A 13-week intravenous toxicity study of GAR-936 in the albino rats. Study # 98211. Serial # 065
10. RPT-41347: GAR-936 a 13-week intravenous toxicity study of GAR-936 in the albino rat (protocol 98211): bioanalytical and toxicokinetic report. Serial # 065
11. GTR-30595: CLX 346,635 and WAY-152,288: a 2-day bolus intravenous tolerability study in beagle dogs. Study # 95378. Serial # 000
12. GTR-30663: WAY 152,288 and CLX 346,635: A 2-week intravenous dose ranging pilot toxicity study in dogs. Study # 96100. Serial # 000
13. GTR-31609: GAR-936: Fourteen day intravenous toxicity and toxicokinetic study in dogs. Study # 96194. Serial # 000
14. RPT-42488: A 14-day intravenous toxicity study of GAR-936 in the beagle dog with a 3-week recovery. Study # 98210.
15. RPT-41664: A 13-week intravenous toxicity study of GAR-936 in the beagle dog. Study # 98212. Serial # 065
16. RPT-42763: GAR-936 a 13 week intravenous toxicity study of GAR-936 in the Beagle dog (protocol 98212): bioanalytical and toxicokinetic report. Serial #065
17. GTR-30594: CLX 346,635/WAY 152,288: a 2-day bolus intravenous tolerability study in cynomolgus monkeys. Study # 95379. Serial # 000

Genotoxicology:

1. GTR-32202: Mutagenicity test on GAR-936 CHO HGPRT forward mutation assay with a confirmatory assay. Study # 96159. Serial # 000
2. GTR-31695: Mutagenicity test of CLX 346,635 in the L5178Y TK +/- mouse lymphoma forward mutation assay. Study # 95393. Serial # 000
3. GTR-32201: Mutagenicity test on GAR-936 in the L5178Y TK +/- mouse lymphoma forward mutation assay with a confirmatory assay. Study # 96157. Serial # 000
4. GTR-32066: Mutagenicity test on GAR-936 measuring chromosomal aberrations in Chinese Hamster Ovary (CHO) cells with a confirmatory assay with multiple harvests. Study # 96156. Serial # 000
5. GTR-31896: Mutagenicity test on GAR-936 in the in vivo mouse micronucleus assay. Study # 96158. Serial # 000

Reproductive Toxicology:

1. GTR-32617: GAR-936: Intravenous fertility and developmental toxicity dose ranging study in rats. Study # 96230. Serial # 015

2. RPT-42298: GAR-036: intravenous injection fertility and embryo-fetal development study in the rat. Study # 98205. Serial # 072
3. RPT-41346: GAR-936: intravenous injection fertility and embryo-fetal development study in the rat (protocol 98205): bioanalytical and toxicokinetic report. Serial # 072
4. GTR-33185: GAR-936: intravenous developmental toxicity dose ranging study in CD-1 mice. Study # 96229. Serial #072
5. GTR-32600: GAR-936: 2-week intravenous dose ranging study in female rabbits. Study # 96228.
6. RPT-33215: GAR-936: Intravenous developmental toxicity dose ranging study in gravid rabbits. Study # 97045. Serial #072
7. GTR-35159: GAR-936: intravenous developmental toxicity dose ranging study in gravid rabbits: bioanalytical and toxicokinetics report (Protocol; 97045). Serial # 015
8. RPT-42304: GAR-936: intravenous injection teratology study in the rabbit. Study # 98206. Serial # 072
9. RPT-41646: GAR-936: intravenous injection teratology study in rabbits (protocol 98206): bioanalytical and toxicokinetic report. Serial # 072
10. RPT-53525: Tigecycline: an intravenous bolus injection pre and postnatal study in the rat (protocol # 03 1633). *Current Submission

Special Toxicology:

1. GTR-33263: GAR-936: passive cutaneous anaphylaxis (PCA) assay in rodents. Study # 97016. Serial #015
2. GTR-33124: GAR-936 ascending intravenous and subcutaneous dose-range finding study in guinea pigs. Study # 97017. Serial # 015
3. RPT-55695: Tigecycline: qualification of the 4-epimer of tigecycline.
4. RPT-54677: Tigecycline: qualification of the 9-aminominocycline.
5. RPT-56037: Tigecycline: 14-day intravenous impurity qualification study in rats (protocol 14- 1696.
6. GTR-33279: GAR-936: 14-day intravenous hematotoxicity study with a recovery period in dogs. Study # 97040. Serial # 000
7. RPT-55059: Tigecycline: single dose phototoxicity study to determine the effects of intravenous administration on the eyes and skin in pigmented male rats. Study # 040001. Current Submission.
8. RPT-39987: Lederle Japan study on the emetogenic potential of GAR-936 in *Suncus murinus* (shrews).
9. GTR-32502: GAR-936: In vitro compatibility testing of the GAR-936 intravenous formulation with rat, dog and human blood. Study # 96199. Serial #000
10. MIRACL-26519: In vitro studies to assess the effects of DMG-DMDOT (CL331, 928) DMG-mino (CL344,677) TBG-mino (CL346-790), minocycline (CL59,806) and tetracycline on cellular and mitochondrial protein synthesis. Study # 93151.
11. MIRACL-24409: A single dose exploratory (gavage) study of CL318,614 (antibacterial) in mice. Study # 90300).
12. MIRACL-25212: A single dose intraperitoneal toxicity study of CL318,614 (9-aminominocycline, an antibiotic agent in mice. Study # 91093.

13. MIRACL-24408: A single dose exploratory (gavage) study of CL318,614 (antibacterial) in rats. Study # 90229.
14. MIRACL-25211: A single dose intraperitoneal toxicity study of CL 318,614 (9-aminomincycline, an antibiotic agent) in rats. Study # 91092.
15. MIRACL-24411: A two week oral toxicity (gavage) study of CL318,614 (antibacterial) in rats. Study # 91024.
16. MIRACL-24488: A single escalating oral (gavage) toxicity study of CL 318,614 (antibacterial) in dogs. Study # 90231.
17. MIRACL-25299: A 2-week oral (gavage toxicity study of CL318,614 (antibacterial) in dogs. Study 91019.
18. MIRACL-26105: Evaluation of CL 318,614 (9-aminomincycline HCL) in a microbial mutagenicity assay. Study # 91074.
19. MIRACL-24694: CHO/HPRT mammalian cell forward gene mutation assay on CL 318,614—9-aminomincycline. Study # 91076.
20. MIRACL-24191: Test for chemical induction of unscheduled DNA synthesis in rat primary hepatocyte cultures by CL318,614 (9-aminomincycline HCL). Study # 91078.

Studies not reviewed within this submission: None of the studies using non-intravenous routes of administration were reviewed.

3.2 PHARMACOLOGY

3.2.1 Brief summary

Tigecycline is a member of the tetracycline family of antibiotics and acts by inhibition of tRNA binding to ribosomes. Tigecycline has activity against Gram positive and negative bacteria as well as against some MRSA and VRE lines.

3.2.2 Primary pharmacodynamics: This information is reviewed by the microbiologist.

3.2.3 Secondary pharmacodynamics

In the — assay, there was no significant interference/binding to the various receptors with tigecycline at concentrations up to 10 uM.

3.2.4 Safety pharmacology

Neurological effects:

Effects were minimal until 30 mg/kg in the rat, where decreased activity, writhing responses, and irritability were noted. In a separate study, 30 mg/kg had no effect on CNS parameters (clinical signs plus grip strength, hindlimb footsplay, and rectal temperature). In a second rat study with 5, 15, and 30 mg/kg tigecycline, no significant changes in behavior or functional parameters were noted.

Cardiovascular effects:

In the telemeterized rats (1 month wash-out from previous drugs), there were no significant effects on blood pressure, heart rate or gross activity over a 24 hour period at

doses of 5 or 25 mg/kg infused over 1 hour. In the dog, a dose of 12 mg/kg was associated with an initial increase in blood pressure, followed by a decrease in blood pressure for the remaining 23 hours; increased activity and increased heart rate in the first hour after infusion; but no changes in ECG. In the rabbit, similar effects were seen at 30 mg/kg.

Pulmonary effects:

Bronchoresistance was fatal in immobilized guinea pig at 30 mg/kg. The response was reduced with anti-histamines. In the rat with 5, 15, or 30 mg/kg tigecycline, no effect on respiratory rate, tidal volume or minute volume were noted.

Renal effects:

With 30 mg/kg, a decrease urinary pH and an increase in potassium excretion was noted in the rat. The findings were not toxicologically relevant.

Gastrointestinal effects:

No effects on transit time was seen with up to 30 mg/kg tigecycline.

Abuse liability: None.

Other: None.

3.2.5 Pharmacodynamic drug interactions: No interactions were investigated.

3.3 PHARMACOKINETICS/TOXICOKINETICS

3.3.1 Brief summary

All of the studies were conducted by the intravenous route using a normal saline vehicle. Tigecycline has a longer half-life in dogs and monkeys than in rats. Gender differences in pharmacokinetics are only briefly explored in the toxicokinetic studies, where there did not appear to be a significant difference between genders. Distribution of tigecycline was widespread, with the exception of not crossing the blood-brain barrier. Like most tetracyclines, tigecycline was bound to bone with the accompanying discoloration (although dental discoloration was not mentioned in the reports from the post-natal rat study. Tigecycline was excreted in milk, but the actual pup plasma exposure to parent compound was extremely low (even the remaining metabolites were just above 10% of the level in the plasma of the dams. Metabolism was not extensive. Excretion was via both the urine and feces.

3.3.3 Absorption

The initial set of single dose pharmacokinetic studies were conducted only in males. No gender comparisons can be made without including the toxicokinetic data. In several studies, both total radioactivity and parent compound by HPLC were measured, suggesting that metabolites do not contribute much to the initial C_{max}, but have longer half-lives and contribute significantly to overall exposure. The results of these studies are shown in the table below.

Ref #	Species	N	Sex	Dose mg/kg	Analysis method	Time course	Cmax ug/mL	AUC ug.hr/mL	T _{1/2} h
1	SD rat	4	M	5	HPLC	0-24 h	7.44±0.59	3.55±0.28	1.0±0.2
				30			120±49	64.6±20.6	2.9±0.1
				70			287±53	227±38	4.3±0.9
2	SD rat	4	M	5	¹⁴ C/HPLC	0-168 h	^t 4.94±0.56	4.28±0.35	3.5±0.2
							^p 3.60±0.70	1.86±0.18	1.1±0.1
5	SD rat		M	3	¹⁴ C	0-168 h	1.14	3.64	36
	Gravid SD rat	1	F	3	¹⁴ C/HPLC	0-72 h	1.35	2.45	7.7
3	Beagle dog	4	M	5	¹⁴ C/HPLC	0-168 h	^t 10.5±3.8	22.2±3.8	30±10
							^p 9.93±4.24	13.2±2.1	8.1±2.1
4	C. monkey	4	M	5 (iv)	HPLC	0-48 h	15.1±6.1	18.3±3.0	14.1±3.4
				15(p.o.)			0.16±0.02	0.16±0.06	---

^t total radioactivity ^p radioactivity from parent drug

The exposure to GAR-936 and metabolites in nursing dams and their pups are shown in the following table. No parent drug was detectable in the pup plasma, and total radiolabel levels in the pups are approximately 1/7th that seen in the dams. The concentration of radioactivity in milk is higher than that in plasma (see table below).

TABLE 7. MEAN (= SE) PHARMACOKINETIC PARAMETERS IN LACTATING RATS AND THEIR NURSING PUPS FOLLOWING A SINGLE 5 MG/KG INTRAVENOUS DOSE OF ¹⁴C-GAR-936 TO LACTATING RATS - PHASE I (PROTOCOL 96664)

		C _{15min} C _{max} (ng/mL)	t _{max} (hr)	AUC ₀₋₄₈ (ng·hr/mL)	t _{1/2} ^a (hr)
Lactating Rats	GAR-936	970 = 512 ^b	NA	2967 ± 362	ND
	Total Radioactivity	1987 = 280 ^{b,c}	NA	5997 = 202 ^d	14.6
Nursing Pups	GAR-936	NC	NC	NC	NC
	Total Radioactivity	39.6 = 2.8 ^c	12 = 3	824 = 92 ^d	ND

a: Half-life was calculated from mean concentration vs time profile using WinNonlin.

b: Concentration at 15 minutes after dosing (1st sampling time point).

c: Units are ng equiv · mL.

d: Units are ng equiv·hr·mL.

NC: Not calculated, all concentrations except two pooled pup serum samples were below the LOQ.

ND: Not determined: the serum concentration-time profiles did not support the estimation of the terminal rate constants.

TABLE 11. MEAN (= SD) CONCENTRATIONS OF TOTAL RADIOACTIVITY AND GAR-936 FOLLOWING A 5 MG/KG INTRAVENOUS DOSE OF ¹⁴C-GAR-936 TO LACTATING RATS - PHASE II (PROTOCOL 96664)

Time (Hr)	Total Radioactivity (ng equiv./mL) Mean ± SD	Unchanged GAR-936 (ng/mL) Mean = SD
Serum^a		
0.25	1670 ± 121	1185 ± 98.5
1	721 ± 113	504 ± 75.6
4	245 ± 32	167 ± 16.6
8	133 ± 34	105 ± 22.1
Milk		
0.25	4814 ± 1495 ^b	ND
1	6648 ± 3057	ND
4	14912 ± 3132	ND
8	6292 ± 4344	ND
Milk-to-Serum Ratio		
0.25	2.84 ± 1.01 ^b	ND
1	9.70 ± 5.16	ND
4	61.1 ± 10.3	ND
8	45.0 ± 21.6	ND

a: Blood sample was taken at end of milk collection.

b: N=3

N = 4 samples per timepoint unless otherwise noted

ND: Not determined

3.3.4 Distribution

Tissue distribution was investigated in the rat with single and daily for 6 or 10 day regimens. Both liquid scintillation counting and whole body autoradiography were used. The duration of dosing did not alter the distribution. The majority of drug after the first hour was found in the bone and persisted there for more than 14 days. Other tissues with exposures to tigecycline exceeding that in plasma included bone marrow, salivary and thyroid glands, kidney and spleen. When gravid rats were examined, the bones in both the dams and feti were obvious in autoradiograms. The AUC in the fetus was 1.5X that of maternal plasma.

Protein binding was investigated by two methods at 0.1 to 15 ug/mL tigecycline. The results are shown in the table below.

Species	% protein binding Filtration	% protein binding Ultracentrifugation
Mouse	13.9	86.2
Rat	49.3	88.5
Rabbit	88.1	80.2
Dog	91.9	84.7
Human	95.3	87.4

3.3.5 Metabolism

The metabolism of tigecycline was investigated in rat and dog by sampling the plasma and urine. Additionally, the effects of Cytochrome P450 enzymes and hepatocyte extracts were studied. The majority of tigecycline in the plasma was in the form of parent compound in both the rat and dog (> 80% of the total dose) with the remainder as the epimer or polar breakdown products. At 0.5 h in the dog, the epimer form accounted for 5% and increased to 15% by the end of 24 hours. Similarly, the amount of "other" polar compounds was initially 2% of the total and increased to 11% of the total at 24 hours. In the urine, 4 other metabolites were found, M1, M2, M3 and M4, where M3 was 9-aminomincycline. These metabolites accounted for less the 2% of the total dose.

In human urine, metabolites M8 and M9, where the label was cleaved, accounted for approximately 11% of the total dose. These were not detected in rat or dog urine, and could be captured when human cytosolic extracts were incubated with tigecycline. M9 was a breakdown product of M3.

3.3.6 Excretion

Excretion patterns of tigecycline were remarkably similar in rat and dog, as is shown in the following table.

Species	N	Interval hours	% of total in 1 st 24 h	% in rinse	% in urine	% in feces	Total radioactivity recovered
Beagle dog	4	0-168	63.8 ±9.3	6.8±1.4	35.5±11.6	46.7±2.6	89.1±10.9
SD rat	4	0-168	62.0±3.6	1.7±1.5	34.4±4.6	53.3±4.9	89.4±2.5

3.3.7 Pharmacokinetic drug interactions:

No interactions (inhibition, stimulation or effects on drug metabolism) with Cytochrome P450 enzymes were noted.

3.3.10 Tables and figures to include comparative TK summary

Toxicokinetics for Tigecycline							
Species	Schedule	Dose mg/kg	AUC _{0-∞} (ug.h/mL)				Half-life (last day) h in M
			Males		Females		
			Day 1	Last Day	Day 1	Last Day	
CD Rat	DX2 wks	5	---	7.1	---	---	6.7
		30	---	65.9	---	50.0	10.2
		70	---	129	---	---	8.1
SD rats	DX13 wks	2	3.4	6.2	---	---	12.3
		6	10.2	19.9	8.5	14.6	13.7
		20	37.9	87.4	---	---	9.0
Beagle Dog	DX2 wks	2	4.9	6.2	5.2	6.0	---
		5	12.5	12.9	11.9	11.8	---
		12	30.1	33.6	33.1	34.4	---
	DX2 wks	2	6.2	6.2	5.9	4.8	7.2
		5	18.6	15.4	18.3	18.7	15.8
		12	49.0	61.4	46.6	58.5	10.8
		20	101	---	91.3	148	---
	DX13 wks	0.5	1.5	1.6	1.4	1.6	14.4
		1.5	4.6	4.5	4.3	4.5	14.5
5.0		15.5	20.4	15.1	18.1	16.8	

---Values not collected

3.4 TOXICOLOGY

3.4.1 Overall toxicology summary

General toxicology:

The toxicology studies for tigecycline were conducted in rat and dog using bolus intravenous dosing with 0.9% saline solution as vehicle. Like other tetracyclines, tigecycline bound to bone and caused discoloration (yellow). A histaminic response was seen in both rat and dog (and was confirmed by measuring histamine levels). Both species also showed significant effects on blood elements (RBCs, WBCs and platelets were all decreased). Minor renal damage was noted (tubular degeneration which resolved within 3 weeks). No effects on the liver were seen. Finally, at higher doses, gastrointestinal effects were seen, primarily on the small intestine. As a secondary effect to vomiting, ulcerations and erosions in the esophagus and mouth were reported (dog only). No additional toxicities were observed with increased duration of administration. No differences in toxicity were noted with gender.

Species	N	Schedule	Doses mg/kg	Results
CD-1 Mouse	3/sex	IX bolus	87.5, 175	LD50=124 mg/kg in males, 98 mg/kg in females; NOEL < 87.5 mg/kg Toxicities: decreased activity, ptosis, dyspnea, exophthalmus
CD rat	3/sex	IX bolus	75, 150, 300	LD50 = 106 mg/kg, NOEL < 75 mg/kg Toxicities: decreased activity, dyspnea, erythema, edema
	5 M	DX3 d bolus	70	Histaminic response, blood in feces, bright yellow urine
	15/sex	DX14d bolus	5, 30, 70	NOAEL = 5 mg/kg. Histaminic response, blood in feces/urine, Decr. in RBC parameters, WBC #, platelets; discoloration of bone, injection site rxn. Histopathology: lymphoid atrophy in bone marrow, thymus, spleen, lymph nodes; atrophy of prostate, seminal vesicles.
SD rat	15/sex	DX14 d bolus+ 3 wk recovery	20, 50, 70	NOAEL < 20 mg/kg; LLD = 20 mg/kg. Main cause of death at 70 mg/kg—marrow hypocellularity, several with cardiac inflammation/mineralization. Clinical signs: histamine release. Hematology: RBCs decreased at 70 mg/kg, WBCs and platelets decreased at all doses. Serum Chemistry: total protein decreased at all doses. Histopathology: yellow discoloration of bone at 50, 70; marrow hypocellularity, lymphoid atrophy in thymus, lymph nodes; myocardial inflammation/myofiber degeneration/ necrosis/mineralization. Kidneys: tubular degeneration. Stomach: ulceration of glandular mucosa. Injection site: hemorrhage, inflammation, thrombosis, necrosis. End of recovery period: bone, injection site and heart effects were still seen.
	15/sex	DX13 wks, bolus	2, 6, 20	NOAEL = 2 mg/kg Clinical signs: histaminic response. Hematology: pancytopenia at 20 mg/kg. Serum chemistry: decreased total protein at 6, 20 mg/kg. Organ weight: decreased spleen and thymus

				weight. Histopathology: yellow bone discoloration at 20 mg/kg. lymphoid atrophy in thymus at 20 mg/kg.
Cyn. Monkey	1/sex	DX2 bolus	5, 15	NOAEL < 5 mg/kg, liquid feces
Beagle dog	1/sex	DX2d Bolus	5, 15	NOAEL < 5 mg/kg; clinical signs: lacrimation, facial erythema, emesis, hypoactivity.
	2/sex	DX 14d Bolus	2, 5, 12	NOAEL < 2 mg/kg, Signs: erythema, changes in feces, salivation and emesis, decreased motor activity and lacrimation (histaminic response) Decr RBC #, no gross pathology
	3/sex	DX14 d bolus	2, 5, 12, 20	LLD= 20 mg/kg, NTEL = 5 mg/kg; histamine response (>2 mg/kg), HD weight loss, blood in feces/urine, decreased motor activity. 12 and 20 mg/kg: pancytopenia w/ marrow hypocellularity. Increases in BUN/creatinine at 12/20 mg/kg, decreased total protein. Thyroxine decreased by 50% at 12, 20 mg/kg. Histopathology at 12/20 mg/kg: lymphoid depletion in lymphoid tissues, atrophy of intestinal mucosa, erosion/ulceration/ inflammation of mouth/esophagus (consistent with vomiting), fatty changes in liver.
	6/sex	DX 14 d bolus + 3 week recovery	5, 12	NOAEL < 5 mg/kg. Clinical signs: histaminic response (measured). Hematology: RBC at 12, WBC at 5, 12, APTT increased at 12 mg/kg males. Serum chemistry: increases in BUN at 12 mg/kg, decreased in total protein at 5, 12. Hematology and serum chemistry resolved by 3 weeks. Histopathology: lymphoid atrophy in the thymus. partially resolved. Tubular degeneration resolved (basophilia) by 3 weeks. No marrow damage found.
	3/sex	DX13 wk, bolus	0.5, 1.5, 5.0	NOEL = 1.5 mg/kg. Clinical signs: histaminic response at HD (confirmed by assay). Histopathology: lymphoid atrophy in thymus at HD

Genetic toxicology:

The full recommended ICH battery of genotoxicity tests was conducted with tigecycline. Tigecycline was negative for mutagenicity in the mouse lymphoma L5178Y and CHO HGPRT assays. The CHO chromosomal aberrations assay demonstrated no genotoxicity for tigecycline. The in vivo mouse micronucleus test was also negative with tigecycline at appropriate doses of 150 mg/kg.

Carcinogenicity: No studies were necessary for the short-duration use of this product.

Reproductive toxicology:

Fertility, fetal toxicity and developmental toxicity were investigated in the mouse, rat and rabbit. Tigecycline was not teratogenic in either the rat or the rabbit; however, there were increased resorptions in both species at doses above the maternally toxic level. The fetotoxic doses and AUCs are shown in the following table. The paternal NTEL in the combined rat fertility/fetal development study was 1 mg/kg. At higher doses, a slight decrement in sperm counts were seen. Other toxicity studies also showed some effects on testicular weights. In the rat development and postnatal study, using the same doses in

the teratology study, there were no effects on the feti and their postnatal development at the highest dose tested, 12 mg/kg. The maternal NTEL was the MD, 4 mg/kg. Based on the pharmacokinetic/distribution studies in the pregnant dams, tigecycline is excreted in the milk and clearly crossed the blood-brain barrier as the fetal skeletons were visible in autoradiographs.

<u>Species</u>	<u>Doses tested</u> <u>mg/kg</u>	<u>Fetal NTEL</u> <u>mg/kg</u>	<u>Fetotoxic Dose</u> <u>mg/kg</u>	<u>AUC @</u> <u>fetotoxic dose*</u> <u>ug.h/mL</u>
Rat	1, 4, 12	4	12	28.5
Rabbit	0.25, 1, 4	4	>4	6.75

AUC on last day of dosing

Special toxicology:

A major issue for tigecycline is whether, based on the myelosuppressive effects, there is also immunosuppression. Consistently in the toxicity studies, bone marrow hypoplasia, and lymphoid atrophy were observed. The passive cutaneous antigenicity study in the rat was negative, but this test would not be expected to predict immunosuppressive potential. The intravenous guinea pig study on airways did show a response, but that may also be associated with the histaminic effects of tigecycline. This is the one area where further pharmacology/toxicology studies might be useful.

Local tolerance was not tested (i.e. skin or eye irritation).

3.4.2 Single-dose toxicity: Previously reviewed by Dr. Terry Peters.

3.4.3 Repeat-dose toxicity: Previously reviewed by Dr. Terry Peters.

3.4.4. Genetic toxicology: Previously reviewed by Dr. Terry Peters.

3.4.5. Carcinogenicity: There were no carcinogenicity studies required due to the short duration of use for this drug.

3.4.6. Reproductive and developmental toxicology

Fertility and early embryonic development: These studies were previously reviewed by Dr. Terry Peters.

Embryofetal development: These studies were previously reviewed by Dr. Terry Peters.

Prenatal and postnatal development

Study title: RPT-53525: Tigecycline: an intravenous bolus injection pre- and postnatal study in the rat (protocol 03_1633).

Conducting laboratory and location: _____

Date of study initiation: 1/26/04

GLP compliance: Yes

QA reports: yes (X) no ()

Drug, lot #, and % purity: Tigecycline, Lot # X42946A, 047ETEC, —

Vehicle: 0.9% sodium chloride

Methods

Doses: 0, 1, 4, 12 mg/kg

Species/strain: Sprague Dawley rats, 11 weeks old, 235-296 g

Number/sex/group: 25 females/dose

Route, formulation, volume, and infusion rate: intravenous, 1 mL/kg/day

Satellite groups used for toxicokinetics: None.

Study design: mated female rats were dosed once daily on presumed gestation day 6 through post-partum day 20.

Parameters and endpoints evaluated: Dams: maternal clinical signs (daily), body weights (twice weekly), food consumption (every 3 days), gross pathology; Pups: malformations, # live/dead, weight (twice weekly), startle response (beginning post-partum day 12, vaginal opening/preputial separation, papillary closure response, passive avoidance, motor activity, water maze swimming, mating indices. F2 generation: malformations and variations.

Results

F₀ in-life: One HD dam died during lactation with no remarkable clinical signs or gross pathology. There were no remarkable differences between treated and control dams in clinical observations. Body weights at the end of gestation decreased with dose, but not to a remarkable extent and are shown in the following table. Body weight gains were decreased to a relevant level in the HD group. Food consumption was increased in the treated groups, but not to a statistically significant extent. There were no significant differences in parturition parameters (length of gestation, duration of parturition).

Body weight and body weight gain in the F0 dams as compared to controls.				
Dose (mg/kg)	End of Gestation		End of lactation	
	Body weight	Body weight gain (GD 6-21)	Body weight	Body weight gain (LD1-21)
1	---	---	↑4%	↑41%
4	↓2%	↓11%	↑2%	↑48%
12	↓5%	↓18%	↑1%	↑70%

F₀ necropsy: There were no remarkable differences between treated and control dams.

F₁ physical development: There were no differences in the number of pups/litter, malformations, or male: female ratios. Pup weights did not differ significantly with dose, nor did weights significantly differ during maturation. At necropsy (following culling at lactation day 4), 4/74 HD females had dilatation of the pelvis. There were no remarkable gross pathology observations.

F₁ behavioral evaluation: Time to auricular startle, papillary closure, time to vaginal opening/preputial separation, passive avoidance, water maze times, and group mean activity counts did not differ significantly between groups. Estrus cycling in females did not differ significantly between groups.

F₁ reproduction: There were no significant differences in the mating performance of the F₁ generation. Maternal weights during gestation did not differ significantly measured as body weight or body weight gain. There were no significant findings at necropsy.

F₂ findings: There were no significant differences between groups in mating/fertility index, total number of corpora lutea, implantation sites, male:female ratio, live feti, resorptions, or gravid uterine weights.

Comments and conclusions:

The fetal NOAEL is the 12 mg/kg/d, while the maternal NOAEL, based on decrements in body weight gain is the 4 mg/kg/d.

3.4.7 Local tolerance: Previously reviewed by Dr. Terry Peters

3.4.8 Special toxicology studies:

1. RPT-55059: Tigecycline: single dose phototoxicity study to determine the effects of intravenous administration on the eyes and skin in pigmented male rats. Study # ADO00001.

Conducting laboratory and location:

Date of study initiation: June 10, 2004

GLP compliance: Yes

QA reports: Yes (X) No ()

Drug, lot #, and % purity: tigecycline (GAR 936), batch # ADO00001-B, C and D.

Formulation/vehicle: 0.9% saline

Doses: 0, 10, 30, 70 mg/kg, intravenous

Study Design: 5 male Long-Evans rats/dose were dosed with drug, then at either 5 minutes or 2 hours exposed to ½ the minimal erythema dose for ½ hour on one eye, one dark patch and one light patch. Positive control was 8-methoxypsoralen (8-MOP) at 1 hour post-dose. Rats were evaluated for mortality, cutaneous response, body weight ophthalmology, and microscopic ocular exams through day 3.

RESULTS:

Mortality and clinical signs: One/5 of the 70 mg/kg rats died on day 1 and was attributed to anesthesia effects. The positive controls had grade 1 erythema and edema at the skin sites. No signs, other than the swelling of mouth/ears/limbs and ataxia, which were expected with the histaminic response to tigecycline, were noted in the tigecycline rats.

Body weights: There were no toxicologically significant changes with treatment.

Eye exams: All of the MOP treated rats showed diffuse superficial corneal edema. One or 2 rats in each dose group with tigecycline showed either corneal edema or focal corneal scarring, but there were no significant dose-related effects.

Conclusions: The study was adequate in that toxic effects from tigecycline were seen at the high dose; no significant increases in UV damage with tigecycline were noted.

2. RPT-39987: Lederle Japan study on the emetogenic potential of GAR-936 in *Suncus murinus* (shrews).

Conducting laboratory and location: Medical Research Laboratories, Wyeth Lederle (Japan), LTD, Saitama, Japan

Date of study initiation: 9/1/98

GLP compliance: No

QA reports: Yes () No (X)

Drug, lot #, and % purity: Gar-936, Lot # OC7650. — pure; also GAR-936 + 4-epimer and GAR-936 + oxidation products (150 mg/kg)

Formulation/vehicle: 0.9% normal saline; positive control: cisplatin, 40 mg/kg

Doses: 100, 300, 600 mg/kg

Study Design: Female shrews (3/dose, weight approximately 40 g) were administered the test compounds and observed for vomiting, # of episodes, and time between episodes for up to 6 hours.

RESULTS:

Doses of 100 or 300 mg/kg GAR-936 had no effect on vomiting or mortality. At 600 mg/kg, 2/4 shrews died while the other 2 vomited. Cisplatin caused vomiting in 2/2 animals. The first episode of vomiting with GAR-936 was at 36 or 73 minutes in the 600 mg/kg group. Copper sulfate (40 mg/kg) caused vomiting in 3/3 animals within an average of 5.7 minutes. Mixtures of the epimer and oxidation products with GAR-936 (150 mg/kg) did cause vomiting in 2/4 and 1/4 animals respectively.

Conclusions: The shrew is not a good model for investigating vomiting with tigecycline.

3.6 OVERALL CONCLUSIONS AND RECOMMENDATIONS

Tigecycline is a minocycline analog and member of the tetracycline antibiotic class. Like other tetracyclines, tigecycline has activity against both Gram positive and negative bacteria. Drug is widely distributed, particularly into bone and teeth (where permanent stains can be seen from prenatal and childhood use). Gastrointestinal irritation (nausea/vomiting, diarrhea with oral administration) are common with the class. Other major toxicities with the class are photosensitivity, hepatic toxicity, and renal toxicity.

The main toxicities from the human clinical trials with tigecycline were nausea, vomiting and diarrhea. Some liver enzyme elevations were observed. However, renal changes and decreases in RBC, WBC and platelet number were rare in the trials.

Tigecycline is administered intravenously. Minimal gender differences were noted in the rat or dog; however, the toxicokinetic studies investigated females only. In humans, gender differences were observed. Distribution was widespread, except for within the blood-brain barrier. The drug did cross the placental barrier. Tigecycline tended to localize in bone and persist there. Excretion was via both urine and feces in both rats and dogs. A similar pattern was seen in humans. Tigecycline was also excreted

in milk in rats but excretion in milk was not investigated in humans. Protein binding was in the range of 80-90% in mouse, rat, rabbit, dog and human. Cytochrome P450 enzyme functions were unaffected by tigecycline.

Toxic effects were extremely similar in the rat and dog with tigecycline. The AUCs at the NOAEL in dogs and rats were within 2 fold of each other. Although no cardiac *in vitro* tests were conducted (e.g. hERG assay), no effects on telemeterized dogs on QT intervals were noted at doses up to 12 mg/kg in the dog in safety pharmacology studies. Further, no significant changes in ECG profiles have been seen in clinical trials. Although tetracyclines are not known for prolonging the QT interval, the class has not been studied extensively. Histamine was released in the rat and dog upon tigecycline administration with confirmation shown by measuring histamine levels in the toxicology studies. Vomiting has been observed in the shorter dog studies, but in the 13 week study, doses were low enough that this was not an issue. Gastrointestinal distress is the major toxicity in the clinical trials. Elevations in liver enzymes were seen in the clinical trials as well, but no liver toxicity (either enzyme elevation or histopathology change) other than occasional decrements in total protein and "fatty changes in the liver" were noted in the 2 week dog at 20 mg/kg. These changes could be attributed to vomiting and diarrhea. Another common human toxicity with tetracyclines, uremia, was not observed with tigecycline.

A major toxicity seen in the animal studies, that did not appear to carry over to humans at the doses in the clinical trials, was myelosuppression. Both rats and dogs had decreased numbers of red and white cells as well as platelets. Marrow hypocellularity, lymphoid depletion and atrophy in the thymus and lymph nodes, indicative of immunosuppression, were also observed.

Tigecycline was not phototoxic and was negative in an antigenicity assay. Local tolerance (eye, skin) was not tested.

Tigecycline affected male fertility at doses of 4 mg/kg in the rat (decreased sperm count). Decreased testes' weights were also noted in dogs treated daily with 20 mg/kg tigecycline for 2 weeks. Tigecycline was not teratogenic in either the rat or the rabbit at maternotoxic doses; decreased fetal viability was seen at 12 mg/kg in the rat (AUC 28.5 ug.h/mL) and > 4 mg/kg in the rabbit (AUC >7 ug.h/mL). There were no effects on post-natal development when dams were administered tigecycline at up to 12 mg/kg through weaning.

Tigecycline was negative for mutagenicity and clastogenicity in the ICH battery of genotoxicity tests including mouse lymphoma L5178Y, CHO HGPRT, CHO chromosomal aberrations, and mouse micronucleus assays. Carcinogenicity testing was not required for the short-term, intermittent use of this drug.

Conclusions: There are no objections to approval from a pharmacology/toxicology standpoint.

Unresolved toxicology issues: In the animals, myelosuppression is the major toxicity with tigecycline; however it is not clear if tigecycline is immunosuppressive.

Recommendations: The drug can be approved from the pharmacology toxicology perspective. No new studies are recommended at this time, especially given that the

decreases in RBCs, WBCs and platelets seen in the rat and dog do not appear to carry over to humans tested in clinical trials.

CURRENT LABELING

Carcinogenesis, Mutagenesis, Impairment of Fertility

Lifetime studies in animals have not been performed to evaluate the carcinogenic potential of tigecycline. No mutagenic or clastogenic potential was found in a battery of tests, including in vitro chromosome aberration assay in Chinese hamster ovary (CHO) cells, in vitro forward mutation assay in CHO cells (HGRPT locus), in vitro forward mutation assays in mouse lymphoma cells, and in vivo micronucleus assay. Tigecycline did not affect mating or fertility in rats at exposures up to 4.7 times the human daily dose based on AUC. In female rats, there were no compound-related effects on ovaries or estrous cycles at exposures up to 4.7 times the human daily dose based on AUC.

Pregnancy



Labor and Delivery

TYGACIL has not been studied for use during labor and delivery.

Nursing Mothers

Results from animal studies using ¹⁴C-labeled tigecycline indicate that tigecycline is excreted readily via the milk of lactating rats. Consistent with the limited oral bioavailability of tigecycline, there is little or no systemic exposure to tigecycline in nursing pups as a result of exposure via maternal milk.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TYGACIL is administered to a nursing woman. (See **WARNINGS**.)

ANIMAL TOXICOLOGY



SUGGESTED LABELING:

The sponsor stated that the human AUC used for comparisons was 6.1 ug.h/mL and noted that a conservative estimate would be obtained with this system. Similar values were obtained when using the human AUC of 4.7 ug.h/mL from the pool efficacy studies in the annotated label, pharmacokinetics section.

- 1) "in vivo micronucleus assay" should read in vivo mouse micronucleus assay".
- 2) Comparison factor for fertility, is 5.
- 3) Teratology should use a comparison factor of 5 for rat, 1 for rabbit.
- 4) "An increased incidence of fetal loss was observed at maternotoxic doses in the rabbits with _____"
- 5) In the animal toxicology section, the AUC comparison for rats and dogs should be _____ . It should be noted that this is from a 2 week study.
- 6) The _____ not as relevant given the difference in infusion times bolus vs. 30-60 minutes and should be deleted.
- 7) Tigecycline should be a Pregnancy Category D, _____ based on tetracycline class effects.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ___ No ___

Deputy Division Director Signature _____

Concurrence Yes ___ No ___

3.7. APPENDIX/ATTACHMENTS: None

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Wendelyn Schmidt
6/14/05 12:37:42 PM
PHARMACOLOGIST

this is the corrected version

Robert Osterberg
6/14/05 01:45:03 PM
PHARMACOLOGIST

Lillian Gavrilovich
6/15/05 04:14:50 PM
MEDICAL OFFICER

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-821

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21, 821
Drug Name:	Tigecycline
Indication(s):	Complicated Skin and Skin Structure Infections (cSSSI), Complicated Intra Abdomen Infections (cIAI)
Applicant:	WYETH RESEARCH
Date of Original Submission	12/15/04
Date of Deadline	06/15/05
Biometrics Division:	Biometrics Division III
Statistical Reviewer:	Thamban Valappil, Ph.D.
Statistical Review TL:	Daphne Lin, Ph.D.
Medical Division:	HFD-520, Division of Anti-Infectives and Ophthalmology Products
Clinical Team:	Charles Cooper, M.D.
Clinical Review TL:	John Alexander, M.D., M.P.H
Project Manager:	Judit Milstein

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

1.1.1 Complicated Skin and Skin Structure Infections (cSSSI)

In the primary efficacy analyses of clinical response at test-of-cure, tigecycline demonstrated noninferiority to vancomycin/aztreonam in the Clinically Evaluable (CE) and Clinical Modified Intent-to-Treat (c-mITT) populations in studies 3074A1-300-US/CA and 3074A1-305-US/WW.

In the FDA analyses of study 3074A1-300-US/CA, clinical response was evaluated for duration of up to 35 days after the last dose of the study drug, as per the protocol. The 95% Confidence Intervals for the difference in clinical cure rates at the TOC (Table 4) in the CE, c-mITT and ITT populations were; CE (95%CI: -7.8, 8.3), c-mITT (95%CI: -8.8, 6.6) and ITT (95% CI: -9.2, 5.6). Based on the 95% Confidence Interval (CI), Tigecycline demonstrated noninferiority to vancomycin/aztreonam using a non-inferiority margin of 15%.

In the FDA analyses of study 3074A1-305-US/WW, clinical response was evaluated for duration of up to 35 days after the last dose of the study drug as in the previous study. The 95% Confidence Intervals for the difference in clinical cure rates at the TOC (Table 9) in the CE, c-mITT and ITT populations were; CE (95%CI: -10.4, 1.0), c-mITT (95%CI: -9.2, 4.0) and ITT (95% CI: -9.0, 3.6). Based on the 95% Confidence Interval (CI), Tigecycline demonstrated noninferiority to vancomycin/aztreonam using a margin of 15%.

1.1.2 Complicated Intra Abdomen Infections (cIAI)

In the primary efficacy analyses of clinical response at test-of-cure, tigecycline demonstrated noninferiority to imipenem/cilastatin in the ME and micro-mITT populations in studies 3074A1-301-WW and 3074A1-306-WW.

In the FDA analyses of study 3074A1-301-WW, clinical response (unadjusted for APACHE scores) was evaluated for duration of up to 35 days after the last dose of the study drug. The 95% Confidence Intervals for the difference in clinical cure rates at the TOC (Tables 16-17) in the ME, micro-mITT and ITT populations were; ME (95%CI: -9.3, 5.3), micro-mITT (95%CI: -11.9, 2.4) and ITT (95%CI: -11.8, 0.3). Tigecycline demonstrated noninferiority to imipenem/ cilastatin in both the ME and micro-mITT using a margin of 15%.

In the FDA analyses of study 3074A1-306-WW, clinical response (unadjusted) was evaluated for duration of up to 35 days based after the last dose of the study drug. The 95% Confidence Intervals for the difference in clinical cure rates at the TOC (Tables 23-24) in the ME, micro-mITT and ITT populations were; ME (95%CI: -4.8, 6.9), micro-mITT (95%CI: -4.6, 7.8) and ITT(95%CI: -5.0, 5.5). Tigecycline demonstrated noninferiority to imipenem/ cilastatin in both the ME and micro-mITT using a margin of 15%.

1.1.3 Safety Issues

Based on the safety review, a total of 57 deaths were reported from studies 3074A1-300-US/CA, 3074A1-301-WW, 3074A1-305-US/WW and 3074A1-306-WW. In studies submitted for Complicated Skin and Skin Structure Infections, there were 6 deaths reported in the Tigecycline arm. Of which, 5 deaths were reported from study 3074A1-300-US/CA and one death in study 3074A1-305-US/WW. In studies submitted for Complicated Intra Abdomen Infections, there were 26 deaths reported in the Tigecycline arm. Of which, 19 deaths were reported from study 3074A1-301-WW and 7 deaths were reported from study 3074A1-306-WW. Based on the review, no specific safety issues could be attributed to the cause of these deaths. The medical officer, Dr. Cooper's clinical review would provide more detailed safety information. Approval of this product would be based on the overall evidence of safety and efficacy and the labeling should indicate all the major safety issues for this product.

1.2 Brief Overview of Clinical Studies

Pivotal Clinical Studies:

There were a total of four (4) phase-3 studies submitted, 2 each for cSSSI and cIAI indications, evaluated the safety and efficacy of tigecycline in the treatment of subjects with complicated and serious infections. The phase 3 studies were conducted worldwide in over 45 countries in North and South America, Europe, Asia, Africa, and Australia. The studies are listed under each of the indications as follows:

I. Complicated Skin and Skin Structure Infections (cSSSI)

1. Study 3074A1-300-US/CA (study 300)

This was a phase-3 multicenter, randomized, double-blind (third-party unblinded) comparison of the safety and efficacy of tigecycline with placebo versus vancomycin/aztreonam in subjects with 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 (1:1 ratio) to receive either tigecycline with placebo or vancomycin with aztreonam intravenously for up to 14 days.

A total of 596 subjects were enrolled in this study; 13 were screen failures and the remaining 583 subjects were randomly assigned to treatment and constituted the intent-to-treat (ITT) population. Ten (10) subjects did not receive study drug. A total of 573 subjects received at least 1 dose of the assigned study drug and constituted the mITT population: 292 subjects received tigecycline and 281 subjects received vancomycin/aztreonam.

2. Study 3074A1-305-US/WW (study 305)

This was a phase-3, multicenter, randomized, double-blind (third-party unblinded), comparison study of the safety and efficacy of tigecycline versus vancomycin/aztreonam in Subjects with cSSSI. cSSSI includes infections that involve deep soft tissue or require significant surgical intervention or are associated with a significant underlying disease state that complicates response to treatment. Subjects were randomly assigned in a 1:1 ratio to receive either tigecycline or vancomycin with aztreonam via intravenous (IV) administration for up to 14 days.

A total of 557 subjects were enrolled into the study; 11 were screen failures. The other 546 subjects were randomly assigned to 1 of the treatment arms and constituted the intent-to-treat (ITT) population. Three (3) subjects did not receive study drug. Altogether, 543 subjects received the study drug and constituted the mITT population: 274 subjects received tigecycline and 269 subjects received vancomycin/aztreonam.

II. Complicated Intra Abdomen Infections (cIAI)

1. Study 3074A1-301-WW (study 301)

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.

A total of 898 subjects were screened into the study; 64 subjects were screen failures and the remaining 834 subjects (ITT) were randomly assigned to 1 of the treatment arms. A total of 825 subjects received the study drug and constituted the mITT population: 413 subjects received tigecycline and 412 subjects received imipenem/cilastatin.

2. Study 3074A1-306-WW (study 306)

This was a phase-3, multi-center, double-blind (third-party unblinded) study comparing the safety and efficacy of tigecycline to imipenem/cilastatin in hospitalized subjects with complicated intra-abdominal infections. 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.

A total of 861 subjects were screened for the study; 37 were screen failures (10 additional subjects were screen failures that were not captured in the database. 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.

1.3 Statistical Issues and Findings

From studies 300, 301, 305 and 306, a total of 54 deaths were reported. In studies submitted for Complicated Skin and Skin Structure Infections, there were 6 deaths reported in the Tigecycline arm. Of which, 5 deaths were reported from study 3074A1-300-US/CA and one death in study 3074A1-305-US/WW. In studies submitted for Complicated Intra Abdomen Infections, there were 26 deaths reported in the Tigecycline arm. Of which, 19 deaths were reported from study 3074A1-301 and 7 deaths reported from study 3074A1-306-WW. Based on the review, no specific safety issues could be attributed to the cause of these deaths. However, medical officer, Dr. Cooper's clinical review would provide detailed safety information.

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ON ORIGINAL**

2. INTRODUCTION

2.1 Overview

Tigecycline is an intravenously administered glycylcycline antibiotic and acts by binding to the 30S bacterial ribosomal subunit and by blocking entry of amino-acyl transfer RNA (tRNA) molecules into the A site of the ribosome. There were four (4) phase 3 studies submitted, 2 each for cSSSI and cIAI indications, evaluated the safety and efficacy of tigecycline in the treatment of subjects with complicated and serious infections. The phase 3 studies were conducted worldwide in over 45 countries in North and South America, Europe, Asia, Africa, and Australia.

Studies 300-US/CA and 305-US/WW were submitted to evaluate the efficacy and safety of tigecycline compared with vancomycin/ aztreonam in complicated subjects with cSSSI. Patients with deep soft tissue infections including wound infections and cellulitis (≥ 10 cm, requiring surgery/drainage or with complicated underlying disease), major abscesses, infected ulcers, and burns were enrolled in these studies.

Studies 301-WW and 306-WW were submitted to evaluate the efficacy and safety of tigecycline compared with imipenem/cilastatin in the treatment of complicated subjects with cIAI. Patients with diagnoses including appendicitis, cholecystitis, diverticulitis, gastric/duodenal perforation, intra-abdominal abscess, perforation of intestine, and peritonitis were enrolled in these studies.

2.2 Data Sources

The review documents and the SAS datasets were available on the EDR at \\CDSESUB1\EVSPROD\N021821\0003.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Complicated Skin and Skin Structure Infections (cSSSI)

3.1.1.1 Study 3074A1-300-US/CA

Study Design:

This was a phase 3 multicenter, randomized, double-blind (third-party unblinded) comparison of the safety and efficacy of tigecycline with placebo versus vancomycin/ aztreonam in subjects with 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 (1:1 ratio) to receive either tigecycline with placebo or vancomycin with aztreonam intravenously for up to 14 days.

Primary Efficacy Endpoint:

The primary efficacy endpoint is the clinical response at the test-of-cure assessment which took place at least 12 days after the last dose of study drug. The efficacy assessments were based on CE and c-mITT (co-primary populations), where c-mITT population consisted of all mITT subjects who received study drug and met the minimum disease criteria for cSSSI. According to the sponsor, 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 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.

Statistical Reviewers Comments:

In an amendment to the protocol, the timing for the TOC assessment was redefined to occur at least 14 days and up to 35 days after the last dose of study drug. However, the sponsor included patients up to 92 days after the last dose of study drug in the primary efficacy analysis. This was discussed with the Sponsor at the teleconference dated February 15, 2005.

Accordingly, in the FDA analysis, the primary efficacy endpoint of clinical response was evaluated for a duration of up to 35 days at the test-of-cure assessment. The primary efficacy assessments were based on CE and c-mITT as co-primary populations and analysis based on the ITT population was also evaluated in this review to assess the robustness of evidence while retaining all randomized patients.

Noninferiority of tigecycline compared with vancomycin/aztreonam for clinical and microbiologic responses was evaluated based on a 2-sided 95% confidence interval (CI) for the true difference in efficacy (tigecycline - vancomycin/aztreonam). Noninferiority was concluded in this review if the lower limit of the 2-sided 95% CI for the true difference in efficacy was higher than -15%.

The sponsor's clinical response based on the submission was as follows:

Cure:

- 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:

- 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.

Patient Disposition, Demographic and Baseline Characteristics

Disposition of Subjects

A total of 596 subjects were enrolled in this study; 13 were screen failures and the remaining 583 subjects were randomly assigned to treatment and constituted the intent-to-treat (ITT) population. Ten (10) subjects did not receive study drug. A total of 573 subjects received at least 1 dose of the assigned study drug and constituted the mITT population: 292 subjects received tigecycline and 281 subjects received vancomycin/aztreonam.

Table 1: Number of Subjects in Each Population Category

	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	91	89	180

Sponsor's Table

Demographic and other baseline characteristics of the mITT population, including age, sex,

ethnicity, weight, and creatinine clearance, are given in Table 2 below.

Table 2: Demographic and Baseline Characteristics: mITT Population

Characteristic	Tigecycline (n = 292)	Vancomycin/ Aztreonam (n = 281)	Total (n = 573)
Age, years			
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 (%)			
Male	180 (61.6)	188 (66.9)	368 (64.2)
Female	112 (38.4)	93 (33.1)	205 (35.8)
Ethnic origin, n (%)			
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			
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			
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

Statistical Reviewer's Comments:

As given in the table above, the demographic and other baseline characteristics of the mITT population (including age, sex, ethnicity, weight, and creatinine clearance) were almost similar in the two treatment groups.

EFFICACY RESULTS:

Table 3: Clinical Response at TOC (CE, c-mITT and ITT Populations)

Visit	Response	Tigecycline		Vancomycin/Aztreonam		95% CI
		n/N	%	n/N	%	
CE Population						
Test-of-Cure	Cure	165/199	82.9%	163/198	82.3%	(-7.4, 8.6)
	Failure	34/199	17.1%	35/198	17.7%	
c-mITT Population						
Test-of-Cure	Cure	209/277	75.5%	200/260	76.9%	(-9.0, 6.1)
	Failure	48/277	17.3%	46/260	17.7%	
	Indeterminate	20/ 277	7.2%	14/ 260	5.4%	
ITT Population						
Test-of-Cure	Cure	217/ 295	73.6%	217/ 288	75.3%	(-9.2, 5.6)
	Failure	53/ 295	18.0%	49/ 288	17.0%	
	indeterminate	25/ 295	8.5%	22/ 288	7.6%	

Sponsor's analysis

Statistical Reviewer's Comments:

In the Sponsor's analysis (Table 3), the clinical response was evaluated at the TOC, 92 days after the last dose of study drug. Based on the 95% Confidence Interval (CI) for the difference in clinical cure rates at the TOC, Tigecycline demonstrated noninferiority to vancomycin/aztreonam using a non-inferiority margin of 15%. The Confidence Intervals in the CE, cmITT and ITT populations were; CE (95%CI: -7.4, 8.6); cmITT (95%CI: -9.0, 6.1) and ITT (95%CI: -9.2, 5.6), respectively.

Table 4: FDA Analysis: Clinical Response (TOC Visit <=35 days post-therapy)

Visit	Response	Tigecycline		Vancomycin/Aztreonam		95% CI
		n/N	%	n/N	%	
CE Population						
Test-of-Cure	Cure	162/196	82.7%	159/193	82.4%	(-7.8, 8.3)
	Failure	34/196	17.3%	34/193	17.6%	

c-mITT Population						
Test-of-Cure	Cure	203/268	75.7%	196/255	76.9%	(-8.8, 6.6)
	Failure	48/268	17.9%	45/255	17.6%	
	Indeterminate	17/ 268	6.3%	14/ 255	5.5%	

Statistical Reviewer's Comments:

In the FDA analyses (Table 4), clinical response was evaluated for duration of up to 35 days at the test-of-cure assessment. The Confidence Intervals in the CE and cmITT populations were; CE (95%CI: (-7.8, 8.3) and cmITT (95%CI: -8.8, 6.6). Based on the 95% Confidence Interval (CI) for the difference in clinical cure rates at the TOC, Tigecycline demonstrated noninferiority to vancomycin/aztreonam using a non-inferiority margin of 15%. The efficacy conclusions were not affected upon evaluating the clinical responses at the TOC<=35 days or TOC<=92 days (sponsor's analysis) after the last dose of study drug.

**Table 5: Clinical Response by Monomicrobial/Polymicrobial Infection:
ME population**

Infection	Response	Tigecycline		Vancomycin/Aztreonam		95% CI
		n/N	%			
Monomicrobial	Cure	56/ 71	78.9%	55/ 69	79.7 %	(-15.2, 13.6)
	Failure	15/ 71	21.1%	14/ 69	20.3%	
Polymicrobial	Cure	37/ 44	84.1%	33/ 44	75.0 %	(-9.5, 27.0)
	Failure	7/ 44	15.9%	11/ 44	25.0%	

Statistical Reviewer's Comments:

At the test-of-cure assessment, the cure rate for monomicrobial infections in the ME population was 78.9% in the tigecycline group and 79.7% in the vancomycin/ aztreonam group. For polymicrobial infections, the cure rate was 84.1% in the tigecycline group and 75.0% in the vancomycin/aztreonam group.

3.1.1.2 Study 3074A1-305-US/WW

Study Design:

This was a phase 3, multicenter, randomized, double-blind (third-party unblinded), comparison study of the safety and efficacy of tigecycline versus vancomycin/aztreonam in Subjects with cSSSI. cSSSI includes infections that involve deep soft tissue or require significant surgical intervention or are associated with a significant underlying disease state that complicates response to treatment. Subjects were randomly assigned in a 1:1 ratio to receive either tigecycline or vancomycin with aztreonam via intravenous (IV) administration for up to 14 days.

Objectives:

The primary objective was to determine the safety and the efficacy of tigecycline as compared with vancomycin/aztreonam in treating hospitalized subjects with complicated skin and/or skin structure infections (cSSSI).

Primary Efficacy Endpoint:

The primary efficacy endpoint was clinical response in the CE and c-mITT populations (co-primary populations) at the test-of-cure assessment.

Patient Disposition, Demographic and Baseline Characteristics**Disposition of Subjects:**

A total of 557 subjects were enrolled into the study; 11 were screen failures. The other 546 subjects were randomly assigned to 1 of the treatment arms and constituted the intent-to-treat (ITT) population. Three (3) subjects did not receive study drug. Altogether, 543 subjects received the study drug and constituted the mITT population: 274 subjects received tigecycline and 269 subjects received vancomycin/aztreonam.

Statistical Reviewers Comments:

Similar to the previous study, the sponsor's analysis at the TOC included patients up to 92 days after the last dose of study drug in the primary efficacy analysis. In the FDA analysis, the primary efficacy endpoint of clinical response was evaluated for duration of up to 35 days at the test-of-cure assessment. The primary efficacy assessments were based on CE and c-mITT as co-primary populations and analysis based on the ITT population was also evaluated to assess the robustness of evidence.

Noninferiority of tigecycline compared with vancomycin/aztreonam for clinical and microbiologic responses was evaluated based on a 2-sided 95% confidence interval (CI) for the true difference in efficacy (tigecycline - vancomycin/aztreonam). Noninferiority was concluded in this review if the lower limit of the 2-sided 95% CI for the true difference in efficacy was higher than -15%.

Table 6: 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 (99.6)	269 (99.3)	543 (99.5)

cSSSI did not meet severity criteria	13	10	23
Clinical mITT (c-mITT)	261 (94.9)	259 (95.6)	520 (95.2)
Did not meet clinical evaluability criteria	38	46	84
Clinically evaluable (CE)	223 (81.1)	213 (78.6)	436 (79.9)
No baseline and/or susceptible pathogens	59	65	124
Microbiologically evaluable (ME)	164 (59.6)	148 (54.6)	312 (57.1)
Microbiologic mITT (m-mITT)	209 (76.0)	203 (74.9)	412 (75.5)
No baseline pathogens (from c-mITT population)	52	56	108

Sponsor's Table: ITT = all randomized subjects; mITT = ITT subjects who received at least 1 dose of study drug; c-mITT = mITT subjects with evidence of cSSSI; m-mITT = mITT subjects with identified baseline pathogen.

The demographic and other baseline characteristics (age, sex, ethnicity, weight, and creatinine clearance) of the mITT population, are given below in Table 7.

Table 7: Demographic and Baseline Characteristics of the mITT Population

Characteristic	Tigecycline (n = 274)	Vancomycin/ Aztreonam (n = 269)	Total (n = 543)
Age, years			
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 (%)			
Male	167 (60.9)	163 (60.6)	330 (60.8)
Female	107 (39.1)	106 (39.4)	213 (39.2)
Ethnic origin, n (%)			
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			
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			
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
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Statistical Reviewer's Comments:

As given in the table 7, the demographic and other baseline characteristics of the mITT population, including age, sex, ethnicity, weight, and creatinine clearance were almost similar in the two treatment groups.

EFFICACY RESULTS:

Table 8: Clinical Response at TOC: (CE, c-mITT and ITT populations)

Visit	Response	Tigecycline		Vancomycin/ Aztreonam		95% CI
		n/N	%	n/N	%	
CE Population						
Test-of-Cure	Cure	200/223	89.7%	201/213	94.4%	(-10.2, 0.8)
	Failure	23/223	10.3%	12/213	5.6%	
c-mITT Population						
Test-of-Cure	Cure	220/261	84.3%	225/259	86.9%	(-9.0, 3.8)
	Failure	31/261	11.9%	26/259	10.0%	
	Indeterminate	10/261	3.8%	8/259	3.1%	
ITT Population						
Test-of-Cure	Cure	231/ 275	84.0%	235/ 271	86.7%	(-9.0, 3.6)
	Failure	33/ 275	12.0%	26/ 271	9.6%	
	Indeterminate	11/ 275	4.0%	10/ 271	3.7%	

Statistical Reviewer's Comments:

In the Sponsor's analysis (Table 8), the clinical response was evaluated at the TOC assessment, 92 days after the last dose of study drug. Based on the 95% Confidence Interval (CI) for the difference in clinical cure rates at the TOC, Tigecycline demonstrated noninferiority to vancomycin/aztreonam using a non-inferiority margin of 15%. Tigecycline demonstrated noninferiority to vancomycin/aztreonam in the CE (95%CI: -10.2, 0.8), cmITT (95%CI: -9.0, 3.8) and ITT (95%CI: -9.0, 3.6) populations.

Table 9: FDA Analysis: Clinical Response (TOC Visit <=35 days post-therapy)

Visit	Response	Tigecycline		Vancomycin/ Aztreonam		95% CI
		n/N	%	n/N	%	
CE Population						
Test-of-Cure	Cure	195/218	89.4%	193/205	94.1%	(-10.4, 1.0)
	Failure	23/218	10.6%	12/205	5.9%	
c-mITT Population						
Test-of-Cure	Cure	212/253	83.8%	216/250	86.4%	(-9.2, 4.0)
	Failure	31/253	12.3%	26/250	10.4%	
	Indeterminate	10/253	4.0%	8/250	3.2%	

Statistical Reviewer's Comments:

In the FDA analyses (Table 9), clinical response was evaluated for duration of up to 35 days at the test-of-cure assessment. The Confidence Intervals in the CE and cmITT populations were; CE (95%CI: (-10.4, 1.0) and cmITT (95%CI: -9.2, 4.0). Based on the 95% Confidence Interval (CI) for the difference in clinical cure rates at the TOC, Tigecycline demonstrated noninferiority to vancomycin/aztreonam using a non-inferiority margin of 15%. The efficacy conclusions were not affected upon evaluating the clinical responses at TOC<=35 days or TOC<=92 days after the last dose of study drug.

**Table 10: Clinical Response by Monomicrobial/Polymicrobial Infection:
ME population**

TOC	Infection	Response	Tigecycline	Vancomycin/ Aztreonam	95% CI
	Monomicrobial	Cure	83/90 (92.2%)	78/81 (96.3%)	(-12.6, 4.6)
		Failure	7/90	3/81	
	Polymicrobial	Cure	65/74 (87.8%)	65/67 (97.0%)	(-19.6, 1.2)
		Failure	9/74	2/67	

Statistical Reviewer's Comments:

At the test-of-cure assessment, the cure rates for monomicrobial infections in the ME population was 92.2% in the tigecycline group and 96.3% in the vancomycin/ aztreonam group. For polymicrobial infections, the cure rate was 87.8% in the tigecycline group and 97.0% in the vancomycin/aztreonam group.

3.1.2 Complicated Intra Abdomen Infections (cIAI)

3.1.2.1 Study 3074A1-301-WW

Study Design:

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.

Duration of Subject Participation (Based on the protocol)

Approximately 4 to 7 weeks: up to 1 day for screening, up to 2 weeks of test article administration, 9 days (+5 days) post therapy for an early follow-up visit, and ≥ 14 days and not more than 35 days after the last dose of test article for the test-of-cure assessment. Subjects who are clinical failures will have the test-of-cure assessment performed prior to the initiation of non-study antibiotic.

Primary Objective:

The primary objective of the study was to determine the efficacy and safety of tigecycline compared with imipenem/cilastatin in treating hospitalized subjects with cIAI. The primary efficacy endpoint was the clinical response within the ME and m-mITT populations (co-primary populations) at the test-of-cure assessment.

Cure: The study medication and the initial intervention (operative or radiologically controlled drainage procedure) resolved the intra-abdominal infection.

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

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.

Statistical Reviewers Comments:

In the FDA analysis, the primary efficacy endpoint of clinical response was evaluated for duration of up to 35 days at the test-of-cure assessment. The primary efficacy assessments were based on ME and micro-mITT as co-primary populations and analysis based on the ITT population was also evaluated in this review to assess the robustness of evidence.

Noninferiority of tigecycline compared with vancomycin/aztreonam for clinical and microbiologic responses was evaluated based on a 2-sided 95% confidence interval (CI) for the true difference in efficacy (tigecycline - imipenem/cilastatin). Noninferiority was concluded in this review if the lower limit of the 2-sided 95% CI for the true difference in efficacy was higher than -15%.

Disposition of Subjects:

A total of 898 subjects were screened into the study; 64 subjects were screen failures and the remaining 834 subjects were randomly assigned to 1 of the treatment arms and constituted the ITT population. A total of 825 subjects received the study drug and constituted the mITT population: 413 subjects received tigecycline and 412 subjects received imipenem/cilastatin.

Table 11: Number of Subjects

Population	Tigecycline n (% ITT)	Imipenem/Cilastatin n (% ITT)	Total n (% ITT)
Screened			898
Screen Failures			64
Intent-to-Treat (ITT)	417	417	834
No treatment received	4	5	9
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

Sponsor's Table

mITT = modified intent-to-treat, ie, all intent-to-treat subjects who received at least 1 dose of study drug, c-mITT = clinical mITT, ie, mITT subjects who met minimal disease requirements with clinical evidence of cIAI, CE = clinically evaluable, ie, c-mITT subjects who met inclusion/exclusion criteria, received appropriate and sufficient treatment to determine cure or failure, had a test-of-cure assessment of cure or failure, and 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.

Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics of the mITT population, including age, sex, ethnicity, weight, Creatinine Clearance (CLCR) and APACHE scores are given below.

Table 12: Demographic and Baseline Characteristics of the mITT Population

Characteristic	Tigecycline (n = 413)	Imipenem/ Cilastatin (n = 412)	Total (n = 825)
Age, years			
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 (%)			
Male	274 (66.3)	263 (63.8)	537 (65.1)
Female	139 (33.7)	149(36.2)	288 (34.9)
Ethnic origin, n (%)			
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			
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			
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			
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)
> 15	16 (3.9)	14 (3.4)	30 (3.6)

Sponsor's Table

Statistical Reviewer's Comments:

Based on the demographic and other baseline characteristics of the mITT population, there were no major differences observed between the two treatment groups. They were almost similar with respect to age, sex, ethnicity, weight, creatinine clearance and APACHE scores were almost similar in the two treatment groups.

Efficacy Analyses:

Statistical Reviewer's Comments:

The efficacy endpoint of clinical response was evaluated based on the co-primary ME and m-mITT populations at the test-of-cure assessment. Non-inferiority of tigecycline to imipenem/cilastatin was concluded, if the lower bound of the 2-sided 95% confidence interval (CI) for the difference in cure proportion was higher than the margin of -15%.

Table 13: Clinical Response: Microbiological Evaluable (ME) Population

TOC	APACHE Score	Tigecycline		Imipenem/Cilastatin		Test for Difference (95%CI)
		n/N	%	n/N	%	
Cure	≤ 15	195/238	81.9	208/247	84.2	(-9.4, 4.8)
	> 15	4/9	44.4	2/8	25.0	(-36.6, 75.5)
Overall	Unadjusted	199/247	80.6	210/255	82.4	(-9.0, 5.4)
	Adjusted					(-8.4, 5.1)
Failure		48/247	19.4	45/255	17.6	

Table 14: Clinical Response at TOC: Microbiological mITT Population

	APACHE Score	Tigecycline		Imipenem/Cilastatin		Test for Difference (95%CI)
		n/N	%	n/N	%	
Cure	≤ 15	219/295	74.2	242/302	80.1	(-13.0, 1.2)
	> 15	8/14	57.1	2/10	20.0	(-7.3, 81.6)
Overall	Unadjusted	227/309	73.5	244/312	78.2	(-11.8, 2.3)
	Adjusted					(-11.0, 2.5)
Failure		63/309	20.4	55/312	17.6	
Indeterminate		19/309	6.1	13/312	4.2	

Table 15: Clinical Response: ITT Population

Test-of-Cure	APACHE Score	Tigecycline		Imipenem/Cilastatin		Test for Difference (95%CI)
		n/N	%	n/N	%	
Cure	≤ 15	295/401	73.6	324/404	80.2	(-12.7, -0.6) (-20.3, 59.5)
	> 15	9/17	52.9	5/15		
Overall	Unadjusted	304/418	72.7	329/419	33.3	(-11.8, 0.3) (-11.5, 0.1)
	Adjusted					
Failure		81/418	19.4	64/419	78.5	
Indeterminate		33/418	7.9	26/419	15.3	

Statistical Reviewer's Comments:

In the Sponsor's analysis (Tables 13-15), the clinical response was evaluated at the TOC assessment, 92 days after the last dose of study drug. Based on the 95% CI for the difference in clinical response (unadjusted) at the TOC, Tigecycline demonstrated noninferiority to imipenem/cilastatin in the ME (95% CI: -9.0, 5.4), micro-mITT (95% CI: -11.8, 2.3) and ITT (95% CI: -11.8, 0.3).

Table 16: FDA Analysis: Clinical Response in the Microbiological Evaluable (ME) Population (TOC Visit ≤35 days post-therapy)

Visit Response	APACHE Score	Tigecycline		Imipenem/Cilastatin		Test for Difference (95%CI)
		n/N	%	n/N	%	
Overall	Unadjusted	193/241	80.1%	206/251	82.1%	(-9.3, 5.3)
Failure		48/241	19.9%	45/251	17.9%	

Table 17: FDA Analysis: Clinical Response in the Microbiological mITT Population (TOC Visit ≤35 days post-therapy)

Visit Response	APACHE Score	Tigecycline		Imipenem/Cilastatin		Test for Difference (95%CI)
		n/N	%	n/N	%	
Overall	Unadjusted	221/302	73.2%	240/308	77.9%	(-11.9, 2.4)
Failure		63/302	20.9%	55/308	17.9%	
Indeterminate		18/302	5.9%	13/308	4.2%	

Statistical Reviewer's Comments:

In the FDA analyses (Tables 16-17), clinical response (unadjusted) was evaluated for a duration of up to 35 days at the test-of-cure assessment. The 95% Confidence Intervals in the ME and micro-mITT populations were; ME (95%CI: (-9.3, 5.3) and micro-mITT (95%CI: (-11.9, 2.4). Tigecycline demonstrated noninferiority to imipenem/cilastatin in the ME and micro-mITT using a margin of 15%. The efficacy conclusions were not changed upon evaluating the clinical responses at TOC<=35 days or TOC<=92 days after the last dose of study drug.

3.1.2.2 Study 3074A1-306-WW**Study Design:**

This was a phase 3, multi-center, double-blind (third-party unblinded) study comparing the safety and efficacy of tigecycline to imipenem/cilastatin in hospitalized subjects with complicated intra-abdominal infections.

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.

Duration of Subject Participation (Based on the protocol)

Approximately 4 to 7 weeks: up to 1 day for screening, up to 2 weeks of test article administration, 9 days (+5 days) post therapy for an early follow-up visit, and ≥ 14 days and not more than 35 days after the last dose of test article for the test-of-cure assessment. Subjects who are clinical failures will have the test-of-cure assessment performed prior to the initiation of non-study antibiotic. No Day 9 post therapy follow-up visit will be performed for subjects who are declared failures.

Primary Efficacy Variables

The primary efficacy endpoint was the clinical response in the ME and m-mITT populations (co-primary populations) at the test-of-cure assessment.

Cure: The study medication and the initial intervention (operative or radiologically controlled drainage procedure) resolved the intra-abdominal infection.

Disposition of Subjects:

A total of 861 subjects were screened for the study; 37 were screen failures (10 additional subjects were screen failures that were not captured in the database. 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 18: Number of Subjects in Each Population Category

Population	Tigecycline n (% ITT)	Imipenem/ Cilastatin n (% ITT)	Total n (% ITT)
Screened			861
Screen failures			37
Intent-to-treat (ITT)	409	415	824
No treatment received	5	2	7
Modified intent-to-treat (mITT)	404 (98.8)	413 (99.5)	817 (99.2)
cIAI did not meet severity criteria Clinical mITT (c-mITT)	11	12	23
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)	322 (78.7)	319 (76.9)	641 (77.8)
No baseline isolate identified (from c-mITT population)	71	82	153

Sponsor's Table. ITT = all randomized subjects , mITT = ITT subjects who received at least 1 dose of study drug
c-mITT = mITT subjects with evidence of cIAI , m-mITT = c-mITT subjects with identified baseline isolate

Statistical Reviewers Comments:

In the FDA analysis, the primary efficacy endpoint of clinical response was evaluated for duration of up to 35 days at the test-of-cure assessment as in the previous study. The primary efficacy assessments were based on ME and micro-mITT as co-primary populations and analysis based on the ITT population was also evaluated in this review to assess the robustness of evidence.

Noninferiority of tigecycline compared with vancomycin/aztreonam for clinical and microbiologic responses was evaluated based on a 2-sided 95% confidence interval (CI) for the true difference in efficacy (tigecycline - imipenem/cilastatin). Noninferiority was concluded in this review if the lower limit of the 2-sided 95% CI for the true difference in efficacy was higher than -15%.

Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics of the mITT population, including age, sex, Ethnicity, weight, and Creatinine Clearance (CLCR) and APACHE-II score are shown below.

Table 19: Demographic and Baseline Characteristics: mITT Population

Characteristic	Tigecycline (n = 404)	Imipenem/ Cilastatin (n = 413)	Total (n = 817)
Age, years			
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 (%)			
Male	239 (59.2)	240 (58.1)	479 (58.6)
Female	165 (40.8)	173 (41.9)	338 (41.4)
Ethnic origin, n (%)			
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			
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 clearance (CLCR) mL/min/1.73m ²			
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			
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 by Category, n (%)			
≤15	395 (97.8)	410 (99.3)	805 (98.5)
>15	9 (2.2)	3 (0.7)	12 (1.5)

Sponsor's Table

Statistical Reviewer's Comments:

There were no major differences observed between treatment groups with respect to the demographic and other baseline characteristics (age, sex, ethnicity, weight, CLCR and APACHE-II scores) in the mITT population.

Table 20: Clinical Response: Microbiological Evaluable (ME) Population

Test-of-cure		Tigecycline		Imipenem/ Cilastatin		Test for Difference (95%CI)
		n/N	%	n/N	%	
	APACHE Score					
Cure	≤15	237/260	91.2%	232/258	89.9	(-4.2, 6.7)
	> 15	5/ 5	100.0%	0/ 0		
Overall	Unadjusted	242/265	91.3%	232/258	89.9	(-4.0, 6.8)
	Adjusted					N/A
Failure		23/265	8.7%	26/258	10.1	

Table 21: Clinical Response: Microbiological mITT Population

Test-of-Cure		Tigecycline		Imipenem/ Cilastatin		Test for Difference (95%CI)
		n/N	%	n/N	%	
	APACHE Score					
Cure	≤ 15	271/314	86.3%	268/316	84.8%	(-4.3, 7.3)
	> 15	8/8	100.0%	2/3	66.7%	(-42.9, 100.0)
	Unadjusted	279/322	86.6%	270/319	84.6%	(-3.7, 7.7)
	Adjusted					(-3.7, 7.5)
Failure		34/322	10.6%	36/319	11.3%	
Indeterminate		9/322	2.8%	13/319	4.1%	

Table 22: Clinical Response: ITT Population

Test-of-Cure		Tigecycline		Imipenem/ Cilastatin		Test for Difference (95%CI)
		n/N	%	n/N	%	
	APACHE Score					
Cure	≤ 15	336/400	84.0%	347/412	84.2%	(-5.5, 5.1)
	> 15	9/9	100.0%	2/3	66.7%	(-42.2, 100.0)
Overall	Unadjusted	345/409	84.4%	349/415	84.1%	(-5.0, 5.5)
	Adjusted					(-4.9, 5.3)
Failure		44/409	10.8%	46/415	11.1%	
Indeterminate		20/409	4.9%	20/415	4.8%	

Statistical Reviewer's Comments:

In the Sponsor's analysis (Tables 20-22), the clinical response (unadjusted) was evaluated at the TOC assessment, 92 days after the last dose of study drug. Based on the 95% CI for the difference in clinical response at the TOC, Tigecycline demonstrated noninferiority to imipenem/cilastatin in the ME (95% CI: -4.0, 6.8), micro-mITT (95% CI: -3.7, 7.7) and ITT (95% CI: -5.0, 5.5).

Table 23: FDA Analysis: Clinical Response in the Microbiological Evaluable (ME) Population TOC Visit <=35 days post-therapy

	APACHE Score	Tigecycline		Imipenem/Cilastatin		Test for Difference (95%CI)
		n/N	%	n/N	%	
Overall	Unadjusted	215/238	90.3%	216/242	89.3%	(-4.8, 6.9)
Failure		23/238	9.7%	26/242	10.7%	

Table 24: FDA Analysis: Clinical Response in the Microbiological mITT Population

Test-of-Cure	APACHE Score	Tigecycline		Imipenem/Cilastatin		Test for Difference (95%CI)
		n/N	%	n/N	%	
Overall	Unadjusted	246/288	85.4%	248/296	83.4%	(-4.6, 7.8)
Failure		34/288	11.8%	35/296	11.8%	
Indeterminate		8/288	2.8%	13/296	4.4%	

Statistical Reviewer's Comments:

In the FDA analyses (Tables 23-24), clinical response (unadjusted) was evaluated for a duration of up to 35 days at the test-of-cure assessment. The 95% Confidence Intervals in the ME and micro-mITT populations were; ME (95%CI: -4.8, 6.9) and micro-mITT (95%CI: -4.6, 7.8). Tigecycline demonstrated noninferiority to imipenem/cilastatin in the ME and micro-mITT using a margin of 15%. The efficacy conclusions were not changed upon evaluating the clinical responses at TOC<=35 days or TOC<=92 days after the last dose of study drug.

3.2 Evaluation of Safety

Mortality Analyses (Overall)

Based on the submission, a total of 57 subject deaths were reported from studies 300, 301, 305, and 306, and 307 (Table 25). This review was only focused on the controlled studies 300, 305, 301 and 306. There were 54 deaths reported in total from these studies.

Table 25: Subjects in the Phase 3 Studies with Adverse Events Resulting in Death: Number (%) of Subjects Who Died

Indication	Tigecycline n/N (%)		Comparator Treatment n/N (%)
			Vancomycin/Aztreonam
cSSSI	6/566	(1.1)	1/550 (0.2)
cIAI	26 ^a /817	(3.2)	Imipenem/Cilastatin 21 ^b /825 (2.5)
cSSSI and cIAI	32 ^a /1383	(2.3)	Combined Comparators 22 ^b /1375 (1.6)
RPc	3/32	(9.4)	0/7 (0.0)

Sponsor's Table: Source: /Clinical R&D/Clinical Programming SAS reports/3074A1 GAR-936/ISS/DEATH DOCUMENT/ae5_dth, 18FEB05, 08:33

a: Includes 2 deaths that occurred after the active reporting period and were not included in the database.

b: Includes 4 deaths that occurred after the active reporting period and were not included in the database.

c: Subjects in this study (RP = resistant pathogen) were randomized 3:1 to tigecycline or an active control.

Statistical Reviewer's Comments:

A total of 54 deaths were reported from studies 300, 301, 305, and 306. In studies submitted for Complicated Skin and Skin Structure Infections, there were 6 deaths reported in the Tigecycline arm. Of which, 5 deaths were reported from study 3074A1-300-US/CA and one death in study 3074A1-305-US/WW. In studies submitted for Complicated Intra Abdomen Infections, there were 26 deaths reported in the Tigecycline arm. Of which, 19 deaths were reported from study 3074A1-301 and 7 deaths reported from study 3074A1-306-WW. Based on the review, no specific safety issues could be attributed to the cause of these deaths. Dr. Cooper's clinical review would provide more detailed safety information.

For Complicated Intra Abdomen Infection studies, increased age, increased APACHE II score, and baseline clinical diagnosis were not the same between subjects who died and subjects who have survived (based on sponsor's submission). The mean age of subjects who died were: 59.4 years in the tigecycline group; 64.4 years in the comparator group and subjects who survived were approximately 47.2 years in both treatment groups. Mean APACHE scores, which are available for subjects in the cIAI studies only, were relatively higher in subjects who died (9.83 in the tigecycline group; 9.18 in the comparator group).

Table 26: Median Days From Start of Treatment to Date of Death: Subjects Who Died in cSSSI Studies

Study Number	Tigecycline		Vancomycin/Aztreonam	
	No. Deaths	Days	No. Deaths	Days
300	5	11	1	11
305	1	8	0	n/a
Total	6	10.5	1	11

Sponsor's Table Source: 3074A1 GAR-936/300/mdeath_onset_3, 17FEB05; 3074A1 GAR-936/305/mdeath_onset_3, 17FEB05; 3074A1 GAR-936/300_305/mdeath_onset_3, 17FEB05.

Statistical Reviewer's Comments:

In study 300, there were 5 deaths reported in the Tigecycline arm and 1 death in the Vancomycin/Aztreonam arm. The median "days to death" was 11 days in the tigecycline arm and for the one death in the Vancomycin/Aztreonam group, the time to death was 11 days. In study 305, 1 death was reported with a time to death of 8 days.

Table 27: 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

Statistical Reviewer's Comments:

Among the 5 deaths reported in study 300, there was no visible trend observed based on the distribution of "days to death" (Table 27). 4/5 deaths were related to non-infection.

Table 28: Median Days From Start of Treatment to Date of Death: Subjects Who Died in cIAI Studies

Median Days From Start of Treatment to Date of Death: Subjects Who Died in cIAI Studies				
Study Number	Tigecycline		Imipenem/Cilastatin	
	No. Deaths	Days	No. Deaths	Days
301	19	10	12	11
306	7	22	5	13
Total	26	12.5	17	11

Statistical Reviewer's Comments:

In study 301, the median "days to death" was 10 days in the tigecycline arm and 11 days in the Imipenem/Cilastatin arm. In study 306, the median "days to death" was 22 days in the tigecycline arm and 13 days in the Imipenem/Cilastatin arm. There were more deaths reported in study 301 compared to study 306.

Table 29: Demographic and Clinical Characteristics of Subjects in the cIAI Studies Who Died

Characteristic	Tigecycline (n = 26)	Imipenem/ Cilastatin (n = 21)
Distribution of Days to Death, n (%)		
1	1	0
2	0	2
3	1	0
4	4	0
6	0	2
8	1	0
9	0	2
10	3	2
11	0	3
12	2	0
13	2	1
15	3	0
16	0	1
17	2	2
20	1	0
22	1	0
27	1	0
30	1	0
31	0	1
32	0	1
41	0	1
45	1	0
49	1	0
53	1	0
93	0	1
unknown	-	2

Statistical Reviewer's Comments:

Based on the distribution of "days to death", there was no clustering of events observed in either of the treatment arms. There was no trend observed in the distribution of days.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Statistical Reviewers Comments:

Clinical responses in the special or subgroup populations (based on Gender, Race and Age) were reviewed to evaluate the evidence comparing tigecycline to imipenem/cilastatin. It should be noted that these subgroup analyses were not powered for non-inferiority testing.

Study 3074A1-300-US/CA:

Table 30: Clinical Response at TOC by Age (<65 or ≥65): c-mITT Population

Age group	Response	Tigecycline		Vancomycin/Aztreonam		95% CI
		n/N (%)		n/N	%	
<65	Cure	175/ 232 (75.4)		165/ 217 (76.0)		(-8.8, 7.7)
	Failure	37/ 232 (15.9)		39/ 217 (18.0)		
	Indeterminate	20/ 232 (8.6)		13/ 217 (6.0)		
≥65	Cure	34/ 45 (75.6)		35/ 43 (81.4)		(-24.0, 13.0)
	Failure	11/ 45 (24.4)		7/ 43 (16.3)		
	Indeterminate	0/ 45 (0.0)		1/ 43 (2.3)		

Table 31: Clinical Response at TOC by Gender: c-mITT Population

Gender	Response	Tigecycline		Vancomycin/Aztreonam		95% CI
		n/N	%	n/N	%	
Male	Cure	127/170	74.7	137/176	77.8	(-12.5, 6.2)
	Failure	29/170	17.1	25/176	14.2	
	Indeterminate	14/170	8.2	14/176	8.0	
Female	Cure	82/107	76.6	63/84	75.0	(-11.0, 14.8)
	Failure	19/107	17.8	21/84	25.0	
	Indeterminate	6/107	5.6	0/84	0.0	

Table 32: Clinical Response by Ethnic Origin: c-mITT Population

Race	Response	Tigecycline n/N(%)	Vancomycin/ Aztreonam n/N (%)	95% CI
White	Cure	107/ 144 (74.3)	109/ 135 (80.7)	(-16.5, 3.9)
	Failure	27/ 144 (18.8)	20/ 135 (14.8)	
	Indeterminate	10/ 144 (6.9)	6/ 135 (4.4)	
Black	Cure	15/ 27 (55.6)	12/ 22 (54.5)	(-27.5, 29.6)
	Failure	7/ 27 (25.9)	7/ 22 (31.8)	
	Indeterminate	5/ 27 (18.5)	3/ 22 (13.6)	
Oriental (Asian)	Cure	1/ 1 (100.0)	1/ 1 (100.0)	
	Failure	0/ 1 (0.0)	0/ 1 (0.0)	
	Indeterminate	0/ 1 (0.0)	0/ 1 (0.0)	
Hispanic	Cure	45/ 52 (86.5)	45/ 50 (90.0)	(-17.8, 11.2)
	Failure	3/ 52 (5.8)	3/ 50 (6.0)	
	Indeterminate	4/ 52 (7.7)	2/ 50 (4.0)	
Other	Cure	41/ 53 (77.4)	33/ 52 (63.5)	(-4.8, 31.5)
	Failure	11/ 53 (20.8)	16/ 52 (30.8)	
	Indeterminate	1/ 53 (1.9)	3/ 52 (5.8)	

Study 3074A1-305-US/WW:

Table 33: Clinical Response at TOC by Age (<65 or ≥65): c-mITT Population

Age group	Response	Tigecycline n/N (%)	Vancomycin/ Aztreonam n/N (%)	95% CI
<65	Cure	181/ 210 (86.2)	167/ 191 (87.4)	(-8.2, 5.9)
	Failure	22/ 210 (10.5)	17/ 191 (8.9)	
	Indeterminate	7/ 210 (3.3)	7/ 191 (3.7)	
≥65	Cure	39/ 51 (76.5)	58/ 68 (85.3)	(-24.8, 6.3)
	Failure	9/ 51 (17.6)	9/ 68 (13.2)	
	Indeterminate	3/ 51 (5.9)	1/ 68 (1.5)	

Table 34: Clinical Response at TOC by Gender (c-mITT Populations)

Gender	Response	Tigecycline		Vancomycin/Aztreonam		95% CI
		n/N	%	n/N	%	
Male	Cure	139/ 162	85.8	134/ 157	85.4	(-7.8, 8.7)
	Failure	14/ 162	8.6	18/ 157	11.5	
	Indeterminate	9/ 162	5.6	5/ 157	3.2	
Female	Cure	81/ 99	81.8	91/ 102	89.2	(-18.0, 3.1)
	Failure	17/ 99	17.2	8/ 102	7.8	
	Indeterminate	1/ 99	1.0	3/ 102	2.9	

Table 35: Clinical Response by Ethnic Origin: c-mITT Population

Race	Response	Tigecycline n/N(%)	Vancomycin/ Aztreonam n/N (%)	95% CI
White	Cure	185/ 218 (84.9)	191/ 219 (87.2)	(-9.2, 4.5)
	Failure	25/ 218 (11.5)	22/ 219 (10.0)	
	Indeterminate	8/ 218 (3.7)	6/ 219 (2.7)	
Black	Cure	17/ 20 (85.0)	19/ 20 (95.0)	(-34.3, 14.6)
	Failure	1/ 20 (5.0)	0/ 20 (0.0)	
	Indeterminate	2/ 20 (10.0)	1/ 20 (5.0)	
Oriental (Asian)	Cure	11/ 15 (73.3)	12/ 16 (75.0)	(-34.7, 31.1)
	Failure	4/ 15 (26.7)	3/ 16 (18.8)	
	Indeterminate	0/ 15 (0.0)	1/ 16 (6.3)	
Other	Cure	7/ 8 (87.5)	3/ 4 (75.0)	(-34.7, 66.9)
	Failure	1/ 8 (12.5)	1/ 4 (25.0)	
	Indeterminate	0/ 8 (0.0)	0/ 4 (0.0)	

Statistical Reviewers Comments:

Based on Tables 30-35, there were numerical differences observed in these subgroups with respect to gender, race and age. However, numbers of subjects were small in the sub groups and were reflected in the wide confidence intervals. Efficacy conclusions based on these subgroups must be drawn with caution.

Study 3074A1-301-WW:

Table 36: Clinical Response by Age (<65 or ≥65): Microbiologically Evaluable Population

Age	Response	Tigecycline		Imipenem/Cilastatin		95%CI
		n/N	%	n/N	%	
<65	Cure	171/210	81.4	188/223	84.3	(-10.4, 4.6)
	Failure	39/210	18.6	35/223	15.7	
≥65	Cure	28/ 37	75.7	22/ 32	68.8	(-15.6, 29.3)
	Failure	9/ 37	24.3	10/ 32	31.3	

Table 37: Clinical Response by Gender: Microbiologically Evaluable Population

Gender	Response	Tigecycline		Imipenem/Cilastatin		95%CI
		n/N	%	n/N	%	
Male	Cure	144/173	83.2	139/166	83.7	(-8.8, 7.9)
	Failure	29/173	16.8	27/166	16.3	
Female	Cure	55/ 74	74.3	71/ 89	79.8	(-19.3, 8.2)
	Failure	19/ 74	25.7	18/ 89	20.2	

Table 38: Clinical Response by Ethnic Origin: Microbiologically Evaluable Population

Ethnic origin	Response	Tigecycline		Imipenem/Cilastatin		95%CI
		n/N	%	n/N	%	
White	Cure	81/104	77.9	82/106	77.4	(-11.4, 12.4)
	Failure	23/104	22.1	24/106	22.6	
Black	Cure	12/ 16	75.0	19/ 25	76.0	(-31.9, 26.2)
	Failure	4/ 16	25.0	6/ 25	24.0	
Asian	Cure	24/ 30	80.0	26/ 30	86.7	(-27.8, 15.0)
	Failure	6/ 30	20.0	4/ 30	13.3	
Hispanic	Cure	44/ 54	81.5	39/ 44	88.6	(-22.3, 9.4)
	Failure	10/ 54	18.5	5/ 44	11.4	
Other	Cure	38/ 43	88.4	44/ 50	88.0	(-15.5, 15.3)
	Failure	5/43	11.6	6/50	12.0	

Study 3074A1-306-WW:

Table 39: Clinical Response by Age (<65 or ≥65): ME Population

Age	Response	Tigecycline		Imipenem/Cilastatin		95% CI
		n/N	%	n/N	%	
<65	Cure	187/202	92.6	192/207	92.8	(-5.8, 5.4)
	Failure	15/202	7.4	15/207	7.2	
≥65	Cure	55/ 63	87.3	40/ 51	78.4	(-6.1, 24.5)
	Failure	8/ 63	12.7	11/ 51	21.6	

Table 40: Clinical Response by Gender: ME Population

Sex	Response	Tigecycline		Imipenem/Cilastatin		95% CI
		n/N	%	n/N	%	
Male	Cure	142/157	90.4	144/161	89.4	(-6.3, 8.2)
	Failure	15/157	9.6	17/161	10.6	
Female	Cure	100/108	92.6	88/ 97	90.7	(-6.6, 10.8)
	Failure	8/108	7.4	9/ 97	9.3	

Table 41: Clinical Response by Ethnic Origin: ME Population

Ethnic origin	Response	Tigecycline		Imipenem/Cilastatin		95% CI
		n/N	%	n/N	%	
White	Cure	222/238	93.3	207/229	90.4	(-2.5, 8.4)
	Failure	16/238	6.7	22/229	9.6	
Black	Cure	4/ 6	66.7	6/ 7	85.7	(-63.7, 32.5)
	Failure	2/ 6	33.3	1/ 7	14.3	
Asian	Cure	12/ 16	75.0	16/ 17	94.1	(-47.3, 10.8)
	Failure	4/ 16	25.0	1/ 17	5.9	
Other	Cure	4/ 5	80.0	3/ 5	60.0	(-39.9, 67.0)
	Failure	1/ 5	20.0	2/ 5	40.0	

Statistical Reviewers Comments:

Based on Tables 36-41, there were numerical differences observed in subgroups with respect to gender, race and age. However, the numbers of subjects in the subgroups were small. Conclusions based on these subgroups must be drawn with caution.

4.2 Other Special /Subgroup Populations

No other special/subgroups were reviewed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Complicated Skin and Skin Structure Infections:

In study 3074A1-300-US/CA, the primary efficacy endpoint was the clinical response at the test-of-cure assessment in the CE and cmITT populations. In the FDA analyses (Table 4), clinical response was evaluated for duration of up to 35 days at the test-of-cure assessment as specified in the protocol. The Confidence Intervals in the CE, cmITT and ITT populations were; CE (95%CI: -7.8, 8.3), cmITT (95%CI: -8.8, 6.6) and ITT (95% CI: -9.2, 5.6). Based on the 95% Confidence Interval (CI) for the difference in clinical cure rates at the TOC in all these three populations, Tigecycline demonstrated noninferiority to vancomycin/aztreonam using a non-inferiority margin of 15%. The efficacy conclusions remained the same based on evaluating the clinical responses at the TOC \leq 35 days or TOC \leq 92 days after the last dose of study drug.

In study 3074A1-305-US/WW, the primary efficacy endpoint was the clinical response at the test-of-cure assessment in the CE and cmITT populations. In the FDA analyses (Table 9), as per the protocol, the clinical response was evaluated for duration of up to 35 days at the test-of-cure assessment. The Confidence Intervals in the CE, cmITT and ITT populations were; CE (95%CI: -10.4, 1.0), cmITT (95%CI: -9.2, 4.0) and ITT (95% CI: -9.0, 3.6). Based on the 95% Confidence Interval (CI) for the difference in clinical cure rates at the TOC in these populations, Tigecycline demonstrated noninferiority to vancomycin/aztreonam using a non-inferiority margin of 15%. The efficacy conclusions were not affected upon evaluating the clinical responses at TOC \leq 35 days or TOC \leq 92 days after the last dose of study drug.

Complicated Intra Abdomen Infections (cIAI)

In study 3074A1-301-WW, the primary efficacy endpoint was the clinical response at the test-of-cure assessment in the ME and m-mITT populations. In the FDA analyses (Tables 16-17), clinical response (unadjusted) was evaluated for a duration of up to 35 days at the test-of-cure assessment. The 95% Confidence Intervals in the ME, micro-mITT and ITT populations were; ME (95%CI: -9.3, 5.3), micro-mITT (95%CI: -11.9, 2.4) and ITT (95% CI: -11.8, 0.3). Tigecycline demonstrated noninferiority to imipenem/cilastatin in the ME and micro-mITT using a margin of 15%. The efficacy conclusions were not changed upon evaluating the clinical responses at TOC \leq 35 days or TOC \leq 92 days after the last dose of study drug.

In study 3074A1-306-WW, the primary efficacy endpoint was the clinical response at the test-of-cure assessment in the ME and m-mITT populations. In the FDA analyses (Tables 23-24), clinical response (unadjusted) was evaluated for a duration of up to 35 days at the

test-of-cure assessment. The 95% Confidence Intervals in the ME, micro-mITT and ITT populations were; ME (95%CI: -4.8, 6.9), micro-mITT (95%CI: -4.6, 7.8) and ITT(95% CI: -5.0, 5.5). Tigecycline demonstrated noninferiority to imipenem/cilastatin in the ME and micro-mITT using a margin of 15%. Assessing efficacy at TOC \leq 35 days or TOC \leq 92 days after the last dose of study drug, provided consistent results.

Based on the safety review, a total of 57 deaths (in total), was reported from studies 300, 301, 305, 306, and 307. However, 54 deaths were from the controlled studies 300, 305, 301 and 306. In studies submitted for Complicated Skin and Skin Structure Infections, there were 6 deaths reported in the Tigecycline arm. Of which, 5 deaths were reported from study 3074A1-300-US/CA and one death in study 3074A1-305-US/WW. In studies submitted for Complicated Intra Abdomen Infections, there were 26 deaths reported in the Tigecycline arm. Of which, 19 deaths were reported from study 3074A1-301 and 7 deaths reported from study 3074A1-306-WW. Based on the review, no specific safety issue could be attributed to the cause of these deaths. However, Dr. Cooper's clinical review would provide detailed safety information.

5.2 Conclusions and Recommendations

Complicated Skin and Skin Structure Infections (cSSSI):

In the primary efficacy analyses of clinical response at test-of-cure, . tigecycline demonstrated noninferiority to vancomycin/aztreonam in the CE and c-mITT populations in studies 3074A1-300-US/CA and 3074A1-305-US/WW.

Complicated Intra Abdomen Infections (cIAI):

In the primary efficacy analyses of clinical response at test-of-cure, tigecycline demonstrated noninferiority to imipenem/cilastatin in the ME and micro-mITT populations in studies 3074A1-301-WW and 3074A1-306-WW.

Safety Issues

A total of 57 deaths were reported from studies 300, 301, 305, 306, and 307. However, 54 deaths were from the controlled studies 300, 305, 301 and 306. In studies submitted for Complicated Skin and Skin Structure Infections, there were 6 deaths reported in the Tigecycline arm. Of which, 5 deaths were reported from study 3074A1-300-US/CA and one death in study 3074A1-305-US/WW. In studies submitted for Complicated Intra Abdomen Infections, there were 26 deaths reported in the Tigecycline arm. Of which, 19 deaths were reported from study 3074A1-301 and 7 deaths reported from study 3074A1-306-WW. Based on the review, no specific safety issues could be attributed to the cause of these deaths. However, medical officer, Dr. Cooper's clinical review would provide more detailed safety information. Approval of this product would be based on the overall evidence of safety and efficacy and the labeling should indicate all the major safety issues for this product.

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Statistical Review of Tigecycline

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