SCIENTIFIC DISCUSSION

1 Introduction

The need for new antibacterial agents is greater than ever because of the emergence of multidrug resistance in common pathogens and the rapid emergence of new infections. Bacterial resistance is associated with treatment failures, increased mortality, and increased costs. Methicillin-resistant *S. aureus* (MRSA), glycopeptide-intermediate *S. aureus* (GISA) and glycopeptide-resistant enterococci (VRE or GRE) are of particular concern. In addition, resistance of gram-negative bacteria to all approved antimicrobials is emerging. Despite the need for new antimicrobial agents, the development of these agents is declining.

Tigecycline, a member of the glycylcycline class of antimicrobial agents, carries a glycylamido moiety attached to the 9-position of minocycline. As a bacteriostatic agent, it inhibits the growth of multiple resistant gram-positive, gram-negative, anaerobic, and atypical bacteria, including methicillin-resistant *Staphylococcus aureus* and extended-spectrum β-lactamase producers. Tigecycline remains vulnerable to the chromosomally-encoded multidrug efflux pumps of Proteeae and *Pseudomonas aeruginosa*. Consequently, tigecycline does not demonstrate significant *in vitro* activity against *Pseudomonas aeruginosa* and demonstrates only moderate *in vitro* activity against microorganisms belonging to Proteeae (*Proteus* spp., *Providencia* spp.and *Morganella morganii*).

Due to the mechanism of action, the antibacterial activity of tigecycline is not expected to be affected by mechanisms that confer specific resistance to beta-lactam drugs, glycopeptides, quinupristin/dalfopristin, linezolid or other agents potentially useful against Gram-positive and Gram-negative bacterial species.

The claimed indications were

- Complicated skin and skin structure infections, including those with methicillin-resistant *Staphylococcus aureus* (MRSA)

- Complicated intra-abdominal infections

The approved indications are:

- Complicated skin and soft tissue infections1

- Complicated intra-abdominal infections

Posology: An initial dose of 100 mg is followed by 50 mg every 12 hours by the intravenous route.

2 Quality aspects

Introduction

Composition

Tygacil contains tigecycline as the active substance. It is presented as a sterile, lyophilised powder for solution for infusion. The product is supplied in single dose type I glass vials sealed with rubber stoppers and each vial contains 53 mg of tigecycline. The product is intended to constitute with 5.3 ml 0.9% sodium chloride injection or 5 % dextrose injection to achieve a concentration of 10 mg / ml of Tigecycline. The 6 % overage facilitates withdrawal and administration of the labeled quantity (50 mg

[1] For the sake of consistency within the EU, the CHMP agreed that the proper denomination of the indication should be “complicated skin and soft tissue infections”(cSSTI) instead of “complicated skin and skin structure infections” (cSSSI). Although acknowledging the difference in the exact meaning of the two wordings, the indication is denoted henceforth as cSSTI.

/ 5 ml). The reconstituted solution should be immediately added to a 100 ml IV bag of solution for infusion (or other suitable infusion container).

Active Substance

Tigecycline is an analogue of minocycline, which is a semi-synthetic tetracycline. It is a t-butylglycyl substituted naphthacenecarboxamide freebase and its chemical name is (4S,4aS,5aR,12aS)-9-[2-(tert-butylamino)acetamido]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide.
Tigecycline is an orange-coloured odourless crystalline powder. It is slightly hygroscopic and highly ionic throughout the entire pH range. In general, tigecycline is less soluble in organic solvents than in water, due its ionic and hydrophilic nature. When the free base is dissolved in water, it is mostly present as zwitterions with a resulting pH around 8.
The structure of the active substance has been characterized by using several spectroscopic techniques including: UV-VIS, mass spectroscopy (ESI-MS and MS/MS), FT-IR and 1H-NMR and C13-NMR. .

- Manufacture

All synthetic steps of the manufacture of tigecycline have been described in detail and appropriate in process controls have been established to ensure that the active substance is consistently produced within the proposed specifications.
The levels of the impurities in active substance are supported by the results of toxicological studies and appropriate specifications have been set.

- Specification

The active substance specification includes tests for assay, identification, impurities, water content, residue on ignition, specific rotation, pH, residual solvents, microbial limits, bacterial endotoxins and heavy metalsThe corresponding analytical methods have been adequately described. At the time of the opinion there were some minor issues concerning aspects of the analytical validation that remained unresolved and will be addressed as post approval commitments.

- Stability

Three batches of the active substance manufactured in accordance with the manufacturing process described were evaluated in stability studies . Samples were stored for up to 12 months at 5°C and up to 6 months at 25°C/ 60% RH. Photostability testing was also performed on the same batches. Data from supporting stability studies on two pilot scale batches of tigecycline have also been presented. Samples were stored for up to 24 months at 5°C and 25°C / 60 % RH and up to 6 months at 40°C / 75 % RH. The following stability indicating parameters were tested: description, strength (HPLC), purity and water. Tests for specific optical rotation, microbial purity and bacterial endotoxines have been added to the stability protocol for the commercial batches.
In all cases the stability results presented were satisfactory and support the proposed shelf life for the active substance.

Medicinal Product

- Pharmaceutical Development

The key characteristics of the active substance were taken into account for the development of the finished product..
Due to the poor gastrointestinal permeability and low bioavailability of tigecycline the development of an oral dosage form was not feasible. Tigecycline was found to be stable, when protected from moisture, oxygen and heat,. Therefore, a lyophilised product has been developed for reconstitution with commonly used intravenous diluents such as 0.9% sodium chloride injection or 5% dextrose injection.

The finished product is manufactured by lyophilising an aqueous solution of the active substance without the use of any excipients. The compatibility of the rubber closure with the lyophilisate and with the reconstituted solution has been sufficiently demonstrated.
During early drug development, different strengths of the product were developed. However, only the 50 mg strength was selected for Phase III clinical studies and commercial development

- Manufacture of the Product

The manufacturing process is a standard process for this kind of formulation and consists of the following main steps: compounding of the bulk product, sterile filtration, vial filling and lyophilisation. All critical process parameters have been identified and controlled by appropriate in process controls. The validation report from three production scale batches demonstrates that the process is reproducible and provides a drug product that complies with the in-process and finished product specifications.

- Product Specification

The specification for the finished product at release and shelf life includes tests for appearance, identification, purity, uniformity of dosage units, water content, pH, residual methylene chloride, particulate matter, bacterial endotoxins, headspace oxygen content, sterility and reconstitution time. All tests included in the specification have been satisfactorily described and validated. At the time of the opinion there were some minor issues concerning aspects of the analytical validation that remained unresolved and will be addressed as post approval commitments.
Batch analysis data from several batches including 3 primary stability and 3 process validation batches have been presented. All batches met the test limits as defined in the release specification and test methodology valid at the time of batch release.

- Stability of the Product

Stability studies were performed on 3 pilot scale batches of powder for infusion according to the ICH requirements . Samples were stored at 5ºC, 25^{o}C/60 % RH and 30^{o}C/70 % RH for up to 12 months and in 40^{o}C/75 % RH for up to 6 months. Supportive stability data have also been provided for two pilot scale batches stored at 5ºC and 25^{o}C/60 % RH for up to 36 months, at 40ºC/75%RH for up to 6/8 months and at 51ºC for up to 2 months. The parameters tested were: physical appearance and description, strength, purity, pH, water content, particulate matter, bacterial endotoxins and sterility. In all cases the stability results presented were satisfactory and support the proposed shelf life for the commercially packaged product under the conditions specified in the SPC.
In addition compatibility studies have been conducted for the product according to the recommended preparation and storage conditions for the intravenous solution intended to be administered through a Y-site. These studies demonstrate that the product remains within the established acceptance criteria, when used as specified in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

The quality of Tygacil is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorization. There are no major deviations from EU and ICH requirements. The active substance is well characterised and documented. It is moisture, oxygen, light and heat sensitive, however the proposed formulation addresses all these issues and the stability data provided demonstrate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life. The packaging material is commonly used and well documented. The manufacturing process of the finished product is a standard process that has been adequately described. The pharmaceutical particulars of the SPC have been adequately discussed.

3 Non-clinical aspects

Pharmacology

- Primary pharmacodynamics (*in vitro/in vivo*)

Tigecycline is a glycylcycline antibiotic derived from the tetracycline group, that acts by inhibiting protein synthesis at the level of the bacterial ribosome. Tigecycline shows higher binding affinity than tetracyclines, being active against bacterial strains with either mechanism of tetracycline resistance (efflux and ribosomal protection). The fact that tigecycline overcomes most of the known tetracycline resistance mechanisms is interpreted as a result of steric hindrance due to the large substituent at position 9. Tigecycline showed a number of differences between the in *vitro/in vivo* antibacterial activity with respect to the tetracycline group that could be attributed to the specific interaction with a different region of the ribosomal A-site. Since mutational resistance to tetracyclines at the A-site is considered extremely rare, it is unlikely that mutational resistance to tigecycline will arise at the A-site. Tigecycline is able to inhibit mitochondrial protein synthesis in eukaryotic cells, which may have some toxicological relevance. However, in this respect tigecycline resembles classical tetracyclines and some other antimicrobial drugs inhibiting prokaryotic protein synthesis. In addition, the *in vitro* data show that tigecycline is active against microorganisms harbouring some tetracycline determinants of resistance.

The *in vitro* activity of tigecycline was tested against a wide range of microorganisms, and especially on those involved in infections for the claimed indications. Susceptibility studies show MIC_{90} values of ≤ 2 µg/ml for many clinically relevant aerobic pathogens. Based on *in vitro* studies, it would appear that tigecycline has bacteriostatic activity**,** it is more active against Gram-positive cocci than against Gram-negative bacilli, it has decreased activity against the Proteeae, and lacks of activity against *Pseudomonas aeruginosa*; being most of these species implicated in complicated intra-abdominal infection. Tigecycline is also active against the antibiotic-resistant gram-positive bacteria methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *S. pneumoniae*, and vancomicin-resistant enterococci and against gram-negative producing ESBLs. A number of isolates of clinical pathogens have been shown to be less susceptible or resistant, such as some strains of *B. fragilis, S. maltophilia and B. cepacia*.

A comprehensive *in vivo* testing program was designed to validate the hypothesis that the *in vitro* activity of tigecycline would translate to broad spectrum *in vivo* activity, including more than 60 different bacterial strains and several animal model diseases (intraperitoneal infection, pneumonia and endocarditis). Tigecycline AUC values in the range of 4 to 9.5 µg•h/ml were efficacious against a wide variety of microorganisms in these animal models. A mean daily AUC value of 6.1µg.h/ml was obtained following a maintenance regimen of tigecycline 50 mg q 12 hours (1-hour infusion) from a Phase I clinical trial data.

- Safety pharmacology

The potential of tigecycline to alter cardiovascular, respiratory and CNS systems was examined as part of the safety pharmacology dossier.

Effects on central nervous system

The CNS safety pharmacology study conducted in rats with single IV (bolus) dosages of 5, 15 or 30 mg/kg showed no significant effects on CNS function. .

Intravenous bolus administration of tigecycline at dosages of 10 mg/kg o greater produced prolongation of thiopental-induced sleeping time and death following thiopental pre-treatment in mice. This issue could be explained by the fact that tigecycline is known to release histamine at high doses. Increased histamine levels are known to decrease blood pressure, which at the same time is also reduced following the administration of an anesthetic dose of thiopental. Consistent with this hypothesis, pre-treatment with antihistamines was related to mortality prevention. Thus, tigecycline and thiopental together may have an additive or synergistic effect, which could be responsible for the additional hypotension and deaths observed after IV administration of thiopental and high doses of tigecycline.

Antihistamines prevented mortality, but did not clearly reverse effects on sleeping time, suggesting that central histaminergic neurons may be involved. There are no clinical observations suggesting that any interactions of tigecycline occur with hypnotics.

Respiratory effects

The respiratory safety pharmacology study conducted in rats with single IV(bolus) dosages of 5,15 or 30mg/kg showed no significant effects on respiratory function.

Bronchoconstriction and hypotension occurred at dose of 30 mg/kg in immobilised guineapigs. . Pre-treatment with H_1 and H_2 histamine antagonists suppressed the increase in bronchoresistance induced by bolus administration of ≥ 10 mg/kg of tigecycline, but did not affect the decrease in mean arterial blood pressure. The ability of tigecycline to decrease mean arterial blood pressure could be attributed to released histamine acting at H3 receptors, which is evident particularly after iv bolus injection but these data would need to be confirmed.

Cardiovascular effects

Regarding cardiovascular safety pharmacology studies, no cardiovascular effects were observed after a 0.5-hour infusion of 5 mg/kg (2.5 times the highest human dose) in dogs, whereas a dosage of 12 mg/kg (6 times the highest human dose) resulted in transient, non-life-threatening changes in heart rate and blood pressure but no effects on ECG (including QT interval). There were also no significant effects on ECG (including QT interval) in dogs at the highest dosage of 20 mg/kg (10 times the highest human dose) administered as an IV bolus in the 2-week toxicology study. These findings were consistent with results from clinical trials,

- Pharmacodynamic drug interactions

There were no pharmacodynamic drug interaction studies conducted in animals. However, adequate information on possible interactions with other medicinal products is included in the SPC (section 4.5).

Pharmacokinetics

The pharmacokinetics of tigecycline has been comprehensively described in animal species used for safety evaluation, especially rats and dogs. Both species share many similarities, the dog being the closest species to human in terms of both pharmacokinetics and metabolism.

- Absorption and Distribution

Tigecycline is not absorbed systemically after oral administration in rats and monkeys.

The pharmacokinetics of tigecycline was characterized by a low to moderate CL_T, a moderate to high Vdss, and short (1-4 hours, rat) to long (8 hours, dog and 14 hours, monkey) $t_{1/2}$ values. Linear kinetics was maintained over a large range of doses. Repeat, daily IV administration of tigecycline to rats and dogs for 13 weeks resulted in only small increases in AUC values (< 2-fold) compared with AUC values after a single dose, similar to that observed in humans after the 14-day IV course of therapy. The large Vdss is consistent with the results from the tissue distribution studies in rats in which [^{14}C] tigecycline was widely distributed to most tissues (the highest exposures seen in bone, bone marrow, thyroid gland, salivary gland, kidney, and spleen).

Tigecycline was found to accumulate in skin and uveal tract of pigmented rats, suggesting that tigecycline and/or its metabolites have an affinity for melanin. However, this is a common property of several drugs including tetracyclines, and is believed to have no toxicological significance per se. Regarding accumulation in bone, taking into account the limited duration of the intended clinical use and the lack of interactions reported in the literature, interaction with bisphosphates is considered negligible.

Tigecycline crossed the placenta and was excreted in the milk of lactating rats although exposure was minimal in nursing pups. Low levels of radioactivity were recovered in brain.

At therapeutic concentrations, plasma protein binding of tigecycline in humans was moderate (from 71% to 89%).

- Metabolism (*in vitro/in vivo*) and Excretion

Tigecycline was minimally metabolised in the animal species tested, consistent with that observed in humans. Consistent with rat and dog data, the 4-epimer of tigecycline (a non-enzymatic epimerization

product) was also the most abundant tigecycline-derived component detected in human serum and urine. The major metabolic pathways for tigecycline in humans were glucuronidation (M7: tigecycline glucuronide metabolite, approximately 12 %, and its epimer M6) and amide hydrolysis of the t-butylaminoacetylamino side chain (M9: N-acetyl-9- aminominocycline, approximately 3 % and its epimer M8, approximately 10% of the administered tigecycline dose). Thehuman metabolites (M7 and M9), have not been observed in rats and dogs, but are present in mice and rabbits. Further studies showed that tigecycline and its epimer as well as M3, M7 and its epimer M6 were detected in both species, mice and rabbits, but M9 and its epimer M8 were only observed in rabbits,although quantitative information on the individual metabolites was not provided. This limitation on the metabolic profile could pose a concern on toxicity assessment, mainly in relation to the genotoxicity potential. This issue has remained as a commitment.

The pharmacokinetics of 4-epimer of tigecycline (both a synthetic impurity and degradation product present in tigecycline drug product) was evaluated in rats following a dosage of 6 mg/kg/day for 4 days of tigecycline containing 0.8 % of 4-epimer (concentration range present in various batches of tigecycline used during the toxicology program). The pharmacokinetics of 9-aminominocycline, a minor metabolite of tigecycline (formed by the loss of the t-butylaminoacetic acid group (M3a) from the TBAAA side chain) is known since a series of studies were previously conducted to support the registration of minocycline.

No significant inhibition was observed on cytochrome P450 CYP3A4, CYP2D6, CYP2C9, CYP2C19, CYP2C8 and CYP1A2 isozymes. However, mechanism based inhibition of CYP450 isoenzymes has not assessed but the potential for tigecycline to inhibit CYP 450 isoenzymes by mechanism based inhibition remains as a post approval commitment.

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The excretion of tigecycline was similar in animals and humans with the predominant mode of excretion being the faeces, via the bile.

Toxicology

- Single dose toxicity

The estimated LD_{50} for tigecycline following intravenous administration ranged from 100-150 mg/kg in mice to 100 mg/kg in rats.

- Repeat dose toxicity (with toxicokinetics)

Repeated-dose toxicity studies of 2-weeks and 13-weeks were conducted in male and female rats and dogs with tigecycline. Separate studies were performed in each species to examine the reversibility of tigecycline -induced adverse effects after 2 weeks of daily IV dosing, followed by a 3-week recovery period. A histamine-type reaction, characterised by clinical signs of an anaphylactoid reaction including oedema/swelling, laboured breathing, salivation and vocalization, was observed following IV administration at dosages ≥20 mg/kg/day in rats and ≥5 mg/kg/day in dogs.

Adverse findings were generally dose related in species, as well as their incidence and severity. There were no sex-related differences in toxicity in either species.

Target organs for tigecycline-induced toxicity in the two-week toxicity studies are bone marrow, kidney, thymus, lymph nodes, gastrointestinal tract, spleen and bone (discolouration) at exposures of 8.1 and 9.8 times the human daily dose (based on AUC) in rats and dogs, respectively.The evaluation of the toxicity was hampered by the low number of animals used in the GLP studies conducted in dogs.

Toxicity to the bone marrow in both rats and dogs manifested as hypoplasia, decreases in RBC parameters and reticulocytes, decreased platelet count and increased platelet volume, and decreases in neutrophils, monocytes, eosinophils, and lymphocytes. Thymic and lymphoid atrophy was noted microscopically for both species. Extramedullary hematopoiesis in splenic red pulp was reduced in treated rats with tigecycline, resulting in a reduced spleen weight.

Renal toxicity was evidenced by cortical tubular degeneration (rats and dogs), increased tubular basophilia (rats), tubular single cell necrosis (rats), granular casts in the kidney (rats), and increases in serum BUN and creatinine (dogs). In the gastrointestinal (GI) tract, tigecycline resulted in erosion of the glandular stomach mucosa in rats and villous atrophy and crypt degeneration in the small intestine of dogs at dosages of 50 and 20 mg/kg/day, respectively. Yellow bone discoloration was noted in rats, a known finding for the tetracycline class. In spite of the known hepatic toxicological liability in animals of tetracyclines, after IV administration of tigecycline for up to 13 weeks, the liver appeared not to be significantly affected in either species based on histopathological examination and serum liver enzymes.

Further observations included macroscopic (pale foci) and microscopic (myocardial inflammation, degeneration/necrosis, and/or mineralization) heart lesions in rats at the highest dosage (70 mg/kg/day) because of histamine release which led to myocardial ischemia. The no-observed-adverse-effect levels (NOAELs) in the 2- and 13-week rat toxicology studies were 5 mg/kg/day and 2 mg/kg/day, respectively. The NOAELs in the 2 and 13-week-week dog studies were 5 and 1.5 mg/kg/day, respectively.

The toxicokinetics of tigecycline were evaluated as part of toxicity studies in rats, rabbits and dogs. Exposure to tigecycline increased with the dose in all species. Although there was an indication of sex-related differences in exposure in rats, there were no sex-related differences in exposure in dogs. Exposure ratios ranged from 0.4 to 6.5 for rats and from 0.7 to 2.8 for dogs. The most relevant exposure ratios to the clinical use duration (up to 14 days) were 1.2 and 2.8 in rats and dogs, respectively.

- Genotoxicity in vitro and in vivo (with toxicokinetics)

Tigecycline did not induce mutations in bacterial or mammalian cells in vitro, nor did it cause clastogenic activity *in vivo* or *in vitro*.However, it emerges from pharmacokinetic studies that M9 metabolite is not present in mouse, and M7 exposure has not been quantified. Genotoxicity of these two metabolites had not been adequately addressed, and therefore further genotoxic testing regarding M7 and M9 metabolites was considered necessary, as a follow-up measure. The Applicant has committed to conduct an in vitro assay to detect point mutations and another to detect chromosomal aberration (according to the ICHS2A and ICHS2B Guidelines).

- Carcinogenicity

No carcinogenicity studies have been conducted since the duration of the therapeutic regimen proposed with tigecycline is 14 days.

- Reproductive and developmental studies

Tigecycline was evaluated in fertility, peri/post-natal and developmental toxicity studies in rats and a developmental toxicity study in rabbits. In rats, decreases in parental body-weight gains were used to establish the NOAEL levels for F_0 males and females at 1 and 4 mg/kg/day, respectively. There were no effects on time to mating, mating or fertility indices, conception rate, pre- or post-implantation loss, numbers of corpora lutea or live and dead foetuses, or percent resorptions. The NOAEL for fertility was 12 mg/kg/day for both sexes. With respect to rat foetal development, there were no effects on foetal sex ratio or on the incidences of foetuses or litters with major malformations or minor external or visceral anomalies. Foetal weights in the 12 mg/kg/day group were reduced compared to controls, with observations of reduced /delayed ossification of the pubic, ischial, and supraoccipital bones and increased incidences of rudimentary 14th rib.
The NOAEL for developmental toxicity in the rat (F_1 litters) was 4 mg/kg/day, based on the reduction in foetal weight at this dosage. The developmental toxicity of tigecycline was also investigated in rabbits dosed IV on days 6 through 18 (inclusive, 13 days) of pregnancy at dosages of 0, 0.25, 1, or 4 mg/kg/day. The administration of 4 mg/kg was associated with foetal loss. The maternal and developmental toxicity NOAELs were 1 mg/kg/day and 4 mg/kg/day, respectively. There was no indication of a teratogenic effect of tigecycline in the rat or rabbit. From results obtained in the

perinatal/postnatal toxicity study conducted in rats, the maternal NOAEL was established at 1 mg/kg/day, and for foetal and offspring (F_1 generation) development, the NOAEL was 12 mg/kg/day. A slight dose-dependent increase in the length of gestation was observed for the tigecycline-treated groups. Distribution studies performed with radiolabeled tigecycline showed that it readily crosses the rat placenta and associates with foetal bone

- Local tolerance

Irritation potential
Local irritation following IV injection was observed in rats given 30 and 70 mg/kg/day. Macroscopical changes at the injection site were observed with a dose of 30 mg/kg/day and microscopic changes at a dose level of 5 mg/kg/day. There were no tigecycline-related injection site lesions in dogs administered tigecycline IV for 2 or 13 weeks at dosages up to 20mg/kg/day. Concentrations of the administered tigecycline solution (30 and 70 mg/ml) were high at the dosages used in these studies compared with 1.2 mg/ml, the highest concentration administered in humans.

Sensitisation potential
Tigecycline was administered by IV or IP to mice in a sensitization phase and IV rats in a challenge phase to assess the antigenic potential using the passive cutaneous anaphylaxis (PCA) assay. Tigecycline showed no antigenic potential. In a single-dose study with guinea pigs, animals at 3 mg/kg IV had adverse clinical signs consistent with an anaphylactoid reaction and histamine release, which precluded an antigenicity study with this species

Phototoxicity
Tigecycline caused no cutaneous or ocular responses following IV administration in rats at 70 mg/kg followed by UVR exposure of both the eyes and skin at 5 minutes and 2 hours after its administration.

- Other toxicity studies

Immunotoxicity
Since tigecycline showed toxicity towards bone marrow, lymph nodes, and the production of red and white blood cells at high doses, it would be expected to be immunotoxic. As immunotoxicity studies were not conducted, the Applicant was requested to conduct an immune function study (e.g. TDAR with KLH as an antigen) as a follow up measure and has agreed to carry it out. Therefore, this issue remains as a post-authorisation commitment and should be included in the Risk Management Plan.

Impurities
The level of structurally-identified impurities and/or degradants, such as 4-epimer, 9-aminominocycline, and others impurities identified by their relative retention time, which may be present in commercial supplies, were qualified with appropriate studies according to ICH guidelines for impurities in new drug substances. The minocycline impurity in tigecycline needs no qualification since it is an antibiotic approved for serious infections. However, no genotoxicity studies have been performed aimed to evaluate three degradation products of tigecycline (RRT 0.55, 1.25, 1.67). The Applicant has agreed to conduct two in vitro studies to detect both point mutations and chromosomal aberrations, as requested as a follow up measure.

Ecotoxicity/environmental risk assessment
The environmental risk assessment of tigecycline followed primarily the draft of guidelines related to this issue. From the results obtained, it is concluded that tigecycline for injection is of no immediate risk to the environment and no proposals for labelling provisions are necessary to reduce any potential environmental risks.

Discussion on the non-clinical aspects
Overall, most of the toxicological effects of tigecycline, with the possible exception of bone discolouration, are likely to be reversible in humans upon cessation of dosing based on recovery studies in rats and dogs. Basically, these findings are qualitatively similar to those known for other tetracyclines.

4 Clinical aspects

Introduction

GCP

The applicant has stated that all clinical trials were performed in accordance with GCP.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

Pharmacokinetic data on tigecycline have been obtained from at least 300 healthy subjects (young and elderly), subjects with mild to severe hepatic disease and severe renal disease and more than 270 patients with complicated skin and soft tissue infections or complicated intra-abdominal infections in Phase 2 and Phase 3 clinical trials.

ADME: Tigecycline is administered IV and therefore has 100% bioavailability.

Following IV administration, the steady-state Cmax was 866 ng/ml for 30-minute infusion and 634 ng/ml for 60-minute infusions. Tigecycline serum concentrations initially decline rapidly while tigecycline is being distributed into the body's tissues with an estimated volume of distribution around 600L. At therapeutic concentrations (0.1 to 1.0 µg/ml) the *in vitro* protein binding increases with increasing concentrations from 71% to 89%.

The tigecycline serum concentration curves often show secondary peaks occurring approximately 12 to 16 hours after administration. Enterohepatic recirculation of tigecycline and a redistribution of tigecycline from the various tissues have been proposed across the dossier to address the "secondary peaks" phenomenon, redistribution being the most likely explanation for the fluctuation observed.

Tigecycline concentrations exhibit a multi-phasic decline, with the final elimination phase generally occurring beyond 24 hours ($t_{1/2}$ of 24 to 48 hours; CV 50%-83%). Following a 100-mg loading dose followed by 50 mg every 12 hours for 5 days, steady-state conditions are met by treatment Day 3. Tigecycline shows to be dose dependent with an accumulation AUC ratio about 1.3. The clinical half-life of tigecycline is above 13 hours.

On average, it is estimated that less than 20% of tigecycline is metabolised before excretion. In healthy male volunteers, following the administration of ^{14}C-tigecycline, unchanged tigecycline was the primary ^{14}C-labelled material recovered in urine and faeces, but a glucuronide, an N-acetyl metabolite and a tigecycline epimer were also present. The recovery of the total radioactivity in faeces and urine following administration of ^{14}C-tigecycline indicates that 59 % of the dose is eliminated by biliary/faecal excretion, and 33 % is excreted in urine. Overall, the primary route of elimination for tigecycline is biliary excretion of unchanged tigecycline. Glucuronidation and renal excretion of unchanged tigecycline are secondary routes.

Cholestasis is a clinical condition that may be frequently associated to cIAI. The potential influence of cholestasis on tigecycline excretion is subject to further studies to be finalised after the marketing authorisation has been granted. Meanwhile a cautionary statement is included in section 4.4 of the SPC.

- Special populations: With regard to weight, gender, age and impaired renal function, the pharmacokinetics of tigecycline is not clinically significant altered. The only significant covariates in the population PK analyses were creatinine clearance, weight and gender; Tigecycline exposure after one single dose is higher among females than males, and in elderly subjects higher than young subjects. All this data are included in section 5.2 of the SPC. The recommended Tygacil dose for patients with severe hepatic insufficiency (Child Pugh C) is a 100-mg loading dose followed by 25 mg every 12 hours. A decrease in the loading dose is not recommended. The volume of distribution in subjects with hepatic insufficiency was observed to be reduced by only

28% compared with healthy subjects with a corresponding increase of 23% in Cmax. Given the importance of quickly providing efficacious concentrations of drug when initiating antimicrobial therapy, the first dose should remain the same.

- Interactions: Due to negligible metabolism and moderate protein binding, pharmacokinetic interactions of clinical relevance are not expected. Two single dose interaction studies with warfarin and digoxin were performed and apparently tigecycline did not affect exposure to digoxin, and vice versa. In the warfarin interaction study, concomitant administration of tigecycline resulted in a 68% increase in R-*warfarin* AUC and 29% increase in S-warfarin AUC, suggesting inhibition of CYP3A4 and CYP2C9, respectively. This is however, inconsistent with *in vitro* studies in human liver microsomes, which suggested a low potential for inhibition of CYP450 isoenzymes. In any case, available data does not suggest that this interaction may result in significant International Normalised Ratio (INR) changes. However, as Tigecycline has been reported to prolong both PT and aPTT, the SPC (sections 4.4 and 4.5) now includes statements about the potential safety implication of tigecycline in this respect.Subject to post authorisation commitment the applicant will further investigate the potential for mechanism-based inhibition of the cytochrome P450 (CYP) isoenzymes CYP2C9 and CYP3A4 by tigecycline.

Pharmacodynamics

Tigecycline is a broad-spectrum primarily bacteriostatic antibiotic, a member of the glycylcycline class of antimicrobial agents. It is a synthetic derivative of minocycline. The bacterial ribosome is the target for the tetracyclines. Binding to the 30S ribosomal subunit at the A-site blocks entry of amino-acyl transfer RNA molecules into the ribosome, preventing incorporation of amino acid residues into elongating peptide chains. Glycylcyclines interact also directly with another region of the 30S A-site.

Tigecycline evades the Tet(A-E) efflux pumps, which account for most acquired resistance to tetracycline and minocycline in Enterobacteriaceae and *Acinetobacter* spp.; also the Tet(K) pumps, which occur widely in staphylococci conferring resistance to tetracycline though not minocycline ordoxycycline. In addition, tigecycline binds to bacterial ribosomes that have been modified by the Tet(M) protein, a mechanism that compromises all available tetracyclines, and which is frequent in Gram-positive cocci and *Neisseria* spp. Evasion of the tet(M) is probably because tigecycline attaches to the ribosome in a different orientation from classical tetracyclines. Tigecycline remains vulnerable to the chromosomally-encoded multidrug efflux pumps of Proteeae and *Pseudomonas aeruginosa*..

Consequently, tigecycline exhibits decreased activity against microorganisms belonging to Proteeae (*P. mirabilis, P. vulgaris, Providencia stuartii, P. rettgeri and Morganella morganii*) and no activity against *Pseudomonas aeruginosa*.

The issue of resistance linked to changes in the A-site has been adequately addressed. Within the risk management plan specific attention is paid to the potential for developing resistance.

The MIC breakpoints (BP) were discussed and agreed with EUCAST in accordance with the standard operating procedure adopted by EMEA, EUCAST and the European Pharmaceutical Industry (EFPIA).
The clinical breakpoints and comments on the antibacterial spectrum of activity are delineated in section 5.1 of the SPC. There is limited in vivo experience with infections caused by enterococci although polymicrobial intraabdominal infections respond to treatment with tigecycline. For anaerobes there is seemingly an absence of correlation between *in vitro* data and clinical outcome and so no BP has been assigned to anaerobic bacteria.

Some microorganisms raise particular concern, i.e. Enterobacteriaceae such as *Klebsiella* spp., *Enterobacter* spp., and *Serratia marcescens* and other Gram-negative organisms such as *Acinetobacter baumannii*, for some of which decreased susceptibility was observed in clinical trials while patients were on therapy. Also, there seems to be some strains of anaerobes with decreased susceptibility to tigecycline, i.e. the MIC distributions for organisms of the genera *Bacteroides* and *Clostridium* are wide and may include values in excess of 2 mg/L tigecycline, which is also mentioned in section 5.1 of the SPC.

An *in vitro* surveillance study (T.E.S.T.) is anticipated to run through 2007-2008 in 600-800 sites worldwide. Furthermore, a specific surveillance study aimed at monitoring emerging resistance in the European Union after the introduction of tigecycline in clinical practise will be conducted as part of a post authorisation commitment. Updated information on the prevalence of resistance as well as further insight into the mechanisms of resistance to tigecycline will be submitted within subsequent PSURs.

The effect of tigecycline on the oropharyngeal and intestinal flora in healthy adults was minor and as could be expected from the antibacterial spectrum. The number of *Bacteroides* isolates in the oropharyngeal microflora was increased and did not return to baseline levels at the end of study period. Also, the number of *Bifidobacterium* in the intestinal microflora was decreased and did not return to baseline levels at the end of study period. Of note, none of the subjects were colonized by C. *difficile* whereas the number of *Bacteroides* isolates in the intestinal microflora was not affected. The remaining intestinal flora returned to normal by the end of the study period.

The issue of potential antagonism between tigecycline (bacteriostatic) and bactericidal antibiotics is addressed in a statement in section 4.5 of the SPC, indicating that in *in vitro* studies no antagonism was shown. No clinical data is available on this issue.

The dosage regimen recommended provides low Cmax and, according to the volume of distribution, extensive tissue penetration. In the PK/PD modelling based on phase 2 data and additional data collected from the phase 3 studies, results are of limited value, partially due to the low MIC range tested and the limited number of isolates available for the modelling. Since tigecycline is bacteriostatic against bacteria causing cSSTIs and cIAIs it is of concern whether adequate and maintained levels are obtained with the dosage regimen recommended, which is particularly relevant for immunocompromised patients. Given the extensive volume of distribution of tigecycline, it is speculated that levels in tissue would be higher than those in serum. However, no adequately validated PK/PD modelling exploring exposure-response in terms of tissue (instead of serum) AUC/MIC ratio is available. Consequently, a warning has been included in section 4.4.to alert physicians on the use of monotherapy with tigecycline in patients presenting with perforation of intestines and/or with incipient sepsis/septic shock. Also, section 5.2. of the SPC addresses the Cmax and AUC reached in serum.

Clinical efficacy

The clinical development program for the claimed indications comprises a Phase 2 study (3074A1-200-US) and 2 pivotal Phase 3 studies (3074A1-300-US/CA and 3074A1-305-WW) for complicated skin and skin soft tissue infection (cSSTI), and for complicated intra-abdominal infection (cIAI) there is one Phase 2 study (3074A1-202-US) and two other pivotal Phase 3 studies (3074A1-301-WW and 3074A1-306-WW).

Protocol Number	Study Description
Efficacy and Safety Studies: Complicated Skin and Skin Structure Infections	
3074A1-200-US	Open-label study of 2 dose levels of tigecycline to treat cSSSI
3074A1-300-US/CA	Double-blind (third-party unblinded), randomized control comparison study of tigecycline + placebo and vancomycin + aztreonam to treat cSSSI
3074A1-305-WW	Double-blind (third-party unblinded), randomized control comparison study of tigecycline + placebo and vancomycin + aztreonam to treat cSSSI
Efficacy and Safety Studies: Complicated Intra-abdominal Infections	
3074A1-202-US	Open-label study of tigecycline to treat cIAI
3074A1-301-WW	Double-blind (third-party unblinded), randomized control comparison study of tigecycline and imipenem/cilastatin to treat cIAI
3074A1-306-WW	Double-blind (third-party unblinded), randomized control comparison study of tigecycline and imipenem/cilastatin to treat cIAI

In addition, 3 studies (3074A1-307-WW, -309-WW, and -310-WW) were ongoing at the time of submission in subjects with serious infections caused by known resistant pathogens (RP).

Table 1-1: Ongoing Phase 3 Studies of Tigecycline to Treat Known Resistant Pathogens

Study (CSR Number)	Targeted Pathogens	Study Populations	Primary Diagnoses	Tigecycline Dose (IV)	Active Control Dose (IV)	Duration of Treatment[a]
3074A1-307-WW (CSR-52112/2)	• Methicillin-resistant *Staphylococcus aureus* (MRSA) • Vancomycin-resistant *Enterococcus* (VRE)	Adults 18 years or older with selected serious infections	Serious infections involving MRSA or VRE, eg, cSSSI, cIAI, bacteremia, HAP, CAP	100 mg, followed every 12 hours by 50 mg	• MRSA: Vancomycin 1 g every 12 hours • VRE: Linezolid 600 mg every 12 hours	7 to 28 days depending on infection site and severity
3074A1-309-WW (CSR-52113)	Gram-negative bacteria, including ESBL-producing strains, eg, • *Enterobacter* species • *Klebsiella pneumoniae* • *Acinetobacter baumannii*	Adults 18 years or older who have failed previous antibiotic therapies or cannot tolerate alternative therapy	Serious gram-negative infections, eg, cSSSI, cIAI, bacteremia, HAP, and CAP	100 mg, followed every 12 hours by 50 mg	NA (noncomparative open-label study)	7 to 28 days depending on infection site and severity
3074A1-310-WW (CSR-52114)	Bacteria (including mycobacteria) resistant to multiple antibiotics or to available, subject-tolerated antibiotics	Adults and children at least 8 years of age (emergency use)	Serious infections caused by multidrug-resistant organisms, including infections requiring long-term treatment, eg, endocarditis, osteomyelitis	100 mg, followed every 12 hours by 50 mg[b]	NA (noncomparative open-label study)	5 to 90 days depending on infection site and severity

CSR = clinical study report; IV = intravenous; WW = worldwide; MRSA = methicillin-resistant *Staphylococcus aureus*; VRE = vancomycin-resistant *Enterococcus*; cSSSI = complicated skin and skin structure infection; cIAI = complicated intra-abdominal infection; HAP = hospital-acquired pneumonia; CAP = community-acquired pneumonia; NA = not applicable.
a: Duration of treatment could be extended based on investigating physician's judgment.
b: Subjects with rapidly growing mycobacterial disease receive a total daily dose of 50 mg (a single 50-mg dose or 25 mg, q12 hr).

- Dose response studies

The Applicant has presented two phase 2 studies for the claimed indications (for cSSTI: Study 200 and for cIAI: Study 202). Study 200 was a randomized, open-label, comparison study of hospitalized subjects with complicated Skin and Soft Tissue infections in which 160 patients received either tigecycline 25 or 50 mg twice daily with an initial dose of 50 or 100 mg, respectively. The clinical data from this study indicated a trend toward a dose-related clinical cure response (67% and 74%, respectively) and dose-related pathogen eradication (56% and 70%). Also dose-safety relationships appeared evident for the adverse events (AEs) of nausea (22% and 35%) and vomiting (13% and 18%). Since tigecycline is intended for use in complicated infections, efficacy was favoured in benefit/risk -balance, and the greater dosage schedule (50 mg twice daily with an initial dose of 100 mg) was used in all consecutive clinical Phase II and III trials.

Study 202 was a phase 2, multicenter, open-label study in hospitalized subjects with complicated intra-abdominal infections in which 111 subjects received an initial IV loading dose of 100 mg of tigecycline followed by 50 mg every 12 hours. Treatment continued for at least 5 days but not more than 14 days. There were no comparator or placebo groups.

Overall, it appears that the choice of the dosage regimen for phase 3 studies is based on pharmacokinetic considerations as well as tolerability. The safety profile in these phase 2 studies is consistent with that seen in the larger database of phase 3 clinical trials. However, it should be highlighted that one case of *Clostridium difficile* associated colitis has been reported in Study 202. Apparently, this was the only one serious case reported of this adverse event for subjects in Phase 2 and 3 trials.

- Main studies

Complicated intra-abdominal infections (cIAI)

Methods

Two pivotal phase 3 trials (studies 301 and 306) have been submitted in support of the indication complicated intra-abdominal infections. Study 301 was carried out in the Western hemisphere, and 306 in worldwide. The study protocols were similar in all essential points. Both phase 3 were multicenter, double-blind (third-party unblinded) studies in which 1568 hospitalised patients

(approximately 800 patients per trial) with complicated intra-abdominal infections who were candidates for or had received a laparotomy, laparoscopy, or percutaneous drainage of an intra-abdominal abscess were randomized.

Key inclusion criteria were the followings:
1. Hospitalized male or female subjects, at least 18 years of age.
2. Candidate for, or had, a laparotomy, laparoscopy, or percutaneous drainage of an intra-abdominal abscess.
3. Complicated intra-abdominal infection, such as:
    a. An intra-abdominal abscess.
    b. An intra-abdominal abscess (including liver and spleen) that developed in a postoperative subject who received more than 48 hours but not more than 5 days of a nonstudy antibiotic and an intraabdominal culture was obtained from the infected site.
    c. Appendicitis complicated by perforation (grossly visible) and abscess or periappendicular abscess.
    d. Perforated diverticulitis complicated by abscess formation or faecal contamination.
    e. Complicated cholecystitis with evidence of perforation or empyema.
    f. Perforation of the large or small intestine with abscess or fecal contamination.
    g. Purulent peritonitis or peritonitis associated with faecal contamination.
    h. Gastric or duodenal ulcer perforation with symptoms lasting at least 24 hours before operation.
    i. Traumatic bowel perforation with symptoms lasting at least 12 hours before operation.

4. No more than 1 dose of an antibiotic (single broad-spectrum agent or 1 dose of each antibiotic in a combination regimen such as metronidazole, ampicillin,gentamicin) after the baseline intra-abdominal culture was obtained from the infected site.

Main exclusion criteria are as follows:
1. Anticipated length of antibiotic therapy less than 5 days.
2. Subjects suspected preoperatively to have had a diagnosis of spontaneous bacterial peritonitis, simple cholecystitis, gangrenous cholecystitis without rupture, simple appendicitis, acute suppurative cholangitis, pancreatic abscess, or infected necrotizing pancreatitis.
3. Neutropenia with absolute neutrophil count less than 1000/mm3. Subjects with neutrophil counts as low as 500/mm3 were permitted if the investigator thought the reduction was due to the acute infectious process.
4. Intra-abdominal infection known to be caused by 1 or more bacterial pathogens not susceptible to both of the study drugs (e.g. *P. aeruginosa, Proteus mirabilis*) and in the investigator's opinion required treatment with an additional antibacterial agent.
5. Presence of hepatic disease:
    a. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels more than 10 times the upper limit of normal (ULN) values.
    b. Bilirubin more than 3 times ULN, unless isolated hyperbilirubinemia was directly related to the acute process.
    c. Acute hepatic failure or acute decompensation of chronic hepatic failure.

Subjects were stratified at randomization according to Acute Physiologic and Chronic Health Evaluation (APACHE) II scores (≤ 15, or > 15 but < 31). Subjects were randomly assigned (1:1) to receive either tigecycline (an initial 100-mg dose, followed by 50 mg twice a day) or imipenem/cilastatin (200 to 500 mg, dose based on body weight and calculated creatinine clearance) every 6 hours via intravenous administration for up to 14 days.

The comparator group in both trials was imipenem/cilastatin that was chosen based on its use worldwide for therapy of cIAI. The total daily dose of imipenem/cilastatin in cIAI was at the lower range of that acceptable for severely ill subjects.

The primary efficacy variable was the clinical response in two co-primary populations, the microbiologically-modified ITT (m-mITT) and the microbiologically evaluable (ME) populations. In

both trials, the objective was to show the non-inferiority of tigecycline vs. imipenem/cilastatin using a delta of 15% (absolute) at the test-of-cure (TOC) assessment.

Results

Demographic and baseline disease characteristics were similar between the treatment groups in each study, excepting differences in ethnic origin. Infection type, etiology of disease, and comorbid conditions were comparable between treatment groups in each study.

In study 301, 39% of subjects were white and 61% were of other ethnic origin (primarily Hispanic). Most of the subjects (88%) in study 306 were white. Approximately 8% (safety population, pooled data of studies 301 and 306) of subjects were older than 75 years.

The most common type of infection was complicated appendicitis (51.4%), followed by other diagnoses less commonly reported such as complicated cholecystitis (13.5%), intra-abdominal abscess (10%), perforation of intestine (10%), and gastric or duodenal ulcer perforation less than 24 hours (4.9%). Of these patients, 76.1% had associated diffuse peritonitis (surgically-apparent peritonitis). Most patients in both studies had APACHE scores < 15 (3.5%). The number of patients with concurrent bacteraemia was limited (6.4%). The number of immunocompromised patients was also limited. Consequently, the limited data on relevant subpopulations (patients with diagnoses other than complicated appendicitis, patients with bacteraemia and with APACHE score > 15) and severely ill patients is stated in section 4.4 of the SPC.

In study 301, 75 (9.1%) subjects received concomitant antibiotics during the on-therapy phase of the study: 44 (10.7%) tigecycline-treated subjects and 31 (7.5%) imipenem/cilastatin-treated subjects. As for study 306, 52 (6.4%) subjects received concomitant antibiotics during the on-therapy phase of the study: 31 (7.7%) tigecycline-treated subjects and 21 (5.1%) imipenem/cilastatin-treated subjects.

Study 301

Table below summarizes the clinical diagnoses for infections in the ME population at baseline.

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

a: p-Value for chi-square.
Source: demo5_diag_me 20OCT04:16:07

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

Study 306

Table below summarizes the clinical diagnoses for infections in the ME population at baseline.

Characteristic	----Tigecycline--- (n = 265)		Imipenem/ Cilastatin (n = 258)		--------Total------- (n = 523)		p-Value[a]
Clinical Diagnosis, n (%)							0.695[a]
Complicated appendicitis	111	(41.9)	117	(45.3)	228	(43.6)	
Complicated cholecystitis	57	(21.5)	58	(22.5)	115	(22.0)	
Complicated diverticulitis	15	(5.7)	17	(6.6)	32	(6.1)	
Gastric/duodenal perforation	12	(4.5)	15	(5.8)	27	(5.2)	
Intra-abdominal abscess	34	(12.8)	28	(10.9)	62	(11.9)	
Perforation of intestine	30	(11.3)	17	(6.6)	47	(9.0)	
Peritonitis	4	(1.5)	4	(1.6)	8	(1.5)	
Other	2	(0.8)	2	(0.8)	4	(0.8)	

a: Chi-square test.
Source: demo5_diag_me, 06OCT04:22:28

ME subjects in the 2 treatment groups had similar clinical diagnoses. Almost half (43.6%) of all infections were diagnosed as complicated appendicitis.

Clinical response

For the primary efficacy analysis results are presented by APACHE score. As the number of patients in the strata > 15 is small, the overall, unadjusted difference has been highlighted in the following figures.

In **study 301,** the cure / failure /completed numbers of the patients in the ME population were 199 / 48 / 247 for tigecycline and 210 / 45 / 255 for the reference therapy. The 95% CI for the difference between treatments at TOC was:-9.0, 5.4. In the m-mITT population, the cure/ failure/ indeterminate/ completed numbers were 227/ 63/ 19/ 309 for tigecycline and 244/ 55/ 13/ 312 for the reference therapy. The 95% CI for the difference between treatments at TOC was:-11.8, 2.3.

Table 9.3.1-1: Clinical Response: Microbiologically Evaluable Population

Visit Response	APACHE Score		----------Tigecycline---------- n/N	%	(95%CI)[a]	-----Imipenem/Cilastatin----- n/N	%	(95%CI)[a]	--------(Tigecycline - Imipenem/Cilastatin)--------- %	(95%CI)	Test for NonInf. p-Value	Test for Difference p-Value
Last day of therapy												
Cure	≤ 15[b]		207/238	87.0	(82.0, 91.0)	225/247	91.1	(86.8, 94.3)	-4.1	(-10.1, 1.9)	0.0001	0.1914
	> 15[b]		7/ 9	77.8	(40.0, 97.2)	3/ 8	37.5	(8.5, 75.5)	40.3	(-14.7, 95.2)	0.0242	0.1961
	Overall	Unadjusted[b]	214/247	86.6	(81.8, 90.6)	228/255	89.4	(85.0, 92.9)	-2.8	(-8.9, 3.3)	<0.0001	0.4128
		Adjusted[c]							-2.8	(-8.5, 2.9)	<0.0001	0.3564
Failure			33/247	13.4	(9.4, 18.2)	27/255	10.6	(7.1, 15.0)				
Test-of-cure												
Cure	**≤ 15[b]**		**195/238**	**81.9**	**(76.4, 86.6)**	**208/247**	**84.2**	**(79.1, 88.5)**	**-2.3**	**(-9.4, 4.8)**	**0.0002**	**0.5840**
	> 15[b]		**4/ 9**	**44.4**	**(13.7, 78.8)**	**2/ 8**	**25.0**	**(3.2, 65.1)**	**19.4**	**(-36.6, 75.5)**	**0.1578**	**0.7549**
	Overall	**Unadjusted[b]**	**199/247**	**80.6**	**(75.1, 85.3)**	**210/255**	**82.4**	**(77.1, 86.8)**	**-1.8**	**(-9.0, 5.4)**	**0.0001**	**0.6892**
		Adjusted[c]							**-1.7**	**(-8.4, 5.1)**	**<0.0001**	**0.6512**
Failure			**48/247**	**19.4**	**(14.7, 24.9)**	**45/255**	**17.6**	**(13.2, 22.9)**				

Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence intervals; Noninf = noninferiority.
a: Treatment group CIs are unweighted and calculated by using the method of Clopper and Pearson.
b: CIs and hypothesis tests are calculated by the asymptotical method, corrected for continuity.
c: Estimates of differences between treatment groups, corresponding CIs, and hypothesis tests are weighted by using minimum risk weights (method of Mehrotra and Railkar).
Source: clin01 28SEP04 09:00

Table 9.3.1-2. Clinical Response: Microbiologic Modified Intent-to-Treat Population

Visit Response	APACHE Score		Tigecycline n/N	Tigecycline %	Tigecycline (95%CI)[a]	Imipenem/Cilastatin n/N	Imipenem/Cilastatin %	Imipenem/Cilastatin (95%CI)[a]	(Tigecycline - Imipenem/Cilastatin) %	(95%CI)	Test for Non-Inf. p-Value	Test for Difference p-Value
Last day of therapy												
Cure	≤ 15 [b]		241/295	81.7	(76.8, 85.9)	268/302	88.7	(84.6, 92.1)	-7.0	(-13.1, -1.0)	0.0042	0.0204
	> 15 [b]		11/ 14	78.6	(49.2, 95.3)	3/ 10	30.0	(6.7, 65.2)	48.6	(4.4, 92.8)	0.0012	0.0277
	Overall	Unadjusted[b]	252/309	81.6	(76.8, 85.7)	271/312	86.9	(82.6, 90.4)	-5.3	(-11.4, 0.7)	0.0007	0.0879
		Adjusted[c]							-5.0	(-10.7, 0.8)	0.0003	0.0938
Failure			45/309	14.6	(10.8, 19.0)	35/312	11.2	(7.9, 15.3)				
Indeterminate			12/309	3.9	(2.0, 6.7)	6/312	1.9	(0.7, 4.1)				
Test-of-cure												
Cure	**≤ 15 [b]**		**219/295**	**74.2**	**(68.8, 79.1)**	**242/302**	**80.1**	**(75.2, 84.5)**	**-5.9**	**(-13.0, 1.2)**	**0.0053**	**0.1049**
	> 15 [b]		**8/ 14**	**57.1**	**(28.9, 82.3)**	**2/ 10**	**20.0**	**(2.5, 55.6)**	**37.1**	**(-7.3, 81.6)**	**0.0086**	**0.1185**
	Overall	**Unadjusted[b]**	**227/309**	**73.5**	**(68.2, 78.3)**	**244/312**	**78.2**	**(73.2, 82.7)**	**-4.7**	**(-11.8, 2.3)**	**0.0019**	**0.1976**
		Adjusted[c]							**-4.3**	**(-11.0, 2.5)**	**0.0009**	**0.2220**
Failure			**63/309**	**20.4**	**(16.0, 25.3)**	**55/312**	**17.6**	**(13.6, 22.3)**				
Indeterminate			**19/309**	**6.1**	**(3.7, 9.4)**	**13/312**	**4.2**	**(2.2, 7.0)**				

Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence intervals; Noninf = noninferiority.
a: Treatment group CIs are unweighted and calculated by using the method of Clopper and Pearson.
b: CIs and hypothesis tests are calculated by the asymptotical method, corrected for continuity.
c: Estimates of differences between treatment groups, corresponding CIs, and hypothesis tests are weighted by using minimum risk weights (method of Mehrotra and Railkar).
Source: clini02 28SEP04 09:00

In **study 306,** the cure / failure /completed numbers of the patients in the ME population were 242 / 23 / 265 for tigecycline and 232 / 26 / 258 for the reference therapy. The 95% CI for the difference between treatments at TOC was:-4.0, 6.8. In the m-mITT population, the cure/ failure/ indeterminate/ completed numbers were 279/ 34/ 9/ 322 for tigecycline and 270/ 36/ 13/ 319 for the reference therapy. The 95% CI for the difference between treatments at TOC was:-3.7, 7.7.

Table 9.3.1-1: Clinical Response: ME Population

Visit Response	APACHE Score		Tigecycline n/N	Tigecycline %	Tigecycline (95%CI)[a]	Imipenem/Cilastatin n/N	Imipenem/Cilastatin %	Imipenem/Cilastatin (95%CI)[a]	(Tigecycline - Imipenem/Cilastatin) %	(95%CI)	Test for Noninf. p-Value	Test for Difference p-Value
Last day of therapy												
Cure	≤15 [b]		243/260	93.5	(89.7, 96.1)	241/258	93.4	(89.7, 96.1)	0.1	(-4.6, 4.7)	<0.0001	1.0000
	>15 [b]		5/ 5	100.0	(47.8,100.0)	0/ 0						
	Overall	Unadjusted[b]	248/265	93.6	(89.9, 96.2)	241/258	93.4	(89.7, 96.1)	0.2	(-4.4, 4.8)	<0.0001	1.0000
		Adjusted[c]							NA	NA	NA	NA
Failure			17/265	6.4	(3.8, 10.1)	17/258	6.6	(3.9, 10.3)				
Test-of-cure												
Cure	**≤15 [b]**		**237/260**	**91.2**	**(87.0, 94.3)**	**232/258**	**89.9**	**(85.6, 93.3)**	**1.2**	**(-4.2, 6.7)**	**<0.0001**	**0.7424**
	>15 [b]		**5/ 5**	**100.0**	**(47.8,100.0)**	**0/ 0**						
	Overall	**Unadjusted[b]**	**242/265**	**91.3**	**(87.3, 94.4)**	**232/258**	**89.9**	**(85.6, 93.3)**	**1.4**	**(-4.0, 6.8)**	**<0.0001**	**0.6904**
		Adjusted[c]							NA	NA	NA	NA
Failure			**23/265**	**8.7**	**(5.6, 12.7)**	**26/258**	**10.1**	**(6.7, 14.4)**				

Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence intervals; Noninf = noninferiority; NA = not applicable because of small sample sizes.
a: Treatment group CIs are unweighted and calculated by using the method of Clopper and Pearson.
b: Between-group CIs and hypothesis tests are calculated by the asymptotic method, corrected for continuity.
c: Estimates of differences between treatment groups, corresponding CIs, and hypothesis tests are weighted by using minimum risk weights (method of Mehrotra and Railkar).
Note: The clinical cure rate at the test-of-cure assessment is the primary endpoint.
Source: 306/clini01 23AUG04 03:22 AM

Table 9.3.1-2. Clinical Response: m-mITT Population

Visit Response	APACHE Score		Tigecycline n/N	Tigecycline %	Tigecycline (95%CI)[a]	Imipenem/Cilastatin a/N	Imipenem/Cilastatin %	Imipenem/Cilastatin (95%CI)[a]	(Tigecycline - Imipenem/Cilastatin) %	(Tigecycline - Imipenem/Cilastatin) (95%CI)	Test for Noninf. p-Value	Test for Difference p-Value
Last day of therapy												
Cure	≤15 [b]		283/314	90.1	(86.3, 93.2)	289/316	91.5	(87.8, 94.3)	-1.3	(-6.2, 3.5)	<0.0001	0.6608
	>15 [b]		8/ 8	100.0	(63.1,100.0)	3/ 3	100.0	(29.2,100.0)	0.0	(-22.9, 22.9)		
	Overall	Unadjusted[b]	291/322	90.4	(86.6, 93.4)	292/319	91.5	(87.9, 94.3)	-1.2	(-5.9, 3.6)	<0.0001	0.7070
		Adjusted[c]							-1.3	(-5.9, 3.3)	<0.0001	0.5995
Failure			28/322	8.7	(5.9, 12.3)	25/319	7.8	(5.1, 11.4)				
Indeterminate			3/322	0.9	(0.2, 2.7)	2/319	0.6	(0.1, 2.2)				
Test-of-cure												
Cure	**≤15 [b]**		**271/314**	**86.3**	**(82.0, 89.9)**	**268/316**	**84.8**	**(80.4, 88.6)**	**1.5**	**(-4.3, 7.3)**	**<0.0001**	**0.6739**
	>15 [b]		**8/ 8**	**100.0**	**(63.1,100.0)**	**2/ 3**	**66.7**	**(9.4, 99.2)**	**33.3**	**(-42.9, 100.0)**	**0.1752**	**0.7019**
	Overall	**Unadjusted[b]**	**279/322**	**86.6**	**(82.4, 90.2)**	**270/319**	**84.6**	**(80.2, 88.4)**	**2.0**	**(-3.7, 7.7)**	**<0.0001**	**0.5406**
		Adjusted[c]							**1.9**	**(-3.7, 7.5)**	**<0.0001**	**0.5130**
Failure			**34/322**	**10.6**	**(7.4, 14.4)**	**36/319**	**11.3**	**(8.0, 15.3)**				
Indeterminate			**9/322**	**2.8**	**(1.3, 5.2)**	**13/319**	**4.1**	**(2.2, 6.9)**				

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

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

b: Between-group CIs and hypothesis tests are calculated by the asymptotic method, corrected for continuity.

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

Source: 306/clini02 23AUG04 03:22

Based on the results, tigecycline has been shown to be non-inferior to imipenem/cilastatin in terms of clinical response at TOC in both the m-mITT and ME populations as the lower limit of the 95% CI for the difference between treatments is within the predefined non-inferiority margin of -15%.

Microbiological response

One hundred ninety (190) patients in study 301, and 153 in study 306 were excluded from the ME population due to the fact that the isolates were not susceptible to the study drugs.

In study 301 the percentage of eradications at the subject level at TOC in the ME population was 80.6% in the tigecycline group vs. 82.4% in the imipenem/cilastatin group, 95% CI for the unadjusted difference: -9.0, 5.4. The rates of persistence were 15.8% vs. 16.5%. In the m-mITT population the figures for eradication were 73.5% and 78.2%, respectively. The unadjusted difference in eradication rates was -4.7% (95% CI, -11.8, 2.3). As for persistence, the percentages were 16.8% for the tigecycline group vs. 16.7 % in the imipenem/cilastatin group. The percentage of patients with indeterminate response in the m-mITT population was 5.5% (tigecycline) and 3.8% (imipenem/cilastatin). As for superinfection, these figures were 4.2% and 1.3%, respectively.

In study 306, the percentage of eradication at the subject level at TOC in the ME population was 91.3% in the tigecycline group vs. 89.9% in the imipenem/cilastatin group (95% CI for the unadjusted difference: -4.0, 6.8). As for persistence, the percentages were 7.9% vs. 10.1%. Within the m-mITT population, infections were eradicated in 86.6% of tigecycline subjects and 84.6% of imipenem/cilastatin subjects at TOC. The difference in eradication rates was 2% (95% CI, –3.7, 7.7, unadjusted). As for persistence, the percentages were 9.9% for the tigecycline group vs. 11.3% in the imipenem/cilastatin group. The percentage of patients with indeterminate response in the m-mITT population was 2.8% (tigecycline) and 4.1% (imipenem/cilastatin). As for superinfection, these figures were 0.6% and 0.0%, respectively.

At the test-of-cure assessment, the difference in eradication rates among ME subjects (pooled data) with monomicrobial infections was 2.6% (92.8% in the tigecycline group and 90.2% in the imipenem/cilastatin group). Among those with polymicrobial infections, the difference was -1.2% (82.5% in the tigecycline group and 83.7% in the imipenem/cilastatin group). When adjusted for type of infection, the difference in eradication rates between the 2 treatment groups was 0.7% (95% CI, -3.3%, 4.8%). In the m-mITT population, the difference in eradication rates of patients with monomicrobial infections at the test-of-cure assessment was -0.4% (85.1% in the tigecycline group and 85.4% in the imipenem/cilastatin group). Among those with polymicrobial infections, the difference was -1.7% (77.2% in the tigecycline group and 78.9% in the imipenem/cilastatin group). When adjusted for type of infection, the difference in eradication rates between the 2 treatment groups was -1.1% (95% CI, -5.4%, 3.2%).

In the m-mITT population of studies 301 and 306 *Escherichia* species (mainly *E. coli*) followed by *Bacteroides* species and *Streptococcus* species were the baseline pathogens most frequently isolated.

To a lesser extent, other isolates found were *Enterococcus* species, *Klebsiella* species and *Staphylococcus* species. No vancomycin resistant enterococci were isolated in these trials.

The pooled results of the microbiological response at the pathogen level at TOC within the ME population is summarised in table below.

Isolate	***Response***	***Tigecycline***		***Imipenem/cilastatin***	
		n/N	%	n/N	%
Bacteroides fragilis	Eradication Persistence	68/87 19/87	78.2 21.8	59/73 14/73	80.8 19.2
Bacteroides thetaiotaomicron	Eradication Persistence	37/41 4/41	90.2 9.8	31/36 5/36	86.1 13.9
Bacteroides uniformis	Eradication Persistence	15/17 2/17	88.2 11.8	14/16 2/16	87.5 12.5
Bacteroides vulgatus	Eradication Persistence	14/16 2/16	87.5 12.5	4/6 2/6	66.6 33.3
Citrobacter freundii	Eradication Persistence	12/16 4/16	75 25	3/4 1/4	75 25
Clostridium perfringens	Eradication Persistence	18/19 1/19	94.7 5.3	20/22 2/22	88.2 11.8
Enterobacter cloacae	Eradication Persistence	14/16 2/16	87.5 12.5	16/17 1/17	90.9 9.1
Escherichia coli	Eradication Persistence	280/325 45/325	86.2 13.8	296/340 44/340	87.1 12.9
Klebsiella oxytoca	Eradication Persistence	19/20 1/20	95 5	17/19 2/19	89.5 10.5
Klebsiella pneumoniae	Eradication Persistence	46/52 6/52	88.5 11.5	54/60 6/60	90 10

Subjects treated with tigecycline who had isolates deemed to have developed indeterminate or resistant susceptibility to tigecycline as defined by the provisional breakpoints, were determined in the cIAI studies. No isolates demonstrated the development of decreased susceptibility to tigecycline in study 301. In study 306, 2 subjects in the study were identified with isolates deemed to have developed indeterminate or resistant susceptibility to tigecycline, as defined by the per-protocol provisional breakpoints. The subjects are listed in the following table along with their isolates, corresponding MIC values, and clinical response to tigecycline therapy.

		MIC	Clinical Response	
Subject Number	Isolate	µg/mL	End of Therapy	Test-of-Cure
306-019-0355	*Morganella morganii*	8	Failure	Failure
306-106-2074	*Klebsiella pneumoniae*	8	Failure	Failure

Source: /draft: CLINICAL R&D/DRAFT CLINICAL STUDY REPORTS/DRAFT 3074A1 TIGECYCLINE (GAR-936)/DRAFT 306/MISC SOURCE DOX FOR 306 CSR/DRAFT 306 T9.3.2.4.3-1-ST9Xdescr.doc

- Subgroup analysis

In the analysis of clinical response by clinical diagnosis, the highest rates of clinical cure were achieved in complicated cholecistytis and gastric and duodenal perforation. In general, these analyses can be considered consistent with the main analysis of clinical response although they should be interpreted with caution due to limited size of patient groups. Additional exploratory analyses for clinical failures were performed and again, although they should be interpreted with caution, it seems that the most consistent independent predictors for failure were APACHE II score and geographic region, although the last factor can be explained by differences in age, APACHE II scores and higher rates of complicated diverticulitis and lower rates of appendicitis and complicated cholecystitis. Immunocompromised patients were excluded from pivotal clinical trials. This is highlighted in section 4.4 of the SPC.

Complicated Skin and Soft Tissue Infections (cSSTI)

Methods

Two pivotal phase 3 trials (study 300 and 305) have been submitted in support of the indication complicated skin and skin structure infection. Study 300 was carried out in the Western hemisphere, and 305 in worldwide. The Study Protocols were similar in all essential points. Both phase 3 studies were multicenter, multinational, double blind (third-party unblinded) in which 1129 patients (approximately 500 patients per trial) were randomised to receive either tigecycline (an initial dose of 100 mg followed by 50 mg every 12 hours, iv) or vancomycin/aztreonam (1 gram of vancomycin iv followed by 2 g of aztreonam iv administered every 12 hours) for up to 14 days.

Key inclusion criteria were:

1. Hospitalized male and female subjects, 18 years of age or older.
2. Anticipated need for intravenous (IV) antibiotic therapy of 5 days' duration or longer.
3. Subjects known or suspected to have a cSSTI, including cSSTI that involved deep soft tissue, or required significant surgical intervention or that was associated with a significant underlying disease state that complicated response to treatment (such as diabetes mellitus, peripheral vascular disease (PVD), peripheral neuropathy, or lower venous insufficiency. This included clinical entities such as 1 of the following:
    a. Infected ulcers that had developed signs of erythema, swelling, tenderness, pus, or warmth.
    b. Burns (less than 5% body surface area, nonfull-skin thickness). In study 300 subjects with burns up to 25% of body surface area (nonfull-skin thickness) could be enrolled at selected study centers.
    c. Major abscess (not treatable through surgery alone).
    d. Deep or extensive cellulitis, either associated with an underlying disease state or greater than 10 cm in width or length.
    e. Peripheral IV catheter sites with documented purulent drainage, provided that the catheter line was removed.
    f. Infected human or animal bites.
4. Subjects with 2 of the following indicators of infection:
    a. Drainage and/or discharge.
    b. Fever: body temperature higher than 37.8°C (100°F) oral, 37.9°C (100.2°F) axillary, 38.2°C (100.8°F) tympanic, or 38.4°C (101.0°F) rectal (core), within 24 hours before enrolment.
    c. Erythema.
    d. Swelling and/or induration.
    e. Localized warmth.
    f. Pain and/or tenderness to palpation.
    g. White blood cell count greater than 10,000/mm3.
5. Subjects who had not received more than 2 doses of any nonstudy antibacterial drug after the original culture of the infected site had been obtained, except for subjects who were considered prior antibiotic failures.
6. For subjects who were considered therapeutic failures for prior antibiotic therapy with another agent at entry, a Gram stain or baseline culture of the infected site showing a potential pathogen was obtained before the first dose of study drug was administered. Once a subject began treatment with study drug, no other concomitant antibiotics could be given.

Main exclusion criteria were as follows:

1. Infected diabetic foot ulcers or decubitus ulcers where the infection was present for longer than 1 week or chronically infected ulcers in subjects who could not be compliant with measures necessary for chronic wound healing.
2. Necrotizing fasciitis or gangrene.
3. An uncomplicated skin and/or skin structure infection (eg, simple abscesses, folliculitis, impetiginous lesions, furunculosis, superficial cellulitis).
4. Subjects with suspected or known infection with *Pseudomonas aeruginosa*. However, subjects in whom the initial wound culture showed evidence of infection with *Pseudomonas aeruginosa* could continue to receive study drug at the investigator's discretion if the subject was showing signs of substantial and continuous clinical improvement on a daily basis.
5. Osteomyelitis contiguous to the infected site.
6. Crepitant cellulitis (gas gangrene).

7. Presence of any of the following laboratory findings:
   a. Neutropenia (absolute neutrophil count less than 1000/mm3).
   b. Presence of hepatic disease:
      i. Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transferase (SGOT) or alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase greater than 10 times the upper limit of normal (ULN) values.
      ii. Bilirubin values greater than 3 times the ULN.
      iii. Subjects with acute hepatic failure or acute decompensation of chronic hepatic failure.

The comparator group in both trials was vancomycin/aztreonam. This is justified based on vancomycin broad activity against aerobic gram-positive pathogen whereas aztreonam provides broad activity against gram-negative pathogens, including some strains of *P. aeruginosa*. The use of vancomycin for treating infections caused by gram-positive cocci susceptible to methicillin is questionable. Currently, the empirical use of vancomycin against gram-positive infections is driven by the knowledge of local prevalence patterns and/or for the presence of certain risk factors. Consequently, whether the use of a beta-lactam would have rendered similar or different results if compared with tigecycline remains unknown. However, from the data submitted and indirect comparisons with data from other drugs in the same indication it seems that tigecycline performs well in cSSTI due to methicillin-susceptible *S. aureus*.

The primary efficacy outcome was the clinical response (cure or failure) for the clinically evaluable (CE) and the clinical response (cure or failure/indeterminate) for the clinical modified intent-to-treat (c-mITT) populations at the test-of-cure (TOC) assessment (which took place at least 12 days but not more than 92 days after the last dose of study drug). In both trials, the objective was to show the non-inferiority of tigecycline vs. vancomycin/aztreonam using a delta of 15% (absolute) at the test-of-cure (TOC) assessment.

Results

Demographic and baseline disease characteristics were similar between the treatment groups in each study, excepting differences in ethnic origin. In study 300, 53% of subjects were white and 38% were of other ethnic origin (primarily Hispanic). More than 80% of subjects in study 305 were white. Approximately 7% of subjects were 75 years or older (safety population, pooled data of studies 300 and 305). The treatment groups (pooled data, CE population) were comparable in terms of their clinical diagnoses, although comorbid conditions between the two studies differed, i.e. in study 305, 11.2% of subjects in the tigecycline arm (12.7% in vancomycin/aztreonam arm) had diabetes mellitus as a comorbid condition compared to 29.1% (29.3% in vancomycin/aztreonam arm) in study 300. In study 305, 4.5% of subjects in the tigecycline arm (5.6% in V/A arm) had peripheral vascular disease as a comorbid condition compared to 9.5% (8.1% in V/A arm) in study 300.

About half of all infections were diagnosed as deep soft tissue infections involving cellulitis covering more than 10 cm in area (where anatomically applicable). Approximately 27.9% of subjects were diagnosed with major abscesses. Limited numbers of patients with co-morbid factors such as diabetes mellitus (20%), peripheral vascular disease (7%) and with bacteraemia (3%) were enrolled. Patients with severe underlying disease, such as immunocompromised, patients with decubitus ulcer infection or patients that had infections requiring longer than 14 days of treatment (e.g. necrotizing fasciitis) were not enrolled. Few patients with diabetic foot infections (5%) were enrolled. Consequently, the limited data on relevant subpopulations (patients with diabetic foot infection, with decubitus ulcer infection, patients with wound infection and patients with bacteraemia) and severely ill patients is stated in section 4.4 of the SPC.

Study 300

Table below summarises the clinical diagnoses for infections in the CE population at baseline.

Table 9.2-2: Clinical Diagnosis of Infections in the CE Population: Number (%) of Subjects

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

a: Subjects with cellulitis could have met more than 1 diagnostic criterion.
Source: demo5_diag_eff1 (rtf in in-text folder), 21JUL04:18:21

Study 305

Table below summarises the clinical diagnoses for infections in the CE population at baseline.

Clinical Diagnosis	Tigecycline (n = 223)	Vancomycin/ Aztreonam (n = 213)	Total (n = 436)	Chi-Square p-Value
Any diagnosis				0.535
Infected ulcers	18 (8.1)	12 (5.6)	30 (6.9)	
Major abscesses	66 (29.6)	75 (35.2)	141 (32.3)	
Burns	9 (4.0)	8 (3.8)	17 (3.9)	
Deep soft tissue infection	130 (58.3)	118 (55.4)	248 (56.9)	
Cellulitis[a]	125 (56.1)	111 (52.1)	236 (54.1)	
Complicated underlying disease	11 (4.9)	20 (9.4)	31 (7.1)	
≥10 cm (where anatomically applicable)	114 (51.1)	103 (48.4)	217 (49.8)	
Requiring surgery/drainage	56 (25.1)	60 (28.2)	116 (26.6)	
Wound infection	5 (2.2)	7 (3.3)	12 (2.8)	

a: Some subjects with cellulitis met more than 1 diagnostic criterion.
Source: demo5_diag_eff1, 21 Jul 2004

Clinical response

In study 300, the cure / failure /completed numbers of the patients in the CE population were 165 / 34 / 199 for tigecycline and 163 / 35 / 198 for the reference therapy. The 95% CI for the difference between treatments at TOC was: -7.4, 8.6. In the c-mITT population, the cure/ failure/ indeterminate/ completed numbers were 209/ 48/ 20/ 277 for tigecycline and 200/ 46/ 14/ 260 for the reference therapy. The 95% CI for the difference between treatments at TOC was: -9.0, 6.1.

The two following tables summarise the clinical response in the CE and in the c-mITT populations.

Table 9.3.1-1: Analysis of Clinical Response: CE Population

		----------Tigecycline---------		----------Vancomycin/Aztreonam---------		Difference (Tigecycline – Vancomycin/Aztreonam			
Visit	Response	n/N	% (95% CI)[a]	n/N	% (95% CI)[a]	%	% (95% CI)[b]	Test for Noninferiority p-Value	Test for Differences p-Value
Last Day of Therapy	Cure	174/199	87.4 (82.0, 91.7)	168/198	84.8 (79.1, 89.5)	2.6	(-4.7, 9.9)	<0.001*	0.5475
	Failure	25/199	12.6	30/198	15.2				
Test-of-Cure	**Cure**	**165/199**	**82.9 (77.0, 87.9)**	**163/198**	**82.3 (76.3, 87.4)**	**0.6**	**(-7.4, 8.6)**	**<0.001***	**0.9816**
	Failure	**34/199**	**17.1**	**35/198**	**17.7**				

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

Table 9.3.1-2: Analysis of Clinical Response: c-mITT Population

		---------Tigecycline---------		-------Vancomycin/Aztreonam-------		Differences (Tigecycline – Vancomycin/Aztreonam)			
Visit	Response	n/N	% (95% CI)[a]	n/N	% (95% CI)[a]	%	95% CI[b]	Test for Noninferiority p-Value	Test for Differences p-Value
Last Day of Therapy	Cure	234/277	84.5 (79.7, 88.5)	212/260	81.5 (76.3, 86.1)	2.9	-3.8, 9.7	<0.001*	0.4291
	Failure	36/277	13.0	41/260	15.8				
	Indeterminate	7/277	2.5	7/260	2.7				
Test-of-Cure	**Cure**	**209/277**	**75.5 (69.9, 80.4)**	**200/260**	**76.9 (71.3, 81.9)**	**-1.5**	**-9.0, 6.1**	**<0.001***	**0.7650**
	Failure	**48/277**	**17.3**	**46/260**	**17.7**				
	Indeterminate	**20/ 277**	**7.2**	**14/ 260**	**5.4**				

a: Treatment group confidence intervals calculated by using the method of Clopper and Pearson.
b: Estimates of differences between treatment groups and corresponding confidence intervals and hypothesis tests are done by using the asymptotic method (corrected for continuity).
*Tigecycline was statistically noninferior to vancomycin/aztreonam.
Source: CMCLIN1_CFI

In study 305, the cure / failure /completed numbers of the patients in the CE population were 200 / 23 / 223 for tigecycline and 201 / 12 / 213 for the reference therapy. The 95% CI for the difference between treatments at TOC was:-10.2, 0.8. In the c-mITT population, the cure/ failure/ indeterminate/ completed numbers were 220/ 31/ 10/ 261 for tigecycline and 225/ 26/ 8/ 259 for the reference therapy. The 95% CI for the difference between treatments at TOC was: -9.0, 3.8.
The following table compares cure and failure rates in the CE population on the last day of therapy and at the test-of-cure assessment.

Table 9.3.1-1: Analysis of Clinical Response Within the CE Population

		——— Tigecycline ———		—— Vancomycin/Aztreonam——		Difference (Tigecycline – Vancomycin/Aztreonam)		
Visit	Response	n/N	% (95% CI)[a]	n/N	% (95% CI)[a]	% (95% CI)[b]	Test for Noninferiority (p-Value)	Test for Differences (p-Value)
Last Day of Therapy	Cure	208/222	93.7 (89.6, 96.5)	204/212	96.2 (92.7, 98.4)	-2.5 (-7.1, 2.0)	<0.001*	0.3219
	Failure	14/222	6.3	8/212	3.8			
Primary Endpoint								
Test-of-Cure	**Cure**	**200/223**	**89.7 (84.9, 93.3)**	**201/213**	**94.4 (90.4, 97.1)**	**-4.7 (-10.2, 0.8)**	**<0.001***	**0.1015**
	Failure	**23/223**	**10.3**	**12/213**	**5.6**			

Note: Two (2) subjects, 1 from each treatment group, had indeterminate responses on the last day of therapy but were clinical cures at the test-of-cure assessment. Subject numbers are 305-057-1045 and 305-082-2002.
a: Treatment group confidence intervals are calculated by using the method of Clopper and Pearson.
b: Estimates of differences between treatment groups and corresponding confidence intervals and hypothesis tests are done by using the asymptotic method (corrected for continuity).
* Tigecycline was statistically noninferior to vancomycin/aztreonam.
Source: ceclin1_cf_2, 31 May 2004

The following table presents comparisons for the treatment groups within the co-primary c-mITT population, including subjects with indeterminate responses.

Table 9.3.1-2: Analysis of Clinical Response Within the c-mITT Population

		Tigecycline		Vancomycin/Aztreonam		Difference (Tigecycline – Vancomycin/Aztreonam)		
Visit	Response	n/N	% (95% CI)[a]	n/N	% (95% CI)[a]	% (95% CI)[b]	Test for Noninferiority (p-Value)	Test for Differences (p-Value)
Last Day of Therapy	Cure	237/261	90.8 (86.6, 94.0)	231/259	89.2 (84.8, 92.7)	1.6 (-3.9, 7.2)	<0.001*	0.6399
	Failure	20/261	7.7	22/259	8.5			
	Indeterminate	4/261	1.5	6/259	2.3			
Primary Endpoint								
Test-of-Cure	**Cure**	**220/261**	**84.3 (79.3, 88.5)**	**225/259**	**86.9 (82.1, 90.7)**	**-2.6 (-9.0, 3.8)**	**<0.001***	**0.4755**
	Failure	**31/261**	**11.9**	**26/259**	**10.0**			
	Indeterminate	**10/261**	**3.8**	**8/259**	**3.1**			

a: Treatment group confidence intervals are calculated by using the method of Clopper and Pearson.
b: Estimates of differences between treatment groups and corresponding confidence intervals and hypothesis tests are done by using the asymptotic method (corrected for continuity).
* Tigecycline was statistically noninferior to vancomycin/aztreonam.
Source: cmclin1 cfi 2. 01 Jun 2004

Using the criteria for non-inferiority of 15%, tigecycline has been shown to be non-inferior to vancomycin/aztreonam in terms of clinical response at TOC in both the CE and c-mITT populations as the lower limit of the 95% CI for the difference between treatments lies within the predefined -15% margin. However, a trend favouring the comparator arm is seen in study 305. In analysis of pooled data (studies 300 and 305) the 95% CI for the difference in cure rates between treatments was -6.8, 2.7 in the CE population and -7.1, 2.8 in the c-mITT population.

Microbiological response

The number (%) of subjects who were microbiologically evaluable for analysis is fairly low (study 300: 39% vs. 39,2% and 305: 59.6% vs. 54.6%.). One hundred and sixty-nine patients in study 300 and 124 in study 305 were excluded from the ME population due to the fact that the isolates were not susceptible to the study drugs.

In study 300 the percentage of eradication at the subject level in the m-mITT population at TOC was 72.6% (135/186) of subjects in the tigecycline group and 73.1% (125/171) of subjects in the vancomycin/aztreonam group. The 95% CI for the difference was -0.5 (-10.3, 9.3). For persistence these figures were 18.3% (34/186) in the tigecycline group and 19.3% (33/171) in the vancomycin/aztreonam group. The rates of indeterminate responses were 6.5% on tigecycline vs. 3.5% on comparator. Superinfection was slightly higher in the vancomycin/aztreonam group (4.1%) than in the tigecycline group (2.7%). Within the ME population, infections were eradicated in 78.3% of tigecycline subjects and 77.0% of vancomycin/aztreonam subjects at the test-of-cure assessment. The between-group difference in eradication rates was 1.3% (95% CI, -0.4, 13.0) at the test-of-cure assessment.

In study 305, the percentage of eradication at the subject level in the m-mITT population at TOC was 79.4% (166/209) of subjects in the tigecycline group and 84.2% (171/203) of subjects in the vancomycin/aztreonam group. The 95% CI of the difference was -4.8 (-12.7, 3.1). For persistence these were 16.3% (34/209) of subjects in the tigecycline group and 10.8% (22/203) of subjects in the vancomycin/aztreonam group. The rates of indeterminate responses were 1.9% on tigecycline vs. 3.0% on comparator. Superinfection was higher in the tigecycline group (2.5%) than in the vancomycin/aztreonam group (2.0%). Within the ME population, infections were eradicated in 84.8% of tigecycline subjects and in 93.2% of vancomycin/aztreonam subjects at the test-of-cure assessment. The between-group difference in eradication rates was -8.5% (95% CI, -16.0, -1.0) at the test-of-cure assessment.

In study 305, the comparison of the percentage of patients for whom eradication was reached at TOC shows that a higher rate of patients in the vancomycin/aztreonam group achieved this endpoint in polymicrobial infections (79.7% vs. 94.0%, 95% CI for the adjusted difference: -15.0, -1.0) within the ME population. In the m-mITT population, these figures were 85.2% vs.74.7%, 95% CI for the adjusted difference:-12.0, 3.0. In analysis of pooled data (studies 300 and 305) the 95% CI for the adjusted difference in eradication rates between treatments was -8.7, 3.1 in the m-mITT population and -10.2, 2.1 in the ME population.

The microbiological response at the pathogen level in the m-mITT population shows that in study 300 the total number of *S. aureus* isolated was 106 in the tigecycline group vs. 95 in the comparator one. The percentage of eradication was 73.6% vs. 78.9%, respectively. Of the total number of isolates, there were 43 MRSA on tigecycline and 39 MRSA on the comparator. The percentage of eradication was 67.4% vs. 82.1%. For non MRSA the percentages of eradication were similar. The same figures in study 305 were as follows: the total number of *S. aureus* isolates was 119 on tigecycline and 104 on comparator study drugs; the percentages of eradication were 80.7% vs. 85.6%; for MRSA the number in each group was 13 isolates and the respective percentages of eradication were 76.9% and 46.2%. In the ME population the percentage of eradication at TOC for MRSA in study 300 was 72.7% (16/22) on tigecycline vs. 80.8% (21/26) on comparator. The same figures in study 305 are 88.9% (8/9) and 57.1% (4/7), respectively. In the case of MSSA, eradication rates in study 300 at TOC (ME population) was 91.1% (41/45) on tigecycline and 81.4% (35/43) on comparator. In study 305 these were as follows: 87.8% (79/90) and 96.1% (74/77) respectively.
As for *S. pyogenes*, in study 300 the percentage of eradication at TOC (ME population) in the tigecycline arm was 87.5% (6/7) vs. 75.0% (6/8) in the comparator. In study 305, the percentage of eradication at TOC (ME population) was 96.0% (24/25) in the tigecycline arm and 100% (19/19) in the comparator.

No vancomycin resistant enterococci (VRE) were isolated in the population recruited in the two pivotal studies.

Subjects treated with tigecycline who had isolates deemed to have indeterminate or resistant susceptibility to tigecycline as defined by the provisional breakpoints were determined in the cSSTI studies. No isolates demonstrated the development of decreased susceptibility to tigecycline during these studies.

- Subgroup analyses

This was performed on pooled data (clinical response) in the CE population to evaluate the consistency of tigecycline cure rates. No significant interactions with treatment were identified, although the amplitude of the 95% confidence intervals is wide for some of the categories within the different subgroups (age≥ 75 years, Asian ethnic origin, clinical diagnosis of infected ulcers and burns, presence of Peripheral Vascular Disease, Cl_{CR} < 30 ml/min, diabetes and baseline bacteraemia). As a consequence it is difficult to draw adequate conclusions based on these results. Immunocompromised patients were excluded from pivotal clinical trials. These aspects are addressed in section 4.4 of the SPC.

Supportive studies

Three (3) studies (3074A1-307-WW, -309-WW, and -310-WW) are currently being conducted in subjects with serious infections caused by known resistant pathogens (RP). Interim data are included from 1 of the ongoing RP studies that specifically enrols cSSTI subjects with MRSA or other resistant pathogens (3074A1-307-WW). This was a phase 3, multicenter, double-blind, randomized (3:1) study to evaluate tigecycline and linezolid for the treatment of selected serious infections in subjects with VRE and to evaluate tigecycline and vancomycin for the treatment of selected serious infections in subjects with MRSA. For this interim analysis (28 May 2004 data cut-off), 5 VRE subjects and 24 MRSA subjects have been enrolled in the modified intent-to-treat (mITT) population. Efficacy evaluations were performed at the end of treatment and at 12 to 37 days after the last dose of study drug for the Test-of-Cure assessment, unless the subject was deemed a clinical failure. Any subject who received at least 1 dose of study drug was included in the evaluation for safety. No formal statistical analysis was planned or conducted. In summary, tigecycline showed moderate efficacy in subjects with MRSA, curing 62.5% and 66.7% of *all infection types* at the test-of-cure assessment within the ME and m-mITT co-primary populations. In subjects with complicated skin and soft tissue infections, tigecycline cured 83.3% and 75.0% of infections in subject groups.

Clinical safety

Patient exposure

A total of 2797 subjects, including 1415 subjects treated with tigecycline and 1382 treated with a comparator received at least 1 dose of tigecycline in the phase 3 clinical trials. In these studies patients were treated with the proposed dosage (100 mg IV followed by 50 mg every 12 hours). The mean duration of therapy was 7 to 8 days for both the total tigecycline and comparator groups. More men than women were enrolled (approximately 62% vs 38%, respectively). The age distribution was similar between the 2 treatment groups, with an overall mean age of 47 years. Approximately 19% of subjects were age 65 or older; about 8% were aged 75 years or older. About 65% of the subjects were white, 7% black, and the remainder Asian and others. The demographic and baseline characteristics were similar for the tigecycline and comparator subjects ($p > 0.05$).

Adverse events

Of these patients 76.6% on tigecycline and 71.1% on comparator reported one or more AEs ($p<0.001$). The adverse events most commonly reported in patients on tigecycline in phase 3 clinical trials were nausea (33.5% vs. 19.9%), vomiting (22.3% vs. 13.4%) and diarrhoea (12.9% vs. 11.9%). Significantly more subjects on tigecycline reported nausea, vomiting, infection, anorexia, dyspepsia, large intestine perforation, jaundice, increased activated partial thromboplastin time (aPTT), Prothrombin Time (PT) prolonged, amylase increased, BUN increased, bilirubinemia, hypoproteinemia, and pneumonia.

Treatment-emergent adverse events (TEAE) were defined as that AE "that was not present when the active (treatment) phase of the study began and was not a chronic condition that was part of the subject's medical history, or was present at the start of the study or as part of the subject's medical history but its severity or frequency increased during the active phase of the study". The Company has presented the incidence of TEAE reported in ≥ 2% of patients treated in phase 3 clinical trials (pooled data).

TEAEs were reported by 71.6% subjects in the tigecycline group and by 67.4% subjects in the comparator group ($p=0.017$). The most common drug-related TEAEs in patients treated with tigecycline were nausea at 20.4% (12.9% mild; 6.6% moderate; 0.8% severe) and vomiting at 13.5% (8.3% mild; 4.5% moderate; 0.6% severe). Discontinuation from tigecycline was most frequently associated with nausea (1.3%) and vomiting (1.0%). The Applicant was requested to further elaborate on the cause of the gastrointestinal adverse effects, in particular to discuss to which extent gastrointestinal symptoms may be due to vestibular toxicity. In this regard, it is likely that the cause of these adverse events is tigecycline's direct effect on the gastrointestinal system rather than vestibular toxicity. No conclusions can be made about the use of prophylactic antiemetic therapy because of the small number of patients who received prophylactic antiemetic medications before tigecycline administration. As a consequence, no recommendation on whether to use antiemetics is made in the SPC. Food seems to improve the gastrointestinal tolerability and therefore, if confirmed, this should be mentioned in the SPC. However, this was no formally assessed in the clinical trials of tigecycline and no recommendation is made in the SPC on this issue.

Clostridium difficile-associated diarrhoea and colitis caused by overgrowth of toxin-producing clostridia, have rarely been reported with the administration of oral or parenteral tetracyclines. No cases of pseudomembranous colitis were reported in patients on tigecycline in phase 3 clinical trials but one case of *Clostridium difficile*-associated diarrhoea, considered as serious, was reported in a phase 2 clinical trial.

Hypersensitivity reactions have rarely been reported with tetracyclines and include a wide variety of symptoms (e.g., rash, dermatitis, urticaria, pruritus, anaphylaxis, fever, headache, arthralgia…). Some TEAEs compatible with hypersensitivity reactions have been reported in patients on tigecycline. This fact may be complicated by the known histamine-release potential of tetracyclines. Allergic reaction was a drug-related treatment emergent adverse event (TEAE) reported infrequently (≥0.2% and <2%) in patients receiving tigecycline. These allergic reactions characterized as rash and/or pruritus and/or generalized redness. One SAE report involved a "possible allergic reaction" occurring in a 49-year old patient enrolled in the RP study. On the 6th day of therapy during the infusion, the patient experienced a "possible allergic reaction" characterized as tachycardia (HR in 120s), with shaking, chills, fever to 103.4 degrees Fahrenheit, and hypotension to "80s/40s." The events were managed with intravenous fluids/volume expanders, packed RBC and platelet transfusions, and diphenhydramine. These events

may have been due to a septic episode. Additionally, the timing of the event (6th day of therapy) complicates causality assessment.

According to clinical evaluation, possible histamine release does not appear likely to be a clinical safety concern when the drug is infused slowly. However, section 5.3 of the SPC warned about the potential occurrence of histaminergic reactions in animals after rapid iv. bolus injections. Section 4.8 also includes treatment emergent adverse reactions compatible with hypersensitivity such as rash and pruritus. Hypersensitivity to tetracycline class of antibiotics is considered a contraindication for tigecycline (section 4.3), given their structural similarity. Finally, hypersensitivity is considered within the Risk Management System (RMS) as an identified risk that requires further evaluation through pharmacovigilance routine activities.

Photosensitivity, manifested as an exaggerated sunburn reaction on sun-exposed areas of the body, has been described with tetracyclines. These reactions, if they occur, develop at any time from within a few minutes up to several hours after exposure to sun and usually persist 1 or 2 days after discontinuance of tetracyclines. No cases of photosensitivity or phototoxicity were reported in phase 3 clinical trials with tigecycline. As most patients included in these clinical trials are likely to be treated in hospital it is unlikely that patients were exposed to the sun. Therefore, at present, photosensitivity cannot be ruled out in patients receiving tigecycline. Nevertheless, because of the structural similarity between tigecycline and tetracycline, the SPC addresses photosensitivity as a possible adverse event in section 4.4 of the SPC.

Infections were reported as TEAE in 7.0% of patients treated with tigecycline versus 4.2% on comparators. This AE was more frequent in patients included in trials assessing tigecycline in complicated intra-abdominal infections (10.2% vs. 5.5 of comparator; $p<0.001$).

Local reactions to procedure were reported as TEAE in 8.2% of patients treated with tigecycline vs., 8.1% treated with comparators. This was an expected AE, as it is well known that IV administration of tetracyclines frequently causes local reactions, especially when this administration is prolonged or when a single vein is used for repeated infusions.

Serious adverse events and deaths

A total of 188 (13.3%) subjects in the combined tigecycline group and 159 (11.5%) subjects in the comparator group had 1 or more SAEs in all phase 3 studies (300, 305, 301, 306, 307, and 309). The total incidence of SAEs was similar between the 2 treatment groups ($p = 0.169$). The most frequently reported SAEs in tigecycline-treated subjects were abscess (25 subjects; 1.8%), infection (24 subjects; 1.7%), and healing abnormal (23 subjects; 1.6%). The most frequently reported SAEs in comparator-treated subjects were also abscess (22 subjects, 1.6%) and infection (15 subjects; 1.1%). Significantly more tigecycline-treated subjects (14, 1%) than comparator-treated subjects (3, 0.2%) reported sepsis as an SAE ($p = 0.013$). Also, the following SAEs were reported more often in the tigecycline groups (n=1383) compared to the reference groups (n=1375): hepatic disorder (9 vs. 1 cases), and renal failure or nephropathy (6 vs. 4 cases). In studies 301 and 306 (cIAI), significantly more subjects treated with tigecycline than imipenem/cilastatin reported treatment emergent adverse events such as infections, including pneumonia (301) and sepsis.

One hundred and eleven (111) patients died during phase 3 trials, 67 in tigecycline group and 44 in comparators group. Although the percentage of death was not statistically different between treatment groups more patients treated with tigecycline died in all indications. In phase 3 cSSTI and cIAI trials, there were 32/1383 (2.3%) deaths in tigecycline vs. 22/1375 (1.6%) in the comparator group. Most of these deaths occurred in patients with intraabdominal infections (26/32). For the patients who died in both groups it was shown that higher age, higher APACHE scores and clinical diagnosis of perforation of intestine were presented. There were no statistically significant differences between groups of treatment. With regard to the infection related deaths, 17/1353 (1.3%) patients on tigecycline died because of this vs. 8/1375 (0.5) patients in the comparator group. A total of 21 patients (14 in the tigecycline group and 7 in the comparator group) died because of worsening of the infection. Of these patients, 12 had sepsis (8 tigecycline and 4 comparator), 5 had pneumonia (all tigecycline-treated), and 3 had both sepsis and pneumonia (all in tigecycline).

In the tigecycline group 10 subjects who died has a clinical diagnosis of perforated intestine or peritonitis due to perforation of the intestine; in the comparator group, 5 subjects who died were diagnosed with peritonitis due to perforation of the intestine. Peritonitis was considered the cause of death in 2 tigecycline-treated patients. Resistance of the baseline isolates do not contribute to these deaths as for the exception of two *P. aeruginosa* isolates all of them were susceptible.
As a consequence, there remains a concern of lack of efficacy in severely ill patients with fulminant and rapid disease. This is proposed to be dealt with appropriate SPC wording in sections 4.4 and 4.8. Furthermore, lack of efficacy in severely ill patients is addressed within the risk management plan and updated information on this issue is expected within the PSURS.

There is a known association between pancreatitis and tetracyclines. Since glycycyclines are structurally similar to tetracyclines, certain adverse reactions such as pancreatitis may be causally associated with tigecycline.

There were 3 cases of pancreatitis reported in the tigecycline-treated subjects versus 3 cases of pancreatitis in the comparator-treated subjects (see also Post-Marketing experience below). Of note, increased amylase was reported in a significantly greater number of tigecycline-treated subjects (38; 2.7%) versus the comparator arm (16 subjects; 1.2%) (p = 0.004). This is mentioned in sections 4.4 and 4.8 of the SPC. Acute pancreatitis will be closely monitored not only as per the Company's pharmacovigilance procedures but also a specific pancreatitis questionnaire to solicit follow-up information from spontaneous AE reports have been created. Additionally, more information regarding pancreatitis may be obtained from the ongoing community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) phase 3 clinical trials as well as the ongoing or planned phase 4 post-marketing studies.

Laboratory findings

More patients treated with comparators had abnormal test results, including: elevated potassium, low phosphorus, high SGOT/AST, high SGPT/ALT, and low lymphocytes (p=0.043 to <0.001). Hepatotoxicity, a known adverse event reported with tetracyclines, was specifically assessed in tigecycline clinical trials. The Applicant tried to identify clinical cases that would satisfy the criteria for "Hy's Law" in the entire phase 1 to 3 safety database. The potential signal of hepatotoxicity examined was the combination of significant transaminase elevation (to at least x 3ULN) accompanied by jaundice or by serum total bilirubin elevations, without evidence of biliary obstruction (significant elevation of ALP) (see Clinical White Paper from FDA Working Group, 2000). Six (6) patients on tigecycline and 5 subjects in the comparators including 3 in the imipenem/cilastatin group in the cIAI studies and 2 in the vancomycin/aztreonam group in the cSSTI studies appeared to satisfy the criteria for "Hy's Law". Although the number of potential Hy's law cases were numerically low, the rate of reported LFT abnormalities (considered isolated) is consistently higher among tigecycline-treated patients as compared to imipenem in both phase 3 studies carried out in patients with cIAI. This trend is observed for almost every individual parameter (bilirubin, alkaline phosphatase, SGOT, and SGPT). Consequently, this issue warrants further investigations and will be addressed within subsequent PSURs. The RMS includes both bilirubinemia and increased Aspartate Aminotransferase (AST)/Alanine Aminotransferase (ALT) as identified risks that deserve further evaluation. Meanwhile, both adverse reactions are mentioned in section 4.8 of the SPC.

There was increase in coagulation parameters (INR, Prothrombin Time and activated Partial Thromboplastin Time) in tigecycline group when compared to comparator group. It is known that certain tetracyclines diminish prothrombin activity and that could imply an increase in bleeding risk in patients. In order to exclude this risk the majority of the reported TEAEs that may indicate bleeding (e.g.,epistaxis, haemorrhage, anaemia) were reviewed and these TEAEs were no more frequent in the tigecycline group. This is mentioned in section 4.4, 4.5 and 4.8 of the SPC. In addition, Prothrombin Time (PT) and Partial Thromboplastin Time (PTT) prolongation are included within the RMS as identified risks that deserve further evaluation.
Increases in the mean BUN/urea in the absence of a consistent increase in the mean creatinine values were observed in patients on tigecycline. These findings, frequently reported with tetracycline class antibiotics, are not usually of clinical importance in patients with normal renal function but further deterioration of renal function has been observed when some tetracyclines are administered to patients with impaired renal function. As most patients receiving tigecycline are likely to be severely ill and

they are treated with concomitant drugs, there is a risk of azotemia, hyperphosphatemia and acidosis in relation to the use of tigecycline in patients with significantly impaired function. This is mentioned in section 4.4 of the SPC. Increased BUN is also mentioned in section 4.8. Finally, it is also included in the RMP as an identified issue that requires further evaluation.

In animal studies it has been shown, that there is bone-marrow toxicity as class-effect of tetracyclines. Bone marrow suppression was not identified as a safety concern during the clinical trials conducted with tigecycline. However, the primary toxicological determinant of the no observed adverse effect level (NOAEL) in both rats and dogs in the repeat-dose IV toxicity studies was bone marrow myelotoxicity. Exposures in animals at the NOAELs ranged from 0.7 to 2.8 times the exposure observed in humans at the proposed dosage (100 mg/day) for registration. At high, suprapharmacological doses, tigecycline would be expected to induce some levelof immunocompetence in animals based on the observation of lymphoid depletion/atrophy of lymph nodes, spleen, and thymus in high-dose animal studies. Since tigecycline demonstrated toxicity towards bone marrow, lymph nodes, and the production of red and white blood cells, an additional non-clinical study [a T-cell dependent antibody response (TDAR) immune function study of tigecycline in rats using keyhole limpet hemocyanin (KLH) as an antigen] has been requested as a follow up measure. The RMP will be updated accordingly provided that the results of this study are of relevance for humans.

Effect of tigecycline on QTc interval

To address the potential effect of tigecycline on the prolongation of the QT interval, standard 12-lead ECGs were performed in phase 3 clinical trials as per protocol, the log-linear correction being considered the primary method of analysis of QT/QTc data. No thorough QTc evaluation has been done in healthy volunteers and therefore a full characterisation of the mean effect of tigecycline on cardiac repolarisation still remains. The data from phase III trials does not suggest a relevant proarrhythmic effect of tigecycline. The low potential for drug interactions further reassures this view. These findings do not suggest that subjects treated with tigecycline are at any increased risk for cardiovascular events compared to comparator-treated subjects. However, because of past concerns of cardiovascular events including QTc prolongation with other antibiotics and drug products, these events are potential risks requiring further evaluation and are included in the RMP.

Safety related to drug-drug interactions and other interactions

Drug-drug interactions were not reported, except for the comment in study 3074A1-300-US/CA related to prolongation of mean aPTT. Of the 12 subjects in the tigecycline group who were flagged in the PCI coagulation profile, 3 had anticoagulants as concomitant medications. No bleeding was associated with this increase and none required treatment/intervention.

Discontinuation due to AES

Regarding discontinuations 12.2% of subjects in the tigecycline group and 10.3% of subjects in the comparator group discontinued study drug during all phase 3 clinical trials (p=0.135). Sixty-nine (4.9%) tigecycline-treated subjects and 58 (4.2%) comparator treated subjects discontinued study drug primarily because of AEs. The rates for discontinuation primarily because of AEs were similar in both the tigecycline and comparator treatment groups (p=0.414). Nine percent (9.0%) of subjects in the tigecycline group and 8.7% of subjects in the comparator group withdrew from the study early. Both in the tigecycline group and comparator group other events and failure/refusal to return for a follow-up visit were the most common reasons for withdrawal. There was no significant difference between the treatment groups for the primary reasons for withdrawal ($p \geq 0.05$).

Post marketing experience

At the time of initial submission of the dossier, tigecycline was not marketed in any country. The FDA granted a Marketing Authorisation in June 2005. Three cases of acute pancreatitis have been reported in the post-marketing setting and considered to be tigecycline-related.

- User consultation

The Applicant has committed to start the Readability User Test prior the Commission Decision and to submit the results of the test as a post-approval commitment.

5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the Applicant fulfils the legislative requirements. The company must ensure that this system is in place and functioning before the product is placed on the market.

Risk Management Plan

A risk management plan was submitted.

The Safety Specification covers all the issues that are considered relevant for the use of tigecycline in clinical practice. Within the Pharmacovigilance Plan most of the activities planned are routine pharmacovigilance practices. From the safety database all the adverse reactions reported in phase III clinical trials and post-marketing have been included in the Summary of Product Characteristics. In addition, the applicant undertook to specifically review the following adverse reactions and report them in the PSUR according to the normal PSUR schedule, using the International birth date of 15th of June 2005.

- Nausea/vomiting
- Hyperbilirubinemia
- Pancreatitis
- PT/PTT increase
- BUN increase
- Hypersensitivity
- QTc prolongation / Cardiovascular effects
- Drug interactions
- Lack of efficacy in severely ill patients
- Development of resistance

A summary of the risk management plan for identified risks associated with the use of tigecycline is summarised in the table below:
Table: Summary of the risk management plan

Safety issue	**Proposed pharmacovigilance activities**	**Proposed risk minimisation activities**
GI effects: Nausea Vomiting	Review of results from ongoing and planned clinical trials Routine PhV	Sub section in 4.8: Nausea, vomiting diarrhoea, anorexia, abdominal pain, dyspepsia Follow up in PSUR
Hepatic effects: Bilirubinemia AST/ALT increase	Review of ongoing trial data Routine PhV	Warning in 4.4 on use in cholestasis Follow up measure for cholestasis (PK and safety) Subsection in 4.8 Hyperbilirubinaemia followed up in PSUR
Pancreatitis	Review of results from ongoing and planned clinical trials Routine PhV using targeted Questionnaires	Warning in 4.4 Mentioned in section 4.8 Follow up in PSUR

PT/PTT increase	Routine PhV	Warning in 4.4. and need for monitoring in 4.5. if used with anticoagulants Mentioned in section 4.8 Follow up in PSUR
BUN increase	Routine PhV	Warning in 4.4 Mentioned in section 4.8. Follow up in PSUR
Hypersensitivity	Routine PhV	Mentioned in section 4.3 and 4.8 Follow up in PSUR
QTc prolongation / cardiovascular effects	Review of results from ongoing and planned clinical trials Routine PhV	Follow up in PSUR
Drug interaction	Investigate the potential for tigecycline to inhibit CYP450 isoenzymes by mechanism-based inhibition	Mentioned in sections 4.5 and 5.2 SPC Follow up measure
Lack of efficacy in severely ill patients	Review of planned/ongoing clinical trial data Routine PhV	SPC section 4.4. and 4.8 Follow up in PSUR
Development of resistance	- Planned European drug utilisation study - Antibiotic surveillance study (T.E.S.T) - New Protocol for a European surveillance study	Section 5.1 Follow up in PSUR

6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues with a negative impact on the Benefit Risk balance of the product

Non-clinical pharmacology and toxicology

Efficacy

Overall, it can be concluded that the efficacy of tigecycline in the claimed indications has been established. The SPC addresses relevant aspects on the representativeness of the population actually enrolled in clinical trials in terms of particular clinical conditions and severity of the disease.

In **complicated intra-abdominal infections** (cIAI) subjects were stratified at randomization according to Acute Physiologic and Chronic Health Evaluation (APACHE) II scores (≤ 15, or > 15 but < 31). Subjects were randomly assigned (1:1) to receive either tigecycline (an initial 100-mg dose, followed by 50 mg twice a day) or imipenem/cilastatin (200 to 500 mg, dose based on body weight and calculated creatinine clearance) every 6 hours via intravenous administration for up to 14 days.

The comparator group in both trials was imipenem/cilastatin. The total daily dose of imipenem/cilastatin in cIAI was at the lower range of that acceptable for severely ill subjects.
The primary efficacy variable was the clinical response in two co-primary populations, the microbiologically-modified ITT (m-mITT) and the microbiologically evaluable (ME) populations.

Tigecycline has been shown to be non-inferior to imipenem/cilastatin in terms of clinical response at TOC in both the m-mITT and ME populations as the lower limit of the 95% CI for the difference between treatments is within the predefined non-inferiority margin of -15%.

Concerns were raised during the CHMP assessment about the efficacy in more severely diseased patients and the limited extent to which these patients were investigated. The most common type of infection was complicated appendicitis (51.4%), followed by other diagnoses less commonly reported such as complicated cholecystitis (13. %), intra-abdominal abscess (10%), perforation of intestine (10%), and gastric or duodenal ulcer perforation less than 24 hours (4.9%). Most patients in both studies had APACHE scores < 15 (3.5%). The number of patients with concurrent bacteraemia was limited (6.4%). The number of immunocompromised patients was also limited. Consequently, the limited data on relevant subpopulations (patients with diagnoses other than complicated appendicitis, patients with bacteraemia and with APACHE score > 15) and severely ill patients is stated in section 4.4 of the SPC.
Tigecycline does not show significant *in vitro* activity against *P. aeruginosa* and demonstrates only moderate *in vitro* activity against *Proteus* species or *Providencia* species. The pharmacodynamic section of the SPC (section 5.1) describes the antibacterial spectrum *in vitro* and *in vivo*.

In **complicated skin and soft tissue infections** the comparator group was vancomycin/aztreonam. The use of vancomycin for treating infections caused by gram-positive cocci susceptible to methicillin is questionable. Currently, the empirical use of vancomycin against gram-positive infections is driven by the knowledge of local prevalence patterns and/or for the presence of certain risk factors. Consequently, whether the use of a beta-lactam would have rendered similar or different results if compared with tigecycline remains unknown. However, from the data submitted and indirect comparisons with data from other drugs in the same indication it seems that tigecycline performs well in cSSTI due to methicillin-susceptible *S. aureus*.

Tigecycline has been shown to be non-inferior to vancomycin/aztreonam in terms of clinical response at TOC in both the CE and the c-mITT populations as the lower limit of the 95% CI for the difference between treatments is within the predefined non-inferiority margin of -15%.

Concerns were raised during the CHMP assessment about the efficacy in more severely diseased patients and the limited extent to which these patients were investigated. Data is limited for some clinically relevant subgroups, e.g., diabetic foot infection, peripheral vascular ulcer infection, sternal wound, and vascular surgery wound infection. In addition limited numbers of patients with co-morbid factors such as diabetes mellitus (20%), peripheral vascular disease (7%) and with bacteraemia (3%) were enrolled. Patients with severe underlying disease, such as immunocompromised, patients with decubitus ulcer infection or patients that had infections requiring longer than 14 days of treatment (e.g. necrotizing fasciitis) were not enrolled. Consequently, the limited data on relevant subpopulations (patients with diagnoses other than cellulites, patients with bacteraemia) and severely ill patients is stated in section 4.4 of the SPC.

Safety

The Safety Specification covers most of the issues that are considered relevant for the use of tigecycline in clinical practice. Within the Pharmacovigilance Plan most of the activities planned are routine pharmacovigilance practices. An appropriate risk management plan for identified risks associated with the use of tigecycline has been agreed upon.

Risk-benefit assessment

The benefits of tigecycline has been sufficiently demonstrated in complicated skin and soft tissue infections and in complicated intra-abdominal infections. Concerns over the severity of disease in

patients enrolled into clinical trials and concerns over the lack of efficacy in such patients have been raised during the CHMP assessment. Also, concerns on whether the patients enrolled in such trials are representative of the target population in terms of the possible clinical diagnoses were raised. These issues are addressed in the SPC and in follow-up measures where the applicant will provide updated information either in the context of subsequent PSURs or as clinical study reports.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that pharmacovigilance activities (in relation with concerns over lack of efficacy) in addition to the use of routine pharmacovigilance were needed to investigate further some of the concerns. No additional risk minimisation activities were required beyond those included in the product information with the exception of a specific surveillance study for the European Union aimed at monitoring emerging resistance. A paediatric study has also been requested as a Follow Up measure to be completed and submitted post-authorisation

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Tigecycline in the treatment of complicated skin and soft tissue infections and complicated intra-abdominal infections was favourable and therefore recommended the granting of the marketing authorisation.