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Post-authorisation Evaluation of Medicines for Human Use

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WITHDRAWAL ASSESSMENT REPORT FOR Tygacil

International Nonproprietary Name:

tigecycline

Procedure No. EMEA/H/C/644/II/13

This withdrawal Assessment Report is based on the latest assessment report adopted by the CHMP prior to the Applicant's withdrawal of the application, with all information of a commercially confidential nature deleted. It may not include all available information on the product in the event that the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application. It should therefore be read in conjunction with the "Questions and Answers" document on the withdrawal of the application, which provides an overview of all available information at the time of the Applicant's withdrawal.

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Table 1-1: List of Abbreviations and Terms

Abbreviations	Definition
Pharmacokinetic	
AUC	area under the serum concentration-time curve ($AUC_{0-\infty}$ for single-dose data or AUC_{τ} for multiple-dose data)
AUC_{τ}	area under the serum concentration-time curve over a dosing interval
CL	systemic clearance (dose/AUC for intravenous administration)
C_{max}	peak concentration
$fuAUC_{0-24h}$	unbound fraction of area under the concentration-time curve over 24 hours
$t_{½}$	apparent terminal-phase disposition half-life
t_{max}	time of peak concentration
V_{ss}	apparent steady-state volume of distribution ($CL \bullet MRT - T_{inf}/2$)
Microbiology	
CFU	colony-forming units
ME	microbiologically evaluable
MIC	minimum inhibitory concentration
MIC_{50}	median MIC for the isolates tested
MIC_{90}	90^{th} percentile of the MICs for the isolates tested
m-mITT	microbiological modified intent-to-treat
MRSA	methicillin-resistant *S. aureus*
MSSA	methicillin-susceptible *S. aureus*
PRSP	penicillin-resistant *S. pneumoniae*
PRSP	penicillin-susceptible *S. pneumoniae*
VRE	vancomycin-resistant enterococci
VSE	vancomycin-susceptible enterococci
Other	
AE(s)	adverse event(s)
ANOVA	analysis of variance
APACHE	Acute Physiology and Chronic Health Evaluation
CART	classification and regression tree
cIAI	complicated intra-abdominal infections
CSF	cerebrospinal fluid
cSSSI	complicated skin and skin structure infections
CV	coefficient of variation
IV	intravenous
LC/MS/MS	liquid chromatography/tandem mass spectroscopy
ROC	receiver operating characteristic
RP	resistant pathogens
SD	standard deviation

I. CHMP RECOMMENDATION PRIOR TO THE WITHDRAWAL

Based on the CHMP review of the data on safety and efficacy, the CHMP considers that the application for extension of the therapeutic indication for tigecycline in the treatment of community-acquired pneumonia (CAP) is not approvable since major objections have been identified, which preclude a recommendation for positive opinion at the present time. The details of the major objections are provided in the follow on request for supplementary information (see paragraph V).

II. EXECUTIVE SUMMARY

Tigecycline is a glycylcycline antibiotic and an analogue of the semi-synthetic tetracycline, minocycline.

It inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino-acyl tRNA molecules into the A site of the ribosome. This prevents incorporation of amino acid residues into elongating peptide chains. In general, tigecycline is considered bacteriostatic. At 4 times the minimum inhibitory concentration (MIC), a 2-log reduction in colony counts was observed with tigecycline against Enterococcus spp., Staphylococcus aureus, and Escherichia coli.

Tygacil is currently approved in:
- Complicated skin and soft tissue infections
- Complicated intra-abdominal infections

The MAH applied here for a new indication for Tygacil (tigecycline) for the treatment of adult patients with Community-Acquired Pneumonia. The proposed posology is an initial dose of 100 mg followed by 50 mg every 12 hours administered intravenously over 30 to 60 minutes for 7 to 14 days.

III. SCIENTIFIC DISCUSSION

III.1 Background

The initial clinical development plans for the tigecycline pneumonia program and subsequently planned submission were to include the data obtained from the 2 community-acquired pneumonia (CAP) studies described in this dossier, as well as the results from hospital-acquired pneumonia (HAP) study in support of obtaining pneumonia indications for both CAP and HAP. However, the results of the HAP study showed that tigecycline met non-inferiority efficacy criteria in comparison to imipenem/cilastatin for only 1 of the 2 co-primary efficacy endpoints, in the clinical modified intent-to-treat (c-mITT) population, but not the clinically evaluable (CE) co-primary population.

Thus, the proposed indication being sought for approval in this dossier is CAP. Pneumonia studies were not undertaken simultaneously with complicated skin and skin structure infections (cSSSI) and complicated intra-abdominal infections (cIAI) because the MAH decided to evaluate the pulmonary pharmacokinetics of tigecycline in healthy subjects before moving into large clinical studies in vulnerable subjects. In addition, because it was unclear whether tigecycline was active against *Legionella pneumophila*, additional work was needed to determine its efficacy in an animal model of *Legionella* pneumonia.

III.2 Clinical Aspects

III.2.1 Clinical pharmacology

III.2.1.2 Introduction

The majority of the information regarding the pharmacokinetic (PK) and pharmacodynamic (PD) properties of tigecycline are based on non-clinical studies and combined (pooled) data from clinical pharmacology studies that were reported in a previous regulatory submission for the complicated skin and soft tissue infection (cSSSI) and complicated intra-abdominal infection (cIAI) indications.

New information on the PK and PD of tigecycline is summarised from the results of a phase 1 study in children that has been submitted since the initial application and from 5 phase 3 studies (CAP studies 308 and 313, HAP study 311, and RP studies 307 and 309).

III.2.1.2 Pharmacokinetics

Pharmacokinetics in Special Populations

The PK profile of tigecycline was investigated in a phase 1 single-dose study in children aged 8 to 16 years. Tigecycline administered to children showed high initial concentrations, followed by rapid distribution and slower elimination. Similar to adults, renal clearance (CL) was relatively small compared with total clearance, 9.3 to 39%. The pharmacokinetic parameters observed in this study were quite variable. The single ascending-dose in adults showed a coefficient of variability (CV) % in weight-normalised Vss (apparent steady-state volume of distribution) and CL of 10 to 31% and 13 to 16%, respectively, after doses of 50 mg to 100 mg. In comparison, the children in this study showed CV% for the same parameters of 10 to 66% and 15 to 73%, respectively.

Several children were observed to have very high maximum concentration (Cmax) values. Results from the statistical analyses investigating the influence of covariates on weight-normalised CL and weight-normalised Vss consistently showed that the younger, smaller children, who received smaller total doses had increased CL and Vss compared with older, larger children who received larger total doses. Race, Tanner scale, and gender were not observed to be important influences on either weight-normalised CL or weight-normalised Vss.

Simulating exposures based upon the children studied, 1-mg/kg doses would be expected to result in a median AUC of 3.2 mg.h/L (range 1.4 to 10.5). Tigecycline is not expected to be used in children less than
8 years of age because of the possibility of damage to forming teeth, and so extrapolation of the pharmacokinetic results to younger subjects was not conducted.

Although the single-dose phase 1 study and pooled analysis in adults did not detect a difference in pharmacokinetics due to age, the population pharmacokinetic analysis of the CAP studies showed a modest decrease in clearance due to age. As may be seen in the equation describing the change:

$$CLj\ (L/h) = 19.1 + 9.7\ (BSAj - 1.73) - 0.103\ (agej - 56),$$

the effect is relatively small and explains at most about 20% of the intersubject variability. It is concluded that there is no suggestion that doses should be different due to age difference in adults.

A second PK and safety/tolerability study (multidose) will be conducted in subjects aged 8 to 11 years to identify the appropriate dose for this age group before enrolling subjects in this age group in subsequent studies. An additional phase 2/3 safety and efficacy study will include subjects aged 8 to 17 years, and will enrol across the currently approved and proposed indications: cSSSI, cIAI, and CAP.

Comparative Pharmacokinetics

PK data were collected for the CAP studies 308 and 313, HAP study 311, and Resistant Pathogen (RP) studies 307 and 309. Steady-state tigecycline concentration data were collected in 566 subjects participating in these phase 3 clinical trials enrolling subjects with CAP (n=290), HAP (n=202), and RP (n=74). Data from the individual studies are described in 2.7.2.2 Summary of Results of Individual Studies.

- Study 308: Noncompartmental analysis results in 180 patients was as follows (mean ± standard deviation): Cmax was 0.66 ± 0.53 mg/l; tmax was 0.64 ± 0.64 h; AUCt was 2632 ± 1179 ng•h/ml; and CL was 22.5 ± 9.28 l/h.

- Study 313: Noncompartmental analysis results (mean ± standard) in 110 patients were as follows: Cmax was 0.60 ±0.60 mg/l; tmax was 1.1 ± 0.5 h; AUCt was 2768 ± 1423 ng•h/ml; and CL was 22.3 ± 10.1 L/h.

- Study 311: Non compartmental analysis results in 202 subjects were as follows: mean ± standard deviation, Cmax was 689 ± 647 ng/ml; tmax was 1.1 ± 0.97 h; AUCt was 3032 ± 1570 ng•h/ml; and CL was 21.6 ± 13.1 L/h. Of the 202 subjects with pharmacokinetic parameters estimated, 71 subjects had been stratified due to ventilator-associated pneumonia (VAP) diagnosis. Their pharmacokinetic parameters (mean ±standard deviation) were as follows: Cmax was 665 ±650 ng/ml; tmax was 1.0 ±0.5 h; AUCt was 2726 ±1424 ng•/ml; and CL was 23.3 ± 12.7 l/h.

The pharmacokinetic parameters (mean ± standard deviation) observed in the 131 subjects with HAP who did not have VAP were as follows: Cmax was 712 ± 647 ng/ml; tmax was 1.1 ± 1.1 h; AUCt was 3198 ± 1625 ng•/ml; and CL was 20.7 ± 13.2 l/h.

The results of the ANOVA comparing the pharmacokinetic parameters in subjects with VAP and those subjects who did not have VAP showed that subjects who had VAP had a significantly lower AUCt (p=0.0407) compared with those who did not have VAP. No other parameters were observed to be different between the 2 groups.

It is concluded that in CAP subjects, the tigecycline dosing regimen of a 100 mg loading dose, followed by 50 mg every 12 hours, provided similar peak concentration (Cmax), AUC, and CL values to that which was observed previously in subjects with cSSSI and cIAI infections. In the HAP studies, the same tigecycline dosing regimen provided similar Cmax, modestly elevated AUCt, and similar CL to what was previously observed in subjects with cSSSI, cIAI, and CAP infections.

- Study 307: Noncompartmental analysis results in the 34 subjects, 3 with VRE infections, for whom pharmacokinetic analysis (mean ± standard deviation) could be performed, were as follows: Cmax was 2006 ± 4116 ng/ml; tmax was 1.3 ± 1.2 h; AUCt was 6940 ± 8049 ng•h/ml; and CL was 12.3 ± 8.4 l/h. The corresponding geometric mean values for the group were: Cmax was 1158 ng/ml; tmax was not applicable; AUC was 4928 ng•h/ml, and CL was 9.6 l/h.

The 3 subjects with VRE received tigecycline over 30 minutes, instead of 60 minutes as was the case for all other subjects, however their observed Cmax values were not lower that the other subjects in the study and fell within the range observed.

Although many of the individuals had exposures comparable to what was observed in patients with cSSSI, cIAI and CAP, the mean Cmax and AUC observed in this study were higher than the mean values observed in other phase 3 studies. No reason for this observation has been identified.

Study 309: Noncompartmental analysis results (mean ± standard deviation) in the 40 subjects for whom pharmacokinetic analysis could be performed, were as follows: Cmax was 1366 ± 1285 ng/ml; tmax was 0.72 ± 0.56 h; AUCt 6081 ± 5249 ng•h/ml; and CL was 15.3 ± 12.2 l/h. The corresponding geometric mean values for the group were: Cmax was 949 ng/ml; tmax was 0.63 h, AUC 4365 was ng•h/ml, and CL was 11.3 l/h.

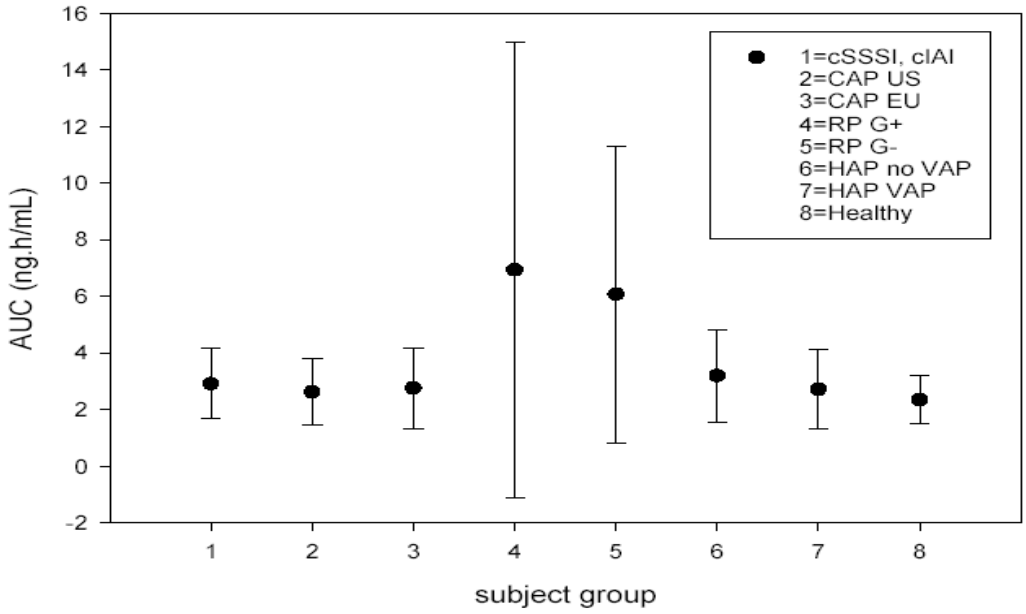
For the RP studies, the observed PK results were more variable compared with that which was reported in subjects with cSSSI, cIAI and CAP infections. The mean Cmax, and AUC values observed in these studies were approximately 2-fold higher than that which was seen in subjects with cSSSI, cIAI and CAP infections, with a corresponding lower clearance (see 2.7.2.3 Comparison and Analysis of Results Across Studies, Table 1-1).

As may be expected in clinical studies involving patients, there was some variability in the way that doses were administered and samples were collected. Most subjects received doses via 30-minute infusions in the RP studies, but some subjects had infusion of at least 60 minutes and several were intermediate in length between 30 and 60 minutes. It was concluded that the difference in mean AUC values for the subjects with resistant pathogens might simply be due to the small number of subjects studied.

Pharmacokinetics Related to Extrinsic and Intrinsic Factors

Comparison of AUC0-12h as calculated using non-compartmental analysis across different groups of subjects shows similar means and standard deviations, with the exception of subjects enrolled in the studies of infections caused by resistant pathogens, as seen in Figure 1-1. The subjects with infections caused by resistant pathogens had mean AUC values that were approximately 2 times what was observed in other studies. Throughout the tigecycline development program, only hepatic impairment has been shown to increase concentrations in a consistent manner requiring a change in dose. It was concluded that the difference in mean AUC values for the subjects with resistant pathogens might simply be due to the small number of subjects studied.

Figure 1-1: Comparison of Mean AUC_{0-12h} Values by Type of Infection: Pooled Phase 3 Study Data



Abbreviations: CAP = community-acquired pneumonia; cIAI = complicated intra-abdominal infections; cSSSI = complicated skin and skin structure infections; EU = European Union; HAP = hospital-acquired pneumonia; HV = healthy volunteers; RP G+ = Gram-positive resistant pathogens; RP G- = Gram-negative resistant pathogens; US = United States; VAP = ventilator-associated pneumonia.
Note: cSSSI, cIAI (n=276), CAP US (n=180), CAP EU (n=110), RP G+ (n=34), RP G- (n=40), HAP no VAP (n=131), HAP VAP (n=71), HV (n=103).

Population Pharmacokinetics

Two population pharmacokinetic (PK) models to describe the disposition of tigecycline in patients with 1) community-acquired pneumonia (CAP); and 2) with hospital-acquired pneumonia (HAP) and CAP were developed. The population for CAP patients consisted of tigecycline-treated patients from two different studies, Studies 3074A1-308W (Study 308) and 3074A1-313-W (Study 313). The population for CAP and HAP analysis consisted of tigecycline-treated subjects from the two CAP studies above mentioned and one HAP study, Study 3074A1-311W (Study 311).

Candidate PK models were fit to serum data using Monte-Carlo parametric expectation maximization (MCPEM) as implemented in the open-source software, S-ADAPT [16]. Given past population analyses of tigecycline, a two-compartment model with short-term IV infusion input was attempted first with plans to investigate other models only if an adequate fit of the data could not be obtained. The two-compartment model was initially parameterised using total clearance (CLt), volume of the

central compartment (Vc), distributional clearance (CLd), and steady-state volume of distribution (Vss). For the second analysis data from the HAP study alone was evaluated first to assure that the structural model adequately fit these data. In all subsequent analyses, the data from the HAP and CAP studies were pooled.

Several demographic and disease characteristics were evaluated for their impact on the primary PK parameters (CLt and Vss). Covariate exploration involved graphical examination of plots of PK parameters versus covariates followed by creation of statistical models to be used as the basis for the development of the population covariate model using S-ADAPT. The entire process was conducted for CLt first. The resultant model then served as the base model during investigation of the covariates that appeared to impact Vss.

The final model was then implemented in S-ADAPT and subjected to a model evaluation process. Model evaluation was accomplished using a bootstrap procedure to examine the amount of bias present in the final mean parameter estimates.

The final analysis dataset for CAP contained a total of 289 patients; 175 came from Study 308 while 114 were from Study 313. The final analysis population for CAP and HAP contained data from a total of 412 subjects; 175 from Study 308, 123 from Study 311 and 114 from Study 313. Two subjects from Study 311, who were included in structural model development, had inadequate covariate information and were excluded from the covariate analysis.

The population pharmacokinetic analysis performed using data collected in subjects with community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) showed both body surface area (BSA) and creatinine clearance as being significant covariates explaining differences between subjects. However, both were of modest magnitude and did not suggest a need for different doses, as seen in the equations used to estimate individual clearance:

From CAP: $CLj(L/h) = 19.1 + 9.97 (BSAj - 1.73) - 0.103 (agej - 56)$

From CAP/HAP: $CLj (L/h) = 19.2 + 10.2 (BSAj - 1.73) + 0.0638 (CrCLj - 100)$

Given that creatinine clearance decreases with advancing age, the changes in predicted tigecycline clearance may actually be related to a common change in physiology observed with these 2 factors.

There were no systematic differences in pharmacokinetics between the subjects the CAP studies and those in the HAP studies. This can be seen implicitly given that the mean and associated interindividual variability of the pharmacokinetic parameters did not differ significantly when the analysis of CAP study data alone was compared with the analysis of the combined CAP and HAP study data. This was also tested explicitly: a model was fit using an indicator variable for subjects from the HAP trial; using systematically different pharmacokinetic parameters for those subjects did not improve the fit.

Looking at all of the population pharmacokinetic analyses performed to date, it is concluded that no infection type seems to be associated with consistent differences in tigecycline pharmacokinetics. It also seems that with advanced age, which is correlated with decreased creatinine clearance, tigecycline clearance is modestly decreased, and that increased size, in the form of BSA, weight, or sex, is significantly related to increased tigecycline clearance, but only to a modest degree.

Results and Discussion on Pharmacokinetics

Results from a pharmacokinetic study in children aged 8 to 16 years showed that the variability of the pharmacokinetic parameters in children is higher than in adults. In addition, several children reached high Cmax concentrations when compared with adult mean values. Given the safety profile of tigecycline (especially the adverse reactions nausea and vomiting), the MAH should take this into account for the upcoming pharmacokinetic study in children.

Pharmacokinetic results of the studies in community-acquired pneumonia (studies 308 and 313), hospital-acquired pneumonia (study 311) and resistant pathogen studies (307 and 309) showed that the pharmacokinetic profile of tigecycline in patients with CAP and HAP is similar to that of patients with infections of the skin and soft tissues or with intra-abdominal infections. However, subjects enrolled in the studies of infections caused by resistant pathogens had mean AUC values that were approximately 2 times the observed in other studies. Although the MAH concludes that this may be due to the small number of subjects studied, these data in fact suggest that the clearance of tigecycline in these subjects is smaller.
The population pharmacokinetic analysis performed in patients with CAP and HAP show that both body surface area (BSA) and creatinine clearance are significant covariates explaining differences between subjects. It seems that with advanced age, which is correlated with decreased creatinine clearance, tigecycline clearance is modestly decreased, and that increased size, in the form of body surface area (BSA), weight, or sex, is significantly related to increased tigecycline clearance, but only to a modest degree. It is also concluded that based on all of the population pharmacokinetic analyses performed to date, no infection type seems to be associated with consistent differences in tigecycline pharmacokinetics.

Whereas it is agreed that the magnitude of these covariates is such that no dose adjustment is considered necessary, it is noted that as in the previous PK pop model in patients with skin and intra-abdominal infections creatinine clearance explains some of the interindividual variability, which is some how paradoxical if it is taken into account that tigecycline is primarily excreted in bile. The explanation of the relevantly different PK profile observed in patients with resistant pathogens is deemed insufficient and it would have been desirable that this patient population was explored in the context of a model for the whole population.

Overall, these raise doubts about the reliability of the different PK pop models and their predictive value.

III.2.1.3 Pharmacodynamics

The MAH has provided within module 2 of the current submission extensive and updated information about the primary pharmacodynamics of tigecycline in support of the following changes in section 5.1 of the SPC (<u>additions underlined</u>):

<u>Mode of action</u>

"Tigecycline, a glycylcycline antibiotic, inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino-acyl tRNA molecules into the A site of the ribosome. This prevents incorporation of amino acid residues into elongating peptide chains.

In general, tigecycline is considered bacteriostatic; however, tigecycline has demonstrated bactericidal activity against common respiratory strains of *S. pneumoniae*, *H. influenzae*, and *L. pneumophila*. At 4 times the minimum inhibitory concentration (MIC), a 2-log reduction in colony counts was observed with tigecycline against *Enterococcus* spp., *Staphylococcus aureus*, and *Escherichia coli*."

<u>Breakpoints</u>

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:
Staphylococcus spp. S ≤ 0.5 mg/l and R > 0.5 mg/l
<u>*Streptococcus pneumoniae* S ≤ 0.12 mg/l and R > 0.12 mg/l</u>
Streptococcus spp. other than *S. pneumoniae* S ≤ 0.25 mg/l and R > 0.5 mg/l
Enterococcus spp. S ≤ 0.25 mg/l and R > 0.5 mg/l
<u>*Haemophilus influenzae* S ≤ 1 mg/l and R > 1 mg/l</u>
Enterobacteriaceae S ≤ 1(^) mg/l and R > 2 mg/l

…

Susceptibility

Inclusion of the following microorganisms in category 1 (Commonly Susceptible Species):

- *S. pneumoniae**
- *H. influenzae**
- *H. parainfluenzae*
- *M. catarrhalis**
- *N. meningitidis*
- *C. pneumoniae**
- *M. pneumoniae**
- *L. pneumophila**
- *Acinetobacter calcoaceticus/baumannii* complex
- *Stenotrophomonas maltophilia*

Microorganisms considered relevant for community-acquired pneumonia are *S. pneumoniae, H. influenzae*, *M. catarrhalis* and those causing "atypical" pneumonia such as *Chlamydophila pneumoniae, Mycoplasma pneumoniae* and *Legionella pneumophila*. Microbiological data on *H. parainfluenzae* and *N. meningitidis* are also discussed due to the MAH's claims for section 5.1.

Haemophilus parainfluenzae is considered to be a component of the normal flora of the human nasopharynx. Because it is normally found in the oral cavity, dental procedures and nasopharyngeal infections seem to be the main risk factor for developing *H. parainfluenzae* infection. *H. parainfluenzae* is mainly a cause of pneumonia in the context of polymicrobial infections. The underlying mechanism is often aspiration of the microbiota from the nasopharynx. Pneumonia is an uncommon manifestation of *Neisseria meningitidis* infection. In a review by Winstead et al (2000) only 58 cases of meningococcal pneumonia were reported in 1974–1998. Given this small incidence as well as the lack of efficacy data for tigecycline, *N. meningitidis* should not be listed although it is fully acknowledged that tigecycline is active *in vitro* against *meningococci*(see below).

Necrotizing or cavitary pneumonia has been described in healthy young adults and can be associated to Community Acquired Methicillin-Resistant *S. aureus* (CA-MRSA) infection, whereas severe COPD and alcoholism are major risk factors for infection with *P. aeruginosa* and other gram-negative pathogens such as *Klebsiella pneumoniae*, an uncommon cause of community-acquired pneumonia except in alcoholics. Nursing home-acquired pneumonia (NHAP) is still a matter for debate with regard to its classification, either as CAP or HAP (Armitage K et al, 2007). The *Enterobacteriaceae* and *Staphylococcus aureus* are now seen more frequently as respiratory tract pathogens in community-acquired pneumonia patients, and they are the major organisms causing pneumonia in residents of homes for the elderly or nursing homes, and in immuno-compromised patients. Anaerobic coverage is clearly indicated only in the classic aspiration pleuropulmonary syndrome in patients with a history of loss of consciousness as a result of alcohol/drug overdose or after seizures in patients with concomitant gingival disease or oesophageal motility disorders.

In vitro, tigecycline has been shown to be active against most of the microorganisms involved in community acquired pneumonia although *H. influenzae* and *Legionella pneumophila* deserve further discussion.

The MIC50 and MIC90 values of tigecycline against 183 strains of penicillin-susceptible (PSSP), 299 strains of penicillin-intermediate (PISP) and 269 strains of penicillin-resistant (PRSP) *S. pneumoniae* were 0.03 and 0.06 µg/ml, respectively. Data from EARS 2005 show that the prevalence of resistance of *S. pneumoniae* to penicillin is variable across Europe, but in general a trend to a decrease was observed. *S. pneumoniae* with intermediate susceptibility to penicillin can be adequately treated with high dose amoxicillin and the presence of resistant isolates is not systematically associated to failure to beta-lactam treatment.

Tigecycline MIC range and MIC90 against 204 recent isolates of *Haemophilus influenzae* were 0.06-1 µg/ml and 0.5µg/ml, respectively using fresh media (reference method). This collection of *H. influenzae* included strains that were resistant to ampicillin, minocycline and tetracycline. Some of

the original studies intended to address the in vitro activity against strains producing beta-lactamase vs. those non-producers seem to have been performed with the non-reference method (Gales, AC, 2000; Zhanel GG, 2003). These non-reference studies showed higher MICs against *H. influenzae* beta-lactamase positive as compared with the values attained against the 204 isolates previously mentioned.

Most recent studies addressing this issue (Fritsche TR, 2005; Bouchillon SK, 2005; Betriu C, 2005; Hoban DJ, 2005) also showed that the MICs of tigecycline are similar for the β-lactamase positive and β-lactamase negative strains and that tigecycline inhibited all of the isolates at concentrations between 0.06 and 2 μg/ml.

In the study by Betriu C et al. (2005) tigecycline MIC50 and MIC90 were 1 mg/L and 2 mg/L (two dilutions higher than the MIC90 reported for the 204 isolates), respectively against ampicillin-resistant isolates. These MIC50 and MIC90 values of tigecycline were 1 dilution lower than those reported by Zhanel et al., but 1 dilution higher than those reported by Fritsche et al. among b-lactamase-positive isolates. The issue is not whether tigecycline MIC differs or not between beta-lactamase positive and negative strains but the fact that there seems to be some discrepancies between MICs in the different studies. In its answer to the RSI adopted in November 2007, the MAH showed that there was no discrepancy in MICs among studies when the reference method is used. With regards to the request for MIC analysis of *H. influenzae* by susceptibility to tetracycline and β-lactamase production the MAH response was limited to the baseline clinical trial isolates (n=39) in patients with CAP that were all susceptible to tetracycline. Therefore, no comparison of tetracycline susceptible and resistant strains can be made for organisms from these trials.

Similarly, 166 isolates of *H. parainfluenzae* were inhibited by 2 μg/ml of tigecycline or less (MIC90 1μg/ml). Tigecycline was also active against the 240 strains of *Moraxella catarrhalis* that were tested. For *Moraxella catarrhalis* (240 isolates), the range of MICs was 0.03-0.25 μg/ml and the MIC90 was 0.12 μg/ml. Finally, all of the 298 strains of *Neisseria meningitidis* tested were susceptible to 0.5 g/ml or less of tigecycline.

Tigecycline MIC range, MIC50 and MIC90 against 180 recent isolates of *Klebsiella pneumoniae* were 0.25-4 μg/ml, 0.5 and 1μg/ml, respectively using fresh media (reference method). Against strains that harbored AmpC-type β-lactamases (100 isolates) and extended spectrum beta-lactamases (ESBLs, 162 isolates) MIC90 values were 2 μg/ml.

Tigecycline was also active against *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae* although the number of isolates is relatively low. The MIC90 and MBC90 values were 0.125 μg/ml for tigecycline when tested against ten *C. pneumoniae* isolates, which were similar to those for clarithromycin and one and two dilutions better than doxycycline and ofloxacin, respectively. Tigecycline MIC range, MIC50 and MIC90 against 25 isolates of *M. pneumoniae* were 0.03-1 μg/ml, 0.06 and 0.25 μg/ml, respectively. With the exception of several macrolide-resistant isolates, the macrolides tested had the best activity against *M. pneumoniae*, whereas tigecycline (MIC90 = 0.25 μg/ml) performed equivalently to doxycycline and better than levofloxacin (MIC90 = 1 μg/ml).

Legionella pneumophila is a leading cause of community-acquired pneumonia. Moreover, *Legionella* is particularly frequent among patients with community-acquired pneumonia who require admission to an intensive care unit. Urinary antigen detection is an effective test for rapid diagnosis of infection caused by *L. pneumophila* serogroup 1. Improved outcomes regarding the time to defervescence, development of complications and length of stay, have been recently observed for patients treated with levofloxacin monotherapy. Current case-fatality rates for hospitalised patients with community-acquired *Legionella pneumonia* are lower than those traditionally reported for this infection.

The susceptibility of *Legionella* spp. to antimicrobial agents is highly dependent on the culture medium used and on the size of the inoculum. Buffered starch-yeast extract (BSYE) is the preferred culture medium and it has been shown to impair the activity of several antimicrobials. As a consequence standard MIC testing against *Legionella* spp. in BSY culture medium does not provide a reliable measure of the *in vitro* activity of tigecycline.

Based on the studies performed in alveolar macrophages and in a guinea pig infection model the MAH claims that tigecycline is bactericidal against *L. pneumophila*, which cannot be agreed by the CHMP**.** Tigecycline has been shown to be inhibitory against intracellular *L. pneumophila*, except when tested against strain F2111, and only at a high concentration (2 mg/l). Moreover, it is clearly ineffective at clearing the bacterium from the lungs in the guinea-pig infection model, and bacterial persistence was observed in the lungs at the end of tigecycline therapy (Edelstein PH et al., 2003).

A time-dependent pattern of bactericidal activity of tigecycline has been demonstrated against *S. pneumoniae* and *H. influenzae*, however, it has been reported to be both bacteriostatic and bactericidal depending on the strains tested; it cannot be assumed as uniformly bactericidal against all strains. In addition, the convenience of conveying information about the bactericidal activity of tigecycline could be misleading as in the neutropenic thigh murine model the range of AUC/MIC ratios is larger than in the intraperitoneal model (non-neutropenic animals) where the ratios are lower and tighter, suggesting that for neutropenic patients tigecycline would not be the first option. In addition, it should be noted that immunodepressed patients were excluded from past and current clinical trials. Theoretically, bactericidal activity is desirable for this type of patients. As a consequence, mentioning bactericidal activity against *S. pneumoniae* and *H. influenzae* is not endorsed by the CHMP as such. Some information on the reduction on colony counts in time kill studies could be considered if a satisfactory answer on the number of experiments conducted and the strains used is provided.

As previously said, *S. pneumoniae*, H. influenzae*, H. parainfluenzae, M. catarrhalis*, N. meningitidis, C. pneumoniae*, M. pneumoniae** and *L. pneumophila** are being requested to be included within category 1 of the SPC. In addition, an asterisk (denoting that clinical efficacy has been shown) is requested for some of them.

Table below shows the number of baseline isolates in the m-mITT and ME populations of studies 308 and 313 pooled.

	m-mITT population		**ME population**	
Baseline pathogens	**TGC (n=225)**	**LVF (n=232)**	**TGC (n=166)**	**LVF (n=179)**
Chlamydia pneumoniae	32	32	19	27
Haemophilus influenzae	18	16	17	18
Haemophilus parainfluenzae	7	11	5	10
Klebsiella pneumoniae	5	8	4	9
Legionella pneumophila	13	11	10	6
Moraxella catarrhalis	4	5	3	5
Mycoplasma pneumoniae	56	65	39	48
Staphylococcus aureus	13	11	12	10
Streptococcus pneumoniae (All)	115	115	91	99
Streptococcus pneumoniae (non PISP, non PRSP)	106	103	84	87
Streptococcus pneumoniae (PISP)	5	6	4	6
Streptococcus pneumoniae (PRSP)	4	6	3	9

Based on the number of isolates as well as on the eradication rates in the ME population, an asterisk could be added to *C. pneumoniae* (tigecycline eradication rate 94.7%), *M. pneumoniae* (94.8%) and *S. pneumoniae* (92.8%). However, for *H. influenzae*, *M. catarrhalis* and *L. pneumophila* it is considered that the efficacy data presented does not support the addition of an asterisk.

Suspicion of *L. pneumophila* pneumonia was an exclusion criterion in studies 308 and 311 (CAP trials). In spite of this the organism was isolated in a very limited number of patients thus hampering the demonstration of efficacy. For *H. influenzae*, the MAH was requested to address the apparently inconsistent results in eradication rates in the tigecycline arm between the two trials (100% in study 308 and 72.7% in study 313). In its answer to the RSI adopted in November 2007, the MAH highlighted that the number of tigecycline-treated patients with *H. influenzae* pneumonia in the individual tigecycline studies was too small to conclude that there is a discrepancy in the results between the studies, which is endorsed by the CHMP. The MAH also stated that eradication rates rate

favourable compared with those of other antibiotics (fluoroquinoles and macrolides). However, the cure rates to compare with are those corresponding to cefotaxime.

However, the NfG on evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 rev 1) states the following:"*The assignment of an asterisk to denote that efficacy has been demonstrated against a particular species in clinical studies can only be decided on a case by case basis. As a general principle, and for commonly encountered pathogens, it would be preferred that clinical efficacy data are available on at least 20 treated cases due to a single species within any one indication. However, it is recognised that it may not always be possible to obtain this minimum number for less commonly encountered pathogens for each indication so that lower numbers or pooling across similar indications may be acceptable in some instances. …*".

- The number of isolates of *M. catarrhalis* is too low to draw proper conclusions. Therefore, the MAH agreed to retain it in the list without adding asterisk.
- Regarding *H. influenzae* the total number of baseline clinical isolates in the ME population of studies 308 and 313 is 17, which is below the minimum of 20 for a common pathogen in a specific indication.
- As for *L. pneumophila* the concern is not only the number (n=10, ME population of studies 308 and 313) but mainly the fact that *Legionella* is particularly frequent among patients with community-acquired pneumonia who require admission to an intensive care unit.

As a consequence, the CHMP is of the opinion that no asterisk should be added to *H. influenzae* and *to L. pneumophila*.

The so-called "resistant pathogens" are those possessing acquired mechanisms of resistance such as *E. coli* and *K. pneumoniae* expressing extended-spectrum-betalactamases (ESBL), vancomycin-resistant *Enterococcus* spp. (VRE), methicillin-resistant *S. aureus* (MRSA) and vancomycin-intermediate *S. aureus* (VISA), multi-drug resistant *Acinetobacter* spp. etc.

Tigecycline inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino-acyl tRNA molecules into the A site of the ribosome. As a consequence, no impact on the *in vitro* activity of tigecycline is expected for the following mechanisms of resistance: resistance to methicillin or intermediate susceptibility to vancomycin in *Staphylococcus* spp., resistance to vancomycin in *Enterococcus* spp., intermediate susceptibility or resistance to penicillin in *S. pneumoniae*, beta-lactamase production in *H. influenzae* and *M. catarrhalis* and beta-lactamase production (including ESBL) in *Enterobacteriaceae*.

However, tigecycline is vulnerable to chromosomally-encoded multidrug efflux pumps of *Proteeae* and *Pseudomonas aeruginosa* (MexXY-OprM efflux system). Pathogens of the family *Proteeae* (*Proteus* spp., *Providencia* spp. and *Morganella* spp.) are generally less susceptible to tigecycline than other members of the *Enterobacteriaceae.* In addition, some acquired resistance has been detected in *Klebsiella pneumoniae*, *Enterobacter aerogenes*, and *Enterobacter cloacae*. Decreased susceptibility in both groups has been attributed to the overexpression of the non-specific AcrAB multi-drug efflux pump. Decreased susceptibility in *Acinetobacter baumannii* has also been reported. During the assessment of the original dossier the MAH was requested to include the AdeAB efflux pump as the underlying mechanism of this decreased susceptibility but as it was felt that little was known at that time no mention in the SPC was finally made. The MAH has submitted more recent data that seems to confirm the role of this efflux pump. As a consequence, the MAH agreed to include thismechanism of resistance in *Acinetobacter baumannii* is in section 5.1 of the SPC.

Tigecycline MIC distribution for 66 *Acinetobacter calcoaceticus*/*baumannii* complex strains isolated from the RP studies ranged from 0.25 to 16 µg/ml. For the majority of the isolates the MIC was 0.5 µg/ml (n=16), 1 µg/ml (n=14), 2 (n=14) and 4 (n=16). Against 609 strains of *Acinetobacter baumannii* the MIC range and MIC 90 were 0.015 to 64 µg/ml and 4 µg/ml. The distribution is described as bimodal, with one mode at 0.25 µg/ml and the second one at 2-4 µg/ml. Looking at the distributions it is clear that some strains of *Acinetobacter* spp. are more susceptible to tigecycline and consequently the *in vitro* activity is not denied. However, this is not considered sufficient to support the inclusion of *Acinetobacter calcoaceticus*/*baumannii* complex in category 1. In its answer to the RSI adopted in

November 2007, the MAH proposed to include *Acinetobacter calcoaceticus*/*baumannii* complex in category 2 (species for which acquired resistance may be a problem) to replace *Acinetobacter baumannii*, which is currently included in this category. The MAH should clarify the nomenclature (taxonomy) of the complex.
Regarding *S. maltophilia* few data has been provided. Tigecycline MIC range, MIC50 and MIC90 against 160 isolates were 0.06-16 µg/ml, 0.5 and 2 µg/ml, respectively. This set of data has been updated and apparently the collection comprises now 169 isolates. Similarly to *Acinetobacter* spp. it is agreed that tigecycline shows *in vitro* activity against *S. maltophilia*. However, the set of data is considered insufficient to support the inclusion in category 1.

Anaerobes are listed within category 1 of the table of relevant microorganisms in section 5.1. In the original assessment it was noted that MIC distribution for them (*Bacteroides* and *Clostridium*) were wide and included values in excess of 2 mg/l tigecycline. Based on the data provided, the MAH agreed to move *Bacteroides fragilis* group to category 2.

The MAH agreed to discuss MIC breakpoints for *S. pneumoniae* and *H. influenzae* with the EUCAST. Tigecycline breakpoints were discussed during the EUCAST Steering Committee Meeting held at Berlin (Germany), 6-7 September 2007. The EMEA has been informed about the EUCAST breakpoint proposal (unratified minutes of the meeting) that is as follows:

S. pneumoniae S≤ 0.25/R>0.5 mg/L; *H. influenzae* S≤ 0.5 /R>0.5 mg/l.

For *S. pneumoniae*, the minutes read as follows: "Differences from other *streptococci* and the non-species related breakpoint are not necessary". In addition, the following comment to the MIC breakpoint table of EUCAST is intended to be added: "Breakpoint increased to avoid splitting the wild type". The CHMP agrees with this proposal. No breakpoint has been requested for *M. catarrhalis* given the low number of clinical isolates.

In conclusion, the MAH should address the changes requested for section 5.1 of the SPC in the light of this discussion and duly clarify the outstanding issues**.**

III.2.1.4 Pharmacokinetic/Pharmacodynamic Relationship

Pharmacokinetic and clinical data from two clinical trials in patients with CAP (see below) were integrated in order to conduct PK-PD analyses of both efficacy and safety. Patient-specific pharmacokinetic (PK) parameter estimates were available from a population PK analysis of these data and were used to provide the most accurate estimates of exposure possible. These exposure estimates were indexed to the MIC of the infecting pathogen(s) and used to explore exposure-response relationships for efficacy. Additionally, these exposure estimates were used to explore exposure-response relationships for safety outcomes of interest.

Model
The population for this analysis consisted of tigecycline-treated patients from two different studies, 3074A1-308W (Study 308) and 3074A1-313-W (Study 313). In brief, both studies were Phase 3, multicentre, randomised, double-blind comparisons of the efficacy and safety of tigecycline with those of levofloxacin in patients initially hospitalised with CAP. Only those patients with PK parameter estimates and a baseline MIC value from one or more pathogens who were clinically and microbiologically evaluable were used for the exposure-response analyses for efficacy. Exposure-response analyses for efficacy undertaken involved the evaluation of three endpoints for efficacy, clinical response (therapeutic success versus failure), microbiological response (pathogen eradication versus persistence), and time to defervescence. Three cohorts of evaluable patients were evaluated:

1) patients with monomicrobial *Streptococcus pneumoniae* infections,
2) patients with either mono- or polymicrobial *S. pneumoniae* infections,
3) all patients, regardless of pathogen.

The value for free fraction of drug was assumed to be 0.20, consistent with the value in the package product information.

Exploratory analyses of clinical and microbiological response were conducted to identify relationships between outcome and fAUC0-24:MIC. This included the examination of the relationship between fAUC0-24:MIC and percent response among patients grouped by quartiles. Threshold values for fAUC0-24:MIC distinguishing cohorts of patients with impressive differences in response were evaluated using classification and regression tree analysis (CART). The relationship between response and certain other independent variables of interest was also examined. Univariate and multivariate logistic regression analyses, with backward elimination ($\alpha = 0.05$), were used to determine whether the above-described independent variables were statistically significant predictors of clinical or microbiological response. The data for time to defervescence were analysed in a similar manner using time-to-event analyses (also referred to as survival analysis).

Two types of safety outcomes were evaluated, dichotomous indications of the occurrence of drug-related adverse events (diarrhoea, headache, nausea and vomiting) and continuous measures (maximum change in total bilirubin and blood urea nitrogen (BUN)). Similar to those conducted for efficacy, exploratory analyses of safety outcomes were conducted to identify relationships between outcome and AUC0-24. The methods for analysis of the safety data were similar to those used for clinical and microbiological outcome with the exception of the continuous safety outcomes, which were evaluated using linear regression.

Efficacy Results

In the two clinical studies, 165 patients randomised to receive tigecycline were clinically and microbiologically evaluable. Of these, a total of 68 patients had at least one pathogen isolated at baseline with a corresponding MIC value and had the requisite PK parameter values. Given that eleven patients had polymicrobial infections, 81 pathogens were isolated from 68 patients. *S. pneumoniae* was the most common pathogen, 34 and 8 patients had monomicrobial and polymicrobial *S. pneumoniae* infections, respectively.

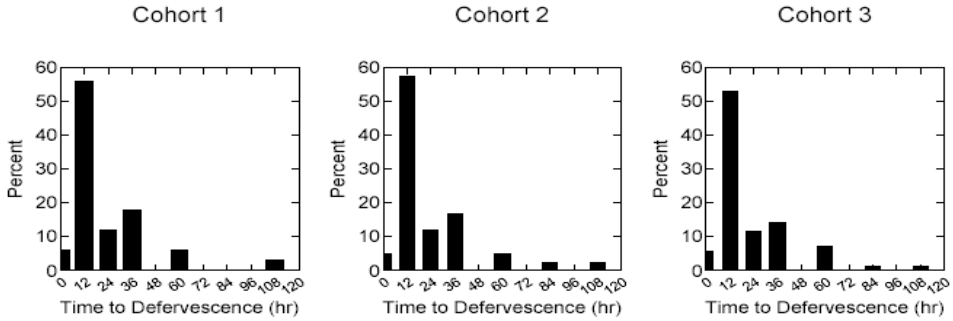
The distribution of successes and failures for the clinical and microbiological outcomes, stratified by cohort, is shown in Table 1-2. Clinical and microbiological outcomes were 100% concordant, thus, only microbiological outcomes were examined in the PK-PD analysis. The distributions of time to defervescence for each cohort are provided in Figure 1-1.

Table 1-2: Distribution of Efficacy Outcomes, Stratified by Cohort

	Clinical Outcome N (%)		Microbiological Outcome[1] N (%)	
Cohort	Success	Failure	Eradicated	Persistent
1 (n=34)	33 (97.1)	1 (2.9)	33 (97.1)	1 (2.9)
2 (n=42)	39 (92.9)	3 (7.1)	39 (92.9)	3 (7.1)
3 (n=68)	63 (92.7)	5 (7.3)	63 (92.7)	5 (7.3)

[1] "Eradicated" includes confirmed and presumed eradicated; "Persistent" includes confirmed and presumed persistent

Figure 1-1: Distribution of Time to Defervescence by Cohort



Note: Two patients do not appear in the distribution for Cohort 3 as they never became afebrile.

The summary statistics for fAUC0-24:MIC values, stratified by cohort, are provided in the table 1-3 below.

Table 1-3: Summary Statistics for *f*AUC$_{0\text{-}24}$:MIC, Stratified by Cohort

Cohort	N	Mean (SD)	Median (Min. – Max.)
1	34	16.3 (6.41)	14.3 (9.22 – 35.9)
2	42	14.7 (6.91)	13.1 (1.64 – 35.9)
3	68	12.2 (8.11)	11.1 (1.04 – 35.9)

Due to the low incidence of microbiological failures (see Table 1-2, above), no statistical analyses were conducted for Cohorts 1 and 2. The details of the demographics and fAUC0-24:MIC for these cases from all Cohorts are provided in table 1-4.

Table 1-4: Selected Characteristics of Patients Classified as Clinical and Microbiological Failures

Case	Cohort	Age (yr)	Sex	FPSI	Pathogen(s)	MIC (mg/L)	*f*AUC$_{0\text{-}24}$:MIC[1]
1	3	28	Female	I	*S. aureus*	0.25	4.02
2	1,2,3	76	Female	IV	*S. pneumoniae*	0.12	18.0
3	2,3	69	Female	IV	*S. pneumoniae* *H. influenzae*	0.12 0.25	4.85
4	2,3	52	Male	III	*S. pneumoniae* *H. influenzae* *Acinetobacter lwolffii*	0.06 0.25 0.12	13.3
5	3	45	Female	IV	*S. oralis*	0.03	24.6

[1]Only one *f*AUC$_{0\text{-}24}$:MIC value is reported as the highest MIC was chosen for those patients with polymicrobial infections

Univariate analysis of data from patients in Cohort 3 revealed that fAUC0-24:MIC was not a significant predictor of response. As might be expected given that patients who failed had fAUC0-24:MIC values throughout the distribution for this measure, a threshold value below which patients were more likely to fail therapy could not be identified. Sex was the only variable with a significant univariate relationship with microbiological outcome; FPSI (Fine Pneumonia Severity Index) and MIC value demonstrated only trends toward significance (see table below for trends toward univariate relationships with microbiological outcome). None of these relationships were significant when analysed using multivariate logistic regression.

Table 4-6: Results of Univariate Analysis of Microbiological Outcome – Cohort 3

Covariate		Microbiological Outcome (N (%))	
		Persistent	Eradicated
Sex			
	Male	1 (2.4)	41 (97.6)
	Female	4 (15.4)	22 (84.6)
FPSI			
	I	1 (8.3)	11 (91.7)
	II	0 (0)	22 (100)
	III	1 (6.7)	14 (93.3)
	IV	3 (15.8)	16 (84.2)
MIC			
	0.03	1 (16.7)	5 (83.3)
	0.06	0 (0)	33 (100)
	0.12	2 (20.0)	8 (80.0)
	0.25	2 (15.4)	11 (84.6)
	0.5	0 (0)	5 (100)
	1	0 (0)	1 (100)

Safety Results

Adverse event and laboratory data were available for all of the 289 patients with PK parameter estimates based on the previously described population PK analysis. The mean (SD) and median (minimum – maximum) values for AUC0-24 were 5.41 (2.50) and 4.75 (1.82 – 17.3), respectively.

When the proportion of individual dichotomous adverse events were evaluated relative to the AUC0-24 values grouped by deciles, no trend for increasing incidence of either diarrhoea or headache with increasing AUC0-24 was evident. However, there was a clear trend for a higher incidence of nausea/vomiting with increasing AUC0-24. Using CART, a threshold AUC0-24 of 6.87 mg•hr/l was found to be predictive of nausea/vomiting; patients with AUC0-24 values above (n=57) and below the threshold value (n=232) had an incidence of nausea/vomiting of 40.4% and 17.2%, respectively (p = 0.00015, Chi-square test).

When other patient characteristics were examined as predictors of nausea/vomiting, only sex and alcohol use were found to be significant. Using multivariate logistic regression with backward stepping, only sex and AUC0-24 categorised (based on the above-described CART-derived threshold) were found to be significant predictors of nausea/vomiting. The final multivariate logistic regression model, with both sex and AUC0-24 evaluated as categorical variables, is shown in table 1-5.

Table 1-5: Final Multivariate Logistic Regression Model for Factors Predictive of Nausea/Vomiting, with Sex and AUC_{0-24} as Categorical Variables

Parameter	Estimate	Odds Ratio (95% CI)	P value
Sex[1]	0.895	2.45 (1.34, 4.47)	0.00414
AUC_{0-24} Threshold[2]	0.955	2.60 (1.35, 4.99)	0.00358

McFadden's $\rho^2 = 0.0712$

[1]Odds ratio is for females versus males

[2]Odds ratio is for $AUC_{0-24} \geq 6.87$ versus < 6.87 mg•hr/L

Table 1-6 illustrates the observed and model-predicted probability of nausea/vomiting based on sex and AUC0-24. The concordance between observed incidence and predicted probabilities for the four different groups suggests that the model adequately predicted the observed data.

Table 1-6: Observed Incidence and Predicted Probability of Occurrence of Nausea/Vomiting Based on Sex and AUC_{0-24} Threshold

AUC_{0-24} Threshold	Male		Female	
	Observed	Predicted	Observed	Predicted
$AUC_{0-24} < 6.87$	0.127	0.121	0.244	0.253
$AUC_{0-24} \geq 6.87$	0.222	0.270	0.487	0.475

Of the 289 patients evaluated for the safety analysis cohort, a total of 270 and 108 patients had the necessary data to examine maximum change from baseline in total bilirubin and BUN, respectively. Despite the lack of an apparent relationship when examined graphically, multivariable linear regression demonstrated that baseline bilirubin and increases in AUC0-24 were significantly associated with larger maximum changes in total bilirubin ($p < 0.001$). However, as evidenced by the shallowness of the slope of the effect of AUC0-24 (an increase in maximum change in bilirubin of 0.046 mg/dl per 1 mg•hr/l increase in AUC0-24) and the size of the adjusted r^2 value (0.053 univariately), the magnitude of impact was not very impressive. None of the other potential predictors (demographics and disease characteristics) showed any trends for relationships with maximum change from baseline in total bilirubin when examined graphically. None of the potential predictors (tigecycline exposure, demographics and disease characteristics) showed any trends for relationships with maximum change from baseline in BUN when examined graphically; thus, no linear regression analyses were conducted.

Conclusion
It is concluded that despite achieving statistical significance, the relationship between AUC0-24 and maximum change in total bilirubin is unlikely to be of clinical significance at clinically achievable tigecycline exposures.

In conclusion, for efficacy analysis of the CAP study data failed to show that the fraction unbound AUC/MIC (fuAUC0-24h/MIC) ratio was a significant predictor of response. Part of the failure might have been because the cSSSI and cIAI data sets included different doses, with some subjects being treated with 50 mg initially, then 25 mg every 12 hours, while others were treated with 100 mg initially, then 50 mg every 12 hours. The CAP studies included only 1 dosing regimen and would therefore more likely have had a narrower range of exposures and consequently a more limited range of values for fuAUC0-24h/MIC ratio. Additional exploration of the data sets revealed that in subjects with mono- or polymicrobial *Streptococcus pneumoniae* infections, an fuAUC0-24h/MIC ratio less than 12.8, which would correspond to an AUC/MIC ratio of 64, was associated with prolonged time to defervescence.

Using univariate logistic analysis of the HAP study data, it was shown that a fuAUC0-24h/MIC ratio of less than 1.15, which would correspond to an AUC/MIC ratio of 5.75, was predictive of microbiological or clinical failure. Characteristics including a higher APACHE II score (≥20.5), lower albumin concentration (< 2.56 g/dl), altered mental status, concomitant antibiotics, a history of smoking, and a diagnosis of ventilator-associated pneumonia (VAP) were also significant predictors of microbiological or clinical failure. However, when multivariate analysis was performed, an fuAUC0-24h/MIC ratio of less than 1.15 was no longer significant when altered mental status and history of smoking were included in the model.

As for safety, an analysis was performed using pooled data from the CAP studies and was repeated with data from the HAP study added. A CART analysis identified AUC0-24h thresholds associated with decreased or increased incidence of nausea and/or vomiting. When CAP study data was analysed, it was shown that there was an increased incidence of nausea and vomiting when the AUC was above 6.87 mg•hr/ml. With the addition of data from subjects with HAP, the threshold was slightly different (6.48 mg•hr/ml) and a lower threshold was identified. When the AUC0-24h was below 3.21 mg•h/l, the incidence of nausea and/or vomiting was 3.8 %, and when the AUC0-24h was above 6.48 mg•h/l, the incidence of nausea and/or vomiting was 27.4 %, while in the intermediate range, the incidence was 17.4%. Results of a univariate logistic regression analysis showed an increased odds ratio for nausea and/or vomiting for the following variables: log-transformed AUC0-24h values, female sex, no history of smoking, and no altered mental status. Results of a multivariate logistic regression analysis showed that sex and AUC0-24h values remained significant. With increased dose or exposure, the incidence of nausea and/or vomiting increases. The incidence predicted from the exposure-response analysis is consistent with the incidence of nausea and vomiting that was reported in the clinical trials.

Discussion
Two PK-PD analyses have been performed aimed at identifying values of fAUC/MIC ratio that correlate with efficacy as well as AUC0-24 for safety. The first analysis is limited to patients with CAP while the second one includes patients with CAP and HAP. The HAP study failed to show non-inferiority of tigecycline vs. comparator agents, at least in patients with ventilator associated pneumonia (VAP). The MAH considers that, although certain degree of overlapping can exist between the two entities, the results of the HAP study do not preclude the demonstration of efficacy in CAP. With this background it is questionable whether the second analysis makes sense given the potential differences between entities (including the microorganisms involved).

In any case, the PK-PD analysis for CAP patients failed to identified a target fuAUC0-24h/MIC ratio that correlates with efficacy and the arguments given, i.e. that there is a narrow distribution of AUC values, is scientifically sound. In addition, tigecycline MIC range of the baseline isolates considered for the analysis is quite narrow, i.e. from 0.03 to 1 mg/L (just 1 patient had a baseline isolate with a MIC of 1 mg/l) and the number of clinical failures is very low (5 out of 68). It should also be taken into account that due to the necessity of a MIC value for each isolate included in the PK-PD analysis, pathogens identified by antigen testing were excluded. Gender was identified as the only variable with

a significant univariate relationship with microbiological outcome, i.e. apparently the percentage of eradication was better in men than in women, which is an unexpected finding if one considers that higher AUC values are expected in women. This seems to be driven by the fact that four out of 5 clinical failures occurred in women, three of which with a Fine Pneumonia Severity Index of IV.

According to the MAH, when exploring the other reasons behind the lack of an identifiable exposure-response relationship for efficacy, it is important to consider previous PK-PD analyses for tigecycline. In analyses conducted using a neutropenic murine - thigh infection model, AUC0-24/MIC ratios of 10-20 (total drug concentration) were associated with a 90% reduction in bacterial burden. In patients with skin and skin structure infections, a significant relationship between total-drug AUC0-24/MIC ratio and microbiological response was identified for patients with either staphylococcal or streptococcal infections. The threshold values for response identified were 12.5 and 16.4. In patients with complicated intra-abdominal infections, Bhavnani et al. have identified a AUC0-24/MIC threshold of 3.1. When expressed as free-drug concentrations, these fAUC0-24:MIC thresholds range from 0.6 and 4. In the current CAP dataset, very few patients (only 16%) had fAUC0-24/MIC values below a value of 4, suggesting that the lack of significant relationships in these analyses may also be attributable to the fact that exposures achieved in the majority of these patients were on the upper relatively flat portion of an exposure-response curve.

As for safety, the PK-PD model identifies a cut-off value of AUC0-24, i.e. 6.87 mg•hr/l, above which the rate of nausea of vomiting is considerably increased (Odds Ratio for AUC0-24 ≥ 6.87 vs. < 6.87 mg•hr/l: 2.60; 95% CI: 1.35, 4.99). Gender is also a variable with a significant relationship with nausea and vomiting (Odds Ratio for females vs. males: 2.45; 95% CI: 1.34, 4.47). This finding has limited practical implications as dosage adjustment for women based on this seems unfeasible. Finally, the relationship between AUC0-24 and maximum change in total bilirubin is unlikely to be of clinical significance at clinically achievable tigecycline exposures although it should be noted that patients with total bilirubin > 3 times the upper limit of niormal at baseline were excluded from the trials.

Previous analyses using data from Phase 2/3 patients treated for complicated intra-abdominal infections or complicated skin/skin structure infections failed to find a relationship between tigecycline exposure and nausea or vomiting. According to the MAH, the reason for this discrepancy is unclear but may be related to smaller sample sizes in the phase 2/3 datasets analysed previously (218 for complicated intra-abdominal, 102 for complicated skin/skin structure). Additionally, the current analyses utilised a categorised exposure variable (based on a CART-derived breakpoint) for the multivariable logistic regression model while the previous analyses only examined exposure as a continuous variable.

Overall, the current PK-PD analyses performed are of limited value, at least regarding efficacy. The MAH has chosen the AUC/MIC ratio as the PK-PD index that best correlates with efficacy based on the findings of the dose fractionation study conducted by van Ogtrop (van Ogtrop ML et al., 2000). However, the results for the strain of *S. pneumoniae* 1199 show a value of R^2 of 0.83 for the AUC and of 0.82 for Time over MIC (T>M). For *K. pneumoniae* these figures are 0.73 and 0.76. In the answer to the RSI adopted in November 2007, the MAH discussed the feasibility of performing a new PK-PD analysis on the clinical dataset including all types of infections that explores the relationship between T>MIC with clinical and microbiological responses. In its answer to the RSI adopted in November 2007, the MAH also justified that there was no need to perform new PK-PD analysis including all infection types or to explore different PK-PD index such as T>MIC. The MAH position is that distribution of tigecycline out of serum occurred so quickly that T>MIC would be very short in most cases and would not allow a sufficient degree of discrimination between patients. The CHMP concluded that according to the answer from the MAH and to the official EUCAST Rational document for tigecycline, there are no evidences of that T>MIC would be a better pharmacodynamic index related to efficacy compared to AUC/MIC.

III.2.2 Clinical efficacy

The clinical development program provided in this variation includes 5 phase 3 studies: Community acquired pneumonia (CAP) studies 308 and 313, and resistant pathogen (RP) studies 307, 309, and

310. In addition, a phase 3 study in patients with hospital acquired pneumonia has been conducted. An overview of these studies is provided in the table below.

Study ID	No. of study centres / locations	Design/ Objective	Tigecycline dose	Comparator	No. subjects	Gender Age
308	54 sites in 8 countries in North, Central, and South America.	Multicenter, randomized, double-blind study to compare tigecycline and levofloxacin to treat CAP requiring hospitalization.	100 mg IV, followed by 50 mg IV every 12 hours Oral switch permitted (open-label levofloxacin) (7-14 days)	Levofloxacin: 500 mg/day IV therapy Oral switch permitted (open-label levofloxacin) (7-14 days)	418 (208 Tigecycline, 210 Levofloxacin)	244 M, 174 W 18-91 (55) years
313	62 sites in 20 countries in Europe, Africa, and Asia Pacific region.	Multicenter, randomized, double-blind study to compare tigecycline and levofloxacin to treat CAP requiring hospitalization	100 mg, followed by 50 mg every 12 hours No oral switch (7-14 days)	Levofloxacin: 500 mg/day or 500 mg twice/day at investigator's discretion. No oral switch (7-14 days)	428 (216 Tigecycline, 212 Levofloxacin)	264 M, 164 W 17-92 (50) years
307	VRE: Argentina, Belgium, Greece Spain, South Africa United States MRSA: Argentina Australia,Belgium Bulgaria, Brazil Chile, Mexico Poland, Romania South Africa, United States	Double-blind, randomized controlled (3:1) study to compare tigecycline and linezolid to treat selected serious infections in subjects with VRE and to compare tigecycline and vancomycin to treat selected serious infections in subjects with MRSA	100-mg loading dose, then 50 mg q12h maintenance (7-28 days)	Vancomycin (for MRSA) 1 g q12h (7-28 days) Linezolid (for VRE) 600 mg q12h (7-28 days)	156 MRSA 15 VRE	99 M, 57 W 19-93 (51) years 7 M, 8 W 23-77 (60) years
309	Argentina, Australia Belgium, Bulgaria Brazil, Chile, Spain Estonia, Greece India, Latvia Mexico, Panama Poland, Romania Russia, South Africa, Ukraine United States	Open label, noncomparative safety and efficacy study of tigecycline to treat serious infections caused by resistant gram-negative bacteria in subjects who have failed or cannot tolerate other antibiotic therapy	100-mg loading dose, then 50 mg q12h maintenance (7-28 days)		112 Tigecycline	69 M, 43 W 21-86 (55) years
310	Germany Poland United States	Open label, noncomparative emergency use study to describe the safety and efficacy of tigecycline to treat serious infections caused by bacteria resistant to multiple antibiotics	100-mg loading dose, then 50 mg q12h maintenance; 50 mg once daily or 25 mg q12h allowed for subjects with rapidly growing mycobacterial infection (duration usually 5-90 days, dependent on type of infection and investigator discretion)		27 Tigecycline	17 M, 10 W 24-72 (51) years
311	Argentina, Australia Belgium, Bulgaria Brazil, Canada Chile, China, Colombia, Croatia	Multicenter, randomized, double-blind study to compare tigecycline with	100 mg, followed by 50 mg every 12 hours, and possibly	Imipenem/cilastatin q8h for 1.5 to 3 g daily of imipenem,	945 (474 Tigecycline 471 Imipenem/	642 M, 292 W 18-102 (58) years

Spain, Finland France, Guatemala Hungary, India Korea, Lithuania Latvia, Morocco Mexico, Panama Peru, Poland, Romania, Russia Slovakia, Taiwan Ukraine, United States, South Africa	imipenem/cilastatin to treat HAP	ceftazidime 1 or 2 g q8-12h and an aminoglycoside (7-14 days)	and possibly vancomycin 1 g q12h and an aminoglycoside (7-14 days)	Cilastatin)

All clinical studies are claimed to have been designed and performed according to the guidelines for Good Clinical Practice.

- ***Main clinical studies***

The MAH has submitted two pivotal phase 3 studies for the claimed indication CAP (Study 308 and Study 313).
As part of the clinical development plan for tigecycline, 3 studies (307, 309 and 310) have been conducted in subjects with serious infections caused by known resistant pathogens (RP). However, only 1 subject with CAP was identified in study 309 and no subjects with PISP, PRSP, or beta-lactamase positive and negative *H. influenzae* infections were identified in these RP studies. Therefore, this section will focus on the 2 CAP studies, 308 and 313.

Methods

Studies 308 and 313 were phase 3, multicenter, randomized, double-blind (third party unblinded) comparative studies of the efficacy and safety of IV tigecycline compared with IV levofloxacin in subjects hospitalized with CAP. Subjects were randomly assigned (in a 1:1 ratio) to receive either tigecycline or levofloxacin for up to 14 days.

The main difference between the 2 studies was that in study 308, the option of a switch to oral antimicrobial therapy was permitted after at least 3 days of intravenous therapy, but was not permitted in study 313. Similarities and differences in design are described in the table below.

Table 1-2: Comparison of Study Designs in the CAP Studies

	Study 308	Study 313
Design	Phase 3, multicenter, multinational, randomized, double-blind comparative trial	Same
Treatment	Tigecycline (IV): 100 mg loading dose followed by 50 mg q12	Tigecycline (IV): Same
	Levofloxacin (IV)[a]: 500 mg/day	Levofloxacin (IV)[a]: 500 mg/day or 500 mg twice/day
	Levofloxacin oral switch permitted after ≥3 days of IV therapy: 500 mg /day	No oral switch
Treatment Duration	7-14 days total (IV, or IV plus oral[b])	Same duration, but no oral switch
	TOC assessment 10-21 days after last dose	Same
Stratification	Fine pneumonia severity index score, geographic region	Fine pneumonia severity index score
Primary Endpoint	Clinical response at the TOC visit in CE and c-mITT populations	Same

Abbreviations: IV = intravenous; TOC = test-of-cure; CE = clinically evaluable; c-mITT = clinical modified intent-to-treat.

a. Levofloxacin dose was 500 mg every 24 hours (or every 12 hours in study 313) for subjects with a CL_{CR} of at least 50 mL/min or an initial IV loading dose of 500 mg followed by 250 mg every 24 hours (or twice daily in study 313) for subjects with a CL_{CR} of 20 to 49 mL/min.

b. Subjects may have been switched to open-label oral levofloxacin therapy after at least 3 days of IV test article administration as per criteria specified in the 308 protocol.

Source: CSRs for studies 308 and 313.

- **Study Participants**

Study 308 was conducted in 54 sites located in Argentina, Brazil, Canada, Chile, Guatemala, Mexico, Panama, Peru and United States.

Study 313 was conducted in 62 sites in Belgium, Bulgaria, Czech Republic, Germany, Denmark, Spain, Estonia, Croatia, Hungary, India, Lithuania, Latvia, Morocco, Poland, Romania, Russia, Slovakia, Taiwan, Ukraine and South Africa.

Subjects with clinical signs and symptoms of CAP who required hospitalization and who required IV antibiotic treatment were considered for enrollment. In study 313 subjects were to have CAP with a severity that required IV antibiotic treatment for at least 7 days.

In study 308 subjects were stratified at randomization by the Fine Pneumonia Severity Index score (Fine score = IV or Fine score < IV) and geographic region (United States/Canada or Mexico/Central America/South America).

In study 313 subject were stratified at randomization by the Fine Pneumonia Severity Index score (Fine score = V; Fine score = IV, Fine score = III, or Fine score less than III).

Key inclusion criteria were:

- The presence of fever (within 24 hours before randomization), defined as:
oral temperature higher than 38°C/100.4°F, axillary temperature higher than 38.1°C/100.6°F, tympanic temperature higher than 38.5°C/ 101.2°F, or rectal/core temperature higher than

39°C/102.2°F, or hypothermia (within 24 hours before randomization), defined as a core temperature less than 35°C/95°F.

- Clinical criteria included the presence of at least 2 of the following signs and symptoms:
    a. Cough.
    b. Production of purulent sputum or a change in the character of sputum consistent with bacterial infection.
    c. Auscultatory findings of rales or evidence of pulmonary consolidation (dullness on percussion, bronchial breath sounds, or egophony).
    d. Dyspnea or tachypnea, particularly if progressive.
    e. Elevated total peripheral WBC count (>10 x 109/l or >10,000/mm3), or more than 15% immature neutrophils (bands) regardless of total peripheral WBC count, or leukopenia (total WBC count <4.5 x 109/l or <4500/mm3).
    f. Hypoxemia, with a partial pressure of oxygen (PO_2) less than 60 mm Hg or oxygen saturation lower than 90% while the subject is breathing room air.
- Chest radiograph (if possible, posteroanterior and lateral) showing the presence of a new infiltrate within 48 hours before the first dose of IV test article.
- Prior antibiotics to treat the current episode of CAP limited to 1 dose of a nonstudy antibacterial agent before the first dose of IV test article. The prior nonstudy antibiotic must have been a drug with a dose administration interval of less than once daily. A single dose of once daily prior antibiotic was not allowed, except subjects who failed a previous course of outpatient therapy with an oral antibiotic for this episode of CAP (ie, clinical symptoms worsened after at least 2 full days of therapy) could be enrolled in the study.

<u>Key exclusion criteria were:</u>

- Hospitalization or residence in a long-term care facility or nursing home within the 14 days before the onset of symptoms.
- Fine Pneumonia Severity Index score of V or required treatment in an intensive care unit.
- Presence of any clinically important central nervous system disease, including seizure disorders or conditions that might predispose the subject to seizures or lower the seizure threshold, or clinically important major psychiatric disorders that might interfere with compliance with the protocol.
- Sustained shock at the time of randomization.
- Risk factors for torsades de pointes, such as hypokalemia, significant bradycardia (as determined by the investigator), or cardiomyopathy. If the hypokalemia was corrected, subjects could be enrolled; however, the potassium level was to be monitored closely.
- Known anatomical or pathological bronchial obstruction, or a history of bronchiectasis or postobstructive pneumonia including end-stage chronic obstructive pulmonary disease (COPD) (forced expiratory volume in 1 second less than 30% predicted). Subjects with less severe COPD were not excluded.
- Immunosuppressive therapy, defined as chronic treatment with known immunosuppressive medications.
- Presence of any of the following:
    a. Known human immunodeficiency virus infection.
    b. Known or suspected *Pseudomonas* infection.
    c. Cystic fibrosis.
    d. Known or suspected *Pneumocystis carinii* pneumonia.
    e. Known *Legionella* pneumonia.
    f. Known or suspected active tuberculosis.
    g. Primary lung cancer.
    h. Any malignancy metastatic to the lungs.
- Presence of any of the following laboratory findings:
    a. Neutropenia (absolute neutrophil count <1 x 109/l or <1000/mm3).
    b. AST or ALT more than 10 times the upper limit of normal, or total bilirubin level more than 3 times the upper limit of normal.
    c. CL_{CR} less than 20 ml/min.
- Outpatient ventilator therapy within the 14 days before the onset of symptoms, or ventilator therapy required at the time of screening.

Note: continuous positive airway pressure (CPAP) therapy was allowed.

- Use of drugs known to prolong the QT interval, including classes Ia and III antiarrhythmics.

- **Treatments and objectives**

Subjects were randomly assigned in a 1:1 ratio to receive 1 of the following test articles:
• Tigecycline: an initial IV loading dose of 100 mg followed by 50 mg IV every 12 hours, or
• Levofloxacin: 500 mg daily in study 308 and 500 mg IV daily or twice a day in study 313 (according to the investigator's decision based upon local practice and recommendation of the local data sheet) for subjects with a CL_{CR} of at least 50 ml/min or an initial IV loading dose of 500 mg followed by 250 mg every 24 hours for subjects with a CL_{CR} of 20 to 49 ml/min.
In study 308 subjects may have been discharged after at least 3 days of IV test article. Investigators then had the option to switch subjects who met the clinical criteria to open-label, oral levofloxacin therapy, to complete a total duration of antimicrobial therapy not to exceed 14 days (IV plus oral).
Subjects must have met each of these criteria to qualify for oral therapy:
1. Cough and shortness of breath were improving.
2. Fever was absent for at least 24 hours (oral temperature <37.8°C).
3. The white blood cell (WBC) count was normalizing.
4. Oral intake and gastrointestinal tract absorption were adequate.

In study 313 oral switch was not allowed. The IV treatment period was to be a minimum of 7 days (unless the subject was declared a clinical failure) but not longer than 14 days.

The **primary objective** was to compare the efficacy and safety of tigecycline with those of levofloxacin in the treatment of subjects with CAP requiring hospitalization.
The primary efficacy analyses were to first determine whether tigecycline was noninferior to levofloxacin. Noninferiority was to be concluded if the lower limit of the 2-sided 95% CI was greater than or equal to -15%.

The **secondary objectives** were
1. To evaluate the microbiologic efficacy of tigecycline.
2. To obtain *in vitro* susceptibility data on tigecycline for a range of bacteria that cause CAP.
3. To compare health care utilization between treatment arms.
4. To determine the PK profile of tigecycline in subjects with CAP.

- **Outcomes/endpoints**

The co primary endpoints were the clinical response in 2 populations, the clinically evaluable (CE) population and the clinical modified intent-to-treat (c-mITT) population, at the test-of-cure (TOC) assessment. The TOC assessment was specified in the protocol as 10 to 21 days and modified in the Statistical Analysis Plan to 7 to 23 days after overall IV and oral therapy.

The populations are defined as follows:

The <u>modified intent-to-treat (mITT) population</u> consists of randomized subjects who receive at least one dose of test article.
The <u>clinical modified intent-to-treat (c-mITT) population</u> consists of mITT subjects who have clinical evidence of CAP, as defined in the inclusion criteria.
The <u>microbiologic modified intent-to-treat (m-mITT) population</u> consists of c-mITT subjects who have one or more baseline isolates identified.
The <u>clinically evaluable (CE) population</u> consists of c-mITT subjects who meet the following criteria:
· meet inclusion and exclusion criteria;
· have a TOC assessment of cure or failure (but not indeterminate);

Clinical response is defined as follows:

<u>Cure</u>
A subject was considered a clinical cure if the following criteria were met:
• All signs and symptoms of pneumonia present at the time of enrollment were improved or resolved at the TOC assessment.

• Chest radiographs were improved or not worse.
• No further antibiotic therapy was necessary for the treatment of pneumonia.
• There was no worsening or appearance of new signs and symptoms of pneumonia.

Failure
A subject was considered a clinical failure if any of the following criteria was met:
• Persistence or worsening in signs and symptoms of the acute process.
• Failure to show improvement in the clinical findings.
• Initial improvement in signs and symptoms followed by clinically important worsening before the TOC assessment.
• Treatment with additional antimicrobial therapy for pneumonia.
• Progression of chest radiograph abnormalities.
• Death after study day 2 because of pneumonia.
• Death resulting from a treatment-related AE (primary reason).
Subjects could be declared a clinical failure after receiving at least 4 doses (2 days) of test article.

Indeterminate
A subject was considered to have an indeterminate response if any of the following criteria were met:
• The subject did not have an outcome determination for reasons unrelated to test article or the infection (eg, lost to follow-up or withdrawal of consent).
• The subject died for any reason other than treatment-related AE within 2 days (≤4 doses of test article) after the first dose of test article.
• The subject died after 2 days but before the TOC assessment for reasons not related to the infection or because of a treatment-related AE (as judged by the investigator).
• The subject died after 2 days but before the TOC assessment because of an infection other than pneumonia (as judged by the investigator).

Secondary efficacy variables:
Microbiologic responses at the subject level and at the pathogen level were considered to be the most important secondary endpoints.
Secondary variables for clinical response included the following:
• Clinical response by baseline isolate for the ME and m-mITT populations at the TOC assessment, summarized overall and by the susceptible and resistant pathogens.
• Clinical response for the ME and m-mITT populations with monomicrobial infections at the TOC assessment.
• Clinical response for the ME and m-mITT populations with polymicrobial infections at the TOC assessment.

The outcome of the microbiologic response at the subject level was described according to the following definitions:
Eradicated (documented or presumed):
• None of the isolates were present in repeat cultures taken from the original site of infection (documented).
• A clinical response of cure precluded the ability to obtain a culturable specimen (presumed).
Persistence (documented or presumed):
• Any baseline isolate was present in a repeat culture obtained from the original site of the infection (documented).
• The subject's clinical response was failure and no repeat microbiologic data were available (presumed).
Superinfection: A new isolate emerged during therapy, at the site of infection with emergence or worsening of signs and symptoms of infection (ie, deemed a clinical failure).
Note: Emergence of a new isolate associated with a clinical event during therapy at a site other than the initial site of infection was considered to be an AE (eg, urinary tract infection, bacteremia).
Indeterminate: Subjects who did not have an outcome determination for a reason unrelated to study drug or the infection such as:
• lost to follow-up;
• withdrew consent;

• did not have a baseline isolate identified;
• died within 2 days after the first dose of IV test article for any reason; or
• died after 2 days (but before the TOC assessment) for non-infection-related reasons or for an infection other than pneumonia (as judged by the investigator).

The microbiologic response at the pathogen level for baseline isolates was described according to the following definitions of microbiologic efficacy:
Eradicated (documented or presumed):
• The baseline isolate was absent in repeat cultures obtained from the original site of infection through the TOC assessment (documented).
• A clinical response of cure precluded the ability to obtain a culturable specimen (eg, sputum) (presumed).
Persistence (documented or presumed):
• Any baseline isolate was present in repeat cultures from the original site of infection during the study (documented).
• Subject's clinical response was failure and no repeat microbiological data were available (presumed).
Indeterminate: Subjects who did not have an outcome determination for reasons unrelated to study drug or the infection such as:
• lost to follow-up;
• withdrew consent;
• did not have a baseline isolate identified;
• died within 2 days after the first dose of test article for any reason;
• died after 2 days (but before the TOC assessment) of non-infection-related reasons or for an infection other than pneumonia (as judged by the investigator).

- **Sample size**

The sample size was calculated to provide enough patients to conclude that tigecycline was at least as effective as levofloxacin based on clinical response rates. The planned enrollment of 400 patients was expected to provide 240 clinically evaluable subjects, with the assumption that at least 60% of enrolled patients were to be clinically evaluable.

If it is assumed that the 2 treatments are equally effective, with clinical cure rates of 85%, 120 clinically evaluable subjects per treatment group are required to ensure with 90% probability (ie, 90% power) that the lower bound of a one-sided 97.5% confidence interval for the true difference in efficacy is not less than -15%. This provides equivalent inference as a two-sided 95% confidence interval.

There were no interim analyses conducted during the course of these studies.

- **Randomisation**

A computerized system of automated telephone randomization (CORE) was used and provided access 24 hours per day. After a subject was screened and deemed eligible for the study, the unblinded dispenser called the provided telephone number to determine the treatment assignment. Knowledge of the treatment assignment was limited to the designated unblinded dispenser/pharmacist.

- **Blinding (masking)**

Subjects received the test article in a double-blind fashion. An unblinded third party prepared the IV test articles. To maintain the blind between tigecycline (q 12 h, 30- minute infusion) and levofloxacin (q 24 h in study 308 and sometimes in study 313, 60-min infusion), placebo dummy infusions were used.

In study 308 the first dose of test article included a 30-minute infusion (either tigecycline or placebo) and a 60-minute infusion (either levofloxacin if the subject had received placebo or placebo if the subject had received tigecycline). Twelve (12) hours later, the subject was to receive a 30-minute infusion of tigecycline or placebo.

In study 313 the first dose of test article was a 60-minute infusion (either tigecycline or levofloxacin). Twelve (12) hours later, the subject received a 60-minute infusion of tigecycline or placebo or levofloxacin.

Since tigecycline has an orange-yellow colour, to preserve the blind, the unblinded third party covered the IV bags and tubing with green plastic sleeves. Alternatively, amber-coloured tubing could have been used to maintain the blind. The person responsible for preparing the IV test article was not to be involved in the assessment or evaluation of the subject for safety or efficacy.

- **Statistical methods**

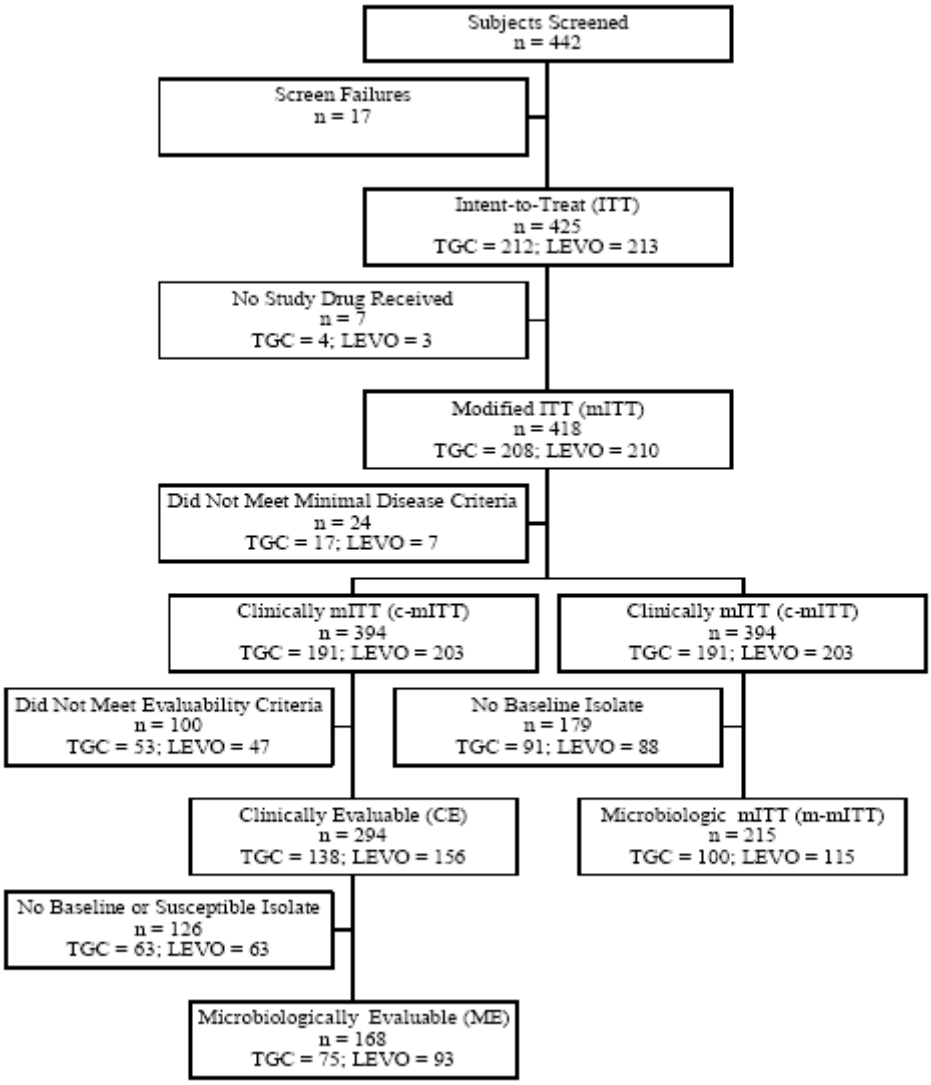
The primary objective was to show the non-inferiority of tigecycline to levofloxacin, using a delta of 15%. If the lower bound of the non-inferiority confidence interval for the true difference in the clinical response had been less than -10% in any population in any protocol, then studies 308 and 313 would have been combined in order to gain power to test for non-inferiority using a delta of 10%.

Results

- **Participant flow**

Study 308:

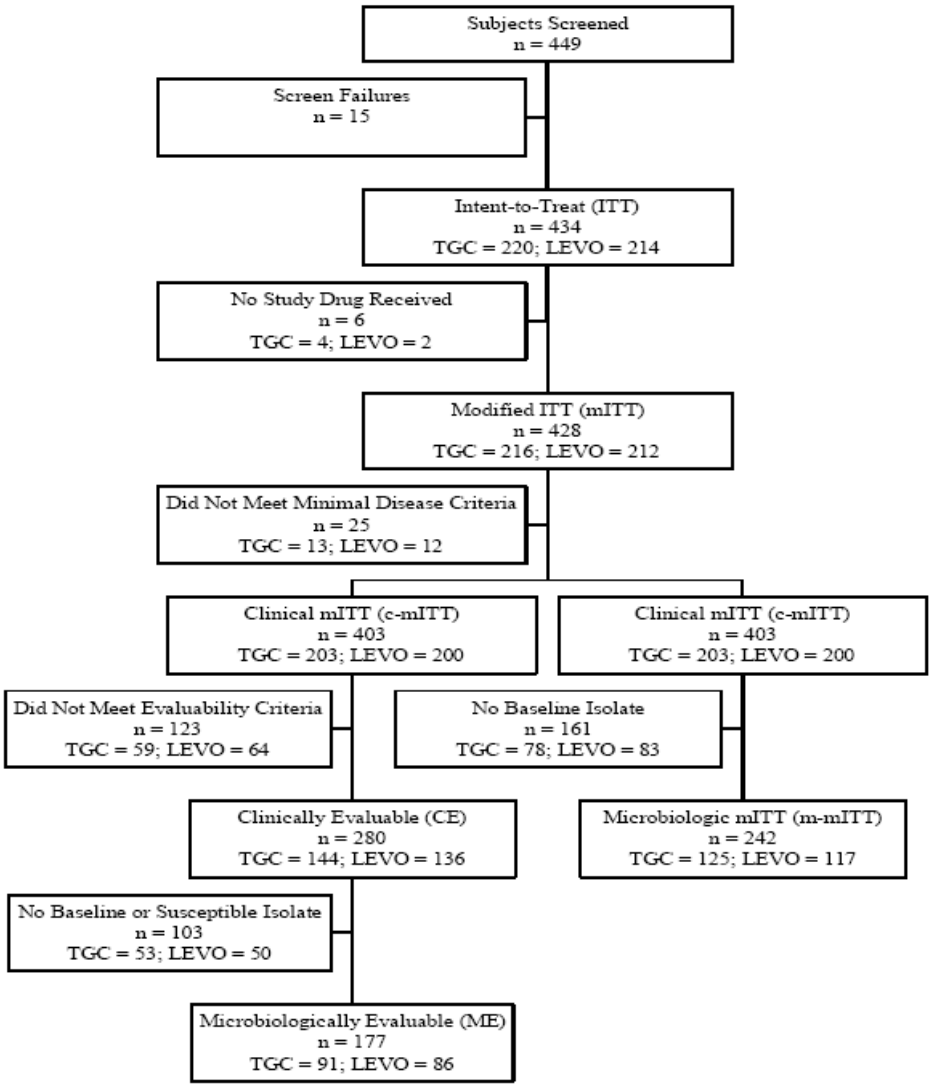
A total of 442 subjects were screened for the study; 17 were screen failures. The remaining 425 subjects were randomly assigned to 1 of the treatment arms and constituted the ITT population. Seven (7) subjects in the 2 treatment groups did not receive test article. Altogether, 418 subjects received the test article and constituted the mITT population: 208 subjects were randomly assigned to and received tigecycline and 210 subjects were randomly assigned to and received levofloxacin. Subject disposition by treatment group is presented in figure below.



Approximately 75% of the Clinically mITT were Clinically Evaluable and 57.14% of the Clinically Evaluable patients were Microbiologically Evaluable.

Study 313:

A total of 449 subjects were screened for the study; 15 were screen failures. The remaining 434 subjects were randomly assigned to 1 of the treatment arms and constituted the intent-to-treat (ITT) population. Six (6) subjects in the 2 treatment groups did not receive study drug. Altogether, 428 subjects received the study drug and constituted the mITT population: 216 subjects received tigecycline and 212 subjects received levofloxacin. Subject disposition by treatment group is presented in figure below.



Abbreviations: ITT = intent to treat; mITT = modified ITT; c-mITT = clinical modified intent-to-treat; m-mITT = microbiologic modified intent-to-treat.

Approximately 70% of the Clinically mITT were Clinically Evaluable and 68.08 % of the Clinically Evaluable patients were Microbiologically Evaluable.

The most common primary reason for discontinuation of test article in both studies was “Adverse event (AEs)”. There were no significant differences between treatment groups in the primary reasons for discontinuation of test article.

The most common reasons for withdrawal from the study before the TOC assessment in study 308 were AEs and “failed to return” in both treatment groups. There were no significant differences between treatment groups in the primary reasons for withdrawal from the study.

The most common reasons for withdrawal from the study before the TOC assessment in study 313 was adverse event. There were no significant differences between treatment groups in the primary reasons for withdrawal from the study.

- **Recruitment**

Study 308 period was from June 2003 to July 2005.
Study 313 period was from January 2004 to January 2005.

- **Conduct of the study**

The original protocol of study 308 was dated on 01 April 2003 and it was amended 3 times. The original protocol of study 313 was dated 19 May 2003 and was amended twice.

- **Baseline data**

In both studies demographic and baseline disease characteristics were similar between the treatment groups, in both the CE and c-mITT Populations. However, because of differences in geographic regions where the studies were conducted, differences in ethnic origin were observed between the 2 studies.

Study 308:
For the CE population, mean age was 56 years for tigecycline and 55 years for levofloxacin. Fifty-three per cent (53%) of the patients were male in the tigecycline group and 61% in the levofloxacin group. The more frequent ethnic origin was white (65% in the tigecycline group and 62% in the levofloxacin group), 10% were black in the tigecycline group and 6% in the levofloxacin group. Mean creatinine clearance was 88 ml/min in the tigecycline group and 81 ml/min in the levofloxacin group.

The data for the c-mITT Population were very similar: mean age was 56 years for tigecycline and 55 years for levofloxacin Fifty-three per cent (53%) of the patients were male in the tigecycline group and 62% in the levofloxacin group. The more frequent ethnic origin was white (61% in the tigecycline group and 59% in the levofloxacin group), 13% were black in the tigecycline group and 12% in the levofloxacin group. Mean creatinine clearance was 87 ml/min in the tigecycline group and 85 ml/min in the levofloxacin group.

Study 313:
For the CE population, mean age was 53 years for tigecycline and 50 years for levofloxacin. Sixty-three per cent (63%) of the patients were male in the tigecycline group and 64% in the levofloxacin group. The more frequent ethnic origin was white (90% in the tigecycline group and 86% in the levofloxacin group), 0% were black in the tigecycline group and 2% in the levofloxacin group. Mean creatinine clearance was 87 ml/min in the tigecycline group and 92 ml/min in the levofloxacin group.

The data for the c-mITT Population were very similar: mean age was 50 years for tigecycline and 49 years for levofloxacin. Sixty per cent (60%) of the patients were male in the tigecycline group and 63% in the levofloxacin group. The more frequent ethnic origin was white (87% in both treatment groups), 3% were black in the tigecycline group and 4% in the levofloxacin group. Mean creatinine clearance was 87 ml/min in the tigecycline group and 91 ml/min in the levofloxacin group.

There were no significant differences between treatment groups in the CE populations in the underlying medical conditions at the time of entry in either study. The most frequent underlying medical conditions are summarised as follows: In study 308, 15.9% of patients in tigecycline group presented with COPD vs. 10.3% in levofloxacin group. In study 313, 6.9% of patients in tigecycline group presented with COPD vs. 10.3% in levofloxacin group. In study 308, 13% of patients in tigecycline group had Diabetes Mellitus vs. 13.5% in levofloxacin group. In study 313, 11.8% of patients in both treatment groups had Diabetes Mellitus. Alcohol abuse was present in 13% of patients in tigecycline group vs. 12.8% in levofloxacin group in study 308 and in 6.9% of patients in tigecycline group vs. 5.1% in levofloxacin group for study 313. In study 308, 64.5% of patients in the tigecycline group had prior smoking history vs. 58.3% in the levofloxacin group. In study 313, 47.2% of patients in the tigecycline group had prior smoking history vs. 47.1% in the levofloxacin group. In study 308, 39.1% of patients in the tigecycline group had current smoking history vs. 28.8% in the

levofloxacin group. In study 313, 34.7% of patients in the tigecycline group had prior smoking history vs. 38.2% in the levofloxacin group.

Only 2.9% (4/138) tigecycline-treated patients in study 308 and 6.9% (10/144) in study 313 had liver disease. 3.8% (6/156) levofloxacin-treated patients in study 308 and 2.9% (4/136) in study 313 had liver disease. The percentages of patients with congestive heart failure were as follows: 6.5% (9/138) tigecycline-treated patients and 7.1% (11/156) levofloxacin-treated patients in study 308 and 9% (13/144) tigecycline-treated patients and 7.4% (10/136) levofloxacin-treated patients in study 313.

In each study, there were no significant differences between treatment groups in the CE populations in the distribution of subjects by Fine pneumonia severity index.

	Study 308		Study 313	
PSI	Tigecycline (n= 138)	Levofloxacin (n= 156)	Tigecycline (n= 144)	Levofloxacin (n= 136)
I	31 (22.5 %)	43 (27.6 %)	18 (12.5 %)	23 (16.9 %)
II	44 (31.9 %)	43 (27.6 %)	49 (34.0 %)	40 (29.4 %)
III	38 (27.5 %)	36 (23.1 %)	40 (27.8 %)	42 (30.9 %)
IV	25 (18.1 %)	34 (21.8 %)	35 (24.3 %)	30 (22.1 %)
V	0	0	2 (1.4 %)	1 (0.7 %)

Calculation of the CURB-65 scores was not performed prospectively in these trials. However, all of the information required for this, other than the assessment of confusion, was collected as part of the baseline information from the subjects in these studies. Thus, an attempt was made to estimate the CURB-65 scores, using the yes/no information about altered mental state from the underlying conditions record of the case report form. In each trial there were no significant differences between the treatment groups in the estimated CURB-65 scores or in the individual criteria (confusion, BUN level, respiratory rate, low blood pressure, age 65 years or greater).

	Study 308		Study 313	
Estimated CURB-65 score	Tigecycline (n= 138)	Levofloxacin (n= 156)	Tigecycline (n= 144)	Levofloxacin (n= 136)
<2	101 (73.2 %)	100 (64.1 %)	97 (67.4 %)	93 (68.4 %)
2	25 (18.1 %)	36 (23.1 %)	36 (25 %)	34 (25 %)
>2	12 (8.7 %)	20 (12.8 %)	11 (7.6 %)	9 (6.6 %)

Regarding signs and symptoms of pneumonia, there were no significant differences between treatment groups in each study for the CE population with respect to the proportions of subjects with WBC > 10 or WBC < 4.5, fever or hypothermia, hypoxemia, *Streptococcus pneumoniae* in blood, cough, pleuritic chest pain, rigors or shaking chills, sputum production, sputum character, and chest auscultation. For study 308, a significant difference was observed for dyspnea, in which more tigecycline-treated subjects had moderate to severe dyspnea compared with levofloxacin-treated subjects.

In study 308, 5.8% tigecycline-treated subjects and 8.6% levofloxacin-treated subjects received concomitant antibiotics during the on-therapy phase of study 308. Significantly ($p = 0.030$) more levofloxacin-treated subjects received macrolides/lincosamides than tigecycline-treated subjects (2.9% vs. 0%). There were no significant differences between treatment groups in the percentages of the individual types of antibiotics received during the on-therapy phase of the study.

In study 313 significantly more levofloxacin-treated subjects received concomitant antibiotics compared with the tigecycline-treated subjects (1.9% tigecycline-treated subjects and 6.6% levofloxacin treated subjects). There were no significant differences between treatment groups in the percentages of the different classes of concomitant antibiotics or of the individual types of antibiotics received during the on-therapy phase of the study.

Switch to oral therapy in study 308:
In the CE population, 124 of 138 tigecycline-treated subjects (89.9%) and 137 of 156 levofloxacin-treated subjects (87.8%) switched to oral levofloxacin. There were no statistically significant differences between the treatment groups. The median number of days to the switch to oral therapy was 3.9 for the tigecycline-treated versus 3.3 days for levofloxacin-treated subjects. There were no statistically significant differences between the treatment groups.

For the c-mITT population these figures were as follows: 81.2% (155/191) tigecycline-treated patients switched to oral levofloxacin vs. 80.8% (164/203) levofloxacin-treated patients. The median number of days to the switch to oral therapy was 3.9 for the tigecycline-treated versus 3.3 days for levofloxacin-treated subjects.

- **Numbers analysed**

In both studies, the treatment groups were comparable with regard to the percentage of patients included in each efficacy analysis populations (CE, c-mITT, ME).

In study 308 a total of 124 mITT subjects were excluded from the CE population (70 in tigecycline group and 54 in levofloxacin group). The most common reason for exclusion from the CE population was that there was no recorded clinical evaluation at the TOC assessment.

In study 313 a total of 148 mITT subjects were excluded from the CE population (72 in tigecycline group and 76 in levofloxacin group). The most common reason for exclusion from the CE population was that the subjects received more than 1 dose of prior antibiotic after baseline culture.

- **Outcomes and estimation**

The primary efficacy variable was Clinical Response at Test-of-Cure in the co-primary analysis populations, the CE and c-mITT populations. In both studies, the lower bound of the 95% CI around the difference in cure rates was greater than -15% in both populations. Thus the primary efficacy endpoint of the study (non-inferiority to levofloxacin in the CE and c-mITT populations) was met. Cure rates were not significantly different between the two treatment groups in both populations in both studies:

In study 308, for the CE population 90.6% (125/138) of tigecycline-treated subjects and 87.2% (136/156) of levofloxacin-treated subjects were considered cured (95% CI -4.4, 11.2) (See table below).

Table 9.3.1-1: Analysis of Clinical Response at the Test-of-Cure Assessment by Geographic Region and Fine Score Category: Clinically Evaluable Population

		-------Tigecycline 50 mg[a] -------			--- -----Levofloxacin[a]----------			----------Difference (Tigecycline–Levofloxacin)----------				
Response	Region and Fine	n/N	%	(95% CI)	n/N	%	(95% CI)	%	(95% CI)	Test for Noninferiority p-Value	Test for Differences p-Value	Test Strat x Trt p-Value
Cure	US/CAN <IV[b]	33/ 37	89.2	(74.6, 97.0)	30/ 38	78.9	(62.7, 90.4)	10.2	(-8.8, 29.3)	0.0034	0.3646	
	US/CAN IV[b]	5/ 6	83.3	(35.9, 99.6)	6/ 11	54.5	(23.4, 83.3)	28.8	(-26.0, 83.6)	0.0741	0.4567	
	MX,CA,SA <IV[b]	71/ 76	93.4	(85.3, 97.8)	81/ 84	96.4	(89.9, 99.3)	-3.0	(-11.1, 5.1)	0.0010	0.6153	
	MX,CA,SA IV[b]	16/ 19	84.2	(60.4, 96.6)	19/ 23	82.6	(61.2, 95.0)	1.6	(-25.8, 29.0)	0.1527	1.0000	
	Overall Unadj[b]	**125/138**	**90.6**	**(84.4, 94.9)**	**136/156**	**87.2**	**(80.9, 92.0)**	**3.4**	**(-4.4, 11.2)**	**<0.001**	**0.4570**	
	Overall Adj[c]							2.3	(-4.5, 9.0)	<0.001	0.5536	0.346
Failure		13/138	9.4	(5.1, 15.6)	20/156	12.8	(8.0, 19.1)					

Abbreviations: CI = confidence interval; Test Strat x Trt = test strata by treatment interaction; US/CAN = United States and Canada; MX,CA,SA = Mexico, Central America, and South America; Unadj = unadjusted; Adj = adjusted.
a. 95% CI within strata are calculated by using the method of Clopper and Pearson.
b. 95% CI for differences within strata are calculated based on 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).

For the c-mITT population, which includes subjects with indeterminate clinical response, 78% (149/191) of tigecycline-treated subjects and 77.8% (158/203) of levofloxacin-treated subjects were considered cured (95% CI -8.5, 8.9).

In study 313, for the CE population 88.9% (128/144) of tigecycline-treated subjects and 85.3% (116/136) of levofloxacin-treated subjects were considered cured (95% CI -5.0, 12.2) (See table below).

Table 9.3.1-1: Analysis of Clinical Response at the Test-of-Cure Assessment by Fine Score Category: Clinically Evaluable Population

		--Tigecycline 50 mg (a)---			--Levofloxacin (a)---			--Difference (Tigecycline-Levo)--			
Response	Fine Score Category	n/N	%	% (95% CI)[a]	n/N	%	% (95% CI)[a]	%	% (95% CI)	Test for Noninferiority (p-Value)	Test for Differences (p-Value)
Final Protocol Amendment											
Cure	< III[b]	60/ 67	89.6	(79.7, 95.7)	55/ 63	87.3	(76.5, 94.4)	2.3	(-10.3, 14.8)	0.0026	0.8993
	III[b]	34/ 40	85.0	(70.2, 94.3)	35/ 42	83.3	(68.6, 93.0)	1.7	(-16.6, 19.9)	0.0388	1.0000
	IV[b]	32/ 35	91.4	(76.9, 98.2)	25/ 30	83.3	(65.3, 94.4)	8.1	(-11.2, 27.4)	0.0079	0.5463
	V[b]	2/ 2	100.0	(15.8,100.0)	1/ 1	100.0	(2.5,100.0)	0.0	(-75.0, 75.0)		
	Overall Unadj[b]	**128/144**	**88.9**	**(82.6, 93.5)**	**116/136**	**85.3**	**(78.2, 90.8)**	**3.6**	**(-5.0, 12.2)**	**<0.001**	**0.4727**
	Overall Adj[c]							3.6	(-4.5, 11.8)	<0.001	0.4025
Failure		16/144	11.1	(6.5, 17.4)	20/136	14.7	(9.2, 21.8)				

a. 95% CI within strata are calculated using the method of Clopper and Pearson
b. 95% CI for differences within strata are calculated based on the asymptotical method corrected for continuity.
c. Estimates of differences between treatment groups, corresponding CIs and hypothesis tests are weighted using minimum risk weights (method of Mehrotra and Railkar).

For the c-mITT population, 83.7% (170/203) of tigecycline-treated subjects and 81.5% (163/200) of levofloxacin-treated subjects were considered cured (95% CI -5.6, 10.1).

Microbiologic response at the subject level for the ME population was as follows: In study 308 eradication rate was 93.3% (70/75) for tigecycline vs. 90.3% (84/93) for levofloxacin. In study 313 eradication rate was 90.1% (82/91) for tigecycline vs. 89.5% (77/86) for levofloxacin (see tables below):

Study 308:

Table 9.3.2.2.1-1: Microbiologic Response at the Subject Level at Test-of-Cure Assessment by Geographic Region and Fine Pneumonia Category: Microbiologically Evaluable Population

		-----Tigecycline 50 mg[a]----			-------Levofloxacin[a]--------			----------Difference (Tigecycline–Levofloxacin)----------				
Response	**Region and Fine**	**n/N**	**%**	**(95% CI)**	**n/N**	**%**	**(95% CI)**	**%**	**(95% CI)**	**Test for Noninferiority p-Value**	**Test for Differences p-Value**	**Test Strat x Trt p-Value**
Eradication	US/CAN <IV[b]	15/16	93.8	(69.8, 99.8)	15/18	83.3	(58.6, 96.4)	10.4	(-16.4, 37.2)	0.0337	0.6722	
	US/CAN IV[b]	3/4	75.0	(19.4, 99.4)	3/4	75.0	(19.4, 99.4)	0.0	(-85.0, 85.0)	0.6280	1.0000	
	MX,CA,SA <IV[b]	43/45	95.6	(84.9, 99.5)	52/55	94.5	(84.9, 98.9)	1.0	(-9.5, 11.5)	<0.001	1.0000	
	MX,CA,SA IV[b]	9/10	90.0	(55.5, 99.7)	14/16	87.5	(61.7, 98.4)	2.5	(-30.3, 35.3)	0.2281	1.0000	
	Overall Unadj[b]	**70/75**	**93.3**	**(85.1, 97.8)**	**84/93**	**90.3**	**(82.4, 95.5)**	**3.0**	**(-6.4, 12.5)**	**<0.001**	**0.6676**	
	Overall Adj[c]							2.6	(-5.3, 10.6)	<0.001	0.5741	0.906
Documented		1/70	1.4	(0.0, 7.7)	0/84	0.0	(0.0, 4.3)					
Presumed		69/70	98.6	(92.3,100.0)	84/84	100.0	(95.7,100.0)					
Persistence		5/75	6.7	(2.2, 14.9)	7/93	7.5	(3.1, 14.9)					
Documented		1/5	20.0	(0.5, 71.6)	0/7	0.0	(0.0, 41.0)					
Presumed		4/5	80.0	(28.4, 99.5)	7/7	100.0	(59.0,100.0)					
Superinfection		0/75	0.0	(0.0, 4.8)	2/93	2.2	(0.3, 7.6)					

Abbreviations: CI = confidence interval; Test Strat x Trt = test strata by treatment interaction; US/CAN = United States and Canada; MX,CA,SA = Mexico, Central America, and South America; Unadj = unadjusted; Adj = adjusted.
a. 95% CI within strata are calculated by using the method of Clopper and Pearson.
b. 95% CI for differences within strata are calculated based on 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).

Study 313:

Table 9.3.2.2.1-1: Analysis of Microbiologic Response at the Subject Level at Test-of-Cure Assessment by Fine Pneumonia Category: Microbiologically Evaluable Population

		----Tigecycline 50 mg----			----Levofloxacin ----			----Difference (Tigecycline-Levo)----			
Protocol Response	Fine Score	n/N	%	(95% CI)[a]	n/N	%	(95% CI)[a]	%	(95% CI)	Test for Non-Inferiority p-Value	Test for Treatment Differences p-Value
Final Protocol Amendment											
Eradication	< III[b]	40/43	93.0	(80.9, 98.5)	35/37	94.6	(81.8, 99.3)	-1.6	(-14.6, 11.5)	0.0212	1.0000
	III[b]	20/23	87.0	(66.4, 97.2)	23/27	85.2	(66.3, 95.8)	1.8	(-21.5, 25.0)	0.0967	1.0000
	IV[b]	22/25	88.0	(68.8, 97.5)	18/21	85.7	(63.7, 97.0)	2.3	(-21.7, 26.3)	0.0991	1.0000
	V[b]	0/0		NA	1/1	100.0	(2.5,100.0)	NA			
	Overall Unadj[b]	**82/91**	**90.1**	**(82.1, 95.4)**	**77/86**	**89.5**	**(81.1, 95.1)**	**0.6**	**(-9.5, 10.6)**	**<0.001**	**1.0000**
	Overall Adj[c]							NA			
Documented		1/82	1.2	(0.0, 6.6)	2/77	2.6	(0.3, 9.1)				
Presumed		81/82	98.8	(93.4,100.0)	75/77	97.4	(90.9, 99.7)				
Persistence		9/91	9.9	(4.6, 17.9)	9/86	10.5	(4.9, 18.9)				
Documented		0/9	0.0	(0.0, 33.6)	1/9	11.1	(0.3, 48.2)				
Presumed		9/9	100.0	(66.4,100.0)	8/9	88.9	(51.8, 99.7)				
Superinfection		0/91	0.0	(0.0, 4.0)	0/86	0.0	(0.0, 4.2)				

NA= not applicable.
a. 95% CI within strata are calculated using the method of Clopper and Pearson.
b. 95% CI for differences within strata are calculated based on the asymptotical method corrected for continuity.
c. Estimates of differences between treatment groups, corresponding CIs and hypothesis tests are weighted using minimum risk weights (method of Mehrotra and Railkar).

Microbiologic response at the subject level for the m-mITT population was as follows: In study 308 eradication rate was 84% (84/100) for tigecycline vs. 82.6% (95/115) for levofloxacin (95% CI -9.5, 12.3). In study 313 eradication rates was 87.2% (109/125) for tigecycline vs. 85.5% (100/117) for levofloxacin (95% CI -7.8, 11.2).

Microbiologic responses at the subject level for ME subjects who had monomicrobial or polymicrobial infections were as follows: **in study 308 eradication rate** was 92.5% (49/53) for tigecycline vs. 92.5% (62/67) for levofloxacin in patients with monomicrobial infection and 95.5% (21/22) for tigecycline vs. 84.6% (22/26) for levofloxacin in patients with polymicrobial infection. Within the m-mITT population eradication rate was 81.6% (62/67) for tigecycline vs. 82.8% (62/67) for levofloxacin in patients with monomicrobial infection and 91.7% (22/24) for tigecycline vs. 82.1% (23/28) for levofloxacin in patients with polymicrobial infection.

In study 313 eradication rate was 88.7% (47/53) for tigecycline vs. 89.3% (50/56) for levofloxacin in patients with monomicrobial infection and 92.1% (35/38) for tigecycline vs. 90% (27/30) for levofloxacin in patients with polymicrobial infection. Within the m-mITT population eradication rate was 87.5% (70/80) for tigecycline vs. 84.8% (67/79) for levofloxacin in patients with monomicrobial infection and 86.7% (39/45) for tigecycline vs. 86.8% (33/38) for levofloxacin in patients with polymicrobial infection.

Microbiologic response at the pathogen level was evaluated for all baseline isolates. Eradication rates at the pathogen level for common CAP pathogens for the ME population were as follows:

Study 308:

Pathogen	**Tigecycline**	**Levofloxacin**
Chlamydia pneumoniae	92.9% (13/14)	93.8% (15/16)
Haemophilus influenzae	100% (6/6)	77.8% (7/9)
Haemophilus parainfluenzae	NA (0/0)	100% (1/1)
Klebsiella pneumoniae	NA (0/0)	50% (1/2)
Legionella pneumophila	100% (7/7)	100% (1/1)
Moraxella catarrhalis	100% (3/3)	66.7% (2/3)
Mycoplasma pneumoniae	92.9% (13/14)	91.7% (22/24)
Staphylococcus aureus	66.7% (2/3)	75% (3/4)
Streptococcus pneumoniae (All)	95.1% (39/41)	92.1% (58/63)
*Streptococcus pneumoniae (*non PISP, non PRSP)	94.9% (37/39)	91.5% 54/59)
Streptococcus pneumoniae (PISP)	100% (1/1)	100% (1/1)
Streptococcus pneumoniae (PRSP)	100% (1/1)	100% (3/3)

Study 313:

Pathogen	**Tigecycline**	**Levofloxacin**
Chlamydia pneumoniae	100% (5/5)	100% (11/11)
Haemophilus influenzae	72.7% (8/11)	100% (9/9)
Haemophilus parainfluenzae	100% (5/5)	100% (9/9)
Klebsiella pneumoniae	100% (4/4)	100% (7/7)
Legionella pneumophila	100% (3/3)	100% (5/5)
Moraxella catarrhalis	NA (0/0)	50% (1/2)
Mycoplasma pneumoniae	96% (24/25)	91.7% (22/24)
Staphylococcus aureus	77.8% (7/9)	100% (6/6)
Streptococcus pneumoniae (All)	92% (46/50)	88.9% (32/36)
*Streptococcus pneumoniae (*non PISP, non PRSP)	91.1% (41/45)	85.7% (24/28)
Streptococcus pneumoniae (PISP)	100% (3/3)	100% (5/5)
Streptococcus pneumoniae (PRSP)	100% (2/2)	100% (6/6)

Eradication was primarily presumed, based on clinical response. Very few *Streptococcus pneumoniae* isolates were PISP or PRSP. All *S. aureus* isolates were non-MRSA.

It should be highlighted that there were consistent lower rates of eradication for *S. aureus* (all non-MRSA). In addition, the results regarding *H. influenzae* are inconsistent between trials. Although suspicion of *L. pneumophila* was an exclusion criteria, there were some isolates. However, the low number of isolates precludes to draw proper conclusions. *S. pneumoniae* isolates were penicillin-susceptible. There were too few PISP or PRSP isolates

Secondary analyses of clinical response at the TOC assessment included assessments of subjects in the ME and m-mITT populations. **In study 308**, for tigecycline-treated subjects in the ME population, 93.3% (70/75) were cured compared with 90.3 % (84/93) of the levofloxacin-treated subjects. For the m-mITT population, 84% (84/100) of the tigecycline-treated subjects were cured compared with 82.6% (95/115) of the levofloxacin-treated subjects. **In study 313**, for the ME population cure rates were 90.1% (82/91) for tigecycline vs. 88.4% (76/86) for levofloxacin. For the m-mITT population cure rates were 86.4% (108/125) for tigecycline vs. 84.6% (99/117) for levofloxacin.

Other secondary analyses of clinical response included assessments of subjects in the ME and m-mITT populations who had monomicrobial or polymicrobial infections. **In study 308**, for the ME population, cure rates were 92.5% (49/53) for tigecycline vs. 92.5% (62/67) for levofloxacin in patients with monomicrobial pneumonia infection and 95.5% (21/22) for tigecycline vs. 84.6% (22/26) for levofloxacin in patients with polymicrobial pneumonia infection. For the m-mITT population, cure rates were 81.6% (62/76) for tigecycline vs. 82.8% (72/87) for levofloxacin in patients with monomicrobial pneumonia infection and 91.7% (22/24) for tigecycline vs. 82.1% (23/28) for levofloxacin in patients with polymicrobial pneumonia infection. The type of infection-by-treatment interaction for clinical response was not significant. **In study 313**, for the ME population, cure rates were 88.7% (47/53) for tigecycline vs. 87.5% (49/56) for levofloxacin in patients with monomicrobial pneumonia infection and 92.1% (35/38) for tigecycline vs. 90% (27/30) for levofloxacin in patients with polymicrobial pneumonia infection. For the m-mITT population, cure rates were 86.3% (69/70) for tigecycline vs. 83.5% (66/79) for levofloxacin in patients with monomicrobial pneumonia infection and 86.7% (39/45) for tigecycline vs. 86.8% (33/38) for levofloxacin in patients with polymicrobial pneumonia infection.

- **Ancillary analyses**

Subgroup analyses of clinical cure rates in subgroups of the CE population were performed in each study in order to evaluate the consistency of treatment effect across various subgroups.

Study 308:

No treatment-by-subgroup interactions were identified for the following subgroups: presence or absence of diabetes, body mass index, creatinine clearance, number of lobes of the lung involved,

deaths, Fine category, age categories (younger than 55 and 55 and older, younger than 65 and 65 and older, and younger than 75 and 75 and older) and sex.

There was a significant interaction for the analysis of clinical cure rates by geographic region. In that analysis, the tigecycline cure rates remained consistent in the United States/Canada and Mexico/Central America/South America regions (88.4% and 91.6%, respectively). However, the levofloxacin cure rates were not consistent (United States/Canada 73.5% and Mexico/Central America/South America 93.5%), thus producing a significant interaction.

Study 313: There were 3 analyses which had statistically significant ($p \leq 0.10$) treatment by subgroup interaction: age (< 55 vs. ≥ 55 years), the subjects with one lobe versus subjects with multilobar pneumonia, and presence or absence of bacteremia at baseline. For these analyses, the clinical cure rates were generally consistent for the tigecycline treatment group across the subgroups; however, the cure rates in the levofloxacin treatment group were variable, thus producing a significant interaction.

Exploratory analysis of clinical response rates for subjects who did or did not switch to oral therapy (study 308 only) was performed. The results were generally similar between the 2 treatment groups. The cure rate was high in those subjects who were switched to oral therapy and low in the small number of subjects who were not switched. The latter would be expected, since subjects could not be switched to oral therapy if they did not demonstrate improvement in their signs and symptoms of pneumonia.

An exploratory analysis of clinical response rates by initial levofloxacin dose was performed for both studies. In study 308 most levofloxacin-treated subjects received 500 mg once daily (78.7%, 122/155). The clinical response rate of CE subjects who received 500 mg daily was 89.3% (109/122) and 78.8% (26/33) for patients who received 250 mg daily. In study 313 most levofloxacin-treated subjects in the CE population received 500 mg BID (63.2%, 91/144). The clinical response rate of CE subjects who received 500 mg twice daily was 87.9% (80/91) and 88.9% (32/36) for patients who received 500 mg daily.

- ***Analysis performed across trials (pooled analyses AND meta-analysis)***

The 2 CAP studies (308 and 313) were generally similar in design, the main differences being the allowance of an oral switch in study 308 and the allowance for dose administration of levofloxacin twice daily in study 313. Because the lower bounds of the confidence intervals for the true difference in cure rates for tigecycline minus levofloxacin were ≥ -10% for clinical response in both protocols, it was determined that a pooled analysis was not required to evaluate non-inferiority with a limit difference of 10% (a preference by some regulatory agencies). Data were pooled for mainly exploratory purposes and to generate hypotheses.

Multiple subgroup analyses were performed. These included subjects with bacteremia, particularly *S. pneumoniae* bacteremia, multilobar disease, bilateral disease, pleural effusions, common respiratory pathogens plus an atypical pathogen, Fine score, estimated CURB-65 scores, underlying conditions (diabetes mellitus, COPD, congestive heart failure, alcohol abuse, witnessed aspiration, neoplastic disease, liver disease, cerebrovascular disease, renal disease, altered mental status, nursing home resident, prior smoking history, and current smoking history), signs and symptoms of pneumonia (sputum character, auscultatory findings, cough, dyspnea, pleuritic chest pain, chills, WBC count, fever/hypothermia, hypoxemia), age, sex, ethnic origin, geographic region, calculated creatinine clearance, and BMI.

The cure rates for tigecycline in the various subgroup analyses were generally similar to the overall results for tigecycline except for lower cure rates observed in subjects with COPD (65.9%, c-mITT) and liver disease (66.7%, c-mITT). Clinical response by geographic region for c-mITT population was low for US/CAN for both treatment groups (66.2% for tigecycline and 56.4% for levofloxacin). The cure rates for levofloxacin-treated subjects in the various subgroup analyses were also generally similar to the overall results for levofloxacin, except for lower cure rates observed in subjects with

diabetes mellitus (75.7%, CE), COPD (68.3%, c-mITT), congestive heart failure (66.7%, CE), renal disease (72.2%, CE), and without fever/hypothermia (67.8, c-mITT).

The treatment-by-Fine score interaction for clinical response was not significant between the 2 treatment groups.

There was a significant interaction for the analysis of clinical cure rates by age for subjects who were <55 and ≥55 years for the CE population. In that analysis, the tigecycline cure rates remained consistent in these age groups (89.3% and 90.1%, respectively). However, the levofloxacin cure rates were not consistent (91.6% for subjects aged <55 years and 80.4% for subjects aged ≥55 years), thus producing a significant interaction.

There was a significant interaction for the analysis of clinical cure rates for estimated creatinine clearance (≤70 ml/min, and >70 ml/min). The tigecycline cure rates remained consistent for the 2 creatinine clearance groups (89.1% and 90.1%, respectively, CE population). However, the levofloxacin cure rates were not consistent with the overall results (78.1% for creatinine clearance ≤70 ml/min, and 91.6% for creatinine clearance >70 ml/min), thus producing a significant interaction.

The clinical response rates were lower in tigecycline-treated CE subjects with multilobar disease (82.5%) compared with unilobar disease (93%) as assessed by the investigator and in levofloxacin-treated subjects with multilobar disease (80.6%) compared with those with unilobar disease (88.2%).

The clinical response rates were lower in levofloxacin-treated subjects with bilateral disease (79.1%, CE, maximum severity assessment) compared with those with unilateral disease (89.3%).

Cure rates were lower for tigecycline (60%, CE) than for levofloxacin (71.4%) for subjects with pleural effusions based on the minimum severity assessment. The clinical response rates were lower in both treatment groups for subjects with pleural effusions (minimum severity) compared with those without pleural effusions. The cure rates for tigecycline were as follows for the CE population: 60% in subjects with pleural effusion and 91.4% in subjects without pleural effusions.

Treatment-by-bacteremia interaction for clinical response was not significant.

- ***Supportive studies***

Study 311 (HAP)

This was a phase 3, multicenter, randomized, double-blind comparative study of the efficacy and safety of tigecycline versus imipenem/cilastatin for the treatment of subjects with hospital-acquired pneumonia. The **primary objective** of this study was to compare the efficacy and safety of the tigecycline regimen with that of the imipenem/cilastatin regimen to treat subjects with HAP. **Secondary objectives** were (1) to evaluate the microbiologic efficacy of tigecycline; (2) to obtain in vitro susceptibility data on tigecycline for a range of bacteria that cause HAP; (3) to compare health care utilization between treatment arms; and (4) to determine the pharmacokinetic profile of tigecycline.

For the HAP indication, a non-inferiority margin of 15% was selected as a balance between the severity of the disease under study and practical considerations regarding study enrollment. Based on an expected response rate of 65% in the HAP population, this absolute limit difference is equal to a relative limit difference of 23%.

After an initial 100-mg dose, subjects received 50 mg tigecycline every 12 hours in a volume of 100 mL normal saline administered IV over a period of 30 to 60 minutes. On each day of treatment, at 8 hours and at 16 hours, subjects received a placebo infusion. Imipenem/cilastatin was administered IV every 8 hours at a total daily dosage of 1.5 to 3 g imipenem. Dosage was at the discretion of the investigator (within local labeling/standard practices) and was to be dependent upon the severity of the infection and the known or suspected organisms and could be adjusted based upon weight and/or

creatinine clearance (CLCR). On each day of treatment, at 12 hours, subjects received a placebo infusion. If appropriate, adjunctive therapy with vancomycin 1 g IV approximately every 12 hours and an aminoglycoside was given.

Adjunctive antibiotics were permitted during the first 72 hours of study treatment if *Pseudomonas aeruginosa* or methicillin-resistant *Staphylococcus aureus* (MRSA) was suspected or cultured (ceftazidime 1 or 2 g IV every 8 or 12 hours for the tigecycline arm for *P. aeruginosa*, vancomycin for the imipenem/cilastatin arm for MRSA, and/or an aminoglycoside for either arm as additional coverage for *P. aeruginosa*). Subjects were stratified at randomization by whether they had ventilator-associated pneumonia (VAP) and by their Acute Physiologic and Chronic Health Evaluation scale (APACHE II) score (≤15 or >15).

The duration of subject participation was approximately 2 to 5 weeks. The duration of therapy was to be a minimum of 7 days and not longer than 14 days. The duration of the adjunctive therapies, if needed, also was not to exceed 14 days.

Eligible subjects were at least 18 years of age with known or suspected acute HAP, defined as pneumonia with onset of symptoms ≥48 hours after admission to and ≤7 days before discharge from an acute care hospital or chronic care facility such as a skilled nursing home facility or rehabilitation unit. The duration of the initial hospitalization must have been ≥3 days. Subjects must have shown the presence of a new or evolving infiltrate on a chest radiograph obtained ≥48 hours after admission.

The co-primary efficacy endpoints were the clinical response (cure, failure, or indeterminate, as assessed by the investigator) at the TOC assessment for the clinically evaluable (CE) and clinical modified intent- to-treat (c-mITT) populations. Microbiologic efficacy was evaluated as a secondary endpoint at both the subject level (eradication, persistence, superinfection, or indeterminate) and at the pathogen level (eradication, persistence, or indeterminate). Subjects were evaluated for microbiologic efficacy if they met all of the criteria for CE subjects and the screening respiratory culture contained at least 1 identified causative pathogen susceptible to at least 1 of the agents used in each treatment arm.

Efficacy results of study 311

At the TOC assessment, 67.9% of tigecycline-treated subjects and 78.2% of imipenem/cilastatin-treated subjects in the CE population were considered cured, and 62.7% of tigecycline-treated subjects and 67.6% of imipenem/cilastatin-treated subjects in the c-mITT population were considered cured. The tigecycline regimen met the statistical criteria of non-inferiority to the imipenem/cilastatin regimen at the TOC assessment (the primary endpoint) for the c-mITT population (p=0.001), but not for the co-primary CE population (p=0.120). The difference in efficacy (ie, tigecycline regimen minus imipenem/cilastatin regimen) for the c-mITT population was –4.8 (adjusted), with the lower limit of the 95% CI not less than -15% in either the adjusted or unadjusted analyses. For the CE population, the difference in efficacy was –10.4, with the lower limit of the 95% CI less than – 15% in both the adjusted and unadjusted analyses.

A statistically significant interaction was noted for the a priori stratification of non-VAP and VAP subjects. The VAP population defines the group of subjects that drove the imbalances in the results between tigecycline and imipenem/cilastatin regimens.

Analyses were performed to try to understand this interaction, with various population and treatment factors assessed individually and in combination. These included such factors as adjunctive therapy, demographic and baseline factors (including co-morbidities), geographic region, incidence of baseline pathogens, and prior antibiotic failure. Despite the multiple analyses performed to attempt to better understand the differences present in the VAP population (both between VAP and non-VAP, and between tigecycline and imipenem/cilastatin regimens), no clear explanation for the differences based on the population could be definitively identified. Even markers for the severity of disease (eg, APACHE II score and being in the ICU) demonstrated that they were predictors of the difficulty of treating/curing the disease, but that their effect was equal in both arms and not a definitive explanation of why the VAP population behaved differently for these two regimens.

It appears that although similar exposure was seen compared to prior experience, when viewed using AUC to MIC as the past best predictor of outcome, the combination with somewhat higher MICs in this population suggests that under-dosing of tigecycline for the VAP subjects may be the underlying issue.

Given the results of the overall analyses, subgroup analysis considering the prespecified VAP and non-VAP populations separately was performed.

Among non-VAP subjects, cure rates in the CE population were 75.4% for the tigecycline group and 81.3% for the imipenem/cilastatin group (95%CI of the difference in cure rates between treatment groups –14.5, 3.0). In the c-mITT population these figures were 69.3% for tigecycline vs. 71.2% for imipenem (95%CI –9.4, 5.6).

Eradication rates at the TOC assessment for non-VAP subjects in the ME population were 76.7% in the tigecycline group and 80.5% in the imipenem/cilastatin group, and in the m-mITT population were 69.1% for the tigecycline group and 73.4% for the imipenem/cilastatin group. The eradication rates were primarily presumed based on clinical response. In both treatment groups, clinical cure rates and microbiologic eradication rates were higher for polymicrobial infections than for monomicrobial infections (ME and m-mITT populations).

Eradication rates at the pathogen level (primarily presumed) were lower than expected for subjects in the tigecycline regimen with MRSA infections (47.1%, 8/17) vs. the comparator (78.9%, 15/19). As a consequence, PVL and mec typing were performed. A total of 162 nonduplicative *S. aureus* isolates with oxacillin MIC ≥ 4 μg/mL were ribotyped, and cluster analysis was performed based on EcoRI and PvuII Riboprint patterns. These isolates were also SCCMec typed, and the PVL status was determined. Of the isolates analyzed, 26, 60, 29, and 28 of the isolates were SCCMec type I, II, III, or IV, respectively. Nineteen (19) could not be typed. Three (3) isolates were PVL positive, and all were SCCMec type IV. Two (2) of the 3 PVL-positive isolates clustered with well-characterized community-acquired MRSA, suggesting that these are community-associated isolates.

Clinical cure rates at the TOC assessment for non-VAP subjects in the ME population treated with tigecycline were 85.7% (6/7) for ESBL-producing *E. coli*; 61.5% (8/13) for ESBL-producing *K. pneumoniae*; 66.7% (6/9) for β-lactamase-negative *H. influenzae*; 100% (8/8) for MDR *A. baumannii*; and 47.1% (8/17) for MRSA. Cure rates for subjects in the imipenem/cilastatin group were similar for ESBL-producing organisms, higher for MRSA, and lower for MDR *Acinetobacter*. MIC values for the resistant organisms were generally lower for tigecycline than for imipenem/cilastatin.

In the non-VAP population, low tigecycline MIC50 and MIC90 values were observed for several key isolates, including *E. coli* (0.25 and 0.5 μg/ml), *H. influenzae* (0.25 and 0.5 μg/ml), *K. pneumoniae* (0.5 and 2 μg/ml), and *S. pneumoniae* (non-PI/PR; 0.06 and 0.12 μg/ml). MIC values for MRSA (n=17) in the tigecycline arm ranged from 0.12 to 2 μg/ml. There were two MRSA baseline isolates with a MIC of 1 μg/ml, one which was eradicated and cured. There was a single MRSA isolate with a MIC of 2 μg/ml which was considered cured but not eradicated. For *S. aureus* (non-MRSA) (n=36) tigecycline MICs ranged from 0.06 to 0.5 μg/ml.

Of the 10 non-VAP ME subjects with monomicrobial MRSA infections, 5 were clinical cures and 6 were microbiologic eradications. Of the 7 non-VAP ME subjects with polymicrobial infections that included MRSA, 3 were clinical cures and 2 were microbiologic eradications. For the 4 clinical failures, the other organisms were *E. cloacae* and *K. pneumoniae* (1 subject each), and *P. aeruginosa* (2 subjects).

An isolate was identified as having decreased susceptibility to one of the study treatments if the MIC increased ≥4-fold from baseline and was not already resistant at baseline. Three (3) subjects in the m-mITT population had isolates that, while not meeting all criteria for decreased susceptibility, did show some alteration in susceptibility to tigecycline (*Acinetobacter baumannii*, *E. cloacae*, and *E. faecalis*).

Study 307 (RP)

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 vancomycin-resistant *Enterococcus* (VRE) and to evaluate tigecycline and vancomycin for the treatment of selected serious infections in subjects with methicillin-resistant *Staphylococcus aureus* (MRSA). Subjects were stratified at randomization by type of infection (VRE or MRSA), by site of infection (VRE subjects: complicated intra-abdominal infection [cIAI] or other infection; MRSA subjects: complicated skin and skin structure infection [cSSSI] or other infection), and by Acute Physiologic and Chronic Health Evaluation (APACHE) II score (>15 or ≤15). Subjects were randomly assigned in a 3:1 fashion (VRE: tigecycline:linezolid; MRSA: tigecycline:vancomycin) for the purpose of an active control.

For VRE subjects, linezolid, IV infusions of 600 mg every 12 hours was administered whereas for MRSA subjects, vancomycin IV infusions of 1 g every 12 hours was administered. Patients in the tigecycline group received an initial 100-mg dose followed by 50 mg every 12 hours administered IV over a period of 30 to 60 minutes. The duration of therapy was to be a minimum of 7 days and not longer than 28 days. Subject participation in the study involved up to 1 day for screening, up to 28 days of study drug administration, and, unless the subject was a clinical failure, 1 post-therapy visit at least 12 days but no more than 37 days after the last dose of study drug for the test-of-cure (TOC) assessment; thus, the maximum duration of participation was 66 days.

Efficacy evaluations were performed at the end of treatment and at 12 to 37 days after the last dose of study drug for the TOC assessment, unless the subject was deemed a clinical failure. The **primary efficacy endpoint** in this study was the clinical response rate in the ME and m-mITT populations at the TOC assessment. The **secondary objectives** of this study were 1) to evaluate the in vitro susceptibility data on tigecycline for these bacteria that are resistant to multiple antibiotics; 2) to evaluate the microbiologic efficacy of tigecycline; 3) to evaluate the safety profile of tigecycline for subjects with serious infections due to VRE or MRSA; 4) to determine the pharmacokinetic profile of tigecycline for subjects with serious infections due to VRE or MRSA; and 5) to characterize the health care utilization profile of tigecycline for subjects with serious infections due to VRE or MRSA.

Safety population includes 156 MRSA and 15 VRE mITT subjects. Co-primary efficacy populations: 117 MRSA microbiologically evaluable (ME) subjects and 6 VRE ME subjects; 133 MRSA microbiologic modified intent-to-treat (m-mITT) subjects and 11 VRE m-mITT subjects.

Efficacy results of study 307

In subjects with MRSA infection (n = 156), clinical cure of MRSA infections at the TOC assessment occurred in 81.4% of ME subjects and 75.0% of m-mITT subjects treated with tigecycline, compared with 83.9% of ME subjects and 81.8% of m-mITT subjects treated with vancomycin. In the MRSA ME population, isolates were eradicated in 80.2% of tigecycline-treated subjects and 83.9% of vancomycin-treated subjects at the TOC assessment.

The tigecycline minimum inhibitory concentration (MIC) range for MRSA was 0.12 to 0.50 µg/mL, and the tigecycline MIC50 and MIC90 values for MRSA were 0.25 and 0.50 µg/mL, respectively.

For VRE subjects, the enrolment was significantly fewer than planned, and evaluability was substantially lower than anticipated (208 enrolled, 70% evaluable). Of the 15 subjects with VRE infection who entered the study, only 40% were evaluable for the ME population. Clinical cure and microbiologic eradication were achieved at the TOC assessment in all 3 VRE ME subjects (each of whom had monomicrobial infection) and 3 of 8 VRE m-mITT subjects treated with tigecycline, compared with 2 of 3 VRE ME and m-mITT subjects treated with linezolid. The tigecycline MIC range for VRE *faecium* was 0.06 to 0.12 µg/mL, and the MIC50 and MIC90 values were each 0.12 µg/mL.

No subjects in this study had an isolate with indeterminate or resistant susceptibility to tigecycline, as defined by the provisional breakpoints.

Pharmacokinetic parameters were assessed in 34 subjects, except for CL, which was assessed in only 31 subjects. The mean (CV%) parameters observed were as follows: Cmax 2006 ng/mL (205%), tmax 1.3 hours (94%), AUC 6940 ng.hr/mL (116%), and CL 12.3 L/hr (67.8%). More variable than previously reported, the Cmax and AUC in this study are also somewhat higher than previously reported for other infected subjects (488 ng/mL [52%] and 2924 ng.hr/mL [42%], respectively) and the CL correspondingly lower (19.9 L/hr [41%]).

Study 309 (RP)

This is a phase 3, open-label, noncomparative study of tigecycline for the treatment of subjects with selected serious infections due to resistant gram-negative organisms such as *Enterobacter* species, *Acinetobacter baumannii*, and *Klebsiella pneumoniae*. For study entry, a subject was considered to have a resistant gram-negative organism if (1) the organism was an extended spectrum beta-lactamase (ESBL)-producing strain, or (2) the subject had clinically failed or the organism was resistant (in vitro) to or the subject could not receive (because of allergy or intolerance) at least 1 antimicrobial agent from 3 or more different classes commonly prescribed for these organisms.

Tigecycline was administered as an initial IV infusion of 100 mg followed by 50 mg every 12 hours. Study drug administration: 7 to 28 days, depending upon the site and severity of infection and based on the investigator's judgment. Subject participation in the study involved up to 1 day for screening, up to 28 days of study drug administration, and, unless the subject was a clinical failure, 1 post-therapy visit at least 12 days but not more than 37 days after the last dose of study drug for the test-of-cure (TOC) assessment; thus, the maximum duration of participation was 66 days.

The **primary efficacy endpoint** was the clinical response in the co-primary populations of the ME and m-mITT subjects at the TOC assessment. Within the ME population, the clinical response was assigned by the investigator as cure or failure; within the m-mITT population, the clinical response was assigned as cure, failure, or indeterminate. Secondary analyses of clinical response (cure vs failure) conducted on the ME and m-mITT populations at the TOC assessment included clinical response excluding subjects whose surgical procedure provided inadequate source control, clinical response by baseline isolate and by minimum inhibitory concentration (MIC) values, and clinical response for subjects with monomicrobial or polymicrobial infections. Microbiologic response was determined programmatically at the subject level (eradication, persistence, superinfection, or indeterminate) and pathogen level (eradication, persistence, or indeterminate) for all baseline isolates. Monomicrobial and polymicrobial infections were also assessed separately. MIC tests were used to evaluate the susceptibility of isolates. **Secondary objectives** were to evaluate microbiologic efficacy of tigecycline, to evaluate in vitro susceptibility data on tigecycline for resistant gram-negative bacteria, to determine the pharmacokinetic (PK) profile of tigecycline for subjects with serious infections caused by these resistant organisms, and to evaluate health care utilization.

Safety population includes 112 subjects in the modified intent-to-treat (mITT) population. Co-primary efficacy populations are: 36 microbiologically evaluable (ME) subjects and 75 microbiological modified intent-to-treat (m-mITT) subjects.

Efficacy results of study 309

For the primary efficacy endpoint, clinical response at the TOC assessment, the cure rate was 72.2% for the ME population and 53.3% for the m-mITT population. Clinical cure rates at the TOC assessment were lower in subjects with monomicrobial infections compared with those who had polymicrobial infections (66.7% vs 76.2% among ME subjects, and 50.0% vs 56.8% among m-mITT subjects). Cure rates at the TOC assessment were generally higher among younger subjects (76.2% of subjects younger than 55 years compared with 66.7% of subjects aged 55 years or older) and lowest (40.0%) among the 5 subjects who were aged 75 years or older. Cure rate was also higher among female subjects than male subjects (83.3% vs 66.7% at the TOC assessment). Among the 11 ME

subjects who had bacteremia at baseline, the clinical cure rate was lower than that of subjects who did not have bacteremia at baseline (63.6% vs 76.0%), as might be expected.

Microbiologic eradication rates at the TOC assessment were 66.7% for the ME population and 49.3% for the m–mITT population. Superinfection occurred in 5 subjects in the ME population and 6 subjects in the m-mITT population. Unlike the clinical cure rates, eradication rates at the TOC assessment were higher in subjects with monomicrobial infections compared with those who had polymicrobial infections (73.3% vs 61.9% among ME subjects, and 52.6% vs 45.9% among m-mITT subjects).

Clinical cure rates at the TOC assessment for resistant pathogens from subjects in the ME population were as follows: 14 of 17 (82.4%) with *A. baumannii*, 3 of 4 (75.0%) with *Enterobacter* species, 4 of 9 (44.4%) with *E. coli*, and 5 of 6 (83.3%) with *K. pneumoniae*. If one excludes cases deemed by the surgical review board to have inadequate source control, the cure rate for *E. coli* was 4 of 6 (66.7%).

Eradication rates for resistant isolates from subjects in the ME population were as follows: 11 of 17 (64.7%) with *A. baumannii*, 3 of 4 (75.0%) with *Enterobacter* species, 6 of 9 (66.7%) with *E. coli*, and 6 of 6 (100%) with *K. pneumoniae*. For the m-mITT population, eradication rates for resistant isolates were as follows: 14 of 32 (43.8%) with *A. baumannii*, 8 of 15 (53.3%) with *Enterobacter* species, 7 of 10 (70.0%) with *E. coli* and 9 of 13 (69.2%) with *K. pneumoniae*.

The cure rate at the TOC assessment for subjects with cSSSI was 83.3% (20/24) in the ME population, with response rates of 84.6% (11/13) for *A. baumannii*, 60.0% (3/5) for *E. coli*, and 100% (3/3 each) for *K. pneumoniae* and *Enterobacter* species. The numbers were small for the other diagnoses in the ME population, although it should be noted that the lower cure rate of 40.0% (2/5) for cIAI overall and 25.0% (1/4) for *E. coli* cIAI infections was impacted by inadequate source control for 3 of these subjects.

Clinical response varied widely across geographic regions, with treatment success occurring more often in eastern Europe (18 of 20 subjects, 90.0%) and Latin America (7 of 7 subjects, 100%) compared with the United States (1 of 4 subjects, 25.0%) and Western Europe (0 of 4 subjects, 0%), although the number of subjects in some of the regions was small. Regional analysis of MIC data suggests that bacterial susceptibility was variable in this study population.

Tigecycline MIC50 and MIC90 values for resistant organisms in the ME population were 1 and 2 mg/mL for *A. baumannii*. For the m-mITT population, the tigecycline MIC50 and MIC90 were 1 and 4 mg/mL for A. *baumannii*, 1 and 2 mg/mL for *E. cloacae*, 0.5 and 0.5 mg/mL for *E. coli*, and 1and 4 mg/mL for *K. pneumoniae*.

There were 2 isolates with a 4-fold or greater increase in tigecycline MIC from baseline: *K. pneumoniae* isolated in a subject who was a clinical cure and microbiological persistence (MIC at baseline 2 µg/mL, on-therapy 8 µg/mL, and at TOC assessment 2 µg/mL); and *M. morganii* isolated in a subject who was a clinical cure and microbiologic eradication (MIC at baseline 8 µg/mL, last day on therapy 32 µg/mL).

Pharmacokinetic parameters were assessed in 40 subjects. The mean (CV%) parameters observed were as follows: max 1366 ng/mL (94%), tmax 0.72 hour (78%), AUC 6081 ng.hr/mL (86%), and CL 15.3 L/hr (79%). More variable than previously reported, the Cmax and AUC values in this study are somewhat higher than previously reported for other infected subjects (488 ng/mL [52%] and 2924 ng.hr/mL [42%], respectively) and the CL correspondingly lower (19.9 L/hr [41%]).

Study 310 (RP)

This is an open-label, noncomparative, multicenter, emergency-use protocol administering tigecycline for the treatment of subjects with infections due to resistant pathogens.

The **primary objective** of this study was to make tigecycline available to patients who have infections due to resistant pathogens and who had failed or could not tolerate other available appropriate antimicrobial therapy. **Secondary objective** of this study was to evaluate the safety and efficacy of tigecycline in these patients.

After an initial 100-mg dose, subjects received 50 mg tigecycline every 12 hours administered IV over a period of 30 to 60 minutes. The duration of therapy was five (5) to 90 days, depending on the site and severity of infection and based on the investigator's judgment; treatment for longer than 90 days was permitted with sponsor approval.

All subjects were to be followed up for safety and efficacy through the test-of-cure (TOC) assessment, which was to take place at least 12 days but not more than 37 days after the last dose of study drug with the following exceptions: endocarditis 3 months, osteomyelitis 6 and 12 months, and mycobacterial infections 6 and 12 months after the last dose of study drug.

The primary efficacy endpoint was the clinical response (cure, failure, or indeterminate) in the mITT population at the TOC assessment. Secondary analyses of clinical response (cure versus failure) performed on the ME and m-mITT populations at the TOC assessment included clinical response by baseline isolate and by minimum inhibitory concentration (MIC) values, and clinical response for subjects with monomicrobial or polymicrobial infections. Microbiologic response was determined programmatically at the subject level (eradication, persistence, superinfection, or indeterminate) and pathogen level (eradication, persistence, or indeterminate) for all baseline isolates. Monomicrobial and polymicrobial infections were also assessed separately. MIC tests were used to evaluate the susceptibility of isolates.

Population enrolled: Safety and primary efficacy population: modified intent-to-treat (mITT) = 27 subjects. Secondary efficacy populations: microbiologically evaluable (ME) = 18 subjects; microbiologic modified intent-to-treat (m-mITT) = 24 subjects.

Efficacy results of study 310

Clinical cure rates at the TOC assessment were 40.7% of the mITT population, 45.8% of the m-mITT population, and 50.0% of the ME population. Clinical cure rates at the TOC assessment were lower in subjects with monomicrobial infections than in those who had polymicrobial infections: 42.9% vs 75.0% among ME subjects and 42.1% vs 60.0% among m-mITT subjects. Clinical cure rates at the TOC assessment were somewhat higher among younger subjects (54.5% of subjects younger than 55 years compared with 42.9% of subjects 55 years or older) and lowest (40.0%) among subjects who were 65 years or older, although there were only 5 subjects in this age group. The clinical cure rate was also higher among male subjects than female subjects (63.6% vs 28.6% at the TOC assessment). The clinical cure rate for the 8 ME subjects who had bacteremia at baseline was higher than that for subjects who did not have bacteremia at baseline (5 of 8 [62.5%] vs 4 of 10 [40.0%]).

Baseline isolates were eradicated (primarily presumed eradication) in 55.6% of ME subjects and 50.0% of m-mITT subjects at the TOC assessment. There were no cases of superinfection in either population. Similar to the clinical responses, eradication rates at the TOC assessment were lower in subjects with monomicrobial infections than in those who had polymicrobial infections: 50.0% vs 75.0% among ME subjects and 47.4% vs 60.0% among m-mITT subjects.

Overall, small numbers of each organism were isolated at baseline. For infection with *Acinetobacter baumannii*, 4 (80.0%) of 5 ME subjects and 5 (62.5%) of 8 m-mITT subjects had clinical cure and microbiologic eradication. For infection with *Mycobacterium abscessus*, none of the 5 ME and m-mITT subjects had clinical cure or microbiologic eradication, although eradication would be unusual with this organism. One subject (310-114-000141) appeared to have some clinical improvement and continued with tigecycline for almost 4 months before discontinuing because of AEs. One (1) other subject (310-129- 000291) with a complicated skin and skin structure infection (cSSSI; wound) and the organism in blood (and previously reported in lung) appeared to have initial clinical improvement

but then developed relapsed bacteremia, sepsis, and multiorgan failure after approximately 5 weeks of treatment.

Tigecycline MIC values were generally low, with most clinical cures and microbiologic eradications at an MIC of 2 mg/mL or less. The MIC values for 50% and 90% of isolates (MIC50 and MIC90) could not be calculated for any of the baseline organisms because none were isolated in 10 or more subjects. There were no isolates with decreased tigecycline susceptibility (ie, a 4-fold or greater increase in MIC from baseline).

- ***Conclusion on clinical efficacy***

Two phase 3 clinical trials have been conducted to support the efficacy of tigecycline in adult patients with community acquired pneumonia (CAP): **studies 308 and 313**.

Design of studies:

Both CAP studies had similar protocol. Main differences were that in study 308 an oral switch to unblinded levofloxacin was allowed after 3 days of IV therapy and in study 313 levofloxacin dose could be 500 mg once daily or twice daily according to the investigator's decision based upon local practice.
They were multicenter, multinational and double blind trials. Patients were randomized to receive either tigecycline (initial dose of 100 mg followed by 50 mg every 12 hours) or levofloxacin (500 mg once daily in study 308 and 500 mg once or twice daily in study 313). Levofloxacin dosage could be adjusted according to creatinine clearance. Duration of treatment was 7-14 days. In both studies subjects were stratified at randomization according to Fine PSI score.

Regarding the choice of the comparator, optimal control drug would have been a betalactam. According to the consensus guidelines on the management of community-acquired pneumonia in adults developed by the *Infectious Diseases Society of America and the American Thoracic Society (CID 2007; 44:S27-72)*, levofloxacin is an acceptable comparator for hospitalized patients (non UCI). However, in *European guidelines (e.g. British Thoracic Society Guidelines for the Management of Community Acquired Pneumonia in Adults- 2004 Update)* the preferred choice for hospital treated non-severe CAP is oral amoxicillin plus a macrolide. The convenience of initial empiric coverage for atypical pathogens has been questioned in recent publications. In fact, what the baseline isolates of trials 308 and 313 show is that a single beta-lactam would have been an adequate choice for most patients. The majority of baseline isolates were penicillin-susceptible *S. pneumoniae*.

Additionally, there was a concern on posology of levofloxacin in pivotal trials. In general, the dose recommended for levofloxacin in the guidelines is 750 mg once daily for 5 days. From a strict regulatory point of view levofloxacin could be accepted as an adequate comparator given that the dosage regimens used in CAP trials 500 mg once or twice daily (depending on the severity of the disease) during 7 to 14 days is authorised in most countries. In addition, its antimicrobial spectrum includes the most frequent pathogens involved in the disease. However, published data (Noreddin AM et al., 2004, 2005) suggest that the dosage regimen used in the pivotal trials could be insufficient for the attainment of an adequate PK-PD target against *S. pneumoniae* in adult patients as compared with elderly patients.

Consequently, the CHMP felt that the dosing schedules of levofloxacin administered in pivotal studies (500 mg once daily in study 308 and 500 mg once or twice daily in study 313 with dose adjustment in case of renal insufficiency) could have ended up in a suboptimal clinical and microbiological outcome, specially considering that the mean age of patients enrolled was around 50 years.

Paradoxically, and despite the above-mentioned published data, the results from tigecycline studies in CAP show a trend toward a lower response in elderly patients treated with levofloxacin. Whether this is a chance finding or not remains unanswered, but is unlikely to be addressed by further analyses.

The MAH performed a subgroup analysis by dose of levofloxacin initially received. In this analysis doses of 250 mg once daily (study 308) and 250 mg once or twice daily (study 313) have been administered to a small number of patients (it is assumed that due to dosage adjustments based on creatinine clearance).

In study 308, the cure rate at TOC in the CE population in the subgroup of patients receiving initially levofloxacin 250 mg once daily was 78.8% (26/33) vs. 90.6% (125/138) for those on tigecycline. For the subgroup of patients receiving the full levofloxacin dose (500 mg once daily) these figures were 89.3% (109/122) vs. 90.6%, respectively.

In study 313, clinical response at TOC in the CE population by levofloxacin dose is shown in table below.

Table 9.3.2.4.1-6: Clinical Response By Initial Levofloxacin Dosage: Clinically Evaluable Population

			----------Tigecycline 50 mg[a]----------		--------Levofloxacin[a]---------		-----Difference-(Tigecycline-Levo[b])------	
Visit	Initial Levo Dosage	Response	N/Total	% (95% CI)	N/Total	% (95% CI)	%	(95% CI)
TOC	Levofloxacin, 250 mg q24h	Cure	128/ 144	88.9 (82.6, 93.5)	1/ 5	20.0 (0.5, 71.6)	68.9	(18.3, 88.3)
		Failure	16/ 144	11.1	4/ 5	80.0		
	Levofloxacin, 250 mg BID	Cure	128/ 144	88.9 (82.6, 93.5)	2/ 3	66.7 (9.4, 99.2)	22.2	(-10.0, 76.5)
		Failure	16/ 144	11.1	1/ 3	33.3		
	Levofloxacin, 500 mg q24h	Cure	128/ 144	88.9 (82.6, 93.5)	32/ 36	88.9 (73.9, 96.9)	0.0	(-10.0, 16.5)
		Failure	16/ 144	11.1	4/ 36	11.1		
	Levofloxacin, 500 mg BID	Cure	128/ 144	88.9 (82.6, 93.5)	80/ 91	87.9 (79.4, 93.8)	1.0	(-7.7, 10.9)
		Failure	16/ 144	11.1	11/ 91	12.1		

a. 95% CI within strata are calculated using the method of Clopper and Pearson.
b. 95% CI for differences within Levo category are calculated based on the Wilson score method corrected for continuity.
Visit: TOC = test-of-cure assessment
SOURCE CODE: ceclin2_levo_cf_1.sas, CONFIDENTIAL: 30SEP05 18:33
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Consequently, the CHMP concluded that the dose of levofloxacin selected by the MAH is supported by the currently approved product information. Moreover, the analyses provided do not suggest that this issue could be seriously hampering the interpretability of the results.

The primary efficacy variable was the clinical response at the test-of-cure (TOC) assessment for the co-primary analysis populations, the clinical-modified intention to treat population (c-mITT) and the clinically evaluable population (CE). The TOC assessment took place 7 to 23 days after end of therapy. Clinical response was categorised as cure, failure and indeterminate. There were two other assessment visits: an early follow up assessment (3 ± 1 days post therapy) and a post therapy serology assessment (6 ± 2 weeks after baseline). The blood sample was tested for IgG and IgM titers for *Chlamydia*, *Mycoplasma* and *Legionella*.

The primary objective was to show the non-inferiority of tigecycline to levofloxacin, using a delta of 15%. According to current guidelines a delta of 10% would have been preferable.

In study 308, 425 subjects were randomized, 212 to tigecycline and 213 to levofloxacin. Of these, 208 subjects received tigecycline and 210 subjects received levofloxacin. 74.62% of the Clinically mITT were Clinically Evaluable and 57.14% of the Clinically Evaluable patients were Microbiologically Evaluable.

A total of 434 subjects were randomized in study 313, 220 to tigecycline and 214 to levofloxacin. Of these, 216 subjects received tigecycline and 212 subjects received levofloxacin. 69.48% of the Clinically mITT were Clinically Evaluable and 68.08 % of the Clinically Evaluable patients were Microbiologically Evaluable.

Regarding switch to oral therapy in study 308, the percentage of patients who switched to oral levofloxacin and the median number of days to the switch were similar in both treatment groups, as follows: In the CE population, 89.9% (124/138) tigecycline-treated patients and 87.8% (137/156) levofloxacin-treated patients switched to oral levofloxacin. The median number of days to the switch was 3.9 for the tigecycline group and 3.3 for the levofloxacin group.

An assessment at the time of switch from parenteral to oral therapy should have been scheduled and the clinical condition of patients at the time of switch should have been recorded in detail and submitted.

Patient population:

Inclusion and exclusion criteria are in general appropriate for the definition of pneumonia as such, but it should be noted that patients with potential Nursing Home Acquired Pneumonia as well as those with suspicion of pneumonia due to *Legionella* were excluded. The same applies to immunodepressed patients and this represents a limitation in order to extrapolate the results.

In both studies demographic and baseline disease characteristics were similar between the treatment groups, in both the c-mITT and CE populations. Pooled data from studies 308 and 313 (CE population) were as follows: mean age was 54.17 years for tigecycline group and 52.9 years for levofloxacin group. Fifty-eight per cent (58%) of the patients were male in the tigecycline group and 62.7% in the levofloxacin group. The most frequent ethnic origin was white (77.3% in the tigecycline group and 72.9% in the levofloxacin group, followed by Hispanic (12.1% in the tigecycline group and 14% in the levofloxacin group). Because of differences in geographic regions where the studies were conducted, differences in ethnic origin were observed between the 2 studies (63% of subjects were white in study 308 vs. 88% in study 313).Mean creatinine clearance was 87.18 ml/min in the tigecycline group and 86.11 ml/min in the levofloxacin group.

Regarding the presence of underlying medical conditions, the proportions of subjects with any of the underlying medical conditions were similar between the treatment groups. Pooled data from studies 308 and 313 (CE population) for the most frequent underlying medical conditions were as follows: 11.3% of patients in tigecycline group presented with COPD vs. 10.3% in levofloxacin group. 12.4% of patients in tigecycline group had Diabetes Mellitus vs. 12.7% in levofloxacin group. Alcohol abuse was present in 9.9% of patients in tigecycline group vs. 9.2% in levofloxacin. 55.7% of patients in the tigecycline group had prior smoking history vs. 53.1% in the levofloxacin group. 36.9% of patients in the tigecycline group had current smoking history vs. 33.2% in the levofloxacin group. Only 5% (14/282) tigecycline-treated patients and 3.4% (10/292) levofloxacin-treated patients had liver disease. Again, the limitations of the study population in terms of relevant co-morbidities should be reflected in the SPC.

Regarding pneumonia characteristics, they were comparable between treatment groups. For the pooled data from both studies (CE population), 24.8% of the tigecycline-treated CE patients and 20.5% of the levofloxacin-treated had multilobar disease. The percentage of patients with bilateral disease was 16.4% in the tigecycline group and 14.7% in the levofloxacin group.

Baseline pathogens as well as their susceptibilities are discussed in the pharmacodynamic section of this assessment report.

The need for hospital admission and intravenous therapy does not seem to be justified. The percentages of patients classified as I or II Fine pneumonia severity index, and thus considered at low risk for death and potential candidates to be safely treated as outpatients, were 55 % in study 308 and around 45% in study 313.

Patients at risk class III are also considered to be at low risk for death and can be treated as outpatients after a brief observation period. The percentages of patients at risk class III were as follows: in study 308, 27.5 % of tigecycline-treated patients and 23.1% levofloxacin-treated patients and in study 313 27.8% of tigecycline-treated patients and 30.9% levofloxacin-treated patients.

According to estimated CURB-65 score, 73.2% tigecycline-treated patients and 64.1% levofloxacin treated patients in study 308 and 67.4% tigecycline-treated patients and 68.4% levofloxacin treated patients in study 313 could have been treated as outpatients.

In addition, intravenous therapy with antibiotics that have high level of oral bioavailability such as fluoroquinolones may not be better than oral therapy with such antibiotics in patients with uncomplicated infections who tolerate the oral route.

The above mentioned findings question the relevance of the enrolled patient population as representative of the real patient population aimed to be targeted with an intravenous antibiotic.

Outcomes:

Tigecycline was shown to be non-inferior to levofloxacin in terms of clinical response using a delta of 15%. In the c-mITT population cure rates were 78% (149/191) for tigecycline vs. 77.8% (158/203) for levofloxacin in study 308 (95% CI -8.5, 8.9) and 83.7% (170/203) for tigecycline vs. 81.5% (163/200) for levofloxacin in study 313(95% CI -5.6, 10.1). For the CE population, cure rates were 90.6% (125/138) for tigecycline vs. 87.2% (136/156) for levofloxacin in study 308 (95% CI -4.4, 11.2) and 88.9% (128/144) for tigecycline vs. 85.3% (116/136) for levofloxacin in study 313 (95% CI -5.0, 12.2). The lower bound of the 95%CI around the difference in cure rates was within the pre-defined 15% in both populations in both studies and in no case lied beyond 10%.

However, the percentage of patients classified as Fine PSI I and II scores, and thus considered potential candidates to be treated as outpatients, was around 50%. Patients with risk class III (25%) can also be treated as outpatients after an observation period. In the RSI adopted in November 2007, the MAH was requested to comment on the relevance of the enrolled patient population, especially those with PSI of I and II, as representative of the real patient population aimed to be hospitalized and treated with an intravenous antibiotic. In its answer, the MAH justified that study design was according to the existing guidelines, that PSI scores and co-morbidities distribution was comparable with published data from global trials and that clinical response by PSI score did not raise cause for concern (see Outcomes below).

Clinical guidelines point out that there are considerations other than pneumonia severity scores that should be taken into account. Objective criteria or scores are usually supplemented with physician's evaluation of subjective criteria, including underlying co-morbidities and the ability to safely and reliably take oral medication.

The CHMP acknowledged that whenever patients need to be hospitalised or given iv therapy, this often requires clinical judgements that in some cases supersede objective scores. Nevertheless, the pneumonia status that led to the hospitalisation of patients with the lower scores was unknown. This aspect is of particular relevance considering the safety concern possibly associated to lack of efficacy in severely affected patients. As a consequence, the MAH was requested to discuss what were the reasons in terms of co-morbidities, pneumonia characteristics, etc of patients with Fine PSI scores of I, II and III that justify the hospitalisation and/or administration of iv therapy in studies 308 and 313 (see paragraph V, follow on RSI, Major objections, Q2, point a).

In addition, only 1.5% (6/393) of patients in the tigecycline arm vs. 1% (4/403) of patients on levofloxacin were admitted to ICU in studies 308 & 313. It is assumed then that very few patients were in need of mechanical ventilation, which is a matter for concern given the results of the study in patients with VAP as well as the safety concerns above mentioned.

Regarding microbiologic results, the by-patient microbiologic response at TOC for the m-mITT population was as follows: In study 308, eradication rate was 84% (84/100) for tigecycline vs. 82.6% (95/115) for levofloxacin. In study 313 these results were 87.2% (109/125) for tigecycline vs. 85.5% (100/117) for levofloxacin. In the ME population, the by-patient microbiologic response at TOC was as follows: In study 308, eradication rate was 93.3%% (70/75) for tigecycline vs. 90.3% (84/93) for levofloxacin. In study 313 these results were 90.1% (82/91) for tigecycline vs. 89.5% (77/86) for levofloxacin. Most eradications and persistences were presumed.

- Microbiologic response at the pathogen level is discussed in the pharmacodynamic section of this assessment report.

Multiple subgroup analyses were conducted to assess the consistency of the results according to age, sex, race, diabetic vs. non-diabetic, creatinine clearance, number of lobes involved, Fine category,

geographic region, occurrence of bacteraemia, switch to oral therapy, levofloxacin dose etc. Although these analyses must be interpreted with caution since the numbers of subjects in some of the subgroups were small, the results were consistent with the findings from the co- primary populations.

Conclusion on supportive studies

The initial clinical development plans for the tigecycline pneumonia program and subsequently planned submission were to include the data obtained from the 2 community-acquired pneumonia (CAP) studies, as well as the results from 1 hospital-acquired pneumonia (HAP) study in support of obtaining pneumonia indications for both CAP and HAP. However, the results of the HAP study showed that tigecycline met non-inferiority efficacy criteria in comparison to imipenem/cilastatin for only 1 of the 2 co-primary efficacy endpoints, in the clinical modified intent-to-treat (c-mITT) population, but not in the clinically evaluable (CE) co-primary population. There was an apparent interaction between tigecycline and ventilator-associated pneumonia (VAP subpopulation).

The MAH position, i.e. that these negative results in the HAP study do not impact the results observed in patients with CAP is not completely endorsed and deserves further comments. It is agreed with the MAH that the clinical picture and causal microorganisms of patients with ventilator-associated pneumonia (VAP) differs from that seen in community-acquired pneumonia. Patients with nursing-home acquired pneumonia (NHAP) were excluded from the pivotal trials similarly with what has been observed in other trials for CAP. In the particular case of Tygacil, given the concerns on lack of efficacy, this information should then be clearly stated in section 4.4 of the SPC. Furthermore, the mean age of patients in the two pivotal trials (around 55 years) for tigecycline, does not provide further reassurance on this issue.

A statistically significant interaction was noted for the a priori stratification of non-VAP and VAP subjects. The MAH has performed several analyses in order to explain the interaction observed, including factors as adjunctive therapy, demographic and baseline factors (including co-morbidities), geographic region, incidence of baseline pathogens, and prior antibiotic failure. Despite the multiple analyses performed attempting to better understand the differences present in the VAP population (both between VAP and non-VAP, and between tigecycline and imipenem/cilastatin regimens), no clear explanation for the differences based on the population could be definitively identified. Even markers for the severity of disease (eg, APACHE II score and being in the ICU) demonstrated that they were predictors of the difficulty of treating/curing the disease, but that their effect was equal in both arms and not a definitive explanation of why the VAP population behaved differently for these two regimens. A potential explanation given is that although similar exposure was seen compared to prior experience (see section "Pharmacokinetics" of the report), when viewed using AUC to MIC as the past best predictor of outcome, the combination with somewhat higher MICs in this population suggests that under-dosing of tigecycline for the VAP subjects may be the underlying issue.

Only the results in the non-VAP population have been highlighted above (Supportive studies, study 311 HAP) as the MAH claims that tigecycline met non-inferiority in both co-primary populations for the non-VAP subset of HAP. However, the clinical cure rates and the lower limit of the 95% CI of the differences between treatments are not completely reassuring in this regard. The unexpected low rate of eradication for *S. aureus* is also worrying, although the low number of isolates should be taken into account.

The so-called "resistant pathogen" studies expand the microbiological database of tigecycline (e.g. efficacy data against MRSA in the original dossier was quite limited and is now complemented with data from study 307), but the small number of patients as well as the uncontrolled design of two of them preclude drawing appropriate conclusions. In addition, the results above shown could not be considered as robust so as to support some of the changes requested by the MAH for section 5.1.

At least for study 307, controlled with linezolid (for VRE) and vancomycin (for MRSA), the population recruited does not seem to differ very much from the population enrolled in the pivotal trials submitted in the original dossier. High cure and eradication rates are generally seen in studies 307 and 309 which is somehow paradoxical, when considering that these are supposed to be patients with "resistant pathogens". Furthermore, higher tigecycline AUC and Cmax have been described in

these patients. It is worrying to note that the lack of efficacy shown by tigecycline in patients with ventilator-associated pneumonia could be attributed to the lack of attainment of an adequate PK-PD target.

III.2.3 Clinical safety

The MAH has provided the safety results from CAP & HAP studies separately and an integrated safety analysis including data from phase 3 clinical trials performed with tigecycline. In all these clinical trials patients were treated with the proposed dosage (100 mg IV followed by 50 mg every 12 hours). Safety results from CAP and HAP clinical trials have been assessed separately. The information coming from the integrated analysis is also assessed separately to compare the results form CAP & HAP population with the general safety profile previously observed for tigecycline.

III.2.3.1 Patient exposure

The safety population consists of all subjects who were randomly assigned to a treatment group (in studies with comparators) and received at least 1 dose of test article. The safety population includes subjects from 9 completed phase 3 studies, which are the following:

- Studies 300 and 305, tigecycline compared with vancomycin and aztreonam in subjects hospitalized with cSSSI.
- Studies 301 and 306, tigecycline compared with imipenem/cilastatin in subjects hospitalized with cIAI.
- Study 307, tigecycline compared with linezolid in subjects with vancomycin-resistant Enterococcus and with vancomycin in subjects with methicillin-resistant Staphylococcus aureus. Interim results from study 307 were presented in the original dossier.
- Study 309, tigecycline in a noncomparative study in subjects with selected serious infections with resistant gram-negative organisms. Interim results from study 309 were presented in the original dossier.
- Studies 308 and 313, tigecycline compared with levofloxacin in subjects hospitalized with CAP; study 308 permitted a switch to oral levofloxacin for some subjects.
- Study 311, a tigecycline regimen compared with an imipenem/cilastatin regimen in subjects hospitalized with HAP.

A total of 2514 subjects in the pooled phase 3 studies received at least 1 dose of tigecycline.

Of the 846 subjects with CAP in the modified intent-to-treat (mITT) population, 424 subjects received tigecycline and 422 subjects received levofloxacin.

Of the 934 subjects with HAP in the mITT population, 467 subjects received tigecycline and 467 subjects received imipenem/cilastatin, including 191 subjects who received placebo for vancomycin and tigecycline, 220 subjects who received vancomycin and imipenem/cilastatin, 185 subjects who received ceftazidime and tigecycline, 177 subjects who received imipenem/cilastatin and placebo for ceftazidime, 67 subjects who received aminoglycosides and tigecycline, and 67 subjects who received aminoglycosides and imipenem/cilastatin.

With regard to the demographic characteristics, basically, the population study enrolled in the studies was under 65 years of age with different degrees of underlying conditions. According to the Fine score, different degrees of pneumonia were reasonably represented, although there were very few patients with Fine score V. According to the CURB score, most of the patient were under score 2 (71%). According to the existing guidelines, if the patient is aged fewer than 50 and there is no co-existing chronic illness, the patient can be managed in the community. This should be properly reflected in the revised proposal of SPC.

III.2.3.2 Adverse events

Nausea, vomiting, abdominal pain, anorexia, bilirubinemia, hypoproteinemia, and increased PT and aPTT have been observed previously with tigecycline and are reflected accordingly in the SPC. Treatment-emergent adverse events (TEAE) were defined as an 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 MAH has presented the incidence of TEAE that occurred in at least 3% of patients treated in CAP, HAP and phases 3 clinical trials, (pooled data).

CAP:
TEAEs were reported by 305 (71.9%) subjects in the tigecycline group and 268 (63.5%) subjects in the levofloxacin group. The frequency of TEAEs was significantly higher in the tigecycline group than in the levofloxacin group ($p = 0.010$).
In the tigecycline group, the most common TEAEs were nausea (103; 24.3%), vomiting (68; 16.0%), headache (40; 9.4%), and diarrhea (39; 9.2%). A significantly higher number of the tigecycline-treated subjects than levofloxacin-treated subjects reported TEAEs of abdominal pain (24; 5.7%; $p = 0.012$), nausea (103; 24.3%; $p < 0.001$), vomiting (68; 16.0%; $p < 0.001$), and leukocytosis (19; 4.5%; $p = 0.027$).
In the levofloxacin group, the most common TEAEs were headache (36; 8.5%), nausea (35; 8.3%), diarrhea (31; 7.3%), and increased ALT (31; 7.3%). A significantly higher number of levofloxacin-treated subjects than tigecycline-treated subjects reported TEAEs of increased AST (29; 6.9%; $p = 0.003$), and increased ALT (31; 7.3%; $p = 0.003$).
The relatedness and severity for subjects with any TEAE were similar between the 2 treatment groups. In the tigecycline group, TEAEs were considered related to test article in 34.9% of subjects and not related in 30.2% of subjects; most were mild or moderate, with 1.4% considered severe and related. In the levofloxacin group, TEAEs were considered related to test article in 32.5% of subjects and not related in 28.4% of subjects; most were mild or moderate, with 1.7% considered severe and related.

HAP:
Overall, TEAEs were reported by 368 (78.8%) subjects in the tigecycline group and 367 (78.6%) subjects in the imipenem/cilastatin group. The frequency of TEAEs was not significantly different between the 2 treatment groups ($p = 1.000$).
In the tigecycline group, the most common TEAEs were nausea (72; 15.4%), vomiting (59; 12.6%), and diarrhea (49; 10.5%). A significantly higher number of the tigecycline-treated subjects than imipenem/cilastatin-treated subjects reported TEAEs of nausea (72; 15.4%; $p < 0.001$), vomiting (59; 12.6%; $p = 0.008$), shock (13; 2.8%; $p = 0.020$), prolonged aPTT (17; 3.6%; $p = 0.033$), somnolence (10; 2.1%; $p = 0.037$), and skin ulcer (25; 5.4%; $p = 0.015$).
In the imipenem/cilastatin group, the most common TEAEs were diarrhea (70; 15.0%), anemia (45; 9.6%), and leukocytosis (42; 9.0%). A significantly higher number of imipenem/cilastatintreated subjects than tigecycline-treated subjects reported TEAEs of headache (23; 4.9%; $p = 0.018$) and diarrhea (70; 15.0%: $p = 0.049$).
The relatedness and severity of the TEAEs were similar between the 2 treatment groups ($p = 0.360$). In the tigecycline group, TEAEs considered related to test article were reported in 25.9% of subjects and those considered not related in 48.4%; most were mild or moderate, with 1.7% considered severe and related. In the imipenem/cilastatin group, TEAEs were considered related to test article in 25.7% of subjects and not related in 51.4%; most were mild or moderate, with 1.5% considered severe and related.

Integrated Phase 3 studies:
Overall, TEAEs were reported by 1840 (73.2%) subjects in the tigecycline group and 1591 (69.0%) subjects in the comparator group. The rate of TEAEs was significantly higher in the tigecycline group than the comparator group ($p < 0.001$). Analysis of the TEAEs by body system indicated that the most common TEAEs occurred in the digestive system in both the tigecycline group (1089; 43.3%) and the comparator group (725; 31.4%) ($p < 0.001$).
The most frequently reported TEAEs in the tigecycline group were nausea (646; 25.7%), vomiting (443; 17.6%), and diarrhea (286; 11.4%). A significantly higher number of tigecycline-treated subjects than comparator-treated subjects reported the following TEAEs:

- Nausea: tigecycline 646 (25.7%), comparator 282 (12.2%), $p < 0.001$.

- Vomiting: tigecycline 443 (17.6%), comparator 201 (8.7%), p < 0.001.
- Abdominal pain: tigecycline 136 (5.4%), comparator 88 (3.8%), p = 0.009.
- Infection: tigecycline 146 (5.8%), comparator 93 (4.0%), p = 0.005.
- Leukocytosis: tigecycline 117 (4.7%), comparator 77 (3.3%), p = 0.023.
- Hypoproteinemia: tigecycline 124 (4.9%), comparator 75 (3.3%), p = 0.004

The most frequently reported TEAEs in the comparator group were nausea (282; 12.2%), diarrhea (241; 10.4%), and vomiting (201; 8.7%). A significantly higher number of TEAEs for comparator-treated subjects occurred as follows:

- Fever: tigecycline 139 (5.5%), comparator 174 (7.5%), p = 0.005.
- Phlebitis: tigecycline 63 (2.5%), comparator 96 (4.2%), p = 0.002.
- Hypokalemia: tigecycline 70 (2.8%), comparator 93 (4.0%), p = 0.020.
- SGOT/AST increased: tigecycline 65 (2.6%), comparator 108 (4.7%), p < 0.001.
- SGPT/ALT increased: tigecycline 66 (2.6%), comparator 112 (4.9%), p < 0.001.
- Insomnia: tigecycline 52 (2.1%), comparator 71 (3.1%), p = 0.028.

III.2.3.3 Serious adverse events and deaths

CAP:

A total of 88 subjects had 1 or more SAEs in the combined studies for CAP: 42 (9.9%) in the tigecycline group and 46 (10.9%) in the levofloxacin group. The incidence of SAEs was similar between the 2 treatment groups (p = 0.654The most frequently reported SAEs in tigecycline-treated subjects were pneumonia and respiratory failure (5 each; 1.2%). The most frequently reported SAEs in the levofloxacin- treated subjects were pneumonia (10; 2.4%) and abscess, infection, and pyothorax (3 each; 7%). These SAEs generally represented progression of the underlying disease and treatment failures.

Twenty-three (23) subjects (2.7%) died during the combined CAP studies (308 and 313): 12 (2.8%) in the tigecycline group and 11 (2.6%) in the levofloxacin group (p = 1.000). None of these deaths were considered by the investigator to be related to treatment.

HAP:

A total of 242 (25.9%) subjects had 1 or more SAEs in the HAP study: 122 (26.1%) in the tigecycline group and 120 (25.7%) in the imipenem/cilastatin group. The incidence of SAEs was similar between the 2 treatment groups (p = 0.940), and no category showed a significant difference between the 2 groups. The most frequently reported SAEs in tigecycline-treated subjects were shock (13; 2.8%) and pneumonia and respiratory failure (11 each; 2.4%). The most frequently reported SAEs in the imipenem/cilastatin-treated subjects were respiratory failure (17; 3.6%) and pneumonia (13; 2.8%). These generally reflect progression of underlying disease states or failure.

A total of 123 deaths occurred in the mITT population. Of these, 66 of 467 (14.1%) were in the tigecycline group and 57 of 467 (12.2%) were in the imipenem/cilastatin group.
Two (2) of these deaths were considered by the investigator to be possibly related to treatment (1 with tigecycline in a subject with “recurrent pneumonia” and 1 with imipenem/cilastatin in a subject with “thrombotic thrombocytopenic purpura”), and 1 death was considered probably related to treatment (with imipenem/cilastatin in a subject with “cardiopulmonary failure”).
Generally, deaths were related to progression of underlying disease or complications of the subject’s underlying state, including those secondary to failed treatment.

Integrated Phase 3 studies:

A total of 408 subjects in the tigecycline group (16.2%) and 334 subjects in the comparator group (14.5%) had SAEs. The incidence of SAEs was similar between the 2 treatment groups (p = 0.094). The most frequently reported SAEs in tigecycline-treated subjects were abscess (36; 1.4%), infection (31; 1.2%), abnormal healing (29; 1.2%), and respiratory failure (29; 1.2%). The most frequently reported SAEs in the comparator-treated subjects were abscess (27; 1.2%), pneumonia (27; 1.2%), and respiratory failure (24; 1.0%).
Significantly more subjects in the tigecycline group than in the comparator group reported heart arrest (tigecycline, 19; 0.8%; comparator, 6; 0.3%; p = 0.025), shock (tigecycline, 22; 0.9%; comparator, 7; 0.3%; p = 0.014), and abnormal healing (tigecycline, 29; 1.2%; comparator, 13; 0.6%; p = 0.030).

During the integrated phase 3 studies, 137 (5.4%) tigecycline-treated and 87 (3.8%) comparator-treated subjects had AEs with outcome of death reported. No significant differences were observed in the mortality rates between the tigecycline and the comparator groups by indication.

Significantly more subjects treated with tigecycline (17.9%) than those treated with comparators (15.3%) reported individual **vital signs** results of PCI ($p < 0.018$). Vital signs values of PCI were reported more frequently with tigecycline than comparators for diastolic blood pressure ($p = 0.024$) and more frequently with comparator than tigecycline for low respiratory rate ($p = 0.044$). Significant ($p \leq 0.05$) differences occurred at the final on-therapy assessment in most within-group comparisons and between-group comparisons for QTc, QTc(L), QTc(F), and QT intervals. Of the tigecycline-treated subjects, 1 subject died because of a TEAE of arrhythmia and 1 subject died because of a ventricular arrhythmia. One (1) subject treated with comparator died because of sudden death. TEAEs of arrhythmia were reported in 6 (0.2%) of subjects treated with tigecycline and 7 (0.3%) of subjects treated with comparators. TEAEs of syncope were reported in 7 (0.3%) subjects treated with tigecycline and 3 (0.1%) subjects treated with comparator; no subjects were discontinued from treatment because of a TEAE of syncope. TEAEs of dizziness were reported in 63 (2.5%) subjects receiving tigecycline and 58 (2.5%) subjects receiving comparators.

III.2.3.4 Laboratory findings

CAP:
A significantly higher number of subjects in the tigecycline group (23; 5.7%) than in the levofloxacin group (11; 2.7%) had Potential Clinical Importance (PCI) results of elevated potassium levels ($p = 0.036$).

Changes in mean laboratory test results were evaluated for significant differences from screening/day 1 to the last day of therapy; laboratory tests were required at the TOC assessment if the prior value was abnormal and considered clinically important. Between-group differences for changes in mean results from screening were also evaluated. Significant ($p \leq 0.05$) within-group variability was observed for most of the chemistry and hematology laboratory test results for both treatment groups.

Most of these changes were small, with the means remaining within normal biologic ranges.

- For **coagulopathy (**aPPT, PT, INR, Coagulation disorder)r, more subjects in the tigecycline group had TEAEs of increases in various coagulation values, although there were no significant differences between treatment groups.
- There was no increase in anemia or bleeding diatheses in the tigecycline group.
- The changes in mean **BUN** and mean urea values appear to be consistent with previously reported minocycline anti-anabolic effects.
- For **total protein**, there was no significant difference in the TEAE of hypoproteinemia between the 2 groups.
- For **liver enzyme measurements** at the final on-therapy assessment, both groups had decreases in mean AST levels. The tigecycline group had a decrease in mean ALT levels, and the levofloxacin group had an increase in the mean level.
- The difference in changes in the **alkaline phosphatase level** was significant ($p = 0.001$).

HAP:
Changes in mean laboratory test results were evaluated for statistically significant differences from screening/day 1 to the last day of therapy; laboratory tests were required at the TOC assessment if the prior value was abnormal and considered clinically important. Between-group differences for changes in mean results from screening were also evaluated. Significant ($p \leq 0.05$) within-group variability was observed for most of the chemistry and haematology laboratory test results. Most of these changes were small, with the means remaining within normal biologic ranges.

Integrated Phase 3 studies:
When the 2 treatment groups were compared (tigecycline and comparator), significant differences ($p \leq 0.05$) occurred at the final on-therapy evaluation with sodium, potassium, carbon dioxide,

bicarbonate, BUN, urea, creatinine, calcium, phosphorus, total bilirubin, direct bilirubin, total protein, albumin, AST, ALT, alkaline phosphatase, INR, PT, prothrombin activity, aPTT, hemoglobin, hematocrit, RBC count, WBC count, granulocytes, neutrophils, lymphocytes, eosinophils, monocytes, and platelets. Although these changes reached statistical significance, in most cases the changes were small. Notable changes with p-values below 0.05 are further summarized below.

- For **coagulopathy**, values of aPTT that met PCI criteria for being abnormally elevated were identified for 23 (2.9%) tigecycline-treated subjects and 13 (1.6%) comparator-treated subjects ($p = 0.129$). Overall, similar percentages of subjects in the tigecycline and comparator groups (4.3% and 3.6%, respectively) had coagulation test results that met PCI criteria. Alterations of coagulation tests (PT/aPTT) have previously been described with tetracycline. Anemia was reported for 114 (4.5%) subjects in the tigecycline group compared with 129 (5.6%) subjects in the comparator group. The laboratory mean change from baseline in hemoglobin at the final on-therapy assessment for tigecycline subjects increased by 1.89 g/L compared with a mean decrease in the comparator group of -4.15 g/L ($p < 0.001$).
- For **BUN**, significantly more subjects in the tigecycline group than in the comparator group had TEAEs of increased BUN ($p < 0.001$). Despite this result, mean creatinine levels decreased in both the tigecycline group and comparator group, and the difference between the groups was significant ($p = 0.003$). Increase in BUN for the tigecycline group has been observed previously with tigecycline.
- For **total protein**, the difference in the TEAEs of hypoproteinemia between the tigecycline group (124; 4.9%) and the comparator group (75; 3.3%) was significant ($p = 0.004$). The changes for albumin (decrease for the tigecycline group compared to the comparator group) have been observed previously with tigecycline and appear consistent with the known anti-anabolic effects of tetracyclines.
- For **liver enzyme** measurements at the final on-therapy assessment, the tigecycline group had a decrease in mean AST level and the comparator group an increase, with a between-treatment $p < 0.001$. The tigecycline group had a decrease in mean ALT levels, and the comparator group had an increase, for a between-treatment $p < 0.001$.
- At the final on-therapy assessment, the tigecycline group had an increase in mean **alkaline phosphatase** levels and the comparator group mean also increased, for a between-treatment $p < 0.001$. For **bilirubin**, the mean level decreased in the tigecycline group and the comparator group, for a between-group $p < 0.001$.

III.2.3.5 Safety in special populations

No unexpected overall differences in safety were observed between these subjects and younger subjects.
No overall differences in safety were observed between men and women.
Pregnant and lactating women were to be excluded from the studies with tigecycline.

III.2.3.6 Discontinuation due to AEs

CAP:
Eleven (11; 2.6%) subjects in the tigecycline group and 12 (2.8%) subjects in the levofloxacin group withdrew from the study because of AEs ($p = 0.836$). Nausea led to the withdrawal from the study of 1 (0.2%) subject in the tigecycline group and 3 (0.7%) in the levofloxacin group ($p = 0.373$). Pneumonia was the only AE resulting in more than 1 withdrawal from the study in the tigecycline group (2 subjects; 0.5%). There were no significant ($p \leq 0.05$) differences between the tigecycline and levofloxacin groups in any AE category.

HAP:
Nine (9; 1.9%) subjects in the tigecycline group and 8 (1.7%) subjects in the imipenem/cilastatin group withdrew from the study because of AEs ($p = 1.000$). Septic shock was the only AE to result in more than 1 withdrawal in the tigecycline group (2 subjects; 0.4%). In the imipenem/cilastatin group, infection was the only AE to result in more than 1 withdrawal (2 subjects, 0.4%). There were no

significant differences ($p \leq 0.05$) between the tigecycline and imipenem/cilastatin groups in any AE category.

Integrated Phase 3 studies:
Sixty (60; 2.4%) subjects in the tigecycline group and 58 (2.5%) subjects in the comparator group withdrew from the study because of AEs ($p = 0.780$). Nausea caused the most withdrawals in the tigecycline group (8; 0.3%); in the comparator group, it caused 6 (0.3%) withdrawals ($p = 0.793$). The tigecycline group had significantly more subjects than the comparator group who withdrew because of septic shock (tigecycline, 7; 0.3%; comparator, 0; $p = 0.016$).

III.2.3.7 Clinical safety in supportive studies

Study 307 (Resistant Pathogens)
Among MRSA subjects, the overall incidence of TEAEs with tigecycline was comparable with that of vancomycin (69.2% vs 66.7%). Nausea and vomiting rates were approximately twice as high in tigecycline-treated subjects (35.9% and 23.9%, respectively) than in vancomycin-treated subjects (15.4% and 12.8%, respectively). Among all subjects treated with tigecycline, nausea and vomiting resulted in study drug discontinuation in 3 subjects, and there was 1 serious event of nausea and vomiting that the investigator considered unrelated to tigecycline.

A total of 13 subjects died, 11 of whom had received tigecycline (6 subjects with MRSA infection, 5 subjects with VRE infection). With 1 exception (death from septic shock in a VRE subject), all deaths in tigecycline-treated subjects were considered by the investigator to be probably not or definitely not related to study drug. A total of 39 subjects had 1 or more SAEs during the study: 19.7% of MRSA subjects treated with tigecycline, 20.5% of MRSA subjects treated with vancomycin, 63.6% of VRE subjects treated with tigecycline, and 25.0% of VRE subjects treated with linezolid.

Almost three fourths of subjects in this study had an on-therapy laboratory test result of potential clinical importance. However, many of the subjects with the most abnormal values were noted to also have abnormal values at baseline. Except for AST, with a significantly higher frequency of vancomycin-treated subjects with values that met PCI criteria, there were no significant differences between the treatment arms for any of the laboratory tests. While there were statistically significant differences between treatment groups with respect to changes from baseline for a number of the laboratory tests, many of the changes were small and probably not clinically meaningful. Approximately one fifth of subjects in the study had an on-therapy blood pressure or heart rate assessment that met PCI criteria. However, many of the subjects with the most abnormal values had abnormalities at baseline. No laboratory or vital sign parameter changes were identified as new safety signals for tigecycline.

Study 309 (Resistant Pathogens)
One or more treatment-emergent adverse events (TEAEs) were reported by 80.4% of subjects. The most commonly reported TEAEs were nausea (29.5%), diarrhea (16.1%), and vomiting (16.1%), similar to what has been reported in other tigecycline studies. Most events of nausea or vomiting were considered by the investigators to be related to study drug. All events of nausea and vomiting were reported as mild to moderate in severity (grades 1 or 2) with the exception of 1 report of severe (grade 3) nausea that was considered by the investigator to be related to tigecycline. Among subjects with nausea or vomiting, median time to nausea onset was 4 days and nausea occurred over a median total duration of 2.5 days; median time to vomiting onset was 3.5 days and vomiting occurred over a median total duration of 3.5 days. In general, the median time to onset of these events is later than what has been reported in other tigecycline studies. Concomitant medications given specifically to treat or prevent nausea or vomiting were received by 22.3% of mITT subjects.

Twenty (20) subjects died during the study. None of these deaths were considered by the investigators to be related to tigecycline treatment. In all cases, cause of death was consistent with the subject's underlying disease or a concomitant medical condition.

Serious adverse events (SAEs) were reported by 30.4% of subjects during the study. SAEs in 2 subjects were considered by the investigator to be related to tigecycline and both resulted in discontinuation from treatment: 1 subject was reported to have a possible allergic reaction on day 7 during infusion of tigecycline, and another subject had thrombocytopenia beginning on day 1 of therapy. Overall, the types of SAEs reported among this study population were consistent with the subjects' severity of illness and the nature of the infections.

Fifteen (15, 13.4%) of the 112 subjects in the mITT population discontinued tigecycline because of an adverse event during the study. Three (3) of these subjects developed new infections. One (1) subject discontinued because of nausea and vomiting, in addition to endocarditis. One (1) subject with hypocalcemia and a history of intracranial bleeding experienced severe convulsions, and another subject had thrombocytopenia.

Three fourths of subjects had an on-therapy laboratory test result of potential clinical importance (PCI). Many of the subjects with the most abnormal values were noted to have had abnormal values at baseline. Although there were statistically significant changes from baseline at various time points for many of the laboratory tests, many of the changes were in a direction that was not clinically important (eg, decreased creatinine, bilirubin, aspartate aminotransferase, lactate dehydrogenase, eosinophils) or that likely reflect improvement in the underlying infection or the overall condition of the subject (eg, decreased white blood cell count, neutrophils, and band neutrophils, increased hemoglobin, hematocrit, and red blood cell count) or that have been observed in other tigecycline studies (eg, increased blood urea nitrogen and urea). One- third of subjects had an on-therapy PCI increase or decrease in blood pressure, respiratory rate, or pulse rate. However, the subjects with the most abnormal values had pre-existing or concurrent conditions that were likely responsible for these abnormal vital signs. No laboratory or vital sign parameter changes were identified as new safety signals for tigecycline.

Study 310 (Resistant Pathogens)
Exposure to tigecycline was longer in this study than in other tigecycline studies. The mean number of days on therapy in this study was almost 24 days. The longer exposure was related to the enrollment of a number of subjects with rapidly growing mycobacterial infections; patients with such infections often remain on antibiotic therapy for prolonged periods.

One (1) or more treatment-emergent AEs (TEAEs) were reported by 85.2% of subjects in the mITT opulation. The most commonly reported TEAEs were sepsis (22.2%), nausea (22.2%), diarrhea (22.2%), vomiting (18.5%), and anemia (18.5%). Most events of nausea and vomiting were considered by the investigators to be related to study drug; however, all events were reported as mild to moderate (grades 1 or 2), and none were considered serious or resulted in study drug discontinuation.

The frequency of the TEAEs of nausea and vomiting was similar to what is reported in the current labeling for tigecycline and higher for diarrhea, although these percentages are based on a small number of subjects. For some of the other most commonly reported TEAEs in this study, such as anemia, fever, sepsis, hypotension, and peripheral edema, the frequency was higher than what is reported in the current labeling, but this is likely to be a reflection of the different severity of illness of this population as well as the small number of subjects. Seven (7) subjects died during the study, and 1 subject died more than a month after having withdrawn from the study for a serious AE (SAE; nodal arrhythmia). None of these deaths were considered by the investigators to be related to tigecycline treatment. In all cases, cause of death was consistent with the subject's underlying disease or a concomitant medical condition.

SAEs were reported by 48.1% of subjects during the study. SAEs in 2 subjects were considered by the investigator to be possibly related to tigecycline and both resulted in withdrawal from treatment. One (1) subject reported ileus and pancreatitis on day 113 (although, of note, the subject had been receiving voriconazole for 76 days prior to entering the study and had started with citalopram on day 106), and another subject had nodal arrhythmia on day 3 (although the subject was also noted to have a mobile mass attached to the right atrial side of the interatrial septum suggestive of aspergilloma). As noted above, this subject died in the poststudy period. Overall, the types of SAEs reported among this study

population were consistent with the subjects' severity of illness and the nature of the infections. A total of 3 subjects discontinued treatment because of AEs: the 2 subjects described above, and a third subject who had chronic sinusitis, frontal and maxillary tenderness, fever, and a history of asthma and allergies to multiple medications and who reported wheezing, headache, bone pain, and worsening fever after approximately 1 week of tigecycline treatment, with resolution of all events after withdrawal of study drug.

Of the 26 subjects with laboratory data, 24 (92.3%) had an on-therapy potentially clinically important (PCI) laboratory test result. The laboratory tests with the most subjects having values meeting PCI criteria were decreased lymphocytes (8/17, 47.1%); increased blood urea nitrogen (BUN; 7/19, 36.8%) and increased urea (2/7, 28.6%); increased platelet count (6/25, 24.0%); and increased creatinine (6/26, 23.1%). Although statistically significant mean changes from baseline were noted at various time points for many of the laboratory parameters, most of the changes were in a direction that was not clinically important (eg, decreased BUN, creatinine, aspartate aminotransferase, amylase, prothrombin time, and eosinophils) or that likely reflect improvement in the underlying infection or the overall condition of the subject (eg, increased hemoglobin, hematocrit, and red blood cells) or that have been observed in other tigecycline studies (eg, increased platelets). Furthermore, the small sample size, lack of a comparative group, and diverse comorbidities of the subject population make it difficult to draw conclusions from these data.

Two (2) subjects had a single on-therapy PCI vital sign value (decreased diastolic blood pressure and increased heart rate); both had abnormal values at baseline and relevant underlying conditions. A significant ($p = 0.007$) mean increase (10.89 mm Hg) from baseline was found for systolic blood pressure on day 5. Significantly decreased temperatures were noted at the final on-therapy, last-day-of-therapy, and TOC assessments, which likely reflect improvement in the subjects' underlying infections.

III.2.3.8 Conclusion on clinical safety

The MAH has provided the safety results pooled by study population (CAP and HAP in support of the indication for CAP) and an integrated safety analysis including data from phase 3 clinical trials performed with tigecycline.

The percentage of patients that report at least 1 AEs was similar to that observed in previous analysis:
CAP: 73.1 % (310 patients) on tigecycline and 69.2% (292 patients) on comparator (p=0.225)
HAP: 81.4% (380 patients) on tigecycline and 80.7% (377 patients) on comparator (p=0.867)
Integrated Phase 3: 76.9% (1934 patients) on tigecycline and 72.6% (1675 patients) on comparator

– The adverse events most commonly reported in CAP patients were nausea (24.5%), vomiting (16%) and headache (9.9%). Significantly more subjects on tigecycline reported nausea, vomiting, abdominal pain (6.4%), leukocytosis (5%), increased BUN (2.6%) and accidental injury (1.9%).
– In HAP population, the most common AEs in the tigecycline group were nausea and vomiting, which were reported by 16.3% and 14.1% of the subjects, respectively. Other AEs that occurred significantly more in tigecycline-treated subjects were shock (3.2%), prolonged activated partial thromboplastin time (aPTT) (3.9%), increased BUN levels (3.4%), somnolence (2.1%), and skin ulcer (5.8%).
– For the integrated phase 3 analyses, the most common AEs in the tigecycline treatment group were nausea (28.7%), vomiting (19.7%), fever (7.2%), and infection (7.1%). The most common AEs in the comparator group were nausea (15.8%), diarrhea (11.4%), vomiting (11.1%), fever (9.4%), infection (7.1%), abdominal pain (6.5%), hypoproteinemia (6.0%), leukocytosis (5.7%) and healing abnormal (2.0%). In general, adverse event profile observed in CAP and HAP studies was also similar.

Nausea, vomiting and some of the other AEs, such as abdominal pain, anorexia, bilirubinemia, hypoproteinemia, and increased PT and aPTT, have been previously observed with tigecycline and are reflected accordingly in the SPC. No specific concerns arise from CAP and HAP studies. Diarrhea is also listed in the SPC. The MAH continues to monitor cases of diarrhea, particularly reports of

Clostridium difficile-associated diarrhea and pseudomembranous colitis, in accordance with the Tigecycline RMP.

In relation to the incidence of AE in CAP studies, the MAH further discussed the statistical difference observed between treatment group at the TOC visit with regard to leukocytosis and its possible implication in a lack of efficacy for tigecycline. Of the 21 tigecycline-treated patients with leukocytosis 13 had a clinical response of cure, 6 had a clinical outcome of failure and 2 were indeterminate. In its answer to the RSI adopted in November 2007, a listing of the clinical response for each patient with leukocytosis was provided, as well as individual WBC counts at baseline, LDOT and TOC. Although not all patients returned to normal values, most of the cases showed improvement on their WBC count at the TOC visit. The increased incidence of leukocytosis does not suggest clinical failure.

TEAEs were reported by 1840 (73.2%) subjects in the tigecycline group and 1591(69.0%) subjects in the comparator group. The rate of TEAEs was significantly higher in the tigecycline group than the comparator group ($p < 0.001$). The most frequently reported TEAEs in the tigecycline group were nausea (646; 25.7%), vomiting (443; 17.6%), diarrhea (286; 11.4%), abdominal pain (136; 5.4%), infection (146; 5.8%), leukocytosis (117; 4.7%), and hypoproteinemia (124; 4.9%).

- In CAP, the frequency of TEAEs was significantly higher in tigecycline group than in levofloxacin. TEAEs were reported by 71.9% subjects in the tigecycline group and by 63.5% subjects in the comparator ($p=0.010$). The most common drug-related TEAEs in patients treated with tigecycline were nausea at 24.3% (14.2% mild; 9.4% moderate; 0.7% severe) and vomiting at 16% (10.4% mild; 4.7% moderate; 0.9% severe). A significantly higher number of the tigecycline-treated subjects than levofloxacin-treated subjects reported TEAEs of abdominal pain (24; 5.7%; $p = 0.012$), nausea (103; 24.3%; $p < 0.001$), vomiting (68; 16.0%; $p < 0.001$), and leukocytosis (19; 4.5%; $p = 0.027$).
- For HAP population, TEAEs were reported by 368 (78.8%) subjects in the tigecycline group and 367 (78.6%) subjects in the imipenem/cilastatin group. The frequency of TEAEs was not significantly different between the 2 treatment groups ($p = 1.000$). A significantly higher number of the tigecycline-treated subjects than imipenem/cilastatin-treated subjects reported TEAEs of nausea (72; 15.4%; $p < 0.001$), vomiting (59; 12.6%; $p = 0.008$), shock (13; 2.8%; $p = 0.020$), prolonged aPTT (17; 3.6%; $p = 0.033$), somnolence (10; 2.1%; $p = 0.037$), and skin ulcer (25; 5.4%; $p = 0.015$).

In relation to the number of deaths reported in clinical trials, in CAP, twenty-three subjects (2.7%) died during the combined CAP studies (308 and 313): 12 (2.8%) in the tigecycline group and 11 (2.6%) in the levofloxacin group ($p = 1.000$). None of these deaths were considered by the investigator to be related to treatment. In HAP, a total of 123 deaths occurred. Of these, 66 of 467 (14.1%) were in the tigecycline group and 57 of 467 (12.2%) were in the imipenem/cilastatin group. One of these dead was considered as possible related to tigecycline by the investigator (treatment failure in recurrent pneumonia). During the integrated phase 3 studies, 137 (5.4%) tigecycline-treated and 87 (3.8%) comparator-treated subjects died. According to the results, there is no difference observed in CAP and HAP studies in deaths between tigecycline and comparators. This is not consistent with the rates previously observed in other indications, where more patients treated with tigecycline died compared with other treatments. Nevertheless, a comparison between rates it is not possible due to the differences in severity of the population studied.

There are class adverse reactions that have rarely been reported with tetracyclines. Such reactions may include photosensitivity, pseudotumor cerebri, pancreatitis, and anti-anabolic action which have led to increased BUN, azotaemia, acidosis, and hyperphosphataemia. Some of these adverse reactions have been reported in patients on tigecycline.

Hepatotoxicity, a known adverse event reported with tetracyclines, was specifically assessed in tigecycline clinical trials. In the integrated phase 3 analysis, significantly more tigecycline-treated subjects reported jaundice or hyperbilirubinemia compared with comparator-treated subjects. On the other hand, AST and ALT abnormalities in comparator-treated patients were numerically reported more frequently than in tigecycline-treated patients. Hepatotoxicity, a known adverse event reported with tetracyclines, was specifically assessed in tigecycline clinical trials. In the integrated phase 3

analysis, more tigecycline-treated subjects reported jaundice [5 (0.2%) vs 0 (0%)] or hyperbilirubinemia [32 (1.3%) vs 4 (0.2%)] compared with comparator-treated subjects. AST and ALT abnormalities in comparator-treated patients were reported more frequently than in tigecycline-treated patients. Overall, there was no difference in the number of patients with potential clinically important (PCI) laboratory values between the 2 groups. PCI results of elevated AST and ALT were similar between groups [AST: tigecycline, 13 (3.3%); comparator, 22 (5.6%); ALT: tigecycline, 4 (3.5%); comparator, 25 (6.3%)]. .

Reports of thrombocytopenia have been reported with minocycline and other tetracyclines. Taking a criteria for PCI values of low platelet counts less than or equal to 100 cells x 109/L, for CAP´s studies, 8 of 377 (2.1%) tigecycline treated subjects met the criteria. For HAP, in the tigecycline group, 33 of 453 (7.3%) of subjects met the criteria. Of note, thrombocytopenia has been including in section 4.8 through the type II variation II/12, which received a positive opinion in November 2007.

A total of 408 subjects in the tigecycline group (16.2%) and 334 subjects in the comparator group (14.5%) had SAEs. The incidence of SAEs was similar between the 2 treatment groups (p = 0.094). The most frequently reported SAEs in tigecycline-treated subjects were abscess (36; 1.4%), infection (31; 1.2%), abnormal healing (29; 1.2%), and respiratory failure (29; 1.2%). Significantly more subjects in the tigecycline group than in the comparator group reported heart arrest (tigecycline, 19; 0.8%; comparator, 6; 0.3%; p = 0.025), shock (tigecycline, 22; 0.9%; comparator, 7; 0.3%; p = 0.014), and abnormal healing (tigecycline, 29; 1.2%; comparator, 13; 0.6%; p = 0.030).

- The most frequently SAEs reported in CAP patients occurred in the respiratory system, with 26 (6.1%) and 22 (5.2%) AEs reported in the tigecycline and levofloxacin treatment groups, respectively. The most frequently reported SAEs in tigecycline-treated subjects were pneumonia and respiratory failure (5 each; 1.2%). groups (p = 0.654). There were no significant differences between treatment groups.
- In HAP, the incidence of SAEs was similar between the 2 treatment groups (p = 0.940), and no category showed a significant difference between the 2 groups. The most frequently reported SAEs in tigecycline- treated subjects were shock (13; 2.8%) and pneumonia and respiratory failure (11 each; 2.4%).

In HAP studies numerically, more subjects in the tigecycline group (13 patients; 2.8%) than in the comparator group (5 patients; 1.1%) reported shock as SAEs. In the tigecycline group, 12/13 patients reporting shock had an outcome of death while in the comparator group 3/5 patients died due to shock. None of these SAEs and deaths were considered as related to study drug. According to the MAH, the observed incidences of SAEs and deaths across all phase 3 studies reflect the progression of underlying disease states. However, this statement is not entirely clear:

- Some differences have been found between the data presented with regard to shock and sepsis shock According to the data presented, there are more cases of septic shock than shock. It is not clear which classification criteria were taken into account to classify the different types of shock.
- There were 9 and 8 cases of septic shock in tigecycline and comparator groups respectively. A pooled analysis of all shock events in HAP studies should be provided.
- As answer to the RSI (Major objections, Q2), the MAH has provided new analyses of the events of shock and heart arrest. These analyses have been performed including not only the terms heart arrest and shock but also combining them with the terms of sepsis and hypotension. To address the impact of severity of disease, analyses comparing events by APACHE score > 10 and >15 have been performed.

To evaluate the effect of the different patient populations on the imbalance in events, analyses were performed as follows:

- Integrated phase 3 studies analyses. Including the following studies: 300 and 305 (cSSSI, 301 and 306 (cIAI), 307 (gram-positive RP), 309 (gram-negative RP), 308 and 313 (CAP), 311(HAP) and 316 (cIAI).
- Analyses by APACHE score (studies 301, 306, 307, 309, 311 and 316)
- Overall analysis of the HAP population, including non-ventilator-associated pneumonia [non-VAP] and VAP subpopulations;

- Excluding HAP and/or resistant pathogen studies as well as overall analyses separately by indication.
- In addition to APACHE score, to further evaluate effects related to severity of infection or other underlying conditions and to help determining their relationship to treatment, analyses were performed evaluating the timing of events in relation to start of therapy and to last day of therapy (LDOT).
- Limited information is available for ongoing post-marketing studies 315 and 400 (cIAI), and 900 (cSSSI) and this is presented separately.
- Finally, cases of heart arrest and shock (excluding septic shock) occurring in tigecycline treated patients were reviewed individually to help evaluating the likelihood that the events were related to tigecycline in terms of the presence or absence of other factors that might explain the events (eg, underlying conditions, response to treatment, timing of the events).

The terms heart arrest and shock included the following verbatim terms:

- *Heart arrest*: cardiac arrest, cardiorespiratory arrest, sinus arrest, asystole, and pulseless electrical activity arrest.
- *Shock*: Shock, cardiogenic shock, multiorgan system failure, multiple organ failure, multiple organ dysfunction, distributive shock, hemodynamic decompensation followed by cardiogenic shock, refractory shock (vasopressor resistant), hemorrhagic shock, and cardiopulmonary failure.
- *Septic shock*: septic shock (this was almost always the verbatim term as well), infectious shock

Integrated phase 3 studies analysis

The safety analysis now submitted shows that there is a statistically significant difference between treatment groups, with more events in tigecycline-treated patients than comparators (53 tigecycline-treated patients vs 27 comparator-treated patients). When sepsis and hypotension are also included, the results are similar (63 vs 27).

Mortality was higher in patients in both treatment arms with higher APACHE scores. There were more tigecycline-treated patients than comparator-treated patients with shock and heart arrest when a cut off of >10 [46 (16.7%) vs 15 (3.9%)] and >15 [26 (15.2%) vs 9 (6.4%)] are used. Only among patients with APACHE score ≤ 10 these differences tend to dilute [12 (1.1%) vs 9 (0.9%).

HAP

When the analyses are performed by the subgroups of NON-VAP or VAP patients, for the VAP subgroup there were significant differences between treatment groups when combining shock and heart arrest (11 vs 2) as well as those terms plus sepsis and hypotension (12 vs 3).

Excluding HAP and/or RP

When HAP study is excluded there are still statistically significant differences between treatment groups for shock and heart arrest with an outcome of death (27 vs 7) and together with sepsis and hypotension (35 vs 10). Excluding HAP and by APACHE scores, the only significant difference between treatment groups for shock and heart arrest was for patients with an APACHE score ≤ 15(15 vs 3). For all the terms together, the significant differences were for patients with APACHE scores > 10 and ≤ 15.

When the analyses are performed excluding HAP and Resistant Pathogens studies, there were only statistically significant difference between treatment groups for patients with APACHE scores <15. In the rest of comparison, there were no statistically significant differences.

Analysis by time to onset of the events

It is mentioned that the majority (70%) of the events in both treatment arms were pre-terminal events. The timing for shock and heart arrest that began during therapy or after LDOT was similar for the 2 treatment groups. In HAP, there were statistically significant differences for the timing of all the deaths

For VAP and Non-VAP subgroups similar results were obtained with mean time to death for tigecycline-treated patients higher than for comparator-treated patients, but with no differences statistically significant.

Ongoing studies

In ongoing post marketing studies were 9/549 tigecycline-treated patients and 5/551 comparator-treated patients who experienced SAEs of shock or heart arrest to date.

Cumulative Review of Information in Global Safety Surveillance and Epidemiology Database

The review of PSUR and of information from Global Safety Surveillance Database identified reports of shock and heart arrest, of which some were considered associated with tigecycline therapy. In some cases, the fatal event occurred after discontinuation of tigecycline. The following conclusions were drawn in the 3rd PSUR AR in relation to these reports:

- The classification of cases and subsequent analysis performed by the MAH doesn't allow for a meaningful evaluation of some of the concerns which are raised from the fatal cases reported. In this regard, the main issue is related to cases in which the death is caused or related to a progression and/or complication of the infectious disease treated with tigecycline.
- According to the MAH, fatal outcome in some of these cases could be attributable to the poor prognosis and medical condition of patients and not to a lack of efficacy of tigecycline. Nevertheless this cannot be differentiated based on the available information of the reported cases. As a conclusion of the analysis of the cumulative review of fatal cases, lack of efficacy and off-label use should continue to be monitored.

In summary,

- The MAH should provide additional information including all deaths occurring across all clinical trials and not limited to those cases associated with particular AEs.
- As for the data provided the complete ascertainment of the reason underlying the increased mortality rate among tigecycline treated patients is not possible. However, considering its stronger association with particular indications (especially HAP) and also the fact that the number of deaths was numerically higher in tigecycline-treated patients, lack of efficacy continues to be the more plausible explanation. Keeping that in mind, this is considered as a potentially serious concern for the currently claimed indication. This aspect was already detected in earlier submissions, but considered to be solvable through SPC refinements highlighting the limitations of the clinical database (specially for cIAI) and specific follow-up measures (monitoring lack of efficacy). In this case, the consequences of the lack of representativeness of the actually enrolled population, the potential overlapping of some cases of CAP/HAP, and the exclusion of patients from nursing centres, lead the CHMP to conclude that SPC wording measures are unlikely to really define a target population without a high risk of ending up in an extremely artificial indication, with serious safety (lack of efficacy) concerns in case of off-label use (see paragraph V, follow on RSI, Major objections, Q1 and Q2 point b).

Cases of shock should be taken as a safety concern that deserves further discussion and elaboration. The MAH should present clearer and concise information related to shock.

Regarding discontinuations 15.5% of subjects in the tigecycline group and 12.7% of subjects in the comparator group discontinued study drug during all phase 3 clinical trials. This difference was significant (p=0.006). 167 (6.6%) tigecycline-treated subjects and 125 (5.4%) comparator treated subjects discontinued study drug primarily because of AEs. Overall, 246 (9.8%) subjects in the tigecycline group and 205 (8.9%) subjects in the comparator group withdrew from the study early. There was not a significant difference (p = 0.299) between the treatment groups for the primary reasons for withdrawal from the studies.

There was increase in coagulation parameters (INR, Prothrombin Time, activated Partial Thromboplastin Time and coagulation disorders) 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. Despite this result, there was no increase in bleeding diathesis or anemia in CAP and HAP studies.

In the integrated phase 3 analysis, significantly more subjects in the tigecycline group (61; 2.4%) than in the comparator group (8; 0.3%) had TEAEs of increased BUN ($p < 0.001$). Increase in BUN for the tigecycline group has been observed previously with tigecycline and is consistent with similar observed effects with tetracyclines. In CAP and HAP similar results were observed. These findings 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. This information is already stated in the SPC.

Overall, no new safety signals have been identified in clinical trials except shock and the confirmation of some safety finding such as hepatotoxicity, thrombocytopenia currently under evaluation.

III.2.4 Risk Management Plan (RMP)

The MAH has submitted a RMP, including the requested parts in the RMP guideline document. A brief overview of the data and issues arising from the clinical trial program as well as a description of the pharmacovigilance ands risk minimization activities is provided.

The MAH has submitted a tabulated summary of the population exposed in clinical trials. This summary has been stratified by indication, dose, subgroups and special populations. It has been also presented data of total exposed patients in clinical trials.

With regard to post marketing exposure (non study), approximately 3 million vials (50mg) of tigecycline injection were distributed between June 2005 and May 2007. The MAH estimate worldwide tigecycline exposure during the 2-year period in approximately 1,487,856 patient-days. The MAH calculation assumes that a typical daily dose of tigecycline is 100 mg. Assuming that each patient received 17 doses (100 mg/day for 8.5 days), there have been approximately 175,042 patients exposed to tigecycline worldwide during this 2-year period.

In general, the identified risks as well as the potential risks and the missing information as proposed by the Applicant cover most of the issues previously identified for tigecycline. There are additional potential risks that should be included in the RMP (cases of severe diarrhea, particularly reports of Clostridium difficile-associated diarrhoea and pseudomembranous colitis).
As stated in safety section, there are pending concerns with regard to the cases of shock reported in HAP studies.
For each important identified or potential risk or missing information, the action plan includes passive surveillance (routine pharmacovigilance and expedited reporting) and discussion of adverse events in PSUR. For some of the specific safety concerns additional data may be obtained from ongoing clinical trials (active surveillance).
At present, no additional safety studies are planned (apart from the ongoing studies). Therefore, additional new data are only expected from the ongoing studies and those generated from the routine pharmacovigilance activities. It is stated that the aggregate information generated would be reviewed on a periodical basis and summarized at the time of the PSUR submission.

In its answer to the RSI adopted in November 2007, the MAH indicated that the risk management plan will be revised to include additional market drug exposure data. This has been obtained from AMR audit data. The data presented includes US Cumulative Patient Projections for 2005, 2006, and the first 6 months of 2007. As requested, the data are stratified by age, indication, dose duration and treatment. European data are only available for the first 6 months of 2007.

According to the MAH, there is no data of the use of tigecycline in children under 8 years. It is likely that tigecycline will not be indicated under this age because of the risk of tooth discoloration and enamel hypoplasia. The MAH will conduct a PK and tolerability study for children aged from 8 to 11 years.
In the initially submitted RMP, the MAH has only listed the population not included in clinical trials. In its answer to the RSI adopted in November 2007, the MAH has specified the inclusion and exclusion criteria for pivotal studies in the RMP. However, there were pending concerns about the

limitations of the population included in the studies that should be further discussed. Therefore the RMP should be revised.

Within the postmarketing regulatory actions taken, sections 4.4 and 4.8 have been updated to included new safety concerns. Information regarding clostridium difficile associated diarrhea, anaphylaxis /anaphylactoid reactions, thrombocytopenia and pancreatitis are being included in the SPC as a result of the ongoing procedures.
As part of the answer to the RSI adopted in November 2007, the MAH submitted a summary of an on-going epidemiological drug utilization study, which is being conducted in the US. A complete description of the study design, data analysis, and limitations is included in the risk management plan. From a regulatory point of view, these new data submitted are in accordance with the RMP guideline.
Thrombocytopenia, anaphylaxis and Hepatic abnormalities have been listed as newly identified safety concerns. QTc prolongation and severe hepatic reactions have been considered as potential risk for tigecycline.
Within the potential risk for tigecycline, the MAH has agreed to consider *Clostridium difficile*-associated diarrhea and pseudomembranous colitis, as a potential risk for tigecycline and these events have been added to the potential risk section of the risk management plan. As stated in safety section, there are still pending concerns with regard to the cases of shock reported in HAP studies. However the MAH has agreed to include information about thrombocytopenia in CAP in the RMP.

Pharmacovigilance Plan
The MAH has a pharmacovigilance system for the collection, verification, evaluation and reporting of adverse drug reactions it receives with the marketed use of its products in accordance with worldwide regulatory reporting requirements for drug safety. New safety information is collected, reviewed and analyzed on an ongoing basis from multiple sources, including spontaneous reports, post-approval clinical studies, reports from Health Authorities, and reports from the published literature.

IV. BENEFIT RISK ASSESSMENT

The MAH has provided an extensive PD dossier, in which a number of issues still need to be modified in section 5.1 of the SPC.

Two pivotal clinical trials in CAP has been presented to support the indication of tigecycline in CAP. Clinical protocols were similar, though in one of them switching to oral levofloxacin at the investigator discretion was allowed. In the 2 studies tigecycline showed statistically convincing non-inferiority to levofloxacine in the enrolled population. However, there are a number of issues related to

- The relevance of the selection criteria defining the study population and the pattern of patients finally enrolled for the claimed indication. In this regard especially relevant concerns are the questionable indication for IV therapy of the majority of the patients, the low number of cases of CAP caused by legionella and the exclusion from pivotal trials of institutionalised patients, who are a relevant target population in terms of relevant prognostic factors, as the severity of the disease, age and microbiological profile.
- The dosing schedule of the comparator arm in both trials may be considered inappropriate in a part of the treated population. Though not in principle relevant for the claimed indication, the results from the submitted study in HAP raise additional concerns on the potential efficacy problems of tygecycline in patients with severe CAP.

The safety profile of tigecycline in patients with CAP is largely consistent with that known for this drug in other indications. In study 311 (HAP study), a surprisingly numerically higher of cases of shock (many of them leading to fatal outcome) observed with tigecycline raises additional concerns regarding its insufficient efficacy in this population, but also potentially on its safety profile.

The proposed RMP is mainly according the EU requirements, however depending on the answer to Q2 listed as a major objection in the follow on RSI (see paragraph V below), the RMP may need further revision.

The remaining concerns do not allow for the time being end up with a positive risk/benefit conclusion for Tygacil in CAP, unless the MAH satisfactorily address the objections listed in the follow on RSI section (see paragraph V below).

V. CHMP FOLLOW ON REQUEST FOR SUPPLEMENTARY INFORMATION AS ADOPTED IN FEBRUARY 2008

The following concerns should be address by the MAH both **in writing** and in an **Oral Explanation** in front of the CHMP.

IV.1 Major Objections

1. The MAH should provide an analogue set of data to that provided as answer to the first RSI adopted in November 2007 with regards to deaths across all tigecycline phase III trials, but including all deaths (independently of the underlying cause). The data should be compared to that of the comparators.

2. Considering the apparent association between the higher rate of deaths observed among tigecycline treated patients with particular indications (especially HAP) and higher APACHE score, lack of efficacy continues to be the more plausible explanation. Keeping that in mind, this is considered as a serious concern for the currently claimed indication. A detailed discussion of these aspects should be provided before a positive benefit/risk conclusion can be reached. The following key aspects will need to be considered in the MAH's answer:

    a. The MAH is requested to discuss what were the reasons in terms of co-morbidities, pneumonia characteristics, etc of patients with Fine PSI scores of I, II and III that justify the hospitalisation and/or administration of iv therapy in studies 308 and 313.

    b. The consequences of the lack of representativeness of the actually enrolled population, the potential overlapping of some cases of CAP/HAP, and the exclusion of patients from nursing centres, lead to the conclusion that SPC wording measures are unlikely to really define a target population without a high risk of ending up in an extremely artificial indication, with serious safety (lack of efficacy) concerns in case of off-label use. The MAH should discuss.

    c. A complete package of risk minimisation measures aimed to avoid the exposure to tigecycline monotherapy of patients not properly represented in the clinical database for CAP should be provided.

IV.2 Other concerns

3. Depending on the MAH responses to the above-mentioned major objection (Q2), the RMP will need further revision.