EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Assessment report

VIBATIV

International Nonproprietary Name: telavancin

Procedure No.: EMEA/H/C/1240

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Astellas Pharma Europe B.V. submitted on 27 October 2009 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Vibativ, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 October 2006.

The applicant applied for the following indication:

VIBATIV is indicated for the treatment of the following infections in adults (see sections 4.4 and 5.1):

- complicated skin and soft tissue infections
- nosocomial pneumonia (including ventilator-associated pneumonia)

Telavancin is bactericidal against susceptible Gram-positive bacteria (see section 5.1).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

The legal basis for this application refers to:

A - Centralised / Article 8(3) / New active substance.

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P127/2009 for the following conditions:

Complicated skin and soft tissue infections

Nosocomial pneumonia

The PIP is not yet completed.

Information relating to orphan market exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable.

Scientific Advice:

The applicant did not seek scientific advice at the CHMP.

Licensing status

Telavancin has been granted a marketing authorization in the USA and Canada. It was launched in the USA in September 2009.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Ian Hudson Co-Rapporteur: Martina Weise

- The application was received by the EMA on 27 October 2009.
- The procedure started on 18 November 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 04 February 2010. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 05 February 2010.
- During the meeting on 18 March 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 19 March 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 09 September 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 October 2010.
- During the CHMP meeting on 18 November 2010 the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 11 February 2011.
- During the CHMP meeting on 11-14 April 2011, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During their 16-19 May 2011 meeting, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to VIBATIV on 19 May 2011. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 19 May 2011.
- The applicant provided the DHCP letter 19 May 2011.

2. Scientific discussion

2.1. Introduction

Among the Gram-positive bacterial pathogens *S. aureus*, particularly MRSA, remains important, especially with the advent of aggressive community-acquired MRSA (CA-MRSA) that express Panton-Valentine Leucocidin (PVL+). In addition, vancomycin-resistant enterococci (VRE) and multidrug-resistant coagulase-negative staphylococci (CoNS) pose problems for antibacterial therapy.

The glycopeptide antibacterial agent vancomycin has been available for systemic therapy of infections due to Gram-positive pathogens for over 40 years. Vancomycin and teicoplanin have been used widely to treat MRSA and enterococcal infections in the last 10 to 15 years. However, vancomycin-insusceptible and -resistant *S. aureus* (VISA and VRSA) have emerged and these are often cross-resistant to teicoplanin. In the last decade other agents have become available for the management of MRSA infections (e.g. daptomycin and linezolid) but there is already some bacterial resistance.

Each of the available agents has its own drawbacks and limitations and there is a need for additional antibacterial agents to manage serious infections due to Gram-positive bacteria.

Telavancin is a semi-synthetic, lipoglycopeptide antibacterial agent with *in-vitro* activity against aerobic and anaerobic Gram-positive pathogens. *In-vitro* data indicate that it may be useful against some staphylococci that are not susceptible to daptomycin and against some bacteria that have reduced susceptibility to vancomycin. The antibacterial activity of telavancin results from inhibition of bacterial cell wall synthesis as observed with other glycopeptides plus an effect on the bacterial cell membrane resulting in disruption of normal functions.

The **claimed indication** at submission of the licensing application was:

VIBATIV is indicated for the treatment of the following infections in adults (see sections 4.4 and 5.1):

- complicated skin and soft tissue infections
- nosocomial pneumonia (including ventilator-associated pneumonia)

Telavancin is bactericidal against susceptible Gram-positive bacteria (see section 5.1).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

The originally recommended dosage regimen was as stated below:

Posology

Adults

The recommended dosage, frequency and treatment duration by infection are shown in the following table:

Table 1:

Infection	Dosage	Frequency	Duration
Complicated skin and soft tissue infections	10 mg/kg	Once every 24 hours	7–14 days
Nosocomial pneumonia (including ventilator-associated pneumonia)	10 mg/kg	Once every 24 hours	7–21 days

Paediatric patients

VIBATIV is not recommended for use in patients below 18 years of age due to a lack of data on safety, efficacy and pharmacokinetics.

Dosage in patients with renal impairment

Patients with renal impairment should receive a dose that has been modified according to estimated or measured creatinine clearance as presented in the table below.

Table 2:

Creatinine clearance* (ml/min)	Dosage regimen
>50	10 mg/kg every 24 hours
30-50	7.5 mg/kg every 24 hours
10-<30	10 mg/kg every 48 hours

*As calculated using the Cockcroft-Gault formula.

There is insufficient information to make specific recommendations for dosage adjustment in patients with end stage renal disease (CrCl <10 ml/min), including patients undergoing haemodialysis.

Dosage in patients with impaired hepatic function

Mild to moderate degrees of hepatic insufficiency (Child-Pugh class B) (see section 5.2) did not result in a relevant change in pharmacokinetics of telavancin. Therefore, no dose adjustment is necessary when administering telavancin to patients with mild or moderate degrees of hepatic insufficiency. No data are available in patients with severe hepatic insufficiency (Child-Pugh class C). Therefore, caution should be exercised if telavancin is given to patients with severe hepatic insufficiency.

Obese patients

Patients with a body weight of ≥90 kg and a Body Mass Index ≥35 kg/m^2 should receive a dosage of telavancin that has been modified as specified in the table below.

Table 3:

	Dose and dosage interval	
Creatinine clearance* (ml/min)	Body weight <90 kg or Body Mass Index <35 kg/m^2	Body weight ≥90 kg and Body Mass Index ≥35 kg/m^2
>50	10 mg/kg once every 24 hours (i.e. no dose adjustment)	900 mg once every 24 hours
30–50	7.5 mg/kg once every 24 hours	675 mg once every 24 hours
10-<30	10 mg/kg once every 48 hours	900 mg once every 48 hours

*As calculated using the Cockcroft-Gault formula.

There is insufficient information to make specific recommendations for dosage adjustment in patients with end stage renal disease (CrCl <10 ml/min), including patients undergoing haemodialysis.

Elderly patients

No clinically significant differences in pharmacokinetics of telavancin were observed between healthy elderly and healthy young subjects. Also, analysis of patient population pharmacokinetic data did not show a relevant effect of age on pharmacokinetics. Therefore, the recommended dose (10 mg/kg once daily) should be used in elderly patients except in those with creatinine clearance of less than or equal to 50 ml/min, or with a body weight ≥90 kg and BMI ≥35 kg/m^2 (see above and section 5.2).

Following assessment of the dossier, based on feedback obtained from CHMP, the applicant **revised the indication and posology section of SmPC** as follows:

VIBATIV is indicated for the treatment of adults with nosocomial pneumonia (NP) including ventilator associated pneumonia, known or suspected to be caused by methicillin-resistant *Staphylococcus aureus* (MRSA).

Vibativ should be used only in situations where it is known or suspected that other alternatives are not suitable (see sections 4.3, 4.4, 4.8 and 5.1).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Posology

Adults

The recommended dosage regimen is 10 mg/kg, once every 24 hours, for 7 to 21 days.

Special populations

Paediatric patients

The safety and efficacy of VIBATIV in children aged below 18 years have not yet been established. No data are available.

Dosage in patients with renal impairment

Patients with renal impairment should receive an initial dose according to calculated or measured creatinine clearance as presented in the table below. During treatment dose adjustments according to the table should be made based on calculated or measured creatinine clearance in patients with clinically relevant changes in renal function.

Table 4:

Creatinine clearance* (ml/min)	Dosage regimen
>50	10 mg/kg every 24 hours
30-50	7.5 mg/kg every 24 hours

*As calculated using the Cockcroft-Gault formula

The use in patients with acute renal failure or creatinine clearance (CrCl) <30 ml/min including patients undergoing haemodialysis is contraindicated (see section 4.3).

Dosage in patients with hepatic impairment

Mild to moderate degrees of hepatic impairment (Child-Pugh class B) (see section 5.2) did not result in a relevant change in pharmacokinetics of telavancin. Therefore, no dose adjustment is necessary when administering telavancin to subjects with mild or moderate degrees of hepatic impairment. No data are available in subjects with severe hepatic impairment (Child-Pugh class C). Therefore, caution should be exercised if telavancin is given to subjects with severe hepatic impairment.

Obese patients

Obese patients should receive a telavancin dose in accordance with their bodyweight and renal function (see section 4.3 and 5.2).

Elderly patients

Elderly patients should receive a telavancin dose in accordance with their bodyweight and renal function (see section 4.3 and 5.2).

Method of administration

VIBATIV must be reconstituted and then further diluted prior to administration by intravenous infusion through a dedicated line or through a Y-site over a 60 minute period. Bolus injections must not be administered. For instructions on reconstitution and dilution see section 6.6.

2.2. Quality aspects

2.2.1. Introduction

Vibativ contains telavancin as an active substance. Telavancin is a semi-synthetic substance derived from vancomycin.

Vibativ is presented as a lyophilisate powder for solution for infusion containing hydroxypropylbetadex (hydroxypropyl ether of β-cyclodextrin, HP-β-CD) and mannitol as solubilisation enhancers.

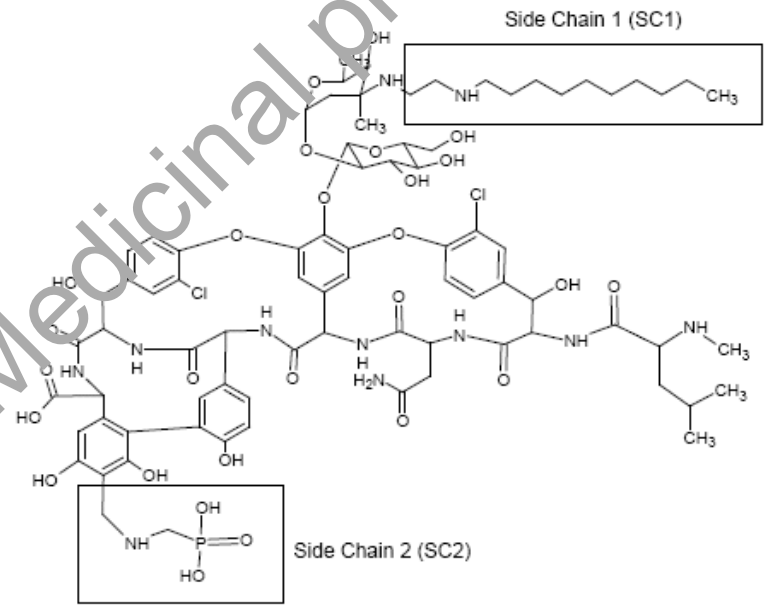
The antibacterial activity of telavancin results from inhibition of bacterial cell wall synthesis as observed with other glycopeptides plus an effect on the bacterial plasma membrane resulting in disruption of normal functions.

The drug product is administered by intravenous infusion over a 60 minute period after reconstitution of the lyophilisate and further dilution into a compatible infusion fluid.

2.2.2. Active Substance

Telavancin is the INN name of the active substance with the chemical name Vancomycin, N3''-[2-decylaminoethyl]-29-[[(phosphonomethyl)amino]methyl]-hydrochloride, corresponding to the molecular formula $C_{80}H_{106}Cl_2N_{11}O_{27}P \cdot x\ HCl$ (where x = 1 - 3) and relative molecular mass 1755.63 (free base). Its structural formula is shown below.

Figure 1:



Telavancin appears as an off-white to pale pink solid hygroscopic powder, sensitive to light. It is sparingly soluble in water (pH 2), slightly soluble in water (pH 4) and very slightly soluble in ethanol. The pH of a saturated aqueous solution is 4.6 to 2.8, depending upon the chloride content. The pKa value cannot be determined due to the close overlap of the multiple pKa. The water/n-octanol distribution coefficients for telavancin ranges from -1.8 to -2.4 in various buffer solutions (pH 4-10). The specific rotation value ($[\alpha]_D^{20}$), of telavancin hydrochloride varies between + 4.1° and +15.6°, due to decreasing specific rotation value with increasing solution concentration. No crystalline forms have been observed.

Manufacture

Telavancin is a semi-synthetic substance derived from the glycopeptide vancomycin by a two-step synthesis followed by purification and isolation. Telavancin contains a lipophilic side chain bond to the amino sugar of vancomycin and an aminomethyl phosphonite group bond to the di-phenol-ring of vancomycin. A detailed description of the synthesis route and detailed flow diagram were presented for each synthesis step. Satisfactory data were provided to support the proposed in-process control limits based on commercial scale batches using the proposed manufacturing process.

Specification

The drug substance specification includes tests for appearance (visual), colour of solution (Ph. Eur.), identification (IR, HPLC), identification of chloride (Ph. Eur.), assay (HPLC), impurities/degradation products (HPLC), residual solvents (GC), water content (Ph. Eur.), chloride content (potentiometric titration), residue on ignition (Ph. Eur.), heavy metals (Ph. Eur.), bacterial endotoxins (Ph. Eur.), and microbial limits (Ph. Eur.).

The justification of specification the drug substance is based on data generated from a large number of batches. Acceptance criteria are based on a full understanding of the process and its impact on the characterization of the drug substance. Historical data, non-clinical safety evaluation, stability, and validation data were utilized in the establishment of the specification addressing all the key attributes necessary to control the quality of the drug substance. A special emphasis was placed on the data from 26 lots manufactured using the current manufacturing process.

Stability

Stability data from four primary stability batches and three validation stability batches all manufactured by the commercial manufacturing process and packed in the intended bulk packaging. The drug substance was tested in line with the ICH stability guidelines. The conditions used were -20°C (long-term) and 5°C (accelerated conditions). For the primary stability studies results up to 48 months at -20° C are provided and for the validation stability studies 24 months data at -20° C are provided. Real time data of the primary lots all comply with the acceptance criteria after 48 months of storage at -20°C.

Furthermore, results from photostability testing undertaken in accordance with ICH Q1B guideline were included. The results of the photostability study showed no significant differences between the light protected and light exposed samples. The combination of storage at -20°C (generally a dark or low light level environment) and the use of the selected packaging have been shown to provide adequate protection from light.

Based on this the proposed re-test period and storage conditions are justified.

2.2.3. Finished Medicinal Product

Vibativ powder for solution for infusion is supplied as a sterile, lyophilized powder, in glass vial, with a stopper and "flip-off" seal. The drug product contains hydroxypropylbetadex (HP-β-CD), mannitol, and may contain sodium hydroxide and/or hydrochloric acid (used to adjust pH).

Pharmaceutical Development

The drug substance has been shown to be unstable in solution even under refrigerated storage conditions. Development work has concentrated on the drug product formulated as a lyophilisate. The formula of Vibativ has remained virtually unchanged over the whole development programme. Telavancin hydrochloride is intended for administration by IV infusion, however, it is poorly soluble at physiological pHs. The product has therefore been formulated with the solubilizer, hydroxypropylbetadex to improve its solubility and to produce a solution that is suitable for manufacturing processing, reconstitution, dilution, storage and intravenous administration. In addition, use of hydroxypropylbetadex in the formulation is stated to offer a degree of nephro-protection from telavancin

Alternative solubilisers could be used to obtain solutions of telavancin, however, the hydroxypropylbetadex was selected because of its ability to protect the kidneys from the toxic effects of the drug substance. While the mechanism by which hydroxypropylbetadex attenuate telavancin associated nephrotoxicity is not clearly understood, the pharmacokinetics and physicochemical properties of the telavancin and hydroxypropylbetadex provides a potential clue.

It has been demonstrated that telavancin and hydroxypropylbetadex readily form a complex upon reconstitution and dilution and that this complex tends to dissociate at around pH 7. It has also been observed that both telavancin and hydroxypropylbetadex are cleared from the circulation by the kidneys.

It is hypothesised that upon infusion dissociation of the complex, possibly due to the pH and/or dilution in the blood stream, makes the telavancin bioavailable to form a new association with plasma proteins, where it is highly bound, the hydroxypropylbetadex remaining free. Once filtered by the glomeruli, both the hydroxypropylbetadex and telavancin enter an environment that favours the re-association of telavancin with hydroxypropylbetadex and it is thought that this complex reduces the tubular injury.

A high ratio of hydroxypropylbetadex relative to telavancin ensures renal tubular hydroxypropylbetadex fluid concentrations that are sufficiently high to support complex formation with telavancin. Data to support these kinetics were provided.

All of the excipients are pharmaceutical materials commonly used to formulate parenteral dosage forms. Compatibility of these excipients with the drug substance has been demonstrated through product stability studies.

Vibativ is reconstituted aseptically in an appropriate solvent and then further diluted aseptically into an IV bag before being administered as an IV infusion. The in-use compatibility of the drug product in a vial has been measured when reconstituted with either 5% Dextrose Injection (D5W), Sterile Water for Injections, (WFI), or 0.9% Sodium Chloride Injection (NS). The data generated support the shelf life for the reconstituted vials.

Vibativ, 250 mg/vial and 750 mg/vial were evaluated for its in-use compatibility, after reconstitution and dilution, following storage at the recommended storage condition and ambient lab conditions.

These dosing solutions were prepared with 5% Dextrose Injection (D5W); 0.9% Sodium Chloride Injection (NS); or Lactated Ringer's Injection (LR) and diluted to 0.6 or 8 mg/ml. The mean values of all samples met the acceptance criteria specified in the protocol and where within the specification

Additionally, no significant changes were observed in appearance (in particular the solutions remained clear and free of particulate matter), pH, assay and colour of solution of the dosing solutions at these conditions. These data support the shelf life for the reconstituted vials. It is concluded that the in-use compatibility of telavancin for infusion after preparation for infusion was not affected by either the telavancin dosing solution concentration or the diluent (D5W, NS, or LR) used to prepare the dosing solution for both the 250 and 750 strengths of drug products. Therefore, telavancin dosing solutions are stable for one day at ambient conditions or three days at refrigerated conditions (when prepared with D5W, NS or LR).

The manufacturing process is considered standard for this type of product. The information provided on the manufacturing process development is considered satisfactory. The manufacturing process has been validated to production scale. Satisfactory validation data have been provided for the sterile filters. The sterile filtration has been addressed and this includes satisfactory information on media fill runs.

Adventitious agents

The bacterial retention filter used to sterilize the Telavancin for Injection bulk solution and the vial stopper are both manufactured using a material of animal origin. Details of both items are provided together with statements from the suppliers confirming that the materials will comply with the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products.

Manufacture of the product

The aseptic production of Vibativ is comprised of several standard unit operations using standard pharmaceutical equipment. The equipment and sequence of the manufacturing process are the same for both presentations (250 mg/vial and 750 mg/vial). The processes for the two presentations differ in the bulk solution concentration, vial size, fill volume and the lyophilisation cycle parameters.

There are no intermediates produced in the manufacture of Vibativ. Processing of the drug product is performed in one continuous process. As part of the manufacturing process defined in-process controls (IPC) are carried out. The IPCs and their acceptance criteria are considered adequate.

Full details on the media fill runs have been provided to demonstrate that all relevant manufacturing steps are tested adequately, including all relevant details. The process parameters used in the media fill runs and the vials are representative of the proposed product manufacture. Assurance that the media fill runs will be carried out at regular intervals has been provided. Based on the satisfactory details of the media fill runs being provided, the process validation data are also considered satisfactory.

Product specification

The release and shelf-life specifications include tests and limits for appearance (visual), reconstitution time (visual), appearance of reconstituted solution (visual, spectro-photometry), pH of reconstituted solution (potentiometry), identification (HPLC, UV), assay (HPLC), degradation products (HPLC), uniformity of dosage units (Ph.Eur.), water content (coulometer), sterility (Ph.Eur.), bacterial endotoxins (Ph.Eur.) and particulate contamination (Ph.Eur.).

Results from six production scale batches used for the process validation studies were summarised meeting the specification to which they were tested against. The proposed drug product specification has tighter limits for certain parameters.

Further details of all batches of Vibativ that have been used in toxicology or clinical studies were included.

Stability of the product

The stability studies were performed on 8 batches of the 250 mg vials and 6 batches of the 750 mg vials, manufactured at pilot and commercial scale using the proposed commercial formulation and manufacturing process. Long-term storage conditions are at 5°C ± 3°C in a refrigerator and accelerated conditions are at 25°C ± 2°C / 60 % ± 5 % RH. Data up to 48 months in long term and 6 months accelerated, respectively, were presented. Results show acceptable levels of potential degradants, whereas all tested parameter were within specifications.

Photostability

Two batches of drug product, one of each strength, were exposed to light according to the ICH guidance Q1B. Samples were presented in the primary packaging (clear glass vial with stopper and seal) as light exposed (naked vial) and light protected controls (foil wrapped vial). There were slight differences between the light exposed and light protected controls, but the differences were not significant. All light exposed samples complied with the specifications in the protocol.

Chemical and physical in-use stability has demonstrated that both the reconstituted solution in the vial and the diluted solution in the infusion bag are stable for 24 hours at room temperature or 72 hours under refrigeration (5°C ± 3°C).

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The quality of Vibativ powder for solution for infusion is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Information on development, manufacture and control of the drug substance has been presented in a satisfactory manner. The quality of the active substance is considered sufficiently described and adequately supported by data. Sufficient chemical and pharmaceutical documentation relating to development, excipients, manufacture and control of the drug product has been presented.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

2.3. Non-clinical aspects

2.3.1. Introduction

GLP

Safety pharmacology studies were carried out in compliance with GLP regulations and to the requirement of ICH S7A. Pharmacokinetic studies were not performed to GLP standards, although an acceptable justification from the applicant has been given. All pivotal toxicity studies were performed in compliance with GLP.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The primary pharmacology of telavancin has been adequately characterised.

Telavancin is a semi-synthetic derivative of the glycopeptide antibiotic vancomycin, possessing a lipophilic side chain attached to the vancosamine sugar. This modification retains the glycopeptide mechanism of action (inhibition of bacterial cell wall synthesis) but introduces a novel mechanism of action whereby telavancin simultaneously interacts with the bacterial cell membrane causing a concentration-dependent loss of membrane potential and increases in membrane permeability.

In vitro bactericidal activity of telavancin

Telavancin possesses in vitro activity against a broad range of clinically relevant Gram-positive bacterial pathogens. Multiple studies, including seven recent, prospective surveillance studies of circulating clinical isolates from around the world, demonstrate the potent in vitro activity of telavancin against Gram-positive species including *S. aureas*, streptococci and *S. pneumoniae*.

Telavancin exerts rapid, concentration-dependent bactericidal activity against Gram-positive organisms including methicillin-susceptible S. aureus (MSSA), methicillin-resistant S. aureus (MRSA), vancomycin-intermediate S. aureus (VISA), coagulase-negative staphylococci, β-haemolytic streptococci and S. pneumoniae. Telavancin, unlike the glycopeptides and most β-lactams, retains bactericidal activity against non-growing S. aureus and shows marked activity against pathogens growing in biofilms. In an in vitro model of staphylococcal biofilm infection, telavancin reduced bacterial load in biofilms established with MSSA, MRSA, VISA and S. epidermidis (methicillin-susceptible S. epidermidis, MSSE and methicillin-resistant S. epidermidis, MRSE), irrespective of phenotype, at drug concentrations that simulated a 10 mg/kg/day dose in humans. Telavancin is actively taken up into macrophages and has been shown to kill intracellular S. aureus to a greater extent than vancomycin, teicoplanin and linezolid.

Telavancin has a prolonged post-antibiotic effect (up to 4-5 h) against S. aureus, including MSSA, MRSA, VISA and VRSA strains, and other Gram-positive pathogens and up to 6.5 h for S. pyogenes. Telavancin is approximately 90% protein bound, primarily to albumin, but the in vitro antibacterial activity of telavancin is affected by the presence of human serum or albumin with increases in MIC and MBC values of 2- to 4-fold. Time-kill studies demonstrate that telavancin remains bactericidal in the presence of high serum concentrations (50 to 70% vol/vol) at drug levels attained with a 10 mg/kg dose.

Resistance induction

There is no known cross-resistance between telavancin and other classes of antibiotics. It should be noted that telavancin is not active against VanA-type vancomycin-resistant enterococci (VRE). Telavancin is an inducer of the VanA but not the VanB operon in VRE. MICs for organisms with the VanB determinant are higher than for glycopeptide-susceptible organisms (e.g. 8 mg/L vs. 0.5 mg/L). Staphylococci that show reduced susceptibility to vancomycin may sometimes remain susceptible to telavancin.

In vitro activity of the main metabolite of telavancin, 7-OH-Telavancin (AMI-11352)

The main metabolite of telavancin, 7-OH-Telavancin (AMI-11352), has antibacterial activity but is 10-fold less potent than telavancin. Due to the low antibacterial activity of AMI-11352 and the low human exposure, this metabolite is not considered to have a relevant contribution to the overall activity of telavancin in vivo.

In vivo efficacy in animal models of infection

Multiple animal models of bacterial infection caused by clinically important Gram-positive pathogens including soft-tissue (neutropenic murine thigh, murine subcutaneous infection), deep-seated (rat and rabbit endocarditis), systemic (murine bacteraemia), lung (murine pneumonia) and brain (rabbit meningitis) have demonstrated telavancin's therapeutic efficacy and confirm the bactericidal activity seen in vitro. Telavancin, at doses that approximate telavancin AUC_{0-24} achieved at human therapeutic doses, was efficacious in these models against clinically-relevant Gram-positive pathogens (MSSA, MRSA, glycopeptide intermediate susceptible S. aureus (GISA), MRSE, MSSE, VRE, penicillin-susceptible S. pneumoniae (PSSP) and penicillin-resistant S. pneumoniae (PRSP).

Secondary pharmacodynamic studies

The applicant has argued that due to the action of telavancin against bacterial pathogens secondary pharmacodynamics studies are not required. This is acceptable.

Safety pharmacology programme

In safety pharmacology studies the systemic exposure in the rat was comparable to that in healthy human volunteers at the proposed dose for therapeutic use. Telavancin did not induce any behavioural changes in rats after slow intravenous single injection of doses up to 50 mg/kg. There were no findings indicative of an effect on gastrointestinal function. Respiratory system function was assessed in anaesthetised dogs and showed no changes of biological significance.

In an in vitro cardiovascular safety study involving hERG channels and using HEK293 cells telavancin drug product exerted concentration-dependent inhibition of the hERG potassium ion channel due to the combined effects of HP-β-CD and telavancin. Telavancin itself inhibited hERG channels in CHO and HEK293 cells by 34-51% at clinically relevant concentrations (15 µg/ml).

The results of studies with isolated Purkinje fibres were inconsistent. In dog Purkinje fibres a prolongation of the action potential duration (APD) by 7 to 11% was observed at telavancin concentrations of 50 and 150 µg/ml and a stimulation frequency of 1 Hz. These increases were not dose-dependent and were not observed at 0.5 Hz. In sheep Purkinje fibres paced at a stimulation frequency of 1 Hz exposure to 5, 50, and 150 µg/ml telavancin had no effect on the resting membrane potential, upstroke amplitude or action potential duration.

In a study by Mikhail et al. (2007) it was demonstrated that HP-β-CD had a direct effect on the hERG current in HEK293 cells. There was a reduction in hERG current amplitude (activating and tail currents) and acceleration of tail current deactivation kinetics. In addition, HP-β-CD attenuated the potency of three structurally diverse hERG blockers to different extents. The authors concluded that complex formation may reduce the free drug available for hERG blockade and has nonlinear effects on assay sensitivity. As a result, the degree of hERG blockade may be underestimated by in vitro studies.

The applicant has provided results of an in vitro GLP study employing the Langendorff heart preparation to assess the torsadogenic potential of telavancin in humans. Results have been provided from 2 studies. The applicant has also provided an independent expert assessment of both Langendorff studies as well as the risk for proarrhythmia, in particular, the risk for Torsades des pointes. The drug product does not appear to be associated with experimental evidence of proarrhythmia in the Langendorff model at concentrations up to 12 times the clinical unbound TLV concentration of 5.5 µM (9.7 µg/ml). However, in summary of the whole database on the cardiotoxic potential of telavancin drug product the expert does not explicitly preclude a torsadogenic risk of telavancin drug product. Associated potential risk of pro-arrhythmia has been highlighted in the risk management plan (RMP) and in the SmPC.

In in-vivo cardiovascular safety studies in anaesthetised and conscious dogs telavancin did not elicit changes in heart rate, in systolic, diastolic and mean systemic blood pressures or in any ECG parameters after repeated (4 days) dosing at 100 mg/kg/day by the IV route. The plasma C_{max} after 4 doses of 100 mg/kg in the conscious dog (389 µg/ml) was approximately 4-fold higher than the Cmax in humans at 10 mg/kg/day (97 µg/ml).

Pharmacodynamic drug interactions

Minimum inhibitory concentration checkerboard and synergy time-kill techniques were used to investigate the potential for *in vitro* synergistic/antagonistic interactions with class representative agents normally prescribed for infections caused by Gram-negative bacteria. Synergistic interactions against *S. aureus*, including MRSA strains, were observed with some β-lactam agents, including imipenem. No interactions have been detected with agents that might be co-administered to treat Gram-negative infections. No antagonistic interactions of telavancin were observed with any of the agents tested, including aztreonam, piperacillin/tazobactam, imipenem, cefepime, amikacin, trimethoprim /sulfamethoxazole, ciprofloxacin and rifampicin.

2.3.3. Pharmacokinetics

Telavancin plasma concentration data were assayed using validated sensitive and specific methods including HPLC with UV detection and LC-MS/MS. The absorption profile of telavancin was evaluated in mice, rats, rabbits, dogs and monkeys. Exposure to telavancin increased with increasing dose levels. There was approximate dose-proportionality across the range 6.25 to 50 mg/kg/day but the increases were less than dose-proportional from 50 to 100 mg/kg/day. There were no marked gender differences in exposure. There was no significant difference observed for the pharmacokinetics of HP-ß-CD when administered alone or with telavancin.

Following single doses of 10 mg/kg telavancin (IV bolus injection or infusion) the serum or plasma concentrations of telavancin declined in all species with $t_{1/2}$ ranging from 1.2 hours in mice to 2.3 hours in monkeys. Accumulation of telavancin was observed after multiple dosing in the rat but was not observed in the dog.

Telavancin is highly protein bound with protein binding in mouse (91.0 to 92.7%), rat (92.0 to 92.9%), dog (88.7 to 89.3%) and rabbit (88.3 to 90.3%) comparable to that in human plasma (86.3 to 89.7%). Telavancin protein binding in human serum was mainly associated with albumin.

At 24 hours following single-dose administration of ^{14}C-telavancin to rats and dogs, telavancin associated radioactivity was detected in all tissues examined. The highest concentrations were observed in kidneys and liver (80-and 70-fold higher, respectively, than the plasma concentration in rats; 20-fold higher than the plasma concentration in dogs) and in rats the concentration in bone was 60-fold higher than in plasma. After repeated-dose administration up to 14 days at 100 mg/kg/day in rats, the liver and kidney concentrations of telavancin increased with the number of doses administered and steady state was not reached after 14 doses. Tissue half-lives of telavancin in the rat liver and kidneys were approximately 10.5 days and 14 days, respectively. No apparent gender related differences in distribution were observed.

In the pigmented rat quantitative whole body autoradiography (QWBA) study the highest levels of radioactivity at 168 hours post dose were observed in liver, spleen and kidney and at 336 hours post dose were observed in spleen, adrenal gland and kidney. The half-life estimated for liver and kidney were 4 and 5 days, respectively. The high levels of radioactivity observed in the bone at all time points appeared to be mainly located in the growth plates and also in the bone marrow with an estimated half-life of 332 hours (~14 days). Penetration into the CNS was minimal.

Telavancin might be considered a weak inhibitor of MDR1, with an IC_{50} > 100 µM for the inhibition of digoxin trans-cellular transport mediated by MDR1.

Telavancin was not extensively metabolised in rats, dogs and monkeys after IV administration. Unchanged telavancin was the predominant component in the serum (99, 89 and 94 % of total AUC for rats, dogs and monkeys, respectively) while 7-OH-telavancin (AMI-11352), telavancin des-phosphonate (AMI-999) and other OH-metabolites were identified. Telavancin accounted for more than 60% (dogs) and 86% (monkeys) of the urinary recoveries. AMI-11352 represented about 17% (dogs) and 5% (monkeys) of total urinary recovery while AMI-999 represented about 1.2% (dogs) and 1.8% (monkeys) and other OH-metabolites represented about 17% (dogs) and 6% (monkey). There was no significant gender-related difference observed for metabolism profiles.

Of the three OH-metabolites of the 2-(decylamino) ethyl side chain of telavancin identified in human urine 7-OH-telavancin (AMI-11352) was the most abundant. The plasma AUC of 7-OH-telavancin (which is much less active against bacteria than telavancin) was about 2-3% of the AUC of telavancin and accounted for 50 % of total peak areas of the three hydroxylated metabolites. AMI-11355 (8-OH metabolite) and AMI-11353 (9-OH metabolite) accounted for 24.2% and 25.3% of the total peak areas of the three hydroxylated metabolites, respectively.

Plasma concentrations of AMI-11352 were low in the rat and increases in C_{max} and AUC_{0-24} were less than dose-proportional. Systemic exposure to AMI-11352 was larger in dogs compared to rats. According to the applicant, saturation of the metabolic pathway at higher doses may be anticipated as the AUC_{0-t} metabolite/telavancin ratio decreased at high doses in both rats and dogs. Systemic exposures to telavancin, AMI-999 and AMI-11352 in rats and/or dogs at steady state exceeded human systemic exposure at the proposed clinical dose of 10 mg/kg/day.

Several cytochrome P450 isoenzymes are able to metabolise telavancin to the 7-OH, 8-OH and 9-OH metabolites. The isoenzymes CYP1A1, 1A2, 2B6, 2C18, 2C19, 2D6, 2E1, 2J2, 3A4, 3A5, and 4F12 participate in the metabolism of telavancin in humans. In vitro drug-drug interaction studies in human liver microsomes showed that telavancin was a direct inhibitor of CYP1A2, 2C9, 2C19, 2D6 and 3A4/5 with IC_{50} values of 40 µM, 89 µM, 54 µM, 35 µM, 25 µM and 14 µM, respectively.

The main route of elimination of telavancin in rats and dogs is renal excretion. After a 24-hour sampling period the mean urinary and faecal recoveries were 62% and 4.5% of the total dose, respectively, for rats and 79% and 1% of the total dose, respectively, for dogs. After a 168-hour sampling period the mean urinary and faecal recoveries were 85.19% and 2.6% of the total dose, respectively, for the dog. The applicant has stated that the prolonged elimination half-life in the liver or kidney explains the incomplete radioactivity recovery. In humans, the main route of elimination was also via the kidneys, with the majority of a dose excreted within 48 hours as unchanged telavancin. Excretion into breast milk of telavancin and its metabolites has not been studied.

A study in female rats showed no consistent drug-drug interactions between telavancin and metronidazole or aztreonam. An *in-vitro* interaction study showed that telavancin (at up to 100 µg/ml) did not affect the binding to plasma proteins of other highly bound drugs such as warfarin, salicylic acid and ibuprofen but clinical doses are likely to provide higher plasma concentrations.

2.3.4. Toxicology

Single dose toxicity

Single dose toxicity studies of telavancin drug product were performed in mice and rats via IV bolus injection. The approximate minimum lethal dose in mice was 100 mg/kg for both sexes. The approximate minimum lethal dose in rats was 100 mg/kg for males and above 150 mg/kg for females.

Repeat dose toxicity

The toxicity after repeated intravenous infusion of telavancin drug product was investigated for up to 3 months in dogs and for up to 6 months in rats (table 1). A chronic non-rodent study (9 months) was not conducted in view of the short treatment duration in humans (up to 21 days).

Table 5: Overview of rat and dog repeated dose toxicity studies

Species	Study Type/Duration	Time of Intravenous Infusion	Dose	Report No	GLP
Rat					
	2-week	2 hours	diluent control, vehicle control, 6.25, 12.5, 25 mg/kg/day	01-001-09	Y
	4-week 4-week Recovery	30 minutes	diluent control, vehicle control, 12.5, 25, 50 mg/kg/day	02-001-01	Y
	13-week 4-week Recovery	30 minutes	diluent control, vehicle control, 12.5, 50, 100 mg/kg/day	02-001-06	Y
	26-week 4-week Recovery	30 minutes	diluent control, vehicle control 6.25, 12.5, 50 mg/kg/day	03-001-07	Y
Dog					
	2- week	2 hours	diluent control, vehicle control, 6.25, 12.5, 25 mg/kg/day	01-001-10	Y
	4-week 4-week Recovery	30 minutes	diluent control, vehicle control, 12.5, 25, 50 mg/kg/day	02-003-01	Y
	13-week 4-week Recovery	1 hour	diluent control, vehicle control, 12.5, 25, 100 mg/kg/day	02-003-05	Y

Diluent control: 4% or 5% dextrose; vehicle: HP-ß-CD at levels that were equivalent to the amount of HP-ß-CD present in the high dose; (fixed ratio 10:1; HP-ß-CD:telavancin); Concentrations of infusion solution (high dose): 25 mg/kg/day: 5 mg/mL; 50 mg/kg/day: 10 mg/mL; 100 mg/kg/day: 10 mg/mL;

Deaths occurred in all rat studies and in the 13-week dog study, at all doses, including the vehicle control. The applicant considered that the deaths were not attributable to treatment with the

telavancin drug product; instead the deaths and the unscheduled sacrifice of moribund animals were caused by catheter related problems.

Target organs of toxicity

There were histopathological changes that suggested toxic effects on the rat and dog kidney. These changes (e.g. renal cortical/proximal tubular degeneration/necrosis, renal cortical tubular vacuolation and necrosis, vacuolation of the renal pelvic and urinary bladder urothelia) were found in almost all telavancin treatment groups and also with hydroxypropylbetadex (HP-ß-CD) administered alone as documented in the literature. With increasing treatment duration there was increased damage apparent in the rat and dog 4-week studies. Most of these histopathological changes were not reversible during the recovery period (4 weeks).

The proposed NOAEL for nephrotoxic effects was 12.5 mg/kg/day for rats and 25 mg/kg/day for dogs. These doses result in exposures (on the basis of the AUC values) that are lower than the human exposure at the recommended clinical dose of 10 mg/kg/day. However, since there was a gradual increase in the severity of the renal changes with the duration of treatment it is expected that the risk of significant or irreversible renal damage during treatment of patients for a maximum of 3 weeks would be limited.

The incidence of the renal observations as well as the severity of the observed changes decreases with increasing ratios of HP-ß-CD to telavancin.

To further substantiate the findings that a formulation of telavancin and HP-ß-CD at a ratio of 1:10 is less toxic than formulations with lower ratios, and to investigate to what extent altered pharmacokinetic parameters and/or an enhanced excretion of telavancin are the reasons for these findings, the applicant has provided results of an additional GLP-compliant 4-week repeated dose study. The results show that the 1:10 ratio (TLV:CD) induces a lower level of renal toxicity than a ratio of 1:4 and 1:2. At a ratio of 1:20 the incidence and severity of the renal histopathological changes were further reduced. Although microscopical alterations associated with the cyclodextrin component (increased diffuse renal cortical tubular vacuolation, urinary bladder urothelial cell vacuolation) animals given TLV:CD 1:20 showed a reduction in the toxic effects seen at a TLV:CD ratio of 1:2 and 1:4, which was observed as a reduction in the increases in urea nitrogen and creatinine concentrations, renal proximal tubular degeneration, tubular basophilia, dilation and casts, and body weight loss.

The concentrations of TLV in the plasma and the kidney decrease with increasing ratios of CD to TLV, while the urinary excretion increases. CD itself accumulates in the kidney, where it is associated with tubular vacuolation without functional changes. When balancing the effects of TLV and CD, the ratio of 1:10 would be the optimal choice, protecting the kidney while limiting the CD accumulation in the renal tubules.

There were also histopathological changes that suggested toxic effects on the rat and dog liver. With increasing treatment duration there was increased damage apparent in the rat and dog 4-week studies. Hepatocellular damage and necrosis were found in 13-week studies in the mid-dose and high-dose groups of rats and in the high-dose group of dogs. At the end of the 4-week recovery period there was good evidence of reversibility with elevations in ALT and AST returning to or near control values and signs of hepatocellular regeneration.

The proposed NOAEL for hepatotoxic effects was 12.5 mg/kg/day for rats and 25 mg/kg/day for dogs. These doses result in exposures (on the basis of the AUC values) that are lower than the human exposure at the recommended clinical dose of 10 mg/kg/day. However, given that there is a gradual increase in the severity of the changes with the duration of treatment the risk of significant or

irreversible liver damage during treatment for up to 3 weeks (as according to the SmPC) is considered to be limited.

In the clinical studies in complicated skin and soft tissue infection (cSSTI) and nosocomial pneumonia (NP), the incidences of hepatic-related adverse events and increases in liver enzyme parameters were low and similar across treatment groups. A statement regarding heptotoxicity is included in section 5.3 of the proposed SmPC.

There was vacuolation of the epididymal tubular epithelium with treatment durations of 13 weeks and longer in rats and dogs. The effect occurred in all treatment groups (HP-ß-CD and telavancin) with a tendency to higher incidence/severity in the telavancin treatment groups and there was no evidence of reversibility following the 28-day recovery period. Seminiferous tubular degeneration was seen in the mid-dose HP-ß-CD group in the 13-week study in rats and to a greater extent in the high-dose telavancin group (see below regarding effects on sperm).

Immunomodulatory effects were produced by HP-ß-CD and by telavancin at doses of 50 and 100 mg/kg. HP-ß-CD induced systemic macrophage hypertrophy/hyperplasia in rats and dogs and pulmonary alveolar histiocytosis in rats but the severity and incidence of the effects were greater in the telavancin treated groups. Macrophages were considered to maintain their function since they responded to stimuli with an increased respiratory burst. The effects were regarded by the applicant as small and evidence of reversibility was seen. The NOAEL for these effects was 12.5 mg/kg/day.

Genotoxicity

Telavancin was considered not to be genotoxic in a standard battery of in vitro and in vivo assays. The exposure level for the clastogenicity study was not determined but may be inferred from the results of standard ADME studies. Based on data from a PK/PD study in mice a dose of 50 mg/kg was estimated to provide an approximate AUC_{0-t} of 600 µg.hr/ml, which is similar to human exposure at the proposed clinical dose of 10 mg/kg/day.

Carcinogenicity

Treatment of telavancin is expected to be up to 21 days and the need for carcinogenicity testing is only required for drugs administered for at least 6 months. Therefore the omission of carcinogenicity testing is acceptable.

Reproduction Toxicity

In studies on potential effects on fertility and early embryonic development, telavancin was administered IV to male rats up to 100 mg/kg and to females up to 150 mg/kg. There were no effects attributed to HP-β-CD in any of the tested species. General toxic effects (pale kidneys, decrease in body weight gain and food consumption) were observed for females and/or males at all dose levels including vehicle controls. Therefore no NOEL could be established for general toxicity.

In the female fertility study there were no compound-related effects on the oestrous cycle, pregnancy rates, and foetal viability at time of caesarean section or live foetuses in any of the dose groups. In addition, there were no effects on the numbers of corpora lutea, implantation sites, resorptions or rates of pre- or post-implantation loss.

In males there was a decrease in sperm motility and epididymal sperm counts and an increase in abnormal sperm. In a 6-week study there was no evidence of testicular degeneration but findings related to gonadal toxicity included reversible sloughed testicular germ cells in the epididymis and

vacuolated macrophages (in vehicle, 50 and 100 mg/kg/day groups) as well as epididymal epithelial vacuolation after recovery (in vehicle and 100 mg/kg/day groups). Telavancin may have the potential to affect male fertility in humans.

The NOEL for effects on fertility indices (embryo-foetal viability) was 150 mg/kg for females and 100 mg/kg for males. From the follow-up gonadal study the NOEL for effects on the male reproductive system was judged to be 25 mg/kg/day.

In the embryo-foetal development studies there were effects on digit formation and limb formation in rats, rabbits and mini-pigs. The NOEL for developmental embryo-foetal toxicity was stated as 150 mg/kg by the applicant but skeletal malformations and decreased foetal weight were seen from 100 mg/kg and consequently the assessor considers the NOEL to be 50 mg/kg. A similar finding occurred in the rabbit with evidence of skeletal variations (ossification delays), increases in dams with non-viable foetuses and visceral variations (dilatation of lateral ventricles) but no NOEL could be established. It was concluded from these data that telavancin has a potential to induce skeletal malformations and therefore has teratogenic potential, with implications for the SmPC.

A study of pre-and postnatal development including maternal function in rats showed a compound-related increase in the number of stillborn pups and a dose-dependent effect of telavancin on F_1 pup viability. There were no treatment-related necropsy observations in F_1 pups. The NOAEL for maternal (F_0) effects was judged to be 50 mg/kg/day. Based on the increase in stillborn-pups and pup clinical findings, the NOAEL for F1 pup development and viability was not established. The NOAEL for motor activity, learning /memory and reproductive parameters of the F_1 offspring was estimated at 150 mg/kg/day.

Since telavancin is not currently proposed for use in paediatric patients the omission of studies in juvenile animals is currently acceptable.

Local Tolerance

Local tolerance tests of telavancin and HP-β-CD have shown that the drug product can be classified as non-irritant to the eye and skin. Injection site reactions were apparent in the vascular irritation study following repeated dosing with 10 mg/kg and these were slightly more severe in the telavancin-treated rabbit ears when compared to the diluent control.

Other toxicity studies

Telavancin did not exhibit cytotoxic activity in Balb/c mouse fibroblasts in the presence or absence of UVA exposure and was considered to have no phototoxic potential.

The data from repeated-dose toxicity studies and the in vivo micronucleus test in mice have been used to qualify the related substances and to set the limits in the drug substance and drug product specifications. Based on the applicant's calculations of dose and exposure in the mouse micronucleus study, a suitable justification has been provided for the proposed specifications with the exception of that for degradant B at end of shelf-life in the drug product. Further justification for the finished product shelf-life specification of NMT 3.0% for Degradant B has been provided, based on the levels in batch 888895 used in the 4-week intravenous study (Study 7668-219). This degradant is now considered to have been adequately justified by the applicant.

The applicant provided a tabulated overview of test substance batches used in all toxicology studies. The specification of batches has changed over the course of the development of the product and there appears to be some discrepancies within the dossier regarding the proposed drug substance

specification. There also appears to be a greater number of specified impurities in the currently proposed drug substance specification than have been included in the toxicology batches.

The impurity profile for batch 888895 used in the 4-week intravenous study (Study 7668-219, 9809-TX-0004) has been provided. Impurity profile for batches used in the toxicology studies was provided along with the calculated qualification levels for each detected impurity in the drug substance.

The applicant has provided a detailed discussion in relation to the limits for impurities at Peak 31B and Peak 32. As has been agreed, the applicant's approach to combine the specification for Peaks 31B and 32 together as a sum (NMT 1.4%) is acceptable. The qualified level in humans for Peaks 31B/32 is 1.38% and this is in line with the new proposed specification.

AMI-999 (telavancin des-phosphonate) has been identified as an impurity produced during the manufacture of telavancin drug substance. Studies to examine the nephrotoxic potential of AMI-999 were undertaken and showed that doses of 50 mg/kg resulted in minimal to marked increases in ALT and AST and increases in BUN and creatinine in association with renal tubular necrosis. These findings were comparable to those seen with telavancin itself.

Telavancin drug product did not induce haemolysis in rat, dog and human whole blood at final concentrations up to 5 mg/ml. Telavancin had no effect on platelet aggregation in vitro up to a final concentration of 200 µg/ml. Several exploratory in vitro studies showed that telavancin interferes with common laboratory tests used to monitor coagulation, such PT and APTT. Telavancin was shown to have no effect on the ability to measure heparin concentrations but interfered with the Heptest, which uses a coagulation endpoint.

HP-ß-CD has been comprehensively investigated for its toxicological properties and the applicant presented a review on the excipient HP-ß-CD using literature information with an adequate discussion of the potential effects on patients of HP-ß-CD in combination with telavancin.

2.3.5. Ecotoxicity/environmental risk assessment

In the Phase I estimation of exposure for telavancin, the $PEC_{surfacewater}$ was above 0.01 µg/l. A Phase II, Tier A assessment (as per EMEA/CHMP/SWP/4447/00 Guideline) was carried out. Three metabolites of telavancin have been identified and are all derivatives of the ethyl side chain of telavancin. The applicant has stated that neither of these metabolites was present at >10% of the dose. This argumentation is acceptable and further refinement of the ERA based on total approach assuming that 100% of excreted material is unchanged telavancin was deemed possible.

The applicant has further refined the PEC in Tier B, by using the information from activated sludge in the adsorption/desorption study to calculate the level of telavancin in the aqueous phase and in sludge. Using the refined data in the SimpleTreat model including estimation of STP parameters, the Expert presents a refined PECsurfacewater of 0.922 µg/L, and a subsequently lower ratio of PECsurface water/PNECsurface water of 0.58. The argumentation for the refined ratio is acceptable and it is agreed that further evaluation on the fate of the drug substance in the aquatic environment is not needed. It was also agreed that further analysis of the cyclised form of telavancin would not be necessary.

2.3.6. Discussion on non-clinical aspects

The primary pharmacology of telavancin has been adequately characterised. It is a semi-synthetic derivative of vancomycin that has a lipophilic side chain attached to the vancosamine constituent that confers not only the expected inhibition of bacterial cell wall synthesis but also an antibacterial effect

resulting from interaction with the bacterial cell membrane to disrupt membrane potential and permeability.

The safety pharmacology programme addressed the cardiotoxic potential of telavancin drug product.

In vivo studies in anesthetised and conscious dogs failed to detect an effect on cardiac repolarisation and no effect was observed in sheep Purkinje fibres. However, two of the *in vitro* assays suggested that a prolongation of the QTc interval in man may be possible. This was further explored in a QTc clinical study (see further). The overall conclusion is that a torsadogenic risk of telavancin drug product cannot be precluded.

The liver, kidney, macrophages and testis were identified as target organs of toxicity in animals.

In the liver, treatment for 13 weeks or longer resulted in reversible degeneration/necrosis of hepatocytes accompanied by elevations in serum AST and ALT in rats and dogs.

Effects on the kidney occurred after a minimum of 4 weeks of dosing and were a combination of renal tubular injury and tubular epithelial vacuolisation. The tubular injury was characterised by degeneration and necrosis of proximal tubular cells, and was associated with increases in BUN and creatinine that reach a maximum of 2 times the control values at the highest doses. The tubular injury was reversible, but not all animals had yet reached full recovery 4 weeks after the end of treatment.

Vacuolisation of tubular epithelium was a common observation in animals treated with the telavancin medicinal product and with the vehicle (HP-β-CD). At higher doses or longer treatment durations, vacuolisation of the urothelium in the bladder also occurred. Vacuolisation was not associated with renal function impairment, but was not reversible after 4 weeks of recovery. Vacuolisation is considered to represent a cytoprotective event and is expected to reverse with the same half-life as the turnover time of the proximal tubular cells. The presence of hydroxypropylbetadex in the formulation at a ratio of 1:10 reduces the incidence and severity of the changes due to telavancin and attenuates the glycopeptides-like toxicity of telavancin.

Systemic macrophage hypertrophy and hyperplasia occurred in rats and dogs, in many organ systems that normally contain macrophages. The macrophages were shown to contain telavancin and HP-β-CD.

In rats and dogs vacuolisation of the epididymal tubular epithelium cells was also noted, and this finding did not show reversibility after a recovery period of 4 weeks. Vacuolisation is considered to be a cytoprotective event, which is not associated with functional impairment.

In embryo-foetal development studies malformations of digits and limbs were observed in rats, rabbits and mini-pigs. In the rat embryo-foetal development study dilatation of lateral ventricles of the brain was observed in the high dose group. An increase in the number of stillborn pups was observed in these pre- and post-natal studies.

2.3.2. Conclusion on the non-clinical aspects

The primary pharmacology of telavancin has been adequately characterised.

The safety pharmacology profile cannot preclude a torsadogenic risk of telavancin drug product. Also, studies in animals have shown reproductive toxicity. Appropriate warnings are added to the SmPC and these safety concerns are included in the Risk Management Plan (RMP) of Vibativ.

The major preclinical toxicity observed relates to the effects on the kidney.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

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

2.4.2. Pharmacokinetics

Telavancin PK was evaluated in 12 studies involving 365 healthy adult volunteers, 23 adult subjects with various degrees of renal impairment and 8 adult subjects with hepatic impairment. Of these, 292 received one or more doses of telavancin. A lyophilised product identical to the final formulation was used in part 2 of the first PK study and in all other clinical studies. Population PK data were also obtained during clinical efficacy studies.

The method for determination of telavancin (free base), the major metabolite AMI-11352 (7-OH telavancin) and the impurity AMI-999 employed liquid chromatography (LC) with a C8 or a C18 column and gradient elution. Detection was by positive ion electrospray (ESI+), tandem mass spectrometry (MS/MS). The assay range for telavancin was 0.25 – 100 mg/L in plasma and 1-1000 mg/L in urine.

Single doses of 0.25 – 12.5 mg/kg were infused over 120 min in healthy male subjects followed by 12.5 mg/kg over 30 and 60 min and 15 mg/kg dose over 30 min. There was dose proportionality of Cmax and AUC in the dose range 5 to 12.5 mg/kg. Mean $t_{1/2}$ ranged between 6.9 and 7.9 h at doses between 5-15 mg/kg and CL was nearly constant (11.3 – 11.9 ml/h/kg) at doses of 5 mg/kg and higher. Mean V_{ss} appeared to be independent of dose and varied between 93.5 and 116 ml/kg. Reducing the infusion period to 60 min had only limited effects while reduction to 30 min increased C_{max}.

Doses of 7.5, 12.5 and 15 mg/kg were infused once daily over 30 min for 7 days. Telavancin PK was linear after the first and last doses. C_{max} was slightly increased and AUC slightly decreased on day 7 vs. day 1 at 2/3 dose levels. Mean t1/2 showed a modest increase on day but there was no consistent trend in mean CL and V_{ss} tended to be higher on day 7.

Table 6: Summary of single and multiple dose PK of telavancin administered over 30 min (part 2)

Dose (mg/kg)	C_{max} (µg/ml)		AUC* (µg.h/ml)		$t_{1/2}$ (h)		CL (ml/h/kg)		V_{ss} (ml/kg)		Excretion (%)
	FD	LD	FD	LD	FD	LD	FD	LD	FD	LD	LD
7.5 (N = 7!)	90.3 (10.7, 12%)	96.7 (19.8, 20%)	668 (137, 21%)	700 (114, 16%)	7.86 (0.90, 11%)	8.83 (1.71, 19%)	11.6 (2.3, 20%)	10.9 (1.6, 15%)	113 (14, 12%)	124 (26, 21%)	68.3 (27.0, 40%)
12.5 (N = 6)	155 (24, 15%)	151 (17, 11%)	1013 (118, 12%)	1033 (91, 9%)	7.26 (1.22, 17%)	9.11 (2.33, 26%)	12.5 (1.5, 12%)	12.2 (1.1, 9%)	121 (14, 12%)	141 (31, 22%)	61.0 (15.8, 26%)
15.0 (N = 7+)	181 (35, 19%)	203 (29, 14%)	1239 (144, 12%)	1165 (232, 20%)	7.33 (0.97, 13%)	8.78 (1.46, 17%)	12.5 (1.7, 14%)	13.3 (2.6, 20%)	117 (18, 15%)	146 (16, 11%)	60.1 (24.4, 41%)

* AUC = AUC_{inf} after the first dose (FD) and AUC_{tau} after the last dose (LD)
! Results of day 7 based on 6 subjects
+ Results of day 7 based on 4 subjects
Values of PK parameters are mean (SD, CV%).

With mean renal clearance (CLR) between 8.3 and 10.2 ml/h/kg and assuming body weight 75 kg and 90% plasma protein binding the unbound renal clearance was estimated to be 6.2 – 7.7 l/h i.e. close to the glomerular filtration rate (7.5 l/h), suggesting that glomerular filtration is the domination excretion mechanism but the data cannot exclude the possibility that active secretion is involved, which is compensated by re-absorption.

PK telavancin was also compared between Caucasian subjects who received telavancin 10 mg/kg daily for 7 days and 16 Japanese subjects who received either 7.5 mg/kg or 10 mg/kg daily doses. Mean $t_{1/2}$, CL and Vss were similar after single and multiple dosing. Mean CLR of telavancin was not affected by dose, treatment duration or race.

Table 7: Summary of telavancin PK in plasma at a dose of 7.5 and 10 mg/kg

Group Treatment	C_{max} (µg/ml)		AUC_{last} (µg.h/ml)		AUC* (µg.h/ml)		$t_{1/2}$ (h)		CL (ml/h/kg)		V_{ss} (ml/kg)	
	FD	LD	FD	LD	FD	LD	FD	LD	FD	LD	FD	LD
Japanese 7.5 mg/kg	69.1 (2.3, 3%)	73.8 (3.7, 5%)	573 (126, 22%)	NA	582 (126, 22%)	581 (127, 22%)	6.05 (0.73, 12%)	6.89 (1.60, 23%)	13.5 (3.2, 23%)	13.5 (3.2, 24%)	112 (12, 11%)	127 (12, 9%)
Japanese 10 mg/kg	84.4 (8.8, 10%)	88.4 (9.0, 10%)	610 (104, 17%)	NA	619 (104, 17%)	686 (99, 14%)	6.28 (0.85, 14%)	7.43 (1.39, 19%)	16.5 (2.6, 13%)	14.8 (2.1, 14%)	142 (14, 10%)	150 (19, 13%)
Caucasians 10 mg/kg	93.6 (15.8, 17%)	104 (14, 13%)	686 (86, 13%)	NA	694 (86, 12%)	710 (76, 11%)	6.34 (1.05, 17%)	6.79 (0.92, 14%)	14.6 (1.7, 12%)	14.2 (1.6, 11%)	126 (12, 10%)	146 (22, 15%)

Values of PK parameters are mean (SD, CV%), N = 8 for all groups at the first dose; N = 7, 8, 7 for Japanese 7.5 mg/kg, Japanese 10 mg/kg, and Caucasians 10 mg/kg, respectively, after the last dose
* AUC = AUC_{inf} after the first dose, AUC_{tau} after the last dose

The amount excreted in urine was about 80% of the dose in Japanese subjects and was about 10% lower in Caucasian subjects. There were no indications of dose or duration of treatment effects.

Table 8: Summary of telavancin PK in urine at a dose of 7.5 and 10 mg/kg

Group Treatment	CL_R (ml/h/kg)		Amount excreted* (mg)		Amount excreted* (% of dose)	
	FD	LD	FD	LD	FD	LD
Japanese 7.5 mg/kg	11.5 (2.0, 17%)	11.3 (3.3, 29%)	437 (17, 4%)	447 (139, 31%)	81.8 (4.3, 5%)	85.1 (20.7, 24%)
Japanese 10 mg/kg	13.3 (3.0, 14%)	11.0 (3.4, 31%)	546 (75, 14%)	485 (144, 30%)	81.6 (10.6, 13%)	74.5 (20.3, 27%)
Caucasians 10 mg/kg	9.63 (1.51, 16%)	10.2 (3.0, 29%)	527 (144, 27%)	561 (97, 17%)	65.6 (11.0, 17%)	70.7 (13.7, 19%)

Values of PK parameters are mean (SD). N = 3, 7, 8 for Japanese 7.5 mg/kg, Japanese 10 mg/kg, and Caucasians 10 mg/kg, respectively, after the first dose; N = 6, 7, 7 for Japanese 7.5 mg/kg, Japanese 10 mg/kg, and Caucasians 10 mg/kg, respectively, after the last dose

* Amount excreted up to the last quantifiable sample after the first dose; over a dosing interval after the last dose

In a mass balance study (10 mg/kg ^{14}C-telavancin over 60 min) plasma concentrations of telavancin and radioactivity were comparable during the first 24 h, after which the concentration of radioactivity started to decline more slowly than the telavancin concentration. Plasma concentration of radioactivity was about twice as high as blood concentration, indicating limited distribution to blood cells. Over 216 h, 76.3% of radioactivity was excreted in urine but < 1% in faeces. The largest part was excreted during the first 48 h. About 82.3% of the radioactivity excreted in urine was unchanged telavancin (60.4% of the administered dose over the first 48 h). However, approximately 20% of the dose was still not recovered after 216 h.

Table 9: Summary of single dose PK of telavancin and ^{14}C radioactivity in plasma and blood at a dose of 10 mg/kg

Matrix, Analyte	t_{max} (h)	C_{max} (µg/ml)	AUC_{last} (µg.h/ml)	AUC_{inf} (µg.h/ml)	$t_{1/2}$ (h)	CL (ml/h/kg)	V_{ss} (ml/kg)
Plasma, telavancin (N = 6)	1.00 (0.00)	93.6 (10.2, 11%)	620 (125, 20%)	649 (103, 16%)	7.08 (0.50, 7%)	15.7 (2.5, 16%)	150 (19, 13%)
Plasma, radioactivity (N = 6)	1.00 (0.00)	89.6 (11.8, 13%)	764 (119, 16%)	827 (120, 15%)	94.2 (17.8, 19%)	12.3 (1.8, 15%)	478 (102, 21%)
Blood, radioactivity (N = 6)	1.00 (0.00)	43.7 (7.0, 16%)	371 (67, 18%)	396 (56, 14%)	9.89 (1.21, 12%)	25.7 (3.8, 15%)	301 (28, 9%)

Values of PK parameters are mean (SD, CV%)

Table 10: Summary of excretion kinetics of telavancin and ^{14}C radioactivity in urine and faeces at a dose of 10mg/kg

Matrix, Analyte	CL_R (ml/h/kg)	Excreted over 48 h (% of dose)	Excreted over 216 h (% of dose)
Urine, telavancin (N = 6)	9.00 (1.32, 15%)	60.4 (7.2, 12%)	Not available
Urine, radioactivity (N = 6)	Not available	73.2 (3.8, 5%)	76.3 (3.6, 5%)
Feces, radioactivity (N = 6)	Not available	0.1 (0.1, 100%)	0.7 (0.2, 29%)

Values of PK parameters are mean (SD, CV%)

Concentrations of the metabolite AMI-11352 and the impurity AMI-999 in plasma were substantially lower compared with telavancin in the mass balance and in other studies in which they were measured. The plasma concentration-time profile of AMI-999 appeared to follow that of telavancin and dropped below LOQ at 12 to 24 h. A flat profile was observed for AMI-11352, for which plasma concentrations were mostly quantifiable only up to 24 h and at most up to 48 h.

Table 11: Summary of single dose PK of AMI-11352 and AMI-999 in plasma at a dose of telavancin 10mg/kg

AMI-11352				AMI-999			
t_{max} (h)	C_{max} (µg/ml)	AUC_{last} (µg.h/ml)	AUC ratio AMI-11352/TLV	t_{max} (h)	C_{max} (µg/ml)	AUC_{last} (µg.h/ml)	AUC ratio AMI-999/TLV
13.8 (8.5)	0.493 (0.107, 22%)	11.6 (6.2, 53%)	0.0185 (0.0068, 37%)	1.00 (0.00)	1.26 (0.14, 11%)	8.49 (2.81, 33%)	0.0136 (0.0029, 21%)

Values of PK parameters are mean (SD, CV%), except for t_{max} [mean (SD)] TLV = telavancin

Although there was no appreciable accumulation of telavancin in plasma on dosing healthy subjects for 7 consecutive days the non-clinical data indicated that accumulation might occur during multiple dosing in several organs and the mass balance study showed that approximately 20% of the dose was still not recovered after 216 h. This raised a theoretical concern that telavancin might accumulate in and have an adverse effect on macrophage function.

Maintenance of functional activity of macrophages was demonstrated by examining the intracellular activity of TLV/CD against *Staphylococcus aureus* in human THP-1 macrophages. No effects on macrophage viability were noted for TLV/CD at concentrations up to 150 µg/ml, a concentration that is approximately 15-fold greater than the observed free plasma concentration in humans at the clinical dose of 10 mg/kg. An increase in phagocytosis but maintenance of respiratory burst after stimulation was not thought likely to cause clinically relevant alterations in phagocyte function.

An *in-vitro* study indicated that P-gp is not a transporter of telavancin but showed that telavancin may act as a weak inhibitor of digoxin transport (IC50 > 100 µmol/l = 175.56 µg/ml). Telavancin binding to plasma proteins (mostly albumin and α-1 acid glycoprotein) varied between 86.3% and 89.7% in the concentration range of 1 – 100 µg/ml. At 100 µg/ml telavancin there were no effects on the binding of other highly bound drugs (warfarin, salicylic acid and ibuprofen) *in vitro*. Overall it was concluded that

telavancin is not likely to interact with other medications as a result of effects on P-gp or protein binding.

CYP 1A1, 1A2, 2B6, 2C18, 2C19, 2D6, 2E1, 2J2, 3A4, 3A5 and 4F12 were all found to be able to metabolise telavancin, involving hydroxylation at the 7, 8 and 9 position of the 2-(decylamino)ethyl side chain. The metabolite AMI-11352 (7-OH-telavancin) is the most abundant.

In-vitro drug-drug interaction studies with human liver microsomes indicated that telavancin has the potential to inhibit several CYP450 isoenzymes and especially CYP3A4/5 with an IC50 of 25 µM (45 µg/ml) measured by testosterone 6β-hydroxylation and 14 µM (25 µg/ml) measured by midazolam 1'-hydroxylation). IC50 values for CYP1A2, CYP2C9, CYP2C19 and CYP2D6 were 40, 89, 54 and 35 µM respectively. In a clinical drug-drug interaction study the administration of telavancin 10 mg/kg daily for 7 days had no effect on the PK of midazolam or 1'-hydroxy midazolam following an IV bolus of 1 mg midazolam after the last infusion. Overall it appeared that telavancin has a low potential to cause clinically meaningful interactions with substrates of CYP450 isoenzymes.

The potential for telavancin to affect the PK of aztreonam and piptazobactam, which depend on urinary excretion for their elimination, and *vice versa* was evaluated in a study in which a dose of telavancin (10 mg/kg over 60 min) was followed by aztreonam (2 g) or piptazobactam (4g/0.5 g) after a 30 minute interval. The PK of telavancin was not affected by aztreonam or piptazobactam and the PK of piptazobactam was not affected by telavancin. There was a small effect of telavancin on the Cmax (90% CI 0.989 – 1.28%) but not AUC of aztreonam that was not considered likely to be of clinical relevance.

In an initial study of PK in renal impairment the administration of a single dose of telavancin (7.5 mg/kg) showed that the telavancin AUC and $t_{1/2}$ increased, CL decreased and C_{max} and V_{ss} were not affected by decreasing renal function. These data plus modelling were used to support the dose modifications for subjects with moderate and severe renal impairment that were used in the Phase 3 efficacy studies when using a routine dose of 10 mg/kg telavancin daily. In this same study:

- Haemodialysis over 4 h removed 5.9% of a dose of telavancin giving an estimated CL of 0.27 l/h. In ESRD subjects CL was 0.61 l/h, so with haemodialysis CL could result in 0.88 l/h (44% increase). In-vitro data indicated that CVVH could efficiently remove telavancin from plasma depending on the type of filter used (CL 5 – 31 l/h). Also, it was established that CVVHD could achieve CL between 4.6 and 10 l/h with AN69 filters and similar CL to CVVH using polysulfone filters.
- The AUC0-48h of 7-OH telavancin (AMI-11352) was 3% of that for telavancin in subjects with normal renal function but increased to 21.5% in subjects with ESRD. Exposure to AMI-999 was low and did not increase with decreasing renal function.

In response to the initial list of questions the applicant provided simulations for dosing in severe renal impairment using reduced daily doses between 5 and 7.5 mg/kg/day vs. 10 mg/kg/2 days (as used in Phase 3 studies). Results showed that 10 mg/kg/2 days gave higher plasma concentrations on the first day but lower concentrations on the second day vs. dosing in those with normal renal function. A daily dose of 5.5 – 6.0 mg/kg gave a daily AUC that was comparable with that in subjects with normal renal function.

In follow-up to these simulations the applicant reported on a study completed during the Marketing Authorisation application procedure in which further data were obtained in subjects with renal impairment who were given a single dose of 10 mg/kg. The table below shows the TLV PK adjusted for the slight under-dosing due to residual fluid in the infusion set. Exposure in the subjects with severe

renal insufficiency was just short of 3-fold higher compared to those with normal renal function and about 1.5-fold that in subjects with moderate renal impairment.

Table 12: Summary Statistics of Dose Corrected Telavancin Plasma and Urine PK Parameters

Parameter Statistic	Normal renal function	Mild renal impairment	Moderate renal impairment	Severe renal impairment
C_{max} (10 mg) (ng/ml)				
Mean (SD, CV)* Min-Max Median N	85616 (10165, 12%) 65088 – 102680 87041 14	83812 (9133, 11%) 66035 – 96025 84674 13	90049 (4804, 5%) 82115 – 96692 89103 7	94081 (15605, 17%) 69943 – 115643 98091 8
AUC_{last} (10 mg) (ng.h/ml)				
Mean (SD, CV)* Min-Max Median N	596775 (112232, 19%) 408112 – 830563 595518 14	676778 (147052, 22%) 479905 – 1002411 676750 13	1075456 (198665, 18%) 895459 – 1499105 1035807 7	1554114 (2[illegible]0, 19%) 117[illegible] – 1951626 1588833 8
AUC_{inf} (10 mg) (ng.h/ml)				
Mean (SD, CV)* Min-Max Median N	600839 (111497, 19%) 411237 – 833749 596974 14	682412 (149887, 22%) 483704 – 1007623 681728 13	1078663 (200540, [illegible]%) 896788 – [illegible]06110 [illegible]89 7	1574669 (315507, 20%) 1181427 – 2048923 1592166 8
Ae_{last} (10 mg) (mg)				
Mean (SD, CV)* Min-Max Median N	436 (91, 21) 281 – 558 451 14	397 (100, 25%) 275 – 595 364 13	368 (91, 25%) 230 – 519 373 8	207 (62, 30%) 139 – 279 206 8
Ae_{inf} (10 mg) (mg)				
Mean (SD, CV)* Min-Max Median N	435 (91, 21%) 279 – 557 449 14	396 (100, 25%) 271 – 592 371 13	375 (96, 26%) 228 – 519 372 7	208 (60, 29%) 139 – 277 209 8

The dose-corrected plasma levels of the metabolite and the impurity also showed increases in plasma exposures with decreasing renal function and a pattern vs. TLV that was similar to that observed in the first study. On the basis also of these additional data the applicant modified the proposal for dosing in severe renal impairment to a daily dose at 5 mg/kg (Note: not further applicable considering that the final SmPC proposal excludes this group of patients).

Hydroxypropylbetadex (HP-ß-CD; in the formulation as a solubiliser in a 10:1 ratio to telavancin) is renally excreted with a shorter t1/2 than telavancin (2 – 3 h vs. 8 h) and therefore higher urinary concentrations would be expected, with a potential to reform HP-ß-CD – telavancin complexes. The role of HP-ß-CD in Vibativ and its potential to exert some nephroprotective effect were further explored as described in the Toxicology section (non-clinical aspects). It was concluded that on administering TLV/CD the majority of the renal histopathological effects appear to be mediated by cyclodextrane (CD).

In the first study in renal impairment plasma exposure to hydroxypropylbetadex (HP-ß-CD) was higher than to free telavancin even in subjects with normal renal function. An increase in exposure with decreasing renal function was observed so that in subjects with ESRD there was a 9-fold increase in

AUCinf compared with subjects with normal renal function. HP-ß-CD was effectively cleared by haemodialysis but removal by CVVH gave even higher CL (13-100 l/h). No data on the removal of HP-ß-CD by CVVHD were available.

The data obtained on plasma exposure in the second study (after a single dose of 10 mg/kg telavancin) followed the same pattern as in the first and were as follows:

Table 13: Summary Statistics of Dose Corrected HP-β-CD Plasma and Urine PK Parameters

Parameter Statistic	Normal renal function	Mild renal impairment	Moderate renal impairment	Severe renal impairment
C_{max} (10 mg) (µg/ml)				
Mean	431	415	521	541
(SD, CV)*	(57, 13%)	(49, 12%)	(61, 12%)	(67, [illegible]%)
Min-Max	301 – 535	354 – 512	443 – 623	[illegible] – 660
Median	431	426	519	[illegible]
N	14	13	8	8
AUC_{last} (10 mg) (µg.h/ml)				
Mean	1056	1191	2793	7038
(SD, CV)*	(217, 21%)	(300, 25%)	(1009, 36%)	(1680, 24%)
Min-Max	643 – 1581	834 – 1936	1909 – 4961	4965 – 10182
Median	1034	1117	252[illegible]	6560
N	14	13	[illegible]	8
AUC_{inf} (10 mg) (µg.h/ml)				
Mean	1082	1221	2877	7162
(SD, CV)*	(219, 20%)	(310, 25%)	(1029, 36%)	(1699, 24%)
Min-Max	664 – 1603	855 – 1988	1985 – 5089	5053 – 10313
Median	1054	1143	2577	6657
N	14	13	8	8
Ae_{last} (10 mg) (mg)				
Mean	4801	[illegible]292	5190	4879
(SD, CV)*	(1390, 29%)	([illegible]449, [illegible]4%)	(709, 14%)	(1112, 23%)
Min-Max	1585 – 6251	[illegible]99 – 6641	3691 – 5916	3377 – 5992
Median	5441	4363	5383	4934
N	14	13	8	6
Ae_{inf} (10 mg) (mg)				
Mean	4786	4274	5257	4969
(SD, CV)*	(1487, 31%)	(1470, 34%)	(773, 14%)	(1070, 22%)
Min-Max	125[illegible] – 6981	1054 – 6652	3712 – 6052	3452 – 6040
Median	52[illegible]0	4358	5354	4984
N	14	13	7	6

Administration of a single dose of telavancin 10 mg/kg over 60 min to subjects with moderate hepatic impairment (Child-Pugh score B) gave a lower C_{max} and AUC_{inf} but higher CL and Vss vs. normal subjects while t1/2 was not affected. Exposure to AMI-999 was comparable while exposure to AMI-[illegible]352 was low but higher than in subjects with normal function (2.8% *vs.* 1.7%). There are no data in severe hepatic insufficiency.

Comparing the plasma concentrations obtained in subjects with a BMI ≥35 kg/m^2 indicated a higher exposure compared to subjects with a lower BMI. Simulations showed that a fixed dose of 900 mg in subjects with a BMI ≥ 35 kg/m^2 and a body weight ≥ 90 kg or dosing with 10 mg/kg at an assumed BMI of 30 kg/m^2 would result in AUC values similar to the values seen in subjects with a BMI < 35 kg/m^2 provided that CLcr exceeds 50 ml/min.

On the basis of these data the applicant initially proposed a fixed dose of 900 mg q.d. for subjects with BMI ≥ 35 kg/m^2 and body weight ≥ 90 kg. However, the applicant was asked to further justify this proposal and provided additional simulations to suggest that the better compromise might be to continue to dose at 10 mg/kg.

A single dose of 10 mg/kg over 60 min administered to subjects aged 65 – 83 years gave generally comparable AUC and CL values vs. younger subjects but V_{ss} and $t_{1/2}$ appeared to be slightly higher in the elderly. AMI-999 and AMI-11352 showed very low plasma exposures compared to telavancin and there were minimal differences between male and female elderly subjects. Dose adjustment was not considered necessary in elderly subjects unless merited based on renal function.

Three population PK analyses were performed using phase 1 data and data from the phase 2 and 3 cSSTI studies. These confirmed the important effect of renal function on PK telavancin such that CL decreased and AUC increased with decreasing CLcr. The central and peripheral (V2) volumes of distribution increased with body weight and one analysis also showed an increase in CL with body weight. Females showed a further 9.3% reduction in CL compared with males. A further analysis that included also the data from the nosocomial pneumonia (NP) studies showed that CLcr and body weight were important covariates for CL telavancin. In the NP studies, using the proposed dose adjustments, PK parameters in three groups delineated by renal insufficiency (CLcr >50, 30-50 and < 30) showed that dose adjustments in the group with CLcr in the 30-50 ml/min range resulted in the lowest plasma exposures.

2.4.3. Pharmacodynamics

Mechanism of action

Telavancin is a lipoglycopeptide antibacterial agent. It is a semi-synthetic derivative of vancomycin that has a lipophilic side chain attached to the vancosamine constituent that confers not only the expected inhibition of bacterial cell wall synthesis but also an antibacterial effect resulting from interaction with the bacterial cell membrane to disrupt membrane potential and permeability.

Primary and Secondary pharmacology

Primary pharmacology

Multiple studies have evaluated the in-vitro activity of telavancin against clinical isolates of Gram-positive cocci including S. aureus and S. pneumoniae. Inoculum, incubation conditions, media pH and Ca^{2+} concentration all have minimal effects on telavancin MIC values. Some typical results for MICs and MBCs against organisms of particular interest are shown below.

Table 14: Telavancin MBC values for *S. aureus* strains including isolates with reduced susceptibility to methicillin, daptomycin, linezolid and vancomycin

Phenotype[a]	N	MIC (mcg/ml)			MBC (mcg/ml)		
		Range	MIC_{50}	MIC_{90}	Range	MBC_{50}	MBC_{90}
All isolates	75	0.25-8	2	2	0.25-64	4	8
MSSA	13	0.25-2	2	2	0.25-8	4	8
MRSA[b]	62	0.25-8	1	2	0.25-64	4	8
Daptomycin-NS	37	0.5-2	2	2	0.5-64	4	8
Linezolid-NS	3	0.25-1	—[c]	—	0.25-2	—	—
VISA[d]	42	0.5-2	2	2	0.5-64	4	8
VRSA	2	2-8	—	—	4-8	—	—

Telavancin is not active against VanA-type vancomycin-resistant enterococci [VRE]. Telavancin is an inducer of the VanA but not the VanB operon in VRE. Telavancin MICs for organisms with the VanB determinant are higher than for glycopeptide-susceptible organisms (e.g. 8 mg/L vs. 0.5 mg/L). The telavancin MIC90 was around 2 mg/mL for anaerobic Gram-positive species while that for *Clostridium difficile* was 0.25 mg/L. The AMI-11352 metabolite of telavancin was at least 10-fold less active than the parent molecule.

Telavancin exerted concentration-dependent bactericidal activity against staphylococci, *S. pyogenes* and *S. pneumoniae in vitro* but drops in cfu/ml were most prominent between 4 and 8 h post-exposure with little discernible change within the first 2 h. It was also actively taken up into macrophages and killed intracellular *S. aureus*.

Serum obtained on dosing healthy subjects with 2.5 mg/kg and 5 mg/kg showed bactericidal activity persisting for 24 h against MRSA and *S. pneumoniae*. A 100-fold dilution of serum obtained at a mean Cmax of 44.9 mg/L reduced the viability of both strains tested by 99.9%. Similarly, a 4-fold dilution of the trough samples (mean ~ 4µg/ml) resulted in bactericidal activity against the same strains. Comparable results were obtained with the sera from day 7.

The post-antibiotic effect of telavancin may be up to about 4 h for *S. aureus* and longer for *S. pyogenes*.

In-vitro drug interaction studies identified additive or indifferent interactions between telavancin and agents that might be co-administered to treat Gram-negative pathogens. Synergistic interactions against *S. aureus*, including MRSA strains, were observed with some β-lactam agents tested, including imipenem.

PK/PD studies in the neutropenic murine thigh infection model suggested that AUC/MIC and T>MIC were equally good predictors of efficacy when total drug concentrations were considered. AUC/MIC was the best predictor of efficacy when free drug concentrations were used (R2 was 0.83, 0.49 and 0.69, respectively for AUC0-24 free/MIC, Cmax free and T>MIC, respectively). These findings suggested that AUC/MIC is the primary PD-linked variable that correlates with efficacy.

An AUC0-24/MIC ratio of 219 (or 14.2 based on unbound telavancin) was required for a one log10 reduction in CFU/g against an MRSA strain with MIC of 1 µg/mL in the murine neutropenic thigh model. This target was used to generate estimates of the doses evaluated in Phase 2 and 3 trials of cSSTI. A 10,000 subject Monte Carlo simulation was performed for at least three drug doses. The simulated AUC24 values per dose were corrected for protein binding and divided by MIC values across the observed distribution to give the AUC24/MIC ratios and to calculate the frequencies with which these

values exceeded the target. Two hypotheses for protein binding were employed: (1) only total drug needs to be considered and (2) free drug is the important entity and telavancin is 90% protein bound in man.

Based on these Monte Carlo simulations with human population PK parameter estimates for a 750 mg dose (approximately 10 mg/kg for average adult body weight) and a range of MICs, a target attainment rate of 99% (based on 1 log drop) was found for organisms with MICs up to 2 mg/L. The susceptibility testing MIC breakpoints recommended by EUCAST are ≤ 1 mg/L for *S. aureus* and ≤0.12 mg/L for the β-haemolytic streptococci and *S. pneumoniae*. These recommendations are now reflected in the SmPC.

The applicant attempted to obtain subject-based AUC/MIC target values by performing a CART analysis for subjects in Phase 3 studies with documented clinical and/or microbiological responses and for whom AUC values could be derived. This assessment focused on subjects infected by *S. aureus* and looked at the possibility of interference from some demographic and baseline subject characteristics that were reasonable likely to interfere with efficacy outcomes (age, renal function and obesity).

No statistically significant association between response to treatment and the quotient of AUC/MIC could be demonstrated in any analysis performed. The major reason for this may be that treated subjects were only infected by "wild type" organisms for which the dose of telavancin used was too high to detect clinical failures associated with the MIC values of the clinical isolates. Thus, no AUC/MIC target value could be derived from the clinical dataset currently available.

Secondary pharmacology

Telavancin, and to a lesser extent HP-ß-CD inhibited the hERG tail current measured in stably transfected HEK293 cells in a concentration-dependent fashion. At 600 µg/ml (~60-fold unbound Cmax on dosing at 10 mg/kg/day [total Cmax ≈ 108 µg/ml, 10% unbound]) there was < 50% inhibition.

In a QTc study (performed before adoption of the current ICH E14 guidance), telavancin was given at 7.5 and 15 mg/kg to parallel groups of 39-40 subjects once daily for 3 days. Reference treatments were placebo and moxifloxacin 400 mg IV. The plasma concentration data resembled the results of the multiple dose PK study. The maximum change in QTcF from baseline coincided with Cmax. The average change and maximum change from baseline in QTcF was comparable in male and female subjects.

The initial analysis of this study concluded that mean increases in placebo-corrected time averaged QTcF were 4.1 ms and 4.5 ms at doses of 7.5 and 15 mg/kg telavancin while moxifloxacin resulted in a 9.2 ms increase. The mean maximum increases in placebo-corrected QTcF were 5.3 and 4.5 ms at doses of 7.5 and 15 mg/kg while moxifloxacin gave an increase by 9.8 ms. Differences between 7.5 and 15 mg/kg were small and not statistically significant. The same analysis of the data using the Bazett's correction for QTc gave comparable results to those observed with Fridericia's correction.

However, in an appendix to the study report the applicant provided a re-analysis of the results on the basis of the criteria in ICH E14. This showed immediate post-infusion changes from baseline relative to placebo of 11.6 to 15.1 ms for 7.5 and 15 mg/kg telavancin dosages, respectively, with upper 90% CI limits on the difference from placebo of 16 ms and 20 ms. The corresponding value in the moxifloxacin group was 21.6 ms, with an upper 90% CI of 26 ms. Statistically significant QTcF increases (relative to placebo) persisted through 7 h following the end of infusion in the 15 mg/kg dose telavancin group. In the 7.5 mg/kg group, significant QTcF increases were observed immediately post-infusion and at 1, 2 and 6 hours post-infusion. Therefore, the study can be considered to provide a positive result for a potentially clinically important effect of telavancin on QTc.

In the 7.5 mg/kg group 10 subjects experienced an increase in QTcF of at least 30 ms but < 60 ms compared to 6 in the 15 mg/kg group, 5 for placebo and 15 for moxifloxacin. The highest individual increase was 63 ms at 17 h after a dose of 15 mg/kg but at all other time points the increase was < 30 ms in this subject. No other treatment groups showed an increase of at least 60 ms.

Further details on the torsadogenic potential of Vibativ are also provided in the safety pharmacology section (non-clinical aspects).

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Telavancin exhibited linear pharmacokinetics at doses up to 15 mg/kg administered as a daily 60 minute intravenous infusion for 7 days in healthy volunteers. The apparent distribution volume of telavancin at steady-state in healthy adult subjects was approximately 133 ml/kg. Human plasma protein binding is approximately 90%, primarily to serum albumin.

In healthy young adults, three hydroxylated metabolites were identified after infusion of telavancin. The AUC of the predominant metabolite accounted for approximately 2-3% of AUC of telavancin.

Renal excretion is the major route of elimination for telavancin in humans. In healthy young adults, after infusion of radiolabelled telavancin, approximately 76% of the administered dose was recovered from urine and less than 1% of the dose was recovered from faeces (collected for up to 9 days), based on total radioactivity. Telavancin is mainly excreted unchanged accounting for approximately 82% of the total amount recovered over 48 hours in urine. The elimination half-life in subjects with normal renal function is approximately 8 hours.

The effect of renal impairment on the pharmacokinetics of telavancin has been evaluated in 2 clinical pharmacology studies in healthy subjects with normal renal function and subjects with mild to severe renal impairment. Both studies consistently showed that the area under the curve (AUC) of telavancin, but not the maximum plasma concentration (C_{max}) increases with decreasing renal function. Changes in AUC only become clinically relevant in patients with moderate and severe renal impairment. Therefore, the same dose of 10 mg/kg/24 hr can be used in patients with normal renal function or mild renal impairment. Dosage adjustment is necessary in patients with a creatinine clearance lower than 50 ml/min.

Pharmacodynamics

Multiple studies, including seven prospective surveillance studies with adequate numbers of isolates from EU study sites, have evaluated the in-vitro activity of telavancin against clinical isolates of Gram-positive cocci including *S. aureus* and *S. pneumoniae*. In light of the consideration to license telavancin exclusively for the treatment of nosocomial pneumonia associated with MRSA, the following comments are pertinent:

S. aureus that show resistance to vancomycin (VRSA or GRSA; typically MICs are 32 mg/L or more) contain a VanA gene similar to that found in enterococci. Telavancin is not active against strains that express the VanA gene. Also, the fact that in-vitro data suggest that telavancin may retain activity against a proportion of enterococci that express the VanB gene is irrelevant to the indication sought since the VanB gene is not detected in *S. aureus*.

There are also some *S. aureus* that show reduced susceptibility but not frank resistance to vancomycin (hetero-resistant vancomycin-insusceptible *S. aureus*: hVISA or hGISA isolates). The exact mechanisms that result in elevated MICs of vancomycin in hVISA are unknown, although they likely

involve alterations in the cell wall and changes in several metabolic pathways. Most of these strains appear to have developed from MRSA. However, to date, there is insufficient and inconclusive evidence regarding the possible clinical efficacy of telavancin against hVISA.

The limited in-vitro data suggest that MRSA that demonstrate reduced susceptibility to linezolid are sometimes inhibited by 1 mg/L telavancin, which is the MIC susceptibility test breakpoint for *S. aureus*. The clinical studies (see further) did not provide any evidence for the efficacy of telavancin against such strains since there were no cases attributable to linezolid-insusceptible staphylococci.

A clinical QTc study with telavancin doses of 7.5 and 15 mg/kg versus vehicle and an active comparator (400 mg moxifloxacin) showed that caution is warranted when using telavancin to treat patients taking medicinal products known to prolong the QT interval. In addition, caution is warranted when using telavancin to treat patients with congenital long QT syndrome, known prolongation of the QTc interval, uncompensated heart failure, or severe left ventricular hypertrophy.

2.4.5. Conclusions on clinical pharmacology

Renal excretion is the major route of elimination for telavancin in humans, prompting dose adjustment in cases of renal impairment.

The antibacterial effects of telavancin have been adequately explored.

Secondary pharmacology stressed the torsadogenic potential of Vibativ. A suitable caution has been added to section 4.4. of SmPC.

2.5. Clinical efficacy

There were two dose-finding Phase 2 cSSTI studies and four Phase 3 studies (two cSSTI and two NP).

Table 15:

Study Identifier	Study Title
cSSTI Phase 2 Studies	
I6424a-202a	A phase 2, randomized, double-blind, multinational trial of intravenous TD-6424 versus standard therapy for treatment of complicated Gram-positive skin and skin structure infections.
I6424a-202b	A phase 2, randomized, double-blind, multinational trial of intravenous telavancin versus standard therapy for treatment of complicated Gram-positive skin and skin structure infections.
cSSTI Phase 3 Studies	
0017	A phase 3, randomized, double-blind, multinational trial of intravenous telavancin versus vancomycin for the treatment of complicated Gram-positive skin and skin structure infections with a focus on patients with infections due to methicillin-resistant *Staphylococcus aureus*.
0018	A phase 3, randomized, double-blind, multinational trial of intravenous telavancin versus vancomycin for the treatment of complicated Gram-positive skin and skin structure infections with a focus on patients with infections due to methicillin-resistant *Staphylococcus aureus*.
NP Phase 3 Studies	
0015	A phase 3 randomized, double-blind, parallel-group, multinational trial of intravenous telavancin versus vancomycin for treatment of hospital-acquired pneumonia with a focus on patients with infections due to methicillin-resistant *Staphylococcus aureus*.
0019	A phase 3 randomized, double-blind, parallel-group, multinational trial of intravenous telavancin versus vancomycin for treatment of hospital-acquired pneumonia with a focus on patients with infections due to methicillin-resistant *Staphylococcus aureus*.

The dose of telavancin was 7.5 mg/kg daily in study 202a and in the original protocols for study 202b (up to 10 days) and the Phase 3 cSSTI studies 0017 and 0018 (up to 14 days), but protocols were amended after enrolment commenced to increase the dose to 10 mg/kg. Following the unblinding of study 202a (with lower cure rates in the telavancin group overall and for those with MSSA), it was considered that the data supported the need to use a higher daily dose in study 202b. This decision was supported by revised Monte Carlo simulations in which 10 mg/kg (but not 7.5 mg/kg) yielded target attainment rates ≥ 99% for organisms with MIC values as high as 2 mg/L.

In cSSTI studies 0017 and 0018 a dose of 10 mg/kg daily for up to 14 days was based on the results of 202b, which showed that clinical cure rates and eradication rates for *S. aureus* (especially MRSA) in evaluable subjects treated with 10 mg/kg were consistently higher and the safety profile was similar to that seen with 7.5 mg/kg.

At the time of the dose amendments there were 32, 143 and 39 subjects randomised into studies 202b, 0017 and 0018, respectively. In study 0017 telavancin 7.5 mg/kg seemed to be at least as efficacious as vancomycin based on cure rates at TOC. For *S. aureus*, 38/40 telavancin subjects and 38/42 vancomycin subjects were clinical cures. In subjects with MRSA cure was reported in 20/20 telavancin subjects and in 27/28 vancomycin subjects compared to rates for MSSA of 19/21 and 12/15. In study 018 cure rates in AT and CE subjects were at least as high in the telavancin group but the numbers were too limited for any interpretation of the findings.

The NP studies 0015 and 0019 used only 10 mg/kg daily for up to 21 days with dose adjustment in subjects with moderate to severe renal insufficiency as recommended in the SmPC.

2.5.1. Dose response studies

Study 202a

This randomised and double blind study was conducted in the US and S. Africa. The primary objective was to compare the safety and tolerability of telavancin 7.5 mg/kg daily for up to 10 days vs. standard therapy and to explore comparative efficacy in cSSTI due to Gram-positive bacteria. Standard therapy was to be either

- Vancomycin 1 g q12 h IV or
- An anti-staphylococcal (semi-synthetic) penicillin – either nafcillin or oxacillin 2 g q6 h IV or cloxacillin 0.5 to 1 g q6 h IV.

In addition, aztreonam was allowed to cover aerobic Gram-negative organisms and /or metronidazole to cover anaerobic Gram-negative bacteria.

The end-of-treatment (EOT) evaluation was to be within 3 days following the last dose with a test-of-cure (TOC) visit between 7 and 21 days post-therapy.

Results

There were 169 patients randomised into the study (84 to telavancin). The majority of patients treated was male (60%), the overall mean age was 44.4 years (range 18 to 89 years) and baseline characteristics were comparable between treatment groups. *S. aureus* patients predominated in the microbiological evaluable (ME) population. The clinical cure rates suggested broadly comparable efficacy based on the limited numbers but the lower 95% CI were around -14% in each population analysed. Also, the cure rates in the clinical evaluable (CE) and eradication rates in the ME populations indicated lower responses to telavancin.

Table 16: Summary of Key Efficacy Endpoints at ToC, Study 202a

Efficacy Parameter	Analysis Population [1]	n/N (%) Patients		
		TLV 7.5 mg/kg	Standard Ther.	Diff (95% CI) [2]
Clinical cure rate	AT	66 /84 (78.6%)	66 /83 (79.5%)	-0.9 (-0.1349, 0.0485) [4]
	CE	66 /72 (91.7%)	66 /69 (95.7%)	-4.0 (-0.1349, 0.0485) [3]
	ME	44 /48 (91.7%)	46 /49 (93.9%)	-2.2 (-0.1465, 0.0959) [3]
By-patient microbiologic eradication rate	ME	36 /48 (75.0%)	41 /49 (83.7%)	-8.7 (-0.2565, 0.0793) [3]

Cure rates among patients with *S. aureus* (MRSA + MSSA) were 91% and 93% in the telavancin and standard therapy groups, respectively. The cure rate among those with MRSA was the same (95%) in each group but rates for patients with MSSA were 88% and 92%. For patients with *S. aureus* and the subset with MSSA the eradication rates were lower in the telavancin group compared with the standard therapy group in both the MAT (64% vs. 69% all; 57% vs. 77% MSSA) and ME populations (73% vs. 81% all; 64% vs. 83% MSSA). In contrast, in the subset with MRSA the eradication rate was higher in the telavancin group in both the MAT and ME populations.

Study 202b

The objectives, design, study population, study drug regimen and methods were generally identical to those in study 202a. For study 202b, randomisation was stratified on the combination of country (US or S. Africa) and the investigator's pre-specified choice of standard therapy (vancomycin or anti-staphylococcal penicillin). Note that the results for the patients that received 10 mg/kg are also shown along with the results from 017 and 018 using this dose in the next section.

Results for 7.5 mg/kg

There were only 32 patients randomised into the study prior to the dose amendment (15 telavancin). The majority of patients treated were male (59%) and the overall mean age was 41.7 years (range 22 to 77 years). *S. aureus* infections predominated, mostly MRSA. There were too few data to draw any conclusions regarding the relative efficacy of telavancin vs. standard therapy.

Table 17: Summary of Key Efficacy Endpoints at ToC, Study 202b (Telavancin 7.5 mg/kg)

Efficacy Parameter	Analysis Population [1]	n/N (%) Patients		
		TLV 7.5 mg/kg	Standard Ther.	Diff (95% CI) [2]
Clinical cure rate	AT	13 /15 (86.7%)	15 /17 (88.2%)	(-0.3103, 0.2523) [4]
	CE	12 /12 (100%)	15 /15 (100%)	(-0.2646, 0.2393) [3]
	ME	9 /9 (100%)	8 /8 (100%)	(-0.3448, 0.3694) [3]
By-patient microbiologic eradication rate	ME	5 /9 (56%)	3 /8 (38%)	(-0.3198, 0.6214) [3]

Results for 10 mg/kg

After the protocol amendment there were 203 patients randomised (103 to telavancin).

Overall, 59% of CE subjects had a major abscess, 30% had cellulitis and 9% had a wound infection. The results suggested that 10 mg/kg provided comparable efficacy to standard therapy with lower 95% CI within -5.3% in the CE and ME populations.

Table 18: Summary of Key Efficacy Endpoints at ToC, Study 202b (Telavancin 10 mg/kg)

Efficacy Parameter	Analysis Population	n/N (%) Patients		
		TLV 10 mg/kg	Standard Ther.	Diff (95% CI) [1]
Clinical cure rate	AT	82 /100 (82.0%)	81 /95 (85.3%)	-3.3 (-0.1418, 0.0744) [3]
	CE	74 / 77 (96.1%)	72 /77 (93.5%)	2.6 (-0.0527, 0.1102) [2]
	ME	59 / 61 (96.7%)	49 /53 (92.5%)	4.2 (-0.0488, 0.1508) [2]
By-patient microbiologic eradication rate	ME	57 / 61 (93.4%)	43 /53 (81.1%)	12.3 (-0.0002, 0.2591) [2]

2.5.2. Main studies

- **cSSTI**

ATLAS I & II:

Study 017: "A Phase 3, Randomized, Double Blind, Multinational Trial of Intravenous Telavancin Versus Vancomycin for Treatment of Complicated Gram-positive Skin and Skin Structure Infections with a Focus on Patients with Infections Due to Methicillin-Resistant *Staphylococcus aureus.*"

Study 0018: "A Phase 3, Randomized, Double Blind, Multinational Trial of Intravenous Telavancin versus Vancomycin for Treatment of Complicated Gram-positive Skin and Skin Structure Infections with a Focus on Subjects with Infections Due to Methicillin resistant *Staphylococcus aureus.*"

These randomised and double-blind studies were of identical design with pre-defined pooling of the data. They were conducted during 2004-2006 across several continents and many countries.

The following relates to the methodology and results obtained after institution of protocol amendment 1, which increased the daily dose from 7.5 mg/kg to 10 mg/kg.

Study Participants

Study sites were selected based on a reported high prevalence of MRSA and subject selection was to take into consideration a range of factors to increase the chance of finding MRSA.

The diagnosis of cSSTI was to be based on the presence of one of:

- Major abscess requiring surgical incision and drainage
- Infected burn (see exclusion criteria for important qualifications)
- Deep/extensive cellulitis
- Infected ulcer (see exclusion criteria for important qualifications)
- Wound infections

There was to be purulent drainage or at least three of: erythema, fluctuance, heat and/or localised warmth, pain and/or tenderness to palpation, swelling and/or induration, fever >38°C, WBC > 10,000/mm^3 and 15% immature neutrophils. The severity of the infection or each local sign/symptom was not evaluated.

Important exclusions were:

- More than 24 hours of potentially effective systemic therapy prior to randomisation unless the pathogen was resistant to prior treatment or the subject was a treatment failure (no clinical improvement after 3 days) and/or required a non-study systemic antibacterial regimen to which the target pathogen is susceptible
- Requirement for concomitant administration of agents containing a cyclodextrin solubiliser (e.g. IV itraconazole or voriconazole
- Baseline QTc > 500 ms, congenital long QT syndrome, uncompensated heart failure, uncorrected abnormal K+ or Mg++ blood levels or severe left ventricular hypertrophy

Excluded were burns involving > 20% of body surface area or third degree/full-thickness, diabetic foot ulcers, ischaemic ulcers/wounds, necrotising fasciitis, gas gangrene or mediastinitis

Treatments

Subjects received treatment for 7-14 days with either telavancin 10 mg/kg once daily (in 100-250 ml over 60 min) or vancomycin 1 g q12 h. Doses were adjusted according to renal function using the recommendations as in the SmPC for telavancin and local routine for vancomycin. Investigators were encouraged to administer aztreonam for suspected or proven polymicrobial infections involving Gram-negative bacteria and /or metronidazole to cover anaerobic Gram-negative bacteria. An Independent Dosing Regimen Adjudicator (IDRA) was responsible for evaluating the appropriateness of initial and subsequent treatment regimens in individual subjects.

Objectives

The primary objective was to compare the efficacy and safety of telavancin to vancomycin in the treatment of cSSTI with an emphasis on infections due to MRSA.

Outcomes/endpoints

All subjects were to have an **EOT** visit within 3 days following the last dose of study medication and a follow-up (**TOC**) visit within 7 to 14 days thereafter for subjects who were clinically cured or indeterminate at the EOT visit. Clinical responses were as follows:

- Cure: Resolution of signs and symptoms associated with the skin infection present at study admission such that no further antibacterial therapy was necessary
- Not Cured: Inadequate response to study therapy
- Indeterminate: Inability to determine outcome
- Missing: no determination reported

A response of "Not Cured" at EOT was carried forward to TOC.

A by-pathogen response was to be determined only for Gram-positive pathogens and primarily based on Central Laboratory data. Subjects with one or more pathogens isolated at baseline were to be assigned a by-subject response.

Sample size

Each study was to enrol 750 subjects (post-amendment) with 300/375 subjects per arm expected to be clinically evaluable. If the population clinical cure rates for telavancin and vancomycin were both 80%, then a one-sided, 0.025 level test of the non-inferiority of telavancin relative to vancomycin, and employing a non-inferiority Δ-criterion of 10%, was to have 86% power.

Randomisation

Subjects were randomised (1:1) using a centralised interactive voice response system (IVRS) stratified for pre-specified country grouping in order to balance potential differences in bacterial strains.

Blinding (masking)

The studies were double-blind.

Statistical methods

There were four efficacy analysis populations:

- All-treated (AT) analysed according to the randomised treatment group
- Modified All-treated (MAT) = AT with a pathogen isolated at baseline from the primary infection site and/or from blood cultures.
- Clinically Evaluable (CE) = AT Population with adherence to the protocol
- Microbiologically Evaluable (ME) = CE with a Gram-positive pathogen recovered from pre-treatment cultures of the primary infection site and/or from blood cultures.

The primary efficacy variable was investigator-assessed clinical response at TOC. In the primary analysis the AT and CE populations were co-primary. The efficacy analysis was to test for the clinical non-inferiority of telavancin relative to vancomycin, employing a non-inferiority Δ-criterion of 10%.

Results

In some of the tables below the results with 10 mg/kg daily in study 202b are also included in the summary tables. There were differences between studies 0017 and 0018 and study 202b in the study design and criteria used to define the analysis populations and therefore no undue weight should be placed on the comparisons.

Participant flow

The numbers enrolled are summarised below by study and for 0017 and 0018 pooled.

Table 19: Randomisation Summary, Studies 0017, 0018 & 202b, AT Population (Telavancin 10 mg/kg

	0017 Post Amendment		0018 Post Amendment		0017 + 0018 Post Amendment		202b Post Amendment	
	TLV 10 mg/kg (N=430)	VAN (N=433)	TLV 10 mg/kg (N=517)	VAN (N=518)	TLV 10 mg/kg (N=946)	VAN (N=951)	TLV 10 mg/kg (N=103)	VAN[1] (N=98)
	Number (%)of Patients							
Randomized	429 (100%)	433 (100%)	517 (100%)	518 (100%)	946 (100%)	951 (100%)	103 (100%)	98 (100%)
Received Study Medication	426 (99%)	429 (99%)	502 (97%)	510 (98%)	928 (98%)	939 (99%)	100 (97%)	95 (97%)
Randomized But Not Treated	3 (1%)	4 (1%)	15 (3%)	8 (2%)	18 (2%)	12 (1%)	3 (3%)	3 (3%)

Study completion (had a follow-up visit) rates were about 90%. The most common reason for early termination was "lost to follow-up". In each study, more AT subjects in the telavancin group (8%) compared to the vancomycin group (5%) discontinued medication due to an AE although no single type of AE accounted for more than 1% of the discontinuations. Comparable (2 to 3%) proportions in each treatment group discontinued study medication due to unsatisfactory therapeutic response.

Conduct of the study

There was one major amendment that was instituted before enrolment of patients to received 10 mg/kg telavancin. This amendment also modified various aspects of the planned analyses. Other changes to the protocol were administrative.

Baseline data

Demographic characteristics were well-balanced between treatment groups with 18% aged at least 65 years and 9% at least 75 years. The majority (65%) had CLcr > 80 ml/min and <5% had severe renal insufficiency (CLcr < 30 ml/min) at baseline with very few on haemodialysis. More than 70% in each study had at least one medical or surgical condition directly associated with cSSTI, most often diabetes mellitus (~24%) and recent trauma (~21%).

The most frequent types of infection were major abscess and deep/extensive cellulitis and the majority affected the lower extremities (next table). More than 95% presented with erythema, localised warmth, pain/tenderness and oedema/induration. Drainage and fluctuance were present in ~ 50-60% in each analysis population, > 95% had at least 4 local signs and symptoms and ~ 80% had 5 or 6. Proportions that had > 24 h prior antimicrobial therapy were consistent across studies (just over 25%), of which nearly all were treatment failures and/or had pathogens resistant to previous treatment.

Table 20: Type and Location of cSSTI, Studies 0017, 0018 & 202b, AT Population (Telavancin 10 mg/kg)

	0017		0018		0017 + 0018		202b	
	TLV (N=426)	VANC (N=429)	TLV (N=502)	VANC (N=510)	TLV (N=928)	VANC (N=939)	TLV (N=100)	VANC[1] (N=95)
	Number (%) of Patients							
Description of complicated skin /soft tissue infection								
Major abscess	179 (42)	193 (45)	209 (42)	209 (41)	388 (42)	402 (43)	58 (58)	55 (58)
Wound infection	72 (17)	60 (14)	72 (14)	64 (13)	144 (16)	124 (13)	11 (11)	10 (11)
Deep /extensive cellulitis	156 (37)	151 (35)	179 (36)	195 (38)	335 (36)	356 (38)	29 (29)	27 (28)
Infected ulcer	16 (4)	12 (3)	29 (6)	36 (7)	45 (5)	48 (5)	2 (2)	1 (1)
Infected burn	3 (< 1)	3 (< 1)	13 (3)	6 (1)	16 (2)	9 (< 1)	0 (0)	2 (2)
- Total -	426 (100)	429 (100)	502 (100)	510 (100)	928 (100)	939 (100)	100 (100)	95 (100)
Location of primary infection site								
Head /neck	29 (7)	33 (8)	36 (7)	31 (6)	65 (7)	64 (7)	10 (10)	7 (7)
Front torso	61 (14)	60 (14)	75 (15)	64 (13)	136 (15)	124 (13)	13 (13)	12 (13)
Back torso	43 (10)	53 (12)	56 (11)	55 (11)	99 (11)	108 (12)	13 (13)	8 (8)
Upper extremities	84 (20)	99 (23)	70 (14)	71 (14)	154 (17)	170 (18)	19 (19)	21 (22)
Lower extremities	209 (49)	184 (43)	265 (53)	289 (57)	474 (51)	473 (50)	45 (45)	47 (49)
- Total -	426 (100)	429 (100)	502 (100)	510 (100)	928 (100)	939 (100)	100 (100)	95 (100)

S. aureus was isolated from 553/928 (59.6%) of telavancin and 590/939 (62.8%) of vancomycin subjects in the pooled AT population while MRSA was found in 348/928 (37.5%) and 369/939 (39.3%), respectively. The Panton-Valentine leukocidin (PVL) gene was present in nearly 80% of MRSA but only 30% of MSSA. A small number per study had a blood pathogen at baseline and most had only *S. aureus*.

Numbers analysed

Across the studies and in the two treatment groups, 80% of the AT population was clinically evaluable and 71% of the CE population was also microbiologically evaluable. Approximately 75% of AT subjects

had a baseline pathogen (as designated by the applicant) and were included in the MATT population while near to 60% were included in the ME population.

Table 21: Data Sets Analysed, Studies 0017, 0018 & 202b, Telavancin 10 mg/kg), N (%) [1]

	0017		0018		0017 + 0018	
	TLV	VANC	TLV	VANC	TLV	VANC
AT	426 (100)	429 (100)	502 (100)	510 (100)	928 (100)	939 (100)
MAT	307 (72)	322 (75)	373 (74)	381 (75)	680 (73)	703 (75)
Infection site pathogens	301 (71)	321 (75)	372 (74)	377 (74)	673 (73)	698 (74)
Blood pathogens only	6 (1)	1 (< 1)	1 (< 1)	4 (< 1)	7 (< 1)	5 (< 1)
CE	346 (81)	349 (81)	399 (79)	395 (77)	745 (80)	744 (79)
ME	237 (56)	255 (59)	290 (58)	281 (55)	527 (57)	536 (57)
Infection site pathogens	234 (55)	255 (59)	290 (58)	277 (54)	524 (56)	532 (57)
Blood pathogens only	3 (< 1)	0	0	4 (< 1)	3 (< 1)	4 (< 1)

Outcomes and estimation

The primary analyses for each of 0017 and 0018 and pooled indicated that telavancin 10 mg/kg was non-inferior to vancomycin with lower 95% CI within -5% for the AT and CE co-primary populations.

Table 22: Clinical Response at Test-of-Cure – Studies 0017, 0018 & 202b, AT and CE Populations, Telavancin, 10 mg/kg)

	0017		0018		0017 + 0018		202b	
	TLV N(%)	VANC N(%)	TLV N(%)	VANC N(%)	TLV N(%)	VANC N(%)	TLV N(%)	VANC[1] N(%)
AT								
Cure	323 (75.8)	321 (74.8)	387 (77.1)	376 (73.7)	710 (76.5)	697 (74.2)	82 (82.0)	81 (85.3)
Not cured[2]	52 (12.2)	58 (13.5)	65 (12.9)	71 (13.9)	117 (12.6)	129 (13.7)	3 (3.0)	6 (6.3)
Indeterminate	23 (5.4)	16 (3.7)	22 (4.4)	20 (3.9)	45 (4.8)	36 (3.8)	15 (15.0)	8 (8.4)
Missing	28 (6.6)	34 (7.9)	28 (5.6)	43 (8.4)	56 (6.0)	77 (8.2)	0 (0.0)	0 (0.0)
- Total -	426 (100.0)	429 (100.0)	502 (100.0)	510 (100.0)	928 (100.0)	939 (100.0)	100 (100.0)	95 (100.0)
Difference (95% CI)[3]	1.0 (-4.8 , 6.8)		3.4 (-1.9 , 8.7)		2.3 (-1.6 , 6.2)		-3.3 (-14.2 , 7.4)	
CE								
Cure	304 (87.9)	302 (86.5)	354 (88.7)	346 (87.6)	658 (88.3)	648 (87.1)	74 (96.1)	72 (93.5)
Not cured[2]	42 (12.1)	47 (13.5)	45 (11.3)	49 (12.4)	87 (11.7)	96 (12.9)	3 (3.9)	5 (6.5)
- Total -	346 (100.0)	349 (100.0)	399 (100.0)	395 (100.0)	745 (100.0)	744 (100.0)	77 (100.0)	77 (100.0)
Difference (95% CI)[3]	1.3 (-3.6 , 6.3)		1.1 (-3.4 , 5.6)		1.2 (-2.1 , 4.6)		2.6 (-5.3 , 11.0)	

The clinical cure rates by pathogen are shown below and indicate that telavancin 10 mg/kg was clinically active against *Staphylococcus aureus* (MSSA and MRSA), *Streptococcus pyogenes*, *Streptococcus agalactiae* and *Streptococcus anginosus*. Within each study there was no clear indication that telavancin was less effective than vancomycin against any specific pathogen based on cure rates in the CE or eradication rates in the ME populations. There were some numerical differences in each direction for specific pathogens but denominators are mostly small and studies were not powered for any formal assessment of non-inferiority. There were small numbers of patients in each study with

both MSSA and MRSA in baseline cultures. These patients are represented twice in the efficacy tables which display all *S. aureus* as well as MRSA and MSSA.

Table 23: Clinical Cure Rates by Pathogen at ToC for the Most Common Pathogens – Studies 0017, 0018 and 202b, MAT Population (Telavancin, 10mg/kg)

	Studies 0017 + 0018		Total (incl Study 202b)	
	TLV (N=680)	VAN (N=703)	TLV (N=760)	VAN (N=773)
S. aureus (all)	433 / 557 (77.7)	438 / 592 (74.0)	482 / 616 (78.2)	478 / 641 (74.6)
S. aureus (MRSA)	265 / 350 (75.7)	277 / 369 (75.1)	290 / 379 (76.5)	295 / 393 (75.1)
S. aureus (MSSA)	170 / 211 (80.6)	164 / 226 (72.6)	194 / 241 (80.5)	186 / 251 (74.1)
Streptococcus pyogenes	21 / 28 (75.0)	25 / 34 (73.5)	30 / 37 (81.1)	34 / 44 (77.3)
Enterococcus faecalis	28 / 33 (84.8)	31 / 43 (72.1)	28 / 33 (84.8)	31 / 43 (72.1)
Streptococcus agalactiae	17 / 23 (73.9)	18 / 23 (78.3)	18 / 25 (72.0)	18 / 23 (78.3)
Streptococcus anginosus	12 / 14 (85.7)	8 / 8 (100.0)	12 / 14 (85.7)	8 / 8 (100.0)
Streptococcus constellatus	4 / 7 (57.1)	6 / 8 (75.0)	4 / 7 (57.1)	6 / 8 (75.0)

By-patient microbiological responses also supported non-inferiority of telavancin compared to vancomycin.

Table 24: By-patient Microbiological Response at ToC – Studies 0017 and 0018, ME Population (Telavancin 10 mg/kg)

	Number of Patients					
	0017		0018		Total	
	Telavancin	Vancomycin	Telavancin	Vancomycin	Telavancin	Vancomycin
By-patient Microbiological Response						
Eradicated	212 (89.5)	219 (82.9)	261 (90.0)	249 (88.6)	473 (89.8)	468 (87.3)
Persisted	25 (10.5)	36 (13.1)	29 (10.0)	32 (11.4)	54 (10.2)	68 (12.7)
- Total -	237 (100.0)	265 (100.0)	290 (100.0)	281 (100.0)	527 (100.0)	536 (100.0)
Difference (95% CI) [1]	3.6 (-2.2 , 9.4)		1.4 (-3.7 , 6.5)		2.4 (-1.4 , 6.2)	

By-pathogen microbiological eradication rates were generally consistent with the by-pathogen cure rates.

Table 25: By-Pathogen Microbiological Eradication Rates at ToC for the Main Gram-positive Pathogens – Studies 0017, 0018 & 202b, ME Population, (Telavancin, 10 mg/kg)

	Studies 0017 + 0018		Total (incl Study 202b)	
	TLV (N=527)	VAN (N=536)	TLV (N=588)	VAN[1] (N=589)
S. aureus (all)	409 / 456 (89.7)	411 / 473 (86.9)	455 / 506 (89.9)	443 / 514 (86.2)
S. aureus (MRSA)	250 / 278 (89.9)	257 / 301 (85.4)	274 / 304 (90.1)	270 / 320 (84.4)
S. aureus (MSSA)	161 / 181 (89.0)	157 / 176 (89.2)	183 / 205 (89.3)	176 / 198 (88.9)
Streptococcus pyogenes	21 / 23 (91.3)	23 / 25 (92.0)	30 / 32 (93.8)	33 / 35 (94.3)
Enterococcus faecalis	25 / 27 (92.6)	31 / 34 (91.2)	25 / 27 (92.6)	31 / 34 (91.2)
Streptococcus agalactiae	17 / 19 (89.5)	18 / 19 (94.7)	18 / 20 (90.0)	18 / 19 (94.7)
Streptococcus anginosus	11 / 11 (100.0)	8 / 8 (100.0)	11 / 11 (100.0)	8 / 8 (100.0)

Ancillary analyses

The majority (84%) of cSSTI AT subjects with normal renal function received the recommended weight-adjusted initial vancomycin dose (59%) or greater than the recommended dose (25%) so that only 16% received less than the recommended dose. Clinical cure rates were generally comparable regardless of the initial dose received. The cure rate in those with mild renal impairment who received lower than the recommended dose was lower vs. those receiving the recommended dose but there were only 7 subjects in this group of which 4/7 were clinical cures.

Data on vancomycin trough levels were available for 29% (298/1027) in cSSTI studies and 55% of AT and 54% of CE subjects achieved an average vancomycin trough level of 5 to < 10 mg/l while 30% and 32% achieved ≥ 10 mg/l compared to 15% and 13% that achieved < 5 mg/l. At the time these studies were conducted 5 – 10 mg/l was considered to be an adequate trough (ASHP Report 2009) so that adequate (i.e. > 5 mg/l) troughs were reached in approximately 85% of subjects.

More recently the ASHP consensus changed to a recommendation for trough levels > 10 mg/l to avoid resistance development and to recommend 15 – 20 mg/l. According to these more recent guidelines trough levels were inadequate in 70% of AT and 67% of CE subjects. Despite this, there was no evidence that the cure rates differed consistently depending on the average trough level achieved. The same pattern and conclusion was obtained for cSSTI subjects with a Gram-positive pathogen at baseline.

There was a marked difference between studies in the proportion of subjects that received an additional antibacterial agent, including those allowed in the protocol. Aztreonam and metronidazole were much less commonly used in study 0018 than 0017. However, comparable percentages received additional antibacterial agents due to lack of efficacy (i.e. around 14%).

Table 26: Concomitant Systemic Antimicrobial Medications ≥5% in any Treatment Group – Studies 0017, 0018 & 202b (Telavancin 10 mg/kg)

	0017		0018		0017 + 0018		202b	
	TLV N(%) (N=426)	VANC N(%) (N=429)	TLV N(%) (N=502)	VANC N(%) (N=510)	TLV N(%) (N=928)	VANC N(%) (N=939)	TLV N(%) (N=100)	VANC[1] N(%) (N=95)
	Number (%) of Patients							
Any systemic antimicrobial	283 (66.4)	271 (63.2)	148 (29.5)	144 (28.2)	431 (46.4)	415 (44.2)	54 (54.0)	46 (48.4)
Protocol-allowed systemic antimicrobials	245 (57.5)	244 (56.9)	81 (16.1)	89 (17.5)	326 (35.1)	333 (35.5)	49 (49.0)	40 (42.1)
Aztreonam	235 (55.2)	231 (53.8)	62 (12.4)	82 (16.1)	297 (32.0)	313 (33.3)	41 (41.0)	35 (36.8)
Metronidazole	173 (40.6)	171 (39.9)	40 (8.0)	34 (6.7)	213 (23.0)	205 (21.8)	44 (44.0)	36 (37.9)
Systemic antimicrobials given for lack of efficacy	59 (13.8)	59 (13.8)	68 (13.5)	74 (14.5)	127 (13.7)	133 (14.2)	12 (12.0)	5 (5.3)
Other reason	31 (7.3)	17 (4.0)	29 (5.8)	15 (2.9)	60 (6.5)	32 (3.4)	3 (3.0)	4 (4.2)

In 92 cases (60 telavancin) it was determined that the additional antibacterial agents were given for reasons other than lack of efficacy. The imbalance between treatment groups was explored but no explanation could be identified and it may have occurred by chance. It is important to note then these subjects were excluded from the CE population if their baseline pathogen(s) were known or suspected to be susceptible to the additional agent.

The clinical cure rates among European subjects (~ 80% in the AT and ~90% in the CE population) were higher than those in the overall population and in some other geographical regions. Cure rates in study 0018 were comparable between treatments in the European AT population (78% and 77%) but numerically higher with vancomycin in 0017 (82% and 86%). The vancomycin group had a numerically higher cure rate than did telavancin in the European CE population in both studies (88% vs. 95% and 85% vs. 91%) but the denominators are relatively small. The European MAT and ME populations showed eradication rates that were higher with vancomycin in study 0017 but higher with telavancin in study 0018. As with cure rate comparisons, the relatively small numbers in this geographical sub-group analysis limit drawing any firm conclusions from these data.

In the elderly the clinical cure rates were lower in the telavancin group compared to vancomycin group with an imbalance that was most apparent in study 0018 for subjects aged ≥ 65 years and in both studies for subjects aged ≥ 75 years. An investigation of these apparent imbalances revealed that slightly more telavancin subjects aged ≥ 65 years had severe renal impairment at baseline while a higher percentage of vancomycin subjects had no or mild renal impairment. Peripheral vascular disease and infected ulcers were more prevalent in the telavancin elderly group, primarily due to a large imbalance in study 0017, and there was a higher rate of infection with Gram-negative bacteria (including *P. aeruginosa*). In contrast, diabetes and MRSA occurred more often in elderly subjects treated with vancomycin.

Table 27: Cure Rates at ToC by Age – Studies 0017 and 0018, CE Population

	Study 0017		Study 0018		Pooled Studies	
	TLV	VANC	TLV	VANC	TLV	VANC
n/N (%Age < 65 y)	251 / 280 (89.6)	257 / 294 (87.4)	307 / 336 (91.4)	270 / 306 (88.2)	558 / 616 (90.6)	527 / 600 (87.8)
n/N (%Age ≥ 65 y)	53 / 66 (80.3)	45 / 55 (81.8)	47 / 63 (74.6)	76 / 89 (85.4)	100 / 129 (77.5)	121 / 144 (84.0)
n/N (%Age ≥ 75 y)	26 / 36 (72.2)	21 / 26 (80.8)	20 / 28 (71.4)	33 / 38 (86.8)	46 / 64 (71.9)	54 / 64 (84.4)

In the cSSTI study 0017, the telavancin cure rate in AT and CE populations with a BMI ≥ 40 was slightly lower vs. the other BMI groups but this pattern was not observed with vancomycin. In study 0018 there was a comparable decrease in cure rate at a BMI ≥ 40 for both treatments. On comparing all those with BMI < 35 or ≥ 35 the cure rate for telavancin among those with BMI ≥ 35 was slightly lower in the AT and CE populations and in each of the studies. Cure rates for vancomycin also tended to be lower in the obese subjects.

Clinical cure rates in both studies showed a trend to be lower with telavancin compared to vancomycin among the subjects with renal impairment (especially in those with CLcr < 30 ml/min at baseline) whereas cure rates were higher with telavancin in subjects with normal renal function.

Table 28: Clinical Cure Rates by Baseline Creatinine Clearance – Studies 0017 and 0018, CE Population

	Study 0017		Study 0018		Pooled Studies	
	TLV	VAN	TLV	VAN	TLV	VAN
n/N (%CE)	304 / 346 (87.9)	302 / 349 (86.5)	354 / 399 (88.7)	346 / 395 (87.6)	658 / 745 (88.3)	648 / 744 (87.1)
n/N (%CLcr ≥ 80)	208 / 224 (92.9)	209 / 240 (87.1)	226 / 246 (91.9)	206 / 233 (88.4)	434 / 470 (92.3)	415 / 473 (87.7)
n/N (%CLcr 50 - <80)	53 / 64 (82.8)	60 / 68 (88.2)	87 / 98 (88.8)	87 / 101 (86.1)	140 / 162 (86.4)	147 / 169 (87.0)
n/N (%CLcr 30 - <50)	28 / 36 (77.8)	23 / 30 (76.7)	21 / 28 (75.0)	33 / 38 (86.8)	49 / 64 (76.6)	56 / 68 (82.4)
n/N (%CLcr < 30)	15 / 22 (68.2)	10 / 11 (90.9)	20 / 27 (74.1)	20 / 23 (87.0)	35 / 49 (71.4)	30 / 34 (88.2)

A univariate analysis by renal subgroups showed that CE subjects with baseline CLcr 30-50 ml/min and CLcr < 30 ml/min were more likely to have lower extremity infections compared to the overall population and these were more frequent in telavancin subjects in both studies. Also, Gram-negative pathogens occurred more often in renally impaired subjects with somewhat higher rates in the telavancin group.

Despite several additional analyses there remains no explanation for the observation that telavancin did not perform as well as vancomycin in the elderly, in those with severe renal impairment or in those with renal insufficiency who only had Gram-positive pathogens.

In the multivariate analysis the major prognostic factors that persistently had a significant impact on clinical outcome were bacteraemia, geographic region, infection site and age. There was no evidence of a treatment by geographic region outcome. The only treatment interaction detected was with age, showing that telavancin was better in the < 65 years age group.

Table 29: Logistic regression factors that were significant in the overall population in the Step 5 analysis for Clinical Cure, AT population

	Odds Ratio		
Prognostic Factor	**Estimate**	**95% CI**	**p-value**
Bacteremia at baseline [NO]	0.323	[0.186, 0.560]	<.0001
Geographic region {Multi-level categorical variable}			0.0004
Infection Site {Multi-level categorical variable}			0.0174
Randomized Treatment			0.8176
Age (2 categories) [<65 years] Interaction with Randomized Treatment			0.0010 0.0197
CONTRAST: VANCOMYCIN vs. TELAVANCIN [VANCOMYCIN] for age=<65 years	1.322	[1.037, 1.686]	0.0245
CONTRAST: VANCOMYCIN vs. TELAVANCIN [VANCOMYCIN] for age>=65 years	0.712	[0.449, 1.127]	0.1473

There were three other retrospective reviews of importance:

- There were 556 subjects across the cSSTI studies (27% of total) with 3, 4 or 5 signs or symptoms of infection at baseline. In this sub-population the clinical cure rates (AT 73.8% vs. 76.5%) and microbiological eradication rates (ME 87.7% and 88%) were comparable between treatments.
- An analysis that took into account pre-enrolment procedures showed that 88% of subjects with abscesses in each treatment group in 0017 and 0018 had at least one surgical procedure before or after the first dose of assigned study drug and in most cases these involved drainage.
- In the combined cSSTI studies consistent clinical cure and microbiologic eradication rates were seen across the range of MICs of telavancin for baseline clinical isolates with no evidence of a relationship between MIC and clinical/microbiologic outcome.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 30: Summary of Efficacy for trial 017

Title: A Phase 3, Randomized, Double-Blind, Multinational Trial of Intravenous Telavancin Versus Vancomycin for Treatment of Complicated Gram-positive Skin and Skin Structure Infections with a Focus on Patients with Infections Due to Methicillin-resistant Staphylococcus aureus		
Study identifier	0017	
Design	Randomised, double blind, active-controlled, parallel-group, multicentre, multinational trial. While the primary objective of Study 0017 is to compare the efficacy and safety of telavancin with vancomycin for the treatment of adults with complicated Gram-positive skin and skin structure infections, a key secondary objective of the study is to assess the superiority of telavancin to vancomycin in patients with skin and skin structure infections caused by MRSA. The secondary objective will be evaluated in the modified all treated population using data from Study 0017 pooled with data from a second study of identical design (Study 0018).	
	Duration of main phase:	7 days - 14 days IV (FU at 7-14 days after last dose)
	Duration of Run-in phase:	Not Applicable

	Duration of Extension phase:		Not Applicable
Hypothesis	Non-inferiority; That is, The lower bound of the 95% CI around the difference between treatments in cure rates exceeded −10%.		
Treatments groups	**Telavancin**		Telavancin 10 mg/kg once a day IV for 7-14 days, 429 randomised
	Vancomycin		Vancomycin 1 g q 12 hr IV for 7-14 days, 433 randomised
Endpoints and definitions	Primary endpoint	**Clinical Response at TOC – AT Population**	Clinical response at Test-of-Cure (Follow-up) evaluation (Cure, Failure or Indeterminate)
	Secondary endpoint	**Clinical Response at TOC – CE Population**	
	Secondary endpoint	**Clinical Response at TOC – MAT Population**	
	Secondary endpoint	**Clinical Response at TOC – ME Population**	
Database lock	10 August 2006		

Results and Analysis

Analysis description	**Primary analysis**		
Analysis population and time point description	Analysis population: • **All-treated (AT)**: Patients who received any amount of study medication. Time point: • **Test-of-Cure**: Only those patients who are evaluated as a clinical "cure" or "indeterminate" at the End-of-Therapy visit will have a Test-of-Cure evaluation during the Follow-up visit.		
Descriptive statistics and estimate variability	Treatment group	**Telavancin**	**Vancomycin**
	Number of subject – AT Population	426	429
	Clinical Response at TOC – AT Population (Cure Rate)	75.8% (323/426)	74.8% (321/429)
	Standard Error	2.07%	2.10%

Effect estimate per comparison	Clinical Response at TOC – AT Population	Comparison groups	Telavancin & Vancomycin
		Difference (TLV-VAN) in Cure Rate	1.0%
		Standard Error	2.95%
		95% CI	(-4.8%, 6.8%)
Notes	P-value is replaced with 95% CI since the study was designed to evaluate the non-inferiority.		

<table>
<tr><th>Analysis description</th><th colspan="3">Secondary analysis</th></tr>
<tr><td>Analysis population and time point description</td><td colspan="3">Analysis population:
• Clinically Evaluable (CE): Patients in the all-treated population who meet all of the following:
o Patient complied with the inclusion criteria #2 and #4. Patient did not violate any of the exclusion criteria: #1, #4, #5, #6, #7, #8, #9 and #10. If a patient appeared to comply with the above inclusion/exclusion requirements at the time of enrolment, but subsequent findings indicate otherwise, the patient will be excluded from this analysis population.
o The patient received at least 72 hours of study medication. If the patient is a clinical "cure," the patient received at least 96 hours of study medication.
o Patient received at least 80% of intended doses of study medication.
o Patient either had a Test-of-Cure evaluation or was previously evaluated as clinically "not cured."
o Patient did not receive a potentially effective non-study antibacterial medication during the study, unless the patient was previously evaluated as clinically "not cured."
• Modified All-treated (MAT): Patients in the all-treated population who have a baseline pathogen identified.
• Microbiologically Evaluable (ME): Patients in the clinically evaluable population who have a Gram-positive pathogen recovered from pre-treatment cultures of the primary infection site that was not resistant to either study medication.
Time point:
• Test-of-Cure: Only those patients who are evaluated as a clinical "cure" or "indeterminate" at the End-of-Therapy visit will have a Test-of-Cure evaluation during the Follow-up visit.</td></tr>
<tr><td rowspan="10">Descriptive statistics and estimate variability</td><td>Treatment group</td><td>Telavancin</td><td>Vancomycin</td></tr>
<tr><td>Number of subject – CE Population</td><td>346</td><td>349</td></tr>
<tr><td>Clinical Response at TOC – CE Population (Cure Rate)</td><td>87.9% (304/346)</td><td>86.5% (302/349)</td></tr>
<tr><td>Standard Error</td><td>1.76%</td><td>1.83%</td></tr>
<tr><td>Number of subject – MAT Population</td><td>307</td><td>322</td></tr>
<tr><td>Clinical Response at TOC – MAT Population (Cure Rate)</td><td>76.5% (235/307)</td><td>74.8% (241/322)</td></tr>
<tr><td>Standard Error</td><td>2.42%</td><td>2.42%</td></tr>
<tr><td>Number of subject – ME Population</td><td>237</td><td>255</td></tr>
<tr><td>Clinical Response at TOC – ME Population (Cure Rate)</td><td>88.6% (210/237)</td><td>86.3% (220/255)</td></tr>
</table>

	Standard Error	2.06%	2.15%
Effect estimate per comparison	Clinical Response at TOC – CE Population	Comparison groups	Telavancin & Vancomycin
		Difference (TLV-VAN) in Cure Rate	1.3%
		Standard Error	2.53%
		95% CI	(-3.6%, 6.3%)
	Clinical Response at TOC – MAT Population	Comparison groups	Telavancin - Vancomycin
		Difference (TLV-VAN) in Cure Rate	1.7%
		Standard Error	3.42%
		95% CI	(-5.0%, 8.4%)
	Clinical Response at TOC – ME Population	Comparison groups	Telavancin - Vancomycin
		Difference (TLV-VAN) in Cure Rate	2.3%
		Standard Error	2.98%
		95% CI	(-3.5%, 8.2%)
Notes	P-value is replaced with 95% CI since the study was designed to evaluate the non-inferiority.		

Table 31: Summary of Efficacy for trial 0018

Title: A Phase 3, Randomized, Double-Blind, Multinational Trial of Intravenous Telavancin Versus Vancomycin for Treatment of Complicated Gram-positive Skin and Skin Structure Infections with a Focus on Patients with Infections Due to Methicillin resistant Staphylococcus aureus			
Study identifier	0018		
Design	Randomised, double-blind, active-controlled, parallel-group, multicentre, multinational trial. While the primary objective of Study 0018 is to compare the efficacy and safety of telavancin with vancomycin for the treatment of adults with complicated Gram-positive skin and skin structure infections, a key secondary objective of the study is to assess the superiority of telavancin to vancomycin in patients with skin and skin structure infections caused by MRSA. The secondary objective will be evaluated in the modified all treated population using data from Study 0018 pooled with data from a second study of identical design (Study 0017).		
	Duration of main phase:		7 days - 14 days IV (FU at 7-14 days after last dose)
	Duration of Run-in phase:		Not Applicable
	Duration of Extension phase:		Not Applicable
Hypothesis	Non-inferiority; That is, The lower bound of the 95% CI around the difference between treatments in cure rates exceeded −10%.		
Treatments groups	**Telavancin**		Telavancin 10 mg/kg once a day IV for 7-14 days, 517 randomised
	Vancomycin		Vancomycin 1 g q 12 hr IV for 7-14 days, 518 randomised
Endpoints and definitions	Primary endpoint	**Clinical Response at TOC – AT Population**	Clinical response at Test-of-Cure (Follow-up) evaluation (Cure, Failure or Indeterminate)

	Secondary endpoint	**Clinical Response at TOC – CE Population**	
	Secondary endpoint	**Clinical Response at TOC – MAT Population**	
	Secondary endpoint	**Clinical Response at TOC – ME Population**	
Database lock	10 August 2006		

Results and Analysis

Analysis description	**Primary analysis**		
Analysis population and time point description	Analysis population: • **All-treated (AT)**: Patients who received any amount of study medication. Time point: • **Test-of-Cure**: Only those patients who are evaluated as a clinical "cure" or "indeterminate" at the End-of-Therapy visit will have a Test-of-Cure evaluation during the Follow-up visit.		
Descriptive statistics and estimate variability	Treatment group	**Telavancin**	**Vancomycin**
	Number of subject – AT Population	502	510
	Clinical Response at TOC – AT Population (Cure Rate)	77.1% (387/502)	73.7% (376/510)
	Standard Error	1.88%	1.95%
Effect estimate per comparison	Clinical Response at TOC – AT Population	Comparison groups	Telavancin & Vancomycin
		Difference (TLV-VAN) in Cure Rate	3.4%
		Standard Error	2.70%
		95% CI	(-1.9%, 8.7%)
Notes	P-value is replaced with 95% CI since the study was designed to evaluate the non-inferiority.		

<table>
<tr><th>Analysis description</th><th colspan="3">Secondary analysis</th></tr>
<tr><td>Analysis population and time point description</td><td colspan="3">Analysis population:
• Clinically Evaluable (CE): Patients in the all-treated population who meet all of the following:
o Patient complied with the inclusion criteria #2 and #4. Patient did not violate any of the exclusion criteria: #1, #4, #5, #6, #7, #8, #9 and #10. If a patient appeared to comply with the above inclusion/exclusion requirements at the time of enrolment, but subsequent findings indicate otherwise, the patient will be excluded from this analysis population.
o The patient received at least 72 hours of study medication. If the patient is a clinical "cure," the patient received at least 96 hours of study medication.
o Patient received at least 80% of intended doses of study medication.
o Patient either had a Test-of-Cure evaluation or was previously evaluated as clinically "not cured."
o Patient did not receive a potentially effective non-study antibacterial medication during the study, unless the patient was previously evaluated as clinically "not cured."
• Modified All-treated (MAT): Patients in the all-treated population who have a baseline pathogen identified.
• Microbiologically Evaluable (ME): Patients in the clinically evaluable population who have a Gram-positive pathogen recovered from pre-treatment cultures of the primary infection site that was not resistant to either study medication.
Time point:
• Test-of-Cure: Only those patients who are evaluated as a clinical "cure" or "indeterminate" at the End-of-Therapy visit will have a Test-of-Cure evaluation during the Follow-up visit.</td></tr>
<tr><td rowspan="10">Descriptive statistics and estimate variability</td><td>Treatment group</td><td>Telavancin</td><td>Vancomycin</td></tr>
<tr><td>Number of subject – CE Population</td><td>399</td><td>395</td></tr>
<tr><td>Clinical Response at TOC – CE Population (Cure Rate)</td><td>88.7% (354/399)</td><td>87.6% (346/395)</td></tr>
<tr><td>Standard Error</td><td>1.58%</td><td>1.66%</td></tr>
<tr><td>Number of subject – MAT Population</td><td>373</td><td>381</td></tr>
<tr><td>Clinical Response at TOC – MAT Population (Cure Rate)</td><td>76.1% (284/373)</td><td>74.0% (282/381)</td></tr>
<tr><td>Standard Error</td><td>2.21%</td><td>2.25%</td></tr>
<tr><td>Number of subject – ME Population</td><td>290</td><td>281</td></tr>
<tr><td>Clinical Response at TOC – ME Population (Cure Rate)</td><td>89.7% (260/290)</td><td>89.0% (250/281)</td></tr>
</table>

	Standard Error	1.79%	1.87%
Effect estimate per comparison	Clinical Response at TOC – CE Population	Comparison groups	Telavancin & Vancomycin
		Difference (TLV-VAN) in Cure Rate	1.1%
		Standard Error	2.29%
		95% CI	(-3.4%, 5.6%)
	Clinical Response at TOC – MAT Population	Comparison groups	Telavancin - Vancomycin
		Difference (TLV-VAN) in Cure Rate	2.1%
		Standard Error	3.15%
		95% CI	(-4.0%, 8.3%)
	Clinical Response at TOC – ME Population	Comparison groups	Telavancin - Vancomycin
		Difference (TLV-VAN) in Cure Rate	0.7%
		Standard Error	2.59%
		95% CI	(-4.4%, 5.8%)
Notes	P-value is replaced with 95% CI since the study was designed to evaluate the non-inferiority.		

- **Hospital acquired pneumonia**

ATTAIN I & II:

Study 015: "A phase 3 randomized, double-blind, parallel-group, multinational trial of intravenous telavancin versus vancomycin for treatment of hospital-acquired pneumonia with a focus on patients with infections due to methicillin-resistant *Staphylococcus aureus.*"

Study 019: "A phase 3 randomized, double-blind, parallel-group, multinational trial of intravenous telavancin versus vancomycin for treatment of hospital-acquired pneumonia with a focus on patients with infections due to methicillin-resistant *Staphylococcus aureus.*"

These randomised and double-blind studies were of identical design with pre-planned data pooling.

- 0015 was conducted at 201 study sites across 25 countries
- 0019 was conducted at 250 study sites across 33 countries

Study Participants

The studies aimed to enrol subjects with NP caused by Gram-positive pathogens and preferably to enrol those with one or more risk factors for MRSA infection. Subjects were to have signs and symptoms consistent with pneumonia acquired after at least 48 h of continuous stay in an insubject acute or chronic care facility or acquired within 7 days after being discharged from a hospitalisation of ≥ 3 days duration. Chest radiographs obtained within 48 hours before randomisation into the study were to show findings consistent with a diagnosis of pneumonia.

At least two of the following were to be present: cough, purulent sputum or other deep respiratory specimen, auscultatory findings of pneumonia, dyspnoea, tachypnoea or hypoxaemia and isolation and identification of a respiratory pathogen from cultures of respiratory tract, sputum or blood.

Subjects were also to have at least two of the following: fever (>38°C) or hypothermia (rectal/core temperature <35°C), respiratory rate >30 breaths/min, pulse rate ≥120 beats/min, altered mental status, need for mechanical ventilation, elevated total peripheral white blood cell (WBC) count >10,000 cells/mm^3, >15% immature neutrophils or total WBC count <4500 cells/mm^3.

Treatments

Telavancin 10 mg/kg (over 60 min in 100-250 ml) was given once daily with dose reduction in renal insufficiency as per the SmPC.

Vancomycin 1 g q 12 h was given with dose adjustments in accordance with local policy. In case of documented MSSA pneumonia the investigators were allowed to replace vancomycin with intravenous nafcillin or oxacillin if desired. Aztreonam and/or metronidazole therapy could be added for suspected or proven infections involving Gram-negative and/or anaerobic bacteria. Piperacillin-tazobactam was allowed for this purpose only if aztreonam was considered to be inappropriate.

Objectives

The primary objective was to compare the efficacy and safety of telavancin with vancomycin in the treatment of NP due to Gram-positive bacteria with an emphasis on infections due to MRSA.

Outcomes/endpoints

All patients were to have an **EOT** visit no later than 3 days after the last dose of study medication at which outcome was assessed. Failure at EOT was carried forward to the TOC evaluation.

The primary efficacy endpoint was the clinical response at the Follow-up (**TOC)** Visit. This was to occur 7 to 14 days after the last dose of study medication or, as necessary, at 7 to 14 days after the last dose of ALL antibacterial therapy administered to treat the pneumonia. Outcomes were defined as follows:

- Failure: Relapsed pneumonia with the same Gram-positive organism or death for any reason on or after Day 3 and before the TOC evaluation or no TOC within 28 days of the last study medication but death was attributable to the HAP episode under study was imputed to be a failure
- Cure: Signs and symptoms of pneumonia resolved and baseline radiographic findings improved or did not progress. A second post-treatment chest X-ray or CT scan was not required at TOC since cure could be assigned only to patients who had an EOT assessment of cure or indeterminate and had already demonstrated resolution or non-progression of radiographic findings.
- Indeterminate: Inability to determine outcome

Other measures:

- For patients who required mechanical ventilation the techniques considered adequate for collecting respiratory specimens were BAL, mini-BAL, PSB, BBS and ETA.
- For non-ventilated patients with HAP an adequate sputum specimen was to be >25 polymorphonuclear leukocytes and <10 squamous epithelial cells per field at 100 × magnification (low-power, 10 × objective). Specimens that were derived by any of the methods listed above were to also be acceptable.

Sample size

Each study was to enrol 312 subjects per treatment group to provide 109 clinically evaluable subjects per group (assuming at least 35% would be clinically evaluable). If the population clinical cure rates for telavancin and vancomycin were both 60%, then a one-sided, 0.025 level test of the non-inferiority of telavancin relative to vancomycin employing a non-inferiority Δ criterion of 20% would have 86% power.

Randomisation

Subjects were randomised (1:1) to telavancin or vancomycin using an interactive voice response system (IVRS) with stratification on geographic region, presence or absence of diabetes and ventilatory status.

Blinding (masking)

The studies had a double-blind design.

Statistical methods

Four analysis populations were defined for efficacy-related summaries:

- All-treated (AT)
- Modified All-treated (MAT): AT patients with a baseline pathogen known to cause pneumonia identified from baseline respiratory cultures from sputum, ETA, BBS, BAL, mini-BAL or PSB
- Clinically Evaluable (CE): AT patients whose adherence to protocol expectations made it reasonable to infer that his/her clinical outcome reflected the effect of study medication
- Microbiologically Evaluable (ME): CE patients with a Gram-positive baseline respiratory pathogen

Baseline respiratory pathogens were to come from sputum, ETA, BBS, BAL, mini-BAL or PSB. If baseline respiratory cultures were not available or did not identify a respiratory pathogen but an organism known to cause pneumonia was identified from baseline blood cultures then this qualified a subject for the MAT Population. If baseline respiratory tract and blood cultures identified different respiratory pathogens, then those from respiratory tract specimens were deemed baseline pathogens.

Testing was to be conducted at a one-sided 0.025 significance level. Testing was to be implemented by the construction of a two-sided 95% confidence interval (CI) on the treatment difference (telavancin vs. vancomycin). If the lower 95% was > -0.20 the null hypothesis of clinical inferiority was to be rejected. The CE and AT analysis populations were considered co-primary.

If the above analysis concluded that telavancin was clinically non-inferior to telavancin, then a superiority analysis was to be conducted to assess whether telavancin was superior to vancomycin based on a lower 95% CI > 0. The primary analysis population in the superiority analysis was to be the CE Population with a supporting analysis in the AT Population.

Results

Participant flow

Disposition was as follows. Note that 40% prematurely discontinued study medication.

Table 32: Study Completion, Studies 0015 and 0019, AT Population

	Number of Patients					
	0015		0019		Total	
	Telavancin (N=372)	Vancomycin (N=374)	Telavancin (N=377)	Vancomycin (N=380)	Telavancin (N=749)	Vancomycin (N=754)
Completed follow-up visit						
All	286 (77%)	299 (80%)	289 (77%)	289 (76%)	575 (77%)	588 (78%)
Number of days after last study drug:						
6 Days or Less	7 (2%)	6 (2%)	7 (2%)	7 (2%)	14 (2%)	13 (2%)
7-14 Days	249 (67%)	265 (71%)	248 (66%)	249 (66%)	497 (66%)	514 (68%)
15 Days or More	30 (8%)	28 (7%)	34 (9%)	33 (9%)	64 (9%)	61 (8%)
Patients who terminated early						
All	86 (23%)	75 (20%)	88 (23%)	91 (24%)	174 (23%)	166 (22%)
Reason for early termination:						
Death	75 (20%)	61 (16%)	67 (18%)	71 (19%)	142 (19%)	132 (18%)
Withdrew consent	9 (2%)	6 (2%)	13 (3%)	11 (3%)	22 (3%)	17 (2%)
Lost to follow-up	0	3 (< 1%)	5 (1%)	8 (2%)	5 (< 1%)	11 (1%)
Transfer to another hospital	0	0	2 (< 1%)	0	2 (< 1%)	0
Other	2 (< 1%)	5 (1%)	1 (< 1%)	1 (< 1%)	3 (< 1%)	6 (< 1%)

Recruitment

Conduct of the study

There was a single protocol amendment (at 7 months after study initiation). The notable changes were:

- Imipenem for Gram-negative coverage was removed as a treatment option on the basis that removing it would reduce the risk of bias in the study results due to potential synergy with either telavancin or vancomycin.
- It was permissible to administer two active doses of telavancin in less than 24 hours provided there was a separation by at least 8 hours.
- The definitions of outcomes at EOT were re-defined to take into account need for further therapy. Indeterminate was added as a possible outcome at TOC and relapse was changed to require isolation of the same Gram-positive organism as at baseline.
- If patients with Gram-negative organisms still required specific coverage they were to remain on study medication and in the study unless they did not require further therapy for Gram-positives.

- Patients with persistent S. aureus infections were to remain on study medication for as long as the local IRB/EC allowed (up to 3 weeks). This made it possible to still assess clinical response of the pneumonia in the AT population.
- The primary analysis was specified to evaluate non-inferiority to vancomycin. In the pooled analysis, the primary analysis was to evaluate superiority to vancomycin in the subset of patients with MRSA pneumonia at baseline in the AT Population.
- Only agents potentially effective against Gram-positive HAP could not be administered for > 24 h pre-randomisation.
- Treatment failure was defined as failure to respond to at least 3 days of therapy.

Baseline data

At least two-thirds of subjects had a baseline pathogen, just over 40% were included in the CE population and around 30% in the ME population.

The majority of subjects (>50%) were 65 years or older and about 30% were 75 years or older. There were more males than females and groups were generally comparable in terms of height, weight, body mass index, ethnicity and smoking status. About one quarter was diabetic and > 40% of subjects were overweight at baseline. Overall, two-thirds had respiratory co-morbidity. Approximately 65% in 0015 and 56% in 0019 already had some degree of renal impairment (CrCl ≤ 80 mL/min) while 10% and 8% in respective studies had acute renal failure and 3% and 1% were on haemodialysis.

The mean elapsed time from diagnosis to randomisation was 1-2 days and the majority was randomised within 1 to 3 days of diagnosis. Approximately half were ventilated at baseline and about 30% per group met the definition for VAP (pneumonia after being ventilated for > 48 hours). Of subjects with complete CPIS, approximately one-third of VAP subjects in each treatment group of the AT Population had scores >6. The proportions of VAP subjects in the CE Population with scores >6 (consistent with a diagnosis of VAP) were 57% and 48% per study in the telavancin group and 32% and 40% in the vancomycin group.

A slightly higher proportion of subjects in the telavancin group had been intubated more than 7 days before randomisation and the median time from intubation to randomisation was longer by 1 day in the telavancin group. Approximately 70-80% of subjects had fever (temperature, >38°C) and approximately 60-70% had a white blood cell (WBC) count >10,000 cells/mm^3. Approximately one-quarter of subjects in each treatment group had APACHE II scores ≥ 20.

In the MATT population about 70% had Gram-positive pathogens isolated from the respiratory tract at baseline and 9% from blood. The majority had *S. aureus* (66%; 16% and 19% per study were PVL+ organisms), of which two-thirds were MRSA (in ~ 40%; 13% and 25% had PVL+ organisms).

Treatment groups were well-balanced with regards to the frequency of pathogens isolated by each respiratory specimen collection method. The majority of respiratory pathogens were collected by ETA. *Staphylococcus aureus* was the most common pathogen isolated by nearly all collection methods in both treatment groups, with MRSA more frequently isolated than MSSA.

Just over half in each study had received >24 h of prior antibacterial therapy. Justification for enrolment of these subjects is shown in the table below.

Table 33:

	Number of Patients						
	0015		0019		Total		
	Telavancin (N=372)	Vancomycin (N=374)	Telavancin (N=377)	Vancomycin (N=380)	Telavancin (N=749)	Vancomycin (N=754)	p-value*
Prior antibiotic therapy (> 24 hrs prior to enrollment)							
All	181 (49%)	209 (56%)	210 (56%)	218 (57%)	391 (52%)	427 (57%)	0.088
Pathogen resistant to this antibiotic	34 (9%)	41 (11%)	58 (15%)	61 (16%)	92 (12%)	102 (14%)	0.935
Failed therapy for NP	88 (24%)	86 (23%)	127 (34%)	125 (33%)	215 (29%)	211 (28%)	0.123
Pneumonia despite prior antibiotics	92 (25%)	110 (29%)	97 (26%)	98 (26%)	189 (25%)	208 (28%)	0.944

The durations of study therapy were comparable between treatment groups in each study. The medians were 9-10 days and the majority received between 7 and 14 days of therapy. Only 9 and 11 subjects per study who were randomised to vancomycin were switched to anti-staphylococcal penicillins when MSSA was recovered.

In 0015 vancomycin serum trough levels were measured in 134 AT subjects and 50% had a first trough ≥ 10 µg/mL. Minimum troughs ≥ 10 µg/mL were documented in 60 (45%), with 16% having minimum levels ≥ 15 µg/mL. Average vancomycin trough levels of ≥ 10 µg/mL were achieved for 86/134 (64%) subjects with 39 (29%) subjects having levels ≥ 15 µg/mL. In 0019 trough levels were measured in 92 AT subjects and 60% had a first trough ≥ 10 µg/mL. Minimum troughs ≥ 10 µg/mL were documented in 51 (55%), with 15% having minimum levels ≥ 15 µg/mL. Average vancomycin trough levels ≥ 10 µg/mL were achieved for 63/92 (68%) subjects and 27 (29%) had ≥ 15 µg/mL.

The number of subjects who received any concomitant systemic antimicrobial was comparable between treatment groups and in most cases these were agents allowed in the protocol to cover other pathogens (aztreonam in about 60%, metronidazole in 23% and piptazobactam in about 21%). Among subjects with only Gram-negative pathogens found there were 87/149 telavancin and 82/143 vancomycin subjects retrospectively judged to have received inadequate therapy for these organisms. Among those with mixed infections the rates were 90/144 and 71/126.

Numbers analysed

Details of patient populations are shown below. Most of the patients excluded from the CE population had an indeterminate outcome (26%) and/or had received additional potentially effective systemic antibacterials (28%).

Table 34: Analysis Population, Studies 0015 and 0019

	Number of Patients					
	0015		0019		Total	
	Telavancin (N=372)	Vancomycin (N=374)	Telavancin (N=377)	Vancomycin (N=380)	Telavancin (N=749)	Vancomycin (N=754)
All-Treated (AT)	372 (100%)	374 (100%)	377 (100%)	380 (100%)	749 (100%)	754 (100%)
Modified All-Treated (MAT)	257 (69%)	247 (66%)	303 (80%)	282 (74%)	560 (75%)	529 (70%)
Respiratory Pathogens	249 (97%)	245 (99%)	297 (98%)	279 (99%)	546 (98%)	524 (99%)
Blood Pathogens Only	8 (3%)	2 (< 1%)	6 (2%)	3 (1%)	14 (3%)	5 (< 1%)
Clinically Evaluable (CE)	141 (38%)	172 (46%)	171 (45%)	170 (45%)	312 (42%)	342 (45%)
Microbiologically Evaluable (ME)	108 (29%)	113 (30%)	135 (36%)	124 (33%)	243 (32%)	237 (31%)
Respiratory Pathogens	105 (97%)	113 (100%)	134 (99%)	123 (99%)	239 (98%)	236 (100%)
Blood Pathogens Only	3 (3%)	0	1 (< 1%)	1 (< 1%)	4 (2%)	1 (< 1%)
ME as % of CE population	77%	66%	79%	73%	78%	69%

Outcomes and estimation

The TOC cure rates were comparable between treatments in both populations and the lower 95% CI in each case was within -10% while the intervals spanned zero. Therefore non-inferiority was demonstrated for telavancin with respect to vancomycin.

Table 35: Clinical Response at Test-of-Cure – Studies 0015 and 0019, AT and CE Populations

	Number of Patients					
	0015		0019		Total	
	Telavancin	Vancomycin	Telavancin	Vancomycin	Telavancin	Vancomycin
All-Treated						
Cure	214 (57.5%)	221 (59.1%)	227 (60.2%)	228 (60.0%)	441 (58.9%)	449 (59.5%)
Failure	46 (12.4%)	68 (18.2%)	53 (14.1%)	52 (13.7%)	99 (13.2%)	120 (15.9%)
Indeterminate	56 (15.1%)	41 (11.0%)	39 (10.3%)	38 (10.0%)	95 (12.7%)	79 (10.5%)
Missing	56 (15.1%)	44 (11.8%)	58 (15.4%)	62 (16.3%)	114 (15.2%)	106 (14.1%)
- Total -	372 (100.0%)	374 (100.0%)	377 (100.0%)	380 (100.0%)	749 (100.0%)	754 (100.0%)
Difference (95% CI) [1]	-1.6% (-8.6% , 5.5%)		0.2% (-6.8% , 7.2%)		-0.7% (-5.6% , 4.3%)	

Clinically Evaluable						
Cure	118 (83.7%)	138 (80.2%)	139 (81.3%)	138 (81.2%)	257 (82.4%)	276 (80.7%)
Failure	23 (16.3%)	34 (19.8%)	32 (18.7%)	32 (18.8%)	55 (17.6%)	66 (19.3%)
- Total -	141 (100.0%)	172 (100.0%)	171 (100.0%)	170 (100.0%)	312 (100.0%)	342 (100.0%)
Difference (95% CI) [1]	3.5% (-5.1% , 12.0%)		0.1% (-8.2% , 8.4%)		1.7% (-4.3% , 7.7%)	

In study 0015 only a higher percentage of AT telavancin subjects had a clinical response of indeterminate at TOC. The most common reason for an indeterminate clinical response was that the subject had an infection due to a Gram-negative pathogen only (4.6% telavancin and 1% vancomycin). Other common reasons included prohibited antibacterial treatment (3.2% and 3.2%), discontinuation due to an AE (3% and 1%) and < 3 days of study medication (2.2% and 1.6%).

Also in trial 0015, only a clinical response at TOC was missing for more AT telavancin subjects than vancomycin subjects. Most of these were subjects who died before TOC (50/56 in the telavancin group and 38/44 in the vancomycin group with missing outcomes).

In a sensitivity analyses in which AT subjects who died were counted as failures at TOC, the cure rates remained comparable in each study and 95% CI were within -10%. The imbalance in proportions with missing outcomes in trial 0015 disappeared.

Table 36: Clinical Response at Test-of-Cure with Any Within Window Death Categorised as Failure – Studies 0015 and 0019, AT Population

	Number of Patients					
	0015		0019		Total	
	Telavancin	Vancomycin	Telavancin	Vancomycin	Telavancin	Vancomycin
All-Treated						
Cure	213 (57.3%)	221 (59.1%)	227 (60.2%)	226 (59.5%)	440 (58.7%)	447 (59.3%)
Failure	101 (27.2%)	109 (29.1%)	101 (26.8%)	110 (28.9%)	202 (27.0%)	219 (29.0%)
Indeterminate	52 (14.0%)	38 (10.2%)	37 (9.8%)	32 (8.4%)	89 (11.9%)	70 (9.3%)
Missing	6 (1.6%)	6 (1.6%)	12 (3.2%)	12 (3.2%)	18 (2.4%)	18 (2.4%)
- Total -	372 (100.0%)	374 (100.0%)	377 (100.0%)	380 (100.0%)	749 (100.0%)	754 (100.0%)
Difference (95% CI) [1]	-1.8% (-8.9% , 5.2%)		0.7% (-6.2% , 7.7%)		-0.5% (-5.5% , 4.4%)	

In a second sensitivity analysis CE subjects were counted as failures at TOC if they originally had a clinical response at TOC of indeterminate or missing or had who died. The applicant considered that the analysis demonstrated non-inferiority of telavancin to vancomycin based on the prospective 20% and the post hoc 14% non-inferiority margins applied. In fact, the lower 95% CI exceeded -10% but were within -12%.

Table 37: Clinical Response at Test-of-Cure – Indeterminate, Missing Responses or Deaths Categorised as Failures – Studies 0015 and 0019, CE Population

	Number of Patients					
	0015		0019		Total	
	Telavancin	Vancomycin	Telavancin	Vancomycin	Telavancin	Vancomycin
Clinically Evaluable						
Cure	118 (65.2%)	138 (67.3%)	139 (64.4%)	138 (67.3%)	276 (67.3%)	257 (64.7%)
Failure	63 (34.8%)	67 (32.7%)	77 (35.6%)	67 (32.7%)	134 (32.7%)	140 (35.3%)
- Total -	181 (100.0%)	205 (100.0%)	216 (100.0%)	205 (100.0%)	410 (100.0%)	397 (100.0%)
Difference (95% CI) [1]	-2.1% (-11.6% , 7.3%)		-3.0% (-12.0% , 6.1%)		-2.6% (-9.1% , 4.0%)	

A third sensitivity analysis applied the ATS/IDSA-recommended diagnostic criteria for HAP to AT subjects (new or progressive radiographic infiltrate plus ≥2 of fever > 38°C, leucocytosis or leucopenia and purulent secretions). These criteria were met for 634/749 (85%) telavancin group and 655/754 subjects (87%) vancomycin subjects. The proportions of subjects who met the ATS/IDSA criteria and who were deemed CE were comparable to those in the AT population.

The analysis gave comparable findings to those of the primary analysis for the AT and CE populations and all 95% CI were within -10%.

Table 38: Clinical Response at ToC – Studies 0015 and 0019, ATS/IDSA Pneumonia Definition, AT and CE Populations

	Number of Patients					
	0015		0019		Total	
	Telavancin	Vancomycin	Telavancin	Vancomycin	Telavancin	Vancomycin
All-Treated						
Cure	182 (58.9%)	184 (58.2%)	194 (59.7%)	202 (59.6%)	376 (59.3%)	386 (58.9%)
Failure	36 (11.7%)	61 (19.3%)	48 (14.8%)	47 (13.9%)	84 (13.2%)	108 (16.5%)
Indeterminate	48 (15.5%)	32 (10.1%)	33 (10.2%)	33 (9.7%)	81 (12.8%)	[illegible]
Missing	43 (13.9%)	39 (12.3%)	50 (15.4%)	57 (16.8%)	93 (14.7%)	96 (14.7%)
- Total -	309 (100.0%)	316 (100.0%)	325 (100.0%)	339 (100.0%)	[illegible]	655 (100.0%)
Difference (95% CI) [1]	0.7% (-7.1% , 8.4%)		0.1% (-7.4% , 7.6%)		0.4% (-5.0% , 5.8%)	
Clinically Evaluable						
Cure	99 (85.3%)	117 (79.1%)	119 (81.0%)	[illegible]	218 (82.9%)	238 (80.1%)
Failure	17 (14.7%)	31 (20.9%)	28 (19.0%)	28 (18.8%)	45 (17.1%)	59 (19.9%)
- Total -	116 (100.0%)	148 (100.0%)	147 (100.0%)	149 (100.0%)	263 (100.0%)	297 (100.0%)
Difference (95% CI) [1]	6.3% (-2.9% , 15.5%)		-0.3% (-9.2% , 8.7%)		2.8% (-3.6% , 9.2%)	

An exploration of the reasons for treatment failure in study 0015 showed that the AT population included 8 telavancin and 10 vancomycin subjects who failed at EOT and who died from day 3 onwards due to NP plus another 5 telavancin subjects who died after EOT due to NP. Of the 162 randomised subjects who died in this study there were 142 who died within the pre-defined data collection window (up to the TOC visit within 28 days after EOT) and 80/142 were in the telavancin group. There were 93/142 (48 telavancin) who died while receiving study medication and 49 (32 telavancin) who died after EOT. Therefore the difference in overall percentages of AT subjects who died from the first day of study medication through the Follow-up period (21.5% telavancin vs. 16.6% vancomycin) was primarily due to the difference between treatment groups in the numbers of deaths that occurred after EOT.

The reasons for treatment failure in study 0019 showed that 14 telavancin and 5 vancomycin subjects in the AT population failed at EOT and died from day 3 onwards due to NP. There was one additional vancomycin subject who died after EOT due to NP. However, this study did not show a higher rate of death in the telavancin group. Mortality rates in both studies are explored further below.

The cure rates by Gram-positive pathogen (whether or not in mixed culture) were generally comparable between treatments although one study showed slightly higher and one showed slightly lower cure rates for telavancin against MRSA.

Table 39: Clinical Cure Rates by Pathogen at ToC for the Most Common Pathogens – Studies 0015 and 0019, ME Population

	Cure Rate n/N (%) [1]					
	0015		0019		Total	
	Telavancin	Vancomycin	Telavancin	Vancomycin	Telavancin	Vancomycin
Gram-positive pathogens at baseline						
Staphylococcus aureus	80 / 98 (81.6%)	81 / 109 (74.3%)	91 / 121 (75.2%)	80 / 105 (76.2%)	171 / 219 (78.1%)	161 / 214 (75.2%)
MRSA	57 / 70 (81.4%)	63 / 84 (75.0%)	47 / 69 (68.1%)	52 / 70 (74.3%)	104 / 139 (74.8%)	115 / 154 (74.7%)
MSSA	26 / 32 (81.3%)	18 / 25 (72.0%)	44 / 52 (84.6%)	29 / 37 (78.4%)	70 / 84 (83.3%)	47 / 6[illegible] (7[illegible].8%)
Streptococcus pneumoniae	9 / 10 (90.0%)	3 / 4 (75.0%)	9 / 10 (90.0%)	15 / 17 (88.2%)	18 / 20 (90.0%)	1[illegible] / 21 (85.7%)
Gram-negative pathogens at baseline						
Pseudomonas aeruginosa	7 / 10 (70.0%)	6 / 8 (75.0%)	13 / 24 (54.2%)	13 / 14 (92.9%)	20 / [illegible] (58.[illegible]%)	19 / 22 (86.4%)
Klebsiella pneumoniae	2 / 3 (66.7%)	7 / 8 (87.5%)	5 / 8 (62.5%)	7 / 12 (58.3%)	7 / 11 (63.6%)	14 / 20 (70.0%)
Acinetobacter calcoaceticus	3 / 5 (60.0%)	3 / 4 (75.0%)	8 / 11 (72.7%)	7 / [illegible] ([illegible]%)	11 / 16 (68.8%)	10 / 12 (83.3%)
Haemophilus influenzae	1 / 1 (100.0%)	3 / 3 (100.0%)	4 / 5 (80.0%)	[illegible] / 1 (100.0%)	5 / 6 (83.3%)	4 / 4 (100.0%)

[1] Cure rate is calculated as the number of patients with the given pathogen and a clinical response of 'cure' divided by the number of patients with the given pathogen.

In both studies cure rates in ME subjects with a single Gram-positive pathogen and no Gram-negative pathogens were numerically higher for telavancin for both MSSA and MRSA. In the MAT population cure rates were comparable between treatments in 0015 and higher with telavancin in 0019. In 0015 and 0019 the numbers with multiple pathogens in the ME population were too small to make reliable comparisons but cure rates were lower with telavancin. The MAT population showed comparable findings.

The reasons for lower cure rates with telavancin in subjects with mixed infections were explored. It was found that telavancin subjects with mixed infections had higher rates of SIRS and multi-lobe involvement (85% and 65% vs. 75% and 44% of vancomycin subjects, respectively) and were more likely to have received > 24 h of antibacterial therapy prior to enrolment (62% vs. 51%). The telavancin subjects had higher rates of infection with MRSA (67.6% vs. 52.4%) and non-fermenting Gram-negative pathogens (79.4% vs. 55.6%) for which they were slightly less likely to have received "adequate" cover (28% vs. 33%) as assessed retrospectively by the applicant's medical monitors.

The "by-subject" microbiological response rates in the ME population were generally comparable between treatments overall. The studies were not powered for a formal comparison between treatments but the 95% CI fell within -12%. The pattern according to types and numbers of baseline pathogens reflected that described above for the clinical responses. The by-pathogen response rates closely followed the by-pathogen cure rates described above. There were no organisms with a > 2-fold increase in telavancin or vancomycin MIC. In the combined NP studies there was no evidence of a relationship between telavancin MIC and clinical or microbiological outcomes.

Table 39: By-patient Microbiological Response at ToC – Studies 0015 and 0019, ME Population

	Number of Patients					
	0015		0019		Total	
	Telavancin	Vancomycin	Telavancin	Vancomycin	Telavancin	Vancomycin
By-patient Microbiological Response						
Eradicated	86 (79.6%)	85 (75.2%)	103 (76.3%)	96 (77.4%)	189 (77.8%)	181 (76.4%)
Persisted	22 (20.4%)	28 (24.8%)	32 (23.7%)	28 (22.6%)	54 (22.2%)	56 (23.6%)
- Total -	108 (100.0%)	113 (100.0%)	135 (100.0%)	124 (100.0%)	243 (100.0%)	237 (100.0%)
Difference (95% CI) [1]	4.4% (-6.6% , 15.4%)		-1.1% (-11.4% , 9.2%)		1.4% (-6.1% , 9.0%)	
Eradication Rate by Number of Pathogens						
Single Gram(+) pathogen only	67 / 82 (81.7%)	66 / 88 (75.0%)	69 / 82 (84.1%)	59 / 77 (76.6%)	136 / 164 (82.9%)	125 / 165 (75.8%)
Difference (95% CI) [1]	6.7% (-5.6% , 19.0%)		7.5% (-4.8% , 19.8%)		7.1% (-1.7% , 15.9%)	
Multiple Gram(+) pathogens only	5 / 6 (83.3%)	0 / 2 (0.0%)	3 / 5 (60.0%)	7 / 7 (100.0%)	8 / 11 (72.7%)	7 / 9 (77.8%)
Mixed Gram(+) /(–)	14 / 20 (70.0%)	19 / 23 (82.6%)	31 / 48 (64.6%)	30 / 40 (75.0%)	45 / 68 (66.2%)	49 / 63 (77.8%)
Difference (95% CI) [1]	-12.6% (-36.8% , 13.2%)§		-10.4% (-29.5% , 8.6%)		-11.1% (-25.8% , 4.8%)§	

The applicant analysed outcomes for those infected only with *S. aureus* according to MICs as shown below. There was a trend for both treatments to have lower success rates against MRSA when the vancomycin MIC was ≥ 1 µg/ml. However, the table indicates a marked imbalance between groups in numbers with MRSA as the sole pathogen (i.e. 70 in the telavancin group and 31 in the vancomycin group). It should be noted that the numbers shown in the table below are limited to those for which MIC data were available (255/298 ME with only *S. aureus* at baseline). However, the fact that the table shows only the subset for which MICs were available does not explain the imbalance.

Table 40: Clinical Cure at TOC According to In-vitro Susceptibility of Baseline *S. aureus* Isolates to Vancomycin Studies 0015 and 0019, ME Population

Treatment Group [2]	Cure Rates (% [n/N]) Stratified by Vancomycin MIC	
	≤0.5 µg/ml [2]	≥1 µg/ml [3]
Telavancin		
S. aureus	89.2% (33/37)	87.1% (74/85) [4]
MSSA	88.0% (22/25)	88.9% (24/27)
MRSA	91.7% (11/12)	86.2% (50/58)
Vancomycin		
S. aureus	78.6% (22/28)	74.3% (78/105) [4]
MSSA	71.4% (10/14)	75.0% (66/88)
MRSA	85.7% (12/14)	70.6% (12/17)

A total of 408 MRSA were screened for vancomycin MIC ≥ 1 µg/mL, growth on VAN-3 or macro E-test method positive. PAP analyses confirmed that 38 subjects (22 telavancin, 16 vancomycin) were

infected with hGISA. Of these 38, there were 18 subjects who had only hGISA isolated at baseline, including 8 telavancin (5 cured, one died) and 10 vancomycin (4 cured, 5 died).

For all 38 subjects with hGISA the clinical outcomes favoured vancomycin, including 8/22 (36%) who died in the telavancin group vs. 5/16 (31%) in the vancomycin group. The applicant pointed out that more telavancin subjects had mixed infections (14 vs. 6) and that telavancin subjects with mixed infections were older (72 vs. 60 years) and had higher mean APACHE II scores (19.8 vs. 15.5). In addition, 8/14 telavancin vs. 2/6 vancomycin subjects had multilobe involvement and 13/14 vs. 3/6 had non-fermenting Gram-negative pathogens.

There was no compelling evidence in either the AT or CE populations that cure or mortality rates differed between those who received the recommended weight-adjusted initial vancomycin dose and those who received above or below this dose. Average vancomycin trough levels achieved tended to be higher in NP vs. those observed in cSSTI subjects so that 66% of AT and 65% of CE subjects had > 10 mg/l and only 6% had < 5 mg/l while 29% had ≥ 15 mg/l. There is no evidence in the NP studies that clinical cure or mortality rate differed depending on the average trough level achieved. The same pattern and conclusion were obtained when only those with a Gram-positive pathogen at baseline were analysed.

In 0015 the incidence of any potential super-infection was higher in the telavancin group (27%) than in the vancomycin group (23%). Approximately 80% of the newly isolated organisms were judged likely to represent super-infection as opposed to colonisation. Most were attributable to Gram-negative pathogens with a higher incidence in the telavancin group (20% vs. 12%) and most were multidrug-resistant pathogens (*P. aeruginosa, Acinetobacter spp.* or *S. maltophilia*).

Similarly, the incidence of any potential super-infection was higher in the telavancin group (37%) than in the vancomycin group (21%) in 0019. Approximately 90% of the newly isolated organisms were judged likely to represent super-infection as opposed to colonisation. Most were attributable to new Gram-negative pathogens with a higher incidence in the telavancin group (30% vs. 18%).

Further exploration of the rates of super-infection across studies showed that in the ME population the rate of super-infection was higher for telavancin (33% vs. 22%) as was the rate for super-infection associated with Gram-negative pathogens (26% vs. 15%). There was much less difference between treatments in super-infection rates in the MAT population (32% vs. 29% overall and 26% vs. 23% for Gram-negative pathogens. Overall, 101/180 (56%) MAT subjects with any potential super-infection in the telavancin group were excluded from the ME population compared to exclusion of 99/151 (65.6%) such subjects in the vancomycin group. Similarly, among those with a potential super-infection associated with a Gram-negative pathogen in the MAT population there were 85/147 (57.8%) telavancin and 84/120 (70%) vancomycin subjects excluded from the ME population. Hence, more vancomycin than telavancin subjects with potential super-infections were not clinically evaluable.

Ancillary analyses

All-cause mortality

The initial analysis of mortality was later superseded by an updated analysis based on a more complete dataset. The data, analyses and main findings are presented in the section of safety below.

In the individual study reports mortality in the AT populations was examined as 'within-treatment' and 'during-or-after treatment' (next table). Only those deaths that occurred before the follow-up visit or within 28 days after last study medication if no follow-up visit occurred were considered. Percentages

of subjects who died between the first study treatment day through the follow-up period as well as while receiving study medication were generally comparable between treatment groups. There was a higher rate of post-treatment deaths in the telavancin group in study 0015 only, resulting in a higher total for deaths during or after study medication. This was not seen in 0019.

As a sensitivity analysis, all-cause mortality was summarised for the AT population of subjects who met the ATS/IDSA diagnostic criteria for pneumonia (second table). In each study and overall, mortality was comparable between treatment groups during the study treatment period and during the entire study.

Table 41: All-cause Mortality – Studies 0015 and 0019, AT Population

	0015		0019		Total	
	Telavancin (N=372)	Vancomycin (N=374)	Telavancin (N=377)	Vancomycin (N=380)	Telavancin (N=749)	Vancomycin (N=754)
Deaths while receiving study medication						
Within-treatment mortality	48 (12.9%)	45 (12.0%)	43 (11.4%)	36 (9.5%)	91 (12.1%)	81 (10.7%)
Difference (95% CI) [1]	0.9 (-3.9 , 5.6)		1.9 (-2.4 , 6.3)		1.4 (-1.8 , 4.6)	
Deaths during or after study medication						
During or after treatment mortality	80 (21.5%)	62 (16.6%)	69 (18.3%)	79 (20.8%)	149 (19.9%)	141 (18.7%)
Difference (95% CI) [1]	4.9 (-0.7 , 10.6)		-2.5 (-8.1 , 3.2)		1.2 (-2.8 , 5.2)	

Table 42: All-cause Mortality – Studies 0015 and 0019, AT Population, ATS/IDSA Pneumonia Definition

	0015		0019		Total	
	Telavancin 10 mg/kg (N=309)	Vancomycin (N=316)	Telavancin 10 mg/kg (N=325)	Vancomycin (N=339)	Telavancin 10 mg/kg (N=634)	Vancomycin (N=655)
Deaths while receiving study medication						
	38 (12.3%)	41 (13.0%)	37 (11.4%)	34 (10.0%)	75 (11.8%)	75 (11.5%)
Difference (95% CI) [1]	-0.7 (-5.9 , 4.5)		1.4 (-3.4 , 6.1)		0.4 (-3.1 , 3.9)	
Deaths during or after study medication						
	61 (19.7%)	57 (18.0%)	61 (18.8%)	72 (21.2%)	122 (19.2%)	129 (19.7%)
Difference (95% CI) [1]	1.7 (-4.4 , 7.8)		-2.5 (-8.6 , 3.6)		-0.4 (-4.8 , 3.9)	

Mortality rates by renal function at baseline gave mostly low denominators and variable findings between studies in each category. The only consistent observation was a difference between treatments in mortality rates in the subgroup of CLcr < 30ml/min in the post-treatment period (24 telavancin and 8 vancomycin; 42.5% vs. 26.8%). The final logistic regression model (see below)

showed that CLcr had a significant interaction with treatment as a predictor of mortality for telavancin in subjects with CLcr < 30ml/min.

Review of the 24 telavancin subjects with CLcr < 30 ml/min who died after the last dose of study medication did not reveal any consistent pattern for cause of death and all deaths were assessed by the investigators as not related to study medication. Of the 24 telavancin subjects:

- 11 were aged at least 80 years, 6 had baseline multi-organ failure and 7 others presented with sepsis/septic shock mostly associated with Gram-negative organisms
- Most had multiple co-morbidities and developed complications related to pre-existing conditions
- Six were assessed as either cured or improved at the time of discontinuation of telavancin
- 17 died between 4-23 days post-therapy while 6 died 2 days and 1 died 3 days post-therapy.

Table 43: All-cause Mortality by Baseline Creatinine Clearance – Studies 0015 and 0019, AT Population

	Study 0015		Study 0019		Pooled Data	
	TLV	VAN	TLV	VAN	TLV	VAN
Within Treatment Mortality						
N (%AT)	48 (12.9)	45 (12.0)	43 (11.4)	36 (9.5)	91 (12.1)	81 (10.7)
N (%CLcr ≥ 80)	9 (6.5)	10 (6.8)	10 (5.6)	10 (5.7)	19 (6.0)	20 (6.2)
N (%CLcr 50 - < 80)	16 (18.6)	8 (9.4)	11 (12.0)	11 (12.5)	27 (15.2)	19 (11.0)
N (%CLcr 30 - < 50)	10 (12.5)	13 (16.3)	11 (18.0)	7 (10.4)	21 (14.9)	20 (13.6)
N (%CLcr < 30)	13 (19.1)	14 (22.2)	11 (24.4)	8 (16.3)	24 (21.2)	22 (19.6)
During or After Treatment Mortality						
N (%AT)	80 (21.5)	62 (16.6)	69 (18.3)	79 (20.8)	149 (19.9)	141 (18.7)
N (%CLcr ≥ 80)	14 (10.1)	18 (12.3)	16 (8.9)	28 (15.9)	30 (9.5)	46 (14.3)
N (%CLcr 50 - < 80)	21 (24.4)	11 (12.9)	18 (19.6)	25 (28.4)	39 (21.9)	36 (20.8)
N (%CLcr 30 - < 50)	19 (23.8)	17 (21.3)	13 (21.3)	12 (17.9)	32 (22.7)	29 (19.7)
N (%CLcr < 30)	26 (38.2)	16 (25.4)	22 (48.9)	14 (28.6)	48 (42.5)	30 (26.8)

There were also some imbalances in all-cause mortality between the two treatment arms for the different age groups with the largest difference observed in study 0019, but not 0015, for within treatment mortality among subjects aged over 75 years (22.2% vs. 9.2%). In 0015, but not 0019, during and after treatment mortality rates were higher in the telavancin group in each age sub-group. In the final multivariate regression analysis model there were no negative treatment-by-covariate interactions including age.

Table 44: All-cause Mortality by Age, Studies 0015 and 0019, AT Population

	Study 0015		Study 0019		Pooled Studies	
	TLV	VANC	TLV	VANC	TLV	VANC
Within Treatment Mortality						
N (%AT)	48 (12.9)	45 (12.0)	43 (11.4)	36 (9.5)	91 (12.1)	81 (10.7)
N (%Age < 65 y)	17 (10.0)	13 (8.0)	14 (7.7)	12 (6.5)	31 (8.8)	25 (7.2)
N (%Age ≥ 65 y)	31 (15.3)	32 (15.1)	29 (14.9)	24 (12.2)	60 (15.1)	56 (13.7)
N (%Age ≥ 75 y)	23 (17.6)	26 (21.0)	22 (22.2)	10 (9.2)	45 (19.6)	36 (15.5)
During or After Treatment Mortality						
N (%AT)	80 (21.5)	62 (16.6)	69 (18.3)	79 (20.8)	149 (19.9)	141 (18.5)
N (%Age < 65 y)	25 (14.7)	17 (10.5)	19 (10.4)	24 (13.0)	44 (12.5)	41 (11.8)
N (%Age ≥ 65 y)	55 (27.2)	45 (21.2)	50 (25.6)	55 (28.1)	105 (26.4)	100 (24.4)
N (%Age ≥ 75 y)	42 (32.1)	34 (27.4)	32 (32.3)	32 (29.4)	74 (32.2)	66 (28.3)

Bacteraemia

The frequency of bacteraemia at baseline (~9%) was comparable between treatment groups (72 vs. 68). In the AT population the clinical cure rates were lower in those with bacteraemia but not lower for telavancin vs. vancomycin. The same observations applied in the CE population except that all six telavancin subjects with bacteraemia in 0019 were clinical cures. In the subset with bacteraemia mortality rates were noticeably higher, especially in the AT population, but with little difference between the two treatments.

Early /late onset NP

In Study 0015 there was a comparable distribution between early onset and late onset NP, although there was a slight imbalance between the treatment groups of about 5%. In Study 0019 there was a good balance between the treatment groups but there were far more with late onset vs. early onset NP (almost 2:1). The clinical cure rates were generally comparable within and between treatments for sub-groups with early onset and late onset NP. The rate of clinical cure in late onset NP in the AT population of Study 0015 showed a slight trend in favour of vancomycin but in the CE population there was a small trend in favour of telavancin. In Study 0019 the cure rates were very comparable between the treatment groups.

Table 45: Numbers and Percentages of Patients with Early/Late Onset HAP in the Nosocomial Pneumonia Studies

	Study 0015				Study 0019			
	TLV n/N	(%)	VAN[1] n/N	(%)	TLV n/N	(%)	VAN[2] n/N	(%)
Early HAP	192/372	(51.6%)	172/374	(46.0%)	137/377	(36.3%)	141/380	(37.1%)
Late HAP	180/372	(48.4%)	199/374	(53.2%)	240/377	(63.7%)	238/380	(62.6%)

Table 46: Cure Rates in Early Onset and Late Onset HAP (AT and CE Populations)

	Study 0015		Study 0019		Pooled Studies	
	TLV n/N (%)	VAN n/N (%)	TLV n/N (%)	VAN n/N (%)	TLV n/N (%)	VAN n/N (%)
AT Population						
Early Onset HAP	110/192 (57.3%)	96/172 (55.8%)	81/137 (59.1%)	84/141 (59.6%)	191/329 (58.1%)	180/313 (57.5%)
Late Onset HAP	103/180 (57.2%)	122/199 (61.3%)	146/240 (60.8%)	141/238 (59.2%)	249/420 (59.3%)	263/437 (60.2%)
CE Population						
Early Onset HAP	63/76 (82.9%)	61/76 (80.3%)	49/58 (84.5%)	52/63 (82.5%)	112/134 (83.6%)	113/139 (81.3%)
Late Onset HAP	55/65 (84.6%)	75/94 (79.8%)	90/113 (79.6%)	85/106 (80.2%)	145/178 (81.5%)	160/200 (80.0%)

VAP

VAP subjects (i.e. interval between intubation and NP diagnosis > 2 days) comprised 427 AT subjects (216 telavancin, 211 vancomycin subjects) with outcomes as follows:

Table 47: Clinical Response at ToC in Patients with VAP – Studies 0015 and 0019, AT, CE, MAT, and ME populations

	Number of Patients					
	0015		0019		Total	
	Telavancin	Vancomycin	Telavancin	Vancomycin	Telavancin	Vancomycin
All-Treated						
Cure	52 (50.5%)	54 (54.0%)	54 (47.8%)	58 (52.3%)	106 (49.1%)	112 (53.1%)
Failure	8 (7.8%)	21 (21.0%)	21 (18.6%)	20 (18.0%)	29 (13.4%)	41 (19.4%)
Indeterminate	25 (24.3%)	13 (13.0%)	13 (11.5%)	13 (11.7%)	38 (17.6%)	25 (11.8%)
Missing	18 (17.5%)	13 (13.0%)	25 (22.1%)	20 (18.0%)	43 (19.9%)	33 (15.6%)
- Total -	103 (100.0%)	100 (100.0%)	113 (100.0%)	111 (100.0%)	216 (100.0%)	211 (100.0%)
Difference (95% CI) [1]	3.5% (-17.2% , 10.2%)		-4.5% (-17.5% , 8.6%)		-4.0% (-13.5% , 5.5%)	
Clinically Evaluable						
Cure	26 (89.7%)	21 (63.6%)	30 (73.2%)	22 (68.8%)	56 (80.0%)	43 (66.2%)
Failure	3 (10.3%)	12 (36.4%)	11 (26.8%)	10 (31.3%)	14 (20.0%)	22 (33.8%)
- Total -	29 (100.0%)	33 (100.0%)	41 (100.0%)	32 (100.0%)	70 (100.0%)	65 (100.0%)
Difference (95% CI) [1]	26.0% (4.4% , 44.1%)§		4.4% (-16.6% , 25.4%)		14.4% (-1.0% , 28.3%)§	

In the VAP CE population 91% telavancin and 83% vancomycin-treated subjects were also included in the ME population. In the AT populations cure rates in VAP subjects were higher with vancomycin in 0015 (with twice the rate of indeterminate outcomes in the telavancin group) but higher with telavancin in 0019. Both studies showed higher cure rates with telavancin in the (much smaller) CE

populations. For MAT subjects with VAP cure rates were comparable between treatments in each study and overall (48% vs. 50%). In the 118 ME subjects with VAP the cure rates followed the same pattern as in CE subjects with VAP (overall 78% vs. 61%) as did cure rates in the 109 ME VAP subjects with *S. aureus* at baseline (76.3% vs. 60%), whether MRSA or MSSA.

Elderly

Regarding the elderly sub-population within study 0015 there was no disadvantage for telavancin in subjects aged over 65 or over 75 years whereas in study 0019 the cure rate was lower with telavancin in the over 75s. The pooled data suggested no important difference between treatments in the < 65, > 65 or > 75 years age groups.

Table 48: Cure Rates at ToC by Age – Studies 0015 and 0019, CE Population

	Study 0015		Study 0019		Pooled Studies	
	TLV	VANC	TLV	VANC	TLV	VANC
n/N (%Age < 65 y)	57 / 68 (83.8)	59 / 67 (88.1)	75 / 89 (84.3)	71 / 83 (85.5)	132 / 157 (84.1)	130 / 150 (86.7)
n/N (%Age ≥ 65 y)	61 / 73 (83.6)	79 / 105 (75.2)	64 / 82 (78.0)	67 / 87 (77.0)	125 / 155 (80.6)	146 / 192 (76.0)
n/N (%Age ≥ 75 y)	37 / 47 (78.7)	44 / 61 (72.1)	29 / 42 (69.0)	35 / 46 (76.1)	66 / 89 (74.2)	79 / 106 (74.5)

A univariate analysis of the baseline demographic characteristics and medical conditions for the different age categories showed that:

- Diabetes was more prevalent in telavancin than in vancomycin subjects aged ≥ 75 years. MRSA was isolated more frequently in telavancin subjects aged ≥75 years, mainly driven by imbalances in study 0019, while Gram-negative non-fermenters were more frequent in the telavancin arm of both studies. In 0019 there was also a higher incidence of mixed Gram-positive/negative infections and isolation of 3 or more pathogens.
- More vancomycin subjects aged ≥ 65 years had severe renal impairment and acute renal failure at baseline and received vasopressor or inotropic agents.
- APACHE II scores were comparable for elderly subjects in the two treatment groups and rates of co-morbidities, multi-lobe infiltrations and pleural effusion showed minor differences between treatment groups.

Vasopressors

With regard to use of vasopressors, these were administered to 12% vancomycin but 7% of telavancin subjects. Among AT subjects the cure rates in those receiving vasopressors were lower than observed for the total population and for those not on vasopressors. The multivariate analysis showed that use of vasopressors predicted a higher risk of not being cured. In the individual studies the cure rates in the two treatment arms were comparable for total subjects and those not on vasopressors but among the small numbers on vasopressors there was a difference between treatments that favoured telavancin in Study 0015 (48.3% vs. 38.6%) and vancomycin in Study 0019 (30.4% vs. 43.2%).

In the AT population the mortality rates in those who were receiving vasopressors were higher than the rates for the total population and for those not on vasopressors and higher for telavancin than for vancomycin among those on vasopressors in both studies. Study 0015 also showed slightly higher mortality rates in the telavancin group regardless of vasopressor use but this was not observed in

study 0019 where mortality rates were slightly higher in the vancomycin group among those not on vasopressors.

Renal insufficiency

Just over half of NP subjects (55%) had some degree of renal insufficiency at baseline (45% had normal function while 24% had mild, 19% moderate and 11% severe impairment). In the CE population there were fewer subjects in the telavancin groups in each study with any degree of renal insufficiency. Cure rates did not show a consistent trend to increase or decrease according to renal function categories. In most comparisons the cure rates were slightly higher for telavancin than for vancomycin, the only exception being in study 0019 in the subgroup of CLcr 30 - < 50 ml/min (68% vs. 91%).

Table 49: Clinical Cure Rates by Baseline Creatinine Clearance, Studies 0015 and 0019, CE Population

	Study 0015		Study 0019		Pooled Studies	
	TLV	VAN	TLV	VAN	TLV	VAN
n/N (%CE)	118 / 141 (83.7)	138 / 172 (80.2)	139 / 171 (81.3)	138 / 170 (81.2)	257 / 312 (82.4)	276 / 342 (80.7)
n/N (%CLcr ≥ 80)	52 / 62 (83.9)	55 / 65 (84.6)	75 / 89 (84.3)	64 / 81 (79.0)	127 / 151 (84.1)	119 / 146 (81.5)
n/N (%CLcr 50 - < 80)	30 / 36 (83.3)	40 / 49 (81.6)	31 / 38 (81.6)	26 / 34 (76.5)	61 / 74 (82.4)	66 / 83 (79.5)
n/N (%CLcr 30 - < 50)	26 / 30 (86.7)	26 / 34 (76.5)	17 / 25 (67.9)	30 / 33 (90.9)	45 / 58 (77.6)	56 / 67 (83.6)
n/N (%CLcr < 30)	10 / 13 (76.9)	17 / 24 (70.8)	11 / 16 (67.5)	18 / 22 (81.8)	24 / 29 (82.8)	35 / 46 (76.1)

Potentially relevant observations included:

- Elderly (≥ 65 years) subjects were slightly more frequent in the vancomycin arm across all sub-groups with renal impairment and there was a higher proportion with acute renal failure already in the ICU at baseline. APACHE II scores increased with decreasing baseline renal function but the only imbalance was for higher scores in vancomycin subjects with CLcr < 30 ml/min in study 0019.
- Diabetes mellitus rates increased with decreasing baseline CLcr and telavancin subjects with CLcr 30 - < 50 ml/min had higher incidence of diabetes compared to vancomycin subjects. Proportions with chronic renal failure were higher in the telavancin group among those with CLcr 30 - < 50 ml/min and in the vancomycin group among those with CLcr < 30 ml/min

The European population included a lower proportion of VAP subjects (15%) compared with almost 30% in the overall population and a lower proportion with multi-lobe involvement (45% vs. 60%). Over 80% of European MAT subjects had Gram-positive pathogens isolated at baseline compared with 72% in each treatment group in the overall population. However, in the European population, MRSA accounted for just less than half of all *S. aureus* compared to over 60% in the overall study population.

Among European AT subjects cure rates were generally higher than those reported in the total populations with a pooled cure rate in the AT population > 70% and about 85% in the CE population. Telavancin had a higher cure rate than vancomycin in 0015 with difference in the opposite direction in 0019 with a higher number of subjects at European sites. There were lower rates of Indeterminate and Missing responses among European subjects than in the study population as a whole.

Cure rates were particularly higher in European subjects compared to North America and the Middle East. This was in part accounted for by a larger rate of shock at baseline and baseline emergency surgery in the latter regions. The trends in the microbiological eradication rates followed those seen for clinical cure rates (pooled rates for both treatments around 70% in the MAT population and around 80% in the ME population).

Table 50: Clinical Response at ToC – Studies 0015 and 0019, European Population

	Study 0015		Study 0019		Pooled NP Studies	
	Telavancin	Vancomycin	Telavancin	Vancomycin	Telavancin	Vancomycin
All-Treated						
Cure	48 (78.7%)	47 (65.3%)	75 (70.1%)	81 (74.3%)	123 (73.2%)	128 (70.7%)
Failure	5 (8.2%)	16 (22.2%)	16 (15.0%)	7 (6.4%)	21 (12.5%)	23 (12.7%)
Indeterminate	3 (4.9%)	4 (5.6%)	5 (4.7%)	7 (6.4%)	8 (4.8%)	11 (6.1%)
Missing	5 (8.2%)	5 (6.9%)	11 (10.3%)	14 (12.8%)	16 (9.5%)	19 (10.5%)
- Total -	61 (100%)	72 (100%)	107 (100%)	109 (100%)	168 (100%)	181 (100%)
Clinically Evaluable						
Cure	30 (90.9%)	37 (77.1%)	55 (80.9%)	65 (92.9%)	85 (84.2%)	102 (86.4%)
Failure	3 (9.1%)	11 (22.9%)	13 (19.1%)	5 (7.1%)	16 (15.8%)	16 (13.6%)
- Total -	33 (100%)	48 (100%)	68 (100%)	70 (100%)	101 (100%)	118 (100%)

BMI ≥ 40

In the NP study 0015 those with a BMI ≥ 40 in the telavancin group had a slightly lower cure rate vs. other BMI groups in the AT population but this was not seen in the CE population or in study 0019. In the vancomycin group the cure rate decreased with a BMI ≥ 40 in study 0015 but not in study 0019. The cure rate for telavancin for those with a BMI ≥ 35 were comparable to or better than for those with a BMI <35 in the AT and CE populations whereas for vancomycin the rates were comparable or lower for the obese subjects. Mortality rates in the NP studies were generally lower in the obese subjects in the AT and CE populations with no trend towards increasing mortality with increasing BMI. In the AT population there were more deaths among those with a BMI ≥ 35 for telavancin vs. vancomycin arm but this was not seen in the CE population where fewer deaths occurred.

The outcome variable used for the initial multivariate analysis was clinical cure at TOC based on investigators' opinions. Responses of indeterminate and missing in the AT population were classed as not cured and those in the CE population with these outcomes were excluded. All-cause mortality was studied as an additional outcome variable, defined as death on or before the TOC visit or before day 28 post-therapy. Prognostic factors that persistently had a significant impact on cure rates are shown below:

- The prognostic factors with the greatest impact on outcomes were APACHE II scores >20 (with more than twice the chance of clinical failure compared to APACHE II scores between 0 and 14), bacteraemia and multi-lobe pneumonia (these characteristics were associated with just under twice the chance of being a clinical failure).
- Whilst "VAP" as a prognostic factor did reach significance in Step 1 it was lost to the model at Step 2. However this may have been because "baseline mechanical ventilation" was in the model throughout and confounded the VAP prognostic factor. This factor did not interact with treatment.

- Geographic region interacted only with study (to be expected as different countries were included in different studies). The impact of Europe did not affect the treatment difference.
- Acute renal failure was lost from the model at Step 2 and creatinine clearance at Step 4, both having less impact on outcome than the final factors. There was no interaction of either with treatment.

There was no significant difference between treatments in the final model. The only interaction with treatment in the model was "inadequate Gram-negative treatment and mixed infection at baseline" at Step 4, which was lost in the final regression model. In all the models vancomycin and telavancin performed similarly except that in mixed infections in the overall model vancomycin did a little better than telavancin (OR 0.608; p value 0.0698).

Table 51: Logistic regression factors that were significant in the overall population in the Step 5 analysis for Clinical Cure, AT population

	Odds Ratio		
Prognostic Factor	**Estimate**	**95% CI**	**p-value**
APACHE II (3 Categories) {Multi-level categorical variable}			<.0001
CONTRAST: 0-14 vs.15-20 [0-14]	0.571	[0.438, 0.744]	<.0001
CONTRAST: 0-14 vs.>20 [0-14]	0.375	[0.273, 0.516]	<.0001
CONTRAST: 15-20 vs.>20 [15-20]	0.657	[0.479, 0.901]	0.0068
Radiography multi-lobe pneumonia [NO]	0.565	[0.444, 0.720]	<.0001
>=2 chronic illnesses [NO]	0.686	[0.539, 0.873]	0.0022
Pseudomonas or Acinetobacter or Stenotrophomonas [NO]	0.663	[0.503, 0.872]	0.0033
Gender [MALE]	1.40	[1.107, 1.790]	0.0053
Bacteremia at baseline [NO]	0.593	[0.404, 0.869]	0.0073
Use of Vasopressors [NO]	0.634	[0.416, 0.967]	0.0345
Mechanical ventilation [NO]	0.770	[0.597, 0.993]	0.0439
Randomized treatment [VANCOMYCIN]	0.991	[0.791, 1.242]	0.9382
Study			0.0649
Geographic region {Multi-level categorical variable}			0.0099
Interaction with study			<.0001
Any shock at baseline [NO]			0.2342
Interaction with study			0.0272
Emergency surgery at baseline [NO]			0.7023
Interaction with study			0.0063

With regard to mortality, the study populations were not markedly different but the mortality rate was higher in Latin America than in Europe.

The initial analysis of mortality in the application dossier was later superseded by an updated analysis based on a more complete dataset. The data, analyses and main findings are presented in the section of safety below.

The inconsistencies in outcomes and death rates in various sub-populations between the two NP studies cannot be dismissed on the basis of pooled data analyses. In addition, it is not possible to disregard deaths that occurred only after EOT since some of these could have been directly related to failure of study therapy and/or adverse reactions resulting from study therapy.

In this regard, it may be relevant to note that a slightly higher proportion of those treated with telavancin reported at least one of multi-organ failure, sepsis or septic shock (as defined/determined by individual investigators) compared with the vancomycin group. Among those who experienced such AEs a higher proportion died in the telavancin group (74.4% [61/82] vs. 67.8% [40/59] for

vancomycin). Not all of the deaths were thought to directly follow on from of one of these three events (as assessed by the investigator) although in many cases they were closely associated. These deaths are also explored further in the clinical safety section.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 52: Summary of Efficacy for trial 015

Title: A Phase 3, Randomized, Double-Blind, Parallel-Group, Multinational Trial of Intravenous Telavancin Versus Vancomycin for Treatment of Hospital-Acquired Pneumonia with a Focus on Patients with Infections Due to Methicillin-Resistant Staphylococcus aureus			
Study identifier	0015		
Design	Multicentre, double-blind, parallel-group, randomised trial comparing telavancin to vancomycin in patients with Gram-positive HAP. The target enrolment is 625 patients; however, additional patients (to total approximately 750 patients) may need to be enrolled to ensure that at least 100 evaluable patients infected with MRSA are available for analysis.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		7-21 days IV (FU at 7-14 days after last dose) Not Applicable Not Applicable
Hypothesis	Non-inferiority; That is, The lower bound of the 95% CI around the difference between treatments in cure rates exceeds −20%.		
Treatments groups	**Telavancin**		Telavancin 10 mg/kg once a day IV for 7-21 days, 381 randomised
	Vancomycin		Vancomycin 1 g q 12 hr IV for 7-21 days, 380 randomised
Endpoints and definitions	Primary endpoint	**Clinical Response at TOC – AT Population**	Clinical response at Test-of-Cure (Follow-up) evaluation (Cure, Failure or Indeterminate)
	Secondary endpoint	**Clinical Response at TOC – CE Population**	
	Secondary endpoint	**Clinical Response at TOC – MAT Population**	
	Secondary endpoint	**Clinical Response at TOC – ME Population**	
	Secondary endpoint	**Clinical Response at TOC for VAP patients – AT Population**	

Database lock	15 November 2007

Results and Analysis

Analysis description	**Primary analysis**		
Analysis population and time point description	Analysis population: • **All-treated (AT)**: All patients who received any amount of study medication. Time point: • **Test-of-Cure**: A blinded Test-of-cure (TOC) assessment was conducted at the Follow-up Visit only for those patients who were evaluated as a clinical cure or indeterminate at the EOT Visit.		
Descriptive statistics and estimate variability	Treatment group	**Telavancin**	**Vancomycin**
	Number of subject – AT Population	372	374
	Clinical Response at TOC – AT Population (Cure Rate)	57.5% (214/372)	59.1% (221/374)
	Standard Error	2.56%	2.54%
Effect estimate per comparison	Clinical Response at TOC – AT Population	Comparison groups	Telavancin & Vancomycin
		Difference (TLV-VAN) in Cure Rate	-1.6%
		Standard Error	3.61%
		95% CI	(-8.6%, 5.5%)
Notes	P-value is replaced with 95% CI since the study was designed to evaluate the non-inferiority.		
Analysis description	**Secondary analysis**		
Analysis population and time point description	Analysis population: • **All-treated (AT)**: All patients who received any amount of study medication. • **Clinically Evaluable (CE)**: Patients in the AT Population whose adherence to protocol expectations made it reasonable to infer that his/her clinical outcome reflected the effect of study medication. • **Modified All-treated (MAT)**: Patients in the AT Population who also had a baseline pathogen identified, defined as an organism known to cause pneumonia identified from baseline respiratory cultures from sputum, ETA, BBS, BAL, mini-BAL, or PSB. • **Microbiologically Evaluable (ME)**: Patients in the CE Population who also had a Gram-positive baseline respiratory pathogen, as defined above for the MAT Population. • **Ventilator-associated pneumonia (VAP)** refers to pneumonia that arises more than 48 hours after endotracheal intubation. Time point: • **Test-of-Cure**: A blinded Test-of-cure (TOC) assessment was conducted at the Follow-up Visit only for those patients who were evaluated as a clinical cure or indeterminate at the EOT Visit.		
Descriptive statistics and estimate variability	Treatment group	**Telavancin**	**Vancomycin**
	Number of subject – CE Population	141	172

	Clinical Response at TOC – CE Population (Cure Rate)	83.7% (118/141)	80.2% (138/172)
	Standard Error	3.11%	3.04%
	Number of subject – MAT Population	257	247
	Clinical Response at TOC – MAT Population (Cure Rate)	56.4% (145/257)	56.3% (139/247)
	Standard Error	3.09%	3.16%
	Number of subject – ME Population	108	113
	Clinical Response at TOC – ME Population (Cure Rate)	81.5% (88/108)	75.2% (85/113)
	Standard Error	3.74%	4.06%
	Number of subject – VAP patients AT Population	103	100
	Clinical Response at TOC for VAP patients – AT Population (Cure Rate)	50.5% (52/103)	54.0% (54/100)
	Standard Error	4.93%	4.98%
Effect estimate per comparison	Clinical Response at TOC – CE Population	Comparison groups	Telavancin & Vancomycin
		Difference (TLV-VAN) in Cure Rate	3.5%
		Standard Error	4.35%
		95% CI	(-5.1%, 12.0%)
	Clinical Response at TOC – MAT Population	Comparison groups	Telavancin - Vancomycin
		Difference (TLV-VAN) in Cure Rate	0.1%
		Standard Error	4.42%
		95% CI	(-8.5%, 8.8%)
	Clinical Response at TOC – ME Population	Comparison groups	Telavancin - Vancomycin
		Difference (TLV-VAN) in Cure Rate	6.3%
		Standard Error	5.52%
		95% CI	(-4.6%, 17.1%)
	Clinical Response at TOC for VAP patients – AT Population	Comparison groups	Telavancin - Vancomycin
		Difference (TLV-VAN) in Cure Rate	-3.5%

		Standard Error	7.01%
		95% CI	(-17.2%, 10.2%)
Notes	P-value is replaced with 95% CI since the study was designed to evaluate the non-inferiority.		

Table 53: Summary of Efficacy for trial 0019

Title: A Phase 3, Randomized, Double-Blind, Parallel-Group, Multinational Trial of Intravenous Telavancin Versus Vancomycin for Treatment of Hospital-Acquired Pneumonia with a Focus on Patients with Infections Due to Methicillin-Resistant Staphylococcus aureus			
Study identifier	0019		
Design	Multicentre, double-blind, parallel-group, randomised trial comparing telavancin to vancomycin in patients with Gram-positive HAP. The target enrolment is 625 patients; however, additional patients (to total approximately 750 patients) may need to be enrolled to ensure that at least 100 evaluable patients infected with MRSA are available for analysis.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		7-21 days IV (FU at 7-14 days after last dose) Not Applicable Not Applicable
Hypothesis	Non-inferiority; That is, The lower bound of the 95% CI around the difference between treatments in cure rates exceeded -20%.		
Treatments groups	**Telavancin**		Telavancin 10 mg/kg once a day IV for 7-21 days, 386 randomised
	Vancomycin		Vancomycin 1 g q 12 hr IV for 7-21 days, 385 randomised
Endpoints and definitions	Primary endpoint	**Clinical Response at TOC – AT Population**	Clinical response at Test-of-Cure (Follow-up) evaluation (Cure, Failure or Indeterminate)
	Secondary endpoint	**Clinical Response at TOC – CE Population**	
	Secondary endpoint	**Clinical Response at TOC – MAT Population**	
	Secondary endpoint	**Clinical Response at TOC – ME Population**	
	Secondary endpoint	**Clinical Response at TOC for VAP patients – AT Population**	
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Results and Analysis

Analysis description	**Primary analysis**		
Analysis population and time point description	Analysis population: • **All-treated (AT)**: All patients who received any amount of study medication. Time point: • **Test-of-Cure**: A blinded Test-of-cure (TOC) assessment was conducted at the Follow-up Visit only for those patients who were evaluated as a clinical cure or indeterminate at the EOT Visit.		
Descriptive statistics and estimate variability	Treatment group	**Telavancin**	**Vancomycin**
	Number of subject – AT Population	377	380
	Clinical Response at TOC – AT Population (Cure Rate)	60.2% (227/377)	60.0% (228/380)
	Standard Error	2.52%	2.51%
Effect estimate per comparison	Clinical Response at TOC – AT Population	Comparison groups	Telavancin & Vancomycin
		Difference (TLV-VAN) in Cure Rate	0.2%
		Standard Error	3.56%
		95% CI	(-6.8%, 7.2%)
Notes	P-value is replaced with 95% CI since the study was designed to evaluate the non-inferiority.		
Analysis description	**Secondary analysis**		
Analysis population and time point description	Analysis population: • **All-treated (AT)**: All patients who received any amount of study medication. • **Clinically Evaluable (CE)**: Patients in the AT Population whose adherence to protocol expectations made it reasonable to infer that his/her clinical outcome reflected the effect of study medication. **Modified All-treated (MAT)**: Patients in the AT Population who also had a baseline pathogen identified, defined as an organism known to cause pneumonia identified from baseline respiratory cultures from sputum, ETA, BBS, BAL, mini-BAL, or PSB. • **Microbiologically Evaluable (ME)**: Patients in the CE Population who also had a Gram-positive baseline respiratory pathogen, as defined above for the MAT Population. • **Ventilator-associated pneumonia (VAP)** refers to pneumonia that arises more than 48 hours after endotracheal intubation. Time point: • **Test-of-Cure**: A blinded Test-of-cure (TOC) assessment was conducted at the Follow-up Visit only for those patients who were evaluated as a clinical cure or indeterminate at the EOT Visit.		
Descriptive statistics and estimate variability	Treatment group	**Telavancin**	**Vancomycin**
	Number of subject – CE Population	171	170
	Clinical Response at TOC – CE Population (Cure Rate)	81.3% (139/171)	81.2% (138/170)

	Standard Error	2.98%	3.00%
	Number of subject – MAT Population	303	282
	Clinical Response at TOC – MAT Population (Cure Rate)	58.4% (177/303)	56.0% (158/282)
	Standard Error	2.83%	2.96%
	Number of subject – ME Population	135	124
	Clinical Response at TOC – ME Population (Cure Rate)	77.0% (104/135)	78.2% (97/124)
	Standard Error	3.62%	3.71%
	Number of subject – VAP patients AT Population	113	111
	Clinical Response at TOC for VAP patients – AT Population (Cure Rate)	47.8% (54/113)	52.3% (58/111)
	Standard Error	4.70%	4.74%
Effect estimate per comparison	Clinical Response at TOC – CE Population	Comparison groups	Telavancin & Vancomycin
		Difference (TLV-VAN) in Cure Rate	0.1%
		Standard Error	4.23%
		95% CI	(-8.2%, 8.4%)
	Clinical Response at TOC – MAT Population	Comparison groups	Telavancin - Vancomycin
		Difference (TLV-VAN) in Cure Rate	2.4%
		Standard Error	4.09%
		95% CI	(-5.6%, 10.4%)
	Clinical Response at TOC – ME Population	Comparison groups	Telavancin - Vancomycin
		Difference (TLV-VAN) in Cure Rate	-1.2%
		Standard Error	5.18%
		95% CI	(-11.3%, 9.0%)
	Clinical Response at TOC for VAP patients – AT Population	Comparison groups	Telavancin - Vancomycin
		Difference (TLV-VAN) in Cure Rate	-4.5%
		Standard Error	6.68%
		95% CI	(-17.5%, 8.6%)

Notes	P-value is replaced with 95% CI since the study was designed to evaluate the non-inferiority.

2.5.3. Discussion on clinical efficacy

Selection of 10 mg/kg once daily

Study 202a cast doubt on the use of 7.5 mg/kg daily while the results of 202b after amendment supported the use of 10 mg/kg. In contrast, the early results from studies 0017 and 0018 suggested that 7.5 mg/kg might be sufficient. However, the PK/PD analyses indicated that 10 mg/kg was likely to be a more reliable dose to cover the less susceptible target pathogens. Based on the results of the Phase 3 studies in cSSTI it was reasonable to proceed with this same dose in the HAP studies. Overall, the selection of 10 mg/kg as the final dose can be accepted.

cSSTI studies

The two Phase 3 studies suffered from a lack of prospective classification of patients according to baseline status and from lack of collection of all the data that would have made it possible to retrospectively categorise the severity of the infections treated. However the applicant provided a detailed summary of the baseline characteristics of these patients, the nature of their baseline infections and their management (e.g. in terms of abscess drainage). Overall, the population enrolled into these studies appears to have been suitable.

About 60% of patients enrolled had *S. aureus* and more than half were MRSA, 80% of which had the gene for PVL. On this basis the choice of vancomycin as the comparator can be accepted. Numbers of *S. pyogenes* were much smaller but the pooled data were sufficient to make some assessment of efficacy. As has been usual in these studies the numbers with bacteraemia were very small.

Cure rates were comparable for each treatment between the two studies. Both studies demonstrated non-inferiority for telavancin based on cure rates at TOC in the AT and CE populations with lower 95% CI around treatment differences that were within -5%. There was no indication within each study or on pooling of the data that telavancin was any less effective than vancomycin in terms of "by-pathogen" or "by-patient" clinical and microbiological outcomes.

Although pooling of data from these studies using the same protocol was planned, it is clear (including evidence from the multivariate analysis) that they were not identical in conduct and case mix. For example, investigators in study 0018 were very much less likely to administer aztreonam or metronidazole than those in study 0017, yet the proportions with infections due to mixed Gram-positive and Gram-negative pathogens and the treatment success rates were comparable between studies. This suggests that there may have been some unnecessary use of additional agents in study 0017 but at the same time the investigation of imbalances in cure rates in sub-populations of elderly patients and those with renal insufficiency suggested that there might be some correlation with an imbalance in Gram-negative pathogens between treatments. Therefore the lower use of Gram-negative cover in 0018 may be pertinent.

In 92 cases (60 telavancin) it was determined that the additional antibacterial agents were given for reasons other than lack of efficacy with higher rates in the telavancin group in each study. The imbalance between treatment groups was explored but no explanation could be identified and it may have occurred by chance. These patients were excluded from the CE population if their baseline pathogen(s) were known or suspected to be susceptible to the additional agent.

The studies provided limited experience with use of telavancin in the elderly. The lower cure rates in the elderly treated with telavancin may be related to differences in rates of renal insufficiency, peripheral vascular disease and ulcers as well as rates of infection with Gram-negative pathogens. Moreover, the lower cure rates seen with telavancin in those with CLcr < 50 ml/min showed the same pattern of differences between treatments and between studies as observed for the elderly sub-populations. Investigation of the latter trend suggested a possible relationship between low cure rates and the frequencies of lower leg infections and Gram-negative pathogens.

Added to these findings, the multivariate analysis showed that the prognostic factors that persistently had a significant impact on clinical outcome were bacteraemia, geographic region, infection site and age. However, the only treatment interaction detected was in subjects aged < 65 years, who as a group had higher cure rates with telavancin.

HAP studies

The study population enrolled into trials 0015 and 0019 appears to have been generally suitable. The mean elapsed time between initial hospitalisation and randomisation was much longer in study 0019 than in study 0015. The clinical cure rates were generally comparable within and between treatments for sub-groups with early onset and late onset NP.

Although the ATS/IDSA 2005 guidance appeared after protocol finalisation, about 85% of patients overall met the criteria for pneumonia (ranging from 73% telavancin and 84% vancomycin in 0015 and 86% and 89% in respective groups in 0019). The applicant reviewed and compared populations that did and did not meet the ATS/IDSA criteria and found that those not meeting the criteria had a higher rate of most signs and symptoms, including pleural effusion. The cure rates in the AT population that met the ATS/IDSA criteria were 58-59% in 0015 and 59-60% in 0019 with lower 95% CI within -10%. Similarly, cure rates in the CE sub-population that met ATS/IDSA criteria were 85% vs. 79% in 0015 and 81% in both treatment groups in 0019 and again the lower 95% CI were within -10%. These cure rates, as well as the all-cause mortality rates, were comparable with those observed in patients that did not meet the ATS/IDSA criteria.

Quantitative cultures were not always attempted in these studies. Variations in sampling and normal error margins in quantitative techniques make these results relatively untrustworthy. Therefore lack of quantisation is not considered to be a major deficit in these studies, in which between two-thirds (0015) and three quarters (0019) had a pathogen at baseline, most of which were Gram-positive species. More important is the risk that the organisms isolated may have represented colonisation (including colonisation of endotracheal tubes) rather than true pulmonary pathogens. However, there is no consensus on how to differentiate colonisers from true pathogens and therefore much reliance is placed on meeting the clinical and radiological criteria.

The pre-determined non-inferiority margin based on comparisons of cure rates has been discussed by the applicant but it remains difficult to wholly accept a margin of -20%. Nevertheless, the actual results gave lower bounds of 95% CI around the differences in cure rates within -10% in each study for the primary analysis in the co-primary populations as well as in the MAT and ME populations (the only exception being the ME population in 0019 with 95% CI -12%, +10%).

Concerns regarding these analyses included the higher rates of indeterminate and missing outcomes in the AT population of study 0015 for telavancin vs. vancomycin. Also in study 0015 there was a higher death rate in the telavancin group that was due to an imbalance in numbers who died after the EOT visit. However, neither of these imbalances between treatment groups was observed in study 0019.

It was also noted that in 0015 the AT population included 8 telavancin and 10 vancomycin patients who failed at EOT with a reason of death due to HAP from day 3 onwards plus another 5 telavancin

patients who died after EOT due to HAP (total 13 telavancin and 10 vancomycin) whereas the totals were 7 and 8 such patients in respective groups in the CE population. In 0019 the AT population included 14 telavancin and 5 vancomycin patients who failed at EOT with a reason of death due to HAP from day 3 onwards and 10 and 4 such patients in the CE population.

It was therefore important that in the sensitivity analyses for both studies (in which all deaths in AT and CE populations were counted as failures and in which all patients with missing or indeterminate outcomes assigned were counted as CE patients who failed) the lower 95% CI were > -9% for the former analyses and ≥ -12% for the latter analyses.

Most patients with a Gram-positive pathogen obtained from the respiratory tract had *S. aureus* and MRSA predominated. Clinical and microbiological outcomes by pathogen did not suggest a consistent advantage or disadvantage for telavancin against MSSA or MRSA. However, in both studies the cure rates in the small numbers of patients with multiple pathogens were lower for telavancin. The explorations of these differences showed that in 0015 the telavancin patients had higher rates of SIRS and multi-lobe involvement, were more likely to have received > 24 h of antibacterial therapy prior to enrolment and had higher rates of infection with MRSA plus non-fermenting Gram-negative pathogens for which they were slightly less likely to have received "adequate" cover as assessed retrospectively by the applicant's medical monitors. In 0019 the telavancin patients with mixed pathogens were more likely to have renal insufficiency, received inadequate therapy for their Gram-negative pathogens and to have *P. aeruginosa*.

Both studies showed higher rates of super-infection (mostly with new Gram-negative pathogens) in the telavancin group.

In both studies the total mortality rates were around 20% regardless of treatment group and despite the differences between studies in mean and median times between hospitalisation and randomisation. While the analyses performed on the pooled study populations showed comparable mortality rates between treatment arms, the subset analyses suggested increased mortality among patients with severe renal impairment in the telavancin arm compared to vancomycin. The multivariate analysis showed no difference between treatments in the final logistic regression model but demonstrated a treatment by (prognostic) factor interaction in the subgroup of patients with CLcr < 30 ml/min.

With two studies in HAP the fact that there are some inconsistencies in outcomes and death rates in various sub-populations between the two is perhaps not surprising but these cannot be dismissed on the basis of pooled data analyses. In addition, it is not possible to disregard deaths that occurred only after EOT since some of these could have been directly related to failure of study therapy and/or adverse reactions resulting from study therapy.

2.5.4. Conclusions on the clinical efficacy

Telavancin demonstrated comparable efficacy vs. vancomycin in cSSTI and NP studies.

2.6. Clinical safety

Patient exposure

Overall, 2264 subjects and subjects were exposed to telavancin up to the cut-off date of 01 July 2009 for the initial application dossier. In the efficacy and safety studies 1780 subjects received 10 mg/kg telavancin daily (or adjusted based on renal function). Almost all comparator subjects (98% in cSSTI and 97% in HAP) in the efficacy studies received vancomycin and therefore the comparator data have been pooled in the tables that follow. The majority of these subjects received 7-14 days of their assigned therapy. An additional 29/58 subjects with S. aureus bacteraemia (not counted in the table) received telavancin 10 mg/kg once daily in study 203a.

Table 54: Exposure of Subjects – All Studies – Safety Population at Data Cut-off – 1 July 2009

	Number of Subjects Exposed	
Study Group	**Telavancin**	**Comparator**
Clinical Pharmacology Studies		
Single Dose Studies[1] (0.25 - 15 mg/kg IV)	124	47
Multiple Dose Studies (7.5 - 15 mg/kg IV)	144	103
Single and multiple dose study (7.5 mg - 10 mg/kg)	24	13
Total Clinical Pharmacology Studies	292	163
Efficacy and Safety Studies in cSSTI		
0017, 0018, 202a, 202b (7.5 mg/kg IV)	192	189
0017, 0018 and 202b (10 mg/kg IV)	1029	1033
Efficacy and Safety Studies in NP		
0015, 0019 (10 mg/kg IV)	751	752
Total Efficacy and Safety Studies	1972	1974
Total Completed Studies	2264	2137

[1] Of the 124 subjects in the telavancin single dose studies, 79 received one single dose, and 45 received single doses on more than one occasion separated by 1 or more weeks.

Adverse events

- Overall rates of AEs were influenced by reports of foamy urine due to the HP-β-CD and by dysgeusia, which accounted for > 650 AEs in telavancin subjects. Removal of these reports from the total resulted in lower total AE reporting rates with telavancin vs. vancomycin.
- SOCs with the most frequent AEs in telavancin subjects were GI disorders and nervous system disorders.
- The GI AEs indicated that nausea and vomiting were responsible for the treatment differences in cSSTI studies but there was no difference in the NP studies. There were three reports of colitis not otherwise specified associated with telavancin in the NP studies and two were considered related to telavancin. In addition, there were 10 case reports of clostridium colitis for telavancin and 9 such reports for vancomycin.

- There were more AEs in the nervous system SOC in the telavancin group in the clinical pharmacology and cSSTI studies but most of the difference vs. vancomycin reflected the rate of dysgeusia.
- Among the infections reported as AEs, urinary tract infection occurred more frequently in the telavancin subjects in the cSSTI studies but rates were low (2% vs. 1%). Sepsis and septic shock occurred more frequently on telavancin (30 and 33 cases vs. 21 and 30 for vancomycin).
- Subjects that received telavancin had fewer rashes and skin events than vancomycin overall.

Table 55: Treatment-Emergent Adverse Events by SOC and Preferred Term – Clinical Pharmacology and Efficacy and Safety Studies in cSSTI and NP – Safety Population

	Clinical Pharmacology Studies		cSSTI Studies 0017, 0018, 202a, 202b		NP Studies 0015, 0079		Totals	
	TLV (N=268)	COMP [1] (N=150)	TLV (N=1221)	VCM [2] (N=1222)	TLV (N=751)	VCM [3] (N=752)	TLV (N=2240)	VCM and COMP [4] (N=2124)
Any Event	214 (80%)	83 (55%)	935 (77%)	868 (71%)	616 (82%)	613 (82%)	1765 (79%)	1564 (74%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	0	47 (4%)	43 (4%)	104 (14%)	118 (16%)	151 (7%)	161 (8%)
CARDIAC DISORDERS	0	1 (<1%)	62 (5%)	41 (3%)	124 (17%)	143 (19%)	186 (8%)	185 (9%)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0	0	0	0	1 (<1%)	0	1 (<1%)	0
EAR AND LABYRINTH DISORDERS	5 (2%)	1 (<1%)	14 (1%)	17 (1%)	4 (<1%)	4 (<1%)	23 (1%)	22 (1%)
ENDOCRINE DISORDERS	0	0	3 (<1%)	1 (<1%)	9 (1%)	6 (<1%)	12 (<1%)	7 (<1%)
EYE DISORDERS	2 (<1%)	1 (<1%)	24 (2%)	26 (2%)	14 (2%)	17 (2%)	40 (2%)	44 (2%)
GASTROINTESTINAL DISORDERS	59 (22%)	17 (11%)	495 (41%)	398 (33%)	260 (35%)	264 (35%)	814 (36%)	679 (32%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	46 (17%)	21 (14%)	292 (24%)	263 (22%)	130 (17%)	137 (18%)	468 (21%)	423 (20%)
HEPATOBILIARY DISORDERS	0	0	8 (<1%)	6 (<1%)	18 (2%)	19 (3%)	26 (1%)	25 (1%)
IMMUNE SYSTEM DISORDERS	4 (1%)	2 (1%)	12 (<1%)	16 (1%)	3 (<1%)	4 (<1%)	19 (<1%)	22 (1%)
INFECTIONS AND INFESTATIONS	8 (3%)	2 (1%)	165 (14%)	124 (10%)	199 (26%)	192 (26%)	372 (17%)	318 (15%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	5 (2%)	1 (<1%)	37 (3%)	35 (3%)	65 (9%)	69 (9%)	104 (5%)	105 (5%)
INVESTIGATIONS	3 (1%)	1 (<1%)	104 (9%)	122 (10%)	107 (14%)	99 (13%)	214 (10%)	222 (10%)
METABOLISM AND NUTRITION DISORDERS	5 (2%)	2 (1%)	121 (10%)	107 (9%)	198 (26%)	206 (27%)	324 (14%)	315 (15%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	16 (6%)	6 (4%)	89 (7%)	93 (8%)	31 (4%)	34 (5%)	136 (6%)	133 (6%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	0	3 (<1%)	1 (<1%)	6 (<1%)	3 (<1%)	9 (<1%)	4 (<1%)
NERVOUS SYSTEM DISORDERS	165 (62%)	47 (31%)	502 (41%)	278 (23%)	89 (12%)	81 (11%)	756 (34%)	406 (19%)
PSYCHIATRIC DISORDERS	7 (3%)	1 (<1%)	189 (15%)	167 (14%)	99 (13%)	113 (15%)	295 (13%)	281 (13%)
RENAL AND URINARY DISORDERS	4 (1%)	1 (<1%)	200 (16%)	79 (6%)	86 (11%)	90 (12%)	335 (15%)	170 (8%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (<1%)	0	27 (2%)	31 (3%)	15 (2%)	8 (1%)	43 (2%)	39 (2%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	18 (7%)	7 (5%)	141 (12%)	101 (8%)	142 (19%)	142 (19%)	301 (13%)	250 (12%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	27 (10%)	11 (7%)	209 (17%)	302 (25%)	130 (17%)	121 (16%)	366 (16%)	434 (20%)
SURGICAL AND MEDICAL PROCEDURES	0	0	1 (<1%)	0	0	1 (<1%)	1 (<1%)	1 (<1%)
VASCULAR DISORDERS	8 (3%)	6 (4%)	77 (6%)	90 (7%)	109 (15%)	105 (14%)	194 (9%)	201 (9%)

In clinical pharmacology studies with dosing up to 15 mg/kg daily the rates of dysgeusia, headache, injection site reactions, nausea, vomiting, pruritus, red man syndrome and psychiatric AEs showed a trend to increase with increasing dose. In cSSTI studies there was no clear trend to increased AE reporting rates between 7.5 mg/kg and 10 mg/kg daily doses.

In cSSTI and NP studies most AEs on telavancin were mild or moderate in intensity. The percentages considered severe were higher in the NP studies than in the cSSTI studies and more subjects in the telavancin group had severe AEs (33% vs. 28%). Severe AEs were predominately infections and respiratory tract disorders and mainly reflected reports of osteomyelitis, sepsis and respiratory failure (cSSTI) or respiratory failure and acute renal failure (NP).

In the cSSTI studies treatment-related AEs occurred in 60% of telavancin and 49% of vancomycin-treated subjects with rates of 61% and 50% in studies that compared 10 mg/kg telavancin with vancomycin. Those reported with a frequency of >1% in telavancin subjects were dysgeusia (31%), nausea (21%), vomiting (11%), urine abnormality (foamy urine, 11%), headache (8%), diarrhoea (5%), constipation (4%), insomnia (4%), pruritus (4%), dizziness (3%), rash (3%), rigors (3%) and fatigue (3%). In the vancomycin group, the commonest treatment-related AEs were nausea (12%), pruritus (10%), diarrhoea (6%) and vomiting (6%).

In the NP studies, treatment-related AEs were reported in 28% of telavancin and 23% of vancomycin-treated subjects. Those in the telavancin group with a frequency > 1% included diarrhoea (4%), nausea (2%), vomiting (2%), acute renal failure (2%), ALT increased (2%), blood creatinine increased (2%) and rash (2%). In the vancomycin group the most common were diarrhoea (3%) and ALT increased (2%).

In the cSSTI studies AE reporting rates were higher in the telavancin group vs. vancomycin and this was especially notable among subjects with CLcr < 50 ml/min. The overall difference between treatments mainly reflected rates of constipation, nausea, vomiting, dysgeusia and urine abnormality. AEs with increased rates as renal function decreased in telavancin subjects included acute renal failure, hypotension and hypertension. In contrast, in the HAP studies the AE reporting rates did not show a notable difference between treatments. Among subjects with CLcr ≥ 80 ml/min there was no apparent difference between treatments for rates of renal AEs in the cSSTI studies or the HAP studies.

Table 56: Number of TEAEs Per Baseline Renal Function in 10 mg/kg Dose Studies (Post-Amendment 202b, 0017 and 0018; 0015 and 0019) – Safety Population

	cSSTI		NP	
Baseline CLcr	TLV N=1029	VAN N=1033	TLV N=751	VAN N=752
Number of patients (%) with at least one AE				
> 80 ml/min	515/655 (79)	489/667 (73)	228/293 (78)	231/300 (77)
> 50-80 ml/min	163/230 (71)	150/228 (66)	163/203 (80)	165/202 (82)
30-50 ml/min	64/78 (82)	55/84 (65)	137/163 (84)	134/161 (83)
< 30 ml/min	33/40 (83)	20/29 (69)	88/92 (96)	83/89 (93)
Missing	16/26 (62)	16/25 (64)	0	0

More than half of the AEs mapped to the renal SOC concerned urine abnormality, largely due to reporting of "foamy urine". After removal of these AEs the rates in this SOC were comparable at

telavancin 7.4% and comparator 8.0%. No renal AEs were seen in the clinical pharmacology studies with doses up to 15 mg/kg for 10 days.

In cSSTI studies the rates of renal AEs were 3% (6/192) for telavancin vs. 1% (2/189) for vancomycin. In NP studies reporting rates were higher but still showed slightly higher rates with telavancin. Overall 13/22 (59%) in the telavancin group vs. 5/13 (38%) in the vancomycin group for whom an AE of renal insufficiency was reported entered the study with baseline CLcr <50 ml/min and all subjects with an AE of chronic renal failure (4 vs. 2) had underlying renal disease at baseline (baseline CLcr 9-44 ml/min). However, there was an excess of renal AEs with telavancin even in those who entered studies with CLcr > 80 ml/min. Among those with decreased renal function at baseline the differences in rates of renal AEs were most marked in those with CLcr 50-79 ml/min. There was also a difference in the rate of worsening of renal insufficiency in subjects with baseline CLcr < 30 ml/min (7 telavancin and one vancomycin).

Table 57: Number of Renal Events in 10 mg/kg Dose Telavancin Studies (Post-Amendment cSSTI 202b, 0017, 0018 and NP 0015, 0019) – Safety Population

	cSSTI		NP		Total	
	TLV N=1029	VAN N=1033	TLV N=751	VAN N=752	TLV N=1780	VAN N=1785
Renal TEAE [1]	35 (3)	12 (1)	74 (10)	57 (8)	109 (6)	69 (4)
Renal ADR [2]	27 (3)	9 (1)	40 (5)	30 (4)	67 (4)	39 (2)
Renal SAE [3]	12 (1)	4 (<1)	26 (3)	17 (2)	38 (2)	21 (1)
Discontinuations [4]	14 (1)	3 (<1)	14 (2)	7 (1)	28 (2)	10 (1)

Table 58: Incidence of Renal TEAEs by Baseline Renal Function cSSTI Studies (202b, 0017, 0018) and NP Studies (0015, 0019)

	cSSTI		NP		TOTAL	
	TLV N=1029	VAN N=1033	TLV N=751	VAN N=752	TLV N=1780	VAN N=1785
<30 ml/min	n=66	n=54	n=113	n=112	n=179	N=166
Any event	8 (12)[1]	3 (6)	17 (15)	12 (11)	25 (14)[1]	15 (9)
Blood Creatinine Increased	2 (3)	1 (2)	4 (4)	3 (3)	6 (3)	4 (2)
Acute renal failure	2 (3)	0	6 (5)	5 (5)	8 (4)	5 (3)
Chronic renal failure	0	1 (2)	3 (2)	1 (1)	3 (2)	2 (1)
Renal impairment	2 (3)	1 (2)	0 (1)	2 (2)	2 (1)	3 (2)
Renal insufficiency	3 (5)	0	4 (4)	1 (1)	7 (4)	1 (1)
30-49 ml/min	n=78	n=84	N=141	n=147	N=219	n=231
Any event	6 (8)	1 (1)	18 (11)	13 (9)[2]	24 (11)	14 (6)[2]
Blood Creatinine Increased	1 (1)	1 (1)	3 (2)	3 (2)	4 (2)	4 (2)
Acute renal failure	2 (3)	0	9 (6)	6 (4)	11 (5)	6 (3)
Chronic renal failure	0	0	1 (1)	0	1 (1)	0
Renal impairment	0	0	2 (1)	1 (1)	2 (1)	1 (<1))
Renal insufficiency	3 (4)	0	3 (2)	4 (3)	6 (3)	4 (2)
50-79 ml/min	n=230	n=228	n=178	n=173	N=408	n=401
Any event	12 (5)[3]	3 (1)	24 (13)[4]	14 (8)	36 (9)[3],[4]	17 (4)
Blood Creatinine Increased	5 (2)	2 (1)	6 (3)	2 (1)	11 (3)	4 (1)
Acute renal failure	3 (1)	0	11 (6)	7 (4)	14 (3)	7 (2)
Chronic renal failure	0	0	0	0	0	0
Renal impairment	2 (1)	0	4 (2)	1 (1)	6 (2)	1 (<1)
Renal insufficiency	3 (1)	1 (<1)	5 (3)	4 (2)	8 (2)	5 (1)
≥80 ml/min	n=554	n=668	N=317	n=322	n=971	n=990
Any event	9 (1)	5 (1)	15 (4)	18 (6)[5]	24 (3)	23 (2)[5]
Blood Creatinine Increased	6 (1)	2 (<1)	5 (2)	4 (1)	11 (1)	6 (1)
Acute renal failure	2 (<1)	1 (<1)	8 (3)	10 (3)	10 (1)	11 (1)
Chronic renal failure	0	0	0	0	0	0
Renal impairment	0	1 (<1)	2 (1)	3 (1)	2 (<1)	4 (<1)
Renal insufficiency	1 (<1)	1 (<1)	0	2 (1)	1 (<1)	3 (<1)

An analysis of subjects with renal AEs according to significant co-morbidities subjects with no other risk factors for renal AEs showed lower rates in each treatment group. Also, those receiving concomitant potentially nephrotoxic medications had an increased risk for renal AEs compared to those not taking such medications. The relative risk for development of renal AEs in subjects not taking these medications was higher in the vancomycin group [RR: (64/967) / (5/818) = 10.8] than the telavancin group [RR: (94/977) / (15/803) = 5.2]. When subjects who had previously or concurrently taken vancomycin were excluded from the analysis the proportional difference between the incidences of renal TEAEs across treatments was attenuated.

Table 59: Renal TEAEs by Baseline Renal Risk Factors and by Concomitant Nephrotoxic Medications – Total Efficacy and Safety Population

	Total cSSTI		Total NP		Total	
	TLV N=1029	VAN N=1033	TLV N=751	VAN N=752	TLV N=1780	VAN N=1785
Number of Patients (%)						
Any Renal AE[1]	35/1029 (3)	12/1033 (1)	74/751 (10)	57/752 (8)	109/1780 (6)	69/1785 (4)
No Baseline Renal Risk Factors[2]	3/519 (<1)	3/532 (<1)	2/141 (1)	5/142 (4)	5/660 (1)	8/674 (1)
Any Baseline Renal Risk Factor[2]	32/510 (6)	9/501 (2)	72/610 (12)	52/610 (9)	104/1120 (9)	61/1111 (5)
No Co-medication[3]	7/595 (1)	3/613 (<1)	8/208 (4)	2/205 (1)	15/803 (2)	5/818 (1)
Co-medication[3]	28/434 (6)	9/420 (2)	66/543 (12)	55/547 (10)	94/977 (10)	64/967 (7)

[1] Includes the following preferred terms: renal failure acute, renal failure chronic, renal insufficiency, renal impairment, blood creatinine increased

Subjects with renal AEs in the 10 mg/kg telavancin studies and/or a Potentially Clinically Significant (PCS) increase in serum creatinine (peak ≥ 133 µmol/l and increase ≥1.5 x baseline) numbered 202 telavancin and 123 vancomycin. Of these 325 subjects, 120 (37%) had a reported renal AE and a PCS increase. Among subjects with a PCS increase in serum creatinine 82 subjects died (57 telavancin).

In the cSSTI studies 10.8% of telavancin subjects in the baseline abnormal serum Cr group experienced >50% increases on treatment or up to 7 days compared to 6.6% in the normal serum Cr group and 2.9% for vancomycin in both abnormal and normal serum Cr groups.

Table 60: Time of first increase in SeCr >50% in cSSTI studies for patients with normal and abnormal SeCr at baseline AT population excluding patient with dialysis

	All patients		Normal SeCr at baseline		Abnormal SeCr at baseline	
Days to first SeCr≥50%	TLV (N=929)	VAN (N=938)	TLV (N=822)	VAN (N=856)	TLV (N=83)	VAN (N=68)
0-7	63 (6.8%)	27 (2.9%)	54 (6.6%)	25 (2.9%)	9 (10.8%)	2 (2.9%)
8-14	35 (3.8%)	23 (2.5%)	34 (4.1%)	21 (2.5%)	1 (1.2%)	2 (2.9%)
15-21	22 (2.3%)	12 (1.3%)	23 (2.8%)	10 (1.2%)	0	2 (2.9%)
22-28	12 (1.3%)	8 (0.9%)	11 (1.3%)	7 (0.8%)	1 (1.2%)	1 (1.5%)
29-35	0	0	0	0	0	0
>35	2 (0.2%)	0	2 (0.2%)	0	0	0
No SeCr≥50%	794 (85.5%)	868 (92.5%)	698 (84.9%)	793 (92.6%)	72 (86.7%)	61 (89.7%)

In the NP studies (see below), the percentage of subjects in the abnormal serum Cr telavancin group that experienced > 50% increases on treatment or up to 7 days follow up (15.4%) was comparable with the rate observed among those with a normal serum Cr at baseline (14.7%). In the vancomycin group 8.4% of subjects with abnormal or normal serum Cr experienced a > 50% increase on treatment. There was no obvious difference in timing of onset of > 50% increases on treatment or up to 7 days follow up in subjects with abnormal and normal serum Cr at baseline.

The applicant concluded that Vibativ induces a response from the kidney during the first few days after start of treatment that manifests as an increase in serum Cr. However, the kidney appears to adapt as a high proportion of the changes do not fall outside the normal range and may decrease while on treatment.

Table 61: Time to first increase in SeCr ≥50% in NP studies for patients with normal and abnormal SeCr at baseline

	All patients		Normal SeCr at baseline		Abnormal SeCr at baseline	
Days to first SeCr≥50%	TLV (N=751)	VAN (N=752)	TLV (N=599)	VAN (N=604)	TLV (N=117)	VAN (N=119)
0-7	106 (14.1%)	61 (8.1%)	88 (14.7%)	51 (8.4%)	18 (15.4%)	10 (8.4%)
8-14	48 (6.4%)	41 (5.5%)	42 (7.0%)	40 (6.6%)	6 (5.1%)	1 (0.8%)
15-21	25 (3.3%)	24 (3.2%)	24 (4.0%)	21 (3.5%)	1 (0.9%)	3 (2.5%)
22-28	12 (1.6%)	10 (1.3%)	10 (1.7%)	10 (1.7%)	2 (1.7%)	0
29-35	2 (0.3%)	4 (0.5%)	2 (0.3%)	4 (0.7%)	0	0
>35	0	1 (0.1%)	0	1 (0.2%)	0	0
No SeCr≥50%	558 (74.3%)	611 (81.3%)	433 (72.3%)	477 (79.0%)	90 (76.9%)	105 (88.2%)

In a detailed exploration (using MVLRA) of subjects who did and did not have > 50% increases in serum Cr on treatment or up to 7 days follow up the cSSTI study data gave a final MVLRA model in which the following had a significant Odds ratio: hypotension (OR 4.5 (CI 95% 1.0, 19.9), hypertension (OR 2.1 CI 95% 1.5, 2.9), gender female (OR 2 CI 95% 1.4, 2.8), anaemia (OR 2 (CI 95% 1.4, 2.8), > 2 chronic illnesses (OR 1.7 (CI 95% 1.1, 2.5) and race non-white (OR 1.5 CI 95% 1.04, 2.19). Telavancin had an OR of 2 (CI 95% 1.4, 2.9) so it had a greater effect on serum Cr than vancomycin and this appeared to be related to the marked increase in frequency of first occurrence of > 50% increases at Day 3/4, which was not reflected in the incidence of renal AEs.

A similar approach was used to explore the NP study data. The MVLRA indicated that a history of renal disease significantly increased the odds of having a renal AE (by 2-fold). The treatment-by-factor interactions detected were geographic region, ventilator status and inadequate therapy for Gram-negative pathogens. There were no treatment-by-factor interactions for telavancin with any baseline renal function variable as measured by CrCl at baseline, age > 65 years, history of diabetes, BMI or any of the nephrotoxic medications. As it is unlikely that telavancin is interacting with geographic region, ventilator status or therapy for Gram-negatives *per se*, the differences in renal AEs have not been explained and may lie in differences in factors not taken into account in the MVLRA.

There were 22 subjects (12 telavancin) who required or were recommended to have renal replacement therapy (RRT). There were also no marked differences in outcomes of renal AEs between treatments with 52% (57/109) telavancin and 52% (36/69) vancomycin subjects recovered or improving. Similarly, 50% of subjects with a PCS in creatinine in each treatment group had recovered while among those that had not recovered 22/74 (30%) telavancin and 13/45 (29%) vancomycin subjects had died.

Of 43 telavancin subjects in NP studies with renal impairment at baseline who died there were 32 who had acute renal failure and 15 with chronic renal failure (including 4 with acute and chronic renal failure at study entry). None of the deaths was considered related to telavancin. The commonest risk factors in these 43 subjects were cardiac co-morbidities [34, (79%)], multilobar pneumonia [31,

(72%)], age > 65 [29, (67%)], ventilation [23, (53%)], APACHE II Score > 20 [19, (44%)], shock [18, (42%)] and inadequate Gram negative treatment [17, (40%)].

Table 62: Mortality Rates in patients with Acute or Chronic Renal Failure

	Death	
	TLV	VAN
Baseline Acute Renal Failure#	32/73 (44%)	15/64 (23%)
Baseline Chronic Renal Failure	15/43 (35%)	11/52 (21%)

In the corresponding subjects in the vancomycin group none of the deaths was considered related to vancomycin. The commonest risk factors were APACHE II score > 20 [19, (86%)], cardiac co-morbidities [20, (91%)], age > 65, ventilation [18, (82%) each] and multi-lobar pneumonia [15, (68%)]. Deaths are considered in more detail below.

Regarding effects on the ECG and QTc interval, the human free fraction of telavancin (10-14 µg/ml at a C_{max} of 97 µg/ml) observed on dosing at 10 mg/kg approximates to concentrations that showed significant effects in in-vitro hERG tests (15 µg/ml). Re-analysis of the thorough QTc study concluded that it was positive for an effect of telavancin on cardiac repolarisation with no evidence of dose response.

In the cSSTI studies higher percentages in the telavancin group had maximum changes in QTcF > 30 ms and > 60 ms. Values > 500 ms occurred in one telavancin subject and three vancomycin subjects.

Table 63: Summary of Post-Drug Changes from Baseline in QTcF Interval (QT Corrected Using Fridericia's Correction Formula) – All Efficacy and Safety Studies in cSSTI – Safety Population

	Studies 0017, 0018, 202 Original Protocol and 202a		Studies 0017, 0018, 202b Post-Amendment		All Efficacy and Safety Studies in cSSTI	
	TLV 7.5 mg/kg (N=192)	Vanc[1] (N=189)	TLV 10 mg/kg (N=1029)	Vanc[1] (N=1033)	TLV (N=1221)	Vanc[1] (N=1222)
Maximum Post-Drug Value, number (%) by category						
≤450 ms	173 (90)	178 (96)	874 (88)	934 (95)	1045 (89)	1112 (95)
>450-≤480 ms	1 (<1)	7 (4)	106 (11)	41 (4)	122 (10)	48 (4)
>480-≤500 ms	0	0	8 (<1)	9 (<1)	10 (<1)	9 (<1)
>500 ms	0	1 (<1)	1 (<1)	2 (<1)	1 (<1)	3 (<1)
Total	189 (100)	186 (100)	989 (100)	986 (100)	1178 (100)	1172 (100)
Maximum Post-Drug Change, number (%) by category						
≤30 ms	141 (75)	161 (88)	789 (81)	885 (90)	930 (80)	1046 (90)
>30-≤60 ms	46 (24)	21 (11)	168 (17)	89 (9)	214 (18)	110 (9)
>60 ms	2 (1)	1 (<1)	14 (1)	5 (<1)	16 (1)	6 (<1)
Total	189 (100)	183 (100)	971 (100)	979 (100)	1160 (100)	1162 (100)

- More subjects with outlying QTc values were observed in the telavancin group (16/1221; 1%) vs. the vancomycin group (6/1222; <1%). Most of these subjects had baseline cardiac disease or concomitant medication that could have contributed to QT prolongation and comparable proportions of those without confounding factors had outlying QTc values (8/64; 13% vs. 9/50; 18% in respective groups).
- Across categories of renal function, the mean and maximum changes in QTcF were higher in the telavancin group except for those with CLCr > 80 ml/L but the incidence of ΔQTcF> 60 ms in this function group was significantly higher in the telavancin group (11/795 vs. 3/808).
- Ten telavancin (9 treated with 10 mg/kg) and 5 vancomycin subjects with outlying ECG QTc values had AEs in the Cardiac Disorders SOC but none had an absolute maximum QTcF > 500 ms while

two telavancin subjects had a change > 60 ms. Of the 10 AEs in the telavancin group the most frequently reported was congestive heart failure (3) and other events occurred only once. None had a ventricular arrhythmic event thought to be induced by effects on QTc and only one telavancin 10 mg/kg subject discontinued therapy due to a cardiac AE.

In the NP studies the proportions with maximum changes in QTcF > 30 or 60 ms and with values > 500 ms were comparable between treatments. There were 1.3 % (8/631) telavancin and 1.2% (8/641) vancomycin subjects with ΔQTcF> 60 ms who also had absolute values > 500 ms.

Across renal function categories similar proportions per treatment group had QTcF changes to > 500 ms and ΔQTcF> 60 ms except that 12/147 vancomycin subjects with moderate impairment had ΔQTcF> 60 ms compared to 3/141 telavancin and the same pattern was seen in those with mild impairment (27/317 vs. 9/322). There was no consistent effect of renal function on rates of QTcF ECG outliers.

Table 64: Summary of On-treatment Changes from Baseline in QTcF Interval (QT Corrected Using Fridericia's Correction Formula) – Safety Population, NP Studies

	0015		0019		0015+0019 Total	
	TLV 10 mg/kg	VAN [1]	TLV 10 mg/kg	VAN [2]	TLV 10 mg/kg	VAN [3]
Summary of QTcF	(N=372)	(N=374)	(N=379)	(N=370)	(N=751)	(N=752)
Maximum Post-Baseline Value, number (%) by category						
≤450 ms	264 (80)	293 (84)	294 (87)	286 (84)	558 (84)	579 (84)
> 450-≤ 480 ms	56 (17)	40 (11)	30 (9)	43 (13)	86 (13)	83 (12)
> 480-≤ 500 ms	6 (2)	10 (3)	6 (2)	5 (1)	12 (2)	15 (2)
> 500 ms	4 (1)	6 (2)	8 (2)	6 (2)	12 (2)	12 (2)
Total	330 (100)	349 (100)	336 (100)	340 (100)	668 (100)	689 (100)
Maximum Post-Baseline Change, number (%) by category						
≤30 ms	213 (69)	242 (76)	226 (70)	236 (74)	439 (70)	478 (75)
> 30-≤ 60 ms	69 (22)	55 (17)	75 (23)	63 (20)	144 (23)	118 (18)
> 60 ms	27 (9)	23 (7)	21 (7)	21 (7)	48 (8)	44 (7)
Total	309 (100)	320 (100)	322 (100)	320 (100)	631 (100)	640 (100)

On-treatment QTcF values > 500 ms and/or a maximum change from baseline > 60 ms were reported for 52 (7%) in the telavancin group and 48 (6%) in the vancomycin group. In the subset with outlying QTc values, 9 (17%) telavancin vs. 17 (35%) vancomycin subjects had cardiac AEs. The most common were atrial fibrillation (4% vs. 8%), bradycardia, cardiac arrest and congestive cardiac failure (1 vs. 2 subjects for each event). Single subjects had ventricular arrhythmia (telavancin group), tachyarrhythmia and tachycardia (each in one subject per group). All of these subjects had one or several pre-existing cardiac conditions at baseline. A search of the total database for Torsade de pointes/QT prolongation turned up 46 subjects (telavancin 18 and vancomycin 28). Three telavancin treated subjects died due to a non-witnessed fatal cardiac event. In these three cases significant co-morbidities and confounding factors were present.

Infusion-related adverse events were less common in the telavancin group compared with the vancomycin group (11% vs. 18%). The most common of these AEs were pruritus (4% and 9%) and generalised pruritus (3% and 6%). AEs specifically noted to be red man syndrome occurred in < 1% of subjects, including 4 treated with 10 mg/kg telavancin and 8 with vancomycin. Drug-related infusion-related SAEs occurred in < 0.5% of subjects with discontinuation of drug or study in 3% telavancin and 2% vancomycin-treated subjects.

Within the telavancin group a higher proportion of females vs. males reported at least one AE in each treatment group but rates of deaths, SAEs and discontinuations due to AEs were generally comparable

between genders. Review of the commonest AEs did not reveal any significant difference in frequency between males and females.

In the cSSTI studies the overall frequencies of AEs were comparable between telavancin-treated subjects aged ≥ 65 years and < 65 years but SAEs and AEs leading to discontinuation were more common in the older cohort. In a detailed evaluation of safety in the four Phase 3 studies according to age and other factors predisposing to higher rates of AEs it was noted that there were fewer subjects with BMI ≥ 35 in the elderly categories (both ≥ 65 and ≥ 75 years) but the distribution of obese subjects within age categories was balanced between the treatment arms. The proportion of diabetic subjects was higher among those aged ≥ 65 years in both treatment groups. Less than 20% of elderly subjects had normal renal function (CLcr > 80 ml/min) compared with approximately 75% of the non-elderly population and there were some imbalances between treatment groups in numbers in each renal impairment category.

Elderly subjects had a higher incidence of SAEs, AEs and AEs resulting in death. The overall incidences in the total elderly population (all ≥ 65 years and those ≥ 75 years) were mostly slightly higher in the telavancin subjects (see below).

AEs within each SOC did not show a consistent trend to higher rates for either treatment within each age category although rates for telavancin were more often slightly higher, even for those < 65 years. Sepsis, septic shock and UTI were slightly more frequent in the elderly telavancin subjects and there was a higher incidence of respiratory failure in telavancin subjects ≥ 75 years (n=15; 4.6%) compared to vancomycin subjects in the same age category (n=10; 3.2%). However, telavancin subjects aged ≥ 75 years presented with more baseline co-morbidities (including, cardiovascular co-morbidity, MRSA infection, APACHE II score > 15, sepsis/shock and bacteraemia) compared to vancomycin subjects in the same age category. Elderly subjects in both age categories in the telavancin arm had a slightly higher incidence of AEs with an outcome of death compared to the vancomycin subjects.

Table 65: Incidence of AEs, SAEs, Discontinuations and Deaths in cSSTI, NP and Total Patient Populations by Indication and Treatment Arm

	cSSTI		NP		Total (cSSTI+ NP)	
	TLV	VAN	TLV	VAN	TLV	VAN
Total Number of Patients (%)						
<65 years	835	844	352	346	1187	1190
>=65 years	186	184	397	408	583	592
>75 years	94	82	230	233	324	315
No. (%) of Patients with at Least One AE						
<65 years	628 (75.2)	626 (74.2)	272 (77.3)	261 (75.4)	900 (75.8)	887 (74.5)
>=65 years	139 (74.7)	113 (61.4)	340 (85.6)	354 (86.8)	479 (82.2)	467 (78.9)
>75 years	73 (77.7)	48 (58.5)	201 (87.4)	207 (88.8)	274 (84.6)	255 (81.0)
No. (%) of Patients with Serious AEs						
<65 years	47 (5.6)	30 (3.6)	78 (22.2)	69 (19.9)	125 (10.5)	99 (8.3)
>=65 years	31 (16.7)	17 (9.2)	159 (40.1)	135 (33.1)	190 (32.6)	152 (25.7)
>75 years	16 (17.0)	11 (13.4)	101 (43.9)	88 (37.8)	117 (36.1)	99 (31.4)
No. (%) of Patients who Discontinued Study Medication Due to AEs						
<65 years	49 (5.9)	44 (5.2)	25 (7.1)	15 (4.3)	74 (6.2)	59 (5.0)
>=65 years	25 (13.4)	11 (6.0)	35 (8.8)	25 (6.1)	60 (10.3)	36 (6.1)
>75 years	12 (12.8)	4 (4.9)	17 (7.4)	14 (6.0)	29 (9.0)	18 (5.7)
No. (%) of Deaths						
<65 years	1 (<1.0)	6 (<1.0)	45 (12.8)	41 (11.8)	46 (3.9)	47 (3.9)
>=65 years	8 (4.3)	2 (1.1)	110 (27.7)	103 (25.2)	118 (20.2)	105 (17.7)
>75 years	5 (5.3)	1 (1.2)	77 (33.5)	67 (28.8)	82 (25.3)	68 (21.6)

Rates of AEs increased with BMI in both treatment groups. Across the four Phase 3 studies, 58% telavancin and 58% vancomycin subjects had a BMI > 25 and 26% and 28% of these were obese (BMI > 35). The proportion of subjects with a BMI ≥ 35 was significantly higher in both treatment groups in the cSSTI study population compared to the NP studies. There was no dose reduction according to BMI alone in the clinical studies.

Among the obese the AE reporting rates were higher with telavancin in the cSSTI studies but slightly higher with vancomycin in the NP studies. The overall proportion of subjects reporting SAEs was mostly lower in the higher BMI categories but rates were consistently higher with telavancin vs. vancomycin (e.g. overall ~16% vs. ~6% for the obese). With increasing BMI, a higher proportion of subjects discontinued treatment due to an AE. In the BMI ≥ 35 category more telavancin than vancomycin treated subjects discontinued due to AEs and this difference was largely driven by the number of discontinuations in cSSTI studies. There were few deaths in the cSSTI studies. In the NP studies the proportions of subjects dying as a result of an AE were comparable across BMI categories in the telavancin group. In the vancomycin group there were fewer deaths in the BMI ≥ 35 category, which gave a treatment difference of ~18% for telavancin vs. ~7% for vancomycin for the obese. In particular, the combined incidence of events of Multi-organ Failure, Sepsis and Septic shock leading to death was higher in obese telavancin subjects compared to vancomycin subjects (8 cases vs. 2).

AEs, SAEs, deaths and discontinuations occurred more frequently in diabetic subjects. In cSSTI studies AE rates were generally higher in telavancin-treated diabetic subjects. Also, rates of deaths and SAEs were higher for telavancin-treated diabetics in the HAP studies.

In cSSTI studies discontinuations due to AEs among diabetics showed notable imbalances for increased creatinine (3 telavancin, one vancomycin), acute renal failure (5 vs. 0), renal insufficiency (2 vs. 0) and osteomyelitis (5 vs. 1). Renal SAEs were also more frequent in this subject group (8 telavancin vs. one vancomycin). Respiratory failure SAEs occurred more frequently in the telavancin treated diabetic subjects. Ten of these 12 subjects in the telavancin treated diabetic group came from the NP studies. The difference between diabetic and non-diabetic subjects and between treatment groups only existed in the NP studies.

Table 66: Overall Incidences of AEs, SAEs, Discontinuations, and Deaths in cSSTI, NP and Total Studies

	cSSTI		NP		TOTAL	
	TLV	VAN	TLV	VAN	TLV	VAN
Total Number of patients (%)						
Diabetic	237	236	169	165	406	401
Non-Diabetic	784	792	580	589	1364	1381
Total	1021	1028	749	754	1770	1782
No. (%) of Patients with at Least One AE						
Diabetic	190 (80.2)	171 (72.5)	148 (87.6)	150 (90.9)	338 (83.3)	321 (80.0)
Non-Diabetic	577 (73.6)	568 (71.7)	464 (80.0)	465 (78.9)	1041 (76.3)	1033 (74.8)
No. (%) of Patients with Serious AEs						
Diabetic	36 (15.2)	19 (8.1)	70 (41.4)	53 (32.1)	106 (26.1)	72 (18.0)
Non-Diabetic	42 (5.4)	28 (3.5)	167 (28.8)	151 (25.6)	209 (15.3)	179 (13.0)
No. (%) of Patients who Discontinued Study Medication Due to AEs						
Diabetic	27 (11.4)	11 (4.7)	13 (7.7)	13 (7.9)	40 (9.9)	24 (6.0)
Non-Diabetic	47 (6.0)	44 (5.6)	47 (8.1)	27 (4.6)	94 (6.9)	71 (5.1)
No. (%) of AEs Resulting in Death						
Diabetic	6 (2.5)	2 (<1.0)	49 (29.0)	36 (21.8)	56 (13.5)	38 (9.5)
Non-Diabetic	3 (<1.0)	6 (<1.0)	106 (18.3)	108 (18.3)	109 (8.0)	114 (8.3)

Serious adverse event/deaths/other significant events

In the initial application dossier the deaths reported within the data capture window (up to 28 days post TOC) for the cSSTI and NP studies were as follows:

Table 67: Overall Summary of Deaths across Studies (cSSTI and NP)

TLV (number of patients)	cSSTI		NP	
	TLV N=1221	VAN N=1222	TLV N=751	VAN N=752
Investigator assessed causality: Related/ possibly probably related	4 † (0.33%)	0	3 (0.40%)	2 (0.27%)
Non related	5 (0.41%)	9 (0.74%)	147 (19.57%)	138 (18.35%)

† Includes one patient on 7.5 mg/kg telavancin in study 0017.
The AE causally related to study therapy was not necessarily the AE causing death in these patients.

In the **cSSTI clinical studies** the 14 events leading to death in the nine telavancin subjects were pulmonary oedema, renal insufficiency (two subjects), respiratory distress, respiratory failure, acute respiratory failure, sepsis, SIRS, cerebrovascular accident, ovarian cancer, ventricular arrhythmia, cardiac arrest, cardio-respiratory arrest and myocardial infarction. Those assessed by the investigator as possibly/probably related to study medication included renal insufficiency, respiratory distress, respiratory failure (all in one subject), ventricular failure, renal insufficiency and cardiac arrest.

There were four out of window deaths in telavancin-treated subjects including a subject who developed renal insufficiency who later died later with VAP, one who developed respiratory distress who died later with ARDS and multi-organ failure, one who discontinued drug due to acute renal failure and hyperkalaemia and later died with a brain stem infarction and a 95-year old who received twice the dose he should have plus aggressive diuresis with furosemide who refused haemodialysis for renal failure.

In the **NP studies** 290 subjects died within the data capture window and almost all had a complex clinical picture with underlying co-morbid conditions at baseline as well as severe pulmonary disease such as acute lung injury (ALI) or acute respiratory distress syndrome (ARDS).

A numerically higher mortality rate was observed in study 0015 in the telavancin group, whereas the opposite was found in study 0019. The largest contribution to the ~5% difference in mortality rate observed in study 0015 was the higher mortality rate in the telavancin group after the EOT. Despite the numerical differences between treatments in mortality rates the lower bound of each 95% CI was within -4% and the intervals all included the value of zero.

Table 68: Analysis of Deaths – Studies 0015 and 0019 (NP) – Safety Population

	0015		0019		Total NP Studies	
	TLV (N=372)	VAN (N=374)	TLV (N=379)	VAN (N=378)	TLV (N=751)	VAN (N=752)
Total Deaths in Window, N (%) [1]	80 (21.5)	62 (16.6)	70 (18.5)	78 (20.6)	150 (20.0)	140 (18.6)
Difference (95% CI) [2]	4.9% (-0.7, 10.6)		-2.2% (-7.8, 3.5)		1.4% (-2.6, 5.3)	
Deaths in Window While Receiving Study Medication, N (%) [3]	48 (12.9)	45 (12.0)	44 (11.6)	35 (9.3)	92 (12.3)	80 (10.6)
Difference (95% CI) [2]	0.9% (-3.9, 5.6)		2.4% (-2.0, 7.7)		1.6% (-1.6, 4.8)	

[1] Deaths based on patients with treatment-emergent adverse events with death as an outcome and death occurred within protocol specified window.
[2] Point estimate and 95% confidence interval on the treatment difference (telavancin - vancomycin) in death rate. The pooled analysis is stratified by study.
[3] Deaths occurred prior to End-of-Therapy (EoT) or 1 day after EoT.

A post hoc analysis of mortality in the NP studies was conducted using additional data at the request of the US FDA. The findings were presented in as a separate paper in the answers to the Day-120 List of Questions posed by CHMP. The rationale was to minimise censored/missing data to support a post-hoc assessment of all-cause mortality. As noted from earlier data Study 0015 showed an excess of deaths in the telavancin group while Study 0019 suggested comparable death rates at D28 and at D49 the rate was slightly lower for telavancin.

Table 69: Summary of Vital Status at 28-, 49-, and 120-Day Time Points – Safety Population

	Study 0015		Study 0019		Total	
	Telavancin 10mg/kg (N=372)	Vancomycin (N=374)	Telavancin 10mg/kg (N=379)	Vancomycin (N=378)	Telavancin 10mg/kg (N=751)	Vancomycin (N=752)
28 Days						
Dead	95 (25.5%)	74 (19.8%)	84 (22.2%)	89 (23.5%)	179 (23.8%)	163 (21.7%)
Alive	258 (69.4%)	272 (72.7%)	278 (73.4%)	269 (71.2%)	536 (71.4%)	541 (71.9%)
Censored	19 (5.1%)	28 (7.5%)	17 (4.5%)	20 (5.3%)	36 (4.8%)	48 (6.4%)
49 Days						
Dead	114 (30.6%)	92 (24.6%)	100 (26.4%)	116 (30.7%)	214 (28.5%)	208 (27.7%)
Alive	234 (62.9%)	242 (64.7%)	257 (67.8%)	231 (61.1%)	491 (65.4%)	473 (62.9%)
Censored	24 (6.5%)	40 (10.7%)	22 (5.8%)	31 (8.2%)	46 (6.1%)	71 (9.4%)
120 Days						
Dead	132 (35.5%)	114 (30.5%)	124 (32.7%)	132 (34.9%)	256 (34.1%)	246 (32.7%)
Alive	88 (23.7%)	87 (23.3%)	89 (23.5%)	76 (20.1%)	177 (23.6%)	163 (21.7%)
Censored	152 (40.9%)	173 (46.3%)	166 (43.8%)	170 (45.0%)	318 (42.3%)	343 (45.6%)

The primary analysis i.e. estimation of Kaplan-Meier (K-M) survival rates in the As-treated (As-Tx) population showed that at 28 days:

- In Study 0015, telavancin was 74.1% and vancomycin was 79.9%.
- In Study 0019, telavancin was 77.6% and vancomycin was 76.0%.

In Study 0015 the curves were initially coincident but diverged at approximately D7 and remained parallel after approximately D13. The log-rank P value for comparison of survival curves was 0.06. The survival curves for Study 0019 were close throughout the 28-day interval (p = 0.75).

Estimation of Kaplan-Meier (K-M) survival rates in the AsTx population showed that at 49 days:

- In Study 0015, telavancin was 68.6% and vancomycin was 74.5%.
- In Study 0019, telavancin was 73.1% and vancomycin was 68.2%.

Table 70: Estimated All-cause Unadjusted Point-wise Mortality Rates at Day 28: As-treated Population

Study	Treatment	Estimated K-M Survival at 28 Days	SE	Diff. Telavancin-Vancomycin (95% CI)	Hazard Ratio (Telavancin/ Vancomycin) (95% CI)	Log-rank P value
0015	Vancomycin	0.7989	0.0209	-0.0579 (-0.119, 0.003)	1.335 (0.985, 1.809)	0.06
	Telavancin	0.7410	0.0229			
0019	Vancomycin	0.7598	0.0222	0.0161 (-0.043, 0.077)	0.952 (0.707, 1.283)	0.75
	Telavancin	0.7759	0.0216			
Combined†	Vancomycin	0.7826	0.0151	-0.0242 (-0.067, 0.018)	1.125 (0.910, 1.390)	0.28
	Telavancin	0.7584	0.0157			

Note: Deaths occurring after Study Day 28 have been censored.
K-M = Kaplan-Meier; Diff = difference.
† Based on proportional hazards regression.

Table 71: Estimated All-cause Unadjusted Point-wise Mortality Rates at Day 49: As-treated Population

Study	Treatment	Estimated K-M Survival at 49 Days	SE	Diff. Telavancin-Vancomycin (95% CI)	Hazard Ratio (Telavancin/ Vancomycin) (95% CI)	Log-rank P value
0015	Vancomycin	0.7450	0.0231	-0.0591 (-0.125, 0.007)	1.289 (0.979, 1.697)	0.07
	Telavancin	0.6859	0.0244			
0019	Vancomycin	0.6816	0.0245	0.0491 (-0.017, 0.115)	0.857 (0.656, 1.120)	0.26
	Telavancin	0.7307	0.0231			
Combined†	Vancomycin	0.7191	0.0166	-0.0123 (-0.059, 0.034)	1.046 (0.864, 1.265)	0.65
	Telavancin	0.7068	0.0169			

Note: Deaths occurring after Study Day 49 have been censored.
K-M = Kaplan-Meier; Diff = difference.
† Based on proportional hazards regression.

The corresponding tables for all patients with a pathogen (MAT population) were as follows:

Table 72: Analysis of Deaths at D28 – Study 0015 and 0019 (NP) MAT Population

	0015		0019		0015+0019	
	TLV (N=257)	VAN (N=247)	TLV (N=304)	VAN (N=281)	TLV (N=561)	VAN (N=528)
Total Deaths in Window [2]	69(26.85%)	52(21.05%)	68(22.37%)	70(24.91%)	137(24.42%)	122(23.11%)
Difference (95% CI) [1]	5.8%(-1.6%, 13.2%)		-2.5%(-9.4%, 4.4%)		1.3%(-3.7%, 6.4%)	
Deaths in Window While Receiving Study Medication [3]	37(14.40%)	30(12.15%)	36(11.84%)	27(9.61%)	73(13.01%)	57(10.80%)
Difference (95% CI) [1]	2.3%(-3.7%, 8.2%)		2.2%(-2.8%, 7.2%)		2.2%(-1.6%, 6.1%)	

Table 73: Analysis of Deaths at D49 – Study 0015 and 0019 (NP) MAT Population

	0015		0019		0015+0019	
	TLV (N=257)	VAN (N=247)	TLV (N=304)	VAN (N=281)	TLV (N=561)	VAN (N=528)
Total Deaths in Window [2]	81(31.52%)	64(25.91%)	82(26.97%)	95(33.81%)	163(29.06%)	159(30.11%)
Difference (95% CI) [1]	5.6%(-2.3%, 13.5%)		-6.8%(-14.3%, 0.6%)		-1.1%(-6.5%, 4%)	
Deaths in Window While Receiving Study Medication [3]	37(14.40%)	30(12.15%)	36(11.84%)	27(9.61%)	73(13.01%)	57(10.80%)
Difference (95% CI) [1]	2.3%(-3.7%, 8.2%)		2.2%(-2.8%, 7.2%)		2.2%(-1.6%, 6.1%)	

A proportional hazards regression analysis for 28-days was conducted to identify prognostic factors and any treatment-effect modifiers related to mortality. Nine factors, all baseline characteristics, were found to be associated with outcome (i.e. APACHE II category, baseline CrCL, cardiovascular disease, MRSA, multilobar pneumonia, bacteraemia, ARDS/acute lung injury [ALI], geographic region and acute renal failure [ARF]). ARF at baseline was the only variable that showed an interaction with treatment.

In Study 0015, 43 in the telavancin group had ARF at baseline compared with 35 in the vancomycin group. In Study 0019 there were 30 and 29 in respective treatment groups.

Across the four studies telavancin-treated subjects with baseline ARF (73) had a lower probability of survival than vancomycin-treated subjects with baseline ARF (64). More of these telavancin-treated subjects had ARDS or ALI at baseline than vancomycin-treated subjects (24% vs. 13%, respectively) but more vancomycin-treated subjects were also in chronic renal failure at baseline than telavancin-treated subjects (23% vs. 14%, respectively).

When the 137 with ARF at baseline (9% of the total study population) were excluded and the survival function was recalculated, the survival functions for each group were nearly identical. Therefore there was an unexplained excess of all cause mortality in those with a clinical diagnosis of acute renal failure at the start of treatment: 41/73 (56.1%) in the telavancin group compared to 21/64 (32.8%) in the vancomycin group. In contrast, all cause mortality in subjects without pre-existing acute renal failure was 137/676 (20.2%) in the telavancin group and 142/688 (20.6%) in the vancomycin group.

All those with ARF who died presented with multiple risk factors independently associated with mortality. Several of the risk factors showed an uneven distribution between treatment groups, including a higher proportion of Gram negative infections in the telavancin group and more subjects in the telavancin group were end of life DNR decisions.

Among subjects with an increase in serum Cr of 50% or more from baseline up to 7 days following treatment cessation the percentages experiencing any AE associated with death were comparable between the two treatment groups (18.3 % telavancin and 20.9% vancomycin for the combined cSSTI and NP study populations).

The frequencies of individual TEAEs leading to death were comparable between the two treatment groups. Of 150 such AEs in the telavancin group the most common were septic shock (16%), multi-organ failure (15%), respiratory failure (11%) and pneumonia (6%). The three 3 deaths assessed by investigators as related to telavancin included two cases of cardiac arrest and an ischaemic stroke.

Deaths considered to follow on from any of multi-organ failure (MOF), sepsis or septic shock numbered 52/150 (35%) in the telavancin group and 31/140 (22%) in the vancomycin group. Review of the cases showed that a substantial proportion had these conditions at baseline and had infections due to mixed Gram-positive/Gram-negative organisms. Such subjects were more frequently randomised to telavancin (15/52 [29%] compared with 5/31 [16%] in the vancomycin group). The applicant proposed that inadequate treatment of baseline Gram-negative pathogens contributed to the development of multi-organ failure, sepsis or septic shock in nine of these subjects (eight telavancin, one vancomycin). It was also noted that among those who experienced AEs of MOF, sepsis or septic shock a higher proportion died in the telavancin group (74.4% [61/82] vs. 67.8% [40/59] for vancomycin but not all of these deaths were considered to follow-on from the AEs.

Across the cSSTI and NP studies there was a slightly higher rate with telavancin vs. vancomycin for all SAEs and those SAEs that were considered related to study drug. The section below shows the tables provided in the study reports included in the application dossier. The numbers were later corrected as described further below.

Table 74: Total Number of Serious TEAEs, per Treatment Received and Relationship

	All Studies in cSSTI[1]		All Studies in NP[2]		All Efficacy and Safety Studies	
	TLV	VAN[3]	TLV	VAN[4]	TLV	VAN[5]
	N=1221	N=1222	N=751	N=752	N=1972	N=1974
Number (%) of Patients						
All Serious TEAE	91 (7)	60 (5)	234 (31)	197 (26)	325 (16)	257 (14)
Related serious TEAE	26 (2)	13 (1)	23 (3)	17 (2)	49 (2)	30 (2)

[1] Includes pooled data from cSSTI Original Protocol and Post-amendment Studies 202a, 202b, 0017 and 0018 (telavancin 7.5 and 10 mg/kg)
[2] Includes pooled data from NP Studies 0015 and 0019
[3] Includes 27 patients (20 in 202a and 7 in 202b post-amendment) who received an antistaphylococcal penicillin instead of vancomycin
[4] Includes 20 patients who received an antistaphylococcal penicillin instead of vancomycin
[5] Includes 47 patients who received an antistaphylococcal penicillin instead of vancomycin

In the cSSTI studies the most frequently reported SAE was acute renal failure (5 treated with 10 mg/kg telavancin). For all SAEs indicating renal impairment rates for the 7.5 mg/kg and 10 mg/kg doses were 1.6% (3/192) vs. 1.2% (12/1029), respectively. The incidence of SAEs in the telavancin group was higher in subjects aged > 65 years vs. those aged < 65 years, in Caucasians vs. other races, in diabetic subjects vs. non-diabetic, in those with BMI ≥ 40 vs. < 40 and in subjects with CLcr < 50 ml/min vs. ≥ 50 ml/min.

In the NP studies SAEs were reported in 234 telavancin-treated subjects (31%) and 197 vancomycin-treated subjects (26%).

Table 75: Most Common Treatment Emergent SAEs in NP Studies

Event	Telavancin N (%)	Vancomycin N (%)
Septic Shock	30 (4)	28 (4)
Respiratory failure	21 (3)	22 (3)
Multi-organ failure	24 (3)	14 (2)
Renal failure acute	18 (2)	11 (1)
Sepsis	12 (2)	9 (1)
Pneumonia	10 (1)	14 (2)
Congestive cardiac failure	< 1%	10 (1)
Acute respiratory failure	< 1%	8 (1)

Multi-organ failure, acute renal failure acute and sepsis were experienced in more telavancin-treated subjects than vancomycin-treated subjects. The incidence of SAEs in the telavancin and vancomycin groups was higher in subjects aged > 65 years, in diabetics, in past smokers and in subjects with decreased CLcr.

In the responses to the list of outstanding issues the applicant acknowledged that there has been a problem of misclassification of serious events as non-serious as reported in all the 4 Phase 3 studies and that this would have led to under-reporting of serious cases to concerned authorities and ethical committees.

The applicant reviewed all case reports received for the adverse events of Acute Renal Failure (ARF), sepsis, septic shock and Multi Organ Failure (MOF) for both telavancin and vancomycin. These are presented by seriousness assessment across both the cSSTI and NP subject populations 1 below. This analysis was performed by preferred term and includes both events and case reports originally classified as serious or as non-serious cases.

In terms of relative risk assessment, both telavancin and vancomycin populations were similarly affected.

Table 76: Reports of ARF, Sepsis, Septic shock and MOF by serious criteria

	cSSSI (Post-Amendment)						HAP					
	Serious		Not Serious		Total		Serious		Not Serious		Total	
Preferred AE Term	TLV	VAN	TLV	VAN	TLV	VAN	TLV	VAN	TLV	VAN	TLV	VAN
ARF	4	0	3	0	7	0	18	11	16	17	34	28
Sepsis/Septic Shock/MOF	1	2	2	2	3	4	65	45	12	9	77	54

Most of the impact of misclassification pertained to NP patient population as expected due to their underlying health problems. The ratio of serious to non-serious assessments was approximately the same in the telavancin and vancomycin groups. A similar review of individual terms of sepsis, septic shock and multi organ failure gave numbers as shown:

Table 77: Reports of Sepsis, Septic shock and MOF in telavancin and vancomycin

	cSSSI (Post-Amendment)						HAP					
	Serious		Not Serious		Total		Serious		Not Serious		Total	
Preferred AE Term	TLV	VAN	TLV	VAN	TLV	VAN	TLV	VAN	TLV	VAN	TLV	VAN
SEPSIS	1	1	2	2	3	3	12	9	14	8	26	17
SEPTIC SHOCK	0	1	0	0	0	1	30	28	2	1	32	29
MULTI-ORGAN FAILURE	0	0	0	0	0	0	24	14	1	0	25	14

There was no evidence to suggest that misclassification of adverse events was related to either country or individual investigation site i.e. there was no clustering of misclassifications according to individual investigators.

While the correction of the numbers of SAEs did not affect the conclusions drawn regarding the excess of all and serious AEs with telavancin vs. vancomycin, nevertheless CHMP raised that it was not possible to verify whether all of the applicant's explorations of factors that might have explained the observed differences were based on the numbers reported as AEs or the total events falling under these terms. The applicant satisfactorily addressed the issue, providing assurance that that the very late recognition of these cases still meant that all the previous and extensive analyses performed at CHMP's request remain valid and do not impact on the conclusions drawn.

Laboratory findings

In cSSTI studies potentially clinically significant (PCS) haematological abnormalities in individual parameters occurred in ≤ 3% with no detectable relationship to telavancin dose. The incidence of PCS abnormalities was higher in NP studies and numerically higher in the vancomycin group. Anaemia was reported as an SAE for one subject in both treatment groups while thrombocytopenia was reported as an SAE in three subjects in the vancomycin group and none in the telavancin group.

In cSSTI studies the incidence of PCS chemistry abnormalities for any individual analyte was 3% or less. In the NP studies proportions with values meeting PCS criteria were comparable between treatment groups except for hypokalaemia (< 3.0 mmol/l), which occurred in 9% of telavancin and 6% of vancomycin subjects. The dose of telavancin did not appear to be a factor.

Table 78: Incidence of Potentially Clinically Significant Changes in Serum Chemistry from baseline – All Efficacy and Safety Studies in cSSTI and NP – Safety Population

	Total cSSTI studies (0017+0018+202b)						Total NP studies (0015+0019)					
	TLV 10 mg/kg			VAN[1]			TLV			VAN[2]		
	Pts with Values[3]	Abnormal[4]		Pts with Values[3]	Abnormal[4]		Pts with Values[3]	Abnormal[4]		Pts with Values[3]	Abnormal[4]	
Parameter and PCS Criteria		N	(%)		N	(%)		N	(%)		N	(%)
LDH > 3 × ULN	794	2	(<1)	822	0		293	2	(<1)	295	2	(<1)
Magnesium-L <0.5 mmol/l	894	10	(1)	911	5	(<1)	603	6	(<1)	586	11	(2)
Magnesium-H > 1.0 mmol/l	894	3	(<1)	911	3	(<1)	603	38	(6)	586	27	(5)
Potassium-L < 3.0 mmol/l	927	17	(2)	928	9	(<1)	587	50	(9)	579	37	(6)
Potassium-H > 5.5 mmol/l	927	24	(3)	928	21	(2)	587	33	(6)	579	32	(6)

Few events related to serum chemistry parameters were reported as SAEs or discontinuations due to AEs. In NP studies one telavancin subject discontinued medication due to increases in all of ALT, AST and ALP while an increase in urea was a contributing event to discontinuation in one other telavancin subject. See also PCS abnormalities related to renal function discussed above.

AEs in the hepatobiliary SOCs were rare and balanced across treatments (cSSTI three per treatment group; HAP 18 telavancin and 19 vancomycin subjects). Two cSSTI and two NP subjects treated with telavancin 10 mg/kg had hepatic SAEs not considered drug-related. The two cSSTI subjects had

hepatic cirrhosis or cholecystitis with concurrent pneumonia at baseline while the two NP subjects had pre-existing liver disease or elevated LFTs at baseline.

One telavancin-treated subject (NP) and 3 vancomycin-treated subjects (2 cSSTI, 1 NP) had hepatic AEs that resulted in death. The telavancin subject had hepatorenal syndrome while the vancomycin subjects died following hepatic failure and/or coma. Two subjects (one per treatment group) discontinued due to a hepatic AE.

In cSSTI and NP studies rates of AEs associated with abnormal LFTs were generally comparable between treatments and between telavancin dose groups. Increases in ALP to ≥ 1.5 x ULN occurred in <1% with 7.5 mg/kg telavancin, 15 (2%) with 10 mg/kg and in 11 (1%) vancomycin-treated subjects in cSSTI studies. There were increases > 2 x ULN in 23 (5%) telavancin and 40 (8%) vancomycin subjects with NP. Concurrence of liver injury (i.e. increased ALT) and reduced function (increased total bilirubin) did not occur in any subject receiving telavancin.

Discontinuation due to adverse events

There were 17 subjects in the clinical pharmacology studies (13 telavancin), 150 subjects in the cSSTI studies and 100 subjects in the NP studies who discontinued study medication due to at least one AE. Overall rates of discontinuations due to AEs were comparable for telavancin doses 7.5 and 10 mg/kg.

In the clinical pharmacology studies the most noteworthy AEs resulting in discontinuation of subjects receiving telavancin were red man syndrome or AEs consistent with red man syndrome.

In cSSTI studies discontinuation of study medication or study due to AEs occurred in 88 (7%) telavancin-treated subjects and 62 (5%) vancomycin-treated subjects. The most frequently reported AEs leading to discontinuation of 10 mg/kg telavancin were nausea (10), rash (9), increased blood creatinine (7), vomiting (7), acute renal failure (6) and osteomyelitis (6). One subject discontinued telavancin due to erythema multiforme but it was thought to be related to iopromide. Discontinuations from vancomycin were most often due to pruritus (7), drug hypersensitivity (5) and rash (5).

In NP studies 60 subjects (8%) subjects in the telavancin group and 40 (5%) in the vancomycin group had at least one AE that resulted in discontinuation. The most common of these AEs were acute renal failure (9 telavancin and 2 vancomycin), QTc prolongation (8 and 2) and blood creatinine increased (6 and 1). Conversely, septic shock (one and 5) and multi-organ failure (one and 4) occurred more often in vancomycin-treated subjects. In 33 (4%) telavancin-treated subjects and 14 (2%) vancomycin-treated subjects the AEs that resulted in discontinuation were assessed by investigators as possibly/probably related to study medication.

Post marketing experience

Telavancin was first marketed in the United States on 5 November 2009. Safety data from 11 September 2009 (date of approval in the US for cSSTI) to 10 March 2010 were summarised in the responses to the CHMP's D120 List of Questions along with the first PSUR. A second PSUR was submitted for data up to 11 September 2010 with the answers to the outstanding issues at Day-180 (of the Marketing Authorisation application procedure). No actions had been taken for safety reasons by regulatory authorities or the MAH and there had been no changes to the CCDS during this period.

There had been 54 medically confirmed case reports and no fatal reports. Notable have been the 15 reports of nephrotoxic renal events as shown in the table. It should be noted that some of these reports were associated with off label use, including three patients with endocarditis who developed renal failure.

Table 79: Nephrotoxicity Cases (under the Renal and Urinary disorders and Investigation SOC)

Case Number	Age Gender	Preferred Term	Outcome	Serious
2010US001126	Unk Unk	Creatinine renal clearance decreased	Unknown	No
2010US001267	57 years Male	Renal failure	Unknown	Yes
2010US001311*	Unk Female	Renal failure acute	Unknown	Yes
2010US001648	Unk Female	Renal impairment	Unknown	No
2010US001728*	Unk Female	Renal failure	Unknown	Yes
2010US001850	Unk Unk	Renal failure acute	Unknown	Yes
2010US002159	Unk Unk	Blood creatinine increased	Unknown	No
2010US002609	83 years Male	Blood creatinine increased	Unknown	Yes
2010US003224	Unk Male	Blood creatinine increased	Unknown	No
2010US003263	38 years Male	Blood creatinine increased	Unknown	Yes
2010US003348	Unk Male	Dehydration Renal failure Rash	Resolved	Yes
2010US003356	Unk Female	Renal disorder	Unknown	Yes
2010US003454	50 years Male	Renal failure acute Pyrexia Nausea Vomiting Cyanosis Heart rate increased Chills	Unknown	Yes
2010US003464	Unk Unk	Renal failure acute	Unknown	Yes
2010US003468	Unk Unk	Renal impairment	Unknown	Yes

*Case 2010US001728 is a duplicate to 2010US001311

Among the targeted medical events there have been two cases of leucopenia and neutropenia and one of decrease WBC and a small number of reports of hepatic events with one case of urticaria and pruritus.

2.6.1. Discussion on clinical safety

While there were some imbalances between treatment groups uncovered that might have contributed to differential risks of AEs (including SAEs and deaths), none of the findings can explain away the differences in safety profile between telavancin and vancomycin. In the additional analysis of mortality, based on a much more complete dataset, the higher rate of deaths in the telavancin group in one NP study persisted but this was not observed in the other NP study. Among the prognostic factors for

mortality that were identified, acute renal failure (ARF) showed an interaction with telavancin treatment and all the analyses presented clearly bear this out.

A summary outlining some of the most pertinent observations is provided below:

- Those entering the studies with pre-existing renal impairment and especially those already in ARF were at particular risk of adverse events and poor outcomes if assigned to telavancin.
- The nephrotoxic effect of telavancin is greater than that associated with vancomycin. Renal AEs occurred in telavancin-treated subjects with or without prior renal insufficiency or risk factors for developing renal injury. The risk seems to be greater in those with some predisposing factors including concomitant use of other nephrotoxic medications.
- With the exception of the rates for subjects with any AE in NP studies, all the comparisons between treatments according to age groups (< 65 years, over 65 and over 75 years) indicated higher rates of AEs, SAEs, deaths and discontinuations due to AEs in elderly subjects who received telavancin compared to those who received vancomycin.
- The tabulation of AEs by BMI mostly showed an excess of AEs, SAEs and discontinuations due to AEs in telavancin subjects who were at least overweight with a particular difference vs. vancomycin in those with the highest BMI values.
- Similarly, there were higher rates of AEs, SAEs, deaths and discontinuations due to AEs in telavancin-treated diabetics in one or both of cSSTI and HAP studies with no obvious explanation at present.
- Telavancin may elicit prolongation of QTc intervals. At present there is no clear evidence that this prolongation is associated with clinically important arrhythmias. Therefore the issue is important but it can likely be dealt with by the usual list of exclusions and warnings to avoid administration of telavancin to subjects potentially at high risk of developing arrhythmias if exposed to a QTc-prolonging agent.

The applicant provided a separate and detailed review of the non-clinical and clinical data regarding the renal effects of telavancin/HP-β-CD. Non-clinical studies showed that there is renal tubular injury and tubular epithelial vacuolisation but, in contrast to vancomycin, telavancin/HP-β-CD has not been shown to exert glomerular damage. Most renal effects of telavancin were the same as for HP-ß-CD. When HP-ß-CD:telavancin ratios of 10:1, 4:1 and 2:1 were tested the 10:1 ratio showed the lowest level of renal degeneration and necrosis. The applicant considers that the presence of HP-ß-CD in the formulation at a ratio of 10:1 reduces the incidence and severity of the observed changes and concludes that HP-ß-CD attenuates glycopeptide-associated toxicity but has distinct effects itself.

The functional changes in the kidney and the histopathological signs of renal damage were reversible after a recovery period of 4 weeks in rats and in some of the dogs. Vacuolisation of the urothelium, especially in the proximal tubular cells, was not reversible after 4 weeks. The applicant proposes that lysosomal vacuolisation represents a cytoprotective event in renal tubular cells after repeated exposure to telavancin/HP-β-CD and is expected to reverse with the same half-life as the turnover time of the proximal tubular cells.

The data indicate that telavancin should not be used in those who have ARF.

The additional post-marketing safety experience indicated that there had been a preponderance of reports of acute renal injury despite the careful advice provided in the US labelling.

In the responses to questioning by CHMP (D-180 outstanding issues), two matters of major importance were analyses of safety and efficacy after excluding patients with pre-existing renal impairment.

However, elimination of these patients did not mitigate the between-treatment differences in safety. Thus it was concluded that attempts to prevent telavancin being used in such patients (i.e. those with pre-existing renal impairment) by means of the SmPC would not satisfactorily address the Major Objection.

Finally, while there are no outstanding major concerns regarding the demonstration of efficacy there remains no sound explanation in terms of patient characteristics and management for the imbalances in mortality rates in HAP/VAP studies (with a higher rate for TLV in one but not the other study but an overall higher rate on pooling the data), for the higher rates of AEs mapping to the infections SOC and for the higher rates of sepsis and septic shock with TLV.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The safety profile of telavancin is inferior to that of vancomycin in subjects with complicated skin and soft tissue infections (cSSTI) and nosocomial pneumonia (NP). The differences observed between treatments cannot satisfactorily be ascribed to imbalances of baseline characteristics or subject management.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, version 1.7 from May 2011, which included a risk minimisation plan.

Table 80: Summary of the risk management plan

Safety issue	**Proposed pharmacovigilance activities**	**Proposed risk minimisation activities**
Identified risks		
Nephrotoxicity	Additional pharmacovigilance: Follow-up questionnaire and post marketing authorization safety study.	Information on nephrotoxicity is included in the SmPC in the sections Posology and method of administration (4.2), Contraindications (4.3), Warnings and precautions (4.4), Undesirable effects (4.8), Pharmacokinetics (5.2) and Preclinical safety (5.3) Additional risk minimization: Educational materials for HCP: DHPC and Healthcare Professional Guide.

Prolongation of cardiac repolarisation	Additional pharmacovigilance: Follow-up questionnaire and post marketing authorization safety study.	Information on prolongation of cardiac repolarisation is included in the SmPC in the sections Warnings and precautions (4.4), Undesirable effects (4.8) and Pharmacodynamic properties (5.1) Additional risk minimization: Educational materials for HCP: DHPC and Healthcare Professional Guide.
Infusion-related reactions (red man syndrome/histamine release/hypersensitivity reactions)	Additional pharmacovigilance: Follow-up questionnaire	Information on infusion-related reactions (red man syndrome/histamine release/ hypersensitivity) AEs is included in the SmPC in the sections Posology and method of administration (4.2), Warnings and Precautions (4.4) and Undesirable effects (4.8). Additional risk minimization: Educational materials for HCP: Healthcare Professional Guide.
Ototoxicity	Additional pharmacovigilance: Post marketing authorization safety study	Information on ototoxicity is included in the SmPC in the sections Warnings and Precautions (4.4), Interactions (4.5) and Undesirable effects (4.8). Additional risk minimization: Educational Materials for HCP: Healthcare Professional Guide
Concomitant administration of nephrotoxic medications	Additional pharmacovigilance: Follow-up questionnaire and post marketing authorization safety study	Warning in Section 4.4 of the SmPC. Additional risk minimization: Educational materials for HCP: Healthcare Professional Guide
Interference with clinical tests	Routine pharmacovigilance	Information on the interference with clinical tests during treatment is included in the SmPC in the section Interactions (Section 4.5). Additional risk minimization: Educational materials for HCP: Healthcare Professional Guide
Antibiotic-associated colitis and pseudomembranous colitis	Routine pharmacovigilance	Information on antibiotic-associated colitis and pseudo-membranous colitis is included in the SmPC in the sections Warnings and precautions (4.4) and Undesirable effects (4.8).
Potential Risks		
Hepatotoxicity	Additional pharmacovigilance: Follow-up questionnaire and post marketing authorization safety study	Information on hepatotoxicity is included in the SmPC in the sections Undesirable effects (4.8) and Preclinical safety (5.3).
Development of drug resistant strains	Additional pharmacovigilance : Participation in microsurveillance program	Information on the potential of development of drug-resistant strains is included in the SmPC in the section Pharmacodynamic properties (5.1).
Overgrowth of nonsusceptible microorganisms	Routine pharmacovigilance	Information on overgrowth of nonsusceptible microorganisms is included in the SmPC in the section Warnings and Precautions (Section 4.4).
Anaphylaxis	Additional pharmacovigilance: Follow-up questionnaire	No additional risk minimization necessary
Thrombocytopenia	Routine pharmacovigilance	No additional risk minimization necessary

Neutropenia	Routine pharmacovigilance	No additional risk minimization necessary
Teratogenicity	Additional pharmacovigilance: Telavancin Pregnancy Exposure Registry	Information on teratogenicity is included in the SmPC in the sections Contraindications (4.3) and Fertility, pregnancy and lactation (Section 4.6). Information on the pre-clinical findings is included in Section 5.3 of the SmPC. <u>Additional risk minimization measures</u> Prescriber checklist Educational materials for HCP: DHPC to be distributed prior to distribution of the product, Healthcare Professional Guide
Off-label Use	Additional pharmacovigilance: Data collected from post-marketing authorization study	Information on the therapeutic indications is included in Section 4.1 of the SmPC. Information on the posology, method of administration and recommended duration of use is provided in Section 4.2 of the SmPC Information on the antimicrobial activity is provided in Section 5.1 of the SmPC. Educational materials for HCP: DHPC to be distributed prior to distribution of the product, Healthcare Professional Guide
Missing information		
Immunocompromised patients	Routine pharmacovigilance	A sentence on the lack of information on immunocompromised patients is included in the SmPC in the section Warnings and Precautions (Section 4.4).
Obese patients	Additional Pharmacovigilance: Pharmacokinetics obese subjects study	Information on obese patients is included in the SmPC in the section Posology and method of administration (Section 4.2).
Interaction with general anaesthetics and muscle relaxants	Routine pharmacovigilance However, this type of reaction would trigger a follow-up questionnaire	Section 4.2 of the SmPC warns against bolus injection, and advises that telavancin should be given over a period of 60 min.

The CHMP, having considered the data submitted in the MA application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:

- **A health care professional educational pack** to be distributed to all physicians who are expected to prescribe or use Vibativ, containing:
  - The Summary of Product Characteristics
  - The Patient Information Leaflet
  - The Healthcare Professional Guide. The Healthcare Professional Guide should contain the following key messages:
    - That Vibativ has a risk of nephrotoxicity including increased risk of mortality in patients with pre existing acute renal failure and is therefore contraindicated in patients with pre-existing acute renal failure and in patients with creatinine clearance < 30ml/min, including patients undergoing haemodialysis. Vibativ should be used with caution with other nephrotoxic drugs.

- That the benefit risk balance for the Complicated Skin and Soft Tissue Infections indication was assessed as negative by the Committee for Medicinal Products for Human Use (CHMP), therefore Vibativ should not be used in this or other indications not approved.
- That patients' renal function should be assessed and monitored and initial dose and dosage adjustments should be calculated based on the creatinine clearance.
- That there is a potential risk of teratogenicity and Vibativ is contraindicated during pregnancy. The pregnancy status of women of childbearing potential must be established prior to dosing with telavancin and women of childbearing potential must use effective contraception during treatment.
- The role and use of the Prescriber Checklist sticker included in the product package to document the established pregnancy status prior to dosing.
- The existence and scope of the pregnancy register and details of how to enter patients into it.
- There is a risk of QTc prolongation and Vibativ should be used with caution in patients taking drugs known to prolong the QT interval.
- That there is a risk of infusion related reactions including red man syndrome-like reactions.
- That there is an identified risk of ototoxicity and patients developing ototoxicity signs or symptoms or patients receiving other drugs with ototoxic potential should be carefully evaluated and monitored.
- Healthcare professionals should be aware that the administration of Vibativ may interfere with some coagulation laboratory tests and qualitative and quantitative urine protein tests.
- The need to counsel patients on important risks associated with Vibativ therapy and appropriate precautions when using the medicine.

- **Direct Healthcare Professional Communication letter** to be distributed to all physicians who are expected to prescribe or use Vibativ, the text of which is appended to the CHMP assessment.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8. Benefit-Risk Balance

Benefits

- Beneficial effects

New antibacterial agents are required, especially for the treatment of resistant pathogens and the treatment of infections in the increasing number of patients with impaired immune systems.

Telavancin demonstrated comparable efficacy vs. vancomycin in complicated skin and soft tissue infections (cSSTI) and nosocomial pneumonia (NP) studies

Non-clinical data suggested that telavancin could be active against hetero-resistant vancomycin-insusceptible *S. aureus* (hVISA) and certain vancomycin resistant enterococci (Non-VanA-VRE).

However, there are no clinical data to indicate whether telavancin could be effective against such organisms.

- Uncertainty in the knowledge about the beneficial effects.

In some patient sub-groups (e.g. elderly, obese and diabetic patients) the efficacy of telavancin was numerically lower than that observed with vancomycin. The applicant has explored risk factors for clinical failure and documented some instances of imbalances in risk factors between treatment groups but these cannot wholly account for the observations made

Risks

- Unfavourable effects

The clinical data point to an overall conclusion that the safety profile of telavancin is not as good as that of vancomycin. This conclusion applies even after removing patients with pre-existing severe renal impairment from the analyses. There is an imbalance in the mortality rates in the combined HAP/VAP studies in favour of the comparator and there are higher rates of AEs mapping to infections, sepsis and shock in telavancin-treated patients. It is not possible to determine to what extent these imbalances may reflect issues of safety or efficacy or both in individual patients

- Uncertainty in the knowledge about the unfavourable effects

The applicant has explored risk factors for various types of AEs, particularly renal AEs, and documented some instances of imbalances in risk factors between treatment groups but these cannot wholly account for the observations made.

Benefit-risk balance

Notwithstanding a non favourable risk-benefit balance in the overall patient population, it is observed that for subjects with nosocomial pneumonia due to Gram-positive pathogens and who cannot receive commonly-used antibacterial agents (e.g. due to hypersensitivity or due to MRSA) there are limited treatment options for this life-threatening infection. Thus, the risk-benefit balance for telavancin may be considered favourable if its use is confined to carefully specified clinical circumstances and with adequate patient monitoring.

2.8.1. Discussion on the benefit-risk balance

The efficacy of telavancin in both adult target populations (cSSTI and NP) has been shown as comparable to vancomycin.

The apparent increased nephrotoxicity of telavancin as compared to vancomycin remains a major safety concern though. Proposed attempts to restrict the patient population eligible for receipt of telavancin do not wholly resolve these concerns.

However, within the framework of robust risk minimization measures to be in place to support the post-marketing use, telavancin could prove valuable in some instances to treat adult patients affected by nosocomial pneumonia known or suspected to be caused by methicillin-resistant *Staphylococcus aureus.* The target patients would likely be severely ill hospitalised patients under close monitoring, subjected to short-tem treatment. In these carefully specified clinical circumstances, a positive B/R balance for the use of telavancin could be entertained.

In conclusion, the overall benefit/risk balance of telavancin is negative for both of the broad indications initially sought by the applicant.

However, the CHMP considers that the benefit/risk balance of telavancin for the treatment of nosocomial pneumonia known or suspected to be caused by MRSA, exclusively in situations where it is known or suspected that other alternatives are not suitable, is favourable.

2.8.2. Risk management plan

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns
- the following additional risk minimisation activities were required
  - **A health care professional educational pack** to be distributed to all physicians who are expected to prescribe or use Vibativ, containing:
    - The Summary of Product Characteristics
    - The Patient Information Leaflet
    - The Healthcare Professional Guide.
  - **Direct Healthcare Professional Communication letter** to be distributed to all physicians who are expected to prescribe or use Vibativ, the text of which is appended to the CHMP assessment

2.9. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority decision that the risk-benefit balance of Vibativ in the treatment of adults with nosocomial pneumonia (NP) including ventilator associated pneumonia, known or suspected to be caused by methicillin-resistant *Staphylococcus aureus* (MRSA), exclusively in situations where it is known or suspected that other alternatives are not suitable was favourable and therefore recommended the granting of the marketing authorisation.