European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 22 December 2009
Doc. Ref: EMA/571673/2009

WITHDRAWAL ASSESSMENT REPORT FOR

RAMVOCID
(Oritavancin)

EMEA/H/C/1025

Day 180 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.europa.eu. http://www.emea.europa.eu

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I. RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the CHMP considers that the application for Ramvocid (oritavancin) in the treatment of cSSTI is not approvable since Major Objections have been identified, which preclude a recommendation for marketing authorisation at the present time.

The Major Objections precluding a recommendation of marketing authorisation pertain to the following principal deficiencies:

Quality

Two specified related substances in the drug substance are not considered to be adequately qualified at the proposed limits.

The limit for total unspecified impurities in the drug product is not considered to be adequately qualified at the proposed limit.

Clinical

The application rests on a single pivotal study (ARRI) that is not considered to provide results that are sufficiently robust and convincing to support approval of oritavancin 200 mg for 3-7 days to treat cSSSI.

There are particular outstanding concerns with regard to the efficacy of oritavancin in cSSTI associated with MRSA and the adequacy of the proposed dose regimen of 200 mg daily for 3-7 days to treat infections due to these organisms.

II. EXECUTIVE SUMMARY

II.1 Problem statement

Complicated skin and skin structure infections are most often caused by Gram-positive organisms and can arise following any breach of the skin or spontaneously. Complicated infections involve deeper skin or soft tissue structures, require significant surgical intervention or arise in the presence of significant co-morbidity. These infections require antimicrobial therapy and, as appropriate, surgical intervention. The possible clinical complications include local spread, secondary bacteraemia, metastatic foci of infection and worsening of systemic signs and symptoms of bacterial infection.

The organisms that are most often responsible for these infections are staphylococci, particularly *S. aureus*. However, the incidence of MRSA has reached 60% to 74% in some large US teaching hospitals and is being reported with increasing frequency in outpatient infections (CA-MRSA), some of which are particularly virulent including the US300 clone of CA-MRSA. Many, but not all, MRSA clones are multi-resistant organisms. Glycopeptide hetero-resistant and resistant strains have also emerged and pose a new threat.

Because the morbidity and mortality of MRSA and of improperly treated or untreated skin and skin structure infections is high, and because gram-positive bacterial pathogens are increasingly resistant to a number of standard antibacterial agents, there is a need to develop new agents that are active against resistant Gram-positive pathogens that have a suitable safety profile.

II.2 About the product

Oritavancin is a semi-synthetic derivative of a naturally occurring glycopeptide antibiotic. It is derived from a component present in the fermentation culture of *Amycolatopsis orientalis*. The presence of a lipophilic aryl side chain classifies oritavancin as a lipoglycopeptide antibiotic and is responsible for the mechanisms of action attributed to oritavancin that the applicant claims distinguish it from vancomycin. Oritavancin is administered intravenously and has activity against Gram-positive bacteria only.

The revised indication proposed by the applicant reads:
NUVOCID is a lipoglycopeptide antibiotic indicated for the treatment of complicated skin and soft tissue infections (cSSTI) caused by susceptible isolates of gram-positive microorganisms (see Section 5.1).

In mixed infections where gram-negative and/or certain types of anaerobic bacteria are suspected, NUVOCID should be co-administered with appropriate antibacterial agent(s).

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

The posology proposed by the applicant reads:
Posology
The recommended dosage is 200 mg (300 mg for patients weighing more than 110 kg) by intravenous (IV) infusion over approximately 60 minutes every 24 hours for 3 to 7 days. Patients with methicillin-resistant *Staphylococcus aureus* (MRSA) should be treated for 7 days (see Section 5.1).

Renal Insufficiency
No dosage adjustment is required for patients with mild, moderate or severe renal impairment. Oritavancin is not removed from blood by the commonly used haemodialysis procedures and can be administered to dialysis patient population without a need for dosage adjustment (see Section 5.2).
Hepatic Insufficiency
No dosage adjustment is required for patients with mild to moderate hepatic impairment (see Section 5.2). The pharmacokinetics (PK) of oritavancin in patients with severe hepatic insufficiency impairment have not been evaluated.

Elderly Patients
No clinically significant age-related differences in the population-predicted PK of oritavancin have been identified. No dosage adjustment is warranted based on age (see Section 5.2).

Children and Adolescents (<18 years old)
Nuvocid is not recommended for use in children and adolescents below 18 years of age due to insufficent data on safety and efficacy (see Section 5.2).

Method of Administration
NUVOCID is given by IV infusion (see Section 6.6) and administered over approximately 60 minutes.

II.3 The development programme/Compliance with CHMP Guidance/Scientific Advice

CHMP scientific advice was sought regarding Oritavancin (LY 333328). Subsequently there was interaction with a small number of EU regulatory agencies. However, the questions posed at the time of the CHMP advice related to a very different overall plan for clinical development and have little relevance to this final application for a single indication of cSSTI. Therefore the features of that CHMP advice will not be further discussed.

II.4 General comments on compliance with GMP, GLP, GCP

GMP
The EMEA Inspections Sector has reviewed the manufacturer information contained in the application form (Module 1) and available information from the EEA National Competent Authorities and determined that all relevant sites underwent GMP inspections by EEA/MRA authorities with a satisfactory outcome within the last 3 years, with the exception of two sites, for which inspection requests were adopted at the March 2008 CHMP meeting. As confirmed by the EMEA, both sites were recently inspected and the outcome was positive.

GLP
In general, the safety pharmacology and pivotal toxicology and toxicokinetic studies were performed in accordance with GLP regulations and were consistent with the Organisation for Economic Cooperation and Development (OECD) standards in effect at that time. However, amongst the safety pharmacology studies battery the *in vitro* cardiac electrophysiology study was non GLP-compliant.

GCP
Module 1 of the submission contains a signed statement regarding compliance with GCP. Some of the clinical studies in the dossier go back to the early 1990s. However, they were conducted in accordance with US Federal regulations operative at that time and as such do not raise concerns regarding GCP.

II.5 Type of application and other comments on the submitted dossier

The application for this new active substance has been filed under Article 8(3) as a Centralised Procedure using the optional scope Art 3(2)(a).

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

Oritavancin diphosphate is a novel drug substance. It is a water soluble crystalline material. The manufacture of the drug substance is adequately described. Controls of the starting materials and critical intermediates are generally sufficient to ensure the quality of the final compound although details of method validation have been requested. A reverse-phase HPLC method has been developed to monitor the purity of the drug substance. Potential impurities of oritavancin have been discussed in relation to their origin and potential carry-over in to the final compound.

The drug substance specification is suitable for this compound although tightening of impurity limits and water content have been requested. Limits for two specified impurities are not considered to be qualified. An additional limits should be included in the final drug substance specification. Inclusion of skip-testing of the drug substance by the finished product manufacturer is unacceptable as part of the MAA and should be agreed with the local GMP inspector.

In order to accept the active substance retest period proposed by the applicant, the limit for a specified impurity should be tightened to avoid out-of-specification results during release testing of the drug product.

Drug Product

The drug product is presented as a 100 mg lyophilised powder for solution for infusion packaged in Type I glass vials with Flurotec-coated stoppers and sealed with an aluminium/polypropylene flip-off seal. The proposed formulation containing mannitol and phosphoric acid has been used for some Phase 1 and all Phase 2 and Phase 3 clinical studies. The development of the product has been adequately described.

The finished product is to be manufactured at two sites for which inspection requests have been approved by the EMEA. The manufacturing process is considered a standard technique for the production of lyophilised products and includes: compounding of solution, sterilisation filtration, vial filling and lyophilisation. In-process controls are described adequately. Process validation data has been submitted but the validation is not entirely satisfactory. Therefore, further process validation should be performed prior to approval of this product.

The control of the drug product is generally acceptable with the exception of impurity specifications. Impurity levels should be tightened in line with data obtained from testing batches manufactured at the commercial sites and qualified at the proposed levels. Analytical methods have been described and suitably validated with the exception of the bioburden and sterility testing. Batch analysis data are provided for both manufacturing sites and for the development site.

Stability studies were performed using 13 primary batches of finished product from both manufacturing sites. Data is also provided from batches manufactured at the development site. However, two batches are considered by the CHMP not to reflect the marketed product. The applicant proposed a shelf-life with no additional storage requirements. The statement 'Store in the original package' will also appear on the labelling. The limit for total unidentified impurities was not considered acceptable and therefore, the shelf-life and storage conditions proposed by the applicant are not acceptable.

Reconstitution stability studies from one manufacturing site are outstanding and a commitment should be provided to submit the data once completed. Based on the stability data provided, the assessors concluded that the product should be used immediately following reconstitution.

III.2 Non clinical aspects

Pharmacology

Overall, the primary pharmacodynamic effect of oritavancin in the non-clinical studies supports its use in the proposed indication.

Oritavancin is a chiral compound. Loss of stereochemical integrity at any of the 22 chiral positions in the molecule would be detected through the high performance liquid chromatography (HPLC) analysis of the drug substance as well as HPLC analysis to detect degradants. No impurities observed at significant levels in the drug substance lots or in the stress studies have been identified as a diastereomer. No impurities resulting from racemisation were observed in stress studies. Crystallinity of oritavancin has only been inferred through the physical characteristic of birefringence of the compound under polarized light and the appearance when examined via a scanning electron microscope. However, crystallinity is unlikely to affect the representativity of the preclinical batches since the product was administrated in dissolution.

The effect of oritavancin on vital systems was assessed in a safety pharmacology studies battery. Oritavancin produced anti-cholinergic and anti-dopaminergic effects at clinically relevant concentration >1 µM *in vitro*. Repeated dose studies in dogs reached exposure multiples of about 6-fold the clinical exposure in terms of AUC (652 µg•hr/ml) without evidence of anti-cholinergic activity or anti-dopaminergic activity. However, the potential to cause anti-cholinergic and anti-dopaminergic effects at

clinically relevant concentrations exists. The Applicant should discuss the clinical relevance of these effects bearing in mind how they could affect patients that already have impairment of dopaminergic or cholinergic transmission. Should potential interactions be predicted with an endogenous level of neurotransmitter in a particular medical condition or with exogenous concomitant medication, they should be addressed as warning in SPC and potential risks at RMP level.

Oritavancin blocked the human cardiac hERG (I_{Kr}) channels with an IC_{50} value of 22 µM which leads to an approximately 10-fold margin between hERG IC_{50}/free C_{max}. According to Redfern et al (2003), a 30-fold margin between C_{max} and hERG IC_{50} may sufficient for drugs undergoing clinical evaluation. Therefore, *in vitro* data do not predict an adequate exposure multiple for interaction with hERG. However, the Applicant conducted a QT safety study (ICH E14) in human subjects in which no clinically or statistically significant changes in QT_{cF} were induced by a clinical (200-mg) or by a four-fold supra-clinical (800-mg) dose of oritavancin. This may be explained by cardiac Na^+ channel blocking properties of oritavancin.

Oritavancin blocked the human cardiac I_{Na} with an IC_{50} value of 0.5 µM in human atrial myocytes. This finding was confirmed in a mouse cardiac cell line (AT-1 sub-clone). This observation suggests that oritavancin induces a nearly complete block of the human I_{Na} within the free therapeutic plasma concentrations (up to 2.7 µM).

The apparent disparity between the observed effect on sodium ion channels in isolated cardiac myocytes and the absence of an electrophysiological effect in both nonclinical *in vivo* and clinical studies is still not sufficiently clarified. Therefore, this aspect should be further investigated in the in the scope of the clinical study which is demanded by the CHMP (ECG measurements at C_{max} with special attention to QRS complex prolongation). Furthermore, mechanistic examinations on a preclinical level would be of great interest. The applicant is asked to work out suggestions on this issue.

In dogs, no effects on cardiac rhythm, conduction, or repolarisation were observed.
Due to the disparity between the observed effect on sodium ion channels in isolated cardiac myocytes and the absence of an electrophysiological effect in both nonclinical *in vivo* and clinical studies APD investigations would have been meaningful to complete the database on cardiotoxicity. The applicant should provide such studies.

Increased arterial pressure and a trend toward decreased heart rate were observed in rats administered bolus intravenous doses of 50 mg/kg. In dogs, a single dose that produced anaphylactoid-like reactions (25 mg/kg) was associated with increased arterial blood pressure, heart rate, and left ventricular inotropic state.

In rats given a single intravenous bolus of oritavancin, doses >15 mg/kg were associated with mildly decreased renal function. At >5mg /kg, red urine was noted. The changes in water and electrolyte excretion and the observations of red urine are attributed to vascular changes and tissue hypoxia after release of histamine.

No changes were observed in charcoal meal transit time in mice, although in sub-chronic toxicity studies, gastrointestinal disturbances were observed in dogs administered doses >15 mg/kg/day.
In the CNS, bolus intravenous doses of 50 mg/kg caused mild hypothermia and increased hexobarbital sleep time in mice; the latter may relate to decreased cytochrome-P450 activity as observed in sub-chronic rat toxicity studies.

Pharmacokinetics

Absorption, distribution, metabolism, and excretion (ADME) characteristics of oritavancin have been investigated in mice, rats and dogs, the same species used for the toxicological evaluation of the

compound. Methods for analysis of oritavancin and radioactive equivalents were developed and validated to detect its presence in whole blood, plasma, urine and bile.

Single IV doses of oritavancin in rats and beagle dogs determined that the plasma half-life was 10.8 hours in rats and 52.5 hours in dogs.

In the repeated dose pharmacokinetic studies in rats and dogs up to 1 month, generally the mean plasma concentration and the AUC increased with dose and the increase was approximately dose-proportional. Overall in rats, C_{max} and AUC_{last} each decreased as the number of doses increased (Day 1 to Day 37 to Day 91), indicating that repeated IV administration of oritavancin resulted in a decrease in daily exposure. In dogs at Day 16 after repeated dose administration, the AUC is halved when compared to the AUC at Day 2. At Day 29, the AUC values returned to levels comparable to those of Day 2. This decrease in the AUC can be observed also in rats when the exposure was measured after longer period of repeated administration, i.e. around Day 37 and not at Day 16. Also in rats, contrary to dogs, the exposure didn't recover the baseline values by Day 91.

Altogether it seems that the absorption of oritavancin after repeated dose in rats and dogs is not simply concentration limited but follows a species-specific fluctuation pattern over the time. Whereas the clinical relevance of the observations at 13 weeks is unclear since it is much longer than the intended treatment duration, the possible cause of the fluctuations observed in the AUC with increasing time of administration and their inter-species differences have been addressed. The observed preclinical findings may be an artefact of the PK analysis method coupled with the limited sampling scheme and toxicity noted in animals treated at doses that attained systemic exposure 4-fold the clinical AUC in dogs and in line or below the clinical exposure in rats. As a result, the preclinical rat data should not be taken as an indicator of oritavancin disposition in humans. The dog data are more relevant, but only at doses and treatment durations which do not exceed the intended therapeutic use. Plasma pharmacokinetics in the dog showed good dose proportionality and reproducibility between studies at well tolerated doses. Deviations from linearity and variability in AUC were observed only at poorly tolerated doses (≥30 mg/kg) corresponding to a systemic exposure 6-fold the clinical AUC.

The human data indicate that oritavancin has linear and dose proportional PK that is not time-dependent for doses up to 1220 mg.

Oritavancin is approximately 80 to 90 % bound to human plasma protein and there are only minor differences in oritavancin protein binding across species.

^{14}C-oritavancin was readily distributed from blood to tissues. The highest concentrations of radiocarbon were quantitated in liver and intestinal wall. Many tissues including adrenal gland, bone marrow, caecal wall, kidney, salivary glands, and spleen, contained moderate concentrations of radioactivity. Brain, eye, and testes contained low or background levels of radioactivity, indicating that oritavancin does not cross the blood-brain and blood-testis barrier in healthy animals. The retention of radiocarbon in tissues following a single IV dose suggests the potential for tissue accumulation after multiple dosing.

In gravid rats, ^{14}C-oritavancin did not appear to have crossed the placenta. No detectable levels were seen in the fetuses by this method of analysis. In lactating rats, radiocarbon associated with ^{14}C-oritavancin was excreted in milk following a single 5 mg/kg IV dose of ^{14}C-oritavancin. The radioactivity associated with ^{14}C-oritavancin excreted in milk was absorbed by nursing pups.

All species showed extensive distribution of oritavancin, mainly into macrophages of the reticulo-endothelial system and excretion extended over several weeks after injection of a single dose, largely via the bile into the faeces.

Oritavancin is excreted unchanged in faeces and urine based on lack of observed additional peaks in HPLC-based assays in plasma and bile. Plasma concentrations of oritavancin and plasma radio equivalents of ^{14}C-oritavancin have been compared. This comparison leads to the suggestion that there are no circulating metabolites in the plasma of rats, dogs or mice. Despite the lack of investigation of the presence of metabolites of oritavancin in urine and faeces, it is concluded that oritavancin is very likely excreted unchanged in faeces and urine. However, the presence of oritavancin metabolite(s) has not been directly addressed in excreta. Due to the very long elimination half-life of oritavancin in humans, it was not feasible to collect urine and faecal samples to investigate multiples of the elimination half-life. The long elimination half-life also prevented administration of radiolabeled drug to humans. Based on estimations of predicted recovery and recovery efficiency, the dog appears to be better model than the rat for the excretion of oritavancin.
All the preclinical species tested demonstrated slow elimination of oritavancin via the bile in the faeces and retention of radioactivity after single doses of ^{14}C-oritavancin. Biliary excretion is a predominant elimination pathway for oritavancin in rats.

The disposition of oritavancin after the cessation of treatment has not been elucidated in animals. Drug accumulation in the liver has been shown 13 week after the end of the repeated dose administration in dogs. Since oritavancin is excreted in milk, the long-lasting persistence in tissues could have consequences in nursing women long time after the treatment cessation.

The potential for oritavancin to affect hepatic drug metabolizing enzymes was assessed in rats after 2 weeks and 1 month of daily IV dosing. Significant decreases were observed in activity of the following cytochrome P450-dependent activities in the 15 mg/kg group: 7-ethoxyresorufin O-de-ethylase (EOD; up to 42%), benzphetamine N-demethylase (BND; by up to 47%), and erythromycin N-demethylase (END; up to 33%). No decreases in P450 were observed.

In beagle dogs after 1 month of daily IV dosing, no significant effects were observed on the hepatic cytochrome P450 content. However, it is noted that in a 13-week repeated dose study, treatment of female dogs with oritavancin caused a significant, dose-dependent decrease in liver microsomal cytochrome P450 content at all doses.

These results suggest that a potential exists for clinical drug-drug interactions.

In vitro, the inhibition by oritavancin of the human cytochrome P450 isoforms was determined to be CYP2D6>CYP3A>CYP1A2>CYP2C9 at 25 μM. Clinical plasma concentration is up to 27 μM.
In an *in vitro* study in Caco-2 cells, oritavancin has showed poor permeability, and was neither a substrate nor inhibitor of P-gp.

Toxicology

Oritavancin has been evaluated in a set of toxicology studies for the assessment of a short-term IV administered therapeutic agent.

Single dose toxicity studies using the IV route of administration were conducted in rats and mice at doses up to 160 mg/kg. Deaths occurred at 80 mg/kg and above dose levels in mice and rats. The median lethal dose in mice was calculated to be 98.5 mg/kg for both sexes. The median lethal dose in rats was estimated to be 63 mg/kg for males and 98 mg/kg for females.

The mortality observed in rat toxicology studies above 40mg/kg can be ascribed to 3 different causes. Deaths following immediately or shortly after dosing in the single dose studies and in the neonatal study are linked to histamine-like infusion reactions, which are related to the administered dose, the infusion rate, and oritavancin concentration of the dosing solution. Deaths in the repeated dose studies are attributable either to severe inflammation reactions to the injection, accompanied by thrombosis and

necrosis or to infections related to infusion catheter problems or cage enhancement devices. Analysis and discussion of the likely causes of mortality observed in rat studies is acceptable but the assessment of the systemic exposures and exposure ratios is not concurred. Calculations on safety margins should not be based on the lower range of clinical exposure.

Noteworthy, neonatal animals showed increased sensitivity to the oritavancin-mediated histamine-like infusion reactions. Despite the reason for the increased sensitivity has not been elucidated, this finding should be reflected in the SPC in order to provide relevant information to prescribers that could be considering the off-label use in paediatric patients.
Given the ability of histamine to cause cardiac arrhythmias and the existence of a large pool of releasable histamine in the myocardium, a causal relationship between increased histamine levels and cardiac arrhythmia is very likely (Wolff and Levi 1986). This indirect pro-arrhythmogenic effect of oritavancin should be taken into consideration in the integrated assessment of the cardiac safety pharmacology.

Ultimately, the causes linked to mortality in rats were not shown to increase mortality in the oritavancin treated patients in clinical trials. This outcome is most likely due to the fact that the conditions (histaminergic effects, injection and catheter-related problems, infections) associated with mortality in the rat toxicity studies did not apply to the clinical studies in terms dose levels, study duration and drug administration parameters. For these reasons, the mortality observed in rats is most likely of no or little relevance to the proposed clinical indication and dosing regimen. However, histamine-like infusion reactions and drug-induced inflammatory responses occurred in animals without safety margin and have been observed in humans with oritavancin administration. There was also an increase in infections in oritavancin-treated animals and a variety of inflammatory findings beyond simply phlebitis at the injection site, including granuloma in adjacent tissues and vasculitis that occurred in animals without safety margin. There was also an increase in infections in oritavancin-treated animals. Therefore, these findings should be taken into account both in the section 5.3 of the SPC and in the RMP.

Mortality affected male at lower dosage than in female rats. The same gender-related differences were not observed in mice. The differences in rats cannot be linked to differences in metabolism since there is no evidence that oritavancin is metabolised in rats. Also, exposure in terms of area under the plasma concentration-versus-time curve (AUC) or maximum concentration (C_{max}) did not show notable gender related differences. The clinical relevance of this finding is not known. This information should be reflected in the section 5.3 of the SPC.

In dogs, the anaphylactoid reactions were manageable with the use of supportive measures such as antihistamines, oxygen, and/or IV fluids.

Repeat-dose studies of 2, 4 and 13 weeks followed by a reversibility phase have been conducted by the IV route in rats and dogs. One-month studies have been conducted in neonatal rats and dogs.

It is noted that the relevance of the findings in the 13-week studies for the intended indication is uncertain, since neither the duration nor the higher dose beyond the limiting toxicity are relevant for the assessment of the potential risk for humans treated with the proposed short duration treatment. Therefore, special consideration is given to the toxicological findings at clinically relevant systemic exposures in animal treated up to 1 month.

In sub-chronic studies in rats and dogs, clinical chemistry parameters indicative of hepatic and renal toxicity were slightly-to-markedly increased. These changes were accompanied by only mild histopathological findings, which showed a trend to recovery at the end of the reversibility periods. Weights of several organs were affected, were generally reversible. In all multiple dose toxicity studies, granules identified as lysosomes containing oritavancin were observed primarily in macrophages at all tested doses (>1 mg/kg).

The NOAEL for repeated dose administration in rats was 1 mg/kg/day, based on the decrease in hematologic parameters and increase in hepatic transaminases after IV administration of daily oritavancin up to 1 month. Therefore, there is no safety margin for the toxicological findings, since animal to human exposure is 0.2. Mortality was observed in rats above 30mg/kg/day, which corresponds with an animal to human exposure margin approximately of 2. Above 40/mg/kg/day, higher mortality was observed in male than in female rats. The cause of death in rodents was often not adequately identified. The necropsy, when performed, often failed to identify a cause of death in rodents. Overall, rodents seem to be more affected by the toxic effects of oritavancin than non-rodents.
Chromodacryorrhea and chromorhinorrhea have been reported in rats as species-specific findings without clinical relevance.

In repeated dose toxicity studies in dogs, the NOAEL was 5 mg/kg/day based on clinical chemistry changes related to liver and kidney toxicity. Accordingly, animal to human exposure to establish the safety margin for toxicity is <2. No mortality was observed in animals treated up to 60 mg/kg/day. Clinical observations were noted in males and females at all doses.

Main clinical signs consistent with histamine-mediated anaphylactoid reactions were observed in the 15-mg/kg group and were dose limiting. In some cases, the extent of these reactions after the first or second dose warranted treatment with antihistamines, oxygen, and/or IV fluids.

Histopathological changes (hepatocellular degeneration/necrosis, eosinophilic deposition) observed in the liver of rats and dogs were dose- and time dependent, with onset after a relatively short treatment period of two weeks. Increases in liver transaminases, with, in general, a more pronounced change in ALT, were the most consistent changes in liver clinical chemistry in rats as well as in dogs. Overall, the liver clinical chemistry and histopathological changes are indicative of liver pathology of hepatocellular origin occurring at systemic exposures in line with the clinical AUC in dogs and below the clinical exposure in rats. Oritavancin accumulates in persistent intracellular eosinophilic granules with phospholipidic envolture in Kupfer cells and hepatocytes, as well as in other tissues. Toxic or functional effects in particular tissues may arise either through excessive accumulation of phospholipids or toxic properties of the drug itself at high intracellular concentrations.

The hepatic effects were either completely or partially reversible in dogs after a period of 4 weeks. Liver chemistry changes had returned to control values and eosinophilic granular deposits were no longer present in hepatocytes, but remained detectable in Kupfer cells. In the 3-month study, liver transaminases had decreased by about half at the end of the reversibility period and degeneration and necrosis were no longer observed in histology. Partial reversibility was observed in the 2-week rat study, with a decrease between 1.5-fold and 2-fold in transaminase levels at the end of the 4 week reversibility period. Histologically, minimal single cell necrosis was still present.

Male rats showed greater sensitivity to the hepatotoxic effects of oritavancin. The cause of this difference remains unexplained since it cannot be linked to differences in metabolism as there is no evidence that oritavancin is metabolised in rats. The clinical relevance of this finding is not known.

The potential risk of hepatotoxicity should be adequately reflected in the SPC and RMP.

Both investigated animal species, rat and dog, showed histopathological changes in the kidney (inflammation, tubular degeneration/necrosis, deposition of granular eosinophilic material). After repeated doses of oritavancin, decreases in urine-specific gravity and pH and increases in BUN and creatinine were present in both rat and dog after treatment of two weeks. Eosinophilic granular deposits were present in the renal tubules in rats and dogs, consistent with secondary lysosomes containing high concentrations of oritavancin. Taken together the clinical chemistry and histological changes are compatible with the presence of tubular lesion, which may have a negative effect on the GFR additional to the decrease of

GFR that oritavancin can cause locally through pre-renal (hemodynamic) or post-renal effect due to histamine release effects rather than tubular dysfunction.

Renal findings were dose- and time-dependent and occurred without safety margin in rats and dogs. The risk of nephrotoxicity has been identified both in animals and humans and therefore it should be adequately reflected in the SPC and RMP.

Myocardial inflammation was observed in some rats at exposure levels from 1.5- to 2-fold the clinical AUC. Degenerative/inflammatory foci in the heart could be linked to a primary cardiac damage induced by oritavancin-mediated histamine-like reactions similar to those reported in rats after administration of doses of 80 mg/kg and 120 mg/kg. Ultimately, the severity of these histaminergic effects in the rat did not apply to the clinical studies and therefore this finding could be considered unlikely to occur in clinical treatment. Despite the clinical relevance is not known, this finding could be linked to the cardiac safety profile of oritavancin and therefore it should be reflected in section 5.3 of the SPC.

Extramedullary haematopoiesis in the spleen was observed in rats from the dose of 5 mg/kg in repeated dose toxicity studies of 2 weeks and 1 month, without safety margin of exposure. This histopathological finding correlated with an enlargement and an increase in the weight of the spleen. The splenic extramedullary haematopoiesis was unrelated to the eosinophilic granules present in the spleen macrophages. However, there was a good correlation with the changes affecting red and white blood cells in treated animals. Given their morphological nature, the treatment related findings in the spleen are not considered to be evidence of splenic damage (no cellular degeneration or cell loss). Extramedullary haematopoiesis in the spleen could be attributed to changes in the demand of blood cell production by the bone marrow, due to increase in infections caused by oritavancin or to inflammatory reactions and haemorrhages induced by catheterisation with oritavancin. Despite the clinical relevance is not known, this finding could be linked to the immunomodulatory effects of oritavancin and therefore it should be reflected in section 5.3 of the SPC.

The basis on which the margins of safety for oritavancin have been estimated in the provided table is not reliable. Actually, based on a human AUC = 652 μg•hr/mL safety margins were ≤ 1 for the toxicological findings.

A standard battery of *in vitro* and *in vivo* test on the genotoxic potential did not reveal any clinically relevant findings. Oritavancin spiked with alkylated Factor A was not mutagenic in a battery of genetic toxicity studies.

Because oritavancin is intended for short-term administration, and there was no evidence of genotoxicity, carcinogenicity studies were not conducted.

There was no indication of reproductive toxicity, selective developmental toxicity, or teratogenicity in the reproductive and developmental studies conducted in rat and rabbit. However, the exposure to the drug attained in the species tested for toxicity to reproduction was below the clinical exposure, based on the AUC. For this reason, the results of the reproductive studies have limited value.

There was no evidence of trans-placental transfer of oritavancin in pregnant rats.

The effects of repeat-dose oritavancin treatment in neonatal rats and dogs were consistent with those observed in adult animals. However, it is noted that mortality occurred at all dose levels and affected only males. This is consistent with the results obtained in the general toxicity studies with adult animals. Moreover, a gender-related difference in exposure is reported that could account for the differential tolerability in males and females. This sex related difference in absorption has not been reported in adult animals. The statement in the SPC regarding equal toxicity in neonatal rats compared to adult rats should be removed.

In repeated dose studies in rats, and to a lesser extent in dogs, an increase in vascular and perivascular inflammation was observed at the injection sites. At the higher concentrations and longer durations, the presence of perivascular histiocytes and granulomas was also noteworthy. Dosing-related masses seen macroscopically correlated with haemorrhage and chronic-active inflammation observed at injection sites. These findings have been attributed to infectious inflammatory changes occurred across all groups and were most likely secondary to trauma and bacterial invasion of the catheterization area. However, it is noted that they were more frequent in treated animals most likely due to the irritant properties and the increase in the infections caused by oritavancin.
Vasculitis has been reported in the 13-week repeated dose study at all dose levels. The term "vasculitis" could have been loosely used for the definition of the inflammatory injection site reactions across the toxicity studies. There was no evidence of systemic vasculitis in the rats affected by vasculitis in the vena cava. However, it remains no clear whether this finding was consistent with phlebitis as consequence of the solitary irritation of the vein injected, or it was consistent with vasculitis. The risk of vasculitis cannot be ruled out.

No specific studies have been conducted on antigenicity.

In the immunotoxicity studies in rats, no consistent effect on antibody response was observed, but a reversible decrease in host resistance was reported.

A comprehensive assessment of the *in vitro* and *in vivo* data on the potential immunotoxic effects of oritavancin showed the potential for an immunomodulatory effect leading to a reversible decrease in host resistance. The presence of eosinophilic granules containing oritavancin in the macrophages has been considered the only finding linked to reduced host-resistance in rats at exposures below the clinical AUC This impairment of the immune response could occur as long as the granules of oritavancin persist in the macrophages.

In the 3-month toxicity study in rats, mortality was higher in the treated animals. These effects were attributed in part to bacterial infections resulting from the glucose infusion. Therefore, it can be concluded that there was also an increase in infections in oritavancin-treated animal. Human data showed a decrease in the TNFα production by LPS-stimulated monocytes in treated patients.

There are residual concerns about the potential immunosuppressive effects of oritavancin not only in the short term, but also in the long term since the product is persistent within the macrophages. Section 5.3 of the SPC and the RMP should adequately reflect the risk of immunosuppression due to the impairment of the functionality of macrophages containing high concentrations of intracellular oritavancin in eosinophilic granules.

The drug substance limits for the impurities with unknown structure are higher than the highest concentration in any of the toxicologically tested batches. The limits should be tightened to the levels found in toxicologically tested batches.

Oritavancin does not exhibit important ultraviolet (UV) or visible absorption in the 290 to 700 nm range. In addition, no evidence of systemic tissue discoloration or photosensitivity reactions has been observed in multiple clinical trials with oritavancin. Based on these data, no photosafety testing of oritavancin was conducted.

Environmental Risk Assessment

According to the Applicant, based on the estimated clinical use of oritavancin the expected environmental concentration is below the 0.01 μg/l threshold for further risk assessment. The log K_{ow} value is -0.11.

The Fpen refinements for the ERA Phase I $PEC_{surface\ water}$ calculation of the applicant are not in line with the current guideline. Because the $PEC_{surface\ water}$ is exceeding the trigger value of 0.01 µg/L, the applicant is asked to provide a Phase II assessment in accordance with the guideline EMEA/CHMP/SWP/4447/00.

III.3 Clinical aspects

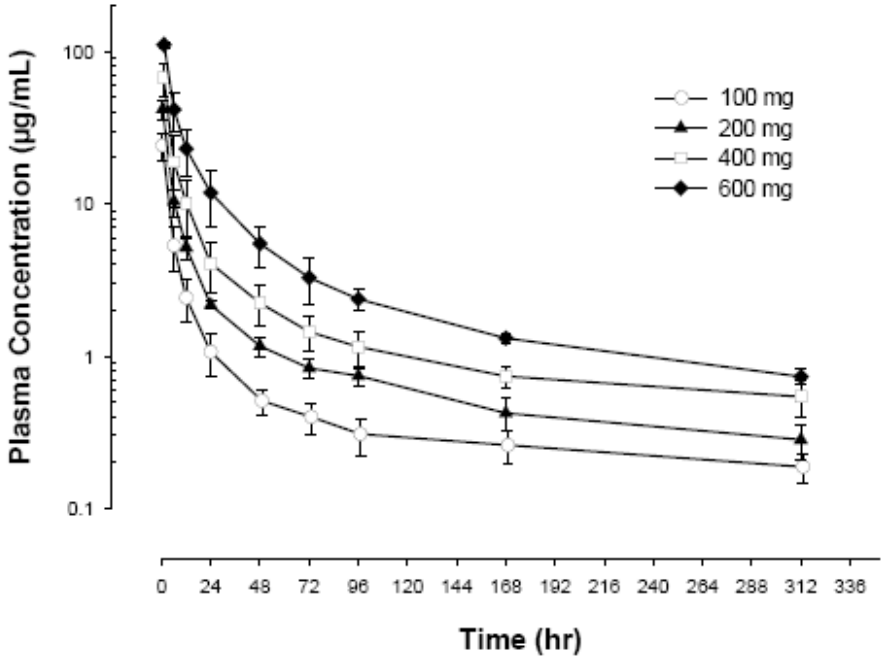
Pharmacokinetics

Oritavancin was administered by infusion over at least 30 min in 5% dextrose in clinical studies. The majority of studies employed LC/MS/MS for determination of plasma concentrations, for which the linear range was from 20 – 2500 ng/ml. Data were provided to demonstrate that appropriate steps were taken to prevent binding of oritavancin in plasma and urine samples to plastic and glass surfaces.

There has been no mass balance study and there remains considerable uncertainty regarding the ultimate fate of oritavancin in man. Taking into account the physicochemical properties of oritavancin and the available PK data a standard 14-day mass balance study would not be sufficient. It was estimated that a study of > 90 days duration would be necessary to recover at least 85% of the total administered dose and it was considered unlikely that there would be reliable collection of urine and faeces over such a period.

Single dose studies used 0.02 mg/kg up to 3 mg/kg or fixed doses up to 600 mg. Dose- and body weight-normalised plasma concentrations were generally consistent across the various doses.

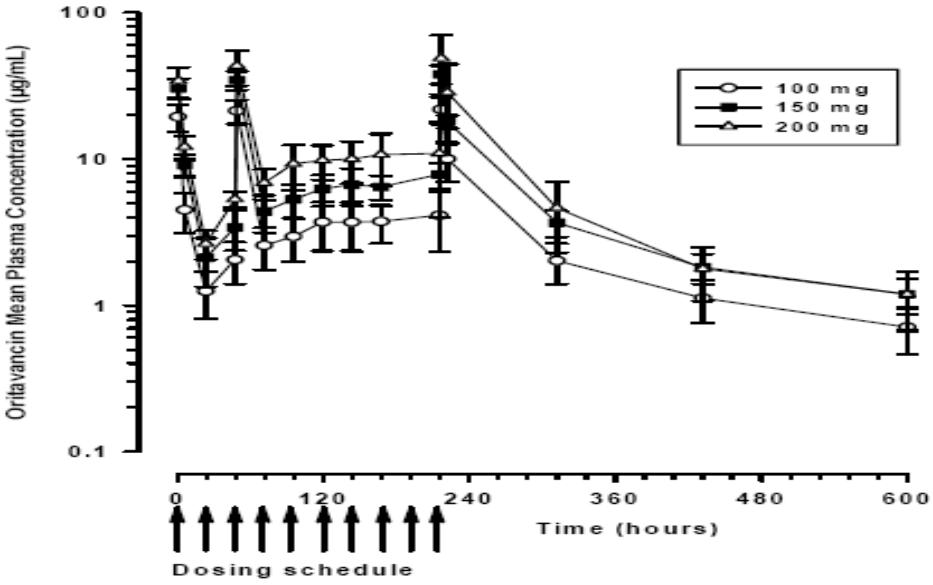
Mean Cmax and AUC0-∞ increased proportionally with dose. Cmax ranged from 24.1 to 111 µg/ml and AUC0-∞ ranged from 280 to 1560 µg•h/ml at doses of 100 mg and 600 mg, respectively. Steady-state Vd and CLp were consistent across the dose range studied. The Vss and mean CLp were 65.8 l (0.83 l/kg) and 0.431 l/h, respectively.



Multiple dose studies used 1.5 to 10.5 mg/kg/day for up to 7 days or up to 200 mg/day for 10 days.

No apparent increase in Cmax was observed with multiple dosing and individual dose/weight-normalised Cmax values were consistent across doses. The mean plasma concentration declined to less than 11% of Cmax within 24 h. There was a modest increase in Cmin (approximately 2.8-fold) after seven to ten daily

doses. After 10 daily doses accumulation in plasma was mostly less than 3-fold (range: 2- to 5-fold) with no significant increase in Cmax. No statistically significant dose effect was observed on the accumulation ratios.



A wide range of oritavancin doses (1 to 1220 mg) was administered across the studies included in the population PK analysis (see below; 42% of 560 subjects received ≥ 400 mg while 25% received ≥ 800 mg). This allowed for an assessment of dose-proportionality from which the applicant concluded that oritavancin pharmacokinetics were linear and predictable over the dose range studied.

Table 2.7.2.3-5 Summary Statistics of Key Pharmacokinetic Parameters and Exposure Estimates, Stratified by Dose Administered

Variable	<180 mg/day (n=181)		180–330 mg/day (n=140)		>330 mg/day (n=239)	
	Mean (SD)	Median (Min–Max)	Mean (SD)	Median (Min–Max)	Mean (SD)	Median (Min–Max)
Dose (mg)	114 (37.9)	113 (1.00 to 179)	239 (40.4)	231 (180 to 330)	682 (179)	800 (333 to 1220)
CL (L/h)	0.558 (0.194)	0.550 (0.169 to 1.40)	0.574 (0.219)	0.544 (0.208 to 1.45)	0.441 (0.202)	0.401 (0.121 to 1.43)
$T_{1/2,\alpha}$ (h)	2.01 (0.467)	1.97 (0.939 to 3.55)	2.13 (0.460)	2.13 (0.910 to 3.27)	2.45 (0.643)	2.35 (1.03 to 4.78)
$T_{1/2,\beta}$ (h)	27.4 (7.89)	27.5 (8.37 to 58.3)	29.7 (9.97)	29.3 (10.4 to 81.5)	31.4 (14.2)	29.3 (9.38 to 99.6)
$T_{1/2,\gamma}$ (h)	376 (71.1)	387 (142 to 567)	376 (77.5)	373 (192 to 545)	353 (80.8)	347 (166 to 302)
$AUC_{0\text{-}24}$ (mg•h/L)	90.0 (61.7)	73.6 (1.02 to 519)	181 (77.1)	171 (46.5 to 424)	750 (412)	712 (109 to 2090)
C_{max} (µg/mL)	17.8 (11.5)	14.3 (0.156 to 87.2)	33.4 (13.2)	30.0 (12.4 to 92.7)	106 (42.2)	105 (20.4 to 251)
C_{min} (µg/mL)	1.17 (0.813)	0.949 (0.016 to 6.78)	2.58 (1.45)	2.20 (0.452 to 8.00)	12.5 (8.74)	11.0 (1.41 to 40.7)

Oritavancin is 85.7%, 88.8%, and 89.9% bound to human plasma proteins at drug concentrations of 1, 10 and 91 µg/ml, respectively. Most binding of oritavancin in serum is to albumin. Oritavancin was found to be excreted in breast milk in non-clinical studies.

Plasma concentrations of oritavancin followed a multi-exponential decline. The mean terminal half-life was estimated to be approximately 15 days. Less than 3.1% of the administered dose was recovered in the urine after 2 weeks of collection in one study and another showed that the overall percent of oritavancin excreted up to 168 h was <5% (approximately 1.9% and 2.4% in urine and faeces, respectively). It was concluded that oritavancin is likely excreted unchanged in faeces and urine based on lack of observed additional peaks in HPLC-based assays, lack of metabolism in animals and the fact that other (lipo)glycopeptides are not or are minimally metabolised.

In an in-vitro study using human liver microsomes there was no detectable depletion of oritavancin due to metabolism. Based on in-vitro studies using human hepatocytes the order of inhibition by oritavancin of cytochrome P450-mediated metabolism of co-administered drugs was determined to be CYP2D6 > CYP3A4 > CYP1A2 > CYP2C9. Oritavancin inhibited CYP2D6 and CYP3A4 in a concentration-dependent manner and was found to be a competitive inhibitor for both isoenzymes with Ki values of 21.9 and 31.7 µM, respectively. Inhibition was non-specific, non-mechanism based and reversible.

The activity of CYP isoforms was not significantly increased by oritavancin at concentrations of up to 50 µM and during incubation over 48 h. At 50 µM there was some increase in CYP2E1 and at 2.5 µM there was some increase in CYP3A4 activity but at higher concentrations there was inhibition of CYP3A4.

Based on these findings a single drug-drug interaction study was performed that found no appreciable effect of oritavancin on the pharmacokinetics of desipramine, a CYP2D6 substrate. In addition, desipramine did not influence the disposition of oritavancin.

The population PK model was developed from pooled data from 560 Phase 1 subjects and Phase 2 and 3 patients with uSSTI, cSSTI or bacteraemia. The most robust fit to the data was obtained using a three-compartment model (one central, two peripheral) with a zero-order IV infusion and first-order elimination. The model fitted the data well, regardless of the observed concentration or administered dose.

The central volume of distribution (Vc) was estimated to be about 6 l (i.e. similar to plasma volume) but the total volume of distribution was approximately 100 l, suggesting wide distribution into tissues. Oritavancin was shown to accumulate in lysosomes of macrophages and fibroblasts by 150- to 350-fold over the extracellular drug concentration within 24 hours, which has been ascribed to the lipophilic side chain and the 4-*epi*-vancosamine sugar. Based on distribution data in rat and dog it has been assumed that the liver is the main tissue store for oritavancin in man when dosed at 200 mg/day for 3 to 7 days.

The model suggested that inter-individual variability was moderate for CL and Vc (34-35%). The dose of oritavancin did not affect CL.

The effect of weight on CL was statistically significant and increased in a linear fashion for those of > 80 kg. CL was significantly higher in the weight categories of ≥ 110 kg (P<0.001) and 80 to 110 kg (P=0.005) compared to the < 80 kg weight category. However, the magnitude of the mean increase in CL relative to the < 80 kg weight category was substantially higher when body weight exceeded 110 kg (42.9%) compared to body weight in the range 80 to 110 kg (8.92%). The relationship between CL and TBW was also apparent when comparing obese individuals (BMI ≥ 30 kg/m^2, n=122) to normal weight (BMI = 18.5-24.9 kg/m^2, n=207) individuals, where the mean oritavancin CL values were 0.616 and 0.497 L/h, respectively. The findings were considered to support the dose recommendations of 300 mg once daily in patients > 110 kg to provide an AUC0-24 comparable to that observed with 200 mg once daily in patients < 110 kg.

The covariate analysis found that CL was increased in Phase 2 and 3 patients compared to Phase I subjects by an average of 30% after accounting for differences in body weight. The higher oritavancin CL observed in patients was thought to be due to enhanced drug distribution as a result of alterations in protein binding and higher intracellular sequestration. The analysis showed that the oritavancin half-life during the distribution phase T1/2,α (mean ± SD) was significantly shorter (p<0.0001) in patients with infection (2.04 ± 0.440 hours) compared to healthy volunteers (2.56 ± 0.653 hours). In contrast, the half life in the terminal phase T1/2,γ was significantly longer (p<0.0001) in patients with infection (393 ± 73.5 hours) compared to healthy volunteers (318 ± 59.1 hours). The findings supported the hypothesis that distribution was likely enhanced in patients with infection compared to healthy volunteers. Other covariate relationships were similar between patients and healthy subjects.

Special populations

Based on the population PK analysis it was considered that dose adjustments are not needed for patients with mild, moderate or severe renal impairment. The pharmacokinetic characteristics of oritavancin have not been studied during haemodialysis. However, since oritavancin has a molecular mass of 1989 Da, shows > 80% protein binding, has a Vd > 100L and CL that is independent of creatinine clearance it was concluded that haemodialysis is unlikely to remove a significant percentage of oritavancin from the plasma compartment.

Single doses of 800 mg oritavancin were given to subjects with Child-Pugh Class B hepatic insufficiency and healthy subjects matched approximately on the basis of sex, ± 5 years of age, ± 30% body weight and smoking habits. At every sampling time point through 45 days post-dose oritavancin plasma

concentrations were approximately 10% to 15% lower and AUCs were more variable in subjects with hepatic insufficiency compared with healthy subjects. Subjects with hepatic insufficiency had increased body weight, lower serum albumin and higher incidence of ascites, which were all thought to contribute to the lower plasma concentrations compared to healthy subjects.

Table 11.2 Arithmetic Mean (Coefficient of Variation) of Pharmacokinetic Parameters (Evaluable Population)

Parameter	Hepatically Impaired Subjects (N = 20)	Healthy Subjects (N = 20)
AUC_{0-24} (µg•h/mL)	877 (37%)	947 (17%)
AUC_{0-t} (µg•h/mL)	1998 (31%)	2265 (19%)
C_{max} (µg/mL)	119 (22%)	145 (33%)
T_{max} (h)	1.66 (1.42 – 2.50)	1.52 (0.75 – 1.73)

When AUC and Cmax values for each subject were adjusted by multiplying by individual body weight and dividing by baseline albumin the adjusted AUC0-t, AUC0-24 and Cmax values were still numerically lower in those with hepatic insufficiency but the 90% CIs around the ratios were within 0.80 to 1.25. It was concluded that the magnitude of the observed differences were less than patient to patient variability and there was no need for dose adjustment for those with mild to moderate hepatic insufficiency.

Gender had no important impact on the pharmacokinetics of oritavancin. There were small differences in the median CL between males and females that were considered likely due to body size differences.

Age had no impact on the CL of oritavancin. There was a statistically significant relationship between oritavancin Vc and age such that Vc decreased in a linear fashion as age increased. Assuming BSA is constant, the population predicted Vc would fall by approximately 35% over the age range of 20 to 85 years. It was concluded that there was no need for dose adjustment as age increases. There were no data from subjects aged < 18 years in this application dossier.

Pharmacodynamics

Microbiology

Oritavancin•2H3PO4 (oritavancin diphosphate) is the *N*-alkyl-p-chlorobiphenyl derivative of chloroeremomycin, a naturally occurring glycopeptide. The core heptapeptide aglycone of oritavancin is shared with vancomycin and it confers inhibition of cell wall (peptidoglycan) synthesis that is characteristic of glycopeptides. Oritavancin has thus been termed a lipoglycopeptide (as have teicoplanin, dalbavancin and telavancin). Unlike vancomycin, oritavancin also disrupts trans-membrane potential leading to rapid killing of susceptible bacteria.

Inclusion of 0.002% polysorbate-80 in broth microdilution susceptibility testing was found necessary to prevent oritavancin binding to plastic and glass. With addition of polysorbate-80 oritavancin MICs against *S. aureus* ATCC 29213 and *E. faecalis* ATCC 29212 decreased by 32- and 16- fold, respectively. The CLSI M7-A8 recommends the inclusion of 0.002% polysorbate-80 throughout oritavancin drug dissolution, dilution and susceptibility testing of staphylococci, enterococci and streptococci. Using the CLSI-recommended method the in-vitro activity of oritavancin was assessed for 8648 geographically diverse clinical isolates collected from 2004 to 2006.

For *Staphylococcus aureus* oritavancin MIC90 values were 0.12 to 0.25 mg/l regardless of oxacillin resistance. Against 16 daptomycin insusceptible (MIC ≥ 2 mg/l) isolates the oritavancin MIC90 was 1 mg/l and against 13 linezolid insusceptible isolates the oritavancin MIC90 was 0.25 mg/l. Against 13

VISA the oritavancin MIC90 was 1 mg/l compared to MICs from 0.12 to 0.5 mg/l for 5 VRSA. The oritavancin MIC90 was 0.25 mg/l against all clinical isolates of *S. pyogenes* (n=287), regardless of erythromycin susceptibility. For *S. agalactiae* the MIC90 was 0.12 mg/l and for Group C, G, and F streptococci MIC90s were 0.25 or 0.5 mg/l. A separate study assessed the in-vitro activity of oritavancin against 139 Gram-positive aerobic bacteria with specific resistance phenotypes or genotypes from worldwide sources.

Table 2.7.2.4-2 Comparative MICs and MBCs using Polysorbate-80 Methodology against *S. aureus*, *S. epidermidis*, Other Coagulase-negative *Staphylococcus*, *E. faecalis* and *E. faecium*, According to Vancomycin Phenotype

Organism	Phenotype	n	Agent	MIC range	MIC_{50}	MIC_{90}	MBC range	MBC_{50}	MBC_{90}	MBC_{90}/MIC_{90}
S. aureus[a]	ALL	31	ORI	0.015-1	0.03	0.5	0.015-4	0.06	1	2
	ALL	31	VAN	0.5->64	0.5	4	0.5->64	0.5	4	1
	VAN S	27	ORI	0.015-1	0.03	0.12	0.015-1	0.03	0.25	2
	VAN S	27	VAN	0.5-1	0.5	1	0.5-1	0.5	1	1
	VAN I	2	ORI	0.5-1	ND	ND	1-4	ND	ND	ND
	VAN I	2	VAN	4-4	ND	ND	4-8	ND	ND	ND
	VAN R	2	ORI	0.25-0.5	ND	ND	0.25-5	ND	ND	ND
	VAN R	2	VAN	>64->64	ND	ND	>64->64	ND	ND	ND
S. epidermidis	ALL	26	ORI	0.03-0.25	0.12	0.25	0.03-0.5	0.12	0.25	1
	ALL	26	VAN	0.5-2	2	2	1-4	2	2	1
Other CoNS[b]	ALL	5	ORI	0.03-0.25	ND	ND	0.03-0.25	ND	ND	ND
	ALL	5	VAN	0.5-2	ND	ND	1-8	ND	ND	ND
E. faecalis[a]	ALL	32	ORI	0.015-1	0.03	0.5	0.015-16	0.25	8	16
	ALL	32	VAN	0.5->256	1	>256	8->256	64	>256	≥1
	VAN S	26	ORI	0.015-1	0.03	0.06	0.015-16	0.12	4	64
	VAN S	26	VAN	0.5-2	1	2	8-256	32	128	64
	VAN NS	6	ORI	0.03-1	ND	ND	0.03-16	ND	ND	ND
	VAN NS	6	VAN	8->256	ND	ND	64->256	ND	ND	ND
E. faecium[a]	ALL	31	ORI	0.004-0.5	0.03	0.12	0.004-16	2	8	64
	ALL	31	VAN	0.25->256	256	>256	2->256	>256	>256	≥1
	VAN S	6	ORI	0.004-0.015	ND	ND	0.004-0.03	ND	ND	ND
	VAN S	6	VAN	0.25-0.5	ND	ND	2-64	ND	ND	ND
	VAN NS	25	ORI	0.004-0.5	0.03	0.12	0.008-16	4	8	64
	VAN NS	25	VAN	32->256	256	>256	>256->256	>256	>256	≥1

Using polysorbate-80 and the CLSI methodology the oritavancin MBC90:MIC90 or MBC:MIC ratios against *S. aureus* and *Staphylococcus epidermidis* ranged from 1 to 4. Time-kill assays confirmed a lack of tolerance to oritavancin by *S. aureus.* At its predicted free peak in plasma after a single 200 mg dose oritavancin reduced viable counts of VanA- and VanB-expressing strains of *E. faecalis* and *E. faecium* by 1 to 2 logs.

Studies in the presence and absence of 4% human serum albumin (HSA) suggested that the impact of 4% human serum albumin on oritavancin activity in-vitro is modest, with MICs elevated maximally 4-fold (against VISA strains) and with bactericidal activity retained in time-kill assays with all but one tested VISA isolate.

At its predicted free peak concentration in plasma oritavancin demonstrated PAEs of 1.5 to 4.5 hours against *S. aureus* and of 3 to 5 hours against enterococci. The oritavancin PAE was concentration-dependent.

Oritavancin accumulates in lysosomes of macrophages and fibroblasts by 150- to 350-fold over the extracellular drug concentration within 24 hours, which has been ascribed to the lipophilic side chain and the 4-*epi*-vancosamine sugar. Oritavancin has been shown to exert bactericidal activity against intracellular staphylococci and enterococci at extracellular drug concentrations that are obtained in serum from 200 mg once daily doses. Bacterial loads were reduced by 2 to 3 log colony-forming unit (CFU) over 24 hours.

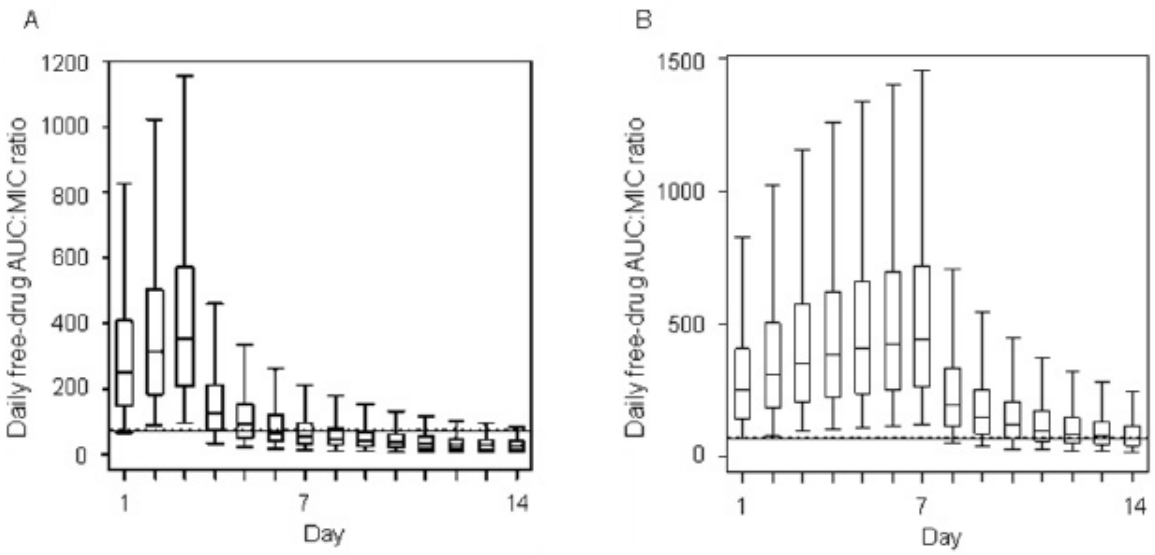
Following 7 daily doses of 1.5 mg/kg oritavancin the evaluation of TNFα measurements of LPS-stimulated monocytes (indicating function of the peripheral cell prior to becoming a tissue-resident macrophage) showed that all subjects had small increases in TNFα release from pre- to post treatment although the increases were not considered to be of clinical significance. The ex-vivo neutrophil production of hydrogen peroxide showed variability but there was no clear trend in the results. The safety database of phase 3 patients did not reveal any evidence of an immunomodulatory effect of oritavancin during post treatment follow-up. At present there is no clear signal for oritavancin to have a detrimental effect on macrophage function as a result of the very high intracellular accumulation that undoubtedly occurs with dosing at the recommended regimen. However, the applicant was asked to discuss how such effects might be investigated further in ongoing and planned studies in patients.

At least two potential routes exist for bacterial resistance to oritavancin – known glycopeptide resistance mechanisms (i.e. Van operons and the VISA-type cell wall thickening) and development of a new mechanism in strains not carrying any other pre-existing glycopeptide resistance. Serial passage experiments using broth microdilution with polysorbate-80 demonstrated that oritavancin MICs of selected *S. aureus* and VanB-expressing *E. faecium* were maximally 8-fold and 64-fold higher, respectively, than those of the parent (naïve) strains.

Animal models that evaluated efficacy suggested that the AUC/MIC ratio and Cmax were the major PK/PD parameters predictive of the efficacy of oritavancin. Monte Carlo simulations based on a dose of 200 mg once daily indicated that the probability of target attainment (net bacterial stasis and 1 and 2 log10 CFU reduction) for oxacillin-susceptible and –resistant *S. aureus* approached 1.0 for MIC values up to 0.12 mg/l. At a MIC of 0.25 mg/l the probability of attaining an AUC/MIC ratio associated with net bacterial stasis ranged from 0.596 to 0.531 while at a MIC of 0.5 mg/l the probability of target attainment was < 0.1. The PK/PD report suggested that the microbiological cut-off for susceptibility was probably 0.25 mg/l whereas the clinical cut-off was 0.12 or 0.25 mg/l.

The breakpoints recommended by EUCAST (finalised May 2009) are as follows:
Non-species related S ≤ 0.12 mg/l, R > 0.12 mg/l
S. aureus S ≤ 0.12 mg/l, R > 0.25 mg/l
Streptococci other than *S. pneumoniae* S ≤ 0.25 mg/l, R > 0.25 mg/l
Regarding the final dose regimen proposed by the applicant to treat cSSSI the figures below show box plots of the daily free-drug AUC:MIC ratios following 200 mg daily for 3 and 7 days, respectively. For each graph, the box plots represent the median and inter-quartile range for daily free-drug AUC:MIC ratios based on simulations of 10,000 patients, which account for population variability in both AUC and MIC values. The horizontal solid and dashed lines for each graph represent the average 24 hour free-drug AUC:MIC targets of 69.0 and 77.1 associated with net bacterial stasis and a 1 log10 CFU decline, respectively, based on data from a murine thigh-infection model for *S. aureus* after 48 hours of study.

Based on these analyses the applicant considered that drug exposures associated with adequate bacterial killing would be expected beyond the 3 to 7 day duration of therapy in the majority of patients and most would be expected to have such exposures for 2 and 5 days following the end of the treatment course.



A Box plots represent the median and interquartile range for daily free-drug AUC:MIC ratios based on simulations of 10,000 patients. The associated whiskers represent the 5th and 95th percentile for the simulated daily free-drug AUC:MIC ratios. The MIC distribution was based on the surveillance data for *S. aureus* from the United States (Study 500275).

B The horizontal solid and dashed lines represent the average 24 hr free-drug AUC:MIC targets of 69.0 and 77.1 associated with net bacterial stasis and a 1 log10 CFU decline, respectively, based on data from a murine thigh-infection model for *S. aureus* after 48 hrs of study (ICPD 00159).

Figure 2.3.1.1-4 **Daily free-drug AUC:MIC ratio corresponding to oritavancin 200 mg administered intravenously once every 24 hours for three (A) or seven (B) days with population variability in AUC and MIC values.**

The Phase 2 study ARRL suggested that seven doses of oritavancin 1.5 mg/kg/day or 3.0 mg/kg/day would be suitable for treatment of cSSSI and were expected to provide plasma concentrations of oritavancin similar to those associated with efficacy in the neutropenic mouse thigh model. Study ARRD compared once-daily oritavancin at 1.5 mg/kg and 3.0 mg/kg to vancomycin/cephalexin in the treatment of patients with cSSSI. Against MRSA oritavancin 1.5 mg/kg showed a numerically lower response rate (8/13) compared to 3.0 mg/kg (10/13) and vancomycin/cephalexin (8/11). The safety profiles of the two oritavancin treatment groups were indistinguishable.

The available data suggested that a fixed dose of oritavancin 200 mg would give adequate drug levels to treat the pathogens involved in cSSSI and this daily dose was used in the pivotal study ARRI (300 mg/day if body weight > 110 kg). With a standard dose of 200 mg daily those weighing < 70 kg could receive perhaps up to 5 mg/kg while those in the range 70-110 kg could receive just under 2 mg/kg.

Effect on cardiac conduction

Non-clinical studies demonstrated a potential for oritavancin to block human cardiac ion channels in an in-vitro protein-free milieu (INa, Ito and hERG). Early investigations of the effect on ECGs (including QTc interval) in man following single and multiple doses of oritavancin showed a trend to increasing change in QTc with higher plasma concentrations of oritavancin but the relationship did not reach significance.

The final report on a thorough QTc study (**QT002**) was provided during the procedure. This was a double blind, randomised, placebo and positive controlled, single dose, parallel design study in healthy adults aged 18-60 years. The treatments were as shown in the table.

Group	Day 0	Day 1
Group 1	Placebo D5W IV	Oritavancin 200 mg IV
Group 2	Placebo D5W IV	Oritavancin 800 mg IV
Group 3	Placebo D5W IV	Moxifloxacin 400 mg po
Group 4	Placebo D5W IV	Placebo D5W IV

The primary analysis was based on comparison of mean QTcIb between groups receiving 800 mg oritavancin and placebo (i.e. ddQTcIb for Group 2 and Group 4) where QTcIb was defined as the QT corrected (Bazett's formula) in each individual subject for heart rate.

In the moxifloxacin group the largest time-matched difference in QTcB (day 1 – day 0) was 12.3 (95% CI 8.5 – 16.2) ms at hour 1. The ddQTcB change in the mixed effects model was positive and the change was statistically significant at all time points except hour 22. The maximum ddQTcB increase was 13.9 (90% CI 10.6 – 17.7) ms at 1 hour. Adequate assay sensitivity was demonstrated by increase of ddQTcIb at one hour with a lower confidence bound exceeding 5 ms (mean 8.23 ms, 90% CI 5.08 – 11.40 ms).

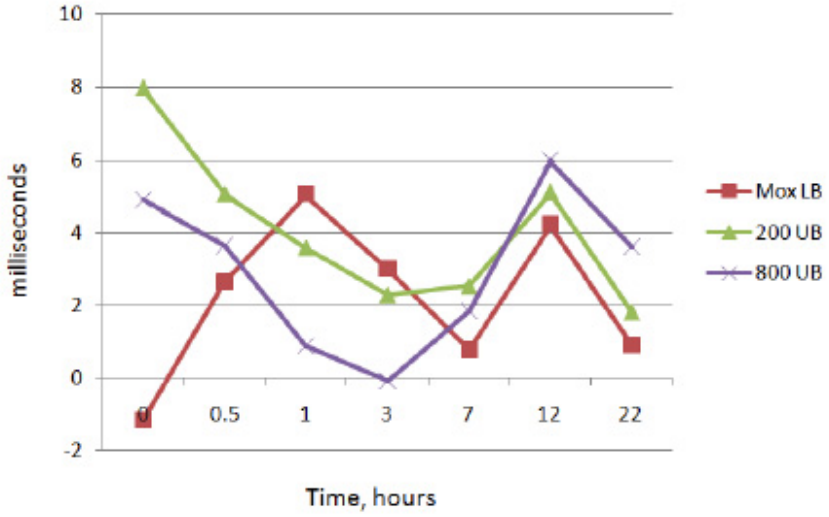
In the 200 mg oritavancin group the largest time-matched increase in QTcB (day 1 – day 0) was 4.6 (95% CI 1.1 –8.0) ms at hour 0. In the mixed effects model the ddQTcB change was positive at five time points and negative at two. The maximum ddQTcB increase was 7.25 (90% CI 3.5 – 11.0) ms at 0 hours. The maximum ddQTcB decrease was -2.04 (90% CI -5.78 – 1.7) ms at 22 hours.

In the 800 mg oritavancin group the largest time-matched increase in QTcB (day 1 – day 0) was 4.0 (95% CI 0.3 – 7.7) ms at hour 12. The ddQTcB change in the mixed effects model was positive at five time points and negative at two. The maximum ddQTcB increase was 4.4 (90% CI .07 – 8.1) ms at 0 hours. The maximum ddQTcB decrease was -1.5 (90% CI -5.3 – 2.2) ms at 22 hours.

In the primary analysis the confidence bounds excluded zero at all time points except hour 0. The upper confidence bound of ddQTcIb for 200 mg and 800 mg oritavancin was < 10 ms at all time points. Zero was excluded by the upper and lower 90% confidence bounds at hour zero for the 200 mg dose (4.85, CI 1.72 – 7.98 ms) and at hour 3 for the 800 mg dose (-3.20, CI -6.32 – -0.09 ms). The upper confidence bound was also below 10 ms for QTcB and QTcF at all time points except for QTcB at hour 0 in the 200 mg group (before drug was administered).

It was concluded that the oritavancin had no clinically significant repolarisation effect when administered intravenously at 200 mg and 800 mg to normal subjects. No other significant electrocardiographic effects were found.

Figure 4: Double Delta QTcIb Lower Confidence Bound for Moxifloaxacin and Upper Bounds for Oritavancin



Clinical efficacy

In the initial application dossier there were five studies that provided data on the efficacy of oritavancin as follows:

H4Q-MC-ARRL	Phase 2 for SSSI	Patients with SSSI (29)
H4Q-MC-ARRC	Phase 2 for bacteremia	Patients with gram-positive bacteremia (27)
H4Q-MC-ARRM	Phase 2 for bacteremia	Patients with gram-positive bacteremia (123)
H4Q-MC-ARRD	Phase 3 Pivotal Study	Patients with cSSSI (517)
H4Q-MC-ARRI	Phase 3 Pivotal Study	Patients with cSSSI (1246)

Studies ARRC and ARRM were conducted in patients with bacteraemia and not in patients with the indication currently sought by the applicant. **ARRL** was a dose-finding study in patients with various types of SSSI but only 29 patients were enrolled.

Only **ARRI** employed the dosing regimen that is proposed in the SPC and this was considered to be the sole pivotal study to support the application. **ARRD** employed mg/kg dosing at two levels and was considered to be a supportive study. The applicant performed some re-analyses of the original study reports on ARRD and ARRI. The following presents the results as shown in the individual study reports prepared by the previous sponsors. Some of the re-analyses based on pooled efficacy data from patients who received 180-330 mg oritavancin daily are also provided.

At the time of responding to the D120 LOQ the applicant provided the report on an additional study **SIMPLIFI** in which three different regimens of oritavancin were compared, one of which involved dosing at 200 mg once daily. The efficacy data from this study have been described below since they have some relevance to the current application and the safety data have been included in the next section.

ARRD and ARRI

These were double-blind (evaluator- and patient-blinded) studies that aimed to demonstrate non-inferiority of clinical responses to oritavancin with respect to vancomycin.

Patients were considered to have complicated SSTI if all three of the following definitions were satisfied:

Severity – based on anticipated need for 3 or more days of parenteral therapy

Complicated - one of the following criteria had to be met:

Infection required significant surgical intervention < 36 h before or after enrolment

Infection process is suspected or confirmed to involve fascia and/or muscle layers

Significant underlying disease that complicated response to treatment

Disease categories - for the purposes of stratified randomisation patients were grouped into:

Wound infection at the site of surgical incision or trauma

Cellulitis

Major abscess including need for intervention within 48 h of enrolment

Patients were excluded if they had been treated for more than 24 h within the last 3 days (ARRD) or 48 h (ARRI) with systemic antimicrobial therapy unless the Gram-positive pathogen was resistant *in vitro* to the previous agent used or the patient had failed to respond.

Oritavancin (with no active oral follow-on therapy) was compared with vancomycin with or without continuation with oral cephalexin (based on pre-defined switch criteria). Patients received up to 7 days of assigned parenteral therapy (oritavancin or vancomycin) except that patients with MRSA received a maximum of 14 days of vancomycin or 7 days of oritavancin. The total duration of treatment (IV/PO) was to be at least 10 days but no more than 14 days. Oritavancin or vancomycin was infused over approximately 60 ± 10 minutes.

- In ARRD oritavancin was dosed at 1.5 mg/kg/day or 3.0 mg/kg/day up to a maximum of 400 mg per day. The randomisation ration (oritavancin 1.5 or 3 mg/kg and vancomycin) was 1:1:1.
- In ARRI the dose of oritavancin was fixed at 200 mg once daily except that patients weighing more than 110 kg were to receive 300 mg once daily. The randomisation ratio was 2:1
- Aztreonam and/or metronidazole could also be administered to any patient suspected or proven to have a polymicrobial infection that included gram-negative pathogens and/or anaerobes.

ARRD allowed an outcome of improvement at the First Follow-Up (=TOC; conducted at D28 = 7-21 days post-therapy). ARRI allowed only the following at TOC:

• Cure: Resolution (cessation) of baseline clinical signs and symptoms of infection such that no further antimicrobial treatment was necessary.
• Failure
• Indeterminate

In ARRD the primary efficacy analysis was based on the investigator-assigned clinical outcomes (IDCO) expressed as success rates (i.e. cure + improvement) in the evaluable population at TOC visit. The non-inferiority margin was -15%. Two interim analyses were planned for this study in which oritavancin patients were compared to vancomycin/cephalexin patients with respect to safety data, clinical response and discontinuations due to AEs. These were conducted under the auspices of the Data Monitoring Board (DMB) and access to patient treatment codes was limited.

In ARRI the following major patient populations were defined:

- Intent-to-treat (ITT) = all randomised and treated
- Intent-to-treat clinical (ITTC) = more severely ill ITT patients who met any of three criteria (fever defined as body temperature > 37.5°C/99.5°F axilla; WBC ≥ 10,000; Bands ≥ 10%) AND had "severe" checked for any one of pain, tenderness, erythema, induration, oedema or purulent drainage
- Modified intent-to-treat (MITT) = ITT patients with cSSTI caused by a gram-positive pathogen
- Clinically evaluable (CE) = met enrolment criteria, received the first six doses of study drug and did not have a Sponsor-defined outcome of indeterminate or missing at TOC (window 21-29 days).
- Bacteriologically evaluable (BE) – CE with a gram-positive pathogen.

The primary efficacy variable was the sponsor-defined clinical outcome (SDCO) in the CE population at TOC although the IDCO was also recorded. The pre-defined non-inferiority margin was 10%.

Results for ARRD

Of the 517 treated patients (ITT population) 384 were qualified for the analysis of clinical outcomes and 256/384 were qualified for the analysis of bacteriological outcomes. There were no differences between treatment groups in age, weight, body mass index, origin, or type of skin infection. The mean and median total durations of treatment (IV+PO) were 10-11 days in each group with 4-5 days IV and 7-8 PO.

For evaluable patients at TOC the combined cure + improvement rates were 75.6%, 75.6%, and 80.2 % for oritavancin 1.5 mg/kg, 3.0 mg/kg, and vancomycin/cephalexin, respectively. The 95% confidence intervals around the treatment difference for oritavancin 1.5 mg/kg versus vancomycin/cephalexin without and with continuity correction were (-0.148 to 0.056) and (-0.155 to 0.064), respectively.

In the comparison between oritavancin 3.0 mg/kg and vancomycin/cephalexin the 95% confidence intervals around the treatment difference without and with continuity correction were (–0.148 to 0.057) and (–0.156 to 0.065), respectively.

Table ARRD.11.17. Clinical Response at First Follow-up (All Clinically Qualified Patients-Failures Carried Forward)

Protocol: H4Q-MC-ARRD
Outcome Variable: CLINICAL RESPONSE

		Cure		Improvement		Failure		Relapse	
THERAPY	N	n	%	n	%	n	%	n	%
A. LY 1.5 mg/kg/d	131	64	48.9	35	26.7	14	10.7	18	13.7
B. LY 3.0 mg/kg/d	127	53	41.7	43	33.9	20	15.7	11	8.7
C. Vancomycin	126	56	44.4	45	35.7	13	10.3	12	9.5

In all clinically qualified patients with a successful clinical response at TOC the clinical success rates at Late Follow-up were 89.9%, 95.5% and 94.5% for oritavancin 1.5 mg/kg, 3.0 mg/kg and vancomycin/cephalexin, respectively. The relapse rate for the oritavancin 3.0 mg/kg group (4.5%) was lower than the rate in the oritavancin 1.5 mg/kg group (10.1%), suggesting that 3.0 mg/kg may be a more efficacious dose.

For all dosed patients, cure or improvement was seen in 62% of oritavancin 1.5 mg/kg patients, 63.4% of oritavancin 3.0 mg/kg patients and 64.7% of vancomycin/cephalexin patients. Since the lower limit of the 95% confidence interval was > -0.15, the applicant concluded that oritavancin at 1.5 mg/kg (95% CI, -0.131 to 0.078) and 3.0 mg/kg (95% CI, -0.118 to 0.094) was non-inferior to vancomycin/cephalexin. After combining data from the two oritavancin dose groups non-inferiority to vancomycin/cephalexin was demonstrated (95% CI, -0.111 to 0.071).

For all bacteriologically qualified patients with *S. aureus* as the only pathogen the cure rates were 43% and 42% for the two oritavancin groups and 53% for vancomycin. For the qualified patients in respective treatment groups with MRSA a successful clinical outcome was reported for 9/13, 8/10 and 8/10. Success rates were 21/32 (66%), 23/33 (70%) and 28/38 (74%), respectively, for the patients with MSSA. Numbers with bacteraemia were not reported.

For all bacteriologically qualified patients, bacteriological response rates (eradication or presumed eradication) at TOC were 72.4%, 71.6% and 75.0% for oritavancin 1.5, 3.0 and vancomycin/cephalexin, respectively. Based on the defined criteria it was concluded that oritavancin 3.0 mg/kg was non-inferior to vancomycin/cephalexin (95% CI, -0.138 to 0.122) but the 95% CI for the difference between 1.5 mg/kg and vancomycin/cephalexin was -0.167 to 0.093.

Results for ARRI

Of 1267 patients enrolled 1246 patients were treated and included in the ITT population. Patient populations (evaluability) and baseline diagnoses were as follows:

Table 11–3 Patient Evaluability by Disease Category and Treatment Group

Population		Wound Infection		Cellulitis		Major Abscess	
	N	Orita n (%)	Vanco n (%)	Orita n (%)	Vanco n (%)	Orita n (%)	Vanco n (%)
ITT	1246	265 (31.9%)	139 (33.5%)	200 (24.1%)	99 (23.9%)	366 (44.0%)	177 (42.7%)
ITTC	574	105 (26.9%)	53 (28.8%)	92 (23.6%)	41 (22.3%)	193 (49.5%)	90 (48.9%)
MITT	850	214 (38.1%)	112 (38.9%)	75 (13.3%)	42 (14.6%)	273 (48.6%)	134 (46.5%)
CE	1000	229 (33.9%)	115 (35.5%)	168 (24.9%)	83 (25.6%)	279 (41.3%)	126 (38.9%)
BE	686	191 (41.4%)	94 (41.8%)	67 (14.5%)	36 (16.0%)	203 (44.0%)	95 (42.2%)

Most patients completed IV therapy (oritavancin 88.6%; vancomycin 87.5%) with means of 6.1 days in the oritavancin group and 6.2 days in the vancomycin group. Discontinuation of IV therapy because of lack of efficacy occurred in 4.0% (33/831) oritavancin and 2.9% (12/415) vancomycin patients.

Most patients (83-85%) who completed IV therapy switched to oral therapy (i.e. placebo or cephalexin) for an average of just over 7 days and a mean time to switch of 4.5 days. The mean duration of total therapy was 10.9 days.

Demographic factors were balanced between treatment groups. In the MITT population 655/850 (77%) had *S. aureus* isolated at baseline and 170/850 (20%) were infected with MRSA. *Streptococcus pyogenes* was found in 17.5% (149/850) while less than 9% in either treatment group had cultures positive for any other baseline pathogen. Numbers of bacteraemic patients were not reported.

Approximately half of the patients in the oritavancin (49.7%) and vancomycin (54.9%) groups received a potentially active antibacterial agent during the 3 days before study drug administration. The duration of pre-treatment and range of agents used were wide but comparable between treatment groups.

Table 2.3.2.3-1 Duration of Treatment with Prior Antibacterial Therapy Study ARRI (ITT)

Duration of Prior Antibacterial Therapy[a]	ORI N=411 % (n)	VAN N=228 % (n)
<24 hours	35.3 (145)	37.7 (86)
1 day	35.8 (147)	32.5 (74)
2 days	4.9 (20)	7.5 (17)
≥3 days[b]	24.1 (99)	22.4 (51)

[a] Calculated as (Stop date – Start date). For patients who took multiple antibiotics, the longest duration was used.

[b] Includes those patients whose medication stop date is missing.

Over 70% (452/639) of these patients had received ≤ 1 day prior therapy. Among those that received ≥ 2 days the majority (171/196, 87.2%) had the prior agent discontinued by the investigator for inadequate response, with or without documented resistance to the previous therapy. Only 16/639 (1.2%; 9 oritavancin and 7 vancomycin) patients did not meet one of permissible explanations for prior therapy.

The primary analysis demonstrated non-inferiority for oritavancin with respect to vancomycin with 95% CI -3.4, 7.8. Note that patients with missing or indeterminate outcomes at TOC were eliminated from the CE population.

A sensitivity analysis was performed to assess the impact of including patients from Site 131, all 20 of whom were excluded from the CE population because of drug accountability and unblinding issues. The cure rates in this sensitivity analysis were 78.4% (540/689) for oritavancin and 76.1% (252/331) for vancomycin. The 95% CI around the difference in cure rates (2.2%; -3.3% to 7.8%) showed consistency with the primary analysis.

Table 11–12 Primary Efficacy Endpoint – Sponsor-Defined Clinical Outcome at First Follow-up: CE Population

Response	Oritavancin N = 676 n (%)	Vancomycin N = 324 n (%)	Difference (Orita–Vanco)	95% CI[a]
Number Assessed	676	324		
Cure	531 (78.6%)	247 (76.2%)	2.3%	(-3.4, 7.8)
Failure	145 (21.4%)	77 (23.8%)		

[a] Mantel-Haenszel CI with stratification method described by Greenland and Robins (Greenland and Robins 1985) and correction to variance estimate described by Sato (Sato 1989). Interval is adjusted for disease category.

Sponsor-defined clinical outcomes (SDCO) at TOC for the other pre-defined patient populations yielded 95% CI that fell within -4.1 and +13.8. Clinical outcomes were comparable between the ITTC and the ITT populations, suggesting that the criteria used to define the ITTC population were not adequate to define a subset of more severely ill patients.

Table 11–13 Sponsor-Defined Clinical Outcome at First Follow-up for MITT, ITT, and ITTC Populations With Missing and Indeterminate Outcomes Classified as Failures

Response	Oritavancin N = 831 n (%)	Vancomycin N = 415 n (%)	Difference (Orita–Vanco)	95% CI[a]
MITT	N = 562	N = 288		
Cure	402 (71.5%)	199 (69.1%)	2.4%	(-4.1, 8.9)
Failure	160 (28.5%)	89 (30.9%)		
ITT	N = 831	N = 415		
Cure	598 (72.0%)	282 (68.0%)	4.0%	(-1.4, 9.4)
Failure	233 (28.0%)	133 (32.0%)		
ITTC	N = 390	N = 184		
Cure	283 (72.6%)	123 (66.8%)	5.7%	(-2.4, 13.8)
Failure	107 (27.4%)	61 (33.2%)		

[a] Two-sided CI constructed using normal approximation to the binomial distribution.

Revisions made when assigning SDCO never improved the IDCO, such that patients with outcomes of cure or indeterminate according to IDCO could be reassigned to a SDCO of failure but not *vice versa*. Cure rates were lower as determined by the SDCO compared to the IDCO. Importantly, the differences between the SDCO and the IDCO were comparable between the oritavancin and vancomycin groups.

Table 2.3.2.3-28 Cure Rates at Test-of-Cure Visit in the Clinically Evaluable Population

Efficacy Endpoint	Oritavancin n/N (%)	Vancomycin n/N (%)
Sponsor-Defined Clinical Outcome	530/675 (78.5)	249/328 (75.9)
Investigator-Defined Clinical Outcome	534/649 (82.3)	254/308 (82.5)

Of the 831 oritavancin and 415 vancomycin patients 36.5% and 37.8%, respectively, had their late follow-up visits conducted by telephone. Of the patients who were cured or improved at the TOC visit 43.9% (261/594) and 44.7% (127/284) in respective groups had their late follow-up visit by telephone. The SDCO at late follow-up for the CE population showed similar relapse rates between treatment groups. Re-hospitalisation occurred in 4.6% oritavancin and 4.9% vancomycin patients with median times to re-hospitalisation of 16 days and 19 days, respectively.

Late Follow-up				
Number Assessed	513	228		
Cure	503 (98.1%)	224 (98.2%)	-0.2%	(-2.3, 1.9)[a]
Relapse	10 (1.9%)	4 (1.8%)		
Indeterminate or Missing	18	19		

The cure rates for patients receiving 8 days or less of study drug were comparable across study populations for the oritavancin and the vancomycin groups and were as follows:

CE - 81.3% (448/551) versus 75.6% (199/263)

MITT - 82.3% (334/406) versus 76.1% (153/201)

ITTC - 82.1% (243/296) versus 73.0% (95/130)
BE with *S. aureus* at baseline - 82.6% (229/277) versus 79.7% (106/133).

Aztreonam was administered to 15.1% (102/676) CE patients in the oritavancin group and 19.8% (64/324) in the vancomycin group with respective cure rates of 76.5% (78/102) and 64.1% (41/64). These rates compared with 78.9% (453/574) and 79.2% (206/260) for patients who did not receive aztreonam. Similar results were observed for the MITT and ITT populations. Cure rates for patients who received aztreonam were lower in both treatment groups (69.6% [39/56]) and 58.1% [18/31]) in the ITTC population, which may reflect a small sub-population with a greater severity of illness.

Metronidazole was administered to 12.0% (81/676) of CE patients in the oritavancin group and 13.3% (43/324) in the vancomycin group with respective cure rates of 75.3% (61/81) and 72.1% (31/43). These rates compare with 79.0% (470/595) and 76.9% (216/281) for patients who did not receive metronidazole. Similar results were observed for patients in the MITT, ITT and ITTC patient populations.

Reflecting the primary analysis, cure rates were comparable between treatments for CE patients with each of cellulitis, major abscess and wound infection and the difference in cure rates was not statistically significant (95% CI = -3.4% to 7.8%) after adjustment for disease category. Similarly in the MITT population the difference in cure rates was not statistically significant (95% CI = -5.5% to 7.0%) when the CI was adjusted for disease category. Relapse rates were low but highest for those with cellulitis (oritavancin 3.1% [4/128]; vancomycin 3.6% [2/56]) compared to < 2% for those with a major abscess or a wound infection.

Table 11–14 Sponsor-Defined Clinical Outcome at First Follow-up by Disease Category: CE Population

Disease Category Response	Oritavancin N = 676 n (%)	Vancomycin N = 324 n (%)	Difference (Orita–Vanco)	95% CI[a]
Cellulitis				
Number	168	83		
Cure	131 (78.0%)	64 (77.1%)	0.9%	(-10.1, 11.9)
Failure	37 (22.0%)	19 (22.9%)		
Major Abscess				
Number	279	126		
Cure	226 (81.0%)	100 (79.4%)	1.6%	(-6.8, 10.1)
Failure	53 (19.0%)	26 (20.6%)		
Wound Infection				
Number	229	115		
Cure	174 (76.0%)	83 (72.2%)	3.8%	(-6.1, 13.7)
Failure	55 (24.0%)	32 (27.8%)		

[a] Two-sided confidence interval constructed using normal approximation to the binomial distribution.

In the overall ITT population:

- Almost 30% of patients met the criteria for Systemic Inflammatory Response Syndrome (SIRS)
- Nearly 45% had deep tissue involvement with infection down to and including the level of the fascia or muscle
- Approximately 60% required a surgical intervention or procedure
- Approximately 40% had at least one co-morbid condition that could complicate the treatment of the infection, including about 20% with diabetes mellitus
- Nearly all patients enrolled (98.3%) had at least 5 signs and symptoms at baseline and approximately 91% had at least 6 signs and symptoms.

When outcomes were examined according to other disease characteristics and severity indicators they did not demonstrate any disadvantage for oritavancin.

Table 2.3.1.1-7 Clinical Cures by SIRS Status and Baseline Signs and Symptoms in Study ARRI (CE population)

	Oritavancin % (n/N)	Vancomycin % (n/N)
SIRS Status[a]		
Without SIRS	80.1% (383/478)	79.8% (186/233)
With SIRS	74.6% (147/197)	66.3% (63/95)
Number of Signs and Symptoms[b]		
Two	---	---
Three	50.0% (1/2)	---
Four	63.6% (7/11)	100% (5/5)
Five	83.3% (40/48)	76.0% (19/25)
Six	72.4% (134/185)	72.3% (60/83)
Seven	83.2% (188/226)	79.6% (86/108)
Eight	77.7% (122/157)	72.9% (62/85)
Nine	82.6% (38/46)	77.3% (17/22)

The applicant reported that differences in cure rates between the oritavancin and vancomycin treatment groups were not statistically significant in the age, gender, or ethnic subgroup analyses.

Table 11–15 Sponsor-Defined Clinical Outcome at First Follow-up by Subgroups: CE Population

Subgroup	Oritavancin N = 676		Vancomycin N = 415		Difference (Orita–Vanco)	95% CI[a]
	Cure rate	Assessed	Cure rate	Assessed		
All Patients	78.6%	676	76.2%	324	2.3%	(-3.4, 7.8[b])
Age Group						
< 65 years	80.5%	548	76.8%	259	3.6%	(-2.5, 9.8)
≥ 65 years	70.3%	128	73.8%	65	-3.5%	(-16.8, 9.8)
Gender						
Female	80.7%	306	74.8%	151	5.9%	(-2.3, 14.1)
Male	76.8%	370	77.5%	173	-0.7%	(-8.3, 6.9)
Ethnic Group						
Caucasian	79.3%	352	82.5%	171	-3.2%	(-10.3, 3.9)
Non-Caucasian	77.8%	324	69.3%	153	8.5%	(-0.1, 17.1)
Region						
South America	78.8%	66	90.0%	30	-11.2%	(-25.8, 3.4)
Europe	85.3%	224	86.4%	110	-1.1%	(-9.0, 6.8)
North America	66.7%	174	64.1%	78	2.6%	(-10.2, 15.3)
S. Africa / Australia	84.6%	169	76.6%	77	8.0%	(-2.9, 18.9)
Asia	67.4%	43	55.2%	29	12.3%	(-10.6, 35.2)

Note: Cure rate = 100 × (number cured/number assessed), where number assessed = number cure + number failure.

[a] Two-sided CI constructed using normal approximation to the binomial distribution.

[b] Mantel-Haenszel CI with stratification method described by Greenland and Robins (Greenland and Robins 1985) and correction to variance estimate described by Sato (Sato 1989). Interval is adjusted for disease category.

As shown above, the cure rates for Europe and N. America in the ITT and CE populations were comparable between treatments within each region but were lower for each treatment in N. America compared to Europe. There was an important and significant difference between the two regions in the percentage of patients assigned to a clinical outcome of failure due to the administration of another antibacterial agent with potential activity against cSSSI associated with Gram-positive bacteria. In Europe 28% of failures had received another agent compared to 45% of failures in North America. This difference most likely reflects the variability in prescribing practices. However, the table below also shows that a higher proportion in Europe were considered to have failed because of need for further intervention, discontinuation due to an AE, death or documented persistence of a pathogen.

Table 2.3.2.3-19 Analysis of Failures (Intent-to-Treat Population)

	Europe % (n/N)	North America % (n/N)
Overall Clinical Failures	71/367 (19.3%)	154/360 (42.8%)
Reasons for Assignment of Clinical Failure		
Concomitant Antibiotic[a]	28.2% (20/71)	44.8% (69/154)
Procedure/Intervention[b]	57.7% (41/71)	45.5% (70/154)
Indeterminate	7.0% (5/71)	13.0% (20/154)
Missing	21.1% (15/71)	28.6% (44/154)
Discontinued study drug due to AE	22.5% (16/71)	3.9% (6/154)
Patient Died	8.5% (6/71)	1.3% (2/154)
Documented Persistence	8.5% (6/71)	0.6% (1/154)
Presumed Persistence	39.4% (28/71)	33.1% (51/154)

Abbreviations: ORI = oritavancin; VAN = vancomycin.

[a] Patient received antibiotic with gram-positive coverage for primary study condition during IV therapy or during post study drug period, excluding late post study drug period.

[b] Patient had their first procedure or intervention for primary study condition starting 48 hours after IV therapy up through post study drug period, excluding late post study drug period.

Further analyses showed that in Europe the mean age was 54 years compared to 46 years in North America. More than twice as many patients in Europe were in the age groups ≥ 65 to < 75 years and ≥ 75 years while 3x as many patients weighing > 110 kg were enrolled in North America (49 patients) as compared to Europe (17 patients). A larger proportion of the enrolled patients in North America were male. However, 8.1% (29/360) of patients in North America had ≥ 3 co-morbidities compared to 2.7% (10/367) in Europe whereas comparable proportions in the two regions had 0-2 co-morbidities.

Tables 2.3.2.3-15 Number of Clinically Relevant Comorbidities per Patient (Intent-to-Treat Population)

Number of Comorbidities	Europe N=367 % (n)	North America N=360 % (n)
Patients with zero	58.6% (215)	56.1 (202)
Patients with one	27.8% (102)	24.7% (89)
Patients with two	10.9% (40)	11.1% (40)
Patients with three or more	2.7% (10)	8.1% (29)

In Europe, 94.3% (346/367) of patients were hospitalised compared to 58.3% (210/360) in North America and mean durations of hospitalisation were 18 days in Europe but only 8 days in North America. Also, a higher proportion of patterns in N. America received aztreonam and/or metronidazole.

Other important differences between populations appear to have concerned the types of infections that were treated and suggest that patients with more complicated infections were enrolled in N. America.

- About 65% (232/360) of patients in North America had deep tissue involvement compared to 44% (162/367) of patients in Europe.
- The incidence of infections due to MRSA in North America was 29% versus 9% in Europe.
- A greater percentage of patients in Europe had a wound infection but a greater percentage of patients in North America had a major abscess.
- Nearly 68% of North America patients had fascia or muscle involvement compared to 44% in Europe.
- There were differences in rates of various procedures and interventions that may reflect the proportions with wounds versus abscesses.

Therefore there were several population differences that seemed likely to have contributed to the differences observed within each treatment group for success rates in N. America versus Europe.

The minority of patients in this study weighed > 110 kg with numbers and success rates in the CE population as shown below.

Table 2.3.1.1-27 Cure Rates at Test-of-Cure Visit by Weight Groupings in Study ARRI (Clinically Evaluable Population)

Weight Grouping	Oritavancin % (n/N)	Vancomycin % (n/N)
≤110 kg (200 mg dose group)	**78.7% (492/625)**	**76.4% (227/297)**
<70 kg	81.6% (208/255)	73.2% (93/127)
70-110 kg	76.8% (284/370)	78.8% (134/170)
>110 kg (300 mg dose group)	**76.0% (38/50)**	**71.0% (22/31)**

A multivariate analysis that compared clinical cure rates between treatment groups with adjustment for baseline weight in patients of ≤ 110 kg did not detect a statistically significant association between body weight and cure rates in the CE population. Clinical cures in oritavancin-treated patients receiving 300 mg daily (weighing > 110 kg) also showed no correlation between outcome and weight (see Figure below).

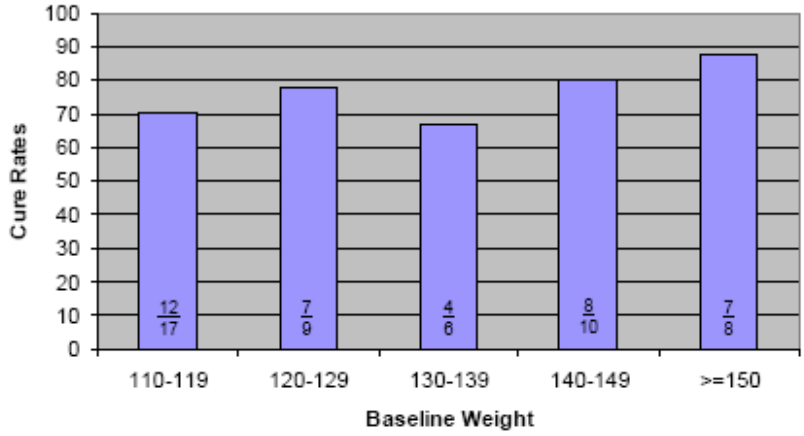


Figure 2.3.1.1-5 Oritavancin clinical cures by baseline weight bands in the oritavancin 300 mg/day patients (clinically evaluable).

When reasons for failures were compared according to oritavancin 200 mg, oritavancin 300 mg and vancomycin groups the results for those who received the higher oritavancin dose were not markedly different to those in the other groups as far as can be determined based on the small number that received 300 mg oritavancin.

As already mentioned the population PK analysis found that CL of oritavancin increased with TBW especially when TBW exceeded 110 kg. It was concluded that the potential risk of underexposure and subsequent treatment failure outweighed the risk of toxicity secondary to repetitive over-exposure with the currently proposed oritavancin dosing regimen. Therefore, it was considered reasonable to use a higher oritavancin dose in patients with high TBW regardless of body composition.

The SDCO at TOC by pathogen showed a lower clinical cure rate for oritavancin compared to vancomycin against MRSA. The table shows the MITT results. Corresponding MRSA cure rates in the BE population were 63.6% of 88 and 73.7% of 38 patients, respectively. This issue is discussed further below.

Table 11–16 Cure Rates for Sponsor-Defined Clinical Outcome at First Follow-up by Pathogen: MITT Population

Pathogen Name	Oritavancin N = 562		Vancomycin N = 288		Difference (Orita–Vanco)	95% CI[a]
	Cure rate	Assessed	Cure rate	Assessed		
S. aureus	78.6%	397	80.7%	192	-2.1%	(-9.0, 4.7)
MSSA	83.5%	266	83.2%	137	0.2%	(-7.4, 7.9)
MRSA	66.0%	100	76.6%	47	-10.6%	(-25.9, 4.7)
S. pyogenes	85.1%	87	68.8%	48	16.3%	(1.2, 31.4)
E. faecalis	72.4%	29	72.7%	22	-0.3%	(-25.0, 24.4)
S. agalactiae	67.9%	28	71.4%	7	-3.6%	(-41.2, 34.1)
S. anginosus	71.4%	21	87.5%	8	-16.1%	(-46.0; 13.9)
S. constellatus	87.5%	8	50.0%	4	37.5%	(-16.6, 91.6)
S. dysgalactiae	50.0%	6	100.0%	2	-50.0%	(-90.0, -10.0)
E. faecium	60.0%	5	100.0%	3	-40.0%	(-82.9, 2.9)
Other enterococci	75.0%	4	0.0%	4	75.0%	(32.6, 100.0)
S. intermedius	75.0%	4	100.0%	4	-25.0%	(-67.4, 17.4)
S. equisimilis	75.0%	4	0.0%	1	75.0%	(32.6, 100)
Peptostreptococcus species	66.7%	3	100.0%	2	-33.3%	(-86.7, 20.0)
Clostridium species	100.0%	1	–	0	–	NA

Sponsor-defined bacteriological outcomes at TOC showed that rates of cure with colonisation or failure with a new pathogen were low and comparable between the treatment groups.

Table 11–20 Success Rates for Sponsor-Defined Bacteriologic Outcome at First Follow-up: BE and MITT Populations

Response	Oritavancin N = 831 n (%)	Vancomycin N = 415 n (%)	Difference (Orita–Vanco)	95% CI[a]
BE Population	**N = 461**	**N = 225**		
Number Assessed	461	225		
Bacteriologic Success	341 (74.0%)	166 (73.8%)	0.2%	(-6.8, 7.2)
Eradication	14 (3.0%)	6 (2.7%)		
Presumed Eradication	306 (66.4%)	158 (70.2%)		
Colonization	21 (4.6%)	2 (0.9%)		
Bacteriologic Failure	120 (26.0%)	59 (26.2%)		
Persistence	43 (9.3%)	19 (8.4%)		
Presumed Persistence	72 (15.6%)	39 (17.3%)		
Reinfection	2 (0.4%)	1 (0.4%)		
MITT Population	**N = 562**	**N = 288**		
Number Assessed	513	256		
Bacteriologic Success	380 (74.1%)	190 (74.2%)	0.1%	(-6.7, 6.4)
Eradication	20 (3.9%)	8 (3.1%)		
Presumed Eradication	338 (65.9%)	179 (69.9%)		
Colonization	22 (4.3%)	3 (1.2%)		
Bacteriologic Failure	133 (25.9%)	66 (25.8%)		
Persistence	46 (9.0%)	21 (8.2%)		
Presumed Persistence	82 (16.0%)	44 (17.2%)		
Reinfection	2 (0.4%)	1 (0.4%)		
Indeterminate or Missing	49	32		

Baseline oritavancin MICs did not appear to explain the documented persistence of baseline pathogens. In the small number of failures with documented persistence on-therapy selection of resistance did not appear to be the cause of failure to eradicate the organism.

Colonisation could be assigned regardless of the presence of a pathogen at baseline and was defined as emergence of a new organism not present at baseline at the site of infection in a patient with a SDCO of cure. While higher colonisation rates were observed in the oritavancin group compared to the vancomycin group among BE and MITT patients the rates for the ITT population were comparable at 4.7% (39/831) and 3.4% (14/415) with organisms as shown below.

Table 2.3.2.3-11 Colonizing Bacteria Identified in Study ARRI (Intent-to-Treat Population)

	Oritavancin N=39 % (n)	Vancomycin N=14 % (n)
Staphylococcus aureus	61.5% (24)	78.6% (11)
Streptococcus pyogenes	15.4% (6)	7.1% (1)
Other Streptococcus spp[a]	10.3% (4)	21.4% (3)
Enterococcus faecalis	10.3% (4)	-
Other Enterococcus spp[b]	5.1% (2)	-

N = total number of patients with a microbiologic response of colonization in the Intent-to-Treat population.

The total number of colonizing pathogens does not equal the total N due to 2 patients (1 oritavancin patient and 1 vancomycin patient) with two identified colonizing pathogens each.

[a] Other *Streptococcus spp* includes one of each of the following: *Streptococcus agalactiae, dysgalactiae, anginosus,* Group B, *equisimilis, milleri,* and *prevoti*.

[b] Other *Enterococcus spp* includes one each of *Enterococcus casseliflavis* and an unspeciated Enterococcus.

Sponsor-Defined Pathogen Level Outcomes at TOC for the BE and MITT populations showed generally comparable eradication rates between treatments. Compared to the differences in cure rates for MRSA noted above there was a lesser difference between treatments for MRSA eradication rates.

Table 11–21 Eradication Rates for Sponsor-Defined Pathogen Level Outcome at First Follow-up: BE Population

Pathogen Name	Oritavancin N = 461		Vancomycin N = 225		Difference (Orita–Vanco)	95% CI[a]
	ER	Assessed	ER	Assessed		
S. aureus	72.7%	355	75.1%	169	-2.5%	(-10.5, 5.5)
MSSA	77.2%	241	78.0%	127	-0.8%	(-9.7, 8.2)
MRSA	63.6%	88	68.4%	38	-4.8%	(-22.7, 13.1)
S. pyogenes	86.6%	82	75.0%	44	11.6%	(-3.2, 26.4)
E. faecalis	88.5%	26	70.0%	20	18.5%	(-5.1, 42.0)
S. agalactiae	73.9%	23	66.7%	6	7.2%	(-34.5, 49.0)
S. anginosus	68.4%	19	87.5%	8	-19.1%	(-50.1, 11.9)
S. constellatus	100.0%	7	33.3%	3	66.7%	(13.3, 100.0)
S. dysgalactiae	50.0%	6	100.0%	1	-50.0%	(-90.0, -10.0)
E. faecium	60.0%	5	100.0%	3	-40.0%	(-82.9, 2.9)
S. intermedius	75.0%	4	100.0%	2	-25.0%	(-67.4, 17.4)
S. equisimilis	100.0%	4	0.0%	1	100.0%	(100.0, 100.0)
Other enterococci	100.0%	3	50.0%	4	50.0%	(1.0, 99.0)
Peptostreptococcus species	66.7%	3	100.0%	2	-33.3%	(-86.7, 20.0)
Clostridium species	100.0%	1	—	0	—	NA

The lower SDCO cure and eradication rates for MRSA with oritavancin were inconsistent with the results for MSSA. The data for the BE population are directly compared below.

Table 2.3.1.1-24 Cure/Success Rates and Pathogen Eradication Rates for *Staphylococcus aureus*, by Oxacillin Susceptibility Phenotype, in Microbiologically Evaluable Patients (Study ARRI)

Organism	Oritavancin % (n/N)	Vancomycin % (n/N)
***Staphylococcus aureus* (All)**		
Sponsor-Defined Clinical Outcome	78.8 (275/349)	81.0 (141/174)
Patient Level Microbiological Outcome	71.9 (251/349)	73.0 (127/174)
Pathogen Level Microbiological Outcome	72.2 (252/349)	74.1 (129/174)
Methicillin-sensitive (MSSA)		
Sponsor-Defined Clinical Outcome	84.6 (203/240)	84.5 (109/129)
Patient Level Microbiological Outcome	76.7 (184/240)	76.0 (98/129)
Pathogen Level Microbiological Outcome	77.1 (185/240)	77.5 (100/129)
Methicillin-resistant (MRSA)		
Sponsor-Defined Clinical Outcome	63.6 (56/88)	73.7 (28/38)
Patient Level Microbiological Outcome	61.4 (54/88)	65.8 (25/38)
Pathogen Level Microbiological Outcome	61.4 (54/88)	65.8 (25/38)

Failure of MRSA to respond to oritavancin could not be explained in terms of baseline MIC or any change in MIC during treatment. In addition, across ARRD and ARRI 42/111 (38%) of all MRSA in the ME subpopulation of oritavancin-treated patients had a susceptibility phenotype consistent with CA-MRSA (clindamycin-susceptible and erythromycin-resistant). The SDCOs and Pathogen-level Microbiological Outcomes were not different between CA-MRSA and all other MRSA.

The majority of patients with MRSA received 10 to 15 days of IV dosing. The cure rates for patients with MRSA that received 10–15 days of IV study drug were 70.8% (34/48) in the oritavancin group and 90.5% (19/21) in the vancomycin group. Therefore there was a difference between treatments even when the maximum duration of oritavancin (i.e. 7 days of active drug) was administered.

The applicant proposed that the finding reflected a specific protocol rule that defined treatment failure in terms of a specified time following initiation of study drug during which surgical intervention was allowed.
The protocol required that patients should not be enrolled unless the required surgical intervention could be completed within 48 h of enrolment. If patients in need of surgery at enrolment did not have the intervention within the 48 h window then they were deemed failures according to the SDCO coding.

Of the ARRI MRSA cases (MITT population) with an SDCO of failure:

- 17/52 oritavancin cases had a clear indication for surgery at baseline including 5 with moderate to severe devitalised tissue. All 17 had moderate to severe purulent drainage
- 2/17 vancomycin cases had a clear indication for surgery at baseline. Only one had mild devitalised tissue at baseline and two had abscesses

These 19 cases received their first surgical intervention after 48 h and received an SDCO coding of failure because of the 48-h window-based protocol rule imposed on investigators and reinforced by the sponsor.

A retrospective analysis of on-therapy assessments of clinical signs and symptoms showed no evidence that any of the 17 oritavancin cases with a clear indication for surgery at baseline received their first surgical intervention after 48 hours because of a deterioration of their clinical status between Visit 1 (baseline) and Visit 2 (before the surgical intervention took place). A case-by-case review indicated that all oritavancin cases had actually improved based on reductions in clinical signs and symptoms.

The imbalance between treatment groups in the proportion of cases who received an SDCO coding of failure because their first surgical intervention occurred > 48 h after initiation of study was restricted to the MRSA subgroup.
In summary, the applicant's explanation for the imbalance was based on the 17 oritavancin and two vancomycin cases in MITT patients with MRSA that had:
1. An indication for surgery at baseline
2. Evidence of improvement before surgery was performed
3. An SDCO coding of failure because of the protocol-defined 48-h window for first surgical intervention

The evolution of these cases in the absence of the imposition of the surgical window protocol rule is impossible to determine because the assignment of failure resulted in the addition of non study antibacterial agents and there was no further recording of clinical symptoms and signs of cSSTI on the case report form.

Additional analyses

The applicant re-analysed data from ARRI and ARRD based on patients that received 180 to 330 mg oritavancin daily, which was designated as the Intended Label Dose Range [ILDR] and was administered to 81.5% [956/1173] of all oritavancin patients (ORI-ALL). Cure rates in the ITT, MITT and ME populations and microbiological success rates for the ME and MITT populations were comparable between treatments.

Table 2.7.3-10 Cure/Success Rates at Test-of-Cure Visit

Efficacy Endpoint (Patient Population)	ORI-ALL n/N (%)		ORI-ILDR[a] n/N (%)	Van n/N (%)
ARRI				
Sponsor-Defined Clinical Outcome (CE)	530/675 (78.5)			249/328 (75.9)
Patient Level Microbiological Outcome (ME)	340/459 (74.1)			170/237 (71.7)
Investigator-Defined Clinical Outcome (CE)	534/649 (82.3)			254/308 (82.5)
ARRD	1.5 mg/kg n/N (%)	3.0 mg/kg n/N (%)		
Sponsor-Defined Clinical Outcome (CE)	98/136 (72.1)	94/128 (73.4)	67/93 (72.0)	98/130 (75.4)
Patient Level Microbiological Outcome (ME)	52/79 (65.8)	56/77 (72.7)	38/52 (73.1)	62/83 (74.7)
Investigator-Defined Clinical Outcome (CE)	100/132 (75.8)	95/126 (75.4)	67/90 (74.4)	100/125 (80.0)
ARRI and ARRD Combined				
Sponsor-Defined Clinical Outcome (CE)	722/939 (76.9)		597/768 (77.7)	347/458 (75.8)
Patient Level Microbiological Outcome (ME)	448/615 (72.8)		378/511 (74.0)	232/320 (72.5)
Investigator-Defined Clinical Outcome (CE)	729/907 (80.4)		601/739 (81.3)	354/433 (81.8)

Cure rates at TOC were comparable between treatments for each of the three disease categories and were generally comparable between disease categories.

Cure rates at TOC for oritavancin were broadly comparable when analysed by duration of therapy with similar findings for all four patient populations. This observation casts some doubt on the minimum necessary duration. The mean duration of active therapy in oritavancin-treated CE patients was 5.2 days compared to 11.3 days for vancomycin/cephalexin (mean duration 6.1 days for vancomycin).

Table 2.7.3-13 Cure Rates for Sponsor-Defined Clinical Outcome by Duration of Active Therapy in Clinically Evaluable Patients (Study ARRI and Study ARRD Combined)

Duration of Active IV Treatment	ORI-ALL n/N (%)	ORI-ILDR n/N (%)
3 Days	84/101 (83.2)	64/75 (85.3)
4 Days	239/285 (83.9)	202/238 (84.9)
5 Days	89/114 (78.1)	77/93 (82.8)
6 Days	71/87 (81.6)	57/70 (81.4)
7 Days	105/133 (78.9)	80/101 (79.2)

Patients weighing ≤ 110 kg had higher cure rates compared to patients weighing > 110 kg in the oritavancin groups but there was no difference in response by weight in the vancomycin group.

Table 2.7.3-12 Cure Rates for Sponsor-Defined Clinical Outcome at Test-of-Cure Visit by Demographic Characteristics in Clinically Evaluable Patients (Study ARRI and Study ARRD Combined)

Demographic Characteristics	ORI-ALL n/N (%)	ORI-ILDR n/N (%)	Van n/N (%)
Sex			
Male	399/526 (75.9)	330/429 (76.9)	203/263 (77.2)
Female	323/413 (78.2)	267/339 (78.8)	144/195 (73.8)
Age Class			
<65	596/764 (78.0)	497/625 (79.5)	287/371 (77.4)
≥65	126/175 (72.0)	100/143 (69.9)	60/87 (69.0)
<75	681/879 (77.5)	564/717 (78.7)	328/427 (76.8)
≥75	41/60 (68.3)	33/51 (64.7)	19/31 (61.3)
Weight			
≤110 kg	664/854 (77.8)	554/708 (78.2)	307/406 (75.6)
>110 kg	58/85 (68.2)	43/60 (71.7)	39/51 (76.5)

Lower response rates were observed in the diabetic patients.

Table 2.7.3-22 Cure Rates at Test-of-Cure Visit for Patients with Diabetes in CE Population (Study ARRI, Study ARRD, and Combined)

Study Patient Population	ORI-ALL n/N (%)		ORI-ILDR[a] n/N (%)	Van n/N (%)
ARRI				
ITT	91/145 (62.8)			50/83 (60.2)
CE	74/120 (61.7)			39/69 (56.5)
ARRD	**1.5 mg/kg n/N (%)**	**3.0 mg/kg n/N (%)**		
ITT	26/39 (66.7)	26/47 (55.3)	14/30 (46.7)	23/30 (76.7)
CE	26/39 (66.7)	25/42 (59.5)	13/26 (50.0)	22/28 (78.6)
ARRI and ARRD Combined				
ITT	143/231 (61.9)		105/175 (60.0)	73/113 (64.6)
CE	125/201 (62.2)		87/146 (59.6)	61/97 (62.9)

There were 21 oritavancin patients and 9 vancomycin patients enrolled in ARRI and ARRD with an associated bacteraemia at baseline who had an assessed outcome for analysis. In this population of MITT patients the cure rates were 61.9% (13/21) in the oritavancin ALL group, 72.2% (13/18) in the oritavancin ILDR group and 66.7% (6/9) in the vancomycin group.
Among the subset with *S. aureus* bacteraemia the cure rates were 9/16, 9/14 and 6/7, respectively, and rates for *S. pyogenes* were 3/4, 3/4 and 2/4. Cure rates for all other *Streptococcus* species isolated in patients with bacteraemia at baseline were 5/7 for oritavancin ALL, 5/6 for oritavancin ILDR and 0/1 for vancomycin-treated patients.

For *S. aureus* and *S. pyogenes* there was no obvious relationship between the oritavancin MICs and the outcomes whether treated with oritavancin or vancomycin. Note that with one exception the highest oritavancin MIC for any *S. aureus* and *S. pyogenes* treated with this drug was 0.25 mg/l.

Increases in oritavancin MIC by >2 dilutions were observed for 16 pathogens treated with oritavancin but final MICs did not exceed 0.25 mg/l. Among the six patients with post-baseline organisms inhibited only at 0.25 mg/l four were failures.

There were only four patients in ARRD or ARRI who received oritavancin (3; all MSSA) or vancomycin (1; MRSA) to treat organisms for which the vancomycin MIC was at the upper end of the observed range

(i.e. 2 mg/l). No isolates required > 2 mg/l vancomycin for inhibition. The MICs of oritavancin for these four isolates were 0.06 mg/l (2) and 012 mg/l (2). All four patients were clinical and microbiological successes.

SIMPLIFI (Study TAR-ORI-SD001)

At the time of answering the D120 LOQ the applicant provided the full study report. This randomised double-blind study was conducted in 2007-2008 at 43 sites across 5 countries. Patients had cSSSI as defined in ARRI and general study design features were as for ARRI except that the IDCOs were used in the primary analysis and patients received one of (1:1:1) the following regimens selected according to PK/PD and clinical data considerations:

- A single dose of 1200 mg oritavancin
- A single dose of 800 mg oritavancin, with an option for a further 400 mg dose at Day 5
- 200 mg oritavancin daily for 3-7 days

In the group that received 800 mg initially an extra dose of 400 mg was given if the investigator decided to continue study drug infusions until at least Day 5. Patients requiring further therapy after Day 7 were considered clinical failures and treated with non-study agents.

Assuming a common expected response rate of 85% and construction of a 2-sided 90% confidence interval for the difference (between groups) in response rates it was estimated that 70 CE patients (total 100 patients) per arm would yield nearly 80% power to declare non-inferiority to within 15%. Overall 302 patients received study medication, of which 210 were enrolled in the United States, and patient populations were as follows:

Table 11-1 Patient Populations

Patient Population	Oritavancin 200 mg N = 100 n (%)	Oritavancin 1200 mg N = 99 n (%)	Oritavancin 800 mg			Total N = 302 n (%)
			Infrequent Dose overall (N=103) n (%)	800 mg only (N=34) n (%)	800 mg + 400 mg (N=69) n (%)	
Intent-to-Treat	100 (100)	99 (100)	103 (100)	34 (100)	69 (100)	302 (100)
Clinically Evaluable	76 (76.0)	81 (81.8)	71 (68.9)	23 (67.6)	48 (69.6)	228 (75.5)
Microbiological Intent-to-Treat	72 (72.0)	68 (68.7)	69 (67.0)	18 (52.9)	51 (73.9)	209 (69.2)
Microbiologically Evaluable	55 (55.0)	58 (58.6)	48 (46.6)	11 (32.4)	37 (56.3)	161 (53.3)

The primary analysis indicated that a single dose of 1200 mg or 800 mg with an optional 400 mg on Day 5 was non-inferior to 200 mg for 3 to 7 days (note the comparisons show 90% CI). Nevertheless, both comparisons suggested that infrequent dosing might be better than 200 mg daily.

Table 11-9 Primary Efficacy Endpoint: Investigator-Defined Clinical Outcome at First Follow-up in the Clinically Evaluable Population

Response	Oritavancin 200 mg N = 76 n (%)	Oritavancin 1200 mg N = 81 n (%)	Oritavancin 800 mg N = 71 n (%)	Estimated Difference[b] 1200 mg – 200 mg (90% CI)	Estimated Difference[b] 800 mg – 200 mg (90% CI)
Cure[a]	55 (72.4)	66 (81.5)	55 (77.5)	8.6 (-2.5, 18.2)	5.2 (-6.8, 15.4)
Failure	21 (27.6)	15 (18.5)	16 (22.5)		

Abbreviations: CI = confidence interval.

[a] Includes cure and improvement outcomes.

[b] Difference in response rate between patients by using Mantel-Haenszel method stratified by disease

The results in the other patient populations supported the conclusions of the primary analysis.

Table 11-10 Investigator-Defined Clinical Outcome at First Follow-up in the ITT, MITT, and ME Populations

Response	Oritavancin 200 mg N = 100 n (%)	Oritavancin 1200 mg N = 99 n (%)	Oritavancin 800 mg N = 103 n (%)	Estimated Difference[b] 1200 mg – 200 mg (90% CI)	Estimated Difference[b] 800 mg – 200 mg (90% CI)
ITT	N = 87	N = 99	N = 103		
Cure[a]	63 (72.4)	72 (81.8)	68 (78.2)	8.7 (-1.7, 17.8)	5.1 (-5.8, 14.6)
Failure	24 (27.6)	16 (18.2)	19 (21.8)		
MITT	N = 64	N = 61	N = 62		
Cure[a]	44 (68.8)	49 (80.3)	50 (80.6)	10.1 (-2.7, 20.9)	11.1 (-1.5, 21.7)
Failure	20 (31.3)	12 (19.7)	12 (19.4)		
ME	N = 55	N = 58	N = 48		
Cure[a]	38 (69.1)	46 (79.3)	39 (81.3)	8.5 (-5.2, 20.0)	11.0 (-2.9, 22.6)
Failure	17 (30.9)	12 (20.7)	9 (18.8)		

It appeared that 34 patients in the 800 mg dose group received only one dose of active treatment but 69 received a second dose of 400 mg on Day 5 and most of these patients continued dosing (i.e. with placebo infusions on Days 6 and 7) to Day 7. Outcomes according to one or two doses were not shown separately.

The SDCOs at first follow-up for the four analysis populations (shown below) were comparable with those of the IDCO-based analysis. The estimated differences in cure rates between each of the single and infrequent doses and the daily dose were not statistically significant according to the applicant. The cure rates within each dose group were comparable across all four analysis populations.

Table 11-15 Sponsor-Defined Clinical Outcome at First Follow-Up in the CE, ITT, MITT, and ME populations

Response	Oritavancin 200 mg n (%)	Oritavancin 1200 mg n (%)	Oritavancin 800 mg n (%)	Estimated Difference[b] 1200 mg – 200 mg (90% CI)	Estimated Difference[b] 800 mg – 200 mg (90% CI)
ITT Population	N=98	N=99	N=103		
Cure	62 (71.3)	70 (79.5)	67 (75.3)	7.7 (-3.1, 17.0)	3.6 (-7.6, 13.3)
Failure	25 (28.7)	18 (20.5)	22 (24.7)		
Missing or indeterminate	11	11	14		
CE Population	N=76	N=81	N=71		
Cure[a]	54 (71.1)	65 (80.2)	54 (77.1)	8.7 (-2.7, 18.4)	6.4 (-5.6, 16.6)
Failure	22 (28.9)	16 (19.8)	16 (22.9)		
MITT Population	N=72	N=68	N=69		
Cure	44 (69.8)	47 (77.0)	50 (79.4)	5.8 (-7.4, 16.9)	8.8 (-4.0, 19.6)
Failure	19 (30.2)	14 (23.0)	13 (20.6)		
Missing or indeterminate	9	7	6		
ME Population	N=55	N=58	N=48		
Cure	38 (69.1)	45 (77.6)	39 (81.3)	6.6 (-7.2, 18.2)	11.0 (-2.9, 22.6)
Failure	17 (30.9)	13 (22.4)	9 (18.8)		

Based on IDCO at first follow-up mean responses were lowest for wound infections and highest for major abscesses. Cure rates were comparable between treatment groups for major abscesses.

In addition to the results for the CE population shown in the table, the cure rates for wound infection were 64.5%, 65.5% and 75.0% in the ITT, 63.0%, 68.2% and 78.9% in the MITT and 65.2%, 68.2% and 75.0% in the ME populations for the daily dose, single dose and infrequent dose, respectively. These data suggest that infrequent dosing might be the best approach to management of wound infections.

A single dose or infrequent dosing appeared to be better for cellulitis and there was a statistically significant difference in the CE (90% CI; 9.2, 49.1) and ITT (90% CI = 8.1, 45.7) populations between the single dose group and daily dose group.

Table 11-11 Investigator-Defined Clinical Outcome at First Follow-up by Disease Category in the Clinically Evaluable Population

Response	Oritavancin 200 mg N = 76 n (%)	Oritavancin 1200 mg N = 81 n (%)	Oritavancin 800 mg N = 71 n (%)	Estimated Difference[b] 1200 mg – 200 mg (90% CI)	Estimated Difference[b] 800 mg – 200 mg (90% CI)
Wound Infection	**N = 26**	**N = 27**	**N = 25**		
Cure[a]	17 (65.4)	18 (66.7)	18 (72.0)	1.3 (-20.1, 22.7)	6.6 (-14.7, 27.9)
Failure	9 (34.6)	9 (33.3)	7 (28.0)		
Major Abscess	**N = 26**	**N = 30**	**N = 24**		
Cure[a]	24 (92.3)	27 (90.0)	21 (87.5)	-2.3 (-14.8, 10.1)	-4.8 (-18.9, 9.2)
Failure	2 (7.7)	3 (10.0)	3 (12.5)		
Cellulitis	**N = 24**	**N = 24**	**N = 22**		
Cure [a]	14 (58.3)	21 (87.5)	16 (72.7)	29.2 (9.2, 49.1)	14.4 (-8.4, 37.2)
Failure	10 (41.7)	3 (12.5)	6 (27.3)		

Abbreviations: CI = confidence interval.

[a] Includes cure and improvement outcomes.

[b] Difference in response rate between patients by using Mantel-Haenszel method stratified by disease.

IDCO at first follow-up in the CE population by patient sub-groups were difficult to interpret due to low denominators and no firm conclusions can be drawn.

Table 11-12 Investigator-Defined Clinical Outcome at First Follow-up by Baseline Subgroup in the Clinically Evaluable Population

Subgroup	Oritavancin 200 mg N = 76 n (%)	Oritavancin 1200 mg N = 81 n (%)	Oritavancin 800 mg N = 71 n (%)	Estimated Difference[b] 1200 mg – 200 mg (90% CI)	Estimated Difference[b] 800 mg – 200 mg (90% CI)
Diabetes					
Cure[a]	6 (60.0)	8 (66.7)	6 (42.9)	6.9 (-39.3, 32.9)	-15.3 (-69.8, 12.8)
Failure	4 (40.0)	4 (33.3)	8 (57.1)		
MRSA					
Cure[a]	18 (78.3)	27 (73.0)	20 (87.0)	-3.8 (-25.1, 12.9)	10.9 (-6.9, 25.3)
Failure	5 (21.7)	10 (27.0)	3 (13.0)		
Bacteremia					
Cure [a]	1 (33.3)	3 (60.0)	1 (100)	60.0 (NA, NA)	NA (NA, NA)
Failure	2 (66.7)	2 (40.0)	0		
Polymicrobial Infection					
Cure [a]	3 (42.9)	6 (100)	6 (100)	52.2 (2.1, 76.6)	50.0 (9.6, 72.3)
Failure	4 (57.1)	0	0		

At the late follow-up visit relapse occurred in three patients. One occurred in a patient in the single dose group who suffered a wound infection while the other two occurred in patients in the infrequent dose group (one with wound infection and one with cellulitis).

Regarding the patients who failed treatment all had at least one planned surgical procedure or intervention. Need for additional antibacterial therapy and unplanned surgical procedures were the main reasons for clinical failure.

- In the ITT population, use of an additional agent was the reason for clinical failure in 21/35 (60%), 20/27 (74.1%) and 24/35 (68.6%) of failed patients in the daily dose, single dose and infrequent dose groups, respectively. Results were comparable in the MITT population.

- The rate of unplanned surgical interventions among failures was highest in the daily dose group in the ITT population (8/35 [22.9%], 4/27 [14.8%] and 2/35 [5.7%]). Again comparable findings were observed in the MITT population.

The finding that both treatment groups with higher and less frequent doses had a lower rate of unplanned surgical intervention may suggest that this concentration profile may be preferred.

Staphylococcus aureus was the most frequently isolated pathogen (in 87.6% of the 209 MITT patients) and 56.3% of these were MRSA. Among patients with MRSA an IDCO of cure was assigned to 78.3% (18/23), 73.0% (27/37) and 87.0% (20/23) in the daily dose, single dose, and infrequent dose groups, respectively. It was unexpected that response rates among MSSA were lower than for MRSA in two treatment groups but the observation may reflect relatively small denominators.

Table 11-13 Investigator-Defined Clinical Outcome at First Follow-up by Pathogen in the Microbiologically Intent to Treat Population

Pathogen Name[a]	% Patients Cured (n of Patients/Total)		
	Oritavancin 200 mg N = 72	Oritavancin 1200 mg N = 68	Oritavancin 800 mg N = 69
Staphylococcus aureus	68.5 (37/54)	79.7 (47/59)	80.0 (40/50)
MRSA	76.9 (20/26)	73.7 (28/38)	83.3 (25/30)
MSSA	60.7 (17/28)	91.3 (21/23)	75.0 (15/20)
Streptococcus pyogenes	66.7 (4/6)	100 (2/2)	100 (3/3)
Streptococcus agalactiae	33.3 (1/3)	100 (1/1)	100 (2/2)
Enterococcus faecalis	50.0 (2/4)	100 (1/1)	100 (3/3)
Streptococcus anginosus	0	100 (1/1)	100 (1/1)
Streptococcus constellatus	0	0	100 (2/2)
Streptococcus parasanguinis	100 (1/1)	100 (1/1)	0
Enterococcus hirae	0	0	100 (1/1)
Enterococcus species	0	0	100 (1/1)
Streptococcus intermedius	0.0 (0/1)	0	0
Streptococcus mitis	100 (1/1)	0	100 (1/1)
Streptococcus salivarius	0	100 (1/1)	0

Cure rates at first follow-up for both the MITT and the ME populations did not suggest a wholly consistent advantage for single dose or infrequent dose regimens but denominators are relatively small.

There was no obvious relationship between oritavancin MIC at baseline and rate of cure at first follow-up for patients in the ME population. Among six pathogens with an increase in oritavancin MIC from baseline five were *S. aureus* and one was *S. intermedius*. Five of these six showed an increase in MIC of 2 doubling dilutions and one *S. aureus* showed an increase by 3 doubling dilutions from baseline. Three of these six patients had an IDCO at first follow-up of failure, two patients were improved and one was cured and they were scattered across dose groups. In no case did the final MIC exceed 0.25 mg/l.

Overall patient-level microbiological success rates in the MITT and ME populations showed a trend to a higher response rates with infrequent dosing. No super-infections were observed.

Table 11-16 Per-Protocol Patient-Level Microbiological Outcome at First Follow-Up in the MITT and ME populations

Response	Oritavancin 200 mg n (%)	Oritavancin 1200 mg n (%)	Oritavancin 800 mg n (%)	Estimated Difference[a] 1200 mg – 200 mg (90% CI)	Estimated Difference[a] 800 mg – 200 mg (90% CI)
MITT Population	N=64	N=61	N=62		
Success	39 (60.9)	40 (65.6)	44 (71.0)	3.7 (-11.7, 16.0)	10.0 (-4.4, 21.6)
Failure	25 (39.1)	21 (34.4)	18 (29.0)		
ME Population	N=55	N=58	N=48		
Success	35 (63.6)	37 (63.8)	34 (70.8)	-0.8 (-17.6, 12.5)	7.3 (-8.8, 20.2)
Failure	20 (36.4)	21 (36.2)	14 (29.2)		

Patient-level microbiological outcomes at first follow-up in the MITT and ME populations suggested an advantage for single dose or infrequent dosing. When clinical outcome was taken into consideration and not just the recovery of a pathogen the success rates approximated to the IDCO at FFU in the MITT population.

Table 11-18 Per-Protocol Patient-Level Microbiological Outcomes by Baseline Pathogen at First Follow-Up in the ME Population

Pathogen Name	% Patients Cured (n of Patients/Total)			Estimated Difference[a] 1200 mg–200 mg (90% CI)	Estimated Difference[a] 800 mg– 200 mg (90% CI)
	Ori 200 mg N=55	Ori 1200 mg N=58	Ori 800 mg N=48		
Staphylococcus aureus	60.9 (28/46)	63.2 (36/57)	65.0 (26/40)	1.8 (-16.1, 15.6)	4.9 (-14.4, 19.5)
MRSA	73.9 (17/23)	59.5 (22/37)	69.6 (16/23)	-12.3 (-36.6, 5.8)	-2.2 (-27.7, 16.6)
MSSA	47.8 (11/23)	68.2 (15/22)	62.5 (10/16)	22.2 (-2.5, 38.3)	16.7 (-17.1, 36.1)
Streptococcus pyogenes	66.7 (4/6)	100 (1/1)	100 (2/2)	NA	NA
Enterococcus faecalis	25.0 (1/4)	100 (1/1)	100 (3/3)	NA	NA
Streptococcus agalactiae	66.7 (2/3)	100 (1/1)	0 (0/1)	NA	NA

The applicant concluded that the single dose or infrequent dose regimens were at least as effective as a daily dose regimen in this study.

Comment on efficacy

The single pivotal study (ARRI) is not considered to provide results that are sufficiently robust and convincing to support approval of oritavancin 200 mg for 3-7 days to treat cSSSI.

It is not possible to agree with the applicant's assertion that the overall imbalance between treatment groups for clinical outcomes in the MITT and ME populations with MRSA resulted from the SDCO coding of failure in accordance with the protocol. The applicant states in the conclusion to the answer that exclusion of these patients from the analysis of clinical response yields cure rates that are comparable between the oritavancin- and vancomycin-treated patients. The results of such an analysis should be supplied for the MITT and ME populations.

The applicant should provide an analysis of clinical outcomes assigned by investigators by baseline pathogen, which might throw further light on the SDCO implementation of the protocol rule.

The results of the SIMPLIFI study indicate that, despite the overall demonstration of non-inferiority for the oritavancin regimen used in ARRI versus comparative therapy, 200 mg for 3-7 days is not the optimal mode of administration of oritavancin. However, the data from this Phase II study would not be sufficient to support approval of 1200 mg as a single dose or 800 mg plus 400 mg on day 5 for treatment of cSSSI. **The findings of this study must be taken into account when considering the overall risk-benefit for the regimen of 200 mg daily for 3-7 days.**

However, the data from this Phase II study would not be sufficient to support approval of 1200 mg as a single dose or 800 + 400 mg for treatment of cSSSI.

Clinical safety

The initial integrated summary of safety encompassed all the data derived from human use except for the Japanese study H4Q-JE-101N, which was omitted due to lack of access to the data base. The summary covered 1540 individuals who had received oritavancin in clinical studies, including 1013 who had received 180 - 330 mg/day (ORI-ILDR). The majority (83.2% ORI-ALL, 94.3% ORI-ILDR) received oritavancin for ≥ 3 days to ≤ 7 days. In cSSSI studies 1173 were treated with oritavancin of which 956 were included in the ORI-ILDR group.

At the time of responding to the D120 LOQ additional safety data were provided from three studies:
- VT001 assessed venous tolerance
- QT002 was a thorough QT study
- SIMPLIFI (TAR-ORI-SD001), which evaluated three dose regimens for cSSSI in 302 patients.

The additional safety data from these studies are mentioned separately under each heading below as appropriate.

Adverse events

During IV therapy a significantly higher percentage of Van (50.0%, 295/590) than ORI-ALL (42.2%, 495/1173) and ORI-ILDR (39.1%, 374/956) cSSTI patients had at least one TEAE. TEAEs mapped to skin and subcutaneous conditions occurred more often in Van patients (14.4%) compared to ORI-ALL (7.2%) and ORI-ILDR (7.0%) patients.

Table 2.7.4-20 Treatment-Emergent Adverse Events of Special Interest, by Decreasing Frequency, Reported in at least 1% of cSSSI ITT Patients in each Treatment Group in the "During IV Therapy" Period

Preferred Term	ORI-ALL N=1173 n (%)	ORI-ILDR N=956 n (%)	Van N=590 n (%)	p-value[a] ORI-ALL vs Van	p-value[a] ORI-ILDR vs Van
Patients with ≥ 1 TEAE	**495 (42.2)**	**374 (39.1)**	**295 (50.0)**	**0.002**	**<0.001**
TEAEs of Interest Reported in ≥1% of Patients in the ORI-ALL Treatment group					
Insomnia	48 (4.1)	**32 (3.3)**	**36 (6.1)**	0.075	**0.015**
Infusion site pain	20 (1.7)	15 (1.6)	11 (1.9)	0.848	0.687
Infusion site phlebitis	19 (1.6)	17 (1.8)	9 (1.5)	1.000	0.840
Pruritus	**19 (1.6)**	**16 (1.7)**	**32 (5.4)**	**<0.001**	**<0.001**
Rash	19 (1.6)	**11 (1.2)**	**15 (2.5)**	0.200	**0.043**
Phlebitis	15 (1.3)	6 (0.6)	10 (1.7)	0.524	0.067
TEAEs of Interest Reported in ≥1% of Patients in the ORI-ILDR Treatment group but not in the ORI-ALL or Van Groups					
Infusion site thrombosis[b]	10 (0.9)	10 (1.0)	1 (0.2)	0.112	0.060
TEAEs of Interest Reported in ≥1% of Patients in the Van Treatment group but not the ORI-ALL or ORI-ILDR Groups					
Erythema	**7 (0.6)**	**5 (0.5)**	**13 (2.2)**	**0.007**	**0.005**
Pruritus generalised	**6 (0.5)**	**6 (0.6)**	**11 (1.9)**	**0.009**	**0.041**
Flushing	**2 (0.2)**	**1 (0.1)**	**8 (1.4)**	**0.003**	**0.003**
Red man syndrome	**0 (0.0)**	**0 (0.0)**	**8 (1.4)**	**<0.001**	**<0.001**
Urticaria	**2 (0.2)**	**2 (0.2)**	**7 (1.2)**	**0.008**	**0.032**
Infusion site pruritus	**1 (0.1)**	**1 (0.1)**	**7 (1.2)**	**0.003**	**0.006**
Infusion site erythema	3 (0.3)	2 (0.2)	6 (1.0)	0.068	0.060

Among the TEAEs of special interest that occurred during IV therapy in ≥ 1% of patients erythema, generalised pruritus, flushing, red man syndrome, urticaria and infusion site pruritus occurred in significantly higher percentages of Van than ORI-ALL and ORI-ILDR patients. Rash and insomnia occurred in significantly higher percentages of Van than ORI-ILDR patients.

A significantly higher percentage of Van (23.2%; 137/590) than ORI-ALL (15.6%; 183/1173) and ORI-ILDR (15.2%; 145/956) patients had at least one TEAE related to study drug. Also eight of the 14 TEAEs of special interest that were considered drug-related occurred at a higher rate with Van than in ORI-ALL and ORI-ILDR patients. Six oritavancin (0.5%) and 3 Van (0.5%) patients had TEAEs of pseudomembranous colitis or *C. difficile* colitis. Onset was between Days 5-48 and all patients had received other systemic antibacterial agents

In a further analysis specific to studies ARRD and ARRI TEAEs were presented according to cumulative doses ≤ 9 mg/kg, > 9 - < 15 mg/kg and ≥ 15 mg/kg. Overall, there was no indication of an increase in the percentage of patients experiencing a TEAE, drug-related TEAE or SAE with increasing cumulative dose in mg/kg. In an extensive analysis there was no unequivocal relationship demonstrable between risk of specific TEAEs and oritavancin dose.

Table 2.3.2.4-1 Patients with Treatment Emergent Adverse Events During Phase 3 cSSTI Studies According to Cumulative Dose in mg/kg Oritavancin (ORI) Treatment Group

	ORI ≤9 mg/kg N=395 % (n)	ORI >9 - <15 mg/kg N=402 % (n)	ORI ≥15 mg/kg N=376 % (n)
Patients with ≥1 TEAE	55.2% (218)	47.5% (191)	58.2% (219)

Table 2.3.2.4-5 Patients with Treatment-Related Adverse Events and Serious Adverse Events during Phase 3 cSSTI Studies According to Cumulative Dose in mg/kg Oritavancin (ORI) Treatment Group

	ORI ≤9 mg/kg N=395 % (n)	ORI >9 - <15 mg/kg N=402 % (n)	ORI ≥15 mg/kg N=376 % (n)
Patients with ≥1 treatment-related adverse event	23.0% (91)	12.9% (52)	18.1% (68)
Patients with ≥1 serious adverse event	10.6% (42)	6.7% (27)	10.1% (38)

In the ARRI and ARRD the percentage of oritavancin-treated patients with ≥ 1 TEAE was 51.8% (555/1071) in patients ≤ 110 kg and 71.6 % (73/102) in patients > 110 kg ($p<0.001$). An analysis was completed that identified 19 TEAEs at the MedDRA preferred term level which occurred in a different percentage of patients in the > 110 kg compared to the ≤ 110 kg weight group ($p<0.05$). All 19 TEAEs occurred at a higher rate among patients > 110 kg. Of these, 10 events occurred in at least 5 patients and these are listed in the table below.

Table 2.3.2.-6 Adverse Events Reported in a Significantly[1] Higher Percentage of Patients >110 kg than Patients ≤ 110 kg and in at Least 5 Patients in the Oritavancin Treatment Group

Preferred Term (MedDRA 10.0)	≤110 kg Group N=1071	>110 kg Group N=102
Diarrhoea	3.5% (37)	10.8% (11)
Infusion site pain	1.4% (15)	5.9% (6)
Oedema peripheral	1.0% (11)	3.9% (4)
Chest pain	0.3% (3)	3.9% (4)
Cellulitis	1.0% (11)	3.9% (4)
Muscle spasms	0.7% (7)	2.9% (3)
Pain in extremity	1.2% (13)	7.8% (8)
Anxiety	1.3% (14)	4.9% (5)
Dyspnoea	0.9% (10)	3.9% (4)
Pruritus	2.1% (22)	5.9% (6)

[1] p<0.05 from Fisher's exact test

Based on further analyses consisting of several multivariate logistic regression models there was a statistically significant difference detected between baseline body weight ≤ 110 kg and baseline body weight > 110 kg for each of the 10 TEAEs included in the table above.

The additional safety data obtained during the SIMPLIFI study did not indicate any new issues and did not preclude further evaluation of any of the dose regimens studied. The single dose group had higher rates of HLIRs while the infrequent dose group had a higher rate of patients with phlebitis. It should be noted that these safety data relate to infusions of 200 mg in 250 ml over 45-60 minutes and to sequential administrations of 400 mg, each in 250 ml over 45-60 minutes. Administration of 400 mg in larger volumes and/or more slowly might improve venous tolerability and potentially affect the incidence of HLIRs.

During oral therapy very few TEAEs occurred in ≥ 1% of patients. Dyspnoea (1.0%; 9/878) occurred in ≥ 1% of ORI-ALL patients but in no Van patients. None of these nine TEAEs of dyspnoea was considered to be related to study drug and four were linked to a specific cause identified by the investigator in the CRF. Onset of dyspnoea ranged from 13.8 hours to 17 days after the last oritavancin infusion.

In the post study drug period four TEAEs occurred at a significantly different rate in the ORI (ALL and/or ILDR) and Van treatment groups, as shown below.

Preferred Term	ORI-ALL N=1173 n (%)	ORI-ILDR N=956 n (%)	Van N=590 n (%)	p-value[a]	
				ORI-ALL vs Van	ORI-ILDR vs Van
Dizziness	35 (3.0)	30 (3.1)	8 (1.4)	0.048	0.028
Osteomyelitis	12 (1.0)	8 (0.8)	0 (0.0)	0.011	0.027
Pruritus	28 (2.4)	22 (2.3)	39 (6.6)	<0.001	<0.001
Rash	26 (2.2)	16 (1.7)	24 (4.1)	0.033	0.005

All of the 35 events of dizziness in the ORI-ALL group were mild (80%, 28/35) or moderate (20%, 7/35) while 6/8 in the Van group were mild and 2/8 moderate in severity. None of these cases was associated with hypotension or clinically significant decrease in blood pressure.

Injection Site Phlebitis (all studies)

Data were reviewed from 962 patients and 243 healthy subjects. In healthy subjects enrolled in multiple-dose cohorts the incidence of injection site phlebitis increased as daily dose (mg/day) increased. In patients with cSSSI and those with bacteraemia the incidence of injection site phlebitis was comparable between oritavancin and vancomycin, including doses up to 10 mg/kg/day for 14 days. Drug administration parameters that appeared to be related to the incidence and severity of injection site phlebitis were:

- The product of drug delivery rate (mg/min) x concentration of the infusate (mg/ml) = (mg2/mL·min)
- The delivery rate of oritavancin to the vein in mg/min
- To a lesser extent the concentration of oritavancin infusate in mg/ml.

Additional data came from study VT-001, which was a double-blind, crossover study that examined venous tolerance of oritavancin based on a modified version of the Maddox Criteria. Healthy subjects (15; 13 completed) were randomised to receive infusions 14 days apart as shown below:

Table 9.1 Study Design for Study Period 1.

Study Groups	Day 1	Day 15
Study Group 1	Oritavancin 800 mg IV (400 mg total volume 500 mL in D5W X2)	500 mL D5W followed by: Oritavancin 200 mg IV (200 mg total volume 500 mL in D5W)
Study Group 2	500 mL D5W followed by: Oritavancin 200 mg IV (200 mg total volume 500 mL in D5W)	Oritavancin 800 mg IV (400 mg total volume 500 mL in D5W X2)

VT-001 employed infusions of oritavancin that were of the same concentration or more dilute than recommended in the draft SPC (i.e. 200 mg or 400 mg doses were both given in 500 ml volumes to maintain the double-blind study design). The infusions were all given over 60 minutes. In contrast, the SIMPLIFI study employed infusions of 200 mg in 250 ml over 45-60 minutes (as in the draft SPC) or sequential administrations of 400 mg, each in 250 ml over 45-60 minutes.

During drug reconciliation and review of the randomisation code it was discovered that the blinded drug preparation for Group 2, Period 1 was performed incorrectly.

There were 27 AEs reported in 9 subjects overall of which 24 AEs were reported in 8 subjects after administration of oritavancin. The adverse events with the highest reported incidence after oritavancin administration included injection site phlebitis, nausea and oedema peripheral. Of the total 27 AEs there were 17 of mild intensity (15 were considered drug-related) and eight of moderate intensity (all considered drug-related). The two severe AEs (phlebitis and pain associated with extravasation of IV fluid) were also considered drug-related.

Injection site reactions and AEs related to the injection site were experienced by five subjects after oritavancin infusions of which three had injection site phlebitis after receiving their second dose.

Table 12.5 Phlebitis Adverse Events by Subject

			Study Group	Study Arm	Study Drug Prior to Onset	Day of Onset	Duration (Days)	Severity	Phlebitis Grade
			2	2	800 mg Oritavancin	Day 23 (8 days	30	Severe	4 (severe)

						postdose)			
			3	2	800 mg Oritavancin	Day 15 (9.5 hours postdose)	19	Mild	3 (moderate)
			4	2	800 mg Oritavancin	Day 15 (2 hours postdose)	7	Mild	3 (moderate)

Two subjects had injection site reactions without phlebitis but including oedema, erythema, swelling and tenderness. One had an extravasation into the subcutaneous tissue resulting in erythema, pain and swelling during the first infusion and thus received only ~20 mg oritavancin. There were no trends with regard to safety relative to oritavancin doses (200 mg or 800 mg) but there was a trend for an increased incidence of AEs during or after the second IV infusion regardless of dose.

Two subjects experienced probable HLIRs after their first exposure to oritavancin with symptoms that included mild urticaria, mild sensation of puffiness in face and moderate hypotension.

Histamine-like Infusion Reactions (HLIRs)

The applicant searched the integrated safety database of the cSSSI ITT population for patients who had one or more AEs consistent with a possible HLIR during or within 6 hours of completion of an oritavancin or vancomycin infusion and resolving within 24 hours. As shown below, HLIRs appeared to occur less often with oritavancin than with vancomycin.

Table 2.7.4-36 Summary of Histamine-Like Infusion Reaction Subgroup Analyses (cSSSI ITT Population)

	ORI-ALL N=1173 n (%)	ORI-ILDR N=956 n (%)	Van N=590 n (%)	p-value[a]	
				ORI-ALL vs Van	ORI-ILDR vs Van
Patients with HLIR	**37 (3.2)**	**31 (3.2)**	**64 (10.8)**	**<0.0001**	**<0.0001**
Patients with > 1 HLIR	4 (0.3)	3 (0.3)	2 (0.3)	--	--
HLIR Subgroup Analyses					
Number of Patients Who	**ORI-ALL N=37 n (%)**	**ORI-ILDR N=31 n (%)**	**Van N=64 n (%)**	**p-value[a]**	
				ORI-ALL vs Van	**ORI-ILDR vs Van**
Received Medications Due to HLIR	9 (24.3)	9 (29.0)	29 (45.3)	0.054	0.180
Had HLIR at First Study Drug Infusion	**13 (35.1)**	11 (35.5)	**37 (57.8)**	**0.039**	0.050
Discontinued Study Drug Due to HLIR-related event	3 (8.1)	3 (9.7)	11 (17.2)	0.245	0.538
Discontinued Study Due to HLIR-related event	0 (0.0)	0 (0.0)	5 (7.8)	0.155	0.169
Discontinued Study Drug and Study Due to HLIR-related event	0 (0.0)	0 (0.0)	4 (6.3)	0.294	0.300

Abbreviations: N = number of patients; n = number of patients with finding; ORI-ALL = oritavancin all doses; ORI-ILDR = oritavancin – intended label dose range (180 to 330 mg/day); HLIR = histamine-like infusion reaction.

[a] p-value from Fisher's exact test. Pairwise comparison is ORI-ALL vs Van and ORI-ILDR vs Van.

[b] More than one distinct reaction.

Note: **Bolded** in-table numbers indicate significant between group differences.

Allergic reactions

AE terms that might represent an allergic reaction were identified and analyses were completed for:

- The entire group of AEs that might represent an allergic reaction to ORI or VAN
- The above group of AEs after subtraction of those events the applicant considered to be possible histamine-like infusion reactions (HLIR).

Analysis of the entire group of events potentially representing allergic reactions demonstrated that 12.0% (141/1173) of ORI and 21.4% (126/590) of VAN patients experienced ≥ 1 such event (p=<0.001). The duration of these events was similar between the treatment groups. In the ORI group, 7.8% (11/141) of these events were severe in intensity compared to 11.1% (14/126) in the VAN group. AEs occurring in ≥ 1% of patients in either treatment group at the MedDRA preferred term level are provided below.

Table 2.3.2.4-7 Adverse Events Possibly Indicating Allergy to Study Drug occurring in ≥1% of ORI and/or VAN Patients

Adverse Event Preferred Term (MedDRA 10.0)	ORI N=1173 % (n)	VAN N=590 % (n)
Infusion site pruritus*	0.1% (1)	1.2% (7)
Oedema peripheral	1.3% (15)	1.7% (10)
Dyspnoea	1.1% (13)	1.2% (7)
Dermatitis allergic*	0.2% (2)	1.2% (7)
Erythema*	0.9% (11)	2.5% (15)
Red man syndrome*	0.0% (0)	1.4% (8)
Pruritus*	2.4% (28)	6.6% (39)
Pruritus generalised*	0.9% (10)	2.0% (12)
Rash*	2.2% (26)	4.1% (24)
Urticaria*	0.2% (2)	1.2% (7)
Flushing*	0.2% (2)	1.4% (8)
Hypotension	1.4% (16)	1.4% (8)

*p<0.05 (Fisher's exact test)

Analysis of this group of AEs after subtraction of those events the applicant considered to be possible HLIRs demonstrated that 9.8% (115/1173) of ORI and 11.9% (70/590) of VAN patients experienced ≥ 1 such event. In the ORI group, 6.9% (8/115) of these events were severe in intensity compared to 11.4% (8/70) in the VAN group. The duration of these events was comparable between the treatment groups.

AEs occurring in ≥ 1% of patients in either treatment group at the MedDRA preferred term level are provided below.

Table 2.3.2.4-8 Adverse Events Possibly Indicating Allergy to Study Drug without Events Considered HLIR occurring in ≥1% of ORI and/or VAN Patients

Adverse Event Preferred Term (MedDRA 10.0)	ORI N=1173 % (n)	VAN N=590 % (n)
Infusion site pruritus*	0.1% (1)	1.2% (7)
Oedema peripheral	1.1% (13)	1.2% (7)
Dyspnoea	1.1% (13)	1.2% (7)
Pruritus*	1.8% (21)	1.9% (11)
Rash	1.6% (19)	2.4% (14)
Hypotension	1.0% (12)	0.7% (4)

*p<0.05 (Fisher's exact test)

Both explorations were designed to be sensitive indicators of hypersensitivity and thus more accurate indicators of the upper limit of the occurrence of hypersensitivity reactions. For example, in an effort not to exclude potentially life-threatening manifestations of hypersensitivity such as angio-oedema and hypotension, these analyses include events of oedema and hypotension related to the patients' presenting infectious process and/or co-morbidities rather than hypersensitivity reactions to either ORI or VAN. AEs that might indicate hypersensitivity may also have been related to exposure to other triggers, including concomitant medications.

Deaths

There were 74 deaths among 2176 patients in the integrated database. Of the 66 deaths recorded in the "during study" integrated safety database, 31 occurred among patients in the cSSSI ITT population (19 ORI, 12 Van), 35 in the Phase 2 ITT population (27 ORI, 8 Van) and none in Phase 1 studies.

In 14/19 ORI patients with cSSSI who died in the "during study" period the AEs that led to death mostly occurred in the "post study drug" period and in only two cases did the AEs leading to death occur in the "during IV therapy" period. The highest percentage of patient deaths in both treatment groups (7/1173 ORI and 5/590 Van) were associated with AEs in SOC cardiac disorders. Many of the deaths were deemed to be due to underlying disease but a number were ascribed to uncontrolled sepsis or to specific infections. However, in a review of these deaths it was not clear if any were directly related to therapeutic failure. One death in a patient treated with oritavancin who died post-study was assessed as related to study drug by the investigator but review of the case indicated that it is unlikely that oritavancin contributed to death.

SAEs

In the cSSSI population "during IV therapy" comparable percentages of patients had at least one SAE (2.6%, 31/1173 ORI-ALL; 2.5%, 24/956 ORI-ILDR and 2.9%, 17/590 Van). Similarly, in the "during oral therapy" period 1.7%, 1.3% and 2.4% in respective groups had an SAE compared to 5.8%, 4.4% and 7.2% in the "post study drug" period. Over the entire study period the rates were 9.1%, 7.4% and 11.4%.

The SOC with the highest percentage of SAEs (4.7%, 3.5% and 3.5%) was infections and infestations, followed by cardiac disorders, gastrointestinal disorders, vascular disorders and respiratory, thoracic & mediastinal disorders. The percentages with drug-related SAEs in the "during IV therapy" were 0.4%, 0.3% and 0.8% compared to 0.9%, 0.4% and 1.2% in the "during study" period.

Laboratory findings

In the cSSTI population "during study" the differences between oritavancin and Van groups of note were:

Mean increases in uric acid concentration from BL to LOV were +41.1 μmol/l in the ORI-ALL group, +44.3 μmol/l for ORI-ILDR and +28.0 μmol/l for Van. There was some suggestion of an increase in mean uric acid concentration as cumulative dose increased. However, the standard laboratory shift table analysis of the serum uric acid data did not demonstrate a difference between the oritavancin and the vancomycin/cephalexin treatment groups in shift from low or normal uric acid levels at baseline to subsequent elevated uric acid levels.

The percentages of ORI-ALL, ORI-ILDR and Van patients who entered these studies with existing hyperuricaemia were 0.7%, 0.8% and 0.3%, respectively, while gout was recorded for 1.2%, 1.3% and 1.4%. Eight oritavancin patients (0.7%) and no Van patient had at least one TEAE potentially associated with hyperuricaemia (blood uric acid increased [3], gout [2], nephrolithiasis [2] and hyperuricaemia [1]) in the "during study" period. None led to discontinuation from the study drug or study. The cases of nephrolithiasis were not considered to be drug-related by investigators.

The applicant does not know of any mechanistic explanation for an increase in serum uric acid level in patients administered oritavancin.

Further exploration of the data revealed a broad variation of laboratory normal ranges of uric acid levels. The upper limit of normal for uric acid in females ranged from 5.5 to 10.4 mg/dl and for males ranged from 6.0 to 10.5 mg/dl. The applicant applied linear transformation of these data in order to "normalise" the values for further safety analysis. The mean change from baseline analysis was repeated using these normalised values and demonstrated no statistically significant (p=0.091) or clinically relevant difference between the oritavancin and vancomycin/cephalexin treatment groups. On this basis the applicant concluded that the greater mean increase in uric acid values in oritavancin-treated patients was an artefact resulting from the broad variation in normal ranges of serum uric acid values. However, this analysis was not considered to be reassuring. The applicant should view the results for oritavancin and vancomycin groups generated by individual central laboratories.

Oritavancin has no effect on the coagulation system but it interferes with the assay for activated partial thromboplastin time (aPTT) due to an interaction with phospholipid reagents. The aPTT is falsely elevated for at least 10 h and up to 32 h post-dose. Therefore, the aPTT should be measured no sooner than 10 h after an infusion of oritavancin and not before plasma concentration is <15 μg/ml. Alternatively, excess phospholipid can be added to the assay or an alternative method of monitoring the effects of heparin therapy may be used, including concentrated thrombin time or plasma heparin assay.

The applicant performed an analysis of potential liver injury cases, defined as having ALT or AST > 3 x ULN and total bilirubin > 34.2 μmol/l. The cases identified are summarised in the table.

Table 2.7.4-41 Incidence of Potential Liver Injury in the "During Study" Period All Studies ITT Population

	ORI-ALL N=1173	ORI-ILDR N=956	Van N=590	p-value[a]	
				ORI-ALL vs Van	ORI-ILDR vs Van
Complicated Skin and Skin Structure Infection Intent-to-Treat Population					
Potential Liver Injury	2/1169 (0.2%)	1/956 (0.1%)	1/587 (0.2%)	>0.999	>0.999
Phase 2 Intent-to-Treat Population					
	ORI-ALL N=142	ORI-ILDR N=35	Van N=34	p-value[a]	
				ORI-ALL vs Van	ORI-ILDR vs Van
Potential Liver Injury	3/135 (2.2%)	0/32 (0.0%)	0/31 (0.0%)	1.000	N/A
Clinical Pharmacology Intent-to-Treat Population					
	ORI-ALL N=225	ORI-ILDR N=22	Van N=12	p-value[a]	
				ORI-ALL vs Van	ORI-ILDR vs Van
Potential Liver Injury	2/225 (0.9%)	0/22 (0.0%)	0/12 (0.0%)	N/A	N/A

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; N/A = not applicable; ORI-ALL = oritavancin all doses; ORI-ILDR = oritavancin – intended label dose range (180 to 330 mg/day).
[a] P-value from Fisher's exact test. Pairwise comparison is ORI-ALL vs Van and ORI-ILDR vs Van. ORI-ILDR is a subgroup of ORI-ALL.

Note: denominator for each set of potential liver injury cases is the number of patients that had a baseline and at least one postbaseline measurement. Potential liver injury defined as ALT or AST > 3 x ULN and Total Bilirubin >34.2 µmol/L (or ≥ 2.0 mg/dL [CN units]).

The two cases in Phase 1 participated in the study in subjects with moderate liver insufficiency and had baseline Child-Pugh scores of 7 to 10. There did not seem to be any marked changes from baseline. Two of the three Phase 2 oritavancin patients had entered study ARRC shortly after liver transplantation (9 days and 21 days previously) and the third entered ARRC with severe alcoholic hepatitis. These were all very complex cases and it does not seem likely that oritavancin was responsible for the changes in LFTs. The two oritavancin patients in cSSTI studies had ongoing, pre-existing liver disease at study entry. In neither case does it appear that oritavancin triggered important changes in LFTs.

Neutropenia, thrombocytopenia and pancytopenia showed a slightly increased frequency in the oritavancin treated patients. Further analysis of these cases showed little, if any, difference between treatment groups in adverse events of neutropenia, thrombocytopenia or pancytopenia. In addition, in most cases there were other reasons for the AEs identified.

In the Phase 3 cSSSI studies 3/1173 ORI patients and none of 590 VAN patients had an AE of neutropenia. One case was mild, one moderate and one severe in intensity according to the investigators. Two were assessed as possibly related to study drug but the severe event was not considered to be drug-related.

In the Phase 2 studies 6/142 ORI patients and none of 34 VAN patients had AEs of neutropenia and/or febrile neutropenia. Five of the six patients were in the non-comparative study ARRC and one came from ARRM. None of these events were assessed as related to study drug and all six patients had medical conditions at baseline that likely caused or contributed to the neutropenia (haematological malignancies in four, metastatic malignant melanoma in one and orthotopic liver transplant in one). In four cases these events were clearly temporally related to cytotoxic chemotherapy.

In the Phase 3 cSSSI studies 2/1173 ORI patients and 1/590 VAN patients had AEs of thrombocytopenia. One of the AEs in the ORI group was mild and possibly related and one was moderate and considered not related to study drug. The VAN event was severe and considered unrelated to study drug. In the Phase 2 studies 4/142 ORI patients and none of 34 VAN patients had AEs of thrombocytopenia. Two cases were mild and considered to be possibly related, one was moderate and unrelated and one was severe and unrelated to study drug.

There were no cases of pancytopenia in the Phase 3 cSSSI studies and only one case in the Phase 2 studies (1/142 ORI patients). The single case was of moderate intensity and was considered to be unrelated to study drug.

Special populations

Rates of TEAEs, SAEs and AEs leading to discontinuation were comparable between ORI-ALL, ORI-ILDR and Van treatment groups when analysed by age < 65 years, ≥ 65 and < 75 years and ≥ 75 years. In all three treatment groups, a higher percentage of patients aged ≥ 65 than < 65 years shifted from normal to substantially abnormal BUN values. The rates of TEAEs and shifts in laboratory values were higher for all treatment groups in those patients aged ≥ 75 years.

About one-fifth of patients in each treatment group had diabetes and these patients had higher rates of TEAS (e.g. 58.5% ORI-ILDR compared to 47.8%) and SAEs (15.9% and 5.3%) compared to those without diabetes. In all three treatment groups, a higher incidence of patients with diabetes than without shifted to substantially abnormal BUN values, which was potentially related to diabetes-associated renal impairment.

Discontinuations in cSSTI studies

In the "during study" period the rates of study drug discontinuation due to an AE without discontinuing from the study were 2.6% (31/1173) in the ORI-ALL group, 2.3% (22/956) for ORI-ILDR and 3.4% (20/590) for Van. A higher percentage of Van (2.4%, 14/590) than ORI-ALL and ORI-ILDR patients (0.3% in each group) discontinued both study drug and study in the "during study" period due to an AE.

Overall, 1.2% (14 of 1173) of ORI- and 2.9% (17 of 590) of Van-treated patients discontinued study drug and/or study in the "during study" period due to an AE that was investigator-assessed as related to study drug.

The three oritavancin patients that discontinued due to possible HLIRs included one with onset of an acute systemic allergic reaction during the first infusion (over 80 min), a case of severe anaphylactoid reaction 15 minutes after the first infusion (over 60 min) and a patient with rigor, chills and rash after the first infusion (over 60 min). The patient with hives is included in the SAE tables.

The patient with facial rash on day 2 had several other possible explanations for this AE. The patient with pruritus had onset at about 14 h after the first dose and resolution on the same day. The AE of vasovagal response commenced 45 min after the start of the second infusion, which was terminated early; the AE resolved within 5 minutes of onset. One patient, listed as having nausea, had a diagnosis of ileus after the 5th dose.

Comment on clinical safety

The safety profile of oritavancin was generally at least as good as that of vancomycin/cephalexin with few instances in which potentially important AEs occurred more often with oritavancin at or around the

selected dose (ORI-ILDR) than with comparative treatment. For the most part the incidence of AEs did not seem to relate strongly to cumulative dose of oritavancin.

The data from Phase III studies did not indicate a higher risk of phlebitis with oritavancin compared with vancomycin. Study VT-001 showed no clear trends with regard to local or general AEs relative to oritavancin doses (200 mg or 800 mg) but there was a trend for an increased incidence of AEs during or after the second IV infusion regardless of dose.

Histamine-like infusion reactions (HLIRs) were anticipated with oritavancin use. On searching for various signs associated with HLIRs specifically with onset < 6 h post-infusion and with rapid resolution (< 24 h) these reactions appeared to occur less often with oritavancin (about 3%) than with vancomycin (about 10%). It can be very difficult to differentiate HLIRs from standard allergic reactions due to the overlap in clinical features and times of presentation and resolution. However, an additional exploration of the database was performed to identify AEs that might represent an allergic reaction to oritavancin regardless of temporal association with dosing and after subtraction of AEs that were considered to represent HLIRs. The findings did not suggest an excess risk of hypersensitivity reactions for oritavancin compared to vancomycin/cephalexin.

There was not an excess of deaths in the oritavancin group and the deaths reported seemed unlikely to be drug-related. Although a few of the deaths were ascribed to uncontrolled sepsis or to specific infections the cases were too complex to draw firm conclusions regarding the possibility that therapeutic failure of oritavancin led to death. There was also no excess of SAEs (all or related) in the oritavancin group versus comparative therapy.

There remains no obvious explanation for the greater mean increase in uric acid with oritavancin compared with vancomycin. However, there was some suggestion of an increase in mean uric acid concentration as cumulative dose increased. The slight baseline imbalance in pre-existing hyperuricaemia (but not gout) would not explain the fact that 8 oritavancin patients (0.7%) and no Van patient had at least one TEAE potentially associated with hyperuricaemia in the “during study” period. The applicant’s proposed explanation is not accepted and further investigations are required.

Based on the applicant’s definition of a potential liver injury case there seemed to be a higher rate of transaminase abnormalities in the oritavancin group. However, the two patients in Phase I, three in Phase II and two in Phase III studies all appeared to have underlying reasons for being at risk of abnormalities and it does not seem likely that oritavancin triggered important changes in LFTs.

Pharmacovigilance system

Targanta Therapeutics Corporation was acquired by the Medicines Company. A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided. The detailed description now provided describes the system in place at the Medicines Company and this has now been assessed.

Provided that the deficiencies (other concerns) are rectified prior to the Applicant placing the medicinal product on the market, the CHMP may consider that the Pharmacovigilance system will fulfil the requirements. The Applicant must ensure that the system of Pharmacovigilance is in place and functioning before the product is placed on the market.

Risk Management Plan

The Risk Management Plan for Ramvocid, complies with the EU-RMP template, where the summary of the safety concerns acknowledged by the Applicant and respective actions proposed are shown in their table 4.1 which is reproduced below.

Table 4.1: Summary of the Risk Management Plan

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Important identified risks		
Histamine-like infusion reactions	• Routine pharmacovigilance practices • Targeted pharmacovigilance follow-up of spontaneous cases • Collection of drug utilisation data • Observational patient registry	None
Injection site phlebitis	• Routine pharmacovigilance practices • Targeted pharmacovigilance follow-up of spontaneous cases • Collection of drug utilisation data • Observational patient registry	None
Interaction with aPPT assay	• Routine pharmacovigilance practices	None
Skin reactions	• Routine pharmacovigilance practices • Collection of drug utilisation data • Observational patient registry	None
Pseudomembranous colitis	• Routine pharmacovigilance practices • Collection of drug utilisation data • Observational patient registry	None
Superinfection	• Routine pharmacovigilance practices • Collection of drug utilisation data • Observational patient registry	None
Important potential risks		
Susceptibility/acquired resistance	• Surveillance of resistance profiles among target organisms through participation in SENTRY Antimicrobial Surveillance Programme. • Collection of drug utilisation data	None
Hepatotoxicity	• Routine pharmacovigilance practices • Collection of drug utilisation data • Observational patient registry	None
Nephrotoxicity	• Routine pharmacovigilance practices • Collection of drug utilisation data • Observational patient registry	None
Immune suppression	• Routine pharmacovigilance practices • Collection of drug utilisation data • Observational patient registry	None
Exposure via breast milk	• Collection of spontaneous reports of exposure via	None

	breast milk, regardless of outcome.	
Osteomyelitis	• Routine pharmacovigilance practices • Collection of drug utilisation data	None
Important missing information		
Use in patients under 18 years of age	• Routine pharmacovigilance practices • Phase 1 single-dose pharmacokinetic and safety study in paediatric patients • Phase 2 multiple-dose pharmacokinetic and safety study in paediatric patients • Phase 3 safety study in paediatric patients	None
Use in pregnancy	• Routine pharmacovigilance practices	None

Since the first submission of the RMP the Applicant has added many additional risks to the safety specification and has indicated how they intend to address these risks through routine Pharmacovigilance and proactive activities. The assessment has questioned whether some of these risks should be classified as important identified, as opposed to important potential. There is also an issue as to whether lack of data in the elderly should be regarded as missing information or not.

In line with the clinical assessment of the available data additional risks have been stipulated that should be addressed in the RMP, namely those of elevated uric acid levels, accumulation of oritavancin in the macrophages, cytopenias, dizziness and allergic reactions. The issue of effects on transaminases should be addressed as the Applicant acknowledges that hepatotoxicity is an important potential risk, but does not consider it is necessary to institute special monitoring, for a variety of reasons argued under the section on preventability in section 1.5.2.8

The Applicant has identified proactive activities of drug utilisation surveys and an observational patient registry to supplement routine Pharmacovigilance activities, but there is a need to address the limitations of these approaches in relation to data capture and study duration that is proposed.

IV. ORPHAN MEDICINAL PRODUCTS

N/A.

V. BENEFIT RISK ASSESSMENT

V.1 Benefits

Oritavancin may represent an additional option for the management of cSSSI. However, the degree of benefit cannot be gauged at present due to ongoing issues regarding the validity of the single pivotal study and remaining concerns that the recommended standard dose regimen is not optimal particularly when treating infections due to MRSA.

V.2 Risks

There are no major objections raised on safety grounds; there are several issues arising from the database that need to be considered further.

It cannot be ruled out that the accumulation of oritavancin within macrophages to give high concentrations potentially over long periods could interfere with normal cell function. The applicant should discuss how

the effects of oritavancin accumulation in macrophages might be investigated further in ongoing and planned studies in patients.

There remains a concern regarding the potential for oritavancin to trigger increases in uric acid levels. Further investigations of the apparent phenomenon are required.

The study of venous tolerance (VT-001) employed infusions of oritavancin that were of the same concentration or more dilute than recommended in the draft SPC, each given over 60 minutes. The SIMPLIFI study employed infusions of 200 mg in 250 ml over 45-60 minutes or sequential administrations of 400 mg, each in 250 ml over 45-60 minutes. It is not clear from these data which concentration and infusion time of oritavancin are optimal for 200 mg daily dosing. This matter should be addressed.

There are also major objections related to insufficient qualification of impurities in the drug substance and the product.

V.3 Balance

At present it cannot be concluded that the risk-benefit relationship is favourable for oritavancin when used at the proposed dose regimen to treat cSSSI.

V.4 Conclusions

The overall B/R of Ramvocid is negative.