22 January 2015
EMA/CHMP/803704/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Orbactiv

International non-proprietary name: oritavancin

Procedure No. EMEA/H/C/003785/0000

Note

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

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Administrative information

Name of the medicinal product:	Orbactiv
Applicant:	The Medicines Company UK Ltd 115L Milton Park Abingdon OX14 4SA UNITED KINGDOM
Active substance:	oritavancin diphosphate
International Nonproprietary Name/Common Name:	oritavancin
Pharmaco-therapeutic group (ATC Code):	oritavancin (J01XA05)
Therapeutic indication(s):	"Orbactiv is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults. (see sections 4.4 and 5.1). Consideration should be given to official guidance on the appropriate use of antibacterial agents."
Pharmaceutical form(s):	Powder for concentrate for solution for infusion
Strength(s):	400 mg
Route(s) of administration:	Intravenous use
Packaging:	vial (glass)
Package size(s):	One pack with 3 vials

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List of abbreviations

Abbreviation	Explanation
ABSSSI	Acute bacterial skin and skin structure infection
AE	Adverse event
AIDS	Acquired Immunodeficiency Syndrome
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BMI	Body mass index
bpm	Beats per minute
BUN	Blood urea nitrogen
CDAD	*Clostridium difficile* associated diarrhea
C. difficile	*Clostridium difficile*
CPK	Creatine phosphokinase
CrCL	Creatinine clearance
CRP	C-reactive protein
CSR	Clinical study report
cSSTI	Complicated skin and soft tissue infection
CYP	Cytochrome P450
DDI	Drug-drug interaction
DSMB	Data Safety Monitoring Board
ECE	Early clinical evaluation
ECG	Electrocardiogram
eDISH	Evaluation of drug-induced serious hepatotoxicity
EMA	European Medicines Agency
EOT	End of treatment
FDA	Food and Drug Administration
HIV	Human immunodeficiency virus
INR	International normalization ratio
ISS	Integrated Summary of Safety
IV	Intravenous
kg	Kilogram
L	Liter
LFT	Liver function test
LLN	Lower limit of normal
max	Maximum
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minimum
mL	Milliliter
mmHg	Milliliters of mercury
MRSA	Methicillin-resistant *Staphylococcus aureus*
ms	Milliseconds
n	Number of patients
NA	Not applicable
PCS	Potentially clinically significant
PT	Prothrombin time
PTE	Post therapy evaluation
Q_1 , Q_3	Quartile range
QTc	Corrected QT
QTcB	Corrected QT according to Bazett
QTcF	Corrected QT according to Fridericia
ROW	Rest of world
SAE	Serious adverse event
SAP	Statistical analysis plan
SCS	Summary of Clinical Safety
SD	Standard deviation

Abbreviation	Explanation
SIRS	Systemic inflammatory response syndrome
SOC	System organ class
S. aureus	*Staphylococcus aureus*
tQT	Thorough QT
ULN	Upper limit of normal
WBC	White blood cells

1. Background information on the procedure

1.1. Submission of the dossier

The applicant The Medicines Company UK Ltd submitted on 4 February 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Orbactiv, through the centralised procedure under Article 3 (2)(a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 30 May 2013.

The applicant applied for the following indication:

Orbactiv is indicated in adults for the treatment of complicated skin and soft tissue infections (cSSTI). Orbactiv is active against Gram positive bacteria only. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that oritavancin was considered to be a new active substance.

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

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0056/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0056/2013 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance oritavancin contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 18 November 2010. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer responsible for batch release

Hälsa Pharma GmbH
Nikolaus Dürkopp Straße 4a
D-33602 Bielefeld
Germany

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP:

Rapporteur: Greg Markey

Co-Rapporteur: Martina Weise

- The application was received by the EMA on 4 February 2014.
- The procedure started on 26 February 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 16 May 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 16 May 2014.
- During the meeting on 12 June 2014 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan
- During the meeting on 26 June 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 27 June 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 September 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 24 October 2014.
- During the meeting on 6 November 2014 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the CHMP meeting on 20 November 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 17 December 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the list of

outstanding issues to all CHMP members on 23 December 2014.

- During the meeting on 08 January 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.

- During the meeting on19 to 22 January 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Orbactiv.

2. Scientific discussion

2.1. Introduction

Problem statement

Acute bacterial skin and skin structure infections (ABSSSI) are among the most common infections seen in clinical practice; these infections may require systemic antibacterial therapy, surgical management and hospitalisation. Untreated infections may become severe or life-threatening, depending on the pathogen [Corey and Stryjewski, 2011; Elston, 2005]. ABSSSIs include cellulitis/erysipelas, wound infections, major cutaneous abscesses, and burn infections. They commonly involve at least a 75 cm^2 surface area of redness, oedema and/or induration accompanied by lymph node enlargement or systemic symptoms such as fever [FDA, 2010].

The morbidity associated with ABSSSI often requires rapid intervention with antibacterial therapy to minimise tissue damage and prevent the spread of infection. The clinical complications of delayed or inappropriate treatment of skin and skin structure infections can be serious, including those resulting from local spread, secondary bacteraemia with potential for distant metastatic foci of infection, and systemic effects [Davis *et al*., 2007]. In a study of 47,219 patients hospitalised for ABSSSI treatment failure occurred in 22.8% of patients and was associated with a 3-fold increase in mortality (OR, 2.91 [95% CI, 2.34-3.62]) [Edelsberg *et al*., 2008]. Treatment failure also increased the duration of both IV therapy and hospital stay by 5 to 6 days. Hence, patients hospitalised with ABSSSI who experience failure of initial therapy have significantly worse clinical outcomes and longer stays.

The most common pathogen is *S. aureus*. The SENTRY programme demonstrated that *S. aureus* was the most prevalent cause of nosocomial and community-acquired skin and skin structure infections and bloodstream infections in almost all geographic regions [Moet *et al.*, 2007; Moellering *et al.*, 2010]. *S. aureus* has developed resistance to all classes of antibacterial agents available for clinical use [Federal Register, 2013]. Numerous resistance mechanisms have been documented in *S. aureus*, including the transmission of resistance that can occur via plasmids shared between bacteria, or even transfer of resistance mechanisms from different genera of bacteria [Pantosti *et al.*, 2007].

Patients infected with drug-resistant pathogens are more challenging to treat than those infected with drug-susceptible pathogens. For example, a patient infected with a drug-resistant pathogen may have a delay in the initiation of effective drug therapy that can result in poor outcomes [Federal Register, 2013]. Additionally, patients and healthcare providers face challenges with the treatments available for ABSSSIs, specifically for the treatment of MRSA. The spectrum of activity and toxicity profiles of available agents indicated for the treatment of ABSSSI contribute to the treatment difficulties [Bishop, 2006].

Current treatments approved for the treatment of ABSSSI include daptomycin, linezolid, tigecycline, ceftaroline and vancomycin. Vancomycin continues to be widely used to cover MRSA. These therapies consist of multi-dose and multi-day regimens with some requiring dosage adjustments for renal

insufficiency (vancomycin), therapeutic monitoring (vancomycin), precautionary use in pregnant women (tigecycline) and myelosuppression (linezolid). Multi-dose therapies may require patients to be hospitalised throughout treatment and could lead to an increased risk of acquiring and spreading infections in the hospital. Treatment non-adherence can also be an issue with these regimens, increasing the potential for pathogen resistance [CDC, 2011]. Additionally, there is a limited armamentarium to treat resistant pathogens such as MRSA that pose an increasingly serious threat to public health.

There is a need for new antibacterial agents that will effectively treat infections caused by Gram-positive bacteria including highly resistant and virulent pathogens such as MRSA. According to the ECDC, the number of patients in Europe that are infected by resistant bacteria is increasing and resistance is a major threat to public health owing to mounting healthcare costs, failed treatments and deaths [ECDC, 2012]. MRSA remains a public health priority because of the substantial resistance burden in Southern and Eastern Europe [ECDC, 2012].

About the product

Oritavancin is a semi-synthetic, lipoglycopeptide the following mechanism of action:

1) Inhibition of the transglycosylation (polymerisation) step of cell wall biosynthesis by binding to the stem peptide of peptidoglycan precursors
2) Inhibition of the transpeptidation (crosslinking) step of cell wall biosynthesis by binding to the peptide bridging segments of the cell wall
3) Disruption of bacterial membrane integrity, leading to depolarisation, increased permeability and rapid cell death.

Oritavancin is a large molecule with a structure that resembles that of vancomycin. It is soluble in water and in acidic solutions. A solution of oritavancin in water has pH 2.8. It is presented for clinical use as the lyophilisate of the dihydrogen phosphate salt. The vials proposed for commercial use contain the equivalent of 400 mg of the free base. The 1200 mg single dose is administered by transferring the contents of three reconstituted vials into a 1000 ml bag of 5% D5W (from which the total reconstitution volume (120 ml) has been withdrawn. The resulting 1.2 mg/ml solution of oritavancin is infused over 3 h.

<u>The revised section 4.1 is as follows:</u>

Orbactiv is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults (see sections 4.4 and 5.1).

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

<u>The revised section 4.2 reads as follows:</u>

<u>Posology</u>
1,200 mg administered as a single dose by intravenous infusion over 3 hours.

<u>Special populations</u>

Elderly (≥ 65 years)
No dosage adjustment is required for patients ≥ 65 years of age (see section 5.2).

Renal impairment
No dosage adjustment is needed in patients with mild or moderate renal impairment (see section 5.2). The pharmacokinetics of oritavancin in patients with severe renal impairment has not been evaluated. Oritavancin is not removed from blood by haemodialysis procedures.

Hepatic impairment
No dosage adjustment is required for patients with mild to moderate hepatic impairment (Child-Pugh Class B) (see section 5.2). The pharmacokinetics of oritavancin in patients with severe hepatic impairment (Child-Pugh Class C) has not been evaluated.

Paediatric population
The safety and efficacy of oritavancin in children and adolescents (<18 years) has not yet been established. No data are available.

Method of administration
Inravenous use.
Intravenous infusion over 3 hours (see section 6.6).

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

2.2. Quality aspects

2.2.1. Introduction

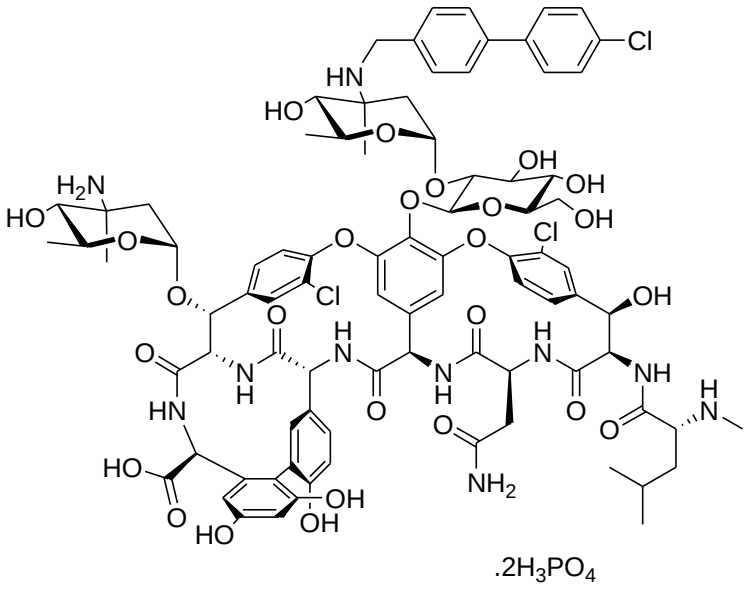
The finished product is presented as a powder for concentrate for solution for infusion containing oritavancin diphosphate equivalent to 400 mg of oritavancin as active substance. The powder must be reconstituted with water for injections and the resulting concentrate must be diluted in glucose 5% intravenous infusion bag prior to use. After reconstitution, 1 ml of the solution contains 10 mg oritavancin. After dilution, 1 ml of the solution for infusion contains 1.2 mg oritavancin.

Other ingredients are: mannitol and phosphoric acid.

The product is available in single-use 50 ml Type 1 glass vials with rubber stoppers and aluminium flip off cap.

2.2.2. Active Substance

General information
The active substance oritavancin diphosphate is a semi-synthetic lipoglycopeptide antibiotic. The chemical name of oritavancin diphosphate is [4"R]-22-O-(3-amino-2,3,6-trideoxy-3-C-methyl- α -Larabino- hexopyranosyl)-N3''-[(4'-chloro[1,1'-biphenyl]-4-yl)methyl] vancomycin phosphate [1:2] [salt] and it has the following structure:



The heptapeptide core has the same structure as Vancomycin. The amino sugars are different but epimeric to the vancosamine contained in Vancomycin.

The structure of oritavancin diphosphate has been confirmed by elemental analysis, mass spectroscopy, ^{1}H and ^{13}C-NMR, IR, UV and X-ray Powder Diffraction.

Oritavancin diphosphate is a hygroscopic white to pale pink solid that is soluble in water (60.75 mg/ml) and 5 % Dextrose (≥33.3 to < 100 mg/ml); however, the solubility is affected by pH and buffer species used. The solubility decreases considerably towards neutral/basic pH. Oritavancin has poor crystallinity; oritavancin cannot be obtained in crystalline form. Therefore polymorphism has not been observed for oritavancin diphosphate. The crystallinity of the drug substance is not critical to the bioavailability of the drug product since the product is administered as an intravenous infusion following reconstitution and dilution of the lyophilized dosage form.

Oritavancin exhibits stereoisomerism due to the presence of 22 asymmetric carbons and three additional chiral elements associated with the restricted rotation of the biphenyl moiety and the 2 diphenyl ether moieties. The stereogenic centers in oritavancin diphosphate are the same as those in Nucleus Factor B (intermediate produced during fermentation to form oritavancin). Both of these compounds share the same chiral elements as vancomycin with the exception of the additional 4-epivancosamine. There are no additional stereogenic centers introduced as a result of the reductive alkylation step that follow the fermentation process. As a fermentation product, Nucleus factor B is synthesised with a high level of stereocontrol by biological processes. The potential for racemisation of any of the chiral elements under the conditions of fermentation, isolation and chemistry used in the manufacturing of oritavancin is extremely low.

Manufacture, characterisation and process controls

Oritavancin diphosphate is manufactured in two steps by one manufacturer using well-defined starting materials with acceptable specifications. The first step involves classical fermentation using *Kibdelosporangium aridum* (formerly referred to as *Amycolatopsis orientalis*) culture to produce the intermediate Nucleus Factor B. The second step is a synthetic step that consists of reductive alkylation of Nucleus Factor B to produce Oritavancin. The crude active substance is purified by column chromatography and ultrafiltration to yield oritavancin which is then converted to the diphosphate salt.

Satisfactory details of phenotypic and genotypic characterisation of Kibdelosporangium aridum Cell Bank are provided.

The applicant has confirmed that the fermentation medium for the commercial process does not contain any animal source material (ASM). However, animal source material was present in the fermentation media used for the production of batches used in the early clinical studies. Comparative data for batches produced with ASM containing fermentation medium and ASM-free fermentation medium confirm that there were no changes in the characteristics of oritavancin.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Specification

The active substance specification includes tests for: appearance, solution colour and clarity (Ph. Eur.), identity (FTIR, HPLC), assay (HPLC), phosphate (IC), impurities (HPLC, GC), residual solvents (GC), water content (KF), heavy metals (Ph. Eur.), residue on ignition (Ph. Eur.), Boron and Copper (ICP), Cyanide (IC), microbial contamination (Ph. Eur) and bacterial endotoxins (Ph. Eur.).

Impurities present at higher than the qualification threshold according to the "Guideline on setting specifications for related impurities in antibiotics" (EMA/CHMP/CVMP/QWP/199250/2009 corr) were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data of the active substance (including 4 batches manufactured at the proposed commercial manufacturing site according to the proposed commercial process) were provided. The results were within the specifications and consistent from batch to batch.

Stability

Stability data on 8 commercial batches of active substance (including 4 batches manufactured without animal sourced material) from the proposed manufacturer stored for 36-48 months under long term conditions at 5 ºC and for up to 6 months under accelerated conditions at 25 ºC / 60% RH according to the ICH guidelines were provided.

The parameters tested were the same as for release. The analytical methods used were the same as for release and were stability indicating.

Oritavancin was exposed to stress conditions as part of the forced degradation specificity study during method validation. The stress conditions used were: Heat (solid) 24 hours, 105 °C; Heat (solution) Reflux, water, 5 hours; UV Light (solid) 24 hours, ambient; Acid (solution) 1 N aqueous H2SO4, 30 hours, ambient; Base (solution) 0.5 N aqueous NaOH, 4 hours, ambient; Oxidative (solution) 30% aqueous H2O2, 43 hours, ambient. The results showed varying degree of degradation under the different conditions and confirmed the analytical methods are stability indicating.

The stability results indicated that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The aim of the pharmaceutical development was to develop a sterile intravenous formulation in single-use vials. The base form of Oritavancin is insufficiently soluble in water. A screening process was undertaken to identify a salt with improved solubility. The diphosphate salt form showed the best solubility and an acceptable pH, therefore it was selected for further development. Due to lack of stability of the Oritavancin solution it was developed as a lyophilized dosage form which requires reconstitution with Sterile Water for Injection and further dilution prior to administration. To provide an acceptable firm homogenous cake structure and also improve stability of the formulation, three bulking/stabilising agents were evaluated during formulation development (mannitol, sucrose, and trehalose). Mannitol was chosen as the bulking/stabilising agent for its physical properties. However, mannitol has a tendency to crystallise, leading to active substance -mannitol phase separation that leaves the active substance unprotected. Therefore, to minimise crystallisation, the ratio of mannitol to active substance was

evaluated. The best ratio of mannitol to drug was found to be 1:2. In addition, phosphoric acid is used during formulation to achieve the desired solution pH (3.6 to 3.8) prior to lyophilisation.

The pharmaceutical development was initiated by a different company for a 100 mg formulation. The 100 mg drug product process was then transferred to two manufacturing sites with minimal changes. The 400 mg drug product formulation, which is the proposed commercial dosage form, was developed later. The same general manufacturing process is used for both drug product strengths. Differences in manufacturing between the two presentations are bulk solution concentration, lyophilisation time, primary drying temperature and batch size. The manufacturing process was later transferred to the proposed manufacturing site with a minor change.

Three different formulations of Oritavancin for Injection have been used in clinical studies and were presented. To support a 1200 mg dose, a formulation containing 400 mg Oritavancin was developed for some of the Phase 3 studies. The differences of the phase 3 and the product for commercial use have been presented and adequately justified

The required administered dose is 1200 mg which is achieved by using three single vials of the 400 mg formulation. Combining three vials bears a risk of microbial contamination during handling.

Therefore a 1200 mg formulation would be more appropriate. However it has been shown that due to the physicochemical properties of the active substance a 1200 mg formulation has not been possible so far. The CHMP considered that the proposed 400 mg formulation can be acceptable and acknowledged the applicant's commitment to explore ways to improve handling or reformulating Orbactiv by developing a 1200mg vial presentation as part of lifecycle management. In addition appropriate handling instructions were included in section 6.6 of the SmPC to address the risk of contamination during handling.

All excipients are well-known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Oritavancin for Injection is prepared by dissolving mannitol and oritavancin diphosphate in water for injection (WFI) which is adjusted to a pH of 3.6-3.8 with dilute phosphoric acid solution. The bulk solution is sterile filtered through 0.22 µm polyvinylidene (PVDF) membrane filters and aseptically filled into sterile vials under sterile nitrogen and lyophilised.

During manufacturing process development, the effect on the stability of the bulk solution of heat and light during manufacture were investigated. The water pH range was determined so that the formulated bulk solution provides acceptable solubility of oritavancin and stability of the lyophilised product.

The order of addition of mannitol and oritavancin diphosphate was found not to affect the solution preparation. Data were provided to support the hold period for bulk solution before sterile filtration and were considered acceptable. Studies for evaluation of extractable substances from the filters were performed. The lyophilisation cycle was developed for the 100 mg strength. The factors affecting that crystallinity of mannitol in the lyophilisate were studied in a number of experiments including a factorial design. It was found that adjusting the lyophilisation parameters was sufficient to control the crystallinity of the mannitol in the lyophilisate.

There is no overage for Oritavancin for Injection. However, a 1.25 % overfill (405 mg) is added for vial retention to ensure labelled content (400 mg) can be withdrawn.

Oritavancin was found to be compatible with Dextrose 5% injection (D5W) but not with 0.9% sodium chloride injection (Normal Saline).

The osmolality of oritavancin reconstituted and admixed with Dextrose 5% injection (D5W) was found to be similar to an isotonic solution of D5W and serum.

Stability of reconstituted solution was investigated. The following precaution was required to be included in the SmPC "The reconstituted solution should be further diluted in glucose 50 mg/mL (5%) intravenous infusion bag immediately."

The chemical stability of reconstituted Oritavancin 400 mg drug product diluted in D5W solutions in PVC bags and PP bags was investigated. A significant assay decrease was observed in the PP bags after 48 hours. Results demonstrated an acceptable chemical stability of 24 hours at room temperature and 2-8 °C in both PVC and PP bags.

Microbial stability of oritavancin in D5W admixture solution was investigated. The applicant initially claimed in-use stability of 48 hours for the diluted drug product in D5W. This was not considered acceptable by CHMP since the drug product does not prevent the growth of at least one microorganism frequently associated with nosocomial infections (Serratia marcescens) in the claimed time.

The following precaution was included in the SmPC "The diluted solution should be used immediately. From a microbiological point of view, the product should be used immediately. If not used immediately storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 12 hours at 25°C and 24 hours at 2-8°C for Orbactiv diluted in glucose 5% intravenous infusion bag, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions."

The primary packaging is a single-use 50 ml Type 1 glass vials with a rubber stopper and an aluminium flip off cap. The material complies with Ph.Eur. requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of 5 main steps: preparation of oritavancin bulk solution, pre-filtration, aseptic filtration and filling, lyophilisation and stoppering, packaging. The process is considered to be a non-standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies on three commercial scale batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: Appearance (visual), Reconstitution Time (Visual), Visible Particulates (Visual), Color of Solution (Ph.Eur.), Clarity of Solution (Ph. Eur.), Identity (HPLC, UV), Assay (HPLC), Uniformity of dosage (Ph.Eur.), Impurities (HPLC), Water content (Karl Fischer), Ethanol (GC), pH (Ph.Eur.), Particulate Matter (Ph.Eur.), Bacterial Endotoxins (Ph.Eur.) and Sterility (Ph.Eur.).

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

The in-house analytical procedures are described and validated. The method for assay as well as related substances was shown to be stability indicating through forced degradation studies.

Batch analysis results are provided for 3 batches (including 1 commercial batch) confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. Additional batch analysis data were provided for 100 mg strength and for the 400mg strength manufactured at different sites.

Stability of the product

Stability data of 3 batches of finished product (including 1 production scale batch) stored for up to 24 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Additional supportive stability data are also provided for 100 mg strength batches and for 400 mg strength batches manufactured at other manufacturing sites.

Samples were tested according to the shelf-life specifications (identical to the release specifications except for assay, impurities and water content were shelf-life limits are different from release limits and except for the uniformity of dosage test only performed at release). The analytical procedures used are stability indicating.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The drug product was shown stable in the clear glass vial without label and is considered not light-sensitive and no special packaging protection from light was considered needed.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

The applicant has proposed that no animal source material will be used for the fermentation step of the manufacturing process of the active substance for commercial batches.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

The required dose is 1200 mg and is administered by using three vials of 400 mg. In this regard appropriate handling instructions were included in section 6.6 of the SmPC to address the risk of contamination during handling. The CHMP considered the handling instructions sufficient and the proposed 400 mg formulation acceptable, and acknowledged the applicant’s commitment to develop a formulation of 1200mg.

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

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:
- explore ways to improve handling or reformulating Orbactiv by developing a 1200mg vial presentation as part of lifecycle management

2.3. Non-clinical aspects

2.3.1. Introduction

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. No issues for GLP compliance have been raised.

2.3.2. Pharmacology

Primary pharmacodynamic studies
See the clinical Pharmacodynamics section regarding antibacterial activity.

Secondary pharmacodynamic studies
In receptor binding assays, oritavancin competed with radioligand binding to dopaminergic D1 and D2 receptors in rat brain homogenates with affinity constants (Ki) of 2.25 µM and 3.46 µM, respectively. Oritavancin (1 µM) exhibited a slight inhibition on the force of acetylcholine-induced contractions of guinea pig ileum tissue.

Safety pharmacology programme
In mice administered a single intravenous (IV) dose of 5, 15 or 50 mg/kg, there were no notable changes in observable behaviour, spontaneous ambulatory or non-ambulatory activity counts, convulsive activity induced by electroshock or pentylenetetrazol, neuromuscular function, or sensorimotor reactivity. Acetic acid-induced writhing was used to evaluate the analgesic potential of oritavancin. There were no statistically significant alterations in acetic acid-induced writhing at any dose level, although reduced writhing was noted in the 50 mg/kg dose group. The 50 mg/kg group also showed a transient reduction of 1.1ºC in body temperature.

Oritavancin increased hexobarbital-induced sleep times in mice dosed 50 mg/kg indicating that oritavancin may produce central nervous system (CNS) depression or inhibit hepatic enzymes involved in hexobarbital metabolism. The applicant states that the latter explanation is more likely because it is supported by the observation that oritavancin inhibited several CYP450 enzymes including those involved

in the metabolism of hexobarbital (CYP2C19, CYP2C9, CYP1A2 and CYP3A4) in human hepatic microsomes.

In-vitro studies indicated oritavancin has the potential to interact with several cardiac ion channels. In HEK293 cells stably transfected with hERG complementary DNA, oritavancin reduced delayed rectifier potassium current (IKr) tail current amplitudes with a low potency (IC50 = 22 μM). In assays conducted with human atrial myocytes oritavancin inhibited the cardiac sodium current (Ina) and transient outward potassium current (Ito) ion channels with IC50s of 0.51 μM and 4.2 μM, respectively. There was no effect of oritavancin on sustained current (Isus) or inwardly rectifying potassium current (Ik1). The translation of single ion channel inhibitory activity is complex and can be influenced by many factors, including the kinetics of channel block, additional pharmacological properties (both known and unknown), and the potential for regional effects on the heart. The applicant proposes to include cardiac conduction events in the Risk Management Plan and should suggest a reasonable approach for routine pharmacovigilance monitoring.

Rats administered 50 mg/kg oritavancin exhibited increased systolic pressure (range 15–22 mmHg), mean arterial pressure (range 13 – 15 mmHg), and aortic pulse pressure (10 mmHg). No cardiovascular effects were observed in rats administered up to 15 mg/kg. Dogs administered IV doses of 25 mg/kg dose groups exhibited increases in systolic, diastolic and mean arterial blood pressures and reduced arterial pulse pressure. The left ventricular inotropic state was significantly higher during and post-infusion. These animals also exhibited an increase in heart rate. There were no treatment-related changes in electrocardiograms (ECGs) in any dose group. Although respiratory sinus arrhythmia (a common occurrence in the dog) was frequently observed, no treatment-related changes in rhythm were observed. There were no treatment-related cardiovascular effects in the 5 and 10 mg/kg dose groups. In the oritavancin clinical program there was no evidence of cardiac toxicity attributable to the administration of oritavancin as demonstrated by clinical cardiac adverse event, serious adverse event and ECG data as well as results from a thorough QTc study.

No respiratory studies with oritavancin were reported. However, following a review of the pivotal non-clinical toxicity studies, no effect on respiratory function was observed. In addition, oritavancin had no effect on respiratory rate in a clinical thorough QTC study. These evaluations showed no evidence of oritavancin-induced effects on respiratory function.

The effect of oritavancin on renal function and water/electrolyte excretion was determined in female rats administered a single dose of 5, 15 or 50 mg/kg oritavancin. Immediately after administration of oritavancin, the rats were administered an oral dose of 25 ml 0.9% saline solution/kg for hydration. Animals in the 50 mg/kg oritavancin dose group exhibited a 27% increase in serum creatinine, and animals in the 15 and 50 mg/kg dose groups exhibited a 2% increase in serum osmolality. In addition, animals in the 15 and 50 mg/kg dose groups exhibited decreases in the total excretion of sodium (56% and 65%, respectively) and its counter ion, chloride (33% and 46%, respectively). Animals in the 50 mg/kg group exhibited a 26% decrease in the total number of osmols, urine volume decreased by 40%, and creatinine clearance was decreased by 33%. The no observed effect level for changes in renal water and electrolyte excretion was 5 mg/kg.

The applicant states that in single and repeat dose toxicity studies, treatment-related haemolysis was not observed. In addition, in the clinical studies, there were no reports of the presence of occult blood in urines, individuals did not exhibit haematological changes or evidence of haemolysis and there was no indication of any adverse renal effects based on the evaluation of serum creatinine calculated and clinical adverse events.

In mice, the administration of a single IV dose of up to 50 mg/kg had no effect on the charcoal meal transit time. This indicates that single therapeutic doses of oritavancin would not be expected to produce constipation or promote diarrhoea.

Pharmacodynamic drug interactions

Oritavancin combinations with gentamicin, linezolid and rifampin were shown to be synergistic *in vitro* against MRSA strains with hVISA and VISA phenotypes. Oritavancin synergises with gentamicin *in vivo* as evidenced by efficacy studies in a rabbit model of VRE endocarditis in which oritavancin alone was poorly active.

2.3.3. Pharmacokinetics

The nonclinical PK and/or toxicokinetics (TK) and metabolism of oritavancin were assessed in a series of in-vitro and in-vivo studies.

Absorption

The pharmacokinetics of IV oritavancin was studied in mice, rats and dogs. Oritavancin exhibited linear, dose proportional plasma kinetics with maximal levels attained at the first sampling time point after the end of infusion. There were no gender differences in the PK among the different species in repeat dose studies and there was no plasma accumulation of oritavancin following multiple dosing.

Oritavancin was originally developed for repeat dose administration in the clinic. Therefore, there are only a limited number of single dose PK studies conducted with oritavancin and often only one animal was sampled per time point. Oritavancin exhibited a terminal plasma half-life that ranged from 8 h to 33 h in mice, from 4 h to14 h in rats and 66.9 h in dogs. The variation in half-lives for oritavancin in all three species was attributed to the heterogeneity from study to study in the data time points used to calculate half-life. The time points used to calculate the terminal half-lives ranged from 4-48 h in mice, 1-60 h in rats and 48-168 h for the dog study. The terminal half-life of oritavancin in humans is 245 h. The difference in sampling time points may explain the shorter terminal half-lives in animals compared to humans.

The PK parameters of oritavancin were determined in neutropenic female mice. The PK profiles were similar in neutropenic and non-neutropenic mice administered oritavancin by the IV route.

Distribution

The serum protein binding of oritavancin was similar (~85%) between mouse, rat, dog, and human matrices. *In vitro* studies indicated that oritavancin was neither a substrate nor an inhibitor of the efflux transporter P-glycoprotein (P-gp). Except for P-gp studies, no transporter protein studies with oritavancin were reported. However, to comply with current guidelines, the applicant will initiate transporter studies. Tissue distribution studies in rats and dogs indicated that oritavancin administered IV is widely distributed throughout the body achieving peak levels by 1-6 h post-dose. There was a long tissue residence time with radioactivity still present at moderate levels 7 days post-dose. These results were consistent with histopathological findings from toxicity studies indicating the presence of macrophages containing eosinophilic granules, presumably from oritavancin uptake, in tissues throughout the body even following treatment-free periods. Studies in pregnant rats indicate no placental transfer of oritavancin to the fetus; however, oritavancin was excreted in milk in lactating dams and orally absorbed by nursing pups and widely distributed to all tissues.

Metabolism

Oritavancin did not appear to be metabolised and was eliminated intact. Comparison of plasma concentrations of oritavancin to plasma radio-equivalent concentrations of ^{14}C-oritavancin suggested that

there were no circulating metabolites of oritavancin in the plasma. Furthermore, analysis of plasma and bile from mice, rats and dogs administered single IV doses of ^{14}C-oritavancin did not indicate the presence of metabolites of oritavancin. In addition, *in vitro* monkey hepatic microsomal metabolism studies did not show any evidence to suggest that oritavancin is metabolised by the CYP system. There were no metabolite peaks observed and there was no depletion of oritavancin over time. These results are consistent with studies of oritavancin incubated in the presence of human liver microsomes that did not show evidence of metabolism.

In human hepatocytes, oritavancin at concentrations ≤ 50 µM did not induce CYP1A2, CYP2A6, CYP2C9, CYP2C19 and CYP2D6 activities. At 50 µM oritavancin slightly increased CYP2E1 activity. At 2.5 µM oritavancin slightly increased CYP3A4 activity but at higher concentrations inhibited CYP3A4 activity. The SmPC states that oritavancin is a weak inhibitor of CYP2C9. No information on the potential for inhibition of CYP2C8 was provided.

Excretion

In rats and dogs, oritavancin is excreted unchanged primarily via the bile into the faeces. After 14 days of administration to rats approximately 50% of the dose was eliminated in the faeces, approximately 5% in the urine and the remaining dose was still in the carcass, reflective of the long tissue retention times. Dogs showed a similar pattern of excretion. However, by 14 days approximately 10% of the dose was recovered in faeces, 6% in the urine and the remaining dose was still in the carcass. The long retention times in animals are consistent with observations in humans where < 5% of the administered dose was recovered in urine and faeces after 14 days of dose administration. In humans, oritavancin is eliminated in the urine and faeces.

Drug interactions

Specific animal studies have not been conducted to evaluate pharmacokinetic drug-drug interactions. In a pharmacodynamic drug interaction study in rabbits, plasma histamine levels of animals treated with oritavancin and desipramine (a CYP2D6 substrate) were similar to those of animals treated with oritavancin alone. In a clinical study, there was no appreciable effect of oritavancin on the pharmacokinetics of desipramine. No other studies were reported in the Non-clinical Overview. The Clinical Report provides an assessment of drug interactions with oritavancin.

2.3.4. Toxicology

Single dose toxicity

A single dose toxicity study was conducted in rats administered an IV dose of 40, 80 or 120 mg/kg oritavancin. Mortality occurred in rats administered 120 mg/kg oritavancin. The clinical findings observed (decreased activity, hunched posture, severely swollen, dark-blue tongues, intermittent tremors, red soiling of perineal and muzzle areas, ataxia, red lacrimation and/or decreased faeces) were consistent with histamine-like infusion reactions.

Repeat dose toxicity

Repeat-dose IV toxicity studies were conducted in rats and dogs. Pivotal toxicology studies were one month and 13 weeks in duration which is acceptable to support the intended single dose IV regimen in humans. In addition, cumulative area under the curve (AUC0-t) exposure levels for oritavancin at the no observed adverse effect levels (NOAELs) were multiples (range: 2.4 to 11.9 fold) higher than human

exposure levels and sufficiently high to qualify impurities in the drug substance. Lower multiples were seen in the 2 week studies.

The results of the repeat dose toxicity studies in rats and dogs indicated that the primary adverse effect was the presence of eosinophilic granules in tissue macrophages throughout the body, including Kupffer cells of the liver, and macrophages of the intestinal mucosa, thymus, spleen, and lymph nodes. The appearance of the granules is most likely the result of oritavancin uptake by the macrophages. The eosinophilic granule containing macrophages were evident following two weeks of dosing, were associated with all dose levels, and were still evident following recovery periods. The eosinophilic granules were occasionally associated with mild inflammatory lesions, particularly in the liver, and some studies in rats showed an increase in serum globulin another indicator of inflammation.

The presence of eosinophilic granules did not occur following single dose administration by either IV bolus or slow infusion. Therefore, the observation of eosinophilic granules in repeated dose studies may have less clinical effect in the single dose setting.

Clinical findings associated with identifying the NOAELs in rats and dogs included decreased mean erythrocytic parameters such as erythrocyte count, haemoglobin and packed cell volume. The decrease in erythrocytes was typically accompanied with a regenerative response, indicated by an increase in reticulocyte count and evidence of increased extramedullary haematopoiesis in the splenic pulp and liver at higher doses. There were also increased levels of serum alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) and bilirubin that was associated with increased liver weights, macroscopic findings of pale livers, microscopic findings of eosinophilic granules in Kupffer cells, and occasional histopathologic findings of hepatocellular vacuolar degeneration and necrosis. There were slight effects in clinical chemistry parameters consistent with minimal effects on renal function including slight increases in blood urea nitrogen, sporadic increases in creatinine, and decreases in urine specific activity. These changes were occasionally associated with histopathologic findings such as renal cortical tubular nephrosis. Increased organ weights (absolute and relative) for liver, spleen and kidney were frequently observed. These findings had partially or completely reversed during the recovery periods. The clinical relevance of the haematology, hepatic and renal effects observed in rats and dogs observed with IV oritavancin was not provided by the applicant. However, the results of the SOLO clinical studies indicate that oritavancin-induced haematological, hepatic or renal effects in humans were similar to those seen in vancomycin-treated subjects.

The applicant states that in a 2 week study in rats, the increase in adrenal weight in the females dosed 15 mg/kg/day was probably secondary to the stress of toxicity.

In a 13-week toxicity study in rats administered IV doses of 5, 15, or 45/30 mg/kg/day oritavancin, mortalities occurred in all dose groups and control animals. The mortalities were attributed to increased bacterial infection in dextrose-vehicle treated animals.

In dogs, the most notable dose limiting toxicity was a moderate to severe histamine reaction that was most pronounced during the first few days of dosing and waned during the study period. The effects were manageable by pre-treatment with anti-histamines such as diphenhydramine hydrochloride and epinephrine, fluid therapy and oxygen. The severity of these reactions increased with higher doses or infusion rates and lessened with repeated administrations. There were no cardiovascular effects in dogs based on ECG recordings that showed normal cardiac rates, rhythm and conduction. ECG analysis was conducted at regular intervals during the 1 month and 13 week studies.

Genotoxicity

In genotoxicity studies conducted with oritavancin, there were no gene mutations or chromosomal damage observed in any of the studies. No mutagenicity or clastogenicity was observed in studies conducted with oritavancin spiked with 4.7% alkylated Factor A. Therefore, neither oritavancin nor the impurities in the drug substance were shown to be genotoxic.

Carcinogenicity

No carcinogenicity studies were conducted with oritavancin. This is acceptable. In view of the results of the genotoxicity studies conducted and the proposed short duration of clinical treatment with oritavancin, in compliance with ICH guidelines, carcinogenicity studies are not required.

Reproduction Toxicity

In rats administered IV doses of ≤30 mg/kg/day oritavancin, there were no adverse effects on gonadal function, mating performance, fertility or early gestation. The NOAEL for reproductive parameters was 30 mg/kg. In female rats administered IV doses of ≤30 mg/kg/day throughout a 2 week premating period, during mating (with groups of untreated males) and through gestation Day (GD) 7, no treatment-related effects on gonadal function, mating behaviour and reproduction was observed. In this study the NOAEL was 30 mg/kg. In another study, IV doses of ≤30 mg/kg/day oritavancin had no effect on implantation or embryo-fetal development when administered to rats during the pre-implantation period of pregnancy (GDs 0 to 5).

Embryo-fetal developmental studies were conducted in rats and rabbits administered IV doses of oritavancin. No embryo-fetal developmental effects were observed in rats administered ≤30 mg/kg oritavancin on GDs 6 to 17 or rabbits administered ≤15 mg/kg oritavancin on GDs 7 to 19.

In a pre and postnatal development study, F0 maternal body weight and food consumption were decreased after oritavancin administration in the 30 mg/kg group during the postnatal period. There were no adverse effects on pregnancy, parturition or lactation. Offspring (F1) of animals in the 30 mg/kg dose group had lower body weights during the study intervals although not during the post-weaning period (postnatal Days (PND) 8 to 57), but had normal physical development. F1 neuro-behavioural and reproductive functions were not affected by oritavancin administration at any dose. There were no oritavancin-related effects observed in the F2 generation. No oritavancin treatment-related effects were observed at doses ≤15 mg/kg/day in the F0 and F1 generations and 30 mg/kg in the F2 generation.

In juvenile toxicity studies in rats, administered oritavancin at doses of ≥15 mg/kg resulted in increased body weight and liver and spleen weights and decreased red blood cell count and haematocrit. Mortalities occurred in the 45/30 mg/kg/day dose group. No treatment-related effects were seen at 5 mg/kg/day.

In a juvenile toxicity study in dogs, oritavancin administered at doses of 15 and 45 mg/kg were associated with clinical observations and decreased mean body weights and body weight gains. Macroscopic and microscopic findings were associated with the injection sites, liver, and lymph nodes in the 45 mg/kg dose group. No oritavancin-related effects were present in the 5 mg/kg dose group. Juvenile dogs administered IV doses of 45 mg/kg for 30 days, showed vacuoles within hepatocyte cytoplasm that is suggestive of diffuse glycogen accumulation. This change was reported to account for the pale livers seen during necropsy. The applicant proposed that the juvenile animals may be more sensitive to anaphylactic-like reactions compared to adult animals. It is noted that the applicant has proposed to conduct 2 clinical studies to provide clinical safety, efficacy and pharmacokinetic data in the paediatric population.

Toxicokinetic data

In general, the systemic exposure of oritavancin increased with dose. However, repeated administration of oritavancin did not lead to an increase in its exposure or accumulation.

At the NOAELs in the pivotal repeated dose toxicity studies conducted with oritavancin in rats and dogs, AUC values achieved at the NOAEL doses were between 0.23 and 11.92x the recommended human AUC value. An adequate discussion of the low multiples of exposure to oritavancin seen in the pivotal repeated-dose toxicity studies in rats and dogs was not provided by the applicant. However, the non-clinical findings did not appear to be clinically relevant since the incidence of correlative findings in subjects in the SOLO clinical trials was low, with comparable rates and severity between the oritavancin and vancomycin-treated groups.

Local Tolerance

Injection site tolerability studies were not conducted with oritavancin. However, injection sites of rats and dogs were examined as part of the toxicity studies. Local irritations at the injection site, in particular during tail vein infusions in rats, were dose-related and often dose-limiting. In local tolerance studies conducted with rabbits, oritavancin had no effect on ear vein irritation and was a slight dermal and ocular irritant.

Antigenicity

No antigenicity studies with oritavancin were reported. Allergic reactions to oritavancin are reflected in section 4.3 and 4.4 of the SmPC.

Immunotoxicity

A series of studies were conducted to determine whether oritavancin affected immune function. In immunotoxicity studies in rats, no consistent effect on antibody response was observed, but evidence of a possible reversible decrease in host resistance was reported. *In vitro* studies were conducted to evaluate the functional status of macrophage cell lines incubated in the presence of oritavancin at concentrations that resulted in intracellular levels that exceeded those anticipated in humans administered the 1200 mg dose. The studies showed that oritavancin-loaded macrophage cells retained full functional capabilities.

Dependence

No dependence studies with oritavancin have been reported. This is acceptable as there is no indication that oritavancin would cause dependence.

Metabolites

No metabolite toxicity studies with oritavancin have been reported. This is acceptable as no circulating metabolites of oritavancin were detected in the plasma of any of the species studied.

Impurities

A study was conducted to qualify impurities present at different levels in different engineered lots of oritavancin in male rats. Oritavancin was administered to rats by IV infusion at dose levels of 28 mg/kg and 60 mg/kg. Mortality was observed at 60 mg/kg (Lot #1169-142) and adverse microscopic findings were observed locally at the infusion site for animals treated at 60 mg/kg (Lot #124RM5 and #23480-134). Based on these findings, there was no systemic toxicity associated with IV infusion of 28 mg/kg (Lot #1169-142) and 60 mg/kg (Lot #124RM5 and #23480-134).

In another study in rats administered IV doses of oritavancin spiked with alkylated Factor A to a level of 4.7% (Lot # FV3-LHK-210*AA) for 14 days, the 15 mg/kg dose group exhibited evidence of mild general toxicity (decreased body weight and food consumption), a mild inflammatory response (slight anaemia, leucopenia, and thrombocytopenia and increased serum globulin), and hepatic effects (increased serum transaminases and liver weight). These effects were generally not present in animals in the 5 mg/kg dose group. In addition, systemic phagocytosis of material presumed to be related to oritavancin (eosinophilic granule deposition) was observed in all dose groups, but was not associated with any evidence of toxicity in the 1 or 5 mg/kg dose groups. The effects noted in the current study were very similar to those observed in prior two week toxicity studies indicating that the presence of alkylated Factor A at a level of 4.7% did not increase toxicity. The NOAEL for oritavancin spiked with alkylated Factor A was considered to be 5 mg/kg.

A toxicity study was conducted in rats administered IV doses of 0 (vehicle), 5, 10, or 15 mg/kg oritavancin (Lot # 73743-196E) containing Total Known Impurities (18.8%), oritavancin Factor C (3.0%) and alkylated Factor A (3.8%) for 28 days. The findings in this study using oritavancin spiked with several impurities were similar to those of the other 28 day toxicity study conducted in rats with oritavancin Lot # 124RM5. The NOAEL for the current study was 5 mg/kg.

An additional 2 week repeat dose toxicity study was conducted in rats administered IV doses of 1, 5, or 15 mg/kg oritavancin that contained higher amounts of the impurities Dev A, oritavancin Factor C, related substance M, and alkylated Factor A compared to Lot 124RM5 that was used in prior toxicity studies. The effects of oritavancin on haematological endpoints, as well as the spleen and upon the liver observed in the 15 mg/kg dose group are generally consistent with prior findings in rats. The effects observed in the 5 mg/kg dose group were slight, more evident in females than males and considered transitional and non-adverse. The NOAEL was considered to be 5 mg/kg which is consistent with other toxicity studies using different lots of material. However, there were three unscheduled deaths in this study. It was stated that the amount of intracytoplasmic granular material within histiocytes/mononuclear cells of the tissues examined suggested that these three animals may have had higher exposure levels than other animals within the 15 mg/kg/day dose group. The three unscheduled deaths were attributed to bacteraemia/septicaemia and not to oritavancin.

Other toxicity studies

In several studies there was an increase in activated partial thromboplastin time (APTT). A subsequent in-vitro study determined that increased APTT is a result of oritavancin binding to phospholipids present in the assay system. Consequently, it should be noted that APTT results are dependent on the timing that blood samples are taken for analysis. An investigative in-vivo study in rats established a direct correlation between oritavancin plasma levels and increased APTT but this result was discounted due to data indicating that oritavancin artificially prolongs APTT.

In an *in vitro* study, the killing of *Candida albicans*, *S. aureus*, and *Acinetobacter baumannii* remained intact after the loading of mouse or human macrophages to substantial intracellular levels of oritavancin or azithromycin. These data indicated that the accumulation of oritavancin in macrophages does not prevent phagocytic killing of key pathogens. In addition, in mouse or human macrophage cell lines, oritavancin did not significantly affect the measured cellular functions i.e. phagocytosis of the Gram-negative pathogen *Pseudomonas aeruginosa*, generation of reactive oxidant species, endocytosis, lysosomal integrity and metabolic activity. The phagocytosis of latex beads by mouse macrophages was reduced by 50 % but was unaffected in human macrophages. In an *in vivo* study in rats, single IV doses of ≤30 mg/kg oritavancin were not associated with eosinophilic granule formation.

Ecotoxicity/environmental risk assessment

Environmental risks from the societal use of oritavancin were characterised using its physical-chemical and environmental fate properties, conservatively predicted environmental exposure levels, and predicted environmental toxicity.

Several studies were conducted previously to assess the environmental fate and effects of oritavancin. However, the underlying study reports were unavailable for several historical studies and no chronic toxicity testing had been conducted to date. As a result, several new studies were completed and results were incorporated into the ERA: Municipal Sewage Sludge Adsorption/Desorption Coefficient (US EPA OCSPP 835.1110); Aerobic Transformation in Aquatic Sediment Systems (OECD 308); Activated Sludge Respiration Inhibition Test (OECD 209); Sediment/Water Chironomid Toxicity Test (OECD 218); Algal Growth Inhibition (OECD 201); Fish, Early Life Stage (OECD 210); and Daphnid Reproduction Test (OECD 211). All final test reports were submitted.

Oritavancin was screened for PBT using a stepwise procedure in accordance with REACH Guidance and was found to not be a PBT substance. In Phase I, a conservatively estimated $PEC_{SURFACEWATER}$ (not accounting for removal during sewage treatment, environmental degradation, or human metabolic losses) was derived. Oritavancin's $PEC_{SURFACEWATER}$ exceeded the action value, triggering a Phase II assessment.

Phase II – Environmental Fate and Effects Analysis

Environmental Fate

Adsorption Desorption behaviour

The submitted test on adsorption is acceptable. The results are mentioned in the table of main study results. The CHMP uses the K_D value of 1375 for the $PEC_{sediment}$ calculation.

Transformation in water-sediment systems

The very low DT50 values in the OECD 308 give the impression that there is a high transformation in water sediment systems. For evaluating these results it should be noted there is a very high amount of the substance or its transformation products (TP) which is partitioning into the sediment compartment where it is not extractable any more. Consequently, it cannot be excluded that the parent compound or some of the TP are persistent in the environment. At the end of the test one TP is increasing which gives further evidence of persistence.

Environmental Effects

Toxicity to aquatic organisms and microorganism

The most sensitive organism is the algae *Anabaena flos-aquae.* The submitted effect test is not valid because the variation coefficient for section-by-section growth rate is clearly higher than required by the OECD protocol 201 (50% in the test, 35% required by the guideline). As it is demonstrated in public available literature the requirements of the OECD guideline are feasible also for *Anabaena flos-aquae (*Ebert et al., 2011)[1]. Therefore the CHMP asks for a new test. The long-term tests on daphnids, fish and sediment organisms (Chironomus riparius) are valid to the requirements of the OECD guidelines and were accepted by the CHMP. The results are included in the summary of main study results.

Table 1. Summary of main study results

Substance (INN/Invented Name):
CAS-number (if available):

[1] I. Ebert, J. Bachmann et al.; Toxicity of the fluoroquinolone antibiotics enrofloxacin and ciprofloxacin to photoautotrophic aquatic organisms; Environmental Toxicology and Chemistry, Vol. 30, No. 12, pp. 2786–2792, 2011

PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	-0.64			Potential PBT (N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	-0.64			not B
	BCF	no data			B/not B
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$, refined (prevalence, dose regime)	0.02	µg/L			> 0.01 threshold (Y)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 or …	*(K_{oc}* = 3620) K_D = 1357			K_{OC} not relevant because no correlation available
Ready Biodegradability Test	OECD 301	No biodegradation			Not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ =2.65 $DT_{50, sediment}$ = not available $DT_{50, whole\ system}$ =2.65 % shifting to sediment = 70 (day 14) Non-Extractable Residues (NER) = 50 – 70% at test end			potentially persistent because of high NER and increasing TP amount (>10%) at the end of the study
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*anabaena flos-aquae*	OECD 201	NOEC		µg/L	**Not valid, open issue**
Daphnia sp. Reproduction Test	OECD 211	NOEC	460	µg/L	Mean measured concentration
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210	NOEC	28	µg/L	Mean measured concentration
Activated Sludge, Respiration Inhibition Test	OECD 209	EC10	14.5	mg/ L	Nominal concentration
Phase IIb Studies					
Sediment dwelling organism, *Chironomus riparius*	OECD 218	NOEC	90	mg/ kg	Mean measured concentration

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points to be addressed:

The ERA cannot be concluded on the risk for surface water. The applicant is asked to provide a new study which meets all validation criteria of the OECD guideline 201.

2.3.5. Discussion on non-clinical aspects

The primary adverse effect of oritavancin administration to rats and dogs was a dose related accumulation of eosinophilic granules in tissue macrophages including hepatocytes, renal cortical epithelial cells, adrenal cells and macrophages of the reticulo endothelial system. The appearance of the eosinophilic granules did not occur following single dose administration and did not significantly affect innate macrophage function *in vitro* at intracellular levels anticipated from a single 1,200 mg dose.

Moderate, dose-related increases in liver enzymes (alanine transaminase and aspartate transaminase) were observed in rats and dogs and were shown to be reversible upon cessation of treatment. Biochemistry changes associated with kidney function including decreases in urine-specific gravity and pH and slight increases in blood urea nitrogen and sporadic increases in creatinine were present in both rat and dog after treatment of two weeks. Extramedullary haematopoiesis in the spleen was observed in rats. This histopathological finding correlated with an enlargement and an increase in the weight of the spleen. The exposure in rats at the no observed adverse effect level (NOAEL) was less to only slightly higher than the human exposure based on the AUC.

Histamine-like infusion reactions following immediately or shortly after dosing with oritavancin occurred in both rats and dogs. These reactions were associated with mortality at lower dosages in male than in female rats in single dose studies; however, the same gender-related differences were not observed in other species. Studies in neonatal rats and dogs for 30 days showed the same tissue effects as those seen in adult animals including sensitivity to the oritavancin-mediated histamine-like infusion reactions. Mortality was observed in neonatal rats at slightly lower dosage levels than in adults.

A standard battery of in-vitro and in-vivo tests on the genotoxic potential did not reveal any clinically relevant findings. Lifetime studies in animals have not been conducted to evaluate the carcinogenic potential of oritavancin.

When administered intravenously at doses up to 30 mg/kg, oritavancin did not affect the fertility or reproductive performance of male and female rats. Studies in pregnant rats and rabbits do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. There was no evidence of transplacental transfer of oritavancin in pregnant rats. The exposure in rats at the NOAEL was less to only slightly higher than the human exposure based on the AUC.

Following a single intravenous infusion in lactating rats, radio-labelled **[14C]**oritavancin was excreted in milk and absorbed by nursing pups.

With regards to the ERA, no final conclusion on environmental risk assessment is possible, because it cannot be concluded on the risk for surface water. The effect test to algae should be repeated.

2.3.6. Conclusion on the non-clinical aspects

The CHMP considers the following measure necessary to address the issue related to non-clinical aspects:

Environmental Risk Assessment

The submitted effect study on algae is not valid. The applicant is asked to provide a new study which meets all validation criteria of the OECD guideline 201.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

In study ARRI 20/21 patients enrolled at site 131 were excluded from the CE population because of drug accountability and unblinding issues. The sponsor audited three sites that participated in the study and the US FDA inspections of the sponsor did not raise any major issues.

In study SOLO II there was one study site (207002) at which patients were screened for study entry but the ruler measurements and planimetry of the index infection site occurred after surgical treatment of the lesion. The signs and symptoms associated with the index lesion and its size prior to surgical treatment were not reported in the eCRF. There were 58 patients enrolled at this site and to compensate for this error an additional 58 patients (over the planned 960 patients) were enrolled at other sites. Sensitivity analyses of early clinical response, investigator-assessed clinical cure at PTE, lesion size reduction ≥ 20% at ECE and sustained clinical response at PTE in the MITT and CE populations were conducted excluding the data from this site.

The development programme/compliance with CHMP guidance/scientific advice

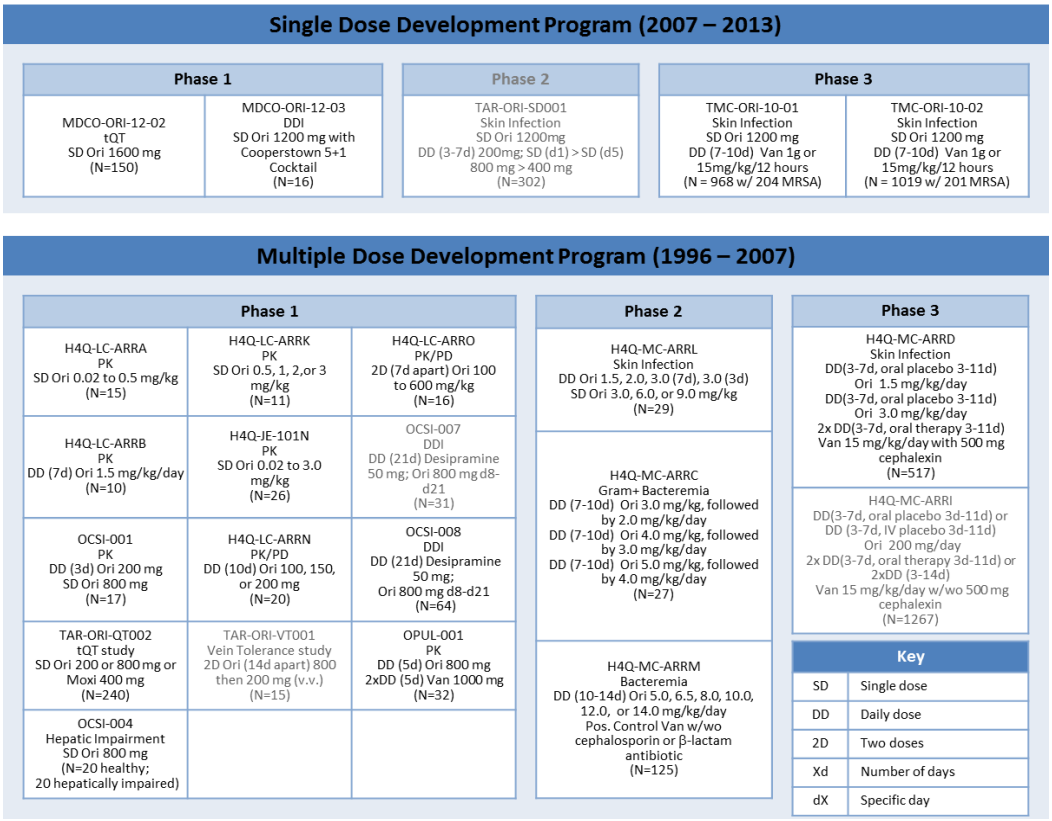
In the initial MAA of 2008, the prior applicant (Targanta) sought approval for oritavancin to treat cSSTI using 200 mg IV daily for 3-7 days. Due to concerns that mainly centred around the single pivotal study and issues raised by the results, including the comparative cure rates for MRSA, as well as new data that became available during the procedure suggesting that the once daily regimen was not optimal, the application was withdrawn. In parallel, the application to FDA was also withdrawn.

Subsequent to this withdrawal, CHMP scientific advice was sought in 2010 mainly to discuss the plans for two new pivotal Phase 3 studies in cSSTI using the 1200 mg single dose regimen. The applicant's justification for pursuing the 1200 mg single dose, based on revised PK/PD analyses and the results of the additional study TAR-ORI-SD001 (SIMPLIFI), was accepted. The design features of the two planned studies were also generally acceptable, with a few suggestions made.

Additional questions concerned the plan for bioburden testing of the drug product, the possible need to conduct additional non-clinical studies and/or a new TQT study with doses adequate to cover the new regimen, the sufficiency of completed and planned investigations to further assess any impact of accumulation within macrophages and the proposal for further evaluation of DDIs.

The two new Phase 3 studies that have assessed a 1200 mg single dose for treatment of cSSTI (SOLO I and II) have been designed in accordance with CPMP/EWP/558/95 Rev 2 and they also comply with the recommendations made in the Addendum to this guideline.

- Tabular overview of clinical studies



Note: Studies in grey did not include PK sampling. Total patient numbers represent randomized patients.

2.4.2. Pharmacokinetics

Oritavancin pharmacokinetics was assessed in subjects and patients in the studies as shown in the above table: Phase 1 (13 trials), 2 (3 trials) and 3 (3 trials).

A range of different assay methods have been used and at different laboratories during the long clinical development period, including initially RIA, HPLC with fluorescence detection and LC/MS/MS. The latter was used in the majority of studies for determining concentrations in plasma and other fluids with a linear range for plasma and urine of 12.5 – 1000 ng/mL. Oritavancin binds to labware surfaces at low drug concentrations. This does not occur in the presence of plasma or 0.002% polysorbate-80. For RIA all assays were performed in a solution that contained 0.05% Tween-20 and 0.05% Triton X-100. In the HPLC-based assays all dilutions were at pH ≤ 3, which prevents binding to surfaces. A cross-study comparison of plasma levels of oritavancin using RIA, LC-fluorescence and LC/MS/MS demonstrated the consistency of the results derived from the three assay methods for similar or identical administered doses.

ADME

Single dose studies

In **ARRK** oritavancin was administered over 30 min in 300 mL D5W at 0.5, 1, 2 or 3 mg/kg. The ranges observed for PK parameters are shown below.

Table 2

Dose range (mg/kg)	C_{max} (µg/mL)	$AUC_{0-\infty}$ (µg•h/mL)	CL_p [a] (L/h/kg)	V_{ss} (L/kg)	$t_{1/2\gamma}$ (h)
0.5 to 3.0	7.17 to 70.7	91.0 to 914	3.3 to 8.3 $x10^{-3}$	0.65 to 1.92	132 to 356

In **JE-101N** the doses ranged from 0.02 up to 3.0 mg/kg. The mean Vss was 65.2 L/kg and t½ ranged from 7-13 days. There was no statistically significant relationship detected between plasma clearance or Vss and body weight. Plasma AUC0-inf and Cmax increased in a dose-proportional fashion over the range 27.5 mg to 208 mg (a 7.6-fold range).

Figure 1

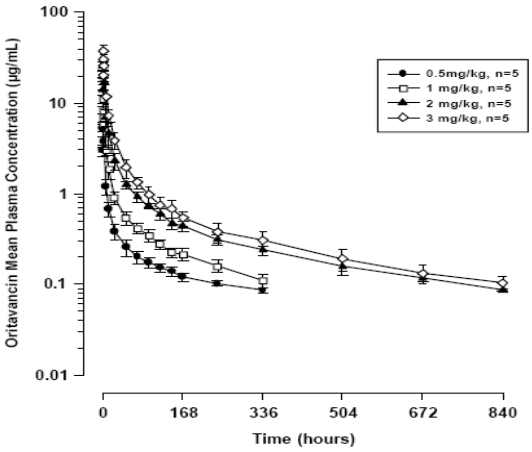


Table 3

Table 101N.11.1. Summary of Descriptive Statistics of Pharmacokinetic Parameters of Oritavancin by Dose Group

Dose (mg/Kg)	Statistics	Total dose (mg)	T_{max} [b] (hr)	C_{max} (µg/mL)	$t_{1/2}$ (hr)	$AUC_{0-\infty}$ (µg*hr/mL)	Cl (L/hr)	Vz (L)	Vss (L)
0.50[a]	Geom. Mean	30.6	--	5.27	239	100	0.306	105	77.9
	Mean	30.7	0.50	5.29	240	101	0.306	106	78.8
	SD	1.98	--	0.455	29.7	11.0	0.0187	14.3	12.4
	Min	27.5	0.50	4.56	202	81.5	0.289	84.1	60.7
	Max	32.8	0.50	5.78	283	109	0.338	122	90.7
	CV%	6.45	--	8.60	12.4	10.9	6.10	13.5	15.7
1.0 [a]	Geom. Mean	59.5	--	11.0	171	177	0.336	82.9	52.2
	Mean	59.8	0.50	11.0	178	179	0.340	85.3	53.7
	SD	5.91	--	1.19	55.9	26.5	0.0595	22.0	13.7
	Min	50.8	0.50	9.71	118	152	0.282	58.3	36.1
	Max	66.2	0.52	12.4	244	222	0.435	105	69.4
	CV%	9.88	--	10.8	31.4	14.8	17.5	25.8	25.5
2.0 [a]	Geom. Mean	131	--	25.5	282	444	0.296	121	66.2
	Mean	131	0.50	25.7	285	448	0.299	121	66.7
	SD	7.71	--	2.57	45.0	67.9	0.0440	9.07	9.56
	Min	124	0.50	21.3	217	357	0.236	109	55.1
	Max	142	0.50	27.8	342	548	0.347	132	77.3
	CV%	5.87	--	10.0	15.8	15.1	14.7	7.50	14.3
3.0 [a]	Geom. Mean	177	--	37.3	318	641	0.276	127	59.2
	Mean	178	0.50	37.7	322	650	0.282	131	61.4
	SD	19.4	--	6.11	58.4	118	0.0655	35.5	17.9
	Min	160	0.50	31.9	257	526	0.207	87.4	41.8
	Max	208	0.50	46.0	392	774	0.375	170	83.9
	CV%	10.9	--	16.2	18.1	18.2	23.2	27.2	29.2

[a] N = 5; [b] Median T_{max} values are shown instead of means.

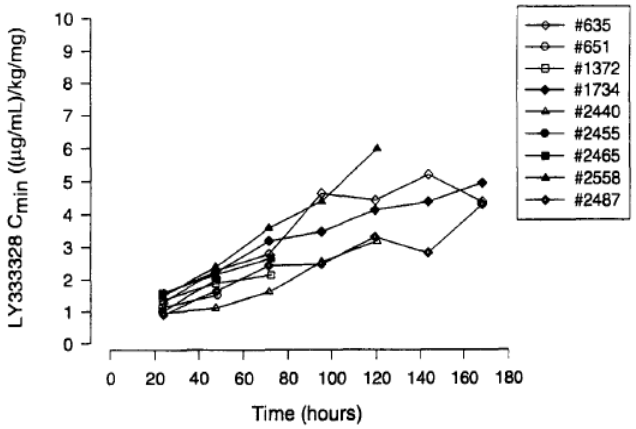
Multiple dose studies

In **ARRB** 1.5 mg/kg/day oritavancin was administered intravenously over 30 min in up to 300 mL D5W once daily for 2-7 days. Based on data from 9 male subjects, Cmax ranged from 14.5 - 28.7 µg/mL after the first dose and concentrations at the end of the first 24-h dosing interval ranged from 0.90 - 1.57 µg/mL. No apparent increase in Cmax was observed with multiple dosing. Individual dose/weight-normalised Cmax values were consistent across doses.

Dose range (mg)	$AUC_{0-\infty}$ (µg•h/mL)	CL_p (L/h)	V_{ss} (L)	$t_{1/2\gamma}$ (h)
99 to 118	297 to 576	0.181 to 0.393	54.8 to 58.4	250 to 356

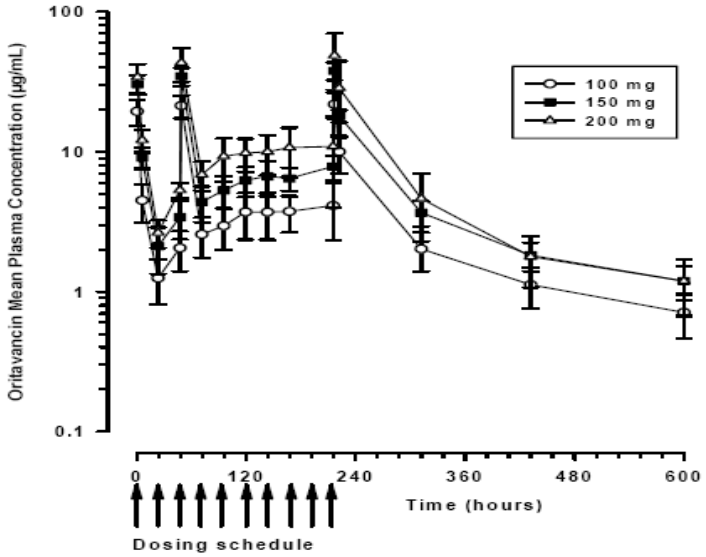
Modest accumulation (approximately 2.83-fold) was observed in Cmin after seven daily doses.

Figure 2



In ARRN the final doses administered were 100, 150 and 200 mg given over 30 or 60 minutes in 50 or 100 mL D5W once a day for 10 days. The mean AUC ratios indicated accumulations of 2.3 to 2.6-fold at the three dose levels. Cmin increased by 2.4 - 2.8-fold and there was no significant increase in Cmax. No statistically significant dose effect was observed on the accumulation ratios.

Figure 3



Protein binding

An initial in-vitro study suggested that oritavancin is 85.7%, 88.8% and 89.9% bound to human plasma proteins at respective drug concentrations of 1, 10 and 91 µg/mL. Most binding of oritavancin in serum was to albumin. The study did not take into account non-specific binding losses but the estimated protein binding was very similar to that obtained in a later study (85%), which used a validated growth-based

method. A further study using a biophysical method that employs cantilever arrays gave an estimated fraction bound to HSA of 0.79 when testing 0.1 µM oritavancin in 600 µM HSA.

Volume of distribution

Based on POPPK analysis, the central volume of distribution (Vc) in humans is 5.9 L, which is similar to plasma volume but the total volume of distribution (Vc + V2 + V3) is approximately 100 L, suggesting that oritavancin is widely distributed to tissues.

Oritavancin was found to be excreted in breast milk in non-clinical studies and data in nursing pups indicated that oritavancin is absorbed by these neonatal animals

OCSI-001 assessed blister fluid levels in healthy male subjects. Oritavancin levels were maximal in blister fluid after 9 to 10 h after the last dose and became undetectable 100 to 150 h after the last dose.

The mean AUC blister/AUC plasma ratios at 24 h were similar at the two dose levels examined, indicating that at both dose levels the blister fluid exposures were ~20% of plasma exposures. Since 10-14% oritavancin is unbound to serum proteins the blister fluid AUC was slightly higher than predicted, suggesting that inflammation might have enhanced the passage of oritavancin from blood to blister fluid. Whether macrophages which accumulate oritavancin and migrate to inflamed tissues contributed to this enhancement is unknown.

Table 4

Table 11.2 Noncompartmental Pharmacokinetic Parameters and Summary Statistics for Oritavancin in Plasma and Blister Fluid

PK Parameters Mean (SD)	Plasma		Blister Fluid	
	200 mg QD x 3d	800 mg x 1	200 mg QD x 3d	800 mg x 1
C_{max} (µg/mL)[a]	46.2 (10.7)	136.6 (28.6)[b]	5.85 (3.05)	12.2 (4.70)[a]
T_{max} (h)	1.00 (0.00)	1.50 (0.00)	10.0 (6.05)	9.50 (3.67)
C_{12} (µg/mL)	17.2 (4.42)	35.4 (11.2)	3.90 (1.53)	11.4 (4.90)
C_{24} (µg/mL)	10.3 (2.99)	19.1 (7.56)	3.12 (1.37)	5.64 (4.0)
AUC_{0-24} (µg·h/mL)[b]	457 (99.4)	1111 (316)[b]	90.7 (35.7)	208 (76.7)[a]
AUC_{0-t} (µg·h/mL)[b]	1146 (277)	2267 (762)[b]	116.1 (84.9)	376.0 (282.76)

Abbreviations: AUC_{0-24} = area under the plasma/blister fluid concentration-time curve from time zero to 24 hours; AUC_{0-t} = area under the plasma/blister fluid concentration-time curve from time 0 to time t; C_{12} = concentration at 12 hours; C_{24} = concentration at 24 hours; C_{max} = maximum concentration; PK = pharmacokinetic; QD = every day; SD = standard deviation

[a] Statistically significant ($p < 0.005$)

[b] PK parameter was tested for a difference between treatment groups

OPUL-001 compared concentrations of oritavancin and vancomycin in plasma, epithelial lining fluid (ELF) and alveolar macrophages (AM). Each subject was to have a single bronchoscopy and BAL performed after the start of the last dose of study drug. Blood was collected for up to 48 h post-last dose. The highest ELF concentration of oritavancin was detected in the samples at 24 h post-dose (6.3 µg/mL) but the highest plasma concentration was detected at 4 h (119.6 µg/mL), which suggested that oritavancin slowly distributed into and out of the ELF. The estimated AUC0-24 in AM was 31-fold that in ELF.

Table 5

Table 9.2 Plasma, ELF, and AM Concentrations (Mean ± SD) at Time of Bronchoscopy and BAL

Sampling time[a]	Plasma (μg/mL)		ELF (μg/mL)		AM (μg/mL)	
	Orit	Vanco	Orit	Vanco	Orit	Vanco
4 hours	119.6 ± 24.58	19.8 ± 3.69	3.1 ± 1.05	5.3 ± 1.48	121.9 ± 69.12[b]	32.0 ± 8.52
12 hours	75.7 ± 16.31[c]	5.1 ± 1.74	3.7 ± 2.45	2.4 ± 0.73	113.1 ± 49.71	45.2 ± 23.28
24 hours	73.7 ± 28.2	ND	6.3 ± 1.46	ND	179.4 ± 76.68	ND
7 days	10.4 ± 3.0	ND	1.7 ± 0.80	ND	557.9 ± 481.42	ND

Note: There were 5 subjects per sampling period, unless otherwise indicated.

Abbreviations: AM = alveolar macrophage; ELF = epithelial lining fluid; ND = not done; Orit = oritavancin; Vanco = vancomycin.

[a] Blood sample collection following completion of last drug infusion.

[b] Two of 5 subjects had concentrations ≥ the quantitative limit of detection and adequate total cell count.

[c] Four of 5 subjects had concentrations ≥ the quantitative limit of detection.

- Excretion

In rats, mice and dogs the mass balance studies demonstrated slow elimination of oritavancin via urine and via bile into the faeces. There was prolonged retention of radioactivity after single doses of [14C]oritavancin.

In **ARRK** (single doses from 0.5 to 3 mg/kg) plasma concentrations of oritavancin followed a tri-exponential decline and were mostly < 10% of Cmax within 24 h. A three-compartment model was selected as the most appropriate for all subjects based on the comparisons of objective function values and standard error of the estimates. The mean t1/2 was estimated to be 251 h (approximately 10.5 days). The area under the terminal phase represented more than 50% of total AUC. Less than 3.1% of the administered dose was recovered in the urine after 2 weeks of collection. The mean systemic plasma clearance (CLp) was estimated at 0.0896 mL/min/kg.

In the multiple dose study **ARRB** plasma concentrations followed a tri-exponential decline to < 20% Cmax within 24 h. The estimated mean terminal half-life of oritavancin was 277 hours (11.5 days). The model-predicted mean clearance was 0.0682 mL/min/kg and mean systemic plasma clearance (CLp) was 0.306 L/h. The applicant has concluded that oritavancin is excreted unchanged in faeces and urine. Mean population-predicted half-lives in patients were similar to those in healthy volunteers with α, β and γ half-lives of approximately 2, 31 and 393 h, respectively.

- Metabolism

A mass balance (metabolite profiling) study using radiolabelled oritavancin has not been performed in man. Oritavancin was not metabolised in studies in dogs and rats.

In human liver microsomes using oritavancin (10 or 100 μM) no unique metabolite peak that was dependent on the NADPH-generating system, microsomal protein and substrate concentrations was detected by fluorescence or UV methods. There was no difference in the area under the peak curve of oritavancin in control experiments compared to those without NADPH or microsomes i.e. no depletion of oritavancin due to metabolism could be detected. The conclusion was that there was no evidence that oritavancin is metabolised by the human cytochrome P450 system.

Dose proportionality and time dependencies

In ARRO after 100 mg and 600 mg doses the mean Cmax and AUC0-∞ increased proportionally with dose from 24.1 to 111 μg/mL and from 280 to 1560 μg•h/mL, respectively. The Vdss and CLp were consistent across the dose range studied (65.8 L [0.83 L/kg] and 0.431 L/h, respectively). No effect of body weight or gender (7/16 with data were female) was observed on CLp or Vdss. The mean documented t1/2 was 194 h (8 days).

Figure 4

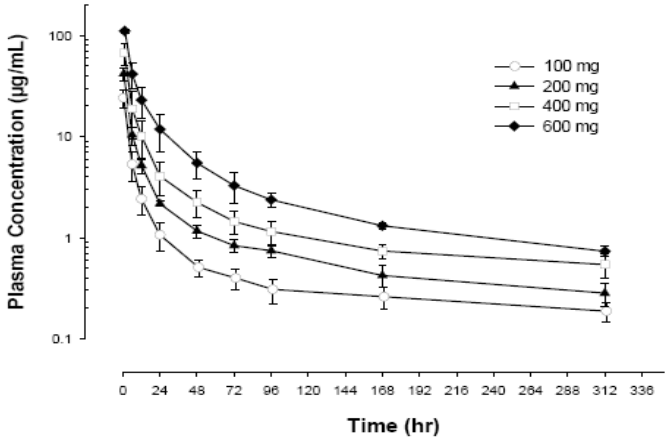


Table 6

Table ARRO.11.2. Oritavancin Dose Proportionality Assessment by Slope of the Power Model

Pharmacokinetic Parameter	Slope of Power Model	95% Confidence Interval for Slope
C_{max} [a]	0.869	0.641, 1.096
AUC_{0-24}	1.018	0.814, 1.222
AUC_{0-t}	1.028	0.841, 1.215
$AUC_{0-\infty}$	0.943	0.759, 1.127

[a] For the C_{max}, 100-mg group was not included in the power model.

Oritavancin does not appear to demonstrate time-dependent PK.

Pharmacokinetics in target population

In SOLO I and II patients enrolled at selected sites underwent PK sampling at 3, 12, 24, 72 and 576 h after the start of the infusion. A pooled analysis was conducted based on a total of 1337 plasma concentrations from 110 patients in SOLO I and 187 in SOLO II, including 4-5 values from the majority of the patients. Plasma exposure and secondary PK parameter estimates were calculated for each patient by simulating a concentration-time profile using the final model or using accepted PK equations. The structure of the previous POPPK model provided an excellent fit to the concentration-time data. Excellent fits to the individual patient PK data were obtained. Summary statistics of the derived PK exposures, stratified by study and pooled across studies, showed a Vss ~100 L, indicating wide distribution. The estimated t1/2 values indicated rapid initial distribution followed by a slower secondary distribution phase and slow terminal elimination.

Table 7

Table 4-9. Summary statistics for individual, model-derived oritavancin plasma exposure and secondary PK parameters for all patients included in the PK population (n = 297)

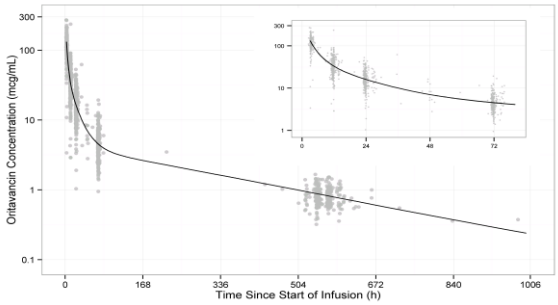
	Mean (CV%)	Median	Min	5th	25th	75th	95th	Max
V_{ss} (L)	97.8 (56.4%)	90.2	15.1	47.3	69.1	115	158	615
C_{max} (µg/mL)	138 (23.0%)	135	11.1	93.9	120	154	187	319
C_{min} (µg/mL)	2.06 (195%)	0.881	0.264	0.645	0.764	1.04	7.69	42.8
T_{min} (h)	482 (39.8%)	555	11.4	71	542	571	597	979
AUC_{0-24} (µg•h/mL)	1110 (33.9%)	1050	109	686	885	1300	1720	4060
AUC_{0-48} (µg•h/mL)	1390 (36.5%)	1310	172	836	1080	1630	2160	5370
AUC_{0-72} (µg•h/mL)	1530 (36.9%)	1430	223	910	1190	1790	2420	5900
AUC_{0-576} (µg•h/mL)	2510 (31.4%)	2350	607	1590	2000	2920	3750	7750
$AUC_{0-\infty}$ (µg•h/mL)	2800 (28.6%)	2640	832	1860	2270	3200	4070	8070
$T_{1/2,\alpha}$ (h)	2.29 (49.8%)	2.01	0.0192	1.01	1.55	2.78	4.43	6.97
$T_{1/2,\beta}$ (h)	13.4 (10.5%)	13.1	7.75	12.0	12.6	14.0	16.2	20.3
$T_{1/2,\gamma}$ (h)	245 (14.9%)	242	139	192	222	262	308	435

Abbreviations:
Vss = Steady-state volume of distribution, C_{max} = Maximum plasma concentration; peak plasma concentration, C_{min} = Minimum plasma concentration, T_{min} = Time of minimum drug concentration, AUC_{0-24} = Area under the plasma concentration-time curve from time zero to 24 hours, AUC_{0-48} = Area under the plasma concentration-time curve from time zero to 48 hours, AUC_{0-72} = Area under the plasma concentration-time curve from time zero to 72 hours, AUC_{0-576} = Area under the plasma concentration-time curve from time zero to 576 hours, $T_{1/2}$ = Half-life, $T_{1/2,\alpha}$ = Half-life for the alpha phase, $T_{1/2,\beta}$ = Half-life for the beta phase, $T_{1/2,\gamma}$ = Half-life for the gamma phase, CV% = Coefficient of variation (percent coefficient of variation)

Mean oritavancin concentration over time, overlaid on the observed concentrations, is shown below.

Figure 5

Mean Concentration-Time Profile Following Oritavancin 1200 mg IV over 3 h – Semi-Log Scale



The POPPK parameter estimates showed that the volume of distribution was about 50% lower in the SOLO vs. previous clinical studies. In addition, the mean T1/2,β and T1/2,γ values in SOLO I and II were substantially lower than those observed in previous Phase 2/3 studies. For example, mean T1/2,β in the 297 patients from SOLO I and SOLO II was 13.4 h vs. a mean of 31.2 h in the 360 Phase 2/3 patients included in the previous analysis while mean T1/2,γ values were 245 and 393 h, respectively. In contrast, the mean T1/2,α values were similar (2.29 h vs. 2.04 h).

The applicant considered that the contrasts may reflect differences in dose regimen, duration of infusion and PK sampling schemes. The duration of PK sampling in ARRL and ARRD (49% of patients in prior analysis) was 24 h vs. 576 h in the SOLO studies. Sampling was also relatively dense in the previous Phase 2/3 studies (> 10 per patient) while a maximum of 5 per patient were obtained in the SOLO studies, albeit at optimal times. Despite the differences in β and γ T1/2 estimates the dose-normalized AUC0-24 values were similar.

Traditional covariate model building techniques identified two statistically significant relationships:

i) A relationship between age and Vc, where Vc decreased with increasing age and

ii) A relationship between height and CL, where CL increased with increasing height

These relationships explained a relatively small amount (<5%) of inter-individual variability in oritavancin PK. Patient age and height were only modestly related to clinically relevant PK parameters (i.e. C_{max} and AUC_{0-72}). Therefore, dose modifications were not considered necessary based on age or height.

Special populations

- Impaired renal function

In the POPPK analysis renal function had no impact on PK oritavancin within the range of CLcr observed in patients (29.8 – 216 mL/min/m^2). The scatterplot of dose-normalized AUC0-72 vs. CLcr showed a lack of any clear relationship between the two parameters. The table shows the summary statistics by renal function category. Note that estimates for severe renal impairment are based on only 3 patients.

Table 8

Table 4-14. Summary statistics of oritavancin plasma exposures for all patients included in the pooled SOLO I and SOLO II PK population, stratified by renal function category (n=297)

Race	Normal >90 mL/min/1.73m² (n=213)		Mild Impairment 60-89 mL/min/1.73m² (n=59)		Moderate Impairment 30-59 mL/min/1.73m² (n=22)		Severe Impairment <30 mL/min/1.73m² (n=3)	
Variable	**Mean (SD)**	**Median (Min- Max)**	**Mean (SD)**	**Median (Min- Max)**	**Mean (SD)**	**Median (Min- Max)**	**Mean (SD)**	**Median (Min- Max)**
C_{max} (µg/mL)	134 (26.2)	133 (49.2 - 210)	143 (36.7)	139 (50.9 - 319)	151 (53)	152 (11.1 - 238)	173 (34.9)	166 (143 - 211)
AUC_{0-24} (µg·h/mL)	1110 (314)	1070 (258 - 2420)	1140 (516)	1010 (320 - 4060)	1110 (512)	996 (109 - 2320)	1190 (394)	1050 (895 - 1640)
AUC_{0-48} (µg·h/mL)	1390 (436)	1330 (298 - 3460)	1400 (676)	1230 (395 - 5370)	1350 (648)	1190 (172 - 3070)	1450 (537)	1250 (1050 - 2060)
AUC_{0-72} (µg·h/mL)	1540 (493)	1470 (325 - 3940)	1530 (739)	1340 (443 - 5900)	1480 (715)	1300 (223 - 3470)	1590 (606)	1350 (1140 - 2280)
AUC_{0-576} (µg·h/mL)	2530 (712)	2390 (607 - 5560)	2460 (941)	2240 (915 - 7750)	2430 (1040)	2120 (818 - 5740)	2600 (979)	2220 (1870 - 3710)
$AUC_{0-\infty}$ (µg·h/mL)	2810 (729)	2670 (832 - 5980)	2760 (955)	2530 (1170 - 8070)	2720 (1040)	2380 (1180 - 5930)	2890 (963)	2500 (2190 - 3990)

An in-vitro study evaluated the clearance of oritavancin by conventional (low-flux), high-flux and CRRT dialysis filters. The mean dialytic clearance value was found to be zero for the low-flux filters (absolute calculated value - 6.0 ml/min), zero for the high-flux filters (absolute calculated value - 5.8 ml/min) and zero for the CRRT dialysis (absolute calculated value - 5.2 ml/min).

- Impaired hepatic function

OCSI-004 was a single-dose, open-label, parallel-group study to compare administration of oritavancin to subjects with Child-Pugh Class B (score 7-10) liver insufficiency and healthy subjects who were matched approximately on the basis of sex, ± 5 years of age, ± 30% body weight and smoking habits. Each subject received a single 800 mg dose of oritavancin.

At every sampling time point oritavancin plasma concentrations were approximately 10% to 15% lower in subjects with hepatic impairment compared with healthy subjects. Mean Cmax, AUC0-24 and AUC0-t were all slightly lower in subjects with hepatic impairment. However, AUCs were more variable than among healthy subjects. The mean Tmax values were similar.

Despite the matching process, the subjects with hepatic impairment had higher body weight, lower serum albumin and higher incidence of ascites, which were all thought to contribute to a larger apparent Vd and hence lower plasma concentrations compared to healthy subjects.

Table 9

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)

In a second statistical analysis (in which PK parameters, including AUC values and Cmax, were adjusted by multiplying the value by the individual body weight and then dividing by the baseline albumin value within each subject) the adjusted AUC0-t, AUC0-24 and Cmax values were still numerically lower in the subjects with hepatic impairment compared to normal subjects but 90% CIs around the ratios were within the range of 0.80 to 1.25. The applicant concluded that the rate and extent of oritavancin exposure was numerically lower in subjects with hepatic impairment but the observed differences were small (the magnitude is less than would be seen in patient to patient variability) and did not indicate a need for dose adjustment. Unbound (free) oritavancin was not measured in this study.

- Elderly

After administration of Oritavancin, C_{max} increased modestly with increasing age, whereas AUC slightly decreased with increasing age. The data suggest that no dose adjustment is needed based on patient age.

- Children

No studies in children were conducted.

- Other factors

From the covariate analysis the applicant concluded that gender does not *per se* have a dramatic impact on the PK of oritavancin. Mean and median Cmax and AUC values were consistently higher in female patients with larger ranges but the applicant proposed this was most likely a reflection of the relationship between height and CL. Based on the results of the covariate analysis the applicant concluded that race has no impact on the PK of oritavancin.

Pharmacokinetic interaction studies

In vitro
Oritavancin was not a substrate for the cytochrome P450 system in human liver microsomes.
The ability of oritavancin to inhibit the metabolism of marker catalytic activities for CYP3A4, CYP2D6, CYP2C9 and CYP1A2 was examined *in vitro* with human hepatocytes. At 25 µM oritavancin:

- Using midazolam 5 µM there was 39% inhibition of CYP3A-mediated metabolism
- Using diclofenac 2.5 µM there was <10% inhibition of CYP2C9-mediated metabolism
- Conversion of phenacetin (at 12.5 µM) to acetaminophen by CYP1A2 was slightly inhibited (21%)
- Modelling the data to conventional enzyme inhibition relationships, the form-selective biotransformation for CYD2D6 (1'-hydroxylation of bufuralol) was non-competitively inhibited by oritavancin yielding a Ki of 12.6 ± 1.3 '-hydroxylation.

The order of potential inhibition by oritavancin of the metabolism of co-administered drugs by the cytochrome P450 isoforms was determined to be CYP2D6>CYP3A4>CYP1A2>CYP2C9.

When HLMs were pre-incubated with oritavancin (2.5 up to 50 µM) and known substrates for CYP2D6 (dextromethorphan) and 3A4 (testosterone) CYP2D6 and CYP3A4 were inhibited in a concentration-dependent manner. Oritavancin was initially reported to be a competitive inhibitor for both isoenzymes with Ki values of 21.9 and 31.7 µM, respectively, but re-analysis of the data indicated that inhibition of CYP3A4 was almost fully non-competitive whereas inhibition of CYP2D6 was mixed.

Table 10

	Substrate	
	Testosterone (CYP3A)	Dextromethorphan (CYP2D6)
In Vitro Technologies analysis		
Inhibition mechanism	Competitive	Competitive
K_i (µM)	31.7	21.9
Tufts University analysis		
V_{max} (pMol/min/mg protein)	13.05	419
K_m (µM)	300	60.6
Inhibition mechanism	Noncompetitive	Mixed
Alpha	1.2	7.3
K_i (µM)	49.0	32.6

A further study compared the abilities of oritavancin and telithromycin to inhibit human CYP enzymes using an in-vitro model based on biotransformation rates of index substrates by human liver microsomes. Oritavancin inhibited all isoforms tested without evidence of a time-dependent (mechanism-based) process, indicating that CYP inhibition is likely to be reversible. The IC50 values relative to typical C_{max} (total drug) based on the POPPK analysis relevant to dosing at 200 QD were > 0.1. For the 1200 mg dose the Cmax/IC50 ratios all exceed 1.5. It was concluded that oritavancin is a relatively nonspecific inhibitor of all human CYP isoforms (similar to efavirenz and isoniazid) and the mechanism is likely to be non-competitive rather than competitive.

Table 11

Summary of CYP Inhibition Characteristics of Oritavancin

CYP isoform and index substrate	**Oritavancin IC50 (µM)**	**C_{max}[(i)]/IC50 – 200 mg daily**	**C_{max}[(ii)]/IC50 – 1200 mg single dose**
CYP3A (triazolam)	16.1	0.85	4.30
CYP2D6 (dextromethorphan)	18.5	0.74	3.75
CYP2C9 (flurbiprofen)	16.7	0.82	4.15
CYP2C19 (S-mephenytoin)	40.3	0.34	1.72
CYP2B6 (bupropion)	31.0	0.44	2.24
CYP1A2 (phenacetin)	40.5	0.34	1.71

(i) Oritavancin mean (±SD) C_{max} of 27.3 (±12.1) µg/mL (equivalent to 13.7 µM) based on population PK analysis of 200 mg once-daily dosing

(ii) Oritavancin mean (±SD) C_{max} of 138 (±31.7) µg/mL (equivalent to 69.3 µM) based on population PK analysis of single 1200 mg dosing

The potential for oritavancin to induce CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 was studied in cryopreserved human hepatocytes. There were no significant increases in enzyme activities over 48 h except that:

- 50 µM oritavancin induced CYP2E1 (activity 150% of vehicle control) whereas 25 µM did not give a significant increase (111% of vehicle control)
- 2.5 µM oritavancin gave some increase in CYP3A4 (117% of vehicle control) but at higher concentrations there was evidence of inhibition of CYP3A4.

The enzyme activity vs. vehicle control decreased as oritavancin concentration increased (2.5, 25 and 50 µM), and especially between the two latter concentrations, for CYP1A2, 2A6, 2C9, 2C19, 2D6 and 3A4. It was demonstrated that 50 µM was not cytotoxic to the hepatocytes. The oritavancin dosing solution was removed prior to adding the substrates for each isoenzyme so inhibition would not be expected after removal. Thus, the report postulated that the finding likely reflects persistence of protein-bound oritavancin in the hepatocytes.

In Caco-2 monolayers and in the absence and presence of the P-gp inhibitors ciclosporin A (10 µM) and verapamil (100 µM) the apparent permeability of oritavancin was lower than that of mannitol (a well-known impermeable marker) in either direction, indicating that oritavancin has poor permeability and is not a P-gp substrate. In addition, oritavancin did not affect the efflux ratio of digoxin, suggesting that oritavancin is not a P-gp inhibitor.

Oritavancin affects the results of the aPTT assay due to an in-vitro interaction with the phospholipids necessary for accurate aPTT estimation. There is no in-vitro or in-vivo evidence that oritavancin affects the coagulation system.

In vivo

OCSI-008 was a parallel-arm, open-label study in which healthy male and female subjects were allocated randomly to either:

Arm A: Desipramine 50 mg administered PO once daily from Day 1 to 7 followed by
Desipramine 50 mg administered PO once daily and oritavancin 800 mg administered IV over 90 minutes once daily for 14 consecutive days (Days 8–21).

Arm B: Placebo administered PO once daily from Day 1 to 7 followed by
Placebo administered PO daily and oritavancin 800 mg administered IV over 90 minutes daily for 14 consecutive days (Days 8–21).

The sponsor terminated the study after most subjects had received only 3 or 4 doses of oritavancin because of the incidence and severity of phlebitis and systemic AEs. There were 29 in each treatment group that completed assessments through Day 8 of the study. There was no effect of desipramine on the mean pharmacokinetic parameters of oritavancin.

Table 12

Table 11-4 Mean Pharmacokinetic Parameters of Oritavancin with and without Desipramine

Pharmacokinetic Parameter	Treatment	Study Day	N	Mean	SD	Minimum	Maximum
$AUC_{(0\text{-}24)}$ (µg·hr/mL)	Desip + Orita	8	29	1159.10	246.59	657.27	1773.3
	Placebo + Orita		26	1184.10	398.68	705.65	2408
C_{max} (µg/mL)	Desip + Orita	8	29	153.21	29.44	94.10	210
	Placebo + Orita		29	163.03	51.94	105.00	313
C_{24} (µg/mL)	Desip + Orita	8	29	18.59	5.45	9.43	29
	Placebo + Orita		26	19.97	10.45	9.53	60.7

There was a numerical decrease in desipramine Cmax and AUC from Day 7 (no oritavancin) to Day 8 (first dose of oritavancin). The sponsor proposed that lack of CYP2D6 inhibition could reflect low levels of unbound oritavancin but did not comment on the possibility of weak induction of 2D6.

Table 13

Table 11-2 Mean Phamacokinetic Parameters of Desipramine with and without Oritavancin

Pharmacokinetic Parameter	Treatment	Study Day	N	Mean	SD	Minimum	Maximum	Geometric Mean
$AUC_{(0-24)}$ (ng·hr/mL)	Desipramine	7	29	534.80	425.66	160.56	2453.84	446.74
	Desipramine with Oritavancin	8	28	503.51	433.58	147.53	2449.41	413.26
C_{max} (ng/mL)	Desipramine	7	30	36.31	21.90	13.54	124.39	31.80
	Desipramine with Oritavancin	8	29	32.35	22.85	11.995	128.60	27.60
C_{24} (ng/mL)	Desipramine	7	29	13.60	14.73	3.35	84.78	10.56
	Desipramine with Oritavancin	8	28	14.16	17.20	3.81	95.75	10.48

The accumulation of 2-hydroxydesipramine was consistent with that of parent drug and there were numerical decreases in Cmax and AUC from Day 7 to Day 8. These decreases, in the absence of any increase in parent drug, do not suggest in-vivo inhibition of CYP2D6 by oritavancin.

Table 14

Table 11-3 Mean Pharmacokinetic Parameters of 2-Hydroxy-Desipramine Pharmacokinetic Parameters with and without Oritavancin

Pharmcokinetic Parameter	Treatment	Study Day	N	Mean	SD	Minimum	Maximum	Geometric Mean
$AUC_{(0-24)}$ (ng·hr/mL)	Desipramine	7	29	288.85	70.32	166.43	461.17	280.88
	Desipramine with Oritavancin	8	28	258.06	72.80	119.40	468.98	248.38
C_{max} (ng/mL)	Desipramine	7	30	20.62	5.26	13.82	31.89	20.03
	Desipramine with Oritavancin	8	29	17.58	4.21	7.60	28.55	17.08
C_{24} (ng/mL)	Desipramine	7	29	6.71	2.24	2.51	13.87	6.36
	Desipramine with Oritavancin	8	28	6.84	3.04	2.78	15.02	6.24

MDCO-ORI-12-03 evaluated the effects of 1200 mg oritavancin infused over 3 h on the activities of CYPs (1A2, 2C9, 2C19, 2D6 and 3A), *N*-acetyltransferase-2 and xanthine oxidase using the Cooperstown 5 + 1 Cocktail (caffeine, warfarin, vitamin K, omeprazole, dextromethorphan and midazolam).

The phenotyping measures used to determine drug metabolizing enzyme activities were as follows:

- CYP1A2 Urinary molar ratio of (1X [1-methylxanthine] + 1U [1-methylurate] + AFMU [(5-acetylamino-6-formylamino-3-methyluracil]) / 17U1 (7-dimethylurate)
- CYP2C9 Plasma *S*-warfarin AUC0-∞
- CYP2C19 Plasma concentration ratio of omeprazole to 5-hydroxyomeprazole
- CYP2D6 Urinary molar ratio of dextromethorphan to dextrorphan
- CYP3A4 Plasma midazolam CL/F
- NAT-2 Urinary molar ratio of AFMU / (1X + 1U)
- XO Urinary molar ratio of 1U / (1X + 1U)

The oritavancin PK data were as expected for the 1200 mg single dose infused over 3 h. The effect of oritavancin on the probe substrates is summarised in the table and forest plot below.

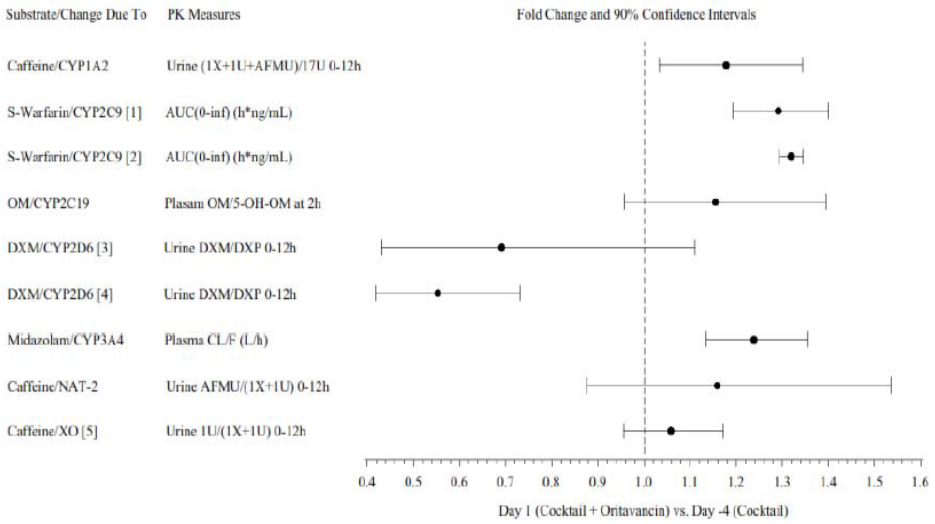
Table 15

Table 10 Summary of the Effect of Oritavancin on the Probe Substrates of the Cooperstown 5 + 1 Cocktail

Substrate	Isozyme	Biological Matrix	PK Parameter	Units	N	Geometric Mean		Ratio	90% Confidence Interval	
						Day -4	Day 1	Day 1/Day-4	Low	High
Midazolam	CYP 3A4	Plasma	CL/F	L/hr	16	79.745	98.814	1.239	1.135	1.353
		Plasma	AUC(0-inf)	hr*ng/mL	16	70.220	57.091	0.813	0.744	0.888
S-Warfarin	CYP 2C9	Plasma	AUC(0-inf)	hr*ng/mL	16	15623	20610	1.319	1.294	1.345
S-Warfarin	CYP 2C9	Plasma	AUC(0-inf)	hr*ng/mL	3	11340	14650	1.292	1.192	1.400
Omeprazole	CYP 2C19	Plasma	OM/5-OM at 2 Hr	Ratio	16	1.501	1.734	1.155	0.957	1.395
Dextromethorphan	CYP 2D6	Urine	Ratio of DXM/DXP in -12Hr Urine	Ratio	13	0.206	0.142	0.692	0.431	1.110
				Ratio	12	0.230	0.127	0.553	0.419	0.731
Caffeine	CYP 1A2	Urine	Ratio of [(1X+1U+AFMU/17U] in -12Hr Urine	Ratio	16	4.125	4.863	1.179	1.033	1.345
Caffeine	NAT-2	Urine	Ratio of [AFMU/(1X+1U)] in -12Hr Urine	Ratio	16	0.180	0.208	1.159	0.875	1.535
Caffeine	XO	Urine	Ratio of [1U/(1X+1U)] in -12Hr Urine	Ratio	14	0.524	0.555	1.058	0.956	1.172

Figure 6

Figure 3 Summary of the Effect of Oritavancin on the Probe Substrates of the Cooperstown 5 + 1 Cocktail Displayed as 90% Confidence Intervals of the Geometric Mean Phenotyping Measure Ratios



The applicant concluded that oritavancin:

- Is a weak inducer of CYP3A4
- May be a weak inhibitor of CYP2C19
- Is a weak inhibitor of CYP2C9
- Is a weak inducer of CYP2D6

There was an increase of 18% in CYP1A2 activity, an increase of 16% in NAT-2 activity and an increase of 6% in XO activity by oritavancin.

Although there were some statistically significant changes in enzyme activities on co-administration of probe substrates with oritavancin the point estimates were all < 1.25 and the upper 90% CI did not exceed 2.00, indicating that oritavancin had a weak inhibitory or inducing effect. The only interaction potential examined considered by the applicant to possibly require action was for warfarin.

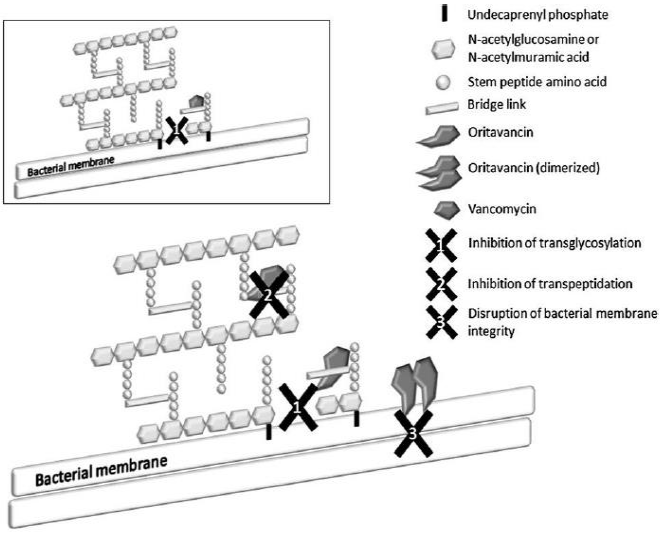
2.4.3. Pharmacodynamics

Mechanism of action

Oritavancin is claimed to exhibit three known mechanisms of action as summarised in the diagram.

Figure 7

Figure 26: Oritavancin Targets the Bacterial Cell Envelope via Three Mechanisms of Action in contrast to vancomycin's single mechanism (inset).



Oritavancin exists primarily as non-covalent dimers that associate strongly with the peptidoglycan precursor-membrane target including those in which the peptidoglycan precursors terminate in acyl-D-Ala-D-Lac. In solution, oritavancin is 12,800-fold more strongly dimerised than vancomycin, which facilitates cooperative binding interactions at the target site. In turn these strengthen the attachment of oritavancin to the cell wall and cell wall precursors, enhancing inhibition of peptidoglycan biosynthesis and cell wall elongation. Consequently, addition of a 284,000-fold molar excess of exogenous peptide ligand *N,N'*-diacetyl-L-Lys-D-Ala-D-Ala was needed to block oritavancin antibacterial activity.

Primary and Secondary pharmacology

The following is a brief summary of the large amount of microbiological data in this application dossier and focuses only on the most pertinent features:

- Information on clinical isolates from the efficacy studies
- The PK/PD analyses supporting the dose and the proposed susceptibility testing breakpoints

Susceptibility testing

With addition of polysorbate-80 oritavancin MICs against *S. aureus* ATCC 29213 and *E. faecalis* ATCC 29212 decrease by 32- and 16-fold, respectively. These MIC shifts are consistent with the differential recovery of oritavancin in the presence and absence of polysorbate-80 and support the idea that the in-vitro activity of oritavancin is best represented with polysorbate-80 at 0.002% during all steps of the broth microdilution assay, as recommended by CLSI. Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

Susceptibility Interpretive Criteria for Oritavancin

- Organism group	- MIC breakpoints - (mg/L)	
	- S ≤	- R >
- *Staphylococcus aureus*	- 0.125	- 0.125
- *Beta-haemolytic streptococci* Groups A, B, C, G	- 0.25	- 0.25
- Viridans group streptococci (*S. anginosus* group only)	- 0.25	- 0.25

- S=Susceptible, R=Resistant

In-vitro activity against the target pathogens

Against *S. aureus* MICs were from ≤ 0.008 - 0.5 µg/mL and the MIC_{90} was 0.06 µg/mL. Oritavancin was active against daptomycin- and linezolid-non-susceptible isolates of *S. aureus* but the MIC_{90} was 8- to 32-fold higher against hVISA, VRSA and VISA (MIC_{90} 0.5 to 2 µg/mL).

Table 16

Table 63 (Appendix): Oritavancin is Active against *S. aureus* Isolates that are non-susceptible to other agents.

Phenotype	N	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC Range (µg/mL)	Source
DAP NS	11	0.5	1	0.12 - 1	5002-87
DAP NS	7	NA	NA	0.06 - 0.5	(Saravolatz, et al. 2010)
DAP NS	5	NA	NA	0.03 - 0.12	12-TMC-02
DAP NS	7	NA	NA	0.06 – 0.25	100948
DAP NS	3	NA	NA	0.06 – 0.25	5002-75
hVISA	100	0.25	0.5	0.03 - 1	(Vidaillac, et al. 2011)
hVISA	11	0.5	1	0.12 - 2	(Arhin, et al. 2009b)
hVISA	5	NA	NA	0.12 - 0.5	MDCO-ORI-M026
LZD NS	9	NA	NA	0.06 - 0.25	5002-87
LZD NS	6	NA	NA	0.015 – 0.03	100948
MDR	651	0.03	0.06	≤0.002 - 0.5	100948
VISA	60	0.5	2	0.12 - 4	(Vidaillac, et al. 2011)
VISA	20	1	2	0.25 - 2	(Saravolatz, et al. 2010)
VISA	14	1	2	0.5 - 4	(Arhin, et al. 2009b)
VISA	13	1	1	0.5 - 1	5002-87
VISA	5	NA	NA	0.5 - 2	MDCO-ORI-M026
VRSA	11	0.5	1	0.25 - 2	(Vidaillac, et al. 2011)
VRSA	10	0.5	1	0.25 - 1	(Saravolatz, et al. 2010)
VRSA	10	0.5	0.5	0.12 - 1	(Arhin, et al. 2009b)
VRSA	5	NA	NA	0.12 - 0.5	5002-87

Abbreviations: DAP NS, daptomycin non-susceptible; hVISA, heterogeneous vancomycin-intermediate *Staphylococcus aureus*; LZD NS, linezolid non-susceptible; MDR, multi-drug resistant (resistant to 3 or more of the following [erythromycin, clindamycin, gentamicin, levofloxacin, and trimethoprim/sulfamethoxazole]); VISA, vancomycin-intermediate *Staphylococcus aureus;* VRSA, vancomycin-resistant *Staphylococcus aureus;* NA, not applicable (MIC_{50} and MIC_{90} were not calculated when n < 10).

The sub-study of clonal diversity by *spa* typing of 1100 isolates of *S. aureus* obtained in SOLO I and SOLO II indicated that nearly all the major clonal complexes associated with human *S. aureus* infections were represented. However, it should be noted that CC239 and CC80 were only represented by 2 isolates.

- Against *S. pyogenes* MICs ranged from ≤0.008 to 0.5 µg/mL and MIC_{90} values were 0.12 or 0.25 µg/mL. Against *S. agalactiae* MICs ranged from ≤0.008 to 0.5 µg/mL and MIC_{90} values were 0.06 or 0.12 µg/mL.
- Against 148 recent isolates of the *S. anginosus* Group (*S. anginosus* 102; *S. constellatus* 33; *S. intermedius* 13) the MIC range was from ≤0.008 to 0.12 µg/mL and the MIC_{50}/MIC_{90} values were ≤0.008/0.0015 µg/mL.

- Oritavancin MICs for 34 *S. dysgalactiae* isolates ranged from ≤0.008 to 0.25 µg/mL, with MIC_{50}/MIC_{90} values of 0.06/0.25 µg/mL.
- For Groups C, G and F streptococci in the US and Europe the MIC_{90} was 0.25 µg/mL regardless of geography or erythromycin susceptibility phenotype.
- The significance of *E. faecalis* in ABSSSI is dubious. Nevertheless, the MIC range was from ≤0.008 to 1 µg/mL with MIC_{90} of 0.06 or 0.12 µg/mL. The MIC_{90} against *E. faecalis* with the VanA phenotype (MIC_{90} = 0.5 µg/mL) was 8-fold higher compared to vancomycin-susceptible isolates.

Table 17

Table 26: Oritavancin is Active against *E. faecalis* Isolates Including Vancomycin-resistant Isolates

Phenotype	N	Geography	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC Range (µg/mL)
All	2132	All	0.015	0.06	≤0.008 – 1
VSE	2088	All	0.015	0.06	≤0.008 – 0.5
VRE (VanA)	37	All	0.25	0.5	0.015 – 1
All	1088	US	0.015	0.06	≤0.008 – 1
VSE	1054	US	0.015	0.06	≤0.008 – 0.5
VRE (VanA)	27	US	0.25	0.5	0.015 – 1
All	1044	EU	0.015	0.06	≤0.008 – 0.5
VSE	1034	EU	0.015	0.06	≤0.008 – 0.25
VRE (VanA)	10	EU	0.25	0.5	0.015 – 0.5

Against linezolid- and daptomycin-non-susceptible *E. faecalis* isolates the MICs were ≤ 0.5 µg/mL.

Table 18

Phenotype	N	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC Range (µg/mL)
LZD NS	11	0.03	0.06	0.015 – 0.25
LZD NS	1	NA	NA	≤0.008
LZD NS	3	NA	NA	0.015 – 0.5
DAP NS	3	NA	NA	0.12 – 0.5

Oritavancin was active against vancomycin-resistant *E. faecium* (due to VanA and VanB) and other enterococci isolated in the US, Europe and Canada.

Table 19

Table 68 (Appendix): Oritavancin is Active against *E. faecium* Isolates Including Vancomycin-resistant Strains

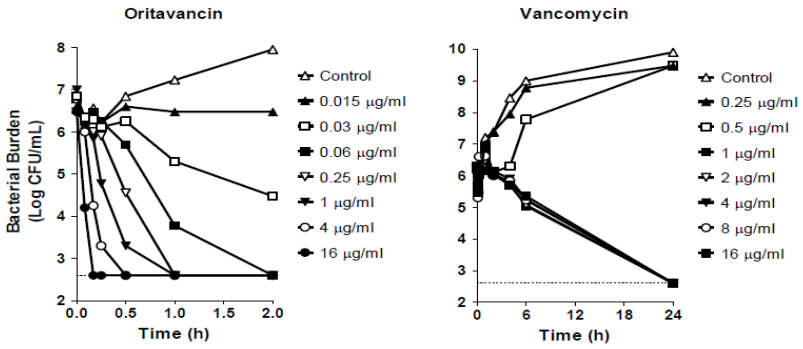
Phenotype	N	Geography	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC Range (µg/mL)
All	1237	All	≤0.008	0.06	≤0.008 – 0.5
VSE	566	All	≤0.008	≤0.008	≤0.008 – 0.015
VRE (VanA)	639	All	0.03	0.12	≤0.008 – 0.5
VRE (VanB)	32	All	≤0.008	≤0.008	≤0.008 – 0.3
All	655	US	0.03	0.12	≤0.008 – 0.5
VSE	138	US	≤0.008	≤0.008	≤0.008 – 0.015
VRE (VanA)	498	US	0.03	0.12	≤0.008 – 0.5
VRE (VanB)	19	US	≤0.008	0.015	≤0.008 – 0.03
All	582	EU	≤0.008	0.015	≤0.008 – 0.12
VSE	428	EU	≤0.008	≤0.008	≤0.008 – 0.015
VRE (VanA)	141	EU	0.015	0.06	≤0.008 – 0.12
VRE (VanB)	13	EU	0.008	0.008	≤0.008 – 0.008

The MBC_{90}:MIC_{90} or MBC:MIC ratios against *S. aureus* ranged from 1 to 2. There were higher MBC:MIC ratios for oritavancin against enterococci, which was suggestive of tolerance.

In time-kill studies there was rapid, concentration-dependent, bactericidal activity against *S. aureus* (including MSSA and MRSA [including *mec*C MRSA]), *S. pyogenes, E. faecalis* and *E. faecium.* An example is shown below for CA-MRSA. Note that the *f*Cmax after a single 1200 mg dose is ~16 µg/mL.

Figure 8

Figure 34: Oritavancin Antibacterial Activity is Concentration-Dependent (Time-kill Study with CA- MRSA strain NRS 384 [USA300])



Oritavancin retained concentration-dependent bactericidal activity against stationary-phase *S. aureus*, including MSSA, MRSA and VRSA. It was also found to sterilise biofilms derived from MSSA, MRSA, VRSA, *S. epidermidis* and *Enterococcus* at minimum biofilm eradication concentrations (MBECs) between 0.5-8 µg/mL.

Resistance to oritavancin

Intrinsic resistance to oritavancin occurs in all Gram-negative organisms and in the Gram-positive organisms of the genera *Leuconostoc*, *Lactobacillus*, *Erysipelothrix* and *Pediococcus* due to alterations in

Lipid II and in peptidoglycan precursors containing acyl-D-Ala-D-Lac or acyl-D-Ala-D-Ser in place of acyl-D-Ala-D-Ala.

Acquired resistance potentially results from altered peptidoglycan precursor formation with diminished affinity for glycopeptides (mediated by the various Van operons in enterococci and VRSA) and changes in cell wall structure and thickness leading to reduced glycopeptide binding (as found in hVISA and VISA). Based on the proposed breakpoint (0.12 µg/mL) these organisms are not expected to be susceptible to oritavancin, with perhaps a few exceptions (see the clinical data for hVISA).

In-vivo efficacy in non-clinical models

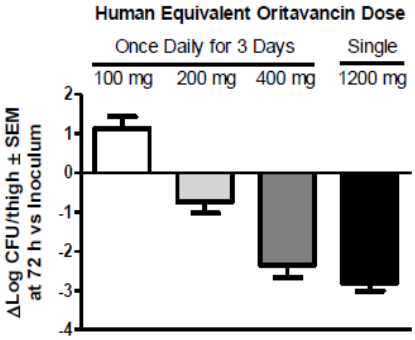
Efficacy of oritavancin has been studied in:
- Murine septicaemia, (neutropenic) thigh infection, inhalational anthrax and lung infection models
- Rat granuloma pouch and bacteraemia models
- Rabbit endocarditis and meningitis models

The AUC/MIC ratio and Cmax were identified as the major PK/PD parameters predictive of efficacy.

An expanded study using 14 *S. aureus* and five *S. pyogenes* simulated the concentration-time profile and AUC achieved in patients after a 1200 mg dose. This showed more rapid and sustained bacterial killing compared with daily regimens, including 400 mg QD for 3 days. An example shows *S. aureus.*

Figure 9

Figure 41: Oritavancin Pharmacodynamics are Optimized with the Humanized Single 1200 mg Dose Compared to Daily Dosing Regimens (Neutropenic Thigh Model of *S. aureus* Infection)



Other microbiological issues

- Oritavancin was shown to have synergistic bactericidal activity in combination with gentamicin, moxifloxacin or rifampicin against MSSA. It also showed synergy with gentamicin or linezolid against MRSA-hVISA, VISA and VRSA. With rifampicin there was synergy against VRSA.
- At its predicted free peak concentration in plasma oritavancin demonstrated PAEs of 1.5 to 4.5 h against *S. aureus* and 3 to 5 h against enterococci. The oritavancin PAE was concentration-dependent.
- Oritavancin is a cationic amphiphatic agent that accumulates in lysosomes of macrophages and fibroblasts by 150- to 974-fold over the extracellular drug concentration within 24 h. This ability to accumulate has been ascribed to the lipophilic side chain and the 4-*epi*-vancosamine sugar.

Effects on cardiac conduction

Non-clinical studies demonstrated that oritavancin blocked human cardiac I_{Na} with an IC50 of 0.5 µM in human atrial myocytes and this was confirmed in a mouse cardiac cell line (AT-1 sub-clone). At free drug therapeutic levels a near complete block of human I_{Na} could be expected, similar to that exerted by Class 1 anti-arrhythmic agents, associated with prolonged QRS complex (which can lead to arrhythmias).

Concurrent blocking of the Ito channel with IC50 4.2 μM could possibly antagonise the effect on sodium channels. Thus, assessing effects on QTc due to the effect on hERG is only a part of the necessary evaluation.

Four studies assessed the effects of oritavancin on cardiac conduction. However, due to the change in regimen over time, the relevant data come from **MDCO-ORI-12-02**, designed as a TQT study in which randomisation was to:

- Oritavancin 1600 mg in 1500 mL of D5W infused over 3 h
- Placebo - D5W administered as for oritavancin
- Moxifloxacin (single 400 mg oral dose)

The primary endpoint (placebo-adjusted change from baseline in QTcF [i.e. ΔΔQTcF]) was analysed using a linear mixed-effect model to evaluate differences between each dose of oritavancin and placebo and between moxifloxacin and placebo. Analysis for QTcB was conducted in the same manner.

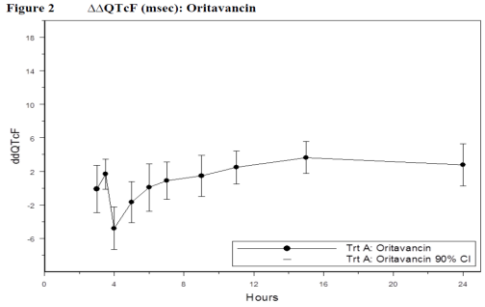
For the 150 enrolled the mean age was 34.9 years and 53.7% were male. Adequate assay sensitivity was demonstrated in the pre-specified mixed-effects model of ΔΔQTcF, as the lower bound of the 90% CI exceeded 5 ms at 2 of the 3 pre-specified time points in the moxifloxacin group after application of the Hochberg procedure (at hours 4 and 6).

Oritavancin did not increase QTc at an IV dose of 1600 mg over 3 h. During the period of highest concentrations of oritavancin, ΔΔQTcF was less than 1.2 msec. After hour 6, positive mean values of 2.6 ms or lower were observed, and the upper boundary of the 90% 2-sided CI was consistently below 6.9 ms in the mixed-effects model.

Table 7 ΔΔQTcF (msec): Mixed-Effects Model

	Oritavancin		Moxifloxacin	
Timepoint (Hour)	Mean	90% CI	Mean	90% CI
3	–0.8	-5.1, 3.5	7.5	3.3, 11.7
3.5	1.2	-3.1, 5.5	15.7	11.5, 19.9
4	–5.8	-10.1, -1.5	10.9	6.7, 15.1
5	–3.0	-7.3, 1.3	9.4	5.2, 13.6
6	–0.3	-4.6, 4.0	11.3	7.1, 15.5
7	0.5	-3.8, 4.8	10.3	6.1, 14.5
9	1.7	-2.6, 6.0	11.4	7.2, 15.6
11	1.3	-3.0, 5.6	9.7	5.5, 13.9
15	2.6	–1.7, 6.9	12.1	7.9, 16.3
24	1.9	–2.4, 6.2	9.9	5.7, 14.1

Figure 2 ΔΔQTcF (msec): Oritavancin

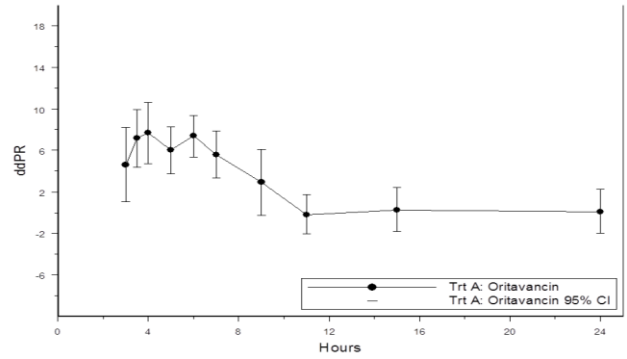


The QTcF did not exceed 480 ms at any time point during any treatment. Values > 450 ms occurred in one placebo, 2 oritavancin and 5 moxifloxacin subjects. Change of QTcF over Baseline exceeded 30 ms at 2 time points in the oritavancin group and at no time points in the other groups. Change in QTcF did not exceed 60 ms at any time point during any treatment.

There was no consistent or clinically significant change in HR associated with any of the treatments. The QRS interval was also not significantly affected by any of the treatments. A modest oritavancin-associated prolongation in PR interval was demonstrated (see figure below). The mean placebo-corrected change in

the oritavancin group was statistically significantly positive at time points from hours 3 to 7 with mean values 4.6 – 7.7.ms. The oritavancin PR interval (ΔPR) returned to baseline by 10 h, when the plasma concentration was ~100 µg/mL.

Figure 4 ΔΔPR (msec): Oritavancin

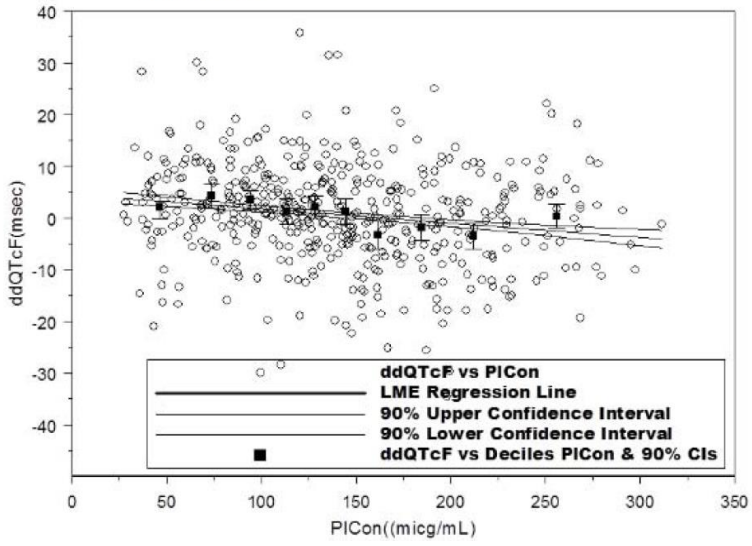


Linear PK/PD modelling of the change in PR showed a statistically significant relationship that predicted a change in PR of 2.347 ms for a 100 µg/mL change in plasma concentration.

The mean moxifloxacin plasma concentration at the single time point was 2274 ng/mL with a range from 1312 to 3693 ng/mL. Following a 3-hour IV infusion of oritavancin, plasma oritavancin concentrations peaked at approximately hour 3 (at the termination of the IV infusion). The mean Cmax was 231.67 µg/mL and the mean AUC_{0-24} was 2420.65 µg·hr/mL. All PK parameters were estimated with low variability (CV% <20%). The linear regression for change in QTc vs. plasma concentration is shown in the figure. The linear slope of the regression was slightly negative and statistically significant.

Figure 10

Figure 9 ΔΔQTcF (msec) Versus Oritavancin Plasma Concentration: Linear Model



The applicant's conclusions were as follows:

- Oritavancin 1600 mg infused over 3 h gave a mean Cmax (at end of infusion) 231.67 µg/mL and mean AUC_{0-24} 2420.65 µg·hr/mL.
- There was no increase in QTc with this dose. In addition, there was no consistent or clinically significant change in HR or QRS interval.
- A modest oritavancin-associated prolongation in PR interval was demonstrated.

Dose selection

Non-clinical data and PK/PD modeling suggested that efficacy would be optimised by pooling rather than fractionating the cumulative dose. The rationale for 1200 mg over 3 h may be summarised as follows:

- Bactericidal activity *in vitro* is concentration-dependent
- C_{max} and AUC are the main PK parameters that predict efficacy *in vivo*
- In animal models front-loaded doses achieved effective exposures earlier in therapy when bacterial burden was greatest when compared to smaller and more frequent doses
- Bacterial regrowth is inhibited after drug concentrations fall below the MIC for the infecting strain
- There is a prolonged tissue residence time and the t1/2 in plasma in patients is ~ 245 h
- In TAR-ORI-SD001 (SIMPLIFI) a single 1200 mg dose had similar efficacy to 200 mg QD

PK/PD analyses

ICPD 00247-02 describes the PK/PD analyses that concern the 1200 mg single dose based on the POPPK relevant to this dose using data collected from the patients enrolled into SOLO I and II. The analysis focussed on the microbiologically-evaluable (ME) population as well as the subset with S. aureus isolated at baseline. Data from patients for whom the primary outcome was determined to be failure not due to study drug were excluded from the analyses. A total of 175 patients treated with oritavancin in SOLO I (n=53) and SOLO II (n=122) were in the ME population and had sufficient PK data. Of these, 154 patients (50 and 104) had S. aureus isolated at baseline. There was a broad distribution of AUC_{0-72}:MIC ratios.

Table 20

Table 4-7. Summary statistics for AUC_{0-72}, baseline MIC, and AUC_{0-72}:MIC ratio for all patients and patients with *S. aureus*

Analysis population	Variable	AUC_{0-72} (mg•h/L)	MIC (mg/L)	AUC_{0-72}:MIC ratio
All patients (N=175)	Mean (%CV)	1,494 (38.5)	-	56,401 (248)
	Median or $MIC_{50/90}$ (min - max)	1,417 (223 – 5,895)	0.06/0.12 (0.001 - 0.25)	33,208 (3,393 – 1,417,272)
	5^{th} – 95^{th} percentile	874.6 – 2,306	-	7,106 – 113,471
	25^{th} – 75^{th} percentile	1,169 – 1,751	-	19,284 – 49,757
Patients with *S. aureus* (N=154)	Mean (%CV)	1,495 (39.0)	-	38,771 (84.0)
	Median or $MIC_{50/90}$ (min - max)	1,424 (325 – 5,895)	0.06/0.12 (0.015 - 0.25)	32,875 (3,393 – 262,629)
	5^{th} – 95^{th} percentile	875 – 2,263	-	7,387 – 90,924
	25^{th} – 75^{th} percentile	1,157 – 1,723	-	18,942 – 48,831

Results for univariable PK-PD analyses generally demonstrated that achieving a higher AUC_{0-72}:MIC ratio was associated with improved response. However, the high success rates for the efficacy endpoints evaluated hindered characterisation of the univariable PK-PD relationships so that continuous functions could not be reliably identified. Instead, step functions describing PK-PD relationships which distinguished patients with lower vs. higher AUC_{0-72}:MIC ratios and success rates could be detected.

An AUC_{0-72}:MIC ratio threshold of 11,982 was found to distinguish clinical responders from clinical non-responders at PTE based on data from all patients and patients with *S. aureus*.

Table 21

Table 4-9. AUC_{0-72}:MIC ratio thresholds for univariable relationships between the probability of achieving dichotomous efficacy endpoints and AUC_{0-72}:MIC ratio evaluated as a two-group variable based on data from all patients and patients with *S. aureus*

Efficacy endpoint	All patients				Patients with *S. aureus*			
	AUC_{0-72}:MIC ratio threshold	Percent of patients < or ≥ AUC_{0-72}:MIC ratio threshold achieving efficacy endpoint		P-value	AUC_{0-72}:MIC ratio threshold	Percent of patients < or ≥ AUC_{0-72}:MIC ratio threshold achieving efficacy endpoint		P-value
		< threshold % (n/N)	≥ threshold % (n/N)			< threshold % (n/N)	≥ threshold % (n/N)	
Primary outcome at ECE	38,951	82.2 (83/101)	98.6 (71/72)	<0.001	24,574	79.6 (43/54)	95.9 (94/98)	0.001
Clinical response at EOT	32,375	96.5 (82/85)	100 (90/90)	0.11	19,111	94.9 (37/39)	100 (115/115)	0.06
Clinical response at Day 10	19,111	92.9 (39/42)	99.2 (132/133)	0.043	19,111	92.3 (36/39)	100 (115/115)	0.015
Clinical response at PTE	11,982	84.6 (22/26)	96.0 (143/149)	0.043	11,982	82.6 (19/23)	96.2 (126/131)	0.029
Sustained clinical response at PTE	23,924	80.0 (48/60)	95.7 (110/115)	<0.001	19,459	80.5 (33/41)	95.6 (108/113)	0.006

The final models for clinical response at PTE based on data from all patients and patients with *S. aureus* contained AUC_{0-72}:MIC ratio evaluated as a two-group variable ($p \leq 0.033$) and BMI evaluated as a three-group variable ($p \leq 0.01$). Univariable relationships between the probability of clinical success at PTE and BMI evaluated as a three-group variable based on data from all patients and patients with *S. aureus* resembled an inverted U-shape.

Tables 23 & 24

Table 4-15. Final multivariable model for the clinical response at PTE based on data from all patients

Independent variable	Parameter estimate (SE)[a]	Odds ratio (95% confidence interval)	P-value[b]
AUC_{0-72}:MIC ratio ≥ 11,982[c]	1.66 (0.747)	5.24 (1.21 – 22.7)	0.033
BMI ≥ 25.0 to < 28.7 kg/m^2[d]	Positive value[e]	> 1[e]	0.009
BMI ≥ 28.7 kg/m^2[d]	-1.24 (0.724)	0.289 (0.070 – 1.20)	

a. The parameter estimate (SE, standard error) for the intercept is 1.83 (0.633).
b. Likelihood ratio p-value.
c. Reference group = patients with AUC_{0-72}:MIC ratio < 11,982.
d. Reference group = patients with BMI < 25.0 kg/m^2.
e. Direction of relationship is indicated but the parameter estimate and odds ratio could not be estimated due to 100% observed success in this BMI range.

Table 4-16. Final multivariable model for clinical response at PTE based on data from patients with *S. aureus*

Independent variable	Parameter estimate (SE)[a]	Odds ratio (95% confidence interval)	P-value[b]
AUC_{0-72}:MIC ratio ≥ 11,982[c]	1.75 (0.764)	5.75 (1.28 – 25.7)	0.028
BMI ≥ 24.8 to < 29.1 kg/m^2[d, e]	Positive value[e]	> 1[e]	0.010
BMI ≥ 29.1 kg/ m^2[d]	-0.976 (0.745)	0.377 (0.087 – 1.63)	

a. The parameter (SE, standard error) for the intercept is 1.58 (0.645).
b. Likelihood ratio p-value.
c. Reference group = patients with AUC_{0-72}:MIC ratio < 11,982.
d. Reference group = patients with BMI < 24.8 kg/m^2.
e. Direction of relationship is indicated but the parameter estimate and odds ratio could not be estimated due to 100% observed success in this BMI range.

Based on data for all patients, percentages of clinical success were 94.7, 100 and 87.8% for BMI < 25.0, ≥ 25.0 to < 28.7 and ≥ 28.7 kg/m^2, respectively. Based on data from patients with *S. aureus*, percentages of clinical success were 93.7, 100 and 86.8% for BMI < 24.8, ≥ 24.8 to < 29.1, and ≥ 29.1 kg/m^2, respectively. As assessed by the degree of agreement between the model-predicted and observed percentages of response the data were well fit by the final models.

PTA and mean percent probabilities of clinical success by oritavancin MIC are shown in the table below.

For *S. pyogenes* PTA based on non-clinical targets for stasis and 1-log kill were evaluated since there were insufficient data from SOLO I and II to evaluate clinical PK-PD relationships. Percent probabilities of PK-PD target attainment were 100% up to MIC values of 0.5 mg/L so the overall percent probability of PK-PD target attainment across the MIC distribution was 100% for both AUC_{0-72}:MIC ratio targets.

Table 25

Table 1-2. Percent probabilities of PK-PD target attainment and mean percent probabilities of clinical success by oritavancin MIC and overall across the MIC distribution for *S. aureus*

Oritavancin MIC (mg/L)	Results based on non-clinical PK-PD data[a]		Results based on clinical PK-PD data[b]	
	Probability of PK-PD target attainment (%)		Probability of PK-PD target attainment (%)	Mean model-predicted probability of clinical success (%)
	Net bacterial stasis	1-log_{10} CFU reduction		
0.06	100	100	96.9	95.8
0.12	99.8	99.4	51.9	89.7
0.25	85.1	74.8	1.9	82.9
0.5	20.0	10.0	0	82.6
Overall[c]	99.8	99.6	94.3	95.4

a. Based on non-clinical PK-PD targets for *S. aureus*.
b. Based on univariable PK-PD relationship for clinical response at PTE for patients with *S. aureus*.
c. Represents the overall (i.e., the weighted average) percent probability of PK-PD target attainment or the average mean model-predicted percent probabilities of clinical success over the MIC distribution for oritavancin against *S. aureus*.

The report concluded that:
Results of univariable analyses based on data from SOLO I and II demonstrated statistically significant PK-PD relationships for a number of efficacy endpoints, including clinical response at PTE. However, the limited number of failures made it difficult to fully characterise the shape of the function for PK-PD relationships.

The majority of all patients and patients with *S. aureus* achieved the AUC_{0-72}:MIC ratio threshold of 11,982 for the univariable relationship for clinical response at PTE. Relatively higher percentages of successful responses were observed for those with higher vs. lower AUC_{0-72}:MIC ratios (96.0 vs. 84.6% for all patients; 96.2 vs. 82.6% for patients with *S. aureus*). On the basis of these findings the analyses provide support for the single 1200 mg oritavancin dose regimen that was studied in SOLO I and II.

Results of PK-PD target attainment and model-predicted clinical response analyses based on non-clinical and clinical PK-PD data provide support for establishing in-vitro interpretive criteria for oritavancin against *S. aureus* and *S. pyogenes*.

The PK-PD target attainment and model-predicted clinical response analyses based on non-clinical and clinical PK-PD data evaluated in the context of the MIC distribution for oritavancin against *S. aureus* and *S. pyogenes* provided further support for the single 1200 mg dose regimen.

2.4.4. Discussion on clinical pharmacology

Non-clinical and clinical data suggest that elimination of oritavancin occurs slowly mostly via the bile into the faeces and to a minor extent via urine. Healthy volunteers were followed for up to 2 months, at which time oritavancin was still detectable in plasma with evidence of slow declining concentrations. Incubation with human liver microsomes did not detect any depletion of oritavancin due to metabolism and non-clinical studies of radiolabelled oritavancin did not point to metabolism in several species.

On the basis of the available information it is agreed that oritavancin is not likely to be involved in clinically significant DDIs with the exception of warfarin, which is mentioned in sections 4.4 and 4.5 of the SmPC. This is due to the effects on S-warfarin resulting from inhibition of CYP2C9. There is also a quite

separate issue for use of warfarin and other anticoagulants for which in-vitro monitoring (using PT or aPTT) is necessary since oritavancin interferes with these tests. Additional information on the duration of interference after a single 1200 mg dose was provided during the procedure and is reflected in the SmPC. The applicant plans additional *in-vitro* and *in-vivo* studies to evaluate these issues.

The potential for oritavancin to inhibit or induce CYP2C8 was not evaluated. The applicant will conduct these studies as a PAM.

The dossier includes relatively recent data on the *in-vitro* activity (using the CLSI-recommended methodology) of oritavancin against geographically diverse clinical isolates. In the case of oritavancin the main interest has to be its activity against staphylococci, especially those that show any degree of reduced susceptibility to other glyco(lipo)peptides, and against the beta-haemolytic streptococci. Taking into account the documented mechanisms of action as well as the applicant's own proposals for the susceptibility test breakpoints applicable to a single 1200 mg dose regimen (≤0.12 mg/L for *S. aureus*) oritavancin is expected to be clinically active against glycopeptide-susceptible MRSA but not against hVISA, VISA or VRSA, although a very few strains may be susceptible.

Oritavancin is also not expected to be clinically active against the majority of daptomycin-insusceptible staphylococci. An association between reduced susceptibility to vancomycin and to daptomycin has been reported in the literature although a correlation is not always observed for individual isolates. Most linezolid-insusceptible strains are likely to be susceptible to oritavancin.

No information was provided on the potential for inhibition of drug transporters other than P-gp. Although the applicant considered that oritavancin is unlikely to interact with other transporters it was agreed that studies will be conducted in compliance with CHMP guidance.

2.4.5. Conclusions on clinical pharmacology

The CHMP considers the following measures necessary to address the issues related to pharmacology:

- To conduct an in-vitro study to assess the ability of oritavancin to inhibit or induce CYP2C8.
- To conduct transporter studies to meet current guidelines. The selection of transporters to be studied will be based upon the recent EMA and FDA guidance and the latest recommendations by the International Transporter Consortium.
- To conduct and complete the following:

Summary of Studies Planned or Ongoing to Further Evaluate Warfarin Interaction and Test Interference

Studies	Objectives	Final Report Submission Timelines
In-vitro study the effects of oritavancin on phospholipid and non-phospholipid based coagulation tests	The objective of this study will be to determine which tests used to monitor anticoagulant therapy may be used in patients following a single 1200 mg dose of oritavancin.	April 2015
Safety of 1200 mg IV dose of Orbactiv in patients on concomitant chronic warfarin therapy who are being treated for ABSSSI	The study will characterize the effect of oritavancin on clinical care and warfarin dosing in patients on chronic warfarin therapy, determine the magnitude and duration of alterations to warfarin dosing and assess safety	August 2016
DDI study of 1200 mg dose of Orbactiv and warfarin in healthy volunteers	This DDI study will evaluate the effects of a single 1200 mg infusion of oritavancin on safety and PK of warfarin and determine the magnitude and duration of this interaction.	June 2015
Effects of 1200 mg dose on multiple coagulation tests in healthy volunteers	The objective of this study is to evaluate the magnitude and duration of any false prolongation of the PT test in healthy volunteers following a single 1200 mg oritavancin infusion.	May 2015

2.5. Clinical efficacy

This section focuses on the three studies in which the 1200 mg single dose was used to treat ABSSSI. These included a dose finding study and two Phase 3 studies as follows:

Table 26

Type of Study; Study Identifier	Study Design and Type of Control	Number of Subjects	Study Status; Type of Report	EU Countries Involved	Other Countries involved
Efficacy and Safety TAR-ORI-SD001 (SIMPLIFI)	Multicenter, Phase 2, randomized, double-blind, parallel, active-comparator controlled study	302	Complete;full	Yes	Yes
Efficacy and Safety TMC-ORI-10-01 (SOLO I)	Multicenter, double-blind, randomized, Parallel, Comparative Efficacy and Safety Study	968	Complete; full	Yes	Yes
Efficacy and Safety TMC-ORI-10-02 (SOLO II)	Multicenter, double-blind, randomized, Parallel, Comparative Efficacy and Safety Study	1019	Complete; full	Yes	Yes

2.5.1. Dose response studies

TAR-ORI-SD001; SIMPLIFI

This randomised double-blind study was conducted in 2007-2008 at 43 sites across 5 countries. Patients with ABSSSI were eligible if they met the protocol-defined criteria for each of severity, complicated disease and disease categories (wound infections at the site of surgical incision or trauma, cellulitis or major abscess).

Randomisation was to one of (1:1:1):

- 200 mg daily for 3-7 days (the prior proposed regimen)
- 1200 mg single dose (the current proposed regimen)
- 800 mg day 1 and 400 mg on day 5 if considered necessary (an alternative exploratory regimen)

A maximum infusion rate of approximately 9 mg/min was selected to minimise the incidence of potential HLIRs. Thus, dosing employed infusions of 200 mg in 250 ml over 45-60 min or sequential administrations of 400 mg, each in 250 ml over 45-60 min (1200 mg was given over 2 h 15 min to 3 h).

Patients requiring further therapy after Day 7 were considered clinical failures.

The primary analysis was based on investigator-determined clinical outcomes (IDCO) at first follow-up (day 21) in CE patients Assuming a response rate of 85% and a 2-sided 90% (note, not 95%) confidence interval around the difference between groups in response rates it was estimated that 70 CE patients per arm would yield nearly 80% power to declare non-inferiority to within 15%. Assuming a clinical evaluability rate of 70%, 300 (100 per treatment group) were to be enrolled. Overall 302 patients (210 USA) received study medication, including 199 males and 103 females with a mean age of 45 years.

Table 27

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)

There was a disproportion between the percentage of patients who discontinued early in the daily dose group (22% [22/78]) compared to single (10.1% [10/89]) and infrequent (9.7% [10/93]) dose groups. The reasons patients were excluded from the CE population included not meeting enrolment criteria, receiving < 80% of intended study medication, having an indeterminate investigator-determined clinical outcome (IDCO) at EOT or first follow-up or not having a first follow-up (TOC) assessment.

The primary analysis indicated that a single dose of 1200 mg or 800 mg with an optional 400 mg dose on Day 5 was non-inferior to 200 mg for 3 to 7 days. Note the comparisons show 90% CI and not 95% CI.

Table 28

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	5.2
Failure	21 (27.6)	15 (18.5)	16 (22.5)	(-2.5, 18.2)	(-6.8, 15.4)

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. In the table below the numbers and percentages do not reflect the total ITT per group because those with missing and indeterminate outcomes have been excluded. A further ITT analysis in which these cases were counted as failures gave cure rates of 63/98 (64.3%), 72/99 (72.7%) and 68/103 (66%) in respective dose groups.

Table 29

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)		

Abbreviations: CI = confidence interval; ITT = intent-to-treat; ME = microbiolgically evaluable; MITT = microbiological intent-to-treat.

[a] Includes cure and improvement outcomes

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

For CE patients the first follow-up response rates were lowest for wound infections and highest for major abscesses. Cure rates were comparable between treatment groups for major abscesses.

Table 30

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.

In addition 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. A single dose or infrequent dosing appeared to be better for cellulitis and there were statistically significant differences 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. IDCO at first follow-up in the CE population by patient sub-groups are difficult to interpret due to low denominators and no conclusions can be drawn.

Table 31

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	-15.3
Failure	4 (40.0)	4 (33.3)	8 (57.1)	(-39.3, 32.9)	(-69.8, 12.8)
MRSA					
Cure[a]	18 (78.3)	27 (73.0)	20 (87.0)	-3.8	10.9
Failure	5 (21.7)	10 (27.0)	3 (13.0)	(-25.1, 12.9)	(-6.9, 25.3)
Bacteremia					
Cure [a]	1 (33.3)	3 (60.0)	1 (100)	60.0	NA
Failure	2 (66.7)	2 (40.0)	0	(NA, NA)	(NA, NA)
Polymicrobial Infection					
Cure [a]	3 (42.9)	6 (100)	6 (100)	52.2	50.0
Failure	4 (57.1)	0	0	(2.1, 76.6)	(9.6, 72.3)

Abbreivations: CI = confidence interval; MRSA = methicillin-resistant *Staphylococcus aureus*.

[a] Includes cure and improvement outcomes.

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

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.

Staphylococcus aureus was the most frequently isolated pathogen (in 183 [87.6%] of the 209 MITT patients) and 103/183 were MRSA. In the ME population the IDCO-assigned by-pathogen cure rates for MRSA were 78.3% (18/23), 73.0% (27/37) and 87.0% (20/23) in the daily dose, single dose and infrequent dose groups, respectively. Similar results applied in the MITT population as shown below.

Table 32

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

There was no obvious relationship between oritavancin MIC and rate of cure at first follow-up in the ME population, including *S. aureus* and MRSA. However, there were only 4 *S. aureus* in the ME population and 5 in the MITT population with oritavancin MICs > 0.12 mg/l. Two *S. aureus* had vancomycin MICs > 1 mg/L (both 2 mg/L) at baseline. Six patients had baseline isolates that showed an increase in oritavancin MIC from baseline (5 with *S. aureus* and one with *S. intermedius*). Three failed at first follow-up, two were improved and one was cured. In no case did the final MIC exceed 0.25 mg/l.

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

Table 33

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)		

Similarly, the patient-level cure rates according to baseline pathogen followed the pattern in the CE population since most outcomes were based on the clinical response.

Table 34

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

2.5.2. Main studies

A MULTICENTER, DOUBLE-BLIND, RANDOMIZED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF SINGLE-DOSE IV ORITAVANCIN VERSUS IV VANCOMYCIN FOR THE TREATMENT OF PATIENTS WITH ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTION (SOLO I)

A MULTICENTER, DOUBLE-BLIND, RANDOMIZED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF SINGLE-DOSE IV ORITAVANCIN VERSUS IV VANCOMYCIN FOR THE TREATMENT OF PATIENTS WITH ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTION (SOLO II)

Methods

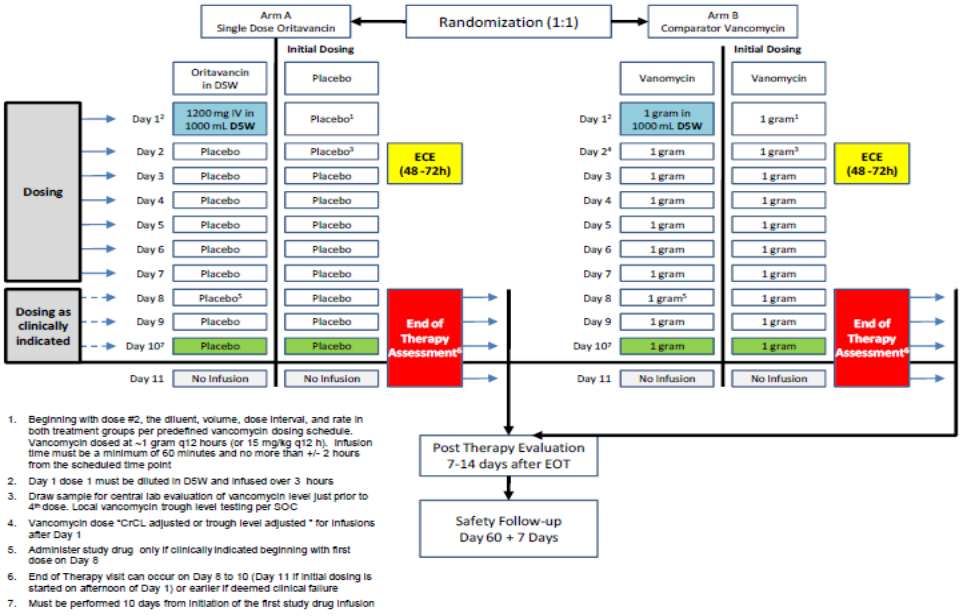
These double-blind studies of identical design were initiated in January 2011. SOLO II completed about 6 months after SOLO I. The geographical locations of sites differed between the two as follows:

- SOLO I was conducted at 46 sites across 9 countries and included 23 sites in the US.
- SOLO II was conducted at 32 sites across 10 countries and included 11 sites in the US
- Both studies included at least one site in India, Israel, Mexico, Romania, Russia, Spain and Ukraine. SOLO I also had a site in Germany while SOLO II had one site in each of Canada and Argentina.

The studies were conducted at a time when new US FDA guidance on studies in ABSSSI had been issued recommending a primary analysis based on early (on-treatment) endpoints as described below whereas the EU guidance continued to request a primary analysis based on the clinical outcome at an appropriate post-therapy test of cure (TOC) visit. However, during this same period the EMA and FDA agreed that the same studies could be used to support applications in each of the US and EU provided that two statistical analyses plans were developed. The applicant followed this strategy as explained below.

The general design features are shown in the figure.

Figure 11



Study Participants

Eligible adult patients were to have a diagnosis of ABSSSI suspected or confirmed to be caused by a Gram-positive pathogen and expected to require at least 7 days of IV therapy. A specimen for culture was obtained within 24 h of the first dose of study drug.

ABSSSI included one of the following infections:

a. Wound infections: either traumatic or surgical with purulent drainage and surrounding erythema, oedema and/or induration of at least 75 cm^2 with onset within 7 days of randomisation and within 30 days of the insult

b. Cellulitis/erysipelas: spreading erythema, oedema and/or induration of at least 75 cm^2 with onset within 7 days of randomisation

c. Major cutaneous abscess: collection of pus accompanied by erythema, oedema and/or induration of at least 75 cm^2

Accompanied by:

At least two of purulent drainage or discharge; erythema; fluctuance; heat or localized warmth; oedema/induration; pain or tenderness to palpation

AND At least one of proximal lymph node swelling and tenderness; increased temperature (≥ 38.0°C oral); decreased temperature (< 36.0°C oral route); increased WBC (≥ 10,000 cells/µL); band forms > 10%; CRP > ULN

OR At least one of age > 70 years; diabetes mellitus requiring treatment; immunosuppressive therapy or chemotherapy in the prior 3 months

Treatments

Oritavancin was given on Day 1 as a single 1200 mg dose in 1000 mL of 5% D5W over 3 h. Vancomycin was administered IV for 7 to 10 days. The first dose on Day 1 was administered as 1 g or 15 mg/kg in 1000 mL D5W over 3 h and then as 1 g or 15 mg/kg q12h in volumes and diluents selected for the individual patient infused over at least 60 min. Subsequent doses could be adjusted by the unblinded pharmacist based on CrCl levels, clinical status or vancomycin trough levels. Aztreonam and metronidazole were allowed for patients with mixed infections.

Objectives

The primary objective as stated in the protocol was to establish non-inferiority of oritavancin vs. vancomycin based on the primary efficacy outcome of cessation of spread or reduction in size of the baseline lesion, absence of fever and no rescue medication at Early Clinical Evaluation (ECE; 48 to 72 h after start of study treatment) in the modified intent-to-treat (MITT) population.

The critical secondary objective was to evaluate the clinical response vs. vancomycin at End of Therapy (EOT) and sustained to Day 10 and the post therapy evaluation (PTE) in the MITT and CE populations.

Outcomes/endpoints

The primary efficacy endpoint as stated in the protocol was early clinical response at the ECE visit. Early clinical response was a composite outcome of the following:

- Cessation of spreading or reduction in the size of baseline lesion
- Absence of fever
- No rescue antibacterial agent given

A patient was a success if all three components were met and failed if ≥ 1 of the following occurred:

- Death (all-cause mortality) during the first 72 h
- Fever defined as at least one oral temperature ≥ 37.7°C between 48 and 72 h
- Spreading of lesion size at 48 to 72 h vs. baseline except that a ≥ 20% reduction in lesion area from baseline was not classed as failure even if there was an increase in lesion length or width
- Administration of rescue antibacterial therapy for ABSSSI during the first 72 h
- Additional, unplanned, surgical procedure during the first 72 h

The key secondary efficacy endpoint was investigator-assessed clinical cure at PTE. This was designated as the primary endpoint for the EMA. This endpoint was pre-specified for non-inferiority testing with a margin of 10% in the MITT and CE populations.

There were two main secondary efficacy endpoints:

i) Lesion size reduction ≥ 20% from baseline at ECE. This is the endpoint currently recommended by FDA and NIH for an ABSSSI treatment. This endpoint was pre-specified for non-inferiority testing with a margin of 10% using the MITT and CE populations.
ii) Sustained clinical response at PTE i.e. EOT cure that is sustained over time. This endpoint was not pre-specified for non-inferiority testing.

There were four visits during the follow-up period:

1. An EOT visit within 24 h of last administration of study drug or change to non-study drug
2. A Day 10 visit at 10 days from initiation of the first dose of study drug, which in some patients was the same as the EOT visit
3. A PTE visit at 7 to 14 days from the EOT visit
4. A safety follow-up visit at 60 days after the first dose of study drug

Each investigational site's laboratory cultured specimens (aerobic and where possible, anaerobic) and identified any pathogen(s). All pathogens obtained from the infection site were sub-cultured and sent to the Central Laboratory for identification to the species level. MICs were determined using broth microdilution by the Central Laboratory. *S. aureus* strains were screened for the Panton-Valentine Leukocidin (*pvl*) by polymerase chain reaction. A subset of *S. aureus* strains (those with vancomycin MICs

of 1 or 2 µg/mL) was screened for the hVISA phenotype with glycopeptide resistance detection (GRD) Etest strips (bioMerieux).

Sample size

For the primary efficacy endpoint (i.e. the FDA-recommended endpoint) the response rates in both treatment groups in the MITT population were assumed to be 75%. A sample size of approximately 960 patients (480 per treatment group) would provide at least 90% power to reject the null hypothesis at the 1-sided alpha level of 0.025. This sample size also provides at least 90% power to demonstrate non-inferiority for the clinical cure at PTE assessment of efficacy at the 1-sided alpha level of 0.025, assuming a clinical cure event rate of 65% in the MITT population in both treatment groups. Patient enrolment was to continue until approximately 175 patients were confirmed with MRSA as a baseline pathogen.

Randomisation

Randomization was stratified by geographic region (North America, South America, Eastern Europe, Western Europe, and Asia), study site and diabetes mellitus diagnosis. An enrolment cap of 30% was maintained for major cutaneous abscesses.

Blinding (masking)

The studies were double-blind.

Statistical methods

The following patient populations were used for the efficacy analyses:

- Intent-to-Treat (ITT) = all randomised
- MITT = primary population for efficacy analyses = all treated (≥ one dose of assigned treatment)
- CE = MITT patients who met the inclusion/exclusion criteria, received at least 7 days of study treatment and had an investigator assessment of clinical outcome.
- MicroITT = MITT patients with baseline Gram-positive pathogen(s) known to cause ABSSSI.
- MicroE = all patients meeting criteria for inclusion in both the MicroITT and CE populations

Unless otherwise specified, missing data was not imputed and was excluded from analysis.

For the EU primary analysis patients with assessments outside the visit window had their responses at PTE imputed as follows:

- If a patient had clinical failure assessed beyond the PTE visit window, the patient was considered as a clinical failure at PTE

- If a patient had clinical success assessed beyond the PTE visit window:

*The patient was a clinical failure at PTE if he/she had failed before the PTE visit
*The patient was a clinical success at PTE if he/she was a clinical success before the PTE visit

After imputation, patients who still had a missing assessment at PTE were treated as failures.

Results

SOLO I

Participant flow

There were 954 treated patients (MITT population). Two patients randomised to oritavancin were inadvertently dosed with vancomycin. The majority (oritavancin 88.6% and vancomycin 83.9%) completed treatment for 7 to 10 days and around 90% completed to the Day 60 safety visit. There were no major protocol violations or deviations from the study eligibility criteria that affected the results.

Table 35

Table 6: Patient Disposition (mITT Population)

	Oritavancin (N=475) n (%)	Vancomycin (N=479) n (%)
Did not receive study drug	8 (1.7)	6 (1.2)
Completed study drug/placebo	421 (88.6)	402 (83.9)
Discontinued study drug/placebo early*	54 (11.4)	77 (16.1)
AE	18 (3.8)	22 (4.6)
Abnormal laboratory value(s)	0	2 (0.4)
Abnormal test procedure result(s)	1 (0.2)	0
Protocol violation	0	4 (0.8)
Patient withdrew consent	14 (2.9)**	22 (4.6)
Administrative problems	8 (1.7)	16 (3.3)
Confirmation of Gram-negative infection only	2 (0.4)	0
Sponsor decision (discontinued by Sponsor)	1 (0.2)	1 (0.2)
Resolution of infection per investigator	1 (0.2)	0
Unsatisfactory therapeutic effect	9 (1.9)	10 (2.1)
Completed the study	433 (91.2)	423 (88.3)
Did not complete the study	42 (8.8)	56 (11.7)
AE	1 (0.2)	1 (0.2)
Patient withdrew consent	16 (3.4)	20 (4.2)
Administrative problems	0	1 (0.2)
Death	1 (0.2)	2 (0.4)
Lost to follow-up	21 (4.4)	32 (6.7)
Other	3 (0.6)	0

Conduct of the study

There were 2 amendments after starting enrolment. The only important change was made in Amendment 1, which removed mandatory 72 h hospitalisation, so allowing an outpatient assessment of ECE.

Baseline data

Most patients were enrolled in North America (62.7%) and Asia (31.0%) and were predominantly white and male. There was no difference in baseline disease or primary infection site characteristics between the treatment groups. Half of the patients had cellulitis/erysipelas, nearly 30% had a major cutaneous abscess and 15% met the SIRS criteria. The median infection area at baseline was 248.0 cm^2 for the oritavancin group and 225.6 cm^2 for the vancomycin group.

In the MITT population *S. aureus* was the most common (MRSA in 204 and MSSA in 230 patients) while *S. pyogenes* was found in 3.3%. For these species MICs of oritavancin were ≤ 0.25 mg/L and mostly did not exceed 0.06 mg/L. MICs of vancomycin did not exceed 1 mg/L for *S. aureus* (in the vancomycin group 14 MRSA and 17 MSSA had MICs = 1 mg/L) or 0.25 mg/L for *S. pyogenes*. There were 18 oritavancin and 9 vancomycin patients with bacteraemia.

Most patients (98.7%) in the oritavancin group received a full dose of 1200 mg on Day 1 and 88.6% completed the twice daily placebo infusions for 7 to 10 days. Slightly fewer (83.9%) in the vancomycin group completed 7 to 10 days of therapy. Less than 10% received aztreonam and/or metronidazole.

Numbers analysed

The percentages in each of the analysis populations were comparable between the treatment groups.

Table 36

Table 10: Analysis Populations

Category	Oritavancin (N=483) n (%)	Vancomycin (N=485) n (%)
Intent–to-Treat (ITT) Population[a]	483	485
Modified ITT (mITT) Population[b]	475 (98.3)	479 (98.8)
Clinically Evaluable (CE) Population[c]	394 (81.6)	397 (81.9)
Microbologically ITT (MicroITT) Population[d]	244 (50.5)	242 (49.9)
Microbiologically Evaluable (MicroE) Population[e]	201 (41.6)	201 (41.4)
Safety Population[f,g]	473	481
PK Population[h]	115	0

Outcomes and estimation

Most patients (98.7%) in the oritavancin group received a full dose of 1200 mg on Day 1 and 88.6% completed the twice daily placebo infusions for 7 to 10 days. Slightly fewer (83.9%) in the vancomycin group completed 7 to 10 days of therapy. Less than 10% received aztreonam and/or metronidazole.

The non-inferiority margin for the primary efficacy analysis of early clinical response was met.

Table 37

Table 11: Early Clinical Response (mITT Population)

Variable	Oritavancin % (proportion)	Vancomycin % (proportion)	Difference (95% CI)
Early Clinical Response	82.3% (391/475)	78.9% (378/479)	3.4 (-1.6, 8.4)

mITT: modified intent-to-treat.

The results in the ITT and CE populations were consistent:

ITT - oritavancin 78.3%; vancomycin 79.0%; difference: -0.7% (95% CI: -5.9, 4.5)

CE - oritavancin 91.9%; vancomycin 93.2%; difference -1.3% (95% CI: -5.0, 2.3)

Investigator-assessed clinical outcome at PTE was missing for 55 oritavancin and 61 vancomycin patients. When patients with missing values were entirely excluded from the analysis the cure rates were 90.0% vs. 91.6% and when they were counted as successes the rates were 91.2% vs. 92.7%.

Percentages with an early clinical response but without cure at PTE were 14.8% for oritavancin and 11.9% for vancomycin. The most frequent reason was the use of non-study antibacterial agents before or at PTE and worsening of erythema/induration or purulent drainage before or at PTE.

A sustained clinical response at PTE was observed for 65.9% oritavancin and 67.2% vancomycin MITT patients (difference -1.3%; 95% CI -7.3, 4.7). Failure was reported for 25.3% and 25.1% while data were missing for 8.8% and 7.7%. If missing values were excluded the rates were 72.3% vs. 72.9% and if they were treated as success the rates were 74.7% vs. 74.9%.

Percentages of patients with microbiological success at PTE were based on the clinical response and therefore were similar between treatments.

Table 38

Table 21: Patient-Level Microbiological Response at PTE (MicroITT Population)

Microbiological Response	Oritavancin (N=244)	Vancomycin (N=242)	Difference (95% CI)
Success	194/213 (91.1)	197/209 (94.3)	-3.2 (-8.1, 1.8)
Eradication	0/213	0/209	
Presumed Eradication	194/213 (91.1)	196/209 (93.8)	-2.7 (7.7, 2.3)
Colonization	0/213	1/209 (0.5)	-0.5 (-1.4, 0.5)
Failure	19/213 (8.9)	12/209 (5.7)	3.2 (1.8, 8.1)
Persistence	0/213	0/209	
Presumed Persistence	18/213 (8.5)	11/209 (5.3)	3.2 (-1.6, 8.0)
Superinfection	0/213	0/209	
Relapse or Recurrence	1/213 (0.5)	1/209 (0.5)	-0.0 (-1.3, 1.3)

The microbiological success rates were comparable between treatment groups by type of infection. Similar results were seen with the MicroE population. In the patients with bacteraemia the patient-level microbiological success rates at PTE were oritavancin 10/15 and vancomycin 3/7 while rates for those with ABSSSI pathogens in blood were 6/9 and 1/3. For patients with MRSA or with MSSA the cure rates at PTE were comparable between treatments in both population subsets with pathogens.

Table 39

Table 25: Primary and Main Secondary Efficacy Endpoints in Patients with ABSSSI caused by MRSA (MicroITT and MicroE Populations)

Variable	Population	Oritavancin % (proportion)	Vancomycin % (proportion)	Difference (95% CI)
Early clinical response	MicroITT	80.8 (84/104)	80.0 (80/100)	0.8 (-10.1, 11.7)
	MicroE	88.4 (76/86)	86.6 (71/82)	1.8 (-8.2, 11.8)
Investigator assessed clinical cure at PTE	MicroITT	82.7 (86/104)	83.0 (83/100)	-0.3 (-10.7, 10.0)
	MicroE	95.3 (82/86)	97.6 (80/82)	-2.2 (-7.8, 3.4)
Lesion size reduction ≥20% from baseline at ECE	MicroITT	90.4 (94/104)	84.0 (84/100)	6.4 (-2.8, 15.5)
	MicroE	96.5 (83/86)	89.0 (73/82)	7.5 (-0.3, 15.3)
Sustained clinical response at PTE	MicroITT	70.2 (73/104)	71.0 (71/100)	-0.8 (-13.3, 11.7)
	MicroE	83.7 (72/86)	86.6 (71/82)	-2.9 (-13.6, 7.9)

In the MicroITT population 291/407 (71.5%) of baseline *S. aureus* screened were positive for the *pvl* gene (100/208 of MSSA and 191/199 of MRSA). The presence of *pvl* had no impact on MICs but there was a noticeable impact on the rates of early clinical response in the oritavancin and vancomycin groups. In contrast the IDCO cure rates at PTE by *pvl* status did not demonstrate such an effect in the MicroITT or ME populations.

Table 40

Table 27: Early Clinical Response at ECE in Patients with *S. aureus* at Baseline by *pvl* Status (MicroITT Population)

	Oritavancin (n/N [%])		Vancomycin (n/N [%])	
Pathogen	*pvl-*	*pvl+*	*pvl-*	*pvl+*
S. aureus	52/60 (86.7)	118/147 (80.3)	50/56 (89.3)	115/144 (79.9)
MRSA	5/5 (100.0)	77/95 (81.1)	3/3 (100.0)	76/ 96 (79.2)
MSSA	47/55 (85.5)	41/52 (78.8)	47/53 (88.7)	39/48 (81.3)

Among the 52 isolates of *S. aureus* screened for the hVISA phenotype by GRD methodology due to having a vancomycin MIC of 1 µg/mL 12 (23.1%) were GRD positive. All the patients with hVISA had an early clinical response. In addition, hVISA did not impact on cure rates at PTE.

Eradication rates (presumed from clinical cure rates) for MRSA are shown as an example below. The pathogen-level microbiological responses generally were not impacted by oritavancin MIC.

Table 41

Table 4.4.12.3 Pathogen-level Microbiological Response by Baseline Pathogen (MicroITT population)

Pathogen: Staphylococcus aureus - MRSA

Clinical Outcome	Oritavancin (N=244)	Vancomycin (N=242)	Diff and 95% CI
Number of Patients with Pathogen	104 (42.6)	101 (41.7)	
Pathogen-level Microbiological Response at EOT			
Eradication*	89/97 (91.8)	86/93 (92.5)	-0.7 (-8.4, 6.9)
Eradication	0/97	0/93	
Presumed Eradication	89/97 (91.8)	85/93 (91.4)	0.4 (-7.5, 8.3)
Persistence*	8/97 (8.2)	7/93 (7.5)	0.7 (-6.9, 8.4)
Persistence	1/97 (1.0)	0/93	
Presumed Persistence	7/97 (7.2)	7/93 (7.5)	-0.3 (-7.7, 7.1)
Pathogen-level Microbiological Response at Day 10			
Eradication*	88/97 (90.7)	87/91 (95.6)	-4.9 (-12.0, 2.3)
Eradication	0/97	0/91	
Presumed Eradication	88/97 (90.7)	86/91 (94.5)	-3.8 (-11.2, 3.6)
Persistence*	9/97 (9.3)	4/91 (4.4)	
Persistence	0/97	0/91	
Presumed Persistence	9/97 (9.3)	4/91 (4.4)	
Pathogen-level Microbiological Response at PTE			
Eradication*	86/93 (92.5)	84/88 (95.5)	-3.0 (-9.9, 3.9)
Eradication	0/93	0/88	
Presumed Eradication	86/93 (92.5)	83/88 (94.3)	-1.8 (-9.1, 5.4)
Persistence*	7/93 (7.5)	4/88 (4.5)	
Persistence	0/93	0/88	
Presumed Persistence	7/93 (7.5)	4/88 (4.5)	
Relapse or Recurrence	0/93	0/88	

A consistent treatment effect was seen for early clinical response and investigator-assessed clinical cure by sex, age, race, geographic region and diabetes mellitus. Consistent effects were also seen by disease category and in the sub-group with SIRS.

SOLO II

Participant flow

There were 1005 treated patients (MITT population). The majority (oritavancin 90.3% and vancomycin 88.8%) completed treatment for 7 to 10 days and around 90% completed to the Day 60 safety visit. There were no major protocol violations or deviations from the study eligibility criteria that affected the safety or efficacy results.

Table 42

Table 6: Patient Disposition (mITT Population)

	Oritavancin (N=503) n (%)	Vancomycin (N=502) n (%)
Did not receive study drug	6 (1.2)	8 (1.6)
Completed study drug/placebo	454 (90.3)	446 (88.8)
Discontinued study drug/placebo early*	49 (9.7)	56 (11.2)
AE	16 (3.2)**	9 (1.8)
Abnormal laboratory value(s)	1 (0.2)	1 (0.2)
Protocol violation	4 (0.8)	4 (0.8)
Patient withdrew consent	12 (2.4)	20 (4.0)
Administrative problems	6 (1.2)	16 (3.2)
Confirmation of Gram-negative infection only	1 (0.2)	0
Sponsor decision (discontinued by Sponsor)	1 (0.2)***	1 (0.2)
Resolution of infection per investigator	1 (0.2)	0
Unsatisfactory therapeutic effect	7 (1.4)	5 (1.0)
Completed the study	455 (90.5)	446 (88.8)
Did not complete the study	48 (9.5)	56 (11.2)
AE	1 (0.2)	0
Patient withdrew consent	14 (2.8)	15 (3.0)
Administrative problems	0	1 (0.2)
Death	1 (0.2)	1 (0.2)
Lost to follow-up	28 (5.6)	36 (7.2)
Other	4 (0.8)	3 (0.6)

Conduct of the study

The same amendments applied as in SOLO I. There were no major protocol violations or deviations from the study eligibility criteria that affected the safety or efficacy results.

Baseline data

Most patients were enrolled in North America (56.9%) and Asia (23.6%) and were predominantly white and male. There was no difference in baseline disease or primary infection site characteristics between the treatment groups. In contrast to SOLO I about one-third of patients had each of the three major diagnoses and the median infection area at baseline was slightly higher in SOLO II. Fewer patients in SOLO II had diabetes but slightly more met the SIRS criteria.

S. aureus was the most common pathogen but a higher proportion were MSSA in SOLO II vs. SOLO I. Also, there was a slightly higher rate of *S. pyogenes* (8.1% and 7.1% per group). MICs of oritavancin did not exceed 0.25 mg/L for these species. MICs of vancomycin were ≤ 1 mg/L but 8 MRSA and 18 MSSA treated with vancomycin had MICs = 1 mg/L. There were 10 oritavancin and 10 vancomycin patients with bacteraemia.

Most patients (93.8%) in the oritavancin group received a full dose of 1200 mg on Day 1 and 90.3% completed the twice daily placebo infusions for 7 to 10 days. Slightly fewer (88.8%) completed 7 to 10 days of vancomycin. Aztreonam was given to ~8% per group and metronidazole to 6.4% and 4.4%.

Numbers analysed

The percentages in each of the analysis populations were comparable between the treatment groups.

Table 43

Table 10: Analysis Populations

Category	Oritavancin (N=509) n (%)	Vancomycin (N=510) n (%)
Intent–to-Treat (ITT) Population[a]	509	510
Modified ITT (mITT) Population[b]	503 (98.8)	502 (98.4)
Clinically Evaluable (CE) Population[c]	427 (83.9)	408 (80.0)
Microbologically ITT (MicroITT) Population[d]	285 (56.0)	296 (58.0)
Microbiologically Evaluable (MicroE) Population[e]	246 (48.3)	247 (48.4)
Safety Population[f, g]	503	502
PK Population[h]	197	0

Outcomes and estimation

The non-inferiority margin for the primary efficacy analysis of early clinical response was met.

Table 44

Table 11: Early Clinical Response (mITT Population)

Variable	Oritavancin % (proportion)	Vancomycin % (proportion)	Difference (95% CI)
Early Clinical Response	80.1% (403/503)	82.9% (416/502)	-2.7 (-7.5, 2.0)

The percentages who failed and reasons for treatment failure were similar between groups. The baseline lesion area was similar between treatment groups for patients with and without an early clinical response.

When early clinical response was calculated using the composite endpoint (cessation of spread or reduction in size and no rescue medication) 90.1% and 89.4% in the oritavancin and vancomycin groups, respectively, had an early clinical response. Early clinical response rates in the ITT and CE populations gave consistent results.

In the primary analysis for the EU non-inferiority was demonstrated.

Table 45

Table 13: Investigator-Assessed Clinical Cure at PTE (mITT Population)

Variable	Oritavancin % (proportion)	Vancomycin % (proportion)	Difference (95% CI)
Investigator-assessed clinical cure	82.7% (416/503)	80.5% (404/502)	2.2 (-2.6, 7.0)

The percentages assessed as treatment failures by investigators were similar in the oritavancin (7.4%) and vancomycin (7.6%) groups. In addition, 9.9% and 12.0% in respective groups had a missing

outcome at PTE and were categorized as treatment failures in the main analysis. The results in the ITT and CE populations were consistent:

ITT - oritavancin 81.7%; vancomycin 79.2%; difference: 2.5% (95% CI: -2.4, 7.4)
CE - oritavancin 93.2%; vancomycin 94.9%; difference -1.6% (95% CI: -4.9, 1.6)
Investigator-assessed clinical outcome at PTE was missing for 50 oritavancin and 60 vancomycin patients. When patients with missing values were entirely excluded from the analysis the cure rates were 91.8% vs. 91.4% and when they were counted as successes the rates were 92.6% vs. 92.4%.

Percentages with an early clinical response but without cure at PTE were 12.2% for oritavancin and 13.5% for vancomycin. The most frequent reason was worsening of erythema/induration or purulent drainage before or at PTE and the use of non-study antibacterial agents before or at PTE.

A sustained clinical response at PTE was observed for 74.4% oritavancin and 73.7% vancomycin patients (difference -0.6%; 95% CI -4.8, 6.1). Failure was reported for 18.1% and 15.7% while data were missing for 7.6% and 10.6%. If missing values were excluded the rates were 80.4% vs. 82.4% and if they were treated as success the rates were 81.9% vs. 84.3%.

Percentages with microbiological success at PTE were similar between treatments.

Table 46

Table 21: Patient-Level Microbiological Response at PTE (MicroITT Population)

Microbiological Response	Oritavancin (N=285)	Vancomycin (N=296)	Difference (95% CI)
Success	240/257 (93.4)	251/271 (92.6)	0.8 (-3.6, 5.1)
Eradication	0/257	0/271	
Presumed Eradication	239/257 (93.0)	251/271 (92.6)	0.4 (-4.0, 4.8)
Colonization	1/257 (0.4)	0/271	0.4 (-0.4, 1.2)
Failure	17/257 (6.6)	20/271 (7.4)	-0.8 (-5.1, 3.6)
Persistence	1/257 (0.4)	0/271	0.4 (-0.4, 1.2)
Presumed Persistence	16/257 (6.2)	20/271 (7.4)	-1.2 (-5.4, 3.1)
Superinfection	0/257	0/271	
Relapse or Recurrence	0/257	0/271	

The microbiological success rates were comparable between treatment groups by type of infection. Similar results were seen with the MicroE population. In the MicroITT population the patient-level microbiological success rates at PTE were 4/8 and 9/9 and for pathogens known to cause ABSSSI the rates were 1/3 and 3/3, respectively. For patients with MRSA or MSSA the cure rates at PTE were comparable between treatments in both populations.

Table 47

Table 25: Primary and Main Secondary Efficacy Endpoints in Patients with ABSSSI caused by MRSA (MicroITT and MicroE Populations)

Variable	Population	Oritavancin % (proportion)	Vancomycin % (proportion)	Difference (95% CI)
Early clinical response	MicroITT	82.0 (82/100)	81.2 (82/101)	0.8 (-9.9, 11.5)
	MicroE	83.0 (73/88)	86.7 (72/83)	-3.8 (-14.5, 6.9)
Investigator assessed clinical cure at PTE	MicroITT	84.0 (84/100)	85.1 (86/101)	-1.1 (-11.1, 8.8)
	MicroE	92.0 (81/88)	96.4 (80/83)	-4.3 (-11.3, 2.6)
Lesion size reduction ≥ 20% from baseline at ECE	MicroITT	96.0 (96/100)	90.1 (91/101)	5.9 (-1.1, 12.9)
	MicroE	96.6 (85/88)	91.6 (76/83)	5.0 (-2.1, 12.1)
Sustained clinical response at PTE	MicroITT	76.0 (76/100)	75.2 (76/101)	0.8 (-11.1, 12.6)
	MicroE	83.0 (73/88)	88.0 (73/88)	-5.0 (-15.5, 5.5)

In the MicroITT population 281/508 (55.3%) of baseline *S. aureus* screened were positive for the *pvl* gene (100/307 MSSA and 181/201 MRSA). The presence of *pvl* had no impact on MICs and only a modest negative effect on early clinical response rates in the oritavancin and vancomycin groups. The IDCO cure rates at PTE by *pvl* status showed no effect or a modest effect.

Tables 48 & 49

Table 4.2.7.5 Investigator-Assessed Clinical Cure at PTE by PVL Status in Strains of Staphylococcus aureus (MicroITT population)

	Oritavancin (N=285)			Vancomycin (N=296)		
Pathogen	PVL Negative	PVL Positive	PVL Total	PVL Negative	PVL Positive	PVL Total
Staphylococcus aureus	95/108 (88.0)	119/142 (83.8)	214/250 (85.6)	104/119 (87.4)	118/139 (84.9)	222/258 (86.0)
MRSA	7/ 8 (87.5)	77/ 92 (83.7)	84/100 (84.0)	11/ 12 (91.7)	75/ 89 (84.3)	86/101 (85.1)
MSSA	88/100 (88.0)	42/ 50 (84.0)	130/150 (86.7)	93/107 (86.9)	43/ 50 (86.0)	136/157 (86.6)

Table 4.2.7.6 Investigator-Assessed Clinical Cure at PTE by PVL Status in Strains of Staphylococcus aureus (MicroE population)

	Oritavancin (N=246)			Vancomycin (N=247)		
Pathogen	PVL Negative	PVL Positive	PVL Total	PVL Negative	PVL Positive	PVL Total
Staphylococcus aureus	93/ 96 (96.9)	112/120 (93.3)	205/216 (94.9)	98/100 (98.0)	111/116 (95.7)	209/216 (96.8)
MRSA	7/ 8 (87.5)	74/ 80 (92.5)	81/ 88 (92.0)	9/ 9 (100.0)	71/ 74 (95.9)	80/ 83 (96.4)
MSSA	86/ 88 (97.7)	38/ 40 (95.0)	124/128 (96.9)	89/ 91 (97.8)	40/ 42 (95.2)	129/133 (97.0)

The early clinical response rates were comparable between treatments for non-hVISA but lower for oritavancin among the very few hVISA. In contrast, all patients with hVISA in both treatment groups (2 and 3 per group) had an investigator-assigned outcome of cure at PTE.

The eradication rates were very predominantly presumed from the clinical cure rates. The data for MRSA are shown as an example below. The pathogen level responses were generally not impacted by MIC.

Table 50

Table 4.4.12.3 Pathogen-level Microbiological Response by Baseline Pathogen (MicroITT population)

Pathogen: Staphylococcus aureus - MRSA

Clinical Outcome	Oritavancin (N=285)	Vancomycin (N=296)	Diff and 95% CI
Number of Patients with Pathogen	100 (35.1)	103 (34.8)	
Pathogen-level Microbiological Response at EOT			
Eradication*	89/97 (91.8)	89/96 (92.7)	-1.0 (-8.5, 6.6)
Eradication	0/97	1/96 (1.0)	
Presumed Eradication	89/97 (91.8)	88/96 (91.7)	0.1 (-7.7, 7.9)
Persistence*	8/97 (8.2)	7/96 (7.3)	1.0 (-6.6, 8.5)
Persistence	4/97 (4.1)	0/96	
Presumed Persistence	4/97 (4.1)	7/96 (7.3)	
Pathogen-level Microbiological Response at Day 10			
Eradication*	89/96 (92.7)	87/94 (92.6)	0.2 (-7.3, 7.6)
Eradication	0/96	1/94 (1.1)	
Presumed Eradication	89/96 (92.7)	86/94 (91.5)	1.2 (-6.5, 8.9)
Persistence*	7/96 (7.3)	7/94 (7.4)	-0.2 (-7.6, 7.3)
Persistence	1/96 (1.0)	0/94	
Presumed Persistence	6/96 (6.3)	7/94 (7.4)	-1.2 (-8.4, 6.0)
Pathogen-level Microbiological Response at PTE			
Eradication*	84/93 (90.3)	86/93 (92.5)	-2.2 (-10.2, 5.9)
Eradication	0/93	1/93 (1.1)	
Presumed Eradication	84/93 (90.3)	85/93 (91.4)	-1.1 (-9.4, 7.2)
Persistence*	9/93 (9.7)	7/93 (7.5)	2.2 (-5.9, 10.2)
Persistence	1/93 (1.1)	0/93	
Presumed Persistence	8/93 (8.6)	7/93 (7.5)	1.1 (-6.7, 8.9)
Relapse or Recurrence	0/93	0/93	

A consistent treatment effect was seen for early clinical response and investigator-assessed clinical cure by sex, age, race and geographic region and also in the sub-group with SIRS. In the MITT population the cure rates at PTE favoured vancomycin in the patients with diabetes mellitus (32/46 [69.6%] for oritavancin and 40/45 [88.9%] for vancomycin).

Ancillary analyses – SOLO 1 & SOLO 2

There were relatively small numbers of some species per study, especially *S. pyogenes* cases. The tables below summarise cure rates by pathogen at PTE in the MicroITT and MicroE populations across SOLO I and II. As far as can be discerned, the species-specific rates were similar between treatments.

Table 51

Table 5.4.1.5 Investigator-Assessment Clinical Cure at Post Treatment Evaluation (PTE) By Baseline Pathogen*
(MicroITT population - Group 2: Patients in SOLO I and SOLO II studies)

	SOLO I		SOLO II		All Patients	
Genus Species	Oritavancin (N=244) n (%)	Vancomycin (N=242) n (%)	Oritavancin (N=285) n (%)	Vancomycin (N=296) n (%)	Oritavancin (N=529) n (%)	Vancomycin (N=538) n (%)
Number of Patients with at Least One Pathogen	194/244 (79.5)	197/242 (81.4)	242/285 (84.9)	252/296 (85.1)	436/529 (82.4)	449/538 (83.5)
Staphylococcus	175/220 (79.5)	174/213 (81.7)	217/253 (85.8)	222/258 (86.0)	392/473 (82.9)	396/471 (84.1)
aureus	175/220 (79.5)	171/210 (81.4)	214/250 (85.6)	222/258 (86.0)	389/470 (82.8)	393/468 (84.0)
MSSA	90/118 (76.3)	91/113 (80.5)	130/150 (86.7)	138/159 (86.8)	220/268 (82.1)	229/272 (84.2)
MRSA	86/104 (82.7)	83/100 (83.0)	84/100 (84.0)	86/101 (85.1)	170/204 (83.3)	169/201 (84.1)
lugdunensis	0	4/ 4 (100.0)	4/ 4 (100.0)	0/ 1	4/ 4 (100.0)	4/ 5 (80.0)
Streptococcus	25/ 31 (80.6)	29/ 38 (76.3)	38/ 48 (79.2)	46/ 57 (80.7)	63/ 79 (79.7)	75/ 95 (78.9)
pyogenes	6/ 8 (75.0)	5/ 10 (50.0)	19/ 23 (82.6)	18/ 22 (81.8)	25/ 31 (80.6)	23/ 32 (71.9)
constellatus	7/ 9 (77.8)	8/ 10 (80.0)	8/ 10 (80.0)	11/ 13 (84.6)	15/ 19 (78.9)	19/ 23 (82.6)
intermedius	3/ 4 (75.0)	3/ 3 (100.0)	5/ 6 (83.3)	10/ 13 (76.9)	8/ 10 (80.0)	13/ 16 (81.3)
agalactiae	6/ 7 (85.7)	7/ 8 (87.5)	1/ 1 (100.0)	4/ 4 (100.0)	7/ 8 (87.5)	11/ 12 (91.7)
dysgalactiae	2/ 3 (66.7)	2/ 3 (66.7)	5/ 6 (83.3)	1/ 3 (33.3)	7/ 9 (77.8)	3/ 6 (50.0)
anginosus	2/ 2 (100.0)	5/ 5 (100.0)	0/ 2	1/ 1 (100.0)	2/ 4 (50.0)	6/ 6 (100.0)
Group F	0	2/ 2 (100.0)	1/ 1 (100.0)	1/ 1 (100.0)	1/ 1 (100.0)	3/ 3 (100.0)
Enterococcus	4/ 7 (57.1)	5/ 5 (100.0)	4/ 6 (66.7)	4/ 7 (57.1)	8/ 13 (61.5)	9/ 12 (75.0)
faecalis	4/ 7 (57.1)	5/ 5 (100.0)	4/ 6 (66.7)	4/ 7 (57.1)	8/ 13 (61.5)	9/ 12 (75.0)
faecium	0	0	0	0/ 1	0	0/ 1

Table 52

Table 5.4.1.6 Investigator-Assessment Clinical Cure at Post Treatment Evaluation (PTE) By Baseline Pathogen*
(MicroE population - Group 2: Patients in SOLO I and SOLO II studies)

	SOLO I		SOLO II		All Patients	
Genus Species	Oritavancin (N=201) n (%)	Vancomycin (N=201) n (%)	Oritavancin (N=246) n (%)	Vancomycin (N=247) n (%)	Oritavancin (N=447) n (%)	Vancomycin (N=448) n (%)
Number of Patients with at Least One Pathogen	187/201 (93.0)	190/201 (94.5)	233/246 (94.7)	238/247 (96.4)	420/447 (94.0)	428/448 (95.5)
Staphylococcus	168/181 (92.8)	168/178 (94.4)	208/219 (95.0)	209/216 (96.8)	376/400 (94.0)	377/394 (95.7)
aureus	168/181 (92.8)	166/175 (94.9)	205/216 (94.9)	209/216 (96.8)	373/397 (94.0)	375/391 (95.9)
MSSA	87/ 97 (89.7)	88/ 95 (92.6)	124/128 (96.9)	130/134 (97.0)	211/225 (93.8)	218/229 (95.2)
MRSA	82/ 86 (95.3)	80/ 82 (97.6)	81/ 88 (92.0)	80/ 83 (96.4)	163/174 (93.7)	160/165 (97.0)
lugdunensis	0	3/ 4 (75.0)	4/ 4 (100.0)	0	4/ 4 (100.0)	3/ 4 (75.0)
Streptococcus	24/ 26 (92.3)	28/ 29 (96.6)	38/ 41 (92.7)	45/ 47 (95.7)	62/ 67 (92.5)	73/ 76 (96.1)
pyogenes	6/ 6 (100.0)	5/ 5 (100.0)	19/ 19 (100.0)	18/ 19 (94.7)	25/ 25 (100.0)	23/ 24 (95.8)
constellatus	7/ 7 (100.0)	7/ 8 (87.5)	8/ 9 (88.9)	11/ 11 (100.0)	15/ 16 (93.8)	18/ 19 (94.7)
intermedius	3/ 3 (100.0)	3/ 3 (100.0)	5/ 5 (100.0)	9/ 9 (100.0)	8/ 8 (100.0)	12/ 12 (100.0)
agalactiae	5/ 6 (83.3)	7/ 7 (100.0)	1/ 1 (100.0)	4/ 4 (100.0)	6/ 7 (85.7)	11/ 11 (100.0)
dysgalactiae	2/ 3 (66.7)	2/ 2 (100.0)	5/ 5 (100.0)	1/ 2 (50.0)	7/ 8 (87.5)	3/ 4 (75.0)
anginosus	2/ 2 (100.0)	5/ 5 (100.0)	0/ 2	1/ 1 (100.0)	2/ 4 (50.0)	6/ 6 (100.0)
Group F	0	2/ 2 (100.0)	1/ 1 (100.0)	1/ 1 (100.0)	1/ 1 (100.0)	3/ 3 (100.0)
Enterococcus	4/ 6 (66.7)	5/ 5 (100.0)	3/ 4 (75.0)	4/ 5 (80.0)	7/ 10 (70.0)	9/ 10 (90.0)
faecalis	4/ 6 (66.7)	5/ 5 (100.0)	3/ 4 (75.0)	4/ 5 (80.0)	7/ 10 (70.0)	9/ 10 (90.0)

The vancomycin trough levels were obtained as a minimum prior to the 4th dose and data were available for 433/481 patients in SOLO I and for 465/502 in SOLO II as shown below.

Table 53

Table 10.3.7 Summary of Vancomycin Trough Levels (mcg/mL) - Central Lab Data (mITT population)

	Vancomycin (N=481)
Trough Level	
n	433
Mean (SD)	15.385 (30.395)
Median	11.100
Q1, Q3	7.600, 16.300
Min, Max	0.35, 595.00

Table 10.3.7 Summary of Vancomycin Trough Levels (mcg/mL) - Central Lab Data (mITT population)

	Vancomycin (N=502)
Trough Level	
n	465
Mean (SD)	14.202 (12.370)
Median	10.500
Q1, Q3	7.500, 16.400
Min, Max	0.35, 122.00

The 2009 IDSA recommendations for trough levels when treating *S. aureus* state that the concentration immediately before the 4th dose should be in the range 15-20 mg/L for the most serious infections and should not be below 10 mg/L.

Summary of main studies

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

Table 54. Summary of Efficacy for trial SOLO 1

Title: A Multicenter, Double-Blind, Randomized Study to Evaluate the Efficacy and Safety of Single-Dose IV Oritavancin versus IV Vancomycin for the Treatment of Patients with Acute Bacterial Skin and Skin Structure Infection (SOLO I)		
Study identifier	TMC-ORI-10-01 (SOLO 1)	
Design	This was a Phase 3, multicenter, double-blind, randomized (1:1) comparative efficacy and safety study of single-dose intravenous (IV) oritavancin versus IV vancomycin for 7 to 10 days in adults with ABSSSI	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	60 days not applicable not applicable
Hypothesis	Non-inferiority	
Treatments groups	Oritavancin	Oritavancin diphosphate 1200 mg single-dose IV followed by placebo infusion q12, 7 to 10 days, 483 patients
	Vancomycin	Vancomycin 1g or 15 mg/kg IV q12, 7 to 10 days, 485 patients

Endpoints and definitions	Primary endpoint	Cessation of spreading or reduction in the size of baseline lesion, absence of fever, and no rescue antibiotics at ECE	Non-inferiority in success rate of oritavancin treatment compared with that of vancomycin treatment at the Early Clinical Evaluation (ECE) Visit of 48-72 hours post start of infusion in the Modified Intent-to-Treat (mITT) analysis population
	Key secondary endpoint	Investigator-assessed clinical cure at PTE	Non-inferiority in clinical cure rate of oritavancin treatment compared with that of vancomycin treatment at the Post-Therapy Evaluation (PTE) Visit in the Modified Intent-to-Treat (mITT) analysis population
Database lock	14/12/2012		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Modified Intent-to-Treat (mITT) at the Early Clinical Evaluation (ECE) visit		
Descriptive statistics and estimate variability	Treatment group	Oritavancin	Vancomycin
	Number of subject	478	481
	Cessation of spreading or reduction in the size of baseline lesion, absence of fever, and no rescue antibiotics at ECE	391 (82.3%)	378 (78.9%)
Effect estimate per comparison	Primary endpoint (for FDA)	Comparison groups	Oritavancin vs Vancomycin
		Difference in success rate in the mITT population	3.4
		95% confidence interval	(-1.6, 8.4)
Analysis description	**Secondary analysis**		
Analysis population and time point description	Modified Intent-to-Treat (mITT) at the Post-Therapy Evaluation (PTE) visit		
Descriptive statistics and estimate variability	Treatment group	Oritavancin	Vancomycin
	Number of subject	478	481
	Investigator-assessed clinical cure at PTE (%)	378 (79.6%)	383 (80.0%)
Effect estimate per comparison	Key secondary endpoint	Comparison groups	Oritavancin vs Vancomycin
		Difference in clinical cure rate in the mITT population	-0.4
		95% confidence interval	(-5.5, 4.7)

Table 55. Summary of Efficacy for trial SOLO 2

Title: A Multicenter, Double-Blind, Randomized Study to Evaluate the Efficacy and Safety of Single-Dose IV Oritavancin versus IV Vancomycin for the Treatment of Patients with Acute Bacterial Skin and Skin Structure Infection (SOLO II)			
Study identifier	TMC-ORI-10-02 (SOLO 2)		
Design	This was a Phase 3, multicenter, double-blind, randomized (1:1) comparative efficacy and safety study of single-dose intravenous (IV) oritavancin versus IV vancomycin for 7 to 10 days in adults with ABSSSI		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		60 days not applicable not applicable
Hypothesis	Non-inferiority		
Treatments groups	Oritavancin		Oritavancin diphosphate 1200 mg single-dose IV followed by placebo infusion q12, 7 to 10 days, 509 patients
	Vancomycin		Vancomycin 1g or 15 mg/kg IV q12, 7 to 10 days, 510 patients
Endpoints and definitions	Primary endpoint	Cessation of spreading or reduction in the size of baseline lesion, absence of fever, and no rescue antibiotics at ECE	Non-inferiority in success rate of oritavancin treatment compared with that of vancomycin treatment at the Early Clinical Evaluation (ECE) Visit of 48-72 hours post start of infusion in the Modified Intent-to-Treat (mITT) analysis population
	Key secondary endpoint	Investigator-assessed clinical cure at PTE	Non-inferiority in clinical cure rate of oritavancin treatment compared with that of vancomycin treatment at the Post-Therapy Evaluation (PTE) Visit in the Modified Intent-to-Treat (mITT) analysis population
Database lock	21/6/2013		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Modified Intent-to-Treat (mITT) at the Early Clinical Evaluation (ECE) visit		
Descriptive statistics and estimate variability	Treatment group	Oritavancin	Vancomycin
	Number of subject	503	502
	Cessation of spreading or reduction in the size of baseline lesion, absence of fever, and no rescue antibiotics at ECE	403 (80.1%)	416 (82.9%)
Effect estimate per comparison	Primary endpoint	Comparison groups	Oritavancin vs Vancomycin
		Difference in success rate in the mITT population	-2.7
		95% confidence interval	(-7.5, 2.0)
Analysis description	**Secondary analysis**		

Analysis population and time point description	Modified Intent-to-Treat (mITT) at the Post-Therapy Evaluation (PTE) visit		
Descriptive statistics and estimate variability	Treatment group	Oritavancin	Vancomycin
	Number of subject	503	502
	Investigator-assessed clinical cure at PTE (%)	416 (82.7%)	404 (80.5%)
Effect estimate per comparison	Key secondary endpoint	Comparison groups	Oritavancin vs Vancomycin
		Difference in clinical cure rate in the mITT population	2.2
		95% confidence interval	(-2.6, 7.0)

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The Phase 3 studies were generally designed and analysed in compliance with CHMP guidance. Since the differential activity against MSSA and MRSA was a concern with daily dosing in the prior application, special attention was paid to enrolling patients with MRSA in the new Phase 3 studies and about half of the patients had this pathogen. The low rate of SIRS, as well as very few bacteraemia cases and <5% with infections due to *S. pyogenes* have been encountered in other relatively recent studies in ABSSSI. These issues do not preclude acceptance of the data but these and some other limitations (e.g. infections studied were confined to cellulitis, abscesses and wound infections only; few elderly patients) should be stated in section 4.4 of the SmPC so that prescribers are warned about the extent of the clinical experience.

Vancomycin was the selected comparator. Dosing of this agent was 1 g or 15 mg/kg q12h and was adjusted according to local practises by designated unblinded personnel at each study site. The lack of standardisation of the approach to dosing and adjustment criteria is not ideal but in a global study with feasibility issues and in which cure rates with vancomycin were in the expected range it can be accepted.

Efficacy data and additional analyses

Both studies demonstrated non-inferiority for oritavancin vs. vancomycin based on the clinical cure rates at PTE in the MITT and CE populations and the sensitivity analyses supported the primary analysis. The lower bounds of the 95% CI were well within -10%. In addition, the results at the ECE visit supported a conclusion of general comparability between treatment groups.

2.5.4. Conclusions on the clinical efficacy

Two Phase 3 RCTs of an appropriate design support a conclusion that a single 1200 mg dose of oritavancin has similar efficacy to twice daily dosing with vancomycin in the treatment of acute bacterial infections of the skin and soft tissues due to recognised Gram-positive pathogens that are susceptible to glycopeptides and lipoglycopeptides.

2.6. Clinical safety

The focus is on the safety profile of the 1200 mg single dose administered over 3 h in patients with ABSSSI, including SOLO I and II. The tabulations compare the pooled data from the SOLO studies with those from Phase 3 daily dosing studies in ABSSSI (ARRD and ARRI) and with the total safety database.

Patient exposure

The total safety database consists of 3017 oritavancin-treated individuals in 22 clinical studies (424 subjects in Phase 1 and 2593 patients in Phase 2/3). In Phase 2/3 ABSSSI studies with the 1200 mg single dose 1075 received oritavancin. In SOLO I and II, 976 patients received oritavancin and 983 received vancomycin.

The overall incidence of AEs, deaths, SAEs and AEs leading to study drug discontinuation were similar for the oritavancin and vancomycin/comparator groups within each of the pools.

Table 56

Table 6: Overview of Adverse Events (Safety Population)

	SOLO Pool		ARRD/I Pool		All Treated Pool	
Category	Oritavancin (N=976) n (%)	Vancomycin (N=983) n (%)	Oritavancin (N=1173) n (%)	Vancomycin (N=590) n (%)	Oritavancin (N=3017) n (%)	Comparator (N=1954) n (%)
No. of Patients with any AE	540 (55.3)	559 (56.9)	627 (53.5)	368 (62.4)	1712 (56.7)	1076 (55.1)
No. of Patients with any AE Leading to Study Drug Discontinuation	36 (3.7)	41 (4.2)	46 (3.9)	40 (6.8)	131 (4.3)	90 (4.6)
No. of Patients with SAE	57 (5.8)	58 (5.9)	107 (9.1)	68 (11.5)	256 (8.5)	144 (7.4)
No. of Patients with any AE Leading to Death	2 (0.2)	3 (0.3)	19 (1.6)	12 (2.0)	53 (1.8)	24 (1.2)

Adverse events

In the SOLO pool the most common AEs in the oritavancin group were nausea, headache and vomiting. The rates for any individual AE in the oritavancin group were ≤ 10% and mostly similar to rates in the vancomycin group. A broadly similar pattern applied in the ARRD/I and All Treated pools.

Table 57

Table 5: Adverse Events that Occurred in ≥2% of Patients in the Oritavancin Treatment Group (Safety Population)

	SOLO Pool		ARRD/I Pool		All Treated Pool	
Preferred Term	Oritavancin (N=976) n (%)	Vancomycin (N=983) n (%)	Oritavancin (N=1173) n (%)	Vancomycin (N=590) n (%)	Oritavancin (N=3017) n (%)	Comparator (N=1954) n (%)
Number of patients with ≥1 AE	540 (55.3)	559 (56.9)	627 (53.5)	368 (62.4)	1712 (56.7)	1076 (55.1)
Nausea	97 (9.9)	103 (10.5)	73 (6.2)	39 (6.6)	238 (7.9)	164 (8.4)
Headache	69 (7.1)	66 (6.7)	63 (5.4)	39 (6.6)	219 (7.3)	129 (6.6)
Vomiting	45 (4.6)	46 (4.7)	48 (4.1)	32 (5.4)	134 (4.4)	95 (4.9)
Cellulitis	37 (3.8)	32 (3.3)	15 (1.3)	13 (2.2)	60 (2.0)	46 (2.4)
Diarrhoea	36 (3.7)	32 (3.3)	48 (4.1)	30 (5.1)	143 (4.7)	75 (3.8)
Constipation	33 (3.4)	38 (3.9)	44 (3.8)	13 (2.2)	106 (3.5)	59 (3.0)
Infusion site extravasation	33 (3.4)	33 (3.4)	7 (0.6)	4 (0.7)	64 (2.1)	38 (1.9)
Pyrexia	30 (3.1)	31 (3.2)	40 (3.4)	27 (4.6)	113 (3.7)	65 (3.3)
Pruritus	29 (3.0)	73 (7.4)	29 (2.5)	40 (6.8)	85 (2.8)	125 (6.4)
Abscess Limb	27 (2.8)	13 (1.3)	22 (1.9)	11 (1.9)	57 (1.9)	24 (1.2)
ALT Increased	27 (2.8)	15 (1.5)	6 (0.5)	3 (0.5)	40 (1.3)	18 (0.9)
Dizziness	26 (2.7)	26 (2.6)	35 (3.0)	8 (1.4)	92 (3.0)	49 (2.5)
Infusion site phlebitis	24 (2.5)	15 (1.5)	18 (1.5)	8 (1.4)	85 (2.8)	28 (1.4)
Tachycardia	24 (2.5)	11 (1.1)	8 (0.7)	3 (0.5)	42 (1.4)	15 (0.8)
Insomnia	21 (2.2)	25 (2.5)	57 (4.9)	45 (7.6)	103 (3.4)	74 (3.8)
Anaemia	13 (1.3)	12 (1.2)	23 (2.0)	13 (2.2)	60 (2.0)	32 (1.6)
Chills	13 (1.3)	16 (1.6)	19 (1.6)	9 (1.5)	62 (2.1)	31 (1.6)
Hypertension	10 (1.0)	14 (1.4)	30 (2.6)	10 (1.7)	52 (1.7)	25 (1.3)
Abdominal pain	9 (0.9)	14 (1.4)	23 (2.0)	15 (2.5)	64 (2.1)	41 (2.1)
Pain in extremity	9 (0.9)	7 (0.7)	21 (1.8)	9 (1.5)	60 (2.0)	21 (1.1)
Infusion site pain	7 (0.7)	15 (1.5)	19 (1.6)	12 (2.0)	81 (2.7)	34 (1.7)
Hypokalaemia	6 (0.6)	5 (0.5)	25 (2.1)	12 (2.0)	50 (1.7)	22 (1.1)
Rash	5 (0.5)	10 (1.0)	25 (2.1)	23 (3.9)	49 (1.6)	40 (2.0)
Phlebitis	0	2 (0.2)	16 (1.4)	12 (2.0)	76 (2.5)	14 (0.7)

Specific analyses of rates of AEs of most interest, including AEs for which reporting rates were higher for oritavancin, were conducted using broad and narrow PTs

Hypersensitivity - The incidence of AEs possibly representing hypersensitivity reactions was lower in the oritavancin group (12.1%) than the vancomycin group (18.6%) in the SOLO pool and in the other pools (12.6% vs. 21.9% in ARRD/I and 14.7% vs. 18% overall). The most frequent (> 2.0%) individual AEs in the SOLO pool were pruritus in the oritavancin group and pruritus and urticaria in the vancomycin group. Broadly consistent findings applied in the ARRD/I and All Treated pools.

The narrow search for AEs that could relate to hypersensitivity in the SOLO pool gave lower rates overall and for most individual terms in the oritavancin group. The median time to onset was 1.2 days (0 to 29) for oritavancin and 0.4 days (0 to 21) for vancomycin and the median durations were 2.4 days (0 to 45) and 1.0 day (0 to 52). These AEs were serious in 0.4% per group while the discontinuation rates were 0.5% vs. 1.4%.

Table 58

Table 13: Hypersensitivity Adverse Events in SOLO Pool – Specific Search (Safety Population)

	Oritavancin (N=976)	Vancomycin (N=983)
Hypersensitivity	75 (7.7)	139 (14.1)
Pruritus	29 (3.0)	73 (7.4)
Pruritus generalised	16 (1.6)	23 (2.3)
Urticaria	11 (1.1)	21 (2.1)
Rash	5 (0.5)	10 (1.0)
Rash papular	4 (0.4)	3 (0.3)
Erythema multiforme	3 (0.3)	2 (0.2)
Hypersensitivity	3 (0.3)	8 (0.8)
Rash macular	3 (0.3)	6 (0.6)
Rash generalised	2 (0.2)	2 (0.2)
Angioedema	1 (0.1)	0
Bronchospasm	1 (0.1)	0
Drug hypersensitivity	1 (0.1)	2 (0.2)
Pharyngeal oedema	1 (0.1)	0
Swelling face	1 (0.1)	2 (0.2)
Rash pruritic	1 (0.1)	1 (0.1)
Anaphylactoid reaction	0	2 (0.2)
Red man syndrome	0	2 (0.2)

Infusion Site Reactions/Phlebitis – When oritavancin 1200 mg was administered in 1000 mL over 3 hours in the SOLO studies the incidence of these AEs was similar between the oritavancin (10.1%) and vancomycin (11.1%) groups. The median time to onset of these AEs was 3.1 days in each group and the median durations of the AEs were comparable (2.0 vs. 1.9 days). None of these AEs was serious and the discontinuation rates were 0.5% for oritavancin vs. 0.1% for vancomycin.

Vestibular Toxicity and ototoxicity – The incidence of vestibular toxicity was similar in the oritavancin (2.0%) and vancomycin (2.8%) groups in the SOLO pool and dizziness was the most frequent individual AE. The median time to onset was 3.0 days for oritavancin and 1.1 days for vancomycin and the median durations were 0.4 (0 to 19) vs. 0.6 (0 to 13) days, respectively. No clinically relevant changes in audiograms were observed in the four Phase 1 studies (ARRA, ARRB, ARRK and JE-101N) that included audiometric testing before and after oritavancin administration. There was one AE of deafness (reported as a mild right ear hearing loss) in SOLO II in a 62-year-old female with onset 12 days after oritavancin but this was assessed as unlikely related to study drug.

Hepatic AEs - In the SOLO pool the overall rates for hepatic AEs (related to liver laboratory abnormalities or clinical AEs) were 4.7% in the oritavancin group and 3.0 % in the vancomycin group. The difference

was driven by AEs of increased ALT in 2.8% oritavancin and 1.5% vancomycin patients. The median times to onset were 6.9 days vs. 6.8 days in respective groups while the median durations were 8.2 days vs. 9.1 days. None of these AEs was serious or led to study discontinuation. In the All Treated pool there was one death due to a hepatic event (hepatic cirrhosis) in the bacteremia study ARRM. This patient already had cirrhosis when she presented with MSSA bacteraemia. She died after completing 9 days of oritavancin 8 mg/kg due to GI bleeding and encephalopathy. Death was not considered to be related to oritavancin.

Renal AEs - The incidence of renal AEs was similar in the oritavancin (0.7%) and vancomycin (0.9%) groups in the SOLO pool. The median time to onset was 8.2 days (0 to 31) for oritavancin and 6.6 days (3 to 22) for vancomycin with median durations of 11.7 and 13.0 days. Renal failure was reported for 3 in the oritavancin group and 5 in the vancomycin group (one of the 5 was serious).

Cardiac and Cardiac Rhythm Disorders - In the SOLO pool cardiac AE rates were 3.4% for oritavancin and 2.7% for vancomycin, with a higher rate of tachycardia with oritavancin (2.5% vs. 1.1%). Cardiac AEs were predominantly within preferred terms of supraventricular arrhythmias but there were no AEs of QT/QTc prolongation, AV block or bundle branch block. One patient died in the oritavancin group due to electromechanical dissociation considered unrelated to study drug by the investigator. Cardiac SAEs occurred in 0.3% oritavancin and 0.6% vancomycin patients. In the oritavancin group these were ventricular tachycardia, congestive heart failure and the case of electromechanical dissociation.

ECG evaluations considered the SOLO pool, the data in the 1200 mg group in SIMPLIFI, the two later TQT studies and ECGs from 69 healthy subjects administered daily oritavancin doses ranging from 100 mg to 800 mg. The results showed that oritavancin had no effect on the QTcF or QRS intervals.

Infections and Infestations - The rates of all AEs in the infections and infestations SOC in the SOLO pool were 16.4% for oritavancin vs. 14.4% for vancomycin. The most frequently reported individual AEs in the SOLO pool were cellulitis and abscesses in limbs. There was no excess of fungal or mycobacterial infections in the oritavancin group. Consistent findings applied in the ARRD/I and All Treated pools. Rates for sepsis, septic shock and related events were low (oritavancin 0.3%; vancomycin 0.7%) with one death in each treatment group. The death in the oritavancin group was at 38 days post-dose and followed hospitalization for severe multi-lobar pneumonia on the same day.

Osteomyelitis occurred more often with oritavancin (6 cases) than vancomycin (one case) in the SOLO studies (including 5 vs. 0 in SOLO II), a pattern which was already apparent from the prior studies that employed daily dosing (13 vs. 0 in ARRD/I). In the SOLO studies the median time to osteomyelitis onset was 4.6 days (0 to 9 days) in the oritavancin group while the single vancomycin patient had an onset at 2.6 days. Four of the 6 cases in the oritavancin group were SAEs, as was the single vancomycin group case. Osteomyelitis was suspected by the investigator to be pre-existing in two of these four patients. An individual patient review of all osteomyelitis cases did not reveal any common factor to explain the imbalance in osteomyelitis between the treatment groups, including diabetes mellitus diagnosis at baseline, diabetic foot, peripheral vascular disease, amputation, primary infection site location, baseline pathogen and region where the study was conducted. The location of the primary infection site in the majority of patients with osteomyelitis in the oritavancin group was the foot and lower leg but no pathogens were isolated from the site of osteomyelitis in any of the cases.

Table 59

Table 44: Osteomyelitis (Safety Population)

Event of Special Interest Preferred Term	SOLO Pool		ARRD/I Pool		All Treated Pool	
	Oritavancin (N=976) n (%)	Vancomycin (N=983) n (%)	Oritavancin (N=1173) n (%)	Vancomycin (N=590) n (%)	Oritavancin (N=3017) n (%)	Vancomycin (N=1954) n (%)
Osteomyelitis	6 (0.6)	1 (0.1)	14 (1.2)	1 (0.2)	23 (0.7)	3 (0.2)
Osteomyelitis	6 (0.6)	1 (0.1)	13 (1.1)	0	22 (0.7)	2 (0.1)
Osteitis	0	0	1 (0.1)	0	1 (0.0)	0
Osteomyelitis Acute	0	0	0	1 (0.2)	0	1 (0.1)

Serious adverse event/deaths/other significant events

Deaths

There were 77 deaths (oritavancin 1.8% [53/3017]; vancomycin/comparator 1.2% [24/1954]) reported across all studies. The median time to death was 17 days (2 to 61 days) in the oritavancin group and 19 days (5 to 48 days) in the vancomycin group and the mean ages of those who died were 58.1 years (19 to 90 years) and 67.3 years (43 to 93 years) in respective groups.

In the SOLO pool, 2 in the oritavancin group and 3 in the vancomycin group died. The causes of death were sepsis and electromechanical dissociation in the oritavancin group and septic shock, acute myocardial infarction and dementia with Parkinsonism in the vancomycin group. None of the deaths was considered related to study drug by the investigator.

The incidence of death was higher in the ARRD/I and the All Treated pools. The higher incidence of death in the All Treated pool was driven by the rates in the bacteremia studies. The most frequent AEs leading to death in both the oritavancin and vancomycin groups were cardiac arrest in the ARRD/I pool and septic shock in the All Treated pool. Three deaths across the clinical development programme were considered related to study drug by the investigator. These were deaths due to hypotension and multi-organ failure in two patients in the oritavancin group in ARRM and a case of ventricular fibrillation in a vancomycin patient in ARRI.

Serious Adverse Events

The overall frequency of SAEs was similar in the oritavancin and vancomycin groups in the SOLO pool. The most frequent SAEs in the oritavancin group were cellulitis, osteomyelitis, abscess limb, pneumonia, skin infection and subcutaneous abscess. The median time to onset of SAEs was 10.6 days (0 to 62 days) in the oritavancin group and 19.6 days (0 to 56 days) in the vancomycin group.

SAEs assessed as related to study drug occurred in 0.5% oritavancin and 0.4% vancomycin patients. Related SAEs in the oritavancin group included leucocytoclastic vasculitis, urticaria, mouth ulceration, drug hypersensitivity and bronchospasm, each of which was reported by 1 patient.

The overall frequency of SAEs in both the oritavancin and vancomycin/comparator groups was lower in the SOLO pool compared to the ARRD/I and All Treated pools.

The SAEs concerning reports that could have reflected hypersensitivity reactions did not suggest an excess risk associated with oritavancin vs. vancomycin/comparators.

Table 60

Table 8: Serious Adverse Events in ≥2 Patients in the Oritavancin Group in Any Pool (Safety Population)

	SOLO Pool		ARRD/I Pool		All Treated Pool	
System Organ Class Preferred Term	Oritavancin (N=976) n (%)	Vancomycin (N=983) n (%)	Oritavancin (N=1173) n (%)	Vancomycin (N=590) n (%)	Oritavancin (N=3017) n (%)	Comparator (N=1954) n (%)
Number of Patients with Any SAE	57 (5.8)	58 (5.9)	107 (9.1)	68 (11.5)	256 (8.5)	144 (7.4)
Cellulitis	11 (1.1)	12 (1.2)	10 (0.9)	4 (0.7)	26 (0.9)	16 (0.8)
Osteomyelitis	4 (0.4)	1 (0.1)	5 (0.4)	0	11 (0.4)	2 (0.1)
Abscess Limb	3 (0.3)	0	6 (0.5)	1 (0.2)	12 (0.4)	1 (0.1)
Pneumonia	3 (0.3)	0	2 (0.2)	2 (0.3)	10 (0.3)	2 (0.1)
Skin Infection	3 (0.3)	3 (0.3)	0	0	3 (0.1)	3 (0.2)
Subcutaneous Abscess	3 (0.3)	1 (0.1)	0	3 (0.5)	4 (0.1)	4 (0.2)
Diabetic Ketoacidosis	2 (0.2)	1 (0.1)	0	0	2 (0.1)	1 (0.1)
Hypoxia	2 (0.2)	1 (0.1)	0	0	2 (0.1)	1 (0.1)
Tenosynovitis	2 (0.2)	0	0	0	2 (0.1)	0
Abdominal Pain	1 (0.1)	0	1 (0.1)	0	5 (0.2)	1 (0.1)
Abscess	1 (0.1)	1 (0.1)	7 (0.6)	2 (0.3)	9 (0.3)	3 (0.2)
Arthritis Bacterial	1 (0.1)	2 (0.2)	0	0	2 (0.1)	2 (0.1)
Asthenia	1 (0.1)	0	1 (0.1)	0	2 (0.1)	0
Bacteraemia	1 (0.1)	0	1 (0.1)	1 (0.2)	4 (0.1)	1 (0.1)
Bipolar Disorder	1 (0.1)	0	0	0	2 (0.1)	0
Bronchitis	1 (0.1)	0	1 (0.1)	0	2 (0.1)	1 (0.1)
Cardiac Failure Congestive	1 (0.1)	1 (0.1)	2 (0.2)	0	4 (0.1)	2 (0.1)
Chest Pain	1 (0.1)	0	3 (0.3)	1 (0.2)	6 (0.2)	1 (0.1)
Deep Vein Thrombosis	1 (0.1)	2 (0.2)	0	1 (0.2)	2 (0.1)	3 (0.2)
Dyspnoea	1 (0.1)	2 (0.2)	0	2 (0.3)	5 (0.2)	4 (0.2)
Gangrene	1 (0.1)	0	1 (0.1)	0	3 (0.1)	0
Necrotising Fasciitis	1 (0.1)	1 (0.1)	1 (0.1)	0	2 (0.1)	1 (0.1)
Peripheral Vascular Disorder	1 (0.1)	0	1 (0.1)	0	2 (0.1)	0
Sepsis	1 (0.1)	1 (0.1)	7 (0.6)	4 (0.7)	11 (0.4)	6 (0.3)
Suicidal Ideation	1 (0.1)	1 (0.1)	0	0	2 (0.1)	1 (0.1)
Urosepsis	1 (0.1)	0	0	0	2 (0.1)	0
Acute Pulmonary Oedema	0	0	2 (0.2)	0	2 (0.1)	0
Acute Respiratory Distress Syndrome	0	0	0	1 (0.2)	2 (0.1)	1 (0.1)
Arteriovenous Graft Site Infection	0	0	2 (0.2)	0	3 (0.1)	0
Ascites	0	0	2 (0.2)	1 (0.2)	3 (0.1)	1 (0.1)
Atrial Fibrillation	0	0	1 (0.1)	0	2 (0.1)	0
Atrial Flutter	0	0	1 (0.1)	0	2 (0.1)	0
Cardiac Arrest	0	0	3 (0.3)	4 (0.7)	9 (0.3)	4 (0.2)
Cardiac Failure	0	0	1 (0.1)	1 (0.2)	2 (0.1)	1 (0.1)
Cardio-Respiratory Arrest	0	1 (0.1)	3 (0.3)	0	5 (0.2)	1 (0.1)
Chronic Obstructive Pulmonary Disease	0	0	1 (0.1)	1 (0.2)	2 (0.1)	1 (0.1)
Dehydration	0	1 (0.1)	1 (0.1)	1 (0.2)	3 (0.1)	2 (0.1)
Depressed Level Of Consciousness	0	0	0	0	2 (0.1)	0
Diabetes Mellitus	0	0	2 (0.2)	0	2 (0.1)	0
Empyema	0	0	2 (0.2)	0	2 (0.1)	0
Febrile Neutropenia	0	0	0	0	3 (0.1)	0
Femoral Artery Occlusion	0	0	2 (0.2)	0	2 (0.1)	0
Gastric Fistula	0	0	2 (0.2)	0	2 (0.1)	0
Gastrointestinal Haemorrhage	0	0	2 (0.2)	0	5 (0.2)	0
Hydronephrosis	0	0	1 (0.1)	0	2 (0.1)	0
Hypotension	0	0	0	1 (0.2)	7 (0.2)	3 (0.2)
Hypovolaemic Shock	0	0	2 (0.2)	0	2 (0.1)	0
Localised Infection	0	0	2 (0.2)	0	2 (0.1)	0
Mental Status Changes	0	0	2 (0.2)	0	2 (0.1)	0
Multi-Organ Failure	0	0	0	0	3 (0.1)	2 (0.1)
Myocardial Infarction	0	0	3 (0.3)	1 (0.2)	7 (0.2)	2 (0.1)
Neoplasm Progression	0	0	0	0	2 (0.1)	0
Pain In Extremity	0	0	1 (0.1)	1 (0.2)	2 (0.1)	1 (0.1)
Peritonitis	0	0	2 (0.2)	1 (0.2)	3 (0.1)	1 (0.1)
Pulmonary Embolism	0	1 (0.1)	1 (0.1)	4 (0.7)	4 (0.1)	5 (0.3)
Pyrexia	0	2 (0.2)	2 (0.2)	2 (0.3)	3 (0.1)	4 (0.2)
Respiratory Arrest	0	0	2 (0.2)	0	2 (0.1)	0
Respiratory Distress	0	0	0	2 (0.3)	2 (0.1)	2 (0.1)
Respiratory Failure	0	2 (0.2)	1 (0.1)	1 (0.2)	3 (0.1)	3 (0.2)
Schizoaffective Disorder	0	0	2 (0.2)	0	2 (0.1)	0
Septic Shock	0	1 (0.1)	4 (0.3)	0	9 (0.3)	2 (0.1)
Staphylococcal Bacteraemia	0	0	0	0	2 (0.1)	0
Tachycardia	0	0	2 (0.2)	0	2 (0.1)	0
Urinary Tract Infection	0	0	1 (0.1)	0	2 (0.1)	0

Laboratory findings

Haematology

Rates of haematological abnormalities reported as AEs were higher for oritavancin in each pool. The differences reflected a range of abnormalities and very small numbers with each.

Table 61

Table 23: Hematologic Effects (Safety Population)

	SOLO Pool		ARRD/I Pool		All Treated Pool	
Event of Special Interest Preferred Term	Oritavancin (N=976) n (%)	Vancomycin (N=983) n (%)	Oritavancin (N=1173) n (%)	Oritavancin (N=590) n (%)	Oritavancin (N=3017) n (%)	Comparator (N=1954) n (%)
Hematologic Effects	23 (2.4)	18 (1.8)	42 (3.6)	14 (2.4)	107 (3.5)	42 (2.1)
Anaemia	13 (1.3)	12 (1.2)	23 (2.0)	13 (2.2)	60 (2.0)	32 (1.6)
Thrombocytosis	1 (0.1)	6 (0.6)	3 (0.3)	0	9 (0.3)	6 (0.3)
Eosinophilia	3 (0.3)	1 (0.1)	6 (0.5)	0	9 (0.3)	1 (0.1)
Thrombocytopenia	3 (0.3)	0	2 (0.2)	1 (0.2)	9 (0.3)	1 (0.1)
Leukocytosis	0	0	4 (0.3)	0	4 (0.1)	2 (0.1)
Leukopenia	2 (0.2)	0	0	1 (0.2)	4 (0.1)	2 (0.1)
Neutropenia	0	0	3 (0.3)	0	5 (0.2)	0
Platelet count decreased	2 (0.2)	0	0	1 (0.2)	3 (0.1)	1 (0.1)
Febrile neutropenia	0	0	0	0	6 (0.2)	0
Haematocrit decreased	1 (0.1)	0	2 (0.2)	0	3 (0.1)	0
Red blood cell count decreased	2 (0.2)	0	0	0	2 (0.1)	0
Anaemia macrocytic	0	0	1 (0.1)	0	1 (0.0)	0
Full blood count abnormal	1 (0.1)	0	0	0	1 (0.0)	0
Neutrophilia	0	0	1 (0.1)	0	1 (0.0)	0
White blood cell count decreased	0 0	1 (0.1)	0	0	0	1 (0.1)
Pancytopenia	0	0	0	0	1 (0.0)	0

The AE of pancytopenia occurred in an oritavancin patient in the bacteremia study ARRM. This AE was serious but was assessed by the investigator as unrelated to study drug.

Thrombocytopenia/decreased platelets was reported as an AE in 5 oritavancin group and no vancomycin patients in the SOLO studies but none of these cases was serious. There was also a higher rate of these AEs for oritavancin vs. comparators in the All Treated pool (12 vs. 2 patients) although none in the oritavancin group was serious.

For each haematology parameter the shifts from normal at baseline to either high or low post-baseline were similar in the oritavancin and vancomycin groups in the SOLO pool. The percentages with PCS values at any time post baseline (in those without PCS at baseline) were similar in the oritavancin and vancomycin groups in the SOLO pool.

Biochemistry

For each biochemistry parameter, shifts from normal at baseline to either high or low post-baseline were similar in the oritavancin and vancomycin groups in the SOLO pool. In addition, the baseline values for each biochemistry parameter, mean change from baseline and percentages with PCS values were similar between treatments at each post-randomisation time point. Hepatic effects were evaluated separately and in accordance with FDA guidance for the detection of drug-induced liver injury.

A higher proportion of patients in both treatment groups in the SOLO pool had PCS LFT values when compared to the ARRD/ARRI pool or the All Treated Pool. For individual parameters the rates were not higher for oritavancin vs. vancomycin except for total bilirubin. Nevertheless, numbers are very small. The mean changes from baseline for each LFT parameter were similar between treatments and none of these changes was clinically significant.

Table 62

Table 25: PCS LFT Results (Safety Population)

	SOLO Pool		ARRD/I Pool		All Treated Pool	
	Oritavancin (N=976) n/N (%)	Vancomycin (N=983) n/N (%)	Oritavancin (N=1173) n/N (%)	Vancomycin (N=590) n/N (%)	Oritavancin (N=3017) n/N (%)	Comparator (N=1954) n/N (%)
ALT ≥ 3X ULN	39/ 911 (4.3)	42/ 911 (4.6)	13/1050 (1.2)	11/ 521 (2.1)	69/2756 (2.5)	53/1776 (3.0)
ALT ≥ 5X ULN	6/ 911 (0.7)	11/ 911 (1.2)	5/1025 (0.5)	2/ 517 (0.4)	12/2756 (0.4)	12/1776 (0.7)
ALT ≥ 10X ULN	2/ 911 (0.2)	0/911 (0.0)	0/1025 (0.0)	1/ 517 (0.2)	3/2756 (0.1)	1/1776 (0.1)
ALT ≥ 20X ULN	0/ 911 (2.7)	0/ 911 (3.7)	0/1025 (0.0)	0/517 (0.0)	0/2756 (0.0)	0/1776 (0.0)
AST ≥ 3X ULN	25/ 921 (2.7)	34/ 921 (3.7)	13/1025 (1.3)	11/ 517 (2.1)	55/2725 (2.0)	45/1781 (2.5)
AST ≥ 5X ULN	6/ 921 (0.7)	11/ 921 (1.2)	5/1025 (0.5)	2/ 517 (0.4)	15/2725 (0.6)	13/1781 (0.7)
AST ≥ 10X ULN	1/ 921 (0.1)	3/ 921 (0.3)	0/1025 (0.0)	1/ 517 (0.2)	3/2725 (0.1)	4/1781 (0.2)
AST ≥ 20X ULN	0/921 (0.0)	0/921 (0.0)	0/1025(0.0)	0/517(0.0)	1/2725 (0.0)	0/1781(0.0)
ALT or AST ≥ 3X ULN	44/ 907 (4.9)	51/ 905 (5.6)	20/1021 (2.0)	13/ 512 (2.5)	89/2704 (3.3)	64/1760 (3.6)
ALT or AST ≥ 5X ULN	10/ 907 (1.1)	14/ 905 (1.5)	6/1021 (0.6)	2/ 512 (0.4)	21/2704 (0.8)	16/1760 (0.9)
ALT or AST ≥ 10X ULN	2/ 907 (0.2)	2/ 905 (0.2)	0/1021 (0.0)	1/ 512 (0.2)	4/2704 (0.1)	3/1760 (0.2)
ALT or AST ≥ 20X ULN	0/907 (0.0)	0/905 (0.0)	0/1021 (0.0)	0/512 (0.0)	1/2704 (0.0)	0/1760(0.0)
TBIL ≥ 1.5X ULN	8/ 895 (0.9)	5/ 902 (0.6)	3/1053 (0.3)	4/ 521 (0.8	24/2741 (0.9)	14/1765 (0.8)
TBIL ≥ 2X ULN	4/ 895 (0.4)	2/ 902 (0.2)	1/1053 (0.1)	2/ 521 (0.4)	10/2741 (0.4)	5/1765 (0.3)
ALT ≥ 3X ULN and TBIL ≥ 1.5X ULN	4/ 928 (0.4)	1/ 927 (0.1)	0/1071 (0.0)	2/ 527 (0.4)	4/2809 (0.1)	3/1798 (0.2)
ALT ≥ 3X ULN and TBIL ≥ 2X ULN	2/ 928 (0.2)	1/ 928 (0.1)	0/1071 (0.0)	1/ 527 (0.2)	2/2809 (0.1)	2/1799 (0.1)
ALT or AST ≥ 3X ULN and TBIL ≥2X ULN	2/ 917 (0.2)	1/ 919 (0.1)	1/1055 (0.1)	1/ 523 (0.2)	6/2777 (0.2)	2/1786 (0.1)
ALT/AST ≥ 3X ULN, TBIL ≥2X ULN, and ALP < 2X ULN	2/ 916 (0.2)	0/919 (0.0)	1/1051 (0.1)	1/ 519 (0.2)	4/2772 (0.1)	1/1781 (0.1)
ALT ≥ 3X ULN, TBIL ≥2X ULN, and ALP < 2X ULN	2/ 914 (0.2)	0/916 (0.0)	0/1052 (0.0)	1/ 519 (0.2)	2/2773 (0.1)	1/1778 (0.1)

Of the 24 patients (10 oritavancin;14 vancomycin) with AST or ALT elevations > 5X ULN in the SOLO pool, 17/24 (8 and 9) returned to baseline levels. For the remaining 7 patients (2 and 5) the AST or ALT values either decreased towards baseline levels or the patients were lost to follow up.

Two outlier analyses evaluated Hy's law and were reviewed by an external independent hepatologist.

AST/ALT ≥ 3X ULN, total bilirubin ≥ 2X ULN and ALP < 2X ULN - Five oritavancin and one vancomycin patients met these criteria.

Medical review of these cases confirmed that none met the criteria for Hy's law due to the lack of evidence of hepatocellular injury, sequence of LFT changes and/or relevant medical history.

eDISH Plot – In the All Treated pool six patients (4 oritavancin; 2 vancomycin) had elevations > 3X ULN in ALT and > 2X ULN in total bilirubin. Two oritavancin group and one vancomycin patients were the same patients described above who met the criteria for AST/ALT ≥ 3X ULN, total bilirubin ≥ 2X ULN, and ALP < 2X ULN (TMC-ORI-10-02/291003016 and TMC-ORI-10-01/101005005 from the SOLO studies and ARRI-229-0003 from ARRI). The other three cases did not meet the criteria for Hy's law.

Safety in special populations

Age - In the SOLO pool the majority of patients were aged < 65 years. Small percentages were aged 65 to < 75 years (oritavancin 7.1%; vancomycin 6.2%) or ≥ 75 years (1.7% vs. 1.6%). Similar percentages by age groups occurred in the ARRD/I and All Treated pools. In both treatment groups the rates for AEs, deaths, SAEs and discontinuations of study drug due to an AE were highest for those aged > 75 years. For most individual AEs the rates were comparable between treatments within each age subset.

In the oritavancin group in the SOLO pool hypersensitivity was reported by a higher percentage of patients aged ≥ 75 years (7/17; 41.2%) compared to those aged < 65 years (11.8%) and 65 to < 75 years (8.7%). In contrast, the rates for vancomycin were similar across the age subsets at 18.7% for those aged < 65 years, 16.4% for those aged 65 to < 75 years and 18.8% (3/16) in the patients aged ≥ 75 years.

In the All Treated pool cardiac rhythm disturbances were more frequent in both the oritavancin and comparator groups in patients aged ≥ 75 years (oritavancin 13.1%; comparator 18.3%) than in patients aged < 65 years (3.3% vs. 2.9%) and 65 to < 75 years (7.1% vs. 3.7%).

Gender - There were more males (oritavancin 65.3%; vancomycin 65.6%) than females enrolled in the SOLO pool as well as in the other pools. Females had a greater percentage of AEs, AEs resulting in death, SAEs and AEs leading to study drug discontinuation than males in both treatment groups in each pool.

Race/Region - Asians had a lower percentage of AEs, SAEs and AEs leading to study drug discontinuation than the other race subgroups in the SOLO and All Treated pools but in the ARRD/I pool Asians had a higher percentage of AEs compared to the other race subgroups and a lower percentage of SAEs than Whites. The percentage of patients with AEs and SAEs was lower in the rest of world vs. N. America in both treatment groups in the SOLO, ARRD/I and All Treated pools but the rates for AEs and SAEs were comparable between treatments within each region.

Weight - In the SOLO pool 67.0% of all patients were 60 to < 100 kg while 17.8% oritavancin and 16.8% vancomycin patients were < 60 kg and 15.5% vs. 16.4% were ≥ 100 kg, respectively. Patients who weighed ≥ 100 kg had the highest rates of AEs, SAEs and AEs leading to study drug discontinuation in both treatment groups.

Safety related to drug-drug interactions and other interactions

Discontinuation due to adverse events

The frequency of AEs leading to study drug discontinuation was comparable in the oritavancin (3.7%) and vancomycin (4.2%) groups in the SOLO pool (see table below). The most frequently reported AEs leading to study drug discontinuation were cellulitis and osteomyelitis in the oritavancin group and cellulitis, hypersensitivity, skin infection and pruritus in the vancomycin group. The median time to onset of AEs leading to study drug discontinuation was 1.7 days (0 to 6 days) and 2.2 days (0 to 9 days) in respective treatment groups.

The frequencies of AEs leading to study drug discontinuation in the ARRD/I pool were oritavancin 3.9% and vancomycin 6.8% while rates in the All Treated pool were 4.3% vs. 4.6%.

Table 63

ıble 9: Adverse Events Leading to Discontinuation of Study Drug in ≥2 Patients in Either Treatment Group in Any Pool (Safety Population)

	SOLO Pool		ARRD/I Pool		All Treated Pool	
	Oritavancin (N=976)	Vancomycin (N=983)	Oritavancin (N=1173)	Vancomycin (N=590)	Oritavancin (N=3017)	Comparator (N=1954)
Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number of Patients with Any AE Leading to Discontinuation of Study Drug	36 (3.7)	41 (4.2)	46 (3.9)	40 (6.8)	131 (4.3)	90 (4.6)
Cellulitis	4 (0.4)	5 (0.5)	0	1 (0.2)	4 (0.1)	6 (0.3)
Osteomyelitis	3 (0.3)	1 (0.1)	2 (0.2)	0	5 (0.2)	1 (0.1)
Abscess Limb	2 (0.2)	0	0	0	2 (0.1)	0
Infection	2 (0.2)	0	0	1 (0.2)	2 (0.1)	1 (0.1)
Infusion Site Phlebitis	2 (0.2)	0	1 (0.1)	0	3 (0.1)	1 (0.1)
Pruritus	2 (0.2)	4 (0.4)	1 (0.1)	1 (0.2)	3 (0.1)	5 (0.3)
Subcutaneous Abscess	2 (0.2)	1 (0.1)	0	0	2 (0.1)	1 (0.1)
Chest Discomfort	1 (0.1)	0	0	0	2 (0.1)	0
Drug Hypersensitivity	1 (0.1)	2 (0.2)	0	1 (0.2)	1 (0.0)	4 (0.2)
Dyspnoea	1 (0.1)	0	0	0	2 (0.1)	0
Hypotension	1 (0.1)	1 (0.1)	0	0	2 (0.1)	1 (0.1)
Infusion Site Thrombosis	1 (0.1)	0	1 (0.1)	1 (0.2)	2 (0.1)	1 (0.1)
Nausea	1 (0.1)	1 (0.1)	1 (0.1)	0	2 (0.1)	2 (0.1)
Rash Macular	1 (0.1)	2 (0.2)	0	0	1 (0.0)	3 (0.2)
Skin Infection	1 (0.1)	4 (0.4)	0	0	1 (0.0)	4 (0.2)
Urticaria	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.2)	6 (0.2)	2 (0.1)
Abscess	0	0	1 (0.1)	0	2 (0.1)	0
Bacteraemia	0	0	1 (0.1)	0	2 (0.1)	0
Cardiac Arrest	0	0	2 (0.2)	3 (0.5)	3 (0.1)	3 (0.2)
Cardiac Failure	0	0	1 (0.1)	0	2 (0.1)	0
Cardio-Respiratory Arrest	0	0	2 (0.2)	0	2 (0.1)	0
Chest Pain	0	0	0	0	2 (0.1)	0
Delirium tremens	0	0	0	2 (0.3)	0	2 (0.1)
Dermatitis Allergic	0	1 (0.1)	0	2 (0.3)	0	3 (0.2)
Drug Exposure During Pregnancy	0	2 (0.2)	0	0	0	2 (0.1)
Empyema	0	0	2 (0.2)	0	2 (0.1)	0
Headache	0	1 (0.1)	2 (0.2)	0	2 (0.1)	1 (0.1)
Hypersensitivity	0	5 (0.5)	1 (0.1)	1 (0.2)	3 (0.1)	6 (0.3)
Infusion Site Urticaria	0	1 (0.1)	0	1 (0.2)	0	2 (0.1)
Pneumonia	0	0	0	2 (0.3)	1 (0.0)	3 (0.2)
Pruritus Generalised	0	0	0	1 (0.2)	2 (0.1)	1 (0.1)
Pulmonary Embolism	0	0	1 (0.1)	1 (0.2)	2 (0.1)	1 (0.1)
Pyrexia	0	2 (0.2)	0	0	6 (0.2)	2 (0.1)
Rash	0	2 (0.2)	2 (0.2)	1 (0.2)	4 (0.1)	4 (0.2)
Red Man Syndrome	0	0	0	4 (0.7)	0	4 (0.2)
Respiratory Arrest	0	0	2 (0.2)	0	2 (0.1)	0
Respiratory Distress	0	0	0	1 (0.2)	2 (0.1)	1 (0.1)
Sepsis	0	2 (0.2)	4 (0.3)	1 (0.2)	4 (0.1)	3 (0.2)
Septic Shock	0	0	3 (0.3)	0	3 (0.1)	0
Skin Bacterial Infection	0	2 (0.2)	0	0	0	2 (0.1)

The most frequent (≥ 0.3%) AEs leading to study drug discontinuation in the ARRD/I pool were sepsis and septic shock in the oritavancin group and red man syndrome, cardiac arrest, pneumonia, allergic dermatitis and delirium tremens in the vancomycin group. The median time to onset of AEs leading to study drug discontinuation was 3.1 days (0 to 43 days) and 0.9 days (0 to 43 days) in respective treatment groups.

In the All Treated pool, the most frequent (≥ 0.2%) AEs leading to study drug discontinuation were pyrexia and urticaria in the oritavancin group and cellulitis, skin infection, rash, red man syndrome, drug hypersensitivity, and hypersensitivity in the vancomycin group. The median time to onset of AEs leading to study drug discontinuation was 2.5 days (0 to 43 days) and 1.9 days (0 to 43 days) in the oritavancin and comparator groups, respectively, in the All Treated pool.

The table below shows all discontinuations (not just those in at least 2 patients) due to AEs that could have been due to hypersensitivity. There was no excess of such AEs in the oritavancin group in any patient pool.

Table 64

Table 12: Hypersensitivity Adverse Events Leading to Study Drug Discontinuation (Safety Population)

	SOLO Pool		ARRD/I Pool		All Treated Pool	
Event of Special Interest Preferred Term	Oritavancin (N=976) n (%)	Vancomycin (N=983) n (%)	Oritavancin (N=1173) n (%)	Vancomycin (N=590) n (%)	Oritavancin (N=3017) n (%)	Comparator (N=1954) n (%)
Hypersensitivity	6 (0.6)	14 (1.4)	13 (1.1)	15 (2.5)	34 (1.1)	33 (1.7)
Pruritus	2 (0.2)	4 (0.4)	1 (0.1)	1 (0.2)	3 (0.1)	5 (0.3)
Bronchospasm	1 (0.1)	0	0	0	1 (0.0)	0
Chest Discomfort	1 (0.1)	0	0	0	2 (0.1)	0
Drug Hypersensitivity	1 (0.1)	2 (0.2)	0	1 (0.2)	1 (0.0)	4 (0.2)
Dyspnoea	1 (0.1)	0	0	0	2 (0.1)	0
Erythema Multiforme	1 (0.1)	0	0	0	1 (0.0)	0
Hypotension	1 (0.1)	1 (0.1)	0	0	2 (0.1)	1 (0.1)
Rash Macular	1 (0.1)	2 (0.2)	0	0	1 (0.0)	3 (0.2)
Urticaria	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.2)	6 (0.2)	2 (0.1)
Anaphylactoid Reaction	0	1 (0.1)	1 (0.1)	0	1 (0.0)	1 (0.1)
Cardiac Arrest	0	0	2 (0.2)	3 (0.5)	3 (0.1)	3 (0.2)
Cardiorespiratory Arrest	0	0	2 (0.2)	0	2 (0.1)	0
Cough	0	0	0	0	1 (0.0)	0
Hypersensitivity	0	5 (0.5)	1 (0.1)	1 (0.2)	3 (0.1)	6 (0.3)
Pruritus Generalised	0	0	0	1 (0.2)	1 (0.0)	1 (0.1)
Rash	0	2 (0.2)	2 (0.2)	1 (0.2)	4 (0.1)	4 (0.2)
Rash Maculo-papular	0	0	0	0	0	1 (0.1)
Red Man Syndrome	0	0	0	4 (0.7)	0	4 (0.2)
Respiratory Arrest	0	0	2 (0.2)	0	2 (0.1)	0
Respiratory Distress	0	0	0	1 (0.2)	2 (0.1)	1 (0.1)
Respiratory Failure	0	0	0	1 (0.2)	0	1 (0.1)
Swollen Tongue	0	0	0	0	1 (0.0)	0
Upper Airway Obstruction	0	0	1 (0.1)	0	1 (0.0)	0

2.6.1. Discussion on clinical safety

The safety database includes 1075 patients with ABSSSI who were treated with a single 1200 mg dose of oritavancin infused over 3 h. With few exceptions there are no marked differences between oritavancin and vancomycin.

Oritavancin is less likely than vancomycin to be associated with HLIRs or true allergic reactions. Cross-hypersensitivity between other glycopeptides and oritavancin seems unlikely but caution is required.

In the SOLO pool cardiac AE rates were 3.4% for oritavancin and 2.7% for vancomycin, with a higher rate of tachycardia with oritavancin (2.5% vs. 1.1%) but further analyses have not explained the imbalance and have shown that events were not clustered around Cmax.

A consistent and very notable higher rate of osteomyelitis cases (total 22 vs. 2 for comparators) has been observed with oritavancin in SOLO I and II (6 vs. 1) and in ARRD/I (13 vs. 0). In addition, in the SOLO studies the rates of abscesses (total of abscess and abscess in limb) were 3.9% for oritavancin vs. 1.9% for vancomycin while the difference in ARRD/I was 3.3% vs. 2.6%. Most of these were treatment-emergent rather than worsening of a baseline abscess. These imbalances have not been explained. The issue has been reflected in the SmPC.

The higher rate of AEs of ALT increased for oritavancin in SOLO I and II influenced the overall higher rates of hepatic events reported as AEs (4.7% vs. 3.0%). There was no imbalance in ARRD/I and a small difference in the All Treated pool (1.3% vs. 0.9%). In contrast, the rates for PCS increases in ALT (or AST) were not higher for oritavancin in the SOLO I and II or other pools. PCS increases in bilirubin occurred more often for oritavancin in SOLO I and II only and this finding was accompanied by more patients (although numbers are very small) with concomitant PCS values for bilirubin and one or more of ALT, AST and ALP. Independent review indicated that no patient fulfilled Hy's law criteria.

The rates for PCS hyponatraemia values were consistently higher for oritavancin vs. vancomycin. This seems to have been related to the higher proportion with diabetes and to the association between hyperglycaemia and hyponatraemia.

Thrombocytopenia (or decreased platelets) was reported as an AE in 5 oritavancin and no vancomycin patients in the SOLO studies and in 12 vs. 2 in the All Treated pool. Counts < 75 x 10^9/L showed a difference only for the All Treated pool (15 vs. 3 cases; 0.6% vs. 0.2%) but missing data and concomitant medications associated with low platelets limit any further comment.

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

2.6.2. Conclusions on the clinical safety

There are several concerns that will be followed up via the RMP. In particular, the consistent imbalances between treatments in the SOLO, and ARRD/I and All Treated pools for AEs of osteomyelitis and abscesses suggest that oritavancin could have some detrimental effect on the migration or function of phagocytic cells in deep seated tissues despite the fact that efficacy against ABSSSI was comparable to that of vancomycin and in-vitro studies showed macrophages to retain functionality.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.2 is acceptable. In addition, minor revisions were recommended to be taken into account with the next RMP update. PRAC endorsed PRAC Rapporteur assessment report is attached.

The applicant implemented the changes in the RMP as requested by PRAC before the CHMP Opinion.

The CHMP endorsed the Risk Management Plan version 1.3 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Hypersensitivity Drug interaction with warfarin Coagulation test interference Limb and subcutaneous abscess
Important potential risks	Pseudomembranous colitis/CDAD Osteomyelitis Development of drug-resistant bacteriae Hyperuricaemia Off-label use for Gram-positive bacterial infections other than ABSSSI Renal impairment

Summary of safety concerns	
	Anticholinergic effects Antidopaminergic effects Cardiac conduction abnormalities Ototoxicity
Missing information	Exposure to oritavancin during pregnancy and lactation Use of oritavancin in the paediatric population (<18 years of age)

Pharmacovigilance plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports
14-TMC-01: International Oritavancin Surveillance Protocol Category 3	To monitor the activity of oritavancin compared to numerous broad- and narrow-spectrum (Gram-positive-targeted) antibacterial agents when tested against contemporary clinical isolates collected in U.S. and European medical centers for the years 2014 to 2019	Development of drug-resistant bacteria	Planned	30 April of each post study year
Open-label trial evaluating the safety of a single 1200 mg IV dose of Orbactiv in patients on concomitant chronic warfarin therapy who are being treated for ABSSSI Category 3	The key objectives of this study are to characterize the effect of oritavancin on clinical care and warfarin dosing in patients on chronic warfarin therapy, to determine the magnitude and duration, if any, of alterations to warfarin dosing, and to determine the safety of and clinically important consequences which may result from the concomitant use of warfarin and oritavancin.	The safety of and clinically important consequences which may result from the concomitant use of warfarin and oritavancin	Planned	August 2016
Open-label trial to assess the clinical significance of the DDI between a single 1200 mg IV dose of Orbactiv and warfarin in healthy volunteers Category 3	The key objectives of this dedicated warfarin drug interaction study are to evaluate the effects of a single 1200 mg infusion of oritavancin on the safety and PK of warfarin and to determine the magnitude and duration of this interaction to gain insights into the possible need for alterations in warfarin dosing.	The magnitude and duration of DDI between a single 1200 mg IV dose of Orbactiv and warfarin	Planned	June 2015
Effects of oritavancin on phospholipid and nonphospholipid	The objective of this study will be to determine which tests used to monitor anticoagulant therapy may be used in patients following a single 1200 mg dose of oritavancin.	Interference with coagulation test	Planned	April 2015

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports
based coagulation test in vitro Category 3				
Single-center, open-label trial to evaluate the effects of a single 1200 mg IV dose of Orbactiv on the results of multiple coagulation tests in healthy volunteers Category 3	The objective of this study is to evaluate the magnitude and duration of any false prolongation of the PT test in healthy volunteers following a single 1200 mg oritavancin infusion.	The magnitude and duration of any false prolongation of the PT test	Planned	May 2015

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risk		
Hypersensitivity	**Information provided in SmPC:** **Section 4.3 Contraindications**: Hypersensitivity to the active substance or to the excipients listed in section 6.1. **Section 4.4 Special warnings and precautions for use**: Hypersensitivity reactions Serious hypersensitivity reactions have been reported with the use of oritavancin. If an acute hypersensitivity reaction occurs during oritavancin infusion, oritavancin should be discontinued immediately and appropriate supportive care should be instituted. No data are available on cross-reactivity between oritavancin and other glycopeptides, including vancomycin. Before using oritavancin it is important to inquire carefully about previous hypersensitivity reactions to glycopeptides (e.g. vancomycin, telavancin). Due to the possibility of cross-hypersensitivity, there should be careful monitoring of patients with any history of glycopeptide hypersensitivity during and after the infusion. Infusion related reactions Oritavancin is given via intravenous infusion over 3 hours to minimise the risk of infusion related reactions. Oritavancin has been shown to cause infusion related reactions including pruritus, urticaria or flushing. If reactions do occur, stopping or slowing the infusion should be considered to mitigate the reaction (see section 4.8). **Section 4.8 Undesirable effects** The pooled ABSSSI Phase 3 clinical trials included 976 adult patients were treated with a single once-only 1200 mg dose of oritavancin. Adverse reactions were reported at similar frequencies for oritavancin and the comparator regimen. The most commonly reported adverse reactions (≥5%) were: nausea, hypersensitivity reactions, infusion site reactions, and headache. The most commonly reported serious adverse reaction was cellulitis (1.1% (11/ 976). The most commonly reported reasons for discontinuation were cellulitis (0.4%, 4/976) and osteomyelitis (0.3%, 3/976). The Patient Information Leaflet (PIL) contains similar information regarding the risk of hypersensitivity.	None
Drug interaction with warfarin	**Information provided in SmPC:** **Section 4.4 Special warnings and precautions for use:** Concomitant use of warfarin	None

	Co-administration of oritavancin and warfarin may result in higher exposure of warfarin (resulting in 31% increase in the mean area under the curve (AUC) of warfarin), which may increase the risk of bleeding (see SmPC section 4.5). Oritavancin should only be used in patients on chronic warfarin therapy when the benefits can be expected to outweigh the risk of bleeding; these patients should be frequently monitored for signs of bleeding. Oritavancin has been shown to artificially prolong prothrombin time (PT) and international normalised ratio (INR) for up to 24 hours, making the monitoring of the anticoagulation effect of warfarin unreliable up to 24 hours after an oritavancin dose. **Section 4.5 Interaction with other medicinal products and other forms of interaction**: Substances metabolised by cytochrome P450 A cocktail drug-drug interaction study was conducted in healthy volunteers (n=16) evaluating the concomitant administration of a single 1,200 mg dose of oritavancin with probe substrates for several CYP450 enzymes. Oritavancin was found to be a nonspecific, weak inhibitor (CYP2C9 and CYP2C19) or a weak inducer (CYP3A4 and CYP2D6) of several CYP isoforms. Caution should be used when administering oritavancin concomitantly with medicinal products with a narrow therapeutic window that are predominantly metabolised by one of the affected CYP450 enzymes (e.g., warfarin), as co-administration may increase (e.g., for CYP2C9 substrates) or decrease (e.g., for CYP2D6 substrates) concentrations of the narrow therapeutic range medicinal product. Patients should be closely monitored for signs of toxicity or lack of efficacy if they have been given oritavancin while on a potentially affected compound (e.g. patients should be monitored for bleeding if concomitantly receiving oritavancin and warfarin) (see section 4.4). The PIL contains similar information regarding the risk of a drug interaction with warfarin.	
Coagulation test interference	**Information provided in SmPC:** **Section 4.3 Contraindications:** Use of intravenous unfractionated heparin sodium is contraindicated for 48 hours after oritavancin administration because the activated partial thromboplastin time (aPTT) test results are expected to remain falsely elevated for approximately 48 hours after oritavancin administration (see sections 4.4 and 4.5) **Section 4.4 Special warnings and precautions for use**: Interference with assay for coagulation tests Oritavancin has been shown to artificially prolong aPTT for 48 hours and the PT and INR for 24 hours by binding to and preventing action of the phospholipid reagents which activate coagulation in commonly used laboratory coagulation tests. For patients who require aPTT monitoring within 48 hours of oritavancin dosing, a non-phospholipid dependent coagulation test such as a Factor Xa (chromogenic) assay or an alternative anticoagulant not requiring aPTT monitoring may be considered. Effects by oritavancin on activated clotting time (ACT) are expected since the phospholipid reagents are also utilized in this coagulation test. Although oritavancin interfered with certain tests used to monitor coagulation, no known effect on the coagulation system has been observed. **Section 4.5 Interaction with other medicinal products and other forms of interaction**: Drug-Laboratory test interactions Oritavancin has been shown to artificially prolong aPTT for 48 hours and PT and INR for up to 24 hours by binding to and preventing action of the phospholipid reagents which activate coagulation in commonly used laboratory coagulation tests. Effects by oritavancin on activated clotting time (ACT) are expected since the phospholipid reagents are also utilised in this coagulation test (see section 4.4). The PIL contains similar information regarding the risk of coagulation test interference.	None
Limb and subcutaneous abscess	**Information provided in SmPC:** **Section 4.4 Special warnings and precautions for use:** Abscess In the Phase 3 clinical trials, slightly more cases of newly emergent abscesses were reported in the oritavancin-treated arm than in the vancomycin-treated arm (4.6% vs 3.4%, respectively) (see section 4.8). If newly emergent abscesses occur, appropriate measures should be taken.	None

	Section 4.8 Undesirable effects: Abscess (limb and subcutaneous) is listed as a common ADR.	
Important potential risk		
Pseudomembranous colitis/*Clostridium difficile*-associated diarrhoea	**Information provided in SmPC:** **Section 4.4 Special warnings and precautions for use**: *Clostridium difficile*-associated diarrhoea Antibacterial-associated colitis and pseudomembranous colitis have been reported for oritavancin and may range in severity from mild to life threatening diarrhoea. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of oritavancin (see SmPC section 4.8). In such a circumstance, the use of supportive measures together with the administration of specific treatment for Clostridium difficile should be considered. **Section 4.8 Undesirable effects**: Diarrhoea is listed as a common ADR.	None
Osteomyelitis	**Information provided in SmPC:** **Section 4.4 Special warnings and precautions for use**: Osteomyelitis In Phase 3 ABSSSI clinical trials, more cases of osteomyelitis were reported in the oritavancin-treated arm than in the vancomycin-treated arm (see section 4.8). Patients should be monitored for signs and symptoms of osteomyelitis after administration of oritavancin. If osteomyelitis is suspected or diagnosed, appropriate alternative antibacterial therapy should be instituted. **Section 4.8 Undesirable effects**: The most common reported reasons for discontinuation were cellulitis (0.4%, 4/976) and osteomyelitis (0.3%, 3/976). Osteomyelitis is listed as an uncommon ADR.	None
Development of drug-resistant bacteria	**Information provided in SmPC:** **Section 4.4 Special warnings and precautions for use:** Superinfection The use of antibacterial agents may increase the risk of overgrowth of non-susceptible micro-organisms. If superinfection occurs, appropriate measures should be taken.	None
Hyperuricaemia	**Information provided in SmPC:** **Section 4.8 Undesirable effects:** Hyperuricemia is listed as an uncommon ADR. The PIL contains similar information regarding the risk of hyperuricaemia.	None
Off-label use for Gram-positive bacterial infections other than ABSSSI	**Information provided in SmPC:** **Section 4.1 Therapeutic indications:** Orbactiv is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults (see sections 4.4 and 5.1). Consideration should be given to official guidance on the appropriate use of antibacterial agents. **Section 4.4 Special warnings and precautions for use:** Need for additional antibacterial agents Oritavancin is active against Gram positive bacteria only (see section 5.1). In mixed infections where Gram negative and/or certain types of anaerobic bacteria are suspected, oritavancin should be co-administered with appropriate antibacterial agent(s). Limitations of the clinical data In the two major trials in ABSSSI the types of infections treated were confined to cellulitis, abscesses and wound infections only. Other types of infections have not been studied. There is limited experience in clinical studies in patients with bacteraemia, peripheral vascular disease or neutropenia, in immunocompromised patients, in patients aged > 65 years and in infections due to *S. pyogenes*. **Section 5.1 Pharmacodynamic properties** Resistance Gram-negative organisms are intrinsically resistant to all glycopeptides, including oritavancin. Resistance to oritavancin was *observed in vitro* in vancomycin-resistant isolates of *Staphylococcus aureus*. There is no known cross-resistance between oritavancin and non-glycopeptide classes of antibiotics. Oritavancin exhibits reduced *in vitro* activity against certain Gram-positive organisms of the genera *Lactobacillus*, *Leuconostoc* and *Pediococcus* that are intrinsically resistant to glycopeptides The PIL contains similar information regarding the risk of off-label use for Gram-positive bacterial infections other than ABSSSI.	None
Renal impairment	Prescription only medicine	None
Anticholinergic effects	**Information provided in SmPC section 4.8 Undesirable effects:** Constipation, tachycardia, and dizziness are listed as common ADRs. The PIL contains similar information regarding the risk of anticholinergic effects.	None
Antidopaminergic effects	Prescription only medicine	None

Cardiac conduction abnormalities	Prescription only medicine	None
Ototoxicity	**Information provided in SmPC section 4.8 Undesirable effects:** Dizziness is listed as a common ADR. The PIL contains similar information regarding the risk of ototoxicity.	None

2.9. Product information

2.9.1. User consultation

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

3. Benefit-Risk Balance

Benefits

Beneficial effects

Oritavancin is a novel antibiotic belonging to the glycopeptide antibacterials. It inhibits bacterial cell wall biosynthesis and disrupts bacterial membrane integrity, leading to rapid cell death. Efficacy has been demonstrated in clinical studies against common aetiological agents of ABSSSI shown to be susceptible to oritavancin *in vitro*. However, in common with all glycopeptides, the spectrum of activity intrinsically excludes Gram-negative organisms. There seems no known cross-resistance between oritavancin and non-glycopeptide classes of antibiotics.

The clinical efficacy of oritavancin in ABSSSI has been evaluated in two phase 3 randomised controlled studies of identical design (SOLO-1 and SOLO-2) that recruited a total of 1987 patients (ITT population). Patients were required to have cellulitis/erysipelas, major cutaneous abscess or wound infection with a minimum total lesion surface area of 75 cm^2 and at least one regional or systemic sign of infection.

Oritavancin was given on Day 1 as a single 1200 mg dose in 1000 mL of 5% D5W over 3 h. Vancomycin was administered IV for 7 to 10 days. Aztreonam and metronidazole were allowed for patients with mixed infections.

Non-inferiority of oritavancin compared to vancomycin was shown, based on the clinical cure rates at post-treatment evaluation (PTE) in the mITT (79.6% vs 80.0% for SOLO-1; 82.7 vs 80.5% for SOLO-2) and CE populations and the sensitivity analyses supported the primary analysis. The lower bounds of the 95% CI were well within -10%. In addition, the results at the early clinical evaluation (ECE) visit supported a conclusion of general comparability between treatment groups.

The microbiological success rates were comparable between treatment groups by type of infection.

Uncertainty in the knowledge about the beneficial effects.

The in-vitro data indicate that very few staphylococci that are of intermediate susceptibility or resistant to glycopeptides would be treatable with oritavancin and there are no clinical data on the use of oritavancin to treat organisms for which the vancomycin MIC exceeds 1 mg/L. It appears unlikely that oritavancin can

be used to treat VISA or VRSA and there are too few data to conclude on hVISA. In addition, it does not appear that oritavancin can be relied upon to treat daptomycin-insusceptible staphylococci.

There are limitations regarding the host and ABSSSI disease aspects of the patients in whom efficacy has been evaluated although there are no clear theoretical reasons to doubt the sufficiency of the dose regimen for a wider population. Indeed, there is limited experience in clinical studies in patients with bacteraemia, peripheral vascular disease or neutropenia, in immunocompromised patients, in patients aged > 65 years and in infections due to *S. pyogenes*. These limitations are noted in section 4.4 of SmPC.

At present it is unclear why there has been a consistent finding of excess treatment emergent infections affecting deep tissues (bones) and abscesses for oritavancin vs. vancomycin but there has to be concern that this reflects some detrimental impact of oritavancin on normal immune defences that may be related to the high degree of intracellular accumulation especially in macrophages.

Risks

Unfavourable effects

The safety profile of oritavancin resembles that for vancomycin and for many SOCs and PTs, the AE rates have been similar or lower for oritavancin. In particular the rates for AEs that may reflect HLIRs or hypersensitivity reactions appear to be lower for oritavancin.

In contrast, the rates for treatment-emergent infections, including osteomyelitis and abscesses, have now been shown to be higher for oritavancin regardless of single or multiple dose regimens. This is of concern, especially when the underlying mechanism(s) for the seemingly consistent difference remains the subject of conjecture (see above).

In addition, the rates for hepatic AEs and for numbers with concomitant PCS values across the LFTs have been higher with oritavancin although no patient has been judged to have met Hy's law and the actual numbers are low. Also, the rates for cardiac AEs, driven by the numbers with tachycardias, have been higher for oritavancin.

Uncertainty in the knowledge about the unfavourable effects

There are some unanswered questions regarding the transport of oritavancin into bile and into various types of cells, which could have possible implications for the safety profile in some individuals.

There are some unexplained apparent anomalies between reporting rates for some types of laboratory abnormalities as AEs vs. the rates for PCS values.

Benefit-risk balance

Importance of favourable and unfavourable effects

Oritavancin does not have any antibacterial properties that could be viewed as definite and proven advantages over other intravenous agents that have antibacterial spectra confined to certain Gram-positive organisms. However, it offers a single parenteral treatment with efficacy against ABSSSI that was shown to be comparable to that of vancomycin in two adequately powered Phase 3 studies.

While it appears that the risk of treatment-emergent infections of bone and abscesses is higher with oritavancin, and this may or may not be a result of its tissue accumulation and effects on normal immune defences, this fact alone would not preclude an approval provided that there are adequate warnings in the SmPC. In addition, although it seems that there could be a slightly higher risk of some other types of AEs vs. vancomycin, the differences do not raise major issues on grounds of safety.

Benefit-risk balance

The overall B/R of Orbactiv is considered as positive in the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults.

Discussion on the benefit-risk balance

Skin infections are among the most common infections seen in clinical practice; these infections may require systemic antibiotic therapy, surgical management, and hospitalization and, if untreated, may become severe or life-threatening depending on the pathogen [Corey and Stryjewski, 2011; Elston, 2005].

The morbidity associated with ABSSSI often requires rapid antimicrobial intervention to minimize tissue damage and prevent the spread of infection. The clinical complications of delayed or inappropriate treatment of skin and skin structure infections can be serious, including those resulting from local spread, secondary bacteraemia with potential for distant metastatic foci of infection, and systemic effects [Davis et al, 2007].

Patients and healthcare providers face challenges with the treatments available for ABSSSI, specifically for the treatment of MRSA infections. Current therapies consist of multi-dose and multi-day regimens with some requiring dosage adjustments for renal insufficiency, therapeutic monitoring, and precautionary use in pregnant women. Multi-dose therapies may require patients to be hospitalized for the course of their antibiotic treatment over multiple days, increasing the risk of acquiring or spreading infection. Treatment non-compliance can also be an issue with these regimens, increasing the potential for pathogen resistance [CDC, 2011]. As demonstrated in the Phase 3 SOLO studies, a single 1200 mg dose of oritavancin is an effective and well-tolerated treatment for ABSSSI, including those caused by MRSA. Single-dose treatment was non-inferior to 7-10 days of vancomycin treatment and showed consistent and reproducible results across all efficacy endpoints, including early clinical response at 48-72 hours and clinical cure at 10-14 days post therapy.

The Phase-3 SOLO studies demonstrated that a single 1200 mg IV dose of oritavancin was well tolerated and had a similar safety profile to 7 to 10 days of vancomycin treatment (1 g or 15 mg/kg twice daily). The most frequently reported AEs were nausea, hypersensitivity reactions, infusion site reactions, and headache. Caution should be used in patients with known hypersensitivity to glycopeptides and patients taking warfarin concomitantly. The risk of treatment-emergent infections of bone and abscesses is higher with oritavancin, warranting adequate warnings in the SmPC.

Oritavancin is a mild inhibitor of CYP2C9 enzymes, and therefore, has the potential to increase warfarin concentrations when administered concomitantly. The potential for oritavancin to inhibit or induce CYP2C8 was not evaluated and will be provided as a PAM. Also, appropriate transporter studies will be provided.

Due to oritavancin's interference with some laboratory coagulation tests, reliable monitoring of coagulation status is not possible. Patients who are on warfarin should be closely monitored for signs of bleeding. Safety of 1200 mg IV dose of Orbactiv in patients on concomitant chronic warfarin who are being treated for ABSSSI, will be further addressed as a PAM.

No adjustment of the oritavancin dose is necessary for age, weight, renal or liver function. No therapeutic drug monitoring for efficacy is required for oritavancin.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Orbactiv in the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that oritavancin is qualified as a new active substance.