CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206334Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

Product Quality Microbiology Review

JULY 03, 2014

NDA: 206334

Drug Product Name
Proprietary: Orbactiv
Non-proprietary: Oritavancin diphosphate

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
December 6, 2013	December 6, 2013	December 16, 2013	December 20, 2013

Submission History (for 2nd Reviews or higher) – N/A

Applicant/Sponsor
Name: The Medicines Company
Address: 8 Sylvan Way,
Parsippany, NJ 07054
Representative: Ketna Patel, Director, Regulatory Affairs,
Phone: 973-290-6031.

Name of Reviewer: Vinayak B. Pawar, Ph.D.

Conclusion: Recommend Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original NDA.

2. SUBMISSION PROVIDES FOR: A new drug product Oritavancin for injection.

3. MANUFACTURING SITE: (b) (4)

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Sterile lyophilized powder, 400 mg per vial, for injection.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Antibiotic for treatment of skin infection.

B. SUPPORTING/RELATED DOCUMENTS: None.

C. REMARKS: The Medicines Company submits an Original NDA 206334 for Oritavancin diphosphate for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by Gram-positive microorganisms. ORBACTIV (oritavancin) for injection is a novel semi-synthetic lipoglycopeptide antibiotic administered as a single intravenous (IV) dose for the treatment of ABSSSI caused by susceptible isolates of Gram-positive pathogens, including MRSA. This is an electronic submission.

filename: **N0206334R1**

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Recommend Approval.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology - The bulk solution is (b) (4) (b) (4)

B. Brief Description of Microbiology Deficiencies – None.

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

D. Contains Potential Precedent Decision(s) - ☐ **Yes** ☒ **No**

III. Administrative

A. Reviewer's Signature _____
Vinayak B. Pawar, Ph.D., Sr. Review Microbiologist, OPS/CDER

B. Endorsement Block _____
Stephen E. Langille, Ph.D., Sr. Review Microbiologist, OPS/CDER

C. CC Block
N/A

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/s/

VINAYAK B PAWAR
07/07/2014

STEPHEN E LANGILLE
07/07/2014

DIVISION OF ANTI-INFECTIVE PRODUCTS CLINICAL MICROBIOLOGY REVIEW

NDA 206334 DATE REVIEW COMPLETED: May 5th, 2014.
Oritavancin/Orbactiv

Date Company Submitted: 12/06/2013
Date received by CDER: 12/06/2013
Date Assigned: March 12/06/2013
Reviewer: Avery Goodwin, Ph.D.

NAME AND ADDRESS OF APPLICANT:

The Medicines Company
8 Sylvan Way
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CONTACT PERSON:

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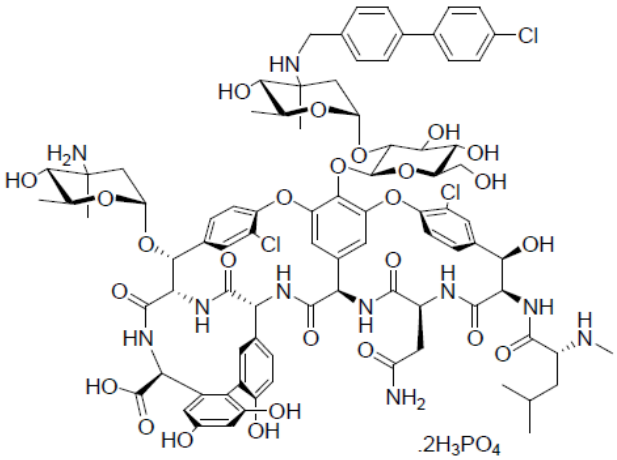
DRUG PRODUCT NAMES:

Proprietary Name:
Established Name: Oritavancin diphospate
Structural Formula:



The oritavancin diphosphate drug substance is obtained by chemical modification of a fermentation product from *Kibdelosporangium aridum* (formerly referred to as *Amycolatopsis orientalis*). It is identified chemically as [4"*R*]-22-*O*-(3-amino-2,3,6-trideoxy-3-*C*-methyl-α-L*arabino*- hexopyranosyl)-*N*3''-[(4'-chloro[1,1'-biphenyl]-4-yl)methyl]vancomycin phosphate [1:2] [salt].

Molecular Formula: $C_{86}H_{97}N_{10}O_{26}Cl_3 \bullet 2H_3PO_4$
Molecular weight is 1989.09 g.mol-1.

DIVISION OF ANTI-INFECTIVE PRODUCTS CLINICAL MICROBIOLOGY REVIEW

NDA 206334 DATE REVIEW COMPLETED: May 5th, 2014.
Oritavancin/Orbactiv

PRODUCT STRENGTH:
Each single-use, clear glass vial contains 400 mg of sterile lyophilized oritavancin powder.

ROUTE OF ADMINISTRATION AND DURATION OF TREATMENT:
Intravenous Injection; the recommended dosage of ORBACTIV is 1200 mg administered as a single dose by intravenous (IV) infusion over 3 hours.

PROPOSED INDICATION:
Oritavancin is indicated for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSIs) caused or suspected to be caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible [MSSA] and –resistant [MRSA] isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus anginosus* group (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), and *Enterococcus faecalis* (vancomycin-susceptible isolates only).

RELATED SUBMISSION REVIEWED:
IND: 51292

STORAGE REQUIREMENT:
Vials should be stored at 20ºC to 25ºC (68ºF to 77ºF); excursions permitted to 15ºC to 30ºC (59ºF to 86ºF) [see USP, Controlled Room Temperature (CRT)].

HOW SUPPLIED AND PACKAGING CONFIGURATION:
400 mg is supplied as sterile oritavancin powder in a 50-mL capacity glass vial.

SUMMARY AND RECOMMENDATIONS:

This Reviewer agrees with the Applicant's list of pathogens in the interpretive criteria Table. Based on the clinical microbiology data submitted by the Applicant, this NDA submission may be approved provided the Applicant makes the changes in the microbiology subsection of the proposed package insert.

Proposed version of the microbiology subsection of the package insert:

12.4 Microbiology
ORBACTIV is a semi-synthetic, lipoglycopeptide antibiotic. ORBACTIV exerts (b) (4) a concentration-dependent bactericidal activity against (b) (4) (b) (4) *S. aureus*

(b) (4)

Mechanism of Action

Oritavancin has three mechanisms of action: (i) inhibition of the transglycosylation (polymerization) step of cell wall biosynthesis by binding to the stem peptide of peptidoglycan precursors; (ii) inhibition of the transpeptidation (crosslinking) step of cell wall biosynthesis by binding to the peptide bridging segments of the cell wall; and (iii) disruption of bacterial membrane integrity, leading to depolarization, permeabilization, and (b) (4) cell death. These multiple mechanisms contribute to the (b) (4) concentration-dependent bactericidal activity of oritavancin.

Mechanism of Resistance

(b) (4)

(b) (4)

Interaction with Other Antimicrobial Agents

In in vitro studies, oritavancin exhibits synergistic bactericidal activity in combination with gentamicin, moxifloxacin or rifampicin against isolates of MSSA, with gentamicin or linezolid against isolates of (b) (4)-hVISA, VISA, and VRSA, and with rifampicin against isolates of VRSA. In vitro studies demonstrated no antagonism between oritavancin and (b) (4) gentamicin, moxifloxacin, linezolid or rifampicin (b) (4)

Antibacterial Activity

Oritavancin has been shown to be active against most isolates of the following bacteria, both in vitro and in clinical infections as described in the Indications and Usage section *[see Indications and Usage (1.1)]*.

Staphylococcus aureus (including methicillin-resistant isolates)
Streptococcus agalactiae
Streptococcus anginosus group (includes *S. anginosus, S. intermedius,* and *S. constellatus*)
Streptococcus dysgalactiae
Streptococcus pyogenes
Enterococcus faecalis (vancomycin-susceptible isolates only)

The following in vitro data are available but their clinical significance (b) (4). At least 90% of isolates of the following (b) (4) exhibit an oritavancin MIC less than or equal to (b) (4) however, the safety and effectiveness of oritavancin in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

Enterococcus faecium (vancomycin-susceptible isolates only)

Susceptibility Testing Methods
When available, the clinical microbiology laboratory should provide cumulative results of in vitro susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial drug for treatment.

Dilution technique
Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds.[1] Oritavancin MICs should be determined using a standardized procedure which are based on a broth microdilution method or equivalent with standardized inoculum concentrations and standardized concentrations of oritavancin. The MIC values should be interpreted according to the criteria provided in the Table (b) (4)

Table (b) (4) Susceptibility Interpretive Criteria for ORBACTIV[a]

Microorganism	**Minimum Inhibitory Concentration (MIC, µg/mL)**		
	S	**I[b]**	**R[b]**
Staphylococcus aureus (including methicillin-resistant isolates)	≤0.12	-	-
Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus anginosus group	≤0.25	-	-

(includes *S. anginosus, S. intermedius,* and *S. constellatus*) *Streptococcus dysgalactiae*			
Enterococcus faecalis (vancomycin-susceptible isolates only)	≤0.12	-	-

Abbreviations: MIC, minimum inhibitory concentration; S, Susceptible; I, intermediate; R, Resistant

[a] As determined by broth microdilution with 0.002% polysorbate-80 during oritavancin dissolution and dilution and in the final assay.

[b] The current absence of resistant isolates precludes defining any results other than "Susceptible". Isolates yielding test results other than "Susceptible" should be retested, and if the result is confirmed, the isolate should be submitted to a reference laboratory for further testing.

(b) (4)

A report of "Susceptible" indicates that the antimicrobial drug is likely to inhibit growth of the (b) (4) if the antimicrobial drug reaches the concentration usually achievable at the site of infection (b) (4)

(b) (4)

Quality Control

Standardized susceptibility test procedures require the use of laboratory control microorganisms to monitor and ensure the accuracy and precision of supplies and reagents used in the assay and the techniques of the individuals performing the test. Acceptable oritavancin MIC ranges for the quality control strains are shown in Table (b) (4) Quality control microorganisms are specific strains of organisms with intrinsic biological properties, and are very stable strains that will give a standard and reproducible susceptibility pattern. The specific strains used for microbiological quality control are not clinically significant.

Table (b) (4) Acceptable Quality Control Ranges for Oritavancin Susceptibility Testing[a]

Quality Control Organism	Minimum Inhibitory Concentration Range (MIC in µg/mL)
Staphylococcus aureus ATCC 29213	0.015 – 0.12
Streptococcus pneumoniae ATCC 49619	0.001 – 0.004
Enterococcus faecalis ATCC 29212	0.008 – 0.03

ATCC = American Type Culture Collection.
[a] As determined by broth microdilution with 0.002% polysorbate-80 during oritavancin dissolution and dilution and in the final assay.[1,2]

Diffusion technique
The use of the disk diffusion method is not recommended since quality control ranges have not been defined for oritavancin.

15 REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard – Ninth Edition. CLSI document M7-A09, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, PA 19087, 2012.
2. CLSI. Performance standards for antimicrobial susceptibility testing; Approved Standard – Ninth Edition. CLSI document M100-S24, Clinical and Laboratory Standards Institute, 2014.

EXECUTIVE SUMMARY

Antimicrobial Spectrum of Activity

The Applicant has submitted data from surveillance and other investigator studies to support the claim that oritavancin demonstrates in vitro activity against selected gram-positive pathogens associated with acute bacterial skin and skin structure infections (ABSSSI).

Staphylococci

Oritavancin demonstrates activity against USA and European staphylococcal isolates with a reported MIC90 of approximately 0.06 mcg/ml (MIC range was ≤0.002 - 0.5 mcg/mL). Among European MRSA the oritavancin MICs that ranged from ≤0.002 to 0.5 mcg/mL; for US isolates the MIC ranged from ≤0.002-0.25 mcg/ml. The presence of pvl did not appear to have an effect on the in vitro activity of oritavancin. Additionally, oritavancin appear to perform well against isolates with a vancomycin MIC of 2 mcg/ml. Against 72 isolates tested, the oritavancin MIC90 was reported to be 0.12 mcg/ml (Mic range ≤ 0.008-0.25 mcg/ml). Against all CoNS isolates tested, the oritavancin MIC90 was reported as 0.12 mcg/mL and the MIC range was 0.004 - 0.25 mcg/mL. The highest MIC observed was 0.25 mcg/mL and was encountered primarily among isolates of *S. epidermidis*.

Streptococci

Oritavancin demonstrates activity in vitro against *S. pneumonia*, including penicillin susceptible, penicillin non-susceptible *Streptococcus pneumoniae* isolates (MIC_{90} 0.15 mcg/ml). Against beta-hemolytic streptococci (Group A: *Streptococcus pyogenes* and Group B: *Streptococcus agalactiae*) the oritavancin MIC90 was 0.25 mcg/mL and the MIC range was ≤ 0.002 - 0.5 mcg/mL. It was noted that 99.7% of all the isolates tested had MICs that ranged from ≤ 0.002 - 0.25mcg/mL. Against Viridans streptococci (alpha-hemolytic streptococci), the oritavancin MIC ranged from ≤ 0.002 - 0.12 mcg/mL and the MIC90 was 0.06 mcg/mL against USA all isolates. Oritavancin MICs against 148 isolates of the three recognized species belonging to the *S. anginosus* Group (*S. anginosus,* n=102; *S. constellatus*, n=33; *S. intermedius,* n=13) ranged from ≤0.008 to 0.12 mcg/mL, with MIC90 of 0.0015 mcg/mL. The in vitro activity of oritavancin was tested against 34 recent *S. dysgalactiae* clinical isolates the MIC ranged from ≤0.008 to 0.25 mcg/mL, with an MIC90 of 0.25 mcg/mL.

Enterococci

Against all *E. faecalis* isolates tested, the Applicant reported an oritavancin MIC90 value of 0.06 mcg/ml (MIC range ≤0.002 – 1.0 mcg/mL). Against USA isolates, the overall oritavancin MIC90 was 0.06 for vancomycin-susceptible isolates and 0.25 mcg/mL for vancomycin-non-susceptible isolates. The highest MIC reported was 1 mcg/ml against one isolate with a VanA phenotype. Against all isolates of *E. faecium* tested the oritavancin MIC90 was reported to be 0.12 mcg/mL and the MIC range was ≤ 0.002 – 1.0 mcg/mL. Higher MIC values were also reported for isolates with the VanA phenotype.

Mechanism of Action

The inhibition of peptidoglycan synthesis via the inhibition of transglycosylation is common to all glycopeptides and lipoglycopeptides. Oritavancin has two cell wall binding sites: the peptidoglycan D-Ala-D-Ala pentapeptide (similar to vancomycin) stem terminus of lipid II, and the pentaglycyl bridging segment (unique to oritavancin). Oritavancin also interferes with gram positive bacterial cell membrane leading to rapid depolarization in staphylococci and enterococci causing a disruption of cellular integrity resulting in bacterial cell death.

Mechanisms of Resistance and Resistance Studies

The mechanism(s) of resistance were not studied. Resistance to oritavancin was examined by serial passage studies using subinhibitory concentrations against staphylococci and enterococci isolates. A 4- to 8-fold increase in oritavancin MIC was observed for other staphylococci isolates of different drug resistance phenotypes and a 4-64 fold increase in oritavancin MIC was reported against enterococci isolates. Results presented in the current study suggest a potential for emergence of oritavancin resistance.

Interaction with other Antimicrobials

In in vitro studies evaluating the inhibitory effects of oritavancin in combination with an array of antimicrobial agents showed that oritavancin exhibits synergistic bactericidal activity in combination with gentamicin, moxifloxacin or rifampicin against isolates of MSSA, with gentamicin or linezolid against isolates of heterogeneous vancomycin intermediate *Staphylococcus aureus* (hVISA), vancomycin intermediate *S. aureus* (VISA), and vancomycin resistant *S. aureus* (VRSA), and with rifampicin against isolates of VRSA.

Intracellular Antimicrobial Concentration Assessment

Oritavancin accumulates substantially in HL-60 cell lines reaching an intracellular concentration of 200-fold higher than the extracellular concentrations following 24 hours incubation. Oritavancin did not affect killing of *C. albicans* but appears to significantly enhance killing of *S. aureus* by macrophages. The results show that oritavancin appears to reduce killing of *A. baumannii* by HL-60 cells but not by RAW 264.7 cells. Macrophage killing of microbes appears to remain intact despite substantial intracellular accumulation with oritavancin. The accumulation of oritavancin did not appear to prevent phagocytic killing of *S. aureus*.

Susceptibility Testing

The in vitro activity of oritavancin varies when tested with and without polysorbate 80 against gram-positive clinical isolates of enterococci, staphylococci, and streptococci. The MICs for vancomycin and teicoplanin, tested by broth microdilution, were generally unaffected by the addition of 0.002% polysorbate 80, based on MIC90s and MIC ranges. However, the addition of 0.002% polysorbate 80 lowered the oritavancin MIC90s by 16- to 32-fold for enterococci and staphylococci as tested by broth microdilution. Oritavancin MIC90 for streptococci did not change in the presence versus absence of 0.002% polysorbate 80.

Animal Studies

The efficacy of oritavancin has been investigated in a number of animal models of infection including 1) staphylococci and enterococci bloodstream infections in mice; 2) endocarditis models of staphylococci and enterococci infections in rabbits and rats; 3) mouse and rat *S. pneumoniae* infection models; 4) biofilm *S. aureus* infection models in mouse; 5) meningitis models of *S. pneumonia* infection in rabbits; and 6) *B. anthracis* mouse infection models.

Pharmacokinetics/Pharmacodynamics

Oritavancin is approximately 85% bound to serum protein. There were no significant differences observed in the binding of oritavancin to serum protein between selected species.

The AUC/MIC has been shown to be the predictor of efficacy in both in vitro and in vivo systems. The probability of PK-PD target arraignment by oritavancin MIC was evaluated

using non-clinical AUC/MIC targets for stasis. The result of the PK-PD target attainment data predict clinical responses and appear to support susceptibility breakpoints of 0.12 mcg/ml for *S. aureus* and 0.5 mcg/ml for *S. pyogenes* and provides support for a single oritavancin dose of 1200 mg.

Clinical Study

The applicant performed two multicenter, double-blind, randomized studies to evaluate the efficacy and safety of single-dose intravenous (IV) oritavancin verses IV vancomycin for the treatment of patients with acute bacterial skin and skin structure infections (SOLO I/SOLO II). The primary objective was to establish non-inferiority of single-dose IV oritavancin compared with IV vancomycin given for 7 to 10 days using the primary efficacy outcome defined as the cessation of spread or reduction in size of the baseline lesion, absence of fever, and no rescue antibiotic medication at the Early Clinical Evaluation (ECE) time-point of 48 to 72 hours in the modified intent-to-treat (mITT) population. The Table below summarizes the efficacy analysis populations in the SOLO I and SOLO II clinical trials.

	SOLO I		SOLO II	
Category	Oritavancin (N=483) n (%)	Vancomycin (N=485) n (%)	Oritavancin (N=509) n (%)	Vancomycin (N=510) n (%)
Intent–to-Treat (ITT) Population[a]	483	485	509	510
Modified ITT (mITT) Population[b]	475 (98.3)	479 (98.8)	503 (98.8)	502 (98.4)
Clinically Evaluable (CE) Population[c]	394 (81.6)	397 (81.9)	427 (83.9)	408 (80.0)
Microbologically ITT (MicroITT) Population[d]	244 (50.5)	242 (49.9)	285 (56.0)	296 (58.0)
Microbiologically Evaluable (MicroE) Population[e]	201 (41.6)	201 (41.4)	246 (48.3)	247 (48.4)
Safety Population[f],	473[g]	481[g]	503	502
Pharmacokinetic (PK) Population[h]	115	0	197	0

[a]The Intent-to-Treat (ITT) population included all patients randomized into the study.
[b]The modified Intent-to-Treat (mITT) population was the primary population for all of the efficacy analyses and included all randomized patients who received any study drug.
[c]The Clinically Evaluable (CE) population consisted of all mITT patients who met the inclusion/exclusion criteria, received the full-course of randomized study treatment (for a minimum of 7 days), and had an investigator assessment for clinical cure at PTE. The CE population was used to confirm the efficacy analyses.
[d]The microbiologically ITT (MicroITT) population consisted of all mITT patients with baseline Gram-positive pathogen(s) known to cause ABSSSI and was used for the secondary efficacy analyses.
[e]The microbiologically evaluable (MicroE) population was used to confirm the secondary efficacy analyses and consisted of all patients who were in both the MicroITT and CE populations.
[f]The Safety population was the primary population for all the safety analyses and consisted of all patients who were dosed with study drug, irrespective of randomization. Treatment classification was based on the actual treatment received.
[g]In SOLO I, two patients randomized to receive oritavancin were inadvertently dosed with vancomycin.
[h]Patients who received at least one dose of oritavancin.
Source: Table 1.2 from CSR SOLO I (TMC-ORI-10-01) and CSR SOLO II (TMC-ORI-10-02).

Proposed In Vitro Susceptibility Interpretive Criteria

Microorganism	**Minimum Inhibitory Concentration (MIC, µg/mL)**		
	S	**I[b]**	**R[b]**
Staphylococcus aureus (including methicillin-resistant isolates)	≤0.12	-	-
Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus anginosus group (includes S. anginosus, S. intermedius, and S. constellatus), Streptococcus dysgalactiae	≤0.25	-	-
Enterococcus faecalis (vancomycin-susceptible isolates only)	≤0.12	-	-

NDA 206334 DATE REVIEW COMPLETED: May 5th, 2014.
Oritavancin/Orbactiv

INTRODUCTION AND BACKGROUND:

In this submission, the Medicines Company has submitted an original New Drug Application (NDA 206334) for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following gram positive organisms: *Staphylococcus aureus* (including methicillin-susceptible [MSSA] and –resistant [MRSA] isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus anginosus* group (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), and *Enterococcus faecalis* (vancomycin-susceptible isolates only). Oritavancin is considered a novel semi-synthetic lipoglycopeptide anti-bacterial agent that will be administered as a single intravenous (IV) dose.

Based on information submitted by the Applicant, oritavancin has multiple mechanism of action, and similar to vancomycin, one of its mechanisms involves the inhibition binding to components in the bacterial cell wall and the subsequent inhibition of peptidoglycan synthesis.

Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

Skin and skin structure infections represent one of the most common indications for antibiotic therapy and skin infections. They are common and range from minor skin infections to severe necrotizing infections which may require surgical intervention such wound drainage[1,2]. Skin and skin structure infection are considered complicated when they involves deeper layers of soft tissue such as fascia and muscle tissue. Infections including extensive cellulitis, abscess, traumatic or surgical wound infections, and foot infections in diabetic patients are both severe and complex to treat. Therefore, one of the most important aspects of treating skin infection is the clinical assessment of the severity of infection[1,4]. The etiological agents associated with Acute Bacterial Skin and Skin Structure Infections (ABSSSI) are predominantly *S. aureus* and streptococci, including Group A and Group B β-hemolytic streptococci (*S. pyogenes* and *S. agalactiae*, respectively). It is also not uncommon to identify *Enterococcus* species, as well as a mixed gram-positive and –negative aerobic and anaerobic bacteria in ABSSSI[4,5].

FACTORS INFLUENCING THE MANAGEMENT OF INFECTIONS

The routes of administration, the pharmacokinetic-pharmacodynamic profile of the antimicrobial agent and the dosing of the drug are some of the factors that must be considered in the treatment and management of infections. Studies have shown that the majority of bacterial infections are present in the extracellular compartment of tissues rather than in the plasma, and in the interstitial fluid of tissues and other body

fluids. Therefore, antibiotic penetration into fluids and tissues at infection sites is valuable in predicting therapeutic outcomes and that successful therapy often relies on the unbound antibiotic concentration at the site of action[6].

For an antimicrobial to be effective it is important that the drug is present at the site of the bacterial infection. In some instances, treatment failures have been attributed to antimicrobials characterized as being highly protein bound in serum despite achieving concentrations in serum that are above the MIC for the target pathogens[7]. For bacterial pneumonia, the delivery of the treatment agent depends on the availability of the unbound concentrations of antibiotic to the infection area. The availability of unbound drug concentrations may also depend on the molecular size, drug diffusion, and a myriad of host factors. Therefore it is also important to measure the concentration of drug from sites including sputum, bronchial secretions, and whole tissue homogenates to determine drug penetration or accessibility[6]. In the case of cSSSI, it is important to obtain culture specimens for documentation of bacteria and for susceptibility testing to guide treatment[12].

Antimicrobial Spectrum of Activity

In this submission, the Applicant has submitted in vitro data from large surveillance and geographically diverse (US and non-US) centers to support the claim that Oritavancin is active against pathogens associated with ABSSSI. The MICs were determined by referenced broth and agar dilution methods with the appropriate quality controls including those established by CLSI and EUCAST. All minimum inhibitory concentration (MIC) data were interpreted according to CLSI M100-S22 criteria (CLSI 2012) and by EUCAST criteria where applicable. The data obtained for isolates were collected in 2011-2012. Oritavancin in vitro activity was also monitored from 2010-2012 as part of the (b) (4)

Activity against *Staphylococcus aureus* (MSSA/MRSA)

Against *Staphylococcus aureus* isolates, the oritavancin MIC90 was reported to be 0.06 mcg/ml (MIC range was ≤0.002 - 0.5 mcg/mL). The in vitro activity of oritavancin and comparator agents against US and European isolates is shown in Table 1. Table 2a and 2b shows the activity against US, and European isolates, respectively. The Applicant indicated that 99.2% of all the isolates tested had oritavancin MICs that ranged from ≤ 0.002 to 0.5 mcg/mL; this included 98.8% of the MRSA and 97.6% of those isolates classified as multi-drug resistant (MDR) MRSA. The results obtained for US and European isolates were similar to each other and to the entire collection tested. The only slight deviation was among European MRSA where oritavancin MICs that ranged from ≤0.002 to 0.5 mcg/mL versus the US isolates where the MIC ranged from ≤0.002-

0.25 mcg/ml.

Table 1: Activity of oritavancin and comparator antimicrobial agents against 4570 isolates of *S. aureus* (USA and Europe)

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %I / %R	EUCAST[b] %S / %I / %R
Oritavancin	0.03	0.06	≤0.002-0.5	- / - / -	- / - / -
Oxacillin	0.5	>4	≤0.06->4	60.9 / - / 39.1	60.9 / 1.9 / 37.2
Vancomycin	0.5	1	≤0.25-2	100.0 / 0.0 / 0.0	100.0 / - / 0.0
Erythromycin	>8	>8	≤0.12->8	39.5 / 3.5 / 56.9	42.1 / 0.2 / 57.6
Clindamycin	0.12	>4	≤0.03->4	84.4 / 0.1 / 15.5	84.0 / 0.4 / 15.6
Gentamicin	0.25	0.5	≤0.06-<16	96.8 / 0.1 / 3.1	96.5 / - / 3.5
Levofloxacin	0.25	32	≤0.03->32	63.9 / 1.8 / 34.4	63.9 / 1.8 / 34.4
Daptomycin	0.5	0.5	≤0.06-4	99.8 / - / -	99.8 / - / 0.2
Linezolid	2	2	≤0.25->4	99.8 / - / 0.2	99.8 / - / 0.2
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5->4	98.7 / - / 1.3	98.8 / 0.0 / 1.2

[a] Criteria as published by the CLSI [2013].
[b] Criteria as published by the EUCAST v 3.1 [2013].

Table 2a: Activity of oritavancin and comparator antimicrobial agents against 3790 isolates of *S. aureus* (USA)

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %I / %R	EUCAST[b] %S / %I / %R
Oritavancin	0.03	0.06	≤0.002-0.25	- / - / -	- / - / -
Oxacillin	0.5	>4	≤0.06->4	57.7 / - / 42.3	57.7 / 2.2 / 40.2
Vancomycin	0.5	1	≤0.25-2	100.0 / 0.0 / 0.0	100.0 / - / 0.0
Erythromycin	>8	>8	≤0.12->8	34.2 / 3.0 / 62.8	36.2 / 0.3 / 63.5
Clindamycin	0.12	>4	≤0.03->4	83.2 / 0.1 / 16.6	82.9 / 0.4 / 16.8
Gentamicin	0.25	0.5	≤0.06-<16	98.3 / 0.1 / 1.6	98.1 / - / 1.9
Levofloxacin	0.25	32	≤0.03->32	62.2 / 2.0 / 35.9	62.2 / 2.0 / 35.9
Daptomycin	0.5	0.5	≤0.06-4	99.8 / - / -	99.8 / - / 0.2
Linezolid	2	2	≤0.25->4	99.9 / - / 0.1	99.9 / - / 0.1
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5->4	98.7 / - / 1.3	98.7 / 0.0 / 1.3

[a] Criteria as published by the CLSI [2013].
[b] Criteria as published by the EUCAST v 3.1 [2013].

Table 2b: Activity of oritavancin and comparator antimicrobial agents against 780 isolates of *S. aureus* (Europe)

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %I / %R	EUCAST[b] %S / %I / %R
Oritavancin	0.03	0.06	≤0.002-0.5	- / - / -	- / - / -
Oxacillin	0.5	>4	≤0.06->4	76.4 / - / 23.6	76.4 / 0.9 / 22.7
Vancomycin	0.5	1	≤0.25-2	100.0 / 0.0 / 0.0	100.0 / - / 0.0
Erythromycin	>8	>8	≤0.12->8	65.4 / 6.3 / 28.3	70.9 / 0.0 / 29.1
Clindamycin	0.12	>4	≤0.03->4	90.0 / 0.3 / 9.7	89.7 / 0.3 / 10.0
Gentamicin	0.25	>16	≤0.06-<16	89.5 / 0.3 / 10.3	88.6 / - / 11.4
Levofloxacin	0.25	32	≤0.03->32	72.1 / 0.9 / 27.1	72.1 / 0.9 / 27.1
Daptomycin	0.5	0.5	≤0.06-4	100.0 / - / -	100.0 / - / 0.0
Linezolid	2	2	≤0.25->4	99.7 / - / 0.3	99.7 / - / 0.3
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5->4	99.0 / - / 1.0	99.0 / 0.4 / 0.6

[a] Criteria as published by the CLSI [2013].
[c]Criteria as published by the EUCAST v 3.1 [2013].

Table 3 shows the activity of oritavancin and comparator agents against 2,186 methicillin susceptible *S. aureus* US isolates while Table 4 shows that activity of oritavancin and comparator agents against another 1,604 isolates of methicillin-resistant *S. aureus* USA isolates. The MIC ranged for this subset of isolates was ≤0.002-0.25 mcg/ml.

Table 3: Activity of oritavancin and comparator antimicrobial agents against 2,186 isolates of methicillin-susceptible *S. aureus* (USA)

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %I / %R	EUCAST[b] %S / %I / %R
Oritavancin	0.03	0.06	≤0.002-0.25	- / - / -	- / - / -
Oxacillin	0.25	0.5	≤0.06-2	100.0 / - / 0.0	100.0 / - / 0.0
Vancomycin	0.5	1	≤0.25-2	100.0 / 0.0 / 0.0	100.0 / - / 0.0
Erythromycin	0.5	>8	≤0.12->8	53.8 / 4.1 / 42.1	56.7 / 0.5 / 42.8
Clindamycin	0.12	0.25	≤0.03->4	93.4 / 0.1 / 6.5	92.9 / 0.5 / 6.6
Gentamicin	0.25	0.5	≤0.06-<16	99.3 / 0.0 / 0.7	98.9 / - / 1.1
Levofloxacin	0.12	4	≤0.03->32	84.1 / 1.6 / 14.3	84.1 / 1.6 / 14.3
Daptomycin	0.25	0.5	≤0.06-2	99.8 / - / -	99.8 / - / 0.2
Linezolid	2	2	≤0.25->4	100.0 / - / 0.0	100.0 / - / 0.0
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5->4	99.6 / - / 0.4	99.6 / 0.0 / 0.3

[a] Criteria as published by the CLSI [2013].
[b]Criteria as published by the EUCAST v 3.1 [2013].

Table 4: Activity of oritavancin and comparator antimicrobial agents against 1,604 isolates of methicillin-resistant *S. aureus* (USA)

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %I / %R	EUCAST[b] %S / %I / %R
Oritavancin	0.03	0.06	≤0.002-0.25	- / - / -	- / - / -
Oxacillin	>4	>4	4->4	0.0 / - / 100.0	0.0 / 5.1 / 94.9
Vancomycin	0.5	1	≤0.25-2	100.0 / 0.0 / 0.0	100.0 / - / 0.0
Erythromycin	>8	>8	≤0.12->8	7.5 / 1.4 / 91.0	8.2 / 0.1 / 91.7
Clindamycin	0.12	>4	≤0.03->4	69.5 / 0.1 / 30.4	69.3 / 0.2 / 30.5
Gentamicin	0.25	0.5	≤0.06-<16	97.1 / 0.1 / 2.8	96.9 / - / 3.1
Levofloxacin	4	>32	0.06->32	32.3 / 2.4 / 65.3	32.3 / 2.4 / 65.3
Daptomycin	0.5	0.5	≤0.06-4	99.8 / - / -	99.8 / - / 0.2
Linezolid	2	2	≤0.25->4	99.8 / - / 0.2	99.8 / - / 0.2
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5->4	97.3 / - / 2.7	97.3 / 0.0 / 2.7

[a] Criteria as published by the CLSI [2013].
[b] Criteria as published by the EUCAST v 3.1 [2013].

Table 5 shows the in vitro activity of oritavancin against *S. aureus* as part of the 2010-2012 international Surveillance (b) (4). A total of 13,336 isolates were tested and the MIC90 was reported as 0.06 mcg/ml (range was ≤0.008-0.25 mcg/ml against all *S. aureus* isolates tested). Oritavancin appear to perform well against isolates with a vancomycin MIC of 2 mcg/ml. Against 72 isolates tested, the oritavancin MIC90 was reported to be 0.12 mcg/ml.

Table: 5 in vitro activities of *S. aureus* (2010-2012 Oritavancin International Surveillance, as part of the (b) (4)

Year	MIC (μg/ml)		Number (cumulative %) of isolates inhibited at each oritavancin MIC (μg/ml)					
Resistant set (number tested)	50%	90%	≤0.008	0.015	0.03	0.06	0.12	0.25
All (13,336)	0.03	0.06	352 (2.6)	3181 (26.5)	5436 (67.3)	3201 (91.3)	968 (98.5)	198 (100.0)
Oxacillin-susceptible (7,800)	0.03	0.06	229 (2.9)	1852 (26.7)	3202 (67.7)	1861 (91.6)	542 (98.5)	114 (100.0)
Vancomycin MIC ≤1 μg/ml (7,726)	0.03	0.06	228 (3.0)	1839 (26.8)	3186 (68.0)	1833 (91.7)	528 (98.6)	112 (100.0)
Vancomycin MIC = 2 μg/ml (74)	0.06	0.12	1 (1.4)	13 (18.9)	16 (40.5)	28 (78.4)	14 (97.3)	2 (100.0)
Oxacillin-resistant (5,536)	0.03	0.06	123 (2.2)	1329 (26.2)	2234 (66.6)	1340 (90.8)	426 (98.5)	84 (100.0)
Vancomycin MIC ≤1 μg/ml (5,419)	0.03	0.06	122 (2.3)	1325 (26.7)	2198 (67.3)	1294 (91.1)	402 (98.6)	78 (100.0)
Vancomycin MIC = 2 μg/ml (117)	0.06	0.12	1 (0.9)	4 (4.3)	36 (35.0)	46 (74.4)	24 (94.9)	6 (100.0)
2010 (5,438)	0.03	0.06	233 (4.3)	2063 (42.2)	2338 (85.2)	635 (96.9)	140 (99.5)	29 (100.0)
Oxacillin-susceptible (3,269)	0.03	0.06	148 (4.5)	1196 (41.1)	1429 (84.8)	396 (96.9)	80 (99.4)	20 (100.0)
Oxacillin-resistant (2,169)	0.03	0.06	85 (3.9)	867 (43.9)	909 (85.8)	239 (96.8)	60 (99.6)	9 (100.0)
2011 (5,337)	0.03	0.12	47 (0.9)	506 (10.4)	2120 (50.1)	1888 (85.5)	656 (97.8)	120 (100.0)
Oxacillin-susceptible (3,155)	0.03	0.12	36 (1.1)	307 (10.9)	1262 (50.9)	1094 (85.5)	384 (97.7)	72 (100.0)
Oxacillin-resistant (2,182)	0.06	0.12	11 (0.5)	199 (9.6)	858 (48.9)	794 (85.3)	272 (97.8)	48 (100.0)
2012 (2,561)	0.03	0.06	72 (2.8)	612 (26.7)	978 (64.9)	678 (91.4)	172 (98.1)	49 (100.0)
Oxacillin-susceptible (1,376)	0.03	0.06	45 (3.3)	349 (28.6)	511 (65.8)	371 (92.7)	78 (98.4)	22 (100.0)
Oxacillin-resistant (1,185)	0.03	0.06	27 (2.3)	263 (24.5)	467 (63.9)	307 (89.8)	94 (97.7)	27 (100.0)

Coagulase negative Staphylococci (CNS)

Against all CoNS isolates tested, the oritavancin MIC90 was reported as 0.12 mcg/mL and the MIC range was 0.004 - 0.25 mcg/mL (Table 6). It was noted that 96.2% of all the isolates tested had oritavancin MICs that ranged from 0.004 to 0.12 mcg/ml; this included 99.1% of the methicillin susceptible (MS)-CoNS and 94.3% of the methicillin resistant (MR)-CoNS. Additionally, the results obtained for US and European isolates appear similar to each other and to the entire collection tested. The highest MIC observed was 0.25 mcg/mL and was encountered primarily among isolates of *S. epidermidis*.

Table 6: Oritavancin activity against coagulase-negative staphylococci in the 2011-2012 (b) (4)

Region	MIC (µg/mL)		Number (cumulative %) of isolates inhibited at each oritavancin MIC (µg/mL)													
Group (number tested)	50%	90%	0.004		0.008		0.015		0.03		0.06		0.12		0.25	
Overall (586)	0.06	0.12	4	(0.7)	20	(4.1)	62	(14.7)	144	(39.2)	218	(76.5)	116	(96.2)	22	(100.0)
Oxacillin-susceptible (233)	0.03	0.12	3	(1.3)	19	(9.4)	45	(28.8)	70	(58.8)	67	(87.6)	27	(99.1)	2	(100.0)
Oxacillin-resistant (353)	0.06	0.12	1	(0.3)	1	(0.6)	17	(5.4)	74	(26.3)	151	(69.1)	89	(94.3)	20	(100.0)
S. capitis (28)	0.03	0.06	1	(3.6)	1	(7.1)	8	(35.7)	9	(67.9)	6	(89.3)	2	(96.4)	1	(100.0)
S. caprae (4)	NA[a]	NA					1	(25.0)	3	(100.0)						
S. cohnii(2)	NA	NA					2	(100.0)								
S. epidermidis (383)	0.06	0.12			4	(1.0)	9	(3.4)	67	(20.9)	186	(69.5)	99	(95.3)	18	(100.0)
S. hemolyticus (32)	0.03	0.12			1	(3.1)	7	(25.0)	10	(56.3)	6	(75.0)	7	(96.9)	1	(100.0)
S. hominis (45)	0.03	0.12					10	(22.2)	21	(68.9)	8	(86.7)	4	(95.6)	2	(100.0)
S. intermedius (7)	NA	NA			1	(14.3)	2	(42.9)	3	(85.7)	1	(100.0)				
S. lugdunensis (29)	0.015	0.03	3	(10.3)	10	(44.8)	10	(79.3)	4	(93.1)	2	(100.0)				
S. pasteuri(1)	NA	NA			1	(100.0)										
S. pettenkoferi(2)	NA	NA			1	(50.0)			1	(100.0)						
S. saprophyticus (15)	0.03	0.06					4	(26.7)	7	(73.3)	4	(100.0)				
S. schleiferi (6)	NA	NA							5	(83.3)			1	(100.0)		
S. sciuri(1)	NA	NA							1	(100.0)						
S. simulans (14)	0.03	0.06					4	(28.6)	7	(78.6)	3	(100.0)				
S. species (3)	NA	NA					1	(33.3)	1	(66.7)			1	(100.0)		
S. warneri (12)	0.03	0.06					5	(41.7)	5	(83.3)	1	(91.7)	1	(100.0)		
S. xylosus(2)	NA	NA									1	(50.0)	1	(100.0)		
USA (480)	0.06	0.12	4	(0.8)	19	(4.8)	53	(15.8)	118	(40.4)	175	(76.9)	92	(96.0)	19	(100.0)
Oxacillin-susceptible (202)	0.03	0.12	3	(1.5)	18	(10.4)	38	(29.2)	59	(58.4)	56	(86.1)	26	(99.0)	2	(100.0)
Oxacillin-resistant (278)	0.06	0.12	1	(0.4)	1	(0.7)	15	(6.1)	59	(27.3)	119	(70.1)	66	(93.9)	17	(100.0)
Europe (106)	0.06	0.12			1	(0.9)	9	(9.4)	26	(34.0)	43	(74.5)	24	(97.2)	3	(100.0)
Oxacillin-susceptible (31)	0.03	0.06			1	(3.2)	7	(25.8)	11	(61.3)	11	(96.8)	1	(100.0)		
Oxacillin-resistant (75)	0.06	0.12					2	(2.7)	15	(22.7)	32	(65.3)	23	(96.0)	3	(100.0)

[a] NA: number of isolates insufficient for this calculation.

Table 7 shows the in vitro activity of oritavancin against additional CoNS isolates obtained from the 2010-2012 international Surveillance; part of the (b) (4) A total of 1664 isolates were tested with a reported MIC90 of 0.06 mcg/ml (range ≤0.008-0.25 mcg/ml.

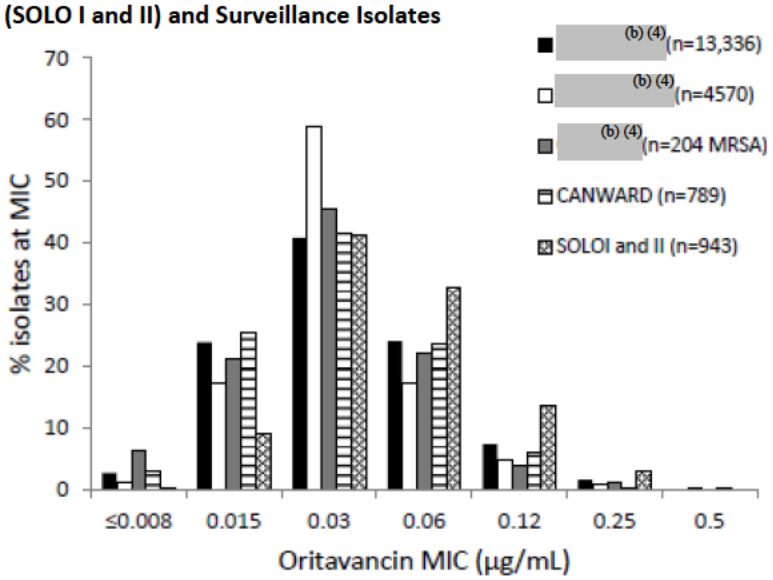
Table 7: Oritavancin activity tested against CoNS and resistant subsets (2010-2012 (b) (4)).

Year	MIC (µg/ml)		Number (cumulative %) of isolates inhibited at each oritavancin MIC (µg/ml)					
Resistant set (number tested)	50%	90%	≤0.008	0.015	0.03	0.06	0.12	0.25
All (1,664)	0.03	0.06	347 (20.9)	282 (37.8)	557 (71.3)	391 (94.8)	80 (99.6)	7 (100.0)
Oxacillin-susceptible (492)	0.03	0.06	123 (25.0)	108 (47.0)	156 (78.7)	88 (96.5)	16 (99.8)	1 (100.0)
Oxacillin-resistant (1,172)	0.03	0.06	224 (19.1)	174 (34.0)	401 (68.2)	303 (94.0)	64 (99.5)	6 (100.0)
2010 (801)	0.03	0.06	170 (21.2)	155 (40.6)	309 (79.2)	139 (96.5)	24 (99.5)	4 (100.0)
Oxacillin-susceptible (230)	0.015	0.06	61 (26.5)	56 (50.9)	79 (85.2)	27 (97.0)	7 (100.0)	
Oxacillin-resistant (571)	0.03	0.06	109 (19.1)	99 (36.4)	230 (76.7)	112 (96.3)	17 (99.3)	4 (100.0)
2011 (642)	0.03	0.06	126 (19.6)	89 (33.5)	166 (59.3)	210 (92.1)	48 (99.5)	3 (100.0)
Oxacillin-susceptible (188)	0.03	0.06	42 (22.3)	37 (42.0)	51 (69.1)	49 (95.2)	8 (99.5)	1 (100.0)
Oxacillin-resistant (454)	0.03	0.06	84 (18.5)	52 (30.0)	115 (55.3)	161 (90.7)	40 (99.6)	2 (100.0)
2012 (221)	0.03	0.06	51 (23.1)	38 (40.3)	82 (77.4)	42 (96.4)	8 (100.0)	
Oxacillin-susceptible (74)	0.03	0.06	20 (27.0)	15 (47.3)	26 (82.4)	12 (98.6)	1 (100.0)	
Oxacillin-resistant (147)	0.03	0.06	31 (21.1)	23 (36.7)	56 (74.8)	30 (95.2)	7 (100.0)	

Oritavancin MIC from the Phase 3 SOLO I and SOLO II studies (*S. aureus*)

Oritavancin MIC frequency distributions for *S. aureus* isolates from recent surveillance studies and the Phase 3 SOLO I and SOLO II studies are similar, with a common modal MIC of 0.03 mcg/mL and a 6-dilution range encompassing the vast majority of isolates (Figure 1). This Reviewer agrees with the observation that suggests oritavancin activity against *S. aureus* as demonstrated in the SOLO studies is relevant to current clinical infections globally. A total of 943 isolates were tested for oritavancin susceptibility.

Figure 1: Comparative Oritavancin MIC Distributions for *S. aureus* Clinical Trial (SOLO I and II) and Surveillance Isolates



Enterococci

Against all *E. faecalis* isolates tested, the Applicant reported an MIC90 value of 0.06 mcg/ml (MIC range 0.002 - 0.25 mcg/mL). Against USA isolates, the overall oritavancin MIC90 was 0.06 for vancomycin-susceptible isolates and 0.25 mcg/mL for vancomycin-non-susceptible isolates. For European isolates the oritavancin MIC90 was reported as 0.03 for vancomycin-susceptible isolates and 0.12 mcg/mL for vancomycin non-susceptible isolates (Table 8). Overall, oritavancin MIC90 values were 2-4-fold higher against vancomycin non-susceptible isolates indicating a common mechanism of action between both antibacterial agents.

Table 8: Oritavancin activity against *E. faecalis* in the 2011-2012 (b) (4)

Region	MIC (µg/mL)		Number (cumulative %) of isolates inhibited at each oritavancin MIC (µg/mL)															
Group (number tested)	50%	90%	≤0.002		0.004		0.008		0.015		0.03		0.06		0.12		0.25	
Europe & USA (665)	0.015	0.06	2	(0.3)	5	(1.1)	105	(16.8)	287	(60.0)	177	(86.6)	53	(94.6)	26	(98.5)	10	(100.0)
Vancomycin-susceptible[a] (635)	0.015	0.03	2	(0.3)	5	(1.1)	105	(17.6)	285	(62.5)	176	(90.2)	43	(97.0)	15	(99.4)	4	(100.0)
Vancomycin-non-susceptible [b] (30)	0.12	0.25							2	(6.7)	1	(10.0)	10	(43.3)	11	(80.0)	6	(100.0)
USA(553)	0.015	0.06	2	(0.4)	4	(1.1)	86	(16.6)	240	(60.0)	147	(86.6)	43	(94.4)	22	(98.4)	9	(100.0)
Vancomycin-susceptible[a] (535)	0.015	0.06	2	(0.4)	4	(1.1)	86	(17.2)	239	(61.9)	147	(89.3)	41	(97.0)	13	(99.4)	3	(100.0)
Vancomycin-non-susceptible [b] (18)	0.12	0.25							1	(5.6)			2	(16.7)	9	(66.7)	6	(100.0)
Europe(112)	0.015	0.06			1	(0.9)	19	(17.9)	47	(59.8)	30	(86.6)	10	(95.5)	4	(99.1)	1	(100.0)
Vancomycin-susceptible[a] (100)	0.015	0.03			1	(1.0)	19	(20.0)	46	(66.0)	29	(95.0)	2	(97.0)	2	(99.0)	1	(100.0)
Vancomycin-non-susceptible [b] (12)	0.06	0.12							1	(8.3)	1	(16.7)	8	(83.3)	2	(100.0)		

[a] Isolates exhibiting vancomycin MIC results of ≤4 (CLSI criteria).
[b] Isolates exhibiting vancomycin MIC results of >4.

Table 9 shows the in vitro activity of oritavancin against *E. faecalis* and resistant subsets part of the 2010-2012 international Surveillance, as part of the (b) (4). The MIC90 was reported as 0.06 mcg/ml. A total of 2,132 isolates were tested. Out of a total of 2,132 isolates, the highest MIC reported was 1 mcg/ml against one isolate with a VanA phenotype.

Table 9: Antimicrobial activity of oritavancin tested against *E. faecalis* and resistant (2010-2012 Oritavancin (b) (4)).

Year	MIC (µg/ml)		Number (cumulative %) of isolates inhibited at each oritavancin MIC (µg/ml)							
Resistant set (number tested)	50%	90%	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1
All (2,132)	0.015	0.06	430 (20.2)	882 (61.5)	529 (86.4)	193 (95.4)	59 (98.2)	30 (99.6)	8 (100.0)	1 (100.0)
Vancomycin-susceptible[a] (2,088)	0.015	0.06	430 (20.6)	875 (62.5)	528 (87.8)	189 (96.8)	55 (99.5)	10 (100.0)	1 (100.0)	
VanA phenotype[b] (37)	0.25	0.5	0 (0.0)	2 (5.4)	1 (8.1)	3 (16.2)	4 (27.0)	19 (78.4)	7 (97.3)	1 (100.0)
2010 (1,069)	0.015	0.03	262 (24.5)	493 (70.6)	224 (91.6)	57 (96.9)	14 (98.2)	13 (99.4)	5 (99.9)	1 (100.0)
Vancomycin-susceptible (1,042)	0.015	0.03	262 (25.1)	487 (71.9)	223 (93.3)	55 (98.6)	11 (99.6)	3 (99.9)	1 (100.0)	
VanA phenotype (21)	0.25	0.5	0 (0.0)	2 (9.5)	1 (14.3)	1 (19.0)	3 (33.3)	9 (76.2)	4 (95.2)	1 (100.0)
2011 (771)	0.03	0.06	112 (14.5)	246 (46.4)	237 (77.2)	118 (92.5)	38 (97.4)	17 (99.6)	3 (100.0)	
Vancomycin-susceptible (755)	0.03	0.06	112 (14.8)	246 (47.4)	237 (78.8)	116 (94.2)	37 (99.1)	7 (100.0)		
VanA phenotype (16)	0.25	0.5	0 (0.0)	0 (0.0)	0 (0.0)	2 (12.5)	1 (18.8)	10 (81.3)	3 (100.0)	
2012 (292)	0.015	0.03	56 (19.2)	143 (68.2)	68 (91.4)	18 (97.6)	7 (100.0)			
Vancomycin-susceptible (291)	0.015	0.03	56 (19.2)	142 (68.0)	68 (91.4)	18 (97.6)	7 (100.0)			

[a] Isolates exhibiting vancomycin and teicoplanin MIC results of ≤4 and ≤8 µg/ml, respectively (CLSI criteria).
[b] Isolates exhibiting vancomycin and teicoplanin MIC results of >4 and >8 µg/ml, respectively.

Against all isolates of *E. faecium* tested the oritavancin MIC90 was reported to be 0.12 mcg/mL and the MIC range was ≤ 0.002 - 0.25 mcg/mL. It was reported that 96.7% of all the strains tested had MICs that ranged from ≤ 0.002 - 0.12 mcg/mL (Table 10). Additionally, for USA *E. faecium* isolates, the oritavancin MIC90 was higher (0.12 mcg/mL) for vancomycin-non-susceptible isolates compared to vancomycin-susceptible isolates (0.015 mcg/mL). However, against European *E. faecium* isolates, the oritavancin MIC90s for vancomycin -non-susceptible and -susceptible isolates were the 0.03 mcg/mL).

Table 10: Oritavancin activity against *E. faecium* in the 2011/2012 (b) (4).

Region	MIC (µg/mL)		Number (cumulative %) of isolates inhibited at each oritavancin MIC (µg/mL)															
Group (number tested)	50%	90%	≤0.002		0.004		0.008		0.015		0.03		0.06		0.12		0.25	
Overall(243)	0.03	0.12	4	(1.6)	23	(11.1)	54	(33.3)	28	(44.9)	52	(66.3)	38	(81.9)	36	(96.7)	8	(100.0)
Vancomycin-susceptible[a] (104)	0.008	0.015	4	(3.8)	20	(23.1)	49	(70.2)	22	(91.3)	5	(96.2)	3	(99.0)	1	(100.0)		
Vancomycin-non-susceptible [b] (139)	0.06	0.12			3	(2.2)	5	(5.8)	6	(10.1)	47	(43.9)	35	(69.1)	35	(94.2)	8	(100.0)
USA(184)	0.03	0.12	1	(0.5)	17	(9.8)	38	(30.4)	12	(37.0)	37	(57.1)	35	(76.1)	36	(95.7)	8	(100.0)
Vancomycin-susceptible[a] (60)	0.008	0.015	1	(1.7)	14	(25.0)	34	(81.7)	8	(95.0)	1	(96.7)	1	(98.3)	1	(100.0)		
Vancomycin-non-susceptible [b] (124)	0.06	0.12			3	(2.4)	4	(5.6)	4	(8.9)	36	(37.9)	34	(65.3)	35	(93.5)	8	(100.0)
Europe(59)	0.015	0.03	3	(5.1)	6	(15.3)	16	(42.4)	16	(69.5)	15	(94.9)	3	(100.0)				
Vancomycin-susceptible[a] (44)	0.008	0.03	3	(6.8)	6	(20.5)	15	(54.5)	14	(86.4)	4	(95.5)	2	(100.0)				
Vancomycin-non-susceptible [b] (15)	0.03	0.03					1	(6.7)	2	(20.0)	11	(93.3)	1	(100.0)				

[a] Isolates exhibiting vancomycin MIC results of ≤4 (CLSI criteria).
[b] Isolates exhibiting vancomycin MIC results of >4.

Table 11 shows the in vitro activity of oritavancin against *E. faecium* and resistant subsets part of the 2010-2012 international Surveillance, as part of the (b) (4) The MIC90 was reported as 0.06 mcg/ml. A total of 1237 isolates were tested and similar to *E. faecalis*, organisms of *E. faecium* with VanA phenotypes was associated with higher oritavancin MIC values.

Table 11. Antimicrobial activity of oritavancin tested against *E. faecium* and resistant subsets submitted to the 2010-2012 Oritavancin International Surveillance as part of the (b) (4)

Year	MIC (µg/ml)		Number (cumulative %) of isolates inhibited at each oritavancin MIC (µg/ml)						
Resistant set (number tested)	50%	90%	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5
All (1,237)	≤0.008	0.06	658 (53.2)	146 (65.0)	174 (79.1)	170 (92.8)	72 (98.6)	16 (99.9)	1 (100.0)
Vancomycin-susceptible[a] (566)	≤0.008	≤0.008	546 (96.5)	20 (100.0)					
VanA phenotype[b] (639)	0.03	0.12	82 (12.8)	125 (32.4)	173 (59.5)	170 (86.1)	72 (97.3)	16 (99.8)	1 (100.0)
VanB phenotype[c] (32)	≤0.008	≤0.008	30 (93.8)	1 (96.9)	1 (100.0)				
2010 (622)	≤0.008	0.06	329 (52.9)	69 (64.0)	96 (79.4)	90 (93.9)	29 (98.6)	8 (99.8)	1 (100.0)
Vancomycin-susceptible (270)	≤0.008	≤0.008	266 (98.5)	4 (100.0)					
VanA phenotype (334)	0.03	0.12	45 (13.5)	65 (32.9)	96 (61.7)	90 (88.6)	29 (97.3)	8 (99.7)	1 (100.0)
VanB phenotype (18)	≤0.008	≤0.008	18 (100.0)						
2011 (456)	≤0.008	0.06	272 (59.6)	51 (70.8)	52 (82.2)	48 (92.8)	26 (98.5)	7 (100.0)	
Vancomycin-susceptible (250)	≤0.008	≤0.008	235 (94.0)	15 (100.0)					
VanA phenotype (194)	0.03	0.12	27 (13.9)	35 (32.0)	51 (58.2)	48 (83.0)	26 (96.4)	7 (100.0)	
VanB phenotype (12)	≤0.008	0.015	10 (83.3)	1 (91.7)	1 (100.0)				
2012 (159)	0.015	0.12	57 (35.8)	26 (52.2)	26 (68.6)	32 (88.7)	17 (99.4)	1 (100.0)	
Vancomycin-susceptible (46)	≤0.008	≤0.008	45 (97.8)	1 (100.0)					
VanA phenotype (111)	0.03	0.12	10 (9.0)	25 (31.5)	26 (55.0)	32 (83.8)	17 (99.1)	1 (100.0)	

[a] Isolates exhibiting vancomycin and teicoplanin MIC results of ≤4 and ≤8 µg/ml, respectively (CLSI criteria).
[b] Isolates exhibiting vancomycin and teicoplanin MIC results of >4 and >8 µg/ml, respectively.
[c] Isolates exhibiting vancomycin and teicoplanin MIC results of >4 and ≤8 µg/ml, respectively.

Streptococcus pneumoniae

Although the Applicant is not targeting *S. pneumonia*, information associated with the in vitro activity against these isolates was reviewed. Among *S. pneumoniae* isolates, oritavancin demonstrated MIC range of ≤0.008-0.12 (MIC90 of 0.015 Table 12.

Table 12: Antimicrobial activity of oritavancin tested against *S. pneumoniae* and resistant subsets submitted as part of the 2010-2012 Oritavancin International Surveillance, as part of the (b) (4)

Year	MIC (µg/ml)		Number (cumulative %) of isolates inhibited at each oritavancin MIC (µg/ml)				
Resistant set (number tested)	50%	90%	≤0.008	0.015	0.03	0.06	0.12
All (4,349)	≤0.008	0.015	3645 (83.8)	505 (95.4)	155 (99.0)	43 (100.0)	1 (100.0)
Penicillin-susceptible[a] (2,739)	≤0.008	0.015	2360 (86.2)	269 (96.0)	83 (99.0)	27 (100.0)	
Penicillin-non-susceptible[b] (1,610)	≤0.008	0.015	1285 (79.8)	236 (94.5)	72 (98.9)	16 (99.9)	1 (100.0)
2010 (1,537)	≤0.008	0.015	1346 (87.6)	162 (98.1)	19 (99.3)	9 (99.9)	1 (100.0)
Penicillin-susceptible (999)	≤0.008	0.015	881 (88.2)	98 (98.0)	12 (99.2)	8 (100.0)	
Penicillin-non-susceptible (538)	≤0.008	0.015	465 (86.4)	64 (98.3)	7 (99.6)	1 (99.8)	1 (100.0)
2011 (2,045)	≤0.008	0.015	1585 (77.5)	305 (92.4)	124 (98.5)	31 (100.0)	
Penicillin-susceptible (1,262)	≤0.008	0.015	1027 (81.4)	149 (93.2)	69 (98.7)	17 (100.0)	
Penicillin-non-susceptible (783)	≤0.008	0.015	558 (71.3)	156 (91.2)	55 (98.2)	14 (100.0)	
2012 (767)	≤0.008	≤0.008	714 (93.1)	38 (98.0)	12 (99.6)	3 (100.0)	
Penicillin-susceptible (478)	≤0.008	≤0.008	452 (94.6)	22 (99.2)	2 (99.6)	2 (100.0)	
Penicillin-non-susceptible (289)	≤0.008	≤0.008	262 (90.7)	16 (96.2)	10 (99.7)	1 (100.0)	

[a] Isolates exhibiting penicillin MIC results of ≤0.06 µg/ml.
[b] Isolates exhibiting penicillin MIC results of >0.06 µg/ml.

Beta-Hemolytic Streptococci

Against beta-hemolytic streptococci the oritavancin MIC90 was 0.25 mcg/mL and the MIC range was ≤ 0.002 - 0.5 mcg/mL. It was noted that 99.7% of all the isolates tested had MICs that ranged from ≤ 0.002 - 0.25mcg/mL. The data showed that the oritavancin MIC against USA isolates were very similar to those obtained with European isolates (Table 13).

Table 13: Oritavancin activity against β-hemolytic streptococci in the 2011-2012 (b) (4)

Region	MIC (µg/mL)		Number (cumulative %) of isolates inhibited at each oritavancin MIC (µg/mL)															
Group (number tested)	50%	90%	≤0.002		0.004		0.008		0.015		0.03		0.06		0.12		0.25	0.5
Europe & USA (1061)	0.06	0.25	1	(0.1)	4	(0.5)	27	(3.0)	94	(11.9)	190	(29.8)	392	(66.7)	241	(89.4)	109 (99.7)	3 (100.0)
Group A (450)	0.06	0.25	1	(0.2)	2	(0.7)	19	(4.9)	62	(18.7)	105	(42.0)	122	(69.1)	87	(88.4)	52 (100.0)	
Group B (556)	0.06	0.12			1	(0.2)	4	(0.9)	20	(4.5)	80	(18.9)	256	(64.9)	143	(90.6)	49 (99.5)	3 (100.0)
Group C[a] (27)	0.12	0.25			1	(3.7)			4	(18.5)	1	(22.2)	7	(48.1)	8	(77.8)	6 (100.0)	
Group F (7)	NA[b]	NA					2	(28.6)	2	(57.1)	1	(71.4)			1	(85.7)	1 (100.0)	
Group G (21)	0.03	0.12					2	(9.5)	6	(38.1)	3	(52.4)	7	(85.7)	2	(95.2)	1 (100.0)	
USA (875)	0.06	0.25	1	(0.1)	3	(0.5)	17	(2.4)	69	(10.3)	153	(27.8)	328	(65.3)	207	(88.9)	94 (99.7)	3 (100.0)
Group A (360)	0.06	0.25	1	(0.3)	2	(0.8)	12	(4.2)	46	(16.9)	86	(40.8)	99	(68.3)	71	(88.1)	43 (100.0)	
Group B (468)	0.06	0.12					2	(0.4)	12	(3.0)	63	(16.5)	218	(63.0)	127	(90.2)	43 (99.4)	3 (100.0)
Group C[a] (26)	0.06	0.25			1	(3.8)			4	(19.2)	1	(23.1)	7	(50.0)	7	(76.9)	6 (100.0)	
Group F (7)	NA	NA					2	(28.6)	2	(57.1)	1	(71.4)			1	(85.7)	1 (100.0)	
Group G (14)	0.03	0.12					1	(7.1)	5	(42.9)	2	(57.1)	4	(85.7)	1	(92.9)	1 (100.0)	
Europe (186)	0.06	0.12			1	(0.5)	10	(5.9)	25	(19.4)	37	(39.2)	64	(73.7)	34	(91.9)	15 (100.0)	
Group A (90)	0.06	0.12					7	(7.8)	16	(25.6)	19	(46.7)	23	(72.2)	16	(90.0)	9 (100.0)	
Group B (88)	0.06	0.12			1	(1.1)	2	(3.4)	8	(12.5)	17	(31.8)	38	(75.0)	16	(93.2)	6 (100.0)	
Group C[a] (1)	NA	NA													1	(100.0)		
Group G (7)	NA	NA					1	(14.3)	1	(28.6)	1	(42.9)	3	(85.7)	1	(100.0)		

[a] Includes *S. dysgalactiae*.
[b] NA: number of isolates insufficient for this calculation.

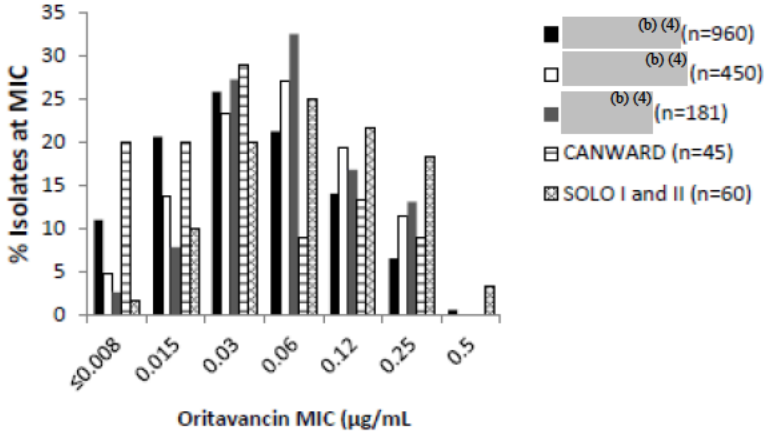
Table 14: Antimicrobial activity of oritavancin tested against β-hemolytic streptococci and resistant subsets submitted as part of the 2010-2012 Oritavancin International Surveillance as part of the (b) (4)

Year	MIC (µg/ml)		Number (cumulative %) of isolates inhibited at each oritavancin MIC (µg/ml)						
Resistant set (number tested)	50%	90%	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5
All (2,281)	0.03	0.12	189 (8.3)	409 (26.2)	553 (50.5)	534 (73.9)	375 (90.3)	194 (98.8)	27 (100.0)
Group A (960)	0.03	0.12	106 (11.0)	198 (31.7)	248 (57.5)	204 (78.8)	135 (92.8)	63 (99.4)	6 (100.0)
Group B (920)	0.06	0.12	32 (3.5)	170 (22.0)	235 (47.5)	238 (73.4)	154 (90.1)	77 (98.5)	14 (100.0)
Group C (115)	0.06	0.12	23 (20.0)	10 (28.7)	24 (49.6)	31 (76.5)	17 (91.3)	10 (100.0)	
Group F (17)	≤0.008	0.12	13 (76.5)	2 (88.2)	0 (88.2)	0 (88.2)	2 (100.0)		
Group G (220)	0.06	0.25	12 (5.5)	24 (16.4)	38 (33.6)	46 (54.5)	54 (79.1)	40 (97.3)	6 (100.0)
2010 (1,108)	0.06	0.25	60 (5.4)	89 (13.4)	224 (33.7)	354 (65.6)	265 (89.5)	113 (99.7)	3 (100.0)
2011 (849)	0.03	0.12	109 (12.8)	247 (41.9)	254 (71.8)	106 (84.3)	72 (92.8)	50 (98.7)	11 (100.0)
2012 (324)	0.03	0.25	20 (6.2)	73 (28.7)	75 (51.9)	74 (74.7)	38 (86.4)	31 (96.0)	13 (100.0)

Streptococcus pyogenes

Oritavancin MIC frequency distributions for *S. pyogenes* isolates from recent surveillance studies and from the Phase 3 SOLO I and SOLO II studies are similar, with modal MIC of 0.03 or 0.06 mcg/mL and a 6-dilution range encompassing the vast majority of isolates (Figure 2). This observation suggests that oritavancin activity against *S. pyogenes* as demonstrated in the SOLO studies is relevant to current clinical infections globally and this Reviewer agrees.

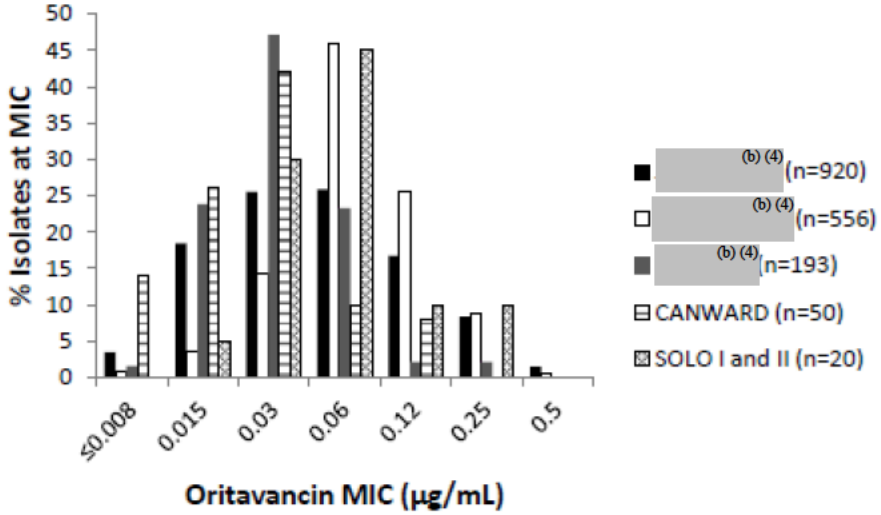
Figure 2: Comparative Oritavancin MIC Distributions for *Streptococcus pyogenes* Clinical Trial (SOLO I and II) and Surveillance Isolates



Streptococcus agalactiae

Oritavancin MIC frequency distributions for *S. agalactiae* isolates from recent surveillance studies and from the Phase 3 SOLO I and SOLO II studies are similar (Figure 3). This observation suggests that oritavancin activity against *S. agalactiae* as demonstrated in the SOLO studies is relevant to current clinical infections globally; the majority of the 20 isolates from the SOLO I and SOLO II demonstrated an MIC of 0.06 mcg/ml.

Figure 3: Comparative Oritavancin MIC Distributions for *Streptococcus agalactiae* Clinical Trial (SOLO I and II) and Surveillance Isolates



Viridans Group Streptococci

Against Viridans streptococci tested, the oritavancin MIC ranged from ≤ 0.002 - 0.12 mcg/mL and the MIC90 was 0.06 mcg/mL against USA all isolates (Table 15).

Table 15: Antimicrobial activity of oritavancin tested against Viridans group streptococci and resistant subsets submitted as part of the 2010-2012 Oritavancin International Surveillance as part of the (b) (4)

Year	MIC (μg/ml)		Number (cumulative %) of isolates inhibited at each oritavancin MIC (μg/ml)						
Resistant set (number tested)	50%	90%	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5
All (835)	≤0.008	0.06	467 (55.9)	134 (72.0)	93 (83.1)	87 (93.5)	46 (99.0)	7 (99.9)	1 (100.0)
Penicillin-susceptible[a] (340)	≤0.008	0.03	237 (69.7)	44 (82.6)	28 (90.9)	21 (97.1)	8 (99.4)	1 (99.7)	1 (100.0)
Penicillin-non-susceptible[b] (111)	0.015	0.06	45 (40.5)	24 (62.2)	17 (77.5)	16 (91.9)	9 (100.0)		
2010 (390)	≤0.008	0.06	250 (64.1)	53 (77.7)	42 (88.5)	30 (96.2)	13 (99.5)	1 (99.7)	1 (100.0)
Penicillin-susceptible (294)	≤0.008	0.03	210 (71.4)	32 (82.3)	27 (91.5)	17 (97.3)	6 (99.3)	1 (99.7)	1 (100.0)
Penicillin-non-susceptible (96)	0.015	0.06	40 (41.7)	21 (63.5)	15 (79.2)	13 (92.7)	7 (100.0)		
2011 (384)	0.015	0.06	185 (48.2)	66 (65.4)	48 (77.9)	50 (90.9)	29 (98.4)	6 (100.0)	
Penicillin-susceptible (270)	≤0.008	0.06	147 (54.4)	42 (70.0)	29 (80.7)	35 (93.7)	15 (99.3)	2 (100.0)	
Penicillin-non-susceptible (114)	0.015	0.12	38 (33.3)	24 (54.4)	19 (71.1)	15 (84.2)	14 (96.5)	4 (100.0)	
2012 (61)	≤0.008	0.06	32 (52.5)	15 (77.0)	3 (82.0)	7 (93.4)	4 (100.0)		
Penicillin-susceptible (46)	≤0.008	0.06	27 (58.7)	12 (84.8)	1 (87.0)	4 (95.7)	2 (100.0)		
Penicillin-non-susceptible (15)	0.015	0.12	5 (33.3)	3 (53.3)	2 (66.7)	3 (86.7)	2 (100.0)		
S. anginosus group[c] (14)	≤0.008	0.06	7 (50.0)	3 (71.4)	1 (78.6)	2 (92.9)	1 (100.0)		

[a] Isolates exhibiting penicillin MIC results of ≤0.12 μg/ml.
[b] Isolates exhibiting penicillin MIC results of >0.12 μg/ml.
c Includes eight *S. anginosus*, and three isolates each of *S. constellatus* and *S. intermedius*.

Streptococcus anginosus Group

Oritavancin MICs against recent 148 isolates belonging to the *S. anginosus* Group (*S. anginosus,* n=102; *S. constellatus*, n=33; *S. intermedius,* n=13) ranged from ≤0.008 to 0.12 mcg/mL, with MIC90 of 0.0015 mcg/mL (Table 16). Oritavancin MIC values didn't appear to be impacted by the higher MICs reported by some of the comparator agents (Table 16).

Table 16: Oritavancin MICs against *Streptococcus anginosus* Group Isolates

Pathogen	N	Agent	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC Range (µg/mL)
S. anginosus Group (all)	148*	Oritavancin	≤0.008	0.0015	≤0.008 – 0.12
		Penicillin	≤0.06	≤0.06	≤0.06 – >4
		Vancomycin	0.5	1	≤0.12 – 1
		Teicoplanin	≤2	≤2	≤2
		Erythromycin	≤0.25	>4	≤0.25 – > 4
		Clindamycin	≤0.25	>2	≤0.25 - >2
		Tetracycline	0.5	>8	≤0.25 – >8
		Levofloxacin	0.5	1	≤0.5 – > 4
		Daptomycin	0.25	0.5	≤0.06 – 2
		Linezolid	1	1	≤0.12 – 2
		TMX	≤0.5	≤0.5	≤0.5 - >4
S. anginosus	102	Oritavancin	≤0.008	0.0015	≤0.008 – 0.12
		Penicillin	≤0.06	≤0.06	≤0.06 – 1
		Vancomycin	0.5	1	≤0.12 – 1
		Teicoplanin	≤2	≤2	≤2
		Erythromycin	≤0.25	>4	≤0.25 – > 4
		Clindamycin	≤0.25	>2	≤0.25 - >2
		Tetracycline	0.5	1	≤0.25 – >8
		Levofloxacin	0.5	1	≤0.5 – > 4
		Daptomycin	0.25	0.5	≤0.06 – 0.5
		Linezolid	1	1	≤0.12 – 2
		TMX	≤0.5	≤0.5	≤0.5 - >4
S. constellatus	33	Oritavancin	≤0.008	0.0015	≤0.008 – 0.015
		Penicillin	≤0.06	≤0.06	≤0.06 – >8
		Vancomycin	0.5	1	0.25 – 1
		Teicoplanin	≤2	≤2	≤2
		Erythromycin	≤0.25	>4	≤0.25 – > 4
		Clindamycin	≤0.25	≤0.25	≤0.25 - >2
		Tetracycline	0.5	>8	≤0.25 – >8
		Levofloxacin	0.5	1	≤0.5 – > 4
		Daptomycin	0.25	0.5	≤0.06 – 0.5
		Linezolid	1	1	≤0.12 – 2
		TMX	≤0.5	≤0.5	≤0.5 - 2
S. intermedius	13	Oritavancin	≤0.008	0.06	≤0.008 – 0.06
		Penicillin	≤0.06	0.25	≤0.06 – >8
		Vancomycin	0.5	1	0.25 – 1
		Teicoplanin	≤2	≤2	≤2
		Erythromycin	≤0.25	>4	≤0.25 – > 4
		Clindamycin	≤0.25	>2	≤0.25 - >2
		Tetracycline	≤0.25	>8	≤0.25 – >8
		Levofloxacin	0.5	1	≤0.5 – 1
		Daptomycin	0.25	0.5	≤0.06 – 1
		Linezolid	0.5	1	≤0.12 – 1
		TMX	≤0.5	≤0.5	≤0.5 - >4

*Comprised of *S. anginosus*, n=102; *S. constellatus*, n=33; *S. intermedius*, n=13. TMX, Trimethoprim/sulfamethoxazole Source: adapted from Table 70 in 12-TMC-02 and compiled from Appendix A in 12-TMC-02.

Streptococcus dysgalactiae

The in vitro activity of oritavancin (and comparators) was tested against 34 recent *S. dysgalactiae* isolates; the MIC ranged from ≤0.008 to 0.25 mcg/mL, with an MIC90 of 0.25 mcg/mL. The results are shown in Table 17.

Table 23: Oritavancin MICs against *Streptococcus dysgalactiae* Isolates (n=34)

Agent	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC Range (µg/mL)
Oritavancin	0.06	0.25	≤0.008 – 0.25
Penicillin	≤0.06	≤0.06	≤0.06 – >8
Vancomycin	0.25	0.5	0.25 – 1
Teicoplanin	≤2	≤2	≤2
Erythromycin	≤0.25	≤0.25	≤0.25 – 4
Clindamycin	≤0.25	≤0.25	≤0.25
Tetracycline	2	>8	≤0.25 – >8
Levofloxacin	≤0.25	1	≤0.5 – 4
Daptomycin	≤0.06	0.5	≤0.06 – 2
Linezolid	1	1	0.5 – 1
TMX	≤0.5	≤0.5	≤0.5

TMX, Trimethoprim/sulfamethoxazole. Source: compiled from Appendix A in 12-TMC-02.

Conclusion: Antimicrobial Spectrum of Activity:

The information submitted by the Applicant from large prospective surveillance studies and other investigations of the in vitro activity of oritavancin supports the Applicant's claim of the activity some of the pathogens shown to be associated with skin structure infections. Oritavancin demonstrates activity against some staphylococci, streptococci, and enterococci isolates with MIC range ≤ 0.002-0.5 mcg/ml.

MECHANISM OF ACTION:

Inhibition of transpeptidation and transglycosylation

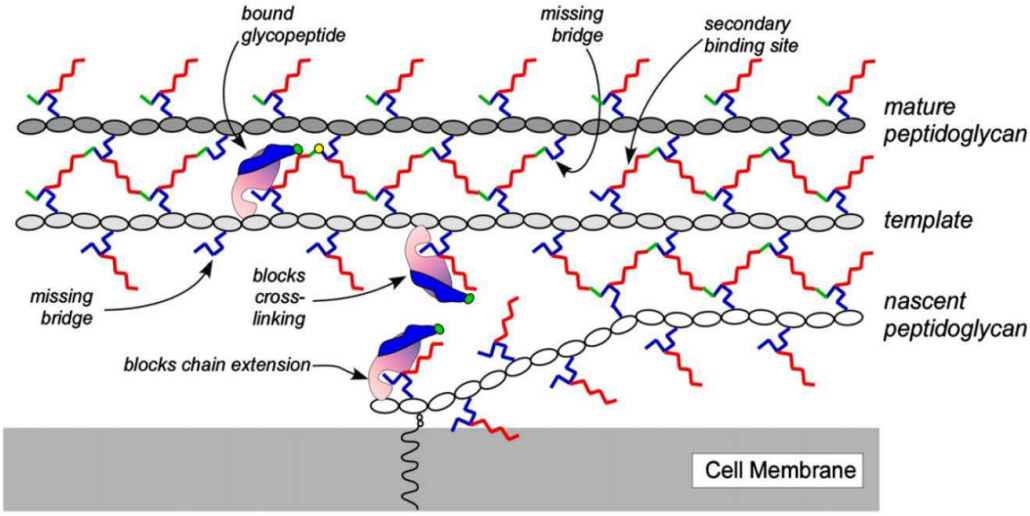
The inhibition of peptidoglycan synthesis via the inhibition of transglycosylation is common to all glycopeptides (vancomycin) and lipoglycopeptides. It was hypothesized that a secondary binding of oritavancin to the pentaglycyl (Asp/Asn) bridging segment in peptidoglycan occurs, and this distinguishes it from vancomycin and contributes to oritavancin activity versus vancomycin-resistant organisms.

Therefore, in this study, the Applicant investigated the mode of action of oritavancin, particularly the binding of oritavancin, in *S. aureus* by solid state nuclear magnetic resonance (NMR). Briefly, *S. aureus* (ATCC 6538P) were grown in a defined medium in which one or two unlabeled amino acids are replaced with labeled amino acids: [1-^{13}C]-glycine and L-[ε-^{15}N]-lysine, or D-[1-^{13}C]-alanine and [^{15}N]-glycine. The Applicant's data demonstrated that oritavancin has two cell wall binding sites: the peptidoglycan D-Ala-D-Ala pentapeptide (similar to vancomycin) stem terminus of lipid II, and the pentaglycyl bridging segment (unique to oritavancin).

It's hypothesized that the binding of oritavancin at the bridging segment of the nascent

peptidoglycan, mediated by the secondary binding site (unique to oritavancin), interferes with crosslinking, and hence leads to inhibition of transpeptidation. This is reported to be consistent with a mode of action where oritavancin is able to bind to nascent peptidoglycan strands beyond lipid II, thereby sequestering the substrates for both cell wall biosynthesis steps. A template model of the interaction between oritavancin and *S. aureus* cell wall biosynthesis is shown in Figure 4.

Figure 4: Template model of cell wall biosynthesis of wild-type *S. aureus*; the figure depicts the interaction of oritavancin with various components of the bacterial cell wall. Addition of a nascent peptidoglycan strand at the membrane exoface is accompanied by partial crosslinking to the bridging segments of the template. (Some stems and bridging segments have been omitted from the figure for clarity.) Interference with template recognition and crosslinking by [^{19}F]-oritavancin results when the drug (purple) attaches to the template proximate to the nascent strand (middle site). Vancomycin bound at the same location does not block crosslinking because the required bulky fluorobiphenyl disaccharide substituent is missing. Both drugs block chain extension when bound to Lipid II (bottom site).



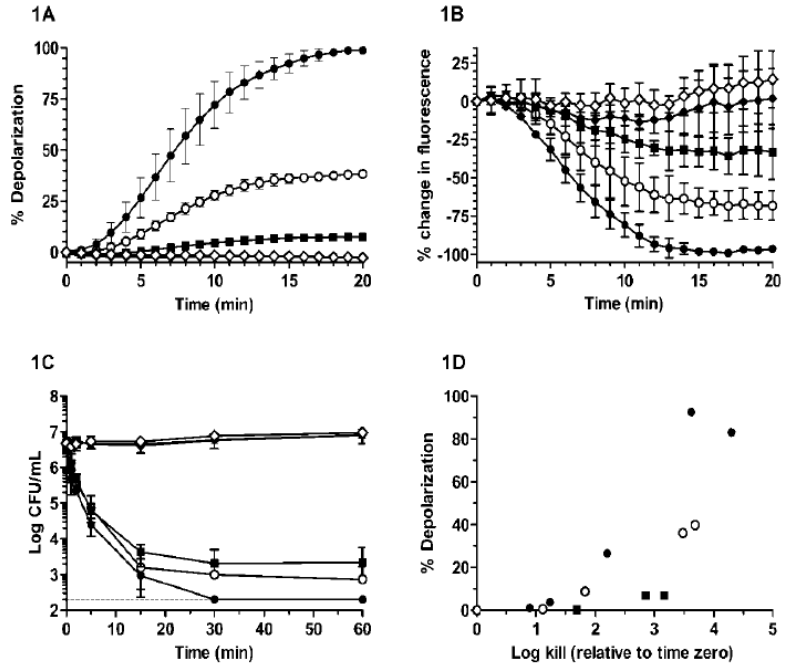
Similar to what was done above with *S. aureus* (above), the Applicant evaluated the effects of oritavancin and vancomycin on bacterial cell wall biosynthesis in *E. faecium* by solid state nuclear magnetic resonance (NMR) techniques. NMR studies demonstrate that the two cell wall binding sites of oritavancin that were characterized in *S. aureus* are still present in *E. faecium* in spite of the structural differences in their respective cell walls. They also demonstrate that, in *E. faecium*, while vancomycin exerts its effect through the inhibition of transglycosylation, oritavancin acts chiefly through the inhibition of transpeptidation, a situation that is explained by the larger proportion of transpeptidation substrate sites found in the cell wall of *E. faecium* compared to *S. aureus*.

Disruption of membrane integrity

In another experiment, the effect of oritavancin on bacterial membrane potential and permeability of exponentially growing gram-positive pathogens were investigated. The bacterial strains used in this study were hVISA ATCC 700698, VISA ATCC 700699, VRSA VRS5 (Network on Antimicrobial Resistance in *S. aureus*), and VRE ATCC 51299 (*E. faecalis*; VanB).

Results from depolarization and permeability experiment are presented as percent depolarization and percent change in fluorescence, respectively, and are relative to the maximal effect observed with oritavancin. Figure 5 shows that the addition of oritavancin to exponential phase hVISA resulted in a concentration dependent increase in fluorescence of an experimental die that was preloaded into cell membranes (Figure 5-1A), indicating an immediate onset of membrane depolarization. Exposure of hVISA to oritavancin caused immediate and concentration dependent increases in membrane permeability (Figure 5-1B).

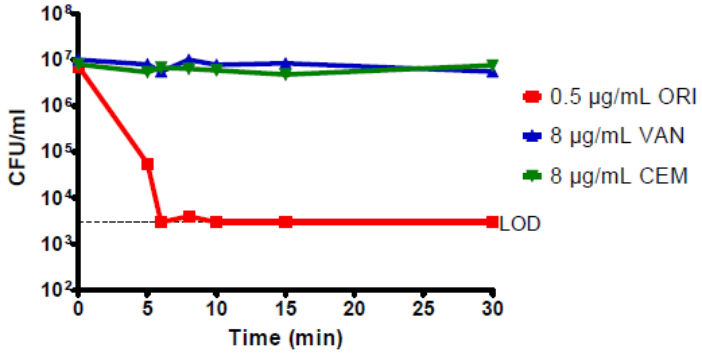
Figure 5: Effect of Oritavancin and Comparator Agents on Membrane Depolarization, Membrane Permeability, Cell Viability, and the Correlation Between Membrane Depolarization and Cell Killing



Oritavancin but not its precursor chloroeremomycin nor vancomycin disrupts bacterial membrane integrity leading to concomitant killing of hVISA ATCC 700698. Effect of oritavancin and comparator agents on membrane depolarization (panel A), membrane permeability (panel B), cell viability (panel C), and the correlation between membrane depolarization and cell killing (panel D). Control (✳); oritavancin at 4 µg/mL (■), 8 µg/mL (○) and 16 µg/mL (●); 16 µg/mL chloroeremomycin (◊); 16 µg/mL vancomycin (◆). Note that the chloroeremomycin and vancomycin curves overlap in panels A and C. The limit of detection (200 CFU) is indicated as a dashed line in panel C.

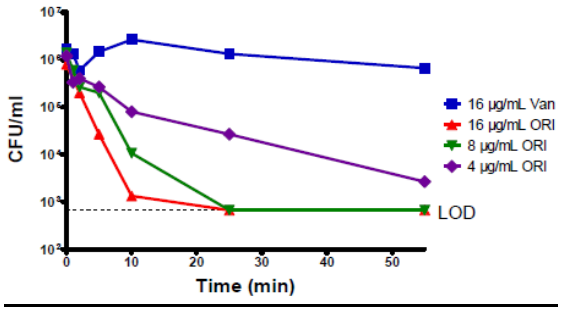
To further elucidate the precise mechanism of action for oritavancin, the Applicant performed cell viability assays on mid-log phase cells of either *S. aureus* on enterococci isolates. Briefly, cells were grown appropriately to OD_{600}~0.3. Assays were initiated by the addition of oritavancin (0.25 to 16 mcg/mL) or comparators at 4-16 mcg/mL. Aliquots were removed at time points (0, 1, 5, 10, 15, 30, 60 min), and serially diluted in sterile saline and 5 mcl was plated growth media. Figure 6 shows that at 0.5 mcg/mL oritavancin caused a 3.5 ± 0.2 log decrease in cell viability for methicillin sensitive *S. aureus* (MSSA) within 10 min.

Figure 6 Oritavancin exerts rapid bactericidal activity against *S. aureus* MSSA (ORI=oritavancin; VAN=vancomycin; CEM=chloroeremomycin Activity over time against MSSA (ORI at 0.5 mcg/mL, VAN and CEM at 8 mcg/mL)



The comparators at a concentration of 8 mcg/mL under similar conditions showed no significant impact upon cell viability over the same period of time. At 16 mcg/mL oritavancin caused a 3.0 ± 0.5 log10 decrease in cell viability for *E. faecium* (VanA) by 10 minutes (Figure 6). Oritavancin cell killing activity was concentration-dependent.

Figure 6 Oritavancin exerts rapid cidal activity against VanA VRE. [ORI=oritavancin; VAN=vancomycin; Activity over time against VRE (ORI at 4 mcg/mL, 8 mcg/mL, 16 mcg/mL, VAN at 16 mcg/mL)]



In another experiment it was shown that oritavancin was capable of rapid

depolarization of MSSA and VanA *E. faecium* upon exposure to 2 or 4 mcg/ml compared to the comparator agents (Figure 7; Figure 8 and 9).

Figure 7 Oritavancin rapidly dissipates Δψ in MSSA. MSSA cultures were treated with oritavancin (ORI) or vancomycin (VAN) at the concentrations indicated in the legend and Δψ was measured using the DiSC3(5) assay as a function of time. RFU, relative fluorescence units.

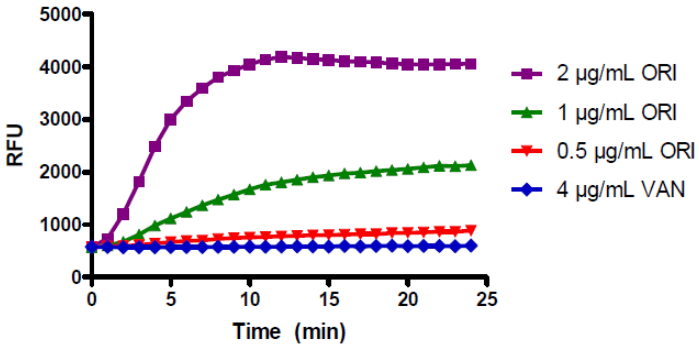


Figure 8 Oritavancin rapidly dissipates Δψ in VRE (VanA). VRE cultures were treated with oritavancin (ORI) or vancomycin (VAN) at the concentrations indicated in the legend and Δψ was measured using the DiSC3(5) assay as a function of time. RFU, relative fluorescence units.

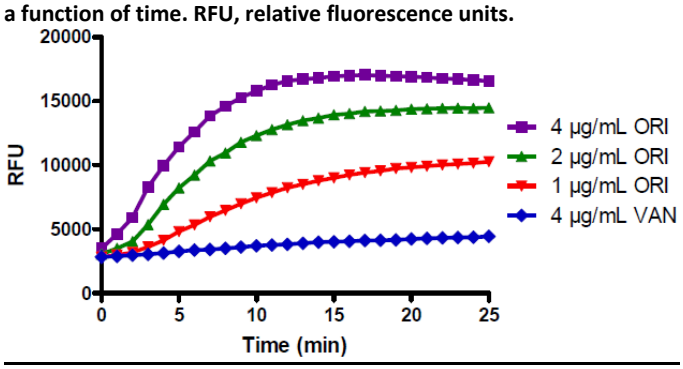
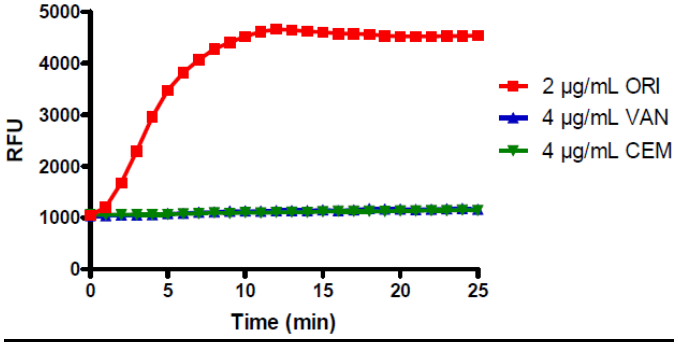


Figure 9 Chloroeremomycin lacks Δψ -dissipating activity against MSSA. MSSA cultures were treated with oritavancin (ORI), vancomycin (VAN), or chloroeremomycin (CEM) at the concentrations indicated in the legend and Δψ was measured using the DiSC3(5) assay as a function of time. RFU, relative fluorescence units.

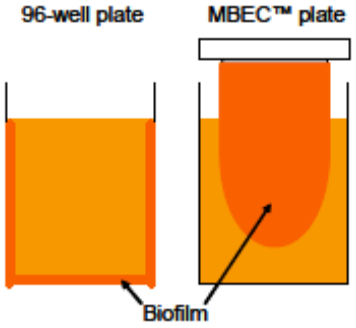


An analysis of the Applicant's data indicate that oritavancin is capable of interfering with some gram-positive bacterial cell membrane leading to a disruption of membrane potential and cell integrity resulting in bacterial cell death. Additional studies have shown that oritavancin is capable of disrupting cell wall synthesis through the interaction of oritavancin with the acyl-D-ala-D-ala portion of the Lipid II structure.

Effect of oritavancin on biofilm in vitro

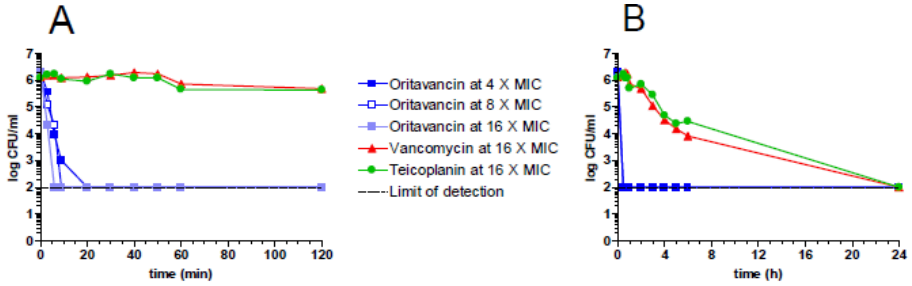
In another study, the Applicant investigated the activity of oritavancin against *S. aureus* in a non-dividing state or growing in a biofilm in vitro. For MIC testing, broth microdilution assays were conducted in accordance to CLSI M7-A7 methods. Susceptibility testing of oritavancin included 0.002% polysorbate-80 and yielded an MIC of 0.06 mcg/ml. Biofilms were established by two methods. Figure 10 shows a representation of method 1 used for biofilm development. For biofilm studies, the adherent biofilms were challenged with 2X, 4X, or 8X MIC of each antibacterial agent in CAMHB for 24 hours.

Figure 10 Methods used to establish *S. aureus* ATCC 29213 biofilms. In method 1, the bacteria were grown in 96-well plates and washed repeatedly to leave adherent cells in a biofilm (indicated by dark orange) that lines the well. In method 2, the MBEC™ system was used, and a biofilm forms on the immersed peg.



In the second approach, biofilm pegs were broken off the MBEC lid (see Figure 10 above), immersed in saline and sonicated then enumerated by serial dilution plating. The data in Figure 11 show that a 3 log10 reduction in viable counts occurred in 20 minutes at 4x 8x and 16x times the MIC.

Figure 11 Oritavancin exhibits rapid bactericidal activity against exponentially growing *S. aureus* ATCC 29213.



Oritavancin was shown to exhibit concentration-dependent bactericidal activity (≥3 log10 reduction in viable cell counts) against stationary-phase cells inoculated into depleted CAMHB (blue curves in left-hand ≤, Figure 12).

Figure 12 bactericidal activities against *S. aureus* ATCC 29213 in depleted CAMHB.

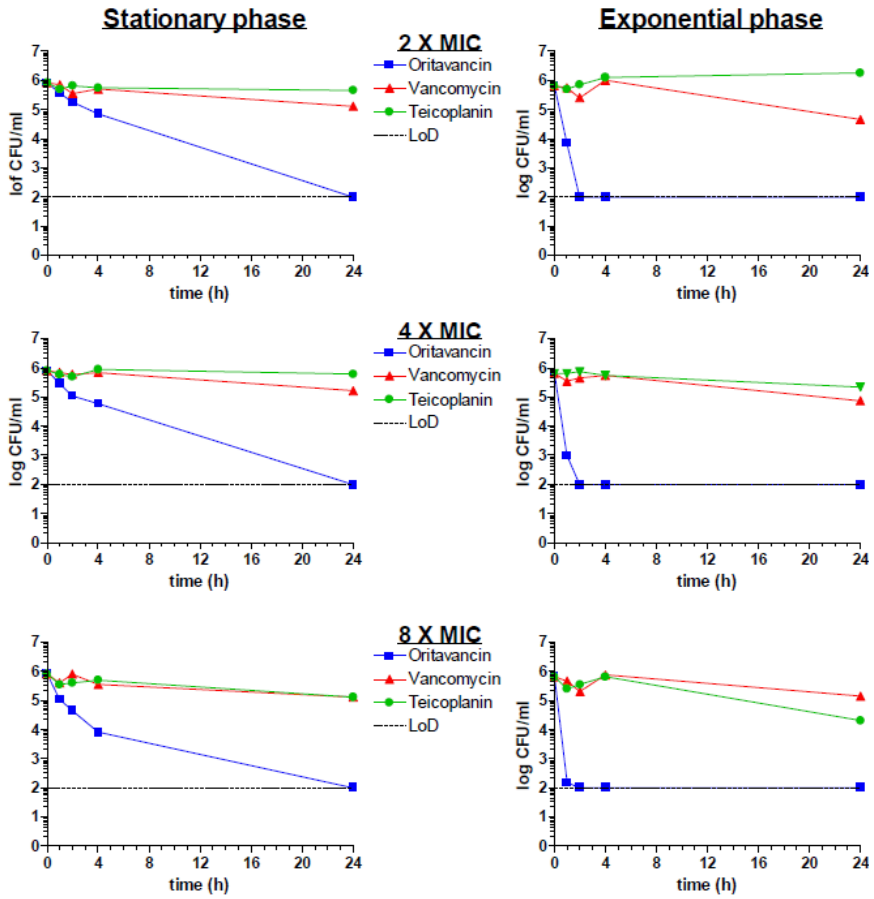


Table 18 shows the assessment of biofilm studies; the two biofilm methods gave similar activity for oritavancin and comparators. For oritavancin, the minimal biofilm inhibitory concentration increased 2-32 folds and was the lowest compared to vancomycin and teicoplanin.

Table 18 Oritavancin Displays Antibacterial Activity Against *S. aureus* ATCC 29213 Biofilms Established in 96-well and MBEC™ Pl

Antibiotic	96-well plate		MBEC™ plate	
	MIC (μg/ml)	MBIC[a] (μg/ml)	MIC[c] (μg/ml)	MBEC[d] (μg/ml)
Oritavancin	0.5	4-16[b]	2-4	4-8
Vancomycin	1	>128[b]	2-4	≥128
Teicoplanin	0.5	64-128[b]	1-2	16-32
Rifampicin	0.008	0.004[b]	<0.125	8

a. MBIC, minimal biofilm inhibitory concentration
b. As assessed 48 hours after addition of fresh CAMHB to the drug-exposed wells, no growth was observed in wells above the oritavancin MBIC breakpoint whereas bacterial regrowth occurred for all other antibiotics.
c. MICs were determined in MBEC™ plates and represent the antibacterial activity against planktonic cells shed from the peg biofilms.
d. The minimal biofilm eradication concentration (MBEC) was determined following the manufacturer's protocol. Biofilms on control pegs contained an average of $8.7 \pm 5.5 \times 10^6$ CFU/peg.

Conclusion:

The Applicant has submitted results from a series of experiments that show oritavancin acts by the inhibition of transpeptidation and transglycosylation. Additionally, oritavancin was shown to disrupt the resting potential of bacterial cells by a mechanism that involves a disruption of membrane potential. The in vitro activity of oritavancin against biofilm *S. aureus* was also demonstrated.

EMERGENCE OF RESISTANCE:

The emergence of resistance to oritavancin was examined by serial passage studies using subinhibitory concentrations against *S. aureus*. High-level resistance may require multiple mutations, which may potentially be revealed by serial-passage studies in which multistep mutations can accumulate during growth at subinhibitory concentrations of antibiotic. Briefly, the Applicant determined the potential for developing reduced susceptibility to oritavancin (ORI) during serial passages of heterogeneous vancomycin-intermediate *Staphylococcus aureus* (hVISA) isolates in sub-inhibitory concentrations of oritavancin for 20 days. Table 19 shows the *S. aureus* strains used in the study.

Table 19: *S. aureus* strains used in the step-wise development of reduced susceptibility to ORI study

Strain	Phenotype	Comments	Source
ATCC 29213	MSSA, VSSA	QC strain	ATCC
ATCC 700698 (NRS 2 or Mu 3)	hVISA	Clinical hVISA reference strain	ATCC
NRS 19	hVISA	Clinical isolate	NARSA

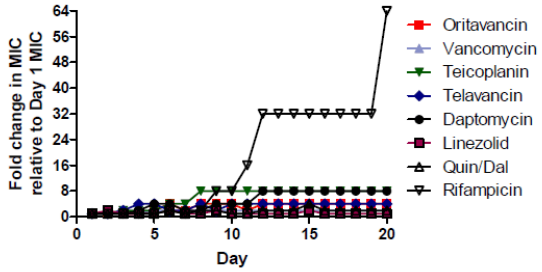
*ATCC, American Type Culture Collection; NARSA, Network on Antimicrobial Resistance in *Staphylococcus aureus*; MSSA, Methicillin-susceptible *Staphylococcus aureus*; MRSA, Methicillin-resistant *Staphylococcus aureus*; hVISA, Heterogeneous vancomycin-intermediate *Staphylococcus aureus*; QC, Quality control.

Test strains were assessed for the propensity to develop reduced susceptibility to challenge drugs by serial passage of the strains in cation-adjusted Mueller-Hinton broth (CAMHB) medium containing doubling dilution concentrations of each drug under standard susceptibility testing broth micro dilution (BMD) MIC assay conditions. For oritavancin, polysorbate-80 (P80) was maintained at 0.002% for drug dissolution, dilution, and in all steps of the BMD assay. For daptomycin (DAP), CAMHB medium was supplemented with $CaCl_2$ at 50 mcg/mL. Twenty cycles of BMD were performed using as inoculum, cells from the 0.5X MIC wells of the previous day's experiment. Each strain was tested in two independent rounds of 20 cycles.

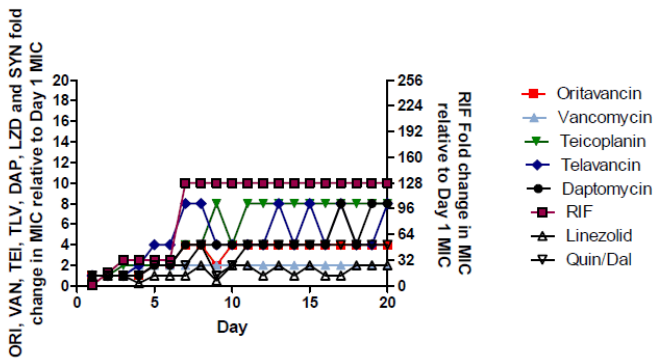
The data in Figure 13 show the MIC changes during the two 20-day (drug challenge) cycles for the methicillin- and vancomycin-susceptible quality control strain *S. aureus* ATCC 29213.

Figure 13: Fold change in MIC for *S. aureus* ATCC 29312 tested against drugs. a, First round; b, Second independent round.

A.



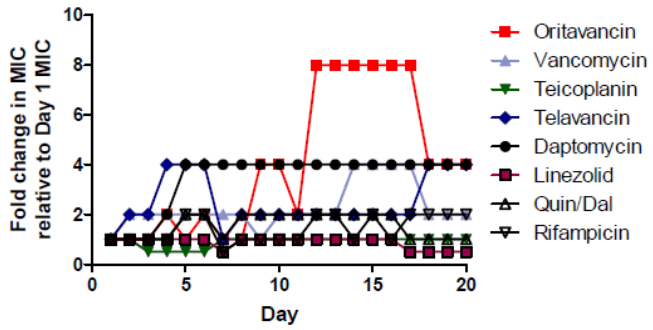
B.



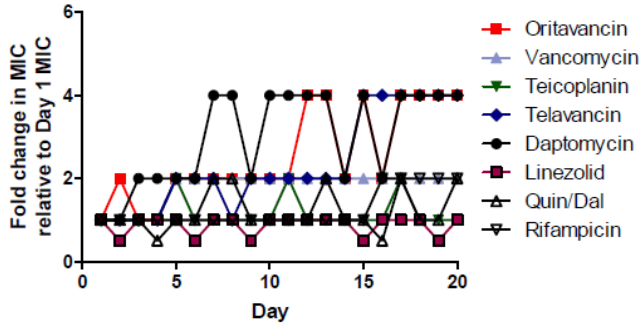
The data in Figure 14 show the MIC changes during the two 20-day (drug challenge) cycles for the hVISA reference strain *S. aureus* ATCC 700698.

Figure 14 Fold change in MIC for *S. aureus* NRS 2 tested against drugs. a, First round; b, Second independent round.

a.



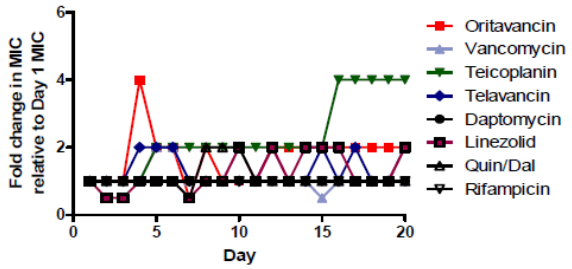
b.



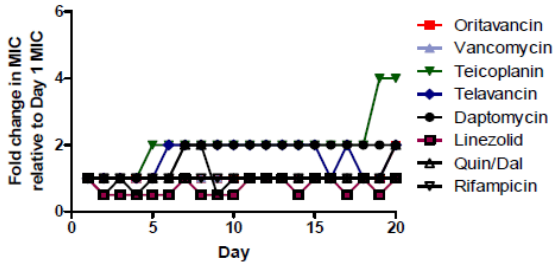
The data in Figure 15 show the MIC changes during the two 20-day (drug challenge) cycles for the hVISA strain *S. aureus* NRS 19.

Figure 15 Fold change in MIC for *S. aureus* NRS 19 tested against drugs. a, First round; b, Second independent round.

a.



b.



Another study was undertaken to determine the potential for resistance development. The procedures were similar to those described above and the bacterial strains used in the study are shown in Table 20.

Table 20 Description of Strains Used to Test Resistance Development to Oritavancin

Test Organism	Description
S. aureus ATCC 29213	Methicillin-sensitive reference strain
S. aureus ATCC 43300	Methicillin-resistant reference strain
S. aureus ATCC 700699 (Mu 50)	Vancomycin-intermediate clinical isolate
S. aureus NRS121	Linezolid-resistant, methicillin-resistant clinical isolate
S. aureus NRS123	Community-acquired methicillin-resistant clinical isolate
S. aureus NRS 402	Vancomycin-intermediate, daptomycin non-susceptible clinical isolate
S. aureus VRS 5	Vancomycin-resistant clinical isolate
E. faecalis ATCC 29212	Vancomycin-sensitive reference strain
E. faecalis ATCC 52199	Vancomycin-resistant (*vanB*) clinical reference isolate
E. faecalis 1059846	Vancomycin-resistant (*vanA*) clinical isolate
E. faecium 1059335	Vancomycin-resistant (*vanB*) clinical isolate
E. faecium ATCC 51559	Vancomycin-resistant (*vanA*) clinical reference isolate

The comparator drugs used in the study were vancomycin (glycopeptide), teicoplanin (glycopeptide), linezolid (oxazolidinone), moxifloxacin (fluoroquinolone) and rifampicin (rifamycin). Minimum inhibitory concentrations and the resistance development studies were conducted in accordance to CLSI methods. Briefly, twenty cycles of broth microdilution MICs were performed using as inoculum, cells from the 0.5X MIC wells of the previous day's experiment. Each strain was tested in two independent rounds of 20

cycles. Any selected isolate with a ≥4-fold increase in MIC to the challenge drug, at day 20, compared to the parental MIC at day 1, was passaged non-selectively (i.e. in the absence of drug) for five days. Following the non-selective growth period, MICs were determined for oritavancin and comparator drugs. Tables 21a and 21b summarize the changes in oritavancin MIC for the oritavancin selection of *S. aureus*.

Table 21a Summary of *in vitro* Step-wise Selection with Oritavancin in *S. aureus* (first round)

Strain	Description	MIC of naïve strain (µg/mL)	MIC (µg/mL) after expt. [a]	Fold increase in MIC from initial MIC
ATTCC 29213	Methicillin-sensitive	0.03	0.12	4
ATCC 43300	Methicillin-resistant	0.03	0.25	8
ATCC 700699	Vancomycin-intermediate	1	1	1
NRS 121	Linezolid-resistant	0.06	0.5	8
NRS 123	Community-acquired Methicillin-resistant	0.06	0.25	4
NRS 402	Vancomycin-intermediate	1	1	1
VRS 5	Vancomycin-resistant	0.25	0.5	2

[a]20 daily cycles with drug followed by 5 days of non-selective growth for those that show ≥4-fold increases in MIC relative to Day 1 MIC

Table 21b Summary of *In Vitro* Step-wise Selection with Oritavancin in *S. aureus* (second round)

Strain	Description	MIC of naïve strain (µg/mL)	MIC (µg/mL) after expt. [a]	Fold increase in MIC from initial MIC
ATTCC 29213	Methicillin-sensitive	0.06	0.25	4
ATCC 43300	Methicillin-resistant	0.06	0.25	4
ATCC 700699	Vancomycin-intermediate	1	1	1
NRS 121	Linezolid-resistant	0.06	0.25	4
NRS 123	Community-acquired Methicillin-resistant	0.03	0.12	4
NRS 402	Vancomycin-intermediate	0.5	1	2
VRS 5	Vancomycin-resistant	0.25	0.5	2

[a]20 daily cycles with drug followed by 5 days of non-selective growth for those that show ≥4-fold increases in MIC relative to Day 1 MIC

Tables 22 and 23 summarize the changes in oritavancin MIC for the oritavancin selection of *E. faecalis* and *E. faecium*.

Table 22 Summary of *In Vitro* Step-wise Resistance to Oritavancin in Enterococci (first round)

Strain[a]	Description	MIC of naïve strain (µg/mL)	MIC (µg/mL) after expt. [b]	Fold change in MIC from initial MIC
Ef ATCC 29212	Vancomycin-sensitive	0.016	0.06	4
Ef ATCC 51299	Vancomycin-resistant (*vanB*)	0.016	0.12	8
Ef 1058946	Vancomycin-resistant (*vanA*)	0.25	1	4
Em 1059335	Vancomycin-resistant (*vanB*)	0.008	0.5	64
Em ATCC 51559	Vancomycin-resistant (*vanA*)	0.06	1	16

[a] Ef, *Enterococcus faecalis*; Em, *Enterococcus faecium*
[b] 20 daily cycles with drug followed by 5 days of non-selective growth for those that show ≥4-fold increases in MIC relative to Day 1 MIC

Table 5.23 Summary of *In Vitro* Step-wise Resistance to Oritavancin in Enterococci (second round)

Strain[a]	Description	MIC of naïve strain (µg/mL)	MIC (µg/mL) after expt. [b]	Fold change in MIC from initial MIC
Ef ATCC 29212	Vancomycin-sensitive	0.016	0.06	4
Ef ATCC 51299	Vancomycin-resistant (*vanB*)	0.016	0.06	4
Ef 1058946	Vancomycin-resistant (*vanA*)	0.25	1	4
Em 1059335	Vancomycin-resistant (*vanB*)	0.008	0.5	64
Em ATCC 51559	Vancomycin-resistant (*vanA*)	0.12	1	8

[a] Ef, *Enterococcus faecalis*; Em, *Enterococcus faecium*
[b] 20 daily cycles with drug followed by 5 days of non-selective growth for those that show ≥4-fold increases in MIC relative to Day 1 MIC

The data show that for oritavancin, a 4- to 8-fold increase in ORI MIC was observed for other *S. aureus* isolates of different drug resistance phenotypes. Results presented in the current study suggest a potential for emergence of ORI resistance during therapy. For *E. faecalis* and *E. faecium* isolates with reduced susceptibility (4-64 fold higher) to oritavancin were selected. In all instances tested, the MIC against the isolates did not exceed 1 mcg/ml. In summary, the mechanisms of resistance to oritavancin have not been established. In in vitro serial passage studies, increase resistance was observed in staphylococcal and enterococcal isolates.

Glycopeptide Resistance Detection (GRD) and PVL Analysis of *S.aureus* Isolates in the clinical studies [SOLO I] [SOLO II]

In this experiment, the Applicant determined levels of GRD resistance in heterogeneous glycopeptide-intermediate *Staphylococcus aureus* (hGISA) and glycopeptide intermediate *Staphylococcus aureus* (GISA) isolates. The study was conducted with *S. aureus* isolates that had vancomycin MICs that were greater than 0.5 mcg/ml. By this method, isolates that had vancomycin or teicoplanin MICs ≥8 mcg/mL are recorded as GRD positive(+). Additionally, if a strain was GRD + and had a standard vancomycin MIC ≥4 mcg/mL then the isolate was considered a GISA; and if an isolate was GRD + and had

a standard vancomycin MIC is < 4 mcg/mL then the isolate was considered an hGISA. The Applicant produced a line listing of GRD results obtained with the *S. aureus* clinical isolates tested. As per the SOLO study protocols only *S. aureus* isolates with vancomycin MICs > 0.5 mcg/mL were selected for GRD testing. All the isolates that met this criteria had a vancomycin MIC of 1 mcg/mL, no isolates were encountered that had vancomycin MICs > 1 mcg/ml. Based on these findings, all GRD positive isolates were classified as being hGISA. Of the 52 SOLO I isolates that were GRD tested 12 (23.1 %) were positive. For SOLO II study, 62 isolates were tested and 9 (14.5%) were GRD-positive.

According to the data presented, the frequency of GRD-positive *S. aureus* isolates in the tested population (VAN MIC = 1 mcg/mL) was relatively low (~23.1%) and no GISA isolates were encountered among the over 1,100 isolates obtained from both trials.

With respect to PVL, for SOLO I, 352 of 513 isolates were PVL-positive (68.6%); for SOLO II, 329 of the 607 (54.2%) isolates were PVL-positive. The prevalence of PVL in the SOLO I and SOLO II populations was relatively common as more than 50% of the isolates were PVL positive in both studies.

Summary and conclusion:

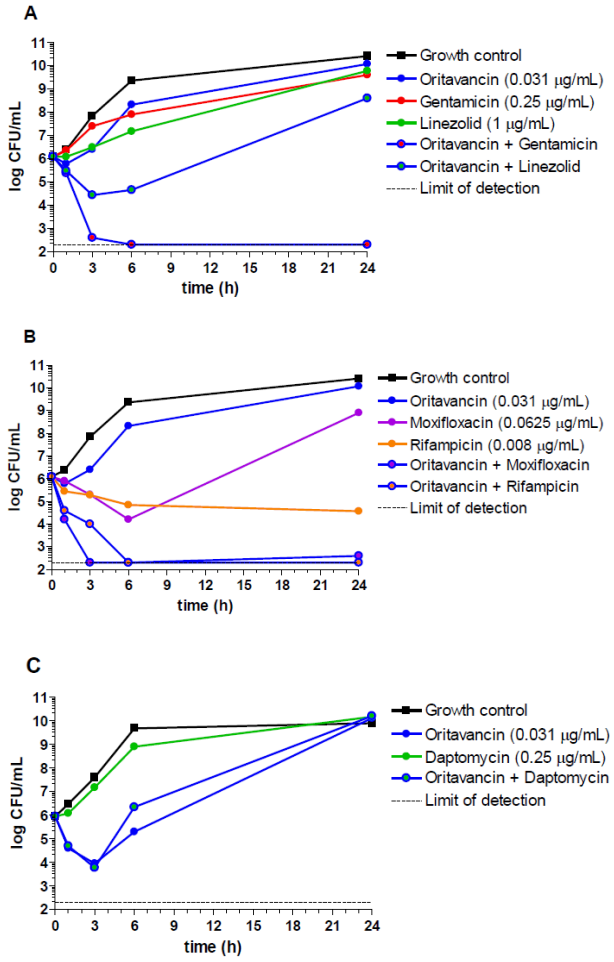
The in vitro studies described within this review indicate a propensity for the development of oritavancin resistance following serial passages. The data show that for *S. aureus* and for enterococci isolates, there is a propensity for the emergence of reduced susceptibility to oritavancin. The in vitro data for *S. aureus*, *E. faecalis* and *E. faecium* strains show a 4-64 fold higher increase in MIC following 20 cycles of oritavancin exposure. No additional data with respect to the genetic nature of the reduce oritavancin susceptibility was provided.

Synergistic Effects of Oritavancin Tested in Combination with Other Agents

Antimicrobial combination and synergy are important for treating pathogens in mixed infection, to enhance the killing of specific pathogens, and to prevent or delay the emergence of drug-resistant populations. The Applicant used a time kill methodology to determine antibacterial synergy. Oritavancin was tested in combination with clinically-used antibacterial agents for synergy against a total of five isolates of *S. aureus*, *E. faecium*, and *E. faecalis*, including strains that spanned a range of vancomycin susceptibility phenotypes. Representative agents from the following classes of antibiotics were tested for synergy with oritavancin: cyclic lipopeptides (daptomycin), aminoglycosides (gentamicin), oxazolidinones (linezolid), fluoroquinolones (moxifloxacin) and rifamycins (rifampicin). Studies were conducted according to CLSI methods. Results of the study show that oritavancin synergizes with gentamicin,

moxifloxacin, and rifampicin against MSSA ATCC 29213. Synergy was not observed with combinations of oritavancin and linezolid, a protein synthesis inhibitor or with combinations of oritavancin and daptomycin, a membrane-perturbing antibiotic (Figure 16).

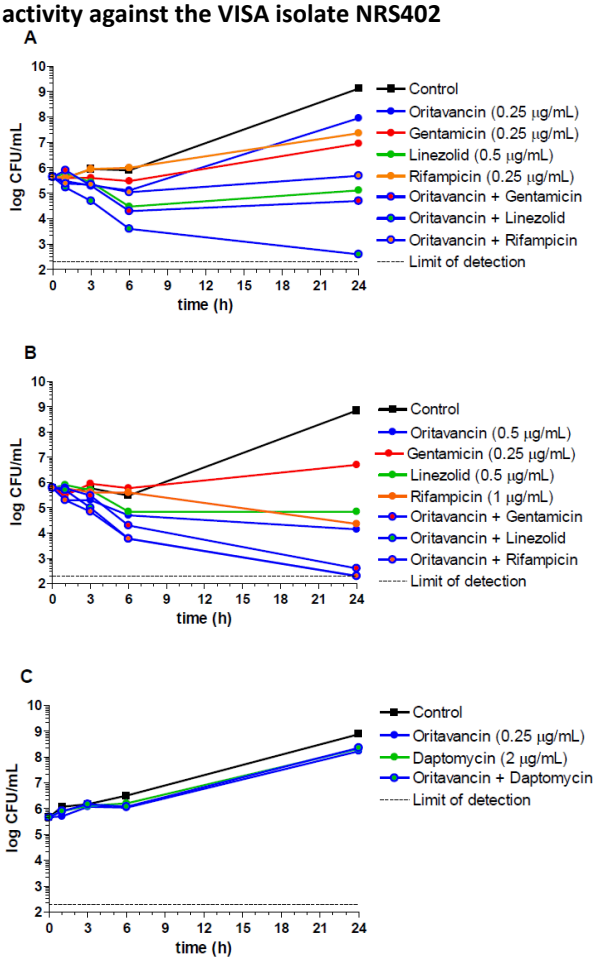
Figure 16 Oritavancin in combination with gentamicin, moxifloxacin or rifampicin displays synergistic bactericidal activity against *S. aureus* ATCC 29213



Against the clinical isolate of VISA used (NRS402; NARSA) sub-MIC concentrations of oritavancin (0.25 mcg/mL) were found to synergize with linezolid or gentamicin. The combinations of oritavancin with linezolid or gentamicin at these concentrations were bactericidal or bacteriostatic, respectively, at the 24-hour time point. The combination of a sub-MIC concentration of oritavancin (0.25 mcg/mL) and rifampicin resulted in additive, bacteriostatic activity. When a 2-fold higher yet still sub-MIC concentration of oritavancin (0.5 mcg/ml) was used in combination with the same concentration of gentamicin or with 1 mcg/mL rifampicin, additive bactericidal activity was observed at

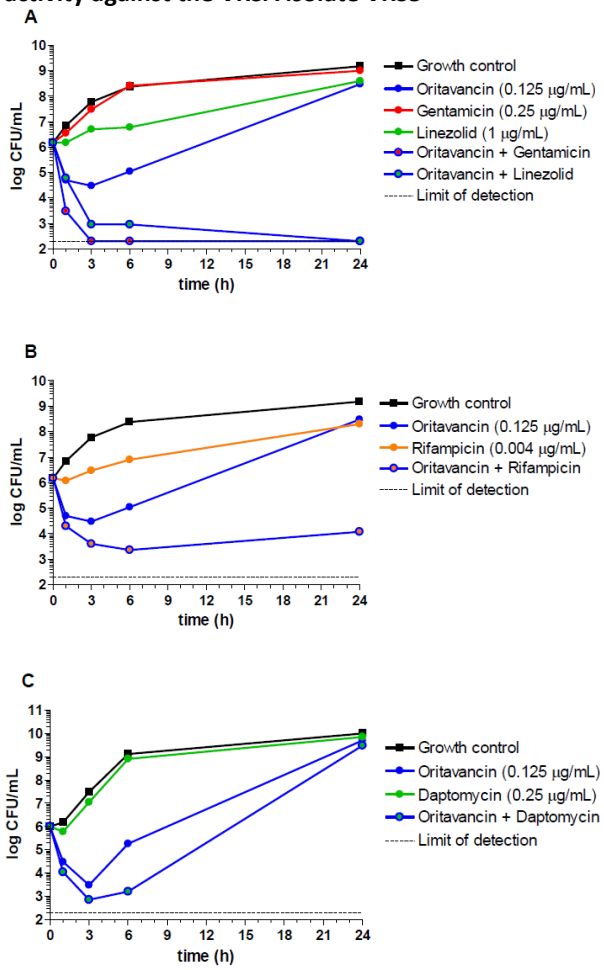
the 24-hour time point, a result that was not seen with either drug alone. Synergistic activity was not observed under these conditions with a combination of oritavancin and daptomycin (Figure 17).

Figure 17 Oritavancin in combination with linezolid, gentamicin or rifampicin displays synergistic activity against the VISA isolate NRS402



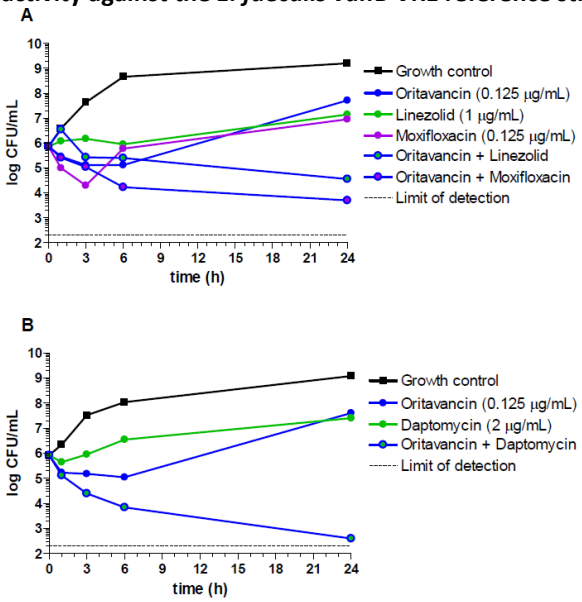
Against VRSA (VRS5; NARSA) a sub-MIC concentration of oritavancin in combination with gentamicin, linezolid or rifampicin was synergistic. The combinations of oritavancin and gentamicin or linezolid were bactericidal whereas the combination of oritavancin and rifampicin was bacteriostatic at the 24-hour time point (Figures 18). Synergistic activity was not observed with a combination of oritavancin and daptomycin under the present conditions.

Figure 18 Oritavancin in combination with gentamicin, linezolid or rifampicin displays synergistic activity against the VRSA isolate VRS5



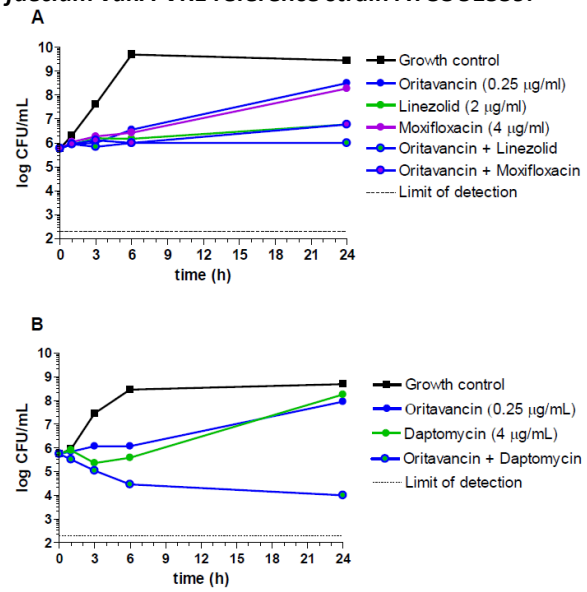
Against VRE *E. faecalis* ATCC 51299 (vanB positive) synergy was observed when a sub-MIC concentration of oritavancin was combined with linezolid, moxifloxacin or daptomycin against this strain. The combination of oritavancin and daptomycin was bactericidal at the 24-hour time point whereas the other combinations were bacteriostatic (Figure 19).

Figure 19 Oritavancin in combination with linezolid, moxifloxacin or daptomycin displays synergistic activity against the *E. faecalis van*B VRE reference strain ATCC 51299.



Against *E. faecium* ATCC 51559 (vanA positive) no synergy or antagonism was detected when oritavancin was used in combination with linezolid or moxifloxacin in time-kill assays. When oritavancin was combined with a sub-MIC concentration of daptomycin, synergy was detected. The activity of these antibiotics in combination was bacteriostatic at the 24-hour time point (Figure 20).

Figure 20 Oritavancin in combination with daptomycin displays synergistic activity against the *E. faecium vanA* VRE reference strain ATCC 51559.



In another experiment, the synergistic effects of oritavancin in combination with gentamycin, linezolid and rifampin were investigated. Table 24 shows that out of eight strains tested with a combination of oritavancin and gentamicin, synergy was observed in 2 strains at 3 hours. At 6 hours, seven strains showed synergy with oritavancin concentrations. By 12 hours and 24 hours, all eight strains showed synergy with oritavancin. The combination of oritavancin and linezolid yielded synergy after 6 hours, 12 hours and 24 hours in all 10 strains tested. Oritavancin and rifampin exhibited synergy against seven of nine strains tested by 24 hours. At 3 hours, two strains showed synergy with oritavancin

Table 24: MICs (mcg/ml) of drugs alone at 24 h and the synergy time-kill results of oritavancin combined with gentamicin, linezolid, and rifampin.

Strain	MIC (µg/ml)[a]				Oritavancin + Gentamicin				Oritavancin + Linezolid				Oritavancin + Rifampin			
	ORI	GEN	LZD	RIF	3h	6h	12h	24h	3h	6h	12h	24h	3h	6h	12h	24h
504	2	256	2	128	NS[b]	Syn 1/128[c]	Syn 0.5/64	Syn 0.5/64	NS	NS	Syn 0.5/0.5	Syn 0.5/0.5	NS	NS	NS	NS
506	1	1	2	256	NS	Syn 0.25/0.25	Syn 0.25/0.25	Syn 0.25/0.25	NS	NS	NS	Syn 0.25/1.0	NS	NS	NS	NS
507	0.5	>1024	2	4	NT[d]	NT	NT	NT	NS	NS	Syn 0.25/1.0	Syn 0.25/1.0	NS	NS	Syn 0.25/ 1.0	Syn 0.12/ 2.0
508	1	>1024	2	0.016	NT	NT	NT	NT	NS	NS	Syn 0.5/1.0	Syn 0.5/1.0	NS	NS	Syn 0.5/ 0.004	Syn 0.5/ 0.008
770	1	1	2	0.016	NS	Syn 0.25/0.25	Syn 0.25/0.25	Syn 0.25/0.25	NS	NS	Syn 0.25/0.5	Syn 0.25/0.5	NS	Syn 0.25/ 0.008	NS	Syn 0.25/ 0.008
710	0.5	512	2	0.016	NS	NS	Syn 0.125/128	Syn 0.125/128	NS	NS	NS	Syn 0.25/0.5	NS	NS	Syn 0.12/ 0.004	Syn 0.12/ 0.008
618	0.25	1	4	0.016	Syn 0.06/ 0.25	Syn 0.06/0.25	Syn 0.06/0.25	Syn 0.06/0.25	NS	NS	Syn 0.12/1.0	Syn 0.12/1.0	Syn 0.06/ 0.008	Syn 0.06/ 0.004	Syn 0.06/ 0.004	Syn 0.06/ 0.008
873	0.5	1	2	0.03	Syn 0.125/ 0.5	Syn 0.125/0.25	Syn 0.125/0.25	Syn 0.125/0.25	NS	NS	Syn 0.12/0.5	Syn 0.12/0.5	Syn 0.12/ 0.008	Syn 0.12/ 0.008	Syn 0.12/ 0.008	Syn 0.12/ 0.008
2222	0.12	1	4	0.008	NS	Syn 0.03/0.25	Syn 0.03/0.25	Syn 0.03/0.25	NS	Syn 0.03/1.0	Syn 0.03/1.0	Syn 0.03/2.0	NS	Syn 0.03/ 0.002	Syn 0.03/ 0.002	Syn 0.03/ 0.004
2223	0.5	32	4	>1024	NS	Syn 0.12/8	Syn 0.12/8	Syn 0.12/8	NS	Syn 0.12/1.0	Syn 0.12/1.0	Syn 0.12/1	NT	NT	NT	NT

Abbreviations: ORI, oritavancin; GEN, gentamicin; LZD, linezolid; RIF, rifampin
[a] MIC reading directly from the time-kill at 24 h
[b] No synergy
[c] Synergy ratio in µg/ml
[d] Not tested because one antibiotic in the pair had the MIC >1024 µg/ml

Summary and conclusions:

The data presented here suggest that oritavancin activity may be enhanced when used in combination with other therapies in the treatment of gram-positive infections. Using time kill methodology, oritavancin was tested in combination with clinically-used antibacterial agents for synergy against a total of five isolates of *S. aureus*, *E. faecium*, and *E. faecalis*. Oritavancin tested in combination with other antibacterial agents against individual representative bacterial strains demonstrated a degree of synergy between gentamycin, linezolid and rifampin. Synergy was dependent on drug exposure time and bacterial strains.

BACTERICIDAL ACTIVITY

Time kill assay

In time-kill assays, concentrations of comparator agents (vancomycin, daptomycin and linezolid) were chosen to approximate their peak concentration of non-protein bound drug (*f*Cmax) and the trough concentration of non-protein bound drug (*f*Cmin) in plasma when administered at approved dosages for acute bacterial skin and skin structure infections, using pharmacokinetic data and protein binding values from their respective package inserts. The concentrations of antibiotics tested in the time-kill assays are shown in Table 25. Oritavancin concentrations were chosen to approximate anticipated plasma *f*Cmax from a single 1200 mg dose and its anticipated free concentration in plasma 24 h after dosing, given that *f*Cmin is not relevant for the single dose.

Table 25: Concentrations of antibiotics tested in time-kill assays

Agent	Representative human dose	Free fraction	fC_{max} (µg/mL)[e]	fC_{min} (µg/mL)[e]
Oritavancin[a]	1200 mg	0.15	16	2[f]
Vancomycin[b]	1000 mg	0.54	16	4
Daptomycin[c]	4 mg/kg	0.08	4	0.5
Linezolid[d]	600 mg	0.69	8	2

[a]Oritavancin, 1200 mg intravenously, single dose (http://clinicaltrials.gov/ct2/show/NCT01252732).
[b]Vancomycin, 1000 mg intravenously, q12h (Vancocin package insert)
[c]Daptomycin, 4 mg/kg intravenously, q24h (Cubicin package insert)
[d]Linezolid, 600 mg orally, q12h (Zyvox package insert)
[d]From package inserts, or, for oritavancin, from dose used in acute bacterial skin and skin structure infection (ABSSSI) clinical trial (http://clinicaltrials.gov/ct2/show/NCT01252732)
[e]Accounting for serum protein binding as noted in package inserts for each drug. fC_{min}, lowest concentration of non-protein bound drug in the approved dosing interval; fC_{max}, maximal [peak] concentration of non-protein bound drug in plasma following approved or recommended dose
[f]fC_{min} is not relevant for oritavancin since it is to be administered as a single 1200 mg dose for treatment of ABSSSI; hence, its estimated free concentration at 24 h following administration of the single dose was used as a representative concentration

In time-kill assays, oritavancin at both *f*Cmax and *f*Cmin was bactericidal when tested against standard and high inoculum densities of ATCC 29213 and ATCC 43300 (Table 19). Against the two daptomycin nonsusceptible VISA strains (NRS 1 and NRS 402) oritavancin was bactericidal at *f*Cmax against standard inoculum density but not against high inoculum density (Table 26). Against both VISA strains, oritavancin at *f*Cmin was bacteriostatic against standard inoculum density but had no substantial growth-inhibitory effect against either strain at high inoculum density. Against the three hVISA strains (NRS 2, NRS 11 and NRS 28), oritavancin at *f*Cmax was bactericidal when tested against both standard and high inoculum densities (Table 26).

Table 26: Activity of oritavancin and comparator agents against *S. aureus* strains in time-kill assays at high (~10^7 CFU/mL) versus standard (std; ~10^5 CFU/mL) inocula.

Strain[b] (inoculum)	Oritavancin (fC_{min})[c]	Oritavancin (fC_{max})[c]	Vancomycin (fC_{min})	Vancomycin (fC_{max})	Daptomycin (fC_{min})	Daptomycin (fC_{max})	Linezolid (fC_{min})	Linezolid (fC_{max})
ATCC 29213 (Std)	15 -30 min	5 – 10 min	6 -24 h	6 -24 h	+ 3.0	1 – 2 h	+ 1.3	- 2.0
ATCC 29213 (High)	30 – 60 min	5 – 10 min	6 -24 h	6 -24 h	+ 2.3	2 – 4 h	+ 2.0	+ 1.2
ATCC 43300 (Std)	5 – 10 min	5 – 10 min	6 -24 h	6 -24 h	+ 3.1	1 – 2 h	+ 1.0	- 1.5
ATCC 43300 (High)	10 – 15 min	5 – 10 min	6 -24 h	6 -24 h	+ 2.4	2 – 4 h	+ 1.5	+ 1.2
NRS 1(Std)	- 2.1	6 - 24 h	+ 3.2	6 -24 h	+ 2.9	+ 2.4	- 1.8	6 – 24 h
NRS 1 (High)	+ 2.2	+ 2.1	+ 2.5	+ 2.3	+ 2.2	+ 2.1	- 0.1	- 1.1
NRS 402 (Std)	- 2.7	6 - 24 h	+ 2.9	6 -24 h	+ 3.0	+ 2.0	-2.1	6 – 24 h
NRS 402 (High)	+ 2.4	+ 2.2	+ 2.6	+ 2.3	+ 2.1	+ 1.9	- 0.5	- 0.1
NRS 2 (Std)	4 - 6 h	2 - 4 h	6 -24 h	6 -24 h	+ 3.1	4 - 6 h	- 1.0	- 1.5
NRS 2 (High)	+ 2.7	6 – 24 h	+ 0.1	-1.1	+ 2.1	+ 1.9	+ 1.9	+ 1.9
NRS 11(Std)	4 - 6 h	2 - 4 h	6 -24 h	6 -24 h	+ 2.5	4 - 6 h	- 0.9	- 1.0
NRS 11 (High)	+ 3.1	6 – 24 h	-1.0	-1.5	+ 1.9	+ 1.5	+ 2.1	+ 1.9
NRS 28 (Std)	4 - 6 h	2 - 4 h	6 -24 h	6 -24 h	+ 2.0	2 - 4 h	- 1.5	- 1.0
NRS 28 (High)	+ 2.5	6 – 24 h	+ 0.1	-1.1	+ 1.5	+ 1.5	+ 2.0	+ 1.5

[a]Time to cidality is indicated for drugs that achieved bactericidal activity (≥ 3 log decrease in cell density relative to initial inoculum). Change in cell density (in log CFU/mL) at 24 h relative to starting inoculum is indicated for drugs with bacteriostatic activity (0 to < 3 log kill at 24 h relative to initial inoculum) and for drugs with little to no inhibition of growth relative to growth control at 24 h.

[b] ATCC 29213, methicillin- and vancomycin-susceptible *S. aureus*; ATCC 43300, methicillin-resistant *S. aureus* (MRSA); NRS 1 and NRS 402, vancomycin-intermediate *S. aureus* (VISA), daptomycin-nonsusceptible; NRS 2, NRS 11 and NRS 28, vancomycin-intermediate *S. aureus* (hVISA).

[c] (fC_{max}), peak concentration of non-protein bound drug; (fC_{min}), trough concentration of non-protein bound drug at approved doses for acute bacterial skin and skin structure infections. For oritavancin, the values are anticipated in patients receiving a single 1200 mg dose. Since fC_{min} is irrelevant for the single oritavancin dose, an estimate of the free oritavancin concentration at 24 h from this 1200 mg dose was used in place of the fC_{min}.

Std, standard inoculum (~ 5 x 10^5 CFU/mL); High, high inoculum (~ 5 x 10^7 CFU/mL)

The data showed that oritavancin retained bactericidal activity against the tested strains of MSSA, MRSA, and hVISA MRSA when it was tested at a concentration reflecting its anticipated *f*Cmax resulting from a single 1200 mg dose. However, at higher bacterial burden against two VISA strains, the oritavancin MIC increases and reduced killing in time-kill assays were observed.

In another experiment, the Applicant conducted additional time kill study against 14 clinical *S. aureus* isolates (three MSSA, nine MRSA and two methicillin- and vancomycin-resistant *S. aureus*). In this study, no comparators were used. The time-kill assays followed M26-A of the CLSI guidelines. Briefly, and similar to above, oritavancin concentrations were chosen to approximate free peak (*f*Cmax; defined as the peak concentration of non-protein bound drug) and free trough levels (*f*Cmin; defined as the trough concentration of non-protein bound drug) [the estimated concentration at 24 hr for a single dose was used since *f*Cmin is irrelevant] in plasma following administration of a single 1200 milligram (mg) dose. The results of the study showed that ORI MIC and time-kill results against the 14 *S. aureus* strains. MICs ranged from 0.015 to 2 mcg/mL (Table 27).

Table 27: Summary of oritavancin MICs and times to ≥99.9% kill against the 14 *S. aureus* isolates used in the study

Strain	Phenotype	ORI MIC (µg/mL)	Time to ≥99.9% kill at free peak	Time to ≥99.9% kill at free trough
ATCC 13709	MSSA	0.06	15 - 30 min	30 - 60 min
NRS123 (USA400)	MRSA	0.03	5 - 10 min	15 - 30 min
NRS384 (USA300)	MRSA	0.03	10 - 15 min	30 - 60 min
VRS1	MR-VRSA	0.5	4 - 6 h	4 - 6 h
VRS 4	MR-VRSA	0.25	15 - 30 min	15 - 30 min
1561603	hVISA-MRSA	2	15 - 30 min	15 - 30 min
1561723	hVISA-MSSA	1	30 - 60 min	30 - 60 in
T972018	hVISA-MSSA	0.5	5 - 10 min	15 - 30 min
U206056	hVISA-DNS-MRSA	0.25	30 - 60 min	60 - 120 min
V406994	MRSA	0.03	5 - 10 min	15 - 30 min
U052219	MRSA	0.03	5 - 10 min	15 - 30 min
Q670504	MRSA	0.015	5 - 10 min	10 - 15 min
R853168	MRSA	0.03	≤5 min	10 - 15 min
T998629	MRSA	0.5	≤5 min	10 - 15 min

*ATCC, American Type Culture Collection; NARSA, Network on Antimicrobial Resistance in *Staphylococcus aureus*; MSSA, Methicillin-susceptible *Staphylococcus aureus*; MRSA, Methicillin-resistant *Staphylococcus aureus*; hVISA, Heterogeneous vancomycin-intermediate *Staphylococcus aureus*; MR, methicillin-resistant; VRSA, vancomycin-resistant *Staphylococcus aureus;* ORI, oritavancin; VAN, vancomycin; DNS, daptomycin nonsusceptible; min, minutes; h, hours.

Based on the data presented by the Applicant, oritavancin MICs against the tested strains ranged from 0.015 to 2 mcg/mL. Oritavancin was bactericidal against all the tested strains, reaching bactericidal concentrations within ≤5 min and 6 hours when tested at pharmacologically-relevant concentrations.

In another experiment, the Applicant performed time-kill assays against *S. aureus* and enterococci isolates in accordance to methods described by CLSI. Time-kill assays were conducted in the presence of presence of 0.002% polysorbate-80. Against all but VISA strains, oritavancin was rapidly bactericidal: viable cell counts decreased by at least 3 log10 within a period of 15 min to 2 hours (Figures 21-24).

Figure 21 Time-kill curves of free peak and free trough concentrations of oritavancin, vancomycin, teicoplanin, linezolid and daptomycin against *S. aureus* ATCC 29213 (MSSA).

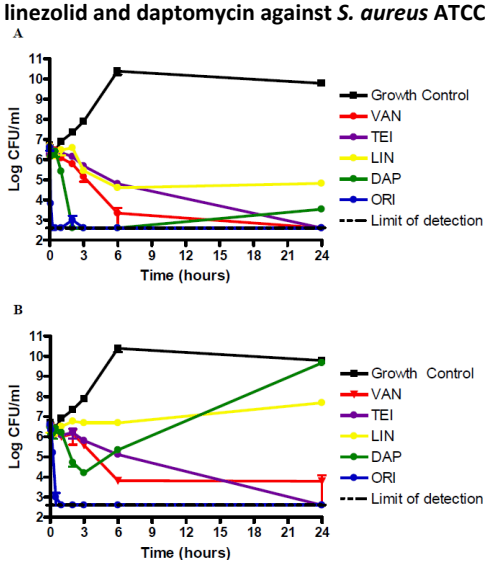


Figure 22 Time-kill curves of free peak and free trough concentrations of oritavancin, vancomycin, teicoplanin, linezolid and daptomycin against *S. aureus* NRS123 (CA-MRSA).

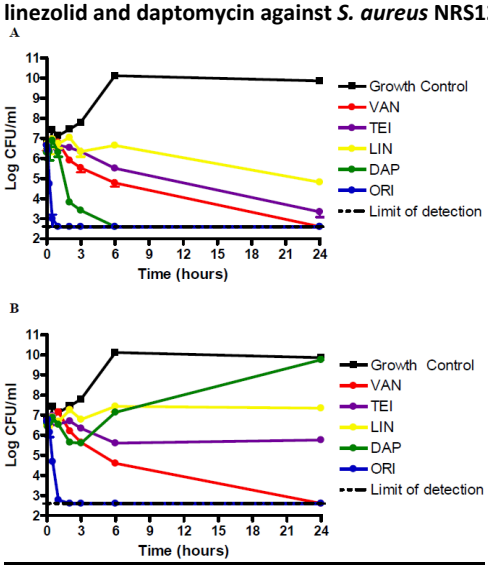


Figure 23 Time-kill curves of free peak and free trough concentrations of oritavancin, vancomycin, teicoplanin, linezolid and daptomycin against linezolid-resistant *S. aureus* NRS121 (MRSA).

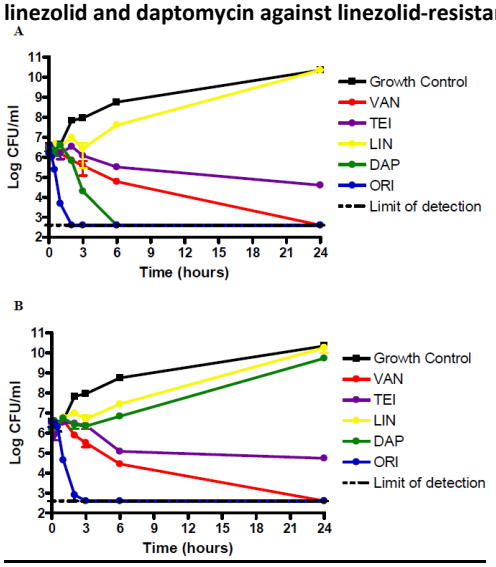
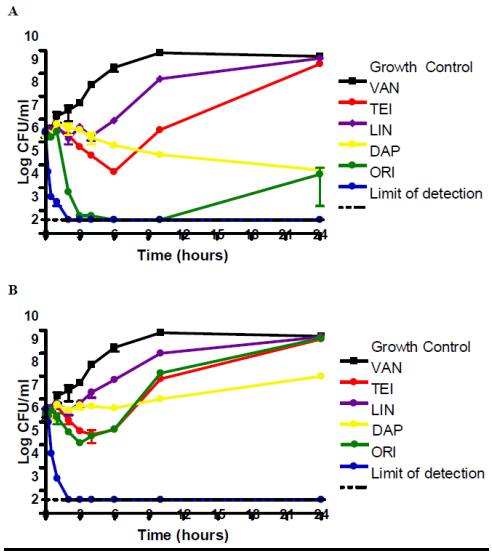


Figure 24 Time-kill curves of free peak and free trough concentrations of oritavancin, vancomycin, teicoplanin, linezolid and daptomycin against vancomycin-resistant *S. aureus* VRS5 (VRSA).



Figures 25- Figures 32 show the time-kill assay for oritavancin against enterococci. Oritavancin was bactericidal (defined as ≥3 log reduction in CFU relative to inoculum at 24 h) at 10 hours against *E. faecalis* ATCC 29212 (VSE) when present at its predicted free peak (fCmax) plasma concentration of 4 mcg/mL while free trough concentrations of oritavancin led to a 1-2 log decrease in viable cell counts at 24 hours.

Figure 25 Time-kill curves of free peak and free trough concentrations of oritavancin, vancomycin, teicoplanin, linezolid and daptomycin against vancomycin-susceptible *E. faecalis* ATCC 29212 (VSE).

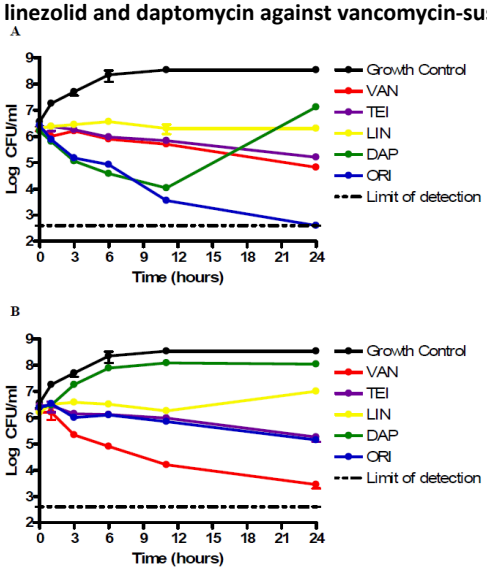


Figure 26 Time-kill curves of predicted free peak concentrations from a 200 mg dose or an 800 mg dose of oritavancin against *E. faecalis* ATCC 29212 (VSE).

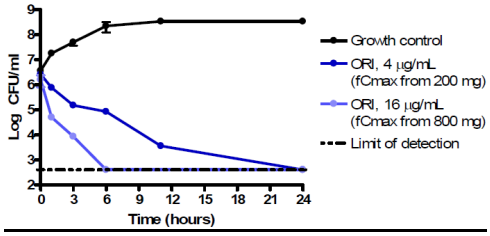


Figure 27 Time-kill curves of free peak and free trough concentrations of oritavancin, vancomycin, teicoplanin, linezolid and daptomycin against VanA expressing vancomycin-resistant *E. faecium* ATCC 51559 (VRE).

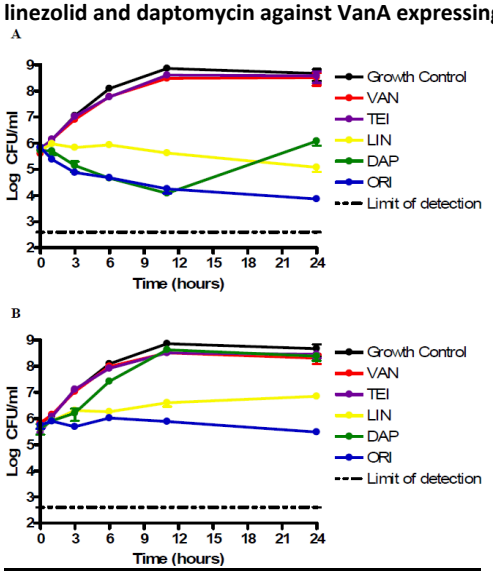


Figure 28 Time-kill curves of free peak and free trough concentrations of oritavancin, vancomycin, teicoplanin, linezolid and daptomycin against VanA expressing vancomycin-resistant *E. faecalis* (VRE).

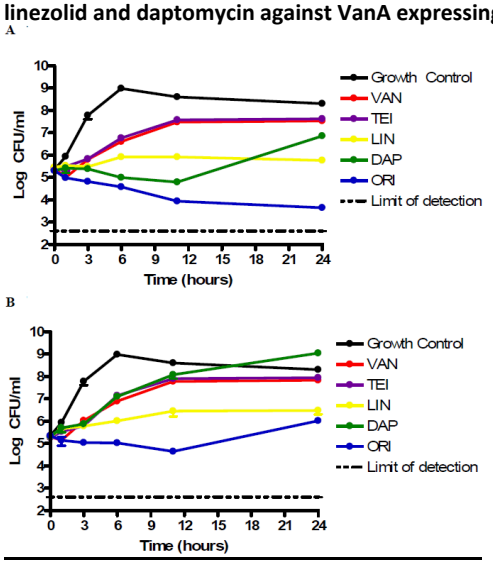


Figure 29 Time-kill curves of free peak and free trough concentrations of oritavancin, vancomycin, teicoplanin, linezolid and daptomycin against VanB expressing vancomycin-resistant *E. faecalis* ATCC 51299 (VRE).

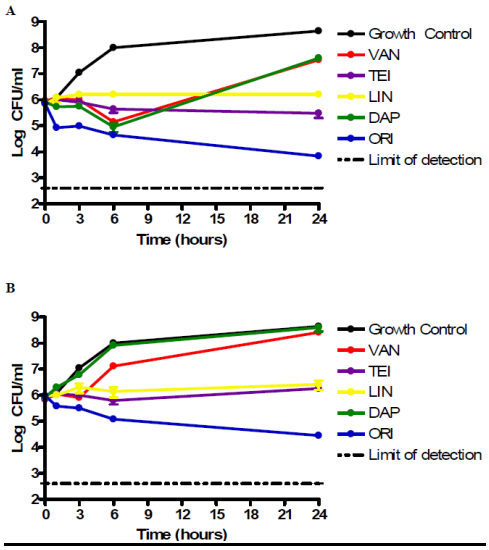
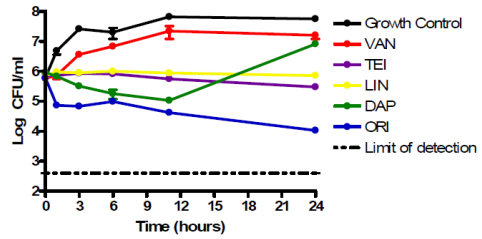


Figure 30 Time-kill curves of free peak and free trough concentrations of oritavancin, vancomycin, teicoplanin, linezolid and daptomycin against VanB expressing vancomycin-resistant *E. faecium* ID1119175 (VRE).

A



B

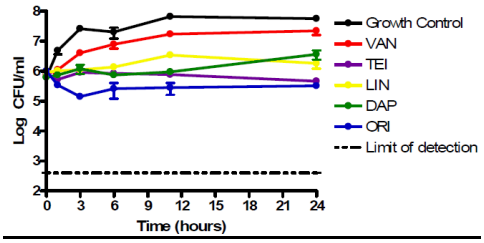
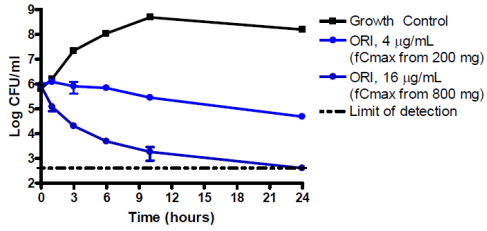


Figure 31 Time-kill curves of predicted free peak concentrations for a 200 mg dose or an 800 mg dose of oritavancin against VanA expressing vancomycin-resistant Enterococcus (VRE).

A



B

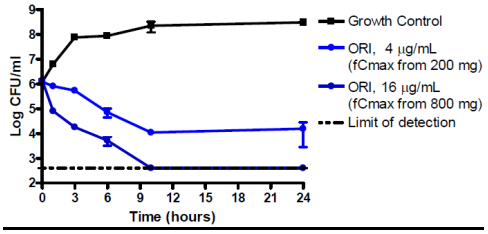
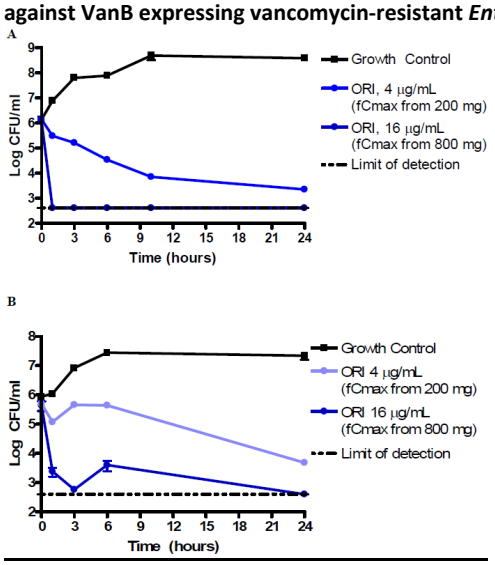


Figure 32 Time-kill curves of predicted free peak concentrations for a 200 mg dose or an 800 mg dose of oritavancin against VanB expressing vancomycin-resistant *Enterococcus* (VRE).

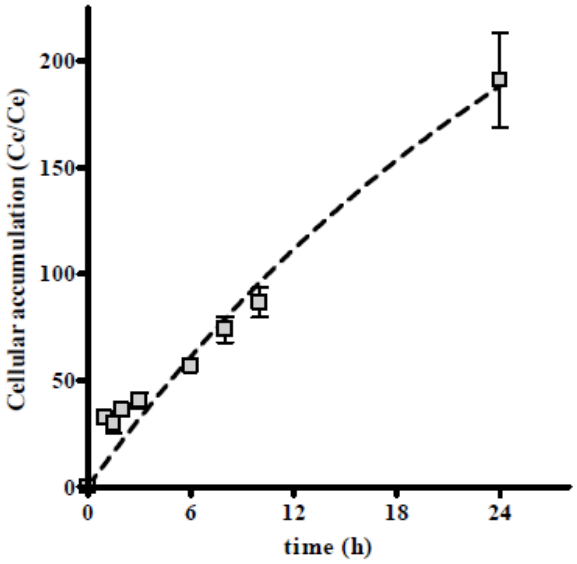


Effect on macrophage killing and intracellular concentration:

The Applicant investigated the impact of oritavancin on macrophage cell lines and its ability to kill *Candida albicans, S. aureus* and A. *baumannii*. Briefly, microbial killing by macrophages in drug-exposed cells was comparatively assessed relative to control, unexposed cells. The test incorporated the use of human HL-60 cells and murine RAW 264.7 macrophage cells. To test macrophage killing, HL-60 cells were cultured at a 200:1 ratio of macrophages to microbes and RAW 264.7 cells were cultured at a 20:1 ratio. After incubation, the tubes were sonicated and quantitatively plated in tryptic soy agar for *S. aureus* and *A. baumannii* or Yeast Extract-Peptone-Dextrose (YPD) agar for *C. albicans*. Colony forming units (CFU) of the co-cultured tubes were compared to CFUs of growth control tubes containing only microbes with no macrophages. Percent killing was calculated as 1 – (CFUs from co-culture tubes / CFUs from growth control tubes).

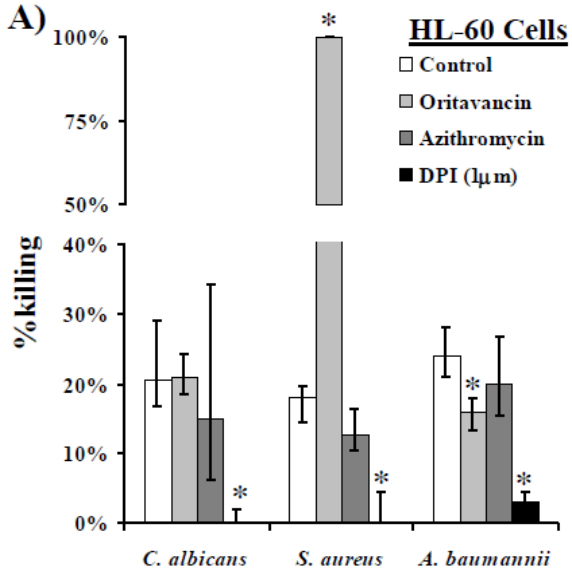
The data showed that oritavancin accumulated substantially in HL-60 cells, reaching intracellular concentrations 200-fold above the extracellular concentrations after 24 hours incubation (Figure 33).

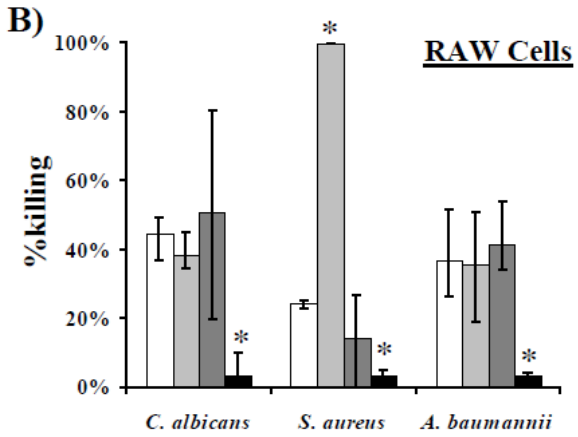
Figure 33: Influence of time on the cellular accumulation of oritavancin in HL-60 cells.



Both HL-60 and RAW 264.7 macrophages killed all three tested pathogens. Macrophage killing of *C. albicans* was not affected by oritavancin, whereas killing of *S. aureus* was substantially enhanced (Figure 34). According to the Applicant's data, the accumulation of oritavancin in macrophages does not appear to be related with the dysfunction of macrophage killing of microbes. Moreover, the accumulation of oritavancin does not appear to prevent phagocytic killing of *S. aureus*.

Figure 34: Macrophage killing of bacterial and fungal pathogens is not inhibited by oritavancin





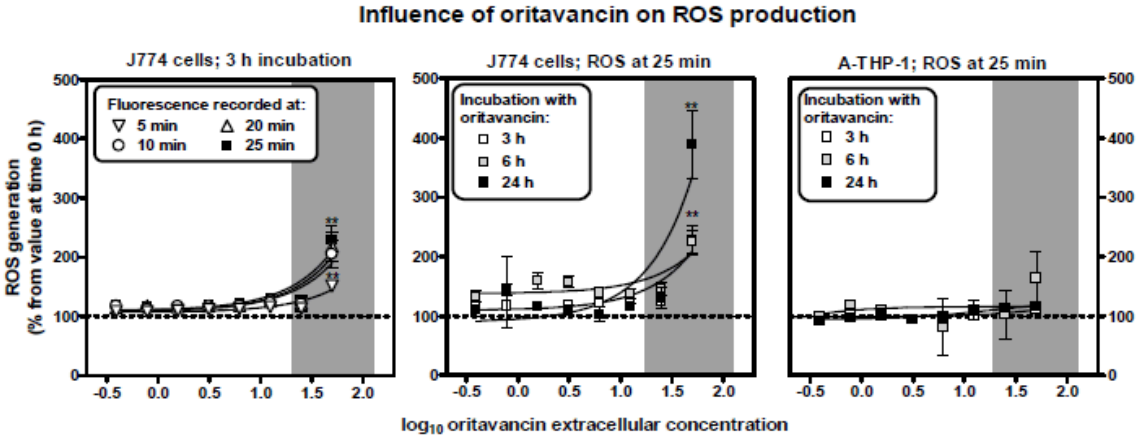
Human HL-60 or mouse RAW 264.7 macrophages were co-cultured with *S. aureus*, *A. baumannii*, or *C. albicans* with or without pre-exposure to oritavancin, azithromycin, or DPI (a superoxide inhibitor). Median and interquartile ranges are shown from 6 to 12 samples each done in duplicate from 2 to 3 separate experiments. *p < 0.05 vs. killing by macrophages without pre-exposure to any substance.

The superoxide inhibitor DPI significantly reduced killing of all three organisms by both HL-60 and RAW 264.7 cells, including compared to oritavancin-preloaded macrophages (Figure 34b).

Influence of oritavancin on ROS production

The Applicant examined the potential influence of oritavancin on the production of reactive oxygen species (ROS) by macrophages (Figure 35). The data in the left panel shows the production of ROS in J774 cells preincubated for 3 hours with oritavancin and then exposed for 5 to 25 minutes to H2O2. Oritavancin caused a concentration-dependent increase of ROS production in cells preexposed to concentrations at ≥ 20 mg/L, which reached a maximum after 10 minutes of incubation with H2O2 (left panel). The middle panel shows ROS production in cells preincubated for 3, 6, or 24 hours to oritavancin and then exposed for 25 minutes to H2O2. Similar effects were observed, however, the amount of ROS produced was higher when cells were preincubated for 24 hours with oritavancin. The right panel shows the result of the same experiment performed with human A-THP-1 cells. In this case, the increase in ROS production induced by oritavancin never reached statistical significance.

Figure 35 Influence of oritavancin on ROS production



The data suggest that oritavancin appear to increase ROS production in the murine J774 cell line but not in human A-THP-1 cell line. The clinical significance of this finding is not known.

Summary and conclusions

Cellular accumulation of oritavancin was first confirmed in HL-60 cells at a fixed extracellular concentration. Oritavancin accumulates substantially in HL-60 cell lines reaching an intracellular concentration of 200-fold higher than the extracellular concentrations following 24 hours incubation. Oritavancin did not affect killing of *C. albicans* but appear to significantly enhanced killing of *S. aureus* by macrophages. The results show that oritavancin appear to reduced killing of *A. baumannii* by HL-60 cells but not by RAW 264.7 cells. Macrophage killing of microbes appears to remain intact despite substantial intracellular accumulation with oritavancin. In short, oritavancin accumulation does not appear to prevent phagocytic killing of *S. aureus*.

EFFECT OF TESTING DYNAMICS ON ORITAVANCIN ACTIVITY

Effect on inoculum density

In another study, the *in vitro* activity of oritavancin and comparators against *S. aureus* strains (Table 28) of different drug resistance phenotypes was determined. The study was designed to evaluate the effect of inoculum density on the in vitro activity of oritavancin and comparators against *S. aureus* strains.

Table 28*: Staphylococcus aureus* strains used in this study

Strain	Phenotype	Comments	Source
ATCC 29213	MSSA, VSSA	QC strain	ATCC
ATCC 43300	MRSA	MRSA Reference strain; clinical isolate	ATCC
ATCC 700699 (Mu 50 or NRS 1)	VISA; DAP NS	VISA Reference strain; clinical isolate	ATCC
NRS 402	VISA; DAP NS	Clinical isolate	NARSA
ATCC 700698 (Mu 3 or NRS 2)	hVISA	hVISA Reference strain; clinical isolate	ATCC
NRS 11	hVISA	Clinical isolate	NARSA
NRS 28	hVISA	Clinical isolate	NARSA

ATCC; American Type Culture Collection; MSSA; Methicillin-susceptible *Staphylococcus aureus*; MRSA, Methicillin-resistant *Staphylococcus aureus*; VSSA, Vancomycin-susceptible *Staphylococcus aureus*; QC, Quality control; VISA, Vancomycin-intermediate *Staphylococcus aureus*; hVISA, heterogeneous Vancomycin-intermediate *Staphylococcus aureus*; NARSA, Network on antimicrobial resistance in *Staphylococcus aureus*; DAP NS, Daptomycin-nonsusceptible

In vitro activities of oritavancin and comparators were tested by broth microdilution and time kill assay under standard conditions using both standard inoculum density of approximately 5 x 10^5 CFU/mL (as per Clinical and Laboratory Standards Institute [CLSI] guidelines) and high inoculum density of approximately 5 x 10^7 colony forming units (CFU)/mL.

Table 29 shows MICs and the fold changes in MIC when oritavancin and comparators were tested in broth microdilution assays at standard versus high inoculum densities. For all tested strains, oritavancin MICs were 16-fold higher at the high inoculum density, relative to values at standard inoculum density. Vancomycin and linezolid MICs increased by 2- to 8-fold against high inoculum density of the tested strains, relative to standard inoculum density. Daptomycin MICs increased 8-fold against MSSA and MRSA at high inoculum density, and 2- to 4-fold against VISA and hVISA strains at high inoculum density, relative to MICs at standard inoculum density.

Table 29: MICs (mcg/mL) and fold increase (Fold Δa) in MICs for *S. aureus* strains when tested at high (~10^7 CFU/mL) and standard (Std., ~10^5 CFU/mL) inocula

	ATCC 43300 (MRSA)			NRS 2 (hVISA)			NRS 11 (hVISA)			NRS 28 (hVISA)			ATCC 29213 (VSSA)			NRS 1 (VISA)			NRS 402 (VISA)		
	Inoculum			Inoculum			Inoculum			Inoculum			Inoculum			Inoculum			Inoculum		
Drug	Std.	High	Fold Δ	Std.	High	Fold Δ	Std.	High	Fold Δ	Std.	High	Fold Δ	Std.	High	Fold Δ	Std.	High	Fold Δ	Std.	High	Fold Δ
ORI	0.06	1	16	0.25	4	16	0.25	4	16	0.25	4	16	0.06	1	16	1	16	16	1	16	16
VAN	1	2	2	1	4	4	1	4	4	1	4	4	1	2	2	8	16	2	4	8	2
DAP	0.5	4	8	1	4	4	2	4	2	1	4	4	0.5	4	8	1	2	2	1	2	2
LZD	2	8	4	2	16	8	2	8	4	2	8	4	2	4	2	0.5	1	4	1	4	4

[a] Fold Δ, ratio of MIC at high inoculum/MIC at standard inoculum; [b] ORI, oritavancin; VAN, vancomycin; DAP, daptomycin, LZD, linezolid

Protein Binding Studies:

Oritavancin is approximately 85% bound to serum protein. There were no significant differences observed in the binding of oritavancin to serum protein between selected species as shown in Table 30.

Table 30: Serum-induced Increases in Broth Microdilution MICs against *S. aureus* ATCC 29213 and Corresponding Protein Binding Estimates for Oritavancin, Ceftriaxone, and Daptomycin

Agent	Human Serum		Mouse Serum		Rat Serum		Dog Serum	
	Mean Fold MIC Increase[a]	% Bound[b]	Mean Fold MIC Increase[a]	% Bound[b]	Mean Fold MIC Increase[a]	% Bound[b]	Mean Fold MIC Increase[a]	% Bound[b]
Oritavancin	5.5	81.9	6.8	85.3	5.7	82.4	7.8	87.1
Ceftriaxone	13.5	92.6	1.6	37.5	1.5	34	1.3	20.9
Daptomycin	5.8	82.9	4.2	76.0	2.9	65.6	3.9	74.5

Source: TT018
[a] Ratio of the mean arithmetic MIC in 95% serum to the mean arithmetic MIC in 95% serum ultrafiltrate.
[b] Calculated from mean MICs using the following formula: percent protein bound = [1- (MIC in ultrafiltrate/MIC in serum)] X 100.

Oritavancin Susceptibility Testing

Susceptibility Test Methods- with and without Polysorbate 80:

MIC and MBC Testing of Oritavancin and Comparators with and without Polysorbate 80

According to the Applicant, it was noted that the in vitro activity of oritavancin varies when tested with and without polysorbate 80 against 301 gram-positive clinical isolates of enterococci, staphylococci, and streptococci collected from the United States and Europe. The MICs for vancomycin and teicoplanin, tested by broth microdilution, were generally unaffected by the addition of 0.002% polysorbate 80, based on MIC90s and MIC ranges. However, the addition of 0.002% polysorbate 80 lowered the oritavancin MIC90s by 16- to 32-fold for enterococci and staphylococci as tested by broth microdilution.

Furthermore, the Applicant noted that oritavancin MIC90 for streptococci did not change in the presence versus absence of 0.002% polysorbate 80. It was also noted that in other studies, polysorbate 80 maintained oritavancin in solution during broth microdilution assays; in its absence, oritavancin is rapidly bound to the surfaces of plastic ware used during MIC testing. Inclusion of polysorbate 80 during broth dilution susceptibility testing should therefore allow for the most accurate representation of the in vitro potency of oritavancin.

In the current study, the Applicant compared the in vitro antibacterial activity of oritavancin in the presence versus absence of 0.002% polysorbate 80 against clinically relevant isolates of staphylococci, enterococci, and streptococci, and (ii) to determine whether the effect of polysorbate 80 additions on *in vitro* susceptibility is specific for oritavancin or shared with other glycopeptides. All broth and agar dilution methods were conducted in accordance with CLSI and in all cases the appropriate quality control strains were used. In assays with P-80, oritavancin and comparator agents were dissolved and diluted in water containing 0.002% P-80 and P-80 was maintained at this concentration throughout all subsequent steps of broth microdilution testing.

Table 31 shows that in the broth dilution MIC testing, vancomycin and teicoplanin MIC values were generally unaffected by the addition of 0.002% P-80. However, the addition of 0.002% P-80 lowered the oritavancin MICs for enterococci and staphylococci tested by broth microdilution.

Table 31 Summary of Oritavancin Activity in vitro by Broth Microdilution Tested with and without 0.002% P-80

			MIC (µg/ml)			
Organism	Agent	Total n	MIC range	MIC mode	MIC_{50}	MIC_{90}
S. aureus	Oritavancin	76	1-8	2	2	4
	Oritavancin/ P-80	76	0.015-0.25	0.03	0.03	0.12
CoNS	Oritavancin	26	0.12-8	2	2	4
	Oritavancin/ P-80	26	0.008-0.5	0.06	0.06	0.25
E. faecalis	Oritavancin	70	0.12-4	2	2	2
	Oritavancin/ P-80	70	0.008-0.5	0.015	0.03	0.12
E. faecium	Oritavancin	30	0.12-4	0.5	1	4
	Oritavancin/ P-80	30	0.004-0.5	0.008, 0.004, 0.12[a]	0.03	0.25
S. agalactiae	Oritavancin	29	0.03-0.5	0.06	0.06	0.25
	Oritavancin/ P-80	29	0.03-0.5	0.06	0.06	0.25
S. pneumoniae	Oritavancin	19	0.00025-0.004	0.002	0.002	0.004
	Oritavancin/ P-80	19	0.0005-0.004	0.002	0.002	0.004
S. pyogenes	Oritavancin	29	0.015-0.5	0.03	0.03	0.25
	Oritavancin/ P-80	29	0.015-0.5	0.03	0.06	0.25
Streptococcus Group C & G	Oritavancin	8	0.004-1	0.008	NA[b]	NA
	Oritavancin/ P-80	8	0.004-1	0.004	NA	NA
Viridans group streptococcus	Oritavancin	14	0.004-2	0.03	0.03	1
	Oritavancin/ P-80	14	0.004-2	0.004	0.03	1

Abbreviations: MIC = minimum inhibitory concentration; CoNS = coagulase-negative staphylococci; P-80 = polysorbate-80
[a]Apparently trimodal
[b]Not applicable for n<10 isolates

The MIC distributions of oritavancin MICs for clinical isolates of *S. aureus* (Figure 36), coagulase-negative staphylococci (Figure 37), and *E. faecalis* (Figure 38) in the presence of P-80 are of approximately 5-7 doubling dilutions as the non- P-80 MICs. Against *E. faecium*, the MICs with P-80 reveal a slightly broadened distribution (Figure 39).

Figure 36 *S. aureus* MIC distribution tested by broth microdilution against oritavancin with and without P-80.

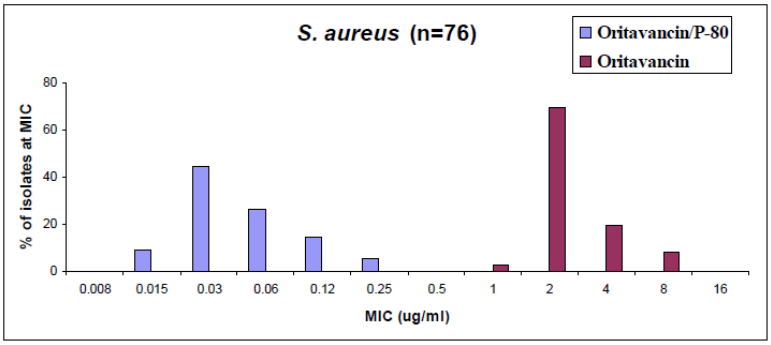


Figure 37 Coagulase-negative staphylococci MIC distribution tested by broth microdilution against oritavancin with and without P-80.

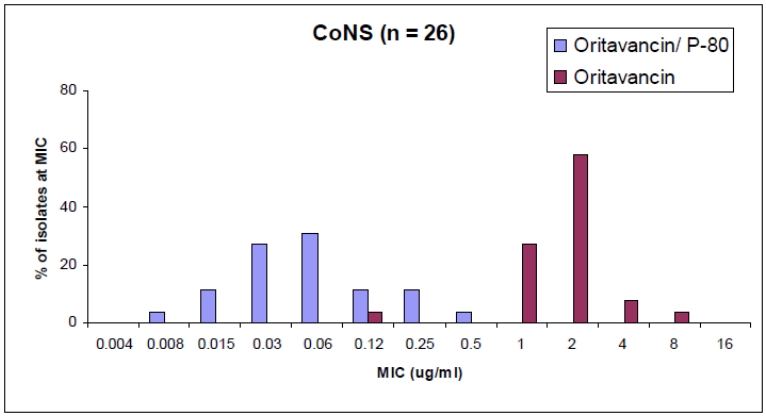


Figure 38 *E. faecalis* MIC distribution tested by broth microdilution against oritavancin with and without P-80.

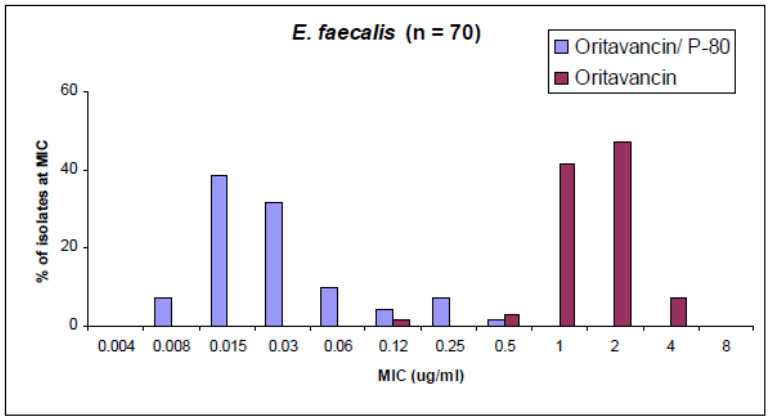
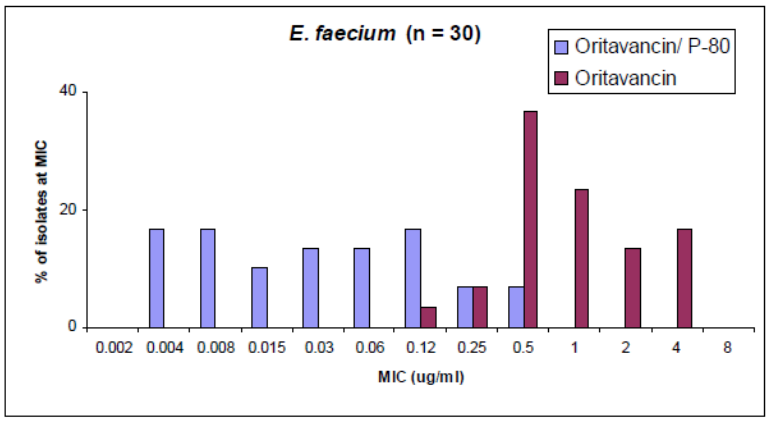


Figure 39 E. faecium **MIC distribution tested by broth microdilution against oritavancin with and without P-80.**



Against streptococci, oritavancin MIC_{90}s and MIC distributions (Figures 40-44) did not change in the presence of P-80 compared with those tested without P-80. The Applicant speculated that this may be due at least in part to the presence of (b) (4) in the testing medium as per CLSI recommendations for propagation of streptococci.

Figure 40 ***S. agalactiae*** **MIC distribution tested by broth microdilution against oritavancin with and without P-80.**

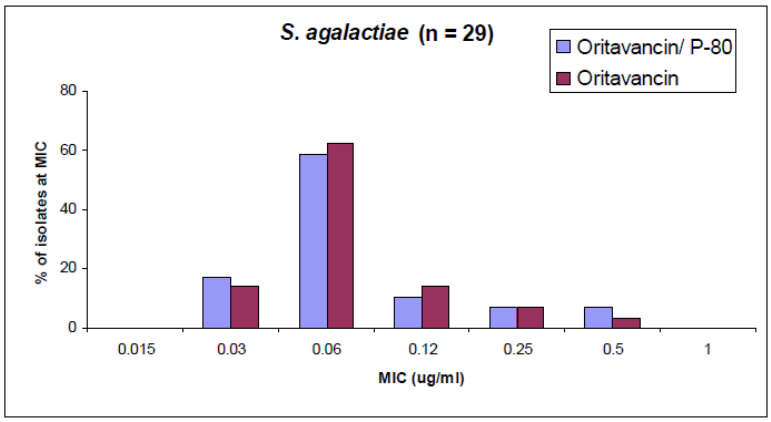


Figure 41 *S. pneumoniae* MIC distribution tested by broth microdilution against oritavancin with and without P-80

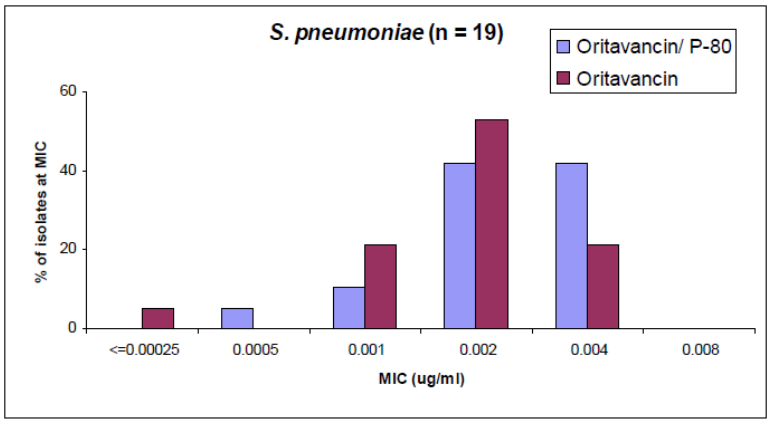


Figure 42 *S. pyogenes* MIC distribution tested by broth microdilution against oritavancin with and without P-80

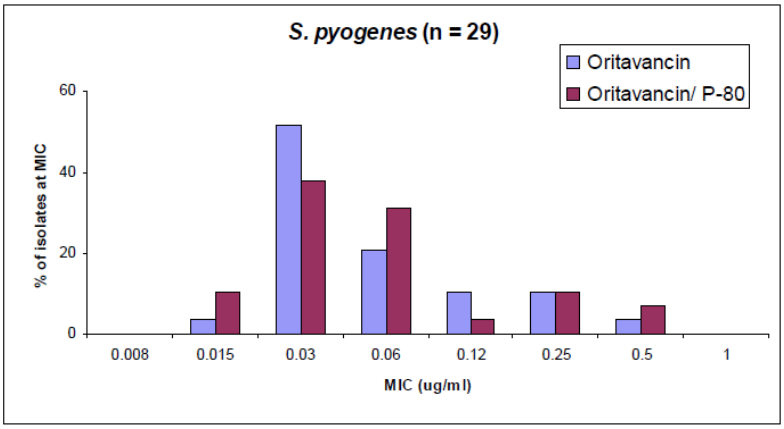


Figure 43 Group C and G streptococci MIC distribution tested by broth microdilution against oritavancin with and without P-80

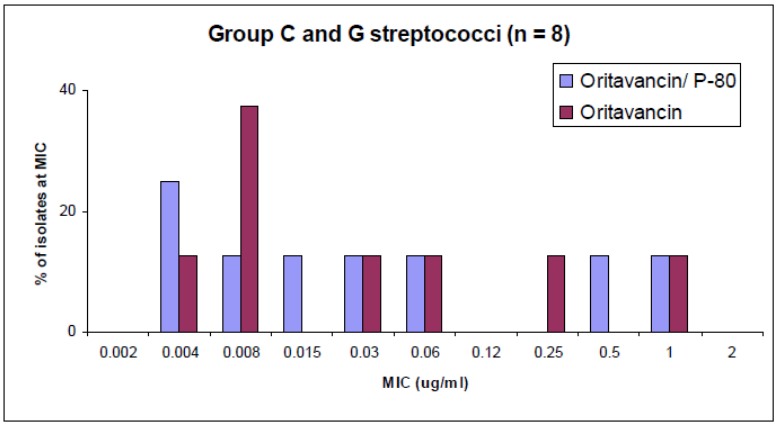
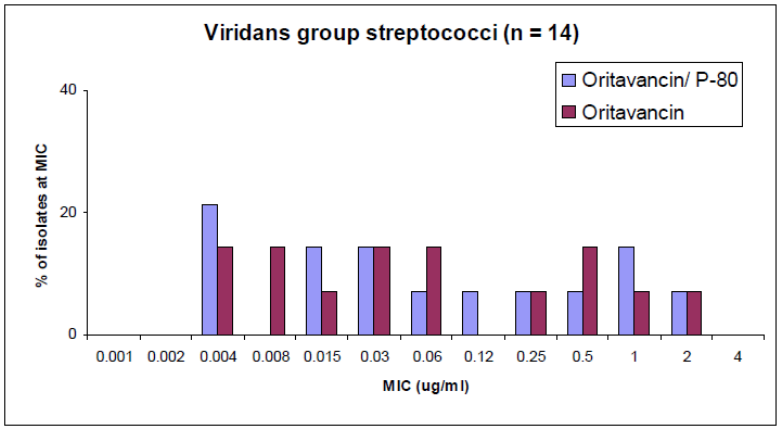


Figure 44 Viridans group streptococci MIC distribution tested by broth microdilution against oritavancin with and without P-80



MBC testing with and without P-80

As shown in Table 31when tested in the presence of 0.002% P-80, seven out of ten isolates of staphylococci and five out of ten isolates of enterococci had MBCs within one doubling dilution of the respective MIC for oritavancin. When tested with 0.002% P-80, all six isolates of streptococci had MBCs equivalent to the MICs for oritavancin. Against clinical isolates of staphylococci, enterococci and streptococci, oritavancin yielded MBCs that were less than or equal to 1, 2, and 0.25 mcg/mL, respectively in the presence of P-80 (Table 5.2). Upper limits of the corresponding vancomycin MBC ranges (without P-80) were 1, >256, and 1 mcg/mL.

Table 31 Comparison of Broth Microdilution MICs and MBCs for Oritavancin and Vancomycin with and without P-80

Genus	Agent	Total n	(µg/mL)							
			MIC range	MBC range	MIC Mode	MBC Mode	MIC_{50}	MBC_{50}	MIC_{90}	MBC_{90}
Staphylococcus	oritavancin	10	1-4	1-4	2	2	2	2	2	2
	oritavancin/P-80	10	0.03-0.06	0.03-1	0.03	0.03	0.03	0.03	0.06	0.25
	vancomycin	10	0.5-1	0.5-1	0.5	0.5, 1	0.5	0.5	1	1
	vancomycin/P-80	10	0.5-1	0.5-1	0.5	0.5	0.5	0.5	1	1
Enterococcus	oritavancin	10	0.25-2	1-8	1, 2	2	1	2	2	8
	oritavancin/P-80	10	0.004-0.12	0.008-2	0.03	2	0.03	0.03	0.06	2
	vancomycin	10	0.5->256	8->256	0.5	16, >256	2	32	256	>256
	vancomycin/P-80	10	0.5->256	4->256	0.5, 1, >256[a]	8, >256	2	16	>256	>256
Streptococcus	oritavancin	6	0.015-0.25	0.03-0.25	NA[b]	NA	NA	NA	NA	NA
	oritavancin/P-80	6	0.015-0.25	0.015-0.25	NA	NA	NA	NA	NA	NA
	vancomycin	6	0.25-0.5	0.25-1	NA	NA	NA	NA	NA	NA
	vancomycin/P-80	6	0.25-0.5	0.25-0.5	NA	NA	NA	NA	NA	NA

Abbreviations: MIC= minimum inhibitory concentration; MBC=minimum bactericidal concentration
[a]Apparently trimodal
[b]Not applicable for n<10 isolates

Agar dilution testing with and without P-80

For oritavancin in the absence of P-80, the MIC mode, MIC50s and MIC90s derived from agar dilution were generally within one dilution of those obtained from broth microdilution in the absence of P-80 (Table 32). In contrast, oritavancin MIC90s with 0.002% P-80 tested by broth microdilution did not correlate with oritavancin MIC90s tested by agar dilution against staphylococci or enterococci, despite the inclusion of P-80 in the agar.

Table 32 Comparison of susceptibility of staphylococci and enterococci to oritavancin with and without P-80 and vancomycin tested by broth microdilution and agar dilution

		Broth microdilution					Agar dilution				
Organism	Agent	Total n	MIC Range	MIC Mode	MIC_{50}	MIC_{90}	Total n	MIC Range	MIC Mode	MIC_{50}	MIC_{90}
S. aureus	oritavancin	76	1-8	2	2	4	76	1-4	2	2	2
	oritavancin/P-80	76	0.015-0.25	0.03	0.03	0.12	11	2-4	2	2	2
	vancomycin	76	0.5-1	0.5	0.5	1	76	0.5-1	1	1	1
CoNS	oritavancin	26	0.12-8	2	2	4	26	0.06-4	4	2	4
	oritavancin/P-80	26	0.008-0.5	0.06	0.06	0.25	3	4-4	4	NA[b]	NA
	vancomycin	26	0.5-2	1	1	1	26	0.5-2	2	1	2
E. faecalis	oritavancin	70	0.12-4	2	2	2	70	0.5-4	0.5	1	1
	oritavancin/P-80	70	0.008-0.5	0.015	0.03	0.12	10	0.25-1	1	1	1
	vancomycin	70	0.12->256	1	1	2	70	0.5->256	1	1	4
E. faecium	oritavancin	30	0.12-4	0.5	1	4	30	0.25-4	1	1	2
	oritavancin/P-80	30	0.004-0.5	0.008, 0.004, 0.12[a]	0.03	0.25	7	0.25-4	1, 4	NA	NA
	vancomycin	30	0.25->256	0.5	128	>256	30	0.5->256	256	128	>256

Abbreviations: MIC= minimum inhibitory concentration; CoNS= coagulase-negative staphylococci
[a]Apparently trimodal
[b]Not applicable for n<10 isolates

Quality control testing with and without P-80

Please note that Tier 1 and Tier 2 quality control parameters were previously conducted and established. Here, the result of the broth microdilution MIC testing under standard (non-P-80) conditions are shown for *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, and *S. pneumoniae* ATCC 49619. The data indicated that they fell within acceptable CLSI M100-S16 standards for vancomycin and teicoplanin (Table 33) (CLSI, 2006b). MIC results for these same organisms tested against oritavancin in the presence of P-80 and they too fell within the CLSI quality control ranges for oritavancin with P-80 (Table 33).

For *S. aureus* ATCC 29213, the oritavancin MICs were 32- to 64-fold lower in the presence of 0.002% P-80 than the MICs tested without P-80 (n=10 replicates; Table 5.4). The oritavancin MICs were 64- to 128-fold lower in the presence of 0.002% P-80 than the MICs tested without P-80 for *E. faecalis* 29212 (n=10, broth microdilution; n=4, agar dilution; Table 33).

For *S. pneumoniae* ATCC 49619, the oritavancin broth microdilution MICs tested in the presence of 0.002% P-80 compared with MICs tested without P-80 were all within one doubling dilution (n=10; Table 5.4). For all ten replicates for each of the three quality

control strains tested, the oritavancin MICs with P-80 fell within the CLSI ranges for oritavancin with P-80 (Table 33). In contrast, the oritavancin MICs for *S. pneumoniae* ATCC 49619 tested in the absence of P-80 f3ll outside the quality control limits.

Table 33 MICs for Oritavancin and Comparators with and without P-80 Tested against Quality Control Strains by Broth Microdilution and Agar Dilution

Organism	Replicate	(µg/ml)				
		Oritavancin Broth MIC	Oritavancin Agar MIC	Oritavancin QC range[c]	Oritavancin/ P-80 Broth MIC	Oritavancin / P-80 QC range[d]
S. aureus ATCC 29213	1	2	2	0.5-2	0.03	0.015-0.12
	2	2	2	0.5-2	0.03	0.015-0.12
	3	2	2	0.5-2	0.03	0.015-0.12
	4	2	2	0.5-2	0.03	0.015-0.12
	5	2	2	0.5-2	0.03	0.015-0.12
	6	2	2	0.5-2	0.03	0.015-0.12
	7	2	2	0.5-2	0.03	0.015-0.12
	8	1	2	0.5-2	0.03	0.015-0.12
	9	2	NT	0.5-2	0.03	0.015-0.12
	10	2	NT	0.5-2	0.03	0.015-0.12
E. faecalis ATCC 29212	1	1	0.5	0.12-1	0.008	0.008-0.03
	2	1	0.5	0.12-1	0.008	0.008-0.03
	3	1	0.5	0.12-1	0.008	0.008-0.03
	5	0.5	0.5	0.12-1	0.008	0.008-0.03
	6	1	NT[a]	0.12-1	0.008	0.008-0.03
	7	1	NT	0.12-1	0.015	0.008-0.03
	8	2[b]	NT	0.12-1	0.015	0.008-0.03
	9	1	NT	0.12-1	0.008	0.008-0.03
	10	1	NT	0.12-1	0.008	0.008-0.03
S. pneumoniae ATCC 49619	1	0.004	NT	0.008-0.06	0.002	0.001-0.004
	2	0.002	NT	0.008-0.06	0.004	0.001-0.004
	3	0.002	NT	0.008-0.06	0.002	0.001-0.004
	4	0.002	NT	0.008-0.06	0.002	0.001-0.004
	5	0.002	NT	0.008-0.06	0.002	0.001-0.004
	6	0.002	NT	0.008-0.06	0.002	0.001-0.004
	7	0.002	NT	0.008-0.06	0.001	0.001-0.004
	8	0.002	NT	0.008-0.06	0.002	0.001-0.004
	9	0.002	NT	0.008-0.06	0.002	0.001-0.004
	10	0.002	NT	0.008-0.06	0.002	0.001-0.004

Abbreviations: MIC= minimum inhibitory concentration
[a]NT=Not tested for that replicate
[b]Gray shading indicates that the agent/organism combination for that replicate fell outside the quality control limit defined by CLSI (without polysorbate-80)
[c]From M100-S16, without polysorbate-80
[d]With polysorbate-80, defined as tentatively appropriate (FDA) and tentatively approved (CLSI), January 2007. Note that for *E. faecalis* ATCC 29212, the CLSI-approved oritavancin QC range (0.008-0.03 µg/mL) is one doubling dilution more restrictive than that from the FDA (0.008-0.06 µg/mL).

Summary of the P-80 susceptibility test methods:

Broth microdilution MIC90s for oritavancin measured in the presence of 0.002% P-80 against clinical isolates of staphylococci (n=102) and enterococci (n=100) were consistently 16- to 32-fold lower than MIC_{90}s determined in the absence of P-80. Against clinical isolates of streptococci (n=99), oritavancin microdilution MICs were unchanged with and without P-80. No correlation was observed for oritavancin broth microdilution MICs tested with P-80 against enterococci and staphylococci compared with oritavancin MICs measured in agar with or without P-80. Oritavancin MICs derived from agar dilution were generally within a doubling dilution of those derived from broth microdilution in the absence of P-80.

Microdilution MICs for oritavancin were consistently lower than MICs for vancomycin or teicoplanin when tested against staphylococci and enterococci, providing oritavancin MICs were measured in the presence of 0.002% P-80. Against streptococci, oritavancin microdilution MICs was comparable to or lowers than those for vancomycin or teicoplanin. In the study, the effect of P-80 was specific to oritavancin since broth microdilution MICs of comparator glycopeptides vancomycin and teicoplanin in the presence of 0.002% P-80 remained generally unchanged or within a doubling dilution of their MIC in its absence. The results presented here demonstrate that the effect of polysorbate 80 addition is specific for oritavancin and does support its inclusion during broth microdilution assays to most accurately represent oritavancin antibacterial activity.

Establishment of Oritavancin Disk Diffusion

Due to the poor diffusion of oritavancin in agar, the Applicant was unable to develop an oritavancin disk diffusion assay for susceptible testing that would agree with CLSI guidelines. (b) (4) No additional information was submitted.

Evaluation of In Vitro Testing Parameters for Oritavancin

Early in the development of oritavancin the Applicant determined the effect of different testing parameters on the in vitro activity of oritavancin. Briefly, test method variations such as inoculum concentration, incubation conditions, media pH, and media cation concentration had minimal effects on the resulting MICs for oritavancin with the exception of increased inoculum size of 10^7 CFU/ml for *E. faecalis, S. pneumoniae* and *S. aureus.* The results of the testing conditions are summarized in Table 34.

In the presence of calcium the MIC against the 3 strains tested remained within one doubling dilution compared with testing done under standard conditions. The data show that decreasing the pH to 5.2 appears to vary MICs by 2-doubling dilution when tested against *S. aureus* ATCC 29213. Likewise, increasing pH to 9.2 resulted in a change in MIC by 2-doubling dilutions. Increasing inoculum size to 10^7 CFU/ml increased the oritavancin MICs by two doubling dilutions for two of three replicates of *E. faecalis* ATCC 29212and by three doubling dilutions for all three replicates of *S. aureus* ATCC 29212. The incubation of the strains in 5% CO_2 did not appear to have an effect on oritavancin MIC compared to control. The 3-months stability study showed that the oritavancin

MICs for *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, and *S. pneumoniae* ATCC 49619 tested after the panels were frozen and stored at –80 °C for three months remained within one doubling dilution compared with the oritavancin MICs obtained under standard conditions.

Table 34 Impact of Testing Parameter Variations on the *In Vitro* Activity of Oritavancin

			MIC (µg/mL)								
Organism	Agent	Replicate	Standard Conditions [a]	48 h Incubation	Calcium (50 µg/mL)	pH 5.2	pH 9.2	Inoculum 10^5 CFU/mL	Inoculum 10^7 CFU/mL	5% CO_2 Incubation	3 month stability
E. faecalis ATCC 29212	ORI	1	0.015	0.015	0.015	0.015	0.015	0.008	**0.06**	0.015	0.015
		2	0.03	0.015	0.015	0.015	0.03	0.015	0.06	0.015	0.015
		3	0.015	0.015	0.015	0.015	**0.03**	0.008	**0.06**	0.015	0.015
	VAN	1	4	4	4	2	8	2	4	4	4
		2	4	4	4	2	**16**	2	4	2	2
		3	4	4	4	2	**16**	2	2	2	2
	TEI	1	0.25	0.25	0.25	0.12	0.25	0.12	0.25	0.25	0.25
		2	0.25	0.25	0.25	0.12	0.25	0.12	0.25	0.25	0.25
		3	0.25	0.25	0.25	0.12	0.25	0.12	0.25	0.25	0.25
S. aureus ATCC 29213	ORI	1	0.03	0.03	0.03	0.06	**0.12**	0.015	**0.25**	0.03	0.03
		2	0.03	0.03	0.03	0.06	0.06	0.015	**0.25**	0.03	0.03
		3	0.03	0.03	0.03	**0.12**	0.03	0.015	**0.25**	0.03	0.03
	VAN	1	1	1	1	1	2	0.5	1	1	2
		2	1	1	1	1	2	1	1	1	1
		3	1	1	1	1	**4**	1	1	1	1
	TEI	1	1	1	0.5	0.5	1	1	1	1	1
		2	1	1	1	0.5	1	0.5	1	1	1
		3	1	1	1	1	1	0.5	1	1	1

Abbreviations: ORI, oritavancin; VAN, vancomycin; TEI, teicoplanin.
[a] Standard Conditions: *S. aureus* and *E. faecalis* were incubated for 18 h and *S. pneumoniae* was incubated for 24 h. The vancomycin MIC was confirmed at 24 h.
[b] NG: no growth observed for any concentration. Additionally, no growth was observed for the growth control well.
[c] Gray shading indicates one doubling dilution difference and **bold** numbers indicate a two- to three doubling dilution difference as compared with standard testing conditions.

			MIC (µg/mL)								
Organism	Agent	Replicate	Standard Conditions [a]	48 h Incubation	Calcium (50 µg/ml)	pH 5.2	pH 9.2	Inoculum 10^5 CFU/ml	Inoculum 10^7 CFU/ml	5% CO_2 Incubation	3 month stability
S. pneumoniae ATCC 49619	ORI	1	0.004	0.004	0.004	NG[b]	NG	0.002	0.008	0.004	0.004
		2	0.004	0.004	0.004	NG	NG	0.002	0.008	0.004	0.004
		3	0.004	0.004	0.004	NG	NG	0.002	0.008	0.004	0.004
	VAN	1	0.25	0.25	0.25	NG	NG	0.25	0.5	0.25	0.25
		2	0.25	0.25	0.25	NG	NG	0.25	0.5	0.25	0.25
		3	0.25	0.5	0.25	NG	NG	0.12	0.5	0.25	0.25
	TEI	1	0.06	0.06	0.06	NG	NG	0.06	0.12	0.06	0.06
		2	0.06	0.06	0.06	NG	NG	0.06	0.12	0.06	0.06
		3	0.06	0.06	0.06	NG	NG	0.03	0.12	0.06	0.06

Abbreviations: ORI, oritavancin; VAN, vancomycin; TEI, teicoplanin.
[a] Standard Conditions: *S. aureus* and *E. faecalis* were incubated for 18 h and *S. pneumoniae* was incubated for 24 h. The vancomycin MIC was confirmed at 24 h.
[b] NG: no growth observed for any concentration. Additionally, no growth was observed for the growth control well.
[c] Gray shading indicates one doubling dilution difference and **bold** numbers indicate a two- to three doubling dilution difference as compared with standard testing conditions.

Susceptibility testing quality control parameters

The Applicant stated that broth microdilution quality control data obtained from the recent surveillance studies were within range. It was stated that 97.9%, 99.5% and 92.6% of MICs for the *S. aureus*, *E. faecalis* and *S. pneumoniae* QC strains, respectively, were within published QC ranges (CLSI 2013) (Table 35). Moreover, it was also indicated that all surveillance studies, MIC results that were out of range were repeated; data on clinical isolates were only accepted when MIC values were within the published QC ranges.

Table 35: Quality Control Data from Recent Surveillance Studies Indicate that Oritavancin Broth Microdilution Methodology Is Robust and Reproducible.

		Oritavancin MIC (µg/mL)*												
QC organism		≤0.0005	0.001	0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2
S. aureus ATCC 29213 (n=373)	n at MIC	0	0	0	0	1	58	174	101	32	6	0	0	1
	% at MIC	0	0	0	0	0.3	15.5	46.6	27.1	8.6	1.6	0	0	0.3
E. faecalis ATCC 29212 (n=213)	n at MIC	0	0	0	1	140	63	9	0	0	0	0	0	0
	% at MIC	0	0	0	0.5	65.7	29.6	4.2	0	0	0	0	0	0
S. pneumoniae ATCC 49619 (n=176)	n at MIC	7	18	107	38	4	1		0	0	0	0	1	0
	% at MIC	4	10.2	60.8	21.6	2.3	0.6	0	0	0	0	0	0.6	0

*Boxed values shaded in grey indicate approved QC ranges for the organism [CLSI, 2013].
Source: Table 1a and Table 1b in12-TMC-02; Table 3.4.1 and Table 3.4.2 in 100948; Table A56 in QBR110399; and MDCO-ORI-M006

In the SOLO I and SOLO II clinical studies, all QC values were within 97.6%, 100% and 98.4% of MICs for the *S. aureus*, *E. faecalis* and *S. pneumoniae* QC strains, respectively, falling within published QC ranges for these organisms (Table 36).

Table 34: Quality Control Data from SOLO I and SOLO II Indicate that Oritavancin Broth Microdilution Methodology Is Robust and Reproducible.

		Oritavancin MIC (µg/mL)*									
QC organism		≤0.0005	0.001	0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25
S. aureus ATCC 29213 (n=165)	n at MIC	0	0	0	1	0	8	49	76	28	3
	% at MIC	0	0	0	0.6	0	4.8	29.7	46.1	17	1.8
E. faecalis ATCC 29212 (n=32)	n at MIC	0	0	0	0	6	12	14	0	0	0
	% at MIC	0	0	0	0	18.8	37.5	43.8	0	0	0
S. pneumoniae ATCC 49619 (n=120)	n at MIC	0	2	95	21	1	0	0	1	0	0
	% at MIC	0	1.7	79.2	17.5	0.8	0	0	0.8	0	0

*Boxed values shaded in grey indicate approved QC ranges for the organism [CLSI, 2013].
Source: (b) (4) Project numbers 57510600001 and 5751060002; data on file.

Final Broth Microdilution Quality Control Ranges for Labeling

A summary of the broth microdilution methodology for oritavancin susceptibility testing of staphylococci, streptococci and enterococci are shown in Table 37. These are quality control (QC) ranges that have been established for testing. A nine-laboratory study (5002-74; CLSI 2008) established oritavancin broth microdilution QC ranges for *S. aureus* ATCC 29213, *S. pneumoniae* ATCC 49619, and *E. faecalis* ATCC 29212. Greater than 95% of replicate oritavancin MIC values were in range for the three QC strains (Table 37).

Table 37: Summary of CLSI Quality Control Ranges for Oritavancin and Vancomycin[a]

	Oritavancin		Vancomycin	
Organism	(with polysorbate-80; µg/mL)	% in range	CLSI range (µg/mL)	% in range
S. aureus ATCC 29213	0.015 - 0.12	95.9	0.5 - 2	100
S. pneumoniae ATCC 49619	0.001 - 0.004	100	0.12 - 0.5	100
E. faecalis ATCC 29212	0.008 - 0.03	96.3	1 - 4	100

Abbreviations: CLSI = Clinical and Laboratory Standards Institute.
[a] Broth microdilution methodology followed M7-A7 guidelines (CLSI 2006); QC ranges appear in CLSI guidance document M100-S23 (CLSI 2013). Oritavancin was dissolved and maintained in 0.002% polysorbate-80 throughout testing (CLSI 2013).
Source: Table 5.1.2 and Table 6.1 in 5002-74.

Postantibiotic Effect of Oritavancin In Vitro in Comparison With Other Agents

The PAE describes the suppression of bacterial growth that occurs after short exposure to an antibiotic. The PAE is a consequence of the initial exposure to high concentrations of antibiotics rather than to persistent sub-inhibitory levels. The subinhibitory MIC effect (SME) is similar to the PAE except that the bacteria are exposed to drug at subinhibitory concentrations. The postantibiotic subinhibitory effect (PA-SME) is similar to a PAE, except that after exposure, the bacteria are further incubated in media containing subinhibitory concentrations of the agent rather than in fresh drug-free media. These effects assess the effect of the agent on bacterial growth during a typical dose interval, where drug concentrations may increase and then decrease to sub-MIC values before subsequent doses.

According to the data presented, five *S. aureus* isolates and three enterococci were selected for PAE studies. Oritavancin and comparators were tested at concentrations (Table 38) approximating their respective free peak (fCmax) concentrations in plasma following normal courses of therapy and taking into account the extent of protein binding of each drug from either their respective package inserts, or, for oritavancin, from published values (86-90% bound to human plasma proteins.

Table 38 Concentrations of Antimicrobial Agents Tested in This Study

Antimicrobial agent	Concentration (µg/mL) representing free peak (fCmax)	Concentration (µg/mL) representing total peak (Cmax)[a]
Oritavancin (200 mg dose)	4	32
Vancomycin	16	64
Teicoplanin	4	32
Daptomycin	4	64
Linezolid	8	16

[a] Provided for reference only

Table 39 shows the result of the PAE study; Oritavancin was found to have a PAE of 2 hour against VISA strain ATCC 700699. The PAE for oritavancin against VRSA (VRS5) was approximately 3.5 hours. The Applicant stated that it was not possible to determine PAEs for oritavancin against MSSA and two of the MRSA strains.

Table 39 PAEa of oritavancin, vancomycin, teicoplanin, linezolid and daptomycin tested against five isolates of *S. aureus*, *E. faecalis* and *E. faecium*

Organism	Oritavancin	Vancomycin	Teicoplanin	Linezolid	Daptomycin
S.aureus ATCC 29213 (MSSA)	ND[b]	-	-	-	-
S. aureus NRS121 (Lin[r] MRSA)	ND[b]	-	-	-	-
S. aureus NRS123 (MRSA)	ND[b]	-	-	-	-
S. aureus ATCC 700699 (VISA)	2	0.25	0	0.25	0.25
S. aureus VRS5 (VRSA)	≥3.5	0.25	0	0.75	0.75
E. faecalis ATCC 29212	≥3.5	0.25	0.5	1.5	0.25
E. faecalis ATCC 51299	≥4	0.5	0.75	0.5	0.5
E. faecium ATCC 51559	≥3	0.25	0.25	1.75	2

Abbreviations: PAE, post antibiotic effect.
[a] PAEs reported are an average of 3 separate experiments. Accompanying figures are for a typical experiment.
[b] Not determined; cultures were sterile following 1 h exposure to oritavancin; PAEs of comparators against these strains were therefore also not determined.

In vitro pharmacokinetics/pharmacodynamics

The objective of this study was to determine the PK associated with free-drug estimates of simulated dosing regimens of a single 1200 dose of oritavancin, once-daily 6 mg/kg daptomycin and 1000 mg vancomycin q12hour against three MRSA isolates over 72 hours. Table 40 shows the susceptibility profiles of the MRSA strains used in the study.

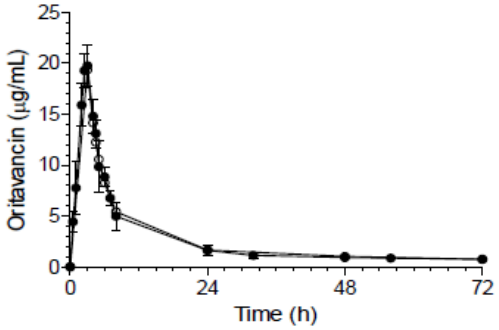
Table 40 Susceptibility profiles of the MRSA strains

Antibacterial agent	MIC (µg/mL)		
	MRSA NRS123	MRSA ATCC 33591	hVISA-MRSA 1561603
Oritavancin	0.12	0.06	0.12-4[a]
Daptomycin	0.5	0.5	1
Vancomycin	1	1	1
Oxacillin	32	128	128

[a] hVISA-MRSA 1561603 exhibited a variable oritavancin broth microdilution MIC ranging from 0.12 to 4 µg/mL.

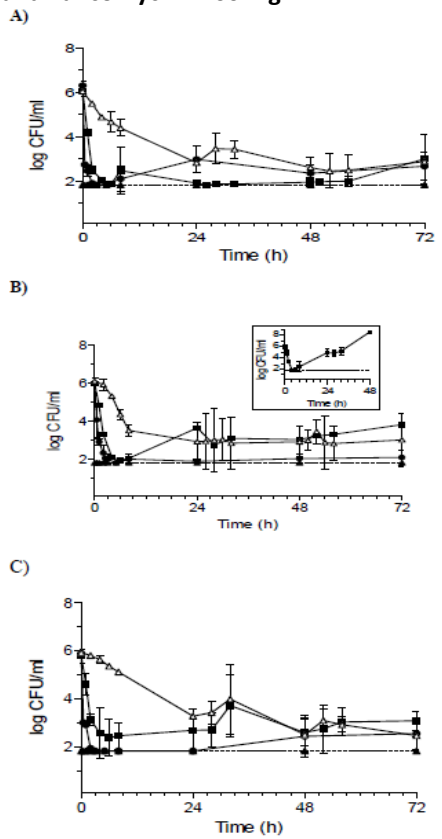
Briefly, Oritavancin was infused at a concentration used in patients (1.2 mg/mL) over 3 hour during. Figure 45 shows the result of a single-dose infusion of oritavancin that approximated the predicted mean drug-free concentration-time profile in patients receiving a single 1200 mg dose exerted rapid bactericidal activity (at least 3 log10 kill relative to inoculum) within the first 2 hour of the 3 hour infusion against the three MRSA isolates.

Figure 45 Mean oritavancin concentration-time profiles for single-dose infusion over 3 hour



Bactericidal activity was sustained over 72 hour against the three tested MRSA strains. The data showed that the bactericidal activity of a single dose of oritavancin provided equal or greater antibacterial effect than either once-daily dosing with daptomycin or twice daily dosing with vancomycin against MRSA in an in vitro PK/PD model over 72 hours (Figure 46).

Figure 46 Pharmacodynamics of simulated dosing regimens of a single dose of oritavancin, daptomycin, and vancomycin 1200 mg



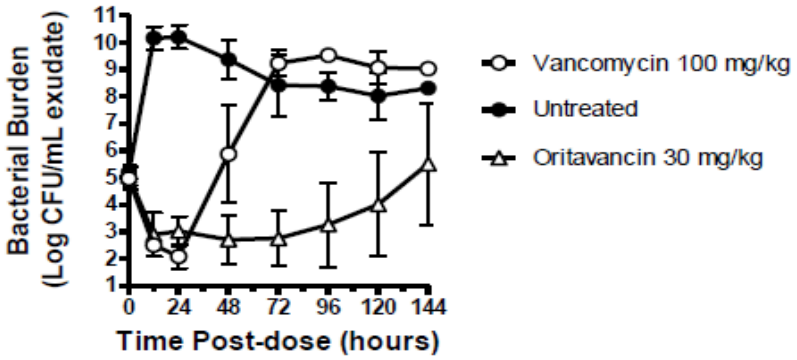
Legend - oritavancin (●), once-daily dosing with 6 mg/kg daptomycin (■) and q12h dosing with 1000 mg vancomycin (▲) against MRSA NRS123

Human and Animal Studies

Granuloma pouch infection model

In this model, granuloma pouches were induced in non-neutropenic rats then inoculated with approximately 10^5 CFU of *S. aureus* ATCC 13709 (oritavancin MIC, 0.06 mcg/mL; vancomycin MIC, 1 mcg/mL). Two hours post-inoculation, treated rats received either single IV doses of oritavancin ranging from 0.25 to 30 mg/kg or a single subcutaneous dose of vancomycin at 100 mg/kg. A single dose of oritavancin at 30 mg/kg delayed regrowth of the infecting *S. aureus* strain for at least 72 hours whereas regrowth began 24 hours after a single dose of vancomycin at 100 mg/kg (Figure 47). This attribute demonstrates that oritavancin efficacy in vivo is sustained for at least 72 hours, under these experimental conditions, following administration of a single IV dose.

Figure 47: Oritavancin Activity is Long-Lived (Rat Granuloma Pouch Infection Model with *S. aureus* ATCC 13709)



Source: adapted from TT012

Bacteremia Models

The efficacy of oritavancin in treating bloodstream infection (against MSSA bacteremia in mice and against both *S. aureus* and VanA *E. faecium* central venous catheter (CVC) infection in rats) was investigated.

Briefly, a bacteremia model was established in normal mice by intraperitoneal injection of 10^7 CFU of *S. aureus.* One hour after infection, mice were treated IV with oritavancin simulating human doses of 100, 400, and 800 mg daily for 3 days or a single dose of 1200 mg. The level of *S. aureus* in blood was approximately 4.8 log10 CFU/mL initially and it increased rapidly in untreated mice, resulting in death by 24 hours. The 100-mg daily human equivalent dose of oritavancin reduced the bacterial burden in blood by 1.7 log10 by 72 hours, whereas the other doses reduced the bacterial burden to the limit of detection or by approximately 2.8 log10.

In the rat CVC infection model, catheters were inserted into the jugular veins and rats were inoculated via the catheter with 10^5 CFU of *S. aureus*. Twenty-four hours after inoculation, groups of 10 animals received IV doses of oritavancin at either 2.5 mg/kg every 12 hours, 5 mg/kg every 24 hours, 10 mg/kg every 48 hours, or 20 mg/kg every 96 hours. The total dose for all animal cohorts was 20 mg/kg over 96 hours. Seven days later, quantitative culturing of blood and catheter demonstrated that higher doses administered less frequently were more effective than lower doses administered more frequently since bacterial counts were reduced most significantly in 20 mg/kg dose group. The dose fractionation design demonstrated that oritavancin C_{max}: MIC and AUC_{0-24}: MIC ratios are the PK-PD indices most closely associated with efficacy, thereby supporting the rationale to administer oritavancin infrequently or as a single dose to optimize its activity against invasive *S. aureus* infections.

In another experiment, oritavancin was shown to demonstrate activity against *E. faecium* in vivo, as was evaluated in a similar CVC-associated bacteremia model to that described for *S. aureus.* Twenty-four hours after inoculation, groups of eight animals received a single 20 mg/kg oritavancin IV dose via the CVC. Seven days later, quantitative culturing of blood and catheter revealed that of the oritavancin-treated animals, only one animal developed CVC infection. In this animal, *E. faecium* was cultured (625 CFU) from the CVC, but not from any tissue. In the control group, six of eight animals were bacteremic and all had metastatic disease compared with none of the oritavancin-treated group ($p<0.01$).

Endocarditis Models

The efficacy of oritavancin against *S. aureus*, whether MSSA or, MRSA, and *E. faecalis*, whether VSE, VanA VRE or VanB VRE, in left-sided models of endocarditis was investigated in rabbits and rats.

In a rabbit endocarditis model, MRSA infection was established by placing a catheter across the aortic value, followed in 3 days by an inoculum of 10^6 CFUs; 16 hours later, animals were treated for 4 days with oritavancin at 25 mg/kg every 24 hours or with vancomycin at 25 mg/kg every 8 hours. Oritavancin and vancomycin each reduced the bacterial burden in the vegetations by approximately 6 log10 CFU and in the kidney and spleen by more than 4 log10 CFU.

In the rat endocarditis model, MSSA infection was established with a catheter that was passed across the aortic value and infected with an inoculum of 10^6 CFU 7 days later. Fourteen hours after infection, rats were treated for 4 days with oritavancin at 80 mg/kg daily, vancomycin at 120 mg/kg every 12 hours, daptomycin at 10 mg/kg daily, and oxacillin at 200 mg/kg every 8 hours. Oritavancin was similar in efficacy to daptomycin

and oxacillin, resulting in a 5 log10 reduction in CFUs in the vegetation from untreated controls at Day 5 whereas vancomycin showed a 3 log10 decrease in CFUs from controls. All antibacterial agents were equally effective in reducing CFUs in the kidney and spleen by 2.5 to 3.5 log10 CFU at Day 5. Oritavancin-treated rats had the lowest density of MSSA in vegetations, kidney and spleen compared to all other regimens at 3 days after the end of therapy.

In another rabbit endocarditis model with glycopeptide-susceptible *E. faecalis* and glycopeptide resistant *E. faecalis* strains with VanA or VanB phenotypes, oritavancin reduced the bacterial density of vegetations (1.8 to 2.8 reduction log10 CFU/g of vegetation compared to control animals after 5 days of therapy) and its activity was not affected by strain phenotype (p=0.45).

In a synergistic VRE rabbit endocarditis model, oritavancin was shown to be synergistic with gentamicin. In this in vivo model oritavancin alone at 20 mg/kg once daily had limited activity (mean bacterial counts in vegetations after 5 days of treatment, 7.9 to 8.1 log10 CFU/g) whereas the oritavancin-gentamicin combination was active against all three tested strains (glycopeptide-susceptible *E. faecalis* and glycopeptide-resistant strains with VanA or VanB phenotypes; 6.1 to 6.8 log10 CFU/g). Compared with bacterial counts in control animals at the end of therapy, the differences were statistically significant for the glycopeptide-susceptible strain and the VanA strain ($p<0.05$), but not the VanB strain (p=0.06).

Pneumonia infection model

The efficacy of oritavancin in a mouse and rat pneumonia model caused by S. pneumoniae and MRSA was investigated. Briefly, in a non-neutropenic mouse model of pneumococcal pneumonia, mice were infected with approximately 10^6 CFU per thigh of penicillin-susceptible *S. pneumoniae* (oritavancin MIC, 0.002 mcg/mL). Groups of 10 mice received single IV doses of 0.25 to 32 mg/kg of oritavancin 1 hour post-infection. These doses were also administered to groups of 5 mice as two, three and four fractionated doses, twice, three times, and four times daily, respectively. At 24 hours post-infection, bacterial counts in lungs of mice that received ≥6.5 mg/kg oritavancin were reduced to the limit of detection. Oritavancin plasma free-drug AUC_{0-24}:MIC (r^2 = 0.92) and C_{max}:MIC (r^2 = 0.89) ratios were the PK-PD indices that best correlated with efficacy.

In a rat model of MRSA pneumonia, oritavancin at 50 mg/kg/day for 6 days reduced the bacterial burden in lungs by 3.5 log10 CFU/lungs compared to the beginning of treatment. The comparators, daptomycin and vancomycin (at 50 and 100 mg/kg/day, respectively, for 6 days), but not nafcillin treatment (150 mg/kg twice daily for 6 days),

were efficacious in the model as judged by statistically significant reductions in bacterial burden relative to the untreated control.

Please note that in the rat MRSA pneumoniae mode, oritavancin MICs increase by approximately 16- to 32-fold in the presence of lung surfactant preparation in vitro. Oritavancin exposure may be limiting for reliable utility against *S. aureus* pneumonia, possibly due to partial inactivation in the presence of lung surfactant; a phenomenon that has been noted for daptomycin.

Biofilm Infection Model

In a mouse model of *S. aureus* biofilm infection, a segment of catheter pre-colonized with 10^5 CFU of MSSA (oritavancin MIC, 0.03 mcg/mL) per catheter was implanted subcutaneously in mice. At 7 days post-infection, animals received either: (1) no therapy (control); (2) oritavancin 80 mg/kg, iv, once daily; (3) vancomycin 120 mg/kg, subcutaneous, bid; (4) daptomycin 10 mg/kg, iv, once daily; or (5) oxacillin 200 mg/kg, intramuscular, tid; all treatments were for 4 days. Potential relapse of infection was also investigated 2 weeks after treatment was discontinued (Table 42).

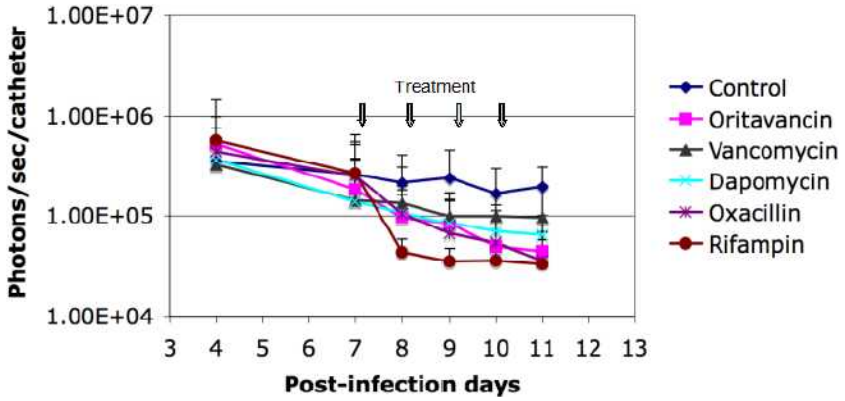
Table 42: *S. aureus* density in catheters in mouse biofilm infection model

Group (no. animal)	Dose	*S. aureus* densities in catheters (log_{10}cfu/catheter)	
TREATMENT			
Control (9)		5.58 ± 0.55	
Oritavancin (7)	80 mg/kg, iv, once daily	3.57 ± 0.52 (*P*=0.000004)	*P*=0.007
Vancomycin (7)	120 mg/kg, subQ, bid	5.37 ± 1.21 (*P*=0.68)	
Daptomycin (7)	10 mg/kg, iv, once daily	4.70 ± 2.01 (*P*=0.30)	
Oxacillin (9)	200 mg/kg, im, tid	3.71 ± 1.08 (*P*=0.0006)	
Rifampin	30 mg/kg, ip, bid	2.83 ± 0.46 (*P*=0.0000004)	
RELAPSE			
Control (9)		6.23 ± 0.59	
Oritavancin (7)	80 mg/kg, iv, once daily	4.91 ± 1.26 (*P*=0.03)	
Vancomycin (7)	120 mg/kg, subQ, bid	5.92 ± 0.99 (*P*=0.53)	
Daptomycin (7)	10 mg/kg, iv, once daily	5.52 ± 0.89 (*P*=0.13)	
Oxacillin (9)	200 mg/kg, im, tid	5.73 ± 0.92 (*P*=0.23)	
Rifampin	30 mg/kg, ip, bid	3.19 ± 0.73 (*P*=0.000002)	

P values vs. untreated control.

Real-time bioluminescence monitoring of *S. aureus* showed that oritavancin and oxacillin significantly ($p<0.05$) decreased *S. aureus* densities in catheters as compared to untreated controls. However, only oritavancin-treated animals had significantly lower *S. aureus* densities on catheters vs. vancomycin-treated animals (Figure 48).

Figure 48: Real-time bioluminescence monitoring of S. aureus in the mouse model of biofilm infection during treatment.



Meningitis model

In two experiments, the Applicant investigated the efficacy of oritavancin in a rabbit model of pneumococcal meningitis. Briefly, in the first experiment, meningitis was induced by intracisternal (cerebellomedullary cistern) injection of 10^6 CFU of penicillin-susceptible *S. pneumoniae*. Twelve hours after inoculation, rabbits received a single IV dose of oritavancin at 1, 2.5, 10, or 40 mg/kg. Cerebrospinal fluid specimens were drawn for CFU determination and for markers of inflammation at 12, 14, 17, 20, and 24 hours post inoculation. Ceftriaxone (20 mg/kg bolus, followed by 10 mg/kg/hour continuous IV infusion) was used as a comparator. Oritavancin at 40 mg/kg decreased the bacterial burden by 0.51 ± 0.54 log10 CFU/mL CSF compared to 0.34 ± 0.15 log CFU/mL CSF by ceftriaxone. The oritavancin results didn't appear to be significantly more superior to the comparator.

In another experiment oritavancin efficacy against cephalosporin-resistant pneumococcal meningitis in rabbits was investigated. Oritavancin (10 mg/kg/day) was administered intravenously alone and in combination with ceftriaxone (100 mg/kg/day) with or without dexamethasone (0.25 mg/day). The reduction in bacterial density was similar (approximately 3.0 to 5.2 log CFU/mL compared to untreated animals) for all cohorts by 6 hours.

Inhalational Anthrax Models

The administration of a single dose of oritavancin was investigated in the mouse aerosol model of *B. anthracis* infection. Three exposure conditions were investigated: (i) post-exposure prophylaxis, (ii) post-exposure treatment, and (iii) pre-exposure prophylaxis.

(i) Post-exposure Prophylaxis

Single IV doses of oritavancin at 15 or 50 mg/kg administered 24 hours after exposure to *B. anthracis* Ames spores protected 70% and 100% of lethally-challenged mice, respectively. The proportional survival provided by ciprofloxacin was similar (90% survival) but required twice daily ciprofloxacin dosing at 30 mg/kg for a duration of 14 days.

(ii) Post-exposure Treatment
In a model of delayed treatment, a single 50 mg/kg IV dose of oritavancin given 42 hours post-exposure protected 56% of lethally-challenged mice. The single dose oritavancin offered protection compared to untreated animals. By comparison, 14 days of twice-daily ciprofloxacin dosing provided 70 to 80% survival following delay of treatment to 36 or 48 hours post-exposure.

(iii) Pre-exposure Prophylaxis
Oritavancin, when administered as a single IV dose of 50 mg/kg either 24 hours or 7 days prior to spore challenge, protected 90% of mice to the 34 day post-challenge endpoint. Ciprofloxacin, when administered either as a single 30 mg/kg IP dose 24 hours before spore challenge or as two 30 mg/kg IP doses, 24 hours and 12 hours before spore challenge appeared ineffective since all mice died from infection by day 4 post exposure. The duration of prophylaxis was further tested by extending the delay between drug administration and lethal challenge. In mice receiving a 50 mg/kg single IV dose, oritavancin prophylactic activity extended to 14 days pre-exposure (100% survival at 22 days post-exposure) and declined when oritavancin was administered 28 days before exposure (20% survival at 22 days post-exposure).

Pharmacokinetic/Pharmacodynamic

Pharmacokinetic-Pharmacodynamic Target Attainment Analyses

According to the data presented by the Applicant, the AUC/MIC has been shown to be the predictor of efficacy in both in vitro and in vivo systems. The probability of PK-PD target arraignment by oritavancin MIC was evaluated using non-clinical AUC/MIC targets for stasis. For oritavancin, the probabilities of PK-PD target attainment by MIC represented the percentage of 5,000 simulated patients with average AUC_{0-}72:MIC ratios at or above the non-clinical target. In addition, probabilities of PK-PD target attainment for the 1 log10 kill target were also determined.

The overall probability of PK-PD target attainment for *S. aureus* considering the oritavancin MIC distribution from surveillance was 99.8% for stasis and 99.6% for 1 log10 kill (Table 42). For *S. pyogenes*, the probability of PK-PD target attainment, whether for stasis or 1 log kill, was 100% at oritavancin MICs up to and including 0.5

mcg/mL as assessed by Monte Carlo simulation.

Table 42: Probability of PK-PD Target Attainment (%) by Oritavancin MIC, and Overall Probability of PK-PD Target Attainment (%), for Nonclinical PKPD Targets against *S. aureus* and *S. pyogenes*

	S. aureus		*S. pyogenes*	
Oritavancin MIC (µg/mL)	**Stasis**	**1-$\log_{10}$ CFU reduction**	**Stasis**	**1-$\log_{10}$ CFU reduction**
0.06	100	100	100	100
0.12	99.8	99.4	100	100
0.25	85.1	74.8	100	100
0.5	20	10	100	100
Overall*	**99.8**	**99.6**	**100**	**100**

*Represents the overall (ie, weighted average) probability of PK-PD target attainment over the oritavancin MIC distribution (12-TMC-02)
Source: ICPD 00247-2

Figure 49 shows the probability of nonclinical PK-PD target attainment by oritavancin MIC are overlaid onto the oritavancin MIC distribution for *S. aureus.* The percent probabilities of PK-PD target attainment by MIC for *S. pyogenes* are shown in Figure 49. The percent probability of PK-PD target attainment by MIC was 100% up to the highest MIC evaluated, 0.5 mg/L, for AUC_{0-72}:MIC ratio targets associated with both net bacterial stasis and a 1-log10 CFU reduction from baseline.

Figure 49: Probability of PK-PD target attainment by oritavancin MIC against *S. aureus* for nonclinical targets, overlaid on the oritavancin MIC distribution against *S. aureus* from surveillance data

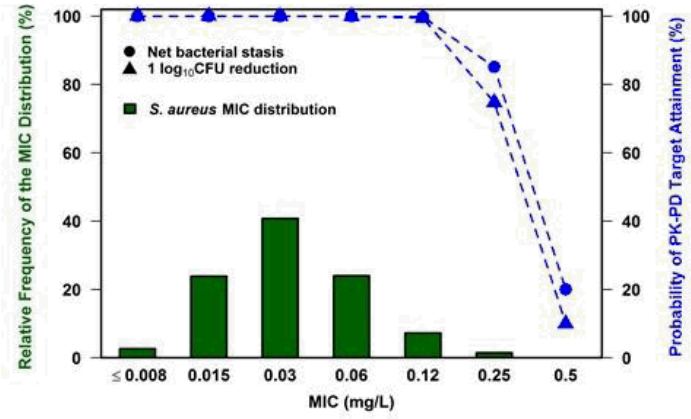
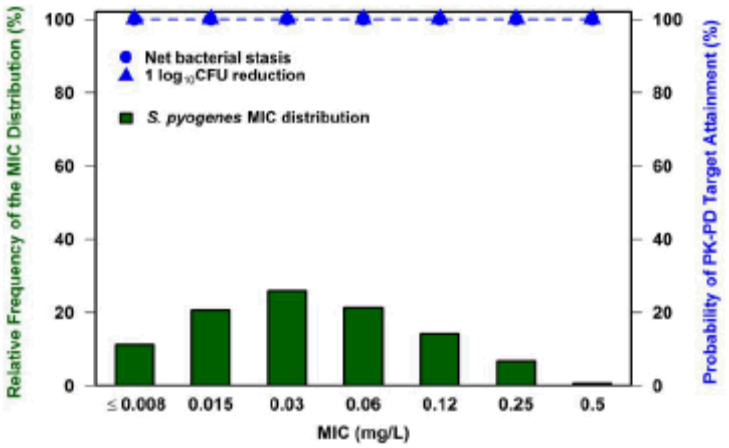


Figure 50. Percent probabilities of PK-PD target attainment by MIC for *S. pyogenes* based on a non-clinical PK-PD relationship



The percent probabilities of PK-PD target attainment based on non-clinical AUC_{0-72}:MIC ratio targets for both net bacterial stasis and a 1-log10 CFU reduction from baseline were ≥ 99.6% for both *S. aureus* and *S. pyogenes*. Moreover, the result of the PK-PD target attainment data predict clinical responses and appear to support susceptibility breakpoints of 0.12 mcg/ml for *S. aureus* and 0.5 mcg/ml for *S. pyogenes* and provides support for a single oritavancin dose of 1200 mg.

SOLO I/SOLO II PHASE 3 CLINICAL TRIALS

SOLO I and SOLO II studies:

The applicant performed two multicenter, double-blind, randomized study to evaluate the efficacy and safety of single-dose intravenous (IV) oritavancin verses IV vancomycin for the treatment of patients with acute bacterial skin and skin structure infections (SOLO I/SOLO II). The primary objectives was to establish non-inferiority of single-dose IV oritavancin compared with IV vancomycin given for 7 to 10 days using the primary efficacy outcome defined as the cessation of spread or reduction in size of the baseline lesion, absence of fever, and no rescue antibiotic medication at the Early Clinical Evaluation (ECE) time-point of 48 to 72 hours in the modified intent-to-treat (mITT) population.

The secondary objectives are as follows:

- To evaluate the clinical response (clinical cure) associated with single dose IV oritavancin compared with IV vancomycin for 7 to 10 days at the End of Therapy (EOT) timepoint and sustained to Day 10 and the post therapy evaluation (PTE) timepoint in the mITT population
- To evaluate the clinical response for the primary efficacy outcome in the

clinically evaluable (CE) population

- To evaluate the clinical response (clinical cure) of treatment with single dose IV oritavancin compared with IV vancomycin for 7 to 10 days at the EOT visit and sustained to Day 10 and the PTE visit in the CE population
- To evaluate the efficacy of single dose IV oritavancin in terms of clinical response (cessation of spread or reduction in size of the baseline lesion, absence of fever, no rescue antibiotic medication, and clinical cure) endpoints by pathogen, compared with vancomycin treatment in the microbiologically intent-to-treat (MicroITT) and microbiologically evaluable (MicroE) populations
- To evaluate the microbiological response, overall and by pathogen, of oritavancin compared with vancomycin treatment in the MicroITT and MicroE populations
- To evaluate the incidence of microbiological relapse or recurrence rates at the PTE visit in the MicroITT and MicroE populations
- To evaluate the clinical response (clinical cure) and microbiological response in patients in the CE and MicroITT populations meeting systemic inflammatory response syndrome criteria at Screening (defined as two of the following: temperature > 38°C, pulse > 90 beats per minute, respiratory rate > 20 breaths per minute, white blood cell count > 12,000 cells/mcL or < 4,000 cells/mcL or > 10%
  bandemia), or with positive blood cultures
- To compare the safety and tolerability of a single IV dose of oritavancin with vancomycin IV dosed for 7 to 10 days
- To examine population pharmacokinetics (PK) and PK/pharmacodynamics (PD) of the oritavancin 1200 mg dose in the PK population

Approximately 1920 patients (960 patients per study) with ABSSSI caused by a gram-positive pathogen were enrolled. ABSSSI included wound infections that were either traumatic or surgical in origin, cellulitis/erysipelas, and major cutaneous abscesses (an enrollment cap of 30% was maintained for major cutaneous abscesses).

Diagnosis and main criteria for inclusion:
The study included patients at least 18 years old with an ABSSSI with a minimum surface area of 75.0 cm^2, suspected or known to be caused by a Gram-positive pathogen requiring at least 7 days of IV therapy. ABSSSI included traumatic and surgical wound infections (onset within 7 days prior to randomization and no later than 30 days following the trauma or surgical procedure); cellulitis/erysipelas (onset within 7 days prior to randomization); and major cutaneous abscesses. Inclusion also required the presence of signs and symptoms of systemic inflammation.

NDA 206334 DATE REVIEW COMPLETED: May 5th, 2014.
Oritavancin/Orbactiv

Test product, dose and mode of administration, batch number:
Oritavancin diphosphate (oritavancin) 1200 mg in mannitol, IV On Day 1, patients randomized to oritavancin/placebo were administered Dose 1, a single 1200 mg IV infusion of oritavancin in 1000 mL 5% dextrose in water (D5W) given over 3 hours. Beginning with Dose 2, placebo infusions were administered to maintain the study blind relative to the active vancomycin treatment group. Starting with Dose 2 and for all subsequent doses of placebo, infusion time was a minimum of 60 minutes.
Dosing was every 12 hours.
The lots of oritavancin used in this study were lot 2042806 and lot 2108927.

Duration of treatment:
Oritavancin: Single dose followed by placebo infusions every 12 hours for 7 to 10 days.
Vancomycin: Twice daily administration for 7 to 10 days

Reference therapy, dose and mode of administration, batch number:
Vancomycin hydrochloride, USP (vancomycin) IV Vancomycin was administered for 7 to 10 days. On Day 1, vancomycin was administered as either a 1 g dose or at 15 mg/kg every 12 hours. After Day 1, the vancomycin dose could be adjusted by the unblinded pharmacist/designee based upon creatinine clearance levels, the patient's clinical status, and/or vancomycin trough levels. Vancomycin trough plasma concentrations were determined and the dose adjusted according to the local standard of care. The first dose of vancomycin on Day 1 was administered in 1000 mL and infused over 3 hours to maintain study blinding. Starting with Dose 2 and for all subsequent doses, infusion time was a minimum of 60 minutes

Criteria for evaluation:
Efficacy
Primary Outcome:

- Early clinical response defined as cessation of spread or reduction in size of baseline lesion, absence of fever, and no rescue antibiotic medication at ECE (48 to 72 hours). The definition of the primary endpoint meets the criteria recommended by the United States Food and Drug Administration (FDA) for the primary efficacy endpoint in ABSSSI studies [FDA, 2010].

Secondary Outcomes:
Key Secondary Efficacy Outcome

- Investigator-assessed clinical cure at the PTE visit in the mITT population. This is the key secondary efficacy endpoint specified in the Statistical Analysis Plan and is the primary endpoint for Europe as recommended by the European Medicine's Agency (EMA) [EMA, 2012].

Main Secondary Efficacy Outcomes

- Lesion area decrease ≥ 20% from baseline at ECE. This is a main secondary

efficacy endpoint because it is the endpoint currently recommended by FDA and the Foundation for the National Institutes of Health as the primary efficacy endpoint for an ABSSSI treatment.

- Sustained clinical response at PTE performed using the mITT population. This is a main secondary efficacy endpoint because it demonstrates the clinical cure at EOT is sustained over time.

Supportive Secondary Efficacy Outcomes

- Investigator-assessed clinical response at EOT and Day 10 using the mITT population
- Sustained lesion area decrease at EOT and PTE using the mITT and CE populations
- Pathogen-level microbiological response at EOT, Day 10, and PTE
- Patient-level microbiological relapse at PTE visit
- Change from baseline in temperature and resolution (absence) of fever (temperature < 37.7°C), at ECE for patients presenting with fever (temperature ≥ 38°C) at baseline
- Rescue medication use
- Unplanned surgical procedures
- Signs and symptoms related to the primary ABSSSI site
- Change in patient's assessment of pain at the primary ABSSSI site

Safety Outcomes:

- Safety endpoints included adverse events (AEs), serious AEs (SAEs), all-cause mortality, premature withdrawals because of AEs, AEs of special interest, clinical laboratory tests (hematology, serum chemistry, and urinalysis), vital signs, and electrocardiograms (ECGs)

PK Outcomes (conducted in a subset of patients)**:**

- PK parameters including area under the plasma concentration-time curve (AUC), half -life (t1/2), clearance (CL), maximum concentration (C_{max}), and steady state volume of distribution (Vss)

Additional Outcomes:

- Association of the genotype in strains of *S. aureus* with clinical response and microbiological response in patients
- Evaluation and comparison of health economic parameters and resource utilization for patients with oritavancin or vancomycin

ABSSSI site specimen

An ABSSSI site specimen for Gram stain, culture, and susceptibility testing was obtained from each patient within 24 hours prior to study drug administration (Table 43).

Table 43: ABSSSI Site Specimen Collection, Culture, and Gram Stain Requirements

Disease Category	If No Drainage, Obtain All of the Following	If Drainage, Obtain All of the Following
Wound or abscess	• Gram stain • Aerobic and anaerobic[a] cultures of material obtained by biopsy, needle aspiration, or deep swab	• Gram stain • Aerobic and anaerobic[a] cultures of purulent material by aspiration (preferred) or deep swab
Cellulitis	• Gram stain • Aerobic culture of punch biopsy (preferred method) or needle aspiration of the leading edge of erythema	• Gram stain • Aerobic cultures of purulent material by aspiration (preferred) or sterile swab

[a]Anaerobic collection and culture where possible.

Gram stains were prepared and interpreted by the local laboratory according to criteria provided in the study laboratory manual. The same Gram stain slide was also sent to the Central Laboratory for independent interpretation; these results were not provided to the investigational site. Each investigational site's laboratory cultured specimens (aerobic and where possible, anaerobic) and identified any pathogen(s). All isolated pathogens obtained from the infection site were subcultured and sent to the Central Laboratory for identification to the species level. Susceptibility testing for MIC values for relevant antibiotics (including oritavancin and relevant comparator antibiotics) was determined by the Central Laboratory

Blood Cultures

Two blood samples from two venipuncture sites were obtained at the Screening visit and divided equally into aerobic and, where possible, anaerobic culture media and incubated for a minimum of 5 days. If a patient was bacteremic, blood cultures were performed until negative results were documented. All isolated pathogens obtained from cultures were subcultured and sent to the Central Laboratory for identification to the species level. Susceptibility testing for MIC values for relevant antibiotics (including oritavancin and relevant comparator antibiotics) was determined by the Central Laboratory.

Microbiological Assessments

S. aureus strains from baseline ABSSSI site cultures were screened for the Panton-Valentine Leukocidin (*pvl*) by polymerase chain reaction. Susceptibility to oritavancin was determined by broth microdilution (CLSI M07-A9). A subset of *S. aureus* strains (those with vancomycin MICs of 1 or 2 mcg/mL) from baseline ABSSSI site cultures was

screened for the heterogeneous vancomycin-intermediate *Staphylococcus aureus* (hVISA) phenotype with glycopeptide resistance detection (GRD) Etest strips (bioMerieux) following manufacturer's instructions.

Clinical Response at EOT and Day 10
Clinical response at EOT and Day 10 was determined by the investigator based on the examination of signs and symptoms of the primary ABSSSI.

Pathogen-Level Microbiological Response at EOT, Day 10, and PTE
The microbiological response for each pathogen was defined as follows:

- Eradication: a culture at the primary ABSSSI site showed that the Gram-positive pathogen present before study drug initiation was eradicated
- Presumed eradication: the patient was assessed as a clinical cure and a culture at the primary ABSSSI site was not obtained because it was not indicated
- Persistence: a culture at the primary site of infection showed continuation of the Gram-positive pathogen that was present before study drug initiation
- Presumed persistence: a culture at the primary site of infection was not obtained and the patient was assessed as a clinical failure
- Relapse or recurrence (only applicable to PTE): the pathogen present at the primary ABSSSI site before initiation of study drug was isolated at the primary ABSSSI site anytime between the EOT and PTE visits after a pathogen response of eradication or presumed eradication at the EOT visit

Patient-Level Microbiological Response
Patient-level microbiological response was categorized as either a success or failure at EOT, Day 10, and PTE using the microbiological response categories defined in the section **Pathogen-Level Microbiological Response at EOT, Day 10, and PTE** above and the following additional categories:

- Super Infection: defined as emergence of a new pathogen at the primary ABSSSI site with a clinical response of failure
- Colonization: defined as emergence of a new pathogen at the primary ABSSSI site with a clinical response of success

Patients who had the ABSSSI categorized as eradicated, presumed eradicated, or colonization were categorized as successes.

Patients who had any of the following outcomes (from worst to least order) were categorized as failures: persistence, presumed persistence, super infection, and relapse/recurrence (PTE only). For each patient, the worst pathogen-level microbiological outcome was selected.

Microbiological Endpoints

Early clinical response at ECE, investigator-assessed clinical cure at PTE, and lesion size reduction ≥ 20% at ECE were assessed for patients with *S. aureus* at baseline by *pvl* status (+/-) and by hVISA status (+/-).

Lesion Size Reduction ≥ 20% From Baseline at ECE

According to the Applicant, lesion size reduction ≥ 20% from baseline at ECE was prespecified in the SAP for noninferiority testing using the mITT and CE populations. The proportion of patients with a lesion size reduction ≥ 20% from baseline at ECE was summarized by treatment group using ruler measurement data, together with the event rate difference between oritavancin and vancomycin and its 95% CI. Analyses were performed for patients who had lesion area assessments at baseline and ECE. If a patient had a missing assessment at baseline or ECE, the patient was treated as a failure in the analyses.

Microbiological Responses: Pathogen-Level Microbiological Response

According to the Applicant, the pathogen-level eradication rate for each baseline pathogen was calculated as follows:

Pathogen– level Eradication rate (%) = *Eradication* / Eradication* +Persistence* x* 100

Where eradication* included the pathogen-level outcomes of eradication or presumed eradication and Persistence* included the pathogen-level outcome of persistence, presumed persistence, or eradication with relapse/recurrence at the primary infection site (only for PTE). The eradication rate was tabulated for each treatment group at EOT, Day 10, and PTE, overall and by baseline pathogen, using the MicroITT and MicroE populations. Table 44 summarizes the efficacy analysis populations in the SOLO I and SOLO II clinical trials.

Table 44: Overview of Analysis Populations in SOLO I and SOLO II

	SOLO I		SOLO II	
Category	Oritavancin (N=483) n (%)	Vancomycin (N=485) n (%)	Oritavancin (N=509) n (%)	Vancomycin (N=510) n (%)
Intent–to-Treat (ITT) Population[a]	483	485	509	510
Modified ITT (mITT) Population[b]	475 (98.3)	479 (98.8)	503 (98.8)	502 (98.4)
Clinically Evaluable (CE) Population[c]	394 (81.6)	397 (81.9)	427 (83.9)	408 (80.0)
Microbologically ITT (MicroITT) Population[d]	244 (50.5)	242 (49.9)	285 (56.0)	296 (58.0)
Microbiologically Evaluable (MicroE) Population[e]	201 (41.6)	201 (41.4)	246 (48.3)	247 (48.4)
Safety Population[f],	473[g]	481[g]	503	502
Pharmacokinetic (PK) Population[h]	115	0	197	0

[a]The Intent-to-Treat (ITT) population included all patients randomized into the study.
[b]The modified Intent-to-Treat (mITT) population was the primary population for all of the efficacy analyses and included all randomized patients who received any study drug.
[c]The Clinically Evaluable (CE) population consisted of all mITT patients who met the inclusion/exclusion criteria, received the full-course of randomized study treatment (for a minimum of 7 days), and had an investigator assessment for clinical cure at PTE. The CE population was used to confirm the efficacy analyses.
[d]The microbiologically ITT (MicroITT) population consisted of all mITT patients with baseline Gram-positive pathogen(s) known to cause ABSSSI and was used for the secondary efficacy analyses.
[e]The microbiologically evaluable (MicroE) population was used to confirm the secondary efficacy analyses and consisted of all patients who were in both the MicroITT and CE populations.
[f]The Safety population was the primary population for all the safety analyses and consisted of all patients who were dosed with study drug, irrespective of randomization. Treatment classification was based on the actual treatment received.
[g]In SOLO I, two patients randomized to receive oritavancin were inadvertently dosed with vancomycin.
[h]Patients who received at least one dose of oritavancin.
Source: Table 1.2 from CSR SOLO I (TMC-ORI-10-01) and CSR SOLO II (TMC-ORI-10-02).

The percentage of patients with an investigator-assessed clinical cure in the CE population is shown in Table 45.

Table 45: Investigator-assessed Clinical Cure at PTE in SOLO I, SOLO II, and the SOLO Pool (CE Population)

	SOLO I		SOLO II		All Patients	
	Oritavancin (N=394) n (%)	Vancomycin (N=397) n (%)	Oritavancin (N=427) n (%)	Vancomycin (N=408) n (%)	Oritavancin (N=821) n (%)	Vancomycin (N=805) n (%)
Clinical Cure Rate at PTE, n (%)	362 (91.9)	370 (93.2)	398 (93.2)	387 (94.9)	760 (92.6)	757 (94.0)
Diff and 95% CI	-1.3 (-5.0, 2.3)		-1.6 (-4.9, 1.6)		-1.5 (-3.9, 0.9)	

CE: Clinically Evaluable; CI: Confidence Interval; PTE: Post Treatment Evaluation
% Success rate is calculated as no. of patients with success/no. of patients with success or failure * 100 (%). Patients with missing outcomes are defined as failure per protocol.
Source: Table 4.5.3

Table 46 shows the percent of patients with a ≥ 20% reduction of lesion size in both oritavancin treatment groups.

Table 46 Patients with >=20% Lesion Size Reduction from Baseline at ECE By Baseline Pathogen* (MicroE population - Group 2: Patients in SOLO I and SOLO II studies)

Genus Species	SOLO I Oritavancin (N=201) n (%)	SOLO I Vancomycin (N=201) n (%)	SOLO II Oritavancin (N=246) n (%)	SOLO II Vancomycin (N=247) n (%)	All Patients Oritavancin (N=447) n (%)	All Patients Vancomycin (N=448) n (%)
Number of Patients with at Least One Pathogen	183/201 (91.0)	177/201 (88.1)	227/246 (92.3)	226/247 (91.5)	410/447 (91.7)	403/448 (90.0)
Staphylococcus	166/181 (91.7)	158/178 (88.8)	204/219 (93.2)	197/216 (91.2)	370/400 (92.5)	355/394 (90.1)
aureus	166/181 (91.7)	156/175 (89.1)	201/216 (93.1)	197/216 (91.2)	367/397 (92.4)	353/391 (90.3)
MSSA	85/ 97 (87.6)	85/ 95 (89.5)	116/128 (90.6)	122/134 (91.0)	201/225 (89.3)	207/229 (90.4)
MRSA	83/ 86 (96.5)	73/ 82 (89.0)	85/ 88 (96.6)	76/ 83 (91.6)	168/174 (96.6)	149/165 (90.3)
lugdunensis	0	3/ 4 (75.0)	4/ 4 (100.0)	0	4/ 4 (100.0)	3/ 4 (75.0)
Streptococcus	22/ 26 (84.6)	26/ 29 (89.7)	36/ 41 (87.8)	44/ 47 (93.6)	58/ 67 (86.6)	70/ 76 (92.1)
pyogenes	5/ 6 (83.3)	3/ 5 (60.0)	17/ 19 (89.5)	16/ 19 (84.2)	22/ 25 (88.0)	19/ 24 (79.2)
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)
agalactiae	6/ 6 (100.0)	7/ 7 (100.0)	1/ 1 (100.0)	4/ 4 (100.0)	7/ 7 (100.0)	11/ 11 (100.0)
intermedius	2/ 3 (66.7)	3/ 3 (100.0)	4/ 5 (80.0)	9/ 9 (100.0)	6/ 8 (75.0)	12/ 12 (100.0)
dysgalactiae	2/ 3 (66.7)	2/ 2 (100.0)	4/ 5 (80.0)	2/ 2 (100.0)	6/ 8 (75.0)	4/ 4 (100.0)
anginosus	1/ 2 (50.0)	5/ 5 (100.0)	2/ 2 (100.0)	1/ 1 (100.0)	3/ 4 (75.0)	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	5/ 6 (83.3)	4/ 5 (80.0)	3/ 4 (75.0)	3/ 5 (60.0)	8/ 10 (80.0)	7/ 10 (70.0)
faecalis	5/ 6 (83.3)	4/ 5 (80.0)	3/ 4 (75.0)	3/ 5 (60.0)	8/ 10 (80.0)	7/ 10 (70.0)

Patients with multiple pathogens are counted once in the rows for each pathogen.
* Includes Gram-positive pathogens known to cause ABSSSI.
Oritavancin (XTRA_NDA), \program\ise-t-ls20path-pop.sas, 23SEP2013 23:16

Table 47 shows the result of the investigator assessed clinical cure rates at the EOT by baseline pathogens in the MicroE population in the SOLO I treatment group. Overall there was a 92% cure rate reported for the oritavancin treatment arm compared to 94% for vancomycin. Similar results were reported for all staphylococcal isolates between both treatment groups. Against *Streptococcus* species, oritavancin reported a success rate of 88.5% compared to 96.6% in the vancomycin treatment group.

Table 47 Investigator-Assessed Clinical Cure at End of Treatment (EOT) by Baseline Pathogen* (MicroE Population)

Genus Species	Oritavancin (N=201) n (%)	Vancomycin (N=201) n (%)	Diff and 95% CI
Number of Patients with at Least One Pathogen	185/201 (92.0)	189/201 (94.0)	-2.0 (-7.0, 3.0)
Staphylococcus	168/181 (92.8)	167/178 (93.8)	-1.0 (-6.2, 4.2)
aureus	168/181 (92.8)	165/175 (94.3)	-1.5 (-6.6, 3.6)
lugdunensis	0	3/4 (75.0)	
Streptococcus	23/26 (88.5)	28/29 (96.6)	-8.1 (-22.1, 5.9)
constellatus	7/7 (100.0)	7/8 (87.5)	12.5 (-10.4, 35.4)
agalactiae	6/6 (100.0)	7/7 (100.0)	
pyogenes	5/6 (83.3)	5/5 (100.0)	-16.7 (-46.5, 13.2)
anginosus	2/2 (100.0)	5/5 (100.0)	
intermedius	3/3 (100.0)	3/3 (100.0)	
dysgalactiae	1/3 (33.3)	2/2 (100.0)	
Group F	0	2/2 (100.0)	
Enterococcus	5/6 (83.3)	5/5 (100.0)	-16.7 (-46.5, 13.2)
faecalis	5/6 (83.3)	5/5 (100.0)	-16.7 (-46.5, 13.2)

Table 78 shows the result of the investigator assessed clinical cure rates at the EOT by baseline pathogens in the MicroE population in the SOLO II treatment group. Overall success rates of 94.7% and 96.4% were reported for the oritavancin and vancomycin treatment groups, respectively. Limited data were reported for *S. agalactiae* in both the SOLO I and the SOLO II treatment groups with respect to the efficacy of oritavancin.

Table 48 Investigator-Assessed Clinical Cure at Post Therapy Response (PTE) By Baseline Pathogen (MicroE Population)

Genus Species	Oritavancin (N=246) n (%)	Vancomycin (N=247) n (%)	Diff and 95% CI
Number of Patients with at Least One Pathogen	233/246 (94.7)	238/247 (96.4)	-1.6 (-5.3, 2.0)
Staphylococcus	208/219 (95.0)	209/216 (96.8)	-1.8 (-5.5, 2.0)
aureus	205/216 (94.9)	209/216 (96.8)	-1.9 (-5.6, 1.9)
lugdunensis	4/4 (100.0)	0	
Streptococcus	38/41 (92.7)	45/47 (95.7)	-3.1 (-12.9, 6.8)
pyogenes	19/19 (100.0)	18/19 (94.7)	5.3 (-4.8, 15.3)
constellatus	8/9 (88.9)	11/11 (100.0)	-11.1 (-31.6, 9.4)
intermedius	5/5 (100.0)	9/9 (100.0)	
dysgalactiae	5/5 (100.0)	1/2 (50.0)	
agalactiae	1/1 (100.0)	4/4 (100.0)	
Group F	1/1 (100.0)	1/1 (100.0)	
anginosus	0/2	1/1 (100.0)	
Enterococcus	3/4 (75.0)	4/5 (80.0)	
faecalis	3/4 (75.0)	4/5 (80.0)	

Treatment outcome: *S. aureus* with/without *pvl*

Table 49 show response in the MicroE population by *S. aureus* patient isolates with *pvl* gene in both treatment groups in the SOLO I study while Table 49 shows the response without the *pvl* gene. The presence of *pvl* did not appear to have an effect on treatment outcome.

Table 49 Patient-level Microbiological Response by Genes in Strains of *S. aureus* (MicroE population) With *pvl* gene

Clinical Outcome	Oritavancin (N=201)	Vancomycin (N=201)	Diff and 95% CI
Number of Patients with Response	123 (61.2)	120 (59.7)	
Patient-level Microbiological Response at EOT			
Success	114/121 (94.2)	115/120 (95.8)	-1.6 (-7.1, 3.9)
Eradication	0/121	0/120	
Presumed Eradication	114/121 (94.2)	115/120 (95.8)	-1.6 (-7.1, 3.9)
Colonisation	0/121	0/120	
Failure	7/121 (5.8)	5/120 (4.2)	1.6 (-3.9, 7.1)
Persistence	0/121	0/120	
Presumed Persistence	7/121 (5.8)	5/120 (4.2)	1.6 (-3.9, 7.1)
Super Infection	0/121	0/120	
Patient-level Microbiological Response at Day 10			
Success	116/123 (94.3)	117/119 (98.3)	-4.0 (-8.7, 0.7)
Eradication	0/123	0/119	
Presumed Eradication	116/123 (94.3)	117/119 (98.3)	-4.0 (-8.7, 0.7)
Colonisation	0/123	0/119	
Failure	7/123 (5.7)	2/119 (1.7)	4.0 (-0.7, 8.7)
Persistence	0/123	0/119	
Presumed Persistence	7/123 (5.7)	2/119 (1.7)	4.0 (-0.7, 8.7)
Super Infection	0/123	0/119	
Patient-level Microbiological Response at PTE			
Success	115/122 (94.3)	114/119 (95.8)	-1.5 (-7.0, 3.9)
Eradication	0/122	0/119	
Presumed Eradication	115/122 (94.3)	114/119 (95.8)	-1.5 (-7.0, 3.9)
Colonisation	0/122	0/119	
Failure	7/122 (5.7)	5/119 (4.2)	1.5 (-3.9, 7.0)
Persistence	0/122	0/119	
Presumed Persistence	6/122 (4.9)	4/119 (3.4)	1.6 (-3.5, 6.6)
Super Infection	0/122	0/119	
Relapse or Recurrence	1/122 (0.8)	1/119 (0.8)	-0.0 (-2.3, 2.3)

Table 50 Patient-level Microbiological Response by Genes in Strains of *S. aureus* (MicroE population) Without *pvl* gene

Clinical Outcome	Oritavancin (N=201)	Vancomycin (N=201)	Diff and 95% CI
Number of Patients with Response	49 (24.4)	46 (22.9)	
Patient-level Microbiological Response at EOT			
Success	46/49 (93.9)	42/45 (93.3)	0.5 (-9.4, 10.5)
Eradication	0/49	0/45	
Presumed Eradication	46/49 (93.9)	42/45 (93.3)	0.5 (-9.4, 10.5)
Colonisation	0/49	0/45	
Failure	3/49 (6.1)	3/45 (6.7)	-0.5 (-10.5, 9.4)
Persistence	0/49	0/45	
Presumed Persistence	3/49 (6.1)	3/45 (6.7)	-0.5 (-10.5, 9.4)
Super Infection	0/49	0/45	
Patient-level Microbiological Response at Day 10			
Success	45/49 (91.8)	42/44 (95.5)	-3.6 (-13.4, 6.2)
Eradication	0/49	0/44	
Presumed Eradication	45/49 (91.8)	42/44 (95.5)	-3.6 (-13.4, 6.2)
Colonisation	0/49	0/44	
Failure	4/49 (8.2)	2/44 (4.5)	3.6 (-6.2, 13.4)
Persistence	0/49	0/44	
Presumed Persistence	4/49 (8.2)	2/44 (4.5)	3.6 (-6.2, 13.4)
Super Infection	0/49	0/44	
Patient-level Microbiological Response at PTE			
Success	45/49 (91.8)	44/45 (97.8)	-5.9 (-14.7, 2.9)
Eradication	0/49	0/45	
Presumed Eradication	45/49 (91.8)	44/45 (97.8)	-5.9 (-14.7, 2.9)
Colonisation	0/49	0/45	
Failure	4/49 (8.2)	1/45 (2.2)	5.9 (-2.9, 14.7)
Persistence	0/49	0/45	
Presumed Persistence	4/49 (8.2)	1/45 (2.2)	5.9 (-2.9, 14.7)
Super Infection	0/49	0/45	
Relapse or Recurrence	0/49	0/45	-0.0 (-2.3, 2.3)

Table 51 shows the result of the MicroE population by *S. aureus* patient isolates with *pvl* gene in both treatment groups in the SOLO II study while Table 52 shows the response without the *pvl* gene. The presence of *pvl* did not appear to have an effect on treatment outcome in the SOLO II trial.

Table 51 Patient-level Microbiological Response by Genes in Strains of *S. aureus* (MicroE population) With *pvl* gene

Clinical Outcome	Oritavancin (N=246)	Vancomycin (N=247)	Diff and 95% CI
Number of Patients with Response	120 (48.8)	116 (47.0)	
Patient-level Microbiological Response at EOT			
Success	116/120 (96.7)	111/116 (95.7)	1.0 (-3.9, 5.9)
Eradication	0/120	0/116	
Presumed Eradication	115/120 (95.8)	111/116 (95.7)	0.1 (-5.0, 5.3)
Colonisation	1/120 (0.8)	0/116	0.8 (-0.8, 2.5)
Failure	4/120 (3.3)	5/116 (4.3)	-1.0 (-5.9, 3.9)
Persistence	2/120 (1.7)	1/116 (0.9)	0.8 (-2.0, 3.6)
Presumed Persistence	2/120 (1.7)	4/116 (3.4)	-1.8 (-5.8, 2.3)
Super Infection	0/120	0/116	
Patient-level Microbiological Response at Day 10			
Success	116/120 (96.7)	111/116 (95.7)	1.0 (-3.9, 5.9)
Eradication	0/120	0/116	
Presumed Eradication	115/120 (95.8)	111/116 (95.7)	0.1 (-5.0, 5.3)
Colonisation	1/120 (0.8)	0/116	0.8 (-0.8, 2.5)
Failure	4/120 (3.3)	5/116 (4.3)	-1.0 (-5.9, 3.9)
Persistence	1/120 (0.8)	0/116	0.8 (-0.8, 2.5)
Presumed Persistence	3/120 (2.5)	5/116 (4.3)	-1.8 (-6.4, 2.8)
Super Infection	0/120	0/116	
Patient-level Microbiological Response at PTE			
Success	112/119 (94.1)	111/116 (95.7)	-1.6 (-7.2, 4.0)
Eradication	0/119	0/116	
Presumed Eradication	111/119 (93.3)	111/116 (95.7)	-2.4 (-8.2, 3.4)
Colonisation	1/119 (0.8)	0/116	0.8 (-0.8, 2.5)
Failure	7/119 (5.9)	5/116 (4.3)	1.6 (-4.0, 7.2)
Persistence	1/119 (0.8)	0/116	0.8 (-0.8, 2.5)
Presumed Persistence	6/119 (5.0)	5/116 (4.3)	0.7 (-4.7, 6.1)
Super Infection	0/119	0/116	
Relapse or Recurrence	0/119	0/116	

Table 52 Patient-level Microbiological Response by Genes in Strains of *S. aureus* (MicroE population)Without *pvl* gene

Clinical Outcome	Oritavancin (N=246)	Vancomycin (N=247)	Diff and 95% CI
Number of Patients with Response	96 (39.0)	100 (40.5)	
Patient-level Microbiological Response at EOT			
Success	91/94 (96.8)	99/99 (100.0)	-3.2 (-6.7, 0.4)
Eradication	0/94	0/99	
Presumed Eradication	91/94 (96.8)	99/99 (100.0)	-3.2 (-6.7, 0.4)
Colonisation	0/94	0/99	0.8 (-0.8, 2.5)
Failure	3/94 (3.2)	0/99	3.2 (-0.4, 6.7)
Persistence	0/94	0/99	0.8 (-2.0, 3.6)
Presumed Persistence	3/94 (3.2)	0/99	3.2 (-0.4, 6.7)
Super Infection	0/94	0/99	
Patient-level Microbiological Response at Day 10			
Success	93/95 (97.9)	100/100 (100.0)	-2.1 (-5.0, 0.8)
Eradication	0/95	0/100	
Presumed Eradication	93/95 (97.9)	100/100 (100.0)	-2.1 (-5.0, 0.8)
Colonisation	0/95	0/100	0.8 (-0.8, 2.5)
Failure	2/95 (2.1)	0/100	2.1 (-0.8, 5.0)
Persistence	0/95	0/100	0.8 (-0.8, 2.5)
Presumed Persistence	2/95 (2.1)	0/100	2.1 (-0.8, 5.0)
Super Infection	0/95	0/100	
Patient-level Microbiological Response at PTE			
Success	92/95 (96.8)	98/100 (98.0)	-1.2 (-5.6, 3.3)
Eradication	0/95	0/100	
Presumed Eradication	92/95 (96.8)	98/100 (98.0)	-1.2 (-5.6, 3.3)
Colonisation	0/95	0/100	0.8 (-0.8, 2.5)
Failure	3/95 (3.2)	2/100 (2.0)	1.2 (-3.3, 5.6)
Persistence	0/95	0/100	0.8 (-0.8, 2.5)
Presumed Persistence	3/95 (3.2)	2/100 (2.0)	1.2 (-3.3, 5.6)
Super Infection	0/95	0/100	
Relapse or Recurrence	0/95	0/100	

Summary of MIC by Baseline Pathogen (SOLO I)

This section provides a summary of the investigator's assessment of the SOLO I clinical response and microbiology outcome by MIC for the microbiologically evaluable (ME) population from the SOLO I controlled study. Microbiology samples were required only at baseline. The distribution of species and the in vitro susceptibility of baseline pathogens in the micro-evaluable (ME) populations are summarized; a summary of the susceptibility profile of all the isolates obtained in the SOLO I trial is presented below Table 53). There were a total of 11 *E. faecalis* isolates obtained in the SOLO I trial, the oritavancin MIC ranged from 0.015-0.12 mcg/ml, with an MIC90 of 0.06 mcg/ml.

Table 53 Summary Statistics of MIC (ug/mL) by Baseline Pathogen (MicroE population)
Pathogen: *Enterococcus faecalis* Medium = MIC-BROTH, Sensititre Plate = Broth microdilution for aerobic Gram-positive organisms

# of Isolates	Antibiotic Test	MIC Min	Max	Mode	MIC50	MIC90
11	AMPICILLIN	<=0.25	1	0.5	0.5	1
	CLINDAMYCIN	>2	>2	>2	>2	>2
	DAPTOMYCIN	1	2	1	1	1
	ERYTHROMYCIN	0.25	>4	2	2	>4
	GENTAMICIN	<=500	<=500	<=500	<=500	<=500
	LEVOFLOXACIN	0.5	>4	1	1	>4
	LINEZOLID	1	2	1	1	2
	ORITAVANCIN	0.015	0.12	0.03	0.03	0.06
	OXACILLIN**	2	>4	>4	>4	>4
	STREPTOMYCIN	<=1000	>1000	<=1000	<=1000	>100
	TEICOPLANIN	0.12	1	0.12	0.25	0.5
	TETRACYCLINE	0.25	>32	32	32	>32
	TRIMETH/ SULFA^	<=0.5	>4	<=0.5	<=0.5	>4
	VANCOMYCIN	0.5	2	2	1	2

There were a total of 168 MRSA isolates and 192 MSSA isolates obtained in the ME population in the SOLO I study (Table 54 and 55). Against all MRSA, the oritavancin MIC ranged from 0.015-0.25 mcg/ml (MIC90=0.12 mcg/ml). Against MSSA, the oritavancin MIC ranged from 0.002-0.25 mcg/ml (MIC90=0.12 mcg/ml).

Table 54 Summary Statistics of MIC (ug/mL) by Baseline Pathogen (MicroE population) Pathogen: Staphylococcus aureus – MRSA Medium = MIC-BROTH, Sensititre Plate = Broth microdilution for aerobic Gram-positive organisms

# of Isolates	Antibiotic Test	MIC Min	Max	Mode	MIC50	MIC90
168	AMPICILLIN	<=0.25	>16	>16	>16	>16
	CLINDAMYCI	0.06	>2	0.12	0.12	0.25
	DAPTOMYCIN	0.25	1	0.5	0.5	0.5
	ERYTHROMYC	0 25	>4	>4	>4	>4
	GENTAMICIN	<=500	>500	<=500	<=500	<=500
	LEVOFLOXACI	0.06	>4	4	3	4
	LINEZOLID	<=0.5	2	2	2	2
	ORITAVANCIN	0.015	0.25	0.03	0.06	0.12
	OXACILLIN	0.12	>4	>4	>4	>4
	STREPTOMYCI	<=1000	>1000	<=1000	<=1000	<=1000
	TEICOPLANIN	0.12	2	0.5	0.5	1
	TETRACYCLIN	<=0.06	>32	0.25	0.25	0.5
	TRIMETH/ SULFA	<=0.5	>4	<=0.5	<=0.5	<=0.5
	VANCOMYCIN	<=0.25	1	0.5	0.5	1

Table 55 Summary Statistics of MIC (ug/mL) by Baseline Pathogen (MicroE population) Pathogen: *Staphylococcus aureus* – MSSA Medium = MIC-BROTH, Sensititre Plate = Broth microdilution for aerobic Gram-positive organisms

# of Isolates	Antibiotic Test	MIC Min	Max	Mode	MIC50	MIC90
192	AMPICILLIN	<=0.25	>16	<=0.25	2	16
	CLINDAMYCIN	0.06	>2	0.12	0.12	0.25
	DAPTOMYCIN	<=0.12	1	0.5	0.5	0.5
	ERYTHROMYCIN	<=0.12	>4	0.5	0.5	>4
	GENTAMICIN	<=500	>500	<=500	<=500	<=500
	LEVOFLOXACIN	<=0.03	>4	0.12	0.5	>4
	LINEZOLID	<=0.5	4	2	2	2
	ORITAVANCIN	0.002	0.25	0.03	0.06	0.12
	OXACILLIN**	<=0.06	2	0.25	0.25	0.5
	STREPTOMYCIN	<=1000	>1000	<=1000	<=1000	<=1000
	TEICOPLANIN	<=0.03	2	0.5	0.5	1
	TETRACYCLINE	<=0.06	>32	0.25	0.25	1
	TRIMETH/ SULFA	<=0.5	>4	<=0.5	<=0.5	2
	VANCOMYCIN	<=0.25	1	0.5	0.5	1

Table 56 Summary Statistics of MIC (ug/mL) by Baseline Pathogen (MicroE population)
Pathogen: *Streptococcus agalactiae* Medium = MIC-BROTH, Sensititre Plate = Streptococci Panel (Frozen, inoculate with CAMHB + LHB)

		MIC				
# of Isolates	Test Antibiotics	Min	Max	Mode	MIC50	MIC90
13	CLINDAMYCIN	0.03	>2	>2	0.06	>2
	DAPTOMYCIN	0.12	0.5	0.25	0.25	0.5
	ERYTHROMYCIN	0.03	>2	>2	0.06	>2
	LEVOFLOXACIN	0.25	1	0.5	0.5	0.5
	LINEZOLID	<=0.25	1	1	1	1
	ORITAVANCIN	0.03	0.25	0.06	0.06	0.25
	PENICILLIN	<=0.03	0.06	<=0.03	<=0.03	0.06
	TEICOPLANIN	0.06	0.12	0.12	0.12	0.12
	TETRACYCLINE	0.12	>16	>16	>16	>16
	TRIMETH/ SULFA	<=0.06	0.12	<=0.06	<=0.06	0.12
	VANCOMYCIN	0.25	0.5	0.25	0.25	0.5

Table 57 Summary Statistics of MIC (ug/mL) by Baseline Pathogen (MicroE population)
Pathogen: *Streptococcus anginosus* Medium = MIC-BROTH, Sensititre Plate = Streptococci Panel (Frozen, inoculate with CAMHB + LHB)

		MIC				
# of Isolates	Antibiotic Test	Min	Max	Mode	MIC50	MIC90
7	CLINDAMYCIN	<=0.015	0.06	<=0.015	0.03	0.06
	DAPTOMYCIN	0.06	1	0.5	0.5	1
	ERYTHROMYCIN	<=0.015	0.03	0.03	0.03	0.03
	LEVOFLOXACIN	0.06	1	0.25	0.25	1
	LINEZOLID	0.5	1	0.5	0.5	1
	ORITAVANCIN	0.002	0.12	0.002	0.03	0.12
	PENICILLIN	<=0.03	0.25	<=0.0	<=0.03	0.25
	TEICOPLANIN	<=0.03	0.25	<=0.0	<=0.03	0.25
	TETRACYCLINE	0.06	>16	0.06	0.25	>16
	TRIMETH/ SULFA	<=0.06	0.25	<=0.0	<=0.06	0.25
	VANCOMYCIN	0.03	0.5	0.5	0.5	0.5

Table 58 Summary Statistics of MIC (ug/mL) by Baseline Pathogen (MicroE population)
Pathogen: *Streptococcus constellatus* Medium = MIC-BROTH, Sensititre Plate = Streptococci Panel (Frozen, inoculate with CAMHB + LHB)

		MIC				
# of Isolates	Antibiotic Test	Min	Max	Mode	MIC50	MIC90
15	CLINDAMYCIN	<=0.015	>2	0.03	0.03	0.06
	DAPTOMYCIN	<=0.03	1	0.5	0.5	1
	ERYTHROMYCIN	<=0.015	>2	<=0.015	0.03	0.03
	LEVOFLOXACIN	<=0.03	1	0.5	0.5	0.5
	LINEZOLID	<=0.25	2	1	1	1
	ORITAVANCIN ^	0.001	0.5	0.015	0.015	0.12
	PENICILLIN	<=0.03	0.12	<=0.03	<=0.03	0.06
	TEICOPLANIN ^	<=0.03	0.12	0.06	0.06	0.12
	TETRACYCLINE	<=0.03	>16	0.25	0.25	16
	TRIMETH/ SULFA^	<=0.06	0.25	<=0.06	<=0.06	0.12
	VANCOMYCIN	<=0.015	0.5	0.5	0.5	0.5

Table 59 Summary Statistics of MIC (ug/mL) by Baseline Pathogen (MicroE population) Pathogen: *Streptococcus dysgalactiae* Medium = MIC-BROTH, Sensititre Plate = Streptococci Panel (Frozen, inoculate with CAMHB + LHB)

# of Isolates	Antibiotic Test	MIC Min	Max	Mode	MIC50	MIC90
5	CLINDAMYCIN	0.03	0.06	0.06	0.06	0.06
	DAPTOMYCIN	0.06	0.12	0.06	0.06	0.12
	ERYTHROMYCIN	0.03	0.06	0.06	0.06	0.06
	LEVOFLOXACIN	0.06	0.5	0.5	0.5	0.5
	LINEZOLID	<=0.25	1	1	1	1
	ORITAVANCIN	0.001	0.5	0.12	0.12	0.5
	PENICILLIN	<=0.03	0.06	<=0.03	<=0.03	0.06
	TEICOPLANIN	0.06	0.06	0.06	0.06	0.06
	TETRACYCLINE	0.06	>16	2	2	>16
	TRIMETH/ SULFA^	<=0.06	0.12	<=0.06	<=0.06	0.12
	VANCOMYCIN	0.03	0.25	0.12	0.12	0.25

Table 60 Summary Statistics of MIC (ug/mL) by Baseline Pathogen (MicroE population) Pathogen: *Streptococcus intermedius* Medium = MIC-BROTH, Sensititre Plate = Streptococci Panel (Frozen, inoculate with CAMHB + LHB)

# of Isolates	Antibiotic Test	MIC Min	Max	Mode	MIC50	MIC90
6	CLINDAMYCIN	<=0.015	0.06	<=0.015	<=0.015	0.06
	DAPTOMYCIN	<=0.03	1	<=0.03	0.09	1
	ERYTHROMYCIN	<=0.015	0.03	<=0.015	<=0.015	0.03
	LEVOFLOXACIN	<=0.03	1	<=0.03	0.155	1
	LINEZOLID	<=0.25	1	<=0.25	<=0.25	1
	ORITAVANCIN	<=0.0005	0.015	<=0.0005	0.00125	0.015
	PENICILLIN	<=0.03	<=0.03	<=0.03	<=0.03	<=0.03
	TEICOPLANIN	<=0.03	0.06	<=0.03	<=0.03	0.06
	TETRACYCLINE	<=0.03	0.12	<=0.03	0.045	0.12
	TRIMETH/ SULFA	<=0.06	0.25	<=0.06	0.09	0.25
	VANCOMYCIN	<=0.015	0.5	<=0.015	0.045	0.5

Table 61 Summary Statistics of MIC (ug/mL) by Baseline Pathogen (MicroE population) Pathogen: *Streptococcus pyogenes* Medium = MIC-BROTH, Sensititre Plate = Streptococci Panel (Frozen, inoculate with CAMHB + LHB)

# of Isolates	Antibiotic Test	MIC Min	Max	Mode	MIC50	MIC90
11	CLINDAMYCIN	0.03	0.25	0.03	0.03	0.25
	DAPTOMYCIN	<=0.03	0.12	0.06	0.06	0.12
	ERYTHROMYCIN	<=0.015	>2	0.06	0.06	>2
	LEVOFLOXACIN	0.25	1	0.5	0.5	0.5
	LINEZOLID	0.5	1	1	1	1
	ORITAVANCIN	0.008	0.25	0.03	0.06	0.25
	PENICILLIN	<=0.03	0.12	<=0.03	<=0.03	<=0.03
	TEICOPLANIN	<=0.03	0.12	<=0.03	<=0.03	0.06
	TETRACYCLINE	0.06	>16	0.12	0.12	16
	TRIMETH/ SULFA	<=0.06	0.25	0.12	0.12	0.25
	VANCOMYCIN	0.25	0.25	0.25	0.25	0.25

MIC with clinical and microbiological outcome (SOLO I)

This section provides a summary of the investigator's assessment of oritavancin clinical response at clinical cure at end of treatment, clinical cure at Day 10 and at the post therapy evaluation (PTE).

There were a total of 6 *Enterococcus faecalis* isolates obtained in the oritavancin treatment arm of the SOLO I study and a positive clinical response was observed for enterococci for MIC values up to 0.06 mcg/ml (Table 62). In the comparator arm, there were a total of 5 *E. faecalis isolates*. At the EOT clinical cure, and at the 10-day clinical cure, the efficacy rate was 83.3 % in the oritavancin treatment group. At the PTE evaluation, one patient with an enterococci isolate with an MIC of 0.06 mcg/ml was considered a failure; thereby lowing the efficacy to 66.7% at the clinical cure at PTE. In the vancomycin treatment arm, the efficacy rate was 5/5 (100%) at EOT, clinical cure at day-10 and at clinical cure at PTE.

Table 62 Investigator-Assessed Clinical Cure at EOT, Day 10 and PTE by Baseline Pathogen and Oritavancin MIC (MicroE population) Pathogen: *Enterococcus faecalis*
Medium = MIC-BROTH, Sensititre Plate = Broth microdilution for aerobic Gram-positive organisms

	Clinical Cure at EOT		Clinical Cure at Day 10		Clinical Cure at PTE	
MIC	Oritavancin (N=201)	Vancomycin (N=201)	Oritavancin (N=201)	Vancomycin (N=201)	Oritavancin (N=201)	Vancomycin (N=201)
Total	5/ 6 (83.3)	5/ 5 (100.0)	5/ 6 (83.3)	5/ 5 (100.0)	4/ 6 (66.7)	5/ 5 (100.0)
<=0.0005	0	0	0	0	0	0
0.001	0	0	0	0	0	0
0.002	0	0	0	0	0	0
0.004	0	0	0	0	0	0
0.008	0	0	0	0	0	0
0.015	1/ 1 (100.0)	1/ 1 (100.0)	1/ 1 (100.0)	1/ 1 (100.0)	1/ 1 (100.0)	1/ 1 (100.0)
0.03	3/ 3 (100.0)	3/ 3 (100.0)	3/ 3 (100.0)	3/ 3 (100.0)	3/ 3 (100.0)	3/ 3 (100.0)
0.06	1/ 1 (100.0)	1/ 1 (100.0)	1/ 1 (100.0)	1/ 1 (100.0)	0/ 1 (0.0)	1/ 1 (100.0)
0.12	0/ 1 (0.0)	0	0/ 1 (0.0)	0	0/ 1 (0.0)	0

A summary of the MIC versus the Investigator's assessment of clinical outcome at EOT, Day-10 and at PTE is provided for MRSA and MSSA in Table 63 and Table 64 below. A positive clinical response was observed against all MRSA of 0.25 mcg/ml. Against MSSA, the highest MIC associated with clinical cure was 0.25 mcg/ml; 4/4 patients were considered to be cure at the EOT, this value decreased at clinical cure at day 10 and at PTE, to 75% and 25%, respectively.

Table 63 Investigator-Assessed Clinical Cure at EOT, Day 10 and PTE by Baseline Pathogen and Oritavancin MIC (MicroE population) Pathogen: *Staphylococcus aureus* - MRSA
Medium = MIC-BROTH, Sensititre Plate = Broth microdilution for aerobic Gram-positive organisms

	Clinical Cure at EOT		Clinical Cure at Day 10		Clinical Cure at PTE	
MIC	Oritavancin (N=201)	Vancomycin (N=201)	Oritavancin (N=201)	Vancomycin (N=201)	Oritavancin (N=201)	Vancomycin (N=201)
Total	83/ 86 (96.5)	79/ 82 (96.3)	82/ 86 (95.3)	81/ 81 (100.0)	82/ 86 (95.3)	80/ 81 (98.8)
<=0.0005	0	0	0	0	0	0
0.001	0	0	0	0	0	0
0.002	0	0	0	0	0	0
0.004	0	0	0	0	0	0
0.008	0	0	0	0	0	0
0.015	4/ 4 (100.0)	2/ 2 (100.0)	4/ 4 (100.0)	2/ 2 (100.0)	4/ 4 (100.0)	2/ 2 (100.0)
0.03	43/ 43 (100.0)	32/ 33 (97.0)	43/ 43 (100.0)	32/ 32 (100.0)	43/ 43 (100.0)	32/ 32 (100.0)
0.06	22/ 25 (88.0)	38/ 38 (100.0)	22/ 25 (88.0)	38/ 38 (100.0)	22/ 25 (88.0)	38/ 38 (100.0)
0.12	13/ 13 (100.0)	6/ 8 (75.0)	12/ 13 (92.3)	8/ 8 (100.0)	12/ 13 (92.3)	7/ 8 (87.5)
0.25	1/ 1 (100.0)	1/ 1 (100.0)	1/ 1 (100.0)	1/ 1 (100.0)	1/ 1 (100.0)	1/ 1 (100.0)

Table 64 Investigator-Assessed Clinical Cure at EOT, Day 10 and PTE by Baseline Pathogen and Oritavancin MIC (MicroE population) Pathogen: Staphylococcus aureus - MSSA
Medium = MIC-BROTH, Sensititre Plate = Broth microdilution for aerobic Gram-positive organisms

	Clinical Cure at EOT		Clinical Cure at Day 10		Clinical Cure at PTE	
MIC	Oritavancin (N=201)	Vancomycin (N=201)	Oritavancin (N=201)	Vancomycin (N=201)	Oritavancin (N=201)	Vancomycin (N=201)
Total	87/ 95 (91.6)	88/ 94 (93.6)	87/ 97 (89.7)	88/ 93 (94.6)	87/ 96 (90.6)	88/ 94 (93.6)
<=0.0005	0	0	0	0	0	0
0.001	0	0	0	0	0	0
0.002	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)
0.004	0	0	0	0	0	0
0.008	0	0	0	0	0	0
0.015	6/ 6 (100.0)	5/ 5 (100.0)	6/ 6 (100.0)	5/ 5 (100.0)	6/ 6 (100.0)	5/ 5 (100.0)
0.03	34/ 39 (87.2)	39/ 41 (95.1)	32/ 39 (82.1)	39/ 41 (95.1)	35/ 39 (89.7)	39/ 41 (95.1)
0.06	34/ 37 (91.9)	28/ 31 (90.3)	36/ 38 (94.7)	28/ 30 (93.3)	37/ 38 (97.4)	30/ 31 (96.8)
0.12	9/ 9 (100.0)	12/ 13 (92.3)	10/ 10 (100.0)	12/ 13 (92.3)	8/ 9 (88.9)	11/ 13 (84.6)
0.25	4/ 4 (100.0)	3/ 3 (100.0)	3/ 4 (75.0)	3/ 3 (100.0)	1/ 4 (25.0)	2/ 3 (66.7)

A summary of the investigator's assessment for oritavancin clinical response and favorable outcome by MIC and clinical cure at EOT, clinical cure at Day-10 and clinical cure at PTE in the SOLO-I study is provided for streptococci is shown in Tables 65-70. There were a total of 57 streptococci isolates obtained from the SOLO I study. In the oritavancin treatment arm, there were a total of 29 streptococci isolates. A positive clinical response was observed up to 0.25 mcg/ml.

Table 65 Investigator-Assessed Clinical Cure at EOT, Day 10 and PTE by Baseline Pathogen and Oritavancin MIC (MicroE population) Pathogen: *Streptococcus agalactiae*

	Clinical Cure at EOT		Clinical Cure at Day 10		Clinical Cure at PTE	
MIC	Oritavancin (N=201)	Vancomycin (N=201)	Oritavancin (N=201)	Vancomycin (N=201)	Oritavancin (N=201)	Vancomycin (N=201)
Total	6/ 6 (100.0)	7/ 7 (100.0)	5/ 6 (83.3)	7/ 7 (100.0)	5/ 6 (83.3)	7/ 7 (100.0)
<=0.0005	0	0	0	0	0	0
0.001	0	0	0	0	0	0
0.002	0	0	0	0	0	0
0.004	0	0	0	0	0	0
0.008	0	0	0	0	0	0
0.015	0	0	0	0	0	0
0.03	2/ 2 (100.0)	2/ 2 (100.0)	2/ 2 (100.0)	2/ 2 (100.0)	2/ 2 (100.0)	2/ 2 (100.0)
0.06	3/ 3 (100.0)	3/ 3 (100.0)	3/ 3 (100.0)	3/ 3 (100.0)	3/ 3 (100.0)	3/ 3 (100.0)
0.12	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)
0.25	1/ 1 (100.0)	1/ 1 (100.0)	0/ 1 (0.0)	1/ 1 (100.0)	0/ 1 (0.0)	1/ 1 (100.0)

Table 66 Investigator-Assessed Clinical Cure at EOT, Day 10 and PTE by Baseline Pathogen and Oritavancin MIC (MicroE population) Pathogen: *Streptococcus anginosus*

	Clinical Cure at EOT		Clinical Cure at Day 10		Clinical Cure at PTE	
MIC	Oritavancin (N=201)	Vancomycin (N=201)	Oritavancin (N=201)	Vancomycin (N=201)	Oritavancin (N=201)	Vancomycin (N=201)
Total	2/ 2 (100.0)	5/ 5 (100.0)	2/ 2 (100.0)	5/ 5 (100.0)	2/ 2 (100.0)	5/ 5 (100.0)
<=0.0005	0	0	0	0	0	0
0.001	0	0	0	0	0	0
0.002	1/ 1 (100.0)	1/ 1 (100.0)	1/ 1 (100.0)	1/ 1 (100.0)	1/ 1 (100.0)	1/ 1 (100.0)
0.004	0	0	0	0	0	0
0.008	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)
0.015	0	0	0	0	0	0
0.03	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0
0.06	0	2/ 2 (100.0)	0	2/ 2 (100.0)	0	2/ 2 (100.0)
0.12	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)

Table 67 Investigator-Assessed Clinical Cure at EOT, Day 10 and PTE by Baseline Pathogen and Oritavancin MIC (MicroE population) Pathogen: *Streptococcus constellatus*

	Clinical Cure at EOT		Clinical Cure at Day 10		Clinical Cure at PTE	
MIC	Oritavancin (N=201)	Vancomycin (N=201)	Oritavancin (N=201)	Vancomycin (N=201)	Oritavancin (N=201)	Vancomycin (N=201)
Total	7/ 7 (100.0)	7/ 8 (87.5)	7/ 7 (100.0)	7/ 8 (87.5)	7/ 7 (100.0)	7/ 8 (87.5)
<=0.0005	0	0	0	0	0	0
0.001	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)
0.002	2/ 2 (100.0)	0	2/ 2 (100.0)	0	2/ 2 (100.0)	0
0.004	0	0	0	0	0	0
0.008	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)
0.015	1/ 1 (100.0)	3/ 4 (75.0)	1/ 1 (100.0)	3/ 4 (75.0)	1/ 1 (100.0)	3/ 4 (75.0)
0.03	3/ 3 (100.0)	0	3/ 3 (100.0)	0	3/ 3 (100.0)	0
0.06	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)
0.12	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0
0.25	0	0	0	0	0	0
0.5	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)

Table 68 Investigator-Assessed Clinical Cure at EOT, Day 10 and PTE by Baseline Pathogen and Oritavancin MIC (MicroE population) Pathogen: *Streptococcus dysgalactiae*

	Clinical Cure at EOT		Clinical Cure at Day 10		Clinical Cure at PTE	
MIC	Oritavancin (N=201)	Vancomycin (N=201)	Oritavancin (N=201)	Vancomycin (N=201)	Oritavancin (N=201)	Vancomycin (N=201)
Total	1/ 3 (33.3)	2/ 2 (100.0)	1/ 3 (33.3)	2/ 2 (100.0)	2/ 3 (66.7)	2/ 2 (100.0)
<=0.0005	0	0	0	0	0	0
0.001	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)
0.002	0	0	0	0	0	0
0.004	0	0	0	0	0	0
0.008	0	0	0	0	0	0
0.015	0	0	0	0	0	0
0.03	0	0	0	0	0	0
0.06	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0
0.12	0/ 1 (0.0)	1/ 1 (100.0)	0/ 1 (0.0)	1/ 1 (100.0)	1/ 1 (100.0)	1/ 1 (100.0)
0.25	0	0	0	0	0	0
0.5	0/ 1 (0.0)	0	0/ 1 (0.0)	0	0/ 1 (0.0)	0

Table 69 Investigator-Assessed Clinical Cure at EOT, Day 10 and PTE by Baseline Pathogen and Oritavancin MIC (MicroE population) Pathogen: *Streptococcus intermedius*

	Clinical Cure at EOT		Clinical Cure at Day 10		Clinical Cure at PTE	
MIC	Oritavancin (N=201)	Vancomycin (N=201)	Oritavancin (N=201)	Vancomycin (N=201)	Oritavancin (N=201)	Vancomycin (N=201)
Total	3/ 3 (100.0)	3/ 3 (100.0)	3/ 3 (100.0)	3/ 3 (100.0)	3/ 3 (100.0)	3/ 3 (100.0)
<=0.0005	2/ 2 (100.0)	1/ 1 (100.0)	2/ 2 (100.0)	1/ 1 (100.0)	2/ 2 (100.0)	1/ 1 (100.0)
0.001	0	0	0	0	0	0
0.002	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)
0.004	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0
0.008	0	0	0	0	0	0
0.015	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)
0.03	0	0	0	0	0	0

Table 70 Investigator-Assessed Clinical Cure at EOT, Day 10 and PTE by Baseline Pathogen and Oritavancin MIC (MicroE population) Pathogen: *Streptococcus pyogenes*

	Clinical Cure at EOT		Clinical Cure at Day 10		Clinical Cure at PTE	
MIC	Oritavancin (N=201)	Vancomycin (N=201)	Oritavancin (N=201)	Vancomycin (N=201)	Oritavancin (N=201)	Vancomycin (N=201)
Total	5/ 6 (83.3)	5/ 5 (100.0)	5/ 6 (83.3)	5/ 5 (100.0)	6/ 6 (100.0)	5/ 5 (100.0)
<=0.0005	0	0	0	0	0	0
0.001	0	0	0	0	0	0
0.002	0	0	0	0	0	0
0.004	0	0	0	0	0	0
0.008	0/ 1 (0.0)	0	0/ 1 (0.0)	0	1/ 1 (100.0)	0
0.015	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)
0.03	1/ 1 (100.0)	2/ 2 (100.0)	1/ 1 (100.0)	2/ 2 (100.0)	1/ 1 (100.0)	2/ 2 (100.0)
0.06	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0
0.12	2/ 2 (100.0)	1/ 1 (100.0)	2/ 2 (100.0)	1/ 1 (100.0)	2/ 2 (100.0)	1/ 1 (100.0)
0.25	1/ 1 (100.0)	1/ 1 (100.0)	1/ 1 (100.0)	1/ 1 (100.0)	1/ 1 (100.0)	1/ 1 (100.0)

Summary of MIC by Baseline Pathogen (SOLO II)

This section provides a summary of the investigator's assessment of the SOLO II clinical response and microbiology outcome by MIC for the microbiologically evaluable (ME) population from the SOLO II controlled study. Microbiology samples were required only at baseline. The distribution of species and the in vitro susceptibility of baseline pathogens in the micro-evaluable (ME) populations are summarized; a summary of the susceptibility profile of all the isolates obtained in the SOLO I trial is presented below.

There were a total of 9 *E. faecalis* isolates obtained in the SOLO II trial, the oritavancin MIC ranged from 0.015-0.06 mcg/ml, with an MIC90 of 0.06 mcg/ml (Table 71).

Table 71 Summary Statistics of MIC (ug/mL) by Baseline Pathogen (MicroE population)
Pathogen: *Enterococcus faecalis* Medium = MIC-BROTH, Sensititre Plate = Broth microdilution for aerobic Gram-positive organisms

# of Isolates	Antibiotic Test	------MIC------ Min	Max	Mode	MIC50	MIC90
9	AMPICILLIN	0.5	1	0.5	0.5	1
	CLINDAMYCIN	>2	>2	>2	>2	>2
	DAPTOMYCIN	0.5	4	1	1	4
	ERYTHROMYCIN	0.5	>4	1	2	>4
	GENTAMICIN	<=500	>500	<=500	<=500	>500
	LEVOFLOXACIN	0.5	2	0.5	0.5	2
	LINEZOLID	1	2	2	2	2
	ORITAVANCIN	0.015	0.06	0.03	0.03	0.06
	OXACILLIN	2	>4	>4	>4	>4
	STREPTOMYCIN	<=1000	<=1000	<=1000	<=1000	<=1000
	TEICOPLANIN	0 25	0.5	0.5	0.5	0.5
	TETRACYCLINE	0 25	>32	32	32	>32
	TRIMETH/ SULFA	<=0.5	1	<=0.5	<=0.5	1
	VANCOMYCIN	0.5	2	0.5	0.5	2

There were a total of 170 MRSA isolates and 262 MSSA isolates obtained in the ME population in the SOLO II study in both the oritavancin and vancomycin treatment arms. Against all MRSA (Table 72), the oritavancin MIC ranged from 0.015-0.25 mcg/ml (MIC90=0.12 mcg/ml). Against MSSA (Table 73), the oritavancin MIC ranged from 0.008-0.25 mcg/ml (MIC90=0.12 mcg/ml).

Table 72 Summary Statistics of MIC (ug/mL) by Baseline Pathogen (MicroE population)
Pathogen: *Staphylococcus aureus* – MRSA Medium = MIC-BROTH, Sensititre Plate = Broth microdilution for aerobic Gram-positive organisms

# of Isolates	Antibiotic Test	------MIC------ Min	Max	Mode	MIC50	MIC90
170	AMPICILLIN	0.5	>16	>16	>16	>16
	CLINDAMYCIN	0.06	>2	0.12	0.12	0.25
	DAPTOMYCIN	0.25	1	0.5	0.5	0.5
	ERYTHROMYCIN	0.25	>4	>4	>4	>4
	GENTAMICIN	<=500	>500	<=500	<=500	<=500
	LEVOFLOXACIN	0.12	>4	4	4	4
	LINEZOLID	<=0.5	4	2	2	2
	ORITAVANCIN	0.015	0.25	0.03	0.03	0.12
	OXACILLIN**	1	>4	>4	>4	>4
	STREPTOMYCIN	<=1000	>1000	<=1000	<=1000	<=1000
	TEICOPLANIN	0.25	2	0.5	0.5	1
	TETRACYCLINE	0.12	>32	0.25	0.25	0.5
	TRIMETH/ SULFA	<=0.5	>4	<=0.5	<=0.5	<=0.5
	VANCOMYCIN	0.5	1	0.5	0.5	0.5

Table 73 Summary Statistics of MIC (ug/mL) by Baseline Pathogen (MicroE population)
Pathogen: *Staphylococcus aureus* – MSSA Medium = MIC-BROTH, Sensititre Plate = Broth microdilution for aerobic Gram-positive organisms

# of Isolates	Antibiotic Test	------MIC------ Min	Max	Mode	MIC50	MIC90
262	AMPICILLIN	<=0.25	>16	<=0.25	2	>16
	CLINDAMYCIN	0.06	>2	0.12	0.12	0.25
	DAPTOMYCIN	0.25	1	0.5	0.5	0.5
	ERYTHROMYCIN	<=0.12	>4	0.5	0.5	>4
	GENTAMICIN	<=500	<=500	<=500	<=500	<=500
	LEVOFLOXACIN	<=0.03	>4	0.12	0.12	4
	LINEZOLID	<=0.5	>4	2	2	2
	ORITAVANCIN	0.008	0.25	0.03	0.06	0.12
	OXACILLIN	<=0.06	0.5	0.25	0.25	0.5
	STREPTOMYCIN	<=1000	<=1000	<=1000	<=1000	<=1000
	TEICOPLANIN	0.25	2	1	0.5	1
	TETRACYCLINE	<=0.06	>32	0.25	0.25	0.5
	TRIMETH/ SULFA	<=0.5	>4	<=0.5	<=0.5	1
	VANCOMYCIN	<=0.25	1	0.5	0.5	1

There were a total of 83 streptococcal isolates obtained from the SOLO II study. The MIC ranged from ≤ 0.0005- 0.5 mcg/ml. Against 5 *Streptococcus agalactiae* isolates (Table 74), the MIC90 ranged from 0.015-0.12 mcg/ml (MIC90=0.12 mcg/ml). Against 20 *S. constellatus* isolates (Table 75), the oritavancin MIC for the baseline pathogens ranged from ≤ 0.0005- 0.25 mcg/ml (MIC90=0.0.045 mcg/ml). Against 7 *S. dysgalactiae* (Table 76), the oritavancin MIC ranged from 0.002-0.5 mcg/ml (MIC90=0.5 mcg/ml). For 14 *S. intermedius* the oritavancin MIC ranged from ≤ 0.0005- 0.06mcg/ml (MIC90=0.03 mcg/ml) (Table 77). For 37 *S. pyogenes* (Table 78) the MIC the oritavancin MIC ranged from 0.015-0.5 (MIC90 0.25 mcg/ml).

Table 74 Summary Statistics of MIC (ug/mL) by Baseline Pathogen (MicroE population)
Pathogen: *Streptococcus agalactiae* Medium = MIC-BROTH, Sensititre Plate = Streptococci Panel (Frozen, inoculate with CAMHB + LHB)

# of Isolates	Antibiotic Test	------MIC------ Min	Max	Mode	MIC50	MIC90
5	CLINDAMYCIN	0.06	>2	0.06	0.06	>2
	DAPTOMYCIN	0.12	0.25	0.25	0.25	0.25
	ERYTHROMYCIN	0.03	>2	0.06	0.06	>2
	LEVOFLOXACIN	0.5	1	0.5	0.5	1
	LINEZOLID	0.5	1	0.5	0.5	1
	ORITAVANCIN	0.015	0.12	0.06	0.06	0.12
	PENICILLIN	<=0.03	<=0.03	<=0.03	<=0.03	<=0.03
	TEICOPLANIN	0.06	0.06	0.06	0.06	0.06
	TETRACYCLINE	8	>16	>16	>16	>16
	TRIMETH/ SULFA^	<=0.06	0.12	<=0.06	<=0.06	0.12
	VANCOMYCIN	0.25	0.5	0.25	0.25	0.5

Table 75 Summary Statistics of MIC (ug/mL) by Baseline Pathogen (MicroE population) Pathogen: *Streptococcus constellatus* Medium = MIC-BROTH, Sensititre Plate = Streptococci Panel (Frozen, inoculate with CAMHB + LHB)

# of Isolates	Antibiotic Test	------MIC------ Min	Max	Mode	MIC50	MIC90
20	CLINDAMYCIN	<=0.015	>2	0.03	0.03	>2
	DAPTOMYCIN	<=0.03	1	0.5	0.5	1
	ERYTHROMYCIN	<=0.015	>2	0.03	0.03	>2
	LEVOFLOXACIN	<=0.03	0.5	0.5	0.5	0.5
	LINEZOLID	<=0.25	1	1	1	1
	ORITAVANCIN	<=0.0005	0.25	0.015	0.015	0.045
	PENICILLIN	<=0.03	0.12	<=0.03	<=0.03	0.06
	TEICOPLANIN	<=0.03	0.12	<=0.03	<=0.03	0.12
	TETRACYCLINE	<=0.03	>16	8	0.375	>16
	TRIMETH/ SULFA	<=0.06	0.25	<=0.06	<=0.06	<=0.06
	VANCOMYCIN	<=0.015	0.5	0.5	0.5	0.5

Table 76 Summary Statistics of MIC (ug/mL) by Baseline Pathogen (MicroE population) Pathogen: *Streptococcus dysgalactiae* Medium = MIC-BROTH, Sensititre Plate = Streptococci Panel (Frozen, inoculate with CAMHB + LHB)

# of Isolates	Antibiotic Test	------MIC------ Min	Max	Mode	MIC50	MIC90
7	CLINDAMYCIN	<=0.015	0.25	0.06	0.06	0.25
	DAPTOMYCIN	0.06	0.5	0.06	0.12	0.5
	ERYTHROMYCIN	<=0.015	1	0.06	0.06	1
	LEVOFLOXACIN	0.06	0.5	0.5	0.5	0.5
	LINEZOLID	0.5	1	1	1	1
	ORITAVANCIN	0.002	0.5	0.002	0.03	0.5
	PENICILLIN	<=0.03	0.12	<=0.03	<=0.03	0.12
	TEICOPLANIN	<=0.03	0.06	<=0.03	<=0.03	0.06
	TETRACYCLINE	0.12	16	0.25	1	16
	TRIMETH/ SULFA^	<=0.06	0.25	<=0.06	<=0.06	0.25
	VANCOMYCIN	0.12	0.5	0.5	0.25	0.5

Table 77 Summary Statistics of MIC (ug/mL) by Baseline Pathogen (MicroE population) Pathogen: *Streptococcus intermedius* Medium = MIC-BROTH, Sensititre Plate = Streptococci Panel (Frozen, inoculate with CAMHB + LHB)

# of Isolates	Antibiotic Test	------MIC------ Min	Max	Mode	MIC50	MIC90
14	CLINDAMYCIN	<=0.015	0.06	<=0.015	<=0.015	0.03
	DAPTOMYCIN	<=0.03	1	0.12	0.12	0.5
	ERYTHROMYCIN	<=0.015	>2	<=0.015	<=0.015	>2
	LEVOFLOXACIN	<=0.03	1	0.25	0.25	0.5
	LINEZOLID	<=0.25	1	<=0.25	<=0.25	1
	ORITAVANCIN ^	<=0.0005	0.06	0.002	0.004	0.03
	PENICILLIN	<=0.03	0.5	<=0.03	<=0.03	0.06
	TEICOPLANIN ^	<=0.03	0.12	<=0.03	<=0.03	0.06
	TETRACYCLINE	<=0.03	>16	<=0.03	<=0.03	>16
	TRIMETH/ SULFA^	<=0.06	0.5	<=0.06	<=0.06	0.25
	VANCOMYCIN	<=0.015	1	0.5	0.5	0.5

Table 78 Summary Statistics of MIC (ug/mL) by Baseline Pathogen (MicroE population) Pathogen: Streptococcus pyogenes Medium = MIC-BROTH, Sensititre Plate = Streptococci Panel (Frozen, inoculate with CAMHB + LHB)

# of Isolates	Antibiotic Test	-----MIC----- Min	Max	Mode	MIC50	MIC90
37	CLINDAMYCIN	0.03	>2	0.03	0.06	>2
	DAPTOMYCIN	<=0.03	0.12	0.06	0.06	0.06
	ERYTHROMYCIN	<=0.015	>2	0.06	0.06	>2
	LEVOFLOXACIN	0.25	2	0.5	0.5	1
	LINEZOLID	0.5	1	1	1	1
	ORITAVANCIN	0.015	0.5	0.06	0.06	0.25
	PENICILLIN	<=0.03	<=0.03	<=0.03	<=0.03	<=0.03
	TEICOPLANIN	<=0.03	0.06	<=0.03	<=0.03	0.06
	TETRACYCLINE	0.06	>16	>16	>16	>16
	TRIMETH/ SULFA	<=0.06	>8	0.12	0.12	0.5
	VANCOMYCIN	0.25	0.25	0.25	0.25	0.25

MIC with clinical and microbiological outcome (SOLO II)

This section provides a summary of the investigator's assessment of oritavancin clinical response at clinical cure at end of treatment, clinical cure at Day 10 and at the post therapy evaluation (PTE).

There were a total of 6 *Enterococcus faecalis* isolates obtained in the oritavancin treatment arm of the SOLO II study and a positive clinical response was observed for enterococci for MIC values up to 0.06 mcg/ml; there were a total of 4 *E. faecalis isolates* (Table 79) At the EOT clinical cure, the 10-day clinical cure and at the clinical cure at PTE, the efficacy rate was 75 % in the oritavancin treatment group. There was one failure reported at an MIC of 0.015 mcg/ml. In the vancomycin treatment group, an 80% (4/5) efficacy rate was reported.

Table 79 Investigator-Assessed Clinical Cure at EOT, Day 10 and PTE by Baseline Pathogen and Oritavancin MIC (MicroE population) Pathogen: *Enterococcus faecalis*

	Clinical Cure at EOT		Clinical Cure at Day 10		Clinical Cure at PTE	
MIC	Oritavancin (N=246)	Vancomycin (N=247)	Oritavancin (N=246)	Vancomycin (N=247)	Oritavancin (N=246)	Vancomycin (N=247)
Total	3/ 4 (75.0)	5/ 5 (100.0)	3/ 4 (75.0)	5/ 5 (100.0)	3/ 4 (75.0)	4/ 5 (80.0)
<=0.0005	0	0	0	0	0	0
0.001	0	0	0	0	0	0
0.002	0	0	0	0	0	0
0.004	0	0	0	0	0	0
0.008	0	0	0	0	0	0
0.015	1/ 2 (50.0)	1/ 1 (100.0)	1/ 2 (50.0)	1/ 1 (100.0)	1/ 2 (50.0)	1/ 1 (100.0)
0.03	1/ 1 (100.0)	4/ 4 (100.0)	1/ 1 (100.0)	4/ 4 (100.0)	1/ 1 (100.0)	3/ 4 (75.0)
0.06	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0
0.12	0	0	0	0	0	0

A summary of the SOLO II MIC versus the Investigator's assessment of clinical outcome at EOT, Day-10 and at PTE is provided for MRSA and MSSA in Table 80 and Table 81 below. A positive clinical response was observed against all MRSA of 0.25 mcg/ml. Against MRSA, the highest MIC associated with clinical cure was 0.25 mcg/ml; 4/5

patients were considered to be cure at the EOT. Against MSSA, the highest MIC associated with clinical cure was also 0.25 mcg/ml.

Table 80 Investigator-Assessed Clinical Cure at EOT, Day 10 and PTE by Baseline Pathogen and Oritavancin MIC (MicroE population) Pathogen: *Staphylococcus aureus* – MRSA

	Clinical Cure at EOT		Clinical Cure at Day 10		Clinical Cure at PTE	
MIC	Oritavancin (N=246)	Vancomycin (N=247)	Oritavancin (N=246)	Vancomycin (N=247)	Oritavancin (N=246)	Vancomycin (N=247)
Total	83/ 88 (94.3)	79/ 82 (96.3)	83/ 88 (94.3)	79/ 82 (96.3)	81/ 88 (92.0)	79/ 82 (96.3)
<=0.0005	0	0	0	0	0	0
0.001	0	0	0	0	0	0
0.002	0	0	0	0	0	0
0.004	0	0	0	0	0	0
0.008	0	0	0	0	0	0
0.015	16/ 16 (100.0)	9/ 9 (100.0)	16/ 16 (100.0)	9/ 9 (100.0)	15/ 16 (93.8)	9/ 9 (100.0)
0.03	36/ 37 (97.3)	30/ 31 (96.8)	36/ 37 (97.3)	30/ 31 (96.8)	36/ 37 (97.3)	30/ 31 (96.8)
0.06	21/ 22 (95.5)	25/ 27 (92.6)	21/ 22 (95.5)	25/ 27 (92.6)	19/ 22 (86.4)	25/ 27 (92.6)
0.12	6/ 8 (75.0)	13/ 13 (100.0)	6/ 8 (75.0)	13/ 13 (100.0)	6/ 8 (75.0)	13/ 13 (100.0)
0.25	4/ 5 (80.0)	2/ 2 (100.0)	4/ 5 (80.0)	2/ 2 (100.0)	5/ 5 (100.0)	2/ 2 (100.0)

Table 81 Investigator-Assessed Clinical Cure at EOT, Day 10 and PTE by Baseline Pathogen and Oritavancin MIC (MicroE population) Pathogen: *Staphylococcus aureus* – MSSA

	Clinical Cure at EOT		Clinical Cure at Day 10		Clinical Cure at PTE	
MIC	Oritavancin (N=246)	Vancomycin (N=247)	Oritavancin (N=246)	Vancomycin (N=247)	Oritavancin (N=246)	Vancomycin (N=247)
Total	125/127 (98.4)	131/133 (98.5)	127/128 (99.2)	132/134 (98.5)	124/127 (97.6)	130/134 (97.0)
<=0.0005	0	0	0	0	0	0
0.001	0	0	0	0	0	0
0.002	0	0	0	0	0	0
0.004	0	0	0	0	0	0
0.008	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0
0.015	8/ 8 (100.0)	16/ 16 (100.0)	9/ 9 (100.0)	16/ 16 (100.0)	9/ 9 (100.0)	16/ 16 (100.0)
0.03	48/ 49 (98.0)	48/ 48 (100.0)	49/ 49 (100.0)	49/ 49 (100.0)	48/ 49 (98.0)	48/ 49 (98.0)
0.06	43/ 44 (97.7)	44/ 45 (97.8)	43/ 44 (97.7)	44/ 45 (97.8)	41/ 43 (95.3)	44/ 45 (97.8)
0.12	19/ 19 (100.0)	19/ 20 (95.0)	19/ 19 (100.0)	19/ 20 (95.0)	19/ 19 (100.0)	18/ 20 (90.0)
0.25	6/ 6 (100.0)	4/ 4 (100.0)	6/ 6 (100.0)	4/ 4 (100.0)	6/ 6 (100.0)	4/ 4 (100.0)

A summary of the investigator's assessment for oritavancin clinical response and favorable outcome by MIC and clinical cure at EOT, clinical cure at Day-10 and clinical cure at PTE in the SOLO-I study is provided for streptococci. There were a total of 57 streptococci isolates obtained from the SOLO I study. In the oritavancin treatment arm, there were a total of 37 streptococci isolates (Tables 82-86). A positive clinical response was observed up to 0.5 mcg/ml.

Table 82 Investigator-Assessed Clinical Cure at EOT, Day 10 and PTE by Baseline Pathogen and Oritavancin MIC (MicroE population) Pathogen: *Streptococcus agalactiae*

	Clinical Cure at EOT		Clinical Cure at Day 10		Clinical Cure at PTE	
MIC	Oritavancin (N=246)	Vancomycin (N=247)	Oritavancin (N=246)	Vancomycin (N=247)	Oritavancin (N=246)	Vancomycin (N=247)
Total	1/ 1 (100.0)	4/ 4 (100.0)	1/ 1 (100.0)	4/ 4 (100.0)	1/ 1 (100.0)	4/ 4 (100.0)
<=0.0005	0	0	0	0	0	0
0.001	0	0	0	0	0	0
0.002	0	0	0	0	0	0
0.004	0	0	0	0	0	0
0.008	0	0	0	0	0	0
0.015	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0
0.03	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)
0.06	0	2/ 2 (100.0)	0	2/ 2 (100.0)	0	2/ 2 (100.0)
0.12	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)
0.25	0	0	0	0	0	0

Table 83 Investigator-Assessed Clinical Cure at EOT, Day 10 and PTE by Baseline Pathogen and Oritavancin MIC (MicroE population) Pathogen: *Streptococcus constellatus*

	Clinical Cure at EOT		Clinical Cure at Day 10		Clinical Cure at PTE	
MIC	Oritavancin (N=246)	Vancomycin (N=247)	Oritavancin (N=246)	Vancomycin (N=247)	Oritavancin (N=246)	Vancomycin (N=247)
Total	8/ 9 (88.9)	11/ 11 (100.0)	8/ 9 (88.9)	11/ 11 (100.0)	8/ 9 (88.9)	11/ 11 (100.0)
<=0.0005	0/ 1 (0.0)	1/ 1 (100.0)	0/ 1 (0.0)	1/ 1 (100.0)	0/ 1 (0.0)	1/ 1 (100.0)
0.001	0	0	0	0	0	0
0.002	0	0	0	0	0	0
0.004	1/ 1 (100.0)	1/ 1 (100.0)	1/ 1 (100.0)	1/ 1 (100.0)	1/ 1 (100.0)	1/ 1 (100.0)
0.008	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0
0.015	4/ 4 (100.0)	4/ 4 (100.0)	4/ 4 (100.0)	4/ 4 (100.0)	4/ 4 (100.0)	4/ 4 (100.0)
0.03	1/ 1 (100.0)	4/ 4 (100.0)	1/ 1 (100.0)	4/ 4 (100.0)	1/ 1 (100.0)	4/ 4 (100.0)
0.06	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)
0.12	0	0	0	0	0	0
0.25	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0

Table 84 Investigator-Assessed Clinical Cure at EOT, Day 10 and PTE by Baseline Pathogen and Oritavancin MIC (MicroE population) Pathogen: *Streptococcus dysgalactiae*

	Clinical Cure at EOT		Clinical Cure at Day 10		Clinical Cure at PTE	
MIC	Oritavancin (N=246)	Vancomycin (N=247)	Oritavancin (N=246)	Vancomycin (N=247)	Oritavancin (N=246)	Vancomycin (N=247)
Total	4/ 4 (100.0)	1/ 2 (50.0)	5/ 5 (100.0)	1/ 2 (50.0)	5/ 5 (100.0)	1/ 2 (50.0)
<=0.0005	0	0	0	0	0	0
0.001	0	0	0	0	0	0
0.002	1/ 1 (100.0)	1/ 1 (100.0)	1/ 1 (100.0)	1/ 1 (100.0)	1/ 1 (100.0)	1/ 1 (100.0)
0.004	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0
0.008	0	0	0	0	0	0
0.015	0	0	0	0	0	0
0.03	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0
0.06	0	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0
0.12	0	0/ 1 (0.0)	0	0/ 1 (0.0)	0	0/ 1 (0.0)
0.25	0	0	0	0	0	0
0.5	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0

Table 85 Investigator-Assessed Clinical Cure at EOT, Day 10 and PTE by Baseline Pathogen and Oritavancin MIC (MicroE population) Pathogen: *Streptococcus intermedius*

	Clinical Cure at EOT		Clinical Cure at Day 10		Clinical Cure at PTE	
MIC	Oritavancin (N=246)	Vancomycin (N=247)	Oritavancin (N=246)	Vancomycin (N=247)	Oritavancin (N=246)	Vancomycin (N=247)
Total	4/ 4 (100.0)	9/ 9 (100.0)	5/ 5 (100.0)	9/ 9 (100.0)	5/ 5 (100.0)	9/ 9 (100.0)
<=0.0005	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)
0.001	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0
0.002	0	4/ 4 (100.0)	0	4/ 4 (100.0)	0	4/ 4 (100.0)
0.004	0	3/ 3 (100.0)	0	3/ 3 (100.0)	0	3/ 3 (100.0)
0.008	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)
0.015	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0
0.03	1/ 1 (100.0)	0	2/ 2 (100.0)	0	2/ 2 (100.0)	0
0.06	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0

Table 86 Investigator-Assessed Clinical Cure at EOT, Day 10 and PTE by Baseline Pathogen and Oritavancin MIC (MicroE population) Pathogen: *Streptococcus pyogenes*

	Clinical Cure at EOT		Clinical Cure at Day 10		Clinical Cure at PTE	
MIC	Oritavancin (N=246)	Vancomycin (N=247)	Oritavancin (N=246)	Vancomycin (N=247)	Oritavancin (N=246)	Vancomycin (N=247)
Total	19/ 19 (100.0)	17/ 18 (94.4)	19/ 19 (100.0)	17/ 18 (94.4)	19/ 19 (100.0)	17/ 18 (94.4)
<=0.0005	0	0	0	0	0	0
0.001	0	0	0	0	0	0
0.002	0	0	0	0	0	0
0.004	0	0	0	0	0	0
0.008	0	0	0	0	0	0
0.015	2/ 2 (100.0)	2/ 2 (100.0)	2/ 2 (100.0)	2/ 2 (100.0)	2/ 2 (100.0)	2/ 2 (100.0)
0.03	4/ 4 (100.0)	2/ 2 (100.0)	4/ 4 (100.0)	2/ 2 (100.0)	4/ 4 (100.0)	2/ 2 (100.0)
0.06	7/ 7 (100.0)	6/ 6 (100.0)	7/ 7 (100.0)	6/ 6 (100.0)	7/ 7 (100.0)	6/ 6 (100.0)
0.12	2/ 2 (100.0)	4/ 4 (100.0)	2/ 2 (100.0)	4/ 4 (100.0)	2/ 2 (100.0)	4/ 4 (100.0)
0.25	4/ 4 (100.0)	2/ 3 (66.7)	4/ 4 (100.0)	2/ 3 (66.7)	4/ 4 (100.0)	2/ 3 (66.7)
0.5	0	1/ 1 (100.0)	0	1/ 1 (100.0)	0	1/ 1 (100.0)

Correlation of microbiological response with in vitro susceptibility results in study SOLO I and SOLOII:

The antimicrobial breakpoint is defined as the drug concentration that differentiates between dissimilar populations of microorganisms and isolates are subsequently classified as susceptible, intermediate or resistant. Additionally, methods using zone diameters to classify bacteria as susceptible or resistant to antibiotics depend on clinically meaningful MICs, a representative sample of bacteria, adequate and reproducible methods for determining MICs and zone diameters and a method for the relation of zone diameters to MICs. The classification scheme for showing a correlation between MIC and zone diameters is referred to as the error-rate bounded method and is presented by scattergrams. However, in this submission, there are no disk susceptibility data to correlate with broth dilution MIC.

The combined microbiological rates for oritavancin against methicillin resistant *S. aureus* (MRSA) isolates as a function of MIC are shown in are shown in Table 87. There were 174 MRSA isolates in the oritavancin treatment arm that had an MIC range from 0.015-0.25 mcg/ml. Of the 174 MRSA isolates, the Applicant reported 8 microbiological failures at clinical cure (1 failure at 0.003 mcg/ml, 4 failures at an MIC of 0.06 mcg/ml, 3 at MIC of 0.12 mcg/ml and one failure at 0.25 mcg/ml). In the vancomycin treatment arm, there were a total of 6 failures between 0.03-0.12 mcg/ml.

Table 87: Microbiological success by Oritavancin (ORI) and Vancomycin (VAN) MIC against *Staphylococcus aureus* MRSA (SOLO I and SOLO II combined)

MIC (mcg/ml) ORI	n/N 166/174	% Clinical Cure at EOT	MIC (mcg/ml) VAN	n/N 150/156	% Clinical Cure at EOT
0.015	20/20	100	0.015	11/11	100
0.003	79/80	99	0.003	62/64	97
0.06	43/47	91	0.06	55/57	96.5
0.12	19/21	83	0.12	19/21	90.5
0.25	5/6	95	0.25	3/3	100

The combined microbiological rates for oritavancin against methicillin resistant *S. aureus* (MSSA) isolates as a function of MIC are shown in are shown in Table 88. There were 221 MSSA isolates in the oritavancin treatment arm that had an MIC range from 0.015-0.25 mcg/ml. Of the 221 MSSA isolates, the Applicant reported 10 microbiological failures at clinical cure (There were 5 failures at an MIC of 0.003 mcg/ml, and 4 failures at an MIC of 0.12. In the vancomycin treatment arm, there were a total of 8 failures between 0.03-0.06 mcg/ml.

Table 88: Microbiological success by Oritavancin (ORI) and Vancomycin (VAN) MIC against *Staphylococcus aureus* MSSA (SOLO I and SOLO II combined)

MIC (mcg/ml) ORI	n/N 211/221	% Clinical Cure at EOT	MIC (mcg/ml) VAN	n/N 219/227	% Clinical Cure at EOT
-	-	-	0.002	1/1	100
0.015	14/14	100	0.015	21/21	100
0.003	82/88	93	0.003	87/89	97.8
0.06	77/81	95	0.06	72/76	94.7
0.12	28/28	100	0.12	31/33	94
0.25	10/10	100	0.25	7/7	100

Table 89 shows the *E. faecalis* success rates for oritavancin and vancomycin, respectively. There were a total of 10 isolates, and an overall success rate of 80% was observed. There was one failure at with an oritavancin MIC of 0.015 mcg/ml. In contrast, the vancomycin treatment arm a success rate of 100% was observed.

Table 89: Microbiological success by Oritavancin (ORI) and Vancomycin (VAN) MIC against *Enterococcus faecalis* (SOLO I and SOLO II combined)

MIC (mcg/ml) ORI	n/N 8/10	% Clinical Cure at EOT	MIC (mcg/ml) VAN	n/N 10/10	% Clinical Cure at EOT
0.015	2/3	67	0.015	2/2	100
0.003	4/4	100	0.003	7/7	100
0.06	2/2	100	0.06	1/1	100
0.12	0/1	0	0.12	-	

Oritavancin demonstrated activity against streptococcal isolates. Against *S. dysgalactiae*, the MIC ranged from 0.002-0.5 mcg/ml. Among baseline isolates, a 71% (5/7) success rate was observed. Additionally, there was one failure at an MIC of 0.12 mcg/ml and at an MIC of 0.5 mcg/ml in the oritavancin treatment group. In the vancomycin treatment group a success rate of 75% (3/4) was observed among baseline isolates at EOT (Table 90).

Table 90: Microbiological success by Oritavancin (ORI) and Vancomycin (VAN) MIC against *Streptococcus dysgalactiae* (SOLO I and SOLO II combined)

MIC (mcg/ml) ORI	n/N 5/7	% Clinical Cure at EOT	MIC (mcg/ml) VAN	n/N 3/4	% Clinical Cure at EOT
0.002	1/1	100	0.001	1/1	100
0.004	1/1	100	0.002	1/1	100
0.008	-	-	0.12	1/2	50

0.015	**-**	**-**
0.03	**1/1**	**100**
0.06	**1/1**	**100**
0.12	**0/1**	**0**
0.25	**-**	**-**
0.5	**1/2**	**50**

Against *S. intermedius*, the MIC ranged from ≤0.0005-0.06 mcg/ml. Among baseline isolates, a 100% (7/7) success rate was observed. In the vancomycin treatment group a success rate of 100% (12/12) was observed among baseline isolates at EOT (Table 91).

Table 91: Microbiological success by Oritavancin (ORI) and Vancomycin (VAN) MIC against *Streptococcus intermedius* (SOLO I and SOLO II combined)

MIC (mcg/ml) ORI	**n/N 7/7**	**% Clinical Cure at EOT**	**MIC (mcg/ml) VAN**	**n/N 12/12**	**% Clinical Cure at EOT**
≤0.0005	**2/2**	**100**	**≤0.0005**	**2/2**	**100**
0.001	**1/1**	**100**	**0.001**	**-**	**-**
0.002	**-**	**-**	**0.002**	**5/5**	**100**
0.004	**1/1**	**100**	**0.004**	**3/3**	**100**
0.008	**-**	**-**	**0.008**	**1/1**	**100**
0.015	**1/1**	**100**	**0.015**	**1/1**	**100**
0.03	**1/1**	**100**			
0.06	**1/1**	**100**			

Against *Streptococcus pyogenes*, an overall cure rate of 96% (24/25) was reported in the combined SOLO I and SOLO II trials. The MIC ranged from 0.008 mcg/ml- 0.25 mcg/ml. A similar cure rate was observed in the vancomycin treatment group (Table 92).

Table 92: Microbiological success by Oritavancin (ORI) and Vancomycin (VAN) MIC against *Streptococcus pyogenes* (SOLO I and SOLO II combined)

MIC (mcg/ml) ORI	n/N 24/25	% Clinical Cure at EOT	MIC (mcg/ml) VAN	n/N 22/23	% Clinical Cure at EOT
0.008	0/1	0	0.015	3/3	100
0.015	2/2	100	0.03	4/4	100
0.03	5/5	100	0.06	6/6	100
0.06	8/8	100	0.12	5/5	100
0.12	4/4	100	0.25	3/4	100
0.25	5/5	100	0.5	1/1	100

A total of 7 patients in both treatment arms were confirmed to have *Streptococcus agalactiae* and 100 % eradication rate was reported. The MIC ranged from 0.015 to 0.06 mcg/ml. In the Vancomycin treatment group, 11/11 or 100% eradication rate was observed (Table 93).

Table 93: Microbiological success by Oritavancin (ORI) and Vancomycin (VAN) MIC against *Streptococcus agalactiae* (SOLO I and SOLO II combined)

MIC (mcg/ml)	n/N 7/7	% Clinical Cure at EOT	MIC (mcg/ml) VAN	n/N 11/11	% Clinical Cure at EOT
0.015	1/1	100	0.03	3/3	100
0.03	2/2	100	0.06	5/5	100
0.06	3/3	100	0.12	2/2	100
0.12	-	-	0.25	1/1	100
0.25	1/1	100			

A total of two patients in the micro-evaluable subjects were confirmed to have *S. anginosus* and a 100% eradication rate was observed. In the vancomycin treatment group, 5/5 or 100% eradication rate was reported (Table 94).

Table 94: Microbiological success by Oritavancin (ORI) and Vancomycin (VAN) MIC against *Streptococcus anginosus* (SOLO I and SOLO II combined)

MIC (mcg/ml) ORI	n/N 2/2	% Clinical Cure at EOT	MIC (mcg/ml) VAN	n/N 5/5	% Clinical Cure at EOT
≤0.0005	-	-	0.002	1/1	100
0.001	-	-	0.008	1/1	100
0.002	1/1	100	0.06	2/2	100
0.03	1/1	100	0.12	1/1	100

Against *Streptococcus constellatus*, an overall cure rate of 94% (15/16) was reported in the combined SOLO I and SOLO II trials. The MIC ranged from ≤0.0005 mcg/ml- 0.25 mcg/ml. A similar cure rate was observed in the vancomycin treatment group (Table 95).

Table 95: Microbiological success by Oritavancin (ORI) and Vancomycin (VAN) MIC against *Streptococcus constellatus* (SOLO I and SOLO II combined)

MIC (mcg/ml) ORI	n/N 15/16	% Clinical Cure at EOT	MIC (mcg/ml) VAN	n/N 18/19	% Clinical Cure at EOT
≤0.0005	0/1	0	≤0.0005	1/1	100
0.001	-	-	0.001	1/1	100
0.002	2/2	100	0.002	0	0
0.004	1/1	100	0.004	1/1	100
0.008	1/1	100	0.008	0	0
0.015	5/5	100	0.015	7/8	87.5
0.03	4/4	100	0.03	4/4	100

0.06	-	-	**0.06**	**2/2**	**100**
0.12	**1/1**	**100**	**0.12**	-	-
0.25	**1/1**	**100**	**0.25**	**1/1**	**100**
			0.50	**1/1**	**100**

The Applicant presented data on two ABSSSI clinical trials and data from these trials revealed that oritavancin is effective against the targeted gram positive pathogens in ABSSSI. Although the in vitro data suggest that there is a propensity for resistance to develop, there was no evidence to suggest that the development of resistance occurred on oritavancin therapy in the SOLO 1 and SOLO II trials.

MIC susceptibility and resistance interpretive criteria are established by using three principles. The first is the MIC distribution patterns from large surveillance studies; second, is the observation of clinical response data with respect to the prescribed drug dose; third, is the PK/PD characteristics of the drug. Based on the information presented in this review, this Reviewer agrees with the Applicant proposed interpretive criteria presented in Table 96..

Table 96: Proposed Susceptibility Interpretive Criteria for oritavancin

Microorganism	**Minimum Inhibitory Concentration (MIC, µg/mL)**		
	S	**I**	**R**
Staphylococcus aureus (including methicillin-resistant isolates)	≤0.12	-	-
Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus anginosus, Streptococcus constellatus, and Streptococcus intermedius.	≤0.25	-	-
Enterococcus faecalis (vancomycin-susceptible isolates only)	≤0.12	-	-

The Applicant's proposed microbiology subsection of the package insert

12.4 Microbiology

ORBACTIV is a semi-synthetic, lipoglycopeptide (b) (4) ORBACTIV exerts (b) (4) concentration-dependent bactericidal activity against (b) (4)

(b) (4) *S. aureus* (b) (4), *S. pyogenes, E. faecalis* (b) (4)

(b) (4)

Mechanism of Action

Oritavancin has three mechanisms of action (b) (4) : (i) inhibition of the transglycosylation (polymerization) step of cell wall biosynthesis by binding to the stem peptide of peptidoglycan precursors; (ii) inhibition of the transpeptidation (crosslinking) step of cell wall biosynthesis by binding to the peptide bridging segments of the cell wall; and (iii) disruption of bacterial membrane integrity, leading to depolarization, permeabilization, and (b) (4) cell death. These multiple mechanisms contribute to the (b) (4) concentration-dependent bactericidal activity of oritavancin.

Mechanism of Resistance

(b) (4)

(b) (4)

Interaction with Other Antimicrobial Agents
In in vitro studies, oritavancin exhibits synergistic bactericidal activity in combination with gentamicin, moxifloxacin or rifampicin against isolates of MSSA, with gentamicin or linezolid against isolates of (b) (4) hVISA, VISA, and VRSA, and with rifampicin against isolates of VRSA. In vitro studies demonstrated no antagonism between oritavancin and (b) (4) gentamicin, moxifloxacin, linezolid or rifampicin).

Antibacterial Activity
Oritavancin has been shown to be active against most isolates of the following bacteria, both in vitro and in clinical infections as described in the Indications and Usage section *[see Indications and Usage (1.1)]*.
Staphylococcus aureus (including methicillin-resistant isolates)
Streptococcus agalactiae
Streptococcus anginosus group (includes *S. anginosus, S. intermedius,* and *S. constellatus*)
Streptococcus dysgalactiae
Streptococcus pyogenes
Enterococcus faecalis (vancomycin-susceptible isolates only)

The following in vitro data are available but their clinical significance (b) (4). At least 90% of isolates of the following (b) (4) exhibit an oritavancin MIC less than or equal to (b) (4) however, the safety and effectiveness of oritavancin in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

Enterococcus faecium (vancomycin-susceptible isolates only)

Susceptibility Testing Methods
When available, the clinical microbiology laboratory should provide cumulative results of in vitro susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial drug for treatment.

Dilution technique
Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds.[1] Oritavancin MICs should be determined using a standardized

procedure which are based on a broth microdilution method or equivalent with standardized inoculum concentrations and standardized concentrations of oritavancin. The MIC values should be interpreted according to the criteria provided in the Table **3**.

Table 3: Susceptibility Interpretive Criteria for ORBACTIV[a]

Microorganism	**Minimum Inhibitory Concentration (MIC, µg/mL)**		
	S	**I[b]**	**R[b]**
Staphylococcus aureus (including methicillin-resistant isolates)	≤0.12	-	-
Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus anginosus, Streptococcus constellatus, and Streptococcus intermedius.	≤0.25	-	-
Enterococcus faecalis (vancomycin-susceptible isolates only)	≤0.12	-	-

Abbreviations: MIC, minimum inhibitory concentration; S, Susceptible; I, intermediate; R, Resistant

[a] As determined by broth microdilution with 0.002% polysorbate-80 during oritavancin dissolution and dilution and in the final assay.

[b] The current absence of resistant isolates precludes defining any results other than "Susceptible". Isolates yielding test results other than "Susceptible" should be retested, and if the result is confirmed, the isolate should be submitted to a reference laboratory for further testing.

A report of "Susceptible" indicates that the (b) (4) is likely to (b) (4) inhibit (b) (4) if the antibacterial compound reaches the concentration at the infection site (b) (4)

Quality Control

Standardized susceptibility test procedures require the use of laboratory control microorganisms to monitor and ensure the accuracy and precision of supplies and reagents used in the assay and the techniques of the individuals performing the test. Acceptable oritavancin MIC ranges for the quality control strains are shown in Table 4. Quality control microorganisms are specific strains of organisms with intrinsic biological properties, and are very stable strains that will give a standard and reproducible susceptibility pattern. The specific strains used for microbiological quality control are not clinically significant.

Table 4: Acceptable Quality Control Ranges for Oritavancin Susceptibility Testing[a]

Quality Control Organism	Minimum Inhibitory Concentration Range (MIC in µg/mL)
Staphylococcus aureus ATCC 29213	0.015 – 0.12
Streptococcus pneumoniae ATCC 49619	0.001 – 0.004
Enterococcus faecalis ATCC 29212	0.008 – 0.03

ATCC = American Type Culture Collection.
[a] As determined by broth microdilution with 0.002% polysorbate-80 during oritavancin dissolution and dilution and in the final assay.[1,2]

Diffusion technique
The use of the disk diffusion method is not recommended since quality control ranges have not been defined for oritavancin.

15 REFERENCES

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