CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206334Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	206334
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Division / Office	Division of Anti-infectives (DAIP)
Reviewer Name(s)	Mayurika Ghosh, MD
Clinical Team Lead	Yuliya Yasinskaya, MD
Review Completion Date	April 23, 2014
Established Name	Oritavancin diphosphate
(Proposed) Trade Name	Orbactiv
Therapeutic Class	Lipoglycopeptide Antibiotic
Applicant	The Medicines Co.
Formulation(s)	Intravenous
Dosing Regimen	1200 mg IV infusion once
Indication(s)	ABSSSI (acute bacterial skin and skin structure infection)
Intended Population(s)	Adults

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on clinical efficacy and safety data submitted by the Applicant from two randomized, double blind, active controlled clinical trials, there is adequate evidence to recommend the approval of oritavancin as a safe and efficacious treatment for *Acute bacterial skin and skin structure infection (ABSSSI).*

1.2 Risk Benefit Assessment

Oritavancin demonstrated non-inferiority to intravenous vancomycin for the treatment of ABSSSI in two phase 3 trials. The primary efficacy outcome was early clinical response (a composite endpoint of cessation of spread or reduction in size of the baseline lesion, absence of fever, and no rescue antibiotic medication) at 48 to 72 hours from initiation of the first infusion of study drug (early clinical evaluation [ECE] in the population of all randomized treated patients (mITT). The prespecified noninferiority (NI) margin was 10%. The trials also satisfied a key secondary endpoint which was lesion size reduction ≥ 20% at ECE and sustained clinical response at PTE in the mITT population.

For the primary efficacy endpoint the success rates in the mITT population at the ECE Visit was 82% (390/473) in the oritavancin group and 79% (379/481) in the vancomycin group in SOLO1. For the primary efficacy endpoint the success rates in the mITT population at the ECE Visit was 80% (403/503) in the oritavancin group and 83% (416/502) in the vancomycin group in SOLO2. The lower bound of the 95% CI around the difference in clinical response rates was greater than -10%.

The percentage of patients with an investigator-assessed clinical cure was similar in the oritavancin (79.9%) and vancomycin groups (79.6%), in SOLO1 and 82.7% in oritavavncin group and 80.5% in the vancomcyin group in SOLO2. The lower bound of the 95% CI around the difference in clinical response rates was greater than -10% for this endpoint as well.

Lesion Size Reduction ≥ 20% at ECE is the recommended primary efficacy endpoint defined in FDA's ABSSSI current guidance. (Guidance for Industry Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment, October 2013).The percentage of patients in SOLO1 with a lesion size reduction ≥ 20% from baseline at ECE was similar in the oritavancin (86.9%) and vancomycin (82.9%) groups, with a treatment difference of 4.1% and 95% CI of (-0.65, 8.6), meeting the prespecified noninferiority margin of -10%. The percentage of patients in SOLO2 with a lesion size reduction ≥ 20% from baseline at ECE was similar in the oritavancin (86%) and vancomycin (85%) groups, with a treatment difference of 0.6% and 95% CI of (-3.7, 5). The lesion size reduction was seen to be consistent across ECE, EOT and PTE. Although the subgroup analysis showed major cutaneous abscesses, cellulitis, SIRS at baseline, Asian sites, age >=65 yrs, and diabetes had a lower primary efficacy rate in oritavancin arm in

SOLO2 compared to vancomycin 81% vs 90%, 67% vs 75%, 69% vs 81%, 78% vs 86%, 69% vs 85%, and 74% vs 84%, respectively, the overall primary and secondary efficacy endpoints meet the prespecified non inferiority margin.

Oritavancin demonstrated an overall favorable safety profile with similar rates of mortality and non-fatal adverse events as the comparator. The major safety findings are: a possibility of artificial prolongation of some laboratory coagulation tests including activated partial thromboplastin time, prothrombin time and international normalized ratio (INR), elevation of liver function tests, an increase in infections, and tachycardia.
In a 1 month long nonclinical toxicity studies in rats and dogs oritavancin at cumulative exposures of 12-70 x human exposure at 1200 mg single dose was associated with increased levels of serum ALT, AST, ALP and bilirubin, increased liver weights, macroscopic findings of pale livers, microscopic findings of eosinophilic granules in Kupffer cells, and occasional histopathologic findings of hepatocellular vacuolar degeneration and necrosis. There were 27 (2.8%) subjects and 16 (1.6%) subjects with elevated ALT in the oritavancin and vancomycin arm respectively. There were 18 (1.8%) subjects and 16 (1.6%) subjects with elevated AST in the oritavancin and vancomycin arm respectively. Although the history of hepatitis or hepatic condition (9 subjects) or intravenous drug use (12 subjects) could have predisposed the subjects to the elevation of transaminases, there were subjects with no such history where the abnormality occurred while on study treatment. The cases do not appear to be a result of severe sepsis or shock liver.None of the subjects met Hy's Law criteria.
Although the frequency LFT elevation from baseline in both arms was balanced, there was 1 subject in the oritavancin arm versus nonein the vancomcyin arm where ALT levels rose to >10xULN from normal baseline. A postbaseline evaluation of LFTs (ALT/AST>3, TB>1.5, and ALP normal) any time during the study for was seen in 2 subjects in the oritavancin arm compared to none in the vancomycin arm. There were 18 subjects in the oritavancin arm versus 14 subjects in the vancomcyin arm where ALT rose from baseline to 3-5xULN and 3 subjects in the oritavancin arm versus 1 subject in the vancomycin arm where TB rose from normal to 1.5-2xULN. Three cases with significant idiosyncratic ALT elevations fell into the Hy's law quadrant; however, upon closer examination none were found to meet the Hy's law criteria. Also, asymptomatic elevations of LFTs were noted in the moderately impaired group in the hepatic impairment study. Given the possibility of oritavancin use in subjects with moderate hepatic impairment or IVDU, this should be noted in the product labeling.
There were 40 (4%) cases of infection in the oritavancin arm versus 31 (3%) cases in the vancomycin arm. These cases included 5 subjects in the oritavancin arm who had osteomyelitis which on further review appeared to be due to lack of efficacy of oritavancin in osteomyelitis or due to failure to diagnose osteomyelitis at screening. There were also 4 cases of pneumonia in the oritavancin arm in subjects who appeared to have a predisposition to develop pneumonia. The cases of subcutaneous abscesses were slightly higher in the oritavancin arm, but appeared to be failure of efficacy as the infection occurred at the site of the index infection. The adverse events of cellulitis were balanced in both arms for the similar reasons:a lack of efficacy or a lack of timely incision and drainage to control the index infection or a recurrence of infection due to underlying comorbidities. Although the host resistance studied in rats showed a dose related

increase in mortality to *C. albicans* infection, there were no increased fungal or mycobacterial infections at 60 day follow up in the SOLO trials.
There were 24 subjects (4.4%) in the oritavancin arm and 11 subjects (1.9%) in the vancomycin arm in the SOLO pool with the adverse event of tachycardia. No specific conclusions can be drawn from further analysis of this adverse event as no clear relationship was seen between occurrence of tachycardia and exposure to the study drug.
In summary, the data submitted by the applicant demonstrate the acceptable safety profile of oritavancin and provide evidence for approval of oritavancin for the treatment of ABSSSI.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None. The reviewer recommends routine pharmacovigilance for oritavancin.

1.4 Recommendations for Postmarket Requirements and Commitments

Required Pediatric Assessments:

- The applicant submitted the phase 1 pharmacokinetic pediatric protocol for PREA on December 16, 2013. This is a Phase 1 Open-label, Dose-finding, Pharmacokinetics, Safety and Tolerability Study of Oritavancin Single-Dose Infusion in Pediatric Subjects <18 Years of Age with Suspected or Confirmed Bacterial Infections.

  The following age cohorts will be recruited in a step-down fashion: 12 to <18 years, 6 to <12 years, 2 to <6 years, 3 months to <2 years, birth to <3 months (includes 0-28 day neonates). The applicant will also collect CSF to determine oritavavncin levels in the CSF.

  Estimated date first subject enrolled: March 2014
  Estimated date last subject completed: March 2017

- A phase 2 efficacy and safety study, multicenter, evaluator blinded randomized safety and tolerability study with 336 patients stratified by age category: 12 to <18 years, 6 to <12 years, 2 to <6 years, 3 months to <2 years, birth to <3 months

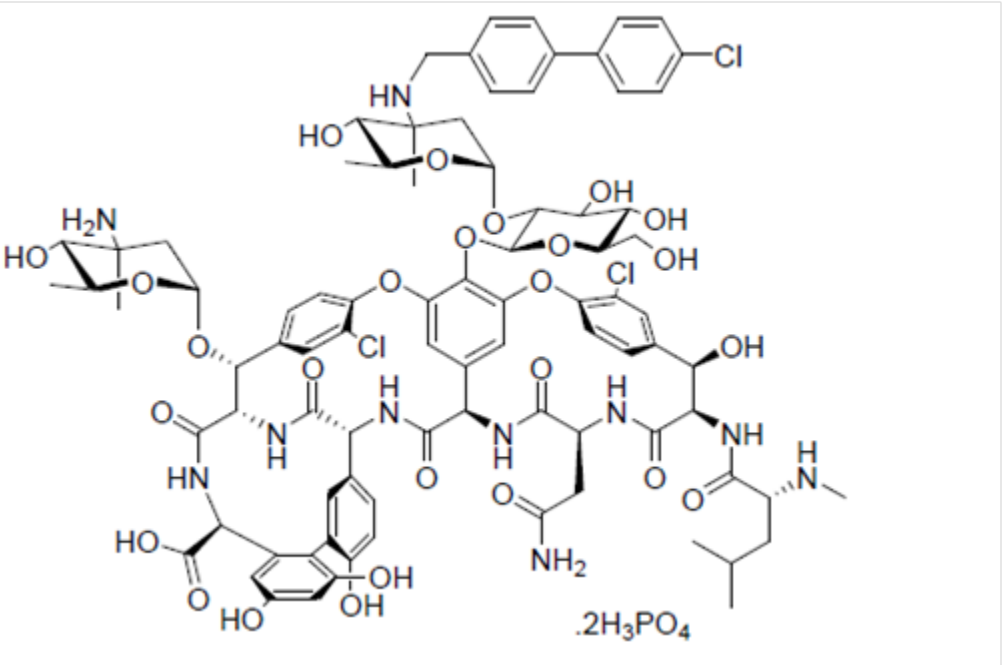
  The Phase 2 trial is to be started upon completion of the Phase 1 trial after the dose and volume to be used in the Phase 2 trial have been determined.
  Estimated protocol submission date - no later than September 2017
  Estimated study initiation - no later than December 2017
  Estimated final report submission - no later than December 2020

2 Introduction and Regulatory Background

2.1 Product Information

Oritavancin diphosphate is a semisynthetic lipoglycopeptide, a derivative of a naturally occurring glycopeptide antibiotic. It is derived from glycopeptide nucleus factor B, a component present in the fermentation culture of *Kibdelosporangium aridum.*

Figure 1: Sturucture of oritavancin



Source: Page 11 of applicant's nonclinical overview

Generic Name: Oritavancin diphosphate

Proposed Trade Name: Orbactiv

Chemical Class: New molecular entity (NME)

Pharmacological class: Lipoglycopeptide (structural similarity to vancomycin, teicoplanin and telavancin).

Proposed indication, age group: Acute bacterial skin and skin structure infections 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).

Dosing regimen: single 1200 mg IV infusion administered over 3 hours. Dosage adjustment is not required for patients with mild, moderate or severe renal insufficiency or mild to moderate hepatic insufficiency.

2.2 Currently Available Treatments for Proposed Indications

The following treatments are FDA approved and available for the treatment of ABSSSI/ cSSSI, including those caused by Gram positive pathogens:

Table 1: FDA approved and available treatments for the treatment of ABSSSI/ cSSSI, including those caused by Gram positive pathogens

Product Generic Name*	**Routes**
AMOXICILLIN AND CLAVULANATE POTASSIUM	Oral
AMIKACIN SULFATE	Intramuscular and Intravenous
AMPICILLIN, SULBACTAM	Intramuscular and Intravenous
AZTREONAM	Intravenous
CEFACLOR	Oral
CEFADROXIL HEMIDRATE	Oral
CEFAZOLIN SODIUM	Intravenous
CEFOTAXIME	Intramuscular and Intravenous
CEFOTETAN	Intravenous
CEFOXITIN	Intravenous
CEFTAROLINE FOSAMIL	Intravenous
CEFTAZIDIME	Intravenous
CEFTRIAXONE	Intramuscular and Intravenous
CEPHALEXIN	Oral
CIPROFLOXACIN	Intravenous and Oral
CLINDAMYCIN	Intravenous and Oral
DAPTOMYCIN	Intravenous
DEMECLOCYCLINE HYDROCHLORIDE	Oral
ERYTHROMYCIN	Oral
ERTAPENEM SODIUM	Intramuscular and Intravenous
GENTAMICIN	Intramuscular and Intravenous
IMIPENEM AND CILASTATIN SODIUM	Intravenous
LEVOFLOXACIN	Intravenous and Oral
LINEZOLID	Intravenous and Oral
MEROPENEM	Intravenous
METRONIDAZOLE	Intravenous and Oral
MINOCYCLINE	Intravenous and Oral
MOXIFLOXACIN HYDROCHLORIDE	Intravenous and Oral
PIPERACILLIN SODIUM,TAZOBACTAM SODIUM	Intravenous
QUINUPRISTIN AND DALFOPRISTIN	Intravenous
TELAVANCIN HYDROCHLORIDE	Intravenous
TETRACYCLINE HYDROCHLORIDE	Oral
TIGECYCLINE	Intravenous
TOBRAMYCIN SULFATE	Intravenous
VANCOMYCIN HYDROCHLORIDE	Intravenous

Of the above listed treatments, the following are approved for treatment of ABSSSI/cSSSI due to methicillin-resistant staphylococcus aureus (MRSA):

- Daptomycin
- Linezolid
- Tigecycline
- Vancomycin
- Ceftaroline

Other medications approved for treatment of "skin and skin structure infection" (treatment indication preceding the separation of skin infections into complicated and uncomplicated categories) include: ampicillin/sulbactam, aztreonam, cefotaxime, ceftazidime, ceftriaxone, ciprofloxacin, minocycline, imipenem and ticarcillin/clavulanate.
Medications approved for "serious skin and soft tissue infections" are cefazolin, clindamycin, and tetracycline.

2.3 Availability of Proposed Active Ingredient in the United States

This product is a NME and is not currently marketed in the United States

2.4 Important Safety Issues with Consideration to Related Drugs

Oritavancin is similar to vancomycin and other glycopeptides like telavancin.

Safety issues associated with vancomycin:
"Red man syndrome" characterized by erythema, pruritus, and flushing and occasionally accompanied by hypotension is an adverse reaction that occurs with infusion of vancomycin. Additional important adverse reactions include hypersensitivity (fever, rash, and pruritus), nephrotoxicity, interstitial nephritis, neutropenia, thrombocytopenia, and otoxicity. Issues with telavancin: adverse reactions include nephrotoxicity (new onset or worsening renal impairment), decreased efficacy with moderate/severe baseline renal impairment, infusion-related reactions, QTc prolongation, coagulation test interference (Prothrombin time, International normalized ratio, Activated partial thromboplastin time Activated clotting time and Coagulation based factor Xa tests).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The presubmission regulatory history and milestones related to the current NDA submission are summarized as follows:

- Oritavancin was under investigation at Eli Lilly and Company (Lilly), InterMune, Inc. and Targanta Therapeutics Corporation (Targanta). In August 1996, the initial IND for oritavancin was submitted to the FDA by Lilly. In January 2002, the sponsorship was transferred from Lilly to InterMune. In February 2006, Targanta became the official sponsor of oritavancin when the product was in late phase 3 development. Targanta was subsequently acquired by The Medicines Co in 2009.

- February 7, 2008: Targanta submitted NDA 22,513 with data from two phase 3 trials (ARRD and ARRI) to evaluate the safety and efficacy of oritavancin in cSSSI. The

primary efficacy endpoint was the Investigator-Defined Clinical Outcome at the test of cure visit.

Study ARRD was a double-blind, randomized, multi-center trial that compared oritavancin intravenously at 1.5 mg/kg/day, oritavancin 3.0 mg/kg/day for 3-7 days , and vancomycin intravenously followed by oral cephalexin for 10-14 days in cSSSI. The study enrolled approximately 170 patients per arm. Study ARRD was powered to show non-inferiority with a margin of -15%. The lower bound of the 95% confidence intervals for the ITT and clinically evaluable populations ranged from -12.5 to -13.8. Excluding patients with abscess (approx. 35 to 40% of the study population) in the 1.5 and 3.0 mg/kg/day dosing regimen resulted in further widening of the 95% confidence limits which ranged from -13.7 to -18.0.

Study ARRI was a double-blind, randomized, multi-center study comparing oritavancin 200mg intravenously once daily (300 mg for patients weighing more than 110 kg) followed by oral placebo, or 15 mg/kg vancomycin intravenously twice daily followed by oral cephalexin (1 gram twice daily). The results of the study were well within a lower bound of -10% for the 95% confidence interval. In study ARRI, the cure rates for the subset of patients with MRSA were less than what was found with vancomycin.

There were a total of 1540 subjects who received oritavancin in the NDA safety database with 50% receiving a cumulative exposure of 600 to 1200 mg. There were (1) the higher rate of study discontinuation for lack of efficacy among oritavancin-treated subjects, (2) the greater number of oritavancin-treated subjects who died or had a serious adverse event (SAE) of sepsis, septic shock, and related events, and (3) more oritavancin-treated subjects who experienced adverse events (AEs) of osteomyelitis and sepsis. In addition, the long terminal half-life of oritavancin, the sequestration of oritavancin in macrophages, the finding of eosinophilic granules in macrophages, and the finding of histiocytosis in multiple organs in animals raised questions about safety.

During review cycle biopharmaceutical and clinical site inspections were conducted and regulatory violations were identified; however DSI inspectors concluded that the reliability of the data was probably intact.

- December 8, 2008: A complete response was issued. The sponsor was asked to assess:

  -Performance of oritavancin in cSSSI due to MRSA by including a significant proportion of patients from whom MRSA is isolated.

  -Effect of oritavancin on macrophage function in a subset of patients from an adequate and well-controlled study. Patients were recommended to be followed for a longer period of time after completion of efficacy assessments in order to monitor for the potential for subsequent infections that could be related to macrophage dysfunction or other adverse events that may be related to the long terminal half-life of oritavancin and its sequestration in macrophages.

  -Identify the rate of phlebitis with more recently manufactured product.

On June 25 2009, the applicant received EMEA's 180-Day List of Outstanding Issues, consistent with FDA's complete response letter and withdrew their MAA on August 20, 2009.

- On July 27, 2009, The Medicines Company (MDCO), the official sponsor of oritavancin after acquiring Targanta, had a Type A meeting with DAIP to discuss the complete response letter. MDCO initiated a new development program to evaluate a single dose administration (1200 mg in 5% dextrose intravenous infusion over a 3 hours) compared to vancomycin (15mg/kg) every 12 hours for (b) (4) to 10 days for the treatment (b) (4) in two Phase 3 studies. The sponsor had conducted a phase 2 trial (SIMPLIFI) from September 9, 2007 to June 3, 2008 to evaluate the efficacy and safety of either single dose 1200 mg or infrequent dosing regimen (a single dose of 800 mg oritavancin, with the option for the investigator to administer a further 400-mg dose at Day 5) of intravenous oritavancin compared with daily intravenous dosing of 200 mg oritavancin for 3 to 7 days in cSSSI in which the single dose was found to be non inferior (estimated differences in cure rates between the daily dose and single dose (8.6%, 90% confidence interval = -2.5, 18.2) to the daily dose.

  DAIP guided the sponsor with the design of the phase 3 trials. DAIP concurred that approximately 330 microbiologically-evaluable MRSA patients in the combined studies was acceptable and with the plan of evaluating oritavancin on macrophage function with in vitro examination of the impact of intracellular accumulation of oritavancin on the ability of macrophages to kill important human pathogens (*Candida albicans, S aureus,* and *Escherichia coli*), monitoring for any indicators of macrophage dysfunction in cSSSI studies and in future studies and a well-designed registry study to assess whether oritavancin has a clinically relevant effect on macrophage function. DAIP recommended that all patients with complicated abscesses should have significant surrounding soft tissue infection; abscesses should be at least 5 cm in size; all patients should be evaluated at 48-72 hours in addition to the test of cure visit; and the primary efficacy analysis should be performed on the full analysis set. The recommendations reflected the divisions existing guidance and thinking at that time.

On March 26, 2010, a Special Protocol Assessment (SPA) request for Phase 3 protocol entitled "A Multicenter, Double-Blind, Randomized Study to Evaluate the Efficacy and Safety of Single-Dose Oritavancin versus Vancomycin for the Treatment of Patients with Acute Bacterial Skin and Skin Structure Infection" submitted. On May 12, 2010, there was no agreement. The Division advised the applicant that:

- Patients should not receive a single dose of a short acting antibacterial therapy within 72 hours of randomization (e.g., surgical prophylaxis) unless the infection is clearly progressing.
- The clinical response should be defined as cessation of the spread of the lesion or reduction in the size (length, width, and area) of redness, edema, and/or induration at 48 to 72 hours after enrollment and resolution (absence) of fever (i.e., temperature less than 37.7 degrees Celsius at the last 3 consecutive recordings by the same route of administration every 6 hours between 48 and 72 hours).

- The primary analysis should be based on the patients with non-missing outcomes at 48-72 hours.
- To evaluate the absolute and percent reduction in lesion size from baseline for day 10 and post therapy visit, assess concordance/discordance of primary outcome rates with investigator assessment of clinical outcome at EOT (day 10), resolution of individual signs/symptoms of infection after the initiation of therapy at 48-72 hours post enrollment, EOT (day 10) and Follow-up Post-Therapy visits to support the primary clinical response analysis of cessation of spread at 48-72 hours and absence of fever after initiation of therapy.
- Any proposed exploratory measure of pain should be based on the pain experienced by the patient at the time of the visit.
- To analyze clinical outcomes stratified by the presence or absence of adjunctive therapies, aztreonam or metronidazole, and number of surgical debridements.
- Analyses of primary endpoint and cessation of spread controlling for baseline fever status
- Analyses of primary endpoint and cessation of spread using risk ratio and odds ratio metrics

- On November 24, 2010, a SPA agreement reached after the protocol was revised by the applicant. These were two identical Phase 3 studies (SOLO I and II) in which the single dose 1200 mg oritavancin treatment is compared to vancomycin given twice daily for 7 to 10 days. The primary efficacy variable in the SOLO studies is a composite outcome of cessation of spreading or reduction of size of baseline lesion, absence of fever, and no rescue antibiotic medication at the ECE visit which is 48-72 hours following initiation of study drug administration. Selected secondary efficacy variables include the clinical response (clinical cure) assessed by the investigators at PTE, which is 7-14 days after end of therapy, and the proportion of patients with ≥20% lesion size reduction from baseline at ECE as requested by the Agency. The SOLO I was initiated in January 12, 2011 and completed on November 30, 2012. The SOLO II was initiated in January 11, 2011 and completed on June 14, 2013.
- The sponsor submitted an initial pediatric development plan under PREA on June 19, 2012. On July 18, 2012, a Type B meeting occurred between the division and the applicant to discuss the pediatric implementation plan for conducting the pediatric studies necessary to meet PREA requirements. Based on FDA recommendations from July 18, 2012 meeting, the applicant submitted a revised pediatric plan on December 5, 2012. The sponsor received the Division's feedback on the pooling strategies for summary of clinical efficacy and safety, safety assessments and presentation of datasets for the NDA submission as well as feedback on the pediatric plan on March 14, 2013. An amended pediatric plan submitted on November 4, 2013. The sponsor intends to start the Phase 2 trial upon completion of the Phase 1 trial and when the dose and volume to be used in the Phase 2 trial have been agreed on by the PDCO. The sponsor also concurred with the Division's suggestions to increase the number of patients in Phase 1 trial to least 48 evaluable patients with at least 8 patients per subgroup and 16 patients in the youngest age group (minimum 5 patients in the 0-28 days of age) and to make every effort to collect data to determine oritavancin levels in the CSF. This was in response to the FDA

comment that insufficient data on CSF penetration may require an additional CSF penetration study in the 0-28 age group prior to the Phase 2 trial. The estimated study initiation for the phase1 trial is March 2014 and December 2017 is for the phase2 trial. The pediatric protocol for PREA, phase 1 trial for TMC-ORI_11-01 was submitted on December 2013.

- The final SAP to SOLO 1 was submitted on 6 December, 2012 and on June 12, 2013 for SOLO 2 trial.
- The MDCO also conducted a thorough QT safety study, MDCO-ORI-12-02, with supratherapeutic dose of oritavancin to assess the cardiac repolarization potential and a drug-drug interaction study MDCO-ORI-12-03.
- MDCO also sought scientific advice from the bfArM on July 18, 2013, MHRA on July12, 2013, ANSM September 20, 2013, and MPA on September 25, 2013 whether they have addressed the major objections from the previous MAA as well as on the efficacy and safety results of the pivotal Phase 3 studies, SOLO I and SOLO II. The agencies generally agreed that the major deficiencies of the previous MAA were met and further review would occur upon submission of the MAA. Of note, ANSM advised the sponsor that it is not known if the non-clinical studies sufficiently addressed the impact on macrophage functions, to consider conducting a Purkinje fiber assay and/or repeating the in vitro sodium channel study. ANSM also stated that results from the first tQT study evaluating a 800 mg dose did not exclude a clinically relevant effect because a lower than expected moxifloxacin response and a mean oritavancin effect of around 5 msec was seen. MPA advised the sponsor that *Enterococcus* is not considered a cSSTI pathogen in the EU and to submit an analysis of oritavancin efficacy by patient body weight, thorough discussion of the three half-lives of oritavancin and an assessment whether the adverse event rate for vancomycin-treated patients in the SOLO studies is higher than in published studies (from literature) in which vancomycin was administered by continuous infusion.MPA also advised evaluating the timing of the tachycardia adverse events and to see if correlated with administration of drug.
- On June 27, 2013 a Pre NDA Chemistry, Manufacturing, and Controls CMC meeting was held to obtain concurrence with the submission strategy for the CMC section of the NDA submission of Oritavancin for Injection. The Agency advised MDCO to structure the microbiological studies with the diluted product in 5% dextrose in support of the requested storage time post constitution studies with several sampling points within the initial 24 hour period.
- On September 11, 2013: A Pre NDA clinical meeting was held between the Agency and the applicant, with the objective of obtaining concurrence on the content and format of the NDA, the planned data analyses and the regulatory timelines. The sponsor was requested to submit the case report forms (CRF) and case narratives in the ISS for 11 patients in the oritavancin group in the SOLO trials who had TEAE of alanine aminotransferase elevated while none had alkaline phosphatase increased. Additional details were requested regarding patient 29100316 who appeared in the Hy's law quadrant in the eDISH plot.

- On September 16, 2013, a Qualified Infectious Disease Product (QIDP) designation request for oritavancin for the treatment of ABSSSI was received by the Agency. This request was reviewed and QIDP granted on October 31, 2013.
- Meetings were held with EUCAST on September 23, 2013 to develop appropriate breakpoints
- On October 2013, FDA's Guidance for Industry- Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment was published which recommends a Primary efficacy endpoint of 20 % lesion size reduction compared to baseline, measured in patients who did not receive rescue therapy and are alive at 48 to 72 hours. The SOLO1 and SOLO 2 trials were conducted with the above response as a secondary endpoint.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was relatively well-organized and based on the electronic common technical document (eCTD) format.
The clinical case summaries were comprehensive. Approximately 10% random sample (181) case report forms (CRFs) were submitted. The review of CRFs and datasets prompted information requests including, but not limited to the following:

- Errors in the TRTEFFE and TRTEFFS variables in the clinsite.xpt dataset were identified and the sponsor submitted corrected dataset on December 19, 2013. A discrepancy regarding the actual treatment arms of two patients (USUBJID TMC-ORI-10-01-101014-006 and TMC-ORI-10-01-191002-094) in the demographics domain of the datasets was noted. The actual treatment arm in the SDTM was listed as oritavancin, while the actual treatment arm in the ADAM dataset is reported as vancomycin. A clarification/information request was sent to the sponsor. The sponsor resubmitted the datasets on December 26, 2013.
- The financial disclosure information reported in Module 1.3.4 was incomplete. It did not contain the attachment listing of investigators with no reportable/reportable disclosures. The sponsor submitted this information on January 10, 2013.
- Amended datasets were requested since there was a problem linking relevant rows in MB and MS properly, the AE domain for all studies needed the EPOCH variable to be populated, there were duplicate rows in the XR and XD domains in study tmc-ori-10-02 and baseline assessments were missing for key labs (ALT, ALP, AST) and ECGs in study tmc-ori-10-02 for a significant number of subjects (32 subjects in LB and 25 subjects in EG). The sponsor submitted updated datasets on February 12, 2014.
- Raw data listings to generate the derived endpoints for sites 101002,191009,101046 (SOLO1) and 201001,201005,201002 (SOLO2) were requested from the sponsor on January 17, 2014. The sponsor submitted this data on January23, 2014.

- Photographs of lesion size for a few subjects with > 1000 cm2 were requested from the sponsor. This was submitted pn March 5, 2014.
- Additional CRFs were requested for AEs of interest as identified by reviewer analysis.The sponsor submitted this on April 4,2014

The applicant provided the responses in a timely fashion without delaying the review.

3.2 Compliance with Good Clinical Practices

The Clinical trials in this program were conducted in adherence with the principles of Good Clinical Practices (GCP), including directions set forth in relevant regulatory guidance (for example, ICH E6) and in keeping with study-subject protection as outlined in the Declaration of Helsinki (1964).

A request for site inspections (4 domestic sites and 1 foreign clinical site) was submitted to the Division of Scientific Investigations for
SOLO I: Site # 101002 due to high enrollment, large site efficacy effect and 100% screened to enroll
Site # 191008 (India) with a 94% efficacy for oritavancin and 88% for vancomycin.
Site # 101046 moderate enrollment, high discontinuation rate, somewhat high efficacy, same address at site 201001 in SOLO2

SOLO II: Site # 201005- high treatment efficacy both arms and high response for oritavancin, low AE
Site # 201002- high efficacy
The site inspections are ongoing at the time of this review.

Of note, there was closing of site #240002 (n=8) in Romania due to GCP noncompliance. This was reported to the IND on September 26, 2012.

3.3 Financial Disclosures

The applicant certified that there were no financial arrangements with clinical investigators that could affect the outcome of the study as defined in 21 CFR 54.2 (a) and that the clinical investigators had no reportable financial disclosures in the SOLO 1 and 2 trials as defined in 21 CFR 54.2 (b). The applicant also certified that no investigator was the recipient of significant payments as defined in 21 CFR 54.2(f). See Appendix 9.4 for detailed review.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Refer to detailed review of this section by Dr Hitesh Shroff. The reviewer concludes that there was sufficient information to assure the identity, strength, purity and quality of the drug product. The manufacturing facilities were examined and found to be acceptable.
Oritavancin diphosphate is a semisynthetic lipoglycopeptide antibiotic (empirical formula: $C_{86}H_{97}N_{10}O_{26}Cl_3 \cdot 2H_3PO_4$, molecular weight: 1989.09). The chemical name for oritavancin is: [4"R]-22-O-(3-amino-2,3,6-trideoxy-3-C-methyl- α -L-arabino-hexopyranosyl)-N3''-[(4'-chloro[1,1'-biphenyl]-4-yl)methyl] vancomycin phosphate [1:2] [salt]
Oritavancin is formulated as a sterile, white to off-white, lyophilized powder for intravenous administration after reconstitution and dilution. The drug product consists of oritavancin diphosphate, mannitol and phosphoric acid (to adjust pH 3.1 to 4.3).

4.2 Clinical Microbiology

Refer to detailed review of this section by Dr Avery Goodwin and breakpoints review by Dr. Ryan Owen. The applicant's proposed breakpoints for *S. aureus* and *S. pyogenes* are supported from a PK/PD standpoint and are acceptable. The highest MIC observed was 0.25 mcg/mL and was encountered primarily among isolates of *S. epidermidis.* The accumulation of oritavancin did not appear to prevent phagocytic killing of *S. aureus*. Due to the lack of sufficient clinical data, the Agency suggests removing *Streptococcus dysgalactiae* from the list of pathogens in the interpretive criteria table.

The spectrum of oritavancin activity includes the key Gram-positive pathogens for ABSSSI, namely staphylococci, streptococci, and enterococci. Oritavancin lacks activity against Gram-negative bacteria (500289), most likely due to an inability to cross the outer membrane permeability barrier. The following table provides in vitro susceptibility data for oritavancin against various bacterial isolates.

Table 2: Spectrum of Activity of Oritavancin

Pathogen	Phenotype	n	Agent	MIC_{50}	MIC_{90}	Range
Staphylococcus	All	13336	Oritavancin	0.03	0.06	≤0.008 – 0.25
aureus						
	MSSA	7800	Oritavancin	0.03	0.06	≤0.008 – 0.25
	MRSA	5536	Oritavancin	0.03	0.06	≤0.008 – 0.25
β-hemolytic	All	2281	Oritavancin	0.03	0.12	≤0.008 – 0.5
streptococci						
Viridans	All	835	Oritavancin	≤0.008	0.06	≤0.008 – 0.5
streptococci						
Enterococcus	All	2132	Oritavancin	0.015	0.06	≤0.008 – 1

Pathogen	Phenotype	n	Agent	MIC_{50}	MIC_{90}	Range
faecalis						
	VSE	2088	Oritavancin	0.015	0.06	≤0.008 – 0.5
	VRE (VanA)	37	Oritavancin	0.25	0.5	0.015 – 1
Enterococcus faecium	All	1237	Oritavancin	≤0.008	0.06	≤0.008 – 0.5
	VSE	566	Oritavancin	≤0.008	≤0.008	≤0.008 – 0.015
	VRE (VanA)	639	Oritavancin	0.03	0.12	≤0.008 – 0.5
	VRE (VanB)	32	Oritavancin	≤0.008	≤0.008	≤0.008 – 0.03

Abbreviations: MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; VSE, vancomycin-susceptible enterococci (strains with vancomycin MIC ≤ 4 µg/mL and teicoplanin MIC ≤8 µg/mL); VRE, vancomycin-resistant enterococci (strains with vancomycin MIC > 4 µg/mL); VanA, strains with vancomycin MIC > 4 µg/mL and teicoplanin MIC > 8 µg/mL; VanB, strains with vancomycin MIC > 4 µg/mL and teicoplanin MIC ≤ 8 µg/mL.
Source: Adapted from applicant's table 2 of clinical overview

4.2.1 Synergy testing

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 MRSA-hVISA, VISA, and VRSA, and with rifampicin against isolates of VRSA.

4.2.2 Resistance

Summary of in vitro stepwise selection of oritavancin in staph aureus showed that for oritavancin, a 4- to 8-fold increase in ORI MIC was observed for *S. aureus* isolates of different drug resistance phenotypes. Results suggested 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.

MO comment: A potential for emergence of resistance to oritavancin exists. Post-approval surveillance studies will be conducted to monitor for decreased susceptibility to oritavancin.By MIC population statistics, oritavancin in vitro potency was similar against S. aureus isolates with and without the pvl gene. Early clinical response rates at ECE for oritavancin-treated patients with pvl+ and pvl- S. aureus strains and hVISA and non h-VISA phenotype were also similar.

4.3 Preclinical Pharmacology/Toxicology

Nonclinical pharmacology review was conducted by Dr. Amy Nostrand. The reviewer concludes thatthere are insufficient nonclinical data to support the proposed dosing for this NDA described

as a single 1200 mg dose, infused over 3 hours. The applicant considered the cumulative dose in repeated dose toxicology studies to support the proposed bolus clinical dose, even though this does not account for the differences in oritavancin concentrations over time, and without actual tissue concentration data, the impact of the bolus dose on incidence and intensity of toxicity findings cannot be certain. In the opinion of the nonclinical reviewer, it does not seem necessary to repeat single dose toxicology studies at doses higher than previously evaluated. Although the slower infusion rate should reduce toxicity, oritavancin safety profile could be determined from the clinical trial data.

The original clinical program for oritavancin involved a daily dosing regimen for multiple days.Therefore, the toxicology program was designed to support repeat dose administration so did not include an extensive investigation of single dose toxicity. However, studies involving daily administration for up to 13 weeks were conducted. Oritavancin has been evaluated in single-dose toxicity in rats, repeat-dose toxicity in rats and dogs, genotoxicity in a comprehensive battery of in vitro and in vivo studies, reproductive and developmental toxicity in rats and rabbits and a series of in vitro studies in macrophage cell lines and in vivo studies in rats were conducted to evaluate immune function.

The safety margins for the SOLO 1 and 2 studies at the NOAEL doses in the pivotal 1 month toxicity studies based on cumulative exposures range from 2.4 to 11.9 fold in rats and dogs, respectively. These safety margins are based on exposures generated from repeat-dose studies of one-month duration.

Clinical findings associated with identifying the NOAELs in rats and dogs included decreased mean erythrocytic parameters such as erythrocyte count, hemoglobin, and packed cell volume. There were also increased levels of serum ALT, AST, ALP and bilirubin that was associated with increased liver weights, macroscopic findings of pale livers, microscopic findings of eosinophilic granules in Kupffer cells, and occasional histopathologic findings of hepatocellular vacuolar degeneration and necrosis.

There were slight effects in clinical chemistry parameters consistent with minimal effects on renal function including slight increases in BUN, sporadic increases in creatinine, and decreases in urine specific gravity. These changes were occasionally associated with histopathologic findings such as renal cortical tubular nephrosis. Increased organ weights (absolute and relative) for liver, kidney and/or spleen were noted.

In dogs, the most notable dose limiting toxicity was a moderate to severe histamine reaction that was most pronounced during the first few days of dosing and waned during the study period. There were no cardiovascular effects in dogs based on ECG recordings.

The NOAEL was 5 mg/kg in repeat dose toxicity in rats. AGLP 1 month toxicity study in beagle dogs showed oritavancin at a dose level of 30 mg/kg produced dose-limiting clinical signs consistent with histamine-mediated reactions. In addition, mild renal toxicity and mild to moderate hepatic toxicity was associated with the 30 mg/kg dose group. Eosinophilic granules were present throughout tissues in animals at all dose levels, but were not associated with any obvious adverse effects.

Another GLP study of oritavancin at doses 5, 15, or 45 mg/kg once daily for 13 weeks in beagle dogs showed decreases in cytochrome P450 content and activity.

There were no gene mutations or chromosomal damage observed in genotoxicity studies.

Fertility studies in male and female rats, embryo-fetal development studies in rats and rabbits

and a prenatal and postnatal development study in rats were conducted. There were no positive signals for selective reproductive or selective developmental toxicity. Immunotoxicity studies are summarized in section 7.4.6 of the review.

MO: No adequate and well-controlled studies with oritavancin have been conducted in pregnant women. The reproductive studies tested a dose equivalent to only 25% of the human clinical dose. The target organs for oritavancin toxicity from nonclinical studies include liver, kidney, and red blood cells (hemolysis).

4.4 Clinical Pharmacology

For detailed clinical pharmacology/pharmacometric review please refer to the reviews by Drs. Ryan Owen and Jeffrey Florian.The reviewers found the submission acceptable and there were no review issues that would preclude oritavancin approval.

4.4.1 Mechanism of Action
Oritavancin has the following three mechanisms of action that target the cell envelope of Gram positive bacteria: (i) inhibition of the transglycosylation step of cell wall synthesis by binding to D-Ala-D-Ala stem termini; (ii) inhibition of the transpeptidation step of cell wall synthesis by binding to the bridging segment of the cell wall and (iii) disruption of bacterial membrane integrity, leading to membrane depolarization and permeabilization resulting in rapid cell death. Oritavavncin has concentration-dependent bactericidal (cell killing) activity against Gram positive pathogens.

4.4.2 Pharmacodynamics
Microbiology data are summarized in section 4.2.

4.4.3 Pharmacokinetics
Oritavancin has extensive tissue distribution, and a long terminal half-life. In oral toxicokinetic studies in rats and dogs there was little, if any, systemic exposure to oritavancin. The mean terminal elimination plasma half-life of oritavancin is 245 hours (14.9% CV) based on population PK analysis of ABSSSI patients receiving a single 1200 mg dose. The population mean total clearance is estimated at 0.445 L/h (percent standard error of the mean, 1.95). Oritavancin has physiochemical properties consistent with long-term tissue sequestration and thus, a slow rate of elimination. Oritavancin is not metabolized and is slowly excreted unchanged in feces and urine; less than 1% and 5% of the dose is recovered in the feces and urine, respectively, after 2 weeks of collection. The PK of oritavancin are linear (independent of dose) and stationary (independent of time). The interindividual variability in oritavancin PK is not related to obesity, renal impairment or hepatic impairment, and weakly related to age and height; dose adjustments are not required for any patient demographic or disease characteristics. The pharmacokinetics of oritavancin in patients with severe hepatic or renal impairment have not been studied. Oritavancin is approximately 85% bound to human plasma proteins. Oritavancin is a weak, non-specific inhibitor or inducer of several CYP450 isoforms. The magnitude of the observed drug interactions do not require dose adjustments; however, caution may be required for the co-administration of narrow therapeutic-range drugs such as warfarin.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The following table summarizes the trials conducted at the various phases of development of oritavancin.

Table 3: Studies/Clinical Trials

Study ID **Locations** **(no. sites)**	**Study start** **Enrollment status and date** **Total enrollment/ enrollment goal**	**Study design**	**Patient population** **Control type** **Duration of follow-up**	**Study and control drugs** **Dose, route and regimen (Duration)**	**Study Objective** **No. patients by arm**	**Overall Sex (M/F): Median age in y (range)**
Phase 1 trials						
H4Q-JE-101N Japan (Single Site)	7 August 1999 Completed 24 October 2000 Planned enrollment: 26 Actual enrollment: 26 subjects	Dose-Ranging (single-dose, open-label, dose escalation study)	Healthy male Japanese subjects No control group 3 months follow-up period.	Oritavancin: Single 0.02, 0.08, 0.2, 0.5, 1.0, 2.0 and 3.0 mg/kg intravenous infusion of oritavancin	Safety and PK Oritavancin: 26 healthy subjects	M: 26 (100%) F: 0 (0%) 20-30 years old
H4Q-LC-ARRA United States (Single site)	Sept 1996 to April 1997 Planned enrollment: 15 subjects Actual enrollment: 15 subjects	Open-label, non-controlled, dose-ranging, single-dose, dose escalation study	Healthy Subjects No control group 8 weeks of outpatient observation after dosing	LY333328: Single doses of 0.02, 0.03, 0.05, 0.08, 0.125, 0.20, 0.325 and 0.5 mg/kg, administered over 1 hr.	Safety and PK Oritavancin: 15 healthy subjects	M: 15 (100%) F: 0 (0%) 24-50 years old
H4Q-LC-ARRB United States (Single site)	August 1997 to February 1998 Planned Enrollment: 12 subjects Actual enrollment: 10 subjects	Open-label, multiple dose escalation study	Healthy subjects No control group Up to 1 year follow-up	LY333328: 1.5 mg/kg IV infusions over 30 minutes for 2, 3, 5, or 7 days	Safety and PK LY333328: 10 healthy subjects	M: 10 (100%) F: 0 (0%) 21-55 years old

Study ID **Locations** **(no. sites)**	**Study start** **Enrollment status and date** **Total enrollment/ enrollment goal**	**Study design**	**Patient population** **Control type** **Duration of follow-up**	**Study and control drugs** **Dose, route and regimen (Duration)**	**Study Objective** **No. patients by arm**	**Overall Sex (M/F): Median age in y (range)**
H4Q-LC-ARRK United States (Single site)	April 1997 to August 1997 Planned enrollment: up to 24 subjects Actual enrollment: 11 subjects	Single-dose, open-label, uncontrolled, dose escalation study	Healthy volunteers No control group 1 month follow-up	LY333328: 0.5, 1.0, 2.0, or 3.0 mg/kg administered as a single 30-minute intravenous infusion.	Safety and PK LY333328: 0.5, 1.0, 2.0, 3.0 mg/kg single doses- 2 subjects per dose	M: 11 (100%) F: 0 (0%) 22-50 years old
OSCI-001 United States (Single site)	29 January 2003 to 29 April 2003 Planned enrollment: 16 subjects Actual enrollment: 17 subjects	Open-label, single-center study designed to characterize the pharmacokinetic profile of oritavancin skin penetration after administration of oritavancin via intravenous infusion in normal healthy male subjects.	Healthy subjects No control group Up to 10 days follow-up	Oritavancin: Group A: 60-minute infusion of 200 mg in 250 ml x 3 days; Group B: 90-minute infusion of 800 mg in 500 ml x 1 day	Safety and PK Oritavancin: 17 Healthy subjects	M: 17 (100%) F: 0 (0%) 19 to 51 years old

Study ID Locations (no. sites)	**Study start Enrollment status and date Total enrollment/ enrollment goal**	**Study design**	**Patient population Control type Duration of follow-up**	**Study and control drugs Dose, route and regimen (Duration)**	**Study Objective No. patients by arm**	**Overall Sex (M/F): Median age in y (range)**
OPUL-001 United States (Single site)	21 November 2002 to 13 June 2003 Planned enrollment: 38 subjects Actual enrollment: 32 subjects	Phase 1, open-label, single-center study, multiple dose comparing the plasma and intrapulmonary concentrations of intravenous oritavancin and vancomycin at steady-state in normal healthy adults	Healthy Subjects Positive Control group 21 days of follow-up from last dose	Oritavancin: 800 mg daily IV infusion for 5 consecutive days Vancomycin: 1000 mg IV infusion every 12 hours for 5 consecutive days	Safety and PK Oritavancin: 20 subjects Vancomycin: 12 subjects	M: 15 (47%) F: 17 (53%) 20-54 years old
MDCO-ORI-12-02 United States (Single site)	27 December 2012 to 11 February 2013 Planned enrollment: 150 subjects Actual enrollment 149 subjects	Double-blind, randomized, placebo- controlled, parallel-design cardiac safety study with an open-label positive control (moxifloxacin) using a supratherapeutic dose of oritavancin in healthy volunteers	Healthy Subjects Placebo Control 7 to 14 days follow-up	Oritavancin, 1600 mg in 1500 mL of 5% dextrose in water (D5W), administered as a constant-rate IV infusion over 3 hours D5W administered as a constant-rate IV infusion over 3 hours as a matching placebo to oritavancin Open-label positive control: A single 400 mg moxifloxacin tablet was administered as an active comparator (unblinded)	Safety TQT Oritavancin: 48 Moxifloxicin: 52 Placebo: 49	M: 80 (53.7%) F: 69 (46.3%) 17 to 61 years old

Study ID Locations (no. sites)	**Study start Enrollment status and date Total enrollment/ enrollment goal**	**Study design**	**Patient population Control type Duration of follow-up**	**Study and control drugs Dose, route and regimen (Duration)**	**Study Objective No. patients by arm**	**Overall Sex (M/F): Median age in y (range)**
OSCI-004 United States (3 sites)	03 October 2002 to 01 February 2003 Planned enrollment: 20 subjects with moderate liver Insufficiency and 20 healthy subjects Actual enrollment: 20 hepatically impaired subjects and 20 healthy subjects.	Phase 1, single-dose, open-label, parallel-group study to compare the safety and pharmacokinetics of oritavancin after a single intravenous infusion in subjects with Child-Pugh Class B (moderate) liver insufficiency and healthy subjects	Healthy subjects Non-controlled 45 days follow-up	Oritavancin, 800 mg, single-dose IV infusion over 90 minutes.	Safety and PK Moderate Liver Insufficiency: 20 Healthy subjects: 20	M: 30 (75%) F: 10 (25%) 19-74 years old
OSCI-007 United States (Single site)	09 Oct 2002 to 24 Dec 2002 Planned enrollment: approximately 30 subjects Actual Enrollment: 31 subjects	This was a Phase 1, open-label, one-sequence group, single-site study designed to investigate the potential of a clinically significant drug interaction between oritavancin and desipramine	Healthy subjects Non-controlled Up to 49 days follow-up after drug discontinuation	Oritavancin, 800 mg, administered intravenously once daily for 14 days (Study Days 8 to 21) Desipramine, 50 mg, administered orally as a tablet, once daily for 21 days (Study Days 1 to 21)	Drug Drug Interaction Received at least one dose of desipramine (50 mg): 31 Completed the desipramine-alone dosing regimen and received at least one daily dose of oritavancin (800 mg) and desipramine (50 mg): 24	M: 22 (70%) F: 9 (30%) 18-45 years old

Study ID **Locations** **(no. sites)**	**Study start** **Enrollment status and date** **Total enrollment/ enrollment goal**	**Study design**	**Patient population** **Control type** **Duration of follow-up**	**Study and control drugs** **Dose, route and regimen (Duration)**	**Study Objective** **No. patients by arm**	**Overall Sex (M/F): Median age in y (range)**
OSCI-008 United States (Single-site)	25 June 2003 to 02 September 2003 Planned enrollment: approximately 70 subjects Actual Enrollment: 64 subjects	Parallel-arm, open-label, randomized, pharmacokinetic, drug interaction study to evaluate the steady-state pharmacokinetics of desipramine po at time points before and after IV oritavancin administration	Healthy Subjects Placebo control Up to 42 days follow-up	Oritavancin 800 mg, administered as a 90-minute IV infusion once daily for 14 days (Days 8-21) with Desipramine, 50 mg, administered po as a tablet, once daily for 21 days (Days 1-21) or Placebo (Cebocap), administered po as capsules, once daily for 21 days (Days 1-21)	Safety and PK Desipramine with Oritavancin: 32 Placebo with Oritavancin: 32	M: 41 (64%) F: 23 (35%) 19 to 64 years old
MDCO-ORI-12-03 United States (Single site)	23 January 2013 to 04 March 2013 Planned enrollment: 16 subjects Actual enrollment: 16 subjects	Open-label, single-dose, PK and drug interaction study	Healthy Subjects Non-controlled 28 day follow-up	Oritavancin: Single 3-hour IV dose of 1200 mg on Day 1 Plus Two doses of Cooperstown 5+1 cocktail administered orally on Day −4 and Day 1	PK and Drug Interaction Oritavancin: 16 subjects	M: 8 (50%) F: 8 (50%) 23-45 years old
H4Q-LC-ARRN United States (Single site)	June 2000 through November 2000 Planned enrollment: 18 subjects Actual enrollment: 20 subjects	Single-blind, non-randomized, multiple dose study	Healthy Subjects Placebo control 6 months follow-up from first dose	Oritavancin: Daily IV infusion of 100, 150 or 200mg with 2 doses of placebo run-in	Safety and QTc 100mg: 6 subjects 200mg: 8 subjects 150mg: 6 subjects	M: 12 (60%) F: 8 (40%) 19-64 years old

Study ID **Locations** **(no. sites)**	**Study start** **Enrollment status and date** **Total enrollment/ enrollment goal**	**Study design**	**Patient population** **Control type** **Duration of follow-up**	**Study and control drugs** **Dose, route and regimen (Duration)**	**Study Objective** **No. patients by arm**	**Overall Sex (M/F): Median age in y (range)**
H4Q-LC-ARRO United States (2 sites)	March 2000 to August 2000 Planned enrollment: 16 subjects Actual Enrollment: 17 subjects	Single-blind, single-dose, dose escalation study	Healthy Subjects Non-controlled Follow-up for 3 months after dosing	Oritavancin: 100, 200, or 400 mg of oritavancin in 100mL of 5% dextrose solution given over 30 or 60 minutes (400mg dose) Placebo: 100 mL or 200 mL (400mg dose group only) of 5% dextrose solution given over 30 or 60 minutes (400 mg dose).	Safety and QTc Oritavancin or Placebo: 100mg: 4 subjects 200mg: 4 subjects 400mg: 4 subjects 600mg: 4 subjects	M: 10 (58%) F: 7 (41%) 23-58 years old
TAR-ORI-VT001 United States (single site)	18 April 2007 to 20 June 2007 Planned enrollment: 15 subjects Actual enrollment: 15 subjects	Phase 1, single-center, randomized, double-blinded, crossover design study to establish the injection site vein toleration of oritavancin, given in two doses 14 days apart via peripheral IV catheters	Healthy subjects Non-controlled Follow-up on Day 23 (+/- 3 days)	Oritavancin: 200mg on Day 1 and 800 mg on Day 15, 800 mg on Day 1 and 200 mg on Day 15, 800 mg on Day 1 and 15 or 200 mg on Day 1 and 15. The 200 mg doses were administered as 2 consecutive 60-minute infusions: one containing 200 mg oritavancin and the other D5W. The 800 mg doses were given as 2 consecutive 400 mg infusions each given over 60 minutes.	Safety Oritavancin (D1/D15) 200mg/800mg: 4 800mg/200mg: 4 800mg/800mg: 3 200mg/200mg: 4	M: 15 (100%) F: 0 (0%) 26-74 years old

Study ID **Locations** **(no. sites)**	**Study start** **Enrollment status and date** **Total enrollment/ enrollment goal**	**Study design**	**Patient population** **Control type** **Duration of follow-up**	**Study and control drugs** **Dose, route and regimen (Duration)**	**Study Objective** **No. patients by arm**	**Overall Sex (M/F): Median age in y (range)**
TAR-ORI-QT002 United States (2 sites)	19 June 2007 to 06 September 2007 Planned enrollment: 240 to yield 208 completed subjects Actual enrollment: 240 subjects	Phase 1, multiple-site, double-blinded, randomized, placebo- and positive-controlled, parallel design study	Healthy Adult Subjects Positive control Follow-up Day 7 ± 3 days	All groups Day 0: placebo (D5W), followed by treatment on Day 1 to one of following: oritavancin 200mg IV, oritavanvin 800 mg IV (2x 400mg infusions), moxifloxacin oral 400 mg po, or placebo D5W IV.	Safety and QTc Oritavancin 200 mg: 60 subjects Oritavancin 800 mg: 60 subjects Moxifloxacin 400 mg po: 60 subjects Placebo D5W: 60 subjects	M: 156 (65%) F: 84 (35%) 18-60 years old
Phase 2 trials						
H4Q-LC-ARRC United States (16 sites)	November 1998 to May 2000 Planned enrollment: 28 patients Actual enrollment: 27 patients	Phase 2, open-label, multi- center, dose- escalation study	Patients with gram-positive bacteremia Non-controlled Follow-up Day 60 (-10 or +30 days)	LY33328: IV dosing 3.0 mg/kg loading dose on Day 1, then 2.0 mg/kg/day 4.0 mg/kg loading dose on Day 1, then 3.0 mg/kg/day 5.0 mg/kg loading dose on Day 1, then 4.0 mg/kg/day All groups were treated for 7-10 days	Efficacy, Safety & PK LY333328: 3/2: 5 patients 4/3: 5 patients 5/4: 17 patients	M: 15 (56%) F: 12 (44%) 29-78 years old

Study ID **Locations** **(no. sites)**	**Study start** **Enrollment status and date** **Total enrollment/ enrollment goal**	**Study design**	**Patient population** **Control type** **Duration of follow-up**	**Study and control drugs** **Dose, route and regimen (Duration)**	**Study Objective** **No. patients by arm**	**Overall Sex (M/F): Median age in y (range)**
H4Q-MC-ARRL United States (6 sites)	March 1998 to March 1999 Planned enrollment: 28 patients Actual enrollment: 29 patients	Open-label, uncontrolled, dose-escalation study	Patients with Skin and skin structure infections No control Follow-up to Day 60	LY333328: treatment groups: 1.5 mg/kg QD for 7 days, 2.0 mg/kg QD for 7 days, 3.0 mg/kg QD for 7 days, 3.0 mg/kg for 3 days, 3.0 mg/kg single dose, 6.0 mg/kg single dose, and 9.0 mg/kg single dose	Safety and PK 1.5 mg/kg QD: 4 2.0 mg/kg QD: 5 3.0 mg/kg QD (7d):4 3.0 mg/kg QD (3d):4 3.0 mg/kg SD: 4 6.0 mg/kg SD: 4 9.0 mg/kg SD: 4	M: 19 F: 10 20-81 years old
H4Q-MC-ARRM 9 countries (23 sites)	7 July 2000 to 14 February 2003 Planned enrollment: 78 patients Actual Enrollment: 125 patients (123 dosed)	Phase 2, randomized, open-label, international, multicenter, active-comparator study	Patients with *S. aureus* bacteremia Positive Control Follow-up (D60 +/- 10 days)	Oritavancin: IV was to be administered every 24 hours (± 2 hours) at the appropriate dose (5.0, 6.5, 8.0, 10.0, 12.0, or 14.0 mg/kg/d) infused for 60 to 90 minutes Vancomycin: IV every 12 hours (± 2 hours)	Safety and Efficacy Oritavancin:86 patients Positive Control group: 37 patients	M: 73 (59%) F: 50 (41%) 18 to 90 years old
TAR-ORI-SD001 5 countries (43 sites)	09 September 2007 to 03 June 2008 Planned enrollment: 294 Actual enrollment: 302 patients	Phase 2, multicenter, randomized, double-blind, parallel, active-comparator controlled trial	Patients with complicated skin and skin structure infections Active control Follow-up to 35 days after last dose	Oritavancin: Either a single dose of 1200 mg plus 2 to 6 infusions of placebo 5% dextrose or a single dose of 800 mg with the option for a further 400-mg dose at Day 5 plus 2 to 5 infusions of placebo 5% dextrose Oritavancin: 200 mg oritavancin daily for a minimum of 3 days and up to a maximum of 7 days	Safety and Efficacy Oritavancin 1200mg: 99 patients Oritavancin 800mg: 103 patients Oritavancin: 200mg: 100 patients	M: 199 (66%) F: 103 (34%) 18-94 years old

Study ID **Locations** **(no. sites)**	**Study start** **Enrollment status and date** **Total enrollment/ enrollment goal**	**Study design**	**Patient population** **Control type** **Duration of follow-up**	**Study and control drugs** **Dose, route and regimen (Duration)**	**Study Objective** **No. patients by arm**	**Overall Sex (M/F): Median age in y (range)**
Phase 3 trials						
H4Q-MC-ARRD 8 countries (107 sites)	2 February 1999 through 6 June 2001 Planned enrollment: up to 675 Actual enrollment: 517 patients	Double-blind, randomized, multicenter study	Patients with complicated skin/skin- structure infections presumed or proved to be caused by gram- positive bacteria Comparator study 60 day follow-up (-10 or +30 d)	Oritavancin 1.5 or 3.0 mg/kg/day followed by oral placebo capsules (1-2 capsules BID) Vancomycin 15mg/kg/dose (Frequency determined by CrCl) followed by oral cephalexin 500 mg capsules (1-2 capsules BID).	Oritavancin 1.5 mg/kg Male: 109, Female: 64, Total: 173 Oritavancin 3.0 mg/kg Male: 106, Female: 63, Total: 169 Vancomycin/cephalexin Male: 116, Female: 59, Total: 175	Male: 331 (64%) Female: 186 (36%) 18-98 years old

Study ID Locations (no. sites)	**Study start Enrollment status and date Total enrollment/ enrollment goal**	**Study design**	**Patient population Control type Duration of follow-up**	**Study and control drugs Dose, route and regimen (Duration)**	**Study Objective No. patients by arm**	**Overall Sex (M/F): Median age in y (range)**
H4Q-MC-ARRI 22 countries (88 sites)	27 June 2001 to 27 November 2002 Planned enrollment: 1250 Actual enrollment: 1267	Phase 3, randomized, double-blind, multicenter, active comparator study	Patients with complicated skin and skin structure infections presumed or proven to be caused by gram- positive bacteria Active control Follow-up 39-46 days after dosing	Oritavancin: IV phase: One daily infusion of oritavancin 200 mg followed by one infusion of 250 mL of 5% dextrose in water (D5W) approximately 12 hours after the first infusion. Oral phase: to maintain the study blind, patients who met the IV-to-oral switch criteria were to receive two placebo capsules every 12 hours. Vancomycin: IV phase: The dose of vancomycin administered was based on creatinine clearance. Patients with normal creatinine clearance received infusions of 15 mg/kg of vancomycin twice daily. Patients with reduced creatinine clearance received 10 to 12 mg/kg. Oral phase: Patients who met the IV-to-oral switch criteria were to receive two 500-mg capsules of cephalexin every 12 hours for up to 11 days.	Safety and Efficacy Oritavancin: 831 patients Vancomycin/cephalexin: 415 patients	M: 693 (56%) F: 553 (44%) 13 to 94 years old

Study ID **Locations** **(no. sites)**	**Study start** **Enrollment status and date** **Total enrollment/ enrollment goal**	**Study design**	**Patient population** **Control type** **Duration of follow-up**	**Study and control drugs** **Dose, route and regimen (Duration)**	**Study Objective** **No. patients by arm**	**Overall Sex (M/F): Median age in y (range)**
TMC-ORI-10-01 9 countries (46 sites)	13 January 2011 to 04 December 2012 Planned enrollment: 960 patients Actual enrollment: 968 patients ITT	This was a Phase 3, multicenter, randomized, double-blind, parallel-group, active-controlled study	Patients with Acute bacterial skin and skin structure infections (ABSSSI), suspected or confirmed to be caused by a Gram-positive pathogen Active Control 60 day follow-up	Oritavancin administered as a single, 1200 mg, IV dose Vancomycin administered IV at a fixed 1 g dose or weight-based at 15 mg/kg every 12 hours for 7 to 10 days	Safety, Efficacy and PK mITT population: Oritavancin: 475 patients Vancomycin: 479 patients	M: 602 (63%) F: 352 (37%) 18-93 years old
TMC-ORI-10-02 10 countries (32 sites)	11 January 2011 to 14 June 2013 Planned enrollment: 960 patients Actual enrollment: 1019patients (ITT)	Phase 3, multicenter, randomized, double-blind, parallel-group, active-controlled study	Patients with Acute bacterial skin and skin structure infections (ABSSSI), suspected or confirmed to be caused by a Gram-positive pathogen Active Control 60 day follow-up	Oritavancin administered as a single, 1200 mg, IV dose Vancomycin administered IV at a fixed 1 g dose or weight-based at 15 mg/kg every 12 hours for 7 to 10 days	Safety, Efficacy and PK mITT population: Oritavancin: 503 patients Vancomycin: 502 patients	M:681 (67.8%) F: 324 (32.2%) 18-92 years old

5.2 Review Strategy

The previous phase 3 trials ARRI and ARRD were reviewed for efficacy and safety by Naseem Moledina, MD (refer to her clinical review from November 28, 2008). Two new phase 3 clinical trials TMC-ORI-10-01(SOLO1) and TMC-ORI-10-02(SOLO2) were conducted by the applicant to evaluate the safety and efficacy of oritavancin in ABSSSI. The Clinical Review is divided into two general parts: the review of efficacy and the review of safety. Both will be conducted by the Medical Reviewer. Statistical analysis of efficacy will be conducted by the statistical reviewer. Efficacy results from the smaller phase 2 SIMPLIFI trial will be considered supportive. The efficacy and safety assessment of oritavancin will be mostly based on the results of two Phase 3(SOLO) clinical trials.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 TMC-ORI-10-01(SOLO 1) and TMC-ORI-10-02(SOLO2)
These are identical double-blind, randomized trials to evaluate the efficacy and safety of single-dose IV Oritavancin vs IV Vancomycin for the treatment of ABSSSI conducted in 46 study centers in Germany, India , Israel, Mexico, Romania, Russia, Spain , Ukraine , United States (SOLO1) and 32 study centers in Argentina, Canada, India, Israel, Mexico, Romania, Russia, Spain, Ukraine, and the United States(SOLO2).

5.3.2 SIMPLIFI trial
This was a multicenter, Phase 2, randomized, double-blind, parallel, active-comparator controlled study was for patients with complicated skin and skin structure infections presumed or proven to be caused by a gram-positive pathogen(s). Patients who met the criteria for enrollment were randomly assigned to receive oritavancin as a single or an infrequent dose, or as a daily dose.

For detailed description of these trials, see section 6.1.1

6 Review of Efficacy

Efficacy Summary

The Applicant performed two Phase 3 clinical trials TMC-ORI-10-01 and TMC-ORI-10-02, also known as SOLO) to demonstrate efficacy in the treatment of acute bacterial skin and skin structure infections (ABSSSI). These trials were of non-inferiority (NI) design assessing the primary efficacy endpoint of early clinical response (a composite endpoint of cessation of spread or reduction in size of the baseline lesion, absence of fever, and no rescue antibiotic medication) at 48 to 72 hours from initiation of the first infusion of study drug (early clinical evaluation [ECE] in the mITT population). The key secondary efficacy endpoints were lesion size reduction $\geq$ 20% at ECE and sustained clinical response at post treatment evaluation (PTE) in the mITT population.

These trials were conducted prior to the Agency's draft guidance for ABSSSI issued on October 2013 where the primary efficacy endpoint of clinical response defined as ≥20 percent reduction in the lesion size at 48 to 72 hours compared to baseline, measured in patients who did not receive rescue therapy and are alive. In the SOLO trials, the applicant evaluated this as a secondary endpoint.

The primary analysis of efficacy included analysis of each trial individually. The applicant also pooled analyses of efficacy from these trials as SOLO 1 and SOLO 2 protocols are identical in patient selection criteria, design, conduct, monitoring, and planned analyses, and the demographic and baseline disease characteristics of the patient populations enrolled in each study are comparable. The main goal of the pooled analyses was to provide a larger sample of patients to improve the precision in the estimate of the treatment differences between oritavancin and vancomycin in the subpopulation of patients with MRSA and to increase power to identify factors that might affect differences between the treatments (i.e., demographics, comorbidities, etc.).

Supportive clinical efficacy data were submitted from the Phase 2 SIMPLIFI trial. Additional trials submitted in support of clinical efficacy in ABSSSI were 1) ARRL, ARRD, and ARRI(complicated skin trials) where oritavancin was used in a daily dose regimen. 2) ARRC and ARRM (bacteremia trials) since they are supportive of the results seen in the bacteremia subgroup in SOLO 1 and SOLO 2. Efficacy data from these studies were not pooled, but were summarized individually for the primary efficacy endpoint. Analysis of dose-response for safety could be found in Dr. Moledina's previous oritavancin NDA 22153 review from December, 2008.

Since pooling of the results of the two pivotal Phase 3 trials, despite their similarity in design and results, is generally inappropriate. Since each trial should provide independent evidence of efficacy of oritavancin in treating ABSSSI and the applicant is still required to demonstrate the efficacy and safety of oritavancin included analysis of each SOLO2 trial separately. In addition to presenting the Applicant's prespecified efficacy analyses, additional sensitivity analyses were conducted by the reviewer to assess the influence of the following factors on the outcome: vancomycin trough levels, unplanned incision and drainage, and low baseline lesion size. These additional analyses do not appear to alter the efficacy results significantly.
Conclusions which can be drawn from primary, secondary and sensitivity analysis are:

- Oritavancin demonstrated non-inferiority to the comparator, vancomycin as evidenced by the lower limit of the 95% CI around the difference in responder rates at early clinical evaluation, being greater than -10%, the pre-specified NI margin for the primary endpoint.

- Investigator measurement error of lesion size did not appear to influence responder rates

- Subjects with low vancomycin trough levels did not appear to influence the primary efficacy rate.

- In addition, there was consistency of clinical response to oritavancin across several time points and varying degree of lesion size reduction at ECE, Day 10 and PTE.

- Major cutaneous abscesses, cellulitis, SIRS at baseline, Asian sites, age >=65 yrs, and diabetes had a lower primary efficacy rate in SOLO2 for oritavancin arm compared to vancomycin 81% vs 90%, 67%vs 75%, 69%vs 81%,78%vs 86%,69%vs 85%,74%vs 84%, respectively. In SOLO 1 these differences were not observed.

6.1 Indication (Acute Bacterial Skin and Skin Structure Infections)

The Applicant seeks the following indication: The treatment of adult patients with acute bacterial skin and skin structure infections caused or suspected to be caused by susceptible isolates of designated Gram-positive microorganisms including *methicillin resistant staphylococcus aureus.*

Acute Bacterial Skin and Skin Structure Infections include cellulitis/erysipelas, wound infection, major cutaneous abscess and burn infections. Among outpatients presenting with purulent ABSSSI to emergency rooms in the US, *Staphylococcus aureus* accounted for approximately 76%, with Methiciliin resistant staphylococcus aureus(MRSA) accounting for approximately 59% (1). Among inpatients, *Staphylococcus aureus* accounted for approximately 70% of cutaneous abscess and ABSSSI with additional complicating factors, with MRSA accounting for approximately 45% (2). ABSSSI range in severity from mild localized infections to severe infections with signs and symptoms of systemic toxicity. Currently, ABSSSI are the most common infections leading to hospitalization (2). Mortality due to untreated ABSSSI in the current era is unknown, but prior to the advent of antibacterial therapy, mortality due to cellulitis/erysipelas is estimated at 10-11% and at 5-8% due to carbuncles and furuncles (3). Therapy may be limited due to emergence of resistant pathogens particularly the emergence of Gram-positive strains displaying reduced susceptibility to vancomycin, including vancomycin intermediate Staphylococcus aureus (VISA) and heterogenous vancomycin intermediate Staphylococcus aureus (hVISA). There are also reports of S. aureus non susceptibility to linezolid. Therefore, there is a need to develop new antibacterials to effectively treat ABSSSI.

6.1.1 Methods

SOLO 1 and SOLO2 Trials

The Applicant performed two identical Phase 3 clinical trials, SOLO 1 and 2, to support the indication of ABSSSI. Description of these trials is in Table xx in section 5.3.

SOLO 1 and SOLO 2 were two large, identically-designed, global, double-blind, randomized, parallel-group, Phase 3 clinical trials intended to enroll approximately 1920 patients (960 patients per study) with an ABSSSI caused by a Gram-positive pathogen, including 350 patients (175 patients per trial) with MRSA. Patients were randomized at a 1:1 ratio to either oritavancin or vancomycin by an interactive voice response system/interactive web response system. 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 in both studies for major cutaneous abscesses).

Randomization was stratified by geographic region, study site, and diabetes mellitus. Stratification by region was done to balance the incidence of MRSA in different regions and at different study sites

across groups. Stratification for diabetes was required to account for an anticipated lower response rate in such patients because of their compromised immune system and peripheral circulation.

Inclusion criteria

- Patients at least 18 years old, consented to study with an ABSSSI with a minimum surface area of 75.0 cm2, suspected or known to be caused by a Gram-positive pathogen requiring at least 7 days of IV therapy.

- ABSSSI -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.

- Presence of signs and symptoms of systemic inflammation.

- ABSSSI must have been presented with at least two of the following signs and symptoms:

  a. Purulent drainage or discharge
  b. Erythema
  c. Fluctuance
  d. Heat or localized warmth
  e. Edema/induration
  f. Pain or tenderness to palpation
  AND
  at least one of the following signs of systemic inflammation*
  a. Proximal lymph node swelling and tenderness
  b. Increased temperature (>38.0°C [100.4°F] oral route; temperature was not obtained by rectal, axillary, or tympanic routes)
  c. Decreased temperature (< 36.0°C [< 96.8°F] oral route; temperature was not obtained by rectal, axillary, or tympanic routes)
  d. Increased WBC (> 10,000 cells/μL)
  e. Bandemia > 10%
  f. C-reactive protein (CRP) > upper limit of normal reference range (ULN)
  *Note: If a patient did not have any of the above signs of systemic inflammation, he/she could have been enrolled if any of the following conditions were met:
  a. Age > 70 years
  b. Diabetes mellitus requiring treatment with insulin and/or oral hypoglycemic medications
  c. Treatment with immunosuppressive therapy or chemotherapy in the prior 3 months

A specimen for culture was obtained 24 hours before the first dose of study drug. Final culture results were not required prior to initiation of study drug.

Exclusion Criteria

- Prior systemic or topical antibacterial therapy with activity against suspected or proven Gram-positive pathogens within 14 days preceding randomization unless:

a. The causative Gram-positive pathogen(s) isolated from the ABSSSI site was resistant in vitro to the antibacterial(s) administered with documented clinical progression
b. Documented failure to previous ABSSSI antibiotic therapy was available (e.g., a record in the patient's medical chart of wound size prior to initial treatment with demonstration of progression on therapy, discussion with prior treating physician, consultation of patient's medical records, and/or consultation of available documentation of treatment, e.g., prescription, before study randomization)
c. Patient received a single dose of a short-acting, antibacterial therapy within 72 hours of randomization (e.g., surgical prophylaxis)

- Infections associated with, or in close proximity to, a prosthetic device
- Severe sepsis or refractory shock
- Known or suspected bacteremia at time of Screening
- ABSSSI, from or associated with, any of the following:

a. Infections suspected or documented to be caused by Gram-negative pathogens (ie, human or animal bites, injuries contaminated with fresh or salt water, external malignant otitis)
b. Wound infections (surgical or traumatic) and abscesses with Gram-negative pathogens only
c. Diabetic foot infections (infection extending distal to the malleoli in a patient with diabetes mellitus, and peripheral neuropathy, and/or vascular insufficiency or any ulceration of their foot)
d. Concomitant infection at another site not including a secondary ABSSSI lesion (eg, septic arthritis, endocarditis, osteomyelitis)
e. Infected burns
f. A primary infection secondary to a pre-existing skin disease with associated inflammatory changes such as atopic dermatitis, eczema, or hidradenitis suppurativa
g. Decubitus or chronic skin ulcer or ischemic ulcer resulting from peripheral vascular disease (arterial or venous)
h. Any evolving, necrotizing process (i.e., necrotizing fasciitis), gangrene, or infection suspected or proven to be caused by the Clostridium species (e.g., crepitance on examination of the ABSSSI site and/or surrounding tissue or radiographic evidence of subcutaneous gas in proximity to the infection)
i. Infections known to be caused by a Gram-positive organism with a vancomycin minimum inhibitory concentration (MIC) > 2 μg/mL or clinically failing prior therapy with glycopeptides
j. Catheter-site infections

- Allergy or intolerance to aztreonam or metronidazole in a patient with a suspected or proven polymicrobial wound infection involving Gram-negative and/or anaerobic bacteria
- Currently receiving chronic systemic immunosuppressive therapy such as chemotherapy or prednisone (prednisone at non immunosuppressive doses of ≤ 15 mg/day was permitted)

- Last known cluster of differentiation antigen 4 count < 200 cells/μL in patients with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome
- Neutropenia with an absolute neutrophil count (ANC) < 500 cells/μL
- Significant or life-threatening condition (e.g., endocarditis) that would have confounded or interfered with the assessment of the ABSSSI
- Women who were pregnant or nursing or who were of childbearing potential and unwilling to use at least two acceptable methods of birth control (e.g., prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, barrier method, or male partner sterilization); women ≥ 2 years postmenopausal or surgically sterile were exempt from this exclusion
- History of immune-related hypersensitivity reaction to glycopeptides (such as vancomycin, telavancin, daptomycin, or teicoplanin) or any of their excipients (note: patients who had histamine-like infusion reactions to a glycopeptide were not excluded)
- Patients that required anticoagulant monitoring with an activated partial thromboplastin time
- Contraindication to vancomycin administration
- Patients unwilling to forego blood and/or blood product donation for at least 3 months from initiation of first study drug treatment
- Treatment with an investigational medicinal product within 30 days before enrollment and for the duration of the study
- Investigational device present or removed within 30 days before enrollment or presence of a device-related infection
- Patients whom the investigator considered unlikely to adhere to the protocol, comply with study drug administration, or complete the clinical study (eg, unlikely to survive 90 days from initiation of study drug)
- Liver function test (LFT) results ≥ 3x the ULN or total bilirubin ≥ 2X ULN
- Presence or history of hyperuricemia or gouty arthritis
- Unwilling to refrain from chronic use of any medication with antipyretic properties
- Patients excluded for any of the above reasons could have been rescreened for participation at any time if the exclusion characteristic changed.

MO comments: Burn wound infections were excluded in the SOLO 1 and 2 trials since a frequent pathogen in burn wounds is Pseudomonas and oritavancin does not have any activity against Pseudomonas.

Concomitant Medications

All non-antibacterial standard of care medications were allowed as concomitant medications, with the exception of antipyretic medications. The following two non-study systemic antibacterial medications were allowed to treat patients with mixed infections: aztreonam (IV) or metronidazole (oral or IV). Narcotics were the only analgesics allowed throughout the treatment period

The use of topical antimicrobials was not permitted from randomization through PTE. The use of acetaminophen was allowed when an antipyretic medication was indicated. However, acetaminophen was not allowed between 36 and 72 hours after initiation of study drug, unless the patient had a documented fever. All other concomitant antipyretics were prohibited from randomization through PTE.

Study Schedule

The Screening period was the period between signing of the informed consent form (ICF) to initiation of the first infusion of study drug. The Screening period lasted no longer than 24 hours.

The Treatment period was the period from initiation of the first infusion of study drug (Day 1) to termination of the last infusion of study drug (Day 7 to Day 10, EOT). The treatment period was no less than 7 days and could have been up to 10 days. Early clinical evaluation [ECE] was at 48 to 72 hours from initiation of the first infusion of study drug.

The Follow-Up period was the period between termination of the last infusion of study drug (Day 7 to Day 10) and a Safety Visit that occurred 60 days after the first administration of study drug. There were four visits during the Follow-up period:

- An end of therapy (EOT) visit that occurred no more than 24 hours from either the last administration of study drug, or a change to a nonstudy drug for the primary ABSSSI (whichever came first)
- A Day 10 visit that occurred 10 days from initiation of the first infusion of study drug; in some patients, the Day 10 visit coincided with the EOT visit, depending on the patient's treatment schedule
- A post-treatment evaluation (PTE) visit that occurred 7 to 14 days from the EOT visit
- A Safety follow-up visit that occurred 60 days after the first administration of study drug
- An additional visit during the Follow-Up Period, the Day 24 visit (24 days [+48/-24 hours] from initiation of the first infusion of study drug) was required for all patients enrolled at investigational sites that agreed to participate in the PK analysis.

Table 4: Schedule of assessments

Study Procedures	**Screening**[c] (≤24 h before first dose)	**Study Visit**						
		Treatment		**Follow-up**				
		Day 1-9	**ECE 48-72 h** after first study drug administration	**EOT** (up to 24 h after last dose)[a]	**Day 10**[s] after first study drug administration	**PTE** 7-14 days after EOT	**Day 24**[j] (+ 48 h/ - 24 h	**Day 60** (+7 d) Safety Visit[b]
Informed consent	x							
Patient inclusion/exclusion criteria	x							
Medical history	x							
Physical exam (including height & weight at Screening only)	x		[x]	[x]	[x]	[x]		
Temperature[o]	x	<----------x---------->						
Vital signs (blood pressure, heart and respiratory rates)	x		x	x	x	x		
Pregnancy test(s)[r]	x							
Record ABSSSI surgical procedures[e]	x	<----------x---------->						
Examination, measurement, and signs & symptoms of ABSSSI[d]	x	<----------x---------->						
Urinalysis (dip stick)	x	<----------[x]---------->						
Clinical Lab Assessments: CBC with differential, & serum comprehensive metabolic panel[k]	x	[x]	x	x	x	x		
Serum uric acid and creatine phosphokinase	x			x				
Hepatitis B surface antigen	x							
Hepatitis C antibodies	x							
HbA_{1C} (if blood glucose level > 170 mg/dL at baseline)		[x]						
Blood for pharmacokinetic analysis[q]		<----------x---------->					x	
Microbiology testing – ABSSSI Gram stain and culture and susceptibility testing[g,l]	x	<----------[x]---------->						
Record prior or concomitant medications[u]	<----------x---------->							
C-reactive protein	x	[x]	x	x	x	x		
Patient Pain Assessment (NRS)[v]	x		x	x	x	x		
Photography and tracing for planimetry of the infection site[m]	x		x	x	x	x		
Health economics	<----------x---------->							
12-lead ECG recording[r]	x	x						
Calculate CrCl	x	[x]	x					

Study Procedures	Screening[c] (≤24 h before first dose)	Study Visit						
		Treatment		Follow-up				
		Day 1-9	ECE 48-72 h after first study drug administration	EOT (up to 24 h after last dose)[a]	Day 10[s] after first study drug administration	PTE 7-14 days after EOT	Day 24[j] (+ 48 h/ - 24 h	Day 60 (+7 d) Safety Visit[b]
Determine dosing schedule with unblinded pharmacist/designee	x							
Randomization via IVRS/IWRS	x							
IV study drug (Days 1-7; Days 8-10 as clinically indicated)		<----------x---------->						
Vancomycin trough level		<----------x[p]---------->						
Assess clinical cure[n]				x	x[l]	x[l]		
Blood for culture (2 sets for anaerobes/aerobes)[h]	x	<----------[x]---------->						
Assess AEs and SAEs[t]	<----------x---------->							
For telephone interview: record questions and patient responses regarding infection								x

AE: adverse event; CBC: complete blood count; CrCl: creatinine clearance; ECE: early clinical evaluation; ECG: electrocardiogram; EOT: end of therapy; h = hour(s); IVRS/IWRS: Interactive Voice Response System/Interactive Web Response System; IV: intravenous; NRS: numerical rating scale; PK: pharmacokinetic; PTE: post therapy evaluation; SAE: serious adverse event.
Note: [x] Test to be performed only if clinically indicated.

a. If a patient discontinued study treatment before Day 10, the EOT assessments were performed within 24 hours after the last dose.
b. A telephone interview was acceptable to record new or ongoing AEs and SAEs. An on-site follow-up visit with a healthcare provider was required to resolve unresolved/ongoing AEs from PTE visit.
c. Assessment was performed prior to treatment in order to determine eligibility for enrollment into the study.
d. Included assessment of signs and symptoms at primary ABSSSI site and the evaluation of the need for continued antibiotic therapy beyond Day 7. When clinically indicated at Screening, osteomyelitis for deep wound infections in proximity to bone or joints was ruled out per standard of care (e.g., X-ray or magnetic resonance imaging scan performed).
e. This included but was not limited to aspiration, debridement, incision and drainage. Incision and drainage after 48 hours of treatment that was unplanned prior to randomization was considered a treatment failure unless it was only superficial, with the exception of cellulitis where there was conversion into an abscess or when an extension of the original incision was indicated. Any planned incision and drainage procedure was documented.
f. A local urine pregnancy test at Screening for female patients of childbearing potential was performed (omitted for females > 2 years postmenopausal or surgically sterile); if negative, a serum test at Screening was performed and sent to the Central Laboratory for eligible patients.
g. An appropriate ABSSSI site specimen (superficial swab was not acceptable) was acquired at baseline and a Gram stain and culture was performed. After interpretation and recording of the Gram stain result, the Gram stain slide was sent to the Central Laboratory for independent interpretation and recording of the result. A specimen was obtained on Day 1 only if the baseline sample was insufficient for required tests or not available for
testing. After baseline, ABSSSI site specimens were only required if clinically indicated (e.g., failure: no improvement in or deterioration of lesion was observed) and the specimen was easily accessible.
h. Blood drawn for aerobes and, where possible, anaerobes, from 2 venipuncture sites at least 5 minutes apart. Blood cultures repeated after baseline only if previously positive or if clinically indicated (e.g., no improvement in or deterioration of lesion). Blood cultures continued to be obtained until negative results were documented.
i. Performed only for patients not categorized as a failure at the EOT visit (If EOT was Day 10, the assessment was performed).
j. In-person visit at Day 24 was required only for patients in the PK Population.
k. Blood chemistry and hematology. Unless otherwise indicated, all laboratory tests were performed by a central laboratory.
l. Confirmatory identification and minimum inhibitory concentration testing of isolated pathogen(s) was performed by the Central Laboratory.

m. If patient failed outside of visit window, photographs, planimetry tracing and measurements were taken at time of failure; photographs and measurements were also taken before and after any surgical procedure. n. Patients were classified as a clinical cure or failure.

o. Preferably taken at the same time on each study day and by same route (oral route only; no temperature was obtained by rectal, axillary or tympanic routes) If additional temperature measurements were taken (e.g., if the patient experienced shaking and/or chills, then the highest temperature for each 24-hour period was also recorded (if not one of the following): For Screening, measurements were obtained prior to initial study drug infusion and just prior to administration of any medication with antipyretic properties. For temperature assessments in the first 72 hours of the Treatment period, measurements were obtained four times per day (e.g., every 6 hours); the schedule started just prior to administration of the first study drug infusion (temperature assessments were taken prior to study drug infusions wherever possible) and just prior to administration of any medication with antipyretic properties. For temperature assessments after the first 72 hour treatment period, measurements were obtained four times per day evenly distributed during waking hours. Two of the four assessments were taken just prior to each study drug infusion and just prior to administration of any medication with antipyretic properties. For EOT, Day 10, and PTE, measurements were obtained once daily at each visit and also just prior to administration of any medication with antipyretic properties.

p. One sample was drawn just prior to administration of the fourth dose of study drug from **all** patients for storage and analysis at the Central Laboratory. Additional sample(s) were drawn and analyzed per standard of care at sites where vancomycin trough testing was locally available.

q. Blood samples were drawn for PK analysis in a subset of patients (PK population) at the following time points: Day 1 at 3 hours (approximately 15 to 30 minutes after the end of first infusion) and at 12 hours (- 1 hour, just prior to second infusion of study drug); Day 2 (24 hours ± 1 hour after initial infusion of study drug); Day 3 (72 hours ± 1 hour after initial infusion of study drug); Day 24 (+ 48 hours/- 24 hours, 576 hours after initial infusion of study drug).

r. ECG recorded at Screening and Day 1 within 30 minutes after termination of study drug.

s. Day 10 visit coincided with the EOT visit depending on the patient's treatment schedule.

t. AEs and SAEs were assessed from the time of informed consent through 60 days (+7 days) post first administration of study drug.

u. Only antipyretic, antibacterial, and immunosuppressive medications were recorded in the eCRF until January 2012 when a decision was made to capture all concomitant medications.

v. See Protocol Appendix 2 for patient self-assessment of pain using NRS

Source: Table 2 of Clinical study report (Page 39 for SOLO1 and Page38 for SOLO2)

Study drug administration
Oritavancin was administered as a single 1200 mg IV dose in 1000 mL 5% dextrose in water (D5W) given over 3 hours on Day 1 followed by twice daily infusions of placebo for 7 to 10 days to maintain the study blind. Vancomycin was administered IV on Day 1 as either a 1 g dose or at 15 mg/kg every 12 hours in 1000 mL D5W and infused over 3 hours. After Day 1, the vancomycin dose could be adjusted by the unblinded pharmacist/designee based upon estimated CrCl, the patient's clinical status, and/or vancomycin trough plasma concentrations. Vancomycin was administered for 7 to 10 days. Starting with Dose 2 and for all subsequent doses, infusion time was a minimum of 60 minutes.

Discontinuation of study drug
Adverse event (AE), Abnormal laboratory value, Abnormal test procedure result, Protocol violation, Patient withdrawal of consent, Administrative problems, Confirmation of Gram-negative infection only, Sponsor decision (study or patient discontinued by the Sponsor), Death, Unsatisfactory therapeutic effect, Loss to follow-up, Other, Resolution of infection per investigator, Unblinding of treatment assignment for any reason (vancomycin dosing change to three times a day).

Lesion size assessment
Lesion size was assessed by both ruler measurement and planimetry tracings, with ruler measurement data used in the primary analysis of lesion size reduction. Planimetry tracing data was used in a concordance analysis between planimetry tracing and ruler measurements.

Efficacy Assessments/Statistical Analyses

Endpoints
The primary endpoint in the SOLO studies was early clinical response (a composite endpoint of cessation of spread or reduction in size of the baseline lesion, absence of fever, and no rescue antibiotic medication) at 48 to 72 hours from initiation of the first infusion of study drug (early clinical evaluation [ECE] in the mITT population).

Main secondary endpoints in SOLO I and SOLO II were: 1) lesion size reduction $\geq$ 20% at ECE, the endpoint currently recommended by FDA and the Foundation for the National Institutes of Health [Talbot et al, 2012] as the primary efficacy endpoint for an ABSSSI treatment; and 2) sustained clinical response at PTE in the mITT population.

Other Secondary endpoints:

- The clinical response ('clinical cure') at the End of Therapy (EOT) timepoint and sustained clinical response to Day 10 and PTE timepoint in the mITT population and the CE population
- The clinical response for the primary efficacy outcome in the clinically evaluable (CE) population
- The 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 and the microbiological response, overall and by pathogen at EOT, Day 10, and PTE in the

microbiologically intent-to-treat (MicroITT) and microbiologically evaluable (MicroE) populations

- The incidence of microbiological relapse or recurrence rates at the PTE visit in the MicroITT and MicroE populations

- 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/μL or < 4,000 cells/μL or > 10% bandemia), or with positive blood cultures

- 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 included population pharmacokinetics (PK) and PK/pharmacodynamics (PD) of the oritavancin 1200 mg dose in the PK population. PK parameters including area under the plasma concentration-time curve (AUC), half -life (t1/2), clearance (CL), maximum concentration (Cmax), and steady state volume of distribution (Vss) were assessed.

Additional objectives:

- To evaluate the ability of a single dose of oritavancin to resolve fever (≤ 37.7°C) at ECE (48 to 72 hours) compared with IV vancomycin for 7 to 10 days in patients presenting with fever (≥ 38°C) at baseline

- To characterize genes in strains of *Staphylococcus aureus* (*S. aureus*) and their association with clinical response and microbiological response in the MicroITT population

- To collect patient-level and hospital-level data to conduct a health economic evaluation of patients in each treatment group

Supportive Secondary Efficacy Outcomes

- Sustained lesion area decrease at EOT and PTE using the mITT and CE populations

- 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

Analysis populations:

- Intent-to-Treat (ITT) population - all patients randomized into the study.
- The mITT population - primary population for all the efficacy analyses included all randomized patients who received any study drug.
- The CE population- 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 investigator assessment for clinical cure at PTE. The CE population was used to confirm the mITT efficacy analyses.
- The MicroITT population - all mITT patients with baseline Gram-positive pathogen(s) known to cause ABSSSI. The MicroITT population was used for the secondary efficacy analyses.
- The MicroE population was used to confirm the secondary efficacy analyses and consisted of all patients who were in both the MicroITT and CE populations.
- 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.
- The PK population consisted of all patients who received at least one dose of oritavancin and had at least one plasma concentration measurement.

Statistical methods:

The primary analysis of early clinical response was performed using the mITT population. For the primary efficacy endpoint, 2-sided 95% confidence intervals (CIs) for the difference in rates of response between the two treatment groups were calculated (oritavancin rate minus vancomycin rate). Non-inferiority of oritavancin was declared at the 1-sided alpha level of 0.025 if the lower bound of the 2-sided 95% CI was more than ‑10%. A 10% non-inferiority margin was selected for investigator-assessed clinical cure at PTE. Supportive analyses were conducted using the ITT and CE populations. For the MRSA subgroup, efficacy was analyzed in the MicroITT population.

Sensitivity analysis:

Sensitivity analyses were performed excluding missing data and treating missing data as success. Investigator-assessed clinical cure rates at PTE and lesion-size reduction $\geq$ 20% at ECE were prespecified for noninferiority testing whereas sustained clinical response was not prespecified for noninferiority testing. Descriptive analyses were performed for safety parameters by treatment group using the Safety population. Unless otherwise specified, the last evaluation prior to the initiation of study drug was considered the baseline evaluation for statistical analysis.

The applicant also evaluated "sustained clinical response-FDA" as a sensitivity analysis. Definition of this secondary endpoint is provided below.

Statistical analysis plan amendments:

- After the database lock that the infusion volume recorded on the study drug administration record (completed by the blinded study personnel who administered drug to the patient) and the total volume on the drug accountability record (completed by the unblinded pharmacist responsible for reconstitution of the study drug) were not always aligned. There were a total of 313 records where the infusion volume on the study drug administration record were not within 20% of the volume recorded on the drug accountability record (<80%: 215 records or >120%: 98 records). This was 2.7% of all study drug administration records for which infusion volumes were recorded. The calculation of study drug exposure was revised such that the calculated infusion volume was capped by the corresponding volume on the drug accountability record with the expectation that the total volume of drug given to the patient could not be more than the volume reconstituted by the unblinded pharmacist and documented on the drug accountability record.

- A sensitivity analysis was performed on the mITT population for the sustained clinical response at PTE for which the condition of "Persistence or worsening of erythema/induration and/or purulent drainage" was revised to simply "Persistence or worsening of purulent drainage as compared to baseline". This was conducted given the variability noted in change of erythema or induration.

The **rate of primary efficacy outcome** was calculated as the number of patients with success divided by number of patients in the mITT population. Patients with missing values were considered as "failures" in the primary efficacy analysis.
Primary efficacy event rate (%)= (Success x 100)/ (Success+ Failure+ Missing). Similar analysis was performed on the CE population and ITT population for confirmation. Primary efficacy analysis was also conducted using the MicroITT and MicroE populations.
The applicant also conducted additional analysis for the following population:

- CE and MicroE populations who met SIRS criteria defined as two of the following: temperature > 38°C, pulse > 90 bpm, respiratory rate >20 breaths per minute, WBC count > 12,000 cells/μL or < 4,000 cells/μL or > 10% bandemia..
- MicroITT and MicroE populations for MRSA patients.
- mITT and CE populations by ABSSSI infection type.
- MicroITT and MicroE populations by baseline pathogen.

Definitions used for primary efficacy analysis
A patient was categorized as a **"success"** if all 3 components of the composite primary endpoint (cessation of spread or reduction in size of the baseline lesion, absence of fever, and no rescue antibiotic medication) at 48 to 72 hours from initiation of the first infusion of study drug were met.
A patient was categorized as a **"failure"** if one or more of the following events occurred:

• Death (all-cause mortality) during the first 72 hours from the initiation of study drug administration.
• Fever (one or more temperature readings of ≥ 37.7°C between 48 and 72 hours)
• Spreading of lesion size defined as an increase in size (length, width, or area [= length X width]) of the redness, edema, and/or induration measured by ruler at 48 to 72 hours, compared to the size at baseline. However, patients with ≥20% reduction in lesion area from baseline were not considered as failure, even if they may have had an increase in lesion length or width. If there were multiple lesion size measurements between 48 and 72 hours, the last measurement was considered.
• Administration of rescue antibacterial drug therapy (any non trial antibacterial drug with gram-positive coverage except metronidazole) during the first 72 hours from the initiation of study drug administration.
• Requirement of an unplanned surgical procedure during the first 72 hours from the initiation of study drug administration.
• A patient with missing data was categorized as a "failure" if any of the above events was unknown or missing.

Fever was further defined as follows:
• A patient was considered as having a fever at ECE if one or more oral temperature (not by rectal, axillary or tympanic routes) measurements were ≥37.7°C at any time between 48 and 72 hours following the initiation of study drug administration.
• A patient was considered as having an absence of fever if the patient received "sufficient" temperature readings during 48-72 hours and none of the temperature readings is ≥37.7°C. Temperature readings were considered as "sufficient" if at least 3 temperatures taken between 48-72 hours.
• If a patient doesn't receive "sufficient" temperature readings between 48-72 hours, the assessment of fever for this patient was considered missing.

Secondary efficacy analysis

The key secondary efficacy outcome was the investigator-assessed **clinical cure at PTE** in the mITT population. Clinical cure was defined as if the patient experiences a complete or nearly complete resolution of baseline signs and symptoms of the primary infection such that no further treatment with antibiotics is needed at end-of-treatment AND sustained/continued resolution of infection at PTE. Patients with assessments outside the visit window had their responses at PTE imputed as follows:

- If a patient had clinical failure assessed beyond the PTE visit window, the patient was considered as clinical failure at PTE as well.
- If the patient had clinical failure before the PTE visit, the patient was considered as clinical failure at PTE.
- If the patient had clinical success before the PTE visit, the patient was considered as clinical success at PTE.
- After the above imputation, patients still with missing assessment at PTE were treated as failure. The rate of clinical cure at PTE was calculated as the number of patients with clinical cure divided by total number of patients in the mITT population:

Clinical cure rate (%) = (Cure x 100) / (Cure + Failure)
Sequential hypothesis tests, sensitivity analyses excluding missing data or treating missing data as success, supportive analyses on the other populations, subgroup analyses and analysis using the odds ratio metric was performed similar to those performed for the primary efficacy endpoint.

Supportive secondary efficacy analysis
Sustained Clinical Response at PTE
Definitions:
Clinical cure: if the patient experiences a complete or nearly complete resolution of baseline signs and symptoms of the primary infection such that no further treatment with antibiotics is needed at end-of-treatment AND sustained/continued resolution of infection at PTE.
Clinical failure at PTE:
• Patient did not fulfill criteria for clinical cure above
• Investigator assigned failure any time prior to EOT
• Patient died (all-cause mortality) following start of study drug
• Incision and drainage after 48 hours of treatment that was unplanned prior to randomization, with the exception of cellulitis where there is a conversion into an abscess or when an extension of the original incision is indicated.
• Persistence of worsening of erythema/induration and/or purulent drainage.
• Initiation of non-study antibacterial drugs for treatment of ABSSSI
• Initiation of non-study antibacterial drugs for treatment of other infections unless antibiotics lack efficacy in the treatment of ABSSSI
• Patients who otherwise do not meet the definition of clinical cure (e.g. lost to follow-up, study drug discontinued secondary to adverse reaction)
• Missing assessment at PTE was treated as failure.

Sustained Clinical Response - FDA
This was defined in a same manner as the parameter "Sustained Clinical Response" except for the criteria of "Persistence or worsening of erythema/induration and/or purulent drainage". Sustained Clinical Response – FDA included "Persistence or worsening of purulent drainage as compared to baseline".

Lesion Area Decrease ≥20% from Baseline at ECE
Proportion of patients with ≥20% decrease in lesion area from baseline at ECE was summarized by treatment group, together with the event rate difference between vancomycin and oritavancin and its 95% CI. If a patient had missing assessment at baseline or ECE, the patient was treated as a failure in the analyses. The main analysis was performed using the mITT and CE populations, with the stepdown approach applied for the primary efficacy endpoint, i.e., sequentially testing for non-inferiority at the 10% margin followed by testing for superiority.

Investigator-Assessed Clinical Cure at EOT and Day 10 and Sustained Lesion Area Decrease at EOT and PTE

The event rate difference of these endpoints between vancomycin and oritavancin and 95% CI was calculated for the same populations and subgroups in the analyses of the primary and key secondary efficacy variables.
Patients who discontinued treatment prior to ECE were treated as failures in the analyses.

Additional analysis:
The applicant submitted the following analyses at the Agency's request at the pre-NDA meeting held on September 16, 2013:

- Histogram of baseline lesion area distribution overall, by ABSSSI infection type, and by the response status of the primary efficacy endpoint at ECE by treatment in the mITT population

- For patients in the CE population who were success for the primary efficacy endpoint at ECE but either failed or had missing value for the sustained clinical response at PTE, a summary of failure reasons were provided by treatment

- Analyses of the primary efficacy endpoint at ECE without the temperature components (i.e., fever or insufficient temperature measurements during 48-72 hours) were performed for the mITT population and in the subgroup of patients with MRSA in the MicroITT population

- A listing was provided for patients in the mITT population who had missing values of sustained clinical response at PTE that included the reason for missing assessment and patient status based on the last investigator assessment of clinical cure before they were missing at PTE

- A flag was included in the listing of surgical procedures to identify those which may affect the endpoints at ECE (i.e., the primary efficacy endpoint and the endpoint of lesion size reduction ≥ 20% from baseline at ECE) if the procedures were performed after the start of treatment and prior to the lesion size assessment at ECE. For patients who had no lesion size assessment at ECE, the upper limit of 72 hours from start of treatment was used. The primary efficacy endpoint was then analyzed for patients in the mITT population who had planned surgery vs. those who did not and by type of planned surgery. Unplanned surgery was not considered in the analysis as any patient who had unplanned surgery during the first 72 hours of treatment was treated as failures for the primary efficacy endpoint. Analyses were also performed for the endpoint of lesion size reduction ≥ 20% from baseline at ECE, for patients in the mITT population who had planned or unplanned surgery vs. those who had no surgery, and by type of surgery.

  Subgroup analysis
  The applicant also conducted primary efficacy and key secondary efficacy analysis in the following subgroups of patients- MRSA and other baseline pathogens, demographic subgroups, including: age (< 65 years, 65 to <75 years, and ≥ 75 years old), gender (males and females), race (White, Black or African American, Asian, and Other), weight (< 60 kg, 60 to < 100 kg, ≥ 100 kg), Body mass index (BMI) (< 25 kg/m2; 25 to < 30 kg/m2, ≥ 30 kg/m2), Geographic region including North America, South America, Eastern Europe, Western Europe, Asia, North America and Rest of World (ROW), baseline signs and symptoms of

ABSSSI and baseline clinical features, including: fever (≥ 38°C) at baseline, bacteremia at baseline, met the criteria for systemic inflammatory response syndrome (SIRS) at baseline, received antibiotics before study drug administration, ABSSSI type (wound infection, cellulitis/erysipelas, major cutaneous abscess), Co-morbid conditions, including diabetes mellitus (with or without), normal renal function (CrCl ≥ 90 mL/min) or mild (CrCl ≥ 60 to < 90 mL/min), moderate (CrCl ≥ 30 to < 60 mL/min), or severe (CrCl < 30 mL/min) renal impairment, hepatic impairment and normal hepatic function, immunodeficient or not. Subgroup analyses were performed using the mITT population, with the exception of the MRSA and other baseline pathogen analyses, which were conducted using the SOLO pool and the MicroITT and MicroE populations.

SIMPLIFI trial

This multicenter, Phase 2, randomized, double-blind, parallel, active-comparator controlled study was for patients with complicated skin and skin structure infections presumed or proven to be caused by a gram-positive pathogen(s). Patients who met the criteria for enrollment were randomly assigned to receive oritavancin as a single or an infrequent dose, or as a daily dose. Randomization was stratified by the following disease categories (in order of priority): wound infection, major abscess, and cellulitis. 302 patients received study drug.

Diagnosis and Inclusion Criteria:

Complicated skin and skin structure infection, presumed or proven to be caused by a Gram-positive pathogen(s) that met disease diagnostic criteria, were age 18 years or older, with a body mass index >17 kg/m^2 and <40 kg/m^2.

A patient was defined as having a complicated skin and skin structure infection if all 3 of the following definitions were satisfied:

1. Severity: The skin and skin structure infection was of sufficient severity for the investigator to anticipate 3 or more days of intravenous antibiotic therapy.
2. Complicated Disease: One of the following criteria was met: 1) infection required significant surgical intervention within 48 hours before or after enrollment; 2) infection process was suspected or confirmed to involve deeper soft tissue, not fascia and/or muscle layers, or: 3) significant underlying disease was present that complicated the response to treatment including, but not limited to diabetes mellitus, bacteremia, corticosteroid therapy, or severe neutropenia.
3. Disease Categories: For purposes of stratified randomization, patients were grouped into 1 of 3 disease categories: 1) wound infection or infected ulcer; 2) major abscess, or; 3) cellulitis.

Exclusion Criteria:

Patients who received systemic antimicrobial agents for more than 24 hours within the 3 days prior to enrollment (unless the Gram-positive pathogen was resistant in vitro to the antimicrobial agent), had a history of severe hypersensitivity reactions to glycopeptides and any of their excipients (patients who had histamine-like infusion reactions to the glycopeptide vancomycin were not excluded), and patients whose investigator anticipated a need for more than 10 days of intravenous antibiotic therapy were not eligible for enrollment in the study.

Study drug

Patients received either a single dose of 1200 mg oritavancin or a single dose of 800 mg oritavancin, with the option for the investigator to administer a further 400-mg dose at Day 5 based on clinical criteria. An appropriate placebo infusion of 5% dextrose in water was given to maintain the blind. Patients in the single dose arm received 1 infusion of 1200 mg oritavancin on Day 1 and 2 to 6 infusions of placebo 5% dextrose in water to maintain the blind. Patients in the infrequent dose arm received 1 infusion of 800 mg oritavancin on Day 1 and 1 infusion of 400 mg oritavancin on Day 5 based on the investigator's assessment. Patients in the infrequent dose arm received 2 to 5 infusions of placebo 5% dextrose in water to maintain the blind. Patients in the control group received 200 mg oritavancin daily for a minimum of 3 days and up to a maximum of 7 days.

Endpoints
The primary efficacy endpoint was the test-of-cure (cure or improvement versus failure) in the clinically-evaluable population at first follow-up. The secondary endpoint was the analysis of safety parameters in the intent-to-treat population

Efficacy variables were clinical response, signs and symptoms of infection and bacteriological response at end-of -therapy, first follow-up day 21(test-of-cure), and late follow-up day 35. Clinical responses included cure, improvement, failure, or indeterminate. Bacteriological responses included eradication, persistence, colonization, superinfection, indeterminate, or eradication with reinfection. Safety evaluations included incidence of adverse events, assessment of vital signs, clinical laboratory tests, electrocardiogram analyses, and concomitant medication usage.

Statistical Methods:
Efficacy Analyses: Efficacy for each test arm was compared against that of the control arm at end-of-therapy, first follow-up (test-of-cure), and late follow-up. Clinical response was calculated for the intent-to-treat, clinically-evaluable, microbiological intent-to-treat and microbiologically-evaluable populations. Two-sided 90% confidence intervals for the difference in response rates (test arm minus control arm) adjusted for disease categories were constructed according to the Mantel-Haenszel methodology. An additional analysis was performed comparing the patients randomized to the 800 mg active treatment arm who received one dose (800 mg) versus 2 doses (800 mg plus 400 mg at Day 5) of the study medication. These results were also examined relative to the patients randomized to receive the 200 mg dose.
Safety: The incidence of adverse events and laboratory toxicities was summarized by dose regimen. Change from baseline in vital signs, QT interval, laboratory tests was summarized by dose regimen.

MO comments: The current FDA draft guidance, October 2013 recommends that the primary efficacy endpoint to be a clinical response defined as greater than or equal to 20 percent reduction in the lesion size at 48 to 72 hours compared to baseline, measured in patients who did not receive rescue therapy and are alive. In the SOLO trials, the applicant evaluated this as a secondary endpoint. In the SIMPLIFI trial, the primary efficacy endpoint was the test-of-cure (cure or improvement versus failure) in the clinically-evaluable population at first follow-up (day 21) while in the SOLO trial the primary efficacy endpoint was early clinical response at 48 to 72 hours after study drug administration. The secondary endpoint in the SIMPLIFI trial was the analysis of safety parameters in the intent-to-treat population while the main secondary endpoints in the SOLO trials were the

investigator-assessed clinical cure at PTE and Lesion Area Decrease ≥20% from Baseline at ECE in the mITT population.

6.1.2 Demographics

The oritavancin and vancomycin groups were similar with respect to demographic and baseline disease characteristics in both SOLO 1 and 2 trials.

MO comment: The clinical reviewer conducted demographic analyses in the mITT population based on the actual treatment received, while the sponsor's analyses were in mITT population based on the planned treatment. Therefore the sponsor's demographic table (Table 2.1.1.1 of clinical study report) reflects 475 subjects in the oritavancin and 479 subjects in the vancomycin group in SOLO1 while reviewer's analysis of SOLO 1 trial reflects 473 subjects and 481 subjects in the oritavancin and vancomycin group, respectively. There were 2 subjects USUBJID TMC-ORI-10-01-101014-006 and TMC-ORI-10-01-191002-094 who were randomized to the oritavancin arm but actually received vancomycin.

SOLO 1 trial: a total of 954 patients (473 in the oritavancin group and 481 in the vancomycin group) received at least one dose of study drug. Most patients in both groups were male (oritavancin, 63.4%; vancomycin, 62.8%), and White (oritavancin, 57.7%; vancomycin, 57.4%). Mean age was 46.2 years (range: 18-89 years) in the oritavancin group and 44.3 years (range: 18-93 years) in the vancomycin group.

SOLO 2: a total of 1005 patients (503 in the oritavancin group and 502 in the vancomycin group) received at least one dose of study drug. Most patients in both groups were male (oritavancin, 67.2%; vancomycin, 68.3%), and White (oritavancin, 70.8%; vancomycin, 70.9%). Mean age was 45.0 years (range: 18-85 years) in the oritavancin group and 44.4 years (range: 18-92 years) in the vancomycin group.

SIMPLIFI trial: A total of 302 patients were enrolled in the SIMPLIFI study: 100 patients in the daily dose group, 99 patients in the single 1200 mg dose group, and 103 patients in the infrequent dose group (34 patients received 800 mg only; 69 patients received 800 mg plus 400 mg). Demographic characteristics were similar in the daily dose, single 1200 mg dose, and infrequent dose groups. The majority of patients were male (daily dose, 76.9%; single 1200 mg dose, 79.2%; infrequent dose, 63.6%). Most patients were White (daily dose, 75.0%; single 1200 mg dose, 59.3%; infrequent dose, 64.0%). Mean age was 44.8 years in the daily dose group, 46.7 years in the single 1200 mg dose group, and 47.3 years in the infrequent dose group. The most common locations of the primary infection in the CE population were the right lower leg (daily dose, 17.1%; single 1200 mg dose, 13.6%; infrequent dose, 11.3%) and left lower leg (daily dose, 15.8%; single 1200 mg dose, 12.3%; infrequent dose, 12.7%)

Approximately 60% of the patients in the SOLO pool were from North America (oritavancin, 59.4%; vancomycin, 59.5%). Demographics, including age, gender, ethnicity, race, weight, height, and body mass index (BMI) and baseline disease characteristics including disease category (i.e., wound,

cellulitis, major abscess), lesion size, signs and symptoms and clinical features of ABSSSI (i.e., fever, bacteremia, SIRS, and antibiotic use before study drug administration), and comorbid conditions are presented for SOLO 1, SOLO 2 and for the SOLO pool using the mITT population in Table xx below. Patient age and BMI were categorized as

• Age: < 65 years, 65 to < 75 years, and ≥ 75 years
• BMI: < 25 kg/m^2; 25 to < 30 kg/m^2; and ≥ 30 kg/m^2 (World Health Organization BMI categories)

Missing values were not imputed and were excluded from analyses of demographics and baseline disease characteristics.

Table 5: Patient Demographics in SOLO I, SOLO II, and the SOLO Pool (mITT Population)

	SOLO 1		SOLO 2		SOLO pool	
	Oritavancin (N=475) n (%)	**Vancomycin (N=479) n (%)**	**Oritavancin (N=503) n (%)**	**Vancomycin (N=502) n (%)**	**Oritavancin (N=978) n (%)**	**Vancomycin (N=981) n (%)**
Age (years)						
Mean (SD)	46.2 (14.20)	44.3 (14.50)	45.0 (13.40)	44.4 (14.29)	45.6 (13.80)	44.3 (14.39)
Median (Range)	46.0(18, 89)	45.0(18, 93)	45.0(18, 85)	44.0(18, 92)	46.0(18, 89)	45.0(18, 93)
Age (yrs) group n(%)						
< 65	428 (90.1)	441 (92.1)	464 (92.2)	463 (92.2)	892 (91.2)	904 (92.2)
65 - <75	35 (7.4)	28 (5.8)	34 (6.8)	33 (6.6)	69 (7.1)	61 (6.2)
≥75	12 (2.5)	10 (2.1)	51.0)	6 (1.2)	17 (1.7)	16 (1.6)
Gender, n (%)						
Male	301 (63.4)	301 (62.8)	338 (67.2)	343 (68.3)	639 (65.3)	644 (65.6)
Female	174 (36.6)	178 (37.2)	165 (32.8)	159 (31.7)	339 (34.7)	337 (34.4)
Race, n (%)						
White	274 (57.7)	275 (57.4)	356 (70.8)	356 (70.9)	630 (64.4)	631 (64.3)
Black or African American	43 (9.1)	40 (8.4)	14 (2.8)	17 (3.4)	57 (5.8)	57 (5.8)
Asian	153 (32.2)	154 (32.2)	122 (24.3)	122 (24.3)	275 (28.1)	276 (28.1)
Other	5 (1.1)	10 (2.1)	11 (2.2)	7 (1.4)	16 (1.6)	17 (1.7)
Weight (kg)						
Mean (SD)	81.9 (24.44)	82.7 (26.52)	76.2 (20.57)	78.0 (23.24)	79.0 (22.70)	80.3 (24.99)
Median(Range)	77.2(35, 200)	78.2(37, 220)	73.1(41, 171)	73.7(36, 189)	75.0(35, 200)	75.4(36, 220)
Weight (kg) Category, n(%)						
< 60	73 (15.4)	72 (15.0)	101 (20.1)	93 (18.5)	174 (17.8)	165 (16.8)
60 - <100	315 (66.3)	314 (65.6)	337 (67.0)	341 (67.9)	652 (66.7)	655 (66.8)
≥ 100	87 (18.3)	93 (19.4)	65 (12.9)	68 (13.5)	152 (15.5)	161 (16.4)
Height (cm)						
Mean (SD)	168.9 (10.88)	169.1 (9.73)	168.5 (10.34)	170.2 (10.21)	168.7 (10.60)	169.6 (9.99)
Median(range)	170.0 (129, 203)	170.0 (135, 195)	169.0 (125, 203)	170.2 (133, 206)	169.5 (125, 203)	170.0 (133, 206)
Body Mass Index (kg/m^2)						
Mean (SD)	28.7 (8.33)	28.8 (8.67)	26.8 (6.74)	26.8 (7.07)	27.7 (7.62)	27.8 (7.95)
Median(range)	27.1(15,74)	26.9 (14, 84)	25.0(16, 58)	25.0(16, 65)	26.29(15,74)	25.9 (14, 84)
Body Mass Index (kg/m^2) Category, n (%)						
< 25	162 (34.1)	175 (36.5)	244 (48.5)	245 (48.8)	406 (41.5)	420 (42.8)
25 – <30	158 (33.3)	138 (28.8)	136 (27.0)	144 (28.7)	294 (30.1)	282 (28.7)
≥ 30	155 (32.6)	166 (34.7)	123 (24.5)	113 (22.5)	278 (28.4)	279 (28.4)

	SOLO 1		SOLO 2		SOLO pool	
	Oritavancin (N=475) n (%)	**Vancomycin (N=479) n (%)**	**Oritavancin (N=503) n (%)**	**Vancomycin (N=502) n (%)**	**Oritavancin (N=978) n (%)**	**Vancomycin (N=981) n (%)**
Region, n (%)						
North American (US and Canada)	298 (62.7)	299 (62.4)	283 (56.3)	285 (56.8)	581 (59.4)	584 (59.5)
Rest of World (ROW)	177 (37.3)	180 (37.6)	220 (43.7)	217 (43.2)	397 (40.6)	397 (40.5)
South America	2 (0.4)	2 (0.4)	2 (0.4)	1 (0.2)	4 (0.4)	3 (0.3)
Eastern Europe	13 (2.7)	15 (3.1)	88 (17.5)	86 (17.1)	101 (10.3)	101 (10.3)
Western Europe	14 (2.9)	13 (2.7)	10 (2.0)	11 (2.2)	24 (2.5)	24 (2.4)
Asia/Pacific	148 (31.2)	150 (31.3)	120 (23.9)	119 (23.7)	268 (27.4)	269 (27.4)
Africa	0	0	0	0	0	0

Source-adapted from Sponsor's Table 5, page 48, of 5.3.5.3 integrated summary for efficacy. Replicated by reviewer.

MO comments: Blacks or African Americans were only 2.8% in the oritavancin arm and 3.4% in the vancomycin arm in SOLO2. However the pooled data showed that around 5.8% were represented in each arm. In the previous ARRI trial, there were 21% subjects of African descent in oritavancin and vancomycin arm while 12-13% in oritavanicn arm and 7% in vancomycin arm in study ARRD.

The following figures demonstrate that the baseline demographics were similar in both the oritavancin and vancomycin arm in the SOLO1 trials. Figure representing the proportion of patients from different regions is also provided below. Around 60% of patients were from US and 30% from Asian sites.

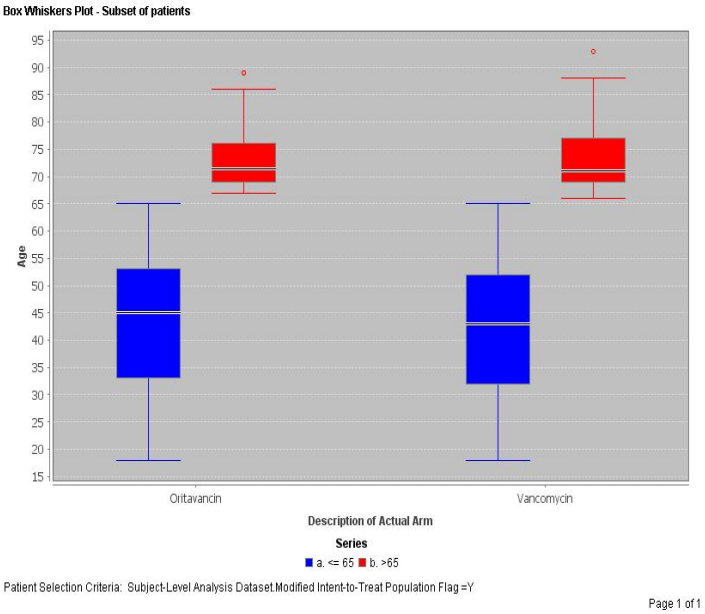


Figure 2: Distribution of age <65 and >65 mITT (SOLO1)

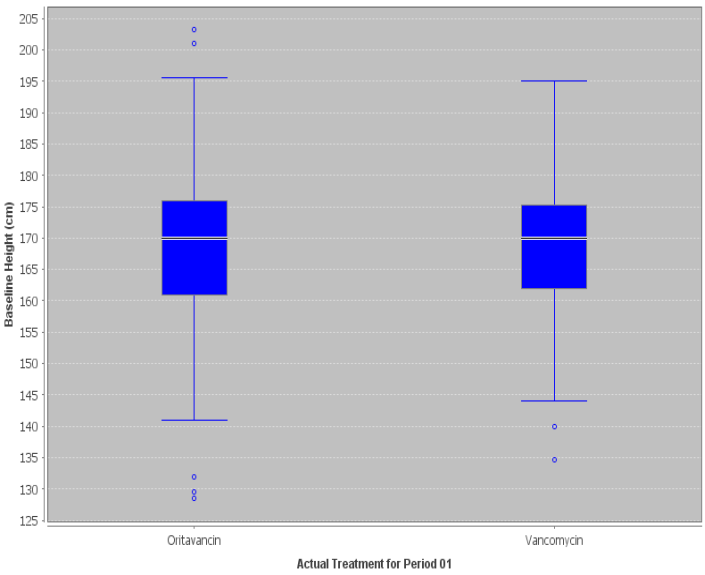


Figure 3: Distribution of baseline height mITT (SOLO1)

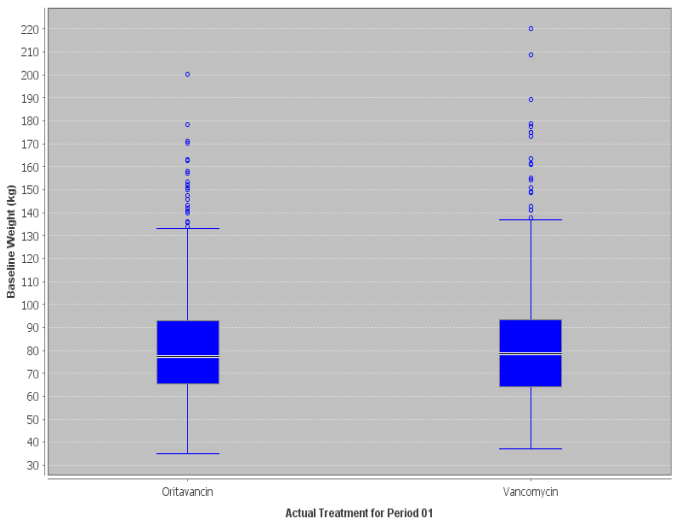


Figure 4: Distribution of baseline weight mITT population (**SOLO1)**

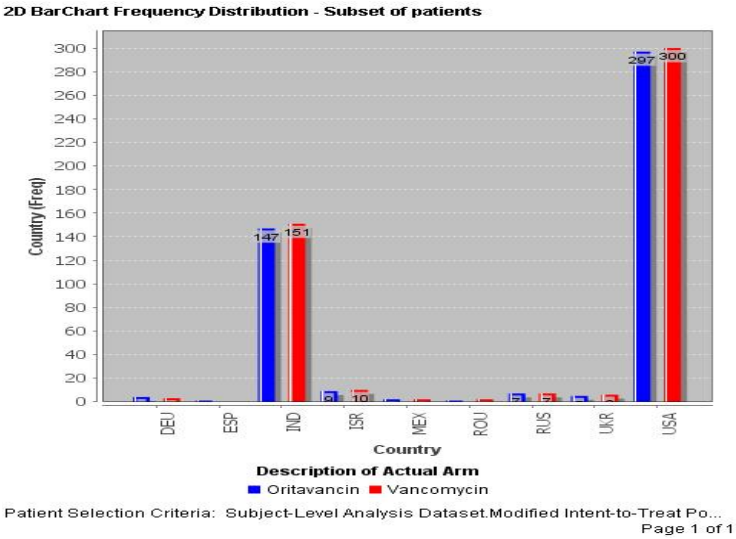


Figure 5: Proportion of patients from different regions in SOLO1

The following figures demonstrate that the baseline demographics were similar in both the oritavancin and vancomycin arm in the SOLO2 trials. Figure representing the proportion of patients from different regions is also provided below. Around 60% of patients were from US and 30% from Asian sites.

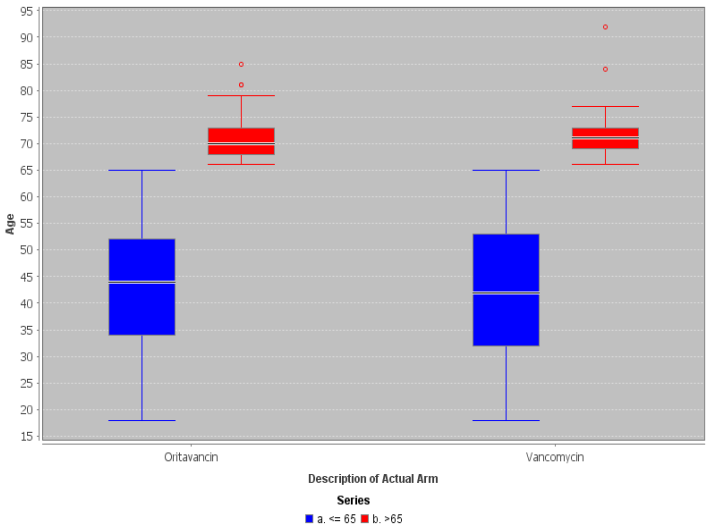


Figure 6: Distribution of age <65 or >65 years by actual treatment mITT population (SOLO2)

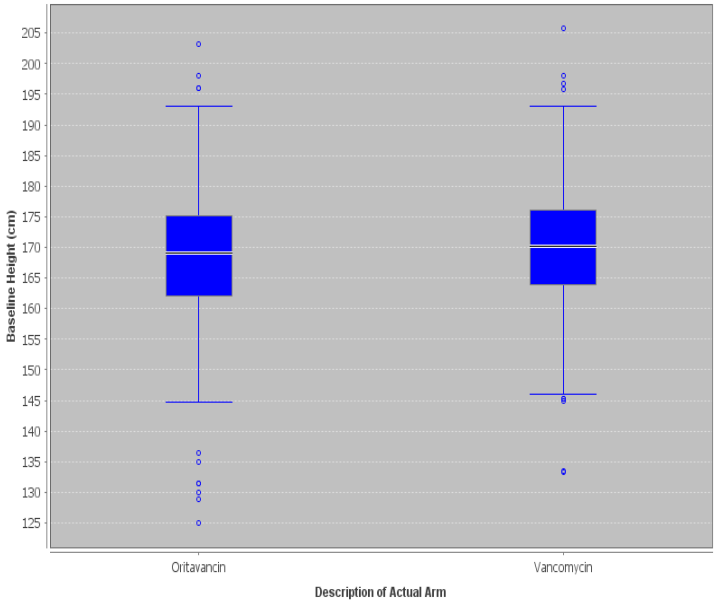


Figure 7: Distribution of baseline height by actual treatment mITTpopulation (SOLO2)

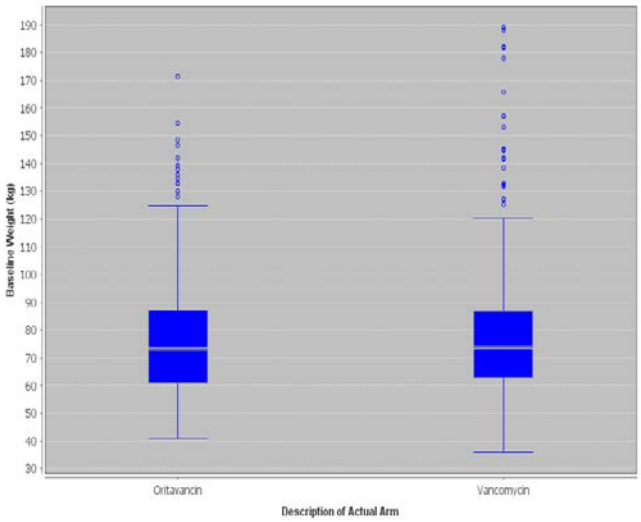


Figure 8: Distribution of baseline weight by actual treatment mITT population (SOLO2)

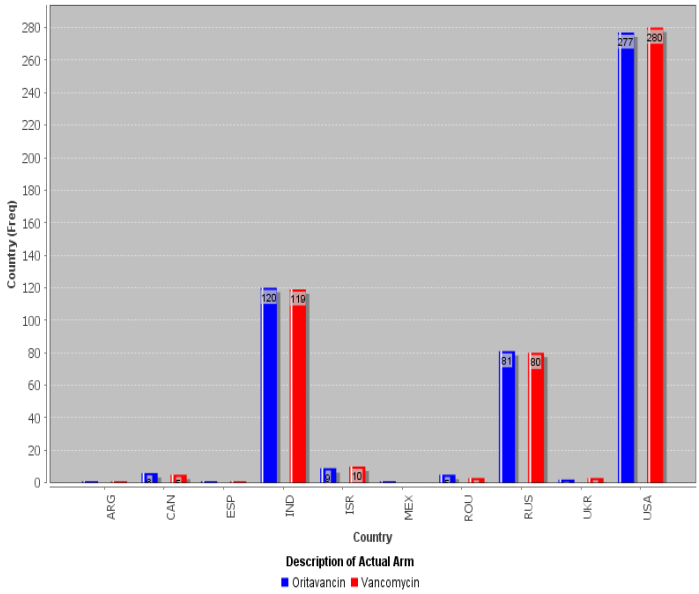


Figure 9: Proportion of patients from different regions (SOLO2)

Table 6: Baseline demographic characteristics in SOLO1 and SOLO2 trials

		SOLO 1				SOLO 2			
Demographic Baseline Characteristics		**Oritavancin N=473**		**Vancomycin N=481**		**Oritavancin N=503**		**Vancomycin N=502**	
Age	Mean (SE)	46.2 (14.2)		44.3 (14.5)		45.0 (13.4)		44.4 (14.3)	
	Min	18		18		18		18	
	Q1	35		33		35		33	
	Median	46		45		45		44	
	Q3	56		54		55		55	
	Max	89		93		85		92	
		Count	%	Count	%	Count	%	Count	%
Age Group	Age under 65 years	426	90.1	443	92.1	464	92.2	463	92.2
	Age 65 and over	47	9.9	38	7.9	39	7.8	39	7.8
Sex	F	173	36.6	179	37.2	165	32.8	159	31.7
	M	300	63.4	302	62.8	338	67.2	343	68.3
Race	American Indian Or Alaska Native	4	0.8	8	1.7	6	1.2	4	0.8
	Asian	152	32.1	155	32.2	122	24.3	122	24.3
	Black Or African American	43	9.1	40	8.3	14	2.8	17	3.4
	Native Hawaiian Or Other Pacific Islander	1	0.2	2	0.4	5	1.0	3	0.6
	White	273	57.7	276	57.4	356	70.8	356	70.9
Ethnicity	Hispanic Or Latino	94	19.9	131	27.2	100	19.9	96	19.1
	Not Hispanic Or Latino	379	80.1	350	72.8	403	80.1	406	80.9

Baseline Disease Characteristics

SOLO pool: approximately 40% of patients had cellulitis/erysipelas, 30% had a major cutaneous abscess, and 30% had a wound infection. Median infection area at baseline in the SOLO pool was 266.6 cm^2 for the oritavancin group and 273.8 cm^2 for the vancomycin group. Within the SOLO pool, greater than 10% of patients were diabetic (oritavancin, 14.2%; vancomycin, 14.3%), met SIRS criteria (oritavancin, 17.3%; vancomycin, 17.6%), had a fever (≥ 38°C) at baseline (oritavancin, 19.0%; vancomycin, 18.9%). Few patients had bacteremia at baseline (oritavancin, 2.9%; vancomycin, 1.9%). MRSA was recovered from the primary ABSSSI site or blood in 204 patients (20.9%) in the oritavancin group and 201 patients (20.5%) in the vancomycin group, and MSSA was isolated from 266 patients (27.2%) in the oritavancin group and 267 patients (27.2%) in the vancomycin group. Around 20% of subjects received an antibiotic within 14 days of study drug: in SOLO1, Bactrim was the most common antimicrobial (4.9% in both arms) followed by aztreonam (oritavancin 3.4%, vancomycin 4.6%) and clindamycin (2% each arm). In SOLO2, metronidazole and azteronam were most common antimicrobials received within 14 days of study drug. Subjects in oritavancin arm received Keflexin (2.1%) and Bactrim (2.2%) more frequently than comparator (0.6% and 1%, respectively). About 37% HIV/AIDS subjects were enrolled in the SOLO pool. Less than 2% of subjects had baseline severe peripheral vascular disease (PVD).

Table 7 Baseline characteristics in SOLO 1 and SOLO 2 trials (mITT population)

	SOLO1		SOLO2	
Baseline Characteristics	**Oritavancin (n=473)**	**Vancomycin (n=481)**	**Oritavancin (n=503)**	**Vancomycin (n=502)**
ABSSSI Category				
Cellulitis/Erysipelas	241 (50.95%)	235 (48.86%)	144 (29%)	167 (33%)
Major Cutaneous Abscess	140 (29.60%)	141 (29.31%)	168 (33%)	159 (32%)
Wound Infection	92 (19.45%)	105 (21.83%)	191 (38%)	176 (35%)
Incision and Drainage Flag				
Y	171 (36.15%)	168 (34.93%)	173 (34.39%)	163 (32.47%)
IV Drug Use Flag				
Y	97 (20.51%)	90 (18.71%)	189(37%)	192(38%)
Pooled Creatinine Clearance Group 2				
< 30 mcmol/L	2 (0.42%)	3 (0.62%)	5 (0.99%)	5 (1.00%)
30 - < 60 mcmol/L	34 (7.19%)	28 (5.82%)	36 (7.16%)	25 (4.98%)
60 - < 90 mcmol/L	99 (20.93%)	88 (18.30%)	92 (18.29%)	94 (18.73%)
>= 90 mcmol/L	331 (69.98%)	357 (74.22%)	356 (70.78%)	360 (71.71%)
(missing)	7 (1.48%)	5 (1.04%)	14(2.78%)	18(3.59%)
Temperature >= 38.0 Celsius Flag				
(missing)	406 (85.84%)	401 (83.37%)	385 (76.54%)	396 (78.88%)
Y	67 (14.16%)	80 (16.63%)	118 (23.46%)	106 (21.12%)
MRSA at Base Flag				
(missing)	369 (78.01%)	381 (79.21%)	403 (80.12%)	401 (79.88%)
Y	104 (21.99%)	100 (20.79%)	100 (19.88%)	101 (20.12%)
MSSA at Base Flag				
(missing)	355 (75.05%)	368 (76.51%)	353 (70.18%)	343 (68.33%)
Y	118 (24.95%)	113 (23.49%)	150 (29.82%)	159 (31.67%)
Diabetes Mellitus Flag				
(missing)	381 (80.55%)	385 (80.04%)	457 (90.85%)	457 (91.04%)
Y	92 (19.45%)	96 (19.96%)	46 (9.15%)	45 (8.96%)
SIRS at Baseline Flag				
(missing)	400 (84.57%)	408 (84.82%)	408 (81.11%)	401 (79.88%)
Y	73 (15.43%)	73 (15.18%)	95 (18.89%)	101 (20.12%)
Any Antibiotics Prior to Study Drug Flag				
(missing)	383 (80.97%)	389 (80.87%)	401 (79.72%)	413 (82.27%)
Y	90 (19.03%)	92 (19.13%)	102 (20.28%)	89 (17.73%)
Any Concomitant Immunosuppressive Flag				
(missing)	465 (98.31%)	477 (99.17%)	498 (99.01%)	498 (99.20%)
Y	8 (1.69%)	4 (0.83%)	5 (0.99%)	4 (0.80%)
Bacteremia Flag				
(missing)	455 (96.19%)	472 (98.13%)	493 (98.01%)	492 (98.01%)
Y	18 (3.81%)	9 (1.87%)	10 (1.99%)	10 (1.99%)
Hepatic impairment				

Source: reviewer generated table

MO comment: Note that theApplicant's demographic table 6 page 51 of ISE 5.3.5.3 has been conducted with randomized patients with planned treatment and the reviewer generated table has the randomized subjects with actual treatment received.

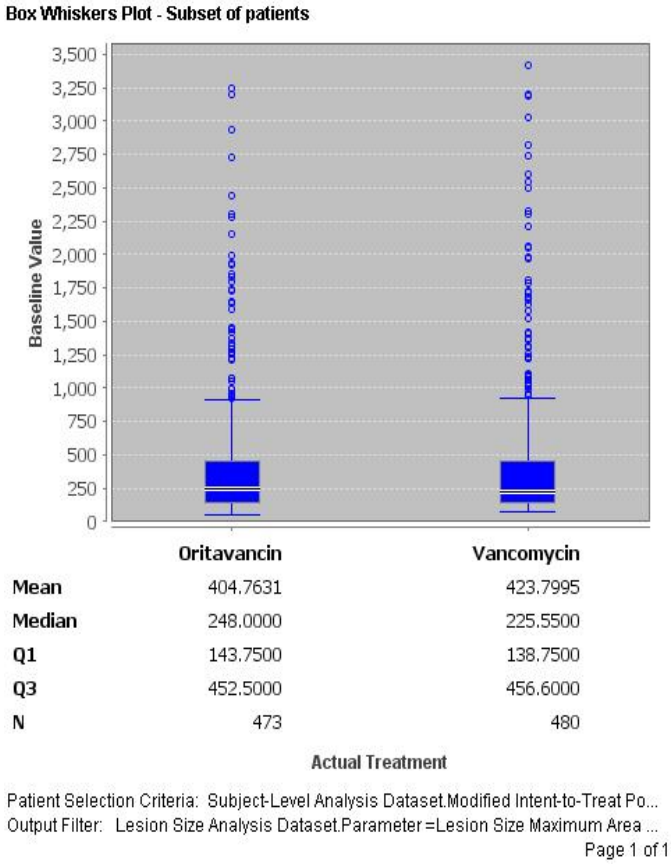
Table 8: Prior concomitant medications with activity against gram positive pathogens in SOLO1 and SOLO2 trials

		SOLO 1			SOLO 2	
Category for Medication	**Standardized Medication Name**	**Oritavancin N=473**	**Vancomycin N= 481**	**Standardized Medication Name**	**Oritavancin**	**Vancomycin**
Prior/concomitant antibiotics and topical antimicrobials	Aztreonam	16 (3.38%)	22 (4.57%)	Metronidazole	24 (4.77%)	24(4.78%)
	Bactrim	23 (4.8%)	23 (4.7%)	Aztreonam	25 (4.9%)	19 (4.1%)
	Keflexin	10 (2.11%)	11 (2.29%)	Keflexin	11 (2.19%)	3 (0.60%)
	Clindamycin	10 (2.11%)	9 (1.87%)	Ceftriaxone	9 (1.79%)	11 (2.19%)
				Bactrim	11 (2.1%)	5 (1%)

MO comment: Prior concomitant medications with activity against gram positive pathogens were few in both arms and fairly balanced in both trials. Note that prior systemic or topical antibacterial therapy with activity against suspected or proven Gram-positive pathogens within 14 days preceding randomization were excluded unless:
a. The causative Gram-positive pathogen(s) isolated from the ABSSSI site was resistant in vitro to the antibacterial(s) administered with documented clinical progression
b. Documented failure to previous ABSSSI antibiotic therapy was available (e.g., a record in the patient's medical chart of wound size prior to initial treatment with demonstration of progression on therapy, discussion with prior treating physician, consultation of patient's medical records, and/or consultation of available documentation of treatment, e.g., prescription, before study randomization)
c. Patient received a single dose of a short-acting, antibacterial therapy within 72 hours of randomization (e.g., surgical prophylaxis)

Baseline lesion size
SOLO1
Thirty eight (8%) subjects treated with Oritavancin had baseline lesion size of >1000 cm^2. Of them, 6 had cutaneous abscesses and 4 with wound infection. The rest had cellulitis or erysipelas. Two subjects TMC-ORI-10-01-101046-025 and TMC-ORI-10-01-197002-006 with Gram negative pathogen *E. coli* and *Acinetobacter wolfi* were considered success primary efficacy outcome. These 2 subjects were concomitantly treated with aztreonam.
Forty seven (9.8%) subjects treated with vancomycin had baseline lesion size of >1000 cm^2.Of them, 3 had wound infection, 4 had major cutaneous abscess. Subject TMC-ORI-10-01-101027-033 with *Pseudomonas aeruginosa* treated with aztreonam as well, was considered a failure. Subject TMC-ORI-10-01-191003-008 with *Acinetobacter baumanii* treated with aztrenoam was considered a success.
SOLO2
Thirty three (6.6%) subjects treated with oritavancin had baseline lesion size of >1000 cm^2. Six had wound infection, 1 had cutaneous abscess. Subjects TMC-ORI-10-02-201035-013, TMC-ORI-10-

02-202001-007, TMC-ORI-10-02-297001-008 had *Acinetobacter baumani*, *Pseudomonas aeruginosa* and *Achromobacter xylosoxidans* isolated and treated with aztreonam. TMC-ORI-10-02-201035-013 had an outcome of success, TMC-ORI-10-02-202001-007 and TMC-ORI-10-02-297001-008 had primary outcomes missing.
Thirty seven (7.4%) subjects treated with vancomycin had a baseline lesion size of >1000 cm^2. Of them, 8 had wound infection, 1 had an abscess. Subject TMC-ORI-10-02-201001-118 with *Enterobacter cloacae* treated with aztreonam had a primary outcome of success.
Graphic representation of the lesion size distribution in the SOLO trials depicted in the figures below.



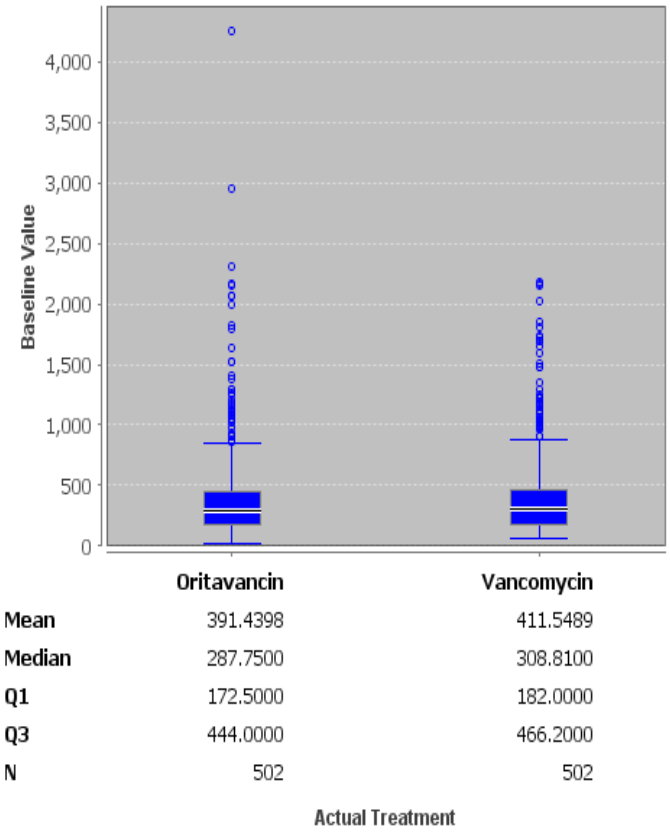


Figure 10: Baseline lesion size SOLO 1 **Figure 11: Baseline lesion size SOLO 2**

MO Comment: A sample of photographs of subjects who had lesion size> 1000 cm^2 was requested from the applicant and reviewed. These outliers were fairly balanced between arms and both SOLO trials.

The following table represents the distribution of sites, percentage of patients enrolled, primary efficacy rates, death, discontinuation, protocol violation rates.

Table 9: Distribution of sites, percentage of patients enrolled, primary efficacy rates, death, discontinuation, protocol violation rates in the SOLO trials

SOLO1 REGION	COUNTRY	# Sites	# Enrolled	Enrolled / Screened %	Treatment Efficacy Result	Site Efficacy Effect Size	NSAE per Enrolled	SAE per Enrolled	Death %	Discontinuation %	PROTVIOL per Enrolled
United States	USA	23	607	100.0%	0.72	-0.01	2.11	0.14	0.5%	16.3%	0.01
United States Total		23	607	100.0%	0.72	-0.01	2.11	0.14	0.5%	16.3%	0.01
Western Europe	DEU	1	8	100.0%	0.38	-0.25	0.50	0.13	0.0%	37.5%	0.25
	ESP	1	1	100.0%	1.00	1.00	5.00	0.00	0.0%	0.0%	0.00
Western Europe Total		2	9	100.0%	0.69	0.38	1.00	0.11	0.0%	33.3%	0.22
Latin America	MEX	2	4	100.0%	0.50	0.00	0.75	0.25	0.0%	0.0%	0.25
Latin America Total		2	4	100.0%	0.50	0.00	0.75	0.25	0.0%	0.0%	0.25
Eastern Europe	RUS	2	14	100.0%	0.69	-0.28	0.36	0.00	0.0%	0.0%	0.00
	UKR	3	11	100.0%	0.81	0.39	0.55	0.00	0.0%	0.0%	0.00
	ROU	2	3	100.0%	0.50	0.50	0.00	0.00	0.0%	33.3%	0.00
Eastern Europe Total		7	28	100.0%	0.68	0.23	0.39	0.00	0.0%	3.6%	0.00
Asia/Pacific	IND	9	300	100.0%	0.92	-0.05	0.98	0.01	0.0%	1.3%	0.00
Asia/Pacific Total		9	300	100.0%	0.92	-0.05	0.98	0.01	0.0%	1.3%	0.00
Middle East/Central Asia	ISR	3	20	100.0%	0.47	0.42	2.60	0.10	0.0%	10.0%	0.05
Middle East/Central Asia Total		3	20	100.0%	0.47	0.42	2.60	0.10	0.0%	10.0%	0.05
SOLO2 REGION	**COUNTRY**	**# Sites**	**# Enrolled**	**Enrolled / Screened %**	**Treatment Efficacy Result**	**Site Efficacy Effect Size**	**NSAE per Enrolled**	**SAE per Enrolled**	**Death %**	**Discontinuation %**	**PROTVIOL per Enrolled**
Canada	CAN	1	13	100.0%	0.38	-0.21	1.08	0.15	0.0%	23.1%	0.23
Canada Total		1	13	100.0%	0.38	-0.21	1.08	0.15	0.0%	23.1%	0.23
United States	USA	11	567	100.0%	0.74	0.06	2.19	0.08	0.2%	15.9%	0.02
United States Total		11	567	100.0%	0.74	0.06	2.19	0.08	0.2%	15.9%	0.02
Western Europe	ESP	1	2	100.0%	1.00	0.00	0.00	0.00	0.0%	0.0%	0.00
Western Europe Total		1	2	100.0%	1.00	0.00	0.00	0.00	0.0%	0.0%	0.00
Latin America	MEX	1	1	100.0%	1.00	1.00	1.00	0.00	0.0%	0.0%	1.00
	ARG	1	2	100.0%	0.50	1.00	5.50	0.00	0.0%	0.0%	0.00
Latin America Total		2	3	100.0%	0.75	1.00	4.00	0.00	0.0%	0.0%	0.33
Eastern Europe	RUS	6	162	100.0%	0.61	-0.02	0.35	0.03	0.6%	5.6%	0.03
	UKR	2	5	100.0%	0.38	-0.50	0.80	0.00	0.0%	20.0%	0.00
	ROU	1	8	100.0%	0.75	0.13	0.25	0.00	0.0%	12.5%	0.13
Eastern Europe Total		9	175	100.0%	0.58	-0.11	0.35	0.03	0.6%	6.3%	0.03
Asia/Pacific	IND	6	240	100.0%	0.75	-0.18	0.50	0.00	0.0%	4.6%	0.04
Asia/Pacific Total		6	240	100.0%	0.75	-0.18	0.50	0.00	0.0%	4.6%	0.04
Middle East/Central Asia	ISR	2	19	100.0%	0.68	-0.14	1.37	0.37	0.0%	10.5%	0.00
Middle East/Central Asia Total		2	19	100.0%	0.68	-0.14	1.37	0.37	0.0%	10.5%	0.00

MO comment: Higher efficacy rates were noted in Asian sites where 30% of enrollment occurred as compared to 70 % efficacy rates in the US sites. The finding is similar in both trials. The division has requested OSI to inspect site (191008) with the largest foreign enrollment.
In SOLO1, 15.6% of subjects were enrolled from site 101002 and 12.5% of subjects were enrolled from 101001. Both these sites were in US. In SOLO2, 10.6% of subjects were enrolled from site 201001 and 20.2% of subjects were enrolled from 201002. Both these sites were in US.

6.1.3 Subject Disposition

The following table depicts the number of subjects and the percentage in the prespecified analysis populations.

Table 10: Number of Subjects in the prespecified analysis populations in SOLO1 and SOLO2 trials

	SOLO1		SOLO 2	
Category	**Oritavancin N=483 n(%)**	**Vancomycin N=485 n(%)**	**Oritavancin (N=509) n (%)**	**Vancomycin (N=510) n (%)**
ITT	483	485	509	510
mITT	475 (98.3)	479 (98.8)	503 (98.8)	502 (98.4)
CE	394 (81.6)	397 (81.9)	427 (83.9)	408 (80.0)
MicroITT	244 (50.5)	242 (49.9)	285 (56.0)	296 (58.0)
MicroE	201 (41.6)	201 (41.4)	246 (48.3)	247 (48.4)
Safety population	473	481	503	502
PK population	115	0	197	0

Source: Adapted from Table 10 of CSR for SOLO1 and SOLO 2.

Of the randomized subjects, only 14 in each trial (SOLO1 and 2) did not receive any study drug. The number of dropouts from the ITT prior to treatment was small. Approximately 80% of subjects were clinically evaluable. Around 50% of mITT in SOLO1 and 60% mITT subjects in SOLO 2 had baseline Gram positive pathogen causing ABSSSI (microITT).

MO comment: 2 subjects in the oritavancin arm in sponsor defined mITT actually received vancomcyin as reflected in the safety population.

The majority of the patients in SOLO I (oritavancin, 88.6%; vancomycin, 83.9%) and SOLO 2 (oritavancin, 90.3%; vancomycin, 88.8%) completed study drug treatment at 7-10 days. About 90% of patients completed the study to Day 60. The primary reason for discontinuing study drug was an adverse event and withdrawal of consent by the patient. The primary reasons for prematurely discontinuing the study were loss to follow-up and withdrawal of consent.

Table 11: Disposition events in the SOLO trials

			SOLO1						SOLO2					
Category of Disposition Event	**EPOCH**	**Disposition Event**	**Not Treated**		**Oritavancin**		**Vancomycin**		**Not Treated**		**Oritavancin**		**Vancomycin**	
			Subject Count	**%**	**Subject Count**		**Subject Count**	**%**	**Subject Count**	**%**	**Subject Count**	**%**	**Subject Count**	**%**
Protocol Milestone	Missing	Informed Consent Obtained	14	100.0	473	100.0	481	100.0	14	100.0	503	100.0	502	100.0
		Randomized	14	100.0	473	100.0	481	100.0	14	100.0	503	100.0	502	100.0
Disposition Event	Follow-Up	Completed	3	21.4	430	90.9	424	88.1	1	7.1	454	90.3	444	88.4
		Lost To Follow-Up	4	28.6	21	4.4	32	6.7	3	21.4	28	5.6	36	7.2
		Withdrawal By Subject	4	28.6	17	3.6	20	4.2	3	21.4	15	3.0	17	3.4
		Administrative Problems	2	14.3	0	0.0	1	0.2	2	14.3	0	0.0	1	0.2
		Other	1	7.1	3	0.6	0	0.0	3	21.4	4	0.8	3	0.6
		Death	0	0.0	1	0.2	2	0.4	0	0.0	1	0.2	1	0.2
		Adverse Event	0	0.0	1	0.2	1	0.2	0	0.0	1	0.2	0	0.0
		Study Terminated By Sponsor	0	0.0	0	0.0	1	0.2	2	14.3	0	0.0	0	0.0
	Missing	Administrative Problems	8	57.1	0	0.0	0	0.0	7	50.0	0	0.0	0	0.0
		Withdrawal By Subject	5	35.7	0	0.0	0	0.0	4	28.6	0	0.0	0	0.0
		Recovery	1	7.1	0	0.0	0	0.0						
		Study Terminated By Sponsor							2	14.3	0	0.0	0	0.0
		Adverse Event							1	7.1	0	0.0	0	0.0
	Treatment	Completed	0	0.0	420	88.8	403	83.8	0	0.0	454	90.3	446	88.8
		Adverse Event	0	0.0	17	3.6	23	4.8	0	0.0	16	3.2	9	1.8
		Withdrawal By Subject	0	0.0	14	3.0	22	4.6	0	0.0	12	2.4	20	4.0
		Administrative Problems	0	0.0	8	1.7	16	3.3	0	0.0	6	1.2	16	3.2
		Lack Of Efficacy	0	0.0	9	1.9	10	2.1	0	0.0	7	1.4	5	1.0

Category of Disposition Event	EPOCH	Disposition Event	SOLO1						SOLO2					
			Not Treated		Oritavancin		Vancomycin		Not Treated		Oritavancin		Vancomycin	
			Subject Count	%	Subject Count		Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
		Protocol Violation	0	0.0	0	0.0	4	0.8	0	0.0	4	0.8	4	0.8
		Recovery	0	0.0	2	0.4	0	0.0	0	0.0	1	0.2	0	0.0
		Study Terminated By Sponsor	0	0.0	1	0.2	1	0.2	0	0.0	1	0.2	1	0.2
		Abnormal Laboratory Value(S)	0	0.0	0	0.0	2	0.4	0	0.0	1	0.2	1	0.2
		Abnormal Test Procedure Result(S)	0	0.0	1	0.2	0	0.0						
		Physician Decision	0	0.0	1	0.2	0	0.0	0	0.0	1	0.2	0	0.0

Note: Disposition events are determined by the standardized disposition term (DSDECOD) and category and subcategory (DSCAT and EPOCH) from the disposition domain (DS) dataset. Treatment arm is determined by the actual treatment arm (ACTARM) from the demographics domain (DM) dataset. Each subject is counted only once per disposition event. Exposure is determined by a subject's presence in the exposure domain (EX) dataset. For Time to Disposition Event, study day is determined by the study day of the start of disposition event (DSSTDY) if available; otherwise, it is calculated by finding the number of days between the subject's reference start date (RFSTDTC) from DM and the start date of disposition event (DSSTDTC).

MO Comment: For SOLO1 trial, the disposition table generated by the reviewer differs from that of the sponsors since 2 subjects were randomized to oritavancin arm but received vancomycin.

Overall, 88% completed treatment in the oritavancin arm and 83% in the comparator. 3.6% of subjects prematurely discontinued oritavancin compared to 4.8% of comparator (due to an AE). Around 3% subjects withdrew from oritavancin compared to 4.6% of vancomycin. Around 2 % had premature discontinuation of drug due to lack of efficacy in each arm.
For SOLO 2 trial**,** 3.2% of subjects prematurely discontinued oritavancin compared to 1.8% of comparator due to an AE. Around 2.4% subjects withdrew from oritavancin compared to 4.0% of vancomycin. Around 1.4 % had premature discontinuation of oritavancin due to lack of efficacy compared to 1% in vancomycin arm.

MO comment: Patient 201002010in SOLO2 had study drug was withdrawn due to an AE; however, there were no active AEs recorded on the AE CRF page at the time the patient's drug was withdrawn. Subject 201001055in SOLO2 was determined by the applicant as to have had drug withdrawn due to an AE -new infection to right arm. Subject 201001055 was a 34-year-old woman, received infusion of oritavancin/placebo over a 7-day period for cellulitis/erysipelas of the right elbow. The patient was discontinued from the blinded study drug infusion after 7 days for infection. The patient with no relevant medical history/concurrent conditions receiving concomitant oxycodone experienced a right arm infection (new infection not at the primary infection site) five days after the start of study treatment. The new infection was treated with oral clindamycin and sulfamethoxazole/trimethoprim. The infection resolved 14 days after study drug was withdrawn. A higher rate of premature discontinuation of the drug occurred in the oritavancin arm due to an AE as compared to vancomycin in SOLO 2 trial. A review of these 16 subjects in the oritavancin arm and 9 subjects in the vancomycin arm shows that the AE were included in the applicant's safety analysis. The subjects (16) on oritavancin arm received study drug but did not complete treatment due to AEs of rash, abscess, tenosynovitis, and osteomyelitis. This is consistent with the higher rate of AE noted in the infection SOC in the safety analysis. These subjects were also appropriately counted as failures for primary and secondary efficacy analyses.

The following table shows the baseline pathogens identified in SOLO trials. Similar percentages of baseline pathogens in oritavancin and vancomycin arm were found in the SOLO trials.

Table 12: Baseline Infection Site Culture positive for Gram-positive Pathogens Known to Cause ABSSSI (MicroITT Population)

	SOLO1		SOLO2	
	Oritavancin N=244	**Vancomycin N=242**	**Oritavancin N=285**	**Vancomycin N=296**
Staphylococcus aureus - MRSA	104 (10.74%)	100 (10.33%)	100 (9.81%)	101 (9.91%)
Staphylococcus aureus - MSSA	118 (12.19%)	113 (11.67%)	150 (14.72%)	159 (15.60%)
Staphylococcus lugdunensis	0 (0.00%)	4 (0.41%)	4 (0.39%)	1 (0.10%)
Streptococcus agalactiae	7 (0.72%)	8 (0.83%)	1 (0.10%)	4 (0.39%)
Streptococcus anginosus	2 (0.21%)	5 (0.52%)	2 (0.20%)	1 (0.10%)
Streptococcus constellatus	9 (0.93%)	10 (1.03%)	10 (0.98%)	13 (1.28%)
Streptococcus dysgalactiae	3 (0.31%)	3 (0.31%)	6 (0.59%)	3 (0.29%)
Streptococcus Group F	0 (0.00%)	2 (0.21%)	1 (0.10%)	1 (0.10%)
Streptococcus intermedius	4 (0.41%)	3 (0.31%)	6 (0.59%)	13 (1.28%)
Streptococcus pyogenes	8 (0.83%)	10 (1.03%)	23 (2.26%)	22 (2.16%)
Enterococcus faecalis	7(0.72%)	5 (0.52%)	6 (0.59%)	7 (0.69%)

MO comment: Enterococcus is not a common pathogen of ABSSSI.MSSA was the most common ABSSSI causing pathogen isolated in both trials followed by MRSA.

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint was early clinical response (a composite endpoint of cessation of spread or reduction in size of the baseline lesion, absence of fever, and no rescue antibiotic medication) at

48 to 72 hours from initiation of the first infusion of study drug (early clinical evaluation [ECE] in the mITT population. A NI margin of 10% was chosen after discussion with FDA to preserve 80% of the estimated M1 of 12%.
The primary efficacy analysis was conducted in the mITT population. However supportive analysis was conducted by the sponsor in the ITT and CE population. The primary efficacy outcome analyzed by the medical reviewer in the modified ITT, ITT with rate of early clinical outcome in CE, microITT and MicroEvaluable population is summarized in table below.

Table 13: Primary efficacy outcomes in the **SOLO** trials in the different analysis populations

Efficacy Endpoint /Analysis Population	**Oritavancin n/N (%)**	**Vancomycin n/N (%)**	**Difference between Oritavancin and Vancomycin**
			(95% CI)
SOLO1 Reviewer Outcome (Primary Endpoint)			
mITT	**390/473 (82%)**	**379/481 (79%)**	**3.7 (-1.4,8.7)**
ITT	390/483 (80.7%)	379/485 (78.1%)	2.6 (-2.5, 7.7)
CE	344/394 (87.3%)	342/397 (86.2%)	1.2 (-3.6, 5.9)
MicroITT	201/244 (82.4%)	196/242 (81%)	1.4 (-5.5, 8.3)
MicroE	177/201 (88.1%)	175/201 (87.1%)	1.0 (-5.5, 7.5)
SOLO2 Reviewer Outcome (Primary Endpoint)			
mITT	**403/503 (80%)**	**416/502 (83%)**	**-2.8 (-7.5, 2.0)**
ITT	403/509 (79.1%)	416/510 (81.5%)	-2.4 (-7.2, 2.5)
CE	357/427 (83.6%)	358/408 (87.8%)	-4.1 (-8.9,0.6)
MicroITT	234/285 (82.1%)	252/296 (85.2%)	-3.0 (-9.1, 3.0)
MicroE	209/246 (85%)	223/247 (90.3%)	-5.3 (-11.1, 0.5)

MO Comment: The applicant conducted the efficacy analysis on the mITT population with the planned arm. The reviewer conducted the efficacy analysis on the mITT population with the actual treated arm. In both SOLO trials oritavancin was showen to be noninferior to vancomycin in mITT, ITT, CE and micro ITT, demonstrating consistency of efficacy finding across different study popultaions.
MO comment: In the CE population, the percentage of patients with an early clinical response was higher in the vancomycin than the oritavancin arm but the treatment difference (-4.1%; 95% CI: -8.9, 0.6) was within 10%NI margin and comparable with the treatment difference in MITT and ITT population. The overall rate of early clinical response of oritavancin group compared to vancomycin group in MITT, ITT, CE, microITT and microE population were lower in SOLO2 compared to SOLO1. The early clinical response for oritavancin (85%) compared to vancomycin (90%) was lower in the microE population in SOLO2 with a treatment difference of -5.3% (95%CI:-11.1%, 0.5%).

The Primary efficacy rates in SOLO2, excluding site 240002 (GCP noncompliant), were as follows:

Table 14: Primary efficacy outcome in SOLO 2 excluding site 240002

	Oritavancin	**Vancomycin**	**Difference (95%CI)**
MITT	**399/498 (80.1%)**	**414/499 (82.97%)**	**-2.85 (-7.6, 1.97)**
ITT	**399/498 (80.1%)**	**414/499 (82.97%)**	**-2.85 (-7.6, 1.97)**
CE	353/423 (83.5%)	358/408 (87.8%)	-4.3 (-9.1,0.5)

	Oritavancin	Vancomycin	Difference (95%CI)
MicroITT	232/283 (82%)	250/294 (85%)	-3.1 (-9.1, 3.0)
MicroE	207/244 (85%)	223/247 (90.3%)	-5.45 (-11.3, 0.4)

MO Comment: The primary efficacy analysis did not change significantly when the 8 subjects from site 240002 were excluded.

Sensitivity analysis:
The applicant performed sensitivity analysis with missing data excluded and treated as success for the primary efficacy endpoint in the mITT population.

Table 15: Primary efficacy outcome in the mITT population (SOLO trials) with missing data excluded and treated as success.

Primary Efficacy Outcome at ECE mITT population	Oritavancin n/N (%)	Vancomycin n/N (%)	Difference between Oritavancin and Vancomycin (95% CI)	Oritavancin n/N (%)	Vancomycin n/N (%)	Difference between Oritavancin and Vancomycin (95% CI)
	SOLO1 Sponsor analysis			SOLO2 Sponsor analysis		
Missing is excluded from analysis	391/459 (85.2)	378/456(82.9)	2.3 (-2.5, 7.0)	403/490 (82.2)	416/487 (85.4)	-3.2 (-7.8, 1.4)
Missing is treated as Success	407/475 (85.7)	401/479 (83.7)	2.0 (-2.6, 6.5)	416/503 (82.7)	431/502 (85.9)	-3.2 (-7.6, 1.3)
	SOLO1 Reviewer analysis			SOLO2 Reviewer analysis		
Missing is excluded from analysis	390/457 (85.3)	379/458(82.7)	2.4 (-2.2, 7.3)	403/490 (82.2)	416/487 (85.4)	-3.2 (-7.8, 1.4)
Missing is treated as Success	406/473 (85.8)	402/481 (83.5)	2.3 (-2.3, 6.8)	416/503 (82.7)	431/502 (85.9)	-3.2 (-7.6, 1.3)

MO Comment: There was no significant difference between the oritavancin or vancomycin arm when subjects who were missing were excluded or treated as success.

Table 16: Reviewer defined efficacy outcome at different visits (mITT population of SOLO trials)

SOLO1				SOLO2			
Analysis Visit	**Outcome**	**Oritavancin N=473**	**Vancomycin N=481**	**Analysis Visit**	**Outcome**	**Oritavancin N=503**	**Vancomycin N=502**
ECE	Failure	67	79	ECE	Failure	87	71
	Success	426*	413		Success	453	449
	Missing	16	23		Missing	13	15
EOT	Clinical Cure	403	393	EOT	Clinical Cure	442	436
	Clinical Failure	71	87		Clinical Failure	53	53
	Failure	0	1		Failure	0	2
					Missing	22	32
	Success	0	1		Success	0	1
DAY 10	Clinical Cure	401	392	DAY 10	Clinical Cure	438	434
	Clinical Failure	80	93		Clinical Failure	58	59
					Failure	0	1

SOLO1				SOLO2			
Analysis Visit	**Outcome**	**Oritavancin N=473**	**Vancomycin N=481**	**Analysis Visit**	**Outcome**	**Oritavancin N=503**	**Vancomycin N=502**
	Missing	44	57		Missing	42	47
	Success	2	1				
PTE	Clinical Cure	378	383	PTE	Clinical Cure	416	404
	Clinical Failure	123	126		Clinical Failure	103	88
	Failure	52	60		Failure	57	55
	Missing	60	63		Missing	54	65
	Success	351	345		Success	385	367

* includes primary efficacy outcome without temperature component at ECE.

MO Comment: Overall the outcomes at different visits were comparable in both trials.

Additional exploratory analysis:
Of the subjects who had success at primary efficacy endpoint, percentage of subjects who went on to have clinical failure at EOT, day 10 and PTE are shown below. The clinical failures were well balanced in both arms.

Table 17: Subjectswho had success at ECE but went on to have clinical failure at EOT, day 10 and PTE (mITT population of SOLO trials)

	SOLO1		SOLO2	
	Oritavancin	**Vancomycin**	**Oritavancin**	**Vancomycin**
n	**473**	**481**	**503**	**502**
Total subjects with success at ECE	390	379	403	416
Clinical failure at				
EOT	31 (8%)	33 (8.7%)	17 (4.2%)	20 (4.8%)
DAY 10	39 (10%)	37 (9.8%)	20 (5%)	24 (5.8%)
PTE	71 (18%)	67 (17.7%)	57 (14%)	48 (11.5%)

Breakdown of failures (146 subjects combined in both arms in SOLO1 and 158 subjects in SOLO2) to achieve an Early Clinical Response (mITT Population, with planned arm).

Table 18: Breakdown of failures in the SOLO trials to achieve an Early Clinical Response (mITT Population, planned arm).

	SOLO1		SOLO2	
	Oritavancin	**Vancomycin**	**Oritavancin**	**Vancomycin**
	475	**479**	**503**	**502**
Treatment failures at ECE	68(14%)	78(16%)	87(17%)	71(14%)
Subjects needing Rescue Medications	14	18	9	14
Unplanned surgical procedure	3	3 [1]	5	1 [3]
Insufficient temperature measurements	16	21	20	11
Temp >37.7	33	35	49 [2]	35
Increase in lesion size(sponsor defined)	15	23	27	22

Adapted from Table 12 of CSR
1 The number of unplanned surgical procedure in vancomycin arm was 9 in sponsor's analysis.
2 Temp >37.7 at ECE in oritavancin arm was 44 by sponsor's analysis.
3. Unplanned surgical procedure was 8 and 10 in oritavancin and vancomycin arm by sponsor's analysis.

MO comments: The applicant's analysis reflects unplanned surgical procedures prior to ECE while reviewer's analysis the same at ECE. There were minor discrepancies in subject numbers; however, a separate unplanned surgical drainage analysis is presented.

SIMPLIFY trial:
The Investigator-defined clinical outcome of cure at first follow-up assessment in the CE population was 55/76 (72.4%), 66/81 (81.5%) and 55/71 (77.5%) in the 200-, 1200-, and 800/400- mg arms, respectively. The treatment difference for the comparison of 1200mg-200 mg (90% CI) was 8.6% (-2.5, 19.2) and for 800mg-200 mg (90% CI) was 5.2% (-6.8, 15.4). Note the NI margin for this study was 15%.

Table 19: The investigator defined clinical response at first follow up visit in the CE population (SIMPLIFI trial).

Parameter	Analysis Visit	Analysis Value (C)	1200 mg ORI Single Dose N=81	200 mg ORI Daily Dose N=76	800 mg ORI Infrequent Dose N=71
Investigator-Defined Clinical Response	FIRST FOLLOW UP	CURE	35 (43.21%)	32 (42.11%)	34 (47.89%)
		IMPROVEMENT	31 (38.27%)	23 (30.26%)	21 (29.58%)

MO comment: The investigator defined cure rate was higher in the 1200 mg dose group and the results of this study most likely resulted in the choice of the current proposed 1200mg single dose regimen. The primary efficacy endpoint was the test-of-cure (cure or improvement versus failure) in the clinically-evaluable population at first follow-up day 21 in the SIMPLIFI trial while the primary endpoint was early clinical response at 48 to 72 hours in the SOLO trials.

6.1.5 Analysis of Secondary Endpoints(s)

The secondary endpoints in the mITT population are summarized in the Table below. The key secondary endpoint was investigator-assessed clinical cure at PTE. The percentage of patients with investigator-assessed clinical cure was similar in the oritavancin (79.9%) and vancomycin groups (79.6%), with a treatment difference of 0.3% and 95% CI of (-4.8, 5.4) in SOLO1. The percentage of patients with an investigator-assessed clinical cure was also similar in the oritavancin (82.7%) and vancomycin groups (80.5%), with a treatment difference of 2.2% and 95% CI of (-2.6, 7.0) in SOLO2.

Table 20: Secondary efficacy outcomes in the mITT population of the SOLO trials

	SOLO1				SOLO2		
	Analysis Visit	Oritavancin N=473 n(%)	Vancomycin N=481 n(%)	Treatment difference 95% CI	Oritavancin N=503 n(%)	Vancomycin N=502 n(%)	Treatment difference 95% CI
Investigator-Assessed Clinical Cure	PTE	378 (79.9%)	383 (79.6%)	0.29(-4.8,5.4)	416 (82.7%)	404 (80.5%)	2.2 (-2.6, 7.0)

		SOLO1			SOLO2		
	Analysis Visit	**Oritavancin N=473 n(%)**	**Vancomycin N=481 n(%)**	**Treatment difference 95% CI**	**Oritavancin N=503 n(%)**	**Vancomycin N=502 n(%)**	**Treatment difference 95% CI**
Sustained Clinical Response		313 (66.17%)	322 (66.94%)	-0.77 (-6.76, 5.22)	374 (74.35%)	370 (73.71%)	0.6 (-4.8, 6.1)
Sustained Clinical Response-FDA		321 (67.86%)	337 (70.06%)	-2.20 (-8.07,3.67)	382 (75.94%)	377 (75.10%)	0.84(-4.47 ,6.16)
Lesion size reduction >=20%	ECE	411 (86.89%)	399 (82.95%)	3.94(-0.59 ,8.47)	432 (85.88%)	428 (85.26%)	0.6 (-3.7, 5.0)

Table is Reviewer generated analysis. Applicant has submitted analysis of secondary endpoints in Table 4.2.2.1. Missing assessment is counted as failure.

Lesion Size Reduction ≥ 20% at ECE is the recommended primary efficacy endpoint defined in FDA's ABSSSI current guidance. (Guidance for Industry Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment, October 2013).

MO comment: In the SOLO trials, oritavancin was non-inferior to vancomycin for this endpoint in the mITTpopulation as well.

The applicant has submitted analysis evaluating lesion size reduction ≥ 20% from Baseline at ECE (mITT Population). The percentage of patients in SOLO1 with a lesion size reduction ≥ 20% from baseline at ECE was similar in the oritavancin (86.9%) and vancomycin (82.9%) groups, with a treatment difference of 4.% and 95% CI of (-0.6, 8.6), meeting the prespecified noninferiority margin of -10%. The percentage of patients in SOLO2 with a lesion size reduction ≥ 20% from baseline at ECE was similar in the oritavancin (86%) and vancomycin (85%) groups, with a treatment difference of 0.6% and 95% CI of (-3.7, 5), meeting the prespecified noninferiority margin of -10%. The medical reviewer generated analysis yielded similar results.

The percentage of patients in SOLO2 with a lesion size reduction ≥ 20% from baseline at ECE (excluding site 240002) was similar in the oritavancin428/498 (85.9%) and vancomycin425/499(85%) groups, with a treatment difference of 0.77 and 95% CI of (-3.6, 5.1).

The applicant has also submitted supportive analysis of the secondary endpoints in the CE population. The data for the CE population is summarized in Table below.

Table 21: Secondary efficacy outcomes in the CE population of the SOLO trials

		SOLO1			SOLO2		
Sponsor analysis	**Analysis Visit**	**Oritavancin N=394 n(%)**	**Vancomycin N=397 n(%)**	**Treatment difference 95% CI**	**Oritavancin N=427 n(%)**	**Vancomycin N=408 n(%)**	**Treatment difference 95% CI**

		SOLO1			SOLO2		
Sponsor analysis	**Analysis Visit**	**Oritavancin N=394 n(%)**	**Vancomycin N=397 n(%)**	**Treatment difference 95% CI**	**Oritavancin N=427 n(%)**	**Vancomycin N=408 n(%)**	**Treatment difference 95% CI**
Investigator-Assessed Clinical Cure	PTE	91.9%	93.2%	-1.3%; (-5.0, 2.3)	93.2%	94.9%	-1.6%: (-4.9, 1.6)
Lesion size reduction >=20%	ECE	90.6%	88.7%	1.9%; (-2.3, 6.2)	85.9%	85.3%	-0.7%: (-5.0, 3.6)
Sustained Clinical Response	PTE	77.9%	84%	-2.4%; (-8.1, 3.2)	88.1%	88.0%	-3.9%; (-8.6, 0.8)
Reviewer analysis	**Analysis Visit**	**Oritavancin N=394 n(%)**	**Vancomycin N=397 n(%)**	**Treatment difference and 95% CI**	**Oritavancin N=427 n(%)**	**Vancomycin N=408 n(%)**	**Treatment difference and 95% CI**
Investigator-Assessed Clinical Cure	PTE	362 (91.88%)	372 (93.70%)	-1.8(-5.4,1.8)	398 (93.21%)	387 (94.85%)	-1.6(-4.9,1.6)
Lesion size reduction >=20%	ECE	357 (90.61%)	352 (88.66%)	1.9(-2.3,6.2)	378 (88.52%)	364 (89.22%)	-0.7(-5,3.6)
Sustained Clinical Response	PTE	307 (77.92%)	319 (80.35%)	-2.4(-8.1,3.2)	359 (84.07%)	359 (87.99%)	-3.9(-8.6, 0.8)

Source: Adapted from the applicant's table 4.2.1.2, 4.2.9.2, 4.2.15.2

MO comment: Cure rate for Sustained Clinical Response at PTE for oritavancin was lower than for vancomycin in both SOLO trials; however, the difference between the treatment arms was still within the prespecified NI margin of -10%.

Sensitivity analyses

The applicant submitted sensitivity analysis for the secondary endpoints with missing data excluded and treated as success in the mITT population.

Table 22: Sensitivity analysis with missing data in the SOLO trials for Investigator assessed clinical cure at PTE and Lesion size reduction>20% at ECE.

	SOLO1			SOLO2		
	Oritavancin n/N (%)	**Vancomycin n/N (%)**	**Difference between Oritavancin and Vancomycin and (95% CI)**	**Oritavancin n/N (%)**	**Vancomycin n/N (%)**	**Difference between Oritavancin and Vancomycin and (95% CI)**
Investigator assessed clinical cure at PTE						
Missing is excluded from analysis	378/420 (90.0)	383/418 (91.6)	-1.6 (-5.5, 2.3)	416/453 (91.8)	404/442 (91.4)	0.4 (-3.2, 4.1)
Missing is treated as Success	433/475 (91.2)	444/479 (92.7)	-1.5 (-5.0, 1.9)	466/503 (92.6)	464/502 (92.4)	0.2 (-3.0, 3.5)

	SOLO1			SOLO2		
	Oritavancin n/N (%)	**Vancomycin n/N (%)**	**Difference between Oritavancin and Vancomycin and (95% CI)**	**Oritavancin n/N (%)**	**Vancomycin n/N (%)**	**Difference between Oritavancin and Vancomycin and (95% CI)**
Lesion size reduction>20% at ECE						
Missing is excluded from analysis	413/459 (90.0)	397 /456(87.1)	2.9 (-1.2, 7.0)	432/490 (88.2)	428/487 (87.9)	0.3 (-3.8, 4.4)
Missing is treated as Success	429/475 (90.3)	420/479 (87.7)	2.6 (-1.3, 6.6)	445/503 (88.5)	443/502 (88.2)	0.2 (-3.7, 4.2)

Adapted from sponsor's table 4.2.1.1and 4.2.9.1 of CSR

MO comment: Analysis of missing data both treated as success and exclusion did not change the clinical response rates for the secondary endpoints in both SOLO trials.

Concordance analysis

The following table summarizes the concordance analysis in the mITT population in the SOLO trials.

Table 23: Concordance analysis demonstrating outcome in the mITT population in SOLO trials.

	Outcome	**SOLO1**		**SOLO2**	
		Oritavancin N=473	**Vancomycin N=481**	**Oritavancin N=503**	**Vancomycin N=502**
Primary Efficacy_>=20% Lesion Size Reduction	Failure _ Failure	40 (8.5%)	56 (11.6%)	47 (4.6%)	44 (4.3%)
	Failure _ Success	43 (9.1%)	46 (9.6%)	53 (5.2%)	42 (4.1%)
	Success _ Failure	22 (4.7%)	26 (5.4%)	24 (2.4%)	30 (2.9%)
	Success _ Success	368 (77.8%)	353(73.4%)	379 (37.2%)	386 (37.9%)
Primary Efficacy: Investigator-Assessed Clinical Response	Failure _ Failure	38 (8%)	52 (10.8%)	38 (7.6%)	42 (8.4%)
	Failure _ Success	45 (9.5%)	50 (10.4%)	62 (12.3%)	44 (8.8%)
	Success _ Failure	57 (12%)	46 (9.6%)	49 (9.7%)	56 (11.2%)
	Success _ Success	333 (70.4%)	333 (69.2%)	354 (70.4%)	360 (71.7%)
Primary Efficacy_Sustained Clinical Response	Failure _ Failure	58 (12.3%)	72 (15%)	52 (10.3%)	48 (9.6%)
	Failure _ Success	25 (5.3%)	30 (6.2%)	48 (9.5%)	38 (7.6%)
	Success _ Failure	102 (21.6%)	87 (18.1%)	77 (15.3%)	84 (16.7%)
	Success _ Success	288 (60.9%)	292 (60.7%)	326 (64.8%)	332 (66.1%)

Source : reviewer generated

MO comment: The outcome by concordance analysis between the primary and secondary endpoints was fairly balanced in both trials.

Other supportive efficacy analyses

The sponsor has submitted analyses of Investigator-Assessed Clinical Cure at EOT and Day 10 and Sustained Lesion Area Decrease as supportive secondary analyses. The percentage of patients with an investigator-assessed clinical cure was similar between the oritavancin and vancomycin groups at EOT and Day 10 and the rates were maintained over time to PTE. The sustained lesion area decrease was also comparable in both arms. This was seen in both SOLO trials. Analyses of these supportive endpoints were conducted in both the mITT and CE population summarized in table below.

Table 24: Investigator-Assessed Clinical Cure and Sustained Lesion Area Decrease (success) at day10, EOT and PTE in the mITT population in the SOLO trials.

		SOLO1		SOLO2	
mITT population		**Oritavancin N=473**	**Vancomycin N=481**	**Oritavancin N=503**	**Vancomycin N=502**
Investigator-Assessed Clinical Cure	DAY 10	401 (84.8%)	392 (81.5%)	438 (87.1%)	434 (86.5%)
	EOT	403 (85.2%)	393 (81.7%)	442 (87.9%)	436 (86.9%)
	PTE	378 (79.9%)	383 (79.6%)	416 (82.7%)	404 (80.5%)
Sustained Lesion Area Decrease success		353 (74.6%)	347 (72.1%)	385 (76.5%)	368 (73.3%)
CE population		**Oritavancin N=394**	**Vancomycin N=397**	**Oritavancin N=427**	**Vancomycin N=408**
Sustained Lesion Area Decrease success		336 (85.3%)	334 (84.1%)	369 (86.4%)	347 (85.1%)
Investigator-Assessed Clinical Cure	DAY 10	368 (93.4%)	370 (93.2%)	404 (94.6%)	388 (95.1%)
	EOT	364 (92.4%)	367 (92.4%)	402 (94.2%)	387 (94.9%)
	PTE	362 (91.9%)	372 (93.7%)	398 (93.2%)	387 (94.9%)

Source: Reviewer generated table

Mean Lesion area in the MITT population at study visits in SOLO1 and SOLO2 is presented below.

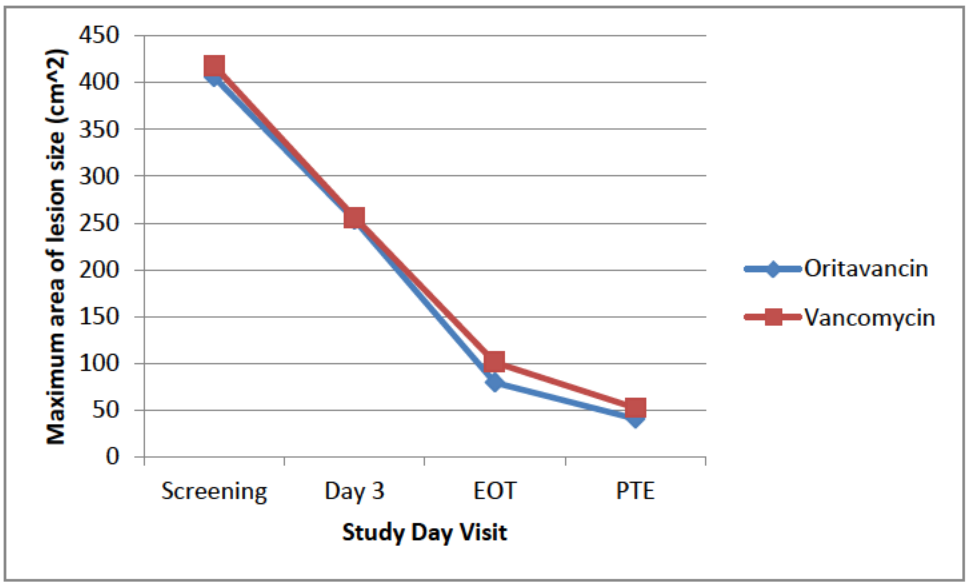


Figure 12: Mean Lesion area in the MITT population at study visits in SOLO1

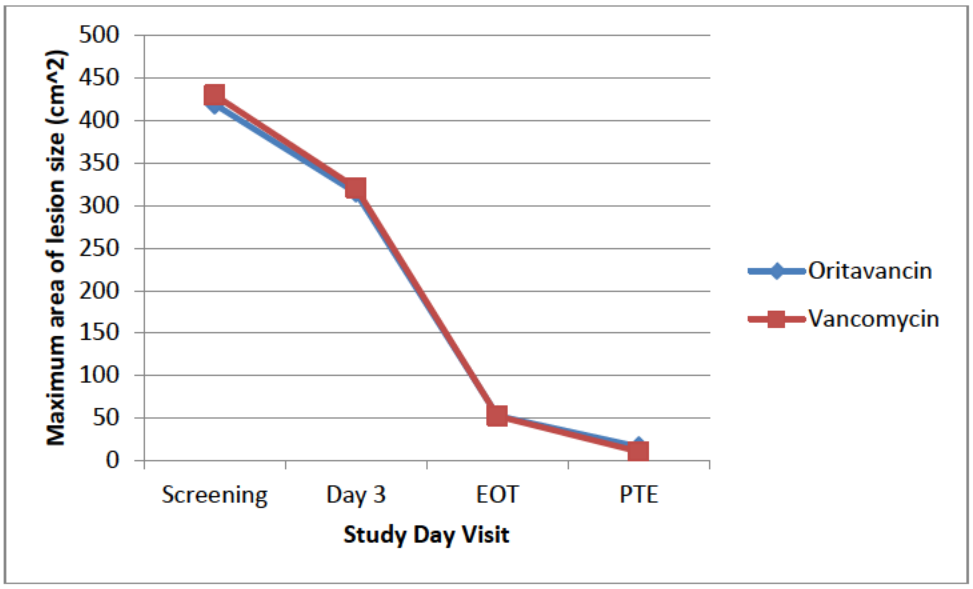


Figure 13: Mean Lesion area in the MITT population at study visits in SOLO2

MO comment: The mean lesion area decreased at different time points consistently in both SOLO trials.

Microbiological response

In the SOLO trials, post baseline specimens for culture were only required if clinically indicated. The patient-level microbiological response was categorized as either success (i.e., eradication, presumed eradication, or colonization) or failure (i.e., persistence, presumed persistence, superinfection, or relapse/recurrence) at EOT, Day 10, and PTE. A similar percentage of patients in the oritavancin and vancomycin groups had a microbiological response of eradication at EOT, Day 10, and PTE pathogen-level microbiological responses. The Patient level Microbiological Response at day 10, EOT and PTE in the MicroITT and MicroEvaluable Population is summarized as below.

Table 25: Patient level Microbiological Response (MicroITT and MicroE Population) in SOLO trials.

		SOLO1		**SOLO2**	
	MicroITT	**Oritavancin N=244**	**Vancomycin N=242**	**Oritavancin N=285**	**Vancomycin N=296**
DAY 10	Success	200(88.9%)	204(94%)	255(95.1%)	263(93.3%)
	Failure	25(11.1%)	13(6%)	13(4.9%)	19(6.7%)
EOT	Success	204(89.9%)	204(90.7%)	255(95.1%)	264(94%)
	Failure	23(10.1%)	21(9.3%)	13(4.9%)	17(6%)
PTE	Success	194(91%)	197(94.3%)	240(93.4%)	251(92.6%)
	Failure	19(9%)	12(5.7%)	17(6.6%)	20(7.4%)
	MicroE	**Oritavancin N=201**	**Vancomycin N=201**	**Oritavancin N=246**	**Vancomycin N=247**
DAY 10	Success	185 (92.0%)	190 (96%)	236(96.7%)	239(97.2%)

	Failure	16 (8.0%)	8(4%)	8(3.3%)	7(2.8%)
EOT	Success	185 (93%)	188 (94%)	234(96.7%)	238(97.1%)
	Failure	14 (7%)	12(6%)	8(3.3%)	7(2.9%)
PTE	Success	187 (93.5%)	192(96.5%)	231(95.1%)	237(96.3%)
	Failure	13(6.5%)	7(3.5%)	12(4.9%)	9(3.7%)

Reviewer generated table. Missing value excluded.

MO comment: A similar percentage of patients in the oritavancin and vancomycin groups had a microbiological response of success at EOT, Day 10, and PTE. The oritavancin arm had a lower percentage of success 88.9% versus 94% in the vancomycin arm in the microITT population at day 10 in SOLO 1 but this was not seen in the SOLO2 trial.

The patient level microbiological response in selected MRSA and MSSA subgroups is presented in Table below.

Table 26: Patient level microbiological response in MRSA and MSSA subgroups at EOT, Day 10 and PTE in the MicroITT population

MicroITT	**SOLO1**			**SOLO2**		
	Oritavancin (N=244)	**Vancomycin (N=242)**	**Diff 95% CI**	**Oritavancin (N=285)**	**Vancomycin (N=296)**	**Diff 95% CI**
MRSA	104 (42.6)	100 (41.3)	1.3 (-7.47,10.08)	100 (35.1)	101 (34.1)	0.97 (-6.77,8.7)
Success at EOT	89/97 (91.8)	85/92 (92.4)	-0.6 (-8.3, 7.1)	89/97 (91.8)	89/96 (92.7)	-1.0 (-8.5, 6.6)
Day 10	88/97 (90.7)	86/90 (95.6)	-4.8 (-12.0, 2.3)	89/96 (92.7)	87/94 (92.6)	0.2 (-7.3, 7.6)
PTE	86/93 (92.5)	83/87 (95.4)	-2.9 (-9.9, 4.0)	84/93 (90.3)	86/93 (92.5)	-2.2 (-10.2, 5.9)
MSSA	118 (48.4)	113 (46.7)	1.7 (-7.21, 10.5)	151 (53.0)	159 (53.7)	-0.7 (-8.8, 7.4)
Success at EOT	99/110 (90.0)	95/103 (92.2)	-2.2 (-9.9, 5.4)	137/140 (97.9)	145/151 (96.0)	1.8 (-2.1, 5.8)
Day10	95/108 (88.0)	95/100 (95.0)	-7.0 (-14.5, 0.4)	137/140 (97.9)	146/154 (94.8)	3.1 (-1.2, 7.3)
PTE	90/101 (89.1)	91/97 (93.8)	-4.7 (-12.4, 3.0)	129/134 (96.3)	138/147 (93.9)	2.4 (-2.6, 7.4)

Missing value was excluded. Similar results noted applicant's table 4.4.3.3., 4.4.6.3.of CSR of SOLO1 and Tables 4.4.3.3., 4.4.3.4., 4.4.6.4 of CSR of SOLO2.

MO comment: Of note, the patient level microbiological success at PTE for the MRSA subgroup was 81/88(92.0%) in the oritavancin arm and 80/83 (96.4%) in the vancomycin arm with a treatment difference of -4.3% and 95% CI of -11.3%, 2.6%. Given the small sample size in the microITT population definitive conclusions cannot be drawn.

Table 27: The Clinical Response Rate at ECE by Baseline Pathogen (Microevaluable population)

	At 48-72 hours(ECE)		
Pathogen	**ORBACTIV n/N (%)**	**Vancomycin n/N (%)**	**Treatment difference(95% CI)**
Staphylococcus aureus	344/397(86.6)	349/391 (89.3)	-2.6(-7.2,1.9)
Methicillin-susceptible *Staphylococcus aureus* (MSSA)	195/223 (87.4)	206/226 (91.2)	-3.7(-9.4,2)
Methicillin-resistant *Staphylococcus aureus* (MRSA)	149/174 (85.6)	143/165 (86.7)	-1(-8.4,6.3)
Streptococcus pyogenes	19/25(76.0)	19/ 24 (79.2)	-3.2(-26.5,20.2)
Streptococcus agalactiae	6/8 (75.0)	11/ 11 (100.0)	
Streptococcus dysgalactiae	7/8(87.5)	4/ 4 (100.0)	
Streptococcus anginosus	3/4 (75.0)	6/ 6 (100.0)	
Streptococcus intermedius	6/8(75.0)	11/ 12 (91.7)	
Streptococcus constellatus	15/16(93.8)	18/ 19 (94.7)	
Enterococcus faecalis	9/10(90.0)	8/ 10 (80.0)	

MO comment: The clinical response rates at ECE for the MSSA subgroup was lower (87.4%) in the oritavancin arm compared to the vancomycin arm (91.2%) however the lower bound of the 95% CI was greater than -10%. Given the small number of pathogens for the streptococcus pyogenes no conclusions can be drawn.

Table 28: The Clinical Response Rate at ECE by Baseline Pathogen (MicroITT population)

	At 48-72 hours (ECE)	
Pathogen	**ORBACTIV n/N (%)**	**Vancomycin n/N (%)**
Methicillin-susceptible *Staphylococcus aureus* (MSSA)	223/269(82.9%)	233/272(85.66%)
Methicillin-resistant *Staphylococcus aureus* (MRSA)	166/204(81.3%)	164/204(80.4%)
Streptococcus pyogenes	21/31(67.7%)	23/32(71.9%)
Streptococcus agalactiae	7/9(77.8%)	12/12(100%)
Streptococcus dysgalactiae	7/9(77.7%)	6/ 6 (100.0)
Streptococcus anginosus	3/4(75%)	6/6(100%)
Streptococcus intermedius	8/10(80%)	13/16(81.25%)
Streptococcus constellatus	17/19(89.4%)	21/23(91.3%)
Enterococcus faecalis	11/13(84.6%)	10/12(83.3%)

MO comment: For Streptococcus agalactiae and treptococcus anginosus the cure rate in the microITT population in the Simplify study 1200 mg dose group was 1/1(100%).

Efficacy in bacteremic patients

In the SOLO trials there were a total 28 subjects in the oritavancin arm and 19 subjects in the vancomycin arm who had bacteremia at baseline in the mITT population. The primary efficacy endpoint rates of early clinical response assessed at ECE (48-72h) were 18/28 (64.3%) for oritavancin arm and 16/19 (84.2%) for vancomycin arm. The investigator-assessed clinical cure at PTE was 17/28 (60.7%) for the oritavancin arm and 15/19 (78.9%) for vancomycin arm. The Agency's review showed that this analysis included non ABSSSI pathogens (*Staphylococcus*

coagulase negative) which may be considered as contaminants. The following table shows updated efficacy rates in the bacteremia trials.

Table 29: Efficacy in bacteremic patients in pooled SOLO trials (ABSSSI pathogens)

FDA	ECE		EOT		PTE (IACC)	
	Oritavancin	Vancomycin	Oritavancin	Vancomycin	Oritavancin	Vancomycin
total ABSSSI pathogens	11	7	11	7	11	7
responders	6 (55%)	5 (63%)	8 (73%)	4 (57%)	6 (55%)	4 (57%)
non responsders	5 (45%)	2(37%)	3 (27%)	2 (43%)	5 (45%)	3 (43%)

6.1.6 Other Endpoints

Primary Efficacy results without the fever component are presented in the Table below.

Table 30: Primary Efficacy without the fever component in the mITT population in the SOLO trials.

	SOLO1			SOLO2		
	Oritavancin	Vancomycin	Difference 95% CI	Oritavancin	Vancomycin	Difference 95% CI
Success at ECE	426 (90.06%)	413 (85.86%)	4.2 (0.08, 8.3)	453 (90.06%)	449 (89.44%)	0.6(-3.1,4.4)
Total number of subjects mITT	473	481		503	502	

MO comment: The success at ECE without the fever component in the mITT population was well balanced in both arms and in both trials.

Resolution of clinical signs and symptoms

The applicant submitted analysis of signs and symptoms related to the primary ABSSSI site (i.e., erythema, induration/edema, purulent drainage, fluctuance, pain, tenderness, local increase in heat/warmth) in both the oritavancin and vancomycin groups from baseline to each day during therapy, ECE, EOT, Day 10, and PTE. Reductions from baseline in each sign and symptom were similar in the oritavancin and vancomycin groups at each assessment. In the mITT population, the most frequent signs and symptoms that remained at PTE were edema (oritavancin, 18.9%; vancomycin, 17.4%), erythema (oritavancin, 22.3%; vancomycin, 20.8%), presence of induration at the edge or overall (oritavancin, 18.4%; vancomycin, 21.3%), mild tenderness at the infection site (oritavancin, 12.7%; vancomycin, 16.9%), and mild pain (oritavancin, 12.3%; vancomycin, 11.2%).
Fewer rescue medications were needed in the oritavancin arm in both the SOLO trials.

Table 31: Rescue medications at ECE, EOT, Day 10 and PTE in the SOLO trials (mITT population).

	SOLO1			SOLO2		
	Oritavancin N=473	**Vancomycin N=481**	**Difference 95% CI**	**Oritavancin N=503**	**Vancomycin N=502**	**Difference 95% CI**
Rescue medications at ECE	18 (3.8)	28 (5.8)	-2 (-4.7,0.7)	13 (2.6)	19 (3.8)	-1.2 (-3.4, 1.0)
Rescue medications at EOT	15 (3.2)	27 (5.6)	-2.4(-5,0.2)	12 (2.4)	17 (3.4)	-1.0 (-3.1, 1.1)
Rescue medications at day10	8 (1.7)	17 (3.5)	-1.8(-3.8,0.2)	6 (1.2)	13 (2.6)	-1.4 (-3.1, 0.3)
Rescue medications at PTE	9 (1.9)	18 (3.8)	-1.8(-3.9, 0.3)	5 (1.0)	12 (2.4)	-1.4 (-3.0, 0.2)

Adapted from sponsor's Table 23 of CSR, replicated by reviewer.

The number of subjects who had unplanned incision and drainage after 48 hours in the mITT population are presented in the Table below.

Table 32: Subjects who had unplanned incision and drainage after 48 hours in the mITT population (SOLO trials).

	SOLO1		SOLO2	
ABSSSI Category	**Oritavancin N=473**	**Vancomycin N=481**	**Oritavancin N=503**	**Vancomycin N=502**
n (%)				
Cellulitis/Erysipelas	6 (1.27%)	5 (1.04%)	3 (1.16%)	3 (1.18%)
Major Cutaneous Abscess	4 (0.85%)	1 (0.21%)	3 (1.16%)	1 (0.39%)
Wound Infection	2 (0.42%)	2 (0.42%)	0 (0.00%)	1 (0.39%)

MO comments: Further analysis of these subjects revealed that a few subjects were classified as success at ECE (TMC –ORI- 10-01-101001-089, 10-01-101003-006, 101003-009,10-01-101014-006, 101034-006,101002-086, 201023-003, 207004-021, 201001-045). Further sensitivity analyses were conducted.

Sensitivity analysis: When primary efficacy at ECE success changed to failure for unplanned I&D, conducted in the ITT and mITT population in SOLO1, 762 total successes (Oritavancin and vancomycin) with 386 in oritavancin arm and 376 in vancomycin arm were noted. In SOLO2, upon similar adjustment 815 total successes (oritavancin and vancomycin) with 401 in the oritavancin arm and 414 in vancomycin arm were noted. Amended primary efficacy analyses are presented below.

Table 33: Primary efficacy at ECE in subjects with adjusted outcome for unplanned I&D (success changed to failure), in mITT population.

	SOLO1			SOLO2		
	Oritavancin N=473	**Vancomycin N=481**	**Diff in % (95% CI)**	**Oritavancin N=503**	**Vancomycin N=502**	**Diff in % (95% CI)**
Primary efficacy endpoint ECE	386 (81.6%)	376 (78.1%)	3.44(-1.65,8.52)	401 (79.7%)	414 (82.5%)	-2.75 (-7.6, 2.1)

MO Comment: The adjustment for unplanned I&D did not significantly affect primary efficacy results.

Baseline lesion size area<75 cm^2

Few subjects in SOLO1 and SOLO2 trials (101027-008, 152002-001, 149003-003, 202001-004, 291002-002, 291002-003, 291002-005, 291002-006, 291002-007, 291002-008, 291002-013) were noted to have baseline lesion size area <75 cm^2. Further sensitivity analysis was conducted to evaluate these subjects.

Sensitivity analysis: When primary efficacy of success at ECE in SOLO1 trial was changed to failure for lesions size <75cm^2 in ITT population of 968, mITT of 954, 768 total successes (oritavancin and vancomycin) with 389 in oritavancin arm and 379 in vancomycin arm was noted. After similar adjustment in SOLO2 trial, in ITT population of 1019 and mITT population of 1005, a total 812 successes (oritavancin and vancomycin with 399 success in oritavancin arm and 413 in vancomycin arm were noted.

Table 34: Amended primary efficacy endpoint, mITT population (lesions size <75cm^2 considered failure or If lesion size were excluded from analysis)

Subjects with lesions size <75cm^2 considered failure, <75cm2, mITT						
	Oritavancin N=473	Vancomycin N=481	Difference (95% CI)	Oritavancin N=503	Vancomycin N=502	Difference (95% CI)
Primary efficacy endpoint ECE	389 (82%)	379 (78.8%)	3.45(-1.57,8.47)	399 (79.3%)	413 (82.3%)	-2.95 (-7.81, 1.92)
Subjects with lesion size<75cm2 excluded from analysis, mITT						
	Oritavancin N=471	Vancomycin N=480	Difference (95% CI)	Oritavancin N=499	Vancomycin N=498	Difference (95% CI)
Primary efficacy endpoint ECE	388 (82.4%)	379 (79%)	3.42(-1.59,8.43)	399 (80%)	413 (82.90%)	-2.97 (-7.79, 1.85)

MO Comments: The adjusted analyses did not affect the primary efficacy results.

Low vancomycin troughs
See Section 6.1.10

Cellulitis, abscess and osteomyelitis as AE
These were 4 subjects in the oritavancin arm who had osteomyelitis which on further review appeared to be due to lack of efficacy of oritavancin in osteomyelitis or due to failure to diagnose osteomyelitis at screening. The cases of subcutaneous abscesses were slightly higher in the oritavancin arm but appeared to be failure of efficacy as the infection occurred at the site of the index infection. The cases of cellulitis were balanced in both arms with similar reasons, which is lack of efficacy or simply needing to have an incision and drainage for control of the infection or recurrent infection due to underlying comorbidities. Further discussion of these cases is in section 7.3.2 of the safety review.

MO comment: Sensitivity analysis was not done as these subjects were appropriately classified in the CRF and clinical response dataset.

The following table presents the lack of efficacy by age, sex and ethnicity in the SOLO trials.

Table 35: Lack of efficacy by age, sex and ethnicity in the SOLO trials (mITT population)

		SOLO 1				SOLO 2			
Standard Disposition Term	**Age Group**	**Oritavancin**		**Vancomycin**		**Oritavancin**		**Vancomycin**	
		N=473		**N=481**		**N=503**		**N=502**	
		Count	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**
Lack Of Efficacy	Age under 65 years	7	11.6	9	22.0	7	11.5	5	11.1
	Age 65 and over	2	44.3	1	22.6	0	0.0	0	0.0
Lack Of Efficacy	F	2	11.2	6	33.4	3	11.8	1	0.6
	M	7	22.3	4	11.3	4	11.2	4	11.2
Lack Of Efficacy	Native Hawaiian Or Other Pacific Islander	1	1100	0	0.0				
	White	6	22.2	9	33.3				
	Black Or African American	2	44.7	0	0.0				
	Asian	0	0.0	1	0.6				
	American Indian Or Alaska Native	0	0.0	0	0.0				
	Hispanic Or Latino					1	11.0	2	22.1
	Not Hispanic Or Latino					6	11.5	3	0.7

MO comment: The subjects were fairly balanced in both trials.

6.1.7 Subpopulations

Table 36: Primary efficacy outcomes in different subgroups in the SOLO trials

Subgroups	**SOLO1**		**SOLO2**	
	Oritavancin	**Vancomycin**	**Oritavancin**	**Vancomycin**
Abscess	115 /140(82%)	110 /141(78%)	136/168(81%)	143/159(90%)
Cellulitis	196/241 (81%)	177 /235(75%)	97/144(67%)	126/167(75%)
Wound infection	79/92(86%)	92/105(88%)	170/191(89%)	147/176(83%)
Male	246/301(82%)	242/301(80%)	273/338(81%)	284/343(83%)
Female	145 /173(84%)	136/179 (76%)	130/165(79%)	132/159(83%)
SIRS at Baseline	50/73 (68%)	45/73 (62%)	66/95(69%)	82/101(81%)
North America	234/298(79%)	224/299(75%)	230/283(81%)	232/285(81%)
Asia	135/148(91%)	137/150(91%)	94/120(78%)	102/119(86%)
>=65 yrs	38/47(81%)	25/38(66%)	27/39(69%)	33/39(85%)
<=65 yrs	353/428(83%)	353/441(80%)	376/464(81%)	383/463(83%)
Causacian	209/274(76%)	197/275(72%)	285/356(80%)	290/356(82%)
Black	38/43(88%)	32/40(80%)	13/14(93%)	15/17(88%)
Asian	140/153(92%)	140/154(91%)	96/122(79%)	104/122(85%)
MSSA at Base.	96 /118(81%)	94/113 (83%)	126/150(84%)	137/157(87%)
MRSA at Base.	84/104 (80%)	80 /100(80%)	82/100(82%)	82/101(81%)
Diabetes Mellitus	76/92 (83%)	78/96 (81%)	34/46(74%)	38/45(84%)
Severe Peripheral Vascular Disease	8/9 (89%)	5/7 (71%)	4/6(67%)	9/10(90%)
Renal Insufficiency or Failure	8 /12(67%)	4/7 (57%)	4/9(44%)	3/5(60%)

MO Comment: Primary efficacy analysis in different subgroups as shown in the table above shows disparity between the 2 SOLO trials in certain subgroups. Major cutaneous abscesses, cellulitis, SIRS at baseline, Asian sites, age >=65 yrs, and diabetes had a lower primary efficacy rate in oritavancin arm compared to vancomycin (81% vs 90%), 67%vs 75%, 69%vs 81%,78%vs 86%,69%vs 85%,74%vs 84%) in SOLO2 trial. The applicant reports in their clinical overview that efficacy was similar in diabetic and non-diabetic patients for the early clinical endpoints (i.e., early clinical response and lesion size reduction ≥ 20%), but lower for oritavancin in diabetics compared to non-diabetics for the later endpoints (i.e., investigator-assessed clinical cure at PTE and sustained clinical response at PTE). There were low number of black population in SOLO 2 but overall efficacy rates were higher in the oritavancin arm. There were minor discrepancies between reviewer generated table and sponsor generated figure (Figure 3, CSR).

The Cure Rates at Test-of-Cure Visit for Patients with Diabetes in ITT in Study ARRI was 63% in oritavancin arm and 60% in vancomycin arm. The Cure Rates at Test-of-Cure Visit for Patients with Diabetes in ITT in Study ARRD was 67% 1.5 mg/kg and 55% with the 3.0 mg/kg dose of oritavancin, while it was 77% in the vancomycin arm(from previous NDA review by Dr. Naseem Moledina, November 28, 2008) in previously submitted NDA review these subgroup analysis.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

In the prior phase 3 trials, the primary efficacy endpoint of sponsor-defined clinical outcome, the success rates in the intent-to-treat (ITT) population at the TOC visit in ARRI were 594/831 (71.5%) in the oritavancin group and 284/415 (68.4%) in the vancomycin group. In ARRI oritavancin 200 mg IV once daily was used. For study ARRD, the primary efficacy endpoint of the investigator-defined clinical outcome, the success rates in the ITT population at the TOC Visit were 58.4% (101/173) in the oritavancin 1.5 mg/kg group, 57.4% (97/169) in the oritavancin 3.0 mg/kg group, and 60.6% (106/175) in the vancomycin group.
When administered parenterally, oritavancin exhibited activity against Gram-positive pathogens in a wide variety of animal models of infection.
The applicant has submitted data where pharmacodynamics are optimized when doses are front-loaded rather than divided and that oritavancin activity is sustained due to its post-antibiotic effects and long half-life in vivo. Such concentration-dependent and persistent effects predicted long-lived activity with infrequent doses and supported the selection of the single 1200 mg dose that was evaluated in the Phase 3 SOLO studies.

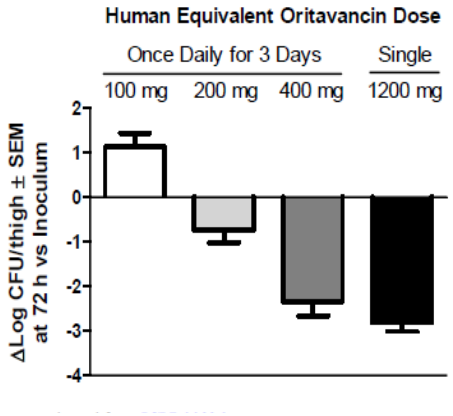


Figure 14: Oritavancin Pharmacodynamics are optimized with the Humanized Single 1200 mg dose Compared to Daily Dosing Regimens (Neutropenic thigh Model of S.aureus infection).
Source: Applicants' Pharmacology summary page 16

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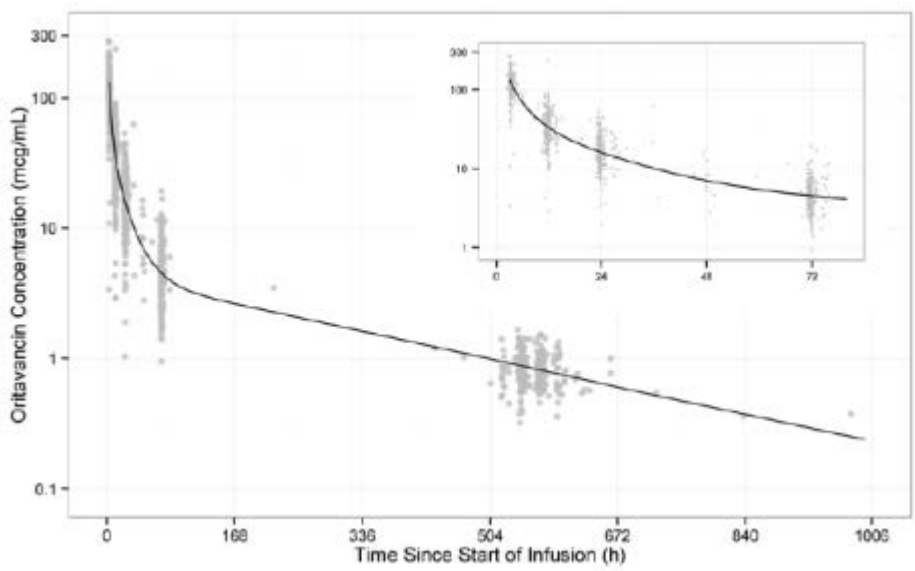


Figure 15: Population mean plasma concentration time profile after a single 1200 mg Dose of Oritavancin Administered IV over 3 hours-Semi-Log scale
Source: Applicant's submission page 15 of clinical overview.

Oritavancin exhibited linear PK at doses up to 1200 mg. The mean, population-predicted oritavancin concentration-time profile displayed a multi-exponential decline and a long terminal plasma half-life of 245 hours, as shown in Figure xx, which supports a single 1200 mg dose.

In the phase 2 SIMPLIFI study, oritavancin given as a single dose of 1200 mg or an infrequent dose of 800 mg with an optional 400 mg on Day 5 was noninferior to a 200-mg daily dose given for 3 to 7 days in the treatment of patients with complicated skin and skin structure infections. The percentage of patients with an investigator-defined clinical outcome of cure at first follow-

up in the clinically evaluable population was 72.4% (55/76), 81.5% (66/81), and 77.5% (55/71) in the daily dose, single dose, and infrequent dose, respectively. The estimated differences in cure rates between the daily dose and single dose (8.6%, 90% confidence interval = -2.5, 18.2) and between the daily dose and infrequent dose (5.2%, 90% confidence interval = -6.8, 15.4) demonstrated noninferiority between the active comparator daily dose group and the 2 testing groups (single dose and infrequent dose groups).

Analysis of dose-response for safety could be found in Dr. Moledina's previous oritavancin NDA 22153 review from December, 2008. AE in the simplify study and the Phase 3 SOLO trials are discussed in the safety section of the review.

MO comment: The pharmacokinetics and pharmacodynamics of oritavancin support the 1200 mg single dose regimen. Efficacy results from 2 adequate and well controlled clinical trials SOLO 1 and 2 also support the 1200 mg single dose regimen for ABSSSI.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The discussion of a potential for the development of resistance is provided in section 4.2 Clinical Microbiology. Oritavancin kills Gram-positive bacteria via three mechanisms of action: inhibition of transglycosylation and transpeptidation processes during cell wall synthesis, and perturbation of cell membrane integrity. Although multiple mechanisms can reduce the propensity of oritavancin to select for resistance, surveillance studies will need to be conducted to monitor for resistance.

6.1.10 Additional Efficacy Issues/Analyses

In SOLO trials in accordance with protocol, vancomycin dosing could have been adjusted by an unblinded pharmacist based upon CrCl levels, the patient's clinical status, and/or vancomycin trough levels (where available) to maintain a steady state trough level of either 10 to 15 μg/mL or a level defined by the site's standard of care.
The sponsor provided vancomycin trough level for 435 subjects in SOLO 1. 194 subjects had vancomycin trough level less than 10, mean 6.3±xx. Of these 194 subjects, 42 subjects were noted as failures at primary efficacy endpoint, ECE. When 42 failures were converted to successes, 193 successes were noted.
The sponsor provided vancomycin trough level of 467 subjects in SOLO 2. 199 subjects had vancomycin trough level less than 10, mean 6.3±2.71. 36 subjects were noted as failures at primary efficacy endpoint, ECE. When 36 failures were converted to success, 198 successes were observed.

Further sensitivity analysis was conducted.

When low vancomycin trough (42) failures were considered as successes in SOLO1, and when low vancomycin trough (36) failures were considered as successes in SOLO2, the primary efficacy analysis was as follows.

Table 37: Primary efficacy in SOLO 1 and SOLO2 in subjects when subjects with low vancomycin trough failures were considered as successes

	SOLO1			SOLO2		
	Oritavancin N=473	**Vancomycin N=481**	**Treatment difference (95% CI)**	**Oritavancin N=503**	**Vancomycin N=502**	**Treatment difference (95% CI)**
Primary efficacy endpoint ECE	390 (82.5%)	421 (87.5%)	-5.07 (-9.60, -0.55)	403 (80%)	452 (90%)	-9.92 (-14.28,-5.56)

194 subjects were identified as having low vancomycin troughs in SOLO1. If these 194 subjects were excluded, the primary efficacy is as follows. In SOLO2, 199 subjects were identified as low vancomycin troughs. If these subjects were excluded, the primary efficacy is as follows.

Table 38: Primary efficacy in subjects excluding low vancomycin troughs in the SOLO trials

SOLO1			**Treatment difference (95% CI)**	**SOLO2**		**Treatment difference (95% CI)**
	Oritavancin N=473	**Vancomycin N=287**		**Oritavancin N=503**	**Vancomycin N=303**	
Success at ECE	390 (82%)	228 (79%)	3.01(-2.79,8.81)	403 (80%)	254 (83%)	-3.7 (-9.1, 1.7)

The following is a comparison of success at ECE of subjects with low vancomycin troughs vs subjects with normal vancomycin troughs.

Table 39: Success at ECE of subjects with low vancomycin troughs vs subjects with normal vancomycin troughs in the SOLO trials.

SOLO1				**SOLO2**		
	Vancomycin Low trough <10 N=194	**Vancomycin Normal troughs>=10 N=241**	**Treatment difference (95% CI)**	**Vancomycin Low trough <10 N=199**	**Vancomycin Normal troughs>=10 N=276**	**Treatment difference (95% CI)**
Success at ECE	151 (77.8%)	209 (86.7%)	-8.89(-16.1,-1.64)	162 (81%)	245 (89%)	-7.36 (-13.93, -0.8)

MO comment: It is expected that patients will have lower cure rates in the setting of low vancomycin troughs. However exclusion of these subjects (low troughs) does not appear to greatly impact the efficacy rates (note: slightly decreased primary efficacy rate in SOLO2).

7 Review of Safety

Safety Summary

The overall safety database consisted of 3017 oritavancin-treated subjects from 22 clinical trials, including 4 Phase 3 studies, 4 Phase 2 studies, and 14 Phase 1 studies. A total of 1075 ABSSSI

patients were treated with the 1200 mg single dose regimen. There were 473 subjects in SOLO 1 and 503 subjects in SOLO2 who were treated with oritavancin. There were 481 subjects in SOLO1 and 502 subjects in SOLO2 who were treated with vancomycin. The safety review focused mainly on the pooled Phase3 SOLO trials. The mean duration of exposure to oritavancin was 8 days. The last follow up visit was a safety visit that occurred 60 days after the first administration of study drug.

In the SOLO pool, 5 patients, 2 in the oritavancin group and 3 in the vancomycin group, died. There were 5/302 (1.7%) deaths in the phase 2 SIMPLIFI study of oritavancin: 3 in the daily dose and 2 in the infrequent dose group. None of the deaths appeared to be related to the study drug.

The incidence of treatment-emergent serious adverse events in phase 3 trials was 55.3% and in 56.9% in the oritavancin and vancomycin groups, respectively. Adverse events of interest that occurred at a higher rate in the oritavancin arm when compared to vancomycin group included the TEAEs in the infections and Infestation SOC. There were 40 cases (4%) in the oritavancin arm versus 31(3%) cases in the vancomycin arm. These cases included 4 subjects in the oritavancin arm who had osteomyelitis which on further review could have been due to lack of efficacy of the proposed oritavancin regimen in osteomyelitis or due to failure to diagnose osteomyelitis at screening. There were also 4 cases of pneumonia in the oritavancin arm in patients who appeared to have underlying risk factors for development of pneumonia, e.g. a history of COPD, a history of aspiration pneumonia).The cases of subcutaneous abscesses were slightly higher in the oritavancin arm representing efficacy failure as the infection occurred at the site of the index infection. The cases of cellulitis were balanced in both arms either representing a lack of efficacy or simply a lack of timely incision and drainage for control of the infection or a recurrent infection due to underlying comorbidities.

For subjects in both the oritavancin and vancomycin groups, the SOC with the highest incidence of TEAEs leading to study drug discontinuation was Infections and Infestations (1.6% versus 1.9% respectively). Twenty one subjects (2.2%) in the oritavancin arm and 19 (1.9%) subjects in the vancomycin arm had a serious AE which lead to treatment discontinuation. The most common TEAEs in both oritavancin and vancomycin groups were nausea (17.7% and 18.3%), headache (12.6% and 11.7%), vomiting (8.2% and 8.2%), diarrhea (6.6% and 5.7%), cellulitis (6.8% and 5.7%), constipation (6% and 6.7%), and infusion site extravasation (6% and 5.9%). The incidence of alanine aminotransferase and aspartate aminotransferase in the investigation SOC, cellulitis, abscess, subcutaneous abscess, abscess limb and infection in the Infections and infestation SOC, tachycardia and myalgia were somewhat higher in the oritavancin-treated patients.
There were 24 subjects (4.4%) in the oritavancin arm and 11 subjects (1.9%) in the vancomycin arm in the SOLO pool with the adverse event of tachycardia. No specific conclusions can be drawn from this analysis as no particular relationship was seen between occurrence of tachycardia and exposure to the study drug.
There were 27 (2.8%) subjects and 16 (1.6%) subjects with elevated ALT in the oritavancin and vancomycin arm respectively. There were 18 (1.8%) subjects and 16 (1.6%) subjects with

elevated AST in the oritavancin and vancomycin arm respectively. Although the history of hepatitis or hepatic condition (9 subjects) or intravenous drug use (12 subjects) could have predisposed the subjects to the elevation of transaminases, there were subjects with no such history where the LFT abnormality occurred. The cases do not appear to be a result of severe sepsis or shock liver. None of the subjects met Hy's Law criteria.
Although the frequency LFT elevation in both arms from baseline was balanced, there was 1 subject in the oritavancin arm versus nonein the vancomcyin arm where ALT levels rose to >10xULN from normal baseline. A postbaseline evaluation of LFTs (ALT/AST>3, TB>1.5, ALP normal) anytime during the study showed 2 subjects in the oritavancin arm compared to none in the vancomycin arm. There were 18 subjects in the oritavancin arm versus 14 subjects in the vancomcyin arm where ALT rose from baseline to 3-5xULN and 3 subjects in the oritavancin arm versus 1 subject in the vancomycin arm where TB rose from normal to 1.5-2xULN. Three cases which fell in the Hy's law quadrant but did not meet the Hy's law criteria appeared to have an idiosyncratic elevation of ALT levels. There were also asymptomatic elevations of LFTs noted in the moderately impaired group in the hepatic impairment study and given the possibility of of use of oritavancin in subjects with moderate hepatic impairment or IVDU, this should be noted in product labeling.

There were slightly higher incidence of serious TEAE in the diabetic subjects 23/138 (16.7%) in the oritavancin arm compared 18/141 (12.8%) in the vancomycin arm. However, the overall number of subjects with >1 TEAE were similar in both arms. In the subjects with baseline CrCl of 30-<60 ml/min, there were 12/70 subjects (%) in the oritavancin arm who had a serious AE as compared to 3/54 subjects (%) in the vancomycin arm.

In summary, the data submitted demonstrates overall similar safety profile of oritavancin and the comparator, vancomycin. No causal relationship between oritavancin and a particular category of adverse events was clearly demonstrated. However, postmarketing monitoring of adverse events such as elevated liver function tests, infections, tachycardia may provide additional information on the safety profile of oritavancin.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary safety data for this review included the new Phase 3 SOLO trials conducted under IND 51292. Safety data was reviewed in relevant sections from the phase 2 SIMPLIFI study and the TQT study (MDCO-ORI-12-02). For the detailed safety review from the prior phase 3 ARRD/ARRI trials the reader is referred to medical review by Dr. Moledina from December 2008 (NDA 22153). The overall safety database consisted of 3017 oritavancin-treated subjects from 22 clinical trials, including 4 Phase 3 studies, 4 Phase 2 studies, and 14 Phase 1 studies. Of the 3017 oritavancin-treated subjects, 2149 were patients from Phase 3 ABSSSI/cSSTI trials, 444 were from Phase 2 studies (331 cSSTI patients and 113 bacteremia patients) and 424 subjects (404 healthy volunteers and 20 moderately hepatically-impaired subjects) were from Phase 1 studies. The safety population in the SOLO trials included subjects who were enrolled and received any amount of study medication.The safety population in the SOLO 1 trial was 954

subjects (473 in oritavancin arm and 481 in the vancomycin arm) and 1005 subjects (503 in the oritavancin arm and 502 in the vancomycin arm) in the SOLO2 trial. 99 subjects received the 1200 mg dose in the SIMPLIFI trial. A total of 1075 ABSSSI patients were treated with the 1200 mg single dose regimen. All safety analyses have been conducted in the safety population or the modified intent to treat population.

7.1.2 Categorization of Adverse Events

An AE was defined as any untoward medical occurrence in a subject administered a medicinal product and which did not necessarily have to have a causal relationship with this treatment. The intensity of each AE was graded as follows:

- Mild: discomfort noticed, but no disruption to daily activity
- Moderate: discomfort sufficient to reduce or affect normal daily activity
- Severe: inability to work or perform normal daily activity

An SAE was defined as any event that fulfilled any of the following criteria:

- Resulted in death
- Was life-threatening (ie, the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred)
- Resulted in persistent or significant disability/incapacity
- Required in-subject hospitalization or prolonged hospitalization
- Was a congenital anomaly/birth defect
- Was another medically significant event that, based upon appropriate medical judgment, jeopardized the subject and required medical or surgical intervention to prevent one of the outcomes listed above

AEs of special interest in the oritavancin clinical development program include AEs related to potential glycopeptide effects, antibiotic-related effects, organ systems (ie, cardiac, renal, and hepatic).

The incidence of TEAEs was summarized based on Medical Dictionary for Regulatory Activities (MedDRA) (Version 13.1) coded terms at the System Organ Class (SOC) and preferred term levels.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The applicant pooled the studies into the following pools

- SOLO pool: two pivotal Phase 3 studies, SOLO I and SOLO II. These studies provide safety data for a single 1200 mg dosing regimen of oritavancin.
- ARRD/I pool: The ARRD and ARRI pooled data set provides safety data for oritavancin as a daily dosing regimen in the treatment of cSSTI.
- All Treated pool: all healthy volunteers, subjects, and patients who received at least one dose of oritavancin in the Phase 1, Phase 2, and Phase 3 clinical studies, including the 20 moderately hepatically-impaired subjects from the Phase 1 study.

The medical reviewer's review mainly focused on the results of the Phase 3 SOLO trials.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In the SOLO studies, patients received either a single 1200 mg oritavancin dose on Day 1 followed by placebo treatment or vancomycin (1 g or 15 mg/kg twice daily) for 7 to 10 days. In the SOLO pool, the median duration of treatment was 8 days in both the oritavancin/placebo and vancomycin groups. Mean cumulative dose (± SD) of oritavancin was 1198.1 mg (± 25.45) with a median of 1200 mg (range 660 to 1200 mg). Mean total daily dose in the vancomycin group was 2229.5 mg with a median of 2000 mg in SOLO I (range, 75 to 5183 mg) and 2131.1 mg with a median of 1954.9 mg (range, 105 to 5625 mg) in SOLO II; equivalent to a total dose of 1 g twice daily.

Table 40 Summary of Study Drug Administration- Safety population SOLO pool

Category	Oritavancin	Vancomycin
Overall Duration of Drug Exposure (days) [1]		
n	976	983
Mean (SD)	8.4(2.05)	8.2 (2.28)
Median	8.0	8.0
Q1,Q3	8.0,10.0	8.0, 10.0
Min, Max	1, 12	1, 11
Overall Duration of Drug Exposure (days) [1], n (%)		
1	13 (1.3)	17 (1.7)
2	17 (1.7)	25 (2.5)
3	14 (1.4)	22 (2.2)
4	19 (1.9)	20 (2.0)
5	9 (0.9)	16 (1.6)
6	8 (0.8)	14 (1.4)
7	77 (7.9)	93 (9.5)
8	447 (45.8)	414 (42.1)
9	62 (6.4)	56 (5.7)
10	146 (15.0)	112 (11.4)
>=11	164 (16.8)	194 (19.7)
Duration of Study Drug Infusion (days) [2]		
	976	983
Mean (SD)	1.0 (0.00)	8.2 (2.29)
Median	1.0	8.0
Q1, Q3	1.0, 1.0	8.0, 10.0
Min, Max	1,1	1,11

[1] Overall duration of drug exposure (days) = Date of last study drug IV/Oral – Date of first study drug IV/Oral + 1.
[2] Duration of study drug infusion (days) = Date of last study drug IV – Date of first study drug IV + 1.
Source: Applicant's Table 02.3.3.P4 of ISS

Medical reviewer comments: The extent and duration of exposure appears to be adequate to assess the safety of oritavancin.

Demographics of the SOLO pool are discussed in section 6.1.2 of the efficacy review. Most patients were male, white, and < 65 years. Disposition of the safety population is discussed in section 7.3.3 of the safety review.

7.2.2 Explorations for Dose Response

Nonclinical PD and PK/PD modeling evidence suggested that oritavancin's effect would be optimized by pooling rather than fractionating the cumulative dose. These properties supported the development of a single dose of 1200 mg regimen. Refer to section 6.1.8 of the efficacy review. In the phase 2 SIMPLIFI study, oritavancin was given as a single dose of 1200 mg or an infrequent dose of 800 mg with an optional 400 mg on Day 5 or a 200-mg daily dose for 3 to 7 days in the treatment of patients with complicated skin and skin structure infections. TEAEs were 56.0% in the daily dose, 55.6% in the single dose, and 61.2% in the infrequent dose groups. Three deaths occurred in the daily dose group, 0 in the single dose group and 2 in the infrequent dose group. The percentage of patients with an SAE was 8.3% (25/302), with 11.0% (11/100), 7.1% (7/99), and 6.8% (7/103) of patients having SAEs in the daily dose, single dose, and infrequent dose groups, respectively.

Medical reviewer comment: A dose dependant increase in incidence of AE was not seen in the SIMPLIFI study.

7.2.3 Special Animal and/or In Vitro Testing

The original clinical program for oritavancin involved a daily dosing regimen for multiple days. Therefore, the toxicology program was designed to support repeat dose administration so did not include an extensive investigation of single dose toxicity. However, studies involving daily administration for up to 13 weeks were conducted. These studies evaluated single-dose toxicity in rats, repeat-dose toxicity in rats and dogs, genotoxicity in Ames and chromosome aberration tests, an in vitro mouse lymphoma assay, and a mouse micronucleus test, reproductive and developmental toxicity in rats and rabbits, and because oritavancin accumulates in macrophages, a series of in vitro studies in macrophage cell lines and in vivo studies in rats were conducted to evaluate immune function. The safety margins for the SOLO I and II studies at the NOAEL doses in the pivotal 1 month toxicity studies based on cumulative exposures that range from 2.4 to 11.9 fold in rats and dogs, respectively. Cumulative exposure safety margins were achieved from the repeat dose studies and are multiples of the exposures achieved at the single 1200 mg dose proposed for use in ABSSSI in patients.

Oritavancin does not undergo metabolism and exhibits long tissue retention times in animals and humans.The primary adverse effect was the presence of eosinophilic granules in tissue macrophages throughout the body, including Kupffer cells of the liver, and macrophages of the intestinal mucosa, thymus, spleen, and lymph nodes. The appearance of the granules was most likely the result of oritavancin uptake by the macrophages. The eosinophilic granule containing macrophages were evident at all dose levels following two weeks of dosing and subsequent recovery periods. The eosinophilic granules were occasionally associated with mild inflammatory lesions, particularly in the liver. Increase in serum globulin, another indicator of

inflammation, was also noted in some rat studies. Eosinophilic granules did not develop following single dose administration by either IV bolus or slow infusion in rats.

The safety pharmacology program included a battery of in vitro and in vivo assays. Effects on the cardiovascular system were assessed in vitro by determining the cardiac ion channel blocking profile using cells expressing the hERG channel and isolated human cardiac myocytes as well as in in vivo studies conducted in rats and dogs. In addition, in vivo studies were conducted in mice and rats to determine effects of oritavancin on behavior, the CNS, gastrointestinal motility, and renal function. The results of the safety pharmacology studies did not indicate a safety risk for oritavancin use in humans.

A host resistance studied in rats showed a dose related increase in mortality to *C. albicans* infection (in the 5 and 15 mg/kg dose groups compared to the vehicle control group). It is unclear if the increased mortality was due to a direct effect on host resistance or an indirect effect of increased susceptibility to infection due to oritavancin-related general toxicity. Importantly, to assess the potential effect of oritavancin accumulation on macrophage function, the pivotal Phase 3 studies (SOLO 1 and 2) were designed to include a long period (60 days) of safety follow-up. The safety evaluations in the Infections and Infestations system organ class showed slight increase in the TEAE 4% in the oritavancin arm versus 3% in the vancomcyin arm without corresponding increase in fungal and mycobacterial infections.

MO comment: The non-clinical program appears adequate to explore potential targets of toxicity; however, an extensive investigation of single dose toxicity was not conducted.

7.2.4 Routine Clinical Testing

The schedule of clinical and laboratory assessments in phase 3 trials presented in section 6.1.1 appear adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

A comparison of the plasma concentrations of oritavancin to plasma radioequivalent concentrations of 14C-oritavancin suggested there were no circulating metabolites of oritavancin in the plasma in any species studied. Evaluation of bile from rats and dogs for metabolites provided no indication of metabolism. In vitro studies with monkey hepatic microsomes did not show any evidence that oritavancin is metabolized by the cytochrome P450 system. Mass balance studies in mice, rats and dogs indicate that the primary route of elimination of oritavancin is via bile into feces. There is considerable retention of oritavancin in tissues. In humans, oritavancin is slowly excreted unchanged in feces and urine with less than 1% and 5% of the dose recovered in feces and urine, respectively, after 2 weeks of collection. The mean terminal elimination plasma half-life of oritavancin is 245 hours (14.9% CV) based on population PK analysis of ABSSSI patients receiving a single 1200 mg dose. The population mean total clearance is estimated at 0.445 L/h (percent standard error of the mean, 1.95).

Drug Drug interaction analysis is discussed in section 7.5.5.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The following AEs were evaluated related to glycopeptide class effects: hypersensitivity, ototoxicity/vestibular toxicity, neutropenia, thrombocytopenia, and infusion site reactions/phlebitis. These AEs are discussed in section 7.4.5.

7.3 Major Safety Results

The overall incidence of TEAEs, SAEs, discontinuation of study drug due to TEAEs, and deaths in the individual and pooled Phase 3 SOLO trials is summarized in Table below.

Table 41: Overview of TEAEs (Safety Population) in the Phase 3 clinical trials

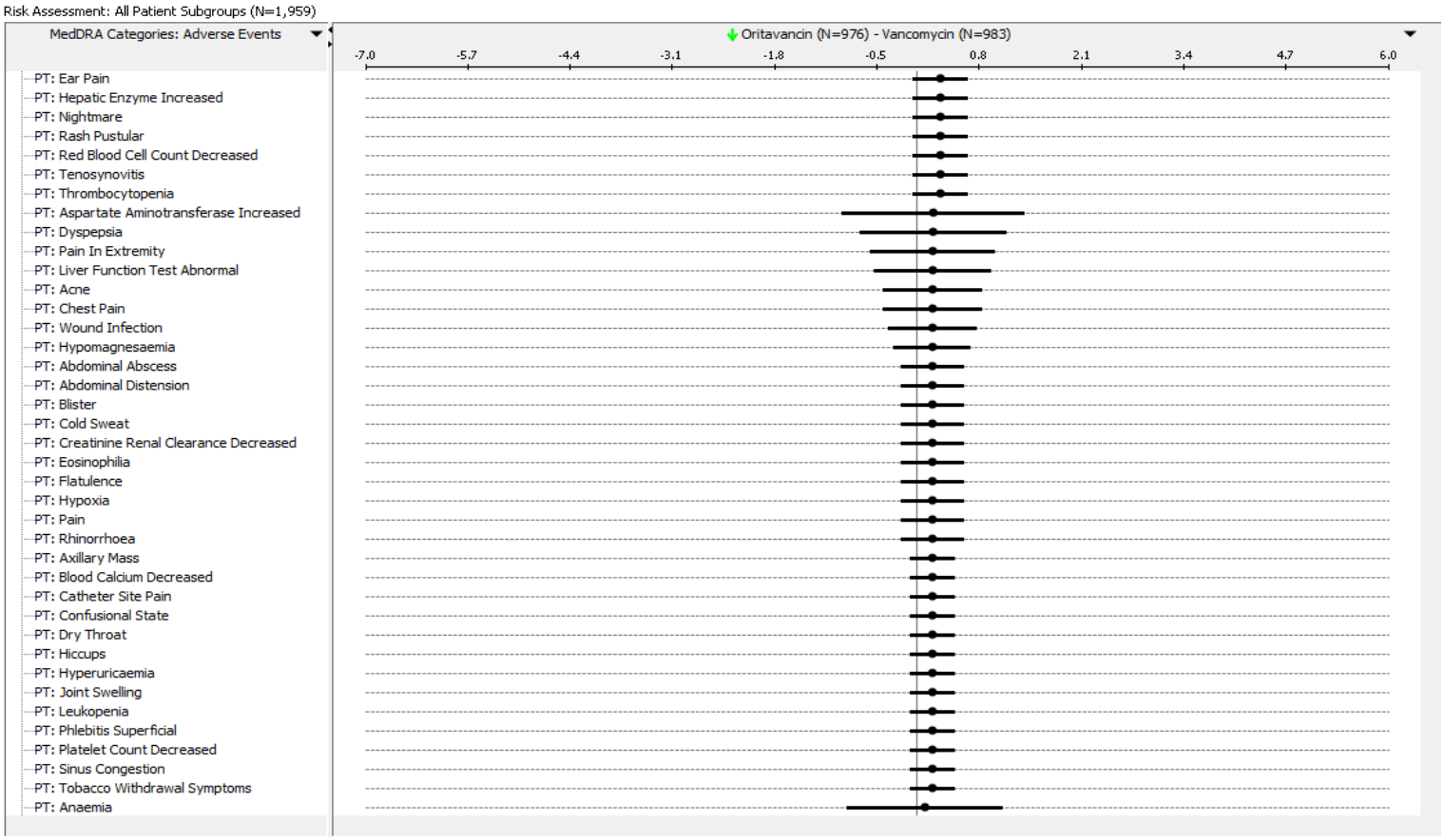
	SOLO pool		SOLO1			SOLO2		
Category	Oritavancin (N=976) n (%)	Vancomycin (N=983) n (%)	Oritavancin (N = 473) n (%)	Vancomycin (N = 481) n (%)	All Patients (N = 954) n (%)	Oritavancin (N = 503) n (%)	Vancomycin (N = 502) n (%)	All Patients (N = 1005) n (%)
No. of Patients with any AE	540 (55.3)	559 (56.9)	284 (60.0)	307 (63.8)	591 (61.9)	256 (50.9)	252 (50.2)	508 (50.5)
No. of Patients with any AE Leading to Study Drug Discontinuation	36 (3.7)	41 (4.2)	18 (3.8)	28 (5.8)	46 (4.8)	18 (3.6)	13 (2.6)	31 (4.5)
No. of Patients with any SAE	57 (5.8)	58 (5.9)	35 (7.4)	35 (7.3)	70 (7.3)	22 (4.4)	23 (4.6)	45 (4.5)
No. of Patients with any AE Leading to Death	2 (0.2)	3 (0.3)	1 (0.2)	2 (0.4)	3 (0.3)	1 (0.2)	1 (0.2)	2 (0.2)
Study drug-related AE			108 (22.8)	151 (31.4)	259 (27.1)	109 (21.7)	128 (25.5)	237 (23.6)

Source: Adapted from sponsor's table ISS page 50 and table 30 of CSR. Replicated by clinical reviewer.

MO Comment: Although minor differences exist in the percentage of patients with TEAE, SAE, AE leeding to discontinuation or death in the individual SOLO trials, the overall pooled results were similar in both arms.

The following Figure shows the risk difference per hundred of adverse events by Preferred term in descending order in the SOLO safety pool (n=1959). The most common adverse event was abscess limb. 44% of PT was missing in the oritavancin arm (429/976) vs 42.6% in the vancomycin arm (419/983). The risk difference less than 0.111 per hundred is not shown.

Figure 16: Risk difference per hundred of adverse events by Preferred term in descending order in the SOLO safety pool



7.3.1 Deaths

From the medical reviewer's safety analysis of deaths for previous NDA by Dr. Moledina, dated December 1, 2008, a total of 74 deaths (66 during study and 8 post study) occurred among oritavancin-and vancomycin-treated patients in the combined phase 3 cSSSI and phase 2 trial populations. Two of the 74 (2.7%) deaths were investigator-assessed as related to study drug. One, multiple organ failure, occurred post study in an oritavancin-treated patient and the other, ventricular fibrillation, occurred during study in vancomycin-treated patient. Overall, the vast majority of deaths were found to be related to the underlying medical conditions of the patients. In study ARRI, there were 16 oritavancin-treated patients and 9 vancomycin-treated patients who died. In study ARRD, there were 7 deaths in oritavancin-treated patients and 5 deaths in vancomycin treated patients.

In the SOLO pool, 5 patients: 2/976 (0.2%) in the oritavancin group and 3/983 (0.3%) in the vancomycin group, died. The causes of death were sepsis and electromechanical dissociation in the oritavancin group and septic shock, acute myocardial infarction, and dementia with Parkinsonism in the vancomycin group. None of these deaths were considered related to study drug by the investigator. There were 5/302 (1.7%) deaths in the phase 2 SIMPLIFI study 3 in the daily dose and 2 in the infrequent dose group. Further discussion of the cases of deaths in SOLO and SIMPLIFI tials are presented in table below.

Per sponsor, the higher incidence of death in the All Treated pool compared to the SOLO pool was due to the higher mortality rate observed in the bacteremia trials (oritavancin, 23.9% [27/113 patients]; comparator, 24.3% [9/37patients]), compared to ARRD/ARRI (oritavancin, 1.6% [20/1173 patients]; vancomycin, 2.0% [12/590 patients]) and SIMPLIFI (oritavancin, 1.7% [5/302 patients: 3 in daily dose and 2 in infrequent dose groups]).

MO comment: The sponsor reported 20 deaths in the oritavavncin arm and 12 deaths in the vancomycin arm in the ARRD/ARRI study however the Agency's previous analysis of study ARRD/ARRI showed 23 deaths/1173 (1.9%) in the oritavancin arm and 14 deaths/590 (2.3%) in the vancomycin group.

Table 42: Cases of death in the SOLO/SIMPLIFI trials

Patient ID/ Age/ Gender/ Treatment	**Cause of Death**	**Study day of Death (days)**	**Association with Study Drug Investigator/ Medical reviewer comments**	**Brief narrative**
SOLO1 101001026 53/M Vancomycin	Septic shock	(b) (6)	Not related/ *In this case death was likely related to the comorbidities and unlikely due to the study drug*	53-year-old man with hepatitis C, Intravenous drug use, cirrhosis received vancomycin for a right hand and lower arm wound infection. Forty-four days after the last dose of vancomycin, the patient experienced septic shock. The patient suffered cardiac arrest and died of septic shock (b) (6) days later. The diagnoses at the time of death included septic shock, community acquired pneumonia, acute renal failure, hyperkalemia, cirrhosis, hepatitis C, poly substance abuse, chronic obstructive pulmonary disorder, and metabolic lactic acidosis. Patient was noted to have *Streptococcus pneumoniae* with *Clostridium perfringens* bacteremia.
SOLO1 101007001 47/F Oritavancin	Sepsis		Not related/ *Not related to the study drug. Remote possibility of selection of Gram negative organisms exists.*	47-year-old woman with history of diabetes, congestive heart failure, known ECG abnormalities, received a single infusion of oritavancin for right lower leg cellulitis. The day of oritavancin infusion she experienced excessive shortness of breath and wheezing, urinary tract infection, abnormal electrocardiogram (ECG) and increased lethargy. The placebo infusions were continued and she improved. (b) (6) days after the single dose of oritavancin, the patient was hospitalized for severe multi-lobar pneumonia with extended spectrum beta-lactamase bacteremia. The patient expired on the same day. The immediate cause of death was sepsis as a consequence of multi-lobar pneumonia.

Patient ID/ Age/ Gender/ Treatment	Cause of Death	Study day of Death (days)	Association with Study Drug Investigator/ Medical reviewer comments	Brief narrative
SOLO1 101027027 93/M Vancomycin	Advanced dementia with Parkinsonism	(b) (6)	Not related/ *Not related, likely death occurred secondary to underlying disease*	93-year-old male with history of Parkinson's dementia, acute delirium, psychosis, acute encephalopathy received 7 days of vancomycin for lower leg cellulitis. On Day 2 of dosing, the patient experienced mental status changes. Seventeen days after the last dose of study drug, he experienced moderate events of congestive heart failure, atrial fibrillation, hematuria, and dehydration. (b) (6) days after the last dose of study drug, the patient was hospitalized because of severe advanced dementia with Parkinsonism, vomiting, gross hematuria, anemia, and acute renal failure. He was discharged to a nursing facility on hospice care. (b) (6) days from the last dose of study drug, the patient reportedly died from advanced dementia with Parkinsonism.
SOLO2 201001019 58/F Oritavancin	Electromechanical dissociation		Not related/ *Not related, likely death occurred as a consequence of the underlying valvular disease and end stage liver disease*	58-year-old female with history of congestive heart failure, heart murmur, hypertension, IV drug use, hepatitis C, end-stage liver disease, vancomycin-resistant enterococcus osteomyelitis, MRSA, severe aortic stenosis received oritavancin for a wound infection of the right knee. An echocardiogram 3 days after the oritavancin dose showed a 20% to 25% ejection fraction, severe aortic stenosis, and pulmonary hypertension. (b) (6) days after oritavancin administration, the patient was hospitalized with altered mental status after a fall. The change in mental status was thought to be due to opiates. She developed decompensated liver failure and worsening left ventricular function and valvular heart disease. She was not a candidate for valvuloplasty. Subsequently she went into cardiogenic shock with concern for sepsis -MSSA in sputum; Escherichia coli in her peritoneal fluid; and MSSA/enterobacter in her right foot wound. The patient experienced electromechanical dissociation (b) (6) after the single dose of oritavancin.
SOLO2 207005003 68/F Vancomycin	Acute myocardial infarction		Not related/ Not related	68 yr old female with history of previous myocardial infarction, congestive heart failure, diabetes mellitus, hepatitis, ischemic heart disease, who received vancomycin over a 10-day period for cellulitis/erysipelas of the right lower leg. (b) (6) days after the last dose of vancomycin, the patient was hospitalized for trophic ulcers of the right lower leg. She had leukocytosis of 20.0 x 10^9/L. She was treated with IV cefoperazone/sulbactam for (b) days. There was insignificant improvement in the ABSSSI, but the ulcers remained. The outcome of the event was reported as not resolving. The patient experienced sudden death from an acute second myocardial infarction (b) (6) days after the last dose of vancomycin.
SIMPLIFI				

Patient ID/ Age/ Gender/ Treatment	Cause of Death	Study day of Death (days)	Association with Study Drug Investigator/ Medical reviewer comments	Brief narrative
SD001-103-07 74/F Oritavancin	Pulmonary embolism	(b) (6)	Not related/ Not related	A 74-year-old female, with history of deep vein thrombosis, coronary artery disease, and pulmonary embolism underwent a laminectomy complicated by a postsurgical wound infection. Incision and debridement of the back wound was performed. She received 800mg of oritavancin intravenously for the back wound infection. During the first infusion of study drug the patient experienced moderate chest pain which was treated by stopping the infusion and oxygen .The adverse event resolved, and the infusion was restarted with no additional events. The study drug was discontinued on Day (b) (6) She was discharged home on oral levofloxacin. On Day (b the patient developed sudden onset of chest pain and bradycardia and went into asystole. The treating emergency room physician's documented opinion was that this event was the result of a massive pulmonary embolism.
SD001-112-06 73/F Oritavancin	Septic shock		Not related/ *Likely unrelated to the study drug given she had several risk factors for developing a myocardial infarction. However it is possible that she had a relapse of her infection after improvement leading to sepsis.*	73-year-old female with history of coronary artery disease, hypertension, congestive heart failure, diabetes mellitus, asthma, and cardiomyopathy developed *S. aureus* wound infection of the left foot. The patient received 200 mg of oritavancin intravenous from Day1 to Day 5.The patient also received piperacillin/tazobactam and vancomycin on Day 1.The investigator defined clinical outcome was improvement on Day 6. On Day (b) (6) the patient presented to the emergency room with severe respiratory distress, severe respiratory acidosis, and moderate hypotension, change in mental status and hypothermia. The patient had a significant lower left leg infection and bilateral cellulitis and was thought to be in septic shock with severe myocardial infarction with elevated cardiac enzymes. On Day (b) (6) the patient died.
SD001-251-02 68/F Oritavancin	Cardiopulmonary failure		Not related/ Not related	68-year-old female with cellulitis of the left lower leg received 200 mg of oritavancin from Day 1 to Day 7 The investigator-defined clinical outcome on Day 8 was improvement. On Day (b) (6) the patient developed cough, breathlessness and had one episode of vomiting. Severe atrial fibrillation was noted. On day (b) (6) she died of cardiopulmonary failure. The cause of death was reported to be atrial fibrillation with rapid ventricular rate with congestive cardiac failure with Type I respiratory failure.
SD001-252-12 47/M Oritavancin	Cardiac arrest		Not related/ Not related	47-year-old male, had cellulitis of the leg received 200 mg of oritavancin daily from Day 1 to Day 5. On Day (b acute respiratory distress syndrome (moderate) was reported. The severe respiratory distress with acidosis, severe sepsis and fever due *to Pseudomonas putida* infection ensued. Patient died on day (b) (6)

Patient ID/ Age/ Gender/ Treatment	Cause of Death	Study day of Death (days)	Association with Study Drug Investigator/ Medical reviewer comments	Brief narrative
SD001-254-09 38/M Oritavancin	Myocardial infarction	(b) (6)	Not related/ Not related His episode of hypoglycemia could be secondary to his development of renal impairment on metformin	38-year-old diabetic male with history of smoking for 20 years, received 800 mg of oritavancin on Day 1 and 400 mg of oritavancin on Day 5 for a right leg wound infection. The patient subsequently developed hypoglycemia, chest discomfort, shortness of breath and into cardiopulmonary arrest (day (b) (6) Of note, the patient developed moderate renal impairment on day 6 while on metforminThe investigator reported that the cause of death as myocardial infarction and this diagnosis was made clinically.

7.3.2 Nonfatal Serious Adverse Events

In the SOLO1 trial, treatment emergent SAEs were found most commonly in the MedDRA system organ class (SOC) of Infections and infestations. About 4.4% of subjects in the oritavancin arm and 3.74% in the vancomycin arm had Treatment emergent SAE in Infections and infestations SOC, followed by Respiratory, thoracic and mediastinal disorders SOC (0.85% oritavancin arm vs 0.62 in vancomycin arm). In the SOLO2 trial, treatment emergent SAEs were found most commonly in the MedDRA system organ class (SOC) of Infections and infestations. About 2.78% of subjects in the oritavancin arm and 1.99% in the vancomycin arm had Treatment emergent SAE in Infections and infestations SOC, followed by Skin and subcutaneous tissue disorders SOC (0.4% oritavancin arm vs 0.2 in vancomycin arm)

For the pooled SOLO trials, the Table below shows the incidence of Treatment emergent SAE by SOCs and PT. The highest incidence of serious TEAE occurred in the Infection and Infestation SOC 4% in the oritavancin arm versus 3 % in the vancomycin arm.

Table 43: Incidence of Treatment emergent SAE by selected SOCs and PT in Pooled SOLO trials

Body organ system class SOC Dictionary-Derived Term	Oritavancin N=976	Vancomycin N=983
Number of patients with ≥ 1serious TEAE	57(5.8%)	58(5.9%)
Infections and infestations	**40(4.08%)**	**31(3.14%)**
Osteomyelitis	4 (0.4%)	1(0.10%)
Abscess Bacterial	0(0.00%)	1(0.10%)
Sepsis	1(0.10%)	1(0.10%)
Septic Shock	0(0.00%)	1(0.10%)
Skin Bacterial Infection	0(0.00%)	3 (0.31%)
Necrotising Fasciitis	1 (0.10%)	1 (0.10%)
Subcutaneous abscess	3 (0.31%)	1 (0.10%)
Bacteremia	1 (0.10%)	0 (0.00%)
Bronchitis	1 (0.10%)	0 (0.00%)
Abscess limb	3 (0.31%)	0 (0.00%)
Lower respiratory tract infection	0 (0.00%)	1 (0.10%)
Abscess	1 (0.10%)	1 (0.10%)
Athritis bacterial	1 (0.10%)	2 (0.20%)
Extradural abscess	0 (0.00%)	1 (0.10%)

Body organ system class SOC **Dictionary-Derived Term**	**Oritavancin** **N=976**	**Vancomycin** **N=983**
Skin infection	3 (0.31%)	3 (0.31%)
Cellulitis	11 (1.13%)	12 (1.22%)
Postoperative wound infection	0 (0.00%)	1 (0.10%)
Intervertebral discitis	0 (0.00%)	1 (0.10%)
Diverticulitis	1 (0.10%)	0 (0.00%)
Gangrene	1 (0.10%)	0 (0.00%)
Infection	1 (0.10%)	0 (0.00%)
Periorbital abscess	1 (0.10%)	0 (0.00%)
Wound infection staphylococcal	1 (0.10%)	0 (0.00%)
Wound infection	1 (0.10%)	0 (0.00%)
Urosepsis	1 (0.10%)	0 (0.00%)
Pneumonia	3 (0.31%)	0 (0.00%)
Skin and subcutaneous tissue disorders	**4(0.4%)**	**1(0.1%)**
Stasis dermatitis	1 (0.10%)	0 (0.00%)
Skin ulcer	0 (0.00%)	1 (0.10%)
Urticaria	1 (0.10%)	0 (0.00%)
Angioedema	1 (0.10%)	0 (0.00%)
Leukocytoclastic vasculitis	1 (0.10%)	0 (0.00%)
Musculoskeletal and connective tissue disorders	**2 (0.20%)**	**0 (0.00%)**
Tenosynovitis	2 (0.20%)	0 (0.00%)
Cardiac disorders	**3(0.3%)**	**6(0.6%)**
Acute myocardial infarction	0 (0.00%)	2 (0.20%)
Atrial thrombosis	0 (0.00%)	1 (0.10%)
Cardiac failure congestive	1 (0.10%)	1 (0.10%)
Cardio-respiratory arrest	0 (0.00%)	1 (0.10%)
Myocardial ischaemia	0 (0.00%)	1 (0.10%)
Ventricular tachycardia	1 (0.10%)	0 (0.00%)
Electromechanical dissociation	1 (0.10%)	0 (0.00%)
Gastrointestinal disorders	**3(0.3%)**	**2(0.2%)**
Constipation	0 (0.00%)	1 (0.10%)
Rectal haemorrhage	1 (0.10%)	0 (0.00%)
Mouth ulceration	1 (0.10%)	0 (0.00%)
Abdominal pain	1 (0.10%)	0 (0.00%)
Oesophagitis	0 (0.00%)	1 (0.10%)
General disorders and administration site conditions	**2(0.2%)**	**3(0.3%)**
Asthenia	1 (0.10%)	0 (0.00%)
Chest pain	1 (0.10%)	0 (0.00%)
Infusion site thrombosis	0 (0.00%)	1 (0.10%)
Pyrexia	0 (0.00%)	2 (0.20%)
Hepatobiliary disorders	**1 (0.10%)**	**0 (0.00%)**
Gallbladder disorder	1 (0.10%)	0 (0.00%)
Immune system disorders	**1(0.10%)**	**5(0.5%)**
Serum sickness-like reaction	0 (0.00%)	1 (0.10%)
Hypersensitivity	0 (0.00%)	1 (0.10%)
Anaphylactoid reaction	0 (0.00%)	2 (0.20%)
Drug hypersensitivity	1 (0.10%)	1 (0.10%)
Metabolism and nutrition disorders	**3(0.3%)**	**5(0.5%)**
Dehydration	0 (0.00%)	1 (0.10%)
Diabetic foot	0 (0.00%)	1 (0.10%)

Body organ system class SOC **Dictionary-Derived Term**	**Oritavancin N=976**	**Vancomycin N=983**
Diabetic ketoacidosis	2 (0.20%)	1 (0.10%)
Hyponatraemia	0 (0.00%)	1 (0.10%)
Metabolic acidosis	0 (0.00%)	1 (0.10%)
Hyperglycaemia	1 (0.10%)	0 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0 (0.00%)**	**1 (0.10%)**
Fibrosarcoma	0 (0.00%)	1 (0.10%)
Nervous system disorders	**2(0.2%)**	**4(0.4%)**
Diabetic neuropathy	1 (0.10%)	0 (0.00%)
Headache	0 (0.00%)	2 (0.20%)
Dementia	0 (0.00%)	1 (0.10%)
Convulsion	1 (0.10%)	1 (0.10%)
Psychiatric disorders	**2(0.2%)**	**3(0.3%)**
Psychotic disorder	0 (0.00%)	1 (0.10%)
Bipolar disorder	1 (0.10%)	0 (0.00%)
Suicidal ideation	1 (0.10%)	1 (0.10%)
Suicide attempt	0 (0.00%)	1 (0.10%)
Renal and urinary disorders	**0 (0.00%)**	**1 (0.10%)**
Renal failure	0 (0.00%)	1 (0.10%)
Respiratory, thoracic and mediastinal disorders	**6(0.6%)**	**6(0.6%)**
Dyspnoea	1 (0.10%)	2 (0.20%)
Hypoxia	2 (0.20%)	1 (0.10%)
Pulmonary embolism	0 (0.00%)	1 (0.10%)
Respiratory failure	0 (0.00%)	2 (0.20%)
Pneumonia aspiration	1 (0.10%)	0 (0.00%)
Bronchospasm	1 (0.10%)	0 (0.00%)
Asthma	1 (0.10%)	0 (0.00%)
Vascular disorders	**2(0.2%)**	**3(0.3%)**
Deep vein thrombosis	1(0.10%)	2 (0.20%)
Phlebitis	0 (0.00%)	1 (0.10%)
Peripheral vascular disorder	1 (0.10%)	0 (0.00%)

The clinically important cases of osteomyelitis, cellulitis, and abscess (Infections and Infestations SOC) are discussed below.

Discussion of the cases of osteomyelitis:

- TMC 10-02 201012-001

A 52-year-old woman with insulin dependent diabetes mellitus, coronary artery disease, triple by-pass surgery (b) (6) chronic renal insufficiency and chronic obstructive pulmonary disease , hypertension, hyperlipidemia, right tibial fracture with plate insertion (b) (6) received a single infusion of oritavancin and 5 subsequent infusions of placebo over a 4-day period for lower leg cellulitis with fever. She experienced osteomyelitis on study day 3, chest pain on study day 15, and bronchitis on day 38. Her CRP was 272 mg/L, elevated, on the day of oritavancin infusion, and she was bacteremic. On day 3 she went on to develop an abscess on her knee requiring incision & drainage and removal of tibial hardware. The study drug was discontinued on the same day.

MO comment: The medical reviewer believes that the patient was at significant risk for coronary artery disease with her underlying disease likely contributing to the onset of chest pain. She developed acute bronchitis with bronchospasm at Day (b)(6) requiring a (b)(6) day hospitalization. Her history of COPD, her symptoms of green sputum with fevers are more suggestive of an acute infection rather than drug induced bronchospasm. The osteomyelitis with hardware infection was likely present at screening and the cellulitis was an early indication of the underlying infection. The case was classified as failure at ECE per sponsor.

- TMC 10-02 202001-003

A 51 year old woman with acquired immunodeficiency syndrome (HIV), IV drug use received a single infusion of oritavancin on (b)(6) for a lower leg abscess. She had a negative bone scan 7 days later. However 9 days after receiving oritavancin, she was diagnosed with osteomyelitis requiring treatment with linezolid and subsequently recovered. The investigator considered the osteomyelitis to be unlikely related to oritavancin.

MO comment: In the opinion of the medical reviewer, occurrence of osteomyelitis after 9 days of study drug is concerning for progression of infection and suggests lack of efficacy. The medical reviewer notes that the case was classified by the applicant as success at ECE, failure for the rest of the efficacy time points.

- TMC 10-02 202001-012

A 73-year-old man with neuropathy, vasculopathy, glucose intolerance received oritavancin and placebo over a 2-day period for lower leg and foot cellulitis and experienced left foot osteomyelitis 1 day after oritavancin infusion. Treatment was discontinued. Imaging showed septic arthritis and joint abscess in the metatarsophalangeal joint resulting in debridement and revascularization. Patient recovered. The investigator considered the osteomyelitis to be unrelated to oritavancin and possibility of misdiagnosed osteomyelitis at screening.

MO comment: The medical reviewer agrees with the investigator assessment.

- TMC 10-02- 207004-021

A 45-year-old man with insulin dependent diabetes mellitus, diabetic neuropathy received a single infusion of oritavancin on and 13 subsequent infusions of placebo over an 8-day period for a right foot abscess and experienced osteomyelitis on Day 7 of blinded study therapy. There were no signs of bacteremia or osteomyelitis at screening. He was diagnosed with osteomyelitis of the proximal phalanges of the third and fourth toes. Treatment included amputation of the toes, IV ciprofloxacin, and oral metronidazole. The investigator considered the osteomyelitis to be unrelated to oritavancin and considered progressive disease to be a contributing factor to the event.

MO comment: In the opinion of the medical reviewer, the case could suggest lack of efficacy of oritavancin given the progression of infection or a failure of treatment due to the lack of early incision and drainage of the abscess. The case was classified as success at ECE and sustained lesion area decrease at PTE classified as cure.

- TMC-10-01-101010002

A 50-year-old man, received 5 days of vancomycin for a lower leg wound infection. 3 days after starting vancomycin infusion, the patient presented with lower leg pain. A magnetic resonance imaging on that day showed osteomyelitis in the vicinity of the medial malleolus of the distal left tibia. Study treatment was discontinued due to the osteomyelitis event. 80 days after the last dose of vancomycin, the osteomyelitis was considered resolved. The investigator considered the osteomyelitis to be unlikely related to vancomycin but related to the patient's underlying disease.

MO comment: In the opinion of the medical reviewer, the case could suggest lack of efficacy of vancomycin given the progression of infection or failure to recognize underlying osteomyelitis at screening. The case was classified by the applicant as success at ECE, then failure at subsequent visits.

MO comment: Overall the TEAE of osteomyelitis suggest a lack of efficacy due to progression of theoriginal infection or failure of recognition at screening. The incidence is slightly higher (0.4% vs 0.1%) in the oritavancin arm versus the vancomycin arm but have different time to event on study drug.

MO comment: An additional case of osteomyelitis was noted from the CRF and narrative in SOLO1. Subject 101001-042 was a 59-year-old man, who received oritavancin/placebo over a 3-day period for a major cutaneous abscess of the right upper arm and elbow. The patient was discontinued from oritavancin due to osteomyelitis of the elbow (index site of infection) 1 day after the single dose of oritavancin. The osteomyelitis AE was considered as nonserious and of moderate intensity.The investigator described osteomyelitis as not related to oritavancin. This case suggests failure to recognize underlying osteomyelitis at screening.

The following TEAE of subcutaneous abscess were noted in cases TMC ORI 10-1-101002-076, 101003-006, and 101005-014.

- TMC ORI 10-1-101002-076

A 33-year-old woman received oritavancin /placebo over an 8-day period for mons pubis cellulitis. 9 days after the single dose of oritavancin she developed a mons pubis abscess which was initially treated with oral antimicrobials then later progressed to require drainage. The investigator felt this was unrelated to oritavavncin.

MO comment: In the opinion of the medical reviewer, onset of the event while on study treatment could suggest decreased efficacy of study drug given the time of occurrence and the location of the abscess at the original site of cellulitis.

- TMC ORI-10-1- 101003-006

A 31-year-old man received a single infusion of oritavancin /placebo over a 10-day period for upper and lower arm cellulitis/erysipelas and experienced progression of axillary abscess 8 days after the single dose of oritavancin. 5 days after the single dose of oritavancin, right arm erythema worsened and followed by the development of abscess seen on MRI. He was treated with IV daptomycin and drainage of the abscess. Although wound culture showed rare Gram

negative rods, the abscess resolved with drainage and daptomycin. The investigator felt abscess was unrelated to oritavavncin.
MO comment" In the opinion of the medical reviewer, this demonstrates a progression of the cellulitis and suggests decreased efficacy of study drug given the onset of the event and the location of the abscess at the original site of infection . The case was classified by the applicant as success at ECE and success for lesion area decrease in PTE.

- TMC ORI-10-1- 101005-014

A 44-year-old man with hidradenitis suppurativa received a single infusion of oritavancin and 10 subsequent infusions of placebo over a 6-day period for the left finger MRSA cellulitis and experienced a subcutaneous buttock abscess on study day 5. The MRSA buttock abscess developed from the small pustule present at screening which the patient failed to report. The abscess was drained and treated. 55 days after the single dose of oritavancin, he reported the development of 6 additional abscesses to his buttocks in the perianal area and scrotum. These were drained and treated with IV vancomycin. On study day 59 a left infra-gluteal abscess and a day later a left medial thigh abscess were observed. The investigator considered the first subcutaneous abscess event as unlikely related to oritavancin, and the second subcutaneous abscess event as unrelated to oritavancin.

MO comment: In the opinion of the medical reviewer, this could suggest decreased efficacy of study drug given it failed to treat the early buttock pustule which has been present at screening. Although the intent of oritavancin was to treat the mrsa finger cellulitis, we would expect it to treat the buttock pustule due to MRSA. The other abscess is likely not related to oritavancin given the patient's history of hidradenitis suppurativa and the predisposition to develop multiple abscesses. The case was classified as success at ECE by the applicant.

Vancomycin arm:

- A 57-year-old woman, with diabetes, received vancomycin for a major cutaneous abscess on the upper arm developed subcutaneous abscess 6 days after starting vancomycin infusion. She presented with foul-smelling, purulent drainage to her left axilla and an indurated area on the anterior chest wall. She was treated with trimethoprim/sulfamethoxazole.

Abscess limb

- TMC ORI-10-1-101001-113

A 53-year-old man with HIV, MRSA, received a single infusion of oritavancin on (b) (6) and 1 subsequent infusion of placebo over a 2-day period for right knee cellulitis/erysipelas that progressed to abscess of the right knee 5 days after the single dose of oritavancin. Study drug was withdrawn due to noncompliance with protocol. His knee abscess was drained and treated. The investigator assessed the abscess limb as unlikely related to the oritavancin.

MO comment: In the opinion of the medical reviewer, this suggests lack of efficacy of the study drug as it failed to prevent progression of the disease. The case was classified as missing as ECE, clinical cure at investigator assessed clinical cure at PTE.

- TMC ORI-10-1-101045-003

A 40-year-old woman recurrent staphylococcal abscesses positive for MRSA, received a single infusion of oritavancin on and 19 subsequent infusions of placebo over an 11-day period for a lower leg cellulitis/erysipelas and experienced *Pseudomonas* bacteremia due to picc catheter 8 days after the single dose of oritavancin. Her right knee MRSA infection resolved and there was no draining fluid. She had another small pustule on the right gluteal area and one on the left axilla.
The medical reviewer agrees that the bacteremia is not drug related. The additional pustules noted could possibly suggest decreased efficacy; however, most likely they were new given the history of recurrent abscesses and the time lapsed since the study drug dicontinuation. The case was classified as success at ECE by the applicant.

Cellulitis:

The case 201002-110 in SOLO2 of **i**nfection was assessed by the medical reviewer as a case of decreased efficacy. Two days after oritavancin progression of left ear cellulitis and the development of abscess despite initial incision and drainage were noted.

Abscess limb: Case 101019-005, a diabetic host developed abscess in the leg 13 days after oritavancin for a distal abscess. The investigator thought this was recurrence due to constant weight bearing.

MO comment: Although the recurrence of abscess is at a more proximal site, relapsed infection could be a possibility.

Additional cases in both oritavancin and vancomycin arm were selected from the Infection and Infestation SOC TESAE of pooled SOLO trials of as having ABSSSI or ABSSSI related complication. The PTs were cellulitis, osteomyelitis, Abscess bacterial, Sepsis, Sepsis shock, Skin bacterial infection, necrotizing fasciitis, Subcutaneous abscess, bacteremia, abscess limb, Abscess, Arthritis bacterial, extradural abscess, skin infection, postoperative wound infection, staphylococcal wound infection, intervertebral discitis, wound infection, infection, periorbital abscess, staphylococcal wound infection, tenosynovitis.
The cases were also reviewed to determine if there was failure of efficacy or recurrence of the index infection. For this purpose, the cases with SAE where the infection was determined not to be directly resulting from a progression of the index ABSSSI being treated were excluded.
11 cases of cellulitis in the oritavancin arm, as SAE were reviewed by the medical reviewer. 5 cases were found in SOLO1 and 6 in SOLO 2. Of these cases, 101002081, 101002-094, 101043-003, 10-01-101003-033, 201034-003, 201034-018 suggest lack of efficacy of oritavancin in the infection under study. Subjects 101002-094 and 101043-003 developed abscesses and it is possible that the infection needed incision and drainage for cure. In all these cases, infection

progressed on average in 2.8 days. The infections that progressed while on treatement did not have a particular body site or pathogen predilection.

MO comment: Upon review of the cases the applicant appropriately classified the efficacy outcomes as failures at the assessment visit, One subject determined by the medical reviewer to have lack of efficacy at in the oritavancin group was counted as success at ECE but failure at day 10 which is appropriate. One subject in vancomycin arm similarly was counted by the applicant as success at ECE, EOT, and PTE. The medical reviewer, therefore, did not conduct further sensitivity analyses.Overall the occurrence of cellulitis appeared to be well balanced between both arms.

Table 44: Subjects in the pooled SOLO trials as having ABSSSI or ABSSSI related complication

Patient ID / Study Drug	Days on Study Drug	Study Day of event	Event Description/location of ABSSSI	Organism	Relationship to study drug: Investigator/ Reviewer comment	Sponsor 's efficacy at ECE
10-01-101002-081 Oritavancin	5	5	Progression of the left anterior shin cellulitis	MRSA	Not related/ *failure of efficacy*	Failure
10-01-101002-094 Oritavancin	2	1	Worsening submandibular cellulitis		Not related/ *failure of efficacy*	Missing
10-01-101003-033 Oritavancin	4	D3 and D52	Worsening periorbital abscess, then right leg cellulitis in setting of MRSA and history of prior abscesses	MRSA,	Not related/ *failure of efficacy*	Failure
10-01-101015-002 Oritavancin	7	16	Progression of right LE cellulitis		Not related/*recurrent cellulitis secondary to underlying PVD, doubt failure of efficacy*	Failure
101043-003 Oritavancin	7	6	Progression of hand cellulitis to hand and wrist abscess requiring I & D		Not related/ *failure of efficacy*	Success at ECE, failure at D10
10-02-201001-032 Oritavancin	11	26	Lower leg cellulitis-index infection developed abdominal wall cellulitis		Not related/ *cellulitis of abdominal wall related to paracentesis*	
10-02-201001072 Oritavancin	8	32	Lower arm cellulitis-index infection, developed lower extremity cellulitis		Not related/*Likely recurrent infection due to history of MRSA recurrent abscess*	
10-02-201002-080 Oritavancin	8	11	Rt hip wound infection-index infection, developed lower left leg cellulitis		Not related/*Recurrent cellulitis due to IV DU*	Success at ECE
10-02-201034-003 Oritavancin	3	2	Worsening Upper arm and chest wall cellulitis		Not related/*failure of efficacy*	Failure
10-02-201034-018 Oritavancin	3	2	Worsening lower arm cellulitis	Gr A streptococcus	Not related/*failure of efficacy. Although Group A streptococcus could be rapidly progressively would classify as lack of efficacy as oritavancin should have activity for GAS*	Failure

Patient ID / Study Drug	Days on Study Drug	Study Day of event	Event Description/location of ABSSSI	Organism	Relationship to study drug: Investigator/ Reviewer comment	Sponsor 's efficacy at ECE
10-02-297001-010 Oritavancin	9	D19, D 62	Recurrent left leg cellulitis, then wound infection same location later	MRSA	Not related/ *recurrent cellulitis due to venous insufficiency*	
10-01-101001-029 Vancomycin	10	D14, D55	Recurrent right lower extremity cellulitis, myositis, abscess	S. aureus, Pseudomonas	Not related/*second episode of cellulitis resolved with treatment with vancomycin therefore doubt lack of efficacy*	Success
10-01-101001-065 Vancomycin	4	4	Left foot cellulitis/erysipelas		Not related/*Lack of efficacy*	Failure
10-01-101002-035 Vancomycin	11	32	Progression of the index infection-cellulitis right foot with osteomyelitis , requiring amputation of foot	Gr B streptococcus and Strep anginosus	Not related/*Lack of efficacy*	Success
10-01-101002072 Vancomycin	2	2	Major cutaneous abscess of rt groin, experienced worsening cellulitis same location	MRSA	Not related/ *failure of efficacy*	Missing
10-01-101014004 Vancomycin	8	D47, D51	Worsening Rt hip abscess-index infection, then lt ankle cellulitis	Klebsiella pneumonia	Not related/*Failure due to gram negative organism*	
10-01-101019006 Vancomycin	8	55	cutaneous abscess of the buttock- index infection, developed leg cellulitis		Not related/*Not related since different sites*	
10-01-101027033 Vancomycin	7	5	Worsening right lower extremity cellulitis)	Pseudomonas aeruginosa	Not related/*Failure due to gram negative organism*	
10-01-197002009 Vancomycin	11	43	Worsening Lower leg cellulitis/erysipelas		Not related/ *Not related as bilateral cellulitis*	
10-02-201001-118 Vancomcycin	10	25	Lower leg cellulitis/erysipelas-index infection, developed bursitis, septic arthritis knee	MSSA	Not related/*history of IVDU, venous insufficiency likely cause of recurrence*	Success
10-02-201002-093 Vancomcycin	1	8	Lower arm wound infection-index infection, developed Rt lower extremity cellulitis		Not related/*received only one dose of vancomycin so doubt failure of efficacy*	Missing
10-02-201034023 Vancomcycin	4	4	Worsening cellulitis of right knee		Not related/*failure of efficacy*	Failure
10-02-297001012 Vancomcycin	8	25	Recurrent cellulitis/erysipelas of the lower leg		Not related/*recurrence due to onycomycosis*	Success

MO comment: Subjects 101001001, 101001050,101001065, 101001101, 101002-072, 101002-086, 201001081, 201034007, 201034014, 201034023, 201035039 in the vancomycin arm and subjects 101002077, 101001-113, 101002094, 101002140, 101003-033, 101014006, 101043003, 201001069, 201001074, 201001107, 201002110, and 201034003 in the oritavancin arm with an AE related to an ABSSSI which lead to treatment discontinuation were treatment failures in the opinion of the medical reviewer. These cases have been reported to be unrelated to study drug.

Pneumonia

In the opinion of the medical reviewer, the cases of pneumonia were unrelated to oritavancin. The 3 cases in the oritavancin arm occurred 7 days, 38 days, and 19 days after oritavancin dose. Each had a risk factor for pneumonia based on their medical history.

The 2 cases of diabetes mellitus 101002-054 and 101019-005 were reviewed by the medical reviewer. Both subjects had a history of insulin dependent diabetes and event occurred 5 days in one subject and 59 days in another which is not suggestive of any specific temporal association with the drug. Given this is a once a day antimicrobial, challenge, dechallenge data is not applicable for determination of causal relationship of drug. The case of hyperglycemia 201002009 in SOLO2 also had insulin dependent diabetes and occurred 61 days later in setting of a shoulder abscess. This was unlikely to be related to oritavancin.

One case of tenosynovitis (subject TMC ORI- 10-02- 201001-074) suggest decreased efficacy per medical reviewer. A 26 yr old man received a single infusion of oritavancin and 5 subsequent infusions of placebo over a 4-day period for an upper leg abscess and experienced tenosynovitis of the left middle finger 3 days after the single dose of oritavancin requiring incision and drainage which grew MRSA.
MO comment: The case was appropriately classified as failure at ECE by the applicant.

The safety databases for trials TMC ORI 10-01 and TMC ORI-10-02 were explored by conducting standardized MedDRA queries. For SOLO1, this search identified a greater number of SAE serious adverse events in the narrow SMQ Asthma/bronchospasm in the oritavancin arm (3 events compared to 0 events in the vancomycin arm) and Hyperglycaemia/new onset diabetes mellitus narrow SMQ (2 events compared to1 event in vancomycin arm). A standardized MedDRA queries (broad SMQ) identified a greater number of SAE adverse events in the SMQ Eosinophilic pneumonia (7 events in oritavancin arm compared to 1 event in vancomycin arm) and broad SMQ of Gastrointestinal nonspecific inflammation and dysfunctional conditions (2 events compared with 0 events in vancomycin arm). The eosinophillic pneumonia SMQ included the subjects with Asthma, bronchospasm, hypoxia and pneumonia (101003034, 101007001, 101015003, 101016008, 101023016, 101025007). A review of the laboratory datasets did not reveal any evidence of eosinophilia in these subjects. Subject 101003034 had aspiration pneumonia 3 days after oritavancin unlikely related to study drug. Subject 101007001, a fatal case of sepsis and multilobar pneumonia, is described in the Deaths (7.3.1) section of the review. Case 101016008, a female with diabetes and COPD, developed pneumonia 7 days after oritavancin, likely unrelated to the study drug. Case 101025007 had hypoxia 19 days after oritavavncin likely due to underlying COPD. There were 2 subjects with gastrointesintinal nonspecific inflammation 101002046 and 101015003. Case 101002046, an 86 year old man with history of diabetes, prostate cancer post radiation treatment, developed diverticulitis (b) (6) days after oritavancin. His age and underlying diseases are likely contributory factors to the development of diverticulitis. Case 101002046, a 48 year old female with diabetes mellitus, developed gallbladder disease requiring cholecystectomy (b) (6) days after oritavancin. Although,the medical reviewer considers this to be unrelated as oritavancin, a possibility of drug induced cholestasis cannot be fully excluded.

For SOLO2, this search identified a greater number of SAE adverse events in the narrow SMQ Oropharyngeal disorders in the oritavancin arm (2 events compared to 0 events in the vancomycin arm). Hyperglycaemia/new onset diabetes mellitus narrow SMQ (1 event compared to 0 events in vancomycin arm.). A standardized MedDRA queries (broad SMQ) identified a greater number of SAE adverse events in the SMQ osteonecrosis (4 cases in oritavancin arm: 201012001,202001003,202001012,207004021 compared to 0 event in vancomycin arm) and broad SMQ of oropharyngeal disorders (2 oritavancin cases: 201034005 and 291005013 compared with 0 events in vancomycin arm). The subjects with osteonecrosis had AE term osteomyelitis and are discussed as above. Case 201034005 was an AE of facial angioedema secondary to lisinopril. Case 291005013 was a case of mouth ulcer described later in the review in section 7.3.3.
The cases of of Asthma and bronchospasm are summarized in the Table below. The case of bronchospasm could be related to oritavancin.

Table 45: Subjects with cases of of asthma and bronchospasm in the SOLO 1 trial.

SOLO1				
Patient ID / Study Drug	**Days on Study Drug**	**Study Day of event**	**Event Description**	**Relationship to study drug: Investigator/Reviewer comment**
101015-003 Oritavancin	8	Day 28, Day 45	48 yr old female with history of COPD developed 2 episodes of severe asthma exacerbation many days after completion of drug treatment, she recovered	Unrelated/ *Likely secondary to asthma and unrelated to study drug*
101023-016 Oritavancin	2	1	A 34-year-old woman developed severe bronchospasm 1 day after study drug, resolved within 24 hours.	Unrelated/*Possibly related to study drug*
101046-042 Oritavancin	8	Day 17	34 year old female with history of COPD developed mild Asthma exacerbation, recovered in 4 days.	Unrelated/*Likely secondary to asthma and unrelated to study drug*

AE of hyperglycemia in the subject 191003006 in SOLO1 was observed after randomization but before administration of oritavancin.. This event is deemed unrelated to the study drug.

7.3.3 Dropouts and/or Discontinuations
The primary reasons for discontinuing study drug in the SOLO pool were AEs (oritavancin, 3.4%; vancomycin, 3.3%) and consent withdrawal (oritavancin, 2.7%; vancomycin, 4.7%). The primary reasons for discontinuing the study prematurely were lost to follow-up (oritavancin, 5.1%; vancomycin, 7.0%) and consent withdrawal (oritavancin, 3.1%; vancomycin, 3.6%).

Table 46: Reasons for treatment discontinuation in the SOLO trials

Reason for Treatment Discontinuation	**Oritavancin N=976**	**Vancomycin N=983**
Subjects n (%)	102 (10.5%)	134 (13.6%)
Patient withdrew consent	26 (2.7%)	46 (4.7%)

Reason for Treatment Discontinuation	Oritavancin N=976	Vancomycin N=983
Adverse events	33 (3.4%)	32 (3.3%)
Lack of efficacy	16 (1.6%)	15 (1.5%)
Lost to follow-up	8 (0.8%)	17 (1.7%)
Other	10 (1.0%)	9 (0.9%)
Protocol violation	4 (0.4%)	8 (0.8%)
Abnormal laboratory value(s)	2 (0.2%)	3 (0.3%)
Sponsor decision	2 (0.2%)	2 (0.2%)
Physician decision	1 (0.1%)	2 (0.2%)

The following table summarizes the AEs which lead to treatment discontinuation by SOCs and PT. The Infusion site reactions were slightly more frequent in the oritavancin arm (5 subjects versus 2 subjects) than in the vancomycin arm. For subjects in study groups, the SOC with the highest incidence of TEAEs leading to study drug discontinuation was Infections and Infestations (1.6% versus 1.9% respectively).There were 8 subjects (0.8%) in the oritavancin arm and 19 subjects (1.9%) in the vancomycin arm who had AE which lead to treatment discontinuation related to study drug in the SOLO pool. Reviewer evaluation of the narratives and case report forms confirmed that the adverse events in these 8 subjects were likely related tooritavancin.. One case of bronchospasm was thought to be related to oritavancinby the investigator but later found to be unrelated given the patient's history of bronchial hyperreactivity. The medical reviewer agrees with that assessment. The remaining AEs which lead to treatment discontinuation and related to oritavancin were pruritis, hypersensitivity, urticaria, leucocytoclastic vasculitis, erythema multiforme, dyspnea, and mouth ulcer. The subjects with AE which lead to treatment discontinuation and related to vancomycin were also reviewed. Twenty one subjects (2.2%) in the oritavancin arm and 19 (1.9%) subjects in the vancomycin arm had a Serious AE which lead to treatment discontinuation.

Table 47: AEs leading to treatment discontinuation by SOCs and PT in the SOLO pool

Body System or Organ Class	Dictionary-Derived Term	ORITAVANCIN N=976 (%)	VANCOMYCIN N=983 (%)
Subjects with Adverse Events resulting in study drug discontinuation		33 (3.4%)	32 (3.3%)
Gastrointestinal disorders	Diarrhoea	0 (0.0%)	1 (0.1%)
	Mouth ulceration	1 (0.1%)	0 (0.0%)
	Nausea	1 (0.1%)	1 (0.1%)
	Rectal haemorrhage	1 (0.1%)	0 (0.0%)
	Vomiting	1 (0.1%)	1 (0.1%)
	Total	4 (0.4%)	3 (0.3%)
General disorders and administration site conditions	Chest discomfort	1 (0.1%)	0 (0.0%)
	Infusion site extravasation	1 (0.1%)	0 (0.0%)
	Infusion site pain	1 (0.1%)	0 (0.0%)
	Infusion site phlebitis	2 (0.2%)	0 (0.0%)
	Infusion site thrombosis	1 (0.1%)	0 (0.0%)
	Infusion site urticaria	0 (0.0%)	1 (0.1%)
	Necrosis	0 (0.0%)	1 (0.1%)
	Pyrexia	0 (0.0%)	2 (0.2%)

Body System or Organ Class	Dictionary-Derived Term	ORITAVANCIN N=976 (%)	VANCOMYCIN N=983 (%)
	Total	6 (0.6%)	4 (0.2%)
Immune system disorders	Anaphylactoid reaction	0 (0.0%)	1 (0.1%)
	Drug hypersensitivity	1 (0.1%)	2 (0.2%)
	Hypersensitivity	0 (0.0%)	5 (0.5%)
	Total	1 (0.1%)	8 (0.8%)
Infections and infestations	Abdominal wall abscess	0 (0.0%)	1 (0.1%)
	Abscess bacterial	0 (0.0%)	1 (0.1%)
	Abscess limb	2 (0.2%)	0 (0.0%)
	Arthritis bacterial	1 (0.1%)	0 (0.0%)
	Bursitis infective	0 (0.0%)	1 (0.1%)
	Cellulitis	4 (0.4%)	5 (0.5%)
	Infection	2 (0.2%)	0 (0.0%)
	Necrotising fasciitis	1 (0.1%)	0 (0.0%)
	Osteomyelitis	3 (0.3%)	1 (0.1%)
	Periorbital abscess	1 (0.1%)	0 (0.0%)
	Sepsis	0 (0.0%)	2 (0.2%)
	Skin bacterial infection	0 (0.0%)	2 (0.2%)
	Skin infection	1 (0.1%)	4 (0.4%)
	Subcutaneous abscess	2 (0.2%)	1 (0.1%)
	Upper respiratory tract infection	0 (0.0%)	1 (0.1%)
	Wound infection	1 (0.1%)	0 (0.0%)
	Total	16 (1.6%)	19 (1.9%)
Injury, poisoning and procedural complications	Drug exposure during pregnancy	0 (0.0%)	2 (0.2%)
Investigations	Urine ketone body present	1 (0.1%)	0 (0.0%)
Metabolism and nutrition disorders	Hyperglycaemia	1 (0.1%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	Tenosynovitis	1 (0.1%)	0 (0.0%)
Nervous system disorders	Convulsion	0 (0.0%)	1 (0.1%)
	Headache	0 (0.0%)	1 (0.1%)
	Somnolence	1 (0.1%)	0 (0.0%)
	Total	1 (0.1%)	2 (0.2%)
Respiratory, thoracic and mediastinal disorders	Bronchospasm	1 (0.1%)	0 (0.0%)
	Dyspnoea	1 (0.1%)	0 (0.0%)
	Hypoxia	1 (0.1%)	1 (0.1%)
	Pneumonia aspiration	1 (0.1%)	0 (0.0%)
	Total	4 (0.4%)	1 (0.1%)
Skin and subcutaneous tissue disorders	Dermatitis allergic	0 (0.0%)	1 (0.1%)
	Erythema multiforme	1 (0.1%)	0 (0.0%)
	Leukocytoclastic vasculitis	1 (0.1%)	0 (0.0%)
	Pruritus	2 (0.2%)	4 (0.4%)
	Rash	0 (0.0%)	2 (0.2%)
	Rash macular	1 (0.1%)	2 (0.2%)
	Urticaria	1 (0.1%)	1 (0.1%)
	Total	6 (0.6%)	10 (1%)

Body System or Organ Class	Dictionary-Derived Term	ORITAVANCIN N=976 (%)	VANCOMYCIN N=983 (%)
Vascular disorders	Hypotension	1 (0.1%)	1 (0.1%)
	Subjects n(%)	36 (3.7%)	41 (4.2%)

Based on the reviewer analysis of the following AE which led to treatment discontinuation, the medical reviewer considers the following ABSSSI cases to be treatment failures. These cases have been reported to be unrelated to study drug. In the vancomycin arm they are subjects- 101001001, 101001050,101001065, 101001101, 101002-072, 101002-086, 201001081, 201034007, 201034014, 201034023, 201035039. In the oritavavncin arm these subjects were 101002077, 101001-113, 101002094, 101002140, 101003-033, 101014006, 101043003, 201001069, 201001074, 201001107, 201002110, and 201034003.
The following subjects had AE which lead to discontinuation from study and death.
Subject 101001026, a 53 yr old man being treated for a wound infection of the extremity died (b) (6) days after vancomycn infusion due to streptococcal pneumonia, *Clostridium perfringens* bacteremia, and septic shock.

MO comment: The medical reviewer agrees with the investigator that the event was unrelated to vancomycin.

Case 201001019- fatal SAE leading to study termination. A 58 yr old female with history of end-stage liver disease (secondary to hepatitis C and alcohol abuse), history of MRSA and VRE infection, and a heart murmur received oritavancin for a wound infection of the right knee. (b) (6) days after oritavancin infusion she had a fall. She was hospitalized for change in mental status subsequently thought to be due to opiates and decompensated liver failure and worsening left ventricular function and valvular heart disease. She was not found to be a candidate for valvuloplasty. Subsequently, she went into cardiogenic shock with concern for sepsis (MSSA in sputum; *Escherichia coli* in her peritoneal fluid; and MSSA/enterobacter in her right foot wound. The patient experienced electromechanical dissociation (underlying etiology unknown) (b) (6) days after the single dose of oritavancin. The investigator considered this event to be unrelated to oritavancin

MO comment: The medical reviewer agrees with the investigator that the event was unrelated to oritavancin.

The following AE was considered not related to the study drug by the medical reviewer.
Subject 201001037- 41-year-old woman developed nausea 3.5 hours before the start of vancomycin infusion in the setting of erysipelas of the abdomen. The patient subsequently developed vomiting after vancomycin and the treatment was discontinued. The investigator considered the nausea to be due to vancomycin.

MO comment: The medical reviewer does not consider the event to be related to vancomcyin as the nausea was present prior to the start of vancomycin.

Clinically important cases with AE which were related to the oritavancin arm and lead to treatment discontinuation are presented below.

Subject 101005-008 developed an urticarial macular rash.-
A 51-year-old man received a single infusion of oritavancin for lower and upper arm cellulitis/erysipelas and experienced uticaria 1 day after the single dose of oritavancin. He was also receiving levofloxacin concomitantly. Pruritis started the day he received oritavancin then developed a macular rash on his arms, trunk, and legs and throat tightness. He denied dyspnea and was hemodynamically stable. The rash consisted of multiple scattered, flat to slightly raised 1 x 2 cm raised macules consistent with uticaria. The study drug was discontinued, and he was treated with prednisone and antihistamines with improvement of the rash. Additional treatment included IV linezolid and after two doses, the rash recurred. He was treated with steroids. Eight days after the single dose of oritavancin, the uticaria, itching, and macular rash resolved. The investigator considered the uticaria possibly related to oritavancin

MO comment: Although the original rash appears to be related to oritavancin given the temporal association, however the recurrence of rash upon switching to linezolid confounds the picture.

Subject 149003007 developed drug hypersensitivity.-
76-year-old diabetic woman received a single infusion of oritavancin for a lower leg wound infection and experienced drug hypersensitivity on the same day as the infusion of oritavancin. Her past history included antibiotic incompatibilities with penicillin, cefuroxime, ciprofloxacin, clindamycin, clarithromycin, and metronidazole. One day after the single dose of oritavancin, she experienced shortness of breath. Study drug was withdrawn. She was noted to have elevated transaminases. She received treatment with prednisolone. The drug hypersensitivity resolved. She was discharged from the hospital following erysipelas treatment. The investigator considered the drug hypersensitivity possibly related to oritavancin.

Pruritus (Itching to back of head)
A 22-year-old woman received a single infusion of oritavancin for a major cutaneous abscess of the back. The patient was discontinued from the study drug due to pruritus during infusion on the same day. The pruritus resolved approximately10 minutes after study drug withdrawn. The investigator considered the pruritus to be possibly related to oritavancin

Subject 201001063- pruritus, chest discomfort, dyspnea, and erythema multiforme
A 37-year-old man with history of COPD received a single infusion of oritavancin for cellulitis/erysipelas of the lower leg. Study drug was discontinued the same day due to pruritus, chest discomfort, dyspnea, and erythema multiforme. The reaction occurred approximately 4 hours after the start of oritavancin infusion and approximately 45 minutes after the conclusion of the oritavancin infusion. She received treatment with intravenous solumedrol. The pruritus resolved 1 day after study drug was withdrawn. The chest discomfort and dyspnea resolved 5 days later and the erythema multiforme resolved subsequently.

Subject- 291005013-mouth ulcers
A 59-year-old diabetic woman received a single infusion of oritavancin for lower leg cellulitis. Two days later, she experienced oral ulcers of the lower lip and tongue. On day 4 she was diagnosed with stomatitis with mucosal ulcerations and complained of nausea and difficulty eating. Study drug was withdrawn due to the mouth ulceration. Mouth ulcerations resolved on study day 10. The investigator considered mouth ulceration to be possibly related to oritavancin.

Subject -297003004-leucocytoclastic vasculitis
A 70-year-old man with history of congestive heart failure, paroxysmal atrial fibrillation, insulin dependent diabetes, renal failure (no dialysis), COPD , and focal segmental glomerular sclerosis with leukocytoclastic vasculitis skin lesion treated with azathioprine off immunosuppression currently, received oritavancin for cellulitis of the lower leg. His cellulitis improved and fever resolved on day 4, but he developed an abscess beneath the cellulitis. On study day 6 the patient experienced a leukocytoclastic vasculitis rash: a diffuse, erythematous, pleomorphic, and pruritic eruption with areas of purpura, petechiae, and ecchymosis. The rash involved both legs, abdomen, back, and hands. Given the patient's past medical history and clinical features, the investigator, along with the dermatologist, felt like a vasculitic process was the most likely etiology. Biopsy ws not performed. 64 days after the single dose of oritavancin, the leukocytoclastic vasculitis rash resolved with sequelae of chronic pigmentation. The investigator considered the leukocytoclastic vasculitis to be possibly related to oritavancin and considered the event possibly related to either an exacerbation of the patient's underlying immune disorder secondary to the cellulitis, the stress of infection, or the antibiotic treatment. The investigator considered the adverse event of congestive cardiac failure exacerbation on study day (b (6) to be unlikely related to oritavancin and considered underlying disease and discontinuation of furosemide at the beginning of hospitalization as contributing factors to the event.

Eighteen subjects in each the oritavancin and vancomycin arm had been classified as treatment discontinuation due to administrative problems. However upon review it was determined that the AEs where the reason for treatment discontinuation.

7.3.4 Significant Adverse Events

Serious TEAE in the Infection and infestation SOC are described in sections 7.3.2.The TEAE leading to treatment discontinuation are described in section 7.3.3 of the review. Analysis of cases of tachycardia and hepatotoxicity are in section 7.4.1 and 7.4.1 of the review respectively. The following discusses clinically important AE cases:

Cases of Convulsion
There were 2 cases of convulsion in each arm in the SOLO pool. In the oritavancin arm, case 101046042 was a 34 year old female with an episode of seizure 4 days after oritavancin infusion, lasting briefly and noted to be mild, non serious in nature with resolution of symptoms.The AE was determined to be unrelated to the study drug by the investigator. Case 201001013 was a 50 year old man with history of polysubstance abuse who developed seizure 30 days after

oritavancin infusion. This serious seizure episode was attributed to illicit drug use and withdrawal and resolved within 3 days.

MO comment: The medical reviewer considers seizures in case 201001013 as unlikely related to the study drug given the delayed onset of the event in relation to the study drug and history of substance abuse.

7.3.5 Submission Specific Primary Safety Concerns
None

7.4 Supportive Safety Results

7.4.1 Common Adverse Events
The incidence of TEAEs in the phase 3 SOLO trials was 55.3% in the oritavancin and 56.9% in the vancomycin group. The most common TEAEs in both oritavancin and vancomycin groups were nausea (10.25% and 10.28%), headache (7.27% and 6.71%), vomiting (4.61% and 4.98%), diarrhea (3.69% and 3.36%), cellulitis (3.89% and 3.36%), constipation (3.38% and 4.07%) and infusion site extravasation (3.38% and 3.36%). These are enumerated in the Table below.
The incidence of alanine aminotransferase and aspartate aminotransferase in the investigation SOC, cellulitis, abscess, subcutaneous abscess, abscess limb and infection in the Infections and infestation SOC, tachycardia and myalgia were somewhat higher in the oritavancin-treated patients. These adverse events discussed in more detail in this section and in sections 7.3.2, 7.3.4 and 7.4.2 of the review. However, TEAE of pruritis was noted to be higher in the vancomycin arm (7.43% compared to 2.97% in the oritavancin arm).

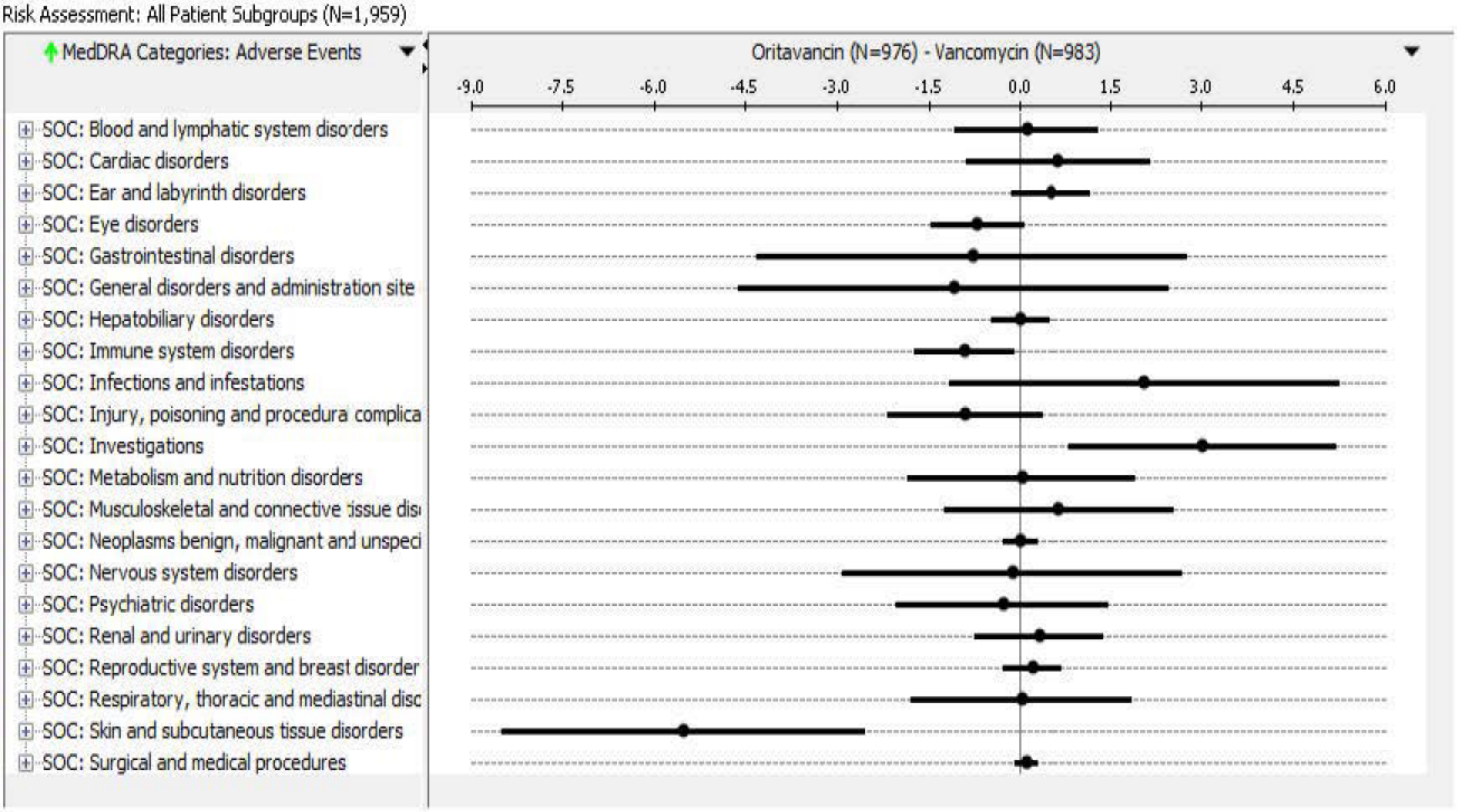
Table 48: Adverse Events That Occurred in ≥1.5% of Patients in the Oritavancin Treatment Group (Safety Population) in the SOLO trials.

	SOLO pool		SOLO1		SOLO2	
Body System or Organ Class	**Oritavancin N=976**	**Vancomycin N=983**	**Oritavancin N=473**	**Vancomycin N=481**	**Oritavancin N=503**	**Vancomycin N=502**
Preferred Term						
Number of patients with ≥1 TEAE	540 (55.3)	559 (56.9)	284 (60.04%)	307(63.83%)	256 (50.89%)	252 (50.20%)
Gastrointestinal disorders						
Constipation	33 (3.38%)	40 (4.07%)	19 (4.02%)	21 (4.37%)	14 (2.78%)	19 (3.78%)
Diarrhoea	36 (3.69%)	33 (3.36%)	23 (4.86%)	18 (3.74%)	13 (2.58%)	15 (2.99%)
Nausea	100 (10.25%)	105 (10.68%)	52 (10.99%)	43 (8.94%)	48 (9.54%)	62 (12.35%)
Vomiting	45 (4.61%)	49 (4.98%)	23 (4.86%)	19 (3.95%)	22 (4.37%)	30 (5.98%)
Nervous system disorders						
Dizziness	26 (2.66%)	26 (2.64%)	15 (3.17%)	15 (3.12%)	11 (2.19%)	11 (2.19%)
Headache	71 (7.27%)	66 (6.71%)	36 (7.61%)	38 (7.90%)	35 (6.96%)	28 (5.58%)
Psychiatric disoders						
Insomnia	22 (2.25%)	25 (2.54%)	14 (2.96%)	13 (2.70%)	8 (1.59%)	12 (2.39%)
General disorders and administration						
Fatigue	15 (1.54%)	11 (1.12%)	10 (2.11%)	6 (1.25%)	5 (0.99%)	5 (1.00%)
Infusion site extravasation	33 (3.38%)	33 (3.36%)	18 (3.81%)	23 (4.78%)	15 (2.98%)	10 (1.99%)
Infusion site phlebitis	24 (2.46%)	15 (1.53%)	8 (1.69%)	10 (2.08%)	16 (3.18%)	5 (1.00%)
Infusion site reaction	19 (1.95%)	34 (3.46%)	19 (4.02%)	34 (7.07%)		
Pyrexia	31 (3.18%)	34 (3.46%)	16 (3.38%)	22 (4.57%)	15 (2.98%)	12 (2.39%)
Oedema peripheral	14 (1.43%)	19 (1.93%)	8 (1.69%)	9 (1.87%)	6 (1.19%)	10 (1.99%)
Chills	13 (1.33%)	16 (1.63%)	10 (2.11%)	12 (2.49%)	3 (0.60%)	4 (0.80%)
Device occlusion	10 (1.02%)	9 (0.92%)	1 (0.21%)	1 (0.21%)	9 (1.79%)	8 (1.59%)
Infections and infestations						
Abscess limb	27 (2.77%)	13 (1.32%)	13 (2.75%)	5 (1.04%)	14 (2.78%)	8 (1.59%)
Cellulitis	38 (3.89%)	33 (3.36%)	20 (4.23%)	17 (3.53%)	18 (3.58%)	16 (3.19%)
Subcutaneous abscess	15 (1.54%)	11 (1.12%)	9 (1.90%)	11 (2.29%)	6 (1.19%)	0 (0.00%)
Infection	12 (1.23%)	2 (0.20%)	8 (1.69%)	2 (0.42%)	4 (0.80%)	0 (0.00%)
Skin and subcutaneous tissue disorders						
Pruritus	29 (2.97%)	73 (7.43%)	16 (3.38%)	44 (9.15%)	13 (2.58%)	29 (5.78%)
Pruritus generalised	17 (1.74%)	25 (2.54%)	11 (2.33%)	9 (1.87%)	6 (1.19%)	16 (3.19%)
Investigations						

Body System or Organ Class	SOLO pool		SOLO1		SOLO2	
	Oritavancin N=976	Vancomycin N=983	Oritavancin N=473	Vancomycin N=481	Oritavancin N=503	Vancomycin N=502
Alanine aminotransferase increased	27 (2.77%)	16 (1.63%)	11 (2.33%)	5 (1.04%)	16 (3.18%)	11 (2.19%)
Aspartate aminotransferase increased	18 (1.84%)	16 (1.63%)	7 (1.48%)	4 (0.83%)	11 (2.19%)	12 (2.39%)
Cardiac disorders						
Tachycardia	24 (2.46%)	11 (1.12%)	9 (1.90%)	4 (0.83%)	15 (2.98%)	7 (1.39%)
Musculoskeletal and connective tissue disorders						
Myalgia	14 (1.43%)	8 (0.81%)	8 (1.69%)	4 (0.83%)	6 (1.19%)	4 (0.80%)
Blood and lymphatic system disorders						
Anaemia	13 (1.33%)	12 (1.22%)	4 (0.85%)	5 (1.04%)	9 (1.79%)	7 (1.39%)
Respiratory, thoracic and mediastinal disorders						
Cough	11 (1.13%)	14 (1.42%)	3 (0.63%)	7 (1.46%)	8 (1.59%)	7 (1.39%)

The following figure shows the risk difference per hundred among the SOCs of MedRA categories in the safety population of the SOLO pool. The highest risk difference was noted in the Infections and Infestations SOC of 2.05 per hundred (16.7% and 14.6% in the oritavavncin and vancomycin arm respectively) and Investigations SOC of 3 per hundred (8.1% and 5.1% in the oritavavncin and vancomycin arm respectively).

Figure 17: Risk assessment in the mITT population in the pooled SOLO trials for common adverse events by SOC.



The following additional subjects (Table below) were noted to have TEAE derived from the SDTM dataset, but not included in the AE analysis dataset. AEs in all these cases were mild in intensity and none required treatment discontinuation. All AE started at study day1.

Table 49: Excluded subjects from the AE dataset identified in SDTM dataset with TEAE in SOLO1 and SOLO 2 trials

SOLO1						SOLO2					
Oritavancin			Vancomycin			Oritavancin			Vancomcyin		
	PT	End date of AE*		PT	End date of AE*		PT	End date of AE*		PT	End date of AE*
TMC-ORI-10-01-101002-014	Haematuria		TMC-ORI-10-01-101001-022	Anxiety	1	TMC-ORI-10-02-201001-024	Hyperglycaemia	2	TMC-ORI-10-02-201001-020	Vomiting	1
TMC-ORI-10-01-101002-071	Pyrexia	1	TMC-ORI-10-01-101002-047	Pyrexia	2	TMC-ORI-10-02-201002-004	Nausea	1	TMC-ORI-10-02-201001-095	Pyrexia	2
TMC-ORI-10-01-101002-138	Hypertension		TMC-ORI-10-01-101002-088	Vomiting	1	TMC-ORI-10-02-201002-010	Breast pain	6	TMC-ORI-10-02-201001-100	Fatigue	4
TMC-ORI-10-01-134003-001	Arthralgia	24	TMC-ORI-10-01-101016-010	Hypoglycaemia	1	TMC-ORI-10-02-201002-010	Nausea	5	TMC-ORI-10-02-201001-102	Vomiting	1
TMC-ORI-10-01-191003-006	Pyrexia	2	TMC-ORI-10-01-101027-033	Hypokalaemia	1	TMC-ORI-10-02-201002-010	Insomnia	1	TMC-ORI-10-02-201001-123	Pruritus generalised	8
TMC-ORI-10-01-191003-006	Urinary tract infection	4	TMC-ORI-10-01-101034-004	Diabetes mellitus	.	TMC-ORI-10-02-201002-036	Diabetes mellitus	.	TMC-ORI-10-02-201001-139	Nausea	1
TMC-ORI-10-01-191003-012	Headache	1	TMC-ORI-10-01-101046-059	Pyrexia	1	TMC-ORI-10-02-201002-089	Abscess	.	TMC-ORI-10-02-201035-019	Constipation	9
TMC-ORI-10-01-191008-029	Dyspepsia	4	TMC-ORI-10-01-149003-006	Fall	1	TMC-ORI-10-02-207002-013	Creatinine renal clearance decreased	19	TMC-ORI-10-02-207002-027	Creatinine renal clearance decreased	4
TMC-ORI-10-01-191010-004	Hypertension	.	TMC-ORI-10-01-191002-038	Vertigo	3	TMC-ORI-10-02-291004-004	Decreased appetite	.	TMC-ORI-10-02-207002-039	Alanine aminotransferase increased	.
			TMC-ORI-10-01-191002-041	Urinary tract infection	10				TMC-ORI-10-02-207002-039	Aspartate aminotransferase increased	.
			TMC-ORI-10-01-191003-008	Diarrhoea	1				TMC-ORI-10-02-207002-049	Blood bilirubin increased	4
			TMC-ORI-10-01-191003-010	Pyrexia	1				TMC-ORI-10-02-297001-001	Constipation	17

MO comment: These additional subjects do not appear to alter the incidence of AEs significantly.

Tachycardia

There were 24 subjects (2.46%) in the oritavancin arm and 11 subjects (1.12%) in the vancomycin arm in the SOLO pool with the adverse event of tachycardia. Further analysis of these cases shows that 3 cases (101046-040, 201001-099, 201001-184) in the oritavancin arm had reported tachycardia 10 mins, 15 mins, and 3 mins prior to treatment. Notably, all cases in SOLO2 were reported from a single site, 201001, the highest enrolling site (n=205). The mean onset of tachycardia in the oritavancin arm was 4.6 days (range:-0.01-28) and 6.1 days (range: 1-24) in the vancomycin arm after administration of the drug. These data are presented in figure below.

The average duration of tachycardia reported was varied from transient to 42 days in the oritavancin arm and 0.42 days to 60 days in the vancomycin arm. Further analysis of the vital signs dataset showed that tachycardia did not occur in the setting of fever. Subject 201001-031 likely had tachycardia in the setting of anxiety. Except for subject 101016-010 who had moderate tachycardia reported all cases were of mild severity. The vital sign dataset did not have evidence of increased pulse rate in many of these subjects however the subjects reported to have elevated pulse rate (oritavancin n=11, vancomycin n=9) had a mean pulse of 110 beats/min in the oritavancin arm and 104 beats /min in the vancomycin arm. Five subjects in the oritavancin arm had elevated pulse rate on day 10 of therapy. Mean heart rate was not noted to be elevated in the ECG dataset.

Figure 18: Onset of tachycardia after oritavancin administration in SOLO

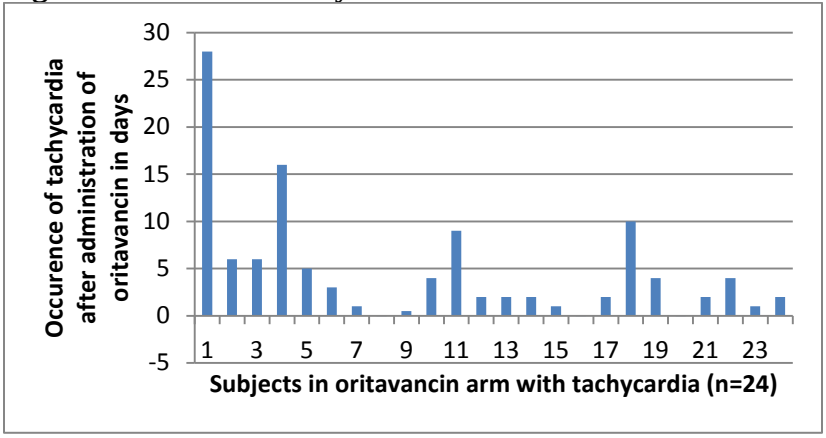
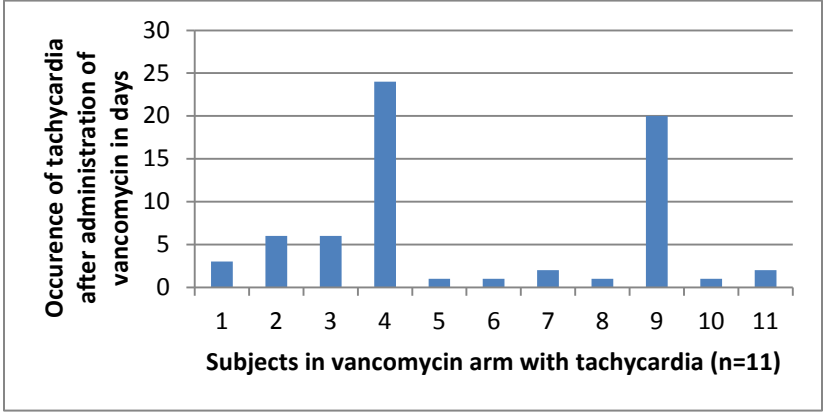


Figure 19: Onset of tachycardia after vancomycin administration (SOLO)



MO comment: No specific conclusions can be drawn from this analysis as no particular relationship was seen between occurrence of tachycardia and timing of exposure to the study drug. Although vancomycin is not known to be associated with the adverse event of tachycardia, several cases had occurred in SOLO trials. Causality for tachycardia TEAE is uncertain, but the incidence of tachycardia was numerically higher in the oritavancin-treated patients than those treated with the comparator.

Myalgia

There were 13 and 8 cases of myalgia in the oritavancin and vancomyicn arm, respectively. None of these cases were serious; all were mild in intensity except for one of moderate intensity in the vancomycin arm. In none of the cases treatment was discontinuation due to myalgia.
MO comment: medical reviewer's examination of the medical history or concomitant medication list did not reveal any specific cause.

7.4.2 Laboratory Findings

Hematology

The incidences of Potentially Clinically Significant (PCS) hematology values were low and similar in both treatment groups.
Baseline values for each hematology parameter and the mean change from baseline at early clinical evaluation (ECE), end of treatment (EOT), and PTE were similar in the oritavancin and vancomycin groups.
Hematology laboratory results (including mean hematology values), box plots, scatter plots, and shift tables revealed similar results between treatment groups.
Aggregated study results show that no findings, trends, or safety concerns in either treatment group.

The following table shows selected PCS laboratory results in the SOLO pool.

Table 50: Potentially Clinically Significant (PCS) hematology values in the pooled SOLO trials

PCS Hematology	Oritavancin n/N(%)	Vancomycin n/N(%)
White blood cells		
≤3x109/L	18/848(2.1)	19/839(2.3)
Neutrophils		
≥90%	18/806 (2.2)	15/813 (1.8)
Eosinophils ≥10%	55/833 (6.6)	50/825 (6.1)
Lymphocytes		
<10%	42/744 (5.6)	35/761 (4.6)
≥80%	0	1/761 (0.1)
Hematocrit		
≤0.75 x LLN	25/829 (3.0)	17/828 (2.1)
Hemoglobin (g/dL)		
Male ≤115 or Female≤95	93/728 (12.8)	73/737 (9.9)
Male ≥180 or Female≥160	4/728 (0.5)	1/737 (0.1)
Red blood cells		
≤0.75 X LLN	19/826 (2.3)	18/829 (2.2)
≥1.25 X ULN	0/826	0/829

PCS Hematology	Oritavancin n/N(%)	Vancomycin n/N(%)
Platelet Count		
>40 - 75 x 10^9/L	2/739 (0.3)	2/763 (0.3)

N=number of patients who had at least one post-baseline measurement and non-PCS value at baseline.
Adapted from Table 59 and Table 44 of the ISS, replicated by reviewer

Chemistry

The incidences of PCS chemistry values were low and similar in both treatment groups. Baseline values for each parameter (serum sodium, potassium, calcium, blood urea nitrogen, creatinine, lipids) and the mean change from baseline at early clinical evaluation (ECE), end of treatment (EOT), and PTE were similar in the oritavancin and vancomycin groups.
Chemistry laboratory results (including mean values), box plots, scatter plots revealed similar results between treatment groups.
Aggregated study results revealed no findings, trends, or safety concerns in either treatment group.

Liver Function test abnormalities

A review of the post baseline liver function tests was conducted. In SOLO 1, 26 (5.50%) subjects in oritavancin arm and 24 subjects (4.99%) in the vancomycin arm had ALT >3 x ULN and that was fairly balanced. In SOLO2, 26 (5.17%) subjects in the oritavancin arm and 25 (4.98%) subjects in the vancomycin arm had ALT >3 x ULN and it was also fairly balanced. In SOLO2, the vancomycin group had slightly higher number of AST elevation >3 x ULN of 22 subjects (4.3%) as compared to 14 (2.7%) subjects in oritavancin arm. In SOLO1, 6 (1.2%) subjects in oritavancin arm and 5 (1%) subjects in vancomycin arm had TB >2 x ULN. In SOLO 2, the oritavancin arm had slightly higher number of subjects with TB > 2xULN as compared to vancomycin arm [4 (0.8%) vs 1 (0.2%)]. Two subjects in the oritavancin arm in the SOLO pool were noted to have ALT>10 x ULN compared to 1 subject in the vancomycin arm. The number of subjects with TB> ULN were slightly higher in the oritavancin arm as compared to the vancomycin arm. The number of subjects with ALT >5xULN in the SOLO pool was 10 (1%) in the oritavancin arm and 17 (1.7%) in the vancomycin arm. The number of subjects with AST >5xULN in the SOLO pool was 7 in the oritavancin arm and 11 in the vancomycin arm. There were 1 subject in the oritavancin arm and 3 in the vancomycin arm with AST >10xULN in the SOLO pool.
Two patients in the oritavancin group (Patients 101014-003 and 191008-057) had an ALT or AST > 10X ULN.Subject 101014-003 was a 42 yr old female with baseline elevated ALT of 51U/L, on codeine and fentanyl, had increases in ALT to 357 U/L (10.8X ULN), AST to 294 U/L (8.2X ULN; reference range: 10 to 43 U/L) and ALP to 365 U/L (3.2X ULN; reference range: 43 to 115 U/L) with an R value of 3.4.. They trended down by day 10 and resolvedby day 16. Treatment was completed. The second subject 191008-057 is a 51 yr old woman on tramadol, she had increases in ALT to 413 U/L (12.5X ULN; reference range: 10 to 33 U/L), AST to 361 U/L (10X ULN; reference range: 10 to 36 U/L) and an R value of 18.22 at ECE visit. On Day 10, she completed treatment and her ALT decreased to 57 U/L (within 2X ULN) and AST normalized (29 U/L).

In SOLO2, there were 12 subjects with total bilirubin level >1.5xULN in the oritavancin arm compared with 2 subjects in the vancomycin arm. Further review showed 3 (subjects 201001-019, 291002-039, 291006-022) of these 12 subjects had normal bilirubin levels at baseline. The elevated bilirubin level was not associated with elevation in transaminases. They were not associated with hemolysis of red blood cells either. In the vancomycin arm, 1 subject had normal bilirubin level at baseline.
Subject 201001019 in the oritavancin arm died from complication of endstage liver disease and electromechanical dissociation. Subject 291002039 in the oritavancin arm was a 45 year old man on tramadol and ceftriaxone concomitantly who developed elevated TB at ECE(29.6) which remained elevated at EOT(22.9) amd PTE(22.4). Subject 291006022 in the oritavancin arm was a 56 year old man on cefotaxime, amoxicillin-clavulanate, diclofenac concomitantly who developed elevation of TB at ECE (29.8) but resolved by EOT.

Table 51: Post baseline liver function tests in the SOLO trials - mITT population)

	SOLO1						SOLO2					
Liver Lab Test	**Oritavancin**			**Vancomycin**			**Oritavancin**			**Vancomycin**		
	N = 473			**N = 481**			**N = 503**			**N = 502**		
ALT ≥ULN	Event Count	Subject Count	%	Event Count	Subject Count	%	Event Count	Subject Count	%	Event Count	Subject Count	%
2x ULN	106	54	11.42	90	52	10.81	114	59	11.73	111	56	11.16
3x ULN	47	26	5.50	42	24	4.99	45	26	5.17	46	25	4.98
5x ULN	10	7	1.48	10	7	1.46	5	3	0.60	13	10	1.99
10x ULN	2	2	0.42	0	0	0.00	0	0	0.00	1	1	0.20
AST ≥ULN												
2x ULN	51	31	6.55	62	44	9.15	72	45	8.95	84	49	9.76
3x ULN	21	15	3.17	22	15	3.12	18	14	2.78	29	22	4.38
5x ULN	4	4	0.85	6	5	1.04	3	3	0.60	7	6	1.20
10x ULN	1	1	0.21	2	2	0.42	0	0	0.00	1	1	0.20
TB≥ULN												
1.5x ULN	11	8	1.69	13	7	1.46	15	12	2.39	2	2	0.40
2x ULN	7	6	1.27	6	5	1.04	4	4	0.80	1	1	0.20
3x ULN	3	2	0.42	2	2	0.42	2	2	0.40	0	0	0.00

Notes: All scores are post-baseline. Subject scores may be counted more than once in that they were counted in all conditions (i.e., 2x, 3x, 5x…) that apply.

This analysis uses the lab test short name variable (LBTESTCD), the numeric results (LBSTRESN) in standard units, the reference range upper limit-Std Units (LBSTNRHI), the sponsor-derived baseline flag (LBBLFL) and study days (LBDY) from the laboratory test results (LB) dataset.

A review of the liver function tests post baseline at the same visit (Table below) shows that the number subjects for the various categories of abnormal liver function tests were fairly balanced in both arms in SOLO1. For the category of ALT or AST ≥ 3 ULN, TB ≥ 1.5 ULN & ALP > normal, there were 2 subjects identified in the oritavancin arm in SOLO 2 and none in the vancomycin arm. For the categories of ALT or AST ≥ 3 ULN, TB ≥ 2 ULN & ALP > normal and ALT or AST ≥ 5 ULN, TB ≥ 3 ULN & ALP > normal in SOLO2, there was 1 subject in the oritavancin arm and none in the vancomycin arm.

An evaluation of the liver function tests at any time during the study shows for category ALT or AST ≥ 3 ULN, TB ≥ 1.5 ULN & ALP > normal in SOLO 2, there were 3 such subjects in the oritavancin arm as compared to none in the vancomcyin arm. For evaluation of Hy's Law (ALT or AST ≥ 3 ULN, TB ≥ 2 ULN & ALP normal), 1 subject was identified in SOLO1 and SOLO2 trials each in the oritavvancin arm.

Table 52: Post baseline liver function tests at the same visit and at anytime during the study (SOLO trials- mITT population)

Liver Lab Test At Same Visit	**Oritavancin N = 473**		**Vancomycin N = 481**		**Oritavancin N=503**		**Vancomycin N=502**	
	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
ALT or AST ≥ 3 ULN, TB ≥ 1.5 ULN & ALP normal	0	0.00	1	0.21	0	0.00	0	0.00
ALT or AST ≥ 3 ULN, TB ≥ 2 ULN & ALP normal	0	0.00	0	0.00	0	0.00	0	0.00
ALT or AST ≥ 5 ULN, TB ≥ 3 ULN & ALP normal	0	0.00	0	0.00	0	0.00	0	0.00
ALT or AST ≥ 3 ULN, TB ≥ 1.5 ULN & ALP > normal	1	0.21	1	0.21	2	0.40	0	0.00
ALT or AST ≥ 3 ULN, TB ≥ 2 ULN & ALP > normal	1	0.21	1	0.21	1	0.20	0	0.00
ALT or AST ≥ 5 ULN, TB ≥ 3 ULN & ALP > normal	0	0.00	1	0.21	1	0.20	0	0.00
Liver Lab Test Any Time During Study	**Oritavancin N = 473**		**Vancomycin N = 481**		**Oritavancin N=503**		**Vancomycin N=502**	
	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
ALT or AST ≥ 3 ULN, TB ≥ 1.5 ULN & ALP normal	1	0.21	0	0.00	1	0.20	0	0.00
ALT or AST ≥ 3 ULN, TB ≥ 2 ULN & ALP normal	1	0.21	0	0.00	1	0.20	0	0.00
ALT or AST ≥ 5 ULN, TB ≥ 3 ULN & ALP normal	0	0.00	0	0.00	1	0.20	0	0.00
ALT or AST ≥ 3 ULN, TB ≥ 1.5 ULN & ALP > normal	1	0.21	1	0.21	3	0.60	0	0.00
ALT or AST ≥ 3 ULN, TB ≥ 2 ULN & ALP > normal	1	0.21	1	0.21	1	0.20	0	0.00
ALT or AST ≥ 5 ULN, TB ≥ 3 ULN & ALP > normal	0	0.00	1	0.21	1	0.20	0	0.00

Notes: All scores are post-baseline. Subjects had the laboratory combinations occurring at any point during the study.

This analysis uses the lab test short name variable (LBTESTCD), the numeric results (LBSTRESN), the reference range upper limit-std units (LBSTNRHI), the baseline flag (LBBLFL), visit number (VISITNUM) and study days (LBDY) from the laboratory test results (LB) dataset. Results are determined to be a baseline value if they have a "Y" in LBBLFL. To determine the count of subjects at any visit, the visit number variable is used. If visit number is unavailable, it is calculated using the variable study days to match up lab results taken on the same day.

The following table shows the distribution of liver function tests in the SOLO trials for subjects with baseline normal liver function tests.

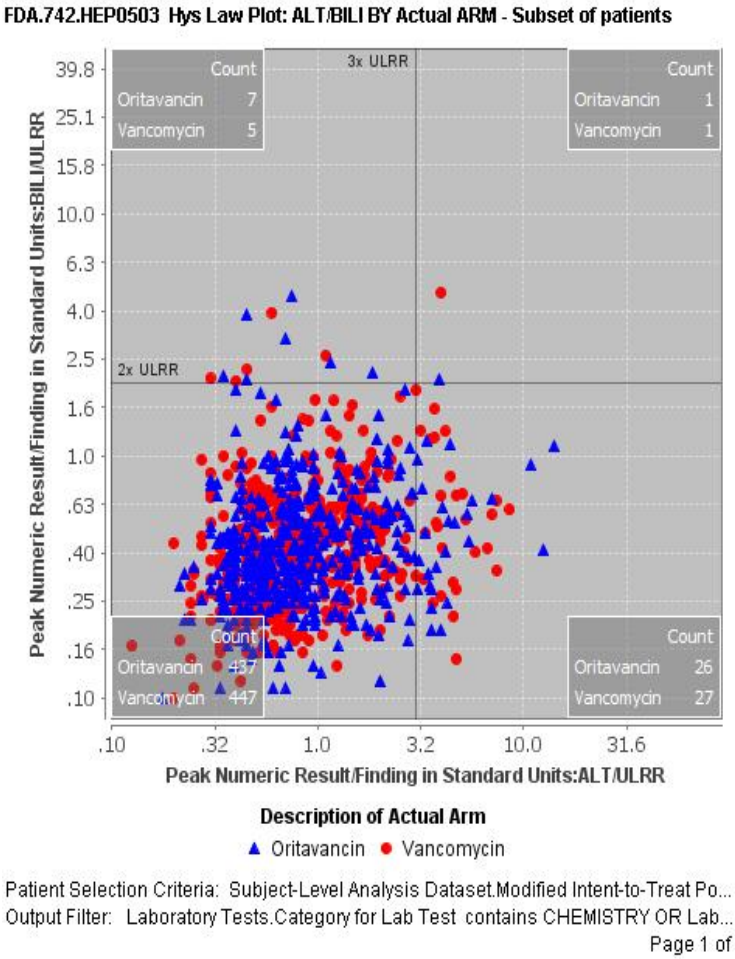
Table 53: Distribution of liver function tests in the SOLO trials for subjects with baseline normal liver function tests.

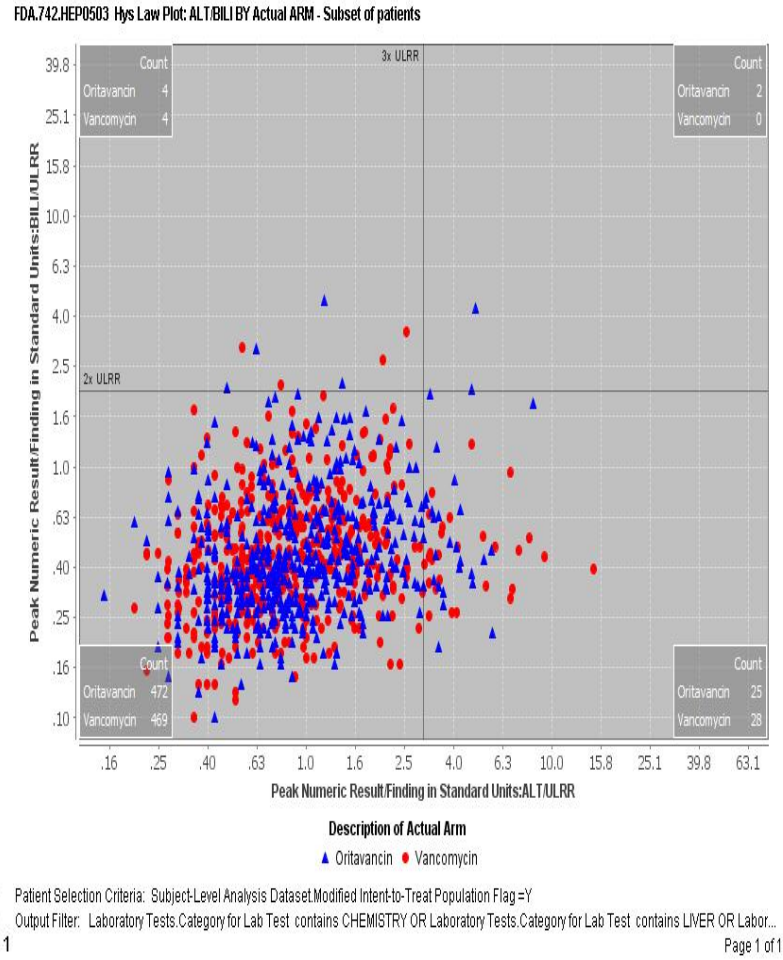
	SOLO pool		
	Shift from normal baseline	**Oritavancin (N=976)**	**Vancomycin (N=983)**
Alanine Aminotransferase (ALT) (U/L)	<ULN to <ULN	765 (78.38%)	771 (78.43%)
	<ULN to 1-<3xULN	174 (17.83%)	180 (18.31%)
	<ULN to 10-<20xULN	1 (0.10%)	0 (0.00%)
	<ULN to 3-5xULN	18 (1.84%)	14 (1.42%)
	<ULN to 5-<10xULN	1 (0.10%)	7 (0.71%)
Alkaline Phosphatase (U/L)	<ULN to <ULN	778 (79.71%)	780 (79.35%)
	<ULN to >=3xULN	2 (0.20%)	3 (0.31%)
	<ULN to 1-<3xULN	95 (9.73%)	92 (9.36%)
Aspartate Aminotransferase (AST) (U/L)	<ULN to <ULN	781 (80.02%)	798 (81.18%)
	<ULN to 1-<3xULN	182 (18.65%)	167 (16.99%)
	<ULN to 10-<20xULN	1 (0.10%)	2 (0.20%)
	<ULN to 3-5xULN	6 (0.61%)	12 (1.22%)
	<ULN to 5-<10xULN	2 (0.20%)	6 (0.61%)

	SOLO pool		
	Shift from normal baseline	**Oritavancin (N=976)**	**Vancomycin (N=983)**
Total Bilirubin (TB) (mcmol/L)	<ULN to <ULN	890 (91.19%)	900 (91.56%)
	<ULN to >=2xULN	4 (0.41%)	2 (0.20%)
	<ULN to 1.5-2xULN	3 (0.31%)	1 (0.10%)
	<ULN to 1-<1.5xULN	15 (1.54%)	21 (2.14%)

MO Comment: There were 4 subjects in the oritavancin arm with TB >2 x ULN compared to 2 subjects in the vancomycin arm. The percentage of subjects with an increase of TB from baseline was similar in both arms in the SOLO pool. The increase of AST from baseline normal value to1-<3xULN was 18.6% in the oritavancin arm versus 16.9% in the vancomycin arm. The ALT levels went from baseline normal values to 3-5xULN in 18(1.8%) subjects of the oritavancin arm versus 14(1.4%) subjects in the vancomycin arm.One subject had Alt level increased from normal to 10-20xULN in the oritvavncin arm but none in the vancomycin arm. ALP levels went from normal baseline to 1-<3xULN in 95 subjects (9.73%) in the oritavvancin arm versus 92 subjects (9.4%) in the vanocmycin arm.

The following figure is a Scatter Plot of Maximum Transaminase versus Maximum Total Bilirubin to evaluate for drug induced Liver injury and Hy's law cases. Further analyses of these cases are presented below.





SOLO1 **SOLO2**

Figure 20: Scatter Plot of Maximum Transaminase versus Maximum Total Bilirubin to evaluate for drug induced Liver injury and Hy's law cases in the SOLO trials.

The following patients were identified as having abnormal LFTS >ULN falling in the Hy's Law quadrant or close to the quadrant in the e dish plot. Hy's Law criteria includes evidence of hepatocellular injury (ALT/AST > 3 ULN) in the drug group than that in control group, and a subject with ALT > 3x ULN and TBL > 2x ULN without notable increase ALP (<2xULN), and when there are no other explanation (liver disease or other drug) [4]. To further evaluate the evidence of DILI (drug induced liver injury) the applicant has provided the R ratio. The R ratio is a ratio of the ALT to the ALP relative to their upper limits of normal, i.e. R= (ALT/ULN) / (ALP/ULN). DILI is categorized as follows:

- Hepatocellular: ALT ≥ 3x ULN and R ≥5

- Cholestatic: ALP ≥ 2x ULN and R≤2
- Mixed: ALT ≥ 3x and ALP > 2x ULN and 2<R<5

Only relevant medical history or concomitant medications are described. R values are reported by the applicant.

Table 54: Description of liver lab abnormality in subject 101005-005 in SOLO1 trial.

Patient ID / Study Drug	Days on Study Drug	Day of event after study drug	Event Description	Event	Outcome	Relationship to study / Reviewer Comments
TMC-ORI-10-01-101005-005: Oritavancin	10	10	31 yr old man with HIV on antiretrovirals (ritonavir, atazanavir, emtricitamine), trazodone , oxycodone who had elevated serum bilirubin at baseline was noted to have ALT> 3 x ULN .	Moderate/ possibly related to study drug per investigator, non serious, completed treatment	ALT trended down by PTE	The subject had elevated TB at baseline possibly due to atazanavir. Although he had an elevation of ALT after 10 days of study drug it trended down by PTE. The case does not meet Hy's law criteria

Visit Date	ALP (ULN =115)		ALT (ULN =40)		AST (ULN=43)		TB (ULN=18.8)		R Value (ALT/ALP)
	Value (U/L)	X ULN	Value (U/L)	XULN	Value (U/L)	X ULN	Value mcmol/L	X ULN	
Baseline	118	1.03	28	0.7	28	0.65	37.8	2.01	0.68
ECE	92	0.8	20	0.5	24	0.56	27.9	1.48	0.63
EOT	128	1.11	155	3.88	93	2.16	39	2.07	3.48
PTE	121	1.05	44	1.1	44	1.02	35.7	1.9	1.05

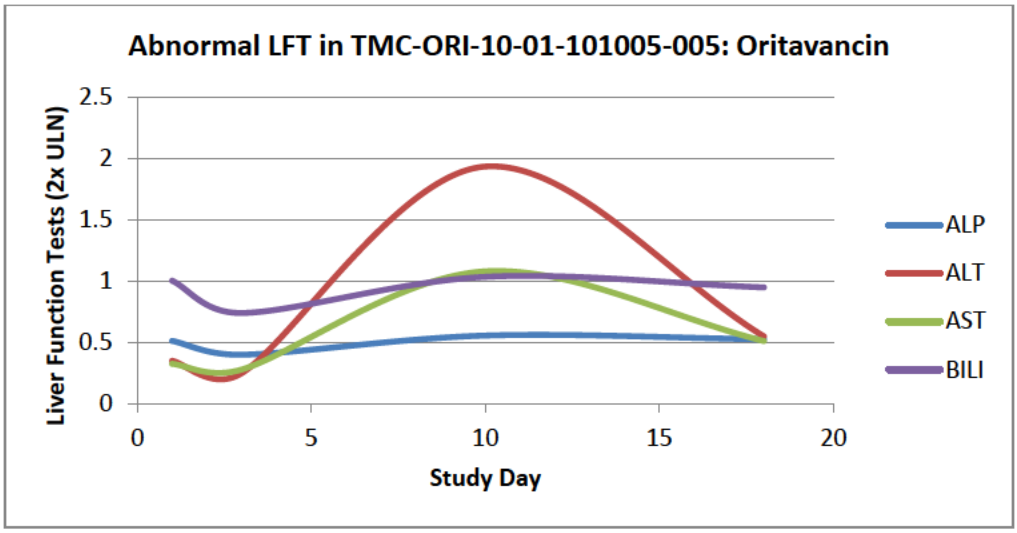


Figure 21: Abnormal LFT in TMC-ORI-10-01-101005-005: Oritavancin

Table 55: Description of liver lab abnormality in subject191002095 in SOLO1 trial.

Patient ID / Study Drug	Days on Study Drug	Day of event after study drug	Event Description	Event	Outcome	Relationship to study / Reviewer Comments
TMC-ORI-10-01/191002095 Vancomycin	10	10	52 year old man with diabetes, on tramadol, received vancomycin for lower leg cellulitis/erysipelas and experienced elevated liver enzymes on the same day as the last dose of vancomycin. At screening, ALP was slightly elevated at 124 U/L .At EOT visit, he experienced elevated ALT 4.0 × ULN, AST 11.4 × ULN), ALP 2.7 × ULN, and total bilirubin 4.8 × ULN. 9 days after the last dose of vancomycin (PTE visit), his LFTs improved and returned to close to normal reference range (resolved without treatment)..	Mild/ unrelated/ nonserious/ completed treatment	ALT trended down by PTE	The patient does not meet Hy's Law criteria. The elevation in serum alkaline phosphatase is suggestive of a cholestatic picture and this marker for elevated at baseline.

Visit Date	ALP (ULN =115)		ALT (ULN =40)		AST (ULN=43)		TB (ULN=18.8)		R Value (ALT/ALP)
	Value (U/L)	X ULN	Value (U/L)	X ULN	Value (U/L)	X ULN	Value mcmol/L	X ULN	
Baseline	124	1.08	14	0.35	22	0.5	2.9	0.15	0.32
ECE	202	1.76	18	0.45	26	0.6	7.4	0.39	0.26
EOT	315	2.74	159	3.98	492	11.4	89.3	4.75	1.45
PTE	141	1.23	35	0.88	52	1.2	4.4	0.23	0.71

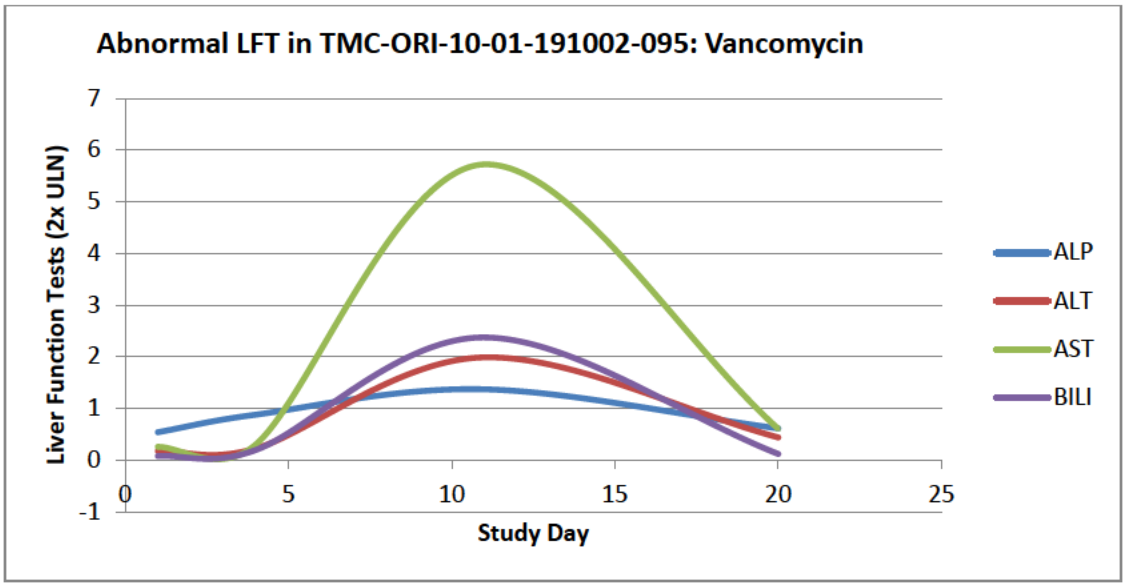


Figure 22: Abnormal LFT in TMC-ORI-10-01-191002-095: Vancomycin

Table 56: Description of liver lab abnormality in subject 207001-002 in SOLO2 trial

Patient ID /Study Drug	Days on Study Drug	Day of event after study drug	Event Description	Event	Outcome	Relationship to study / Reviewer comment
TMC-ORI-10-02-207001-002: Oritavancin	7	9	A 58-year-old man received oritavancin for cellulitis and had increased AST and ALT on study day 9. No relevant medical history was reported for this patient. Relevant concomitant medications included aztreonam and metronidazole. At screening, his total bilirubin was elevated at 2.02 × ULN. At the EOT visit study day 9, his AST was 4.12 × ULN and ALT was 4.70 × ULN, but ALP and Tb were normal. His AST and ALT were trending down and almost resolved 16 days after oritavancin infusion.	Mild/non-serious/ completed treatment	The liver function tests trended down by PTE	The subject had transient elevation of ALT and AST which resolved by the end of treatment. Although no other etiology of this elevation was found, metronidazole could have had a contributory effect. There is a possibility of drug related mild hepatocellular injury but does not meet the Hy's law criteria.

Visit Date	ALP (ULN=115)		ALT (ULN=40)		AST (ULN=43)		TB (ULN=18.8)		R Value (ALT/ALP)
	Value (U/L)	X ULN	Value (U/L)	X ULN	Value (U/L)	X ULN	Value (mcmol/ L)	X ULN	
Baseline	83	0.72	34	0.85	56	1.30	38	2.02	1.18
ECE	71	0.62	38	0.95	60	1.40	9.6	0.51	1.54
EOT	116	1.01	188	4.70	177	4.12	7.5	0.40	4.66
Day 10	109	0.95	116	2.90	100	2.33	8.6	0.46	3.06
PTE	93	0.81	50	1.25	53	1.23	6.5	0.35	1.55

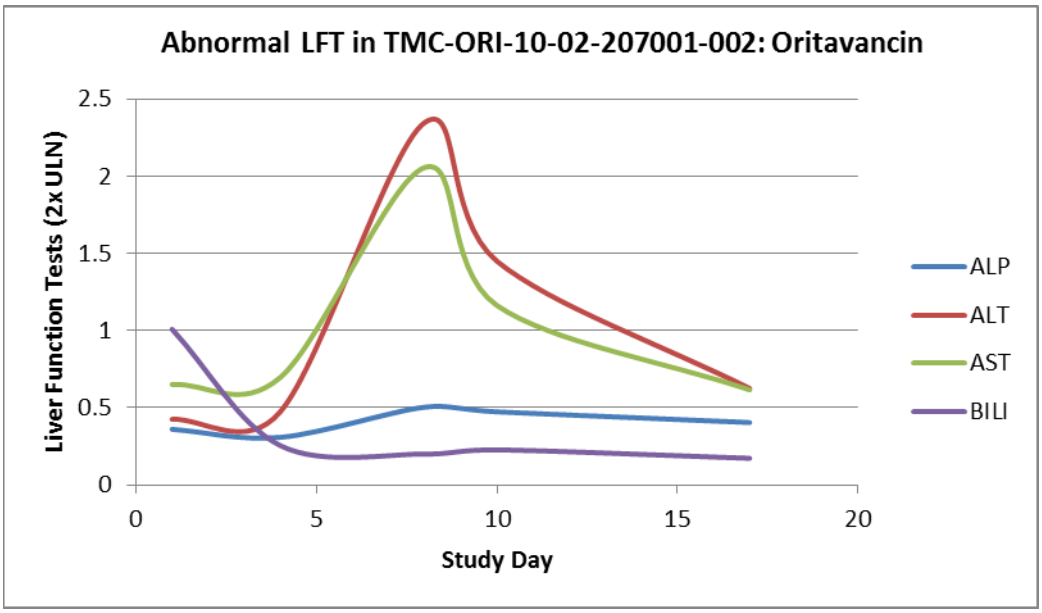


Figure 23: Abnormal LFT in TMC-ORI-10-02-207001-002: Oritavancin

Table 57: Description of liver lab abnormality in subject 291003-016 in SOLO2 trial

Patient ID /Study Drug	Days on Study Drug	Day of event after study drug	Event Description	Event	Outcome	Relationship to study / Reviwer comment
TMC-ORI-10-02-291003-016 Oritavancin	10	3	23 year old male with no past history on tramadol, noted to have elevated TB, AST and ALP at baseline. Elevated AST of 8.3xULN, ALT 4.9XULN, elevated TB of 4xULN and elevation of ALP were noted at ECE.	Mild/ nonserious/ no discontinuation of treatment	The liver function tests trended down by PTE	The applicant states that this was a largely cholestatic process. The medical reviewer notes that AST/ALT ratio was almost 2:1 although report of alcohol was not noted. Given the rise of AST, ALP and elevated baseline TB this does not meet Hy's law criteria. However a brief transaminase elevation accompanied by doubling of bilirubin level could have been related to oritavancin and is of concern.

Visit Date	ALP (ULN=115)		ALT (ULN=40)		AST (ULN=43)		TB (ULN=18.8)		R ratio (ALT/ALP)
	Value (U/L)	X ULN	Value (U/L)	X ULN	Value (U/L)	X ULN	Value (mcmol/ L)	X ULN	
Baseline	160	1.4	26	0.7	56	1.3	32.0	1.7	0.47
ECE	212	1.8	196	4.9	353	8.2	80.5	4.3	2.66
EOT	198	1.7	48	1.2	57	1.3	14.5	0.8	0.7
PTE	140	1.2	30	0.8	28	0.7	9.9	0.5	0.62

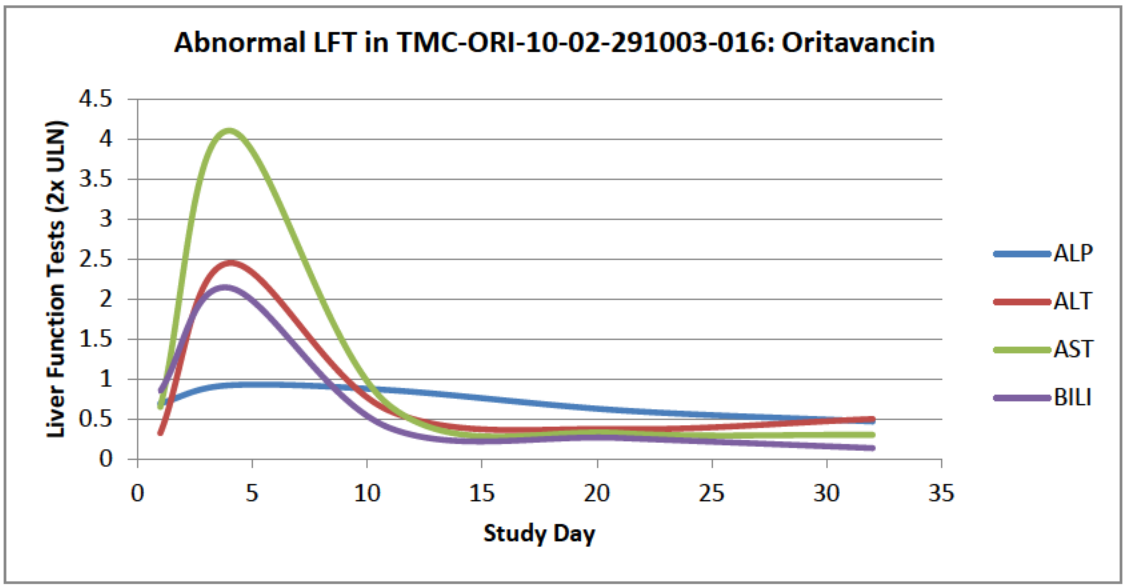


Figure 24: Abnormal LFT in TMC-ORI-10-02-291003-016: Oritavancin

Table 58:Description of liver lab abnormality in subject 291002-022 in SOLO2 trial

Patient ID / Study Drug	Days on Study Drug	Day of event after study drug	Event Description	Event	Outcome	Relationship to study / Reviewer comment
TMC-ORI-10-02-291002-022 Oritavancin ALT was elevated but did not fit the criteria ALT /ALT ≥ 3x ULN, TBIL ≥ 2x ULN, and ALP < 2x ULN	9	15 days after PTE	56 year old female with history of hepatitis or other hepatic condition received oritavancin for an abscess. She had baseline elevated ALP and TB suggestive of a cholestatic picture. She received concomitant ceftriaxone. She was noted to have elevation of ALP peaking at 1560, 15 days after PTE however her TB was trending down. ALT was noted to be elevated >2.6 x ULN at 15 days after PTE which resolved on its own however her TB was noted to be rising again.	Mild/ nonserious completed treatment	The liver function tests trended down by PTE	This case does not meet Hy's law criteria. Her liver function tests suggest more of a cholestatic picture rather than hepatocellular injury. Of note a transient elevation was seen 15 days after PTE which resolved on its own. Concomitant ceftriaxone use and history of hepatitis/hepatic condition are likely confounders.

Visit Date	ALP (ULN=115)		ALT (ULN=40)		AST (ULN=43)		TB (ULN=18.8)	
	Value (U/L)	X ULN	Value (U/L)	X ULN	Value (U/L)	X ULN	Value (mcmol/ L)	X ULN
Baseline Study drug	535	4.7	14	0.4	38	0.9	35.1	1.9
ECE	863	7.5	14	0.4	47	1.1	30.1	1.6
EOT	1157	10.1	22	0.6	55	1.3	22.6	1.2
PTE	1390	12.1	32	0.8	75	1.7	20	1.1
15 days after PTE	1560	13.6	105	2.6	169	3.9	16.2	0.9
18 days after prior visit	957	8.3	37	0.9	48	1.1	36.4	1.9

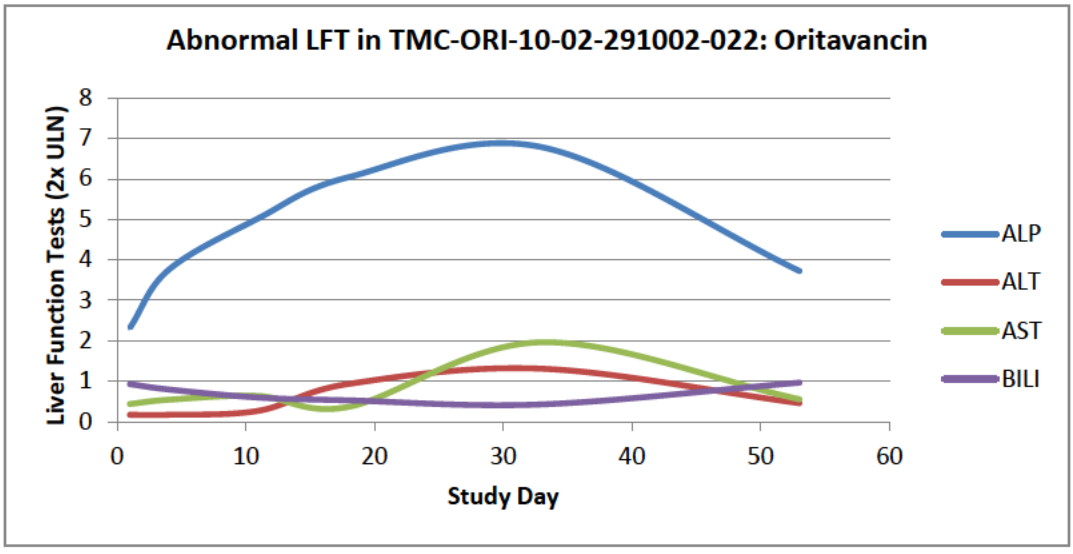


Figure 25: Abnormal LFT in TMC-ORI-10-02-291002-022: Oritavancin

MO comment: None of these cases strictly met the Hy's Law criteria. However subject 101005005 had abnormal LFTs attributed to oritavancin by the investigator. Although the R ratio remained <5 for subjects 207001002 and 291003016, the abnormalities of liver function tests are suggestive of hepatocellular injury and are of concern.

Hepatic impairment study

The applicant had conducted a Phase 1 study (OCSI-004) comparing the safety and pharmacokinetics of a single 800 mg IV infusion of oritavancin in healthy subjects and subjects with moderate hepatic impairment The percentage of patients with at least one AE was 10% (2/20) in healthy subjects and 25%(5/20) in subjects with moderate hepatic impairment. A total of 13 adverse events was reported, and the incidence was higher in the hepatically impaired subjects (8 events in 5 hepatically-impaired subjects) compared with healthy subjects (5 events in 2 healthy subjects). The majority of events reported in both groups were mild or moderate in severity as assessed by the investigator. Of the eight adverse events reported in the hepatically impaired subjects, four were considered possibly or probably related to study drug. These events were sedation, diarrhea, elevated ALT, and elevated AST. In both groups, most clinical laboratory mean results did not change substantially. Clinically asymptomatic elevations in liver function tests (ALT, AST, alkaline phosphatase, GGT, and bilirubin) were noted in individual subjects in the hepatically impaired group. There were transitory, sporadic, clinically asymptomatic, post baseline elevations in hepatic enzymes for 2 healthy subjects

Two subjects in the hepatically impaired group (Subject 02-51A and Subject 02-54A) were considered to have clinically significant elevations in hepatocellular enzymes (ALT and AST) by the investigator. Subject 02-51A, a 38-year-old African American male with hepatitis B, hypertension, gastroesophageal reflux disease, depression and anxiety, on atenolol, entered the study with clinically significant elevated LFTs (screening: GGTP 962 U/L [>10 times ULN], ALT 350 U/L [>5 times ULN], and AST 412 U/L [>10 times ULN]). His hepatocellular enzymes decreased during the study (Day 8: ALT 57 U/L and AST 45 U/L), then increased by Day 45 (ALT 126 U/L [>2 times ULN] and AST 261 U/L [>5 times ULN] although lower than baseline levels).

Subject 02-54A, a 48-year-old Caucasian female, with hepatitis B and C and hyperglycemia on Amaryl, benzodiazepines, and methadone, entered the study with elevated LFTs (screening: GGTP 81 U/L, ALT 81 U/L, and AST 78 U/L); hepatocellular enzymes increased to a peak on Day 3 (ALT 237 U/L and AST 284 U/L) and decreased over the remainder of the study (Day 45, ALT 79 U/L and AST 81 U/L)Two SAEs were reported: ascites exacerbation in the moderate hepatic impairment group and severe cholecystitis in the healthy subjects group; neither event was related to study drug. Severe cholecystitis resulted in study discontinuation. Oritavancin plasma concentrations were approximately 10-15% lower at every time point in the population of subjects with hepatic impairment. The mean Cmax and AUC0-24 were 18% and 12% lower in subjects with hepatic impairment compared to healthy subjects with normal hepatic function. Severe hepatic impairment was not evaluated.

MO comment: The liver function test abnormalities in Subject 02-54A could be related to the underlying hepatitis; however, temporary association with oritavancin was present.

SIMPLIFI trial
Subject TAR-ORISD001256-04 was a 49 year old man who received oritavancin and had elevated ALP of 221 (1.9xULN), AST 51(1.2xULN) and TB 11.8xULN at baseline. The next day he had ALP 278(2.4xULN), ALT of 45(1.1xULN) AST of 89(2.1xULN) and TB 10.5xULN.

MO comment: Given the abnormal baseline LFTs the subject did not meet the Hy's law criteria.

Hepatic AE
There was a greater incidence of AEs of elevated transaminases noted in the oritavancin treated subjects as compared to those treated with vancomycin in SOLO trials (see Table of common adverse events). There were 27(2.77%) subjects and 16 (1.63%) subjects with elevated ALT in the oritavancin and vancomycin arm, respectively. There were 18 (1.84%) subjects and 16 (1.63%) subjects with elevated AST in the oritavancin and vancomycin arm, respectively. The following Table) discusses the 24 cases of hepatic AE with increased ALT in the oritavancin arm excluding the cases already discussed above in the Hy's law case analysis.Only relevant clinical data for evaluation of these AEs are provided in the table below. In these subjects the abnormal LFTs (ALT and AST elevations) occurred as early as 2 days or as late as 19 days after oritavancin dose. The abnormalities resolved the same day in some cases or were still apparent as late as 68 days after dosing. Five subjects had ALT elevations which have not resolved. There were 7 subjects where the investigator thought the AE was unrelated. None of the AEs required study drug discontinuation. Seven subjects had increased ALT and 3 had increased ALP at baseline. Ten of 27 subjects had hepatitis or hepatic condition and 12 subjects a history of intravenous drug use at baseline. In the vancomycin arm, 5 /16 subjects had elevated baseline ALT.

Table 59: Selected subjects with increased ALT in the oritavancin arm in the SOLO trials

Patient ID	Day of event after study drug	Event Description	Investigator defined causality	Medical Reviewer comment
101001018	2	38 yr old man with history of diabetes mellitus, hepatitis or other hepatic condition, IV drug use on heroin, had baseline elevated ALT 107 U/L (2.68 x ULN), AST 142 U/L (3.30 x ULN) and ALP 169 U/L . Two days after oritavancin he developed elevated ALT 153 U/L (3.83 × ULN) and AST 237 U/L (5.51 × ULN); additional LFTs showed ALP 178 U/L and total bilirubin of 20.9 mcmol/L. After EOT visit, the LFTs started trending down but remained somewhat elevated at 30 day follow up- ALT 134 U/L (3.35 × ULN) and AST 134 U/L (3.12 × ULN).	Possibly related per investigator	*The patient's history of hepatitis and intravenous drug use are confounders. The AE was not resolved by 30 day follow up.*
101003026		ALT 1.33xULN at PTE. Other enzymes unremarkable, patient was on linezolid concomitantly.	Possibly related per investigator	
101003033	15	15 days after the single dose of oritavancin, he experienced elevated AST 60 U/L (1.40 × ULN) and elevated ALT 114 U/L (2.85 × ULN). Had vancomycin and Bactrim in interim.	Possibly related per investigator	

Patient ID	Day of event after study drug	Event Description	Investigator defined causality	Medical Reviewer comment
101005003	10	32 yr old man with baseline ALT 81 U/L developed elevated ALT 212 U/L (5.3 × ULN) and AST 71 U/L at day 10 visit.	Possibly related per investigator	
101025011	19	35 yr old man, who 24 days after the single dose of oritavancin and 5 days before the onset of the event of increased ALT) his LFTs showed ALT 54 U/L (1.35 × ULN)	Unrelated per investigator	
101025012	3	33 yr old 3 days after the single dose of oritavancin (ECE visit), she experienced increased ALT 50 U/L (1.52 × ULN. 9 days later this resolved.	Unrelated per investigator	
101046011	7	28 yr old man 7 days after the single dose of oritavancin (EOT visit), he experienced increased ALT 168 U/L (4.20 × ULN) and AST 101 U/L (2.35 × ULN). Resolved same day.	Unrelated per investigator	
101046012	3	55 yr old man with positive hepatitis C antibody serology, IVDU at screening had elevations of ALT 100 U/L (2.5 × ULN) and AST 94 U/L (2.2 × ULN). At ECE visit, the LFTs showed ALT 218 U/L (5.5 × ULN), AST 145 U/L (3.4 × ULN). Seven days later the ALT elevation resolved. On study day 9 after oritavancin dose, the ALT again increased to 157 U/L (3.9 × ULN) and AST increased to 99 U/L (2.3 × ULN). 17 days after study drug, ALT decreased to 96 U/L (2.4 × ULN) and AST decreased to 73 U/L (1.7 × ULN); ALP and total bilirubin remained normal	Unrelated per investigator	*The fluctuating transaminase level, underlying hepatitis and IVDU are confounders to assess causality .However the R value was 6.67 at ECE and 5.6 at day 10. The transaminases did not resolve after 17 days of study drug administration*.
197002016	3	48 yr old man, at (ECE visit), experienced increased ALT 53 U/L (1.33 × ULN) and AST 58 U/L (1.35 × ULN). On study day 6 after oritavancin dose (EOT visit), his LFTs had increased further, with ALT 118 U/L (2.95 × ULN) and AST 65 U/L (1.51 × ULN). Eight days after study drug, ALT and AST elevations resolved.	Unrelated/	*Possibly related given the temporal association with the study drug*
201001008	10	34 yr old female with IVDU 10 days after the single dose of oritavancin (Day 10 visit), she experienced increased ALT 157 U/L (4.76 × ULN) and AST 129 U/L (3.58 × ULN. 4 days later the transaminases normalized.	Possibly related per investigator	
201001029	10	37 yr old man, at Day 10 visit, he experienced increased ALT 118 U/L (2.95 × ULN) and AST 52 U/L (1.21 × ULN). 17 days after study drug, they resolved	Possibly related per investigator	
207004018	3	30 yr old man: ALT/AST started rising 3 days after oritavancin administration.At PTE visit, his LFTs were elevated:ALT 138 U/L (3.45 × ULN) and AST 65 U/L (1.51 × ULN. 27 days later they resolved.	Possibly related per investigator	
207004002	3	46 yr old man, 3 days after the single dose of oritavancin (ECE visit), his AST was 66 U/L (1.53 × ULN), ALT was 81 (2.03 × ULN); additional LFTs showed ALP 187 U/L (1.63 × ULN). At EOT they remain elevated, but resolved by PTE	Unrelated, resolved.	*There appears to be cholestatic component in this AE.*
207002036	9	43 yr old man, 9 days after the single dose of oritavancin (EOT visit), his AST was 65 U/L (1.51 × ULN) and ALT was 168 (4.2 × ULN. At PTE, ALT remained elevated at 1.6xULN. Subject's baseline LFTs were within normal limits.	unrelated	*The ALT remained elevatedat PTE.*

Patient ID	Day of event after study drug	Event Description	Investigator defined causality	Medical Reviewer comment
201005073	3	22 yr old female with hepatitis C and IVDU, at baseline, ALT 141 U/L (4xULN), AST 68 U/L. 3 days after the single dose of oritavancin (ECE visit), her AST was 167 U/L (4.64 × ULN) and ALT was 174 (5.27 × ULN. On study day 7 after oritavancin dose (EOT visit), AST 74 U/L (2.06 × ULN) and ALT 156 (4.73 × ULN). On study day 10 AST was 50 U/L (1.39 × ULN) and ALT was 95 (2.88 × ULN). Eight months later LFTs remained elevated at AST 92 U/L (2.56 × ULN) and ALT 139 (4.21 × UL).	Possibly related, event ongoing	*The transaminitis had not resoved by day 10.His history of hepatitis with baseline elevated LFTS are confounders.*
201005023		35 yr old female with hepatitis and IVDU, at EOT visit she had increased ALT 44 U/L (1.33 x ULN); 2 days later showed ALT 37 U/L (1.12 x ULN). At PTE visit AST was 59 U/L (1.64 x ULN); ALT remained elevated at 119 U/L (3.61 x ULN). 38 days after the single dose of oritavancin- LFT abnormalities resolved.	Possibly related per investigator	
201005001	7	34 yr old male with hepatitis and IVDU At 7 days after oritavancin, he had increased ALT 49 U/L (1.23 x ULN) and AST 53 U/L (1.23 x ULN) and resolved 4 days later.	Possibly related per investigator	
201002087	10	34 yr old male with hepatitis C and IVDU at screening, his LFTs showed ALT 88 U/L (2.20 x ULN), AST 54 U/L (1.26 x ULN). At study day 10 visit he experienced elevated ALT 132 U/L (3.30 x ULN) and AST 58 (1.35 x ULN. Forteen days after study drug, the event resolved.	Possibly related per investigator	
201002004	3	57 yr old man with with hepatitis and IVDU on tramadol, aztreonam, flagyl, with baseline ALP 169 U/L, At ECE visit, he experienced increased ALT 132 U/L (3.30 x ULN) and AST 175 U/L (4.07 x ULN). LFTs at EOT visit showed ALT 162 U/L (4.05 x ULN) and AST 76 (1.77 x ULN). LFT abnormalities resolved by PTE.	Possibly related per investigator	
201001200	3	27 yr old female with IVDU, 3 days after the single dose of oritavancin, she had increased AST 59 U/L (1.6 x ULN) and increased ALT 71 U/L (2.2 x UL. 2 days later they resolved. 59 days after study drug, she was diagnosed with pregnancy.	Possibly related per investigator	
201001059	3	46 yr old female on Bactrim, metformin, had baseline elevated ALP 122 U/L. At ECE visit she had increased ALP 128 U/L (1.11 x ULN) and ALT 38 U/L (1.15 x ULN). 2 days later they resolved	Possibly related per investigator	*There appears to be cholestatic component in this AE.*
201001048	7	30 yr old man with history of hepatitis, or other hepatic condition, IVDU on methadone at screening had ALT 66 U/L AST 51 U/L. At EOT visit ALT increased to 144 U/L (3.60 x ULN) and AST to 109 U/L (2.53 x ULN). At PTE, they were trending down. 27 days after the single dose of oritavancin LFTs showed ALT 96 U/L (2.40 x ULN) and AST 64 U/L (1.49 x ULN).	Possibly related per investigator	*ALT and AST remained elevated 27 days after study drug.*
201001046	10	45 yr old female with history of hepatitis or other hepatic condition and IV drug use at screening, had ALT of 59 U/L (1.79 x ULN) and AST of 57 U/L (1.58 x ULN). After oritavancin dose on day 10 visit, she had increased ALT 132 U/L (4.00 x ULN) and AST 118 U/L (3.28 x ULN). At PTE the LFTs remained elevated, but resolved 2 weeks later.	Possibly related per investigator	

Patient ID	Day of event after study drug	Event Description	Investigator defined causality	Medical Reviewer comment
201001038		33 year old man with history of IVDU, baseline ALP of 95, at PTE visit he had increased ALT 49 U/L (1.23 x ULN) and ALP 130 (1.13 x ULN). 68 days after the single dose of oritavancin (unscheduled visit), LFTs were normal.	Possibly related per investigator	

MO comment: Although the subjects with history of hepatitisC or hepatic condition or intravenous drug use could have predisposed the subjects to the elevation of transaminases, there were subjects with no such history and normal baseline LFT values where the abnormality occurred. The cases do not appear to be a result of severe sepsis/shock liver.

7.4.3 Vital Signs

In the SOLO trials, vital signs, including temperature, pulse rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP) and weight were monitored for PCS changes. Values meeting both the observed value criteria and the change from baseline criteria were classified as low or high PCS.

No meaningful differences were reported in either mean baseline or mean change from baseline values between treatment groups in the SIMPLIFI or the SOLO trials. No clinically relevant differences were noted in vital signs in the ARRI and ARRD trials (refer to clinical review by Dr. Moledina, December 1, 2008).

There was one subject with AE of hypotension in the oritavancin arm where study drug was discontinued.

Subject 101010003 was a 35-year-old woman, who received a single infusion of oritavancin for lower leg cellulitis/erysipelas. The patient was discontinued from the study drug due to hypotension of 83/52 mmHg 1 day after the single dose of oritavancin. No relevant medical history/concurrent conditions were reported for the patient. Relevant concomitant medications included morphine, drospirenone with ethinylestradiol, arixtra, and odansetron. Study treatment was withdrawn due to the hypotension. The hypotension resolved without treatment 1 day after the study drug discontinuation. Eight days after withdrawal of the study drug, her blood pressure was 119/74 mmHg. The investigator considered the hypotension to be unlikely related to oritavancin.

MO comment: The subject had a low BP of 106/71 mm Hg at start of study drug and the infection can cause SIRS contributing to low blood pressure. Morphine could also have a contributory lowering effect on BP. The medical reviewer considers the hypotension to be unrelated to the study drug.

7.4.4 Electrocardiograms (ECGs)

In the SOLO pool, the mean heart rate, QT, QTcF, QTcB, QRS, PR durations were not prolonged (that is clinically meaningful) and similar in the oritavancin and vancomycin groups. No notable trends were observed between groups for post baseline mean and median values of

heart rate, QT, QTc, PR, QRS, and RR. Treatment-emergent abnormal ECG morphologies at 30 minutes post baseline were comparable between the oritavancin and vancomycin groups.

From the QT-IRT consult review by Dr. Moh Jee Ng dated December 16, 2013, there were no significant QTc prolongation effects of oritavancin 1600 mg infusion detected in the TQT study (MDCO-ORI-12-02). The largest upper bounds of the 2-sided 90% CI for the mean difference between oritavancin and placebo were below 10 ms. Five subjects had HR > 100 bpm, none of them exceed 105 bpm. Five subjects had PR > 200 ms, three of them at baseline, none were clinically meaningful. Six subjects had post-dose QRS >110 ms (< 120 ms).

Review of the cases of death does not reveal a proarrythmogenic etiology. QTcF Fridericia's correction is presented in the table below.

Table 60: QTcF - Fridericia's Correction (millisec) in the mITT population in the SOLO trials

QTc (msec)	Oritavancin N=976	Vancomycin N=983
>500	3 (0.3%)	5 (0.5%)
481-500	11 (1.1%)	6 (0.6%)
451-480	35 (3.6%)	28 (2.8%)

7.4.5 Special Safety Studies/Clinical Trials

Adverse Events of Special Interest:

Glycopeptide class effects-

- **Hypersensitivity**

Overall the incidence of hypersensitivity was lower in the oritavancin group 119/976(12.2%) than the vancomycin group 184/983 (18.7%) in the SOLO study pool. The most frequent (> 2.0%) hypersensitivity reactions in the SOLO pool were pruritus in the oritavancin group and pruritus, pruritis generalized, and urticaria in the vancomycin group. The following table summarizes the hypersensitivity events by PT in the SOLO pool. The median time to onset of hypersensitivity was 2.2 days (range, 0 to 29 days) and 0.6 days (range, 0 to 63 days) in the oritavancin and vancomycin groups, respectively, in the SOLO pool. The median duration of hypersensitivity was 2.4 days (range, 0 to 55 days) and 1.5 days (range, 0 to 69 days) in the oritavancin and vancomycin groups, respectively.

Table 61: Hypersensitivity events by PT in the SOLO pool (Safety population)

Preferred Term	Oritavancin N=976 (%)	Vancomycin N=983 (%)
Pruritus	29 (3.0%)	73 (7.4%)
Pruritus generalized	17 (1.7%)	25 (2.5%)
Oedema peripheral	14 (1.4%)	19 (1.9%)
Urticaria	11 (1.1%)	21 (2.1%)
Cough	11 (1.1%)	14 (1.4%)

Preferred Term	Oritavancin N=976 (%)	Vancomycin N=983 (%)
Dyspnoea	11 (1.1%)	8 (0.8%)
Rash	5 (0.5%)	10 (1.0%)
Hypersensitivity	3 (0.3%)	8 (0.8%)
Hypotension	8 (0.8%)	3 (0.3%)
Erythema	1 (0.1%)	9 (0.9%)
Rash macular	3 (0.3%)	6 (0.6%)
Chest discomfort	4 (0.4%)	4 (0.4%)
Rash papular	4 (0.4%)	3 (0.3%)
Infusion site rash	1 (0.1%)	5 (0.5%)
Erythema multiforme	3 (0.3%)	2 (0.2%)
Infusion site pruritus	1 (0.1%)	4 (0.4%)
Rash generalised	2 (0.2%)	2 (0.2%)
Flushing	1 (0.1%)	3 (0.3%)
Wheezing	4 (0.4%)	0 (0.0%)
Swelling face	1 (0.1%)	2 (0.2%)
Asthma	2 (0.2%)	1 (0.1%)
Drug hypersensitivity	1 (0.1%)	2 (0.2%)
Generalised oedema	1 (0.1%)	1 (0.1%)
Rash pruritic	1 (0.1%)	1 (0.1%)
Sneezing	1 (0.1%)	1 (0.1%)
Respiratory failure	0 (0.0%)	2 (0.2%)
Red man syndrome	0 (0.0%)	2 (0.2%)
Oedema	1 (0.1%)	1 (0.1%)
Rash maculo-papular	0 (0.0%)	2 (0.2%)
Anaphylactoid reaction	0 (0.0%)	2 (0.2%)
Eyelid oedema	0 (0.0%)	1 (0.1%)
Infusion site vesicles	0 (0.0%)	1 (0.1%)
Localised oedema	0 (0.0%)	1 (0.1%)
Penile oedema	0 (0.0%)	1 (0.1%)
Pharyngeal oedema	1 (0.1%)	0 (0.0%)
Bronchospasm	1 (0.1%)	0 (0.0%)
Angioedema	1 (0.1%)	0 (0.0%)
Cardio-respiratory arrest	0 (0.0%)	1 (0.1%)

The following is reviewer generated summary of serious hypersensitivity reactions grouped by PT. 6 subjects in the oritavancin arm and 9 subjects were identified in the vancomycin arm in the SOLO pool.

Table 62: Serious Adverse Events Related to Hypersensitivity (Safety Population) of SOLO pool

PT	Oritavancin (N = 976) Number of subjects	Vancomycin (N = 983) Number of subjects
Respiratory failure	0	2
Drug hypersensitivity	1	1
Anaphylactoid reaction	0	2
Cardio-respiratory arrest	0	1
Hypersensitivity	0	1

PT	Oritavancin (N = 976) Number of subjects	Vancomycin (N = 983) Number of subjects
Asthma	1	0
Bronchospasm	1	0
Urticaria	1	0
Angioedema	1	0
Dyspnoea	1	2

The number of hypersensitivity AEs in the oritavancin arm was lower than in the vancomycin arm and differed only slightly with the sponsor analysis.

Table 63: Hypersensitivity AEs in the SOLO pool (safety population)

	Sponsor		Reviewer	
SOLO pool	**Oritavancin (N=976)**	**Vancomycin (N=983)**	**Oritavancin (N=976)**	**Vancomycin (N=983)**
SAE related to Hypersensitivity	4 (0.4)	4 (0.4)	6 (0.61%)	7 (0.71%)
Hypersensitivity AEs Leading to Study Drug Discontinuation	5 (0.5)	14 (1.4)	6 (0.61%)	14 (1.42%)

Adapted from ISS: Table 20, Table 21.

Reviewer analysis of the SIMPLIFI study identified four subjects in the 1200 mg oritavancin arm (hot flush-2, dyspnea-2), 10 subjects in the 200 mg oritavancin arm (cough-3, hot flush-1, erythema -2, hypotension -2, urticarial -1, swelling-1) and 4 subjects in the 800 mg oritavancin arm (cough-4, hot flush-4, erythema -3, hypotension-2, dyspnea-2, urticarial-1, eye swelling-1, swelling-1) who developed hypersensitivity related events.

- **Infusion Site Reactions/Phlebitis**

There was a greater incidence and severity of infusion site reactions/phlebitis in the Phase 1 studies (OCSI-007 and OCSI-008), compared to the Phase 2 and Phase 3 clinical studies where multiple daily doses were administered. These reactions appeared related to the concentration of the oritavancin solution and rate of infusion in these volunteers (800 mg of oritavancin was infused in 267-533 mL of D5W, over 86-105 minutes). To decrease infusion site reactions/phlebitis, a decreased infusion rate and concentration of oritavancin 1200 mg was administered in 1000 mL D5W over 3 hours in the SOLO trials. The following Table summarizes the infusion site reactions/phlebitis in the SOLO pool. As noted in the table, The incidence of infusion site reactions/phlebitis was comparable in both oritavancin (10%) and vancomycin arm(11%).

Table 64: Infusion site reactions/phlebitis in the SOLO pool

Preferred Term	Oritavancin N=976 (%)	Vancomycin N=983 (%)
n(%)	99 (10.1%)	109(11.1%)
Infusion site extravasation	33 (3.4%)	33 (3.4%)
Infusion site reaction	19 (1.9%)	34 (3.5%)

Preferred Term	Oritavancin N=976 (%)	Vancomycin N=983 (%)
Infusion site phlebitis	24 (2.5%)	15 (1.5%)
Infusion site pain	7 (0.7%)	15 (1.5%)
Infusion site erythema	8 (0.8%)	8 (0.8%)
Infusion site thrombosis	7 (0.7%)	7 (0.7%)
Infusion site swelling	7 (0.7%)	6 (0.6%)
Infusion site rash	1 (0.1%)	5 (0.5%)
Infusion site pruritus	1 (0.1%)	4 (0.4%)
Phlebitis	0 (0.0%)	2 (0.2%)
Infusion site urticaria	0 (0.0%)	2 (0.2%)
Infusion site induration	1 (0.1%)	1 (0.1%)
Phlebitis superficial	2 (0.2%)	0 (0.0%)
Infusion site discomfort	0 (0.0%)	1 (0.1%)
Infusion site inflammation	0 (0.0%)	1 (0.1%)
Infusion site anaesthesia	0 (0.0%)	1 (0.1%)
Infusion site vesicles	0 (0.0%)	1 (0.1%)
Vessel puncture site pain	0 (0.0%)	1 (0.1%)
Infusion site scar	1 (0.1%)	0 (0.0%)
Infusion site irritation	1 (0.1%)	0 (0.0%)

The incidence of Infusion Site Reaction/Phlebitis Leading to Study Drug Discontinuation was 0.5% in the oritavancin arm and 0.1% in the vancomcyin arm.

Table 65: Infusion site reactions/phlebitis leading to study drug discontinuation in the SOLO pool

Dictionary-Derived Term	Oritavancin N=976	Vancomycin N=983
n(%)	5 (0.5%)	1 (0.1%)
Infusion site phlebitis	2 (0.2%)	0 (0.0%)
Infusion site pain	1 (0.1%)	0 (0.0%)
Infusion site thrombosis	1 (0.1%)	0 (0.0%)
Infusion site urticaria	0 (0.0%)	1 (0.1%)
Infusion site extravasation	1 (0.1%)	0 (0.0%)

The sponsor reported that the median time to onset of an infusion site reaction/phlebitis was 3.1 days (range, 0 to 26 days in the oritavancin group and 0 to 15 days in the vancomycin group) in each group in the SOLO pool. Median duration of infusion site reactions/phlebitis was 2.0 days (range, 0 to 25 days) and 1.9 days (range, 0 to 512 days [imputed]) in the oritavancin and vancomycin groups, respectively.
No deaths or SAEs related to infusion site reactions/phlebitis occurred in the SOLO pool in the oritavancin arm.

- **Vestibular Effects/Ototoxicity**

The incidence of vestibular toxicity was similar in the oritavancin (3%) and vancomycin (2.9%) groups in the SOLO pool.

Table 66: Vestibular effects in the SOLO pool

Preferred Term	Oritavancin N=976	Vancomycin N=983
n(%)	30 (3%)	29 (2.9%)
Dizziness	26 (2.7%)	26 (2.6%)
Motion sickness	1 (0.1%)	0
Vertigo	2 (0.2%)	3 (0.3%)
Tinnitus	1(0.1%)	0

MO comment: The adverse event of tinnitus was added to the group of vestibular effects. The subject with tinnitus (201001-106) was a 41 year old while female who developed symptoms 3 days after infusion of oritavancin. Symptoms resolved in 2 days and the investigator thought this was related to the study drug. The AE was classified as mild.

There was a single case of deafness in SOLO 2 (Subject 202001-007). This was a 62-year-old, white female who had cold/flu-like symptoms (ie, runny nose, sore throat, aches all over body) before the onset of the hearing loss at day 12 post oritavancin infusion. The AE was assessed by the investigator as mild and unlikely related to study drug. The AE resolved.

MO comment: The duration of the AE was not reported, however the patient was started on dimenhydrinate 10 days after the onset of the event for dizziness and tinnitus. The AE may be related to viral labrynthitis. Of note the patient also received ciprofloxacin prior to the onset of symptoms which has been reported to cause hearing loss and tinnitus.

The percentage of patients with AEs in the ear and labyrinth disorders SOC was similar in the oritavancin and vancomycin/comparator groups in the SOLO pool.

- **Neutropenia and thrombocytopenia**

There were no cases of neutropenia or febrile neutropenia reported as AEs in the SOLO pools. The mean change from baseline, the percentages of patients with a PCS change in neutrophils or a shift from normal at baseline to low post baseline in neutrophils was similar between the oritavancin and vancomycin groups in the SOLO pool and was not clinically significant.

The sponsor reports six cases of febrile neutropenia from the bacteremia studies (ARRC, 5 patients; ARRM, 1 patient) and all patients had medical conditions at baseline that likely caused or contributed to neutropenia (hematological malignancies in 4 patients, metastatic malignant melanoma in 1 patient, and orthotopic liver transplant in 1 patient).
In the SOLO pool, there were 5 patients in the oritavancin group and no patients in the vancomycin group had AEs of thrombocytopenia/platelet count decreased. There were 2 patients in each group in the ARRD/I pool reported to have thrombocytopenia/platelet count decreased. None of these AEs resulted in death, were serious, or led to study drug discontinuation.

MO comment: The analysis of these cases of thrombocytopenia /decreased platelet count in the oritavancin arm the decreased counts ranged from 55000-119000, mean 136,000. Most were mild in intensity except one case which was associated with hepatitis C and rectal bleeding.

None were serious. The investigators reported these cases were unliked drug related. Mean onset was 12.4 days (range 2-30). Data on length of resolution was missing in some cases. It is difficult to draw conclusions from these small numbers.

- **Antibiotic related effects**

No events related to pseudomembranous colitis/*Clostridium difficile* associated diarrhea or superinfection were reported in the SOLO pool. The percentage of patients with a superinfection was similar in the oritavancin and vancomycin/comparator groups in the ARRD/I pool.

- **Renal Effects**

The incidence of renal AEs was similar in the oritavancin (0.8%) and vancomycin (0.9%) groups in the SOLO pool. Median time to renal AE onset was 8.2 days (range, 0 to 31 days) and 6.6 days (range, 3 to 22 days); median duration of renal AEs was 11.7 days (range, 4 to 37 days) and 13.0 days (range, 3 to 28 days) for the oritavancin and vancomycin groups, respectively, in the SOLO pool. No deaths or discontinuation of study drug due to a renal AE occurred in the SOLO pool Consistent findings for renal AEs were seen in the ARRD/I trials.

Table 67: Renal AEs (Safety Population)

Event of Special Interest Preferred Term	Oritavancin (N=976) n (%)	Vancomycin (N=983) n (%)
Renal AEs	7 (0.7)	9 (0.9)
Blood Creatinine Increased	2 (0.2)	3 (0.3)
Creatinine Renal Clearance		
Decreased	2 (0.2)	0
Renal Failure Acute	2 (0.2)	3 (0.3)
Renal Failure	1 (0.1)	2 (0.2)
Azotaemia	0	0
Haematuria	0	1 (0.1)
Urine flow decreased	1(0.1)	0

Adapted from Sponsor's table 37of ISS.

MO comment: One additional subject with PT urine flow decreased was identified and added to the oritavancin arm.

Hepatic Effects

A review of the hepatic effects is presented in section 7.4.2.

Cardiac effects

In the SOLO pool, the incidence of cardiac AEs in the SOC of cardiac disorders was 3.4% in the oritavancin group and 2.7% in the vancomycin group. There was a higher rate of tachycardia noted in the oritavancin arm (Table below and further analysisof these cases in section 7.4.1, common adverse events). Cardiac effects are also discussed in section 7.4.4 (ECG).

Table 68: Cardiac Adverse events in the SOLO pool (safety population)

PreferredTerm	Oritavancin N=976	Vancomycin N=983
Subjects n (%)	33 (3.4%)	27 (2.7%)
Tachycardia	24 (2.5%)	11 (1.1%)
Palpitations	4 (0.4%)	3 (0.3%)
Bradycardia	1 (0.1%)	2 (0.2%)
Cardiac failure congestive	1 (0.1%)	2 (0.2%)
Ventricular tachycardia	1 (0.1%)	2 (0.2%)
Acute myocardial infarction	0	2 (0.2%)
Atrial fibrillation	0	2 (0.2%)
Atrial thrombosis	0	1 (0.1%)
Cardiac flutter	0	1 (0.1%)
Cardio-respiratory arrest	0	1 (0.1%)
Electromechanical dissociation	1 (0.1%)	0 (0.0%)
Myocardial ischaemia	0	1 (0.1%)
Paroxysmal arrhythmia	1 (0.1%)	0 (0.0%)
Sinus bradycardia	1 (0.1%)	0 (0.0%)

Serious cardiac AEs were ventricular tachycardia, congestive heart failure, and electromechanical dissociation in the oritavancin group. Patient 201001019 in SOLO II with electromechanical dissociation was assessed as unrelated to study drug by the investigator. The incidence of cardiac AEs in the ARRD/I was similar to the SOLO trials.

MO Comment: The medical reviewer agrees with the investigator assessment that electromechanical dissociation was unrelated to the study drug. Details of the case can be found under section 7.3.1(death).

Infections and Infestations
Oritavancin has been shown to accumulate in macrophages; therefore, fungal/mycobacterial infections were assessed. Selected incidences of fungal infections are presented in table below. In the SOLO pool, there were no reported AEs of mycobacterial infections.

Table 69: Selected incidences of fungal infections in the SOLO pool (Safety population)

Dictionary-Derived Term	Oritavancin N=976	Vancomycin N=983
n(%)	15(1.5)	15(1.5)
Fungal infection	5 (0.5%)	5 (0.5%)
Vulvovaginal mycotic infection	5 (0.5%)	5 (0.5%)
Vulvovaginal candidiasis	1 (0.1%)	3 (0.3%)
Oral candidiasis	1 (0.1%)	1 (0.1%)
Candidiasis	1 (0.1%)	0 (0.0%)
Fungal skin infection	1 (0.1%)	0 (0.0%)
Tinea cruris	0 (0.0%)	1 (0.1%)
Tinea infection	1 (0.1%)	0 (0.0%)

Due to reports of sepsis/septic shock and osteomyelitis in previous multi-dose regimen trials, these events were also evaluated specifically in the SOLO trials.

The percentage of patients with sepsis, septic shock, and related events was 0.3% in the oritavancin group and 0.7% in the vancomycin group in the SOLO pool. Median duration of AE (see figure below) was 7.2 days (range, 0 to 73 days) and 1.5 days (range, 0 to 2 days) the oritavancin and vancomycin groups, respectively, in the SOLO pool. The percentage of patients with SAEs was similar in the oritavancin (0.3%) and vancomycin (0.4%) groups. Details about the deaths due to sepsis in the oritavancin arm (subject 101007001) and vancomycin arm (subject 101001226) are in section 7.3.1.

The sponsor reports the median time to onset of sepsis and septic shock AEs of 30.7 days (range, 1 to 39 days) and 8.1 days (range, 0 to 51 days) in the oritavancin and vancomycin groups, respectively, in the SOLO pool.

The cases of osteomyelitis, cellulitis and abscess limb are reviewed in section 7.3.2.

Anticholinergic Effects

In nonclinical safety pharmacology studies, oritavancin exhibited slight inhibition on the force of acetylcholine induced contractions of guinea pig ileum tissue. The percentage of patients with an anticholinergic AE was similar in the oritavancin (8.8%) and vancomycin (7.9%) groups in the SOLO pool. Pyrexia was the most frequently reported anticholinergic AE in the SOLO pool. Consistent findings for anticholinergic AEs were seen in the ARRD/I.
Subject 201001-076 had reduced visual acuity in the oritavancin arm. He was a 42 yr old male who reported squinting while reading a day after receiving oritavancin. The AE was mild and lasted 2 days.

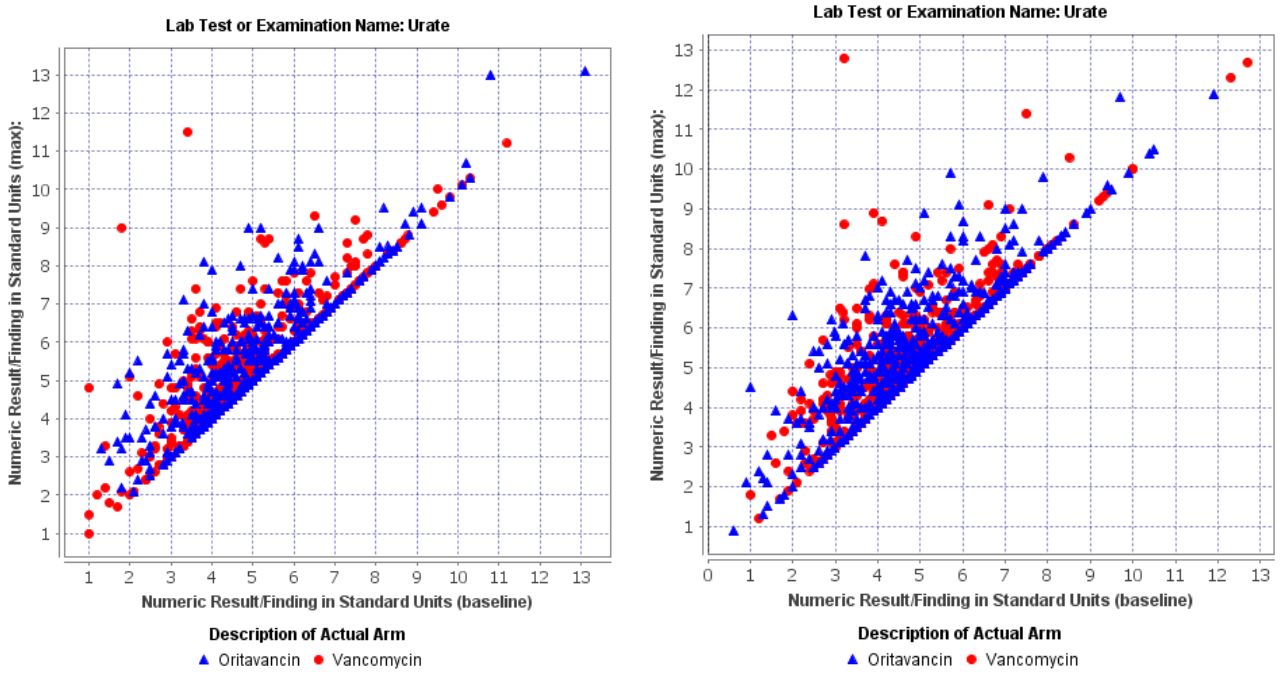
MO Comment There is insufficient information to assess causality in this subject.

Antidopaminergic Effects

In nonclinical studies, oritavancin inhibited radioligand binding to dopaminergic D1 and D2 receptors. However, in subsequent behavioral and central nervous system studies and toxicity studies and in the SOLO trials no safety signals of antidopaminergic effects were noted.

Hyperuricemia

Two cases of hyperuricemia were found in the oritavancin arm in the SOLO trial. The baseline vs maximum scatter plot shows the uric acid level in the SOLO trials were comparable in both arms.



SOLO1 **SOLO2**

Figure 26: The baseline vs maximum scatter plot showing the uric acid level in the SOLO trials

7.4.6 Immunogenicity

Refer to nonclinical review by Amy C Nostrandt. Briefly, toxicity studies in rats and dogs revealed a dose-related accumulation of eosinophilic granules in macrophages of several tissues. The applicant conducted three studies to determine if oritavancin altered the primary antibody (measured as IgM) or secondary antibody (measured as IgG) response to a Tcell dependent sheep erythrocyte-derived protein test antigen (SRBC) administered in Freund's adjuvant. In two of these studies, a delayed response to an oritavancin effect on primary antibody production was noted. There were no significant effects on the secondary antibody (IgG) response in the test or recovery phases of either study, suggesting that the ability to produce antigen specific memory cells remained intact under conditions that resulted in depressed primary IgM antibody response. The third study did not reproduce these results. Also, an in vitro study to determine if intracellular accumulation of oritavancin alters macrophage functions (mdco-ori-m002). Based on the findings from this study the sponsor concluded that oritavancin-loaded macrophage cells retained full functional capabilities.

Clinical hypersensitivity reactions are discussed in section 7.4.5 of the review.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In the Phase 2 SIMPLIFI trial, the cumulative dose of oritavancin received was as follows:

Table 70: Cumulative dose of oritavancin received in the SIMPLIFI Trial

	200 mg Ori Daily Dose (N=100)	1200 mg Ori Single Dose (N=99)	800 mg Ori Infrequent Dose			Total (N=302)
			Infrequent Dose overall (N=103)	800 mg only (N=34)	800 mg + 400 mg (N=69)	
Mean	1064.0	1185.8	1044.7	782.4	1173.9	1097.3
SD	354.1	86.6	205.7	75.8	96.5	248.8
Median	1200.0	1200.0	1200.0	800.0	1200.00	1200.0
Minimum	200.0	488.0	400.0	400.0	800.0	200.0
Maximum	1400.0	1200.0	1200.0	800.0	1200.0	1400.0

Abbreviations: Ori = oritavancin; SD = standard deviation. Source: Table 14.1.40.1

In this trial, 57% of patients had TEAEs. Of them, 42.0% (73/174) had at least 1 event investigator-assessed as being related to study medication.56.0% in the daily dose, 55.6% in the single dose, and 61.2% in the infrequent dose groups. Three deaths occurred in the daily dose group, 0 in the single dose group and 2 in the infrequent dose group. The percentage of patients with an SAE was 8.3% (25/302), with 11.0% (11/100), 7.1% (7/99), and 6.8% (7/103) of patients having SAEs in the daily dose, single dose, and infrequent dose groups, respectively.

The TEAEs in the individual SOCs in the different dose groups are presented in the Table below.

Table 71: TEAEs in the individual SOCs in the different dose groups (SIMPLIFI trial)

System or Organ Class	1200 mg ORI Single Dose N=99	200 mg ORI Daily Dose N=100	800 mg ORI Infrequent Dose N=103
Gastrointestinal disorders	23 (23.2%)	22 (22.0%)	19 (18.4%)
General disorders and administration site conditions	14 (14.1%)	17 (17.0%)	19 (18.4%)
Infections and infestations	14 (14.1%)	22 (22.0%)	13 (12.6%)
Vascular disorders	13 (13.1%)	12 (12.0%)	19 (18.4%)
Nervous system disorders	13 (13.1%)	9 (9.0%)	7 (6.8%)
Skin and subcutaneous tissue disorders	6 (6.1%)	12 (12.0%)	8 (7.8%)
Investigations	9 (9.1%)	8 (8.0%)	4 (3.9%)
Metabolism and nutrition disorders	7 (7.1%)	6 (6.0%)	7 (6.8%)
Musculoskeletal and connective tissue disorders	6 (6.1%)	6 (6.0%)	6 (5.8%)
Respiratory, thoracic and mediastinal disorders	6 (6.1%)	6 (6.0%)	6 (5.8%)
Cardiac disorders	1 (1.0%)	6 (6.0%)	6 (5.8%)
Psychiatric disorders	4 (4.0%)	4 (4.0%)	3 (2.9%)
Renal and urinary disorders	4 (4.0%)	2 (2.0%)	4 (3.9%)
Blood and lymphatic system disorders	4 (4.0%)	1 (1.0%)	4 (3.9%)
Eye disorders	1 (1.0%)	1 (1.0%)	4 (3.9%)
Injury, poisoning and procedural complications	1 (1.0%)	2 (2.0%)	3 (2.9%)
Immune system disorders	3 (3.0%)	0 (0.0%)	0 (0.0%)
Reproductive system and breast disorders	1 (1.0%)	1 (1.0%)	0 (0.0%)
Hepatobiliary disorders	0 (0.0%)	1 (1.0%)	0 (0.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.0%)	0 (0.0%)	0 (0.0%)
Subjects n(%)	56 (56.6%)	56 (56.0%)	63 (61.2%)

The most common TEAEs (200 mg daily dose, 1200 mg single dose, 800 mg infrequent dose groups, respectively) were nausea (6.0%, 9.1%, and 6.8%), phlebitis (5%, 5.1%, and 9.7%) and diarrhea (6.0%, 6.1% and 3.9%). TEAE in >3% of subjects by SOC and PT is presented below.

Table 72: Treatment-Emergent Adverse Events During Study in ≥3% of Patients in any of the Treatment Groups by System Organ Class and Preferred Term in the ITT Population

System Organ Class and Preferred Term	200 mg Ori Daily Dose N = 100 n (%)	1200 mg Ori Single Dose N = 99 n (%)	800 mg Ori Infrequent Dose N = 103 n (%)	Total N = 302 n (%)
Musculoskeletal and Connective Tissue Disorders	6 (6.0)	6 (6.1)	6 (5.8)	18 (6.0)
Respiratory, Thoracic, and Mediastinal Disorders	6 (6.0)	6 (6.1)	6 (5.8)	18 (6.0)
Cough	4 (4.0)	1 (1.0)	1 (1.0)	6 (2.0)
Cardiac Disorders	6 (6.0)	1 (1.0)	6 (5.8)	13 (4.3)
Psychiatric Disorders	4 (4.0)	4 (4.0)	3 (2.9)	11 (3.6)
Insomnia	3 (3.0)	4 (4.0)	2 (1.9)	9 (3.0)
Renal and Urinary Disorders	2 (2.0)	4 (4.0)	4 (3.9)	10 (3.3)
Eye Disorders	1 (1.0)	1 (1.0)	4 (3.9)	6 (2.0)
Blood and Lymphatic System Disorders	1 (1.0)	4 (4.0)	4 (3.9)	9 (3.0)
Immune System Disorders	0	3 (3.0)	0	3 (1.0)
Hypersensitivity	0	3 (3.0)	0	3 (1.0)

Source: Applicant's Table 12-4 of the study report.

MO comment: A dose dependant increase in incidence of AE was not seen in the SIMPLIFI study.

In the TQT study (MDCO-ORI-12-02) with the 1600 mg dose of oritavancin in healthy subjects, 30.9% reported at least 1 TEAE, with a higher percentage of TEAEs reported in the oritavancin group (41.7%) compared with the placebo (28.6%) and moxifloxacin (23.1%) groups. TEAE reported in > 2 subjects in the oritavancin group were oral paresthesia in 5 subjects (10.4%), nausea (8.3%), and headache, vomiting, and infusion site pain (6.3% each); in the placebo group were headache (8.2%) and dizziness (6.1%), and in the moxifloxacin group was nausea (7.7%).One subject in the oritavancin group had TEAEs of generalized pruritus, rash, cough, dizziness, and tachycardia that led to discontinuation of study drug.

MO comment: 2 additional subjects- MDCO-ORI-12-02-2037, MDCO-ORI-12-02-2044 with oral hypoaesthesia was also identified in the oritavancin arm with the 1600 mg dose.

MO comment: The overall incidence of TEAE as stated above were similar in the oritavancin and vancomycin arm and no dose dependencyfor AE was noted.

7.5.2 Time Dependency for Adverse Events

Oritavancin is being proposed to be used for an acute infection as a single dose, thus time dependency for AEs is not relevant in this submission. A 60 day follow up in the SOLO trials did not reveal additional AEs.

7.5.3 Drug-Demographic Interactions

Clinical safety results in subgroups of subjects were analyzed for drug-demographic interactions by age (< 65 years and ≥ 65-75 years and ≥ 75 years), gender (male and female), race (White and non-White), and country (Asia, Eastern Europe, South America, Western Europe). Overall, no clinically significant differences with regard to drug-demographic interactions were observed in Phase 3 trials.

Treatment emergent adverse events occurred in similar frequencies in patients <65 years of age (56%, 498/890) compared to patients ≥ 65 years of age (48.8%, 42/86). Higher rates of treatment emergent adverse events were reported in >75 years of age however occurred in similar frequencies between oritavancin vs vancomycin treatment groups (64.7%, 11/17 vs 68.8%, 11/16; respectively).

MO comment: Upon review of the TEAE in age group >75 years they were determined not to be clinically significant (fatigue, asthenia).

7.5.4 Drug-Disease Interactions

The overall incidence of ≥ 1TEAEs and serious TEAEs in explored drug disease categories were similar between the oritavancin and vancomycin groups. The incidence of serious adverse events and ≥ 1 TEAE is presented in Table below. The explored drug-disease categories were as follows:

- ABSSSI category

- Renal insufficiency (Estimated Creatinine Clearance mild <30ml/min, 30-59, 60 to <90)
- Hepatic impairment (baseline ALT or AST > 3X ULN or total bilirubin > 2X ULN)
- Diabetes status
- Immunodeficiency
- Baseline MRSA or MSSA category

Table 73: Incidence of serious adverse events and > 1 TEAE

	No of subjects with Serious TEAE n(%)		Subjects with ≥1 TEAE n(%)	
	Oritavancin	**Vancomycin**	**Oritavancin**	**Vancomycin**
Diabetes	23 (16.7)	18 (12.8)	87 (63.0)	89 (63.1)
Non diabetics	34 (4.1)	40 (4.8)	453 (54.1)	470 (55.8)
Abscess	16 (5.2)	11 (3.7)	175 (56.8)	172 (57.3)
Cellulitis	31 (8.1	34 (8.5)	222 (57.7)	237 (59.0)
Wound infection	10 (3.5)	13 (4.6)	143 (50.5)	150 (53.4)
Renal impairment				
Crcl <30	1 (3.6%)	2 (6.7%)	1 (14.3)	3 (42.9)
Crcl 30-59	12 (17.1)	3 (5.6)	40 (57.1)	25 (46.3)
Crcl 60-90	8 (4.2)	8 (4.4)	85 (44.7)	90 (49.2)
Crcl >90	36 (5.2)	45 (6.3)	405 (58.9)	435 (60.8)
Hepatic impairment	2 (6.9)	1 (3.7)	20 (69.0)	12 (44.4)
No hepatic impairment	55(5.8)	57 (6.0)	520 (54.9)	547 (57.2)
Immunodeficiency	3 (18.8)	4 (16.7)	9 (56.3)	10 (41.7)
No Immunodeficiency	54 (5.6)	54 (5.6)	531 (55.3)	549 (57.2)
Baseline MRSA	12 (5.88%)	14 (6.97%)	139(68.1%)	136(67.7%)
Baseline MSSA	9 (3.36%)	10 (3.68%)	127(47.4%)	135(49.6%)

Adapted from reviewer generated tables and applicant's table 65,66,67,71.

There were slightly higher incidence of serious TEAE in the diabetic subjects 23/138 (16.7%) in the oritavancin arm compared 18/141 (12.8%) in the vancomycin arm. However the overall number of subjects with ≥1 TEAE were similar in both arms. In the subjects with baseline Crcl of 30-<60 ml/min, there were 12/70 subjects in the oritavancin arm who had a serious AE as compared to 3/54 subjects in the vancomycin arm. Further analyses of these cases are presented in table below. Out of these 12 subjects in the oritavancin arm 6 had an AE related to infection. There was one death in each arm.

Table 74: Subjects with serious AE in category of baseline Crcl of 30-<60 ml/min in SOLO trials

	Subject ID	**History of renal insufficiency**	**AE**	**Outcome**	**Treatment discontinuation**
Oritavancin	101001-002	None	Worsening of skin infection	Resolved	Yes (lack of efficacy)
	101002-030	None	Urosepsis	Resolved	No
	101002-046	None	Diverticulitis	Resolved	No
	101014-002	Yes	Ventricular tachycardia	Resolved	No
	101015-002	None	Progression of cellulitis (index infection), PVD		No
	201001-001	None	Shortness of breath	Resolved	No

	Subject ID	History of renal insufficiency	AE	Outcome	Treatment discontinuation
	201001-019	None	PEA, electromechanical dissociation	Death	Yes
	201001-144	None	Pneumonia	Resolved	No
	201002-105	None	Rectal bleeding	Resolved	Yes
	202001-003	None	Osteomyelitis	Resolved	No
	291005-013	Unknown	Mouth ulcer, stomatitis	Resolved	Yes
	297003-004	Yes	CHF, Leucocytoclastic vasculitis, constipation	Resolved	Yes
Vancomycin	101027-027	None	Dementia, parkinsonism	Resolved	No
	191005-015	None	hypersensitivity reaction	Resolved	Yes
	207005-003	None	acute mi, trophic ulcer ext	Death	No

The investigator thought the hypersensitivity vasculitis was related to the study drug.

MO comment: The applicant has conducted Population PK analysis and indicated that renal impairment had no clinically relevant effect on the exposure of oritavancin. However, no dedicated studies in dialysis patients have been conducted. Dosage adjustment of oritavancin is not needed in patients with mild, moderate, and severe renal impairment.

7.5.5 Drug-Drug Interactions

In vitro studies with human liver microsomes showed that oritavancin inhibited the activities of cytochrome P450 (CYP) enzymes 1A2, 2B6, 2D6, 2C9, 2C19, and 3A4. The observed noncompetitive inhibition of multiple CYP isoforms is likely to be reversible. In vitro studies indicate that oritavancin is neither a substrate nor an inhibitor of the efflux transporter P-gpp. The applicant has conducted a Drug Drug Interaction study in healthy volunteers (MDCO-ORI-12-03) that utilized the Cooperstown 5+1 cocktail with the probe drugs midazolam, warfarin, caffeine, omeprazole, and dextromethorphan. A single 1200 mg dose of oritavancin was shown to be a weak inhibitor of CYP2C9 (31%) and CYP2C19 (15%) and a weak inducer of CYP2D6 (31%) and CYP3A4 (18%). Oritavancin had no effect on CYP1A2, N-acetyltransferase-2 enzyme activity, or xanthine oxidase activity.

In the SOLO Trials, patients who had concomitant administration of a CYP2C9 or CYP2D6 substrate had higher rates of AEs, SAEs and AEs leading to study drug discontinuation compared to those who did not in both the oritavancin and vancomycin groups (Table below).

Table 75: AEs with Drug Drug Interactions for CYP2C9 and CYP2D6

	Co-administered with a CYP2C9		Co-administered without a CYP2C9	
	Oritavancin (N=92) n (%)	Vancomycin (N=96) n (%)	Oritavancin (N=884) n (%)	Vancomycin (N=887) n (%)
Any AEs	67 (72.8)	75 (78.1)	473 (53.5)	484 (54.6)
AEs resulting in death	0	0	2 (0.2)	3 (0.3)
Any SAEs	12 (13.0)	11 (11.5)	45 (5.1)	47 (5.3)
AEs leading to study drug discontinuation	3 (3.3)	3 (3.1)	18 (2.0)	16 (1.8)

	Co-administered with a CYP2C9		Co-administered without a CYP2C9	
	Oritavancin (N=92) n (%)	**Vancomycin (N=96) n (%)**	**Oritavancin (N=884) n (%)**	**Vancomycin (N=887) n (%)**
	Co-administered with a CYP2D6		**Co-administered without a CYP2D6**	
	Oritavancin (N=475) n (%)	**Vancomycin (N=475) n (%)**	**Oritavancin (N=501) n (%)**	**Vancomycin (N=508) n (%)**
Any AEs	325 (68.4)	342 (72.0)	215 (42.9)	217 (42.7)
AEs resulting in death	2 (0.4)	1 (0.2)	0	2 (0.4)
Any SAEs	4 (0.8)	2 (0.4)	1 (0.2)	2 (0.4)
AEs leading to study drug discontinuation	23 (4.8)	28 (5.9)	13 (2.6)	13 (2.6)

Source: applicant's table 72 and 73.

MO comment: Vancomycin is not a known CYP450 inhibitor. There is no difference in the incidence of AE appear between oritavancin and comparator arms and, therefore, this potential interaction may not be clinically meaningful.

Safety evaluation for subjects taking concomitant warfarin therapy with oritavancin was conducted. Reviewer analysis generated 14 subjects with warfarin and oritavancin treatment and 16 subjects with warfarm and vancomycin. There were 7 subjects who had TEAE however none of the AE reported were specific for any clinical interaction with warfarin in the oritavancin arm. No bleeding was reported. Results from a drug-drug interaction study in healthy volunteers showed that oritavancin is a weak inhibitor of CYP2C9 (approximately 30% increase in the mean AUC of warfarin); therefore, changes in the metabolism of warfarin when combined with oritavancin may result in higher concentrations of warfarin.

aPTT assay

Oritavancin interferes with the aPTT assay due to an in vitro interaction with the phospholipids necessary for accurate aPTT estimation. In vitro studies indicate that aPTT results after an oritavancin dose may remain falsely elevated until oritavancin concentrations fall below 15 µg/ml. Oritavancin concentrations are expected to fall below 15 µg/mL in 50% and 90% of patients within 25 and 40 hours, respectively, after the start of a single 1200 mg IV infusion as reported in the Study ICPD 00247-1.

Medical reviewer comment: Oritavancin artificially prolongs PTT and is expected to prolong other laboratory coagulation tests: PT and INR, making monitoring of tanticoagulant effect of warfarin unreliable. It is particularly of concern as oritavancin increases warfarin exposure by 30% when administered concomitantly. It may be difficult to evaluate aPTT levels in patients on oritavancin and intravenous heparin concomitantly.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Oritavancin is given in single dose infusion and not administered chronically. Therefore carcinogenicity studies were not conducted.

7.6.2 Human Reproduction and Pregnancy Data

No adequate and well-controlled studies with oritavancin have been conducted in pregnant women. Oritavancin did not affect the fertility or reproductive performance of male rats (exposed to daily doses up to 30 mg/kg for at least 4 weeks) and female rats (exposed to daily doses up to 30 mg/kg for at least 2 weeks prior to mating). However, these daily doses would be equivalent to a human dose of 300 mg, or 25% of the proposed clinical dose. The human plasma cumulative AUC after a 1200 mg single dose was 1530 μg*h/ml while the cumulative plasma AUC in non pregnant rats for a NOAEL of 1mg/kg was 357 μg*h/ml with a margin of safety of 0.23. For pregnant rats the plasma AUC at 24 hrs was 503 at 30 mg/kg dose at study day 6. Five pregnancies were reported in oritavancin-treated patients. Three of the pregnancies in the oritavancin group were reported in the Phase 3 SOLO studies that utilized the single 1200 mg dose and two of the pregnancies were reported in the Phase 1 studies in healthy subjects. There were two miscarriages, one elective termination, and one healthy birth; one pregnancy is ongoing at the time of the NDA review.

- Patient 101005032 in SOLO I: A 31-year-old female who received a single infusion of oritavancin /placebo over a 10-day period for a neck abscess and experienced pregnancy and spontaneous abortion 15 days after the single dose of oritavancin. Relevant medical history/concurrent conditions included hypertension, spontaneous abortions (b) (6) gestational diabetes, obesity, and urinary tract infection. Relevant concomitant medications included morphine, ceftriaxone, cephalexin, mupirocin, metoprolol, and oxycodone. 13 days after receiving a single infusion of oritavancin she developed abdominal pain, 15 days after receiving a single infusion of oritavancin, the patient was noted to have a low beta-HCG level but no intrauterine pregnancy on an abdominal and endovaginal sonogram. 18 days after the single dose of oritavancin, she experienced vaginal bleeding and subsequently the serum beta HCG progressively declined.

- Patient 201001200 in SOLO II: 27 year old with wound infection received oritavancin. Pregnancy exposure to oritavancin occurred at day 8 after oritavancin was administered. Relevant medical history/concurrent conditions included IV drug use, obesity, rosacea, placenta previa. 59 days after the single dose of oritavancin, a 7 week pregnancy was detected when she presented with a 3 day history of vaginal bleeding and suprapubic cramping. Final outcome of the pregnancy is unknown, pending an anticipated (b) (6) delivery date.

- Patient 201001122 in SOLO II: 41 year old female with pregnancy detected 44 days following a single infusion of oritavancin. Relevant medical history/concurrent conditions included IV drug use, hypertension, depression, anxiety, chest pain, homelessness, alcohol ingestion, and smoking (20 cigarettes per day). Relevant concomitant medications included penicillin V potassium and acetaminophen/hydrocodone. On Day 57, the patient fell down. On the following day, the patient had a miscarriage.

- Subject OCSI-007 001-0003: This was a drug interaction study with oritavancin and desipramine. A 20-year-old healthy female, received oral desipramine from Study Days 1

to 13 and 800 mg administered intravenously once daily oritavancin from study days 8 to 12. 3 days after the fifth and final oritavancin infusion the subject had a positive urine test for pregnancy. The patient was determined to be within 2 to 3 weeks into her pregnancy. Oritavancin was discontinued. Subject terminated pregnancy electively.

- Subject OPUL-00101-016: became pregnant approximately 7 weeks after completing her last dose of oritavancin. She gave birth to a healthy male child.

  MO comment: Patient 101005032 had a history of spontaneous abortions and therefore more susceptible to miscarriages. There could be a possible relation of the abortion to oritavancin, but it is more likely related to her prior history. Patient 201001122's miscarriage is likely related to her fall and unlikely related to oritavancin. No conclusions regarding relationof the pregnancy outcome to oritavancin can be drawn from the subject OCSI-007 001-0003 who terminated her pregnancy electively.

7.6.3 Pediatrics and Assessment of Effects on Growth

Oritavancin has not been evaluated to date in children below 18 years of age and is not proposed for use in the pediatric population in this application.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

With a single dose infusion, no withdrawal or rebound effects have been observed; no such effects are anticipated.

In the tQT study MDCO-ORI-12-02, healthy subjects received a supratherapeutic single 1600 mg dose of oritavancin. The AEs seen with 1600 mg of oritavancin were consistent with those in patients who received the therapeutic dose of 1200 mg, with the exception of paraesthesia oral (10.4% [5/48 patients]) and hypoaesthesia oral (4.2% [2/48 patients]) which were more frequent with 1600 mg.

7.7 Additional Submissions / Safety Issues

The Applicant submitted a 120-day Safety Report on April 4, 2014 indicating that there was no new safety information to report.

8 Postmarket Experience

None

9 Appendices

9.1 Literature Review/References

References

1. Talan DA et al. Comparison of Staphylococcus aureus from skin and soft tissue infections in US emergency department patients, 2004 and 2008. Clinical Infectious Diseases 2011; 53: 144-149
2. Jenkins TC et al. Skin and soft tissue infections requiring hospitalization at an academic medical center: opportunities for antimicrobial stewardship. Clinical Infectious Diseases 2010; 51:895-901
3. Spellberg B et al. Antimicrobial agents for complicated skin and skin structure infections: justifications of non-inferiority margins in the absence of placebo-controlled trials. Clinical Infectious Diseases 2009; 49: 383-391
4. Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf
5. Leise MD, Poterucha JJ, Talwalkar JA. Drug-Induced Liver Injury. Mayo Clin Proc. 2014 Jan; 89 (1):95-106

9.2 Labeling Recommendations

At the time of the review preparation the reviewer had no specific comments on labeling.

9.3 Advisory Committee Meeting

An Advisory Committee Meeting was not held to discuss this application.

9.4 Financial disclosure form

Clinical Investigator Financial Disclosure Review

Application Number: NDA 206334

Submission Date(s): December 6, 2013

Applicant: The Medicines Co.

Product: ORBACTIV

Reviewer: Mayurika Ghosh, MD

Date of Review: April 23, 2014

Covered Clinical Study (Name and/or Number): TMC-ORI-10-01 and TMC –ORI-10-02

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 69 for TMC-ORI-10-01 and 60 for TMC –ORI-10-02		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): N/A Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements: N/A	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:N/A	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from applicant)

The financial disclosure information reported in Module 1.3.4 was incomplete. It did not contain the attachment listing of investigators with no reportable/reportable disclosures. The sponsor submitted this information on January 10, 2013 in response to an information request.
The applicant certified that there were no financial arrangements with clinical investigators that could affect the outcome of the study as defined in 21 CFR 54.2 (a) and that the clinical investigators had no reportable financial disclosures in the SOLO 1 and 2 trials as defined in 21 CFR 54.2 (b). The applicant also certified that no investigator was the recipient of significant payments as defined in 21 CFR 54.2(f).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAYURIKA GHOSH
05/08/2014

YULIYA I YASINSKAYA
05/08/2014