CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	206334
Drug Name:	Oritavancin diphosphate (single 1200 mg dose of IV)
Indication(s):	Acute Bacterial Skin and Skin Structure Infection (ABSSSI)
Applicant:	The Medicines Company
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Keywords:	Noninferiority trial, Active Control, Confidence Interval, Noninferiority margin, Sensitivity Analyses, Concordance Analyses

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1. EXECUTIVE SUMMARY

Introduction:

In this submission, the applicant has provided findings from two independent and identically-designed phase 3 trials, SOLO I and SOLO II, to establish efficacy and safety of a single 1200 mg dose of intravenous Oritavancin for the treatment of acute bacterial skin and skin structure infections (ABSSSI). Both SOLO I and SOLO II are global, multicenter, randomized, double-blind, active-controlled, parallel-group clinical trials in patients with an ABSSSI suspected or confirmed to be caused by a Gram-positive pathogen. The SOLO I and SOLO II protocols were designed using the *2010 FDA Guidance for Industry: Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment*.

The primary objective of the SOLO trials was to establish noninferiority of single-dose intravenous (IV) Oritavancin compared with IV Vancomycin given for 7 to 10 days. The primary efficacy endpoint was a composite endpoint defined as the cessation of spread or reduction in size of the baseline lesion, absence of fever, and no rescue antibiotic medication at the Early Clinical Evaluation (ECE) time point of 48 to 72 hours after study drug infusion. The primary analysis population was the modified intent-to-treat (mITT) population, which included all randomized patients who were treated.

The definition of the primary endpoint met the criteria recommended by the *2010 FDA Guidance for Industry: Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment*. Moreover, this endpoint was pre-specified for noninferiority testing using a margin of 10%. Although the primary endpoint used in SOLO I and SOLO II was previously agreed upon by the Agency through a Special Protocol Agreement, this endpoint is no longer recommended for non-inferiority trials in ABSSSI. Instead, current recommendations are based on the *2013 FDA Guidance for Industry: Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment.* The guidance recommends a primary endpoint evaluating at least 20% reduction in lesion size from baseline at 48-72 hours.

Both SOLO trials included an additional secondary efficacy endpoint of investigator-assessed clinical cure at the Post Therapy Evaluation (PTE) at 7 to 14 days from end of therapy (EOT) at 7 to 10 days. Inferential testing based on a non-inferiority hypothesis for clinical cure at PTE was not considered acceptable due to lack of a scientifically justifiable non-inferiority margin.

Conclusions and Recommendations

This reviewer concludes that both SOLO I and SOLO II trials provided sufficient evidence that a single 1200 mg Oritavancin dose is noninferior to 7 to 10 days of Vancomycin (1g or 15 mg/kg twice daily) for the treatment of ABSSSI in adult patients. The prespecified noninferiority margin for the cessation of spread or reduction in size of the baseline lesion, absence of fever, and no rescue antibiotic medication at 48-72 hours and the lesion size reduction ≥ 20% at 48-72 hours from baseline was met in both trials. The findings are summarized below.

Based on the reviewer's analysis of the primary endpoint, responder rates at 48-72 hours, SOLO I and SOLO II provided adequate evidence supporting the efficacy of Oritavancin in treating patients with ABSSSI infections. Responder rates were similar between Oritavancin and the comparator groups: 82.3% [391/475] vs.78.9% [378/479], a 3.4% difference (95% CI:-1.6%, 8.4%) in Trial SOLO I and 80.1% [403/503] vs.82.9%[416/502], a -2.7% difference (95% CI: -7.5%, 2.0%) in Trial SOLO II.

The reviewer's analysis of a lesion size reduction ≥ 20% from baseline at 48-72 hours provided evidence supporting the efficacy of Oritavancin in treating patients with ABSSSI infections in both SOLO I and SOLO II trials. The percentage of patients with lesion size reduction ≥ 20% from baseline at 48-72 hours were similar between Oritavancin and the comparator: 86.9%[413/475] vs.82.9%[397/479], a 4.1% difference (95% CI: -0.5%, 8.6%) in Trial SOLO I and 85.9 % [432/503]vs. 85.3%[428/502], a 0.6% difference (95% CI: -3.7%, 5.0%) in Trial SOLO II.

The reviewer's analysis of an additional secondary efficacy endpoint, the investigator-assessed clinical cure at PTE in the Oritavancin and the comparator groups were 79.6% [378/475] vs.80.0%[383/479], a 0.4% difference (95% CI: -5.5%, 4.7%) in Trial SOLO I and 82.7% [416/503] vs.80.5%[404/502], a 2.2% difference (95% CI: -2.6%, 7.0%) in Trial SOLO II.

The safety data from SOLO I and SOLO II demonstrated that a single 1200 mg IV dose of Oritavancin had a similar safety profile to 7 to 10 days of Vancomycin treatment (1 g or15 mg/kg twice daily). Most of the AEs were mild or moderate in severity. The incidences of deaths, SAEs, and discontinuation of trial drug due to an AE in Oritavancin-treated patients were low and similar to the incidences seen in patients receiving Vancomycin. Please see the clinical review of safety by Dr. M. Ghosh for further detail.

2. INTRODUCTION

2.1Overview

The Applicant's current submission includes two pivotal phase 3 trials, SOLO I and SOLO II based on the 2010 FDA regulatory guidance (a Special Protocol Agreement on November 24, 2010 for SOLO I and SOLO II protocols) for ABSSSI. SOLO I and SOLO II were two identical trials in which the single dose 1200 mg Oritavancin treatment is compared to Vancomycin given twice daily for 7 to10 days.

The following table provides the description of the two pivotal phase 3 trials:

Table 1: List of Phase 3 trials reviewed

Trial #	Phase/Design	Treatment Period	Follow-up Period	Number of Subjects per Treatment Group (mITT)	Trial Population
SOLO I	Phase 3; Multicenter (32 centers: Argentina, Canada, India, Israel, Mexico, Romania, Russia, Spain, Ukraine, and United States), randomized (1:1), double-blind, active-controlled, parallel-group trial	7 to 10 days	60 days (+ 7 days) post first administration of trial drug	Treatment group 1(n=475): Oritavancin: 1200 mg IV over 3 hr. for the first dose followed by IV placebo infusions over 60 min every 12 hour for 7-10 days Treatment group 2(n=479): Vancomycin: 1 g or 15 mg/kg every 12 hr. for 7-10 days	Adults with ABSSSI suspected to be caused by Gram-positive pathogens, including MRSA
SOLO II	Phase3; Multicenter (46 centers: Germany, India, Israel, Mexico, Romania, Russia, Spain, Ukraine, and United States), randomized (1:1), double-blind, active-controlled, parallel-group trial	7 to 10 days	60 days (+ 7 days) post first administration of trial drug	Treatment group 1(n=503): Oritavancin: 1200 mg IV over 3 hr. for the first dose followed by IV placebo infusions over 60 min every 12 hr. for 7-10 days Treatment group 2(n=502): Vancomycin: 1 g or 15 mg/kg every 12 hour for 7-10 days	Adults with ABSSSI suspected to be caused by Gram-positive pathogens, including MRSA

Source: Reviewer's Table

SOLO I and SOLO II enrolled patients with a mixture of ABSSSIs including cellulitis/erysipelas (40%), wound infection (29%), and major cutaneous abscesses (31%). The SOLO protocols closely followed the 2010 guidance for ABSSSI. The patient population was representative of ABSSSIs with *Staphylococcus aureus* (*S. aureus*) and a subset of patients (N=405 from both trials) with documented MRSA infections.

The primary efficacy endpoint in SOLO I and SOLO II was a composite endpoint defined as the cessation of spread or reduction in size of the baseline lesion, absence of fever, and no rescue antibiotic medication at ECE 48 to 72 hours from initiation of drug infusion. The definition of the primary endpoint meets the criteria recommended in the 2010 *FDA Guidance for Industry: Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment*. This endpoint was prespecified for noninferiority testing with a margin of 10% using the modified Intent-to-Treat (mITT) populations which includes all randomized patients who were treated.

A Qualified Infectious Disease Product (QIDP) Designation for the treatment of ABSSSI was granted on October 31, 2013.

2.2 Data Sources

The primary efficacy data (including demographic data) and the baseline characteristics datasets were provided, respectively, in *ADCR.XPT* and *ADLS.XPT* under the network drive:

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The treatment group was denoted by TRTP (Oritavancin and Vancomycin).The data for primary efficacy (*clinical cure at ECE: PEO under column PARAMCD*) with Success or Failure in column AVALCAT2 (analysis category 2). The key secondary endpoint (*investigator-assessed clinical cure(IACC) at EOT, Day 10 and PTE* visits) were also provided in ADCR.XPT dataset The data for percentage lesion area decrease from baseline (Variable name: PCHG) at ECE visit were provided in ADLS.XPT.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The applicant has stated that the data for SOLO I and SOLO II were collected using an electronic data capture system developed by (b) (4) called (b) (4) The applicant states the following:

> (b) (4) is the client-side component of the (b) (4) electronic data capture system which allows Investigators and Trial Coordinators to enter patient data via the internet. The data entered in (b) (4) was loaded and transferred immediately to a secured site at (b) (4) Site personnel also resolved queries on discrepant data by accessing the electronic data capture system via the internet.
>
> The first level of checking for data validity was done through defining mandatory fields and consistency and range checks residing in the (b) (4) system. These checks identified potentially discrepant data entered during the data entry session. After data were entered, edit checks were then run automatically across fields to ensure consistency within the eCRF. Finally, when all data were entered into the system, monitors and data managers had the ability to manually review patient data and to generate notes for any remaining discrepant data.

> The Applicant conducted audits at the trial centers. Audits included, but were not limited to, review of drug accountability, presence of required documents, the informed consent process, and comparison of eCRFs with source documents.

The review team identified that there were two foreign sites (Site 191008 and Site 191009 in India) in SOLO I where the efficacy rates of the primary endpoint were higher (compared to overall rates as well as to other sites) in both treatment groups. The Office of Scientific Investigations (OSI) is currently investigating Site 191008. OSI could not inspect Site 191009 for logistical reasons. This reviewer analyzed the primary efficacy endpoint by excluding both sites to examine any potential impact on overall analyses. See Section 5.1 for details.

The quality and integrity of the submission are acceptable. The submission uses the electronic common technical document (eCTD) format. The submission is well organized and easy to navigate. Submitted Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets meet the Clinical Data Interchange Standards Consortium (CDISC) standards. It is possible to reproduce the primary endpoint and the secondary endpoints from both the SDTM and ADAM datasets that the applicant provided.

3.2. Evaluation of Efficacy

3.2.1 Trial Design and Endpoints

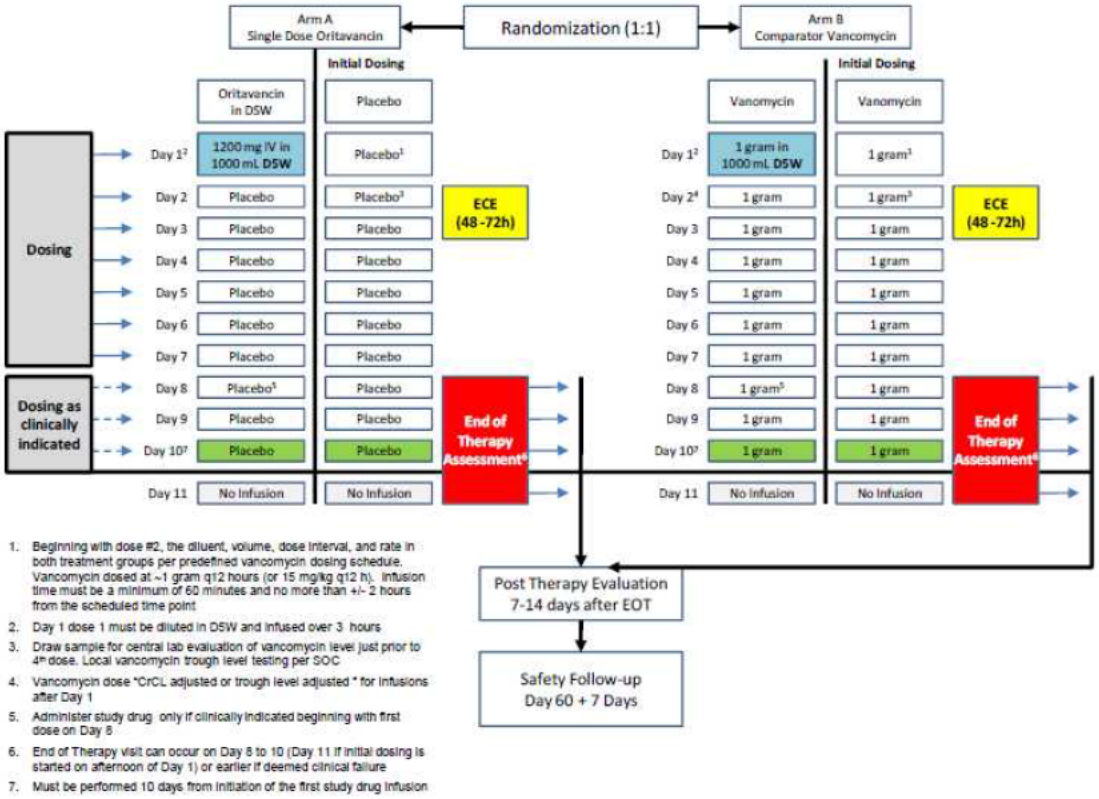
SOLO I and SOLO II were two large*, identically-designed*, global, double-blind, randomized, parallel group, phase 3 clinical trials which included patients with an ABSSSI caused by a Gram-positive pathogen. The primary objective of the SOLO trials was to establish noninferiority of single-dose IV Oritavancin compared with IV Vancomycin given for 7 to 10 days using the primary efficacy outcome defined as the cessation of spread or reduction in size of the baseline lesion, absence of fever, and no rescue antibiotic medication at the Early Clinical Evaluation (ECE) time point of 48 to 72 hours in the modified intent-to-treat (mITT) population

In SOLO I, 968 patients were randomized (1:1; Oritavancin, 483 patients; Vancomycin, 485 patients) in 46 trial centers in 9 countries (number of centers in parentheses): Germany (1), India (9), Israel (3), Mexico (2), Romania (2), Russia (2), Spain (1), Ukraine (3), and United States (23).

In SOLO II, 1019 patients were randomized (1:1; Oritavancin, 509 patients; Vancomycin, 510 patients) in 32 trial centers in 10 countries (# of centers in parentheses): Argentina (1), Canada (1), India (6), Israel (2), Mexico (1), Romania (1), Russia (6), Spain (1), Ukraine (2), and United States (11).

The overview of the design of both SOLO trials is provided in Figure 1:

Figure 1: Overview of Study Design



Source: Applicant's clinical trial report, Figure 1, page 26 (SOLO I)

Schedule of Assessments:

The schedule of assessments of both SOLO I and SOLO II trials consisted of a Screening period (Screening period lasted no longer than 24 hours), a Treatment period, and a Follow-Up period as described below:

The Treatment period was the period between initiation of the first infusion of trial drug (Day 1) to termination of the last infusion of trial drug (either Day 7 or Day 10). The Treatment period was no less than 7 days and could have been up to 10 days. During the Treatment period, efficacy was assessed at 48 to 72 hours following initiation of trial drug administration; this was defined as the Early Clinical Evaluation (ECE).

The Follow-Up period was the period between termination of the last infusion of trial drug (either Day 7 or Day 10) and a Safety Visit that occurred 60 days after the first trial drug administration. There were three visits during the Follow-up period when efficacy was assessed:

> An end of therapy (EOT) visit that occurred no more than 24 hours from either the last administration of trial drug or a change to a non-trial drug for the primary ABSSSI (whichever came first);
> A Day 10 visit that occurred 10 days from initiation of the first infusion of trial drug; in some patients, the Day 10 visit coincided with the EOT visit, depending on the patient's treatment schedule;
> A post therapy evaluation (PTE) visit that occurred 7 to 14 days from the EOT visit.

According to the applicant, throughout each of these periods, the size (i.e., size of erythema and/or edema/induration) of the primary ABSSSI site was monitored to determine the cessation of spread or reduction in the size of the baseline lesion. The presence or absence of local signs and symptoms of infection, pain, and temperature were also monitored as efficacy assessments.

Diagnosis and main criteria for inclusion:

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

Randomization and Treatment Administration:

According to the applicant:

> Randomization was accomplished by an automated Interactive Voice/Web Response System (IVRS/IWRS). A dynamic/adaptive randomization method was utilized with stratification of patients by geographic regions (e.g., North America, Eastern Europe, Western Europe, South America and Asia), sites, and presence of diabetes mellitus to minimize any potential biases intentionally or unintentionally introduced during the overall trial conduction and ensure the validity of treatment comparisons. Stratification for a diabetes mellitus diagnosis was required to account for an anticipated lower response rate in patients with diabetes mellitus because of their compromised immune system and decreased peripheral circulation. An enrollment cap of 30% was maintained for major cutaneous abscesses.

Although, in general, balance is achieved through randomization, this reviewer opines that stratification provided additional assurance, over and above that provided by randomization, that important factors (e.g., diabetic mellitus for SOLO trials) would be equally represented in the two treatment groups.

Trial drug (i.e., Oritavancin, placebo extension of Oritavancin for blinding purposes, or Vancomycin) was initiated via a dedicated IV line within 24 hours after the patient was first seen, and was administered for 7 to 10 days. Prior to trial drug administration on Day 8, and

each subsequent day thereafter, the investigator examined the patient and determined whether or not further doses of trial drug were indicated.

Oritavancin/Placebo:

Oritavancin IV was given on Day 1 of the trial as a single, 1200 mg dose in 1000 mL of 5% dextrose in water (D5W) over 3 hours. Beginning with the second dose, and for all subsequent doses, placebo infusions were administered over a minimum of 60 minutes to maintain the trial blind.

Vancomycin:

Vancomycin was administered IV for 7 to 10 days. On Day 1, Vancomycin was administered as either a 1 g dose or at 15 mg/kg every 12 hours. After Day 1, the Vancomycin dose could be adjusted by the unblinded pharmacist/designee based on CrCl levels, the patient's clinical status, or Vancomycin trough levels. The mean total daily dose for the Vancomycin group was equivalent to a total dose of 1 g twice daily.

Rescue Medication Use:

The use of rescue medication for the primary ABSSSI site, defined as any non-trial, systemic or topical antibiotic medication with a known or proven effect on Gram-positive pathogens (including Vancomycin if it was administered as a non-trial drug), was assessed at ECE, EOT, Day 10, and PTE.

Efficacy Assessments:

Efficacy assessments of the primary ABSSSI site included size (i.e., size of erythema and/or edema/induration), presence or absence of local signs and symptoms of infection, and pain. Temperature was also measured as an efficacy assessment. Detailed descriptions of the efficacy endpoints are provided later.

A microbiological assessment was also conducted using both infection site specimens and blood.

Lesion Size Measurement

According to the applicant:

> Lesion size was assessed by both ruler measurement and planimetry tracing. Ruler measurements (in centimeters) included the maximum length (A) and width (B) of the primary site of infection. Each measurement included the furthest point incorporating the surrounding erythema and/or edema/induration. The axes of maximum length and width were identified at Screening with reference marks that were used for subsequent measurements of the primary infection. A measurement of the maximum width (C) of erythema or edema/induration from the edge of the wound (surgical or traumatic) or abscess was recorded. For abscesses, measurements were from

the end of the fluctuance before drainage or from the edge of the drainage site following drainage. Lesion size was assessed by digital planimetry of acetate tracings of the infection site.

ABSSSI site specimen

According to the applicant:

An ABSSSI site specimen for Gram stain, culture, and susceptibility testing was obtained from each patient within 24 hours prior to trial drug administration. If the Screening visit sample was inadequate or not available for testing, additional samples were obtained, if accessible, on Day 1. During the Treatment Period, additional ABSSSI site specimens were obtained only if clinically indicated (e.g., no improvement in, or deterioration of, lesion) and the specimen was easily accessible

Efficacy Endpoints:

A short summary of the primary and main secondary efficacy endpoints and analyses is presented below:

Primary Efficacy Endpoint

The primary efficacy endpoint was early clinical response at the ECE visit (48-72 hours following the initiation of trial drug administration). Early clinical response was defined as a composite outcome of the following:

Cessation of spreading or reduction in the size of baseline lesion;

Absence of fever (defined as no temperature ≥ 37.7°);

No rescue antibiotic medication.

A patient was categorized as a success if all of the above three components 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 initiation of trial drug administration;

Fever, defined as one or more oral temperature readings ≥ 37.7°C at any time between 48 and 72 hours following initiation of trial drug;

Spreading of lesion size defined as an increase in size (length, width, or area) of the redness, edema, and/or induration measured by ruler at 48 to 72 hours compared with the size at baseline; however, patients with ≥ 20% reduction in lesion area from baseline were not considered as failures even if they might 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, or any nontrial antibacterial drug therapy, for the treatment of ABSSSI during the first 72 hours from initiation of trial drug administration;

An additional, unplanned, surgical procedure during the first 72 hours from initiation of trial drug.

Secondary Endpoints:

1) Lesion area decrease ≥ 20% from baseline at ECE:

This is the endpoint currently recommended by FDA and the Foundation for the National Institutes of Health as the primary efficacy endpoint for an ABSSSI treatment. The agency will recommend inclusion of this endpoint in the label.

It is noted earlier that SOLO 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.

2) Investigator-assessed clinical cure at PTE visit from EOT:

One of the secondary efficacy endpoints proposed for a labeling claim was investigator-assessed clinical cure at PTE visit from EOT. A patient was categorized as clinically cured if the patient experienced a complete or nearly complete resolution of baseline signs and symptoms of the primary infection such that no further treatment with antibiotics was needed. Signs and symptoms related to the primary ABSSSI infection site included erythema, induration/edema, purulent drainage, fluctuance, pain, tenderness, and local increase in heat/warmth.

According to the applicant, a patient was classified as a clinical failure at PTE if any of the following occurred:

- Did not fulfill criteria for clinical cure;
- Investigator assigned failure any time prior to PTE;
- Patient died (all-cause mortality) following the start of trial drug;
- Incision and drainage after 48 hours of treatment that was unplanned prior to randomization, with the exception of cellulitis where there was a conversion into an abscess or when an extension of the original incision was indicated;
- Persistence or worsening of erythema/induration and/or purulent drainage;
- Initiation of non-trial, antibacterial drugs for treatment of ABSSSI;
- Initiation of non-trial, antibacterial drugs for treatment of other infections, unless antibiotics lacked efficacy in the treatment of ABSSSI;
- Otherwise did not meet the definition of clinical cure (e.g., lost to follow-up, trial drug discontinued because of an adverse reaction).

3) Sustained clinical response at PTE:

This endpoint demonstrates that the clinical cure at EOT is sustained over time (at PTE). According to the applicant, this endpoint was not prespecified for noninferiority testing.

Supporting endpoints:

SOLO I and SOLO II trials also had a number of applicant-defined supportive secondary efficacy endpoints as follows. Note that these secondary endpoints are

considered as exploratory and are not used for making any inferences using non-inferiority hypotheses. The supporting endpoints are provided below:

• Clinical response at EOT and Day 10 as determined by the investigator;

• Pathogen-level microbiological response at EOT, Day 10, and PTE;

• Patient-level microbiological response at EOT, Day 10, and PTE;

• Change from baseline in temperature at ECE, EOT, Day 10, and PTE;

• Reduction in lesion size of the primary ABSSSI site at ECE, EOT, Day 10, and PTE;

• Rescue medication usage at ECE, EOT, Day 10, and PTE;

• Unplanned surgical procedures at ECE, EOT, Day 10, and PTE;

• Signs and symptoms related to the primary ABSSSI site (i.e., erythema, induration/edema, purulent drainage, fluctuance, pain, tenderness, local increase in heat/warmth) at ECE, EOT, Day 10, and PTE;

• Deaths through Day 60 Follow-Up Safety Visit;

• Change in the patient's assessment of pain at the primary ABSSSI site at ECE, EOT, Day 10, and PTE.

Safety Endpoints:

Safety endpoints included AEs, SAEs, all-cause mortality, and premature withdrawals due to AEs, clinical laboratory tests (hematology, serum chemistry, and urinalysis), vital signs, and ECGs.

Definitions of Trial Populations:

According to applicant, both trials have the same analysis populations defined as follows:

> The Intent-to-Treat (ITT) population included all patients randomized into the trial;
>
> The modified ITT (mITT) population was the primary population for all the efficacy analyses and included all randomized patients who received any trial drug;
>
> The CE population consisted of all mITT patients who met the inclusion/exclusion criteria, received the full-course of randomized trial treatment (for a minimum of7 days), and had investigator assessment for clinical cure at PTE. The CE population was used to confirm the efficacy analyses;
>
> The MicroITT population consisted of 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;

The Safety population was the primary population for all the safety analyses and consisted of all patients who were dosed with trial drug, irrespective of randomization. Treatment classification was based on the actual treatment received.

Table 2 below summarizes the analysis populations for both trials.

Table 2 (SOLO I and SOLO II): Analysis Populations

	SOLO I		SOLO II	
Population	Oritavancin (N=483) n (%)	Vancomycin (N=485) n (%)	Oritavancin (N=509) n (%)	Vancomycin (N=510) n (%)
ITT	483 (100)	485 (100)	509 (100)	510 (100)
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)
Safety	473*	481*	503	502

Source: Reviewer's Table

* Note that two patients randomized to Oritavancin were dosed with Vancomycin; thus, 473 patients in the Oritavancin group and 481 patients in the Vancomycin group were included in the Safety Population.

Table 2 shows that the percentage of patients in each of the analysis populations was comparable between the Oritavancin and Vancomycin groups in both SOLO trials.

3.2.2 Statistical Methodologies

Primary analysis:

The primary analysis of early clinical response was performed using the mITT population in both SOLO trials. 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). Noninferiority of Oritavancin was declared at the 1-sided alpha level of 0.025 if the lower bound of the 2-sided 95% CI (based on the normal approximation to Binomial distribution) was more than -10%. If noninferiority of Oritavancin was declared, superiority was tested using the same 2-sided 95% CI and a lower limit of 0%. Supportive analyses were conducted using the ITT and CE populations. Sensitivity analyses were conducted: (1) excluding missing data and (2) treating missing data as treatment successes.

Analysis of secondary endpoints:

Investigator-assessed clinical cure rates at PTE, lesion-size reduction ≥ 20% at ECE, and sustained clinical response at PTE were analyzed using the mITT population. The former two

variables were prespecified for noninferiority testing whereas sustained clinical response was not.

The aforementioned secondary efficacy endpoints and microbiological responses were summarized and compared between treatment groups. Unless otherwise specified, two-sided 95% confidence intervals (CI) based on the normal approximation to Binomial distribution for the difference in outcome rates between the two treatment groups were derived. The SOLO protocols prespecified the analyses of the secondary endpoints.

Note that the SOLO protocols did not mention any adjustment of overall type I error rate for testing the secondary endpoints. This reviewer opines that the overall type I error rate would not require adjustment for multiple tests provided the secondary endpoints were tested after noninferiority of the primary endpoint was established (based on gate keeper method).

Supporting analyses:

The following supporting analyses were also proposed in the SOLO protocols:

•Concordance/discordance tables were generated by treatment groups for the mITT and CE populations.

•The absolute and percent reduction of the lesion size from baseline (length, width, and surface area analyzed separately) at ECE, EOT, Day 10 and PTE were calculated by treatment group using mITT and CE populations In addition, the various percentage reductions from baseline (e.g., ≥10%, ≥20%, ≥30% for ECE; ≥50%, ≥80%, ≥90%, ≥95% for EOT, Day 10 and PTE visits) were summarized by treatment group for the mITT and CE populations.

•Resolution of individual signs and symptoms related to skin infections (erythema, induration, edema, purulent drainage, fluctuance, pain, tenderness, heat or localized warmth) after the initiation of study drug were summarized at each of the following visits: ECE, EOT, Day 10 and PTE by treatment group on mITT and CE populations.

•Time to complete resolution of signs/symptoms of ABSSSI was analyzed.

•Patient's self-assessment of pain (measured on a 0 to 10 point Numeric Rating Scale) was summarized at each of the following visits: Screening, ECE, EOT, Day 10 and PTE by treatment group on mITT and CE populations.

Analyses of Safety endpoints:

Descriptive analyses were performed for safety parameters by treatment group.

Missing data:

In the analysis of the primary and secondary efficacy endpoints in SOLO I and SOLO II, patients who had missing outcomes were treated as failures since all these analyses were based on responder rates.

Sensitivity analyses were performed, using the mITT population and treating missing data as successes, to confirm that the results were not influenced by how missing data was handled.

Noninferiority Margin and Sample Size Calculation:

The applicant states the following:

> Based on the draft guidance of "Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment" released in August 2010 by FDA and the recommendation by FDA Anti-infective Drug Advisory Committee [FDA, 2008], a control effect (M1) of 12% for the active comparator drug was estimated for patients with an ABSSSI using an endpoint of cessation of spread of lesion and resolution of fever at 48 to 72 hours of therapy. The noninferiority margin (M2) of 10% chosen was thus justified and would represent approximately 80% preservation of the estimated control effect. The chosen noninferiority margin was also accepted by FDA under the SPA…
>
> Although the primary analysis was based on the mITT population and the primary efficacy outcome (of cessation of spread or reduction in size of the baseline lesion, absence of fever, and no rescue antibiotic medication) at ECE, the sample size estimate was also intended to provide sufficient power for determining the treatment efficacy on the primary efficacy endpoint and clinical cure at PTE in the mITT population. The primary efficacy outcome (cessation of spread or reduction in size of the baseline lesion, absence of fever, and no rescue antibiotic medication) rates in both Oritavancin and Vancomycin treatment groups in the mITT population were assumed to be 75%. A sample size of approximately 960 patients (480 per treatment group) would provide at least 90% power to reject the following null hypothesis (H0) against the alternative hypothesis (HA) at the 1-sided alpha level of 0.025 using a two-group large-sample normal approximation test of proportions:
>
> $H_{0:}\ P_{Vancomycin} - P_{Oritavancin} \geq 0.10$ (The rate of the primary outcome in the Vancomycin group is greater than or equal to that in the Oritavancin group by 10%).
>
> versus:
>
> $H_A: P_{Vancomycin} - P_{Oritavancin} < 0.10$ (The rate of the primary outcome in the Vancomycin group is less than that in the Oritavancin group by 10%)

According to the applicant, this sample size also provided at least 90% power to demonstrate noninferiority for the clinical cure assessment of efficacy at the 1-sided alpha level of 0.025, assuming the margin of 10% and a clinical cure event rate of 65% in the mITT population in both the Oritavancin and Vancomycin treatment groups. However, patient enrollment was not to stop until approximately 175 patients were confirmed with MRSA as a baseline pathogen.

Subgroup Analyses:

Early clinical response, investigator-assessed clinical cure at PTE, lesion size reduction ≥ 20% at ECE and sustained clinical response were analyzed for the following subgroups of patients:

1) MRSA and other baseline pathogens;

2) Demographic subgroups, including:

a) Age (< 65 years, 65 to <75 years, and ≥ 75 years old);

b) Gender (males and females);

c) Race (White, Black or African American, Asian, and Other);

d) Weight (< 60 kg, 60 to < 100 kg, ≥ 100 kg)) Body mass index (BMI) (< 25 kg/m^2; 25 to < 30 kg/m^2, ≥ 30 kg/m^2);

3) Geographic region including

a) North America, South America, Eastern Europe, Western Europe, Asia;

b) North America and all other regions;

4) Baseline signs and symptoms of ABSSSI and baseline clinical features, including:

a) Fever (≥ 38°C) at baseline;

b) Bacteremia at baseline;

c) Met the criteria for systemic inflammatory response syndrome (SIRS) at baseline;

d) Received antibiotics before trial drug administration;

5) ABSSSI type (wound infection, cellulitis/erysipelas, and major cutaneous abscess)

6) Co-morbid conditions, including

a) 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;

b) Hepatic impairment (alanine aminotransferase or aspartate aminotransferase > 3X upper limit of normal [ULN] at baseline or total bilirubin > 2X ULN at baseline) and normal hepatic function;

c) Immunodeficient (yes or no where immunodeficiency was defined as patients who had baseline absolute neutrophil count [ANC] < 1000 cells/μL, or took any immunosuppressive

medications prior to treatment, or had a history of acquired immunodeficiency syndrome [AIDS] or other immune deficiency state).

Note that the above subgroup analyses were prespecified. However, the protocols did not mention whether the above subgroup analyses would be conducted subject to meeting the primary hypothesis.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics, and Analysis Populations

Patient disposition:

Patient disposition for SOLO I and SOLO II are provided below.

SOLO I:

In SOLO I, 968 patients were randomized (Oritavancin, 483 patients; Vancomycin, 485 patients). Of the 968 patients randomized, a total of 954 patients (Oritavancin, 475 patients; Vancomycin, 479 patients) received trial drug and were included in the mITT population The majority of these patients (Oritavancin, 421 patients [88.6%]; Vancomycin, 402 patients [83.9%]) completed trial drug treatment for 7 to 10 days .The primary reason for discontinuing trial drug was an AE (Oritavancin, 3.8%; Vancomycin, 4.6%). See Table 3 for further details.

Table 3(SOLO I): Patient disposition (mITT population)

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

mITT: modified Intent-to-Treat; AE: adverse event.
*Reasons as recorded in the IV Therapy Summary page of the eCRF.
**One patient was determined by Sponsor to have had drug withdrawn due to an adverse event.
Source: Applicant's clinical trial report, Table 6. Page 70

SOLO II:

In SOLO II, 1019 patients were randomized (Oritavancin, 509 patients; Vancomycin, 510 patients). Of these 1019 patients, a total of 1005 patients (Oritavancin, 503 patients; Vancomycin, 502 patients) received trial drug and were included in the mITT population. The majority of these patients (Oritavancin, 454 patients [90.3%]; Vancomycin, 446 patients

[88.8%]) completed trial drug treatment for 7 to 10 days. The primary reason for discontinuing trial drug was an AE in the Oritavancin group (Oritavancin, 3.2%; Vancomycin, 1.8%). See Table 4 for further details.

Table 4 (SOLO II): Patient disposition (mITT population)

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

mITT: modified Intent-to-Treat; AE: adverse event.
*Reasons as recorded in the IV Therapy Summary page of the eCRF.
**One patient (201002010) had recorded in the IV Therapy Summary eCRF page that 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.
***One patient (201001055) was determined by Sponsor to have had drug withdrawn due to an AE.
Source: Applicant's clinical trial report, Table 6. Page 69

Demographic and baseline characteristics (SOLO I and SOLO II):

There are no noticeable imbalances between treatment groups with respect to demographic and baseline characteristics in either trial. Demographic and baseline characteristics are provided below:

SOLO I:

Demographic and baseline characteristics for the patients in SOLO I are summarized in the following table:

Table 5: Demographic and baseline characteristics

	Oritavancin (N=475) n (%)	**Vancomycin (479) n (%)**
Age (years) ≥65 years <65	 47(9.9) 428(90.1)	 38(7.9) 441(92.1)
Male Female	301(63.4) 174/(36.6)	301(62.8) 178(37.2)
Race: White Black or African American Asian Other	 274(57.7) 43(9.1) 153(32.2) 5 (1.0)	 275(57.4) 40(8.4) 154(32.2) 10(2.1)
Region: USA South America Eastern Europe Western Europe	298(62.1) 2(0.04) 13(2.7) 14(2.9) 148(31.2)	299(62.4) 2(0.04) 15(3.1) 13(2.7) 140(29.2)
Infection type: Wound Infection Cellulitis/erysipelas Major cutaneous abscess	 92/475 (19.4) 243/475(51.2) 140/475(29.5)	 105/479 (21.9) 233/479(48.6) 141/479(29.4)
Meets SIRS*criteria at baseline [n (%)]	74(15.6)	72(15.0)

Table 5 (Continued): Demographic and baseline characteristics

	Oritavancin (N=475) n (%)	Vancomycin (479) n (%)
Lesion Area (cm^2):		
Mean (SD)	405.6(467.76)	423.0(524.13)
Median (Min, Max)	248.0(47, 3249)	225.6(75, 3417)
Q1, Q3	140.0, 456	140.4, 453.1
≥ 75 $cm^2$2 (n[%]))	473/475 (99.6)	478/478 (100)_
Infection site culture (proportion [%])	290/475(61.1)	290/479 (60.5)
Any Gram-positive pathogen	279/290(96.2)	277/290 (95.5)
S. aureus	218/279(78.1)	210/277 (75.8)
MRSA	104	100
MSSA	116)	110
Status in baseline diabetes: diabetes	93(19.6)	95(19.5)
Renal Function, CrCl (mL/min)		
< 30	2 (0.4)	3 (0.6)
30 - < 60	35 (7.4)	27 (5.6)
60 - < 90	99 (20.8)	89 (18.6)
≥ 90	332 (69.9)	355 (74.1)
Missing	7 (1.5)	5 (1.0)

Source: Applicant's Table 8, Clinical Trial Report, Page 73

[a]SIRS criteria is defined as two of the following: temperature > 38.0□C, pulse > 90 beats per minute, respiratory rate > 20 breaths per minute, WBC count >12,000 cells/μL or WBC count < 4,000 cells/μL, or> 10% bandemia.

In the mITT population, the Oritavancin and Vancomycin groups were similar with respect to demographics, type of ABSSSI, and relevant medical or surgical history. Most patients in both groups were less than 65 years of age (balanced between two treatment groups). Patients in both groups were predominantly male (Oritavancin, 63.4%; Vancomycin, 62.8%), and White (Oritavancin, 57.7%; Vancomycin, 57.4%). Patients in the trial were primarily

enrolled in North America (62.7%) and Asia (31.0%). Infection types were balanced in the Oritavancin and Vancomycin groups. The distribution of lesion area at baseline was similar in the Oritavancin and Vancomycin groups. The proportion patients who met SIRS criterion were well balanced between two treatment groups (Oritavancin vs. Vancomycin: 15.6% vs. 15%). The proportion of patients in different levels of creatinine clearance was also balanced between the two treatment groups.

Table 6 provides the signs and symptoms at baseline for both treatment groups.

Table 6: Signs and symptoms rate at baseline in SOLO I trial

	SOLO II	
Signs and symptoms	Oritavancin (N=475) n (%)	Vancomycin (N=479) n (%)
Edema(absent)	16/475 (3.4)	14/478 (2.9)
Erythema(absent)	12/475 (2.5)	12/478 (2.5)
Fluctuance(absent)	295/475 (62.1)	294/477 (61.6)
Local increase in heat and warmth(absent)	16/475 (3.4)	12/478 (2.5)
Induration(absent)	39/475 (8.2)	45/477 (9.4)
Purulent drainage(none)	259/475 (54.5)	227/478 (47.5
Pain(none)	3/475 (0.6)	8/478 (1.7)
Tenderness(none)	4/475 (0.8)	216/477 (45.3)

Source: Applicant's Clinical study report, Table 4.9.1.1, page 1063

As shown in Table 6 that proportion of patients with signs and symptoms at baseline is comparable between two treatment groups.

SOLO II:

Demographic and baseline characteristics for the patients in SOLO II are summarized in the Table 7:

Table 7: Demographic and baseline characteristics

Disease	Oritavancin (N=503) n (%)	Vancomycin (N=502) n (%)
Age (years) <65 >65 years	 464(92.2) 39 (7.8)	 463(92.2) 39 (7.8)
Gender: Male Female	 338 (67.2) (32.8)	 343 (68.3) 159(31.7)
Race: White Black or African American Asian Other	 356 (70.8) 14 (2.8) 122 (24.3) 11 (2.2)	 356 (70.9) 17(3.4) 122 (24.3) 7 (1.4)
Region: USA South America Eastern Europe Western Europe Asia	 283(56.3) 2(0.04) 88(17.5) 10(2.1) 120(23.9))	 285(56.8) 1(0.02) 86(17.1) 11(2.2) 119(23.7)
Wound Infection Cellulitis/erysipelas Major Cutaneous Abscess	191/503 (38.0) 144/503 (28.6) 168/503(33.4)	176/502 (35.1) 167/502 (33.3) 159/502(31.7)
Meets SIRS criteria at baseline [n (%)]	95(18.9)	101 (20.1)

Table 7 (Continued): Demographic and baseline characteristics

	Oritavancin (N=503) n (%)	Vancomycin (N=502) n (%)
Lesion Area (cm^2): Mean (SD)	391.4 (397.38)	411.5 (355.70)
Median (Min, Max)	287.8 (19, 4250)	308.8 (57, 2184)
Q1, Q3	172.5444.0	182.0, 464.1
≥ 75 cm^2 (n[%])	498/502 (99.2)	498/502 (99.2)
Infection site culture (proportion [%]):	351/503 (69.8)	352/502 (70.1)
Any gram-positive ABSSSI pathogen	340/351 (96.8)	344/352 (97.7)
S. aureus	250/340 (73.5)	258/344 (75.0)
Methicillin-resistant S. aureus MRSA	100	101
MSSA	150	157
Status in baseline diabetes: diabetes	46/503(9.1)	45/502(9.0)
Renal Function, CrCl (mL/min)		
< 30	5 (1.0)	4 (0.8)
30 - < 60	36 (7.2)	26 (5.2)
60 - < 90	91 (18.1)	94 (18.7)
≥ 90	357 (71.0)	360 (71.7)
Missing	14 (2.8)	18 (3.6)

Source Applicant's Table 8, Clinical Trial Report, and Page 72

[a]SIRS criteria is defined as two of the following: temperature > 38.0□C, pulse > 90 beats per minute, respiratory rate > 20 breaths per minute, WBC count >12,000 cells/μL or WBC count < 4,000 cells/μL, or> 10% bandemia

In the mITT population, the Oritavancin and Vancomycin treatment groups were similar with respect to demographics, type of ABSSSI, and relevant medical or surgical history Most patients in both groups belong to age group <65 (balanced between the two treatment

groups). Patients in both groups were predominantly male (Oritavancin, 67.2%; Vancomycin, 68.3%), and White (Oritavancin, 70.8%; Vancomycin, 70.9%). Patients in the trial were primarily enrolled in North America (56.9%) and Asia (23.6%). Infection types were balanced in the Oritavancin and Vancomycin groups. . The distribution of lesion area at baseline was similar in the Oritavancin and Vancomycin groups in the overall population.

The proportion patients who met SIRS criterion were well balanced between two treatment groups (Oritavancin vs. Vancomycin: 18.9% vs. 20.1%). The proportion of patients in different levels of creatinine clearance was also balanced between the two treatment groups.

Table 8 provides the signs and symptoms at baseline for both treatment groups.

Table 8(SOLO II): Signs and symptoms rates at baseline

	SOLO II	
Signs and symptoms	**Oritavancin (N=503) n (%)**	**Vancomycin (N=502) n (%)**
Edema (absent)	17/503 (3.4	16/502 (3.2)
Erythema(absent)	7/500 (1.4)	5/500 (1.0)
Fluctuance (absent)	339/498 (68.1)	349/499 (69.9)
Local increase in heat and warmth(absent)	7/498 (1.4)	11/501 (2.2)
Induration(absent)	36/498 (7.2)	45/499 (9.0)
Purulent drainage(none)	155/501 (30.9	160/501 (31.9)
Pain(none)	1/500 (0.2	4/501 (0.8)
Tenderness(none)	3/503 (0.6)	2/502 (0.4)

Source: Applicant's Clinical study report, Table 4.9.1.1, page 1015

Table 8 shows that proportion of patients with signs and symptoms at baseline is comparable between two treatment groups.

3.2.4 Results and Conclusions

This reviewer conducted analyses of the primary and the secondary endpoints using datasets provided in the applicant's submission. The reviewer's findings were consistent with the Applicant's findings. The efficacy results of SOLO I and SOLO II are provided below.

SOLO I:

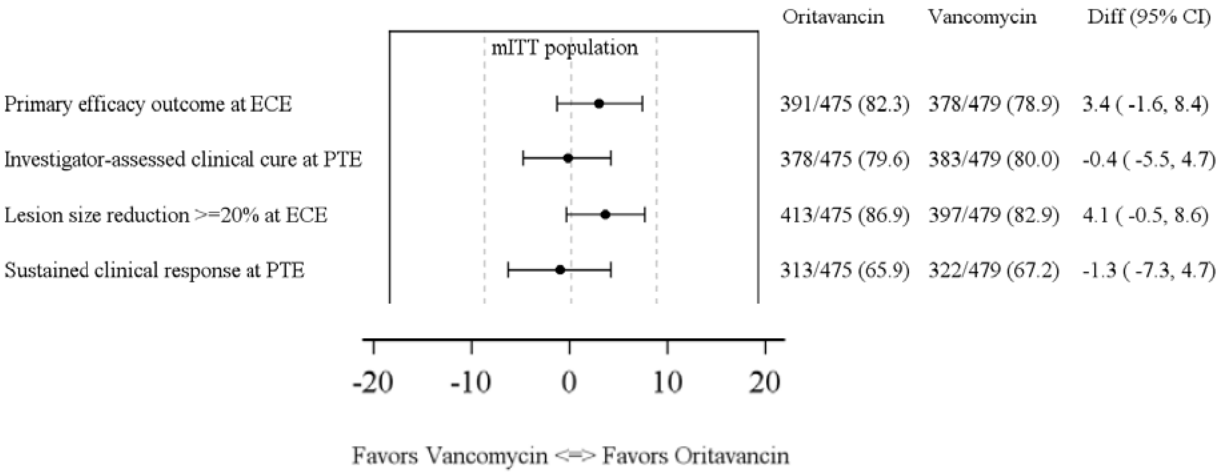
In SOLO I, Oritavancin has comparable clinical efficacy to the comparator regimen Vancomycin for the primary efficacy outcome measure of early clinical response at 48 to 72 hours. Oritavancin has also comparable clinical efficacy to the comparator regimen Vancomycin for the secondary endpoints. Table 9 and Figure 2 provide efficacy results of the primary endpoint and secondary endpoints of SOLO I.

Table 9(SOLO I): Summaries of the efficacy analyses for the mITT population

Endpoints	Oritavancin (N=475) n (%)	Vancomycin (N=479) n (%)	Difference (%) (95% CI*)
Early clinical response (primary endpoint specified in the protocol)	391(82.3)	378(78.9)	3.4 (-1.6, 8.4)
Investigator assessed clinical cure ta PTE	378 (79.6)	383 (80.0)	-0.4(-5.5, 4.7)
Lesion size reduction≥20% at ECE (current primary endpoint-FDA)	413 (86.9)	397 (82.9)	4.1 (-0.5, 8.6)
Sustained clinical response at PTE	313 (65.9)	322 (67.2)	-1.3 (-7.3,4.7)

Source: Applicant's clinical trial report: Tables 11, 13, 14 and 15
*Based on the normal approximation to Binomial distribution

Figure 2 (SOLO I): Forest Plot of Primary Endpoint (mITT Population)



Source: Applicant's Figure 7, Clinical Trial report, page 102

Primary endpoint:

In the mITT population, it is seen from the Table 9 that the rate of early clinical response was similar in the Oritavancin (82.3%) and Vancomycin (78.9%), groups. The lower limit of the 95% CI (-1.6, 8.4) for the rate difference was above the -10% margin, demonstrating that a single dose of Oritavancin is noninferior to 7-10 days of IV Vancomycin.

Note that in the ITT population, the percentages of patients with an early clinical response in the Oritavancin and Vancomycin groups (Oritavancin, 391/483(81%); Vancomycin, 378/485(77.9%) were similar to the percentages seen in the mITT population with a similar treatment difference and 95% CI (difference: 3.0%; 95% CI: -2.1, 8.1).

Secondary Efficacy Endpoints:

Investigator-assessed clinical cure (IACC) at PTE:

As shown in Table 9, the percentage of patients with an investigator-assessed clinical cure at PTE was 79.6% in the Oritavancin and 80.0% in the Vancomycin groups , with a treatment difference of -0.4% and 95% CI of (-5.5, 4.7).

Table 10 shows that the percentage of patients with an investigator-assessed clinical cure was similar between the Oritavancin and Vancomycin groups at EOT (Oritavancin, 84.8%; Vancomycin, 82.0%) and Day 10 (Oritavancin, 84.4%; Vancomycin, 81.8%), and the rates were maintained over time to PTE.

Table 10 (SOLO I): Investigator-Assessed Clinical Cure at EOT, Day 10, and PTE (mITT Population)

Visit	Oritavancin (N=475) n (%)	Vancomycin (N=479) n (%)	Difference (95% CI*) n (%)
EOT	403(84.8)	393(82.0)	2.8 (-1.9, 7.5)
Day 10	401 (84.4)	392 (81.8)	2.6 (-2.2, 7.3)
PTE	378 (79.6)	83 (80.0)	-0.4(-5.5, 4.7

Source: Applicant's clinical trial report: Clinical trial report, Table 19
*Based on the normal approximation to Binomial distribution

Percentage of patients with a lesion size reduction ≥ 20% from baseline at ECE:

As shown in Table 9, the percentage of patients 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 (-0.5, 8.6). Based on these data, Oritavancin was noninferior to Vancomycin because the lower limit of the 95% CI is greater than the prespecified noninferiority margin of -10%. Note that clinical response rates at 48-72 hours defined as a ≥20% reduction in lesion area from baseline was considered a key secondary endpoint by the FDA.

Table A.1 in the appendix shows the various reductions from baseline at ECE at intervals: ≥20% - <30%, ≥30% - <40%, ≥40% - <50%, ≥ 50% - <60%, ≥60% - <70%, ≥70% - <80%, ≥90% - <95% and ≥95%. These reductions from baseline at ECE were similar between the two treatment groups.

Sustained clinical response at PTE:

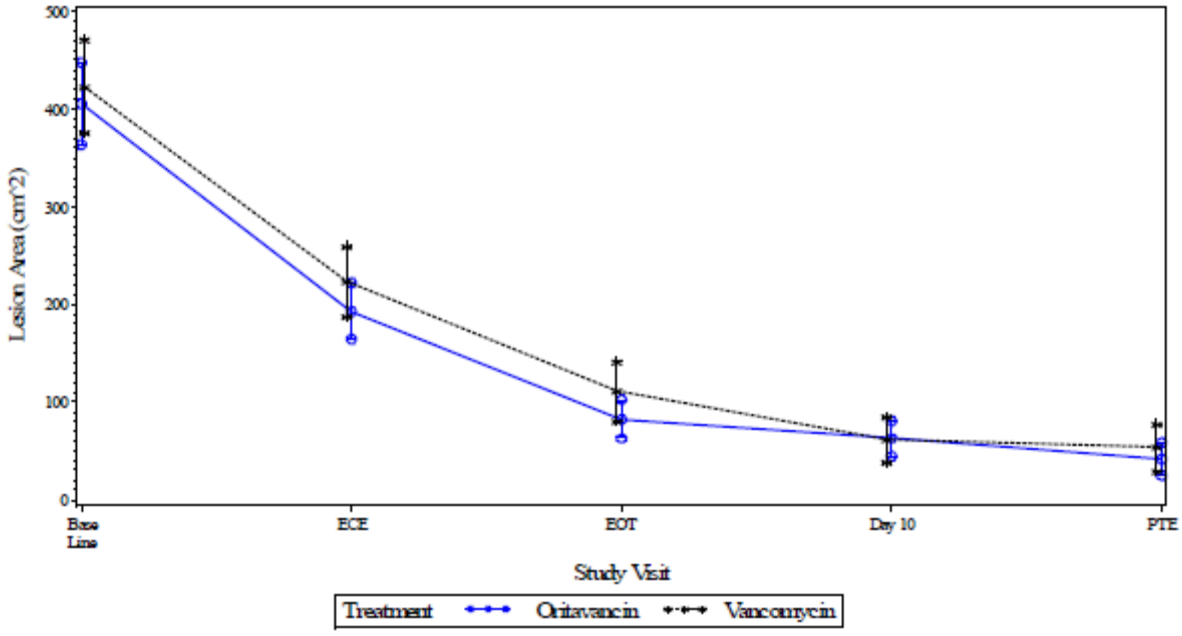
As shown in Table 9, the percentage of patients with a sustained clinical response at PTE in the Oritavancin group was 65.9% and Vancomycin group was 67.2% , with a treatment group difference of -1.3% and 95% CI of (-7.3, 4.7).

Supportive analyses:

Mean lesion area at ECE, EOT, Day 10, and PTE:

Mean Lesion Area and 95% Confidence Intervals in the mITT Population at Baseline, ECE, EOT, Day 10, and PTE are provided in the figure below:

Figure 3(SOLO I): Mean Lesion Area and 95% Confidence Intervals in the mITT Population at Baseline, ECE, EOT, Day 10, and PTE



Source: Applicant's clinical trial report, Figure 2, page 90

It can be seen from Figure 3 that the mean lesion size in Oritavancin treated group and Vancomycin treated groups at ECE, EOT, Day 10 and PTE was similar. Note that at PTE, the difference in mean reduction from baseline lesion area between Oritavancin and Vancomycin groups (Oritavancin vs. Vancomycin: -361.9 vs. -355.1) was -6.8 cm^2 with 95% CI (-66.5, 52.9).

Sensitivity/Exploratory Analyses:

Sensitivity/exploratory analyses were conducted by the applicant to assess the robustness of the findings for rates for early clinical response and clinical cure rate at PTE. These analyses considered the following:

- Missing data at ECE;
- Missing data at PTE;
- Early clinical response excluding fever component;
- Concordance between the Primary and Secondary Efficacy Endpoints.

Missing data at ECE:

Table 11 summarizes failures and missing data at ECE and PTE, respectively.

Table 11(SOLO I): Failure and Missing data at ECE and PTE in the mITT population

Failure/missing		Treatment Group	
		Oritavancin (N=475) n (%)	Vancomycin (N=479) n (%)
ECE	Failure	68(14.3)	78(16.3)
	Missing	16(3.4)	23(4.8)
PTE	Failure	42(8.8)	35(7.3)
	Missing	55(11.6)	61(12.7)

Source: Reviewer's Table

The applicant conducted a sensitivity analysis to explore the impact of missing values for early clinical response on the robustness of the conclusions from the primary analysis. The percentage of patients with an early clinical response was similar in the Oritavancin and Vancomycin groups if missing values were treated as success (Oritavancin 85.7% vs. Vancomycin 83.7%; 95% CI: (-2.6, 6.5)). Thus, the sensitivity analysis showed that the treatment difference and the associated 95% CI were similar to those seen in the primary analysis where missing data were treated as failure**.**

The applicant also conducted a sensitivity analysis to explore the impact of missing values for IACC at PTE on the robustness of the conclusions from the primary analysis. It was found that the percentage of patients with an IACC was similar in the Oritavancin and Vancomycin groups if missing values were treated as success (Oritavancin, 91.2%; Vancomycin, 92.7%; 95% CI (-5.0, 1.9)). Thus, the results seen in the sensitivity analyses demonstrated similar conclusions from the original analysis.

This reviewer opines that because the number missing values were similar in both treatment groups, classification of missing data as success did not change the original analyses. Thus, the analyses treating missing data as success were not informative.

Early clinical response excluding fever component:

When early clinical response was calculated as a composite endpoint of cessation of spread or reduction in size of the baseline lesion and no rescue antibiotic medication at ECE, and excluding fever as part of the composite, 90.1% and 85.8% of the Oritavancin and Vancomycin groups, respectively, had an early clinical response. The efficacy rates were similar in both treatment groups.

Concordance between the Primary and Secondary Efficacy Endpoints

Concordance/discordance of early clinical response at ECE with investigator-assessed clinical cure at EOT, PTE, and at least 20% reduction in lesion area from baseline at ECE are provided in the following table by treatment group using the mITT population.

Table 12 (SOLO I): Concordance of early clinical response with secondary endpoints in mITT population

Endpoint	Outcome	Responders		Non-Responders	
		Oritavancin	Vancomycin	Oritavancin	Vancomycin
Investigator-assessed clinical cure at EOT	Success	362/391(92.6)	345/378(91.3)	41/84(48.8)	48/101(47.5)
	Failure	29/391(7.4)	33/378(8.7)	43/84 (51.2)	53/101(52.5)
Investigator-assessed clinical cure at PTE	Success	333/391 (85.2)	333/378(88.1)	45/84(53.6)	50/101(49.5)
	Failure	58/391(14.8	45/378(11.9)	39/84 (46.4)	51/101(50.5)
lesion size reduction ≥ 20% at ECE	Success	369/391 (94.4)	352/378 (93.1)	44/84 (52.4)	45/101(44.6)
	Failure	22/391 (5.6)	26/378(6.9)	40/84 (47.6)	56/101 (5.9)

Source: Applicants clinical trial report: Table 16 (page 84), Table 18 (page 85)

Table 12 shows that most patients in both groups (Oritavancin, 92.6%; Vancomycin, 91.3%) who had an early clinical response also had an IACC at EOT (i.e., success for both endpoints) in the mITT population. Only a small percentage of patients in both groups who had an early clinical response did not have an IACC at EOT (Oritavancin, 7.4%; Vancomycin, 8.7%) in the mITT population. Thus, for the majority of patients, an early clinical response was maintained through EOT.

Additionally, most patients in both groups (Oritavancin, 85.2%; Vancomycin, 88.1%) who had an early clinical response also had an IACC at PTE (i.e., success for both endpoints) in the mITT population. Only a small percentage of patients in both groups who had an early clinical response did not have an investigator-assessed clinical cure at PTE (Oritavancin, 14.8%; Vancomycin, 11.9%) in the mITT population. Thus, for the majority of patients, an early clinical response was maintained for 7-14 days after the end of treatment.

In addition, most patients in the mITT population with an early clinical response also had a lesion size reduction ≥ 20% at ECE (Oritavancin, 94.4%; Vancomycin, 93.1%).

Concordance/discordance of early clinical response with complete resolution at PTE and Complete resolution <5% with residual lesion size:

Exploratory analyses of concordance/discordance of responder rates at ECE with complete resolution and complete resolution/<5% residual lesion size at PTE showed that responder outcomes at PTE diverged from the outcomes at ECE. This divergence could not be interpreted meaningfully due to missing data at PTE. However, concordance/discordance rates of early clinical response were similar with (1) complete resolution and (2) complete resolution/<5% residual lesion size. These analyses are provided in Table 13.

Table 13 (SOLO I): Concordance of early clinical response with complete resolution at PTE and Complete resolution <5% with residual lesion size in mITT population

Endpoint	Outcome	Responders		Non-Responders	
		Oritavancin	Vancomycin	Oritavancin	Vancomycin
Complete resolution at PTE	Success	213/391(54.5)	207/378(54.8)	27/84(32.1)	32/101(31.7)
	Failure	126/391(32.2)	131/378(34.7)	42/84 (50.0)	37/101(36.6)
	Missing	52/391(13.6)	40/378 (10.6)	15/84(17.9)	32/101(31.7)
Complete resolution at PTE and <5% with residual lesion size	Success	212/391(54.5)	207/378(54.8)	26/84(31.0)	32/101(31.7
	Failure	126/391(32.2	130/378(34.4)	43/84(51.2)	37/101(36.6)
	Missing	53/391(13.6)	41/378(10.8)	15/84(17.9)	32/101(31.7)

Source: Applicant's submission (dated March 07, 2014) Table 4.12.1.3a and Table 4.12.1.4a

Statistical Reviewer's Conclusions:

Based on the reviewer's analysis of the primary endpoint, SOLO I provided adequate evidence supporting the efficacy of Oritavancin (administered a single-dose 1200 mg IV infusion) in treating patients with ABSSSI. Responder rates (based on early clinical response) at ECE were similar between Oritavancin and the comparator: 82.3% [391/475] vs.78.9% (378/479], a 3.4% difference (95% CI: -1.6%, 8.4%).

The reviewer analysis of the lesion size reduction ≥ 20% at ECE from baseline (the primary endpoint currently recommended by FDA) demonstrated evidence to support the efficacy of Oritavancin (administered a single-dose 1200 mg IV infusion) in treating patients with ABSSSI. The percentage of patients using this endpoint was similar between Oritavancin and the comparator: 86.9% [413/475] vs. 82.9% [397/479], a 4.1% difference (95% CI: -0.5%, 8.6%).

The reviewer analysis of the investigator-assessed clinical cure at PTE resulted in clinical cure rates at PTE of 79.6% [378/475] in the Oritavancin group vs.80.0%[383/479] in the comparator group, with a 0.4% difference (95% CI: -5.5%, 4.7%).

The SOLO I protocol prespecified the analyses of the secondary endpoints. However, the protocol did not mention any adjustment method for controlling overall type I error rate for testing the multiple secondary endpoints. Based on a gatekeeper strategy, the overall type I error rate did not require adjustment for multiple tests since they were tested after noninferiority for the primary endpoint was established. Thus, the inferences from the secondary endpoints are acceptable.

In summary, this reviewer concludes that the trial provides sufficient evidence that a single 1200 mg Oritavancin dose is noninferior to 7 to 10 days of Vancomycin (1g or 15 mg/kg twice daily) for the treatment of ABSSSI in adult patients.

SOLO II:

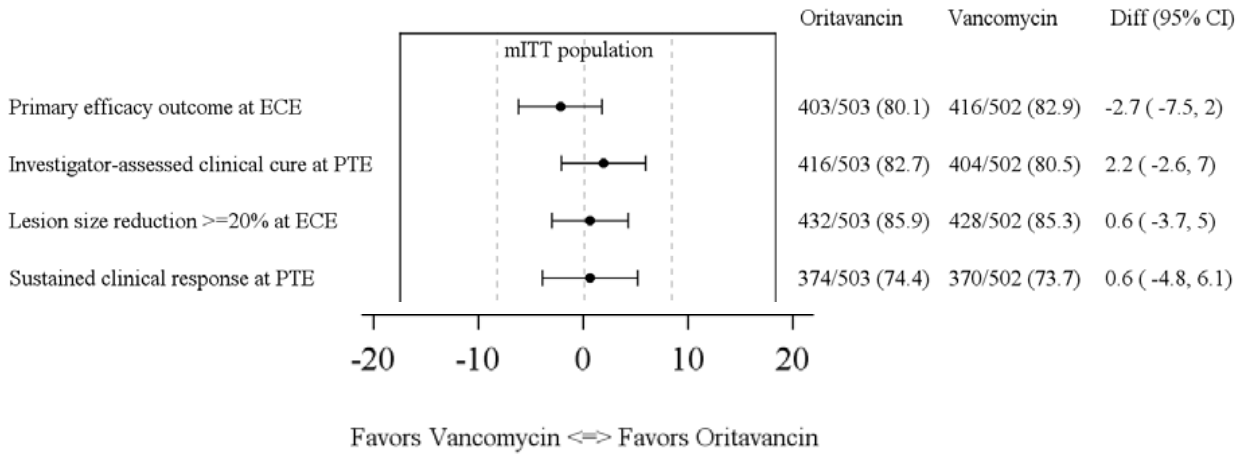
In SOLO II, Oritavancin has comparable clinical efficacy to the comparator regimen Vancomycin for the primary efficacy outcome measure of early clinical response at 48 to 72 hours. Oritavancin has also comparable clinical efficacy to the comparator regimen Vancomycin for the secondary endpoints. Table 14 and Figure 4 provide efficacy results of the primary endpoint and secondary endpoints of SOLO II.

Table 14(SOLO II): Summaries of the efficacy analyses for the mITT population

Endpoints	Oritavancin (N=503) n (%)	Vancomycin (N=502) n (%)	Difference (95% CI*)
Early clinical response (primary endpoint specified in the protocol)	403(80.1)	416(82.9)	-2.7(-7.5, 2.0)
Investigator assessed clinical cure ta PTE	416 (82.7)	404(80.5)	2.2 (-2.6, 7.0)
Lesion size reduction≥ 20% at ECE (current primary endpoint-FDA)	432(85.9)	428(85.3)	0.6 (-3.7, 5.0)
Sustained clinical response at PTE	313 (65.9	322 (67.2)	-1.3 (-7.3,4.7)

Source: Applicants clinical trial report: Tables 11, 13, 14, and 15
*Based on the normal approximation to Binomial distribution

Figure 4(SOLO II): Forest Plot of Primary Endpoint (mITT Population



Source: Figure 7, Applicant's Clinical Trial Report, Page 101.

Primary endpoint:

In the mITT population, it is seen from Table 14 that the rate of early clinical response was similar in the Oritavancin (80.1%) and Vancomycin (82.9%), groups. The lower limit of the 95% CI (-7.5, 2.0) for the rate difference was above the -10% margin, demonstrating that a single dose of Oritavancin is noninferior to 7-10 days of IV Vancomycin.

Note that in the ITT population, the percentage of patients with an early clinical response in the Oritavancin and Vancomycin groups (Oritavancin, 416/509(79.2%); Vancomycin, 403/510(81.6%) was similar to the percentages seen in both groups in the mITT population with a similar treatment difference and 95% CI (-2.4%; 95% CI: -7.3, 2.5).

Secondary Efficacy Endpoints:

Investigator-assessed clinical cure (IACC) at PTE:

As shown in Table 14, the percentage of patients with an investigator-assessed clinical cure at post-therapy evaluation (PTE) was 82.7% in the Oritavancin and 80.5% in the Vancomycin groups with a treatment difference of 2.2% and 95% CI of (-2.6, 7.0).

Table 15 shows that the percentage of patients with an investigator-assessed clinical cure was similar between the Oritavancin and Vancomycin groups at EOT (Oritavancin, 87.9%; Vancomycin, 86.9%) and Day 10 (Oritavancin, 87.1%; Vancomycin, 86.5%) and the rates were maintained over time to PTE.

Table 15: Investigator-Assessed Clinical Cure at EOT, Day 10, and PTE (mITT Population)

Visit	Oritavancin (N=502) n (%)	Vancomycin (N=503) n (%)	Difference (95% CI)* n (%)
EOT	442(87.9	436(86.9	1.0 (-3.1, 5.1)
Day 10	438 (87.1)	434(86.5)	0.6 (-3.6, 4.8)
PTE	416 (82.7)	404 (80.5)	2.2(-2.6, 7.0)

Source: Applicants clinical trial report, Table 19, page 85
*Based on the normal approximation to Binomial distribution

Percentage of patients with a lesion size reduction ≥ 20% from baseline at ECE:

As shown in Table 14, the percentage of patients with a lesion size reduction ≥ 20% from baseline at ECE was similar in the Oritavancin (85.9%) and Vancomycin (85.3%) groups, with a treatment difference of 0.6% and 95% CI of (-3.7, 5.0). Based on these data, Oritavancin is noninferior to Vancomycin because the lower limit of the 95% CI is greater than the prespecified noninferiority margin of -10%.

Table A.2 in the appendix shows the various reductions from baseline at ECE at intervals: ≥20% - <30%, ≥30% - <40%, ≥40% - <50%, ≥ 50% - <60%, ≥60% - <70%, ≥70% - <80%, ≥90% - <95% and ≥95%. These reductions form baseline at ECE were similar between the two treatment groups.

Percentage of patients with a sustained clinical response at PTE:

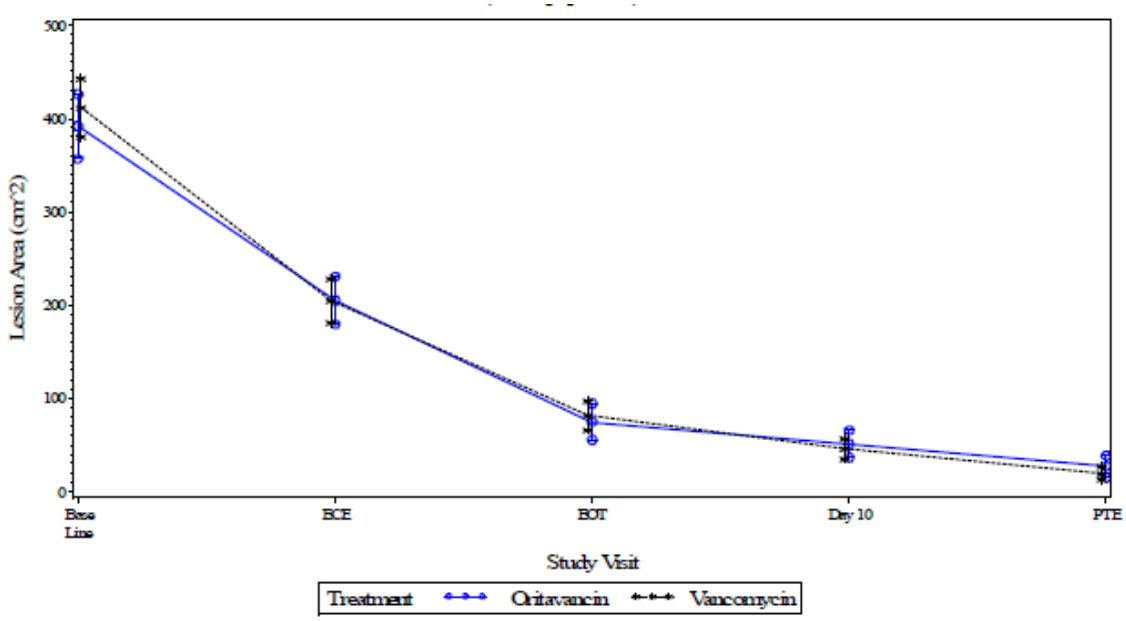
As shown in Table 14, the percentage of patients with a sustained clinical at PTE in the Oritavancin group was 74.4% and Vancomycin group was 73.7%, with a treatment group difference of 0.6% and 95% CI of (-4.8, 6.1).

Supportive analyses:

Mean lesion area at ECE, EOT, Day 10, and PTE:

Mean Lesion Area and 95% Confidence Intervals in the mITT Population at Baseline, ECE, EOT, Day 10, and PTE are plotted in Figure 5.

Figure 5(SOLO II): Mean Lesion Area and 95% Confidence Intervals in the mITT Population at Baseline, ECE, EOT, Day 10, and PTE



Source: Applicant's clinical trial report, Figure 2, page 89

Figure 5 shows that the mean lesion size in Oritavancin treated group and Vancomycin treated groups at ECE, EOT, Day 10 and PTE was similar, Note that at PTE the difference in mean reduction from baseline lesion area between Oritavancin and Vancomycin groups (Oritavancin vs. Vancomycin: -358.1 vs. -386.7) was 28.6 cm^2 with 95% CI (-16.9, 74.1)

Sensitivity/Exploratory Analyses:

Sensitivity/exploratory analyses were conducted by the applicant to assess the robustness of the findings for rates for early clinical response and clinical cure rate at PTE. These analyses considered the following:

- Missing data at ECE;
- Missing data at PTE;
- Early clinical response excluding fever component;
- Concordance between endpoints.

Missing data at ECE and PTE:

Table 16 summarizes failures and missing data at ECE and PTE, respectively.

Table 16(SOLO II): Failure and Missing data at ECE and at PTE for the mITT population

Failure/missing		Treatment Group	
		Oritavancin (N=503) n (%)	Vancomycin (N=502) n (%)
ECE:	Missing	87(17.3)	71(14.1)
	Failure	13(2.6)	15(3.0)
PTE:	Missing	37(7.4)	38(7.6)
	Failure	50(9.9)	60(11.9)

Source: Reviewer's Table

The applicant conducted a sensitivity analysis to explore the impact of missing values for early clinical response on the robustness of the conclusions from the primary analysis. The percentage of patients with an early clinical response was similar in the Oritavancin and Vancomycin groups if missing values were treated as success (Oritavancin, 82.7%; Vancomycin, 85.9%; 95% CI (7.6, 1.3)). Thus, the sensitivity analysis showed that treatment differences and the associated 95% CIs were similar to those seen in the primary analysis where missing data were treated as failure**.**

The applicant also conducted a sensitivity analysis to explore the impact of missing values for investigator-assessed clinical cure at PTE on the robustness of the conclusions from the primary analysis, The percentage of patients with an investigator-assessed clinical cure was similar in the Oritavancin and Vancomycin groups if missing values were treated as success (Oritavancin, 92.6%; Vancomycin, 92.4%; 95% CI (-3.0, 3.5)). Thus, the results seen in the sensitivity analyses demonstrated similar conclusions from the original analysis.

This reviewer opines that because missing patterns were similar in both treatment groups, classification of missing data as success did not change the original analyses. Thus, the analyses by treating missing data as success were not informative.

Early clinical response excluding fever component:

When early clinical response was calculated as a composite endpoint of cessation of spread or reduction in size of the baseline lesion and no rescue antibiotic medication at ECE, and excluding fever as part of the composite, 90.1% and 89.4% of the Oritavancin and Vancomycin

groups, respectively, had an early clinical response. The efficacy rates were similar in both treatment groups.

Concordance between the Primary, and Secondary Efficacy Endpoints

Concordance/discordance of early clinical response at ECE with investigator-assessed clinical cure at EOT, PTE, and at least 20% reduction in lesion area from baseline at ECE are provided in the Table 17 by treatment group using the mITT population.

Table 17 (SOLO II): Concordance of early clinical response with secondary endpoints in mITT population

Endpoint	Outcome	Responders		Non-Responders	
		Oritavancin	Vancomycin	Oritavancin	Vancomycin
Investigator-assessed clinical cure at EOT	Success	382/403(94.8)	392/416(94.2)	60/100(60.0)	44/86(51.2)
	Failure	21/403(5.2	24/416(5.8%)	40/100(40.0)	42/86(5.8)
Investigator-assessed clinical cure at PTE	Success	354/403(87.8)	360/416(86.5)	62/100 (62.0)	44/86 (51.2)
	Failure	49/403 (12.2)	56/416(13.5)	38/100 (38.0)	42/86 (48.8)
lesion size reduction ≥ 20% at ECE	Success	379 /403(94.0)	386/416 (92.8)	53/100 (53.0)	42/86 (48.8)
	Failure	24/403 (6.0)	30/416 (7.2)	47/100 (47.0)	44/86 (51.2)

Source: Applicants clinical trial report: Table 16 (page 83), Table 18 (page 84)

Most patients in both groups (Oritavancin, 94.8%; Vancomycin, 94.2%) who had an early clinical response also had an investigator-assessed clinical cure at EOT (i.e., success for both endpoints) in the mITT population. Only a small percentage of patients in both groups who had an early clinical response did not have an investigator-assessed clinical cure at EOT (Oritavancin, 5.2%; Vancomycin, 5.8%) in the mITT population. Thus, for the majority of patients, an early clinical response was maintained for EOT.

Additionally, most patients in both groups (Oritavancin, 87.8%; Vancomycin, 86.5%) who had an early clinical response also had an investigator-assessed clinical cure at PTE (i.e., success for both endpoints) in the mITT population. Only a small percentage of patients in both groups who had an early clinical response did not have an investigator-assessed clinical cure at PTE (Oritavancin, 12.2%; Vancomycin, 13.5%) in the mITT population. Thus, for the majority of patients, an early clinical response was maintained for PTE.

In addition, most patients in the mITT population with an early clinical response also had a lesion size reduction ≥ 20% at ECE (Oritavancin, 94.4%; Vancomycin, 92.8%).

Concordance/discordance of early clinical response with complete resolution at PTE and Complete resolution <5% with residual lesion size:

Exploratory analyses of concordance/discordance of responder rates at ECE with complete resolution and complete resolution/<5% residual lesion size at PTE showed that responder outcomes at PTE diverged from the outcomes at ECE. This divergence could not be interpreted meaningfully due to missing data at PTE. However, concordance/discordance rates of early clinical response were similar with (1) complete resolution and (2) complete resolution/<5% residual lesion size. These analyses are provided in the Table 18.

Table 18 (SOLO I): Concordance of early clinical response with complete resolution at PTE and Complete resolution <5% with residual lesion size in mITT population

Endpoint	**Outcome**	**Responders**		**Non-Responders**	
		Oritavancin	Vancomycin	Oritavancin	Vancomycin
Complete resolution at PTE	Success	231/403 (57.3)	241/416(57.9)	40/100 (40.0	34/86(39.5)
	Failure	134/403(33.3)	119/416(28.6)	37/100 (37.0)	32/86(37.2)
	Missing	38/403(9.4)	56/416(13.5)	23/100(23.0)	20/86(23.3)
Complete resolution and <5% with residual lesion size	Success	231/403(57.3)	240/416(57.7)	40/100(40.0)	33/86(38.4
	Failure	134/403(33.3)	120/416(28.8)	37/100(37.0)	32/86(37.2)
	Missing	38/403(9.4)	56/416 (13.5)	23/100(23.0)	21/86(24,4)

Source: Applicant's submission (dated March 07, 2014) Table 4.12.1.3a and Table 4.12.1.4a

Statistical Reviewer's Conclusions

Based on the reviewer's analysis of the primary endpoint, SOLO II provided adequate evidence supporting the efficacy of Oritavancin in treating patients with ABSSSI infections. Responder rates at ECE were similar between Oritavancin and the comparator: 80.1% [403/503] vs.82.9%[416/502], a-2.7% difference (95% CI: -7.5%, 2.0%).

The reviewer analysis of lesion size reduction ≥ 20% at ECE from baseline also demonstrated evidence to support the efficacy of Oritavancin in treating patients with ABSSSI infections. The percentages of patients using this endpoint were similar between Oritavancin group and the comparator group (85.9 % [432/503] vs. 85.3% [428/502]) with a 0.6% difference (95% CI: -3.7%, 5.0%)

The reviewer analysis of the investigator-assessed clinical cure at PTE resulted in clinical cure rates at PTE of 82.7% [416/503] in the Oritavancin group vs.80.5%[404/502] in the comparator group with a 2.2% difference (95% CI: -2.6%, 7.0%).

The SOLO II protocol prespecified the analyses of the secondary endpoints. However, the protocol did not mention any adjustment method for controlling overall type I error rate for testing the multiple secondary endpoints. Based on gatekeeper methodology (step-down testing), the overall type I error rate did not require adjustment for multiple tests since the endpoints were tested after noninferiority of the primary endpoint was established. Thus, the inferences from the secondary endpoints are acceptable.

In summary, this reviewer concludes that the trial provides sufficient evidence that a single 1200 mg Oritavancin dose is noninferior to 7 to 10 days of Vancomycin (1g or 15 mg/kg twice daily) for the treatment of ABSSSI in adult patients.

3.3 Evaluation of Safety

The applicant has stated that the primary safety analysis population was the pooled data for the Phase 3 trials, SOLO I and SOLO II, because it provides safety data for the proposed single 1200 mg dose of Oritavancin for the treatment of ABSSSI suspected to be caused by Gram-positive pathogens. This reviewer opines that pooling of the data for SOLO I and SOLO II was appropriate because of the identical design of the SOLO protocols. Note that the SOLO pool includes 976 patients treated with Oritavancin and 983 patients treated with Vancomycin. Patients were followed for 60 days following trial drug administration because of the long half-life of Oritavancin.

The applicant has mentioned that the overall frequency of SAEs was similar in the Oritavancin and Vancomycin groups in the SOLO trials (Oritavancin, 5.8%; Vancomycin, 5.9%). See Table A.3 (SOLO I) and Table A.4 (SOLO II) for details. See also clinical review for further details.

The most frequent SAEs ($\geq$ 0.3%) in the SOLO pool were cellulitis, osteomyelitis, abscess limb, pneumonia, skin infection, and subcutaneous abscess in the Oritavancin group and cellulitis, skin infection, and skin bacterial infection in the Vancomycin group .The percentage of patients with any SAE assessed as related to trial drug was similar in the Oritavancin (0.5%) and Vancomycin (0.4%) groups

Five patients, two in the Oritavancin group and 3 in the Vancomycin group, died in the SOLO trials. Causes of death were sepsis and electromechanical dissociation in the Oritavancin group and septic shock, advanced dementia with Parkinsonism, and acute myocardial infarction in the Vancomycin group.

In summary, Oritavancin demonstrated an overall comparable safety profile with similar rates of mortality and non-fatal adverse events as the comparator.

3.4 Benefit-Risk Assessment

As noted earlier, the SOLO trials demonstrated that a single 1200 mg IV dose of Oritavancin was well tolerated and had a similar safety profile to 7 to 10 days of Vancomycin treatment (1 g or15 mg/kg twice daily).

Overall, the safety of Oritavancin has been characterized in over 3000 subjects throughout the development program. The safety of Oritavancin across different subpopulations and different doses (multiple or single) was consistent with the safety results observed in the SOLO trials at the intended treatment dose of 1200 mg.

4 Findings in Special/Subgroup Populations

The applicant's subgroup analyses included the following factors: demographics and baseline characteristics (age, sex, race, body mass index [BMI], disease type), region, baseline pathogen (e.g., MRSA vs. MSSA), diabetes mellitus diagnosis, underlying medical conditions and previous infection history, baseline fever status, antibiotics prior to trial drug, and planned surgical procedure s for the primary ABSSSI.

It is to be noted that subgroup analyses were limited by a high degree of variability resulting from the small number of subjects included in each subgroup. Both SOLO trials were not powered to test the effectiveness of the drug for the subgroups. In addition, there was a problem (inflation of type I error) of multiple hypotheses testing related to subgroup analyses. For these reasons, confidence intervals for treatment differences in subgroups were not considered to be informative. Therefore, the subgroup analyses have to be interpreted very cautiously.

4.1Gender, Race, Age, and Geographic Region

The applicant's subgroup analyses for the primary endpoint are provided in Figure A.1 (SOLO I) and A.2 (SOLO II) in the Appendix. These analyses showed consistent treatment effect in the Oritavancin and Vancomycin groups for the primary endpoint of early clinical response by gender, age, race, and geographic region and in patients with diabetes mellitus. A few of these subgroup analyses are provided below.

Analysis by gender:

The following table (See also Figure A.1 and A.2 in the Appendix) provides responder rates at ECE by gender for both SOLO I and SOLO II trials.

Table 19: Early clinical response rates (primary efficacy endpoint) by Gender in mITT population

	SOLO I		SOLO II	
Gender	Oritavancin **(N= 475)** n/N (%)	**Vancomycin (N=479)** n/N (%)	Oritavancin **(N=503)** n/N (%)	**Vancomycin (N=502)** n/N (%)
Male	246/301 (81.7)	242/301 (80.4)	273/ 338(80.8)	284/343(82.8)
Female	145/174 (83.3)	136/ 178(76.4)	130/1 6 5 (78.8)	132/ 159(83.0)

Source: Reviewer Table

Table 19 shows that responder rates (regardless of treatment) at ECE in each trial were comparable between two treatment groups with respect to each gender.

Analysis by race:

The following table (See also Figure A.1 and A.2 in the Appendix) provides responder rates at ECE by race for both SOLO I and SOLO II trials.

Table 20: Early clinical response rates (primary efficacy endpoint) by Race in mITT population

	SOLO I		SOLO II	
	Oritavancin (N= 475) n/N (%)	Vancomycin (N=479) n/N (%)	Oritavancin (N=503) n/N (%)	Vancomycin (N=502) n/N (%)
White	209/274 (76.3)	197/275 (71.6)	285/ 356(80.1)	290/ 356(81.5)
African American	38/43 (88.4)	32/ 40(80.0)	13/14 (92.9)	15/ 17(88.2)
Asian	140/ 153(91.5)	140/ 154(90.9)	96/122 (78.7)	104/122 (85.2)

Source: Reviewer's
Note: Efficacy results for other races were not included because of small sample sizes (5 patients in Oritavancin group and 10 patients in Vancomycin group in SOLO I; 11 patients in Oritavancin group and 7 patients in Vancomycin group in SOLO II)

In trial SOLO I, somewhat higher rates were observed Oritavancin treated group than Vancomycin treated group in all the races. In trial SOLO II, somewhat lower rates were observed in all the races as except African American population.

Analysis by age-group:

The following table (See also Figure A.1 and A.2 in the Appendix) provides responder rates at ECE by age-group (≤65 and >65) for both SOLO I and SOLO II trials.

Table 21: Early clinical response rates (primary efficacy endpoint) by age-group in mITT population

	SOLO I		SOLO II	
Age-group	Oritavancin (N= 475) n/N (%)	Vancomycin (N=479) n/N (%)	Oritavancin (N=503) n/N (%)	Vancomycin (N=502) n/N (%)
≤65	353/428(82.5)	353/441(80.0)	376/ 464(81.0)	383/ 463(82.7)
>65	38/47(80.9)	25/ 38(65.8)	27/3 9 (69.2)	33/39(84.6)

Source: Reviewer's Table

In SOLO trials, similar rates of early clinical response were seen in the Oritavancin and Vancomycin groups in patients ≤65 years. In trial SOLO I, higher rate of early clinical response was observed in Oritavancin treated group than that of Vancomycin treated group (80.9% versus 65.8%) in patients >65 years whereas in trial SOLO II, lower rates of early clinical response observed in Oritavancin treated group than that of Vancomycin treated group (69.2% versus 84.6%) in patients >65 years.

Analysis by geographic region:

Early clinical response rates (See also Figure A.1 and A.2 in the Appendix) in the U.S., Eastern Europe, Western Europe and Asia are provided in the following table:

Table 22: Early clinical response rates (primary efficacy endpoint) by Region in the mITT population

	SOLO I		**SOLO II**	
	Oritavancin **(N= 475)** n/N (%)	**Vancomycin (N=479)** n/N (%)	Oritavancin **(N=503)** n/N (%)	**Vancomycin (N=502)** n/N (%)
USA	234/298 (78.5)	224/299 (74.9)	230/ 283(81.3)	232/ 285(81.4)
Eastern Europe	10/13 (76.9)	9/ 15(60.0)	70/88 (79.5)	72/ 86(83.7)
Western Europe	11/ 14(78.6)	7/ 13(53.8)	7/10 (70.0)	10/11 (90.9))
Asia	135/148 (91.2)	137/150 (91.3)	94/120(78.3)	102/119(85.7)

Source: Reviewer's Table

Note: Efficacy results for other region/countries were not included because of small sample sizes (South America: 2 patients in Oritavancin group and 2 patients in Vancomycin group in SOLO I; 2 patients in Oritavancin group and 1patients in Vancomycin group in SOLO II. Canada: 4 patients in Oritavancin group and no patients in Vancomycin group in SOLO I; no patients in Oritavancin group and no patients in Vancomycin group in SOLO II)

Table 22 shows that responder rates (regardless of treatment) at ECE in SOLO I were substantially higher in the Asia versus other regions. In North America, responder rates comparable between two treatment groups in both trials. In trial SOLO I, because of small sample sizes in Eastern Europe (Oritavancin vs. Vamcomycin: 13 vs. 15) and Western Europe (Oritavancin vs. Vamcomycin: 14 vs. 13), there are increased uncertainties in response rates comparing two treatment groups. See also Figure A.2 in the Appendix for further details.

In trial SOLO II, because of small sample sizes in Western Europe (Oritavancin vs. Vamcomycin: 10 vs. 11), the response rates at ECE are not interpretable for comparing two treatment groups. However, the response rates in Eastern Europe were similar between two treatment groups. See Figure A.2 in the Appendix for further details.

Table 22 also shows that the response rates were also higher in Asia in SOLO I than those of SOLO II. See also Figure A.1 and Figure A.2 in the Appendix for further details.

4.2 Other Special/Subgroup Analyses

Analyses by infection type:

Early clinical response rates by infection types are provided in the following table:

Table 23: Responder Rates (primary efficacy endpoint) by Infection Type in mITT population

	SOLO I		SOLO II	
	Oritavancin **(N= 475)** n/N (%)	**Vancomycin (N=479)** n/N (%)	Oritavancin **(N=503)** n/N (%)	Vancomycin (N=503) n/N (%)
Wound Infection	79/92(85.9)	92/105 (87.6)	170/191 (89.0)	147/176(83.5)
Cellulitis/erysipelas	197/243(81.1)	176/233(75.5)	97/146 (67.4)	126/167 (75.4)
Major Cutaneous Abscess	115/140 (82.1)	110/141(78.)	136/168(81.0)	143/159 (89.9)

Source: Figure A.1 (SOLO I) and Figure A.2 (SOLO II)

In trial SOLO I, a consistent treatment effect was seen in the Oritavancin and Vancomycin groups for early clinical response for each infection type. However, in trial SOLO 2, in patients with a major cutaneous abscess and Oritavancin had lower early clinical response rates than Vancomycin (Oritavancin, 81.0%; Vancomycin, 89.9%). See Figure A.1 and Figure A.2 in the Appendix for further details.

Analyses by Diabetic mellitus:

Early clinical response rates for the diabetic mellitus patients are provided in the following table:

Table 24: Analyses of the Primary Endpoint by Diabetic mellitus in mITT population

	SOLO I		SOLO II	
	Oritavancin n/N (%)	Vancomycin n/N (%)	Oritavancin n/N (%)	Vancomycin n/N (%)
Diabetic mellitus	76/93(81.7)	78/95 (82.1)	34/ 46(73.5)	38/45(84.4)

Source: Figure A.1 (SOLO I) and Figure A.2 (SOLO II)

Table 24 shows that in trial SOLO I, the percentage of patients with an early clinical response in the patients with diabetic mellitus was similar in the Oritavancin (81.7%) and Vancomycin (82.1%) groups.

However, in trial SOLO II, the percentage of patients with an early clinical response in the patients with diabetic mellitus was somewhat lower in the Oritavancin (73.5%) arm as compared to Vancomycin (84.4%) arm. Because of small sample sizes, this difference cannot be meaningfully interpreted.

Analyses by Baseline Pathogen:

Efficacy was analyzed for patients with ABSSSI infections in the MicroITT population caused by MRSA and MSSA. Table summarizes Clinical Response Rate at 48-72 hours and Clinical Success Rate at follow-up visit (7 to 14 days after end of therapy) by Baseline Pathogen (MRSA and MSSA subgroups) in SOLO trials.

Table 25: Analyses of the Primary Endpoint by Baseline Pathogen

	SOLO I		SOLO II	
Baseline Pathogen	Oritavancin n/N (%)	Vancomycin n/N (%)	Oritavancin n/N (%)	Vancomycin n/N (%)
MRSA	84/104(80.8)	80/100 (80.0)	82/100(82.0)	82/101(81.2)
MSSA	96/116 (82.8)	92/110(83.6)	126/150(84.0)	137/157(87.3)

Source: Figure A.1 (SOLO I) and Figure A.2 (SOLO II)

As shown in Table 25, within the MRSA subgroup in SOLO I, the percentage of patients with an early clinical response in the MicroITT population was similar in the Oritavancin (80.8%) and Vancomycin (80.0%) groups. Within the MSSA subgroup in SOLO I, the percentage of patients with an early clinical response in the MicroITT population was similar in the Oritavancin (82.8%) and Vancomycin (83.6%) groups.

As shown in Table 25, within the MRSA subgroup in SOLO II, the percentage of patients with an early clinical response in the MicroITT population was similar in the Oritavancin (82.0%) and Vancomycin (81.0%) groups. Within the MSSA subgroup in SOLO II, the percentage of patients with an early clinical response in the MicroITT population was similar in the Oritavancin (84.0%) and Vancomycin (87.3%) groups.

Pooled Analyses by pathogen:

Note that *S. aureus* was the most common pathogen in this submission. MRSA was recovered from the primary ABSSSI site or blood in 204 and 201 patients in the Oritavancin and Vancomycin groups, respectively, in the SOLO pool whereas MSSA was recovered from the primary ABSSSI site or blood in 266 and 267 patients in the Oritavancin and Vancomycin groups, respectively, in the SOLO pool.

The primary efficacy analysis of each SOLO trial was conducted individually. However, the applicant also conducted pooled analyses (which will be put in the label) to provide a larger sample of patients to improve the precision in the estimate of the treatment differences between Oritavancin and Vancomycin based on microITT population. Table 26 provides the pooled analyses by pathogen for clinical response rate at ECE and clinical success rate at PTE by pathogen type.

Table 26: Clinical Response Rate at 48-72 hours and Clinical Success Rates at Follow-up visit (7 to 14 days after end of therapy by Baseline Pathogen

	At 48-72 hours[1]		**At 7-14 days after End-of-Therapy[2]**	
Pathogen	**ORBACTIV n/N (%)**	**Vancomycin n/N (%)**	**ORBACTIV n/N (%)**	**Vancomycin n/N (%)**
Staphylococcus aureus	388/470(82.6)	391/468 (83.5)	389/470 (82.8)	393/468 (84.0)
Methicillin-susceptible (MSSA)	222/266 (83.5)	229/267 (85.8)	219/266 (82.3)	224/267 (83.9)
Methicillin-resistant (MRSA)	166/204 (81.4)	162/201(80.6)	170/204 (83.3)	169/201 (84.1)
Streptococcus pyogenes	21/31(67.7)	23/ 32(71.9)	25/31 (80.6)	23/32 (71.9)
Streptococcus intermedius	8/10(80.0)	13/ 16 (81.3)	8/10 (80.0)	13/16 (81.3)
Streptococcus constellatus	17/19(89.5)	21/ 23 (91.3)	15/19 (78.9)	19/23 (78.3)
Enterococcus faecalis	11/13(84.6)	10/ 12 (83.3)	8/13 (61.5)	9/12 (75.0)

Source: Applicant's submission (dated May 09, 2014) Table 1

MRSA subgroup:

Table 26 shows that within the MRSA subgroup, the percentage of patients with an early clinical response in the SOLO pool was similar in the Oritavancin (81.4%) and Vancomycin (80.6%) groups, with a treatment difference of 0.8% and 95% CI of (-6.9, 8.4) in the MicroITT population.

Table 26also shows that within the MRSA subgroup, the percentage of patients with an investigator-assessed clinical cure in the SOLO pool was similar in the Oritavancin (83.3%) and Vancomycin (84.1%) groups (treatment difference of -0.7% and 95% CI of (-7.9, 6.4)) in the MicroITT population.

This reviewer concludes that within the SOLO pool, the rates of early clinical response and investigator-assessed clinical cure at PTE in the MicroITT population were similar in the Oritavancin and Vancomycin groups for MRSA patients.

MSSA subgroup:

Table 26 shows that within the MSSA subgroup, the percentage of patients with an early clinical response in the SOLO pool was similar in the Oritavancin (83.5%) and Vancomycin (85.8%) groups (treatment difference of -2.3% and 95% CI of (-8.4, 3.8)) in the MicroITT population.

Table 26 also shows that within the MSSA subgroup, the percentage of patients with an investigator-assessed clinical cure in the SOLO pool was similar in the Oritavancin (82.3%) and Vancomycin (83.9%) groups (treatment difference of -1.1% and 95% CI of (-7.3, 5.1)) in the MicroITT population.

This reviewer concludes that within the SOLO pool, the rates of early clinical response and investigator-assessed clinical cure at PTE in the MicroITT population are similar in the Oritavancin and Vancomycin groups for MSSA patients.

Other pathogen types:

Table 26 also shows that Clinical Response Rate at 48-72 hours and Clinical Success Rate at follow-up visit (7 to 14 days after end of therapy) by baseline pathogen (Pathogen type with sample size <10 were not included in Table 26) are similar between the two treatment groups.

Analyses of Signs and Symptoms:

The Applicant reported that signs and symptoms related to the primary ABSSSI site (i.e., erythema, induration/edema, purulent drainage, fluctuance, pain, tenderness, local increase in heat/warmth) were reduced in frequency and severity 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. See following table for absence (rates) of signs and symptoms at PTE.

Table 27: Absence of Signs and symptoms at PTE

	SOLO I		SOLO II	
Signs and symptoms	**Oritavancin (N=475) n (%)**	**Vancomycin (N=479) n (%)**	**Oritavancin (N=503) n (%)**	**Vancomycin (N=502) n (%)**
Edema (absent)	331/408 (81.1)	336/407(82.6)	400/444 (90.1)	391/427 (91.6)
Erythema(absent)	317/408 (77.7)	323/408 (79.2)	348/444 (78.4)	349/426 (81.9)
Fluctuance (absent)	403/408 (98.8)	403/407 (99.0)	442/444 (99.5)	424/426 (99.5)
Local increase in heat and warmth(absent)	394/408 (96.6)	393/408(96.3)	433/444 (97.5)	419/426 (98.4)
Induration(absent)	333/408 (81.6)	321/408 (78.7)	341/444 (76.8)	330/427 (77.3)
Purulent drainage(none)	399/408(97.8)	399/408(97.8)	427/444 (96.2)	416/426 (97.7)
Pain(none)	352/408 (86.5)	357/409 (87.3)	365/444 (86.7)	381/426 (89.4)
Tenderness(none)	349/408 (85.5)	332/409(81.2)	400/444(90.1)	387/427 (90.5)

Source: Table 1 of Applicant's submission, dated May 09, 2014

Patients with a rescue antibiotic:

The percentage of patients treated with a rescue antibiotic (i.e., non-trial antibiotic medication with an effect on Gram-positive pathogens) was similar in the Oritavancin and Vancomycin groups at ECE, EOT, Day 10, and PTE in both trials. See Table A.5 (SOLO I) and Table A.6 (SOLO II) in the Appendix for details.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are no major statistical issues that impacted the overall conclusions. However, this reviewer has identified the following minor issues which have not impacted the overall conclusions.

Analyses by excluding patients who did not satisfy main inclusion criterion:

In both SOLO trials, according to the protocol, all the patients dosed in the trial must have had baseline lesion area at least 75 cm^2. However, there were patients who did not satisfy the main inclusion criterion and who had missing baseline lesion measurement. The following table summarizes these patients:

Table 28: Baseline lesion area in the mITT population (Trials SOLO I and SOLO II)

Baseline lesion area	SOLO I		SOLO II	
	Oritavancin (N=475)	Vancomycin (N=479)	Oritavancin (N=503)	Vancomycin (N=502)
Baseline lesion area <75 cm^2	2	0	4	4
Baseline lesion area≥75 cm^2	473	477	498	497
Missing baseline area	0	1	0	0
Total	475	478	502	501

Source: Reviewer's Table

This reviewer conducted the analyses of the primary endpoint for both trials by deleting the subjects who had baseline lesion area <75 cm^2 and whose baseline lesion were missing (if any). The overall findings remained unchanged.

Analyses by excluding sites in SOLO I trial (Site 191008 and Site 191009) with high efficacy rates:

There were two foreign sites, Site 191008 and Site 191009 in India, in SOLO I where the efficacy rates of the primary endpoint were higher compared to overall rates as well as to rates in other sites in both treatment groups. OSI is currently investigating Site 191008. OSI could not inspect Site 191009 for logistical reasons. In Site 191008, the efficacy rates were 93.6% (29/31) in the Oritavancin treated group and 87.5% (28/32) in the Vancomycin treated group. In Site 191009, the efficacy rates were 100% (29/29) in the Oritavancin treated group and 96.7% (29/30) in the Vancomycin treated group. This reviewer analyzed the primary efficacy endpoint by excluding a) Site 191008, b) Site 191009 and c) both sites (Site 191008 and Site 191009) to examine whether these two sites had an impact on overall analyses. The efficacy rates for the primary endpoint are summarized in Table 29:

Table 29(SOLO I): Efficacy analyses in the mITT population excluding sites 191008 and 191009

Population	Oritavancin n/N (%)	Vancomycin n/N (%)	Diff (95% CI)
Overall	391/475 (82.32)	378/479 (78.91)	3.4(-1.6, 8.4)
Excluding Site 191008	362/444 (81.53)	350/447 (78.3)	3.2 (-2.0, 8.4)
Excluding Site 191009	362/446 (81.17)	349/449 (77.73)	3.4 (-1.8, 8.7)
Excluding Sites 191008 and 191009	333/415 (80.4)	321/417 (77.0)	3.3 (-2.3, 8.8)

Source: Reviewer's Table

Table 29 shows that results for the primary endpoint first excluding each site and then both sites were similar to the overall mITT population.

Primary analysis population:

Although the current FDA guidance for ABSSSI recommends that the ITT population in general should be considered the primary analysis population, the Applicant's SPA agreement with the agency included mITT population as the primary analysis population. However, in the ITT population for each SOLO trial, the percentages of patients with an early clinical response in the Oritavancin and Vancomycin groups were similar to the percentages seen in the mITT population with a similar treatment difference and 95% CI.

Note that in SOLO I, 8 (1.66%) patients in Oritavancin treated group and 6 (1.24%) patients in the Vancomycin did not receive the study medication whereas in SOLO II, 6 (1.18%) patients in Oritavancin treated group and 8 (1.57%) patients in the Vancomycin treated group did not receive the study medication. The number of patients who did not receive study drug was similar in each SOLO trial by the treatment groups. This reviewer opines that use of mITT population as the primary analysis population is not a major issue with this submission.

Missing data:

In SOLO I, Oritavancin arm had slightly less missing data, 16(3.4%) versus 23(4.8%) at ECE. In SOLO 2, both treatment arms had similar rates of missing data, 13(2.6%) vs. 15(3.0%) at ECE. In SOLO protocols, it was mentioned that missing data would be imputed as failures. In both trials, the handling of missing data as 'responders' in sensitivity analyses at ECE did not appear to substantially favor either treatment.

In SOLO I, Oritavancin arm had less missing data, 55(11.6%) versus 61(12.7%), at PTE. In SOLO II, Oritavancin arm had less missing data, 50(9.9%) versus s. 60(11.9%). The number of

patients missing at PTE was similar in each SOLO trials by the treatment groups. In both trials, the handling of missing data as 'responders' in sensitivity analyses at PTE did not appear to substantially favor either treatment.

This reviewer opines that because the number missing values were similar in both treatment groups, classification of missing data as success did not change the conclusions. Thus, the analyses treating missing data as success were not informative.

Multiplicity issues:

The SOLO protocols prespecified the analyses of the secondary endpoints. However, the protocols did not mention any adjustment method of controlling overall type I error rate for testing the multiple secondary endpoints. Note that that based on a gatekeeper method, the overall type I error rate did not require adjustment for multiple tests since endpoints were tested after noninferiority for the primary endpoint was established. Thus, the inferences from the secondary endpoints are acceptable.

5.2 Collective Evidence

The reviewer's summary of the collective evidence of effectiveness and/or safety is a compilation of the main findings from SOLO I and SOLO II and is provided below.

The rate of early clinical response was similar in the Oritavancin and Vancomycin groups in SOLO I (Oritavancin, 82.3%%; Vancomycin, 78.9%) and SOLO II (Oritavancin, 80.1%; Vancomycin, 82.9%). The lower limit of the 95% CI for the treatment group difference was greater than the prespecified noninferiority margin of -10% in both studies.

The percentage of patients with a lesion size reduction ≥ 20% at ECE was similar in the Oritavancin and Vancomycin groups in SOLO I (Oritavancin, 86.9%; Vancomycin, 82.9%) and SOLO II (Oritavancin, 85.9%; Vancomycin, 85.3%). The lower limit of the 95% CI for the treatment group difference was greater than the prespecified noninferiority margin of -10% in both studies.

The rate of investigator-assessed clinical cure at PTE was similar in the Oritavancin and Vancomycin groups in SOLO I (Oritavancin, 79.6%; Vancomycin, 80.0%) and SOLO II (Oritavancin, 82.7%; Vancomycin, 80.5%).

The percentage of patients with a sustained clinical response at PTE was similar in the Oritavancin and Vancomycin groups in SOLO I (Oritavancin, 65.9%; Vancomycin, 67.2%) and SOLO II (Oritavancin, 74.4%; Vancomycin, 73.7%).

The patient population in SOLO I and SOLO II was representative of ABSSSI patients that required IV therapy. There was no notable imbalance between treatments groups in most subgroups. Consistent results were shown across all efficacy endpoints for patient subgroups in the SOLO pools, including patients with microbiologically-confirmed MRSA.

In summary, SOLO trials support Oritavancin's indication for the treatment of ABSSSI caused by susceptible isolates of Gram-positive microorganisms including *S. aureus* (methicillin-susceptible and -resistant isolates), *S. pyogenes*, *Streptococcus constellatus*, and *Enterococcus faecalis*(Vancomycin-susceptible isolates only).

5.3 Conclusions and Recommendations

Oritavancin demonstrated non-inferiority to the regimen of intravenous (IV) Vancomycin for the treatment of ABSSSI in two phase 3 trials. The primary efficacy outcome was responder rates at 48-72 after study drug initiation defined as the cessation of spread or reduction in size of the baseline lesion, absence of fever, and no rescue antibiotic medication.

Efficacy was further demonstrated via evaluation of the clinical response defined as a ≥20% reduction in lesion area from baseline. Currently, this endpoint is recommended by the Agency as the primary endpoint for ABSSSI trials. The lower bound of the 95% CI around the difference in clinical response rates was greater than -10 for this endpoint as well.

The analysis of an additional secondary efficacy endpoint, investigator-assessed clinical cure at post treatment evaluation from end of therapy also supported the efficacy of Oritavancin in treating patients with ABSSSI infections at PTE in both trials.

The safety data from SOLO I and SOLO II demonstrated that a single 1200 mg IV dose of Oritavancin had a similar safety profile to 7 to 10 days of Vancomycin treatment (1 g or15 mg/kg twice daily). Most of the AEs were mild or moderate in severity. The incidences of deaths, SAEs, and discontinuation of trial drug due to an AE in Oritavancin-treated patients were low and similar to the incidences seen in patients receiving Vancomycin. Please see the clinical review of safety by Dr. M. Ghosh for further detail.

Overall, this reviewer concludes that a single-dose IV Oritavancin was effective in treating ABSSSI and well tolerated with a safety profile similar to IV Vancomycin.

5.4 Labeling Recommendations

The division's labeling meetings (internal) are still ongoing. However, some of the changes based on statistical recommendations include the following:

●Inclusion of a separate table for the following endpoints:

1) Early clinical response rates evaluated at 48-72 hours;

2) Percentage of patients with a lesion size reduction ≥ 20% from baseline at 48-72 hours;

3) Investigator assessed clinical cure rate at PTE from EOT.

•Inclusion of a table of early clinical response rates (by pathogen) evaluated at both 48-72 hours and investigator assessed clinical cure rate (by pathogen) at PTE from EOT for the microITT population.

APPENDIX:

The following entry criteria were based on the trial protocol for SOLO 1 and SOLO II clinical trials:

Inclusion Criteria:

For inclusion into the trial, patients were required to fulfill all of the following criteria:

1. Male or female ≥ 18 years old

2. Diagnosis of ABSSSI suspected or confirmed to be caused by a Gram-positive pathogen requiring at least 7 days of IV therapy. A specimen for culture was obtained by an approved protocol method 24 hours before the first dose of trial drug. Final culture results were not required prior to initiation of trial drug.

3. An ABSSSI which included one of the following infections:

    a. Wound infections: either traumatic or surgical in origin defined as an infection characterized by purulent drainage from a wound with surrounding erythema, edema, and/or induration of a minimum surface area of 75 cm^2 (e.g., the shortest distance of erythema, edema, and/or induration extending at least 5 cm from the peripheral margin of the wound), accompanied by the signs and systemic inflammation symptoms listed below; onset must have occurred within 7 days prior to randomization and no later than 30 days following the trauma or surgical procedure

    b. Cellulitis/erysipelas: a diffuse skin infection characterized by spreading areas of erythema, edema, and/or induration of a minimum surface area of 75 cm^2 (e.g., minimum length of 10 cm and width of 7.5 cm), accompanied by the signs and systemic inflammation symptoms listed below; onset of cellulitis must have occurred within 7 days prior to randomization

    c. Major cutaneous abscess: an infection characterized by a collection of pus within the dermis or deeper that was accompanied by erythema, edema, and/or induration of a minimum surface area of 75 cm^2 (e.g., the shortest distance of erythema, edema, and/or induration extending at least 5 cm from the peripheral margin of the abscess), accompanied by the signs and systemic inflammation symptoms listed below

4. 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)

5. Patient provided informed consent and was willing to comply with all required trial procedures (if necessary, informed consent was obtained from the patient's legal representative with a witness present)

Exclusion Criteria:

Patients who met any of the following criteria were excluded from the trial:

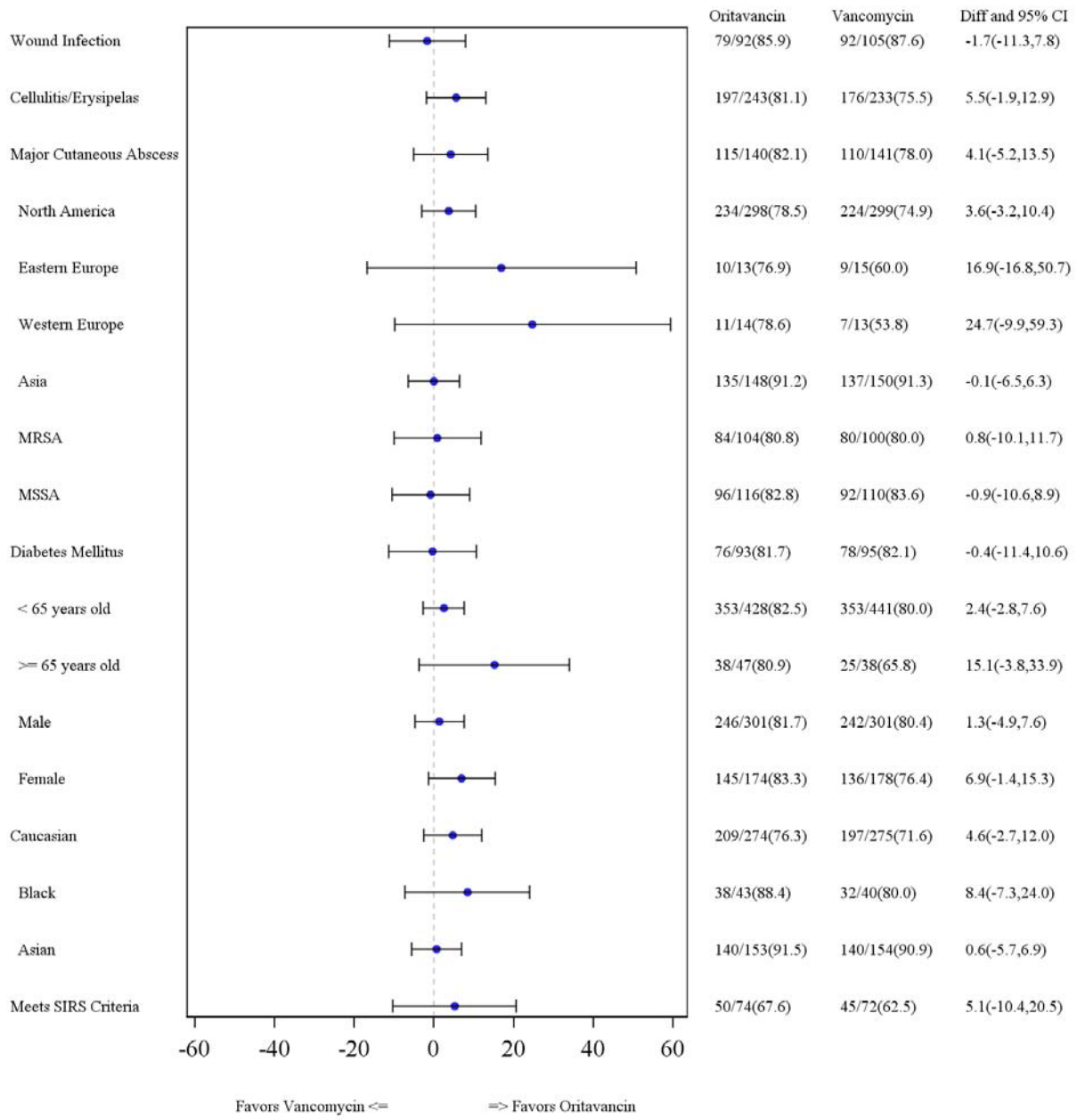
1. Prior systemic or topical antibacterial therapy with activity against suspected or proven Gram-positive pathogens within 14 days preceding randomization unless:
    a. The causative Gram-positive pathogen(s) isolated from the ABSSSI site was resistant in vitro to the antibacterial(s) administered 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 trial randomization)
    c. Patient received a single dose of a short-acting, antibacterial therapy within 72 hours of randomization (e.g., surgical prophylaxis)
2. Infections associated with, or in close proximity to, a prosthetic device
3. Severe sepsis or refractory shock
4. Known or suspected bacteremia at time of Screening
5. ABSSSI, from or associated with, any of the following:
    a. Infections suspected or documented to be caused by Gram-negative pathogens (i.e., 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 (e.g., 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

6. 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
7. Currently receiving chronic systemic immunosuppressive therapy such as chemotherapy or prednisone (prednisone at nonimmunosuppressive doses of≤ 15 mg/day was permitted)
8. Last known cluster of differentiation antigen 4 count < 200 cells/μL in patients with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome
9. Neutropenia with an absolute neutrophil count (ANC) < 500 cells/μL
10. Significant or life-threatening condition (e.g., endocarditis) that would have confounded or interfered with the assessment of the ABSSSI
11. 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
12. 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)
13. Patients that required anticoagulant monitoring with an activated partial thromboplastin time
14. Contraindication to Vancomycin administration
15. Patients unwilling to forego blood and/or blood product donation for at least 3 months from initiation of first trial drug treatment
16. Treatment with an investigational medicinal product within 30 days before enrollment and for the duration of the trial
17. Investigational device present or removed within 30 days before enrollment or presence of a device-related infection
18. Patients whom the investigator considered unlikely to adhere to the protocol, comply with trial drug administration, or complete the clinical trial (e.g., unlikely to survive 90 days from initiation of trial drug)
19. Liver function test (LFT) results ≥ 3x the ULN or total bilirubin ≥ 2X ULN
20. Presence or history of hyperuricemia or gouty arthritis
21. 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.

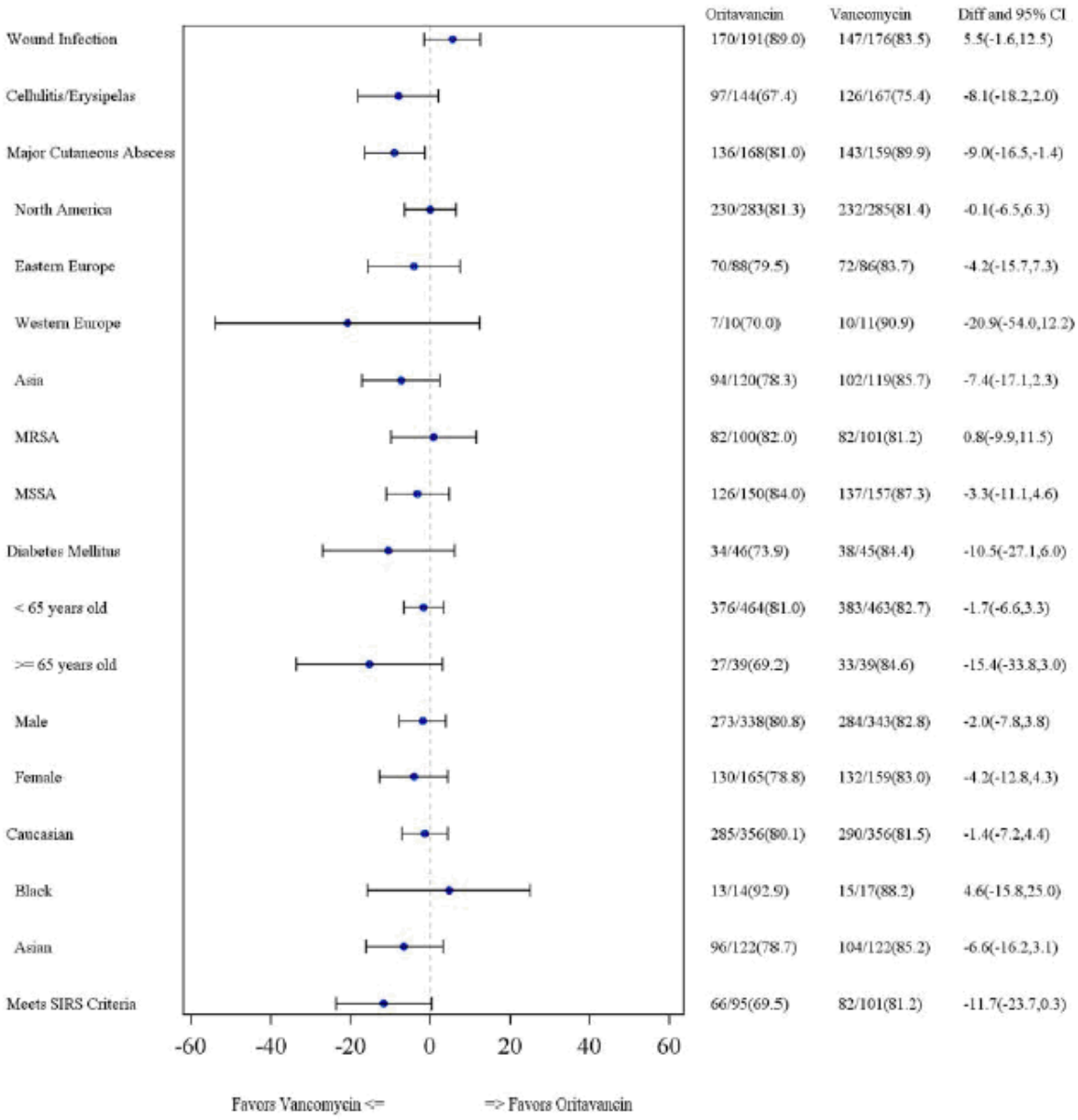
Figure A.1: Forest Plot of Early Clinical Response by Subgroup (mITT Population)



mITT: modified Intent-to-Treat; MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin susceptible *Staphylococcus aureus*; SIRS: systemic inflammatory response syndrome.

Source: Applicant's Figure 3, Clinical Trial report, page 97

Figure A.2 (SOLO II): Forest PLOT of Early Clinical; Response by Subgroups (mITT Population)



mITT: modified Intent-to-Treat; MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin susceptible *Staphylococcus aureus*; SIRS: systemic inflammatory response syndrome.

Source: Figure 3, Applicant's Clinical Trial Report, Page 96.

Table A.1: Lesion Size Area (A*B) of Primary ABSSSI Site at Baseline at ECE in the mITT population (SOLO I)

Timepoint	Oritavancin (N=475)	Vancomycin (N=479)	Diff and 95% CI
Baseline			
Maximum Area (A*B) at Baseline (cm^2)			
n	475	478	
Mean (SD)	405.6 (467.76)	423.0 (524.13)	-17.4 (-80.6, 45.7)
Median	248.0	225.6	
Q1, Q3	140.4, 453.1	140.0, 456.0	
Min, Max	47, 3249	75, 3417	
ECE			
Maximum Area (A*B) at ECE (cm^2)			
n	459	456	
Mean (SD)	193.1 (315.12)	223.5 (393.19)	-30.5 (-76.7, 15.8)
Median	80.0	89.8	
Q1, Q3	40.0, 210.0	42.8, 218.4	
Min, Max	0, 2788	0, 2750	
Absolute Reduction from Baseline			
n	459	456	
Mean (SD)	-218.1 (310.72)	-197.2 (276.17)	-20.9 (-59.1, 17.2)
Median	-132.3	-112.4	
Q1, Q3	-249.4, -68.1	-254.0, -61.5	
Min, Max	-2540, 731	-2183, 1354	
% Reduction from Baseline			
<0% (increase)	11 (2.4)	17 (3.7)	-1.3 (-3.6, 0.9)
>= 0% - <10%	12 (2.6)	17 (3.7)	-1.1 (-3.4, 1.2)
>=10% - <20%	23 (5.0)	25 (5.5)	-0.5 (-3.4, 2.4)
>=20% - <30%	41 (8.9)	41 (9.0)	-0.1 (-3.8, 3.6)
>=30% - <40%	39 (8.5)	30 (6.6)	1.9 (-1.5, 5.3)
>=40% - <50%	47 (10.2)	53 (11.6)	-1.4 (-5.4, 2.7)
>=50% - <60%	43 (9.4)	59 (12.9)	-3.6 (-7.6, 0.5)
>=60% - <70%	63 (13.7)	60 (13.2)	0.6 (-3.9, 5.0)
>=70% - <80%	79 (17.2)	69 (15.1)	2.1 (-2.7, 6.8)
>=80% - <90%	54 (11.8)	47 (10.3)	1.5 (-2.6, 5.5)
>=90% - <95%	24 (5.2)	21 (4.6)	0.6 (-2.2, 3.4)
>=95%	23 (5.0)	17 (3.7)	1.3 (-1.4, 3.9)
Missing	0	0	

Source: Applicant's clinical study report, Table 4.6.7.1, page 887.

Table A.2: Lesion Size Area (A*B) of Primary ABSSSI Site at Baseline at ECE in the mITT population (SOLO II)

Timepoint	Oritavancin (N=427)	Vancomycin (N=408)	Diff and 95% CI
Baseline			
Maximum Area (A*B) at Baseline (cm^2)			
n	426	408	
Mean (SD)	389.2 (396.57)	402.2 (344.12)	-13.0 (-63.4, 37.4)
Median	282.8	303.0	
Q1, Q3	180.0, 440.0	180.9, 461.0	
Min, Max	71, 4250	76, 2184	
ECE			
Maximum Area (A*B) at ECE (cm^2)			
n	426	408	
Mean (SD)	195.5 (252.28)	195.8 (251.47)	-0.3 (-34.5, 33.9)
Median	112.7	125.8	
Q1, Q3	63.0, 238.0	60.0, 213.5	
Min, Max	0, 2236	0, 1924	
Absolute Reduction from Baseline			
n	425	408	
Mean (SD)	-193.9 (237.31)	-206.4 (230.88)	12.4 (-19.4, 44.3)
Median	-133.7	-139.1	
Q1, Q3	-234.0, -78.5	-264.0, -85.5	
Min, Max	-2768, 611	-1507, 919	
% Reduction from Baseline			
<0% (increase)	17 (4.0)	13 (3.2)	0.8 (-1.7, 3.3)
>= 0% - <10%	10 (2.3)	10 (2.5)	-0.1 (-2.2, 2.0)
>=10% - <20%	20 (4.7)	21 (5.1)	-0.4 (-3.4, 2.5)
>=20% - <30%	35 (8.2)	31 (7.6)	0.6 (-3.0, 4.3)
>=30% - <40%	48 (11.3)	38 (9.3)	2.0 (-2.1, 6.1)
>=40% - <50%	48 (11.3)	45 (11.0)	0.3 (-4.0, 4.5)
>=50% - <60%	68 (16.0)	54 (13.2)	2.8 (-2.0, 7.6)
>=60% - <70%	57 (13.4)	66 (16.2)	-2.8 (-7.6, 2.1)
>=70% - <80%	43 (10.1)	59 (14.5)	-4.3 (-8.8, 0.1)
>=80% - <90%	45 (10.6)	36 (8.8)	1.8 (-2.3, 5.8)
>=90% - <95%	14 (3.3)	17 (4.2)	-0.9 (-3.4, 1.7)
>=95%	20 (4.7)	18 (4.4)	0.3 (-2.5, 3.1)
Missing	1 (0.2)	0	

Source: Applicant's clinical study report, Table 4.6.7.1, page 843

Table A.3: Overall summary of safety events (SOLO I)

Category	Oritavancin (N = 473) n (%)	Vancomycin (N = 481) n (%)	All Patients (N = 954) n (%)
Patients with any AE	284 (60.0)	307 (63.8)	591 (61.9)
Study drug-related AE[a]	108 (22.8)	151 (31.4)	259 (27.1)
AE leading to study drug discontinuation	18 (3.8)	28 (5.8)	46 (4.8)
SAE	35 (7.4)	35 (7.3)	70 (7.3)
AE leading to fatal outcome	1 (0.2)	2 (0.4)	3 (0.3)

[a]Includes AEs considered by the investigators as definitely related or possibly related to study drug.

Source: Applicant's clinical trial report, page 7

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Table A.4: Overall summary of safety events (SOLO II)

Category	**Oritavancin (N = 503) n (%)**	**Vancomycin (N = 502) n (%)**	**All Patients (N = 1005) n (%)**
Patients with any AE	256 (50.9)	252 (50.2)	508 (50.5)
Study drug-related AE[a]	109 (21.7)	128 (25.5)	237 (23.6)
AE leading to study drug discontinuation	18 (3.6)	13 (2.6)	31 (3.1)
SAE	22 (4.4)	23 (4.6)	45 (4.5)
AE leading to fatal outcome	1 (0.2)	1 (0.2)	2 (0.2)

[a]Includes adverse events considered by the investigators as definitely related or possibly related to the study drug.

Source: Applicant's clinical trial report, page 6

Table A.5: Patients with rescue antibiotics in trial SOLO I (mITT population)

Patients with Rescue Antibiotics at	Oritavancin (N=475) n (%)	Vancomycin (N=479) n (%)	% Difference (95% CI)
ECE	18 (3.8)	28 (5.8)	-2.1 (-4.8, 0.7)
EOT	15 (3.2)	27 (5.6)	-2.5 (-5.1, 0.1)
Day 10	8 (1.7)	17 (3.5)	-1.9 (-3.9, 0.2)
PTE	9 (1.9)	18 (3.8)	-1.9 (-4.0, 0.2)

ECE: early clinical evaluation; EOT: end of therapy; mITT: modified Intent-to Treat; PTE: post therapy evaluation.
Note: Includes any Gram-positive antibiotic

Source: Applicant's clinical study report, page 91.

Table A.6: Patients with rescue antibiotics in trial SOLO II (mITT population)

Patients with Rescue Antibiotics at	Oritavancin (N=503) n (%)	Vancomycin (N=502) n (%)	% Difference (95% CI)
ECE	13 (2.6)	19 (3.8)	-1.2 (-3.4, 1.0)
EOT	12 (2.4)	17 (3.4)	-1.0 (-3.1, 1.1)
Day 10	6 (1.2)	13 (2.6)	-1.4 (-3.1, 0.3)
PTE	5 (1.0)	12 (2.4)	-1.4 (-3.0, 0.2)

ECE: early clinical evaluation; EOT: end of therapy; mITT: modified Intent-to Treat; PTE: post therapy evaluation.
Note: Includes any Gram-positive antibiotic
Source: Applicant's clinical study report, page 90.

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/s/

MUSHFIQUR M RASHID
05/27/2014

DIONNE L PRICE
05/28/2014
Concur with overall conclusion. Normally, Dr. Valappil would sign as team leader. However, he is on leave; therefore, I am both the secondary and tertiary signoff.